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Practical Use of Continuous Processing in Developing and Scaling Up Laboratory Processes

Neal G. Anderson*

Anderson's Process Solutions, P.O. Box 782, Nicasio, California 94946, U.S.A.

Abstract:

Continuous operations can be used for the efficient scale-up of many processes that cannot be carried out through batch operations. Rapid reactions with reactive intermediates and products can be scaled up in the laboratory using continuously stirred tank reactors (CSTR) and plug flow reactors (PFR). Continuous processing in small reactors allows for better control of exothermic processing, creating a larger margin of safety for scale-up. This review also discusses the advantages of continuous processing for thermochemical rearrangements, immobilized catalysts, and microwave, photochemical, electrochemical, and sonochemical processes. Many of these continuous operations can be performed using equipment readily available for the laboratory, and can be readily scaled up in the laboratory and pilot plant.

Introduction

Batch operations, routinely used in the pharmaceutical and fine chemicals industries, can lead to problems with scale-up. Continuous operations can avoid scale-up difficulties in two types of processes. The first involves relatively fast reactions with reactive intermediates or products that can degrade under extended batch processing. In this case continuous processing is used to control mixing during critical additions, or dispersal or quenching of the product stream. Continuous processing can also be used to tightly control reaction temperature, pH, or other process conditions. The second type of processes aided by continuous processing are those requiring close contact of process streams with a localized area of a specialized reactor. The desired reaction in such processing is not always rapid, and the process stream may be recycled through the reactor to increase process yields. This review outlines continuous processes that use relatively common laboratory equipment for effective scale-up of some processes that would be difficult or impossible to scale up using batch operations.[1]

One may appreciate potential limitations of batch operations by considering common round-bottomed flasks (Table 1). In a 25-mL flask rapid top-to-bottom mixing is possible, but such mixing is slower in a 22-L vessel, in part due to the taller reactor height. Clearly micromixing[2,3] is more of a concern in the larger vessel. Loss of selectivity when scaling up the processing of multifunctional molecules often indicates that rapid mixing is an important control element. The high surface area-to-volume ratio of the 25-mL flask permits rapid heat transfer through external cooling; the heat transfer burden (cal/cm^2) is about 10 times higher in the larger vessel, and raises concerns for tight heat control during rapid additions. Heat control in a larger vessel is difficult if ineffective mixing creates localized hot spots. Concerns about micromixing and heat transfer are exacerbated with further scale-up of batch operations in larger flasks and reactors, and small reactors afford the best opportunities to control reaction conditions. As logical extensions of this reasoning, microreactors (vide infra) are being developed.[4−6]

Most reactions developed by discovery chemists in small flasks cannot be scaled up by simple multiplication without incident. Generating large amounts of material by repeatedly running batch operations in a small reactor is a tedious approach that allows room for many errors. An alternative approach has been to continuously pass process streams through small reactors where the process conditions are tightly controlled. Operations in small reactors run in parallel can produce larger amounts of material by a "numbering up" approach.[7] Benefits of continuous processing include control of product yields and quality, improved productivity, decreased safety concerns, and others.

Continuous operations may not be considered for some processes until scale-up difficulties occur. Then it may be discovered that rapid reactions are involved, and that mixing, the most common cause of scale-up difficulties, is very important. Warning signs are a change in product yield or quality with laboratory mixing speed, with the addition rate or the position of a feed stream, or with scale-up in a vessel of a different geometry.[8] For effective scale-up in batch operations, it may not be enough to vary the addition mode (extended, split, and inverse additions; spraying and subsurface additions, etc.). Such processes may be best scaled up using continuous operations. Other reactions requiring close

(1) Anderson, N. G. *Practical Process Research & Development*; Academic Press: San Diego, 2000. This review expands upon material found primarily in Chapter 13.

(2) For discussion of micromixing, mesomixing, and macromixing, see: Baldyga, J.; Pohorecki, R. Turbulent micromixing in chemical reactors: a review. *Chem. Eng. J.* **1995**, *58*, 183; Baldyga, J.; Bourne, J. R. *Turbulent Mixing and Chemical Reactions*; Wiley: New York, 1999; Atherton, J. H.; Carpenter, K. *Process Development: Physicochemical Concepts*; Oxford University Press: Oxford, 1999; *Handbook of Batch Process Design*; Sharratt, P. N., Ed.; Blackie/Chapman & Hall: New York, 1997; Genck, W. J. Crystallization's Forgotten Facet. *Chem. Eng.* **1997**, *104(10)*, 94.

(3) On a large scale, minutes of mixing may be required to reach equilibrium conditions throughout a vessel. For instance, as much as 5 min may be needed for pH stabilization in a 200-gal reactor.

(4) Ehrfeld, W.; Hessel, V.; Löwe, H. *Microreactors: New Technology for Modern Chemistry*; Wiley-VCH: Weinheim, 2000.

(5) See review of ref 4: Laird, T. *Org. Process Res. Dev.* **2001**, *5*, 89.

(6) Ondrey, G. Mastering Microengineering. *Chem. Eng.* **2001**, *108(7)*, 27.

(7) Reference 4, p 9.

(8) Crabb, C. Controlling Fast Reactions. *Chem. Eng.* **1999**, *106(6)*, 30.

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Table 1. **Physical characteristics of small and large glass vessels**

	25-mL round-bottomed flask	22-L round-bottomed flask
height (sphere, cm)	3.6	34.8
speed of top-to-bottom mixing	very rapid mixing possible	mixing not always rapid
surface area/volume[a] (cm^2/mL)	1.66	0.17
heat generated/surface area[b] (cal/g)	36.2	347.1

[a] As a sphere, neglecting thickness of glass wall. [b] For a full reactor with a reaction mass generating 60 cal/g of heat.

contact of the process stream with specialized areas of a reactor, for example, photochemical and sonochemical reactions, are best scaled up using continuous-flow reactors. While continuous processes have long been employed for the manufacture of commodity chemicals, such processes can also be implemented in the laboratory, allowing for scale-ups that would be difficult to effect under batch processing.

Batch, Semi-Continuous, and Continuous Processing. In the pharmaceutical and fine chemicals industries, most processes are developed for batch or semi-continuous operations. In a batch process all the reaction components are combined and held under controlled conditions until the desired process endpoint has been reached. Reactions are typically slow, taking hours, and the product is isolated at the end of the process cycle. Unit operations, such as fermentation and crystallization, can be carried out on the entire batch with fine control. Because the product output, typically no more than hundreds of kilos, can be readily correlated with input materials, batch operations are suited for cGMP considerations. For these reasons batch processing is commonly used in the pharmaceutical and fine chemicals industries.

Semi-continuous operations, also known as semi-batch, batch-flow, or (in the biotechnology industry) fed-batch[9] processes, combine aspects of both batch and continuous operations. For example, a reactor may be gradually filled with process streams, with none of the mixture being displaced. After a suitable time the product is isolated. An example of this is the controlled crystallization of a product by slow pH adjustment or addition of an antisolvent. The output from continuous operations can also be combined and treated as a batch, for example, recrystallized; such processing is also considered semi-continuous. The distinction between batch and semi-continuous operations is often blurred, and strictly speaking many processes used in the pharmaceutical and fine chemicals industries are semi-continuous processes.

Continuous processing is typically used to prepare commodity chemicals on a tonnage basis. There are two primary types, continuously stirred tank reactors (CSTR) and plug flow reactors (PFR),[10] along with the recently developed microreactors.[4] In CSTR processing, process streams are continuously mixed in reactors and continuously harvested; after a vessel is filled the output streams overflow into another reactor at the same rate as the input streams are added, thus maintaining a constant volume under steady-state conditions. On a microscopic scale there is a range of residence times for molecules as they enter and leave such a mixed vessel, and as more mixed vessels are added in series the reactor train becomes more characteristic of a batch system.[11] The continuous, controlled movement of the process streams through equipment increases the product throughput on a space-time basis, allowing more material to be made from a smaller plant with smaller capital investment than would be possible under batch conditions. Typically continuous processes are used for fast reactions, requiring minutes or less. For the preparation of high-quality material it is essential that the process be conducted with little variation from optimal conditions; such steady state conditions should be reached quickly upon start-up of the processing for optimal yields.

PFRs are tubes commonly constructed of metal or plastic. As narrow-bore tubes, the high surface area-to-volume ratio allows for rapid heat transfer and control of reaction temperature. Mixing in PFRs occurs radially, not axially,[11] making PFRs useful for minimizing side reactions in which reagents react with the product. PFRs that are run at elevated temperatures are sometimes called hot tube reactors, and they have many uses in industry. Other PFRs are static mixers, inexpensive tubes with stationary internal elements that split and sometimes rotate the streamflow, producing intimate mixing.[12] Static mixers are powerful tools, with diverse applications ranging from mixing solutions in low-viscosity solvents to blending peanut butter.[13] Most PFRs are relatively inexpensive, portable, and useful for the laboratory, pilot plant, and manufacturing.

Microreactors, miniaturized systems produced by microtechnology and precision engineering, have fluid channels in the range of submicrometers to submillimeters, and reactors at the higher end of this range are sometimes referred to as minireactors.[14] The structural elements of microreactors include static mixers, reactors, microseparators, heat ex-

(9) For an example, see: Zimmermann, Th. P.; Robins, K. T.; Werlen, J.; Hoeks, F. W. J. M. H. Bio-transformation in the Production of L-Carnitine. In *Chirality in Industry II*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; John Wiley & Sons: New York, 1997; p 287.

(10) For detailed discussions, see Oldshue, J. Y. *Fluid Mixing Technology*; McGraw-Hill: New York, 1983; Levenspiel, O. *Chemical Reaction Engineering*, 3rd ed.; John Wiley & Sons: New York, 1999; Denbigh, K. G.; Turner, J. C. R. *Chemical Reactor Theory*, 3rd ed.; Cambridge University Press: Cambridge, 1984; Walas, S. M. Chemical Reactors. In *Perry's Chemical Engineer's Handbook*, 7th ed.; Perry, R. H., Green, D. W., Maloney, J. O., Eds.; McGraw-Hill: New York, 1997; pp 23−61; *Scaleup of Chemical Processes. Conversion from Laboratory Scale Tests to Successful Commercial Size Design*; Bisio, A., Kabel, R. L., Eds.; Wiley: New York, 1985.

(11) Michel, B. J. How Mixing Helps and Hurts Continuous Processing. *Chem. Processing* **1989**, *July*, 24.

(12) For a thorough discussion see May 1988 bulletin for Kenics Static Mixers KTEK Series. Information and equipment is also available from http://www.komax.com, http://www.chemineer.com, http://www.kenics.com, and others.

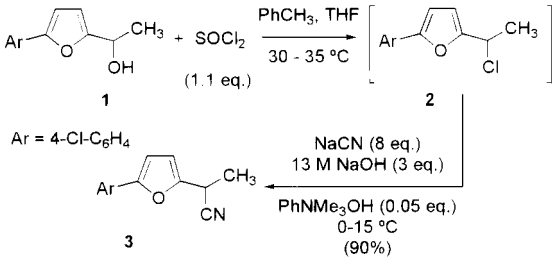
(13) Chemineer Sanitary Mixer Bulletin 820.

(14) Reference 4, p 6.

changers, pumps, and other components,[6] and the primary focus is to intensify mass transport and heat exchange.[15] Microreactors have been used for peptide synthesis[16] and PCR amplification,[17] and hold promise for commercial applications.[4] As the microreactor field is an emerging technology, few devices are commercially available.[6,18] This review examines continuous processing with equipment more commonly available for the laboratory, and does not include microreactors.

Power and Productivity of Continuous Processing. Financial considerations have led to the development of large-scale continuous processing. High-volume solvents such as MTBE[19] and EtOAc[20] have been produced by continuous contact of starting materials with an immobilized acidic catalyst. Simulated moving bed chromatography (SMB) is a powerful technique for cost-effective, continuous purification.[21] Continuous processing has been used in the manufacture of silanes and siloxanes.[22] In the manufacture of cyclopropylamine by Hofmann rearrangement of cyclopropylcarboxamide, CSTR processing has been developed to control the exothermic hydrolysis of the intermediate isocyanate,[23] and PFR technology is claimed to increase productivity.[24] Highly reactive compounds such as diazomethane[25] and phosgene[26] are generated continuously in small volumes due to safety considerations. Polyacrylate resins have been made by PFR technology with improved productivity.[27] A continuous photochemical process is used to manufacture cyclohexanone oxime, a precursor to caprolactam.[28] In the solid-phase manufacture of oligonucleotides, continuous processing using axial-flow packed bed reactors is markedly more efficient than processing using stirred-bed reactors.[29] An excellent review on industrial and laboratory applications of continuous processing was published in 1992.[30]

Scheme 1. **CSTR processing to generate an unstable chloride**



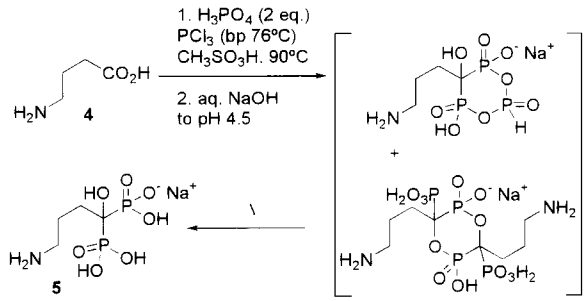
Continuous processes have been used for scale-up in the laboratory and pilot plant. The feasibility of continuous processing can often be assessed with a modicum of effort, and sometimes batch processing cannot effectively scale up some processes (vide infra). For initial laboratory work and scale-up to the pilot plant, reactors are smaller than those used in manufacturing settings. Despite their small size, continuous flow reactors can lead to large productivity due to rapid flow rates. M. A. Poliakoff, in describing his 5-mL reactor used for continuous hydrogenation in super-critical fluids, was quoted: "With our 5-mL reactor, we have achieved a throughput that is larger than that required by most synthetic organic laboratories."[31] Examples below describe the power and productivity of continuous processing applied in the laboratory, using equipment that is readily available.

Continuous Processing that has been Applied to Laboratory Operations

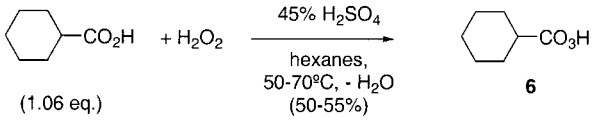
CSTR and Semi-Continuous Operations. The chlorination of the furfuryl alcohol **1** (Scheme 1) provides one of the most powerful examples of how continuous processing can be readily applied in the laboratory.[32] The chloride **2** was an intermediate in the preparation of the nitrile **3**. When the chlorination was scaled up to more than 100 g in a batch mode, unacceptable yields of **3** were obtained. The poor stability of **2** ($t_{1/2}$ at room temperature of only 20 min) was the cause of poor yields upon scale-up of the batch process. A CSTR process was set up to convert **2** to **3** soon after **2** had been generated, using two 10-mL round-bottomed flasks with magnetic stirrers. Separate solutions of **1** and $SOCl_2$ were charged to a flask by ganged syringe pumps, and the

(15) Reference 4, p 6.
(16) Watts, P.; Wiles, C.; Haswell, S. J.; Pombo-Villar, E.; Styring, P. The synthesis of peptides using micro reactors. *Chem. Commun.* **2001**, 990.
(17) Kopp, M. U.; de Mello, A. J.; Manz, A. Chemical Amplification: Continuous-Flow PCR on a Chip. *Science* **1998**, *280*, 1046.
(18) The SELECTO modular microreactor system is available from Cellular Process Chemistry Control GmbH: http://www.CPC-net.com.
(19) Smith, L. A. Catalytic distillation process. (Chemical Research & Licensing Company.). U.S. 4,307,254, 1981.
(20) Weissermel, K.; Arpe, H.-J. *Industrial Organic Chemistry*, 3rd ed.; VCH Publishers: New York, 1997; pp 186−187.
(21) Strube, J.; Haumreisser, S.; Schmidt-Traub, H.; Schulte, M.; Ditz, R. Comparison of Batch Elution and Continuous Simulated Moving Bed Chromatography. *Org. Process Res. Dev.* **1998**, *2*, 305.
(22) Klokov, B. A. Continuous and Batch Organomagnesium Synthesis of Ethyl-Substituted Silanes from Ethylchloride, Tetraethoxysilane, and Organotrichlorosilane for Production of Polyethylsiloxane Liquids. 2. Continuous One-Step Synthesis for Ethylethoxy- and Ethylchlorosilanes. *Org. Process Res. Dev.* **2001**, *5*, 234; Klokov, B. A. Continuous Single-Stage Organomagnesium Synthesis of a Mixture of Ethylethoxysilanes and Dimethylethylethoxysilane. *Org. Process Res. Dev.* **2000**, *4*, 122.
(23) Diehl, H.; Blank, H. U.; Ritzer, E. Process for the preparation of cyclopropylamine (Kernforschunganlage Julich Gesellschaft). U.S. 5,032,687, 1991.
(24) Kleemiss, W.; Kalz, T. Process for the preparation of cyclopropanamine (Huels Aktiengesellschaft). U.S. 5,728,873, 1998.
(25) Warr, A.; Proctor, L. D. Generation of Diazomethane (Phoenix Chemicals Ltd.). GB 2357501A, 2001. See also Archibald, T. G.; Barnard, J. C.; Reese, H. F. Continuous process for diazomethane from an *N*-methyl-*N*-nitrosoamine and from methylurea through *N*-methyl-*N*-nitrosourea (Aerojet-General Corporation). U.S. 5,854,405, 1998.
(26) Stinson, S. C. Custom Chemicals. *Chem. Eng. News* **1999**, *77*, 69; http://www.kvaerner.com/kpt/ch.
(27) Roth, G.; Smith, G. A.; Grinstein, R.; Whyzmuzis, P. D.; Singhal, S.; Boucher, S.; Lovald, R.; Devore, D.; Fischer, S. A.; Wiggins, M. S. Bulk polymerization process for preparing solid acrylic resin (Cook Composites and Polymers). U.S. 6,160,059, 2000.
(28) Weissermel, K.; Arpe, H.-J. *Industrial Organic Chemistry*, 3rd ed.; VCH Publishers: New York, 1997; p 254.
(29) Sanghvi, Y. S.; Ravikumar, V. T.; Scozzari, A. N.; Cole, D. L. Applications of green chemistry in the manufacture of oligonucleotide drugs. *Pure Appl. Chem.* **2001**, *73*, 175.
(30) Tundo, P. *Continuous Flow Methods in Organic Synthesis*; Prentice Hall PTR: Upper Saddle River, NY, 1992. See also: Moulijn, J. A.; Makkee, M.; Van Diepen, A. *Chemical Process Technology*; Wiley: Chichester, 2001; *Third International Conference on Process Intensification for the Chemical Industry*; Green, A., Ed.; Professional Engineering Publishing: Suffolk, 1999.
(31) Freemantle, M. Cleaning Up Hydrogenations. *Chem. Eng. News* **2001**, *79(22)*, 31.
(32) Foulkes, J. A.; Hutton, J. A Simple Laboratory Procedure for the Preparation of Nitriles from Alcohols via Unstable Chlorides in Large Quantities. *Synth. Commun.* **1979**, *9*, 625.

Scheme 2. **Use of CSTR to control exothermic operations with a volatile reagent**



Scheme 3. **Generation of cyclohexaneperoxycarboxylic acid**

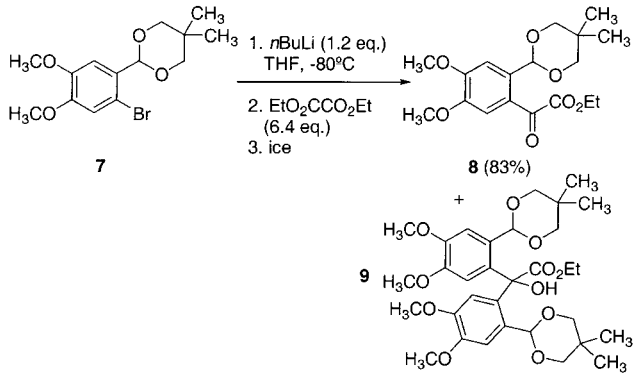


reaction stream overflowed into a second flask and then into a reactor charged with an excess of NaCN. PTC conditions rapidly converted **2** to **3**. *Continuous operations for one week produced 10 kg of **3** using this train of two 10-mL reactors!*

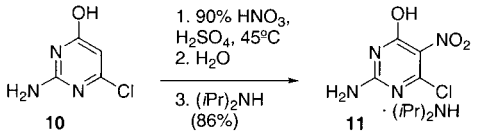
Alendronate sodium (**5**) has also been prepared using CSTR operations (Scheme 2).[33] Studies had shown that 90 °C was the desired temperature for reacting the starting material **4** with H_3PO_4 and PCl_3. Under conventional batch operations, charging and containing PCl_3 (bp 76 °C) was difficult at this temperature, and yields and quality of **5** suffered as the stoichiometry of the reagents changed. In addition, the process was known to be very exothermic at 90 °C. The Merck co-workers addressed the quality, yield, and safety problems by CSTR processing. PCl_3 and a solution of **4** and H_3PO_4 in methanesulfonic acid were continuously fed into the reactor at 90 °C, and the batch overflowed to a quench vessel containing H_2O. Heat transfer was more efficient by operating in the small reactor, and the reaction temperature could be more readily controlled. The authors stated that the severity of any runaway reaction was reduced since only a small portion of the batch could be heated at any time in the CSTR reactor, and that the reactor contents could be transferred to the quench vessel in the event of an adverse thermal event. The PCl_3 charge was adjusted for vapor loss. As the phosphonation stream entered the quench vessel, the pH was maintained by the addition of aqueous NaOH. With heating the intermediates were hydrolyzed to **5**. In addition to the increased safety margin conferred by CSTR processing, product yields were raised by as much as 10% over batch processing.

Cyclohexaneperoxycarboxylic acid (**6**, Scheme 3) has been developed as a safe, inexpensive oxidant, with demonstrated utility in a Baeyer−Villiger rearrangement.[34] Solutions of cyclohexanecarboxylic acid in hexane and 50% aqueous H_2O_2 were continuously added to 45% H_2SO_4 at 50−70 °C and slightly reduced pressure. The byproduct H_2O was removed azeotropically, and the residence time in the reactor was 3 h. Processing was adjusted to maintain a

Scheme 4. **Preparation of a ketoester aided by PFR**



Scheme 5. **Continuous nitration under PFR conditions**



concentration of **6** at 17−19%, below the detonable level, and the product was kept as a stable solution in hexane. These operations enhanced the safety margin in preparing **6**.

Plug Flow Reactors. In the preparation of the ketoester **8** (Scheme 4), simple laboratory equipment was adapted for effective processing under PFR conditions.[35] When a solution of the lithio derivative of **7** was added to diethyl oxalate in THF, a 23% yield of **8** was obtained, with the primary product being the double addition byproduct **9**. Intimate mixing of lithiated **7** with diethyl oxalate and a rapid quench were necessary to minimize the reaction of lithiated **7** with **8**, which is more reactive than diethyl oxalate. As a reactor the authors used the barrel of a 1-mL syringe, fitted with a T-junction. The syringe barrel drained through tubing into a suction flask charged with crushed ice. Suction from a vacuum line simultaneously pulled a preparation of the lithium salt of **7** and a solution of diethyl oxalate through Teflon lines into the T-junction. The streams mixed in the syringe barrel and were rapidly pulled into the quench vessel. With transfer times of about 1 min (50 mmol charge of **7**), **8** was isolated in 83% yield, with negligible amounts of the double adduct **9**.

Safety studies showed that nitration of the pyrimidine **10** (Scheme 5) was highly exothermic and generated a large amount of gases upon decomposition at a relatively low temperature.[36,37] Due to safety considerations this reaction was run on scales no larger than 22 L in a batch mode. The

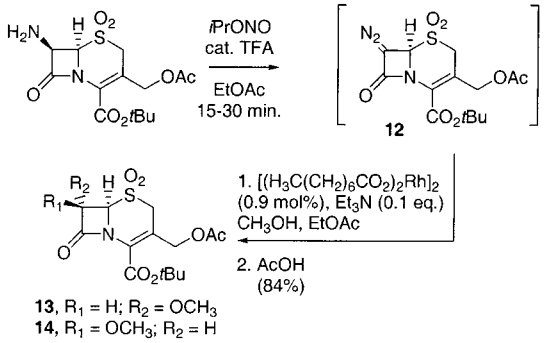
(33) Dauer, R. R.; DiMichele, L.; Futran, M.; Kieczykowski, G. R. Process for producing *N*-amino-1-hydroxy-alkylidene-1,1-bisphosphonic acids (Merck). U.S. 5,510,517, 1994.

(34) Cotarca, L.; Delogu, P.; Nardelli, A.; Maggioni, P.; Bianchini, R.; Sguassero, S.; Alini, S.; Dario, R.; Clauti, G.; Pitta, G.; Duse, G.; Goffredi, F. Efficient and Scaleable Methods for ω-Functionalized Nonanoic Acids: Development of a Novel Process for Azelaic and 9-Aminononanoic Acids (Nylon-6.9 and Nylon-9 Precursors. *Org. Process Res. Dev.* **2001**, *5*, 69; Cotarca, L.; Delogu, P.; Maggioni, P.; Bianchini, R.; Sguassero, S. Efficient Synthesis of ω-Functionalized Nonanoic Acids. *Synthesis* **1997**, 328.

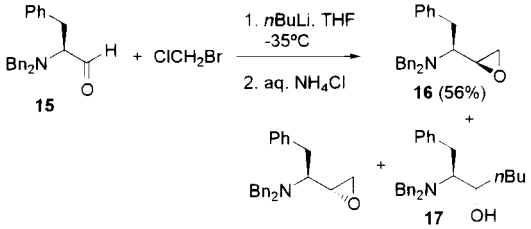
(35) Hollwedel, F.; Kossmehl, G. A Simple Method for the Preparation of New α-Oxoacetic Acid Esters with a Plug Flow Reactor. *Synthesis* **1998**, 1241.

(36) De Jong, R. L.; Davidson, J. G.; Dozeman, G. J.; Fiore, P. J.; Giri, P.; Kelly, M. E.; Puls, T. P.; Seamans, R. E. The Development of CI-972 and CI-1000; A Continuous Nitration, A $MgCl_2/Et_3N$-Mediated C-Alkylation of a Chloronitropyrimidine, A Catalytic Protodedizaotization of a Diazonium Salt, and an Air Oxidation of an Amine. *Org. Process Res. Dev.* **2001**, *5*, 216.

Scheme 6. **Use of a static mixer to control reaction of a diazo-ss-lactam**



Scheme 7. **Use of a static mixer in the Kowalski reaction**

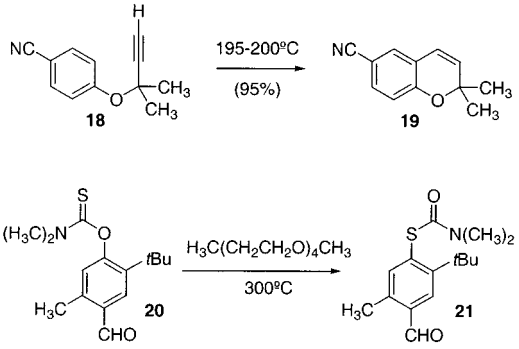


nitration was found to be rapid and was adapted for PFR processing. Using a translucent Teflon tube, at 45 °C a solution of **10** in H_2SO_4 was combined with 90% HNO_3. Residence time in the reactor was about 2.5 min, and the use of the open-ended tube decreased concerns of any gas build-up. The reaction was quenched into cold H_2O, and the salt **11** was isolated in 85% yield from 45 kg of **10**.

Static mixers have been used for intimate mixing in the reaction of a diazo-*β*-lactam (Scheme 6) and in a Kowalski reaction (Scheme 7). EtOAc−MeOH solutions of **12** and the rhodium catalyst were combined in a static mixer (residence time of 1−3 min), producing the methyl ethers in a combined yield of 84% (**13**:**14** ratio of 17:1).[38] A solution of the aldehyde **15** and bromochloromethane was treated at −35 °C with a solution of *n*-BuLi, leading to the isolation of the epoxide **16** in 56% yield.[39,40] Efficient mixing was needed to minimize formation of **17** from reaction of *n*-BuLi with **15** and the reaction of the intermediate chloromethyllithium with bromochloromethane. Rapid phase-transfer catalyzed reactions may also benefit by the use of static mixers.[41]

Hot tube reactors have been used for thermal rearrangements. Thermal rearrangement of the acetylenic ether **18** to the chromene **19** (Scheme 8) was found to be quite exothermic, and safety concerns were alleviated by heating only a small portion of the batch at any time in a hot tube reactor.[42] A coiled steel tube (0.125 in internal diameter) was heated in a modified GC oven for the rearrangement. Passing melted

Scheme 8. **Rearrangements under hot tube conditions**



18 through the tube at 195−200 °C (residence time of about 4 min) afforded kilos of **19** in 95% yield. Newman−Kwart rearrangement of **20** to **21** took place at 300 °C in tetraethylene glycol dimethyl ether (bp 275−276 °C).[43] Use of this water-soluble solvent minimized process impurities. The process stream was quenched into water, and **21** was isolated by filtration. A hot tube reactor afforded better temperature control than batch processing (50% yield), with yields of over 72%.[44] In early investigations a tubular reactor (0.75 in internal diameter, 0.5-L volume, 15−20 min residence time) was used in a modified GC oven. Scale-up to a 5-L reactor increased production from 6 to 50 kg/day.

Reactors Involving Immobilized Catalysts. Immobilized catalysts allow for ready recovery and recycle of valuable reagents, with decreased contamination of product. The use of immobilized TADDOLate catalysts contained in "tea bags" has been described for the addition of dialkyl zinc reagents to aldehydes.[45] Operationally simple is the process of passing a reaction stream through a catalyst contained in a column. Resin-mediated epimerization has been studied in detail.[46] Recirculating an aqueous DMSO solution of fructose (**22**) through a bed of strongly acidic ion-exchange resin led to isomerization and dehydration, producing the aldehyde **23** (Scheme 9).[47] Passing a solution of **24** in *i*-PrOH−heptane through a chromatography column containing a rhodium catalyst and chiral amine adsorbed to silica gel produced the chiral alcohol **25**.[48]

(37) Brummel, R. Contribution presented at the 219th National Meeting of the American Chemical Society, San Francisco, CA, March 26−30, 2000; American Chemical Society: Washington, DC, 2000.

(38) Blacklock, T. J.; Butcher, J. W.; Sohar, P. Lamanec, T. R.; Grabowski, E. J. J. *J. Org. Chem.* **1989**, *54*, 3907.

(39) Liu, C.; Ng, J. S.; Behling, J. H.; Yen, C. H.; Campbell, A. L.; Fuzail, K. S.; Yonan, E. E.; Mehrotra, D. V. Development of a Large-Scale Process for an HIV Protease Inhibitor. *Org. Process Res. Dev.* **1997**, *1*, 45.

(40) Presumably further optimization of this process could have taken place, but development of this compound was discontinued. Personal communication from J. Ng.

(41) Halpern, M. Personal communication.

(42) Bogaert-Alvarez, R. J.; Demena, P.; Kodersha, G.; Polomski, R. E.; Soundararajan, N.; Wang, S. S. Y. Continuous Processing to Control a Potentially Hazardous Process: Conversion of Aryl 1,1-Dimethylpropargyl Ethers to 2,2-Dimethylchromenes (2,2-Dimethyl-2*H*-1-Benzopyrans). *Org. Process Res. Dev.* **2001**, *5*, 636; Soundararajan, N.; Colandrea, V. J.; Sedergran T. C.; Fox, R. T.; Godfrey, J. D., Jr.; Mueller, R. H. Poster presentation at International Conference on Organic Synthesis, Bangalore, India, December 11−16, 1994.

(43) Lin, S.; Moon, B.; Porter, K. T.; Rossman, C. A.; Zennie, T.; Wemple, J. A Continuous Procedure for Preparation of *para* Functionalized Aromatic Thiols Using Newman-Kwart Chemistry. *Org. Prepr. Proced. Int.* **2000**, *32*, 547.

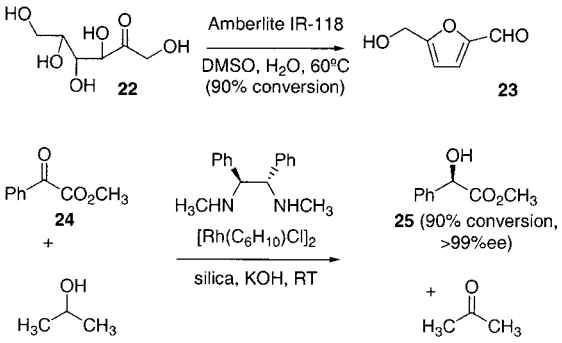
(44) The yield of **21** via hot tube reactor was not available from the paper. Preparations of **21** were telescoped into three other steps, affording the desired drug intermediate in 70−72% yield.

(45) Comina, P. J.; Beck, A. K.; Seebach, D. A Simple Batch Reactor for the Efficient Multiple Use of Polymer-bound α,α,α′,α′-Tetraaryl-1,3-dioxolane-4,5-dimethanol Titanates in the Nucleophilic Addition of Dialkylzinc Reagents to Aldehydes. *Org. Process Res. Dev.* **1998**, *2*, 18.

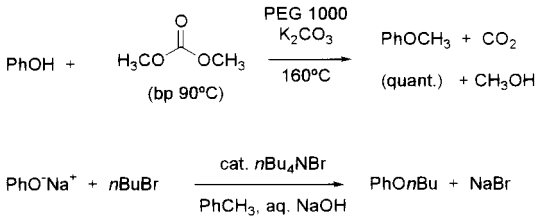
(46) Cerami, J.; Gala, D.; Hou, D.; Kalliney, S.; Mas, J. L.; Nyce, P.; Peer, L.; Wu, G. Delevalol via Resin-Mediated Epimerization: A Case Study. Reaction Mechanism to Reactor Design to a Viable Process. *Org. Process Res. Dev.* **2000**, *4*, 107.

(47) Nakamura, Y.; Morikawa, S. The Dehydration of D-Fructose to 5-Hydroxymethyl-2-furaldehyde. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3705.

Scheme 9. **Continuous processing with immobilized catalysts**



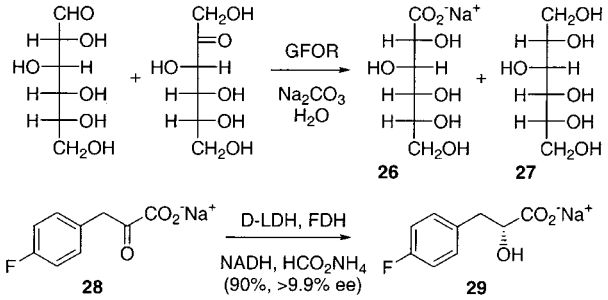
Scheme 10. **Catalytic processing through "captive" catalysts**



Glass reactors have been developed for more specialized continuous processing with immobilized catalysts. Phenol was methylated with dimethyl carbonate (bp 90 °C) using K_2CO_3 on melted PEG-1000 at 160 °C (Scheme 10). The relatively high temperature was needed for one-pass methylation. A solution of phenol and dimethyl carbonate was fed into the bottom of a glass cylindrical vessel containing the melted catalyst, and the volatilized products were collected at the top of the vessel.[49] A similar approach was used in the alkylation of phenol with *n*-BuBr in a stirred glass reactor[50] (Scheme 10). Under PTC conditions with concentrated aqueous NaOH and $(n\text{-Bu})_4$NBr as phase transfer catalyst, a reactive third phase formed at the aqueous−organic interface.[51] An aqueous solution of sodium phenoxide and NaOH was continuously added in the top third of the reactor, as a toluene solution of *n*-BuBr was continuously fed into the bottom third of the reactor. During continuous operations the aqueous phase was withdrawn from the bottom and the organic phase from the top of the reactor, with the reactive third phase being "held captive" in the middle of the reactor.

Immobilized catalysts have been developed and used in continuous reactors, often termed "bioreactors" when enzymes or cells are used. Enzymes have been immobilized to increase enzymatic stability, ease workup, and allow for convenient continuous processing.[52] Cell cultures attached

Scheme 11. **Continuous enzyme-catalyzed processes**



to porous materials have been claimed to continuously produce metabolites.[53] Workers at Degussa have developed soluble polymer-bound catalysts contained by membranes, with the smaller product molecules permeating the membranes.[54] Cross-linked enzyme crystals (CLECs) have been used in the hydrolytic kinetic resolution of *sec*-phenethyl acetate, with recycle of the CLECs affording a semi-continuous process.[55] A continuous bioreactor was used for the enzymatic transformation of glucose and fructose to gluconic acid (**26**) and sorbitol (**27**, Scheme 11).[56] Under the latter conditions a portion of the process stream was continuously withdrawn and passed into a reactor fitted with tangential ultrafiltration; the products permeated the membrane, and the larger enzyme was returned to the reactor. Nanofiltration similarly retained the enzymes used in the reduction of the α-ketoester **28** (Scheme 11).[57] The alcohol **29** was obtained in 90% yield on a 10-kg basis, using equipment in two adjacent walk-in hoods.

Scale-Up of Continuous Microwave Processes. Microwaves are known to markedly accelerate reactions,[58] and recently the value of microwaves in developing discovery libraries has been discussed.[59] Due to the shortened reaction times, larger amounts of material can be prepared by running successive batches in a conventional microwave reactor. Batch processing has been scaled up under neat conditions, producing as much as 620 g of an ester by PTC alkylation[60] and 269 g of a dithioketal by ketal exchange.[61] Microwave

(48) Gamez, P.; Fache, F.; Lemaire, M. Asymmetric catalytic reduction of prochiral ketones with supported metal complexes. *Bull. Soc. Chim. Fr.* **1994**, *131*, 600.

(49) Bomben, A.; Selva, M.; Tundo, P.; Valli, L. A Continuous-Flow O-Methylation of Phenols with Dimethyl Carbonate in a Continuously Fed Stirred Tank Reactor. *Ind. Eng. Chem. Res.* **1999**, *38*, 2075.

(50) Weng, H.-S.; Wang, C.-M.; Wang, D.-H. A Preliminary Study on a Continuous Flow Stirred Vessel Reactor for Tri-Liquid-Phase Phase Transfer Catalysis. *Ind. Eng. Chem. Res.* **1997**, *36*, 3613.

(51) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase Transfer Catalysis, Fundamentals, Applications and Industrial Perspectives*; Chapman & Hall: New York, 1994; pp 10, 252−258.

(52) Faber, K. *Biotransformations in Organic Chemistry*, 4th ed.; Springer-Verlag: Berlin, 2000; pp 384−402.

(53) Endo, I.; Nagamune, T.; Kobayashi, T. Fluidized bed cell culture apparatus with a drain valve for the removal of support material (Rikagaku Kenkyusho and Shinko-Pfaudler). U.S. 5,043,283, 1991.

(54) Wöltinger, J.; Bommarius, A. S.; Drauz, K.; Wandrey, C. The Chemzyme Membrane Reactor in the Fine Chemicals Industry. *Org. Process Res. Dev.* **2001**, *5*, 241.

(55) Collins, A. M.; Maslin, C.; Davies, R. J. Scale-Up of a Chiral Resolution Using Cross-Linked Enzyme Crystals. *Org. Process Res. Dev.* **1998**, *2*, 400.

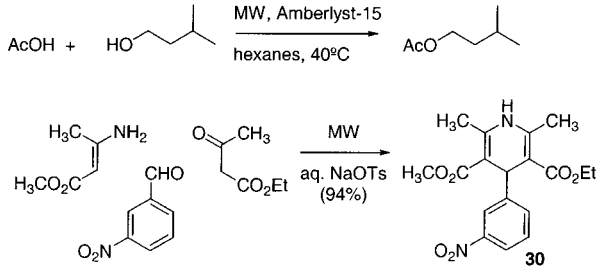
(56) Silva-Martinez, M.; Haltrich, D.; Novalic, S.; Kulbe, K. D.; Nidetzky, B. Simultaneous Enzymatic Synthesis of Gluconic Acid and Sorbitol. *Appl. Biochem. Biotech.* **1998**, *70−72*, 863.

(57) Tao, J.; McGee, K. *Abstracts of Papers*, 221st National Meeting of the American Chemical Society, San Diego, CA, April 1−5, 2001; American Chemical Society: Washington, DC, 2001; ORGN 0326.

(58) *Microwave-Enhanced Chemistry*; Kingston, H. M., Haswell, S. J., Eds.; Oxford University Press: Oxford, U.K., 1997; Langa, F.; de la Cruz, P.; de la Hoz, A.; Diaz-Ortiz, A.; Diez-Barra, E. Microwave irradiation: more than just a method for accelerating reactions. *Contemp. Org. Synth.* **1997**, 373; Caddick, S. Microwave Assisted Organic Reactions. *Tetrahedron* **1995**, *51*, 10403.

(59) Sarko, C. Microwave Technology: A Tool to Reduce the Library Development Bottleneck. *Abstracts of Papers*, 221st National Meeting of the American Chemical Society, San Diego, CA, April 1−5, 2001; American Chemical Society: Washington, DC, 2001; ORGN 0049. For commercial applications of this approach, see: http://www.personalchemistry.com.

Scheme 12. **Continuous microwave dehyration processes**



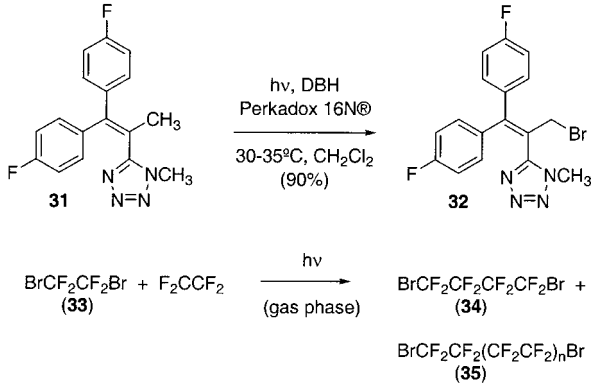
processes can produce localized high temperatures and pressures, and any scale-up operations must consider these potential dangers and limitations.

Strauss and co-workers described a continuous microwave reactor in 1994,[62] and a continuous reactor is commercially available.[63] Low-temperature Fischer-type esterification has been carried out by microwave irradiation of a polyethylene tube as a hexane solution of acetic acid and isopentyl alcohol was recirculated through an acidic ion-exchange resin in the tube (Scheme 12).[64] In a continuous microwave process dihydropyrimidines (e.g., **30**) have been prepared in high yield by condensation of three components (Scheme 12).[65]

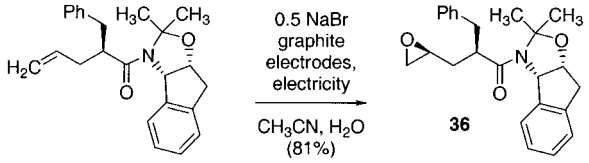
Photochemical Processes. Conventional multipurpose reactors are not prepared for immersion of a light source or transmission of light through the vessel walls. Continuous operations permit the effective scale-up of some photochemical processes, with process streams being circulated within close proximity to light sources in specially designed transparent cells. Many of these cells are made of glass or Teflon,[66] and can be fabricated by local craftsmen. Continuous photolytic reactors have been described for the photochemical degradation of wastewater containing dichloromethane[67] or inorganic salts[68] and photochemical iodide/bromide exchange.[69]

Continuous photobromination was used to convert the olefin **31** to the allylic bromide **32** (Scheme 13).[70] 1,3-Dibromo-5,5-dimethyl hydantoin (DBH) was used as the bromine source, and Perkadox 16N was the radical initiator.

Scheme 13. **Continuous photochemical processes**



Scheme 14. **One-step electrochemical epoxidation**



The reaction mixture was pumped through a helical Teflon coil winding upward around the light source. In one pass **31** was converted to **32** in a yield of of 89.9% (28-kg scale). In the radical-induced telomerization of **33**, vapor-phase photobromination reactions were carried out in cylindrical glass tubes, glass desiccators, or 100-dm^3 stainless steel vessels.[71] The key feature is that under irradiation from a low-pressure Hg lamp tetrafluoroethylene reacted with volatilized **33** to form **34**, while the heavier oligomers (such as **35**) were held as liquids and not subjected to irradiation. Vapor-phase irradiation decreased the formation of oligomers.

Electrochemical Processes. Electrochemical reactions[72,73] have wide application for the commercial preparation of commodity chemicals, such as the reductive dimerization of acrylonitrile to produce the nylon-6 precursor adiponitrile.[74] Reactions, especially oxidations, can be readily carried out in the laboratory and scaled up.[75] An intriguing example is the electrochemical formation of the epoxide **36** using catalytic amounts of NaBr (Scheme 14).[76] Continuous equipment is available for laboratory scale-up of electrochemical processes.[77]

Sonochemical Processes. Sonication converts electrical energy into mechanical energy, with localized high temperatures and pressures and improved phase mixing.[78,79] Sonolysis of aqueous solutions produces reactive species arising

(60) Cléophax, J.; Liagre, M.; Loupy, A.; Petit, A. Application of Focused Microwaves to the Scale-Up of Solvent-Free Organic Reactions. *Org. Process Res. Dev.* **2000**, *4*, 498.

(61) Perio, B.; Dozias, M.-J.; Hamelin, J. Ecofriendly Fast Batch Synthesis of Dioxolanes, Dithiolanes, and Oxathiolanes without Solvent under Microwave Irradiation. *Org. Process Res. Dev.* **1998**, *2*, 428.

(62) Cablewski, T.; Faux, A. F.; Strauss, C. R. Development and Application of a Continuous Microwave Reactor for Organic Synthesis. *J. Org. Chem.* **1994**, *59*, 3408.

(63) See: http://www.milestonesci.com.

(64) Kabza, K. G.; Chapados, B. R.; Gestwicki, J. E.; McGrath, J. L. Microwave-Induced Esterification Using Heterogeneous Acid Catalyst in a Low Dielectric Constant Medium. *J. Org. Chem.* **2000**, *65*, 1210.

(65) Khadilkar, B. N.; Madyar, V. R. Scaling Up of Dihydropyridine Ester Synthesis by Using Aqueous Hydrotrope Solutions in a Continuous Microwave Reactor. *Org. Process Res. Dev.* **2001**, *5*, 452.

(66) For a picture of The European Photo Reactor, made of Teflon, see *Chem. Eng. News* **2001**, *79(22)*, 55.

(67) Mass, B. Chamber Design and Lamp Configuration for an Ultraviolet Photochemical Reactor (Purus, Inc.). U.S. 5,151,252, 1992.

(68) Pareek, V. K.; Brungs, M. P.; Adesina, A. A. Continuous Process for Photodegradation of Industrial Bayer Liquor. *Ind. Eng. Chem. Res.* **2001**. ASAP article, May 19, 2001.

(69) Oliveros Braun, E.; Wohlers, M.; Drivon, G.; Kervennal, J. Synthèse d'un bromure de perfluoroalkyle par bromation photochimique de l'iodure correspondent (Elf Atochem S.A.). Eur. Pat. Appl. EP 604,256, 1994.

(70) Chan, Y.; Kotnis, A.; Vanyo, D.; Wei, C.-K. Presentation at the 210th National Meeting of the American Chemical Society, Chicago, IL, August 26−30, 1996; American Chemical Society: Washington, DC, 1996.

(71) Zhang, L.; Zhang, J.; Yang, W.; Wang, Y.; Fuss, W.; Weizbauer, S. Highly selective photochemical synthesis of perfluoroalkyl bromides and iodides. *J. Fluorine Chem.* **1998**, *88*, 153.

(72) Fry, A. J. *Synthetic Organic Electrochemistry*, 2nd ed.; John Wiley & Sons: New York; 1989.

(73) Shono, T. *Electroorganic Synthesis*; Academic Press: San Diego, 1991.

(74) Danly, D. E. Development and Commercialization of the Monsanto Electrochemical Adiponitrile Process. In *Electrosynthesis: From Laboratory to Pilot to Production*; Genders, J. D., Pletcher, D., Eds.; The Electrosynthesis Company Inc.: Elmhurst, New York, 1990; pp 147−164.

(75) Enders, J. D.; Pletcher, D. Electrosynthesis: A Tool for the Pharmaceutical Industry Today? *Chem. Ind.* **1996**, *18*, 682.

(76) Rossen, K.; Volante, R. P.; Reider, P. J. A Highly Diastereoselective Electrochemical Epoxidation. *Tetrahedron Lett.* **1997**, *38*, 777.

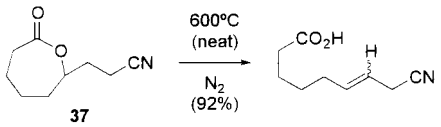
(77) Suppliers include The Electrosynthesis Company Inc.: http://www.electrosynthesis.com; and Ionics, Inc., Watertown, Massachusetts.

from HO•,[78] and sonication of organic solutions accelerates reactions through single-electron-transfer processes.[79] Organometallic reactions are often aided by sonication, one example being the ultrasonic "cleaning" of mossy zinc to control cyclopropanation reactions.[80−82] Synthetic applications of ultrasonic chemistry have been reviewed.[83−85]

Examples of successful scale-up of sonochemical processes are not widely known, but large-scale applications have been used for degassing, improved mass transport, crystallization, and low-temperature extraction of natural products.[86] A continuous-flow apparatus has been claimed for blood hemolysis.[87] In the biotech industry process streams may be pumped past sonic horns to disrupt cells and facilitate product isolation.[88] In the simplest laboratory applications, scale-up is limited by the concentration of the reactants and by the size of the reactor that fits into an ultrasonic bath.[89] Further scale-up can be carried out in commercially available continuous-flow reactors.[79,89,90]

Impinging Jet Reactors. Impinging jet technology, widely used in the plastic industry,[91] affords vigorous, intimate mixing. Using a glass tangential-flow reactor, a stream of glucose was mixed with immobilized glucose isomerase, and conversion to fructose was higher than expected for conventional reactors.[92] Jet crystallization[93] has been employed to control crystallization: contact of a finasteride solution in aqueous acetic acid with water (as antisolvent) gave finasteride with average particle size of 10−15 μm.[94,95] In addition to eliminating the need for milling, the finasteride crystals displayed particle size distribution ranges narrower than those resulting from standard batch crystallization. The mixers used for the latter crystallizations were engineered from tubes.

Scheme 15. **Hot-tube pyrolysis of a lactone**



37

Other Approaches. As other techniques become more widely used, equipment will become more readily available. The promise of scaling up continuous-flow processes with immobilized catalysts and super-critical fluids has been demonstrated for hydrogenations,[96] organometallic synthesis,[97] acid-catalyzed dehydrogenations,[98] and hydrovinylation.[99] Continuous asymmetric hydrogenation at 270 bar has been carried out using two autoclaves connected in series.[100] These conditions require components for controlling high pressure and are outside the sphere of most organic chemistry labs. SMB, which has been shown to be very cost-effective as a tool for resolution,[101] requires an appreciable investment of time and money. Mechanochemistry[102] has been used for the solvent-free preparation of BH_3 for the semiconductor industry.[103] Such ultrahigh-intensity grinding can lead to internal temperatures above 500 °C, and vibratory ball mills were used for the solvent-free preparation of calixarenes.[104] Furnaces have been built for high-temperature pyrolyses, as in the pyrolysis of lactone **37** (Scheme 15).[35] A spinning disc reactor is useful for reactions needing 0.1−1 s residence times. In the latter reactor process streams are pumped into a well in the center of a rotating disc, and are thrust centrifugally to the edge of the disc. The spinning disc reactor

(78) Ince, N. H.; Tezcanli, G.; Belen, R. K.; Apikyan, I. G. Ultrasound as a catalyzer of aqueous reaction systems: the state of the art and environmental applications. *Appl. Catal. B* **2001**, *29*, 167.

(79) Thompson, L. H.; Doraiswamy, L. K. Sonochemistry: Science and Engineering. *Ind. Eng. Chem. Res.* **1999**, *38*, 1215.

(80) Repic, O.; Vogt, S. Ultrasound in Organic Synthesis: Cyclopropanation of Olefins with Zinc-Diiodomethane. *Tetrahedron Lett.* **1982**, *23*, 2729.

(81) Repic, O.; Lee, P. G.; Giger, U. Large-Scale Cyclopropanation. *Org. Prepr. Proced. Int.* **1984**, *16*, 25.

(82) For discussions on developing a Simmons−Smith cyclopropanation that could be engineered for plant design, see: Repic, O. *Principles of Process Research and Chemical Development in the Pharmaceutical Industry*; John Wiley & Sons: New York, 1997; pp 14−16.

(83) Mason, T. J. Ultrasound in Synthetic Organic Chemistry. *Chem. Soc. Rev.* **1997**, *26*, 443−451.

(84) Cains, P. W.; Martin, P. D.; Price, C. J. The Use of Ultrasound in Industrial Chemical Synthesis and Crystallization. 1. Applications to Synthetic Chemistry. *Org. Process Res. Dev.* **1998**, *2*, 34.

(85) Luche, J.-L.; Bianchi, C. *Synthetic Organic Sonochemistry*; Plenum: New York, 1998.

(86) Crabb, C.; D'Aquino, R. Ultrasound Makes Waves in the CPI. *Chem. Eng.* **1999**, *106(8)*, 26.

(87) Eppes, W. R. Apparatus for ultrasonc agitation of liquids (Corning Glass Works). U.S. 4,764,021, 1983.

(88) For a perspective on the scalability of ultrasonic disruption of cells, see: Lanfear, D.; Hassler, R.; Sitney, K.; Curless, C.; Patro, S.; Tsai, L.; Ogez, J. Protein Drug Manufacturing. In *Biopharmaceutical Drug Design and Development*; Wu-Pong, S., Rojanasakul, Y., Eds.; Humana: Totowa, NJ; 1999; p 274.

(89) Ultrasonic baths are available in a range of sizes. See: http://www.misonix.com and http://www.bransoncleaning.com.

(90) See http://www.sodeva.com for further information on the Sonitube reactor.

(91) Kirwan, D. J.; Orella, C. J. Crystallization of Biological Molecules. In *Handbook of Industrial Crystallization*; Myerson; A. S., Ed.; Butterworth−Heinemann: Boston, 1993; p 234.

(92) Sohrabi, M.; Marvast, M. A. Application of a Continuous Two Impinging Streams Reactor in Solid−Liquid Enzyme Reactions. *Ind. Eng. Chem. Res.* **2000**, *39*, 1903.

(93) Midler, M., Jr.; Paul, E. L.; Whittington, E. F.; Futran, M.; Liu, P. D.; Hsu, J.; Pan S. H. Crystallization method to improve crystal structure and size (Merck). U.S. 5,314,506, 1994.

(94) Dauer, R.; DiMechele, L.; Futran, M.; Kieczykowski, G. R. Dual Jet Crystallizer Apparatus (Merck). U.S. 5,578,279, 1996.

(95) For a mathematical approach to controlling particle size using seed crystals, see footnote 22 in Cook, D. M.; Jones, R. H.; Kabir, H.; Lythgoe, D. J.; McFarlane, I. M.; Pemberton, C.; Thatcher, A. A.; Thompson, D. M.; Walton, J. B. Process Development of the PDE Inhibitor 3-(Cyclopentyloxy)-*N*-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide. *Org. Process Res. Dev.* **1998**, *2*, 157.

(96) Hitzler, M. G.; Smail, F. R.; Ross, S. K.; Poliakoff, M. Selective Catalytic Hydrogenation of Organic Compounds in Supercritical Fluids as a Continuous Process. *Org. Process Res. Dev.* **1998**, *2*, 137.

(97) King, J. L.; Molvinger, K.; Poliakoff, M. Organometallic Synthesis as a Continuous Process: The Synthesis and Isolation of $Cr(CO)_5(\eta^2\text{-}C_3H_6)$ and $(C_5R_5)Mn(CO)_2(\eta^2\text{-}C_3H_6)$ (R = H and Me) from Superheated Liquid Propene. *Organometallics* **2000**, *19*, 5077.

(98) Gray, W. K.; Smail, F. R.; Hitzler, M. G.; Ross, S. K.; Poliakoff, M. The Continuous Acid-Catalyzed Dehydration of Alcohols in Supercritical Fluids: A New Approach to the Cleaner Synthesis of Acetals, Ketals, and Ethers with High Selectivity. *J. Am. Chem. Soc.* **1999**, *121*, 10711.

(99) Bösmann, A.; Franciò, F.; Janssen, E.; Solinas, M.; Leitner, W.; Wasserscheid, P. Activation, Tuning, and Immobilization of Homogeneous Catalysts in an Ionic Liquid/Compressed CO_2 Continuous-Flow System. *Angew. Chem., Int. Ed.* **2001**, *40*, 2697.

(100) Wang, S.; Kienzle, F. Development of a Continuous Homogeneous Metal Complex Catalyzed, Asymmetric Hydrogenation under High Pressure (270 bar). *Org. Process Res. Dev.* **1998**, *2*, 226.

(101) Juza, M.; Mazzotti, M.; Morbidelli, M. Simulated moving bed chromatography and its application to chirotechnology. *Trends Biotechnol.* **2000**, *18(3)*, 108; Nicoud, R.-M. The Separation of Optical Isomers by Simulated Moving Bed Chromatography. *Pharm. Technol. Eur.* **1999**, March−April.

(102) Fernandez-Barton, J. F. Mechanochemistry: an overview. *Pure Appl. Chem.* **1999**, *71*, 581.

(103) Volkov, V. V.; Myakishev, K. G. Mechanochemical reactions in the chemistry of boranes. *Inorg. Chim. Acta* **1999**, *289*, 51.

(104) Atwood, J. L.; Mardie, M. J.; Raston, C. L.; Sandoval, C. A. Convergent Synthesis of *p*-Benzylcalix[7]arene: Condensation and UHIG of *p*-Benzylcalix[6 or 8]arenes. *Org. Lett.* **1999**, *1*, 1523.

was useful in controlling particle size distribution in crystallization, and in minimizing hydrolysis of a nitrile formed under PTC conditions.[105] Further development of these and other techniques is expected.

Limitations of Continuous Processing. Physical factors can limit the development of continuous processes. Continuous processes are ideal for liquids and gases, but efficient fluid flow can be limited by the presence of solids[65] and bubbles, disrupting processing productivity. Such difficulties may be exacerbated by small apertures and by the narrow channels of microreactors. Pressure drops through tubular reactors and narrow apertures can pose safety concerns and limit productivity. Some of these difficulties can be eliminated by adjusting flow rates, by selecting solvents to ensure good dissolution, or by selecting higher-boiling solvents so that vaporization does not increase reactor pressures. With the continuous transfer of reaction streams, the risk of leaks, physical losses, and contamination is always present. Some continuous reactors operate at high temperatures and pressures and can pose safety concerns. Equipment manufacturers should always be consulted for safe operating guidelines, potential for corrosion, and compatibility of process streams with the materials of construction. It may be necessary to consult those with an engineering background for the design and smooth assembly or construction of continuous reactors.

Developing optimal conditions for a continuous process may require more time than that for the more familiar practice of developing a batch process. Empirical investigations are needed to determine the optimal residence time/flow rate, temperature, concentrations, and other parameters. Optimal conditions may be different than those for batch operations; for instance, the optimal temperature in the continuous thermal rearrangement of **20** (Scheme 8) was higher than that in batch processing.[43] Designed experiments may be useful to decrease the development time.[106]

Additional concerns of developing continuous processes are related to cGMP. In the start-up (and sometimes continuation) of continuous operations there are portions of the process streams that were not subjected to optimal, steady-state conditions: what is the disposition of these materials? With efficient process control, only a small proportion of the total process stream would fall into this category. In principle the rejected streams can be fed back into an earlier stage of operations, in effect performing an in situ rework of the suboptimal material if suitable purification is effected at the conclusion of processing. A less attractive approach is to reprocess (e.g., recrystallize) the entire output of a continuous operation to upgrade the quality and to ensure batch homogeneity. Although the latter approach may be considered blending, in some cases it may be found that despite such semi-continuous operations the quality is higher than that from batch processing. Overall, cGMP considerations are important to most processes and should not pose an insurmountable barrier for developing most continuous processes.

Continuous operations are not necessary or suitable for all operations. In some cases it may be a waste of time and resources to develop a continuous process; however, in other cases considerable time may be spent trying to identify suitable conditions to scale up a batch operation when continuous processing would afford an attractive alternative. Sometimes for scale-up there are no good alternatives to continuous operations, and the benefits must be contrasted with the limitations mentioned above. Many of the limitations of continuous processing are analogous to those encountered when using an unfamiliar technique or instrument, and may not be significant barriers. In the words of the Nike commercials, sometimes it is appropriate to "just do it" and try continuous processing.

Summary

Continuous processing, long established as cost-effective in the commodity chemicals sector, has been shown to be useful in the laboratory and pilot-plant scale-up of pharmaceuticals and fine chemicals. The benefits of continuous processing include greater process control, enhanced margins of safety, increased productivity, and improved quality and yields. Many processes that cannot be scaled up using batch operations can be readily scaled up in the laboratory and pilot plant through continuous operations. Continuous processing will be more commonly used in the future for scale-up in the lab and pilot plant.

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(105) Brechtelsbauer, C.; Lewis, N.; Oxley, P.; Ricard, F. Evaluation of a Spinning Disc Reactor for Continuous Processing. *Org. Process Res. Dev.* **2001**, *5*, 65.

(106) See Lendrem, D.; Owen, M.; Godbert, S. DOE (Design of Experiments) in Development Chemistry: Potential Obstacles. *Org. Process Res. Dev.* **2001**, *5*, 324, and other papers in issue 3, for the Special Feature Section: Laboratory Automation in Process R&D.