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Noninnocent Role of *N*-Methyl Pyrrolidinone in Thiazolidinethione-Promoted Asymmetric Aldol Reactions

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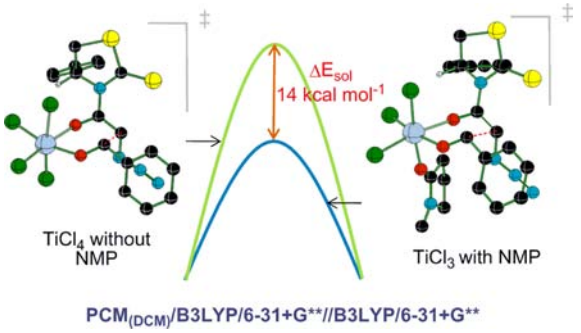
ABSTRACT



The origin of stereoselectivity in the reaction between α-azido titanium enolate derived from chiral auxiliary *N*-acyl thiazolidinethione and benzaldehyde is established using the DFT(B3LYP) method. A nonchelated transition state with *N*-methyl-2-pyrrolidinone (NMP) bound to a $TiCl_3$ enolate is found to be energetically the most preferred model responsible for the formation of an Evans *syn* aldol product. The TS model devoid of NMP, although of higher energy, is found to be successful in predicting the right stereochemical outcome.

Chiral auxiliaries such as oxazolidinones and thiazolidinethiones are widely used in asymmetric synthesis, in both industry and academia.[1] Since the days of early developments in chiral auxiliaries, several modifications have been tried to steer the stereochemical course of such reactions.[2] Aldol reactions using chlorotitanium enolates of thiazolidinethione generally yield Evans *syn* products with 2 equiv of base while a non-Evans *syn* aldol product can be obtained by lowering the loading of the base to 1 equiv.[3] Similarly, the use of *N*-methyl pyrrolidinone (NMP), as a cosolvent or additive, is known to alter the stereochemical course of asymmetric aldol reactions. For instance, chlorotitanium enolates of thiazolidinethione provide access to Evans *syn* and non-Evans *syn* products, respectively, in the presence and absence of NMP.[4] This observation evidently suggests a noninnocent role of NMP toward influencing the stereoselectivity. Since NMP is a commonly used additive in asymmetric aldol reactions,[5] the molecular origin of such stereochemical differences are of inherent interest.

Recently, Franck and co-workers reported the formation of an Evans *syn* product in an aldol reaction between the α-azido enolates derived from *N*-acyl thiazolidinethione and aldehydes (Scheme 1).[6] The stereoselectivity in such reactions is generally rationalized with the help of a working hypothesis relying on qualitative transition state

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(6) (a) Patel, J.; Clave, G.; Renard, P.-Y.; Franck, X. *Angew. Chem., Int. Ed.* **2008**, *47*, 1. (b) The reaction holds promise in providing easier access to a *syn* α-amino-β-hydroxy acid or acid derivatives. Such structural elements are known to be important in several biologically active compounds.

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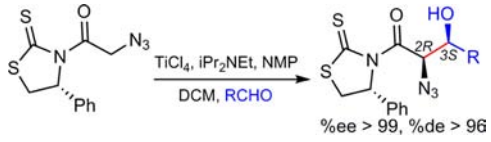
(TS) models. In the recent past, quantitative TS models for asymmetric aldol reactions for the commonly employed chiral auxliaries were reported from this laboratory.[7] However, the role of NMP in the stereochemical course of asymmetric aldol reactions thus far remains largely speculative. The TS models aimed at exploring the origin of stereoselectivity under such conditions have not yet been reported. As part of our continued interest toward understanding the controlling factors that influence stereoselectivity in organic reactions,[8] we decided to examine the role of NMP using TS models for stereoselective C−C bond formation between benzaldehyde and chlorotitanium α-azido enolates using the $PCM_{(DCM)}$/B3LYP//B3LYP/6-31+G** level of theory.[9] The electronic energies obtained in the dichloromethane solvent continuum are employed for discussions. The trends as well as the conclusions are found to remain the same with the Gibbs free energies as well, in both the gas phase and the solvent continuum.

Scheme 1. Aldol Reaction between (*R*)-*N*-2-Azidoacetyl-4-phenylthiazolidine-2-thione and RCHO (ref 6)



The reaction can be envisaged to involve the addition of a $TiCl_4$-bound enolate (**1**) to benzaldehyde. Both *cis* and *trans* orientations of the enolate oxygen with respect to the thiocarbonyl group as well as the *E* and *Z* configurations across the C−C double bond are considered. The addition of the *si* or *re* prochiral face of the enolate to that of benzaldehyde can lead to four key stereoisomeric products, as shown in Scheme 2. The notations **a** and **b** respectively denote the *cis* and *trans* orientations of the enolate while **rr**, **rs**, **sr**, and **ss** respectively represent the *re-re*, *re-si*, *si-re*, and *si-si* stereochemical modes of approach between the enolate and benzaldehyde.[10]

The energies of the TSs with both *E* and *Z* configurations of the enolate are provided in Table 1.[11] The most preferred TS in the case of the *Z*-enolate involves the addition of the *re*-face of the *trans* enolate to the *re*-face of benzaldehye (**TS1b$_{rr}$**). Such an approch corresponds to the formation of an Evans *syn* product, consistent with the experimental observation.[6] More significantly, the energy difference between the lowest energy **TS1b$_{rr}$** and diastereomeric **TS1b$_{rs}$** is higher than 3 kcal mol^{-1}, which is in full accordance with the experimental observation of *de* > 96%. Similarly, the predicted *ee* > 99% is in concert with the high enantiomeric excess noted by Franck et al.

The optimized geometry of **TS1b$_{rr}$** exhibits a chairlike arrangement with a fully staggered disposition of the substituents around the developing C−C bond (Figure 1). This is a *nonchelated* TS without any thiocarbonyl or azide coordination to titanium wherein the chiral auxliary and the benzaldehyde phenyl group remain in a *transoid* arrangement. TSs with the *cis* enolate (**TS1a$_{rr}$**, **TS1a$_{rs}$**, and **TS1a$_{sr}$**) conformation are found to be of higher energy, presumably due to the unfavorable Columbic interaction

Scheme 2. Different Likely Stereoisomeric Products Formed by the Addition of Prochiral Enolate to Benzaldehyde

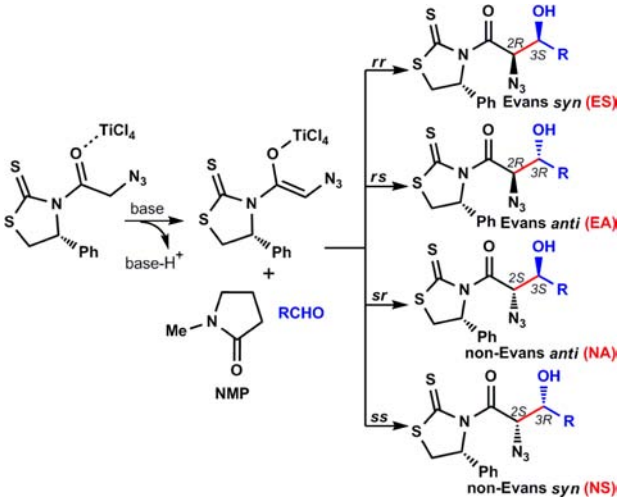


Table 1. Computed Relative Energies[a] (in kcal mol^{-1}) of $TiCl_4$ Coordinated Transition States for *Z*- and *E*-Enolates

Z-enolate			*E*-enolate	
TS	ΔE_{sol}	product	TS	ΔE_{sol}
1a$_{rr}$	11.3	ES	**1a′$_{rr}$**	5.4
1a$_{rs}$	15.9	EA	**1a′$_{rs}$**	–[b]
1a$_{sr}$	9.9	NA	**1a′$_{sr}$**	5.0
1a$_{ss}$	–[b]	NS	**1a′$_{ss}$**	0.8
1b$_{rr}$	**0.0**	ES	**1b′$_{rr}$**	2.0
1b$_{rs}$	4.1	EA	**1b′$_{rs}$**	**0.0**
1b$_{sr}$	6.5	NA	**1b′$_{sr}$**	0.7
1b$_{ss}$	12.5	NS	**1b′$_{ss}$**	3.2

[a] Computed with respect to the lowest energy TS in each enolate configuration (*E* or *Z*). [b] **TS1a$_{ss}$** and **TS1a′$_{rs}$** could not be optimized as the initial guess geometry with a *cis* orientation converged to an *anti* conformer.

(7) (a) Shinisha, C. B.; Sunoj, R. B. *J. Am. Chem. Soc.* **2010**, *132*, 12319. (b) Shinisha, C. B.; Sunoj, R. B. *Org. Lett.* **2010**, *12*, 2868.

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(9) (a) All calculations were performed using Gaussian09. Frisch, M. J. et al. *Gaussian 09*, revision A.02; Gaussian, Inc.: Wallingford, CT, 2004. See Supporting Information (SI) for full citation. (b) Full details of computational methods, including at the mPW1K level of theory, are provided in the SI. The gas-phase free energies exhibit identical trends. See SI (Tables S1−S5). (c) The asymmetric carbon in the chiral auxiliary is in the *R* configuration.

(10) More details on terminologies are described in Figure S1 in the SI.

(11) (a) As the energy difference between *Z* and *E* enolates is only 0.1 kcal mol^{-1}, both of these configurations are considered in this study.

between the thiocarbonyl and the axial chloride ligand on titanium.

In the case of the *E*-enolate, TSs are generally found to be lower in energy than that of the corresponding *Z*-enolate. However, the lowest energy **TS1b′$_{rs}$** in this group corresponds to the Evans *anti* product, contrary to the experimental observation. This implies the involvement of either (a) the higher energy *Z*-enolate as a reactive conformer of the $TiCl_4$-enolate, which is successful in predicting the correct stereochemical course of the reaction, or (b) an alternative TS model in the stereocontrolling step.

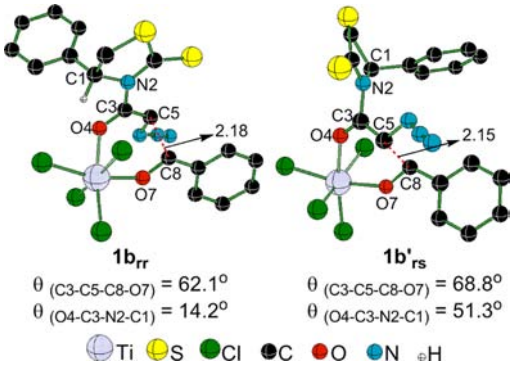

Figure 1. The lower energy diastereomeric transition states with $TiCl_4$ coordination. Only select hydrogens are shown. Distances are in Å and angles in deg.

It is important to consider that, besides the reactants and $TiCl_4$, a tertiary amine (iPr_2NEt) is employed for *in situ* generation of the enolate. The protonated base, released as a result of the enolate formation, can help displace one of the labile chloride ligands on titanium to provide a neutral $TiCl_3$-bound enolate with a vacant coordination site at the metal. Either the thiocarbonyl of the chiral auxiliary or the azide group of the nucleophilic moiety could now bind to the metal resulting in a *chelated* TS.[12]

Alternatively, NMP can be considered as a ligand capable of occupying the open coordination site. TS models with four different relative positions of NMP, as shown in Figure 2, with the *Z*-enolate configuration are examined.[13] In these TSs, the axial and equatorial positions are defined with respect to benzaldehyde and the enolate oxygens. In TS models **N$_a$** and **N$_{a'}$** NMP is axial, while in **N$_e$** and **N$_{e'}$** it is equatorial.

The relative energies of important TSs, as summarized in Table 2, indicate a general preference for an axial

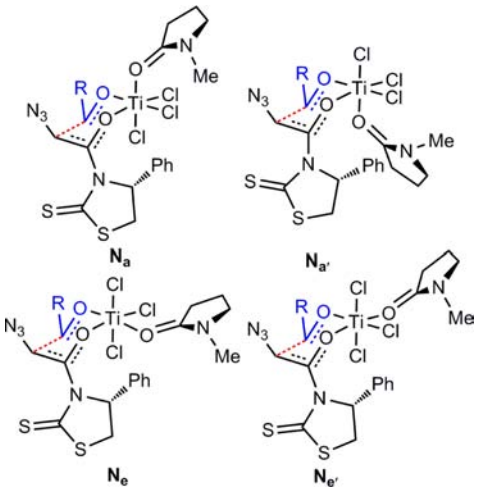

Figure 2. NMP-bound TSs differing in the site of coordination to titanium.

disposition of NMP.[14] **TSN$_a$b$_{rr}$** is found to be the most preferred TS, which is in conformity with the formation of the Evans *syn* product. **TSN$_a$b$_{rr}$** presents a chairlike geometry with a fully staggered arrangement of the substituents around the developing C−C bond and involves a sterically more preferred approach between the reactants as compared to the other stereochemical modes of addition (Figure 3). The nearest diastereomeric TS **TSN$_a$b$_{rs}$** in the NMP-bound model, leading to the Evans *anti* product, is 2.7 kcal mol^{-1} higher in energy. The NMP-bound TS model offers both *de* and *ee* values greater than 99%, which is in accordance with the experimental observation. Other likely TSs such as **TSN$_{a'}$b$_{rr}$**, **TSN$_e$b$_{rr}$**, and **TSN$_{e'}$b$_{rr}$** for the same *re-re* mode of addition differing in the position of NMP coordination are about 1.4 to 3.7 kcal mol^{-1} higher in energy.[14]

Table 2. Comparison of Relative Energies (in kcal mol^{-1}) of Important Transition States with the NMP-Bound $TiCl_3$ to the Corresponding $TiCl_4$ Coordinated Transition States Devoid of NMP Coordination

TS	ΔE_{sol}	product	TS	ΔE_{sol}
N$_a$b$_{rr}$	**0.0**	ES	**1b$_{rr}$**	14.6
N$_a$b$_{rs}$	2.7	EA	**1b$_{rs}$**	15.9
N$_{e'}$b$_{sr}$	7.1	NA	**1b$_{sr}$**	14.4
N$_{a'}$b$_{ss}$	6.3	NS	**1b$_{ss}$**	20.7

To gain additional insights into the origin of the differential stabilization of the stereocontrolling TSs, *activation-strain analysis* is carried out for the NMP-bound TSs.[15] **TSN$_a$b$_{rr}$** is found to be the TS with the least amount of distortion in its reacting partners such as the titanium

(12) Although the relative energies of the TSs with azide coordination are of lower energy than the thiocarbonyl coordination, the predicted product stereochemistry (Evans *anti*) is in contrast with the experimental observation (see Table S2 in the SI).

(13) The formation of the desired Evans *syn* product demands the approach of benzaldehyde through the hindered face when the *E*-enolate configuration is considered. Such a pathway would obviously be of higher energy, as evident from $TiCl_4$ bound enolate (see Table S1 in the SI).

(14) Although the site of NMP coordination is important, different orientations of NMP did not bring any appreciable energy difference (see Tables S3−S4 in the SI).

enolate and benzaldehyde. Other stereochemical modes such as **rs**, **sr**, and **ss** are found to exhibit a larger distortion of their nucleophilic titanium enolate. The reduced interaction energy, between the electrophilic and nucleophilic partners, as compared to the total distortion renders these three modes of approach higher in energy.

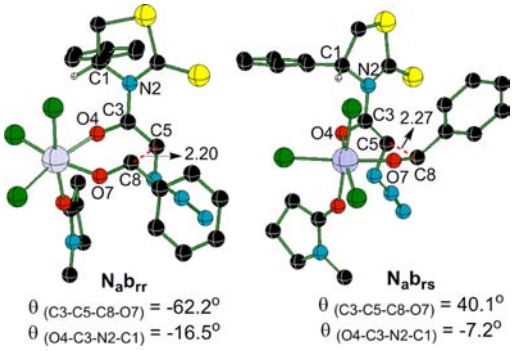

Figure 3. Optimized geometry of the lower energy transition states for NMP-bound TS.

A comparison between $TiCl_4$ and NMP-bound $TiCl_3$ TS models would be of considerable interest at this juncture. Both of these are *nonchelated* TSs consisting of a hexacoordinate titanium, which is found to be effective toward rationalizing the formation of the Evans *syn* product. The weak stabilizing interactions in the lowest energy transition states $\mathbf{TSN_ab_{rr}}$ and $\mathbf{TS1b_{rr}}$, respectively with and without NMP coordination, are analyzed using the Atoms-In-Molecule formalism.[9b] It is noted that, in $\mathbf{TSN_ab_{rr}}$, NMP develops weak interactions with an equatorial chloride ligand, the enolate oxygen, and the azide group nearby.[16] However, in the case of $\mathbf{TS1b_{rr}}$, the equivalent position is occupied by a chloride ligand, which does not exhibit any such stabilizing interactions with the other atoms. This could be regarded as a favorable situation for the chloride ligand to become dislodged in the presence of a protonated base (*vide supra*).

A more important question here relates to the suitability of the above-mentioned *nonchelated* TS models in the absence of NMP in the reaction mixture. It is possible that the thiocarbonyl of the chiral auxiliary, as well as the azide group of the enolate, can coordinate to the vacant site on titanium generated by the displaced chloride ligand. Thus reaction under such conditions could exhibit a propensity to proceed through a *chelated* TS. When a strongly coordinating NMP is introduced, it is likely to win over the competitive chelation by the thiocarbonyl or azide group. This situation promotes a *nonchelated* TS which is key to the formation of the Evans *syn* product.

The TSs with the NMP-bound $TiCl_3$ enolate are found to be energetically more preferred over the corresponding $TiCl_4$ enolate as summarized in Table 2. For instance, TSs with $TiCl_3$ maintaining azide group coordination is 7 kcal mol^{-1} higher, while the $TiCl_4$ model is 14 kcal mol^{-1} higher in energy as compared to the most favored NMP-bound $TiCl_3$ TS. Such energetic features evidently indicate that NMP can prevent the chelation of the azide or thiocarbonyl group with titanium thereby steering the reaction through a *nonchelated* TS. On the basis of these insights, it can be concluded that the NMP-bound $TiCl_3$ TS is the most suitable model toward rationalizing the formation of the Evans *syn* aldol product in the reaction between α-azido enolates derived from *N*-acyl thiazolidinethione and benzaldehydes.

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Supporting Information Available. Cartesian coordinates of optimized transition states and other relevant information are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) (a) Details of the *activation-strain analysis* (wherein the activation barrier is partitioned into interaction energy between the reacting partners and distortion energy within each partner at the TS as a result of the bond formation) are provided in Tables S6 and S7 in the SI. (b) van Zeist, W. J.; Bickelhaupt, F. M. *Org. Biomol. Chem.* **2010**, *8*, 3118. (c) Legault, C. Y.; Garcia, Y.; Merlic, C. A.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 12664.

(16) See Figure S9 in the SI for additional details.

The authors declare no competing financial interest.