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DFT Modeling of the Enantiomeric Excess in Asymmetric Transfer Hydrogenation Reaction of Prochiral Ketones in Water Promoted by Chiral Proline (Amide/Amine) Ruthenium (II) Complexes.

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ABSTRACT

Recently, a proline amide/amine derived amino acid has been experimentally employed as an effective chiral catalytic precursor in the ruthenium-mediated asymmetric reduction of prochiral ketones in water to produce the corresponding secondary alcohols, which provides the products in 80% ee. In this paper, We show that transition state modeling according to the outer-sphere reaction mechanism at the PBE-GD3BJ/LANL2DZ/6-31G (d,p) level of theory can accurately model enantioselectivity for various proline-catalyzed asymmetric transfer hydrogenation.

Keywords: asymmetric transfer hydrogenation, ruthenium, DFT, Dispersion, enantioselectivity.

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INTRODUCTION

Asymmetric transfer hydrogenation of ketones is an important transformation in the production of many fine chemical compounds at both laboratory and industrial level [1-2].Therefore, many studies have been undertaken to develop new highly selective catalyst [3-4]. Noyori et al [5-6] Showed that a ruthenium complex containing monotosylated 1, 2-diamines could serve as efficient catalyst for the ATH of ketones.

Amino acids are inexpensive chiral materials that have been used for the synthesis of optically active transition metal complexes [7-9]. In 2001, the group of Faller reported a in situ generated (*p*-cymene) Ru (L-proline amide) Cl_2 catalyst that gave excellent yields, 70-90%, with moderate enantiocontrol, 68-93%, in hydrogenations of a variety of ketones at -24 C° [10]. In the same year, Chung reported the first example of the asymmetric hydrogen-transfer reductions of aromatic ketones in an aqueous solution, with enantiomeric excesses up to 95.3 % using a functionalized proline amide as ligand [11]. Zeror and others have constructed active and selective ATH-catalysts based on the use of proline amides [12-14].

Based on literature reports [15-17], a plausible mechanism for the ATH of ketones in aqueous media can follow an outer-sphere pathway analogous to that proposed by Noyori and al [18-19] fig1.

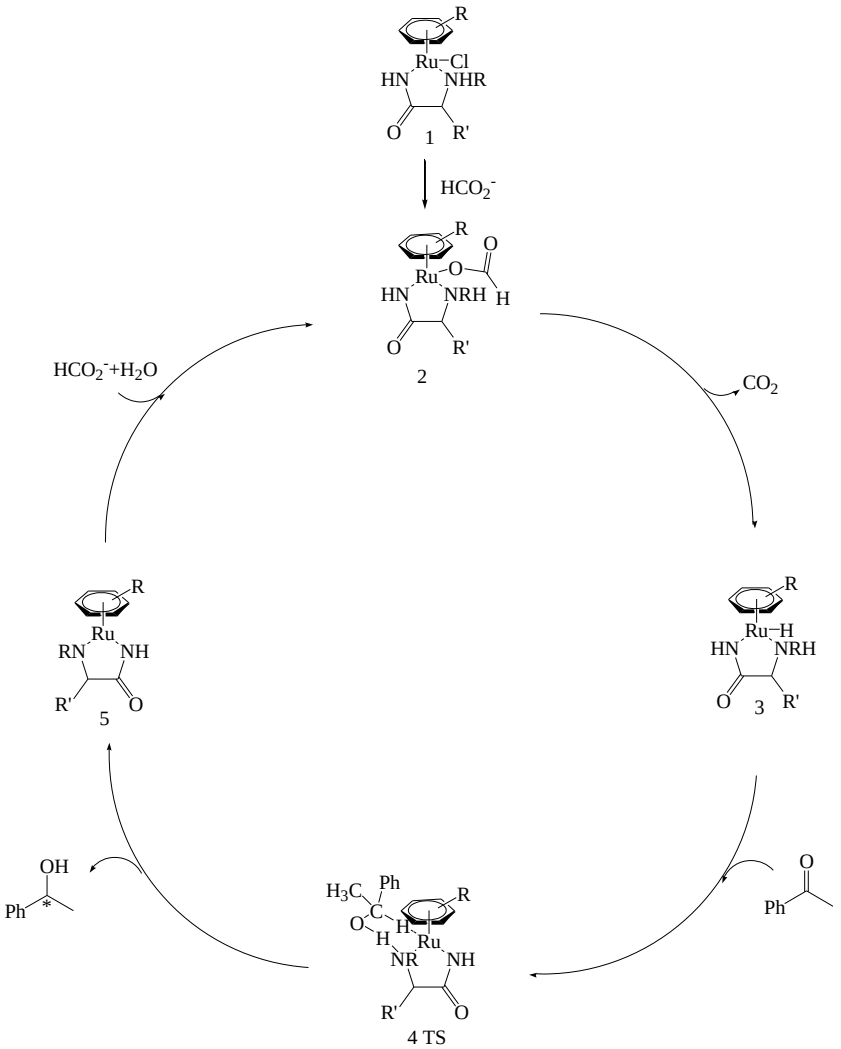

Figure 1: Plausible mechanism for transfer hydrogenation of acetophenone catalyzed by Ru (II) complexes containing amino amide ligands in aqueous media.

Percatalyst Ru-proline amide is generated *in situ* from [Ru (p-cymene) $cl_2]_2$ and proline amide in water and then it reacts with HCOOHNa forming formato complex 2 the reduction prooceeds via the formato intermediate 2, followed by decarboxylation to give Ru-hydride intermediate 3, The key step is the

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simultaneous transfer of the hydritic H (Ru–H) and the protic H (N–H) to the C=O functional group via a six-membered transition state 4 TS. Last, the active intermediate 5 is regenerated with the liberation of the chiral alcohol, closing the catalytic cycle.

Recently, Serpil Denizaltı et al. [20] compared the proline amine ligands with amide analogues in asymmetric transfer hydrogenation reaction of prochiral ketones in water (figure 2). In this work we have rationalized the enantioselectivity observed experimentally using Density functional theory.

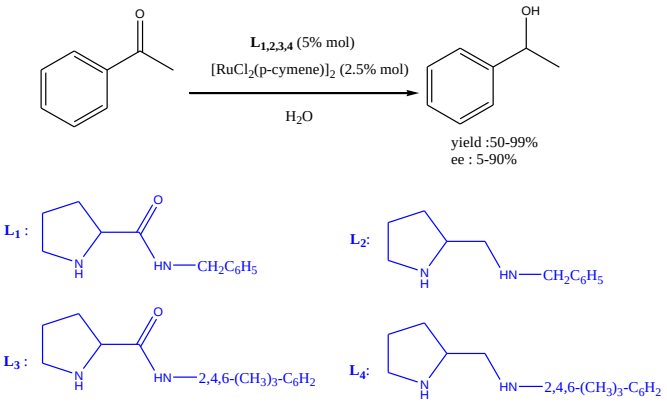

Figure 2: Ru-catalyzed ATH of ketones with [Ru (p-cymene)Cl_2]$_2$ and ($L_{1,3}$) proline amide or ($L_{2,4}$) proline amine. ee is the enantiomeric excess.

EXPERIMENTAL SECTION

Computational details

All calculations were performed at the density functional theory (DFT) level, using the PBE [21] functional by addition of the D3 version of Grimme's dispersion with Beck-Johnson Damping functions [22] as implemented in the Gaussian 09 D01 software package [23]. For all atoms except ruthenium, the 6-31G (d,p) basis set was used [24-25]; ruthenium was treated with the LANL2DZ basis set and effective core potential (ECP) [26].geometries for the transition state were located either by QST2 or by QST3 procedures, or by the guess based on the structure of the previously found TS. Vibrational frequency calculations were then performed at the optimized geometry of transition structure. We confirmed that all transition structures have one, and only one, imaginary frequency. The intrinsic reaction coordinate (IRC) calculations, at the same level of theory, were performed to ensure that the transition structures led to the expected reactants and products. The reported energies are Gibbs free energies, which include zero-point vibrational corrections, thermal corrections at 298 K and solvation free energies. The solvation energies were calculated as single point corrections on the optimized structures using the conductor-like polarizable continuum model method [27], with dielectric constant ε=78.3553 for water.

RESULTS AND DISCUSSION

In acetophenone hydrogenation catalyzed by chiral proline (amide/amine) ruthenium (II) complexes, the hydride transfer can occur via two different pathways, each having a diastereotopic transition state. One pathway corresponds to the attack of the hydride at the *Re* face of acetophenone while the other pathway involves an attack at the *Si* face.

According to eqn (1) and the Arrhenius equation, we could obtain eqn (2) to calculate the ee values (ee Calculated).

$$ee = \frac{R-S}{R+S} \qquad (1)$$

$$ee_{\text{calculated}} = \frac{e^{\Delta\Delta Ga/RT}-1}{e^{\Delta\Delta Ga/RT}+1} \qquad (2)$$

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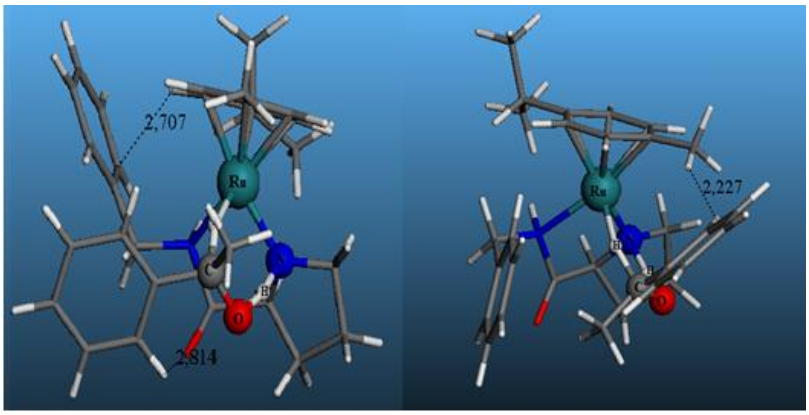
Stereoselectivity with Ligand 1, 2 (proline amide/amine)

TS1(*S*) results from the approach of Ru-hydride intermediate to the *Re* face of the acetophenone and leads to (active catalyst + phenylethanol). In TS1(*S*), the free energy of TS1(*S*) is calculated to lie +8.4 kcal/mol above that of the separate reactants (Ru-hydride + acetophenone). TS1(*R*) results from the approach of Ru-hydride intermediate to the *Si* face of the acetophenone and lies +7.9 kcal/mol above the free energy of the reactants and leads to the other configuration of phenylethanol + active catalyst. The optimized structures of these transition states are collected in Figure 3.



TS1(*R*) **TS1(*S*)**
+7,9 **+8,4**

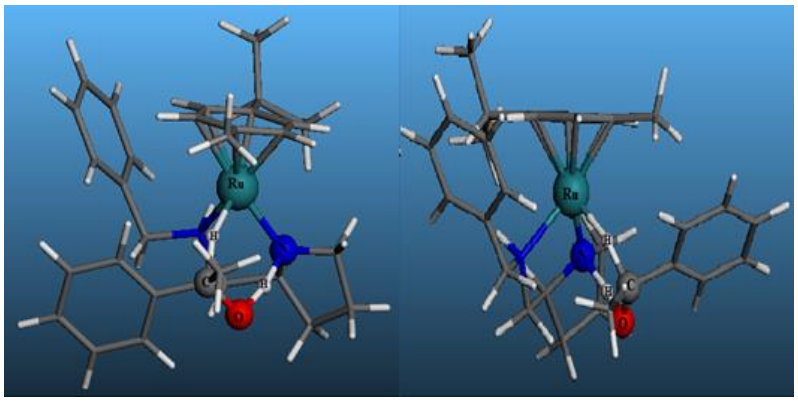
ee experimental= 28%
ee calculated= 35%

Figure 3: Optimized geometries of the PBE-GD3BJ level of transition states with ligand 1. free energies are in kcal mol^{-1} and relative to the separate reactants.

The reason for this preference is that

- In transition state TS1(*R*) a stabilizing NH–p interaction between the phenyl group of the catalyst and the cymene of the catalyst.
- And in TS1(*S*) the clashes of the methyl groups of cymene with the phenyl ring of the acetophenone; this is not present in the TS1(*R*).

Optimized structures of transition states with ligand 2 (proline amine) are collected in Figure 4.



TS2(*R*) **TS2(*S*)**
+8.5 **+8,75**

ee experimental= 14%
ee calculated= 18%

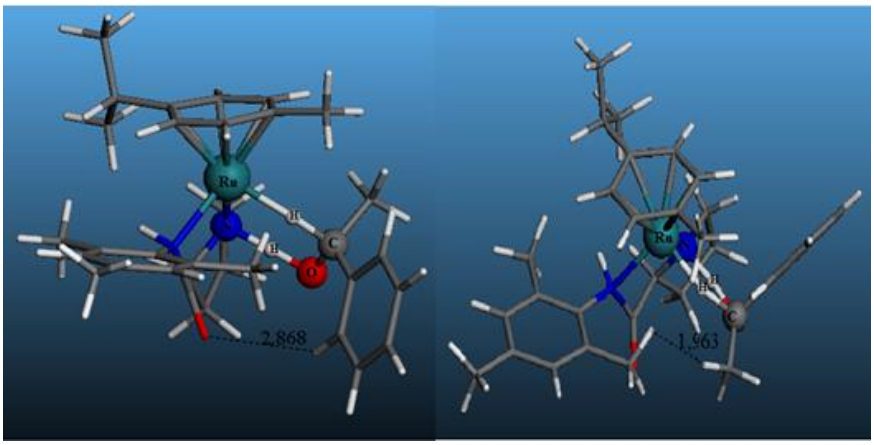
Figure 4: Optimized geometries of the PBE-GD3BJ level of transition states with ligand 2. free energies are in kcal mol^{-1} and relative to the separate reactants.

The calculations correctly reproduce the fact that this ligand affords the *R* form of the product. TS2(*R*)

Is 0.25 kcal mol^{-1} lower than TS2(*S*) wich corresponds quite well with the experimental findings. Both of these transition states have the advantageous stabilizing CH–p electrostatic interaction between the Cymene of the catalyst and the phenyl ring of the catalyst. However, in the case of TS1(*R*) there is an additional similar attractive interaction between the oxygen and the hydrogen of the acetophenone (see Figure 3), which causes the energy of this TS to be lower and, thus, determines the selectivity. These results, in particular the fact that the calculations reproduce and rationalize the stereoselectivity of ligand 1 and 2.

Stereoselectivity with Ligand 3, 4 (proline amide/amine)

TS3(*S*) results from the approach of Ru-hydride intermediate to the *Re* face of the acetophenone and leads to (active catalyst + phenylethanol). In TS3(*S*), the free energy of TS3(*S*) is calculated to lie +11.3 kcal/mol above that of the separate reactants (Ru-hydride + acetophenone). TS3(*R*) results from the approach of Ru-hydride intermediate to the *Si* face of the acetophenone, and lies +9.6 kcal/mol above the free energy of the reactants and leads to the other configuration of phenylethanol+ active catalyst. The optimized structures of these transition states are collected in Figure 5.



TS3(*R*) **TS3(*S*)**
+9,6 **+11,3**

ee experimental= 80%
ee calculated= 89%

Figure 5: Optimized geometries of the PBE-GD3BJ level of transition states with ligand 1. free energies are in kcal mol^{-1} and relative to the separate reactants.

The reason for this preference is that

- In transition state TS3(*R*) a stabilizing interaction between the oxygen of the catalyst and the hydrogen of the acetophenone.
- And in TS3(*S*) the clashes of the methyl groups of acetophenone with the phenyl ring of the catalyst; this is not present in the TS3(*R*).

Optimized structures of transition states with ligand 4 (proline amine) are collected in Figure 6.

Concerning the pro-(R) pathways, free energy barrier for the H transfer, TS4(*S*), is 10.9 $kcalmol^{-1}$. This value is the one corresponding to the approach of Ru-hydride intermediate to the *Re* face of the acetophenone. On the other hand, free energy barrier for the pro-(S) pathways, TS4(*R*), is 9.2 $kcalmol^{-1}$ and corresponds to the approach of Ru-hydride intermediate to the *Re* face of the acetophenone. Since the difference between these free energy barrier values is 1.7 $kcalmol^{-1}$, the theoretical calculations predict a 74% ee of the (*R*)-product, which is consistent with the experimental results.Therefore, our theoretical model seems to be appropriate for explaining the stereoselectivity of this transfer-hydrogenation process.

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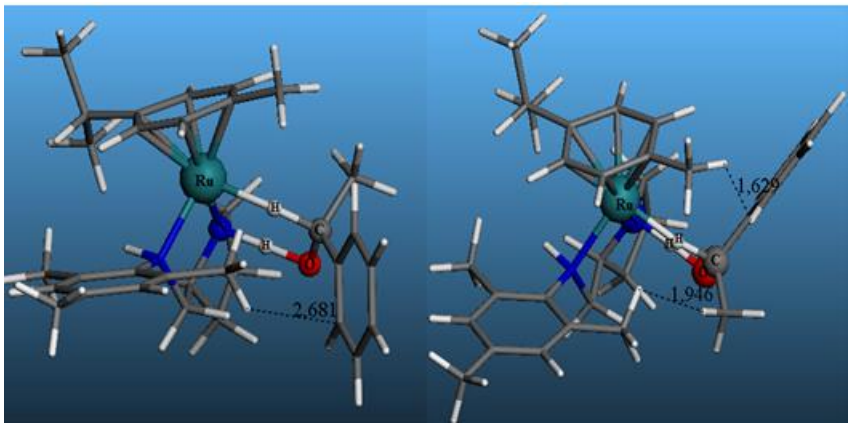

TS4(*R*) **TS4(*S*)**

+9,2 **+10,9**

ee experimental= 71%
ee calculated= 74%

Figure 6: Optimized geometries of the PBE-GD3BJ level of transition states with ligand 2. free energies are in kcal mol-1 and relative to the separate reactants.

CONCLUSION

A theoretical investigation of the factors that affect the enantioselective outcome of ruthenium (II) proline (amide/amine) catalysed transfer hydrogenation allowed the determination of a ligand structure-enantioselectivity relationship. It was shown that the chiral proline amide ligands gave better enantiomeric excess as compared with the corresponding amine derivatives and the bulk of the aryl substituents on the ligand increased the enantioselectivity, all the synthetically useful high selectivities are successfully predicted. In addition, our results showed that important insights can be obtained with such a theoretical approach, particularly the origin of enantioselectivity. This can help experimentalists to design new active catalysts.

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