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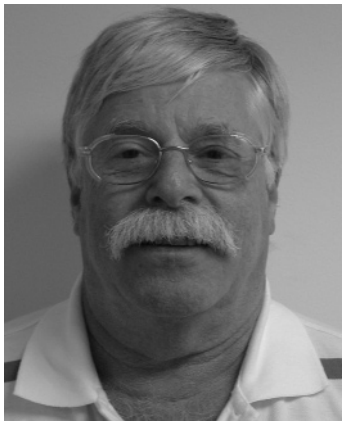
Introduction: Process Chemistry



Michael Lipton joined Schering-Plough Research Institute as a Senior Development Fellow in Chemical and Physical Sciences in 2006. He received a B.S. in Chemistry from Purdue University in 1972 and a Ph.D. in Chemistry in 1976 from the University of Colorado, where he worked on tosylhydrazones with Professor Robert H. Shapiro. Following a postdoctoral stint with Professor Steven M. Weinreb, conducting research in total synthesis and synthetic methods, he joined the faculty at Michigan State University as an Assistant Professor of Chemistry in 1978. From there he went to The Upjohn Company (in 1980), where his affiliation with process chemistry began. Mike stayed on in Kalamazoo, MI, through the changing regulatory landscape and the flurry of mergers and acquisitions, working on a variety of process chemistry problems and rising to the level of Research Fellow, electing early retirement from Pfizer in 2006. He was Chairman of the Organic Reactions and Processes Gordon Research Conference in 2001 and has been a member of the Editorial Advisory Board of Organic Process Research and Development since 2001. He was also a member of the organizing committee of *Building Bridges, Forging Bonds for 21st Century Organic Chemistry and Chemical Biology*, a joint conference sponsored by the American Chemical Society and India's Council on Scientific Research, in early 2006.

Tony Barrett started his academic career at Imperial College London (B.Sc., 1973; Ph.D., 1975, with Derek H. R. Barton; Lecturer, 1975; and Senior Lecturer, 1982). He was appointed a Full Professor of Chemistry at Northwestern University, Evanston, IL (1983), and at Colorado State University (1990). In 1993 he returned to his alma mater, IC, as Glaxo Professor of Chemistry, Sir Derek Barton Professor of Synthesis, Director of the Wolfson Centre for Organic Chemistry in Medical Science, and Head of Synthesis. His research interests include the total synthesis of bioactive natural products, porphyrazine chemistry, and the design of methods for organic synthesis including novel catalysis, enantioselective transformations, and supported reagents.

There are myriad synthetic organic reactions that are widely applied in small-scale synthesis. Much of the chemical literature over the last century has been devoted to the invention and application of new synthetic methodology. Nonetheless, there are so very few reactions that stand up to the most stringent of tests: scale-up and manufacture. Process chemistry is the practical application of organic synthesis. For a chemical process to be functional on large scales, it not only needs to be robust and predictable; it should also be operationally simple, safe, and straightforward. Ideally, reactions should use inexpensive, environmentally benign starting materials, reagents, and solvents and produce the target compound not only in high yield but also in very high quality as well, with a minimum of impurities that are easily removed, preferably by crystallization. If the process is catalytic, turnover numbers and turnover frequencies must be high and the product must be free of trace contaminants such as heavy metal salts or complexes. Few synthetic transformations meet these rigorous criteria. During development, the process chemist seeks to understand completely the chemistry involved and conducts reactions aimed at finding the limits of acceptability of critical variables. In the current view, the process chemist develops not only commercial routes but also enabling and supply routes as a drug candidate, agrochemical, or fine chemical moves from the laboratory to full-scale production. Good process chemistry is necessarily green chemistry; it always has been, long before this phrase became fashionable.

This thematic issue of *Chemical Reviews* brings together a series of articles generally drawn from the pharmaceutical and fine chemical areas with a focus on reactions that are highly efficient on a large scale. They represent not only structural motifs and synthetically useful reagents, reactions, and processes important to the field, but also the modern spirit and philosophy of process development. Throughout the last 30 years, the importance of good process chemistry

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has been increasingly recognized, with numerous books and short courses now offered. However, since no formal training at the university level yet exists, we hope that academic researchers and students will gain both an appreciation and an interest in process chemistry as a result of this issue of *Chemical Reviews*.

The first article by Zhang provides an outline of the underlying principles of process research with a focus on safety, cost, environmental issues, and the robustness of synthesis. The importance of mass throughput, the correct ordering of steps in a sequence, factors that control the costs of starting materials, the design of experiments, and the relative merits of linear and convergent syntheses are described. The papers by Wu and Huang and Burkhardt and Matos describe the use of stoichiometric main-group organometallic reagents in large-scale synthesis. The first article provides convincing examples of the scalability of enantioselective alkylations, aminoalkylations, aldol reactions, and Michael addition reactions, among others, using organolithium reagents. The use of organoboron reagents in process chemistry is illustrated with examples of hydroboration reactions and the application of the derived organoboron compounds in diverse reactions from alcohol synthesis to Suzuki−Miyaura coupling reactions. In addition, the use of organoboron reductants for the large-scale synthesis of alcohols, lactols, amines, and other classes of products is described. Corbet and Mignani provide an overview of palladium-, nickel-, copper-, and iron-catalyzed coupling reactions that provide many valuable and versatile pathways for discovery chemistry as well as large-scale synthesis and manufacture. Many important classes of pharmaceuticals would be difficult to prepare without reactions such as the Heck, Negishi, and Sonogashira reactions.

Few chemists in academia or in industrial discovery laboratories really understand and appreciate crystallization. It is, however, of vital importance in scale-up synthesis and in the separation of enantiomers. Brands and Davies provide an overview of the resolution of racemic compounds by the formation of salts or other derivatives, which for many classes of compounds is far more effective, both cost- and otherwise, on scale-up than alternative processes such as enantioselective synthesis. The article by Farina, Reeves, Senanayake, and Song complements the preceding review with a focus on enantioselective synthesis using chiral auxiliaries, stoichiometric chiral additives, or chiral catalysts. The juxtaposition of these two articles will guide the reader as to the relative merits of resolution and enantioselective synthesis for a diverse range of compounds. In a related vein, the role of physical organic chemistry as a mainstay of process research cannot be underestimated. Delaney and coworkers overview a range of techniques that underpin process optimization, including design of experiments, parallel measurements, kinetic analysis, continuous processing, and process intensification.

The second part of this thematic issue is devoted to four articles concerning the large-scale synthesis of important classes of pharmaceuticals or key intermediates. Izawa and Onishi review the industrial synthesis of HIV protease inhibitors with a focus on the diverse methods for the assembly of both *erythro* and *threo N*-protected 3-amino-1,2-epoxides. The article is enhanced with descriptions of the manufacturing processes for the commercial drugs Ritonavir and Lopinavir. Reeder and Anderson describe methods for the synthesis of chiral α-amino-α′-halo-ketones and their conversion into pharmaceuticals such as saquinavir, palinavir, Viracept, and Agenerase. Gallou and Senanayake describe large-scale synthesis of *cis*-1-amino-2-indanol. This versatile compound is a key building block in pharmaceuticals including HIV protease inhibitors and antimalarials, and is also commonly employed as a resolving agent for substrates such as racemic carboxylic acids or secondary alcohols, as a chiral auxiliary, and in catalytic enantioselective synthesis. The indole ring system occurs in many biologically important natural products and is a key constituent of many pharmacophores. Humphrey and Kuethe discuss the myriad of reactions for the synthesis of this ubiquitous heterocycle. The importance of indoles is heavily underscored by the many named reactions, from the Fischer indole synthesis to the Leimgruber−Batcho reaction, that are described in this article.

While there are many small-scale reactions for oxidations and reductions, few pass the strict criteria needed for large-scale use. Jäkel and Paciello describe high-throughput and parallel screening methods for the selection of homogeneous catalysts for enantioselective hydrogenation reactions. Such reductions are especially valuable as a consequence of their excellent enantioselectivities, broad substrate applicability, and high turnover numbers and frequencies. The article is illustrated with examples from the large-scale synthesis of diverse pharmaceuticals. Ripin and colleagues describe the currently acceptable methods for large-scale oxidations of alkenes, arenes, alkylarenes, alcohols, amines, sulfides, and other substrates. For example, the Moffatt oxidation and TEMPO-based oxidants are shown to be especially valuable for the conversion of primary alcohols into aldehydes. Van Ornum, Champeau, and Pariza describe in detail examples of total syntheses including (+)-artemisin, indolizidine 251F, camptothecin, and vitamin D metabolites and large-scale ozonolysis reactions illustrated by cefaclor, indane derivatives, and oxandrolone. The last article, written by Butters, Catterick, Gillmore, and colleagues, reviews the criteria by which process routes are assessed, with a focus on safety, environmental issues, legal issues, economics, process control, and throughput.

In summary, this thematic issue provides a series of highly informative reviews on an area of synthetic chemistry of immense economic value. It illustrates the types of synthetic organic transformations that have proven to be sufficiently robust and reliable for use in large-scale synthesis. We have both been fortunate in working either directly in scale-up synthesis (M.F.L.) or as a consultant (A.G.M.B.) and have experienced the challenges and rewards of the field. We hope that this issue will provide guidance to graduate students and postdoctoral research associates in academia considering a career in process research.

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