DOI: 10.1002/ejoc.200700409

Organocatalytic Asymmetric Mannich Reactions: New Methodology, Catalyst Design, and Synthetic Applications

Amal Ting[a] and Scott E. Schaus*[a]

Keywords: Organocatalysis / Enantioselective synthesis / Asymmetric catalysis / Mannich reaction / Imines

The direct, asymmetric Mannich reaction catalyzed by small organic molecules offers a facile route to optically active α- or β-amino acid derivatives and 1,2- and γ-amino alcohols. One-pot reactions of unmodified carbonyl donors with preformed or in situ generated imines can be stereochemically controlled with Organic catalysts such as proline, chiral pyrrolidines, chiral Brønsted acids, and *Cinchona* alkaloids. The generated Mannich adducts can be further functionalized towards a variety of bioactive molecules. In this Microreview, recent contributions are discussed to present the methodology and synthetic advantages achieved so far in the asymmetric Mannich reaction.

1. Introduction

The use of small organic molecules as catalysts has become a powerful strategy in the construction of chiral building blocks for synthesis. The developments in this area have had a profound effect on the Mannich reaction with the use of proline, chiral pyrrolidines, and *Cinchona* alkaloid-derived catalysts being significant contributing areas of research and development.

The Mannich reaction is a useful transformation to access amine-containing building blocks.[1] In the classical Mannich reaction,[2] the Mannich bases afforded from the reaction have been key synthetic intermediates in the synthesis of diverse alkaloids.[3] Similar Mannich adducts have found multiple uses in product synthesis. Both metal-based and metal-free asymmetric catalysis has contributed to the development of asymmetric Mannich reactions. Initially, the development of metal-catalyzed asymmetric Mannich reactions afforded valuable chiral intermediates for synthesis.[4] Complimentary metal-free organocatalytic methods have been developed to supplement the pool of available building blocks; suggestive of a biomimetic approach towards the bond construction.[5] Alkaloid synthesis has particularly been influenced by biomimetic approaches and illustrates the utility of the asymmetric Mannich reaction. For example, the alkaloid (+)-geissoschizine proved to be a

[a] Department of Chemistry, Boston University, Life Science and Engineering Building,
24 Cummington Street, Boston, MA 02215, U. S. A.
Fax: +1-617-353-6466
E-mail: seschaus@bu.edu

Amal Ting earned her B.S. degree in Biology from Univeristy of Chicago in 2000. Between 2000 and 2004, she worked as a clinical research associate with hospitals and pharmaceuticals at Theseus Imaging Corp., North American Scientific. Amal is currently pursuing her Ph.D. in organic chemistry under the direction of Prof. Scott E. Schaus, at Boston University's Department of Chemistry. Her research interests include the new methodology development of asymmetric catalysis.

Scott E. Schaus studied chemistry at Boston University, Boston, Massachusetts where he completed his undergraduate degree in 1995. He received his Ph.D. in organic chemistry from Harvard University in 1999 under the direction of Professor Eric N. Jacobsen. His graduate work focused on the development of chiral salen transition metal catalysts and reactions for use in synthesis. He carried out his postdoctoral research as an NIH Postdoctoral Fellow in Professor Andrew G. Myers's laboratories studying the use of genomic technologies to facilitate drug target identification. In 2001 he joined the Department of Chemistry at Boston University as an Assistant Professor and, in 2002, he became one of the co-principal investigators of the Center for Chemical Methodology and Library Development at Boston University. His research interests include the development of asymmetric catalytic reactions for synthesis, new methodologies for library synthesis, and drug target identification and validation.

key precursor in the total synthesis of of (+)-*N*-methylvellosimine.[6] A notable step in the synthesis involves a biomimetically inspired intramolecular asymmetric Mannich reaction. The stereochemistry of a corynantheane intermediate common to both (+)-geissoschizine and (+)-*N*-methylvellosimine was also established by an alternative Mannich route. Biomimetic synthesis continues to inspire the development of methods and advances in organic catalysis in many respects embodies that inspiration.

The recent advances made in the development of organocatalytic asymmetric Mannich reactions demonstrate novel approaches to methodology, catalyst design, and synthetic accomplishments. These advances, new catalysts, and notable contributions to the area, including aza-variants like the nitro-Mannich (aza-Henry) reaction, are highlighted in this Microreview.

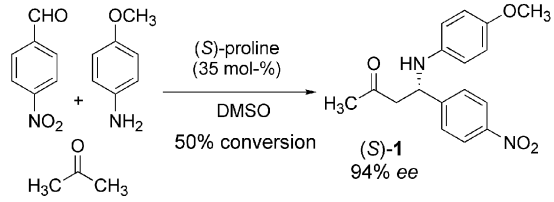
2. One-Pot Three-Component Mannich Reaktion

2.1 One-Pot Three-Component Mannich Reaction: Simple Ketones

Recent advances in Mannich-type reactions have been driven by the prevalence of nitrogen synthons in drugs and natural products as well as by the potential of this multicomponent reaction to generate diversity. Early catalytic methods have been introduced by groups directed by Kobayashi,[7] Sodeoka,[8] Lectka,[9] Trost,[10] Shibasaki,[11] and Jørgensen.[12] All of these variants use preformed imine and enol derivatives combined with a metal-based catalyst. Asymmetric organocatalysis of Mannich-type reactions was first realized in the Hajos–Parrish–Eder–Sauer–Wiechert reaction.[13] The basis of these reactions is the facile in situ generation of chiral enolate equivalents (enamines) from ketones and aldehydes using pyrrolidine-based catalysts.[14]

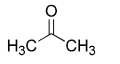
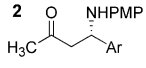
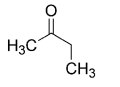
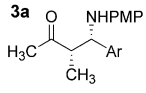
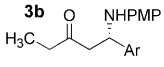
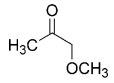
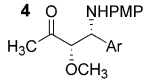
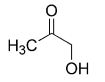
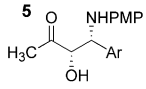
Building on earlier proline-catalyzed direct asymmetric intermolecular aldol reactions[15] and the report of Kobayashi's three-component Mannich reactions,[16] List examined chiral amines as catalysts for Mannich-type reactions. List found that after stirring proline (35 mol-%), *p*-nitrobenzaldehyde (1.0 equiv.), and *p*-anisidine (1.1 equiv.) in acetone/DMSO (1:4) for 12 h, the corresponding Mannich product was formed in 50% yield and 94% *ee* (Scheme 1).[17] This reaction constitutes the first organocatalytic asymmetric three-component Mannich reaction of a free aldehyde with an unmodified ketone and an amine. Aldol addition and condensation products were observed as side products in this reaction. The PMP (*p*-methoxyphenyl) amine protecting group was chosen because of its facile deprotection under oxidative conditions.[18] Proline as the catalyst is available in both enantiomeric forms and can be recovered from the reaction mixture via filtration.

Subsequent studies[19] with oxygenated ketones revealed that high regioselectivities generally favoring Mannich products result from the higher substituted α-side of the ketone (Table 1, products **4**, **5**). Excellent enantioselectivities yet modest yields were obtained in reactions of aromatic aldehydes; α-unbranched aldehydes were found to be efficient substrates. Various aniline derivatives were studied, including *p*-anisidine, *o*-anisidine, *p*-chloroaniline, and *o*-aminophenol. Yields and enantiomeric excess were optimal with *o*-anisidine; these results suggest the electronic properties of the aromatic moiety strongly affect on the stereoselectivity. The *syn*-diastereoselctivity and absolute configuration of the products were assigned on the basis of X-ray structural analysis of the Mannich products. These Mannich reactions can be considered a regiospecific alternative to the Sharpless asymmetric aminohydroxlyation reaction (AA).[20] An important utility of the enantiomerically enriched *syn*-1,2-amino alcohols would be their use in synthesis of α-amino acid derivatives.[21]



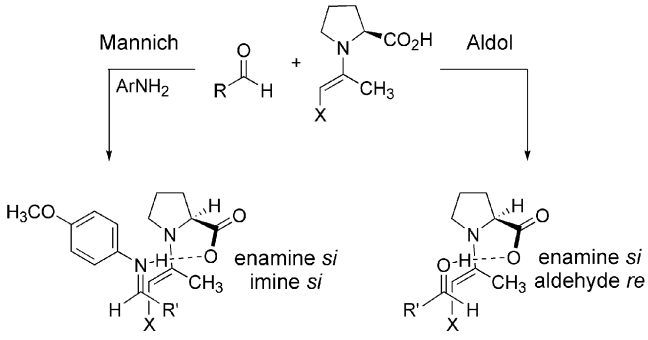
Scheme 1. Proline-catalyzed catalytic one-pot asymmetric three-component Mannich reaction.

Table 1. One-pot asymmetric three-component Mannich reactions with different ketones (PMP = *p*-methoxyphenyl, Ar = *p*-NO_2-C_6H_4).

Ketone	Product	Yield (%)	*de* (%)	*ee* (%)
	**2** 	50	-	94
	**3a** 	96 (**3**/**3b** = 2.5:1)	> 95	99
	3b 		-	94
	**4** 	93	> 95	98
	**5** 	92	> 95	> 99

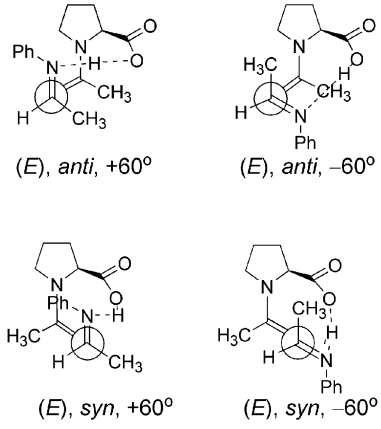
The difference in mechanisms between the proline-catalyzed aldol and Mannich reactions is the stereoselectivity (Scheme 2).[22] Aldols typically generate a *re*-enantiofacial attack on the aldehyde, whereas Mannich products are formed through a *si*-face attack on an imine. The additional factor that both enamine and imine may adopt (*E*)- or (*Z*)-configurations complicates the possible variants of transition states.[23] Although it is known that imines may undergo (*E*)/(*Z*) isomerization,[24] the (*Z*)-imines are present in only low equilibrium concentrations. Accordingly, in the Mannich reaction transition state, it is assumed that (*E*)

configurations are adopted by both proline-enamine and imine. The *si*-face of the imine is selectively attacked by the enamine to allow for protonation of its lone pair. Attack of the *re*-face would result in unfavorable steric interactions between the pyrrolidine and aromatic ring.



Scheme 2. Stereoselectivity of proline catalysis in aldol and Mannich reactions.

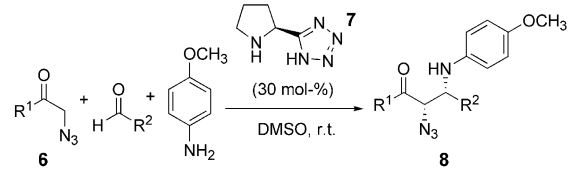
The first computational studies that present insight into the stereoselectivity of the proline-catalyzed direct Mannich reaction were presented by Houk using density functional theory (B3LYP/6-31G*).[22b] Transition-state geometries were optimized and characterized by frequency analysis to show the possible proline-enamine activation of (*E*)-imine and (*Z*)-imine (Scheme 3). In the transition states for the reaction of proline-enamine of acetone with *N*-phenyl imine of acetaldehyde, the lowest energy transition state involves an *anti*-enamine with the double bond away from the proline carboxylic acid. The corresponding *anti*-transition state with an (*Z*)-imine is calculated to be 1.6 kcal/mol higher in energy. When the enamine double bond is *syn* to the proline carboxylate, the energy for (*E*)- and (*Z*)-imine is 1.7 and 4.9 kcal/mol higher, respectively. Other transition states presented by Houk involved energies that were 2.0–5.7 kcal/mol higher. The percentage of predicted enantioselectivity excess that results from the transition state energy calculation is consistent with experimental results.



Scheme 3. Possible proline-enamine transition states.

Although oxygenated ketones were employed in organocatalytic Mannich reactions, use of amino ketones was not reported due to their instability. Barbas' group envisioned the use of azido ketones and protected amino ketones as surrogates for amino ketones (Tables 2, 3).[25] Direct, regiospecific, asymmetric synthesis of 1,2- and 1,4-diamines based on the Mannich reactions of imines with azido ketones **6** and with protected amino ketones **9** were presented by Barbas' group. Under optimized conditions, the (*S*)-proline-derived tetrazole **7** was investigated as the catalyst. Vicinal 1,2-diamine products **8** from azido ketones were obtained regiospecifically with good diastereoselectivity (*syn*:*anti* 70:30 to 91:9) and enantioselectivity (82–99% *ee*). In

Table 2. Protected 1,2-azido amines by three-component Mannich reaction.



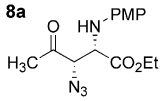
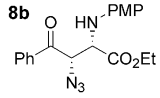
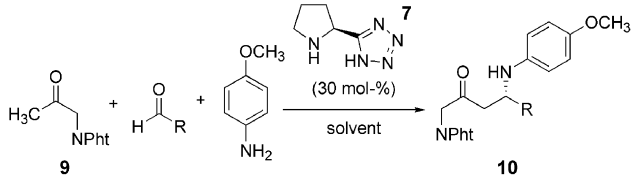
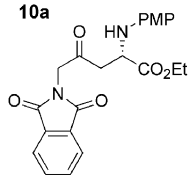
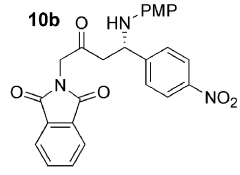
Product	Time (h)	Yield (%)	*dr* *syn/anti*	*ee* (%) (*syn/anti*)
8a 	0.5	96	91:9	99/99
8b 	40	87	88:12	99/64

Table 3. Protected 1,4-diamines by three-component Mannich reaction.



Product	Conditions	Yield (%)	*ee* (%)
10a 	DMSO, r.t., 16 h	85	64
	DMF, 4 °C, 40 h	83	90
	NMP, 4 °C, 60 h	88	91
	NMP, r.t., 48 h	95	83
10b 	DMSO, r.t., 45 h	53	57
	DMF, 4 °C, 72 h	41	93
	NMP, 4 °C, 84 h	68	97

contrast to the azido ketones **6**, the phthalimido-acetones **9** provided only the 1,4-diamine derivatives **10**.

This methodology demonstrated, for the first time, direct asymmetric Mannich reactions of imines with varied protected amino ketones to afford selective access to chiral 1,2- and 1,4-diamines with excellent yields and enantioselectivities.

2.2 One-Pot Three-Component Mannich: Cyclic Ketones

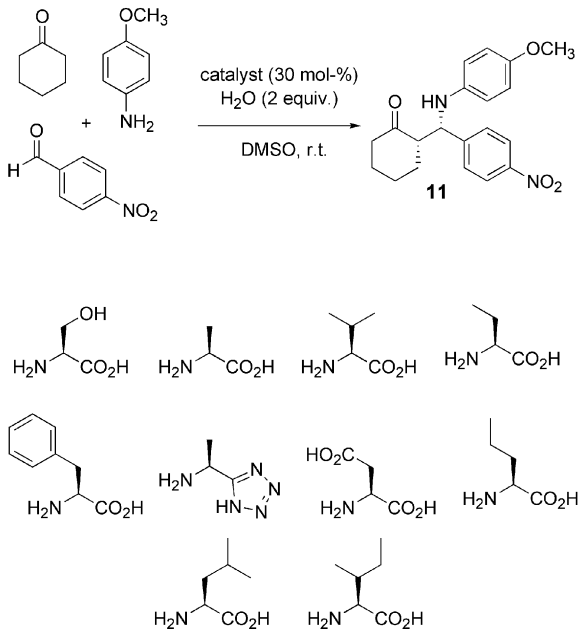
Enders et al.[26] reported a direct, organocatalytic synthesis of carbohydrates starting with a cyclic dihydroxyacetone equivalent, 2,2-dimethyl-1,3-dioxan-5-one. Various protected carbohydrates and amino sugars could be assembled in a one step proline-catalyzed aldol reaction. The group subsequently followed up with a Mannich variant of this reaction employing 2,2-dimethyl-1,3-dioxan-5-one, dimethoxyacetaldehyde, and *p*-anisidine.[27] With 30 mol-% loading of proline or proline derivative in aqueous DMF at 2 °C, the Mannich product was obtained in 91% yield and excellent stereoselectivities (> 99% *de*, and 98% *ee*).

Córdova disclosed the proline-catalyzed reaction between cyclohexanone, aqueous formaldehyde, and *p*-anisidine.[28] With 30 mol-% loading of proline in DMSO for 16 h, the *syn*-selective PMP-protected Mannich base was isolated in 94% yield and at least 99% *ee*. Different aliphatic linear ketones and cyclic ketones were studied and all provided modest to high yields with excellent enantioselectivities, typically at least 99%.

Whereas the enantioselectivities for the three-component reactions of List,[17,19] Barbas,[25] and Córdova[28] are impressive, two other factors of this catalysis are noteworthy: first the catalyst loading is generally high (≥10 mol-%), and second, the overall reaction time is long (typically 16 to 48 h). With the goal of improving upon these limitations, Bolm et al. began to investigate the potential of an optimized protocol using microwave irradiation.[29] The proline-catalyzed reaction between cyclohexanone, formaldehyde, and various anilines were thermally accelerated. With catalyst loadings as low as 0.5 mol-% of catalyst, Mannich products with up to 98% *ee* were obtained after a short period of time. To increase the yield of the reaction, either catalyst loading or reaction time had to be increased. Optimal conditions of the reaction gave 84% yield, 98% *ee* in 6 h, with 5 mol-% proline, at 75–77 °C and constant microwave (MW) irradiation at low power (10–15 W). Although no specific MW effect[30] has been found for this particular organocatalytic case, these results are synthetically promising.

2.3 One-Pot Three-Component Mannich Reaction: Non-Proline-Derived Catalysts

In the development of several stereoselective Mannich reactions catalyzed by amino acids, proline and proline derivatives have been utilized as highly stereoselective catalysts.[31] However, acylic amino acids were the first to be investigated by Córdova (Scheme 4).[32]



Scheme 4. One-pot three-component Mannich: aliphatic amine catalysts screen.

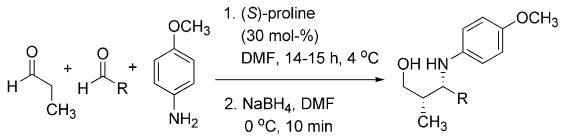
Using serine as the catalyst, cyclohexanone, *p*-nitrobenzaldehyde, *p*-anisidine, and aqueous DMSO, the corresponding Mannich product **11** was formed in 60% yield, 6:1 *dr* (*syn*:*anti*) and 94% *ee* after 48 h with only trace amounts of aldol products. The primary amine did not act as the amine component under reaction conditions. In comparison, proline catalyzed the formation in 50% yield, 2:1 *dr* and 84% *ee*. All amino acids that were tested catalyzed the reaction with excellent chemoselectivity. Simple aliphatic acyclic amino acids such as alanine, valine, serine, and isoleucine provided high chemo-, regio-, and enantioselectivity with yields up to 90%, 95:5 *dr*, and > 99% *ee*.

2.4 One-Pot Three-Component Mannich Reaction: Two Aldehydes and an Aniline

Córdova[33] developed the first organocatalytic asymmetric three-component Mannich reaction with unmodified aldehydes as donors (Table 4). On the basis of preliminary studies,[34] the role of the aldehyde components could be directed by adding the donor slowly to the reaction mixture. Hence, slow addition of propionaldehyde (1.0 M), to the reaction mixture containing *p*-methoxyaniline (0.1 M), *p*-nitrobenzaldehyde (0.1 M), and (*S*)-proline followed by in situ reduction with $NaBH_4$ afforded the γ-amino alcohol **14** in 75% yield and 95% *ee*. The amine component was versatile enough with various *p*-substituted anilines to give higher yields and *ee* than corresponding *m*-substituted anilines. The reaction presented excellent chemoselectivity with other aromatic aldehyde acceptors without any formation

of cross-aldol or self-Mannich adducts. Reactions with aliphatic acceptor aldehydes, however, only afforded trace amounts of the corresponding Mannich adducts.

Table 4. Proline-catalyzed one-pot three-component Mannich reaction with unmodified aldehdyes.



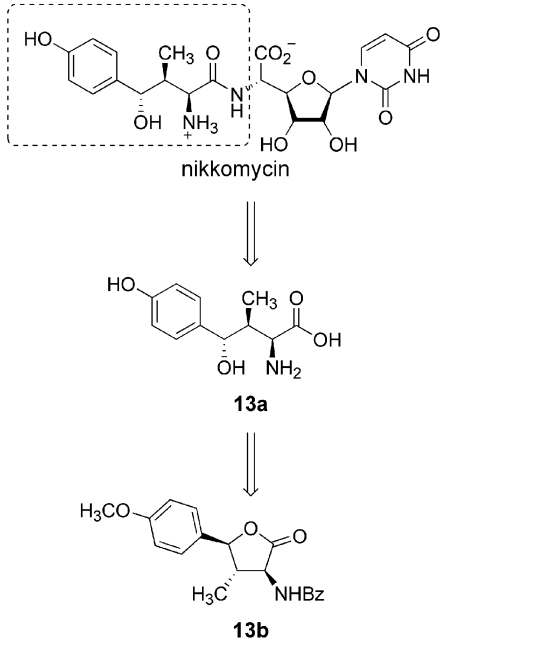
12

Entry	R	Yield (%)	*dr*	*ee* (%)
1	*p*-$NO_2C_6H_4$	75	> 10:1	99
2	*p*-CNC_6H_4	65	5:1	93
3	*p*-BrC_6H_4	81	10:1	91
4	*p*-ClC_6H_4	65	6:1	93
5	C_6H_5	62	4:1	75
6	*m*-BrC_6H_4	77	4:1	97
7	Et	55	>10:1	81

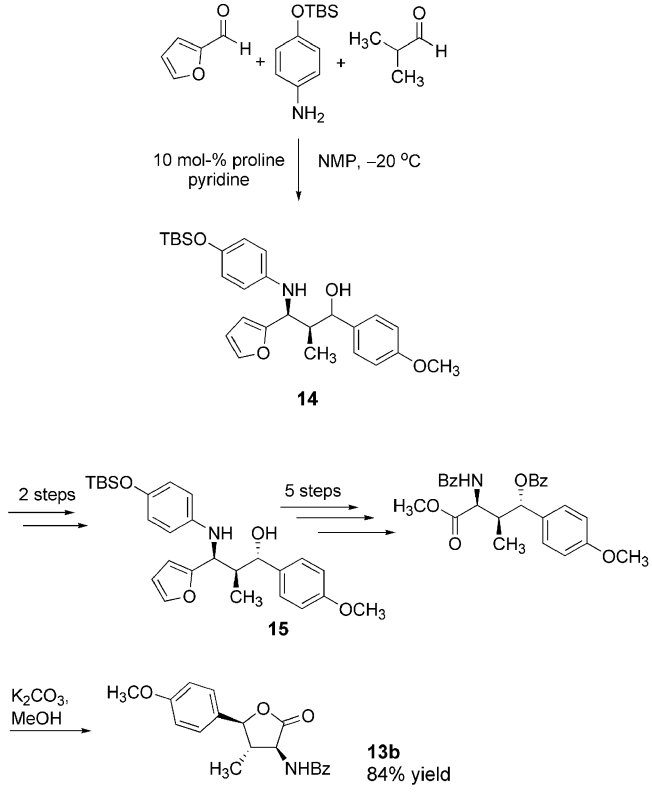
Right around the same time, Hayashi also developed similar protocols for the proline-catalyzed three-component Mannich reaction involving two different aldehydes.[34b] NMP was used as a solvent and heteroaromatic aldehydes were examined. Furfural and *p*-pyridinecarbaldehdye as Mannich acceptors were investigated with propanal to afford adducts in good yield with high *syn*-diastereo- and enantioselectivity.

2.5 One-Pot Three-Component Mannich Reaction: Application to Synthesis of Nikkomycins

Nikkomycins are nucleoside peptide antibiotics isolated from *Streptomyces tendae*.[35] Nikkomycins contain two structural units, the C-terminal nucleoside amino acid and the N-terminal amino acid **13a** that contains three contiguous stereocenters of an α-methyl β-amino secondary alcohol moiety (Scheme 5). The synthetic challenge of accessing the N-terminal amino acid has been accomplished by several groups.[36] In the formal total synthesis of nikkomycin, Hayashi's group[36c] synthesized the synthetic equivalent of the N-terminal amino acid moiety **13b** by the Mannich reaction of 2-furaldehyde, propanal, 4-(*tert*-butyl)dimethylsiloxysilane, and (*S*)-proline, with pyridine as an additive. The reaction proceeded with high selectivity (96% *ee*, vide infra) to afford a crude β-amino aldehyde that was immediately reduced to a β-amino alcohol (Scheme 6, **14**) for stability. After simple modifications that include oxidation and diastereoselective reduction, 1,2-*anti* amino alcohol **15** was generated in excellent yield and diastereoselectivity (98%, 1,2-*syn*/1,2-*anti* = 1:32). The remaining steps after setting the key three contiguous stereocenters involve only the oxidation of the furan to a carboxy group, followed by treatment of K_2CO_3 in methanol to afford the lactone **13b** in 84% yield.



Scheme 5. Retrosynthetic analysis of nikkomycin.



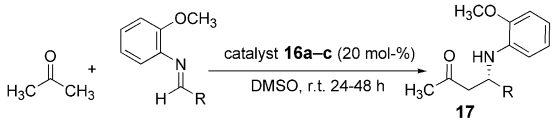
Scheme 6. Synthesis of Nikkomycin's N-terminal moiety.

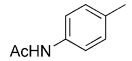
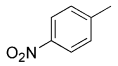
3. Aldimine and Simple Ketones

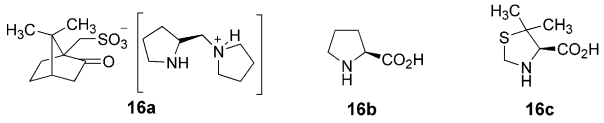
The direct asymmetric Mannich reaction of acetone with a variety of preformed aldimines was discovered during the one-pot three-component reaction of an aldehyde, acetone, *p*-anisidine, and amine catalyst.[37] In a catalyst screen for the addition of acetone to *N*-PMP-aldimines in DMSO/ace-

tone (4:1) with 20 mol-% of catalysts **16a**–**c**, all three catalysts afforded the β-amino ketone in modest yield after 48 h (Table 5). In particular, DMTC **16c** provided the desired product in 80% *ee*.

Table 5. β-Amino ketone adducts from preformed aldimines.



Entry	R	Catalyst	Yield (%)	*ee* (%)
1	 **a**	**16a**	43	2
		16c	45	15
2	 **b**	**16a**	50	67
		16b	48	51
		16c	48	60
3	 **c**	**16a**	40	55
		16b	50	40
		16c	48	80
4	 **d**	**16a**	32	25
		16b	42	86
		16c	56	88
5	 **e**	**16c**	47	75

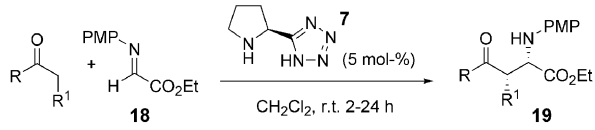


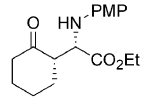
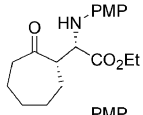
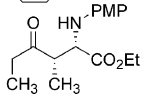
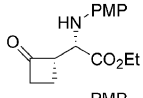
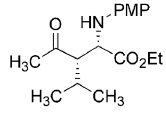
According to previously established amino acid catalysis involving enamine intermediates,[17,19] the enamine formed between a ketone and proline might serve as a nucleophile to stereoselectively add to α-imino esters. In an initial experiment,[38] *N*-PMP-protected ethyl iminoglyoxylate (0.1 M) and (*S*)-proline (20 mol-%) were subjected to previously established standard conditions. After 2 h, the aldimine was consumed and the corresponding α-amino acid was formed in 82% yield and 95% *ee*. The scope of this reaction was expanded to other ketones (both cyclic and acyclic) such as 3-pentanone, cyclohexanone, and 5-hexen-2-ones, affording Mannich adducts in excellent stereoselectivities.

In considering optimization of a reaction, attention must also be paid to the practical aspects of the reaction that go beyond the products themselves; specifically, solvent choice[39] and recycling of non-consumed materials. In recent years, ionic liquids[40] have attracted a great deal of attention from synthetic chemists as novel, green reaction media. Barbas et al.[41] reported the proline-catalyzed direct asymmetric Mannich reaction of the *N*-PMP-iminoglyoxylate with cylohexanone in [bmim]BF_4 at room temperature. In contrast to previously reported proline-catalyzed Mannich-type reactions, the reaction was complete within 30 min with 5 mol-% catalyst, affording the desired *syn* adducts in quantitative yield, excellent *ee* (>99%), and diastereoselectivity (>19:1). The recovered ionic liquid containing (*S*)-proline was used in a subsequent reaction run without any compromise of yield or stereoselectivity. Based on these results, various aldehydes and ketones as nucleophile or donors were examined. In all cases, the reactions were complete within 30 min to furnish functionalized amino acids with excellent yields and enantioselectivity. Reducing the catalyst loading to 1 mol-% using ionic liquid solvent did not compromise the enantioselectivity of the reaction but required longer reaction time of 2 h.

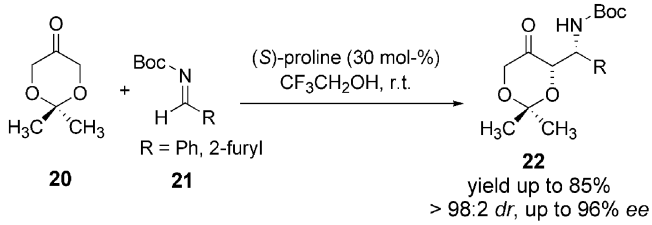
Although proline-based catalysis has proved to be highly enantioselective in a range of transformations, these transformations all rely on fairly polar solvents such as DMSO due to the insoluble nature of proline itself. Proline alternatives with greater solubility in conventional solvents were investigated in the reaction of cyclohexanone to *N*-PMP-iminoglyoxylate.[42] The highest yielding reaction at 2 h was found to be that carried out in dichloromethane with catalytic loading of tetrazole **7** at 5 mol-% (Table 6). Lower catalyst loadings of 1 mol-% required longer reaction times (16 h). These catalytic amounts are significant in that proline is routinely used at levels of 20 mol-%.

Table 6. Tetrazole-catalyzed addition of ketones to *N*-PMP-protected ethyl iminoglyoxylate.



Product	Reaction time (h)	Yield (%)	*dr*	*ee* (%)
	2	65	> 19:1	> 99
	8	59	> 19:1	> 99
	16	63	> 19:1	> 99
	24	74	> 19:1	> 94
	24	75	> 7:1	95

Due to the reactivity and pure (*E*) geometry, the *N*-PMP-imines **18** have so far dominated this area of research. Shortly after Westermann's use of dihydroxyacetone (DHA) as Mannich donors,[43] the accessibility of amino sugar derivatives from Mannich adducts was also examined by Enders[44] using 2,2-dimethyl-1,3-dioxan-5-one (**20**) as the nucleophile (Scheme 7). The selection of electrophile, however, focused on the use of (*E*)-*tert*-butyloxycarbonyl (Boc) imines **21**.



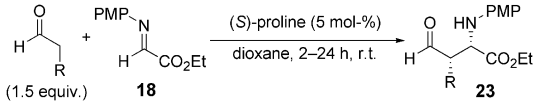
Scheme 7. Organocatalytic Mannich reaction of **20** with *N*-Boc imines.

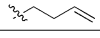
4. Aldimine and Aliphatic Aldehydes

Significant advances have been achieved with unmodified ketones in the catalytic asymmetric Mannich reaction. Subsequently, the extension to aldehyde donors was investigated. On the basis of previous research, Barbas et al.[45] disclosed the first unprecedented use of enamine intermediates formed from aliphatic aldehydes to serve as nucleophiles in a stereoselective Mannich addition to imines. In their initial experiment, isovaleraldehyde (0.2 M), *N*-PMP ethyl iminoglyoxylate (0.1 M), and (*S*)-proline (10 mol-%) were stirred in DMSO at room temperature.

After 8 h, the Mannich adduct was isolated in 80% yield, with *dr* > 10:1 and 87% *ee*. A subsequent solvent screen identified dioxane as the ideal solvent, providing the highest *ee* of 93% (Table 7). To broaden the scope of the investigation, various aliphatic aldehydes were investigated. Higher diastereoselectivities were achieved with increased bulkiness of the substituents on the aldehydes donor in the order of R = Me < Et < *i*Pr < *n*Pent (Table 7, Entries 1–7). This result demonstrates an excellent route to sterically demanding amino acid derivatives.

Table 7. Proline-catalyzed Mannich reaction of unmodified aldehydes and *N*-PMP-protected ethyl iminoglyoxylate.

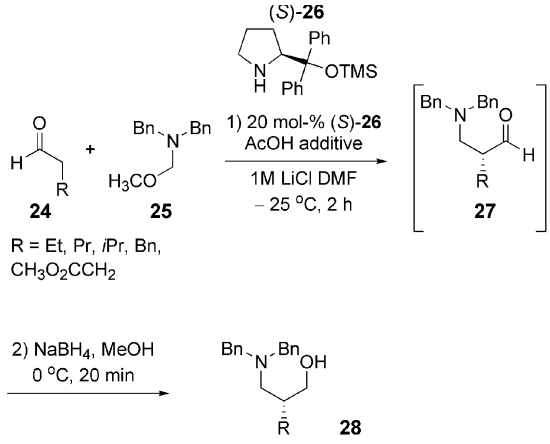


Entry	R	Yield (%)	*dr*	*ee* (%)
1	*i*Pr	81	> 10:1	93
2	CH_3	72	1.1: 1	99
3	Et	57	1.5: 1	99
4	*n*Bu	81	3:1	99
5	*n*Pent	81	> 19: 1	> 99
6		89	> 19: 1	99
7		71	> 19: 1	> 99

The use of *N*-PMP-protected aromatic aldimines instead of iminoglyoxylates was subsequently presented for the first time by Córdova in proline-catalyzed enantioselective Mannich reactions with aliphatic aldehydes[46] and α-oxyaldehydes.[47] Recently, Córdova and List separately applied *N*-Boc-protected aromatic imines in proline-catalyzed enantioselective reactions with aliphatic aldehydes.[48]

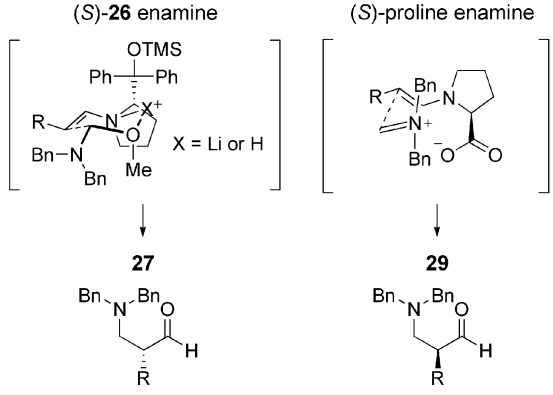
4.1 In situ Iminium Ions and Aliphatic Aldehydes

An enantioselective Mannich reaction of aldehydes with formaldehyde imines is an attractive method for the construction of α-substituted β^2-amino acids. In an effort to synthesize these amino acids, Gellman et al.[49] developed an in situ method for the preparation of formaldehyde iminium as electrophiles for the Mannich reaction. Similar to Cordova's earlier work on the α-aminomethylation of ketones,[28] Gellman used the aminomethyl ether **25** to form iminium ions in situ for the aminomethylation of aldehydes. The method utilizes the diaryl-prolinol catalyst (*S*)-**26** with a salt additive (1 M LiCl) and acetic acid additive to enhance enantioselectivity of the (*S*)-aminoaldehyde products **27** (Scheme 8). The aminoaldehdye adducts were immediately reduced to the corresponding stable β-substituted γ-amino alcohols **28**.[49]



Scheme 8. Chiral pyrrolidine-catalyzed aminomethylation of aldehydes.

Closely following Gellman's report, Cordova[50] also reported the aminomethylation of aldehydes also using (*S*)-**26** catalyst and salt additives. In a complimentary approach, proline was used to access (*R*)-amino aldehdyes **29**. Cordova proposes two transition states that explain the difference in facial selectivity of (*S*)-**26** vs. (*S*)-proline catalysts



Scheme 9. Proposed transition states for enantioselectivity of (*S*)-**26** and (*S*)-proline enamines in the α-aminomethylation of aldehdyes by in situ iminium ions.

(Scheme 9).[50] In the case of (*S*)-**26**, the *Re*-face of the pyrrolidine enamine is approached by aminomethyl ether via a six-membered transition state through activation of the methoxy leaving group. With (*S*)-proline-catalyzed α-aminomethylation, *Si*-face of the chiral enamine is approached by the in situ generated iminium ion that forms an ionic intermediate with the carboxylate group of the catalyst. Essentially, two different mechanistic explanations for the individual processes account for the enantioselectivity of the reaction.

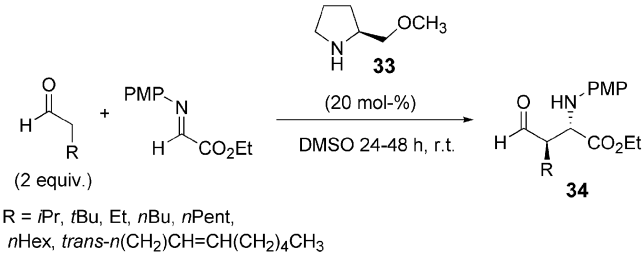
4.2 Mannich Reaction of Aldimine and Aliphatic Aldehdyes: Synthesis of DPP-IV Inhibitor

The glucagon-like peptide 1 (GLP-1) has been the focus of type-2 diabetes research for reducing the risk of hypoglycemia.[51] GLP-1 regulates insulin in a glucose-dependent manner and is readily degraded in vivo by dipeptidyl peptidase IV (DPP-IV), a serine protease. Inhibition of the DPP-IV enzyme increases the level of GLP-1, which could offer alternative therapeutic routes to type 2 diabetes.[52] Medicinal chemists at Merck Research identified molecules with structural analogues of **32** as novel inhibitors of DPP-IV.[53] The diamide aspartic acid derivative **32** can be accessed by a proline-catalyzed Mannich reaction of *N*-PMP-protected ethyl iminoglyoxylate and phenylacetaldehyde (Scheme 10). Excellent stereoselectivity (92:8 *syn*/*anti* and > 90% *ee*) was achieved in the *syn*-β-phenyl-substituted homoserine which underwent immediate reduction to prevent epimerization at room temperature (**30**). Workup with AcOH followed by $NaBH_4$ provided the amino alcohol **31** as the only product that retained stereoselectivity.

Further modification by heating in THF with pyrrolidine and catalytic K_2CO_3 provided amide **32** with optical purity > 99:1 *dr* and > 99% *ee* by crystallization from *tert*-butyl methyl ether (MTBE). Deprotection of *N*-PMP with $PhI(OAc)_2$, followed by treatment with carbonyldiimidazole and dimethylamine gave the desired diamide aspartic acid derivative.

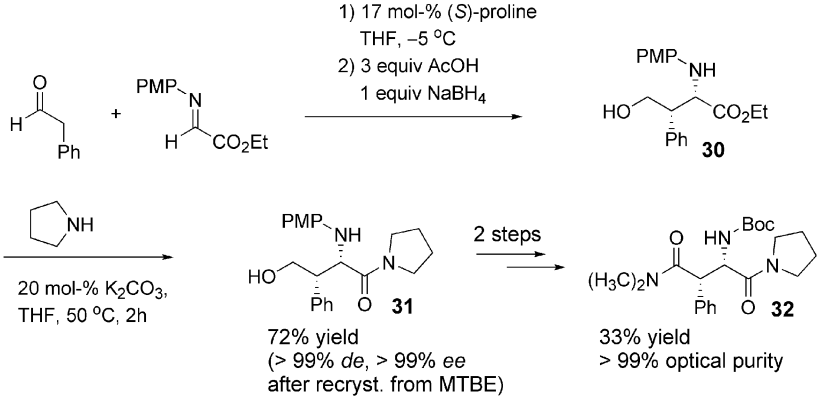
5. *anti*-Selective Mannich Adducts from Aldimines with Aldehydes or Ketones

Progress in the use of unmodified ketones and aldehydes in organocatalytic asymmetric Mannich reactions demonstrates the potential for extending the versatility of this methodology. Another aspect of the Mannich reaction that warrants further exploration is the development of protocols that provide for the directed synthesis of all possible stereoisomers in asymmetric catalysis. Based on earlier studies of chiral pyrrolidine derivatives, Barbas reported the first direct (*S*)-(2-methoxymethyl)pyrrolidine (SMP, **33**), catalyzed asymmetric Mannich reactions with unmodified aldehydes to afford the *anti*-selective products **34** (Scheme 11).[54] Several aliphatic aldehydes were treated with *N*-PMP-protected ethyl iminoglyoxylate in DMSO to afford β-formyl functionalized amino acid derivatives in moderate yield. The reaction afforded enantioselectivity between 74% and 92% with an *anti*-diastereoselectivity that increased with the bulkiness of the aldehyde donor. In the Mannich-transition state, (*E*)-configurations of both enamines and imine are assumed.



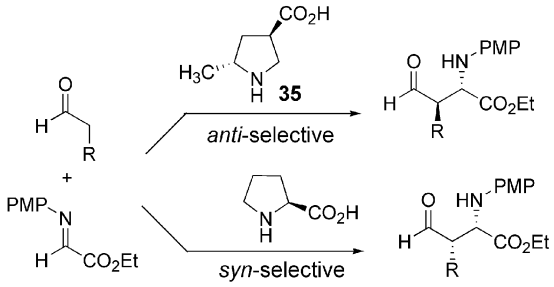
Scheme 11. *anti*-Selective SMP-catalyzed Mannich reaction.

Further investigations by Barbas were made to optimize pyrrolidinone catalysts that are *anti*-selective for the Mannich.[55] Previous results with the SMP catalyst **33** generated *anti*-Mannich adducts in only moderate yield and enantioselectivity. Certain key considerations regarding steric features of the catalyst to fix the conformation of facial selectivity of either the enamine or imine were explored. Functional features at the 5-position of the pyrrolidine were in-



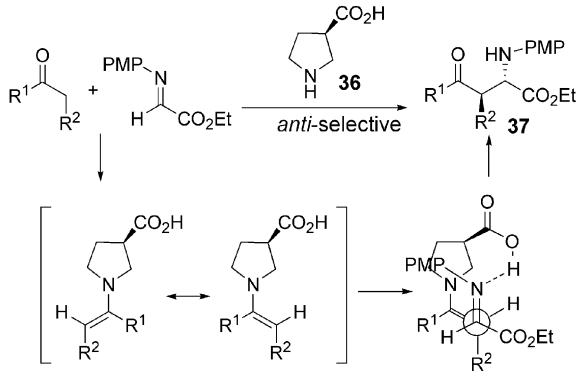
Scheme 10. Synthesis of a DPP-IV inhibitor via a proline-catalyzed Mannich reaction.

stalled to fix the enamine conformation by preventing initiation of proton transfer to the imine. Acid functionality was placed at the 3-position of the ring to affect control of enamine and imine facial selection. To avoid steric interactions between the substituents at the 5-position of the catalyst and the imine, substituents 3- and 5- are in *trans*-configuration. On the basis of these parameters, a new catalyst (3*R*,5*R*)-5-methylpyrrolidine-3-carboxylic acid (**35**) was designed (Scheme 12). In accordance with design principles and computational calculations, the reactions catalyzed by **35** afforded high *anti*-amino aldehyde products in excellent stereoselectivities and high yield under 1–5 mol-% catalyst loading.



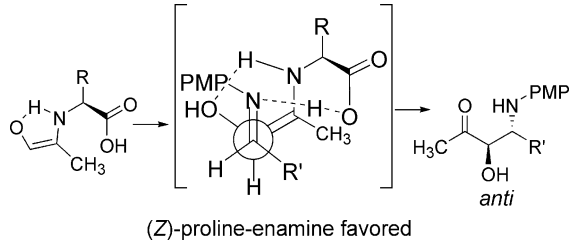
Scheme 12. *syn*-/*anti*-Directing pyrrolidine catalysts in the asymmetric Mannich reaction.

The catalyst **35**, however, was ineffective in the Mannich reactions of ketones. Upon consideration of transition states, it was hypothesized that the low efficiency of catalyst **35** with ketones originated from the relatively slow formation of the enamine intermediates due to steric interaction with the methyl group of the catalyst. Barbas subsequently designed the unmethylated catalyst (*R*)-pyrrolidine-3-carboxylic acid (**36**, Scheme 13).[56] Consistent with their hypothesis and computational studies, when the position of the carboxylic acid group on (*S*)-proline was changed from the 2- to 3-postion, the stereochemistry of the product **37** was altered from *syn* to *anti*. A variety of acyclic and cyclic ketones were examined, all offering good yields and high stereoselectivities in most cases. For reactions with unsymmetrical ketones, the reaction occurred predominantly at the more substituted α-position of the ketone.



Scheme 13. *anti*-Directing (*R*)-pyrrolidine-3-carboxylic acid (**36**).

The catalysts (3*R*,5*R*)-5-methylpyrrolidine-3-carboxylic acid (**35**) and (*R*)-pyrrolidine-3-carboxylic acid (**36**), however, were not optimal catalysts with α-hydroxy ketone donors. Application of α-hydroxy ketone donors in the Mannich reaction generates 1,2-amino alcohols. Current organocatalytic procedures allow access to *syn*-1,2-amino alcohols and *anti*-1,2-diols.[57] An organocatalytic *anti*-1,2-amino alcohol procedure was subsequently investigated by Barbas.[58] On the basis of their prior understanding of *anti*-selective Mannich catalysts **35** and **36**, (*Z*)-enamines in the transition state should generate *anti*-Mannich adducts. With primary amine catalysts, the (*Z*)-enamines of α-hydroxy ketones should predominate over the (*E*)-enamine configuration (Scheme 14).[59] On the basis of this consideration, natural acyclic amino acids and their derivatives were screened. Under optimized conditions, primary amine catalysts L-tryptophan and *O*-*t*Bu-L-threonine generated the desired *anti*-amino alcohols in good yields and excellent diastereoselectivities.

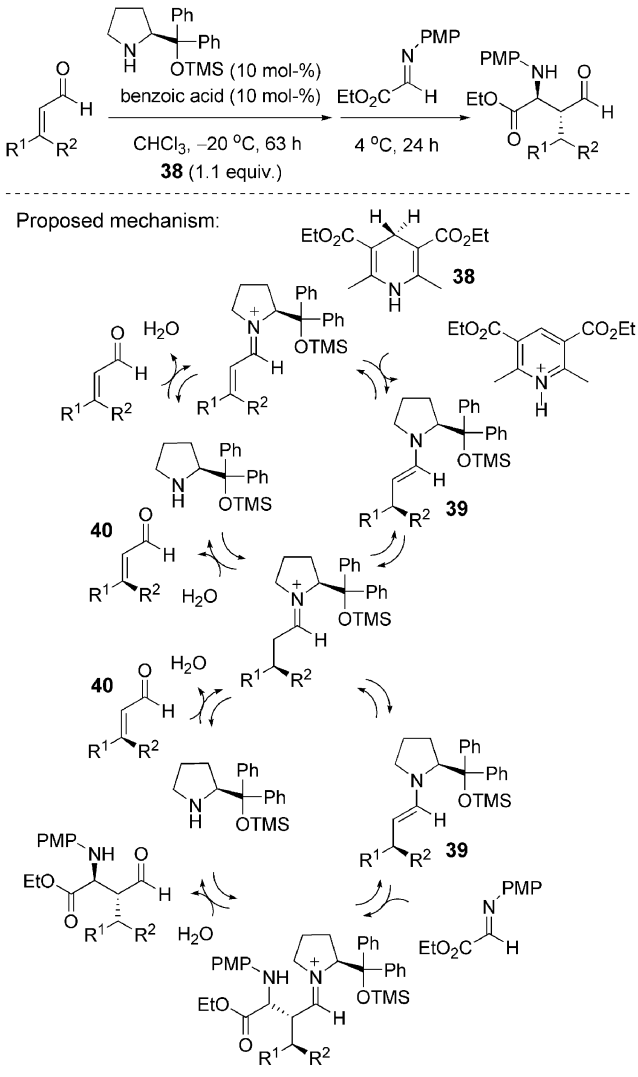


Scheme 14. (*Z*)-Enamine transition state favors *anti*-Mannich adduct.

For Mannich reactions involving in situ generated enamines, pyrrolidine-based catalysts have been extensively examined. The six-membered analogue, pipecolic acid, was relatively unexplored as a catalyst due to its inefficiency in aldol reactions.[60] Houk and Barbas recently reported (*S*)-pipecolic acid-catalyzed Mannich reactions between aldehydes and *N*-PMP-protected ethyl iminoglyoxylate.[61] Both *syn* and *anti* products could be isolated in good yields and excellent enantioselectivities. Experimental and computational investigation of the transition states account for the observed selectivities. The piperidine ring holds the carboxylic acid more rigidly than the more flexible pyrrolidine. This rigidity alters electrostatic interactions with the ester of the iminoglyoxylate and with the protonated imine. Such differences allow the (*S*)-*trans*- or (*S*)-*cis*-enamines to react accordingly to give roughly equal amounts of both *syn*-product and *anti*-product in high enantioselectivity excess.

Recently, Córdova reported a direct catalytic asymmetric reductive Mannich reaction that could be either *syn*- or *anti*-selective (Scheme 15).[62] An additional advantage of this transformation would be that three contiguous stereocenters could be constructed by an organocatalytic asymmetric domino reaction sequence. On the basis of the List–MacMillan transfer hydrogenation reaction,[63] the chi-

ral pyrrolidine enamine **39** catalyzed the transfer hydrogenation of the aldehydes **40** using the Hantzsch ester **38** as a hydrogen source to give chiral aldehydes. Taking advantage of these chiral aldehydes, *N*-PMP-protected α-iminoglyoxylate was selected as the electrophile for the subsequent in situ Mannich reaction. Carbon–carbon bond formation in the Mannich step displayed increased enantioselectivity as compared to the transfer hydrogenation step. The reactions afforded Mannich adducts in high chemo- and enantioselectivity; *syn*- or *anti*-selectivity could be easily steered using either (*S*)- or (*R*)-pyrrolidine **39**.

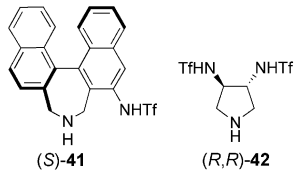


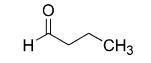
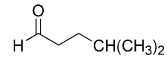
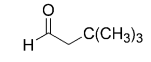
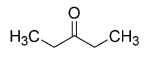
Scheme 15. Enantioselective reductive Mannich reaction.

Further catalyst design of chiral amino acid and chiral pyrrolidines were explored by other groups. Hayashi[64] first applied TMS-protected (*S*)-2-(diphenylmethyl)pyrrolidine as an active catalyst in the Mannich reaction. Jørgensen[65] and Córdova[66] separately discovered the application of Hayashi's TMS-protected (*S*)-2-(diphenylmethyl)pyrrolidine as an active catalyst for *anti*-selective Mannich reactions of aliphatic aldehdyes with PMP-iminoglyoxylates. Córdova further investigated the reactions in water. Reactions were fast (1 h) due to the hydrophobic effect; although conversion was low (< 40%), high enantioselectivities were achieved (90–98% *ee*). Stabilization of the *trans*-configuration and efficient shielding of the *si*-face of the chiral enamine explains the high stereoselectivity of the reaction. Coulombic interactions between the imine and the nitrogen of the pyrrolidine moiety of the chiral enamine (generated during the nucleophilic attack) contribute to the stabilization of *si*-facial attack on the electrophile.

Maruoka, et al., based their catalyst design on achieving an *anti*-Mannich adduct via the *syn*-enamine intermediate.[67] Catalyst (*S*)-**41** was discovered to reduce steric repulsion between the enamine and carboxylic acid moiety of **18**. In addition, the imine activated by the remote acidic proton is expected to react preferentially with the *syn*-enamine intermediate to give the desired *anti*-selective adduct of aldehyde and the iminoglyoxylate **18**. The efficiency of this catalyst, however, is sterically hindered by bulky aldehydes and ketones. In this context, the group designed a new chiral amino sulfonamide catalyst possessing highly nucleophilic pyrrolidine core and acidic triflamide groups, (*R*,*R*)-**42** (Table 8).[68] The catalyst proved to afford excellent yields and stereoselectivities with bulky aliphatic aldehydes and simple acyclic or cyclic ketones.

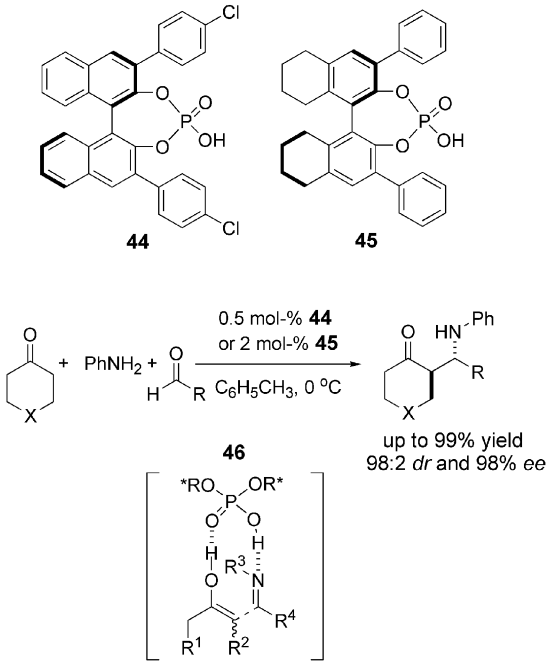
Table 8. *anti*-Selective Mannich reaction catalyzed by (*R*,*R*)-**42**.



Entry	Substrate	Conditions (°C, h)	Yield (%) (*anti*:*syn*)	*ee* (%)
1		–20, 2	82 (16:1)	94
2		–20, 1	93 (11:1)	95
3		–20, 24	88 (18:1)	90
4		r.t., 1	99 (>20:1)	95
		r.t., 4	95 (>20:1)	95
5		r.t., 35	98 (>20:1)	93
		r.t., 70	56 (4.8:1)	92

Up to this point, *anti*-selective direct Mannich reactions have employed the use of imino-esters based on enamine catalysis. In a recent report,[69] aldimines were used under a Brønsted acid-catalyzed Mannich mechanism (Scheme 16). On the basis of the mechanistic proposal that an acid-promoted ketone enolization delivers a nucleophilic attack of

a Brønsted acid activated aldimine, Gong[69] looked at the *anti*-selective three-component Mannich[70] reaction of ketones, primary amines, and aldehydes in toluene.



Scheme 16. Chiral Brønsted acid-catalyzed *anti*-selective Mannich reaction.

The optimal phosphoric acid catalysts identified were **44** and **45**. The primary amine component contributed much to the enantioselectivity of the reaction, with phenylamine selected as the best candidate. Electronic properties of the aromatic aldehyde contributed to stereoselectivity, where electron-donating groups eroded the enantioselectivity. Cycloketones bearing heteroatoms required relatively higher catalytic loadings of 2 mol-% to restore yield and selectivity.

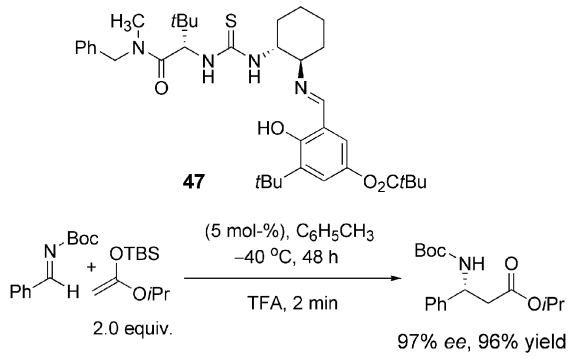
With low catalytic loadings (0.5 mol-%) of a chiral phosphoric acid, **44** or **45**, *anti*-selective Mannich adducts were obtained with cycloketones in high diastereo- (*anti*/*syn*, 98:2) and enantioselectivity (up to 98% *ee*). Aliphatic and aromatic ketone donors also provided good selectivity with moderate yield.

6. Bifunctional Brønsted Acid Activation of the Mannich Reaction

Much of the organocatalysis discussed so far has focused on activation of a carbon nucleophile by the formation of an enamine intermediate via the nucleophilic attack of a secondary amine on a carbonyl compound. Although electrophilic activation of a substrate by Brønsted acid has been a classical approach to promotion of a reaction, the development of effective asymmetric Brønsted acid transformations has been relatively limited.[71]

6.1 Chiral Thiourea Catalyst

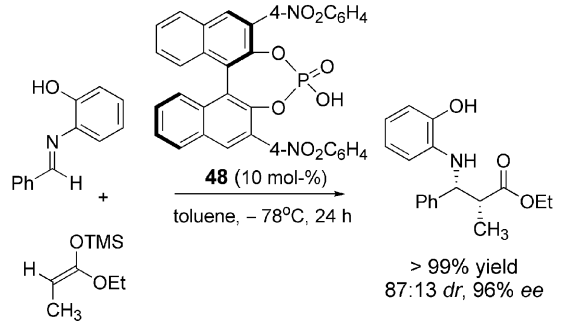
Significant advances were made by Jacobsen's highly enantioselective Strecker and Mannich reactions catalyzed by chiral thiourea-derived Brønsted acid catalysts (Scheme 17, **47**).[72] The achievement presented new avenues in asymmetric catalysis at an early stage illustrating that a chiral Brønsted acid could distinguish the enantiotopic faces of an imine substrate via hydrogen bonding.



Scheme 17. Chiral thiourea-catalyzed asymmetric Mannich reaction of silyl enol ether addition to imines.

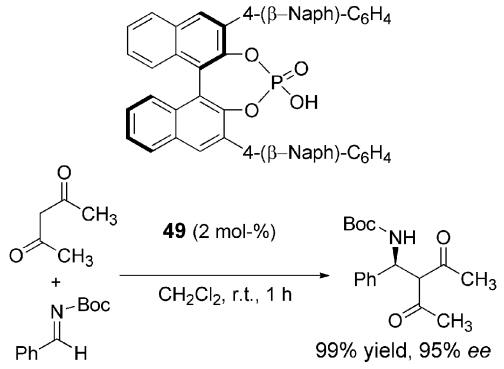
6.2 Chiral Brønsted Acid Catalysts

Chiral phosphoric acids have proven to be useful catalysts in the asymmetric Mannich reaction. Akiyama[73] developed bulky chiral phosphoric acid catalysts in the Mannich reaction (Scheme 18). The chiral acids were used for activation of *N*-*o*-hydroxyphenyl imines in the Mannich reaction with silyl enol ethers. Almost simultaneous to the introduction of Akiyama's chiral phosphoric acid catalysts, Terada[74] employed similar chiral phosphoric acids with *N*-Boc imines, demonstrating the first example of *N*-Boc imines in the organocatalytic Mannich reaction (Scheme 19).



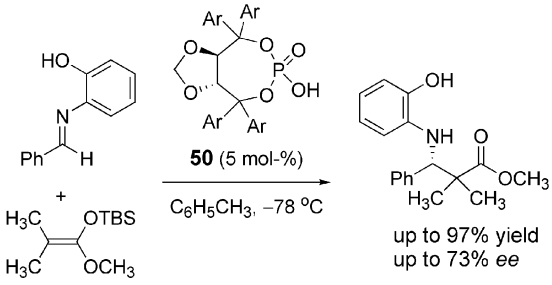
Scheme 18. Akiyama's chiral phosphoric acid-catalyzed addition of silyl enol ethers to imines.

Further chiral phosphoric acid development for activation of *N*-*o*-hydroxyphenyl imines includes Akiyama's TADDOL-derived phosphoric acid[75] (**50**, Scheme 20). The phosphate hydrogen atoms are imine activating, while the phosphoryl oxygen plays the key hydrogen-bonding role with the imine's hydroxyphenyl group. Yamamoto's[76] chiral Brønsted acid employs the use of *N*-phenyl aldimines in the Mannich reaction with silyl ketene acetals (Scheme 21). An achiral proton source, 2,6-xylenol was used to generate

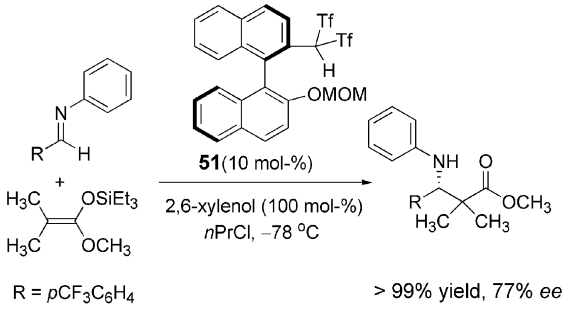


Scheme 19. Terada's chiral phosphoric acid-catalyzed addition of β-diketone addition to *N*-Boc-imines.

the catalytic cycle. These catalytic systems are bifunctional, either in a Brønsted acid–Lewis basic fashion or a Brønsted acid assisted chiral Brønsted fashion.



Scheme 20. Akiyama's TADDOL-derived phosphoric acid-catalyzed Mannich reaction of silyl enol ether addition to imines.

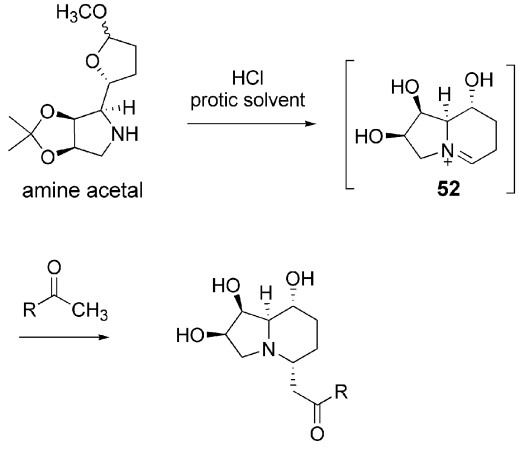


Scheme 21. Yamamoto's chiral Brønsted acid-catalyzed enantioselective Mannich reaction.

6.3 Acid-Catalyzed Mannich Reaction: Synthesis of New Mannosidase Inihibitors, 5-Substituted Swainsonine Analogues

(–)-Swainsonine is an immunomodulatory agent that has been found to reduce tumor growth and metathesis in clinical trials.[77] Swainsonine is a potent inhibitor of golgi α-mannosidase II (GM II), an enzyme that plays a key role in the biosynthesis of N-linked glyocoproteins[78] that are commonly and characteristcally expressed in various tumor cell lines.[79]

Many efforts have been directed toward structural modification of swainsonine in efforts to achieve more potent immunomodulatory activity.[80] Nagasawa's group investigated the stereoselective synthesis of 5-substituted swainsonine analogues via an iminium ion **52** generated in situ from an amine acetal (Scheme 22).[81] The possibility for a Mannich reaction became apparent during the acid-catalyzed cleavage of protective groups of an amine acetal in protic solvents. The iminium salt **52** derived from the amine acetal under acid conditions was treated with various ketones in a stereoselective Mannich reaction to produce 5-substituted analogues.

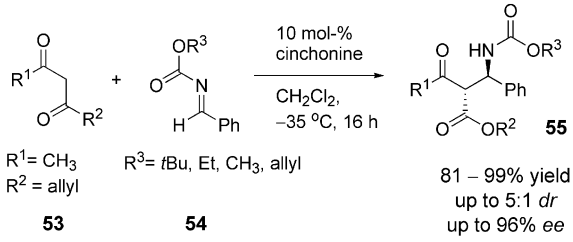


Scheme 22. Key synthetic steps for swainsonine analogues.

Aromatic ketones were more reactive than the less-stabilizing enol forms of aliphatic ketones. Unsymmetrical dialkyl ketones gave a single regioisomer at the less substituted α-carbon. The less stable 5α-diastereomer resulting from an axial attack of enols were formed selectively over the equatorial, 5β-analogues. Interestingly, the 5α-swainsonine analogues displayed significantly higher inhibitory activity than the corresponding 5β-epimers.

7. 1,3-Dicarbonyls and Acyl Aldimines with Bifunctional Catalysts

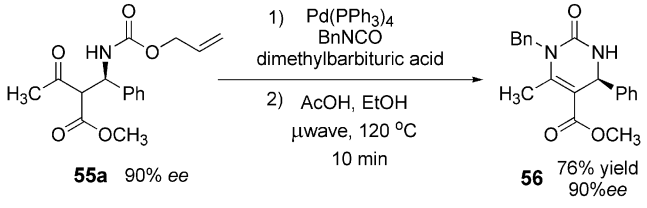
Highly enantioselective organocatalytic Mannich reactions of aldehydes and ketones have been accomplished with catalysts derived from chiral secondary amines, chiral thioureas, and phosphoric acids. Hydrogen-bond acceptors (chiral Brønsted acid-Lewis-base) such as *Cinchona* alkaloid catalysts were previously shown to be effective activators of malonates in conjugate additions.[82] However, the enantioselective Mannich reaction of malonates and β-keto esters with acyl imines is relatively unexplored.[83] This observation led Schaus et al. to investigate *Cinchona* alkaloid-catalyzed addition of β-keto esters **53** to various acylaryl imines **54**.[84] Highly enantioselective multifunctional secondary amine products **55** were obtained in under 16 h using 10 mol-% cinchonine in dichloromethane (Scheme 23).



Scheme 23. Cinchonine-catalyzed asymmetric Mannich reaction of β-keto esters.

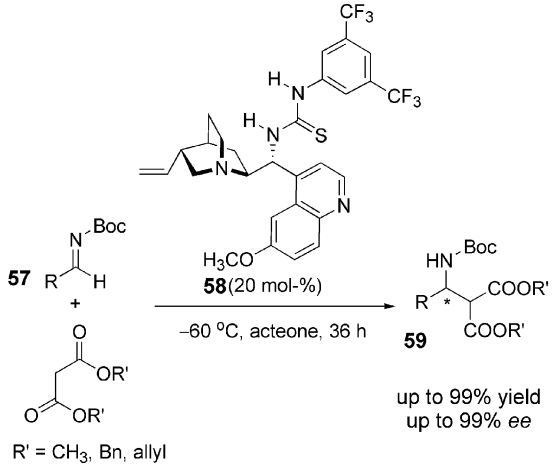
The opposite enantiomer of the product could be accessed by using the pseudoenantiomer of the catalyst, cinchonidine. High functional group tolerance of the catalytic system was displayed in the use of methoxycarbonyl and allyloxycarbonyl (Alloc) *N*-protecting groups of the imines.

The Mannich adducts obtained provide ready access to highly functionalized building blocks, notably demonstrated in the subsequent synthesis of enantio-enriched dihydropyrimidones[85] (Scheme 24). Deprotection of the allyl carbamate on **55a** was accomplished by treatment with catalytic $Pd(PPh_3)_4$ and dimethylbarbituric acid as the allyl scavenger; benzyl isocyanate was added to afford the corresponding unsymmetrical urea (85% yield). Ring closure was promoted by AcOH in ethanol under microwave conditions to afford the 5-benzylpyrimidone **56** in 76% yield and 90% *ee*.



Scheme 24. Mannich route to chiral pyrimidones.

Shortly after Schaus's work,[84] Deng et al. explored the use of bifunctional *Cinchona* alkaloids **58** in the efficient catalysis of malonate addition to carbamate-protected imines. The *N*-Boc imines **57** (Scheme 25) and α-amido sulfones (via in situ generation of carbamate-protected imines) were used to access enantioselective β-amino acid products.[86]



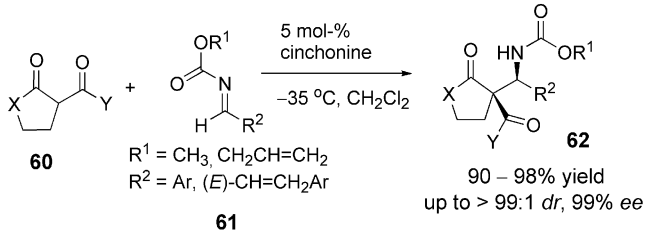
Scheme 25. Bifunctional *Cinchona* alkaloid-catalyzed asymmetric Mannich reaction of malonates.

8. α-Substituted 1,3-Dicarbonyl Donors: Asymmetric Mannich Adducts with Quaternary Carbon Centers

The asymmetric synthesis of quaternary amino acid derivatives remains a challenging task.[87] With the recent success in organocatalysis of enantioselective Mannich reactions involving ketone, aldehyde, and 1,3-dicarbonyl donors, an asymmetric synthesis of quaternary amino acid Mannich adducts has generated much interest.

Barbas, for the first time, applied the use of (*S*)-proline with α,α-disubstituted aldehydes donors and *N*-PMP-iminoglyoxylates to generate enantioselective products with quaternary carbon stereogenic centers.[88] Jørgensen investigated the use of α-substituted cyanoacetates as nucleophiles in the β-isocupreidine-catalyzed Mannich to generate all-carbon quaternary adducts.[89]

Schaus et al.[90] further investigated the prospects of accessing *cyclic* all-carbon quaternary amino acid[91] derivatives (Scheme 26). On the basis of earlier results with cinchonine-catalyzed direct asymmetric Mannich reactions,[84,86a] the cyclic 1,3-dicarbonyl compound **60** was added to the acyl imine **61** to afford the corresponding α-quaternary carbon-bearing product **62** in yields up to 98%, up to > 99:1 *dr*, and enantioselectivities up to 98% *ee*. No erosion of yield or stereoselectivity was observed with electron-rich or electron-poor aromatic, heteroaromatic, and arylpropenyl imines – a new class of imine acceptors not previously used in Mannich reactions.



Scheme 26. Cyclic Mannich adduct with all-carbon quaternary centers.

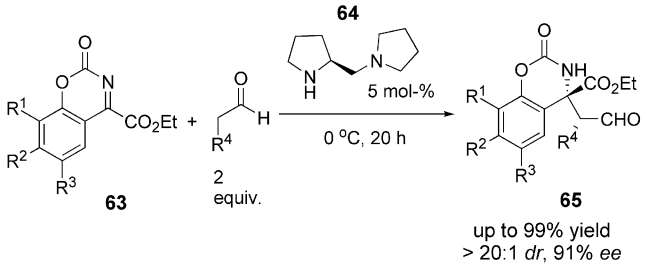
At around the same time, Dixon et al.[92] published their work on Mannich reactions of malonate and β-keto esters to *N*-Boc and *N*-Cbz aldimines catalyzed by a cinchonine-derived thiourea catalyst.

9. Asymmetric Mannich Adducts with Ketimines

With the tremendous progress in the development of the Mannich reaction, the imine acceptor has been limited to only aldimines. The organocatalytic enantioselective Man-

nich reaction of ketimines was first achieved by Jørgensen's group as an alternative route to the synthesis of α-quaternary amino acids.[93]

Because ketimines are less reactive towards nucleophilic addition owing to steric hindrance as well as electronic effects, Jørgensen's group anchored the protecting group on the nitrogen atom to the α-aryl substituent of a ketimino ester (Scheme 27, **63**). This application minimizes rotational freedom by blocking *E*/*Z* isomerization of the ketimines; the induced ring-strain also increased reactivity towards nucleophiles. A survey of chiral pyrrolidine catalysts identified diamine **64** as the optimal catalyst.



Scheme 27. Ketimines in the direct organocatalytic asymmetric Mannich reaction.

10. Asymmetric Nitro-Mannich Reaction

A variant of the Mannich reaction involves the conjugate addition of nitronates to imines. Known as the nitro-Mannich or aza-Henry reaction,[94] this variation of the Mannich affords β-nitroamines that could be further reduced to generate vicinal diamines.[95] These β-nitroamine adducts can also be converted via the Nef reaction to give α-amino acids.[96] The asymmetric nitro-Mannich has generated particular interest owing to its versatile accessibility to 1,2-diamino moieties prevalent in biologically active molecules, chemotherapeutic agents, medicinal drugs, chiral ligands, and chiral auxiliaries in stereoselective synthesis.[97]

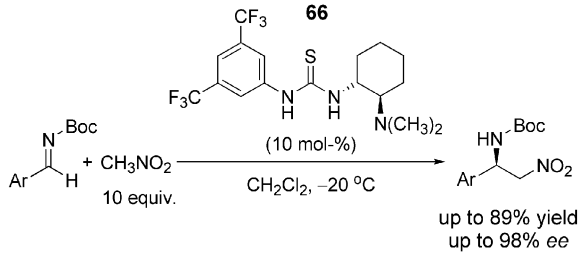
Development of an asymmetric metal-catalyzed nitro-Mannich[98] that is both diastereoselective and enantioselective was first achieved by Shibasaki's[98a,98b] report of heterobimetallic complexes with lanthanide-BINOL systems. Jørgensen[98c] also developed a catalytic asymmetric version of the reaction with bisoxazoline copper(II) complexes.

With the progress made in the organocatalytic field of the Mannich reaction, metal-free versions of the nitro-Mannich have recently evolved. On the basis of Lewis acid activation of the imines and Brønsted base activation of the nucleophile, several organocatalytic methods have been developed.

10.1 Nitro-Mannich Reaction of Acyl Imines

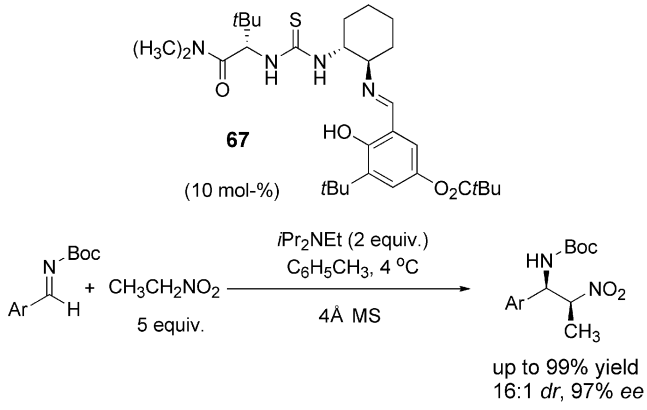
10.1.1 Thiourea-Based Bifunctional Organocatalysis

Chiral urea and thioureas catalysts[99] have recently contributed to a variety of enantioselective conjugate reactions in the Mannich, nitro-Michael addition, Strecker reaction, hydrophosphonylation of imines, and acyl-Pictet–Spengler (Scheme 28).[100] The first example of an α-nitro-Mannich reaction with an organocatalyst was presented by Takemoto's chiral thiourea **66** with a dimethylamino group.[101] The best results were obtained from aromatic *N*-Boc aldimines and *N*-phosphonylimines.



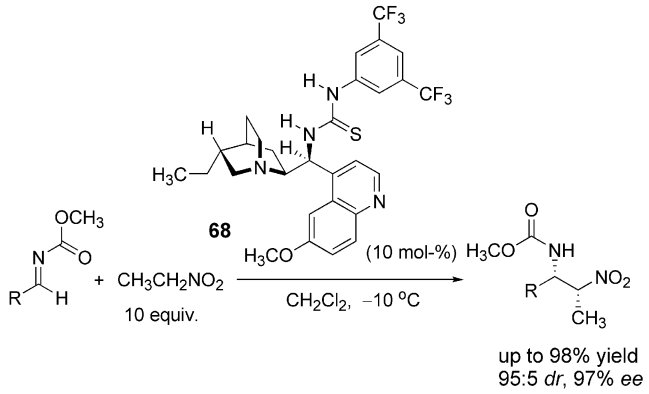
Scheme 28. Takemoto's thiourea Catalyzed nitro-Mannich reaction.

Jacobsen also identified a highly stereoselective chiral thiourea[102] catalyst **67** (Scheme 29) based on their previous work for the asymmetric Strecker reaction.[100c,100d] In the presence of the catalyst **67**, a base additive (*i*Pr_2NEt), and molecular sieves, various nitroalkanes were employed in the addition to aromatic and heteroaromatic *N*-Boc imines.



Scheme 29. Jacobsen's thiourea-catalyzed nitro-Mannich reaction.

Cinchona alkaloid modified chiral thiourea catalysts were recently used by Ricci[103] and Schaus.[104] Ricci's procedure, with the addition of nitromethane to *N*-Boc and *N*-CBz imines with 20 mol-% of a thiourea derivative,[103] afforded β-nitroamines in moderate yield and selectivity. Schaus' group turned to a hydroquinine-derived thiourea **68** previously identified by Connon and Soos.[105] This asymmetric nitro-Mannich reaction catalyzed by **68** was highly selective with methyl *N*-alkylidenecarbamates (Scheme 30). While nitromethane has been utilized in the addition to acyl imines, the use of nitroethane has yet to be thoroughly investigated with various aromatic imines, including heteroaromatic and arylpropenyl imines. Subsequently, the scope of investigation included nitro-Mannich addition of nitroethane to a variety of methylcarbamate imines to afford *syn*-β-nitroamines in high yield and stereoselectivity.

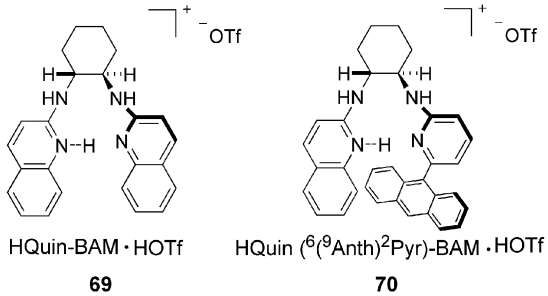


Scheme 30. Hydroquinine-derived thiourea-catalyzed nitro-Mannich reaction with methyl carbamate imine.

The proposed mode of reactivity up to this point includes two possible routes,[101] either by nitroalkane activation from binding thiourea to the nitronate anion, or by co-activation of both reaction partners (imine and nitroalkane). Based on their methodology,[104] Schaus proposed a model that accounts for the observed diastereo- and enantioselectivity. Using a MMFF conformation search,[106] the lowest energy conformer complex was identified. The nitromethane catalyst complex was modelled with *re*- and *si*-facial attack of the nucleophile. The calculated energy difference between the binding modes was found to be 1.6 kcal/mol in favor of *si*-facial attack of the nucleophile. Modelling of the catalytically active thiourea–nitromethane complex approach of the *re*-face of methyl carbamate imine was in agreement with energy calculations and observed selectivity.[105,107]

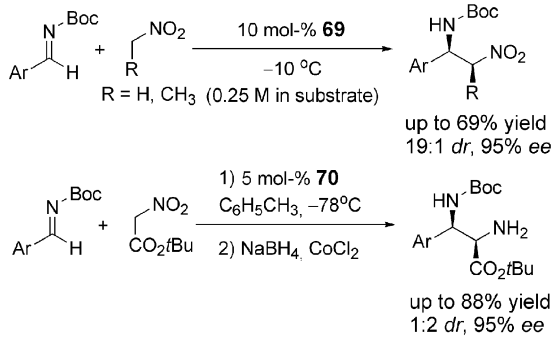
10.1.2 Chiral Proton Catalysis

Based on the concept of polar ionic hydrogen bonds, Johnston reported a highly enantioselective chiral proton-catalyzed nitro-Mannich reaction without use of a base additive (Scheme 31).[108] In the manner of a Brønsted acid, symmetrical bidentate ligand **69** was synthesized as a single enantiomer. Activation of *N*-Boc imines by the bis(amidine) ligand affords *syn*-secondary amine adducts in moderate yield. Following this work, the group also identified an unsymmetrical bis(amidine) complex **70** for highly *anti*-selective α-nitroester addition to *N*-Boc aldimines (Scheme 32). Although the mechanism for the observed stereocontrol is



Scheme 31. Bis(amidine) catalysts developed by Johnston.

not yet thoroughly understood, there is evidence that the *anti* adducts are based on kinetic selectivity. When the *anti* adduct is left at room temperature with catalyst, the *syn*-enriched product can be obtained following silica gel filtration with identical enantiomeric ratio.



Scheme 32. Bis(amidine) complex-catalyzed nitro-Mannich reactions.

10.2 Nitro-Mannich Reaction of *N*-Phosphinoylimines

With the purpose of developing an environmentally friendly and economically accessible protocol, Ricci's group[109] presented a solvent-free procedure with an organic base as the catalyst. The nitronate anion generated from nitroalkane deprotonation would need an imine moiety that is sufficiently reactive, particularly as the catalytic system lacks a strong Lewis or Brønsted acidic site. Consequently, 1,1,3,3-tetramethylguanidine (TMG) was selected as the organic base component and *N*-(diphenylphosphinoyl)imines were the selected electrophiles. *anti*-Nitro Mannich adducts were obtained in high yields and high selectivity, including adducts generated from lesser explored donors nitropropane (no selectivity) and nitrobutane.

Conclusions

The use of small organic molecules such as proline, cyclohexane diamine, and *Cinchona* alkaloid-derived catalysts has proven extraordinarily useful for the development of asymmetric Mannich reactions. The utility of the products afforded by the reactions highlighted by this review provides a small but significant indication of how powerful the approach will be in providing ready access to chiral amine-containing building blocks. Significant advances in new methodologies have been the result of insightful consideration of the limitations afforded by previous methods and innovative catalyst development to address those limitations. As the area of organic catalysis matures, more consideration will be devoted to the synthetic utility of the products afforded by new methodologies. It is clear that the synthetic challenges and utility of the asymmetric Mannich reaction have inspired the creativity of chemists and continue to be an area of active investigation.

Acknowledgments

The authors would like to gratefully acknowledge support from Amgen, Inc., the National Science Foundation (CHE-0349206), and the National Institutes of Health (P50 GM067041) and (R01 GM078240).

[1] a) E. F. Kleinmann, in *Comprehensive Organic Synthesis* (Eds: B. M. Trost, I. Flemming), Pergamon Press: New York, **1991**; vol. 2, chapter 4.1; b) L. Mei, M. P. Sibi, *Tetrahedron* **1992**, *58*, 7991–8035; c) *Enantioselective Syntheses of β-Amino Acids* (Ed.: E. Juaristi) Wiley-VCH: New York, **1997**; d) M. Arend, B. Westermann, N. Risch, *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070; e) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069–1094; f) S. Denmark, O. J.-C. Nicaise, in *Comprehensive Asymmetric Catalysis* (Eds: E. N. Jacobsen, A. Pfaltz, H. Yamamoto) Springer: Berlin, **1999**; vol. 2, p. 93; g) S. C. Bergmeier, *Tetrahedron* **2000**, *56*, 2561–2576; h) A. Córdova, *Acc. Chem. Res.* **2004**, *24*, 102–112; i) H. Pellissier, *Tetrahedron* **2006**, *62*, 2143–2173; j) G. K. Friestad, A. K. Mathies, *Tetrahedron* **2007**, *63*, 2541–2569.

[2] a) C. Mannich, W. Krosche, *Arch. Pharm.* **1912**, *250*, 647; b) First example of the Mannich reaction in natural product synthesis: R. Robinson, *J. Chem. Soc.* **1917**, 762–768; c) S. Kobayashi, M. Ueno, *Mannich Reaction. Comprehensive Asymm. Catal. Suppl.* **2004**, *1*, 143–150; d) G. Friestad, A. K. Mathies, *Tetrahedron* **2007**, *63*, 2541–2569.

[3] a) E. Leete, *Tetrahedron* **1958**, *3*, 313–314; b) H. Conroy, *Tetrahedron Lett.* **1960**, *1*, 34–37; c) E. E. Van Tamelen, R. L. Foltz, *J. Am. Chem. Soc.* **1960**, *82*, 2400; d) E. Wenkert, *J. Am. Chem. Soc.* **1962**, *84*, 98–102; e) E. Leete, *Annu. Rev. Plant Physiology* **1967**, *18*, 179–196; f) M. Hesse, *Dtsch. Apoth. Ztg.* **1968**, *108*, 1480–1482; g) H. Liebisch, *Biosyn. Alkaloids* **1969**, 101–122; h) K. F. Maclure, C. H. Heathcock, *J. Am. Chem. Soc.* **1989**, *111*, 1530–1531; i) S. F. Martin, *J. Heterocycl. Chem.* **1994**, *31*, 679–686; j) S. F. Martin, *Pure Appl. Chem.* **1997**, *69*, 571–576; k) J. C. Lanter, H. Chem, X. Zhang, Z. Sui, *Org. Lett.* **2005**, *7*, 5905–5907; l) K. Nagata, K. Nishimura, M. Yokoya, T. Itoh, *Heterocycles* **2006**, *70*, 335–344; m) X. Chen, J. Chen, J. Zhu, *Synthesis* **2006**, *23*, 4081–4086; n) F. A. Davis, M. Santhanaraman, *J. Org. Chem.* **2006**, *71*, 4222–4226.

[4] a) M. Ueneo, H. Kitagawa, H. Ishitani, S. Yasuda, K. Hanada, S. Kobayashi, *Tetrahedron Lett.* **2001**, *42*, 7863–7865; b) S. Kobayashi, R. Matsubara, H. Kitagawa, *Org. Lett.* **2002**, *4*, 143–145; c) D. E. DeMong, R. M. Williams, *J. Am. Chem. Soc.* **2003**, *125*, 8561–8565; d) Y. Nakamura, R. Matsubara, H. Kitagawa, S. Kobayashi, K. Kumagai, S. Yasuda, K. Hanada, *J. Med. Chem.* **2003**, *46*, 3688–3695; e) H. Liu, S. Cai, J. Xu, *J. Pept. Sci.* **2006**, *12*, 337–340.

[5] U. Scholz, E. Winterfield, *Nat. Prod. Rep.* **2000**, *17*, 349–366.

[6] A. Delters, K. Chen, C. T. Early, S. F. Martin, *J. Am. Chem. Soc.* **2003**, *125*, 4541–4550.

[7] a) H. Ishitani, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **1997**, *119*, 7153–7154; b) S. Kobayahi, T. Hamada, K. Manabe, *J. Am. Chem. Soc.* **2002**, *4*, 5640–5641; c) H. Ishitani, M. Ueno, S. Kobayashi, *Org. Lett.* **2002**, *4*, 143–145; d) H. Ishitani, S. Ueneo, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 8180–8186.

[8] a) E. Hagiwara, A. Fujii, M. Sodeoka, *J. Am. Chem. Soc.* **1998**, *120*, 2474–2475; b) A. Fujii, E. Hagiwara, M. Sodeoka, *J. Am. Chem. Soc.* **1999**, *121*, 545–556; c) Y. Hamashima, K. Yagi, H. Tamas, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 14530–14531; d) Y. Hamashima, M. Hotta, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 11240–11241.

[9] a) D. Ferraris, B. Young, T. Dudding, T. Lectka, *J. Am. Chem. Soc.* **1998**, *120*, 4548–4549; b) D. Ferraris, B. Young, C. Cox, W. J. Drury III, T. Dudding, T. Lectka, *J. Org. Chem.* **1998**, *63*, 6090–6091; c) D. Ferraris, B. Young, C. Cox, T. Dudding, W. J. Drury III, L. Ryzhkow, T. Taggi, T. Lectka, *J. Am. Chem. Soc.* **2002**, *124*, 67–77.

[10] B. M. Trost, L. M. Terrell, *J. Am. Chem. Soc.* **2003**, *125*, 338–339.

[11] a) S. Matsunaga, N. Kumagai, N. Harada, S. Harada, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 4712–4713; b) T. Yoshida, H. Morimoto, N. Kumagai, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2005**, *44*, 3470–3474; c) S. Harada, S. Handa, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2005**, *44*, 4365–4368.

[12] a) K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2001**, *40*, 2995–2997; b) M. Marigo, A. Kjaersgaard, K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Eur. J.* **2003**, *9*, 2359–2367; c) L. Bernardi, A. S. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 2583–2591.

[13] a) Z. G. Hajos, D. R. Parrish, *Asymmetric Synthesis of Optically Active Polycylic Organic Compounds.* German Patent DE 2102623 Jul 29, **1971**; b) U. Eder, G. Sauer, R. Wiechert, *Optically Active 1,5-Indanone and 1,6 Naphthalenedione.* German Patent DE 201475557, Oct 7, **1971**; c) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496–497; d) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615–1621.

[14] a) D. A. Evans, S. G. Nelson, *J. Am. Chem. Soc.* **1997**, *119*, 6452–6453; b) B. List, *Synlett* **2001**, 1675–1686; c) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580–591.

[15] a) T. Hoffman, G. Zhong, B. List, D. Shabat, J. Anderson, S. Gramatikova, R. A. Lermer, C. F. Barbas III, *J. Am. Chem. Soc.* **1998**, *120*, 2768–2779, and references cited therein; b) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; c) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387.

[16] M. Manabe, S. Kobayashi, *Org. Lett.* **1999**, *1*, 1965–1967.

[17] B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337.

[18] P. Bravo, M. Guidetti, F. Viani, M. Zanda, A. L. Markovsky, A. E. Sorochinsky, I. V. Solochonok, V. A. Soloshonok, *Tetrahedron* **1998**, *54*, 12789–12806.

[19] B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827–833.

[20] a) G. Li, T.-H. Chang, B. K. Sharpless, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451–454; b) P. O'Brien, *Angew. Chem. Int. Ed.* **1999**, *38*, 326–329.

[21] J.-A. Ma, *Angew. Chem. Int. Ed.* **2003**, *42*, 4290–4299.

[22] a) D. Seebach, J. Golinski, *Helv. Chim. Acta* **1981**, *64*, 1413–1423; b) S. Bahmanyar, K. N. Houk, *Org. Lett.* **2003**, *5*, 1249–1251.

[23] R. Hoffman, *Angew. Chem. Int. Ed.* **2001**, *40*, 3337–3340.

[24] a) J. Bjoergo, D. R. Boyd, C. G. Watson, W. B. Jennings, D. M. Jerina, *J. Chem. Soc. Perkin Trans. 2* **1974**, 1081–1084; b) H. Kessler, *Tetrahedron* **1974**, *30*, 1861–1870.

[25] N. S. Chowdari, M. Ahmad, K. Albertshofer, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2006**, *8*, 2839–2842.

[26] D. Enders, C. Grondal, *Angew. Chem. Int. Ed.* **2005**, *44*, 1210–1212.

[27] D. Enders, C. Grondal, M. Vrettou, G. Raabe, *Angew. Chem. Int. Ed.* **2005**, *44*, 4079–4083.

[28] a) I. Ibrahem, J. Casas, A. Córdova, *Angew. Chem. Int. Ed.* **2004**, *43*, 6528–6531; b) I. Ibrahem, W. Zou, J. Casas, H. Sundén, A. Córdova, *Tetrahedron* **2006**, *62*, 357–364.

[29] B. Rodriguez, C. Bolm, *J. Org. Chem.* **2006**, *71*, 2888–2891.

[30] a) L. Perreux, A. Loupy, *Tetrahedron* **2001**, *57*, 9199–9223; b) P. Lidström, J. Tierney, B. Wathey, J. Westman, *Tetrahedron* **2001**, *57*, 9225–9283; c) H. Blackwell, *Org. Biomol. Chem.* **2003**, *1*, 1251–1255; d) A. Lew, P. P. Krutzik, M. E. Hart, A. R. Chamberlin, *J. Comb. Chem.* **2004**, *4*, 95–105.

[31] For excellent reviews, see: a) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748; b) B. List, *Synlett* **2001**, *11*, 1675–1686; c) E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**,

58, 2481–2495; d) B. List, *Tetrahedron* **2002**, *58*, 5573–5590; e) R. O. Duthaler, *Angew. Chem. Int. Ed.* **2003**, *42*, 975–978; f) S. France, D. J. Guerin, S. J. Miller, T. Lectka, *Chem. Rev.* **2003**, *103*, 2985–3012; g) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; h) A. J. A. Cobb, A. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84–96; i) B. List, *Chem. Commun.* **2006**, 819–824.

[32] I. Ibrahem, W. Zou, M. Engqvist, Y. Xu, A. Córdova, *Chem. Eur. J.* **2005**, *11*, 7024–7029.

[33] A. Córdova, *Chem. Eur. J.* **2004**, *10*, 1987–1997.

[34] a) A. Córdova, W. Notz, C. F. Barbas III, *Chem. Commun.* **2002**, *67*, 3034–3035; b) Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, N. Shoji, K. Sakai, *Angew. Chem. Int. Ed.* **2003**, *42*, 3677–3680.

[35] a) H. Hagemaier, A. Keckeisen, H. Zahner, W. A. Konig, *Liebigs Ann. Chem.* **1979**, 1494–1502; b) W. A. Konig, W. Hass, W. Dehler, H. P. Fiedler, H. Zahner, *Liebigs Ann. Chem.* **1980**, 1016–1027.

[36] Total synthesis: a) H. Hahn, H. Heitsch, R. Rathmann, G. Zimmerman, C. Bormann, H. Zahner, W. A. Konig, *Liebigs Ann. Chem.* **1987**, 803–805; b) A. G. M. Barrett, S. A. J. Lebold, *J. Org. Chem.* **1991**, *56*, 4875–4884; c) Y. Hayashi, T. Urushima, N. Shin, M. Shoji, *Tetrahedron* **2005**, *61*, 11393–11404 and references cited therein.

[37] W. Notz, K. Sakthivel, T. Bui, G. Zhong, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 199–201.

[38] A. Córdova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1824–1825.

[39] Use of aqueous media in direct organocatalytic asymmetric Mannich reaction: A. Córdova, C. F. Barbas III, *Tetrahedron Lett.* **2003**, *44*, 1923–1926.

[40] a) T. Welton, *Chem. Rev.* **1999**, *99*, 2071–2084; b) P. Wasserscheid, W. Kein, *Angew. Chem. Int. Ed.* **2000**, *39*, 3772–3789; c) R. A. Sheldon, *Chem. Commun.* **2001**, 2399–2407.

[41] N. S. Chowdari, D. B. Ramachary, C. F. Barbas III, *Synlett* **2003**, *12*, 1906–1909.

[42] A. J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett* **2004**, *3*, 558–560.

[43] B. Westermann, C. Neuhaus, *Angew. Chem. Int. Ed.* **2005**, *44*, 4077–4079.

[44] a) D. Enders, M. Vrettou, *Synthesis* **2006**, *13*, 2155–2158; b) D. Enders, C. Grondal, M. Vrettou, *Synthesis* **2006**, *21*, 3597–3604.

[45] a) A. Córdova, S. Watanabe, F. Tanaka, W. Notz, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1866–1867; b) W. Notz, F. Tanaka, S. Watanabe, N. S. Chowdari, J. M. Turner, R. Thayumanawan, C. F. Barbas III, *J. Org. Chem.* **2003**, *68*, 9624–9634.

[46] A. Córdova, *Synlett* **2003**, *11*, 1651–1654.

[47] I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2005**, *46*, 2839–2843.

[48] a) J. Vesely, R. Rios, I. Ibraheim, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 421–524; b) J.-W. Yang, M. Stadler, B. List, *Angew. Chem. Int. Ed.* **2007**, *46*, 609–611.

[49] Y. Chi, S. H. Gellman, *J. Am. Chem. Soc.* **2006**, *128*, 6804–6805.

[50] I. Ibrahem, G.-L. Zhao, A. Córdova, *Chem. Eur. J.* **2007**, *13*, 683–688.

[51] For review of GLP-1, see: L. B. Knudsen, *J. Med. Chem.* **2004**, *47*, 4128–4134.

[52] For review of DPP-IV inhibitors, see: A. E. Weber, *J. Med. Chem.* **2004**, *47*, 4135–4141.

[53] a) S. D. Edmondson, A. Mastracchio, J. L. Duffy, G. J. Eiermann, H. He, I. Ita, B. Leiting, J. F. Leone, K. A. Lyons, A. M. Makarewicz, R. A. Patel, A. Petrov, J. K. Wu, N. A. Thornberry, A. E. Weber, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3048–3052; b) J. M. Janey, J. D. Armstrong III, *J. Org. Chem.* **2006**, *71*, 390–392.

[54] A. Córdova, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 7749–7752.

[55] H. Zhang, M. Mifsud, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 9630–9631.

[56] S. Mitsumori, H. Zhang, P. H.-Y. Cheong, K. N. Houk, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 1040–1041.

[57] a) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387; b) K. Sakthievel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; c) W. Notz, S. Watanabe, N. S. Chowdari, G. Zhong, J. M. Betancourt, F. Tanaka, C. F. Barbas III, *Adv. Synth. Catal.* **2004**, *346*, 1131–1140.

[58] S. S. V. Ramasastry, H. Zhang, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2007**, *129*, 288–289.

[59] a) T. Hoffman, G. Zhong, B. List, D. Shabat, J. Anderson, S. Gramatikova, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **1998**, *120*, 2768–2779; b) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170–7171; c) S. B. Tsogoeva, S. Wei, *Chem. Commun.* **2006**, 1451–1453.

[60] a) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, R. Terrell, *J. Am. Chem. Soc.* **1963**, *85*, 207–222; b) P. W. Hickmott, *Tetrahedron* **1982**, *38*, 1975–2050; c) K. Sakthivel, N. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; d) B. Kempf, N. Hampel, A. R. Ofial, H. Mayr, *Chem. Eur. J.* **2003**, *9*, 2209–2218.

[61] P. H.-Y. Cheong, H. Zhang, R. Thayumanavan, F. Tanaka, K. N. Houk, C. F. Barbas III, *Org. Lett.* **2006**, *8*, 811–814.

[62] G. L. Zhao, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 7417–7421.

[63] a) J. W. Yang, M. T. Hechevarria Fonseca, N. Vignola, B. List, *Angew. Chem. Int. Ed.* **2005**, *44*, 108–110; b) S. G. Gudlet, J. B. Tuttle, D. W. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 32–33; c) S. Mayer, B. List, *Angew. Chem. Int. Ed.* **2006**, *45*, 4193–4195; d) H. Adolfsson, *Angew. Chem. Int. Ed.* **2005**, *44*, 3340–3342.

[64] a) Y. Hayashi, J. Yamaguchi, K. Hibino, T. Sumiya, T. Urushima, M. Shoji, D. Hashizume, H. Koshimo, *Adv. Synth. Catal.* **2004**, *346*, 1435–1439; b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215.

[65] J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, Z. Kjaersgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304.

[66] I. Ibrahem, A. Córdova, *Chem. Commun.* **2006**, 1760–1762.

[67] T. Kano, Y. Yanaguchi, O. Tokuda, K. Maruoka, *J. Am. Chem. Soc.* **2005**, *127*, 16408–16409.

[68] T. Kano, Y. Hato, K. Maruoka, *Tetrahedron Lett.* **2006**, *47*, 8467–8469.

[69] Q.-X. Guo, H. Liu, C. Guo, S.-W. Luo, Y. Gu, L.-Z. Gong, *J. Am. Chem. Soc.* **2007**, *129*, 3790–3791.

[70] First *anti*-selectvie three-component Mannich reaction: L. Cheng, X. Wu, Y. Lu, *Org. Biomol. Chem.* **2007**, *5*, 1018–1020.

[71] a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289–296; b) Y. Huang, A. K. Unni, A. N. Thadani, V. H. Rawal, *Nature* **2003**, *424*, 146; c) N. T. McDougal, S. E. Schaus, *J. Am. Chem. Soc.* **2003**, *125*, 12094–12095; d) A. L. Tillman, D. J. Dixon, *Org. Biomol. Chem.* **2007**, *5*, 606–609.

[72] a) A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965; b) A. G. Wenzel, M. P. Lalonde, E. N. Jacobsen, *Synlett* **2003**, *12*, 1919–1922.

[73] a) T. Akiyama, J. Itoh, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, *43*, 1566–1568; b) M. Yamanaka, J. Itoh, K. Fuchibe, T. Akiyama, *J. Am. Chem. Soc.* **2007**, *129*, 6756–6764.

[74] a) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357; b) M. Terada, K. Sorimachi, D. Uraguchi, *Synlett* **2006**, *1*, 133–136.

[75] T. Akiyama, Y. Saitoh, H. Moriat, K. Fuchibe, *Adv. Synth. Catal.* **2005**, *347*, 1523–1526.

[76] A. Hasegawa, Y. Naganawa, M. Fushimi, K. Ishihara, H. Yamamoto, *Org. Lett.* **2006**, *8*, 3175–3178.

[77] a) P. E. Goss, R. L. Reid, D. Bailey, J. W. Dennis, *Clin. Cancer Res.* **1997**, *3*, 1077–1086; b) P. E. Goss, J. Baptiste, B. Fer-

nandes, M. Baker, J. W. Dennis, *Cancer Res.* **1994**, *54*, 1450–1457.
[78] J. W. Dennis, M. Granovsky, C. E. Warren, *Biochim. Biophys. Acta* **1999**, *1473*, 21–34.
[79] a) P. E. Goss, M. A. Baker, J. P. Carver, J. W. Dennis, *Clin. Cancer Res.* **1995**, *1*, 935–944; b) J. D. Roberts, J. L. Kelin, R. Palmantier, S. T. Dhume, M. D. George, K. Olden, *Cancer Detect. Prev.* **1998**, *22*, 455–462.
[80] a) J. P. Michael, *Nat. Prod. Rep.* **2003**, *20*, 458–475; b) N. Asano, A. Kato, A. A. Watson, *Mini-Rev. Med. Chem.* **2001**, *1*, 145–154; c) A. El Nemr, *Tetrahedron* **2000**, *56*, 8579–8629; d) W. H. Pearson, L. Guo, *Tetrahedron Lett.* **2001**, *42*, 8267–8271; e) A. T. Carmona, J. Fuentes, I. Robina, E. R. Garcia, R. Demange, P. Vogel, A. L. Winters, *J. Org. Chem.* **2003**, *68*, 3874–3883.
[81] T. Fujita, H. Nagasawa, Y. Uto, T. Hashimoto, Y. Asakawa, H. Hori, *Org. Lett.* **2004**, *6*, 827–830.
[82] M. Mango, A. Kjaersgaard, K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Eur. J.* **2003**, *9*, 2359–2367.
[83] a) H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907; b) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, *35*, 4481–4483.
[84] S. Lou, B. M. Taoka, A. Ting, S. E. Schaus, *J. Am. Chem. Soc.* **2006**, *127*, 11256–11257.
[85] a) P. Bignelli, *Gazz. Chim. Ital.* **1893**, *23*, 360. Reviews: ; b) C. O. Kappe, *QSAR Comb. Sci.* **2003**, *22*, 630–645; c) C. O. Kappe, *Eur. J. Med. Chem.* **2000**, *35*, 1043–1052; d) C. O. Kappe, A. Stadler, *Org. React.* **2004**, *63*, 1–116; e) C. O. Kappe, *Tetrahedron* **1993**, *49*, 6937–6963.
[86] a) J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 6048–6049; b) J. Song, H.-W. Shih, L. Deng, *Org. Lett.* **2007**, *9*, 603–606.
[87] a) C. Cativiela, M. D. Diaz-de-Villegas, *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599; b) M. Moreno-Mañas, E. Trepat, R. M. Sebastián, A. Vallribera, *Tetrahedron: Asymmetry* **1999**, *10*, 4211–4224; c) P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867–870; d) B. M. Trost, K. Dogra, *J. Am. Chem. Soc.* **2002**, *124*, 7256–7257; e) W. Liu, J. F. Hartwig, *Org. Lett.* **2003**, *5*, 1915–1918; f) T. Kawabata, S. Kawakami, S. Majumdar, *J. Am. Chem. Soc.* **2003**, *125*, 13012–13013; g) C. Spino, C. Gobdout, *J. Am. Chem. Soc.* **2003**, *125*, 12106–12107; h) D. B. Berkowitz, R. de la Salud-Bea, W.-J. Jahng, *Org. Lett.* **2004**, *6*, 1821–1824; i) T. Ooi, T. Miki, K. Maruoka, *Org. Lett.* **2005**, *7*, 191–193.
[88] N. S. Chowdari, J. T. Suri, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 2507–2510.
[89] T. B. Poulsen, C. Alemparte, S. Saaby, M. Bella, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 2896–2899.
[90] A. Ting, S. Lou, S. E. Schaus, *Org. Lett.* **2006**, *8*, 2003–2006.
[91] a) D. Seebach, J. L. Matthews, *Chem. Commun.* **1997**, 2015–2022; b) R. P. Chen, S. H. Gellman, W. F. DeGrado, *Chem. Rev.* **2001**, *101*, 3219–3232; c) A. Avenoza, J. H. Busto, F. Corzana, G. Jimènez-Osès, J. M. Peregrina, *Chem. Commun.* **2004**, 980–981; d) A. E. Porter, B. Weisblum, S. H. Gellman, *J. Am. Chem. Soc.* **2005**, *127*, 11516–11529; e) J. D. Sadowsky, M. A. Schmitt, H.-S. Lee, N. Umezawa, S. Wang, Y. Tomita, S. H. Gellman, *J. Am. Chem. Soc.* **2005**, *127*, 11966–11968; f) M. A. Schmitt, S. H. Choi, I. A. Guzei, S. H. Gellman, *J. Am. Chem. Soc.* **2005**, *127*, 13130–13131.
[92] A. L. Louise, J. Ye, D. J. Dixon, *Chem. Commun.* **2006**, *11*, 1191–1193.
[93] W. Zhuang, S. Saaby, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2003**, *43*, 4476–4478 and references cited therein.
[94] a) H. H. Baer, L. Urbas, *The Chemistry of the Nitro and Nitroso Groups* (Ed.: S. Patai), Interscience, New York, **1970**, part 2, p. 117; b) N. Onon, *The Nitro Group in Organic Synthesis*, 1st ed., Wiley, New York, **2001**; c) B. Westermann, *Angew. Chem. Int. Ed.* **2003**, *42*, 151–153; d) C. Palomo, M. Oiarbide, A. Mielgo, *Angew. Chem. Int. Ed.* **2004**, *43*, 5442–5444; e) J. C. Anderson, A. J. Blake, G. P. Howell, C. Wilson, *J. Org. Chem.* **2005**, *70*, 549–555.
[95] a) D. N. Sarma, R. P. Sharma, *Tetrahedron Lett.* **1985**, *26*, 371–372; b) D. H. Lloyd, D. E. Nichols, *J. Org. Chem.* **1986**, *51*, 4294–4295; c) A. G. M. Barrett, C. D. Spilling, *Tetrahedron Lett.* **1988**, *29*, 5733–5734; d) A. D. Kende, J. S. Mendoza, *Tetrahedron Lett.* **1991**, *32*, 1699–1702; e) M. A. Sturgess, D. J. Yarnberry, *Tetrahedron Lett.* **1993**, *34*, 4743–4746; f) D. Enders, J. Wiedemann, *Synthesis* **1996**, 1443–1450; g) D. Lucet, L. Toupet, T. Le Gall, C. Kioskowski, *J. Org. Chem.* **1997**, *62*, 2682–2683; h) H. Adams, J. C. Anderson, S. Peace, A. M. K. Pennell, *J. Org. Chem.* **1998**, *63*, 9932–9934; i) S. R. S. Saibabu Kotti, C. Timmons, G. Li, *Chem. Biol. Drug Design*, *67*, 101–114.
[96] a) H. W. Pinnick, *Org. React.* **1990**, *38*, 655–792; b) C. Matt, A. Wagner, C. Moiskowski, *J. Org. Chem.* **1997**, *62*, 234–235; c) J.-A. Ma, *Angew. Chem. Int. Ed.* **2003**, *42*, 4290–4299; d) R. Ballini, M. Petrini, *Tetrahedron* **2004**, *60*, 1017–1047.
[97] a) E. T. Michalson, J. Szmuszkovicz, *Prog. Drug Res.* **1989**, *33*, 135–149; b) D. Lucet, T. Le Gall, C. Mioskowski, *Angew. Chem. Int. Ed.* **1998**, *37*, 2580–2587.
[98] a) K. Yamada, S. K. Harwood, H. Gröger, M. Shibasaki, *Angew. Chem. Int. Ed.* **1999**, *38*, 3504–3506; b) K. Yamada, G. Moll, M. Shibasaki, *Synlett* **2001**, 980–982; c) N. Nishiwaki, K. R. Knudsen, K. V. Gothelf, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2001**, *40*, 2992–2995; d) K. R. Knudsen, T. Risgaard, N. Nishiwaki, K. V. Gothelf, K. A. Jørgensen, *J. Am. Chem. Soc.* **2001**, *123*, 5843–5844; e) K. R. Knudsen, K. A. Jørgensen, *Org. Biomol. Chem.* **2005**, *3*, 1362–1364; f) J. C. Anderson, A. J. Blake, G. P. Howell, C. Wilson, *J. Org. Chem.* **2005**, *70*, 549–555; g) J. C. Anderson, G. P. Howell, R. M. Lawrence, C. J. Wilson, *J. Org. Chem.* **2005**, *70*, 5665–5670; h) C. Palomo, M. Oiarbide, R. Halder, A. Laso, R. López, *Angew. Chem. Int. Ed.* **2006**, *45*, 117–120.
[99] a) D. P. Curran, L. H. Kuo, *Tetrahedron Lett.* **1995**, *36*, 6647–6650; b) M. S. Sigman, E. N. Jacbosen, *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902; c) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289–296; d) M. Pihko, *Angew. Chem. Int. Ed.* **2004**, *43*, 2062–2064; e) G. D. Joly, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 4102–4103; f) D. E. Fuerst, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 8964–8965; g) D. J. Dixon, R. D. Richardson, *Synlett* **2006**, *1*, 0081–0085.
[100] a) D. P. Curran, L. H. Kuo, *J. Org. Chem.* **1994**, *59*, 3259–3261; b) B. R. Linton, S. M. Goodman, A. D. Hamilton, *Chem. Eur. J.* **2000**, *6*, 2449–2455; c) P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867–890; d) P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014; e) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12671–12673; f) A. G. Wenzel, M. P. Lalonde, E. N. Jacobsen, *Synlett* **2003**, 1919–1922; g) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 10558–10559; h) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299–4306; i) S. H. Cooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 2–6; j) B. Vakulya, S. Varga, A. Csampai, T. Soos, *Org. Lett.* **2005**, *7*, 1967–1969; k) Y. Hoashi, T. Okino, Y. Takemoto, *Angew. Chem. Int. Ed.* **2005**, *44*, 4032–4035; l) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481–4483; m) S. B. Tsogoeva, D. A. Yalalov, M. J. Hateley, C. Weckbecker, K. Huthmacher, *Eur. J. Org. Chem.* **2005**, *45*, 4995–5000; n) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125; o) X. Xu, T. Yabuta, P. Yuan, Y. Takemoto, *Synlett* **2006**, *1*, 137–140.
[101] a) T. Okino, A. Nakamura, T. Furukawa, Y. Takemoto, *Org. Lett.* **2004**, *6*, 625–627; b) X. Xu, T. Furukawa, T. Okino, H. Miyabe, Y. Takemoto, *Chem. Eur. J.* **2006**, *12*, 466–476.
[102] T. P. Yoon, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2005**, *44*, 466–468.
[103] L. Bernardi, F. Fini, R. P. Herrera, A. Ricci, V. Sgarzani, *Tetrahedron* **2006**, *62*, 375–380.
[104] C. M. Bode, A. Ting, S. E. Schaus, *Tetrahedron* **2006**, *62*, 11499–11505.
[105] B. Vakulya, S. Varga, A. Csampai, T. Soos, *Org. Lett.* **2005**, *7*, 1967–1969.

[106] a) Moeluclar Operating Environment 2004.03, MOE, Chemical Computing Group: Montreal, Quebec, Canada; b) T. A. Halgreen, *J. Comput. Chem.* **1996**, *17*, 490–519.
[107] Similar models have been proposed for diastereoselective β-keto ester additions to nitrooelfins, see: a) H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907; b) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem. Int. Ed.* **2005**, *44*, 105–108. For conformational studies of cinchona alkaloid catalyst reactions, see: c) G. S. Cortez, S. H. Oh, D. Romo, *Synthesis* **2001**, 1731–1736; d) A. E. Taggi, A. M. Hafez, T. Dudding, T. Lectka, *Tetrahedron* **2002**, *58*, 8351–8356.
[108] a) B. M. Nugent, R. A. Yoder, J. N. Johnston, *J. Am. Chem. Soc.* **2004**, *126*, 3418–3419; b) A. Singh, R. A. Yoder, B. Shen, J. N. Johnston, *J. Am. Chem. Soc.* **2007**, *129*, 3466–3467.
[109] L. Bernardi, B. F. Bonini, E. Capitò, G. Dessole, M. Comes-Franchini, M. Fochi, A. Ricci, *J. Org. Chem.* **2004**, *69*, 8168–8171.

Received: May 6, 2007
Published Online: August 28, 2007

