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Project Title: Dehydrogenative Amide Synthesis Utilizing Ruthenium and Iron Catalysts via Traditional and Microwave techniques

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Our research group focuses on the synthesis of mid-transition metals for catalytic dehydrogenative amide synthesis. The first year of this project was used to synthesize and characterize Ru^{II} complexes of a variety of motifs and to start testing preliminary catalytic reactions. Students began by synthesizing the organic ampy (2-aminomethylpyridine) ligand with electronic variation of the substituent on the 4-position, and then coordinating the ligand to a Ru^{II} metal center (Figure 1). These complexes were targeted since previous research showed that the parent complex, *cis*-Ru(dppb)(ampy-Y)Cl₂ (dppb = diphenylphosphinobutane, Y = MeO, H, and Cl) is capable of catalytic dehydrogenative amidation.^{1,2} The new set of complexes would provide insight into the effect of secondary sphere electronic tuning on catalysis and, at the same time, would be compatible with the skills of an undergraduate researcher. The 4-OMe and 4-Cl complexes were fully characterized spectroscopically, as well as by cyclic voltammetry and X-ray diffraction methods. The data were compared to examine the differences in electron density and structure around the metal center (Figure 1).

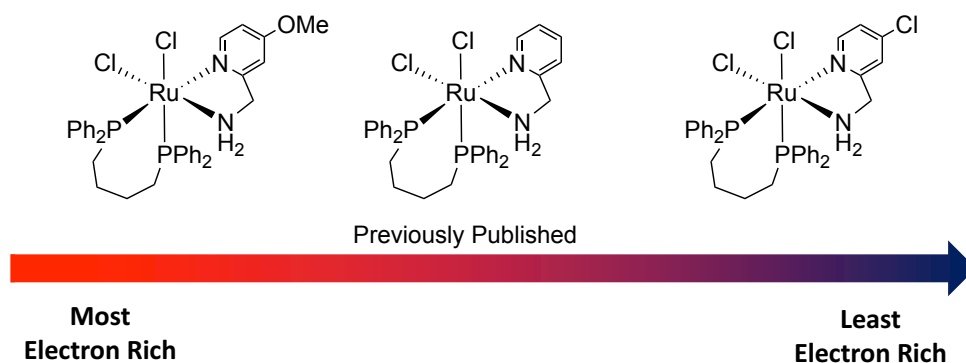
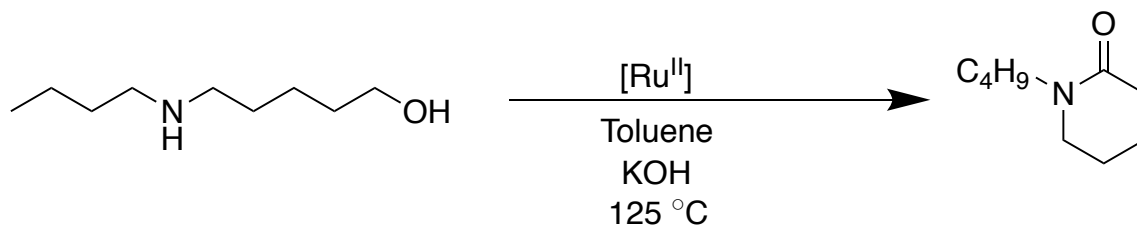


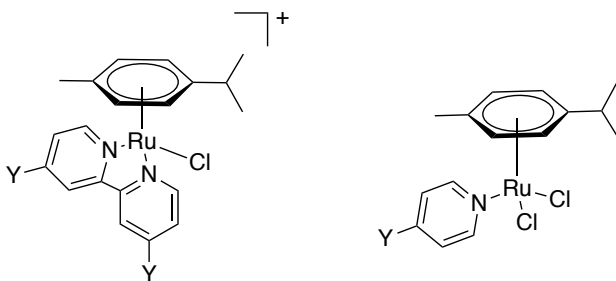
Figure 1: *cis*-Ru(dppb)(ampy-Y)Cl₂ complexes synthesized and characterized.

X-ray crystallographic data indicate that the steric profile around the metal center is retained, and electrochemical data show that the complexes vary in electron density to some extent. Preliminary data on the rates of isomerization were also obtained to probe the effects of substitution on the 4-position on reactivity. All three complexes were tested for catalytic activity and preliminary data show that, although the substituted complexes are both catalytically active, they do not generate yields of amide as high as the parent complex. Preliminary catalytic reactions were also conducted to examine the effects of catalysis under microwave conditions versus traditional thermal conditions.



Scheme 1: Catalytic Reaction for the Dehydrogenation of *N*-Butyl-5-amino-1-pentanol using [Ru^{II}].

Our group also used the first year of funding to synthesize substituted [(η⁶-*p*-cymene)Ru(4Y,4'-Y-bpy)Cl]⁺ (bpy = bipyridine, Y = MeO, ^tBu, and H) and [(η⁶-*p*-cymene)Ru(4Y-py)Cl₂] (py = pyridine, Y = MeO, ^tBu, and H) complexes (Figure 2) to examine the effects of monodentate and bidentate ligands on dehydrogenative amide synthesis. Although these complexes have been previously synthesized using traditional thermal methods, one of my newer students has started to investigate if a standardized method using microwave synthesis could be used for shorter reaction times. Preliminary intramolecular catalysis was conducted using *N*-butyl-5-amino-1-pentanol to examine the reactivity of these complexes. Initial results using [(η⁶-*p*-cymene)Ru(^tbpy)Cl]⁺ does not catalytically form the desired amide but another apparently pure product is formed according to the GC-MS. The identity of the product is still being examined and other reaction conditions are being explored.



Y = OMe, ^tBu, and H

Figure 2: Synthesized and characterized $[(\eta^6\text{-}p\text{-cymene})\text{Ru}(4\text{Y},4'\text{-Y-bpy})\text{Cl}]^+$ and $[(\eta^6\text{-}p\text{-cymene})\text{Ru}(4\text{Y-py})\text{Cl}_2]$.

Impact

The funding obtained from this grant has had a significant impact on both my and my students' careers. A portion of the grant funds were used to purchase an Anton-Parr Monowave 400 microwave reactor. This purchase allowed us to pursue research in the third aim of this research grant without having to travel to MTSU 45 minutes away from campus which would be difficult with my students' research schedules. This past year my research student attended SERMACS to present a research poster and the 2018 Spring ACS National Meeting to give an oral presentation on his research. These opportunities are invaluable to him because it gave him an opportunity to attend the graduate school fair (he is now pursuing his Ph.D. at NC State University) and to gain confidence in presenting his data to the scientific community. As a pre-tenured faculty member, this research project will have a significant impact on my tenure packet. As stated above, this year's funding has allowed for the generation of new molecules and preliminary catalysis data which will lead towards publications needed for the tenure requirement. The grant has also allowed me to increase my lab's capacity to mentor more undergraduate students because of the funding to purchase the required supplies and chemicals.

References:

- (1) Nova, A.; Balcells, D.; Schley, N. D.; Dobereiner, G. E.; Crabtree, R. H.; Eisenstein, O. An Experimental–Theoretical Study of the Factors That Affect the Switch between Ruthenium-Catalyzed Dehydrogenative Amide Formation versus Amine Alkylation. *Organometallics* **2010**, *29* (23), 6548–6558. <https://doi.org/10.1021/om101015u>.
- (2) Schley, N. D.; Dobereiner, G. E.; Crabtree, R. H. Oxidative Synthesis of Amides and Pyrroles via Dehydrogenative Alcohol Oxidation by Ruthenium Diphosphine Diamine Complexes. *Organometallics* **2011**, *30* (15), 4174–4179. <https://doi.org/10.1021/om2004755>.