

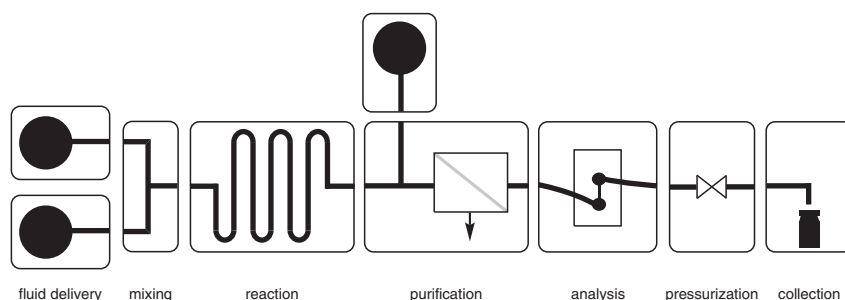
Abstracts

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2 Flow Chemistry System Design and Automation

C. W. Coley, J. Imbrogno, Y. Mo, D. A. Thomas, and K. F. Jensen

Organic chemistry performed in continuous-flow equipment, flow chemistry, has emerged as a complementary tool to traditional batch synthesis. This chapter describes typical components of a flow chemistry platform (e.g., pumps, mixers, reactors, and separators), reviews reaction engineering fundamentals as they apply to flow chemistry (e.g., mixing, dispersions, mass and heat transfer), summarizes laboratory and production reactors for single-phase, multiphase, thermal, photochemical, and electrochemical reactions, and describes strategies for separation with a focus on extraction. The chapter also reviews systems for multistep reactions along with integrated flow platforms comprising flow reactors, analytics, and computer control for automation, screening, and optimization.

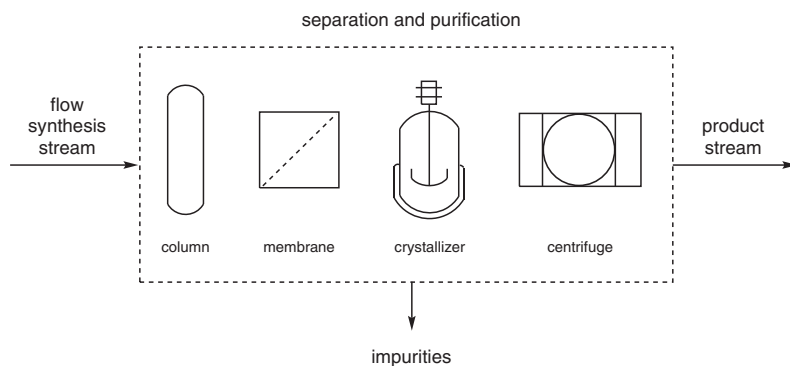


Keywords: flow chemistry · fluid delivery · pumps · laboratory reactor · commercial reactor · photochemistry · electrochemistry · multiphase reactions · extraction · multistep reactions · automation · reaction screening · reaction optimization

3 Separation and Purification in the Continuous Synthesis of Fine Chemicals and Pharmaceuticals

M. O'Mahony, S. Ferguson, T. Stelzer, and A. Myerson

Of use to both chemists and chemical engineers working in flow synthesis, this chapter provides a summary of separation and purification operations that can be applied to flow synthesis reaction streams. Both single and biphasic separations for the liquid phase are detailed. Separation and purification by continuous crystallization of a solid phase is covered. Continuous solid-liquid separation and drying technologies for the isolation of a fine-chemical or pharmaceutical product are also reviewed.



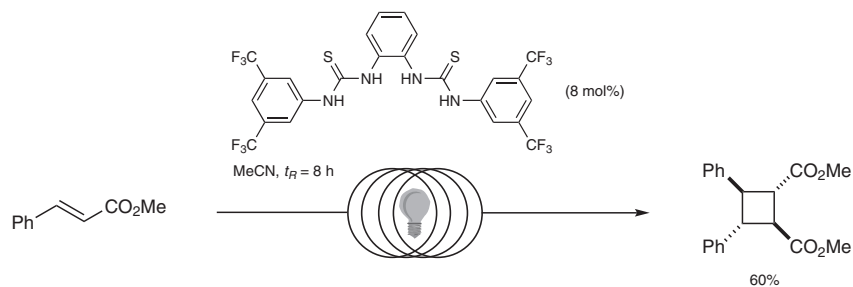
Keywords: flow chemistry · continuous separation · pharmaceuticals · nanofiltration · membrane extractors · continuous crystallization · integrated continuous manufacturing · continuous solid-liquid separation · filtration · continuous filtration · continuous isolation and drying

4 Flow Photochemistry in Organic Synthesis

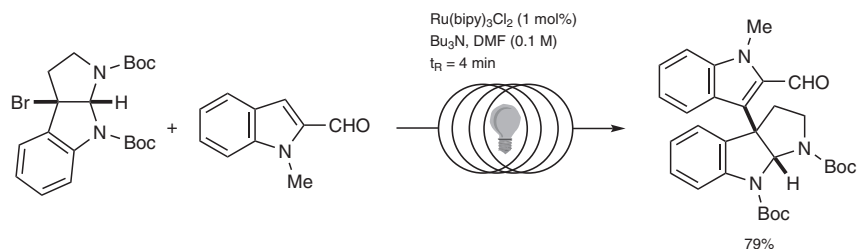
R. Telmesani, A. C. Sun, A. B. Beeler, and C. R. J. Stephenson

Performing photochemical reactions in flow has helped increase their efficiency, scalability, and utility. These efforts have brought photochemistry back to prominence as a powerful tool for synthesis. This chapter outlines the most important procedures and flow setups that can be used to perform photochemical transformations. Examples include ultraviolet-light-driven photocycloadditions and reactions with reagents such as singlet oxygen and transition-metal catalysts. Applications of visible-light photoredox catalysis in continuous-flow systems are discussed in the context of late-stage fluorination, natural product synthesis, alkyl–aryl cross coupling, and lignin fragmentation.

UV photochemistry



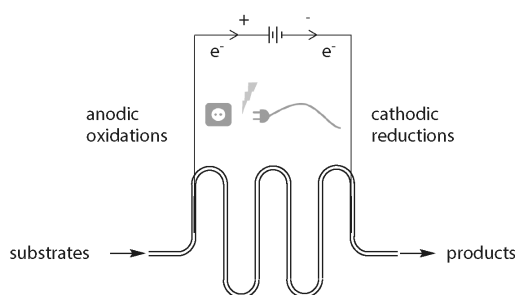
visible-light photoredox catalysis



Keywords: photochemistry · flow chemistry · photocycloaddition · singlet oxygen · photochemical rearrangements · polymer modification · immersion well · fluorination · photoredox catalysis · perfluoroalkylation · natural product synthesis · lignin

5 Electroynthesis in Continuous Flow*A. A. Folgueiras-Amador and T. Wirth*

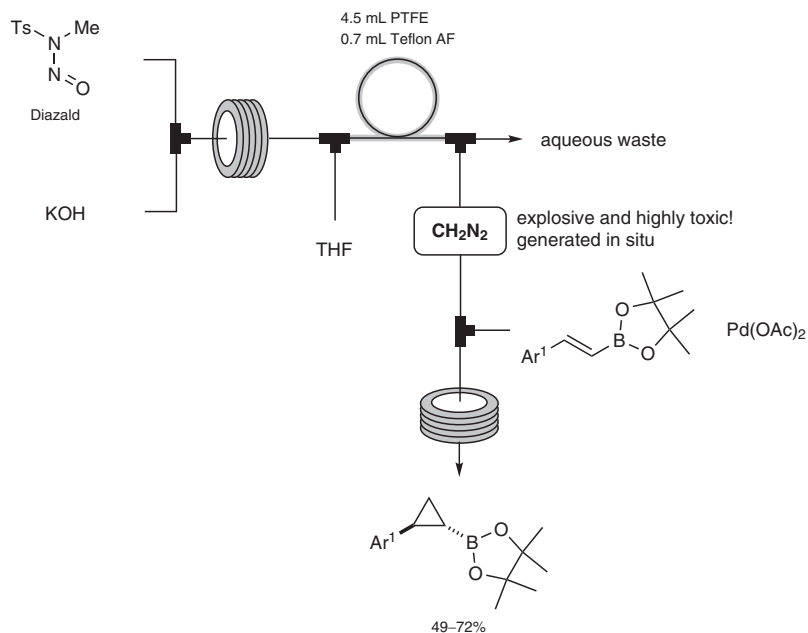
Organic electroynthesis is recognized as a green enabling methodology to perform reactions in an efficient and straightforward way. Electrons are used as the reagent to form anionic and cationic radical species from neutral organic molecules, achieving oxidations and reductions and replacing toxic and dangerous reagents. Within this field, the use of microreactors in continuous flow is particularly compatible with electrochemistry because of the convenient advantages of flow over batch, including: (i) low loading or no supporting electrolyte at all, due to the small distance between electrodes, providing significant advantages in downstream processing; (ii) high electrode surface-to-reactor volume ratio; (iii) short residence time; and (iv) improved mixing effects. In this chapter, the most relevant electrochemical flow reactors and electrochemical transformations performed in continuous flow are presented and discussed.



Keywords: flow electroynthesis · electrochemical microreactors · flow chemistry · electrochemistry · anodic oxidations · cathodic reductions · divided cells · undivided cells

6 Hazardous Reagents in Continuous-Flow Chemistry*R. W. Hicklin, A. E. Strom, E. D. Styduhar, and T. F. Jamison*

Continuous-flow technology enables the use of hazardous reagents and the safe handling of hazardous intermediates. This chapter focuses on the application of continuous-flow techniques in reactions involving reactive organometallic reagents, hazardous nitrogen- and halogen-based reagents, oxidants, and toxic low-molecular-weight reagents.

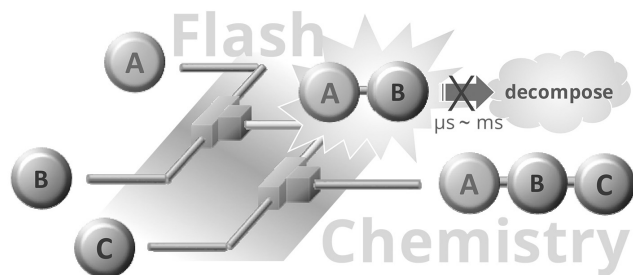


Keywords: continuous-flow chemistry • hazardous reagents • diazo compounds • halogenation • explosive reagents • pyrophoric reagents • acutely toxic reagents • reactive organometallic reagents • toxic low-molecular-weight reagents • oxidation

7 Very Fast Reactions and Extreme Conditions

H. Kim and J. Yoshida

Microreaction technology represents a powerful and unique tool for the control of extremely fast reactions and reactions under extreme conditions. In this chapter, fast flow reactions such as Swern–Moffatt oxidations, diisobutylaluminum hydride reductions, reactions involving organolithiums and organomagnesiums, and Friedel–Crafts alkylations are presented. Moreover, this chapter also covers examples of reactions performed under extreme reaction conditions of high temperature and high pressure, which cannot be easily conducted in flasks.

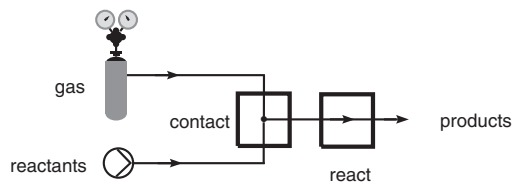


Keywords: fast reactions · unstable intermediates · organolithiums · extreme conditions · high temperature · high pressure · flow chemistry · microreactors · flash chemistry

8 Gaseous Reagents in Continuous-Flow Synthesis

M. O'Brien and A. Polyzos

Although reactive gases facilitate a wide range of important synthetic transformations, their use is often not straightforward. Significant safety issues arise from the highly mobile nature of gases, both in terms of the rapidity with which they can spread throughout the laboratory and also because of the frequent need to use pressurized containment. Additionally, as surface-area-to-volume ratios tend to decrease as reactor dimensions are increased, gas–liquid transformations carried out in batch mode are often accompanied by scale-dependent performance. This chapter highlights some of the benefits that continuous flow chemistry can bring to gas–liquid synthetic chemistry. A number of flow chemical reactor systems are described, including microfluidic devices which enhance the mechanical mixing of gas and liquid phases, as well as systems based on the use of gas-permeable membrane materials.

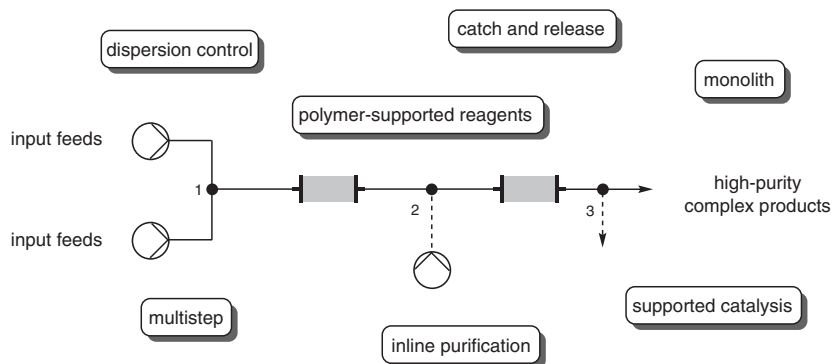


Keywords: gas–liquid · flow chemistry · falling film · cyclone · H-Cube · Teflon AF-2400 · tube-in-tube · biphasic flow · microfluidic · membranes

9 Immobilized Reagents and Multistep Processes

S. V. Ley, D. L. Browne, and M. O'Brien

Multistep continuous-flow processing enables the direct preparation of complex chemical materials from simple input streams through a series of complexity-adding reaction steps. The use of polymer-supported reagents can greatly facilitate this process through the inline hosting of reagents or catalysts, the scavenging of spent materials or impurities, or even the temporary hosting of reactive intermediates prior to their reaction and release from the support. This chapter provides a comprehensive overview of such polymer-supported techniques.

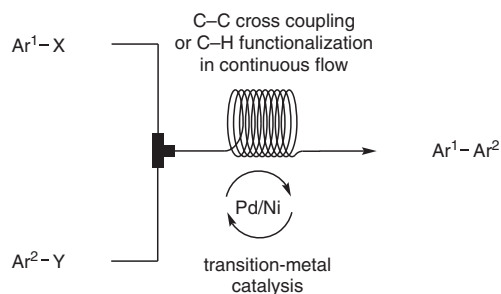


Keywords: polymer-supported reagents · multistep flow synthesis · natural products · pharmaceutical agents · catch and release

10 Intermolecular Transition-Metal-Catalyzed C–C Coupling Reactions in Continuous Flow

C. Bottecchia and T. Noël

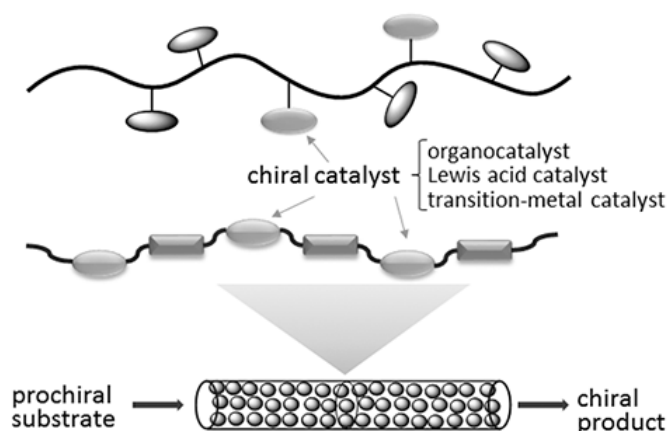
This chapter provides an up-to-date collection of prominent examples of intermolecular transition-metal-catalyzed C–C coupling reactions performed in continuous-flow systems. The advantages offered by flow technology for the implementation of traditional cross-coupling methods are discussed. Moreover, recent examples of the successful application of flow reactors for C–H functionalization strategies (including C–H activation and dual photoredox transition-metal catalysis) are reviewed.



Keywords: transition-metal catalysis · cross coupling · Suzuki–Miyaura coupling · Negishi coupling · Mizoroki–Heck coupling · carbonylative coupling · continuous flow · C–H functionalization · dehydrogenative coupling · C–H activation · dual catalysis

11 Immobilized Catalysts for Asymmetric Reactions*S. Itsuno and M. S. Ullah*

Recent applications of polymer-immobilized catalysts for asymmetric reactions are described in this chapter. The chiral catalysts covered include organocatalysts, Lewis acid catalysts, and transition-metal catalysts. Preparation of these chiral polymer-immobilized catalysts and their use in asymmetric reactions are described. The polymer-immobilized catalysts are insoluble in the solvent used for asymmetric reactions and are easily separated from the reaction mixture; the recovered polymeric catalysts can be reused many times without any loss of the catalytic performance. Some of these polymeric catalysts have been used in continuous-flow systems, potentially providing a powerful tool for the synthesis of optically active fine chemicals.

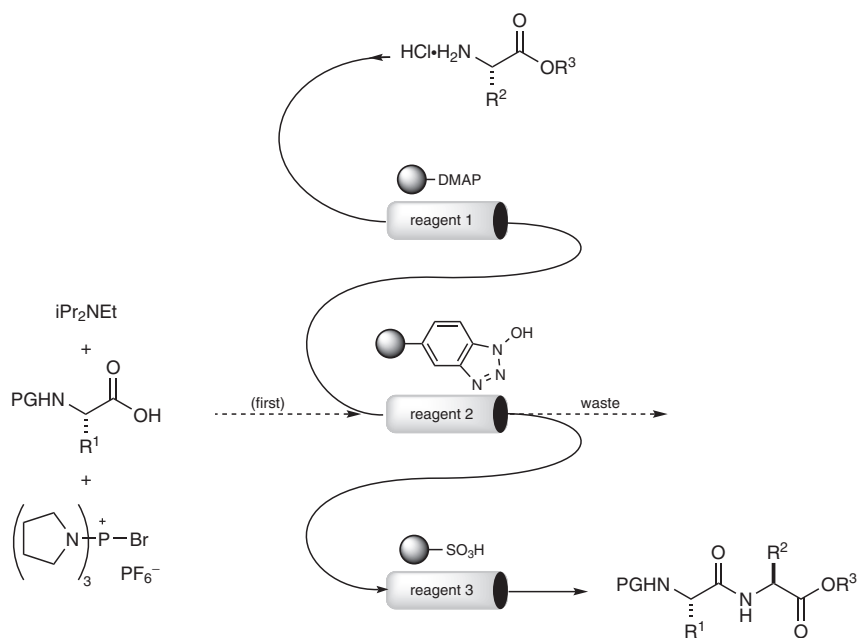


Keywords: polymer-immobilized catalysts · organocatalysts · cinchona alkaloids · Lewis acid catalysts · transition-metal catalysts · asymmetric reactions · flow chemistry

12 Pushing the Limits of Solid-Phase Peptide Synthesis with Continuous Flow

A. J. Mijalis, A. Steinauer, A. Schepartz, and B. L. Pentelute

Since its invention by Bruce Merrifield, solid-phase peptide synthesis has conventionally been performed in batch reactors. With systems created by Atherton, Dryland, and Shepard in the 1980s, flow-chemistry techniques began to be applied to enhance solid-phase peptide synthesis, improving mixing and enabling time-resolved monitoring of Fmoc removal. Here, we review the history of flow-chemical techniques for solid-phase peptide synthesis, advances in solid supports that make flow chemistry on the solid phase feasible, the rationale behind using flow chemistry for amino acid activation, and other techniques for synthesizing peptides in flow, including the use of solid-supported coupling reagents and soluble macromolecular supports. Advantages of flow-chemistry techniques for both solid- and liquid-phase peptide synthesis include precise control of reagent heating and chiral integrity of incorporated amino acids, improvements in amino acid coupling times, and in-process detection of problematic peptide sequences.

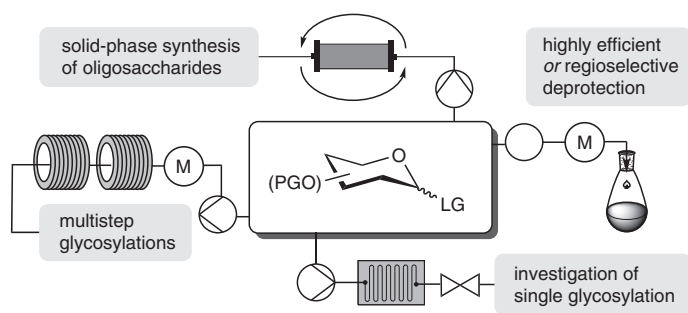


Keywords: peptide synthesis · flow chemistry · amides · amino acids · activation · automation · solid phase

13 The Controlled Synthesis of Carbohydrates

S. Moon, K. Gilmore, and P. H. Seeberger

While the formation of the glycosidic bond is the key transformation in the synthesis of polysaccharides, a dominant class of biopolymer, the reaction is poorly understood and remains highly challenging to perform reliably and selectively in a laboratory setting. This is due to the numerous intermediates and competing mechanistic pathways present, all of which are extremely sensitive to the environmental conditions of the reaction. This sensitivity and irreproducibility is an excellent opportunity to take advantage of the inherent control over reaction conditions achievable in micro- and meso-flow reactors. In this chapter, the range of transformations performed under continuous-flow conditions related to the synthesis of carbohydrates, including glycosidic bond formation, functional-group manipulations, and multistep synthesis, are presented and discussed. The advantages gained in flow are highlighted and, where available, directly compared to the respective batch process.

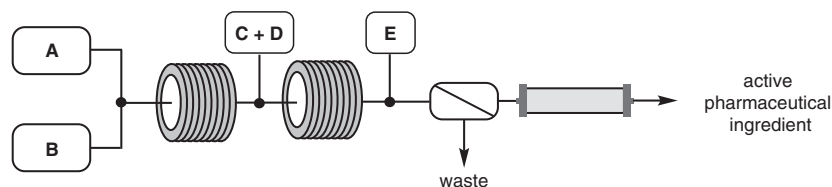


Keywords: carbohydrates · flow chemistry · mixing · multistep · stereoselective · glycosylation · glycosidic bond · micromixer · microfluidic · monosaccharide · oligosaccharide · polysaccharide · automation · solid-phase synthesis

14 Continuous-Flow Syntheses of Active Pharmaceutical Ingredients

R. L. Beingessner, A. R. Longstreet, T. A. McTeague, L. P. Kelly, H. Seo, T. H. Tran, A. C. Wicker, and T. F. Jamison

This chapter describes synthetic strategies and technologies used to perform multistep flow syntheses of active pharmaceutical ingredients (APIs). The APIs or potential drug candidates highlighted are efavirenz, imatinib, (–)-oseltamivir, ibuprofen, rolipram, methylphenidate hydrochloride, and rufinamide.

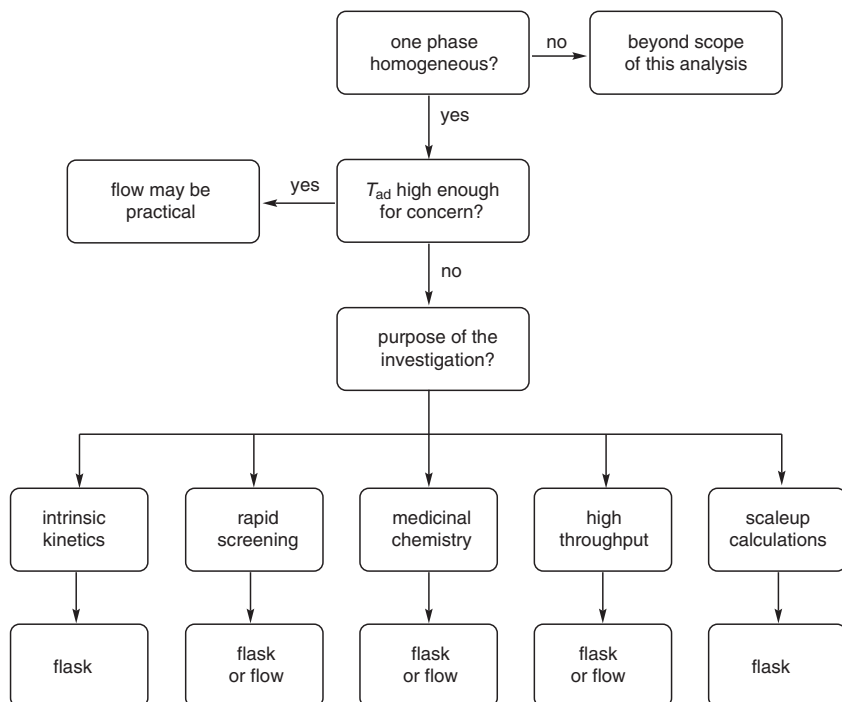


Keywords: multistep processes · continuous-flow synthesis · essential medicines · polymer-supported catalysts · packed-bed reactors · copper tubing reactors · inline purification · biphasic synthesis · inline separation · semi-continuous · fully continuous

15.1 Flow Chemistry in the Pharmaceutical Industry: Part 1

A. G. O'Brien

The use of flow chemistry in the single- and multistep synthesis of active pharmaceutical ingredients has been well demonstrated. The pharmaceutical industry is now taking the next steps towards integration of flow chemistry into large-scale commercialized processes, which can effectively supply patient populations. This chapter details advances in this area, and outlines the data and knowledge required to select, develop, scale, and commercialize an efficient flow process.

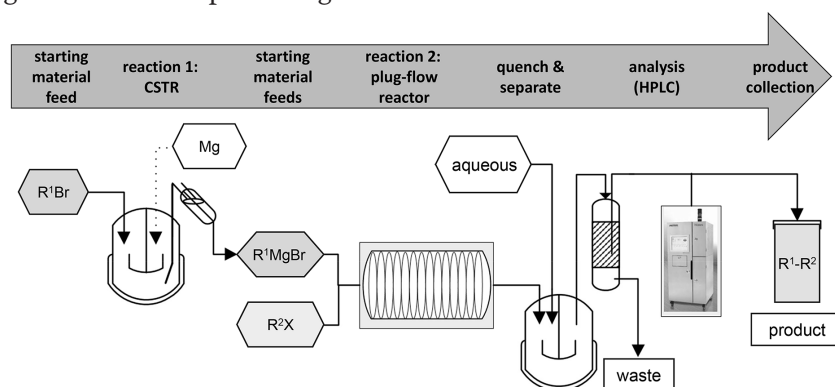


Keywords: continuous-flow processes · pharmaceuticals · multistep processes · process selection · process development · scaleup · process optimization

15.2 Flow Chemistry in the Pharmaceutical Industry: Part 2

S. A. May and M. S. Kerr

The development and application of continuous-flow drug-substance manufacturing at Eli Lilly is described. A series of examples are provided in which a continuous process was developed to solve problems associated with an existing batch process. The three distinct areas of focus are: facilitation of early phase delivery, hybrid batch/flow processes at manufacturing scale, and small-volume continuous manufacturing (linked multiunit operation processes at 10 kg/day throughput). An overview is provided of the types of reactors implemented in our program and the chemistries they enable. The use of online process analytical technology is also described for each of these systems. Special emphasis is placed on the examples pertaining to increased safety and improved product quality gained from flow processing.

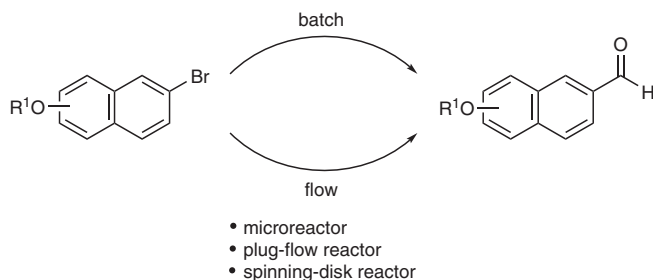


Keywords: continuous processing · flow technologies · process analytical technology · plug-flow reactors · continuous stirred-tank reactors · intermittent stirred tanks · small-volume continuous manufacturing · process development · continuous crystallization

15.3 Flow Chemistry in the Pharmaceutical Industry: Part 3

S. M. Opalka, W. F. Kiesman, and D.-I. A. Kwok

When considering whether to develop a flow-chemistry approach to a particular synthetic route, the criteria of safety, quality, cost, sustainability, scalability, and speed are all considered. This chapter presents a case study of a single reaction, the formylation of an aryl bromide, being performed in a batch reactor, a microreactor, a plug-flow reactor, and a spinning-disk reactor. An assessment of the various technologies is made with respect to the abovementioned criteria.



Keywords: flow chemistry · scale-up · batch reactions · microreactors · plug-flow reactors · spinning-disk reactors · process development · optimization