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Preface

Asymmetric synthesis on a process scale

Many complex organic molecules used as pharmaceuticals have resulted from the requirement for more exquisitely potent and selective structural motifs, designed to present a set of chiral pharmacophores, to interact with a variety of receptor subtypes. In process chemistry, discovery and development of asymmetric methods has largely paralleled the medicinal chemist's capability to identify these three-dimensional problems in molecular recognition. Consequently, contemporary research in the pharmaceutical industry has become an arena for asymmetric synthesis, and to some degree, modern drug targets have replaced natural products as models for the demonstration of innovative methods. This *Special Issue* of *Tetrahedron: Asymmetry* provides a snapshot of contemporary asymmetric synthesis on a process scale, with direct or potential application to commercial scale production of the current drug portfolio.

The topics reported here cover many aspects of asymmetric synthesis. Protocols that involve **classical resolution** are still pivotal for access to enantiomerically enriched materials, and some of the contributions reflect this. Separation of diastereomeric salts through crystallization using the eutectic point has proven to be a powerful tool, and analytical and automation technologies have simplified the screening and optimization of classical resolutions. Other contributions in this *Issue* focus on the **chiral pool** for enantiomerically enriched materials, either as building blocks or for chirality transfer. Further architectural elaboration from these predisposed homochiral substrates has relied upon intrinsic **diastereocontrol** elements—either cyclic or acyclic, to complete an assemblage. There is an excellent example of a highly diastereoselective vinylogous Mannich reaction to highlight this point. Additionally, there are two examples employing ring opening of aziridinium building blocks with high regio- and enantiocontrol. Carbon–carbon bond formation through enolate alkylation is further highlighted herein. Another route to enantiopure materials is exemplified via **enzyme** mediated ester hydrolysis and acylation. The combination of the above requisites into a unified strategy has furnished the **racemization resolution** protocol, relying upon solubility differences to drive equilibria.

Organometallic catalysts feature prominently in asymmetric synthesis, and in this issue. **Desymmetrization** of *meso*-substrates employing chiral catalysts has provided ready access to enantiomerically enriched compounds; one example given here is the hydrolytic kinetic resolution of terminal epoxides using chiral (salen)Co(III) catalysts demonstrated at the kilogram level for access to enantiopure epoxides and diols. There is a practical, large-scale preparation of a **cyclopropanation** catalyst, providing ready access to this structural motif. Catalytic asymmetric cyclopropanation coupled with diastereoselective crystallization has been utilized as a strategy for optimal production of a critical drug subunit. Asymmetric catalytic **hydrogenation** continues to be a keystone for the synthesis of highly enantiopure materials. Excellent examples of this protocol are provided, including ligand survey and experimental design to optimize process parameters, en route to drug candidates and pharmacophores. An excellent **characterization** of the Ru(II)-BINAP precatalyst is presented. As is often the case, we turn to academic laboratories to provide an advanced prospective for new, and even more powerful tools in catalytic, asymmetric synthesis. There is a novel, nickel catalyzed, reductive **carbon–carbon** bond forming reaction with high enantioselectivity. Better-designed catalysts to emulate enzymatic transformations continue to provide more general solutions to what has traditionally been very substrate specific. The mechanistic understanding offers insights into the design principles for better asymmetric processes.

Finally, we have endeavored to assemble a set of protocols/methods that have been tested on large-scale reactions, and that could be scaled down for use in academic or drug discovery laboratories. With the demand for asymmetric synthesis growing at a rapid rate, the task rests upon process chemists to either identify existing technologies or develop new asymmetric methods for chemical processes. This trend has increased tremendously in recent years, especially in the pharmaceutical industry, and many process chemists are facing these intense challenges. Thus we hope the general scientific community will find this *Special Issue* to be a valuable collection in the field of asymmetric chemistry.

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