Asymmetric Enamine Catalysis

Santanu Mukherjee, Jung Woon Yang, Sebastian Hoffmann, and Benjamin List*

Max-Planck-Institut für Kohlenforschung, D-45470 Mülheim an der Ruhr, Germany

Received August 28, 2007

Contents

* E-mail: list@mpi-muelheim.mpg.de.

1. Introduction

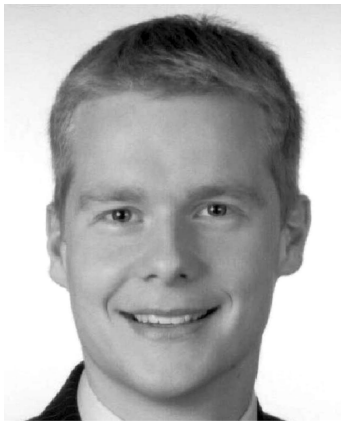
The catalysis by primary and secondary amines of electrophilic substitution reactions in the α-position of carbonyl compounds and related reactions via enamine intermediates is called enamine catalysis.[1,2] To a large degree this chemistry can be considered the catalytic variant of the classical preformed enamine chemistry (Scheme 1) pioneered by Stork.[3−5] In such transformations an enamine (**III**) is generated by reacting a carbonyl compound (**I**) with an amine (**II**) under dehydration conditions. Reaction of the enamine (**III**) can proceed via an addition (route **A**) or substitution (route **B**) route depending on the nature of the reaction partner (electrophile). In either case, iminium ions (**IV**) are usually formed, which are then hydrolyzed to afford the products (**V**). A vast array of transformations has been achieved via preformed enamine chemistry.[5] Therefore, a catalytic version of this chemistry was highly desirable.

Recent years have witnessed an explosive growth in the field of enamine catalysis and, particularly, asymmetric enamine catalysis, and it became apparent that, in addition to being almost ideally atom economic and step economic, the scope of the catalytic version (Scheme 2) and its potential for enantioselective synthesis by far exceeds those of the stoichiometric approach (Scheme 1). The basis of enamine catalysis is the reversible generation of enamines from a catalytic amount of an amine and a carbonyl compound. Key to enamine formation is the LUMO lowering effect and the resulting dramatic increase in C−H acidity upon initial conversion of the carbonyl compound into an iminium ion. There are two modes of enamine catalysis, depending on the class of electrophile used. On the one hand, double bond containing electrophiles such as aldehydes, imines, Michael

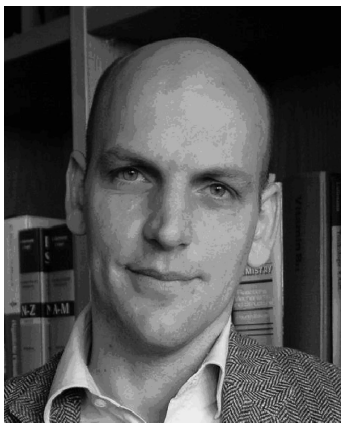
10.1021/cr0684016 CCC: $65.00
Published on Web 12/12/2007

Santanu Mukherjee was born in Hooghly, India, in 1980. After obtaining his B.Sc. (Chemistry Honors) from Ramakrishna Mission Residential College, Narendrapur, in 2000, he moved to the Indian Institute of Technology, Kanpur, where he finished his M.Sc. in 2002. Immediately afterward, he started his Ph.D. at the University of Cologne, Germany, under the supervision of Professor Albrecht Berkessel, where he worked on the enantioselective synthesis of amino acids, applying the emerging concepts of asymmetric organocatalysis. He completed his Ph.D. (*summa cum laude*) in February 2006 and joined Professor List's group for postdoctoral research. He is currently working on widening the scope of asymmetric counteranion directed catalysis in the domain of transition metal chemistry.

Jung Woon Yang was born in Jeju, Korea, in 1973. He received his Ph.D. degree in 2003 under the supervision of Drs. Choong Eui Song and Hogyu Han, working on the heterogeneous asymmetric catalysts for dihydroxylation, aminohydroxylation, allylic substitution reactions, and synthesis of DNA triangles with vertexes of bis(terpyridine)iron(II) complexes at the Korea Institute of Science and Technology (KIST) and Korea University, respectively. He undertook postdoctoral studies at the Max-Planck-Institut für Kohlenforschung, in Germany, with Prof. Benjamin List, where he worked on the development of asymmetric organocatalytic reactions, including transfer hydrogenation, the Mannich reaction, and cascade reactions. In 2006, he became a senior scientist in the List group.



Sebastian Hoffmann was born in 1979 in Aachen, Germany. He studied chemistry at Clausthal University of Technology and the University of Florida. After completing his master's thesis on "Pd-Catalyzed Reactions of Bicyclic Azetidines" in 2005 under the direction of Prof. D. Kaufmann, he joined the group of Prof. B. List, where he is currently working as a Ph.D. student. His research interests include both metal-free and metal-mediated asymmetric transformations.

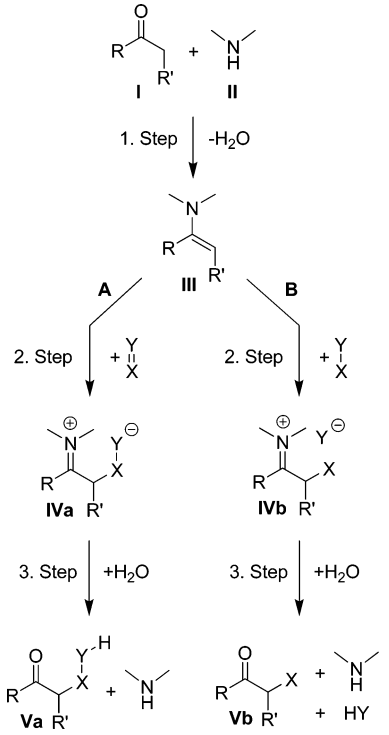


Benjamin List was born in 1968 in Frankfurt, Germany. He graduated from Freie University Berlin (1993) and received his Ph.D. (1997) from the University of Frankfurt (Mulzer). After postdoctoral studies (1997–1998) as a Feodor Lynen Fellow of the Alexander von Humboldt Foundation at The Scripps Research Institute (Lerner), he became a Tenure Track Assistant Professor there in January 1999. Subsequently, he developed the first proline-catalyzed asymmetric intermolecular aldol, Mannich, Michael, and α-amination reactions and received a grant on *Asymmetric Aminocatalysis* from the National Institutes of Health. He moved to the Max-Planck-Institut für Kohlenforschung in 2003 as an associate professor (2003–2005) and currently is a director (full professor) there and an honorary professor at the University of Cologne. His research interests are new catalysis concepts, bioorganic chemistry, and natural product synthesis. He has received several awards, including the Carl-Duisberg-Memorial Award of the German Chemical Society (2003), the Degussa Prize for Chiral Chemistry (2004), the Lecturer's Award of the Endowment of the Chemical Industry (2004), the Lieseberg-Prize of the University of Heidelberg (2004), The Society of Synthetic Chemistry, Japan Lectureship Award (2005), the Novartis Young Investigator Award (2005), the OBC-Lecture Award (2007), and, most recently, the AstraZeneca Award in Organic Chemistry. He is currently an editor of *Synfacts* and coordinates the DFG-priority program "*Organocatalysis*".

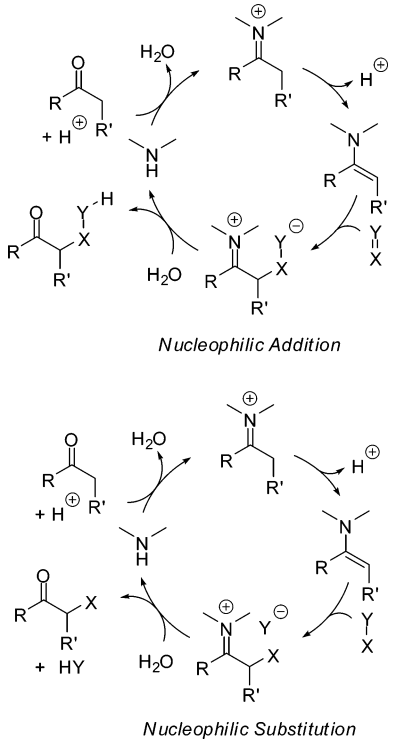
acceptors, etc. are inserted into the α-C−H bond of the carbonyl compound via a nucleophilic *addition* reaction of the enamine intermediate. Single bond containing electrophiles such as alkyl halides on the other hand react in a nucleophilic *substitution* reaction and lead to a stoichiometric byproduct.

The concept of enamine catalysis has three fundamental roots: (1) the stoichiometric chemistry of enamines as developed by Stork and others,[5] outlining the general utility of enamines as nucleophiles in organic synthesis, (2) enamine catalysis as a biological approach to carbon−carbon bond formation as used by aldolases[6] and more recently by designed catalytic antibodies[7,8] to catalyze the direct asymmetric aldol reaction (the aldolase reaction), and (3) the Hajos−Parrish−Eder−Sauer−Wiechert reaction, a proline-catalyzed aldol reaction (see section 2.2.1) that proceeds via enamine intermediates and in turn has its own roots in the chemistry of Knoevenagel.[9] Although this reaction was discovered in early 1970s, its potential has not been realized until recently and remained little more than a laboratory curiosity. A revival of this chemistry was initiated, at the

Scheme 1. Chemistry of Preformed Enamines



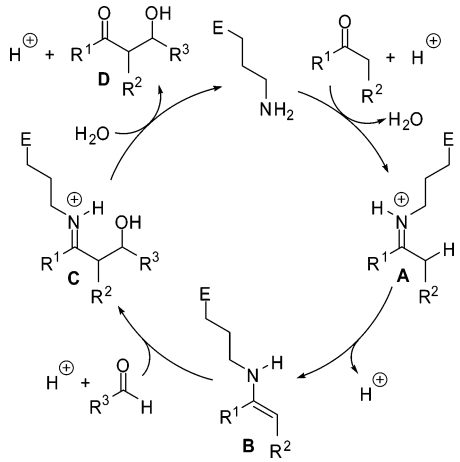
Scheme 2. Enamine Catalysis



beginning of this century, with the discovery of the proline-catalyzed direct asymmetric intermolecular aldol reaction by List et al.[10] Since then, the general field of asymmetric organocatalysis[11−13] and, particularly, asymmetric amine catalysis has unfurled at a breathtaking pace: new catalysts are being designed, new reactions are being discovered and applied in asymmetric synthesis, and the mechanistic picture is becoming increasingly clear.

Enamine catalysis has developed into a powerful strategy for asymmetric synthesis. The area is still extremely active,

Scheme 3. Nature's Strategy of Aminocatalytic Aldolization (E = Enzyme)



and publications are coming up at an amazing pace. Here we cover only the literature until the year 2006.

2. Asymmetric Aldol Reactions

2.1. Introduction

The aldol reaction is among the most commonly applied C−C bond forming reactions.[14] The versatility of this reaction stems from its utility in constructing chiral building blocks (via the stereoselective formation of C−C bonds) for the synthesis of structurally complex molecules, namely natural products or non-natural drug molecules.

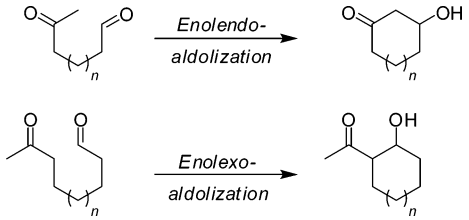
Aldol reactions combine a nucleophilic addition, which is acid-catalyzed, with an enolization, which is catalyzed by both acids and bases.[15,16] These properties make it possible for the aldolization to be catalyzed by both Lewis and Brønsted acids and bases.

Chemically, this reaction is dominated by approaches that employ preformed enolate equivalents in combination with a chiral catalyst (indirect aldol reaction).[6,17−19] Typically, a metal is involved in the reaction mechanism, with the notable exception of chiral Lewis base-catalyzed Mukaiyama aldol-type reactions.[19] The direct aldol reaction between two unmodified carbonyl compounds is of great importance, especcasprially due to practical reasons, as it avoids the formation and/or isolation of an enolate equivalent.[20,21]

Nature's aldolases use combinations of acids and bases in their active sites to accomplish the direct asymmetric aldolization of unmodified carbonyl compounds. Class I aldolases use the Lewis base catalysis of a primary amino group (Scheme 3). To realize enolization under essentially neutral, aqueous conditions, these enzymes decrease the pK_a of the carbonyl donor (typically a ketone) by converting it into an iminium ion (**A**). A relatively weak Brønsted base cocatalyst then generates the nucleophilic species, an enamine (**B**), via deprotonation (Scheme 3). Subsequent addition to the carbonyl acceptor leads to another iminium ion (**C**), which upon hydrolysis regenerates the amine catalyst and liberates the aldol product (**D**).

Although acids and bases are used for catalyzing aldolizations, the aldolase-like direct catalytic asymmetric aldol reaction remained an elusive challenge for a long time. Chemists became inspired by nature and developed catalysts that mimic the functional concept of aldolases for this purpose. One such approach includes antibody-catalyzed

Scheme 4. The Two Modes of Intramolecular Aldolization



direct asymmetric aldol reactions developed by Lerner, Barbas, and Reymond.[22,23] Purely chemical direct catalytic asymmetric aldol reactions were achieved by multifunctional heterobimetallic complexes reported by the Shibasaki group[24−28] and dinuclear Zn complexes reported by Trost et al.[29,30] and Shibasaki et al.[28,31]

Both class I aldolases and even more so Knoevenagel's chemistry[9] may have stimulated chemists to employ amino acids for the catalysis of the aldol reaction. Initial efforts in *asymmetric* catalysis have concentrated on proline-catalyzed enantiogroup differentiating intramolecular aldolizations.

2.2. Intramolecular Aldolizations

There are two types of intramolecular aldol reactions, namely enolendo and enolexo aldolizations (Scheme 4). Both types can be catalyzed by amines, and examples of amine-catalyzed nonasymmetric as well as asymmetric enolendo and enolexo aldolizations have been published.[32]

The first example of an aminocatalytic asymmetric aldol reaction was the Hajos−Parrish−Eder−Sauer−Wiechert cyclization,[33−35] a proline-catalyzed enantiogroup-differentiating 6-enolendo aldolization of di- and triketones. Discovered in the early 1970s, this reaction was the first example of a highly enantioselective organocatalytic process, although neither its mechanism was well understood nor its potential for other reactions was realized.

2.2.1. Enolendo Aldolizations

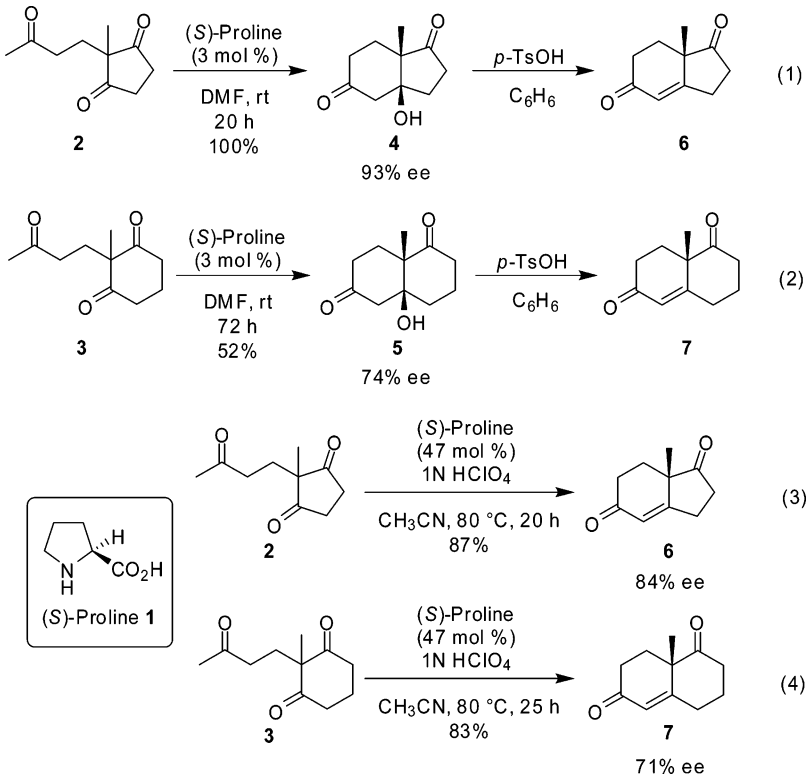
The Hajos−Parrish−Eder−Sauer−Wiechert reaction is a 6-enolendo aldolization. Hajos and Parrish discovered that proline (**1**) is an effective catalyst for the intramolecular aldol reaction of triketones such as **2** and **3**, furnishing aldols **4** and **5** in good yields and in one case with high enantioselectivity (Scheme 5).[33,35] Acid-catalyzed dehydration of the aldol addition products gave condensation products **6** and **7** (eqs 1 and 2). Independently in the same year, Eder, Sauer, and Wiechert directly isolated the aldol condensation products when the same cyclizations were conducted in the presence of proline (10−200 mol %) and an acid cocatalyst (eqs 3 and 4).[34]

Proline-catalyzed enolendo aldolizations have been applied to certain other substrates, since their invention over 30 years ago, most often in steroid synthesis. Selected products from such Hajos−Parrish−Eder−Sauer−Wiechert reactions are shown in Scheme 6.[36−43]

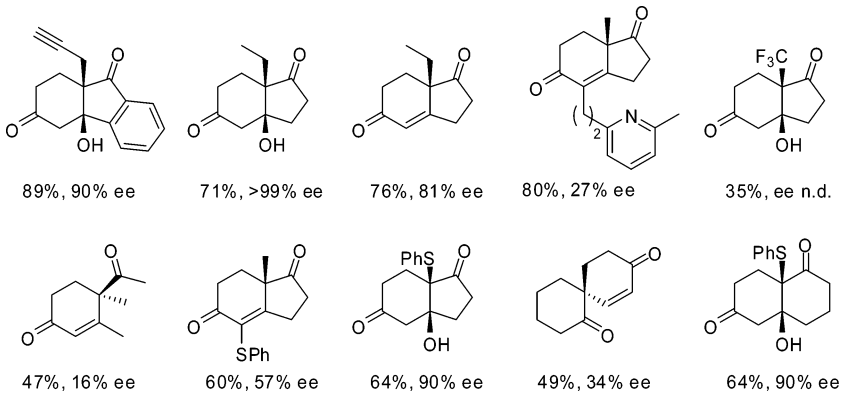
This reaction has been used not only in steroid syntheses but also in other natural product syntheses.[44] The reaction has also been studied using polymer-bound (*S*)-proline as the catalyst. Already in 1985, Takemoto and co-workers linked 4-hydroxyproline derivative **8** to a polystyrene resin and the resulting material **9** was shown to catalyze the reaction, albeit in low yield and with low enantioselectivity (Scheme 7).[45]

Although several different catalysts have been studied in such enolendo aldolizations, proline has typically been preferred. It can, however, be advantageous to use primary amino acid catalysts such as phenylalanine, particularly when non-methyl ketones are employed as substrates. For example, Danishefsky et al. found that the proline-catalyzed cyclization of triketone **10** furnished product **11** in 27% ee whereas 86% ee was obtained when phenylalanine was used as the catalyst (Scheme 8, eqs 1 and 2).[46] Agami et al. made

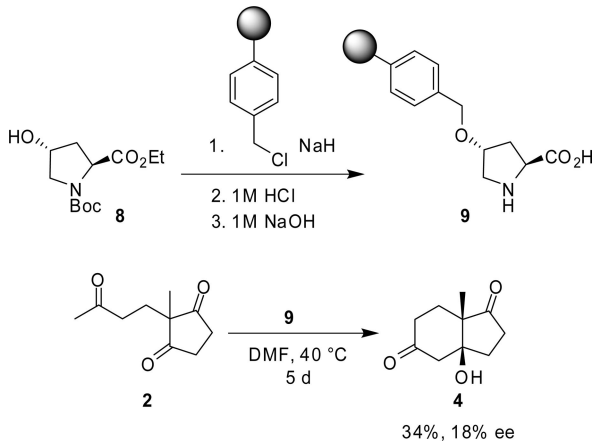
Scheme 5. Hajos−Parrish−Eder−Sauer−Wiechert Reactions



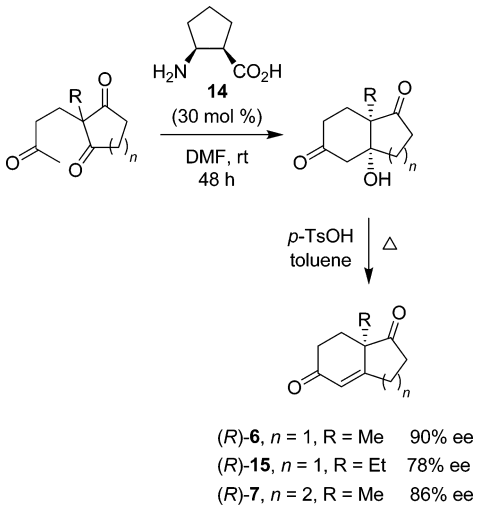
Scheme 6. Selected Products from Proline-Catalyzed 6-Enolendo Aldolizations



Scheme 7. The First Polymer-Supported Proline Catalyst for the Hajos−Parrish−Eder−Sauer−Wiechert Reaction



Scheme 9. Cispentacin-Catalyzed Hajos−Parrish−Eder−Sauer−Wiechert Reactions



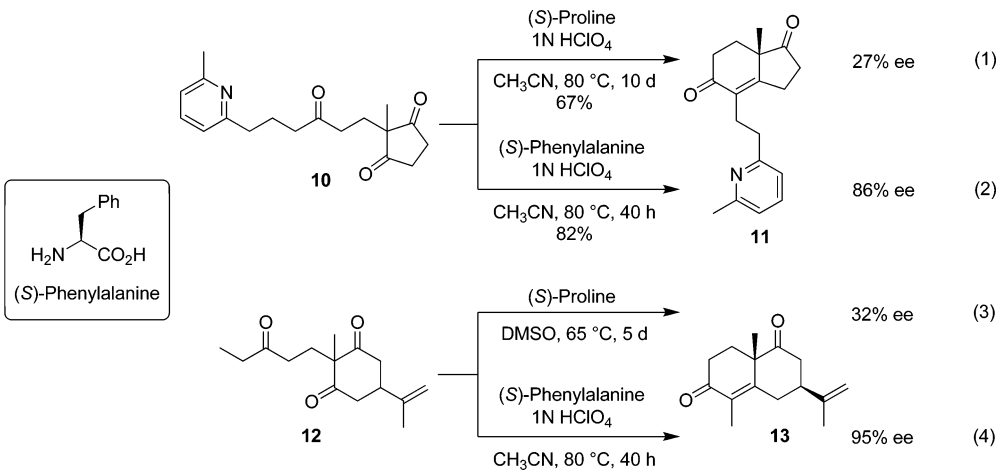
similar observations in the cyclization of ketone **12** (eqs 3 and 4).[47]

Davies, Smith, and co-workers reported a β-amino acid (1*R*,2*S*)-cispentacin **14** as catalyst for Hajos−Parrish−Eder−Sauer−Wiechert reactions (Scheme 9).[48] Using 30 mol % amino acid **14** in DMF at room temperature, product diketones **6**, **7**, and **15** were obtained in enantioselectivities comparable to or even higher (in the case of **7** and **15**) than those obtained by proline-catalyzed reactions.

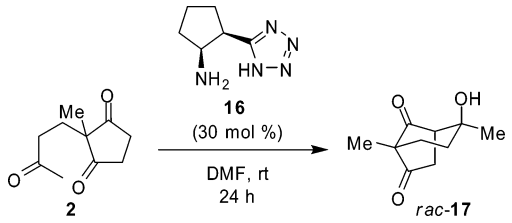
The authors also studied the ability of cispentacin-derived tetrazole **16** as a catalyst for the same cyclization reaction (Scheme 10).[48] Surprisingly, although **16** turned out to be a very efficient catalyst, the replacement of the carboxylate functionality of cispentacin with the tetrazole moiety changed the reaction manifold completely. Using 30 mol % catalyst **16** under identical reaction conditions, the bicylic product **17** was obtained in racemic form as the exclusive product.

Very recently, Inomata, Paquette, and co-workers reported a detailed study of an α-amino acid-mediated intramolecular asymmetric aldol reaction for the construction of 6−7 fused bicyclic enones.[49] A modest level of enantioselectivity was obtained using different α-amino acids and acid cocatalysts. The authors also observed a crossover in enantioselectivity as a function of differing ring size.

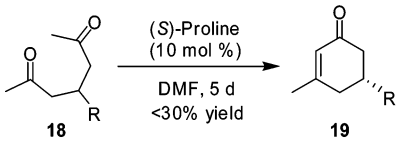
Scheme 8. Compared to Proline, Phenylalanine is a Superior Catalyst for Some Intramolecular Aldolizations



Scheme 10. Cispentacin-Derived Tetrazole-Catalyzed Cyclization of Triketone 2



Scheme 11. Enantiogroup-Differentiating Aldol Cyclodehydrations of 4-Substituted 2,6-Heptandiones



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

Attempts have been made to expand the scope of the Hajos−Parrish−Eder−Sauer−Wiechert reaction to an enantiogroup differentiating aldolization of acyclic diketones.[50] Agami et al. described the proline-catalyzed aldol-cyclodehydration of acyclic 4-substituted 2,6-heptandiones **18** (Scheme 11).[51,52] The efficiency and enantioselectivity of this reaction are modest compared to those of the parent cycloaldolization.

2.2.2. Enolexo Aldolizations

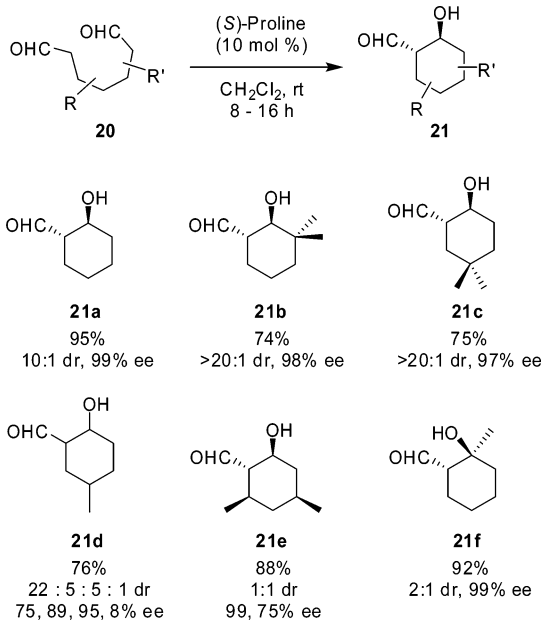
Although amine-catalyzed nonasymmetric enolexo aldolizations are relatively common and catalytic asymmetric enolendo aldolizations have been known for three decades (section 2.2.1), the first catalytic asymmetric enolexo aldolizations were developed only recently. List and coworkers reported a highly enantioselective enolexo aldolization of dicarbonyl compounds.[53] It was discovered that a variety of achiral heptanedials (**20**) and 7-oxoheptanal on treatment with a catalytic amount (10 mol %) of (*S*)-proline furnished *anti*-aldols **21** with excellent enantioselectivity (Scheme 12). Differently substituted heptanedials can be used in this reaction. However, a single substituent in the 4 position has an unfavorable effect on the stereoselectivity of the cycloaldolization. The substrate scope is not limited to dialdehydes; ketoaldehydes can also be used in this reaction. The products of this reaction, β-hydroxy cyclohexane carbonyl derivatives, may find use in target-oriented synthesis. This *anti*-diastereoselective reaction nicely complements alternative methodologies such as highly enantioselective- and *syn*-diastereoselective baker's yeast reduction of β-keto esters.[54,55]

While nonasymmetric amine-catalyzed enolexo-aldolizations often give aldol condensation products, the corresponding proline-catalyzed process selectively provides the aldol addition products.

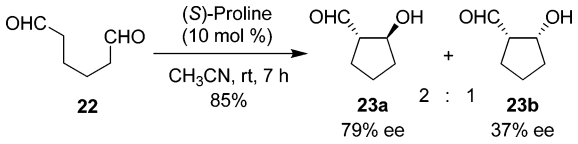
The corresponding 5-enolexo aldolizations are less stereoselective. For example, treating hexanedial (**22**) with a catalytic amount of (*S*)-proline furnished aldol **23** with only modest diastereo- and enantioselectivities (Scheme 13).[32]

The proline-catalyzed 6-enolexo-aldolization has been utilized for the desymmetrization of *meso*-dialdehyde **24** in the total synthesis of (+)-cocaine **25** (Scheme 14).[56] A 1:1 mixture of epimeric aldol product **26**, an important intermediate of cocaine, was obtained in 91% yield when 20 mol % proline was used as catalyst in toluene at 25 °C.

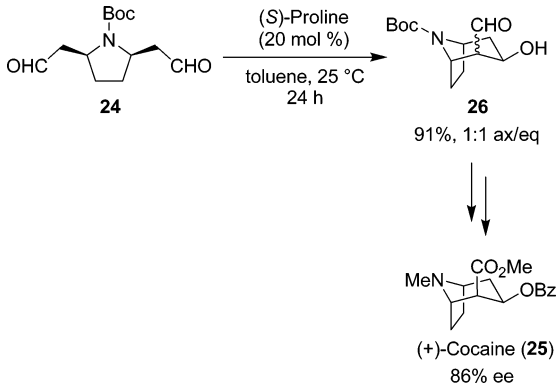
Scheme 12. Proline-Catalyzed Enantioselective 6-Enolexo-Aldolizations of Dialdehydes



Scheme 13. Proline-Catalyzed 5-Enolexo-Aldolization of Hexanedial 22



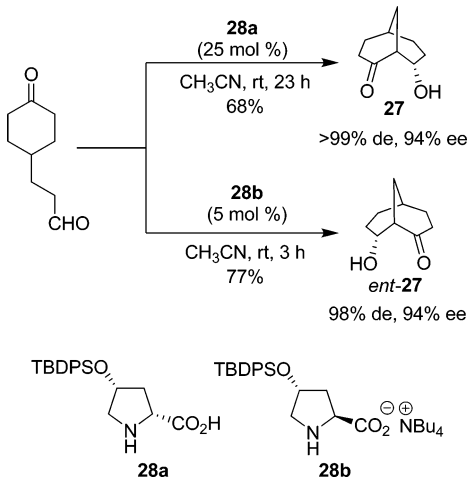
Scheme 14. Proline-Catalyzed Desymmetrization of *meso*-Dialdehyde in the Total Synthesis of (+)-Cocaine



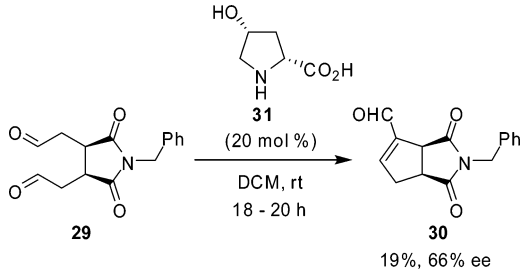
Quite recently, Iwabuchi et al. applied an intramolecular enolexo aldolization of σ-symmetric keto-aldehydes in the synthesis of *endo*-8-hydroxybicyclo[3.3.1]nonan-2-one **27**.[57] Proline derivatives **28a** and **28b** were used as highly efficient catalysts for this synthetically useful asymmetric transformation (Scheme 15). Both enantiomers of **27** could be accessed in excellent diastereo- and enantioselectivities. The higher catalytic activity of tetrabutylammonium salt **28b** compared to the free acid catalyst **28a** could be due to the higher effective concentration of the catalytically active nucleophilic secondary amine form.

A direct intramolecular asymmetric aldol cyclodehydration of *meso*-3,4-disubstituted-1,6-dialdehyde **29** to the corresponding cyclopentene carbaldehyde **30** (Scheme 16) was reported by Kurteva and Afonso in 2005.[58] 4-Hydroxyproline (**31**) was found to be one of the better catalysts among a broad range of catalysts tested. Using 20 mol % catalyst,

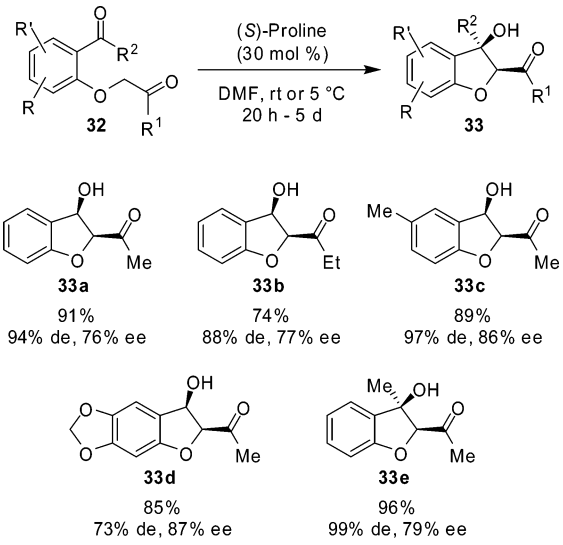
Scheme 15. Asymmetric Intramolecular Aldolization for the Synthesis of *endo*-8-Hydroxybicyclo[3.3.1]nonan-2-one



Scheme 16. Intramolecular Asymmetric Aldol Cyclodehydration of *meso*-Dialdehyde 29



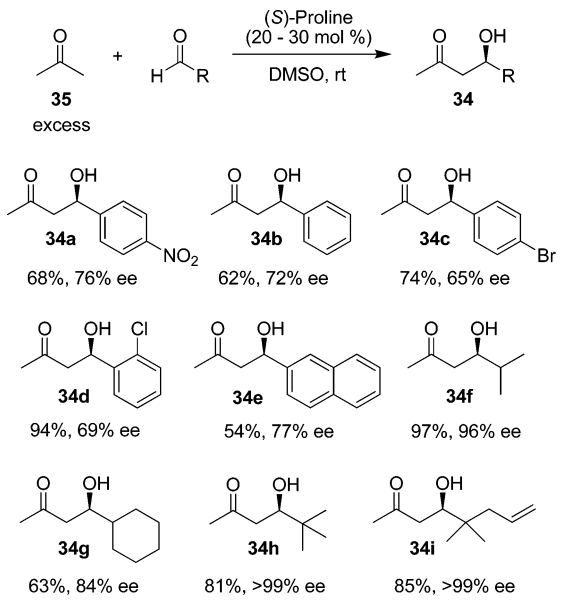
Scheme 17. Proline-Catalyzed Asymmetric 5-Enolexo Aldolization of Dicarbonyl Compounds



modest yield and moderate enantioselectivity were obtained. Although proline itself is an excellent catalyst for this transformation, surprisingly no stereoinduction was observed. The authors proposed that the presence of the hydroxyl group in the catalyst is crucial for obtaining stereocontrol in this transformation.[58]

In 2006, Enders and co-workers reported an asymmetric intramolecular *cis* 5-enolexo aldolization of dicarbonyl compounds **32**, that leads to 2,3-dihydrobenzofuranols **33**, the core structure of some antimicrobial compounds (Scheme 17).[59] Among a number of catalysts screened, (*S*)-proline once again turned out to be the optimum. In the presence of

Scheme 18. Proline-Catalyzed Direct Asymmetric Intermolecular Aldol Reactions of Acetone with Aromatic and α-Branched Aldehydes



30 mol % proline in 0.1 M DMF, several dicarbonyl compounds undergo *cis*-selective intramolecular aldolization in moderate to high diastereoselectivities and good enantioselectivities. In most of the cases, the products could be obtained in diastereo- and enantiopure form after recrystallization from a *n*-hexane/EtOAc mixture.

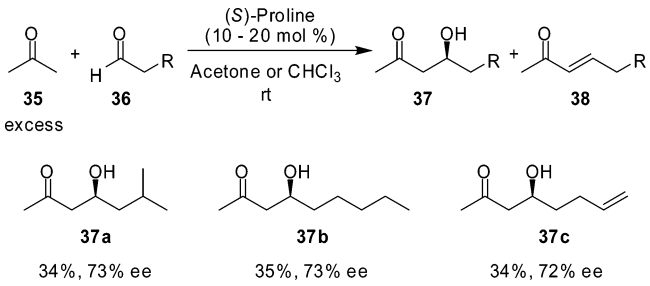
2.3. Intermolecular Aldolizations

2.3.1. Ketone Donors

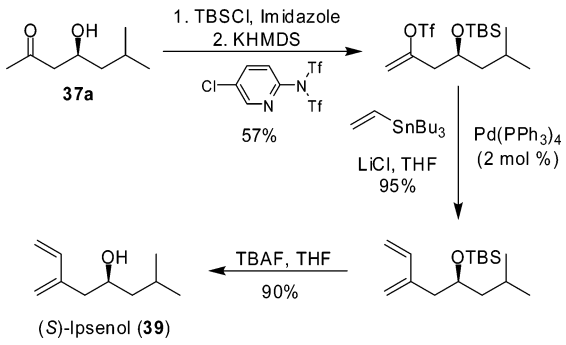
A. Proline as Catalyst. The first amine-catalyzed, asymmetric direct intermolecular aldol reaction was developed by List et al. in 2000.[1,10,60−62] The reaction of excess acetone with some aromatic and α-branched aldehydes was found to proceed in the presence of a catalytic amount of (*S*)-proline (typically 20−30 mol %) in DMSO to provide the corresponding acetone aldols **34** with good yields and enantioselectivities (Scheme 18). Several other amino acid derivatives, including primary and both cyclic and acyclic secondary amino acids, were screened as catalysts.[10] Proline, however, turned out to be the most efficient and practical catalyst for this reaction.[63] In fact, both the pyrrolidine ring and the carboxylate are found to be essential for effective catalysis to occur.[64] Yields and enantioselectivities depend on the aldehyde component and are typically in the seventies with aromatic aldehydes and in the nineties with α-branched and α-trisubstituted aldehydes. The only side products in this reaction are the aldol condensation products (α,β-unsaturated ketones), possibly formed via Mannich condensation.

α-Unbranched aldehydes **36** proved to be an extremely challenging substrate class and did not provide the corresponding aldol products under the original conditions.[10] Homo-aldol addition and condensation of the aldehyde or elimination of the cross-aldol product appeared to be the main side reactions in DMSO. It was found later that by using acetone or acetone/chloroform mixtures instead of DMSO as solvent, and 10−20 mol % proline as catalyst, the cross-aldol product **37** could be isolated in modest yields and with acceptable enantioselectivities (Scheme 19).[61] The new reaction conditions effectively suppressed aldehyde self-

Scheme 19. Proline-Catalyzed Aldol Reactions of Acetone with α-Unbranched Aldehydes



Scheme 20. Asymmetric Synthesis of (*S*)-Ipsenol



aldolization. The main side product was now the corresponding acetone cross-aldol condensation product **38**, typically formed in comparable yields along with the desired aldol addition product.

These relatively modest results represented the state-of-the-art in direct catalytic asymmetric aldolizations with α-unbranched aldehyde acceptors at the time.[61] Even non-asymmetric amine-catalyzed cross-aldolizations with α-unbranched acceptors were still largely unknown. In some cases, the practicality of this process can compensate for the modest yield and enantioselectivity. This was illustrated by a straightforward synthesis of the natural pheromone (*S*)-ipsenol **39**, a major component of the sex pheromone of the bark beetle that is needed in kilogram quantities for insect traps. The synthesis was achieved starting from aldol **37a** and features a high yielding Stille coupling (Scheme 20).[61]

Other aliphatic aldehydes have also been employed as the acceptor components for the acetone aldol reaction. Varying results were obtained depending on the catalyst when proline and its derivatives were used as catalysts.[65] The proline-catalyzed intermolecular aldol reaction with acetone has been utilized in the highly diastereoselective synthesis of complex sugar derivatives.[66]

Recently, Chandrasekhar and co-workers reported a proline-catalyzed asymmetric transfer aldol reaction.[67] Using diacetone alcohol instead of acetone in DMSO at room temperature, aldol products were obtained in moderate to high yields and with good enantioselectivities (up to 86% ee) when the reaction was conducted with 30 mol % (*S*)-proline.

B. Mechanism of the Proline-Catalyzed Aldol Reaction. Extensive research has been conducted by several research groups to elucidate the mechanism of proline-catalyzed aldol reactions.[2,35,68−87]

Initially, only limited mechanistic information was available for the proline-catalyzed intermolecular aldol reaction, most of which came from a closer look at the studies of alternative catalysts in the intermolecular aldolizations (see Table 2).[10,88] Simple primary amino acids are poor catalysts for the intermolecular aldol reaction, even though phenylalanine was known to be a good catalyst for Hajos−Parrish−Eder−Sauer−Wiechert reactions (Scheme 8). This suggested the apparent requirement of a secondary amine in the intermolecular reaction. However, acyclic secondary amino acids such as *N*-methylvaline are not catalytic, and from the studies of cyclic amino acids of different ring sizes, proline proved to be the best catalyst while six-membered pipecolic acid is found to be inactive. From Stork's seminal work on the chemistry of enamines,[3] it was known that pyrrolidines much more readily form enamines with carbonyl compounds when compared to piperidines and also the corresponding pyrrolidine enamines are more nucleophilic. Additional evidence for covalent catalysis and an enamine mechanism came from the result obtained with *N*-methylproline, which proved to be completely inactive as catalyst. Support for the role of carboxylate came from the fact that prolinamide is an inferior catalyst compared to proline itself in terms of both activity and enantioselectivity.

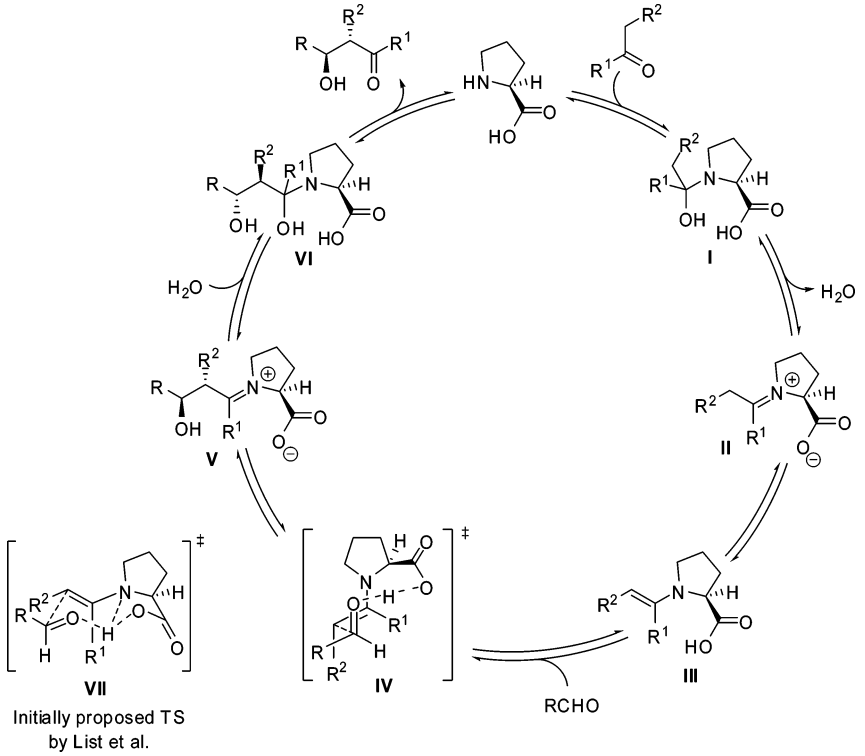
With these limited studies in hand, an enamine catalysis mechanism was initially proposed (Scheme 21)[10] involving carbinolamine (**I** and **VI**), iminium ion (**II** and **V**), and enamine (**III**) intermediates. This mechanism is essentially identical to the accepted mechanism of class I aldolases. The carboxylic acid was proposed to act as a general Brønsted cocatalyst, replacing the several acid/base functional groups involved in the aldolase mechanism. In the transition state of the carbon−carbon bond formation (**IV**), protonation of the acceptor carbonyl group occurs by the carboxylic acid, which is *anti* with respect to the (*E*)-enamine double bond. In this context, proline not only acts as an enamine catalyst but also brings along its own Brønsted acid cocatalyst and therefore can be regarded as a "bifunctional catalyst". Later on, Houk and co-workers proposed a similar transition state for the intramolecular variant and also showed that a simultaneous hydrogen bond to the enamine nitrogen (**VII**, Scheme 21), which was initially invoked,[10] does not further contribute to lowering the energy of the transition state.[77,78,83,85,89]

Quite recently, Marquez and Metzger were able to intercept and characterize intermediates **I**, **III**, **V**, and **VI** (Scheme 21) with an ESI-MS study,[90] supporting the enamine mechanism proposed by List et al.[10]

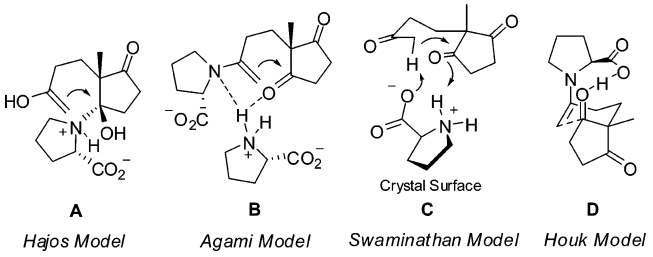
Although this mechanistic proposal seemed plausible according to both theory and experiment and similar to the known class I aldolase mechanism, it stood against the previously accepted mechanism of the Hajos−Parrish−Eder−Sauer−Wiechert reaction. In addition, a number of different models have been proposed for this intramolecular aldol reaction (Scheme 22).

In their original report,[35] Hajos et al. proposed an alternative mechanism that does not involve enamine intermediates. Accordingly, proline "activates" one of the two enantiotopic acceptor carbonyl groups as a carbinol amine (**A**, Scheme 22). The basis of the Hajos model was the surprising observation that if the reaction was conducted in the presence of ^{18}O-enriched water, no ^{18}O was apparently incorporated into the product. However, important details of these experiments have never been published. Unless unusual effects were operative, the proposed enamine mechanism requires ^{18}O-incorporation, since a hydrolysis step completes the catalytic cycle (Scheme 23). Experiments conducted by List and co-workers under carefully controlled conditions showed high ^{18}O incorporation (ca. 90%) in the aldol

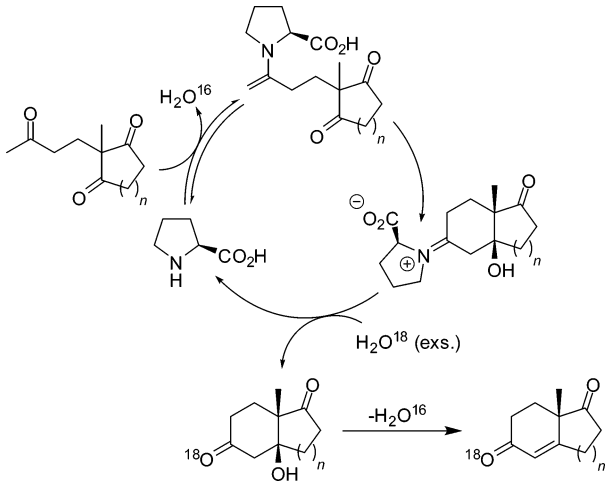
Scheme 21. Proposed Mechanistic Cycle for the Proline-Catalyzed Intermolecular Aldol Reaction



Scheme 22. Mechanistic Models Proposed for the Hajos−Parrish−Eder−Sauer−Wiechert Reaction



Scheme 23. ^{18}O-Incorporation in the Enamine Catalysis Cycle of the Hajos−Parrish−Eder−Sauer−Wiechert Reaction



products, consistent with the proposed enamine mechanism.[81] Parallel theoretical calculations by Clemente and Houk also support the enamine mechanism.[80,85]

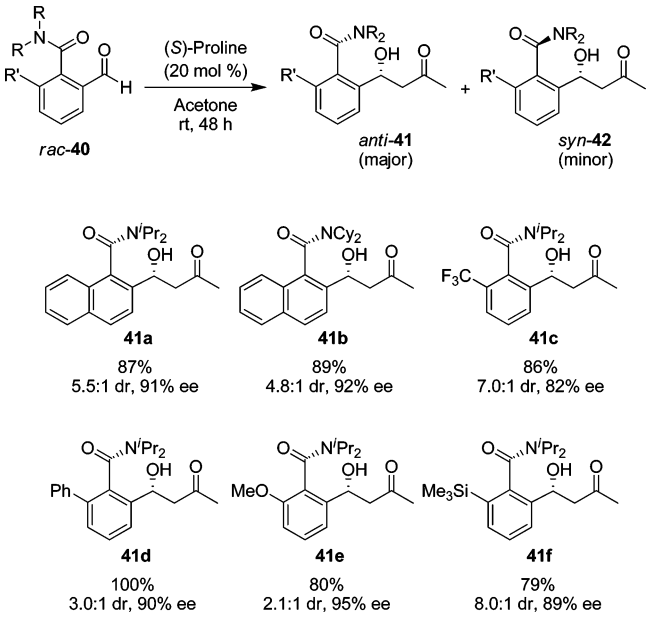
Swaminathan et al. suggested a heterogeneous aldolization mechanism on the surface of the crystalline proline (**C** in Scheme 22).[87] However, many proline-catalyzed aldolizations are completely homogeneous.

On the basis of an observed small negative nonlinear effect in the asymmetric catalysis, Agami et al. proposed a side-chain enamine mechanism involving two proline molecules in the C−C bond forming transition state (**B** in Scheme 22).[69−74] One proline molecule is engaged in enamine formation whereas the second one acts as a proton-transfer mediator. However, in a recently conducted study, a nonlinear effect could not be confirmed in both inter- and intramolecular aldol reactions.[79] Theoretical studies by the Houk group also support a one-proline mechanism in which the side-chain enamine reacts with the ring acceptor carbonyl group, under concomitant activation via hydrogen bonding to proline's carboxylic acid group (model **D** in Scheme 22).[78,91,92]

Blackmond and co-workers very recently demonstrated that, under heterogeneous conditions, a nonlinear effect was indeed observed in proline-catalyzed aldol reactions.[93−97] The origin of this nonlinear effect stems from the physicochemical phase behavior of proline in heterogeneous solid-solution systems in different solvents and not from the mechanism of the reaction itself.

C. Proline as Catalyst (Continued). In 2004, Walsh et al. utilized the proline-catalyzed aldol reaction for the dynamic kinetic resolution (DKR) of a series of atropisomeric benzamides and naphthamides.[98] The process simultaneously established the stereochemistry of the atropisomeric amide's chiral axis and a stereogenic center. In the presence of 20 mol % (*S*)-proline in neat acetone, aldehyde substrates *rac*-**40** undergo direct aldol reaction to generate a diastereomeric mixture. The *anti*-isomer was obtained as the major product in high (combined) yield, good diastereoselectivity, and excellent enantioselectivity (Scheme 24). The reaction can also be performed in a DMSO/acetone (4:1) mixture; however, the selectivities are somewhat lower in this case.

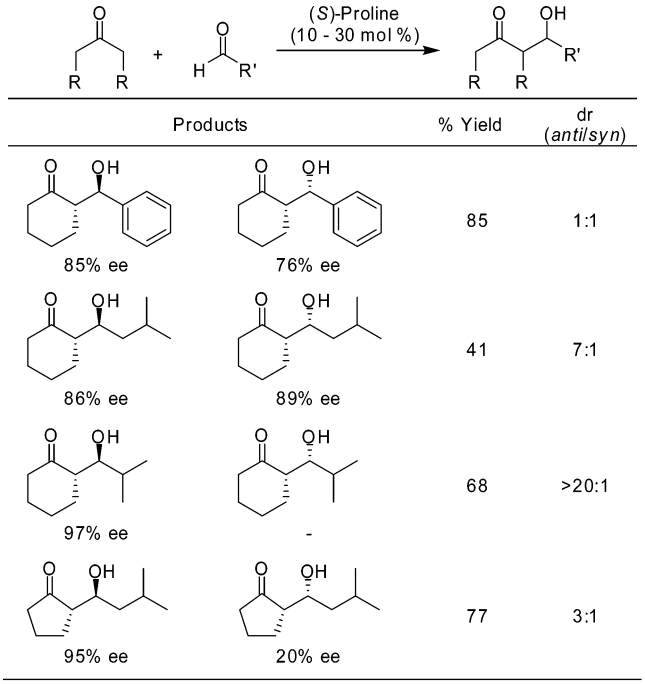
Scheme 24. Application of the Proline-Catalyzed Acetone Aldol Reaction for the DKR of Atropisomeric Amides



The use of ketones other than acetone in proline-catalyzed aldolizations has also been described.[60,61,99] In those reactions, that require a large excess of the ketone component, one is limited to readily available and inexpensive smaller ketones such as butanone, cyclopentanone, and cyclohexanone. Depending on the aldehyde component, excellent enantio- and (*anti*)-diastereoselectivity can be achieved in such reactions (Table 1).[61,99]

Interestingly, the stereoselectivity of reactions of cyclohexanone (**43**) with isobutyraldehyde (**44**) and benzaldehyde (**45**) were first predicted[99] by using density functional theory (DFT) calculations on models based on Houk's calculated transition state of the Hajos−Parrish−Eder−Sauer−Wiechert reaction (see Scheme 22).[78] The transition states of inter- and intramolecular aldol reactions are almost superimposable and readily explain the observed enantiofacial selectivity.

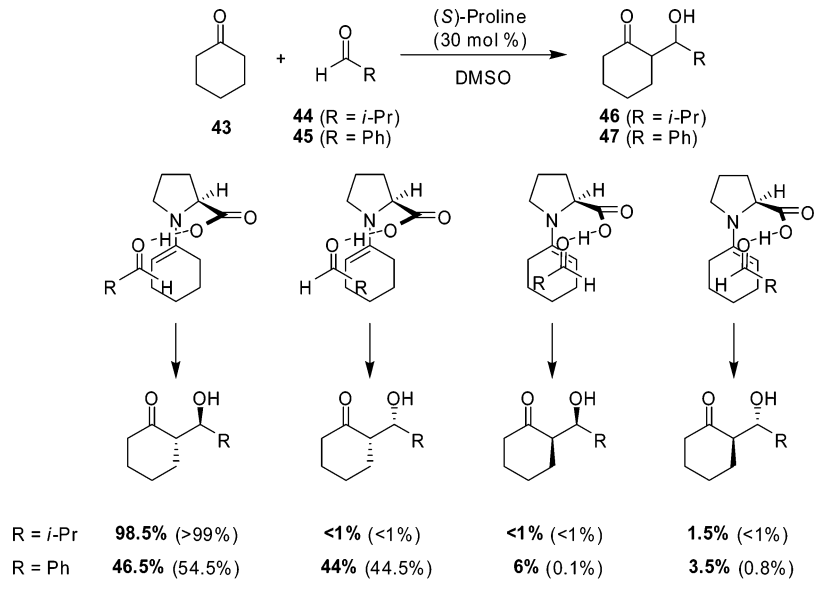
Table 1. Proline-Catalyzed Intermolecular Aldolization with Cyclic Ketone Donors



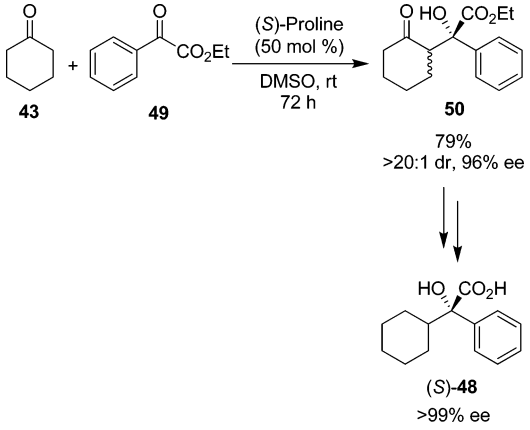
Relative transition state energies were then used to predict the diastereo- and enantioselectivities of the proline-catalyzed reactions of cyclohexanone **43** with isobutyraldehyde (**44**) and benzaldehyde (**45**) (Scheme 25).[99] The predictions are compared with the experimental studies and provide support for the proposed mechanism.

The utility of cyclohexanone as a donor unit in combination with an activated ketone acceptor in the proline-catalyzed asymmetric direct aldol reactions is nicely demonstrated by Maruoka and co-workers for the enantioselective sythesis of (*S*)-2-cyclohexyl-2-phenylglycolic acid [(*S*)-**48**] (Scheme 26).[100] (*S*)-**48** is a key intermediate of the muscarinic receptor antagonist (*S*)-oxybutynin. As an initial step of the synthesis, reaction of cyclohexanone **43** with ethyl phenylglyoxalate

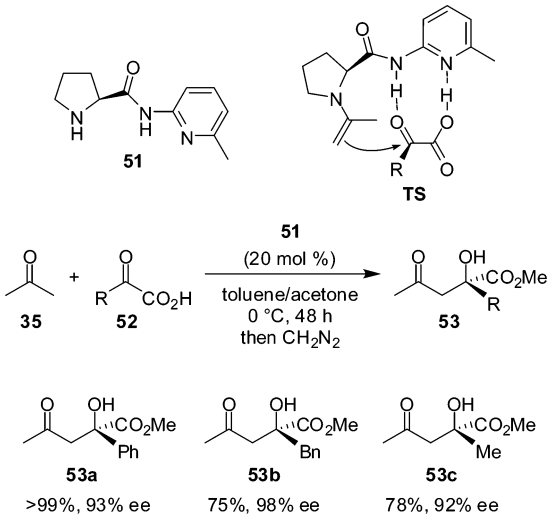
Scheme 25. Theoretical Prediction (within Parentheses) and Experimental Verification (Values in Bold) of Diastereo- and Enantioselectivities of Proline-Catalyzed Aldolizations



Scheme 26. Proline-Catalyzed Aldol Reaction of Cycloehxanone with Ethyl Phenylglyoxalate



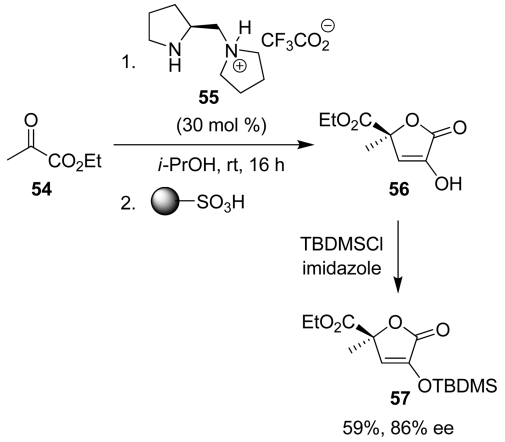
Scheme 27. Novel Prolinamide Organocatalyst for the Direct Asymmetric Aldol Reaction of Acetone and α-Keto Acids



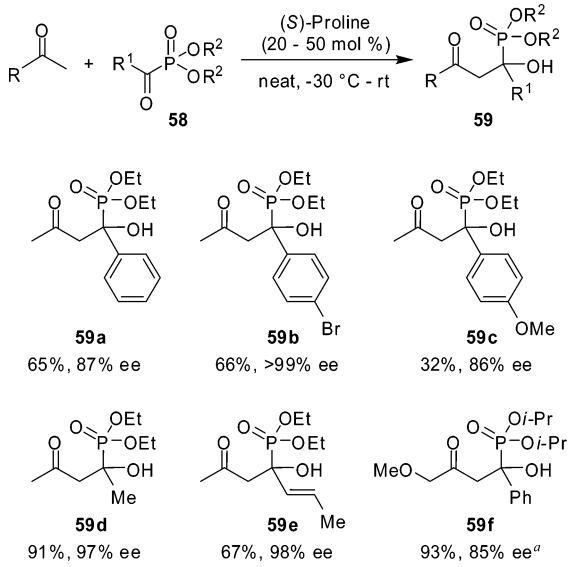
49 with a catalytic amount of (*S*)-proline in DMSO at room temperature afforded the aldol product **50** in good yield with excellent diastereo- and enantioselectivities. This reaction represents one of the rare examples of aldol reactions where ketones act both as the acceptor and the donor (see below). The product contains a quaternary stereogenic center and was manipulated in a few steps to the desired target molecule in almost perfect enantioselectivity. Other phenylglyoxalate derivatives have also been tested in this reaction with even superior results (up to >99% yield, >20:1 dr, and >99% ee).[100]

One year later, Gong et al. designed a novel 2-aminopyridine-derived prolinamide catalyst **51** for the direct asymmetric aldol reaction between a ketone and an α-keto acid **52** (Scheme 27).[101] The catalyst was designed on the basis of molecular recognition, where the keto acid was expected to be activated by hydrogen bonding with the catalyst as in **TS**. Mostly, acetone was used as the ketone component. Using 20 mol % catalyst **51**, the product *β*-hydroxy carboxylic acids (isolated as methyl esters **53**) were obtained in good to excellent yields and high enantioselectivities. Cyclopentanone can also be used as the donor; the product was obtained in diminished stereoselectivity. The authors also demonstrated catalyst recovery by a simple acid−base extraction strategy which enables catalyst recycling without affecting the ee significantly; however, the yield dropped drastically after the second run.[101]

Scheme 28. Homoaldol Reaction of Ethyl Pyruvate 54 for the Synthesis of an Isotetronic Acid Derivative



Scheme 29. Proline-Catalyzed Aldol Reactions of α-Keto Phosphonates as Acceptors[a]

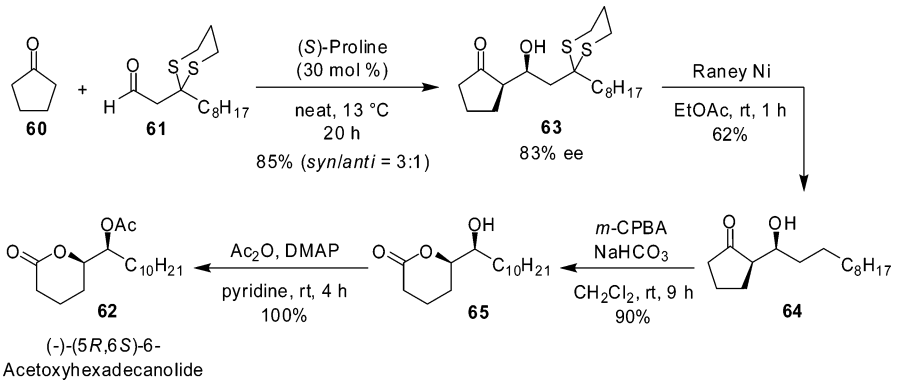


[a] (*S*)-Prolinamide was used as the catalyst.

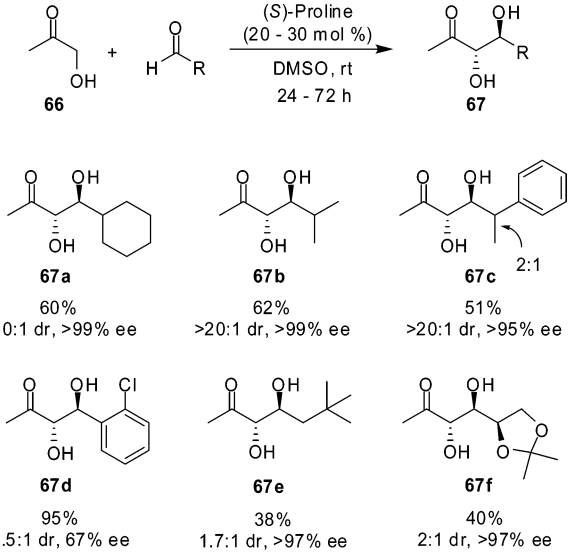
The homoaldol reaction of ethyl pyruvate (**54**) has also been described.[102] Dondoni and co-workers reported that in the presence of 30 mol % of a diamine-TFA salt (**55**) the homoaldol reaction of ethyl pyruvate **54** produces isotetronic acid derivative **56** after treatment with an acidic resin (Scheme 28). Protection of the enol moiety by TBDMS led to stable adduct **57** in 59% yield and 86% ee.

A related class of ketone acceptors are α-keto phosphonates **58**. However, this class of compounds poses a considerable challenge as substrate due to its susceptibility toward nucleophilic attack and the leaving group ability of the phosphonate group. Proline-catalyzed enantioselective aldol reaction between ketones and α-keto phosphonates **58** was reported by Samanta and Zhao (Scheme 29).[103] The produced α-hydroxy phosphonates **59** and the corresponding phosphonic acids are biologically active. Alkyl, aryl, and alkenyl α-keto phosphonates were used as substrates, affording the aldol products in high yields (up to 94%) and enantioselectivities (up to >99%) in most cases. When prolinamide was applied as the catalyst, ketones other than acetone can also be used and the aldol products were formed regioselectively at the methyl carbon in high yields but with relatively lower enantioselectivities.

Scheme 30. Synthesis of (−)-(5*R*,6*S*)-6-Acetoxyhexadecanolide 62 Using the Proline-Catalyzed Direct Aldol Reaction



Scheme 31. Proline-Catalyzed Intermolecular Aldolization Using Hydroxyacetone 66 as the Donor



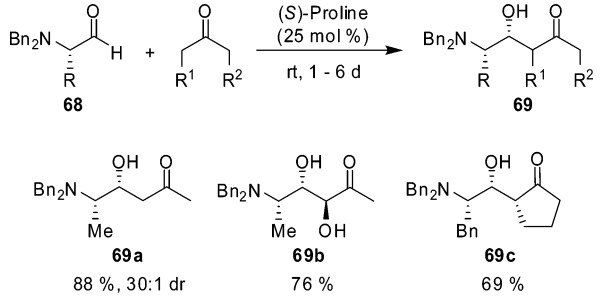
Recently, Kotsuki et al. applied the proline-catalyzed aldol reaction between cyclopentanone **60** and aliphatic aldehyde **61** for the synthesis of (−)-(5*R*,6*S*)-6-acetoxyhexadecanolide **62**, an oviposition attractant pheromone of the female *Culex* mosquito (Scheme 30).[104] (*S*)-Proline (30 mol %) under solvent-free conditions at 13 °C gave the *syn*-adduct **63** as the major diastereomer in 3:1 dr and 83% ee. Simple functional group transformations afforded the target molecule **62**.

Another interesting and particularly noteworthy ketone donor in the cross-aldol reaction is hydroxyacetone **66**.[60] This is the first application of an unprotected hydroxyketone as a donor in a nonenzymatic aldol reaction. In this case, *anti*-diols **67** are formed in excellent regioselectivities and up to very high diastereo- and enantioselectivities (Scheme 31). Although *anti*-diols are accessible by Sharpless asymmetric dihydroxylation (AD),[105] the required (*Z*)-olefins are more difficult to obtain and show reduced enantioselectivity in the AD to *anti*-diols. Therefore, this process provides a complimentary approach to Sharpless-AD for the synthesis of *anti*-diols.

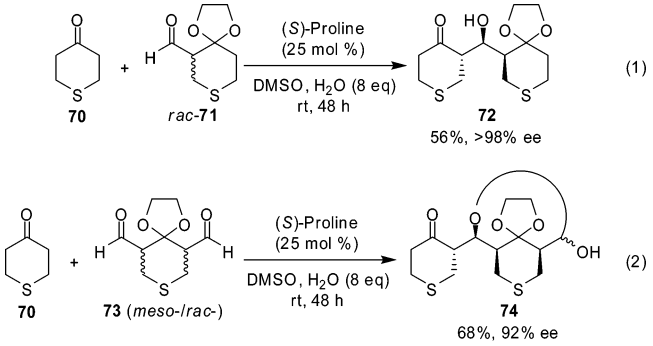
The exceptionally high stereoselectivity found in proline-catalyzed aldol reactions involving hydroxyacetone **66** has been explored during the total synthesis of brassinolide, a steroidal plant-growth regulator.[106]

Ma et al. reported a proline-catalyzed diastereoselective direct aldol reaction of L-amino acid-derived *N*,*N*-dibenzyl α-amino aldehydes **68** with ketones (Scheme 32).[107] In the

Scheme 32. (*S*)-Proline-Catalyzed Diastereoselective Aldol Reactions of *N*,*N*-Dibenzyl α-Amino Aldehydes



Scheme 33. Application of Proline-Catalyzed Aldolization in Dynamic Kinetic Resolution of Aldehydes

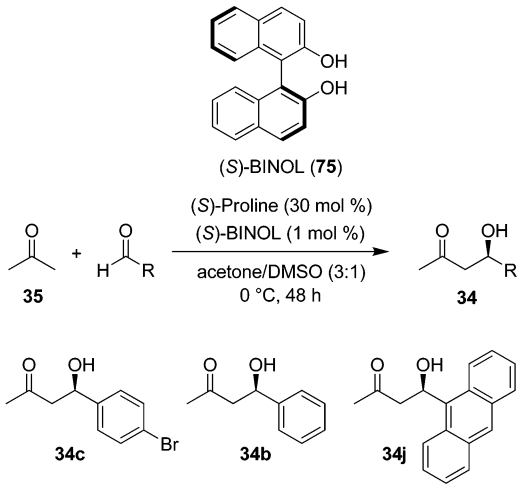


presence of 25 mol % (*S*)-proline, the aldol products γ-amino-β-hydroxy- and γ-amino-α,β-dihydroxy ketones (**69a**−**c**) were obtained in good to excellent yields in most cases and in excellent diastereoselectivities.

Ward and co-workers applied the proline-catalyzed aldolizations for the dynamic kinetic resolution (DKR) of racemic and *meso*-aldehydes (Scheme 33).[108] When reacted with tetrahydro-4*H*-thiopyranone **70**, racemic aldehyde **71** afforded the aldol **72** as a single diastereomer in 56% yield and >98% ee (eq 1). Addition of a small amount of water improved both yield and ee. Similarly, when a mixture of dialdehyde **73** (*rac*-/*meso*- = 3.5) was used as the acceptor component, aldol hemiacetal **74** was formed exclusively in 68% yield and 92% ee (eq 2). Interestingly, in both cases, proline catalyzes the isomerization of aldehydes and, since these isomerizations are faster than the aldol addition, the reaction proceeds with DKR. Both the aldol products are useful tetrapropionate synthons, and their synthetic potential has also been explored by the authors.[108]

Additive effects on the proline-catalyzed aldol reactions have also been tested. Pikho and co-workers studied the effect of acids, bases, and water as additives in the proline-

Scheme 34. Proline-Catalyzed Direct Aldolizations Assisted by BINOL



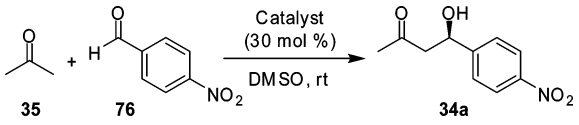
Without BINOL	82%, 75% ee	43%, 72% ee	10%, 92% ee
With BINOL	76%, 97% ee	56%, 98% ee	23%, 87% ee

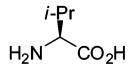
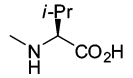
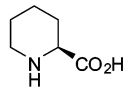
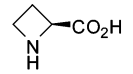
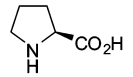
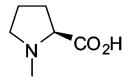
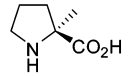
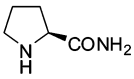
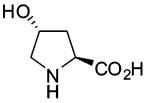
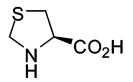
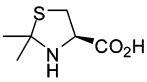
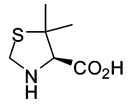
catalyzed aldol reactions and reported that small amounts of tertiary amine bases or weak acids have little influence on this reaction.[109] Strong acids, however inhibit the reaction completely. Interestingly, water as an additive has a beneficial influence on both the reactivity and stereoselectivity of the reaction. This enables the use of only a stoichiometric amount of the reaction partners in contrast to the standard reaction conditions, where the donor component (particularly ketones) is typically used in excess.

Recently, Zhou and Shan achieved significant improvement of reaction rate, yield, and enantioselectivity in proline-catalyzed aldolizations using different diols as additive.[110] (*S*)-BINOL (**75**) was found to be the best choice for the reactions catalyzed by (*S*)-proline. Significant enhancement in enanatioselectivities was observed in most of the cases with 1 mol % (*S*)-BINOL (**75**) when 30 mol % (*S*)-proline was used as the catalyst, except for the reaction of 9-anthracenylaldehyde with acetone (Scheme 34). All the reactions afforded the aldol products with the same configuration **34** regardless of the chirality of the additives. This indicates that the chiral induction stems from the chirality of (*S*)-proline and that the additive (*S*)-BINOL only augments the inductive ability of proline by forming a chiral supramolecular system through hydrogen bonding interactions.[110]

D. Catalyst Development for the Asymmetric Direct Aldol Reaction. Other catalysts besides proline have also been investigated. A particularly large amount of data has been collected for the aldol reaction of acetone (**35**) with *p*-nitrobenzaldehyde (**76**) (Table 2).[10,88] Simple primary α-amino acids (e.g., **77**) and acyclic *N*-methylated α-amino acids (e.g., **78**) are not catalytically active under standard reaction conditions (entries 1 and 2). Of the simple cyclic amino acids studied, azetidine (**80**), pyrrolidine (**1**), and piperidine 2-carboxylate (**79**), proline is clearly the best catalyst (entries 3−5).[63] Among the "proline-type" cyclic α-amino acids, only 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC, **87**) was found to provide yields and enantioselectivities superior to those provided by proline itself with aromatic aldehydes (entry 12). α-, α′-, and, in particular, *N*-methylation reduce the efficiency, whereas substitution at the 3- and 4-positions is tolerated without dramatic effects. Proline amide (**83**) is essentially catalytically inactive under the standard reaction conditions (DMSO, rt, 2 h), but after 3 days, the aldol could be isolated in good yield, albeit with very low enantioselectivity (entry 8).

Table 2. Amino Catalysts Studied for Direct Aldol Reaction of Acetone 35 with *p*-Nitrobenzaldehyde 76

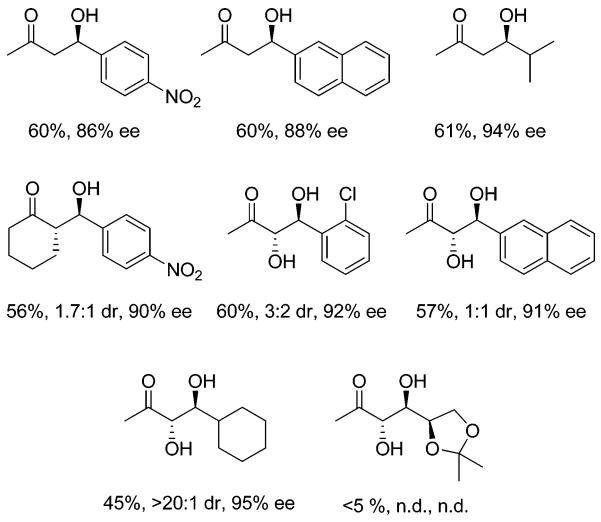


Entry	Catalyst		% Yield	% ee
1		**77**	<10	n.d.
2		**78**	<10	n.d.
3		**79**	<10	n.d.
4		**80**	55	40
5		**1**	68	76
6		**81**	<10	n.d.
7		**82**	26	61
8		**83**	80	20
9		**84**	85	78
10		**85**	67	73
11		**86**	<10	n.d.
12		**87**	60	86

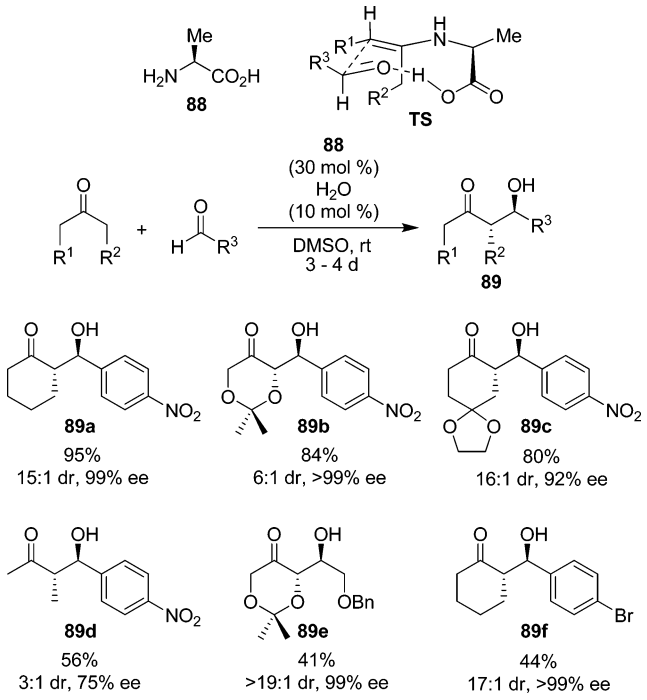
Barbas and co-workers exploited the potential of 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC, **87**) for the direct aldol reaction of other substrates after it had first been used by List[111] in an asymmetric Mannich reaction.[88,112] Whereas DMTC (**87**) was found to afford superior results in the cases of aromatic aldehydes, proline (**1**) is usually the catalyst of choice for linear and α-branched aldehydes. Scheme 35 represents a selection of products obtain by direct aldol reactions, catalyzed by 20 mol % DMTC (**87**).

Córdova et al. recently reported the application of simple acyclic α-amino acids as catalysts for the asymmetric direct aldol reaction.[113] The reactions of cyclic ketones and butanone with electron-deficient aldehydes were found to proceed in wet DMSO with 30 mol % simple primary amino acids (Scheme 36). (*S*)-Alanine (**88**) and especially (*S*)-valine (**77**) proved to be effective and stereoselective catalysts for

Scheme 35. Selected Products Obtained by Direct Aldol Reactions Catalyzed by DMTC



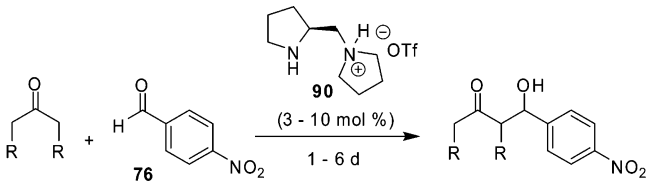
Scheme 36. Alanine-Catalyzed Direct Asymmetric Aldol Reactions of Ketones to Aldehydes

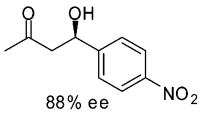
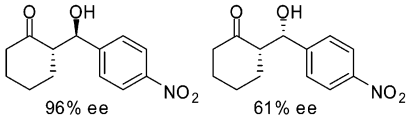
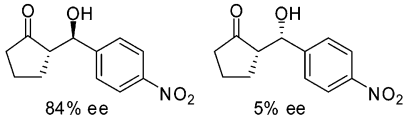
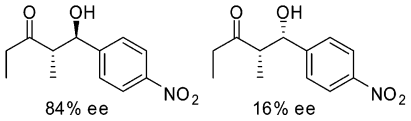


this reaction; however, alanine (**88**) was used by the authors for examination of the substrate scope due to its small size and simplicity. *Anti*-aldol products were obtained preferentially with very high enantioselectivites in most cases along with good diastereocontrol, but only in moderate to good yields. Water plays an important role, rendering high yields and stereoselectivities in this reaction. The authors proposed a Houk-type[79] transition state (**TS** in Scheme 36) to account for the observed stereoselectivities.[113] This proposal was later on supported by combined experimental and DFT calculations.[82] The scope of primary α-amino acids and their derivatives to catalyze the aldol reaction has recently been explored by Córdova and co-workers.[114]

Similar to the observation by Córdova and co-workers, Amedjkouh showed that the efficiency of primary amino acid-catalyzed asymmetric aldol reactions can be enhanced in the presence of a small amount of water.[115] Using (*S*)-valine as catalyst, aldol products were obtained in moderate

Table 3. Diamine Salt 90-Catalyzed Asymmetric Direct Aldolization of Various Ketones



Products	% Yield	dr (*anti*/*syn*)
	60	-
	97	74:26
	88	43:57
	81	54:46

to good yields (48−83%) and enantiomeric excesses (42−72% ee) when the reactions were conducted in DMF or DMSO.

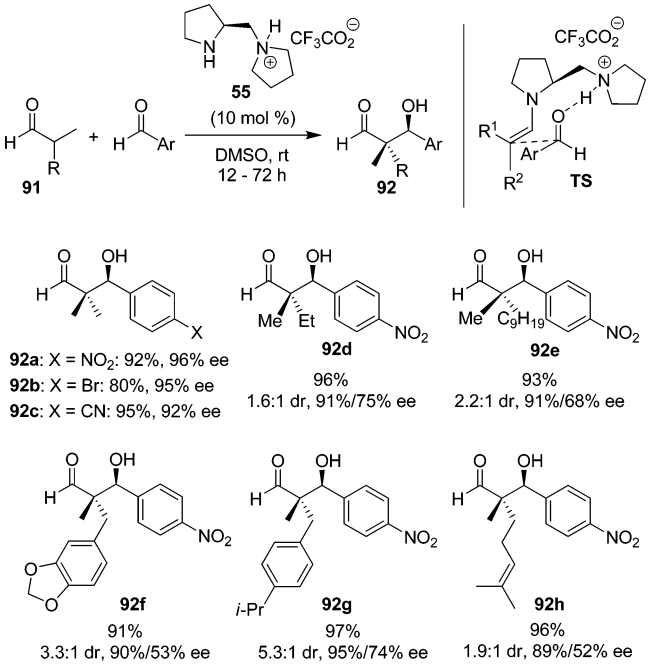
Intense research has focused on discovering even more efficient catalysts for the direct asymmetric aldol reactions. Although most of these catalysts somewhat structurally differ from the amino acids, their mode of action remains the same as that of proline itself.

Yamamoto et al. screened a wide variety of diamine salts to show that the secondary−tertiary diamine salt **90** catalyzes the aldol reaction of different ketones with *p*-nitrobenzaldehyde **76** to give aldols in good yields and enantioselectivities (Table 3).[116−118] However, the diastereoselectivities of the aldol products obtained are rather low.

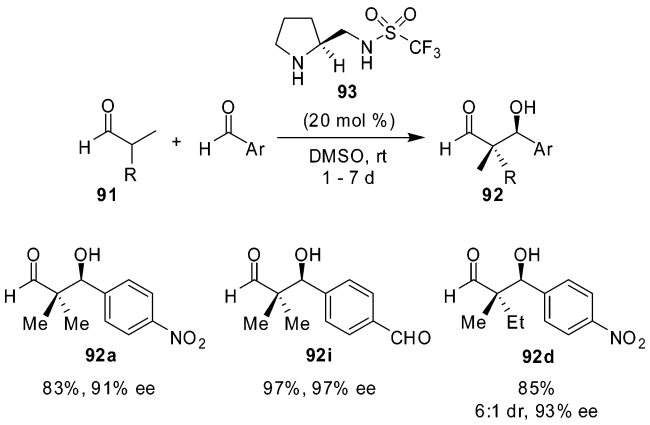
The scope of this type of diamine-acid salt catalyst was further extended to the construction of quaternary stereogenic centers. Diamine-trifluoroacetic acid salt **55** was identified as an efficient catalyst for the direct aldol reaction of α,α-disubstituted aldehydes **91** with aromatic aldehydes (Scheme 37).[119,120] The aldol products were obtained in excellent yields and very high enantiomeric excesses. The observed stereoselectivity was explained with transition state **TS** (Scheme 37), where the *re*-face attack on the aromatic aldehyde occurs via an enamine intermediate.[120] It is worth mentioning that proline is not an effective catalyst for this type of aldol reaction.

Wang et al. also reported a similar aldol reaction of α,α-dialkyl aldehydes **91** with electron-deficient aromatic aldehydes that generates quaternary carbon-containing *β*-hydroxycarbonyl compounds **92** using bifunctional pyrrolidine sulfonamide **93** as catalyst (Scheme 38).[121] The corresponding products **92** were obtained in high yields with excellent enantioselectivities (91−97% ee) using 20 mol % **93** despite the fact that longer reaction times are required in most cases.

Scheme 37. Diamine Salt 55-Catalyzed Asymmetric Direct Aldol Reactions for the Synthesis of α,α-Disubstituted Aldols



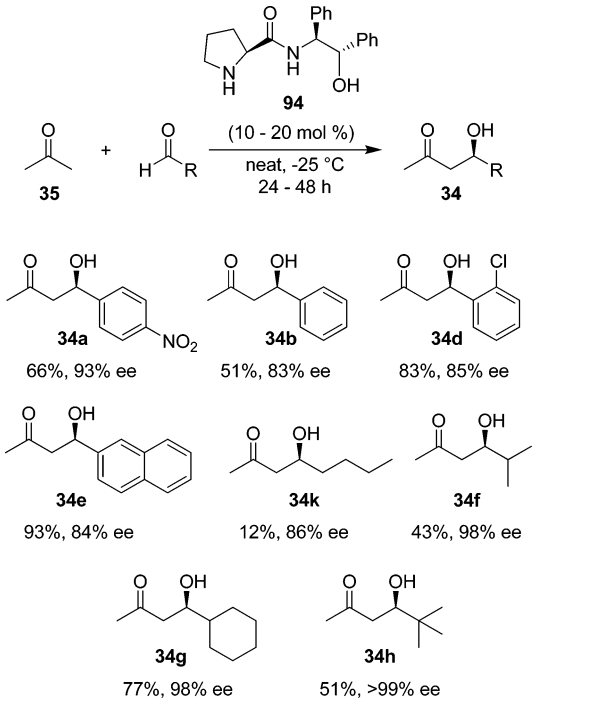
Scheme 38. Pyrrolidine Sulfonamide-Catalyzed Enantioselective Direct Aldol Reaction of α,α-Dialkyl Aldehydes



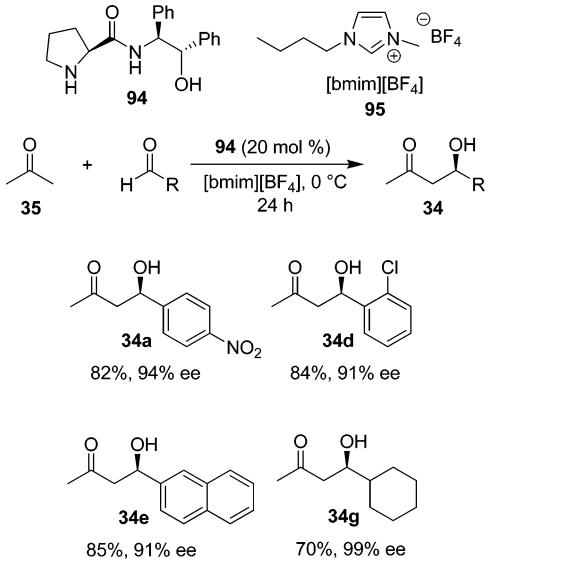
Interestingly, only one aldehyde group of terephthalaldehyde underwent aldol reaction with isobutyraldehyde even when an excess of isobutyraldehyde (product **92i**) was employed. An analogous Houk model (Scheme 37)[120] was invoked to rationalize the observed selectivity.[121]

Gong, Wu, and co-workers presented the first successful application of (*S*)-proline-derived amino alcohol amides as catalysts for highly enantioselective direct aldol reactions of aldehydes with neat acetone.[122,123] After studying a selection of proline-derived amides, the authors identified the hydroxyl amide **94** as an excellent catalyst for reactions of acetone with a variety of aldehydes (Scheme 39). Although (*S*)-prolinamides have been shown to be ineffective for the direct aldol reaction,[88] (*S*)-prolinamides with a terminal hydroxyl group exhibited increased catalytic activity and enantioselectivity. Typically, 20 mol % catalyst **94** provides aldol products **34** in high enantioselectivities of up to 93% ee for aromatic aldehydes and up to >99% ee for aliphatic aldehydes. Even though the yields are usually slightly better when proline is used as the catalyst, the enantioselectivity is invariably higher with amide **94**.

Scheme 39. Hydroxyamide-Catalyzed Aldolizations of Acetone with Different Aldehydes



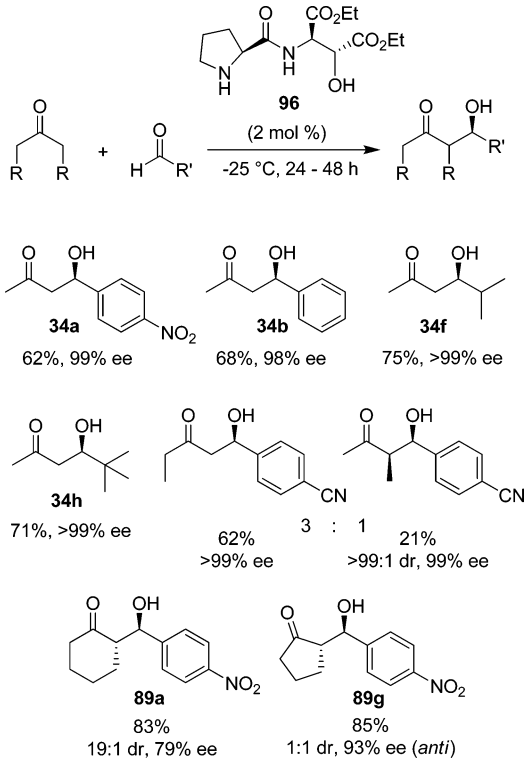
Scheme 40. Hydroxyamide-Catalyzed Acetone Aldolizations in Ionic Liquid



The authors also investigated the mechanism of this reaction based on quantum mechanical calculations.[122,123] Density functional theory calculations support the activation of the aldehyde substrate by simultaneous hydrogen bonds from the amide N−H and the terminal hydroxyl group in the transition state.

Gong, Jiang, and co-workers have also examined amide **94**-catalyzed aldol reactions in ionic liquids.[124] In general, higher yields and enantioselectivities were obtained (cf. Scheme 39) when the reactions were conducted with 20 mol % catalyst **94** in [bmim][BF_4] (**95**) at 0 °C (Scheme 40). The authors also showed that recycling of the catalyst is possible at least two times without affecting the efficiency or enantioselectivity of the reaction. The improved catalytic performance of amide **94** in ionic liquid was explained as a

Scheme 41. Substrate Scope of the Hydroxyl-amide 96-Catalyzed Direct Asymmetric Aldol Reaction



result of either stabilization of the iminium ion intermediate or enhanced nucleophilicity of the enamine.[124]

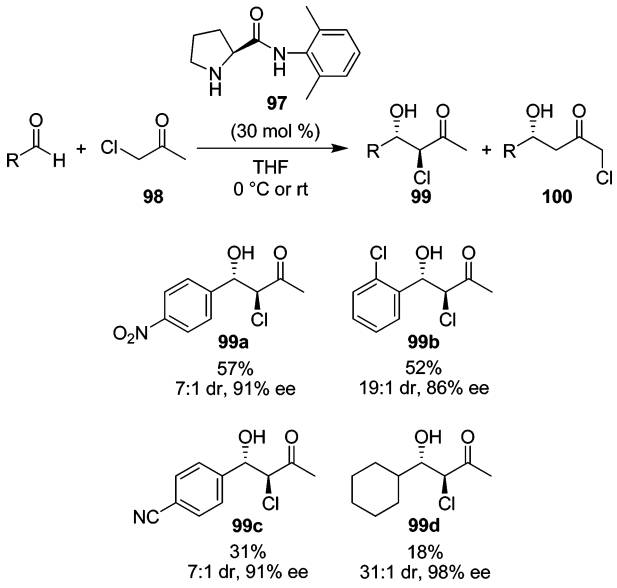
After continuous studies toward the improvement of the prolinamide catalyst, Gong et al. found that catalysts incorporating electron-withdrawing groups exhibit much higher catalytic activity and enantioselectivity than their analogues with electron-donating groups.[125] As low as 2 mol % of the newly identified catalyst **96** significantly catalyzes the direct aldol reactions of a wide range of aldehydes with acetone and butanone (Scheme 41). The products, β-hydroxy ketones, were obtained in very high enantioselectivities, ranging from 96% to >99% ee. Cyclic ketones have also been used: cyclohexanone led to the formation of *anti*-aldol product in high diastereoselectivity, but only with moderate enantioselectivity, whereas high enantioselectivity of the *anti*-aldol product was obtained with cyclopentanone. In the later case, however, the *anti*/*syn* ratio is 1:1.

Recently, the Gong group applied simple prolinamide **97** for the direct asymmetric aldol reaction of chloroacetone (**98**) with aldehydes (Scheme 42).[126] Electron-deficient aromatic aldehydes and one aliphatic aldehyde were used as the aldol acceptors. The corresponding *anti*-aldol products **99** were obtained in low to moderate yields and with good to excellent diastereo- and enantioselectivities. The main side products in this case are the other regioisomers **100**.

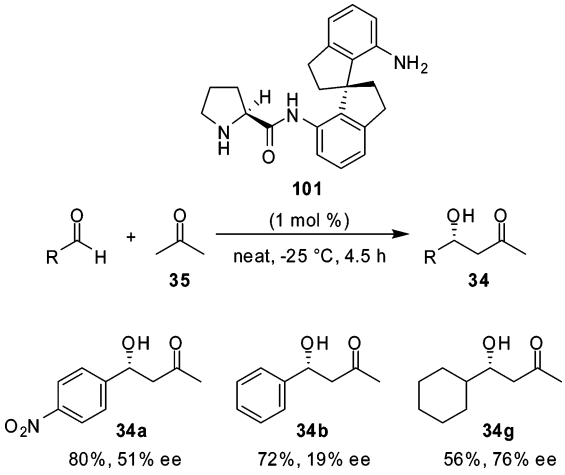
Zhou, Zhou, and co-workers introduced a remarkably active proline-derived spiro diamine catalyst **101** for direct asymmetric acetone aldol reactions (Scheme 43).[127] Different aromatic and aliphatic aldehydes were used as aldol acceptors. Only 1 mol % catalyst is required to obtain the aldol products in moderate to good yields and modest enantioselectivities within a short reaction time, even at −25 °C.

Chimni and co-workers showed the potential of protonated chiral prolinamides in the enantioselective direct aldol reaction of acetone and 4-nitrobenzaldehyde when water was

Scheme 42. Prolinamide 97-Catalyzed Asymmetric Direct Aldol Reactions of Chloroacetone with Aldehydes



Scheme 43. A New Spiro Diamine Catalyst for the Direct Asymmetric Acetone Aldol Reactions

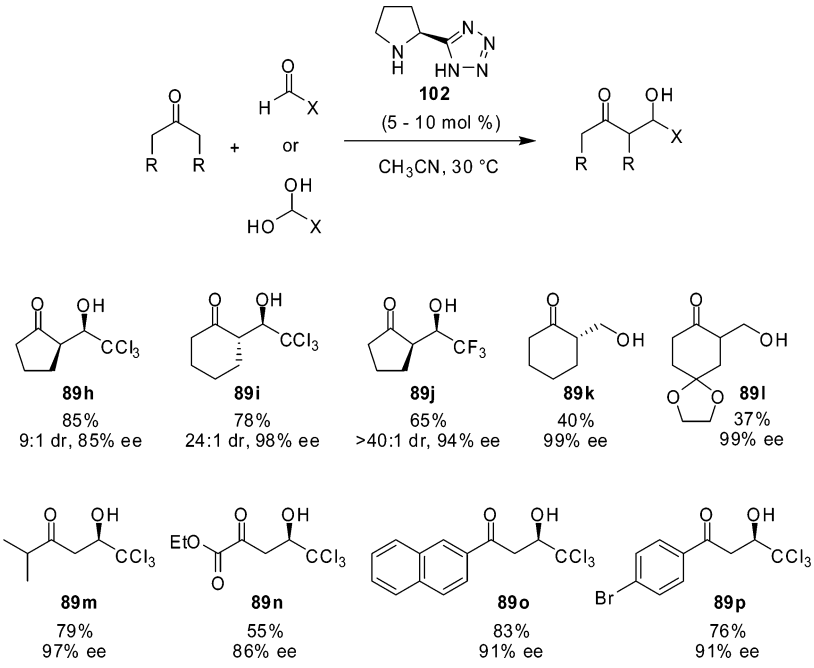


used as the cosolvent.[128] Although the aldol product was obtained in high yields in most cases, the enantioselectivities were only modest.

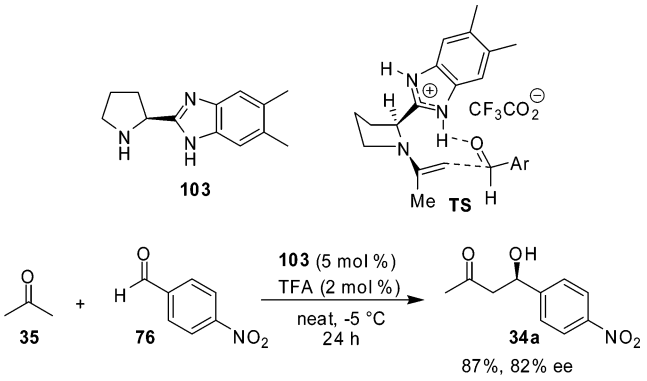
Saito, Yamamoto, and co-workers reported that a proline-derived tetrazole catalyst **102** (Scheme 44), that was independently developed by Ley et al.,[129] functions as a highly efficient catalyst for the asymmetric direct aldol reaction of ketones to reactive aldehydes, when the overall reaction conditions are adjusted precisely.[118,130] Interestingly, this reaction is significantly assisted by water: almost no product formation was observed when the reaction was performed under anhydrous conditions or with a catalytic amount of water. The enantioselectivities of the aldol products increase with an increasing amount of water, albeit at the expense of the diastereoselectivity. Three reactive aldehydes, namely chloral, trifluoroacetaldehyde, and formaldehyde, were used; several aliphatic and aromatic ketones were employed with chloral as acceptor. Good to excellent enantioselectivities along with high diastereoselectivities were obtained in all cases.

Shortly afterward, Hartikka and Arvidsson demonstrated the increased solvent scope and higher catalytic efficiency of the proline-derived tetrazole catalyst **102** compared to

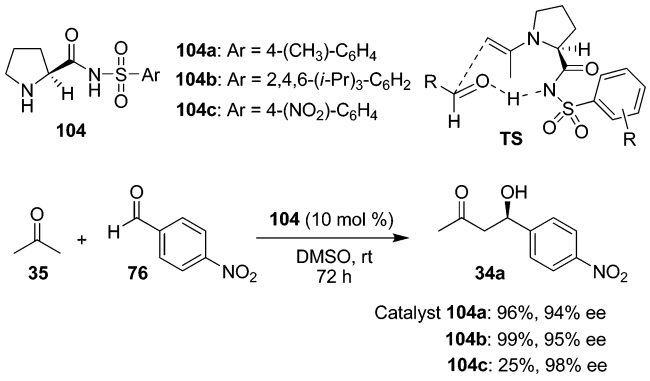
Scheme 44. Water-Assisted Asymmetric Direct Aldol Reactions of Ketones to Reactive Aldehydes



Scheme 45. Benzoimidazole-pyrrolidine (103)-Catalyzed Direct Aldol Reaction of Acetone to 4-Nitrobenzaldehyde



Scheme 46. Proline-Derived *N*-Acylsulfonamide Catalysts in Direct Aldol Reaction of Acetone to 4-Nitrobenzaldehyde



those of proline itself for the direct aldol reaction between acetone and different aldehydes.[131] Recently, an explanation for such differences in catalytic behavior between proline and its tetrazole derivative **102** was provided by Domingo and co-workers based on their DFT study.[86,132] Formation of an intermolecular hydrogen bond between the acidic hydrogen of tetrazole and the carbonyl oxygen of the aldehyde was proposed, and a larger solvation of the transition state involved in the tetrazole-catalyzed reaction due to the larger charge transfer accounts for the higher catalytic efficiency of the tetrazole catalyst.[86]

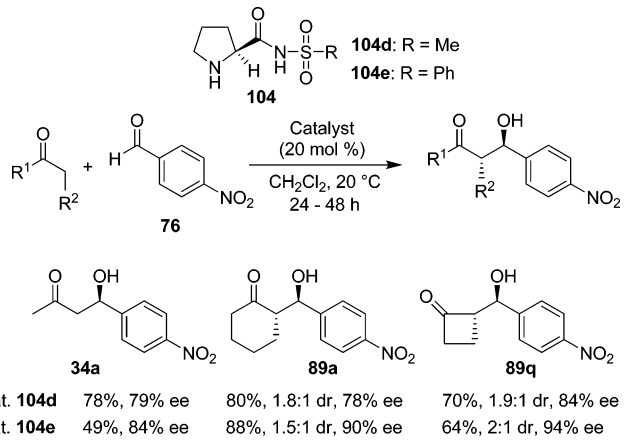
Landais, Vincent, and co-workers reported an easy to prepare benzoimidazole-pyrrolidine **103**, which in combination with trifluoroacetic acid (TFA) catalyzes the direct aldol reaction of acetone (**35**) with 4-nitrobenzaldehyde (**76**) (Scheme 45).[133] A combination of only 5 mol % **103** and 2 mol % TFA is enough to catalyze the aldol reaction at −5 °C, affording the aldol product in 87% yield with 82% ee. A transition state **TS** was proposed to explain the observed stereochemical outcome of the reaction (Scheme 45). Cyclopentanone was also employed in this reaction. In this case, the aldol product was obtained in moderate yield and good ee, despite almost 1:1 dr.

In the same year, Berkessel et al. introduced proline-derived *N*-acylsulfonamide catalysts **104** for the asymmetric direct aldol reaction of acetone (**35**) to 4-nitrobenzaldehyde (**76**) (Scheme 46).[134] These catalysts showed superior results compared to those of proline itself, in terms of both catalytic activity and enantioselectivity in this reaction. Using 10 mol % catalyst in DMSO, the aldol product **34a** was obtained in moderate to high yield and high enantioselectivity (up to 98% ee). Further lowering of the catalyst loading (up to 5 mol %) is possible without influencing the enantioselectivity, albeit at the expense of reaction rate. The authors proposed the transition state **TS** and explained the improved enantioselectivity by a better shielding of one of the enantiotopic faces of the aldehyde by the aryl ring.[134]

Soon after the report of Berkessel et al.,[134] the Ley group independently developed similar proline-derived *N*-acylsulfonamides (**104**) that catalyze asymmetric direct aldol reactions of different ketones with 4-nitrobenzaldehyde (**76**) (Scheme 47).[135] Enantioselectivities vary markedly depending on the solvent used. Even though dichloromethane was reported as the solvent of choice for these catalysts, when acetone was used as the solvent, aldol product **34a** was obtained in quantitative yield with 92% ee. In the case of cyclic ketones, *anti*-aldols were obtained in moderate to good enantioselectivities, but only with poor *anti*/*syn* ratios.

Kokotos et al. also described a series of proline and 4-substitited proline-derived *N*-acylsulfonamides for the

Scheme 47. Direct Asymmetric Aldol Reactions of Ketones and 4-Nitrobenzaldehyde Catalyzed by Proline-Derived *N*-Acylsulfonamides

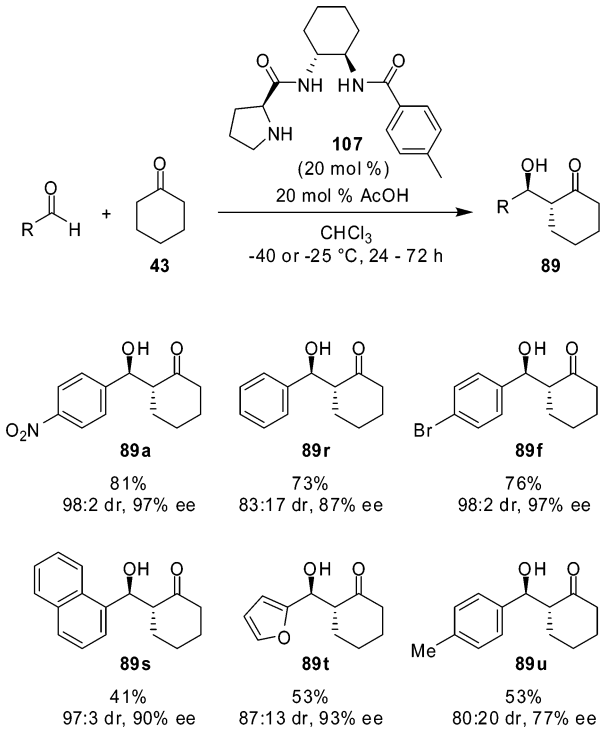


direct aldol reaction of acetone and 4-nitrobenzaldehyde.[136] Similar to the results reported by Berkessel[134] and Ley,[135] catalytic efficiency was found to vary depending on the nature of the substituents. Kokotos' group also synthesized a series of 4-substitued prolines and applied them for the direct aldol reactions.[137] Although the catalytic activity was not much influenced by the nature of the substituents, the enantioselectivity varied markedly depending on the substituents.

Recently Gouverneur et al. applied proline-derived *N*-acylsulfonamide catalyst **104e** (Scheme 47) for the enantioselective direct aldol reaction of ynones **105** to aromatic aldehydes (Scheme 48).[138] This is first time unmodified ynones were used as the donor in organocatalytic direct aldol reactions. In the presence of 20 mol % amine **104e**, monoprotected *anti*-α,*β*-dihydroxyynones **106** were obtained in moderate to high yields and high enantioselectivities (up to 95% ee) in most cases. The synthetic utilities of these products have also been demonstrated by the authors: the products were manipulated into enantioenriched *anti,anti*-triols and a novel class of oxygenated heterocycles in two steps.[138]

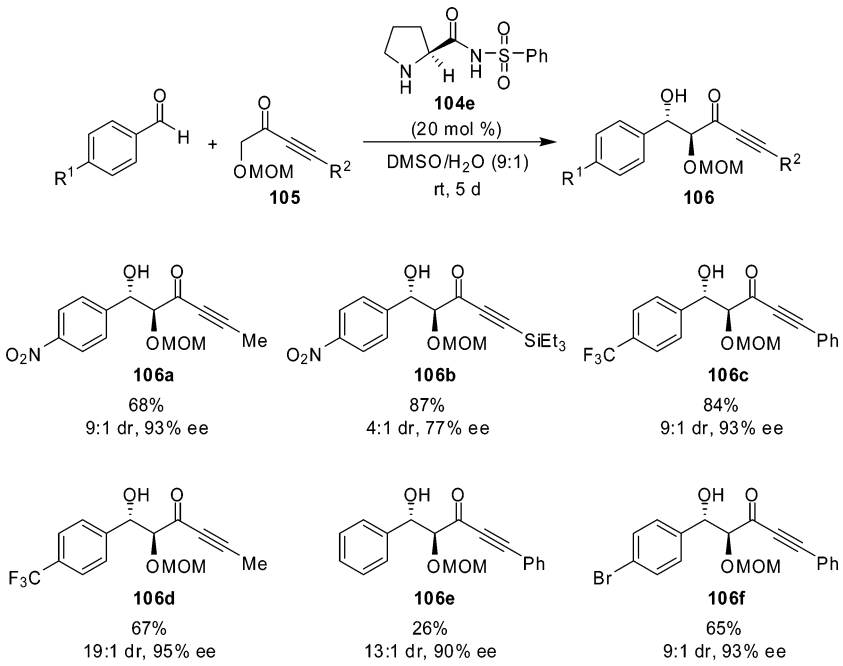
Xiao et al. reported a readily tunable (*S*)-prolinamide **107** as bifunctional organocatalyst for asymmetric direct aldol reactions of cyclohexanone (**43**) and various aromatic aldehydes (Scheme 49).[139] Acetic acid was used as a cocatalyst

Scheme 49. Bifunctional Prolinamide-Catalyzed Aldol Reactions of Cyclohexanone with Aromatic Aldehydes

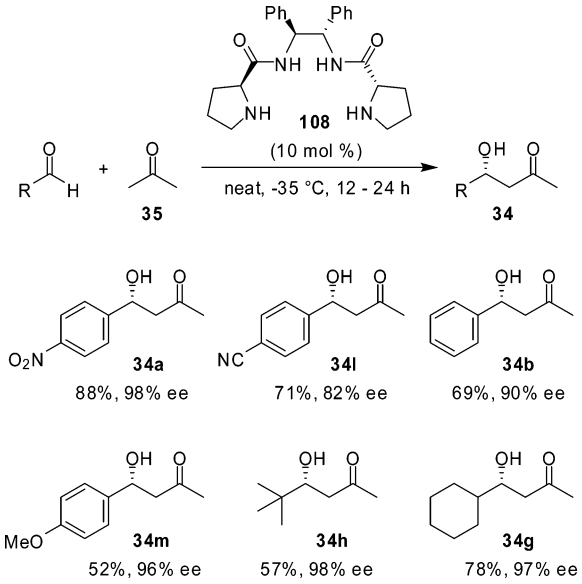


in this reaction. In the presence of 20 mol % of each **107** and AcOH at −25 °C (or −40 °C) in chloroform, aldol products **89** were obtained in moderate to good yields, and excellent diastereo- and enantioselectivities. The aldol reaction of 4-nitrobenzaldehyde with butanone was also explored: the regioselective *anti*-aldol product at the C-3 position of butanone was obtained in 63% yield and in high diastereo- (95:5) and enantioselectivities (99% ee).

Scheme 48. Enantioselective Direct Aldol Reaction of Ynones to Aromatic Aldehydes



Scheme 50. C_2-Symmetric Bisprolinamide Catalyst for the Direct Aldol Reaction of Acetone with Aldehydes

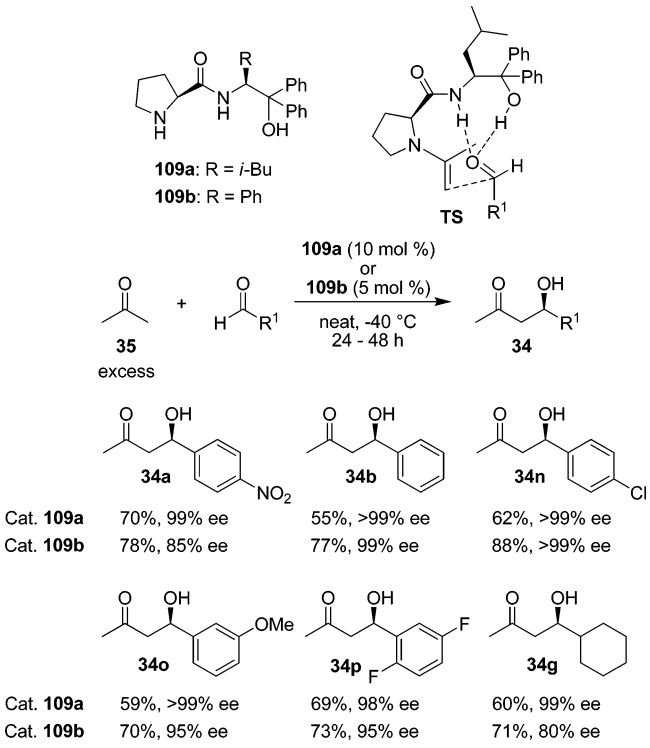


Xiao and co-workers have recently described a detailed study exploring the steric and electronic properties of this type of catalysts, and their efficacy in the direct aldol reaction of cyclic and heterocyclic ketones with various aldehydes.[140] Excellent diastereo- (up to >99:1 dr) and enantioselectivities (up to >99% ee) were achieved when hetereocyclic ketones were used as donors with aromatic and some aliphatic aldehyde acceptors. For any given heterocyclic ketone, a suitable catalyst has been identified.

A similar but C_2-symmetric bisprolinamide catalyst **108** was developed by Zhao et al.[103] for the improvement of the catalytic activity of prolinamide-type catalysts[122,123,125,139,141] (Scheme 50). Direct aldol reactions of acetone with various aromatic and aliphatic aldehydes were found to take place quite efficiently in the presence of 10 mol % of this catalyst at a temperature as low as −35 °C. Very high enantioselectivities (up to 98% ee) of aldol products **34** were obtained in moderate to good yields (up to 88%) in most cases. Other acyclic and cyclic ketones, besides acetone, have also been used as the ketone component for the reaction with 4-nitrobenzaldehyde: moderate to high enantio- and diastereoselectivities were obtained in these cases along with rather poor regioselectivity in the case of hydroxyacetone.[103]

Nájera et al. reported a conceptually related C_2-symmetric bisprolinamide catalyst bearing a binaphthyl backbone for the direct aldol reaction between ketones and various aldehydes.[142] Enantioselectivities of the aldol products in the range of 78−96% ee were obtained with moderate to excellent yields and good diastereoselectivities when cyclohexanone was used as the ketone partner. The catalyst can be recovered by simple extraction and can be reused without significant changes in the reactivity or enantioselectivity.[142] Gryko and co-workers used the same catalyst for the acetone aldol reaction with moderate enantioselectivities.[143] The Nájera group showed that this catalyst can also be applied for the aldol reaction of α-oxygenated acetones with electron-deficient aromatic aldehydes.[144] Products were obtained with good to high regio- and diastereoselectivities as well as with moderate to excellent enantioselectivities. The same group demonstrated that, when used together with benzoic acid cocatalyst, the C_2-symmetric bisprolinamide catalyst can effectively increase the reaction rate as well as the product

Scheme 51. (*S*)-Proline-Based Small Molecules as Catalyst for the Direct Aldol Reaction of Acetone as Donor

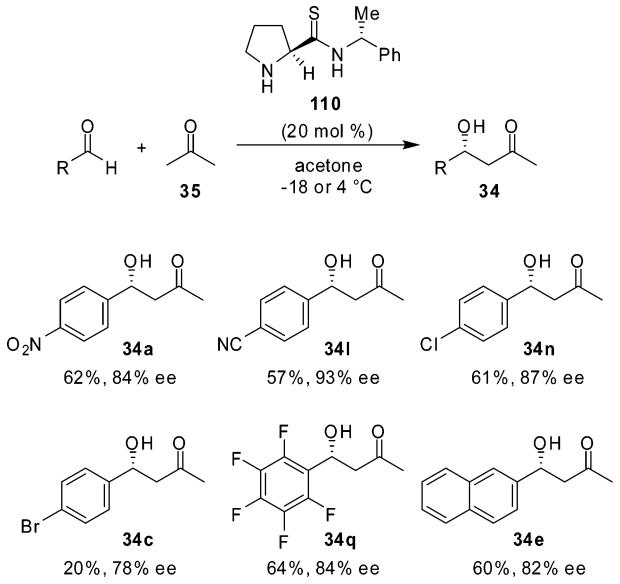


yield for the reaction in DMF/H_2O or neat water.[145] Very recently, Shi et al. applied a combination of this C_2-symmetric bisprolinamide catalyst and acetic acid for the asymmetric intermolecular aldol reaction of acetone and cyclohexanone with various aromatic aldehydes.[146] Very high diastereoselectivities and enantioselectivities were obtained together with good yields. Benaglia and co-workers used related non-C_2-symmetric mono- and bisprolinamide catalysts for the aldol reaction with mixed results.[147]

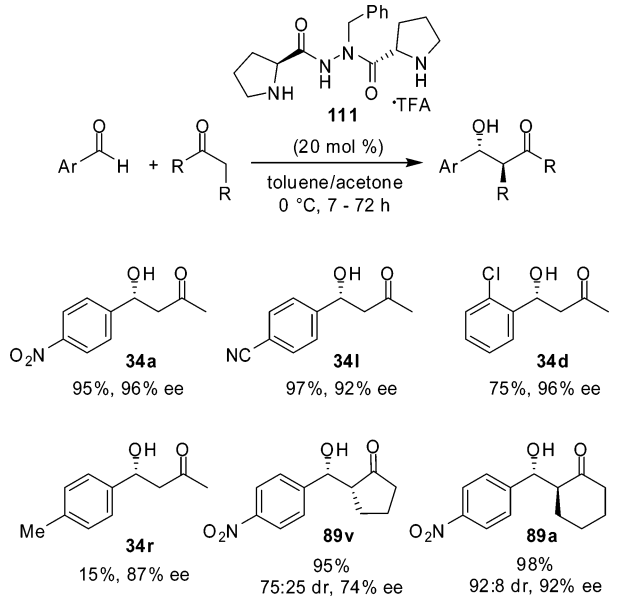
To date, the best enantioselectivity in aminocatalytic intermolecular acetone aldolizations has been achieved by Singh and co-workers.[148] They reported a class of (*S*)-proline-based, Gong-like small organic molecules **109** for the direct aldol reaction between acetone and various aldehydes (selected examples are shown in Scheme 51). The reaction is efficient with 5−10 mol % catalyst even at very low reaction temperature (−40 °C). Excellent enantioselectivities (up to >99% ee) were obtained with numerous aromatic aldehydes and cyclohexane carbaldehyde. The presence of a *gem*-diphenyl group at the β-carbon is necessary for high enantioselectivities. The stereogenic center at the β-carbon atom is not essential but beneficial for high optical purity. The authors explained the stereochemical outcome of the reaction by a transition state model **TS** (Scheme 51) similar to the one proposed by Gong and Wu.[123] Higher reactivity of the catalyst can be rationalized by the double hydrogen bond activation of the aldehyde carbonyl group.

Although prolinamide itself[88] or unfunctionalized prolinamide derivatives[123] were reported to be either poorly active or little enantioselective catalysts for direct aldol reactions, the corresponding prolinethioamides are shown to be rather efficient catalysts for the same reaction. Gryko and Lipinski demonstrated the potential of unfunctionalized prolinethioamides as enantioselective catalysts for the direct aldolization of acetone to reactive aromatic aldehydes.[149,150] In most of the cases, the aldol adducts were generated in good yields

Scheme 52. Prolinethioamide-Catalyzed Direct Acetone Aldolization with Reactive Aromatic Aldehydes



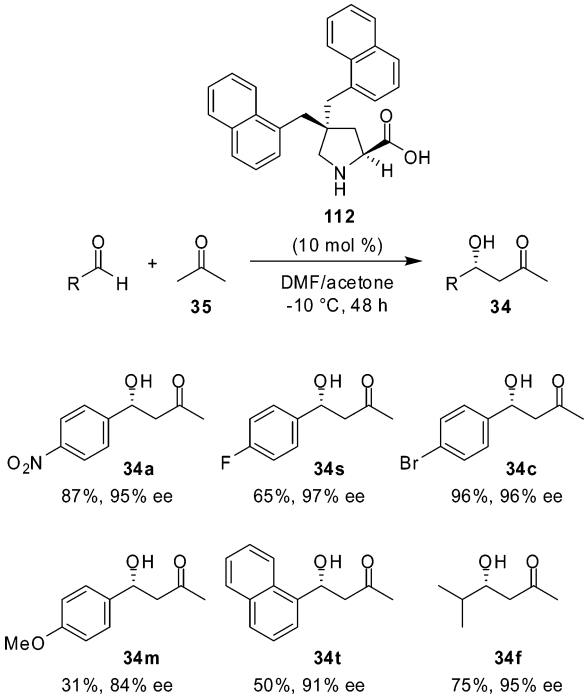
Scheme 53. Protonated Proline-hydrazides for the Asymmetric Direct Ketone Aldol Reactions with Aromatic Aldehydes



and enantioselectivities with 20 mol % thioamide **110** (Scheme 52). The enantioselectivity could be improved up to 100% ee at −78 °C, although at the expense of reaction rates. A catalytic amount of acid was shown to have a beneficial influence on both the yield and enantioselectivity of the reaction.[149] Such a difference in catalytic efficiency between prolinamides and prolinethioamides is presumably due to the higher acidity of the thioamide proton (the pK_a of CH_3CSNH_2 is 18.5 compared to 25.5 for CH_3CONH_2).[151]

Very recently, Sun, Wu, and co-workers reported chiral proline hydrazides as highly efficient catalysts for the direct aldol reaction between ketones and aromatic aldehydes.[152] With the help of thorough structure-based optimization studies, the hydrazide−TFA combination **111** was identified as the optimal catalyst for the reaction (Scheme 53). At 0 °C in toluene with 20 mol % catalyst **111**, electron-deficient aromatic aldehydes were found to provide the aldols in excellent yields and enantioselectivities with acetone as the donor unit. Nonactivated and electron-rich aromatic aldehydes afforded somewhat inferior results, particularly in terms of reaction rate and product yield. The *anti*-aldol product was obtained predominantly when cyclohexanone was used as the ketone partner, whereas cyclopentanone generated the *syn*-aldol product selectively. Theoretical calculations as well as experimental observations established that the enamine generated from one of the proline NHs (the one on the left side in Scheme 53) participates in the catalytic cycle.[152]

Scheme 54. 4,4′-Disubstituted (*S*)-Proline 112 for the Direct Aldol Reactions of Acetone with Various Aldehydes

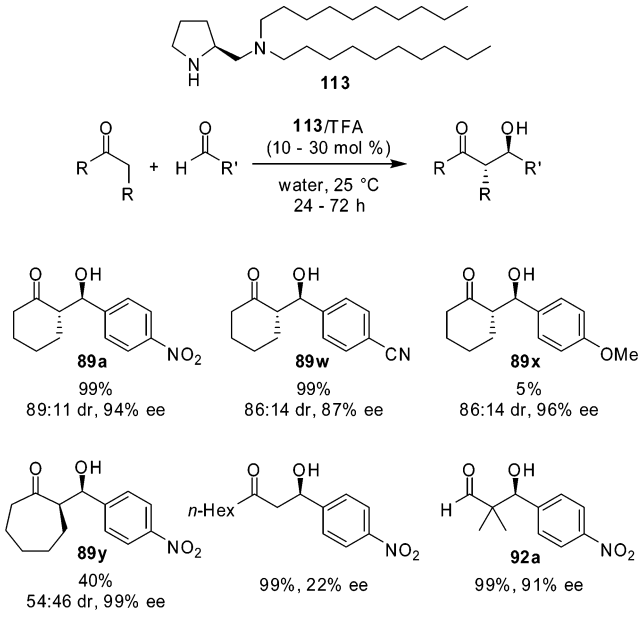


Almost all the catalysts described above rely on the same catalyst design concept, namely the replacement of the carboxylic acid group of proline with another functionality. Modification of the five-membered ring of proline has attracted less attention, except for the case of 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC) catalyst **87**.[111]

Quite recently, Zhao et al. reported 4,4′-disubstituted (*S*)-prolines as highly enantioselective catalysts for direct aldol reactions.[153] The authors synthesized a series of 4,4′-disubstituted (*S*)-prolines and applied them for the aldolization between aliphatic ketones and various aldehydes (Scheme 54). Among all the catalysts studied, 1-naphthlenylmethyl-substituted catalyst **112** turned out to be optimal. With 10 mol % **112** in DMF at −10 °C, aldol products were obtained in excellent enantioselectivities, although in varying yields depending on the nature of the aldehydes. Other ketones besides acetone have also been used, namely cyclohexanone, cyclopentanone, and 2-butanone. Whereas the cyclic ketones provided the *anti*-products in 94% ee, 2-butanone gave a mixture of regioisomers.[153] In all cases, the enantioselectivities obtained are very high.

Although the majority of aldol reactions reported so far use conventional organic solvents as reaction medium, water, due to its economical viability and environmental affability, remains one of the most attractive solvents. Therefore, efforts have been made to develop catalysts that would allow for the aldol reactions to be conducted in water containing solvents.

Scheme 55. Diamine 113/TFA-Catalyzed Aldol Reactions in Water



In 2006 Takabe et al. developed a diamine-based catalyst for the direct asymmetric aldol reactions in the presence of water.[154] Diamine **113** with long hydrocarbon tails in combination with TFA (typically 10 mol %) catalyzed the aldol reaction of various ketones or isobutyraldehyde with aromatic aldehydes in water at room temperature to provide the products, usually in high yield, good diastereoselectivity, and excellent enantioselectivity of up to 99% ee (Scheme 55). Electron-deficient aromatic aldehydes once again proved to be the best acceptors. Nonactivated and electron-rich aromatic aldehydes have also been used, however with somewhat inferior results. Particularly, *p*-methoxybenzaldehyde afforded the aldol products in poor yield, but still with high diastereo- and enantioselectivities. The aqueous reaction in general provided superior results compared to when standard solvent (DMSO) was used for the same catalyst system. The authors also provided an explanation involving hydrophobic interactions for such high catalyst efficiency.[154]

At the same time, Hayashi et al. independently reported the development of a proline-based catalyst *trans*-4-silyloxyproline **114** for the direct aldol reactions of ketones and aldehydes in the presence of water (Scheme 56).[155] Almost all kinds of aldehydes, including electon-rich and electon-poor aromatic, heteroaromatic, and aliphatic aldehydes and even formaldehyde, were employed as the acceptor component. Excellent enantioselectivities of the *anti*-aldol products were obtained in conjunction with high diastereoselectivities for the reactions with cyclic ketones using 10 mol % catalyst **114**. Acyclic ketones such as acetone and hydroxyacetone, however, afforded only a moderate level of enantio- and diastereocontrol (1:1 dr and up to 67% ee). Lowering of the catalyst loading down to 1 mol % is possible without any influence on enantioselectivity, even though longer reaction times are required. The authors explained the effectiveness of the catalyst based on its solubility property: the partly water-soluble catalyst **114** together with the substrates forms a separate organic phase where the aldol reaction proceeds efficiently.[155−157]

Next to the designed small molecule catalysts, peptides, particularly *N*-terminal prolyl peptides, have emerged as another attractive class of catalysts for asymmetric aldol

Scheme 56. *trans*-4-Silyloxyproline-Catalyzed Direct Aldol Reactions in Water

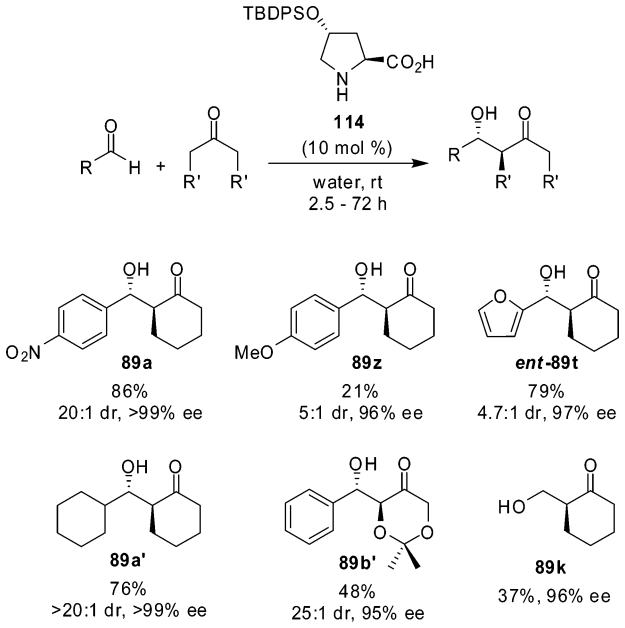
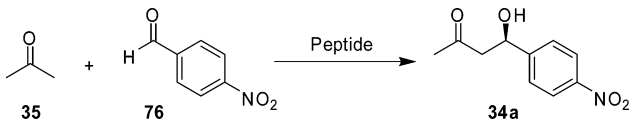


Table 4. *N*-Terminal Prolyl Peptides Catalyze Enantioselective Aldolizations

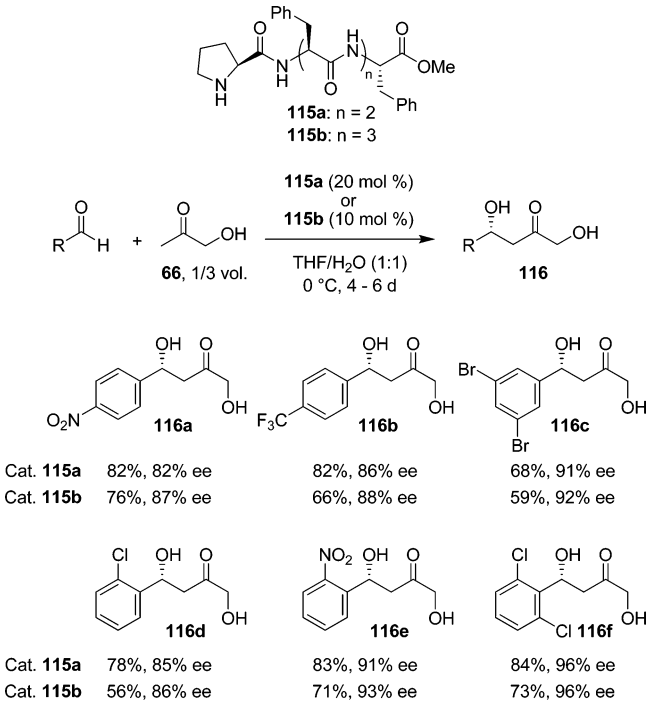


peptide	% yield	% ee	ref
H-Pro-Thr-OMe	n.r.	69	122
H-Pro-Gly-OH	99	46	158
H-Pro-Glu-Leu-Phe-OH	96	66	158
H-Pro-Aib-Glu-Phe-OH	94	37	158
H-Pro-Asp-Leu-Phe-OH	95	50	158
H-Pro-Aib-Asp-Phe-OH	97	12	158
H-Pro-Ala-OH	90	70	159
H-Pro-Trp-OH	77	65	159
H-Pro-Asp-OH	75	74	159
H-Pro-Glu-OH	72	68	159
H-Pro-Val-OH	89	70	159
H-Pro-Arg-OH	91	31	159
H-Pro-Ser-OH	87	77	159
H-Pro-Lys-OH·HCl	62	66	159
H-Pro-Gly-Gly-OH	68	53	159
H-Pro-His-Ala-OH	85	56	159

reactions. Although small molecules such as proline and its derivatives are excellent catalysts for direct aldol reaction and provide for many substrates good enantioselectivities, relatively high catalyst loadings are often required. Catalyst optimization by structural modifications of small molecules such as proline can be difficult. Besides, there are several interesting enamine involving reactions that cannot be catalyzed by proline. Peptides with their structural and chemical diversity, accessibility, and inherent chirality present an attractive alternative solution to these problems.

Gong, Wu, and co-workers mentioned in a footnote[122] that the dipeptide ester H-Pro-Thr-OMe catalyzes the aldolization of acetone with 4-nitrobenzaldehyde to generate the corresponding aldol adduct in 69% ee. In 2003, Reymond et al. reported the first example of *N*-terminal prolyl peptides as catalysts for asymmetric aldol reactions (Table 4).[158] After studying a peptide library, they found that the peptide H-Pro-Glu-Leu-Phe-OH catalyzes the reaction of acetone with

Scheme 57. Small Peptide-Catalyzed Direct Aldol Reactions of Hydroxyacetone with Aldehydes



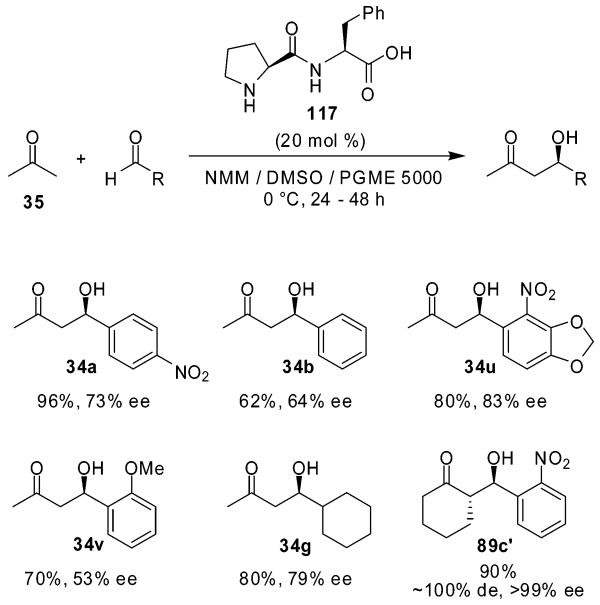
4-nitrobenzaldehyde with good activity and moderate enantioselectivity (66% ee). The authors showed that an acidic side chain and/or *C*-termini are essential for catalysis. In the same year, Martin and List demonstrated that *N*-terminal prolyl peptides (both di- and tripeptide) catalyze this reaction in moderate to good yields and moderate enantioselectivities up to 77% ee (Table 4).[159]

These results are particularly remarkable in light of the observation that catalysis by proline amide is much less efficient and that it provides the product in only up to 30% ee.[123]

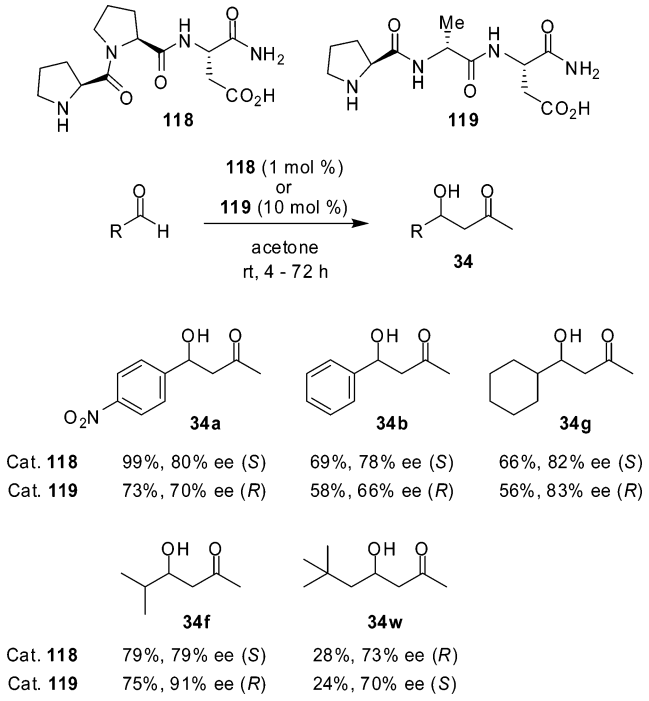
Gong et al. developed small *N*-terminal prolyl peptides **115** as efficient catalysts for the asymmetric direct aldol reactions of electron-withdrawing aromatic aldehydes with hydroxyacetone **66** at its methyl group (Scheme 57).[141] The products chiral 1,4-diols **116**, which are disfavored in aldolases or proline-catalyzed aldol reactions, were obtained in high yields and enantioselectivities up to 96% ee. This kind of regioselectivity is unprecedented in enamine-catalyzed aldol reactions and provides access to optically active 1,4-diols, an otherwise difficult to synthesize compound class. This reaction works in aqueous media, and the peptide chain length plays an important role in the stereo- and regioselectivities of the reaction.

Li et al. reported a dipeptide H-Pro-Phe-OH (**117**) as efficient catalyst for the asymmetric direct aldol reaction between acetone (**35**) and aldehydes (Scheme 58).[160] This catalyst can be considered as the minimal version of Reymond's tetrapeptide catalyst H-Pro-Glu-Leu-Phe-OH,[158] where the two intervening amino acid residues are omitted. Although catalyst **117** itself is less active and enantioselective than the tetrapeptide, both the catalytic activity and enantioselectivity can be significantly increased by adding *N*-methylmorpholine (NMM) and the surfactant polyethylene glycol monoethyl ether 5000 (PGME 5000). Under these conditions in DMSO at 0 °C, 20 mol % amide **117** catalyzes the aldol reaction of acetone and several aromatic as well as

Scheme 58. Dipeptide-Catalyzed Asymmetric Direct Aldol Reaction of Ketone to Aldehydes



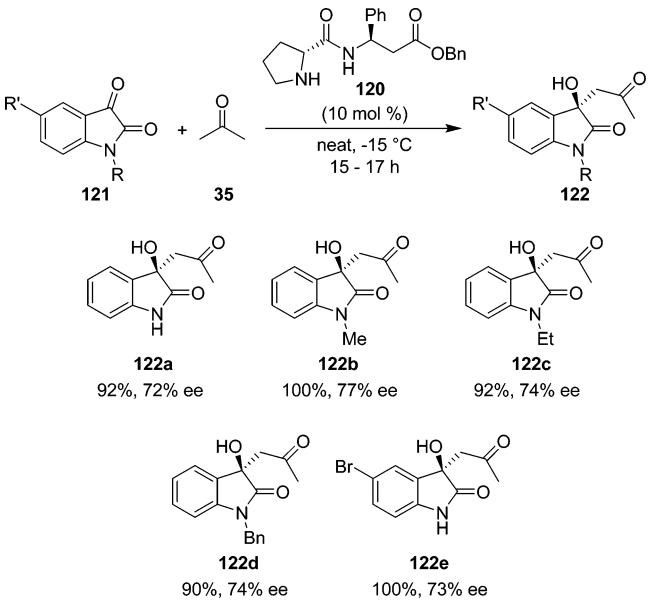
Scheme 59. Peptide-Catalyzed Aldolization of Acetone and Aldehydes



some aliphatic aldehydes to furnish the aldol products in moderate to good yields and up to 83% ee. When cyclohexanone was used as the ketone component, the *anti*-aldol product was obtained almost exclusively in 90% yield with >99% ee. An interesting aspect of this process is the catalyst recovery: it can be recovered by precipitating with aqueous ammonium chloride solution and reused without any loss of catalytic activity and enantioselectivity.

Wennemers and co-workers elegantly employed the combinatorial method of "catalyst−substrate co-immobilization"[161] to develop two tripeptide catalysts **118** and **119** (Scheme 59) for the direct asymmetric aldol reaction of acetone and aldehydes.[162] Both peptides contain a secondary amine and a carboxylic acid, and the peptides were identified from a library of 3375 different tripeptides. The authors

Scheme 60. Dipeptide-Catalyzed Acetone Aldolizations with Isatins



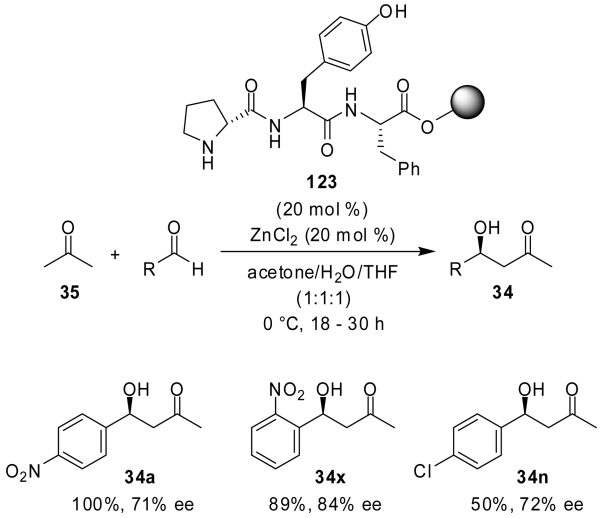
pointed out that the complexity of the tripeptides is a good trade-off for higher activity, and they correlate enantioselectivity with secondary structure: peptide **118** is >30-fold more active than peptide **119**, and the two catalysts generate aldol products with opposite absolute configurations. Both aromatic and aliphatic aldehydes are used as the acceptor component, and the aldol products are obtained in moderate to good yields and enantioselectivities. According to the conformational analysis, the opposite sense of stereoinduction stems from the oppositely handed turn conformations of the two peptides.

Combinations of α- and β-amino acids have also been used in the design of peptide catalysts. After systematic screening of several *N*-terminal prolyl dipeptides, Tomasini and co-workers identified a dipeptide (H-D-Pro-L-β^3-hPhg-OBn) containing (*R*)-proline and β^3-homophenylglycine **120** as a highly efficient catalyst for the direct acetone aldol reaction with isatin and its derivatives **121** (Scheme 60).[163] This reaction represents one of those few examples[100,164] where ketones were employed as the acceptor unit and enabled the formation of a quaternary stereogenic center. The catalyst is effective in only 10 mol % loading at −15 °C and afforded the aldol products **122** in excellent yields, although the enantioselectivities are in the range 72−75% ee. The absolute configuration of proline dictates the absolute configuration of the products, whereas the choice of the second amino acid is crucial for the selectivity.[163] Recently, this method was applied for the first total synthesis of (*R*)-convolutamydine A.[452]

Solid-supported *N*-terminal prolyl peptides have also been utilized as catalysts for direct asymmetric aldol reactions. In 2005, Andreae and Davis reported the application of PEG−polystyrene (TG)-supported peptides for the direct aldol reactions of acetone with *p*-nitrobenzaldehyde.[165] The dipeptide H-Pro-Ser-NH-TG was found to be the optimum among other peptides studied, giving the aldol product in 82% ee when the reaction was conducted in acetone at −25 °C.

Kudo et al. showed that polymer-supported *N*-terminal prolyl tripeptide H-D-Pro-Tyr-Phe-PEG-PS (**123**) effectively catalyzes acetone aldolizations with electron-deficient aromatic aldehydes (Scheme 61).[166] Aldol products were obtained in high yields and moderate enantioselectivities when the reactions were performed with 20 mol % peptide **123** and 20 mol % $ZnCl_2$ in an acetone/H_2O/THF (1:1:1) mixture. The solid-supported peptide catalyst can be recovered and reused at least five times without any influence on efficiency or selectivity. The role of $ZnCl_2$ in this reaction was not explained.

Scheme 61. Polymer-Supported Prolyl Tripeptide-Catalyzed Acetone Aldolizations in Aqueous Media

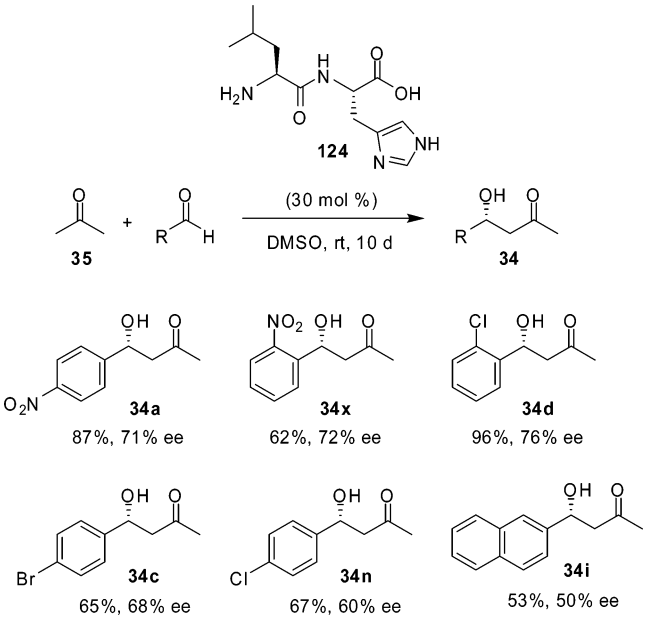


Peptides containing α-amino acids other than proline are also found to be active catalysts for asymmetric direct aldol reactions. Tsogoeva and Wei described the structure−activity relationship of some (*S*)-histidine-based dipeptide catalysts in this reaction.[167] They showed that the reactivities and enantioselectivities depend on the intermolecular cooperation of side chain functional groups and, particularly, on the appropriate combination and sequence of amino acids. The dipeptide H-Leu-His-OH (**124**) was identified as the optimum catalyst for the direct aldol reaction of acetone and aromatic aldehydes (Scheme 62). With 30 mol % peptide **124** in DMSO at room temperature, the aldol products were typically obtained in moderate to good yields (up to 96%) and moderate enantioselectivities (up to 76% ee). Significant rate enhancement was observed with different additives, albeit at the expense of enantioselectivities.

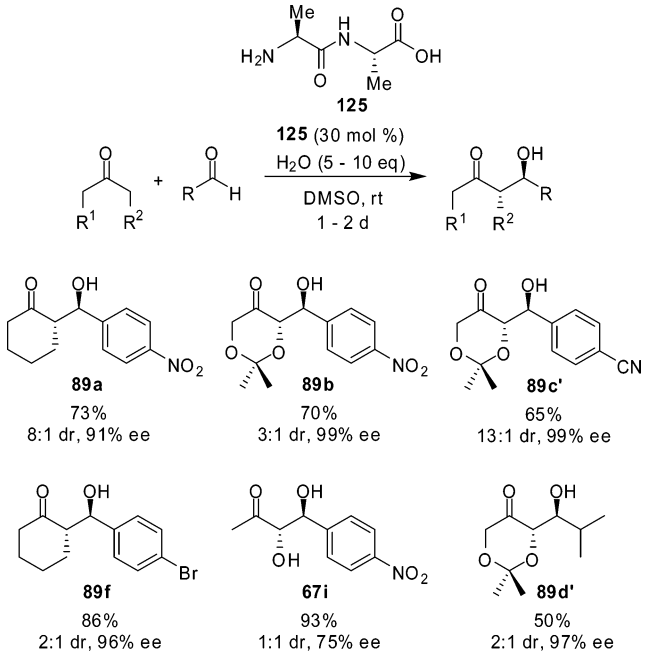
Córdova and co-workers showed that simple dipeptides containing primary α-amino acids can catalyze the asymmetric direct aldol reaction, albeit slowly.[168] From a collection of small peptides, the simplest dipeptide H-Ala−Ala-OH (**125**) was identified as a highly enantio- and diastereoselective catalyst for the reaction (Scheme 63). Addition of a small amount of water was found to be beneficial for both catalytic efficiency and stereoselectivity of the reaction. Excellent enantioselectivities (up to 99% ee) were obtained in most cases with 30 mol % peptide **125** along with moderate to excellent diastereoselectivities (1:1 to 13:1 dr) of the *anti*-aldol products. A transition state (see Scheme 36) similar to the one proposed by the same authors for the alanine-catalyzed aldol reaction[113] was invoked to rationalize the observed stereochemical outcome of the reaction. The authors have also studied the substrate scope for other dipeptides and suggested that for a given pair of substrates an optimum peptide catalyst can be generated.[168]

The Córdova group also demonstrated the potential of small dipeptides to catalyze stereoselective aldol reactions

Scheme 62. Direct Aldol Reaction between Acetone and Aromatic Aldehydes Catalyzed by the Dipeptide H-Leu-His-OH



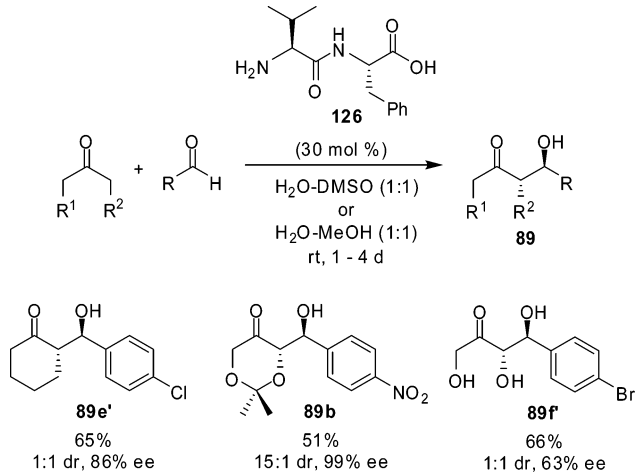
Scheme 63. Dipeptide H-Ala−Ala-OH-Catalyzed Asymmetric Direct Aldol Reactions



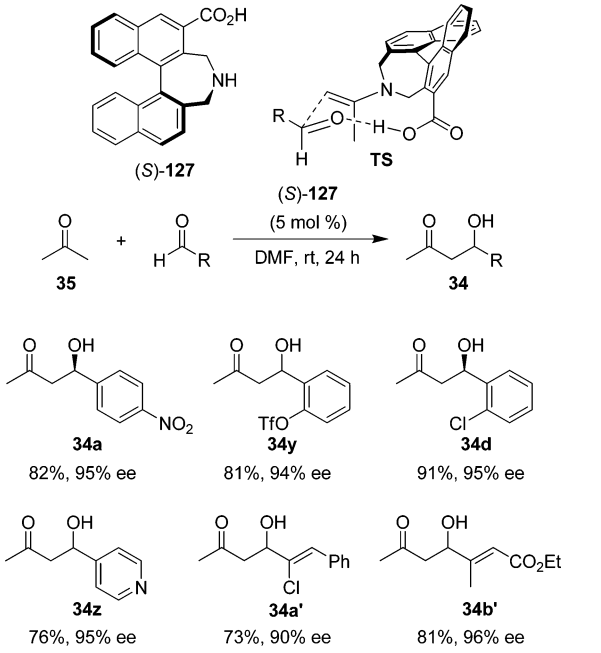
in aqueous media.[169] This time, H-Val-Phe-OH (**126**) was the catalyst of choice (Scheme 64). When the reactions were conducted in a H_2O−MeOH or H_2O−DMSO mixture (1:1) with 30 mol % peptide **126**, the aldol products were obtained in moderate to excellent enantioselectivities. Simple amino acids have also been tested in aqueous media, where they proved to be inefficient. Such a difference in catalytic behavior between amino acids and small peptides was explained in terms of structural complexity of peptides and their effectiveness in stabilizing the generated alkoxide product by hydrogen bonding.[169] Recently, Córdova and co-workers have explored the scope of small peptide-catalyzed enantioselective direct aldol reactions, with mixed results.[114]

Maruoka et al. reported the successful application of novel, robust axially chiral amino acid catalyst **127** to the direct

Scheme 64. Dipeptide H-Val-Phe-OH-Catalyzed Asymmetric Aldol Reactions in Aqueous Media



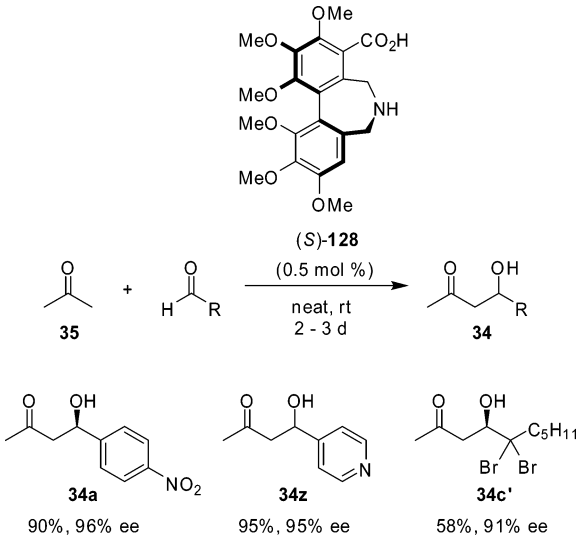
Scheme 65. Application of Binaphthyl-Based Axially Chiral Amino Acid to Direct Aldol Reactions



asymmetric acetone aldol reaction with aldehydes (Scheme 65).[170] In the presence of 5 mol % **127** in DMF, acetone (27 equiv compared to the aldehyde) undergoes an aldol reaction with olefinic, heteroaromatic, and aromatic aldehydes to provide products in good yields and excellent enantioselectivities. The limitation of the multistep catalyst synthesis is at least partially compensated by the fact that a relatively low catalyst loading is required for this reaction. Recently, the Maruoka group extended the substrate scope from acetone to cyclic ketones with excellent diastereo- and enantioselectivities.[171] To explain the observed stereoselectivity, the authors invoked a transition state (**TS** in Scheme 65) that is similar to the transition state[79] of the proline-catalyzed aldol reactions.[171]

Later on, the Maruoka group developed a more powerful biphenyl-based axially chiral amino acid catalyst **128** that promotes the acetone aldol reaction efficiently at a catalyst loading as low as 0.5 mol % (Scheme 66).[172] Excellent yields and enantioselectivities were obtained when the reaction was performed in neat acetone at room temperature. The catalyst loading can be further reduced to 0.1 mol % without affecting

Scheme 66. Biphenyl-Based Axially Chiral Amino Acid for Asymmetric Direct Acetone Aldol Reactions



the yield and ee, provided a longer reaction time (4 days vs 2 days with 0.5 mol %) is used. The superior catalytic efficiency of **128** (compared to **127** in Scheme 65) is presumably due to the higher nucleophilicity of its secondary amine because of the highly substituted electron-donating methoxy groups (Scheme 66).[172]

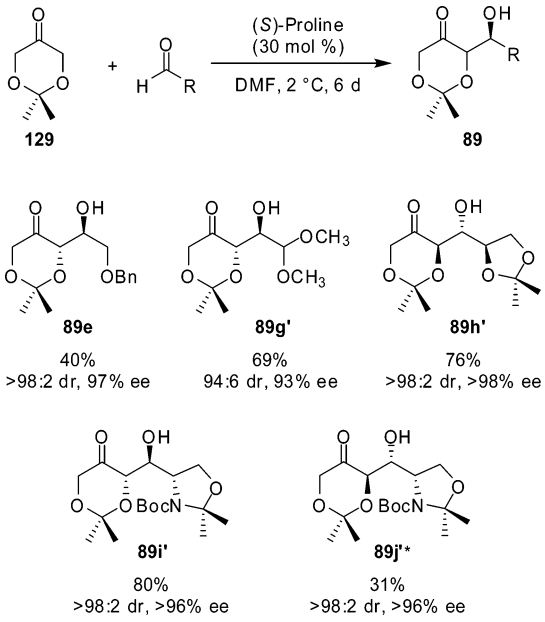
Very recently, Luo, Cheng, and co-workers synthesized proline-derived functionalized ionic liquids for asymmetric direct aldol reactions.[173] However, the selectivities obtained in this case were rather low (up to 4.8:1 dr and 63% ee).

E. Proline-Catalyzed Ketone Aldol Reaction in Carbohydrate Synthesis. Complementing MacMillan's two-step carbohydrate synthesis (see below), Enders and Grondal adopted a different strategy for the de novo synthesis of carbohydrates using the aldol reaction as a key step.[174,175] In their biomimetic approach, dioxanone **129**, the acetonide-protected dihydroxy acetone (DHA),[176] was employed as the donor unit (Scheme 67). When reacted with suitable aldehydes in the presence of 30 mol % proline in DMF at 2 °C, *anti*-aldol products were obtained in moderate to good yields and excellent diastereo- and enantioselectivities: a direct C_3+C_n assembly to selectively protected ketoses in one step. The products represent protected sugars and aminosugars: L-ribulose (**89e**), D-*erythro*-pentos-4-ulose (**89g′**), D-psicose (**89h′**), 5-amino-5-deoxy-L-psicose (**89i′**), and 5-amino-5-deoxy-L-tagatose (**89j′**). The formation of the *anti*-aldol product and the absolute configurations are in agreement with the Houk model.[99] The deprotection of the acetonides in **89h′** was achieved quantitatively with an acidic ion-exchange resin Dowex W50X2-200 to obtain the parent D-psicose.[174] The authors also described the stereoselective ketone reduction of **89g′** to obtain protected aldopentoses D-ribose and L-lyxose.[175]

Self-aldolization of dioxanone **129** is also possible using (*S*)-proline as catalyst to afford the aldol adduct **130** with 94% ee, but only in moderate yield (57%).[174] The product **130** represents a direct precursor of (*S*)-dendroketose (Scheme 68).

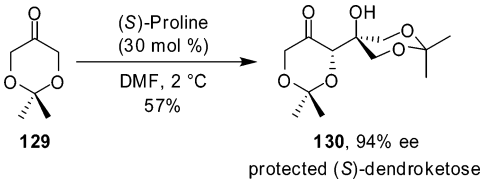
In the same year, Barbas and co-workers reported a proline-catalyzed aldol reaction of dioxanone **129** with various different aldehydes (Scheme 69).[177] Excellent enantio- and diastereoselectivities were obtained with aromatic, aliphatic, and oxy- and amine-substituted aldehyde acceptors

Scheme 67. Proline-Catalyzed Asymmetric Aldol Reaction of Dioxanone with Aldehydes[a]

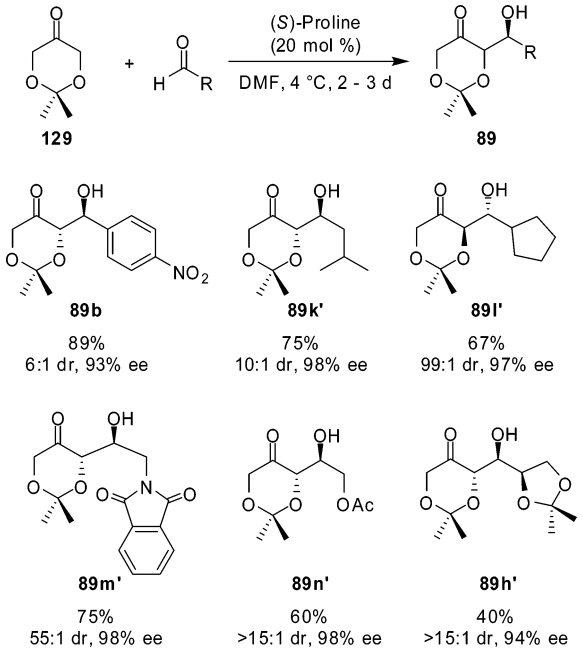


[a] The * indicates (*R*)-proline as catalyst.

Scheme 68. Proline-Catalyzed Asymmetric Self-aldolization of Dioxanone to Protected (*S*)-Dendroketose

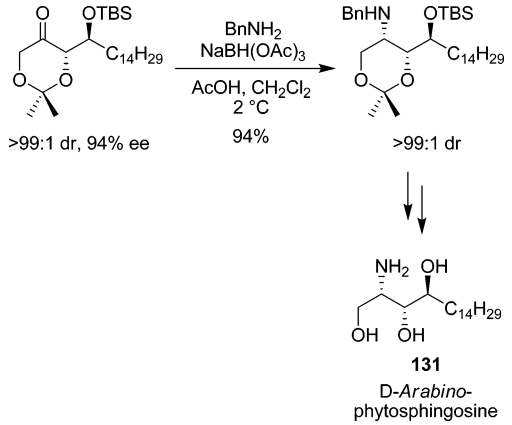


Scheme 69. Proline-Catalyzed Direct Aldol Coupling of Dioxanone with Various Aldehyde Acceptors

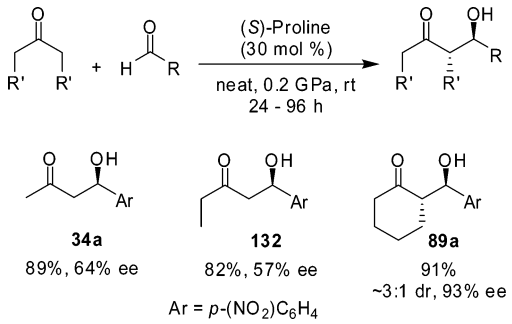


with 20 mol % (*S*)-proline as catalyst in DMF at 4 °C. When cyclopentane carboxaldehyde was used as the acceptor, the *anti*-aldol product was obtained in diastereomerically pure form with an ee of 97%. The aldol products obtained from oxy- and amine-substituted aldehydes are the protected azasugar and carbohydrates. The authors also elaborated the

Scheme 70. Asymmetric Synthesis of D-*arabino*-Phytosphingosine



Scheme 71. Proline-Catalyzed Asymmetric Aldolizations at High Pressure



aldol products to carbohydrate architectures by simple functional group manipulations.[177]

Recently, Córdova et al. reported similar observations for the de novo synthesis of ketoses by direct aldol reaction of dioxanone **129** as the donor and various aldehydes as acceptors catalyzed by proline and other cyclic five-membered amino acid derivatives.[178,179] The beneficial effect of water on the reaction rate and enantioselectivity was also studied by the same authors.

Enders et al. described the utility of this type of aldols[174] for a direct and flexible synthesis of phytosphingosine via a diastereoselective reductive amination of the aldol followed by deprotections (Scheme 70).[180]

Recently, the asymmetric synthesis of carbasugars has also been achieved by the Enders group starting from the aldol products of type **89h′** (Scheme 67) by using simple functional group transformations and ring closing metathesis (RCM) as the key step.[181]

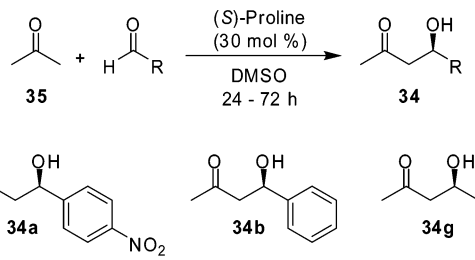
F. Unconventional Reaction Conditions for the Proline-Catalyed Asymmetric Direct Aldol Reaction. In addition to studying alternative catalysts and substrate variations, new reaction conditions have also been investigated by several research groups for the proline-catalyzed aldolizations. For example, reactions conducted at high pressure have been reported by two research groups. Kotsuki and co-workers found that the reaction between ketones and aldehydes can be promoted efficiently by applying high pressure.[182] When the reactions were conducted using 30 mol % proline at room temperature under a pressure of 0.2 GPa, the aldol products were obtained in improved yields, although nearly comparable enatioselectivities were obtained (Scheme 71). The main advantage of applying high pressure is that the formation of undesired condensation products was almost suppressed. However, as pointed out later on by Hayashi et al.,[183] the improvement of yield and enantioselectivity can be attributed not only to the pressure effect but also to the solvent effect, as the reactions were performed under neat conditions instead of DMSO.[10]

Whereas Kotsuki et al. preferred the conventional method for applying high pressure, the Hayashi group extended their water freezing-induced high-pressure technique from previously reported Mannich reactions[184] to aldol reactions.[183] The reactions were conducted at 200 MPa using the same conditions as those used by List et al.[10] except for a temperature of −20 °C. The reactions were accelerated, and the aldol products were obtained with improved enantioselectivities (Scheme 72). As in the report of Kotsuki et al.,[182] the condensation products were formed only in trace amount. The authors ascribed the rate acceleration to the pressure effect and the ee increment to the low reaction temperature.[183]

Aldol reactions have also been performed in unconventional reaction media. It has been found that the commonly used solvent DMSO could be replaced by the room-temperature ionic liquid [bmim][PF_6] (**133**) or [emim][OTf] (**134**) with comparable yields and selectivity (Scheme 73, eq 1).[185−187] The effect of solvent structure on the regioselectivity can, apparently, be quite strong, as is illusatrated in the case of the reaction of butanone (**135**) with *p*-trifluoromethylbenzaldehyde (**136**) (Scheme 73, eqs 2 and 3).

Chandrasekhar and co-workers reported a proline-catalyzed acetone aldol reaction in poly(ethylene glycol)-400.[67] The reactions were found to proceed rapidly (in general 30 min) in PEG-400 at room temperature when 10 mol % (*S*)-proline was used as the catalyst to afford the products in high yields (Scheme 74). The enantioselectivities of the products were found to be only moderate. The authors also demonstrated the reusability of both catalyst and solvent over ten runs without influencing the activity.

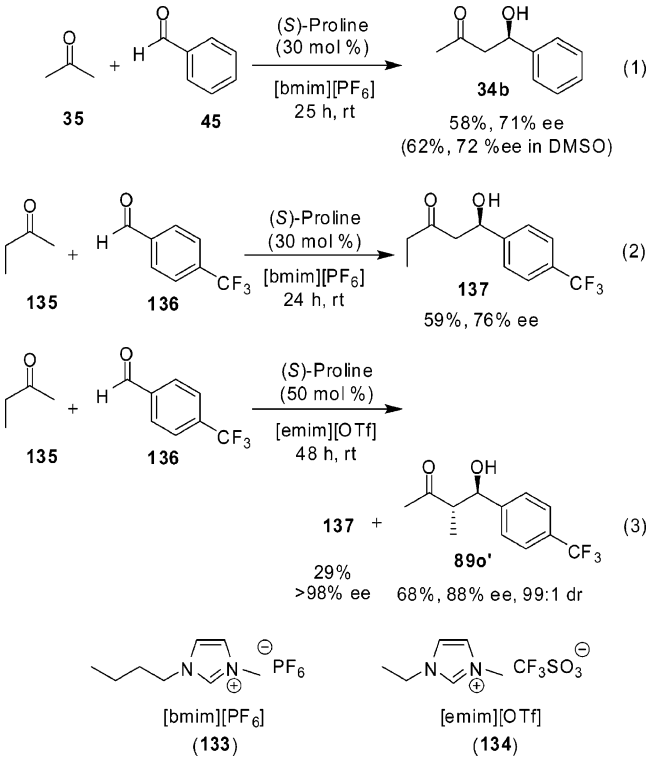
Scheme 72. Application of Water Freezing-Induced High Pressure to Proline-Catalyzed Asymmetric Aldol Reactions



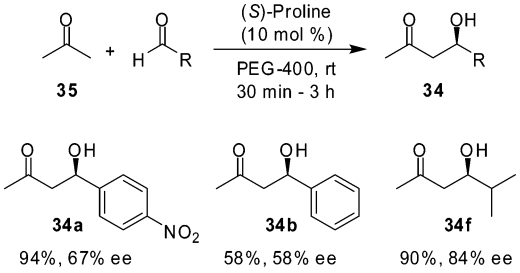
	34a	34b	34g
Conditions **A**	63%, 69% ee	62%, 69% ee	46%, 88% ee
Conditions **B**	57%, 75% ee	40%, 78% ee	6%, 90% ee
Conditions **C**	75%, 75% ee	78%, 75% ee	21%, 96% ee

Conditions **A**: 0.1 MPa, 23 °C; Conditions **B**: 0.1 MPa, -20 °C; Conditions **C**: 200 MPa, -20 °C.

Scheme 73. Proline-Catalyzed Aldolizations in Ionic Liquids



Scheme 74. Proline-Catalyzed Acetone Aldol Reactions in Poly(ethylene glycol)

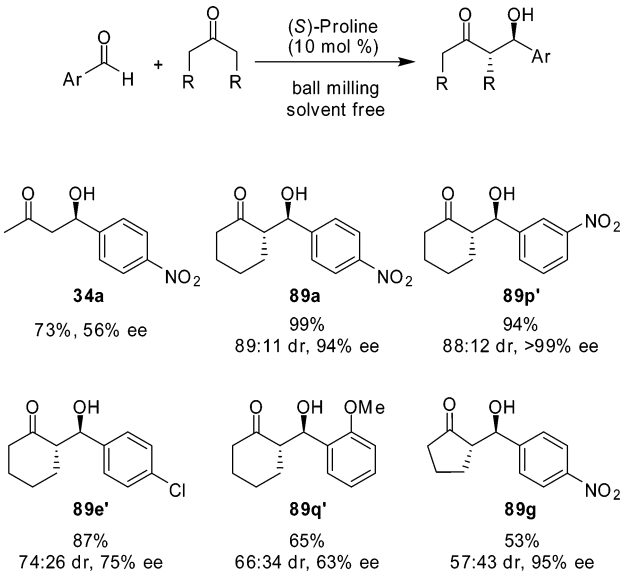


Even solvent-free conditions have been employed for the proline-catalyzed aldol reactions. Bolm et al. applied the ball milling technique for the solvent-free asymmetric direct aldolizations of ketones with aromatic aldehydes catalyzed by 10 mol % (*S*)-proline (Scheme 75).[188] Aldol products were obtained, typically in high yields within a short reaction time, with a varying range of selectivities depending on the nature of the substrates. Reactions under solvent-free conditions can also be conducted using conventional magnetic stirring, although with inferior results in most cases.

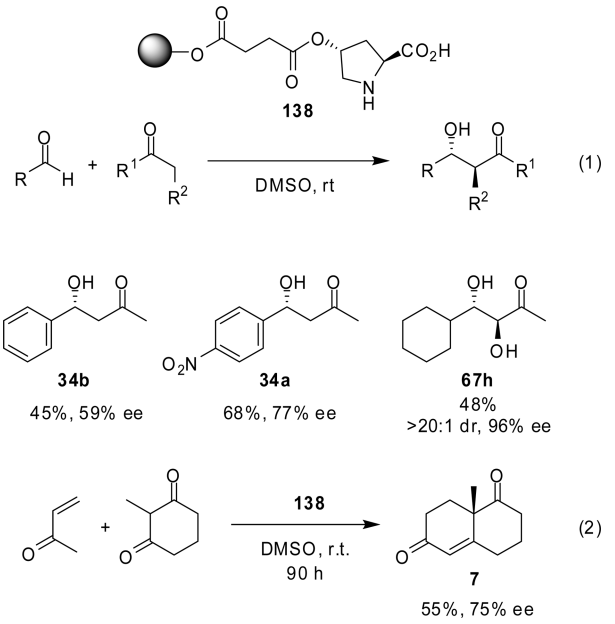
G. Supported Proline and Derivatives as Catalysts. Proline and its derivatives have also been attached to polymer supports. This approach permits recycling and reuse of catalysts. Even though for proline itself, because of its easy accessibility and ease of recycling via aqueous extraction or precipitation, such need of recycling can be questioned, attaching proline derivatives (that require multistep synthesis to obtain) to polymer supports definitely makes such processes more attractive. Takemoto et al. described the first example of this approach back in 1985 for the Hajos−Parrish−Eder−Sauer−Wiechert reaction (vide supra).[45]

Benaglia, Cozzi, and co-workers recently attached 4-hydroxyproline to a succinic acid-modified poly(ethylene glycol) support and applied the resulting soluble, polymer-

Scheme 75. Solvent-free Proline-Catalyzed Asymmetric Aldolizations under Ball-Milling Conditions



Scheme 76. Poly(ethylene glycol)-Supported Proline Catalysis in Aldol Reactions

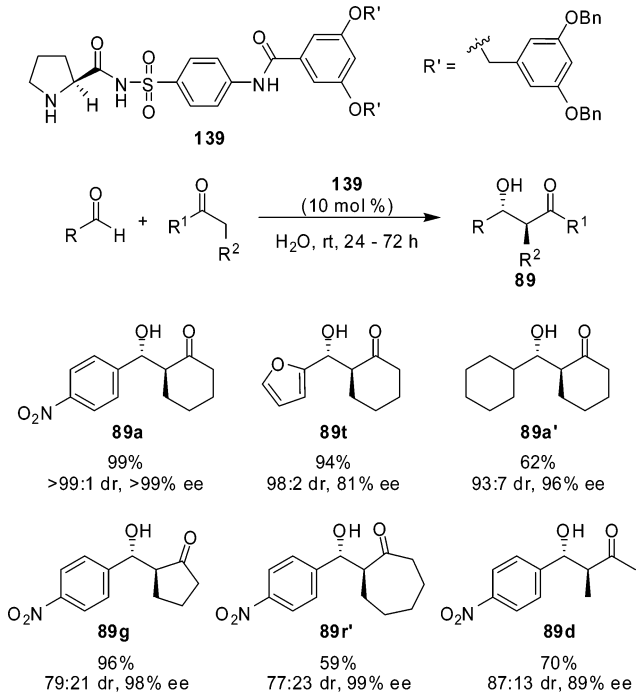


supported proline **138** for asymmetric intermolecular direct aldol reactions of ketones to aldehydes (Scheme 76, eq 1) and also for Robinson annulation (eq 2).[189,190] Yields and ee's are comparable to those obtained by proline itself. The reaction proceeds under homogeneous conditions; the catalyst was then precipitated by solvent change and reused without a major drop of catalytic activity and enantioselectivity.[189]

Kokotos et al. reported the synthesis of a surface-functionalized poly(propyleneimine) dendrimer based on proline and its application for the intermolecular aldol reaction.[191] The dendritic catalyst contains eight proline residues at its periphery. This soluble dendrimer (6.5 mol %, which is equivalent to 52 mol % proline) catalyzes the intermolecular acetone aldol reaction with comparable yields and enantioselectivities within a short reaction time (2 h).

Recently, Zhao, Wang, and co-workers reported a chiral amphiphilic dendritic catalyst **139** derived from prolyl *N*-sulfonamide for the asymmetric direct aldol reactions in

Scheme 77. Dendritic Prolyl *N*-Sulfonamide Catalyst for Direct Asymmetric Aldolizations in Water

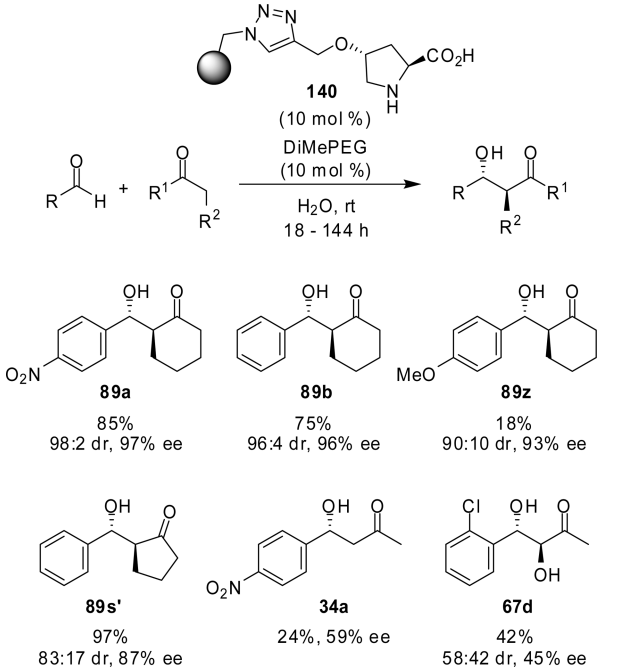


water (Scheme 77).[192] Using water as the only reaction medium, 10 mol % compound **139** at room temperature afforded the *anti*-aldol adducts in high yields with superb diastereo- and enantioselectivities. Both aromatic and aliphatic aldehydes were used as the acceptor whereas cyclic or acyclic ketones served as the donor unit. One attractive feature of this dendritic catalyst is that it can be recovered quantitatively by simply adding 1:1 *n*-hexane/EtOAc to the reaction mixture. The authors reported the recycling of the catalyst five times without any loss of activity and enantioselectivity.[192] This property of the catalyst will at least partially counterbalance the disadvantage of its multistep synthesis.

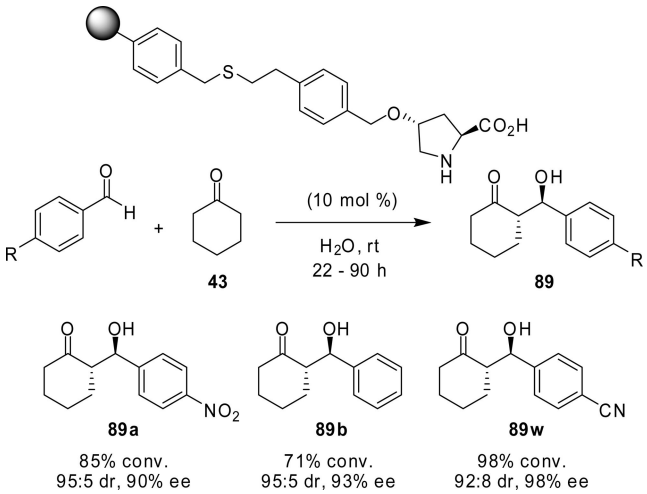
Pericàs et al. anchored 4-hydroxyproline to the polystyrene resin through click chemistry and applied the resulting polystyrene-supported proline **140** successfully to the direct aldol reaction in water (Scheme 78).[193] Only 10 mol % resin-bound catalyst is required to obtain the *anti*-aldol products in good yield and high diastereo- and enantioselectivities. A catalytic amount of water-soluble DiMePEG (MW ~ 2000) proved to be beneficial for obtaining an improved yield in a short reaction time. Both electron-deficient and electron-rich aromatic aldehydes were used as the aldol acceptors; however, the electron-rich aromatic aldehyde gave only a modest yield after a long reaction time, although the dr and ee remained high. Only a moderate level of selectivities was achieved with acyclic ketones as the donor. The favorable influence of the polymer backbone was established by comparing the results with those of a soluble analogue of **140**, which were inferior.[193]

Very recently, Gruttadauria et al. reported another polystyrene-supported proline for the asymmetric direct aldol reaction of cyclohexanone **43** with various aromatic aldehydes in water (Scheme 79).[194] Aldol products **89** were obtained with high diastereoselectivities and enantioselectivities. The authors also showed the recyclability of the supported catalyst up to four cycles: although the selectivities remain unaffected, conversion decreases with every recycling. Interestingly, no reaction was observed in the absence

Scheme 78. Polystyrene-Supported 4-Hydroxyproline for Direct Asymmetric Aldol Reactions in Water



Scheme 79. Polystyrene-Supported Proline Catalyst for the Asymmetric Direct Aldol Reaction of Cyclohexanone in Water



of water. The authors hypothesized the formation of a microenvironment with a hydrophilic proline moiety at the resin/water interface which promotes the aldol reaction with high stereoselectivity.

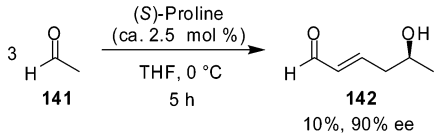
Fache and Piva prepared a polyfluorinated proline starting from *trans*-4-hydroxy-(*S*)-proline and applied it for the direct aldol reaction of acetone with 4-nitrobenzaldehyde.[195] A similar level of enantioselectivity to that of (*S*)-proline itself was obtained when the reaction was performed in benzenetrifluoride.

Some other supports for proline have also been employed in the asymmetric direct aldol reactions with varying success. These include supported ionic liquids,[196] a polyelectrolyte system,[197] and even anionic clays as intercalated support.[198]

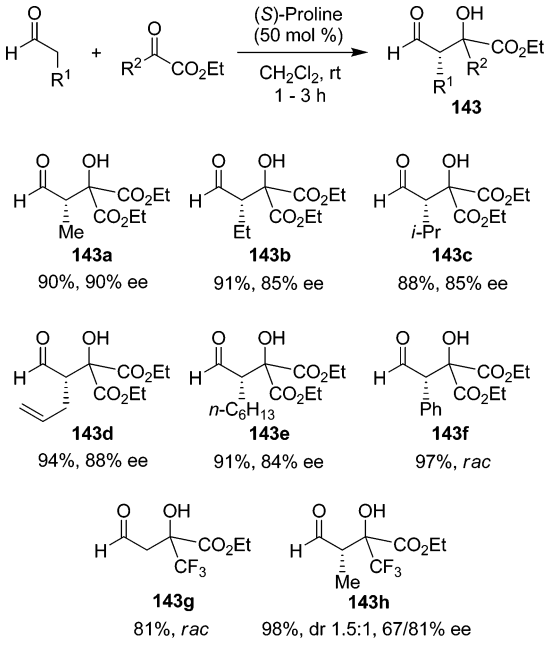
2.3.2. Aldehyde Donors

Recently, the scope of the proline-catalyzed aldol reaction was extended with respect to the donor carbonyl compounds.

Scheme 80. Proline-Catalyzed Direct Asymmetric Self-aldolization of Acetaldehyde



Scheme 81. First Proline-Catalyzed Intermolecular Direct Aldol Reactions with Aldehyde Donors



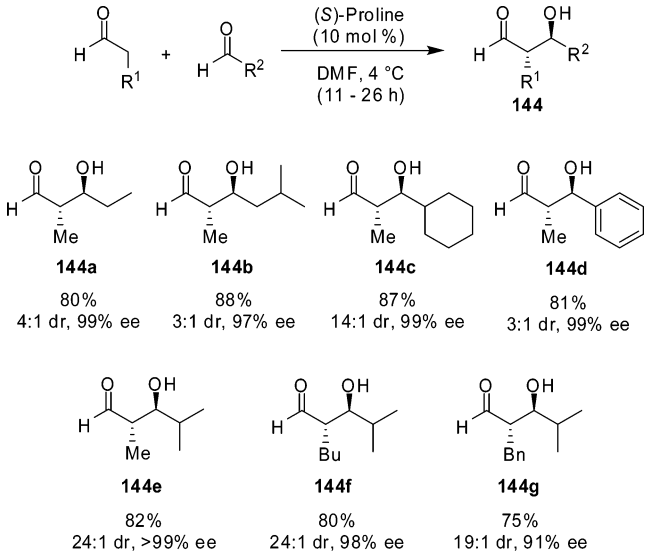
Besides ketones, aldehydes are an interesting class of donors in proline-catalyzed aldol reactions.[199] One challenge in using aldehyde donors in direct catalytic enantioselective aldolization is the lower reactivity of aldehyde-derived enamines as compared to those derived from ketones. More importantly, the aldol products, being aldehydes themselves, may undergo further aldolization.

In 2002, Barbas et al. reported an enantioselective proline-catalyzed self-aldolization of acetaldehyde (**141**).[200] Treating acetaldehyde solutions in THF (20 vol %) with proline provided 5-hydroxy-(2*E*)-hexenal (**142**), an aldol trimer of acetaldehyde, with up to 90% ee in low yield (Scheme 80).

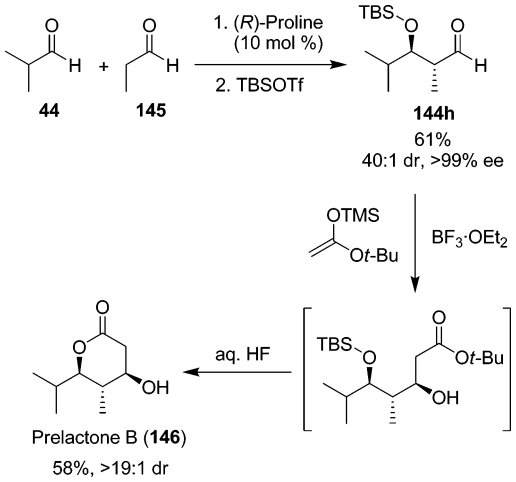
The first direct catalytic asymmetric cross-aldol reaction using aldehydes as donor component was reported by Jørgensen et al.[164] Simple α-unbranched aldehydes were used as donors in proline-catalyzed cross-aldolizations with highly activated nonenolizable ketone acceptors such as ketomalonates (Scheme 81). In the presence of a substoichiometric amount (50 mol %) of (*S*)-proline, the aldol products **143** were obtained in high yields within a short reaction time. High enantioselectivities were obtained in most of the cases, except with phenylethanal and acetaldehyde, which afforded racemic products. Ethyl trifluoropyruvate ($R^2 = CF_3$) also reacts with propionaldehyde ($R^1 = Me$) to give a mixture of two diastereomers (**143h**) with moderate dr (1.5:1) and with 67% and 81% ee of the two diastereomers. The potential of this process was demonstrated by simple conversion of the aldol products (when $R^2 = CO_2Et$) into optically active β-hydroxy carboxylic acid derivatives.[164]

A useful variant of the proline-catalyzed intermolecular aldol reaction was introduced by Northrup and MacMillan,[201] who demonstrated that α-unbranched aldehydes can be used as donors in the reaction with aldehyde acceptors. Proline catalyzed the cross-aldolizations of two different aldehydes under carefully developed conditions using syringe pump techniques to furnish *anti*-aldols **144** in excellent enantioselectivities and good yields and diastereoselectivities (Scheme 82). Although the aldolizations were performed with only 10 mol % proline in DMF, the reaction can be readily accomplished in a wide array of solvents with varying polarity, from benzene to DMSO. The products of this cross-aldolization, the β-hydroxy aldehydes, are important building blocks of polypropionate and polyacetate natural products.

Scheme 82. First Direct Asymmetric Cross-aldol Reactions of Aldehydes



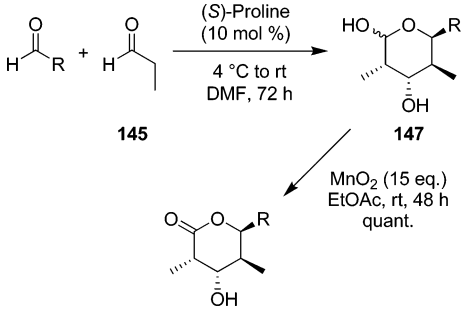
Scheme 83. Proline-Catalyzed Direct Asymmetric Cross-aldolization of Aldehydes in a Synthesis of Prelactone B



The discovery of the direct enantioselective cross-aldolization of aldehydes, which until quite recently would have probably been regarded as impossible by many, can be viewed as a major breakthrough in the field of the aldol reaction. One product of this reaction has recently been used in an extremely efficient and short synthesis of prelactone B (**146**) by Pikho et al. (Scheme 83).[202]

Barbas et al. described proline-catalyzed assemblies of polyketides by direct aldol reactions involving three aldehyde components.[203] Slow addition of propionaldehyde **145** into the acceptor aldehyde and 10 mol % (*S*)-proline in DMF generates the lactols **147**, which were converted to the

Scheme 84. Proline-Catalyzed Assembly of Pyranoses by the Aldol−Aldol Reaction Cascade



R	% yield	α/β	% ee (**148**)
Et	53	1:2.2	33
i-Pr	32	1:2.0	12
i-Bu	24	1:2.5	11

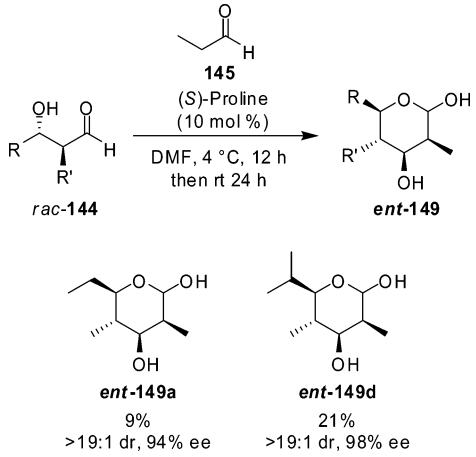
corresponding δ-lactones **148** (Scheme 84). The product pyranoses contain four stereogenic centers and are obtained with excellent diastereoselectivity but only with modest enantioselectivity.

This reaction was recently revisited by Córdova and coworkers.[204] Improved enantioselectivities were achieved using proline or 4-hydroxyproline as catalyst under modified reaction conditions. Isolation of the β-hydroxy aldehyde intermediate **144** from the first aldol step was proposed to be beneficial: this allows the application of two different catalysts for two aldol steps (Scheme 85). Irrespective of the aldehydes used, almost perfect enantioselectivities (99 to >99% ee) were obtained in all cases, although the overall yields are only in the range 15−42%.[204]

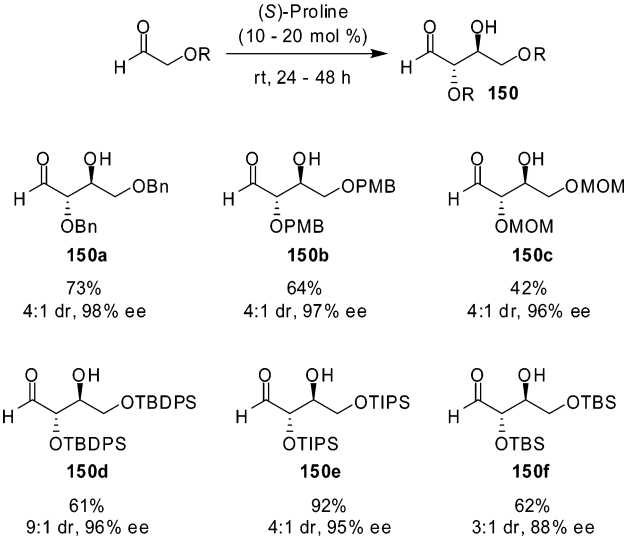
The same group demonstrated a proline-catalyzed dynamic kinetic asymmetric transformation (DYKAT) involving racemic β-hydroxy aldehydes **144** (Scheme 86).[205] Proline-mediated racemization of **144** via retro-aldol aldol addition followed by a subsequent proline-catalyzed stereoselective direct aldol addition generates the triketide- and deoxysugars ***ent*-149** in highly stereoselective fashion.

The MacMillan group extended the scope of the proline-catalyzed aldehyde cross-aldolization reaction to an important class of substrates and developed an enantioselective aldol union of α-oxyaldehydes (Scheme 87).[206] In this reactions, α-oxyaldehydes were used both as donor and acceptor. In the case of the homocoupling aldol reaction, the electronic nature of the oxyaldehyde substituent (R in Scheme 87) has

Scheme 86. Proline-Catalyzed DYKAT of Racemic β-Hydroxy Aldehydes to Polyketides

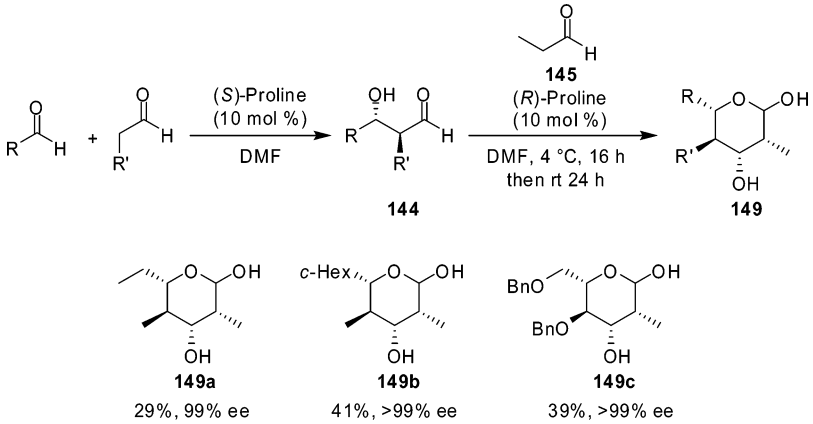


Scheme 87. Proline-Catalyzed Enantioselective Direct Homocoupling Aldol Reactions of α-Oxyaldehydes

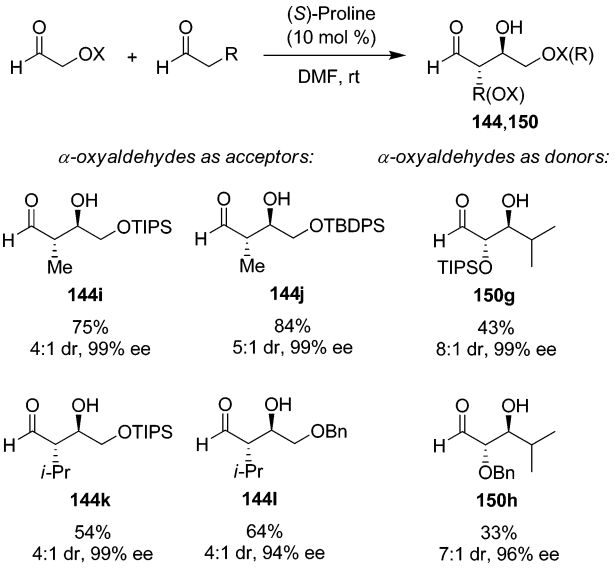


a prominent influence on the overall efficiency of the process. Electron-rich oxyalkyl groups are necessary for the reaction to proceed and also to have practical levels of enantio- and diastereocontrol. In most cases, 10 mol % proline is sufficient to catalyze the homocoupling of α-oxyaldehydes containing bulky α-silyl substituents as well as the commonly used protecting groups (Bn, PMB, or MOM). In all cases, products were obtained in useful yields and diastereoselectivities along

Scheme 85. Amino Acid-Catalyzed Asymmetric Two-Step Direct Polyketide Synthesis



Scheme 88. Proline-Catalyzed Enantioselective Direct Heterocoupling Cross-aldol Reactions of α-Oxyaldehydes



with good to excellent enantioselectivities. This reaction provides a straightforward access to stereochemically controlled polyol architectures.[207]

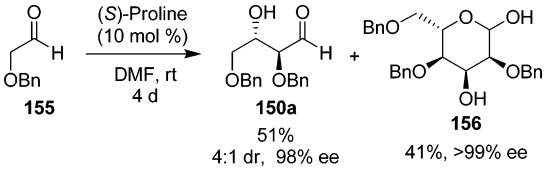
In the case of the enantioselective heterocoupling cross-aldol reaction, α-oxyaldehydes react with α-alkyl-substituted aldehydes in the presence of 10 mol % proline as catalyst. Although both aldehyde partners bear enolizable protons, the glycolaldehyde invariably acts as the acceptor component in the reaction with alkyl aldehydes that contain α-methylene protons (Scheme 88).[206] However, in the presence of aldehydes that do not readily participate in enamine formation (α-branched aldehydes), α-oxyaldehydes can act as aldol donors. In the later case, the yields are relatively lowered due to formation of significant quantities of the oxyaldehyde homodimers. Excellent enantioselectivities were obtained in both cases.

MacMillan et al. successfully transformed α-oxyaldehyde dimer **150e** (Scheme 87) to the polyol differentiated hexoses by a tandem Lewis acid-catalyzed Mukaiyama aldol addition−cyclization reaction with an α-oxy-enolsilane **151** (Scheme 89).[208] Selective access to each of differentially protected glucose (**152**), allose (**153**), and mannose (**154**) was realized in high yield and stereochemical purity by careful choice of Lewis acid and reaction solvent. The authors also applied this reaction sequence for the synthesis of ^{13}C-labeled hexoses as well as 2-amino- and 2-thio-substituted derivatives.[208]

The significance of this de novo carbohydrate synthesis[209] and other proline catalyzed reactions has been luminously demonstrated by Mangion and MacMillan for the total synthesis of brasoside and littoralisone.[210]

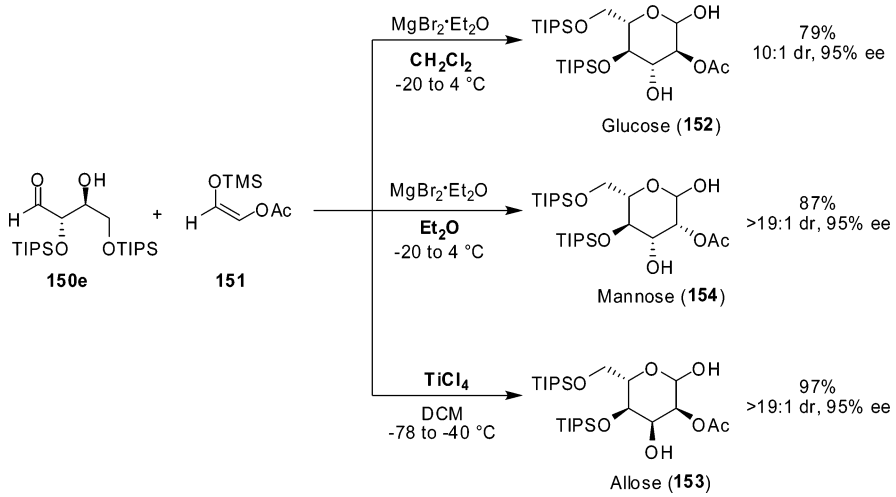
Recently, the Córdova group accomplished MacMillan's concept of two-step carbohydrate synthesis under complete proline catalysis in a single reaction sequence.[211,212] Proline catalyzed the asymmetric conversion of protected glycolaldehydes into hexoses in one step in almost perfect enantioselectivity. For example, 10 mol % (*S*)-proline in DMF at room temperature transformed α-benzyloxy acetaldehyde (**155**) to a mixture of tetrose (**150a**) and 2,4,6-tri-*O*-benzyl allose (**156**) (Scheme 90). Although tetrose (**150a**) is the major product in this reaction, protected allose **156** was obtained in an excellent ee of >99%. The authors observed a significant nonlinear effect for this reaction: only 40% ee of (*S*)-proline is sufficient to induce >99% ee in the product allose.[211] This is by far the largest permanent nonlinear effect observed for a proline-catalyzed reaction. Considerable asymmetric amplification of enantiomeric excess (vide supra) in the formation of allose was also demonstrated. Based on these two observations, the authors proposed a model for the evolution of homochirality.[211]

Scheme 90. Proline-Catalyzed Neogenesis of Allose from α-Benzyloxy Acetaldehyde

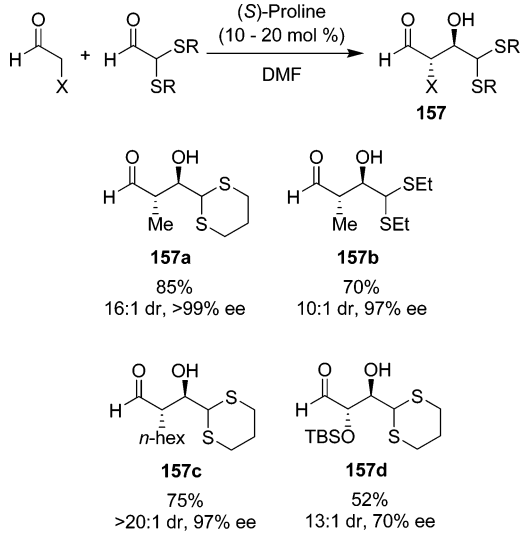


MacMillan and co-workers also showed the potential of α-thioacetal aldehydes as versatile acceptor units in proline-catalyzed aldolizations with a variety of aldehyde and ketone donors (Scheme 91).[213] Different α-branched aldehydes and ketones and also acetone were used as donor unit to generate *β*-hydroxy and α,*β*-dihydroxy aldehydes **157** and ketones in highly diastereoselective (up to >20:1 dr) and enantioselective (up to >99% ee) fashion. Considering the synthetic

Scheme 89. One-Step Synthesis of Hexoses by Tandem Mukaiyama Aldol Addition−Cyclization



Scheme 91. Proline-Catalyzed Cross-aldol Reactions of α-Thioacetal Aldehydes as Aldol Donors



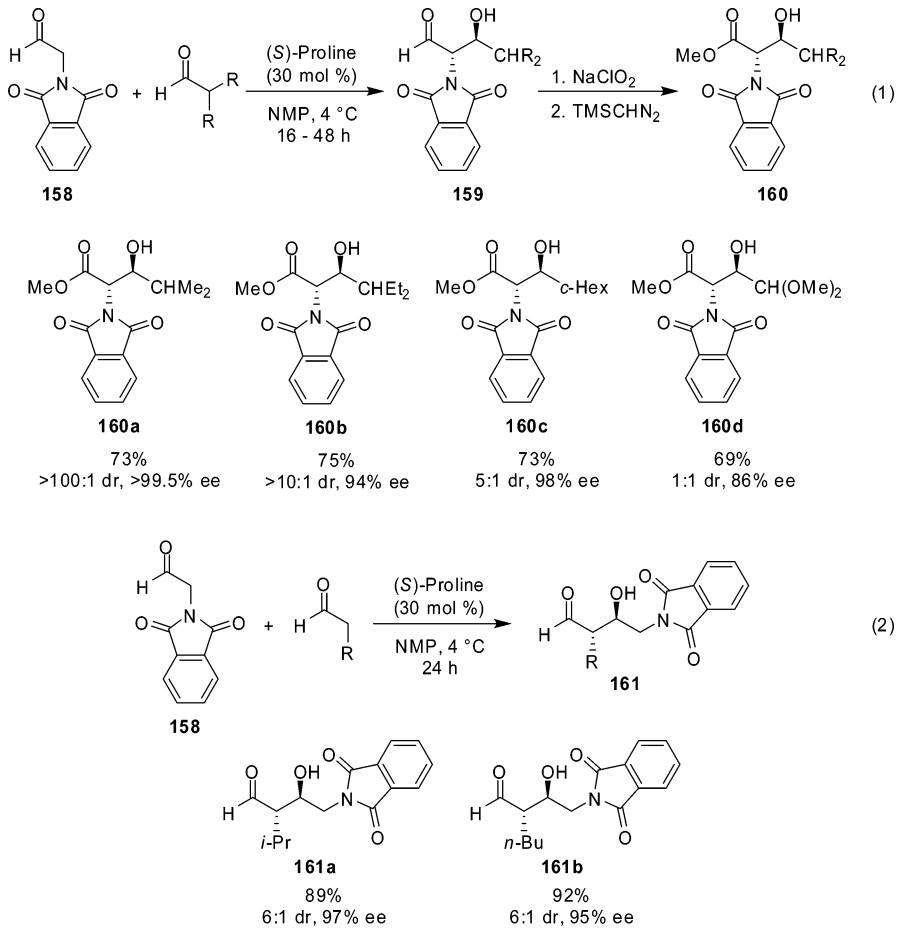
value of thioacetals as latent carbonyl and alkyl equivalents,[214] the products are of potential as synthons for complex targets.

Tanaka, Barbas, and co-workers reported a proline-catayzed asymmetric direct aldol reaction of protected glycine aldehyde **158** (Scheme 92).[215] They showed that the aldehyde **158** can act as both an acceptor and a donor depending on the nature of the second aldehyde present. In combination with α-branched aldehydes, aldehyde **158** acts as donor (eq 1), whereas when α-unbranched aldehydes are used it acts as acceptor (eq 2). The use of the phthalimide protecting group is important for achieving regioselectivity in this reaction. In the first case (eq 1), the product β-hydroxy-α-amino aldehydes **159** were converted to the corresponding esters **160**, which were obtained in good yields and with excellent diastereo- and enantioselectivities in most cases. In the second case (eq 2), the product β-hydroxy-γ-amino aldehydes **161** were obtained in similar yields and selectivities.

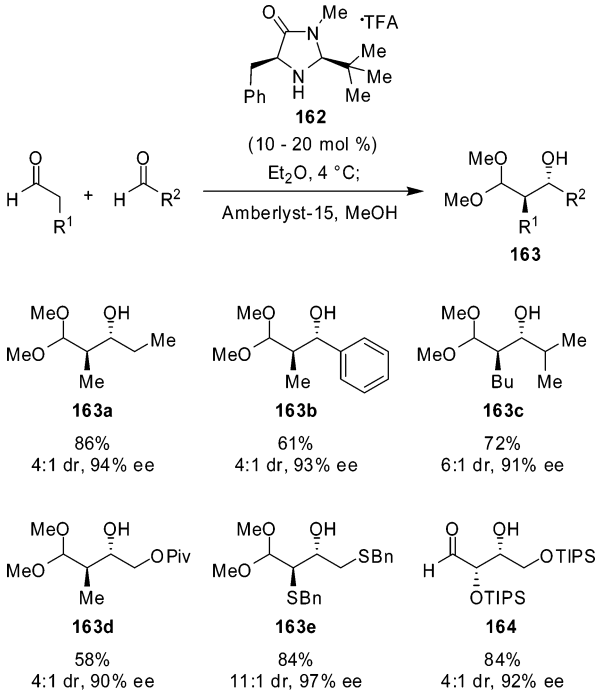
Catalysts other than proline have also been successfully applied for the asymmetric direct aldehyde cross-aldol reactions. The MacMillan group reported the first asymmetric aldol reaction in the presence of an imidazolidinone catalyst.[216] Aldol self-couplings as well as cross-aldol reactions between two different aldehydes were found to proceed efficiently in the presence of 10 mol % (2*S*,5*S*)-5-benzyl-2-*tert*-butylimidazolidinone-TFA salt (**162**) (Scheme 93). β-Hydroxy dimethoxyacetals **163** were obtained after methanolysis of the initially formed aldol hemiacetals. Good yields and excellent enantioselectivities (up to 97% ee) were obtained in all cases along with decent diastereoselectivities. α-Pivaloyloxy-substituted acetaldehyde, an otherwise inert substrate for the proline-catalyzed aldol reaction,[206] was found to undergo smooth aldolization with propinaldehyde to afford the aldol adduct **163d** in moderate yield (58%) and good enantioselectivity (90% ee). Surprisingly, α-silyloxy aldehydes provide the *syn*-aldol adduct in 4:1 dr and 92% ee (see Scheme 93).

Hayashi and co-workers recently developed a combined proline−surfactant organocatalyst **165** for the highly stereoselective direct cross-aldol reactions of two different alde-

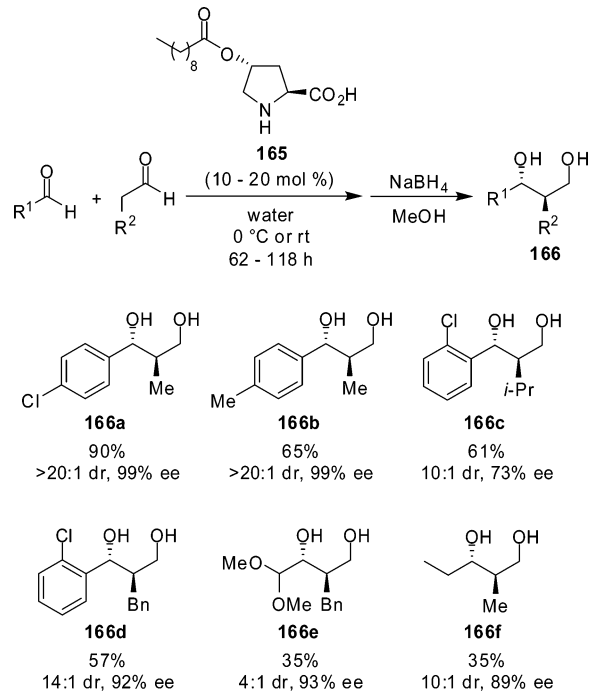
Scheme 92. Proline-Catayzed Asymmetric Direct Aldol Reactions of Protected Glycine Aldehyde



Scheme 93. Imidazolidinone-Catalyzed Direct Aldol Reactions of Aldehydes

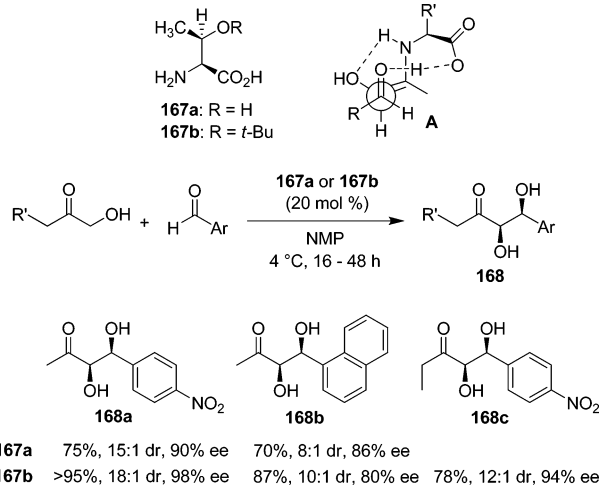


Scheme 94. Proline−Surfactant Organocatalyst 165 for Asymmetric Direct Cross-aldolizations of Aldehydes



hydes in aqueous media (Scheme 94).[217] The catalyst was identified by a systemic optimization process. The chain length has a dramatic influence on the yield, although the selectivities remain the same. Both aromatic and aliphatic aldehydes were equally efficient as the acceptor when propanal, isovaleraldehyde, and 3-phenylpropanal served as the donor unit. Excellent diastereo- and enantioselectivities were achieved using typically 10 mol % catalyst in water at 0 °C. According to the authors' proposal, "emulsions seem to offer an ideal reaction environment in the presence of water, in which organic molecules can be assembled through hydrophobic interactions thus enabling the aldol reaction to proceed efficiently".[217]

Scheme 95. Primary Amino Acid-Catalyzed *syn*-Aldol Reactions of α-Hydroxyketones and Aromatic Aldehydes



2.3.3. Direct Catalytic Asymmetric syn-Aldol Reactions

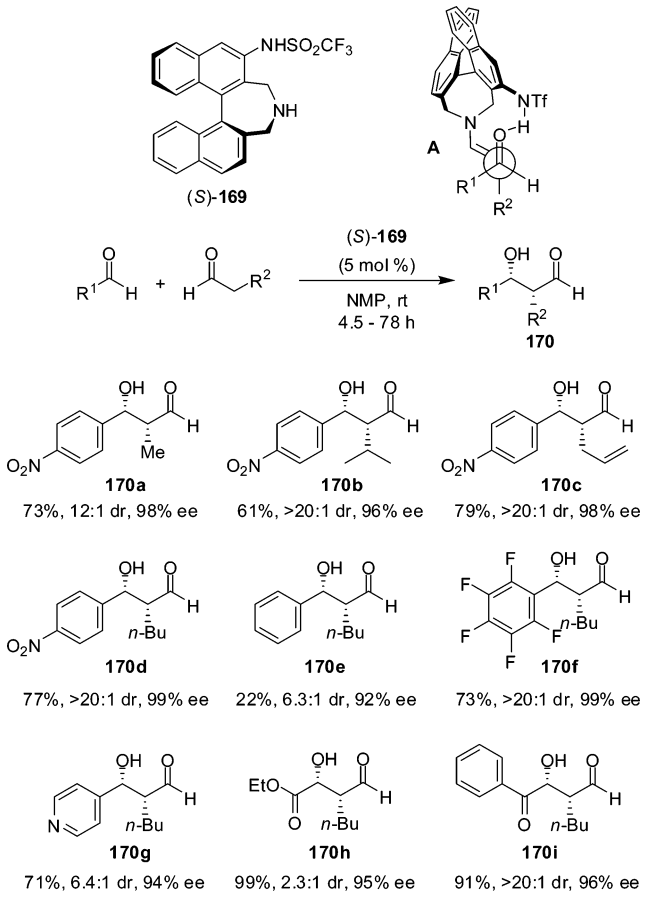
Most of the aldol reactions described above produce the *anti*-aldol as the major diastereomer irrespective of the nature of the donor component. There has been no report of a highly enantioselective and exclusively *syn*-selective direct aldol reaction so far. Only a few exceptions giving *syn*-aldol adducts, mostly depending on the substrate type, have been described.[117,152,154,216]

Very recently, Barbas et al. reported a *syn*-selective aldol reaction between α-hydroxyketones and aromatic aldehydes catalyzed by the primary amine containing acyclic amino acid (*S*)-threonine **167a** and its derivative O^{t}Bu-(*S*)-threonine (**167b**) (Scheme 95).[218] When the reactions were performed in NMP with 20 mol % catalyst at 4 °C, *syn*-diols were obtained in good yields, high *syn*/*anti* ratios (up to 18:1), and high enantioselectivities (up to 98% ee). 1-Hydroxy-2-butanone was used as the donor component in the aldol reaction with good results. According to the authors' rationalization, the observed *syn*-selectivity stems from the reaction of a (*Z*)-enamine in the C−C bond forming transition state **A** (Scheme 95). The (*Z*)-enamine intermediate predominates due to hydrogen bonding of the hydroxyl oxygen with the amine hydrogen.

Although the Barbas et al. report on the *syn*-aldol reaction provides excellent diastereo- and enantioselectivities, the substrate scope of this process is limited to α-hydroxyketones as donors and only aromatic aldehydes as acceptors. The development of an asymmetric direct *syn*-selective aldol reaction of general substrate scope, especially for the aldehyde cross-aldol reaction, has been a considerable challenge since the discovery of proline-catalyzed intermolecular direct aldol reactions.[10]

Maruoka and co-workers developed a highly *syn*-selective and enantioselective direct cross-aldol reaction between two different aldehydes catalyzed by the axially chiral amino sulfonamide (*S*)-**169** (Scheme 96).[219] Using only 5 mol % (*S*)-**169**, aldol adducts were obtained in good yields in most cases, along with up to >20:1 diastereoselectivity and excellent enantioselectivities (92 to 99% ee) in all cases. With respect to the *syn*/*anti* selectivity, this process complements the proline-catalyzed cross-aldol reaction between two different aldehydes. The drawback of multistep catalyst synthesis is compensated not only by low catalyst loading but

Scheme 96. *syn*-Selective Direct Aldol Reactions between Various Aldehydes Catalyzed by (*S*)-169



also by 95% catalyst recovery by column chromatography. The authors explained the observed *syn*-selectivity with the help of transition state **A** (Scheme 96), where the hydrogen bonding activation of the acceptor aldehyde by the acidic proton of triflamide triggers the reaction to proceed via the *syn*-enamine intermediate.[219]

Even though Maruoka's *syn*-aldol reaction significantly improves the substrate generality, a truly general *syn*-selective variant still remains to be discovered. Nevertheless, these two processes can be viewed as a first step in this direction.

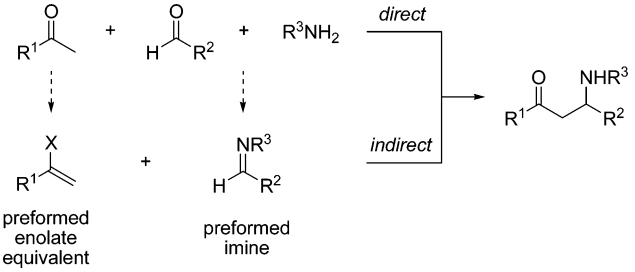
After the discovery of the proline-catalyzed intermolecular aldol reaction by List et al. in 2000,[10] enamine catalytic chemistry has witnessed enormous development in terms of both new catalyst design and new aldol reactions. Some of the challenges of aldol reactions (e.g., aldehyde cross-aldol reaction) have been solved by the design of new catalysts or reaction engineering. However, despite such massive research in this area, a number of aldol reactions still remain considerably challenging to the aldol researchers. A few of these include the use of acetaldehyde as an aldol partner or the development of efficient transannular aldol reactions. With the power of enamine catalysis and the ever increasing discoveries of new amine catalysts, it does not seem to be overenthusiastic to believe that solutions to these problems are just around the corner.

3. Asymmetric Mannich Reactions

3.1. Introduction

The Mannich reaction is a highly useful transformation for the construction of nitrogenous molecules.[220−225] In this transformation, three components, namely two carbonyl compounds and an amine, react to form a β-amino-carbonyl compound. The increasing popularity of the Mannich reaction has been fueled by the ubiquitous nature of nitrogen in drugs and natural products as well as by the potential of this multicomponent reaction to generate diversity. Both *direct* variants with unmodified ketone donors and *indirect* variants utilizing preformed enolate equivalents have been described. In addition, the imine intermediate may be preformed or its amine and aldehyde precursors may be used directly (Scheme 97). Enantioselective variants are especially attractive. For

Scheme 97. Direct and Indirect Mannich Reactions



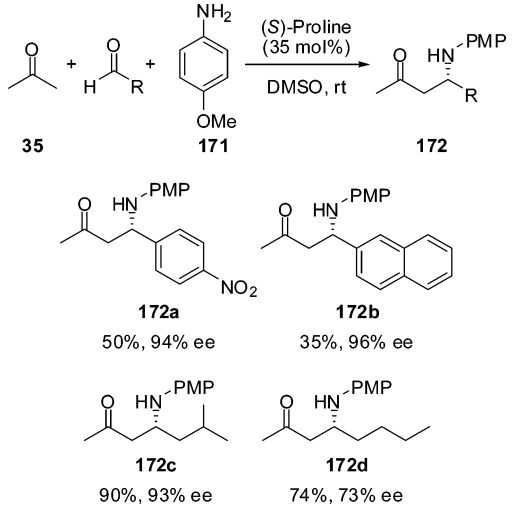
example, Kobayashi and co-workers reported the first catalytic enantioselective Mannich-type reactions of imines with silyl ketene acetals as preformed enolates using a chiral zirconium catalyst.[226] Trost and co-workers recently reported zinc-catalyzed asymmetric Mannich reactions to furnish 1,2-amino alcohols.[227] In the latter case, aromatic hydroxy ketones react with α-imino esters or imines derived from aromatic aldehydes in the presence of a catalytic amount of the dinuclear zinc catalyst. Sodeoka and co-workers reported the first late transition metal-catalyzed Mannich-type reactions of silyl enol ethers with α-imino esters.[228] The reaction involves slow addition of the silyl enol ether to a solution of α-imino ester in the presence of 5 mol % catalyst. β-Amino esters were obtained in excellent yields with varying levels of diastereoselectivity and enantioselectivity. A direct Mannich reaction of unmodified ketones using a lanthanum catalyst was discovered in 1999 by Shibasaki and co-workers.[229]

3.2. Direct Asymmetric Mannich Reactions of Ketones

In 2000, List discovered the first efficient proline-catalyzed asymmetric three-component Mannich reactions of different ketones with *p*-anisidine (**171**) and aldehydes in DMSO.[1,2,111,230] In the presence of 35 mol % (*S*)-proline, aromatic and α-substituted and α-unsubstituted aliphatic aldehydes were reacted with acetone (**35**) to give the corresponding β-amino ketones **172** in good to excellent yields with enantioselectivities as high as 99% ee (Scheme 98). The author found that the aldol addition and condensation products were observed as side products during the Mannich reaction.

High pressure (200 Mpa), realized by freezing water (−20 °C) in a sealed autoclave, has been successfully applied to the direct asymmetric three-component Mannich reactions of various aldehydes, *p*-anisidine (**171**), and acetone (**35**).[184] Hayashi and co-workers showed that, under high pressure, Mannich adducts were obtained in better yields and higher enantioselectivities than under normal pressure. For example, electron-rich aldehydes such as *p*-anisaldehyde, 3,4-dimethoxybenzaldehydes, and *N*-acetyl-(4-formyl)aniline are poor substrates under normal atmosphere even with 0.1 MPa at room temperature, while high yields and excellent enantioselectivities have been achieved under water-freezing high-pressure conditions (200 MPa) (Scheme 99).

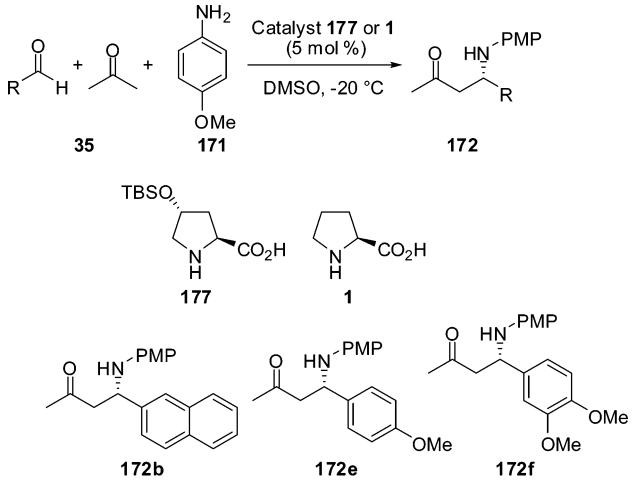
Scheme 98. Proline-Catalyzed Asymmetric Three-Component Mannich Reactions



The authors also showed that the (*S*)-proline-catalyzed Mannich reaction between acetone (**35**), 3,4-dimethoxybenzaldehyde (**175**), and 4-*tert*-butyldimethylsiloxyaniline (**176**) followed by reduction with $LiAlH_4$ and cleavage of the *N*-aryl moiety with $PhI(OCOCF_3)_2$ gave *syn*- and *anti*-1,3-amino alcohols in excellent enantioselectivities (Scheme 100).[184] This procedure provides an alternative method for the protecting group cleavage, which is normally PMP removed with cerium(IV) ammonium nitrate (CAN).

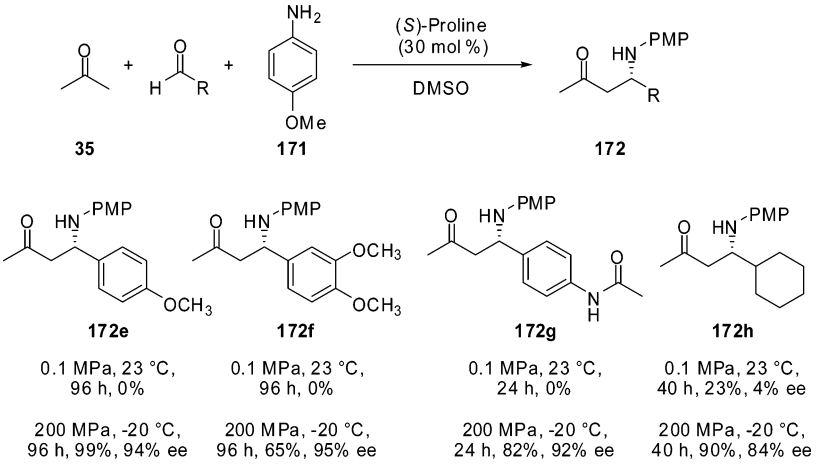
Hayashi et al. used *trans*-4-siloxyproline (**177**)[231] as an efficient and enantioselective organocatalyst for the direct

Scheme 101. Comparison between *trans*-4-Siloxyproline 177 and Proline 1 in Mannich Reactions

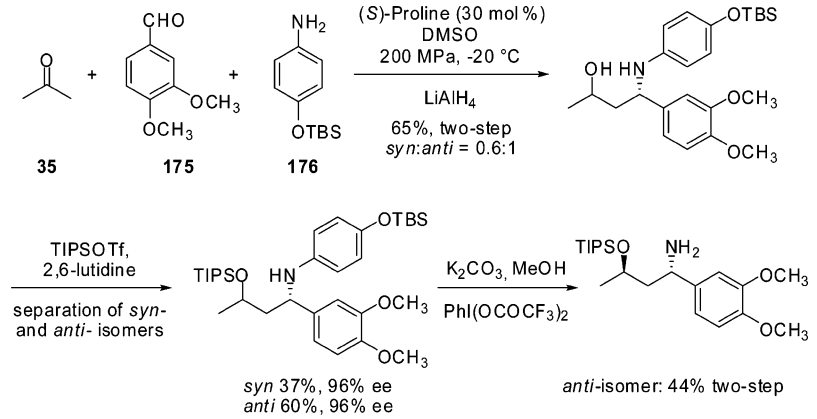


asymmetric Mannich reaction.[232] Due to the higher activity of 4-siloxyproline (**177**) compared to proline, the catalyst loading could be reduced to 5 mol % without reducing the enantioselectivity (up to 98% ee). Generally, proline is inefficient for the direct catalytic asymmetric three-component Mannich reaction using electron-rich aldehydes: For example, *p*-anisaldehyde and 3,4-dimethoxybenzaldehyde are poor substrates (Scheme 101).[184] The corresponding siloxyproline **177** is quite effective with these substrates, and

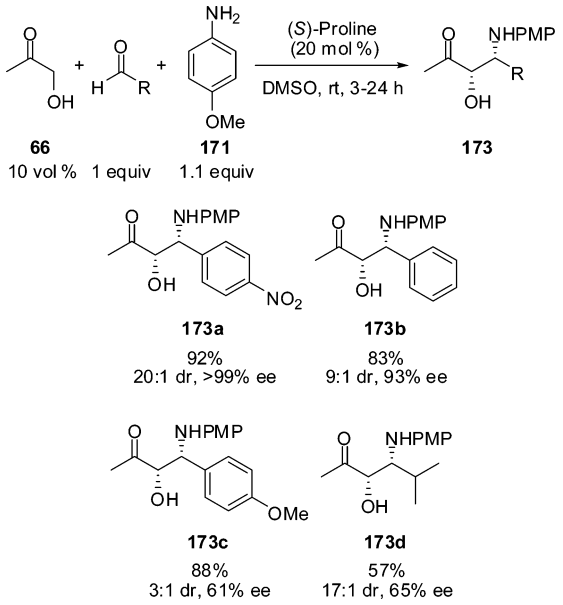
Scheme 99. Mannich Reaction of Various Aldehydes, *p*-Anisidine, and Acetone Catalyzed by (*S*)-Proline under Ambient and High Pressure: A Comparison



Scheme 100. Synthesis of *syn*- and *anti*-1,3-Amino Alcohols via Mannich Reaction



Scheme 102. Catalytic Enantioselective Synthesis of *syn*-1,2-Amino Alcohols



resulting products were obtained in moderate yield (48−55%) and high enantioselectivity (90−98% ee).

Using hydroxyacetone (**66**) as the ketone component, the reaction provides the corresponding *syn*-1,2-amino alcohols **173** in high yields and excellent levels of diastereo- and enantioselectivities.[233] Aliphatic branched aldehydes were tolerated but gave lower yields and selectivities (Scheme 102).[1,2,62,63,234]

These Mannich reactions constitute a regiospecific alternative to the Sharpless asymmetric aminohydroxylation reaction (AA) of enones.[235]

In order to explain the observed stereoselectivity, it was proposed that the reaction follows an enamine mechanism and involves a transition state similar to the earlier proposed transition state of the corresponding aldol reaction (Figure 1). (*E*)-Configurations are assumed for both the enamine and the imine. The two components react, to avoid unfavorable steric interaction between the *N*-substituent of the imine and the proline ring and to allow for a stabilizing hydrogen bond between the carboxylate and the protonated imine. Approach of the *si*-face of the imine to the *si*-face of the enamine results if R^2 is highest priority and leads to the observed stereochemistry (Figure 1).

List and co-workers developed a new asymmetric synthesis of oxazolidin-2-ones, demonstrating the utility of Mannich product **173** (Scheme 103).[237] The sequence is based on the chemistry of previously unknown 5-acyloxy-oxazolidin-2-ones **174**. Oxazolidinones **174** were obtained via the proline-catalyzed direct asymmetric three-component Mannich reaction, protecting group manipulations, and a subsequent Baeyer−Villiger oxidation.

These 5-acyloxy-oxazolidin-2-ones **174** can readily be transformed into many interesting optically active synthons such as oxazolidinones and amino alcohols (Scheme 104).

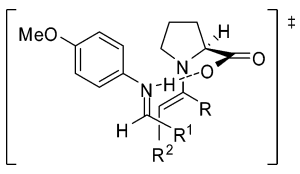
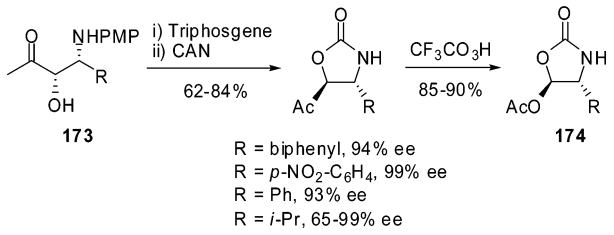
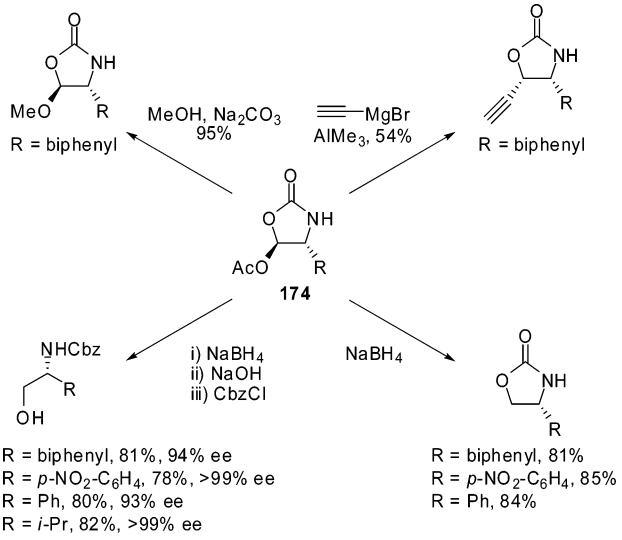


Figure 1. Mannich transition state.[111,234,236]

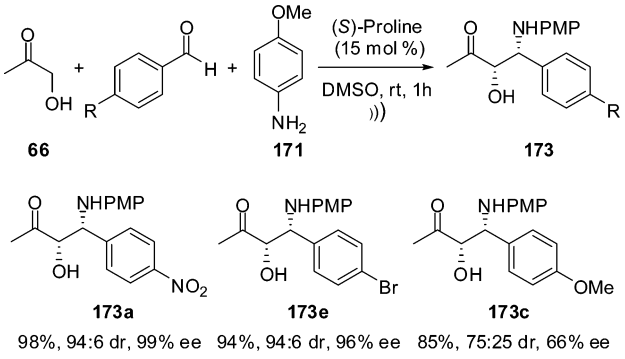
Scheme 103. Synthesis of 5-Acyloxy-oxazolidin-2-ones



Scheme 104. Transformation of 5-Acyloxy-oxazolidin-2-ones



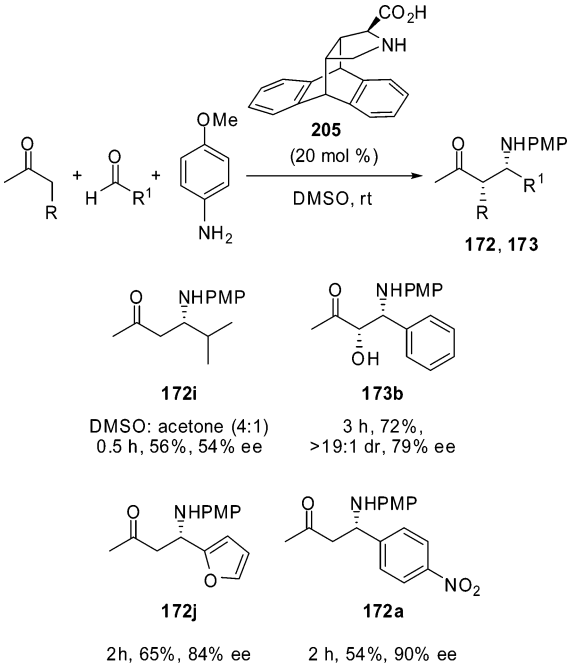
Scheme 105. Three-Component Asymmetric Mannich Reaction of Aromatic Aldehydes and *p*-Anisidine with Hydroxyacetone Catalyzed by (*S*)-Proline under Ultrasonic Conditions



Kantam and Choudary described the effect of ultrasound on proline-catalyzed three-component asymmetric Mannich reactions.[238] The asymmetric Mannich reaction of various aromatic aldehydes and *p*-anisidine (**171**) with hydroxyacetone (**66**) was carried out in the presence of 15 mol % proline under ultrasonic conditions (40 Hz) for 1 h (Scheme 105). The authors emphasized that ultrasonic conditions not only promoted the asymmetric reaction but also promoted imine formation between the aromatic aldehydes and *p*-anisidine.

Kotsuki and co-workers have developed an anthracene-fused chiral proline catalyst **205** that has been shown to accelerate the asymmetric three-component Mannich reaction of aldehydes, methyl ketones, and *p*-anisidine (**171**).[239] The catalyst was synthesized in racemic form from the Diels−Alder reaction of anthracene and maleic anhydride via lithiation/carbonylation followed by resolution with (−)-

Scheme 106. Asymmetric Three-Component Mannich Reaction between Ketones, *p*-Anisidine, and Aldehydes Using Catalyst 205



menthol.[240] With 5−20 mol % organocatalyst **205**, *N*-PMP-protected β-amino ketones **172** and **173** were formed in good yields (54−76%) with good enantioselectivities ranging from 54% to 90% ee (Scheme 106).

Using the Ti-catalyzed Sharpless asymmetric epoxidation of allylic alcohol as the key step, Sudalai and co-workers synthesized (−)-cytoxazone,[453] a cytokine modulator in 83% ee and 23% overall yield via nine steps from commercially available 4-iodophenol. The proline-catalyzed Mannich reaction has also been applied in the enantioselective synthesis of (+)-*epi*-cytoxazone (**188**)[454] by the same authors. The reaction provided (+)-*epi*-cytoxazone (**188**) with 35% overall yield and 81% ee in six-steps starting from readily available *p*-anisaldehyde (**189**) (Scheme 107).[241]

Itoh et al. described an asymmetric synthesis of *ent*-sedridine (**199**) applying the proline-catalyzed Mannich reaction of 4-hydroxybutanal (**200**), *p*-anisidine (**171**), and acetone (**35**) in the key step (Scheme 108).[242] The resulting compound **201** was reduced using $LiAlH_4$ to give diol **202** as a mixture of diastereomers. Upon treatment with DEAD and PPh_3, the amino alcohol ring-closed to give a mixture of cyclized products **203** in 88% total yield (major/minor = 1.2:1), which underwent an oxidative cleavage reaction of the PMP group followed by reprotection with a Cbz group. Piperidine **204** was subjected to $Pd(OH)_2$-catalyzed hydrogenation to provide *ent*-sedridine (**199**) in 34% overall yield from *p*-anisidine **171** in six steps (Scheme 108).

Córdova and co-workers have used chiral acyclic primary amino acids to catalyze the direct asymmetric three-component Mannich reaction between unmodified acyclic and cyclic ketones, *p*-anisidine, and aldehydes with high chemo-, diastereo- and enantioselectivities (up to >99% ee).[243] Interestingly, in contrast to that of *p*-anisidine, the primary amino group of the catalyst is not incorporated into the product. Encouraged by this observation, the authors screened several acyclic amino acids, such as serine (**184**), valine (**77**), isoleucine (**185**), and leucine (**186**), as catalyst. (*S*)-Alanine (**88**) and alanine-based tetrazole **187** were found to be the most active amino acid catalysts (Scheme 109). Addition of water (5 equiv) to the reaction mixture slightly improved the yield; however, the ee decreased. The alanine-based tetrazole catalyst **187** exhibited the highest efficiency for the reaction.

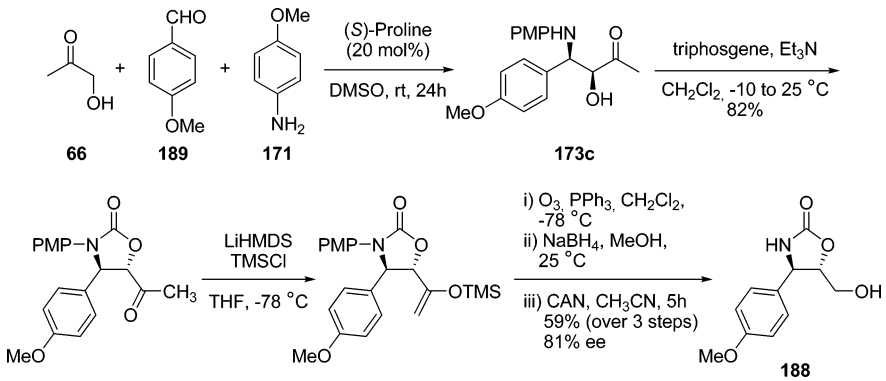
Córdova and co-workers reported the use of protected dihydroxyacetone **129**, *p*-anisidine, and an aldehyde in the direct amino acid-catalyzed enantioselective synthesis of protected carbohydrate derivative **180**.[178] For example, the (*R*)-proline-catalyzed three-component Mannich reaction between dioxanone **129**, *p*-anisidine (**171**), and D-isopropylidene-glyceraldehyde (**181**) proceeded to afford protected 4-amino-4-deoxy-D-fructose (**180**) in 55% yield with >19:1 dr and >98% ee (Scheme 110).

Enders and co-workers have also described the synthesis of selectively protected amino sugars **182** via an organocatalytic asymmetric three-component Mannich reaction of dioxanone **129** and *p*-anisidine (**171**) with different aldehydes.[244] Generally, the *syn*-configurated Mannich products **182** were obtained in good to high yields and with high diastereoselectivities (up to >99% de) and enantioselectivities (up to ≥98% ee) in the presence of 30 mol % proline (**1**) or 20 mol % TBS-protected hydroxyproline **177** in DMF at 2 °C (Scheme 111).

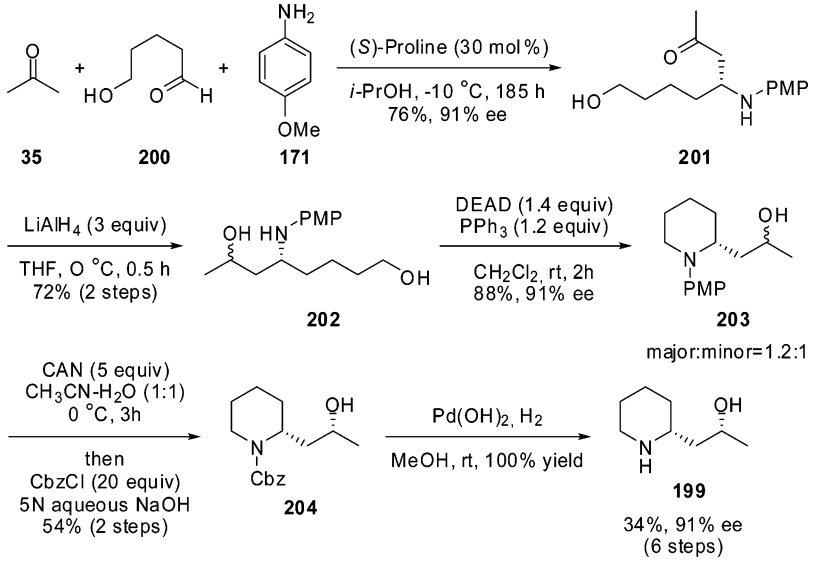
The presence of water (1−10 equiv) normally led to increased stereoselectivity, independent of solvent. Interestingly, TBS-protected hydroxyproline catalyst **177** led to an improvement of reaction rate due to its higher solubility. When TBS-protected hydroxyproline **177** is employed, the addition of water (3−5 equiv) improved the stereoselectivity.

To expand the synthetic utility of this direct Mannich reaction, a new synthetic approach to biologically active 2-amino-2-deoxy sugar derivatives **183** was developed (Scheme 112).

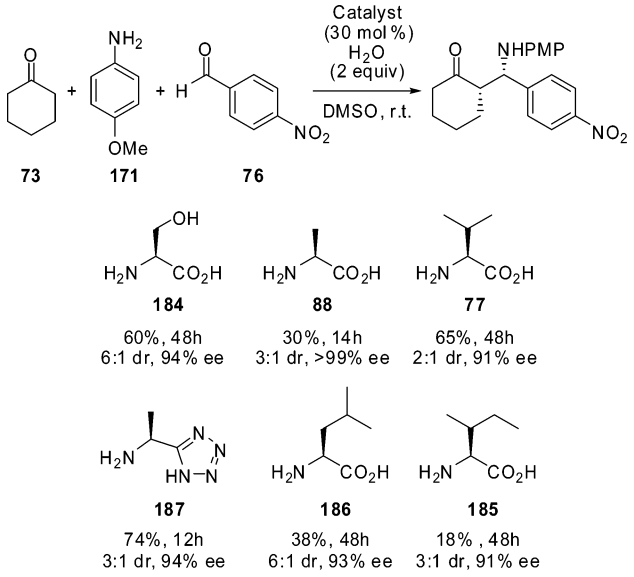
Scheme 107. Synthesis of (+)-*epi*-Cytoxazone 188



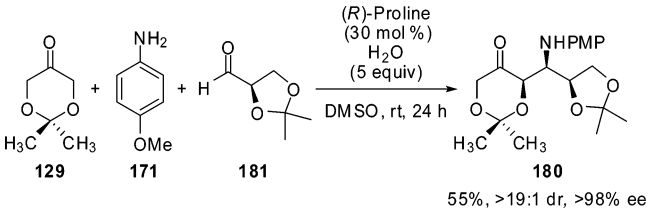
Scheme 108. Total Synthesis of *ent*-Sedridine 199



Scheme 109. Catalyst Screening for the Asymmetric Mannich Reaction



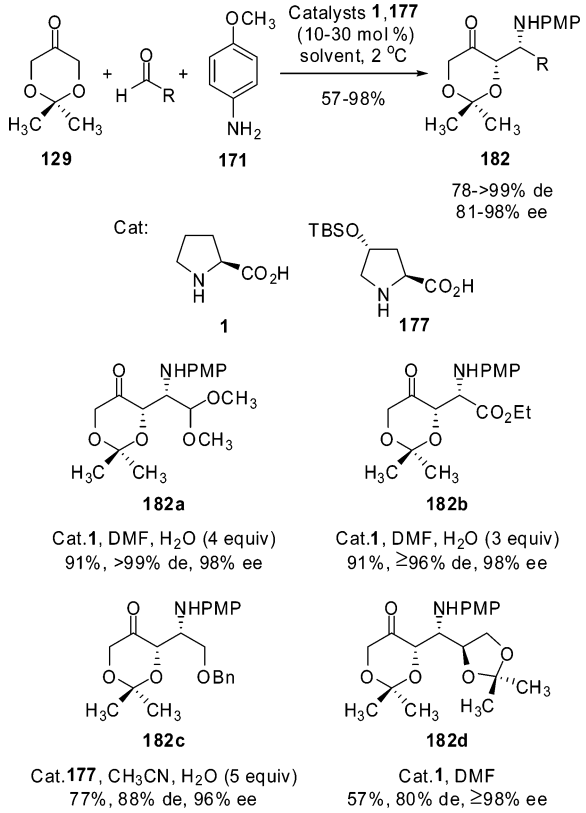
Scheme 110. Direct Proline-Catalyzed Asymmetric Synthesis of Protected 4-Amino-4-deoxy-D-fructose



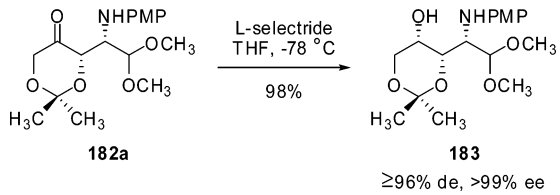
During the course of the development of a practical synthesis of polyoxamic acid,[245] which is a unique polyhydroxyamino acid constituting the side chain moiety of the antifungal polyoxin antibiotics, Córdova and co-workers reported a Mannich reaction between dioxanone (**129**), glyoxylate (**197**), and *p*-anisidine (**171**) as the key step (Scheme 113).[179]

The organocatalytic asymmetric three-component Mannich reaction has significantly expanded the synthetic scope and value of this transformation. Mannich reactions of protected amino ketones, different aldehydes, and *p*-anisidine in the presence of pyrrolidine-based tetrazole catalyst **102** have been realized. These reactions provide highly enantioselective (up to 99% ee) and regioselective, efficient methods for the

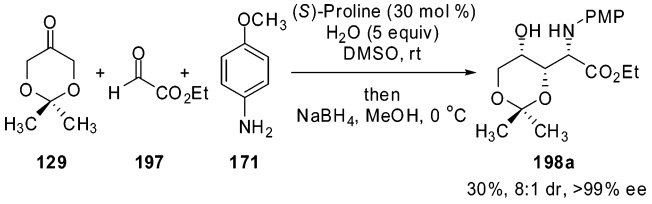
Scheme 111. Organocatalytic Asymmetric Three-Component Mannich Reaction of Dioxanone with Different Aldehydes and *p*-Anisidine



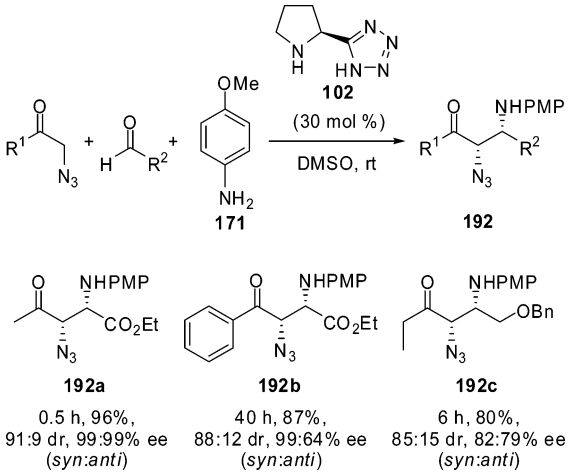
Scheme 112. Synthesis of the Biologically Active 2-Amino-2-deoxy Sugar Derivative



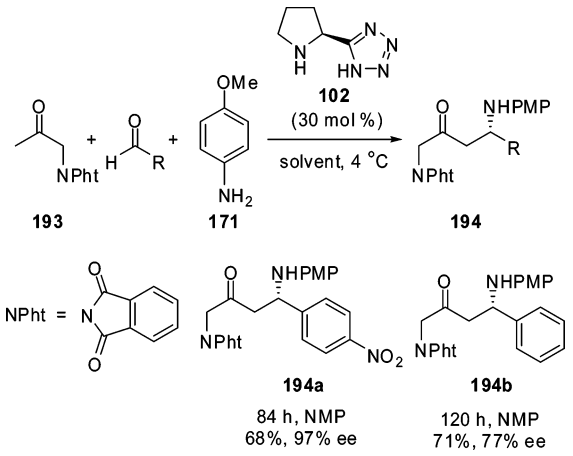
Scheme 113. Highly Chemo- and Enantioselective One-Step Synthesis of Protected Polyoxamic Acid



Scheme 114. Mannich Reactions for the Synthesis of Various 1,2-Azidoamines



Scheme 115. Mannich Reactions for the Synthesis of Protected 1,4-Diamines

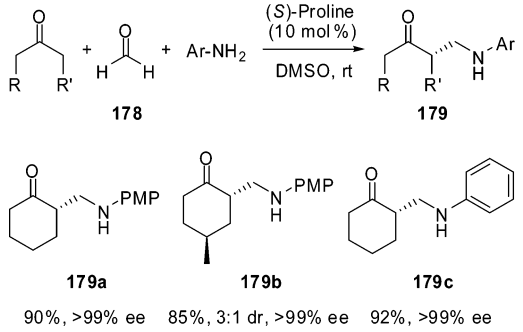


asymmetric synthesis of 1,2-diamines **192** from azido ketones (Scheme 114) and 1,4-diamines **194** from phthalimido ketones **193** (Scheme 115).[246] This represent the first example of highly stereoselective catalytic access to chiral 1,2- and 1,4-diamines using the Mannich reaction.

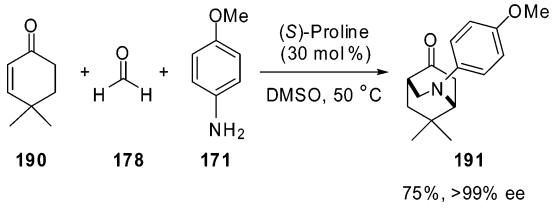
Recently, Córdova and co-workers reported a proline-catalyzed, one-pot, three-component asymmetric α-aminomethylation of ketones. Typically, the reactions were performed with unmodified ketones, aqueous formaldehyde (**178**) and aromatic amines in DMSO or DMF.[247] In most cases, the reaction furnished α-aminomethylated ketones **179** with >99% ee using 10 mol % catalyst (Scheme 116).

Córdova and co-workers extended the scope of enamine catalysis of proline, realizing an efficient method for the direct catalytic asymmetric α-aminomethylation between aqueous formaldehyde (**178**), *p*-anisidine (**171**), and α,β-unsaturated cyclic ketones **190**.[248,249] Inspired by this methodology, the authors reported a direct catalytic enantioselective aza-Diels−Alder reaction that yields the corresponding product **191** with excellent enantioselectivity (>99% ee) (Scheme 117).

Scheme 116. Direct Catalytic One-Pot Three-Component α-Aminomethylation of Ketones



Scheme 117. Proline-Catalyzed One-Pot Three-Component Asymmetric Aza-Diels−Alder Reaction



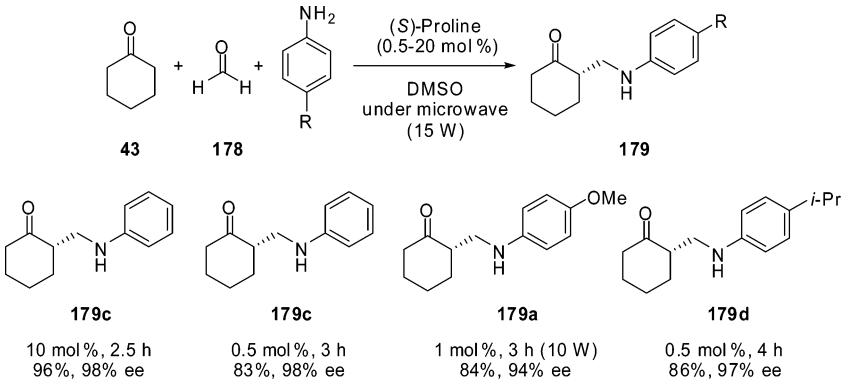
Bolm and Rodríguez investigated thermal effects in the (*S*)-proline-catalyzed enantioselective α-aminomethylation between ketone, aqueous formaldehyde, and aniline.[250] By applying microwave irradiation power heating with simultaneous air-cooling, reaction times and catalyst loadings could be reduced. For example, complete consumption of cyclohexanone (**43**), formaldehyde (**178**), and aniline occurred within 2.5 h in the presence of 10 mol % (*S*)-proline in DMSO under a microwave power of 15 W, giving the corresponding product **179c** in 96% yield with 98% ee. Interestingly, the authors found that, even with 0.5 mol % proline, product **179c** was obtained in 83% yield with the same ee after 3 h (Scheme 118).

Similar results were also achieved by heating in an oil bath for 23 h at the same temperature (45−50 °C) using 1 mol % proline. The corresponding reduced aminoalcohol **196** was obtained in 82% yield with 97% ee (Scheme 119).

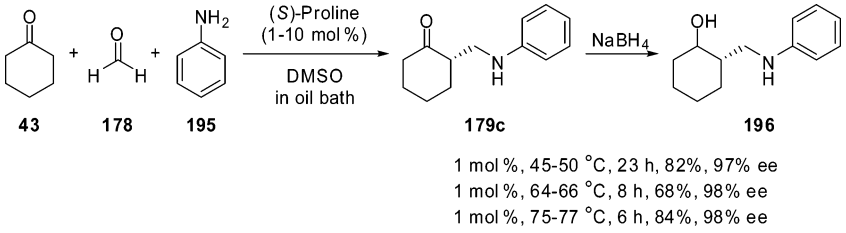
3.3. Direct Asymmetric Mannich Reactions of Aldehydes

Hayashi et al. reported proline-catalyzed asymmetric three-component, one-pot cross-Mannich reaction of different aldehydes with *p*-anisidine (**171**).[251] Initially, the reaction was carried out at room temperature and the desired amino alcohol **221** was formed (after reduction with $NaBH_4$) in less than 10% yield; significant improvements were obtained at 0 °C and −10 °C. To avoid the unwanted cross-aldol or self-Mannich adducts, the reaction was performed at −20 °C in *N*-methyl-2-pyrrolidinone (NMP) as solvent. Under these conditions, the desired products were obtained in excellent yield with high enantioselectivity and diastereoselectivity even if all three components are mixed together at −20 °C. This modified method is attractive in terms of generality, high selectivity, ease of operation, and practicality for the synthesis of *syn*-γ-amino alcohols **221** (Scheme 120).

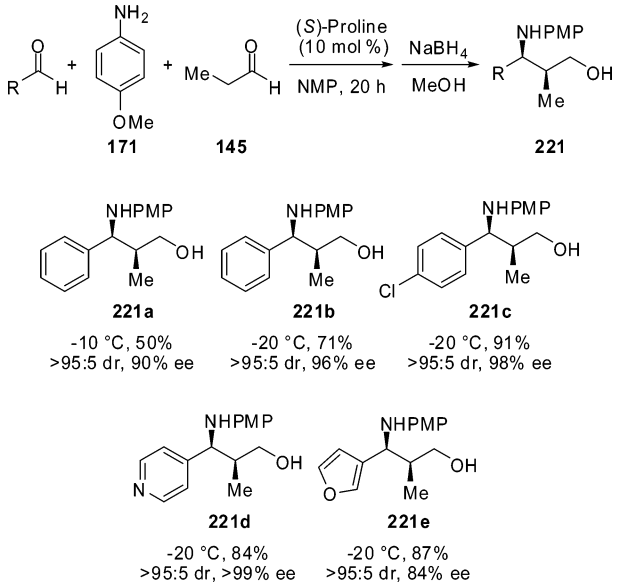
Scheme 118. Microwave-Assisted Direct Asymmetric Mannich Reaction Catalyzed by (*S*)-Proline



Scheme 119. (*S*)-Proline-Catalyzed Direct Asymmetric Mannich Reaction Using Conventional Heating



Scheme 120. Three-Component Mannich Reaction with Various Acceptor Aldehydes

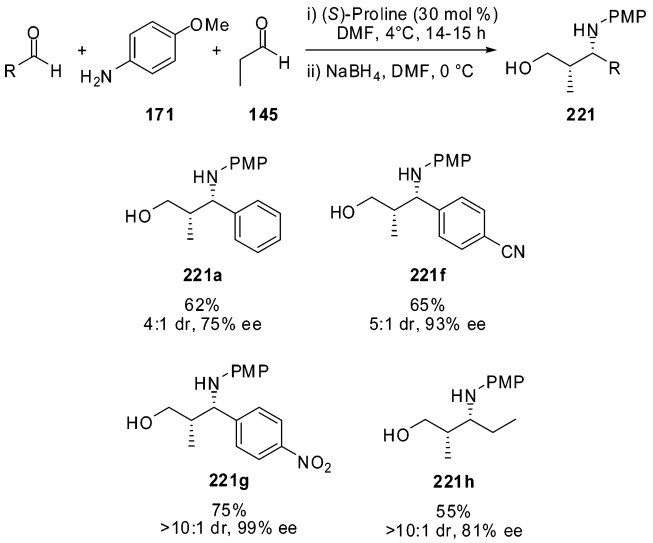


Barbas[252] and Córdova[253] also reported a similar three-component, one-pot Mannich reaction. To avoid the formation of cross-aldol or self-Mannich adducts, propionaldehyde **145** (1 M) in DMF was added slowly via syringe pump into the reaction mixture containing *p*-anisidine **171** (0.1 M), the aldehyde (0.1 M), and (*S*)-proline in DMF. This protocol provided *syn*-γ-amino alcohols **221** in good yield with up to >10:1 dr and 99% ee (Scheme 121).

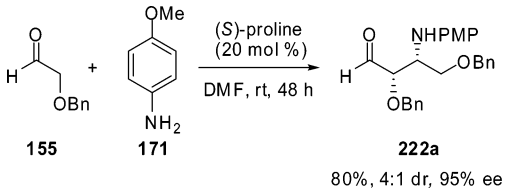
Córdova et al. reported the one-step asymmetric synthesis of protected amino-tetroses **222a** using the cross-Mannich reaction. The product was obtained in high yield with up to >99% ee and moderate dr (Scheme 122).[254]

Córdova and co-workers developed a stereoselective catalytic one-pot tandem reaction that involves a Mannich, Horner−Wadsworth−Emmons (HWE), and subsequent Sharpless dihydroxylation sequence to provide optically active amino- and iminosugar derivatives.[255] For example, in the

Scheme 121. One-Pot Direct Three-Component Asymmetric Proline-Catalyzed Mannich Reactions with Unmodified Aldehydes

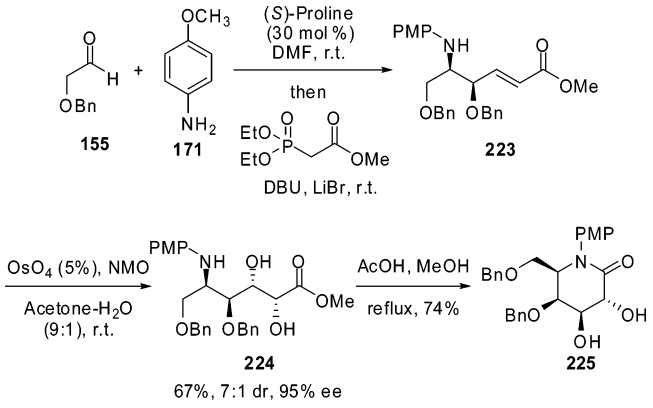


Scheme 122. One-Step Asymmetric Synthesis of Protected Amino-tetrose

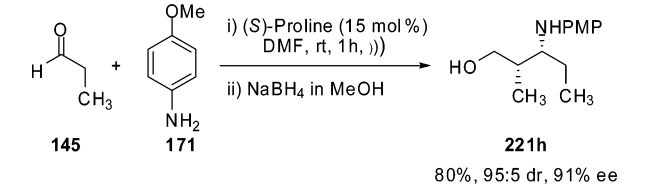


presence of (*S*)-proline (30 mol %), α-benzyloxyacetaldehyde (**155**) reacted with *p*-anisidine (**171**) to give the corresponding homo-Mannich product, which was treated with methyl diethylphosphono acetate (2.2 equiv), DBU (2.2 equiv), and LiBr (2.2 equiv) to provide protected vicinal amino alcohol **223** with two stereogenic centers in good yield (64%), enantioselectivity (95% ee), and diastereoselectivity (4:1 dr). Subsequent Sharpless dihydroxylation to galactonic ester **224**

Scheme 123. Synthesis of Galactolactam 225



Scheme 124. Self-Mannich Reaction of Aldehyde with *p*-Anisidine under Ultrasonic Conditions



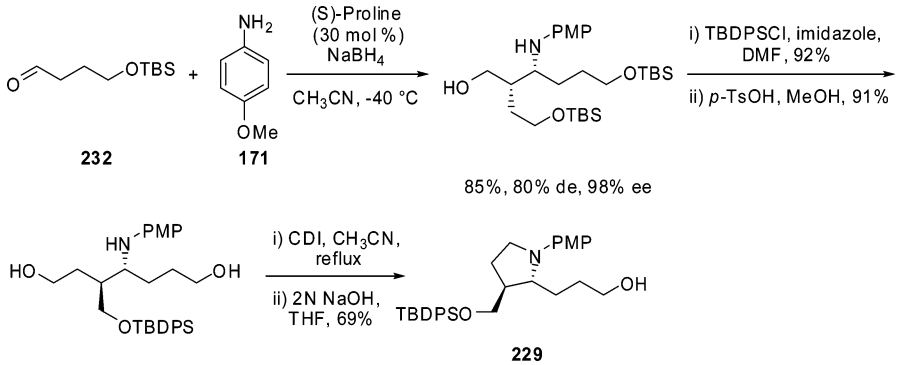
followed by acid-catalyzed cyclization provided the galactolactam **225** in good yield (74%) with 95% ee (Scheme 123).

Kantam and Choudary demonstrated the self-Mannich reaction of propionaldehyde (**145**) with *p*-anisidine (**171**) at room temperature under ultrasonic conditions to give the corresponding *syn*-γ-amino alcohol **221h** after $NaBH_4$ reduction in 80% yield with 91% ee (Scheme 124).[238]

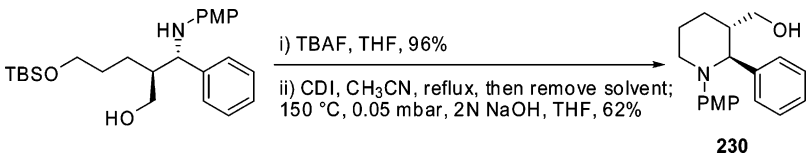
For the synthesis of nitrogen-containing heterocycles such as pyrrolidines **229** (Scheme 125), piperidines **230** (Scheme 126), and azetidines **231** (Scheme 127), which are of considerable significance in antibiotics and related biologically active targets, a catalytic enantioselective direct Mannich reaction of functionalized aldehydes **232** with *p*-anisidine (**171**) served as a key step; this is followed by a novel dehydrative cyclization mediated by the Staab reagent (1,1′-carbonyldiimidazole, CDI).[256]

Córdova and co-workers reported that, if subjected to Mannich conditions, aqueous formaldehyde (**178**), isovaleraldehyde (**226**), and *p*-anisidine (**171**) gave only the self-Mannich product of isovaleraldehyde (**227a**). Mannich adduct **227a** was obtained in 75−95% yield with high stereoselectivities (up to >10:1 dr and 99% ee). Only trace amounts of the desired cross-Mannich products **228** were detected (Scheme 128).[249]

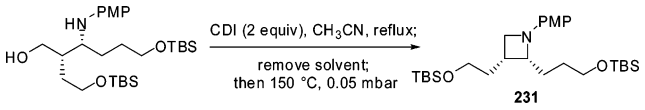
Scheme 125. Synthesis of Pyrrolidine Derivative



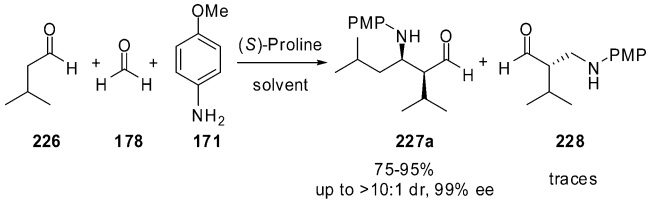
Scheme 126. Synthesis of Piperidine Derivative



Scheme 127. Synthesis of Azetidine Derivative



Scheme 128. Chemoselectivity in the Proline-Catalyzed Asymmetric α-Aminomethylation of Aldehydes



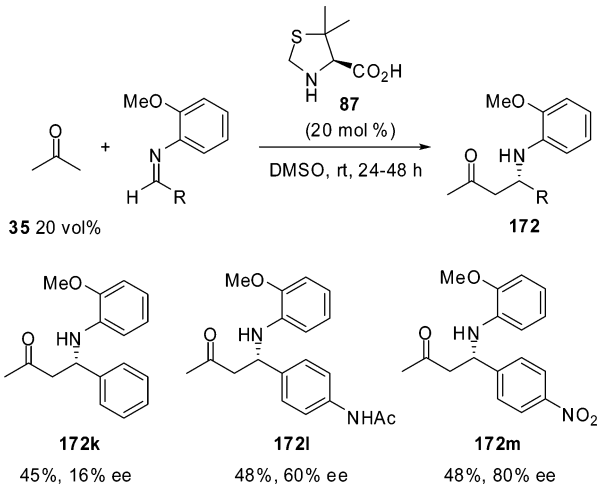
3.4. Indirect Asymmetric Mannich Reactions of Preformed Aldimines with Ketones

Barbas and co-workers reported (*S*)-5,5-dimethylthiazolidine-4-carboxylic acid (DMTC, **87**)-catalyzed asymmetric Mannich reactions of acetone with a variety of preformed or in situ-generated aldimines derived from *o*-anisidine (Scheme 129).[88,257] This catalyst was first used by List.[111]

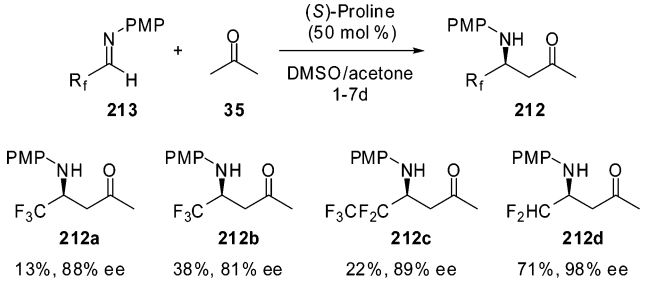
Funabiki et al. reported a highly enantioselective synthesis of β-amino-β-polyfluoroalkyl ketones **212**, via Mannich reaction of polyfluoroalkylated aldimines **213** with acetone (**35**) using (*S*)-proline with up to 98% ee (Scheme 130).[258] The reaction showed limited scope and modest chemical yields.

Barbas and co-workers used *N*-PMP-protected α-imido ethyl glyoxylate **206** as a Mannich acceptor, in the presence of a catalytic amount of (*S*)-proline with a number of ketones, forming the corresponding functionalized α-amino esters **172**, **173**, **207**, and **208** with high stereoselectivities (Scheme 131).[230,259]

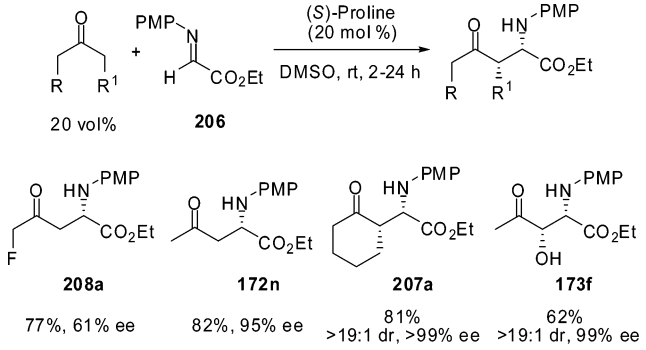
Scheme 129. β-Amino Ketones Obtained from the Reaction of Acetones with Preformed Aldimines



Scheme 130. Asymmetric Synthesis of β-Amino-β-polyfluoroalkyl Ketones via the Catalytic Asymmetric Mannich Reaction



Scheme 131. Proline-Catalyzed Mannich Reaction of Unmodified Ketones with *N*-PMP-Protected α-Imino Ethyl Glyoxylate

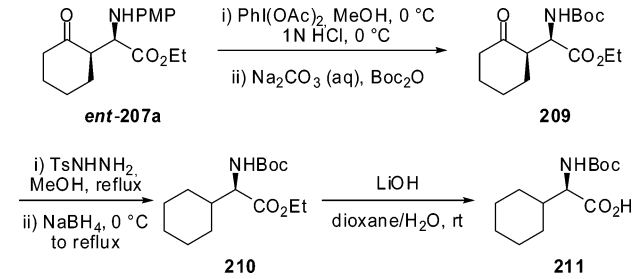


A synthesis of the unnatural amino acid (*R*)-cyclohexylglycine (**211**) using this reaction has also been developed. The product obtained (***ent*-207a**) from the (*R*)-proline-catalyzed reaction of cyclohexanone with α-imino ester (see Scheme 131) was elaborated to **211** via simple functional group manipulations (Scheme 132).[260]

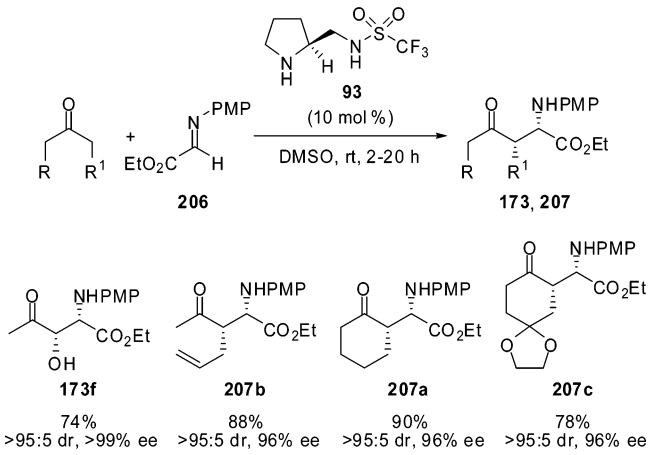
Wang et al. reported chiral proline-derived pyrrolidine-sulfonamide **93** as an excellent catalyst of the Mannich reaction of ketones with α-imino ester **206**.[261] For example, the Mannich reaction of cyclohexanone with *N*-PMP-protected α-imido ethyl glyoxylate **206** was completed within 2 h at room temperature with 10 mol % catalyst to afford product **207a** in 90% yield with 96% ee and >95:5 dr (Scheme 133).

A highly enantioselective Mannich reaction of carbonyl compounds with α-imino esters **206** was achieved by Ley

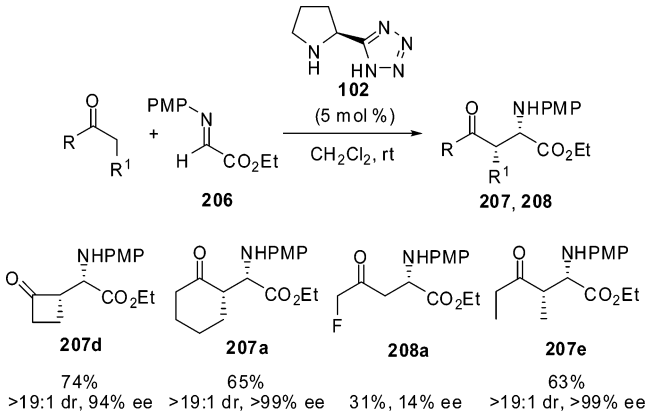
Scheme 132. Synthesis of the Unnatural Amino Acid Cyclohexyl Glycine



Scheme 133. Pyrrolidine-sulfonamide Catalyzed the Reactions of Ketones with α-Imino Ester



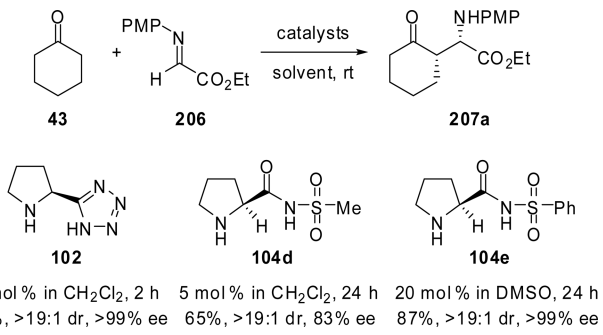
Scheme 134. 5-Pyrrolidin-2-yltetrazole-Catalyzed Asymmetric Mannich Reactions



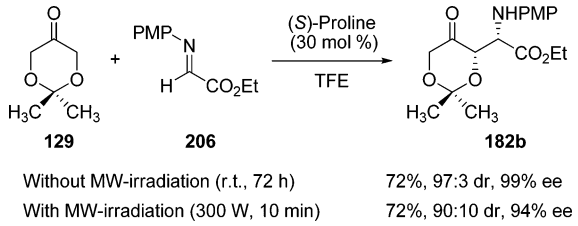
and co-workers using the chiral pyrrolidine-based tetrazole catalyst **102**.[129] The catalytic activity as well as solubility of tetrazole catalyst **102** is better than that of proline. Reaction with different cyclic as well as acyclic carbonyl compounds provided a high degree of stereochemical control (95 to >99% ee and >19:1 dr) (Scheme 134).

Ley and co-workers investigated tetrazole **102** and acylsulfonamides **104** as catalysts for the asymmetric Mannich reaction. For example, the reaction of cyclohexanone **43** with α-imino ester **206** catalyzed by 5 mol % tetrazole organocatalyst **102** in CH_2Cl_2 at room temperature gave the corresponding product **207a** in 65% yield with >19:1 dr and >99% ee after 2 h. In comparison, 65% yield, >19:1 dr, and 83% ee after 24 h were achieved using methyl sulfonamide catalyst **104d** under the same conditions. Most importantly, the tetrazole organocatalyst **102** showed a high level of enantioselectivity (>99% ee) and reactivity even at low

Scheme 135. Comparing Proline Variants for the Asymmetric Mannich Reaction



Scheme 136. Comparison of Microwave-Assisted and Original Mannich Reactions



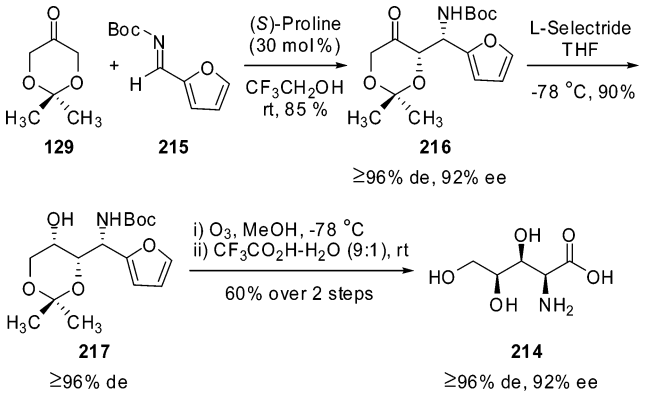
catalyst loading (1 mol %). On the other hand, the phenyl sulfonamide catalyst **104e** was much less reactive and 20 mol % catalyst loading is required. However, the level of selectivity is the same as that of tetrazole catalyst **102** (Scheme 135).[135]

Westermann et al. investigated the proline-catalyzed asymmetric Mannich reaction of protected dihydroxyacetone **129** and various imines in 2,2,2-trifluoroethanol (TFE).[262] For example, the asymmetric Mannich reaction of ketone **129** with *N*-PMP-protected α-imido ethyl glyoxylate **206** in the presence of proline (30 mol %) to the corresponding product **182b** proceeded with up to 72% yield and up to 99% ee after 72 h. Interestingly, the authors pointed out that the reaction was accelerated under the action of microwave (MW) irradiation. The best results were obtained using 30 mol % catalyst with 300 W of irradiation power. Under these conditions, the product was obtained in only 10 min in 72% yield with 90:10 dr and 94% ee (Scheme 136).

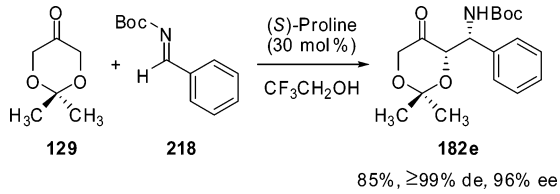
Enders et al. reported the synthesis of (+)-polyoxamic acid **214** employing the Mannich reaction of *N*-Boc-protected imine **215**[263] with 2,2-dimethyl-1,3-dioxan-5-one (**129**).[264] The reaction occurred with excellent stereoselectivity in 85% yield with >96% de and 92% ee. Subsequent reduction with L-Selectride in THF at −78 °C afforded the alcohol **217**. Oxidation of the furyl group to the carboxylic acid via ozonolysis[265] followed by treatment with $CF_3CO_2H-H_2O$ (9:1) gave enantiomerically pure (+)-polyoxamic acid (**214**) in 60% yield over two steps with >96% de and 92% ee (Scheme 137).

Enders et al. also reported the synthesis of various synthetically important amino sugars and derivatives via three-component, direct Mannich reaction of a variety of aldehydes, including heteroatom containing ones, *p*-anisidine (**171**), and 2,2-dimethyl-1,3-dioxan-5-one (**129**) in high yields with high stereoselectivities (78 to >99% de, 81−98% ee) when (*S*)-proline or TBS-protected hydroxy proline (**177**) was used.[266] The authors also reported the use of *N*-Boc

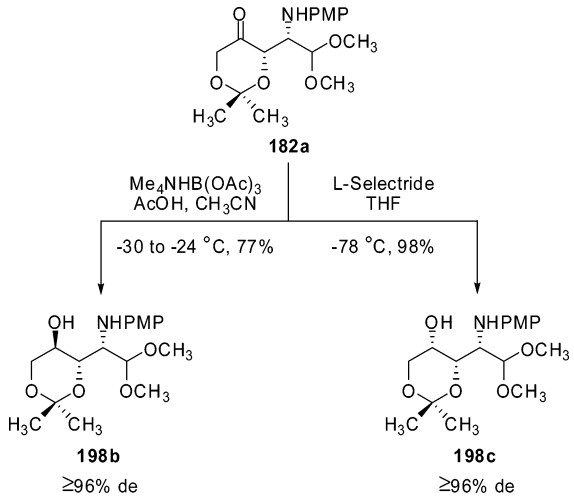
Scheme 137. Synthesis of (+)-Polyoxamic Acid via Mannich Reaction of *N*-Boc-imine with Ketone



Scheme 138. Organocatalytic Mannich Reaction Using an *N*-Boc-imine



Scheme 139. Diastereoselective *syn*- and *anti*-Reduction of the Mannich Product



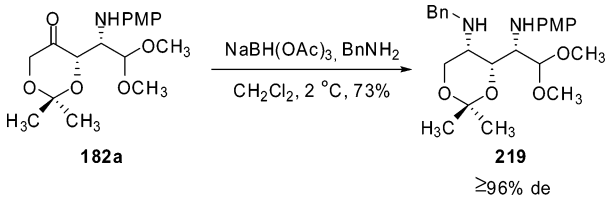
imine **218** as Mannich acceptor instead of the *N*-PMP imine, giving the corresponding *syn*-Mannich product **182e** in almost perfect diastereoselectivity (≥99% de) (Scheme 138).

The Enders group also examined reduction of Mannich product **182a** into the corresponding diastereomeric *β*-amino alcohols **198b**−**c** using $Me_4NHB(OAc)_3$ or L-Selectride as reducing reagent. The $Me_4NHB(OAc)_3$-mediated reduction of the Mannich product produced highly *anti*-selectively protected 2-amino-2-deoxyaldopentose 2-amino-2-deoxy-D-arabinose (**198b**) (≥99% de), whereas L-Selectride afforded the *syn*-isomer **198c** selectively (Scheme 139).

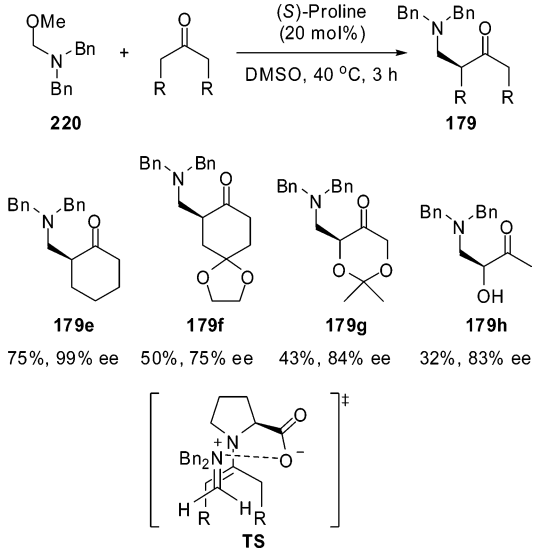
Enders et al. developed an elegant method for the highly *syn*-diastereoselective direct reductive amination of the Mannich product **182a** using $NaBH(OAc)_3$, $BnNH_2$, and AcOH (Scheme 140).[267]

Based on important contributions by Gellman et al.,[268] Córdova and co-workers reported the asymmetric α-aminomethylation of cyclohexanone with dibenzyl aminomethyl

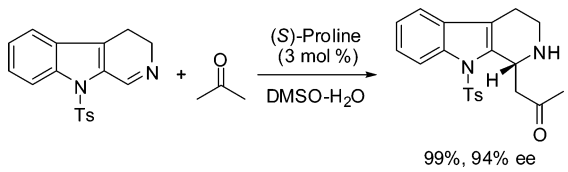
Scheme 140. *syn*-Selective Direct Reductive Amination of the Mannich Product



Scheme 141. Organocatalytic Asymmetric α-Aminomethylation of Ketones



Scheme 142. Reaction of 9-Tosyl-3,4-dihydro-*β*-carboline with Acetone in the Presence of (*S*)-Proline



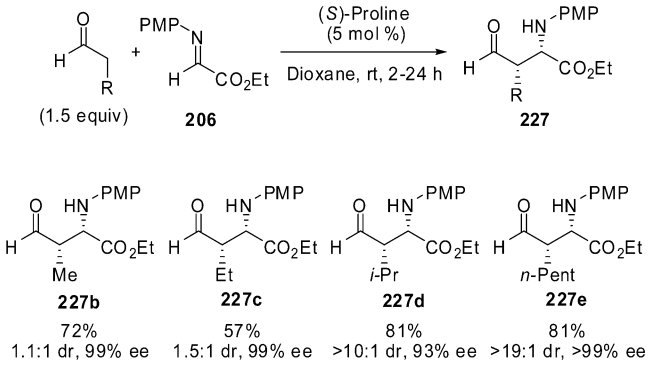
ether **220** using (*S*)-proline and proline derivatives as catalyst.[269] Screening of solvents and catalysts revealed that this reaction proceeds best in DMSO at 40 °C in the presence of 20 mol % (*S*)-proline to give the corresponding α-aminomethylated ketones **179** in generally modest yields (32−75%) with high enantioselectivities (75−99% ee) (Scheme 141). A possible transition state **TS** is also suggested.

A highly enantioselective proline-catalyzed Mannich reaction of ketones with 9-tosyl-3,4-dihydro-*β*-carboline has also been developed (Scheme 142).[242]

3.5. Indirect Asymmetric Mannich Reactions of Preformed Aldimines with Aldehydes

Barbas et al. explored the possibility of using unmodified aldehydes in catalytic asymmetric Mannich reactions. This Mannich reaction was initially examined using isovaleraldehyde. Under optimized reaction conditions, treatment of the aldehydes with *N*-PMP-protected α-imido ethyl glyoxylate **206** using 5 mol % (*S*)-proline in dioxane at room temperature provides the desired aldehyde-substituted α-amino esters **227** in high yields with high diastereo-

Scheme 143. Proline-Catalyzed Mannich Reaction of Unmodified Aldehydes with *N*-PMP-Protected α-Imino Ethyl Glyoxylate



selectivities (up to >19:1 dr) and enantioselectivities (up to >99% ee) (Scheme 143).[230,252,270,271] The bulkiness of the substituent of the aldehyde donor influences the diastereoselectivities.

The authors applied this method in the synthesis of α-alkyl-*β*-lactam (**233**), which is used as a carbapenem antibiotic PS-6 precursor[272−274] (Scheme 144).

One-pot enantioselective Mannich-hydrocyanation reactions, to give *β*-cyanohydroxymethyl α-amino acid derivatives **234** with three stereogenic centers as single diastereomers in high yield and with excellent enantioselectivity, have also been developed. Under elevated temperature, the reaction product cyclizes to the lactone **235** (Scheme 145).[271,275]

With an in situ similarly, the Mannich reaction can be combined with indium-promoted allylation to give *γ*-allyl substituted α-amino acid derivatives **236** (Scheme 146).[271,276]

In the synthesis of the DPP-IV inhibitor **247**,[277] which belongs to one of several new classes of antidiabetic medications,[278] a catalytic enantioselective direct Mannich reaction between a glyoxalate-derived imine **206** and phenyl acetaldehyde **248** served as a key step (Scheme 147).[279]

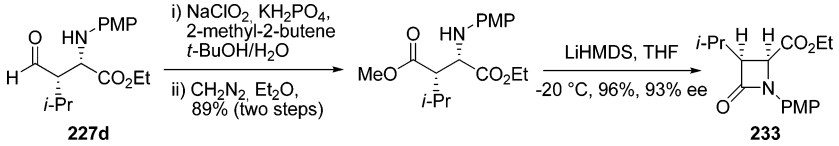
Fustero and Sanz-Cervera reported that the combination of a proline-catalyzed Mannich reaction between protected fluorinated aldimines **213** and unbranched aldehyde propanal **145** followed by reduction with $NaBH_4$ in MeOH gives fluorinated *β*-alkyl *γ*-amino alcohols **221** in highly diastereo- (up to 97:3 dr) and enantioselective fashion (99% ee in all cases) (Scheme 148).[280]

Using a ruthenium-catalyzed aerobic oxidation of amines **245** to imines **246**,[281] Bäckvall and Córdova investigated proline-catalyzed asymmetric tandem Mannich reactions (Scheme 149).[281] In the presence of (*S*)-proline, a single operation provided *β*-amino aldehydes **227** in high yields with excellent enantioselectivities (up to >99% ee) (Scheme 150).

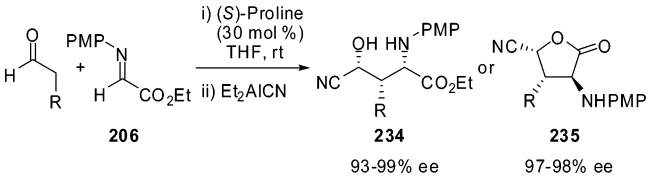
Córdova et al. reported the asymmetric syntheses of α-oxy-*β*-aminoaldehydes **222** using the cross-Mannich reactions of imines with protected glycolaldehydes (Scheme 151).[254] Potentially, the differently protected α-oxy-*β*-aminoaldehydes **222** could be easily converted to the corresponding amino alcohols and *β*-amino-α-hydroxy acids.[224] This methodology provides a complementary and metal-free approach to Trost's[227] and Shibasaki's[31] methods.

Gellman and co-workers identified an α-aminomethyl ether **220** as the key reagent[229,282] in the catalytic α-aminomethylation of aldehydes. In the presence of 20 mol %

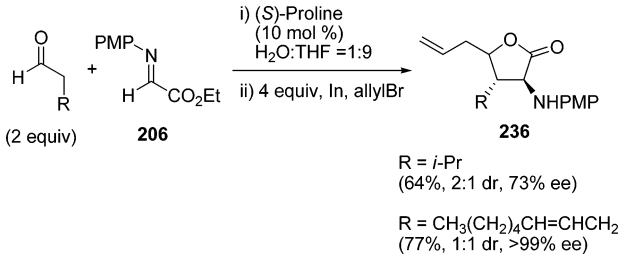
Scheme 144. Synthesis of α-Alkyl-β-Lactam



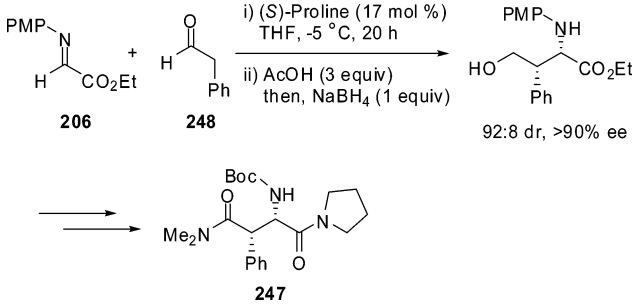
Scheme 145. Asymmetric One-Pot Mannich-Cyanation Reactions



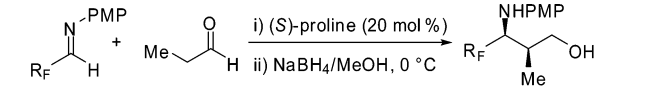
Scheme 146. One-Pot Asymmetric Synthesis of γ-Allyl-Substituted α-Amino Acid Derivatives



Scheme 147. Enantioselective Synthesis of DPP-IV Inhibitor



Scheme 148. Preparation of Fluorinated γ-Amino Alcohols from Propanal and Aldimines



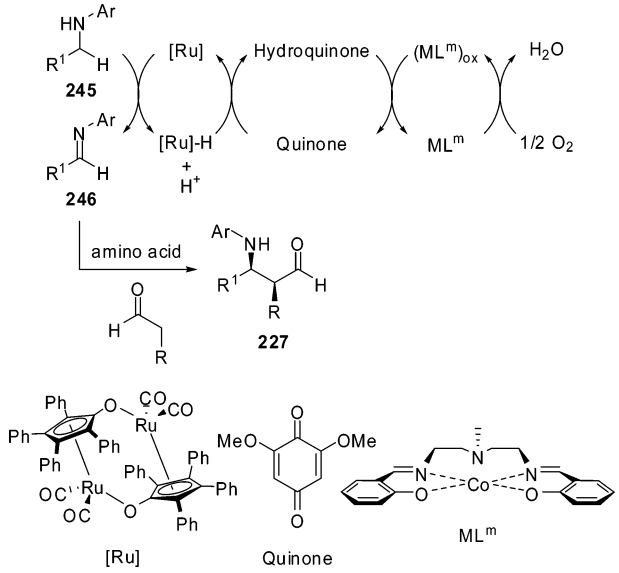
diaryprolinol-acetic acid salt **249** in DMF containing 1 M LiCl, a methylene iminium species is generated in situ and converted to α-substituted β-amino aldehydes, which after reduction afforded alcohols **250** in high yields with excellent enantioselectivities (Scheme 152).[268]

This Mannich reaction was used in an efficient synthesis of β^2-amino acids **251** (Scheme 153).[283]

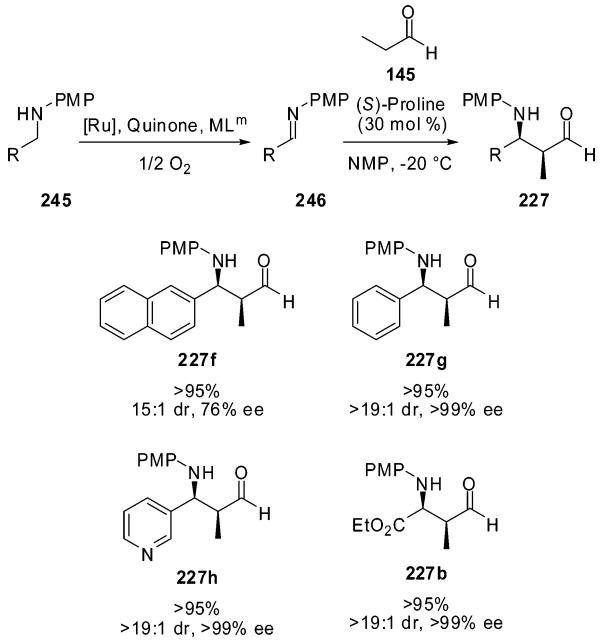
This asymmetric α-aminomethylation reaction was revisited by Córdova and co-workers using the same catalyst **249**.[284] In the presence of 20 mol % catalyst **249**, simple unmodified aldehydes were found to react smoothly with dibenzyl aminomethyl ether **220** in DMF and LiBr (2 equiv) at −25 °C, and the corresponding amino alcohols **250** were isolated in high yields with up to 98% ee (Scheme 154).

Córdova and co-workers observed that the inorganic salt exerts a significant influence on enantioselectivity, and the

Scheme 149. Combination of Catalytic Aerobic Oxidation of Amines with Organocatalytic Mannich Reactions



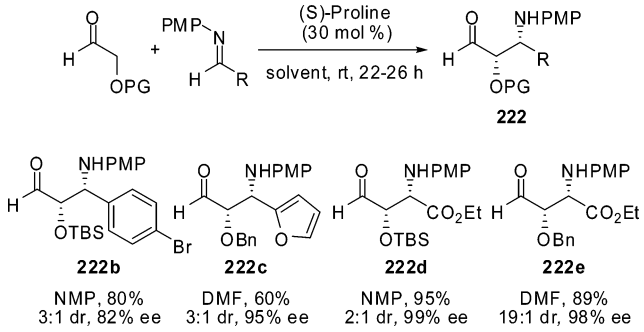
Scheme 150. Catalytic Aerobic Oxidation of Amines with Organocatalytic Mannich Reactions



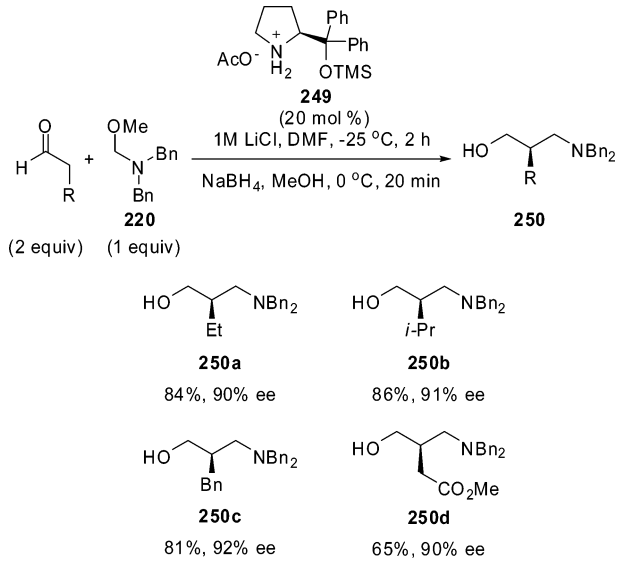
ee follows the order following: LiBr > LiCl > LiI ≫ without salt. For example, when LiBr was added into the reaction mixture, the optical purity of the isovaleraldehyde product was increased from 78% to 96% ee. Gellman and Córdova proposed that the mechanism may involve an ion pair interaction between the carboxylate and the iminium ion, while the diaryprolinol reaction induced a nonbonding interaction, forcing an electrophile to approach from the opposite face.[268,284]

Córdova and Zhao reported an organocatalytic asymmetric reductive Mannich reaction of α,β-unsaturated aldehydes

Scheme 151. Catalytic Cross-Mannich Reactions with Protected Glycol Aldehydes

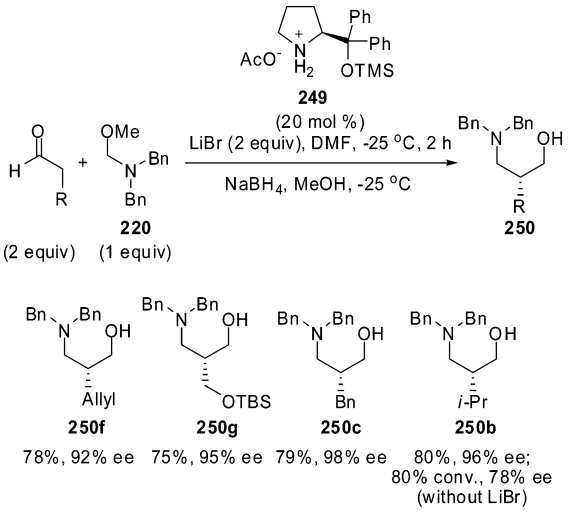


Scheme 152. Enantioselective Aminomethylation of Aldehydes



with a Hantzsch ester as a hydrogen donor.[285] The authors presumed that exposure of α,β-unsaturated aldehydes to chiral (*S*)-diphenylprolinol catalysts **252** would generate an activated iminium species, and then subsequent hydride transfer to an iminium intermediate from Hantzsch ester **253** presumably gives the enamine intermediate. This enamine activation would enable addition to a wide array of *N*-PMP-protected α-iminoglyoxylates **206** to give the corresponding *anti*-amino acid derivatives **254** in good yields with up to 50:1 dr and up to 99% ee (Scheme 155).

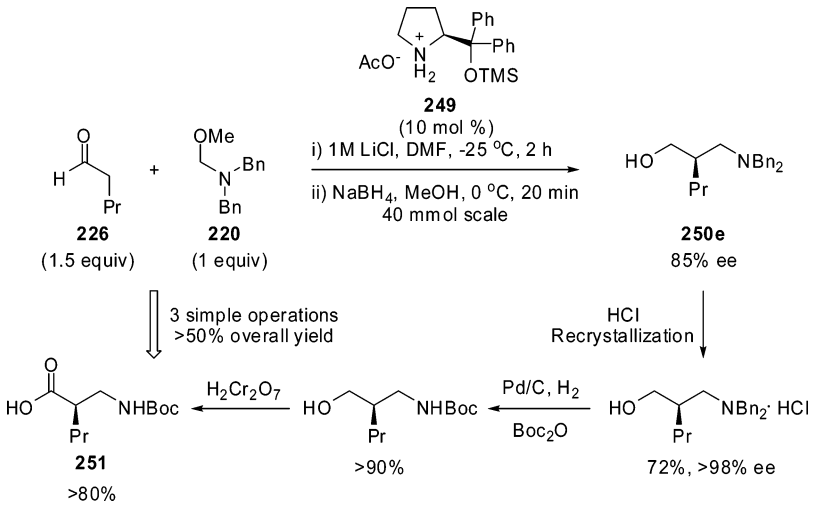
Scheme 154. Chiral Diphenyl Prolinol Silyl Ether-Catalyzed Asymmetric α-Aminomethylation of Aldehydes



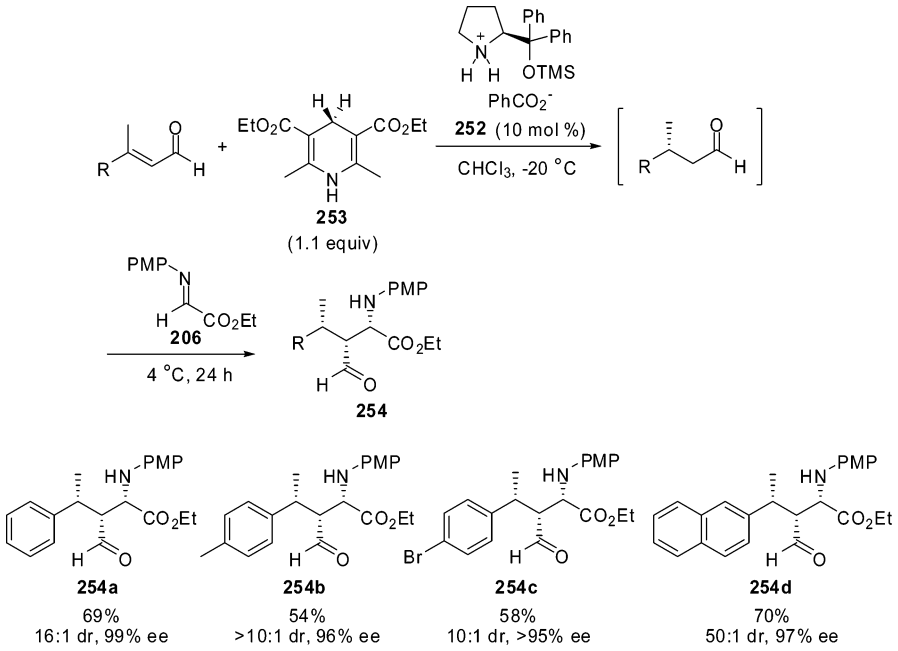
To achieve *syn*-selective Mannich product **255** with high enantioselectivity, the reaction mixture together with *N*-PMP-protected α-iminoglyoxylate **206** in the presence of a catalytic amount of (*R*)-proline was added (Scheme 156).[285]

A highly diastereo- and enantioselective Mannich reaction of unmodified aldehydes with *N*-Boc imines[286,263,287] using (*S*)-proline as catalyst was recently reported by List and co-workers.[288] Originally, the proline-catalyzed Mannich reaction required the use of anilines as the amine component. Since the N-substituent is usually employed as protecting group, it should be easily removable after the reaction has taken place. However, the removal of the most commonly used *p*-methoxyphenyl (PMP) group from nitrogen often requires drastic oxidative conditions involving harmful reagents such as ceric ammonium nitrate (CAN) that are not compatible with all substrates. List et al. have employed the *tert*-butoxycarbonyl (Boc) group as an easily removable protecting group in order to overcome this drawback. In general, the *syn*-Mannich products directly precipitated from the reaction mixtures to give high yields and stereoselectivities or alternatively can be isolated by crystallization

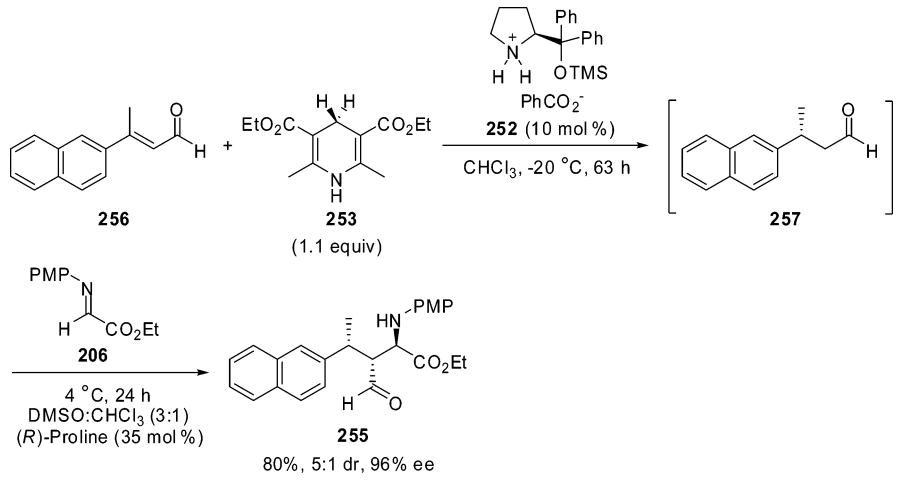
Scheme 153. Concise Synthesis of Boc-β²-homonorvaline



Scheme 155. Direct Catalytic Enantioselective Reductive Mannich Reactions



Scheme 156. Direct Catalytic Enantioselective Reductive Mannich Reaction with a Diphenyl-Prolinol Derivative and (*S*)-Proline as Catalyst



induced by trituration with hexanes (Scheme 157 and Figure 2).

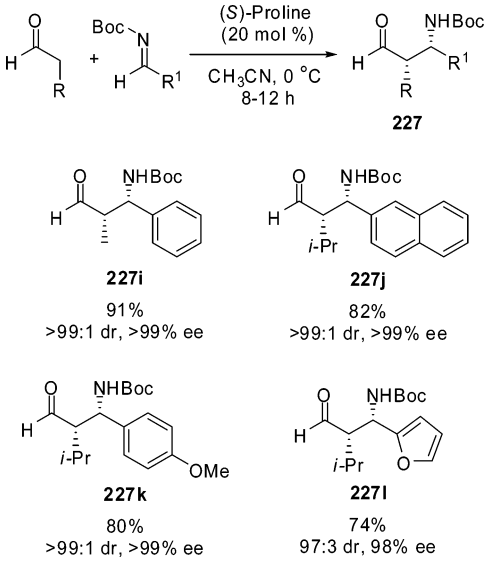
The authors also showed that an application of this methodology to the synthesis of α,*β*-branched *β*-amino acids, which are of great potential for the synthesis of peptide derivatives and related biologically active compounds, is possible (Scheme 158).[289,290] Córdova et al. also reported this reaction.[291]

3.6. Indirect Asymmetric Mannich Reactions of Preformed Aldimines with α-Branched Aldehydes

Barbas and co-workers reported (*S*)-proline-catalyzed asymmetric Mannich reactions of *N*-PMP-protected α-imido ethyl glyoxylate **206** with α,α-disubstituted aldehydes to give quaternary *β*-formyl α-amino acid derivatives **240** with excellent yields and enantioselectivities (Scheme 159).[292]

The Mannich adduct **241** can be converted into the corresponding quaternary α- and *β*-amino acids **242** and the *β*-lactam **243** (Scheme 160).

Scheme 157. Proline-Catalyzed Asymmetric Mannich Reaction of Aldehydes with *N*-Boc-imines



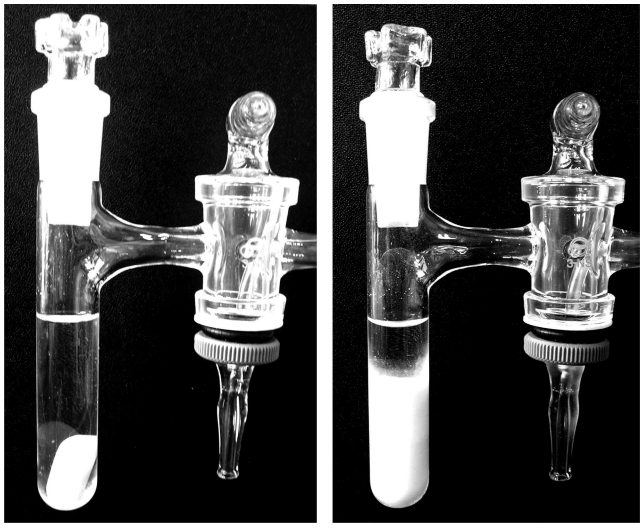
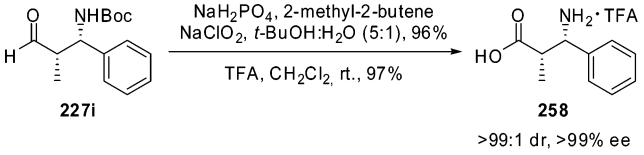
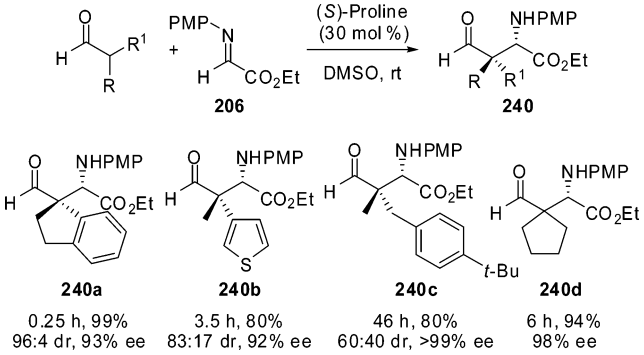


Figure 2. Reaction of isovaleraldehyde with 2-naphthyl *N*-Boc-imine in the presence of (*S*)-proline (20 mol %) in CH_3CN. Homogeneous reaction mixture after mixing all compounds (left). Reaction mixture after completion of the reaction (10 h) (right).

Scheme 158. Synthesis of α,*β*-Branched *β*-Amino Acid



Scheme 159. α,α-Disubstituted Aldehydes as Donors in the Synthesis of Quaternary *β*-Formyl-Substituted α-Amino Acid Derivatives



3.7. Indirect Asymmetric Mannich Reactions of Preformed Ketimines with Aldehydes

Ketimines can be used in organocatalytic Mannich reactions with aldehydes. Jørgensen and co-workers reported an effective method for the construction of asymmetric quaternary carbons using the enantioselective Mannich reaction of ketimines and unmodified aldehydes.[293] (*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine (**237**) proved to be the best catalyst and provided quaternary α-amino acid derivatives **238** and **239** with excellent yields (72−99%) and enantioselectivities (83−98% ee) (Scheme 161).

3.8. Asymmetric *anti*-Mannich Reactions

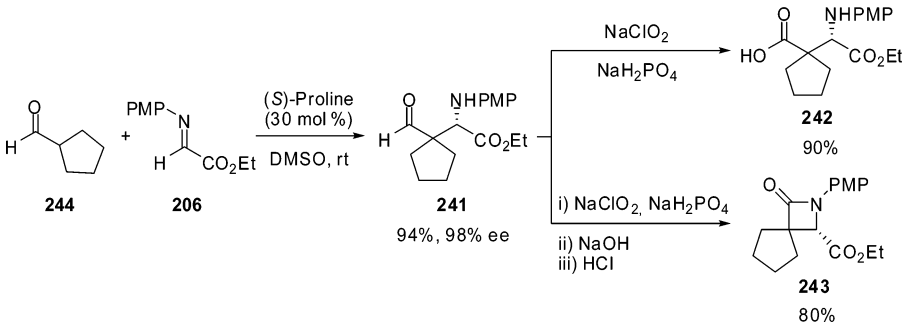
In 2002, Barbas and co-workers reported an (*S*)-2-methoxymethylpyrrolidine (SMP) **259**-catalyzed Mannich reaction between unmodified aldehydes and *N*-PMP-protected α-imino ethyl glyoxylate **206** which gave the products **260** in good yields (44−78%) with *anti*-selectivities ranging from 1:1 to >19:1 dr and good enantioselectivities (74−92% ee) (Scheme 162).[252,294] The authors proposed that the *anti*-selectivity was achieved because the s-*cis*-(*E*)-enamine could be attacked to the *si*-face of imine by a favorable Coulombic interaction[221,295] between the ethereal oxygen group of the catalyst and the nitrogen group of the imine (**TS-A**). An alternative transition state (**TS-B**) based solely on steric considerations may also be operative.

A highly *anti*-selective and enantioselective asymmetric Mannich reaction using a novel axially chiral amino trifluoromethanesulfonamide **169** has been developed by Maruoka and co-workers.[296] Reactions between aldehydes and *N*-PMP-protected α-imino glyoxylates proceed smoothly to give *β*-amino aldehydes **260** with a high *anti*/*syn* ratio and enantioselectivity (Scheme 163). Maruoka's studies provide a plausible mechanistic insight that may ultimately be utilized in the design and development of other *anti*-selective organocatalysts.

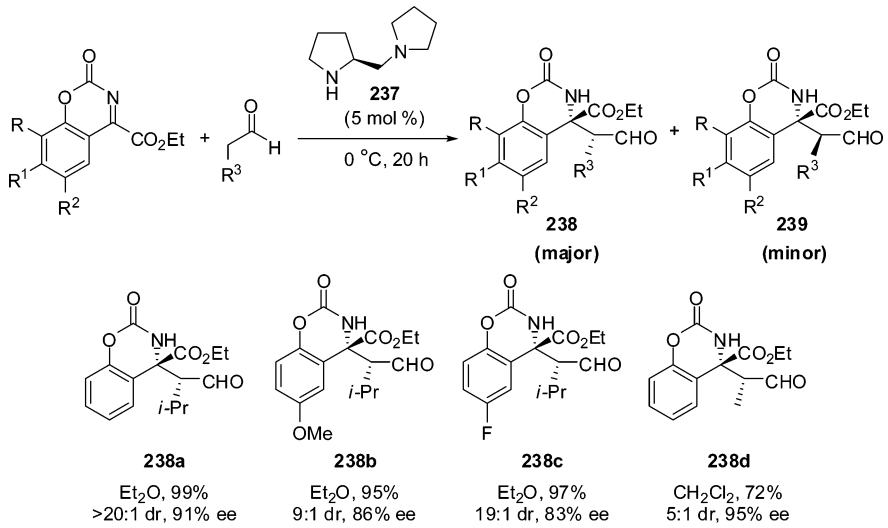
The authors proposed that the key for the formation of the *anti*-Mannich product is an s-*cis* configurated (*E*)-enamine. The activation of the imine occurs by hydrogen bonding from the acidic proton of the sulfonamide moiety. Since in the s-*cis* configured (*E*)-enamine, the imine nitrogen was brought into closer proximity to the sulfonamide proton compared to that in the s-*trans* configured (*E*)-enamine, a stronger hydrogen bonding and therefore higher activation of the imine is possible in the s-*cis* configured one (Scheme 164).

Later, the same group developed an even simpler organocatalyst for the *anti*-selective asymmetric direct Mannich reaction. The novel C_2-symmetric pyrrolidine-based amino sulfonamide **261** was prepared from L-tartaric acid in seven steps and used in the Mannich reaction of aldehydes and ketones.[297] The carbonyl compounds were treated with α-imino ester **206** in the presence of pyrrolidine-based amino sulfonamide **261** (10 mol %) to afford the corresponding Mannich products **260** and **262** in good yield with high *anti*-diastereoselectivities and enantioselectivities (Scheme 165).

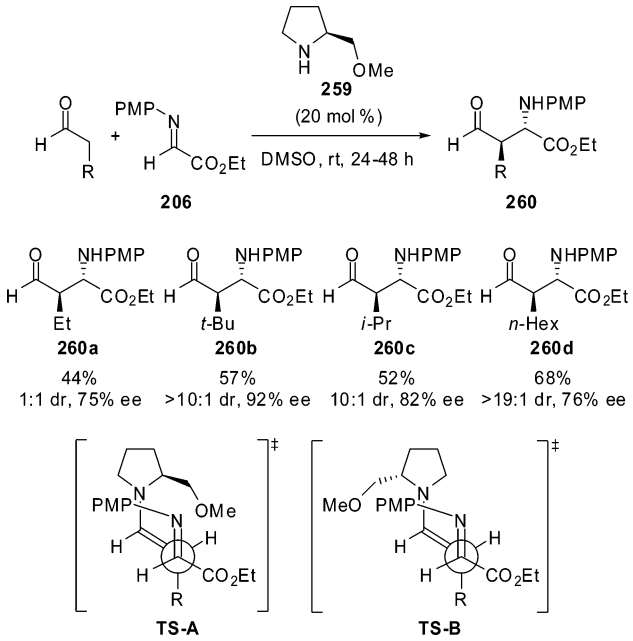
Scheme 160. Synthesis of Quaternary α- and *β*-Amino Acids and Spiro *β*-Lactams from Mannich Products



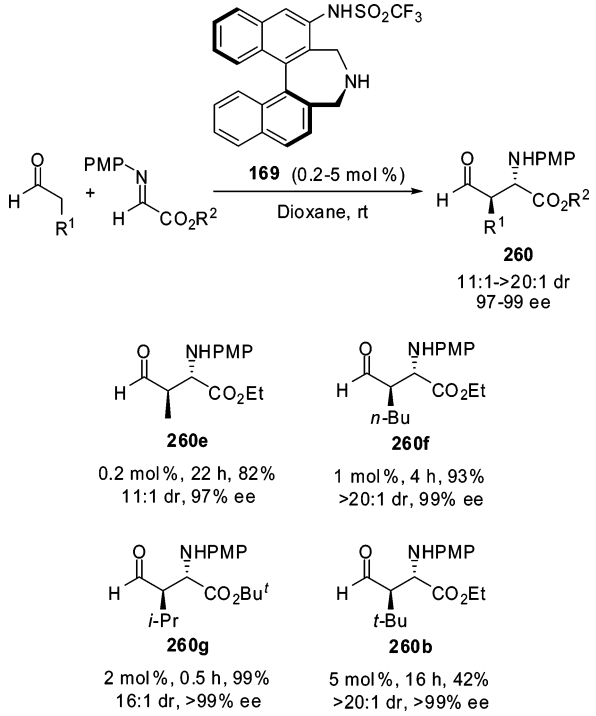
Scheme 161. Direct Organocatalytic Asymmetric Mannich Reactions of Ketimines with Aldehydes



Scheme 162. SMP-Catalyzed Mannich Reactions of Unmodified Aldehydes with *N*-PMP-Protected α-Imino Ethyl Glyoxylate



Scheme 163. *anti*-Selective Mannich Reactions between Various Aldehydes and α-Imino Esters Catalyzed by Axially Chiral Amino Trifluoromethanesulfonamide



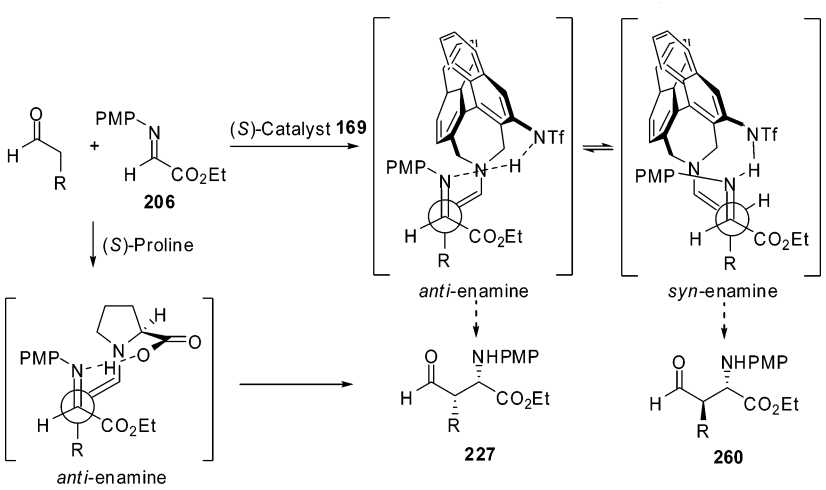
Barbas, Tanaka, and Houk reported a highly *anti*-selective and enantioslective Mannich reaction catalyzed by a designed amino acid. The Mannich reaction between aldehydes and *N*-PMP-protected imines catalyzed by (*S*)-proline derivative **263** affords the *anti*-amino aldehydes **260** with high stereoselectivities (Scheme 166).[298]

Here the designed new catalyst induces a preferred s-*cis* configuration of the (*E*)-enamine to the carboxylate in the transition state to avoid 1,3-allylic strain between the enamine and the methyl substituent at the 5-position of the proline-type catalyst. The *si*-face of the enamine attacks the *si*-face of the (*E*)-imine (Scheme 167). Remarkably, even if the Mannich reaction was carried out in the presence of 1 or 2 mol % catalyst **263**, the desired product was obtained in good yield with high diastereoselectivity (up to 98:2 dr) and enantioselectivity (up to >99% ee) within a few hours.

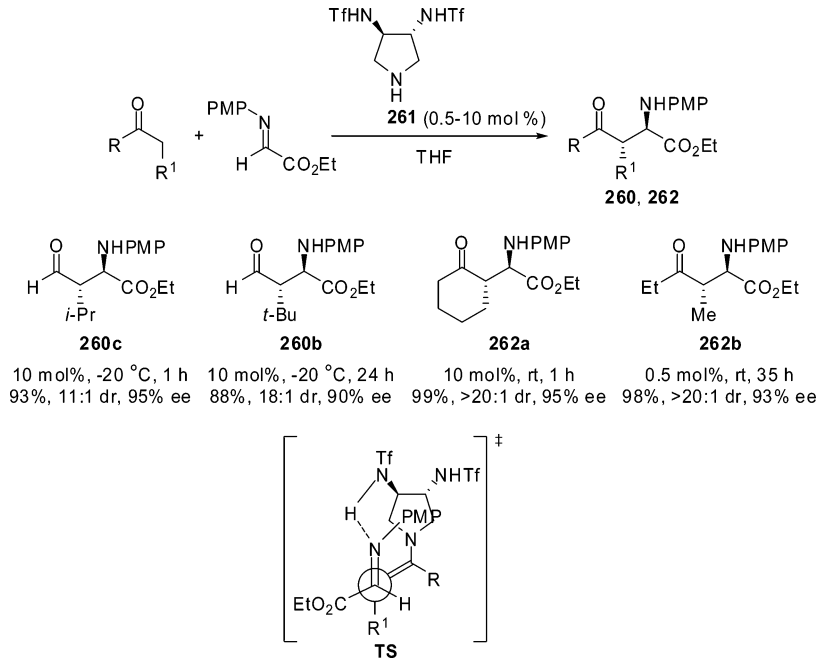
A highly *anti*-diastereoselective and enantioselective β-amino ketone synthesis with preformed *N*-PMP-imines using 3-pyrrolidinecarboxylic acid **264** as catalyst has also been developed.[299] Here the authors rationalized the observed *anti*-Mannich product based on the conformation of the (*E*)-enamine. The free enamine conformers **265** and **266** should have similar free energies. However, in the transitions state for the Mannich reaction involving s-*cis*-(*E*)-enamine **266**, formation of a stronger hydrogen bonding (compared to the TS involving the s-*trans*-enamine) from the carboxyl group of the catalyst to the imine nitrogen is expected due to the proximity of these functionalities. Subsequently, the s-*cis* conformation of the (*E*)-enamine attacks the *si*-face of the (*E*)-imine to give the *anti*-Mannich products in good yields with high diastereo- and enantioselectivities in most cases (Schemes 168 and 169).

Córdova and co-workers have examined catalytic asymmetric *anti*-selective Mannich reactions in which TMS-protected α,α-diphenyl-2-pyrrolidinemethanol **265** is utilized as organocatalyst.[300] The corresponding β-formyl-α-amino-

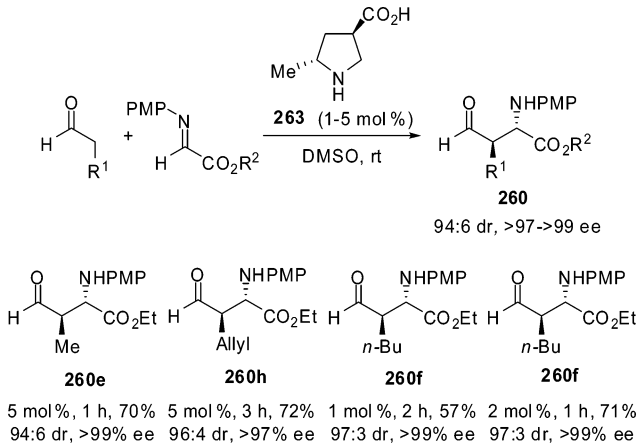
Scheme 164. Proposed Transition States of the *anti*-Selective Mannich Reaction



Scheme 165. *anti*-Selective Mannich Reactions Catalyzed by C_2-Symmetric Chiral Pyrrolidine-Based Amino Sulfonamide

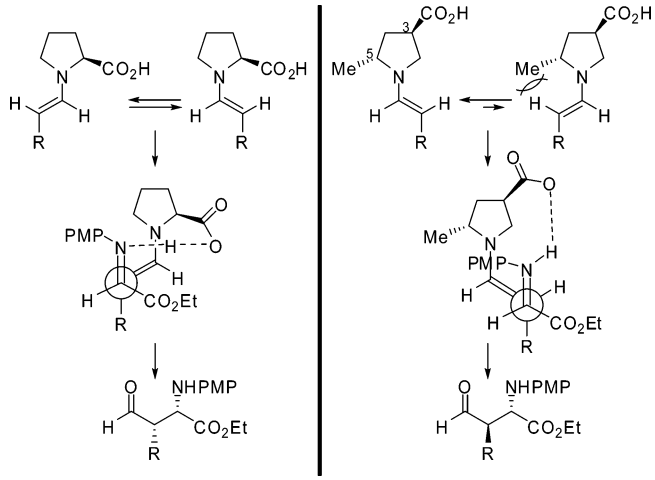


Scheme 166. 5-Methyl-3-pyrrolidinecarboxylic Acid-Catalyzed Mannich Reactions

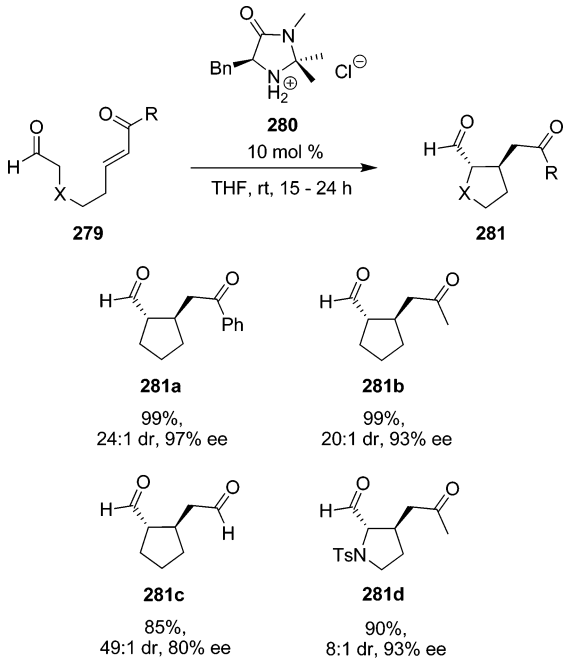


esters **260** are obtained in good yields (45−75%), with high diastereoselectivities (14:1 to >19:1 dr) and enantioselectivities (97−99% ee) (Scheme 170). The authors invoked

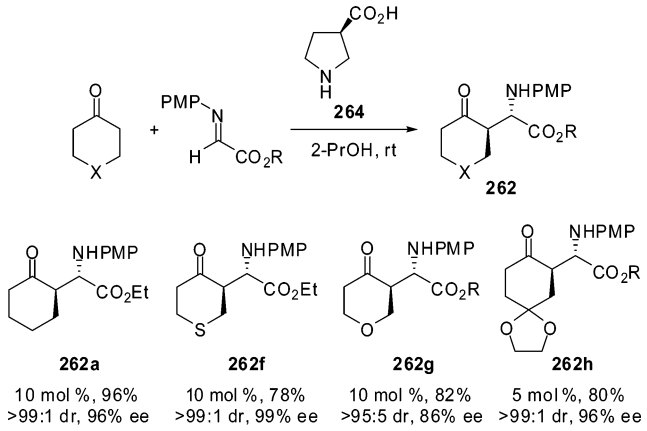
Scheme 167. Proposed Transition States for the *anti*-Selective Mannich Reaction and the Proline-Catalyzed *syn*-Selective Mannich Reaction



Scheme 168. 3-Pyrrolidinecarboxylic Acid-Catalyzed *anti*-Mannich Reactions of Ketones



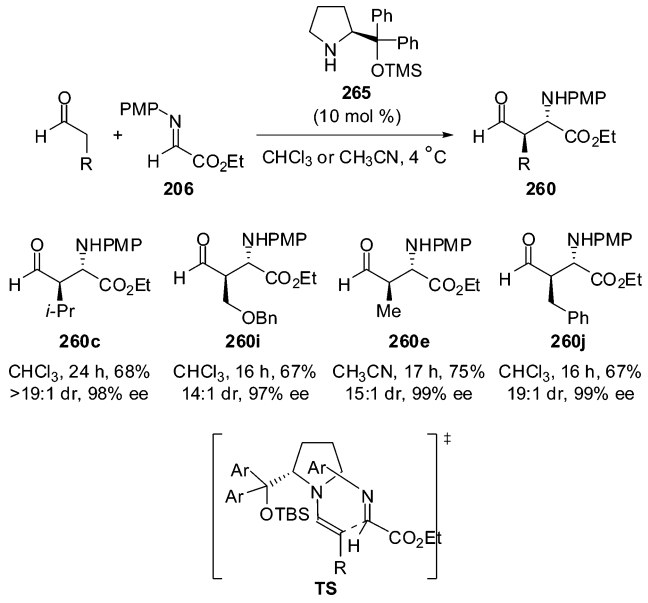
Scheme 169. 3-Pyrrolidinecarboxylic Acid-Catalyzed *anti*-Mannich Reactions of Cyclic Ketones



the transition state **TS** based on steric and Coulombic interactions to account for the observed stereoselectivity.

Very recently, an *anti*-selective three-component Mannich reaction between α-hydroxy ketones, aromatic aldehydes, and *p*-anisidine (**171**) catalyzed by primary amine containing acyclic amino acids was reported.[218] When the reaction was performed in DMF or *N*-methylpyrrolidinone (NMP) with 20 mol % O-*t*-Bu-(*S*)-threonine (**167b**) as catalyst at 4 °C, *anti*-Mannich adducts **266** were obtained in good yields with high diastereoselectivities (1.3:1 to >19:1 dr) and enantioselectivities (53−98% ee) (Scheme 171). The reaction with (*S*)-tryptophan **267** was found to be faster than that with O-*t*-Bu-(*S*)-threonine (**167b**). The observed *anti*-Mannich adducts **266** are proposed to arise from the reaction of a (*Z*)-enamine in the C−C bond forming transition state. The (*Z*)-configuration of the enamine is favored over its (*E*)-counterpart due to an internal hydrogen bonding between the hydroxyl oxygen of the substrate and the amine NH of the catalyst. Although excellent stereoselectivity was obtained, the process is limited to α-hydroxy ketones.

Scheme 170. Catalytic *anti*-Selective Asymmetric Mannich Reactions



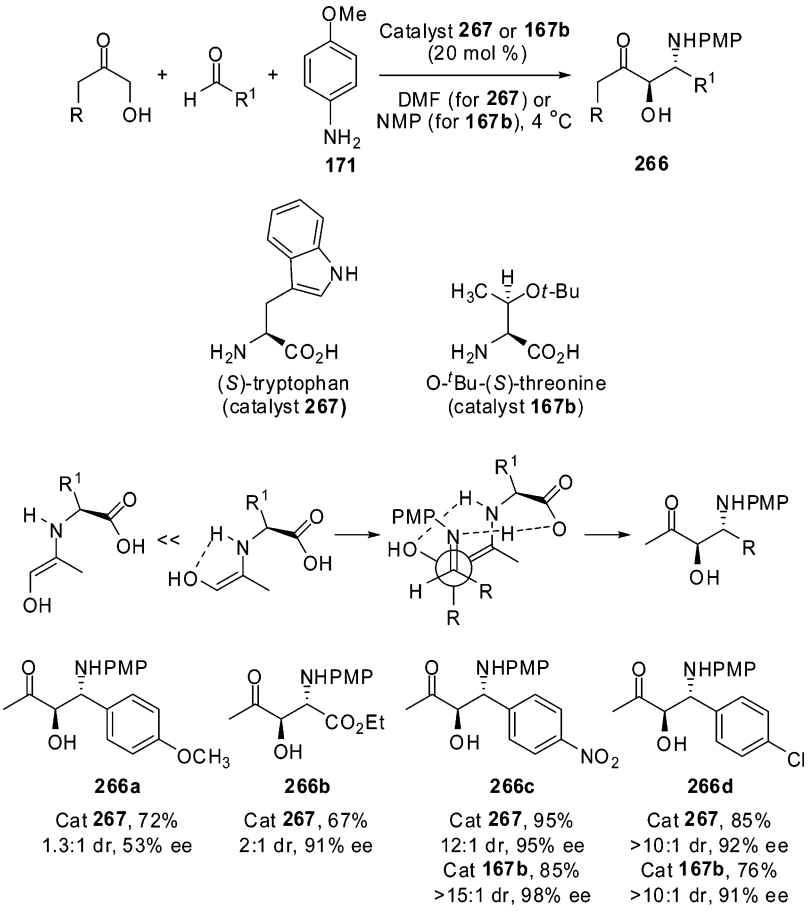
3.9. Immobilized Catalysts for Mannich Reactions

Benaglia and Puglisi investigated a PEG-bound chiral proline catalyst. The immobilized PEG−proline catalyst was prepared from (2*S*,4*R*)-4-hydoxyproline, and the Mannich reaction between an *N*-PMP-imine **268** and acetone **35** investigated.[190] The reaction proceeded smoothly at room temperature in the presence of 30 mol % catalyst **269**, affording the β-aminoketone **172a** in yields and enantioselectivities that depend on reaction conditions. The best result was observed in DMSO after 72 h, which gave an 81% yield of β-aminoketone **172a** in 96% ee (Scheme 172).

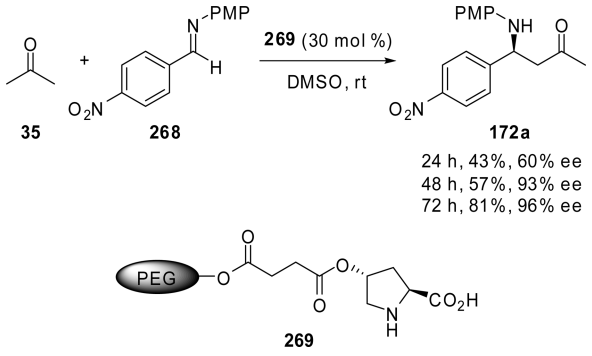
The PEG-supported catalyst was recycled by simple filtration and extraction, and used three times without significant loss of enantioselectivity (96−97% ee). However, subsequent uses of recycled catalyst led to diminished activity (from 81% to 64% yield). The same authors also reported three-component a direct asymmetric Mannich reaction between aliphatic aldehyes, acetone **35**, and *p*-anisidine **171** to afford the corresponding products **172** in modest yields (from 35% to 51%) and enantioselectivities (from 40 to 83% ee) (Scheme 173).[190] However, the PEG-supported proline-catalyzed reaction of 4-nitrobenzaldehyde **76** instead of the aliphatic aldehyde for the three-component reaction in DMSO provided a 50:50 mixture of Mannich product and aldol product in only 20% combined yield.

Ionic liquids can accelerate the asymmetric Mannich reaction of *N*-PMP-protected α-imino ethyl glyoxylate **206** with aldehydes and ketones catalyzed by (*S*)-proline.[301] For example, the Mannich reaction of cyclohexanone **46** with *N*-PMP-protected α-imino ethyl glyoxylate **206** using 5 mol % (*S*)-proline in the presence of [bmim][BF_4] **95** was completed within 30 min and provided the Mannich products **207** in quantitative yield with excellent ee (>99%) and diastereoselectivity (>19:1 dr), whereas the same reaction in traditional organic solvent required 2−24 h using 5−20 mol % (*S*)-proline to achieve complete conversion (Scheme 174). This rate acceleration effect induced by the ionic liquid was shown even more dramatically when the amount of the catalyst was reduced to 1 mol %. The authors mentioned that

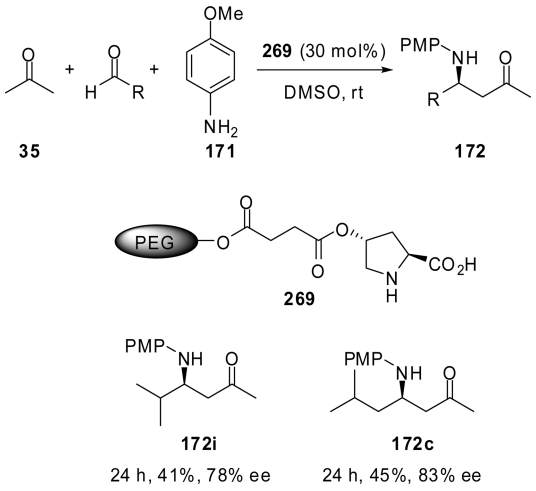
Scheme 171. Direct Asymmetric Mannich Reactions



Scheme 172. Poly(ethylene glycol)-Supported Proline Catalyst for the Enantioselective Mannich-Type Reaction



Scheme 173. Catalytic Enantioselective Three-Component Synthesis of β-Aminoketones



the use of an ionic liquid solvent allows for easier catalyst recycling without the need for catalyst modification. However, no data on recycling experiments have been reported.

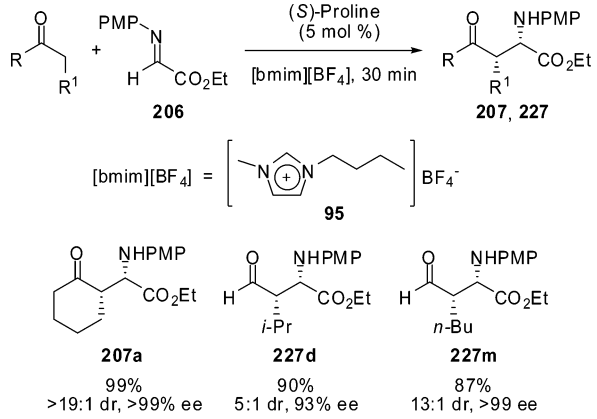
The authors also investigated the three-component Mannich reactions in [bmim][BF_4] ionic liquid **95** (Scheme 175).[301] These results are comparable with respect to yields and enantioselectivities with those of the reactions conducted in normal organic solvents.

The (*S*)-proline-catalyzed asymmetric Mannich reaction of *N*-PMP-protected α-imino ethyl glyoxylate **206** with hydroxyacetone (**66**) in the presence of [bmim][BF_4] ionic liquid **95** (Scheme 176) has also been developed.[301] A significant decrease of enantioselectivities (24−39% ee) and diastereoselectivities (58:42−68:32 dr) was observed compared with those obtained in organic solvent.

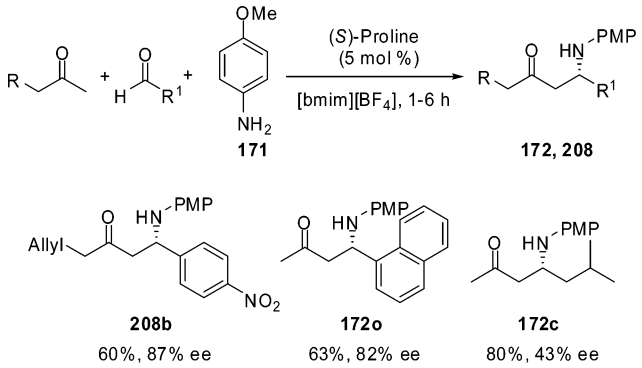
3.10. Computational Studies

The use of computational chemistry to understand and predict the stereoselectivity and transition states of catalytic asymmetric reactions has undergone rapid development in recent years. Some recent examples are Houk and co-workers studies on the enantioselective proline-catalyzed direct Mannich reaction using DFT (density functional theory; B3LYP/6-31G*).[302] Using this tool, a transition state could be provided to explain the origin of the opposite stereoselec-

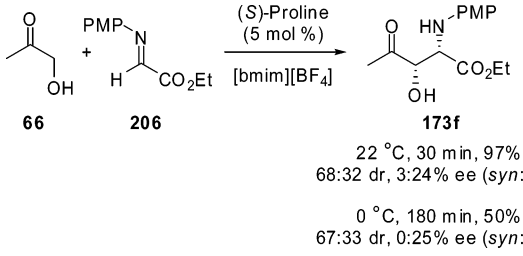
Scheme 174. (*S*)-Proline-Catalyzed Direct Asymmetric Mannich Reactions in [bmim][BF_4]



Scheme 175. (*S*)-Proline-Catalyzed Direct Asymmetric Three-Component Mannich Reactions in [bmim][BF_4]



Scheme 176. (*S*)-Proline-Catalyzed Direct Asymmertric Mannich Reactions in [bmim][BF_4] with Hydroxyacetone

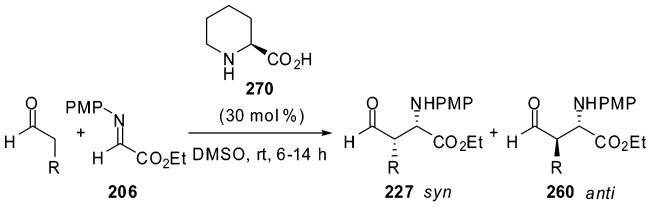


tivities of the proline-catalyzed Mannich and aldol reactions. The results confirmed the initial proposal by List et al.[234]

Houk and Barbas reported the experimental and computational investigation of the (*S*)-pipecolic acid **270**-catalyzed Mannich reaction between aldehydes and *N*-PMP-protected α-imino ethyl glyoxylate **206**.[303] The reactions provided both *syn*-**227** and *anti*-products **260** (1.4−2:1 dr) with high enantioselectivities (>98% ee) (Scheme 177). In contrast, (*S*)-proline-catalyzed reactions give mainly *syn*-products **227** with high enantioselectivities.

Computational studies using HF/6-31G(d) revealed the energy difference for the proline-catalyzed reaction between the s-*cis*- and s-*trans*-(*E*)-enamine conformations to be 1.0 kcal/mol. On the other hand, the computed energy difference of the competing conformation for the pipecolic acid-catalyzed reaction is only 0.2 kcal/mol (Scheme 178). These calculations predict that approximately equal amounts of *syn*- and *anti*-product (2:1 dr) will be formed by this reaction. Indeed, this is consistent with experimental results, where the reaction of propionaldehydes with *N*-PMP-protected

Scheme 177. (*S*)-Pipecolic Acid-Catalyzed Mannich Reaction of Aldehydes and α-Imino Ethyl Glyoxylate to Afford *syn*- and *anti*-Mannich Products



R = Me; 80%, 2.0:1 (*syn*:*anti*) dr, >99% ee (*syn*), >99% ee (*anti*)
R = *i*-Pr ; 82%, 1.4:1 (*syn*:*anti*) dr, >99% ee (*syn*), 98% ee (*anti*)
R = *n*-Bu, 83%, 1.5:1 (*syn*:*anti*) dr, >99% ee (*syn*), >99% ee (*anti*)

α-imino ethyl glyoxylate using (*S*)-pipecolic acid led to the formation of *syn*- and *anti*-products in a 1.4:1 ratio.[303]

4. Asymmetric Michael Reactions

4.1. Introduction

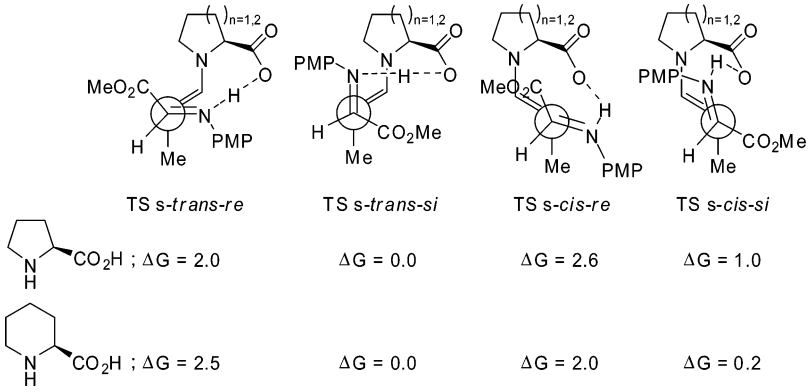
C−C bond formations by conjugate addition of nucleophiles to the *β*-position of α,*β*-unsaturated carbonyl compounds (Michael reaction) are frequently used in organic synthesis.[304−307] An increasing demand for optically active compounds has aroused considerable interest, since stereogenic centers can be created in the course of the Michael reaction. Thus, much effort has been made to develop efficient catalytic stereoselective methods.[308−312] Though remarkable advances have been made in the design of asymmetric catalysts containing metals, only recently have asymmetric transformations been reported which employ small organic molecules as catalysts.[11,13,313]

Carbon nucleophiles that contain active methylene centers were widely applied in direct Michael additions, whereas simple carbonyl compounds had generally to be converted into more reactive species such as enol ethers and enamines prior to use (Scheme 179). Since chemical transformations that avoid additional reagents, waste, and working time are highly desirable, a more promising and atom-economic strategy would involve direct addition of unmodified carbonyl compounds to Michael acceptors.

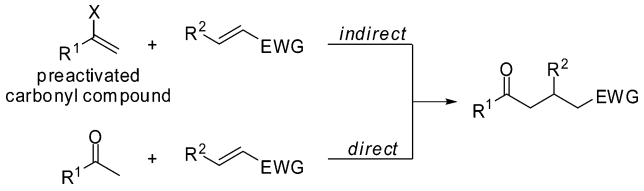
Consequently, aminocatalysis has gained considerable attention. The Michael donor can be catalytically activated either through enamine or enolate formation for the addition to a Michael acceptor (Scheme 180, paths a and b). Complementary, carbonyl-derived Michael acceptors can be activated via formation of an iminium species (Scheme 180, path c). For instance, early asymmetric attempts have been made to use active methylene compounds as Michael donors in the presence of chiral proline-derived catalysts.[314−320] In these cases, the α,*β*-unsaturated carbonyl compounds are most likely activated via iminium ion intermediates. On the other hand, chiral tertiary amines are known to catalyze the in situ formation of enolates.[321−323]

In contrast, enamine-catalyzed enantioselective addition reactions have only recently attracted considerable attention. The use of preformed enamines in the Michael reaction has been pioneered by Stork et al.,[3] and ever since, several nonasymmetric as well as asymmetric examples have been reported. For example, asymmetric Michael additions of preformed enamines derived from chiral amines to conjugated nitroalkenes and alkylidene malonates have been extensively studied by Seebach et al.[324−326] Yamada and coworkers reported early examples of the asymmetric Michael

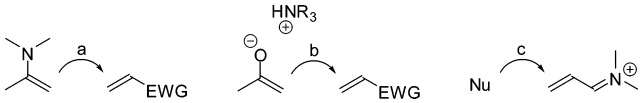
Scheme 178. Transition Structures for the C−C Bond Formation of the (*S*)-Proline and (*S*)-Pipecolic Acid-Catalyzed Mannich Reaction between Propionaldehyde and *N*-PMP-Protected α-Imino Methyl Glyoxylate



Scheme 179. Indirect and Direct Michael Reaction



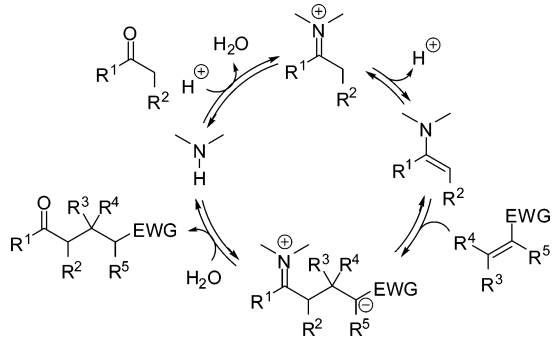
Scheme 180. Enamine-, Enolate-, and Iminium-Catalytic Michael Reactions



addition of (*S*)-proline-derived preformed enamines to acrylonitriles, acrylates and methyl vinyl ketone.[327,328]

Enamines can also be formed reversibly from amines and carbonyl compounds and used as intermediates in a catalytic cycle (Scheme 181). In analogy to the well-studied reactions

Scheme 181. Enamine-Catalyzed Michael Reaction

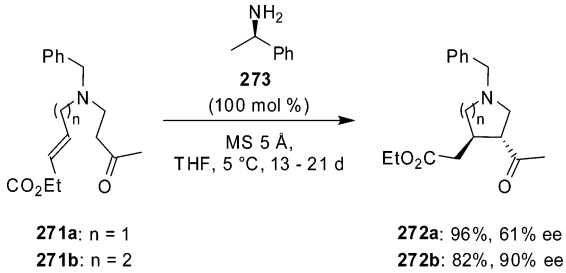


of preformed enamines, further reaction with an acceptor leads to the desired Michael adduct. Importantly, hydrolysis with in situ-generated water liberates the product and regenerates the catalyst. In the present overview, these enamine catalytic enantioselective Michael additions will be discussed.

4.2. Intramolecular Reactions

Early examples of intramolecular Michael additions catalyzed by stoichiometric amounts of chiral amines were reported by Hirai, Kozikowski, and Momose.[329−331] Hirai, Momose, and co-workers were interested in the construction of chiral building blocks for alkaloid synthesis via an asymmetric Michael reaction.[330,331] Inspired by an auxiliary-based work of Stork and Saccomano, the authors examined the intramolecular cyclization of esters **271a** and **271b** using stoichiometric amounts of chiral amines to form the corresponding enamines in situ (Scheme 182). Initial attempts with

Scheme 182. Asymmetric Intramolecular Michael Reaction Using Stoichiometric Amounts of an Amine

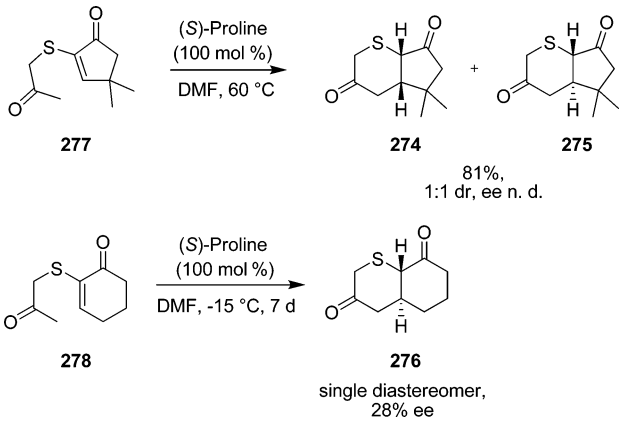


1 equiv of (*S*)-proline in DMF at room temperature furnished product **272a** in 34% enantiomeric excess (45% yield, 7 days). Under optimized conditions, (*R*)-1-phenylethylamine (**273**) was shown to be superior in terms of both yield and enantioselectivity (up to 90% ee). Additionally, the authors could recover the chiral amine **273** in quantitative yield without any loss of optical purity. To obtain a "truly" catalytic Michael reaction, only 30 mol % catalyst **273** was employed under otherwise identical conditions. However, low turnover was achieved, presumably because molecular sieves were added, preventing the hydrolysis step of the catalytic cycle.

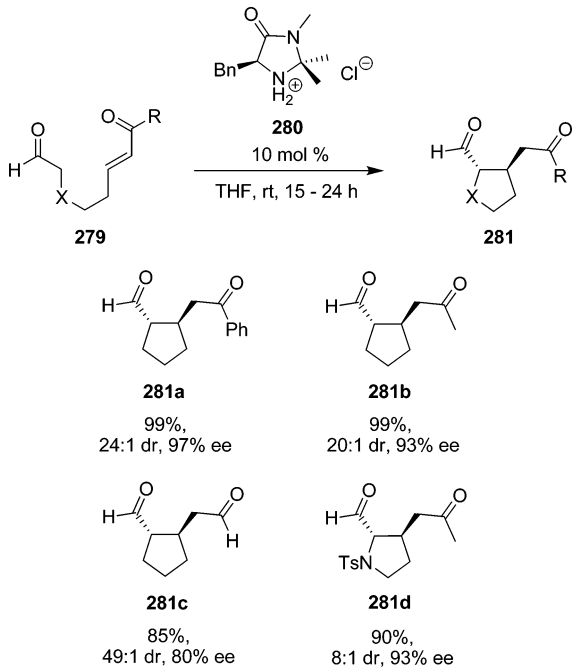
Toward the synthesis of medium-sized ring compounds, Kozikowski and Mugrage needed sulfur-containing diketones **274**−**276** in optically active form.[329] Enones **277** and **278** turned out to readily cyclize in the presence of 1 equiv of (*S*)-proline in DMF (Scheme 183). Although the enantiomeric excess of Michael adducts **274** and **275** could not be determined, ketone **276** was obtained as a single diastereomer with 28% ee.

Recently, Fonseca and List reported the first catalytic asymmetric intramolecular Michael reaction of aldehydes.[332] Formyl enones **279** were shown to readily cyclize in the presence of 10 mol % of the commercially available MacMillan imidazolidinone **280** in THF under mild reaction conditions (Scheme 184). The Michael addition furnished *trans*-disubstituted cyclic five-membered ketoaldehydes **281** in excellent yields and very good stereoselectivities (up to 49:1 dr and 97% ee). The method proved to be quite general, since aromatic enones as well as aliphatic enones could be used and even an enal furnished the desired dialdehyde **281c**

Scheme 183. Asymmetric Intramolecular Michael Reaction Using Stoichiometric Amounts of Proline



Scheme 184. Catalytic Asymmetric Intramolecular Michael Reaction of Aldehydes

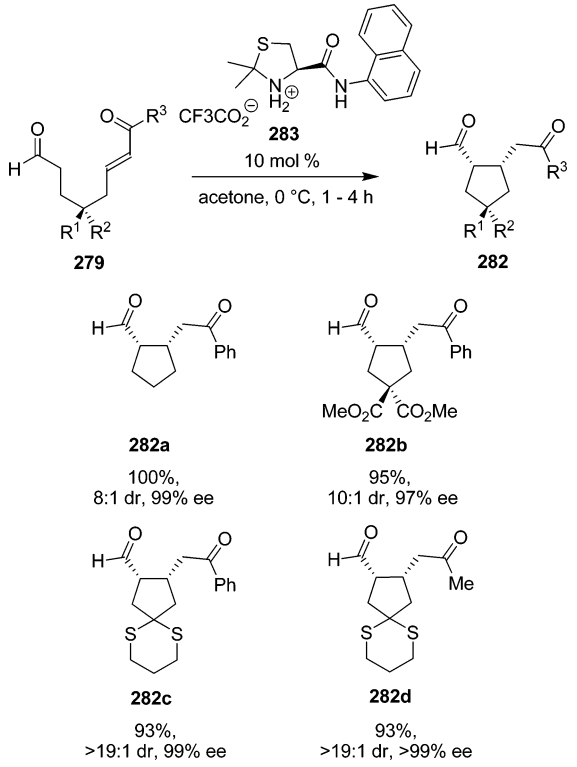


in good yield and stereoselectivity. Additionally, a heteroatom containing formyl enone was shown to give the corresponding pyrrolidine **281d**. To point out the utility of the primary Michael adducts, potential precursors for natural products could be synthesized via subsequent in situ aldol or HWE transformations. The above-mentioned Michael reaction is assumed to proceed through an enamine activation of the aldehyde followed by intramolecular 1,4-addition to the α,β-unsaturated carbonyl function. Furthermore, an inverse-electron-demand hetero-Diels−Alder mechanism toward intermediary hemi-aminals should also be considered.

List and co-workers further expanded this methodology to a catalytic highly stereoselective reductive Michael cyclization of enal enones to give *trans*-disubstituted cyclic keto aldehydes (up to >50:1 dr and 97% ee).[455] In this tandem sequence, an initial iminium catalytic nonasymmetric conjugate reduction is followed by an enamine catalytic asymmetric Michael cyclization using a single catalyst. Besides enal enones, an alkylidene malonate emerged as a suitable Michael acceptor (>50:1 dr, 86% ee).[455]

Complementarily, Hayashi and co-workers reported an enantioselective intramolecular Michael reaction of formyl

Scheme 185. Asymmetric Intramolecular Michael Reaction



enones **279**, giving *cis*-disubstituted cyclopentanes **282** as kinetic products (up to >19:1 dr, up to >99% ee) (Scheme 185).[332−334] Since these products could be completely isomerized to the thermodynamic *trans*-adducts without loss of optical purity, the method allows access to both diastereomers with very high optical purity. Pyrrolidine and imidazolidinone catalysts gave unsatisfactory results, whereas a new cysteine-derived organocatalyst **283** was found to give superior activity as well as selectivity. Importantly, both aromatic and aliphatic α,β-enones turned out to be suitable substrates. Starting from enals, the authors reported the formation of a hemi-aminal incorporating the catalyst. This suggests that a chiral enamine is involved in the reaction and that the mechanism may include an inverse-electron-demand Diels−Alder reaction.[335,336]

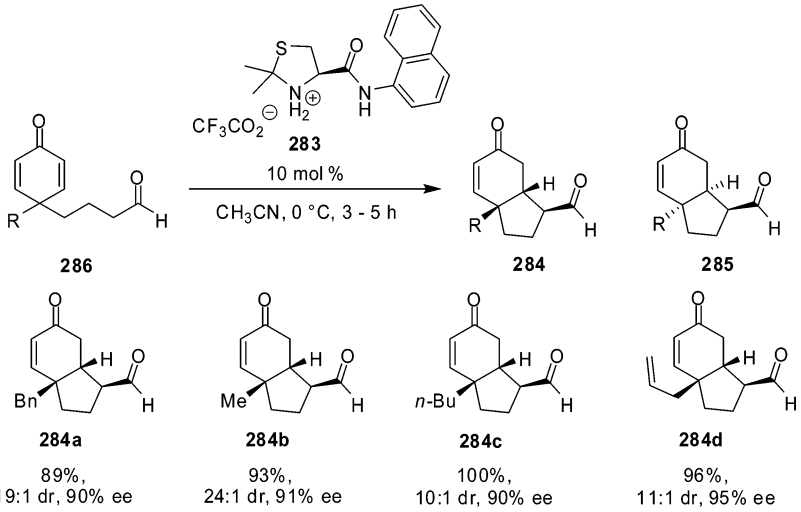
Furthermore, bicyclo[4.3.0]nonenes **284** and **285** could be synthesized from 4-substituted-4-(3-formylpropyl)cyclohexa-2,5-dien-1-ones **286** with creation of three contiguous chiral centers (up to 24:1 dr, 95% ee) (Scheme 186).[333] Only 10 mol % catalyst **283** was sufficient to promote the reaction at 0 °C in acetonitrile.

4.3. Intermolecular Reactions

4.3.1. Nitroolefins as Acceptors

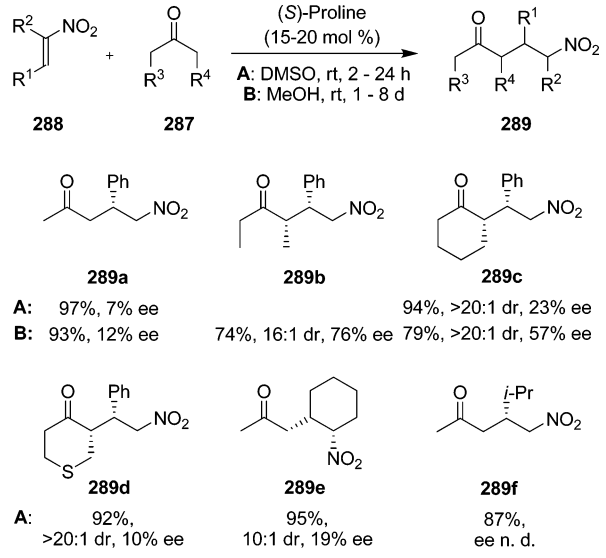
The enamine−catalytic Michael addition of carbon nucleophiles to nitroalkenes is a useful synthetic method for the preparation of γ-nitrocarbonyl compounds. Owing to the various possible transformations, for example to aminocarbonyl compounds, aminoalkanes, or pyrrolidines, 1,4-addition adducts are important precursors in organic synthesis.[337] In organocatalysis, a number of different Michael acceptors have already been used. Among them, nitroalkenes are the most prominent ones, because of their high acceptor reactivity and the possible conversion into other useful functionalities.[310]

Scheme 186. Asymmetric Intramolecular Michael Reaction



The first enamine−catalytic asymmetric intermolecular Michael reaction was developed by List et al. in 2001.[2,338] The addition of unactivated symmetric ketones **287** to nitroolefins **288** was found to proceed in the presence of catalytic amounts of (*S*)-proline in DMSO to furnish the desired γ-nitro ketones **289** in generally high yields and good diastereoselectivities but only low enantioselectivities ($\leq$23%) (Scheme 187, method A). In general, proline-catalyzed Michael reactions seem to be less enantioselective than Mannich or aldol reactions, which might be due to less efficient hydrogen bonding between the catalyst and the Michael acceptor or might be because a different mechanism is operative. This highly efficient and operationally simple process served as proof of principle for enamine catalysis of the Michael reaction.

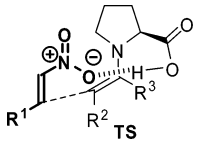
Scheme 187. Proline-Catalyzed Michael Addition of Unmodified Ketones to Nitroolefins



Barbas and co-workers reported catalytic acetone addition reactions to β-nitroolefins and alkylidene malonates in DMSO, using (*S*)-proline as catalyst. However, only racemic products were obtained.[88]

Most commonly, aprotic solvents are used in proline-catalyzed reactions. Enders et al. anticipated that alcohols, which can homogenize the reaction mixture, may be effective for this reaction by increasing the amount of dissolved proline. Indeed, the enantioselectivity of the reaction could be increased by using methanol as the solvent (Scheme 187, method B, up to 65:1 dr and 76% ee).[339] To explain the *syn*-diastereoselectivity and the absolute configuration observed, Enders et al. proposed an acyclic synclinal transition state (**TS**) based on Seebach's model (Scheme 188).[324,340] At this, all bonds around the newly formed bond are staggered, with a gauche relationship of the donor and the acceptor π-systems. Additionally, the partially positive nitrogen of the enamine and the partially negative nitro group should be situated close to each other, due to favorable elecrostatic interactions. An intermolecular hydrogen bond between the carboxylic acid moiety and the nitro group was assumed to further fix the conformation (Scheme 188).

Scheme 188. Proposed Transition State

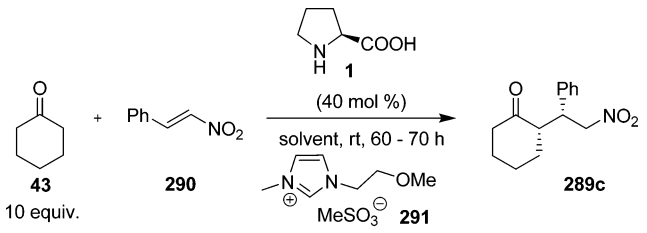


The application of ionic liquids to the Michael reaction of different aldehydes and ketones was reported by Toma and co-workers.[341] Screening different secondary amines as catalyst in ionic liquids revealed that (*S*)-proline **1** is the most active among them. Similar enantioselectivities (up to 60% ee) and diastereoselectivities (up to $\geq$25:1) were reached and shorter reaction times (1 day instead of 2−3 days) are possible compared to previously reported reactions in DMSO and methanol.

Analogously, Salunkhe et al. also investigated the proline-catalyzed asymmetric Michael-type reaction of various ketones to nitrostyrene **290** in ionic liquids.[342] Interestingly, they pointed out that the enantioselectivity was clearly enhanced in comparison to that reported in organic solvents (Scheme 189; [moemim][OMs] **291**: 1-methoxyethyl-3-methylimidazolium methanesulphonate).[338,339] The product can be obtained by simple extraction with ether, and the ionic liquid layer (containing proline) can be reused. Though the isolated yields of the products were similar to that obtained in the first run, a significant decrease of the enantiomeric excess was already observed in the second run (first run, 73% ee; second run, 47% ee; third run, 26% ee).

Diamine catalysts have also been used.[343] (*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine (**237**) was found to be an effective

Scheme 189. (*S*)-Proline-Catalyzed Asymmetric Michael Addition



solvent:	yield:	dr:	ee:
[moemim][OMs]	75%	19:1	75%
DMSO	65%	12:1	20%
MeOH	85%	19:1	50%

catalyst. Mainly applied to the addition of ketones to alkylidene malonates, the addition of cyclopentanone **60** to *trans*-β-nitrostyrene **290** was also accomplished, leading to improved results in comparison with those for (*S*)-proline (Scheme 190).

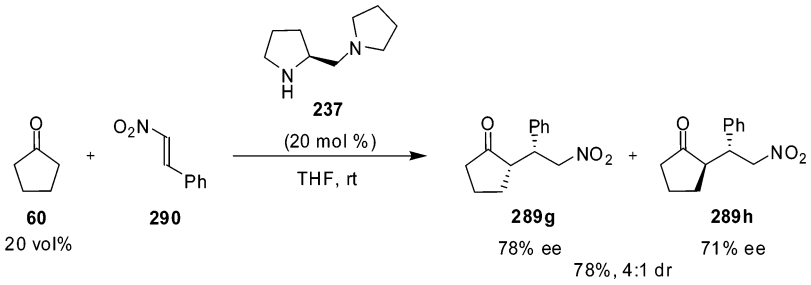
Due to the difficulty in controlling reactions of enolates or enols of aldehydes, there had been no examples of direct catalytic asymmetric conjugate additions of naked aldehydes.[344,345] The first utilization of unmodified aldehydes as donors in the catalytic asymmetric Michael reaction was accomplished by Barbas and co-workers.[346] A highly diastereoselective direct catalytic Michael reaction involving the addition of aldehydes to nitroolefins **288** was reported. Whereas proline **1** furnished the Michael adduct of isovaleraldehyde **226** and *trans*-β-nitrostyrene **290** in low yield with low enantioselectivity (<5%, 13:1 dr, 25% ee), better results were obtained using pyrrolidine-type diamine catalysts. The authors found (*S*)-2-(morpholinomethyl)pyrrolidine (**292**) as the best catalyst in terms of selectivity (78%, 12:1 dr, 72% ee). Using this catalyst, the reactions generally proceed in good yields in a highly *syn*-selective manner with moderate to good enantioselectivities (Scheme 191). For aldehydes, higher enantioselectivities were observed with increasing substituent bulk on the Michael donor in the order Me < Et < Bu < *i*-Pr (up to 49:1 dr and 78% ee).[456]

Aliphatic nitroolefins also provided Michael adducts, but in low yields, and enantioselectivities were not determined. Since isovaleraldehyde **226** was a suitable substrate and no reaction took place with the sterically more congested 3,3-dimethylbutyraldehyde, steric factors seem to play an important role. The same is true for the nitroolefins. An isopropyl substituent on the nitroolefin renders the reaction impossible (Scheme 191).[346] Furthermore, pyrrolidine itself catalyzes the Michael reaction, whereas *N*-methylpyrrolidine is ineffective. This is in agreement with the proposed enamine mechanism.

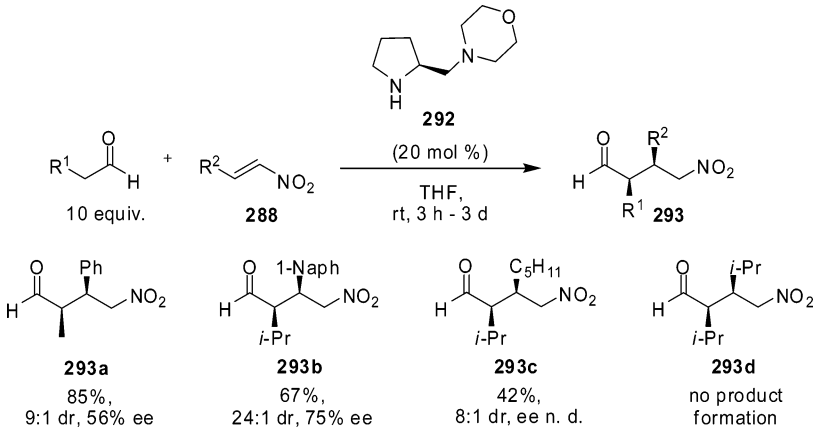
Alexakis and co-workers reported *N*-*i*-Pr-2,2′-bipyrrolidine (*i*-PBP, **294**), which was successfully used in the asymmetric Michael addition of aldehydes (symmetrical as well as unsymmetrical), ketones, and α-hydroxyketones to nitrostyrenes.[347−350] Satisfying reaction rates, even at −25 °C, and the best stereoselectivities were obtained for propionaldehyde as Michael donor (19:1 dr, 83% ee) (Scheme 192).[347] Higher aldehyde homologues reacted more slowly, and the corresponding Michael adducts were obtained in lower enantioselectvity. In a search for improved reaction conditions, they found that the hydrochloride salt of the free diamine **294** significantly improved the enantioselectivity and diastereoselectivity, whereas the reaction rate was slower (Scheme 192).[347] Later, the authors reported improved diastereoselectivities (up to 24:1) and enantioselectivities (up to 96%) for the Michael addition of different aldehydes to various nitroolefins.[349]

In contrast, acyclic ketones turned out to be more challenging substrates. The best outcome for the addition to *trans*-β-nitrostyrene (**290**) was reached with cyclohexanone (**43**) (16:1 dr, 81% ee). Acidic additives accelerated the

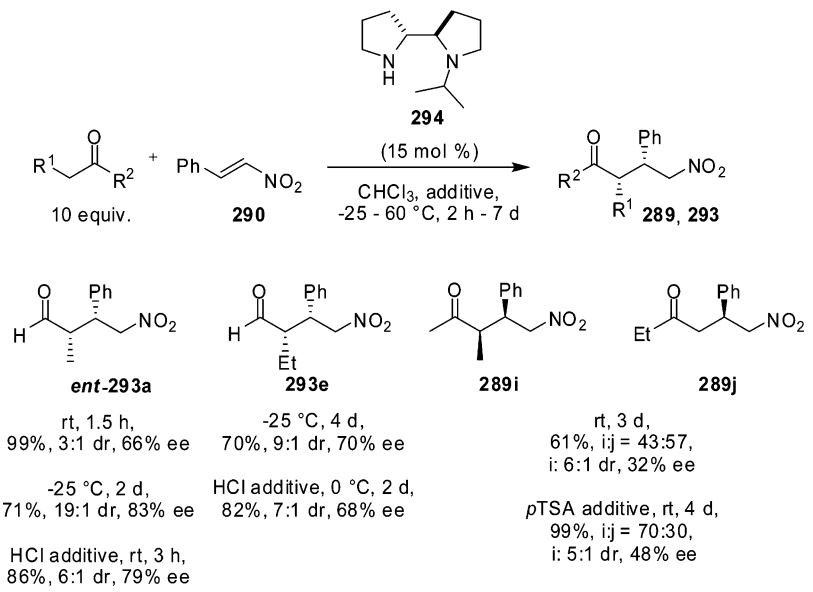
Scheme 190. Michael Reaction of Cyclopentanone



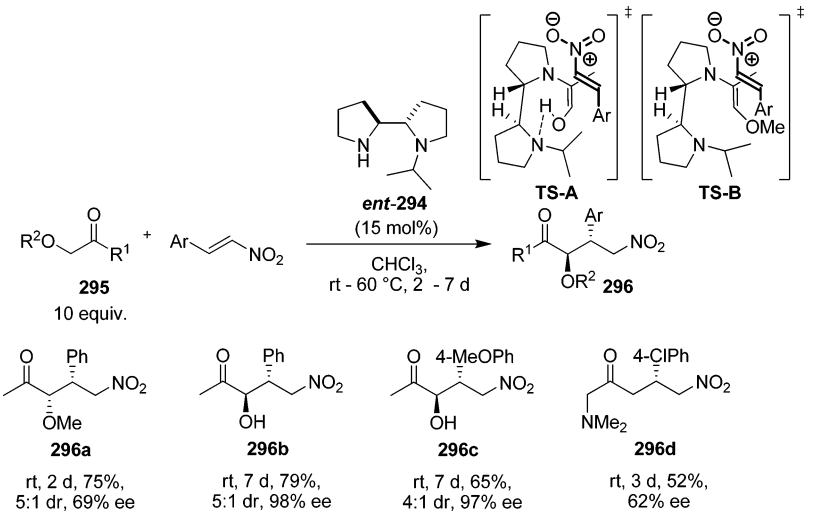
Scheme 191. Michael Addition of Unmodified Aldehydes to Nitroolefins



Scheme 192. Additive Effect in Asymmetric Michael Additions of Aldehydes and Ketones



Scheme 193. Asymmetric Michael Addition of α-Heterosubstituted Ketones to Nitroolefins



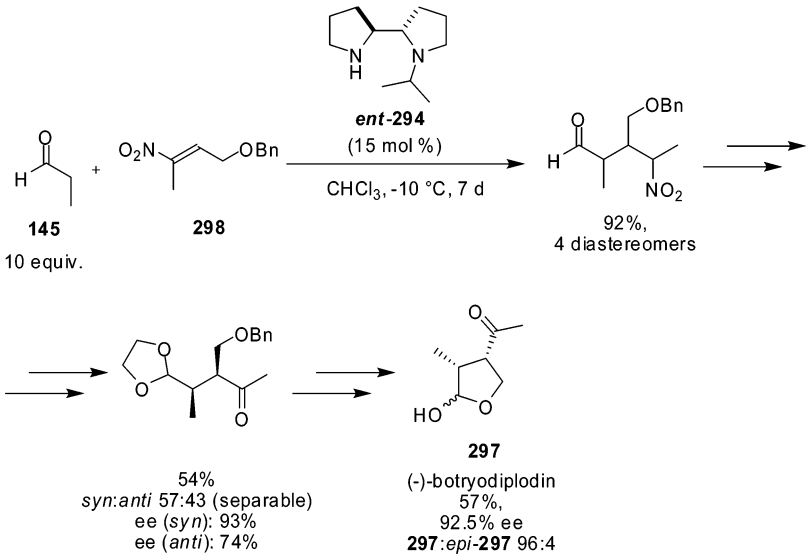
reaction by facilitating enamine formation and suppressing side reactions. Additionally, the use of *p*-toluenesulfonate or hydrochloride affected the regioselectivity for nonsymmetrical ketones (Scheme 192).[347] Again, the observed *syn*-selectivity was explained by an acyclic synclinal model with favorable electrostatic interactions between the nitro group and the nitrogen of the enamine.

To further investigate the regioselectivity problems associated with nonsymmetrical ketones, the authors decided to evaluate α-hydroxy- and α-alkoxycarbonyl compounds **295**.[348] This is the first report on organocatalytic asymmetric additions of α-hydroxyketones to nitroolefins. Interestingly, the expected *syn*-isomer was only obtained using α-methoxyacetone, whereas α-hydroxyacetone yielded mainly the unexpected *anti*-isomer. This was explained by an additional hydrogen bond between the OH group of the substrate and the tertiary amine of the catalyst which leads to the *cis*-instead of the *trans*-enamine (see **TS-A** and **TS−B** in Scheme 193). In general, the products were obtained in excellent enantioselectivities (Scheme 193). When the oxygen is replaced by the nitrogen of the dimethylamino group, linear addition products were obtained. The balance between steric effects and acidity presumably favors the terminal enamine formation (Scheme 193).[349]

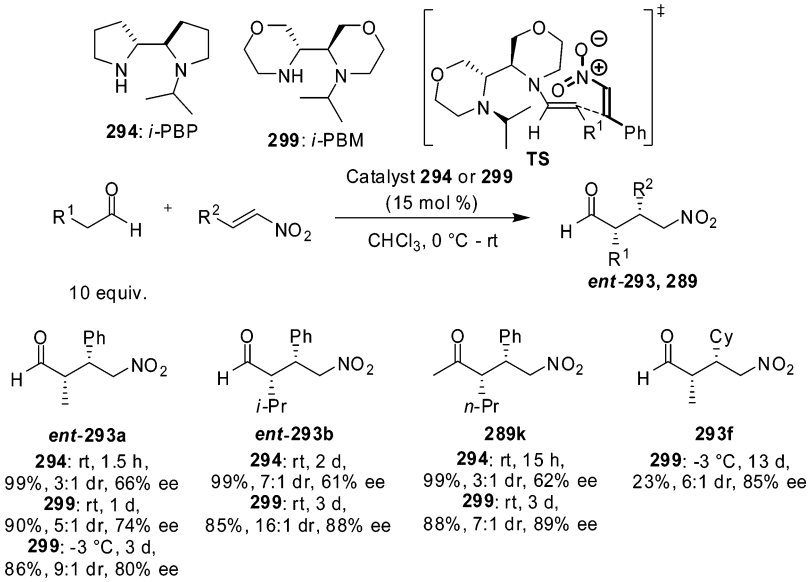
To demonstrate the potential of organocatalysis in asymmetric total synthesis, Alexakis and co-workers described the first enantioselective synthesis of (-)-botryodiplodin (**297**) (Scheme 194).[351] The asymmetric Michael addition of propionaldehyde (**145**) to (2*E*)-(3-nitrobut-2-enyloxymethyl)-benzene (**298**) served as the key step, using the previously reported *N*-*i*-Pr-2,2′-bipyrrolidine (*i*-PBP) ***ent*-294** catalyst.

In order to make the reaction more efficient and viable, Mossé and Alexakis investigated microwave heating.[352] By applying constant microwave irradiation (15 W) and simultaneous air cooling, reaction times and, most importantly, catalyst loadings could be reduced. For example, complete conversion of hydroxyacetone and *trans*-*β*-nitrostyrene occurred within 4 h instead of 7 days (Scheme 193), giving the corresponding product in 83% yield without loss of selectivity. Similiar results were obtained using isovaleraldehyde and isobutyraldehyde as Michael donors, showing that microwave irradiation seems to be general with regard

Scheme 194. Asymmetric Synthesis of (−)-Botryodiplodin



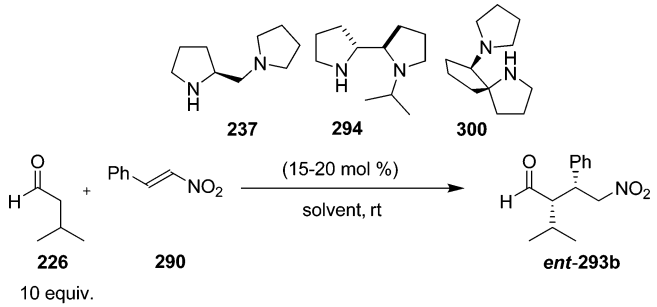
Scheme 195. 3,3′-Bimorpholine Derivative as a New Organocatalyst



to Michael donors. Moreover, the catalyst loading could be decreased from 15 to 5 mol %, maintaining good reactivity and selectivity.

A new class of efficient six-membered ring organocatalysts was recently applied by Alexakis and co-workers.[353] In analogy to the previously reported chiral pyrrolidine-type catalyst *i*-PBP **294**, the new *N*-*i*Pr-3,3′-bimorpholine catalyst (*i*-PBM) **299** also promotes the asymmetric direct Michael addition of aldehydes to nitroolefins (Scheme 195). Moderately hindered aldehydes proved to be suitable substrates in terms of conversion and stereoselectivity (100% conversion, up to 19:1 dr and 90% ee), whereas bulkier aldehydes such as isobutyraldehyde and 3,3-dimethylbutyraldehyde did not react with *trans*-*β*-nitrostyrene (**290**). Irrespective of the nitroolefin, good stereoselectivities were obtained and, except for aliphatic nitroolefins, the yields were generally good. The newly reported *i*-PBM (**299**) showed better performance in the asymmetric Michael addition of various aldehydes to nitroolefins in comparison to *i*-PBP (**294**) (Scheme 195).[347,353] A transition state **TS** was proposed in which the isopropyl group promotes the selective formation of the *anti*-enamine. Hence, the *si*−*si* transition state should be favored, leading to the *syn*-adduct.

Scheme 196. Chiral Diamines as Catalysts for Michael Reaction

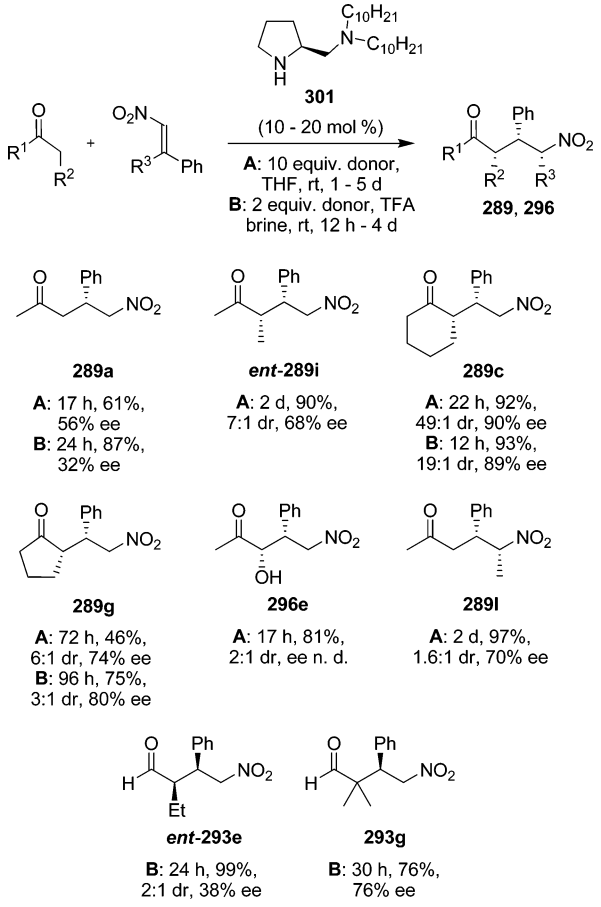


Inspired by Alexakis results and reports by Barbas et al.,[346] Royer and co-workers envisioned preparing similar catalysts containing a constrained structure (Scheme 196, **300**).[354] Focusing on the access to a new rigid bi-pyrrolidine, the authors prepared catalyst **300**, whose efficiency was tested in the addition of isovaleraldehyde (**226**) to *trans*-*β*-nitrosty-

rene (**290**). The corresponding γ-nitro aldehyde ***ent*-293b** was obtained in poor diastereoselectivity but encouraging enantioselectivity under nonoptimized conditions (1.4:1 dr, 47% ee).

Previous success using pyrrolidine-based chiral diamine catalysts has prompted Barbas et al. to explore other diamines and to show the full scope of the aldehyde and ketone addition to nitroolefins.[343,346,456] Generally, (*S*)-proline and analogues lacking the tertiary amine were less effective catalysts. Superior results for the ketone addition to *trans*-β-nitrostyrenes (**290**) in THF were obtained with the new catalyst **301** (Scheme 197). Whereas cyclic ketones turned out to be good substrates, with cyclohexanone and cyclopentanone giving reasonable yields and high enantioselectivities, the reaction with cycloheptanone was sluggish (after 5 days, 32%, 7:1 dr, 53% ee). Interestingly, *trans*-β-methyl-β-nitrostyrene (**302**) was also used as an acceptor. The product, bearing a stereogenic center α to the nitro group, was obtained in high yield with poor diastereoselectivity (1.6:1 dr, Scheme 197).

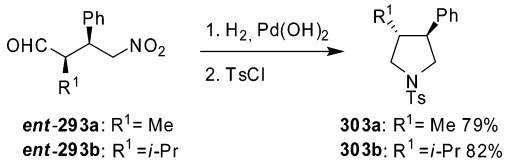
Scheme 197. Addition of Ketones and Aldehydes to Nitroolefins



The same hydrophobic catalyst (**301**) has also been used for the asymmetric direct Michael reaction of ketones and aldehydes with *trans*-β-nitrostyrene in brine (Scheme 197).[457] Initial attempts showed a similar conversion in pure water and in brine but significantly lower isolated yields due to an amine initiated polymerization of the nitroolefin. Hypothesizing that the anion intermediate could be stabilized by metal complexation the authors found that polymer propagation can be inhibited in brine, and addition of TFA further improved the yield by facilitating the enamine formation. Using brine as the only reaction medium, 10 mol % diamine **301**/TFA at room temperature afforded the expected *syn*-Michael adducts with high yields and excellent stereoselectivities for cyclohexanone and tetrahydrothiopyran-4-one (up to 49:1 dr, 97% ee), whereas somewhat reduced stereoselectvities were obtained for α,α-disubstituted aldehydes (up to 1.5:1 dr, 76% ee) (Scheme 197). Catalyst **301** turned out to be less efficient for α-substituted aldehydes and acetone (up to 38% ee). Similar or slightly lower stereoselectivities were obtained to those in organic solvents (Schemes 197 and 199).[456,458] Importantly, only 2 equiv of the carbonyl compounds had to be used and a multigram-scale synthesis revealed the practicability of the process, since no washing or chromatography was necessary to obtain the pure product.

Furthermore, the 2,3-disubstituted γ-formyl nitro Michael adducts ***ent*-293a−b** were shown to be easily converted to substituted pyrrolidines **303** (Scheme 198), as had been previously shown by List et al. using analogous γ-nitro ketones.[456,459]

Scheme 198. Hydrogenation of Optically Active γ-Formyl Nitro Compounds

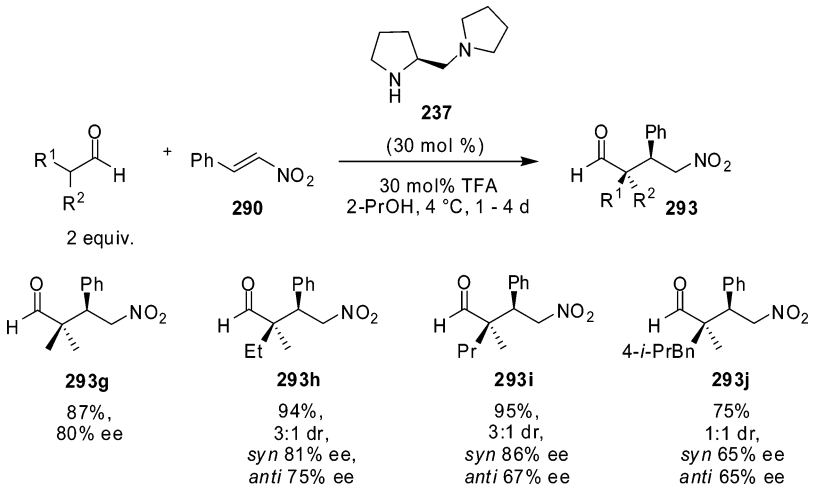


Other interesting and particularly noteworthy aldehyde donors are α,α-dialkylaldehydes. Barbas and co-workers showed that Michael adducts bearing an all-carbon quaternary stereogenic center are formed in moderate diastereoselectivities and with good enantioselectivities (up to 91% ee) (Scheme 199).[458] This is the first application of α,α-dialkylaldehydes as donors in asymmetric organocatalytic Michael reactions. Before, this substrate class had been used by Bräse in α-aminations.[355] The addition of a Brønsted acid slightly improved the enantioselectivity but prolonged the reaction time. This is in contrast to previously reported aldol reactions,[460] in which the enantioselectivity and activity of the catalyst were dramatically increased. (*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine (**237**), in combination with an equal amount of TFA, turned out to be the best catalyst system (Scheme 199).

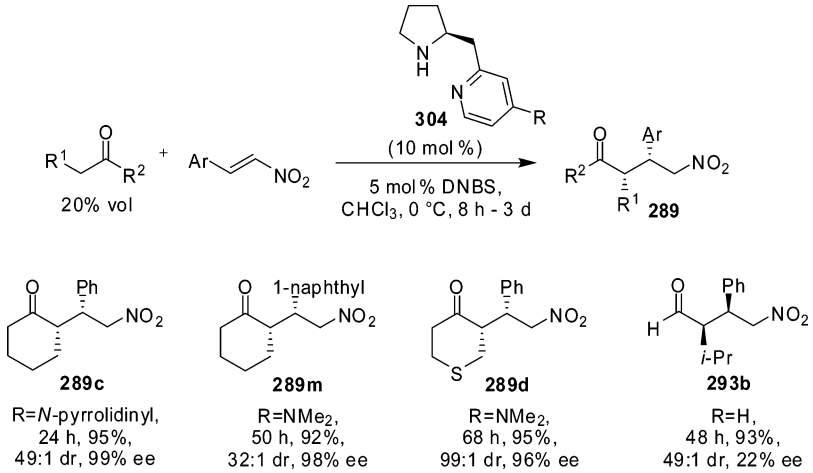
In search of new chiral catalysts and additives, Kotsuki and co-workers designed pyrrolidine−pyridine conjugate base catalysts **304**, which are easily prepared from (*S*)-prolinol and are effective for the asymmetric Michael addition reaction of ketones to nitroolefins.[356] They anticipated that incorporation of a pyridine moiety in close proximity to the pyrrolidine function should facilitate the enamine formation from ketone precursors and efficiently shield one side of the enamine double bond. Indeed, the reaction conducted in chloroform as a solvent at 0 °C proceeded with exceptionally high yields, diastereoselectivities (up to 99:1), and enantioselectivities (up to 99%) for cyclohexanone and tetrahydrothiopyran-4-one, but only with modest enantioselectivity in the case of aldehydes (isovaleraldehyde, 22% ee) (Scheme 200). As had been shown before, an acid additive was needed to improve the catalytic activity.[116,117,347,357]

Tetrazoles are commonly used as bioisosteres for carboxylic acids due to their increased solubility and the similarity in pK_a. The combination of the pyrrolidine core with a tetrazole moiety as an organocatalyst **102** for asymmetric

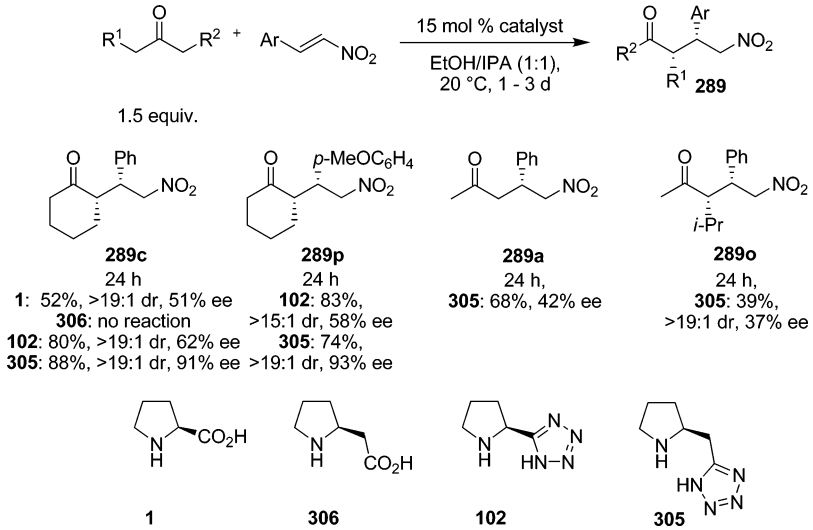
Scheme 199. Asymmetric Organocatalytic Michael Reaction of α,α-Disubstituted Aldehydes



Scheme 200. Pyrrolidine−Pyridine Conjugate Base Catalysts for Use in Asymmetric Michael Addition Reactions

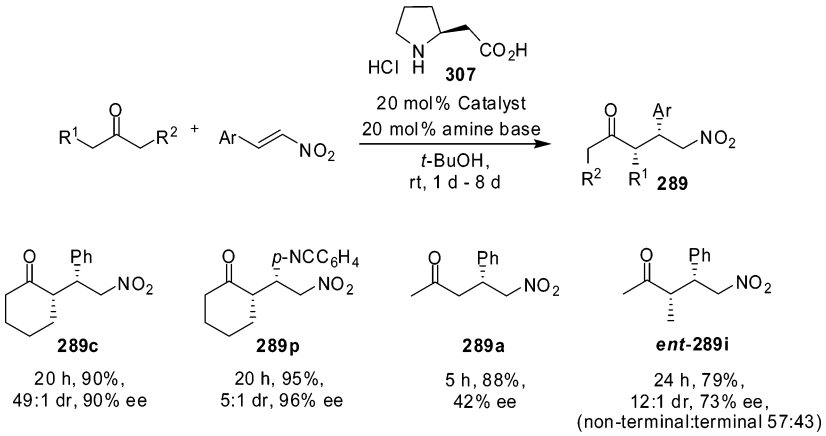


Scheme 201. Tetrazole Organocatalysts for the Addition of Ketones to Nitroolefins



Michael reactions was introduced by the group of Ley.[135,461] Due to the higher solubility of this "modified proline" catalyst, a greater range of solvents can be used. In the presence of tetrazole **102**, the authors were able to achieve the asymmetric Michael addition of a ketone to aromatic nitroolefins in a 1:1 mixture of ethanol and isopropanol (Scheme 201, **102**). The reactions proceeded in moderate to good diastereoselectivities (up to >19:1) and moderate enantioselectivities (up to 73%), and the best results were observed for cyclic ketones. Nevertheless, in alcoholic solvents, this catalyst is more active than (*S*)-proline (Scheme 201). The authors suggest this to be the result of differences in hydrogen bonding strengths, or they suggest the increased size of the tetrazole moiety to be responsible. Most importantly, the amount of ketone could be reduced to 1.5 equiv without affecting the outcome of the reaction; lowering the catalyst loading had little effect on the enantioselectivity but decreased the yield significantly.

Scheme 202. (*S*)-Homoproline-Catalyzed Michael Addition Reaction

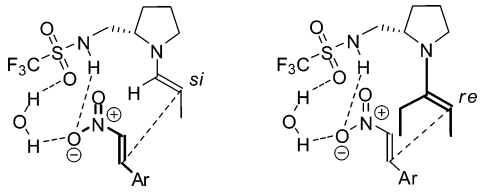


Inspired by these results, the preparation of a new homoproline tetrazole derivative **305** was undertaken.[358] Compared to tetrazole **102**, this new catalyst gave similiar diastereoselectivities and higher enantioslectivities (up to 93% ee) in the Michael addition of ketones to aromatic nitroolefins (Scheme 201, **305**). Two possible transition states were discussed accounting for the improved enantioselectivity. Most likely, the facial bias is more efficiently induced by the more bulky homo-tetrazole side chain.[358]

No reaction has been observed using (*S*)-homoproline (**306**) itself (Scheme 201).[358] However, Oriyama could show that (*S*)-homoproline hydrochloride (**307**) in the presence of a base (NEt_3 or morpholine) efficiently catalyzes the addition reaction of ketones to β-nitrostyrene and its derivatives (up to 49:1 dr and 96% ee) (Scheme 202).[359] Again, alcohols turned out to be the solvents of choice in terms of both chemical yield and stereoselectivity. The influence of substituents on aromatic nitroolefins was negligible. The best results were obtained using symmetrical cyclic ketones, whereas the regioisomeric ratios were moderate in the case of unsymmetrical acyclic ketones (nonterminal−terminal up to 61:39).

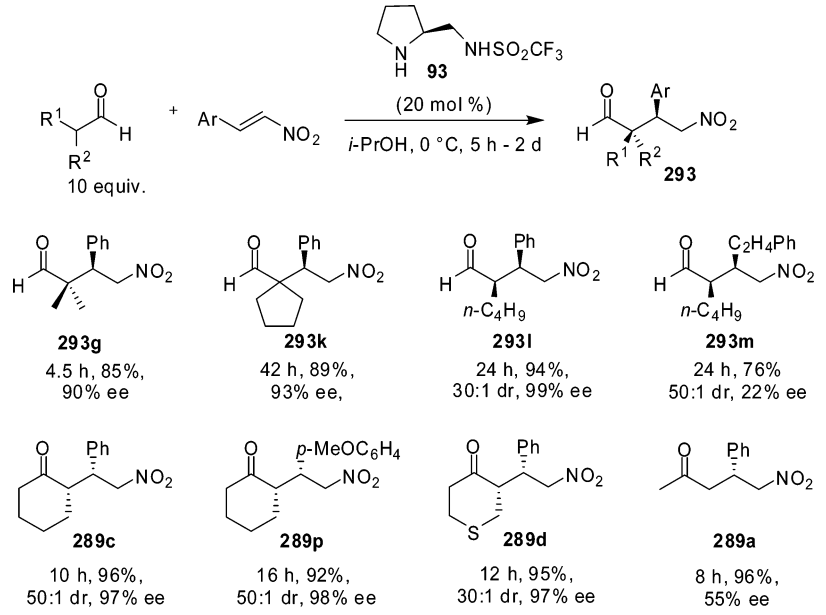
Pyrrolidines containing sulfonamides were also found to be active catalysts for the asymmetric conjugate additions of aldehydes to nitrostyrenes. Wang et al. described pyrrolidine sulfonamide **93** as an efficient catalyst for α-aminoxylation, α-sulfenylation, α-selenenylation, and also aldol, Mannich, and Michael reactions.[360] Based on calculations, the authors proposed transition states for the rate-limiting C−C bond forming steps in which the preferential (*E*)-enamines of both aldehydes and ketones would add to the less hindered face of a nitroolefin (Scheme 203). Lower

Scheme 203. Proposed Transition States



energy barriers for the *si*-face attack in reactions of aldehydes (leading to 2*R*,3*S* products) and for *re*-face additions in reactions of ketones (leading to 2*S*,3*R* products) were calculated, which is in agreement with the experimental results (Scheme 204).[361] The authors found by DFT calculations higher rate-limiting reaction barriers for *syn*-enamines than for *anti*-enamines. Consequently, only the *anti*-enamine conformers are presented (Scheme 203). This is consistent with studies on proline-catalyzed aldol reactions but in

Scheme 204. Pyrrolidine Sulfonamide-Catalyzed Michael Addition to Nitrostyrenes

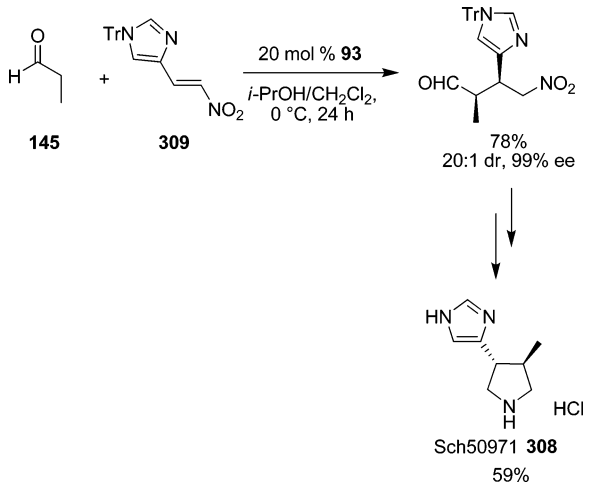


contrast to previously evaluated Michael reactions via *syn*-enamines.[347,356,456]

With 20 mol % catalyst **93** in *i*-PrOH at 0 °C, the α-alkyl as well as α,α-dialkyl aldehyde-derived Michael adducts were typically obtained in good yields (up to 99%) with excellent diastereoselectivities (≥20:1, up to 50:1 dr) and excellent enantioselectivities (up to 99% ee) (Scheme 204).[360] Additionally, the reactions of both symmetrical cyclic ketones (up to 50:1 dr, up to 99% ee) and acyclic ketones (up to 50:1 dr, up to 93% ee) with aromatic nitroolefins demonstrate that (*S*)-pyrrolidine trifluoromethanesulfonamide **93** can catalyze the reaction of a wide range of Michael donors in high diastereo- and enantioselectivities (Scheme 204).[361]

Wang's catalyst **93** was also successfully employed in the synthesis of the potent H_3 agonist Sch50917 **308**, previously prepared by applying an Evan's auxiliary controlled Michael reaction.[362] A route to this target was designed with the stereoselective addition of propionaldehyde **145** to nitroolefin **309** as a key step (Scheme 205).

Scheme 205. Synthesis of Sch50971 308

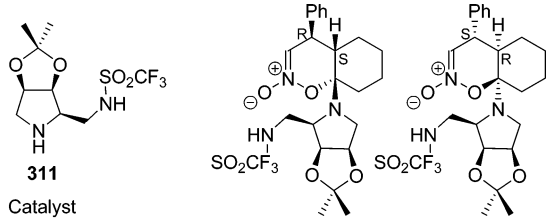


Based on their previous achievements, the authors recently developed a recyclable and reusable chiral fluorous pyrrolidine sulfonamide containing a more lipophilic and strongly electron withdrawing fluorous tag (*n*-C_4F_9 group) for catalyzing the Michael addition of ketones and aldehydes to nitroolefins.[462] Remarkably good results were obtained in water at room temperature (up to 50:1 dr, up to 95% ee), although the stereoselectivities were slightly lower compared to previous results achieved in organic solvents.[360,361] The catalyst was shown to be readily separated (>90%) by fluorous solid-phase extraction and was reused four times without significant loss of activity and stereoselectivity.

Recently, Enders and Chow evaluated different proline-based catalysts for the addition of 2,2-dimethyl-1,3-dioxan-5-one (**129**) to various nitroalkenes (Scheme 206).[179,363] Initial investigations revealed pyrrolidine sulfonamide **93**, previously used by Wang et al., as the catalyst of choice. The addition of water accelerated the reaction and furnished higher yields. Generally, a long reaction time was needed and the desired products were obtained in high *syn*-selectivity and good enantioselectivities (77−86% ee), but only in moderate yields (Scheme 206). Accordingly, the reaction did not proceed with sterically more demanding aliphatic nitroalkenes (R^1 = *i*-Pr, *t*-Bu).

A modified pyrrolidine sulfonamide catalyst **311** was reported by Diez and Broughton (Scheme 207).[364] Since

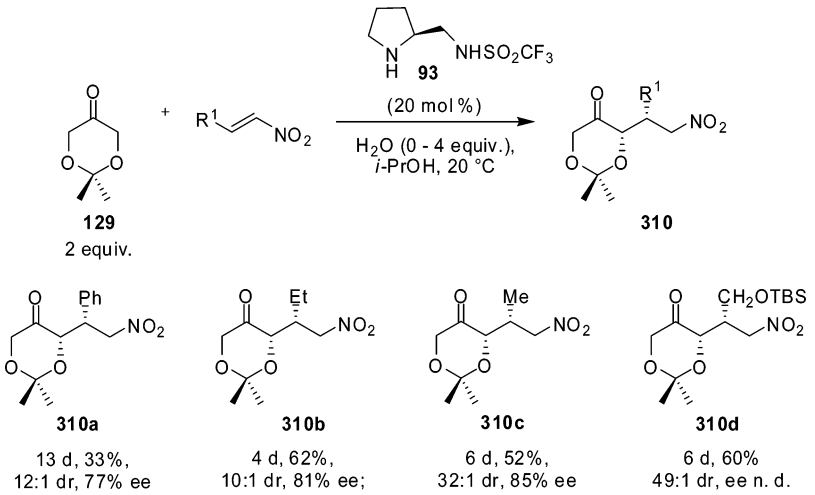
Scheme 207. Energies of the Putative Intermediates with Solvent Model for Chloroform



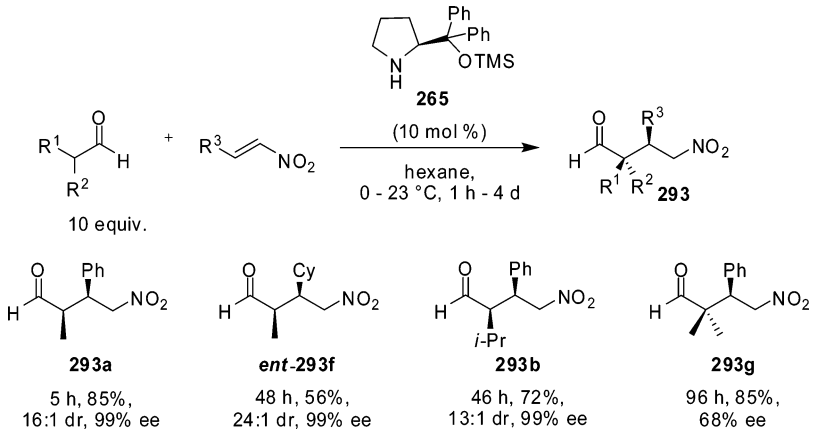
SCF energy (hartrees)	-2208.1774	-2208.1674
Zero point energy (kcal/mol)	350.1	350.3
Gibbs free energy $Gtot_{298}$	-2207.6839	-2207.6734
Free energy relative to minimum (kcal/mol)	0	6.7

Wang's catalyst was mainly used in isopropanol, the authors envisioned to increase the solubility of the catalyst in nonpolar solvents without affecting the acidity of the sulfonamide in order to obtain superior results. Indeed, in the presence of 15 mol % catalyst **311** in chloroform as the solvent at room temperature, they could obtain ketone-derived Michael adducts in moderate yields with excellent diastereoselectivities (>32:1 dr) and moderate to good enantioselectivities (up to 94% ee). Cyclic six-membered ketones and ethyl methyl ketone proved to be the best

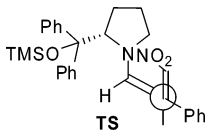
Scheme 206. Michael Addition of Dioxanone 129 to Nitroalkenes



Scheme 208. Diphenylprolinol Silyl Ether as Organocatalyst for the Asymmetric Michael Reaction



Scheme 209. Transition State Model



Michael donors, whereas acetone gave diminished enantioselectivity (20% ee).

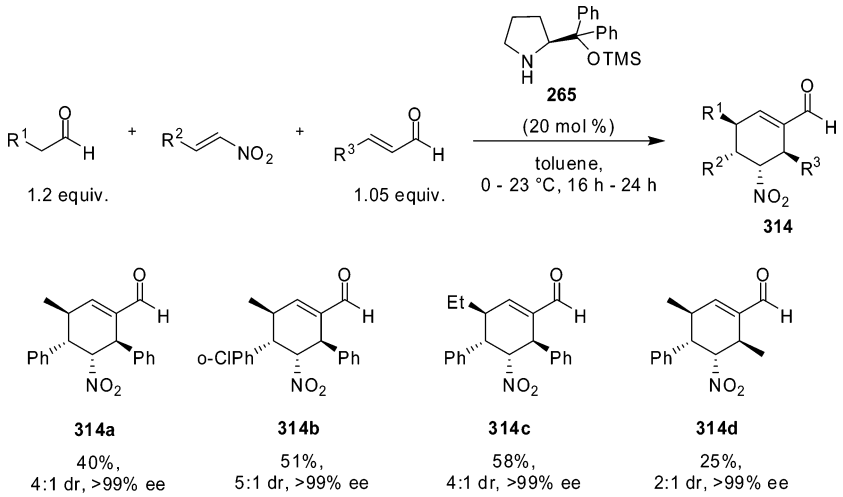
A detailed molecular modeling study, leading to the proposal of Diels−Alder-type intermediates, was included. Studying the addition process of the enamine derived from catalyst **311** and cyclohexanone to nitrostyrene, geometry optimization gave rise to unexpected cyclic intermediates **312** and **313** (Scheme 207). Such cyclic intermediates are known, but only compounds where the nitroolefin is α-substituted could be isolated.[365] In cases without an α-substituent, the mechanism either could be a simple Michael addition or could involve a rapid breakdown of the cyclic intermediates. However, Diez and Broughton reasoned that the cyclic structures are possible intermediates which could be stabilized by a hydrogen bond between the sulfonamide and the nitro group. Although this could not be proven unequivocally, the experimental stereochemical outcome (nonpolar media, absolute configuration, high diastereoselectivity) was consistent with the proposed Diels−Alder-type intermediates, in particular with the calculated preference for the *S*,*R*-product (**312**, Scheme 207). The idea of a change of mechanism may be further supported by the fact that the results in chloroform are superior to those in isopropanol.

Using the diphenylprolinol silyl ether **265**, Hayashi and co-workers developed a highly enantioselective Michael reaction of aldehydes and nitroolefins.[366,367,463] Though diphenylprolinol itself also catalyzes the Michael reaction of propanal and nitrostyrene in high enantioselectivities (23 °C, 24 h, 29%, 6:1 dr, 95% ee), the catalytic activity and enantioselectivity were dramatically increased by forming the corresponding more soluble silyl ether **265** (23 °C, 1 h, 82%, 6:1 dr, 99% ee). Catalyst **265** is easily prepared from diphenylprolinol, and the products of α-monosubstituted aldehydes were obtained in nearly optically pure form (99% ee) (Scheme 208). A limitation is the application of α,α-disubstituted aldehydes, since the products were obtained with inferior stereoselection. Interestingly, both aryl- and alkyl-substituted nitroalkenes are suitable Michael acceptors.

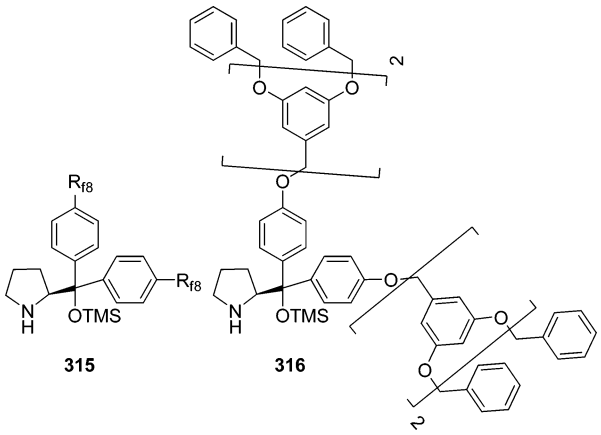
An acyclic synclinal transition state **TS** was proposed, involving an electrostatic interaction between the nitrogen of the enamine and the nitro group.[340] The bulky diphenylsiloxymethyl group affects the selective formation of the *anti*-enamine and efficiently shields the *re*-face of the enamine (Scheme 209).

Later on, Enders and co-workers developed a chemo- and stereoselective three-component domino reaction leading to tetrasubstituted cyclohexane carbaldehydes using the same catalyst **265** (Scheme 210).[368] In the course of the reaction, three carbon−carbon bonds were formed consecutively, starting with the activation of linear aldehydes by enamine formation, which then add to various nitroalkenes.

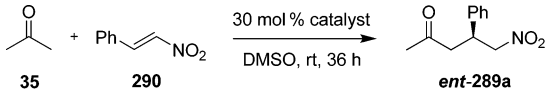
Scheme 210. Triple Cascade Organocatalytic Reaction



Scheme 211. Recyclable Catalysts



Scheme 212. *N*-Terminal Prolyl Peptide-Catalyzed Michael Reaction



Pro-Val (**317**): 65%, 31% ee
Proline (**1**): 97%, 7% ee

Very recently, Wang and co-workers developed a recyclable and reusable diphenylprolinol TMS ether containing two R_{f8} fluorous tags (n-C_8F_{17}) (**315**, Scheme 211).[464] Compared with Hayashi's previous results,[366] the Michael adducts of aldehydes were obtained with similar stereoselectivities (up to 29:1 dr, 97 to >99% ee) using 20 mol % of the modified fluorous organocatalyst in trifluoromethylbenzene. The catalyst was shown to be readily recovered (>90%) and reused without significant loss of activity and stereoselectivity.

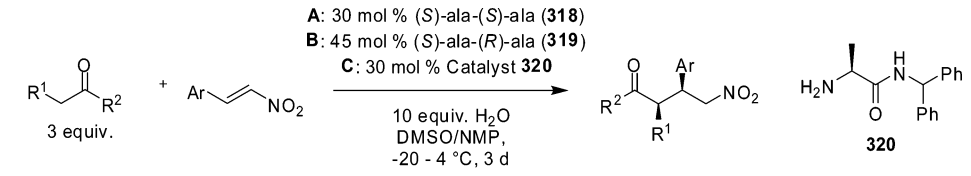
Along those lines, Zhao and co-workers developed a recyclable diphenylprolinol TMS ether-based dendritic catalyst **316** for the asymmetric Michael addition of aldehydes to nitrostyrenes (10 mol % **316**, up to 19:1 dr and 99% ee) (**316**, Scheme 211).[369] The catalyst was easily separated from substrates and products through precipitation and could be reused five times with only a slight loss of activity.

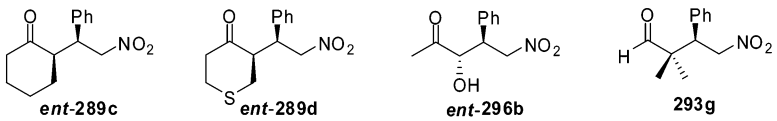
That *N*-terminal prolyl peptides efficiently catalyze enantioselective Michael reactions between acetone (**35**) and *trans*-β-nitrostyrene (**290**) was shown by List and Martin.[159] Though only modest enantioselectivites were observed (up to 31% ee), these enantioselectivities constitute an improvement compared to those of proline-catalyzed Michael reactions in DMSO (Scheme 212).[338]

Later on, Córdova and co-workers demonstrated that simple di- and tripeptides derived from alanine with a primary amine residue can catalyze the direct asymmetric Michael addition of ketones and aldehydes to nitroolefins.[370] *N*-Terminal alanyl peptides with increased structural complexity as compared to the parent amino acid provided superior reactivity and stereoselectivity. Again, the best stereoselectivities were obtained with symmetrical cyclic six-membered ketones as the donors (dr's ≥ 12:1, ee's ≥ 90%), whereas diminished results were obtained with symmetrical cyclic five-membered ketones, acyclic ketones, and aldehydes (Scheme 213, **A** and **B**). It turned out that the acid moiety of the dipeptide was crucial to achieve reasonable yields. Both the acid and the amide moiety are supposed to assist in the stabilization of the transition state, and the addition of a small amount of water not only increases the observed yield but also facilitates hydrogen bonding, which improves the stereoselectivity. Moreover, they could also show that simple linear amino acid amides catalyze the direct asymmetric addition of ketones to aromatic nitroolefins, giving similar results (Scheme 213, (*S*)-alanine amide **320**, up to >38:1 dr, up to 99% ee).[371] In this case, the addition of a small amount of a Brønsted acid additive accelerated the reactions.

Gong et al. reported triamine **321**, which emerges to be an efficient catalyst for the Michael addition of cyclic ketones to nitroolefins.[372] Triamine **321** contains a diamine substructure, previously used for the addition of ketones and aldehydes to aromatic nitroolefins.[346,456,458] The authors reasoned that the larger substituent on the pyrrolidine core should occupy a larger space to more efficiently shield one side of the enamine. As has been already reported, the usage of an acidic additive enhanced the catalytic activity (Scheme 214).[347,356] Performing the reaction in toluene at 0 °C, the Michael adducts derived from symmetrical cyclic six-membered ketones were obtained in good yields and with good to excellent stereoselectivities (up to 49:1 dr, up to 91% ee) (Scheme 214). Modification of the aromatic nitroolefin had no remarkable effect on the stereochemical outcome. In the cases of tetrahydropyran-4-one and tetrahydrothiopyran-4-one, somewhat lower enantioselectivities were observed (Scheme 214).

Scheme 213. Primary Amine-Catalyzed Asymmetric Michael Reaction





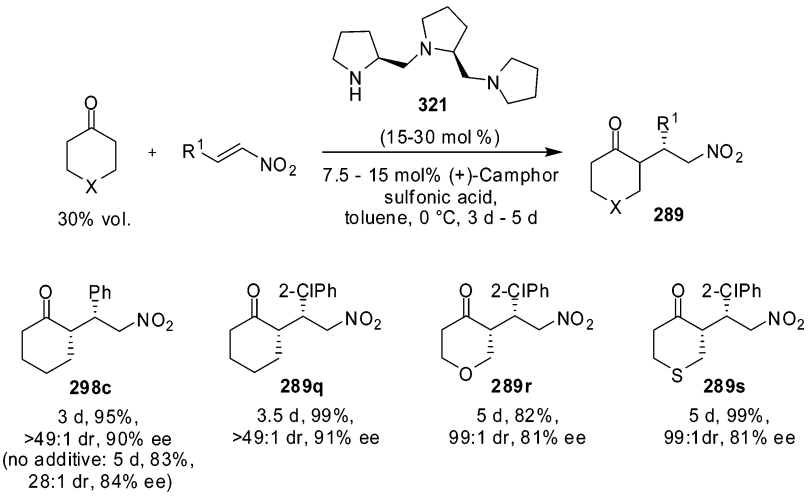
A: 67%, 22:1 dr, 91% ee
B: 62%, 17:1 dr, 97% ee
C: 15 mol % *p*-TsOH 92%, 27:1 dr, 93% ee

B: 66%, 25:1 dr, 98% ee
C: 45%, 38:1 dr, 99% ee

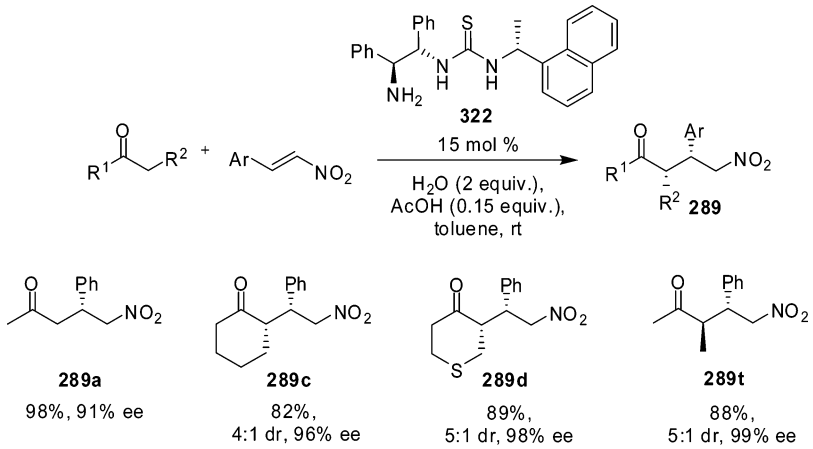
A: -20 °C, 23%, 1:2 dr, 40% ee
A: 4 °C, 60%, 1:2 dr, 29% ee
C: 15 mol % *p*-TsOH 83%, 1:2 dr, 27% ee

B: 57%, 58% ee

Scheme 214. Michael Addition of Cyclic Ketones to Nitroolefins



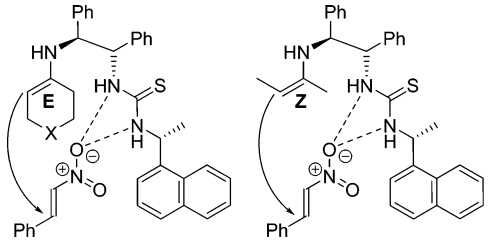
Scheme 215. A Thiourea-Amine-Catalyzed Addition of Ketones to Nitroolefins



Tsogoeva, Schmatz, and co-workers reported primary amine-derived chiral thiourea catalysts.[373,374] They demonstrated that these catalysts catalyze the Michael reaction of nonactivated ketones to aromatic nitroolefins via enamine intermediates. While a proline-based chiral thiourea gave the Michael adducts in racemic form and low yields, outstanding activity as well as selectivity was observed for thiourea **322**, bearing a primary amine, for a wide range of ketones and aromatic nitroolefins (82−99%, up to 6:1 dr, up to 99% ee) (Scheme 215). Inspired by the fact that the imine formation is accelerated by acidic additives and that water plays an important role in the regeneration of the catalyst, the authors examined various additives. Finally, the addition of 0.15 equiv of acetic acid and 2 equiv of water significantly improved the catalytic activity and slightly increased the enantioselectivity (Scheme 215).

The thiourea moiety of bifunctional organocatalyst **322** presumably interacts with a nitro group via hydrogen bonding, whereas the primary amine group forms an enamine (Scheme 216). Enamine formation of catalyst **322** and acetone could be detected by ESI-MS. Furthermore, it was shown that the 1,2-diphenylethylenediamine alone does not act as an efficient catalyst in the presence of acetic acid. The authors proposed plausible transition states to explain the diastereoselectivity (*anti* for ethyl methyl ketone, otherwise *syn*) and the absolute configuration observed (Scheme 216). Cyclic ketones capable only of forming (*E*)-enamines afforded *syn*-products, whereas the acyclic ethyl methyl ketone presumably reacts via a (*Z*)-enamine to give the *anti*-

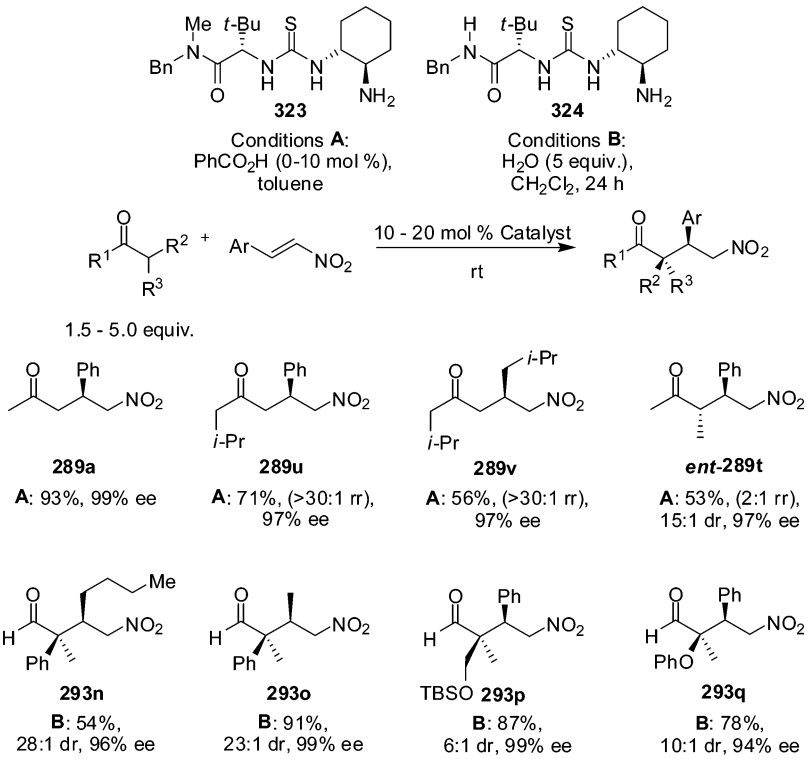
Scheme 216. Proposed Transition States for the Michael Reaction of Symmetrical and Nonsymmetrical Ketones



Michael product. Additionally, their results suggest that only one oxygen atom of the nitro group is bound to the thiourea moiety.[373]

Huang and Jacobsen also reported direct conjugate additions of ketones to nitroalkenes promoted by a similar primary amine thiourea catalyst **323**.[375] While reactions performed in polar and/or protic solvents proceeded slowly, nonpolar solvents and high concentrations turned out to be beneficial. A broad range of acyclic ketone substrates as well as both aromatic and aliphatic nitroolefins furnished the desired Michael adducts with remarkable *anti*-selectivity (up to 20:1 dr) and excellent enantioselectivities (86−99% ee) (Scheme 217). It is noteworthy that the challenging Michael products obtained from acetone and various nitroolefins were almost enantiomerically pure and aliphatic β-substituted nitroalkenes proved to be excellent Michael acceptors (up to 98% ee). Similar to the results of Tsogoeva[374] and in contrast to previous reports using secondary amine catalysts,

Scheme 217. Primary Amine-Thiourea-Catalyzed Michael Reactions of Ketones and Aldehydes



acyclic ketones furnished mainly the *anti*-diastereomers (Scheme 217). A (*Z*)-enamine intermediate was proposed to be responsible for the observed *anti*-diastereoselectivity (Scheme 216).[374,375] Previously, only Alexakis et al. had reported an *anti*-selective Michael addition using a pyrrolidine-derived catalyst, but only α-hydroxyacetone afforded *anti*-products (Scheme 193).[348]

Recently, Jacobsen et al. could show that the slightly modified primary amine thiourea catalyst **324** is suitable for the direct conjugate addition of racemic α,α-disubstituted aldehydes to *β*-substituted Michael acceptors (Scheme 217).[376] Very good results (up to >50:1 dr, up to 99% ee) for a broad range of α,α-disubstituted Michael donors and Michael acceptors were obtained using 20 mol % catalyst **324**, 5 equiv of water, and 2 equiv of the aldehyde in dichloromethane as a solvent. The highest diastereoselectivities were obtained for aldehydes bearing a phenyl or ethereal α-substituent (up to >50:1 dr). In contrast, lower diastereoselectivities were obtained for aldehydes bearing alkyl substituents (up to 4:1 dr). In all cases, the enantioselectivities observed are excellent. Interestingly, essentially racemic aldehyde was recovered, indicating that a dynamic kinetic resolution process took place. According to the stereochemical outcome of the reaction (*syn*-products predominate), Jacobsen and co-workers proposed the reaction taking place via an (*E*)-enamine.

A secondary amine-derived bifunctional thiourea catalyst **325** was reported by Tang and co-workers for the Michael addition of cyclohexanone to nitroolefins.[377] Pyrrolidine-thiourea **325** afforded the desired *γ*-nitroalkanes of both aryl and alkyl nitroolefins with high diastereo- and enantioselectivities under solvent-free conditions (10:1−99:1 dr, 88−98% ee). Products derived from other carbonyl compounds were obtained in lower stereoselectivities (Scheme 218). To illustrate the potential usefulness of the process, the *γ*-nitroalkane derived from cyclohexanone and *trans*-*β*-nitrostyrene was converted to the corresponding nitrone in 95% yield without loss of ee.

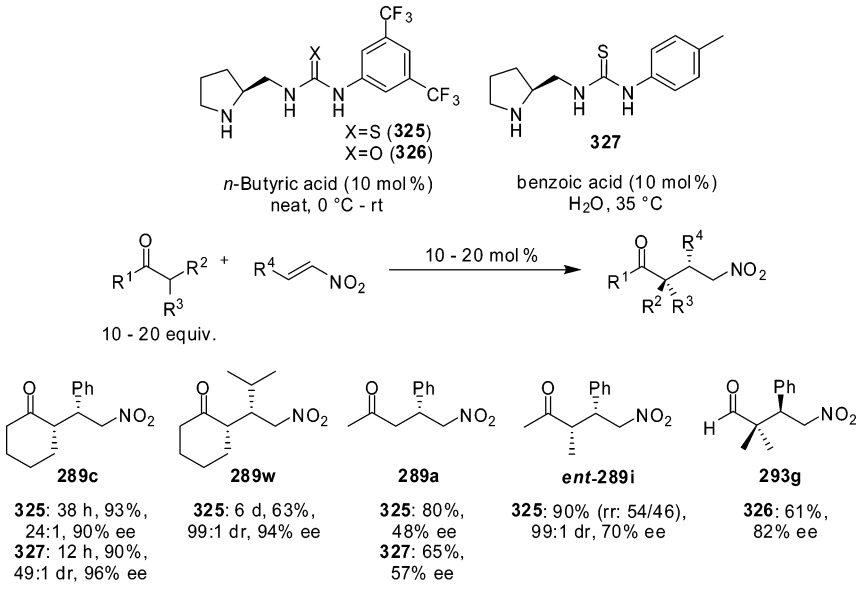
Independently, Xiao and co-workers described bifunctional pyrrolidine-thiourea **327**, which slightly improved the stereoselectivity of ketone-derived Michael adducts (up to 99:1 dr and 99% ee) (Scheme 218).[378,379] Comparable results were observed in both aqueous media and organic solvents.

Luo and Cheng developed a novel asymmetric catalytic system composed of functionalized chiral ionic liquids and showed their potential as catalysts for asymmetric Michael reactions.[380] The attachment of a pyrrolidine moiety onto the side chain of an ionic liquid produced a powerful catalyst **328**. At this, the former can act as the catalytic site, whereas the latter serves as the chiral-induction group and the phase tag, which facilitates catalyst recycling. A broad range of both ketone- and aldehyde-derived Michael donors were shown to yield the addition products with high yields and moderate to excellent stereoselectivities (up to 99:1 dr, up to 99% ee) (Scheme 219). Again, acetone turned out to be a challenging donor substrate for the Michael addition to *trans*-*β*-nitrostyrene. However, better results were obtained using acetone and a cyclic nitroolefin. Precipitation with diethyl ether allowed recycling of the catalyst **328**, which was reused three times. In subsequent runs, the reaction time was increased and the stereoselectivities were slightly lower.

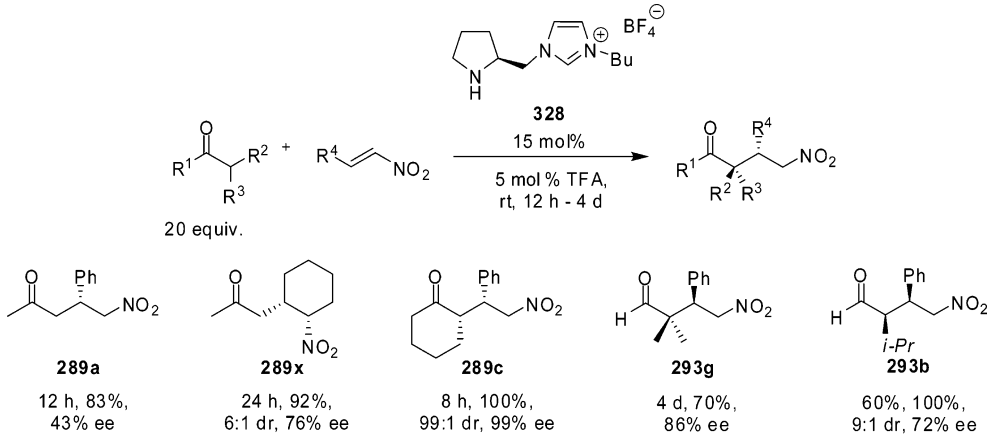
A similar catalyst was reported by Xu and co-workers.[381] Instead of using a large excess of the carbonyl component, additional solvents were explored. Much better yields and stereoselectivities (up to 99% ee) could be obtained in ionic liquids than in conventional organic solvents. The amount of the carbonyl compound could be decreased to 2 equiv.

Further interested in the environmental impact of the Michael addition process, Luo and Cheng developed surfactant-type asymmetric organocatalyst **329** by replacing the anions with surfactant sulfonate (compare Scheme 219 with Scheme 220), since chiral ionic liquid-type catalysts were ineffective in water.[382] These compounds were expected to promote the reaction and simultaneously act as a surfactant to help solubilizing the organic substrates. Indeed, **329**

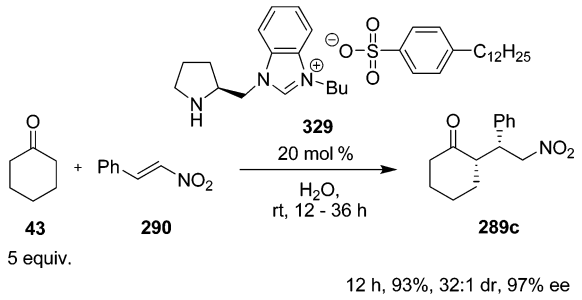
Scheme 218. Pyrrolidine-Thioureas as Bifunctional Organocatalysts



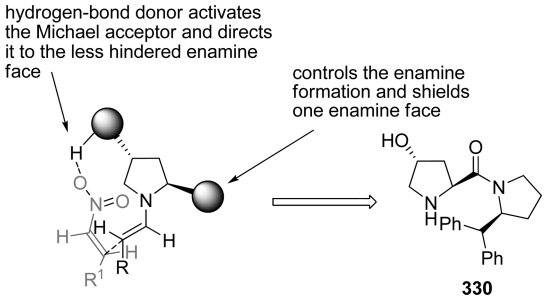
Scheme 219. Functionalized Chiral Ionic Liquids as Efficient Organocatalysts



Scheme 220. Michael Addition in Water Using a Surfactant-Type Asymmetric Organocatalyst



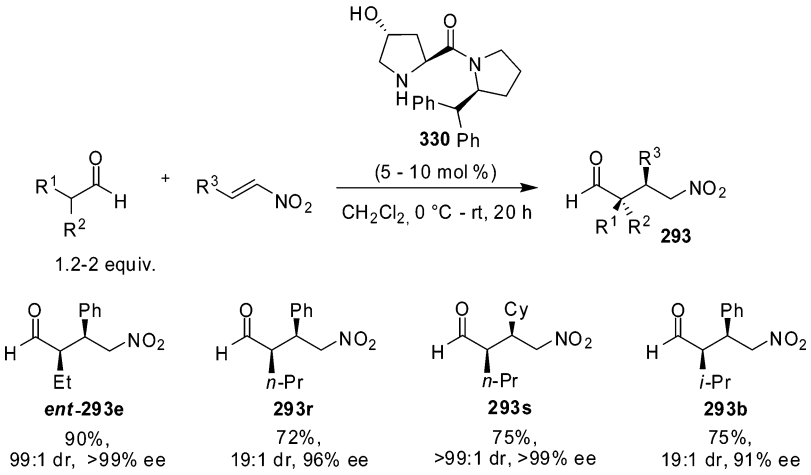
Scheme 221. Catalyst Design



catalyzes the asymmetric Michael addition of cyclohexanone **43** to aromatic nitroolefins efficiently in pure water in the absence of organic solvents and acid cocatalysts (Scheme 220). Cyclohexanone-derived Michael adducts were obtained in good yields and excellent stereoselectivities (>16:1 dr, >91% ee). However, isovaleraldehyde proved to be a less suitable donor in terms of enantioselectivity (80%, 32:1 dr, 61% ee), and the reaction of acetone resulted in a trace amount of product. Importantly, the Michael products could be readily separated from the reaction mixture by simple phase separation without using any organic solvent.

A very recent example of enantioselective conjugate addition of aldehydes to nitroalkenes was reported by the group of Palomo.[465] By introducing a new model for the asymmetric Michael addition, the authors designed an efficient and powerful catalyst **330** (Scheme 221). The authors assumed to activate and direct the Michael acceptor to the less hindered enamine face by introducing a hydrogen bond donor in the 4-position. Complementarily, the substituent in the 2-position shields the opposite side and controls the enamine formation. Accomplished experiments showed that the introduction of a hydroxyl group was essential to obtain adequate enantioselectivities. Moreover, DFT calculations at the B3LYP/6-31G* level showed that the OH group accelerates the Michael addition and helps to discriminate between possible transition state structures.

Scheme 222. *trans*-4-Hydroxyprolylamide-Catalyzed Michael Addition



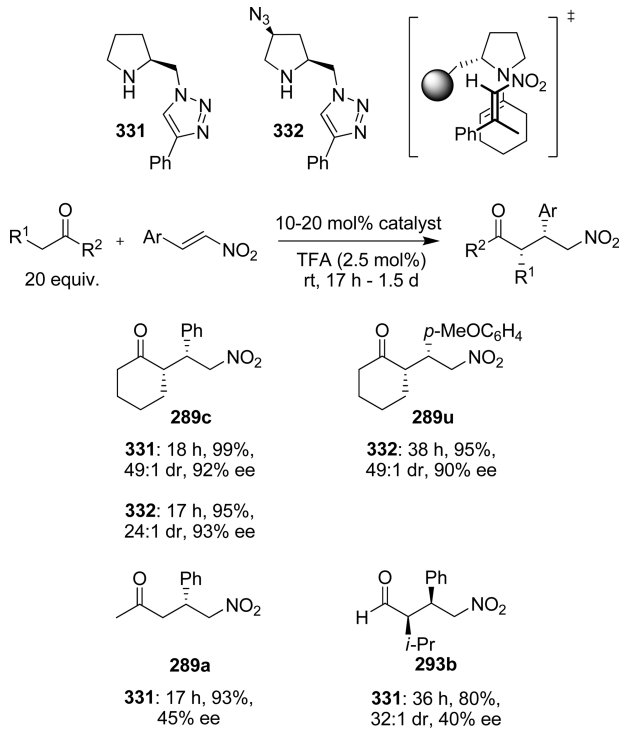
Optimal results were achieved for linear chain aldehydes when the reactions were carried out in the presence of only 5 mol % catalyst **330** in dichloromethane at 0 °C (up to 99:1 dr and 99% ee), whereas 10 mol % catalyst at room temperature was best for β-substituted aldehydes (up to 19:1 dr, 92% ee) (Scheme 222). As control experiments revealed the absence of self-aldol adducts, only a small excess of the aldehyde had to be used (1.2−2 equiv). Furthermore, the reaction can be performed on a 20 mmol scale and the catalyst was shown to be easily recovered by acid/base extraction in 70−80% yield. α,α-Disubstituted aldehydes were not reported, and the catalytic system seems to be less effective for ketones, since cyclohexanone afforded the product in 5:1 dr and 20% ee.

Since pyrrolidine-based catalytic systems are among the best asymmetric organocatalysts known for this reaction, Luo, Cheng, and co-workers reported in 2006 a modular and efficient approach for the discovery of new chiral pyrrolidines.[383] Using "click" chemistry, a chiral pyrrolidine library was prepared starting from azido-pyrrolidine and evaluated in asymmetric Michael additions of aldehydes and ketones to nitroolefins. Similar to the case of tetrazole-derived catalysts, the polar and planar triazole ring was supposed to be efficient for space shielding, which is regarded as a key factor for stereocontrol. In fact, potent catalysts **331** and **332** were found to give very good results for cyclohexanone as a Michael donor (up to 99:1 dr, up 96% ee). However, other ketone and aldehyde Michael donors gave diminished results (Scheme 223). A gram-scale synthesis of compound **289c** (95%, 49:1 dr, 91% ee), with only 5 mol % catalyst **331** employed, demonstrated the potential usefulness for organic synthesis.

Complementing other reports mainly dealing with privileged catalyst backbones such as pyrrolidine or imidazolidine, Barros and Phillips have recently introduced chiral piperazines as organocatalysts for the asymmetric Michael addition of aldehydes to aromatic nitroalkenes.[384] Dibenzylpiperazine (**333**) was found to catalyze the addition of aldehydes to aromatic nitroolefins with moderate to good yields (up to 78%), diastereoselectivities (up to 32:1 dr), and enantioselectivities (up to 85%) (Scheme 224). However, α- and β-branched aldehydes retarded the reaction considerably, and longer reaction times were needed to obtain reasonable yields. Achiral unsubstituted piperazine was shown to efficiently furnish the racemic γ-nitro aldehydes.

Recently, prolinol (**334**) was shown to efficiently promote the addition of aldehydes to β-nitroacrolein dimethyl acetal

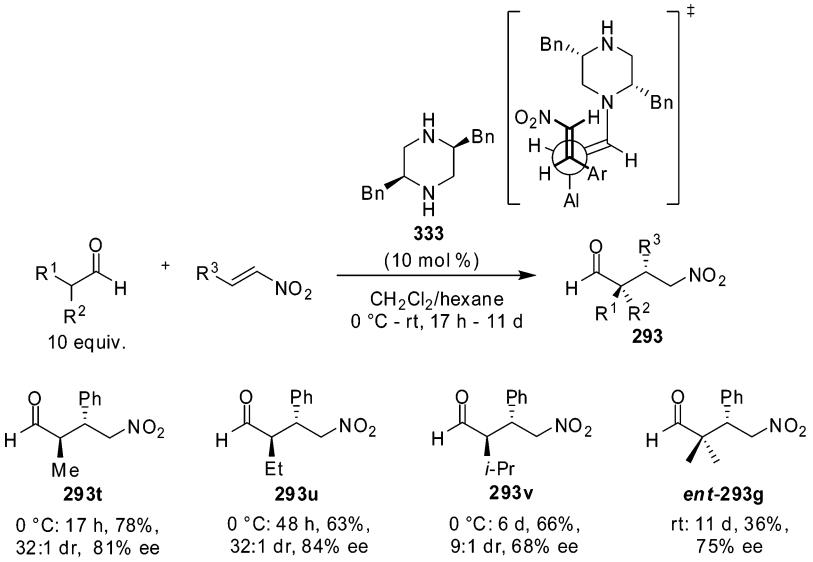
Scheme 223. Pyrrolidine Triazole Organocatalyst for Asymmetric Michael Additions



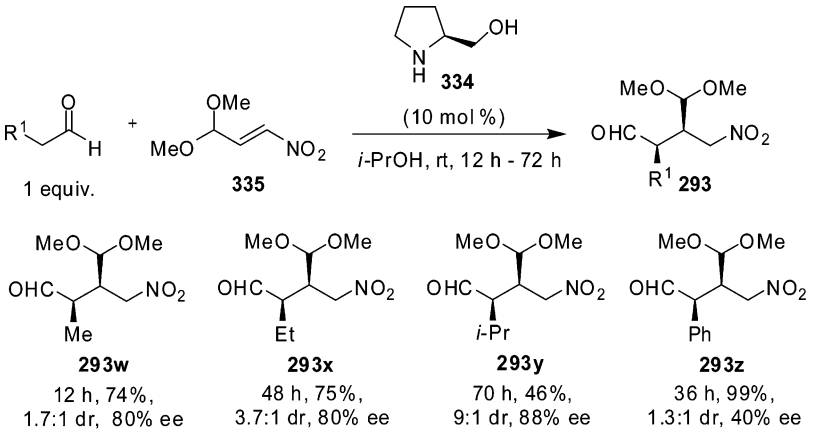
(**335**).[466] This is a rare example of functionalized nitroalkenes being used as Michael acceptors. Vicario and co-workers could obtain the enantioenriched highly functionalized Michael products containing a second chemically differentiated formyl group using equimolar amounts of aldehyde donor and nitroalkene and 10 mol % prolinol (**334**) in isopropanol (Scheme 225). The products were obtained with only moderate diastereoselectivity (typically ~2:1, up to 9:1 dr) and good enantioselectivity (up to 88% ee). Similar results were obtained using only 1 mol % catalyst, and most importantly, the catalyst is inexpensive and readily available in both enantiomeric forms.

Pansare et al. investigated proline-derived triamines, readily prepared from (*S*)-Boc-proline in three steps, as potential promoters for the direct asymmetric Michael reaction (Scheme 226).[385] Initial experiments with cyclohexanone and *trans*-β-nitrostyrene revealed that the use of *p*-TsOH has a strong effect on the outcome of the reaction. In addition, the secondary−secondary diamine motif was

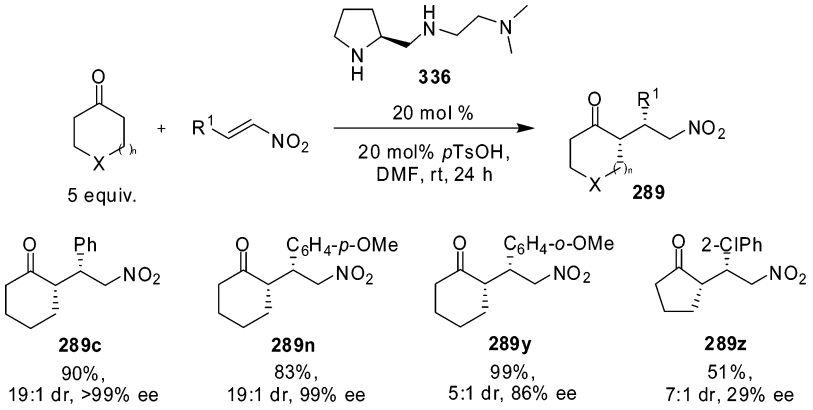
Scheme 224. Chiral Piperazine as Catalyst for the Addition of Aldehydes to Nitroalkenes



Scheme 225. Michael Addition of Aldehydes to *β*-Nitroacrolein Dimethyl Acetal



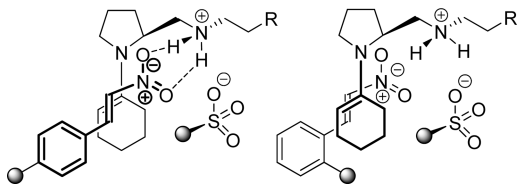
Scheme 226. Amine-Protonic Acid Catalyst for the Michael Addition of Cyclic Ketones to Nitroalkenes



found to be essential for good selectivities. Using DMF as the solvent, 20 mol % protonated triamine catalyst **336** at ambient temperature afforded the cyclic ketone-derived *syn*-Michael adducts in high yields with good diastereo- and enantioselectivities (up to 50:1 dr, up to >99% ee) (Scheme 226). Cyclopentanone proved to be a more challenging substrate in this case. Although 5 equiv of the cyclic ketones were usually used, it was shown that in some cases equal amounts were sufficient.

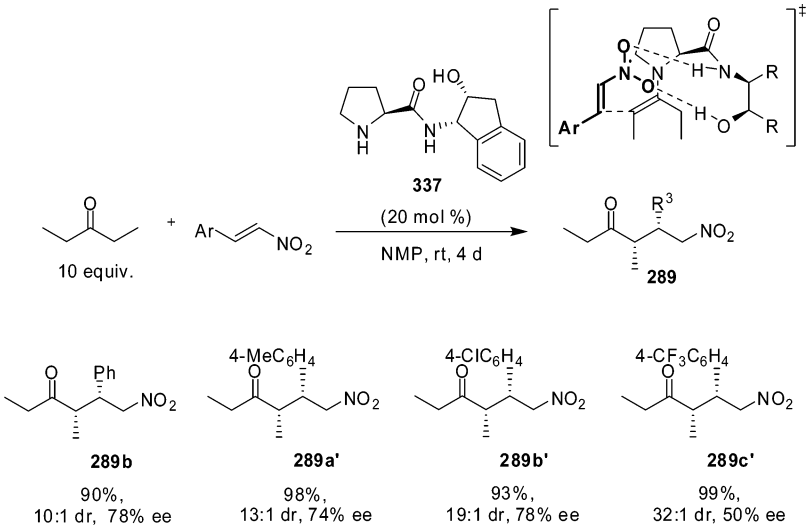
The authors proposed a synclinal transition state assembly, in which the protonated secondary amine activates the

Scheme 227. Transition State Assemblies

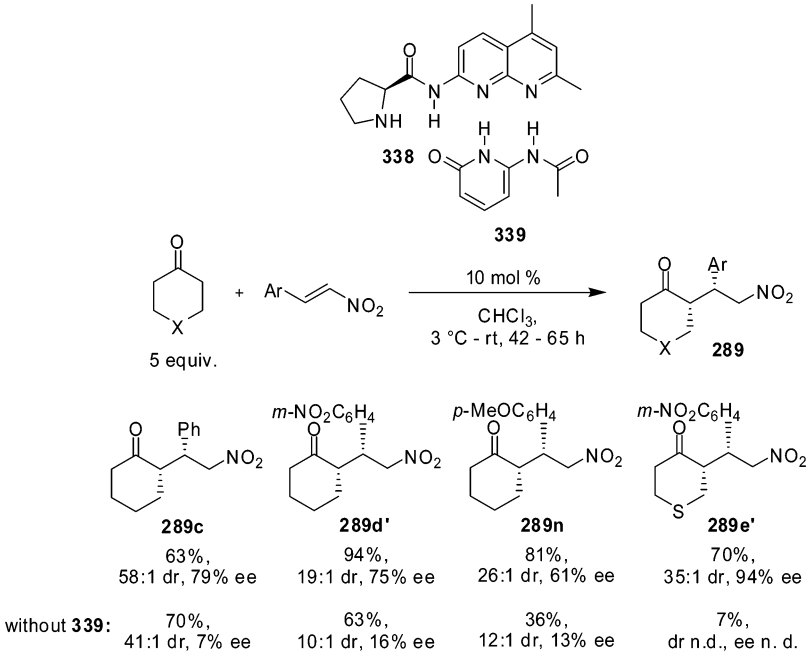


nitroolefin by hydrogen bonding (Scheme 227[243]). Interestingly, the authors could show that the stereoselectivities were very high for nitroalkenes with substitution at the 4-position

Scheme 228. Enantioselective Addition of Ketones to β-Nitrostyrenes



Scheme 229. Michael Addition Promoted by Self-assembled Organocatalyst



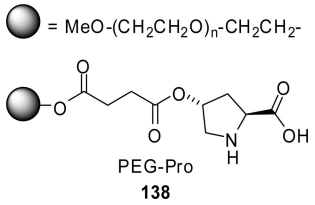
of the phenyl ring, whereas the enantioselectivity was lowered by moving the substituent to the 2-position. Here, a non-hydrogen-bonded transition state may compete, due to steric interactions between the 2-substituent and the counteranion of the acidic additive, which would reduce the enantioselection.

(*S*)-Prolinamides, prepared from (*S*)-proline and β-amino alcohols, were recently introduced as catalysts for the addition of 3-pentanone to β-nitrostyrenes by Alonso and co-workers.[386] Using 20 mol % **337** in NMP, the Michael adducts were obtained in high yields with moderate to good diastereo- and enantioselectivities (up to 32:1 dr and 80% ee) (Scheme 228). Experiments showed that the presence of both the secondary amide and the alcohol functionality is important for good catalyst activity and selectivity. Hence, the amide and the hydroxyl group were expected to interact with the nitroolefin via double hydrogen bonding (Scheme 228).

Typically, catalyst structures are optimized through covalent structure modifications in order to obtain high activities as well as selectivities. Even with modular structures, the approach to catalyst libraries can be time-consuming. However, Clarke and Fuentes could modulate the catalyst activity of a chiral pyrrolidine-derived precatalyst by combination with a library of achiral additives.[387] This concept is based on self-assembly of the new catalyst by complementary hydrogen bonding between precatalyst and additive in order to alter the precatalyst environment. A combination of 10 mol % precatalyst **338** and 10 mol % pyridinone **339** (Scheme 229) catalyzed the addition of cyclic ketones to aromatic nitroolefins, giving the Michael adducts **289** in high yields with moderate to excellent stereoselectivities (up to 58:1 dr and 94% ee).

In 2003, Benaglia et al. utilized poly(ethylene glycol)-supported proline (PEG-Pro) **138** as a catalyst for the already discussed diastereo- and enantioselective addition of cyclohexanone to *trans*-β-nitrostyrene (Scheme 230).[388] Fair yields and good diastereoselectivities were observed, and the successful recovery and recycling of the supported catalyst was reported. Nevertheless, the PEG-supported catalyst **138**

Scheme 230. Structure of Immobilized Proline Catalyst



is less efficient than nonsupported proline in terms of enantioselectivity (in MeOH: 57% vs 35% ee; in DMSO: 23% vs 22% ee).[62,339]

4.3.2. α,β-Unsaturated Carbonyl Compounds as Acceptors

In most organocatalytic Michael additions, either highly activated nucleophiles or electrophiles have been used. The addition of unactivated carbonyl compounds to nitroalkenes, for instance, is well established (section 4.3.1.), whereas fewer examples are known dealing with the addition to simple enone acceptors.

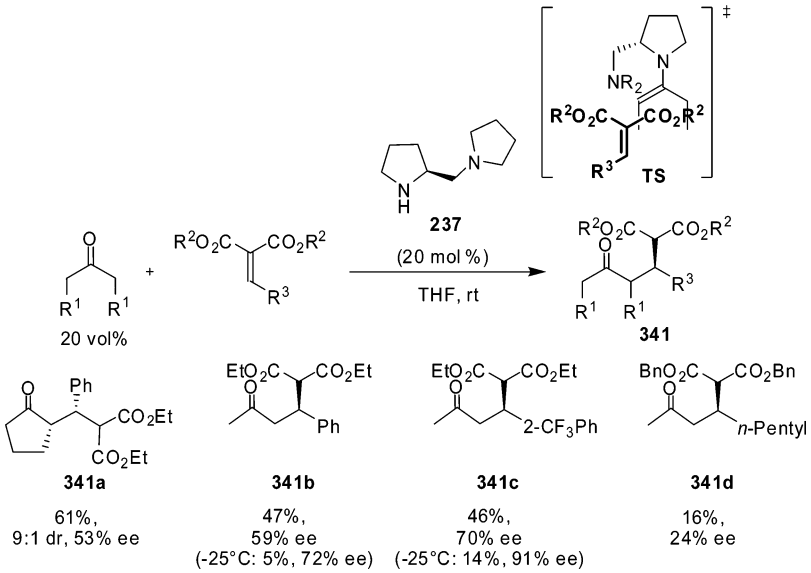
Barbas et al. investigated the Michael addition of acetone **35** to highly activated diethyl benzalmalonate (**340**) in DMSO as a model transformation.[112,343] Since the desired Michael adducts were obtained in racemic form,[88] a variety of chiral amines were screened as catalysts for the reaction. The best overall results were obtained using 20 mol % (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine (**237**) in THF at room temperature (rt, 47%, 59% ee) (Scheme 231). Although higher enantioselectivities were observed at lower temperatures, no reasonable yield of the Michael product could be isolated (−25 °C, 5%, 72% ee). A variety of both aromatic and aliphatic alkylidene malonates were evaluated as Michael acceptors, with an excess of acetone, cyclopentanone, and cyclohexanone as Michael donors (Scheme 231). Generally, the products **341** were obtained in moderate yields (16−84%) and enantioselectivities (up to 70% ee). In contrast, the aliphatic alkylidene malonates furnished the Michael adducts in low enantioselectivities (up to 24% ee) and, due to their instability under the reaction conditions (retro-Knoevenagel), also in low yields (up to 27%). The observed stereochemistry was rationalized with a transition state (**TS**, Scheme 231), where the alkylidene malonate approaches the enamine from the less hindered *re*-face. Furthermore, a three-component, one-pot reaction of benzaldehyde, diethylmalonate, and acetone was established that directly converts an aldehyde into the final Michael adduct via amine catalysis of both steps (Knoevenagel and Michael reaction, 52%, 49% ee). The Michael adducts could be further converted to 3-substituted-5-keto esters after monodecarbomethoxylation under Krapcho conditions.

Other promising catalysts arose from a catalyst screening reported later by the same group.[456] In terms of both yield and enantioselectivity, diamine **301** turned out to be superior to previously reported (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine (**237**) (Scheme 232).

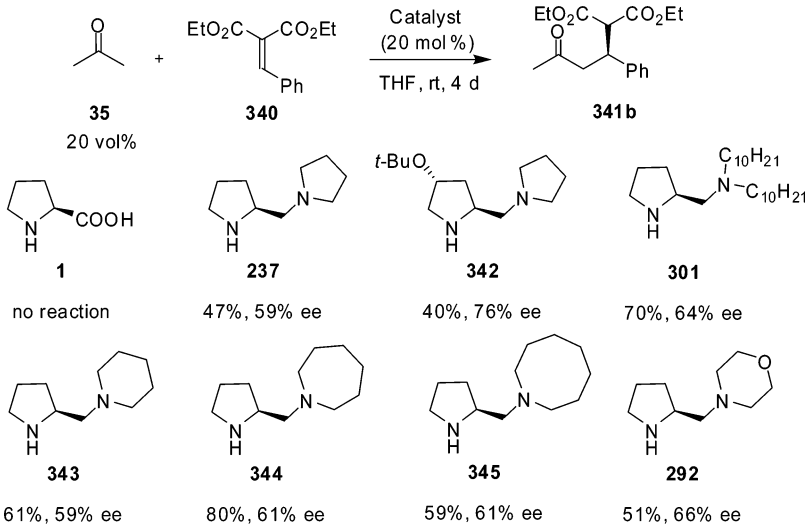
List and co-workers treated a mixture of acetone **35** (20 vol %) and proline **1** (35 mol %) in DMSO with an aromatic alkylidene malonate **346** and cyclohexenone **347**.[1] While the expected Michael adducts (**341e** and **348**, respectively) were formed (Scheme 233), the enantioselectivities remained unsatisfactory (90%, 14% ee; 15%, 20% ee). As an extension, a novel proline-catalyzed three-component domino reaction between ketones, aldehydes, and Meldrum's acid was described.[389] Two new carbon−carbon *σ*-bonds are formed in the course of the reaction, but the enantioselectivity is generally low and products were typically obtained with ee's under 5%.

Recently, Wang et al. developed a highly enantioselective, organocatalytic Michael addition reaction of cyclic ketones with α,β-unsaturated ketones **349**.[390] The process is catalyzed by 10 mol % (*S*)-pyrrolidinesulfonamide **93** and leads to synthetically useful 1,5-dicarbonyl compounds **350** in good yields and with high degrees of stereoselectivity (>40:1 dr, up to 97% ee). Superior results were observed for cyclic six-membered ketones, whereas cyclopentanone appears to be more challenging (Scheme 234). In addition, structural variation of the α,β-unsaturated aromatic ketones was well tolerated without affecting the stereoselection. Among other catalysts, proline, diphenylprolinol silyl ethers, and imidazolidinones were not effective. No Michael addition occurred with acyclic ketones including acetone, 3-pentanone, and acetophenone. Similar to the case of proline-catalyzed reactions, the NH proton is believed to stabilize the transition state through hydrogen bonding interactions with the chalcone carbonyl group in which an additional solvent molecule might be involved (Scheme 234).

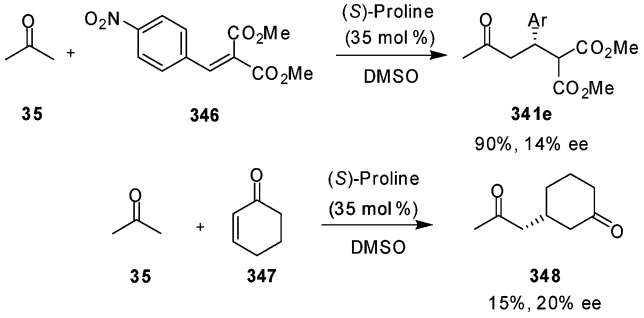
Scheme 231. Catalytic Enantioselective Direct Michael Additions of Ketones to Alkylidene Malonates



Scheme 232. Catalyst Screening for Enantioselective Direct Michael Additions of Acetone to Alkylidene Malonate 340



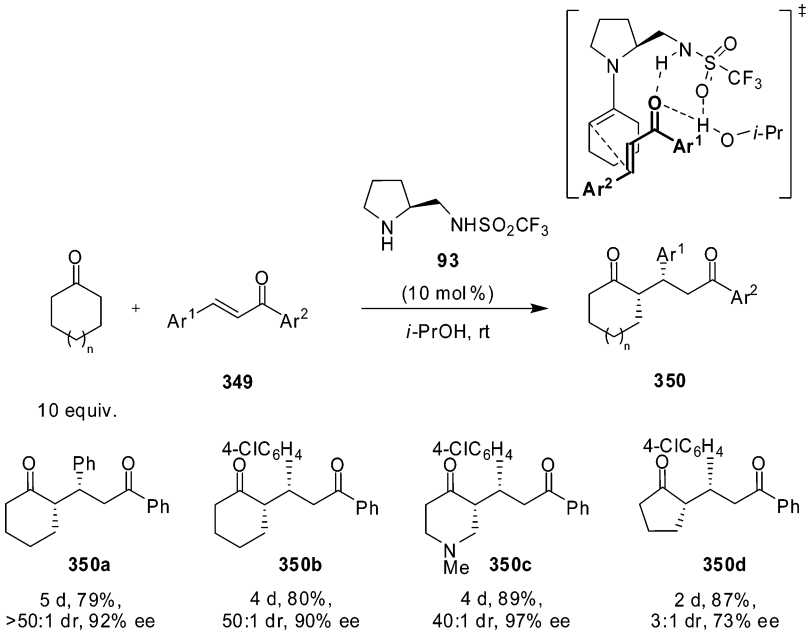
Scheme 233. Proline-Catalyzed Michael Reactions



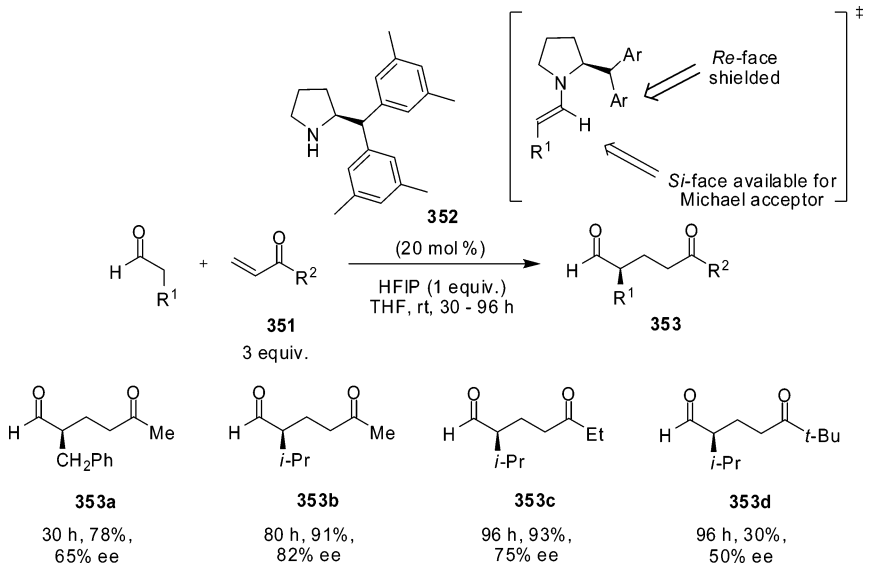
Aldehydes were introduced as feasible Michael donors by Melchiorre and Jørgensen, who developed organocatalytic direct enantioselective Michael addition of simple aldehydes to vinyl ketones **351**.[391] Using (*S*)-2-[bis(3,5-dimethylphenyl)methyl]pyrrolidine (**352**) as the catalyst in THF, optically active substituted 5-keto aldehydes **353** were formed in good yields and moderate to good enantioselectivities (up to 82% ee) (Scheme 235). Methyl vinyl ketone and ethyl vinyl ketone smoothly reacted with different aliphatic aldehydes, giving similar selectivities. For the more sterically hindered *tert*-butyl vinyl ketone, the reaction proceeded more slowly and the enantiomeric excess was lowered. The catalyst **352** is expected to shield the *re*-face of the enamine intermediate, so that the major reaction path is the addition to the *si*-face (Scheme 235). Later, a similar catalyst was used by Gellman and co-workers for the Michael addition of aldehydes to alkyl vinyl ketones (up to 83% ee).[392]

In order to understand the catalytic effect of the chiral catalyst **352**, a series of experimental and theoretical investigations were conducted.[391] A negative nonlinear effect had been observed for the reaction of butanal (R^1 = Et) with methyl vinyl ketone (R^2 = Me), which indicates that probably more than one molecule of the catalyst is involved in the enantiodifferentiating step. To account for this and based on other experiments, the authors proposed that the catalyst activates the aldehyde via enamine (**354**) formation, which can add both to the vinyl ketone **351** itself and to the iminium intermediate **355** derived from the Michael acceptor (Scheme 236, paths a and b). In contrast, the reaction of *tert*-butyl

Scheme 234. Michael Addition of Ketones to Chalcones

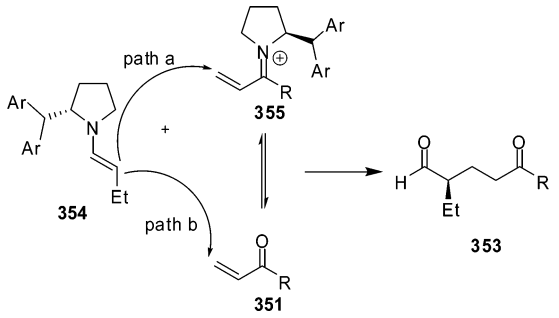


Scheme 235. Direct Enantioselective Michael Addition of Aldehydes to Vinyl Ketones



vinyl ketone shows no nonlinear effect. Presumably, the formation of iminium ion intermediates can be excluded for sterically hindered substrates (Scheme 236, path b).

Scheme 236. Proposed Reaction Course

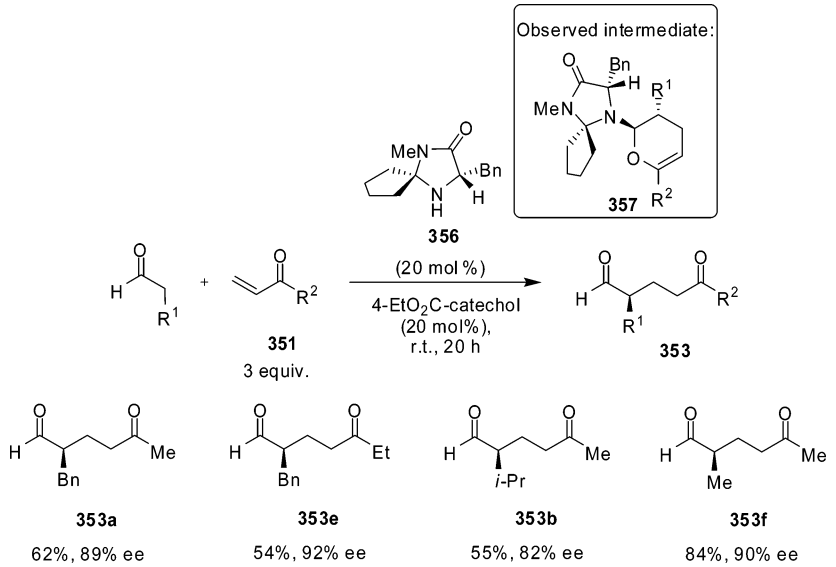


Along those lines, Gellman and co-workers could show that the intermolecular addition of aldehydes to vinyl ketones can be catalyzed with an imidazolidinone catalyst **356**.[393] A combination of **356** and 4-EtO_2C-catechol afforded the addition of a variety of aldehydes to methyl vinyl ketone (R^2 = Me) and ethyl vinyl ketone (R^2 = Et) in very good enantioselectivities (up to 92% ee) (Scheme 237). Gellman et al. provided clear evidence for an imidazolidinone-derived enamine. A preformed enamine was shown to react smoothly with methyl vinyl ketone in the presence of catechol to provide dihydropyrane **357** (Scheme 237), which is hydrolyzed to the desired keto-aldehyde. Consequently, the reaction of imidazolidinone-derived enamines was proposed to take place with hydrogen-bond-activated enones. The observed dihydropyrane can be formed either by conjugate Michael addition and subsequent hemi-aminal formation or directly by an inverse-electron-demand hetero-Diels−Alder reaction.

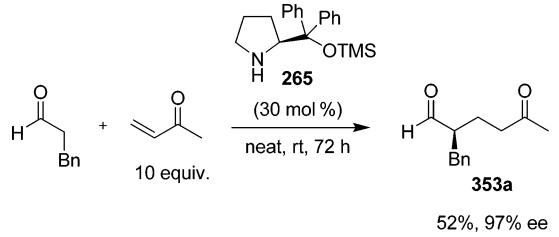
Hayashi and co-workers could show that not only nitroalkenes but also α,β-unsaturated ketones can be employed as Michael acceptors using diphenylprolinol silyl ether **265** as catalyst.[366] The addition of 3-phenylpropanal to methyl vinyl ketone under neat conditions led to the Michael adduct in moderate yield with excellent enantioselectivity (Scheme 238).

After having developed α,α-diarylprolinol silyl ethers for stereoselective C−F and C−S bond formation, Jørgensen

Scheme 237. Imidazolidinone Catalyzed Michael Addition

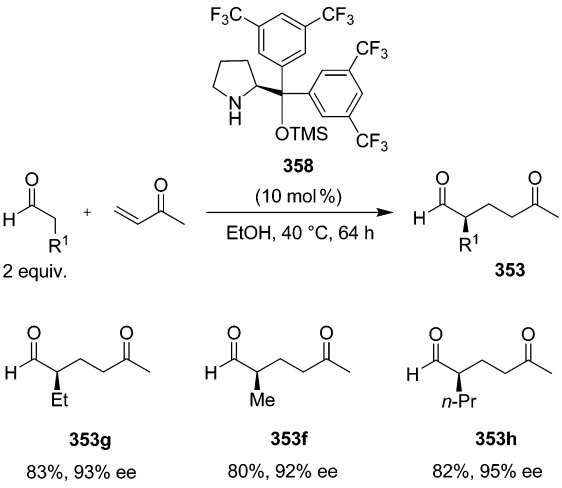


Scheme 238. Highly Enantioselective Michael Addition to Methyl Vinyl Ketone



and co-workers could show the ubiquitous application of **358** for α-functionalization of aldehydes.[394,463] Characteristic is the high stereoselectivity of all these functionalizations, since the catalyst controls the enamine geometry and efficiently shields one enamine face. Michael addition of aldehydes to methyl vinyl ketone in the presence of 10 mol % **358** proceeded in a highly enantioselective manner, and all products (**353**) were obtained in good yields (≥80%, up to 95% ee). Compared to catalyst **352** used in their initial study (Scheme 235),[391] catalyst **358** improved the enantiomeric excess significantly (Scheme 239).

Scheme 239. Organocatalytic Enantioselective Michael Addition



Chi and Gellman reported a very efficient diphenylprolinol ether for the asymmetric Michael reaction.[395] A study of different potential pyrrolidine catalysts revealed that quaternary substitution adjacent to the nitrogen was beneficial for both reactivity and enantioselectivity, since catalysts lacking this substitution gave inferior results.[391,392] Since the reaction appears to proceed via an enamine intermediate, especially the higher reactivity was an unforeseen result. The catalyst etherification was necessary, as a diphenylprolinol-derived catalyst was inactive. Instead, a catalyst deactivation through formation of stable cyclic aminals was proposed to take place. Various aldehydes were used as donors in the diphenylprolinol methyl ether **359**-catalyzed Michael reaction with methyl vinyl and ethyl vinyl ketones (Scheme 240). In the presence of only 5 mol % **359** and a small excess of the vinyl ketone **351** (1.5 equiv) under neat conditions, the Michael adducts (**353**) were obtained in good yields and excellent enantioselectivities (>95% ee, up to 99% ee). Less reactive substrates required the use of an acidic additive in order to activate the enone as well. Although the reaction is faster in the presence of 20 mol % pyrrolidine catalyst **359**, modest enantioselectivity was observed, whereas the best results could be obtained in the presence of ≤5 mol %. This trend suggests that the catalyst not only catalyzes the Michael addition but also the product epimerization via enamine formation with the product aldehyde **353**.

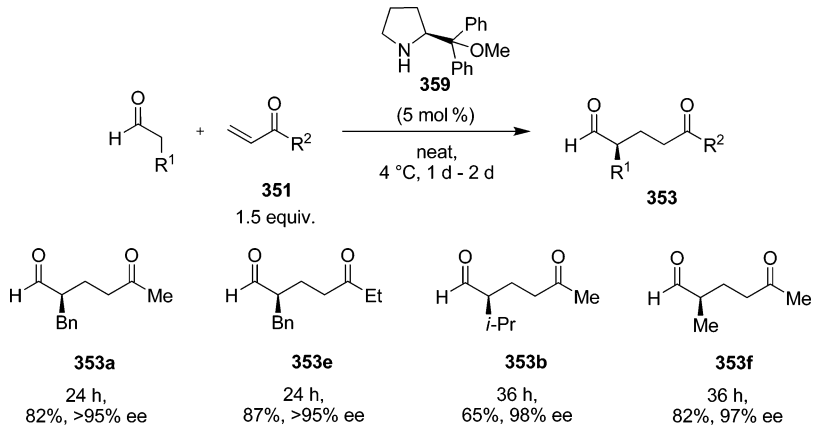
A preliminary study of aldehyde addition to β-substituted alkylidene malonates revealed good stereoselectivities but only poor results for the addition to cyclopentenone or acyclic β-substituted enones (results not specified).

Asato and Liu reported the proline-mediated self-condensation reaction of α,β-unsaturated aldehydes **360** (2 equiv of (*S*)-proline, up to 65% ee).[396] Very recently, this reaction was investigated in detail by Watanabe and co-workers.[397] (*S*)-Proline (1.5 equiv) effected the asymmetric formation of trisubstituted cyclohexadienes **361** under mild reaction conditions in high yields with up to 62% enantioselectivity (Scheme 241).

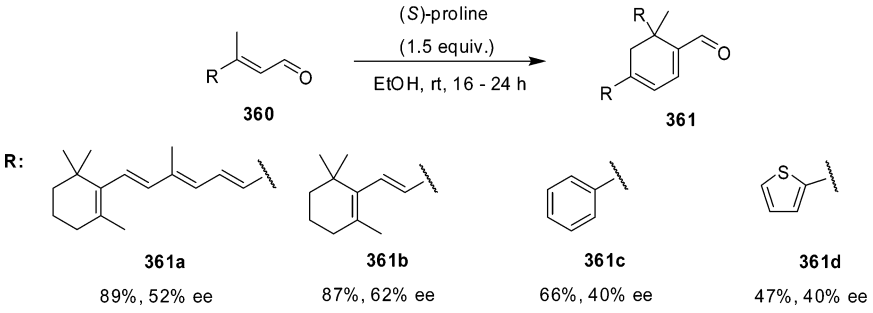
A time course analysis by NMR and MS provided evidence that a two-proline adduct-based mechanism occurs, which involves substrate activation through both enamine **I** and iminium-ion **II** formation (Scheme 242). The moderate enantioselectivities obtained with different proline analogues support a Michael-like imine addition (Scheme 242) rather than a Diels−Alder reaction, since the involvement of two reaction centers (the Diels−Alder mechanism would involve the enamine- and the γ-position of the diene **I**) should show a more pronounced auxiliary effect. However, a stepwise mechanism involving only a remote carbon center of diene **I** (γ-position, Scheme 242) could explain the moderate enantioselectivities.

A related Michael-type reaction is the enamine-catalytic asymmetric inverse-electron-demand hetero-Diels−Alder (HDA) reaction developed by Juhl and Jørgensen.[398] A

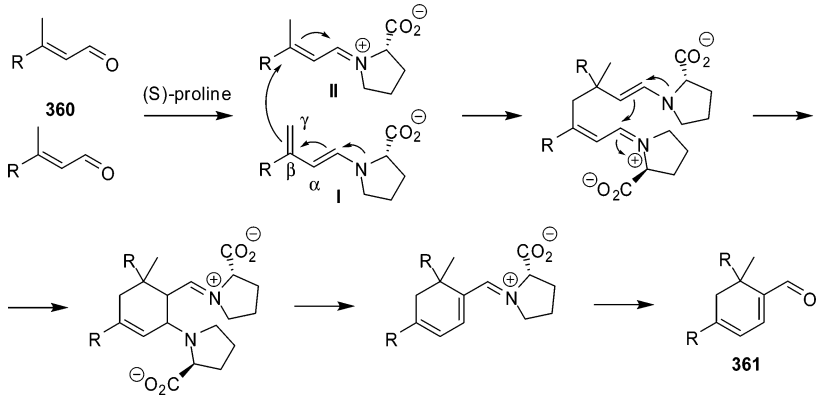
Scheme 240. A Highly Enantioselective Catalyst for Michael Addition of Aldehydes to Enones



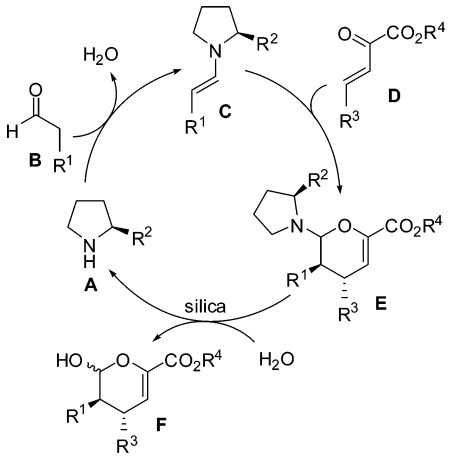
Scheme 241. Self-condensation of α,*β*-Unsaturated Aldehydes



Scheme 242. Proposed Route to 1,2,4-Trisubstituted Cyclohexadienals



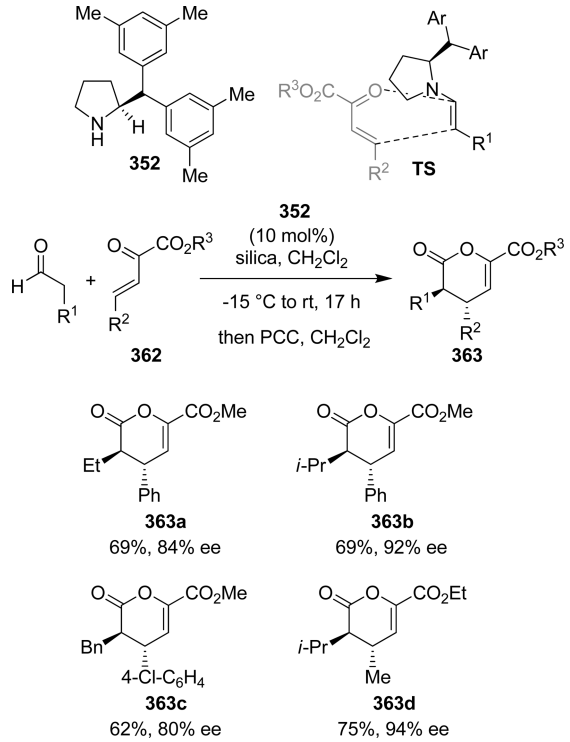
Scheme 243. Plausible Catalytic Cycle for the Enamine-Catalytic HDA Reaction



plausible catalytic cycle is depicted in Scheme 243. The enamine **C**, which is generated from the amine catalyst **A** and the aldehyde **B**, acts as an electron-rich dienophile for the reaction with electron-deficient "diene" **D** to produce the aminal **E**. Hydrolysis of **E** gives hemiacetal **F** and regenerates the catalyst. The presence of silica was found to facilitate the hydrolysis step in the catalytic cycle.

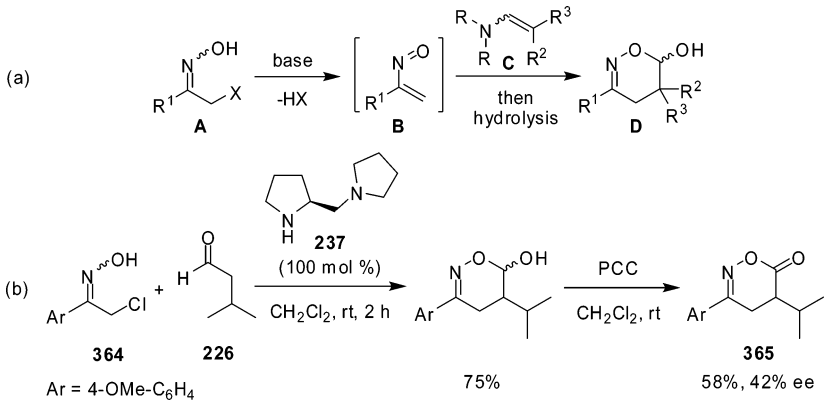
After screening various cyclic secondary amines, the authors found the pyrrolidine derivative **352** to be the most efficient catalyst for this reaction (Scheme 244).[398] *β*,*γ*-Unsaturated α-ketoesters **362** were used as the "diene" for this reaction. The products were isolated as lactone **363** after subsequent PCC oxidation of the crude HDA adducts. In the presence of 10 mol % **352**, lactones **363** were obtained in good yield and high enantioselectivity. In almost all cases, only one diastereomer of the products was obtained. A transition state model **TS** was proposed by the authors to rationalize the observed stereochemistry of the reaction

Scheme 244. First Organocatalytic Asymmetric Inverse-Electron-Demand HDA Reaction

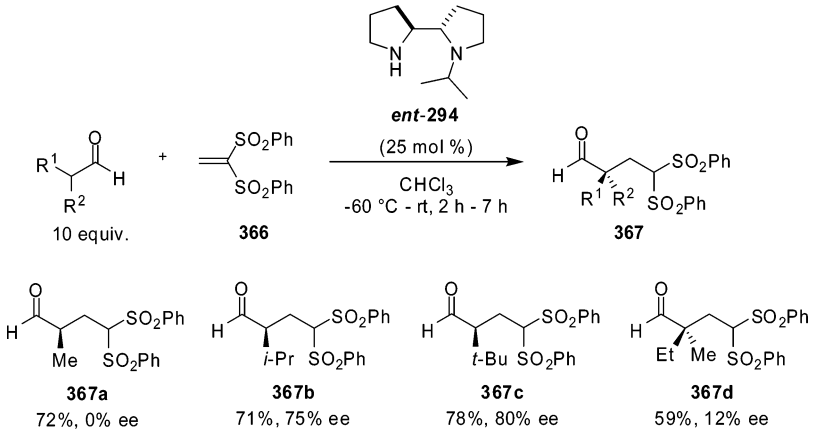


(Scheme 244). The diarylmethyl substituent of the catalyst **352** shields the *si*-face of the enamine, which makes the approach of the enone possible only from the *re*-face in an *endo*-selective fashion. The regioselectivity of the reaction is dictated by the electronic properties of the enamine. Although a concerted mechanism is assumed for this reaction, a stepwise Michael-type mechanism cannot be ruled out.[398] Similarly, several enamine catalytic Michael reactions may actually be [4+2]-cycloadditions.

Scheme 245. Inverse-Electron-Demand HDA Reaction of Nitroso Alkene



Scheme 246. First Organocatalytic Asymmetric Michael Addition to Vinyl Sulfones



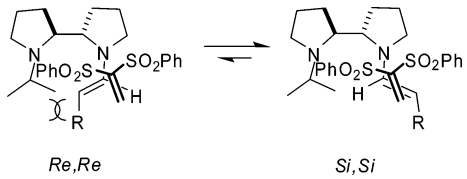
The Jørgensen group also showed that the scope of this reaction in terms of the "diene" unit can be extended beyond enones.[399] Nitroso alkenes **B**, which can be in situ-generated from α-halooximes **A**, can react with enamine **C** to generate 5,6-dihydro-4*H*-oxazines **D** (Scheme 245a). Using a stoichiometric amount of chiral amine **237**, the reaction between isovaleraldehyde (**226**) and the aromatic α-halooxime **364** was found to generate, after oxidation, the oxazinone **365** in moderate (42%) ee (Scheme 245b). This is the first example of an asymmetric inverse-electron-demand HDA reaction of a nitrosoalkene.

4.3.3. Vinyl Sulfones as Acceptors

The reaction of preformed enamines with vinyl sulfones has been known for some time.[400] Although advancement has been made using chiral auxiliaries to develop asymmetric conjugate additions to vinyl sulfones,[401−404] the direct asymmetric catalytic conjugate addition of carbonyl compounds to vinyl sulfones would be desirable.[405] Since sulfones are widely useful intermediates of unique synthetic versatility in organic synthesis,[406] the desired 1,4-Michael adducts could further react as nucleophilic reagents or be involved in reductive alkylations and Julia-type reactions, among others. The first direct catalytic asymmetric Michael addition of aldehydes to vinyl sulfones was reported in 2005 by Mossé and Alexakis.[350,407] In contrast to the case of phenylvinyl sulfone, the first promising results could be obtained using the more reactive Michael acceptor 1,1-bis(benzenesulfonyl)-ethylene (**366**). Among the catalysts screened, *N*-*i*Pr-2,2′-bipyrrolidine (*i*-PBP) ***ent*-294** turned out to be most suitable (Scheme 246). Interestingly, neither (*S*)-proline nor (*S*)-(+)-(1-pyrrolidinylmethyl)pyrrolidine (**237**) furnished the desired adduct in a sufficient amount. In the presence of catalyst ***ent*-294**, good yields and enantioselectivities could be obtained using sterically hindered α-monosubstituted aldehydes (up to 80% ee), whereas smaller substrates such as propionaldehyde (−60 °C, racemic) and α,α-disubstituted aldehydes (rt, up to 12% ee) showed similar reactivity but no pronounced enantioselection (Scheme 246). To further illustrate the utility of the current process, the authors could remove the sulfone groups of **367** in 45% yield without loss of enantioselectivity.

As shown previously for nitroolefins, an acyclic synclinal transition state model was postulated, in which the *trans*-enamine intermediate is favored (Scheme 247). The less hindered *si*−*si* transition state is assumed to be favored, leading to (*R*)-adducts.

Scheme 247. Proposed Transition State



Recently, the authors have used *i*-PBM (**299**) to catalyze the addition of isovaleraldehyde (**226**) to vinyl sulfone (**366**) in 79% yield and 55% ee.[353]

5. Asymmetric α-Functionalization of Carbonyl Compounds

5.1. Introduction

α-Functionalizing carbonyl compounds is particularly important, owing to its value in the synthesis of a wide range

Scheme 248. α-Functionalization of Unmodified Carbonyl Compounds

of α-heteroatom-substituted carbonyl compounds.[408,409] Since optically active α-functionalized carbonyl compounds find application in nearly all fields of organic chemistry,[408] the synthesis of such targets from unmodified carbonyl compounds via the transformation of a C−H bond adjacent to the carbonyl functionality into a stereogenic C−X (X = C, N, O, P, F, Cl, Br, I, S, Se) bond (Scheme 248) became a major area of research in recent years.

The emergence of organocatalysis and, particularly, enamine catalysis has prompted chemists to consider these transformations as a group of mechanistically related reactions. Such amine-catalyzed transformations proceed via an enamine intermediate, whose reaction with electrophiles generates α-functionalized carbonyl compounds after hydrolysis of the corresponding iminium ion. The choice of appropriate electrophiles is crucial for such transformations, and depending on the nature of the electrophile, two types of reactions are possible, namely the addition and substitution reactions (see Scheme 2).

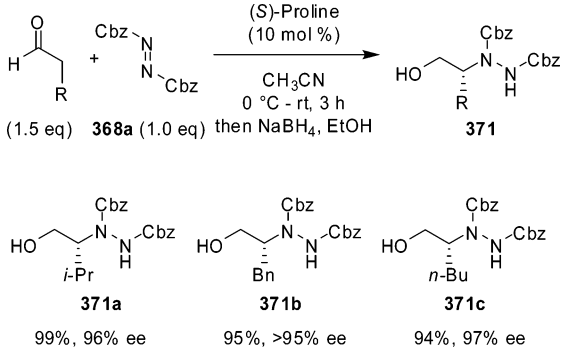
The following sections illustrate the use of enamine catalysis for the direct α-functionalization of carbonyl compounds with a wide range of electrophiles. A review on this topic has recently been published by Jørgensen et al.[408]

5.2. α-Amination

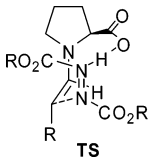
Catalytic asymmetric C−N bond forming reactions are highly attractive in organic synthesis due to their potential in giving access to a broad diversity of structural elements, which are also present in many biologically active compounds. In this context, the direct stereoselective introduction of a nitrogen functionality in the α-position of carbonyl compounds leads to valuable optically active synthetic targets such as α-amino aldehydes, α-amino acids, and *β*-amino alcohols. Employing an appropriate nitrogen electrophile, chiral amine catalysts were found to afford asymmetric α-amination of aldehydes and ketones via enamine intermediates.[230]

The first direct catalytic α-amination of aldehydes was reported simultaneously and independently by Jørgensen et al.[467] and List[410] in 2002. Using azodicarboxylates **368** as the nitrogen electrophile with a slight excess of aldehyde, 10 mol % (*S*)-proline afforded the α-hydrazino aldehydes

Scheme 250. Proline-Catalyzed Direct Asymmetric α-Amination of Aldehydes by List



Scheme 251. Proposed Transition State for the Proline-Catalyzed Asymmetric α-Amination of Aldehydes



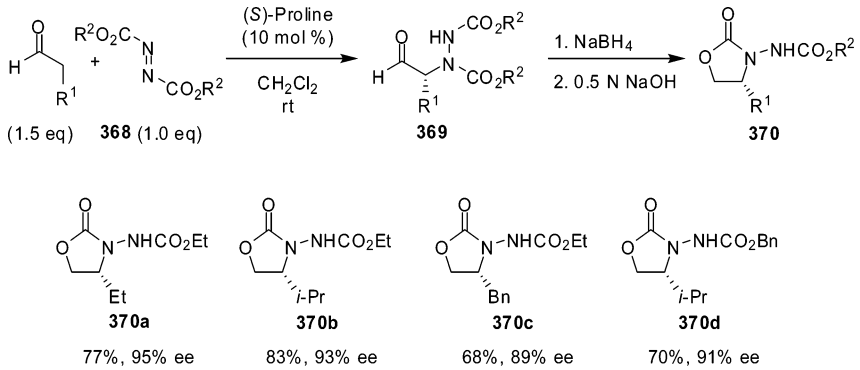
369 in moderate to high yields and excellent enantioselectivities (Schemes 249 and 250). Due to the configurational lability of the produced aldehydes **369,** Jørgensen and co-workers preferred to isolate the corresponding *N*-amino oxazolidinones **370** formed via reduction and cyclization (Scheme 249).[467]

Unlike Jørgensen et al., List chose to isolate the α-amination products as their corresponding configurationally stable crystalline 2-hydrazino alcohols **371** (Scheme 250).[410]

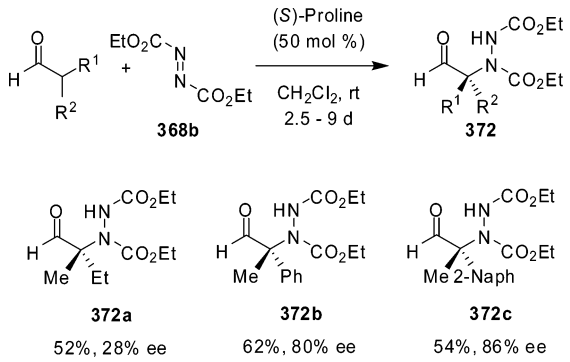
In both cases, the authors demonstrated the utility of the method by converting the products into synthetically useful 4-substituted 2-oxazolidinones (Evans' auxiliary) after N−N bond cleavage.[410,467] Furthermore, Jørgensen and co-workers showed that this α-amination method can be an easy and attractive way for obtaining optically active non-proteinogenic α-amino acids.[467] List explained the observed product stereochemistry by invoking a transition state **TS** (Scheme 251), which is similar to Houk's transition state of the Hajos−Parrish−Eder−Sauer−Wiechert reaction.[410]

Blackmond and co-workers recently disclosed an autoinduction mechanism to account for the observed higher turnover frequencies of this reaction as compared to those of other proline-catalyzed processes such as aldol or Mannich reactions.[411] An interaction of the reaction product with proline through complex hydrogen bonding was proposed which led to better solubilization of proline.[411] The catalytic

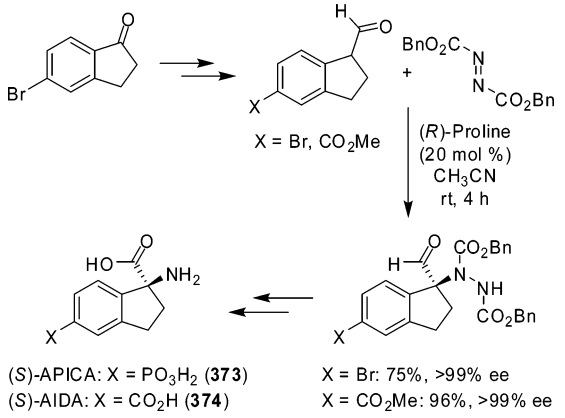
Scheme 249. Proline-Catalyzed Direct Asymmetric α-Amination of Aldehydes by Jørgensen et al.



Scheme 252. Proline-Catalyzed Direct Asymmetric α-Amination of α,α-Disubstituted Aldehydes



Scheme 253. Application of Proline-Catalyzed Direct Asymmetric α-Amination to the Synthesis of APICA and AIDA



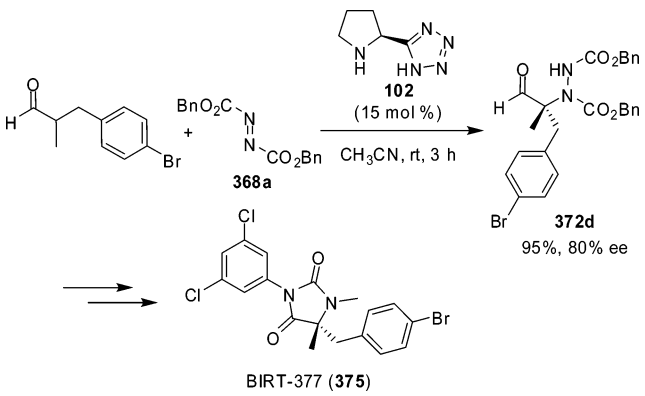
cycle invoked by the authors is essentially identical to the generally accepted enamine mechanism except for the fact that it circumvents free proline and the reaction proceeds via product displacement from the hydrogen-bonded adduct by the aldehyde.[411]

The substrate scope of the proline-catalyzed direct α-amination reaction was extended to include racemic α,α-disubstituted aldehydes. In 2003, Bräse and co-workers reported the direct asymmetric α-amination of α,α-disubstituted aldehydes with DEAD (**368b**) using 50 mol % (*S*)-proline in dichloromethane at room temperature.[355] Reaction times are relatively long, and the products were obtained in moderate yield with up to 86% ee (Scheme 252). This method is particularly suitable for α-alkyl-α-aryl-substituted aldehydes and useful for accessing α-alkyl-α-aryl-substituted α-amino acids. As in the above cases, the authors showed facile oxazolidinone formation from the products.

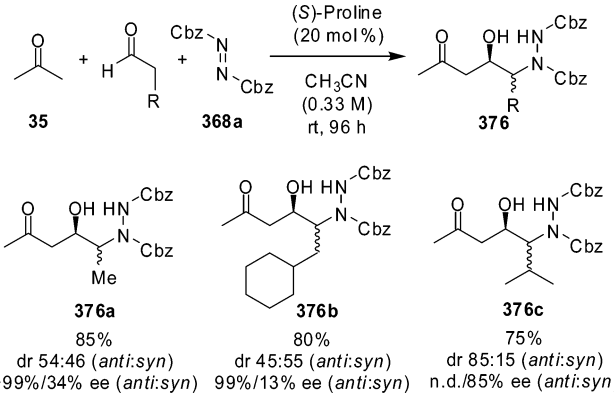
The utility of the proline-catalyzed direct asymmetric α-amination of α,α-disubstituted aldehydes was illustrated in an application to the synthesis of the metabotropic glutamate receptor ligands (*S*)-APICA (**373**) and (*S*)-AIDA (**374**) by Barbas et al. using List's conditions[410] (Scheme 253).[468]

Another application of this simple yet useful transformation for the construction of a quaternary stereocenter was developed for the total synthesis of the LFA-1 antagonist BIRT-377 (**375**).[412] This time, proline was not an appropriate catalyst: after 5 days, the amination product **372d** was obtained in 90% yield, but only with moderate enantioselectivity (44% ee). However, (*S*)-proline-derived tetrazole **102** turned out to be a good choice, affording the product

Scheme 254. Enantioselective Total Synthesis of LFA-1 Antagonist BIRT-377 through Direct Asymmetric α-Amination of a Branched Aldehyde



Scheme 255. Proline-Catalyzed Assembly Reactions of Acetone, Dibenzyl Azodicarboxylate, and Aldehydes



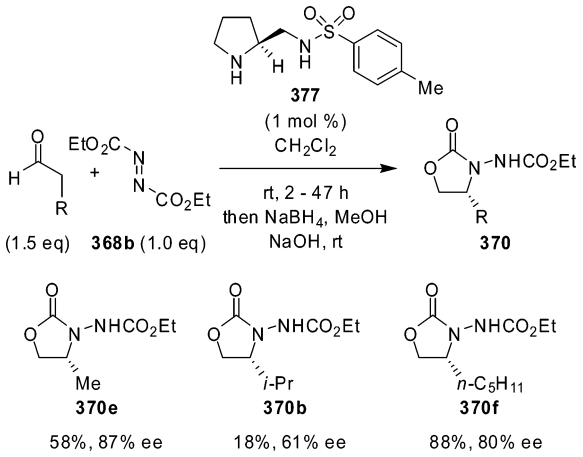
372d in 95% yield after 3 h with 80% ee (Scheme 254). α-Aminated aldehyde **372d** was elaborated to BIRT-377 (**375**) by standard transformations.

The proline-catalyzed α-amination of aldehydes can be combined with an acetone aldol reaction to produce optically active β-hydrazino alcohols **376**.[469] Both acetone (**35**) and the aldehydes act as nucleophiles. In the presence of 20 mol % (*S*)-proline, a number of aldehydes were found to undergo facile reaction to produce β-aminated alcohols **376** in high yields (Scheme 255). In most cases the products were obtained as an ~1:1 mixture of two diastereomers with excellent ee's for the *anti*-diastereomers.

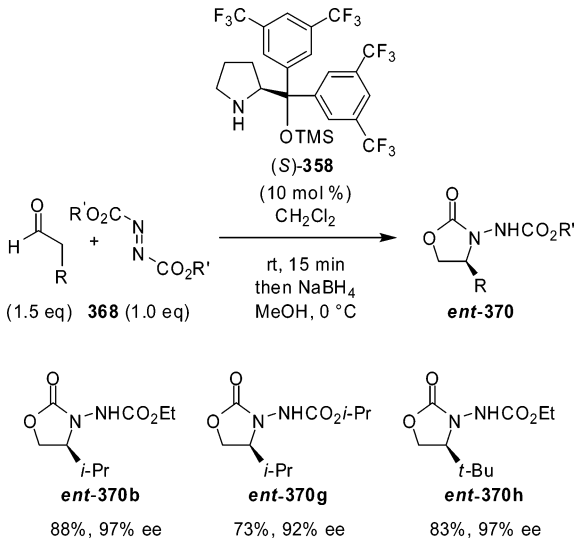
Likewise for aldol, Mannich, and Michael reactions, catalysts other than proline have also been used for the α-amination reaction. After screening a series of monosulfonyl-2-aminomethylpyrrolidines, Adolfsson and co-workers found sulfonamide **377** as the optimum catalyst for the direct asymmetric α-amination of aldehydes with DEAD (Scheme 256).[413] Only 1 mol % **377** is enough to bring about the transformation, and the products were isolated as *N*-amino oxazolidinones **370** in moderate to good yields and enantioselectivities. Although the enantioselectivities are lower as compared to proline itself, the attractive feature of the Adolfsson method is the low catalyst loading.

The Jørgensen group developed a proline derivative (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]-pyrrolidine (**358**) (Scheme 257) based on the steric shielding mechanism (vide infra) as a general catalyst for a number of α-functionalizations of aldehydes.[394] A similar silyloxy-lated catalyst containing phenyl instead of bistrifluoromethylphenyl groups (**265**) has independently been developed by

Scheme 256. Pyrrolidine Sulfonamide-Catalyzed Enantioselective α-Amination of Aldehydes



Scheme 257. Diarylprolinol Silyl Ether as Catalyst for the Enantioselective α-Amination of Aldehydes

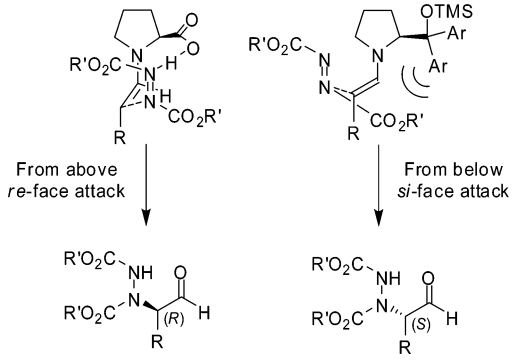


Hayashi and co-workers for the Michael reaction (vide supra).[366] This diarylprolinol silyl ether **358** was found to be an active catalyst for the direct α-amination of aldehydes.[394] A number of aldehydes underwent α-amination within 15 min in the presence of 10 mol % catalyst **358** to afford the products (isolated as *N*-amino oxazolidinones ***ent*-370**) in good yields and high enantioselectivities (Scheme 257).

Besides the high activity and high selectivity obtained with this catalyst, an intriguing feature of **358** is that the aminated products were obtained with the opposite configuration compared to those obtained with proline. The authors explained this observation based on the nature of the transition states (Scheme 258). While in the case of proline-catalyzed reactions, the *re*-face attack to the electrophile azodicarboxylate is driven by hydrogen bonding from the carboxylic acid group of proline, one of the 3,5-bistrifluoromethyl phenyl groups in catalyst **358** efficiently covers the *re*-face of the enamine.[394] Therefore, the electrophilic attack to the enamine must occur from the *si*-face, resulting in the formation of the (*S*)-product.

Shortly after their first report of the proline-catalyzed direct asymmetric aldehyde α-amination,[467] the Jørgensen group extended the scope of this reaction to ketone substrates.[470] Similar reaction conditions to those for the aldehyde were

Scheme 258. Transition State Model for the α-Amination Catalyzed by Proline and Diarylprolinol Silyl Ether (*S*)-358



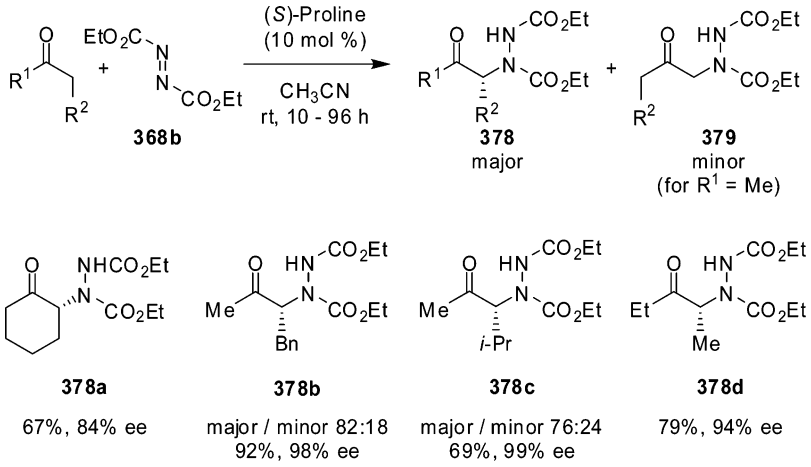
employed to obtain α-hydrazino ketones (**378** and **379**) in good yields and excellent enantioselectivities (Scheme 259). The reaction occurs in a highly regioselective fashion (major/minor up to 10:1): Amination takes place at the higher substituted α-position. In most cases, these products, after silica gel column chromatographic purification, were obtained with slightly decreased optical purities. Using different reducing agents, the authors presented the diastereoselective reduction of the keto functionality to acquire both *syn*- and *anti*-*β*-amino alcohols, which can easily be converted to the corresponding oxazolidinones.

Further developments in the α-amination include the performance of the reaction in unconventional reaction media such as ionic liquids instead of conventional organic solvents. Ionic liquids have previously been used in other organocatalytic reactions such as aldol and Michael addition reactions with variable results.[185,186,414] Toma and co-workers thoroughly investigated the scope of various ionic liquids, catalysts, substrates, and other reaction parameters.[415] (*S*)-Proline was chosen as the catalyst at room temperature in the ionic liquid [bmim][BF_4] to demonstrate the aldehyde substrate scope for the reaction with DEAD (**368b**). Unlike the case in conventional organic solvents, only a slight excess of aldehyde (1.1 equiv) is sufficient to obtain the aminated products (isolated as *N*-amino oxazolidinones **370**) in good yields in the presence of 5 mol % (*S*)-proline within a relatively short period of time (Scheme 260). Although the enantioselectivities are lower in most cases as compared to the reaction in organic solvents, one example showed that the use of higher catalyst loading (10 mol %) and 1.5 equiv of aldehyde can lead to even higher enantioselectivity. Ketones proved to be incompatible substrates in this reaction media: inseparable mixtures of mono- and bis-aminated products were obtained in almost all cases. Catalyst recycling is possible, however with somewhat lower yields and selectivities, presumably due to partial loss of catalyst during the extraction.

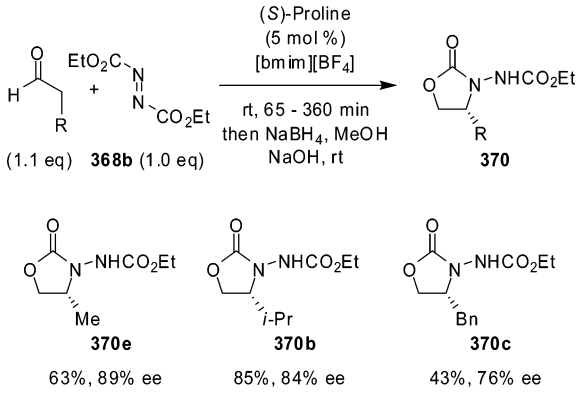
All the α-amination reactions discussed so far rely on diazodicarboxylate as the nitrogen source. Easier to handle nitroso compounds are mostly neglected for this purpose, mainly due to their tendency to react at oxygen to generate aminoxylation products in the enamine-catalytic mode (see section 5.3) rather than forming hydroxyamination products.

Gong, Jiang, and co-workers showed for the first time that nitrosobenzene (**380**) can be used for asymmetric hydroxyamination of carbonyl compounds via enamine catalysis.[416] In the presence of 10 mol % prolinamide derivative **381**, some α-branched aldehydes underwent α-hydroxyamination (nitroso aldol reaction) with nitrosobenzene **380** (Scheme

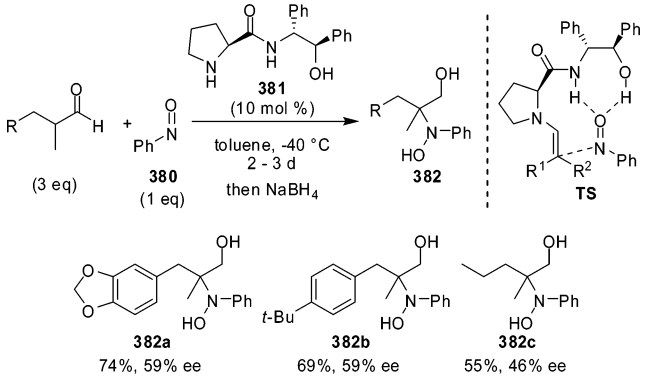
Scheme 259. Proline-Catalyzed Direct Asymmetric α-Amination of Ketones



Scheme 260. Proline-Catalyzed α-Amination of Aldehydes in Room-Temperature Ionic Liquid [bmim][BF_4]

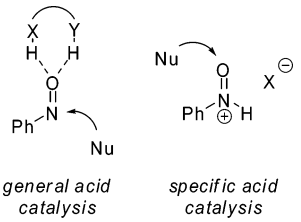


Scheme 261. First Asymmetric Enamine Catalytic Hydroxyamination (Nitroso Aldol Reaction) of Aldehydes

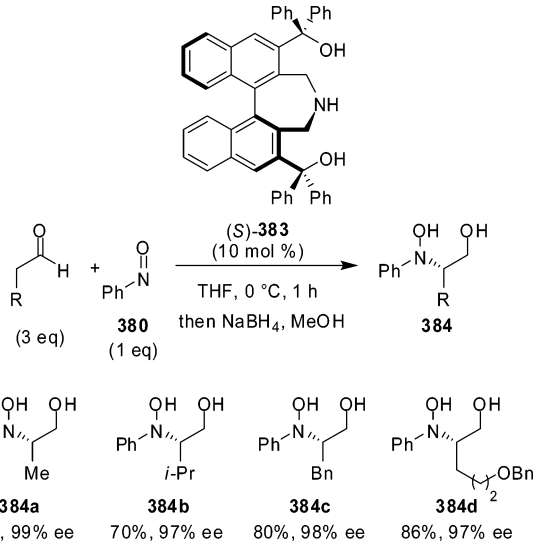


261). After reduction with $NaBH_4$, the corresponding alcohols **382** were obtained in moderate yield and enantioselectivity. No oxyamination products were observed. Despite the moderate enantioselectivities obtained in this reaction, it represents the first enamine catalytic hydroxyamination of carbonyl compounds with nitrosobenzene. The authors provided a transition state model **TS** to explain the reactivity pattern with catalyst **381** compared to that with proline, where aminoxylation occurs exclusively (see section 5.3). In contrast to the proline-catalyzed reaction, where protonation at the more basic nitrogen of nitrosobenzene activates its oxygen toward nucleophilic attack (vide infra), double hydrogen bonding from catalyst **381** to the oxygen of nitrosobenzene activates its nitrogen (Scheme 262).[416] This is due to the difference in acidity between the carboxyl group of

Scheme 262. Difference in Nitrosobenzene Reactivity under General and Specific Acid Catalysis



Scheme 263. Catalytic Asymmetric α-Hydroxyamination of Aldehydes by Maruoka et al.

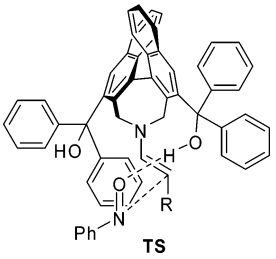


proline, and the amide and hydroxyl groups of catalyst **381**.

Quite recently, Maruoka and co-workers reported a highly enantioselective α-hydroxyamination of aldehydes with nitrosobenzene catalyzed by a designed chiral secondary amine.[417] The authors introduced a new C_2-symmetric binaphthyl-based secondary amine catalyst **383** containing hydroxyl groups for the α-hydroxyamination of a number of unbranched aldehydes using nitrosobenzene (**380**) as the reagent (Scheme 263). The pronounced effect of the hydroxyl group on both the reactivity and the enantioselectivity was demonstrated. After in situ reduction of the aldehyde group, products **384** were obtained in good yield and excellent enantioselectivity (up to 99% ee).

The authors also showed that the synthetic utility of this reaction could be enhanced if an easily cleavable group was

Scheme 264. Proposed Transition State Model for the Asymmetric α-Hydroxyamination of Aldehydes



TS

used in the reagent instead of phenyl; 4-methoxynitrosobenzene served as the reagent, and the product was manipulated to afford *β*-amino alcohol or 1,2-diamine in good yield with a similar level of enantioselectivity.[417] A transition state model **TS** was proposed to account for the observed stereoselectivity (Scheme 264). One bulky hydroxydiphenylmethyl group of the catalyst shields the *re*-face of the enamine while the other directs and activates the nitrosobenzene toward nucleophilic attack via hydrogen bonding to its oxygen atom.[417]

Kim and Park showed that when proline-derived tetrazole catalyst **102** was used for the reaction of nitrosobenzene (**380**) with α-branched aldehydes, selective formation of the α-hydroxyamination product (**382**) over the α-aminoxylation product (**385**) was observed in some cases (Scheme 265).[418] However, the selectivity varies dramatically depending on the nature of the substrates. Remarkably high *N*- vs *O*-addition selectivity was observed for α-methyl-α-aryl-substituted aldehydes, although the enantioselectivities are only moderate. Other substrates afforded both the products in almost equal amounts, but the hydroxyaminated products were obtained with up to 90% ee. The preferential formation of the hydroxyaminated products was explained on the basis of steric congestion in the transition state.[418]

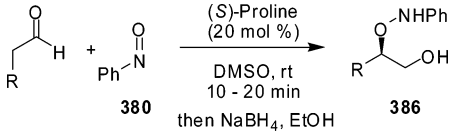
5.3. α-Oxygenation

α-Oxygenated carbonyl compounds are important not only due to their presence in many natural and non-natural biologically active compounds but also because of their utility for the synthesis of other useful building blocks such as diols. Obtaining α-hydroxy carbonyl compounds in enantiomerically pure form poses a natural attraction to the synthetic organic chemists. With the breathtaking applications of asymmetric enamine catalysis in hand for the α-functionalization of carbonyl compounds with a variety of electrophiles, a natural extension was to use this concept in combination with a suitable oxygen electrophile.

Following the discovery of Yamamoto and co-workers of the use of nitrosobenzene as the electrophilic source of oxygen in the asymmetric metal-catalyzed α-oxygenation of tin enolates in 2003,[419] three different groups almost contemporaneously reported the direct α-aminoxylation of aldehydes using (*S*)-proline as catalyst.[420−422]

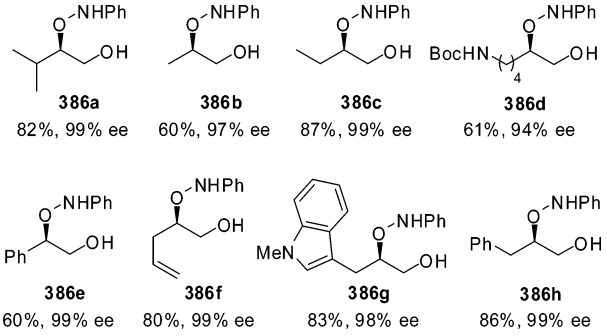
Zhong described that, in the presence of 20 mol % (*S*)-proline in DMSO at room temperature, a series of unbranched aldehydes rapidly react with nitrosobenzene (**380**) to generate the α-aminoxylated aldehydes with excellent enantioselectivity (Schemes 266 and 267).[420] After in situ reduction with

Scheme 266. Proline-Catalyzed α-Aminoxylation of Aldehydes by Zhong



380 **386**

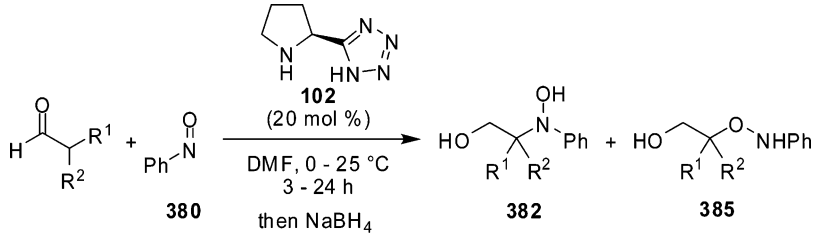
Scheme 267. A Selection of Products Obtained from the Proline-Catalyzed α-Aminoxylation of Aldehydes



386a 82%, 99% ee
386b 60%, 97% ee
386c 87%, 99% ee
386d 61%, 94% ee
386e 60%, 99% ee
386f 80%, 99% ee
386g 83%, 98% ee
386h 86%, 99% ee

$NaBH_4$, the products **386** were generally isolated in high yield. A transition state model similar to the one initially proposed for the proline-catalyzed intermolecular aldol reaction[10] was invoked to rationalize the observed selectivity.

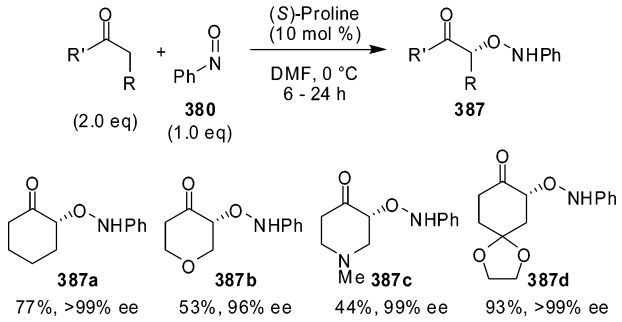
Scheme 265. Proline Tetrazole-Catalyzed Asymmetric α-Hydroxyamination of α-Branched Aldehydes



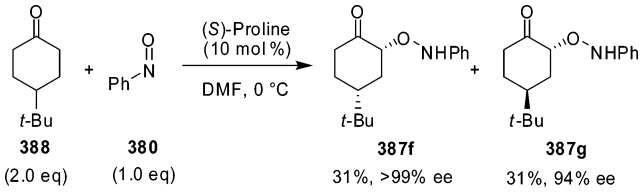
380 **382** **385**

R^1	R^2	Yield (%)	**382**/**385**	ee **382** (%)	ee **385** (%)
Me	4-(OMe)-Bn	75	1.7:1	90	35
Me	Ph	83	20:1	64	n.d.
Me	4-(OMe)-Ph	65	10:1	45	n.d.
Me	CH_2OBn	89	0.8:1	79	5
Me	Et	76	1.7:1	70	8
Et	Bn	67	1.3:1	25	11

Scheme 268. Proline-Catalyzed Asymmetric α-Aminoxylation of Cyclic Ketones



Scheme 269. An Example of Proline-Catalyzed Asymmetric Desymmetrization of 4-Substituted Cyclohexanone



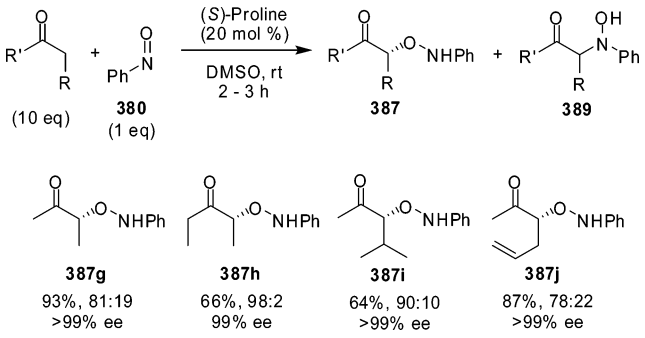
MacMillan and co-workers showed that the same level of enantioselectivity could be achieved using much lower catalyst loading (typically 2−5 mol %, but 0.5 mol % is also possible) when the reaction was conducted in chloroform at 4 °C.[421] Hayashi et al., on the other hand, preferred to use 30 mol % (*S*)-proline in acetonitrile at lower temperature (−20 °C), leading to a similar level of enantioselectivities.[422] A selection of products obtained by these methods are shown in Scheme 267. Cleavage of the O−N bond was also illustrated under catalytic hydrogenation to obtain the diol without loss of optical purity.[420,421]

The Hayashi group successfully extended the scope of this reaction to ketone substrates.[422−424] A major problem for ketone substrates is their low reactivity as compared to aldehydes, which leads to homodimerization of nitrosobenzene as well as α,α′-diaminoxylation. The authors showed that both of these side reactions could be circumvented by carrying out slow addition of nitrosobenzene at low temperature. Under these conditions, a number of six-membered cyclic ketones were α-aminoxylated in good yield and with nearly perfect enantioselectivity (Scheme 268). Typically the reactions were conducted in DMF in the presence of 10 mol % (*S*)-proline with an excess of ketone at 0 °C. In the case of 2-butanone, a ∼1:1 mixture of 2-aminoxylated 3-butanone and 2-hydroxyaminated 3-butanone was obtained.[423] Whereas the aminoxylated product was obtained with >99% ee, the ee of the hydroxyaminated product was found to be only 4%. Partial racemization was observed when cleaving the O−N bond with $CuSO_4$.

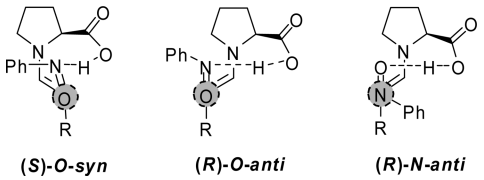
Hayashi et al. also demonstrated an application of asymmetric α-aminoxylation of 4-substituted cyclohexanones **388** (Scheme 269).[423] Here an asymmetric desymmetrization takes place during the enamine formation followed by a diastereoslective α-aminoxylation of the enamine. Although the selectivity of the initial step is not high, that of the second step is excellent.

At the same time as Hayashi et al., Córdova and co-workers developed a proline-catalyzed α-aminoxylation of ketones.[425,426] Besides cyclohexanone, which provided excellent levels of selectivity (see Scheme 268), the authors mainly focused on acyclic ketones as substrates. Both aminoxylated and hydroxyaminated products (**387** and **389**, respectively) were formed with fairly good selectivity in favor of aminoxylated products, and the reaction occurred exclusively on the methylene carbon of ketones (Scheme 270). Almost perfect enantioselectivity was observed for the aminoxylated products **387** whereas the hydroxyaminated products **389** were obtained with only low ee. The authors showed that when cyclohexanone was used as the substrate, the corresponding C_2-symmetric α,α′-diaminoxylated ketone could also be obtained with >99% ee.[425]

Scheme 270. Proline-Catalyzed Asymmetric α-Aminoxylation of Acyclic Ketones (The Ratios Indicate the Ratio of 387 to 389)



Scheme 271. Calculated Transition State Models for the Proline-Catalyzed α-Aminoxylation of Aldehydes

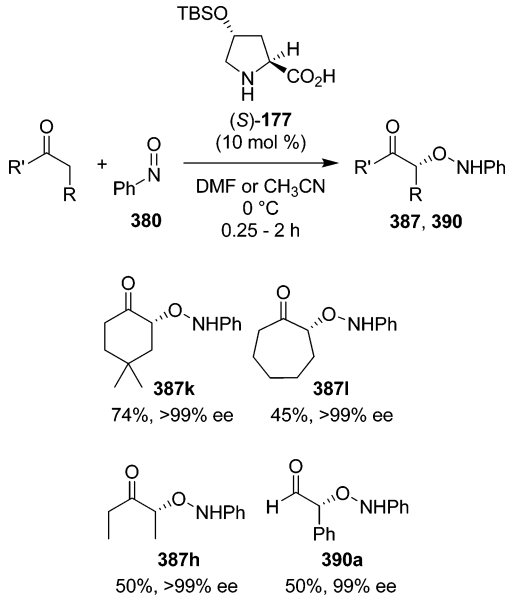


Both the Córdova group[426] and Houk et al.[471] conducted quantum mechanical computational studies to understand the mechanism of proline-catalyzed α-aminoxylation reactions as well as to explain the observed selectivity of aminoxylation products over hydroxyamination products. The transition state for attack at nitrogen (***N-anti***) is higher in energy (2.6 kcal/mol) than the one for attack at oxygen (***O-anti***) (Scheme 271).[471] The higher basicity of nitrogen accounts for its preferential protonation, rendering the oxygen atom to become electrophilic. Among the two transition state structures for the attack at oxygen, ***O-syn*** is 3.3 kcal/mol higher in energy than ***O-anti*** and gives the minor enantiomeric product.

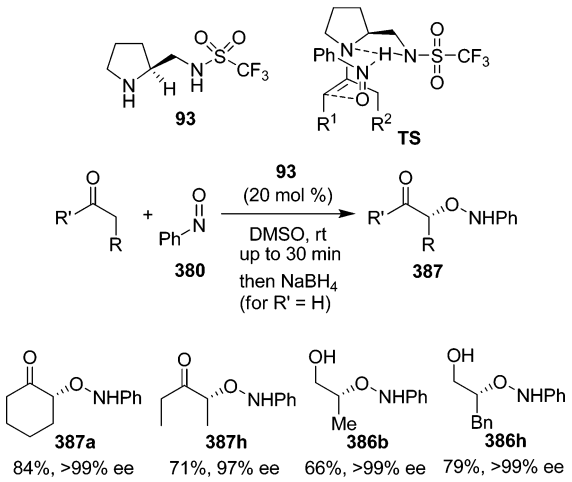
Blackmond and co-workers studied the kinetic behavior of this reaction experimentally and reported some interesting observations.[472] In the absence of a long preequilibration of proline with an excess of aldehyde, the authors found pronounced rate acceleration and, in contrast to the report of Córdova et al.,[426] a positive nonlinear effect. Based on these findings, an alternative and more complex mechanism was proposed where equilibration between proline and the product generates an improved catalyst, which accounts for the dramatic rate acceleration.[472] Further experimental as well as computational studies by the Blackmond group led to a mechanistic proposal involving only soluble proline complexes or adducts formed by a series of hydrogen bonding between proline and the reaction products.[473]

Other catalysts besides proline have also been used for asymmetric α-aminoxylation reactions. In 2004, Hayashi and co-workers reported the application of *trans*-4-*tert*-butyldim-

Scheme 272. 4-Silyloxy Proline-Catalyzed Asymmetric α-Aminoxylation of Aldehydes and Ketones



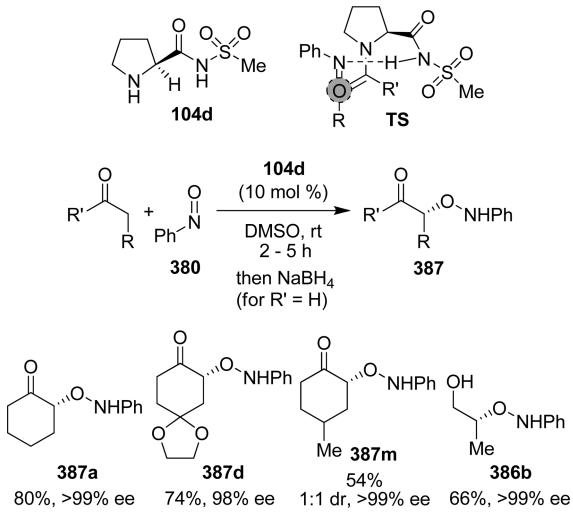
Scheme 273. Pyrrolidine Sulfonamide-Catalyzed Asymmetric α-Aminoxylation of Aldehydes and Ketones



ethylsilyloxy-(*S*)-proline (**177**) for this reaction (Scheme 272).[232] Introduction of the bulky silyloxy group at the 4-position of proline greatly enhances its solubility in a wide range of organic solvents, which enables faster reaction with lower catalyst loading. The remarkable catalytic efficiency of this proline derivative was evident from the fact that α-aminoxylation of cyclohexanone was complete within *1 min* in the presence of 30 mol % **177** and the product was obtained in 68% yield and >99% ee.[232] A number of aldehydes and ketones were aminoxylated using 10 mol % **177** within a short period of time to obtain products in moderate to good yields and with excellent enantioselectivities (Scheme 272).

Wang et al. applied the pyrrolidine sulfonamide catalyst **93** for the aminoxylation of a number of aldehydes and ketones (Scheme 273).[427] In the presence of 20 mol % catalyst, the reaction was found to undergo completion within 30 min to afford the products in good yield and excellent enantioselectivity. The authors showed that the catalyst loading could be decreased to 1 mol % without any loss in enantioselectivity. A transition state model (**TS**) was also

Scheme 274. Proline-Derived *N*-Methylsulfonylcarboxamide in Asymmetric α-Aminoxylation of Aldehyde and Ketones



proposed to rationalize the observed stereoselectivity of the reaction.

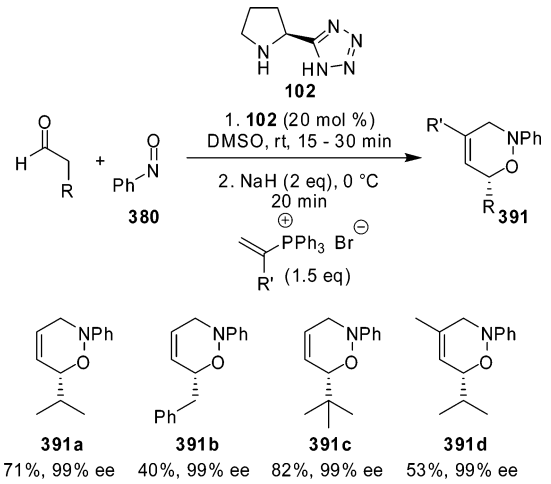
Córdova and co-workers showed that the catalytic efficiency of proline could be greatly improved by converting it to *N*-methylsulfonylcarboxamide **104d** (Scheme 274).[428] A number of cyclic ketones and propionaldehyde were aminoxylated with 10 mol % **104d** in DMSO at room temperature. The reaction was found to undergo completion within 2−5 h to afford the products **387** in good yield and excellent enantioselectivity (Scheme 274). Similar to the proline-catalyzed reaction, in the case of ketones, the formation of α,α′-diaminoxylated products was suppressed by slow addition of nitrosobenzene. A transition state model **TS** similar to the one for the proline-catalyzed reaction (see Scheme 271) was invoked to account for the stereochemical outcome of the reaction (Scheme 274).[428]

Although proline-derived tetrazole **102** as catalyst afforded selectively the hydroxyaminated products with α-branched aldehydes (see Scheme 265), Ley and co-workers showed that this catalyst could be applied successfully for aminoxylation of unbranched aldehydes.[429] Instead of aldehyde reduction as the commonly used product isolation method, Ley et al. introduced a sequential intramolecular Wittig olefination protocol to produce synthetically useful dihydro-1,2-oxazines **391** (Scheme 275). A number of unbranched aldehydes were employed as substrates to obtain the corresponding dihydro-1,2-oxazines with excellent ee in moderate to good yield. Reductive cleavage of the N−O bond with Zn/HCl afforded *cis*-allylic alcohols in excellent yields.[429]

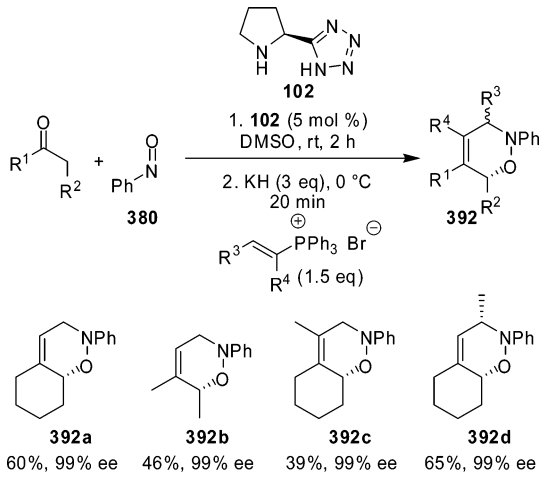
The extension of this methodology for ketone substrates has also been demonstrated by Ley et al.[430] This time, a lower catalyst loading (5 mol %) was sufficient to induce excellent enantioselecivity. A number of six-membered cyclic ketones and butanone were used as substrates, and the corresponding dihydro-1,2-oxazines **392** were obtained in moderate yields (Scheme 276).

Jiang, Wang, and co-workers performed the proline-catalyzed asymmetric α-aminoxylation reaction at room temperature in the ionic liquid [bmim][BF_4].[431] A number of aldehydes and ketones were aminoxylated using 20 mol % proline at room temperature with high yields and excellent enantioselectivities (Scheme 277). The authors showed that the catalyst loading could be reduced to 1 mol % without any loss of enantioselectivity. Products were isolated by

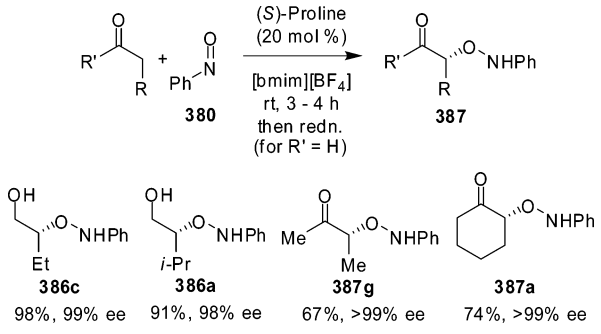
Scheme 275. Asymmetric Aldehyde Aminoxylation/ Intramolecular Wittig Olefination Sequence to Dihydro-1,2-oxazines



Scheme 276. Asymmetric Ketone Aminoxylation/ Intramolecular Wittig Olefination Sequence to Dihydro-1,2-oxazines



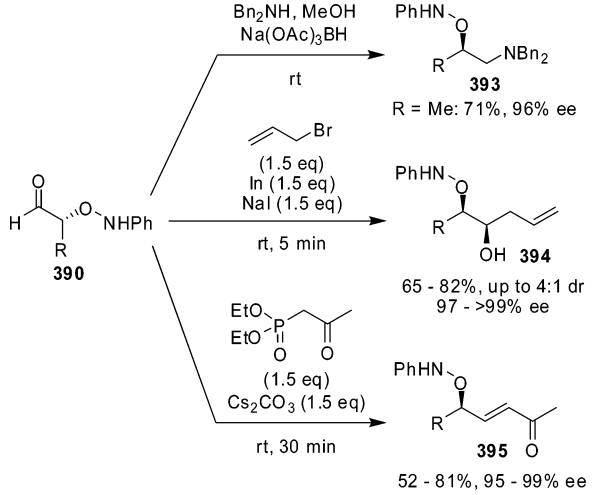
Scheme 277. Proline-Catalyzed Asymmetric α-Aminoxylation in Room-Temperature Ionic Liquid



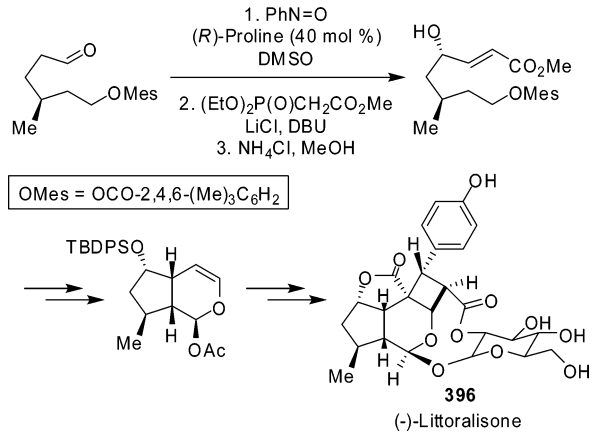
simple extraction, which leaves the catalyst in the ionic liquid phase; this enables catalyst recycling at least four times without sacrificing the yield or enantioselectivity.[431]

When aldehydes were used as substrates for the asymmetric aminoxylation reaction, the corresponding products α-aminoxy aldehydes **390** (Scheme 278) are relatively unstable. The most commonly used method for isolation of such compounds comprised reduction to the alcohol as described above. However, several research groups have illustrated in situ functionalizations of **390**, which not only enables the isolation of the products as stable compounds

Scheme 278. Further in Situ Transformation of α-Aminoxy Aldehydes to Chiral Building Blocks



Scheme 279. Proline-Catalyzed α-Aminoxylation/HWE Olefination in the Total Synthesis of Littoralisone



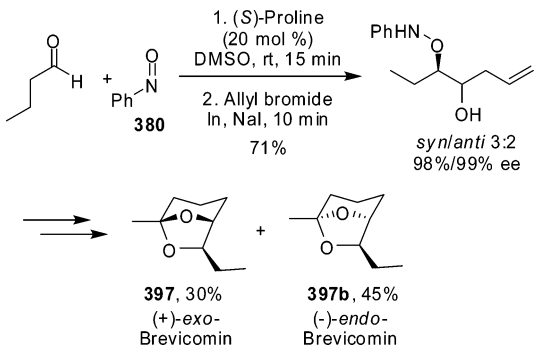
but also allows for the construction of important chiral building blocks, particularly after cleavage of the O−N bond (Scheme 278). The aminoxylation/intramolecular Wittig olefination sequence[429] has already been depicted above (see Scheme 275). MacMillan et al. described the in situ transformation to 1,2-amino alcohol **393** in good yield by treatment with dibenzylamine under reductive conditions.[421] Zhong reported a tandem allylation reaction to obtain monosubstituted *syn*-1,2-diols **394** in good yield with moderate dr.[474] Later on, Zhong and Yu showed that sequential α-aminoxylation/Horner−Wadsworth−Emmons (HWE) olefination can be carried out to obtain *O*-amino-substituted allylic alcohols **395** in good yields.[475] It is worth mentioning that all these subsequent reactions can be performed without any loss in optical puritiy of the initial product **390**.

A successful application of the sequential proline-catalyzed α-aminoxylation/HWE olefination methodology[475] can be seen in the elegant total synthesis of the structurally related compounds brasoside (not drawn) and littoralisone (**396**) by MacMillan and Mangion (Scheme 279).[210]

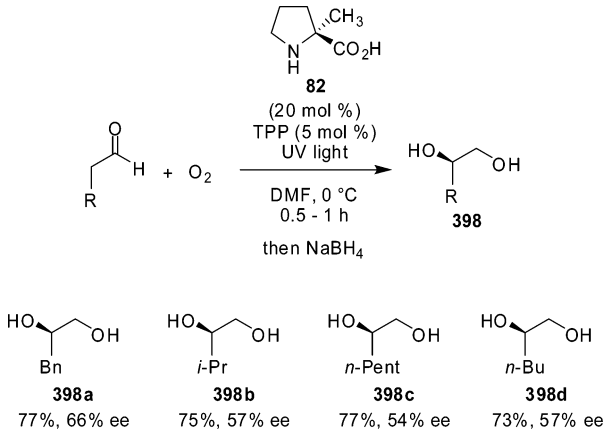
Similarly, the importance of the tandem aminoxylation−allylation reaction[474] was recently demonstrated by Kim et al. during a short and efficient total synthesis of (+)-*exo*- and (-)-*endo*-brevicomin (**397a** and **397b**, respectively) (Scheme 280).[432]

Although nitrosobenzene has emerged as the source of electrophilic oxygen and has been successfully implemented

Scheme 280. Application of the Tandem Aminoxylation−Allylation Reaction to the Total Synthesis of Brevicomin



Scheme 281. α-Methyl Proline-Catalyzed Asymmetric α-Oxygenation of Aldehydes Using Molecular Oxygen

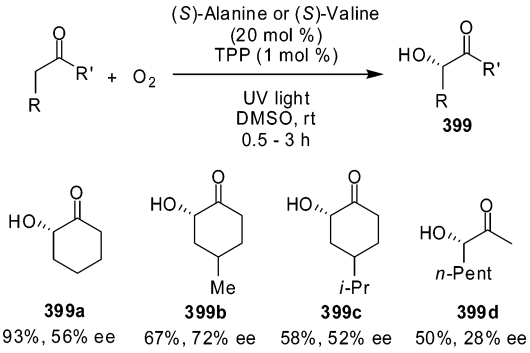


for the highly enantioselective α-aminoxylation of carbonyl compounds, the application of an atom-economic oxygen source is highly desirable. In this context, molecular oxygen as the electrophilic oxygen source for the α-oxygenation of carbonyl compounds would be particularly useful. In 2004, Córdova and co-workers reported the first organocatalytic asymmetric incorporation of molecular oxygen into organic compounds.[433,476] Singlet oxygen ($^1O_2$) was generated from oxygen or air with a catalytic amount of tetraphenylporphine (TPP) in the presence of UV light. Using 20 mol % α-methylproline (**82**) as the catalyst, several unbranched aldehydes were α-oxygenated to obtain the diols (after reduction) in good yields and moderate ee's (Scheme 281).[433]

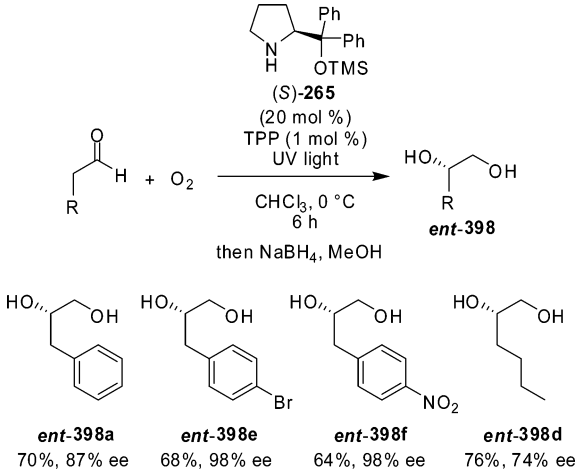
This reaction has also been applied to ketone substrates.[476] This time, the primary α-amino acids (*S*)-alanine and (*S*)-valine proved to be the most efficient catalysts. Both cyclic and acyclic ketones were α-oxygenated under similar reaction conditions to directly obtain α-hydroxy ketones **399** as products after silica gel chromatography (Scheme 282). Alanine turned out to be the catalyst of choice for cyclic ketones, whereas valine was used for the acyclic ketone. Although high yields were obtained in most cases, enantioselectivities were once again only moderate.

Despite the moderate level of enantioselectivities initially obtained in these reactions, these reports[433,476] represent a remarkable advancement in the field of organocatalysis, since the incorporation of molecular oxygen into organic compounds was considered to only be possible by enzymes and transition metal complexes. A mechanistic explanation was also provided by the authors where the attack of the initially generated enamine intermediate to the singlet oxygen fol-

Scheme 282. Primary α-Amino Acid-Catalyzed Asymmetric α-Oxygenation of Ketones Using Molecular Oxygen



Scheme 283. Diphenylprolinol Silyl Ether-Catalyzed Asymmetric α-Oxygenation of Aldehydes Using Molecular Oxygen



lowed by proton transfer from the catalyst carboxyl group produces the α-hydroperoxy carbonyl compounds. Reductive cleavage of the O−O bond during silica gel chromatography then yields the reaction products.[433,476]

Quite recently, the Córdova group improved the enantioselectivity of the aldehyde α-oxygenation reaction by using diphenylprolinol silyl ether **265** as the catalyst (Scheme 283).[434] Excellent enantioselectivities (up to 98% ee) were obtained, in most cases maintaining good yields.

5.4. α-Halogenation

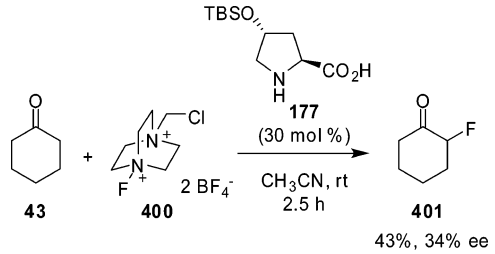
The formation of C−halogen bonds with the simultaneous generation of a stereogenic center at the carbon atom leads to optically active halogen compounds, which are unique targets that can be further manipulated to other important functionalized compounds. This led to increased research toward the development of new methods for catalytic asymmetric C−halogen bond forming reactions.

Enamine-catalyzed asymmetric α-halogenation of carbonyl compounds can be regarded as an important breakthrough in this area. Employing appropriate halogen electrophiles, these elegant reactions give direct access to stereogenic C−halogen centers.

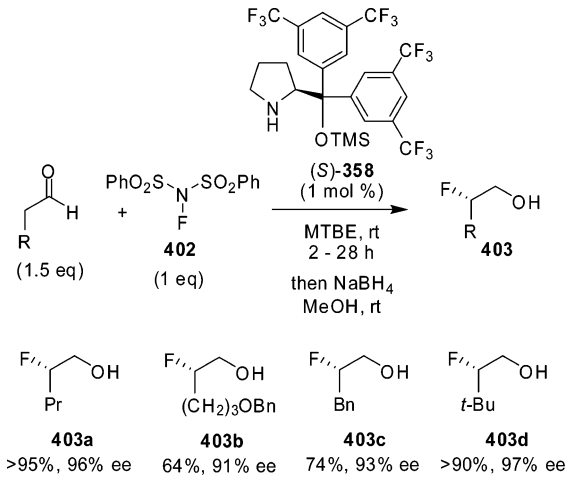
5.4.1. α-Fluorination

Besides being attractive in organic synthesis due to the electronegativity of the fluorine atom and the strength of the C−F bond, fluorinated organic compounds are extremely important in medicinal chemistry due to their exceptional

Scheme 284. The First Enantioselective α-Fluorination of Ketone by Enders et al.



Scheme 285. Diarylprolinol Silyl Ether-Catalyzed Asymmetric α-Fluorination of Aldehydes by Jørgensen et al.



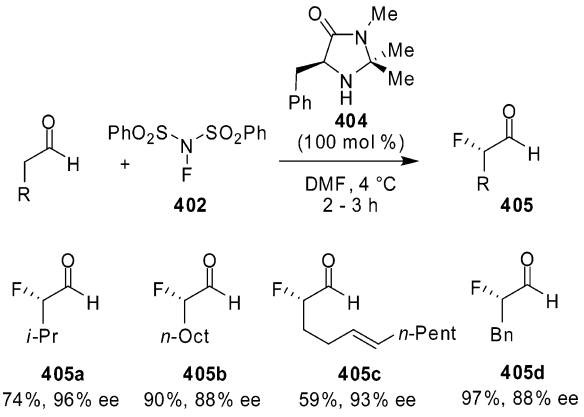
metabolic stability. Therefore, the stereoselective synthesis of fluorinated compounds poses a considerable challenge for synthetic organic chemists. In this respect, enantioselective C−F bond formation is particularly noteworthy due to the difficulty of selective monofluorination. This problem, particularly the α-fluorination of carbonyl compounds, was successfully addressed by several organocatalytic approaches.[409,435]

At the beginning of 2005, Enders et al. reported the first organocatalytic enantioselective α-fluorination of aldehydes and ketones.[436] Selectflour (**400**) (Scheme 284) was applied as the electrophilic fluorine source in the presence of chiral secondary amines. (*S*)-Proline was employed as the catalyst for aldehyde α-fluorination: moderate to good yields were obtained for various aldehydes; the enantioselectivities of the products were not reported. Cyclohexanone **43** was chosen as the substrate for asymmetric α-fluorination (Scheme 284). A number of chiral amines were tested, but the enantioselectivity remained rather low (0−36% ee).

Soon after the report of Enders et al., three research groups independently reported highly enantioselective α-fluorination of aldehydes.[437,438,477] In all these cases, *N*-fluorodibenzenesulfonimide (NFSI, **402**) (Scheme 285) was employed as the fluorinating agent; however, the optimized reaction conditions in each case were quite different.

Jørgensen and co-workers applied the diarylprolinol silyl ether **358** as catalyst.[477] The resulting α-fluorinated aldehydes are rather prone to racemization on silica gel and more volatile than the starting aldehydes. Therefore, the products were isolated as the corresponding alcohols **403** after in situ reduction with $NaBH_4$. A series of unbranched aldehydes were subjected to α-fluorination. **358** turned out to be an efficient catalyst for this reaction, as only 1 mol % catalyst is sufficient for obtaining the products in good to high yields

Scheme 286. Chiral Imidazolidinone-Promoted Asymmetric α-Fluorination of Aldehydes by Barbas et al.



and excellent enantioselectivities (Scheme 285). Catalyst loading can be further lowered to only 0.25 mol % without any effect on conversion and enantioselectivity.[477] With the help of computational studies, the authors also explained the observed product stereochemistry of the α-fluorinated products based on the steric shielding from one of the catalyst aryl groups.

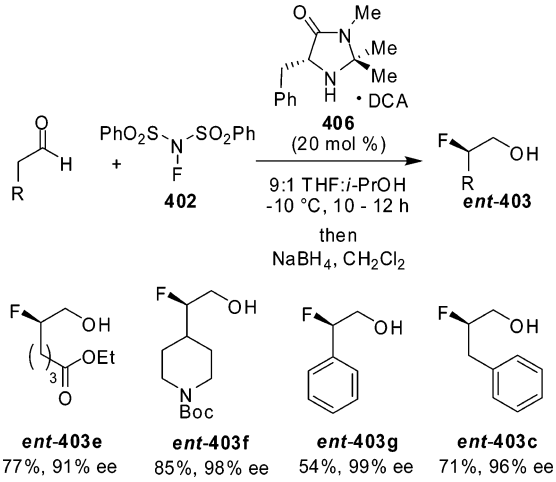
The scope of the reaction has also been extended to branched aldehydes: With a sterically less hindered desilyloxy catalyst, 2-phenylpropanal was successfully α-fluorinated, albeit with only moderate enantioselectivity (48% ee).[477]

Both Barbas' and MacMillan's groups applied the same imidazolidinone to their α-fluorination reactions. After screening a number of different chiral amines, Barbas and co-workers used a stoichiometric amount of the chiral imidazolidinone **404** as chiral promoter in DMF at 4 °C, to observe moderate to excellent yield and good to excellent enantioselectivity for a series of unbranched aldehydes within a short period of time (Scheme 286).[437] Barbas et al. also showed that when a substoichiometric amount (30 mol %) of prolinol triisopropylsilyl ether was used as catalyst, branched aldehydes can be α-fluorinated with excellent yield but only with moderate ee (up to 66% ee).[437]

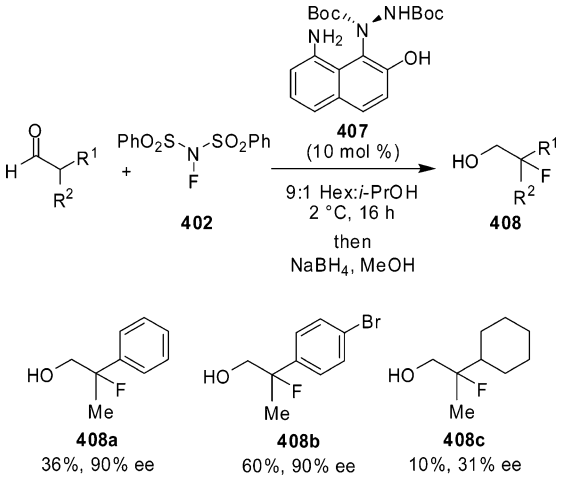
In contrast to the report of Barbas et al., MacMillan and co-workers showed that the chiral imidazolidinone can be employed in a catalytic amount when used in combination with an equimolar amount of acid.[438] Thus, 20 mol % dichloroacetic acid (DCA) salt **406** catalyzed the reaction of a series of linear aldehydes with NFSI in a 10% *i*-PrOH/THF mixture to afford the fluorinated products in good to high yields and excellent enantioselectivities (Scheme 287). The reaction can be performed in a variety of different organic solvents without significant influence on enantioselectivity; even acetone can be used as the solvent without any observable solvent fluorination or aldol reaction. The catalyst loading can be decreased to as low as 2.5 mol % when the reaction was carried out at an appropriate temperature without any loss in enantiocontrol.[438] The resulting α-fluoro aldehydes were found to be configurationally stable under the mild reaction conditions.

Quite recently, the Jørgensen group applied their newly developed non-biaryl atropisomeric amine **407** (Scheme 288) to the asymmetric α-fluorination of α-branched aldehydes.[439] In the presence of 10 mol % catalyst (with 96% ee), a number of aliphatic and aromatic α-branched aldehydes were α-fluorinated in moderate yields (10−60%) and moderate to high

Scheme 287. Chiral Imidazolidinone Salt-Catalyzed Asymmetric α-Fluorination of Aldehydes by MacMillan et al.



Scheme 288. Asymmetric α-Fluorination of α-Branched Aldehydes Catalyzed by a Non-biaryl Atropisomeric Amine



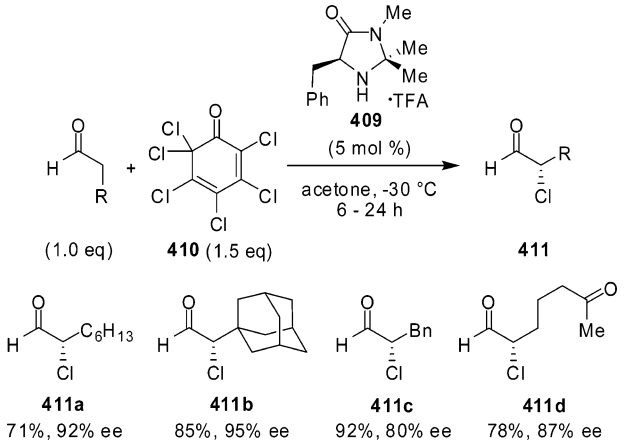
enantioselectivities (7−90% ee) using NFSI (**402**) as the fluorine source. This represents the first example of an organocatalyst where the chirality originates from non-biaryl atropisomerism.

5.4.2. α-Chlorination

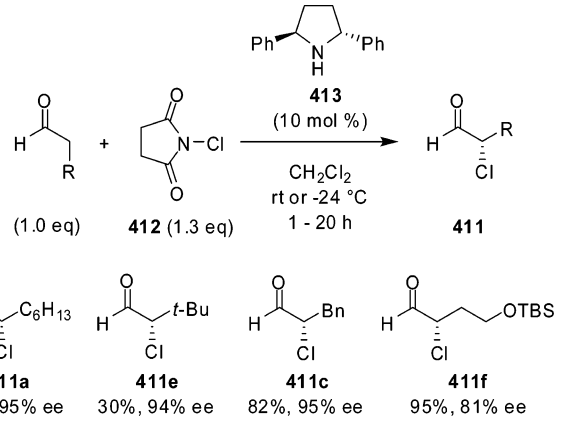
Chiral α-chloro carbonyl compounds are particularly versatile synthetic intermediates due to their potential for further synthetic transformations. For instance, chiral α-chloro aldehydes are excellent substrates for the synthesis of optically active epoxides, amino acid derivatives, and amino alcohols. The direct organocatalytic asymmetric α-chlorination represents the first approach toward α-halogenation reactions and opened up the route for other related α-functionalizations (e.g., α-selenylation).

The direct organocatalytic enantioselective α-chlorination of aldehydes was independently reported by the MacMillan[440] and Jørgensen[441] groups in 2004. MacMillan et al. applied the TFA salt of chiral imidazolidinone **409** as the catalyst for the direct α-chlorination of aldehydes with the electrophilic chlorinating agent perchlorinated quinone **410** (Scheme 289).[440] Proline proved to be an extremely active catalyst for the chlorination with *N*-chlorosuccinimide (NCS, **412**), but the product was obtained with very low ee. In the presence of only 5 mol % catalyst **409**, a variety of linear

Scheme 289. Chiral Imidazolidinone-Catalyzed Direct Asymmetric α-Chlorination of Aldehydes by MacMillan et al.



Scheme 290. Direct Asymmetric α-Chlorination of Aldehydes Catalyzed by C_2-Symmetric Diphenylpyrrolidine

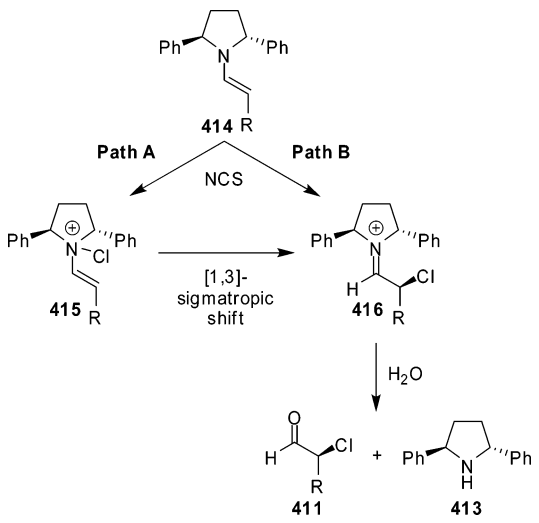


aldehydes underwent facile α-chlorination in acetone at −30 °C to afford the products in high yields and enantioselectivities. No chlorination of acetone was observed under the applied reaction conditions. The reaction can be performed in various organic solvents without significant alteration of yield and enantioselectivity. The authors also demonstrated the synthetic advantage of this method by chlorinating an enantiopure *β*-chiral aldehyde: depending on the catalyst enantiomer, *syn*- or *anti*-adducts were obtained in high diastereoselectivity.

Jørgensen and co-workers utilized NCS (**412**) as the chlorinating agent for aldehydes in a reaction catalyzed by either prolinamide or (2*R*,5*R*)-diphenylpyrrolidine (**413**) (Scheme 290).[441] The catalyst (10 mol %) was used in combination with 1.3 equiv of NCS (**412**) to afford the products in high yields and excellent enantioselectivities. Although prolinamide is a more active catalyst than C_2-symmetric diphenylpyrrolidine **413**, the latter was found to induce higher enantioselectivity in most cases. The authors established the synthetic utility of α-chloro aldehydes by transforming them into a variety of chiral building blocks such as a terminal epoxide, 2-amino alcohols, and non-proteinogenic α-amino acid derivatives under perpetuation of the optical purity.[441]

During the mechanistic studies of 2,5-diphenylpyrrolidine (**413**)-catalyzed enantioselective α-chlorination of aldehydes by Jørgensen and co-workers, DFT studies showed the absence of any face shielding in the enamine intermediate

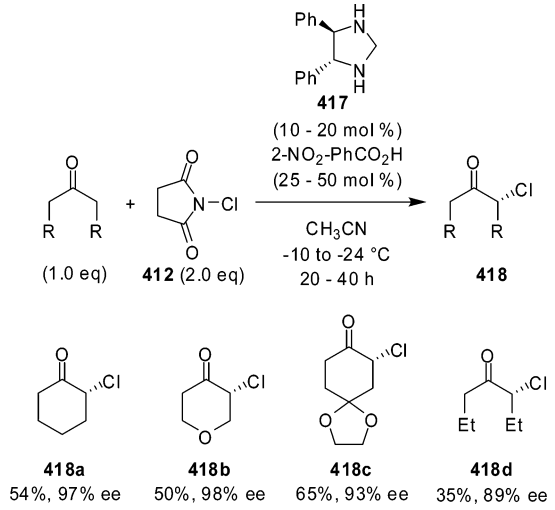
Scheme 291. Mechanistic Proposals for the Diphenylpyrrolidine-Catalyzed α-Chlorination of Aldehydes by Jørgensen et al.



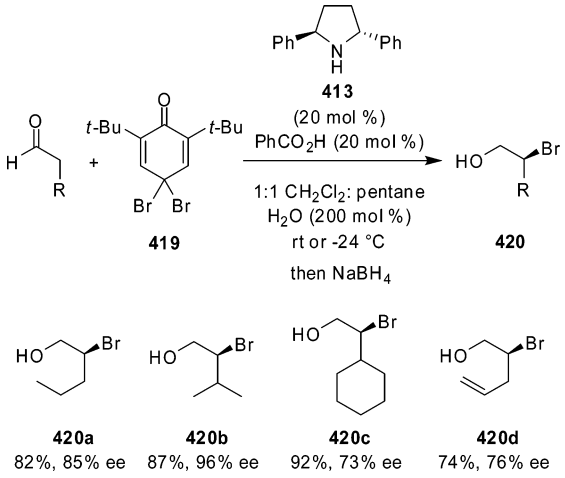
414 (Scheme 291).[442] This interesting observation led the authors to thoroughly investigate the origin of stereoinduction by means of combined experimental and computational studies. As opposed to the commonly accepted enamine mechanism (path B, Scheme 291), an alternative pathway (path A) was proposed where the reaction proceeds via the formation of a kinetically controlled *N*-chlorinated species **415**, which upon rapid [1,3]-sigmatropic shift leads to the energetically favorable iminium intermediate **416**. The rate determining hydrolysis of this iminium intermediate **416** liberates the product and regenerates the catalyst. The DFT calculation for this pathway not only accounts for the formation of the observed product enantiomer, but the experimental optical purity was also predicted with high accuracy. Although sufficient theoretical and experimental evidence supports this mechanism, the direct C−Cl bond formation from the enamine intermediate **414** has not been completely excluded.[442]

The identification of appropriate conditions for the α-chlorination of ketones was rather challenging due to their inherent lower reactivity as compared to aldehydes as well as the possibility of polychlorination. Nevertheless, the Jørgensen group reported the first organocatalytic direct α-chlorination of ketones shortly after their report of aldehyde α-chlorination.[443] Interestingly, their best catalyst for the aldehyde α-chlorination proved to be unproductive for ketone substrates. After carefully screening different catalyst systems, a combination of 4,5-diphenylimidazolidine **417** and 2-nitrobenzoic acid turned out to be an efficient system for the α-chlorination of various cyclic and acyclic ketones, with NCS (**412**) as the chlorinating agent (Scheme 292). Using 10−20 mol % catalyst **417**, the chlorinated products were obtained in excellent enantioselectivities in most cases. Low yields are due to formation of a considerable amount of polychlorinated ketones and partial chlorination of the catalyst. This also explains the requirement of an excess of NCS in the reaction. Intrigued by the formation of polychlorinated products, the authors also investigated the kinetic resolution of racemic 2-chlorocyclohexanone, with fruitful results. The synthetic usefulness of the products was also demonstrated by their conversion into other functionalized compounds.[443]

Scheme 292. The First Organocatalytic Asymmetric Direct α-Chlorination of Ketones



Scheme 293. The First Asymmetric Organocatalytic α-Bromination of Aldehydes

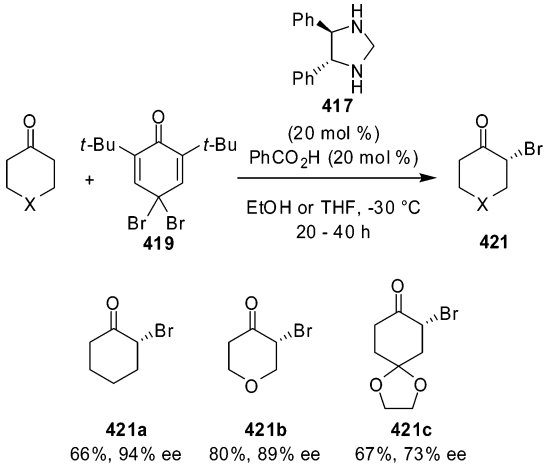


5.4.3. α-Bromination

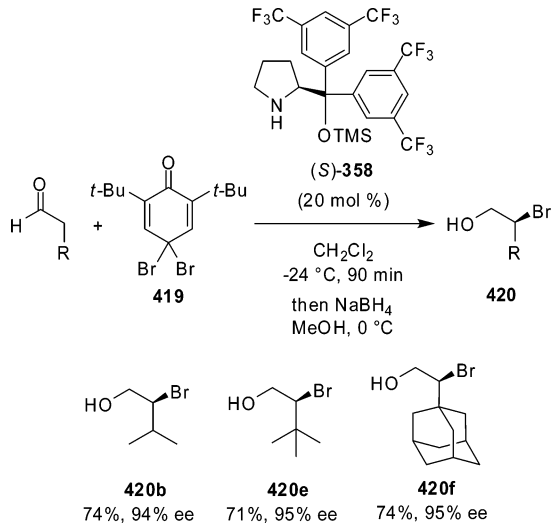
The first direct asymmetric organocatalytic α-bromination of aldehydes and ketones was reported by Jørgensen and coworkers.[441,444] Among different brominating agents tested, the easily accessible and air stable 4,4-dibromo-2,6-di-*tert*-butylcyclohexa-2,5-dienone (**419**) (Scheme 293) proved to be the reagent of choice for both aldehyde and ketone substrates.[444] The same diphenylpyrrolidine catalyst (**413**) that was used for the aldehyde α-chlorination (see Scheme 290) was applied in combination with an equimolar amount of benzoic acid for the α-bromination of aldehydes. Different linear, branched, cyclic, and unsaturated aldehydes were α-brominated using 20 mol % catalyst **413** to afford the products (isolated as the corresponding alcohols **420** after in situ $NaBH_4$ reduction) in high yields and moderate to high enantioselectivities (Scheme 293). The product yield was found to be strongly solvent dependent, and a mixture of CH_2Cl_2 and pentane (1:1) proved to be the optimum solvent for this reaction.[444]

While the C_2-symmetric pyrrolidine **413** was the catalyst of choice for the α-bromination of aldehyde substrates, C_2-symmetric imidazolidine catalyst **417** (see Scheme 292) once again proved to be suitable for ketones, this time in combination with benzoic acid.[444] Only cyclic ketones were used as substrates, and the brominated products were

Scheme 294. The First Asymmetric Organocatalytic α-Bromination of Ketones



Scheme 295. Application of Diarylprolinol Silyl Ether Catalyst for the Asymmetric α-Bromination of Aldehydes



obtained in moderate to good yields and enantioselectivities (Scheme 294).

In the same year, the Jørgensen group applied diarylprolinol silyl ether **358** for the α-bromination of aldehydes, with significantly improved results: products were obtained in uniformly good yields and excellent enantioselectivities within a short period of time (Scheme 295).[394] The low temperature is necessary to suppress undesired side reactions such as catalyst bromination.

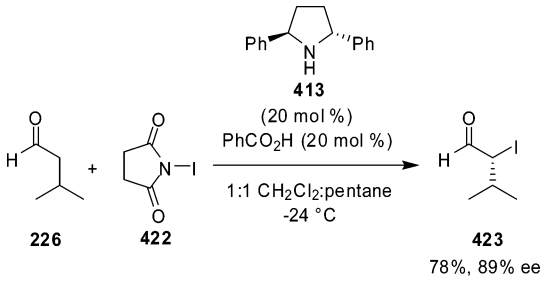
5.4.4. α-Iodination

To date, only one example of the enantioselective α-iodination has been reported. In an extension of their previous α-bromination protocol, the Jørgensen group found that, when using *N*-iodosuccinimide (NIS) **422** as the iodinating agent, 3-methylbutanal **226** underwent facile α-iodination within 20 min in the presence of the C_2-symmetric pyrrolidine catalyst **413** to afford 2-iodo-3-methylbutanal **423** in 78% yield and 89% ee (Scheme 296).[444] When butanal was employed as the substrate, the iodination product was obtained in significantly lower yield and enantioselectivity (30%, 60% ee).

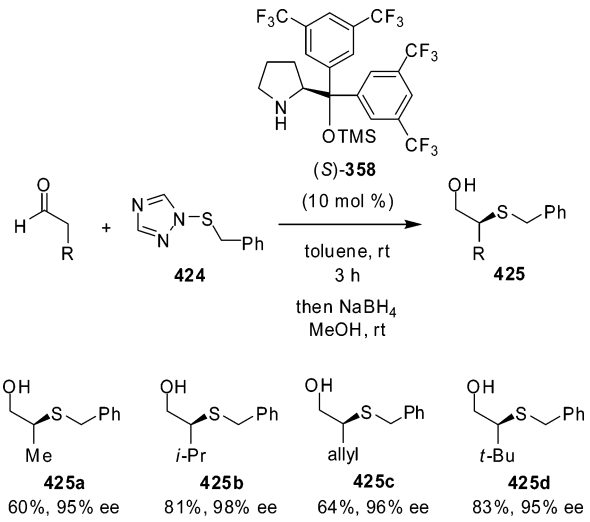
5.5. α-Sulfenylation

Chiral thiol compounds are an interesting class of compounds due to their potential inhibition properties toward

Scheme 296. Asymmetric α-Iodination of 3-Methylbutanal



Scheme 297. First Direct Asymmetric α-Sulfenylation of Aldehydes



Zn containing enzymes. Despite the synthetic potential of α-sulfenylated compounds, their asymmetric syntheses rely either on auxiliary-based approaches or multistep synthesis. Therefore, direct α-sulfenylation of unmodified carbonyl compounds remained a long-neglected synthetic challenge.

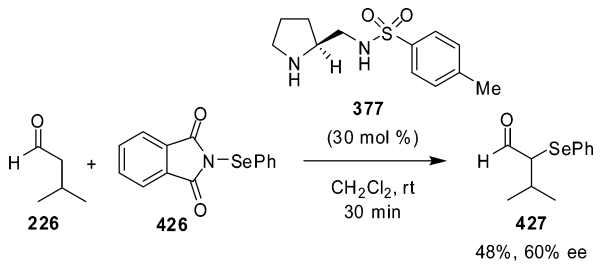
In 2004, Wang and co-workers reported a pyrrolidine trifluoromethanesulfonamide-catalyzed α-sulfenylation of aldehydes and ketones using commercially available *N*-(phenylthio)phthalimide as the electrophilic sulfur source.[445] Although good yields were obtained in many cases, enantioselectivities were not reported.

Soon after the report of Wang et al., Jørgensen and coworkers reported the first asymmetric α-sulfenylation of aldehydes.[367] After optimization of several reagents and catalysts, 1-benzylsulfanyl-1,2,4-triazole (**424**) was chosen as the electrophilic sulfur source and diarylprolinol silyl ether **358** as the catalyst (Scheme 297). A number of unbranched aldehydes underwent facile α-sulfenylation in the presence of 10 mol % catalyst **358** to generate the products **425** (after reduction) in good yields and excellent enantioselectivities.[367,394] The authors showed that the formation of a quaternary stereogenic center is possible using a branched aldehyde as substrate in the presence of 2-nitrobenzoic acid cocatalyst: 2-phenylpropanal gave the corresponding α-sulfenylated product in good yield (84%), but only with moderate ee (61%) after 16 h.[367] The reductive cleavage of the benzyl group was also demonstrated with Na/NH_3 (I) when the alcohol functionality was protected as *tert*-butyldimethylsilyl (TBDMS) ether.

5.6. α-Selenylation

Catalytic α-selenylation of carbonyl compounds can be viewed as an extension of the α-sulfenylation reaction. In

Scheme 298. Catalytic Asymmetric α-Selenylation of Isovaleraldehyde



2004, Wang and co-workers reported the first catalytic α-selenylation of aldehydes using chiral secondary amines as catalyst and *N*-(phenylseleno)phthalimide (**426**) as the electrophilic selenium source (Scheme 298).[446] A number of different secondary amines were screened, and (*S*)-prolinamide proved to be the most effective catalyst. Various unbranched and some α-branched aldehydes were selenylated rapidly (10 min for unbranched and 1 h for branched aldehydes) to obtain the products in very high yields. However, the enantioselectivities were not reported in most of the cases. When pyrrolidine tosylsulfonamide **377** was used as the catalyst, isovaleraldehyde (**226**) was selenylated with moderate yield and enantioselectivity (Scheme 298).[446] Nevertheless, this reaction represents the first and to date the only direct catalytic asymmetric α-selenylation of aldehydes.

The authors extended this method to ketone substrates.[447] Once again, rather high yields were reported for a number of ketone substrates, but no enantioselectivity was reported, with one exception. An 18% ee was obtained when cyclohexanone was used as the substrate.[447]

6. Other Asymmetric C−C Bond Forming Reactions

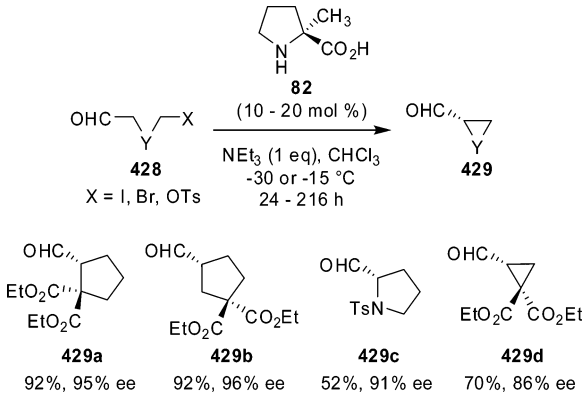
6.1. Intramolecular α-Alkylation of Aldehydes

α-Alkylations of carbonyl compounds are important C−C *σ*-bond forming reactions in organic synthesis. Asymmetric variants mostly rely on the use of chiral auxiliaries. Although two catalytic asymmetric α-alkylation strategies based on chiral phase transfer catalysts and chiral oligoamines are reported, these methods are most commonly applied in the synthesis of α-amino acids via alkylation of glycine derivatives and are by no means general.

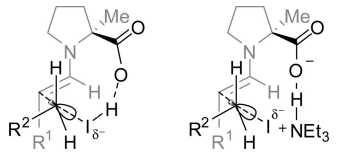
In 2004 List et al. reported an organocatalytic approach for catalytic asymmetric intramolecular α-alkylation of aldehydes.[448] This reaction not only shows the potential of general applicability but represents the first example in the realm of enamine catalysis where a nucleophilic substitution reaction takes place. Among the catalysts screened, proline showed rather high activity and only moderate enantioselectivity under standard reaction conditions (Scheme 299), but (*S*)-α-methylproline (**82**) turned out to be an efficient and highly enantioselective catalyst, furnishing several chiral substituted cyclopentanes **429a-b**, cyclopropane (**429d**) and pyrrolidine (**429c**).[448] Yields are generally high and enantioselectivities are excellent for five-membered rings. The use of a stoichiometric amount of triethylamine is crucial for the reaction.

Recently, Thiel, List, and co-workers investigated the mechanism of this α-alkylation reaction on the basis of computational studies.[449] The influence of the amine base

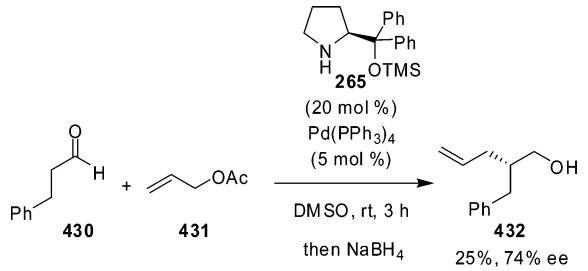
Scheme 299. Catalytic Asymmetric Intramolecular α-Alkylation of Aldehydes by List et al.



Scheme 300. Comparison between the Transition States of Base-free and Base-Assisted α-Alkylation of Aldehydes



Scheme 301. Enantioselective α-Allylic Alkylation of 3-Phenylpropanal



was studied in great detail. It turned out that the base-free α-alkylation reaction is in principle possible, but the base has a substantial influence on the C−C bond forming process. By forming triethylammonium carboxylate, it provides an enhanced electrostatic stabilization of the developing negative charge at the leaving halide (Scheme 300).[449] This in turn lowers the overall activation barrier and determines the stereoselectivity by stabilizing the *anti*- and *syn*-transition states to a different extent.

6.2. Asymmetric α-Allylation of Aldehydes and Ketones

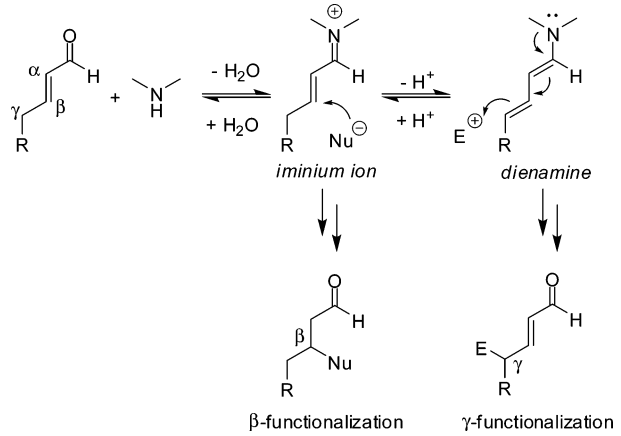
Recently, Córdova et al. reported an intermolecular α-allylic alkylation of aldehydes and ketones.[450] This procedure applied combined enamine/Pd catalysis. Using chiral diphenylprolinol silyl ether **265**, asymmetric allylation of aldehyde was possible with moderate enantioselectivity (Scheme 301).[450] Asymmetric α-allylic alkylation of cyclohexanone was also investigated by applying both chiral amine and chiral diphosphine ligands for palladium: although good enantioselectivity was obtained in some cases (88% ee), the yield was rather low (20%).[450]

7. Asymmetric γ-Functionalization of Carbonyl Compounds

7.1. Introduction

Asymmetric γ-functionalization of α,β-unsaturated carbonyl compounds can be regarded as the logical extension

Scheme 302. β- and γ-Functionalization via Iminium Ion and Dienamine Catalysis



of α- and β-functionalization which have been achieved by enamine and iminium ion catalysis of simple and α,β-unsaturated carbonyl compounds, respectively. Formation of enamines from amines and simple carbonyl compounds, and their subsequent α-functionalization reactions have been described above. On the other hand, amines can react with α,β-unsaturated carbonyl compounds to generate iminium ions, which, due to their electron-deficient nature, can be attacked by nucleophilic reagents, leading to β-functionalization (Scheme 302). Another, much ignored, possibility is the formation of dienamine by deprotonation of the iminium ion. The resulting dienamine, being an electron-rich species, can react with electrophiles at its γ-position, leading to γ-functionalization (Scheme 302).

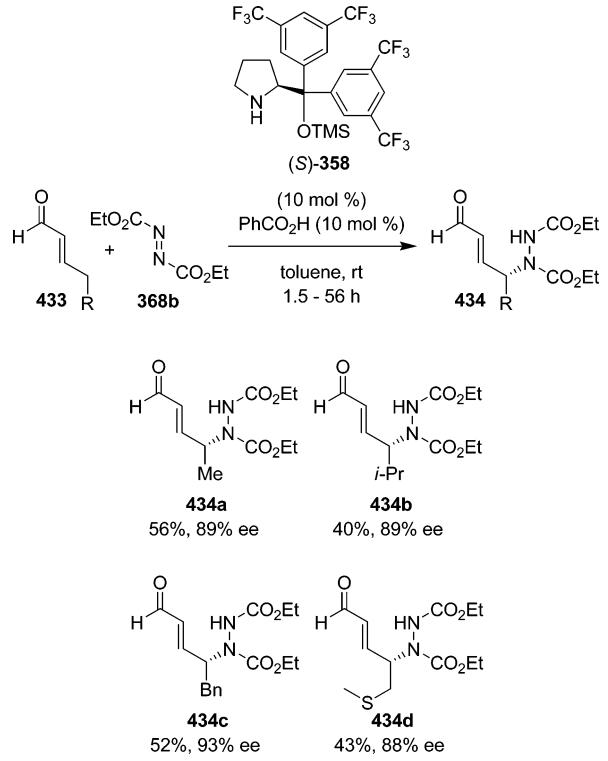
Despite being well-known organic compounds, the potential of dienamines in asymmetric catalysis has not been realized so far. Quite recently, Jørgensen and co-workers introduced this new concept of organocatalysis for the γ-amination of α,β-unsaturated aldehydes.[451]

7.2. γ-Amination of α,β-Unsaturated Aldehydes

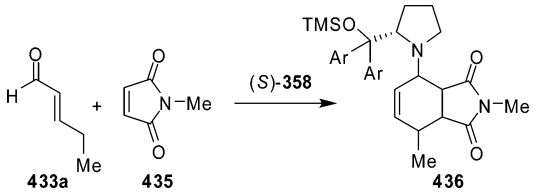
γ-Amination of α,β-unsaturated aldehydes reported by Jørgensen and co-workers represents the first and so far only example of the newly introduced concept of dienamine catalysis.[451] Among many different chiral pyrrolidine derivatives screened, 2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilyloxymethyl]pyrrolidine [(*S*)-**358**] once again turned out to be the best catalyst for γ-amination of a series of α,β-unsaturated aldehydes **433** with DEAD (**368b**) as the electrophilic nitrogen reagent (Scheme 303). The products γ-hydrazino-α,β-unsaturated aldehydes **434** were obtained in moderate yields and with good enantioselectivities. Interestingly, the sense of stereoinduction obtained in this reaction was found to be opposite to that of other enamine- or iminium-catalytic reactions promoted by the same catalyst. This led the authors to explore the reaction course thoroughly based on theoretical calculations. A mechanism involving a concerted [4+2]-cycloaddition reaction between the in situ-generated chiral dienamine and DEAD was proposed which also accounts for the observed stereochemistry of the products.[451]

As a further experimental proof for the proposed mechanism, the Jørgensen group carried out a reaction of 2-pentenal (**433a**) and *N*-methylmaleimide (**435**) in the presence of catalyst (*S*)-**358** (Scheme 304).[451] The [4+2]-cycloaddition product **436** was isolated with dr 2:1 after flash

Scheme 303. First Asymmetric γ-Amination of α,β-Unsaturated Aldehydes



Scheme 304. Reaction of 2-Pentenal with *N*-Methylmaleimide in the Presence of the Amine Catalyst (*S*)-358



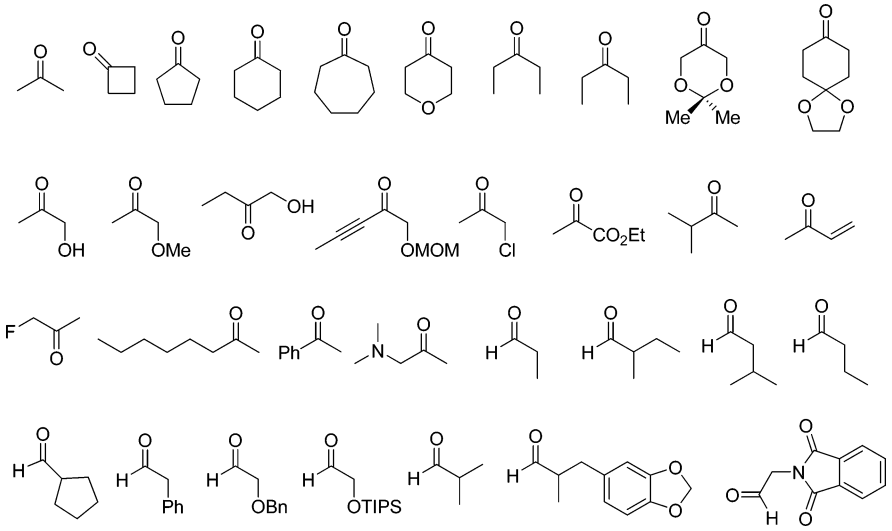
chromatography. This reaction not only supports the proposed mechanism for the γ-amination but also indicates the potential of asymmetric dienamine catalysis for other γ-functionalization reactions.

8. Summary and Outlook: Current Status and Future Challenges of Asymmetric Enamine Catalysis

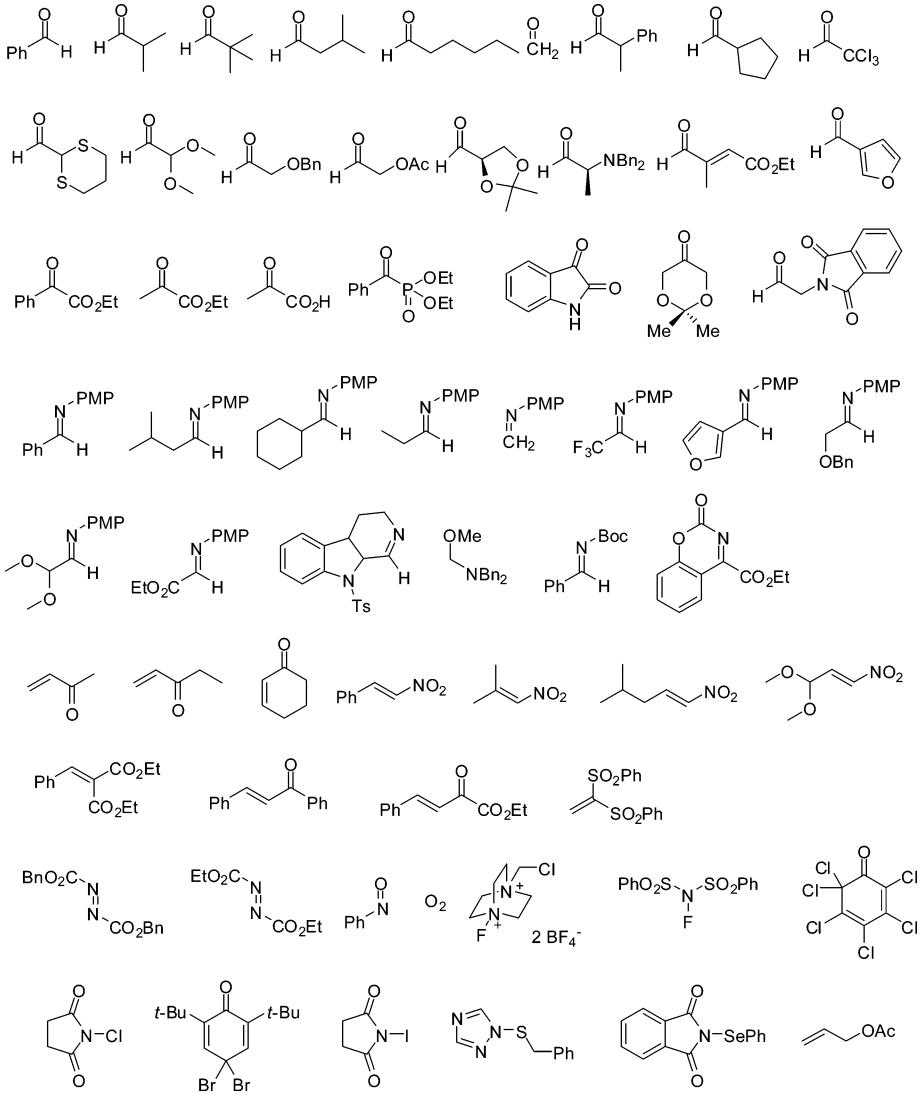
Within only a few years since its conceptualization in 2000, enamine catalysis has developed into a flourishing field of research and established itself as a powerful methodology for asymmetric synthesis. Essentially all types of ketones and aldehydes have been used as nucleophiles (Scheme 305) in reactions with a broad range of electrophile classes (Scheme 306) and an ever increasing number of aminocatalysts (Scheme 307). With roots in the biocatalytic aldol reaction, Stork's enamine chemistry, and the Hajos−Parrish−Eder−Sauer−Wiechert reaction, asymmetric enamine catalysis is a new concept that has delivered profoundly useful and rather unexpected reactions. It is interesting to speculate about the future development of this area. Despite the great achievements already accomplished, a number of challenges remain, and selected ones will be mentioned here:

In the aldol area, major breakthroughs have been achieved and essentially all possible combinations of intermolecular

Scheme 305. Typical Nucleophiles Used in Asymmetric Enamine Catalysis

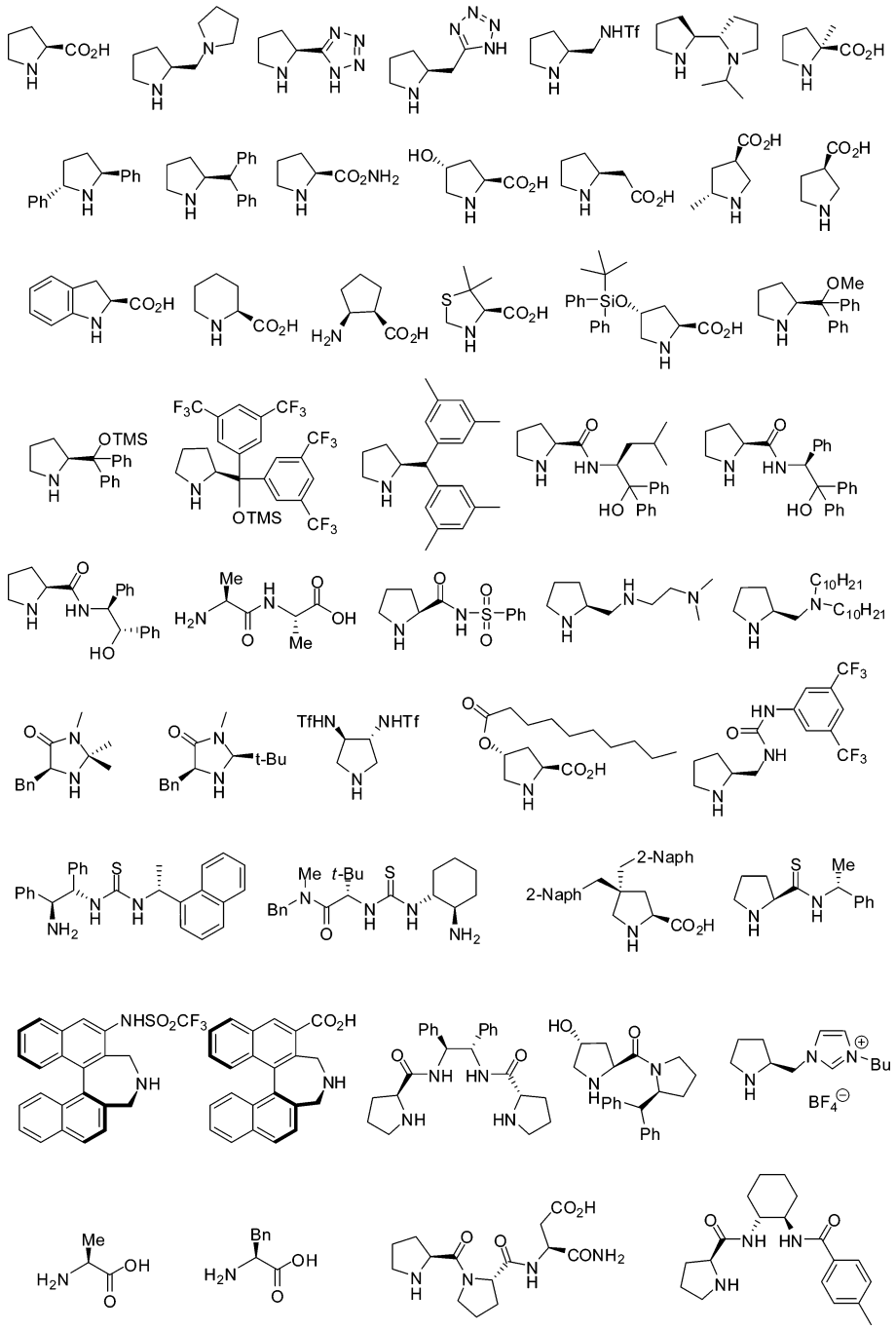


Scheme 306. Typical Electrophiles Used in Asymmetric Enamine Catalysis



aldolizations (ketone/aldehyde, aldehyde/ketone, aldehyde/aldehyde, ketone/ketone), as well as both intramolecular enolexo- and enolendo-aldolizations, have been realized with high *anti*-diastereoselectivity and enantioselectivity. The discovery of a highly efficient, general, and enantioselective catalyst of the *syn*-diastereoselective aldol reaction still remains to be announced as yet another milestone in organocatalysis. Also, it seems that formaldehyde has not been fully explored as an electrophile in enamine catalytic asymmetric aldol reactions of aldehydes. Such a transforma-

Scheme 307. Typical Catalysts Used in Asymmetric Enamine Catalysis



tion would lead to highly valuable aldols for natural product synthesis. Similarly, enantioselective transannular aldolizations via enamine catalysis might both be envisioned and of use in the construction of complex oligocyclic natural products.

A difficult challenge would be the development of a direct catalytic asymmetric *intermolecular* α-alkylation of ketones and aldehydes. Such processes would clearly be extremely useful.

More atom-economic α-functionalizations also seem to be desirable. For example, is it possible to use elemental chlorine in highly enantioselective α-chlorinations?

Despite the great advancements already made with regard to catalyst amounts (e.g., <1% loadings have already been occasionally realized!), very high turnover numbers might be considered yet another challenge. This is clearly an important goal if complex multistep syntheses requiring catalysts are used but obviously a less dramatic issue with easily recyclable and inexpensive catalysts such as proline. Clearly, production costs rather than catalyst loadings alone are critical for industrial applications of any catalysis methodology. Already now, several large-scale applications of enamine catalysis are being pursued in industry. It is certainly not unreasonable to assume significant growth in this area, both in industry and in academic research.

9. Acknowledgments

We would like to thank Sonja Mayer for her help in the preparation of this manuscript and Daniela Kampen and Corinna Reisinger for their careful proofreading. B.L. acknowledges the numerous contributions from all current

and previous members of his laboratory to the development of the enamine catalysis concept and methodology. Generous funding of these studies has been provided by the Max-Planck-Society, by the DFG, by the VCI, and by Novartis.

10. References

(1) List, B. *Synlett* **2001**, 1675.
(2) List, B. *Acc. Chem. Res.* **2004**, *37*, 548.
(3) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.
(4) Stork, G.; Saccomano, N. A. *Tetrahedron Lett.* **1987**, *28*, 2087.
(5) *The Chemistry of Enamines*; Rappoport, Z., Ed.; Wiley: New York, 1994.
(6) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352.
(7) Barbas, C. F., III; Heine, A.; Zhong, G.; Hoffmann, T.; Gramatikova, S.; Bjoernstedt, R.; List, B.; Anderson, J.; Stura, E. A.; Wilson, I.; Lerner, R. A. *Science* **1997**, *278*, 2085.
(8) Turner, J.; Bui, T.; Lerner, R. A.; Barbas, C. F., III; List, B. *Chem.—Eur. J.* **2000**, *6*, 2772.
(9) Knoevenagel, E. *Chem. Ber.* **1898**, *31*, 2596.
(10) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.
(11) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Application in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005.
(12) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719.
(13) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138.
(14) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 133.
(15) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004; Vols. 1 and 2.
(16) Tanaka, F.; Barbas, C. F., III. In *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007; pp 19.
(17) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2001**, *33*, 325.
(18) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65.
(19) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432.
(20) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595.
(21) Alcaide, B.; Almendros, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 858.
(22) Reymond, J.-L.; Chen, Y. *J. Org. Chem.* **1995**, *60*, 6970.
(23) Tanaka, F.; Barbas, C. F., III In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004; Vol. 1, pp 273.
(24) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1871.
(25) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168.
(26) Kumagai, N.; Matsunaga, S.; Yoshikawa, N.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 1539.
(27) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466.
(28) Shibasaki, M.; Matsunaga, S.; Kumagai, N. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004; Vol. 2, pp 197.
(29) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003.
(30) Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497.
(31) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169.
(32) List, B. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004; Vol. 1, pp 161.
(33) Hajos, Z. G.; Parrish, D. R. German Patent DE 2102623, 1971.
(34) Eder, U.; Sauer, G. R.; Wiechart, R. German Patent DE 2014757, 1971.
(35) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.
(36) Gutzwiller, J.; Buchschacher, P.; Fürst, A. *Synthesis* **1977**, 53.
(37) Takano, S.; Kasahara, C.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1981**, 635.
(38) Blazejewski, J. C. *J. Fluorine Chem.* **1990**, *46*, 515.
(39) Terashima, S.; Sato, S.; Koga, K. *Tetrahedron Lett.* **1979**, *36*, 3469.
(40) Przézdziecka, A.; Stephanenko, W.; Wicha, J. *Tetrahedron: Asymmetry* **1999**, *10*, 1589.
(41) Kwiatkowska, S.; Syed, A.; Brock, C. P.; Watt, D. S. *Synthesis* **1989**, 818.
(42) Rajagopal, D.; Narayanan, R.; Swaminathan, S. *Tetrahedron Lett.* **2001**, *42*, 4887.
(43) Ramamurthi, N.; Swaminathan, S. *Indian J. Chem., Sect. B* **1990**, *29*, 401.
(44) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Grandi, M. J. D. *J. Am. Chem. Soc.* **1996**, *118*, 2843.
(45) Kondo, K.; Yamano, T.; Takemoto, K. *Makromol. Chem.* **1985**, *186*, 1781.
(46) Danishefsky, S. J.; Cain, P. *J. Am. Chem. Soc.* **1976**, *98*, 4975.
(47) Agami, C.; Meynier, F.; Puchot, C. *Tetrahedron* **1984**, *40*, 1031.
(48) Davies, S. G.; Sheppard, R. L.; Smith, A. D.; Thomson, J. E. *Chem. Commun.* **2005**, 3802.
(49) Nagamine, T.; Inomata, K.; Endo, Y.; Paquette, L. A. *J. Org. Chem.* **2007**, *72*, 123.
(50) List, B.; Lerner, R. A.; Barbas, C. F., IIII. *Org. Lett.* **1999**, *1*, 59.
(51) Agami, C.; Sevestre, H. *J. Chem. Soc., Chem. Commun.* **1984**, 1385.
(52) Agami, C.; Platzer, N.; Sevestre, H. *Bull. Soc. Chim. Fr.* **1987**, *2*, 358.
(53) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785.
(54) Spiliotis, V.; Papahatjis, D.; Ragoussis, N. *Tetrahedron Lett.* **1990**, *31*, 1615.
(55) Bertau, M.; Bürli, M.; Hungerbühler, E.; Wagner, P. *Tetrahedron: Asymmetry* **2001**, *12*, 2103.
(56) Mans, D. M.; Pearson, W. H. *Org. Lett.* **2004**, *6*, 3305.
(57) Itagaki, N.; Kimura, M.; Sugahara, T.; Iwabuchi, Y. *Org. Lett.* **2005**, *7*, 4185.
(58) Kurteva, V. B.; Afonso, C. A. M. *Tetrahedron* **2005**, *61*, 267.
(59) Enders, D.; Niemeier, O.; Straver, L. *Synlett* **2006**, 3399.
(60) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.
(61) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573.
(62) List, B. *Tetrahedron* **2002**, *58*, 5573.
(63) Movassaghi, M.; Jacobsen, E. N. *Science* **2002**, *298*, 1904.
(64) Hiroi, K.; Yamada, S. I. *Chem. Pharm. Bull.* **1975**, *23*, 1103.
(65) Szöllosi, G.; London, G.; Baláspiri, L.; Somlai, C.; Bartók, M. *Chirality* **2003**, *15*, S90.
(66) Izquierdo, I.; Plaza, M. T.; Robles, R.; Mota, A. J.; Franco, F. *Tetrahedron: Asymmetry* **2001**, *12*, 2749.
(67) Chandrasekhar, S.; Reddy, N. R.; Sultana, S. S.; Narsihmulu, C.; Reddy, K. V. *Tetrahedron* **2006**, *62*, 338.
(68) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *108*, 2353.
(69) Agami, C.; Levisalles, J.; Sevestre, H. *J. Chem. Soc., Chem. Commun.* **1984**, 418.
(70) Agami, C.; Levisalles, J.; Puchot, C. *J. Chem. Soc., Chem. Commun.* **1985**, 441.
(71) Agami, C.; Puchot, C.; Sevestre, H. *Tetrahedron Lett.* **1986**, *27*, 1501.
(72) Agami, C.; Puchot, C. *J. Mol. Catal.* **1986**, *38*, 341.
(73) Agami, C.; Puchot, C. *Tetrahedron* **1986**, *42*, 2037.
(74) Agami, C. *Bull. Soc. Chim. Fr.* **1988**, *3*, 499.
(75) Arnó, M.; Domingo, L. R. *Theor. Chem. Acc.* **2002**, *108*, 232.
(76) Rankin, K. N.; Gauld, J. W.; Boyd, R. J. *J. Phys. Chem. A* **2002**, *106*, 5155.
(77) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273.
(78) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911.
(79) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16.
(80) Clemente, F. R.; Houk, K. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 5766.
(81) List, B.; Hoang, L.; Martin, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5839.
(82) Bassan, A.; Zou, W.; Reyes, E.; Himo, F.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7028.
(83) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558.
(84) Cheong, P. H.-Y.; Houk, K. N. *Synthesis* **2005**, 1533.
(85) Clemente, F. R.; Houk, K. N. *J. Am. Chem. Soc.* **2005**, *127*, 11294.
(86) Arnó, M.; Zaragozá, R. J.; Domingo, L. R. *Tetrahedron: Asymmetry* **2005**, *16*, 2764.
(87) Rajagopal, D.; Moni, M. S.; Subramanian, S.; Swaminathan, S. *Tetrahedron: Asymmetry* **1999**, *10*, 1631.
(88) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260.
(89) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 9922.
(90) Marquez, C.; Metzger, J. O. *Chem. Commun.* **2006**, 1539.
(91) Jung, M. E. *Tetrahedron* **1976**, *32*, 3.
(92) Brown, K. L.; Damm, L.; Dunitz, J. D.; Eschenmoser, A.; Hobi, R.; Kratky, C. *Helv. Chim. Acta* **1978**, *61*, 3108.
(93) Klussmann, M.; White, A. J. P.; Armstrong, A.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7985.
(94) Klussmann, M.; Mathew, S. P.; Iwamura, H.; WellsJr., D. H.; Armstrong, A.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7989.
(95) Klussmann, M.; Iwamura, H.; Mathew, S. P.; WellsJr., D. H.; Pandya, U.; Armstrong, A.; Blackmond, D. G. *Nature* **2006**, *441*, 621.
(96) Blackmond, D. G.; Klussmann, M. *AIChE J.* **2007**, *53*, 2.

(97) Kellogg, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 494.
(98) Chan, V.; Kim, J. G.; Jimeno, C.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2004**, *6*, 2051.
(99) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475.
(100) Tokuda, O.; Kano, T.; Gao, W.-G.; Ikemoto, T.; Maruoka, K. *Org. Lett.* **2005**, *7*, 5103.
(101) Tang, Z.; Cun, L.-F.; Cui, X.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2006**, *8*, 1263.
(102) Dambruoso, P.; Massi, A.; Dondoni, A. *Org. Lett.* **2005**, *7*, 4657.
(103) Samanta, S.; Liu, J.; Dodda, R.; Zhao, C.-G. *Org. Lett.* **2005**, *7*, 5321.
(104) Ikishima, H.; Sekiguchi, Y.; Ichikawa, Y.; Kotsuki, H. *Tetrahedron* **2006**, *62*, 311.
(105) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(106) Peng, L.; Liu, H.; Zhang, T.; Zhang, F.; Mei, T.; Li, Y. *Tetrahedron Lett.* **2003**, *44*, 5107.
(107) Pan, Q.; Zou, B.; Wang, Y.; Ma, D. *Org. Lett.* **2004**, *6*, 1009.
(108) Ward, D. E.; Jheengut, V.; Akinnusi, O. T. *Org. Lett.* **2005**, *7*, 1181.
(109) Pikho, P. M.; Laurikainen, K. M.; Usano, A.; Nyberg, A. I.; Kaavi, J. A. *Tetrahedron* **2006**, *62*, 317.
(110) Zhou, Y.; Shan, Z. *J. Org. Chem.* **2006**, *71*, 9510.
(111) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.
(112) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580.
(113) Córdova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W.-W. *Chem. Commun.* **2005**, 3586.
(114) Córdova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. *Chem.—Eur. J.* **2006**, *12*, 5383.
(115) Amedjkouh, M. *Tetrahedron: Asymmetry* **2005**, *16*, 1411.
(116) Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* **2001**, 1245.
(117) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167.
(118) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570.
(119) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2003**, *5*, 4369.
(120) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420.
(121) Wang, W.; Li, H.; Wang, J. *Tetrahedron Lett.* **2005**, *46*, 5077.
(122) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262.
(123) Tang, Z.; Jiang, F.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5755.
(124) Guo, H.-M.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Chem. Commun.* **2005**, 1450.
(125) Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285.
(126) He, L.; Tang, Z.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Tetrahedron* **2006**, *62*, 346.
(127) Jiang, M.; Zhu, S.-F.; Yang, Y.; Gong, L.-Z.; Zhou, X.-G.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2006**, *17*, 384.
(128) Chimni, S. S.; Mahajan, D.; Babu, V. V. S. *Tetrahedron Lett.* **2005**, *46*, 5617.
(129) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558.
(130) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983.
(131) Hartikka, A.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1831.
(132) Hartikka, A.; Arvidsson, P. I. *Eur. J. Org. Chem.* **2005**, 4287.
(133) Lacoste, E.; Landais, Y.; Schenk, K.; Verlhac, J.-B.; Vincent, J.-M. *Tetrahedron Lett.* **2004**, *45*, 8035.
(134) Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004**, *346*, 1141.
(135) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84.
(136) Bellis, E.; Vasilatou, K.; Kokotos, G. *Synthesis* **2005**, 2407.
(137) Bellis, E.; Kokotos, G. *Tetrahedron* **2005**, *61*, 8669.
(138) Silva, F.; Sawicki, M.; Gouverneur, V. *Org. Lett.* **2006**, *8*, 5417.
(139) Chen, J.-R.; Lu, H.-H.; Li, X.-Y.; Cheng, L.; Wan, J.; Xiao, W.-J. *Org. Lett.* **2005**, *7*, 4543.
(140) Chen, J.-R.; Li, X.-Y.; Xing, X.-N.; Xiao, W.-J. *J. Org. Chem.* **2006**, *71*, 8198.
(141) Tang, Z.; Yang, Z.-H.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Org. Lett.* **2004**, *6*, 2285.
(142) Guillena, G.; Hita, M. C.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 729.
(143) Gryko, D.; Kowlaczyk, B.; Zawadzki, L. *Synlett* **2006**, 1059.
(144) Guillena, G.; Hita, M. C.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1027.
(145) Guillena, G.; Hita, M. C.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1493.
(146) Ma, G.-N.; Zhang, Y.-P.; Shi, M. *Synthesis* **2007**, 197.
(147) Guizzetti, S.; Benaglia, M.; Pignataro, L.; Puglisi, A. *Tetrahedron: Asymmetry* **2006**, *17*, 2754.
(148) Raj, M.; Vishnumaya; Ginotra, S. K.; Singh, V. K. *Org. Lett.* **2006**, *8*, 4097.
(149) Gryko, D.; Lipinski, R. *Adv. Synth. Catal.* **2005**, *347*, 1948.
(150) Gryko, D.; Lipinski, R. *Eur. J. Org. Chem.* **2006**, 3864.
(151) Bordwell, F. G.; Ji, G. Z. *J. Am. Chem. Soc.* **1991**, *113*, 8398.
(152) Cheng, C.; Sun, J.; Wang, C.; Zhang, Y.; Wei, S.; Jiang, F.; Wu, Y. *Chem. Commun.* **2006**, 215.
(153) Gu, L.; Yu, M.; Wu, X.; Zhang, Y.; Zhao, G. *Adv. Synth. Catal.* **2006**, *348*, 2223.
(154) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 734.
(155) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958.
(156) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 8100.
(157) Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8103.
(158) Kofoed, J.; Nielsen, J.; Reymond, J.-L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2445.
(159) Martin, H. J.; List, B. *Synlett* **2003**, 1901.
(160) Shi, L.-X.; Sun, Q.; Ge, Z.-M.; Zhu, Y.-Q.; Cheng, T.-M.; Li, R.-T. *Synlett* **2004**, 2215.
(161) Krattiger, P.; McCarthy, C.; Pfaltz, A.; Wennemers, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1722.
(162) Krattiger, P.; Kovasy, R.; Revell, J. D.; Ivan, S.; Wennemers, H. *Org. Lett.* **2005**, *7*, 1101.
(163) Luppi, G.; Cozzi, P. G.; Monari, M.; Kaptein, B.; Broxterman, Q. B.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 7418.
(164) Bøgevig, A.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Commun.* **2002**, 620.
(165) Andreae, M. R. M.; Davis, A. P. *Tetrahedron: Asymmetry* **2005**, *16*, 2487.
(166) Akagawa, K.; Sakamoto, S.; Kudo, K. *Tetrahedron Lett.* **2005**, *46*, 8185.
(167) Tsogoeva, S. B.; Wei, S. *Tetrahedron: Asymmetry* **2005**, *16*, 1947.
(168) Zou, W.; Ibrahem, I.; Dziedzic, P.; Sundén, H.; Córdova, A. *Chem. Commun.* **2005**, 4946.
(169) Dziedzic, P.; Zou, W.; Háfren, J.; Córdova, A. *Org. Biomol. Chem.* **2006**, *4*, 38.
(170) Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3055.
(171) Kano, T.; Tokuda, O.; Takai, J.; Maruoka, K. *Chem. Asian J.* **2006**, *1*, 210.
(172) Kano, T.; Tokuda, O.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 7423.
(173) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Tetrahedron* **2007**, *63*, 1923.
(174) Enders, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210.
(175) Grondal, C.; Enders, D. *Tetrahedron* **2006**, *62*, 329.
(176) Enders, D.; Voith, M.; Lenzen, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1304.
(177) Suri, J. T.; Ramachary, D. B.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 1383.
(178) Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 3363.
(179) Ibrahem, I.; Zou, W.; Xu, Y.; Córdova, A. *Adv. Synth. Catal.* **2006**, *348*, 211.
(180) Enders, D.; Palecek, J.; Grondal, C. *Chem. Commun.* **2006**, 655.
(181) Grondal, C.; Enders, D. *Synlett* **2006**, 3507.
(182) Sekiguchi, Y.; Sasaoka, A.; Shimomoto, A.; Fujioka, S.; Kotsuki, H. *Synlett* **2003**, 1655.
(183) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *Tetrahedron Lett.* **2004**, *45*, 4353.
(184) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208.
(185) Kotrusz, P.; Kmentová, I.; Gotov, B.; Toma, S.; Solcániová, E. *Chem. Commun.* **2002**, 2510.
(186) Loh, T.-P.; Feng, L.-C.; Yang, H. Y.; Yang, J.-Y. *Tetrahedron Lett.* **2002**, *43*, 8741.
(187) Kitazume, T.; Jiang, Z.; Kasai, K.; Mihara, Y.; Suzuki, M. *J. Fluorine Chem.* **2003**, *121*, 205.
(188) Rodríguez, B.; Rantanen, T.; Bolm, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 6924.
(189) Benaglia, M.; Celentano, G.; Cozzi, F. *Adv. Synth. Catal.* **2001**, *343*, 171.
(190) Benaglia, M.; Cinquini, M.; Cozzi, F.; Puglisi, A.; Celentano, G. *Adv. Synth. Catal.* **2002**, *344*, 533.
(191) Bellis, E.; Kokotos, G. *J. Mol. Catal. A: Chem.* **2005**, *241*, 166.
(192) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417.
(193) Font, D.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2006**, *8*, 4653.
(194) Giacalone, F.; Gruttadauria, M.; Marculescu, A. M.; Noto, R. *Tetrahedron Lett.* **2007**, *48*, 255.
(195) Fache, F.; Piva, O. *Tetrahedron: Asymmetry* **2003**, *14*, 139.
(196) Gruttadauria, M.; Riela, S.; Aprile, C.; Meo, P. L.; D'Anna, F.; Noto, R. *Adv. Synth. Catal.* **2006**, *348*, 82.
(197) Kucherenko, A. S.; Struchkova, M. I.; Zlotin, S. G. *Eur. J. Org. Chem.* **2006**, 2000.

(198) An, Z.; Zhang, W.; Shi, H.; He, J. *J. Catal.* **2006**, *241*, 319.
(199) Orsini, F.; Pelizzoni, F.; Forte, M. *Heterocycl. Chem.* **1989**, *26*, 837.
(200) Córdova, A.; Notz, W.; Barbas, C. F., III. *J. Org. Chem.* **2002**, *67*, 301.
(201) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798.
(202) Pikho, P. M.; Erkkilä, A. *Tetrahedron Lett.* **2003**, *44*, 7607.
(203) Chowdari, N. S.; Ramachary, D. B.; Córdova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 9591.
(204) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343.
(205) Reyes, E.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 6605.
(206) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152.
(207) Sorensen, E. J.; Sammis, G. M. *Science* **2004**, *305*, 1725.
(208) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752.
(209) Kazmaier, U. *Angew. Chem., Int. Ed.* **2005**, *44*, 2186.
(210) Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696.
(211) Córdova, A.; Engqvist, M.; Ibrahem, I.; Casas, J.; Sundén, H. *Chem. Commun.* **2005**, 2047.
(212) Córdova, A.; Ibrahem, I.; Casas, J.; Sundén, H.; Engqvist, M.; Reyes, E. *Chem.—Eur. J.* **2005**, *11*, 4772.
(213) Storer, R. I.; MacMillan, D. W. C. *Tetrahedron* **2004**, *60*, 7705.
(214) Yus, M.; Najera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147.
(215) Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 3541.
(216) Mangion, I. K.; Northrup, A. B.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 6722.
(217) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5527.
(218) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2007**, *129*, 288.
(219) Kano, T.; Yamaguchi, Y.; Tanaka, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1738.
(220) Mannich, C.; Krosche, W. *Arch. Pharm.* **1912**, *250*, 647.
(221) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044.
(222) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348.
(223) Shibasaki, M.; Matsunaga, S. *J. Organomet. Chem.* **2006**, *691*, 2089.
(224) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102.
(225) Kobayashi, S.; Ueno, M. In *Comprehensive Asymmetric Catalysis Supplement I*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 2003; Chapter 29.5.
(226) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153.
(227) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338.
(228) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474.
(229) Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 307.
(230) Duthaler, R. O. *Angew. Chem., Int. Ed.* **2003**, *42*, 975.
(231) Ohtake, H.; Imada, Y.; Murahashi, S.-I. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2737.
(232) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M.; Hashizume, D.; Koshino, H. *Adv. Synth. Catal.* **2004**, *346*, 1435.
(233) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561.
(234) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827.
(235) O'Brien, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 326.
(236) Bahmanyar, S.; Houk, K. N. *Org. Lett.* **2003**, *5*, 1249.
(237) Pojarliev, P.; Biller, W. T.; Martin, H. J.; List, B. *Synlett* **2003**, 1903.
(238) Kantam, M. L.; Rajasekhar, C. V.; Gopikrishna, G.; Reddy, K. R.; Choudary, B. M. *Tetrahedron Lett.* **2006**, *47*, 5965.
(239) Sasaoka, A.; Uddin, M. I.; Shimomoto, A.; Ichikawa, Y.; Shiro, M.; Kotsuki, H. *Tetrahedron: Asymmetry* **2006**, *17*, 2963.
(240) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.
(241) Paraskar, A. S.; Sudalai, A. *Tetrahedron* **2006**, *62*, 5756.
(242) Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2003**, *5*, 4301.
(243) Ibrahem, I.; Zou, W.; Engqvist, M.; Xu, Y.; Córdova, A. *Chem.—Eur. J.* **2005**, *11*, 7024.
(244) Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4079.
(245) Casiraghi, G.; Rassu, G.; Spanu, P. *Chem. Rev.* **1995**, *95*, 1677.
(246) Chowdari, N. S.; Ahmad, M.; Albertshofer, K.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2006**, *8*, 2839.
(247) Ibrahem, I.; Casas, J.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6528.
(248) Sunden, H.; Ibrahem, I.; Eriksson, L.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4877.
(249) Ibrahem, I.; Zou, W.; Casas, J.; Sundén, H.; Córdova, A. *Tetrahedron* **2006**, *62*, 357.
(250) Rodríguez, B.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 2888.
(251) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677.
(252) Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III. *J. Org. Chem.* **2003**, *68*, 9624.
(253) Córdova, A. *Synlett* **2003**, *11*, 1651.
(254) Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 2839.
(255) Liao, W.-W.; Ibrahem, I.; Córdova, A. *Chem. Commun.* **2006**, 674.
(256) Münch, A.; Wendt, B.; Christmann, M. *Synlett* **2004**, *15*, 2751.
(257) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 199.
(258) Funabiki, K.; Nagamori, M.; Goushi, S.; Matsui, M. *Chem. Commun.* **2004**, 1928.
(259) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842.
(260) Notz, W.; Watanabe, S.; Chowdari, N. S.; Zhong, G.; Betancort, J. M.; Tanaka, F.; Barbas, C. F., III. *Adv. Synth. Catal.* **2004**, *346*, 1131.
(261) Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett.* **2004**, *45*, 7243.
(262) Westermann, B.; Neuhaus, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 4077.
(263) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.
(264) Enders, D.; Vrettou, M. *Synthesis* **2006**, *13*, 2155.
(265) Koriyama, Y.; Nozawa, A.; Hayakawa, R.; Shimizu, M. *Tetrahedron* **2002**, *58*, 9621.
(266) Enders, D.; Grondal, C.; Vrettou, M. *Synthesis* **2006**, *21*, 3597.
(267) Baxter, E. W.; Reitz, A. B. *Org. React. (N. Y.)* **2002**, *59*, 1.
(268) Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804.
(269) Ibrahem, I.; Dziedzic, P.; Córdova, A. *Synthesis* **2006**, *23*, 4060.
(270) Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866.
(271) Córdova, A. *Chem.—Eur. J.* **2004**, *10*, 1987.
(272) Manhas, M. S.; Ghosh, M.; Bose, A. K. *J. Org. Chem.* **1990**, *55*, 575.
(273) Greff, Z.; Hoirvath, Z.; Nyitrai, J.; Kajtar-Peredy, M.; Brlik, J. *J. Chem. Res.* **1990**, *S*, 170.
(274) Greff, Z.; Horvath, Z.; Nyitrai, J.; Kajtar-Peredy, M.; Brlik, J. *J. Chem. Res.* **1990**, *M*, 1201.
(275) Watanabe, S.; Córdova, A.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2002**, *4*, 4519.
(276) Córdova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2003**, *44*, 1923.
(277) Edmondson, S. D.; Mastracchio, A.; Duffy, J. L.; Eiermann, G. J.; He, H.; Ita, I.; Leiting, B.; Leone, J. F.; Lyons, K. A.; Makarewicz, A. M.; Patel, R. A.; Petrov, A.; Wu, J. K.; Thornberry, N. A.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3048.
(278) Knudsen, L. B. *J. Med. Chem.* **2004**, *47*, 4128.
(279) Janey, J. M.; Hsiao, Y.; Armstrong, J. D., III. *J. Org. Chem.* **2006**, *71*, 390.
(280) Fustero, S.; Jiménez, D.; Sanz-Cervera, J. F.; Sánchez-Roselló, M.; Esteban, E.; Simón-Fuentes, A. *Org. Lett.* **2005**, *7*, 3433.
(281) Ibrahem, I.; Samec, J. S. M.; Bäckvall, J. E.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 3965.
(282) Enders, D.; Ward, D.; Adam, J.; Raabe, G. *Angew. Chem., Int. Ed.* **1996**, *35*, 981.
(283) Seebach, D.; Abele, S.; Gademann, K.; Jaun, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1595.
(284) Ibrahem, I.; Zhao, G.-L.; Córdova, A. *Chem.—Eur. J.* **2007**, *13*, 683.
(285) Zhao, G.-L.; Córdova, A. *Tetrahedron Lett.* **2006**, *47*, 7417.
(286) Kanazawa, A. M.; Denis, J.-N.; Greene, A. E. *J. Org. Chem.* **1994**, *59*, 1238.
(287) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048.
(288) Yang, J. W.; Stadler, M.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 609.
(289) Porter, E. A.; Wang, X.; Lee, H.-S.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 565.
(290) Seebach, D.; Jacobi, A.; Rueping, M.; Gademann, K.; Ernst, M.; Jaun, B. *Helv. Chim. Acta* **2000**, *83*, 2115.
(291) Vesely, J.; Rios, R.; Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 421.
(292) Chowdari, N. S.; Suri, J. T.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2507.
(293) Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4476.
(294) Córdova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 7749.
(295) Vinkovic, V.; Sunjic, V. *Tetrahedron* **1997**, *53*, 689.
(296) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408.
(297) Kano, T.; Hato, Y.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 8467.
(298) Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 1040.
(299) Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 9630.
(300) Ibrahem, I.; Córdova, A. *Chem. Commun.* **2006**, 1760.

(301) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F., III. *Synlett* **2003**, *12*, 1906.
(302) Bahmanyar, S.; Houk, K. N. *Org. Lett.* **2003**, *5*, 1249.
(303) Cheong, P. H.-Y.; Zhang, H.; Thayumanavan, R.; Tanaka, F.; Houk, K. N.; Barbas, C. F., III. *Org. Lett.* **2006**, *8*, 811.
(304) Komnenos, T. *Liebigs Ann. Chem.* **1883**, 145.
(305) Michael, A. *J. Prakt. Chem.* **1887**, *36*, 349.
(306) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.
(307) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992.
(308) Tomioka, K.; Nagaoka, Y.; Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. III, pp 1105.
(309) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171.
(310) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877.
(311) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688.
(312) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033.
(313) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701.
(314) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1176.
(315) Yamaguchi, M.; Shiraishi, T.; Igarashi, Y.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 8233.
(316) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520.
(317) Yamaguchi, M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hirama, M. *Tetrahedron* **1997**, *32*, 11223.
(318) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975.
(319) Kawara, A.; Taguchi, T. *Tetrahedron Lett.* **1994**, *47*, 8805.
(320) Belokon, Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Orlova, S. A.; Kuzmina, N. A.; Bodrov, D. E. *Russ. Chem. Bull.* **1993**, *42*, 1525.
(321) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, *46*, 4057.
(322) Herrman, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238.
(323) Latvala, A.; Stanchev, S.; Linden, A.; Hesse, M. *Tetrahedron: Asymmetry* **1993**, *4*, 173.
(324) Blarer, S. J.; Seebach, D. *Chem. Ber.* **1983**, *116*, 2250.
(325) Seebach, D.; Missbach, M.; Calderari, G.; Eberle, M. *J. Am. Chem. Soc.* **1990**, *112*, 7625.
(326) Blarer, S. J.; Schweizer, W. B.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 1637.
(327) Yamada, S.; Hiroi, K.; Achiwa, K. *Tetrahedron Lett.* **1969**, *10*, 4233.
(328) Yamada, S.; Otani, G. *Tetrahedron Lett.* **1969**, *10*, 4237.
(329) Kozikowski, A. P.; Mugrage, B. B. *J. Org. Chem.* **1989**, *54*, 2274.
(330) Hirai, Y.; Terada, T.; Yamazaki, T.; Momose, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 509.
(331) Hirai, Y.; Terada, T.; Yamazaki, T. *J. Am. Chem. Soc.* **1988**, *110*, 958.
(332) Fonseca, M. T. H.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3958.
(333) Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* **2005**, *127*, 16028.
(334) Enders, D.; Scherer, H. J.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1664.
(335) Schreiber, S. L.; Meyers, H. V.; Wiberg, K. B. *J. Am. Chem. Soc.* **1986**, *108*, 8274.
(336) Schreiber, S. L.; Meyers, H. V. *J. Am. Chem. Soc.* **1988**, *110*, 5198.
(337) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: Weinheim, 2005.
(338) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423.
(339) Enders, D.; Seki, A. *Synlett* **2002**, 26.
(340) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.
(341) Kotrusz, P.; Toma, S.; Schmalz, H.-G.; Adler, A. *Eur. J. Org. Chem.* **2004**, 1577.
(342) Rasalkar, M. S.; Potdar, M. K.; Mohile, S. S.; Salunkhe, M. M. *J. Mol. Catal. A* **2005**, *235*, 267.
(343) Betancort, J. M.; Sakthivel, K.; Thayummanavan, R.; Barbas, C. F. *Tetrahedron Lett.* **2001**, *42*, 4441.
(344) Hagiwara, H.; Okabe, T.; Hakoda, K.; Hoshi, T.; Ono, H.; Kamat, V. P.; Suzuki, T.; Ando, M. *Tetrahedron Lett.* **2001**, *42*, 2705.
(345) Hagiwara, H.; Komatsubara, N.; Ono, H.; Okabe, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 316.
(346) Betancort, J. M.; Barbas, C. F. *Org. Lett.* **2001**, *3*, 3737.
(347) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611.
(348) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559.
(349) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernarddinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147.
(350) Mossé, S.; Andrey, O.; Alexakis, A. *Chimia* **2006**, *60*, 216.
(351) Andrey, O.; Vidonne, A.; Alexakis, A. *Tetrahedron Lett.* **2003**, *44*, 7901.
(352) Mossé, S.; Alexakis, A. *Org. Lett.* **2006**, *8*, 3577.
(353) Mossé, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559.
(354) Planas, L.; Viret, J. P.; Royer, J. *Tetrahedron: Asymmetry* **2004**, *15*, 2399.
(355) Vögt, H.; Vanderheiden, S.; Bräse, S. *Chem. Commun.* **2003**, 2448.
(356) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558.
(357) Vogel, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570.
(358) Mitchell, C. E. T.; Cobb, A. J. A.; Ley, S. V. *Synlett* **2005**, 611.
(359) Terakado, D.; Takano, M.; Oriyama, T. *Chem. Lett.* **2005**, *34*, 962.
(360) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369.
(361) Wang, J.; Li, H.; Lou, B.; Zu, L.; Guo, H.; Wang, W. *Chem.—Eur. J.* **2006**, *12*, 4321.
(362) Aslanian, R.; Lee, G.; Iyer, R. V.; Shih, N.-Y.; Piwinski, J. J.; Draper, R. W.; McPhail, A. T. *Tetrahedron: Asymmetry* **2000**, *11*, 3867.
(363) Enders, D.; Chow, S. *Eur. J. Org. Chem.* **2006**, 4578.
(364) Diez, D.; Gil, M. J.; Moro, R. F.; Marcos, I. S.; Garcia, P.; Basabe, P.; Garrido, N. M.; Broughton, H. B.; Urones, J. G. *Tetrahedron* **2007**, *63*, 740.
(365) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137.
(366) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.
(367) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794.
(368) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861.
(369) Li, Y.; Liu, X. Y.; Zhao, G. *Tetrahedron: Asymmetry* **2006**, *17*, 2034.
(370) Xu, Y.; Zou, W.; Sunden, H.; Ibrahem, I.; Córdova, A. *Adv. Synth. Catal.* **2006**, *348*, 418.
(371) Xu, Y.; Córdova, A. *Chem. Commun.* **2006**, 460.
(372) Zhu, M. K.; Cun, L. F.; Mi, A. Q.; Jiang, Y. Z.; Gong, L. Z. *Tetrahedron: Asymmetry* **2006**, *17*, 491.
(373) Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Adv. Synth. Catal.* **2006**, *348*, 826.
(374) Tsogoeva, S. B.; Wei, S. *Chem. Commun.* **2006**, 1451.
(375) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170.
(376) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366.
(377) Cao, C. L.; Ye, M. C.; Sun, X. L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901.
(378) Cao, Y. J.; Lu, H. H.; Lai, Y. Y.; Lu, L. Q.; Xiao, W. J. *Synthesis* **2006**, 3795.
(379) Cao, Y. J.; Lai, Y. Y.; Wang, X.; Li, Y. J.; Xiao, W. J. *Tetrahedron Lett.* **2007**, *48*, 21.
(380) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093.
(381) Xu, D.; Luo, S.; Yue, H.; Wang, L.; Liu, Y.; Xu, Z. *Synlett* **2006**, 2569.
(382) Luo, S.; Mi, X.; Liu, S.; Xu, H.; Cheng, J. P. *Chem. Commun.* **2006**, 3687.
(383) Luo, S.; Xu, H.; Mi, X.; Li, J.; Zheng, X.; Cheng, J. P. *J. Org. Chem.* **2006**, *71*, 9244.
(384) Barros, M. T.; Phillips, A. M. F. *Eur. J. Org. Chem.* **2007**, 178.
(385) Pansare, S. V.; Pandya, K. *J. Am. Chem. Soc.* **2006**, *128*, 9624.
(386) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 2064.
(387) Clarke, M. L.; Fuentes, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 930.
(388) Benaglia, M.; Cinquini, M.; Cozzi, F.; Puglisi, A.; Celentano, G. *J. Mol. Catal. A* **2003**, *204−205*, 157.
(389) List, B.; Castello, C. *Synlett* **2001**, 1687.
(390) Wang, J.; Li, H.; Zu, L.; Wang, W. *Adv. Synth. Catal.* **2006**, *348*, 425.
(391) Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4151.
(392) Chi, Y.; Peelen, T. J.; Gellman, S. H. *Org. Lett.* **2005**, *7*, 3469.
(393) Peelen, T. J.; Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11598.
(394) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296.
(395) Chi, Y.; Gellman, S. H. *Org. Lett.* **2005**, *7*, 4253.
(396) Asato, A. E.; Watanabe, C.; Li, X. Y.; Liu, R. S. H. *Tetrahedron Lett.* **1992**, *33*, 3105.
(397) Bench, B. J.; Liu, C.; Evett, C. R.; Watanabe, C. M. H. *J. Org. Chem.* **2006**, *71*, 9458.
(398) Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498.
(399) Wabnitz, T. C.; S. Saaby; Jørgensen, K. A. *Org. Biomol. Chem.* **2004**, *2*, 828.
(400) Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6951.
(401) Pinheiro, S.; Guingant, A.; Desmaële, D.; d'Angelo, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1003.
(402) d'Angelo, J.; Revial, G. *Tetrahedron: Asymmetry* **1991**, *2*, 199.
(403) Enders, D.; Müller, S. F.; Raabe, G.; Runsink, J. *Eur. J. Org. Chem.* **2000**, 879.
(404) Sanki, A. K.; Suresh, C. G.; Falgune, U. D.; Pathak, T. *Org. Lett.* **2003**, *5*, 1285.

(405) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948.
(406) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, 1993.
(407) Mossé, S.; Alexakis, A. *Org. Lett.* **2005**, *7*, 4361.
(408) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001.
(409) Guillena, G.; Ramón, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465.
(410) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656.
(411) Iwamura, H.; Mathew, S. P.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 11770.
(412) Chowdari, N. S.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 867.
(413) Dahlin, N.; Bøgevig, A.; Adolfsson, H. *Adv. Synth. Catal.* **2004**, *346*, 1101.
(414) Dere, R. T.; Pal, R. R.; Patil, P. S.; Salunkhe, M. M. *Tetrahedron Lett.* **2003**, *44*, 5351.
(415) Kotrusz, P.; Alemayehu, S.; Toma, S.; Schmalz, H.-G.; Adler, A. *Eur. J. Org. Chem.* **2005**, 4904.
(416) Guo, H.-M.; Cheng, L.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Chem. Commun.* **2006**, 429.
(417) Kano, T.; Ueda, M.; Takai, J.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 6046.
(418) Kim, S.-G.; Park, T.-H. *Tetrahedron Lett.* **2006**, *47*, 9067.
(419) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038.
(420) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247.
(421) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808.
(422) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293.
(423) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112.
(424) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Hibino, K.; Shoji, M. *J. Org. Chem.* **2004**, *69*, 5966.
(425) Bøgevig, A.; Sundén, H.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109.
(426) Córdova, A.; Sundén, H.; Bøgevig, A.; Johansson, M.; Himo, F. *Chem.—Eur. J.* **2004**, *10*, 3673.
(427) Wang, W.; Wang, J.; Li, H.; Liao, L. *Tetrahedron Lett.* **2004**, *45*, 7235.
(428) Sundén, H.; Dahlin, N.; Ibrahem, I.; Adolfsson, H.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 3385.
(429) Kumarn, S.; Shaw, D. M.; Longbottom, D. A.; Ley, S. V. *Org. Lett.* **2005**, *7*, 4189.
(430) Kumarn, S.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2006**, 3211.
(431) Guo, H.-M.; Niu, H.-Y.; Xue, M.-X.; Guo, Q.-X.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Wang, J.-J. *Green Chem.* **2006**, *8*, 682.
(432) Kim, S.-G.; Park, T.-H.; Kim, B. J. *Tetrahedron Lett.* **2006**, *47*, 6369.
(433) Córdova, A.; Sunden, H.; Engqvist, M.; Ibrahem, I.; Casas, J. *J. Am. Chem. Soc.* **2004**, *126*, 8914.
(434) Ibrahem, I.; Zhao, G.-L.; Sunden, H.; Córdova, A. *Tetrahedron Lett.* **2006**, *47*, 4659.
(435) Pikho, P. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 544.
(436) Enders, D.; Hüttl, M. R. M. *Synlett* **2005**, 991.
(437) Steiner, D. D.; Mase, N.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706.
(438) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826.
(439) Brandes, S.; Niess, B.; Bella, M.; Prieto, A.; Overgaard, J.; Jørgensen, K. A. *Chem.—Eur. J.* **2006**, *12*, 6039.
(440) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108.
(441) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790.
(442) Halland, N.; Lie, M. A.; Kjaersgaard, A.; Marigo, M.; Schiøtt, B.; Jørgensen, K. A. *Chem.—Eur. J.* **2005**, *11*, 7083.
(443) Marigo, M.; Bachmann, S.; Halland, N.; Braunton, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5507.
(444) Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K. A. *Chem. Commun.* **2005**, 4821.
(445) Wang, W.; Li, H.; Wang, J.; Liao, L. *Tetrahedron Lett.* **2004**, *45*, 8229.
(446) Wang, W.; Wang, J.; Li, H. *Org. Lett.* **2004**, *6*, 2817.
(447) Wang, J.; Li, H.; Mei, Y.; Lou, B.; Xu, D.; Xie, D.; Guo, H.; Wang, W. *J. Org. Chem.* **2005**, *70*, 5678.
(448) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450.
(449) Fu, A.; List, B.; Thiel, W. *J. Org. Chem.* **2006**, *71*, 320.
(450) Ibrahem, I.; Córdova, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1952.
(451) Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973.
(452) Luppi, G.; Monari, M.; Correa, R. J.; Violante, F. A.; Pinto, A. C.; Kaptein, B.; Broxterman, Q. B. Gardenb, S. J.; Tomasini, C. *Tetrahedron* **2006**, *62*, 12017.
(453) Kim, J. D.; Kim, I. S.; Jin, C. H.; Zee, O. P.; Jung, Y. H. *Org. Lett.* **2005**, *7*, 4025.
(454) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777.
(455) Yang, J. W.; Fonseca, M. T. H.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036.
(456) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Synthesis* **2004**, 1509.
(457) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966.
(458) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2527.
(459) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423.
(460) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420.
(461) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2004**, 1808.
(462) Zu, L.; Wang, J.; Li, H.; Wang, W. *Org. Lett.* **2006**, *8*, 3077.
(463) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876.
(464) Zu, L.; Li, H.; Wang, J.; Yu, X.; Wang, W. *Tetrahedron Lett.* **2006**, *47*, 5131.
(465) Palomo, C.; Vera, S.; Mielgo, A.; Gomez-Bengoa, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 5984.
(466) Reyes, E.; Vicario, J. L.; Badia, D.; Carrillo, L. *Org. Lett.* **2006**, *8*, 6135.
(467) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *41*, 1790.
(468) Suri, J. T.; Steiner, D. D.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 3885.
(469) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F., III. *Org. Lett.* **2003**, *5*, 1685.
(470) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254.
(471) Cheong, P. H.-Y.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 13912.
(472) Mathew, S. P.; Iwamura, H.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3317.
(473) Iwamura, H.; Wells, D. H.; Mathew, S. P.; Klussmann, M.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 16312.
(474) Zhong, G. *Chem. Commun.* **2004**, 606.
(475) Zhong, G.; Yu, Y. *Org. Lett.* **2004**, *6*, 1637.
(476) Sunden, H.; Engqvist, M.; Casas, J.; Ibrahem, I.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6532.
(477) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjaersgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703.

CR0684016