Asymmetric Organocatalysis

Direct Organocatalytic Enantioselective Mannich Reactions of Ketimines: An Approach to Optically Active Quaternary α-Amino Acid Derivatives**

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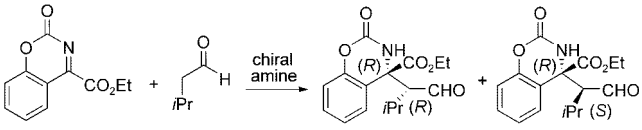
The Mannich reaction is an effective C–C bond-forming process for the construction of nitrogen-containing compounds, such as α- and β-amino acid derivatives, as well as a variety of natural products.[1] The catalytic enantioselective addition of preformed nucleophiles, such as silyl ketene acetals and silyl enol ethers, to imines is well established,[2] but only recently were the first examples of direct enantioselective Mannich reactions reported. By the use of either bifunctional chiral Lewis acid complexes[3] or secondary chiral amines[4] as the catalyst for the reaction of imines with unmodified carbonyl donors, the formation of the corresponding optically active Mannich bases has been reported.

However, despite the tremendous amount of work and effort devoted to the development of efficient and versatile Mannich reactions, the structure of the electrophile has been restricted to imines derived from aldehydes. The organocatalytic enantioselective Mannich reaction of imines derived from ketones (ketimines) is to date unprecedented,[5] although substrates such as α-substituted α-ketimino esters would constitute an interesting template for the synthesis of quaternary α- and β-amino acids.[6,7]

As a result of the tetrasubstituted asymmetric carbon atom, quaternary α-amino acids are considerably more stable than tertiary α-amino acid derivatives, and therefore problems of metabolic degradation, for example, of peptidomimetics, may be avoided. Moreover, α,α-disubstituted α-amino acids exert a remarkable influence on the conformation of peptides into which they are incorporated.[8] Finally, non-natural α-aryl α-alkyl α-amino acid derivatives have shown strong inhibitory effects on aldose reductases, that is, as potential drugs for the treatment of various diabetes-related diseases.[9] Herein the development of the first direct organocatalyzed enantioselective Mannich reaction of ketimines and unmodified aldehydes is presented.

Ketimines are in general less reactive towards nucleophilic additions than aldimines owing to steric hindrance in the C–C bond-forming step, as well as electronic effects. A series of ketimines **1a–f** (see Supporting Information) in which the protecting group on the nitrogen atom is intrinsically bound to an α-aryl substituent of the imine were prepared.[5] The anchoring of the protecting group in this way overcomes the above-mentioned problems by minimizing the degree of rotational freedom and by blocking the *E*/*Z* isomerization of the imine double bond. Consequently, and also as a result of the induced ring strain, ketimines **1a–f** showed high reactivity towards a variety of nucleophiles, in striking contrast to their non-anchored analogues.[5,10] The reaction of ketimine **1a** with isovaleraldehyde (**2a**) was investigated as the model reaction, and a survey of different chiral amines as catalysts was carried out (Table 1).

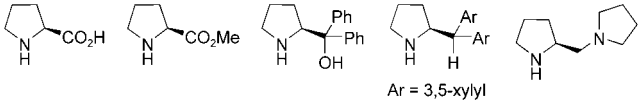
Table 1: Direct organocatalytic asymmetric Mannich reaction of ketimine **1a** with **2a**.



1a **2a** **3a** **4a**

Entry	Catalyst (mol%)	*T* [°C]	**2a** [equiv]	Solvent	Yield[a] [%]	**3a**/**4a**[b]	*ee*[c] [%]
1	**5a** (30)	0	5	CH_2Cl_2	84	1:8	82
2	**5b** (30)	0	5	CH_2Cl_2	11	>20:1	7
3	**5c** (30)	0	5	CH_2Cl_2	trace	>20:1	–
4	**5d** (30)	0	5	CH_2Cl_2	39	>20:1	80
5	**5e** (30)	0	5	CH_2Cl_2	56	15:1	86
6	**5e** (5)	0	5	CH_2Cl_2	73	2:1	88
7	**5e** (5)	0	5	Et_2O	74	19:1	90
8	**5e** (5)	0	2	Et_2O	99	>20:1	91
9	**5e** (5)	−24	2	Et_2O	51	17:1	92
10	**5e** (2)	0	2	Et_2O	93	18:1	91

[a] Combined yield of the two isolated diastereomeric products. [b] The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product mixture. [c] The *ee* of the major product was determined by HPLC on a Daicel Chiralpak AS column.



5a **5b** **5c** **5d** **5e**

Initial experiments were performed with L-proline (**5a**; 30 mol%) as the catalyst and with 5 equivalents of the aldehyde donor. The reaction proceeded smoothly to afford the desired Mannich products in a combined yield of 84% with a diastereomeric ratio of 1:8 in favor of **4a** (82% *ee*; Table 1, entry 1). The more soluble methyl ester of L-proline also promoted the reaction of ketimine **1a** with **2a**, but the yield dropped to 11%, the diastereoselectivity was inversed (>20:1), and the enantioselectivity was almost completely eroded (7% *ee*) (Table 1, entry 2). The L-proline-derived catalyst **5c** was a poor catalyst for this reaction (Table 1, entry 3). However, the removal of the hydroxy group and introduction of sterically demanding aryl substituents provided the catalyst **5d**, which showed good stereoselectivity

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[**] This work was made possible by a grant from The Danish National Research Foundation. We are grateful to Dr. R. G. Hazell for X-ray crystallographic analysis.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  DOI: 10.1002/ange.200460158

(d.r. > 20:1, 80% *ee*), although it had only a moderate turnover number (39% yield). The chiral diamine (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine (**5e**) finally proved to be the catalyst of choice, and under the same conditions afforded the Mannich product in 56% yield, with a d.r. of 15:1 and with 86% *ee* for the major diastereomer (Table 1, entry 5). By lowering the amount of catalyst and aldehyde to 5 mol% and 2.0 equivalents, respectively, and changing the solvent to Et_2O, it was possible to prepare **3a** in almost quantitative yield (99%), with excellent diastereoselectivity (> 20:1), and with 91% *ee* (Table 1, entries 6–8). Lowering of the temperature only had a minimal effect on the enantioselectivity (Table 1, entry 9), but the Mannich reaction could be carried out in the presence of only 2 mol% of the catalyst without compromising the yield or enantioselectivity (Table 1, entry 10).

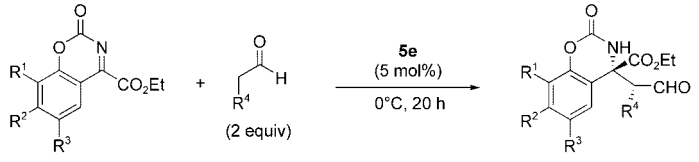
Having optimized the reaction conditions, we investigated the scope of the reaction by treating a series of ketimines **1a–f** with aldehyde donors **2a–c**, as summarized in Table 2. Imines bases **3e**,**f** with 87 and 84% *ee*, respectively (Table 2, entries 5 and 6).

The best results with propionaldehyde (**2b**) as the substrate in the reaction with ketimine **1a** were obtained in CH_2Cl_2. The major diastereomer **3g** (d.r. 5:1) was formed in good yield and with high enantioselectivity (95% *ee*; Table 2, entry 7). Finally, when unsaturated 4-pentenal (**2c**) was used as the aldehyde donor, the Mannich base **3h** was isolated in 82% yield with an excellent optical purity of 98% *ee* (Table 2, entry 8).

It was demonstrated previously that these cyclic carbamates are readily cleaved under basic solvolytic reaction conditions to liberate the phenolic hydroxy group.[5] By this protocol, triflate-substituted aryl compounds are potentially accessible for further elaboration, such as palladium-catalyzed cross-coupling reactions and deoxygenation.

The absolute and relative configuration of the Mannich products **3** and **4** was determined by X-ray crystallography and by comparison of HPLC traces and signs of optical rotation (see Supporting Information). The condensation of **3f** (84% *ee*) with 2,4,6-trichlorophenylhydrazine and subsequent crystallization from acetone provided optically pure crystals of the corresponding chiral hydrazone which were suitable for X-ray crystallographic analysis.

Table 2: Reaction of ketimines **1a–f** with aldehydes **2a–c** under the optimized reaction conditions.



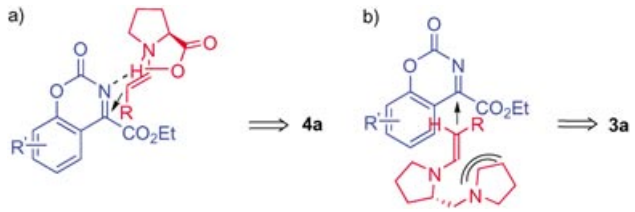
Entry	Imine	Solvent	R^1	R^2	R^3	R^4	Product	Yield [%][a]	**3**/**4**[b]	*ee* [%][c]
1	**1a**	Et_2O	H	H	H	*i*Pr	**3a**	99	> 20:1	91
2	**1b**	Et_2O	H	H	Me	*i*Pr	**3b**	98	6:1	89
3	**1c**	Et_2O	H	H	OMe	*i*Pr	**3c**	95	9:1	86
4	**1d**	Et_2O	H	H	F	*i*Pr	**3d**	97	19:1	83
5	**1e**	Et_2O	H	OMe	H	*i*Pr	**3e**	90	> 20:1	87
6	**1f**	Et_2O	$-C_4H_4-$		H	*i*Pr	**3f**	93	> 20:1	84
7	**1a**	CH_2Cl_2	H	H	H	Me	**3g**	72	5:1	95
8	**1a**	CH_2Cl_2	H	H	H	allyl	**3h**	82	4:1	98

[a] Combined yield of the two isolated diastereomeric products. [b] The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product. [c] The *ee* value for the major product (with *R* configuration at the quaternary stereocenter) was determined by HPLC on a chiral stationary phase (see Supporting Information for details).

Based on the absolute configuration of the product, attack at the *Si* face of the ketimine was observed for all catalysts **5a–e** tested. However, a very interesting reversal of diastereoselectivity was found when the carboxylic acid functionality of L-proline (**5a**) was substituted for a non-acidic or basic substituent (Table 1, entry 1 versus entries 2–5). The observed stereoselectivity with L-proline as the catalyst is in good agreement with the transition-state models proposed by Córdova and Barbas,[4f] List et al.,[4d] and Bahmanyar and Houk[11] for the catalytic enantioselective Mannich reaction of imines derived from glyoxylic aldehydes. We propose that L-proline directs reaction at the *Re* face of the enamine, and the transition-state model in Scheme 1a may account for the stereochemistry of the Mannich product **4a** observed.

with an electron-donating substituent (a methyl or a methoxy group) in the 4-position underwent a clean reaction with isovaleraldehyde (**2a**) in the presence of the catalyst **5e** (5 mol%). Upon filtration of the reaction mixture through a column of silica gel, the corresponding products **3b**,**c** were isolated in very high yields, with good diastereomeric ratios of 6:1 and 9:1, and with 89 and 86% *ee*, respectively (Table 2, entries 2 and 3). The reaction of the 4-fluoro-substituted ketimine **1d** afforded the Mannich product **3d** in nearly quantitative yield (97%) with excellent diastereoselectivity (19:1) and 83% *ee* (Table 2, entry 4). The 3-methoxy-substituted and 1-naphthol-derived ketimines **1e**,**f** were also successfully employed as substrates in the reaction with aldehyde **2a** to give the diastereomerically pure Mannich

In contrast, when **5e** was used as the catalyst, interactions such as hydrogen bonding between the enamine intermediate and the lone pair of electrons on the nitrogen atom of the ketimine can not occur, as the reaction is conducted under neutral conditions.[12] The concept of intrinsic protecting-group anchoring inherently rules out the possibility of *E*/*Z* isomerization of the ketimine, and a linear transition state in which the *Si* face of the enamine approaches the *Si* face of the imino electrophile may explain the observed stereochemistry



Scheme 1. A schematic representation of the approach of the ketimine to two enamine intermediates that accounts for the observed diastereoselectivities: a) reaction occurs at the *Si* face of the imine and the *Re* face of the enamine; b) reaction occurs at the *Si* face of the imine and the *Si* face of the enamine.

(Scheme 1b).[13] An *E* geometry of the enamine double bond is anticipated on the basis of energy calculations, and an antiperiplanar approach of the reaction partners would minimize steric repulsions in the C–C bond-forming step.

In conclusion, we have reported the first organocatalytic enantioselective Mannich reaction of ketimines and unmodified aldehydes based on the concept of intrinsic protecting-group anchoring. Under the catalysis of chiral secondary amines (2–5 mol%), optically active quaternary α-amino acid derivatives were formed in high yields (72–99%) with optical purities ranging from 83 to 98% *ee*. Depending on the choice of catalyst, either diastereomer of the Mannich base can be prepared.

Received: March 30, 2004 [Z460158]

Keywords: amino acids · chiral amines · Mannich bases · organocatalysis · quaternary stereocenters

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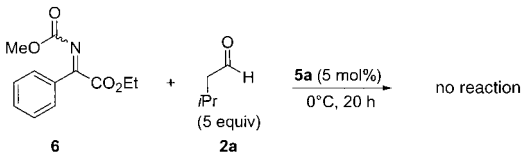
[10] The ketimine **6**, without intrinsic protecting-group anchoring, did not react with isovaleraldehyde (**2a**) in the presence of 5 mol% of L-proline (**5a**).



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