The ying and yang of asymmetric aminocatalysis

Benjamin List

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During the last six years the asymmetric catalysis of carbonyl transformations *via* iminium ion and enamine intermediates using chiral amines as organocatalysts has grown most remarkably. In this personal account an overview of this area is given. The field can be divided into two sub areas: (a) Iminium catalysis, which is typically used for cycloadditions and conjugate additions to enals and enones and (b) Enamine catalysis, which is commonly used in electrophilic α-substitution reactions of ketones and aldehydes. A common origin of the two catalysis principles is proposed and their recent merger in tandem sequences is discussed.

Introduction

Although discovered in the early 1970s by two industrial groups, the proline-catalyzed intramolecular aldol reaction remained little more than a laboratory curiosity for almost thirty years.[1] Its scope had not been explored, its mechanism was poorly understood, and its use was limited to a narrow context.[2] Thirty years later, a revival of this chemistry was initiated with the discovery of the proline-catalyzed direct asymmetric intermolecular aldol reaction.[3] Since then, an explosive growth in the general area of organocatalysis and particularly in asymmetric amine catalysis could be witnessed.[4] Here I will try to give an overview of the fascinating chemistry that has evolved over the last five years. Naturally, I will focus on the contributions from my laboratory but I will also include examples from other groups working in the area, the number of which seems to be increasing at an amazing pace.

Max-Planck-Institut für Kohlenforschung, 45470, Mülheim an der Ruhr, Germany. E-mail: list@mpi-muelheim.mpg.de

The proline-catalyzed asymmetric aldol reaction: scope, mechanism and consequences

In addition to catalyzing the well-known Hajos–Parrish–Eder–Sauer–Wiechert reaction (eq. 1), we found in early 2000 that proline also catalyzes intermolecular aldolizations (*e.g.* eq. 2). Thereafter, our reaction has been extended to other substrate combinations (aldehyde to aldehyde, aldehyde to ketone, and ketone to ketone, eq. 3–5) and to enolexo-aldolizations (eq. 6).[5–8] Proline seems to be a fairly general, efficient, and enantioselective catalyst of the aldol reaction and the substrate scope is still increasing continuously (Fig. 1).

Both experimental and theoretical studies have contributed significantly to the elucidation of the reaction mechanism. We found that in contrast to earlier proposals,[9] proline-catalyzed aldol reactions do not show any non-linear effects in the asymmetric catalysis.[10] These lessons as well as isotope incorporation studies provided experimental support for our previously proposed single proline enamine mechanism and for Houk's similar DFT-model of the transition state of the intramolecular aldol reaction.[11,12] On the basis of these results we proposed the mechanism shown in Fig. 2. Key intermediates are the iminium ion and the enamine. Iminium ion formation effectively lowers the LUMO energy of the system. As a result, both nucleophilic additions and α-deprotonation become more facile. Deprotonation leads to the generation of the enamine, which is the actual nucleophilic carbanion equivalent. Its reaction with the aldehyde then provides, *via* transition state **TS** and hydrolysis, the enantiomerically enriched aldol product (Fig. 2).

For us, the intriguing prospect arose, that the catalytic principle of the proline-catalyzed aldol reaction may be far more general than originally thought. We reasoned that simple chiral amines including proline should be able to catalytically generate chiral enamines as carbanion equivalents, which then may

Benjamin List

Benjamin List received his PhD from Johann-Wolfgang-Goethe University in Frankfurt, Germany in 1997. After postdoctoral studies at The Scripps Research Institute, he became an Assistant Professor at the same institution in January 1999. He moved to the Max-Planck-Institut für Kohlenforschung in 2003, initially as an Associate Professor. In 2004 he became an Honorary Professor at the University of Cologne and was promoted to the post of Director of the Department of Homogenous Catalysis at the Max-Planck-Institut für Kohlenforschung in 2005. His research interests include developing new organic reactions, total synthesis, bioorganic chemistry, and organocatalysis.

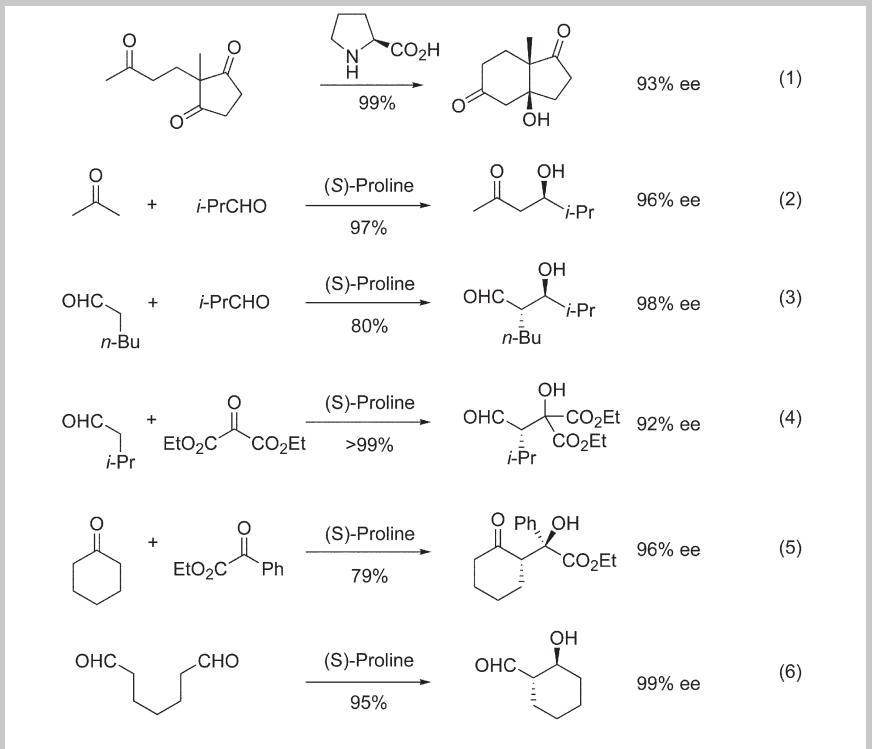

Fig. 1 Proline-catalyzed aldol reactions.

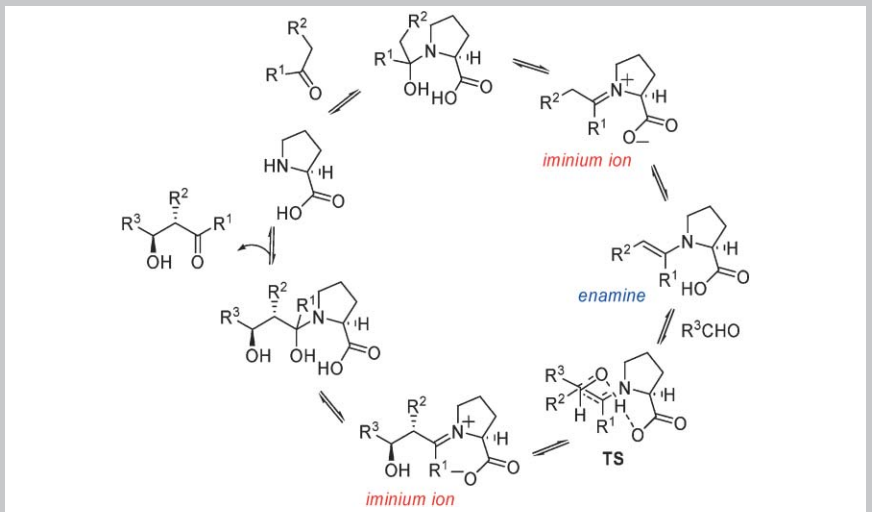

Fig. 2 The proposed mechanism and transition state of proline-catalyzed aldolizations.

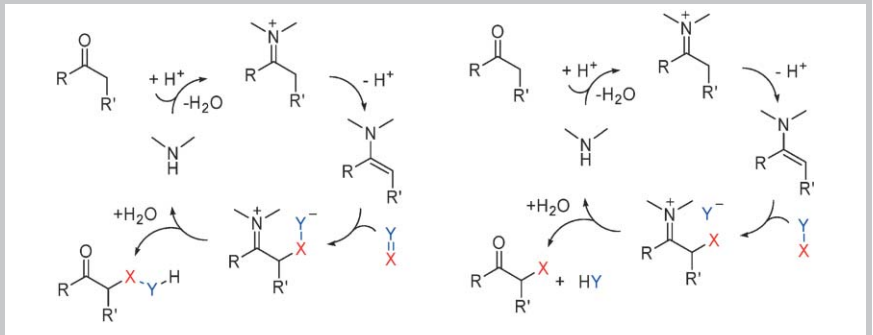

Fig. 3 Enamine catalysis of nucleophilic addition and substitution reactions (arrows may be considered equilibria).

undergo reactions with various electrophiles. We termed this catalytic principle *enamine catalysis* (Fig. 3).[13] Accordingly, the enamine, which is generated from the carbonyl compound *via* iminium ion formation can react with an electrophile X=Y (or X–Y) *via* nucleophilic addition (or substitution) to give an α-modified iminium ion and upon hydrolysis the α-modified carbonyl product (and HY).

Enamine catalysis has developed dramatically in the last few years and it turns out that its scope not only exceeds our most optimistic expectations but also that of the traditional stoichiometric enamine chemistry by far.[14]

Enamine catalysis of nucleophilic addition reactions

Enamine catalysis using proline or related catalysts has now been applied to both intermolecular and intramolecular nucleophilic addition reactions with a variety of electrophiles. In addition to carbonyl compounds (C=O), these include imines (C=N) in Mannich reactions,[15] azodicarboxylates (N=N),[16] nitrosobenzene (O=N),[17] and Michael acceptors (C=C) (see Fig. 4 for selected examples).[18]

Enamine catalysis often delivers valuable chiral compounds such as alcohols, amines, aldehydes, and ketones. Many of these are normally not accessible using established reactions based on transition metal catalysts or on preformed enolates or enamines, illustrating the complementary nature of organocatalysis and metallocatalysis.

Enamine catalysis of nucleophilic substitution reactions

The first example of an asymmetric enamine catalytic nucleophilic substitution was a reaction that may have been considered impossible only a few years ago. We found that proline and certain derivatives such as α-methyl proline efficiently catalyze the asymmetric α-alkylation of aldehydes.[19] Catalytic α-alkylation reactions of substrates other than glycine derivatives had been rare and those of aldehydes completely unknown before. In our process we

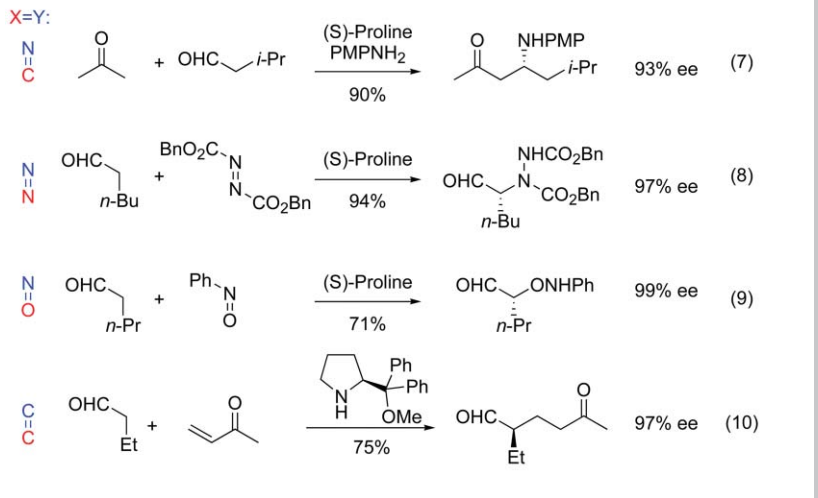

Fig. 4 Enamine catalysis of nucleophilic additions.

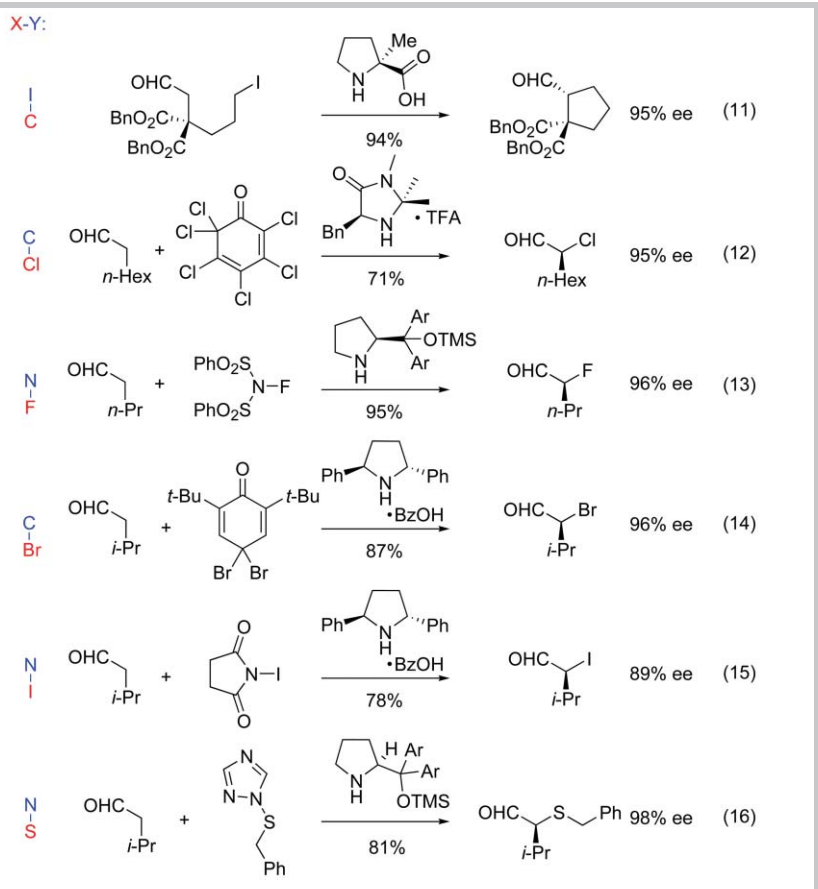

Fig. 5 Enamine catalysis of nucleophilic substitution reactions.

could cyclize 6-halo aldehydes to give cyclopentanecarbaldehydes in excellent yields and *ee*s (eq. 11, Fig. 5). Other important and remarkably useful enamine catalytic nucleophilic substitution reactions have been developed subsequently and include enantioselective α-chlorinations,[20] α-fluorinations,[21] α-brominations,[22] α-iodinations, and α-sulfenylations (eq. 12–16).[23]

Once again, most of these reactions have never been realized before using preformed enamines or any other methodology but lead to highly valuable products of potential industrial relevance.

Iminium catalysis

The *in situ* generation of an iminium ion from a carbonyl compound lowers the LUMO energy of the system. *Iminium catalysis* is comparable to Brønsted or Lewis acid activation of carbonyl compounds.[24] The LUMO energy is lowered, the α-CH-acidity increases, and nucleophilic additions including conjugate additions as well as pericyclic reactions are facilitated (Fig. 6).

The first highly enantioselective examples of this catalysis strategy were reported by MacMillan *et al.* in 2000,[25,26] only shortly after our first paper on the proline-catalyzed intermolecular aldol reaction had appeared. The MacMillan group has quickly established that Diels–Alder reactions, 1,3-dipolar cycloadditions,[27] and conjugate additions of electron rich aromatic and heteroaromatic compounds can be catalyzed using chiral amino acid derived imidazolidinones as catalysts.[28] In addition, highly enantioselective epoxidations,[29] cyclopropanations,[30] and conjugate reductions have recently been developed (eq. 17–21, Fig. 7).[31] Like enamine catalysis, this field is attracting an ever increasing number of research groups.

The ying and yang of aminocatalysis

The iminium catalytic cycle for nucleophilic additions is shown in Fig. 8. It is initiated *via* iminium ion formation from an α,β-unsaturated aldehyde and the catalyst. Conjugate addition of a nucleophile gives an enamine intermediate, which upon hydrolysis provides the product (Fig. 8).

Enamine and iminium catalysis are two divergent reaction modes in organocatalysis. In iminium catalysis on the one hand, carbonyl compounds are activated by lowering the LUMO energy of the system, which makes it more electrophilic, acidic, and prone to certain pericyclic reactions. In enamine catalysis

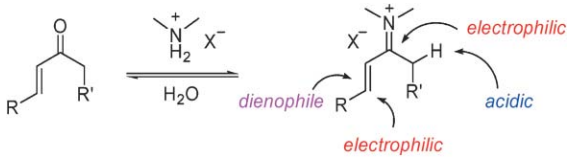

Fig. 6 Iminium catalysis.

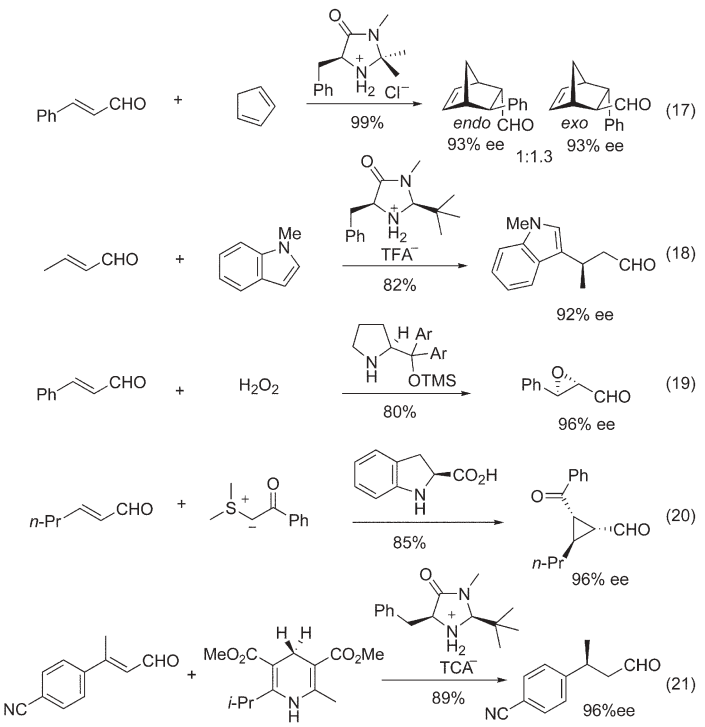

Fig. 7 Examples of asymmetric iminium catalysis.

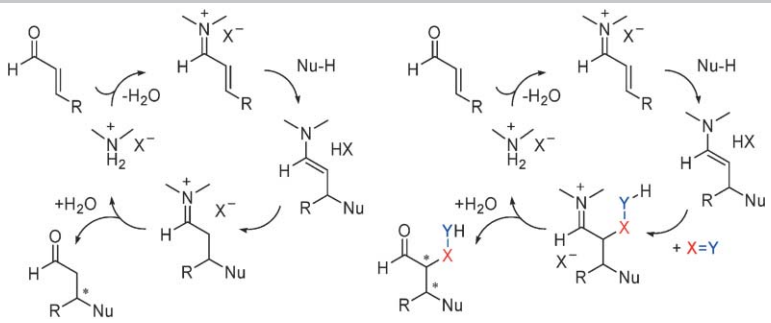

Fig. 8 The iminium catalytic cycle and its extension to tandem iminium–enamine catalysis sequences (arrows may be considered equilibria).

on the other hand, carbonyl compounds are converted into the more nucleophilic enamines, a transformation that overall increases the energy of the HOMO.

However, it is apparent that enamine and iminium catalysis are based on the same origin. Enamine catalysis *proceeds via* iminium ion formation and almost always *results* in iminium ion formation. In an opposing but complementary fashion, iminium catalysis typically results in the formation of an enamine intermediate. Like the ying and yang,[32] the two catalytic intermediates are opposites, yet interdependent, and they consume and support each other.

Combining the two catalysis principles in tandem sequences is obviously attractive and worth pursuing. Very recently, the first approaches appeared in two simultaneous communications (Fig. 9). We have described a highly enantioselective reductive Michael cyclization consisting of an iminium catalytic conjugate reduction and an enamine catalytic Michael cyclization (*e.g.* eq. 22).[33] At the same time the MacMillan group discovered similar sequences that are initiated by an iminium catalytic conjugate addition (or reduction) and that terminate in an enamine catalytic α-halogenation (*e.g.* eq. 23–24).[34] As pointed out by MacMillan *et al.*, an attractive feature of these reactions is the exquisite enantioselectivity, a mathematical requirement resulting from sequencing two asymmetric processes.

It is clear that such tandem sequences can be quite powerful for the generation of molecular complexity in a simple one flask operation. They should be modular and many of the reactions presented in eq. 1–21 should be combinable in double, triple, and multiple cascades.[35]

In summary, enamine catalysis and iminium catalysis turn out to be useful new strategies for organic synthesis and their arising combinations in tandem sequences are promising. The catalysts are usually bench stable, easy to synthesize from readily available amino acids, and will likely evolve with regard to their catalytic efficiency as many of the reactions discussed here still require catalyst loadings between 5 and 30 mol%. Keeping in mind that the field is still in its infancy there can be little doubt that it will continue to excite many of us for some time to come.

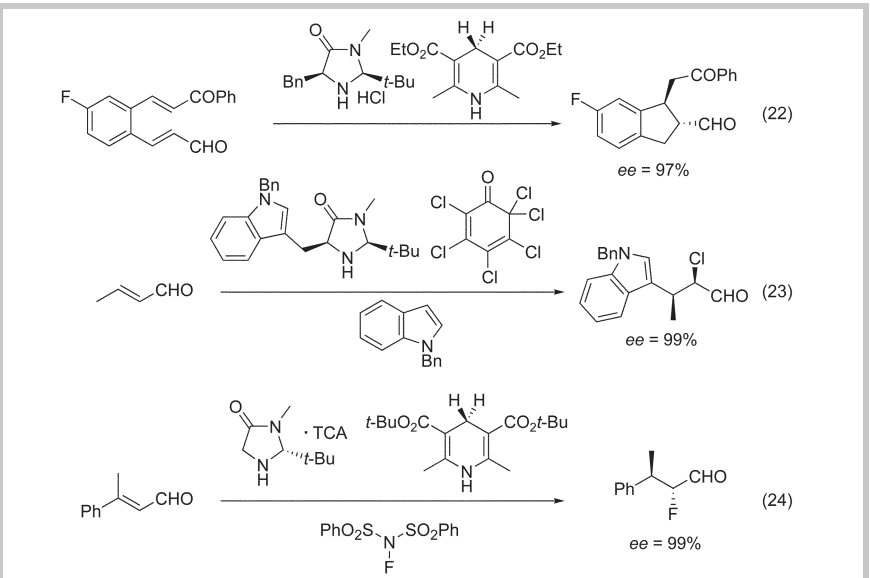

Fig. 9 Tandem iminium–enamine catalysis.

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