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Pipecolic Acid-Catalyzed Direct Asymmetric Mannich Reactions

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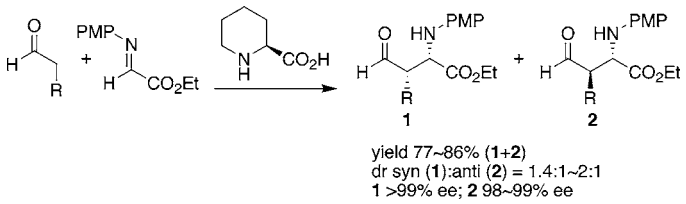
ABSTRACT



Mannich reactions between aldehydes and *N*-*p*-methoxyphenyl-protected α-imino ethyl glyoxylate have been performed using (*S*)-pipecolic acid as catalyst. The reactions give both *syn*- and *anti*-products (dr = 1.4–2:1) with high enantioselectivities (>98% ee). In contrast, (*S*)-proline-catalyzed reactions give mainly *syn*-products with high enantioselectivities. Computational studies reveal that the energetic preference between the transition structures involving the s-*cis*-enamine and the s-*trans*-enamine is smaller for the pipecolic acid as compared to proline, yielding the (2*S*,3*R*)-*anti* and the (2*S*,3*S*)-*syn* Mannich product in nearly equal amounts.

Preformed enamines of both five-membered pyrrolidine and six-membered piperidine rings have been used as nucleophiles in many reactions.[1,2] For the reactions involving in situ-generated enamines, pyrrolidine-based catalysts have been extensively examined.[3−5] One of the most effective routes for the synthesis of enantiomerically enriched α- and β-amino acid derivatives is pyrrolidine derivative-catalyzed Mannich-type reactions of an aldehyde donor. (*S*)-Proline and various (*S*)-proline derivatives give the *syn*-product (2*S*,3*S*)-**1** as the major product with high diastereo- and enantioselectivity (Scheme 1).[4] The six-membered analogue, pipecolic acid, has received little attention as a catalyst for asymmetric reactions and has proven to be ineffective for aldol reactions involving acetone as donor.[3a,6] Here we report the experimental and computational investigation of (*S*)-pipecolic acid-catalyzed Mannich reaction between aldehydes

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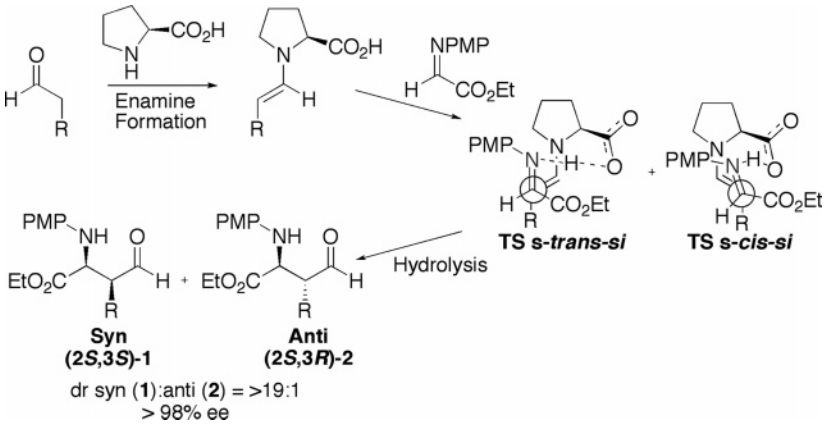
Scheme 1. Mechanism of the (*S*)-Proline-Catalyzed Mannich Reaction of Aldehydes with α-Imino Ethyl Glyoxylate



and *N*-*p*-methoxyphenyl (*N*-PMP)-protected α-imino ethyl glyoxylate.[4]

Pipecolic acid-catalyzed Mannich reactions provide both the *syn*-product **1** and the *anti*-product **2** in good yields (Table 1). The reaction rates were similar to that of proline-catalyzed reactions under the same conditions. The enantioselectivities of the *syn*-product (2*S*,3*S*)-**1**[4] and *anti*-product (2*S*,3*R*)-**2**[4,6] were both typically greater than 98% ee. The diastereomeric ratio of *syn*-product **1** to *anti*-product **2** ranged from 2:1 to 1:1, regardless of the bulkiness of the aldehyde substituent (Table 1). The insensitivity of the diastereoselectivity to steric bulk is in sharp contrast to the proline-catalyzed reactions, in which bulky R groups often led to excellent enantio- and diastereoselectivity.[4] (*S*)-Pipecolic acid catalysis provides a route to highly enantiomerically pure products of both diastereomers.

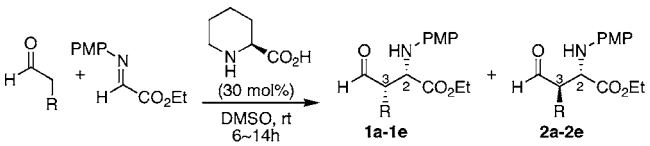
This unusual change in diastereoselectivity upon increase in the ring size of the catalyst caused us to investigate these reactions computationally. The enamine of propionaldehyde, *N*-PMP-protected α-imino methyl glyoxylate, and the transition structures leading to the four possible stereoisomeric products for both proline and pipecolic acid were calculated at the HF level of theory with the 6-31G(d) basis set.[7] We have previously used density functional theory to study related organocatalytic reactions.[8] However, HF/6-31G(d) was used over B3LYP/6-31G(d) in this study for rapidly computing the stereoselectivity.

The s-*cis*- or s-*trans*-enamine attack on the *re* or *si* face of the imine acceptor is the stereo- and rate-determining step of this reaction. Four possible diastereomeric transition structures are possible that allow for intramolecular proton transfer. The four lowest energy transition structures involving (*S*)-proline and (*S*)-pipecolic acid are shown in Figure 1.

The *syn*-product **1** arises from the s-*trans*-*si* transition state and the *anti*-product **2** from the s-*cis*-*si*. The conformations of the proline enamine were previously discussed as *anti*- and *syn*-enamine.[8] These notations are changed to s-*trans*- and s-*cis*-enamine, respectively, in this work to distinguish from *anti* and *syn* diastereoselective products. In the proline-catalyzed reaction, the computed energy difference between these transition structures, **TS-(*S*,*S*)-4** and **TS-(*R*,*S*)-6**, is 1.0 kcal/mol. The corresponding energy difference for the pipecolic acid-catalyzed reaction between **TS-(*S*,*S*)-8** and **TS-(*R*,*S*)-10** is only 0.2 kcal/mol. This decrease in energetic difference reflects the experimentally observed decrease in diastereoselectivity for the pipecolic acid-catalyzed reaction.

The computed selectivities arising from the relative energies for all transition structures are summarized in Table 2.

Table 1. (*S*)-Pipecolic Acid-Catalyzed Mannich Reaction of Aldehydes and α-Imino Ethyl Glyoxylate to Afford Products *syn*-**1a**−**e** and *anti*-**2a**−**e**[a]



Entry	R	Product	Yield (%)	dr *syn*(**1**):*anti*(**2**)	ee (%) *syn*(**1**)	ee (%) *anti*(**2**)
1	Mc	**1a** + **2a**	80	2.0:1	>99	>99
2	*i*-Pr	**1b** + **2b**	82	1.4:1	>99	98
3	*n*-Bu	**1c** + **2c**	83	1.5:1	>99	>99
4	*n*-Pent	**1d** + **1d**	86	1.4:1	>99	>99
5		**1e** + **2e**	77	1.6:1	>99	99

[a] Typical conditions: To a solution of *N*-PMP-protected α-imino ethyl glyoxylate (0.5 mmol) and aldehyde (1.0 mmol) in anhydrous DMSO (5 mL) was added (*S*)-pipecolic acid (0.15 mmol), and the mixture was stirred for 6−14 h at room temperature. The diastereomeric ratio was determined without purification by ^{1}H NMR. The enantiomeric excess was determined by chiral-phase HPLC analysis.

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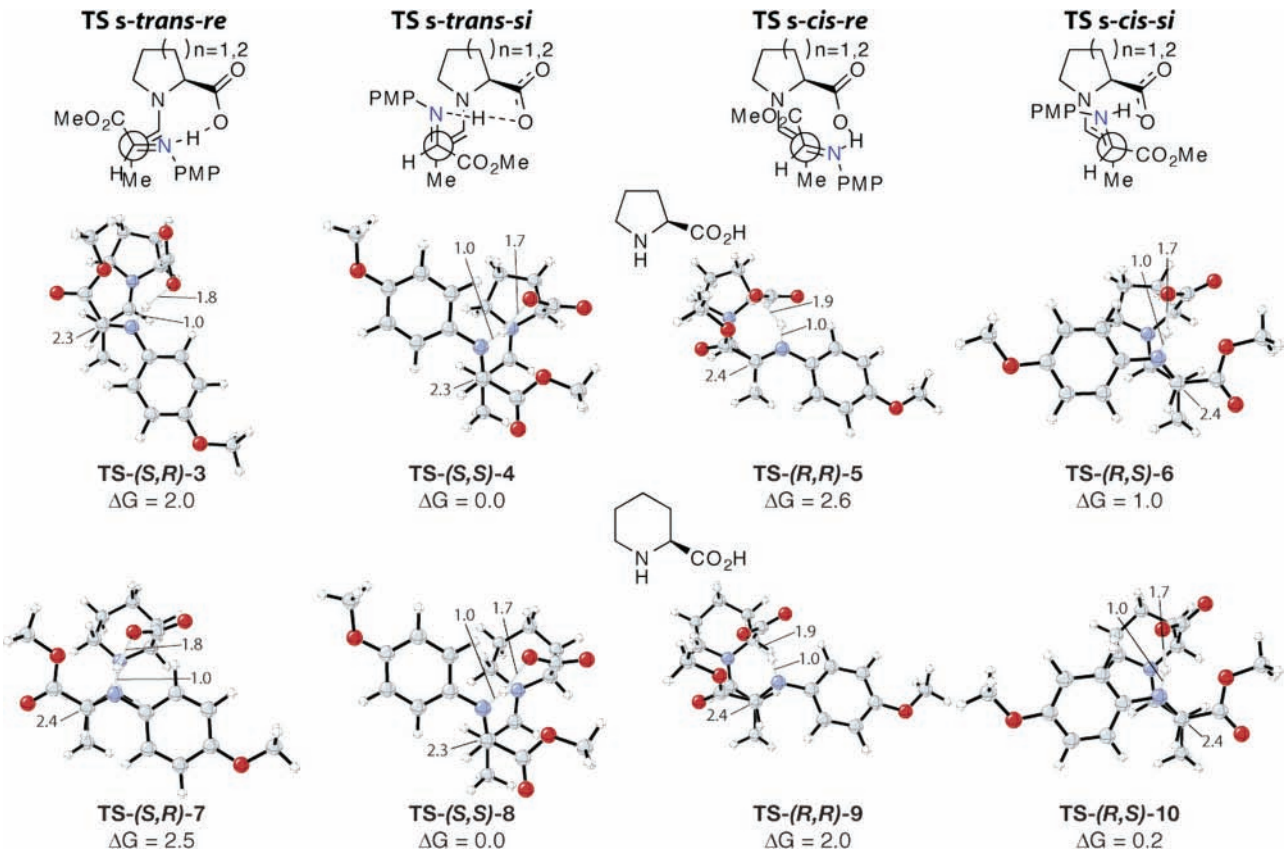

Figure 1. Transition structures for the C−C bond formation of the (*S*)-proline and (*S*)-pipecolic acid-catalyzed Mannich reaction between propionaldehyde and *N*-PMP-protected α-imino methyl glyoxylate; s-*trans*-*si* transition structures **TS-(*S*,*S*)-4** and **TS-(*S*,*S*)-8** give rise to product **1a**, while **TS-(*R*,*S*)-6** and **TS-(*R*,*S*)-10** gives rise to **2a**.

There is an excellent agreement between the computed stereoselectivity and the observed product ratios.

The facial *re* or *si* selectivity of the imine acceptor is governed by the necessity for intramolecular proton transfer and minimization of steric interactions between the imine and the reactive enamine. The (*E*)-imine is more stable than the (*Z*)-imine. Combined with the observation that transition structures involving intramolecular proton transfer are favored, the *re* face attacks necessitate substantial eclipsing of the imine and enamine [**TS-(*S*,*R*)-3**, **TS-(*S*,*R*)-7**, **TS-(*R*,*R*)-5**, and **TS-(*R*,*R*)-9**, Figure 1]. Consequently, as shown in Figure 1, the s-*trans*-*re* and s-*cis*-*re* transition structures are higher in energy by >1 kcal/mol than the s-*trans*-*si* or s-*cis*-*si* transition structure, for both proline and pipecolic acid.

Table 2. Comparison of the Experimentally Observed Product Ratios Involving Reaction of Propionaldehyde with *N*-PMP-Protected α-Imino Ethyl Glyoxylate with Computed Stereoselectivities Based on Transition State Theory Predictions Involving *N*-PMP-Protected α-Imino Methyl Glyoxylate

Entry	Catalyst	Type	dr *syn*(**1**):*anti*(**2**)	ee (%) *syn* (*anti*)
1	proline	exp.	3:1	>99
2	proline	computed	3.5:1	97
3	pipecolic acid	exp.	2:1	>99 (>99)
4	pipecolic acid	computed	1.4:1	93 (96)

The *re* or *si* attack on the enamine is determined by whether the s-*cis* or s-*trans* enamine conformer is favored in the transition state. In the case of proline, the transition structures involving the s-*trans*-enamine are favored over those that involve the s-*cis*-enamine. The latter involves distortions of the developing iminium from planarity to accommodate proton transfer. Thus proline provides the *syn*-product (2*S*,3*S*)-**1** as the major product.[8]

This differentiation is weakened in the case of pipecolic acid. The piperidine ring has steric interactions with the s-*trans*- or s-*cis*-enamines that are different than those of the pyrrolidine ring of proline. The relatively rigid piperidine ring holds the carboxylic acid more rigidly than the more flexible pyrrolidine. This alters electrostatic interactions with the ester of the iminoglyoxylate and with the protonated imine. These differences allow the imine to react via both the s-*trans*- and s-*cis*-enamine, giving rise to roughly equal amounts of both *syn*-product (2*S*,3*S*)-**1** and *anti*-product (2*S*,3*R*)-**2**.

The (*S*)-pipecolic acid-catalyzed Mannich reactions of aldehydes afford ready access to both syn- and *anti*-products

with high enantioselectivities. In contrast, proline-catalyzed reactions yield primarily the *syn*-product. Work is underway to further develop *anti*-selective Mannich catalysts based on these discoveries.[9,10]

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Supporting Information Available: Experimental procedures, characterization of compound, Cartesian coordinates, energies, thermodynamic corrections for all reported structures, full authorship of Gaussian and Q-Chem. This material is available free of charge via the Internet at http://pubs.acs.org.

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