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Introduction: Frontiers in Organic Synthesis

It is an exciting time for science and one of unprecedented opportunity for chemistry. Over the past two centuries, chemistry has evolved from a relatively isolated pursuit to a position of central importance in the physical and life sciences. It has provided a language and methodology that have unified the sciences in the pursuit of a molecular understanding of our world, thereby shaping the direction, development, and destiny of scientific research. Molecular medicine, molecular biology, and nano (molecular) technology are but a few of the significant scientific fusions that have resulted. From new materials to new medicinal agents, the investment in molecular science has provided returns of fundamental and technological significance, profoundly impacting all facets of our global community.

This issue of *Chemical Reviews* provides an exciting illustration of how the central role of chemistry in the sciences is being expanded through research on the frontiers of organic synthesis. Driven by remarkable improvements in our understanding of structure and reaction mechanisms and by increasingly powerful instrumentation and analytical tools, the reach of organic synthesis has been extended to virtually all of science. This breadth is reflected in part in the 24 reviews in this issue which include studies on reactive intermediates, organometallic chemistry, photochemistry, natural products chemistry, catalysis, solid-phase synthesis, chemical libraries, electrochemistry, novel materials, enzyme-mediated transformations, biochemistry, medicinal chemistry, biology, and virology.

The range of organic synthesis has been significantly influenced by the increasing ability to address molecular complexity which, over the past two centuries, has evolved from largely empirical approaches toward the preparation of relatively simple molecules to highly sophisticated strategies yielding molecules of considerable complexity. Recent reviews and lead references contained therein further address this significant point and provide an important foundation for the analyses provided herein.[1-6] Practicality has also played an important role in defining the impact of synthesis. Many complex molecules can now be prepared in a practical fashion, ensuring their availability for scientific, technological, and commercial purposes. Practical syntheses are, however, not common, calling attention to the need for new science directed at this globally significant objective. This issue appropriately starts with an elegant and insightful overview on this point by T. Hudlicky, addressing concerns and illustrating advances pertinent to the design and development of practical organic syntheses.

An ideal (the ultimate practical) synthesis is generally regarded as one in which the target molecule (natural or designed) is prepared from readily available, inexpensive starting materials in one simple, safe, environmentally acceptable, and resource-effective operation that proceeds quickly and in quantitative yield. Because most syntheses proceed from simple starting materials to complex targets, there are two general ways of approaching this ideal synthesis (i.e., achieving maximum relevant complexity increase while minimizing step count): the use of strategy-level reactions (e.g., the Diels–Alder reaction) that allow in one step for a great increase in target-relevant complexity or the use of multistep processes (e.g., polydirectional synthesis, tandem, serial, cascade, domino, and homo- and heterogenerative sequences) that produce similar or greater complexity changes in one operation. The design and development of new reactions and reaction sequences that allow for a great increase in target-relevant complexity are clearly essential for progress toward the next level of sophistication in organic synthesis.[1-4]

Salient examples of such powerful complexity-increasing addition and cycloaddition reactions are comprehensively documented in this issue in reviews by J. A. Marshall; M. Lautens, W. Klute, and W. Tam; and R. D. Little. When such strategy-level reactions are conducted in a serial fashion (multistep, one operation processes) dramatic increases in com-

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(1) Hudlicky, T.; Natchus, M. G. Modern Synthetic Design: Symmetry, Simplicity, Efficiency, and Art. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, pp 1–26.

(2) Ho, T. L. *Tandem Reactions in Organic Synthesis*; Wiley-Interscience: New York, 1992.

(3) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131–163.

(4) Wendor, P. A.; Miller, B. L. Toward the Ideal Synthesis: Connectivity Analysis and Multibond-Forming Processes. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, pp 27–66.

(5) Hall, N. *Science* **1994**, *266*, 32–34.

(6) Bertz, S.; Sommer, T. J. Applications of Graph Theory to Synthesis Planning: Complexity, Reflexivity, and Vulnerability. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, pp 67–92.

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plexity can be produced in impressively concise sequences. Such serial processes based principally on pericyclic reactions are superbly treated by several contributors. L. F. Tietze provides an insightful overview of domino reactions. The significant complexity changes attending tandem cycloadditions is further developed in impressively effective routes to hetero- and carbocycles addressed by S. E. Denmark and A. Thorarensen and by J. D. Winkler.

In addition to pericyclic cascades, in which the product of a first thermal transformation serves as the starting material for a second step of the same overall operation, serial processes have also been designed and developed around most reactive intermediates. Nature's cationic cascades are remarkable examples of the utility of this strategy, mimicked with considerable success by many groups including notably that of the late W. S. Johnson. Such strategies have been extended with great effectiveness in recent years to include radical, anion, radical anion, radical cation, carbenoid, diradical, zwitterionic, and organometal cascades. In these serial multistep, multibond-forming events, a starting reactive intermediate is generated and used in a first bond-forming step which *generates* a second but *like* reactive intermediate (*homogenerative* series),[4] thereby creating a second bond-forming event in a sequence that can be continued further in what is effectively a controlled oligomerization. The spectacular utility of this approach to the synthesis of complex molecules involving radical intermediates is effectively represented in contributions by I. Ryu, N. Sonada, and D. P. Curran and by P. J. Parsons, C. S. Penkett, and A. J. Shell. While relatively less studied, biradicals are also beginning to provide significant service as intermediates in notably concise routes to polycycles, as insightfully covered by K. K. Wang.

In addition to the regeneration of like intermediates (homogenerative processes), serial processes can also be achieved through sequences which proceed with the *generation* of *different* intermediates (*heterogenerative* series).[4] A. Padwa and M. D. Weingarten and D. F. Harvey and D. M. Sigano provide impressive illustrations of this strategy in which the synthetic utility of carbenoid chemistry is coupled serially to a variety of pericyclic and metal-mediated reactions. This theme is further elaborated by M. Malacria in connection with novel mixed cascades based on radical and transition metal-mediated reactions. Dramatically effective examples of sequenced reactions in which radical chemistry is coupled to cationic and anionic processes are superbly illustrated by G. A. Molander and C. R. Harris and by B. B. Snider. Further examples of mixed-intermediate cascades are also found in the treatment of diyl and electrochemically generated intermediates provided by R. D. Little.

Organometallic compounds, another highly significant and useful class of *reactive intermediates* that can be sequenced to achieve impressive increases in structural complexity, have greatly extended the palette of organic synthesis to virtually all available elements of the periodic table. Exemplifying the notable advances in this area are overviews by E. Negishi, C. Coperet, S. Ma, S.-Y. Liou, and F. Liu on palladium-mediated cascades and the thematically related treatments by D. Harvey and D. Sigano; A. Padwa and M. D. Weingarten; M. Malacria; and M. Lautens, W. Klute, and W. Tam. B. M. Trost and D. L. Van Vranken provide a noteworthy analysis of highly effective approaches to asymmetric control based on transition metal-mediated bond-forming reactions. Further demonstrating the scope and value of organometallic chemistry are the novel examples of lactone and lactam syntheses based on organoiron complexes described by S. V. Ley, L. R. Cox, and G. Meek.

Enzymes provide another notable class of catalysts that can be coupled in serial fashion for complex molecule synthesis, an exciting theme covered by H. J. M. Gijsen, L. Qiao, W. Fritz, and C.-H. Wong. The interplay of biology, chemistry, medicine, and synthesis that attends much of natural products chemistry is also very much in evidence in this issue in exciting accounts of studies on the structurally and biochemically novel ellagitannins and pumiliotoxins covered by S. Quideau and K. S. Feldman and by A. S. Franklin and L. E. Overman, respectively. The interface between chemistry and biology is further illuminated in studies by G. A. Kraus, W. Zhang, M. J. Fehr, J. W. Petrich, Y. Wannemuehler, and S. Carpenter, inspired by the natural product hypericin and directed at the development of antiviral agents involving the design of molecular flashlights. The power of organic synthesis to address problems in the materials area is effectively captured and exemplified in an analysis provided by J. M. Tour. Finally, our emerging capacity to produce the chemical and functional diversity long provided only by Nature is insightfully analyzed by L. A. Thompson and J. A. Ellman in a review on chemical libraries.

While space restrictions preclude an exhaustive analysis of the range of subjects covered, requiring the authors to emphasize insights from their own work and its scholarly context, this collection of reviews and perspectives provides an exciting vision of chemistry and organic synthesis. It illustrates the breadth of the field and the role that synthesis plays in advancing the frontiers of chemistry as well as other sciences whose further development is heavily coupled to molecular understanding. This issue provides a panoramic snapshot of the field and a preview of its future directions. It will hopefully serve as a current textbook on the subject of contemporary organic synthesis as well as a book of reference and inspiration for those aspiring to further advance its frontiers. I am most grateful to the authors for the considerable effort and thought that they invested in producing this information- and idea-rich collection and for the enduring inspiration and pedagogical value it will provide.

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