

Why Is Copper(I) Complex More Competent Than Dirhodium(II) Complex in Catalytic Asymmetric O–H Insertion Reactions? A Computational Study of the Metal Carbenoid O–H Insertion into Water

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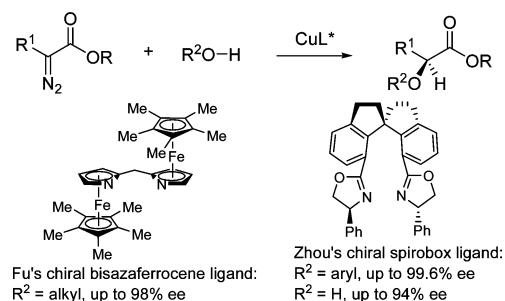
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Transition-metal-catalyzed insertions of α -diazocarbonyl compounds into X–H (X = C, O, N, etc.) bonds have drawn considerable interest because these methods provide direct and efficient processes for the creation of carbon–carbon or carbon–heteroatom bonds.¹ In this field, many efforts have been devoted to the development of chiral transition-metal catalysts for asymmetric versions of these important reactions. Among them, chiral dirhodium(II) catalysts have been shown to be powerful for catalytic asymmetric insertions into C–H bonds, which have been utilized in syntheses of natural products and pharmaceutical targets.² On the other hand, the asymmetric O–H insertion reaction is an ideal synthetic strategy for preparing optically pure α -alkoxy, α -aryloxy, and α -hydroxy carboxylic acid derivatives, which are valuable building blocks for the construction of natural products and other biologically active molecules.³ Surprisingly, although many groups have tried to achieve asymmetric O–H insertion using various chiral dirhodium(II) catalysts, to date there have been no reports of a significant level of enantiocontrol.⁴ Only recently, through the use of copper catalysts carrying chiral ligands, have the groups of Fu and Zhou independently made remarkable advances in highly enantioselective insertions of α -diazocarbonyl compounds into the O–H bonds of alcohols,^{5a} phenols,^{5b} and water.^{5c} (Scheme 1). Why are chiral copper catalysts more competent than chiral dirhodium catalysts in asymmetric O–H insertions? This is an unresolved question. The answers to this question will not only provide a comprehensive and deep understanding of the insertions of metal carbenoids into O–H bonds at the molecular level but also guide further rational design of new catalysts for asymmetric X–H insertions.

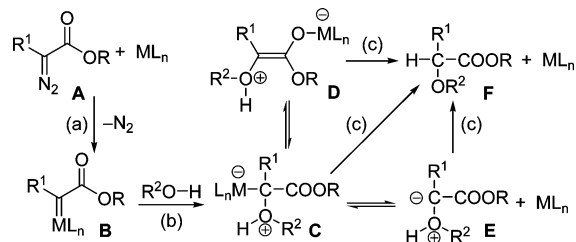
The commonly accepted mechanism for the O–H insertion reaction is given in Scheme 2.^{6,7a} The whole reaction includes three main processes: (a) metal-catalyzed nitrogen extrusion from α -diazocarbonyl compound **A** to form metal carbenoid **B**; (b) generation of metal-associated oxonium ylide **C** from metal carbenoid **B** and R²OH; and (c) [1,2]-hydrogen shift of the metal-associated ylide (**C** or **D**) or free oxonium ylide **E** to give product **F** and regenerate the metal catalyst. Although several experimental results have provided evidence of oxonium ylide formation,⁷ there are still two pivotal questions to be answered: (1) Which oxonium ylide is the reactive precursor for the [1,2]-H shift process, a metal-associated one or a metal-free one? (2) How does the [1,2]-H shift occur? In particular, the answer to the first question is critical to the asymmetric O–H insertions using chiral metal catalysts. Only when the stereodetermining [1,2]-H shift occurs via the metal-associated ylide pathway can the stereocenter formation be induced by the chirality of the catalyst. This is the prerequisite for achieving enantioselectivity.

Here we communicate the results of our mechanistic study of copper(I)- and rhodium(II)-catalyzed O–H insertion reactions of methyl α -diazophenylacetate with water using density functional theory (DFT) calculations with the B3LYP functional.^{8,9} We have found that the reaction pathway for Cu(I)-catalyzed O–H insertion is quite

Scheme 1. Catalytic Highly Enantioselective O–H Insertion Reactions Using Chiral Copper Catalysts



Scheme 2. The Commonly Accepted Mechanism for the O–H Insertion Reaction



different from that for the Rh(II)-catalyzed one, and the widely accepted direct [1,2]-proton shift should be corrected to a water-catalyzed [1,2]-proton shift.

Our mechanistic studies of the O–H insertion focus on the catalytic cycle starting from the metal carbenoids, since previous DFT calculations have documented the detailed processes of Cu(I) and Rh(II) carbenoid formation from α -diazocarbonyl compounds.^{10–12} First we investigated the reaction between water and the Cu(I) carbenoid complex **1** ligated by a 2,2-dimethylmalonic acid-derived bisoxazoline. The computed free energy surface is given in Figure 1. The calculations show that the nucleophilic attack of water to copper carbenoid **1** is very facile, requiring an activation free energy of only 9.3 kcal/mol via transition state **TS-1**. Formation of copper-associated oxonium ylide **2-C** is endergonic by 8.6 kcal/mol. According to the previously proposed mechanism,^{6,7a} the subsequent step is an intramolecular [1,2]-proton shift that converts the oxonium ylide intermediate into the final O–H insertion product **4**. However, the exact reactive precursor for this [1,2]-proton shift process is not clear. To solve this problem, we located the direct [1,2]-H shift transition states from copper-associated oxonium ylides **2-C** (having carbon anion as the coordinating atom) and **2-O** (having oxygen anion as the coordinating atom) and free oxonium ylide **2-F** (for details, see Table S1 in the Supporting Information). The computational results indicate that the lowest-energy route among them is from copper-associated ylide **2-C** to **TS-2-C**. However, the overall activation free energy to reach **TS-2-C** is still as

high as 32.7 kcal/mol in CH_2Cl_2 (Figure 1). Therefore, this direct intramolecular [1,2]-proton shift pathway is kinetically unfeasible, in view of the fact that the O–H insertion of copper carbenoid into water can smoothly occur even at 10 °C.^{5c} Inspired by computational and experimental studies of the phosphine-catalyzed [3 + 2] reaction,¹³ in which a water-catalyzed [1,2]-proton shift is favored over the direct [1,2]-proton shift, we hypothesized that the reactant water may also act as a proton-transport catalyst to facilitate the [1,2]-proton shift in the present reaction. To test this hypothesis, we computed the activation free energies of the water-catalyzed [1,2]-H shift pathways and found that the energy barriers for these transition states **TS-3-C**, **TS-3-O**, and **TS-3-F** are all substantially lower than those for the corresponding direct [1,2]-H shift transition states **TS-2-C**, **TS-2-O**, and **TS-2-F** (for details, see Table S1). The most favored transition state among them is **TS-3-O** from copper-associated intermediate **3-O**. The overall energy barrier for this water-catalyzed [1,2]-H shift pathway is only 19.8 kcal/mol (Figure 1). In contrast, the pathway involving the free ylide is energetically disfavored. DFT calculations show that the dissociation of copper-associated ylide **3-C** to give free ylide **3-F** is endergonic by 15.1 kcal/mol, and the subsequent water-catalyzed [1,2]-H shift via **TS-3-F** requires an activation free energy of 4.7 kcal/mol. This means that the free-ylide pathway has an overall activation free energy of 29.4 kcal/mol, which is ~ 10 kcal/mol higher than that for the copper-associated ylide pathway (Figure 1).^{12,14} Therefore, we conclude that the stereodetermining [1,2]-H shift process requires the catalysis of water and that the involved intermediate in this step is the copper-associated ylide.

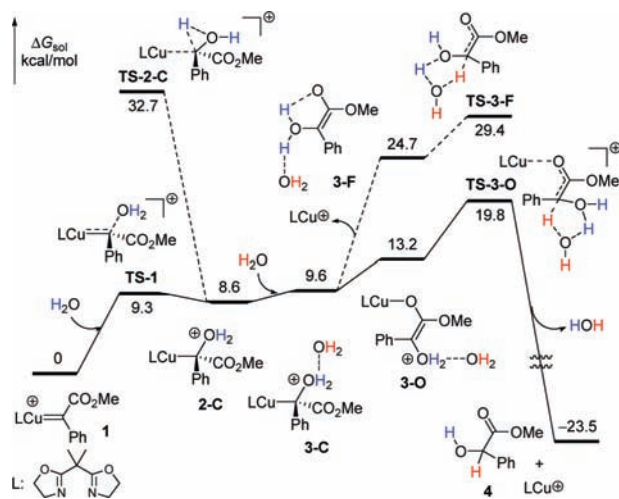


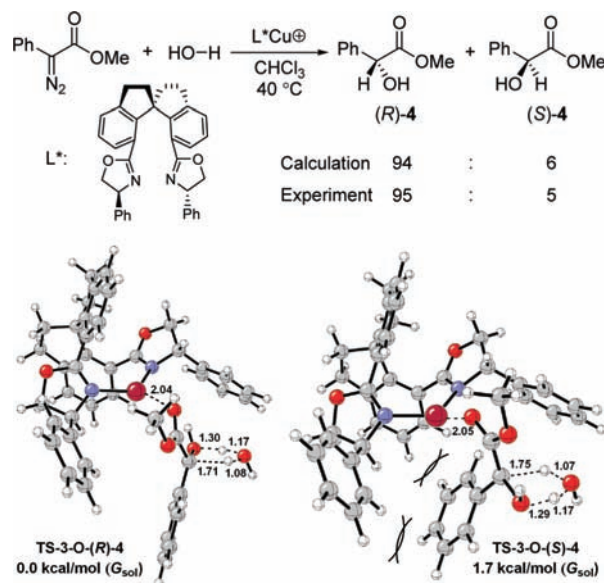
Figure 1. DFT-computed free energy surface for the Cu(I) carbenoid insertion into the O–H bond of water.

We further conducted a preliminary investigation of the asymmetric version of this O–H insertion reaction (Scheme 3). In the Cu(I)-catalyzed O–H insertion, the stereocenter-formation transition state is **TS-3-O** (Figure 1). Therefore, we replaced the achiral ligand in **TS-3-O** by a chiral ligand, (*S,S,S,S*)-Ph-spirobox, and optimized the two stereocenter-formation transition states corresponding to the generation of (*R*)-**4** and (*S*)-**4**. It was found that the generation of (*R*)-**4** is favored over that of (*S*)-**4**. This is because the phenyl group of the ylide has steric repulsions with the two phenyl groups of the ligand in **TS-3-O-(S)-4**, whereas these are absent in **TS-3-O-(R)-4** (Scheme 3). The computed free energy difference between these two transition states is 1.7 kcal/mol in CHCl_3 , giving a predicted ee of 88% at 40 °C, which is close to the experimentally observed ee of 90%.^{5c}

We also investigated the reaction of methyl α -diazophenylacetate with water employing dirhodium tetraformate as the catalyst. The computed free energy surface is given in Figure 2. In the rhodium(II)-catalyzed O–H insertion, the formation of rhodium-associated ylide

6-C is also facile, with an activation free energy of 8.7 kcal/mol. The subsequent [1,2]-proton shift process is catalyzed by water as well

Scheme 3. DFT Study of an Asymmetric O–H Insertion Reaction



(for details, see Table S2), but the reactive precursor for this process is different from that in the copper-catalyzed reaction. The energy barrier for transition state **TS-7-O** from rhodium-associated ylide **7-O** is 19.3 kcal/mol (Figure 2). However, free ylide **7-F** is 6.5 kcal/mol more stable than **7-O**, and the subsequent water-catalyzed [1,2]-H shift via **TS-7-F** requires an activation free energy of only 4.7 kcal/mol. This means that the free-ylide pathway has an overall activation barrier of 13.6 kcal/mol,¹⁵ which is ~ 6 kcal/mol lower than the energy required in the rhodium-associated ylide pathway (Figure 2). Thus, the reactive precursor for the [1,2]-H shift process is the free ylide in the Rh(II)-catalyzed O–H insertion. This implies that when a chiral dirhodium(II) complex is used as the catalyst, the Rh-coordinated ylide first dissociates to form a free ylide, so the subsequent stereodetermining transition state is not influenced by the chiral ligand. Therefore, it is not surprising that to date there has been nearly no enantioselectivity observed when chiral dirhodium(II) catalysts are used.⁴

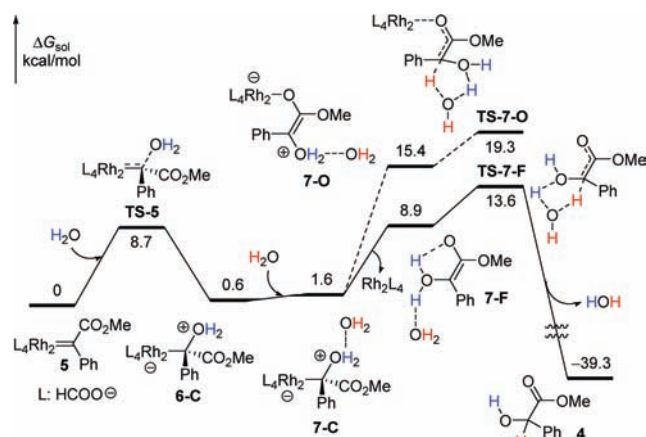
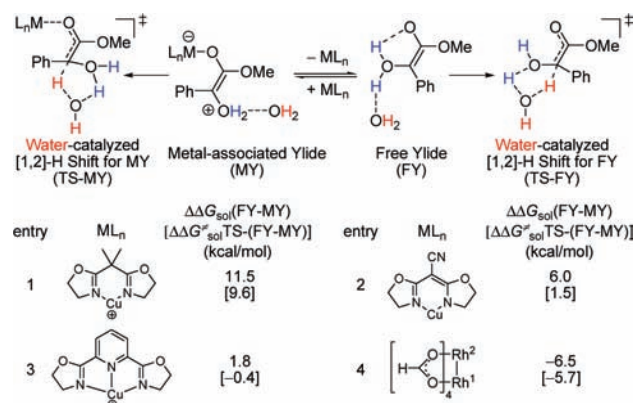


Figure 2. DFT-computed free energy surface for the Rh(II) carbenoid insertion into the O–H bond of water.

Reviewing the aforementioned energy surfaces (Figures 1 and 2), we find that whether the key [1,2]-H shift proceeds via the metal-associated ylide (MY) pathway or the free-ylide (FY) pathway mainly depends on the relative stability of the corresponding ylide intermedi-

ates (Scheme 4). When the cationic Cu(I) complex of bisoxazoline is used as the catalyst, the metal-associated ylide is much more stable than the free one, leading exclusively to the copper-associated ylide pathway (entry 1). In contrast, the free ylide is more favored when the neutral dirhodium(II) complex is used as the catalyst, making the

Scheme 4. Relative Free Energies of the Two Competing Pathways for Various Catalyst Systems



FY pathway predominant (entry 4). To further probe the factors that influence the energy difference between the MY and FY pathways, we investigated two other Cu(I) catalysts.¹⁶ For the neutral Cu(I) complex of semicorrin (entry 2), the metal-associated ylide is still favored, but this preference is much smaller than that using the cationic Cu(I) complex of bisoxazoline (6.0 vs 11.5 kcal/mol). This indicates that the cationic metal catalyst can lead to a stronger electrostatic attraction between the metal center and the enolate moiety of the ylide, which remarkably enhances the stability of the MY. For the Cu(I) complex of Pybox (entry 3), albeit in a cationic form, the metal-associated ylide is only 1.8 kcal/mol more stable than the free one. This much lower binding energy of the metal catalyst and the ylide is attributed principally to the trans effect of the ligand in the catalyst. There is a pyridine ligand positioned trans to the ylide in the MY, and this trans effect (the lone pair of the nitrogen atom donating to the Cu–O σ^* orbital) facilitates the dissociation of the ylide from the metal center. On the basis of these two factors, the strong propensity of the dirhodium(II) complex to release the ylide can be explained well: (1) the neutral dirhodium(II) complex has a weaker electrostatic attraction between the metal catalyst and the ylide than in the cationic complex; (2) in the dirhodium(II) complex, there are two Rh atoms close in a line (Rh¹ and Rh², see entry 4), so the trans effect of the Rh² atom (the Rh² nonbonding 4d_{z²} orbital donating to the Rh¹–O σ^* orbital)^{11a} can greatly promote the dissociation of the ylide from the Rh¹ atom.

In summary, the detailed mechanisms of copper(I) and rhodium(II) carbenoid insertions into O–H bond of water have been investigated using DFT calculations, from which some new insights into these reactions have been obtained. It has been found that in the Cu(I)-catalyzed system, the [1,2]-H shift process (the stereocenter-formation step) favors the copper-associated ylide pathway. This ensures that when a chiral copper complex is used as the catalyst, the stereocenter forms in a chiral environment, which is the prerequisite for achieving enantioselectivity. In contrast, the free-ylide pathway is favored in the Rh(II)-catalyzed system. This significant difference renders copper(I) complexes more competent than dirhodium(II) complexes in catalytic asymmetric O–H insertion reactions. In addition, it is found for the first time that in transition-metal-catalyzed X–H insertions, water can act as an efficient proton-transport catalyst for the [1,2]-H shift. These findings will be helpful in understanding other insertion reactions of heteroatom–hydrogen bonds in a wide range of substrates¹⁷ and provide useful information for the design of new chiral catalysts.

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Supporting Information Available: Computational details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (12) The formations of Cu(I) carbenoid **1** (Figure 1) and Rh(II) carbenoid **5** (Figure 2) are exergonic by 20.0 and 4.2 kcal/mol, respectively, in CH₂Cl₂. In Figures 1 and 2, the regenerated metal catalysts are coordinatively unsaturated, and they can be coordinated by α -diazoester to start another catalytic cycle or stabilized by solvent CH₂Cl₂. However, these processes are all slightly endergonic, suggesting that the catalyst resting states shown in Figures 1 and 2 are reasonable. These computational details are given in the Supporting Information.
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- (16) The enantioselectivities of the O–H insertions using copper catalysts carrying the chiral semicorrin ligand and Pybox ligand were evaluated in ref 5. It was found that only low enantioselectivity could be achieved. These experimental findings can be rationalized by the computational results in Scheme 4. The energy differences between the FY and MY pathways are very close for Cu–semicorrin (1.5 kcal/mol; entry 2) and Cu–Pybox (–0.4 kcal/mol; entry 3), suggesting that the generation of racemic products via the FY pathway cannot be suppressed in these two systems.
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