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Origins of Opposite Absolute Stereoselectivities in Proline-Catalyzed Direct Mannich and Aldol Reactions

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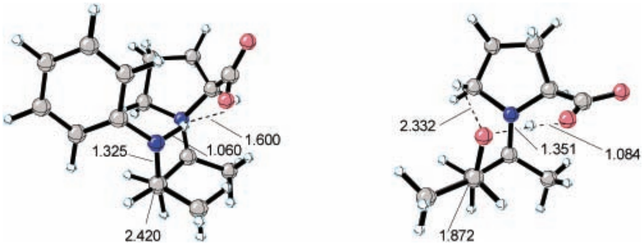
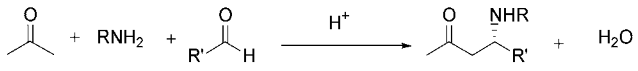
ABSTRACT



The first computational studies to elucidate the stereoselectivity of the proline-catalyzed direct Mannich reaction have been performed using density functional theory (B3LYP/6-31G*). The transition states for the proline-catalyzed direct Mannich reaction of the proline enamine of acetone with the *N*-phenyl imine of acetaldehyde are reported here. The computed transition states provide a general model that explains the origin of the opposite stereoselectivities of proline-catalyzed Mannich and aldol reactions.

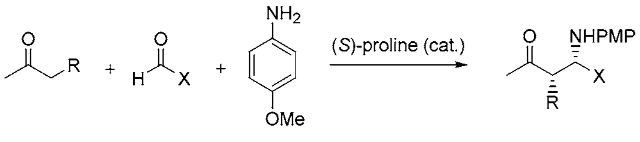
The Mannich reaction is a versatile three-component reaction involving C−C bond formation and chiral amine production from a ketone, aldehyde, and amine (Scheme 1).[1]

Scheme 1



List[2] and Barbas[3] recently showed that proline catalyzes the *direct* asymmetric Mannich reactions of a broad range of ketones and aldehydes. β-Amino ketones and aldehydes can be synthesized in good yields and stereoselectivities as shown in Scheme 2.[4]

Scheme 2



R = H, OH, Me, OMe; X = PNP, ^{n}Bu, ^{i}Bu, ^{i}Pr, CO_2ET; 50-92% yield; > 95% de; 70-99% ee.[4]

Remarkably, these reactions form the β-amino ketones with stereochemistry opposite to that of β-hydroxy ketones found in the proline-catalyzed aldol reaction as shown in Table 1.[2−6]

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(1) (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044−1070. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094.

(2) (a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336−9337. (b) List, B. *Synlett* **2001**, *11*, 1675−1686. (c) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827−833.

(3) (a) Notz, W.; Sathivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 199−201. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260−5267. (c) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842−1843. (d) Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866−1867.

(4) List, B. *Tetrahedron* **2002**, *58*, 5573−5590.

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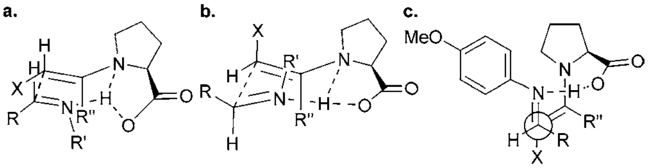
Table 1. Yields and Enantioselectivities for Proline-Catalyzed Direct Mannich Reactions (Scheme 2)[a]

R	X	% yield	% ee
H	PNP[b]	50 (68)	94 (76)
H	^{n}Bu	74 (31)	73 (67)
H	^{i}Bu	90 (34)	93 (73)
H	^{i}Pr	56 (97)	70 (96)

[a] Yields and enantioselectivities (with opposite configuration) for the corresponding aldol reaction are in parentheses. [b] *para*-Nitrophenyl.

Several models have been proposed to explain the stereoselectivity for this reaction. The first model postulated the reaction of (Z)-imines with proline enamines in chair- and boat-like transition states (Scheme 3a,b).[2a,3a]

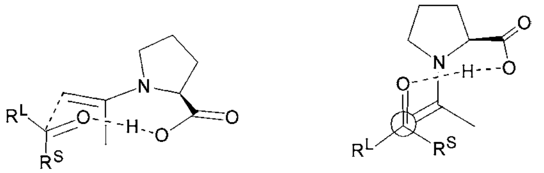
Scheme 3



This model emphasized a six-membered transition state where the (*Z*)-imine is held together by N−H interactions from the proline carboxylic acid group to the forming amine. Later, a Newman projection-like transition state was proposed (Scheme 3c)[2b,c,4] in analogy to our theoretical calculations on the transition states for proline- catalyzed aldol reactions.[7−9] Indeed, there is ample experimental evidence that (*E*)-imines are more stable than (*Z*)-imines.[10,11]

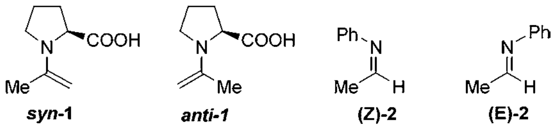
Our theoretical studies of proline-catalyzed aldol reactions demonstrated that proton transfer from the proline carboxylic acid to the forming alkoxide is essential for C−C bond formation.[7−9] In the preferred transition state for the aldol reaction, the carboxylic acid group is anti to the forming C−C bond, and the aldehyde substituent is pseudo-equatorial.[7−9] The large group (R^L) prefers to be pointing away from the enamine substituents leading to the observed re-facial selectivity (Scheme 4). This model has been used to predict[8] and rationalize[9,12] the outcome of the proline-catalyzed aldol reactions of a variety of ketones with a variety of aldehydes.

Scheme 4. Two Views of the Preferred Aldol Transition State



We have now explored the transition state of proline-catalyzed Mannich reactions with quantum mechanical methods. The model system we studied involves the reaction of the syn and anti proline enamines of acetone, **1**, with the (*Z*) and (*E*) *N*-phenyl imines of acetaldehyde, **2** (Scheme 5).

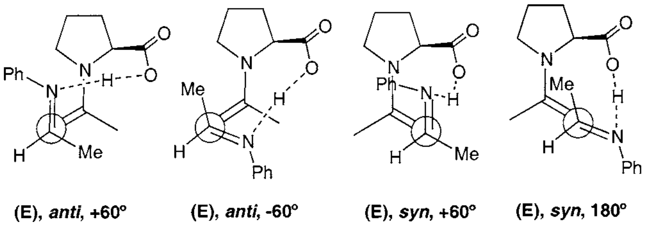
Scheme 5



All ground state and transition state geometries were located using hybrid density functional theory (B3LYP),[13] and the 6-31G*[14] basis set as implemented in Gaussian 98.[15] All of the transition states geometries were fully optimized and characterized by frequency analysis.[16]

Only the transition states that allow for intramolecular acid catalysis from the proline carboxylic acid group to the forming amine were considered. The four transition structures for the reaction of the (*E*)-imine are shown in Scheme 6.

Scheme 6



The corresponding transition structures were studied for the (*Z*)-imine also.

All of the transition states have the carboxylic acid proton completely transferred to the imine, with forming C−C single-bond lengths of 2.4−2.6 Å and forming C−N iminium bond lengths of 1.33 Å as shown in Figure 1. By contrast,

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(5) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396.

(6) Córdova, A.; Notz, W.; Barbas, C. F., III. *J. Org. Chem.* **2002**, *67*, 301−303.

(7) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911−12912.

(8) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475−2479.

(9) Bahmanyar, S.; Alleman, C.; Houk, K. N. Manuscript in preparation.

(10) Yeh, H. J. C.; Ziffer, H.; Jerina, D. M.; Boyd, D. R. *J. Am. Chem. Soc.* **1973**, *95*, 2741−2743.

(11) List, B. Unpublished results discussed in ref 4.

(12) Arno, M.; Domingo, L. R. *Theor. Chem. Acc.* **2002**, *108*, 232−239.

(13) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372−1377. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.

(14) (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724−728. (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257−2261. (c) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213−223.

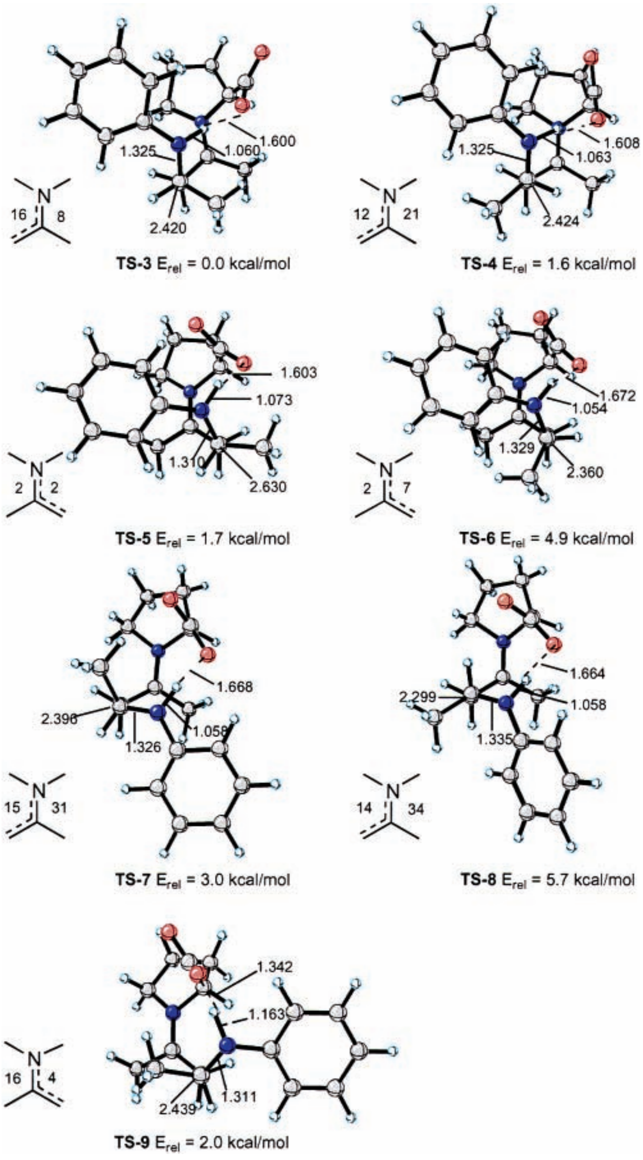

Figure 1. Transition states for the reaction of the proline-enamine of acetone with *N*-phenyl imine of acetaldehyde. Insets show the dihedral angles about the partial CN double bond in the transition states.

the more reactive and less basic aldehydes involve less proton-transfer in the transition state for aldol reactions.[17]

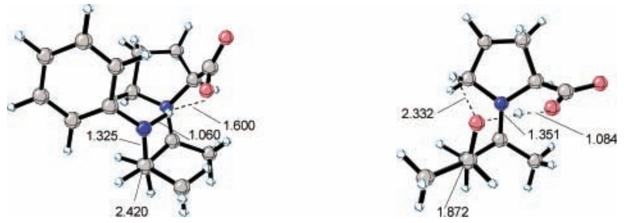

Figure 2. Comparison of the transition states for the reaction of the proline-enamine of acetone with *N*-phenyl imine of acetaldehyde (left) and with acetaldehyde (right).

Transition state **3** is the lowest in energy. It involves the anti enamine that has the double bond away from the proline carboxylic acid. The corresponding anti transition state involving the (*Z*)-imine is 1.6 kcal/mol higher in energy. Transition states **5** and **6**, with the enamine double bond syn to the carboxylate, are 1.7 and 4.9 kcal/mol higher in energy than transition state **3**, respectively. Transition states, **7**−**9**[17] all have repulsive steric interactions, and the forming iminium is distorted out of planarity. Consequently, these transition states are 2.0−5.7 kcal/mol higher in energy than the transition state **3**. These calculations predict that product of this model reaction involving acetaldehyde will be formed in 88% ee. This is consistent with experimental results where the reaction of acetone with a variety of aldehydes (butanal, benzaldehyde, 3-methyl-butyraldehyde, and isobutyraldehyde) led to the formation of products with this stereochemistry in 70−94% ee.

The models that emerge from theory for both the aldol and Mannich transition states involve intramolecular proton transfer from the carboxylic acid to O or N, and this occurs most easily when the enamine double bond is anti to the proline carboxylic acid (Figure 2).

For the aldol reaction, the aldehyde substituent assumes the pseudoequatorial conformation, while in the Mannich reaction, the substituent is forced into the pseudoaxial arrangement, since the (*E*)-imine is more stable than the (*Z*)-imine. These differences explain the reversal of selectivity for the proline-catalyzed Mannich reaction.

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Supporting Information Available: Cartesian coordinates of all reported structures, as well as the total electronic (HF) and zero-point vibrational (ZPE) energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.11; Gaussian, Inc.: Pittsburgh, PA, 1998.

(16) Reported energies include zero-point energy corrections and are scaled by 0.9806. Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502−16513.

(17) Transition state corresponding to the (*Z*) syn −60° rotamer was never successfully located.