Enantioselective Organocatalyzed Reactions II

Rainer Mahrwald
Editor

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Asymmetric C-C Bond Formation Processes

Springer

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Foreword

It is part of the human experience to wonder and marvel at the beauty of life in the world around us. An astronomer might look up in awe and question the size, shape and age of the universe. A biologist might pay keen attention to the anatomical features unique to a given organism and see the beauty in the organism's adaptability. The organic chemist, however, tends to look deeper and ponder the actual molecules, focusing on the unique mechanisms that create a wide array of complex molecules that in turn conspire to create life itself. This is as true today as it was more than a century ago when the great organic chemist Emil Fischer stated "If we wish to catch up with Nature, we shall need to use the same methods as she does, and I can foresee a time in which physiological chemistry will not only make greater use of natural enzymes, but will actually resort to creating synthetic ones."[1] Fischer foresaw that if we could understand how Nature's enzymes catalyze reactions, we could create our own synthetic catalysts. Indeed, it was in recreating Nature's aldolase enzymes that we were led to re-examine the chemistry of Hajos and Parrish in a new light. Through experimentation, we realized that the simple amino acid proline could recapitulate the 'complex' chemistry of an aldolase enzyme thereby providing a stunningly simple solution to the direct asymmetric aldol, Michael, Mannich and other reactions. Indeed, catalytic activity of amino acids, particularly in enamine and iminium chemistry, is not restricted to the amino acid proline but rather is a feature that most, if not all, amino acids have in common.

A decade has now passed since the studies of my laboratory and those of David MacMillan's refocused the considerable attention of the community on the profound potential of small organic molecules to catalyze asymmetric reactions. In this time, the scope of organocatalysis has enlarged considerably with respect both to the type of reactions catalyzed (aldol, cycloaddition, redox, asymmetric assembly and domino reactions, conjugate addition reactions, etc.) and the mechanisms used

[1] Fischer E: Synthesen in der Purin- und Zuckergruppe. In Les Prix Nobel en 1902. Edited by Cleve PT, Hasselberg C-B, Morner K-A-H: P-A Norstedt & Fils; 1905.

to affect catalysis (enamine, iminium, hydrogen bonding, Bronsted or Lewis acid/base chemistry, SOMO activation, etc.). With each new reaction and mechanistic lever applied, "the veil behind which Nature has so carefully concealed her secrets is being lifted."[1] Indeed, there is much to be gained in envisioning an enzyme as an organic flask that affects catalysis through the side chains of amino acids, their intervening amide linkages, organic cofactors, and the flask itself.

Although the notion of organocatalysis has been with us since the very beginnings of organic chemistry, in the last decade organocatalysis has created a sea change with respect to our abilities both to synthesize molecules asymmetrically and to understand how these molecules were synthesized in a prebiotic world before enzymes themselves existed. We speculate that the first carbohydrates might have been first synthesized via amino acid catalysis and can envision a route to homochirality that might have been exploited to create life. Thus organocatalysis might have been the key chemistry available in the prebiotic word and might have provided the homochiral building blocks that allowed life to form. Indeed, biosynthetic reactions occurring in organisms today that are catalyzed by small organic molecules might explain our inability to find protein enzymes for certain reactions. The secret of life now feels a bit closer. Organocatalysis has also changed our notions concerning what is possible in catalytic asymmetric synthesis. We are not so much concerned with creating a single stereogenic center now or a single bond connection, but with creating arrays of 2, 3, 4, 5, or more stereocenters and bond connections under organocatalysis in a single pot with excellent control of enantio- and diastereoselectivity. Such reports are now becoming commonplace whereas a decade ago they would have been greeted as major triumphs. This has led many to suggest that we are in the golden age of organocatalysis, that the creative stage of this endeavor has somehow now passed. I believe we are just at the beginning of this endeavor and that much fascinating and unexpected chemistry lies ahead of us.

The explosive growth of asymmetric organocatalysis has been driven by a newfound appreciation for reactivity among small organic molecules, but we have barely begun to explore this space. How big is this space and what might we find? It is easier to answer the first part of this question. It is vast indeed. If we consider calculations performed to define the space of small molecules of molecular weight of less than 500 Da that consist of only C, H, N, O, P, S, Cl, and Br and are stable at room temperature and to oxygen and water, the number is unimaginable – more than 10^{63} molecules.[2] With this in mind, I believe that the organocatalysts known today represent islands of reactivity or catalytic potential in a near infinite sea. The discovery of new islands of catalytic potential will rely on the scientific method, chemical intuition, and luck but they are out there to be discovered and they promise new and ever more stunning catalytic syntheses of complex molecules and ever greater understanding of how atoms born in stars eventually conspired to create life.

[2] W.C. Guida et al. (1996) Med. Res. Rev. 16, 3–50.

As Emil Fischer told us more than a century ago, progress towards this goal will "not so much be determined by brilliant achievements of individual workers, but rather by the planned collaboration of many observers."[1] And so, the future of organocatalysis is vast and bright and will continue to benefit from the community of chemists that join this endeavor. Stunning reactions and reactivities await us.

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Carlos F. Barbas, III

Preface

Without any doubt organocatalysis belongs to the most exiting and innovative chapters of organic chemistry today.

Since this chapter was first opened systematically 10 years ago, a plethora of methods and catalysts have been developed to solve problems of organic chemistry. More and more these methodologies have been applied in total syntheses of natural products. This is what this two-volume book set wants to demonstrate - the full power of organocatalysis.

Asymmetric C-C bond formation processes form the subject of the second book while functionalization, catalysts and general aspects of organocatalysis are covered in the first one. Overlappings cannot be entirely avoided by such an approach. However, often these overlappings are desirable and valuable in order to illustrate a methodology by different views as this is true for asymmetric hydrogenation, enantioselective conjugate hydride addition, oxidation or transfer hydrogenation catalyzed by chiral primary amines.

It took great pleasure in working together with a team of leading experts in this field. I have to thank them for organizing these overviews.

Also, I thank the team at Springer UK to help us to publish these results.

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