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Review

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Using Continuous Processes to Increase Production

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ABSTRACT: Continuous operations have become popular in both academia and the pharmaceutical industry. Continuous operations may be developed to make high-quality material safely, or because continuous operations are the only effective and economical way to make larger quantities of material. This review surveys the area of continuous processes used to make larger quantities of material and discusses the feasibility of developing economical continuous operations.

1. INTRODUCTION

Multikilogram amounts of drug candidates are needed in drug development, increasing from perhaps 10 kg needed for phase 2 studies up to manufacturing batches that may be hundreds of kilograms. Batch operations, routinely used in the pharmaceutical and fine chemicals industries, are not always easy to scale-up.[1] Warning signs may be seen in the laboratory if there is a change in product yield or quality with a change in (a) mixing speed, (b) additions (portionwise or continuous, rapid, or slow), (c) the position of a feed stream, (d) scale-up to a vessel with different geometry, or (e) holding time before workup. In such cases micromixing,[2] poor heat transfer, or the stability of intermediates or products is the cause. These issues may be identified early in laboratory development, through exploratory experiments run on a small scale and discarded after in-process monitoring. If micromixing is an issue, suitable approaches may include increasing the agitation rate,[3] extending the addition time of a key reagent, diluting reagent solutions for the addition, cooling the reaction or adjusting the pH to moderate the reaction, employing an inverse addition, resorting to a less reactive reagent, such as Ac_2O instead of AcCl, or using continuous operations. Other processes that are candidates for continuous operations are those requiring close contact with sources of energy, such as photolyses, sonochemical reactions or microwave reactions, where the power of the energy source falls off as a function of the square of the distance from the energy source. Continuous operations, which may require some time initially to set up equipment and find optimal concentrations, temperatures, and flow rates, may provide the only practical approach.

In continuous operations, or flow operations, process streams flow through reactors where mixing, temperature, and other parameters can be tightly controlled. Continuous operations can use energy efficiently and produce materials with less waste, an approach to processing which has been termed process intensification.[4] Often these reactors need only small footprints on a bench or plant floor, although continuous stirred tank reactors (CSTRs) may be quite large. For decades continuous operations have been used to economically manufacture high-volume compounds in sectors such as the petrochemical and food processing industries, as with sucrose.[5] High-volume continuous processes within the chemical industries include the manufacture of 1,2-propanediol from glycerol,[6] the manufacture of (*S*)-3-hydroxy γ-butyrolactone from (*S*)-malic acid,[7] and the preparations of cyclopropylamine[8] and solketal.[9] The pharmaceutical industry has been using continuous operations as early as 1962,[10] and the use of continuous processing to streamline the manufacture of drugs has been increasing.[11]

Five considerations primarily drive the development of continuous processes.

- First, by efficiently mixing process streams and controlling reaction temperatures, side products from micromixing and temperature excursions can be minimized,[12] possibly reducing the number of rejected batches in manufacturing. For instance, static mixers are often tubular reactors that that create turbulent mixing through internal elements that split and twist the flow of streams. Due to the high surface area-to-volume ratios inherent in small reactors the application and removal of heat can be very efficient, allowing for fine control of reaction temperatures. Through efficient mixing, continuous operations may decrease solvent usage if high dilution had formerly been employed to decrease the formation of side products. The energy for mixing and temperature control can be applied more directly to a small reactor than to a large reactor, increasing the efficiency of energy usage.[13]
- Second, continuous operations can be applied economically for both cryogenic and high-temperature processes. Sometimes processes requiring cryogenic temperatures in batch mode can be carried out using higher temperatures with short contact times; such operations may eliminate the need for expensive reactors for cryogenic temperatures. These higher-temperature conditions are a variant of high temperature−short time (HTST) processing, which has been used for decades, as in the pasteurization of milk. Processes requiring high temperatures, such as 140−300 °C, can be carried out in coiled tubes immersed in heat transfer fluids or inserted in GC ovens; by constraining hot reaction streams to a small area the damage from any unexpected incidents can be localized and ideally minimized.
- Third, reactive species can be separated, thus minimizing side products and raising yields. For instance, if

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polymerization is an issue, unstable intermediates can be removed from reactors as they are formed and then be subjected to reaction conditions to generate the desired product. Alternatively, if a starting material is reactive towards both the product and another starting material, by efficiently mixing the two starting materials a rapid reaction can be carried out, and the product can then be continuously removed from the entry point of the reactive starting material.

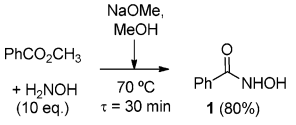
- Fourth, by continuously circulating reaction streams past an energy source such as a lamp or a sonic horn, or through a bed of an immobilized catalyst, the forced contact can ensure rapid reactions. Continuous operations may be the only practical approach to generate large amounts of products from photolyses or sonochemical reactions.
- Finally, the above characteristics of continuous operations may be applied to develop safe processes. Toxic or highly energetic compounds, such as HCN,[14] phosgene[15,16] and diazomethane,[17] may be generated in the quantities needed for complete consumption, or consumed as they are formed, so that large amounts of such materials cannot accumulate and lead to an accident. For instance, Sigma-Aldrich markets a laboratory reactor for the continuous generation of phosgene from triphosgene.[18,19] Continuous flow operations can safely control processes that are exothermic slightly above the desired reaction temperature.[20,21] By using a heat exchanger to cool a reaction mixture immediately after passage through a heated zone, at any moment only a small amount of a reaction mixture may be subjected to high temperatures, thus lessening potential damage from any uncontrolled temperature excursions. Hence for safety reasons continuous operations may be preferred over batch or semibatch operations.

Other potential benefits and disadvantages of developing continuous processes may not be as obvious as those above. For instance, continuous operations may create the opportunity for intellectual property, which the inventors may elect not to disclose by patent or journal publication. A further benefit of continuous operations is that process streams can be continuously monitored using process analytical technology (PAT), fitting well into the quality by design (QbD) initiatives promoted by regulatory authorities.[22,23] The impurity profile of continuous operations may be different from that of batch operations; perhaps the level of unreacted starting material will be higher. A different impurity profile may prompt bridging toxicology studies. Reaction times may be shorter, as heat may be more efficiently removed from reaction streams. Unfortunately, developing the initial continuous process may require more time than desired. To summarize, the primary advantages of continuous operations are safety, yield, quality, and economics.[24]

To generate large amounts of product using continuous operations, three approaches are possible. The simplest approach is to run the process longer, "scaling out." Another approach is to run multiple processes in parallel, "numbering up";[25] complications can arise in simultaneously controlling conditions in multiple reactors. Significantly, no further process development is needed to generate larger amounts of products using those two approaches. The third approach is to develop a process in a larger, continuous reactor, and then scale up, exploiting other benefits of continuous operations.

The equipment and thinking used to develop continuous operations is slightly different from that used to develop batch or semibatch operations. Unless a commercial unit with all components is purchased,[26] more pieces of equipment are needed for continuous operations than for batch operations. Minimal needs include a pump, a reactor, and a vessel to collect the product, along with secure fittings, a device to prevent backflow, a pressure gauge, and a pressure relief valve. Additional components might include vessels, pumps and static mixers for adding starting materials, reagents, or quenches; heat exchangers; probes for in-line analyses, and separators. A reaction can be said to begin when the desired steady-state conditions are reached, which could include temperature, flow rate, or other parameters. For simplicity processes are generally developed to be complete after one passage through a continuous reactor, so the end of the reaction may be determined by the mean residence time, τ (tau), which is essentially the average time needed for a molecule to pass through the reactor. To increase the turbulence in a static mixer a process stream is pumped more rapidly through the mixer, decreasing the τ; however, a decreased τ may not afford enough time for sufficient reaction completion. For example, the hydroxamic acid **1** was prepared in coiled tubing in a Vapourtec system with 0.5 mm internal diameter (ID) PFA (perfluoroalkoxy copolymer resin) tubing (Scheme 1).[27] The authors described

Scheme 1. Variables examined in optimizing the preparation of a hydroxamic acid using continuous operations



flow rate (mL / min)	τ (min)	temperature (°C)	conversion, %
0.5	5	50	52
0.5	5	70	65
0.5	5	80	58
1.0	20	60	76
1.0	20	70	74
1.0	30	70	80

how τ and the temperature of the coiled tubing influenced the yield.[28] To change the stoichiometry streams may be pumped into a reactor at different rates. Other considerations to optimize continuous processes, such as concentration of reactants, equivalents of reagents, quenching or inverse quenching, are similar to those of optimizing batch processes.

Types of continuous reactors are classified in Figure 1. The first division is based on the concentration of molecules in the reactors. In CSTRs the contents exit from the tank at the same rate as process streams are continuously added, thus holding the volume constant. For the ideal CSTR the material being added to the reactor is evenly dispersed instantly. In contrast to CSTRs, in plug flow reactors (PFRs) the concentration of starting materials and products varies with the distance in the path of flow between the inlet and the outlet. As a simple illustration of a PFR, a bolus of starting material might be injected into the inlet of a small-diameter tube and through pressure and heat emerges from the outlet of the tube as a bolus of product. Other divisions of continuous reactors are shown in Figure 1 and discussed in this review. Nomenclature is summarized at the end of this review.

Upon scrutiny, what has been termed a continuous process can be seen to be a semi-batch or semi-continuous process. For instance, the feed solutions of starting materials and reagents may be prepared in the fashion of batch operations. The output from a continuous reaction may be combined and worked up and crystallized as batch operations. The terms "continuous reaction," "continuous process," and "continuous processing"

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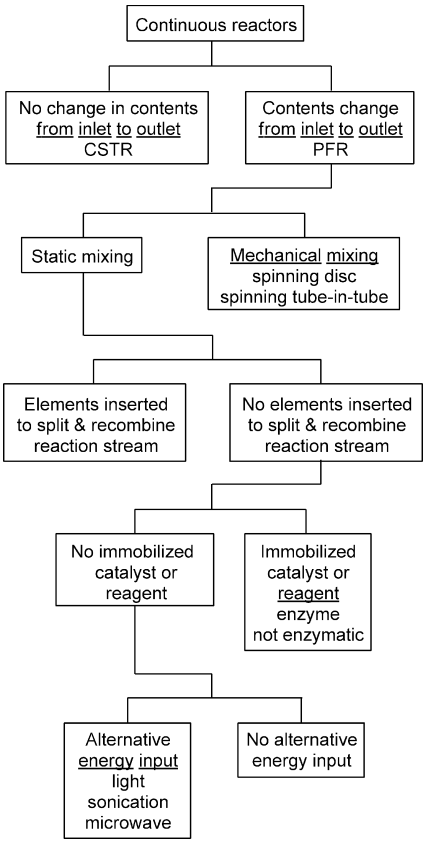


Figure 1. Classification of continuous reactors.

may be used to describe a process that includes a continuous operation.

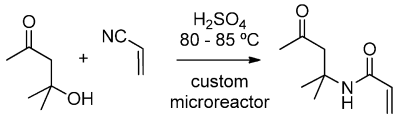
Continuous operations have been reviewed.[29−44] This review focuses on continuous processes used to make products on scale.[45] The following two sections are loosely based on the size and type of the continuous processing equipment. Section 1.1 discusses microreactors and reactors using small-diameter tubing. Microreactors may be used to demonstrate proof of concept for continuous operations, for initial process optimization for scale-up, and to prepare large amounts of material. The size of a continuous reactor is determined by the τ: longer residence times require reactors of larger volumes. Larger reactors may also be employed for increased throughput (kg/hour). Section 1.2 discusses continuous operations using larger-diameter reactors to prepare large quantities of material, without using commercial microreactors. Many of the operations in the Section 1.2 can be performed using equipment that is relatively common to laboratories and pilot plants.

1.1. Microreactors and Small-Diameter Tubing for Scale-Up. Microreactors may first come to mind for continuous operations.[44,46−48] Microreactors are manufactured by precision engineering from metal, glass, or ceramics, with the width of fluid channels generally ranging from submicrometers to submillimeters. Operations conducted in reactors larger than the channels of microreactors may be called mesofluidics. Mixing and heat exchange are efficient in these small channels. Components of microreactors include mixers for liquids and gases,[49] areas with immobilized reagents,[50] separators,[51] heat exchangers,[52] and gas separators;[53] to conserve space these components may be stacked on top of each other.[54] Many microreactors have become commercially available over the past 10 years.

Diverse applications have been demonstrated and promised for microfluidics. Biodiesel has been prepared using microreactors,[55−57] and the yield of crude oil may be increased by gas-to-liquid conversion using microreactors.[58] Velocys has developed microchannel reactors with immobilized catalysts to produce synthetic fuels.[59] Drug discovery and analyses have been carried out on a "lab on a chip".[60] Microreactors have been used in peptide synthesis,[61] polymerase chain reactions,[62] glycosylations,[63] and fluorinations.[64] Microreactors have been used for on-demand production of hazardous materials, such as H_2O_2[65−67] and methyl ethyl ketone peroxide.[68] Trimethyl orthoacetate has been manufactured using tubes of 1 mm diameter.[69] Microreactors can be rugged; for instance, aminolyses in EtOH were carried out in a microreactor at 245 °C.[70,71] Using glass microreactors, Corning and DSM carried out a hazardous nitration under cGMP conditions, manufacturing more than 25 tons in four weeks.[72] A custom ceramic microreactor was used to generate 100 kg/week of a product from an exothermic Grignard reaction.[73] All types of PFRs shown in Figure 1 have been used in microreactors.

A striking example of an economical application of continuous operations using a microreactor is shown in Scheme 2. Custom

Scheme 2. Continuous manufacture of a monomer by Ritter reaction



2 (40 tons/day)

metal microreactors were developed to manufacture the monomer **2**. Using continuous operations DSM was able to control the exothermic Ritter reaction, decrease exposure to acrylonitrile, and rapidly process the product streams to decrease decomposition. Yields rose by 15%, waste decreased by 15%, and 40 tons/day of this monomer could be manufactured.[74,75]

Some compounds made by commercially available microreactors on small scale are shown in Scheme 3. Quantities of oxadiazoles such as **3** were prepared as a library for discovery compounds.[76] Thales Nanotechnology developed the H-Cube Continuous-Flow Hydrogenation Reactor, which uses disposable packed catalyst cartridges and generates H_2 by electrolysis.[77] Faster reductions are afforded by forcing contact of the reaction stream with the catalyst.[78] A group from Thales described reductions of nine functional groups,[79] and the Ley group has also described reductions of imines and hydrogenolyses.[80] In the example shown in Scheme 3 a benzyl group on amine **4** was removed;[81] a drug discovery group used this equipment routinely for such hydrogenolyses.[82] The pyrrole **5** was generated in essentially quantitative yield through an exothermic Paal−Knorr reaction run at 20 °C; with four microreactors running in parallel, in one hour 55.8 g of the pyrrole was produced.[83] Nitration of a sildenafil intermediate was carried out at about 90 °C, showing proof of concept; tight temperature control was necessary, as the reaction was exothermic and the product **6** decomposed above 100 °C.[21] In the reduction of methyl butyrate using diisobutylaluminum hydride Lonza researchers showed that continuous reactions at −20 °C could be used to produce butyraldehyde **7** in a yield equivalent to batch operations in the laboratory at −65 °C; these researchers had found that in batch operations at −78 °C

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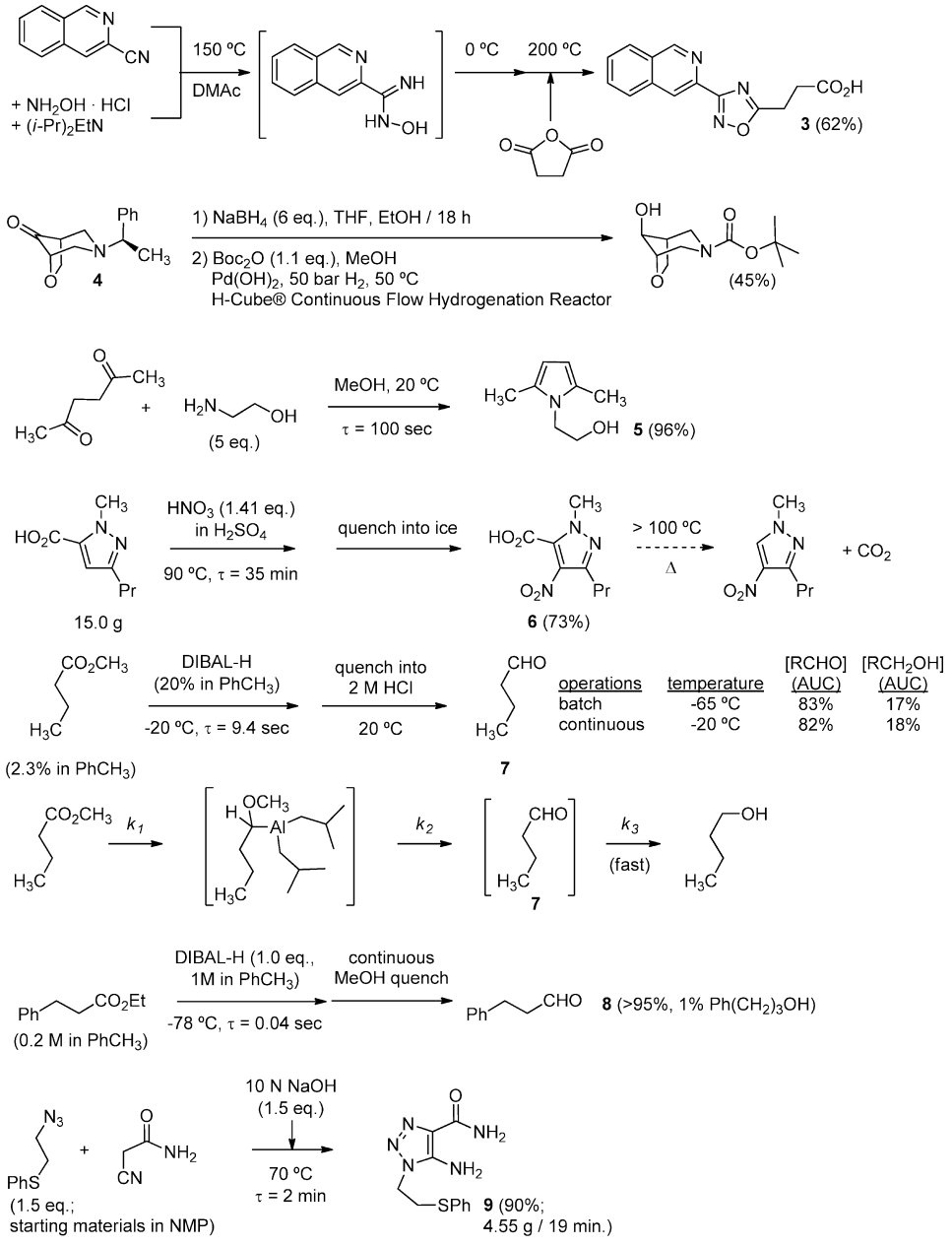
Scheme 3. Some reactions carried out in commercially available microreactors



DIBAL-H reduction of another ester in the pilot plant generated more impurities than did similar reduction in the laboratory at −78 °C. Over-reduction to the primary alcohol could be a problem if k_2 was fast relative to k_1, as shown for the reduction of methyl butyrate.[84] The Jamison group found that with cryogenic temperatures, a short residence time and continuous quenching with MeOH they could reach excellent yields and selectivities for the DIBAL-H reduction of esters to aldehydes, as with the generation of **8**.[85] The aminotriazole **9** was prepared from cyanoacetamide and *β*-azidoethyl phenyl sulfide, as a safe synthon for ethyl azide; proof of concept for scale-up was demonstrated with the partial output from an input of about 5 g of cyanoacetamide.[86] Phenols have been converted to the triflates and then to biaryls by Suzuki-Miyaura couplings using an immobilized catalyst in a packed-bed reactor; the liquid−liquid extraction unit in the microreactor was critical to purify the intermediate triflate and allow the reaction sequence to proceed in good yield.[87,88] Using microreactors the Yoshida group developed a Swern oxidation at 20 °C,[89] as opposed to the cryogenic conditions usually employed for a Swern oxidation.[90,91] A group from N. V. Organon showed that Swern oxidation processes were effective at −20 to 0 °C, probably because the short reaction times limited the formation of the side products from Pummerer rearrangement.[92] Wiles and Watts carried out Strecker reactions in a microreactor using TMSCN.[93] Peptides have been synthesized using triphosgene to activate the carboxylic acid.[94,95]

Thales Nanotech's X-Cube Flash reactor, which can operate continuously up to 200 bar and 350 °C,[96] has been used in a number of high-temperature applications, some of which were more efficient than the original microwave processes.[97] One application was the formation of the nitrophenyl pyrazole **10** in Scheme 4.[98] Contact of the process streams with the stainless steel (SS) tubing that was part of the X-Cube reactor led to the

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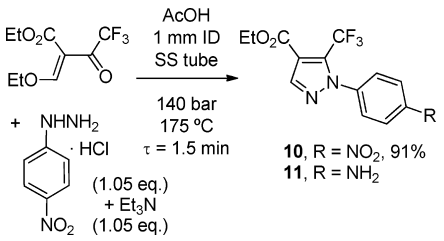
Scheme 4. A reaction carried out in a commercially available continuous reactor at high temperature



formation of the corresponding aniline side product, **10**. By reducing the residence time the formation of **11** was minimized; however, pyrazole formation by reaction of *p*-nitrophenylhydrazine with another ketone gave the corresponding aniline as the primary product, despite a shortened residence time.

Reactors made of small-diameter coiled tubing have been used to prepare quantities of material through continuous operations (Scheme 5). In an example showing the promise of sequential operations, the McQuade group prepared ibuprofen (**12**) through the sequence of acylation, oxidative rearrangement, and hydrolysis.[99] Using 1 mm ID tubing substituted pyrrolidine **13** was prepared in high yield through a [3 + 2] dipolar cycloaddition.[100] Reactions with hydrazine and methylhydrazine were carried safely and rapidly at 150−250 °C in a coiled tube reactor, affording benzopyrazoles such as **14**.[101] When a Newman-Kwart rearrangement in DME was heated to 300 °C, pressures of 1000−1100 psi resulted, causing the solvent to become supercritical and double in volume. DME was chosen because the solvent could be readily chased by heptanes for extractive workup, and at the reaction temperature both starting material and product (**15**) were very soluble. A syringe pump that operated under pressure was used to charge the solution of starting material.[102] In batch operations the yield of a bromide-lithium exchange and subsequent reaction gave decreasing yields with increasing scale-up, probably due to the stability of the lithiated thiophene, and continuous operations were investigated. Conditions were developed that gave 92% overall conversion to **16**, suitable for preparing larger amounts of material.[103,104] The rapid optimization of these conditions was limited by the time needed to prepare and run NMR samples to monitor the reaction.[105] Researchers from the Stahl group and Lilly developed continuous operations for an O_2-mediated oxidation of alcohols such as **17** using a soluble palladium catalyst and a reactor made of 0.305 in ID SS tubing. To preclude combustion of the solvent vapors with O_2[106−108] the researchers used 8% O_2 in N_2.[109] Using a syringe pump, a Y-mixer and a reaction coil of 0.5 mm ID PFA tubing, Leduc and Jamison developed conditions for the NaOCl-mediated oxidation of alcohols under biphasic conditions. A catalytic charge of tetrabutylammonium bromide was necessary for the oxidation; these flow conditions eliminated the need for passing the reaction streams through a bed of an immobilized catalyst.[110] Continuous nitrations were safely carried out in 1 mm ID PFA tubing to control the reaction temperatures below the temperature of decomposition, resulting in high yield and high productivity for **18** and other nitroarenes.[111] 1-Decene was ozonolyzed in a Vapourtec R4 unit (1 mm ID tubing), giving productivity comparable to batch operations. Continuous operations were preferred for safety reasons because the temperature of potentially exothermic reactions could be readily controlled, and because reactive ozonides could be continuously quenched. Continuous ozonolyses could be run at −10 °C instead of temperatures of about −78 °C routinely used for batch operations; the authors also described the fluid behavior of the reaction stream in the presence of this gas.[112,113] Researchers from the Kuraray Company developed a continuous process for a hetero-Diels−Alder reaction using a 4 mm ID Teflon tube, 8 ft long; semibatch operations gave a slightly lower yield of **19**.[114,115] Researchers from Actelion Pharmaceuticals and ZHAW Zurich University of Applied Sciences noted an exothermic polymerization in a Diels−Alder reaction between acrylonitrile and diene **20**, and they developed a continuous process to control the reaction temperature and minimize the danger from polymerization. After carrying out scoping studies in a microwave oven, they developed a continuous process using 2.2 mm ID SS tubing.[116] Using a 2.0 mm ID stainless steel tube coiled in a GC oven, researchers from Lilly carried out a continuous Claisen rearrangement to prepare **22**.[117] Continuous operations were chosen for safety; the authors mentioned that stainless steel tubing that they used could withstand pressures of 110−300 bar. Lilly researchers also prepared benzyl azide **23** in a hot tube reactor (0.64 mm ID); further research indicated that a phase transfer-catalyzed continuous process may be more economical for manufacturing the product azide.[118] For safe operations in a cyclopropanation using dimethylsulfoxonium methylide at high temperatures, Lilly researchers found continuous operations to be promising for safe scale-up.[119] A series of 12- to 22-membered macrocycles was formed in good yields by acetylene−azide cycloaddition, catalyzed by flow through 0.75 mm ID copper tubing.[120] These processes indicate the success possible with relatively simple equipment, using tubing no bigger than 4 mm ID.

Solids can clog or even plug microchannel reactors, tubing, and static mixers, prompting many researchers to develop homogeneous solutions for continuous processing. Some manufacturers of microreactors have approached this problem by constructing microreactors with deeper channels.[75] The McQuade group has developed a system to encapsulate solids in mineral oil in tube reactors, and prevent plugging on a small scale.[121] Eliminating constrictions and sonicating at key points can help prevent plugging.[122] Merck researchers have shown that on a small scale magnetic stirbars in tubes can prevent plugging.[123] Wiles and Watts have given a number of examples where operations using reaction streams with some insoluble components were carried out successfully in microreactors.[124]

Many have promoted microreactors for rapid process optimization.[75,125−127] Sigma-Aldrich researchers discussed using microreactors for reaction screening and production in 2004.[128] Seeberger was quoted as saying that "Microreactors will become the round-bottom flasks of the 21st century."[126,129] Microreactors have been used to demonstrate the feasibility of making large amounts of material through continuous operations.

1.2. Continuous Operations Using Larger Reactors. Other types of continuous reactors include PFRs such as static mixers and simple tubing, CSTRs, spinning discs, and spinning tube-in-tube reactors. These reactors are discussed below.

The operation of spinning disk reactors and spinning tube-in-tube reactors can produce thin films, permitting rapid heat exchange and promoting contact of the materials with the surface of the reactors. Solutions applied to the center of a spinning disk are driven to the edges by centrifugal forces, and the contact time with the disk is inversely proportional to the

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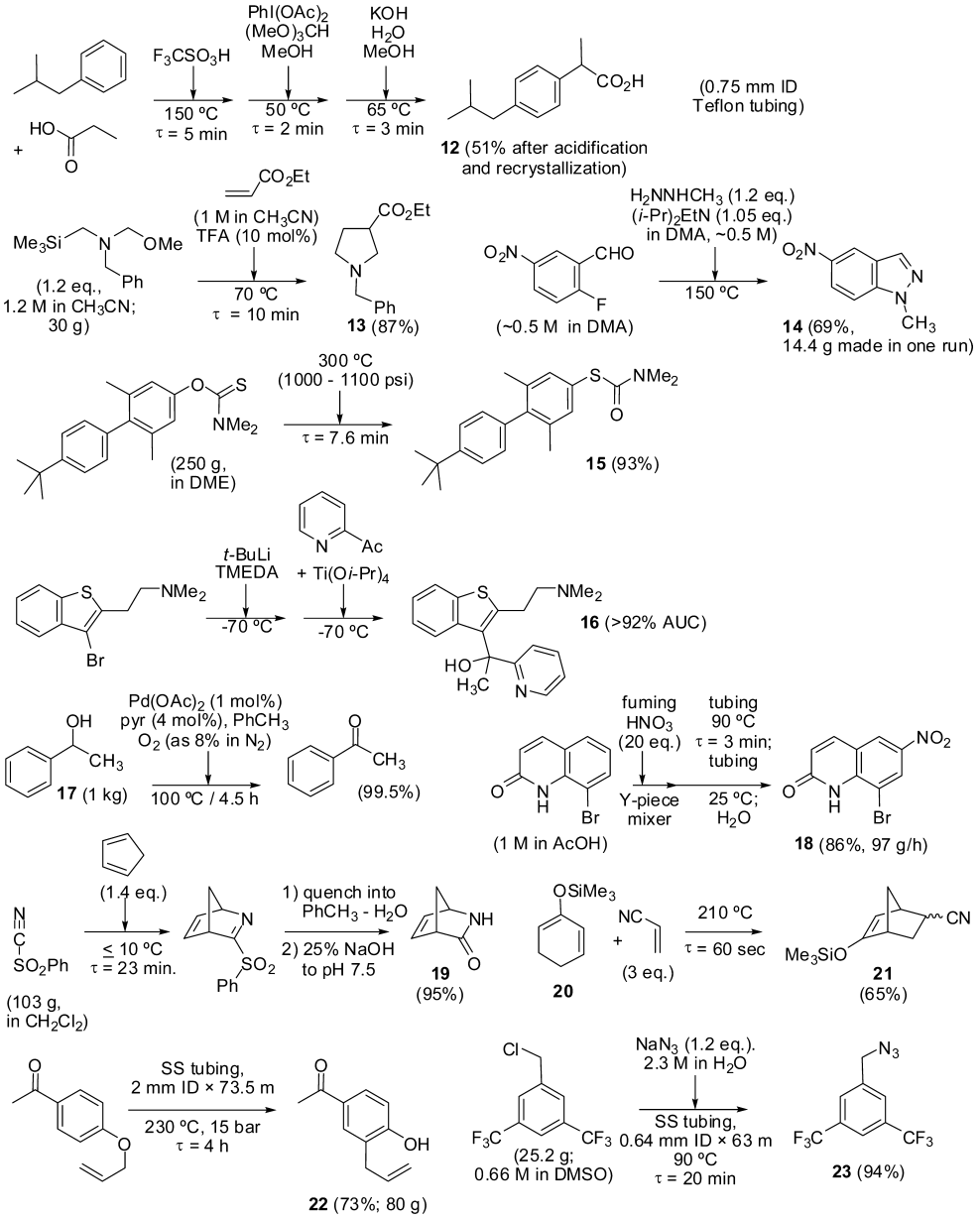
Scheme 5. Some continuous processes carried out in coiled tubing



angular velocity.[130,131] A group from the University of Newcastle upon Tyne demonstrated the potential of a spinning disk reactor for the catalytic isomerization to afford campholenic aldehyde **25**.[132] Solutions of α-pinene oxide **24** in 1,2-dichloroethane (DCE) were applied to the surface of a disk coated with $Zn(OTf)_2$-silica catalysts, and isomerization to **25** was completed in less than 0.5 s (Scheme 6). The short contact time minimized further reactions of the product. The coated discs were reused 14 times with no decrease in selectivity, perhaps because the high-shear forces of the system promoted the movement of the molecules away from the surface of the disk. A spinning disk reactor was very effective with an intrinsic phase transfer-catalyzed Darzen's condensation, minimizing hydration of the desired nitrile **26** to the amide **27**.[133] Under optimized conditions for continuous operations the desired epoxynitrile was 88% of the product composition; for some comparison, the epoxynitrile was isolated in 73% yield from batch operations.[134] The SmithKline Beecham group estimated that by using spinning disk technology a throughput of 8 tons/year of the epoxynitrile was possible. These researchers also presented data that an API could be crystallized with a small particle size and with a narrow particle size distribution using a spinning disk reactor. Nanoparticles of trans-β-carotene have been prepared through processing with spinning discs.[135] Other uses may be developed for spinning discs, such as liquid−liquid separation; for instance, a device with vertically spinning grooved discs rapidly recovers oil from oil spills at sea.[136] A microreactor spinning disk reactor is commercially available.[137]

A spinning tube-in-tube reactor (STT) has been developed to make biodiesel, with a stated capacity of 110,000 tons/year. Such reactors increase reaction rates by improved mixing through high shear rate, which is independent of the residence time and dependent upon the angular velocity and the gap

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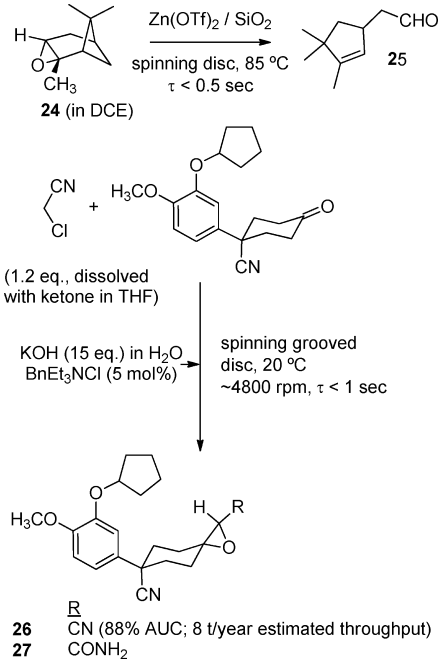
Scheme 6. Some continuous processes carried out in spinning disc reactors



between the spinning internal tube and the stationary external tube (Figure 2).[138] A STT has been used in biphasic

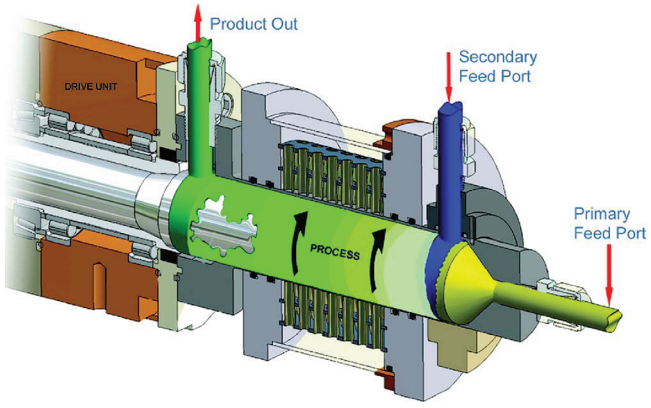
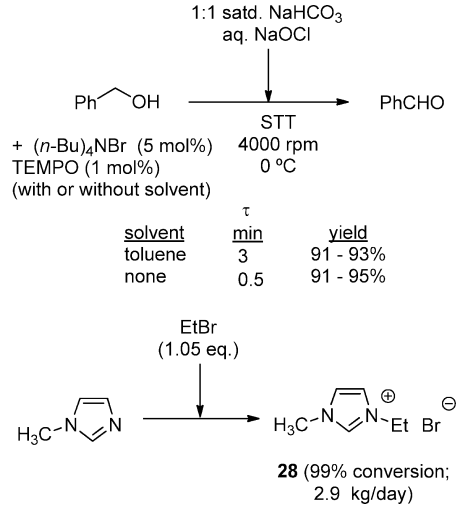


Figure 2. Diagram of a spinning tube-in-tube reactor. *Reprinted with permission from Gonzalez, M. A.; Ciszewski, J. T. Org. Process Res. Dev. 2009, 13, 64. Copyright 2008 American Chemical Society.*

TEMPO-mediated oxidations of benzylic and aliphatic alcohols to aldehydes and ketones in excellent yields.[139] Perhaps the high shear of that reactor minimized the formation of side products seen with poor agitation in some TEMPO oxidations.[140] Most of those oxidations in the STT were carried out using toluene and 3−6% aq NaOCl, but solvent-free oxidation of benzyl alcohol using 13% NaOCl gave benzaldehyde in a comparable yield.[139,141] A STT was used to prepare ionic liquids such as **28** (Scheme 7) under solvent-free conditions, with production rates as high as 18 kg/day.[142] STTs can also be used for processes that generate solids. STTs may be considered as true instruments of process intensification.[143] Both spinning disk reactors and STTs have considerable potential for generating large amounts of materials through continuous operations.

Scheme 7. Some continuous processes carried out in spinning tube-in-tube reactors



1.2.1. Use of CSTRs and Bubble Reactors. CSTRs can improve operations and quality of crystallized products, as described by Genck[144] and Tung and coauthors.[145] Ozonolyses can be hazardous, as both the addition of ozone to olefins and quenching the intermediate ozonides can be exothermic, and the ozonides can be reactive in high concentrations.[106] Abbott researchers developed CSTR conditions for the safe ozonolysis of styrene, as a model for the ozonolysis of an API intermediate (structure not disclosed).[146] To minimize the release of unreacted ozone to the atmosphere, styrene was charged to the reactor based on the theoretical rate of ozone generation, so that 1.2 equivalents of O_3 was available for reaction. The reaction mixture containing ozonides overflowed from the 100 mL reactor into a quench solution, thus avoiding accumulation of the ozonides (Scheme 8). Using this reactor about 90 g/day of the API intermediate was generated (98% conversion, 81% isolated product). To increase the amount of material that could be produced daily an ozone generator with an output of about 15 mol/h was then used. With the increased flow of gases the loss of solvents through entrainment was a concern using the CSTR mentioned above, so a "bubble reactor" was designed and built to accommodate a higher gas flow. The O_3−O_2 mixture was introduced at the bottom of the reactor through a coarse frit, generating fine bubbles to improve the reaction rate. The product stream overflowed through a valve on the side of the reactor. Under these conditions an output of about 80 g/h of the product was generated. Scaling up the size of the reactor was considered to be less complicated than numbering up, as running multiple reactors in parallel would have required multiple controls for safely handling ozone.[147] Using a bubble reactor constructed from a chromatography column packed with glass beads, Pfizer researchers ozonolyzed styrene **29**. In this counter-current flow reactor the O_3−O_2 mixture was introduced at the bottom of the column and the solution of the olefin was pumped into the top. The output solution of the ozonide was quenched into Me_2S in MeOH. In this fashion 1 kg of the styrene was ozonolyzed.[148,149] For safe operations using O_2 BMS researchers scaled up a continuous oxidation to **30** in a stainless steel tube (0.875 in ID) filled with packings.[150] Using a microreactor the researchers had demonstrated the feasibility of continuous operations for this oxidation. In runs with a larger trickle bed reactor controlling the temperature of

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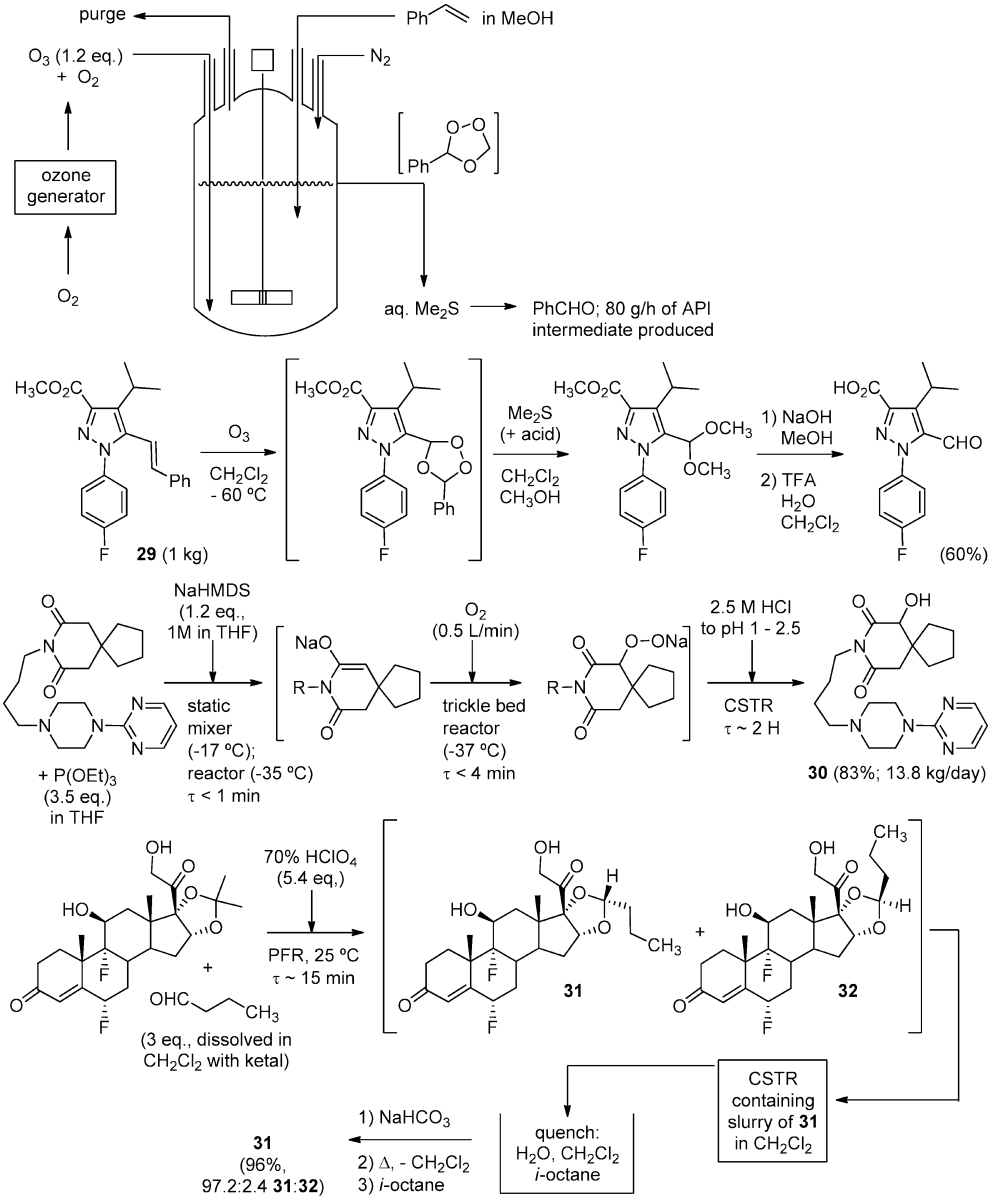
Scheme 8. Continuous reactions carried out in CSTRs and bubble reactors



this exothermic oxidation was difficult, and increased levels of impurities were expected; to make larger amounts of material the operation was numbered up to four parallel tube reactors clustered inside a heat exchanger. Pfizer researchers used a CSTR to crystallize the desired acetal diastereomer **31** through a rapid crystallization-induced asymmetric transformation.[151,152] The acetal formation was carried out in a PFR for safety reasons, as the isolated semisolid mixture of **31, 32** and excess $HClO_4$ was highly explosive.[153]

1.2.2. Plug Flow Reactors to Generate Large Amounts of Material. Laminar flow and turbulent flow are the two primary types of liquid flow in tubes. Laminar flow is motion mostly parallel to the axis of the tube, and can provide efficient mixing on the scale of microreactors but usually not for larger reactors. Turbulent flow is vigorous, random flow, and through turbulent flow both mass transfer and heat transfer can be efficient. In the ideal PFR mixing occurs only radially, not axially; conceptually reactants mix in thin discs moving away from the entry point, and the composition changes until a plug of product emerges from the reactor.[154,155] Turbulent flow can be measured by the dimensionless Reynolds number (*Re*), and for turbulence in PFR operations *Re* should be greater than 3500−4000 (eq 1).[156,157] To reach the same *Re* in a reactor of twice the diameter the linear velocity would be halved; however, under these conditions the flow rate (liters/sec) would double. For effective scale-up to a larger PFR, calculations using both *Re* and the residence time distribution are key.[158]

$$Re = du\rho/\mu \quad (1)$$

where d = tube diameter (m), u = mean linear velocity (m/sec), ρ = bulk density of fluid (kg/m^3), and μ = dynamic viscosity (Newton·s/m^2)

Static mixers, a type of PFR, create turbulence as materials flow past internal stationary elements that split and sometimes twist the flow of the stream (Figure 3). Static mixers are energy-saving devices that can mix materials as diverse as hydrocarbons and tomato paste. Static mixers range in size from 3/16 in. ID to 10 ft ID, with larger custom sizes possible,[159] and can be

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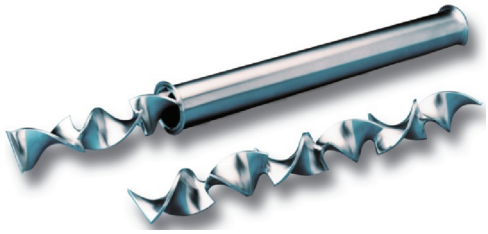

Figure 3. Sanitary static mixer, showing removable internal mixing elements. *(Used by permission of Chemineer, Inc.).*

used in settings from the laboratory to the pilot plant to manufacturing. Applications include mixing low-viscosity or high-viscosity solutions, gases in liquids, suspensions of solids, or even solids.[160] A static mixer made of Pyrex glass was used to observe the formation of solid hydrates.[161] A specialized static ozone mixer is available that introduces ozone to process streams through a fritted tube oriented perpendicular to the axis of the PFR;[162] ozone is used to sterilize water in municipal water treatment plants.[163−165] Compact mixers can also be clamped between the flanges of two pipes, and other mixers have been developed to disperse gases in liquids.[166] Small static mixers are portable and could be considered cGMP friendly, as a new mixer could be used for each campaign. Many of the operations in the examples following could be carried out using static mixers.

1.2.3. Applications of Static Mixers in the Pharmaceutical Industry. Static mixers have been used to separate reactive starting materials, intermediates and products, as in Scheme 9. Merck researchers described the preparation of L-alanyl-L-proline (**34**), a penultimate intermediate for enalapril, using the *N*-carbonic anhydride derivative (NCA) of L-alanine (**33**).[167] This approach avoided the protection and deprotection of L-alanine. With batch operations the yield was 90% when the NCA was added in less than 5 s; the yield dropped to 65% when the addition was extended to 3 min. Unfortunately reduced yields resulted upon 50-fold scale-up.[168] In another publication E. Paul, an engineer involved with the project, explained that under batch operations the reduced yields resulted from formation of the tripeptide **35** from reaction of the product with the NCA.[169] A static mixer was used to thoroughly mix the starting materials and remove **34** from the entry point of the NCA, reducing the formation of impurity **35**. Continuous operations were scaled up from 0.8 cm ID in the laboratory to 1 in. ID in the plant with no change in selectivity. Researchers have also shown that for the highly exothermic reaction of Boc_2O with an amine static mixers could provide temperature control that was superior to batch operations, with better selectivity.[170] For instance, at 20−25 °C the biphasic reaction mixture generated the protected enamine **36** in almost quantitative yield; higher temperatures led to some hydrolysis.[171] Static mixers have also been used to produce solutions of sodium γ-hydroxybutyrate (**37**); by controlling the mixing of aqueous NaOH and the temperatures no further adjustment of the pH was needed for subsequent formulation.[172] A Grignard reagent of pentafluorobenzene was generated by a bromide−metal exchange reaction using ethyl magnesium bromide, because the product Grignard **38** cannot be readily prepared using magnesium metal.[173] In pilot-plant trials, a static mixer was used to control the reaction temperature, and the product was generated in high yield. A Lilly group has also used continuous operations to prepare a Grignard reagent.[174] In a striking example of practical scale-up of continuous operations, a continuous Swern oxidation was carried out at 40 °C with a residence time of 0.1 s.[175] The reactor for this high-throughput process was only a 2.1 in. ID pipe with two 90° bends to increase turbulence. The 61% isolated yield of **39** was only slightly better than the batch yield of 55%,[176] but continuous operations afforded better control of the processing.[177] The latter is a good example of HTST processing.

1.2.4. Continuous Processing Using Immobilized Catalysts. The use of immobilized catalysts and flow-through chemistry has been reviewed,[178,179] along with processes to immobilize catalysts.[180] By passing reaction streams through a bed of catalyst reaction rates often increase, due to the forced contact. Using Jones reagent (H_2CrO_4) supported on silica, benzylic alcohols were oxidized to aldehydes or acids; longer contact times with the reagent selectively produced the acids.[181] Researchers in the Poliakoff group have used fixed catalyst beds and supercritical CO_2 (sc CO_2) to methylate amines, alcohols, and carboxylic acids by reaction with dimethyl carbonate,[182,183] and to hydrogenate isophorone to the saturated ketone.[184] Suzuki−Miyaura couplings were carried out in a fixed-bed reactor containing Pd(II)EnCat 40 catalyst using either toluene−MeOH or sc CO_2−MeOH solutions (Scheme 10). With the latter solvent mixture, two passages through the catalyst were required for quantitative conversion to the biphenyl product **40**.[185] Using immobilized Pd(0) nanoparticles a Heck reaction was conducted in DMF or EtOH at 130 °C.[186] The Lectka group has used resin-bound reagents for synthesis by continuous flow through sequential columns.[187] The Jacobsen group immobilized salen complexes onto silica for hydrolytic kinetic resolution of epoxides.[188] Boc-proline has been immobilized on silica for catalytic aldol reactions, using packed columns.[189,190] Acidic Amberlyst resins were used to catalyze the Michael addition of 2-methylindole to enones.[191] Immobilized Pd has been used in microreactors for Suzuki−Miyaura couplings[192] and C−N cross-couplings.[193] The Ley group has developed many processes for continuous flow synthesis.[194] Borane-based chemistry in a fixed bed reactor has been proposed as the most economically feasible route for the isomerization of linear internal olefins to linear alpha olefins.[195] The Poliakoff group and others have investigated the use of sc CO_2 for hydrogenations in flow-through operations; H_2 dissolves readily in sc CO_2, facilitating reductions.[196]

1.2.5. Continuous Processing Using Enzymes. Reactions of immobilized enzymes may be considerably faster when the reactant streams flow through a packed bed of catalyst rather than in batch processing. Subjecting an immobilized enzyme to high shear in a stirred tank can also shorten the effective lifetime of an enzyme, making a packed bed reactor more attractive for long-term manufacturing.[197] For example, for two of three secondary alcohol substrates resolution using vinyl acetate and *Candida antarctica* lipase B (CAL-B) was faster when the immobilized enzyme was contained in columns.[198] Using an immobilized CAL-B in a packed bed reactor, a dynamic kinetic resolution was optimized to prepare chiral ester **41** (Scheme 11).[199] Tao and co-workers provided more details on the reduction of an α-keto acid to the chiral alcohol **42** using a two-enzyme system.[200] A solution of the starting material was pumped into a reservoir containing D-lactate dehydrogenase (LDH), formate dehydrogenase (FDH), and NADH, and the reaction stream exited through a nanofiltration membrane, which retained the enzymes. (NAD(P)H cofactors have been regenerated electrochemically in a microreactor,[201] which could

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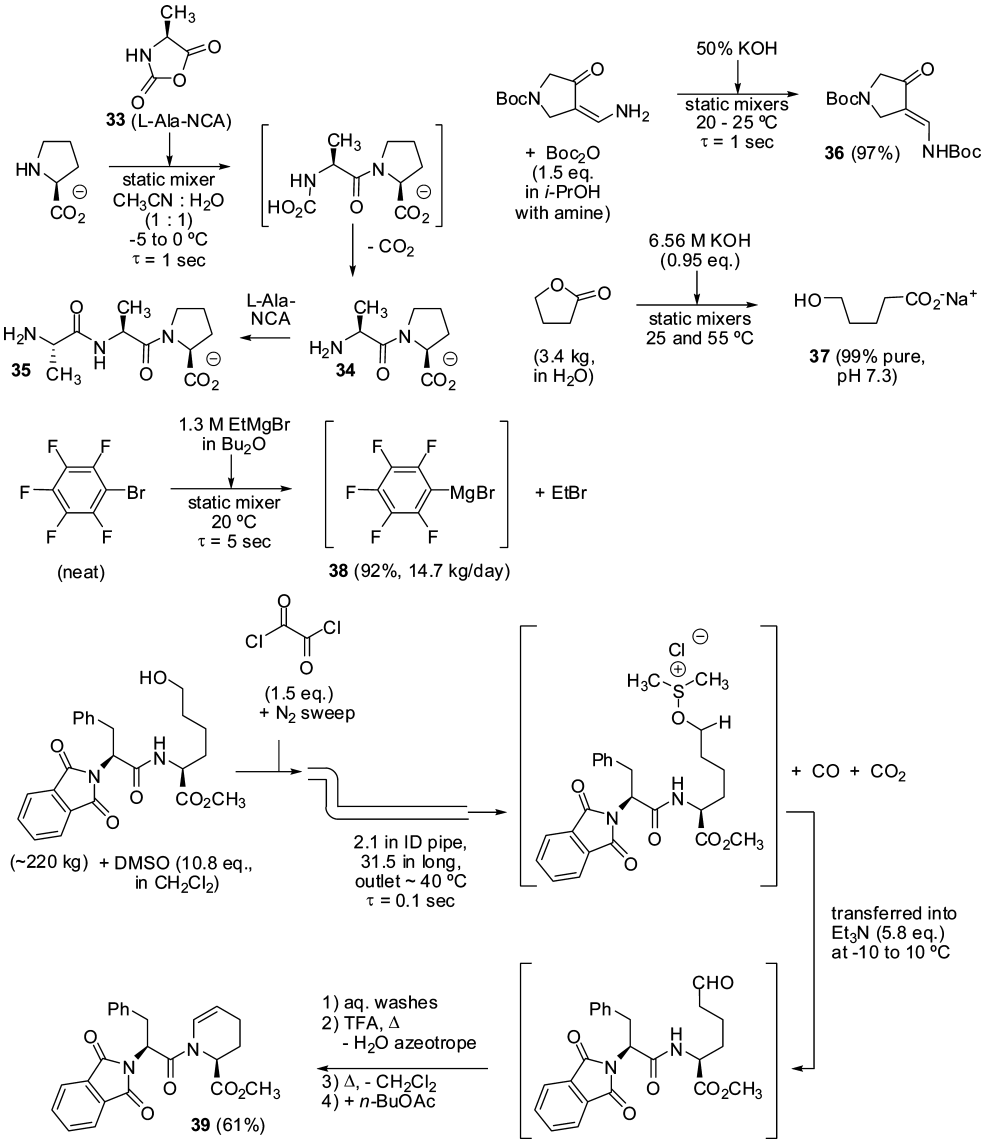
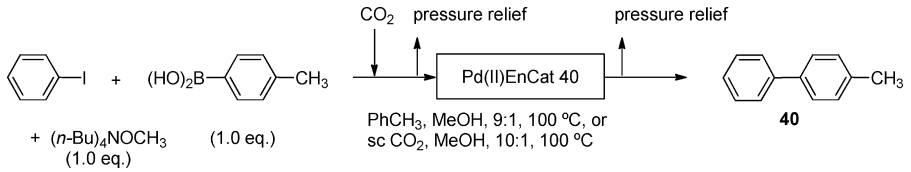
Scheme 9. Some continuous operations using static mixers



Scheme 10. Continuous Suzuki–Miyaura coupling with an immobilized catalyst



eliminate the need for FDH.) Using an enzyme reactor, nanofiltration, and simulated moving bed chromatography, an efficient epimerization of D-fructose to D-psicose was demonstrated on a laboratory scale.[202] A column packed with raw almond meal, a source of oxynitrilases, was eluted with a solution of aromatic aldehydes and HCN in diisopropyl ether.[203] Chiral cyanohydrins such as **43** were prepared in as high as 99% ee, demonstrating the utility of continuous flow operations for crude enzyme preparations.[204] An immobilized mutase was used to convert aryl hydroxylamines to *o*-aminophenols.[205] Response surface methodology was used to optimize the esterification of stearic acid with racemic 1,2-isopropylidene glycerol, using an immobilized lipase and an X-Cube.[206] Enzymes may also be immobilized in microreactors, as with a ß-glycoside hydrolase that was immobilized in a silicon rubber microreactor.[207]

1.2.6. Continuous Operations for Photolysis, Sonication, Microwave Chemistry, and Hot-Tube Reactions. Since the intensity of energy falls off with the square of the distance from a point source, reaction streams are best positioned close to the light source or sonic horn for photolysis and sonochemistry, respectively. Continuous operations are probably the most effective way to make more material through photolysis and sonication. Continuous operations can also localize the energy needed for microwave processes and hot-tube reactions.

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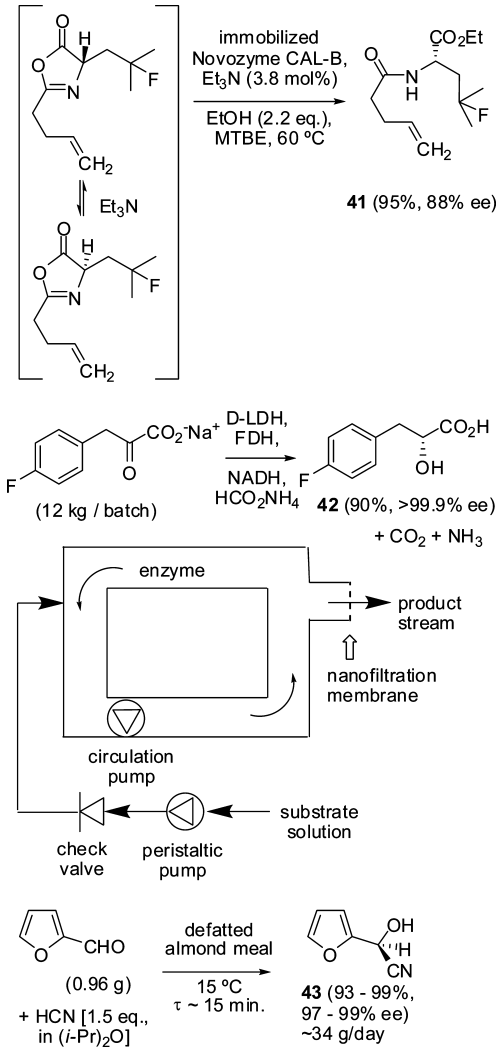
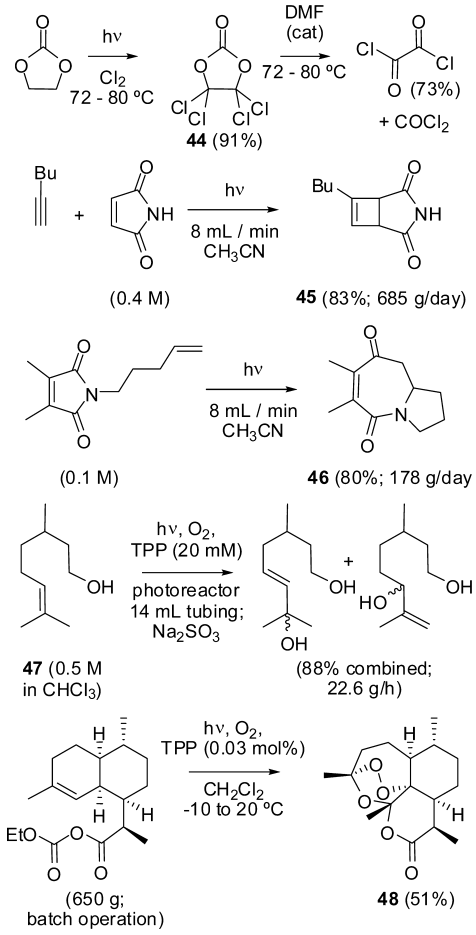
Scheme 11. Continuous catalytic operations using enzymes



1.2.7. Photochemistry. Photochemistry can provide some powerful transformations[208−210] and has numerous applications. For instance, ultraviolet light can be used to purify water for injection.[211] Continuous photo-oxidation has been used to purify wastewater: sunlight excites a metal−porphyrin dye immobilized onto beads of an ion-exchange resin, generating singlet oxygen from oxygen bubbled through the reactor.[212] Photobioreactors have been used to grow algae, a source of energy as an alternative to petroleum distillates.[213,214] Exhaustive photolytic chlorination of dimethyl carbonate produces triphosgene.[210] Continuous photochemical chlorination of ethylene carbonate produced the tetrachloro derivative **44,** and then heating in the presence of DMF formed oxalyl chloride and phosgene (Scheme 12).[215] Continuous "two-wavelength photolysis"[216] was used to prepare vitamin D3.[217] By coiling four layers of solvent-resistant, UV-transparent fluoropolymer tubing around a lamp, researchers passed streams of starting materials close to the light source and generated photolysis products in high yields; curiously, a lower yield of **45** was obtained when the solution of starting materials for the [2 + 2] reaction entered the inner layer instead of the outer layer of the coiled tubing. A high yield was also obtained for the intramolecular [2 + 2] reaction to afford **46.**[218] The Seeberger group constructed a similar photoreactor for the

Scheme 12. Photolyses



singlet oxygen oxidation of citronellol (**47**) and other alkenes, using tetraphenylporphyrin (TPP) as a sensitizer.[219] A commercial falling film microreactor made of glass was used in the singlet oxygen-mediated oxidation of cyclopentadiene; the reactive peroxide intermediate was quenched as it was generated.[220] Artemisinin (**48**), a stable peroxide[221] and antimalarial compound,[222] may be manufactured by photochemistry.[223,224] A photoreactor for continuous operations is commercially available.[225]

1.2.8. Sonochemistry. Sonication produces microcavitation, or the formation and implosion of microbubbles, which can enhance mixing, raise temperatures microscopically, and exert considerable force on reaction components. The theory and applications of sonochemistry have been reviewed.[226−228] Continuous sonication at room temperature has been examined to oxidize sulfurous contaminants in marine gas oil.[229] Biodiesel and fine emulsions can be produced through sonication.[230] In an example from the pharmaceutical industry, on-scale sonication fractured large crystals, facilitating filtration and handling; Ostwald ripening subsequently removed the fines, making the crystals more uniform.[231] Such sonication and temperature cycling has been used to prepare irbesartan on large scale.[232] Sonication has been used to enhance crystallization by impinging jets,[233,234] and to generate particles small enough for inhalation.[235] Crystal slurries may be circulated from a vessel past a sonic probe, or passed through a flow cell fitted with external sonic sources mounted annularly or radially.[226] In the laboratory agitation was shown to have a significant effect in the sonochemistry of suspensions.[236]

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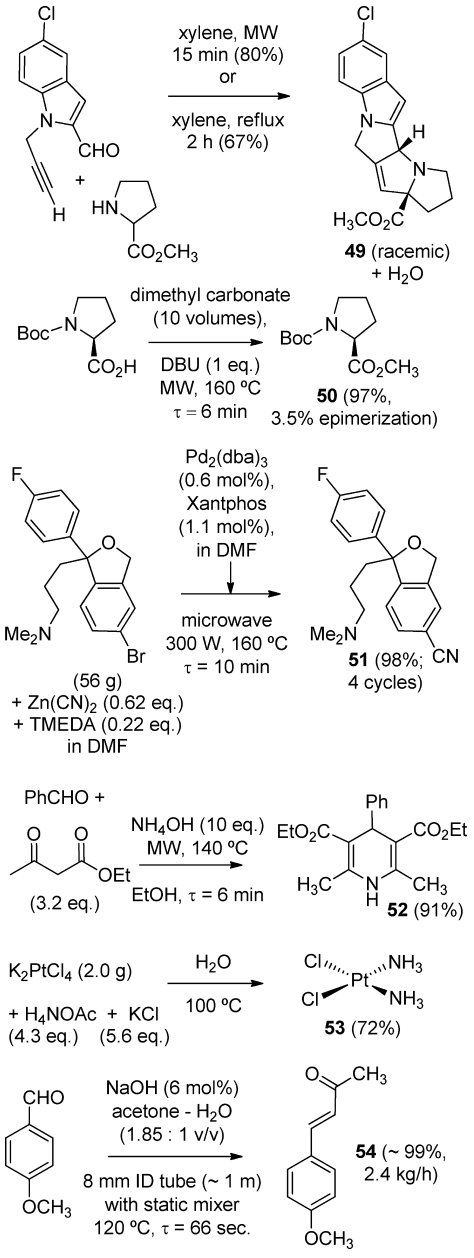
1.2.9. Microwave Processes. Microwave-assisted chemistry has been powerful for drug discovery and organic synthesis.[237−239] In what are essentially HTST conditions, microwave (MW) processes can dramatically speed up and improve the yield of reactions.[240] For instance, under microwave irradiation the proline adduct **49** was formed by dipolar cycloaddition in significantly higher yield than by reaction under thermal conditions (Scheme 13).[241] Under

Scheme 13. Some continuous microwave and hot-tube reactions



microwave irradiation esterification of Boc-L-proline with dimethyl carbonate to afford **50** was about 80 times faster than esterification at 90 °C, the boiling point of dimethyl carbonate.[242,243] Using stop-flow conditions citalopram **51** was prepared in almost quantitative yield.[244] The Kappe group found that under continuous microwave processing Pd was leached from an insoluble (Pd/C) catalyst, and $Pd(OAc)_2$ was preferred as a precatalyst for continuous Mizoroki−Heck reactions.[245] Microwave-assisted Suzuki−Miyaura couplings were carried out using continuous-flow conditions through an immobilized Pd catalyst; under the conditions employed the Pd catalyst became extremely hot, melting the polymer matrix. To prevent the reactor from plugging due to extended heating, a cycle of microwave radiation, then cooling was developed.[246] Using flow conditions the Leadbeater group prepared the 1,4-dihydropyridine **52** in high yield,[247] and they also carried out carbonylations.[248] The Leadbeater group has described approaches to scale-up microwave reactions in continuous or batch mode.[249] Microwave chemistry and hot-tube reactions may be considered together, as the Kappe group has shown that high temperatures are the essential part of microwave reactions.[250] By substituting heat for microwave irradiation cisplatin **53** was prepared using continuous operations.[251] The Kappe group showed that an aldol-Claisen reaction could be carried out in essentially quantitative yield without microwave irradiation, affording the chalcone **54**.[252] Groups have discussed how to translate high-temperature microwave processes in batch mode to continuous-flow operations for the production of larger amounts of material.[253−255] Commercial units are available for making larger amounts of material through continuous-flow and stop-flow microwave techniques, and for continuous-flow high-temperature reactions under PFR conditions.[256]

As with microreactors, plugging of microwave reaction tubing can be an issue. In one approach to this issue, the Leadbeater group has shown that under continuous operations process streams emerging from a reactor can be diluted with a suitable solvent to dissolve the product.[257] Precipitation need not be an issue that prevents microwave and hot-tube reactions from rapidly providing larger amounts of material.

2. SUMMARY AND PERSPECTIVE

Continuous operations may be the best way to generate large amounts of products when micromixing or rapid heat transfer is an issue, or when reactions on scale require the application of external energy, as with photolysis or sonication. Some processes benefit from the physical separation of reactants and products that is possible through continuous operations. Significantly, continuous operations may be employed for safe operations on scale.

Equipment for many continuous operations is simple and readily available, but some additional considerations may be warranted. Microreactors and other PFRs may inhibit the volatilization of low-boiling components, thus speeding reactions that might be slowed in a batch mode because a volatile component was localized in the headspace of the reactor.[70] Despite the fact that high pressures can be generated under some flow conditions, processes can be carried out safely through pressure regulators and pressure relief valves. If high temperatures and pressures are anticipated, the safety of the equipment can be assessed with initial trials using an inert solvent. Corrosion may be accelerated under reaction conditions, and equipment suppliers may have some data that can be applied to the reaction conditions. For safe operations most reactors for continuous operations can be heated or cooled to control reaction temperatures; in-line heaters or chillers can also be used before and after the reactors. Lapkin and Plucinski have discussed engineering factors for efficient continuous processes.[4] Reactors designed for large-scale continuous operations are commercially available.[258]

In selecting equipment for continuous operations a number of factors should be considered. With the passage of a suspension of solids in liquid, a microreactor may plug, and larger scale (mesofluidic)

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reactors may be preferred. For reactions with gaseous reagents many reactors could be used, such as microreactors, static mixers, and CSTRs. PFRs may be preferred to contain volatile reagents and solvents in processes accelerated by heating, as mentioned earlier. PFRs would be a logical choice for reactions involving immobilized catalysts, photolysis, sonication, microwave irradiation, and high temperatures and low temperatures. STTs may be preferred to force intimate mixing of suspensions or viscous liquids. If extremely short residence times are needed, such as <1 s, a spinning disk reactor may be preferred; small-diameter discs may be necessary in this case, so that large quantities of product would be made by scaling out or numbering up. PFRs can also be employed for reactions with short residence times; high back-pressure due to rapid flow may determine the practicability of such conditions. As discussed earlier, reaction temperatures can influence reaction kinetics, and correlating τ with reaction kinetics is key for efficient operations. The Kirschning group has recently highlighted current issues in flow chemistry.[259]

Some researchers may be dissuaded from developing continuous operations due to concerns about portions of process streams that were generated from nonsteady state operations and may be out of specification. Ideally only small amounts of such process streams would be generated in any run, perhaps two residence times at the beginning and end of the operation. At least three approaches are practical for cGMP manufacturing under continuous operations. First of all, an inert solvent could be pumped through a reactor until the desired parameters have been met, and then streams of reactants could be directed into the reactor. Second, substandard portions of the process streams, as detected by online analyses, could be separated from the main portion of the batch. Those portions could be reworked or sent for disposal. Alternatively, if the fate of the impurities were well understood, for instance if high levels of starting materials were present, then the subpar portions of the process streams could be returned to the continuous reactor for further processing. A third approach is to collect the entire process stream from continuous operations and process further to ensure homogeneity and high quality, such as by recrystallization. Collectively those operations become semicontinuous or semibatch. Although blending *batches* that fail specifications with acceptable batches in order to meet specifications is not acceptable,[260] semicontinuous operations to process the entire output of a batch could be successfully validated, once the ability of processing to tolerate impurities was well understood.[261]

Another cGMP-related concern may be how to define a batch generated under continuous operations. The output from semicontinuous operations, as mentioned above, could constitute a batch. The output generated every day or the output generated from a given quantity of a starting material could also constitute a batch. As long as a batch is logically defined, it is unlikely to fail regulatory approval.

Continuous processes are not suitable for all reactions. There may be little incentive to change batch operations, such as crystallizations, that routinely perform well. Reactions requiring hours, such as fermentations, multicomponent reactions, and crystallization-driven processes,[151,152] might be inappropriate, unless some advantages were available through CSTR.

The impact of continuous operations in the pharmaceutical industry has been debated. For example, in 2009 Federsel estimated that 10−20% of the processes in both the fine chemicals and pharmaceutical industries were continuous.[262] In 2005 Roberge and co-workers estimated that half of the processes used in the pharmaceutical industry could benefit from continuous operations.[263] Dowle, of the Center for Process Innovation, stated that continuous processing would greatly reduce both operating expenses and capital expenses.[264] Cue and co-workers feel that continuous operations will decrease the percentages of rejected batches in manufacturing, in concord with PAT.[265,266] In 2005 a group of researchers from CPC Cellular Process Chemistry GmbH estimated that only a few microreactor plants were manufacturing products,[267] and in 2011 Ondrey estimated that worldwide 20−30 plants were using microstructured reactors for manufacturing.[75] Although the data above are only estimates, clearly the development of continuous processes within the pharmaceutical and associated industries has grown recently. Experienced CROs and CMOs are available to develop continuous processes. The push towards continuous processing as the means for cost-effective manufacturing operations will continue.

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Notes

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NOMENCLATURE

CAL-B	*Candida antarctica* lipase B
CSTR	continuous stirred tank reactors
HTST	high temperature−short time processing
ID	internal diameter
LDH	D-lactate dehydrogenase
FDH	formate dehydrogenase (FDH)
MW	microwave
NCA	*N*-carbonic anhydride
PAT	process analytical technology
PFA	perfluoroalkoxy copolymer resin tubing
PFR	plug flow reactor
QbD	quality by design
Re	Reynolds number
sc CO_2	supercritical CO_2
SS	stainless steel
STT	spinning tube-in-tube reactor
τ	residence time (tau)
TPP	tetraphenylporphyrin

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