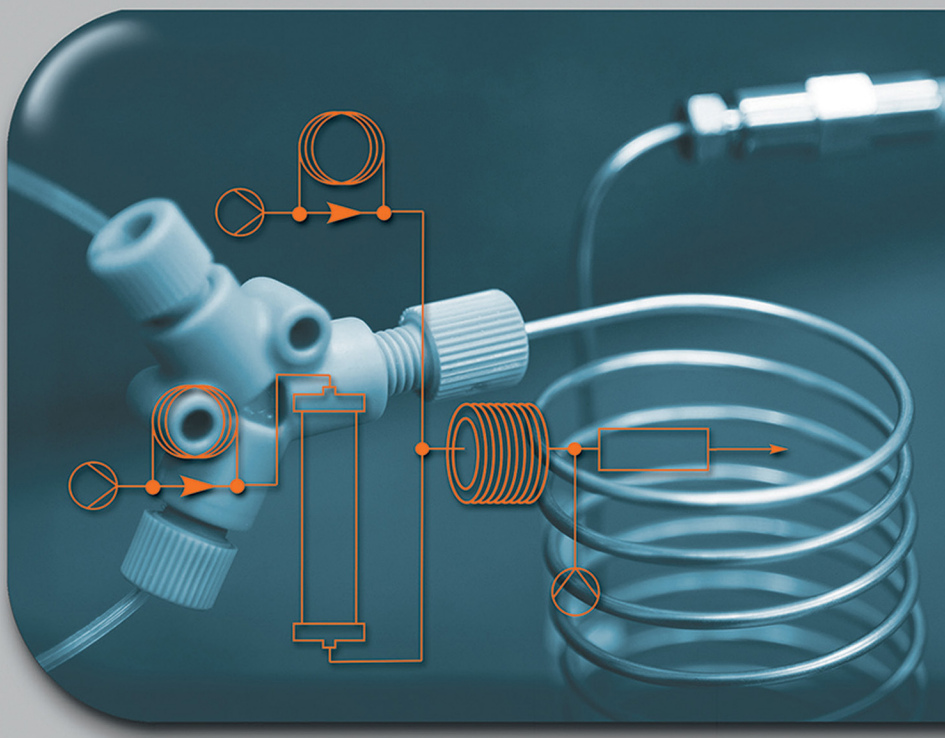
Science of Synthesis

Flow Chemistry in Organic Synthesis

Volume Editors
T. F. Jamison
G. Koch



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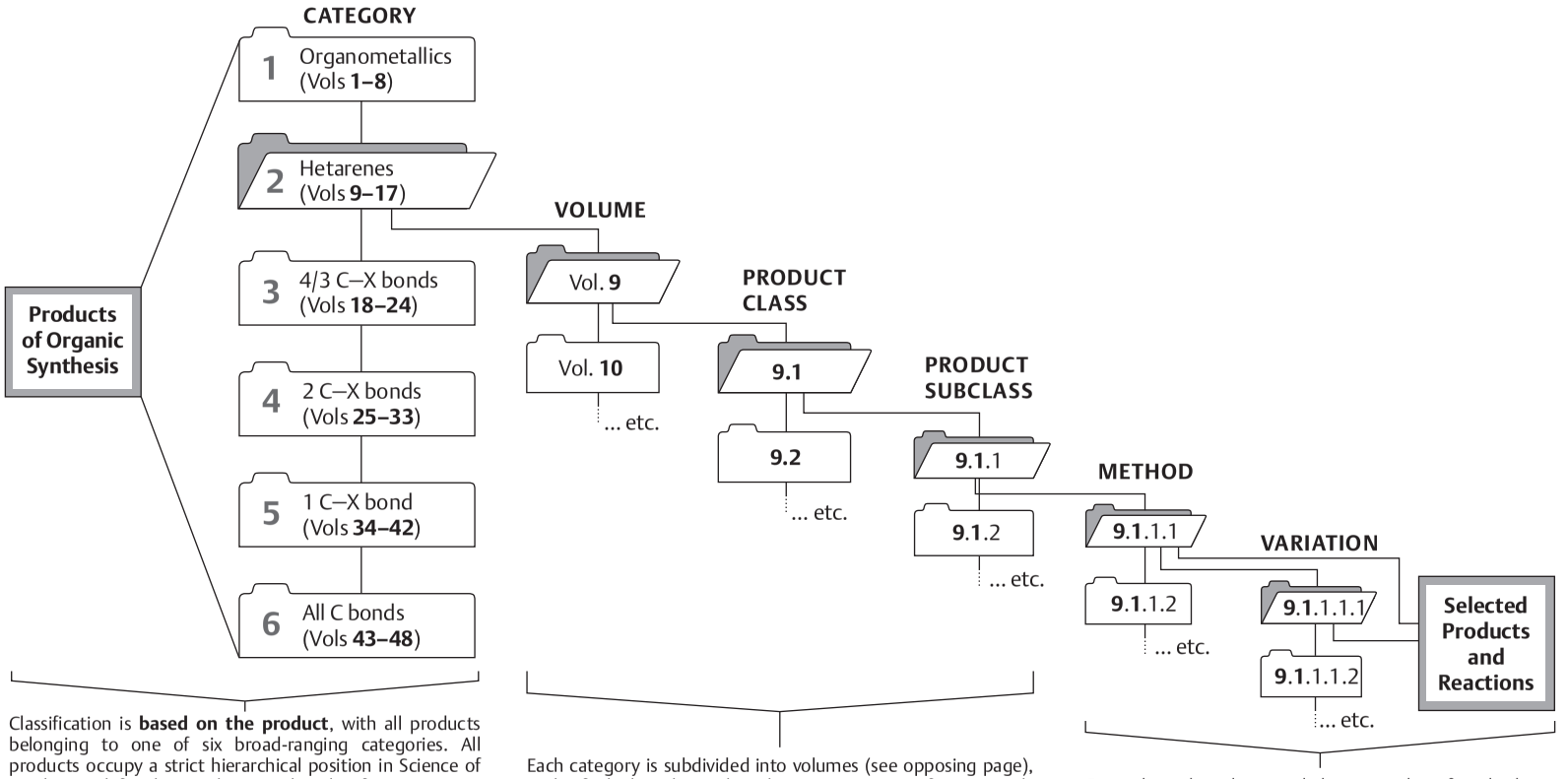
Organizational Structure of Science of Synthesis*

* A complete description of the full classification principles can be found in the **Science of Synthesis Guidebook.**



Classification is **based on the product**, with all products belonging to one of six broad-ranging categories. All products occupy a strict hierarchical position in Science of Synthesis, defined according to the classification principles*. Products in Categories 3–6 are organized according to oxidation state, with products containing the greatest number of carbon–heteroatom (C—X) or C—C π-bonds to a single carbon occupying the highest positions (e.g., carboxylates, enolates, and alcoholates are covered in Categories 3, 4, and 5, respectively).

Each category is subdivided into volumes (see opposing page), each of which is devoted to discrete groupings of compounds called **product classes** (e.g., "Thiophenes" is Product Class 10 of Volume 9). Product classes may be further subdivided into **product subclasses**, (e.g., "Thiophene 1,1-Dioxides" is Product Subclass 3 of Product Class 10 of Volume 9). Consequently, the relationship between heading name and heading number varies below product class level within individual volumes.

For each product class or subclass, a number of methods are described for synthesizing the general product type. Often there are variations on a method given. Both methods and variations contain experimental procedures with relevant background information and literature references. **Selected products and reactions** display the scope and limitations of the methods.

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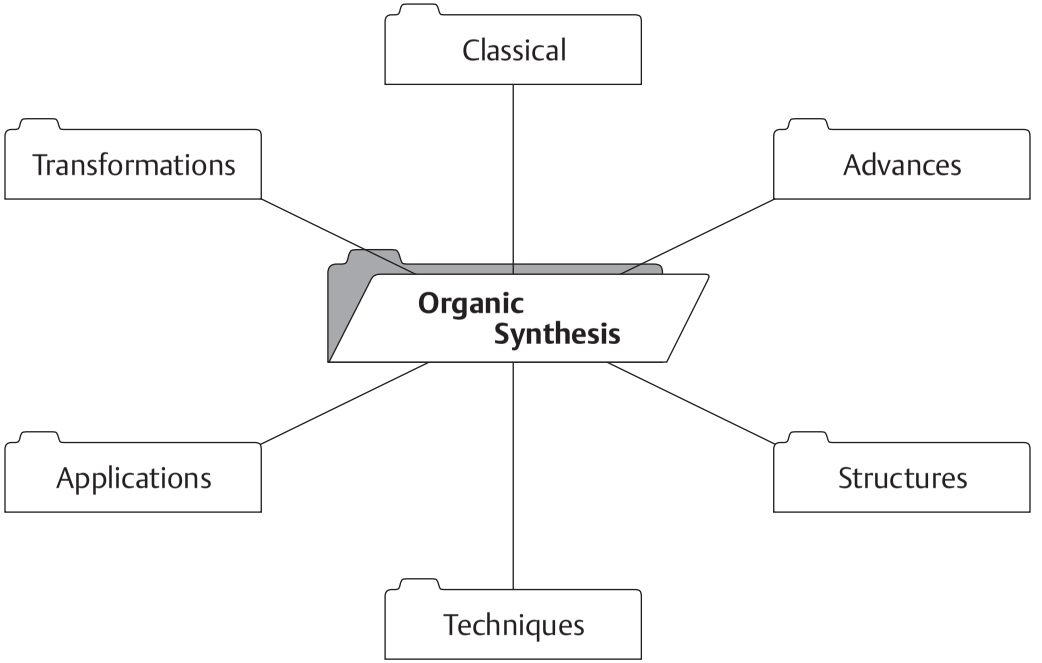
The **Science of Synthesis Reference Library** comprises volumes covering special topics of organic chemistry in a modular fashion, with six main classifications: (1) Classical, (2) Advances, (3) Transformations, (4) Applications, (5) Structures, and (6) Techniques. Volumes in the **Science of Synthesis Reference Library** focus on subjects of particular current interest with content that is evaluated by experts in their field. **Science of Synthesis**, including the **Knowledge Updates** and the **Reference Library**, is the complete information source for the modern synthetic chemist.



Science of Synthesis

Science of Synthesis is the authoritative and comprehensive reference work for the entire field of organic and organometallic synthesis.

Science of Synthesis presents the important synthetic methods for all classes of compounds and includes:

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- Background information and detailed experimental procedures
- Schemes and tables which illustrate the reaction scope

Science of Synthesis

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Flow Chemistry in Organic Synthesis

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Preface

As the pace and breadth of research intensifies, organic synthesis is playing an increasingly central role in the discovery process within all imaginable areas of science: from pharmaceuticals, agrochemicals, and materials science to areas of biology and physics, the most impactful investigations are becoming more and more molecular. As an enabling science, synthetic organic chemistry is uniquely poised to provide access to compounds with exciting and valuable new properties. Organic molecules of extreme complexity can, given expert knowledge, be prepared with exquisite efficiency and selectivity, allowing virtually any phenomenon to be probed at levels never before imagined. With ready access to materials of remarkable structural diversity, critical studies can be conducted that reveal the intimate workings of chemical, biological, or physical processes with stunning detail.

The sheer variety of chemical structural space required for these investigations and the design elements necessary to assemble molecular targets of increasing intricacy place extraordinary demands on the individual synthetic methods used. They must be robust and provide reliably high yields on both small and large scales, have broad applicability, and exhibit high selectivity. Increasingly, synthetic approaches to organic molecules must take into account environmental sustainability. Thus, atom economy and the overall environmental impact of the transformations are taking on increased importance.

The need to provide a dependable source of information on evaluated synthetic methods in organic chemistry embracing these characteristics was first acknowledged over 100 years ago, when the highly regarded reference source **Houben–Weyl Methoden der Organischen Chemie** was first introduced. Recognizing the necessity to provide a modernized, comprehensive, and critical assessment of synthetic organic chemistry, in 2000 Thieme launched **Science of Synthesis, Houben–Weyl Methods of Molecular Transformations**. This effort, assembled by almost 1000 leading experts from both industry and academia, provides a balanced and critical analysis of the entire literature from the early 1800s until the year of publication. The accompanying online version of **Science of Synthesis** provides text, structure, substructure, and reaction searching capabilities by a powerful, yet easy-to-use, intuitive interface.

From 2010 onward, **Science of Synthesis** is being updated quarterly with high-quality content via **Science of Synthesis Knowledge Updates**. The goal of the **Science of Synthesis Knowledge Updates** is to provide a continuous review of the field of synthetic organic chemistry, with an eye toward evaluating and analyzing significant new developments in synthetic methods. A list of stringent criteria for inclusion of each synthetic transformation ensures that only the best and most reliable synthetic methods are incorporated. These efforts guarantee that **Science of Synthesis** will continue to be the most up-to-date electronic database available for the documentation of validated synthetic methods.

Also from 2010, **Science of Synthesis** includes the **Science of Synthesis Reference Library**, comprising volumes covering special topics of organic chemistry in a modular fashion, with six main classifications: (1) Classical, (2) Advances, (3) Transformations, (4) Applications, (5) Structures, and (6) Techniques. Titles will include *Stereoselective Synthesis*, *Water in Organic Synthesis*, and *Asymmetric Organocatalysis*, among others. With expert-evaluated content focusing on subjects of particular current interest, the **Science of Synthesis Reference Library** complements the **Science of Synthesis Knowledge Updates**, to make **Science of Synthesis** the complete information source for the modern synthetic chemist.

The overarching goal of the **Science of Synthesis** Editorial Board is to make the suite of **Science of Synthesis** resources the first and foremost focal point for critically evaluated information on chemical transformations for those individuals involved in the design and construction of organic molecules.

Throughout the years, the chemical community has benefited tremendously from the outstanding contribution of hundreds of highly dedicated expert authors who have devoted their energies and intellectual capital to these projects. We thank all of these individuals for the heroic efforts they have made throughout the entire publication process to make **Science of Synthesis** a reference work of the highest integrity and quality.

The Editorial Board September 2018

Science of Synthesis Reference Library

Flow Chemistry in Organic Synthesis
Catalytic Reduction in Organic Synthesis (2 Vols.)
Catalytic Oxidation in Organic Synthesis
N-Heterocyclic Carbenes in Catalytic Organic Synthesis (2 Vols.)
Metal-Catalyzed Cyclization Reactions (2 Vols.)
Applications of Domino Transformations in Organic Synthesis (2 Vols.)
Catalytic Transformations via C—H Activation (2 Vols.)
Biocatalysis in Organic Synthesis (3 Vols.)
C-1 Building Blocks in Organic Synthesis (2 Vols.)
Multicomponent Reactions (2 Vols.)
Cross Coupling and Heck-Type Reactions (3 Vols.)
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Asymmetric Organocatalysis (2 Vols.)
Stereoselective Synthesis (3 Vols.)

Abstracts

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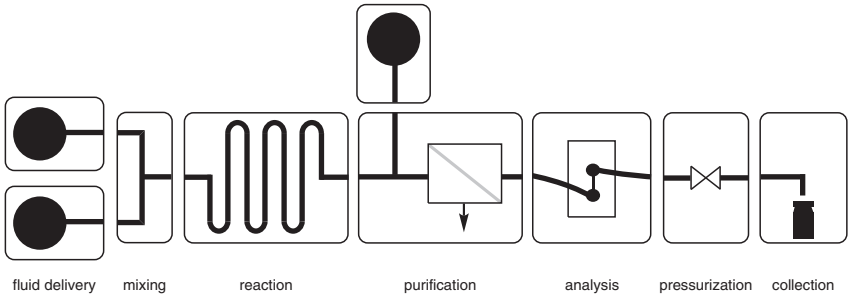
2 Flow Chemistry System Design and Automation

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

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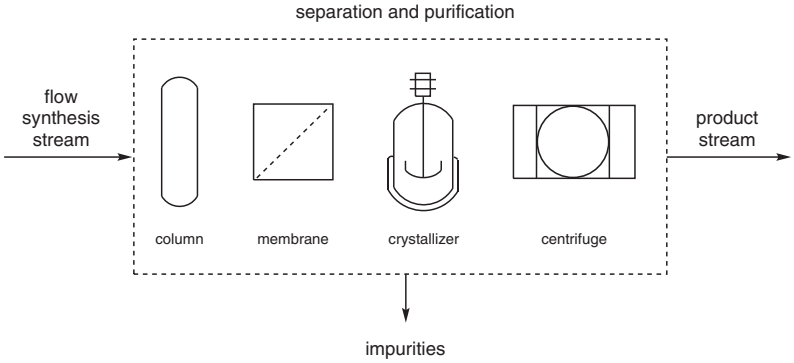
3 Separation and Purification in the Continuous Synthesis of Fine Chemicals and Pharmaceuticals

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.

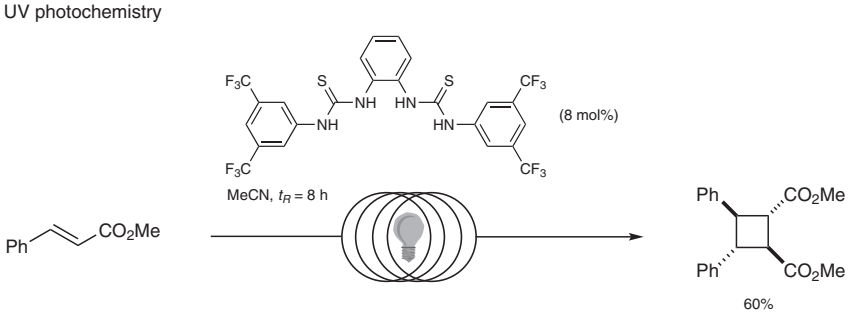


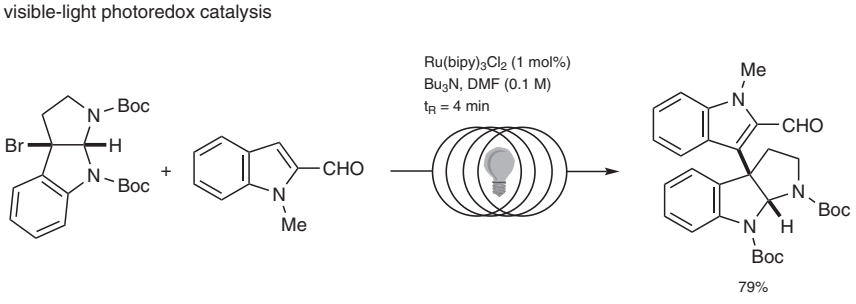
Keywords: flow chemistry · continuous separation · pharmaceuticals · nanofiltration · membrane extractors · continuous crystallization · integrated continuous manufacturing · continuous solid–liquid separation · filtration · continuous filtration · continuous isolation and drying

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.





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

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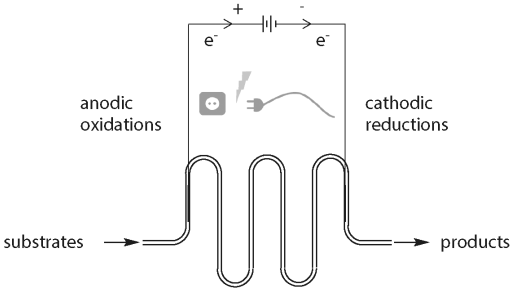
5 Electrosynthesis in Continuous Flow

A. A. Folgueiras-Amador and T. Wirth

Organic electrosynthesis 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 electrosynthesis · electrochemical microreactors · flow chemistry · electrochemistry · anodic oxidations · cathodic reductions · divided cells · undivided cells

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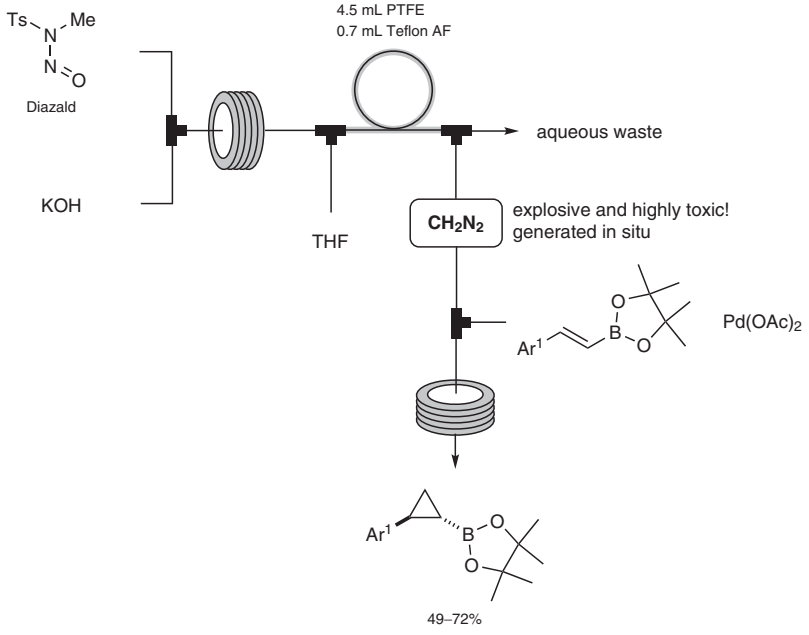
6 Hazardous Reagents in Continuous-Flow Chemistry

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

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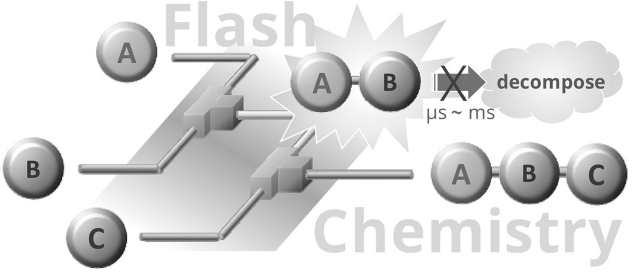
7 Very Fast Reactions and Extreme Conditions

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

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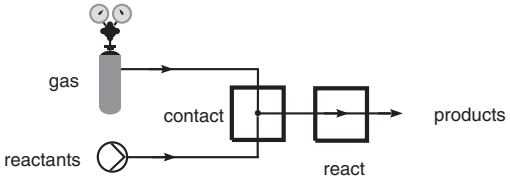
8 Gaseous Reagents in Continuous-Flow Synthesis

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

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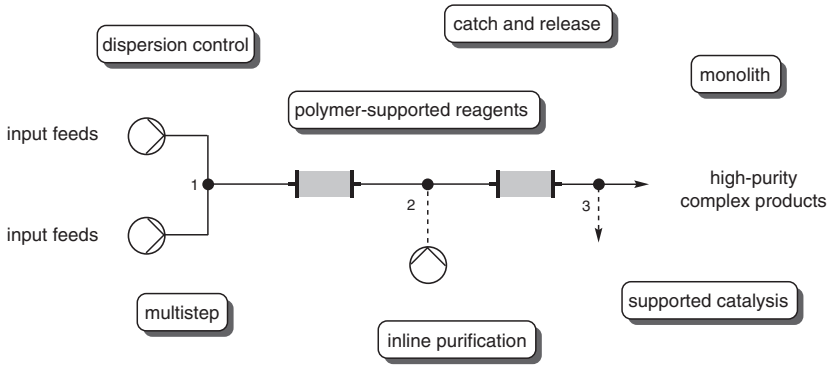
9 Immobilized Reagents and Multistep Processes

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

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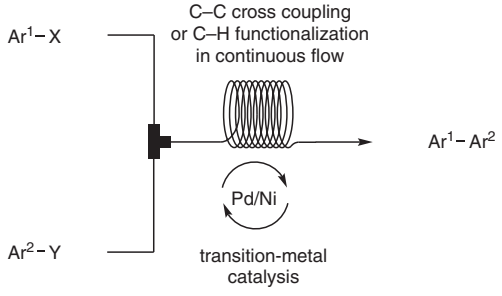
10 Intermolecular Transition-Metal-Catalyzed C—C Coupling Reactions in Continuous Flow

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

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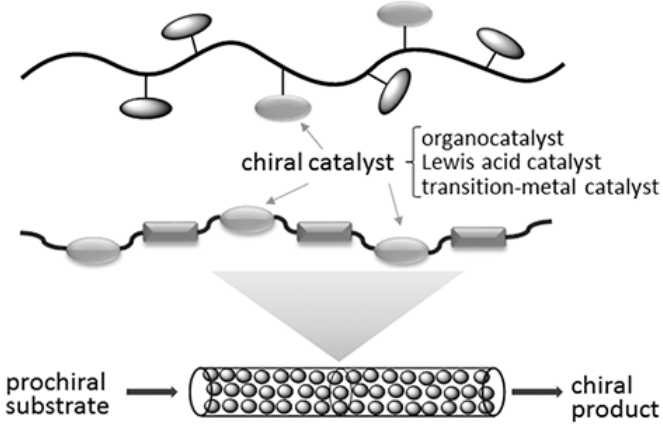
11 Immobilized Catalysts for Asymmetric Reactions

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

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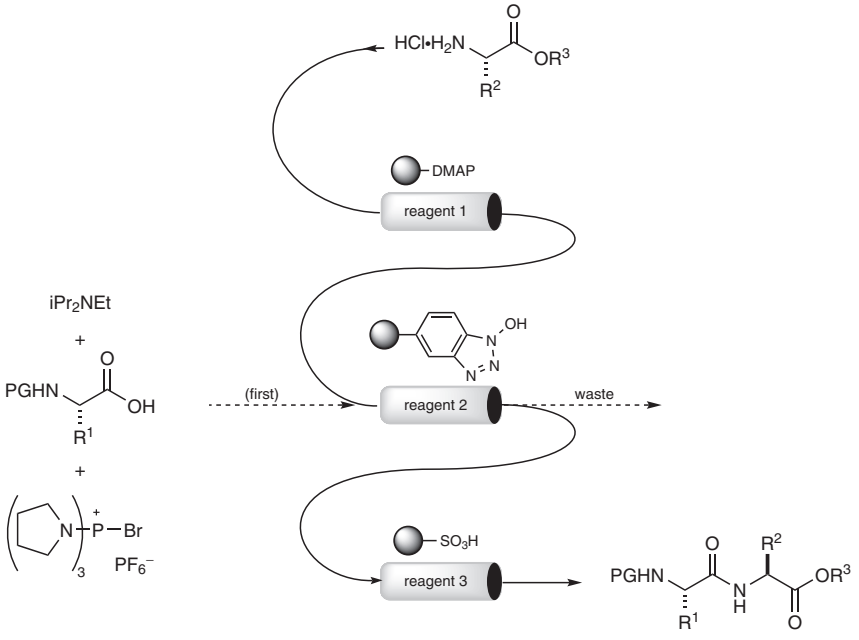
12 Pushing the Limits of Solid-Phase Peptide Synthesis with Continuous Flow

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 Sheppard 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

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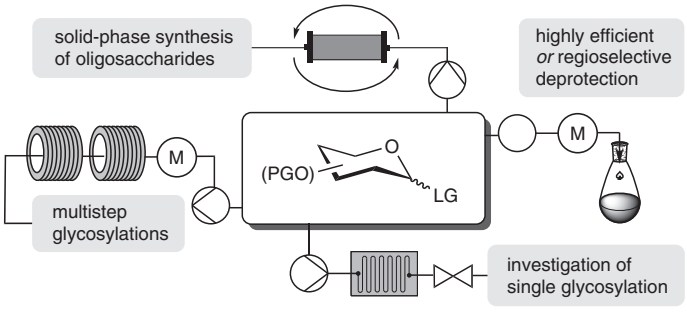
13 The Controlled Synthesis of Carbohydrates

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

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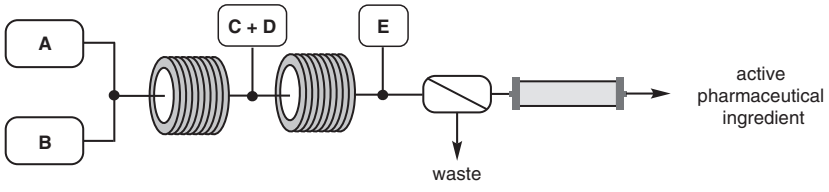
14 Continuous-Flow Syntheses of Active Pharmaceutical Ingredients

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

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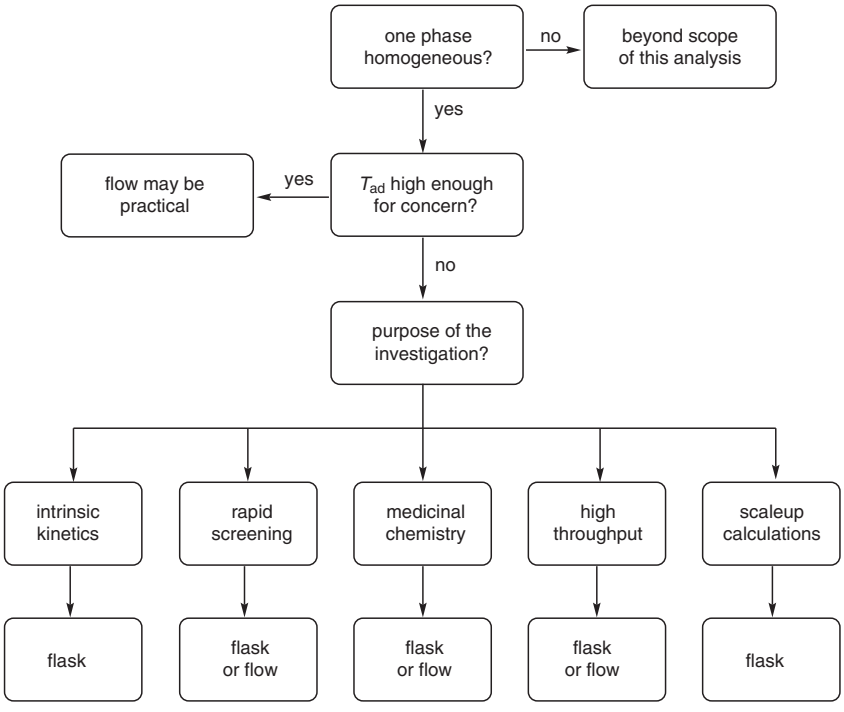
15.1 Flow Chemistry in the Pharmaceutical Industry: Part 1

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

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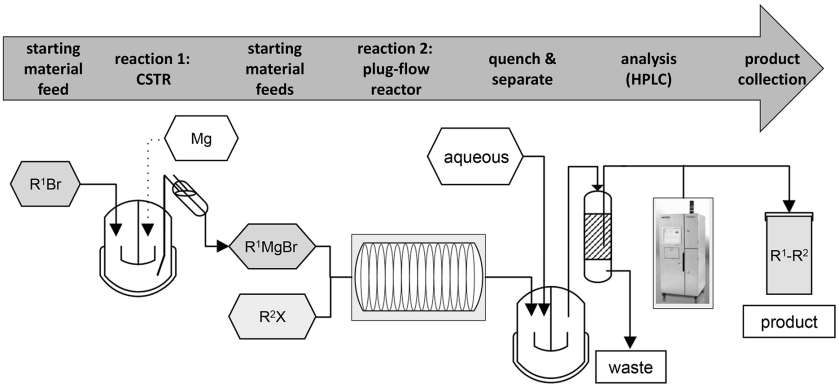
15.2 Flow Chemistry in the Pharmaceutical Industry: Part 2

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

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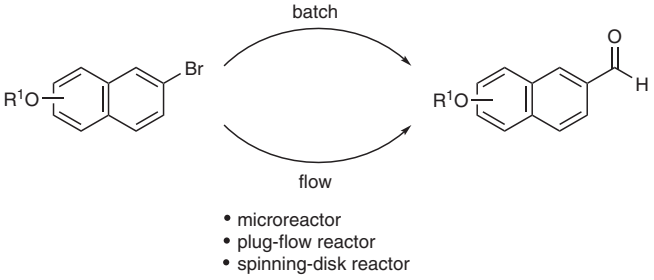
15.3 Flow Chemistry in the Pharmaceutical Industry: Part 3

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

Flow Chemistry in Organic Synthesis

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