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Enamine-Based Organocatalysis with Proline and Diamines: The Development of Direct Catalytic Asymmetric Aldol, Mannich, Michael, and Diels−Alder Reactions

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ABSTRACT

Enamines and imines have long been recognized as key intermediates in enzyme catalysis, particularly within a class of enzymes organic chemists would very much like to emulate, the aldolases. Here we summarize the contributions of this laboratory to converting enzymatic enamines, and in some cases imines, into a versatile catalytic asymmetric strategy powered by small organic molecules.

Introduction

As chemists, we often turn to nature for inspiration since nature provides a nearly limitless fount of stereochemically complex molecules. To advance our understanding of how nature accomplishes such awesome synthetic feats, we have studied approaches aimed at recreating nature's aldolase enzymes,[1] and it is through these studies that we have developed our organocatalytic methodologies. From a synthetic perspective, the appealing features of aldolases are that they efficiently catalyze aldol reactions under mild ambient conditions and often use nonactivated unprotected polyfunctionalized substrates to form a new carbon−carbon bond in a stereospecific fashion. These same features are typically absent in traditional synthetic asymmetric aldol methodologies.[2,3]

Our ideal synthetic catalyst would be one that could generate enamines from any number of aldehydes or ketones and then direct bond-forming reactions with a wide variety of electrophiles beyond the carbonyl electrophiles of the aldol reaction. Further, since these catalysts also generate imines as part of their reaction mechanism, electrophilic catalysis might facilitate diverse reactions with nucleophiles. Such an antibody might be termed an "open-active site" catalytic antibody. Indeed, we were able to demonstrate that our aldolase antibodies could catalyze not only a wide range of intra- and intermolecular aldol reactions but also decarboxylation reactions via imine catalysis and certain Michael reactions as well.[2] Significantly for what would become our studies in organocatalysis, in our search for "open-active site" antibody catalysis, we studied the potential of aldolase antibodies to catalyze the addition of ketones to nitrostyrenes in Michael reactions, the addition of ketones to imines in Mannich-type reactions, and Diels−Alder reactions through the generation of antibody-bound 2-amino-1,3-butadienes or antibody-bound iminium-activated α,β-unsaturated ketone dienophiles.[2f] These studies provided significant conceptual models and preliminary results, stimulating our interest to create catalysts for these important reactions. Our interest in organocatalysis was piqued in 1997 when we initiated comparative studies of aldolase antibodies with L-proline,[2b] the well-known catalyst of the intramolecular Hajos−Eder−Sauer−Wiechert reaction,[4] an enantiogroup-differentiating aldol cyclodehydration reaction. Evidence suggests that this intramolecular proline-catalyzed reaction proceeds via an enamine reaction mechanism much like our aldolase antibodies. Mechanistically then, catalysis with antibody aldolases and the simple amino acid proline are very similar. This study would serve as foreshadowing of our reinvestigation of the Hajos−Eder−Sauer−Wiechert reaction and proline and launch our studies in organocatalysis.

To understand the features of aldolase enzymes that make them exceptional catalysts, we have taken constructive and deconstructive approaches, studying antibodies, designed peptides, amines, and amino acids to deduce the features of these families of catalysts essential for their activity, stereocontrol, and chemoselectivity (Figure 1). A methodological advance in reaction screening came in our design of a UV-sensitive reporter aldol based on 4-dimethylaminocinnamaldehyde that allowed for rapid and quantitative study of retro-aldol reactions.[2c,d] This powerful tool inspired us to screen a wide variety of commercially available amino acids and chiral amines with and without additives for catalysis of the retro-aldol reaction. To our surprise, L-proline remained the most promising catalyst. This result immediately suggested the application of all active catalysts to intermolecular aldol

Wolfgang Notz received his Ph.D. in organic chemistry at the University of Konstanz, Germany, where he developed a novel general strategy toward C-ketosides of sialic acids under the supervision of Richard R. Schmidt. He then joined the laboratories of Carlos F. Barbas, III, for two years as a postdoctoral fellow at The Scripps Research Institute, studying organocatalysis. He is currently a process research scientist at Pfizer Global Research and Development in La Jolla.

Fujie Tanaka received her Ph.D. from Kyoto University, Japan, under the direction of Kaoru Fuji. For postdoctoral studies, she joined Chi-Huey Wong in the Frontier Research Program, Riken, Ikuo Fujii, at the Protein Engineering Research Institute (Biomolecular Engineering Research Institute), and Carlos F. Barbas, III, at The Scripps Research Institute. She is currently an Assistant Professor in the Department of Molecular Biology at The Scripps Research Institute.

Carlos F. Barbas, III, received his B.S. degree in Chemistry and Physics from Eckerd College and his Ph.D. in Chemistry with Chi-Huey Wong at Texas A&M University. He completed his postdoctoral studies with Richard Lerner in 1991 and began his academic career as an Assistant Professor in the same year. He is now Kellogg Professor and Chair in Molecular Biology and Chemistry at The Scripps Research Institute. His research interests lie at the interface of chemistry, biology, and medicine, and he is a cofounder of Prolifaron Inc., now Alexion Antibody Technologies, and the founder of CovX Pharmaceuticals.

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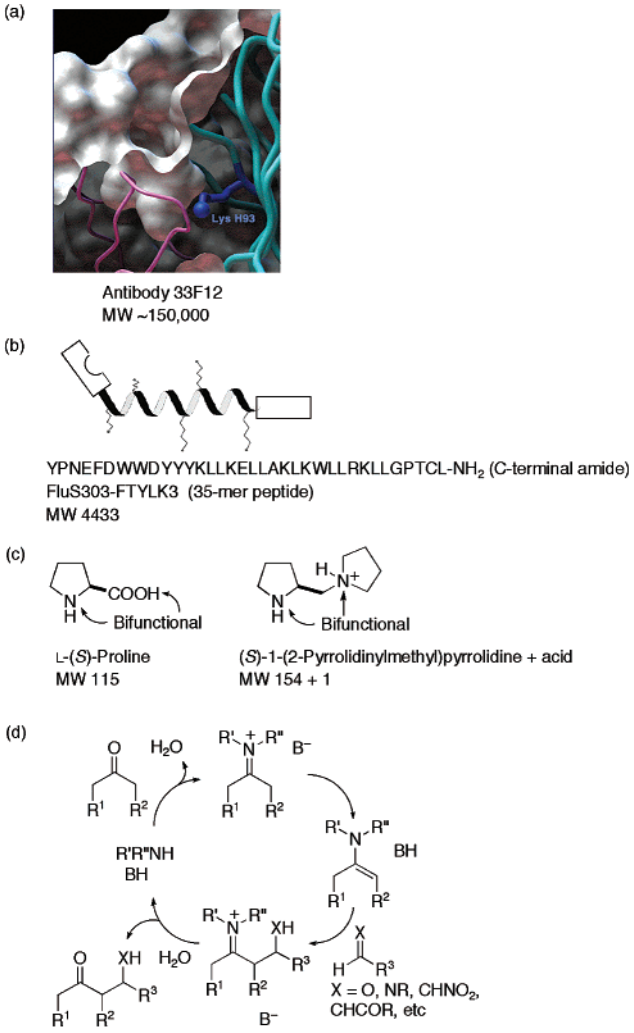


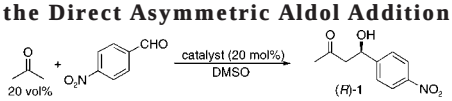
FIGURE 1. Structurally complex and simple catalysts studied in our laboratory and the enamine-based catalytic cycle: (a) a view of the active site of an aldolase antibody;[2] (b) a structured peptide catalyst;[3] (c) two common organocatalysts; (d) enamine reaction cycle.

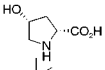
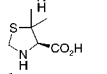
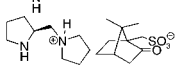
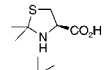
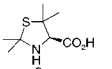
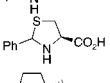
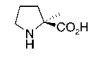
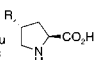
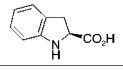
addition reactions because this reaction is characteristically reversible and varying the concentrations of the reactant with respect to the equilibrium constant allows the reaction to be driven to completion in either direction. In proline chemistry, we began to realize our dream of "open-active site catalysis" with a molecule of stunning simplicity.

1. Direct Organocatalytic Asymmetric Aldol Reactions

With proline as the most promising catalyst as identified in retro-aldol and Robinson annulation screens (vide infra), we embarked on a broad survey for new catalysts with structural features common with proline (Table 1), anticipating that we might identify a more promising catalyst with respect to both rate and enantioselectivity. The reaction of 4-nitrobenzaldyde and excess acetone in DMSO served as a model reaction.[5] In accord with our earlier UV-based screening, simple linear amino acids were poor catalysts of the reaction (entry 1). This study revealed a structure/activity relationship involving a cyclic

Table 1. Exploration of Various Amino Acids and Commercially Available Derivatives as Catalysts for the Direct Asymmetric Aldol Addition



Entry	Catalyst	Yield	ee	Entry	Catalyst	Yield	ee
1	(*L*)-His, (*L*)-Val, (*L*)-Tyr, (*L*)-Phe	< 10%	n.d.	9		> 50%	-62%
2		68%	76%	10		66%	86%
3		< 10%	n.d.	11		41%	81%
4		55%	40%	12		<10%	n.d.
5		< 10%	n.d.	13		< 5%	n.d.
6		< 10%	n.d.	14		<10%	n.d.
7		67%	73%	15		26%	61%
8a R=OH **8b** R=O*t*Bu **8c** R=OAc		85% > 50% 70%	78% 62% 74%	16		<10%	n.d.

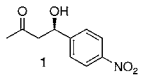
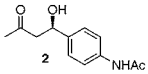
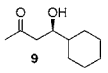
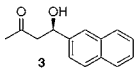
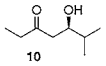
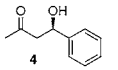
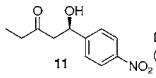
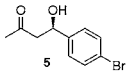
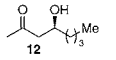
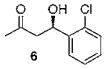
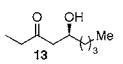
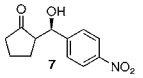
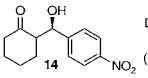
secondary amine moiety and an acidic proton in appropriate spatial proximity for efficient catalysis to occur with the five-membered pyrrolidine ring as the best secondary cyclic amine moiety (entries 4 and 5 versus entry 2). In particular L-proline and 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC) were very effective. We also identified significant activity in the diamine−acid combination of (*S*)-1-(2-pyrrolidinylmethyl)-pyrrolidine and camphorsulfonic acid, which was better behaved in our studies than several other salts tested (entry 11).

Whereas DMTC provided improved results in the cases of aromatic aldehydes, L-proline generally proved superior in the cases of linear and α-branched aldehydes (Table 2). The latter generally provides aldol products with higher enantioselectivities, and most notably, isobutyraldehyde afforded the desired aldol product with 96% ee!

With unsymmetrical 2-butanone as donor a highly regioselective nucleophilic attack of the methyl group of the ketone occurred, presumably due to sterics. In contrast to 2-butanone, hydroxyacetone[5,6] exclusively affords the corresponding anti aldol products arising from a nucleophilic attack of the more substituted carbon atom, in most cases with excellent enantioselectivities (Table 3). The stereochemical outcome of hydroxyacetone donors can be accounted for by favorable interactions of the π-donating OH-group with the π^*-orbital of the C=C bond of the enamine intermediate thereby stabilizing the hydroxyl enamine[7] and furthermore by minimization of 1,3-allylic strain,[8] which forces the enamine double bond to preferentially adopt an (*E*)-configuration. We first noted the special characteristics of hydroxyacetone as an aldol donor in our aldolase antibody studies years earlier.[2]

The construction of quaternary carbon centers has long been a challenging topic in asymmetric organic synthesis.[9] We examined α,α-disubstituted aliphatic aldehydes as potential donors instead. Proline was not an efficient

Table 2. Direct Asymmetric Aldol Reactions Catalyzed by L-Proline and DMTC

Product	Catalyst	Yield	ee	Product	Catalyst	Yield	ee
 1	DMTC	60%	86%	 8	DMTC	61%	94%
	(*L*)-Pro	68%	76%		(*L*)-Pro	97%	96%
 2	DMTC	60%	80%	 9	DMTC	45%	83%
	(*L*)-Pro	62%	69%		(*L*)-Pro	60%	85%
 3	DMTC	60%	88%	 10	DMTC	<5%	n.d.
	(*L*)-Pro	54%	77%		(*L*)-Pro	60%	80%
 4	DMTC	60%	89%	 11	DMTC	57%	74%
	(*L*)-Pro	62%	60%		(*L*)-Pro	61%	59%
 5	DMTC	65%	67%	 12	(*L*)-Pro	75%	73%[a]
	(*L*)-Pro	74%	65%		(*L*)-Pro	56%	68%[b]
 6	DMTC	71%	74%	 13	DMTC	<5%	n.d.
	(*L*)-Pro	94%	69%		(*L*)-Pro	65%	58%[b]
 7	DMTC	*syn* 24%	60%	 14	DMTC	*syn* 21%	69%
		anti 39%	65%			*anti* 35%	90%
	(*L*)-Pro	*syn* 27%	36%		(*L*)-Pro	*syn* 24%	36%
		anti 46%	53%			*anti* 41%	63%

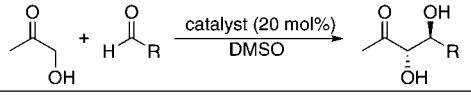
[a] Reaction in neat acetone. [b] Chloroform as solvent

catalyst for this type of aldol reaction, so we searched for superior organocatalysts, using our fluorescence-based detection assay[2g,10] that allows the progress of carbon−carbon bond formation to be monitored in a high-throughput fashion invoking the Michael-type reaction of a maleimide and acetone as a surrogate reporter reaction for other enamine-based reactions. From this screen, diamine **23** and trifluoroacetic acid as additive emerged as a superior bifunctional catalyst system, which efficiently catalyzed the direct aldol reaction of α,α-disubstituted aldehydes with arylaldehydes providing aldol products **24** in excellent yield and very high enantiomeric excess (Table 4).[10]

2. Direct Organocatalytic Asymmetric Mannich Reactions

Mannich Reactions with Ketone Donors. Realizing that our concept of amine-catalyzed addition of enamines formed in situ could be extended to imines as acceptors, we initially studied the reaction of acetone with a number of aromatic aldimines preformed with *o*-anisidine,[11] thus evading concerns regarding chemoselectivity. The three catalysts identified in our aldol studies, L-proline, 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC), and (*S*)-1-(2-pyrrolidinylmethyl)-pyrrolidine/camphorsulfonic acid, afforded the Mannich products with various degrees of enantioselectivity in comparable yields, which were mainly compromised by the formation of the corresponding aldol condensation product. Attempts to prepare preformed aldimines derived from *o*-anisidine and cyclohexanecarboxaldehyde or isobutyraldehyde proved troublesome. We therefore switched to a more convenient one-pot three-component reaction protocol using a 1:1 mixture of aldehyde and *p*-anisidine. In the presence of L-proline, a variety of ketone donors afforded Mannich products in

Table 3. Synthesis of Anti Diols from Hydroxyacetone



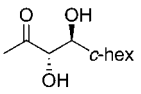
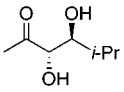
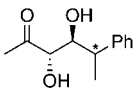
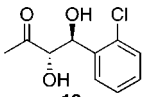
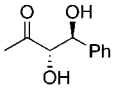
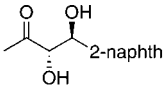
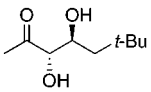
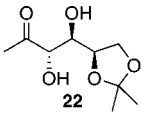
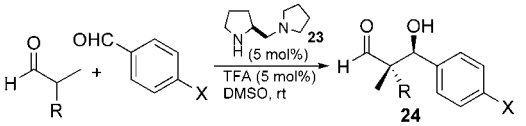
Product	Catalyst	anti:syn	Yield	ee
 **15**	(*L*)-Pro	>20:1	60%	>99%
	DMTC	>20:1	45%	95%
 **16**	(*L*)-Pro	>20:1	62%	>99%
	DMTC	n.d.	<5%	n.d.
 **17a** + **17b** (2:1)	(*L*)-Pro	>20:1	51%	>95%
	DMTC	n.d.	<5%	n.d.
 **18**	(*L*)-Pro	3:2	95%	67% (32%)
	DMTC	3:2	60%	92% (76%)
 **19**	(*L*)-Pro	1:1	83%	80% (n.d.)
	DMTC	1:1	52%	95% (50%)
 **20**	(*L*)-Pro	3:1	62%	79% (33%)
	DMTC	1:1	57%	91% (36%)
 **21**	(*L*)-Pro	1.7:1	38%	>97% (84%)
	DMTC	n.d.	<5%	n.d.
 **22**	(*L*)-Pro	2:1	40%	>97% (97%)
	DMTC	n.d.	<5%	n.d.

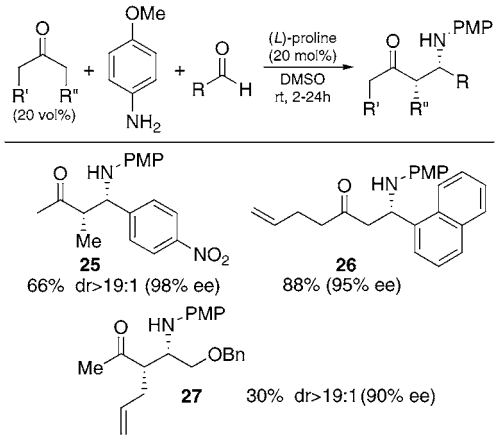
Table 4. Synthesis of α,α-Disubstituted Aldol Products



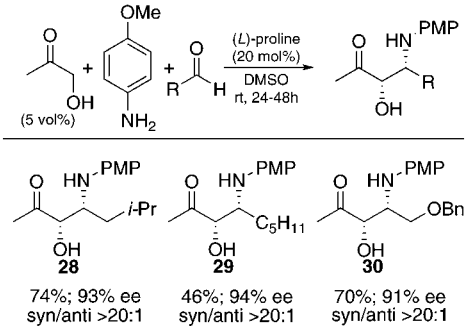
Entry	R	X	Time	Yield[a]	*anti:syn*[b]	ee *(anti/syn)*[c]
(1)	Me	NO_2	24h	92%	-	96%
(2)	Me	CN	12h	95%	-	92%
(3)	Me	Br	72h	80%	-	95%
(4)	Et	NO_2	48h	96%	1.6:1	91%/75%
(5)	Pr	NO_2	48h	92%	1.9:1	89%/66%
(6)	nonyl	NO_2	48h	93%	2.2:1	91%/68%
(7)		NO_2	48h	96%	1.9:1	89%/52%
(8)		NO_2	48h	97%	5.3:1	95%/74%

30−88% yield and 40−98% ee (Scheme 1).[12] Aromatic and linear as well as branched aliphatic aldehydes can be employed in this protocol furnishing the desired Mannich products with (*S*)-stereochemistry at the newly generated

Scheme 1. One-Pot Three-Component Mannich-type Reaction between Selected Ketone Donors, Aldehyde Acceptors, and *p*-Anisidine



Scheme 2. Formation of Vicinal Syn Amino Alcohols via Catalytic Mannich Reaction of Hydroxyacetone



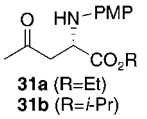
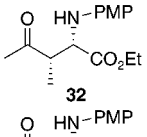
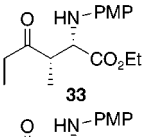
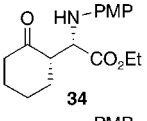
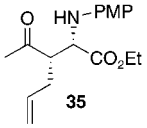
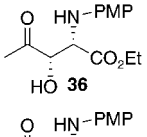
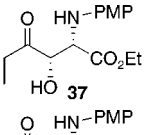
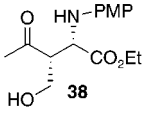
stereocenters.[11,12] Compared to the related aldol reaction, this constitutes a switch in the facial selectivity of the imine attack. In cases of ketone donors that give rise to the formation of syn/anti diastereomers, the corresponding syn diastereomer was formed predominantly.

As in the related aldol reaction, hydroxyacetone can also be employed as donor in the one-pot three-component Mannich reaction (Scheme 2).[12] In all cases, the vicinal syn hydroxy amino compound was formed as the only regioisomer with high diastereoselectivity (syn/anti typically >20:1), as well as excellent enantioselectivity (86−94% ee).

We deemed our proline-catalyzed Mannich-type reactions a suitable strategy to accomplish a stereoselective entry to functionalized α-amino acids.[13] With the use of preformed *N*-PMP-protected α-imino ethyl glyoxylate as imine component, a series of structurally diverse ketones provided the corresponding Mannich products **31**−**38** with exceptional ee's (Table 5).[14]

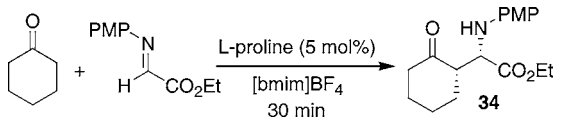
All the donors studied provided a single reaction product. In particular, in the case of unsymmetrical ketones, the regioselective attack of the more substituted α-carbon atom of the ketone afforded predominantly the syn diastereomers (dr typically >19:1) with excellent enantioselectivities (ee > 98%). The newly formed α-stereocenter exhibited the anticipated (*S*)-stereochemistry. These reactions are well-behaved in a wide variety of organic solvents with dioxane and THF providing the best

Table 5. Formation of Functionalized γ-Oxo-α-Amino Acids

Entry	Product	Yield	syn/anti	ee
(1)	 **31a** (R=Et) **31b** (R=*i*-Pr)	**31a**: 82% **31b**: 85%	- -	95% 97%
(2)	 **32**	72%	>19:1	>99%
(3)	 **33**	47%	>19:1	>99%
(4)	 **34**	81%	>19:1	>99%
(5)	 **35**	79%	>19:1	>99%
(6)	 **36**	62%	>19:1	99%
(7)	 **37**	68%	~4:1	98%
(8)	 **38**	59%	>19:1	>99%

results. In these solvents, the amount of proline or ketone donor can be reduced to 5 mol % and 2 equiv, respectively, whereas reducing both catalyst loading and the amount of ketone donor led to a significantly reduced reaction rate. A significant improvement in this reaction came with the introduction of ionic liquids as solvents. The Mannich reaction of *N*-PMP-protected α-imino ethyl glyoxylate with cyclohexanone using a catalytic amount of L-proline (5 mol %) in [bmim]BF_4 (bmin = 1-butyl-3-methylimidazolium) at room temperature was studied (Table 6).[12b] Significantly, the reaction was complete within 30 min and provided Mannich product **34** in quantitative yield with excellent ee (>99%) and diastereoselectivity (>19:1). To study catalyst and solvent recycling, the product was extracted with ether. The recovered ionic liquid containing L-proline was then used for the next reaction run. Following four consecutive reaction cycles, there was no diminution in ee and a slight decrease in yield when the 30 min reaction time was strictly maintained. In further studies, we found that our Mannich-type reactions were generally accelerated from 4- to

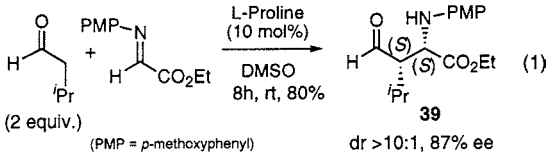
Table 6. Catalyst and Ionic Liquid Solvent Recycling



no. of runs	yield (%)	dr	ee (%)
1	99	>19:1	>99
2	92	>19:1	>99
3	87	>19:1	>99
4	83	>19:1	>99

50-fold using ionic liquids as solvents, and the products were obtained in high yield with excellent enantioselectivity with catalyst loadings as low as 1%.

The First Direct Asymmetric Mannich-type Reactions with Enolizable Aliphatic Aldehyde Donors. In the reaction of isovaleraldehyde, L-proline, and *N*-PMP-protected α-imino ethyl glyoxylate (0.1 M) in DMSO (eq 1), we found



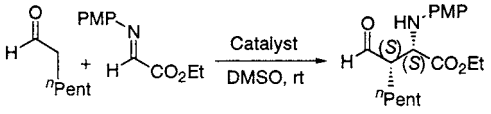
that amino acid **39** was formed as the sole product in 80% yield as its syn diastereomer (dr > 10:1) with 87% ee.[15,16] *This constituted the first example of an unmodified enolizable aliphatic aldehyde being successfully used in a catalytic asymmetric Mannich-type reaction*. A comprehensive screen of amine catalysts (Table 7) revealed L-proline, hydroxyproline, and its *tert*-butyl ether derivative as promising catalysts for this reaction.[15] This reaction proved to be tolerant of a wide range of solvents including ionic liquids and aqueous conditions (Table 8).

Reactions of aldehydes with *N*-PMP-protected α-imino ethyl glyoxylate afforded Mannich-products with excellent enantioselectivities (91−99% ee) (Scheme 3). The diastereoselectivities obtained were found to be dependent on the chain length as well as the bulkiness of the substituents of the aldehyde donors.

Reactions with preformed α-imino glyoxylates have been limited in that only the syn diastereomers are selectively accessible. Intrigued by the result of SMP in the catalyst screen (Table 7, entry 3), we revisited this catalyst and found that it provided the corresponding anti diastereomers **43** with 74−92% ee as the major products (Scheme 4).[17]

We then succeeded in broadening the scope of this reaction to preformed imines beyond imino glyoxylates, and ultimately established a more general and efficient one-pot three-component protocol. Initially, we focused on Mannich-type reactions with preformed aldimines. It turned out to be crucial that the aldehyde donor be added very slowly to the reaction mixture, thus avoiding the formation of undesired side products, particularly those arising from self-aldolization. Upon in situ $NaBH_4$ reduction of the Mannich products, the corresponding β-amino alcohols **44**−**50** were isolated predominantly as one

Table 7. Catalyst Screen for the Mannich-Type Reaction of Heptanal with α-Imino Ethyl Glyoxylate



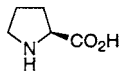
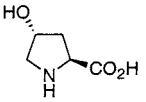
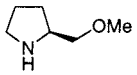
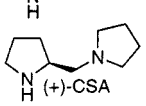
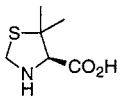
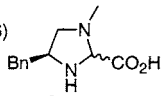
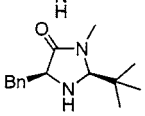
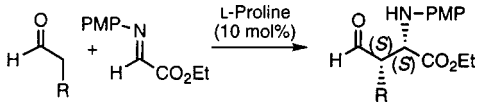
Entry	Catalyst	Time	Yield	dr syn:anti	ee (%) syn(anti)
(1)		3h	88%	32:1	>99(31)
(2)		26h	85%	32:1	99(20)
(3)		22h	40%	<1:10	-- (76)
(4)		2h	14%	2.8:1	57(32)
(5)		18h	78%	19:1	62(18)
(6)		22h	56%	1.7:1	64(4)
(7)		4h	<5%	1.3:1	11(27)

Table 8. Solvent Screen for the Mannich-Type Reaction of Aldehydes with α-Imino Ethyl Glyoxylate

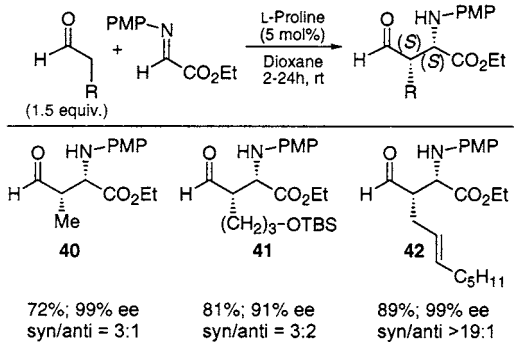


R	solvent	yield (%)	ee (%)
i-Pr	DMSO	81	87
i-Pr	Et_2O	70	80
i-Pr	$CHCl_3$	62	74
i-Pr	EtOAc	75	88
i-Pr	THF	79	88
	THF (4 °C)	75	92
i-Pr	dioxane	81	93
	dioxane (4 °C)	82	96
i-Pr	$[bmim]BF_4$	90	93
pent	dioxane/H_2O (4:1)	44	>99

diastereomer in 57−89% yield and ee = 90−99% (Table 9).[15]

These results eventually led to the successful development of a one-pot three-component protocol for the challenging task of directing the role of the aldehyde components. Slow addition of aldehyde donor to various substituted aromatic aldehydes gave, after in situ $NaBH_4$ reduction, β-amino alcohol derivatives **44**−**50** with excellent enantioselectivities (Table 10).[15] When performed at lower temperatures and with water as a cosolvent, respectively, an increase in diastereoselectivity and enantiomeric excess can be observed for electron-deficient aromatic systems (Table 10, entries 1, 2, and 7), whereas

Scheme 3. β-Formyl-Substituted α-Amino Acids from Unmodified Aldehydes as Donors



Scheme 4. SMP-catalyzed Mannich-type Reactions of Unmodified Aldehydes with *N*-PMP-Protected α-Imino Ethyl Glyoxylate

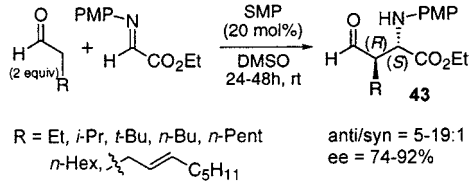
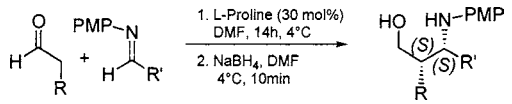


Table 9. Mannich Reactions of Unmodified Aldehydes with Preformed Aldimines



entry	R	R′	product	yield (%)	dr	ee (%)
1	Me	*p*-$NO_2C_6H_4$	**44**	81	>10:1	99
2	Me	*p*-CNC_6H_4	**45**	72	7:1	98
3	Me	*p*-BrC_6H_4	**46**	57	6:1	95
4	Me	*p*-ClC_6H_4	**47**	81	>10:1	93
5	Me	Ph	**48**	65	4:1	93
6	Me	*m*-BrC_6H_4	**49**	89	3:1	96
7	pent	*p*-$NO_2C_6H_4$	**50**	60	>19:1	90

in the cases of halogen-substituted aromatic systems, the results remain inconclusive. In the absence of a second aldehyde, proline did catalyze the direct asymmetric self-Mannich reaction using the same aldehyde both as donor and acceptor component, which furnished self-Mannich adducts **51**−**55** in good yields and, with the exception of isovaleraldehyde, good enantioselectivities (Table 11).[15]

3. The First Direct Organocatalytic Asymmetric Michael Reactions

To further expand the scope of enamine-based carbon−carbon bond-forming reactions, we sought to apply our concept of amine-catalyzed enamine generation to asymmetric Michael reactions.[18−20] A complementary mode of activation is iminium-based activation of the Michael acceptor (Figure 2).

Our first studies of organocatalytic Michael reactions in 2000 involved a reexamination of proline as applied to the Wieland−Miescher ketone synthesis.[18] We found that proline catalyzed the Michael reaction of 2-methylcyclohexane-1,3-dione with methyl vinyl ketone to form 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione that then underwent the ring-closing aldol reaction. Application of this transformation in screening revealed catalysts that distinguished themselves in their ability to catalyze the Michael addition step, the Michael and aldol addition steps, or the complete transformation. Several of the key catalysts unveiled here were later exploited in our studies as well as in the studies of others in the area of imine and enamine-based catalysis (Figure 3).

Extending our enamine-based activation strategy common to our earlier antibody studies, we found that in the presence of chiral amines both ketones and aldehydes can be used as nucleophiles without preactivation.[19,20] As a model, we studied the proline-catalyzed Michael reaction of acetone and cyclopentanone with benzalmalonate and nitrostyrene (Scheme 5) affording the Michael product as a racemate and with only modest enantiomeric excess, respectively. Yet, these constituted the first examples of a direct asymmetric Michael reaction employing an enamine-activated donor.[20]

When we switched to diamine **23** (revealed first in our Wieland−Miescher ketone studies), however, the ee was improved significantly with both nitrostyrene and alkylidene malonates as acceptors (Scheme 6). Thus, we focused on this diamine as catalyst of choice for Michael reactions employing ketone donors. Using alkylidene malonates **66** as acceptors (Scheme 6), the corresponding Michael adducts **67** could be obtained with up to 91% ee at −25 °C.[19] In the unprecedented reactions of unmodified aldehydes with nitrostyrenes **68**, amine catalyst **69** proved superior and provided Michael products **70** with high syn diastereoselectivity and up to 78% ee.[20] These stereochemical results were accounted for by assuming acyclic transition states **I** and **II**. *These Michael reactions constituted the first direct catalytic asymmetric reactions—of any type—involving aldehyde donors and encouraged the development of aldehyde-based reactions with a range of electrophiles.*

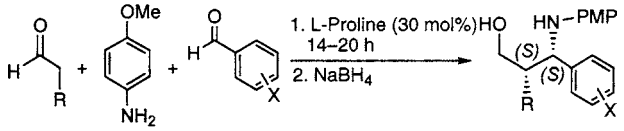
4. Diels−Alder Reactions

The concept of amine-catalyzed activation as described for Michael reactions can also be applied to Diels−Alder reactions. Recently, the activation of α,β-unsaturated carbonyl compounds as dienophiles via LUMO-lowering iminium formation has been described.[21] Alternatively, we have developed a protocol involving in situ enamine activation of α,β-unsaturated ketones (Scheme 7). In the amine-catalyzed Diels−Alder reaction (or double Michael reaction) with nitro-olefins as dienophiles, cyclohexanone derivatives **71**−**74** were obtained in an efficient single-step process (Scheme 8).[22] In the absence of a nitro-olefin as dienophile, iminium activation of the α,β-unsaturated ketone as dienophile together with in situ generation of a 2-amino-1,3-butadiene diene provided cyclohexanone derivatives by self-Diels−Alder reactions.[23]

5. One-Pot Multicomponent Asymmetric Assembly Reactions

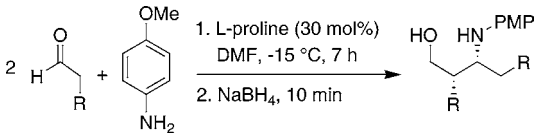
Direct asymmetric assembly of simple achiral building blocks into stereochemically complex molecules has long

Table 10. Direct One-Pot Three-Component Asymmetric Proline-Catalyzed Mannich Reactions



				at 4 °C in DMF			at −20 °C in DMF			at −20 °C in DMF/H_2O (95:5)		
entry	R	X	product	yield (%)	dr	ee (%)	yield (%)	dr	ee (%)	yield (%)	dr	ee (%)
1	Me	*p*-NO_2	**44**	85	>10:1	>99	87	65:1	98	90	25:1	99
2	Me	*p*-CN	**45**	65	5:1	93	83	65:1	99	79	21:1	97
3	Me	*p*-Br	**46**	81	10:1	91	77	16:1	89	80	29:1	93
4	Me	*p*-Cl	**47**	65	6:1	93	92	12:1	84	88	6:1	76
5	Me	H	**48**	65	4:1	93	82	4:1	94	89	24:1	88
6	Me	*m*-Br	**49**	77	4:1	97	86	11:1	90	83	17:1	87
7	*n*-pent	*p*-NO_2	**50**	73	4:1	75	87	138:1	>99	85	11:1	>99

Table 11. Formation of Self-Mannich Products



entry	R	product	yield (%)	syn/anti	ee (%)
1	Me	**51**	85	4:1	82
2	*n*-Bu	**52**	51	5:1	85
3	*n*-octyl	**53**	90	4:1	81
4	allyl	**54**	92	5:1	87
5	*i*-Pr	**55**	64	2:1	18

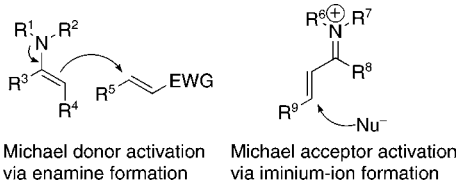


FIGURE 2. Modes of activation for amine-catalyzed Michael reactions.

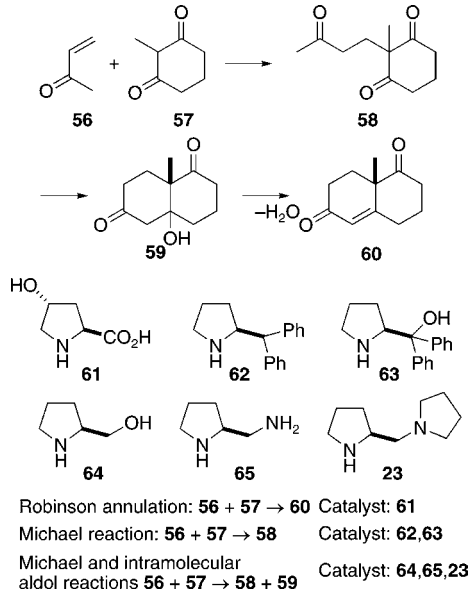


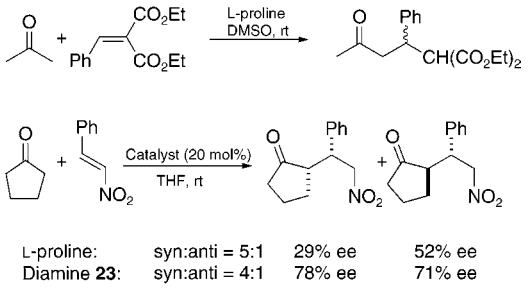
FIGURE 3. Amine-catalyzed Michael reaction and Michael−aldol sequence.

been the purview of nature's enzymes. Considering the versatility of the aldehyde functionality with respect to reaction coupling, we have developed a number of one-pot assembly reactions that exploit our aldol, Mannich, and Diels−Alder reactions.

Aldol−Aldol Reactions. A series of triketides was prepared by slow addition of propionaldehyde into acceptor aldehyde and L-proline in DMF, and the isolated lactols were readily converted to the corresponding δ-lactones (Table 12).[24] These results are significant in terms of asymmetric formation of carbohydrates from aldehydes and comparable to the DERA (deoxyribose 5-phosphate aldolase)-catalyzed reaction of propionaldehyde, which afforded the trimerized product in only 13% yield after 2 weeks.[25] These results may prove to be significant with respect to amine-catalyzed prebiotic syntheses of carbohydrates.

Despite reports of well-controlled L-proline-catalyzed aldehyde−aldehyde aldol reactions providing aldol products with high enantioselectivity,[26] epimerization of **77** occurred easily during the second aldol reaction upon increasing reaction times (Table 12, entry 1), giving rise to trimeric isomer **79** (Scheme 9).[24] If propionaldehyde is simply mixed together with L-proline in DMF, the major product is dimer **77** due to its lower reactivity compared to propionaldehyde itself. In contrast to propionaldehyde, however, a simple mixture of acetaldehyde and L-proline provided **80** in 90% ee (Scheme 9).[27]

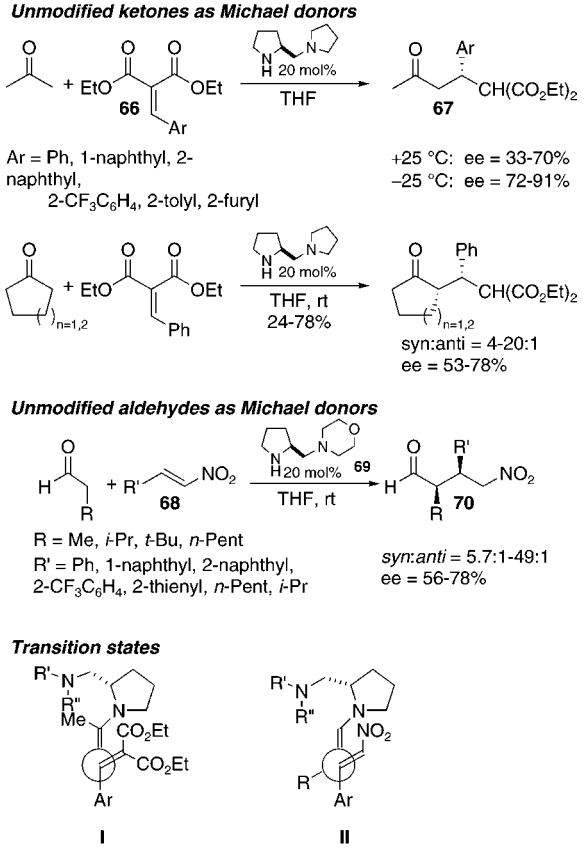
Scheme 5. First Examples of Enamine-Activated Donors in Michael Reactions



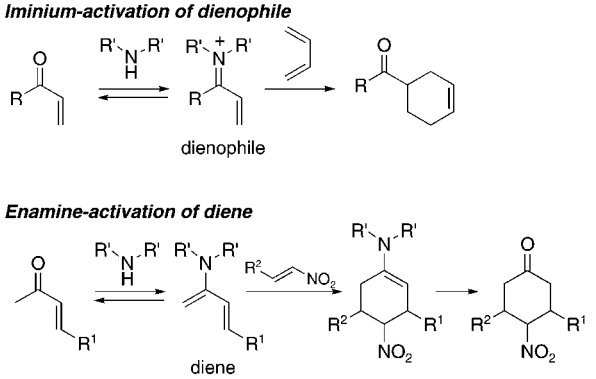
Mannich Oxime Formation, Mannich Allylation, and Mannich Cyanation Reactions. The aldehyde products from Mannich-type reactions of aldehydes with *N*-PMP-protected α-imino ethyl glyoxylate can be directly transformed to oximes **81**[15] or subjected to In-mediated allylation[28] providing lactones **82** (Scheme 10).

Upon treatment with Et_2AlCN in a one-pot fashion, these Mannich products can also be converted to β-cy-

Scheme 6. Amine-Catalyzed Michael Reactions via Enamine-Activation and Related Transition States



Scheme 7. Amine-Catalyzed Activation Modes of Diels−Alder Reactions



anohydroxymethyl α-amino acid derivatives, for example, **83**−**85** (up to >99% ee) as single diastereomers in up to 68% yield over two steps (Table 13).[29]

Amination−Aldol Reactions. Exploiting the reactivity difference between ketones and aldehydes, we accomplished a one-pot amination−aldol sequence affording *β*-amino alcohols from acetone, aliphatic aldehydes, and azodicarboxylates (Table 14).[30] Although the amination product itself was formed with high enantioselectivity,[31] the net diastereoselectivities observed are low due to rapid proline-mediated racemization of the amination product prior to the relatively slow aldol reaction.

Knoevenagel−Diels−Alder Reactions. Combining our enamine-based activation of enones in Diels−Alder reactions with the amine-catalyzed Knoevenagel reaction of malonates with aromatic aldehydes, we developed a strategy for the one-pot reaction of an aromatic enone

Scheme 8. Amine-Catalyzed Diels−Alder Reactions via Enamine Activation

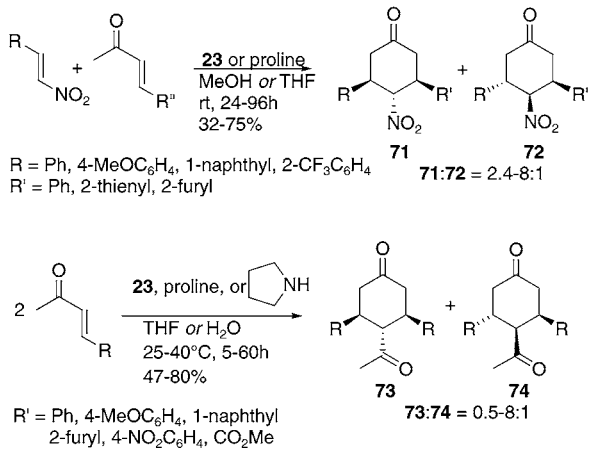
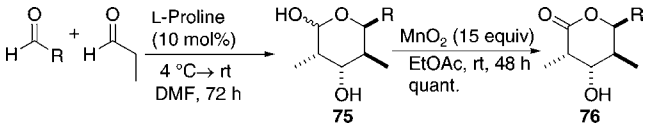


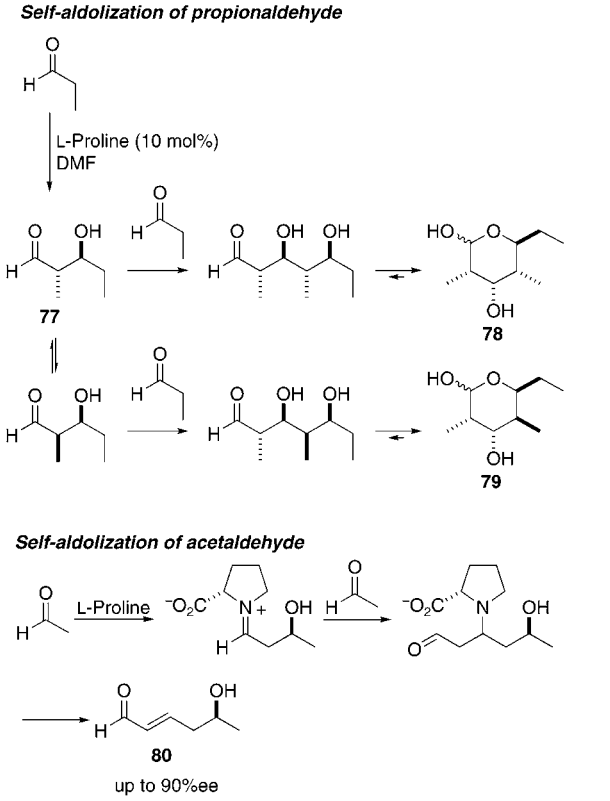
Table 12. L-Proline-Catalyzed Assembly of Pyranoses



entry	R	yield (%)	α/β	ee of **76** (%)
1	Et	53	1:2.2	11 (47,[a] 33[b])
2	*i*-Pr	32	1:2.0	12
3	*i*-Bu	24	1:2.5	11

[a] ee after 10 h at 4 °C. [b] ee after 72 h at 4 °C.

Scheme 9. Self-Aldolization of Propionaldehyde and Acetaldehyde



Scheme 10. One-Pot Oxime Formation and Allyation

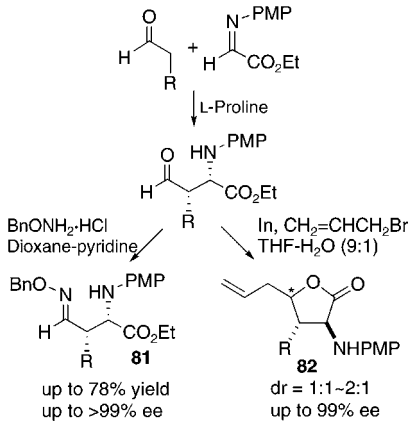


Table 13. One-Pot Mannich−Cyanation Reactions

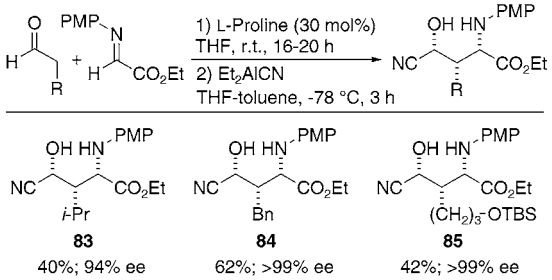
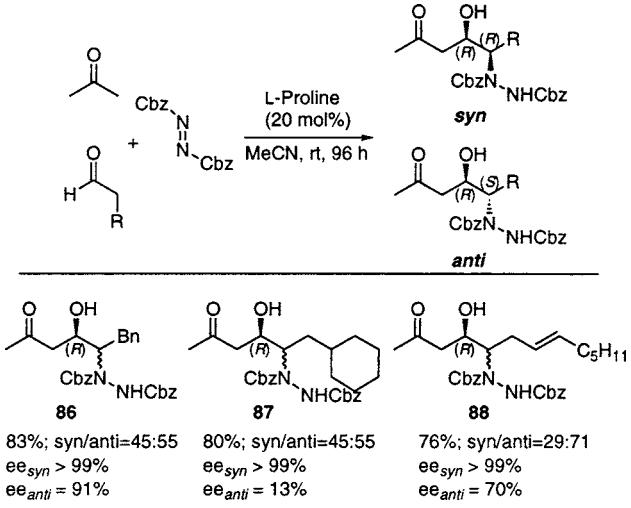


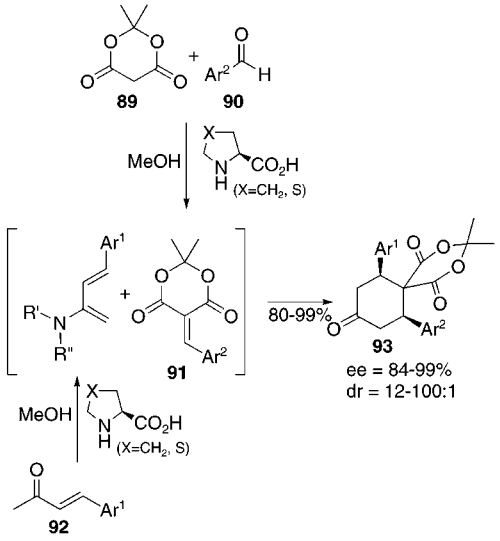
Table 14. L-Proline-Catalyzed Amination−Aldol Assembly Reaction



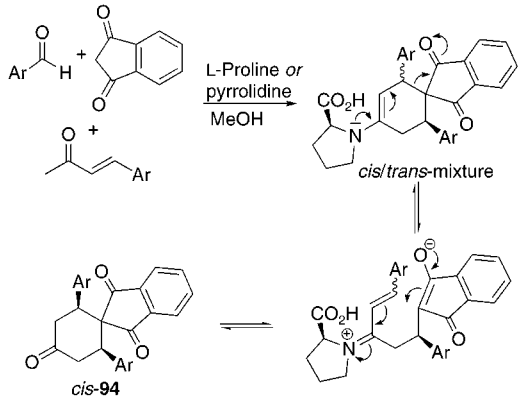
92 with an aromatic aldehyde and Meldrum's acid, which upon catalysis by L-proline or L-DMTC afforded spirocyclic ketones **93** with high diastereoselectivities and up to 99% ee (Scheme 11).[32] The Knoevenagel reaction of Meldrum's acid and arylaldehydes provided alkylidene derivatives **91**, which reacted as dienophile of the Diels−Alder reaction with the enamine of arylenone. This Knoevenagel−Diels−Alder reaction sequence formed three new carbon−carbon bonds in one pot.

If 1,3-indandione is used instead of Meldrum's acid, a variety of aromatic aldehydes afforded, after thermodynamic equilibration, the cis-configured Knoevenagel−

Scheme 11. Amine-Catalyzed Asymmetric Knoevenagel−Diels−Alder Reaction



Scheme 12. Heterodomino Knoevenagel−Diels−Alder Epimerization Reaction



Diels−Alder products **94** in almost quantitative yields (Scheme 12).[33]

6. Reaction Mechanisms and Transition States

Invoking the Hajos−Eder−Sauer−Wiechert reaction, we assume that the key intermediate of the direct intermolecular asymmetric aldol, Mannich, and Michael reactions is an enamine formed between L-proline or a diamine and the corresponding donor substrate. In the aldol reaction, this enamine attacks the carbonyl group of the aldehyde acceptor with high enantiofacial selectivity, provided by a highly organized hydrogen-bonded framework resembling a metal-free Zimmerman−Traxler-type transition state (Scheme 13). Recently, computational studies by Houk and co-workers confirmed[34] that this transition state is energetically the most favorable, predicting the stereochemistry observed correctly.

This mechanism reflects our observation that both a base and an acidic proton are required for effective catalysis to occur. Further support for hydrogen bonding

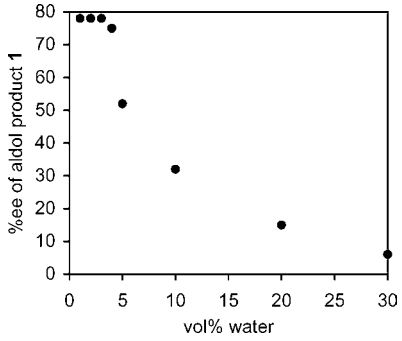
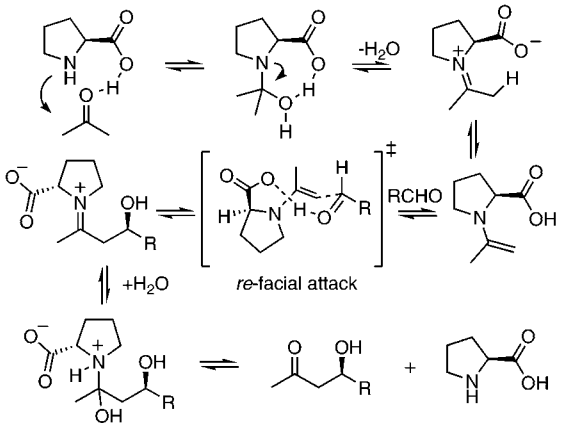


FIGURE 4. Effect of water on the enantiomeric excess of aldol product **1**.

Scheme 13. Enamine Mechanism of the Direct Catalytic Asymmetric Aldol Reaction Catalyzed by L-Proline



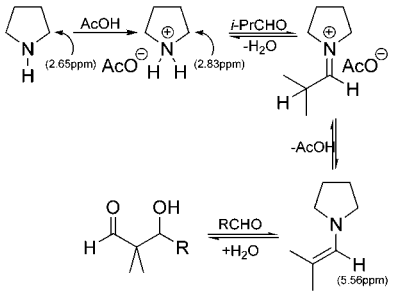
as an essential feature of the transition state of the aldol reaction comes from our findings that the addition of water severely compromises the enantioselectivity of aldol product formation (Figure 4). Nonetheless, while enantioselectivity of the aldol reaction is compromised in aqueous media synthesis, the reaction still proceeds. We have exploited this observation with the synthesis of polyhydroxylated aldols in aqueous reaction media[35] with unprotected donors such as dihydroxyacetone.

While the prolyl-enamine intermediate has not been directly observed, in a recent mechanistic study of the reaction of isobutyraldehyde with pyrrolidine/acetic acid, we were able to confirm the formation of an enamine intermediate by ^{1}H NMR spectroscopy. When isobutyraldehyde was added to a solution of pyrrolidine/acetic acid in d_6-DMSO, within 5 min the formation of a new peak at $\delta = 5.56$ ppm was observed corresponding to the presumed enamine intermediate (Scheme 14).[10a]

Further insight into the mechanism of the aldol reaction could be gained by the observation of a linear effect for the reaction of acetone and 4-nitrobenzaldehyde in DMSO with L-proline as a catalyst (Figure 5), which is consistent with the transition state proposed above involving a single molecule of catalyst at the carbon−carbon bond-forming step.

In Mannich-type reactions, the stereochemical results are explained best by invoking chairlike transition states similar to those for the related aldol reaction with L-proline directing a nucleophilic *si*-facial attack of an (*E*)-imine by

Scheme 14. Enamine Formation by ^{1}H NMR



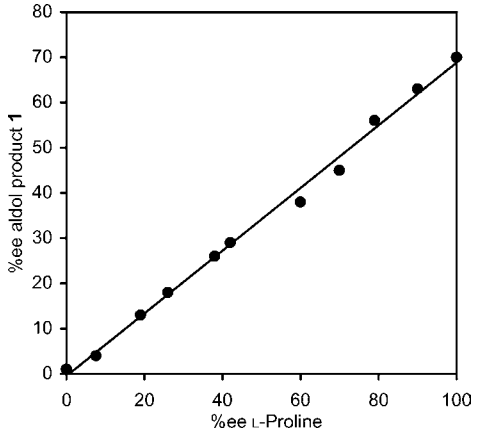


FIGURE 5. Linear effect in the L-proline-catalyzed aldol reaction of acetone with 4-nitrobenzaldehyde in DMSO. The line fits the equation $y = 0.69x - 0.47$, $R^2 = 0.995$.

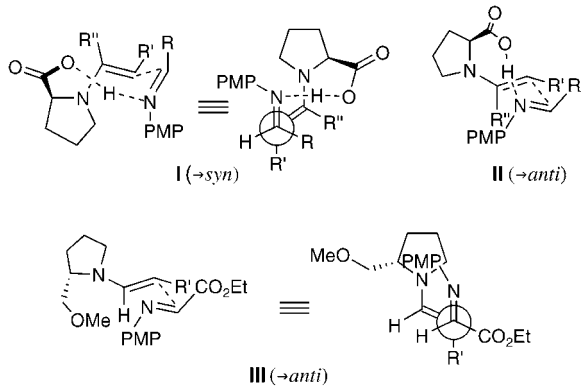


FIGURE 6. Transition States for the direct asymmetric Mannich-type reaction.

the *si*-face of an aldehyde-derived enamine intermediate (Figure 6, **I** and **II**).[11,16] A key feature of these transition states is an enamine the double bond of which points away from the proline carboxylic acid, thus facilitating the essential intramolecular proton transfer from the carboxylic acid to the nitrogen of the forming amine. Unlike the aldol reaction, the Mannich reaction with aldehyde nucleophiles proceeds in a highly enantioselective fashion even in reaction media containing a high concentration of water. Computational studies by Houk suggest that proton transfer to the imine is virtually complete in the TS of the Mannich reaction implying a substantial ionic interaction between an iminium and the carboxylate that is less perturbed in protic solvents than the corresponding aldol interaction.[36] Since the (*E*)-imine is more stable than

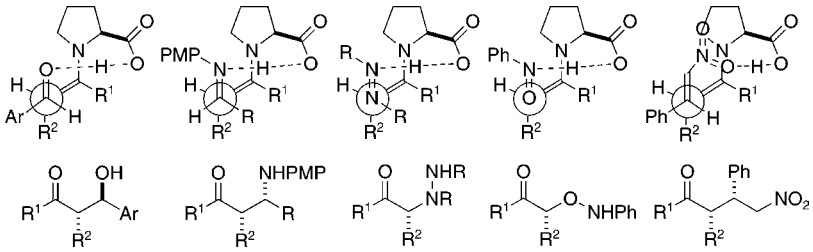


FIGURE 7. Comparison of transition states of proline-catalyzed reactions.

the corresponding (*Z*)-imine, the substituent R of the imine is forced into a pseudoaxial arrangement. This explains the reversal of stereoselectivity for the proline-catalyzed Mannich reaction as compared to the aldol reaction, where this substituent can adopt a pseudoequatorial position.[36] Lacking the stereodirecting carboxylate of proline, the topicity of the transition state for the SMP-catalyzed reaction is altered (Figure 6, **III**).

Significantly, our proline- and diamine-catalyzed asymmetric aldehyde addition reactions have been extended in reactions with azodicarboxylates[30,31,37] and nitrosobenzene electrophiles[38] to affect asymmetric α-amination and α-oxyamination reactions. The unifying features of proline-catalyzed asymmetric enamine-based reactions are best seen in the Newman projections of Figure 7.

Common to the Mannich, α-amination, and α-oxyamination reactions is a hydrogen bond involving an amine on the electrophile with the stereodirecting carboxylate of proline. This interaction, which may be significantly ionic in character, enforces excellent enantiofacial discrimination with these electrophiles. In contrast, in the Michael reaction involving a nitrostyrene electrophile, the interaction between the nitrostyrene electrophile and the carboxylate of proline is not optimal and the enantioselectivity is very modest.

Outlook

L-Proline and other chiral amines have been shown to be efficient asymmetric catalysts of a variety of significant imine- and enamine-based reactions. Studies from our laboratory and the contributions of others have advanced one of the ultimate goals in organic chemistry, the catalytic asymmetric assembly of simple and readily available precursor molecules into stereochemically complex products under operationally simple and in some cases environmentally friendly experimental protocols. One of the significant findings of these studies is the development of catalysts that allow aldehydes, for the first time, to be used efficiently as nucleophiles in a wide-variety of catalytic asymmetric reactions. Previously, only nature's enzymes were thought capable of this chemical feat. With future efforts, small organic catalysts may match some of nature's other heretofore unmatched synthetic prowess, and in doing so, they may help explain the development of complex chemical systems in the prebiotic world and provide hints toward yet to be discovered mechanisms in extant biological systems.

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