

Asymmetric Aminocatalysis

Benjamin List*

Departments of Chemistry and Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, USA

Fax +1(858) 784 7028; E-mail: blist@scripps.edu

Received 13 August 2001

Abstract: This account focuses on novel amine-catalyzed reactions recently discovered in our laboratories. Among the newly developed transformations are efficient proline-catalyzed intermolecular aldol, Mannich, Michael reactions and a novel three-component reaction.

- 1 Introduction
- 2 The Intermolecular Hajos–Parrish–Eder–Sauer–Wiechert Reaction
- 3 Proline-Catalyzed Direct Asymmetric Aldol Reactions
- 3.1 Acetone as the Aldol Donor
- 3.2 Proline-Catalyzed Aldol Reactions with Other Ketones
- 4 Mechanism of the Proline-Catalyzed Aldol Reaction
- 5 Potential and Limitations of Enamine Catalysis
- 6 The Direct Asymmetric Three-Component Mannich Reaction
- 7 Enamine Catalysis of the Michael Reaction
- 8 Combining Enamine and Iminium Catalysis in the Design of a Novel Multicomponent Reaction
- 9 Conclusions

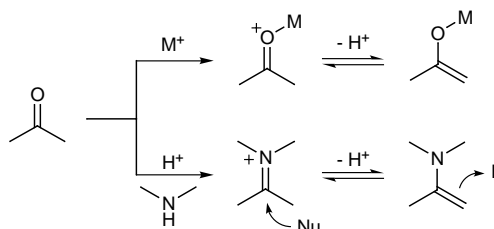
Key words: aminocatalysis, organocatalysis, asymmetric Catalysis, aldol reactions, Mannich reactions, Michael reactions, Multi-component reactions

1 Introduction

Modern organic synthesis is very efficient in constructing functional molecules of enormous complexity. Nevertheless, it seems to rely on only a relatively short list of privileged chemical reactions.¹ Our interest in developing new synthetic methodologies is fueled by an ever-increasing demand for practically useful transformations to extend this list.

Several important processes utilize the chemistry of carbonyl compounds. These reactions typically involve metals and can be catalyzed by Lewis- or Brønsted acids and bases. We recently embarked upon the question whether or not several carbonyl transformations could also be catalyzed by amines. This concept is based on electronic similarities between a protonated (or Lewis-acid activated) carbonyl group and an iminium ion. The reactivity of these species is dramatically enhanced and both, electrophilicity and α -C-H-acidity increase (Scheme 1).^{2,3}

There are two aminocatalytic pathways. Iminium catalysis directly utilizes the higher reactivity of the iminium



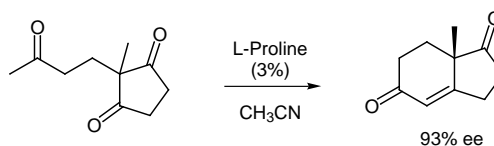
Scheme 1 Activation of the carbonyl group by acids (M^+) and by amines

ion in comparison to the carbonyl species and facilitates Knoevenagel-type condensations,⁴ cyclo- and nucleophilic additions,^{5,6} and cleavage of σ -bonds adjacent to the α -carbon.^{7,3c} Enamine catalysis on the other hand involves catalytically generated enamine intermediates that are formed via deprotonation of an iminium ion, and react with various electrophiles or undergo pericyclic reactions.^{8,2b}

Several valuable and broadly applicable transformations, including, aldol, Michael, Mannich, and Diels–Alder reactions are amenable to aminocatalysis. This account summarizes recent contributions from our laboratory to this exciting area of organocatalysis.

2 The Intermolecular Hajos–Parrish–Eder–Sauer–Wiechert Reaction

Aminocatalysis is a biomimetic strategy used by important enzymes such as class I aldolases (enamine catalysis) and ketoacid decarboxylases (iminium catalysis).^{9,3c} Applications in asymmetric organic synthesis are relatively rare despite the well-known Hajos–Parrish–Eder–Sauer–Wiechert process,^{10,11} a proline-catalyzed reaction that most likely involves enamines (Scheme 2).^{12,13}

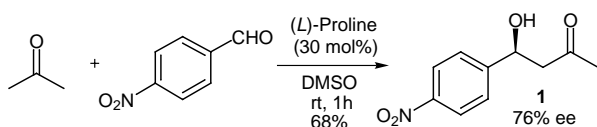


Scheme 2 The Hajos–Parrish–Eder–Sauer–Wiechert reaction

Our interest in aminocatalysis is based on this remarkable reaction and on studying enamine catalytic aldolase antibodies developed in the laboratories of Lerner.^{14–19} Like natural class I aldolases these antibodies catalyze asym-

metric aldol reactions between ketones and aldehydes. This “direct” approach to the catalytic asymmetric aldol reaction has recently been introduced as a synthetic method by Shibasaki et al.^{20,21,22}

We initially asked a seemingly simple question: If proline catalyzes *intramolecular* aldol reactions using an enamine mechanism like natural and antibody aldolases, could it also catalyze the *intermolecular* aldol reaction? The Hajos–Parrish–Eder–Sauer–Wiechert reaction is an intramolecular process and the type of enantioselectivity (enantioselectivity) is distinct from the π -enantioselectivity required for asymmetric aldol addition reactions. Furthermore, it is known that proline reacts with both aliphatic and aromatic aldehydes.²³ These facts considered, it was by no means clear that proline would also catalyze intermolecular aldol reactions. Nevertheless, in May 1999 we conducted the experiment and were delighted to find that (L)-proline catalyzed the reaction of *p*-nitrobenzaldehyde with an excess of acetone to furnish the aldol product in 76% ee (Scheme 3).²⁴



Scheme 3 The first proline-catalyzed asymmetric intermolecular aldol reaction

This particular experiment constitutes the first low molecular weight amine-catalyzed direct asymmetric aldol reaction and was the starting point for the experiments described in this account.

3 Proline-Catalyzed Direct Asymmetric Aldol Reactions

3.1 Acetone as the Aldol Donor

We have studied the proline-catalyzed aldol reaction of acetone with several aromatic aldehydes and found the products to be formed with good ee's (Table 1, entries 1–5). α -Substituted aliphatic aldehydes gave the products in

even higher enantioselectivities (entries 6–9). For example the use of isobutyraldehyde resulted in the formation of aldol **6** in 96% ee and 97% yield. Later we observed excellent (>99%) enantioselectivities in aldol reactions of acetone with tertiary aldehydes.^{25,27} Direct and indirect asymmetric aldol reactions with acetone (or equivalents) as the donor are generally considered to be very challenging and our results compare well with many of the best known catalyst- or auxiliary based procedures.^{20,21,26,28}

α -Unbranched aldehydes did not produce the desired products under our standard conditions using DMSO as the solvent. Homo-aldol-addition- and condensation of the aldehyde or elimination of the cross-aldol product to the α,β -unsaturated ketone appeared to be the main side reactions. However, after screening several solvents, we found that by using acetone or acetone/ CHCl_3 mixtures, the cross-aldol products were obtained in modest yields and good enantioselectivities (Table 2).²⁷ The only substantial side-products observed in these reactions, are the cross-aldol *condensation* products and the homo-aldol addition product of acetone. Yields and ee's are rather modest but comparable to those obtained using Shibasaki's and Trost's catalysts.^{20,21,28} Advantages of the proline-catalyzed reactions include operational simplicity and availability of both enantiomeric catalysts. The reactions can easily be performed on a multi-gram scale, required for complex molecule syntheses. This was demonstrated with a short synthesis of (*S*)-ipenol (**17**), a major component of the sex pheromone of the bark beetle and needed in kg-quantities for insect traps.^{29,30} Our synthesis used aldol **13** as the starting material, which was protected and converted to enoltriflate **15**. Subsequent Stille coupling with vinyltributylstannane furnished known diene **16**, which after deprotection gave natural (*S*)-ipenol (Scheme 4). This synthesis is one of the shortest disclosed and highlights the potential of the proline-catalyzed aldol reaction for the asymmetric synthesis biologically active compounds.

3.2 Proline-Catalyzed Aldol Reactions with Other Ketones

After evaluating the acceptor-scope of the proline-catalyzed aldol reaction we next focused on the use of other

Biographical Sketch

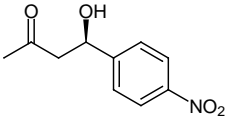
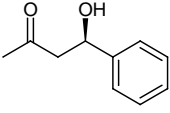
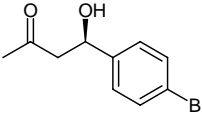
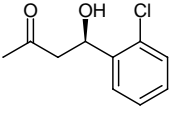
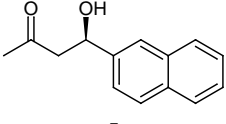
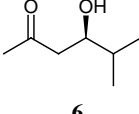
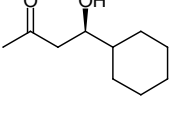
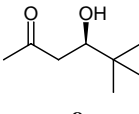
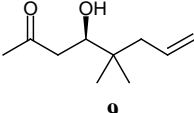


Benjamin List was born in Germany in 1968. He studied chemistry at the Free University of Berlin where he obtained a Diploma (*summa cum laude*) in 1993. He received his Ph.D. in 1997 from the Johann Wolfgang Goethe-University in

Frankfurt working in the field of natural product synthesis under the supervision of Prof. J. Mulzer. He spent nearly two years as a post-doctoral research associate in the laboratories of Prof. R. A. Lerner at the Scripps Research Institute studying

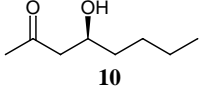
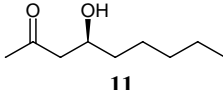
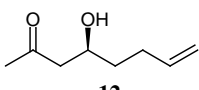
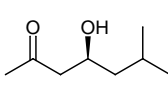
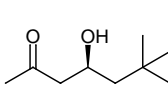
catalytic antibodies. In January 1999 he became an Assistant Professor at Scripps. His research interests include catalysis, new reaction methodologies and bioorganic chemistry.

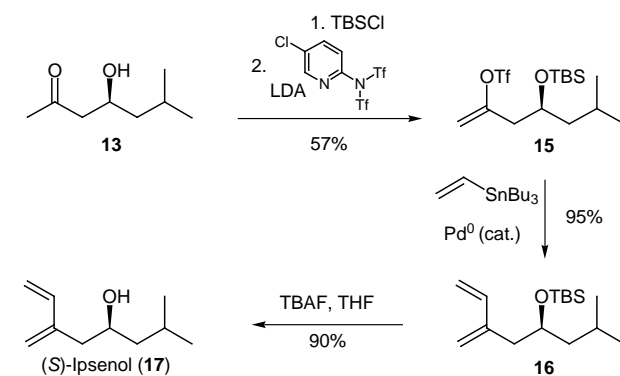
Table 1 Proline-Catalyzed Aldol Reactions of Acetone with Several Aldehydes

Entry	Product	Yield	ee
1		68%	76%
2		62%	60%
3		74%	65%
4		94%	69%
5		54%	77%
6		97%	96%
7		63%	84%
8		81%	>99%
9		85%	>99%

donors. We could establish that a variety of cyclic and acyclic ketones including butanone, cyclopentanone, and cyclohexanone furnish the products in useful regio-, dia-

Table 2 Proline-Catalyzed Aldol Reactions of Acetone with α -Unbranched Aldehydes

Entry	Product	Yield	ee
1		31%	67%
2		35%	73%
3		34%	72%
4		34%	73%
5		22%	36%

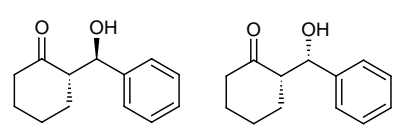
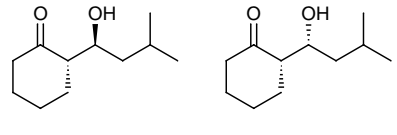
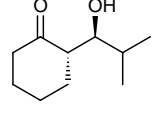
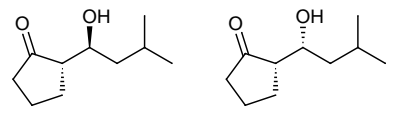
**Scheme 4** Asymmetric total synthesis of (*S*)-iposenol

stereo-, and enantioselectivities (Table 3).^{25,27} Unfortunately, other important ketones, including acetophenone and 3-pentanone failed in these reactions.

Among the ketones studied so far, remarkable results were obtained with hydroxyacetone. We found that hydroxyacetone typically reacts with aldehydes to furnish the corresponding *anti*-1,2-diols in high regio-, diastereo- and enantioselectivities (Table 4).³¹

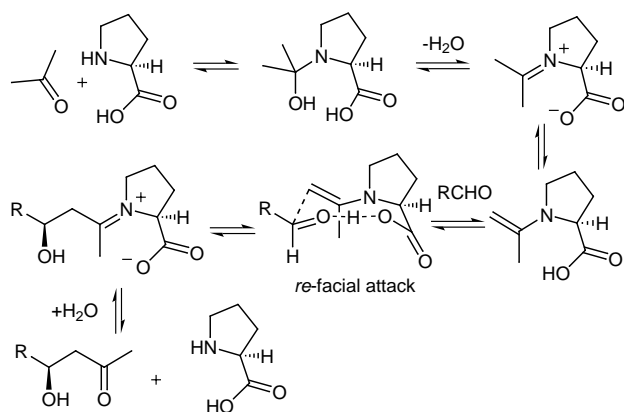
Our method represents the first catalytic asymmetric synthesis of *anti*-1,2-diols and complements the Sharpless asymmetric dihydroxylation, which provides *syn*-diols from (*E*)-olefins in high ee's but gives rather low ee's in the synthesis of *anti*-diols from (*Z*)-olefins.³²

Table 3 Some Proline-Catalyzed Aldol Reactions with Cyclic Ketones

Products	Yield	<i>anti:syn</i>
 <i>anti</i> - 18 (85% ee) <i>syn</i> - 18 (76% ee)	85%	1:1
 <i>anti</i> - 19 (86% ee) <i>syn</i> - 19 (89% ee)	41%	7:1
 <i>anti</i> - 20 (97% ee)	68%	>20:1
 <i>anti</i> - 21 (95% ee) <i>syn</i> - 21 (20% ee)	77%	2.5:1

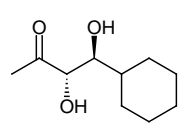
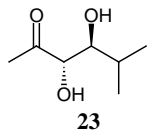
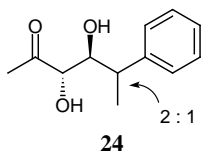
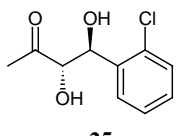
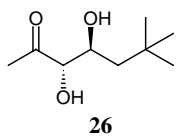
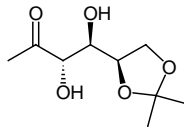
4 Mechanism of the Proline-Catalyzed Aldol Reaction

We proposed that proline-catalyzed intermolecular aldol reactions follow an enamine mechanism that is closely related to the one used by natural aldolases (Scheme 5).

**Scheme 5** Proposed mechanism of the proline-catalyzed aldol reaction

According to our proposal, proline functions as a *microaldolase* with the secondary amine as a nucleophilic enamine catalyst and the carboxylic acid as general Brønsted cocatalyst. Our mechanism is based on concepts on the Hajos-Parrish-Eder-Sauer-Wiechert reaction that were originally proposed by Eschenmoser³³ and have

Table 4 Products from Proline-Catalyzed Aldol Reactions with Hydroxyacetone

Entry	Product	Yield	dr	ee
1	 22	60%	>20:1	>99%
2	 23	62%	>20:1	>99%
3	 24	51%	>20:1	>95%
4	 25	95%	1.5:1	67%
5	 26	38%	1.7:1	>97%
6	 27	40%	2:1	>97%

been experimentally supported by Agami.^{12,13} Although, an alternative ammonium enolate mechanism can not be ruled out at the present time, several indirect pieces of evidence for the proposed covalent aminocatalysis can be found in the literature. Among those are the rapid formation of covalent products from reactions of proline with β -ketoesters, β -diketones, and both aromatic and aliphatic aldehydes.^{34,23} It is furthermore known that proline can be reductively alkylated with unactivated ketones.³⁵ This observation parallels reductive alkylation of an active site lysine residue in class I aldolases, a result that has been interpreted as evidence for enamine catalysis by these enzymes.³⁶ We have obtained additional indirect support for the proposed mechanism, including the fact that *N*-methyl proline is not catalytically active at all, which is consistent with iminium and enamine intermediates. Furthermore, we found that in contrast to acetone and 2-butanone, 3-pentanone is inactive as an aldol donor, which may be explained with the characteristic sensitivity of enamine reactions to sterical hindrance.³⁷ A final piece of evidence comes from the observation that like 3-pentanone, ace-

tophenone is ineffective as a donor. This result is inconsistent with an enolate mechanism, according to which acetophenone, based on its lower pK_a (24.7, DMSO) should be more reactive than acetone (26.5, DMSO).³⁸

An uncertainty still concerns the number of proline molecules that participate in the transition-state. According to the Eschenmoser-Agami-mechanism, two proline molecules are involved in the *intramolecular* aldol reaction, while we have speculated that only one proline molecule is required for the *intermolecular* reaction. In contrast to Agami's studies, we found a linear relationship of proline ee vs. aldol ee for the intermolecular aldol reaction between acetone and *p*-nitrobenzaldehyde to aldol **1** (Figure 1).³⁹

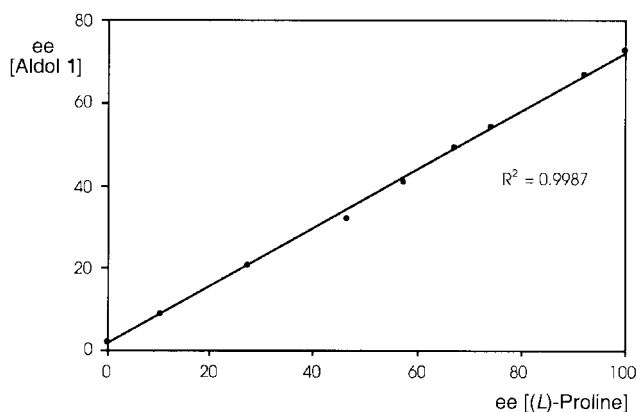


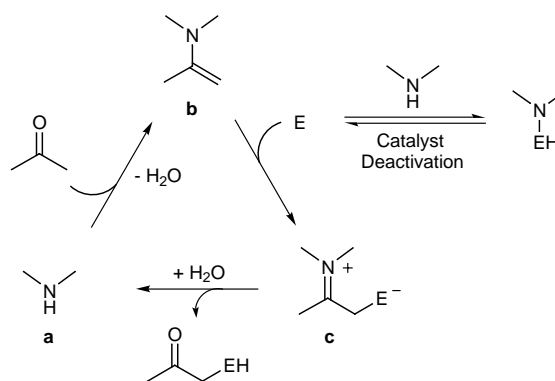
Figure 1 Proline vs. aldol enantiomeric excess in an intermolecular aldol reaction

This behavior is consistent with the proposed first order mechanism but has to be interpreted with caution. While a nonlinear relationship provides clear evidence for higher order mechanisms, the observed linear relationship alone does not prove a first order mechanism. Additional catalyst molecules may be involved in the transition-state without influencing enantioselectivity. Clearly, more research is needed to gain further understanding of the details of this operationally simple yet mechanistically complex reaction.

5 Potential and Limitations of Enamine Catalysis

An important consequence of the proposed aminocatalytic mechanism is the potential for catalysis of other transformations that involve enolate equivalents. We have developed a generalized enamine catalysis cycle that describes amine-catalyzed reactions of carbonyl compounds with electrophiles (Scheme 6).

According to this scheme, a secondary (or primary) amine (**a**) reacts reversibly with a ketone or aldehyde to furnish, via carbinolamine and iminium ion, an enamine (**b**) and water. This enamine reacts with an electrophile to give a modified iminium ion (**c**) that upon hydrolysis furnishes



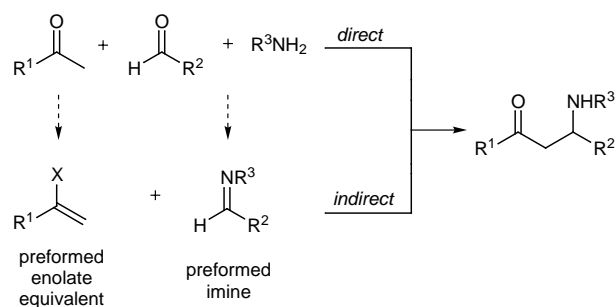
Scheme 6 The enamine catalysis-cycle

the product and regenerates the aminocatalyst. A potential limitation of this cycle would be the irreversible deactivation of the nucleophilic aminocatalyst by the electrophile. For example, the use of alkyl halides as electrophiles in a potential catalytic asymmetric ketone alkylation may lead to alkylation of the aminocatalyst and subsequent inhibition of the reaction. However, if the aminocatalyst reacts only reversibly with the electrophile, catalysis can proceed. For example, if aldehydes are used as electrophiles, iminium ions, carbinolamines, or in the case of proline, oxazolidinones are formed *reversibly*. These “side reactions” may best be described as *parasitic equilibria*⁴⁰ since they can limit reaction rates but still allow for turnover. Other electrophiles that can react reversibly with the aminocatalyst include Michael acceptors and imines. Again other useful electrophiles may not react with amines at all, but only with enamines. Further potential applications of enamine catalysis are pericyclic reactions,⁸ including sigmatropic rearrangements.

6 The Direct Asymmetric Three-Component Mannich Reaction

Realizing the potential of enamine catalysis, we immediately focused our attention on the Mannich reaction.⁴¹ While this reaction is enormously useful for the construction of nitrogenous molecules, first catalytic asymmetric Mannich variants were only developed in recent years.⁴² Despite some earlier attempts,⁴³ all of these variants are indirect, and either the enolate equivalent and/or the imine have to be preformed (Scheme 7). The direct three-component Mannich reaction stood as a major challenge for asymmetric catalysis.

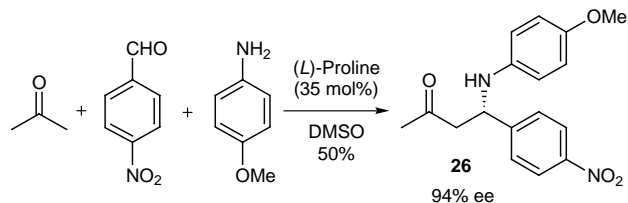
Aldol and Mannich reactions principally compete if the imine is not preformed but present in equilibrium with the free aldehyde. We hoped that nucleophilic addition of the proline enamine would be faster to an imine than to an aldehyde. Consequently, we believed that Mannich reactions catalyzed by a chiral aminocatalyst could be performed directly as a three-component reaction utilizing an aldehyde, a ketone and a primary amine.⁴⁴ We



Scheme 7 Direct and indirect Mannich reactions

found that this concept worked extremely well. Reacting *p*-nitrobenzaldehyde (1 equiv) with proline (0.35 equiv) and *p*-anisidine (1.1 equiv) in DMSO–acetone (4:1) furnished Mannich product **26** in excellent enantioselectivity (Scheme 8).^{45,46}

We found that several other ketones can be used in proline-catalyzed Mannich three-component reactions with excellent results (Table 5). In reactions of three different ketones with *p*-anisidine and *p*-nitrobenzaldehyde not one product was formed with an ee below 94%! In addition very high diastereoselectivities and regioselectivities could be obtained.



Scheme 8 The first highly enantioselective three-component Mannich reaction

Several aldehydes have been successfully studied. Most importantly, aliphatic α -unbranched aldehydes can readily be used in this novel reaction (Table 6, entries 1–3).

Interestingly and in contrast to the proline-catalyzed aldol reactions, the best enantioselectivities in these Mannich reactions were obtained with *aromatic* aldehydes.

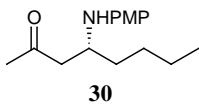
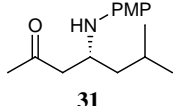
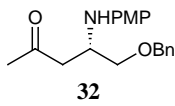
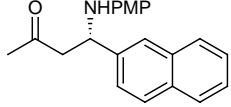
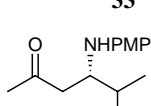
We have studied several commercially available proline derivatives (including a thiaproline derivative, entry 6) as catalysts for the reaction leading to ketone **31** (Table 7). So far, proline is still the most efficient catalyst for aldol and Mannich reactions.

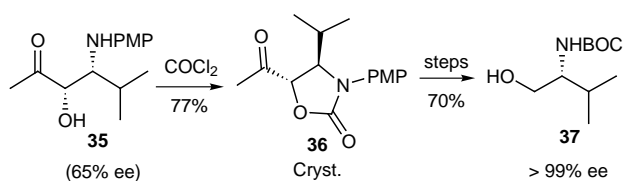
The potential of hydroxylated products such as ketone **35** as precursor for α -amino acid derivatives was illustrated by converting **35** into (D)-*N*-BOC-valinol (**37**) in >99% optical purity after one recrystallization of intermediate **36** (Scheme 9).

Table 5 Three-Component Mannich Reactions with Different Ketones

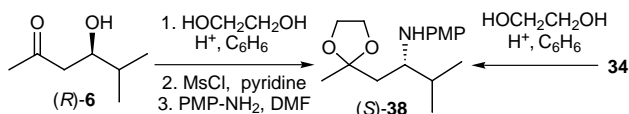
Ketone	Yield	Products	Ee
	50%		94%
	96% (27a / 27b = 2.5:1)		99% (de >95%) 94%
	93%		98% (de >95%)
	92%		>99% (de >95%)

Table 6 Three-Component Mannich Reactions with Different Aldehydes

Entry	Product	Yield	ee
1	 30	74%	73%
2	 31	90%	93%
3	 32	82%	75%
4	 33	35%	96%
5	 34	56%	70%

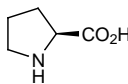
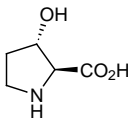
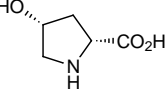
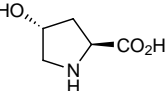
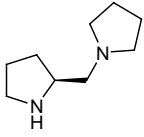
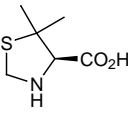


The absolute configuration of the Mannich products was determined via comparison of the optical rotation of **37** with an authentic sample (obtained from Aldrich) and by correlation of amino ketone **34** with aldol **6** (Scheme 10).

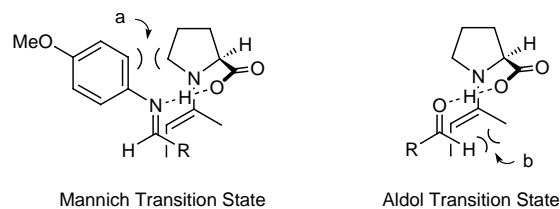


Remarkably, the products from proline-catalyzed Mannich reactions had the *opposite* absolute configuration from the aldol products. This means that Mannich and aldol reactions have opposite enantiofacial selectivities (*si* and *re* respectively). Currently, we speculate that both reactions follow an enamine mechanism but the transition states of the enantioselectivity determining steps differ because of the additional imine nitrogen substituent in the Mannich reaction (Scheme 11).

Table 7 Some Catalysts that were Studied for the Three-Component Mannich Reaction

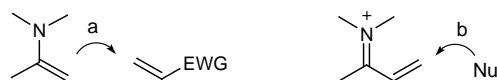
Entry	Catalyst (35 mol%)	Yield	ee
1		90%	93%
2		56%	76%
3		22%	12%
4		22%	15%
5		26%	0%
6		60%	16%

We assume a fixed (*E*)-configuration of both the proline enamine and the imine.⁴⁷ The enamine selectively attacks the *si*-face of the imine to allow protonation of its lone pair. Access to the corresponding *re*-face is limited by unfavorable steric interactions between the pyrrolidine and aromatic ring (a). These interactions do not exist in the aldol reaction and steric repulsion between aldehyde and enamine carbon substituents dominates (b).



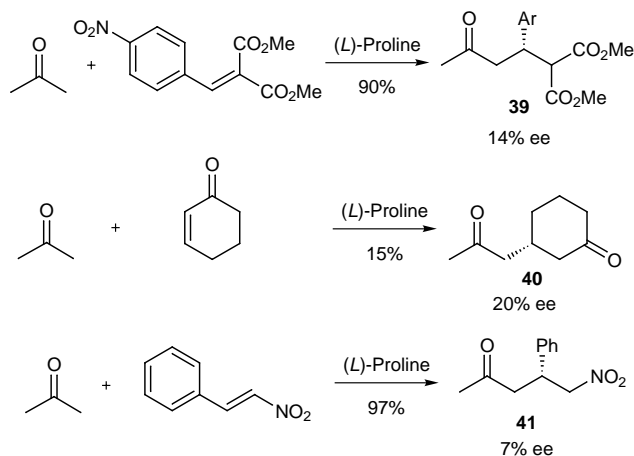
7 Enamine Catalysis of the Michael Reaction

The Michael reaction is another excellent candidate for aminocatalysis. Two different modes can be envisioned: (a) An unmodified ketone donor may be activated as an enamine and (b) an acceptor α,β -unsaturated carbonyl-compound may be activated as an iminium ion (Scheme 12). Both strategies could potentially be combined.



Scheme 12 Enamine (a) and iminium catalysis (b) of the Michael reaction

Only strategy (b) has been used thus far.⁶ We are particularly interested in intermolecular aminocatalyzed Michael reactions according to strategy (a), that follow in an enamine mechanism. To our surprise, we found this reaction to be essentially unknown. Initial experiments strongly suggested the feasibility of this new strategy. Treating a mixture of acetone (20 vol%) and proline (35 mol%) in DMSO with Michael-acceptors, including enones, nitro olefins and alkylidene malonates resulted in the formation of the expected products. While some of these reactions are rapid and efficient, enantioselectivities are still unsatisfactory (Scheme 13).



Scheme 13 Proline-catalyzed intermolecular Michael reactions

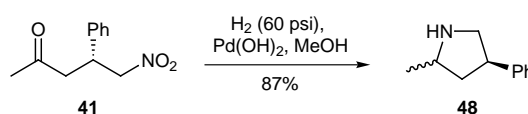
The remarkable efficiency of the proline-catalyzed Michael addition of acetone to β -nitrostyrene combined with the value of the produced γ -nitro ketones such as **41** as pyrrolidine precursors prompted us to further study the scope of this reaction (Table 8).^{48,49}

Typically, very good yields but low enantioselectivities were obtained. However, excellent regio- and diastereoselectivities were observed (entries 2–4). Both aromatic (entries 1–4) and aliphatic nitro olefins, either saturated (entries 5,6) or conjugated (entry 7), may be used efficiently. Nitroketones such as **41–47** are valuable precursors

Table 8 Proline-Catalyzed Michael Reactions of Ketones to Nitro Olefins

Entry	Product	Yield	Selectivity
1	41	97%	<i>ee</i> = 7%
2	42	85%	<i>rr</i> > 20:1 <i>dr</i> = 3:1 <i>ee</i> = 10%
3	43	94%	<i>dr</i> > 20:1 <i>ee</i> = 23%
4	44	92%	<i>dr</i> > 20:1 <i>ee</i> = 10%
5	45	95%	<i>dr</i> = 10:1 <i>ee</i> = 19%
6	46	87%	not determined
7	47	85%	not determined

for several functionalized organic compounds,⁵⁰ including pyrrolidines.⁵¹ As an illustration, nitroketone **41** was hydrogenated to give pyrrolidine **48** in 87% yield as a mixture of diastereomers (Scheme 14). Pyrrolidine **48** and similar compounds are pharmacologically active and selectively block presynaptic dopamine receptors.



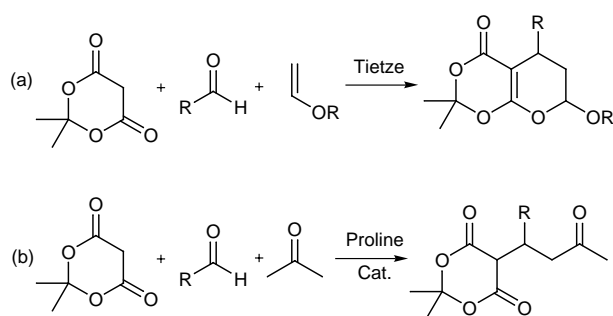
Scheme 14 Reductive cyclization of **41** to pyrrolidine **48**

Future studies will focus on the design of new catalysts to improve the level of enantioselectivity in these efficient enamine catalytic Michael reactions.

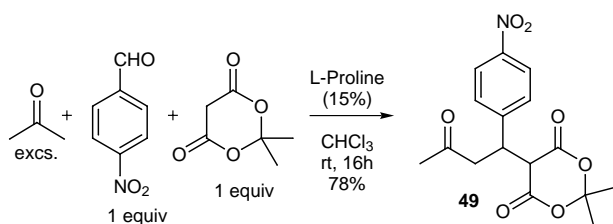
8 Combining Enamine and Iminium Catalysis in the Design of a Novel Multicomponent Reaction

Our observation that alkylidene malonates are efficient acceptors in proline-catalyzed Michael reactions with unactivated ketones becomes more interesting in the context that alkylidene malonates themselves can be prepared in a proline-catalyzed Knoevenagel reaction.⁵² It occurred to us that proline-catalyzed Knoevenagel and Michael reactions may be combined to an in situ sequence related to the Tietze reaction (Scheme 15).^{53,54} Tietze's domino Knoevenagel–hetero-Diels–Alder reaction uses aldehydes, Knoevenagel nucleophiles (typically Meldrum's acid) and preformed enolate equivalents (a). In contrast, the proposed three-component reaction (b) would directly use *unmodified* ketones instead of preformed enolate equivalents (Scheme 15). The overall transformation could be described as carba-analogue Mannich reaction or as carba-acetalization. We realized this concept for the first time when we discovered the proline-catalyzed reaction of *p*-nitrobenzaldehyde with acetone and Meldrum's acid (Scheme 16). Crystalline product **49** was formed in essentially racemic form but in good yield considering that two new carbon-carbon bonds from three different components are formed in the process. We have studied this reaction in some more detail with the following results: Other aldehydes including α -branched (entry 4), α -unbranched (entries 2 and 3) and cyclic aldehydes (entry 5) as well as cyclic ketones (entries 6 and 7) can readily be used to give the products in good yields and diastereoselectivities (Table 9). Unfortunately, the reactions are not enantioselective.⁵⁵

We assume the reaction involves a Knoevenagel–hetero-Diels–Alder sequence,⁵⁶ in which proline uses both iminium- and enamine-catalysis (Scheme 17). Accordingly, the initial Knoevenagel condensation (a–c) proceeds via



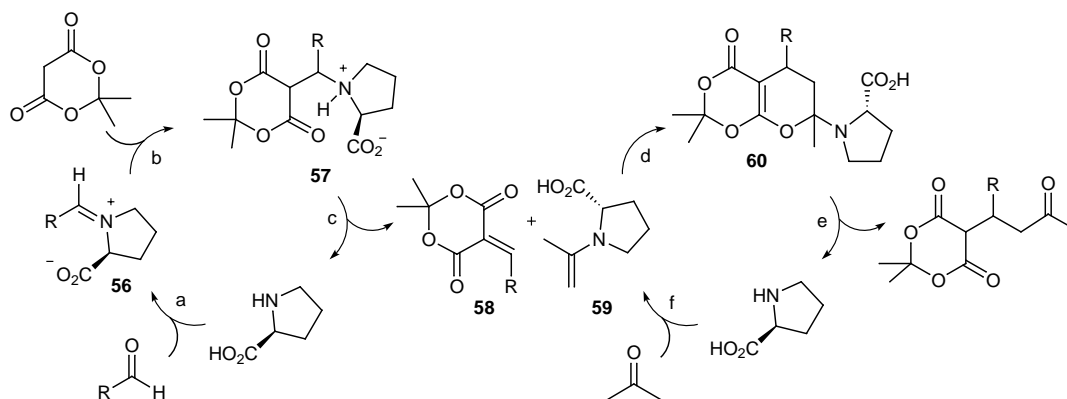
Scheme 15 Proposed three-component reaction and Tietze reaction



Scheme 16 Carba-acetalization of *p*-nitrobenzaldehyde

iminium ion **56** and ammonium ion **57** to give olefin **58**. The role of proline in the hetero-Diels–Alder step (d–f) is to generate the dienophile, enamine **59**, which reacts with hetero diene **58** furnishing cyclo-adduct **60** and upon hydrolysis the final product under concomitant regeneration of the catalyst.

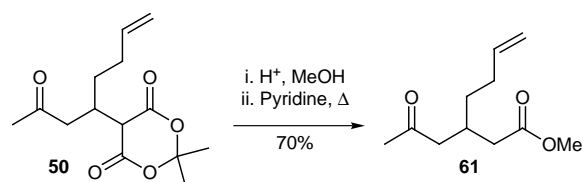
Meldrum's acid derivatives such as **49–55** are valuable precursors of 3-substituted-1,5-dicarbonyl derivatives including 3-alkyl-5-oxo-hexanoates. This was demonstrated by methanolysis and in situ decarboxylation of compound **50** to give keto ester **61** in good yield (Scheme 18).



Scheme 17 Proposed mechanism of the proline-catalyzed carba-acetalization

Table 9 Proline-Catalyzed Carba-Acetalizations

Entry	Product	R ¹	R ²	R ³	Yield	de
1	49	H	H		78%	
2	50	H	H		83%	
3	51	H	H		79%	
4	52	H	H		51%	
5	53	H	H		65%	
6	54				69%	>95%
7	55				75%	>95%

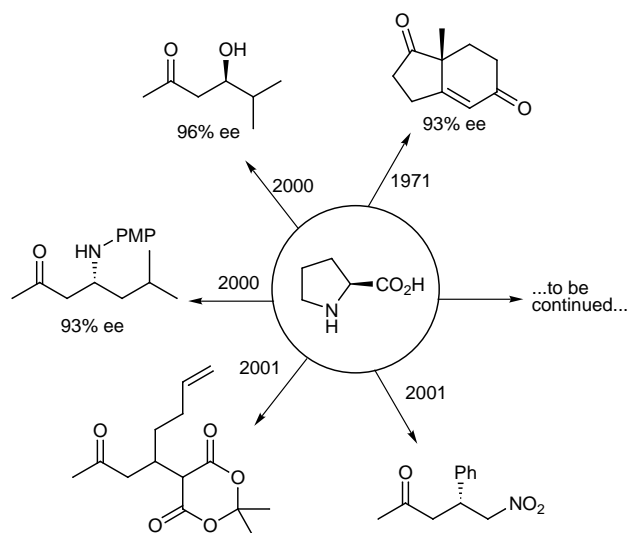
**Scheme 18** Methanolysis and decarboxylation of compound **50**

We currently search for new aminocatalysts that provide the products of our new three-component reaction enantioselectively.

9 Conclusions

This account focused on novel amine-catalyzed reactions recently discovered in our laboratories.⁵⁷ Among the newly developed transformations are efficient proline-catalyzed intermolecular aldol, Mannich and Michael reactions and a novel three-component reaction (Scheme 19).

Designing new catalytic reactions is a domain of organometallic chemistry and we agree with Seebach's analysis

**Scheme 19** New and old proline-catalyzed reactions

that truly novel reactions are to be expected from this area.⁵⁸ However, despite some promising exceptions, organocatalysis in general and aminocatalysis in particular seem to be neglected fields.^{59,60} While the unique reactivity of iminium ions and enamines has long been used in organic synthesis, most of these reactions use stoichiometric quantities of the amine. Amines have rarely been used catalytically despite the fact that they are readily available in enantiomerically pure form from several sources including the chiral pool. We hope this account contributes to a greater realization that aminocatalysis could complement transition metal catalysis in many aspects and ultimately might expand the list of privileged chemical reactions.

Acknowledgment

The author thanks his creative and dedicated colleagues William Biller, Chris Castello, Harry J. Martin, Wolfgang Notz, and Peter Pojarliev. Gratefully acknowledged is furthermore Peter Guthrie (University of Western Ontario, Canada) for his advice and Ken Houk and Sami Bahmanyar (University of California, Los Angeles) for sharing their mechanistic insights. Our results would not have been possible without the guidance and support by Richard A. Lerner.

References

- (1) Most of these reactions can be found in the excellent book: *Classics in Total Synthesis*; Nicolaou, K. C.; Sorensen, E. J., Eds.; VCH: Weinheim, **1996**.
- (2) It has been estimated that the p*K*_a of acetone decreases by about 12 units (from p*K*_a ≈ 20 to p*K*_a ≈ 8) after conversion to an iminium ion. Depending on the strength of the base, the rate of proton removal from the α-carbon increases by a factor of 10⁵–10⁸, see: (a) Bender, M. L.; Williams, A. J. *Am. Chem. Soc.* **1966**, *88*, 2502. (b) Roberts, R. D.; Ferran, H. E.; Gula, M. J.; Spencer, T. A. *J. Am. Chem. Soc.* **1980**, *102*, 7054.

- (3) For selected early studies on aminocatalytic principles, see: (a) Kayser, R. H.; Pollack, R. M. *J. Am. Chem. Soc.* **1975**, *97*, 952. (b) Hine, J. *Acc. Chem. Res.* **1978**, *11*, 1. (c) Tagaki, W.; Guthrie, J. P.; Westheimer, F. H. *Biochemistry* **1968**, *7*, 905. (d) Coward, J. K.; Bruce, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 5329.
- (4) Knoevenagel reaction, review: Tietze, L. F. In *Comprehensive Organic Synthesis*, Vol. 2; Trost, B. M., Ed.; Pergamon Press: New York, **1991**, 341–394.
- (5) (a) Diels–Alder Reaction: Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) 1,3-Dipolar Cycloaddition: Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.
- (6) Asymmetric iminium catalytic Michael reactions: (a) Belokon, Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Orlova, S. A.; Kuz'mina, N. A.; Bodrov, D. E. *Russ. Chem. Bull.* **1993**, *42*, 1525. (b) Yamaguchi, M.; Shiraiishi, T.; Hiram, M. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1176. (c) Yamaguchi, M.; Shiraiishi, T.; Hiram, M. *J. Org. Chem.* **1996**, *61*, 3520. (d) Kawara, A.; Taguchi, T. *Tetrahedron Lett.* **1994**, *47*, 8805. (e) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975; Iminium catalytic (Michael-type) Friedel–Crafts reaction. (f) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.
- (7) Iminium catalytic decarboxylation: Guthrie, J. P.; Jordan, F. *J. Am. Chem. Soc.* **1972**, *94*, 9136.
- (8) For a pioneering example, see: Boger, D. L.; Panek, J. S.; Meier, M. M. *J. Org. Chem.* **1982**, *47*, 895.
- (9) (a) Marsh, J. J.; Leberherz, H. G. *TIBS* **1992**, *17*, 110. (b) Lai, C. Y.; Nakai, N.; Chang, D. *Science* **1974**, *183*, 1204. (c) Morris, A. J.; Tolan, D. R. *Biochemistry* **1994**, *33*, 12291.
- (10) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496.
- (11) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.
- (12) Agami, C.; Meynier, F.; Puchot, C.; Guilhem, J.; Pascard, C. *Tetrahedron* **1984**, *40*, 1031.
- (13) Agami, C.; Puchot, C.; Sevestre, H. *Tetrahedron Lett.* **1986**, *27*, 1501.
- (14) Barbas, C. F. III.; Heine, A.; Zhong, G.; Hoffmann, T.; Gramatikova, S.; Bjornestedt, R.; List, B.; Anderson, J.; Stura, E. A.; Wilson, I. A.; Lerner, R. A. *Science* **1997**, *278*, 2085.
- (15) List, B.; Shabat, D.; Barbas, C. F. III.; Lerner, R. A. *Chem.–Eur. J.* **1998**, *4*, 881.
- (16) List, B.; Barbas, C. F. III.; Lerner, R. A. *Proc. Natl. Acad. Sci.* **1998**, *95*, 15351.
- (17) List, B.; Lerner, R. A.; Barbas, C. F. III. *Org. Lett.* **1999**, *1*, 59.
- (18) List, B.; Shabat, D.; Zhong, G.; Turner, J. M.; Li, T.; Bui, T.; Anderson, J.; Lerner, R. A.; Barbas, C. F. III. *J. Am. Chem. Soc.* **1999**, *121*, 7283.
- (19) Turner, J. M.; Bui, T.; Lerner, R. A.; Barbas, C. F. III; List, B. *Chem. Eur. J.* **2000**, *6*, 2772.
- (20) (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1871. (b) Yamada, Y. M. A.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 5561. (c) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168.
- (21) For more recent work by the Shibasaki group, see: (a) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466. (b) Kumagai, N.; Matsunaga, S.; Yoshikawa, N.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 1539. (c) Yoshikawa, N.; Shibasaki, M. *Tetrahedron* **2001**, *57*, 2569. (d) Suzuki, T.; Yamagiwa, N.; Matsuo, Y.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M.; Noyori, R. *Tetrahedron Lett.* **2001**, *42*, 4669.
- (22) For an earlier partially successful direct catalytic asymmetric aldol reaction, see: (a) Nakagawa, M.; Nakao, H.; Watanabe, K.-I. *Chem. Lett.* **1985**, 391. (b) Yamada, Y.; Watanabe, K.-I.; Yasuda, H. *Utsunomiya Daigaku Kyoikugakubu Kiyō, Dai-2-bu* **1989**, *39*, 25.
- (23) (a) Orsini, F.; Pelizzoni, F.; Forte, M.; Destro, R.; Gariboldi, P. *Tetrahedron* **1988**, *44*, 519. (b) Rizzi, G. P. *J. Org. Chem.* **1970**, *35*, 2069. (c) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390. (d) Orsini, F.; Pelizzoni, F.; Forte, M.; Sisti, M.; Bombieri, G.; Benetollo, F. *J. Heterocycl. Chem.* **1989**, *26*, 837.
- (24) List, B.; Lerner, R. A.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.
- (25) List, B.; Castello, C.; Pojarliev, P.; Martin, H. J., unpublished results.
- (26) For representative examples, see: (a) Eichenauer, H.; Friedrich, E.; Lutz, W.; Enders, D. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 206. (b) Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649. (c) Ramachandran, P. V.; Xu, W.; Brown, H. C. *Tetrahedron Lett.* **1996**, *37*, 4911. (d) Denmark, S. E.; Stavenger, R. A.; Wong, K. J. *Org. Chem.* **1998**, *63*, 918.
- (27) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573.
- (28) (a) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (b) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367. (c) Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497.
- (29) Wood, D. L.; Stark, R. W.; Silverstein, R. M.; Rodin, J. O. *Nature* **1967**, *215*, 206.
- (30) Oertle, K.; Beyeler, H.; Duthaler, R. O.; Lottenbach, W.; Riediker, M.; Steiner, E. *Helv. Chim. Acta* **1990**, *73*, 353.
- (31) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.
- (32) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
- (33) Brown, K. L.; Damm, L.; Dunitz, J. D.; Eschenmoser, A.; Hobi, R.; Kratky, C. *Helv. Chim. Acta* **1978**, *61*, 3108.
- (34) Vargha, E.; Gonczy, F.; Balog, A. *Stud. Univ. Babeş-Bolyai, Ser. Chem.* **1972**, *17*, 125.
- (35) Toth, G.; Kovacs, A.; Tarnai, T.; Tungler, A. *Tetrahedron: Asymmetry* **1993**, *4*, 331.
- (36) See for example: (a) Lia, C. Y.; Oshima, T. *Arch. Biochem. Biophys.* **1971**, *144*, 363. (b) Schettino, C. M.; Lima, D. F.; Leyton, J. F.; El-Dorry, H. A.; Bacila, M. *Biochim. Biophys. Acta.* **1981**, *667*, 411.
- (37) Whitesell, J. K.; Whitesell, M. A. *Synthesis* **1983**, 517.
- (38) pK_a Table, Homepage D. A. Evans group, <http://daer1.harvard.edu/index.html>
- (39) This experiment and several proline-catalyzed aldol reactions originally published by us have recently been repeated by others: Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2001**, *123*, 5260.
- (40) This appropriate term has been coined by Professor J. P. Guthrie, University of Western Ontario, Canada.
- (41) Reviews: (a) Kleinnmann, E. F. In *Comprehensive Organic Synthesis*, Vol. 2; Trost, B. M., Ed.; Pergamon Press: New York, **1991**, Chap. 4.1. (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044.

- (42) (a) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060. (b) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153. (c) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431. (d) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474. (e) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548.
- (43) (a) Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 307. (b) Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron* **1999**, *55*, 8857.
- (44) For an elegant example of non-asymmetric three-component Mannich reactions, see: Manabe, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 1965.
- (45) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.
- (46) After our results were published, others submitted a related manuscript: Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F. III. *Tetrahedron Lett.* **2001**, *3*, 2423.
- (47) We have advanced our originally proposed transition states that invoked a (Z)-imine.
- (48) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423.
- (49) Some encouraging enantioselective enamine catalytic Michael reactions have been described in parallel with our efforts: Betancort, J.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F. III. *Tetrahedron Lett.* **2001**, *3*, 4441.
- (50) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1.
- (51) Svensson, K. A. I. et al. PCT Int. Appl. WO 9218475, **1992**.
- (52) In contrast to some organic chemistry textbooks, Knoevenagel himself speculated that his reaction involves iminium intermediates and we classify his reaction as an iminium catalytic transformation, see: Knoevenagel, E. *Chem. Ber.* **1898**, *31*, 2585.
- (53) (a) Tietze, L. F. *J. Heterocyclic Chem.* **1990**, *27*, 47. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (c) For a recent example, see Tietze, L. F.; Evers, T. H.; Töpken, E. *Angew. Chem. Int. Ed.* **2001**, *40*, 903.
- (54) For a related three-component reaction, see: (a) Oikawa, Y.; Hirasawa, H.; Yonemitsu, O. *Tetrahedron Lett.* **1978**, 1759. (b) Oikawa, Y.; Hirasawa, H.; Yonemitsu, O. *Chem. Pharm. Bull.* **1982**, *30*, 3092.
- (55) List, B.; Castello, C. *Synlett* **2001**, *in press*.
- (56) A similar mechanism has been postulated for the Tietze-three-component reaction.
- (57) Some of our results have been reviewed elsewhere: (a) Gröger, H.; Wilken, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 529. (b) Albus, S. *Nachr. Chem. Techn. Lab.* **2000**, *48*, 1459. (c) Bahmanyar, S.; Houk, K. N. *Chemtracts* **2000**, *13*, 904. (d) Doye, S. *Chem. Unserer Zeit* **2001**, *35*, 62.
- (58) Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1320.
- (59) For a selection of enantioselective organocatalytic reactions, see: Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, Chap. 7; John Wiley & Sons: New York, **1994**, 323–345.
- (60) The following statement by Nicolaou and Sorensen illustrates this point: “In a catalytic asymmetric reaction, a small amount of an enantiomerically pure catalyst, either an enzyme or a synthetic, soluble transition metal complex, is used to produce large quantities of an optically active compound from a precursor that may be chiral or achiral.” See Ref.¹, p. 344.