

Enamine Catalysis Is a Powerful Strategy for the Catalytic Generation and Use of Carbanion Equivalents

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ABSTRACT

The chemistry of preformed enamines, especially their use as enolate equivalents, has been a well-investigated area of research since the early 1950s. However, *enamine catalysis*, the catalysis of carbonyl transformations via enamine intermediates by using primary and secondary amines as catalysts, has only been fully appreciated as a powerful strategy for asymmetric synthesis since the beginning of this century. Contributions from this laboratory to the revitalized interest in asymmetric enamine catalysis are summarized in this Account.

Introduction

Carbanions and their equivalents are important intermediates in organic synthesis, and many exceptionally useful reactions rely on their utilization. Examples include classic carbon–carbon bond-forming reactions, such as the Grignard, aldol, and Wittig reactions, but also many modern catalytic asymmetric transformations. The carbanion equivalent is typically generated in an individual step that requires stoichiometric reagents, while the actual bond-forming event with the electrophile takes place in a separate second reaction. Processes in which the carbanion equivalent is not preformed stoichiometrically but generated in situ and catalytically are less studied but have distinct inherent advantages such as atom economy. A main challenge of these *direct* catalytic strategies is that the carbanion generation has to be compatible with the presence of an electrophile. In recent years several attractive solutions to this challenge have been developed and a number of efficient direct catalytic asymmetric reactions, which merge the formation of a carbanion equivalent with its reaction with an electrophile, have been reported. In general, these processes are mediated by either Brønsted- or Lewis bases.

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Brønsted-Base Catalysis

Catalysis with Brønsted bases is initiated via deprotonation of a C–H bond followed by reaction of the resulting carbanion with an electrophile. The direct catalytic aldol reaction of ketones is an important example, and elegant asymmetric Brønsted-base-catalyzed variants have recently been realized.¹ In addition to ketones, other C–H-acidic pro-nucleophiles such as nitroalkanes,² amides,³ alkynes,⁴ isonitrile acetate esters,⁵ amino esters,⁶ and lactones⁷ have been successfully used in direct catalytic asymmetric reactions with different electrophiles. One is not limited to using aldehydes as the electrophile; imines, Michael-acceptors, azodicarboxylates, alkyl halides, or even aryl halides have also been used in such Brønsted-base-catalyzed asymmetric merged carbanion generation, electrophile bond constructions with various C–H-acidic pro-nucleophiles. Selected examples are shown in Scheme 1.

Lewis Base Catalysis

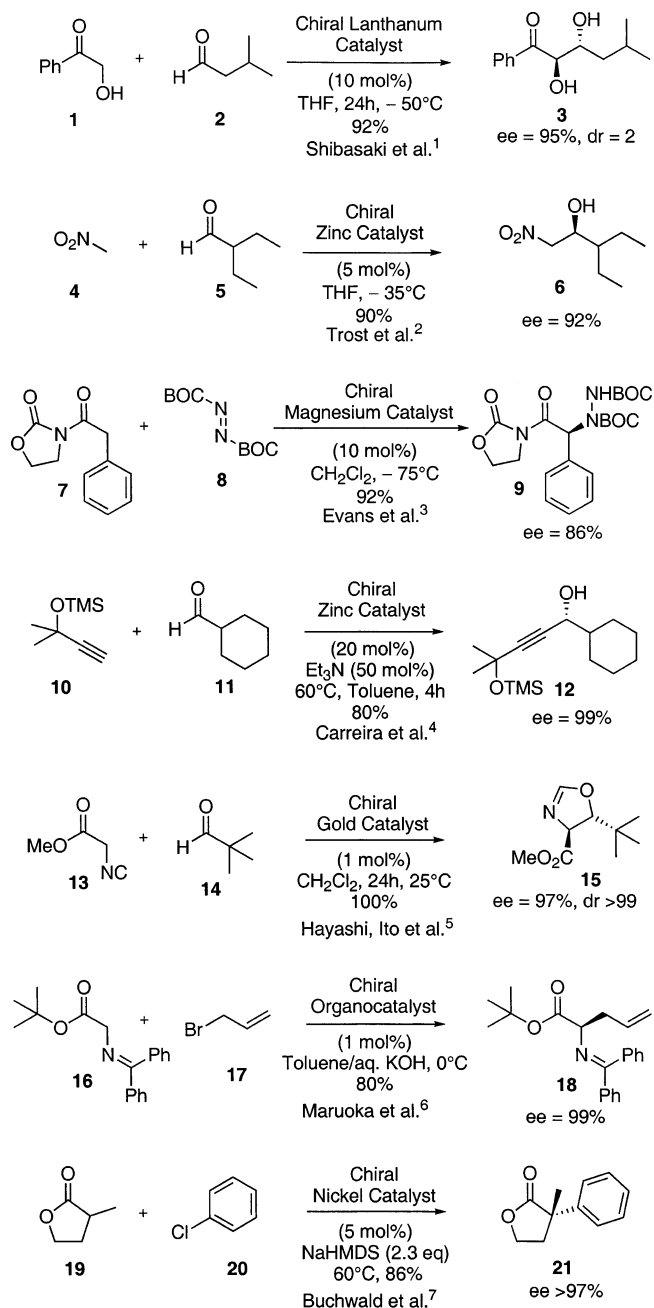
An alternative strategy for the catalytic in situ generation of carbanion equivalents that does not require strong Brønsted bases is *Lewis*-base catalysis. An illustrative example is the Morita–Baylis–Hillmann reaction and its many variations in which a nucleophilic enolate is generated in a reversible conjugate addition of a Lewis-base catalyst to an enone or enoate.⁸ Another example is the chiral Lewis-base-catalyzed reaction of ketenes with electrophiles such as aldehydes or imines that also involve zwitterionic enolate intermediates.⁹

A particularly useful strategy for the catalytic generation and use of carbanion equivalents involves the catalysis of carbonyl transformations by primary and secondary amines via enamine intermediates.¹⁰ The basis of *enamine catalysis* is the reversible and catalytic generation of enamines (**25**) from amines (**22**) and carbonyl compounds (**23**) (Scheme 2). Enamine formation is facilitated by the dramatic increase in C–H-acidity upon initial conversion of the carbonyl compound into an iminium ion (**24**). The catalytically generated enamine (**25**) should be able to undergo addition reactions with various electrophiles ($X = Y$), similarly to the well-studied chemistry of preformed enamines.¹¹ The resulting new iminium ion **26** furnishes, after hydrolysis with in-situ-generated water, the α -substituted carbonyl products **27**.

Enamine catalysis is used by aldolase enzymes,¹² which catalyze direct asymmetric aldol reactions of ketones with aldehydes ($X = Y = RCHO$), and few nonasymmetric variants have been developed as synthetic transformations for the laboratory but have rarely been used during the last century.

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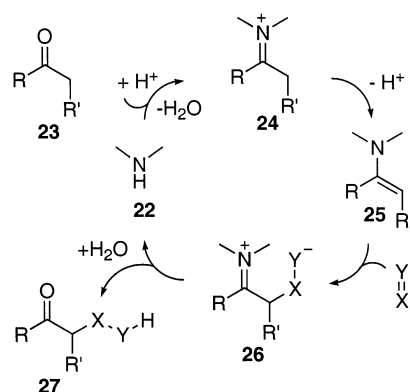
Scheme 1. Examples of Brønsted-Base-Catalyzed Direct Asymmetric Reactions That Merge Carbanion Generation and Bond Construction with an Electrophile



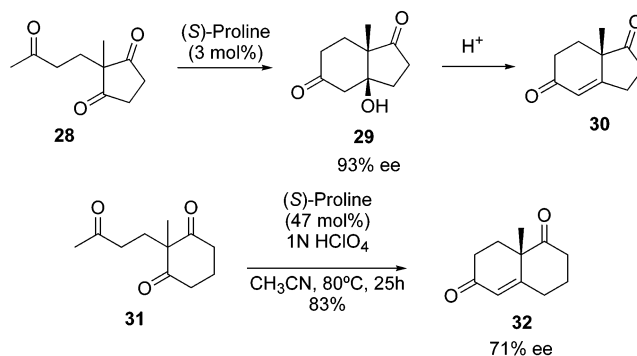
Asymmetric Enamine Catalysis

In 1999 we became interested in using enamine catalysis as a novel strategy for asymmetric synthesis. Our interest in this area was inspired by Class I aldolase enzymes and powerful aldolase catalytic antibodies developed by Lerner and Barbas at The Scripps Research Institute.¹³ We were so fortunate to contribute to parts of these studies, which demonstrated that an efficient enamine catalyst of the direct asymmetric intermolecular aldol reaction could potentially have great synthetic value. Clearly, the development of even more efficient systems that would allow extending this remarkable bioorganic catalytic strategy to a preparatively useful synthetic methodology would be

Scheme 2. Enamine Catalysis



Scheme 3. Hajos–Parrish–Eder–Sauer–Wiechert Reactions



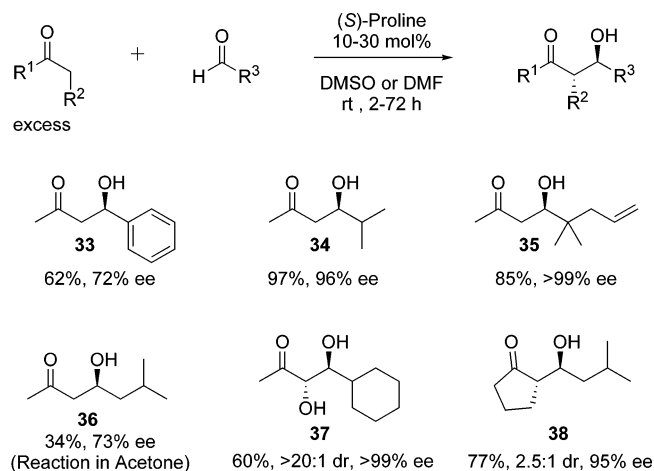
highly desirable. However, at the time, to the best of our knowledge, there was not a single report on using chiral low molecular weight amines as catalysts of the aldolase-like direct catalytic asymmetric intermolecular aldol reaction. We therefore chose as our research program to solve just this problem: Designing and identifying novel small-molecule amine catalysts, now appropriately termed organocatalysts, of the direct asymmetric aldol reaction.

While there were no asymmetric amine catalysts of the intermolecular aldol reaction, an exceptionally elegant approach to intramolecular aldolizations, the Hajos–Parrish–Eder–Sauer–Wiechert reaction, had already been developed by two industrial laboratories in the early 1970s (Scheme 3).¹⁴

The proline-catalyzed intramolecular aldol reaction of triketones to give aldol addition or condensation products such as aldol **29** or enone **32** in good enantioselectivities is the first asymmetric aldol reaction mediated by a small-molecule catalyst instead of an enzyme. As one of the first highly enantioselective catalytic carbon–carbon bond-forming reactions, together with important catalytic asymmetric hydrogenations and oxidation reactions, development of the Hajos–Parrish–Eder–Sauer–Wiechert reaction marks the beginning of not only organocatalysis but modern asymmetric catalysis in general.

For us the most logical starting point in our search for organocatalysts of the intermolecular aldol reaction was therefore the proven catalyst (*S*)-proline. Thus, combining lessons learned from studying aldolase antibodies and the roots of asymmetric catalysis, we decided to investigate proline catalysis of the direct asymmetric aldol reaction, the actual aldolase reaction.

Scheme 4. Proline-Catalyzed Direct Asymmetric Aldol Reaction of Ketones with Aldehydes



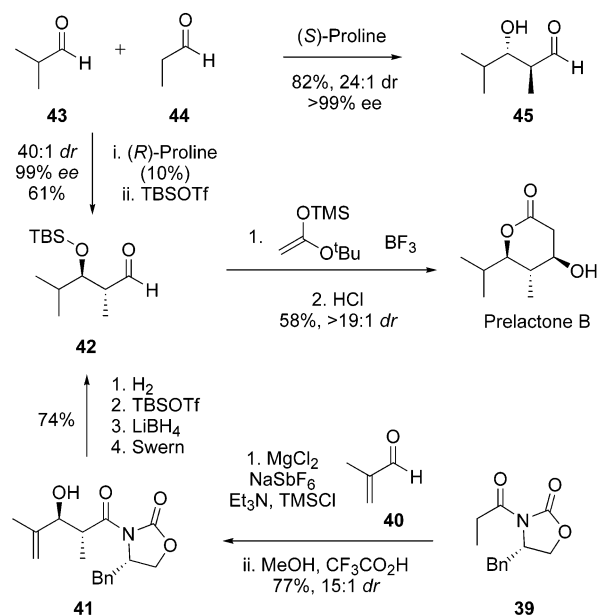
Proline-Catalyzed Direct Asymmetric Intermolecular Aldol Reaction

We found proline to be an efficient catalyst of the direct asymmetric aldol reaction of ketones with aldehydes.¹⁵ Using an excess of the ketone donor component allowed us to isolate cross-aldolization products in good yields and high enantioselectivities in many cases (Scheme 4).

Yields and enantioselectivities depend on the aldehyde component and are typically in the seventies with aromatic aldehydes and in the nineties with α -branched and α -trisubstituted aldehydes. Even α -unbranched aliphatic aldehydes can be used when acetone or ketone/chloroform mixtures were used as the solvent. In this case the yields of the aldol addition products are rarely higher than 40%, and the ee's are also typically in the seventies with acetone. The main side product in these and all other proline-catalyzed aldolizations is the aldol condensation product presumably formed via a Mannich-type mechanism. While clearly far from perfect, the results with α -unbranched aldehydes represented the state-of-the-art in the field and alternative catalysts by no means outperformed proline catalysis. Besides acetone, other ketones that can generally be used include cyclopentanone, cyclohexanone, and hydroxyacetone.

An exceptionally useful variant of the proline-catalyzed intermolecular aldol reaction was recently introduced by MacMillan et al.,¹⁶ who demonstrated that α -unbranched aldehydes can be used as donors in the reaction with aldehyde acceptors. For example, propionaldehyde (**44**) reacts with isobutyraldehyde (**43**) to give the corresponding aldol (**45**) in >99% ee (Scheme 5). The product of this reaction has recently been used in an extremely efficient and short synthesis of prelactone B (Scheme 5).¹⁷ For comparison, a state-of-the-art synthesis that appeared shortly thereafter utilizing an Evans auxiliary strategy is shown as well.¹⁸ By removing several of the protecting and functional-group interchanges, the proline-catalyzed route shortens the required steps to the natural product from a total of eight to only three steps, illustrating significant advancements of proline catalysis.

Scheme 5. Proline-Catalyzed Direct Asymmetric Aldol Reaction in a Synthesis of Prelactone B



First Catalytic Asymmetric Enolexo Aldol Reactions

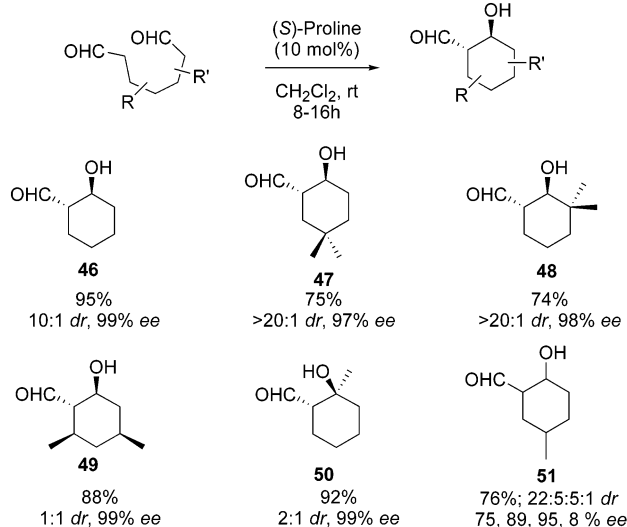
The Hajos–Parrish–Eder–Sauer–Wiechert reaction is a 6-enolendo aldolization, and all described intramolecular proline-catalyzed aldolizations follow this cyclization mode. However, the alternative enolexo–aldolization is also a favored process and nonasymmetric enamine catalytic variants are known. We found that proline catalyzes the enolexo–aldolization of heptanedials and keto aldehydes with high enantioselectivity.¹⁹ The corresponding cyclohexane products are obtained with excellent enantioselectivities (Scheme 6).

Mechanism of the Proline-Catalyzed Aldol Reaction

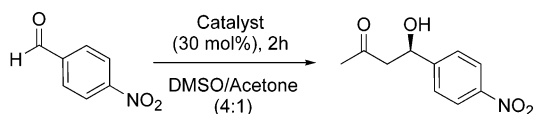
Initially, only limited mechanistic information was available on the proline-catalyzed intermolecular aldol reaction. Most of what we knew came from an investigation of alternative catalysts (Scheme 7).

We found that simple primary amino acids did not catalyze the intermolecular aldol reaction of acetone with *p*-nitrobenzaldehyde, although it was known that phenylalanine could be a good catalyst for Hajos–Parrish–Eder–Sauer–Wiechert reactions. Thus, apparently a secondary amine is required at least in the intermolecular reaction. However, acyclic secondary amino acids such as *N*-methyl valine are not catalytic, and from the studied cyclic amino acids, proline, azetidine carboxylic acid, and pipercolic acid, proline proved to be the best catalyst. That pipercolic acid is not catalytic may be viewed as surprising. However, from Stork's seminal work on the chemistry of enamines, it was known that pyrrolidines much more readily form enamines with carbonyl compounds if compared to piperidines.¹¹ In addition, the corresponding pyrrolidine

Scheme 6. Proline-Catalyzed Enolexo–Aldolizations



Scheme 7. Selected Catalysts Investigated

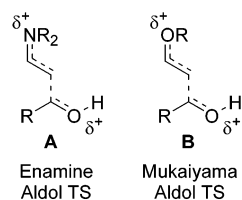


Catalyst	Yield	ee
(L)-His, (L)-Val (L)-Tyr, (L)-Phe	< 10%	n. d.
	< 10%	n. d.
	55%	40%
	68%	76%
	< 10%	n. d.
	< 10%	n. d.
	< 10%	n. d.

enamines are more nucleophilic. Additional evidence for covalent catalysis and an enamine mechanism came for the result with *N*-methyl proline, which proved to be completely inactive as catalyst. Concerning the role of the carboxylate, we found that proline amide is an inferior catalyst showing essentially no product after 2 h, and only after several days was the aldol product obtained with low enantioselectivity (22% ee).

With these limited studies in hand, we proposed an enamine catalysis mechanism involving carbinoamine, iminium ion, and enamine intermediates, which is essentially identical to the accepted mechanism of class I aldolases (Scheme 8). The carboxylic acid was proposed

to act as a general-purpose Brønsted cocatalyst, replacing the several acid/base functional groups involved in the aldolase mechanism. In the transition state of the carbon–carbon bond formation we proposed protonation of the acceptor carbonyl group by the carboxylic acid, which is anti with respect to the (*E*)-enamine double bond. We later learned from the work of K. N. Houk and his group who proposed a similar transition state for the intramolecular variant that a simultaneous hydrogen bond to the enamine nitrogen, which we initially invoked, does not further contribute to lowering the energy of the transition state.²⁰ Their DFT calculations seemed plausible to us, particularly as the enamine nitrogen becomes partially positively charged in the transition state. Earlier, our introduction of the additional NH hydrogen led to a metal-free version of the familiar Zimmermann–Traxler-type transition state. However, the general transition state of the secondary amine-catalyzed aldol reaction (A) seems to be instead related to the open transition state of an acid-catalyzed Mukaiyama aldolization (B).



In this context, proline happens to not only act as an enamine catalyst, but also brings with it its own Brønsted-acid cocatalyst. While the resulting transition state is a nine-membered ring, it is still superior to alternative open transition states involving intermolecular acid catalysis.

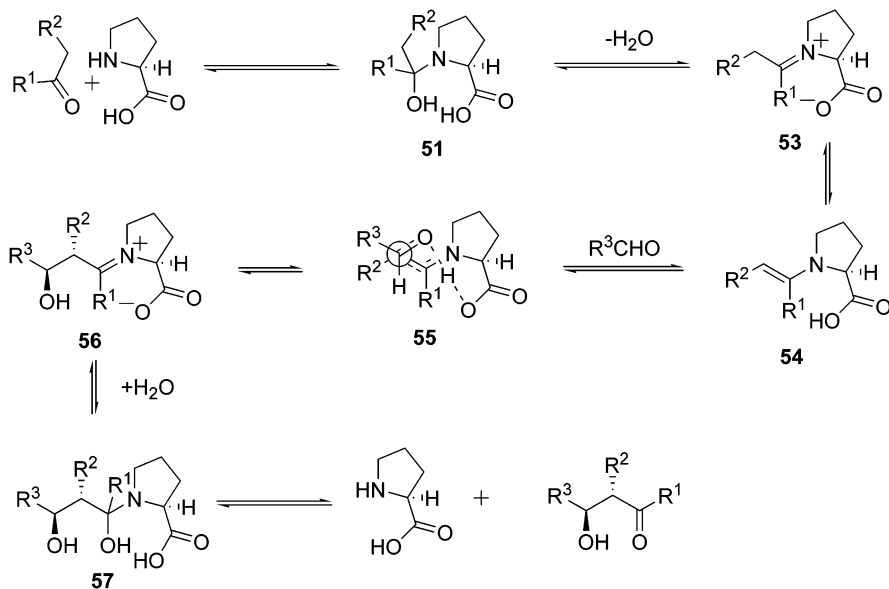
Although our mechanistic proposal seemed both plausible according to theory and similar to the known mechanism of class I aldolases, it stood against the formerly accepted mechanism of the intramolecular Hajos–Parrish–Eder–Sauer–Wiechert reaction. On the basis of an observed small negative nonlinear effect in the asymmetric catalysis, Agami et al. proposed a transition state that involved two proline molecules (B, Scheme 9).²¹

However, in a recent carefully conducted study, nonlinear effects could not be confirmed in both inter- and intramolecular aldol reactions (Scheme 10).²² Theoretical studies by the Houk group also supported a one-proline mechanism.

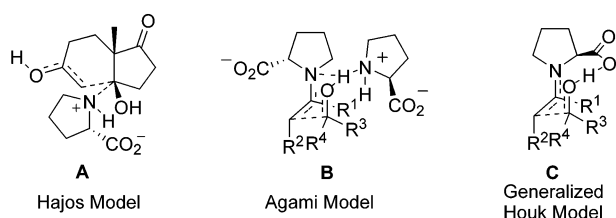
Hajos et al. proposed an alternative mechanism that does not involve enamine intermediates.^{14a} Accordingly, proline “activates” one of the two enantiotopic acceptor carbonyl groups as a carbinol amine (A, Scheme 9). The basis of the Hajos model was the surprising observation that if the reaction was conducted in the presence of O-18-enriched water, no O-18 was incorporated into the product. However, important details of these experiments have never been published. Unless unusual effects were operative, the proposed enamine mechanism requires O-18 incorporation since a hydrolysis step is involved (Scheme 11).

We studied the Hajos–Parrish–Eder–Sauer–Wiechert cyclization of ketones **28** and **31** to give the corresponding

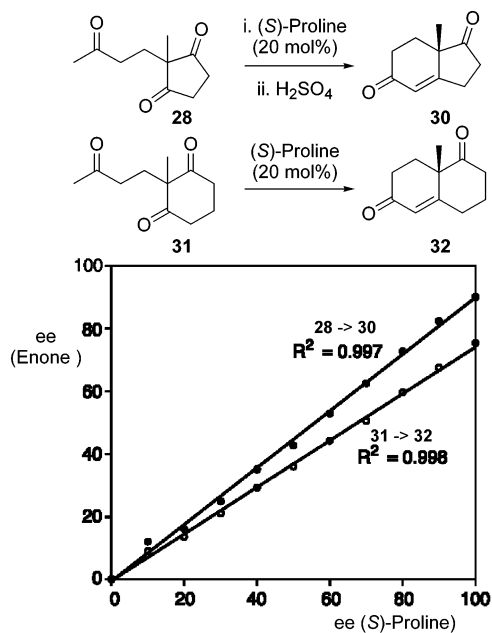
Scheme 8. Proposed Mechanism of the Proline-Catalyzed Intermolecular Aldol Reaction



Scheme 9. Selected Transition-State Models for the Proline-Catalyzed Aldol Reaction

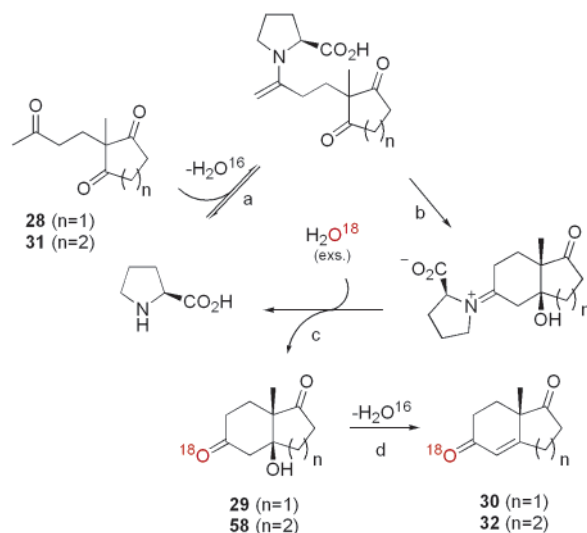


Scheme 10. No Nonlinear Effects in the Hajos–Parrish–Eder–Sauer–Wiechert Reaction



aldol addition (**29** and **58**) or condensation products (**30** and **32**) in the presence of O-18-enriched water (Aldrich 95% O-18). When the reactions were performed under completely air- and moisture-free conditions (except, of course, for the purposely added water), high O-18 incorporation was observed.²³ According to a GCMS experi-

Scheme 11. Proposed Enamine Catalysis Cycle of the Hajos–Parrish–Eder–Sauer–Wiechert Reaction Requires O-18 Incorporation When the Reaction Is Performed in the Presence of O-18-Enriched Water

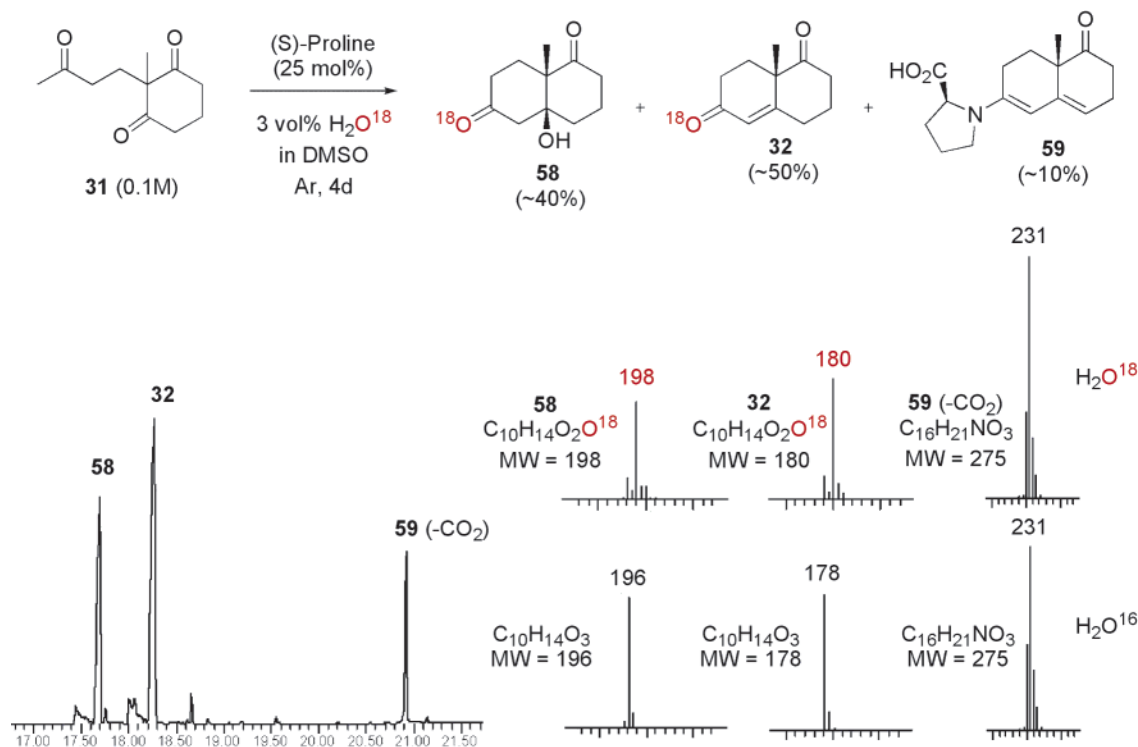


ment, triketone **31** in the presence of proline (25 mol %) and O-16- or O-18-enriched water (3 vol %) gave, after 4 days reaction time, ca. 40% of the aldol addition product **58**, 50% of the aldol condensation product **32**, and 10% of dienamine **59** as detected by GC (Scheme 12). In the H₂O¹⁸ experiment, the aldol products were O-18 labeled (ca. 90%) at the side-chain oxygen, consistent with the proposed enamine mechanism.

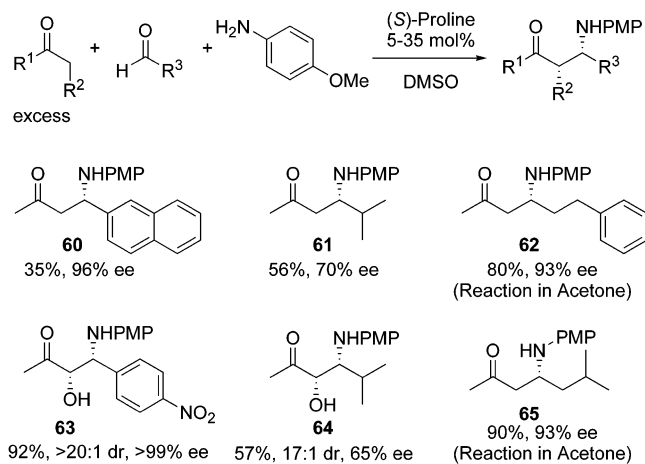
First Proline-Catalyzed Mannich Reaction

With an increased mechanistic understanding of the proline-catalyzed aldol reaction, we wondered whether the principle of asymmetric enamine catalysis could be extended beyond nature's aldol reaction. We were particularly fascinated by the prospect of replacing the aldehyde with other electrophilic components, and the

Scheme 12. O-18-Incorporation Experiment



Scheme 13. Proline-Catalyzed Direct Asymmetric Three-Component Mannich Reaction



next logical step for us was to look at imines. Specifically, we hoped that the mild conditions of proline catalysis would be compatible with an in-situ generation of the imine, realizing a direct asymmetric three-component Mannich reaction. Only Shibasaki et al. have previously approached this transformation with partial success.²⁴

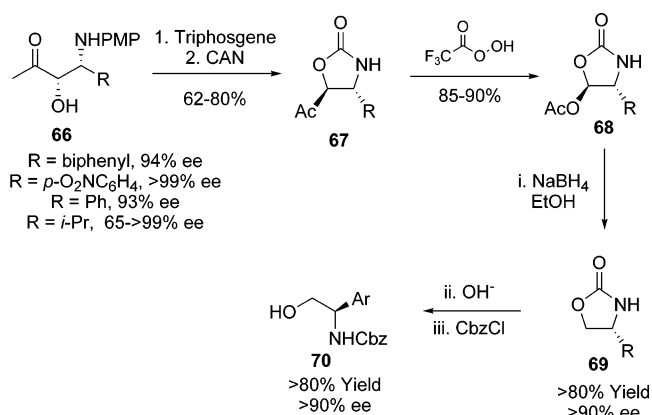
We found that proline indeed catalyzes the direct asymmetric three-component Mannich reaction of ketones (used in excess) with aldehydes and *p*-anisidine with remarkable results.²⁵ Generally, high ee's and dr's could be achieved, again strongly depending on the aldehyde component. However, all trends previously observed in the proline-catalyzed aldol reaction were now inverted (Scheme 13). First, the enantiofacial selectivity of the imine was *si*, opposite to the observed aldehyde *re* faciality of

the aldol reaction. Consequently, the major product had the opposite absolute configuration at the stereogenic center bearing the heteroatom. The diastereoselectivity was also inverted with *syn*-products in the Mannich and *anti*-products in the aldol reaction. Moreover, aromatic aldehydes gave high ee's (>90%) in the Mannich reaction but only around 70% in the aldol reaction. With branched aldehydes the situation was opposite with 70% ee or even lower in the Mannich reaction and high ee's (>90%) in the aldol reaction. Excitingly, α -unbranched aldehydes typically gave very good ee's and yields in the Mannich reaction whereas in the aldol reaction they proved to be a most challenging substrate class.

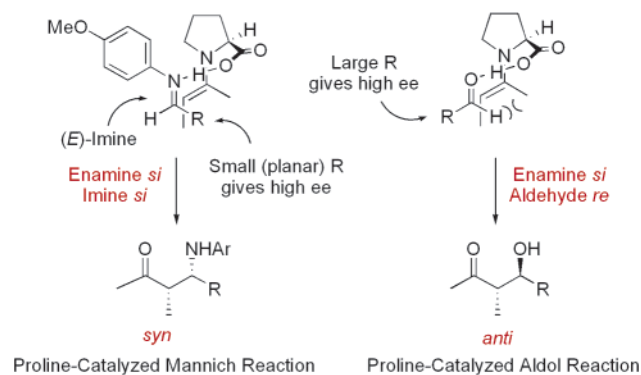
We developed a novel synthesis of amino acid derivatives from the β -amino alcohol products of the highly efficient and selective proline-catalyzed Mannich reactions with hydroxy acetone as the ketone component (Scheme 14).²⁶ Treatment of the produced amino alcohols **66** with triphosgene followed by cerium ammonium nitrate gave 5-acyl oxazolidinones **67**. Bayer–Villiger oxidation provided 5-acetoxy oxazolidinones **68**, which represent a novel synthetic equivalent of α -amino aldehydes. Interestingly, treatment with NaBH₄ furnished unsubstituted oxazolidinones **69** in high yields. The workup can also be modified to give protected aryl glycinols **70** in good yields and ee's.

A mechanistic model that accounts for the observed inverse trends in proline-catalyzed aldol and Mannich reactions is shown in Scheme 15. The in-situ-formed *E*-imine can approach the proline-derived enamine only with its *si* face because in the alternative *re* approach the *N*-aryl substituent underwent nonbonding interactions with the carboxylic acid moiety. Our proposed transition-

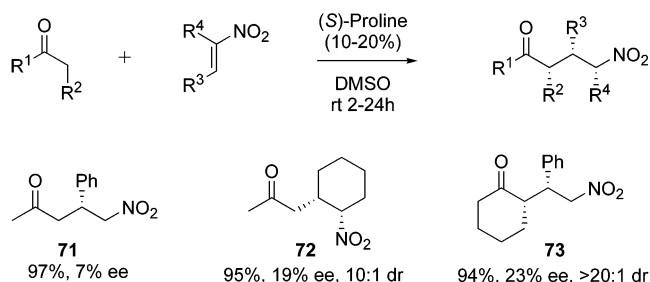
Scheme 14. New Synthesis of Protected Amino Alcohols and Oxazolidinones



Scheme 15. Transition-State Models for Proline-Catalyzed Aldol and Mannich Reactions



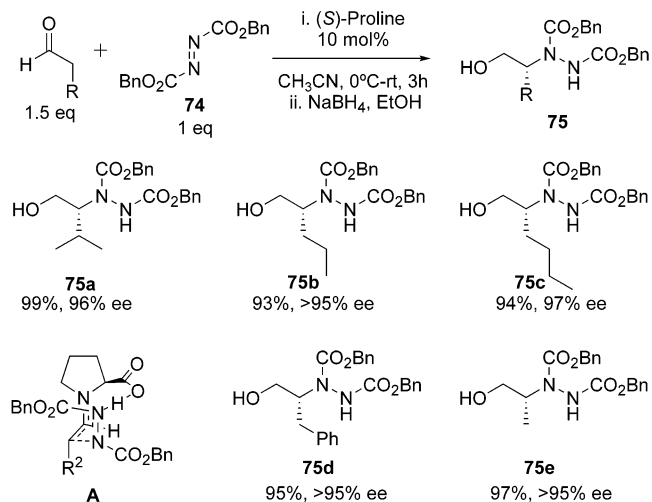
Scheme 16. First Proline-Catalyzed Direct Asymmetric Michael Reaction Was Only Modestly Enantioselective



state model is consistent with recent calculations by Houk et al.²⁷

First Direct Asymmetric Proline-Catalyzed Michael Reaction

As an alternative electrophilic species, Michael acceptors seemed promising. However, it turned out that the reaction of ketones with nitro olefins, although highly efficient, was only poorly enantioselective (Scheme 16).²⁸ In general, proline-catalyzed Michael reactions via enamine mechanisms seem to be less enantioselective than aldol and Mannich reactions, independent of the Michael acceptor. We published our studies nonetheless as they demonstrated for the first time that it is possible to perform

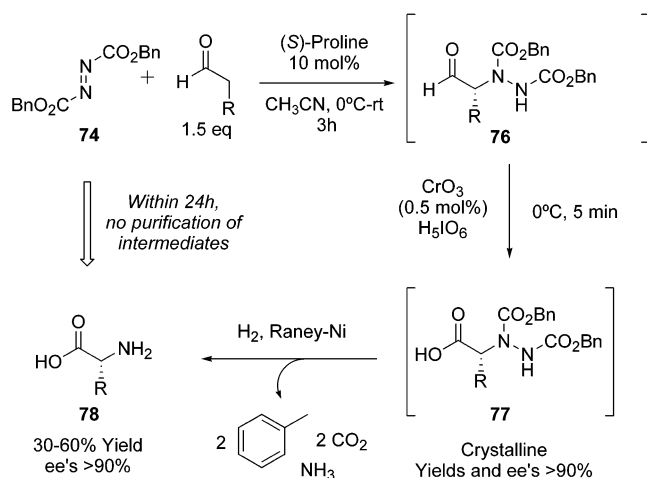
Scheme 17. First Direct Asymmetric α -Amination of Aldehydes

asymmetric enamine-catalytic Michael reactions and also because the produced γ -nitro ketones are valuable synthetic intermediates, for example, in the synthesis of pyrrolidines. Later work by several other groups including those of Enders, Barbas, and Alexakis further improved the reaction by either optimizing the reaction conditions or designing novel catalysts.²⁹

First Direct Asymmetric α -Amination of Aldehydes

One conclusion we drew from our studies on the Michael reaction was that in general the electrophile $X = Y$ should have an electron lone pair at Y. This lone pair may be crucial for effective asymmetric induction in proline-catalyzed reactions with carbonyl compounds presumably to induce effective H-bonding to proline's carboxylate in the transition state. Consistent with this notion were the exceptionally high enantioselectivities we observed when we used dialkyl azodicarboxylates as the electrophile in the reaction with α -unbranched aldehydes.³⁰ Previous studies established that, in addition to ketones, α -unbranched aldehydes can be used as donors in enamine catalysis both with aldolase enzymes as well as with proline and other aminocatalysts.³¹ We found that when a mixture of proline (10 mol %), the α -unbranched aldehyde (1.5 equiv), and dibenzyl azodicarboxylate (**74**, 1 equiv) reacted at 0 °C, the corresponding α -hydrazino aldehydes are obtained in high yields and ee's. Since α -hydrazino aldehydes tend to racemize upon standing at room temperature, they were generally isolated as the corresponding stable and crystalline α -hydrazino alcohols **75** in excellent yields and ee's (Scheme 17). Similar results were independently reported by Jørgensen et al.³²

The observed enantioselectivity of the reaction is consistent with transition-state **A** (Scheme 17), which is very similar to the proposed transition state of the proline-catalyzed Mannich reaction. Currently, we establish a novel straightforward synthesis of amino acids and related derivatives via a proline-catalyzed α -amination reaction. A simple oxidation of the aldehyde intermediate **76** gives

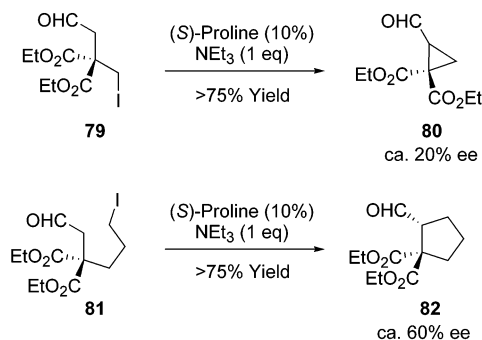
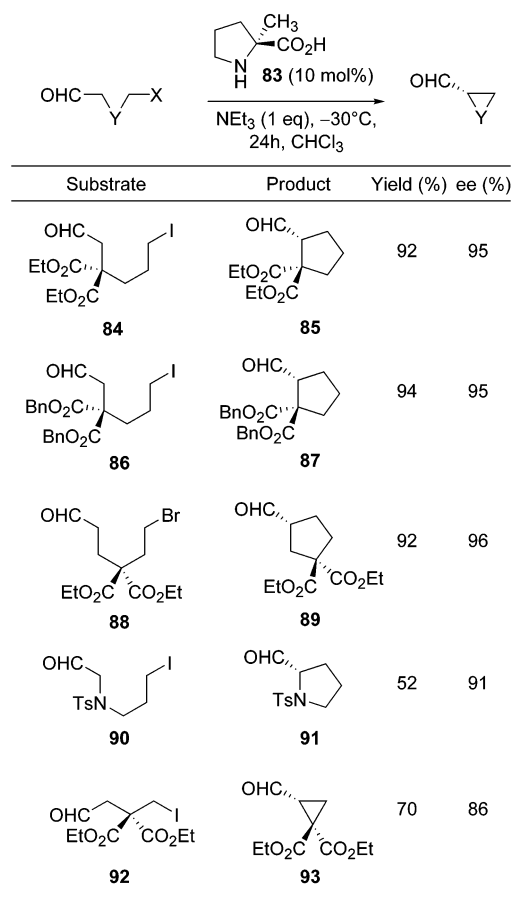
Scheme 18. Direct Catalytic Asymmetric α -Amination in the Synthesis of α -Amino Acids

chiral nonracemic α -hydrazino carboxylic acids **77**, which found interesting applications themselves in certain peptidomimetics. Reductive N–N bond cleavage and simultaneous protecting-group removal provides unprotected α -amino acids **78** with excellent ee's together with only volatile material (Scheme 18).³³ The currently developed route is highly enantioselective and practical and delivers the desired novel amino acid in less than 24 h. However, the critical step at this point is not the organocatalysis or the oxidation, but rather the reductive hydrazine cleavage, which requires further optimization.

Beyond Enamine Catalysis of Nucleophilic Additions: First Catalytic Asymmetric α -Alkylation of Aldehydes

We recently embarked upon a challenging reaction: the enamine-catalytic α -alkylation of carbonyl compounds with alkyl halides. Catalytic asymmetric α -alkylation reactions are highly desirable as they lead to α -branched carbonyl compounds of great value for organic synthesis. Current enantioselective approaches are mostly based on auxiliary technologies such as those developed by Meyers, Evans, and Enders.³⁴ While few reports exist on catalytic asymmetric α -alkylations of ketones and glycine-derived esters,³⁵ catalytic asymmetric α -alkylations of aldehydes are completely unknown. There are several problems associated with a potential amine-catalyzed version, including (1) self-aldolization of the aldehyde, (2) N-alkylation of the enamine intermediate or the amine catalyst, and (3) racemization of the product.

Not surprisingly, initial experiments failed: for example, reacting propionaldehyde with benzylbromide in the presence of a catalytic amount of proline and 1 equiv of triethylamine furnished only the products of proline alkylation, *N*-benzylproline and *N*-benzylproline benzy-lester. We therefore focused on an intramolecular variant, which should be more facile. Indeed, the proline-catalyzed reaction of 3- and 5-halo aldehydes in the presence of 1 equiv of triethylamine readily provided the corresponding cyclic products in good yields (Scheme 19).

Scheme 19. Two Proline-Catalyzed Intramolecular α -Alkylations of AldehydesScheme 20. Catalytic Asymmetric α -Alkylation of Aldehydes

Although the enantioselectivity was still modest, these experiments showed that asymmetric catalysis of the reaction was indeed possible and that the development of highly enantioselective systems may be just a matter of optimizing the reaction conditions or screening for alternative catalysts. After some experimentation we found that commercially available α -methyl proline catalyzes the intramolecular alkylation of various halo aldehydes to the corresponding formyl-substituted cyclopentanes, cyclopropanes, or pyrrolidines in excellent yields and enantioselectivities (Scheme 20).³⁶

Developing an intermolecular variant of this reaction as well as establishing other cyclization modes is currently of high interest in our laboratory.

Summary and Outlook

Taken together, the results we and others have obtained over the past few years convinced us that asymmetric enamine catalysis is not only an elegant catalytic strategy of certain enzymes but also a quite powerful approach for the catalytic generation and use of chiral, nonracemic carbanion equivalents. The scope of enamine catalysis is increasing constantly, and new catalysts are being developed.³⁷ Already it has become clear that the versatility of this approach is broader than anticipated and enamine catalysis is compatible with an increasing number of electrophiles including aldehydes, ketones, imines, Michael acceptors, dialkyl azodicarboxylates, nitrosobenzene,³⁸ and, last but not least, alkyl halides.

Clearly, the Hajos–Parrish–Eder–Sauer–Wiechert reaction is not confined to what it was originally conceived. Rather than a mechanistically poorly understood industrial steroid process that never became a reality, it constitutes the tip of the iceberg of a novel catalytic principle, of which the entire scope still remains to be fully uncovered.

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