Asymmetric Catalysis

DOI: 10.1002/anie.200803515

Proline-Catalyzed Highly Enantioselective and *anti*-Selective Mannich Reaction of Unactivated Ketones: Synthesis of Chiral α-Amino Acids**

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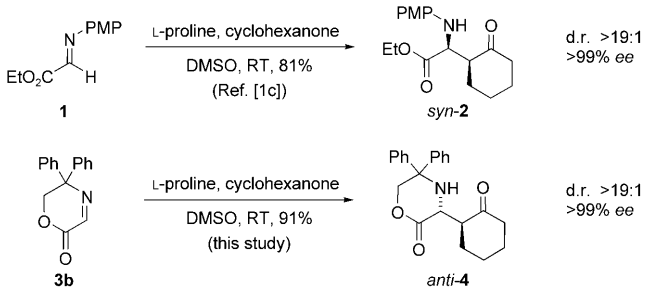
Dedicated to Professor Manfred T. Reetz on the occasion of his 65th birthday

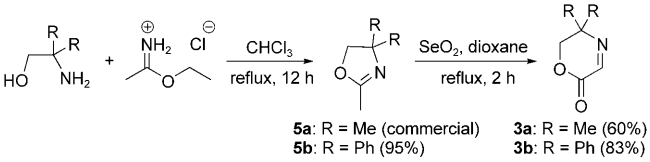
Mannich reactions have proved very useful for the synthesis of enantiomerically pure amino alcohol, aminocarbonyl, and amino acid derivatives, which are important structural motifs of biologically active molecules. In this respect, the development of enantioselective organocatalytic Mannich reactions, particularly those catalyzed by proline, represents a major advancement.[1,2] In contrast to metal-catalyzed methods that require the use of enol ethers and other preformed nucleophiles, pyrrolidine-based catalysts enable the direct and atom-economical coupling of aldehydes or ketones with imines by in situ enamine formation. Furthermore, by using proline or related amine organocatalysts, Mannich products can be formed with two adjacent stereocenters, predominantly in the *syn* configuration.[3] The use of iminoglyoxylates, such as **1**, as electrophiles is of particular interest, as valuable α-amino acid derivatives, such as **2**, are formed (Scheme 1).[3c–e] The development of a direct *anti*-selective Mannich reaction has been a longstanding challenge. Interestingly, the use of 3-pyrrolidinecarboxylic acid (β-proline) in place of 2-pyrrolidinecarboxylic acid (proline or α-proline) leads to an inversion of the selectivity and, thus, the preferential formation of *anti* products.[4] However, β-proline, although of low structural complexity, requires a 5- to 10-step synthesis.[5]

We have developed a highly enantio- and *anti*-selective Mannich reaction of unactivated ketones and readily available cyclic imines **3** with simple L-proline as the catalyst (Scheme 1). The Mannich products are interesting α-amino acid derivatives that contain a new protecting group. Facile hydrogenolytic one-step cleavage of the protecting group under mild conditions provides free α-amino acids with unchanged stereoisomeric purity, as indicated by NMR spectroscopy.



Scheme 1. Proline-catalyzed Mannich reactions with representative selectivities. DMSO = dimethyl sulfoxide, PMP = *p*-methoxyphenyl.

Typically, acyclic imines are employed as substrates in organocatalytic Mannich reactions. We reasoned that cyclic iminoglyoxylates **3**[6] would be useful alternative imine substrates locked in a *Z* configuration.[7,8] The change in the configuration of the imine double bond should result in the formation of *anti*-configured amino acid derivatives. Imines **3** can be prepared readily from commercially available starting materials (Scheme 2). The key step of the synthesis is the SeO_2-mediated rearrangement of the 4,4-disubstituted 2-methyl-1,3-oxazoline **5** to the desired 5,5-disubstituted 5,6-dihydro-1,4-oxazin-2-one **3**.[8]



Scheme 2. Synthesis of the acceptors.

At the outset of our study, we compared the 5,5-dimethyl- and 5,5-diphenyl-substituted imine substrates **3a** and **3b**. Both imines reacted with cyclohexanone to give the corresponding Mannich product with high diastereo- and enantioselectivity (Table 1, entries 1 and 2). Owing to the higher levels of selectivity observed with dihydrooxazinone **3b**, this imine was selected for further L-proline-catalyzed reactions

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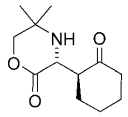
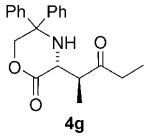
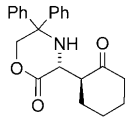
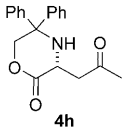
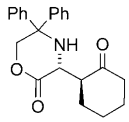
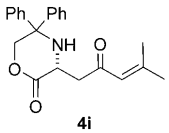
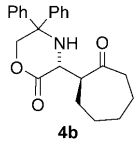
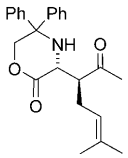
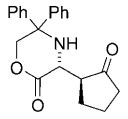
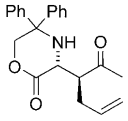
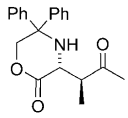
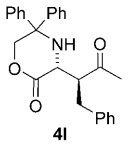
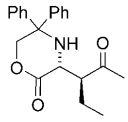
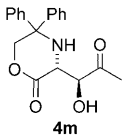
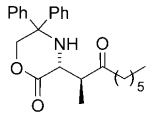
[**] We thank the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft for generous financial support. The research of F.G. was supported by the Alfried Krupp Prize for Young University Teachers of the Alfried Krupp von Bohlen und Halbach Foundation.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200803515.

Table 1: Scope and selectivity of the *anti*-selective Mannich reaction.[a]

Entry	Product	Yield[b] [%]	d.r.[c]	*ee* [d] [%]	Entry	Product	Yield[b] [%]	d.r.[c]	*ee*[d] [%]
1[e]	 **6**	80	10:1	95	9	 **4g**	73	12:1	>99
2[f]	 **4a**	91	>20:1	>99	10[f]	 **4h**	75	–	81
3[g]	 **4a**	78	20:1	99	11	 **4i**	30	–	80
4	 **4b**	60	>20:1	97	12[h]	 **4j**	59	>20:1	98
5[h]	 **4c**	30	>20:1	99	13	 **4k**	91[i]	>20:1	>99
6	 **4d**	70	>20:1	>99	14	 **4l**	70[j]	>20:1	>99[j]
7	 **4e**	90[i]	>20:1	94	15	 **4m**	84[k]	10:1	98
8[h]	 **4f**	40	10:1	>99					

[a] Reaction conditions: **3b** (1 mmol), L-proline (0.3 mmol), ketone (3 mmol), anhydrous DMSO (10 mL), 24 h. [b] Yield of the isolated product. [c] The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product. [d] The *ee* value was determined by HPLC or GC on a chiral stationary phase. [e] Imine **3a** was used. [f] Proline: 0.2 equivalents. [g] (*S*)-5-Pyrrolidin-2-yl-1*H*-tetrazole and the solvent CH_2Cl_2 were used instead of L-proline and DMSO. [h] Ketone: 5 equivalents. [i] A mixture of regioisomers was obtained. [j] The *ee* value after crystallization is given. [k] A mixture of diastereomers was obtained.

with a series of different ketones in dry DMSO. Clean product formation was observed, as well as high levels of stereoselectivity. The use of cyclic ketones with different ring sizes led to the desired products with very high selectivities (Table 1, entries 2–5). When the more lipophilic catalyst 5-pyrrolidin-2-yl-1*H*-tetrazole was used in CH_2Cl_2,[9a] cyclohexanone reacted smoothly with the same levels of stereoselectivity as observed with proline (Table 1, entry 3). When cyclopentanone, which is known for its relatively low reactivity in related studies,[9] was used, the product was formed in low yield, but the high selectivity was maintained (Table 1, entry 5). Acyclic aliphatic ketones reacted highly selectively to form the desired amino acid derivatives (Table 1, entries 6–9). Typically, small amounts of regioisomers were also formed. Interestingly, with the methyl ketones acetone and mesityl oxide, which give rise to products with one stereocenter, lower levels of enantioselectivity were observed (Table 1, entries 10 and 11). Finally, very high levels of selectivity were observed with a number of functionalized ketones (Table 1, entries 12–15). Especially noteworthy is the high enantioselectivity of the reaction with hydroxyacetone to form **4m** (98% *ee*; (Table 1, entry 15).

The absolute and relative configurations of some representative products (Table 1, entries 1, 2, 6, and 15) were

established by X-ray crystallography (Figure 1).[10] The expected α(*R*),β(*S*) configuration was found in all cases. The absolute configuration of the other Mannich products was assigned by analogy and through comparison of their sign

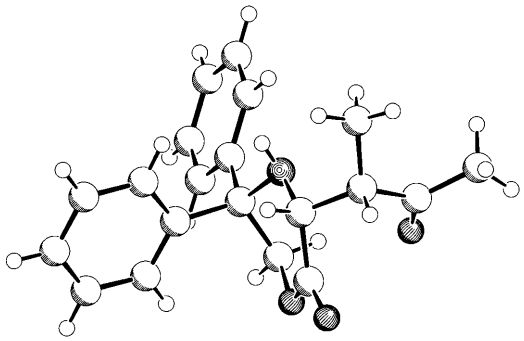
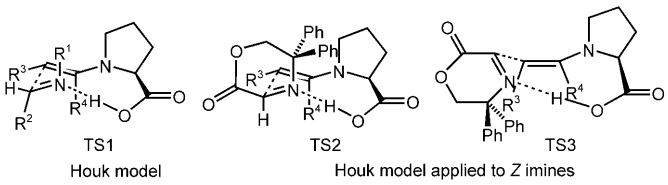


Figure 1. Crystal structure of the morpholinone **4d**.

of optical rotation.[11] This stereoselectivity is in agreement with the predicted attack of the enamine at the *Re* face of the imine to provide the *anti*-configured products (Scheme 3).

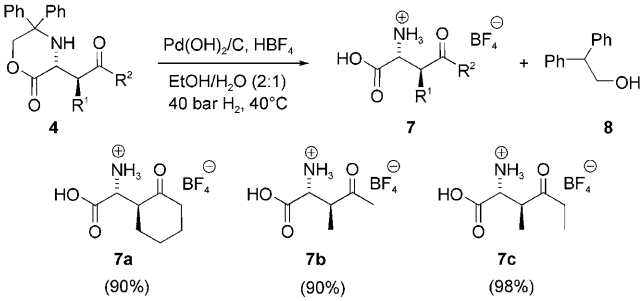


Scheme 3. Houk model of the transition state of the proline-catalyzed Mannich reaction (TS1) applied to the cyclic imine **3b**.[12]

The application of the generally accepted model for the transition state of the proline-catalyzed Mannich reaction of acyclic imines (TS1)[12] to the corresponding reaction of the cyclic imine **3b** is informative (Scheme 3). For **3b**, a reasonable chairlike transition state (TS2) and a boatlike transition state (TS3) can be envisaged. Comparison of TS1 and TS2 shows that products with opposite (*syn* versus *anti*) configurations result. We were surprised to find that the bulky geminal diphenyl group does not negatively affect the selectivity, although it comes into close proximity with the proline ring. However, the geminal diphenyl group might increase the energy of undesired transition states, such as TS3, and thus favor the desired transition state TS2. In T3, there is an unfavorable steric interaction between the geminal diphenyl group and R^3. The absence of this interaction might explain the low levels of selectivity observed for the reactions of acetone and mesityl oxide ($R^3 = H$; Table 1, entries 9 and 10).

Not only does the diphenylethylene group have a stereodirecting effect, but it also functions as a new protecting group that can be cleaved readily to give the free α-amino acids. For reasons of substrate and product stability and activity, *N*-aryl imines are often used as electrophiles in known organocatalytic Mannich reactions, generally with the *para*-methoxyphenyl group.[2] Oxidative conditions are required to deprotect the nitrogen atom.[3d] A complementary and readily cleavable protecting group would greatly expand the usefulness of organocatalytic Mannich reactions in complex multistep syntheses. The diphenylethylene group in our Mannich products acts as a protecting group for both the N and the O terminus of an α-amino acid.[13]

Deprotection of the chiral 1,4-morpholin-2-one products is possible under mild conditions by simple hydrogenolysis. This simultaneous deprotection of the N and the O terminus provided the free amino acids without any epimerization, as indicated by NMR spectroscopy (Scheme 4). The lipophilic by-product 2,2-diphenylethanol (**8**) can be removed easily with organic solvents; protonated amino acids **7** were obtained as white solids after lyophilization.



Scheme 4. Hydrogenative cleavage of the diphenylethylene protecting group. General procedure: The 5,5-diphenyl-1,4-morpholin-2-one was stirred with concentrated aqueous HBF_4 (1 equiv) and 20% (w/w) $Pd(OH)_2/C$ in $EtOH/H_2O$ (2:1) at 40°C under H_2 (40 bar). Without HBF_4, the reaction is slower.

In summary, we have developed a highly enantio- and *anti*-selective proline-catalyzed Mannich reaction of unactivated ketones. We demonstrated that the use of cyclic acceptors enables the highly stereoselective synthesis of chiral 3-substituted 1,4-morpholin-2-ones. These products correspond to α-D-amino acids that are protected at the N and O terminus by the diphenylethylene group. This protecting group for α-amino acids can be cleaved readily by hydrogenolysis in aqueous ethanol to furnish the free amino acid. In combination with asymmetric catalysis, these cyclic iminoglyoxylates should become versatile building blocks for the synthesis of chiral α-amino acids.

Received: July 19, 2008
Published online: November 12, 2008

Keywords: amino acids · asymmetric catalysis · Mannich reaction · organocatalysis · proline

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[10] CCDC 694197 (**4d**), 694198 (**4m**), 694199 (**4a**), and 694982 (**6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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