Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 3229

www.rsc.org/obc

PAPER

(*S*)-Proline-catalyzed nitro-Michael reactions: towards a better understanding of the catalytic mechanism and enantioselectivity†

Hui Yang and Ming Wah Wong*

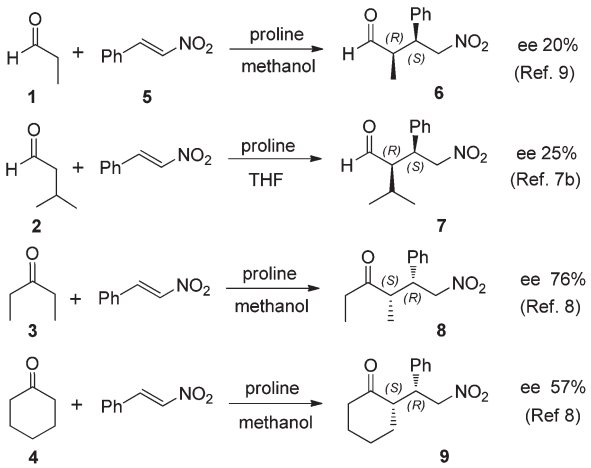
Received 28th November 2011, Accepted 20th February 2012
DOI: 10.1039/c2ob06993h

(*S*)-Proline-catalyzed nitro-Michael additions of aldehydes and ketones to β-nitrostyrene were investigated computationally (MP2/6-311+G**//M06-2X/6-31G**). Contrary to what is usually assumed in organocatalysis, the lowest-energy transition states of proline-catalyzed nitro-Michael reactions do not necessarily involve the carboxylic acid group of the proline moiety directing the incoming nitroalkene to the same face through hydrogen bonding. For the aldehyde substrates examined, the TS leading to the major (*R,S*) product was found to involve the *anti*-enamine and nitroalkene approaching from the opposite face of the carboxyl group. In the case of ketone substrates, the lowest-energy TSs leading to both enantiomeric products are characterized by the absence of hydrogen bonds and s-*cis* conformation of the carboxyl group, which functions as an electron donor to stablize the developing iminium. When both hydrogen bonded and non-hydrogen bonded types of TSs are considered, the calculated enantioselectivities for Michael additions of aldehyde and ketone substrates are in good agreement with experimental findings.

Introduction

Organocatalysis has achieved remarkable success during the last decade in catalytic asymmetric transformations.[1] One of the key milestones of organocatalysis is the discovery of (*S*)-proline catalyzed intermolecular aldol reactions *via* an enamine mechanism by List *et al*. in 2000.[2] Subsequent mechanistic studies by Bahmanyar and Houk,[3] Arno and Domingo,[4] Boyd *et al.*,[5] and List *et al*.[6] revealed that proton transfer from the α-carboxyl group of the proline to the developing alkoxide during the C–C bond-forming step is crucial to stabilize the transition structures and is responsible for the energetic differences among the different approaches of enamine to electrophile. However, when (*S*)-proline catalyst was applied to conjugated additions such as Michael reactions, poor yields and low enantioselectivities were obtained, despite high observed diastereoselectivities.[7–9] Unsatisfactory enantioselectivities are persistent in ionic liquids for both aldehyde and ketone substrates.[10] In contrast to the proline-catalyzed aldol reactions, theoretical understanding of such low enantioselectivities in proline-catalyzed Michael reactions is somewhat limited.[11]

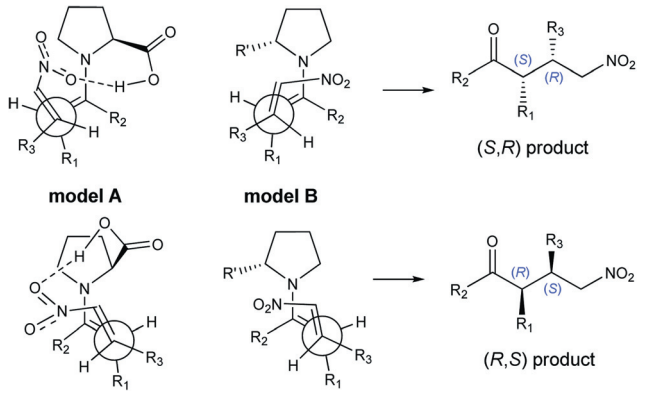
Experimentally, (*S*)-proline promotes *syn* (*R,S*) Michael product for aldehyde substrates and *syn* (*S,R*) product for ketone substrates (Scheme 1).[7–9] This reversal of enantioselectivity from aldehyde to ketone substrate was also observed for other proline derived organocatalysts bearing an acid functional group.[11c,12] The exact origin of such reversal has remained controversial.



Scheme 1 Proline-catalyzed Michael additions of aldehydes and ketones to *trans*-β-nitrostyrene.

Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore. E-mail: chmwmw@nus.edu.sg; Fax: +65 67791691; Tel: +65-65164320

† Electronic supplementary information (ESI) available: Total energies and cartesian coordinates of all optimized structures (Table S1), NBO charges of selected transition states (Table S2), and results of conformational studies (Fig. S1), structures and energies of *E*- and *Z*-enamine conformers (Fig. S2), and transition states derived from *Z*-enamine (Fig. S3). See DOI: 10.1039/c2ob06993h



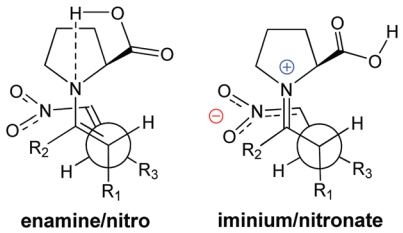
Scheme 2 Two models of transition state for organocatalyzed nitro-Michael additions: hydrogen bonded model A and non-hydrogen bonded model B.

As for proline-catalyzed aldol reactions, it is generally believed that hydrogen bond in the C–C bond-forming transition state (TS) between the α-carboxyl group of (*S*)-proline and nitroalkene (model A, Scheme 2) is crucial for Michael reactions.[13] Based on this hydrogen bonding mode, a recent DFT study of proline-catalyzed nitro-Michael addition by Patil and Sunoj concluded that explicit inclusion of methanol solvent molecules in transition state hydrogen bond network is required to reliably reproduce the observed enantioselectivities.[14]

Alternative non-hydrogen bonded types of transition state (model B, Scheme 2) have been proposed by Barbas *et al.*,[15] Alexakis and Bernardinelli[16] and Kotsuki *et al.*[17] to rationalize product stereochemistry of Michael reactions catalyzed by diamine organocatalysts. However, there has been no literature report applying this non-hydrogen bonded model to rationalize stereoselectivity of proline-catalyzed Michael reactions, presumably due to the conceivable "strong" hydrogen bond in the transition states.

In our ongoing effort towards understanding the mechanism and origin of stereoselectivities of organocatalyzed Michael reactions,[18] we find that it is necessary to go beyond the simple hydrogen bond catalysis to offer a satisfactory explanation to observed enantioselectivity. In particular, we note that Michael reactions can be catalyzed by amine catalysts that lack a hydrogen bond donor, such as diarylprolinol ethers[19] and the above mentioned diamine catalysts,[15–17] without significant lost of catalytic efficiency or enantioselectivity compared to proline. This prompts us to carefully investigate the non-hydrogen bonded type of transition state. Here, we hypothesize that this type of transition state is essential to understand catalytic Michael reactions. This implies that both types of C–C bond-forming transition state, hydrogen bonded and non-hydrogen bonded, based on an enamine mechanism,[20] are necessary to explain the observed enantioselectivities in Michael additions catalyzed by proline.

In their pioneering studies, Seebach *et al*. proposed synclinal transition states for the major *syn* diastereomers of Michael reactions in which developing nitronate group interact favorably with developing iminium moiety.[21] This hypothesis has been supported by both experimental and theoretical studies.[22] However, in these TSs, charge transfer from enamine moiety to



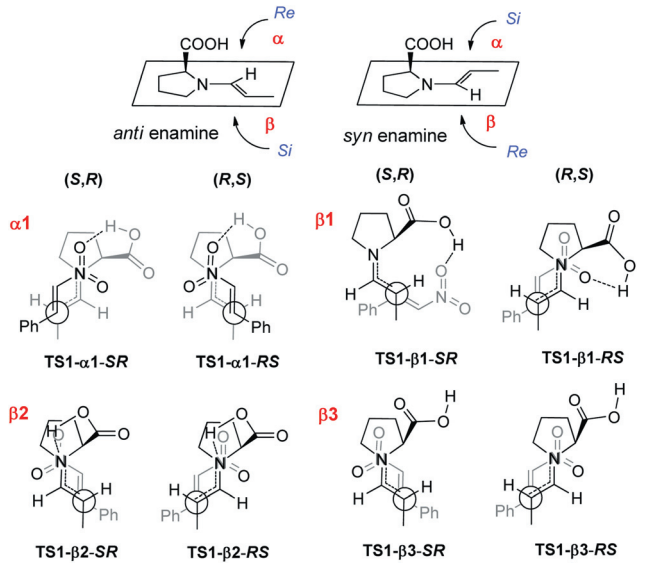
Scheme 3 Two possible modes of electrostatic interaction in the transition states of proline-catalyzed Michael reactions. Note the difference in conformation of the α-carboxyl group of the pyrrolidine moiety.

nitrostyrene is only partially completed. One would envisage two plausible modes of electrostatic interaction, namely enamine–nitro and iminium–nitronate interactions (see Scheme 3). The nature of this electrostatic interaction would have a profound influence on the conformational preference of the α-carboxyl group in the transition states, especially for the TSs of model B (Scheme 2). It is important to point out that previous approach of analyzing the conformation of α-substituent in TSs for pyrrolidine-based catalysts is based solely on conformational studies of enamine intermediates.[11,23] To the best of our knowledge, there has been no report in the literature studying the nature of electronic interaction in the transition structures of proline-catalyzed Michael reaction and investigating the effect of this interaction on the conformational space of the α-carboxyl group of the pyrrolidine moiety.

To further shed light on the origin of enantioselectivities of proline-catalyzed Michael reactions and to test our hypothesis, we have studied systematically all transition states of models A and B for several proline-catalyzed Michael reactions, namely reactions (1)–(4) (Scheme 1). In particular, we examined in detail the conformations of the α-carboxyl group in the C–C bond-forming transition states.

Computational methodology

Geometry optimizations were carried out with the M06-2X[24] density functional method together with the 6-31G** basis set.[18,25] Frequency calculations were performed on the optimized geometries to establish the nature of stationary points as transition states (with only one imaginary frequency) or equilibrium structures (with all real frequencies). Higher-level relative energies were obtained through MP2/6-311+G** single-point calculations. The polarizable continuum model (PCM)[26] was employed to investigate the effect of solvation. MP2/6-311+G** single-point energy PCM calculations (methanol, $\varepsilon = 32.6$) were carried out based on the gas-phase M06-2X/6-31G** geometries. The UAKS radii and solvent accessible surface (SAS) options were employed for the PCM calculations. Only the electrostatic term is included in the solvation calculations. Unless otherwise noted, the relative energies reported in the text correspond to relative enthalpies at 298 K (ΔH_{298}). Previous study has suggested that computed relative enthalpy provides a better comparison with observed enantioslectivity.[6,27] Charge density analysis was carried out using the natural bond orbital (NBO) method.[28] All calculations were performed using the Gaussian 09 suite of program.[29]



Scheme 4 Various transition states of (*S*)-proline catalyzed Michael addition between **1** and **5** leading to the two *syn* products (*R*,*S*) and (*S*,*R*). Definition of α and β faces.

Results and discussion

Michael reactions of aldehydes

The Michael reaction between propanal (**1**) and β-nitrostyrene (**5**) was studied initially. Two conformations of enamine intermediate, derived by condensation of **1** with (*S*)-proline catalyst, are possible: *anti* and *syn*. Here, we designate the face with the α-carboxyl group as α face and the opposite side as β face (see Scheme 4). Those TSs involving nitrostyrene attacking from the α face are designated as α TSs. β TSs are defined in a similar manner. All TSs are assumed to be the Seebach type of TSs unless hydrogen bond formation is required.

To examine the nature of electrostatic interaction between developing iminium and nitronate groups in transition state, relaxed potential energy surface scan was performed first to determine the lowest-energy conformation of the carboxyl group in enamine and iminium (see Fig. S1, ESI†). Based on the results obtained, we envisaged that 3 types of β transition state were possible (Scheme 4): β1 TS with hydrogen bond between the carboxyl group and nitro group, while β2 and β3 TSs have the most favorable conformations of the carboxyl group of enamine and iminium ion. Thus, both α1 and β1 TSs correspond to model A TSs while β2 and β3 TSs are model B TSs. Considering there are two possible enantiomeric products (*RS* and *SR*), a total of eight transition states are identified (Scheme 4). All eight TSs were considered in this study. The *E* conformation is assumed to be the active form of enamine. This is readily confirmed by calculation of the *Z* conformation, which is 11 kJ mol^{-1} less stable than the *E* form (Fig. S2, ESI†). Hence, only transition structures derived from the *E*-enamine are considered here. Further calculations of selective TS's derived from *Z*-enamine indicate they are indeed significantly higher in energy, by at least 59 kJ mol^{-1} (Fig. S3, ESI†).

For reaction (1), the lowest-energy TSs leading to the major (*R*,*S*) and minor (*S*,*R*) products are **TS1-β1-*RS*** and **TS1-β3-*SR***

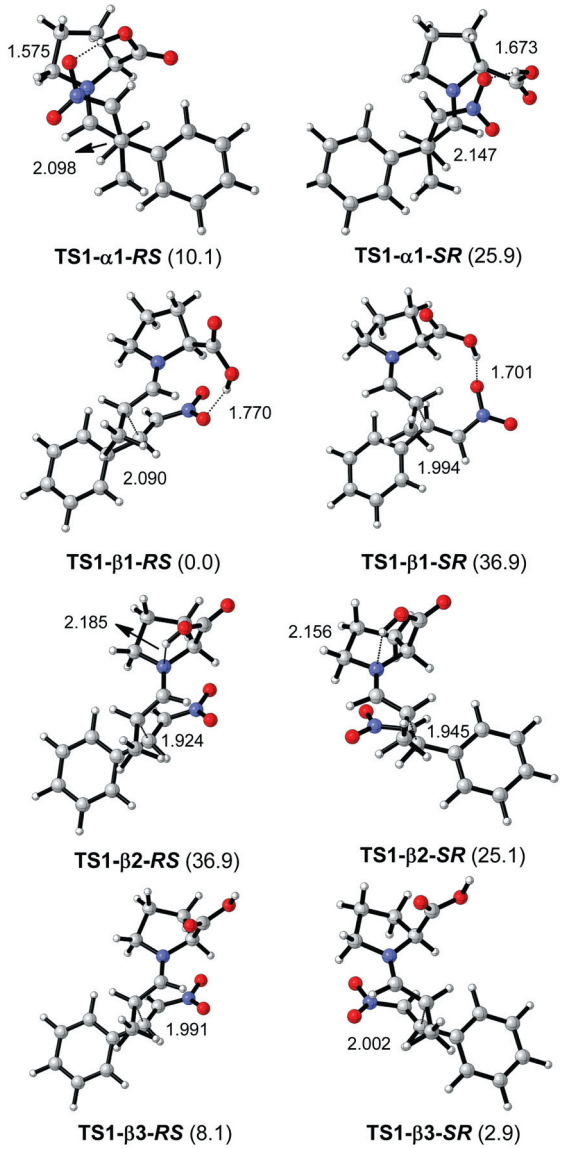
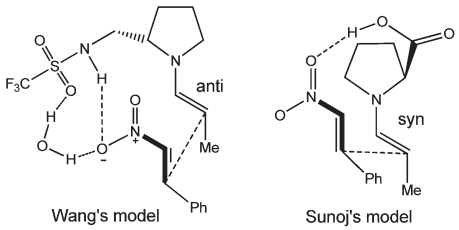


Fig. 1 Optimized (M06-2X/6-31G**) geometries of transition states of Michael reaction (1), hydrogen bonding distances in Å. Calculated relative enthalpies (ΔH_{298}, kJ mol^{-1}) are in parenthesis.

(Fig. 1), respectively, with the former being 2.9 kJ mol^{-1} more stable. This result is in pleasing accord with the observed small preference of the (*R*,*S*) product for the aldehyde substrates.[9] The calculated activation barrier ($\Delta H^{\dagger}_{298\ K}$) for the (*R*,*S*)-induced TS, *via* **TS1-β1-*RS***, is small (12.5 kJ mol^{-1} with respect to the pre-transition state complex of enamine and nitrostyrene), which is consistent with the room-temperature requirement of this catalytic addition.[9] The calculated structure of **TS1-β1-*RS*** (Fig. 1) involves *anti*-enamine and nitrostyrene attacking from the β face, which agrees with the model proposed by Wang *et al.* for pyrrolidine sulfonamide catalyzed Michael reactions,[11c] but differs from Sunoj's TS model[14] for proline-catalyzed Michael reactions (Scheme 5). The calculated (*R*,*S*) transition state corresponding to Sunoj's model is **TS1-α1-*RS***, which lies 10.1 kJ mol^{-1} higher in energy than **TS1-β1-*RS***. This demonstrates that unlike proline-catalyzed aldol reactions,[3–6,30] where the electrophile always attacks from the same face as the carboxyl group in



Scheme 5 Wang's and Sunoj's TS models for Michael reaction (1) catalyzed by proline derivatives.

major transition states, for Michael reactions of aldehydes, there is a slight preference for nitrostyrene to attack from the β face. The hydrogen bond is stronger in **TS-α1-*RS*** than in **TS-β1-*RS***, indicating that carboxyl group is probably too close to nitrostyrene in **TS-α1-*RS*** to cause significant steric repulsion.

Contrary to a previous theoretical study of proline-catalyzed Michael reactions,[14] our calculated lowest-energy TS leading to (*S,R*) product, namely **TS1-β3-*SR*** (Fig. 1), does not have a hydrogen bond between the carboxyl group and the incoming nitrostyrene. In comparison, the hydrogen bonded transition state **TS1-α1-*SR*** is 23.0 kJ mol^{-1} higher in energy than **TS1-β3-*SR***. It is also 15.8 kJ mol^{-1} higher than the corresponding *RS* TS, *i.e.* **TS-α1-*RS***. The higher relative energy of **TS1-α1-*SR*** can be attributed to the close contact of the two electron-negative oxygen atoms found only in **TS1-α1-*SR***. This finding supports our initial hypothesis that the non-hydrogen bonded transition states are also important to consider, even for catalysts bearing acidic functional groups such as proline. Furthermore, in **TS1-β3-*SR***, the α-carboxyl group of pyrrolidine moiety adopts the most stable conformation of carboxyl group found for an iminium ion rather than for an enamine. Transition state leading to (*S,R*) product with corresponding enamine-like carboxyl conformation, namely **TS1-β2-*SR*** (Fig. 1), is 22.2 kJ mol^{-1} higher in energy than **TS1-β3-*SR***, despite the observed hydrogen bond between carboxyl group and pyrrolidine nitrogen atom in **TS1-β2-*SR***. To account for this seemingly unexpected result, we firstly calculated NBO charge of the pyrrolidine nitrogen atom in both **TS1-β2-*SR*** and **TS1-β3-*SR***. The NBO results (Table S2, ESI†) show that in both transition states, the atomic charge of nitrogen is closer to that of an iminium ion rather than an enamine. This clearly indicates that the electronic interaction in the TSs of Michael reaction is better described as an iminium ion interacting with a nitronate. Thus, the hydrogen bond to an "iminium" nitrogen in **TS1-β2-*SR*** is expected to be fairly weak.

Interestingly, the conformation of the α-carboxyl group is s-*cis* in **TS1-β3-*SR*** and s-*trans* in **TS1-β2-*SR*** (Fig. 1). S-*cis* HOCO conformation is generally preferred in carboxylic acids. For instance, the s-*cis* conformer of acetic acid is significantly more stable than the s-*trans* conformer, by 24.6 kJ mol^{-1} at the same level of theory, which is in agreement with the literature values.[31] However, the s-*trans* conformation of carboxyl group is structurally more suited to hydrogen bonding and is found in all hydrogen bonded transition states for reaction (1). We note that this subtle difference between the conformational preference of the carboxyl group in free state and in hydrogen-bonded state has prompted one study to use 1H-tetrazole as a conformational rigid substitute for carboxyl group in designing new sensors for anions.[32] However, we are unable to find such examples in organocatalysis, despite there having been continuous efforts to design new organocatalysts bearing carboxyl group(s).[9,27b,33] Thus, caution shall be taken when proposing mechanism and transition state for this type of organocatalyst or designing new organocatalyst.

Table 1 Calculated relative energies (ΔH_{298} and ΔG_{298}, kJ mol^{-1}) of various transition states for reactions (1)–(4)[a,b]

TS	Reaction (1)		Reaction (2)		Reaction (3)		Reaction (4)	
	ΔH	ΔG	ΔH	ΔG	ΔH	ΔG	ΔH	ΔG
α1-*RS*	10.1	14.7	10.0	14.1	11.8	20.4	8.3	17.8
α1-*SR*	25.9	25.9	23.8	24.1	32.9	37.3	26.7	30.6
β1-*RS*	0.0	0.0	0.0	0.0	27.0	32.1	17.2	21.8
β1-*SR*	36.9	33.9	36.1	34.2	26.9	27.3	23.3	27.0
β2-*RS*	36.9	34.0	36.9	34.2	39.8	44.4	38.1	41.2
β2-*SR*	25.1	20.5	28.2	26.0	21.6	22.7	25.4	25.3
β3-*RS*	8.1	4.2	8.6	5.4	7.8	11.6	7.0	9.4
β3-*SR*	2.9	−1.2	3.1	−0.7	0.0	0.0	0.0	0.0

[a] MP2/6-311+G**//M06-2X/6-31G** level of theory. [b] The lowest enthalpy of activation ($\Delta H^{\ddagger}_{298\ K}$) and activation free energy ($\Delta G^{\ddagger}_{298\ K}$), with respect to enamine-nitrostyrene pre-transition state complex, for reactions (1)–(4) are 12.5 and 25.7 (**TS1-α1-*RS***), 10.2 and 25.0 (**TS2-α1-*RS***), 22.8 and 35.1 (**TS3-β3-*SR***), and 34.1 and 47.1 (**TS4-β3-*SR***) kJ mol^{-1}, respectively.

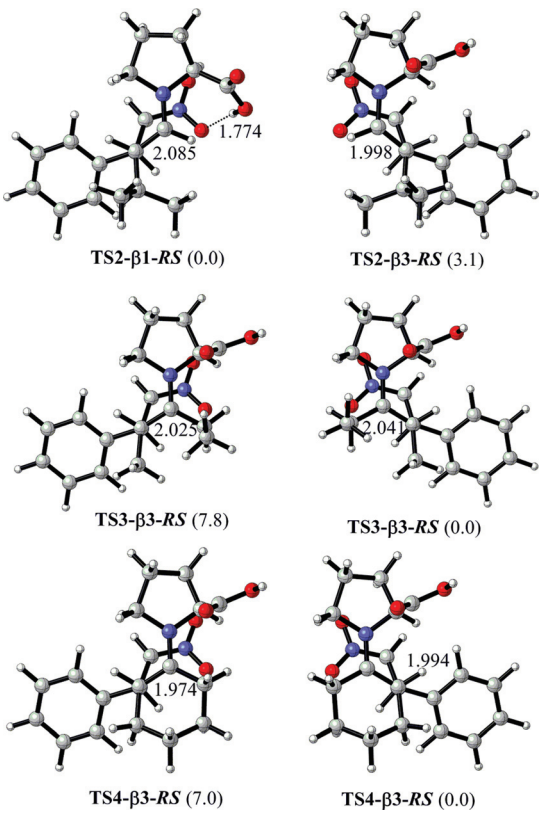


Fig. 2 Optimized (M06-2X/6-31G**) geometries of transition states of Michael reactions (2)–(4), hydrogen bonding distances in Å. Calculated relative enthalpies (ΔH_{298}, kJ mol^{-1}) in parenthesis.

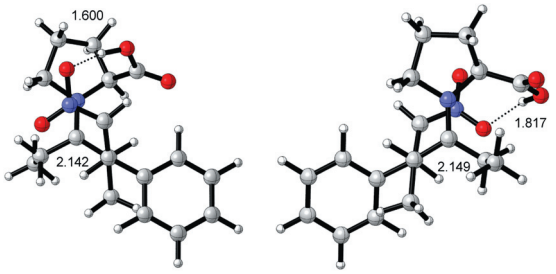


Fig. 3 Optimized (M06-2X/6-31G**) geometries of hydrogen bonded TSs for reaction (3), **TS3-α1-*RS*** and **TS3-β1-*RS***, hydrogen bonding distances in Å. Calculated relative enthalpies (ΔH_{298}, kJ mol^{-1}) in parenthesis, with respect to **TS3-β3-*SR***.

Table 2 Comparison of calculated enantiomeric excess (ee)[a] with known experimental results

Reaction	Observed ee[b] (%)	Calculated ee[c] (%)
(1)	20	54
(2)	25	57
(3)	−76	−92
(4)	−57	−89

[a] *RS* product as reference. [b] From ref. 7b, 8, and 9. [c] Based on contributions of 8 transition states (Scheme 4) at MP2/6-311+G**//M06-2X/6-31G** level.

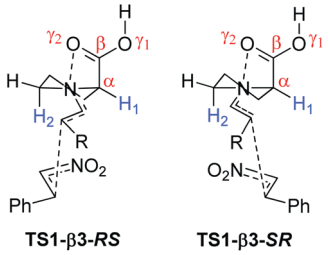
Similar result is obtained for aldehyde **2**, i.e reaction (2), (Scheme 1). In agreement with experiment, the (*R,S*) product is preferred (Table 1). As with aldehyde **1**, the lowest-energy TS leading to the (*S,R*) product is **TS1-β3-*SR*** (Fig. 2), a non-hydrogen bonded TS. Consistent with the observed low enantioselectivity,[7b] small energy difference of 3.1 kJ mol^{-1} (Table 1) is predicted for the lowest-energy *SR* and *RS* TSs.

Michael reactions of ketones

Michael reactions of the ketone substrates were also explored, namely reactions (3) and (4) (Scheme 1).[8] Intriguingly, the lowest-energy TSs leading to both enantiomeric products correspond to the non-hydrogen bonded β3 type of transition states (Fig. 2). For comparison, the two hydrogen bonded *RS* TSs of reaction (3) (**TS3-α1-*RS*** and **TS3-β1-*RS*** Fig. 3) are significantly higher in energy than the non-hydrogen bonded β3-*RS* transition state (Table 1). The hydrogen bonding distance in **TS3-β1-*RS*** (1.817 Å) is significantly longer than that in the corresponding aldehyde analogue (1.770 Å in **TS1-β1-*RS***). It is rather surprising that for a supposedly "hydrogen-bond" catalytic reaction, the mechanism changes from the hydrogen bond and enamine catalysis for aldehyde substrates to simple enamine catalysis for ketone substrates. This is probably due to the presence of one more alkyl group in the case of ketone substrate which impedes the formation of β1-*RS* type of transition state.

Overall, there is close agreement between computed enantiomeric excess (ee), using the gas-phase enthalpy of activation ($\Delta H^{\dagger}_{298\ K}$), and known experimental results for both aldehyde and ketone substrates (Table 2). Most importantly, the computed ee successfully predict the correct enantioselectivity for each substrate and the reversal of enantioselectivity on going from aldehyde to ketone substrates (Table 2). As with previous theoretical studies,[6,27] calculated activation enthalpies yield better agreement with experiment than computed activation free energies.

Finally, we examined the effect of solvation (in methanol solvent) using the implicit PCM solvation model.[26] The PCM calculations indicate that the solvent influence is small. The calculated solvation energies, $\delta\Delta G = \Delta G_{solution} - \Delta G_{gas}$, for the energy difference (ΔG) between the lowest-energy *SR* and *RS* transition states of reactions (1)–(4) are −0.6, 0.9, −0.9 and −0.1 kJ mol^{-1}, respectively. Thus, explicit solvation, as proposed by Patil and Sunoj,[14] is likely not to be required to explain the observed low enantioselectivities. This is further supported by the experimental results that low enantioselectivities were also observed in ionic liquids.[10]



Scheme 6 Conformations of **TS1-β3-*RS*** and **TS1-β3-*SR*** transition states.

Stereoselectivity in β3 type transition states

The general preference for *SR* over *RS* type for the β3 transition state warrants further investigation. In the observed conformation of the pyrrolidine backbone in the β3 TSs (Scheme 6), the carboxyl group and H_1 are in an equatorial position while H_2 is in an axial position. Intriguingly, a small $NC_\alpha C_\beta O_{\gamma 1}$ torsional angle (<20°) is observed in both *RS* and *SR* forms of TS. As a result, the carboxyl oxygen ($O_{\gamma 2}$) is in close contact with the nitrogen atom, *e.g.* 2.756 Å in **TS1-β3-*SR***. However, there is no direct favorable interaction between the N and O atoms. Energetic analysis of NBO interactions based on second-order perturbation theory[28] reveals that the near collinear axial arrangement maximizes the donor–acceptor interactions from C_β–$O_{\gamma 1}$ σ and $O_{\gamma 1}$ lone pair orbitals to the N–C_α σ* orbital and from the N lone pair to the C_α–C_β σ* orbital simultaneously (Fig. 4). In other words, the conformational preference is attributed to several favorable donor–acceptor interactions.

The observed preference of **TS1-β3-*SR*** over **TS1-β3-*RS*** is firstly attributed to the adoption of the conformation shown in Fig. 4. **TS1-β3-*RS*** is expected to experience greater steric repulsion of the axial hydrogen. This is readily confirmed by calculations of 2 modeled transition states without the α-carboxyl group. In this case, the *SR*-type TS is more stable than the sterically more hindered *RS*-type TS by 3.2 kJ mol^{-1}. For comparison, **TS1-β3-*SR*** is more stable than **TS1-β3-*RS*** by 5.2 kJ mol^{-1}, which suggests additional factors of stabilization of the

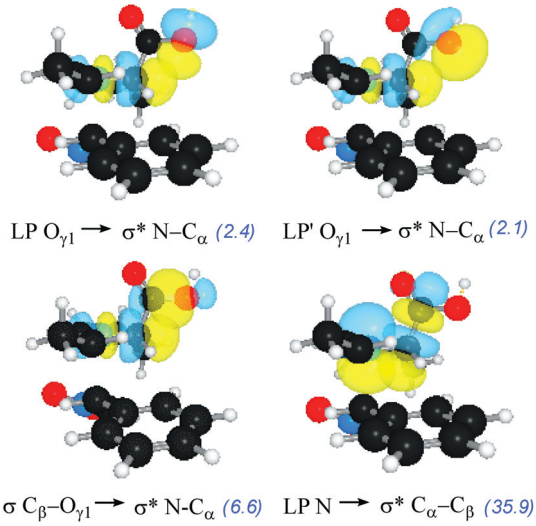


Fig. 4 NBO donor–acceptor interactions in the near-collinear axial conformation of the α-carboxyl group in **TS-β3-*SR*** transition state, interaction energies (kJ mol^{-1}) in parenthesis.

SR-type TS. Secondly, electron donation from the π orbital of α carbon of nitrostyrene to the C_α–C_β σ* bond in **TS1-β3-*SR***, as revealed by NBO analysis, further stabilizes *SR* TS over *RS* TS. Thus, when a stronger electron-withdrawing nitro group is substituted at the α position of pyrrolidine moiety, a larger energetic preference of 8.4 kJ mol^{-1} for the *SR*-type TS is predicted.

Conclusions

In summary, we have systematically examined all possible transition states of models A and B for (*S*)-proline-catalyzed Michael addition of several aldehydes and ketones to β-nitrostyrene. The most favorable reactive channel does not always correspond to the formation of an intramolecular hydrogen bond (*i.e.* α1 and β1). Transition state of model B without the COOH···N hydrogen bond (*i.e.* β2 and β3) is best described as an iminium ion, stabilized by neighbouring carboxyl group *via* charge transfer, interacting with nitronate. These non-hydrogen bonded transition states provide the key to understand the observed low enantioselectivities and the preference of different stereoisomeric products in aldehyde and ketone substrates.

Acknowledgements

This research was supported by the National University of Singapore (Grant No: R-143-000-481-112).

Notes and references

1 (*a*) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471; (*b*) D. W. C. MacMillan, *Nature*, 2008, **455**, 304; (*c*) C. F. Barbas III, *Angew. Chem., Int. Ed.*, 2008, **47**, 42; (*d*) S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178; (*e*) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167; (*f*) E. N. Jacobsen and D. W. C. MacMillan, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 20618; (*g*) B. R. Buckley and M. M. Farah, *Annu. Rep. Prog. Chem., Sect. B*, 2011, **107**, 102.
2 B. List, R. A. Lerner and C. F. Barbas III, *J. Am. Chem. Soc.*, 2000, **122**, 2395.
3 (*a*) S. Bahmanyar and K. N. Houk, *J. Am. Chem. Soc.*, 2001, **123**, 9922; (*b*) S. Bahmanyar and K. N. Houk, *J. Am. Chem. Soc.*, 2001, **123**, 11273.
4 M. Arno and L. R. Domingo, *Theor. Chem. Acc.*, 2002, **108**, 232.
5 K. N. Rankin, J. W. Gauld and R. J. Boyd, *J. Phys. Chem. A*, 2002, **106**, 5155.
6 S. Bahmanyar, K. N. Houk, H. J. Martin and B. List, *J. Am. Chem. Soc.*, 2003, **125**, 2475.
7 (*a*) B. List, P. Pojarliev and H. J. Martin, *Org. Lett.*, 2001, **3**, 2423; (*b*) J. M. Betancort and C. F. Barbas III, *Org. Lett.*, 2001, **3**, 3737.
8 D. Enders and A. Seki, *Synlett*, 2002, 26.
9 J. Xiao, F.-X. Xu, Y.-P. Lu and T.-P. Loh, *Org. Lett.*, 2010, **12**, 1220.
10 (*a*) P. Kotrusz, S. Toma, H.-G. Schmalz and A. Adler, *Eur. J. Org. Chem.*, 2004, 1577; (*b*) M. S. Rasalkar, M. K. Potdar, S. S. Mohile and M. M. Salunkhe, *J. Mol. Catal. A: Chem.*, 2005, **235**, 267.
11 (*a*) R. Zhu, D. Zhang, J. Wu and C. Liu, *Tetrahedron: Asymmetry*, 2006, **17**, 1611; (*b*) A. Hamza, G. Schubert, T. Soos and I. Papai, *J. Am. Chem. Soc.*, 2006, **128**, 13151; (*c*) J. Wang, H. Li, B. Lou, L. Zu, H. Guo and W. Wang, *Chem.–Eur. J.*, 2006, **12**, 4321; (*d*) M. Arno, R. J. Zaragoza and L. R. Domingo, *Tetrahedron: Asymmetry*, 2007, **18**, 157.
12 (*a*) W. Wang, J. Wang and H. Li, *Angew. Chem., Int. Ed.*, 2005, **44**, 1369; (*b*) Y. Hayashi, H. Gotoh, T. Tamura, H. Yamaguchi, R. Masui and M. Shoji, *J. Am. Chem. Soc.*, 2005, **127**, 16028; (*c*) D. Diez, M. J. Gil, R. F. Moro, I. S. Marcos, P. García, P. Basabe, N. M. Garrido, H. B. Broughton and J. G. Urones, *Tetrahedron*, 2007, **63**, 740; (*d*) X. J. Zhang, S. P. Liu, X. M. Li, M. Yan and A. S. C. Chan, *Chem. Commun.*, 2009, 844; (*e*) C. Palomo, S. Vera, A. Mielgo and E. Gómez-Bengoa, *Angew. Chem., Int. Ed.*, 2006, **45**, 5984.
13 P. H. Cheong, C. Y. Legault, J. M. Um, N. Celebi-Olcum and K. N. Houk, *Chem. Rev.*, 2011, **111**, 5042.
14 M. P. Patil and R. B. Sunoj, *Chem.–Eur. J.*, 2008, **14**, 10472.
15 J. M. Betancort, K. Sakthivel, R. Thayumanavan, F. Tanaka and C. F. Barbas III, *Synthesis*, 2004, **9**, 1509.
16 A. Alexakis and G. Bernardinelli, *Org. Lett.*, 2003, **5**, 2559.
17 T. Ishii, S. Fujioka, Y. Sekiguchi and H. Kotsuki, *J. Am. Chem. Soc.*, 2004, **126**, 9558.
18 (*a*) H. Yang and M. W. Wong, *J. Org. Chem.*, 2011, **76**, 7399; (*b*) Z. Jiang, H. Yang, X. Han, J. Luo, M. W. Wong and Y. Lu, *Org. Biomol. Chem.*, 2010, **8**, 1368.
19 E. Marques-Lopez and R. P. Herrera, *Curr. Org. Chem.*, 2011, **15**, 2311.
20 (*a*) B. List, *Acc. Chem. Res.*, 2004, **37**, 548; (*b*) W. Notz, F. Tanaka and C. F. Barbas III, *Acc. Chem. Res.*, 2004, **37**, 580; (*c*) B. List, *Chem. Commun.*, 2006, 819; (*d*) S. Sulzer-Mossé and A. Alexakis, *Chem. Commun.*, 2007, 3123; (*e*) P. M. Pihko, I. Majander and A. Erkkilä, *Top. Curr. Chem.*, 2010, **291**, 29.
21 (*a*) D. Seebach and J. Goliński, *Helv. Chim. Acta*, 1981, **64**, 1413; (*b*) S. J. Blarer, W. B. Schweizer and D. Seebach, *Helv. Chim. Acta*, 1982, **65**, 1637; (*c*) R. Haner, T. Laube and D. Seebach, *Chimia*, 1984, **38**, 255; (*d*) D. Seebach, A. K. Beck, J. Goliński, J. N. Hay and T. Laube, *Helv. Chim. Acta*, 1985, **68**, 162.
22 (*a*) J. Bures, A. Armstrong and D. G. Blackmond, *J. Am. Chem. Soc.*, 2011, **133**, 8822; (*b*) M. Hutka, V. Polackova, J. Marak, D. Kaniansky, R. Sebesta and S. Toma, *Eur. J. Org. Chem.*, 2010, 6430; (*c*) D. Seebach, R. Gilmour, U. Groselj, G. Deniau, C. Sparr, M. Ebert, A. K. Beck, L. B. McCusker, D. Sisak and T. Uchimaru, *Helv. Chim. Acta*, 2010, **93**, 603; (*d*) S. Belot, A. Massaro, A. Tenti, A. Mordini and A. Alexakis, *Org. Lett.*, 2008, **10**, 4557; (*e*) H. Uehara and C. F. Barbas III, *Angew. Chem., Int. Ed.*, 2009, **48**, 9848; (*f*) J. M. Um, D. A. DiRocco, E. L. Noey, T. Rovis and K. N. Houk, *J. Am. Chem. Soc.*, 2011, **133**, 11249.
23 (*a*) M. P. Patil, A. K. Sharma and R. B. Sunoj, *J. Org. Chem.*, 2010, **75**, 7310; (*b*) M. B. Schmid, K. Zeitler and R. M. Gschwind, *Chem. Sci.*, 2011, **2**, 1793.
24 Y. Zhao and D. G. Truhlar, *Theor. Chem. Acc.*, 2008, **120**, 215.
25 B. Cho, C.-H. Tan and M. W. Wong, *Org. Biomol. Chem.*, 2011, **9**, 4550.
26 (*a*) M. Cossi, V. Barone, R. Cammi and J. Tomasi, *Chem. Phys. Lett.*, 1996, **255**, 327; (*b*) V. Barone, M. Cossi and J. Tomasi, *J. Chem. Phys.*, 1997, **107**, 3210–3221.
27 (*a*) S. E. Wheeler, A. J. McNeil, P. Müller, T. M. Swager and K. N. Houk, *J. Am. Chem. Soc.*, 2010, **132**, 3304; (*b*) C. B. Shinisha and R. B. Sunoj, *Org. Biomol. Chem.*, 2007, **5**, 1287.
28 A. E. Reed, L. A. Curtiss and F. Weinhold, *Chem. Rev.*, 1988, **88**, 899.
29 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov,

J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, *GAUSSIAN 09 (Revision A.1)*, Gaussian, Inc., Wallingford CT, 2009.

30 A. K. Sharma and R. B. Sunoj, *Angew. Chem., Int. Ed.*, 2010, **49**, 6373.

31 (*a*) S. Amiri, H. P. Reisenauer and P. R. Schreiner, *J. Am. Chem. Soc.*, 2010, **132**, 15902; (*b*) M. L. Senent, *Mol. Phys.*, 2001, **99**, 1311.

32 A. H. McKie, S. Friedland and F. Hof, *Org. Lett.*, 2008, **10**, 4653.

33 (*a*) D. Terakado, M. Takano and T. Oriyama, *Chem. Lett.*, 2005, **34**, 962; (*b*) D. Roca-López, P. Merino, F. J. Sayago, C. Cativiela and R. P. Herrera, *Synlett*, 2011, 249; (*c*) A. Armstrong, Y. Bhonoah and A. J. P. White, *J. Org. Chem.*, 2009, **74**, 5041; (*d*) S. G. Davies, A. J. Russell, R. L. Sheppard, A. D. Smith and J. E. Thomson, *Org. Biomol. Chem.*, 2007, **5**, 3190.