Organocatalysis

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Organocatalysis Lost: Modern Chemistry, Ancient Chemistry, and an Unseen Biosynthetic Apparatus

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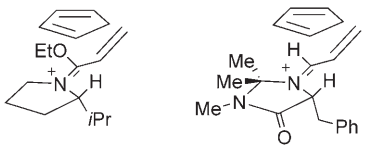
aldolases · asymmetric synthesis · biosynthesis · catalytic antibodies · organocatalysis

In memory of Frank H. Westheimer (1912–2007)

Since the year 2000 there has been explosive growth in an area of catalytic asymmetric synthesis now known as organocatalysis, catalysis mediated solely by small organic molecules.[1] A large number of powerful asymmetric bond-forming reactions and stunning cascade reactions have been reported that allow for the enantioselective synthesis of molecules with unprecedented ease. A substantial portion of this new work is founded on enamine and iminium ion based catalysis. Given the historically deep roots of this type of catalysis, why did decades pass before the basic concepts, hidden in the landmark work of Hajos and Parrish, were unveiled and exploited? I believe the answer is complex and unknowable with complete certainty, but likely involves both culture and the actual chemical mechanisms. I believe that this chemistry not only provides for fascinating and efficient syntheses of chiral molecules but may serve to explain the emergence of homochirality in the prebiotic world and may constitute an unseen biosynthetic mechanism functioning in today's cells in support of metabolism.

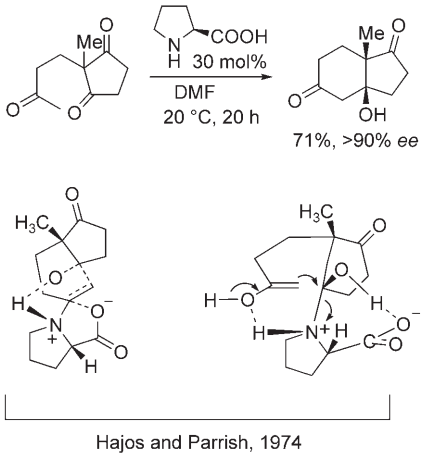
Let us consider the reports from the year 2000 that marked the ascendance of enamine/iminium ion based organocatalysis and their literature antecedents. For our studies concerning the aldol and Robinson annulation,[2] the Hajos–Wiechert[3] reaction (1971) provides the proper foreshadowing. The MacMillan iminium ion based Diels–Alder reaction[4] is foreshadowed by the iminium ion Diels–Alder reaction of Baume and Viehe (1976) and the chiral alkoxy iminium salt asymmetric Diels–Alder reaction of Jung et al. (1989).[5] The breakthrough in the MacMillan approach is the conversion of the stable alkoxy iminium salt of Jung into a labile iminium compound suitable for catalysis. Significantly, the Jung and MacMillan reports are in agreement with respect to the presumed transition state of the reaction, probably owing to the already substantial body of work on the Diels–Alder reaction (Scheme 1).



Jung et al., 1989 MacMillan et al., 2000

Scheme 1. Proposed transition states for the iminium ion based Diels–Alder reactions of Jung et al. and MacMillan et al.[4,5b]

With the realization of an approach to a labile iminium ion, the reaction could be further generalized and iminium ion based organocatalysis could be further developed. In contrast, the general mechanism of the Hajos–Wiechert reaction and a reasonable and exploitable transition-state proposal remained an enigma for decades despite the fact that the reaction has been performed on an industrial scale since its invention thirty years prior (Scheme 2).[3,6]



Scheme 2. Top: Hajos–Wiechert reaction. Bottom: Proposed transition states and intermediates for this reaction.[3,6]

Why did the Hajos–Wiechert reaction remain an enigma until 2000?

Why were the fascinating organocatalytic transformations published in recent years not discovered in the intervening 30 years? We can come closer to understanding this enigma by looking back at the literature concerning iminium ion and enamine based catalysis. Although studies concerning the nature of imines and enamines can undoubtedly be found earlier, the studies of K. J. Pedersen and Frank Westheimer concerning amine catalysis of the decarbox-

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ylation of β-keto acids (iminium catalysis, 1934) and the Westheimer work concerning the retro-aldol reaction of diacetone aldol (iminium ion/enamine based catalysis 1940) mark a modern formalism of catalysis in these systems.[7] Iminium ion and enamine based catalysis are clearly illustrated in these works. These studies provided the framework for the elucidation of the mechanisms of the enzymes acetoacetate decarboxylase (iminium ion based catalysis) by Westheimer[8] and the aldolase family of enzymes (iminium ion/enamine based catalysis) by others.[9] Significantly, many of the mechanistic subtleties of iminium ion/enamine based enzymes were already textbook knowledge in 1969 when William Jenks published his landmark work entitled *Catalysis in Chemistry and Enzymology*.[10] The prototypical iminium ion/enamine based mechanism had also been extended to other systems like 2-keto-3-deoxy-L arabinate dehydrase,[11] and by 1974 the complete amino acid sequence of rabbit muscle aldolase had been determined and amino acid residues critical to the catalytic mechanism had been assigned.[9b] Key features of the aldolase mechanism are activation of the ketone's α proton through imine formation and subsequent generation of an enzyme-bound enamine that is a nascent carbon nucleophile. General-acid-catalyzed activation of the aldehyde electrophile then facilitates its reaction with the enzyme-bound enamine. Indeed, this experimentally supported mechanism (Figure 1), clearly postulated by Rutter in 1964[9a] (the year of my birth) has for the most part stood the test of time. If so much could be known about the complex rabbit muscle aldolase enzyme (160000 g mol^{-1}), why did the mechanism involving proline (115 g mol^{-1}) prove so elusive and therefore so unexploitable? Why did the proline-catalyzed reaction stump so many when the mechanistic underpinnings of nature's complex and efficient aldolases were well understood in the 1960s?

Part of the answer presumably lies in the compartmentalization of ideas in the cultures of organic chemistry and biochemistry. This cultural isolationism often inhibited the flow of information between the organic chemist and the biochemist and visa versa. Whereas the biochemists would turn to the teachings of Westheimer, Rutter, and Jenks—to name a few—for a foundation in imine and enamine chemistry, the traditional organic chemists turned to the studies of Robinson and Stork and their landmark use of enamines to form new C–C bonds.[12] Historically, cross-referencing between these two cultures tended to be rare.[13] Although the emergence of the new field of chemical biology (also called bioorganic chemistry) has merged the fields of organic chemistry and biochemistry, it also threatens a rekindling of isolationist thinking in the chemical sciences that we vigilantly need to guard against.

Perhaps, while marveling at the stunning efficiency of enzymes, early investigators were unable to imagine that the chemical principles that drive them might also be manifested by a simple amino acid. Doing so ignores da Vinci's tenant that "simplicity is the ultimate sophistication"—an idea manifested in the principle of Occam's razor.[14] Indeed, the presumed structural complexity required for aldolase enzyme action together with the infrequent communication between biochemical and organic communities were likely the major roadblocks to the construction of an exploitable mechanism for asymmetric catalysis by proline. Our proposal for the exploitable transition state in proline catalysis of the aldol reaction (Figure 1) became possible through the uniting of the chemical and biochemical literature as we learned to recreate nature's aldolase enzymes as

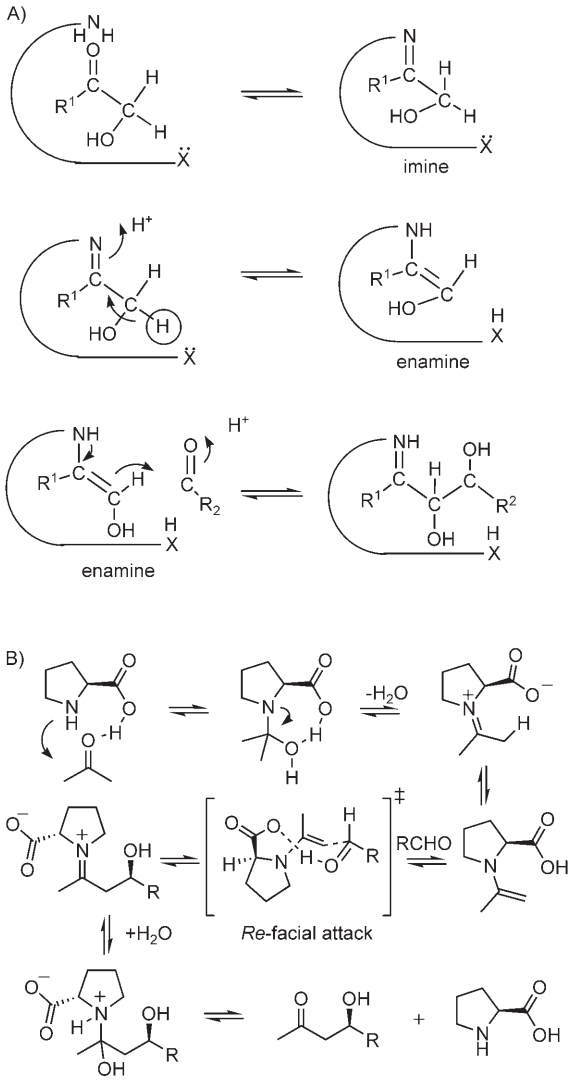


Figure 1. A) Rutter's 1964 mechanism for aldolase enzymes and B) the proline-catalyzed aldol reaction.

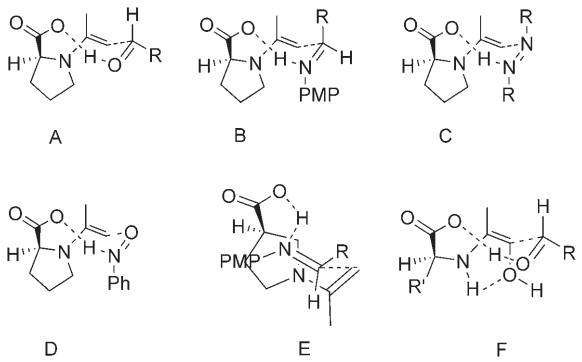
catalytic antibodies. Our studies provided us with a perspective not available through the study of nature's existing enzymes or organic chemistry alone. Drawing on the studies of Westheimer and our recognition of the similarities between the reaction coordinates of the enzymatic aldol reaction and covalent inhibition of enzyme action via 1,3-diketones, we were able to recreate the mechanism of class I aldolases in catalytic antibodies.[15] These antibodies not only captured the mechanism of nature's "sophisticated" aldolases, but also provided a new perspective on this chemistry.

We demonstrated that not only could antibody-based enamines be challenged with a wide variety of electrophiles to effect bond-forming reactions but also that these antibodies could catalyze the decarboxylation of β-keto acids thereby mimicking the acetoacetate decarboxylase enzyme studied by Westheimer.[15b] We further exploited iminium catalysis to facilitate retro-Michael reactions for drug-delivery and cancer-therapy approaches.[15e,f] In 1997, we challenged our aldolase antibodies to catalyze the Hajos–Wiechert reaction.[15g] The aldolase antibodies were able to catalyze this ring-closing aldol reaction. We then studied catalysis of the Michael reaction essential for the synthesis of the triketone substrates of the Hajos–Wiechert reactions. Indeed, as we predicted based on mechanism, aldolase antibodies could catalyze both steps of the Robinson annulation reaction. These experiments led us to suspect that proline mimicked aldolase enzymes more closely than had been suggested previously, and our studies of this analogy continued.[16]

The final step in confirming this hypothesis came with our development of UV-sensitive reporter retro-aldol substrates based on 4-dimethylaminocinnamaldehyde, which was devised to study aldol kinetics as well as to discover new aldol catalysts.[17] Given the intrinsic reversibility of the aldol reaction, screening for either the synthetic aldol or the retro-aldol reaction is possible. We found that proline was the most active of the amino acid catalysts evaluated; this immediately suggested that proline mimics the mechanism of natural aldolase antibodies, albeit without the structural confines of a protein catalyst. Therefore we posited that proline was an "open active-site catalyst" meaning that whereas steric constraints posed limitations to protein-catalyzed reactions arising from the geometric confines of protein active sites, the small molecule proline should accept a wider range of substrates.[18] We proposed a simple aldolase-enzyme/antibody-inspired mechanism for proline-catalyzed reactions that was unlike those proposed before: We suggested that proline's carboxylate was used for general acid/base catalysis and that a single molecule of proline was present in the transition state. Our mechanism directly converted the mechanism of Rutter (founded on the Westheimer work) and incorporated a modified Zimmerman–Traxler-type transition state that had been the working model for our aldolase antibodies. In support of this mechanism, we did not find the nonlinear effect that had led Agami and co-workers mechanistically astray in their proline studies.[19] Indeed, later studies have since supported our one-proline model in both intra- and intermolecular aldol reactions.[20] Demonstrating the potential of proline to catalyze intermolecular aldol reactions with the same broad scope we had noted for aldolase antibodies, we completed the aldolase–proline analogy by demonstrating that proline could, like aldolase antibodies before them, catalyze both the iminium ion Michael and the enamine aldol steps.[2b,15g] *Thus, although the proline-catalyzed Hajos–Wiechert reaction had been performed on an industrial scale since its invention, the potential of proline to catalyze the preceding Michael step had been overlooked owing to the plethora of confounding mechanisms for this chemistry.*

While the mechanism we proposed in 2000, founded on our aldolase antibody studies and ultimately on the studies of Westheimer, will undoubtedly be further refined, a test of a mechanistic proposal is the advances in chemistry that it enables. In this sense, exploitation of the enzymatic iminium ion/enamine based mechanism in organocatalysis has been unusually successful. Our transition-state model has led to the exploitation of Mannich, Michael, amination,[1b,d] α-aminoxylation,[1b,d] and a wide variety of other reactions,[1b,d] including the coupling of iminium ion and enamine based catalysis as we demonstrated first with aldolase antibodies[15g] and later with proline,[2b] a concept that has now become key in the design of asymmetric reaction cascades in organocatalysis (Scheme 3).[1,21] A further test of a mechanistic proposal regarding a specific catalyst is how it informs the construction of new catalysts. Here too the proline mechanism has been exploited to design novel catalysts that provide access to *anti*-Mannich and *syn*-aldol products not accessible through proline as well as catalysts that act effectively with water.[22]

While it is not the goal of this essay to provide a complete review of studies that support and refine the mechanism of the proline-catalyzed aldol reaction we first reported, the reader is directed to additional computational and kinetic studies that have further enriched our



Scheme 3. Generalization of the proline aldol transition state to other the transition states of other reactions and catalysts, including A) aldol, B) Mannich, C) amination, and D) α-aminoxylation reactions, and its redesign to provide access to *anti*-Mannich (E) and *syn*-aldol (F) products. PMP = *para*-methoxyphenyl.

understanding of this and related reactions.[23]

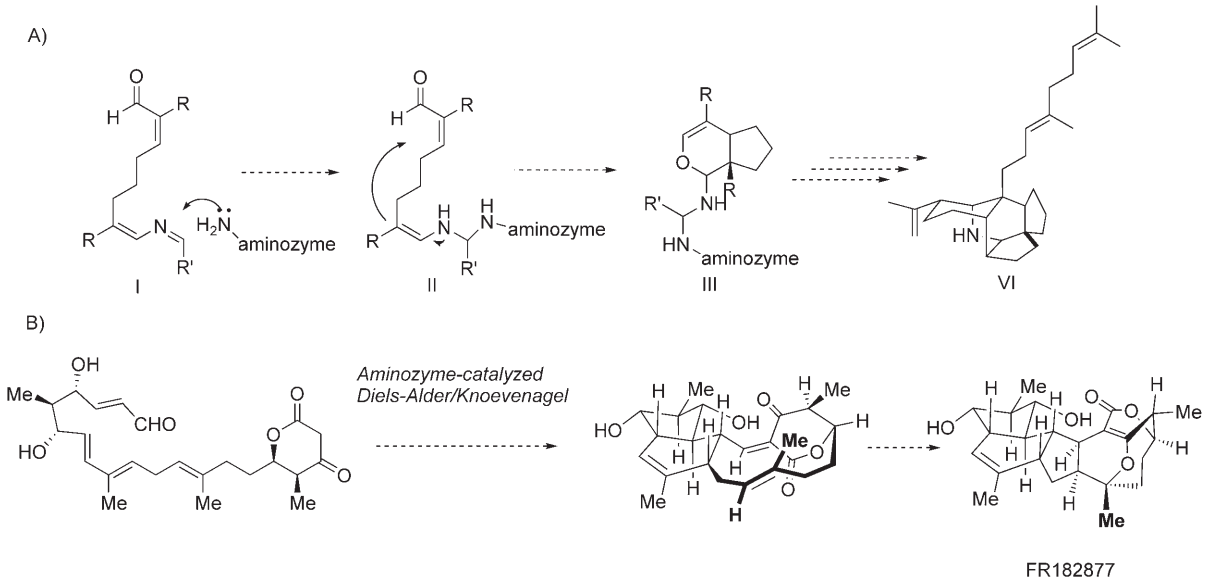
Organocatalysis is an ancient strategy in asymmetric synthesis

Humans discovered the use of asymmetric organocatalysis only recently, and enzymes "discovered" and exploited these concepts much earlier; however, amino acids might be the key primordial prebiotic asymmetric catalysts. In 2002, after our experiments demonstrated that molecules such as carbohydrates, polyketides, and unusual amino acids could be synthesized using organocatalytic asymmetric aldol, Mannich, Diels–Alder, and other reactions, I proposed that organocatalysis might be a key chemistry that could enable the asymmetric prebiotic synthesis of the building blocks of life.[1c,24] Although this hypothesis points to the origin of homochirality through asymmetric synthesis and has subsequently drawn much attention,[25] the question remained how the scales of chirality might be tipped to release the watershed of homochirality we see in the biological world. We know that meteorites carry only slightly enantiomerically enriched amino acids.[26] How then were the first homochiral catalysts made available to the primordial world for asymmetric organocatalysis? The solution of this problem might be at hand in the work of Blackmond, Hayashi, and Breslow, who have demonstrated in complementary studies how even only slightly enantiomerically favored amino acid mixtures can provide access to nearly enantiomerically pure forms of amino acids that might then act to propagate their handedness through asymmetric organocatalysis.[27] Indeed, this simple thermodynamic mechanism, coupled with asymmetric organocatalytic reactions, might have pulled the finger out of the dike of the prebiotic world of molecules, resulting in the flood of homochirality necessary for life as we know it.

Is primordial asymmetric organocatalysis an extant biosynthetic mechanism?

I believe that, in time, research will show that organocatalysts or "aminozymes" (chiral amines or amino acids that play biosynthetic roles) constitute components of an unseen biosynthetic apparatus at work in cells today. As we begin to appreciate the fascinating chemical transformations that are now possible through organocatalysis, and amino acid catalysis in particular, we need to look at cellular metabolism and biosynthesis in a new light. Classically, we are trained to search for a "protein" enzyme for each and every step in the synthesis of a natural product in vivo. I suggest that many of the more elusive metabolic enzymes are likely to be organocatalysts and, in many cases, simple amino acids. Given that intracellular concentrations of amino acids can exceed 1M, many wonderful and diverse exotic natural products may actually be synthesized in vivo with the aid of aminozymes and other forms of organocatalysts more complicated than amino acids.

Clearly, aldol, Michael, and Mannich-type reactions, as well as cascades of such reactions, facilitated in living cells by natural organocatalysts must now be considered. When one revisits previous biogenic posits, with this new perspective, it is easy to see where aminozymes might intervene in biosynthesis. One illustrative example can be found in the Heathcock's proposal for the biosynthesis of the *Daphniphyllum* alkaloids.[28] Here an aminozyme might intervene to affect an enamine-based asymmetric Michael reaction, like those that we have previously described, through the Heathcock intermediate II (Scheme 4). Other interesting examples concerning a particularly elusive class of in vivo reactions that might be catalyzed by aminozymes are Diels–Alder-type reactions. There has been much speculation concerning protein enzymes that catalyze the Diels–Alder reaction that might intercede in the synthesis of



Scheme 4. Potential roles of aminozymes in the biosynthesis of A) the *Daphniphyllum* alkaloids and B) the potential anticancer compound FR182877.

hundreds of known natural products, including polyketides, terpenoids, phenylpropanoids, and alkaloids.[29a–c] Some of these "enzymes" may not be proteins at all. One can predict that the list of biosynthetic routes that incorporate Diels–Alder chemistry will grow significantly with the simple inclusion of the new organocatalytic Diels–Alder reactions, namely the iminium ion based Jung–MacMillan Diels–Alder reaction[4,5b] and our own enamine-based Diels–Alder reaction.[24b,e,f] One potential candidate biogenic reaction of this type is the intramolecular Diels–Alder reaction proposed in the biosynthesis of the potential anticancer natural product FR182877 (Scheme 4).[29d,e] Catalysis mediated by an aminozyme would be expected to facilitate this biosynthetic step, as well as the subsequent Knoevenagel cyclization. Indeed tandem reactions involving Knoevenagel reactions in organocatalysis are now well-known.[21,24e,f,g] Thus one might imagine that amino acids and other aminozymes play an ongoing role in the biosynthesis of molecules in living organisms today.

In conclusion, organocatalysis has made impressive strides in the past seven years. While it is impossible to know with certainty why the Hajos–Wiechert reaction posed an enigma that went unsolved and unexploited for almost 30 years, it is clear that the catalytic asymmetric assembly of complex products from simple starting materials is no longer just in the purview of nature's protein enzymes and perhaps never was. In providing new and highly efficient routes to complex chiral molecules, organocatalysis has made significant inroads into unveiling the source of homochirality in the biological word, and I suggest that organocatalysis may be a yet-to-be-discovered biosynthetic mechanism at work in living organisms today.

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[1] a) The intent of this essay is not to provide an up-to-date survey of the field but rather to provide historical context to the development of enamine/iminium ion based organocatalysis and a perspective regarding its potential importance beyond synthetic organic chemistry. It should be noted that the roots of organocatalysis run as deep as organic chemistry itself (J. von Liebig, *Justus Liebigs Ann. Chem.* **1860**, *113*, 246) and that the area of asymmetric catalysis based on purely organic molecules had been recognized earlier, see R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**; b) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; c) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580 and accompanying articles in this special issue on organocatalysis; d) *Enantioselective Organocatalysis, Reactions and Experimental Procedures* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**.

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