Organic Process Research & Development

EDITORIAL

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Guest Editorial for Asymmetric Synthesis on Large Scale Special Issue

It has been four years since our last special feature on asymmetric synthesis on large scale. Thus, it is time to once again dedicate an issue to this topic and to see if the favored methods from 2007 are still the favored methods today. In the past four years the chemical and, in particular, the pharmaceutical industry has faced ever increasing challenges of addressing not only economics and process safety but also to deliver on:

- "green" or more sustainable processes (special feature 2011, issue 4)
- the tighter regulations around control of genotoxic impurities (special feature 2010, issue 4)
- the trend towards greater complexity in pharmaceutically active molecules.

For these reasons the bar to define an acceptable large scale synthesis continues to rise and in turn provides the driver to develop more efficient methods for delivery of chiral molecules. A recent review (*J. Med. Chem.* **2011**, *54*, 3451) indicated that at least a third of compounds generated by medicinal chemistry groups contain at least one chiral centre, highlighting the importance of the controlled introduction of such chiral centres on large scale.

In reading the submitted papers, we see the majority of papers are from the Pharmaceutical industry; however there are also contributions from academic laboratories and chemical companies. The most prevalent reaction presented is the catalytic asymmetric hydrogenation, and the most common structural motif targeted is an amino acid (either α or β). Asymmetric hydrogenations in various different guises feature in the papers by Praquin, Grayson, Campeau, Challenger, Matsumura, Fox, and Goto. Substrates for the hydrogenation include enamides, enamines, benzophenones, and a tetrasubstituted alkene. Two papers use chiral pool starting material in their approaches, either to introduce the single stereocentre (Scott) or to build additional stereocentres via diastereoselective transformations (Tang). Single examples use Sharpless asymmetric dihydroxylation (Erhard), chiral cyclopropanation (Pibworth), and Ellman chemistry (Pibworth). A nice example of Seebach's self-regeneration of stereocenters procedure is illustrated in the paper by Wang. The two papers from Wulff are different in approach, in that they focus on ligand design and synthesis, followed by application to two different catalytic reactions.

We were interested to note that for the most part asymmetric biocatalytic reactions were largely absent from the papers we have received for this issue. Grayson et al. compare an asymmetric hydrogenation approach to β-phenylalanine derivatives with enzymatic resolutions using either lipases or acyclases. However no examples of the more recently developed asymmetric reduction or nonresolution approaches using enzymes were submitted (although a number of papers did appear in the special issue on biocatalysis earlier this year, 2011, issue 1). This suggests that despite the considerable advances that have occurred in the area of ketoreductase and transaminase reactions over the past five years, these reactions have yet to feature significantly in larger scale reactions. In a similar way, transformations employing organocatalysis are also not seen in this collection of papers, despite the large number of academic groups working in the area.

We hope the readership of OPRD will find this collection of papers both interesting and inspiring, and that the process community continues to work towards solving the remaining challenges around asymmetric synthesis. We will be particularly keen to see if a comparable issue five years from now embraces a larger range of asymmetric transformation than we see today.

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