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Asymmetric Induction with a Chiral Amine Catalyzed by a Ru-PNP Pincer Complex: Insight from Theoretical Investigation

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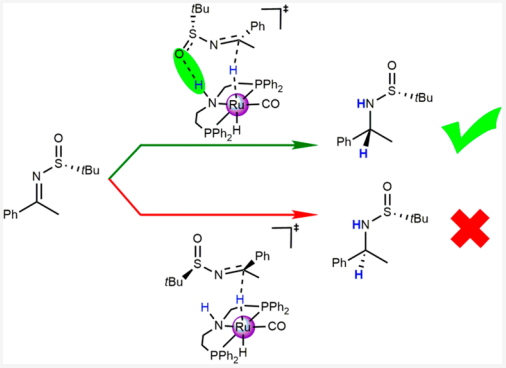
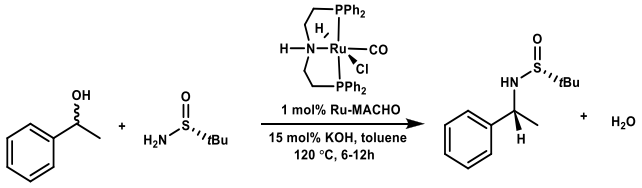
ABSTRACT: In this paper, the mechanism of asymmetric amination of a racemic alcohol with Ellman's sulfinamide and the origin of diastereoselectivity catalyzed by a Ru-PNP pincer complex were studied using density functional theory (DFT). The mechanism involves dehydrogenation of the racemic alcohol, C−N coupling, and hydrogen transfer from the catalyst to the in situ formed imine. The calculated results indicate that both the alcohol dehydrogenation and imine hydrogenation are stepwise. The hydride transfer from a Ru hydride complex to the imine is shown to be the chirality-determining step in the whole catalytic cycle. It was found that the diastereoselectivity mainly stems from the hydrogen bonding interactions between the oxygen atom of the sulfinyl moiety and the hydrogen atom of the NH group of the ligand.



1. INTRODUCTION

A vast number of drugs and fine chemicals are chiral amines or contain functional groups derived from chiral amines. Thus, the development of many biologically active molecules relies on the development of general and efficient methods to prepare chiral amines.[1] With this in mind, there remains a need to develop more efficient methods for the stereoselective construction of C−N bonds. One of the most explored reaction types for this purpose is the asymmetric hydrogenation of imines, which can be achieved with purely organic catalysts or with transition-metal complexes.[2] In transition-metal-catalyzed hydrogenations, the hydrogen source can either come from molecular hydrogen (direct hydrogenation) or organic molecules such as 2-propanol or formic acid (transfer hydrogenation).[3] In particular, Ru, Rh, and Ir complexes bearing chiral ligands have been successfully used as catalysts for asymmetric transfer hydrogenation (ATH).[4] Amines have also been prepared by the condensation or amination of alcohols with amines catalyzed by transition-metal complexes,[5] which has been recognized as a highly atom economical and green method.[6] We have recently shown that such a hydrogen borrowing (or hydrogen autotransfer) reaction is feasible even under transition-metal-free conditions.[7]

Scheme 1. Ru-catalyzed Diastereoselective Amination of Racemic Alcohols to Afford Chiral Amines



Among the amino substrates, Ellman's sulfinamide has become a widely used reagent for the synthesis of α-chiral primary amines since its discovery in 1997.[8] Over the past decade, an increasing collection of methods based upon the chiral amine reagent *tert*-butanesulfinamide has been used for both the discovery and production of drug candidates and agrochemicals product.[9] The *tert*-butylsulfinyl group is a particularly interesting chiral auxiliary, since it has shown high levels of asymmetric induction in a variety of processes and can be easily removed under mildly acidic conditions, leading to the corresponding primary amines.[10] An excellent example is seen in the work of Dong, Guan, and co-workers,[11] who reported the direct synthesis of α-chiral amines from Ellman's sulfinamide and racemic alcohols catalyzed by the Ru-MACHO[12] catalyst (Scheme 1). This amination reaction transforms inexpensive racemic alcohols into diastereopure amines and generates H_2O as the only byproduct. The

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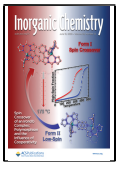

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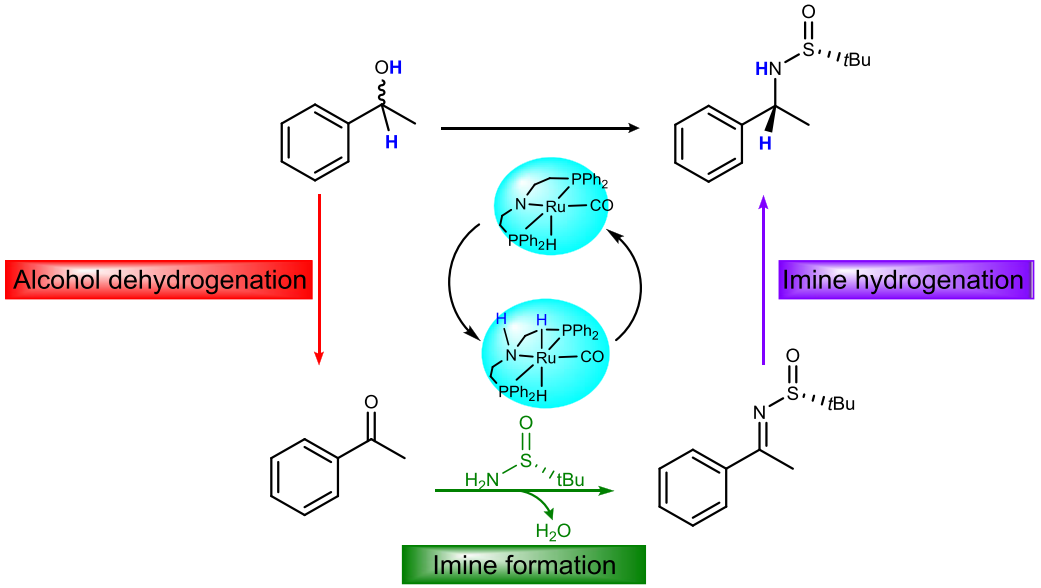
Scheme 2. Proposed Mechanism for the Diastereoselective Hydrogen-Borrowing Reaction Catalyzed by Ru-MACHO Complex



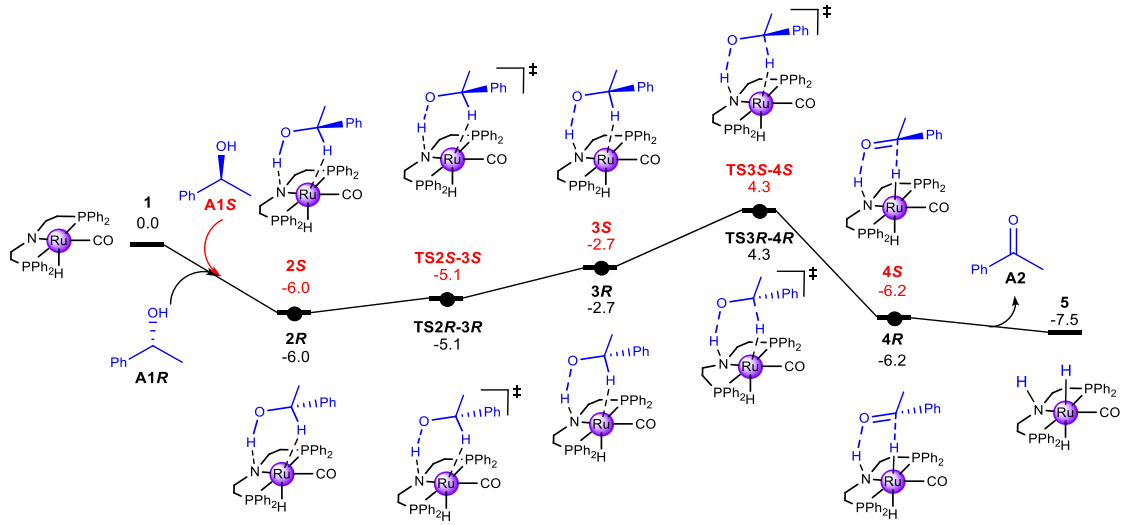


Figure 1. Free energy profiles for the alcohol dehydrogenation (in kcal/mol). The energies of stationary points are free energies relative to (PNP)RuH(CO) (structure **1**). The *S* path indicates that alcohol is *S*-chiral (in red), while the *R* path means *R*-chiral alcohol (in black).

mechanism of this interesting reaction has not been reported, however.

Detailed mechanistic studies will help to promote the development of more efficient catalytic systems. In 2012, Yus and co-workers[13] reported an excellent Ru catalyst for the ATH of N-(*tert*-butylsulfinyl)imines with high diastereoselectivities. DFT studies showed that the imine reduction occurs through a stepwise mechanism and that the origin of diastereoselectivity is derived from steric repulsions and attractive hydrogen bonding interaction. In 2015, Yang and co-workers[14] performed DFT calculations to study the mechanism of the N-alkylation of amines with alcohols using $[Cp^*IrCl_2]_2$ ($Cp^* = \eta^5$-C_5Me_5) as the precatalyst. The results showed that the most favorable pathway involves inner-sphere hydrogen transfer under the catalysis of Cp*Ir(NHPh)Cl with $KHCO_3$ as the proton donor.

Following from our study of the asymmetric formation of chiral amines from Ellman's sulfinamide and racemic alcohols which requires no transition-metal catalysts,[7] we carried out a DFT study on the borrowing hydrogen reaction of Dong and Guan, which involves Ru-catalyzed asymmetric hydrogenation of in situ generated imines. As shown in Scheme 2, the catalytic cycle of the amination reaction could be divided into three parts, i.e., a racemic alcohol is oxidized by the Ru-pincer complex to form ketone and Ru hydride; the ketone then undergoes condensation with sulfinamide to form the sulfinylimine; and hydrogenation of the imine via the Ru hydride finally generates the α-chiral sulfinylamine. The staring ruthenium monohydride species could be formed from the corresponding chloride complex, Ru-MACHO, by treating with a base and using hydrogen gas or 2-propanol as hydrogen resources.[15] In this work, we use the hydrides as active catalyst for imine reduction.

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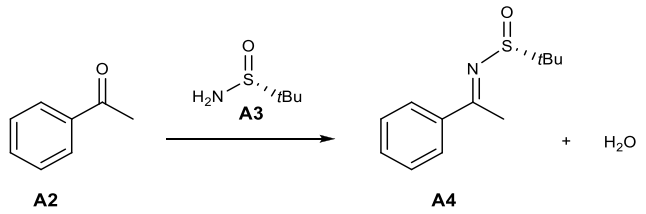

Figure 2. Formation of an imine from acetophenone and Ellman's sulfinamide.

2. COMPUTATIONAL DETAILS

On the basis of previous computational studies on hydrogenation and dehydrogenation reactions catalyzed by transition-metal complexes, all calculations were performed in the continuum solvent reaction field of implicit toluene at the ωB97X-D/BS-I[16] level using the Gaussian 09 program.[17] The SMD polarizable continuum model[18] was employed in the calculations. BS-I denotes the LANL2DZ basis set for Ru and the 6-31G* basis set for the other atoms.[19] In addition, we have calculated the single-point energy data using ωB97X-D/BS-II//ωB97X-D/BS-I (BS-II denotes LANL2DZ for the Ru center and 6-31++G** for the other atoms) on the basis of stationary points. Free energies were calculated at 298.15 K. All transition states were further confirmed by vibrational analysis and characterized by the only imaginary frequencies mode.[20] Intrinsic reaction coordinates (IRC) calculations were performed in order to confirm intermediates along the reaction pathway. The atomic polar tensor (APT) charge was calculated.[21] All energies discussed in the following parts are free energies unless otherwise stated. Free energies at 393.15 K were also calculated for comparison (see Supporting Information). Figure 4 and Figure 6 were generated using CYLview.[22] All relative energies of stationary points along the reaction pathway are relative to **1** unless otherwise stated.

3. RESULTS AND DISCUSSION

As shown in Scheme 2, the catalytic cycle of the diastereoselective amination reaction catalyzed by the Ru-MACHO complex consists of three key steps, namely, alcohol dehydrogenation, imine formation, and imine hydrogenation.

3.1. Alcohol Dehydrogenation. In the alcohol dehydrogenation process, we set the monohydride **1** as zero point reference (Figure 1). First, we investigated the racemic alcohol dehydrogenation process shown in Scheme 2. As Figure 1 shows, the *S* and *R* alcohols can interact with **1** through an outer-sphere mechanism to form **2*R*** and **2*S***, and the free energies are both −6.0 kcal/mol. On going from **2** to **3**, the proton transfers from the alcohol to the N atom of **1**, with energy barriers of 0.9 kcal/mol for both. It should be pointed out that the transition state **TS2*S*-3*S*/TS2*R*-3*R*** is slightly lower (by 2.4 kcal/mol) in free energy than **3*S*/3*R*** However, **TS2*S*-3*S*/TS2*R*-3*R*** is higher than **3*S*/3*R*** by 0.3 kcal/mol in electronic energy. The hydride transfer occurs from the step of **3** to **4** via the transition state **TS3*S*-4*S*/TS3*R*-4*R***, and the energies of **4*R*** and **4*S*** are both −6.2 kcal/mol. The free energy barriers for the dehydrogenation of *S* and *R* benzylalcohol, from **2*S*/2*R*** to **TS3*S*-4*S*/TS3*R*-4*R***, are both 10.3 kcal/mol. Finally, **5** is formed after **4** releases one molecule of ketone, the energy of **5** being −7.5 kcal/mol.

The product of alcohol dehydrogenaiton, acetophenone **A2**, reacts with Ellman's sulfinamide **A3** to form imine **A4** (Figure 2) under the experimental conditions (see Scheme 1). The mechanism of imine formation was studied by Wang et al.[23] using the DFT method. The formation of imine includes two steps, i.e., coupling of the ketone with amine to form hemiaminal and dehydration of hemiaminal to give the product imine. The calculated results show that the hemiaminal dehydration step is the rate-determining step in the formation of imine assisted by water, alcohol, or base.[23,24] Although the imine formation from amine and ketone is a routine condensation reaction, we investigated this condensation mechanism using ωB97X-D. The mechanism of imine

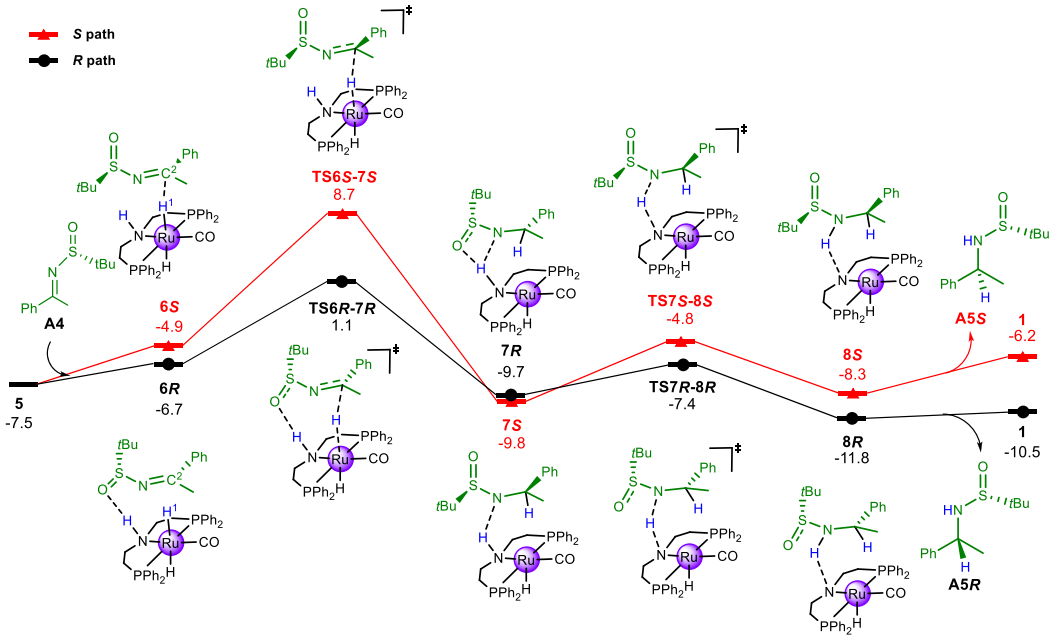

Figure 3. Free energies (in kcal/mol) for the hydrogenation of imine. The energies of stationary points are free energies relative to (PNP)RuH(CO) (structure **1**). *S* path indicates that final product is (*R*,*S*)-amine (in red), while *R* path means (*R*,*R*)-amine (in black).

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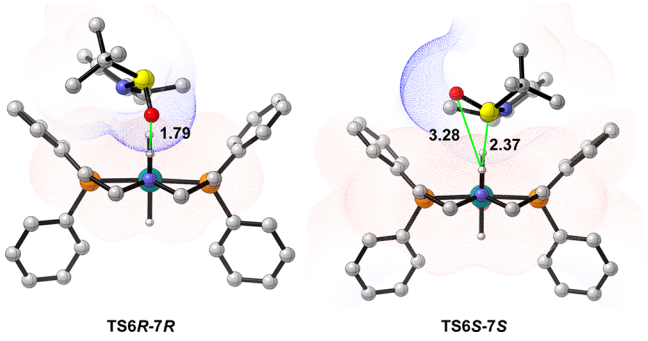

Figure 4. Optimized geometries of **TS6*R*-7*R*** and **TS6*S*-7*S***. Electrostatic potential surfaces are shown.[25] Key bond lengths are given in angstroms, and less relevant H atoms are omitted for clarity.

formation catalyzed by KOH involves two steps, i.e., amine couples with acetophenone to form a hemiaminal imtermediate, and KOH mediated hemiaminal dehydration to give product imine and byproduct H_2O. The calculated results indicate that the hemiaminal dehydration is the rate-determining step owning to a free energy barrier of 14.9 kcal/mol (see SI).

3.2. Imine Hydrogenation. The energy profiles of the reaction between **5** and imine in continuum toluene are shown in Figure 3. The reaction starts with the formation of the hydrogen-bonding complexes, formed between **5** and imine substrate along the *R* and *S* pathways. From the resulting intermediate **6*R***, the hydride transfer occurs via the transition state **TS6*R*-7*R***, in which the O atom of the sulfinyl forms a hydrogen bond with the NH moiety of the PNP ligand of the catalyst with the dihedral angle of C−N−S−O being −88°. The O−H distance in **TS6*R*-7*R*** is much shorter than that in **TS6*S*-7*S***, which shows that the *R* path involves N−H···O hydrogen bonding interaction, but there is no such interaction in the *S* path (Figure 4).

The transition state **TS6*R*-7*R*** leads to the formation of complex **7*R***, which lies 2.2 kcal/mol below **5**. The transfer of the hydrogen from the nitrogen atom of the ligand takes place via **TS7*R*-8*R***, with an energy barrier of 2.3 kcal/mol. The transition state **TS7*R*-8*R*** evolves into complex **8*R***, which is −11.8 kcal/mol relative to **1.** In this intermediate, the (*R*,*R*)-amine product is connected to the active catalyst **1** through a hydrogen bond between the N−H group of the product and the nitrogen atom of the ligand. Finally, the (*R*,*R*)-amine is released with the regeneration of catalyst **1**, and the whole process is exergonic, by 10.5 kcal/mol. Figure 3 further shows that the *R* pathway is favored energically, and the (*R*,*S*)-amine is less stable than the (*R*,*R*)-analogue, which is consistent with the experimental observations.[11] Free energies at experimental temperature (393.15 K) were also calculated (Figure S5). At 393.15 K, the whole process is exergonic by 10.6 and 6.2 kcal/

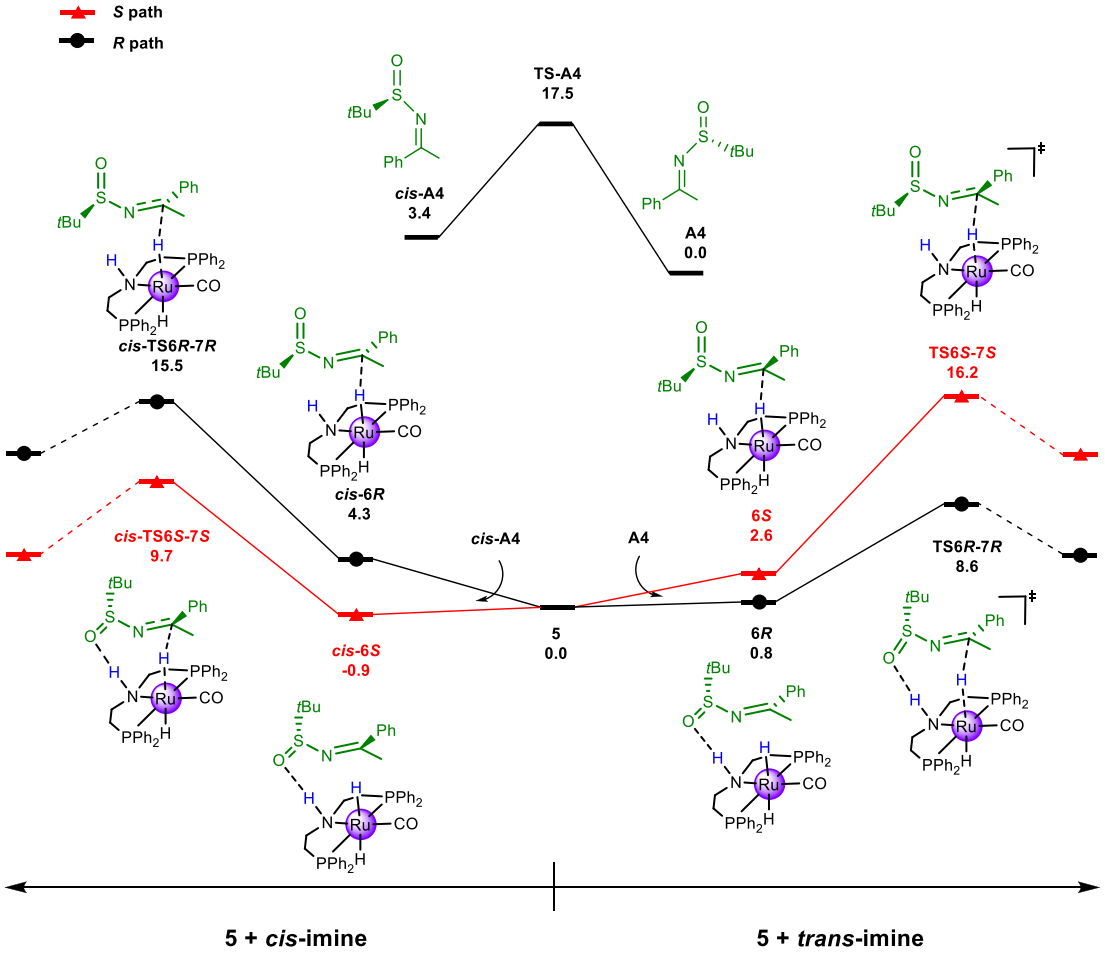

Figure 5. Free energy profiles (in kcal/mol) of the first hydrogen transfer with *cis*- and *trans*-imine. The energies of stationary points are free energies relative to (PNHP)RuH(CO) (structure **5**). The *S* path is drawn in red and the *R* path in black.

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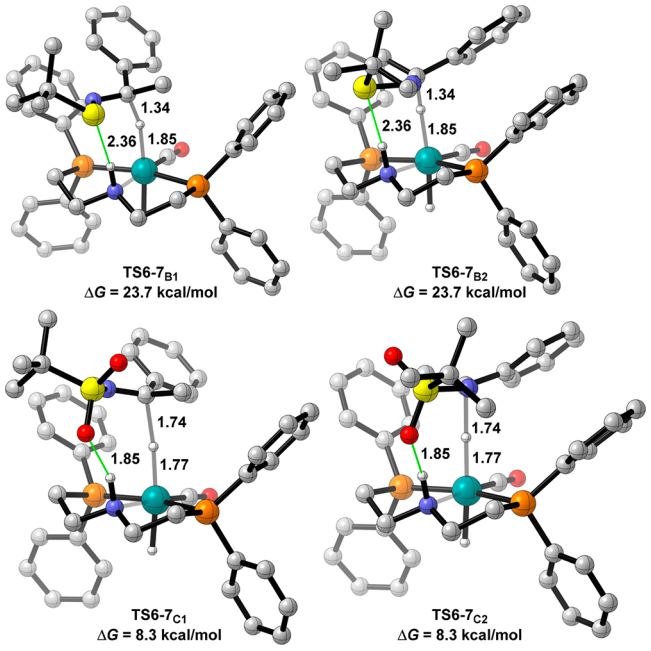

Figure 6. Optimized geometrical structures of transition states and corresponding free energy barriers of the hydride transfer step from **6** to **7** for the hydrogenation of the imine with *tert*-butyl thiamine group (**B**) and that with *tert*-butanesulfonyl group (**C**) (**TS6−7$_{B1}$** denotes the transition state for the *Si* pathway of **B** system, and **TS6−7$_{B2}$** denotes the transition state for the *Re* pathway of **B** system).

mol in *R* and *S* paths, respectively. Compared with the results calculated at 298.15 K, the energy barrier of alcohol dehydrogenation increased slightly. As for the chirality-determining step, from **5** to **7*R***/**7*S***, the energy barrier increased from 8.6/16.2 kcal/mol to 13.7/21.1 kcal/mol.

3.3. The Origin of Diastereoselectivity. It is important to understand the factors governing the diastereoselectivity in the mechanism. In this work, we have shown that enantioselection takes place when hydride transfer occurs. Concerning the *R* pathway, the energy barrier of the hydride transfer is 8.6 kcal/mol. On the other hand, the energy barrier for the *S* pathway is 16.2 kcal/mol (Figures 3 and 5), showing the former to be more feasible.

We also considered the hydrogenation of the *cis*-imine. When the reduction occurs on the *R* pathway, the energy barrier of the hydride transfer is 15.5 kcal/mol; analogously, the energy barrier is 10.6 kcal/mol on the *S* pathway. The imine **A4** can transfer to ***cis*-A4** through a transition state **TS-A4** with an energy barrier of 17.5 kcal/mol, which is higher than the energy barrier of hydride transfer. This means that the isomerization between **A4** and ***cis*-A4** is slower than the hydride transfer, so the Curtin−Hammet principle[26] is not applicable for this reaction. Our calculations show that the free energy of the *trans*-imine, **A4**, is 3.4 kcal/mol lower than that of ***cis*-A4**. It is obvious that *trans*-imine is more stable. This is consistent with the experimental results[7] that only **A4** is observed. It is clear that the lowest energy barrier of the hydride transfer is 8.6 kcal/mol along the *R* pathway with **A4** as the substrate, leading to the (*R*, *R*)-product. This is also consistent with the experimental results (Scheme 1).

Our previous works[27] suggest that the charge of H^1 in complex **6*S***/**6*R*** (Figure 3) is a good manifestation of the difficulty of hydride transfer. In this study, the charge of H^1 in complex **6*S***/**6*R*** could still be used as an important factor to evaluate the hydride transfer process. The APT charge of H^1 in **6*R*** and **6*S*** is −0.195 and −0.172, respectively. The APT charge of C^2 atom in **6*R*** is 0.932 and that in **6*S*** is 0.846. And, the energy barrier of hydride transfer in the *R* path and *S* path is 8.6 and 16.2 kcal/mol, respectively. Thus, it is tempting to conjecture that the effect caused by the more negative charge of H^1 and more positive charge of C^2 in intermediate **6*R*** compared to those in **6*S*** makes the following hydrogen transfer easier, which is consistent with results from our previous works.[27] Meanwhile, some other factors, such as steric effect and hydrogenation bond interactions, may decrease or increase the hydride transfer energy barriers.

As we can see from Figure 5, **TS6*R*-7*R*** involves attractive interactions between O(δ^-) of the sulfinyl moiety of the imine and H of the NH moiety of Ru complex. These attractive interactions are strong hydrogen bonds, in which the O(δ^-) acts as an electron donor and H atom behave as electron acceptors (d_{N-H} = 1.03 Å, d_{O-H} = 1.79 Å, ∠N−H−O = 160°). Such interactions can stabilize **TS6*R*-7*R*** in comparison with **TS6*S*-7*S***, in which there is no O···H hydrogen bonding. It thus appears that it is the NH···O hydrogen bonding that stabilizes the transition state **TS6*R*-7*R***, affording the observed diastereoisomer. The results are also consistent with Yus and co-workers' calculations[13] on Ru-catalyzed ATH of N-(*tert*-butylsulfinyl)ketimine, which showed that the NH···O hydrogen bonding interactions play a key role in the origin of diastereoselectivity. In our recent theoretic study of the same reaction but under transition-metal-free conditions, the sodium cation from the base used is shown to play a similar critical role in the hydride transfer step, bonding with both the nitrogen and oxygen atoms of the intermediate sulfinamide in the transition state and thereby accelerating the hydrogen transfer reaction while dictating its diastereoselectivity.[7]

To further understand the importance of hydrogen bonding network for the hydride transfer, we then changed the *tert*-butanesulfoxyl group of substrate imine into a *tert*-butyl thiamine group (**B**) and *tert*-butanesulfonyl group (**C**) as shown in Figure 6. As we can see, both **TS6−7$_{B1}$** and **TS6−7$_{B2}$** involve weak N−H···S hydrogen bonding interactions, leading to *R* and *S* amine, respectively, and the energy barriers are both 23.7 kcal/mol. In contrast, both **TS6−7$_{C1}$** and **TS6−7$_{C2}$** involve strong hydrogen bond interactions, and the energy barriers are much lower, both at 8.3 kcal/mol. With an achiral catalyst, two reaction pathways have no difference in energy as we expected. The results show that the hydrogen bond interactions involving the sulfinyl group are the main driving force in accelerating the reaction and determining the diastereoselectivity.

4. CONCLUSIONS

The mechanism of the amination of a racemic alcohol with Ellman's sulfinamide and the origin of diastereoselectivity catalyzed by a ruthenium PNP complex were studied. The calculated results indicate that both alcohol dehydrogenation and imine hydrogenation are stepwise. It was found that the energy barrier for the favorable pathway leading to the (*R*,*R*)-amine is 8.6 kcal/mol, while the energy barrier for the unfavorable pathway leading to the (*R*,*S*)-product is 16.2 kcal/mol. The difference between the free energy of activation is 7.6 kcal/mol, and so, the theoretical calculation is consistent with the experimental results.[11] The origin of the diastereoselectivity appears to stem mainly from the hydrogen bonding interactions between the O of the sulfinyl moiety and the H

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atom of the NH group of the ligand, which may shed light on the asymmetric imine hydrogenation induced by sulfinamide in the future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.inorgchem.0c00823.

Electronic energies in toluene solvent and thermal correction energies, geometric parameters of a typical structure, and Cartesian coordinates of stationary points (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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