

**PRF# 56371-DN11, Early/Late Heterobimetallic Complexes for Catalytic Alkene and Alkyne Functionalization, David Michaelis, Brigham Young University**

Transition metal-catalyzed reactions of olefins and alkynes are particularly important in modern synthesis because a late transition metal can serve as a  $\pi$ -acid to activate them towards nucleophilic additions. The *objective* of this project is to develop heterobimetallic Ti-M catalysts capable of novel reactivity in C-N and C-C bond forming reactions via electrophilic olefin and alkyne activation. During the past 12 months of this project, we have continued to focus on two different directions in heterobimetallic catalysis. First, we have continued to synthesize and test chiral titanium ligands for enantioselective allylic amination reactions with hindered amine nucleophiles. These efforts include strategies to characterize and determine the structure of these new ligands. Second, we have developed N-heterocyclic carbene ligands (NHC) containing pendant coordinative groups for heterobimetallic nickel catalysis and developed and published two nickel-catalyzed processes as a result of these efforts

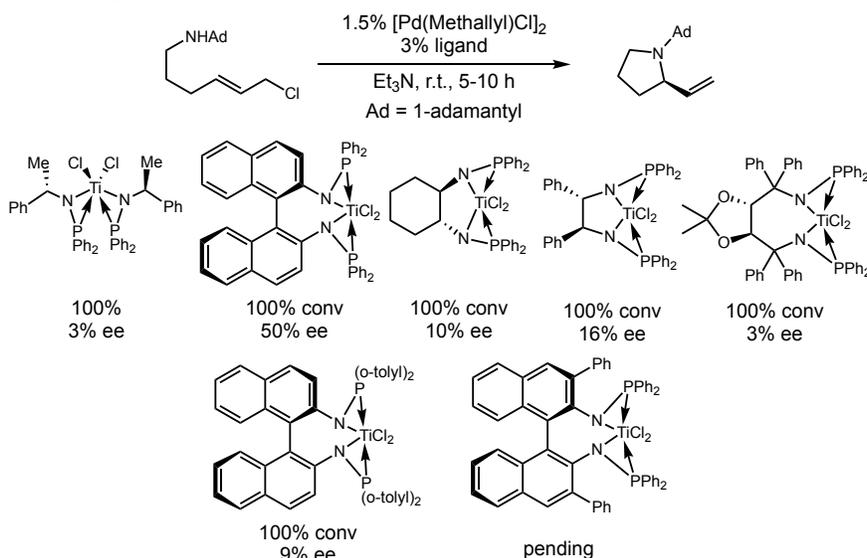
**Enantioselective Bimetallic Catalysis:** One aim of our research is to develop chiral titanium-containing ligands that assemble heterobimetallic complexes in situ to provide highly active and selective catalysts for organic transformations with alkenes and alkynes. In our previously described work, we demonstrated that various titanium containing ligands assemble bimetallic Pd-Ti catalysts in situ and enable fast allylic amination catalysis with hindered amine nucleophiles. Importantly, this allylic amination with hindered amines does not proceed at room temperature with any phosphine ligands that we have screened to date.

In our previous work, we synthesized a variety of chiral bisphosphine titanium ligands for use in enantioselective reactions. We then screened these ligands in allylic amination reactions that generate piperidine products (Figure 1). Due to the variability in the yield and enantioselectivity in these reaction, we set out this year to more completely characterize the structure of these titanium-containing ligands. As such, we crystallized each of these ligands and obtained single crystal x-ray structures for each ligand (Figure 2). Importantly, each titanium atom is coordinated to both amines in each of these ligand structures. In addition, the phosphorous atoms are transiently bound to the titanium, allowing them to dissociate and coordinate with our palladium catalyst. With this structural data in hand, we have begun to perform reaction optimization studies to improve the enantioselectivity of these ligands in allylic amination reactions. This work will be submitted for publication shortly. We have also begun to optimize the structure of this binaphthyl ligand to improve this modest enantioselectivity. For example, we have initiated computation studies with the Ess laboratory to calculate the enantioselectivity of different ligand scaffolds. These efforts are guiding our synthetic efforts in the design of ligands for enantioselective catalysis.

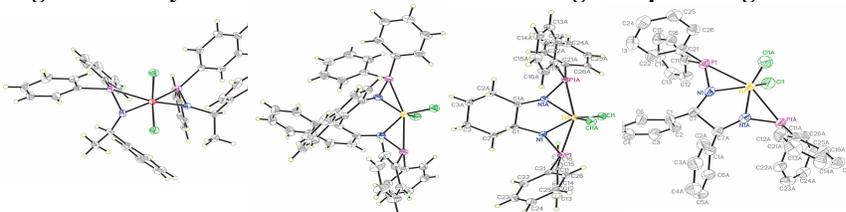
**Heterobimetallic Nickel**

**Catalysis:** The results presented above focus on the use of titanium-containing ligands for heterobimetallic catalysis. During the last year, we have continued to pursue efforts to develop bidentate N-heterocyclic carbene (NHC) ligands for bimetallic catalysis. Our hypothesis is that a NHC-metal complex containing a labile coordinating group could recruit a second metal and enable bimetallic catalysis. This would allow us to screen second metal effects in catalysis. In our initial efforts, we have synthesized various bidentate NHC ligands and screened their activity in nickel-catalyzed Suzuki reactions with simple allylic alcohols. Importantly,

**Figure 1. Enantioselective Heterobimetallic Catalysis.**



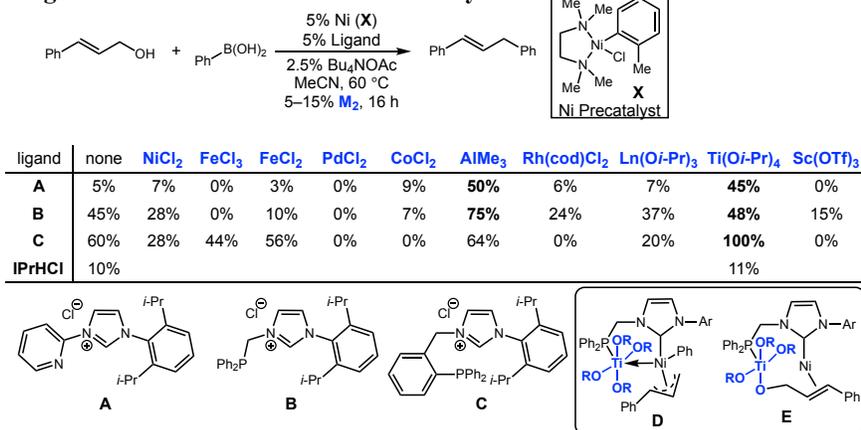
**Figure 2. X-ray Structures of Titanium-Containing Phosphine Ligands.**



this transformation has not been reported with nickel catalysts, giving us an opportunity to explore new reactivity with nickel catalysts.

In our optimization studies, we screened a variety of metal precursors in combination with our nickel NHC complexes (Figure 3). Importantly, we found several positive effects when Lewis acidic metals such as aluminum and titanium were employed. We were intrigued by that fact that many of the second metal effects, such as with titanium, iron, and aluminum were actually ligand dependent. This suggests that the ligand structure is important to influencing the impact of the second metal in catalysis. In particular, we observed that with ligand C, we could obtain 100% conversion to the cross coupled product when titanium isopropoxide was employed. While we do believe that activation of the alcohol substrate by titanium is likely increasing the rate of catalysis, we are currently investigating the formation of bimetallic

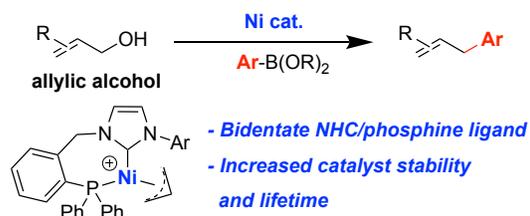
**Figure 3. Heterobimetallic Nickel Catalysis.**



complexes such as **D** and **E** to determine if the ligand scaffold is increasing reactivity via interactions with nickel (**D**) or by binding to and activating the alcohol substrate in close proximity to nickel (**E**).

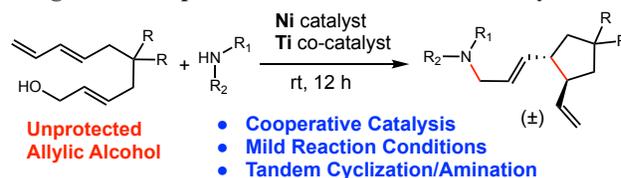
As a result of the preliminary data described above, during the past year we published two studies in nickel catalysis. The first publication describes the use of bidentate N-heterocyclic carbene (NHC) ligands to enable Nickel-catalyzed Suzuki reactions with unprotected allylic alcohols (Figure 4). In our bimetallic optimization studies described above (Figure 3), we found that the bidentate NHC ligands we had developed enabled highly efficient catalysis in the absence of any second metal effect. Thus, while we continue to investigate the heterobimetallic catalysis system, we published these highly practical results relying on the stability of Nickel catalysts containing these bidentate ligands.

**Figure 4. A Nickel-Catalyzed Suzuki Reaction with Unprotected Allylic Alcohols.**



We also recently published a dual catalytic approach to nickel catalysis that we discovered as we optimized the above strategy for nickel heterobimetallic catalysis (Figure 5). In this report, we demonstrated that the addition of 30% titanium isopropoxide would greatly accelerate the allylic amination of allylic alcohols and enable catalysis under mild conditions at room temperature. In these studies, the addition of titanium was shown to activate the alcohol substrate toward oxidative addition and greatly accelerate the transformation.

**Figure 5. Cooperative Nickel-Titanium Catalysis**



Importantly, our new catalyst system also enabled tandem cyclization/amination reactions, which could not be performed by other nickel catalysts. These results provide a new strategy for converting unprotected allylic alcohols to amines under mild conditions with cheap nickel catalysts and enables access to a new class of cyclic amine products.

**Conclusion:** The results presented above confirm the potential of heterobimetallic catalysts to contribute new and important reactivity to organic transformations. In addition, our studies have led to the development of new and efficient nickel-catalyzed transformation, including Suzuki reactions and allylic aminations. These new reactions were developed as we pursued our goals in heterobimetallic catalysis. We have also demonstrated several strategies for employing heterobimetallic catalysis in organic reactions, and have developed new methods for enantioselective catalysis with heterobimetallic complexes. The successes of this work have led to invitations to give scientific seminars at 26 universities and companies over the last 12 months. Also, myself and 3 students have attended Gordon Research Conferences and ACS national meetings over the last year to present results on this project.