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Origin of Enantioselection in Hetero-Diels−Alder Reactions Catalyzed by Naphthyl-TADDOL

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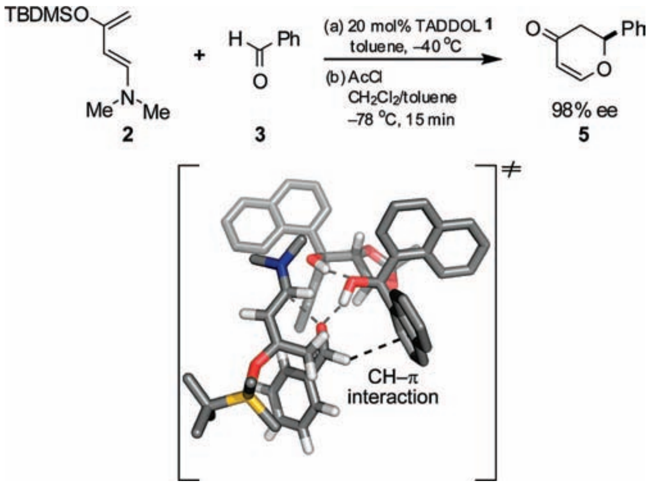
ABSTRACT



The asymmetric hetero-Diels−Alder reaction of benzaldehyde with 1-dimethylamino-3-*tert*-butyldimethylsiloxy butadiene catalyzed by (*R*,*R*)-1-Np-TADDOL was studied using computational methods. A theoretical rationale was developed through the combined use of molecular mechanics and ONIOM(B3LYP/6-31G(d):AM1) calculations. The origins of stereoselection in this process were identified, and excellent correlation between experiment and theory was found.

The hydrogen bond (H-bond) is a recurring structural element in nature and is of fundamental importance in maintaining the native structure and function of enzymes and other biologically significant molecules. Despite its ubiquitous presence, only recently have chemists begun to harness the synthetic potential of the H-bond for asymmetric catalysis.[1] For example, Rawal and co-workers have reported the use of TADDOL derivatives such as **1**[2] as catalysts for the enantioselective hetero-Diels−Alder (hDA) reactions between the electron-rich diene **2** and aldehydes **3** to afford dihydropyranones **5** after workup (Scheme 1).[3]

Several models for stereoselection in these reactions have been proposed. On the basis of the available TADDOL and

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(1) For recent reviews of organocatalysis see: (a) List, B. *Acc. Chem. Res.* **2004**, *37*, 548–557. (b) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558–569. (c) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062–2064. (d) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Cat.* **2006**, *348*, 999–1010. (e) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543. (f) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418–5427.

(2) Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92–138.

(3) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146.

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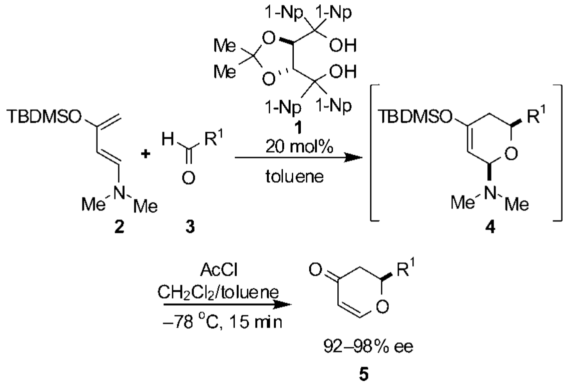
Scheme 1. TADDOL-Catalyzed hDA Reaction[a]



[a] R^1 = Ph, 4-MeOPh, 4-CF_3Ph, 1-Np, 2-Np, 2-furyl, *trans*-styryl, cyclohexyl.

TADDOL complex X-ray crystal structures, Rawal and coworkers have proposed aldehyde−TADDOL complex **6** as an important precursor to the enantiodetermining cycloaddition step, where π−π stacking is central to obtaining high stereoselectivity (Figure 1).[3,4] In addition to Rawal's proposal, two computational models for stereoselection have appeared in the recent literature. Wu and co-workers studied the related TADDOL-catalyzed hDA reaction between 1,3-dimethoxy-1,3-butadiene and benzaldehyde using ONIOM-(B3LYP/6-31G(d):PM3) and found that *si*-face addition is favored by 2.6 kcal/mol.[5] The low energy transition structure (TS) obtained from this calculation has a π−π stacking interaction analogous to Rawal's model. Deslongchamps and co-workers used a molecular mechanics based docking approach to fit TADDOL **1** to hDA transition structures; the low energy TS geometry had the benzaldehyde coordinated syn to the phenyl ring, which corresponds to TADDOL−aldehyde complex **7**.[6]

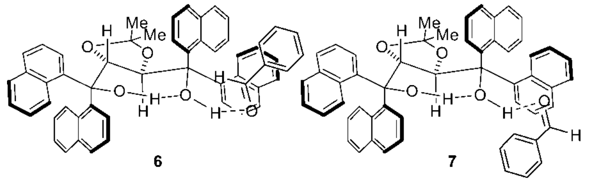


Figure 1. TADDOL−aldehyde complexes.

On the basis of our previous mechanistic studies of the reactions,[7] we initiated an investigation employing both Monte Carlo conformational searches[8] (MCCS) and density functional theory within the context of ONIOM (layered molecular orbital method) calculations to provide an understanding of the origin of stereoselection in the TADDOL-catalyzed hDA reaction.[9]

We previously demonstrated that the hDA reaction between benzaldehyde and model diene **8** catalyzed by 1,4-butanediol proceeds through an *endo*-selective cooperative H-bond transition structure **TS1** (Figure 2).[7] The reaction proceeds through the initial formation of an aldehyde−1,4-butanediol H-bond complex, followed by reaction of the resulting complex with diene **8**. The transition structure **TS1** is highly asynchronous with a forming C−C bond distance of 1.94 Å and a long forming C−O distance of 2.78 Å. Catalysis by hydrogen bond donors was demonstrated to be the result of charge stabilization in the zwitterionic transition structures by strong hydrogen bonding.

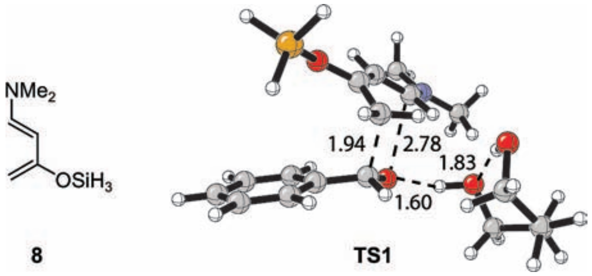


Figure 2. Model diene **8** and transition structure **TS1** for a hDA reaction catalyzed by 1,4-butanediol. Select bond distances are shown in angstroms.

Due to the relatively large size of this reaction system, both MCCS and mixed QM/QM calculations were employed. Transition structures for all combinations of *re*- and *si*-face addition and *exo*- and *endo*-approach of the aldehyde, obtained from calculations on simplified model systems, were used as structural templates from which the remaining architecture of the catalyst and the diene were derived.[7,10] For each structure, the internal coordinates of the diene−aldehyde π system were frozen, the hydrogen bond distances of TADDOL **1** were constrained, and a series of MCCS were conducted. Structures with energies within 4 kcal/mol of the global minimum conformation were then optimized with

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(4) Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5846–5850.

(5) Zhang, X.; Du, H.; Wang, Z.; Wu, Y.-D.; Ding, K. *J. Org. Chem.* **2006**, *71*, 2862–2869.

(6) (a) Harriman, D. J.; Lambropoulos, A.; Deslongchamps, G. *Tetrahedron Lett.* **2007**, *48*, 689–692. (b) An earlier protocol used by the Deslongchamps group provided a unique transition structure. Harriman, D. J.; Deslongchamps, G. *J. Mol. Model.* **2006**, *12*, 793–797. See Supporting Information for further details.

(7) Gordillo, R.; Dudding, T.; Anderson, C. D.; Houk, K. N. *Org. Lett.* **2007**, *9*, 501–503.

(8) Monte Carlo conformational searches utilized the MMFF force field as implemented in Macromodel. *Macromodel V.8.6*; Schrödinger, LLC: New York, 2004.

(9) The ONIOM method represents a viable solution for calculating stereoselectivity for large reaction systems; see: (a) Dudding, T.; Houk, K. N. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5770–5775. (b) Cheong, P. H.-Y.; Yun, H.; Danishefsky, S. J.; Houk, K. N. *Org. Lett.* **2006**, *8*, 1513–1516.

(10) See Supporting Information for details.

(11) Frisch, M. J. et al. *Gaussian 03, Revision C.02*; Gaussian, Inc.: Wallingford, CT, 2004. Full reference for Gaussian programs provided in Supporting Information.

ONIOM(B3LYP/6-31G(d):AM1). Finally, single point energy calculations (B3LYP/6-31G(d)) were performed on the ONIOM transition structures. The ONIOM and DFT calculations were performed with the Gaussian suite of programs.[11]

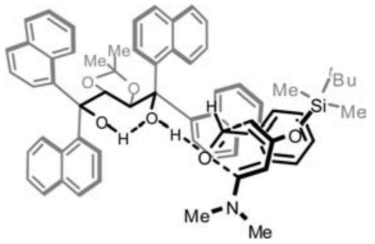

Figure 3. ONIOM partitioning scheme. The black region was modeled with B3LYP/6-31G(d), whereas the grey region was modeled with AM1.

Figure 3 illustrates the partitioning scheme utilized in this investigation. The alkyl groups on the silyl ether, the acetal atoms (-OC(CH_3)$_2$O-) and the aromatic portions of TADDOL **1** were treated at the AM1 level of theory, while the remainder of the system was optimized with B3LYP/6-31G(d).

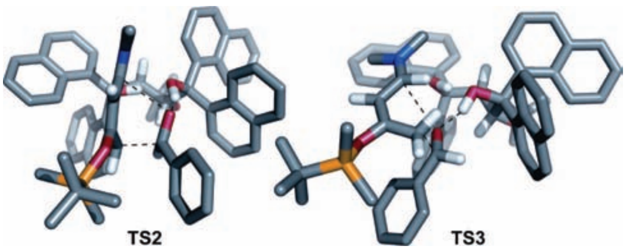

Figure 4. Enantiodetermining transition structures **TS2** and **TS3** for (*R*,*R*)-1-Np-TADDOL-catalyzed hDA of diene **2** and benzaldehyde. Select hydrogen atoms have been removed for clarity. **TS3** is 1.5 kcal/mol more stable than **TS2**.

Figure 4 shows the two lowest energy transition structures **TS2** and **TS3** for *re*-face and *si*-face addition, respectively. Both of the low energy transition structures are *endo*. Inspection of **TS2** and **TS3** reveals that both transition structures are highly asynchronous with forming C−C bond distances of 1.99 and 2.03 Å and C−O distances of 2.83 and 2.86 Å, respectively. The hydrogen atoms of the naphthyl groups in **TS2** are within van der Waals radius of the diene moiety, and the naphthyl moieties restrict the approach of the diene to the coordinated aldehyde, disfavoring *re*-face addition. *Si*-face addition in **TS3** has no steric repulsions of this type. Transition structure **TS3** also benefits from the presence of a stabilizing CH-π interaction (3.19 Å) between the aldehyde CH and the pseudoequatorial naphthalene ring of TADDOL **1** (Figure 5).[12,13] **TS2** lacks this stabilizing CH−π interaction and instead possesses a π−π stacking interaction that is reminiscent of the models proposed by others.[3–6] The calculated difference between **TS2** and **TS3** ($\Delta E = 1.5$ kcal/mol (B3LYP[14]/6-31G(d)[15])) corresponds to an *S*:*R* product ratio of 97:3 at −40 °C, which is in reasonable agreement with the experimentally observed enantiomer ratio of 99:1.

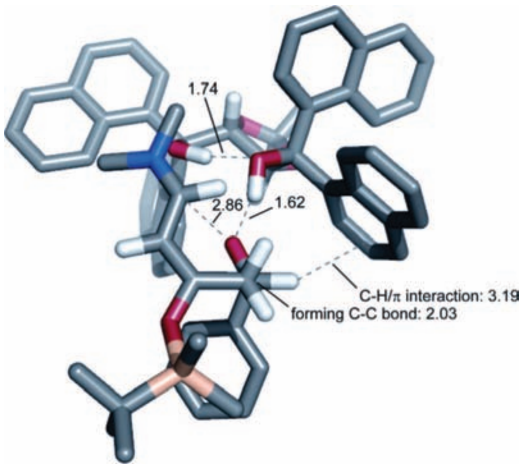

Figure 5. Stabilizing CH−π interaction in **TS3**.

To compare this model directly to the earlier computational models, the ONIOM(B3LYP/6-31G(d):AM1) transition structures reflecting the Wu π-stacking model and the Deslongchamps *syn*-phenyl geometry for the hDA reaction between benzaldehyde and diene **2** catalyzed by TADDOL **1** were located (Figure 6).[5,6] Subsequently, single point energy calculations were performed at the B3LYP/6−31G(d) level of theory. The π-stacking TS **TS4** is 2.9 kcal/mol less favorable than the CH−π TS **TS3**. Both **TS2** and **TS4** have similar aldehyde−naphthyl π-stacking, but diene addition occurs on opposite faces of aldehyde. The *syn*-phenyl TS **TS5** is 2.9 kcal/mol higher in energy than the π-stacking TS **TS4**. This observation draws attention to the importance of using conformational searches in conjunction with relatively accurate calculations to locate transition structures.

In an effort to thoroughly account for dispersion interactions, single point energy calculations were performed on

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[12] For a review of CH−π interactions in organic chemistry, see: Nishio, M. *Tetrahedron* **2005**, *61*, 6923–6950.

[13] For recent theoretical discussions of CH−π interactions: (a) Kobayashi, Y.; Saigo, K. *J. Am. Chem. Soc.* **2005**, *127*, 15054–15060. (b) Takahashi, O.; Kohno, Y.; Saito, K. *Chem. Phys. Lett.* **2003**, *378*, 509–515. (c) Ujaque, G.; Lee, P. S.; Houk, K. N.; Hentemann, M. F.; Danishefsky, S. J. *Chem. Eur. J.* **2002**, *8*, 3423–3430. (d) Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 104–112. (e) Ribas, J.; Cubero, E.; Luque, F. J.; Orozco, M. *J. Org. Chem.* **2002**, *67*, 7057–7065. (f) Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. *J. Am. Chem. Soc.* **2000**, *122*, 3746–3753.

[14] (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372–1377. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.

[15] (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724–728. (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257–2261. (c) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213–222.

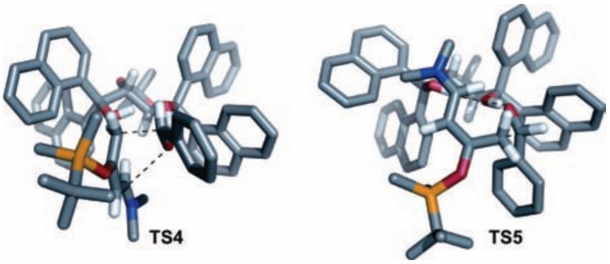

Figure 6. ONIOM(B3LYP/6-31G(d):AM1) transition structures for the π-stacked and *syn*-phenyl TS models for the TADDOL-catalyzed hDA.

Table 1. Relative Energies of Transition Structures (kcal/mol)[a]

	TS2	**TS3**	**TS4**	**TS5**
B3LYP/6-31G(d)	1.5	0.0	2.9	5.8
MPWB1K/6-31G(d)	2.4	0.0	2.8	5.3
M06-2X/6-31+G(d)	3.4	0.0	4.2	2.5

[a] Based upon single point energy calculations on the ONIOM(B3LYP/6-31G(d):AM1) transition state geometries.

the ONIOM(B3LYP/6-31G(d):AM1) geometries using two different meta-hybrid DFT functionals. The MPWB1K[16]/6-31G(d) energies reflect the same trend that is observed for the B3LYP/6-31G(d) single point energies. This method predicts a larger preference for the formation of the *S* enantiomer of product. The M06-2X[17]/6-31+G(d) single point energies also rank **TS3** as the most favorable transition structure.[18] Interestingly, the second most stable transition structure is **TS5**, the *syn*-phenyl model of Deslongchamps and co-workers. The M06-2X method has been found to accurately compute weak dispersion interactions of the type present in these transition structures.[17]

In summary, a combined MM and QM/QM study of the TADDOL **1**-catalyzed hDA reaction of diene **2** and benzaldehyde provides a model for selectivity that correctly predicts the sense and relative magnitude of product stereoinduction. TADDOL **1** promotes the reaction by coordination of the carbonyl oxygen through a cooperative hydrogen bonding motif and orientation of the aldehyde by CH−π interaction.

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Supporting Information Available: Complete references 11 and 18, details of the computational methods employed, Cartesian coordinates and energies for the computed structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2004**, *108*, 6908–6918.

(17) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2007**, published online ahead of print. DOI: 10.1007/s00214-007-0310-x.

(18) M06-2X single point energies were calculated using NWChem. (a) Bylaska, E. J. et al. *NWChem, A Computational Chemistry Package for Parallel Computers, Version 5.0*; Pacific Northwest National Laboratory: Richland, WA, 2006. Full reference for the NWChem program is provided in Supporting Information. (b) Kendall, R. A.; Apra, E.; Bernholdt, D. E.; Bylaska, E. J.; Dupuis, M.; Fann, G. I.; Harrison, R. J.; Ju, J.; Nichols, J. A.; Nieplocha, J.; Straatsma, T. P.; Windus, T. L.; Wong, A. T. *Comput. Phys. Commun.* **2000**, *128*, 260–283.