

CATALYTIC ENANTIOSELECTIVE MANNICH REACTIONS

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INTRODUCTION

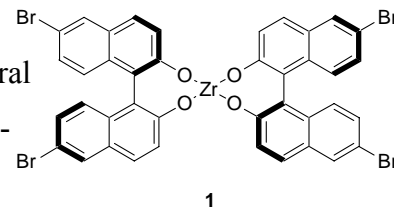
Enantiomerically pure natural and nonnatural α -amino acids, β -amino carbonyl compounds, and β -amino alcohols are useful chiral building blocks for biologically active compounds.¹ Of the many methods which have been developed for the synthesis of these compounds, catalytic asymmetric processes are most promising.^{2,3} To date, the majority of the efforts directed toward the construction of these compounds by asymmetric catalysis have focused on C-C and C-N bond forming reactions. Among catalytic asymmetric C-C bond forming reactions, the Strecker and Mannich reactions have received the most attention. Catalytic asymmetric Mannich-type reactions are perhaps the most versatile with the potential to set two adjacent stereocenters simultaneously during C-C bond formation.⁴

The classic Mannich reaction involves the reaction of an imine or iminium ion with a C-H acidic compound such as a ketone or ester to afford an aminoalkylated product. While Carl Mannich was not the first to describe the reaction that bears his name, he is credited with being the first to recognize the reaction's enormous significance and developing it into a useful synthetic methodology.⁵ Several diastereoselective variants of the Mannich-type reaction have been reported,⁶ but enantioselective variants have only recently been explored. Corey and coworkers⁷ in 1991 and Yamamoto and coworkers⁸ in 1994 reported the first cases of enantioselective Mannich-type reactions; however, in both of these cases stoichiometric amounts of chiral sources were required. This review focuses on recent developments in metal- and non-metal-catalyzed asymmetric Mannich-type reactions.

METAL-CATALYZED MANNICH-TYPE REACTIONS

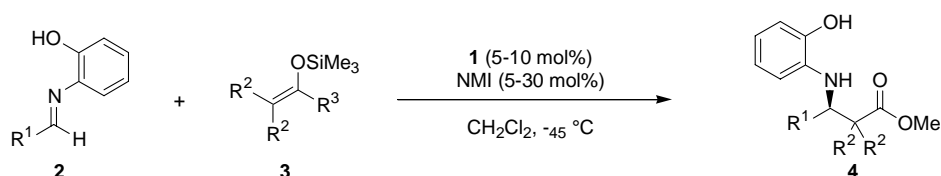
Zirconium-Catalyzed Mannich-Type Reaction

Kobayashi and co-workers reported the first catalytic enantioselective Mannich-type reactions of imines with silyl ketene acetals using chiral zirconium catalyst **1**.^{9, 10} Aryl imines derived from aryl aldehydes and 2-amino phenol were treated with silyl ketene acetals in the presence of 5-10 mol % of zirconium catalyst **1** and 5-30 mol % of N-methyl imidazole (NMI) to provide β -amino esters in high yields and excellent enantiomeric ratios (Table 1). Imines derived from 2-amino phenol were necessary presumably to ensure bidentate chelation to the catalyst. It was thought that two-point binding of the imine to the catalyst would prevent *E/Z* isomerization of the imine and thus reduce the number of possible transition states and possible erosion of enantioselectivity. While the role of NMI is



not fully understood, it was shown to be necessary to obtain high levels of enantioselectivity. The authors proposed that NMI was responsible for generating a monomeric catalyst in solution. This hypothesis was supported by the observation that a white precipitate formed upon combining $Zr(OtBu)_4$ and 6,6'-dibromo-1,1'-bi-2-naphthol in dichloromethane, and the precipitate dissolved completely when NMI was added. This methodology, while providing good yields and excellent enantiomeric ratios, suffers from a lack of substrate scope in that only imines derived from 2-amino phenol were functional. In addition, this methodology suffers from the need to pre-form silyl ketene acetals and is thus not a direct Mannich method in which enolate formation and subsequent aminoalkylation occur in the same reaction vessel.

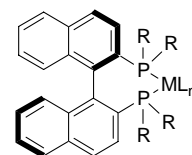
Table 1. Zr-Catalyzed Asymmetric Mannich-Type Reaction



entry	R ¹	R ²	R ³	% yield	er
1	Ph	Me	OMe	70	94: 6
2	1-naphthyl	Me	OMe	quant	96: 4
3	Ph	H	SEt	78	94: 6
4	1-naphthyl	H	SEt	quant	99:1
5	C ₆ H ₁₁	H	SEt	89	95: 5

Late Transition Metal-Catalyzed Asymmetric Mannich-Type Reaction of α -Imino Esters

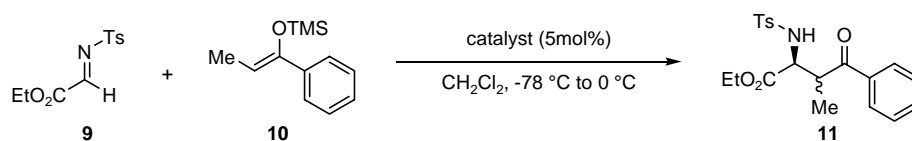
Lectka and coworkers reported the first late transition metal-catalyzed Mannich-type reactions of silyl enol ethers with α -imino esters.^{11,12} The reaction involves slow addition of the silyl enol ether to a solution of α -imino ester in the presence of 5 mol % of catalyst (Table 2). α -Amino esters were obtained in excellent yields with varying levels of diastereoselectivity and enantioselectivity. α -Imino esters are excellent substrates for this reaction for two reasons. The electron withdrawing nature of an α -ester provides additional activation of the imine for nucleophilic attack. In addition, the imine nitrogen and the carbonyl oxygen of the ester are capable of two point binding to the catalyst, this five membered chelate ring should provide additional rigidity to the activated complex and thus enhance selectivity. Lectka and coworkers supported their proposal of chelate formation between the α -imino ester and the Cu(I) catalyst by FTIR studies. Upon addition of one equivalent of catalyst **7**, the ester carbonyl band of **9** shifted from 1735 cm^{-1} to 1697 cm^{-1} , while the



- 5, R = Ph, ML_n = AgSbF₆
 6, R = Ph, ML_n = Pd(ClO₄)₂
 7, R = Ph, ML_n = CuClO₄
 8, R = 4-MePh, ML_n = CuClO₄

imine absorption band shifted from 1630 cm^{-1} to 1618 cm^{-1} . They also demonstrated that without possible chelate formation, much of the selectivity was lost as was the case with simple imines that reacted sluggishly and produced products with nearly no enantiomeric enrichment. While a number of ligands were screened the highest levels of diastereo- and enantioselectivities were observed when Tol-BINAP (**8**) was used as the ligand. A reversal of diastereoselectivity, from *anti* to *syn*, was observed when Pd-complex **6** was employed in the reaction to afford the desired product in a 1:4 *anti/syn* ratio with modest enantioselectivity. This methodology lacks substrate scope as only α -imino esters react efficiently and, like the Kobayashi methodology described previously, suffers from the drawback of requiring pre-formed silyl enol ethers rather than a direct Mannich protocol.

Table 2. Late Transition Metal-Catalyzed Asymmetric Mannich Reaction



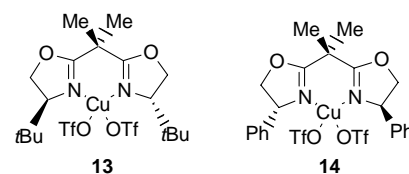
entry	catalyst	% yield	anti:syn	er
1	7	80	10:1	96:4
2	8	86	25:1	99:1
3	12	86	1.3:1	-
4	6	81	1:4	69:31

12 = $\text{CuClO}_4 \cdot (\text{PPh}_3)_2 \cdot (\text{CH}_3\text{CN})_2$

Chiral Copper (II) Complex-Catalyzed Asymmetric Mannich-Type Reaction of α -Imino Esters

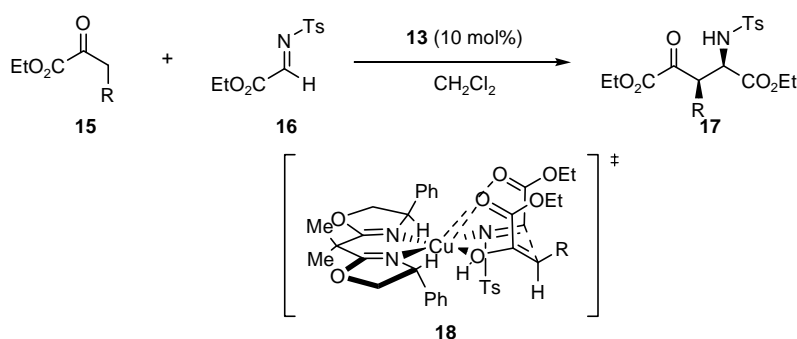
Jørgensen and coworkers recently demonstrated the first catalytic diastereo- and enantioselective Mannich-type reactions of pyruvates with α -imino esters using chiral copper complexes.¹³ They had previously demonstrated the utility of these catalysts in enantioselective homo-aldol reactions of pyruvates¹⁴ and asymmetric

α -amination reactions of β -keto esters.¹⁵ A variety of chiral Lewis acids were screened and copper (II) was found to possess the properties necessary to catalyze this asymmetric Mannich-type reaction. The procedure affords 4-oxo-glutamic acid ester derivatives in good yields and diastereoselectivities, and with excellent enantioselectivities. In this reaction, the chiral copper complex acts both as a catalyst for the *in situ* generation of the enol pyruvate, and as a catalyst for the stereoselective addition step (Table 3). In sharp contrast to the previous examples by Kobayashi and Lectka where the catalyst is believed to complex only the imine and directs the approach of the enolate, the copper catalyst in this system is believed to complex both the enolate and imine. In this reaction, catalyst **14** proved superior in terms of



yields, *syn/anti* selectivities, and enantioselectivities. Jørgensen proposed transition state **18** in which both the enol and imino ester are coordinated to copper. In the proposed six-membered chairlike transition state, the enol coordinates to the metal in a bidentate fashion with the R substituent of the enol in the less sterically encumbered equatorial position. The (*E*)-configured imine coordinates to the copper in a bidentate manner with the tosyl group in a pseudo axial position. This methodology provides 4-oxo-glutamic acid ester derivatives without the need for pre-formed enolates. However, it suffers from lack of substrate scope in that only activated carbonyl compounds such as pyruvates in combination with α -imino esters provide products in high yields.

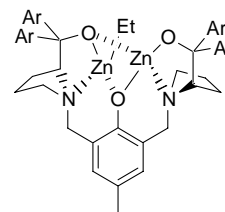
Table 3. Cu (II)-Catalyzed Direct Asymmetric Mannich-Type Reaction with Imino esters



entry	R	% yield	dr	er
1	H	70	-	95:5
2	Me	89	>10:1	99:1
3	Bn	94	>10:1	99:1
4	Br	79	3:1	89:11

Zinc-Catalyzed Direct Asymmetric Mannich-Type Reaction of α -Imino Esters

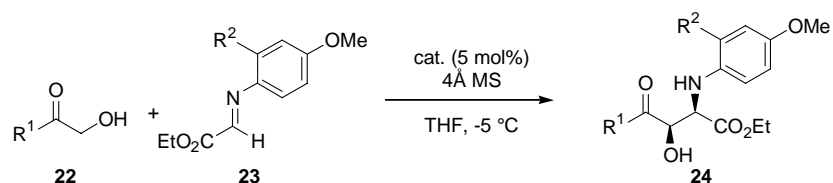
Trost and coworkers recently reported the first example of zinc catalyzed direct asymmetric Mannich-Type reactions to furnish 1,2 amino alcohols.¹⁶ In these reactions, aromatic hydroxy ketones react with α -imino esters or imines derived from aromatic aldehydes in the presence of a catalytic amount of the dinuclear zinc catalyst **19**. This affords 1,2 *syn*-amino alcohols in good yield and high levels of diastereo- and enantioselectivities (Table 4). The dinuclear zinc catalyst was originally developed for a direct catalytic enantioselective aldol reaction.¹⁷ It is believed that reaction of hydroxy ketone **22** with the bimetallic catalyst **20** liberates one equivalent of ethane and initiates the catalytic cycle. The role of the two proximal zinc centers is to provide both a zinc atom to form the required enolate and a second zinc atom to coordinate to the imine as a Lewis Acid. During optimization of this reaction, it was discovered that the highest yields and diastereoselectivities were obtained with



19, Ar = phenyl
20, Ar = 4-biphenyl
21, Ar = β -naphthyl

dinuclear zinc catalyst **20**. It is interesting to note that the absolute stereochemistry of the Mannich products is opposite of that observed for the aldol products. Trost and co-workers propose that this observation might arise from the fact that lone pair coordination in the case of aldehydes occurs anti to the bulky group but is syn in the case of imines. This methodology, like that of Jørgensen, does not require pre-formed enolates and suffers from being limited to N-aryl α -iminoesters.

Table 4. Zn-Catalyzed Direct Asymmetric Mannich-Type Reaction

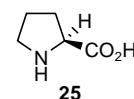


entry	R ¹	R ²	cat.	% yield	dr	er
1	Ph	H	19	76	6.5: 1	98: 2
2	Ph	CH ₃	20	92	12: 1	99: 1
3	<i>p</i> -MeO-Ph	CH ₃	19	75	2: 1	97: 3
4	<i>2</i> -furyl	CH ₃	20	81	8: 1	99: 1

NON-METAL CATALYZED MANNICH-TYPE REACTIONS

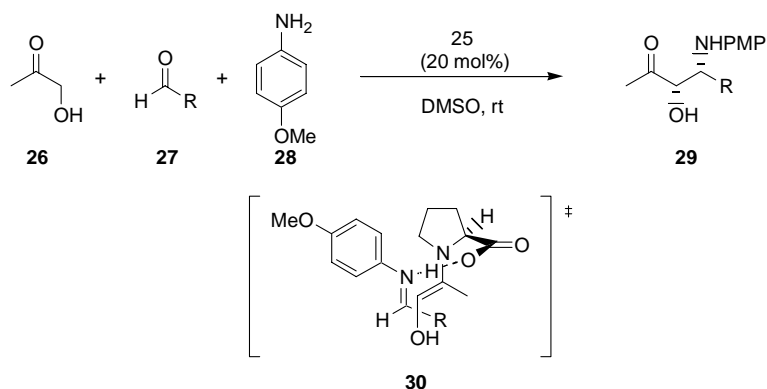
Proline Catalyzed Asymmetric Mannich-Type Reaction

Proline has been shown to catalyze a variety of important transformations including direct aldol reactions, α -aminations of aldehydes and ketones, and Diels Alder reactions.¹⁷ Several groups, including those of List¹⁸ and Barbas¹⁹, have reported the use of proline as a catalyst for direct asymmetric Mannich-type reactions. While these approaches parallel each other in the use of proline as a catalyst, they differ in the imine component used. Perhaps the most valuable of these methodologies was developed by List and co-workers. They reported the first proline catalyzed direct asymmetric three-component Mannich reaction. As opposed to many other catalytic asymmetric Mannich-type reactions that utilize pre-formed enolates, pre-formed imines, or both, this methodology requires neither. Direct aldol and Mannich reactions typically compete with one another if imines and enol equivalents are not pre-formed. Therefore, List and coworkers carefully selected amines and aldehydes that had good rates of reaction and large equilibrium constants favoring imine formation. The procedure involves addition of (S)-Proline (**25**) to a solution of aryl aldehyde **27**, *p*-methoxyaniline (**28**), and a simple aliphatic ketone in DMSO. When hydroxyacetone (**26**) is used as the ketone component, the reaction provides the corresponding *syn*-1,2-amino alcohols (**29**) in high yields and excellent levels of diastereo- and enantioselectivities (Table 5). Aliphatic aldehydes were tolerated but gave lower yields



and selectivities. In order to explain the observed stereoselectivity, it was proposed that the reaction follows an enamine mechanism and involves open transition state **30**. In transition state **30**, (*E*)-configurations are assumed for both the enamine and the imine. These two components interact in such a way as to avoid steric interaction between the N-substituent and the proline ring. Approach of the imine to the *si*-face of the enamine is potentially assisted by hydrogen-bonding between the proline carboxylate and the imine. While this reaction provides product in good yields and excellent diastereo- and enantioselectivities, it suffers from being limited to imines generated from anilines and aryl aldehydes.

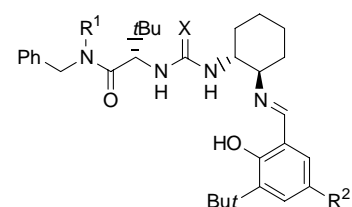
Table 5. Proline-Catalyzed Asymmetric Mannich Reaction



entry	R	% yield	dr	er
1		92	20:1	99:1
2		88	15:1	99:1
3		83	9:1	97:3
4		88	3:1	81:19
5		57	17:1	83:17

Urea-Catalyzed Asymmetric Mannich-Type Reaction

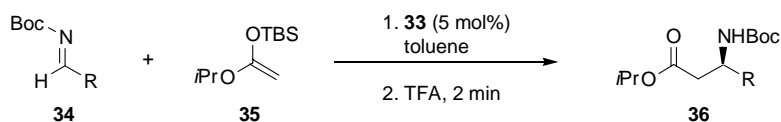
One major drawback of all metal-catalyzed and proline-catalyzed asymmetric Mannich-type reactions is that they are restricted to imines bearing N-aryl substituents. Often these aryl groups can be difficult to remove from the amine products. Therefore a catalytic asymmetric Mannich-type reaction that employs imines with easily removable protecting groups would be an attractive methodology. Jacobsen and co-



- 31:** R¹ = H, R² = OCO(^tBu), X = O
32: R¹ = H, R² = OCO(^tBu), X = S
33: R¹ = Me, R² = ^tBu, X = S

workers recently reported a urea-catalyzed asymmetric Mannich-type reaction employing N-Boc imines.^{20,21} The procedure consists of reaction between silyl ketene acetals (**35**) and N-Boc aryl imines (**34**) catalyzed by thiourea **33** (Table 6). Urea derivatives of general structure **31** have been used as catalysts for asymmetric Strecker reactions.²² It was found that the rate of the uncatalyzed racemic Mannich-type reaction was substantial at 23 °C. During optimization of this reaction, several factors were found to increase the rate of the catalyzed reaction, in particular catalyst structure. Replacement of the urea moiety in **31** with a thiourea group, as in **32**, resulted in a dramatic increase in the rate of the catalyzed reaction. The increased rate of reaction with **32** permitted the use of lower reaction temperatures and thus increased the yields and enantioselectivities of the products. Further catalyst optimization was achieved through systematic variation in salicyladimine, diamine, amino acid, and amide components. The resulting small library of 22 catalysts revealed with thiourea catalyst **33**, which achieved the highest levels of enantioselectivity. This catalytic asymmetric Mannich-type reaction, unlike previously discussed reactions, provides N-Boc protected β -amino acid derivatives in excellent yields and enantioselectivities. Although this reaction relies on pre-formed silyl ketene acetals, and thus is not a direct Mannich-type reaction, the use of N-Boc protected imines represents a major advance.

Table 6. Urea-Catalyzed Asymmetric Mannich-Type Reaction with N-Boc Imines



entry	R	temp (°C)	% yield	er
1	Ph	-40	95	99:1
2	<i>p</i> -OMeC ₆ H ₄	4	91	93:7
3	1-naphthyl	-30	93	94:6
4	3-pyridyl	-30	99	99:1

CONCLUSION

Significant advances in the development of efficient methods for the synthesis of enantiomerically pure α -amino acids, β -amino carbonyls, and β -amino alcohols by way of catalytic asymmetric Mannich-type reactions have recently been made. Metal catalyzed asymmetric Mannich-type reactions utilizing zirconium, copper, and zinc complexes in combination with various asymmetric ligands offer powerful catalytic methods for the construction of these desired building blocks. The recent addition of the asymmetric Mannich reaction to the ever increasing list of proline catalyzed reactions offers a method in which an inexpensive organocatalyst can be used to construct the aforementioned products. While all of these methods represent major advances in the development of

efficient catalytic asymmetric Mannich-type reactions, there are still several areas that need improvement. Future work should focus on the development of direct catalytic methodologies that utilize structurally diverse imines with easily removable N-protecting groups.

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