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# Theory of Asymmetric Organocatalysis of Aldol and Related Reactions: Rationalizations and Predictions

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**ABSTRACT**

Computational studies have led to models to understand some classic and contemporary asymmetric reactions involving organocatalysts. The Hajos−Parrish−Eder−Sauer−Wiechert reaction and intermolecular aldol reactions as well as Mannich reactions and oxyaminations catalyzed by proline and other amino acids, and Diels−Alder reactions catalyzed by MacMillan's chiral amine organocatalysts have been studied with density functional theory. Quantitative predictions for several new catalysts and reactions are provided.

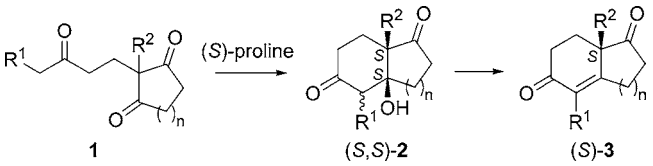
## Introduction

The discovery of asymmetric organocatalysts usually comes from experimental studies involving serendipity, enlightened trial and error, or combinatorial screening methods. The fruits of such explorations are described throughout this Special Issue. We use theory to probe how asymmetric catalysts work. We strive to predict stereoselectivities, suggest promising leads for experimental study, and eventually design new catalysts. This Account describes how quantum mechanical methods have been used in our laboratory to understand how organocatalysts cause rate acceleration and induce stereoselectivity. The research described here emphasizes proline but includes other amino acids and MacMillan's imidazolidinone organocatalysts.

We have not only reproduced experimental results in many cases but have successfully predicted the products of a complicated reaction. We make some additional predictions and show how ambitious predictions will be made in the future.

Quantum mechanical methods have matured into a hierarchical set of methods suitable for very accurate results for small molecules (a few heavy atoms) to rather approximate methods that can be applied to molecules with thousands of atoms. Methods of intermediate accuracy that can be applied to significant organic reactions have been used in our work. The absolute accuracy of hybrid density functional theory methods such as B3LYP[1] is only moderate (mean average error ≈ 3 kcal/mol; maximum error ≈ 20 kcal/mol).[1d] However, the method can be used to compute activation energies on reactions involving around 25 heavy atoms with accuracies of a few kcal/mol and stereoselectivities with errors of less than 0.5 kcal/mol; the method and related newly developed functionals are the methods of choice for the exploration of problems in organic stereoselectivity.

Scheme 1




## Amino Acid Catalysis of Aldol, Mannich, and Oxyamination Reactions

**Mechanism.** The proline-catalyzed intramolecular aldol cyclization of triketones **1** (Scheme 1) is recognized today as one of the early discoveries of effective enantioselective organocatalysis. In the early 1970s, Hajos and Parrish[2] and, independently, Eder, Sauer, and Wiechert[3] published a series of papers and patents involving this transformation. This discovery made possible the asymmetric synthesis of enediones **3**, useful building blocks in natural product total syntheses.[4,5] In all cases, (*S*)-proline induces the formation of (*S*)-enediones.

At that time, Hajos and Parrish proposed two mechanisms. One of them involves the formation of a carbinolamine intermediate, followed by the displacement of the proline moiety by nucleophilic attack of the enol from the

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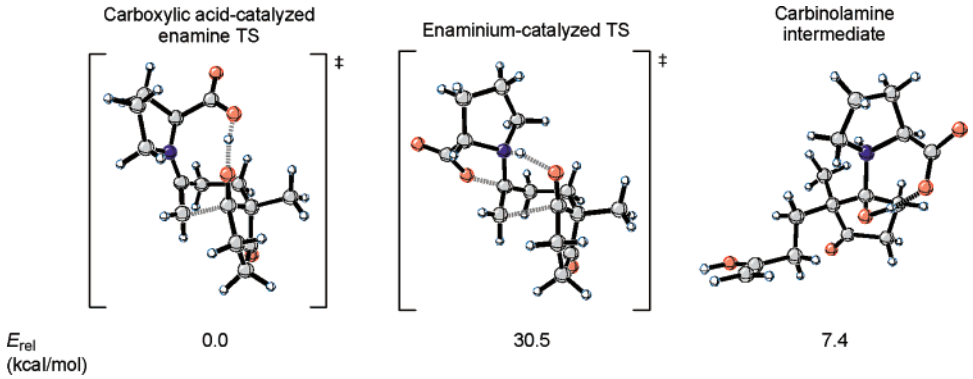
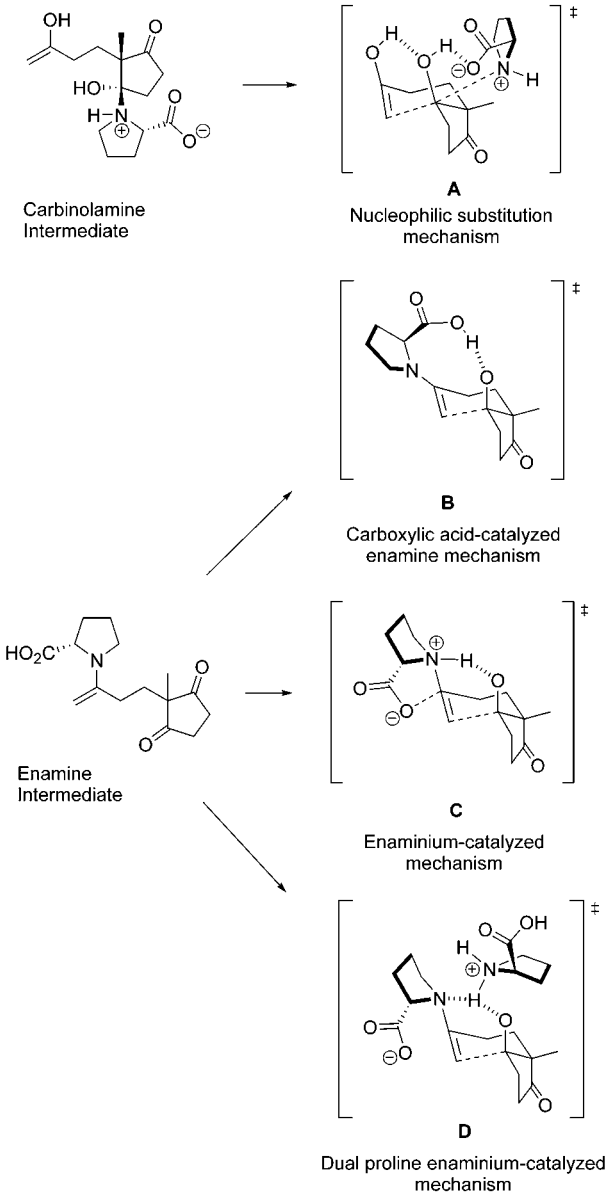


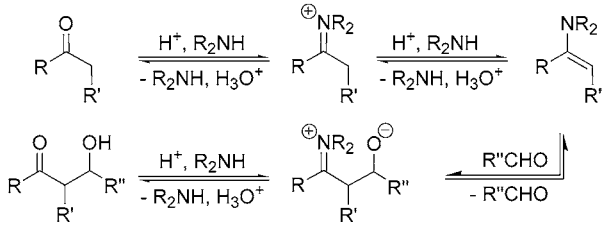

**FIGURE 1.** Transition states or intermediates of three proposed proline-catalyzed aldolization mechanisms.

**Scheme 2. Mechanisms Proposed for the Proline-Catalyzed Intramolecular Aldol Reactions**




side chain ketone (Scheme 2, **A**).[6] The other involves an enaminium intermediate acting as a nucleophile in the C−C bond formation with concomitant N−H···O hydrogen transfer (Scheme 2, **C**).

**Scheme 3. Amine-Catalyzed Aldol Reaction**




Although Hajos expressed a preference for the nucleophilic substitution mechanism (**A**), experimental evidence presented by Spencer,[7] Wakselman,[8] and Eschenmoser[9] supported the involvement of enamine intermediates in amine- and amino-acid-catalyzed aldolizations. The general enamine mechanism is depicted in Scheme 3. Proline provides the acid catalysis for many of the steps, including the C−C bond formation shown in Scheme 2 (**B**). Agami et al.[10−12] proposed a modified version of the enaminium mechanism involving a second proline molecule assisting in the N−H···O hydrogen transfer (Scheme 2, **D**). However, recent experimental studies by List's group and theory by ours support a one-proline mechanism; nonlinear effects are actually not present in proline-catalyzed intramolecular aldolizations.[13]

Computations with the B3LYP/6-31G(d) density functional theory method have been employed to determine which of these mechanisms is more likely.[14a] These computations suggest that the mechanism of the proline-catalyzed aldol cyclization is best described by the nucleophilic addition of the neutral enamine to the carbonyl group together with hydrogen transfer from the proline carboxylic acid moiety to the developing alkoxide (Scheme 2, **B**, and Figure 1). The idea of intramolecular carboxylic acid catalysis can be traced back to Jung[6] in a review in 1976. This transition-state model was almost abandoned in favor of the dual proline enaminium mechanism until List's experiments and our calculations established the participation of only one proline molecule.[13] The enaminium TS is 30.5 kcal/mol higher in energy than the carboxylic acid catalysis TS, a clear disadvantage of a zwitterionic enaminium in a nonpolar environment. The transition structure for the C−C bond-forming process via the carbinolamine intermediate could not be located, but this intermediate is 7.4 kcal/mol higher in energy than the most favorable enamine TS. Therefore, the transition

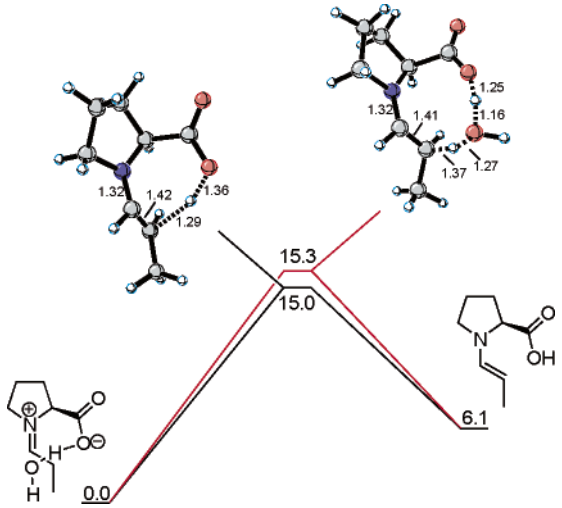
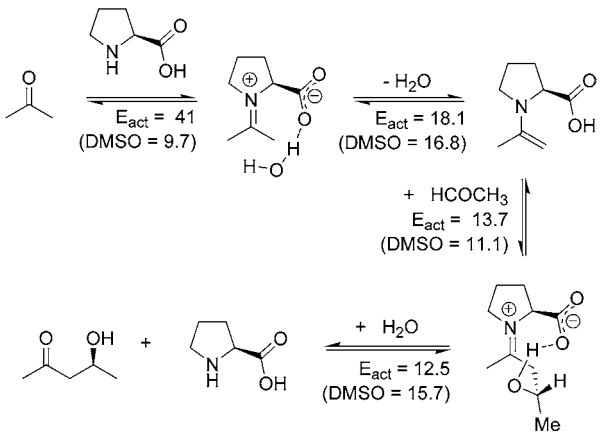



**FIGURE 2.** B3LYP/6-31+G(d,p) transition states for the formation of proline enamine of propionaldehyde from an iminium intermediate in DMSO, with and without water assistance (enthalpies in kcal/mol).

**Scheme 4. Proposed Pathway for Aldol Reaction. Formation of Iminium, Enamine, and Aldol Product in the Gas Phase (and in DMSO)[a]**




[a] Energies in kcal/mol from ref 15

structure leading to the aldol product is likely to be much higher in energy.

For the reaction of acetone with acetaldehyde catalyzed by proline, Boyd et al.[15] studied all the steps in the reaction (Scheme 4). The formation of enamine and its reactions all have similar barriers in DMSO. One intriguing aspect of the mechanism is the role of the water molecule formed during the reaction. Experimental evidence indicates that water influences the reaction rate.[16] We studied all the steps in the aldolization of propionaldehyde and isobutyraldehyde. Enamine formation can occur through either direct deprotonation or a water-assisted deprotonation of the iminium (Figure 2).[17] The two have very similar activation energies, but the free energies of activation are substantially in favor of the intramolecular process not involving water.

Calculations by Sevin et al.[18] and our group[19] show that acid catalysis is necessary to facilitate the enamine−aldehyde reaction, since otherwise a high-energy zwitterion must be formed. For example, the hydronium-

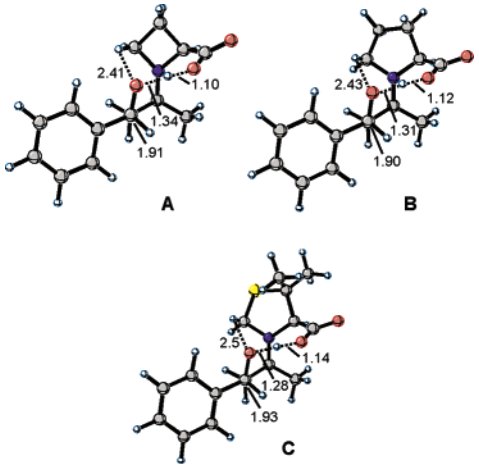



**FIGURE 3.** Most stable transition states for the aldol reaction of acetone with benzaldehyde catalyzed by 2-azetidine carboxylic acid (A), proline (B), and 5,5-dimethylthiazolidine-4-carboxylic acid (C). Newman projections along the C−C bond forming are shown (B3LYP/6-31G(d,p)).

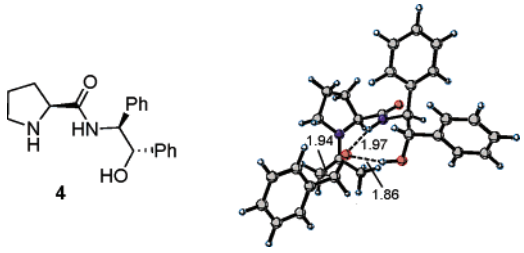



**FIGURE 4.** Most favorable transition state (anti-re) for the reaction of the enamine of the pyrrolidine carboxamide **4** with benzaldehyde (HF/6-31G(d), ref 20).

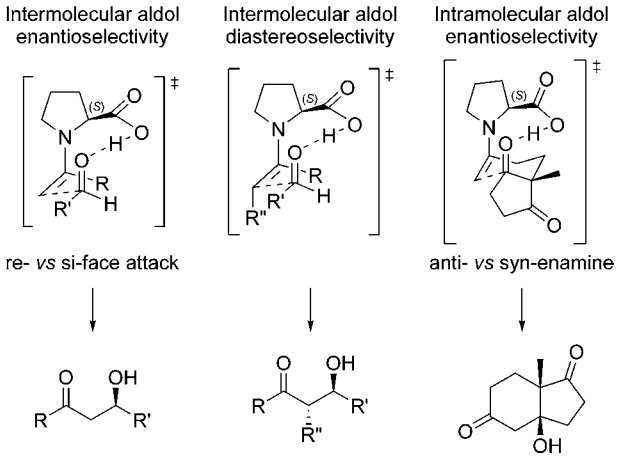



**FIGURE 5.** Stereoselectivity models for proline-catalyzed aldol reactions.

catalyzed reaction of acetaldehyde with *N*,*N*-dimethylvinylamine has no barrier of activation, while without acid catalysis, the activation barrier is 33 kcal/mol.[19] Amino acids readily provide intramolecular proton transfer from the carboxylic acid group. Figure 3 shows some examples.[17]

Good hydrogen bonding has been shown to be sufficient in some cases. For example, the (*S*)-pyrrolidine-2-carboxamide **4** catalyzes the reaction of benzaldehyde with acetone in modest to good yield and in higher ee

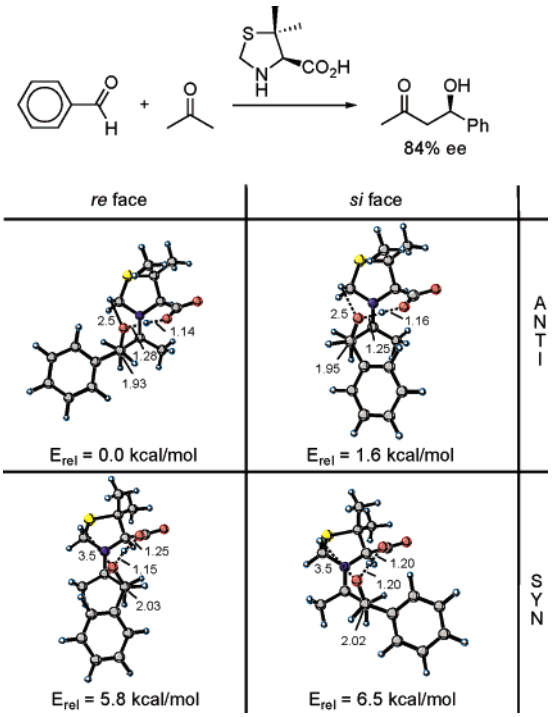



**FIGURE 6.** Transition states for the reaction of benzaldehyde with acetone catalyzed by 5,5-dimethylthiazolidine-4-carboxylic acid (B3LYP/6-31G(d,p)).

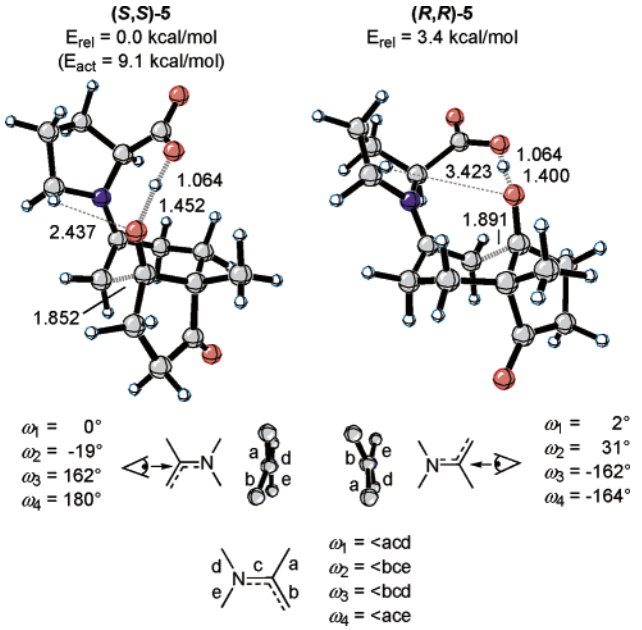



**FIGURE 7.** Transition states for a proline-catalyzed Hajos–Parrish–Eder–Sauer–Wiechert reaction.

than proline (Figure 4).[20] With this catalyst, the transition states computed by Wu et al. are similar to those with proline as catalyst, except that both the terminal hydroxyl and the amide groups are hydrogen bonded with the aldehyde.[20]

**Stereoselectivity Model.** Computations of a variety of systems have led to the model depicted in Figure 5 to explain the major products formed in proline-catalyzed aldol reactions.[2,3,21,22] These drawings combine the simplicity of the Newman projections, such as in the computer renderings of transition states given before (Figure 3), with the partial Zimmerman–Traxler-like transition state involving a chair-like arrangement of enamine and carbonyl atoms. The model can be used to rationalize and predict enantioselectivity and diastereoselectivity in diverse aldolizations. In each reaction studied so far,[13,14,17,19,23–25] transition states involving the *syn*-enamine are 2–10 kcal/mol higher in energy than the transition states involving the *anti*-enamine, shown in Figure 5. Lack of $^{\delta+}$NCH···O$^{\delta-}$ electrostatic stabilization, distortion of the developing iminium double bond to achieve favorable proton transfer from the carboxylic acid, and a partially eclipsed arrangement of the substituents about the forming C–C bond contribute to the destabilization of the syn transition states.

In general, the aldehyde acceptor is attacked on the *re*-face to place the aldehyde substituent in a pseudoequatorial arrangement.[17,24,25] A more detailed example is shown in Figure 6. Here the syn and anti transition states with an axial or equatorial arrangement of phenyl (labeled as *re* and *si*, respectively) are shown. The experimental 84% ee (*R*) corresponds nicely to the 1.6 kcal/mol preference calculated for anti-*re* attack.

Enantioselectivity of proline-catalyzed intramolecular aldol reactions is governed by the same type of effects (Figure 7).[23] In the (*S*,*S*)-TS, the carboxylic acid group and the enamine double bond are anti with respect to the C–N axis, while in the (*R*,*R*)-TS, this relationship is syn. In a syn disposition, the two oxygen atoms involved in the hydrogen transfer are too close to each other for ideal proton transfer. To achieve an optimal O–H···O arrangement, the developing iminium double bond is forced out of planarity. This can be measured by dihedral angles $\omega_{2(syn)} = 31°$ and $\omega_{2(anti)} = -19°$ (Figure 7).[9] In addition, in the anti arrangement, a $^{\delta+}$NCH···O $^{\delta-}$ stabilizing electrostatic interaction also contributes to the lower energy of such transition structures ($d_{CH-O(anti)} = 2.44$ Å vs $d_{CH-O(syn)} = 3.42$ Å).[23,26] While concerns have been expressed about the anti carboxylic acid geometry present in the TS, proline itself actually prefers this anti carboxylic acid to promote hydrogen bond to the N.

This computational study also explained why the proline-catalyzed cyclizations of the acyclic diketones **8** studied by Agami et al.[12] give lower ee's than the hydrindan/decalin system (42% ee with R = Me, Figure 8). The alkyl group R adopts an equatorial position in the chair transition structure; the geminal H in the axial disposition interacts unfavorably with the proline carboxylic acid group ($d_{H-O(anti)} = 2.35$ Å, $d_{H-C(anti)} = 2.83$ Å).[23]

**Predictions of Aldol Product Ratios.** While understanding the origins of stereoselectivity in these proline-catalyzed aldol reactions was a pleasing accomplishment, the ability to predict the results of experiments beforehand is the ultimate goal of any theoretical model. Benjamin List, then at Scripps, challenged us to predict the enantio- and diastereoselectivities of the proline-catalyzed aldol reactions of cyclohexanone with benzaldehyde and with isobutyraldehyde. There are more than 24 reasonable diastereomeric transition states for these reactions even

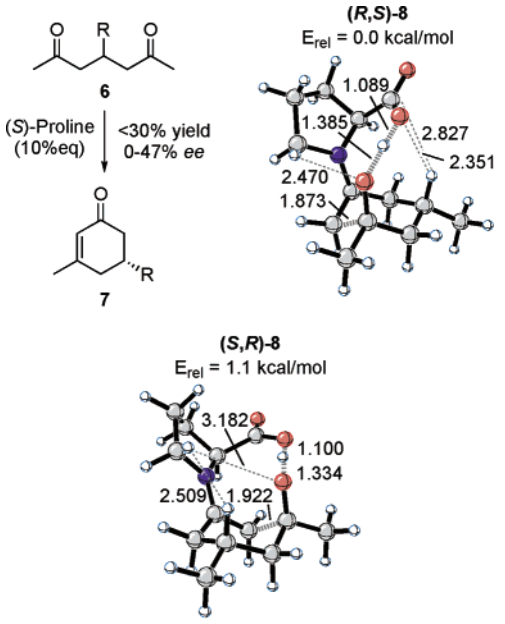



**FIGURE 8.** Transition states for the Agami aldol cyclizations.

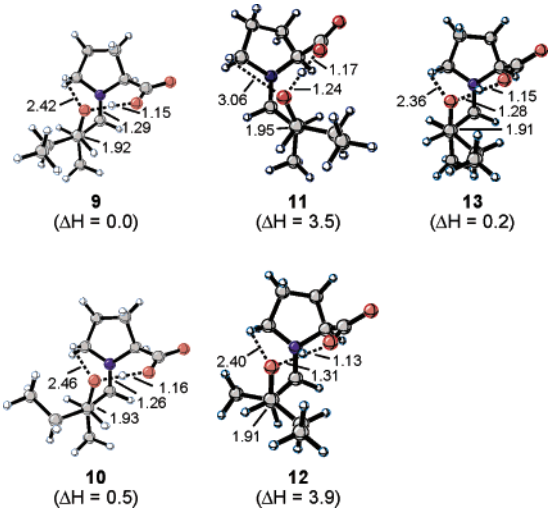



**FIGURE 9.** Most significant transition states for the proline-catalyzed dimerization of propionaldehyde (B3LYP/6-31G(d)).

when intramolecular acid catalysis is assumed, resulting from *re* or *si* attack on both enamine and aldehyde, three staggered arrangements of aldehyde with respect to enamine along the forming bond, and two-half-chair conformations of the cyclohexene. We also found that boat conformers are not much higher in energy. Our model studies[25] allow us to reduce this number to eight since the staggered conformations with angles of 180° (TSs lacking a hydrogen-bonding activation of the aldehyde) or −60° are about 19 and 5−10 kcal/mol higher in energy than those with +60°, respectively. List's experimental results were in excellent agreement for the isobutyraldehyde reaction with cyclohexanone and followed the general trend of lower stereoselectivity predicted for reactions of benzaldehyde.[24]

The scope of the model has been extended successfully to the proline-catalyzed aldol reaction of propionaldehyde with itself and with isobutyraldehyde.[22] In these reactions, the sterically least hindered transition state involves the less-substituted enamine with the more substituted aldehyde. Isobutyraldehyde proline enamine formation is at least 5 kcal/mol less favored than the same process with propionaldehyde. Many more conformations are possible with aldehydes such as propionaldehyde. Only the 5 TSs shown in Figure 9 of the 18 transition states explored computationally for the propionaldehyde self-aldol[25] are significant for the prediction of stereoselectivity. Conformers **9** and **10** give the major (2*S*,3*S*)-anti product, while the enantiomer (2*R*,3*R*)-anti comes from the less favored *syn*-(*E*)- and *anti*-(*Z*)-enamines with equatorial- and axial-ethyl conformers, respectively (**11** and **12**). The (2*S*,3*R*)-syn product from TS **13** is formed as a significant byproduct. Despite these complexities, computed dr and ee (2:1 and 99%) are close to experiments (4:1 and 99%).

**Other Amino Acids.** Although proline has received the most press, other amino acids are capable of stereoselective catalysis of the Hajos−Parrish−Eder−Sauer−Wiechert reaction. The highest ee's (75−95%) in the cyclization of methyl ketones (**1**, $R^1$ = H) were obtained using secondary cyclic amino acids[2,3,13,27−29] as catalysts (Table 1). In contrast, the reactions with primary amino acids[2,27] proceeded with much lower enantioselectivity (~25%).

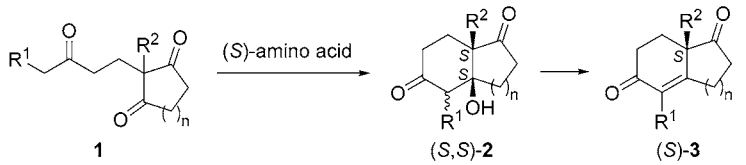
Figure 10 shows the computed transition states for the phenylalanine-catalyzed Hajos−Parrish−Eder−Sauer−Wiechert reaction (cf. the proline-catalyzed TSs in Figure 7).[14b] The relative rigidity of the pyrrolidine ring enforces stereoselectivity, but the flexibility of phenylalanine produces lower levels of asymmetric induction. The 3.4 kcal/mol energy difference between the (*S*,*S*) and (*R*,*R*) transition states in the proline-catalyzed process drops to 1.7 kcal/mol with phenylalanine. With acyclic amino acids, the carboxylic moiety can achieve favorable proton-transfer geometries in both syn and anti transition states. Figure 10 shows small and similar values of $\omega_2$ for both (*S*,*S*)- and (*R*,*R*)-**14**. These transition structures, with proton transfer from the carboxylic acid moiety, are lower in energy (>4 kcal/mol) than those where the enamine NH proton is transferred to the carbonyl acceptor.

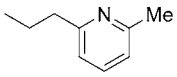
With larger than methyl ketones (**1**, $R^1 \neq$ H), the acyclic primary amino acids[3,4,10,29,30] are able to catalyze the formation of enediones **3** ($R^1 \neq$ H) in 75−95% optical yields (Table 1), in fact better than proline, which gives good enantioselectivity (72−100% ee) but low chemical yields.[2,31] As shown in Figure 11, the anti transition state from the (*Z*)-enamine is now highly favored with phenylalanine.[14b] The anti-(*E*) or syn transition states shown are much higher in energy due to steric hindrance.

With proline, steric hindrance disfavors both (*Z*) and (*E*) anti transition states (Figure 12), which accounts for the substantial increase in the activation energy as compared with (*S*,*S*)-**9** (see Figure 10).[14b] In agreement with experiments,[31] similar ee's are expected for the major ketol in proline-catalyzed cyclizations of substrate **1** regardless of the $R^1$ group.

Unpublished experimental work performed by the Hanessian group indicates that the *cis*-4,5-methanoproline (Figure 13) behaves much like proline, whereas *trans*-4,5-

**Table 1. Examples of Intramolecular Aldol Cyclizations Catalyzed by Amino Acids**




| | n | $R^1$ | $R^2$ | ee (%) | $R^3$ | ee (%) | Amino acid ($R^3$) |
|---|---|---|---|---|---|---|---|
| **a** | 1 | —H | —Me | 90-96 | H | 25 | (*S*)-Phe ($CH_2Ph$) |
| **b** | 2 | —H | —Me | 76 | H | | |
| | | | | 60-75 | OH, OAc, O$^t$Bu | | |
| **c** | 1 | —Me | —Me | 72-100 | H | 66 | (*S*)-Phe ($CH_2Ph$) |
| | | | | | | 71 | (*S*)-Ala ($CH_3$) |
| | | | | | | 74 | (*S*)-Val ($CH(CH_3)_2$) |
| **d** | 1 |  | —Me | | | 80-86 | (*S*)-Phe ($CH_2Ph$) |
| | | | | | | 84 | (*S*)-Tyr-OMe ($CH_2$-$C_6H_4$-*p*-OMe) |
| | | | | | | 78 ((*R*)-**3d**) | (*R*)-Trp ($CH_2$-(indol-3-yl)) |

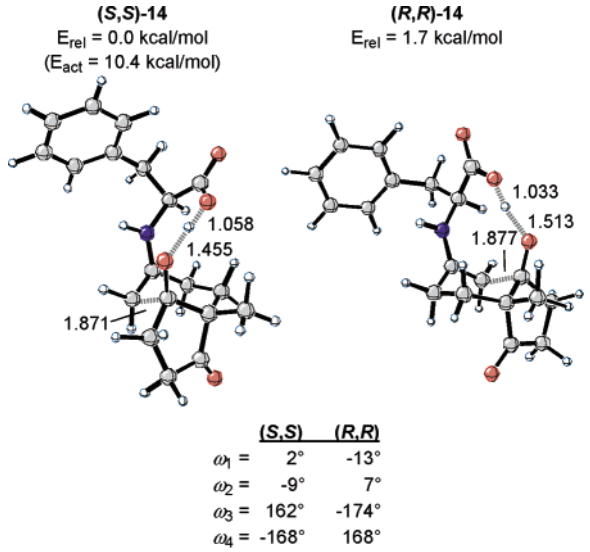



**FIGURE 10.** B3LYP/6-31G(d)-optimized TSs for the (*S*)-phenylalanine-catalyzed cyclization of **1a**.

methanoproline is a poorer catalyst and less enantioselective than either proline or the cis derivative.[32a] This seems opposite to our idea of the role of the C−H···O hydrogen bond. The transition states and activation energies for reactions catalyzed by proline (Figure 7) and *cis*-4,5-methanoproline (Figure 13) are virtually identical. By contrast, the *trans*-4,5-methanoproline-catalyzed reaction is predicted to be more than 1 order of magnitude slower and the anti−syn transition state energy difference drop by 0.6 kcal/mol (Figure 13). The calculations agree with experiments that the trans isomer is a poorer catalyst. Bicyclo[3.1.0]hexane systems favor the boat conformation (shown at the top of Figure 13) over the usual chair due to torsional strain introduced by the ring fusion.[33] The cis isomer can easily achieve the ideal transition state, while the trans stereoisomer cannot.

**Other Reactions Catalyzed by Proline.** The models of stereoselectivity proposed in Figure 5 not only predict successfully the stereoselectivities of aldol reactions catalyzed by proline but can also be used to rationalize stereoselectivities of other reactions. For the closely related Mannich reaction,[34] our calculations showed why opposite enantiofacial selectivities are observed for the proline-catalyzed Mannich and aldol reactions.[35] Figure 14 sketches the preferred transition state. Proton transfer to the nitrogen atom occurs most easily when the enamine double bond is anti to the proline carboxylic acid, but proton transfer requires the *N*-phenyl group to be anti to the acid. *E*-Imines are more stable than *Z*-imines, and this energy difference is maintained in the transition state. Consequently, the *C*-substituent of the imine acceptor adopts a pseudoaxial arrangement, in contrast to the equatorial arrangement favored in the aldol reaction.

MacMillan,[36] Zhong,[37] and Hayashi[38] all recently reported the use of proline to catalyze asymmetric α-oxyaminations with modest to high yield and high enantioselectivity. Different transition-state models were proposed by MacMillan (enaminium-catalyzed TS) and Zhong (carboxylic-acid-catalyzed enamine TS) as shown in Figure 14. Our calculations demonstrate that the most favorable transition structure (B3LYP/6-31G(d)) involves proton transfer from the carboxylic acid (as in aldol reactions), with anti addition of the enamine to the oxygen atom of the nitroso compound.[32b] The corresponding syn transition structure is 3.6 kcal/mol higher in energy, in good agreement with the experimental 97% ee. The regioselectivity is also reproduced: the most favorable nitrogen-addition TS, the anti one, lies 2.8 kcal/mol above the oxygen-addition anti TS. The greater basicity of the nitrogen of the nitroso compound causes the O attack on the enamine to be favored over N attack. This is consistent

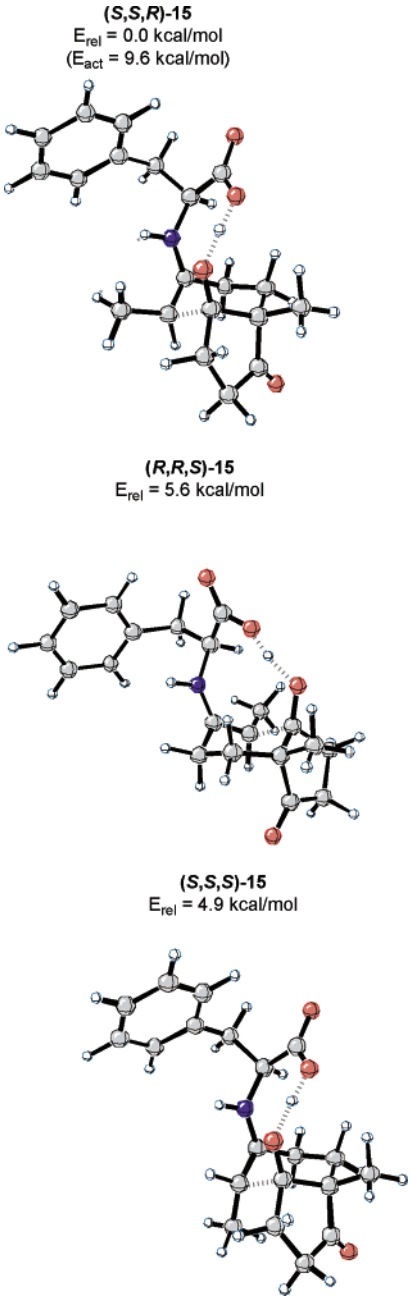



**FIGURE 11.** B3LYP/6-31G(d)-optimized TSs for the (*S*)-phenylalanine-catalyzed cyclization of **1c**.

with reversal of regioselectivity of attack on nitroso compounds by silyl enol ethers with Lewis acids.[39]

**Predictions of Amino-Acid-Catalyzed Processes.** Intermolecular aldol reactions of acetone with benzaldehyde catalyzed by several catalysts have also been investigated, as presented in Table 2.[40] Using the model described throughout this section, under kinetic control conditions, we predict that all the catalysts will be more enantioselective than proline, whereas *trans*-4,5-methanoproline is expected to be roughly the same as proline. Pyrrolidines with heteroatoms (S or O) are predicted to be the most enantioselective, with an efficiency closely related to that of 5,5-dimethylthiazolidine-4-carboxylic acid. This organocatalyst was also predicted (B3LYP/6-31G(d,p)) to be more stereoselective than proline by 0.5 and 0.9 kcal/mol

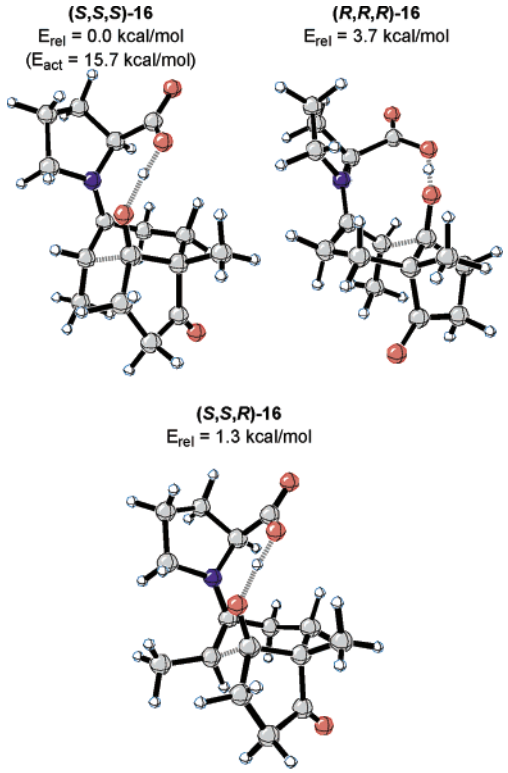



**FIGURE 12.** B3LYP/6-31G(d)-optimized TSs for the (*S*)-proline-catalyzed cyclization of **1c**.

in the intramolecular aldol cyclizations of **1a** and **1b** (Table 1), respectively.

## Imidazolidinone as Organocatalysts

MacMillan and co-workers have been developing a series of chiral imidazolidinones as powerful enantioselective catalysts for carbon−carbon bond-forming reactions. The authors hypothesized that formation of the iminium compound from enones would lead to LUMO lowering and facilitate reaction with nucleophiles much as Lewis-acid catalysis activates enones toward Diels−Alder reactions and electrophilic substitutions (Scheme 5).[41−47]

All the conformations of iminium intermediates formed from reactions of catalysts **17**−**19** with model α,β-unsaturated aldehydes and ketones were explored computationally with B3LYP/6-31G(d).[48] In the case of (*E*)-crotonaldehyde, this analysis involves the (*E*) and (*Z*) conformations about the $^{+}$N═C bond and conformations around the bond from the ring to the benzyl group. The (*Z*)-iminium complexes are always less stable than the (*E*), as shown in Figure 15.[48a] Contrary to force-field energy minimizations reported by MacMillan[41−45,47] and Kozlowski,[49] conformer **20a** is more stable, a result of a C−H···π interaction between a C2-methyl group and the phenyl ring of the C5-benzyl group. The distance between methyl carbon and the center of the aromatic ring in **20a** is 3.8 Å, close to that reported by Tsuzuki et al. for the benzene−methane complex.[50] Even the (*Z*)-isomer **20c** is close enough in energy to the (*E*)-isomers to be considered for further studies, since it is 1.2 kcal/mol higher in energy than **20a**.

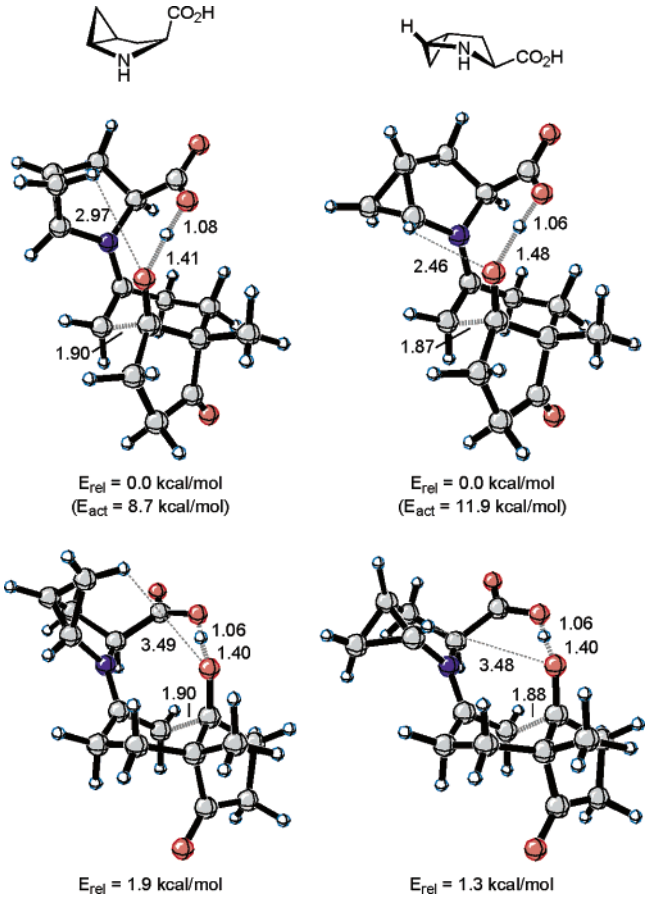



**FIGURE 13.** B3LYP/6-31G(d) anti and syn transition states and activation energies for *cis*- and *trans*-4,5-methanoproline-catalyzed Hajos–Parrish–Eder–Sauer–Wiechert reaction.

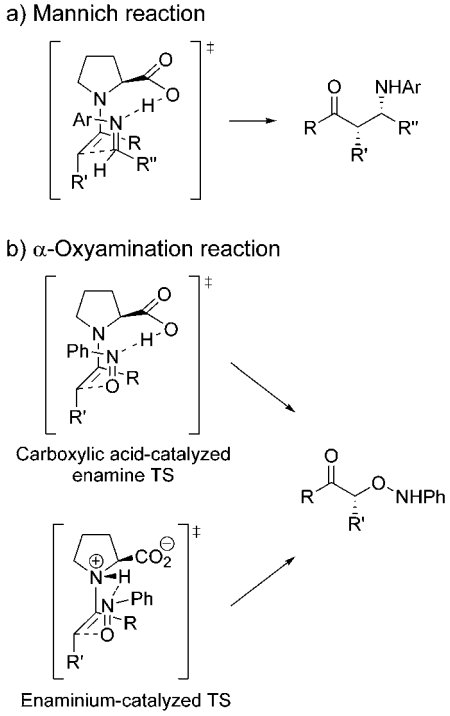



**FIGURE 14.** Proposed transition states for Mannich and α-oxyamination reactions catalyzed by proline.

In the case of iminium intermediates **21**, the most stable isomer (**21a**) has a structure similar to that predicted by MacMillan et al. based on MM3 force-field calculations (Figure 16).[44,45] Again, there are several low-energy conformers including the almost eclipsed conformer, **21b**.[48a]

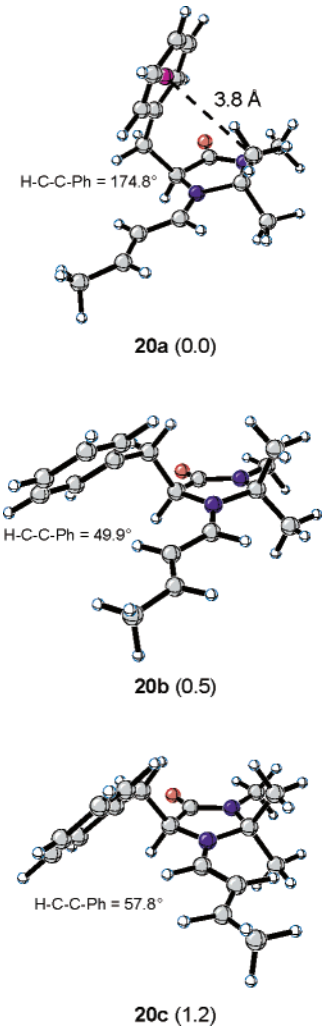
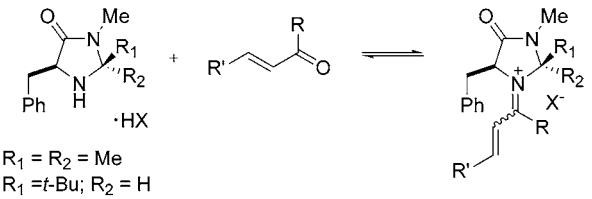



**FIGURE 15.** Optimized geometries and relative energies (kcal/mol) for the most stable iminium intermediates formed from catalyst **17** and (*E*)-crotonaldehyde.

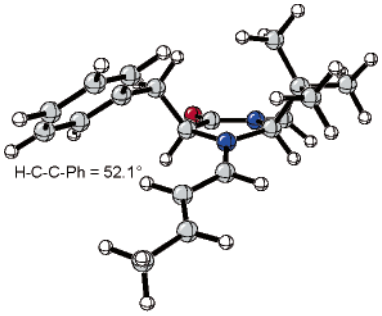
**Scheme 5**



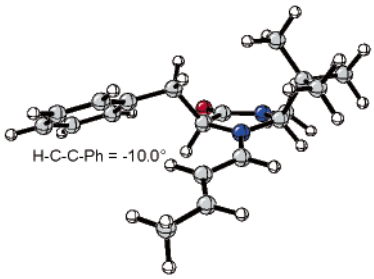

**17** $R_1 = R_2 =$ Me
**18** $R_1 =$ *t*-Bu; $R_2 =$ H
**19** $R_1 =$ 5-Me-furyl; $R_2 =$ H

Catalyst **19** gives the best results for the Diels–Alder reaction of cyclopentadiene with α,β-unsaturated ketones (89% yield, endo:exo 25:1, 90% ee).[47] Structural study of iminium complexes **22** formed from 4-hexen-3-one and imidazolidinone **19** shows that **22c** and **22d** are strongly destabilized due to the repulsion between the oxygen lone pair of the furan ring and the π system of the benzene ring.[48b]

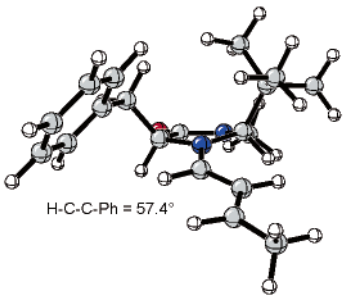
Considering the transition structures of the Diels–Alder reaction of cyclopentadiene with the most stable iminium




**21a** (0.0)




**21b** (0.9)




**21c** (1.4)

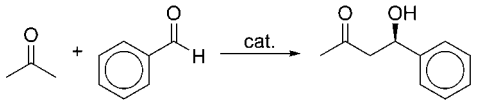
**FIGURE 16.** Optimized geometries and relative energies (kcal/mol) for the most stable iminium intermediates formed from catalyst **18** and (*E*)-crotonaldehyde.

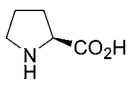
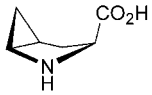
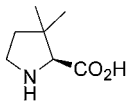
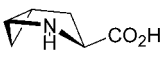
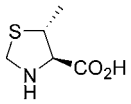
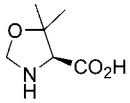
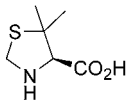
intermediates **22a** and **22b** (Figure 18), an ee of 86% and an endo:exo ratio of 8:1 were predicted[48b] (experimental: 90% ee, endo:exo 25:1). Despite the good agreement with experiments, the calculations of other transition states and solvent effects are underway in order to refine the predictions. All the transition structures shown in Figure 18 are concerted but very asynchronous as indicated by the nearly 1 Å difference between the two forming bond lengths (d1−2 and d3−4). Endo and exo approach to (*Z*)-isomer **22b** give the most stable transition states, ***endo***- and ***exo*-24** (Figure 18). The lowest energy conformer of the iminium, **22a**, gives transition states, **23**, that produce the minor enantiomer in this reaction.

**Predictions about Amine Catalysts.** Relative populations (%) of iminium intermediates **20**−**22** were predicted at 298 K from electronic energy differences and based on the Boltzmann distribution analysis (Table 3).

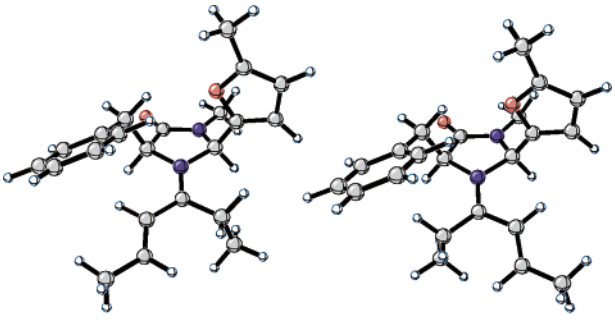
Iminium ion **20a**, which is stabilized by a C−H···$\pi$ interaction between a C2-methyl group and the phenyl ring of the C5-benzyl substituent, is predicted to constitute 60% of all the existing (*E*)- and (*Z*)-isomers at room temperature, in contrast to the sole **20b** reported.[46] Contrary to hydrogen-bonded complexes, C−H···$\pi$ complexes can exist in polar protic media such as water since they are mostly stabilized by dispersion interactions.[51] Interactions of this nature can be detected by $^1$H NMR.[52] Suezawa et al. employed NOE[53] experiments to determine intramolecular C−H···$\pi$ interactions.[54] In addition, the two benzylic protons must show very different chemical shifts

**Table 2. Predicted Stereoselectivities (B3LYP/6-31G(d,p)) by Potential Catalysts of Intermolecular Aldol Reactions under Kinetic Control**

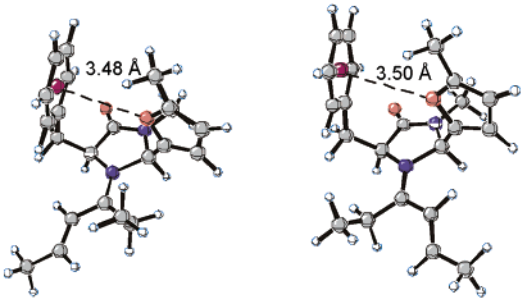



| Catalyst | Predicted ee (%) | Catalyst | Predicted ee (%) |
|---|---|---|---|
|  | 53-80 (72)[a] 53-85[b] |  | 73-92[b] |
|  | 62-84 |  | 53-85[b] |
|  | 78-91 |  | 73-92[b] |
|  | 80-92 (89)[a] | | |

[a] Experimental ee in parentheses. [b] B3LYP/6-31G(d).



**22a** (0.0) **22b** (0.4)




**22c** (4.1) **22d** (5.1)

**FIGURE 17.** Optimized geometries and relative energies (kcal/mol) for the (*E*) (**22a** and **22c**) and (*Z*) (**22b** and **22d**) conformers of the iminium formed from catalyst **19** and 4-hexen-3-one.

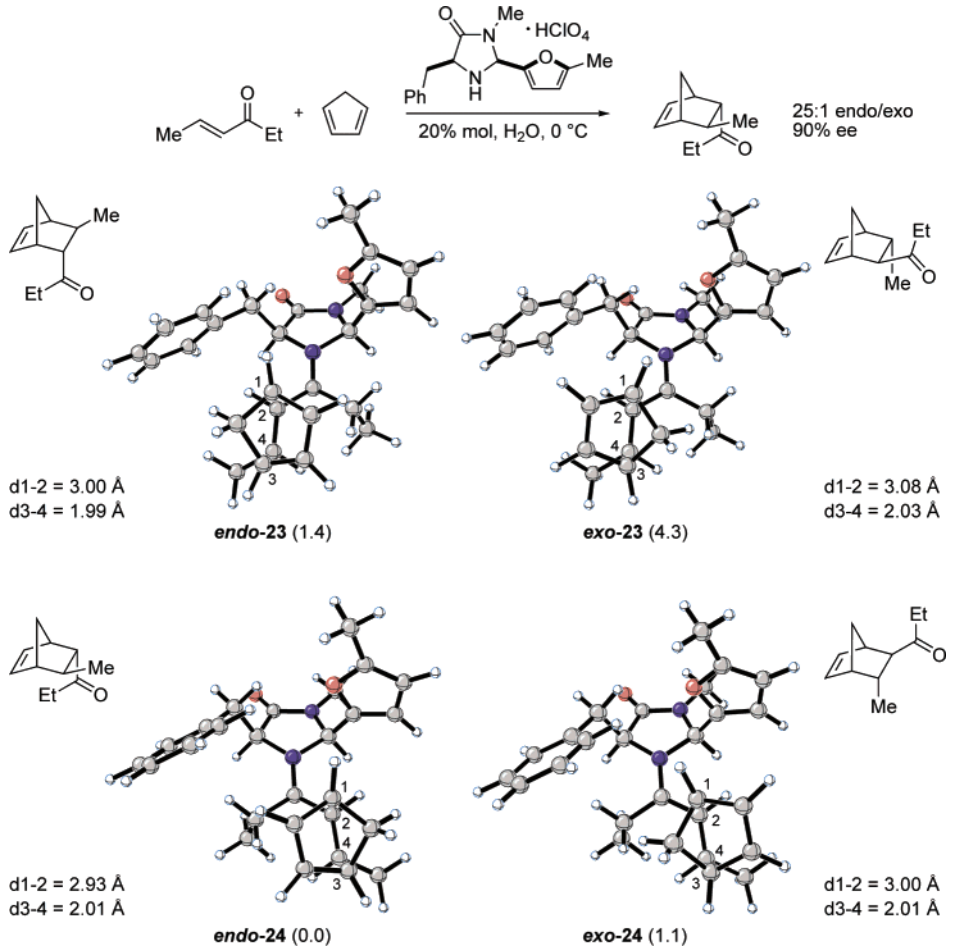



**FIGURE 18.** Optimized geometries, bond-forming distances, and relative energies (kcal/mol) for located transition structures at the B3LYP/6-31G(d) level.

**Table 3. B3LYP-6-31G(d)-Calculated Relative Populations of the Most Stable Iminium Intermediates**

| iminium intermediate | % (298 K) |
|---|---|
| **20a** | 60 |
| **20b** | 27 |
| **20c** | 7 |
| **21a** | 76 |
| **21b** | 17 |
| **21c** | 7 |
| **22a** | 32 |
| **22b** | 7 |

caused by restricted rotation of the benzyl group;[52] this fact can also be employed to demonstrate the most stable situation for compound **21**. In the case of isomer **21a** (76% of all the possible isomers at 298 K), NOE enhancement of one of the benzyl hydrogen signals is likely when the methyl signals of the *tert*-butyl moiety are irradiated (and/or vice versa).

## Conclusion

Quantum mechanical calculations have advanced to the point where semiquantitative calculations are possible on real systems studied by experiments. Rationalization of the outcome of reactions and the successful prediction of the product ratios of complex reactions are now feasible. A thorough consideration of all the possible transition states is needed in order to make those predictions, and this becomes tedious as the size and flexibility of the system increases. Very often, several interactions control the transition-state energies, and these may be only slightly different for stereoisomeric transition states. More efficient methods to search complex conformational spaces, faster computers, and improved algorithms will make quantitative studies of asymmetric organocatalysis a common procedure.

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