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The Pivotal Role of Chelation as a Stereochemical Control Element in Non-Evans *Anti* Aldol Product Formation

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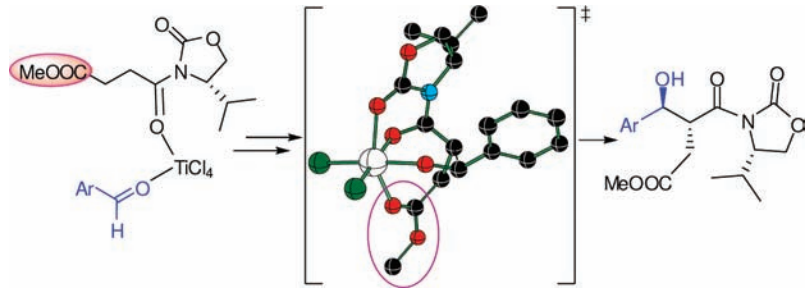
ABSTRACT



The origin of stereoselective formation of Evans *syn* and non-Evans *anti* aldol products in the reaction between titanium enolate derived from *N*-succinyloxazolidinone and benzaldehyde is established by using transition-state modeling. The chelated transition-state model is found to hold the key to otherwise less likely non-Evans *anti* aldol product, whereas the nonchelated model offers a convincing rationalization toward Evans *syn* aldol product. The computed results are in agreement with the reported experimental observations.

Asymmetric aldol reactions employing oxazolidinones as chiral auxiliaries have been a domain of considerable activity in organic chemistry for nearly three decades.[1] The use of oxazolidinones and its variants has found an increasingly large number of applications in total synthesis of natural products and compounds of pharmaceutical significance.[2] The precedence in oxazolidinone-mediated aldol reactions encompasses the synthesis of both *syn* and *anti* aldol products.[3,4] While most of the early efforts provided access to *syn* aldol products, the synthesis of *anti* aldol received great attention in more recent times. The approach toward the latter generally relies on stoichiometric control, changes in the nature of reagents, and the chiral auxiliaries.[5] For example, *anti*-selective aldol reactions were achieved by (a) varying the nature of Lewis acids in boron enolate mediated reactions,[5c] (b) introducing magnesium halide as catalyst,[5d] and (c) using thiazolidinethione as the chiral auxiliary.[5e] It

(1) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. (c) Evans, D. A.; Urpi, F.; Somers, T. D.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215. (d) Evans, D. A.; Starr, J. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1787.

(2) (a) Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998**, *120*, 9084. (b) Hawkins, J. M.; Watson, T. J. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3224. (c) Crimmins, M. T.; Christie, H. S.; Chaudhary, K.; Long, A. *J. Am. Chem. Soc.* **2005**, *127*, 13810. (e) Patel, J.; Clavé, G.; Renard, P.-Y.; Franck, X. *Angew. Chem., Int. Ed.* **2008**, *47*, 4224. (f) Tessier, A.; Lahmar, N.; Pytkowicz, J.; Briguad, T. *J. Org. Chem.* **2008**, *73*, 2621.

(3) (a) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23. (b) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047. (c) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894.

(4) Details of the stereochemical descriptions and product nomenclature are provided in the Supporting Information.

(5) (a) Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173. (b) Bonner, M. P.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 1299. (c) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747. (d) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392. (e) Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127. (f) Crimmins, M. T.; McDougall, P. J. *Org. Lett.* **2003**, *5*, 591. (g) Itoh, Y.; Yamanaka, M.; Mikami, K. *J. Am. Chem. Soc.* **2004**, *126*, 13174.

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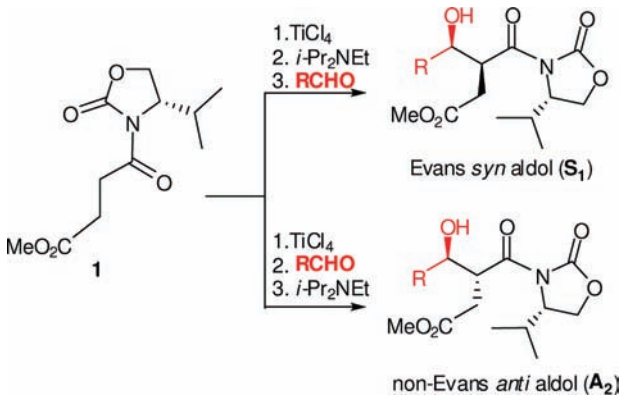
is noteworthy that large majority of oxazolidinone mediated aldol reactions offer access to *syn*-diastereoselectivity.

In a very recent study, Hajra et al. reported the synthesis of both *syn* and *anti* aldol products, beginning from the same substrates, just by altering the sequence of generation of the enolate.[6] The reaction was performed by using *N*-acyloxazolidinones bearing a γ/δ-chelating functional group, as shown in Scheme 1. What is interesting here is that when the normal sequence of addition of reagents was followed, Evans *syn* aldol (**S**$_1$) was formed. More intriguing, however, was the formation of non-Evans *anti* aldol (**A**$_2$), when the electrophile was introduced prior to the addition of base (inverse sequence of addition). Further, with unfunctionalized substrates Evans *syn* aldol only was isolated, irrespective of whether a normal or an inverse sequence of additions of reagents were followed. This observation evidently alludes to the potential role of the pendent functional group in steering the stereochemical course of the reaction.

It is surprising to note that the very premise on which the stereochemical outcome of oxazolidinone based asymmetric induction have been thus far rationalized relies on qualitative transition state (TS) models.[5b] The insights on the electronic structure of such crucial TSs are seldom found in literature.[7] We have recently examined the nature of stereocontrolling TSs in the reaction of titanium enolates, derived from Evans as well as Crimmins chiral auxiliaries, with benzaldehyde.[8] In this paper, we intend to shed light on the molecular origin of stereoselectivity-controlling chelation in *N*-acyloxazolidinones bearing a pendent functional group.

Scheme 1. Oxazolidinone-Mediated Aldol Reaction Yielding *Syn* and *Anti* Aldol Products (See Ref 6)



The key intermediates and TSs associated with the reaction of titanium enolate derived from *N*-succinyl-2-oxazolidinone (**1** in Scheme 1) and benzaldehyde is identified by using the density functional theory calculations. Computations are performed at the B3LYP/6-311+G**//B3LYP/6-31G* level of theory.[9,10] All calculations were carried out by using Gaussian03 suite of quantum chemical programs.[11] To establish the influence of different coordination patterns around the oxophilic titanium, several likely possibilities are analyzed and their effect on the stereochemical course of the reaction is delineated herein.

One of the most important roles of the titanium center is to anchor together the reactants viz., **1** and benzaldehyde, through coordination. The coordinations that can most readily occur is between titanium and the carbonyl oxygens of the (i) *N*-acyl group and (ii) benzaldehyde. Additional coordination possibilities as well are likely with the carbonyl of the oxazolidinone ring or/and the pendent ester group.[12] The terminologies "chelated" and "nonchelated", respectively, refer to the presence or absence of coordination between the ring carbonyl of oxazolidinone and titanium.[13] The effect of such preorganization is expected to be critical in the stereocontrolling C−C bond formation step. The TSs for the addition of *si*/*re* face of chiral titanium enolate on the *si*/*re* face of benzaldehyde are identified.[14] To distinguish different TSs arising as a result of differing chelation modes, following scheme is adopted in the TS notations. The representations are as follows: **2**, nonchelation, **3**, chelation with the ring carbonyl of the oxazolidinone, **3′**, chelation with the pendent group, and **4**, chelation with both ring carbonyl and the pendent groups.

Under the conditions of normal sequence of addition of reagents, it is logical to assume that the titanium enolate will be generated from a precoordinated $TiCl_4$ substrate complex.[15] It is identified that when a nonchelated TS model is employed for the stereoselective C−C bond formation, the computed relative energies of the TSs indicate the formation of Evans *syn* aldol product as most likely.[16] The addition by the less hindered *re* face of the enolate on the *si* face of benzaldehyde is found to be the most favored mode. The lowest energy TS **TS-S$_1$-2** leads to the formation of Evans *syn* aldol (**S**$_1$) (Table 1, entry 1).[8]

(6) Hajra, S.; Giri, A. K.; Karmakar, A.; Khatua, S. *Chem. Commun.* **2007**, 2408.

(7) Except for a rare account on oxazolidinone based stereoinduction by using boron enolates, see: Goodman, J. M.; Paton, R. S. *Chem. Commun.* **2007**, 2124.

(8) Our efforts toward rationalizing the formation of Evans and non-Evans *syn* aldol products through chelated and nonchelated transition-state models to date is the only computational study on oxazolidinone mediated asymmetric aldol reaction between Ti-enolate and aldehydes. Shinisha, C. B.; Sunoj, R. B. Manuscript in preparation.

(9) All the intermediates and TSs were respectively characterized as minima and first-order saddle points by using frequency calculations. Further, intrinsic reaction coordinate (IRC) calculations were performed to authenticate the TSs. Calculations on the critical TSs were further repeated at the mPW1K level of theory. See the Supporting Information for further details.

(10) The solvent effects were incorporated with the continuum solvation model by using the SCRF-PCM framework. Dichloromethane was taken as the continuum solvent dielectric ($\varepsilon = 8.93$). The results are tabulated in Tables S1 and S2 in the Supporting Information.

(11) Frisch, M. J. *Gaussian 03*, Revision C.02; Gaussian, Inc.: Wallingford, CT, 2004. See the full citation in the Supporting Information.

(12) The TSs **S**$_1$, **S**$_2$, **A**$_1$, and **A**$_2$ correspond to Evans *syn*, non-Evans *syn*, Evans *anti*, and non-Evans *anti* products.

(13) Qualitative models that are generally employed in rationalizing the stereoselectivity in oxazolidinone mediated aldol reaction are summarized in Scheme S1 in the Supporting Information.

(14) A schematic representation of all these modes of addition are given in Scheme S2 in the Supporting Information.

(15) Marrone, A.; Renzetti, A.; De Maria, P.; Gérard, S.; Sapi, J.; Fontana, A.; Re, N. *Chem.—Eur. J.* **2009**, *15*, 11537.

(16) Such a nonchelated working model has been documented: (a) Nerz-Stormes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, *56*, 2489. (b) Siegel, C.; Thornton, E. R. *J. Am. Chem. Soc.* **1989**, *111*, 5722. (c) Crimmins, M. T.; Shamszad, M. *Org. Lett.* **2007**, *9*, 149. (d) See Scheme S1 in the Supporting Information.

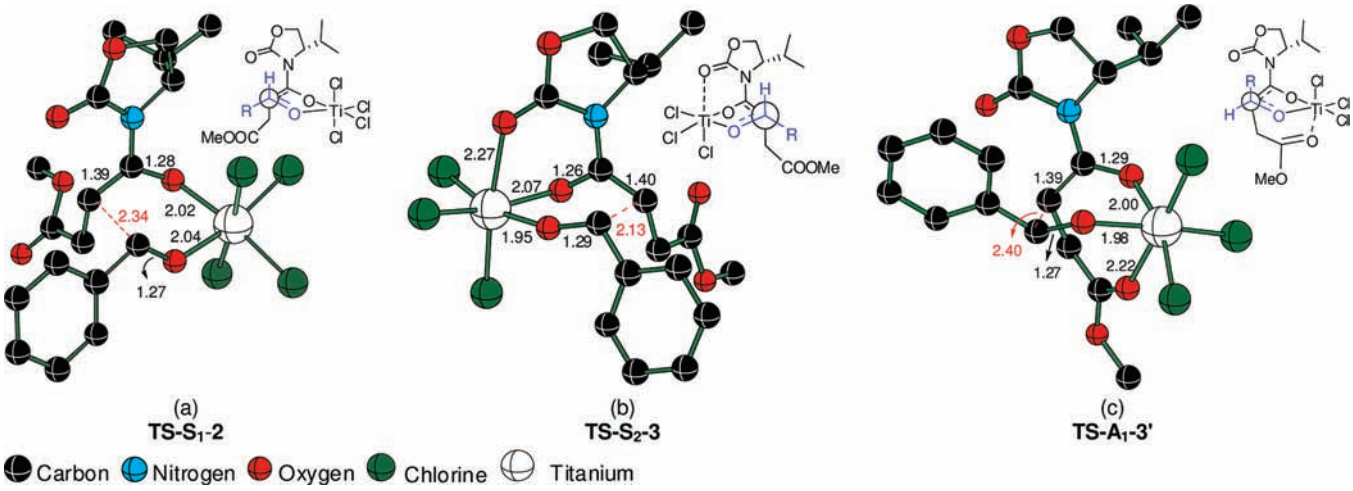


Figure 1. B3LYP/6-31G*-optimized geometries of lower energy diastereomeric transition states for the addition of titanium enolate (derived from *N*-succinyl-2-oxazolidinone) to benzaldehyde. Different coordination modes are depicted by using the lowest energy transition state in each case.

The optimized geometry of the lowest energy **TS-S$_1$-2**, as given in Figure 1a, reveals a chairlike structure, wherein the phenyl group occupies a pseudoequatorial position. It can further be noticed that the pendent group in this nonchelated model is oriented away from the aryl group as well as from the coordination sphere of titanium. This implies that under the conditions of normal sequence of addition of reagents, a nonchelated pathway guiding toward Evans *syn* aldol product is quite likely to operate. Further, the presence of potential chelating group in the pendent arm might not directly influence the stereoselectivity in this TS model.

Next, the chelated TSs wherein the ring carbonyl is coordinated to titanium are identified, and the associated energetics are summarized in Table 1. The addition by nonhindered *si* face of the enolate on the *re* face of benzaldehyde is identified as the most favored mode. The optimized geometry of the lowest energy **TS-S$_2$-3** is provided in Figure 1b. The lowest energy TS exhibits a chairlike geometry with the phenyl group on benzaldehyde positioned farther from the chiral auxiliary. The preferred diastereofacial approach through **TS-S$_2$-3** would lead to non-Evans *syn* aldol product. From these results it is evident that the presence of the pendent group is perhaps not influencing in the stereodifferentiation, so long as a conventional chelated and nonchelated TS model is invoked. In fact, our prediction concurs with the literature precedence, where the chelated TS model is proposed to be responsible for the formation of non-Evans *syn* aldol (**S$_2$**), under suitable reaction conditions.[3c,5b]

With the chelated TS model suggesting the formation of non-Evans *syn* aldol, we turned our attention to another model as follows. As mentioned earlier, a non-Evans *anti* aldol (**A$_2$**) product is produced, upon following an inverse sequence of addition of reagents. Besides the aforementioned chelations, a new TS model where the additional functionality from the pendent group coordinates to titanium is studied.[17]

Table 1. Relative Energies (in kcal/mol) of Important Transition States Obtained at the B3LYP/6-311+G**//B3LYP/6-31G* Level of Theory for the C−C Bond Formation between Titanium Enolate and Benzaldehyde

transition states	$\Delta E^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$
	(a)		
TS-S$_1$-2	**0.0**	**0.0**	**0.0**
TS-S$_2$-2	4.8	4.8	5.0
TS-A$_1$-2	[a]	[a]	[a]
TS-A$_2$-2	8.7	8.5	8.8
	(b)		
TS-S$_1$-3	4.8	4.7	5.4
TS-S$_2$-3	**0.0**	**0.0**	**0.0**
TS-A$_1$-3	2.8	2.7	3.3
TS-A$_2$-3	0.2	0.2	0.3
	(c)		
TS-S$_1$-3′	1.1	1.4	1.5
TS-S$_2$-3′	3.5	3.4	3.3
TS-A$_1$-3′	**0.0**	**0.0**	**0.0**
TS-A$_2$-3′	2.7	2.7	3.1

[a] The transition state could not be located after repeated attempts.

The stereochemical course could be quite different when the second scenario, as described in Scheme 1, is operating. When benzaldehyde is introduced prior to the generation of titanium enolate, different coordination possibilities can arise. The TSs exhibiting coordination of the pendent carbonyl group are located and the relative energies are provided in Table 1. In this model, the addition of the *re* face of the enolate on the *re* face of benzaldehyde through a boat-like

(17) Several key possibilities belonging to this category are presented in Scheme S2 of the Supporting Information.

TS (**TS-A_1-3′** in Figure 1c) is identified as the most preferred mode. The **TS-A_1-3′** can lead to Evans *anti* aldol (**A_1**) product. In the next higher energy TS, namely **TS-S_1-3′**, the aryl group occupies a pseudoequatorial position in a chairlike conformation and is oriented toward the pendent coordination.[18] It is of significance, at this juncture, to reckon that the predicted stereochemical outcome is at variance with the reported experimental results (Scheme 1). Refinements to TS models hitherto considered are therefore evidently in order.

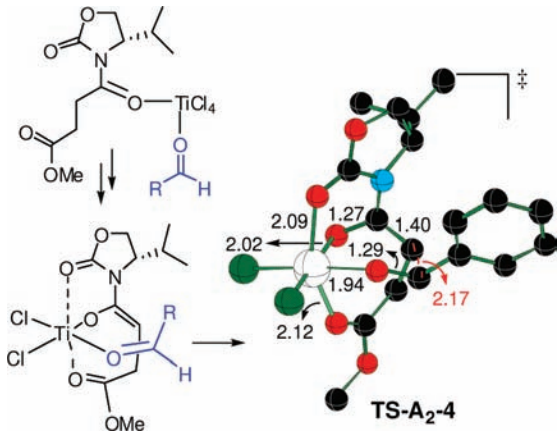


Figure 2. B3LYP/6-31G*-optimized geometry of the TS for the C−C bond formation wherein the pendent group is coordinated. Distances are given in angstroms.

Further refinements have been done in which the coordination of both carbonyl groups of oxazolidinone ring and the pendent group with titanium is included. The optimized TS geometry, as given in Figure 2, reveals a six-membered boatlike arrangement. The carbonyl groups of oxazolidinone, enolate, pendent ester group, and benzaldehyde together constitute a distorted octahedral topology around the titanium center.[19] The relative energies of the key TSs with respect to the lowest energy TS are summarized in Table 2.[20] The lowest energy **TS-A_2-4** is found to involve the addition of *si* face of enolate on the *si* face of benzaldehyde. The next higher energy TS (**TS-S_2-4**) presents a chairlike conformation with the phenyl group occupying a pseudoequatorial position.[21] The higher energy of this TS perhaps is due to the destabilizing interaction with the pendent carboxylic group coordinated to titanium.[22] The resulting product from **TS-S_1-4** would be Evans *syn* aldol and involves the attack by the hindered face of enolate on the electrophile. Hence, when both the ring carbonyl and pendent carbonyl groups are in coordination with titanium, the stereoselective C−C bond formation would lead to non-Evans *anti* aldol (**A_2**) as the most favored product.

Since TSs in this model is most vital to the conclusions, we have examined how the predicted trends hold across different levels of theory and basis set combinations. The results provided in Table 2 readily suggest a close mutual agreement between the computed values.

Table 2. Computed Relative Energies (in kcal/mol) of Important Transition States with Pendent Group Coordination[a] for the C−C Bond Formation between Titanium Enolate and Benzaldehyde

	relative energy (in kcal/mol)					
	L1		L2		L3	
transition states	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$
TS-A_2-4	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
TS-S_2-4	1.1	1.0	1.6	1.1	1.3	1.2
TS-S_1-4	2.6	3.2	[b]	[b]	2.8	3.2

[a] L1 = B3LYP/6-311+G**//B3LYP/6-31G*; L2 = mPW1K/6-311+G**//mPW1K/6-31G*; L3 = B3LYP/LANL2DZ(Ti), 6-31+G** [b] Transition state could not be located after repeated attempts.

In summary, we could rationalize the formation of non-Evans *anti* aldol (**A_2**) product by invoking a chelated TS model in which the metal is coordinated with ring carbonyl and the γ-functionality. The formation of Evans *syn* aldol, on the other hand, is explained through nonchelated transition states. Our results are in accordance with the known experimental results.

Acknowledgment. Computing resources from the IITB computer center, Center for Modeling Simulation and Design Hyderabad, and a fellowship from CSIR New Delhi (S.C.B) are acknowledged. We are thankful to Prof. S. Hajra (IIT Kharagpur) for bringing our attention to the reagent sequence-dependent product variations.

Supporting Information Available: Details on computational methods, full citation of ref 11, and optimized coordinates of various transition states and their energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Optimized TS geometries are given in Figure S1 in the Supporting Information.

(19) (a) The axial ligands are found to be tilted toward the substrate. (b) Similar topologies around titanium have earlier been noticed for $TiCl_4$-promoted C−C bond formation reactions. See: Patel, C.; Sunoj, R. B. *J. Org. Chem.* **2010**, *75*, 359.

(20) The relative energies obtained from single-point calculations by using the PCM model at various levels of theory are provided in Table S2 of the Supporting Information.

(21) See Figure S2 in the Supporting Information.

(22) **TS-S_2-4** appears to be more constrained (Figure S2, Supporting Information), leading to a higher degree of destabilization between the ester and the phenyl groups. It is to be noted that the computational methodology employed here, although adequate for the assessment of relative energies, may not provide an accurate description of van der Waals repulsions.