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Proline-catalyzed asymmetric reactions

Benjamin List*

Department of Molecular Biology, The Scripps Research Institute, 10550 N. Torrey Pines Rd., La Jolla, CA 92037, USA

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Contents

1. Introduction

Several strategies are available for enantioselective catalysis, including heterogeneous catalysis, Brønsted or Lewis acid and base catalysis, homogeneous transition-metal catalysis, and biocatalysis. One remarkable molecule, the amino acid proline, has become a crucial component in examples of all of the catalytic strategies listed above. Proline can be a ligand in asymmetric transition-metal catalysis, a chiral modifier in heterogeneously catalyzed hydrogenations, and, most importantly, proline itself can be an effective organocatalyst of several powerful asymmetric transformations, such as the aldol, Mannich, and Michael reactions.

In the focus of this review are proline-catalyzed asymmetric reactions. Covered are those reactions that are either catalyzed by proline alone, or by proline in combination with cocatalysts such as metal salts. Selected non-enantioselective proline-catalyzed reactions have also been included. However, the present review does not cover the use of important proline-*derived* auxiliaries or catalysts including the Enders-hydrazones or the Corey–Bakshi–Shibata-catalyst, which have been reviewed elsewhere.[1,2] Furthermore, other remarkable and useful amino acid-based catalysts such as MacMillan's iminium catalysts and Miller's peptide catalysts are beyond the scope of this review.[3]

1.1. Proline—a universal asymmetric catalyst?

There are several reasons why proline has become an important molecule in asymmetric catalysis. Not least is the

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* Fax: +1-858-784-7028; e-mail: blist@scripps.edu

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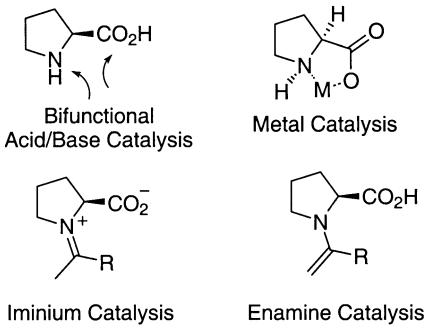


Figure 1. Modes of action in proline-catalysis.

fact that proline is an abundant chiral molecule that is inexpensive and available in both enantiomeric forms. Additionally, there are various chemical reasons that contribute to proline's role in catalysis. Proline is bifunctional, with a carboxylic acid and an amine portion. These two functional groups can both act as acid or base and can also facilitate chemical transformations in concert, similar to enzymatic catalysis. While enzymes typically use several different functional groups in their catalytic machinery, bifunctional asymmetric catalysis has become a very successful strategy in the laboratory.[4] In addition, proline is a chiral bidentate ligand that can form catalytically active metal complexes (Fig. 1).

While all of these criteria apply for all amino acids, proline is a secondary, cyclic, pyrrolidine-based amino acid. A unique consequence of this property is the increased pK_a value of its amine compared to primary amino acids. Another consequence of proline's pyrrolidine portion is the bicyclo[3.3.0]octane ring system ('open book structure') of its metal complexes. The most important difference to other amino acids is proline's effective aminocatalysis—a Lewis-base-type catalysis that facilitates iminium- and enamine-based transformations.[5] Proline's unique nucleophilic reactivity is primarily a consequence of the pyrrolidine portion, which forms iminium ions and enamines with carbonyl compounds more readily than most other amines, including cyclic ones such as piperidine.[6] The carboxylate further contributes to proline's aminocatalysis by acting as a general Brønsted cocatalyst.

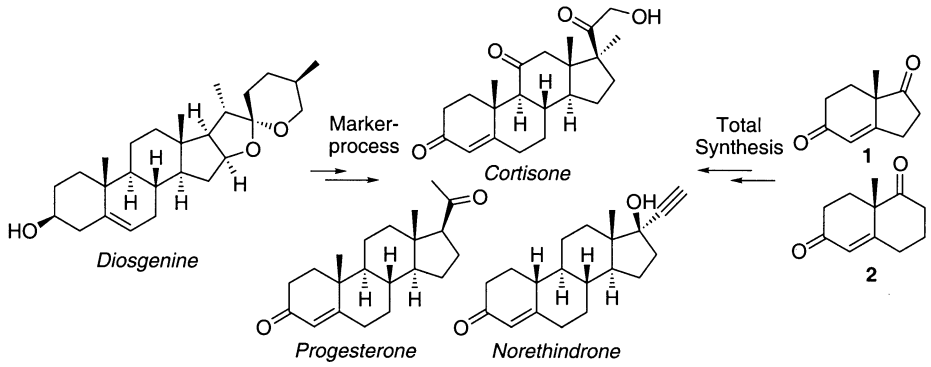
2. The Hajos–Parrish–Eder–Sauer–Wiechert reaction

2.1. Background

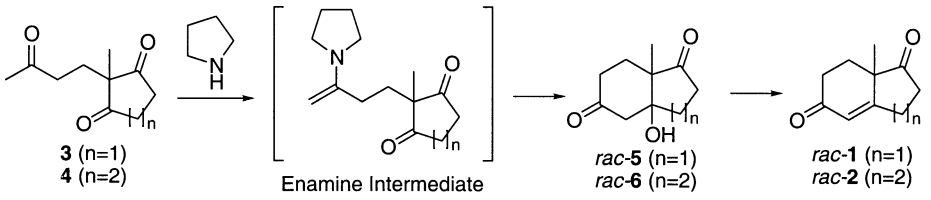
The 1960s witnessed a strong interest in efficient and economic steroid syntheses. This development was fueled by the commercial success of steroidal contraceptive agents (in 1969, 7.5 million American women were taking the pill) and the promise of other pharmaceutically active steroids such as the 'wonder drug', cortisone. The best way to synthesize steroids at the time was the Marker process, a sequence of reactions that led from diosgenin, a plant steroid isolated from Mexican wild yams, to cortisone and other important steroids such as norethindrone.[7] Early on, alternative synthetic schemes that would not require the use of a potentially rare resource were envisioned. For example, racemic tetrahydroindandione **1** and octahydronaphtalenedione **2** (the Wieland–Miescher ketone) have been resolved and used in asymmetric steroid total syntheses (Scheme 1).[8]

Ketones **1** and **2** can be made from symmetric monocyclic triketones **3** and **4** via intramolecular aldol condensation (Scheme 2). These reactions can be catalyzed by amines such as pyrrolidine,[9] and Spencer et al. convincingly demonstrated that they involve enamine intermediates similar to certain enzymatic reactions.[10]

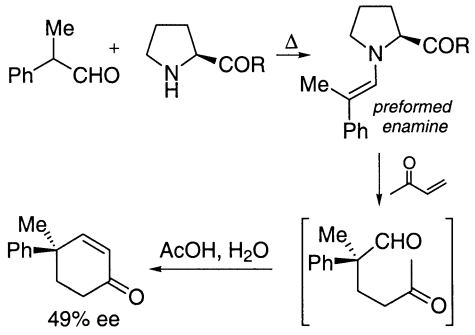
Contemporaneous to these experiments were Yamada's studies on asymmetric synthesis with amino acids. For example, asymmetric Robinson-annulations have been



Scheme 1. Synthesis of medicinally relevant steroids.



Scheme 2. Pyrrolidine-catalyzed intramolecular aldol reactions for the synthesis of diketones **1** and **2**.



Scheme 3. Yamada's asymmetric Robinson-annulation.

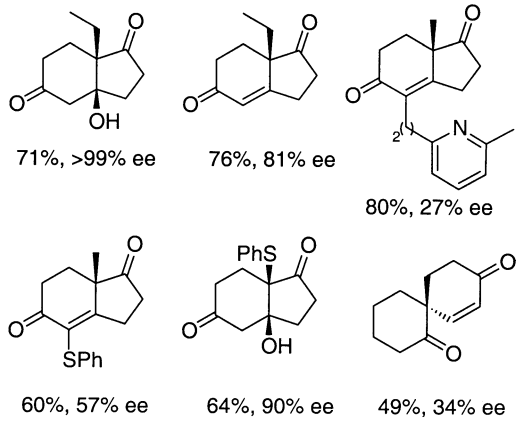


Figure 2. Selected products from Hajos–Parrish–Eder–Sauer–Wiechert reactions.

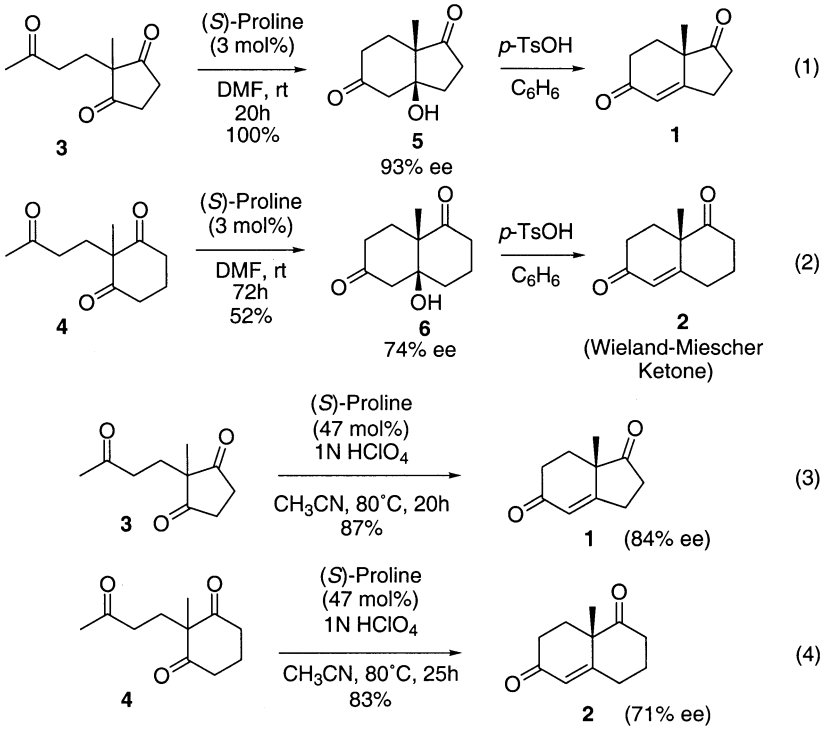
developed that are based on preformed proline-derived enamines (Scheme 3).[11]

Asymmetric enamine catalysis was first realized with the discovery of the proline-catalyzed asymmetric intramolecular aldol reaction by two industrial groups in the early 1970s. Hajos and Parrish at Hoffmann La Roche reported proline-catalyzed intramolecular aldol reactions of triketones such as **3** and **4** to give aldols **5** and **6** in good yields and ees (Scheme 4).[12] Acid-catalyzed dehydration furnished aldol condensation products **1** and **2** in a second step (Eqs. (1) and (2)). As shown by Eder, Sauer, and Wiechert at Schering, the aldol condensation products can also be obtained directly from triketones **3** and **4** if the cyclization is performed in the presence of proline (10–200 mol%) and an acid-cocatalyst (Eqs. (3) and (4)).[13]

2.2. Scope and applications

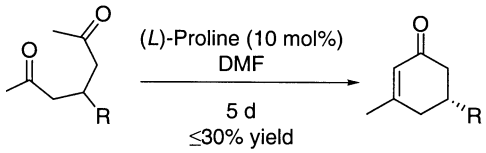
The asymmetric proline-catalyzed intramolecular aldol cyclization, also termed the Hajos–Parrish–Eder–Sauer–Wiechert reaction,[14] has been applied to several substrates since its invention over 30 years ago.[15] A small selection of products obtained using proline-catalyzed intramolecular aldolizations is shown in Fig. 2.[16]

The Hajos–Parrish–Eder–Sauer–Wiechert reaction has not only been used in steroid syntheses but also in several other natural product total syntheses.[17] The reaction has been studied using polymer-bound (*S*)-proline as the catalyst[18] and Agami et al. described conceptually related proline-catalyzed enantiogroup differentiating aldol-cyclodehydrations of acyclic diketones (Table 1).[19] When compared to the Hajos–Parrish–Eder–Sauer–Wiechert reaction, the efficiency and enantioselectivity of Agami's desymmetrization reaction are generally lower.



Scheme 4. Hajos–Parrish–Eder–Sauer–Wiechert reactions.

Table 1. Agami's enantiogroup differentiating aldol cyclodehydration



R	ee (%)
Ph	47
n-C_5H_{11}	20
Me	42
i-Pr	8
t-Bu	0

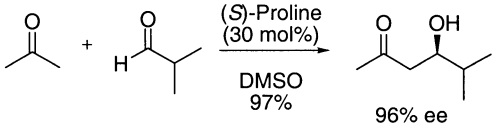
2.3. Mechanism

While realizing that their "results may be considered an example of a simplified model of a biological system in which (*S*)-proline plays the role of an enzyme", Hajos and Parrish initially rejected the aldolase-type enamine mechanism in their seminal work.[12] According to the proposed alternative mechanism, one of the enantiotopic ring carbonyl-groups is activated as a carbinolamine, which undergoes a C–C-bond-forming nucleophilic substitution reaction reaction with a side-chain enol (**A** in Fig. 3). This model is consistent with the low ^{18}O-incorporation into the product, an observation made if the reaction was conducted in the presence of ^{18}O-labeled water. However, the Hajos-mechanism has been rejected by Jung because it involves retention of configuration in an S_N2-like process.[20] Jung and later Eschenmoser et al.[21] first discussed a 'one proline-mechanism' involving a side-chain enamine intermediate and Agami et al. proposed model **B** in which a second proline molecule is involved.[22] Kinetic studies and an observed non-linear effect in asymmetric catalysis supported the involvement of two proline molecules in the enantioselectivity-determining step.[23] Heterogeneous catalysis involving a concerted bifunctional acid/base-mechanism (**C**) has also been suggested as a possible mechanism on the basis of the observation that proline is often not completely soluble in organic solvents.[24] Using quantum mechanical calculations, Houk et al. recently proposed a new model (**D**) that readily explains the observed enantioselectivity.[25] This elegant model is also consistent with the original Spencer-mechanism of the pyrrolidine-catalyzed intramolecular aldolization.

3. The direct intermolecular aldol reaction

3.1. Background

The direct intermolecular aldol reaction between two carbonyl compounds is central to sugar metabolism. Class I aldolases catalyze this process by using an enamine mechanism.[26] Several early bioorganic studies appeared in which simple small molecule amines and amino acids served as aldolase models.[27] Aldolase-like catalytically active amines, amino acids, and amine/antibody systems have been studied by Reymond et al.[28] In addition, catalytic antibodies have been generated which also use an enamine mechanism.[29] These important studies in particular have taught us the potential of enamine catalysis for asymmetric synthesis. Lessons learnt from the aldolase antibodies, the Hajos–Parrish–Eder–Sauer–Wiechert reaction, and the discovery of non-proteinogenic, metal complex-catalyzed direct asymmetric aldol reactions,[30] led to the development of the first proline-catalyzed direct asymmetric aldol reaction.[31] Initially, it was shown that, although proline typically reacts unproductively with aldehydes, the intermolecular reaction between a ketone and an aldehyde is possible if a large excess of the ketone donor is used. For example, acetone (20 vol.%, ca. 27 equiv.) reacts with isobutyraldehyde in DMSO to give the corresponding aldol in excellent yield and ee (Scheme 5).



Scheme 5. Highly enantioselective proline-catalyzed intermolecular aldol reaction.

3.2. Scope and applications

Several other aldehydes have been used in proline-catalyzed aldol reactions with acetone (Table 2). In general, aromatic aldehydes furnish aldols with ees of around 70% and in varying yields (54–94%). Higher enantioselectivities and yields were obtained when α-branched aldehydes were used and tertiary aldehydes gave exceptionally high ees of up to >99%. The only significant side-product in these reactions (and also in the Hajos–Parrish–Eder–Sauer–Wiechert reaction) is the aldol-condensation product.

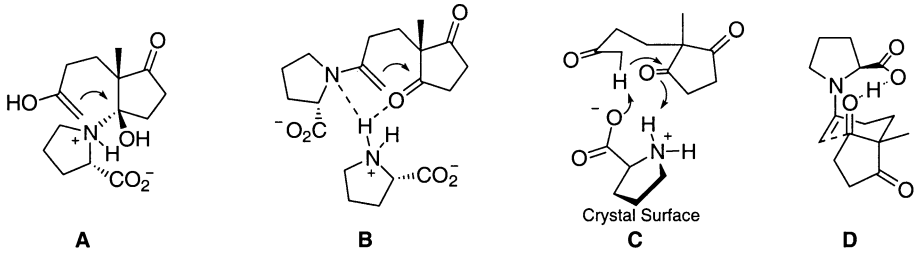
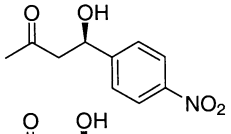
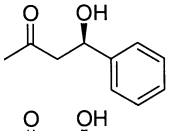
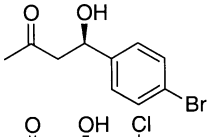
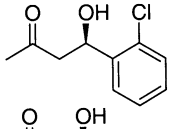
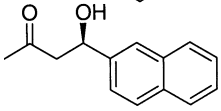
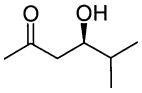
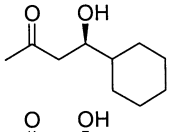
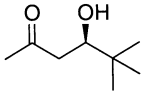
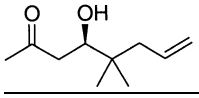


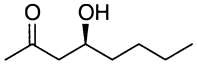
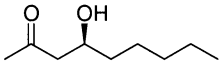
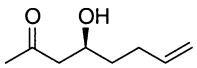
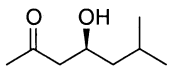
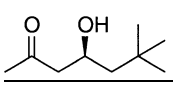
Figure 3. Proposed mechanisms of the Hajos–Parrish–Eder–Sauer–Wiechert reaction.

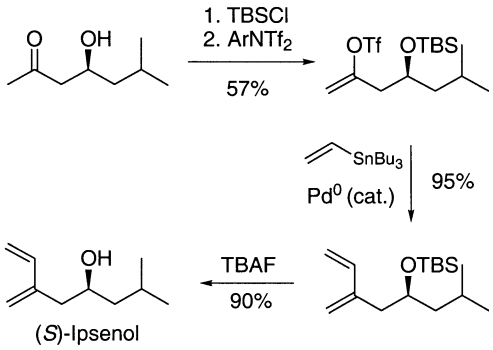
Table 2. Proline-catalyzed direct asymmetric aldol reactions using acetone as the donor

Product	Yield (%)	ee (%)
	68	76
	62	60
	74	65
	94	69
	54	77
	97	96
	63	84
	81	>99
	85	>99

α-Unbranched aldehydes turned out to be a difficult substrate class and did not provide the corresponding aldol products under standard conditions. Only homo-aldol-addition- and condensation of the aldehyde or elimination of the cross-aldol product to the α,β-unsaturated ketone were observed in DMSO. Using acetone or acetone/$CHCl_3$ mixtures as solvents and 10–20 mol% of proline as the catalyst allowed isolation of the cross-aldol products in modest yields and good enantioselectivities (Table 3).[32]

Table 3. Proline-catalyzed direct asymmetric aldol reactions using α-unbranched aldehydes as acceptor

Product	Yield (%)	ee (%)
	31	67
	35	73
	34	72
	34	73
	22	36

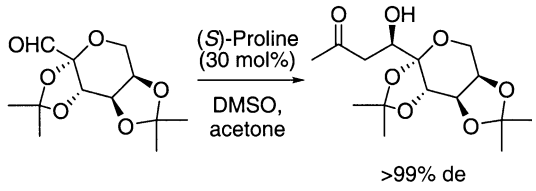


Scheme 6. Catalytic asymmetric total synthesis of (*S*)-ipsenol.

Observed side-products are the cross-aldol condensation products and the homo-aldol addition product of acetone.

The proline-catalyzed aldol reaction of acetone with α-unbranched aldehydes has been used in a short synthesis of the natural pheromone (*S*)-ipsenol (Scheme 6).

Recently, the proline-catalyzed intermolecular aldol reaction with acetone has been applied to the highly diastereoselective synthesis of complex sugar derivatives (Scheme 7).[33]



Scheme 7. The proline-catalyzed intermolecular aldol reaction in the synthesis of complex sugars.

Table 4. The proline-catalyzed intermolecular aldol reaction using cyclic ketones as donors

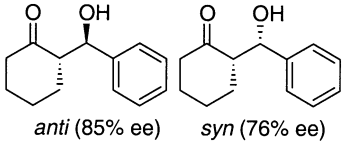
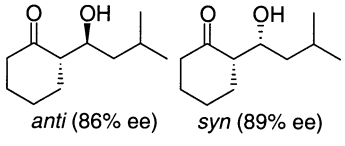
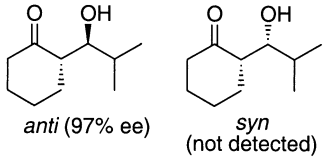
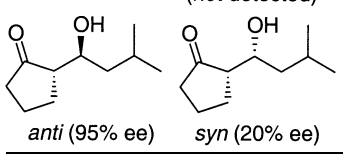
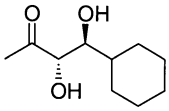
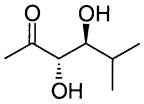
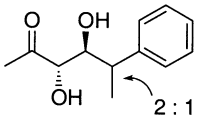
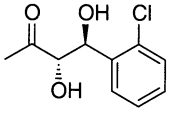
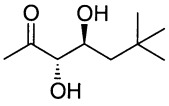
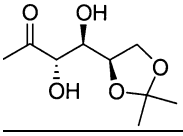
Product	Yield (%)	dr
 *anti* (85% ee) *syn* (76% ee)	85	1:1
 *anti* (86% ee) *syn* (89% ee)	41	7:1
 *anti* (97% ee) *syn* (not detected)	68	>20:1
 *anti* (95% ee) *syn* (20% ee)	77	2.5:1

Table 5. The proline-catalyzed intermolecular aldol reaction using hydroxyacetone as the donor

Product	Yield (%)	dr	ee (%)
	60	>20:1	>99
	62	>20:1	>99
	51	>20:1	>95
	95	1.5:1	67
	38	1.7:1	>97
	40	2:1	>97

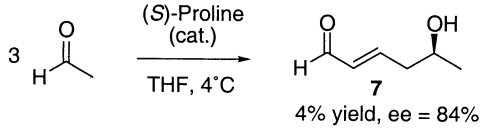
A general limitation of the method is the scope of the ketone component. Since a large excess of the ketone is often required, small and inexpensive ketones such as acetone, butanone, and cyclohexanone are typically used. Selected reaction products from proline-catalyzed aldol reactions with ketones other than acetone are provided in Table 4. Other ketones such as 3-pentanone and cetophenone have not been successfully used yet.

Excellent results have also been obtained with hydroxyacetone as the donor. In this case, anti-diols are formed in high regioselectivities, diastereoselectivities and enantioselectivities (Table 5).

Several proline-catalyzed intermolecular aldol reactions have recently been successfully repeated, both with proline itself and with poly(ethylene glycol)-supported proline.[34,35]

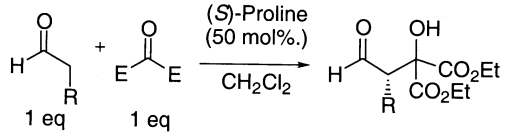
In addition to serving as acceptors in proline-catalyzed aldol reactions, aldehydes can also act as donors under certain conditions. For example, acetaldehyde trimerizes in the presence of (*S*)-proline to give aldehyde **7** in low yield but relatively high enantioselectivity (Scheme 8).[36]

Furthermore, it was found that several α-unbranched alde-



Scheme 8. Proline-catalyzed asymmetric acetaldehyde trimerization.

Table 6. The proline-catalyzed direct asymmetric intermolecular aldol reaction using aldehydes as donors



R	Yield (%)	ee (%)
Me	90	90
Et	91	85
i-Pr	88	85
$CH_2CH{=}CH_2$	94	88
n-C_6H_{13}	91	84
Ph	97	0

hydes react with activated non-enolizable ketones to give aldols in good yields and ees (Table 6).[37]

3.3. Mechanism

The originally proposed mechanism of the proline-catalyzed intermolecular aldol reaction[31] was based on the established class I aldolase-mechanism that involves carbinolamine, imine or iminium, and enamine intermediates.[26] The catalytically active functional groups in class-I aldolases are an ε-amino group of a lysine residue and, depending on the enzyme subtype, a set of Brønsted cocatalysts required for the various proton-transfers of the multi-step reaction mechanism. In the proline-catalyzed version, the catalytic amine is proline's pyrrolidine. The carboxylate could function as a multi-purpose Brønsted cocatalyst for the proton-transfers (Scheme 9).

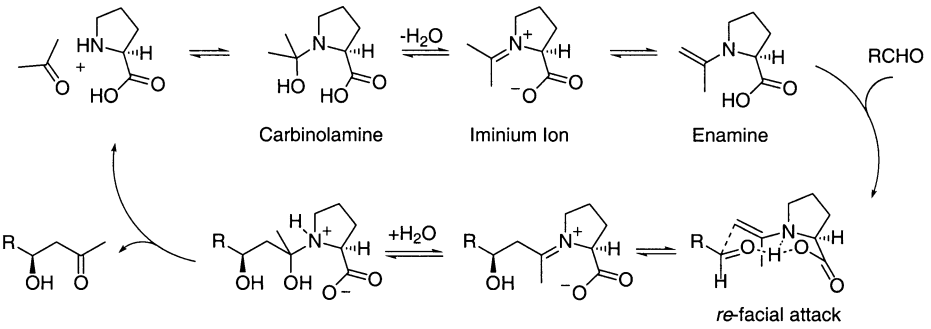
The enantioselectivity was explained with a transition state (**E**) that can be described as a metal-free version of the classical Zimmermann–Traxler model (**F**),[38] which successfully explains stereoselectivities of metal enolate aldol reactions. Furthermore, model **E** is similar to Houk's recently calculated transition state of the Hajos–Parrish–Eder–Sauer–Wiechert reaction (**D**).[25] However, according to these calculations, an N–H hydrogen bond does not lower the energy of the transition state and model **E** has consequently been advanced to model **G**,[5] which is superimposable to the calculated transition state of the proline-catalyzed intermolecular aldol reaction (Fig. 4).

The proposed multi-step reaction mechanism (Scheme 9) has very recently been confirmed using density functional theory calculations.[39a] Moreover, the validity of transition state **G** has been demonstrated by using density functional theory predictions followed by experimental verification of stereoselectivities of proline-catalyzed aldol reactions.[39b]

4. Mannich reactions

Proline-catalysis has recently been extended to the direct asymmetric three-component Mannich reaction of ketones, aldehydes, and amines to give β-amino ketones in high yields and enantioselectivities (Scheme 10).[40]

Prior examples of catalytic asymmetric Mannich reactions



Scheme 9. Originally proposed mechanism of the proline-catalyzed direct asymmetric aldol reaction.

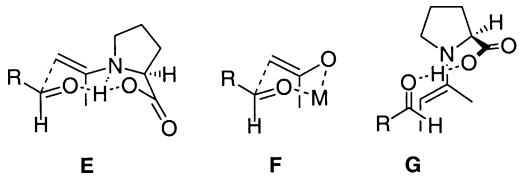
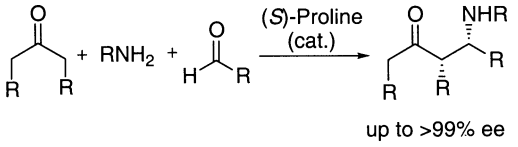


Figure 4. Transition states.

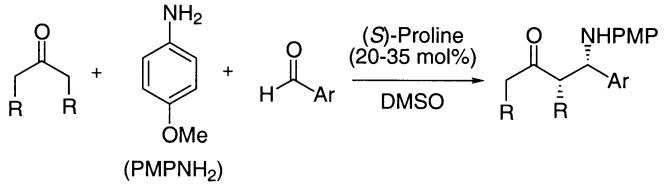


Scheme 10. Proline-catalyzed direct asymmetric Mannich reaction.

typically were indirect and required the use of preformed imine- and enol equivalents.[41] In contrast, the proline-catalyzed version constitutes a rare example of a catalytic asymmetric multi-component reaction. The substrate scope of this reaction has recently been explored.[42] Various ketones can be employed in proline-catalyzed Mannich reactions with *p*-anisidine ($PMPNH_2$) and *p*-nitrobenzaldehyde with excellent results (Table 7).

Catalyst and amine-component have also been varied and so far proline seems to be the optimal catalyst while *p*-anisidine turned out to be the most useful amine-component. A remarkable aspect of the reaction is its tolerance to a broad range of diverse aldehydes as substrates. Both aromatic and aliphatic aldehydes can be used. Aromatic aldehydes generally give the Mannich products in high ees yet modest yields.[43] Most importantly, and in contrast to the proline-catalyzed aldol reactions and to all other catalytic asymmetric Mannich reactions, α-*unbranched* aldehydes were

Table 7. Proline-catalyzed direct asymmetric Mannich reactions varying the ketone component



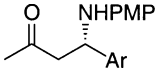
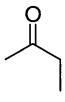
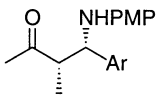
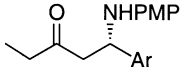
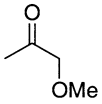
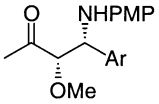
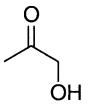
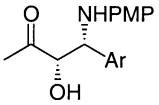
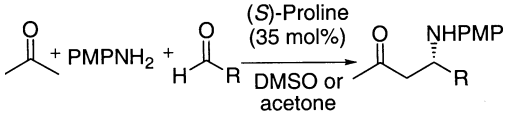
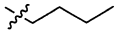
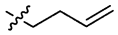
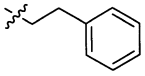
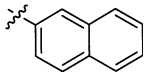
Ketone	Products	Yield (%)	de (%)	ee (%)
		50	–	94
	 (2.5:1)	96	>95	99
			–	94
		93	>95	98
		92	>95	>99

Table 8. Proline-catalyzed direct asymmetric Mannich reactions varying the aldehyde component



R	Yield (%)	ee (%)
	74	73
	90	93
	82	75
	60	80
	80	93
	35	96
	56	70

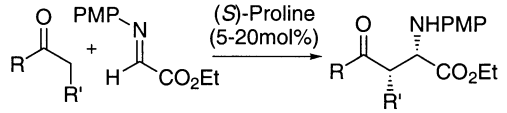
efficient substrates in the proline-catalyzed variant. Here, acetone or a chloroform/acetone mixture was used as the solvent instead of the commonly used DMSO (Table 8).

Recently, ethyl glyoxylate has been added to the list of aldehydes that may be used.[44] Functionalized α-amino acid esters were obtained in high stereoselectivities in such reactions if the preformed imine of ethyl glyoxylate was used. Both ketones and α-unbranched aldehydes could be utilized as donors to give the products in high enantioselectivities (Table 9).

Because of the exceptionally high regio-, diastereo-, and enantioselectivities observed in the Mannich reaction with hydroxyacetone, reactions with this ketone as the donor component were studied with several different aromatic aldehydes and isobutyraldehyde (Table 10).[42]

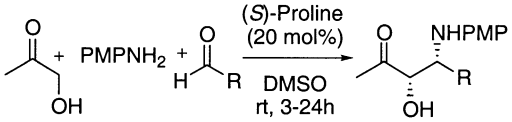
Good yields and diastereoselectivities and excellent regioselectivities were generally observed. Enantioselectivities were typically very high (up to >99%), yet dependent on the electronic nature of the aldehyde component. A good

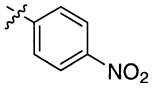
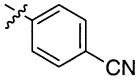
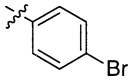
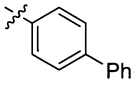
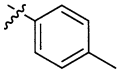
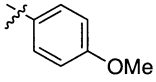
Table 9. Proline-catalyzed asymmetric Mannich reactions involving an ethyl glyoxylate derived imine



R	R′	Yield (%)	dr	ee (%)
Me	H	86	–	99
Me	Me	72	>19:1	>99
Et	Me	47	>19:1	>99
Me	OH	62	>19:1	99
H	*i*-Pr	81	>10:1	93
H	Me	72	1.1:1	99
H	*n*-Bu	81	3:1	99
H	*n*-Pent	81	>19:1	<99

Table 10. Proline-catalyzed direct asymmetric Mannich reactions involving hydroxyacetone as the donor



R	Yield (%)	dr	ee (%)
	92	20:1	>99
	88	15:1	99
	90	15:1	98
	79	8:1	94
	83	9:1	93
	85	5:1	86
	88	3:1	61
	57	17:1	65

R	σ_p	Yield %	dr	ee %	er
NO_2	0.81	92	20:1	>99	332
CN	0.70	88	15:1	99	199
Br	0.26	90	15:1	98	99
Ph	0.05	79	8:1	94	32
H	0	83	9:1	93	28
Me	-0.14	85	5:1	86	13

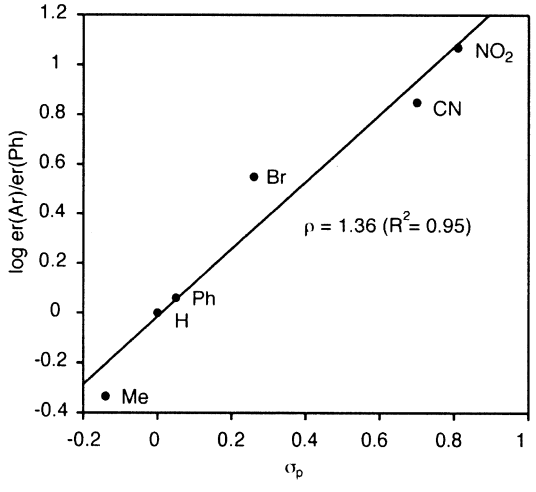
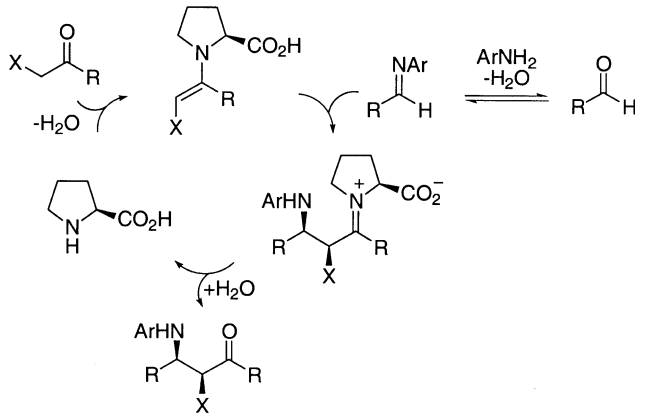


Figure 5. Hammett linear free energy correlation in the proline-catalyzed direct asymmetric three-component Mannich reaction.



Scheme 11. Proposed mechanism of the proline-catalyzed direct asymmetric three-component Mannich reaction.

correlation of enantioselectivities with Hammett σ_p-values was observed, and a linear Hammett plot was obtained with a reaction constant ρ for the proline-catalyzed three-component Mannich reaction of 1.36 (R^2=0.95) (Fig. 5).

The positive reaction constant is consistent with partial negative charge formation in the transition state and with the proposed mechanism that involves nucleophilic addition of a proline–enamine to an imine (Scheme 11).

According to the mechanistic proposal, a proline–enamine reacts with an imine in the C–C-bond forming and enantioselectivity-determining step. Both the imine and enamine intermediates are formed in situ from an aldehyde and a ketone in two separate pre-equilibria.

One of the intriguing aspects of the proline-catalyzed Mannich reaction is its stereoselectivity. Diastereo- and enantioselectivities are opposite to those observed in proline-catalyzed intermolecular aldol reactions. This result was initially explained with transition states that involved (*Z*)-imines. However, (*E*)-aldimines strongly predominate equilibria with the corresponding (*Z*)-imines. For example, only the (*E*)-aldimine can be detected ^{1}H NMR-spectroscopically in the reaction of *p*-nitrobenzaldehyde with *p*-anisidine in DMSO-d_6.[42b] Therefore, although (*Z*)-imines cannot be excluded, it seems more likely that (*E*)-imines are involved in the reaction mechanism. The currently preferred transition state models for the proline-catalyzed Mannich reaction (**H**) and intermolecular aldol reaction (**G**) are shown in Fig. 6.

The assumed transition states reflect the fact that enantiofaciality of the electrophile (imine *si* vs aldehyde *re*), but not that of the enamine, is reversed in aldol vs Mannich

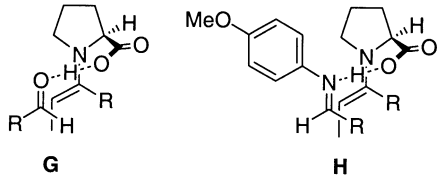
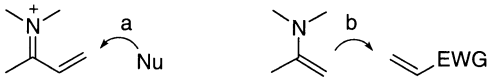


Figure 6. Proposed transition states of proline-catalyzed aldol and Mannich reactions.



Scheme 12. Iminium and enamine catalysis of the Michael reaction.

reactions and in order to allow for protonation of its lone pair, an (*E*)-imine has to approach the enamine with its *si*-face to avoid unfavorable steric interactions between the pyrrolidine and aromatic ring.

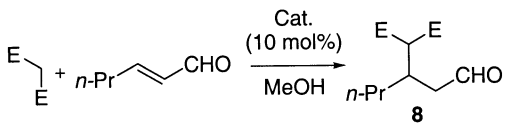
5. Michael reactions

The Michael addition is a particularly interesting reaction because proline-catalysis may proceed by both aminocatalytic pathways, iminium (a) and enamine catalysis (b) (Scheme 12); both reaction types have been realized.

5.1. Iminium catalysis of the Michael reaction

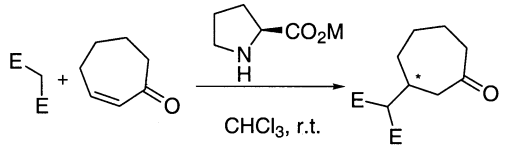
Yamaguchi et al. found the Michael addition of malonates to α,β-unsaturated aldehydes to be catalyzed by secondary amines, including (*S*)-proline.[45] For example, dimethyl malonate reacts with hex-2-enal in the presence of pyrrolidine or proline to furnish Michael adduct **8**. It was noted that triethylamine and *N*-methyl proline are inactive and that lithium prolinate is superior to proline itself (Table 11).

Table 11. Initial study by Yamaguchi et al. on iminium catalysis of the Michael reactions



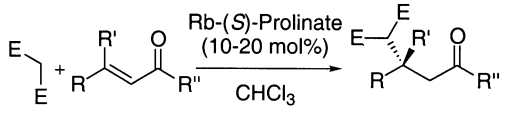
Catalyst	Yield (%)
NEt_3	No reaction
Pyrrolidine	33
(*S*)-Proline	44
(*S*)-Proline Li salt	93
(*S*)-Valine Li salt	32

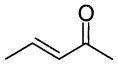
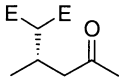
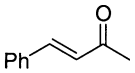
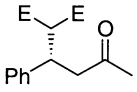
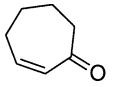
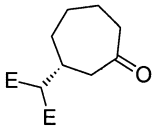
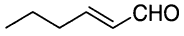
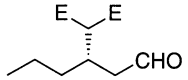
Table 12. Studied metal prolinates



M	Cat. mol%	Yield (%)	ee (%)	Abs. config.
Li	100	23	28	(*S*)
Na	5	72	29	(*R*)
K	5	72	51	(*R*)
Rb	5	91	59	(*R*)
Cs	5	73	56	(*R*)
$Mg_{1/2}$	200	8	31	(*S*)
$Ca_{1/2}$	20	41	22	(*S*)
$Sr_{1/2}$	20	39	12	(*S*)
$Ba_{1/2}$	20	48	1	(*S*)
Nme_4	10	33	41	(*R*)

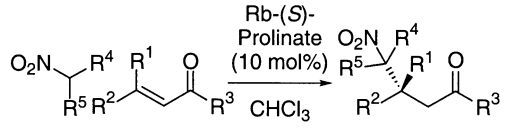
Table 13. Rubidium prolinate-catalyzed Michael additions of diisopropyl malonate

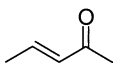
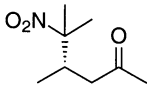
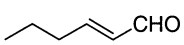
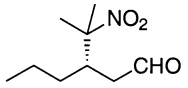
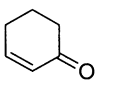
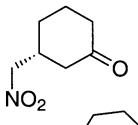
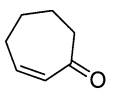
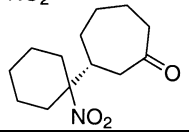


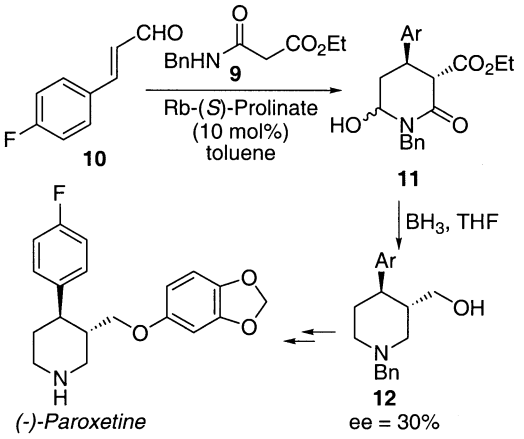
Enone or enal	Product	Yield (%)	ee (%)
		71	76
		79	53
		91	59
		58	41

The lithium prolinate-catalyzed reaction has been performed with several different α,β-unsaturated aldehydes in good yields. However, only racemic products were obtained. The authors proposed iminium intermediates to be involved in the mechanism of this novel Michael reaction. Later, the same group observed asymmetric induction if the reactions were performed in chloroform instead of methanol. After screening several different metal and ammonium prolinates as catalysts for the Michael addition of diisopropyl malonate to cycloheptenone, it was found that enantioselectivity and yield were optimal with the rubidium salt (Table 12).[46] Interestingly, the lithium and alkaline earth metal prolinates provided the product with reversed absolute configuration. The optimized conditions with rubidium prolinate as the catalyst have been applied to

Table 14. Rubidium prolinate-catalyzed Michael additions of nitroalkanes



Enone or enal	Product	Yield (%)	ee (%)
		74	68
		61	29
		55	45
		84	84



Scheme 13. Catalytic asymmetric synthesis of (−)-paroxetine.

Michael additions of diisopropyl malonate and also of nitroalkanes to a variety of unsaturated ketones and aldehydes to give the products in good yields and ees (Tables 13 and 14).[47]

Recently, an industrial group applied the Yamaguchi–Michael addition to an elegant yet only modestly enantioselective synthesis of the selective serotonine re-uptake inhibitor (SSRI) (−)-paroxetine (Scheme 13).[48]

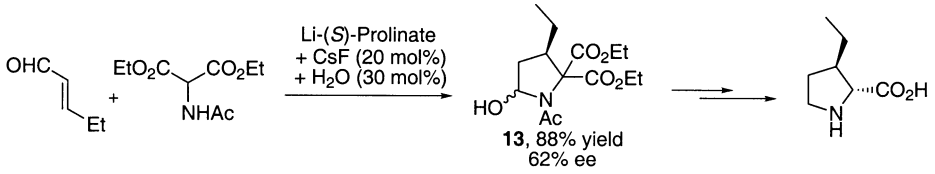
The rubidium prolinate-catalyzed Michael addition of a malonamide **9** to cinnamic aldehyde **10** gave *trans*-piperidinone **11**, which was reduced to give piperidine **12** in 30% ee. (−)-Paroxetine was obtained from piperidine **12** straightforwardly.

Yamaguchi et al. further demonstrated that the enantioselectivities of the malonate Michael additions could be further improved by using di(*tert*-butyl) malonate as the donor and cesium fluoride as a cocatalyst.[47b] Related conditions have been used in Merck's approach to the synthesis of substituted proline-derivatives (Scheme 14).[49]

Accordingly, treating α,β-unsaturated aldehydes with diethylacetamidomalonate furnished pyrrolidines such as **13**. These can be converted to 3-substituted proline derivatives in three steps. As has been noted before by Yamaguchi et al., addition of a small amount of water to the Michael reaction mixture was found to be essential for effective catalysis to occur.

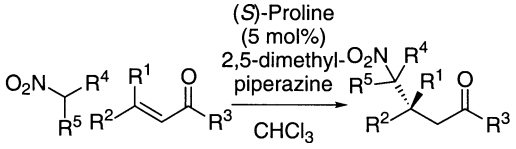
High enantioselectivities (up to 93% ee) in prolinate-catalyzed Michael additions of nitroalkanes to enones have recently been obtained by Hanessian and Pham by using a combination of proline (3–7 mol%) with a stoichiometric amount of *trans*-2,5-dimethylpiperazine as the catalyst (Table 15).[50]

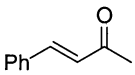
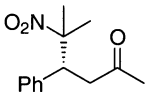
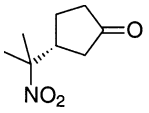
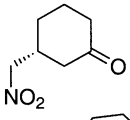
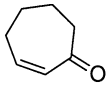
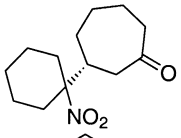
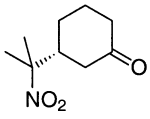
It is likely that these reactions and those that are catalyzed by metal prolinates are facilitated by an iminium mechanism. Evidence obtained by Yamaguchi et al. includes that tertiary amines such as *N*-methyl proline are inactive, and that in contrast to (*E*)-4-phenyl-3-buten-2-one, its iminium salt readily undergoes a Michael reaction with dimethyl malonate. Proline's function could be two-fold in providing

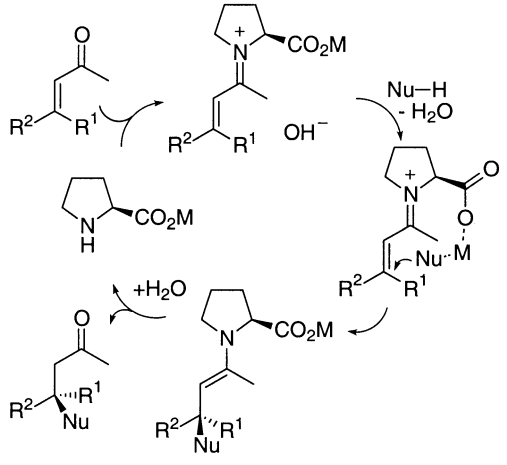


Scheme 14. Merck's synthesis of substituted prolines.

Table 15. Proline-catalyzed asymmetric Michael reactions that use an organic base as the cocatalyst



Enone or enal	Product	Yield (%)	ee (%)
		n.r.	61
		66	75
		61	71
		49	89
		88	93



Scheme 15. Possible iminium catalysis mechanism of proline-catalyzed Michael reactions.

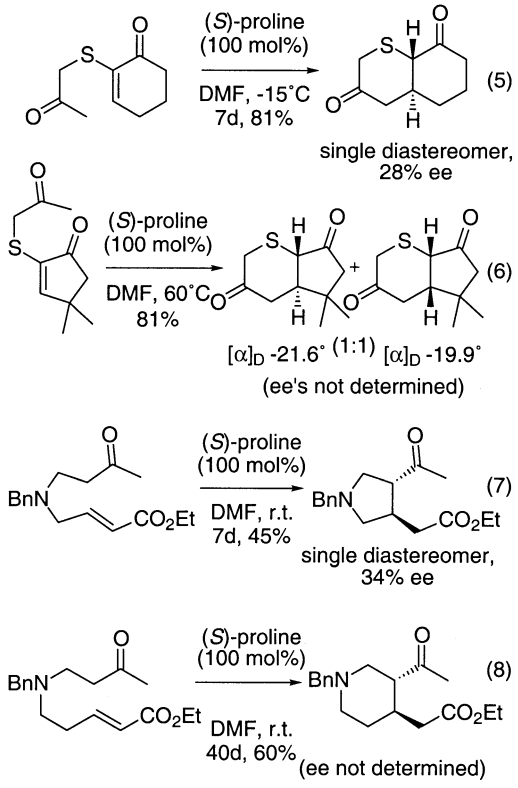
a secondary amine for iminium catalysis as well as the carboxylate as a cocatalyst that helps in binding the nucleophilic nitronate or malonate anion via the metal (or ammonium ion). In turn, this could determine the enantiofacial selectivity (Scheme 15).

An explanation of why different metals furnish enantiomeric products is not provided by this mechanism. However, it should be noted that the enantiofacial selectivity could readily reverse if the geometry of the presumed iminium ion was switched from (*E*) to (*Z*).

5.2. Enamine catalysis of the Michael reaction

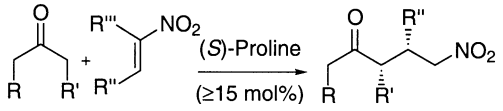
Intramolecular proline-catalyzed Michael reactions of unactivated ketones to α,β-unsaturated carbonyl compounds have been described by Kozikowski et al.[51] (Eqs. (5) and (6)) and Momose et al.[52] (Eqs. (7) and (8)) (Scheme 16).

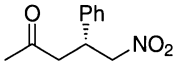
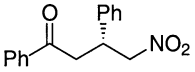
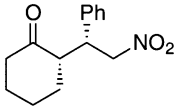
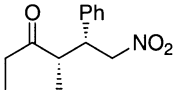
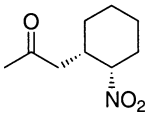
These reactions require a stoichiometric amount of the catalyst, long reaction times, and provide cyclic Michael products in only modest ees. In analogy to the Hajos–Parrish–Eder–Sauer–Wiechert reaction, a proline enamine



Scheme 16. Proline-catalyzed intramolecular Michael reactions.

Table 16. The proline-catalyzed intermolecular Michael reaction of unactivated ketones with nitro olefins



Product	Yield (%)	Selectivity	Method
	97 93	7% ee 12% ee	A B
	30	42% ee	B
	94 79	dr>20:1, 23% ee dr>20:1, 57% ee	A B
	74	dr=16:1, 76% ee	B
	95	dr=10:1, 19% ee	A

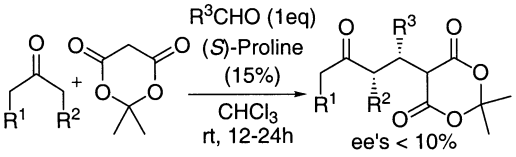
intermediate has been proposed to be involved in the mechanism.

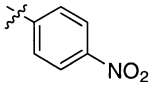
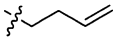
The first proline-catalyzed enantioselective intermolecular Michael reactions that use simple unactivated ketones as donors have recently been described.[53] Reacting selected small ketones (in excess) with nitro olefins and (*S*)-proline (15 mol%) in DMSO gave the corresponding Michael adducts in generally high yields but only low enantioselectivities (≤23%) (Method A, Table 16). Enders et al. could further improve the enantioselectivity of the process by using methanol as the solvent (Method B).[54]

A novel proline-catalyzed three-component reaction between ketones, aldehydes, and Meldrum's acid has also been developed.[55,56] The reaction presumably involves a Knoevenagel reaction followed by a non-enantioselective Michael-type hetero-Diels–Alder reaction (Table 17).

Why proline-catalyzed enamine catalytic Michael reactions (in contrast to Yamaguchi's iminium catalytic Michael reactions) generally showed lower enantioselectivities than the corresponding Mannich and aldol processes remains an open question. The basic lone pair of aldehydes and imines may be partially responsible for π-facial enantioselectivity by providing an additional point of interaction with the chiral proline enamine intermediate through hydrogen bonding to proline's carboxylic acid. Consistent with this concept is the fact that enantioselectivities in aldol and Mannich reactions are reduced in protic solvents such as methanol. Interestingly, *improved* enantioselectivities were observed in proline-catalyzed Michael reactions in methanol.

Table 17. A novel proline-catalyzed three-component reaction

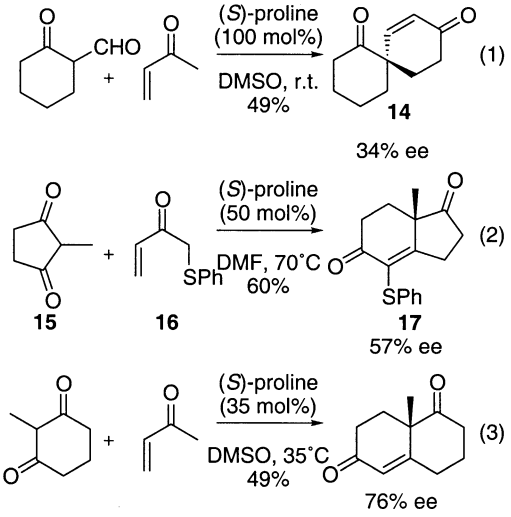


R^1	R^2	R^3	Yield (%)	de (%)
H	H		78	
H	H		83	
H	H		79	
H	H		51	
H	H		65	
			69	>95
			75	>95

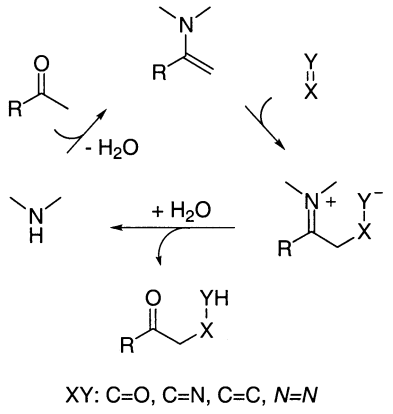
5.3. One-pot Robinson-annulations

The first proline-catalyzed asymmetric Robinson-annulation (intermolecular Michael reaction followed by intramolecular aldol reaction) has been developed by Swaminathan et al.[57] Reacting 2-formylcyclohexanone with methyl vinylketone (MVK) directly gave spirocyclic product **14** in modest enantioselectivity (Eq. (1) in Scheme 17). The scope of the reaction has been extended to other cyclic formylketones.[58] Wicha et al. found the proline-catalyzed reaction of diketone **15** with unsaturated ketone **16** to directly give Hajos–Parrish–Eder–Sauer–Wiechert-type product **17** (Eq. (2)).[59] This reaction has recently been extended to the Wieland–Miescher-ketone (Eq. (3)).[60]

While the proline-catalyzed one-pot Robinson-annulations are experimentally simpler than the original two-step



Scheme 17. Proline-catalyzed Robinson-annulations.



Scheme 18. The enamine catalysis cycle.

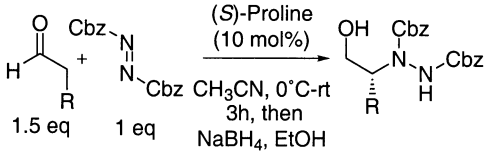
processes, it has been pointed out that the two-step procedures require significantly less catalyst and generally provide better yields and ees.[58]

6. The direct electrophilic α-amination

Proline-catalysis in aldol, Mannich, and Michael reactions can be rationalized with a general enamine catalysis cycle (Scheme 18).[5]

Accordingly, carbonyl compounds react with proline to generate an enamine intermediate and water. This enamine reacts with an electrophile X=Y, which may be an aldehyde, an imine, or an activated olefin in an aldol, Mannich, or Michael reaction. Hydrolysis of the iminium intermediate then gives the product under regeneration of the proline catalyst. An alternative electrophilic species could be a dialkyl azodicarboxylate (X=Y: $RCO_2N{=}NCO_2R$). The overall transformation would result in an electrophilic α-amination of the carbonyl compound.[61] The products of this reaction, if produced enantioselectively, could be useful precursors for various amino acid derivatives.

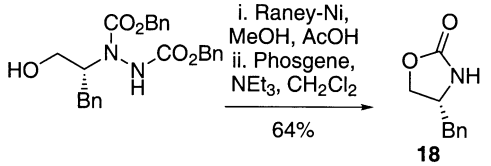
Table 18. The first direct catalytic asymmetric electrophilic α-amination of aldehydes



Product	R	Yield (%)	ee (%)
1	*i*-Pr	99	96
2	*n*-Pr	93	>95
3	*n*-Bu	94	97
4	Me	97	>95
5	Bn	95	>95

Very recently, this reaction has been realized for the first time.[62] It was found that proline catalyzes the direct electrophilic α-amination of unbranched aldehydes highly effectively and enantioselectively. Because the produced α-hydrazino aldehydes are configurationally labile, they were in situ reduced to the corresponding alcohols (Table 18).

The potential of the produced amino alcohol derivatives as precursors for the asymmetric synthesis of α-amino acid derivatives was demonstrated with a straightforward synthesis of Evans-type oxazolidinone **18** via hydrogenation and work-up with phosgene (Scheme 19). The hydrogenation removes both Cbz-protecting groups and simultaneously cleaves the N–N bond.



Scheme 19. Synthesis of an Evans-auxiliary.

The observed stereoselectivity can be explained with transition state **J** (Fig. 7), which again is superimposable with Houk's transition states of the Hajos–Parrish–Eder–Sauer–Wiechert reaction (**D**) and Agami's diketone-cyclization (**D′**). A comparison of the assumed preferred transition states of the proline-catalyzed enamine-involving intramolecular aldol reaction (**D**, **D′**),[25] intermolecular aldol reaction (**G**),[5] Mannich reaction (**H**),[42] Michael reaction (**I**),[53,54] and α-amination (**J**)[62] reveals three important and general structural elements: (1) The assumed proline–enamine is always in a conformation in which the carboxylate is *anti* to the enamine–olefin. (2) The enamine–olefin geometry is always (*E*). (3) The carboxylic acid protonates the electrophile to compensate negative charge formation. A generalized transition state (**K**) that combines these elements may be constructed (Fig. 7).

7. Miscellaneous proline-catalyzed asymmetric reactions

In addition to aldol, Mannich-, Michael and electrophilic α-amination reactions, proline has been used as a catalyst in several other asymmetric transformations such as allylic oxidations, transfer-hydrogenations, and Diels–Alder-type reactions. In these reactions, proline is not only used as an aminocatalyst but also as a chiral ligand in metal-mediated asymmetric processes.

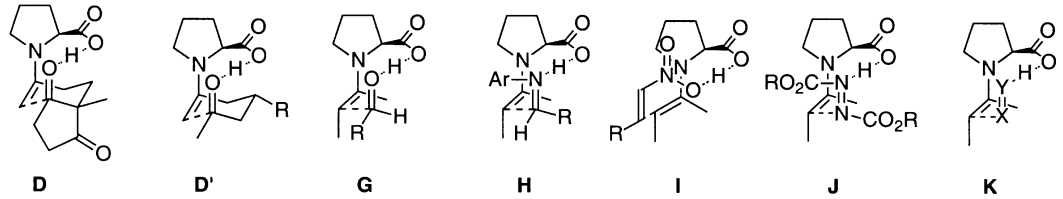
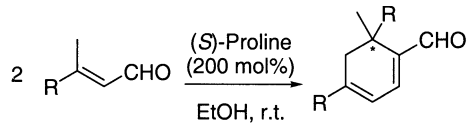
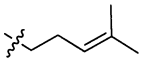
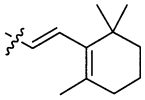
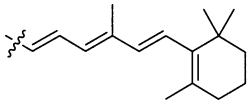


Figure 7. Postulated transition states of proline-catalyzed reactions.

Table 19. Dimerizations of unsaturated aldehydes (n.r.=not reported)



R	Yield (%)	ee (%)
CH_3	n.r.	–
	n.r.	n.r.
	52	43
	76	33

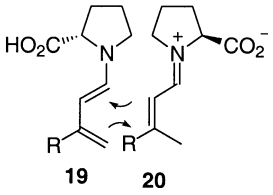


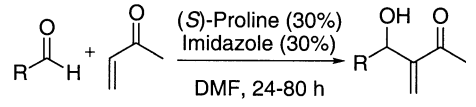
Figure 8. Possible intermediates.

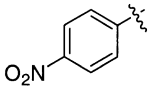
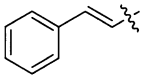
7.1. Diels–Alder-type dimerizations of α,β-unsaturated aldehydes

Asato and Liu et al.[63] found that upon treating α,β-unsaturated aldehydes with (*S*)-proline in ethanol, cyclic optically active dimers were obtained (Table 19).

Such dimerizations were known to occur under basic conditions, and to give racemic products.[64] The proline-catalyzed reactions furnish the products in encouraging enantioselectivity and it may be worthwhile to study other chiral amines as potential catalysts for this interesting reaction. Mechanistically, the reaction could proceed via dienamine **19** and/or iminium ion **20**. These intermediates may undergo a Diels–Alder-reaction followed by elimination and hydrolysis to give the observed products (Fig. 8).

Table 20. Proline-catalyzed Baylis–Hillman reactions

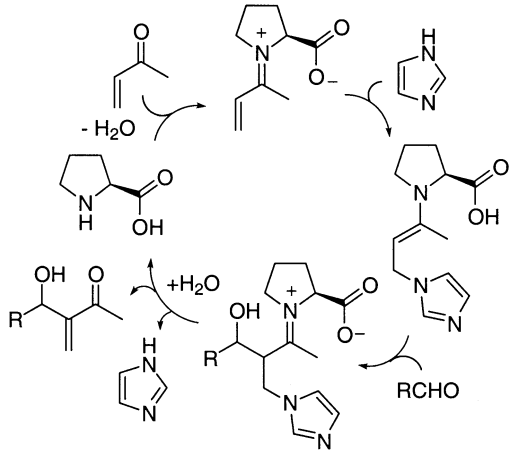


R	Yield (%)
	91
	90
	43
	46

7.2. Baylis–Hillman reactions

Very recently, a mixture of proline and imidazole (each 30 mol%) has been found to catalyze Baylis–Hillman reactions of aldehydes with MVK (Table 20).[65]

Essentially, no asymmetric induction was observed (ees 5–10%). According to the proposed mechanism, proline activates MVK as the iminium ion, facilitating conjugate addition of the imidazole. The resulting enamine reacts with the aldehyde in an aldol reaction. The Baylis–Hillman product is then formed via elimination and hydrolysis. That imidazole alone (in contrast to other nucleophiles such as DABCO) is not sufficiently reactive to induce the Baylis–Hillman process can be interpreted as evidence for the proposed iminium catalysis (Scheme 20). It will be interesting to note whether the use of other chiral amines or different reaction conditions may lead to a new catalytic asymmetric Baylis–Hillman variant.

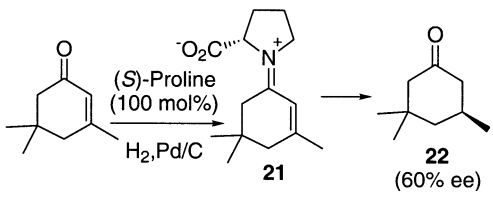


Scheme 20. A mechanism of the proline/imidazole-catalyzed Baylis–Hillman reaction.

7.3. Reductions

Several reductions involving proline as the source for asymmetric induction have been developed. These include hydrogenations, epoxide reductions, borane and boranate reductions, and ruthenium-catalyzed transfer hydrogenations.

Ethyl acetoacetate has been enantioselectively reduced with

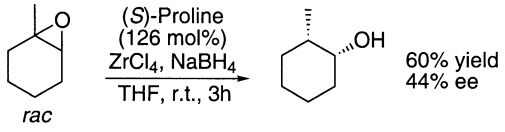


Scheme 21. Proline-catalyzed asymmetric hydrogenation.

a Raney Cu-catalyst modified with (*S*)-proline.[66] Other heterogeneous catalysts in combination with proline have also been used, but typically reduce ketones with low enantioselectivities.[67] Tungler et al. described the Pd/C-catalyzed reduction of isophorone in the presence of (*S*)-proline to give saturated ketone **22** in low yield and ca. 60% ee. The main side product results from a reductive amination of ketone **22** with proline. The reaction may involve iminium intermediate **21** (Scheme 21).[68]

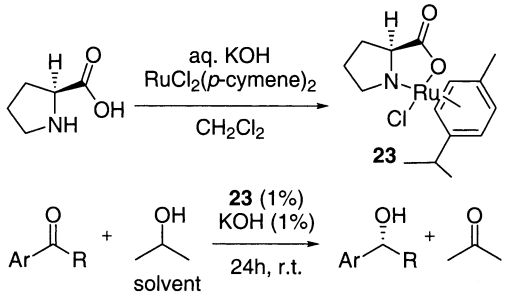
An equimolar mixture of $NaBH_4$ and (*S*)-proline in THF reduces ketones to secondary alcohols in ees of up to 62%.[69] Martens et al. used a mixture of borane with proline for the similar reactions and obtained enantioselectivities of up to >95%.[70] Presumably, proline is initially converted to prolinol, which then forms an oxazaborolidine, derivative of the well-known CBS-reduction catalyst.

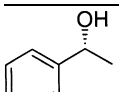
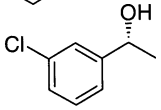
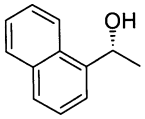
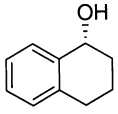
Racemic epoxides have been reductively cleaved with a mixture of zirconium tetrachloride, sodium borohydride, and (*S*)-proline to give enantioenriched alcohols (Scheme 22).[71] Apparently, these reactions are not kinetic resolutions and the authors speculate that they may involve zirconium enolates.

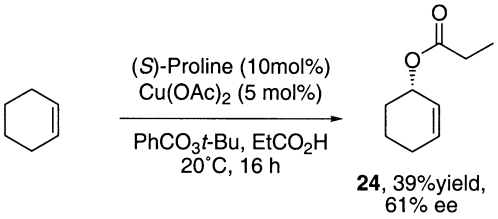


Scheme 22. Proline-catalyzed reductive epoxide-opening.

Table 21. Proline-catalyzed asymmetric transfer hydrogenation



Product	Yield (%)	ee (%)
	72	81
	74	68
	64	82
	8	92



Scheme 23. Proline-catalyzed asymmetric allylic oxidation.

An interesting Noyori-type asymmetric transfer hydrogenation has been developed by Furukawa et al.[72] The catalyst is prepared by mixing potassium prolinate with $RuCl_2$ (p-cymene)$_2$, and reduces aromatic ketones with isopropanol to give secondary alcohols in good yields and ees (Table 21).

7.4. Oxidations

One of the first catalytic asymmetric allylic oxidations was based on a copper catalyst combined with (*S*)-proline. Disclosed in a patent by Sumitomo Chemical Co., Ldt.,[73] this system was investigated by Muzart and Ferringa.[74] An example is the oxidation of cyclohexene with $PhCO_3t$-Bu in the presence of propionic acid and catalytic amounts of $Cu(OAc)_2$ and (*S*)-proline to give ester **24** in acceptable enantioselectivity (Scheme 23). Improved catalyst systems have recently been described.[75]

8. Conclusions

It is remarkable that despite the diversity of reactions discussed in this review, ranging from carbon–carbon bond-forming aldol-, Mannich-, and Michael reactions, to electrophilic aminations, transfer-hydrogenations, and allylic oxidations, the catalytically active species and source of asymmetry is a small and simple amino acid. While proline may not be the 'universal asymmetric catalyst' for all reactions, it clearly is a privileged molecule for enantioselective synthesis. Not only is proline inexpensive, available in both enantiomeric forms, stable, non-toxic, and a powerful catalyst for a number of asymmetric reactions; it also has a multifaceted mechanistic complexity hidden underneath its 'simple' structure. It would seem daring to expect anything less than the discovery of several new proline-catalyzed reactions in the future.

9. Note added in proof

Three important publications that highlight the vitality of the reviewed field have appeared while proof reading this article: MacMillan et al. describe proline-catalyzed highly enantioselective intermolecular aldol reactions between two aldehydes (Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, *ASAP*), and Jørgensen and coworkers describe proline-catalyzed electrophilic alpha-amination reactions (also see chapter six) of both aldehydes (*Angew. Chem. Int. Ed.* **2002**, *41*, 1790–1793) and ketones (*J. Am. Chem. Soc.* **2002**, *124*, 6254–6255).

Acknowledgements

Some of the experiments described herein were done in the laboratories of the reviewer and would not have been possible without the dedication and enthusiasm of his co-workers William Biller, Chris Castello, David Goldsheft, Linh Hoang, Harry Martin, Wolfgang Notz, and Peter Pojarliev. We gratefully acknowledge our collaborator K. N. Houk and his colleagues at the University of California, Los Angeles for sharing the results of their brilliant computational studies. We further thank Richard A. Lerner for his support and inspiration and the National Institutes of Health for generous funding of our studies.

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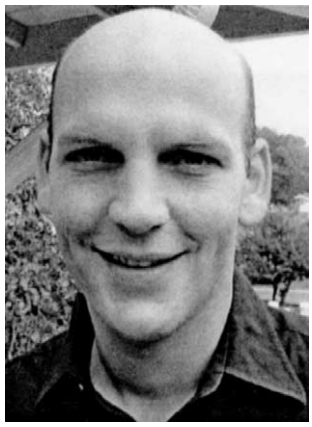
Biographical sketch



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 PhD (*summa cum laude*) in 1997 from the Johann Wolfgang Goethe University in Frankfurt working in the field of natural product synthesis under the supervision of Professor J. Mulzer. He spent nearly two years as a postdoctoral research associate in the laboratories of Professor 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.