Organocatalysis

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Emil Knoevenagel and the Roots of Aminocatalysis**

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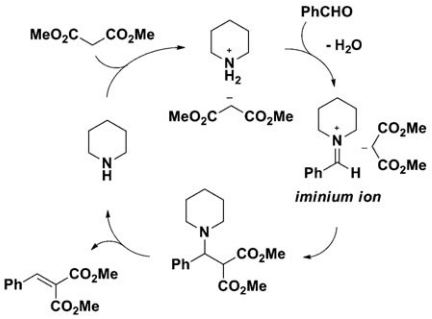
The progress of organocatalysis over the last ten years has been breathtaking. From a small collection of exotic and underdeveloped transformations that were mechanistically poorly understood, the area has grown into one of the three pillars of asymmetric catalysis, complementing bio- and metal catalysis.[1] The developments in aminocatalysis,[2] which comprises reactions catalyzed by secondary and primary amines via enamine and iminium ion intermediates, have been particularly exciting. What are the roots of aminocatalysis, though? Why is this field only blossoming now and not earlier?

Here I will take a look back at the origins of aminocatalysis and its development over the last century, maybe revealing some surprises.

The Knoevenagel Reaction and the Aldolase Mechanism

In general, enzyme mechanisms are based on chemical experiments and reasoning. The aldolases have been no exception. Throughout his investigations on amine catalysis in biology, which paved the way for the formulation of the class I aldolase mechanism, Westheimer was well aware of the synthetic organic roots of his proposals. His studies on the mechanism of the amine-catalyzed retro-aldol reaction not only led to the conclusion that it involves iminium ion and enamine intermediates but also that "*the idea of a ketimine as intermediate in condensations similar to the aldol is not new.*"[3]

To which ideas was he referring? It was to those of the organic chemist Emil Knoevenagel (Scheme 1). Long before anything was known about the chemistry of the aldolases, Knoevenagel found that primary and secondary amines, as well as their salts, catalyze the aldol condensation of β-ketoesters or malonates with aldehydes or ketones.[4] He realized that his amines were truly catalytic ("*Contactsubstanz*"), and even by today's standards Knoevenagel achieved remarkably high turnover numbers. More importantly, while he of course did not formulate the modern catalytic cycle shown in Scheme 1, in the case of imines—and in the case of β-ketoesters also with enamines—he suggested the same intermediates that Westheimer later proposed in his retro-aldolization studies.[4b–d]



Scheme 1. Emil Knoevenagel (1865–1921) and his reaction (1896).

In addition to inspiring bioorganic chemists, Knoevenagel's seminal discovery and mechanistic interpretation of his reaction over 100 years ago laid the historical foundation for the development of modern aminocatalysis. As will be shown below, there is a direct connection between the seminal work of Knoevenagel and our own studies on amine catalysis, and probably also those of MacMillan and co-workers in 2000.[5,6]

One Hundred Years of Aminocatalysis

A long time passed between the discovery of the Knoevenagel reaction and the development of modern aminocatalysis. What happened during those decades? First of all, it should be noted that the Knoevenagel reaction has always been an extremely important and reliable method for the formation of C–C bonds and is frequently used in industry. However, Knoevenagel's chemistry also had a strong influence on other researchers. For example, in 1910 Dakin found that primary amino acids catalyze the Knoevenagel condensation.[7] Twenty years later, Kuhn and Hoffer made the important observation that secondary amines not only catalyze the Knoevenagel condensation but also the self- and cross-aldol condensations of aldehydes,[8] reactions which are still used on an industrial scale. Similarly inspired by

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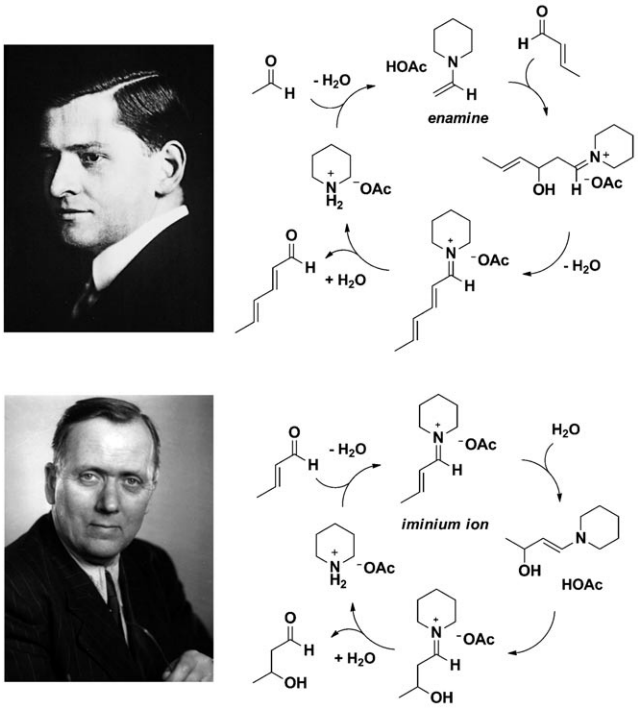
Knoevenagel were Fischer and Marshall when they used primary amino acids to catalyze aldol addition and condensation reactions of acetaldehyde.[9] In 1936, Kuhn et al. also found that carboxylic acid salts of amines catalyze the aldol condensation of aldehydes more effectively, and introduced piperidinium acetate as a particularly active catalyst for this reaction (Scheme 2).[10] Interestingly, piperidinium acetate was shortly after also used by Langenbeck and Sauerbier in their studies on the catalytic hydration of crotonaldehyde.[11] Langenbeck suggested a Kuhn–Knoevenagel-type covalent catalysis mechanism ("*Hauptvalenzkatalyse*"), and was probably the first chemist who had an entire research program devoted to studying organocatalysts ("*die Organischen Katalysatoren*"),[12] their mechanisms, and their relationship to enzyme action (Scheme 2). He also introduced secondary amino acids, most notably sarkosine (but not yet proline!) as catalysts for aldolizations.[13]

Kuhn and Langenbeck also did not formulate the modern catalytic cycles shown in Scheme 2; but isn't it still remarkable how Knoevenagel, Kuhn, and Langenbeck were already aware of mechanistic details of their catalytic reactions, and how naturally they utilized the iminium ion and the enamine activation modes of aminocatalysis?

These studies clearly encouraged Wieland and Miescher as well as Woodward et al. to investigate intramolecular aldol reactions of diketones and dialdehydes catalyzed by piperidinium acetate.[14,15] These experiments were made in the context of the total syntheses of steroids and delivered methods that continue to be used today. In line with the ideas of Knoevenagel, Kuhn, and Langenbeck, Woodward, Wieland, and Miescher believed that their aldolizations would proceed via enamine intermediates, which has subsequently been confirmed by the mechanistic studies carried out by Spencer et al in 1965.[16]



Scheme 2. Richard Kuhn (1900–1967, top) and Wolfgang Langenbeck (1898–1967): Piperidinium acetate catalyzed aldehyde aldolization (1936) and crotonaldehyde hydration (1937) by enamine and iminium ion catalysis.[10,11]

The Hajos–Parrish–Eder–Sauer–Wiechert Reaction

This background set the stage for the discovery of the first asymmetric amine-catalyzed aldolization—the proline-catalyzed intramolecular aldol reaction—by Hajos and Parrish and by Eder, Sauer, and Wiechert in the early 1970s (Scheme 3).[17] Their "catalyst design" is apparent: while piperidinium and pyrrolidinium salts were established achiral catalysts of inter- and intramolecular aldolizations, such as those described by Wieland and Miescher,[15] and amino acids had already shown their potential,[7,9,13] proline was an obvious choice as an abundantly available chiral secondary amino acid catalyst.

The Hajos–Parrish–Eder–Sauer–Wiechert reaction has previously been discussed in detail.[1e] In the present context it is sufficient to remember two remarkable facets of this

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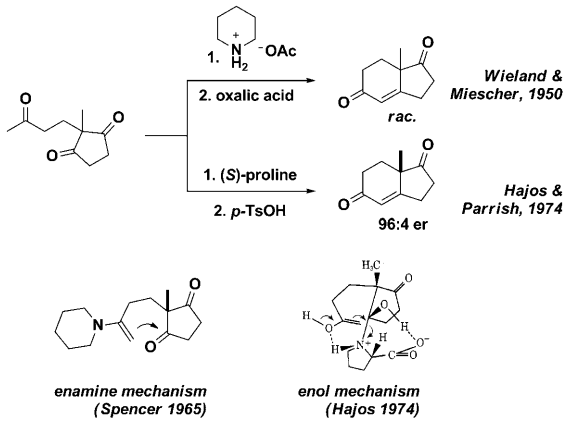


Scheme 3. The reactions of Wieland and Miescher and of Hajos, Parrish, Eder, Sauer, and Wiechert. Suggested mechanisms (the Hajos mechanism is taken from Ref. [17b]).

discovery: First, the Wiechert research group at Schering, in contrast to Knoevenagel more than 70 years earlier, neither discussed any mechanism nor realized or at least mentioned that their process was an early example of asymmetric catalysis. Secondly, and more perplexing, is the discussion but rejection of an enamine mechanism by Hajos. Instead, a mechanism involving the reaction of a weakly nucleophilic enol with a weakly electrophilic and sterically hindered hemiaminal (with retention of configuration!) is proposed. This is, to say the least, surprising considering the mechanistic studies mentioned above, particularly the piperidine-catalyzed enamine mechanism proposed by Spencer et al. for the same reaction (Scheme 3).

After Hajos–Parrish–Eder–Sauer–Wiechert

Why was this reaction not fully explored in the following three decades? To answer this question, we shall first evaluate the few studies conducted subsequently to the Hajos–Parrish–Eder–Sauer–Wiechert observation. First of all, Eschenmoser and co-workers,[18] in mostly unpublished experiments, investigated the reaction mechanism in the 1970s. One of the most pressing concerns for Eschenmoser and co-workers was whether or not putative proline enamines are pyramidalyzed. Such a pyramidalization was speculated to be involved in communicating the α-chirality of the proline to the newly created stereocenters several atoms apart.

Contemporarily, Woodward et al. applied proline catalysis in their synthesis of erythromycin published in 1981.[19] Woodward et al. used proline in the critical stereochemistry-determining step of the synthesis to mediate an intriguing retro-Michael-Michael-aldol triple organocascade.[20] The authors suggested their poorly enantioselective transformation to involve iminium ions and enamines. In retrospect, it seems that among the chemists of the time, Woodward may have had the clearest imagination of the potential of proline catalysis.

Agami et al. examined proline catalysis in the 1980s.[21] Their studies include the application of proline as a catalyst for other, significantly less enantioselective and efficient 6-*enolendo* aldolizations as well as mechanistic experiments. The seemingly nonlinear and dilution effects found in these studies suggested the reactions proceed by yet another complex mechanism involving two proline molecules.

Finally, some less noticed but nonetheless important progress came in the early 1990s from the research groups of Yamaguchi and Taguchi. They used proline derivatives in enantioselective Michael additions and, following Knoevenagel's tradition, suggested iminium ion activation as the catalytic principle.[22] Their work was clearly inspired by the proline-catalyzed aldolization. However, it also reflects an early awareness of the connection between enamine and iminium catalysis, the two fundamental principles ("Yin and Yang") of *asymmetric* aminocatalysis.[2]

Real progress, however, towards the generalization of aminocatalysis and a more complete mechanistic understanding of proline catalysis was not made during these years. Some more plausible reasons why proline catalysis and its underlying reactivity principles have not been explored further are: 1) the reaction was developed in an industrial setting, where the "academics" of a discovery are rarely fully explored; 2) the suggested mechanisms by Hajos and Agami were counterintuitive and could not easily be generalized such that new reactions and catalysts could be designed; 3) the scope of highly enantioselective aldol variants appeared to be very narrow; and finally 4) the trends of the time were simply different: Pioneering studies by Noyori, Knowles, and Sharpless as well as others on asymmetric transition-metal catalysis led to a whole new area of research. This field has inspired and fascinated organic chemists deeply—possibly to the extent that catalysis with "their own" purely organic molecules appeared somewhat less exciting—at least for a few decades.

The Proline-Catalyzed Direct Asymmetric Aldol Reaction: Asymmetric Aminocatalysis

What then let to our proline catalysis study in 2000? These experiments were stimulated by two developments. First, between 1997 and 1998 we investigated the aldolase catalytic antibodies developed by Lerner and Barbas. Realizing possible similarities between the aldolases and proline, it was Danishefsky who encouraged the successful exploration of the Hajos–Parrish–Eder–Sauer–Wiechert reaction with antibody 38C2.[23] One of my ideas involved the use of antibody catalysis for the desymmetrizing aldolizations described by Agami et al.[21a,24] Attempts to repeat their experiments first exposed me to proline catalysis in the laboratory. We also tried to use antibody catalysis in natural product synthesis and on a preparative scale.[25,26] Our research then aimed at highlighting the power and scope of antibody catalysis. These experiments also revealed certain limitations, however, which encouraged me to investigate small organic molecules as catalysts in my independent work.

A second stimulation came from the discovery by Shibasaki and co-workers of direct asymmetric aldol reactions catalyzed by a metal complex in 1997.[27] These important experiments showed that it is possible to catalyze direct enantioselective intermolecular aldol reactions with a designed transition-metal catalyst.

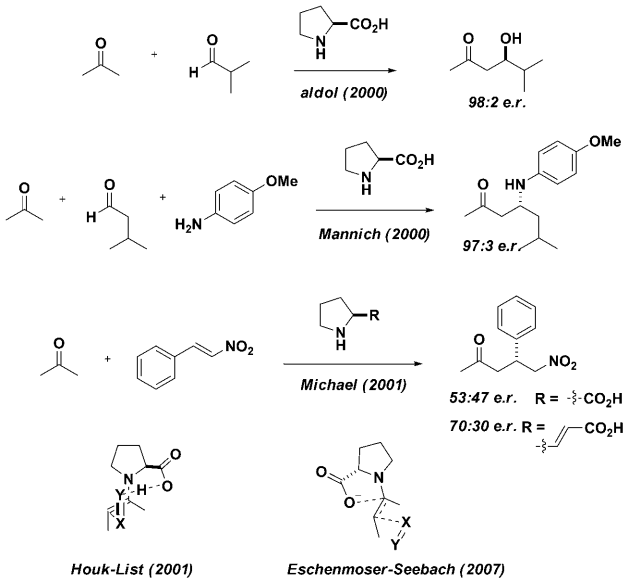
In 1999, I began wondering whether chiral, low-molecular-weight amines could also catalyze direct asymmetric *intermolecular* aldol reactions. In retrospect, and considering the historical studies mentioned above, this question should have been approached with confidence; yet skepticism was the most common reaction I received when proposing this idea to colleagues. I was, therefore, delightfully surprised when I found that the proline-catalyzed direct aldol reaction of acetone with aldehydes furnished the desired products in good yields and high enantioselectivity.[5]

Could the mechanistic proposals of Hajos or Agami explain these exciting results? After some deliberation, I formulated a different mechanism. The first, maybe more apparent assumption was that proline forms an enamine intermediate. Secondly, keeping the wise words of my PhD mentor Johann Mulzer in mind that nucleophilic attack at a

carbonyl group requires an acid to neutralize the "oxyanion", in "statu nascendi" so to speak, I reasoned that the carboxylic acid of proline might play exactly that role. Accordingly, proline would be a bifunctional catalyst acting both as Lewis base and Brønsted acid. A mechanism very similar to this was subsequently supported by DFT calculations by Houk and co-workers and by further mechanistic studies.[28]

The newly developed mechanistic proposal suggested to me that this type of organocatalysis may be a universal strategy for the catalytic generation of chiral carbanion equivalents from carbonyl compounds. Inspired by studies by Kobayashi et al. and Hayashi et al.,[29] we investigated in situ generated imines and nitroolefins which led to the first proline-catalyzed asymmetric intermolecular Mannich and Michael reactions.[30,31] All three new asymmetric transformations catalyzed by a chiral amine—the intermolecular aldol, Mannich, and Michael reactions—have a remarkable substrate scope that continues to be expanded today, not only by my research group but also by many others (Scheme 4).[32] The mechanism and stereoselectivity of these (and many other) proline-catalyzed reactions can be wonderfully explained and even predicted with the Houk–List transition state. Recently though, Eschenmoser, Seebach, and co-workers have challenged this model and proposed an alternative transition state.[33] I am very curious about further mechanistic studies that will hopefully answer all the remaining questions about this fascinating catalysis principle.

In retrospect, I think that it really was the experiments shown in Scheme 4 and our transition-state model that opened our eyes to the enormous possibilities of the catalysis principle that I have (admittedly slightly inaccurately) called "enamine catalysis".[2b,31] This concept has inspired several dozens of different reactions and literally hundreds of variations over the last decade, including C–C bond-forming reactions and α-functionalizations.[32] Some of these reactions have the potential to change the way we synthesize organic molecules. Spectacular advancements have also been made in the area of iminium catalysis, the second subarea of aminocatalysis during those years—but that is another story.[34]



Scheme 4. Examples of the first chiral-amine-catalyzed asymmetric intermolecular aldol, Mannich, and Michael reactions.[5,30,31]

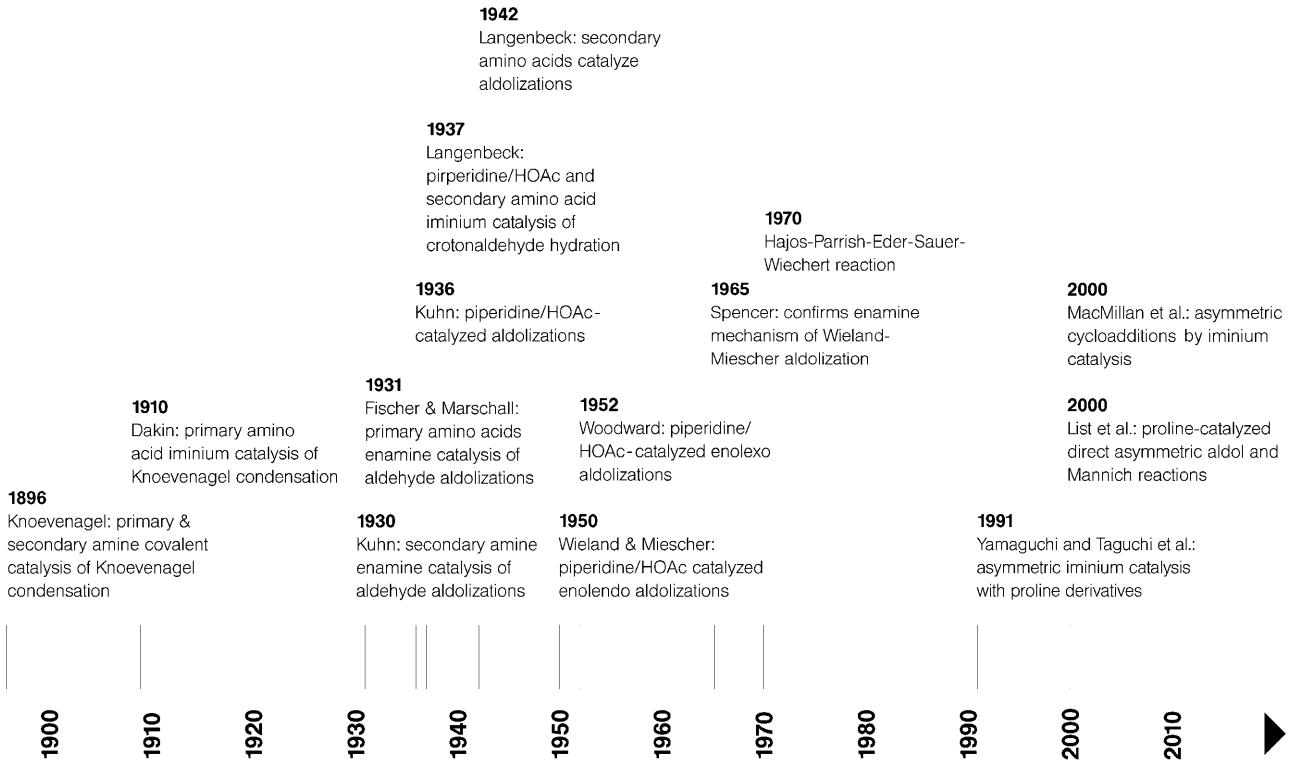


Figure 1. Milestones in the development of aminocatalysis over the last 114 years.

Conclusions

After a decade of highly active research in asymmetric aminocatalysis, the time has come to take a look at its historical origins and further advancement (Figure 1). Interestingly, Wu and Schultz have recently traced the roots of proline organocatalysis back to antibody catalysis by stating that "*mechanistic studies of this aldolase antibody led […] investigators to the discovery that the simple amino acid proline could act as an asymmetric organocatalyst.*"[35]

But was that really so? After exploring the roots of aminocatalysis, the pioneering studies of Knoevenagel, Kuhn, Langenbeck, and others, and also recapitulating our own contributions I developed a slightly different view. Both the protein-catalyzed direct asymmetric aldol reaction[36] and the rare earth metal catalyzed version developed by Shibasaki and co-workers[27] have clearly triggered and accelerated the advancement of asymmetric aminocatalysis. The true origins of this fascinating catalysis principle, however, go back to the pioneering and insightful contributions of Emil Knoevenagel over 100 years ago.

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