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Faculty Sabbatical Leave Report

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Mini Review

General Outcome of Sabbatical

Research was performed in the laboratories of Nobel Laureate Dr. Robert Grubbs, (Nobel Prize in Chemistry 2005) at CALTECH during the Spring 2016. Rivas successfully completed the goal of becoming familiar with olefin metathesis reactions using Ru-based catalysts. Rivas is now better prepared to continue developing his research expertise with a new emphasis on the use of olefin metathesis reactions for the synthesis of molecules with biological activity. Rivas performed olefin metathesis on a model substrate that is similar to those found in peptides as proposed in the original sabbatical request. The model system was synthesized by Rivas according to established procedures which exposed Rivas to new synthetic methods. Once the model system was synthesized various Z-selective olefin metathesis catalysts were explored for the generation of Z-alkenes. The goal of studying the Z-selective catalysts became the research focus and it required most of the time available for the sabbatical. Studying olefin metathesis with Ru-based catalysts in the laboratory of Dr. Grubbs exposed Rivas to first-hand experience with this important reaction. The study of the proposed system revealed that the steric environment next to the alkene has a significant impact on the outcome of the reaction. It was discovered that the Z-selective catalysts are less reactive and therefore yielded no product or low yield on the selected model system. Consequently, our approach to the synthesis of the desired molecules such as 4 (Figure 1) will require a modified cross metathesis or ring closing metathesis instead of homo-coupling (metathesis with two of the same molecules).

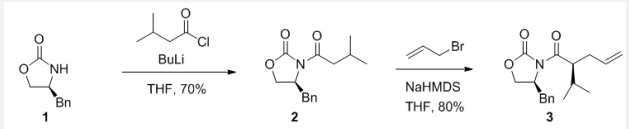

Figure 1

A side project that became of interest due to the potential generation of publications was also investigated. This side project although not in the original proposed request has significant scientific impact and is of mutual interest between Dr. Grubbs and Dr. Rivas. It also served as a contribution to Dr. Grubbs laboratory in return for allowing Dr. Rivas to use the research facilities and chemical supplies. In retrospect, the other goals of the sabbatical require a longer period to be completed. They will become part of the future research goals.

I am very thankful to Chicago State University and his administration for allowing me to have the experience to perform research during the sabbatical period. I am also thankful for my colleagues in the department who cover my other responsibilities while I was away.

Attended Meetings

During the sabbatical period I attended a weekly Research Group Meetings in which different members of the Grubbs group presented their research findings. The meetings were held every Friday at 11:00 am. During the period of the sabbatical I presented my research results from my work at Chicago State University. This consisted of an oral presentation of the research performed at Chicago State University. I also shared with the group members my experiences teaching at a primarily undergraduate institution that serves mostly an underrepresented population in the sciences. At the end of the sabbatical I presented my research results to the Caltech researchers. The attached Power Point slides were used to present and discuss my results. In addition to the research group meeting I also attended weekly Literature Group Meetings in which different members of the Grubbs Group presented various topics from current peer review scientific articles. Caltech is an excellent place to learn about the research that is performed all around the world due to the many scientists that visit the university and share their research results. I also had the opportunity to attend many seminars during the sabbatical period that helped me expand my scientific knowledge of various other research areas.

Research Project I: Studies in Selective Olefin Metathesis using Ru-Based Catalysts

In order to study the selectivity of the Olefin Metathesis reaction a model system was first studied. This model system is similar in complexity and functional group content as the peptides proposed on the sabbatical proposal. Using a model study will allowed for the selectivity studies to be performed without investing significant amount of time on the more complex and time consuming peptide compounds. The findings in this study will then allow the application of the optimized conditions to the synthesis of the stapled peptides proposed on the sabbatical proposal. The compoundselected to study the reaction selectivity was compound 3 shown in Figure 1. This intermediate is also an intermediate toward the synthesis of Aliskiren which is a renin inhibitor for the treatment of hypertension [1]. If successful, the results from this study could also be apply to the synthesis of Aliskiren.

The synthesis of compound 3 started with the acylation of oxazolidinone 1 with the corresponding acid chloride (Figure 1). This step required dry solvents and purification of the acid chloride before the reaction could be performed. The acid chloride was purified by treatment with base followed by filtration through basic alumina. The reaction worked in good yield (70%) and the only by product observed were unreacted oxazolidinone 1. The yield could be improved by further purification of the acid chloride. The acylated oxazolidinone 2 was purified by column chromatography to remove any unreacted oxazolidinone 1. During the next step allyl bromide was used to alkylate acylated oxazolidinone 2 by reacting it first with sodium bis (trimethylsilyl)amide (NaHMDS). The reaction generated the desired product 3 in 80% yield. Purification of compound3 from the starting acylated oxazolidinone was performed by column chromatography. Having compound3 allowed us to study the selectivity of the Olefin Metathesis.

The olefin metathesis requires a catalyst to perform the formation of a disubstituted double bond (e.g. 4) from the terminal double bond found in 3. These compounds with a double bond present are commonly referred to as olefins. This reaction is known as a homo-couplingolefin metathesis since one molecule of 3 has to react with another molecule of 3 to generate compound 4 (Figure 2). This is one of the most challenging olefin metathesis to carry out. The reaction requires concentrated solutions of the reaction in order to speed up the olefin metathesis. This becomes a challenge since a higher concentration means less solvent to properly mix the reactants and the catalyst. In addition, to drive the reaction to completion the CH2=CH2 generated during the reaction has to be remove by evaporation which in turn makes keeping the small amount of solvent present challenging.

The first reaction investigated was the cross metathesis of 3 using the 2nd Generation Grubbs catalyst (Figure 2). This reaction occurred in more than 95% conversion of the starting material 3 when performed using the 2nd Generation Ru-catalyst. The reaction was performed at a concentration of 1 M during 24 hours at 50° C. The starting material, catalyst and solvent were mixed inside a glove box inside a vial equipped with magnetic stirrer and a lid with a Teflon septum. The vial was then taken out of the glove box and placed under an atmosphere of inert gas and heated to 50° C using a silicon oil bath. The reaction progress was monitored using H-NMR by taking aliquots of the reaction mixture using a syringe equipped with a needle. The reaction reached a greater than 95% conversion after 24 hours. The H-NMR analysis indicated that with this catalyst, which tends to be E-selective, the new alkene in 4 was produced as a mixture of isomers (E and Z). The ratio of these two isomers was close to 1:1 with a slight preference for the E isomer. The goal of this study is to identify a catalyst that can perform the formation of the disubstituted double bond with the Z configuration as the major or only isomer. The Z isomer is the most difficult to generate because is the least stable isomer. The Z-configuration will be a desirable configuration to have in stapled peptides to allow the control of the peptide's conformation.

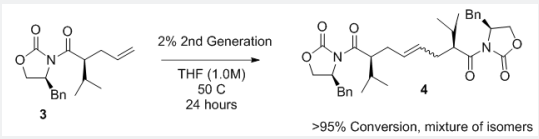

Figure 2

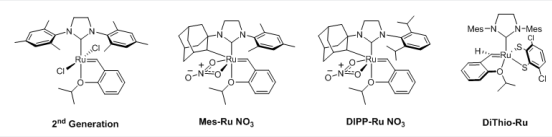

Figure 3

Figure 3 shows the catalysts used during this study. The 2nd Generation Grubbs catalyst is regarded as a better catalyst than its precursor because it tolerates a greater number of functional groups and is more robust in the presence of moisture and oxygen. It has also been demonstrated that this 2nd Generation Catalyst can perform metathesis reactions that do not work well with the 1st Generation Catalyst [2].

Having shown that the reaction of 3 with the 2nd generation catalyst worked, we tried the catalysts that are Z-selective. Catalyst Mes-Ru NO3 has been shown to generate the Z-double bond to generate 6 with 76% of its configuration as the Z-isomer (Figure 4). Using catalyst Mes-Ru NO3 for the olefin metathesis of 3 for 22 hours with the temperature going from 32° to 50° C gave no evidence of product 4 formation. Only the starting material was observed (Figure 5).

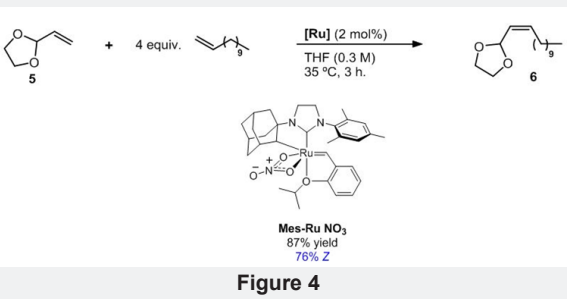

Figure 4

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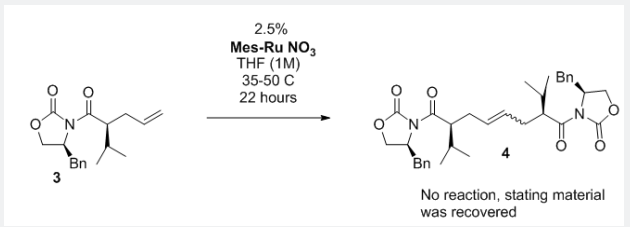

Figure 5

The next catalyst used was DIPP-Ru NO3 which is similar to Mes-Ru NO3 but have a more sterically hindered ligand. This more sterically hindered ligand is expected to slow down the reaction but increased selectivity for the Z-isomer. Unfortunately, the reaction outcome was similar to that of using catalyst Mes-Ru NO3. The starting material was recovered and no evidence of the product was observed. Both Mes-Ru NO3 and DIPP-Ru NO3 appear to be less reactive with 3 than the 2nd Generation Catalyst. This has been observed during the homo-coupling of double bonds with allylic substituents [3-5]. The binding in Mes-Ru NO3 and DIPP-Ru NO3 is different than the binding in 2nd Generation catalyst. The combine effect of different binding and increased steric interactions are believed to be responsible for the change in selectivity from E to Z selectivity.

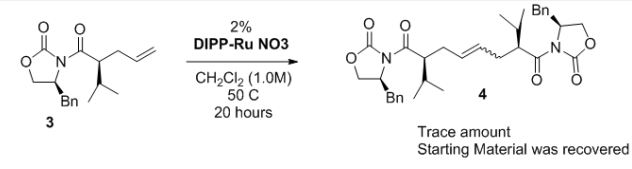

Figure 6

Next, the catalyst DIPP-Ru NO3was studied using CH2Cl2 as a solvent instead of THF (Figure 6). Changing the solvent used for olefin metathesis has been shown to affect the outcome of the reaction. We selected CH2Cl2 as a solvent because of the precedent of using this solvent by Nam and Ko during the synthesis of Aliskiren [1]. In their case the reaction was performed at 40° C for 27 hours with a 0.25 M concentration and the 2nd Generation catalyst. In our study using CH2Cl2 with DIPP-Ru NO3 at 50° C for 20 hours in a sealed vial generated trace amount of the desired product 4. From the trace amount it was not possible to determine the selectivity for the reaction. Studies on this reaction with the Z-selective catalysts give a very slow reaction. This outcome could be explained by the combining steric effects presented by the catalyst and compound 3. The Isopropyl group on compound 3 could be interfering with the mesityl and isopropyl groups found in Mes-Ru NO3and DIPP-Ru NO3.

Because of the low reactivity observed with Mes-Ru NO3 and DIPP-Ru NO3 we decided to look into alternative Z-selective catalyst with a different set of ligands. We try the dithiolate catalyst DiThio-Ru developed by Hoveyda [6]. In this case the catalyst appears to be more active with our compound 3 providing a 40% conversion (Figure 7). The H-NMR analysis of 4 shows signals that correspond to the E-isomer. This is an interesting result since DiThio-Ru is a Z-selective catalyst [6]. The configuration was tentatively assigned as the E based on the similar signals for the major isomer obtained with the 2nd Generation catalyst. The 2nd generation catalyst is E-selective and the major isomer observed for 4 in this study was assumed to be that of the E-isomer. Isolation of the product 4 from the unreacted compound 3 was not possible due to their close proximity during chromatography. Further studies on the isolation of 4 should help determine what the configuration of compound 4 is. The Dithio-Ru catalyst has not been used for the homo-coupling of hindered substrates. There is an example of a hindered allylic substrate that has been used in cross metathesis with an unhindered allylic substrate [6]. In their studies Hoveyda and coworkers observed a 68% conversion for this reaction. The fact that we are observing40% conversion with our reaction despite the increased hindrance in compound 3 is an encouraging result. Further studies with this system will need to be performed in order to improve on the reactivity and selectivity of the reaction.

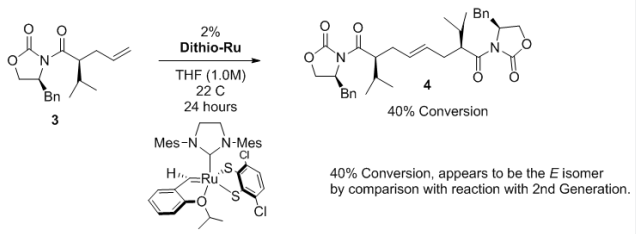

Figure 7

Research Project II: Oxidation of Cyclooctadiene into Cyclooctenone

The oxidation of cyclooctadiene 7into cyclooctenone 8 became of interested during the sabbatical period (Figure 8). Cyclooctenone 8 is the precursor of (Z)-5,5-dimethylcyclooct-1-ene (9, Me2COE) which is the monomer for the synthesis of polyisobutylene polymers (PIB). Polyisobutylene polymers have many industrial applications due to its many desirable properties. PIBs have extremely low permeability, excellent oxidative stability and chemical resistance. PIBs were also shown to be biocompatible and approved by the Food and Drug Administration (FDA) for food-related applications [7]. Recent interest in these polymers as part of thermoplastic polyurethane (PU) elastomers prompted us to investigate the first step to generate 8 in large amounts [8].

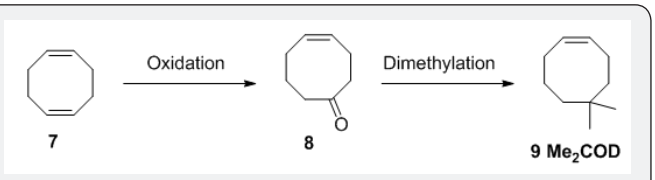

Figure 8

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For the generation of cyclooctenone 8 Rivas investigated the direct oxidation from COD 7. The reaction involves the oxidation of 7 in the presence of hydrogen peroxide, palladium acetate and benzoquinone (Figure 9) [9]. The reaction is a heterogeneous reaction and requires intense stirring and mild heating. The reaction was monitored by H-NMR and after 3-5 days the reaction reached greater than 95% conversion to cyclooctenone 8 as the major product. During the optimization of the reaction Rivas discovered that excess of hydrogen peroxide is needed to force the reaction to completion. Accordingly, the reported procedure was modified to include two additional portions of hydrogen peroxide. This reaction was performed many times before a reproducible result was obtained. In general the product was obtained in 48% to 63% yield. Most of the product was lost during the purification process. The product 8 was purified by a careful distillation under reduced pressure. Because of the viscous nature of the product the distillation under reduced pressure became a challenge. Multiple attempts were performed before suitable conditions were developed for the distillation of 8. At the end pure product was successfully obtained. Initial attempts to perform the direct dimethylation of 8 to generate 9 in one step were not straightforward. Previous syntheses of 9 involved many steps which prevent access to 9 in significant amounts [8]. Additional time is needed to investigate this second step to generate the desired key intermediate 9. A shorter synthesis of 9 from 8 will greatly contribute to the availability of 9 for the synthesis of important polymers with biomedical applications.

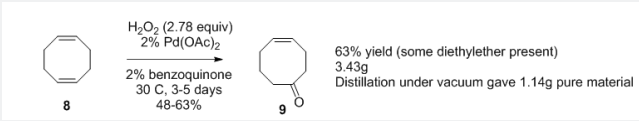

Figure 9

Figure 10

Future Work

Research Project I: Studies in Selective Olefin Metathesis using Ru-Based Catalysts

Future work for in the synthesis of Z-selective alkenes will focus on the cross-metathesis of precursor 3 with less hindered alkenes (Figure 10). A less challenging steric environment is expected to improve the activities of the Z-selective catalysts. If successful, methods to convert the product of this Z-selective reaction into the symmetrical alkene found in 4 could be investigated.

Research Project II: Oxidation of Cyclooctadiene into Cyclooctenone

Future work in the oxidation of cyclooctadiene 8 into 9 will involve further optimization of the reactions conditions such as the catalyst amount, type of catalyst, the type of oxidant, the oxidant addition sequence and improving the purification procedure.

Incorporation of Olefin Metathesis in Organic Chemistry Curriculum

Future plans include addition of laboratory experiments where the students at Chicago State University will be exposed to Olefin Metathesis reactions. Initial experiments will focus on established reactions with known outcomes. As we become proficient at performing the olefin metathesis reactions here at Chicago State University we will try to incorporate more challenging and novel experiments. The students will be experiencing a teaching environment that is closer to that of a research laboratory. This will help encourage students to pursue further studies.

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