

**Ligand Effects on Reactivity and Selectivity of Transition-Metal Catalyzed Asymmetric  
C-C and C-N Bond Forming Reactions**

by

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# **Ligand Effects on Reactivity and Selectivity of Transition-Metal Catalyzed Asymmetric C-C and C-N Bond Forming Reactions**

Luke Thomas Jesikiewicz, MS

University of Pittsburgh, 2020

Homogenous catalysis using transition metals has grown to be one of the most common ways of forming chemical bonds in an enantioselective and regioselective manner. The role of the ancillary ligand in these processes is crucial in determining the desired stereochemical outcome. The origins of the effects of ligands that influence reactions to yield a specific product are not yet well understood. Herein, three studies that combine density functional theory (DFT) calculations and experimental data to further understand the role of the ligand in transition metal catalyzed reactions are reported. In the first study, the mechanisms and rate- and selectivity-determining steps of the copper-catalyzed asymmetric coupling of ketones and 1,3-butadiene were examined. The product selectivity is controlled by steric interactions from a combination of chiral ligand-substrate interactions and steric repulsions about the forming carbon-carbon bond in the Zimmerman-Traxler type ketone addition transition state. Next, a mechanistic study of the copper-catalyzed coupling of 1,3-enynes and nitriles demonstrated the selectivity was determined through steric interactions in the nitrile addition and cyclization steps of the reaction. Lastly, the study of the rhodium-catalyzed Pauson-Khand reaction of 1,6-enynes identified a key steric interaction between the substrate and the ligand in the oxidative cyclization transition state that controls the enantioselectivity. Additionally, this study demonstrated the importance of accounting for experimental conditions when performing DFT calculations. Taken together, these computational

studies demonstrated the effective use of DFT calculations to study mechanisms, and the effects of ligands and substrates on reactivity and selectivity in transition metal-catalyzed reactions.

## Table of Contents

|                                                                                                                                                                   |           |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| <b>1.0 Introduction.....</b>                                                                                                                                      | <b>1</b>  |
| <b>2.0 Mechanism and Origin of Diastereo- and Enantioselectivity in the CuH-Catalyzed Enantioselective Ketone Allylation with 1,3-Dienes .....</b>                | <b>5</b>  |
| <b>2.1 Background.....</b>                                                                                                                                        | <b>5</b>  |
| <b>2.2 Computational Details.....</b>                                                                                                                             | <b>9</b>  |
| <b>2.3 Results and Discussion .....</b>                                                                                                                           | <b>10</b> |
| <b>2.3.1 Key Experimental Results .....</b>                                                                                                                       | <b>10</b> |
| <b>2.3.2 SL-J011-1 Ligand Catalytically Active Conformation Search .....</b>                                                                                      | <b>11</b> |
| <b>2.3.3 Selectivity in the Hydrocupration Step .....</b>                                                                                                         | <b>13</b> |
| <b>2.3.4 Mechanistic Consequences of 1,3-Migration .....</b>                                                                                                      | <b>14</b> |
| <b>2.3.5 Origin of Enantio- and Diastereoselectivity in Ketone Addition Step .....</b>                                                                            | <b>15</b> |
| <b>2.4 Synthesis of Pyrroles from Cu-H Catalyzed Coupling of 1,3-Enynes and Nitriles</b>                                                                          | <b>21</b> |
| <b>2.5 Conclusion .....</b>                                                                                                                                       | <b>24</b> |
| <b>3.0 Mechanism and Origins of Enantioselectivity in the Rh(I)-catalyzed Pauson–Khand Reaction: Comparison of Bidentate and Monodentate Chiral Ligands .....</b> | <b>25</b> |
| <b>3.1 Introduction .....</b>                                                                                                                                     | <b>25</b> |
| <b>3.2 Computational Details.....</b>                                                                                                                             | <b>29</b> |
| <b>3.3 Results and Discussion .....</b>                                                                                                                           | <b>32</b> |
| <b>3.3.1 Substrate Binding Energies for Four Different (R)-BINAP-Rh(I) Complexes .....</b>                                                                        | <b>32</b> |
| <b>3.3.2 Calculated Mechanism for PKR with (R)-BINAP Ligand .....</b>                                                                                             | <b>34</b> |

|                                                                                               |    |
|-----------------------------------------------------------------------------------------------|----|
| 3.3.3 Origin of Enantioselectivity with ( <i>R</i> )-BINAP .....                              | 35 |
| 3.3.4 Calculated ( <i>S</i> )-MonoPhos Mechanism and Origin of Enantioselectivity .....       | 38 |
| 3.3.5 Effects of Corrections for Experimental Conditions .....                                | 46 |
| 3.3.6 Full Potential Energy Surface of PKR with CO as the Only Ligand .....                   | 49 |
| 3.3.7 Comparison of Calculated Oxidative Cyclization Barriers and Experimental<br>Rates ..... | 51 |
| 3.4 Conclusions .....                                                                         | 55 |
| Bibliography .....                                                                            | 57 |

## **List of Tables**

|                                                                                                |           |
|------------------------------------------------------------------------------------------------|-----------|
| <b>Table 1: Experimental rate studies of cationic Rh catalysts in the PKR of enyne 1. ....</b> | <b>52</b> |
|------------------------------------------------------------------------------------------------|-----------|



## List of Figures

|                                                                                                                                                                                                                                                                                                 |    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Figure 1: Overview of projects including the a) Cu-catalyzed asymmetric coupling of ketones to dienes, b) Cu-catalyzed enyne-nitrile coupling, and the c) Asymmetric Pauson-Khand reaction.....                                                                                                 | 4  |
| Figure 2: Overview of the use of 1,3-dienes in industry and in catalytic allylation processes. ....                                                                                                                                                                                             | 6  |
| Figure 3: Overview of relevant previous computational studies on TM-catalyzed allylations by a former member of our group, Gang Lu et. al. (a) and the Houk group (b).....                                                                                                                      | 8  |
| Figure 4: Proposed catalytic cycle for copper-catalyzed ketone allylation.....                                                                                                                                                                                                                  | 9  |
| Figure 5: Optimized reaction conditions for the CuH-catalyzed allylation of 4-methoxyacetophenone performed by Chenxi Li and Richard Liu at MIT. ....                                                                                                                                           | 11 |
| Figure 6: The conformations of the SL-J011-1 ligand supported Cu-H catalyst.....                                                                                                                                                                                                                | 11 |
| Figure 7: The lowest energy transition state geometries for hydrocupration step. ....                                                                                                                                                                                                           | 13 |
| Figure 8: Computed free energy profile of diene-ketone coupling with SL-J011-1 ligand..                                                                                                                                                                                                         | 14 |
| Figure 9: Lowest energy Zimmerman-Traxler type transition state structures.....                                                                                                                                                                                                                 | 16 |
| Figure 10: Effects of ligand conformation on the stability of the ketone addition transition state. Gibbs free energies and enthalpies (in parenthesis) are in kcal/mol with respect to the separated reactants (1b and 28a) and the CuH catalyst (25a).....                                    | 18 |
| Figure 11: Additional isomers of the ketone addition transition states that involve addition to the ( <i>Re</i> )-face of the ketone. Gibbs free energies and enthalpies (in parenthesis) are in kcal/mol with respect to the separated reactants (1b and 28a) and the CuH catalyst (25a). .... | 19 |

|                                                                                                                                                                                                                                                                                                     |    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Figure 12: Additional isomers of the ketone addition transition states that involve addition to the ( <i>Si</i> )-face of the ketone. Gibbs free energies and enthalpies (in parenthesis) are in kcal/mol with respect to the separated reactants (1b and 28a) and the CuH catalyst (25a).<br>..... | 20 |
| Figure 13: Enyne nitrile coupling reaction conditions performed by Yujing Zhou at MIT.                                                                                                                                                                                                              | 21 |
| Figure 14: Proposed catalytic for copper-hydride catalyzed coupling of enynes and nitriles.<br>.....                                                                                                                                                                                                | 22 |
| Figure 15: Potential energy surface of Cu-H catalyzed enyne-nitrile coupling. ....                                                                                                                                                                                                                  | 23 |
| Figure 16: Overview of previous relevant computational studies on Pauson-Khand and Rh-catalyzed cyclization reactions by the Baik group (a) and the Patton group (b). ....                                                                                                                          | 26 |
| Figure 17: Allenic Pauson-Khand reaction conditions and ligand scope. ....                                                                                                                                                                                                                          | 27 |
| Figure 18: Proposed catalytic cycle for PKR with 1,6 Enynes. ....                                                                                                                                                                                                                                   | 28 |
| Figure 19: Enyne binding energies ( $\Delta G$ Values) for four (R)-BINAP-Rh(I) complexes.<br>.....                                                                                                                                                                                                 | 32 |
| Figure 20: Calculated free energy profile of PKR with (R)-BINAP (L1). ....                                                                                                                                                                                                                          | 34 |
| Figure 21: (R)-BINAP oxidative cyclization transition state structures. ....                                                                                                                                                                                                                        | 35 |
| Figure 22: 3D view of lowest energy oxidative cyclization transition states. ....                                                                                                                                                                                                                   | 36 |
| Figure 23: Substrate binding energies to possible (S)-MonoPhos CO-coordinated complexes. ....                                                                                                                                                                                                       | 38 |
| Figure 24: Partial free energy profiles showing the oxidative cyclization steps for One-(S)-MonoPhos (A) and two-(S)-MonoPhos pathway (B). ....                                                                                                                                                     | 40 |

|                                                                                                                                                                                                                                                                                                |    |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Figure 25: 4-coordinate isomers of the oxidative cyclization transition states. The Gibb's free energy and the enthalpy in parenthesis are reported in kcal/mol relative to structure 16 (1 ligand) or structure 21 (2 ligands). .....                                                         | 42 |
| Figure 26: 5-coordinate isomers of the oxidative cyclization transition states. The Gibb's free energy and the enthalpy in parenthesis are reported in kcal/mol relative to structure 16 (1 ligand) or structure 21 (2 ligands). .....                                                         | 43 |
| Figure 27: Lowest energy oxidative cyclization transition states leading to the major and minor products with one-(S)-MonoPhos and two-(S)-MonoPhos. ....                                                                                                                                      | 45 |
| Figure 28: Energy difference between 4-coordinate and 5-coordinate oxidative cyclization transition states at standard Gaussian09 conditions and the effect of correcting for experimental conditions.....                                                                                     | 48 |
| Figure 29: Optimized free energy profile for the Pauson-Khand reaction using carbon monoxide in place of a phosphine ligand. ....                                                                                                                                                              | 50 |
| Figure 30: Comparison of calculated barriers of activation for oxidative cyclization step.                                                                                                                                                                                                     | 51 |
| Figure 31: Linear correlation observed between (S)-MonoPhos (L2) (%ee) and product 2 (% ee) in PKR of enyne 1. Reaction conditions performed by Lauren C. Burrows are as follows; Rh(cod)2SbF6 (0.10 equiv), (S)-MonoPhos (L2) (0.11 equiv), mesitylene (1.0 equiv), DCE (0.05 M), 80 °C. .... | 54 |

## 1.0 Introduction

Homogenous transition metal catalysts have become amongst the most popular tools in modern organic synthesis due to their ability to catalyze reactions enantioselectively, and in high yields. Additionally, these catalysts have been able to functionalize previously inaccessible starting materials like C-C/C-H bonds, and unactivated olefins. These homogeneous transition metal catalytic systems are remarkably complex consisting of multiple interacting components including a substrate, a transition metal center, an ancillary ligand, solvent, and other reaction additives. The particular influence of the ancillary ligand has been posited since the dawn of asymmetric catalysis. The choice of ancillary ligand is crucial to enabling the desired increase in reactivity, regio-, diastereo-, enantio-, and chemo selectivity often associated with these systems. The process of selecting the correct ligand during reaction development is commonly expensive and time consuming experimentally as it involves the screening of large ligand libraries<sup>1-3</sup>. Developing an understanding of the ligand effects on the reactivity and selectivity is a crucial component to streamlining the reaction development process. In order to understand these ligand effects, numerous different qualitative and quantitative methods have been developed. Among the oldest, and most popular is the quadrant diagram<sup>4</sup>, which breaks the steric environment created by the ligand into blocked and open quadrants. The incoming substrate will typically orient itself in such a way that it places its bulkiest components in the open quadrants where there is less interference from the ligand.

The development of functionals like B3LYP<sup>5</sup>, have allowed density functional theory (DFT) to be used to examine larger, more mechanistically complex systems like asymmetric organic catalysis. DFT calculations can provide important information that can be used to elucidate

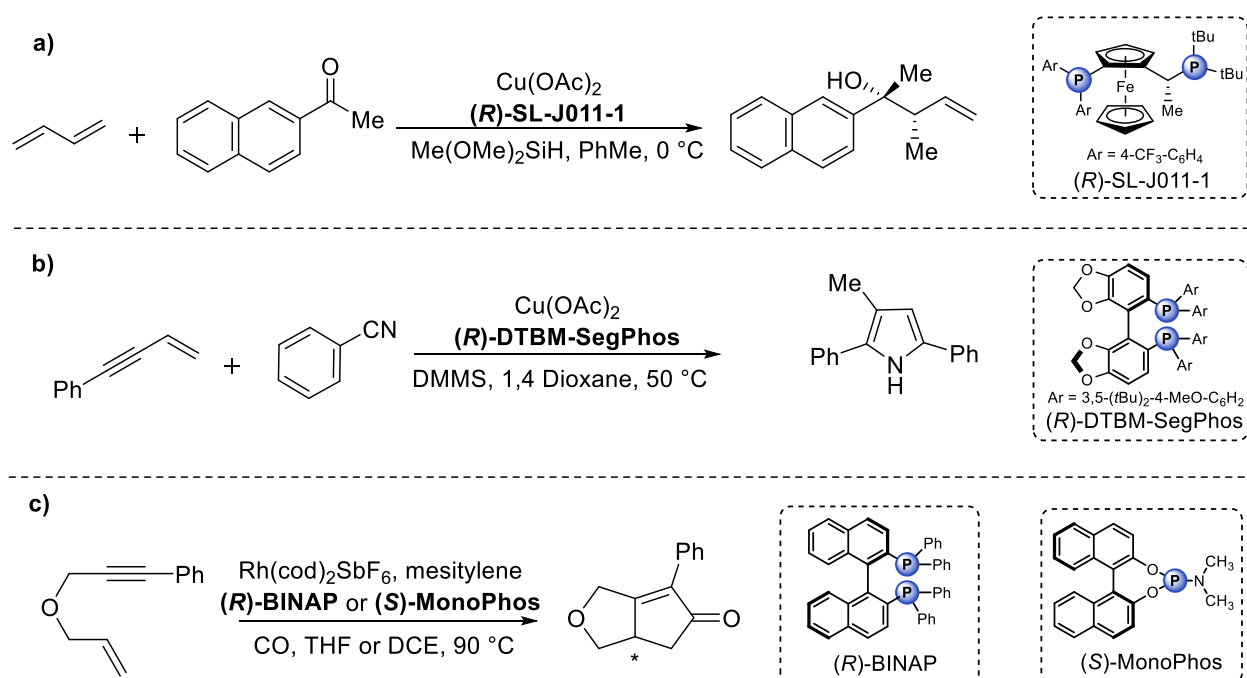
the mechanism and deduce the nature of enantio-, regio-, and diastereoselectivity in the reaction. These computational insights have informed smaller experimental screenings and the rise of “rational design” of catalysts<sup>6,7</sup>. We have chosen to employ B3LYP in the case of geometry optimizations due to its ability to elucidate reasonable energies when coupled with an appropriate single point method for transition states and intermediates alike. By combining B3LYP with a more sophisticated functional for single point calculations we can strike a balance between computational cost and relative accuracy<sup>8</sup>. We’ve chosen the M06 functional<sup>9</sup> for single point calculations used in all studies to achieve a more accurate value for the free energies. Implicit solvation models, like SMD<sup>10</sup>, and corrections for experimental temperature and concentrations were employed to better mimic the experimental conditions when necessary.

Many transition-metal catalyzed asymmetric reactions employ the use of a C<sub>2</sub>-symmetric bidentate phosphine ligand like BINAP or Ph-BPE. The ligand effects on reactivity and selectivity of these types of ligands have been well studied computationally<sup>11,12</sup>. Several classes of ligands including C<sub>1</sub>-symmetric, chiral monodentate, and phosphoramidite have received less attention and their mechanisms of chiral induction and reactivity aren’t as well understood as their C<sub>2</sub>-symmetric counterparts<sup>13</sup>. These ligand classes present additional computational challenges due to their additional conformational flexibility. Additionally, in the case of monodentate ligands the challenge of whether the mechanism prefers to proceed with a one or two of the chiral ligands coordinated to the rhodium center. This coordination preference can be further complicated by considering relative ligand concentrations and reaction temperature.

We plan to construct free-energy surfaces of mechanisms by determining the nature of the resting state of the catalyst by calculating multiple different isomers and determining the effects of ligand exchange. Then, all possible intermediates and transition states will be calculated to

determine the rate-determining and stereochemistry-determining steps. Competing transition states in key steps will be subject to further analysis to determine a rationale for energy differences leading to a certain selectivity. We will further examine the structure to identify specific steric interactions that destabilize one competing structure relative to the other. Additional tools such as steric-quadrant analysis were employed to gain further insights in the forces contributing to mechanism of selectivity.

This thesis details the use of DFT calculations along with various quantitative and qualitative computational models to better understand the reactivity and selectivity of  $C_1$ -symmetric and chiral monodentate ligand classes. I hypothesize that the existing stereochemical models, like quadrant diagrams, used to describe  $C_2$ -symmetric ligands will be sufficient to describe the behavior of  $C_1$ -symmetric and chiral monodentate ligands. These models can lead to straightforward and insightful chemical understanding about factors that control reactivity and selectivity. This chemical understanding can be applied in conjunction with experimental collaborators to rationally design new catalysts in a resource and time efficient manner.



**Figure 1: Overview of projects including the a) Cu-catalyzed asymmetric coupling of ketones to dienes, b) Cu-catalyzed enyne-nitrile coupling, and the c) asymmetric Pauson-Khand reaction.**

The first study documents the effects of the non- $C_2$ -symmetric, SL-J011-1 ligand on the copper-catalyzed asymmetric reductive coupling of ketones to 1,3-dienes (Figure 1a). The second study is a further investigation into the effect of ligand on the cyclization and nitrile addition steps in the copper catalyzed enyne-nitrile coupling (Figure 1b). The final study was a joint computational and experimental study into the mechanism of the asymmetric Pauson-Khand with 1,6-enynes (Figure 1c). This study documents the impact of the  $C_2$ -symmetric BINAP ligand, monodentate phosphoramidite MonoPhos ligand, and carbon monoxide ligands on the rate and selectivity of the reaction. Corrections for experimental concentrations and temperature played a key role in the computational mechanistic study.

## 2.0 Mechanism and Origin of Diastereo- and Enantioselectivity in the CuH-Catalyzed Enantioselective Ketone Allylation with 1,3-Dienes

Section adapted from the publication: Li, C., Liu, R. Y., Jesikiewicz, L. T., Yang, Y., Liu, P., & Buchwald, S. L., *J. Am. Chem. Soc.*, **2019** *141*(12) 5062-5070.

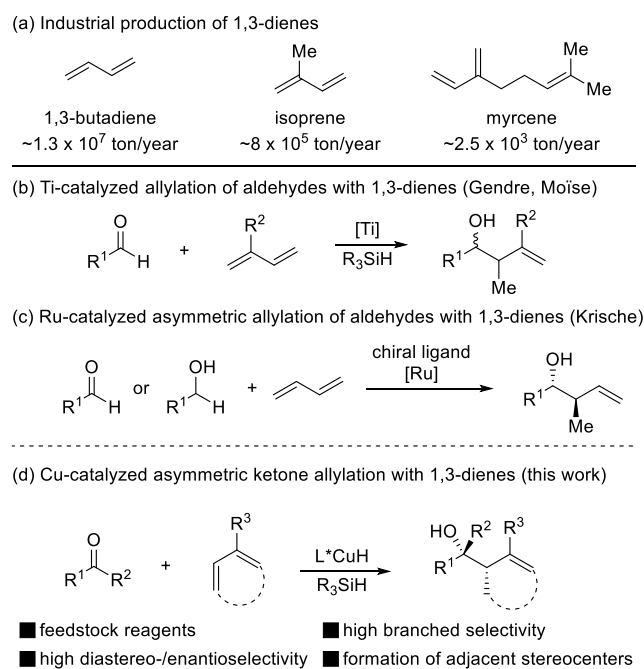
### 2.1 Background

The synthesis of enantiomerically enriched tertiary alcohols is highly sought-after due to their prevalence in a variety of pharmaceutical agents and complex natural products<sup>14,15</sup>. The most common practice traditionally for synthesizing this motif has been organomagnesium, Grignard-type reagents<sup>16</sup>. These reactions however, have significant limitations. The organomagnesium reagents need to be synthesized under harsh conditions and once synthesized are unstable and highly reactive. As a result, they have very limited use in the presence of polar functional groups. The reaction also produces a racemic mixture and achieving an enantioselective process requires the addition of chiral auxiliaries which further add to reaction complexity. There is a need to develop simple, highly efficient catalytic strategies to asymmetrically construct tertiary alcohols<sup>17–24</sup>.

1,3-Dienes provide an excellent starting material as they are produced in massive quantities every year industrially<sup>25,26</sup>. Recently, several groups have considered the use of these stable, inexpensive starting materials as replacements for organometallic reagents in carbonyl addition chemistry. In 2005, Gendre and Moise presented a titanium-catalyzed aldehyde allylation of



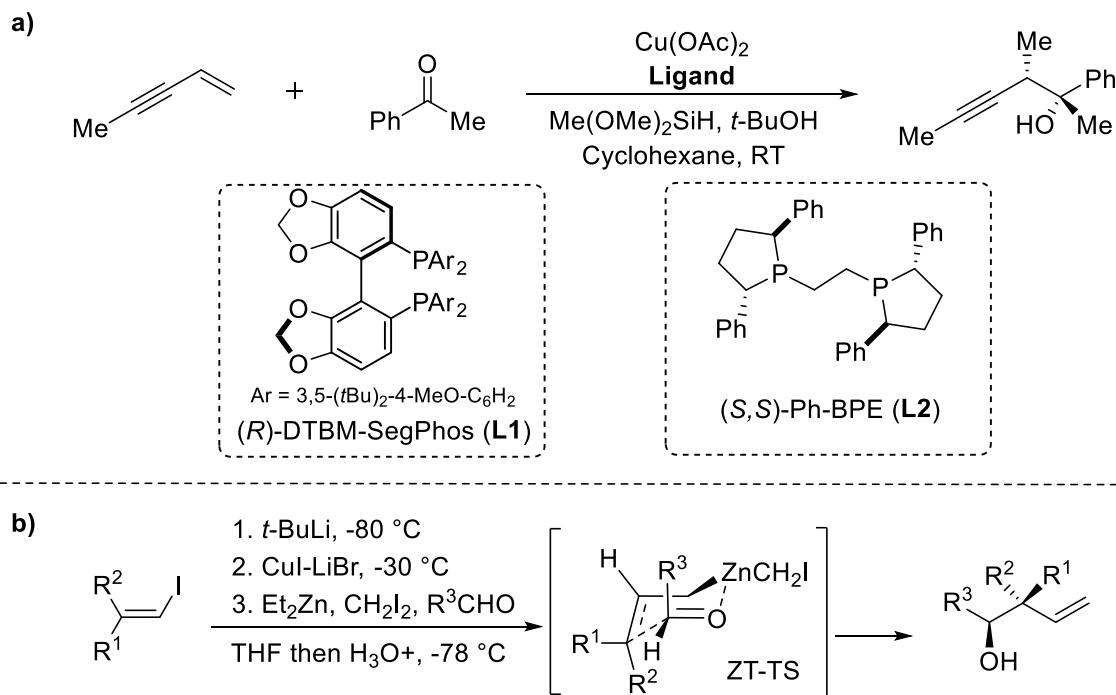
conjugated dienes which presented a step forward in metal catalyzed allyl-ketone coupling but was held back by the high reactivity of the allyl-titanium species<sup>27</sup>. Krische developed a protocol for the stereoselective aldehyde or alcohol allylations with 1,3-butadiene using a ruthenium catalyst. Consequently, this protocol is limited by the fact that it cannot be applied to ketones thus synthesizing tertiary alcohols<sup>25,26</sup>. Even with the report of multiple cases of transition metal catalyzed reductive coupling with conjugated dienes using nickel<sup>28–31</sup>, ruthenium<sup>32–37</sup>, rhodium<sup>38</sup>, and iridium<sup>39–41</sup>; the challenge of developing reaction protocols that can tolerate ketones instead of aldehydes remains.



**Figure 2: Overview of the use of 1,3-dienes in industry and in catalytic allylation processes.**

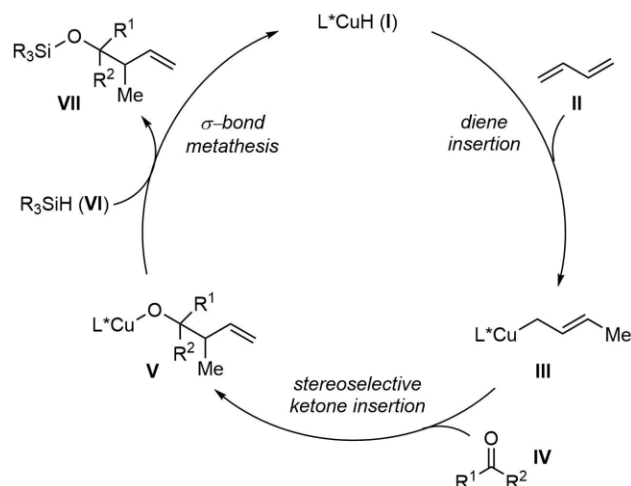
Recently, several groups, including the Buchwald group, have published work on copper-catalyzed hydroamination of unsaturated substrates via the in-situ generation of alkylcopper nucleophiles<sup>42–48</sup>. This methodology was also utilized with pronucleophiles such as allenes and enynes for nucleophilic addition to ketones<sup>49–53</sup>. The aforementioned reaction methodology with allenes and enynes has been adapted for use with imines as well<sup>54–57</sup>.

Initial computational investigations into this process were conducted in the Liu lab published in 2016 (Figure 3, A). The initial study focused on the reductive coupling of ketones to 1,3-enynes with Ph-BPE and DTBM-SegPhos ligands<sup>50</sup>. Changing the ligand from (*S,S*)-Ph-BPE to DTBM-SegPhos in experiments decreased both the yield and enantioselectivity. Computationally, It was found the (*S,S*)-Ph-BPE ligand played a crucial directing role in the hydrocupration and ketone addition steps. The steric environment created by the (*S,S*)-Ph-BPE favors hydrocupration forming the (*S*)-alkylcopper species and ketone addition forming the (*S,R*)-tertiary alcohol product. The ketone addition proceeds through a six-membered ring transition state similar to the Zimmerman-Traxler type transition state studied by Houk et. al. (Figure 3, B)<sup>58,59</sup>. The lowest energy transition states of this type are typically those who minimize the number of gauche interactions along the forming C-C bond. The above studies have either focused on enynes or substituted alkenes, no investigation has been conducted on the copper-catalyzed allylation with diene starting materials.



**Figure 3: Overview of relevant previous computational studies on TM-catalyzed allylations by a former member of our group, Gang Lu et. al. (a) and the Houk group (b).**

This project overviews a copper-catalyzed allylation of ketones using readily available 1,3-dienes that demonstrated high levels of enantio- and regioselectivity. The computational end of this project saw a study of the mechanism of this process yielding insight into the complex kinetic basis for enantio- and regioselectivity. Additionally, we proposed a stereochemical model for this allylation process using a non-C<sub>2</sub>-symmetric JOSIPHOS-derived chiral ligand. The experimental end of this project saw application of this allylation protocol on route to a concise synthesis of pharmaceutical agent (R)-procyclidine and key intermediates in the syntheses of (R)-oxyphencyclimine, (R)-oxybutynin, and (R)-oxyphenonium bromide.



**Figure 4: Proposed catalytic cycle for copper-catalyzed ketone allylation.**

The proposed catalytic cycle is depicted in figure 4. We believed the primary alkylcopper intermediate (**III**) would be formed through a hydrocupration of the diene. The alkylcopper intermediate would then undergo stereoselective ketone addition with **IV** to yield the copper alkoxide (**V**).  $\sigma$ -Bond metathesis would rapidly happen with silane (**VI**) to rapidly regenerate the original copper hydride catalyst (**I**) with the simultaneous formation of the silylated homoallylic alcohol (**VII**). The mechanism for this process has been previously presented<sup>50</sup>

## 2.2 Computational Details

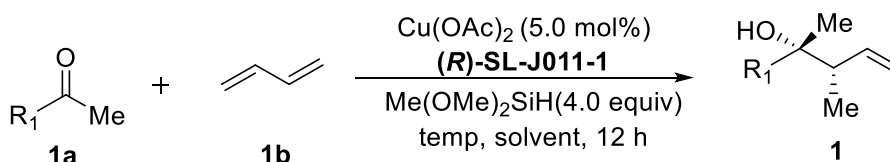
All calculations were performed with the Gaussian 09 software package<sup>60</sup>. Geometry optimizations were performed in the gas phase using the B3LYP functional<sup>5</sup> and a mixed basis set of SDD to evaluate Cu and Fe atoms and 6-31G(d) for all other atoms. Single point calculations were performed using the M06 functional<sup>9</sup> with a mixed basis set of SDD to evaluate Cu and Fe atoms and 6-311+G(d,p) for all other atoms. The implicit SMD solvation model<sup>10</sup> was used to correct the energies for the effects of the toluene solvent.

This methodology was built from previous study on copper catalyzed reductive coupling of ketones and enynes done by Lu et. al. in 2016<sup>50</sup>. The study tested several different functionals and basis sets and found that the above computational methodology demonstrated accurate correlation with experimentally determined enantio- and diastereoselectivities.

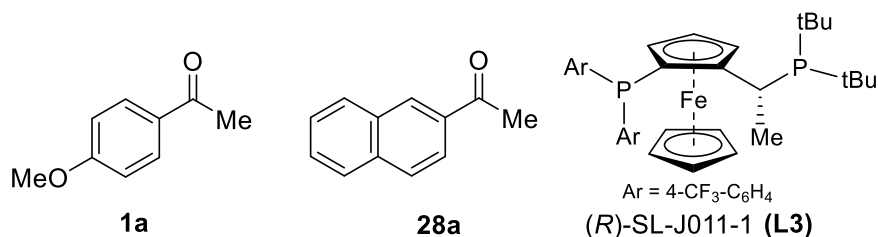
## 2.3 Results and Discussion

### 2.3.1 Key Experimental Results

The experimental study began with the reaction of 4-methoxyacetophenone (**1a**) with 1,3-butadiene (**1b**) under previously reported reaction conditions for copper-catalyzed reductive coupling reactions<sup>49–51,53</sup>. The optimized experimental conditions were performed with SL-J011-1 and toluene as the solvent at 0 °C provided compound **1** in 94% yield with excellent diastereoselectivity (4:1). The major and minor diastereomers were both afforded with high enantiomeric ratios.



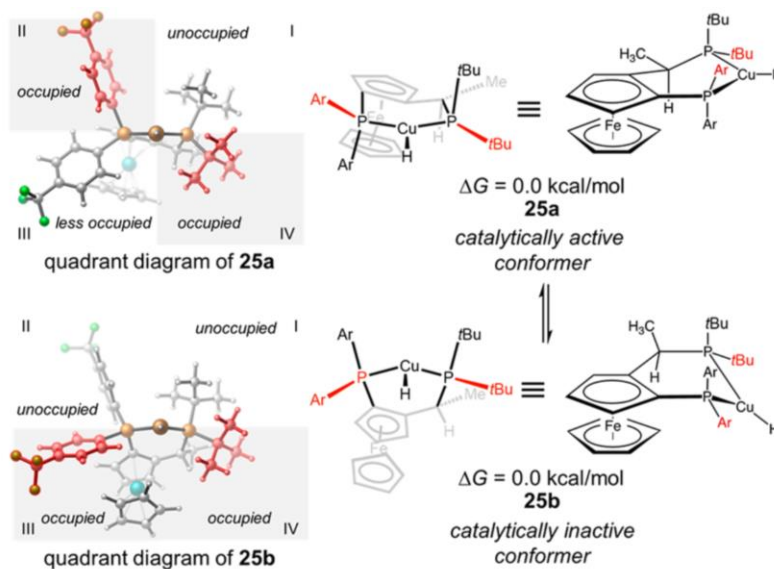
| Ketone     | Solvent | Temp<br>(°C) | Yield <sup>b</sup><br>1 (%) | dr    | er <sup>c</sup><br>major<br>(minor) |
|------------|---------|--------------|-----------------------------|-------|-------------------------------------|
| <b>1a</b>  | PhMe    | 0            | 94                          | 4:1   | 98:2<br>(97:3)                      |
| <b>28a</b> | PhMe    | 0            | 95                          | 2.5:1 | 93.7<br>(90.5:9.5)                  |



**Figure 5: Optimized reaction conditions for the CuH-catalyzed allylation of 4-methoxyacetophenone performed by Chenxi Li and Richard Liu at MIT.**

The next step was further expanding the substrate scope to include cyclic and noncyclic dienes. Excellent selectivity along with high functional group tolerances were demonstrated in this portion of the study. We selected the reaction 2-acetonaphthone and 1,3-butadiene with SL-J011-1 under the standard reaction conditions as our model system for the computational investigation. Experimentally it was determined that this pair of substrates reacts to give a 95% yield, 2.5:1 dr, and 93:7 er for the major diastereomer (the minor diastereomer had a 90.5:9.5 er).

### 2.3.2 SL-J011-1 Ligand Catalytically Active Conformation Search



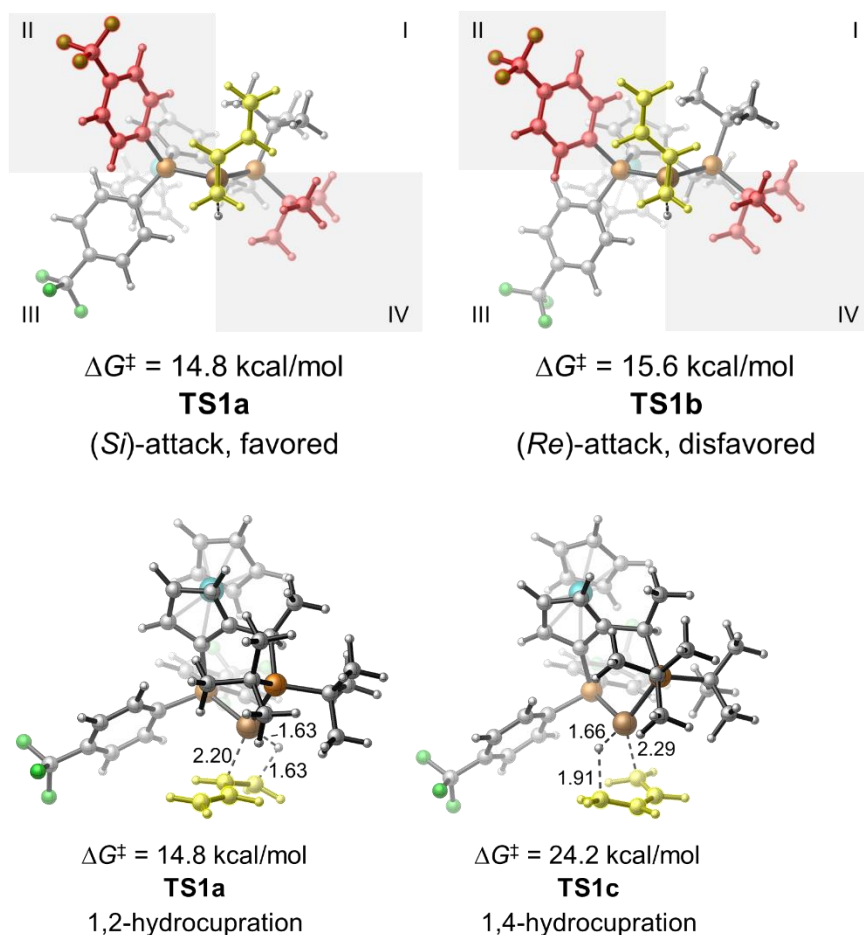
**Figure 6: The conformations of the SL-J011-1 ligand supported Cu-H catalyst.**

The first step of the mechanistic investigation began with determining the catalytically active conformer of the Cu-H catalyst. The flexibility of the six-membered ring formed with the copper led to us considering four possible conformers, two of which were located, **25a** and **25b** (Figure 6). The other two conformers were presumably higher in energy as geometry optimization led to convergence to either **25a** or **25b**. Conformers **25a** and **25b** differ in their orientations of the aforementioned six-membered ring. **25a** sees the chiral carbon in the ligand puckered out of the plane leaving the two phosphorus atoms and the copper in the plane with the Cp ring on the ferrocene. Structure **25b** has the copper atom puckered out of the plane and the two phosphorus atoms and the chiral carbon are co-planar with the Cp ring.

The conformational differences in the six-membered ring of the two structures leads to unique steric environments created by the arms of the ligand. Structure **25a** adopts a C<sub>2</sub>-symmetric type conformation placing one aryl group and one t-Bu in equatorial positions pointing out towards the copper center. The other two groups are axial and point away from the copper center. Quadrants II and IV are sterically occupied and quadrants I and III are relatively sterically unencumbered (Figure 6, top). In contrast, structure **25b**'s ring structure leads to the aryl group in quadrant III and the t-Bu group in quadrant IV oriented towards the copper. This leaves quadrants I and II unoccupied (Figure 6, bottom).

Both **25a** and **25b** were considered when investigating the transition states in the proposed mechanistic pathway. It was found the pseudo-C<sub>2</sub> symmetric structure of **25a** was energetically preferable in the case of hydrocupration, 1-3 migration, ketone addition transition states (see Figure 6). This was consistent with previous successful Cu-H catalysts promoting similar chemical transformations that employed C<sub>2</sub>-symmetric ligands such as Ph-BPE.

### 2.3.3 Selectivity in the Hydrocupration Step



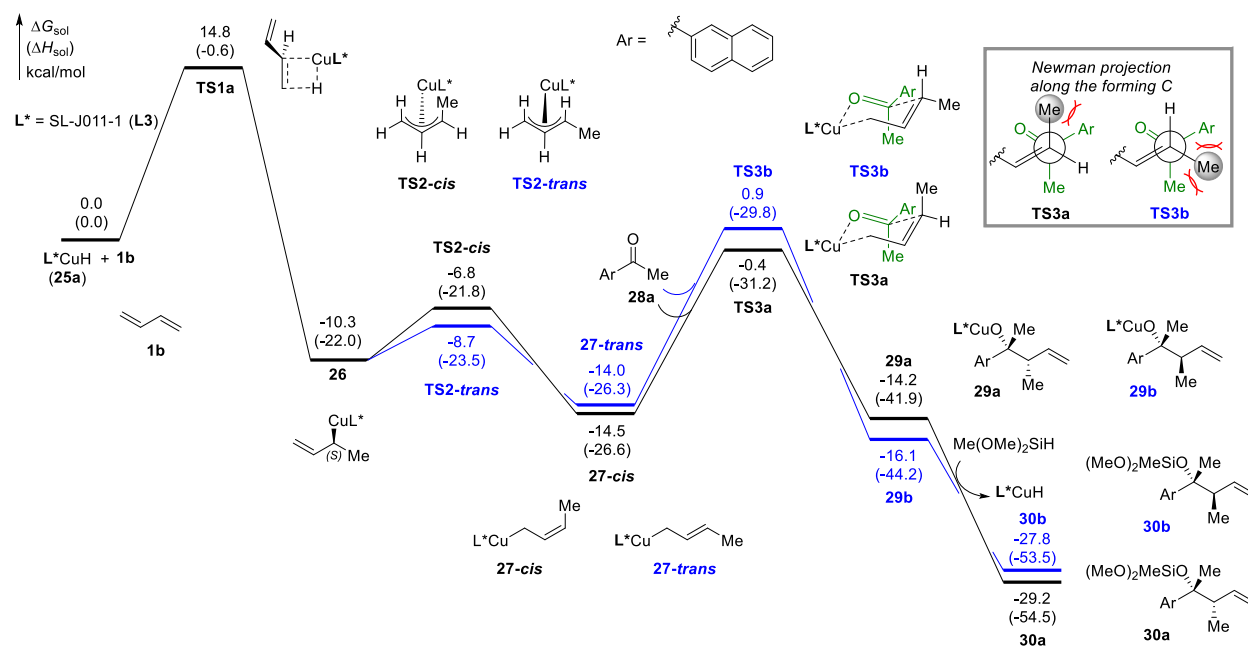
**Figure 7: The lowest energy transition state geometries for hydrocupration step.**

We hypothesized that the hydrocupration step with 1,3-butadiene can proceed through a direct 1,4-hydrocupration or via a 1,2-hydrocupration followed by a 1,3-migration to yield a primary alkylcopper species. It was found through calculation that there was a strong preference to proceed through the 1,2-hydrocupration pathway (**TS1a**). The 1,4-hydrocupration pathway (**TS1c**) requires 9.6 kcal/mol more energy than the 1,2-pathway (Figure 7, bottom). Additionally, **TS1a** shows modest  $\pi$ -facial selectivity (0.8 kcal/mol relative to **TS1b**) for forming the (*S*)-alkylcopper intermediate. This selectivity originates from **TS1a** placing the alkyl chain of the 1,3-



butadiene in the unoccupied first quadrant in comparison to **TS1b**, which places the chain in the occupied second quadrant. Transition state isomers occupying quadrant III and IV were found to both be higher in energy.

### 2.3.4 Mechanistic Consequences of 1,3-Migration

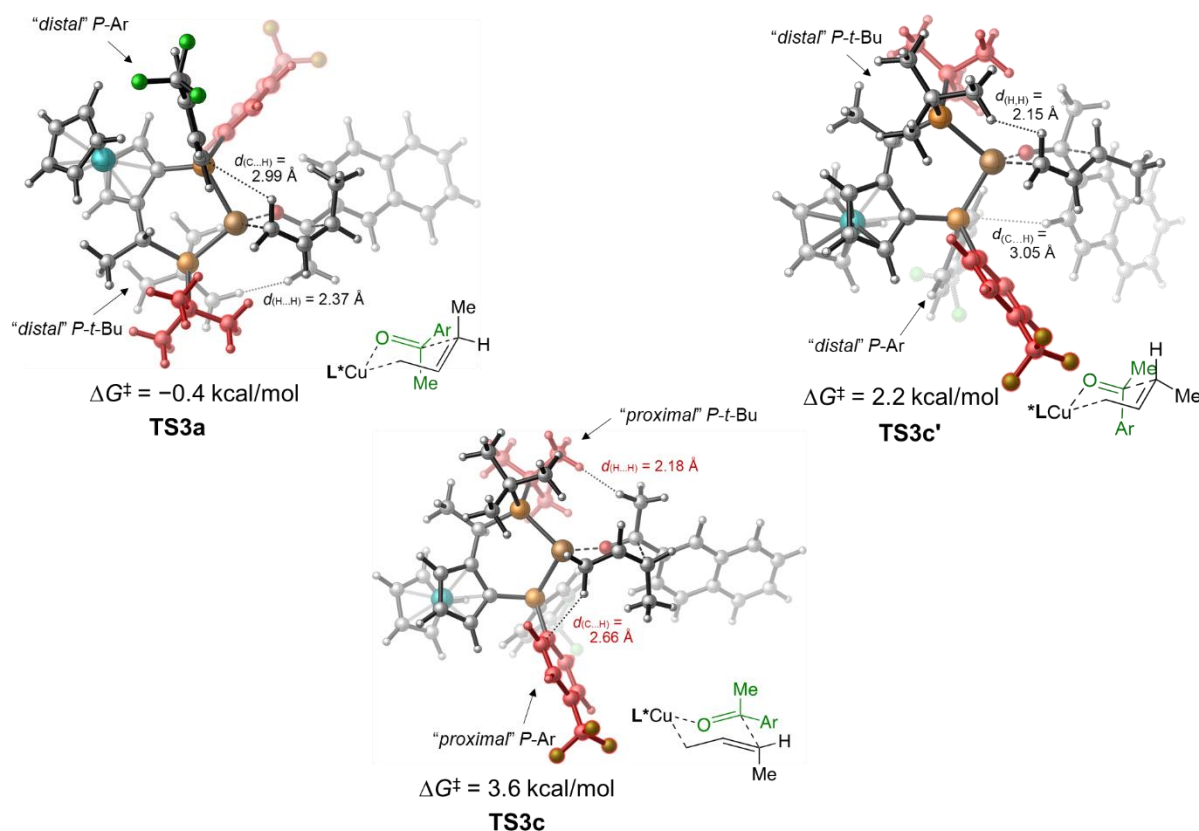


**Figure 8: Computed free energy profile of diene-ketone coupling with SL-J011-1 ligand.**

The (S)-alkylcopper species formed from TS1a rapidly ablates to give the primary alkylcopper intermediate **27-cis** or **27-trans**. The 1,3-migration transition states (**TS2-cis** and **TS2-trans**) both have low barriers from **26**. Additionally, **27-cis** and **27-trans** are slightly lower in energy but not to the point where 1,3-migration process is irreversible. As a result, prior to the ketone addition step, there is a mixture of cis/trans primary alkylcopper species and the other branched isomers.

### 2.3.5 Origin of Enantio- and Diastereoselectivity in Ketone Addition Step

Due to the equilibrium mixture of *cis*, *trans*, and branched isomers, the enantio- and diastereoselectivity are both determined in the step involving the addition of the organocopper species to the ketone (**28a**) which occurs through a six membered Zimmerman-Traxler type transition state<sup>58,59,61</sup>. Sixteen different transition state isomers were considered and the lowest energy transition state structures are depicted in Figure 5. Additional higher energy transition state structures are included in Figure 7. The lowest energy isomer was found to be **TS3a** which proceeds from the **27-cis isomer**. **TS3a** places the terminal methyl group of the 1,3-butadiene substrate in the pseudo-axial position in contrast with **TS3b** which places the same group in the pseudo-equatorial position leading to more *gauche*-type interaction during the C-C bond forming process. As a result, **TS3b** is destabilized by 1.3 kcal/mol relative to **TS3a**. (Figure 8, Box). Furthermore, placing the Ar group at the axial position (**TS3a-2** and **TS3b-2**) (Figure 11) leads to much higher transition state energies. In addition, the di-*tert*-butyl substituted phosphorus atom on the ligand prefers to be *syn* to the methyl on the ketone (see **TS3a** and **TS3b**). Consequently, placing the di-aryl substituted phosphorus atom *syn* to the methyl on the ketone (**TS3a-1** and **TS3b-1**) is slightly less favorable. Additionally, the 1,3-diaxial interaction with the terminal methyl group in **TS3a** are going to be relatively weak due to only H-Me interactions contributing. **TS3b** is disfavored because experiences much stronger 1,3-diaxial interactions (Figure 8, box). **TS3a** gives way to form **29a**, which rapidly undergoes sigma-bond metathesis to yield **30a**. This is consistent with previous work in which sigma-bond metathesis with copper alkoxides was found to be very fast, rendering the ketone addition step irreversible<sup>50</sup>.

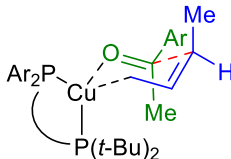
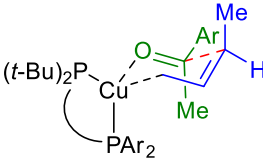
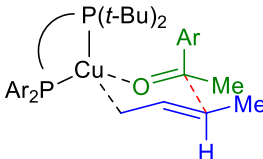


**Figure 9: Lowest energy Zimmerman-Traxler type transition state structures.**

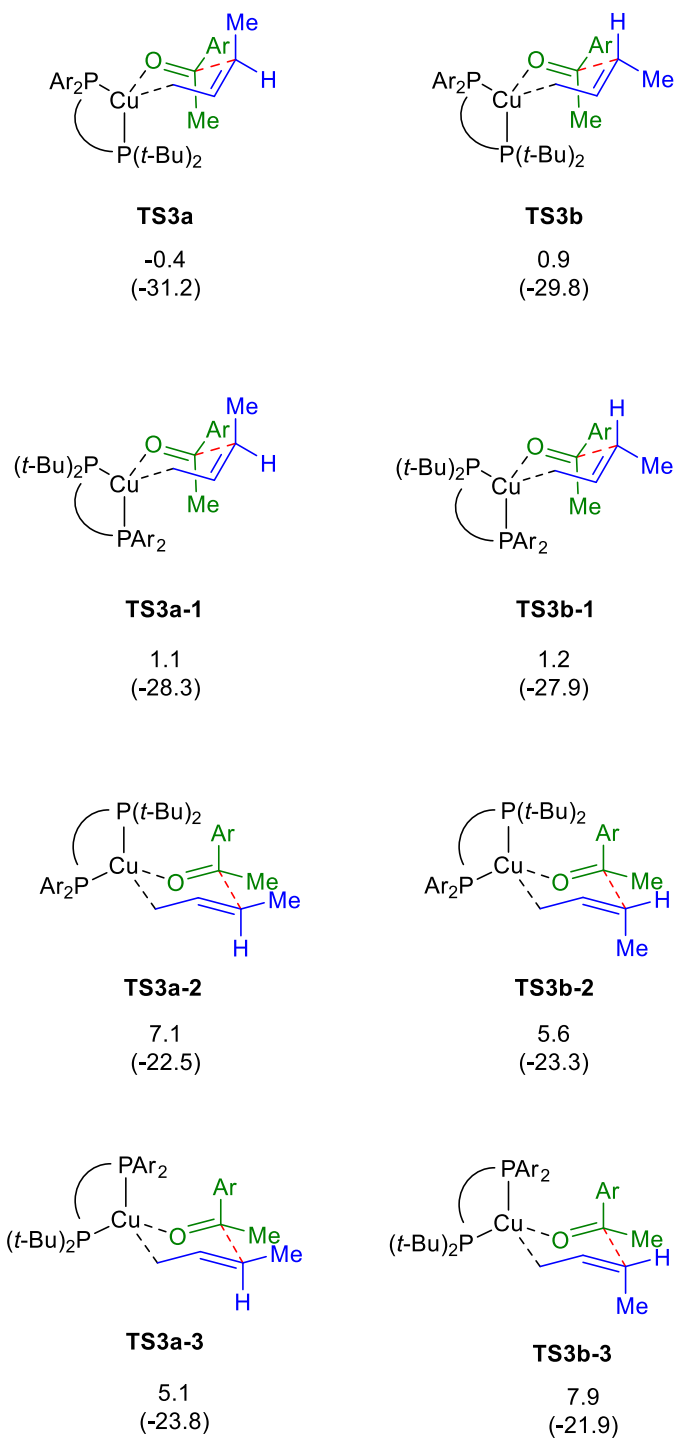
The enantioselectivity of the process was found to be a result of pi-facial selectivity as influenced by the ligand. Disfavored transition state structures **TS3c** and **TS3c'**, involve addition to the opposite face of the ketone relative to the favored **TS3a**. **TS3c** has the pseudo-axial methyl group and the  $\alpha$ -methylene group placed in quadrants that contain the "proximal" p-aryl and P-tBu groups (Figure 9). This interaction results in steric repulsion which destabilizes **TS3c** relative to **TS3a**. **TS3a** alleviates these unfavorable interactions by placing the pseudo-axial methyl group and the  $\alpha$ -methylene group in the unoccupied "distal" quadrants in which the P-aryl and P-tBu are angled further away from the substrate and Cu center. **TS3c'** also alleviates some steric strain by placing the bulky substituents of the substrate in unoccupied quadrants. However, this transition state is destabilized relative to **TS3a** due to greater 1,3-diaxial interactions making it 2.6 kcal/mol less stable. This combined with the energy difference of 4.0 kcal/mol between **TS3c** and **TS3a**,

shows agreement with the experimentally observed high levels of enantioselectivity for this process.

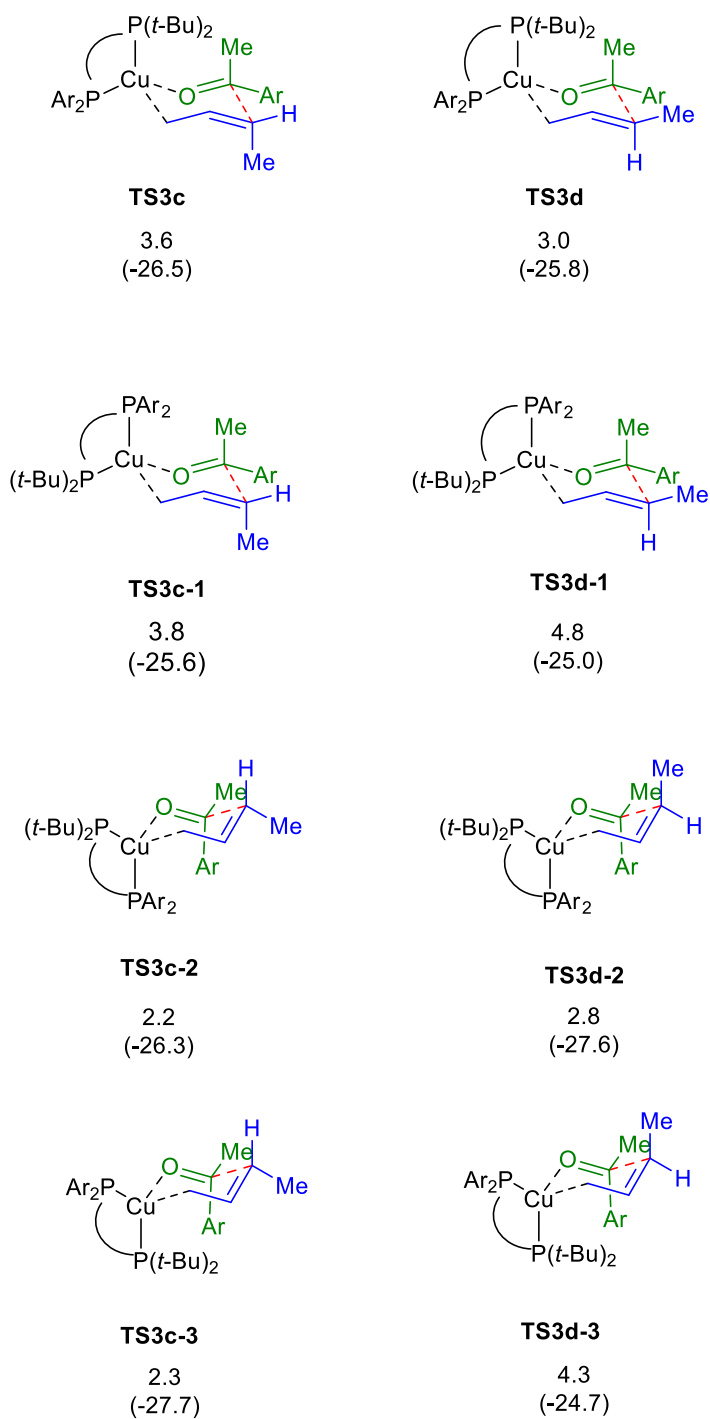
In addition, we evaluated ketone addition transition states with the two different ligand conformations as in **25a** and **25b**. In **25a**, the chiral carbon center is puckered out-of-plane, while the two phosphorus atoms and the Cu are nearly co-planar with one of the Cp rings of the ferrocene. In contrast, in **25b**, the Cu is puckered out-of-plane, while the two phosphorus atoms and the chiral carbon are nearly co-planar with the ferrocene Cp ring. We considered both ligand conformations in the ketone addition transition state isomers that lead to the experimentally observed diastereomeric product (Figure 10). It was observed that the ligand conformation as in **25a** is more favored in the ketone addition transition state.

|                                                                                   | ligand conformation <b>a</b><br>(as in <b>25a</b> ) | ligand conformation <b>b</b><br>(as in <b>25b</b> ) |
|-----------------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|
|  | <b>TS3a</b><br>-0.4<br>(-31.2)                      | <b>TS3a-3</b><br>7.6<br>(-23.0)                     |
|  | <b>TS3a-1</b><br>1.1<br>(-28.3)                     | <b>TS3a-4</b><br>9.1<br>(-19.8)                     |
|  | <b>TS3a-2</b><br>7.1<br>(-22.5)                     | <b>TS3a-5</b><br>7.3<br>(-21.5)                     |

**Figure 10: Effects of ligand conformation on the stability of the ketone addition transition state. Gibbs free energies and enthalpies (in parenthesis) are in kcal/mol with respect to the separated reactants (1b and 28a) and the CuH catalyst (25a).**



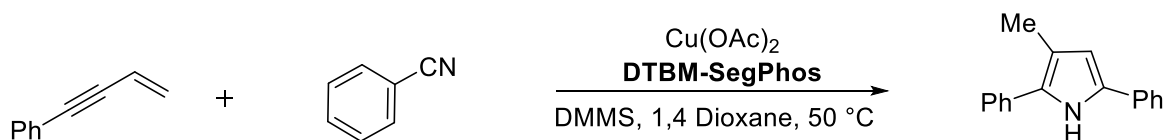
**Figure 11: Additional isomers of the ketone addition transition states that involve addition to the (*Re*)-face of the ketone. Gibbs free energies and enthalpies (in parenthesis) are in kcal/mol with respect to the separated reactants (1b and 28a) and the CuH catalyst (25a).**



**Figure 12: Additional isomers of the ketone addition transition states that involve addition to the (Si)-face of the ketone. Gibbs free energies and enthalpies (in parenthesis) are in kcal/mol with respect to the separated reactants (1b and 28a) and the CuH catalyst (25a).**

## 2.4 Synthesis of Pyrroles from Cu-H Catalyzed Coupling of 1,3-Enynes and Nitriles

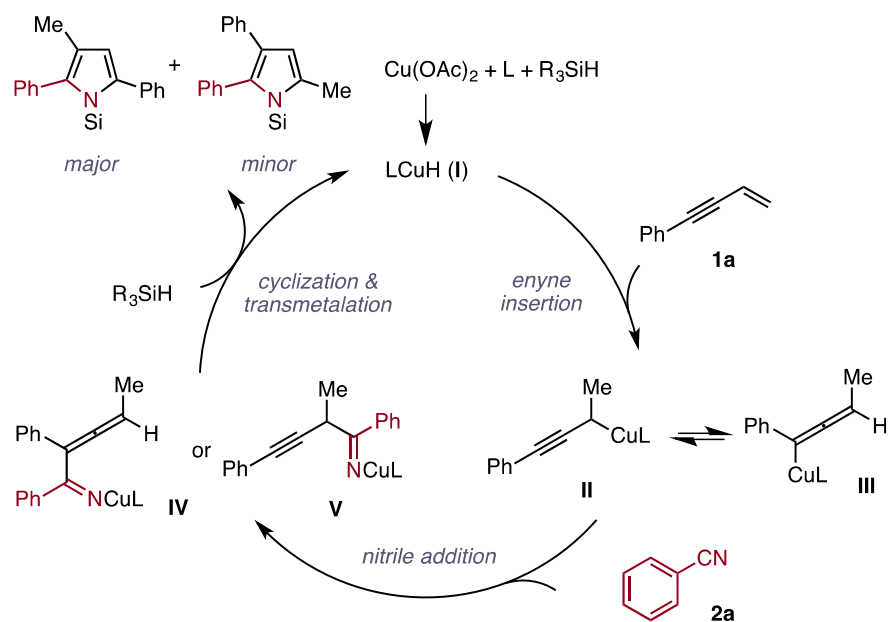
Section adapted from the publication: Zhou, Y.; Zhou, L.; Jesikiewicz, L.T.; Liu, P.; and Buchwald, S.L. *J. Am. Chem. Soc.* **2020** 142 (22), 9908-9914



**Figure 13: Enyne nitrile coupling reaction conditions performed by Yujing Zhou at MIT.**

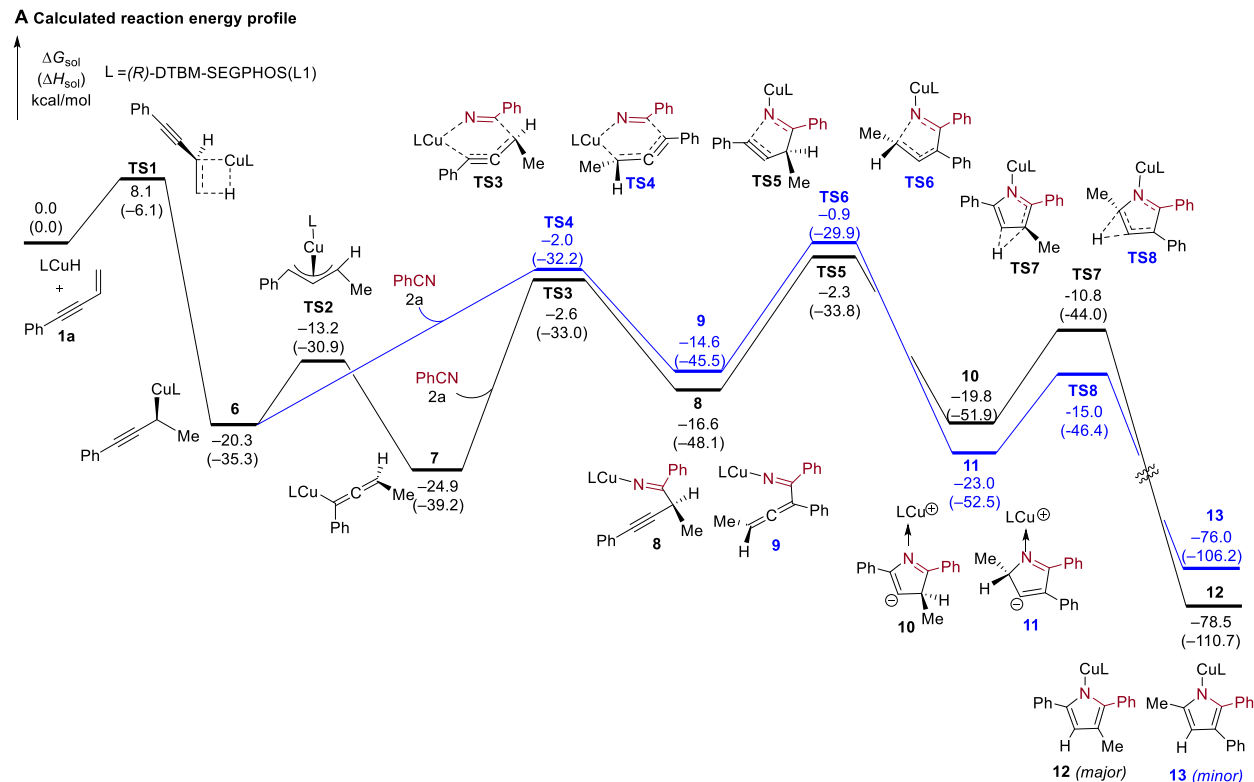
The most recent collaboration between the Buchwald and ourselves has seen adaption of the reaction protocol used in the ketone coupling reactions described earlier in this document for nitriles yielding pyrroles (Figure 12). Pyrroles are a highly sought-after synthetic target due to their prevalence as a motif in important natural products<sup>62,63</sup>. The proposed catalytic cycle for this process is similar to that of the ketone coupling, with a few key differences later in the pathway. The hydrocupration, 1,3-migration steps will likely proceed in an identical fashion to the ketone case. We suspect that the nitrile addition step will be the area where the regioselectivity is determined as this was the case with the ketone. The ligand effects on the transition states in this portion of the pathway are a key area of interest. Additionally, the mechanism for the subsequent cyclization step is unknown. We propose a closed shell, stepwise cyclization from complex IV and V to yield the major and minor products.





**Figure 14: Proposed catalytic for copper-hydride catalyzed coupling of enynes and nitriles.**

The primary goals the computational investigation will be understand the mechanism of regioselectivity in this reaction by examining the nitrile addition and cyclization steps with DFT calculation and qualitative tools in order to gain chemical understanding. This understanding will then be passed on to our collaborators as they continue to optimize the reaction conditions. The DFT methods used were identical to the previous study with the exception that Gaussian 16<sup>64</sup> was used instead of Gaussian 09.



**Figure 15: Potential energy surface of Cu-H catalyzed enyne-nitrile coupling.**

We performed density functional theory (DFT) calculations to validate the proposed mechanism (Figure 14). Consistent with previous DFT studies<sup>50,65,66</sup>, the hydrocupration of enyne (**TS1**) and the subsequent 1,3-Cu shift (**TS2**) are both exothermic and have relatively low barriers. The addition of the allenyl- and propargylcopper intermediates to the nitrile occur via six-membered cyclic transition states (**TS3** and **TS4**, respectively). The resulting Cu-imine species (**8** and **9**) undergo facile cyclization via **TS5** and **TS6** to form 3H-pyrrol-4-yl and 2H-pyrrol-3-yl anions (**10** and **11**), respectively, which upon 1,5-H shift yield the more stable 1-pyrrolylcopper species **12** and **13**. It is conceivable that a small amount of Lewis acidic copper species could be formed under the experimental conditions<sup>67</sup>, which will further accelerate this nucleophilic

cyclization process via coordination with the alkyne or allene to enhance the electrophilicity of the  $\pi$  bond<sup>68–71</sup>.

## 2.5 Conclusion

Computationally, we provided a rationale explaining the factors controlling observed enantio- and diastereoselectivity of a copper-catalyzed allylation of ketones with conjugated dienes. From a rapidly equilibrating mixture of alkylcopper intermediates, all of similar energy, a selective addition to the cis-allyl complex generated the experimentally observed diastereomer. We also proposed a model for the enantioselectivity for the addition of allyl-copper intermediates to ketones in the case of reactions utilizing the non-C2-symmetric JOSIPHOS type ligand. Experimentally, our collaborators succeeded in expanding the substrate scope to include a variety of functional groups, cyclic, and non-cyclic dienes. Using an optimized method, they were able to concisely and efficiently synthesize (R)-procyclidine and a key intermediate for anticholinergic drugs (R)-oxyphencyclimine, (R)-oxybutynin, and (R)-oxyphenonium bromide. Presently, a joint computational and experimental study into the mechanism of Cu-catalyzed nitrile coupling with 1,6-enynes. Initial calculations into the nitrile addition step of the pathway have identified a steric interaction between the incoming nitrile and the enyne substrate as influencing the preferential formation of the experimentally observed major regioisomer. Concerted [3+2] cycloaddition/1,2-Cu migration has been ruled out due to its high energetic barrier. Further investigations into the nature of the cyclization step are the next step computationally with the goal being to confirm that the regioselectivity is determined in the nitrile addition step.

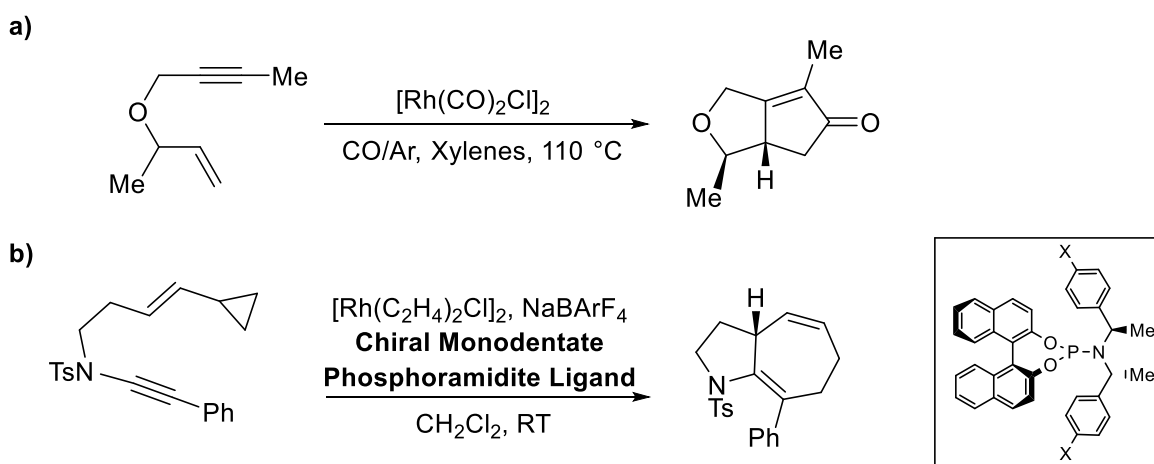
### 3.0 Mechanism and Origins of Enantioselectivity in the Rh(I)-catalyzed Pauson–Khand Reaction: Comparison of Bidentate and Monodentate Chiral Ligands

#### 3.1 Introduction

The Pauson-Khand (PKR) remains among the most popular methods to synthesize cyclopentanones<sup>72-76</sup>. The PKR methodology has been further utilized to achieve highly diastereoselective bond formation<sup>77-82</sup>. Chiral ligand bound Rh(I)-complexes have emerged as the most effective tools for accomplishing enantioselective intramolecular PKR<sup>83</sup>. The highest enantioselectivities for these reactions has been achieved using sterically bulky BINAP-type ligands with aryl-substituted phosphine groups<sup>84,85</sup>. These ligands afford 99% ee's on unsubstituted alkene substrates, but the steric demands of the ligand limit the expansion of the scope to larger substrates. There has been little expansion of the substrate scope beyond 1,6-enynes with –O–, –NTs, or –C(CO<sub>2</sub>R)<sub>2</sub> tethers, and monosubstituted alkenes.

We recently demonstrated that enantioselective PKR with allenes can be achieved using a cationic Rh(I)-catalyst and a chiral monodentate phosphoramidite ligand<sup>6</sup>. This ligand class has a large number of benefits from a synthetic perspective. First, the synthesis of the ligand itself can be completed in 1-2 steps where bidentate phosphine ligands like (*R*)- or (*S*)-BINAP require multiple steps. Monodentate ligands have been often overlooked in catalysis due to the perception that by allowing more conformational freedom they would be less effective for enantioselective catalysis. As of late, the phosphoramidite ligand class has been battling back that assumption<sup>86-89</sup>. A vast majority of these reactions employ a ligand-to-metal of 2:1<sup>86,90-95</sup>, but whether one or two monodentate ligands are bound to the metal center during the reaction is still unclear. Despite

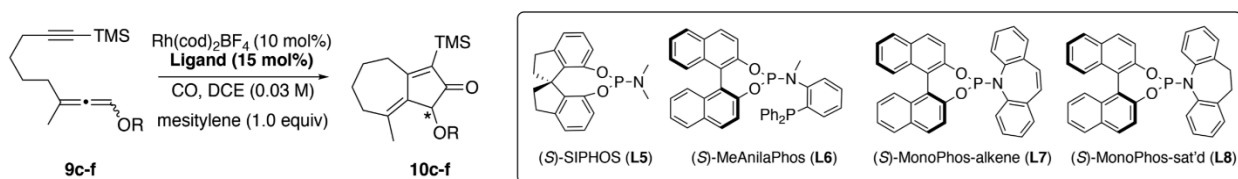
bidentate and monodentate P-containing ligands often being used interchangeably in catalysis, the impact of ligand denticity on the mechanism of chiral induction is rarely studied<sup>93,96</sup>. In particular, it is not clear whether monodentate C1-symmetric ligands operate via a bis-ligated process to mimic the steric environments of bidentate C2-symmetric ligands or manifest the chiral induction via a unique mono-ligated mechanism. Clarification of this will provide useful insight for the rational design of future catalysts.



**Figure 16: Overview of previous relevant computational studies on Pauson-Khand and Rh-catalyzed cyclization reactions by the Baik group (a) and the Patton group (b).**

Previous computational studies have been conducted in order to further clarify the underlying mechanism of the Pauson-Khand reaction. Mu-Hyun Baik's group conducted computational investigations on the reaction with a neutral rhodium catalyst in absence of a chiral ligand (Figure 16, a). They found that the diastereoselectivity of this reaction is highly dependent on the concentration of CO. Lower CO concentration leads to the predominance of a 4-coordinate pathway where there is a smaller energy difference between the transition states leading to the major and minor diastereomer relative to the 5-coordinate pathway<sup>97</sup>. Additionally, they report the origin of diastereoselectivity is an additional stabilization of the developing positive charge on alkyne carbon in the oxidative cyclization transition state of the major diastereomer<sup>98</sup>.

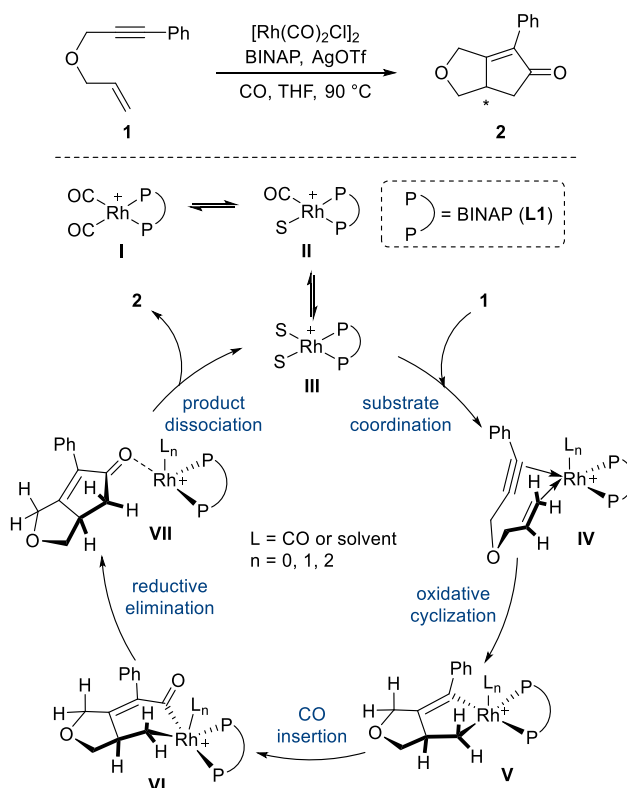
However, no computational study of the Pauson-Khand reaction with 1,6-enynes has been conducted with a chiral ligand. The ligand's role in the reactivity and selectivity of this reaction is still relatively unclear. Patton et. al. studied the ligand effects of a similar phosphoramidite ligand on an enantioselective [5+2] Rh-catalyzed cycloaddition of ynamides (Figure 16, b)<sup>96</sup>. The lowest energy isomer of the rate-limiting, oxidative cyclization transition state is stabilized by a dispersive ( $\pi$ - $\pi$ ) interaction between the naphthyl portion of the backbone of the ligand and the phenyl group of ynamide. The study does not address the possibility of the reaction proceeding with two monodentate ligands coordinated to the rhodium instead of one.



**Figure 17: Allenic Pauson-Khand reaction conditions and ligand scope.**

In 2017, we published a joint experimental and computational study of the Rh-catalyzed asymmetric Pauson-Khand reaction of allenyl carboxy groups (Figure 17)<sup>6</sup>. In this study, we deployed an iterative synergistic methodology for rational catalyst design which allowed for rapid development of a reactive and enantioselective catalyst. The computational study addressed a series of mechanistic questions that are critical for the proper prediction of ligand effects on reactivity and enantioselectivity of APKR, including facile catalyst rearrangement, the number of CO ligands bound to the Rh center, and the binding mode of a hemilabile phosphoramidite ligand. It was found that oxidative cyclization proceeds preferentially with a five-coordinated rhodium and the enantioselectivity is controlled through steric interactions with the TMS group of the alkyne and the naphthalene backbone of the (S)-MonoPhos-alkene ligand. After obtaining these mechanistic insights, the calculated reactivity and selectivity ( $\Delta G^\ddagger$  and  $\Delta\Delta G^\ddagger$ ) were used as a guide to understand the experimental yield and er and to make rational prediction of a more selective

and reactive (S)-MonoPhos-alkene ligand. The enantioselectivity of hemilabile (S)-MonoPhos-alkene was accurately predicted by computation and the absolute configuration of the major enantiomer was confirmed by X-ray crystallography.



**Figure 18: Proposed catalytic cycle for PKR with 1,6 Enynes.**

The proposed catalytic cycle for the (R)-BINAP rhodium-catalyzed PKR is shown in Figure 18<sup>99,100</sup>. There exists an equilibrium between CO and solvent-coordinated Rh-BINAP complexes (**I**, **II**, and **III**). The coordination of enyne substrate **1** proceeds by the displacement of a solvent molecule from active catalyst **III** to yield  $\pi$ -coordinated complex **IV**. The five-coordinated complex **IV** will undergo oxidative cyclization to afford Rh-metallacycle **V**. The Rh-metallacycle then undergoes CO insertion to yield a Rh(III) acyl complex **VI**, followed by reductive elimination to yield Rh(III) complex **VII**. Lastly, the product dissociates to yield cyclopentanone product **2** and return the active catalyst.

Despite the above catalytic cycle being widely accepted, there are still persistent mechanistic questions. The rate and enantioselectivity determining step of the catalytic cycle are still unknown. In addition, the active form of the catalyst from the equilibrium mixture at the beginning of the cycle has not yet been determined. The Rh-catalyst can be four, five, or six coordinated with up to two CO or solvent molecules present. Lastly, the role of the ligand in the enantioselectivity of this process is at this point unclear. We undertook a computational study of the mechanism and key steps in order to clarify these questions.

### 3.2 Computational Details

All calculations were performed using the Gaussian 09 software package<sup>60</sup>. Molecular geometries were optimized using the B3LYP functional<sup>5</sup> and the 6-31G(d) basis set for all non-metal atoms and LANL2DZ for rhodium in the gas phase. Single point energy calculations were performed using the M06 functional<sup>9</sup> and 6-311+G(d,p) for all non-metal atoms and SDD for rhodium with the SMD solvation model<sup>10</sup> in dichloroethane (DCE).

The computed Gibbs free energy values for all optimized transition state and intermediate structures were computed at the experimental temperature (353 K unless otherwise noted). Corrections were applied to the computed Gibbs free energy values for all relevant structures using the experimental concentrations of CO and (S)-MonoPhos (see later for details). When considering the substrate binding to replace solvent molecules in the rhodium(solvent) complexes, corrections were applied to the computed Gibbs free energy values using experimental concentrations of COD, THF, or DCE. The methods used to obtain the corrected standard Gibbs free energy values are detailed below.



In addition to the concentration and thermal corrections, a correction to the translational entropy in solution was applied to all structures. The methodology for this was adapted from a series of equations originally developed by Whitesides et. al.<sup>101</sup>. A calculation of the volume using Gaussian09 was run and found to be 100.058 Å<sup>3</sup>/mol for dichloroethane ( $V_{DCE}$ ). This value was then placed into equation S1 along with the molar concentration of solvent ( $[X] = 12.7$  M see eq. S4) and Avogadro's number ( $N_0$ ) to obtain the free volume in solution ( $V_{free}^{DCE}$ ).  $C_{free}$  in equation S1 is equal to 8 due to the system being treated as 3D cubic array.

$$V_{free}^{DCE} = C_{free} \left( \sqrt[3]{\left( \frac{10^{27}}{[X]N_0} \right)} - \sqrt[3]{V_{DCE}} \right)^3 = 0.7877 \text{ Å}^3/\text{mol} \quad (S1)$$

The  $V_{free}$  term is then implemented in equation S2 with the molecular weight of DCE (M) and the reaction temperature to yield the new corrected translational entropy ( $S_{trans}^{new}$ ).

$$\begin{aligned} S_{trans}^{new} &= 11.1 + 12.5 \ln(T) + 12.5 \ln(M) + 8.3 \ln(V_{free}^{DCE}) \\ &= 139.789 \text{ J/mol} * K \end{aligned} \quad (S2)$$

The  $S_{trans}^{new}$  value is used in place of the original translational entropy value at the temperature of 353 K. The new  $\Delta S$  term is used to determine the new adjusted  $\Delta G$  value using the Gibb's free energy equation. This value was found to be -2.352 kcal/mol and was applied to all structures. The correction of the Gibb's free energies for translational entropy primarily become evident in the case where there is a relative change in entropy from what we treated as the zero point in the reaction.

The CO concentration in DCE solution ( $c_{CO}$ ) under the experimental conditions was estimated by using Henry's law:

$$\begin{aligned} c_{CO} &= \frac{P_{CO}}{k} = \frac{10132.5 \text{ Pa}}{16930 \frac{\text{Pa} * \text{m}^3}{\text{mol}}} = 0.5985 \frac{\text{mol}}{\text{m}^3} \\ &= 0.0006 \text{ M CO} \end{aligned} \quad (S3)$$

where  $k$  is Henry's constant for CO in DCE<sup>102</sup> and  $P_{CO}$  is the CO pressure in pascals in experiment (Table 1).

The concentrations of (S)-MonoPhos, cod, THF, and DCE were calculated using the relevant experimental conditions (SI) using the equations shown below. The Gibbs free energies and enthalpy at the experimental temperature (353 K) and concentrations were then calculated using the GoodVibes software package<sup>103</sup>.

The concentration of liquid DCE ( $C_{DCE}$ ) was calculated from

$$C_{DCE} = \frac{\rho_{DCE}}{MW_{DCE}} = \left( \frac{1256 \text{ g/L}}{98.96 \text{ g/mol}} \right) = 12.700 \text{ M DCE} \quad (S4)$$

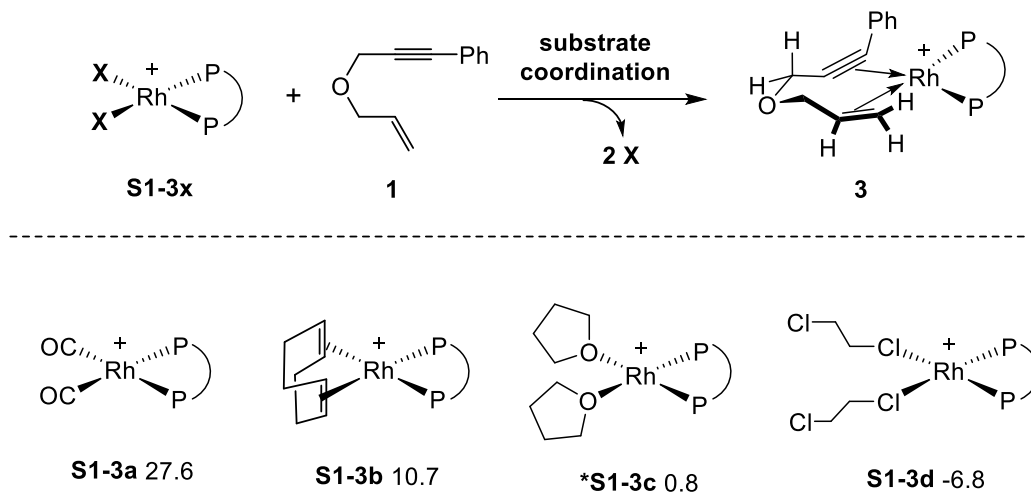
where  $\rho_{DCE}$  and  $MW_{DCE}$  are the density in g/L and molecular weight of DCE, respectively. The same method was used to determine the concentration of liquid THF (12.385 M).

The concentration of total cod and (S)-MonoPhos ligand in solution were determined using the initial amounts of Rh catalyst added to the reaction. The initial loading of the reaction had 0.01 mmol of Rh(cod)<sub>2</sub>SbF<sub>6</sub> pre-catalyst. There should be 0.02 mmol of cod in the vial, dividing this by the reaction volume of 2 mL gives a total concentration of cod of 0.01 M. For (S)-MonoPhos, we assuming the targeted 1.1 L/Rh ratio with 0.01 mmol of Rh would yield 0.011 mmol of (S)-MonoPhos ligand. Dividing this number by the total reaction volume of 2 mL gives us total (S)-MonoPhos concentration (at the 1.1 L/Rh loading) of 0.0055 M.

### 3.3 Results and Discussion

#### 3.3.1 Substrate Binding Energies for Four Different (R)-BINAP-Rh(I) Complexes

We began the computational investigation by attempting to establish the identity of the cationic Rh-complex **3** to which enyne **1** coordinates to form **4**. We proceeded by computing the substrate binding energies using four different Rh-BINAP complexes: X=CO, **3a**; 1,5-cyclooctadiene (cod), **3b**; THF, **3c**; and DCE, **3d** (Figure 19). These complexes were hypothesized to all be present in solution and represented a spectrum of different ligand coordinating abilities. CO was assumed to be the strongest coordinating ligand, DCE the weakest, and cod and THF having moderate coordinating ability towards the Rh(I) center.

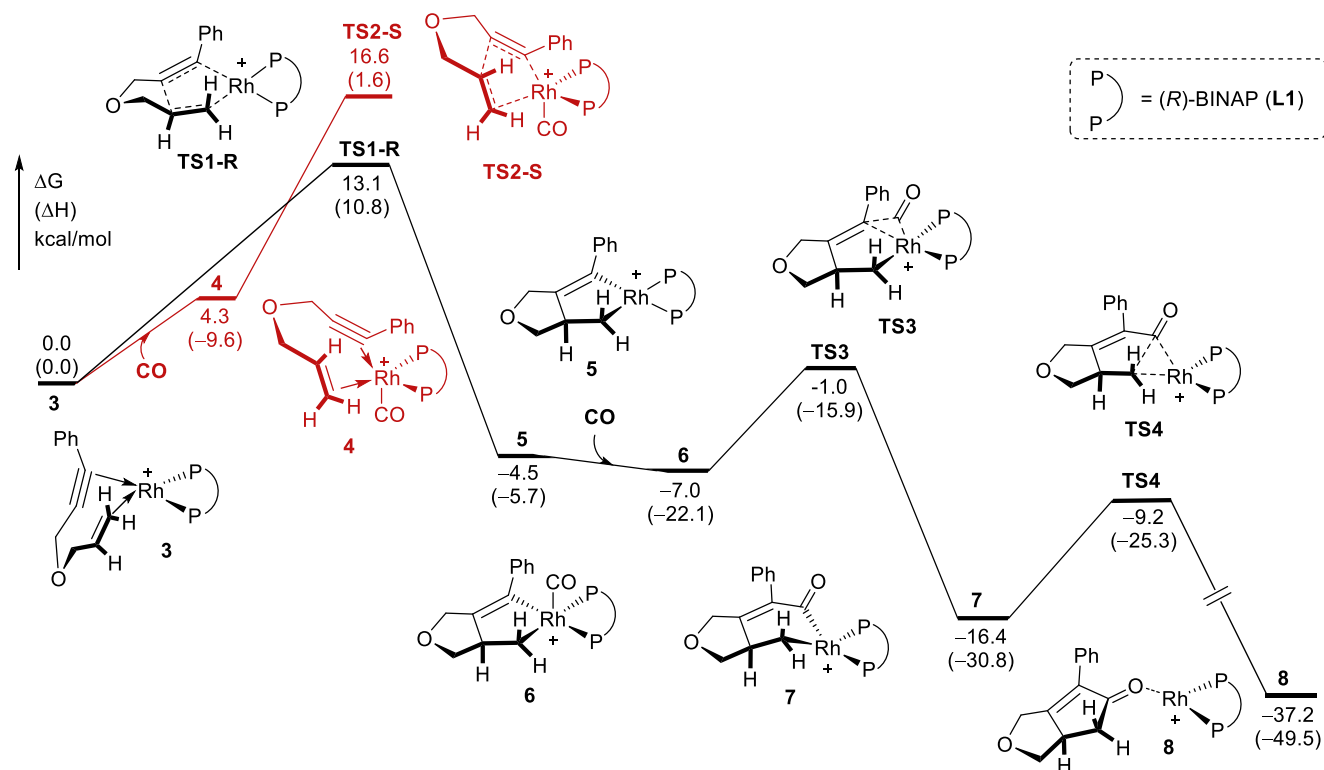


**Figure 19: Enyne binding energies (Delta G Values) for four (R)-BINAP-Rh(I) complexes.**

Substitution of two CO ligands of **S1-3a** with enyne **1** to give complex **3** is endothermic by 27.6 kcal/mol of energy; while substitution of cod ligand complex **S1-3b** to give **3** is endothermic by only 10.7 kcal/mol. Substitution of the THF's of **S1-3c** with **1** is endothermic by

0.8 kcal/mol; while the reaction of **S1-3d** to form **3** is exothermic by 6.8 kcal/mol. These calculated substrate binding energies reflect the relative coordinating ability of these ligands (CO > cod > THF > DCE) and indicate the importance of the starting catalyst identity on the reaction pathway<sup>104</sup>. For example, the solvent coordinated and Rh-cod complexes (**S1-3b**, **S1-3c**, **S1-3d**) are relatively similar in energy relative to **3** and will likely not be in competition with the reaction pathway. However, the thermodynamic stability of the CO-bound catalyst **S1-3a** supports this as an off-cycle energetic sink for the Rh catalyst. The computed endothermicity of the reaction to afford **3** is supported by experiments where lower CO concentration (10% CO, 90% argon) and a coordinating solvent (THF) showed significantly faster reaction rates<sup>84</sup>. This was explained by an equilibrium shift of the CO-bound catalyst to solvent-bound to accounting for the faster reaction rate. This was further validated by an experiment that monitored the catalyst structure by <sup>31</sup>P NMR during a Rh-bisphosphine-catalyzed PKR. There was substantial evidence that the reaction proceeded rapidly from a solvent-bound catalyst<sup>105</sup>.

### 3.3.2 Calculated Mechanism for PKR with (R)-BINAP Ligand

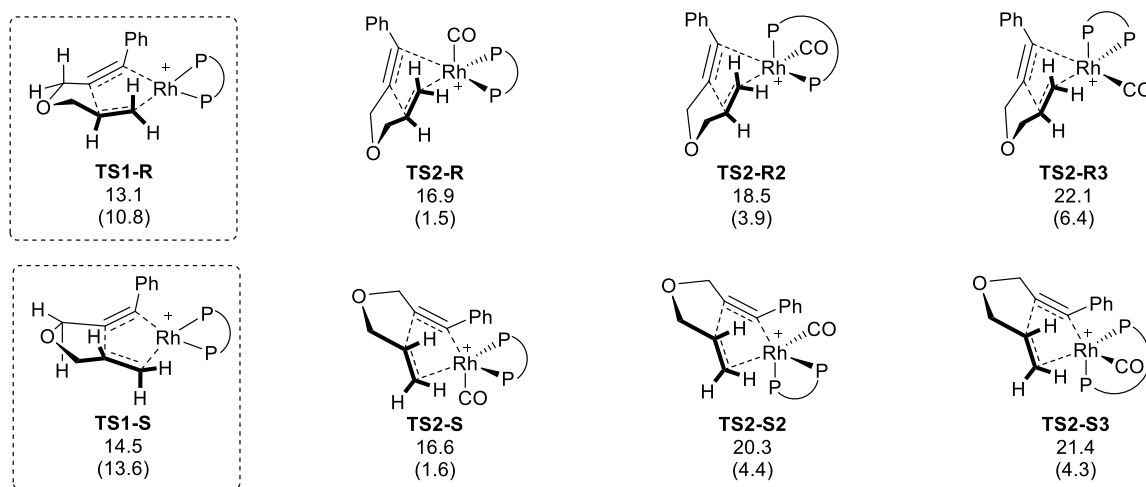


**Figure 20: Calculated free energy profile of PKR with (R)-BINAP (L1).**

The free energy profile is reported relative to the lowest energy substrate coordinated  $\pi$ -complex **3**. Both four-coordinate and five-coordinate oxidative cyclization pathways were calculated. The lowest energy isomer for the four-coordinated pathway was **TS1-R** which yields an (*R*)-stereocenter. The five-coordinate pathway proceeds from **3** by binding an additional CO molecule to form **4** which is 4.3 kcal/mol higher in energy. This complex will then undergo oxidative cyclization through the lowest energy isomer **TS2-S** which will yield the (*S*)-isomer. The calculations show that the four-coordinated oxidative cyclization pathway is favored by 3.5 kcal/mol. This directly contradicted our previous study on the Pauson-Khand reaction of allenyl carboxy substrates, which indicated that the five-coordinate pathway would be strongly preferred (further discussion in section 3.3.5).

Following oxidative cyclization **TS1-R** affords Rh-metallocycle **5**, which is significantly downhill. **5** will then bind an additional molecule of CO to yield **6**, which subsequently undergoes CO insertion via **TS3** affording Rh-acyl metallocycle **7**. Complex **7** then quickly undergoes reductive elimination via **TS4** to give product coordinated complex **8**. Since the subsequent CO insertion and reductive elimination have lower barriers than oxidative cyclization, the oxidative cyclization step is rate-determining. Additionally, the oxidative step is irreversible making it the enantioselectivity determining step. These findings were all consistent with previously reported computational studies on the Pauson-Khand reaction.<sup>6,97-98</sup>

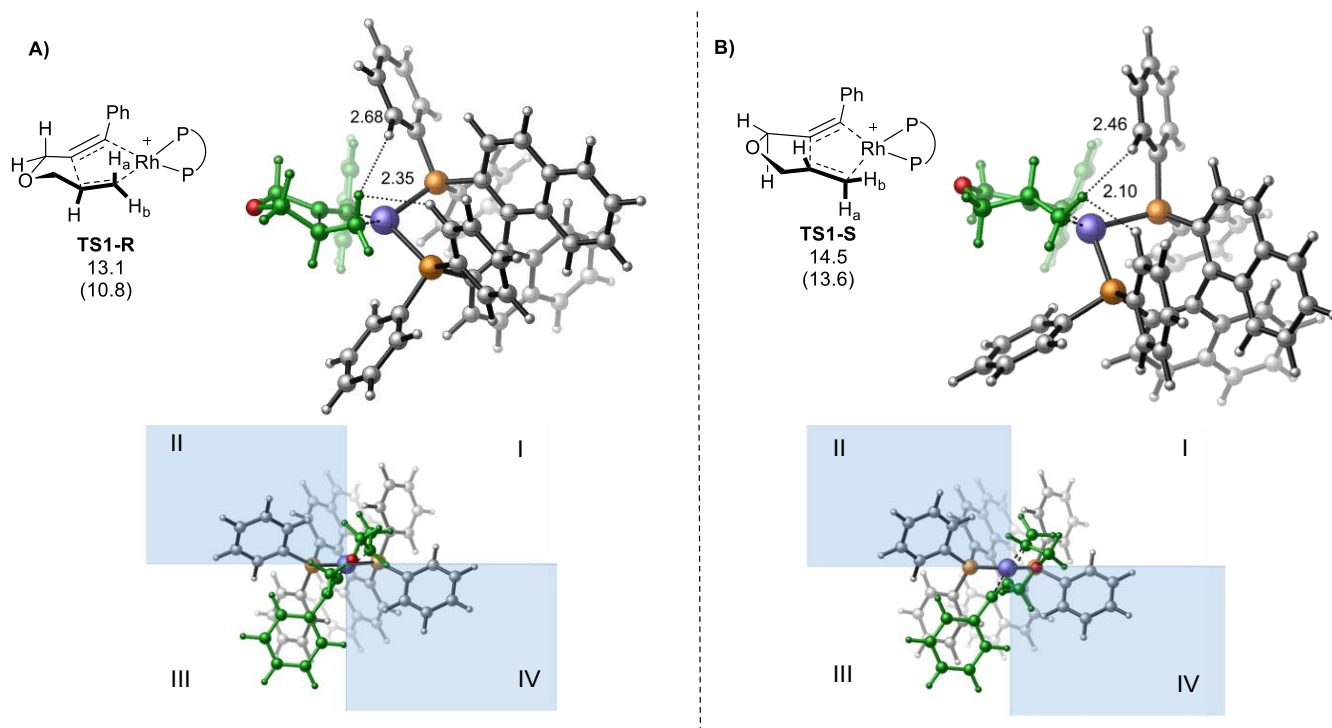
### 3.3.3 Origin of Enantioselectivity with (*R*)-BINAP



**Figure 21: (*R*)-BINAP oxidative cyclization transition state structures.**

We calculated all the possible transition state isomers considering both four-coordinate and five coordinate transition states with (*R*)-BINAP leading to both the (*R*) and (*S*) products (Figure 21). The overall lowest energy transition state isomer is the four-coordinate **TS1-R** with a  $\Delta G^\ddagger$  of 13.1 kcal/mol. The second lowest four-coordinate transition state is **TS1-S** which has a  $\Delta G^\ddagger$  of 14.5 kcal/mol. The formation of the (*R*) isomer is favored by 1.4 kcal/mol over the (*S*) isomer. All

of the possible five-coordinate transition state isomers (**TS2-R**, **TS2-R2**, **TS2-R3**, **TS2-S**, **TS2-S2**, **TS2-S3**) were all found to be substantially higher in energy than the four-coordinate transition states. The lowest energy five-coordinate transition state (**TS2-S**  $\Delta G^\ddagger = 16.6$  kcal/mol) yielded the (*S*)-product and was 0.3 kcal/mol lower in energy than the lowest energy five-coordinate transition state yielding the (*R*)-product (**TS2-R**  $\Delta G^\ddagger = 16.9$  kcal/mol).



**Figure 22: 3D view of lowest energy oxidative cyclization transition states.**

The steric environment can be visualized by using the quadrant diagrams (Figure 22, bottom). The substrate is highlighted in green, the rhodium center is blue, and the phosphorus atoms are yellow. In the case of **TS1-S** and **TS1-R**, the equatorial phenyl groups block quadrants II and IV leaving quadrants I and III unoccupied and where the substrate is aligned. The steric environment created by the (*R*)-BINAP ligand is very similar and the alkene facial selectivity is the only significant difference between these transition states leading to stereo-induction. The  $\pi$ -

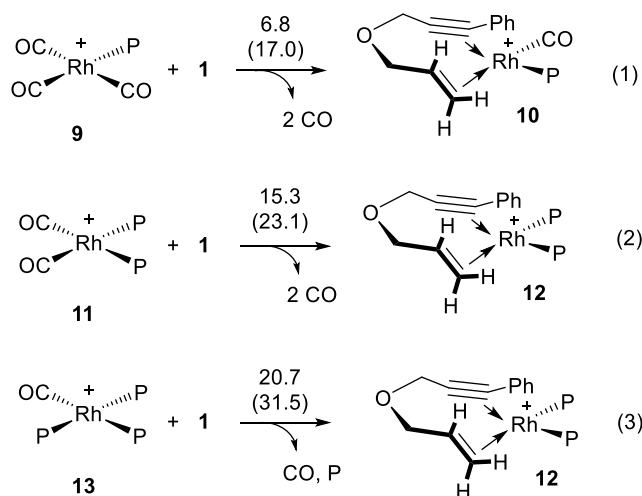
facial selectivity of the alkene determines how the terminal CH<sub>2</sub> group (H<sub>a</sub> and H<sub>b</sub>) is oriented in the puckered five-membered cycle, and thus affects the steric repulsions with the BINAP ligand. **TS1-R** places the oxygen tether downwards and **TS1-S** places the oxygen upwards. The alkene facial selectivity of **TS1-S** places the terminal hydrogens on the alkene towards the ligand causing an adverse steric interaction. This is demonstrated in Figure 22 B with the H-H interactions between H<sub>b</sub> on the substrate and phenyl groups of the ligand labeled 2.10 Å and 2.46 Å. The alkene facial selectivity in the lower energy transition state (**TS1-R**), alleviates this steric interaction demonstrated in figure with longer H-H interactions with H<sub>a</sub> of 2.68 Å and 2.35 Å. This demonstrates the ability of the aryl groups of the (R)-BINAP ligand to affect the stereochemical outcome of the PKR. This conclusion is supported experimentally, as there are examples of highly enantioselective Pauson-Khand reactions achieved using bulky BINAP-derived ligands<sup>84,106</sup>.

Previous mechanistic experiments<sup>107</sup> lead to the conclusion that there is no solvent (THF) coordinated to rhodium in the rate-limiting transition state. The relative steric bulk from the substrate and ligand in the computational structures leaves very little room for solvent coordination making it likely very high in energy and extremely unlikely. Additionally, another prior study<sup>108</sup> proposed the possible chelation of the oxygen tether to rhodium during oxidative cyclization. Computationally, we found the steric strain required to bring the oxygen tether within coordinating distance was very high as our attempted optimizations consistently converged to **TS1-S** or **TS1-R**. This result suggests that the higher rates and enantioselectivities observed in the PKR using O-tethered substrate **1** are *not* caused by chelation of the heteroatom tether. Instead, the tether may be facilitating the substrate coordination step.



### 3.3.4 Calculated (*S*)-MonoPhos Mechanism and Origin of Enantioselectivity

Building on the mechanistic clues and mode of stereochemical induction with the bidentate (*R*)-BINAP ligand, we turned see if we could apply our findings to the PKR with the monodentate phosphoramidite ligand (*S*)-MonoPhos. Having previously identified the oxidative cyclization step as rate and enantioselectivity determining, we omitted subsequent steps from our calculations with (*S*)-MonoPhos. In addition to comparing the five and four-coordinate pathways, we also examined one chiral ligand and two chiral ligand pathways. The two different ligand pathways were largely treated as independent. The Gibb's free energy and enthalpy values were adjusted to account for the experimental temperature (80 °C), CO concentration (0.0006 M), and (*S*)-MonoPhos concentration (0.0055 M, or 0.011 M) using the Goodvibes software package<sup>103</sup>.

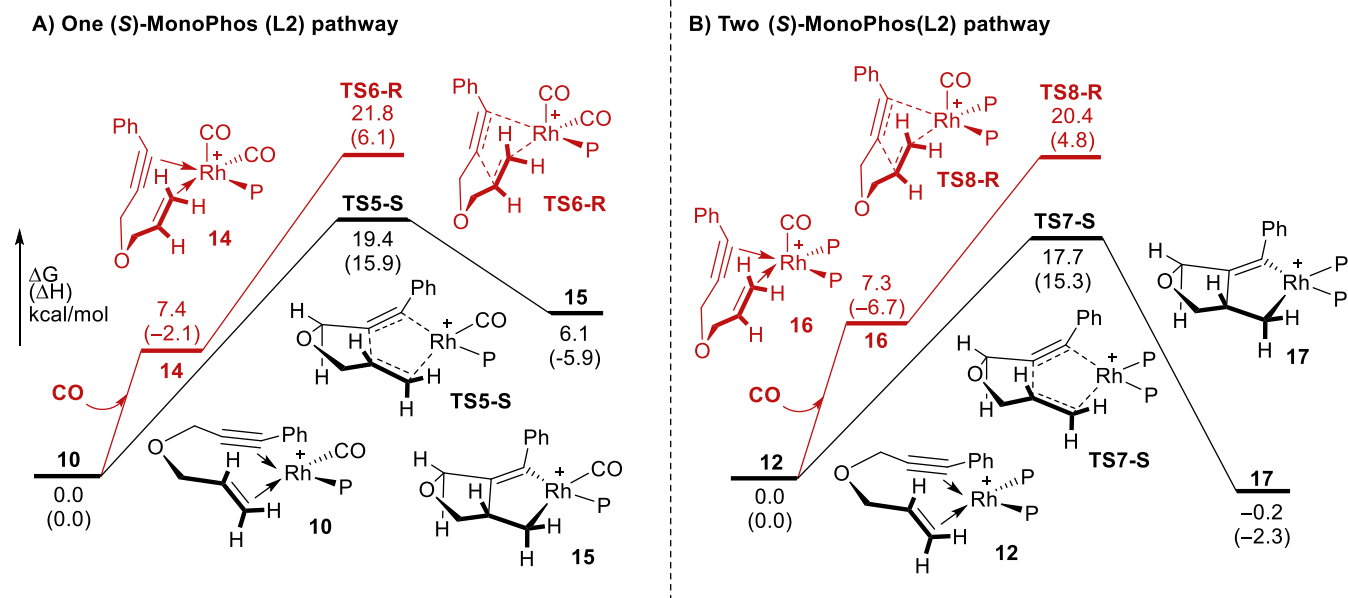


**Figure 23: Substrate binding energies to possible (*S*)-MonoPhos CO-coordinated complexes.**

We began by calculating the substrate binding energy between resting (*S*)-MonoPhos and CO-coordinated Rh catalysts and substrate-coordinated complexes to investigate the effect of the starting Rh catalyst structure on substrate coordination. In the presence of CO and an excess of (*S*)-MonoPhos (**L2**), the Rh catalyst can exist as one-, two- or three-(*S*)-MonoPhos (**L2**) coordinated species (**9**, **11**, and **13**, respectively). The four-(*S*)-**L2** Rh complex can also be formed,

but this species is unlikely to facilitate the PKR and was not included in this study. Resting catalysts and substrate-coordinated complexes are shown in Figure 23.

The replacement of two CO molecules on the one-(S)-MonoPhos (**L2**) resting catalyst **9** to afford the substrate-coordinated complex **10** is endothermic by 6.8 kcal/mol (Figure 23, eq 1). The replacement of two CO molecules on the two-(S)-MonoPhos (**L2**) resting catalyst **11** to afford substrate-coordinated complex **12** is endothermic by 15.3 kcal/mol (Figure 23, eq 2). The replacement of one CO molecule and one (S)-MonoPhos (**L2**) ligand on the three-(S)-MonoPhos (**L2**) resting catalyst **13** is endothermic by 20.7 kcal/mol (Figure 23, eq 3). Substrate binding to the one-(S)-MonoPhos (**L2**) resting catalyst **12** is less endergonic than substrate binding to the two-(S)-MonoPhos (**L2**) resting catalyst **11** (6.8 vs. 15.3 kcal/mol). The catalyst with fewer (S)-MonoPhos (**L2**) ligands and more CO ligands is more electrophilic due to the  $\sigma$ -donating ability of (S)-MonoPhos (**L2**) and the  $\pi$ -accepting ability of CO. Therefore, the more electrophilic one-(S)-MonoPhos (**L2**) resting catalyst **9** undergoes more facile coordination to the enyne substrate. Additionally, the enyne coordinates is aided in cases where the catalyst possesses fewer sterically-encumbering (S)-MonoPhos (**L2**) ligands.



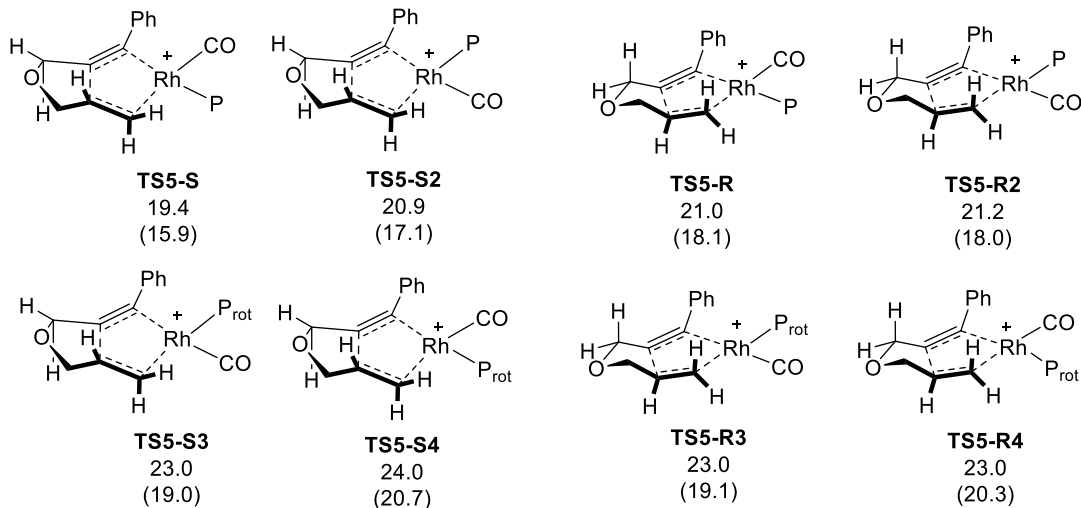
**Figure 24: Partial free energy profiles showing the oxidative cyclization steps for One-(S)-MonoPhos (A) and two-(S)-MonoPhos pathway (B).**

Figure 24 shows the possible pathways for the reaction with pathway A One-(S)-MonoPhos on the left and pathway B two-(S)-MonoPhos on the right. In pathway A, substrate coordinated complex **10** can either undergo direct cyclization via a four-coordinate transition **TS5-S** ( $\Delta G^\ddagger$  of 19.4 kcal/mol rel. to **10**) or bind an additional CO molecule to yield complex **14**. Complex **14** then proceeds to oxidative cyclization through five-coordinate transition state **TS6-R** ( $\Delta G^\ddagger$  of 21.8 kcal/mol). In the One-(S)-MonoPhos pathway, the four-coordinate pathway is favored over the five-coordinate pathway by 2.4 kcal/mol. Pathway B begins from substrate coordinated complex **12**. Complex **12** undergoes direct oxidative cyclization via **TS7-S** ( $\Delta G^\ddagger$  of 17.7 kcal/mol rel. to **12**) to yield Rh-metallocycle **17**. Alternatively, the higher energy pathway involves the binding of an additional CO molecule to afford complex **16** which proceeds to oxidative cyclization via **TS8-R** ( $\Delta G^\ddagger$  of 20.4 kcal/mol rel. to **12**). In the two-(S)-MonoPhos pathway the five-coordinate transition state is disfavored by 2.7 kcal/mol. The oxidative cyclization barrier is substantially lower in the

case of the two-(*S*)-MonoPhos pathway because the additional  $\sigma$ -donating phosphoramidite ligand further stabilizes the transition from a Rh (I) to a Rh (III) species.

To investigate the enantioselectivity we calculated a total of 34 different transition state isomers leading to the (*S*) and (*R*)-isomers of the product (Figures 25 and 26). This list comprised of 20 One-(*S*)-MonoPhos transition states (8 four-coordinated and 12 five-coordinated) and 14 two-(*S*)-MonoPhos transition states (8 four-coordinated and 6 five-coordinated). The higher number of one-(*S*)-MonoPhos isomers is due to the formation of two low-energy rotamers about the phosphorus-rhodium bond. The two-(*S*)-MonoPhos isomers were too sterically crowded to undergo this rotation.

4 Coordinate 1 (S)-MonoPhos Ligand @ 353.15 K



4 Coordinate 2 (S)-MonoPhos Ligands @ 353.15 K

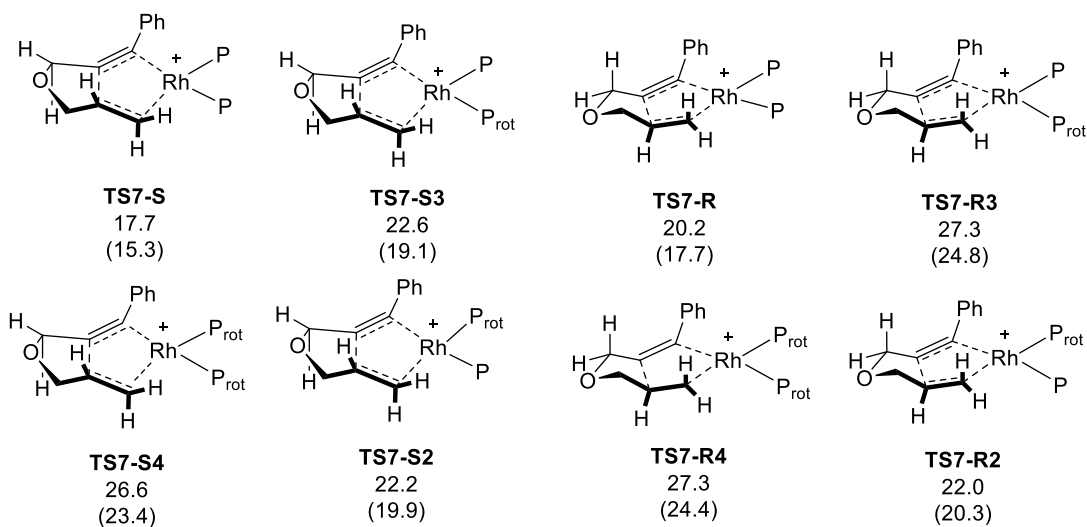
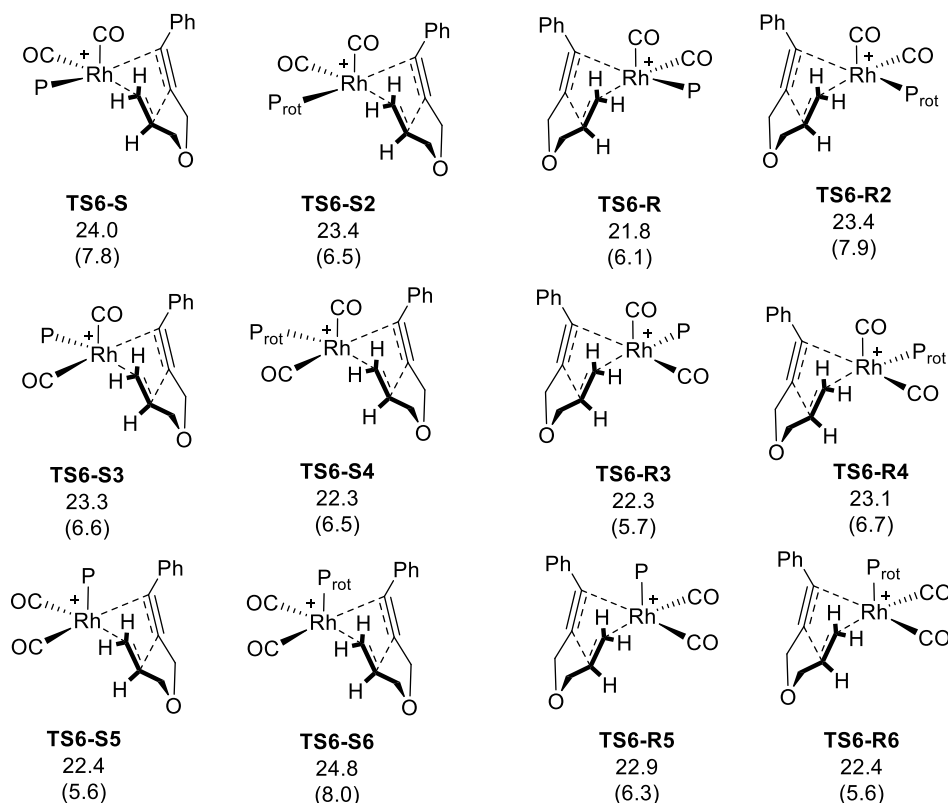


Figure 25: 4-coordinate isomers of the oxidative cyclization transition states. The Gibb's free energy and the enthalpy in parenthesis are reported in kcal/mol relative to structure 16 (1 ligand) or structure 21 (2 ligands).

5 Coordinate 1 (S)-MonoPhos Ligand TS @ 353.15 K



5 Coordinate 2 (S)-MonoPhos Ligands TS @ 353.15 K

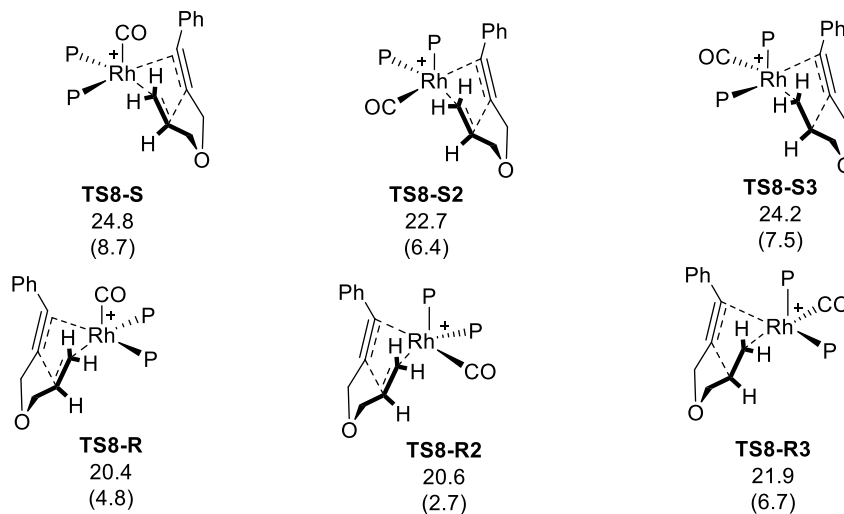
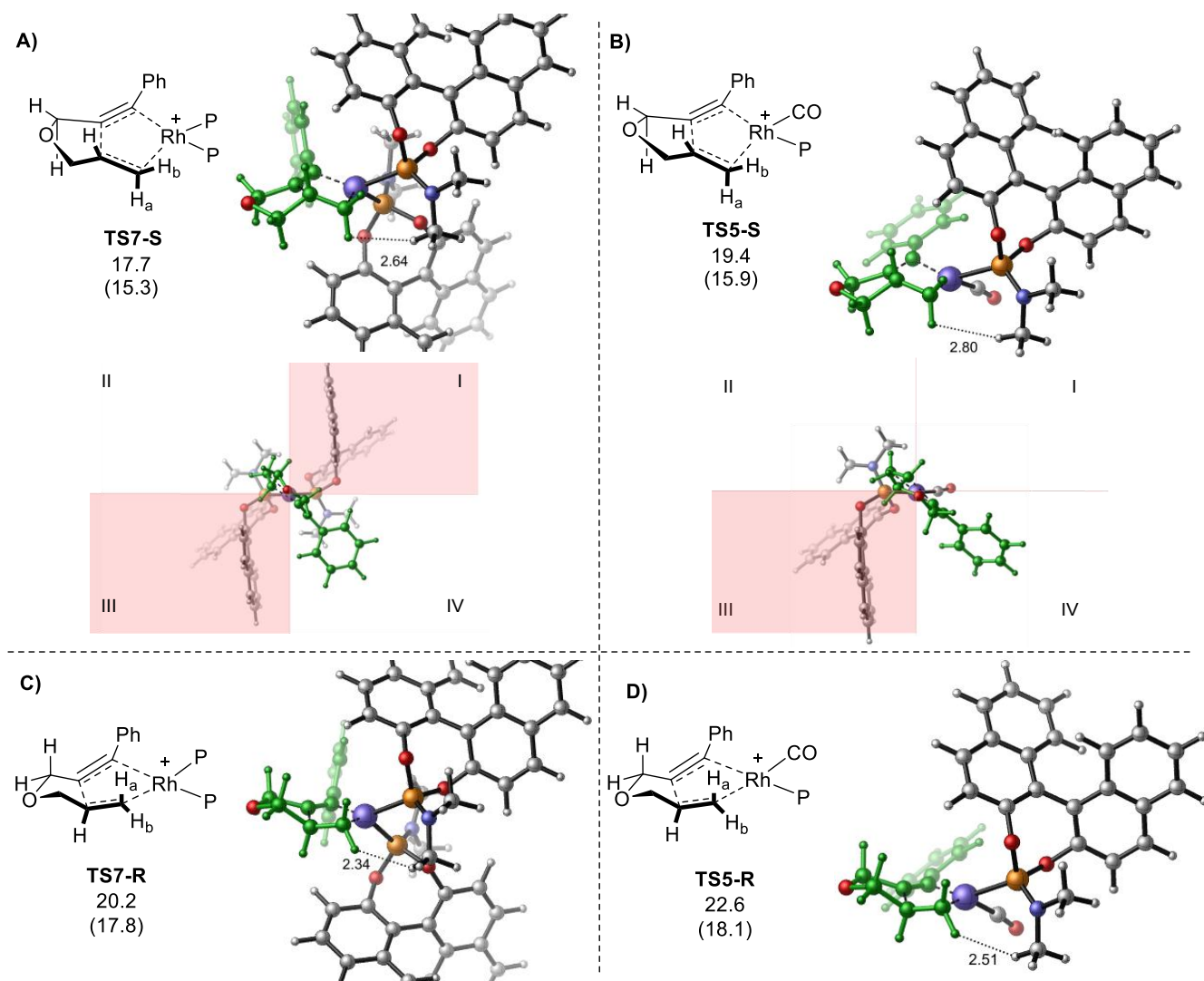


Figure 26: 5-coordinate isomers of the oxidative cyclization transition states. The Gibb's free energy and the enthalpy in parenthesis are reported in kcal/mol relative to structure 16 (1 ligand) or structure 21 (2 ligands).

Figure 27 shows the lowest energy isomers for the oxidative cyclization transition state with the isomers leading to the major (S)-product on the top two panels (A and B) and the isomers

leading to the minor (R)-product on the bottom two panels (C and D). The transition state isomers leading to the (S)-product (**TS7-S** and **TS5-S**) adopt a different alkene facial selectivity than the transition states leading to the (R)-product (**TS7-R** and **TS5-R**). The alkene facial selectivity of **TS7-R** and **TS5-R** causes the terminal hydrogens to be placed close to the N-Me group on the (S)-MonoPhos ligand. This causes an adverse steric interaction that is demonstrated by the short H-H distances for **TS7-R** and **TS5-R** (2.34 and 2.51 Å, respectively). This steric interaction is largely alleviated in **TS7-S** and **TS5-S** (2.64 and 2.80 Å, respectively). This mechanistic conclusion is in agreement with previous experimental work that showed that changing the dimethylamino group on another monodentate phosphoramidite ligand to a diisopropylamino or a 1-phenyl ethylamino groups led to low yield and ee<sup>109</sup>.



**Figure 27: Lowest energy oxidative cyclization transition states leading to the major and minor products with one-(S)-MonoPhos and two-(S)-MonoPhos.**

The structures for the two lowest-energy (S)-MonoPhos transition states **TS7-S** and **TS5-S** were analyzed using quadrant diagrams. In the lowest-energy two-(S)-L2 transition state **TS7-S** (Figure 27, A), quadrants I and III are blocked by the binaphthyl group of the ligand and the substrate fills unoccupied quadrants II and IV. Similarly, in the one-(S)-MonoPhos (L2) transition state **TS5-S** (Figure 27, B), the substrate preferentially occupies quadrant II and IV, despite quadrant I being empty.



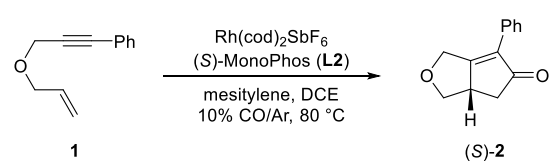
Despite (R)-BINAP and (S)-MonoPhos ligands differing in structure, they both impose a similar chiral environment on the Rh catalyst. Both ligands interact with the terminal vinyl proton. These interactions are observed between the phenyl group of the (R)-BINAP ligand and terminal vinyl protons and between the dimethylamino group of the (S)-MonoPhos ligand and the terminal vinyl protons. Further, the chiral environments effected by both ligands can both be described using quadrant diagrams. The phenyl groups of the (R)-BINAP (**L1**) ligands block quadrants II and IV, and the binaphthyl groups of the (S)-MonoPhos (**L2**) ligand blocks quadrants I and III (or if only one (S)-MonoPhos (**L2**) ligand is involved, quadrant III is blocked). Therefore, these transition state structures suggest that monodentate phosphoramidite ligands create a similar steric environment to bidentate phosphine ligands thus enabling stereo-directing ability in the PKR.

### 3.3.5 Effects of Corrections for Experimental Conditions

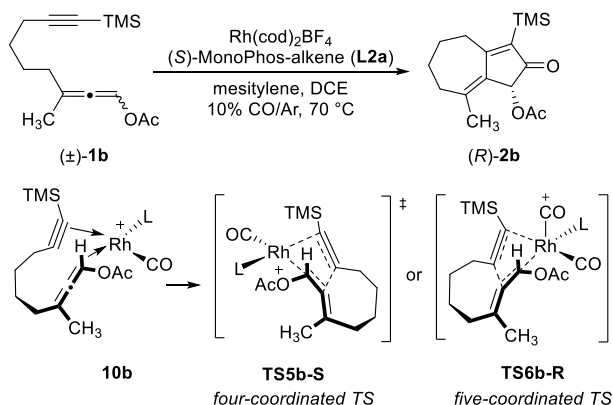
Although the majority of computational studies in recent literature report Gibbs free energies computed under standard conditions (25 °C, 1.0 atm), the effects of concentration and temperature are apparent and have been widely recognized.<sup>110,111</sup> In addition, the common practice of computing entropies in solution is flawed, because the translational entropies ( $S_{\text{translation}}$ ) are often calculated using gas phase formulas, which lead to overestimation of the computed entropy values for species in solution.<sup>101</sup> These errors usually cancel out when the enantioselectivity is determined by transition states via the same mechanism and thus will not affect the validity of the computational predictions in these scenarios. However, in the present study, the concentration, temperature, and entropic effects need to be carefully considered because the five- and four-coordinated cyclization pathways are competing and favor different major enantiomeric products (*vide supra*). The Gibbs free energy values reported in the above sections were computed under

the experimental conditions (80 °C, 0.1 atm CO, which is equivalent to 0.0006 M of dissolved CO in DCE). Here, the effective concentration of CO was estimated from the saturated concentration of dissolved CO in DCE using Henry's law (see the "Computational Methods" section for details).<sup>102</sup> In addition, translational entropies in DCE solution were calculated using the free volume theory proposed by Whitesides *et al.*<sup>101</sup> In Scheme 8a, we compared the Gibbs free energies computed using this approach and the commonly applied approach that calculates the thermodynamic parameters under standard conditions (25 °C, 1.0 atm CO or 0.045 M, and without the free volume theory corrections for translational entropies). Activation free energies calculated using the standard conditions show that the lowest-energy 5-coordinate oxidative cyclization transition state via **TS6-R** is 0.5 kcal/mol more favorable than the lowest-energy 4-coordinate transition state via **TS5-S**, and thus a slight preference for (*R*)-**2**, having the opposite configuration of the experimentally observed major enantiomer, would be predicted using this computational approach. By contrast, calculations using the actual experimental temperature and concentration and the solution translational entropy corrections show that the four-coordinated **TS5-S** is 2.4 kcal/mol lower in energy than **TS6-R**, predicting the selective formation of (*S*)-**2**, which agrees with experiment.

(A) Rh-catalyzed asymmetric PKR of enyne **1**



(B) Rh-catalyzed asymmetric PKR of allenyl acetate ( $\pm$ )-**1b**



|                         | T<br>(°C) | P(CO)<br>(atm) | [CO]<br>(mol/L)     | $S_{\text{translation}}$  | $G^{\ddagger}_{4\text{-coord}}$<br>(kcal/mol) | $G^{\ddagger}_{5\text{-coord}}$<br>(kcal/mol) |  | T<br>(°C)               | P(CO)<br>(atm) | [CO]<br>(mol/L) | $S_{\text{translation}}$ | $G^{\ddagger}_{4\text{-coord}}$<br>(kcal/mol) | $G^{\ddagger}_{5\text{-coord}}$<br>(kcal/mol) |      |
|-------------------------|-----------|----------------|---------------------|---------------------------|-----------------------------------------------|-----------------------------------------------|--|-------------------------|----------------|-----------------|--------------------------|-----------------------------------------------|-----------------------------------------------|------|
| “standard conditions”   | 25        | 1.0            | 0.045 <sup>a</sup>  | gas-phase formulas        | 18.8                                          | 18.3                                          |  | “standard conditions”   | 25             | 1.0             | 0.045 <sup>a</sup>       | gas-phase formulas                            | 11.2                                          | 7.6  |
| experimental conditions | 80        | 0.1            | 0.0006 <sup>b</sup> | free-volume theory in DCE | 19.4                                          | 21.8                                          |  | experimental conditions | 70             | 0.1             | 0.0006 <sup>b</sup>      | free-volume theory in DCE                     | 11.5                                          | 10.0 |

<sup>a</sup> Calculated using the ideal gas law. <sup>b</sup> Calculated using Henry's law.

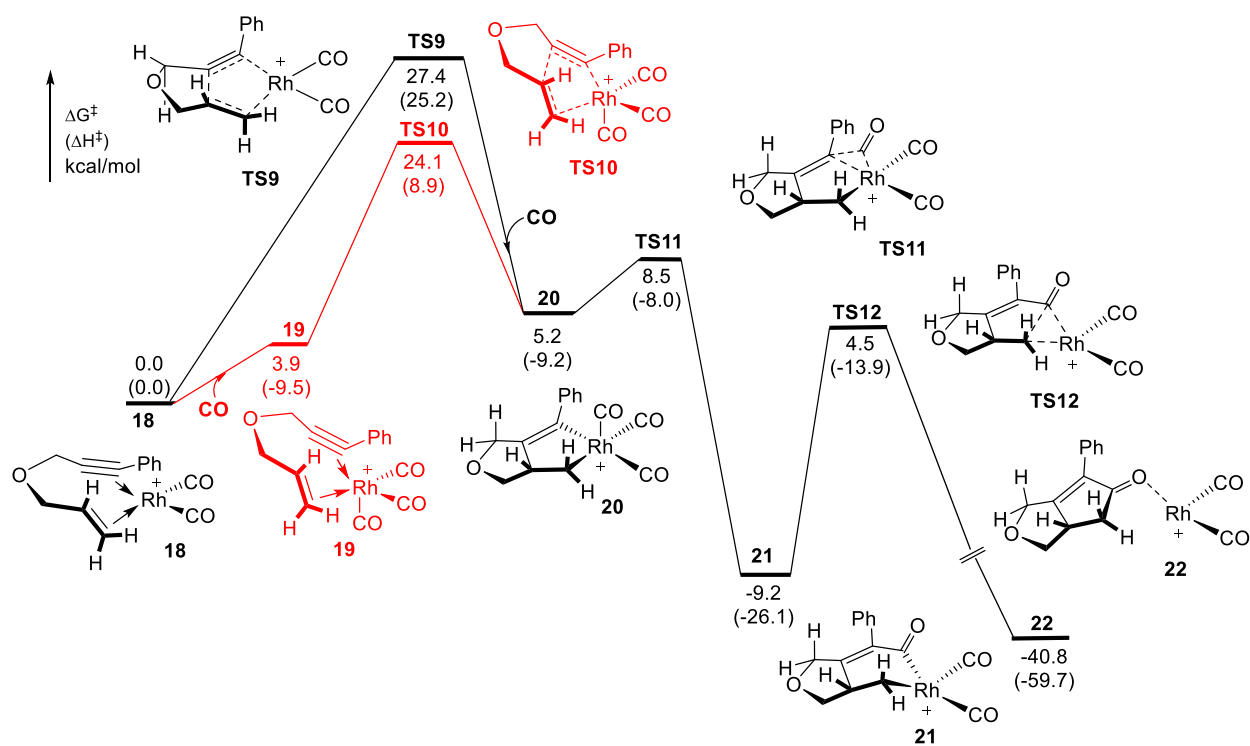
**Figure 28: Energy difference between 4-coordinate and 5-coordinate oxidative cyclization transition states at standard Gaussian09 conditions and the effect of correcting for experimental conditions.**

We surmised that the identity of the substrate may also affect the relative activation energies of the competing four- and five-coordinated oxidative cyclization pathways. In our previous computational study, we predicted that the enantioselective PKR of allenyl acetate **1b** prefers the five-coordinated pathway based on activation free energies calculated under standard conditions (Figure 28). To determine to what extent corrections for experimental parameters might affect the conclusions for this reaction, we applied the concentration, temperature, and translational entropy corrections to reflect the actual experimental conditions (70 °C, 0.1 atm of CO, which is equivalent to 0.0006 M of CO in DCE). After these corrections, these calculations predicted that the five-coordinated **TS6b-R** is still favored over **TS5b-S**, indicating the previously reported mechanism was not affected by these corrections, but the energy difference between the two competing transition states decreased from 3.6 kcal/mol before the corrections to 1.5 kcal/mol after the corrections.

Taken together, the computational results suggest that reaction conditions and the identity of the PKR substrate may both affect the mechanism of Rh-catalyzed PKR. Under the experimental conditions, the reaction with allenyl acetate **1b** prefers the five-coordinated oxidative cyclization while the reaction with enyne **1** prefers the four-coordinated pathway. The four-coordinated transition state with allenyl acetate (**TS5b-S**) is destabilized by the steric repulsions between the acetate group on the allene and the Rh, which force the allene and alkyne  $\pi$  bonds to be perpendicular to the Rh center, rather than adapting the co-planar geometry as seen in the four-coordinated transition state with the enyne (**TS5-S**).

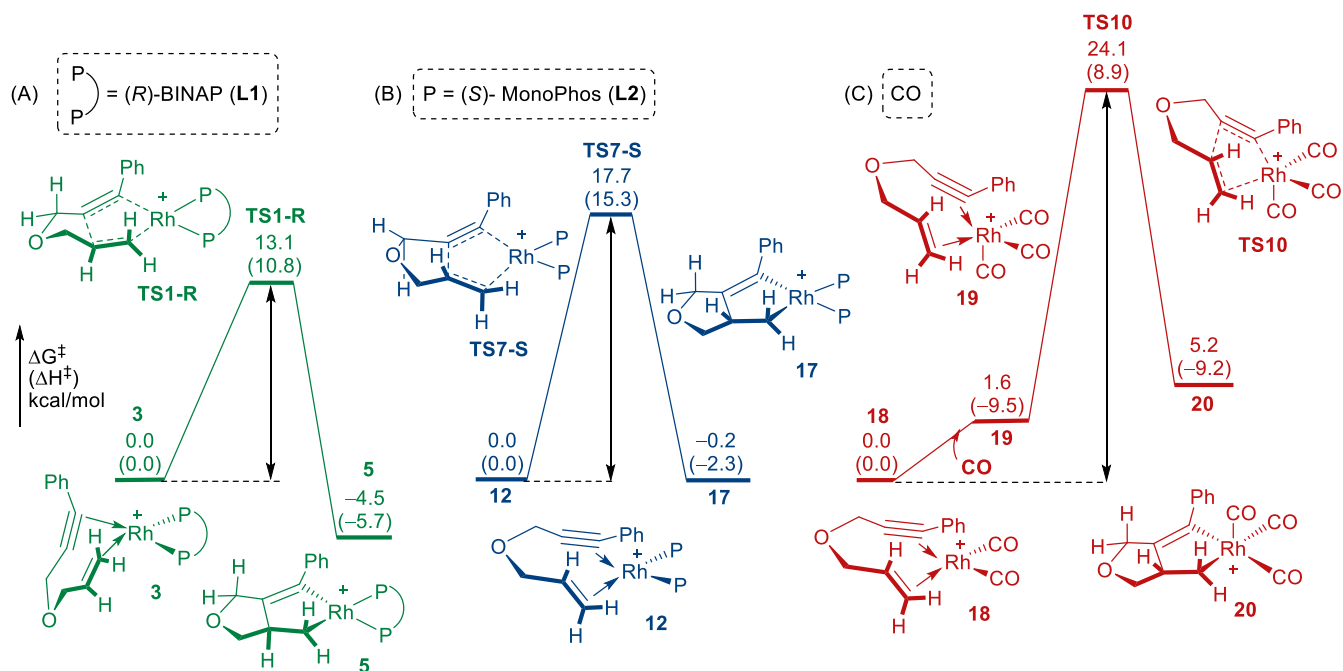
### 3.3.6 Full Potential Energy Surface of PKR with CO as the Only Ligand

The full potential energy surface with CO as the on ancillary ligand was also calculated (Figure 29). It was found that the reaction pathway proceeds through a 5-coordinate oxidative cyclization transition state (**TS10**) when CO acts as the ligand. The preferential of 5-coordinate complex likely due to the CO being less sterically encumbered than with the phosphine ligands. Additionally, since CO is a worse electron donor than the phosphine ligands, the rhodium in 4-coordinate transition state (**TS9**) is likely more electron deficient than in the other 4-coordinate transition states with the phosphine ligands.



**Figure 29: Optimized free energy profile for the Pauson-Khand reaction using carbon monoxide in place of a phosphine ligand.**

### 3.3.7 Comparison of Calculated Oxidative Cyclization Barriers and Experimental Rates



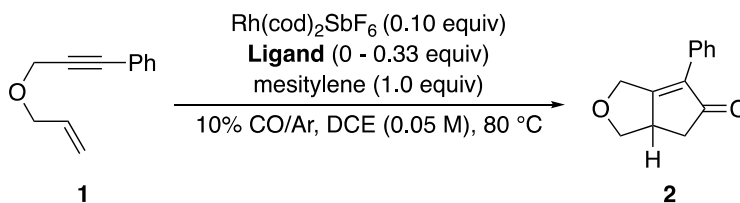
**Figure 30: Comparison of calculated barriers of activation for oxidative cyclization step.**

The calculated activation energies ( $\Delta G^\ddagger$ ) of the oxidative cyclization step provide some evidence of a ligand effect on the overall rate of the PKR. The calculated activation energies led to development of a hypothesis that states the Rh-(R)-BINAP-catalyzed PKR would have a high rate due to its low activation energy barrier ( $\Delta G^\ddagger = 13.1$  kcal/mol **TS1-R**). Likewise, the Rh-(S)-MonoPhos-catalyzed PKR will proceed at a moderate rate ( $\Delta G^\ddagger = 17.7$  kcal/mol, **TS7-S**) and the chiral ligand free, Rh-“CO-only”-catalyzed PKR would proceed at a very low rate ( $\Delta G^\ddagger = 25.7$  kcal/mol, **TS10**). Additionally, since the activation energy for the Rh-two-(S)-MonoPhos-catalyzed PKR (17.7 kcal/mol, **TS7-S**) was lower than the Rh-one-(S)-MonoPhos (L2)-catalyzed PKR (19.4 kcal/mol, **TS5-S**), it was anticipated that rate would be higher with an increased initial ligand load of (S)-MonoPhos/Rh > 2. Experimental rate studies were conducted in order to benchmark the calculations and provide further evidence to support the claim that the oxidative

cyclization step is rate determining. Experimental rates were determined using the cationic Rh conditions with no phosphorus ligand, (R)-BINAP ligand, and various (S)-MonoPhos ligand/Rh ratios (0.5, 1.1, 2.2 and 3.3). The purpose varying the (S)-MonoPhos ligand was to examine the effects of shifting the form of the active catalyst from containing one to two ligands on the rate, yield, and product ee (%). The results of these experiments can be seen in table 1.

The PKR under cationic Rh conditions with no phosphorous ligand proceeded very slowly, with a half-life of 301 h ( $k = 6.39 \times 10^{-7} \text{ s}^{-1}$ , entry 1, Table 1). The reaction of 1 with added (R)-BINAP (L1/Rh = 1.1) proceeded rapidly, with a half-life of only 6 min ( $k = 1.88 \times 10^{-3}$ ) and afforded a 41% yield of (S)-2 in 77% ee (entry 2). Next, the effect of the (S)-MonoPhos (L2) ligand on the PKR rate was examined. Performing the PKR with a (S)-L2/Rh ratio of 0.5 afforded a 59% yield of (S)-2 in 79% ee and a  $t_{1/2} = 6.4 \text{ h}$  (entry 3). A (S)-L2/Rh ratio of either 1.1 or 2.2 gave (S)-2 in nearly identical yields, ee's and half-lives (entries 4 and 5). Finally, performing the PKR using a L2/Rh ratio of 3.3 afforded (S)-2 in 90% yield with a 79% ee with a  $t_{1/2} = 30.5 \text{ h}$  (entry 6).

**Table 1: Experimental rate studies of cationic Rh catalysts in the PKR of enyne 1.**



| entry | ligand (L/Rh) | rate ( $\text{s}^{-1}$ ) | $\Delta G^\ddagger$ (kcal/mol) | time (h) <sup>a</sup> | $t_{1/2}$ (h) | yield (SM) <sup>b</sup> | ee (%), absolute configuration |
|-------|---------------|--------------------------|--------------------------------|-----------------------|---------------|-------------------------|--------------------------------|
| 1     | none          | $6.39 \times 10^{-7}$    | 24.1                           | 245                   | 301           | 11 (56)                 | -                              |
| 2     | (R)-L1 (1.1)  | $1.88 \times 10^{-3}$    | 13.1                           | 1.0                   | 0.10          | 41 (0)                  | 77 (R)                         |
| 3     | (S)-L2 (0.5)  | $3.03 \times 10^{-5}$    | -                              | 48                    | 6.4           | 59 (1)                  | 79 (S)                         |
| 4     | (S)-L2 (1.1)  | $1.10 \times 10^{-4}$    | 19.4                           | 18                    | 1.6           | 61 (4)                  | 82 (S)                         |
| 5     | (S)-L2 (2.2)  | $1.15 \times 10^{-4}$    | 17.7                           | 18                    | 1.7           | 60 (0)                  | 83 (S)                         |
| 6     | (S)-L2 (3.3)  | $6.32 \times 10^{-6}$    | -                              | 101                   | 30.5          | 90 (0)                  | 79 (S)                         |

<sup>a</sup> Time reaction was monitored. <sup>b</sup> Yields determined by  $^1\text{H}$  NMR by comparing integral intensities of product (2, 4.9 ppm) to mesitylene (6.8 ppm). Conditions: rhodium bis(cyclooctadiene) hexafluoroantimonate ( $\text{Rh}(\text{cod})_2\text{SbF}_6$ , 0.1 equiv), phosphorus ligand (0-0.33 equiv), and mesitylene (1.0 equiv) under 10% CO/Ar in dichloroethane (0.05 M). In each PKR rate experiment, Rh precatalyst and ligand were reacted under nitrogen at 60 °C for 1 h, at which time the reaction atmosphere was changed to 10%

CO/Ar. After an additional 1 h, the oil bath temperature was increased to 80 °C and enyne **1** was added all at once. (**Experiments Performed by Lauren C. Burrows**)

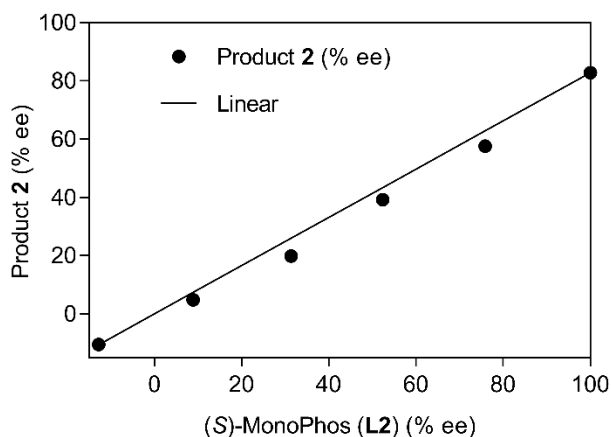
The experimental reaction rate experiments showed that switching from no phosphorus ligand (Table 1, entry 1) to (R)-BINAP ligand (table 1, entry 2) caused a nearly 3,000-fold increase in rate. Similarly, (S)-MonoPhos in a ligand/Rh ratio of 1.1 increased the rate nearly 180-fold (table 1, entry 1 and 4). This is evidence of phosphorus ligand accelerated catalysis, which has not been reported in the case of PKRs utilizing neutral Rh(I) catalysts<sup>100</sup>. The general experimental trend of a very low rate with no phosphorus ligand, a moderate rate with (S)-MonoPhos, and a high rate with (R)-BINAP showed good agreement with the calculated free energy barriers for oxidative cyclization (25.7, 17.7, and 13.1 kcal/mol, respectively). This correlation between the calculated activation energies and the experimental reaction rates supports oxidative cyclization being the rate determining step of the reaction.

The experiments that varied of the initial concentration of (S)-MonoPhos ligand are detailed in the bottom of table 1 (entry 4 – 6). It was found that both the rate and enantioselectivity remained relatively the same despite changing the (S)-MonoPhos/Rh from 1.1 to 2.2 (table 1, entry 4 and 5). This shows that despite a difference in the calculated activation energy between the one-(S)-MonoPhos and two-(S)-MonoPhos (20.9 and 17.7 kcal/mol respectively), these two reactions proceed similarly. We observed a reduction in rate when the (S)-MonoPhos/Rh ratio was reduced to 0.5 (table 1, entry 3). The reason for the rate reduction in this case is that the equilibrium of Rh-(S)-MonoPhos complexes shifts towards the one-(S)-MonoPhos complexes which have a higher barrier of activation (20.9 kcal/mol). Additionally, half of the complexes when the ligand/Rh = 0.5 are the Rh-“CO-only” complex which reacts much more slowly than the phosphorus ligand bound complexes. The low rate observed in the case of ligand/Rh = 3.3 (table 1, entry 6) was unexpected as we anticipated these conditions would form more of the two-(S)-MonoPhos complexes with the



lower activation barrier leading to an overall rate increase. The low observed rate could be due to the formation of  $\text{RhL}_3$  and  $\text{RhL}_4$  complexes. We demonstrated that the  $\text{RhL}_3\text{CO}$  has a higher barrier to substrate coordination relative to  $\text{RhL}_2[\text{CO}]_2$  and  $\text{RhL}_1[\text{CO}]_3$ , thus leading to a rate reduction for these complexes. The high yield of 90% can be attributed to additional free (S)-MonoPhos ligand coordinating to coordinatively unsaturated Rh(III) complexes, thus preventing any undesired side reactions.

Additional rate experiments were conducted to further resolve the question of how many (S)-MonoPhos ligands were present on Rh center in the oxidative cyclization transition state. To resolve this, an experiment was conducted where the ee (%) of the (S)-MonoPhos ligand was varied and the dependence of the product ee (%) was measured. A direct linear correlation would suggest one (S)-MonoPhos ligand coordinated in the oxidative cyclization transition state. A nonlinear correlation would suggest two (S)-MonoPhos ligands coordinated in this transition state. The resulting product ee vs. (S)-MonoPhos ee is shown in Figure 31.



**Figure 31: Linear correlation observed between (S)-MonoPhos (L2) (%ee) and product 2 (% ee) in PKR of enyne 1. Reaction conditions performed by Lauren C. Burrows are as follows;  $\text{Rh}(\text{cod})_2\text{SbF}_6$  (0.10 equiv), (S)-MonoPhos (L2) (0.11 equiv), mesitylene (1.0 equiv), DCE (0.05 M), 80 °C.**

Figure 31 depicts a linear correlation observed between the product ee and the ee of the (S)-MonoPhos ligand. This evidence suggests the PKR proceeds with one ligand bound to the catalytically active species<sup>112</sup>, despite this pathway having a higher energy of activation (20.9 kcal/mol). This experiment also shows that a single monodentate chiral ligand can create a suitable environment for highly enantioselective catalysis.

### 3.4 Conclusions

This study was a thorough investigation into the mechanism of the enantioselective PKR using experimental and computational tools. We conducted an exhaustive search of transition state structures with Rh-(R)-BINAP and Rh-(S)-MonoPhos catalysts. VCD was used to assign the absolute configuration of the cyclopentanone products. The computational study revealed evidence of ligand accelerated catalysis. This computational claim was validated experimental rate studies which also showed a ligand acceleration effect of phosphorus ligands in the cationic Rh-catalyzed PKR of enynes. The Rh-(R)-BINAP catalyst had the highest rate of reaction, and the Rh-(S)-MonoPhos catalyst delivered the highest yield (Ligand/Rh = 3.3, 90% yield). Both the BINAP and MonoPhos catalysts afforded similar enantioselectivities (77-82 % ee). A rate experiment with (S)-MonoPhos where the ee of the ligand was varied, this experiment revealed high yields and enantioselectivities can be achieved with only one-(S)-MonoPhos ligand on the catalyst. This may allow for future expansion of the reaction scope of the enantioselective PKR to include more sterically bulky substrates.

The study highlighted the importance of integrating experimental reaction conditions in computations. In calculating the reaction energy profile of the Rh-(R)-BINAP-catalyzed PKR, the

correct enantiomer of the product was predicted only with the incorporation of parameters for experimental CO concentration and temperature using Goodvibes software. In the case of the Rh-(S)-MonoPhos-catalyzed PKR, the concentration of the (S)-MonoPhos ligand was also taken into account. Applying these conditions also led to unexpected predominance of the four-coordinated pathway in this study, which was counter to previous PKR studies. Therefore, by incorporating key experimental reaction conditions, experimental and computational expertise can be combined to understand reaction mechanism and design better enantioselective catalysts.

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