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# Density Functional Study of Enantioselectivity in the 2-Methylproline-Catalyzed α-Alkylation of Aldehydes

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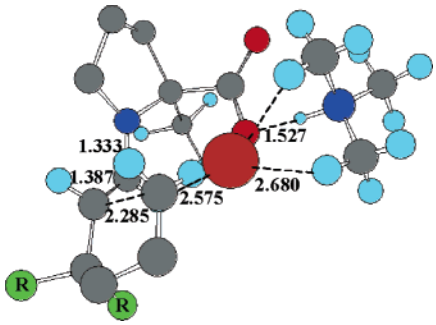
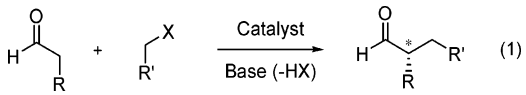



An organocatalytic asymmetric α-alkylation of aldehydes has recently been shown to provide cyclic aldehydes in high yields and enantioselectivities upon treating substituted acyclic halo-aldehydes with a catalytic amount of 2-methylproline in the presence of 1 equiv of triethylamine. Here, we report a density functional study on the mechanism of this reaction. The crucial step is an intramolecular nucleophilic substitution in the enamine intermediate. The added base accelerates the reaction through the electrostatic activation of the leaving group and affects the stereoselectivity by stabilizing anti and syn transition states to a different extent. On the basis of the computed barriers and transition states, we provide an explanation for the remarkable and unexpected increase in enantioselectivity that is observed when using 2-methylproline instead of proline as the catalyst. Calculated and observed enantiomeric excess values are in good agreement.

## I. Introduction

The catalytic asymmetric α-alkylation of carbonyl compounds represents a profoundly challenging yet highly valuable reaction for organic synthesis. While this transformation has been significantly advanced in the synthesis of α-amino acids via phase-transfer catalytic α-alkylation of glycine derivatives[1] and also for selected other substrates,[2] catalytic asymmetric α-alkylations of aldehydes (eq 1) have been completely unknown until very recently.




(1)

On the basis of our previous studies on enamine catalysis,[3] we have initiated a program toward using this powerful strategy for the α-alkylation of carbonyl compounds. As part of these studies, we reported the first and highly enantioselective organocatalytic intramolecular α-alkylation of aldehydes.[4] In the presence of a catalytic amount of proline (**1**) or 2-methylproline (**2**) and stoichiometric quantities of triethylamine, substituted 6-halo-aldehydes (**3**) react to furnish the corresponding (hetero)cyclopentane carbaldehydes (**4**) in good yields and enantioselectivities (eq 2), and substituted 4-halo-aldehydes (**5**)

(1) For reviews, see: (a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013−3028. (b) O'Donnel, M. *Acc. Chem. Res.* **2004**, *37*, 506−517. (c) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518−525. (d) Ooi, T.; Maruoka, K. *Acc. Chem. Res.* **2004**, *37*, 526−533. Also see: (e) Dolling, U.-H.; Davis, P.; Grabowski, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 446−447. (f) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595−8598. (g) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414−12415. (h) Park, H.-G.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-K.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036−3038. (i) Ohshima, T.; Shibuguchi, T.; Fukuta, Y.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 7742−7754.

(2) For catalytic asymmetric alkylations of preformed lithium enolates with oligoamine catalysts, see: (a) Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, *116*, 8829−8830. For catalytic asymmetric alkylations of preformed tin enolates with a transition-metal catalyst, see: (b) Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62−63.

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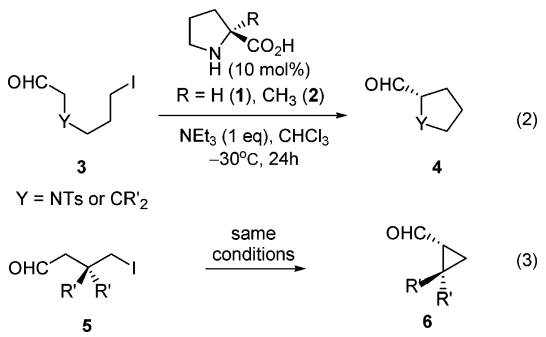
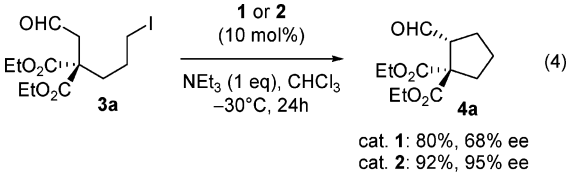
are converted into cyclopropane carbaldehydes (**6**) in an analogous manner (eq 3).




Complementing previous enamine catalytic *nucleophilic additions*,[5] our alkylations represent the first asymmetric enamine catalytic *nucleophilic substitutions*.[6] In addition to these formal mechanistic differences, an intriguing stereochemical observation was made: in contrast to previous results with the proline-catalyzed aldol reaction, in the alkylations, 2-methylproline generally gave significantly higher enantioselectivities than proline itself. For example, the cyclization of iodo aldehyde **3a** furnished product **4a** in 68% enantiomeric excess (ee) when proline was used as the catalyst, whereas **4a** was obtained in 95% ee with 2-methylproline as the catalyst (eq 4).




These interesting observations call for mechanistic and theoretical investigations. A number of other proline-catalyzed reactions have previously been studied by DFT.[7−9] In a series of pioneering contributions, Houk and co-workers have investigated the mechanism of proline-catalyzed aldol, Mannich, and related reactions.[7] These theoretical and concomitant experimental studies[3g,h] have established that the reactions proceed via enamine intermediates and involve one proline molecule in the crucial C−C bond-forming step (nucleophilic addition of the enamine intermediate to an electrophile). The transition states (TSs) for this step show an arrangement of the reacting atoms that is stabilized by a hydrogen-bonding interaction between the proton of the proline carboxylic acid moiety and an oxygen or nitrogen atom of the electrophile.[7] On the basis of this concept, it has been possible to rationalize and even predict the enantioselectivity and diastereoselectivity for these proline-catalyzed reactions.[7]

To extend our general understanding of the mechanism of enamine catalytic reactions, the present theoretical investigation addresses the following questions: (a) what is the mechanism of the enamine catalytic asymmetric α-alkylation reaction and how does it differ from other proline-catalyzed reactions, and (b) what is the origin of the remarkable increase in enantioselectivity when switching from proline to 2-methylproline?

## II. Computational Methods

All ground state and TS geometries were located using DFT and the B3LYP hybrid functional.[10,11] The standard 6-31G* basis set[12] was employed throughout, except for iodine, which was described by the effective core potential of Hay and Wadt with the associate valence basis set.[13] All TS geometries were fully optimized and characterized by frequency analysis. Bulk effects of the solvent, $CHCl_3$, on the enamine mechanism have been taken into account by means of a dielectric continuum represented by the Onsager model[14] and the polarizable continuum model (PCM).[15] As a result of occasional convergence problems in PCM-based optimizations, we used the Onsager model for geometry optimization and the PCM model for subsequent single-point energy calculations [conductor-like PCM (CPCM) calculations with united-atom Kohn−Sham (UAKS) radii]. The continuum calculations were done with a dielectric constant $\epsilon = 4.9$ for $CHCl_3$. Natural bond orders were calculated[16,17] at the B3LYP/6-31G* level. All calculations were

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(4) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450−451.

(5) See ref 3. For α-oxidations and α-aminations, see: (a) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2003**, *125*, 10808−10809. (b) Zhong, G. F. *Angew. Chem., Int. Ed*. **2003**, *42*, 4247−4250. (c) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett*. **2003**, *44*, 8293−8296. (d) Cordova, A.; Watanabe, S.-I.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc*. **2002**, *124*, 1866−1867. (e) Momiyama, N.; Yamamoto, H. *Angew. Chem., Int. Ed*. **2002**, *41*, 2986−2988. (f) Juhl, K.; Jorgensen, K. A. *Angew. Chem., Int. Ed*. **2003**, *42*, 1498−1501.

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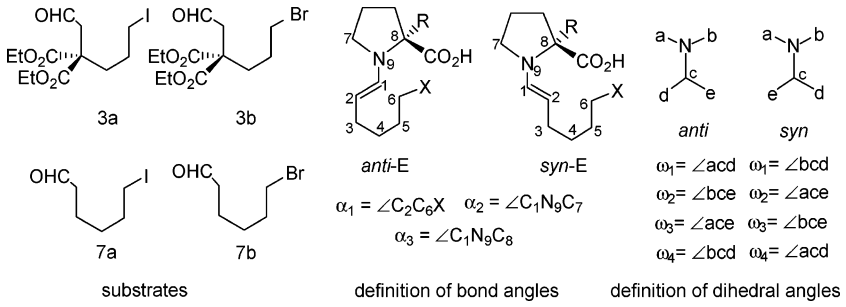
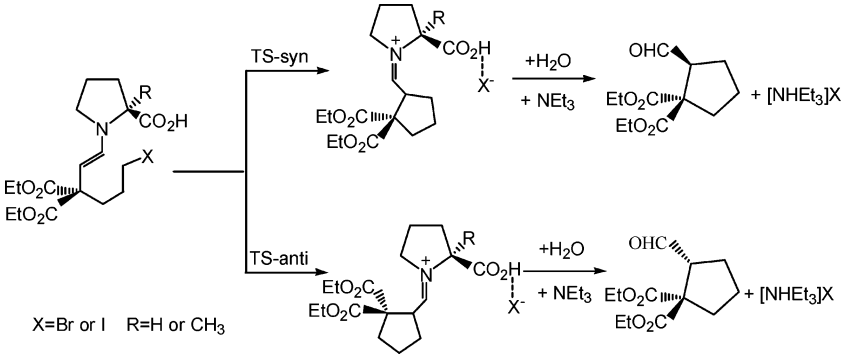
**SCHEME 1**




**SCHEME 2**




carried out using the Gaussian 03 program.[18] The chosen computational approach is analogous to the one used in previous studies.[7]

## III. Results

To investigate the proline- and 2-methylproline-catalyzed reactions according to the enamine mechanism, we have used **3a** (eq 4), **3b** (with Br replacing I in **3a**), and the simplified aldehydes **7a**,**b** as prototype substrates. Scheme 1 shows these substrates and the numbering conventions and notation used for the enamine intermediate. All calculations refer to the *S* enantiomers of proline and 2-methylproline.

**A. Transition States.** Similar to the investigation of the aldol reaction,[7] we have focused on the TSs for enamine attack on the alkyl halide. This is expected to be the rate-determining step of the reaction because all previous steps leading to enamine are reversible.[3,4] Test calculations for **7b** confirm that C−C bond formation is indeed more facile than the preceding enamine formation in this system under all conditions studied (with 2-methylproline, with and without solvent, and with and without added base). More importantly, the C−C bond-formation step controls the stereochemistry of the proline-catalyzed reaction and thus needs to be studied to understand the observed enantioselectivities.

We have considered several stereochemical pathways for this step, first without involving the auxiliary base (Scheme 2). The enamine may in principle have an *E* or *Z* configuration. The TSs involving the *Z* enamine are computed to be more than 30 kJ/mol higher in energy than those of the *E* enamine (see Supporting Information) and are, therefore, not discussed further. During the attack of the nucleophilic $C_2$ carbon atom of the *E* enamine at the $C_6$ carbon atom of the alkyl halide, the enamine may be oriented syn and anti relative to the carboxylic acid group of proline (Scheme 1). In both cases, the transition structure can adopt a conformation with attractive electrostatic interactions between the leaving halide and the carboxylic acid proton. Other TS conformations are conceivable which lack such stabilization of the developing negative charge at the halogen atom (e.g., when C−C bond formation occurs on the opposite side of the proline plane), but they are expected to be unfavorable, as in the case of the aldol reaction.[7] Hence, we have investigated in each reaction only two possible pathways, syn *E* and anti *E*, which will simply be labeled as syn and anti. The initially formed intermediate is a hydrogen-bonded complex, with the leaving halide attached to the carboxylic group (Scheme 2).

Figure 1 presents the transition structures for cyclization of the (*S*)-proline enamines of **3a**. The forming five-membered ring systems assume envelope-like conformations in the transition structures, with one carbon atom ($C_4$) being above (or below) the others. We have investigated different conformers that differ in the orientation of this carbon atom: the results for the more stable conformer are shown here and in the following, while those for the less stable conformers are given in Supporting Information (labeled by a prime, **3a′**, etc.). In the cases of **3a**,**b**, the conformers with $C_4$ above are always the more stable ones due to less steric hindrance.

Figure 1 provides numerical values for several geometric parameters that are relevant for the relative stability of the TSs. These include the length of the forming $C_2-C_6$ and the breaking $C_6-X$ bond, the associated angle $\alpha_1$ ($C_2-C_6-X$, ideally 180° in an $S_N2$ reaction), the dihedral angles $\omega_{1-4}$ that measure the deviation of the developing iminium bond from planarity (ideally 0, 0, 180, and 180°, see Scheme 1), the angles $\alpha_2$ and $\alpha_3$ at nitrogen (ideally almost equal, see Scheme 1), and the distance $d_{H\cdots H}$ between the relevant vinylic hydrogen (at $C_1$ in the anti TS and at $C_2$ in the syn TS) and the hydrogen at $C_8$ that reflects the steric congestion at the reaction center.

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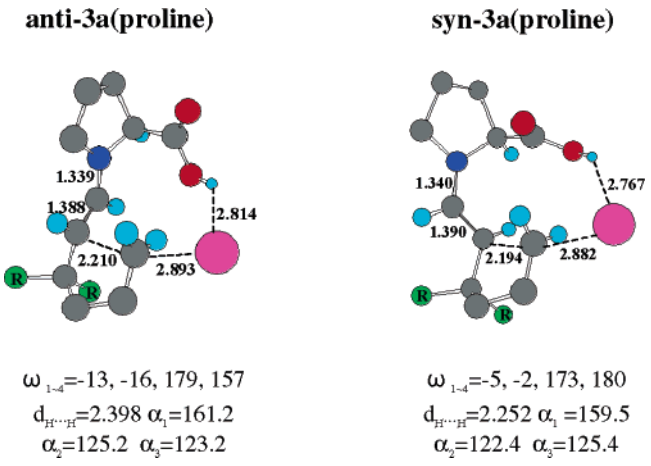


**FIGURE 1.** Transition structures for the cyclization of the (*S*)-proline enamines of **3a**. Distances in Å and angles in deg (see Scheme 1 and text for definitions). For clarity, hydrogen atoms at the periphery are omitted, and substituents R = COOEt are represented by the directly bound C atom only. Color code: C, black; N, blue; O, red; H, light blue; I, pink; R, green.

In the enamine-mediated aldol and Mannich reactions,[7] the TSs are stabilized by hydrogen bonding between the carboxylic acid proton and an oxygen or nitrogen atom of the electrophile. In the presently studied alkylation reaction, the negative charge at the leaving iodine atom is stabilized in a similar manner, but the electrostatic interaction with the rather distant carboxylic acid proton is relatively weak. The corresponding TS stabilization may be estimated from the relative energy of the syn TS for the cyclization occurring on the opposite side of the proline ring (with negligible charge stabilization), which is computed to be 14.6 kJ/mol in the case of the unsubstituted substrate **7a**.

When the calculated transition structures for the (*S*)-proline enamines of anti and syn **3a** are compared (Figure 1), the syn TS benefits from a somewhat shorter distance between iodine and the carboxylic acid proton and from a "more planar" iminium moiety. It is computed to lie 2.6 kJ/mol below the anti TS. This energy order is incompatible with the 68% ee anti preference found experimentally.[4]

We have, therefore, studied an alternative mechanism where the added base (triethylamine) participates in the cyclization step (Scheme 3). It has been suggested in the original experimental work[4] that triethylammonium carboxylate is involved in the ionic activation of the leaving group, and it is clear that this may significantly affect the stereoselectivity in this intramolecular nucleophilic substitution. For the sake of simplicity, trimethylamine has been used instead of triethylamine in the calculations (Scheme 3).

The reactant in these base-assisted cyclizations is a hydrogen-bonded complex between the enamine intermediate and trimethylamine, which is favored over the corresponding trimethylammonium carboxylate ion pair that would arise from proton transfer. This is consistent with high-level ab initio calculations[19] that predict the prototypical hydrogen-bonded HCOOH···$NMe_3$ complex to be more stable than the $HCOO^-$···$HNMe_3^+$ ion pair in the gas phase (by almost 30 kJ/mol) and also in a low-dielectric solvent [up to $\epsilon = 9$, self-consistent isodensity PCM (SCI−PCM)]. By contrast, the TS and the resulting intermediate in these base-assisted cyclizations are computed to be ion pairs containing a $HNMe_3^+$ moiety. The most important TSs are shown in Figures 2−4, while the less favored ones are documented in Supporting Information. In analogy to Figure 1, the conformers with the $C_4$ carbon atom above the other atoms in the forming five-membered ring are usually slightly lower in energy than those with $C_4$ below for steric reasons, but there are exceptions (syn **7a**,**b**) where the "below" conformer, with a chairlike arrangement [20] of atoms $C_1$ to $C_6$, is favored in the TS.

As discussed in more detail below, upon inclusion of trimethylamine, the anti TSs are lower in energy than the syn TSs for all substrates (**3a**,**b** and **7a**,**b**) and both catalysts (proline and 2-methylproline). This anti preference is in qualitative agreement with experiment, where the product resulting from an enamine *re*-facial attack is always found to be favored, both for proline and for 2-methylproline as catalysts.

The TSs of the base-assisted reactions contain a $HNMe_3^+$ cation; that is, the carboxylic acid proton has been transferred to the base. This cation forms a strong hydrogen bond to the carboxylate and provides an effective electrostatic stabilization of the negative charge that is developing at the leaving halogen atom during the $S_N2$ reaction. The transition structures share several common features (Figures 2−4). The length of the forming C−C bond is generally around 2.2−2.4 Å, thus, somewhat shorter than in the Mannich reaction[7d] and much longer than in the aldol reaction.[7a−c,f] The lengths of the breaking $C_6$−I (Br) bonds in the anti and syn TSs are about 2.8 (2.6) Å (i.e., larger than those found[21] in the $S_N2$ reaction; $X^- + CH_3X$, with X = Br, I). Closer inspection of these distances ($C_2$−$C_6$ and $C_6$−X) reveals that the more favorable anti TS occurs generally slightly earlier than the syn TS. The $C_2$−$C_6$−X angle ($\alpha_1$) is always in the range of 165−170°. The bond lengths of typically 1.33−1.35 Å for $C_1$−$N_9$ and 1.38−1.39 Å for $C_1$−$C_2$ indicate that the iminium bond is about to form while the olefinic double bond is being converted into a single bond (Figures 2−4).

Comparison of the transition structures for the base-free and base-assisted proline-catalyzed reactions (Figures 1 and 2) shows that the $C_2$−$C_6$ forming bonds are longer in the presence of trimethylamine, while the breaking $C_6$−X bonds are shorter (by about 0.1 Å in each case). The addition of base thus leads to an earlier and structurally more favorable TS: the $C_2$−$C_6$−X angle ($\alpha_1$) is closer to linearity (166−168° vs 160−161°) and there is less steric congestion (larger $d_{H\cdots H}$ values). The more stable TS is in each case associated with a "more planar" iminium moiety (syn in Figure 1, anti in Figure 2).

When replacing catalyst proline **1** by 2-methylproline **2**, the additional methyl group introduces more steric repulsion, which affects the syn TS more strongly than the anti TS, according to the calculated transition structures (Figure 3). The iminium moiety is still nearly planar in the anti TS but deviates strongly from planarity in the syn TS (more so than in the proline case, Figure 2). Moreover, the $C_2$−$C_6$−X angle ($\alpha_1$) is somewhat closer to linearity in the anti TS compared with that observed in the syn TS (again, slightly more so than in the proline case). Finally, the angles ($\alpha_2$, $\alpha_3$) at nitrogen differ by more than 10° in the syn TS, indicating a significant distortion that is present neither in the anti TS (Figure 3) nor in the proline case (Figure 2). As mentioned before, the distance $d_{H\cdots H}$ between the relevant

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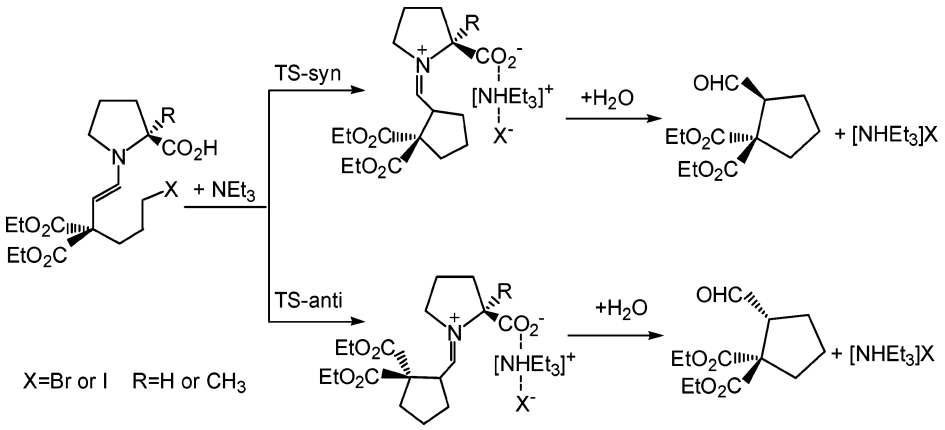
**SCHEME 3**




vinylic hydrogen (at $C_1$ in the anti TS and at $C_2$ in the syn TS) and the hydrogen at $C_8$ (closest methyl hydrogen in the case of **2**) may serve as a diagnostic measure of steric hindrance at the reaction center: it is obvious that $d_{H\cdots H}$ is particularly low in the case of the syn TS (Figure 3). In summary, when going from proline to 2-methylproline, the distortions in the syn TS of the base-assisted reaction become more pronounced as compared with those of the anti TS as a consequence of increased steric hindrance due to the additional methyl group and the increased steric repulsion between the vinyl and the carboxylate moieties. These factors combine to enhance the enantioselectivity.

The results for the unsubstituted substrates **7a**,**b** (Figure 4) are analogous to those for substrates **3a**,**b** (Figures 2 and 3) and will, therefore, not be discussed in detail. The anti TSs are again favored strongly with 2-methylproline (much more so than with proline), and the syn TSs are again significantly more distorted.

The discussion in this section so far has only addressed gas-phase transition structures. The inclusion of solvent effects (chloroform) during optimization using the Onsager model does not substantially modify these geometries: the forming C−C bond becomes slightly larger, while the breaking C−X bond becomes slightly shorter in all cases studied (see Tables S2−S4 of Supporting Information). Hence, when including solvent effects, the TSs occur slightly earlier but do not change their character in a qualitative sense.

Finally, it has been confirmed that all TSs considered have one single imaginary frequency (typically of the order of 300−400 i $cm^{-1}$). The predominant motions in this mode correspond to $C_2-C_6$ bond formation and $C_6-X$ bond rupture (X = Br, I).

**B. Activation Barriers and Enantioselectivities.** The calculated activation energies are given in Table 1. They refer to the enamine intermediate in the base-free reaction and to a hydrogen-bonded complex between the enamine intermediate and trimethylamine in the base-assisted reaction. The barriers

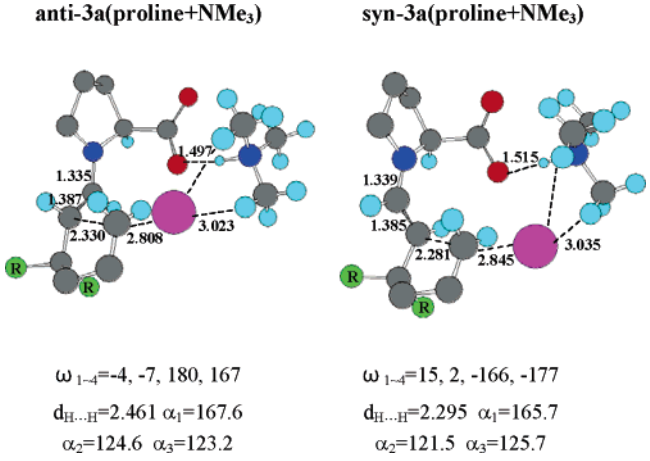



**FIGURE 2.** Transition structures for the cyclization of the (*S*)-proline enamines of **3a** in the presence of trimethylamine. For conventions, see Figure 1.

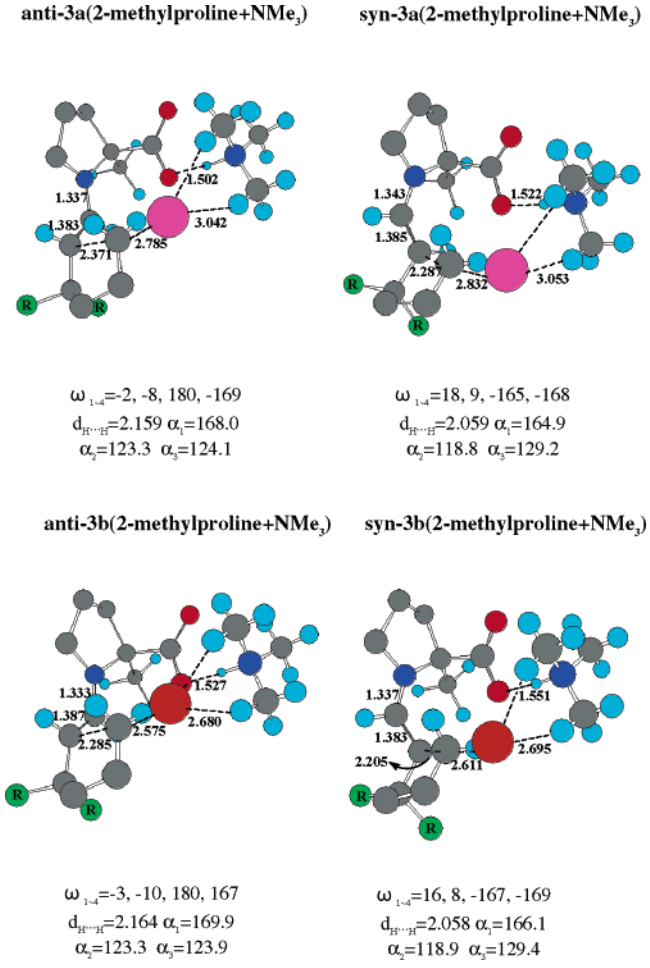



**FIGURE 3.** Transition structures for the cyclization of the 2-methylproline enamines of **3a**,**b** in the presence of trimethylamine. For conventions, see Figure 1.

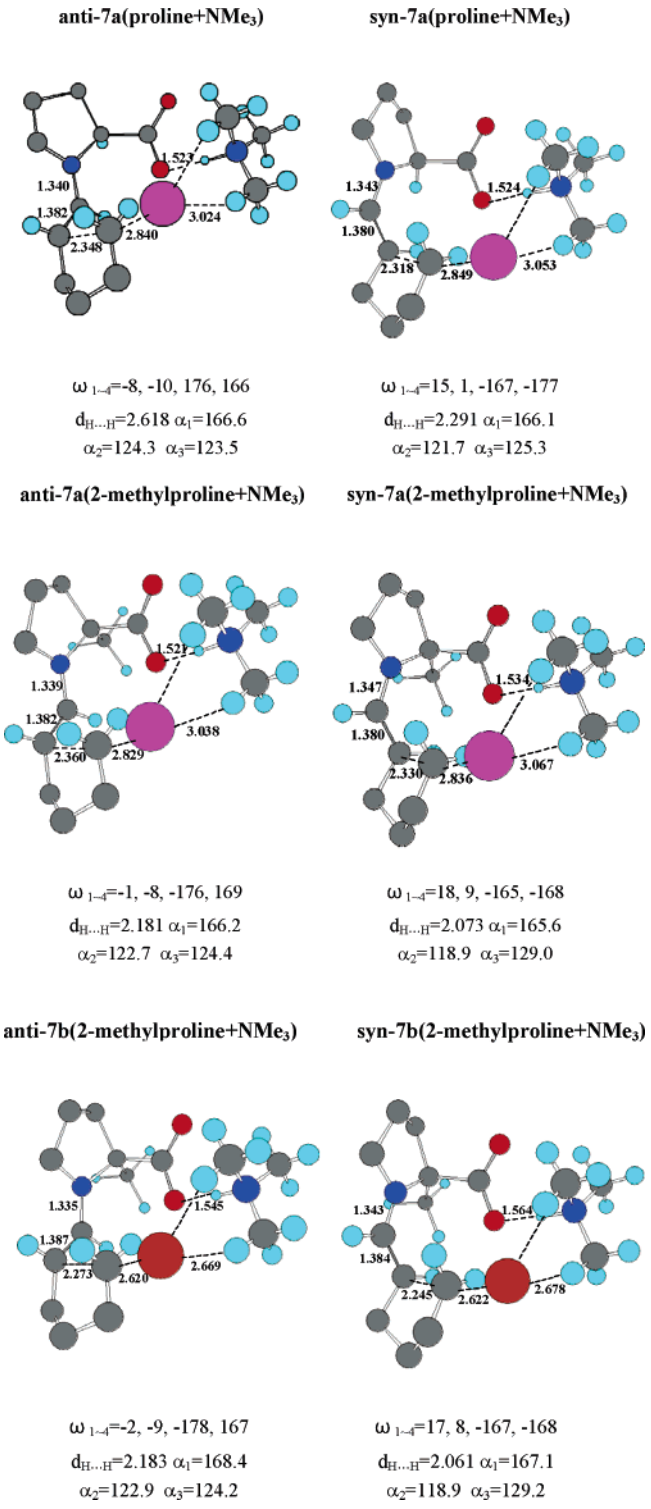



**FIGURE 4.** Transition structures for the cyclization of the (*S*)-proline and the 2-methylproline enamines of **7a**,**b** in the presence of trimethylamine. For conventions, see Figure 1.

for the I-substituted enamine **3a** are computed to be about 20 kJ/mol smaller than those of the Br-substituted enamine **3b**. This is in qualitative agreement with the experimentally observed reactivity (Br < I).[4]

Inclusion of trimethylamine in the TS lowers the calculated activation energies significantly, by 9−21 kJ/mol, compared with those of the base-free case (9−16 kJ/mol for **3a**, 15−21 kJ/mol for **3b**). The largest reduction is found for the 2-methylproline enamine of **3b**, where the barrier changes from 101 to 80 kJ/mol upon addition of trimethylamine. The anti TSs are generally affected more strongly than the syn TSs, with a differential stabilization of the anti TSs of about 4−7 kJ/mol relative to the corresponding syn TSs. According to the calculations, the presence of trimethylamine thus accelerates the reaction significantly by a large TS stabilization and modifies the enantioselectivity at the same time (anti vs syn). This is consistent with our observation that cyclization is not occurring to any significant extent in the absence of base.

**TABLE 1. Computed Activation Barriers $\Delta E_0^{\ddagger}$ of Aldehydes 3a,b**

| | | $\Delta E_0^{\ddagger a,b}$ (kJ/mol) | |
|---|---|---|---|
| catalyst | substrate | absolute | relative |
| proline | anti **3a** | 73.3 (50.3) | 2.6 (2.5) |
| | syn **3a** | 70.7 (47.8) | 0 |
| 2-methylproline | anti **3a** | 73.3 (54.7) | 0 |
| | syn **3a** | 81.2 (58.5) | 7.9 (3.8) |
| | anti **3b** | 101.3 (83.4) | 0 |
| | syn **3b** | 108.0 (87.5) | 6.7 (4.2) |
| proline + $NMe_3$ | anti **3a** | 57.0 (40.1) | 0 |
| | syn **3a** | 61.6 (44.5) | 4.6 (4.1) |
| 2-methylproline + $NMe_3$ | anti **3a** | 58.4 (37.4) | 0 |
| | syn **3a** | 70.3 (48.5) | 11.9 (11.1) |
| | anti **3b** | 80.1 (59.1) | 0 |
| | syn **3b** | 93.0 (72.5) | 12.9 (13.4) |

[a] From total energies, including zero-point vibrational energies. [b] PCM values in chloroform solution are shown in parentheses.

When the barriers in the gas phase and in chloroform solution (values in parentheses in Table 1) are compared, it is obvious that the solvent facilitates the reaction. In the case of the base-assisted proline (2-methylproline) catalysis, the calculated activation energies are lowered by 17 (21−22) kJ/mol, while the syn/anti preference is not affected much (by 0.5−0.8 kJ/mol). The main role of the bulk solvent is thus to accelerate the reaction. The TSs for nucleophilic substitution are significantly more polar than the starting enamines (larger dipole moments) so that the inclusion of a polar solvent environment leads to significant TS stabilization. The anti TS occurs only slightly earlier than the syn TS and shows only slightly less charge separation (according to natural population analysis) so that it is stabilized almost as well by the polar environment, resulting in only minor enantiodifferentiation by the solvent. The product of the base-assisted reaction is an ion-pair complex (Scheme 3) that is even more polar than the TS and can thus be stabilized even better by a polar solvent (e.g., by almost 40 kJ/mol relative to the reactant in the case of anti **3a**, yielding an exothermicity of 86 kJ/mol in chloroform solution).

As pointed out before, the enantiopreference of the proline-catalyzed reaction of **3a** is switched upon addition of trimethylamine, and the observed anti preference[4] is reproduced only when trimethylamine is present. In the case of 2-methylproline, the anti TS is always computed to be lower than the syn TS, but their energy difference increases by 4−6 kJ/mol upon inclusion of trimethylamine. The differences in the calculated free-activation enthalpies $\Delta\Delta G^{\ddagger}$ (syn/anti) can be used to predict absolute stereoselectivities and the associated ee from absolute rate theory, $\ln(k_{anti}/k_{syn}) = \Delta\Delta G^{\ddagger}/RT$. Table 2 lists the corresponding $\Delta\Delta G^{\ddagger}$ and ee values in the gas phase and in chloroform solution and compares them with the published experimental data.[4] There is obviously good agreement between the predicted and the observed enantioselectivities. It should be pointed out that this might be fortuitous to some extent

**TABLE 2. Free-Activation Enthalpies $\Delta\Delta G^{\ddagger}$ (kJ/mol) and ee Values versus Experimental ee Results**

| | | theory (gas phase) | | theory ($CHCl_3$) | | experiment[a] |
|---|---|---|---|---|---|---|
| catalyst | substrate | $\Delta\Delta G^{\ddagger}$ | ee | $\Delta\Delta G^{\ddagger}$ | ee | ee |
| **1** + $NMe_3$ | **3a** | 4.0 | 67% | 3.9 | 66% | 68% |
| **2** + $NMe_3$ | **3a** | 14.5 | 99% | 13.5 | 99% | 95% |
| **2** + $NMe_3$ | **3b** | 12.6 | 99% | 12.3 | 99% | 94% |

[a] Experimental data from ref 4.

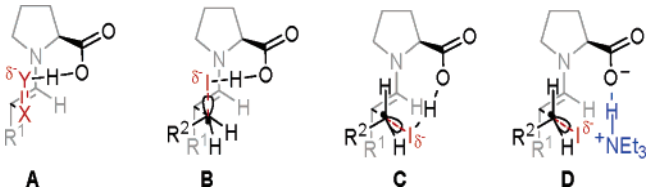
because the added base is trimethylamine in the calculations and triethylamine in the experiment. On the other hand, an inspection of Figures 2 and 3 shows that the relevant TSs should be able to accommodate larger alkyl groups in the base without causing steric problems. Previous studies on proline-catalyzed aldol reactions[7b,c,e] have also reported excellent agreement between predicted and measured enantioselectivities.

## IV. Discussion and Conclusions

In this section, we give a brief comparison with previous computational results on other proline-catalyzed reactions,[7] in particular, the aldol and Mannich reactions. The currently studied α-alkylation of aldehydes follows the same general enamine mechanism. As before, the TSs for the C−C bond-forming step are stabilized by electrostatic interactions involving neighboring groups. The enantioselectivity is governed by the strength of these interactions, the steric situation, and the degree of planarity of the forming iminium moiety. The resulting anti preference is a general feature of the proline-catalyzed asymmetric aldol, Mannich, and α-alkylation reactions.

There are, of course, also significant mechanistic differences. Formally, the aldol and Mannich reactions are nucleophilic addition processes, while the α-alkylation involves a nucleophilic substitution. More importantly, it is the only proline-catalyzed reaction investigated so far where an added base is essential and participates in the TS of the C−C bond formation. The calculations show that a base-free α-alkylation is possible in principle, but the base-assisted reaction is more facile and exhibits a different stereoselectivity: only in the latter case are the computed ee values consistent with the experimental observations. In the TS of the base-assisted α-alkylation the added base is present as a trialkylammonium carboxylate, which activates the leaving group in the nucleophilic substitution by providing an enhanced electrostatic stabilization of the developing negative charge at the halide. The base-assisted α-alkylation thus involves an intramolecular $S_N2$-type reaction coupled with a proton transfer from the carboxylic acid to trimethylamine. This process appears to be concerted: in the case of the unsubstituted substrate **7b**, we have followed the intrinsic reaction path starting from the anti and syn TSs (Figure 4, bottom entries) and reached, after subsequent optimization, the hydrogen-bonding reactant complex between the enamine intermediate and trimethylamine without encountering another intermediate.

**SCHEME 4**




Scheme 4 sketches the relevant TSs for the aldol and Mannich reactions (A), for the base-free α-alkylation with retention (B) and inversion (C), and for the base-assisted α-alkylation (D). A chairlike arrangement of the reacting atoms, as in A, can be envisioned in an intramolecular $S_N2$-type reaction with retention (B) but not with inversion (C). However, as expected, B is much less favorable than C because the difference in the computed barriers exceeds 80 kJ/mol (see Supporting Information). The TSs for the base-free (C) and base-assisted (D) α-alkylation are thus qualitatively different from A because the electronic requirements for an intramolecular $S_N2$-type reaction demand an essentially linear rearrangement of the reacting atoms.

In summary, aldehydes **3a**,**b** and **7a**,**b** have been used as prototype substrates to investigate the rate-determining C−C bond-formation step in the proline-catalyzed and 2-methylproline-catalyzed α-alkylation reactions. The geometries and relative energies of the anti and syn TSs have been computed in the presence and absence of trimethylamine. The calculations show that trimethylamine plays an important role in the C−C bond-formation process because it lowers the overall barriers and determines the stereoselectivity by stabilizing the anti and syn TSs to a different extent. An analysis of the theoretical results allows us to rationalize the origin of the remarkable increase in enantioselectivity when changing the catalyst from proline to 2-methylproline.

**Acknowledgment.** This work was supported by the Fonds der Chemischen Industrie. We thank Abdul M. Seayad for technical assistance.

**Supporting Information Available:** Structures and Cartesian coordinates of all relevant species, total electronic energies, and zero-point vibrational energies; comments on bond orders in selected TSs; and the complete ref 18 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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