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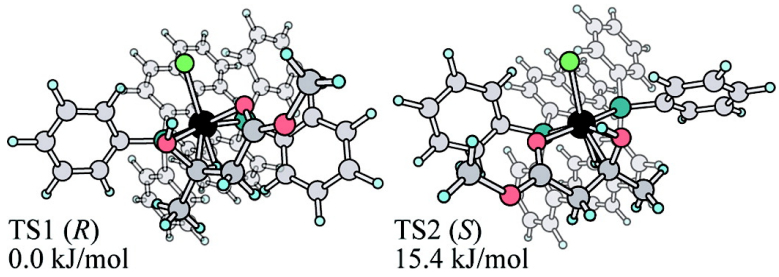

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Lowest Transition State for the Chirality-Determining Step in Ru((*R*)-BINAP)-Catalyzed Asymmetric Hydrogenation of Methyl-3-Oxobutanoate

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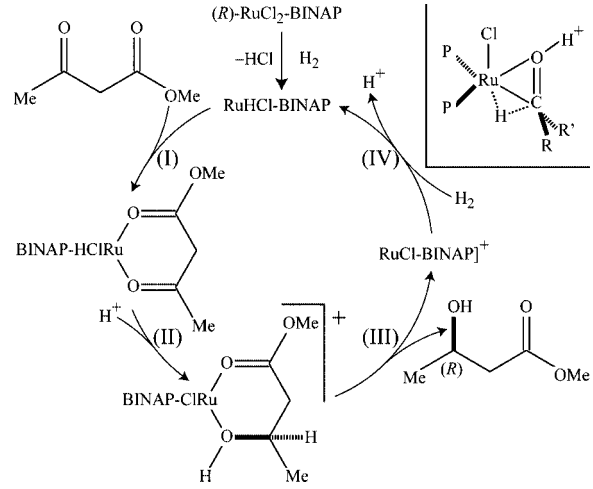
Asymmetric hydrogenation[1−3] is a very powerful approach to produce the desired enantiomer with the smallest amounts of waste. It was suggested by Noyori et al. that deep mechanistic insight is indispensable for developing truly efficient asymmetric hydrogenation reactions.[4] Theoretical studies of the asymmetric reaction mechanisms[5−7] have been made for this purpose in addition to the experimental studies.

Theoretical calculations have become a powerful tool because of recent developments of computation techniques. Introduction of the quantum-mechanics and molecular-mechanics (QM/MM) hybrid methods such as the ONIOM[8] method was one of the most remarkable progresses. In the QM/MM approaches, both the chemical bond rearrangements at the reaction center and the steric repulsions determining the selectivity can be taken into account with a desired accuracy and a reasonable computation cost. The QM/MM methods have been employed to investigate mechanisms of a [Rh((*R*,*R*)-Me-DuPHOS)]$^+$-catalyzed reaction[5] and a [Rh((*R*)-BINAP)]$^+$-catalyzed reaction,[7] and experimental selectivity has been explained successfully. Previous theoretical studies[5−7] considered a few transition state (TS) structures for each elementary step by using a geometry optimization technique which depends on initial guesses. However, there are numerous TS structures for just one elementary step of an asymmetric hydrogenation reaction due to the complexity of its potential energy surface (PES), as demonstrated here. The complexity is caused by introduction of bulky ligands in the asymmetric catalysts for high selectivity. Hence, systematic analysis of the PES[9] is necessary to determine the lowest TS structure, for understanding and for prediction of selectivity of a newly designed catalyst. For this purpose, we have successfully developed the anharmonic downward distortion following (ADD-following) method, which enables one to globally explore reaction pathways on the PES by noting the ADDs as a signpost of chemical reactions.[10]

In this study, we performed a systematic search for TS structures of the chirality-determining elementary step in the $RuCl_2$-((*R*)-BINAP)-catalyzed asymmetric hydrogenation of methyl-3-oxobutanoate by using the ADD-following method. A set of 68 TS structures (first-order saddle points in the 288-dimensional PES) were obtained for the step. A comparison between the lowest TS structures for the *R*- and *S*-type products showed a reason for the high enantioselectivity of the reaction.

Scheme 1 shows the catalytic cycle of the reaction, which was reproduced based on ref 4. In the cycle, the RuHCl compound is the actual catalyst. The chiral-carbon atom is generated in step (II), and steps (I), (III), and (IV) do not change the product's chirality. A schematic illustration of the reaction center for the chiral-carbon generation step is shown in an inset of Scheme 1, where the H atom on the Ru atom transfers to the C atom of the carbonyl group.

Scheme 1. Catalytic Cycle[4] and Reaction Center (Inset)



We investigated TS structures with this reaction center by using the ADD-following method.

Figure 1A lists the seven lowest TS structures among the 68 TSs obtained in this study. All 68 TSs are for the hydrogen abstraction from the Ru atom by the carbonyl carbon in the reactant. Energy values in the figure are the relative free energy at 100 °C with respect to the lowest TS1. The lowest TS1 leads to the *R*-type product, while the lowest TS for the *S*-type (TS2) is 15.4 kJ mol^{-1} higher in energy than TS1. Figure 1B presents the relative free-energy distribution of 10 *R*-type TSs and 52 *S*-type TSs under 100 kJ/mol. Although there are many energetically similar TSs, a comparison between the lowest TSs for each product type clearly shows that the *R*-type is the main product in this reaction in agreement with the experiment.[11] Boltzmann distribution shows that relative population of TS1 and TS2 is 143:1, which is also in line with the experimental enantioexcess of >99% ee[11] qualitatively.

The mechanistic reason for the high selectivity can be discussed based on the lowest TS structures of each product type. Chart 1 shows a schematic illustration of RuHCl-((*R*)-BINAP) and the reactant molecule, where binaphthyl in BINAP is simplified with a thin line. There are four phenyl groups: two (Ph1 and Ph2) are sticking out toward the reactant molecule, and others (Ph3 and Ph4) are lying backward without a strong interaction with the reactant. Coordination of one of the O atoms in the ester group stabilizes the TS structures, and both TS1 and TS2 experience this coordination. It follows that TS1 and TS2 exhibit the same coordination except for their adsorption faces. However, the Me1−Ph1 and Me2−Ph2 distances in TS1 are 4.64 and 4.27 Å, respectively, which are longer than the Me1−Ph2 and Me2−Ph1 distances in TS2 of 4.28 and 3.96 Å, respectively. Although it was proposed that repulsion between Me1 and Ph1/Ph2 is responsible for the selectiv-

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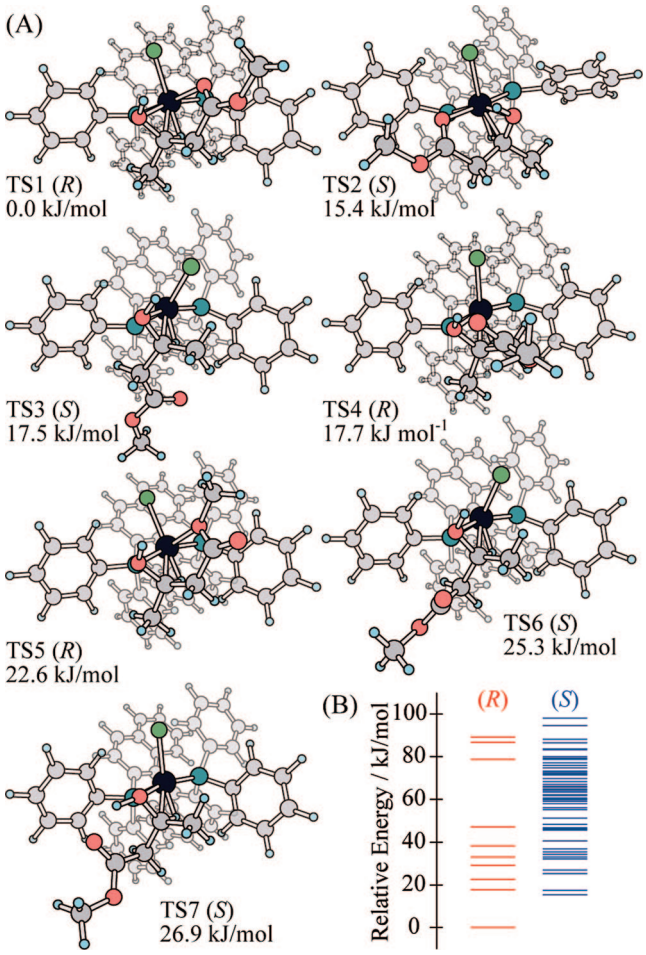
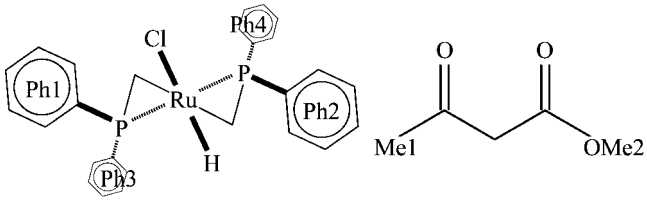


Figure 1. (A) Seven lowest TS structures (in terms of free energy at 100 °C) among 68 TSs located in this study, and (B) free-energy distribution of 10 (*R*)-type TSs and 52 (*S*)-type TSs below 100 kJ/mol.

Chart 1. RuHCl-((*R*)-BINAP) and the Reactant Molecule



ity,[4] these results show that repulsion between Ph1/Ph2 and Me2 next to the ester group is the more important factor because of the shorter distance. Me1 and Me2 in TS1 can stay above Ph3 and Ph4, respectively, and can avoid repulsion with Ph1 and Ph2, respectively, with a "lock-and-key" motif at the TS structure. To abstract the H atom on the Ru atom, the carbonyl has to coordinate along the Ru−H bond. Hence, the direction of the Ru−H bond determines the relative Me1/M2−Ph1/Ph2 arrangements when the TSs are stabilized by the ester-oxygen coordination. In other words, these two restrictions in the stable TS structures, i.e., the carbonyl coordination direction and the ester-oxygen coordination, may be microscopic causes of the selectivity.

There are many TSs without the ester-oxygen coordination such as TS3, TS4, TS6, and TS7, although they are not directly related to the selectivity in the present system. In contrast to TSs with the coordination, *S*-type TSs without the coordination are more stable than *R*-type ones. This is because the *S*-type TSs can locate the ester group above Ph3, while the *R*-type TSs have strong repulsion between the ester group and Ph2. Since TSs without the ester coordination are much more flexible than TSs with the coordination, there are many such TSs for the *S*-type in the high-energy region, while there are few *R*-type ones because of their instability. This is the reason why the density of TSs for the *S*-type is much higher than the *R*-type in the high energy region of Figure 1B. It follows that the selectivity could be different when the catalyst was designed to prevent the ester-oxygen coordination.

In summary, we searched for TS structures of the chirality-determining elementary step in a $RuCl_2$-((*R*)-BINAP)-catalyzed asymmetric hydrogenation reaction. Experimental selectivity was reproduced by a semiautomated systematic exploration on the PES by using the ADD-following method, which may be promising for screening newly designed asymmetric catalysts as well as searching for mechanistic insight about the selectivity. From the present results, a "lock-and-key" motif at the TS structure was discovered to be the origin of the excellent selectivity in the $RuCl_2$-((*R*)-BINAP)-catalyzed asymmetric hydrogenation reaction.

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Supporting Information Available: Descriptions about the ADD-following method, computation details, and computation costs. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
(2) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998.
(3) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008.
(4) Noyori, R.; Kitamura, M.; Ohkuma, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5356.
(5) (a) Landis, C. R.; Feldgus, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2863. (b) Feldgus, S.; Landis, C. R. *J. Am. Chem. Soc.* **2000**, *122*, 12714.
(6) Gridnev, I. D.; Imamoto, T. *Acc. Chem. Res.* **2004**, *37*, 633.
(7) Mori, S.; Vreven, T.; Morokuma, K. *Chem. Asian J.* **2006**, *1*, 391.
(8) (a) Svensson, M.; Humbel, S.; Froese, R. D. J.; Matsubara, T.; Sieber, S.; Morokuma, K. *J. Phys. Chem.* **1996**, *100*, 19357. (b) Dapprich, S.; Komáromi, I.; Byun, K. S.; Morokuma, K.; Frisch, M. J. *THEOCHEM* **1999**, *461*−*462*, 1. (c) Vreven, T.; Morokuma, K. *J. Comput. Chem.* **2000**, *21*, 1419. (d) Vreven, T.; Morokuma, K.; Farkas, Ö.; Schlegel, H. B.; Frisch, M. J. *J. Comput. Chem.* **2003**, *24*, 760. (e) Morokuma, K.; Wang, Q.; Vreven, T. *J. Chem. Theory Comput.* **2006**, *2*, 1317.
(9) Kolossváry, I.; Guida, W. C. *J. Am. Chem. Soc.* **1996**, *118*, 5011. Schlegel, H. B. *J. Comput. Chem.* **2003**, *24*, 1514. Wales, D. J. *Int. Rev. Phys. Chem.* **2006**, *25*, 237. Jensen, F. *Introduction to Computational Chemistry*, 2nd ed.; Wiley: Chichester, U.K., 2007.
(10) (a) Ohno, K.; Maeda, S. *Chem. Phys. Lett.* **2004**, *384*, 277. (b) Maeda, S.; Ohno, K. *J. Phys. Chem. A* **2005**, *109*, 5742. (c) Ohno, K.; Maeda, S. *J. Phys. Chem. A* **2006**, *110*, 8933. (d) Maeda, S.; Ohno, K. *J. Phys. Chem. A* **2007**, *111*, 4527. (e) Maeda, S.; Ohno, K. *J. Phys. Chem. A* **2007**, *111*, 13168.
(11) (a) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth. Collect.* **1998**, *9*, 589. (b) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth. Collect.* **1993**, *71*, 1.

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