DOI: 10.1002/cmdc.200700109

Asymmetric Organocatalysis

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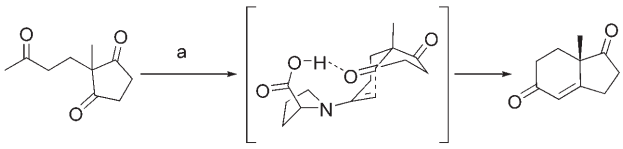
Chemical synthesis is one of the key technologies underlying modern drug discovery and development. For the design and accessibility of novel structures and the rapid preparation of new test compounds and development candidates with often highly complex chemical architecture, it is essential to use state-of-the-art chemical synthesis technologies. As the number of chiral drugs is increasing, asymmetric synthesis and efficient chiral separation technologies are steadily gaining importance. Regarding asymmetric catalysis, enzymatic transformations, and reactions employing metal, catalysts are important tools for organic synthesis and invaluable to pharmaceutical industry. Recent developments in the field of asymmetric catalysis point to a third class of catalysts besides the established enzymes and metal complexes, the so-called organocatalysts. In an effort to increase the awareness within the community of medicinal and process chemists as well as to learn more about recent developments in this rapidly evolving field, the Schering Foundation organized a symposium on "Organocatalysis", which took place in Berlin on April 18–20, 2007. This minireview summarizes some of the important results presented at the symposium.

Introduction

Chemical synthesis is one of the key technologies underlying modern drug discovery and development. For the design and accessibility of novel structures and the rapid preparation of new test compounds and development candidates with often highly complex chemical architecture, it is essential to use state-of-the-art chemical synthesis technologies. As the number of chiral drugs is increasing,[1] asymmetric synthesis[2] and efficient chiral separation technologies[3] are steadily gaining importance. With respect to the first, (diastereoselective) asymmetric syntheses[4] the application of chiral auxiliaries or chiral pool strategies has become well implemented into the arsenal of industrial processes. Regarding asymmetric catalysis, enzymatic transformations[5] and reactions employing metal catalysts are important tools for organic synthesis and invaluable to the pharmaceutical industry.[6,7] Recent developments in the field of asymmetric catalysis point to a third class of catalysts, besides the established enzymes and metal complexes, the so-called organocatalysts. These low-molecular weight organic molecules can even contain a metal possibly playing a structure defining, but not a catalytic, role. Essentially, organocatalysts can be considered as small molecule enzymes.[8]

As for metal and enzyme-mediated asymmetric catalysis,[9] the utility and efficiency of organocatalysts has been impressively illustrated with the de novo synthesis of carbohydrates.[10] Despite that and the considerable efforts to explore and extend the scope of asymmetric organocatalytic reactions throughout the last years, their use in medicinal and process chemistry is still rather low. This is even more surprising as the field was pioneered by the medicinal chemistry laboratories of Schering AG and Hoffmann La Roche in the late 1960s and early 1970s by using proline as asymmetric catalyst for a Robinson annulation (see Scheme 1).[11]

In an effort to increase the awareness within the community of medicinal and process chemists as well as to learn more about recent developments in this rapidly evolving field, the Schering Foundation organized a symposium on "Organocatalysis", which took place in Berlin on April 18–20, 2007.



Scheme 1. Asymmetric Robinson annulation catalyzed by L-proline leading to the steroid CD fragment. a) 1) 3 mol% L-Pro, DMF, 20 °C, 2) TosOH, benzene, quant., 93% *ee*.

Developments and Applications

Amine Catalysis

The Hajos-Parrish-Eder-Sauer-Wiechert reaction[11] involves an enamine catalysis increasing the HOMO of the nucleophile and additionally, due to the bifunctional character of proline, the LUMO of the electrophilic reaction partner is lowered through

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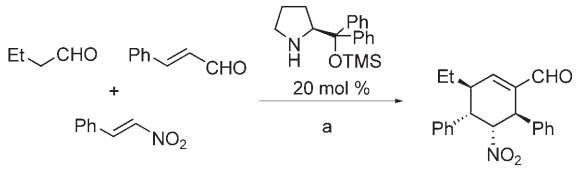
a hydrogen bond interaction with the proline carboxylic acid moiety.[12] Starting from the extension of proline-mediated enamine catalysis to intermolecular processes and its generalization to different electrophiles as a means to access α-functionalized aldehydes, Benjamin List presented a straightforward classification of organocatalysts. Whereas secondary amines (Lewis base catalysts) can provide alternate modes of activation through iminium ion formation, he stressed the increasing importance of Brønsted acid catalysis. With respect to the crucial formation of close-contact chiral ion pairs within the proposed mechanisms, Brønsted acid catalysis can be seen as a specialized case of a more general strategy, named asymmetric counterion-directed catalysis (ACDC),[13] which is related to the already established chiral phase-transfer catalysis.

Dieter Enders elegantly employed the different modes of enamine and iminium activation in domino reactions leading to highly functionalized cyclohexenes (see Scheme 2).[14] Starting

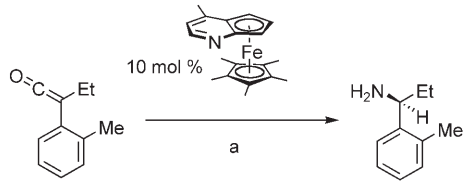


Scheme 2. Domino reaction using enamine and iminium activation for the construction of highly functionalized cyclohexenes. a) toluene, 0 °C, (58%, >99% *ee*).

from dihydroxyacetone acetonide the amine organocatalyst functions like an artificial aldolase eventually leading to carbohydrates,[15] sphingolipids,[16] and carbasugars.[17]

Nucleophilic Catalysis

One of the most acclaimed and applied nucleophilic organocatalyst is dimethylaminopyridine (DMAP).[18] Greg Fu[19] has introduced planar-chiral versions of DMAP and pyrrolidinopyridine (PPY)[20] and has reported their versatility for various applications, such as Staudinger reactions. Careful selection of the imine protecting groups, that is, tosyl versus triflyl, allows for directing the stereochemistry at the β-lactam from *cis*- to the unusual *trans*-stereochemistry with the more electrophilic triflylimine.[21] Interestingly, Fu presented a further switch in stereoselectivity for reactions involving ketenes by changing the reaction mechanism from standard Lewis base conditions (addition to ketene) to a Brønsted acid catalytic cycle with proton-



Scheme 3. Asymmetric catalysis of addition of hydrazoic acid to ketenes. a) 1) HN_3, toluene/hexane, -90 °C, 2) Δ, H_2O/H^+, (97%, 93% *ee*).

ated planar-chiral pyridine (formation of chiral ion pairs) as postulated for the asymmetric addition of NH_3 to ketenes (see Scheme 3).[22] Such chiral ion pairs might also play a role for a novel route to enantiopure tertiary α-chlorinated esters.[23]

Besides amines another privileged class of Lewis basic organocatalysts are nucleophilic carbenes,[24] which have been proven to be extremely versatile for different transformations, albeit strongly dependent on the electronic and steric nature of the catalyst. Apart from the well-known Stetter reaction,[25] Frank Glorius applied N-heterocyclic carbenes (NHCs) for a conjugate umpolung[26] of α,β-unsaturated aldehydes into homoenolates, which are then reacted with aldehydes or ketones to γ-butyrolactones or β-lactones depending on the reaction conditions;[27] the reaction can be monitored via important intermediates with MS techniques.[28] Whereas for α-substituted enals, a dimethylbenzimidazolium-derived carbene proved to be an ideal catalyst, the sterically demanding *N*,*N*′-bismesitylimidazolium (IMes) carbene is otherwise the reagent of choice.

A nitrogen-free nucleophilic catalyst is Varinder Aggarwal's chiral [2.2.1] bicyclic sulfide, synthesized from camphorsulfonyl chloride, which is a powerful catalyst in the catalytic asymmetric synthesis of epoxides[29] and aziridines,[30] and Morita-Baylis–Hillman reactions of enones with acyliminium species.[31] The asymmetric epoxidation of olefins of various geometry using chiral ketones derived from D-fructose as catalysts is constantly enhanced by Yian Shi (see Figure 1).[32] His reliable, stereopre-

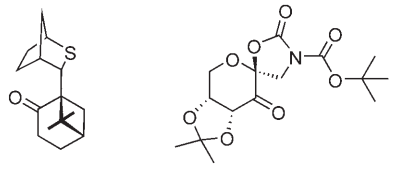
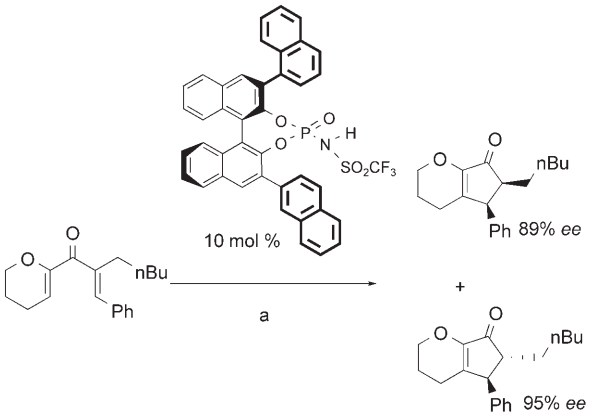


Figure 1. Aggarwal's sulfide catalyst for Corey-Chaykovsky-type epoxidation and Morita-Baylis–Hillman reaction and Shi's ketone organocatalysts for stereoselective oxidation of *cis*-disubstituted and terminal olefins.

dictable method is often complementary to metal-catalyzed epoxidations and has attracted wide spread application in different total syntheses. As the reaction can be conducted with simple hydrogen peroxide as oxidant, large amounts of inorganic byproducts are avoided, which makes the process amenable for larger scale.[33]

Mathias Christmann showed examples for organocatalytic key steps in the total synthesis of the natural product and telomerase inhibitor UCS 1025A.[34] In addition to an intramolecular Diels–Alder reaction for the formation of the decaline framework using MacMillan's imidazolidinone catalyst,[35] an unprecedented alkaloid-mediated lactone formation was applied to build up the tricyclic part of the target molecule. During this investigation an useful enantioenrichment of scalemic mixtures of the key intermediate in solution could be observed, which is interesting in the context of the current discussion on the solid-liquid equilibrium of scalemic amino acid mixtures and their role in asymmetric amine catalysis.[36] More examples for "applied organocatalysis" were presented by Harald Gröger



Scheme 4. Chiral Brønsted acid-catalyzed Nazarov cyclization. a) $CHCl_3$, 0 °C, (86%; *cis*:*trans* 2:1)

within an overview on organocatalytic methods already applied on a technical scale. Based on case studies he showed several examples that satisfy the criteria of a technically feasible process such as high catalyst activity and stability, economic access, sustainability, atom economy, and high volumetric productivity.

Hydrogen Bonding

The use of organocatalysts in radical reactions appears to be a novel trend.[37] The first radical reactions catalyzed by a chiral organic additive were documented with a piperidone and dihydroquinolinone synthesis by Thorsten Bach.[38] The Kemp's triacid derived organocatalyst interacts with the secondary lactam or amide substrates through double hydrogen bonding in contrast to the previous mentioned amine organocatalysts, which generally function through covalent interactions. Relying on H-bonding interactions affords the choice of nonpolar solvents, such as trifluorotoluene, to achieve high *ee* values. Hydrogen bonding networks are also used by Albrecht Berkessel in the kinetic resolution of azlactones and oxazinones.[39] A thiourea moiety as hydrogen bond donor is connected through a chiral spacer to a Lewis basic head group allowing for bifunctional catalysis activating both substrate and reagent. Bifunctionality is also a key feature of a "minizyme", that is, a helical oligoleucyl peptide with at least five amino acids, which is an effective catalyst for the epoxidation of chalcones. The "NH-binding motif" for the Julia-Colonna reaction is similar to the so-called "nest and egg motif" which can be found as an oxyanion hole in several serine hydrolases.

Complementary to the great variety of Lewis basic organocatalysts Brønsted acids gain increasing importance and significantly expand the scope of organocatalytic processes. As thiourea moieties generally work through hydrogen bonds and therefore can be considered as general acid catalysts, the stronger phosphoric acids act similarly to specific acids if compared to enzymatic reactions. Magnus Rueping demonstrated the versatiliy of chiral BINOL-phosphate based Brønsted acids in the asymmetric hydrogenation of quinolines, benzoxazines and pyridines and highlighted the potential of this method in an alkaloid total synthesis.[40] The scope is not limited to transfer hydrogenations, but is well suited for Strecker syntheses[41] and Nazarov cyclizations.[42] Even more importantly, with catalyst loadings lower than 0.01 mol%[43] this class of catalysts has already reached the power to compete with established transition metal-complexes (see Scheme 4).

Larger Molecules

Hydrogen bonding interactions are also considered to be of importance in organocatalysis involving peptides. In the context of developing efficient methods for selective functionalization of complex molecules (for example, natural products) Scott Miller has developed efficient peptidic acylation catalysts employing split-and-pool combinatorial chemistry techniques for optimization.[44] The common chiral scaffold for such site-selective catalysis is a nucleophilic histidine-based building block. These small peptide catalysts are not only effective for various group transfers (acylations, phosphorylations etc.), but also for Morita-Baylis–Hillman reactions.

Possible benefits from immobilization approaches for organic catalysts were pointed out by Maurizio Benaglia.[45] Apart from catalyst recycling or simplified workup procedures, catalyst immobilization can be additionally advantageous in terms of catalyst development and optimization.[46] The use of soluble supports, such as polyethylene glycol (PEG), often allows the direct transfer and application of already optimized reaction conditions.

In the field of enzyme catalysis, some of the major drawbacks, such as narrow substrate scope, or low selectivity and thermostability can be successfully addressed by using directed evolution.[47] In contrast to a rational design, which uses site-specific mutagenesis, these studies utilize genomic technologies like saturation mutagenesis and gene shuffling to create powerful, tailor made protein catalysts.[48] An even more effective strategy to enhance enzyme catalysis is the symbiosis of rational design and randomization, as applied in CASTing (combinatorial active-site saturation test)[49] in combination with iterative saturation mutagenesis (ISM) which was introduced by Manfred Reetz.

Outlook

Although organocatalysis is still in its infancy compared to metal-catalyzed processes or enzyme-mediated transformations, there has been tremendous progress within the last few years. New reactions have been developed and applied for technical processes. Novel types of catalysts are constantly introduced expanding the scope of organocatalytic methodology. Moreover, increasing mechanistic insights will help to further improve known catalytic transformations and to exploit reactivity. The Schering workshop offered a broad overview on organocatalytic processes, mechanisms, and possible applications and provided an outlook for the future establishment of organocatalysis as a third important strategy in asymmetric catalysis, complementing metal- and biocatalysis not only in academia, but also in industry.

Acknowledgements

We are grateful to the Ernst Schering Foundation for sponsoring and organizing an exciting workshop.

Keywords: amines · Brønsted acids · enantioselectivity · enzymes · organocatalysis

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Received: May 10, 2007
Published online on July 3, 2007

