

Stereochemistry of Titanium-N-salicyl-β-aminoalcohol Complexes as Catalysts for Strecker Reaction

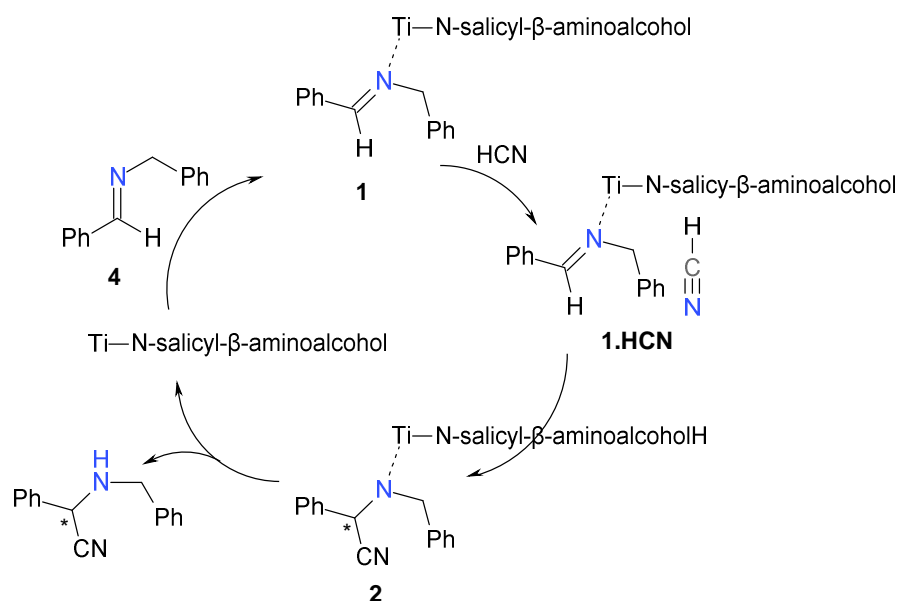
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Titanium-N-salicyl-β-aminoalcohol complexes have been reported as stereoselective catalysts for the Strecker reaction, an efficient procedure for amino acid synthesis.^{1, 2} However, the catalytic mechanism of this Strecker reaction is not yet fully understood. The stereochemistry of Ti-catalyst with imine substrate complexes, as well as their reactions with HCN, was investigated by density functional theory using the B3LYP functional. The 6-31G(d, p) basis was applied for C, H, N, O atoms and LanL2DZ basis with effective core potential was employed for Ti atom. The N-salicyl-β-aminoalcohol, which acts as the ligand, binds its two oxygen and nitrogen atoms to Ti and forms the octahedral-like complex. However, this octahedral-like structure would change during the reaction process, which affects the outcome of the reaction.



Proposed mechanism of Strecker reaction catalyzed by Ti- N-salicyl-β-aminoalcohol complex³

1. V. Banphavichit, W. Mansawat, W. Bhanthumnavin, and T. Vilaivan *Tetrahedron* **60** 10559 (2004).
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3. S. Qin, C. Hu, H. Yang, Z. Su, and D. Tang, *J. Org. Chem.* **73** 4840 (2008).

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Introduction Titanium-N-salicyl-β-aminoalcohol complexes have been reported as efficient catalyst for the stereoselective Strecker reaction, which is an important reaction for amino acid synthesis.[1,2] The proposed mechanism of Ti complex catalyzed Strecker reaction is displayed in Fig 1.

Computational details The geometries of reactants, catalyst complexes, and intermediates involved in the C-CN bond formation step were optimized using B3LYP with LanL2DZ basis set and effective core potential for Ti atom and 6-31G(d,p) basis set for other atoms. The transition state structures were located using QST3 algorithm. All the calculations were performed using Gaussian09 program.

Results and Discussions

Ti catalyst complexes Fig. 2 exhibits the optimized octahedral-like complexes of Ti-catalyst **1**, and the substrate imine **4**. The N atom of imine **4** bound with titanium in the catalyst complex with Ti-N imine distance of 2.59, 2.78, and 2.60 Å in complex **1a**, **1b**, and **1c**.

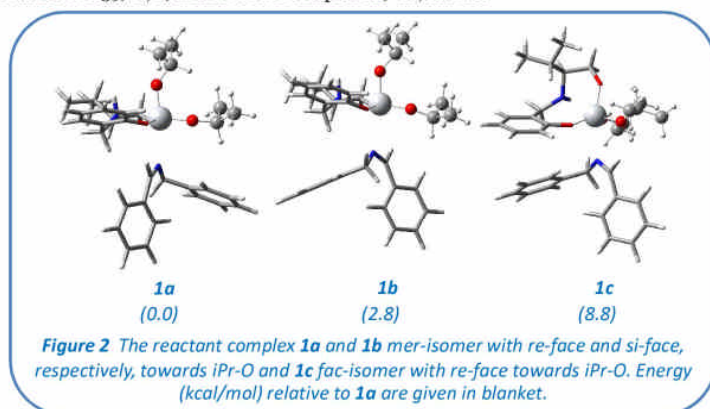


Figure 1 Proposed mechanism of Ti-complex catalyzed Strecker reaction

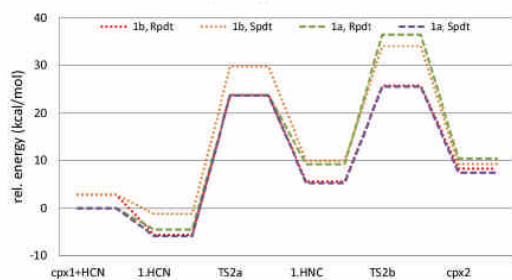
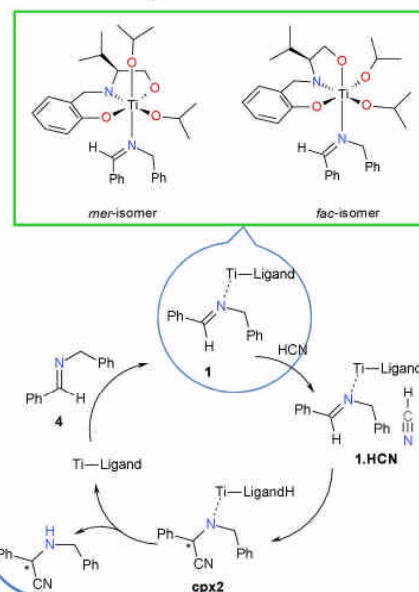


Figure 3 Energy profiles of the C-CN two-step bond formation of mer-isomer of the reactant complex **1a** and **1b** with HCN

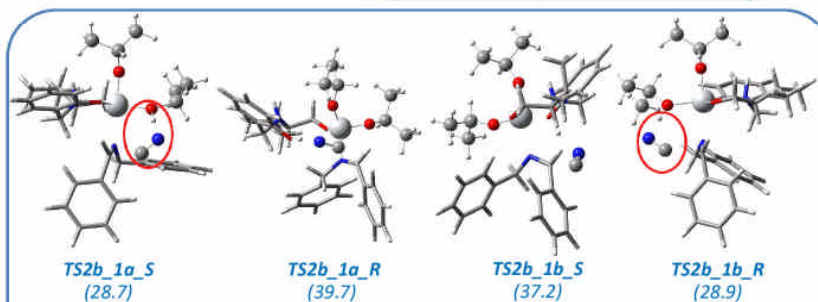
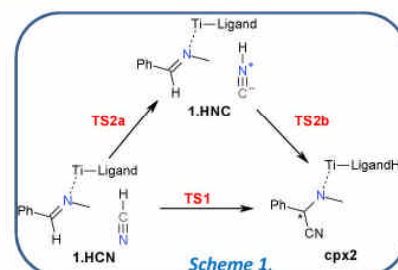


Figure 4 Transition states of the C-CN bond formation step of the reactant complex **1a** and **1b**. Proton transfer to the iPr-O are circled. Energy (kcal/mol) relative to **1a** are given in blanket.

Energy Profiles During the search for the transition state of the C-CN bond formation step of the complex **1.HCN**, the HCN to HNC isomerization was observed from the mode of the imaginary vibrational frequency. Moreover the energies of both **TS2a** and **TS2b** were lower than that of **TS1**. Thus, an additional HCN isomerization step as shown in Scheme 1 was considered in the catalytic cycle. The energy profile in Fig. 3 hinted that from the more stable reactant complex **1a**, the intermediate **cpx2** with (S)- configuration of is the major product of the C-CN bond formation step. From the transition state structures displayed in Fig. 4, the HNC binding to the iPr-O leads to a transition state with lower energy than the one binding to the ligand oxygen.

Conclusions Several geometries of the octahedral Ti catalyst reactant complexes can be formed. From the most stable reactant complex, the proposed reaction mechanism proceeds to (S)- intermediate as it was reported experimentally.



References 1) a) V. Banphavichit, W. Mansawat, W. Bhanthumnavin, and T. Vilaivan, *Tetrahedron* 2004, 60, 10559. b) V. Banphavichit, W. Mansawat, W. Bhanthumnavin, and T. Vilaivan, *Tetrahedron* 2009, 65, 5849. 2) S. J. Zuend, M. P. Coughlin, M. P. Lalonde, E. N. Jacobsen, *Nature* 2009, 968. 3) H. Groeger, *Chem. Rev.* 2003, 103, 2795. 4) S. Qin, C. Hu, H. Yang, Z. Su, D. Tang, *J. Org. Chem.* 2008, 73, 4840. 5) A. Paerssinen, T. Luhtanen, M. Klinga, T. Pakkanen, M. Leskelae, and T. Repo, *Organometallics* 2007, 26, 3690. 6) A. Gama, L. Z. Flores-Lopez, G. Aguirre, M. Parra-Hake, R. Somanathan, and T. Cole, *Tetrahedron: asymmetry* 2005, 16, 1167. 7) R. M. Moreno, M. Rosol, and A. Moyano, *Tetrahedron: asymmetry* 2006, 17, 1089. 8) N. S. Josephsohn, K. W. Kuntz, M. L. Snapper, and A. H. Hoveyda, *J. Am. Chem. Soc.* 2001, 123, 11594.

Acknowledgements **Financial support** : 1 Thailand Research Fund (TRF: RTA5380010), 2 Faculty of Science, Kasetsart University, 3 Kasetsart University Research and Development Institute **Computing facilities** : TKK-2555, Computational Chemistry Unit Cell (CCUC) of Department of Chemistry, Faculty of Science, Chulalongkorn University

