The Direct Catalytic Asymmetric Mannich Reaction

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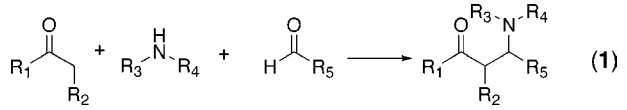
Received July 25, 2003

ABSTRACT
The direct catalytic asymmetric addition of unmodified carbonyl compounds to preformed or in situ-generated imines has emerged as a promising new route to optically enriched α- and *β*-amino acid derivatives, *β*-lactams, and 1,2- and *γ*-amino alcohols. The direct catalytic asymmetric Mannich reactions are mediated by small organometallic and organic amine catalysts that can achieve levels of selectivity similar to those possible with natural enzymes. The different small-molecule catalysts described here are complementary in their applications. They also complement each other in *syn* or *anti* selectivity of the direct asymmetric Mannich reaction. In this Account, we highlight the recent developments in and contributions to this research.

Introduction

One of the ultimate goals and challenges in chemistry is to develop stereoselective transformations for the creation of functionalized optically active molecules with structural diversity from simple and easily available starting materials. Hence, during the past two decades, the synthesis of enantiomerically pure or enriched compounds has emerged as one of the most important fields in organic synthesis. Several procedures to generate optically active molecules are known, and among these, asymmetric catalysis plays an important role and is a highly active research area.[1]

The Mannich reaction is a classic method for the preparation of *β*-amino carbonyl compounds and therefore a very important carbon−carbon bond-forming reaction in organic synthesis. The versatility and potential to create both functional and structural diversity using this reaction have long stimulated the creativity of chemists.[2] For example, the Mannich reaction has been employed numerous times successfully as a key step in natural product synthesis as well as in medicinal chemistry.[3] The first asymmetric Mannich reactions were diastereoselective and involved the addition of preformed enolates and enamines to preformed imines using stoichiometric amounts of chiral auxiliaries.[4] Only recently, the first successful examples of catalytic asymmetric additions of enolates to imines were reported by the groups of Kobayashi,[5] Sodeoka,[6] Lectka,[7] and Jacobsen.[8] However, a disadvantage of these stereoselective Mannich reactions can be the preparation and instability of the preformed enolates used. The most effective and atom-economic asymmetric Mannich reaction would be a catalytic process that involves the same number of equivalents of unmodified carbonyl donor, amine, and acceptor aldehyde (eq 1).[9]

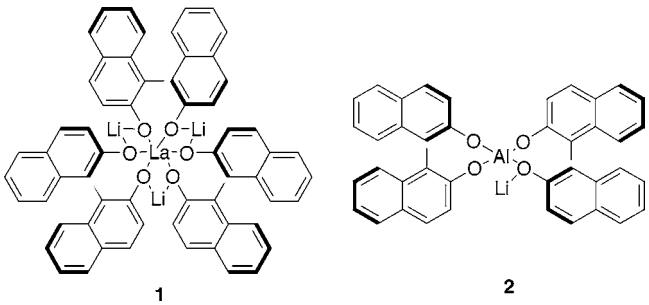


(1)

Recently, direct catalytic asymmetric Mannich-type reactions were reported. The transformations are catalyzed by both organometallic complexes and metal-free organic catalysts. The different catalysts are highly stereoselective and complementary in their applicability and selectivity. The direct catalytic Mannich reaction has opened the path to new routes for the synthesis of α- and *β*-amino acid derivatives, *γ*-amino alcohols, *syn*- and *anti*-1,2-amino alcohols, and *β*-lactams. It is apparent that the exploitation of the direct catalytic asymmetric Mannich-type reaction has begun and further advances are on the horizon.[10] Here, we highlight the recent developments in and contributions to this research.

Discussion

Organometallic Catalysts. Shibasaki and co-workers have conducted extensive research on the use of heterobimetallic complexes as catalysts for asymmetric synthesis.[11] The reactions are catalyzed by heterobimetallic complexes that function as both a Lewis acid and a Brønsted base. Among them, $LaLi_3$tris(binaphthoxide) **1** (LLB) was proven to be an effective catalyst in direct asymmetric aldol reactions (Figure 1).[12] On the basis of this research,



1 2

FIGURE 1. $LaLi_3$tris(binaphthoxide) catalyst **1** and AlLibis(binaphthoxide) (ALB) **2**.

Shibasaki et al. disclosed the first report of a direct catalytic asymmetric Mannich reaction.[13]

In their initial one-pot, three-component experiment, propiophenone, $(CH_2O)_n$, and pyrrolidine were reacted in the presence of a catalytic amount of LLB, affording the corresponding Mannich product with an ee of 64% (Scheme 1).

Armando Córdova grew up in Stockholm and received his M. S. in 1995 from the Royal Institute of Technology, KTH. He acquired his Ph. D. from KTH in 1998 under the direction of Tommy Iversen and Karl Hult. After accomplishing research at the Swedish Pulp and Paper Research Institute he joined the laboratory of Kim Janda in 1999 at the Scripps Research Institute with Wennergren and Skaggs postdoctoral fellowships. He conducted research at Scripps until 2002. He is currently Assistant Professor at Arrhenius laboratory, Stockholm University. His research interests include development of catalytic asymmetric reactions, biocatalysis and asymmetric synthesis.

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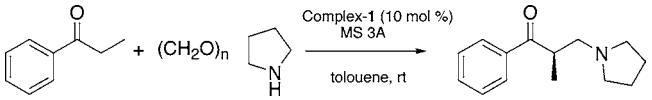
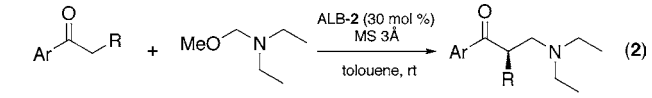
10.1021/ar030231l CCC: $27.50
Published on Web 01/13/2004

Scheme 1. The First Direct Catalytic Asymmetric Mannich Reaction



The yield of the Mannich product was only 16%, due to competing formation of $C_4H_8NCH_2NC_4H_8$. However, the chemoselectivity of the Mannich reaction can be significantly increased by in situ generation of the iminium ion using aminomethyl ethers in combination with rare earth metal triflates and AlLibis(binaphthoxide) (ALB) **2** (Figure 1) as the catalyst (eq 2). The cooperative complex of ALB **2** and $La(OTf)_3 \cdot nH_2O$ catalyzes direct asymmetric Mannich-type reactions with good selectivity, providing β-amino aryl ketones in good yields and with 31−44% ee.



Ar	R
C_6H_5	Me
4-$MeOC_6H_5$	Et
2-Napht	
6-MeO-2-Napht	

65-76% yield
31-44% ee

Recently, Shibasaki et al. reported that the Et_2Zn/linked-BINOL complex **3** is an excellent catalyst for the direct asymmetric Mannich-type reaction (Figure 2).[14]

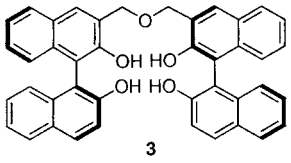


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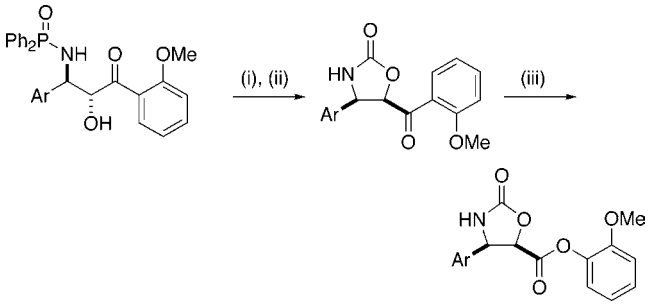
FIGURE 2. (*S*,*S*)-Linked BINOL complex **3**.

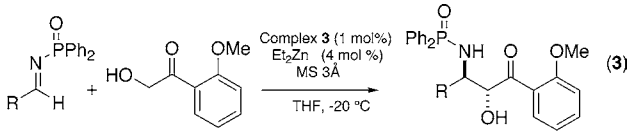
The Et_2Zn/linked-BINOL complex **3** was investigated as a catalyst due to its high selectivity in direct asymmetric *syn*-selective aldol reactions and Michael reactions with aryl hydroxyketones as the donors.[15] Mannich reactions between imines with various *N*-protective groups, hydroxyaceto-2-methoxyphenone, and Et_2Zn/linked-BINOL complex **3** revealed that *N*-diphenylphosphinoyl (Dpp)-protected imines were the most promising with regard to stereoselectivity. Thus, *N*-Dpp-protected imines are employed as acceptors, and the corresponding Mannich adducts are isolated in high yield and excellent enantioselectivity (eq 3).

High *anti*-diasteroselectivity is observed for several aromatic imines. For ortho-substituted aromatic imines, the two newly formed stereocenters are created with almost absolute stereocontrol. Aliphatic imines can also be used as substrates, and the reaction is readily performed on a gram scale with as little as 0.25 mol % of catalyst loading. Furthermore, the Mannich adducts are readily transformed to protected α-hydroxy-β-amino acids in high yield. This is achieved by deprotection of the *N*-Dpp group under acidic conditions, followed by carbamate formation and Baeyer−Villiger oxidation with *m*CPBA without epimerization (Scheme 2).

Scheme 2. Synthesis of Protected α-Hydroxy-β-amino Acids[a]



[a] Reagents and conditions: (i) HCl(aq), THF, room temperature; (ii) triphosgene, pyridine, CH_2Cl_2, −78 °C; (iii) *m*CPBA, $Cl(CH_2)_2Cl$, 60 °C.



R
4-MeC_6H_4
2-MeC_6H_4
C_6H_4
4-$NO_2C_6H_4$
4-$MeOC_6H_4$
4-ClC_6H_4
1-Naphtyl
2-furyl
E-cinnam
cyclo-propyl

96-98% yield
3:1- >49:1 dr
98->99.5% ee

The absolute stereochemistry of the Mannich adducts was determined by the Mosher method and X-ray analysis. The analysis revealed that Et_2Zn/linked-BINOL complex **3** affords Mannich and aldol adducts with the same absolute configuration (2*R*). However, the diastereoselectivity of the amino alcohol derivatives is *anti*, which is opposite to the *syn*-1,2-diol aldol products. Hence, the electrophiles approach the *re* face of the Zn-enolate in the Mannich reactions and the *si* face in the aldol reactions. The *anti* selectivity is due to the bulky Dpp group of the imine nitrogen, and to avoid steric repulsion, the Mannich-type reaction proceeds via the transition state **4** (Figure 3).

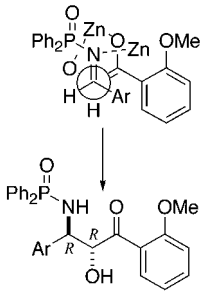
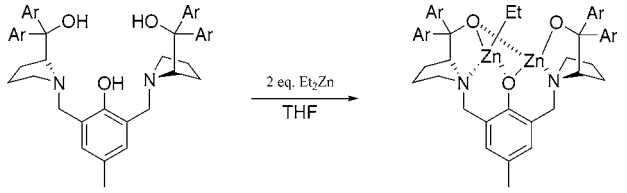


FIGURE 3. Plausible transition state.

Trost et al. have discovered a novel design of dinuclear zinc catalysts that can catalyze diasteroselective and enantioselective direct aldol reactions.[16] The dinuclear zinc catalysts **5a**−**7a** are generated in situ by exposing the appropriate ligand **5**−**7** to 2 equiv of diethylzinc in THF (Scheme 3).

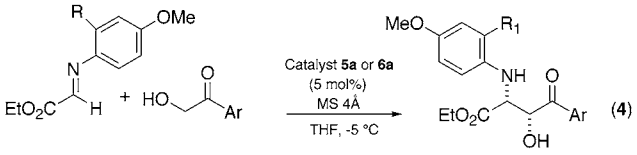
Scheme 3. Generation of Dinuclear Zn Catalysts 5a−7a



5 Ar = phenyl
6 Ar = 4-biphenyl
7 Ar = β-naphtyl

5a Ar = phenyl
6a Ar = 4-biphenyl
7a Ar = β-naphtyl

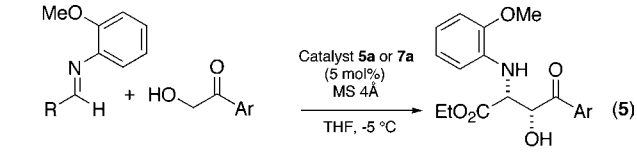
Recently, Trost and co-workers reported that the dinuclear zinc complexes catalyze Mannich reactions with unmodified aromatic hydroxy ketones as donors with excellent enantioselectivity.[17] Mannich-type reactions between *N*-*p*-methoxyphenyl (PMP)-protected α-ethyl glyoxalate and hydroxyacetophenone in the presence of a catalytic amount of catalyst **5a** afford the desired *N*-PMP-protected amino acid derivative in 76% yield, with a dr of 7:1 and 95% ee (eq 4).



R	Ar
H	C_6H_5
Me	4-$MeOC_6H_4$
	3-$MeOC_6H_4$
	2-$MeOC_6H_4$
	2-furyl

76 - > 97% yield
2:1 - >20:1 dr
98 - >99% ee

Imines derived from the more sterically demanding 2-methyl-4-methoxyaniline derivatives and ethyl glyoxylate provide even higher selectivity. The reaction also exhibits a significant ligand effect, and when ligand **6** is used, the yield and diastereoselectivity are further improved. Hence, the biphenyl ligand **6** is used as the standard ligand for reactions with glyoxylate imines. The Zn_2/linked complex **6a** catalyzes Mannich reactions with more electron-rich aromatic hydroxy ketones, and a single diastereoisomer is formed with ortho-substituted methoxy hydroxy ketone as the donor. Furthermore, reaction with 2-hydroxyacetylfuran proceeds smoothly and furnishes amino alcohols with a new element of diversity. The dinuclear zinc complex-catalyzed reactions are also highly enantioselective for acceptor imines derived from aromatic aldehydes (eq 5). In this case, *β*-naphthyl ligand **7**

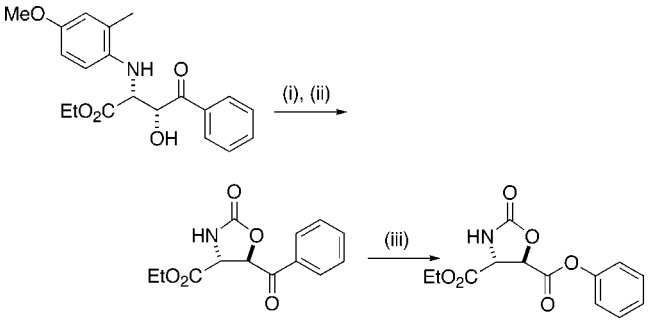


R	Ar
C_6H_5	C_6H_5
4-ClC_6H_5	4-$MeOC_6H_4$
	3-$MeOC_6H_4$
	2-$MeOC_6H_4$
	2-furyl

66 - 90% yield
> 15:1 dr
99- > 99% ee

significantly increases the diastereoselectivity of the reaction. The employment of *o*-methoxyaniline-derived acceptor imines also dramatically increases the diestereoselectivity of the reaction. This is explained by a bidentate binding model with the ortho-substituted derivative, where a two-point binding of the imine through the nitrogen and the methoxy group helps rigidify the dynamic nature of the imine−Lewis acid complex, preventing *E*/*Z* isomerization of the carbon−nitrogen double bond. Importantly, a nearly atom-economic process can be achieved, using 1.1 equiv of ketone, with no change in chemoselectivity by addition of "zincaphilic" additives such as Ph_3PS and Ph_3AsO. The *β*-amino alcohol derivatives are valuable synthetic intermediates. For example, a three-step procedure including Baeyer−Villiger oxidation and oxidative dearylation provides protected *syn*-α-hydroxy-*β*-amino acids that are constituents of natural products, e.g., Taxol (Scheme 4).[3d]

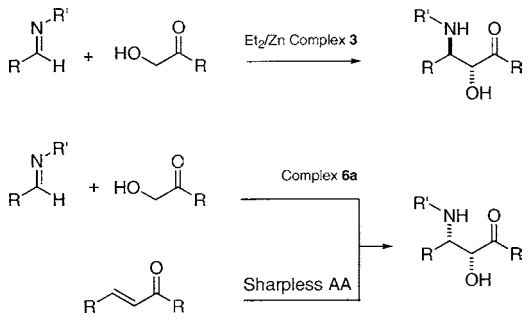
Scheme 4. Synthesis of *syn*-α-Hydroxy-*β*-amino Acids[a]



[a] Reagents and conditions: (i) triphosgene, *i*-Pr_2NEt; (ii) CAN, H_2O/CH_3CN, 0 °C; (iii) TMSO−OTMS, sulfonamide, $SnCl_4$.

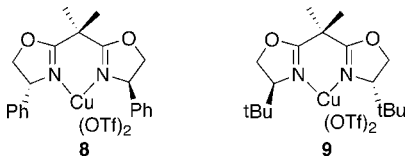
NOE experiments on the oxazolidinone confirmed that *syn*-1,2-amino alcohols are formed. This is opposite to the dinuclear zinc complex-catalyzed direct asymmetric aldol reaction, where vicinal diols are obtained with an *anti* configuration.[16] *Trost's and Shibasaki's zinc complexes are complementary in their selectivity and provide new routes to either syn- or anti-1,2-amino alcohol derivatives, respectively.* The dinuclear zinc complex-catalyzed Mannich reactions can be considered as a regiospecific alternative to the Sharpless asymmetric aminohydroxylation reaction (AA) (Scheme 5).[18]

Scheme 5. Complementary Routes to 1,2-Amino Alcohols



Jørgensen and co-workers have developed direct asymmetric reactions that are catalyzed by chiral copper(II)

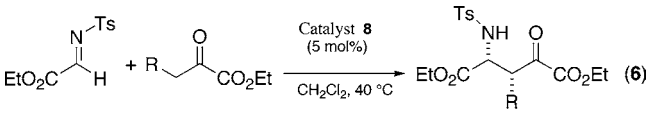
bisoxazoline (BOX) complexes.[19] On the basis of this research, they disclosed the first chiral copper(II)/BOX complex-catalyzed direct asymmetric Mannich reaction of activated carbonyl compounds and α-imino esters.[20] A screen of different C_2-symmetric ligands with copper(II) as the metal ion revealed that $Cu(OTf)_2$/BOX complexes **8** and **9** are catalysts in the reaction between pyruvate and *N*-tosyl-protected α-imino ethyl glyoxylate (Figure 4).



8 **9**

FIGURE 4. $Cu(OTf)_2$/BOX complex **8** and **9**.

Different α-carbonyl esters can be used as nucleophiles, providing functionalized α-amino acid derivatives with excellent diastereoselectivity and enantioselectivity (eq 6).

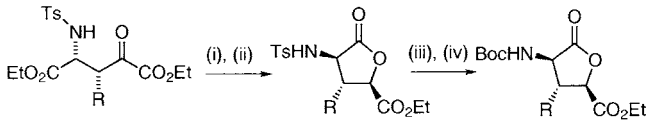


R
H
Me
Bn
Br

70 - 94% yield
> 10:1 dr
78 - >98% ee

The Mannich adducts are readily transformed to optically active α-amino-γ-lactones via a one-pot diastereoselective reduction and lactonization sequence (Scheme 6). The tosyl group can also be removed and exchanged

Scheme 6. Synthesis α-Amino-γ-lactones[a]



R
Me
Bn

70-90% yield
>98% de
97-98% ee

[a] Reagents: (i) L-Selectride, THF; (ii) PTSA; (iii) $(Boc)_2O$, DMAP catalyst; (iv) Mg/MeOH.

with a Boc group via a two-step procedure.

The copper(II) ion is crucial for the success of this reaction.[21] It has the properties necessary to both generate the enol species in situ and, in combination with the C_2-symmetric ligand, coordinate it as well as the imine in a bidentate fashion. The reaction proceeds via a cyclohexane-like transition state with the R substituent of the enol in the less sterically crowded equatorial position, which is required to obtain the observed diastereoselectivity (Figure 5).

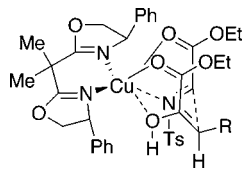
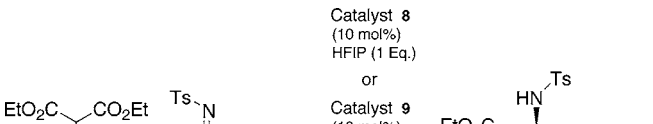


FIGURE 5. Plausible transition state.

The chiral $Cu(OTf)_2$/BOX complexes **8** and **9** are also catalysts for the asymmetric Mannich-type additions of unmodified malonates and β-ketosters to activated *N*-tosyl-α-imino esters.[22] Reactions with substituted diethyl malonates in the presence of a catalytic amount of $Cu(OTf)_2$/BOX complex **8** proceed smoothly at −20 °C, giving Mannich adducts in good yield with 61−87% ee (eq 7).



R
H
Me
Bn
Et
i-Bu
n-Bu

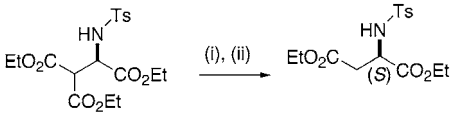
Catalyst **8** 73 - 88% yield
61 - 87% ee

Catalyst **9** 60 - 99% yield
74 - 94% ee

The addition of the electron-poor alcohol 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) is necessary to improve the enantioselectivity of the $Cu(OTf)_2$/BOX complex **8**-catalyzed reactions. Interestingly, there is no improvement of the stereoselectivity when HFIP is added to the $Cu(OTf)_2$/BOX complex **9**-catalyzed reactions (eq 7).

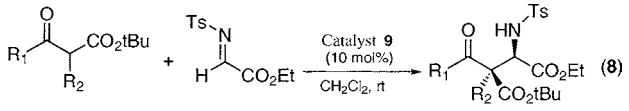
The direct catalytic asymmetric Mannich reaction with substituted malonates is a new entry to optically active β-carboxylic ester α-amino acid derivatives. Synthesis of *N*-tosyl-protected aspartic acid diethyl ester via decarboxylation revealed that both $Cu(OTf)_2$/BOX catalysts **8** and **9** provide L-amino acid derivatives, even though the catalysts have the opposite configurations (Scheme 7).

Scheme 7. Synthesis of Aspartic Acid Derivatives[a]



[a] Reagents: (i) 0.5 M NaOH (ii) EtOH, H_2SO_4.

$Cu(OTf)_2$/BOX complex-catalyzed Mannich reactions with substituted β-ketoesters are especially interesting since they provide a new entry for the formation of chiral quaternary carbon centers (eq 8).[23]



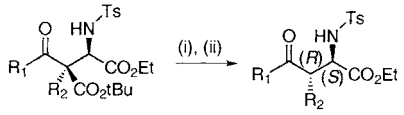
R_1	R_2
Me	Me
Bn	$(CH_2)_4$
Et	Allyl
i-pr	

55 - 89% yield
dr > 10:1
86- 95% ee

In particular, the $Cu(OTf)_2$/BOX **9**-catalyzed Mannich reactions with β-ketoesters including a *tert*-butyl ester group are highly selective, providing amino acid derivatives with a chiral quaternery center with excellent diastereoselectivities and enantioselectivities. In addition, treatment of the products with TMSOTf, followed by addition of $NaHCO_3$, affords a convenient approach to

valuable γ-keto-functionalized α-amino acid derivatives with *anti* relative configuration (Scheme 8).

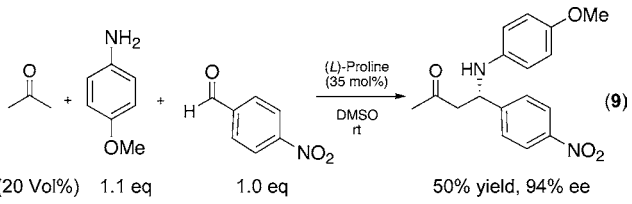
Scheme 8. Synthesis of γ-Keto-Functionalized α-Amino Acid Derivatives[a]



[a] Reagents: (i) 1.5 equiv of TMSOTf; (ii) saturated $NaHCO_3$.

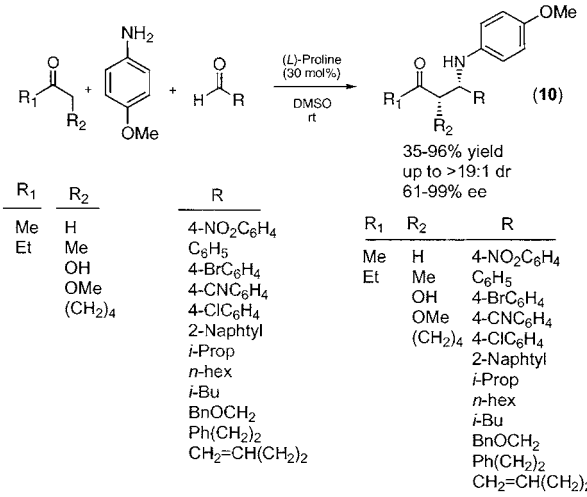
Metal-Free Organocatalysis. Asymmetric reactions catalyzed by metal-free organic catalysts have received increased attention in recent years.[24] Interestingly, since the discovery of amino acid-catalyzed stereoselective Robinson annulations in the early 1970s, there was no intensive research on this concept for other C−C bond-forming reactions for several decades, even though the reaction is frequently used in the preparation of building blocks for the total synthesis of natural products.[25,26] It was not until almost three decades later that researchers demonstrated that amino acid derivatives function as catalysts for direct asymmetric intermolecular C−C bond-forming reactions.[24]

Recently, List and co-workers reported the first direct organocatalytic asymmetric Mannich reaction.[27] The design and support for such transformations were based on Kobayshi and co-workers' report of one-pot, three-component Mannich reactions and previous research on proline-catalyzed direct asymmetric aldol reactions.[28,29] Hence, they envisioned that a small chiral amine would be able to form enamines with unmodified ketones and mediate stereoselective additions to in situ-generated imines in one pot. In an initial experiment, L-proline (35 mol %), excess acetone, *p*-nitrobenzaldehyde, and *p*-anisidine were dissolved in DMSO and stirred for 12 h (eq 9).

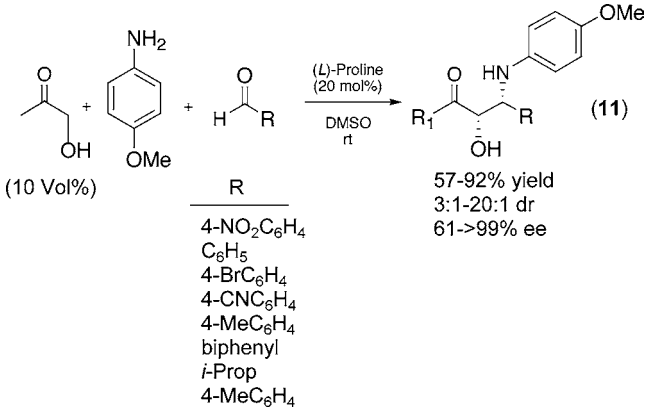


The reaction was quenched, and after standard workup, the corresponding Mannich adduct was isolated in 50% yield with an ee of 96%, together with a 20% yield of the aldol adduct. The proline-catalyzed one-pot, three-component reactions with acetone, *p*-anisidine, and aliphatic aldehydes proceed with excellent chemoselectivity, affording Mannich adducts in high yield with 73−93% ee (eq 10).

The L-proline-catalyzed Mannich reaction also takes place with other ketones as donors, where aliphatic ketones provide two regioisomers with good enantioselectivity. The Mannich reaction is regiospecific for oxygen-substituted ketones, providing one single regioisomer in good yield with high ee. In particular, the reaction with hydroxyacetone as the donor provides a new highly

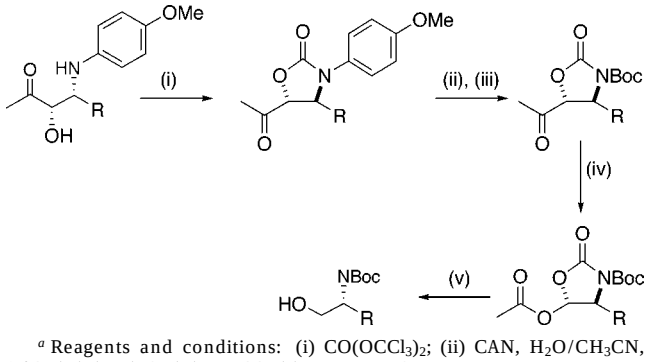


chemo-, regio-, diastereo-, and enantioselective entry to chiral 1,2-amino alcohols (eq 11).



The highest selectivity is observed when aromatic imines with electron-withdrawing groups are used as acceptors. The relative and absolute configuration was determined by X-ray analysis, confirming that *syn*-1,2-amino alcohols are formed. The amino alcohol products can also be converted to Boc-protected oxazolidinones in three steps (Scheme 9). Baeyer−Villiger oxidation of the

Scheme 9. Synthesis of α-Amino Alcohol Derivatives[a]



[a] Reagents and conditions: (i) $CO(OCCl_3)_2$; (ii) CAN, H_2O/CH_3CN, 0 °C; (iii) $(Boc)_2O$; (iv) TFPAA; (v) $NaBH_4$, EtOH.

oxalidinones affords acetal products instead of protected α-hydroxy-β-amino acid esters, which are obtained in oxidations of aryl hydroxy ketone-derived oxalidinones (see Schemes 2 and 4). Reduction of the acetals yielded

Boc-protected 2-amino 1-alcohols and revealed that L-proline affords β-amino ketones with *S* configuration.

Barbas and co-workers later demonstrated that other amino acid derivatives, in addition to proline, can catalyze the direct asymmetric Mannich-type reaction with good enantioselectivity (Figure 6).[30]

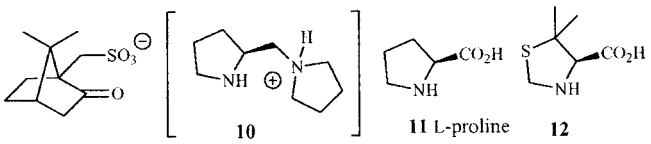
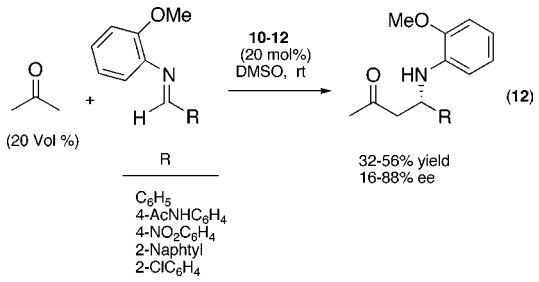


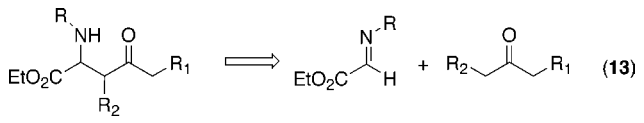
FIGURE 6. Organic catalysts **10**, **11**, and **12**.

Their previous catalyst screens of aldol reactions and Robinson annulations suggested the possibility of chiral amines being able to catalyze the Mannich reaction as well.[31,32] Thus, a catalyst screen of Mannich-type reactions between *N*-OMP-protected aldimines and acetone revealed that chiral diamine salt **10**, L-proline **11**, and 1-5,5-dimethylthiazolidine-4-carboxylic acid (DMTC) **12** are catalysts for the Mannich-type reaction, affording Mannich adducts in moderate yields with 60−88% ee (eq 12).

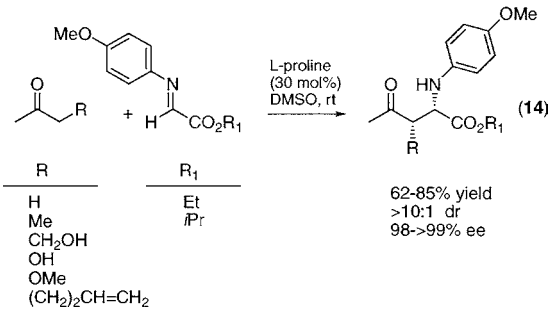


To extend the Mannich-type reactions to aliphatic imines, the DMTC **12**-catalyzed reactions are performed as one-pot, three-component procedures. The *o*-anisidine component has to be exchanged with *p*-anisidine for the one-pot reactions to occur. The DMTC **12**-catalyzed one-pot, three-component direct asymmetric Mannich reactions provide Mannich adducts in moderate yield with 50−86% ee.

Addition of nucleophiles to electrophilic glycine templates has served as an excellent entry for the synthesis of α-amino acid derivatives.[3c,5−7] In particular, imines derived from α-ethyl glyoxylate are excellent electrophiles for the stereoselective construction of optically active molecules.[33] This research and retrosynthetic analysis led us to believe that amine-catalyzed asymmetric Mannich-type additions of unmodified ketones to glyoxylate-derived imines would be an attractive route for the synthesis of γ-keto-α-amino acid derivatives (eq 13).[34]

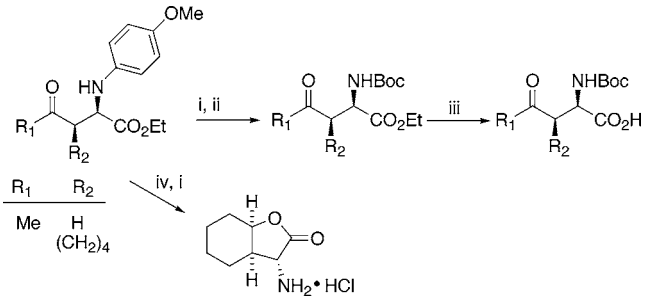


Initially, an L-proline-catalyzed direct asymmetric Mannich reaction with acetone and *N*-PMP-protected α-ethyl glyoxylate was examined in different solvents. The Mannich-type reaction was effective in all solvents tested, and the corresponding amino acid derivative was isolated in excellent yield and enantioselectivity (ee >95%). Direct asymmetric Mannich-type additions with other ketones afford Mannich adducts in good yield and excellent regio-, diastereo-, and enantioselectivities (eq 14).



The reaction is regiospecific, and C−C bond formation exclusively occurred on the most substituted side of the ketone donor. In contrast, the corresponding Mannich addition of non-oxygen-substituted ketones to other imines resulted in a mixture of regioisomers.[27] The amino acid derivatives can be further manipulated, and the PMP group can be exchanged with a Boc protective group via a one-pot dearylation carbamate-formation procedure without racemization (Scheme 10).

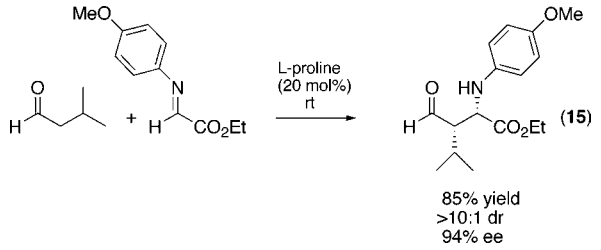
Scheme 10. Further Synthetic Manipulations of the *N*-PMP-Protected γ-Keto-α-amino Acid Derivatives[a]



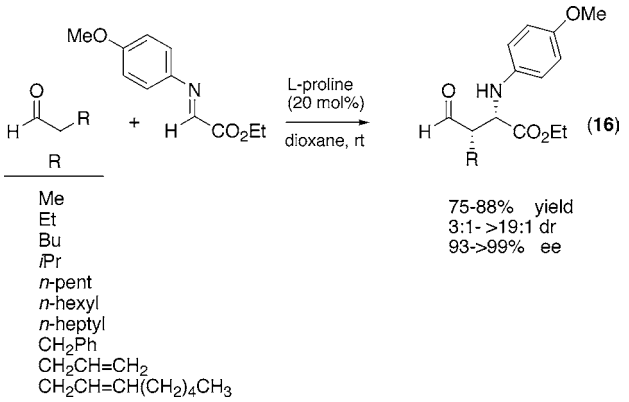
[a] Reagents: (i) CAN, H_2O/CH_3CN; (ii) $(Boc)_2O$; (iii) LiOH, H_2O/dioxane; (iv) L-Selectride, THF.

The corresponding Boc-protected γ-keto-α-amino acid derivatives are useful building blocks in peptide chemistry and medicinal chemistry. Determination of the absolute and relative configuration revealed that L-proline provides L-amino acids with *syn* relationship between the alkyl and amino groups.

The similarity in reaction mechanisms between proline- and 2-deoxyribose-5-phosphate aldolase-catalyzed direct asymmetric aldol reactions with acetaldehyde made us postulate that a chiral amine would be able to catalyze stereoselective C−C bond formation between unmodified aldehydes and other electrophiles, such as imines.[35,36] Thus, we disclosed the first report of a direct catalytic asymmetric Mannich reaction with unmodified aldehydes as nuchleophiles.[37] Initially, isovaleraldehyde and *N*-PMP-protected α-ethyl glyoxylate were reacted in the presence of a catalytic amount of L-proline in different solvents (eq 15).

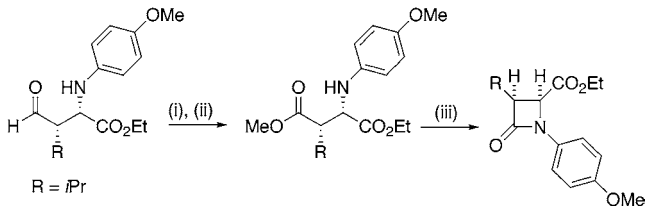


The highest enantioselectivity is achieved in dioxane and THF, affording the corresponding β-formyl-functionalized amino acid derivative in high yield and stereoselectivity. The proline-catalyzed direct asymmetric Mannich-type reaction with other aldehydes as nucleophiles proceeds with excellent chemo-, diastereo-, and enantioselectivity (eq 16).



The diastereoselectivity of the Mannich reaction increases with enhanced chain length of the donor, and for aldehydes with more than six carbon atoms, the two stereocenters are formed with almost absolute stereocontrol. The reaction is readily performed on a multigram scale, and only 2 equiv of aldehyde and 10 mol % of catalyst were used. Mannich-type additions with unmodified aldehydes add a new dimension to the direct asymmetric Mannich reaction, since the aldehyde moiety allows further chemical manipulations and linkage to tandem reactions. For example, the β-formyl amino acid derivatives can be converted to aspartic acid derivatives and β-lactams in three steps (Scheme 11).

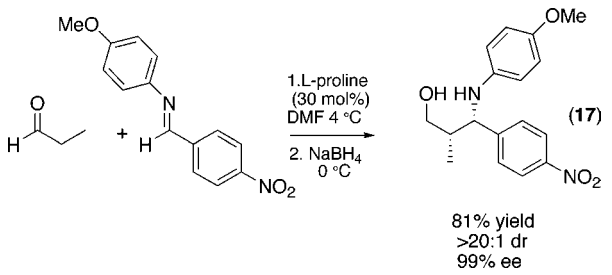
Scheme 11. Asymmetric Synthesis of β-Amino Acid and β-Lactam Derivatives[a]



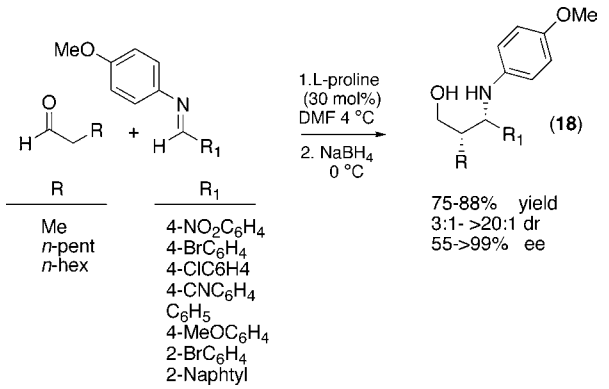
[a] Reagents: (i) $NaOCl_2$, KH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O; (ii) CH_2N_2, Et_2O; (iii) LHMDS, THF.

NOESY experiments on the isovaleraldehyde-derived lactam revealed that L-proline catalyzes the creation of L-amino acid derivatives with *syn* relative configuration. In addition, the proline-catalyzed direct asymmetric Mannich-type reaction has been connected to one-pot tandem cyanation and allylation reactions in THF and aqueous media, affording functional α-amino acid derivatives (Scheme 12).[38,39]

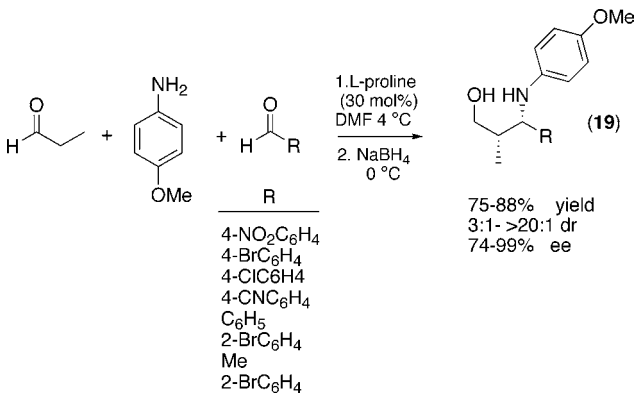
L-Proline is not able to catalyze the addition of aldehydes to aromatic imines under set stir-and-mix reaction conditions. However, addition of propionaldehyde with a syringe pump to a vial containing *N*-PMP-protected 4-nitrobenzaldimine and a catalytic amount of L-proline in DMF at 4 °C provides the desired Mannich adduct that is reduced in situ with excess $NaBH_4$ (eq 17).[40,41] The corresponding γ-amino alcohol adduct is isolated in 81% yield, >20:1 dr, and 99% ee.



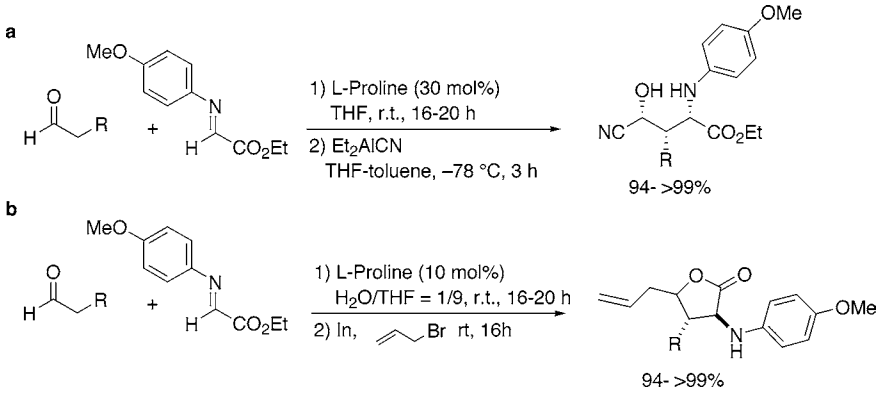
The direct catalytic asymmetric Mannich-type reactions with aldehydes and aromatic imines furnish γ-amino alcohol derivatives in high yield with 54 → 99% ee (eq 18).



The reaction can be considered as a regiospecific asymmetric synthesis of 3-amino 1-alcohols. The direct asymmetric synthesis of γ-amino alcohols can also be performed as a one-pot, three-component cross-Mannich reaction, starting with two unmodified aldehydes and *p*-anisidine (eq 19).[40]

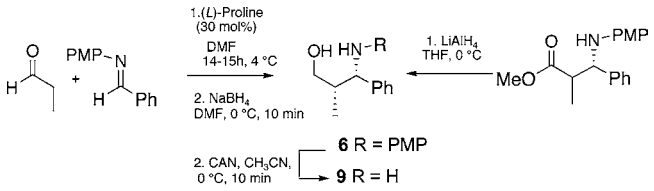


Scheme 12. (a) One-Pot Tandem Direct Asymmetric Mannich Cyanation and (b) Mannich Allylation Reactions



The corresponding β-amino aldehydes are reduced in situ, and the corresponding amino alcohols are isolated in good yield with high enantioselectivity. The Mannich reactions proceed with excellent chemoselectivity, and imine formation occurs with the acceptor aldehyde at a faster rate than C−C bond formation. Furthermore, the cross one-pot, three-component direct asymmetric Mannich reaction allows for aliphatic aldehydes to serve as acceptors. The absolute stereochemistry of the reaction was determined by synthesis and revealed that L-proline provides *syn*-β-amino aldehydes with *S* stereochemistry of the amino group (Scheme 13).

Scheme 13. Deprotection and Confirmation of the Absolute Stereochemistry by Synthesis



The mechanism of the proline-catalyzed Mannich reactions is depicted in Scheme 14. Accordingly, the ketone or aldehyde donor reacts with proline to give an enamine. Next, the preformed or in situ-generated imine reacts with the enamine to give, after hydrolysis, the enantiomerically enriched Mannich adduct, and the catalytic cycle can be repeated.

The stereochemical outcome of the L-proline-catalyzed direct asymmetric Mannich reactions is explained by an *si*-facial attack on the imine that has a trans configuration by the *si* face of the enamine, which also has a trans configuration (Figure 7). The six-membered transition

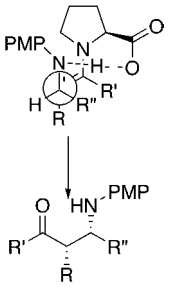
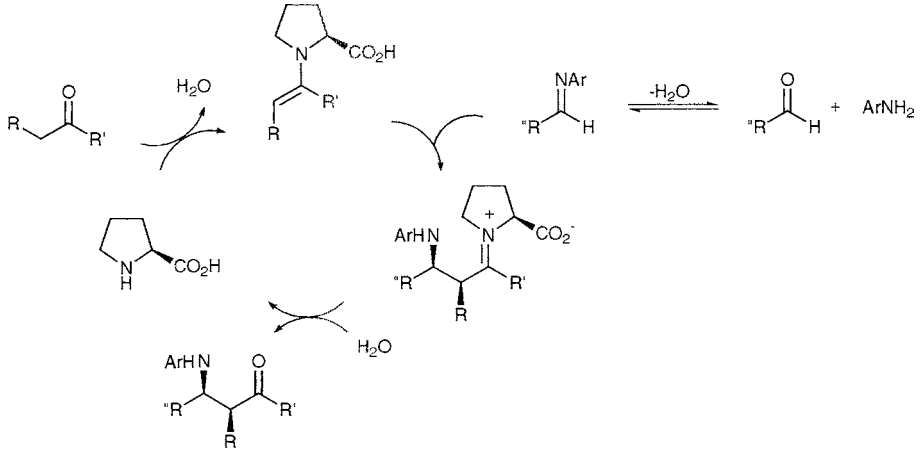


FIGURE 7. Transition state of the proline-catalyzed direct asymmetric Mannich reaction.

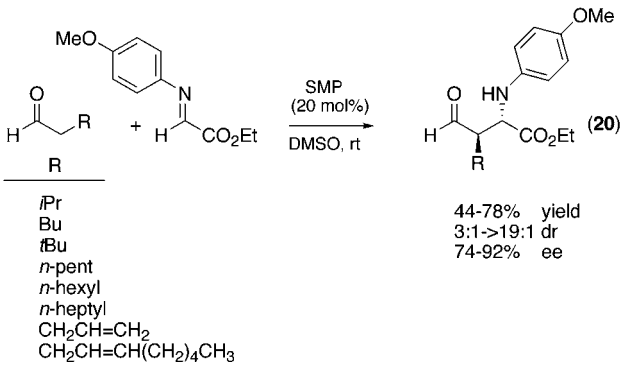
state is stabilized by hydrogen-bonding between the nitrogen of the imine and the carboxylic group of proline. A switch of the facial selectivity is disfavored due to steric repulsion between the PMP group of the imine and the pyrrolidine moiety of the enamine. This is opposite to the similar direct asymmetric aldol reaction, where an *re*-facial attack occurs.[28,31,35]

Scheme 14. Mechanism of the Proline-Catalyzed Direct Asymmetric Mannich Reactions[a]



[a] R′ = Me, alkyl, H or CH_2F; R = OH, OR, alkyl.

On the basis of previous reports of *anti*-selective Mannich-type reactions with preformed chiral enamines or imines,[4d,e,47] we theorized that it would be possible for a chiral amine to catalyze a similar *anti*-selective direct asymmetric Mannich transformation.[4,42] A screen of chiral amines of the reaction between unmodified aldehydes and *N*-PMP-protected α-ethyl glyoxylate revealed that ether- and ester-functionalized proline-derived secondary amines are able to mediate the transformation, albeit in lower yields than proline.[43] The premium catalyst (*S*)-2-methoxymethylpyrrolidine (SMP) is able to catalyze the direct asymmetric Mannich reaction with high *anti* selectivity, affording α-amino acid derivatives in moderate yield with 74−92% ee (eq 20).



Synthesis and NMR analysis confirmed that L-amino acid derivatives with *anti* relative configuration are obtained by SMP catalysis. Hence, the *re* face of the imine is attacked from the *si* face of the enamine, in contrast to the *si* facial attack of enamines derived form L-proline (Figure 8).

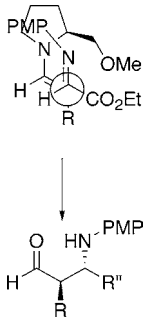


FIGURE 8. Transition state of the SMP-catalyzed direct asymmetric Mannich reaction.

In this case, Coulombic interactions between the pyrrolidine ring and the aromatic moiety of the imine stabilize the transition state, favoring the *re*-facial attack. An *si*-facial attack of the imine is less favorable due to the lack of hydrogen-bonding.

Conclusion

This Account focuses on recent advances in small-molecule-catalyzed direct catalytic asymmetric Mannich reactions. Mannich reactions with dinuclear Zn complexes that incorporate a center acting as a Lewis acid, together with a metal moiety that acts as a Brønstedt base, are described. This cooperative mode of action enables the use of unmodified donors for stereoselective Mannich-type reactions. Another important class of catalysts that mediate the direct asymmetric Mannich reaction are chiral copper(II) bisoxazoline complexes. Chiral cyclic five-membered secondary amines, particularly proline, are able to catalyze the direct asymmetric Mannich reaction without the use of metals via an enamine mechanism. In fact, enamine catalysis enables unmodified aldehydes to be used as nucleophiles, adding a new chemical diversification point to the asymmetric Mannich reaction. The enantioselectivity of these small-molecule-catalyzed C−C bond-forming reactions can approach and even sometimes match the stereoselectivity of natural enzymes. The different small-molecule catalysts described here are complementary in their applications. They also complement each other in *syn* or *anti* selectivity of the direct asymmetric Mannich reaction. The direct catalytic Mannich reactions are new highly stereoselective and economic entries for the synthesis of chiral synthons and amino acid derivatives.

A.C. thanks the Swedish Natural Science Research Council for financial support.

References

(1) (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999. (b) Noyori, R. *Asymmetric Catalysis in Asymmetric in Organic Synthesis*; John Wiley & Sons: New York, 1994. (c) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*, 2nd ed; Wiley-VCH: New York, 2000.

(2) The first example of the application of the Mannich reaction to natural product synthesis is attributed to Robinson in his synthesis of tropinone: Robinson, R. Synthesis of Tropinone. *J. Chem. Soc.* **1917**, 762−768.

(3) For excellent reviews, see: (a) Kleinmann, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 4.1. (b) Arend, M.; Westerman, B.; Risch, N. Modern Variants of the Mannich Reaction. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044−1070. (c) Kobayashi, S.; Ishitani, H. Catalytic Enantioselective Addition to Imines. *Chem. Rev.* **1999**, *99*, 1069−1094. (d) Denmark, S.; Nicaise, O. J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamomoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, p 93. (e) For examples, see: *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; VCH: Weinheim, 1997.

(4) (a) Seebach, D.; Hoffmann, M. Preparation and Use of a New Chiral Glycine Derivative, (*R*)- and (*S*)-tert-Butyl 2-tert-butyl-4-methoxy-2,5-dihydroimidazole-1-carboxylate (BDI), in Amino Acid Synthesis. *Eur. J. Org. Chem.* **1998**, 1337−1351. (b) Aoyagi, Y.; Jain, R. P.; Williams, R. M. Stereocontrolled Asymmetric Synthesis of α-Hydroxy-β-Amino Acids, a Stereodivergent Approach. *J. Am. Chem. Soc.* **2001**, *123*, 3472−3477 and references therein. (c) Schöllkopf, U. In *Topics in Current Chemistry*; Boschke, F. L., Ed.; Springer-Verlag: Berlin, 1983; Vol. 109, pp 45−85. (d) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. New Procedure for the Direct Generation of Titanium Enolates. Diastereoselective Bond Construction with Representative Electrophiles. *J. Am. Chem. Soc.* **1990**, *112*, 8215−8216. (e) Kober, R.; Papadopoulos, K.; Miltz, W.; Enders, D.; Steglich, W.; Reuter, H.; Puff, H. Synthesis of Diastereo- and Enantiomerically Pure α-Amino-γ-Acid Esters by Reaction of Acyl Imino-Acetates with Enamines Derived from 6-Membered Ketones. *Tetrahedron* **1985**, *42*, 1693−1701. (f) Palomo, C.; Oiarbide, M.; Landa, A.; Gonzales-Rego, M. C.; Garcia, J. M.; Gonzales, A.; Odriozola, J. M.; Martin-Pastor, M.; Linden, A. Design and Synthesis of a Novel Class of Sugar-Peptide Hybrids: C-linked Glyco-β-Amino Acids through a Stereoselective "Acetate" Mannich Reaction as the Key Element. *J. Am. Chem. Soc.* **2002**, *124*, 8637−8643 and references therein.

(5) (a) Ishitani, H.; Ueno, M.; Kobayashi, S. Catalytic Enantioselective Mannich-type Reactions using a Novel Chiral Zirconium Catalyst. *J. Am. Chem. Soc.* **1997**, *119*, 7153−7154. (b) Kobayashi, S.; Hamada, T.; Manabe, K. The Catalytic Asymmetric Mannich-type Reaction in Aqueous Media. *J. Am. Chem. Soc.* **2002**, *124*, 5640−5641. (c) Ishitani, H.; Ueno, S.; Kobayashi, S. Enantioselective Mannich-type Reactions using a Novel chiral Zirconium Catalyst for the Synthesis of Optically β-Amino Acid Derivatives. *J. Am. Chem. Soc.* **2000**, *122*, 8180−8186.

(6) (a) Hagiwara, E.; Fujii, A.; Sodeoka, M. Enantioselective Addition of Enol Silyl Ethers to Imines Catalyzed by Palladium Complexes: A Novel Way to Optically Active Acylalanine Derivatives. *J. Am Chem. Soc.* **1998**, *120*, 2474−2475. (b) Fujii, A.; Hagiwara, E.; Sodeoka, M. Mechanism of Palladium Complex-Catalyzed Enantioselective Mannich-Type Reaction: Characterization of A Novel Binuclear Palladium Enolate Complex. *J. Am Chem. Soc.* **1999**, *121*, 545−556.

(7) (a) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. A Novel Synthesis of α-Amino Acid Derivatives through Catalytic, Enantioselective Ene-Reactions of α-Imino Esters. *J. Am. Chem. Soc.* **1998**, *120*, 4548−4549. (b) Ferraris D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J., III; Ryzhkov, L.; Taggi, T.; Lectka, T. Catalytic, Enantioselective Alkylation of α-Imino Esters: The Synthesis of Nonnatural α-Amino Acid Derivatives. *J. Am Chem. Soc.* **2002**, *124*, 67−77 and references therein.

(8) Wenzel, A G.; Jacobsen, E. N. Asymmetric Catalytic Mannich Reactions Catalyzed by Urea Derivatives: Enantioselective Synthesis of β-Aryl-β-Amino Acids. *J. Am Chem. Soc.* **2002**, *124*, 12964−12965.

(9) Trost, B. M. The Atom Economy: A Search for Synthetic Efficiency. *Science* **1991**, *254*, 1471−1477.

(10) For a new catalytic asymmetric Mannich-type reaction, see: Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. Catalytic Asymmetric Mannich Reactions of Glycine Derivatives with Imines. A New Approach to Optically Active α,β-Diamino Acid Derivatives. *J. Org. Chem.* **2003**, *69*, 2583−2591.

(11) See: Shibasaki, M.; Sasai, H.; Arai, T. Direct Catalytic Asymmetric Aldol reactions of Aldehydes with Unmodified Ketones. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871−1873 and references therein.

(12) (a) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. Direct Catalytic Asymmetric Aldol Reaction. *J. Am. Chem. Soc.* **1999**, *121*, 4168−4178. (b) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. Direct Catalytic Asymmetric Aldol Reaction: Synthesis of Either *syn*- or *anti*-α,β-Dihydroxy Ketones. *J. Am. Chem. Soc.* **2001**, *123*, 2466−2467. (c) Sawada, D.; Shibasaki, M. Enantioselective Total Synthesis of Epothilone A using Multifunctional Asymmetric Catalyses. *Angew. Chem., Int. Ed.* **2000**, *39*, 209−213.

(13) Yamasaki, S.; Iida, T.; Shibasaki, M. Direct Catalytic Asymmetric Mannich Reaction of Unmodified Ketones: Cooperative Catalysis of an AlLibis(binaphthoxide) Complex and La(OTf)$_3$·nH2O. *Tetrahedron Lett.* **1999**, *40*, 307−310.

(14) Matsunaga, S.; Kumagai, N.; Harada, N.; Harada, S.; Shibasaki, M. anti-Selective Direct Catalytic Asymmetric Mannich-type Reaction of Hydroxyketone Providing β-Amino Alcohols. *J. Am. Chem. Soc.* **2003**, *125*, 4712−4713.

(15) (a) Matsunaga, S.; Das, J.; Roels, J.; Vogel, E. M.; Yamomoto, N.; Iida, T. Yamaguchi, K.; Shibasaki, M. Stable, Storable, and Reusable Asymmetric Catalyst: A Novel La-linked-BINOL Complex for the Catalytic Asymmetric Michael Reaction. *J. Am. Chem. Soc.* **2000**, *122*, 6506−6507. (b) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K. Shibasaki, M. Direct Catalytic Asymmetric Aldol Reaction of Hydroxyketones: Asymmetric Zn Catalysis with a Et$_2$Zn/Linked-BINOL Complex. *J. Am. Chem. Soc.* **2003**, *125*, 2169−2178 and references therein. (c) Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. Direct Catalytic Asymmetric Michael Reaction of Hydroxyketones: Asymmetric Zn Catalysis with a Et$_2$-Zn/Linked-BINOL Complex. *J. Am. Chem. Soc.* **2003**, *125*, 2582−2590 and references therein.

(16) (a) Trost, B. M.; Ito, H. A Direct Catalytic Enantioselective Aldol Reaction via a Novel Catalyst Design. *J. Am. Chem. Soc.* **2000**, *122*, 12003−12004. (b) Trost, B. M.; Ito, H.; Silcoff, E. Asymmetric Aldol Reaction via a Dinuclear Zinc Catalyst: α-Hydroxy Ketones as Donors. *J. Am. Chem. Soc.* **2001**, *123*, 3367−3368. (c) Trost, B. M.; Silcoff, E.; Ito, H. Direct Asymmetric Aldol Reactions of Acetone using Bimetallic Zinc Catalysts. *Org. Lett.* **2001**, *3*, 2497−2500.

(17) Trost, B. M.; Terrell, L. M. A Direct Catalytic Asymmetric Mannich-type Reaction to *syn*-Amino Alcohols. *J. Am. Chem. Soc.* **2003**, *125*, 338−339.

(18) (a) Andersson, M. A.; Epple, R.; Fokin, V. V.; Sharpless, K. B. "Second-Cycle"-Ligands: The Next Generation for Amino- and Dihydroxylation. *Angew. Chem., Int. Ed.* **2002**, *41*, 472−475 and references therein. (b) Li, G.; Chang, H.-T.; Sharpless, K. B. Catalytic Asymmetric Aminohydroxylation (AA) of Olefins. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451−454.

(19) (a) Juhl, K.; Gathergood, N.; Jørgensen, K. A. Catalytic Asymmetric Homo-Aldol Reaction of Pyruvate—a Chiral Lewis Acid Catalyst that Mimics Aldolase Enzymes. *Chem. Commun.* **2000**, 2211−2212. (b) Juhl, K.; Jørgensen, K. A. Catalytic Asymmetric Direct α-Amination Reactions of 2-Keto Esters: A Simple Synthetic Approach to Optically Active *syn*-β-Amino-α-hydroxy Esters. *J. Am. Chem. Soc.* **2002**, *124*, 2420−2421.

(20) Juhl, K.; Gathergood, N.; Jørgensen, K. A. Catalytic Asymmetric Direct Mannich Reactions of Carbonyl Compounds with α-Imino Esters. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995−2997.

(21) For reviews of C_2-bisoxazoline−Lewis acid complexes, see: (a) Johnson, J. S.; Evans, D. A. Chiral Bis(oxazoline) Copper(II) Complexes: Versatile Catalysts for Enantioselective Cycloaddition, Aldol, Michael, and Carbonyl Ene Reactions. *Acc. Chem. Res.* **2000**, *33*, 325−335. (b) Jørgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. Catalytic Asymmetric Addition Reactions of Carbonyls. A Common Catalytic Approach. *Acc. Chem. Res.* **1999**, *32*, 605−613.

(22) Marigo, M.; Kjaersgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. Direct Catalytic Asymmetric Mannich Reactions of Malonates and β-Keto Esters. *Chem.−Eur. J.* **2003**, *9*, 2359−2367.

(23) (a) Corey, E. J.; Guzman-Perez, A. The Catalytic Enantioselective Construction of Molecules with Quaternary Carbon Stereocenters. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (b) Christoffers, J.; Mann, A. Enantioselective Construction of Quaternary Stereocenters. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597.

(24) (a) Dalko, P. I.; Moisan, L. Enantioselective Organocatalysis. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726−3748. (b) List, B. Proline-Catalyzed Asymmetric Reactions. *Tetrahedron* **2002**, *58*, 5573−5590. (c) Gröger, J.; Wilken, J. The Application of L-Proline as an Enzyme Mimic and Further New Asymmetric Synthesis using Small Organic Molecules as Chiral Catalysts. *Angew. Chem., Int. Ed.* **2001**, *40*, 529−532. (d) Jarvo, E. R.; Miller, S. J. Amino Acids and Peptides as Asymmetric Organocatalysts. *Tetrahedron* **2002**, *58*, 2481−2495. (e) Duthaler, R. O. Proline-Catalyzed Asymmetric α-Amination of Aldehydes and Ketones-An Astonishingly Simple Access to Optically Active α-Hydrazino Carbonyl Compounds. *Angew. Chem., Int. Ed.* **2003**, *42*, 975−978.

(25) (a) Hajos, Z. G.; Parrish, D. R. Asymmetric Synthesis of Optically Active Polycyclic Organic Compounds. German Patent DE 2102623, Jul 29, 1971. (b) Hajos, Z. G.; Parrish, D. R. Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry. *J. Org. Chem.* **1974**, *39*, 1615−1621. (c) Eder, U.; Sauer, G.; Wiechert, R. Optically Active 1,5-Indanone and 1,6-Naphthalenedionene. German Patent DE 2014757, Oct 7, 1971. (d) Eder, U.; Sauer, G.; Wiechert, R. Total synthesis of optically active steroids. 6. New Type of Asymmetric Cyclization to Optically Active Steroid CD Partial Structures. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496−497. (e) Agami, C. Mechanism of the Proline-Catalyzed Enantioselective Aldol Reaction. Recent advances. *Bull. Soc. Chim. Fr.* **1988**, 499−507.

(26) For example, for the total synthesis of Taxol, see: Danishefsky, S. J.; et al. Total Synthesis of Taxol and Analogs. *J. Am. Chem. Soc.* **1996**, *118*, 2843−2859.

(27) (a) List B. The Direct Catalytic Asymmetric Three-Component Mannich Reaction. *J. Am. Chem. Soc.* **2000**, *122*, 9336−9337. (b) List B.; Porjalev, P.; Biller, W. T.; Martin, H. J. The Proline-Catalyzed Direct Asymmetric Three-Component Mannich Reaction: Scope, Optimization, and Application to the Highly Enantioselective Synthesis of 1,2-Amino Alcohols. *J. Am. Chem. Soc.* **2002**, *124*, 827−833.

(28) (a) List, B.; Lerner, R. A.; Barbas, C. F., III. Proline-Catalyzed Direct Asymmetric Aldol Reactions. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396. (b) Notz, W.; List, B. Catalytic Asymmetric Synthesis of anti-1,2-Diols. *J. Am. Chem. Soc.* **2000**, *122*, 7386−7387.

(29) Manabe, K.; Kobayashi, S. Mannich-Type Reactions of Aldehydes, Amines, and Ketones in a Colloidal Dispersion System Created by a Brønsted Acid-Surfactant-Combined Catalyst in Water. *Org. Lett.* **1999**, *1*, 1965−1967 and references therein.

(30) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III. Amine-Catalyzed Direct Asymmetric Mannich-type Reactions. *Tetrahedron Lett.* **2001**, *42*, 199−201.

(31) Saktihvel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. Amino Acid-Catalyzed Direct Asymmetric Aldol Reactions: A Bioorganic Approach to Catalytic Asymmetric Carbon−Carbon Bond-Forming Reactions. *J. Am. Chem. Soc.* **2001**, *123*, 5260−5267.

(32) Bui, T.; Barbas, C. F., III. A Proline-Catalyzed Asymmetric Robinson Annulation Reaction. *Tetrahedron Lett.* **2000**, *41*, 6951−6954.
(33) (a) Taggi, A. E.; Hafez, A. M.; Lectka, T. α-Imino Esters: Versatile Substrates for the Catalytic, Asymmetric Synthesis of α- and β-Amino Acids and β-Lactams. *Acc. Chem. Res.* **2002**, *36*, 10−19. (b) Yao, S.; Johannsen, M.; Hazell, R. G.; Jørgensen, K. A. Catalytic Enantioselective Aza Diels−Alder Reactions of Imino Dienophiles. *Angew. Chem., Int. Ed.* **1998**, *37*, 3121−3124.
(34) Córdova, A.; Notz. W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. A Highly Enantioselective Amino Acid-Catalyzed Route to Functionalized α-Amino Acids. *J. Am. Chem. Soc.* **2002**, *124*, 1844−1845.
(35) Córdova, A.; Notz, W.; Barbas, C. F., III. Proline-Catalyzed One-Step Asymmetric Synthesis of 5-Hydroxy-(2*E*)-hexenal from Acetaldehyde. *J. Org. Chem.* **2002**, *67*, 301−303. See also later important reports: (a) Bøgevig, A.; Kumaragurubaran, N.; Jørgensen, K. A. Direct Catalytic Asymmetric Aldol Reactions of Aldehydes. *Chem. Commun.* **2002**, 620−621. (b) Northrup, A. B.; MacMillan, D. W. C. The First Direct and Enantioselective Cross-Aldol Reaction of Aldehydes *J. Am. Chem. Soc.* **2002**, *124*, 6798−6799. (c) Chowdari, N. S.; Ramachary, D. B.; Córdova, A.; Barbas, C. F., III. Proline-Catalyzed Asymmetric Assembly Reactions: Enzyme-like Assembly of Carbohydrates and Polyketides from Three aldehyde Substrates. *Tetrahedron Lett.* **2002**, *43*, 9591−9595. (d) Córdova, A.; Notz, W.; Barbas, C. F., III. Direct Organocatalytic Aldol Reactions in Buffered Aqueous Media. *Chem. Commun.* **2002**, *67*, 3024−3025. (e) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. Direct Organo-Catalytic Asymmetric α-Amination of Aldehydes—A Simple Approach to Optically Active α-amino Aldehydes, α-Amino Alcohols, and α-Amino Acids. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790−1793. (f) List, B. Direct Catalytic α-Amination of Aldehydes. *J. Am. Chem. Soc.* **2002**, *124*, 5656−5657. (g) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. Direct L-proline Catalyzed Asymmetric α-Amination of Ketones. *J. Am. Chem. Soc.* **2002**, *124*, 6254−6255.
(36) Machajewski, T. D.; Wong, C.-H. The Catalytic Asymmetric Aldol Reaction. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352−1374 and references therein.
(37) Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III. A Highly Enantioselective Route to Either Enantiomer of Both α- and β-Amino Acid Derivatives. *J. Am. Chem. Soc.* **2002**, *124*, 1866−1867.
(38) Watanabe, S.-i.; Córdova, A.; Tanaka, F.; Barbas, C. F., III. One-Pot Asymmetric Synthesis of β-Cyanohydroxymethyl α-Amino Acid Derivatives: Formation of Three Contiguous Stereogenic Centers. *Org. lett.* **2002**, *4*, 4519−4522.
(39) Córdova, A.; Barbas, C. F., III. Direct Organocatalytic Asymmetric Mannich-type Reactions in Aqueous Media: One-Pot Mannich-Allylation Reactions. *Tetrahedron Lett.* **2003**, *44*, 1923−1926.
(40) (a) Córdova, A. Amine-Catalyzed Direct Asymmetric Mannich-type Reactions: Enanioselective Synthesis of Amino acid and Amino Alcohol Derivatives. Presented at the 225th ACS National Meeting, New Orleans, LA, Spring 2003. (b) Córdova, A. One-Pot Direct Organocatalytic Asymmetric Synthesis of γ-Amino Alcohol Derivatives. *Synlett* **2003**. 1651−1654. (c) Córdova, A. The Direct Catalytic Asymmetric Cross-Mannich reaction: A Highly Enantioselective Route to 3-Amino Alcohols and α-Amino Acid Derivatives. Manuscript submitted.
(41) The Mannich adducts are reduced to the more stabile β-amino alcohols prior to isolation and ee determination due to their lower risk of decomposition, epimerization, and racemization.
(42) Vinkovic, V.; Sunjic, V. A Highly Stereocontrolled Synthesis of (S)-(−)-3-(4-tert-Butyl)phenyl-1-*N*-(cis-2,6-dimethyl)morpholinyl-2-methylpropane via Asymmetric Mannich Reaction. *Tetrahedron* **1997**, *53*, 689−696.
(43) Córdova, A.; Barbas, C. F., III. *Anti*-Selective SMP-Catalyzed Direct Asymmetric Mannich-type Reactions: Synthesis of Functionalized Amino Acid Derivatives. *Tetrahedron Lett.* **2002**, *43*, 7749−7752.

AR030231L