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Introduction to Facilitated Synthesis

Dave Bergbreiter arrived at Texas A&M University as an Assistant Professor in 1974 after education at Michigan State University (B.S. 1970) and Ph.D. training in Whitesides' laboratory at MIT (1970−1974). In the following 35 years, he and his group have been involved in a variety of research including seminal studies of enolate and related azaallyl anion chemistry, studies of polymer surface modification, studies of responsive polymers, and studies that use soluble polymers as phase anchors. This latter work included inventing the concept of "smart" catalysts as well as developing various phase-separation strategies that use soluble polymers to recover conventional homogeneous catalysts. He was named a Presidential Professor of teaching excellence in 2006 and was recognized in 2008 with the ACS Southwest Regional award.

Shu Kobayashi was born in 1959 in Tokyo, Japan. He studied at the University of Tokyo, receiving his Ph.D. in 1988 working under the direction of Professor T. Mukaiyama. Following an initial period as assistant professor, he was promoted to lecturer and then associate professor at Science University of Tokyo (SUT). In 1998, he moved to the Graduate School of Pharmaceutical Sciences, University of Tokyo, as full professor. In April 2007, he was appointed to his current position as professor of organic chemistry in the Department of Chemistry, Faculty of Science, The University of Tokyo. Professor Kobayashi is also director of the ERATO project of the Japan Science Agency (JST). He has held various visiting professorships, including the Universite Louis Pasteur, Strasbourg (1993), Kyoto University (1995), Nijmegen University (1996), and Philipps-University of Marburg (1997). Professor Kobayashi has wide-ranging research interests that include the development of new synthetic methods and novel catalysts, organic reactions in water, solid-phase synthesis, total synthesis of biologically interesting compounds, and organometallic chemistry. He has held numerous named lectureships and is a recipient of many prestigious awards, including the Chemical Society of Japan Award for Young Chemists (1991), Ciba-Geigy Research Foundation Award (1994), Springer Award in Organometallic Chemistry (1997), IBM Science Award (2001), Organic Reactions Lecturer (2002), Nagoya Silver Medal (2002), Mitsui Chemical Catalysis Science Award (2005), JSPS Prize (2005), the Arthur C. Cope Scholar Award from the American Chemical Society (2006), Howard Memorial Lecturer (2006), C.S. Hamilton Award (2007), and Merck-Cambridge Lecturer (2007).

The classical ways to improve a synthetic reaction are either to invent a new reagent, to invent a new catalyst, or to elucidate details about the mechanism that in turn enable one to judiciously modify conditions to increase a reaction's rate and/or yield. However, in recent years, a variety of emerging scientific and methodological developments have been reported that aim to improve the ease and practicality of synthesis and related separation processes. These developments can facilitate how synthetic targets or catalysts are prepared and used. Just as earlier developments in the 1960s and 1970s in separation and analytical chemistry enabled the development of a greatly expanded suite of modern synthetic and catalytic reactions, these new developments have the potential to broadly impact the art and practice of synthesis and catalysis. While they can involve "new" chemistry, they often do not necessarily require "new" reactions. In many cases, they simply use "old" chemistry in a new way. Often they focus on how phase properties can be used to advantage in existing chemistry. The recent attention afforded to concepts like Green Chemistry and sustainability have served to heighten interest in this second round of developments of strategies and technologies that improve the ease and practicality of synthesis and catalysis. This topical issue of *Chemical Reviews* includes 15 articles from a broad spectrum of experts from laboratories around the world that highlight these developments.

Specific topics addressed in this issue of *Chemical Reviews* often use some sort of phase behavior wherein a macromolecular support, an insoluble solid, or an immiscible solvent mixture facilitates a particular chemical process. This is illustrated with reviews that deal with methodology, synthesis, or catalysis, though the individual articles often overlap two or even all three of these areas. The potential for such strategies to extend beyond methodology is also

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seen in a review by Mintzer and Simanek that discusses issues of how to facilitate gene and drug delivery with nonviral vectors. While the topics covered tend to focus on smaller-scale synthesis related to the pharmaceutical and agrochemical areas, the concepts discussed are not by any means limited to these areas. Indeed, developments relevant to all scales of synthesis and catalysis up to bulk chemical production fall within the purview of the reviews in this special issue.

Developing practical catalysts is receiving increasing attention, and several of the reviews in this volume focus on specific types of catalysts or specific methodologies that are useful in improving the practicality of catalysts. A review by Buchmeiser comprehensively reviews the state of the art in the design of recoverable, reusable olefin metathesis catalysts. These catalysts are widely used both in the synthesis of materials and in the synthesis of complex natural products, but are at present difficult to recover and reuse. Three reviews, one by Wang, Chen, and Ding, a review by Fraile, García, and Mayoral, and another review by Trindade, Gois, and Afonso, describe the use of self-supporting, noncovalent, and a variety of phase immobilization strategies wherein useful chiral catalysts are recoverable as insoluble, separable solids or within a separable immiscible liquid phase. Asymmetric catalysis, like metathesis, was recently recognized with a Nobel prize because of the importance of such chemistry in academic and pharmaceutical syntheses. However, like metathesis, the recovery and reuse of both the metals used and the ligands in asymmetric catalysis can still be problematic. The use of insoluble ion exchange resins is old technology in chemistry. It is chemistry that has been the focus of study in areas as diverse as the Manhattan project or in water purification, chemistry that seemingly has little overlap with sophisticated organic synthesis and catalysis. However, this chemistry was a logical predecessor of solid-phase synthesis—chemistry that has significantly changed the synthetic landscape both in the areas of the synthesis of biologically important peptides, nucleotides, and oligosaccharides and in the broader area of combinatorial chemistry. Ion exchange resins have recently experienced a renaissance of interest themselves, and the use of these materials to recover and separate catalysts is reviewed by Barbaro and Liguori. Two reviews, one by Bergbreiter, Tian, and Hongfa and another by Ikegami and Hamamoto, describe the use of other sorts of polymers in catalytic chemistry. Their reviews describe work where responsive organic polymers' solvation properties usefully affect the activity and recoverability of homogeneous catalysts as well as chemistry where the phase-selective solubility of polymers usefully leads to efficient and practical product/catalyst separations. Another review by Akiyama and Kobayashi discusses still other types of polymer-supported, microencapsulated, and related catalysts, detailing their applications to organic synthesis and to processes important in the synthesis of fine chemicals. Using multiple phases with different densities as a separation step is an elementary process in working up most syntheses—a process that dates back to the 19th century or earlier. However, the concept of using a separate phase like water to advantage in organometallic catalysis is much more recent. It is an idea with demonstrated industrial practicality. Recent developments in this are reviewed by Shaughnessy. The theme of the utility or influence of water on reactions is further addressed in a review by Minakata and Komatsu, who discuss organic reactions on inorganic solids in water, and in a review by Chanda and Fokin, where recent studies that highlight the advantages of carrying out reactions on water are discussed. Fluorous phase chemistry has become a practical alternative to aqueous phase chemistry. Though it is an area that is only 15 years old, fluorous chemistry continues to develop. New developments in this area where fluorous phases and fluorous tags facilitate synthesis and separations are reviewed by Zhang. New reactions or new strategies that use existing reactions are often used to facilitate synthesis, and such chemistry saw an explosion of interest as combinatorial chemistry developed. Examples of using such chemistry in macrocycle synthesis are reviewed by Wessjohann, Rivera, and Vercillo, who review the advantages and limitations of multiple multicomponent strategies that lead to diversity in macrocycle synthesis. Finally, the roles of cross-linked polymeric supports in synthesis and catalysis are discussed in a review by Lu and Toy. This review critically highlights recent developments in solid-phase chemistry, discussing how both catalytic and synthetic chemistry can be facilitated by focusing on the use of various sorts of cross-linked polystyrene polymers.

While this thematic issue highlights a wealth of strategies that facilitate chemistry as diverse as catalysis, synthesis, and gene delivery, it only provides a taste of the various new strategies that are being developed to facilitate chemistry in its broadest sense. Chemistry will always be mainly focused on reactions, mechanisms, and properties of molecules and materials. However, the many ways inventive chemists are combining chemistry from biological sciences, inorganic chemistry, analytical chemistry, materials chemistry, and organic chemistry promise to continue to make it simpler to prepare new compounds, to separate compounds one from another, or to affect how compounds are ultimately used. Such developments have the potential to significantly expand both the capabilities of synthesis and the potential for chemistry as a tool in medicine or materials chemistry. Just as Merrifield's use of a solid-phase resin for peptide synthesis developed into an enabling technology for the biotechnology revolution, new developments in areas like those discussed in this thematic issue or in a host of other areas like microfluidics, microreactors, magnetic separations, enzymatic chemistry, and smart materials can be expected to expand and facilitate the ways in which catalytic and synthetic chemistry are performed and the ways in which the products of synthetic chemistry are employed.

As coeditors, we are most grateful to the authors of these reviews. They and the staff at *Chemical Reviews* made assembling this topical issue a relatively simple task. Their efforts do not only provide the community with timely and authoritative reviews that illustrate a few of the ways one can facilitate synthesis; they will hopefully stimulate others' creativity and lead to further strategies that facilitate synthesis. A casual reader can see even by just perusing the articles that there is a wealth of chemistry here—chemistry that many times in very simple ways uses ideas from one branch of chemistry to impact the ways in which molecules are made or used. It is an area ripe for further development by a new generation of imaginative chemists.

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