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Synthesis of Phenoxides with Pendant Amines and Catalytic Intramolecular Hydroaminations

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Kenneth is a senior Chemistry major who conducted his research under the mentorship of Dr. Stephen Waratuke. He presented his research at the 2008 National meeting of the American Chemical Society in New Orleans. This work is part of an honors thesis which will be defended in April of 2008.

Abstract

One core focus of my research project, (my 2007 summer research) is to make structural analogs of substituted phenols to support the titanium catalysis of organic compounds. The synthesis and study of these and related ligands, (pyrrolyls, aldimines, salens, and other nitrogen/oxygen heterocycles) is a major field of organometallic chemistry. Bulky phenols and their analogs serve as highly effective ligands to support catalysis due to their sterics and electronics.[1] I have been designing and have begun synthesizing phenol analogs using a series of aldol condensations and michael additions and other organic chemistry methodology to generate new substituted phenols. Our method is centered on the synthesis of known phenols and I have worked on the generation of four modified phenols that would represent novel compounds and could serve as ligands to enable transition metal catalysis for a broad range of chemical reactions.[2]

My second core focus has been to develop known and novel phenol compounds to serve as catalysts for a specific type of hydroamination reaction. In my current honors thesis work I am exploring the usage of titanium phenoxide catalyzed intra-molecular hydroaminations of amino alkenes. My progress on phenoxide ligand synthesis, intra-molecular hydroaminations, and their planned combination represent my ongoing exploration of these three phases that has evolved over the last 3 years of my collaborative undergraduate research with Professor Waratuke and my fellow group members. This paper serves as a preliminary report of our work and the prospective of my senior thesis, (Spring 2008).

Introduction

The regio-selective and stereo-selective coupling of organic molecules can often best be achieved at reasonable conditions and yields using early transition metal catalysts which contain bulky electron donating oxygen and nitrogen functionalities. In our research group we are specifically interested in the usage and synthesis of titanium phenoxide type compounds to catalyze a range of hydroamination reactions. The sub-field of asymmetric catalysis within organometallic chemistry has grown substantially over the last decade and has been recognized widely by chemists and science in general as a highly versatile and practical methodology for cleanly synthesizing more complex organic molecules. The 2001 Nobel Prize in chemistry was awarded to Knowles,

Noyori, and Sharpless for their work in the field of catalytic asymmetric synthesis. The products of these types of catalytic reactions can then be used for an entire spectrum of applications ranging from academics to commercial usage as building blocks for other molecules. For example in the pharmaceutical industry, the synthesis of many blockbuster drugs involve multiple synthetic steps and require some type of catalytic methodology to ensure that several key reaction steps generate the correct three dimensional reaction product, (enantiomeric excess), at an acceptable high yield. Often these three-dimensional products and "unwanted by-products" will have vastly different reactivity with biological systems and can be serious health hazards if they are present as impurities in a marketed drug. Many of the recent asymmetric catalysis publications also make note of the sustainable nature of these methods as they often strive to incorporate 100% atom economy into the desired reaction products.

Early transition metals have found utility as powerful asymmetric catalysts capable of yielding more complex organic products with a high efficiency and control. This has been accomplished for a rapidly growing number of titanium and zirconium catalysts supported with pyrrolls, salens, aldimines, and phenols as ancillary ligands.[3] The metal centers are known to be sufficiently lewis acidic to bind with the pi bonds of organic molecules and the lone pairs of oxygen and nitrogen functionalities. In order for the metal center to "perform catalysis" the usage of an ancillary ligand that is sufficiently bulky and electron donating is crucial. A catalyst comprised of the needed arrangement of sterics and electronics will be able to temporarily bind to organic substrates, perform sigma bond formation on the substrates in a highly specific manner, and then release the substrate in order for the catalyst to begin the cycle anew on the next round of substrates. (This is commonly referred to as a catalytic cycle).

Considering the massive complexity of organic molecules and the potential organometallic applications, it is not surprising that no one catalyst can serve all applications. Within very specific sub-applications such as the intra-molecular hydroamination of amino alkenes, even the most promising catalysts range in performance depending on the exact substrate. There is still a great deal of scope to develop catalysts capable of broader usage, catalysts that are more effective for highly specialized usage, and to better understand how these catalysts work on the molecular level.

Background of ligand models and hydroamination chemistry

A large number of Schiff base type compounds have shown significant promise for supporting early transition metal catalysis especially. Of specific interest to our group are the nitrogen and oxygen heterocycle titanium compounds, (Figure 1), that have been found to be especially useful for performing and understanding a range of catalytic hydroaminations of unsaturated compounds with amines. In considering the three titanium compounds, each has multi-dentate electron donating ligands that enable the catalyst and the probable catalytic species of a cycle to fluctuate and enable bond formation and breakage to generate hydroamination products. It is important to realize that the catalyst structures have been drawn using ChemDraw software and do not accurately represent the most correct depictions of these compounds. These structures have been reported in the solid state as X-ray crystal structure and these are contained within the appropriate references. Also of note is that once these catalysts are subjected to solvent, reagents, and begin to perform catalysis, a great deal is unknown about the true nature of the actual structure of these compounds.

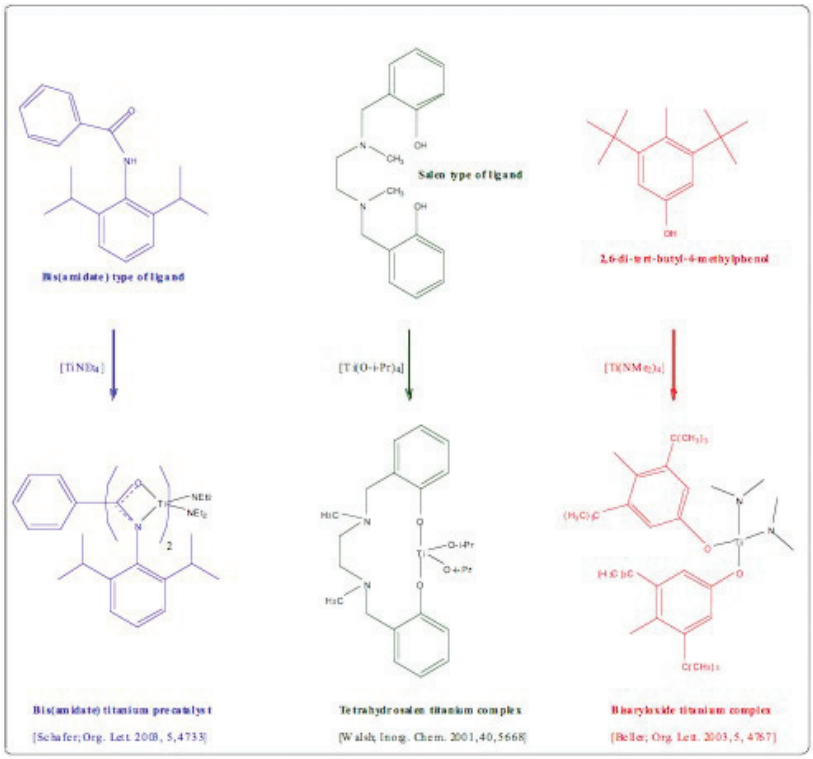


Figure 1 (Examples of nitrogen and oxygen containing ligands bound and unbound to titanium)

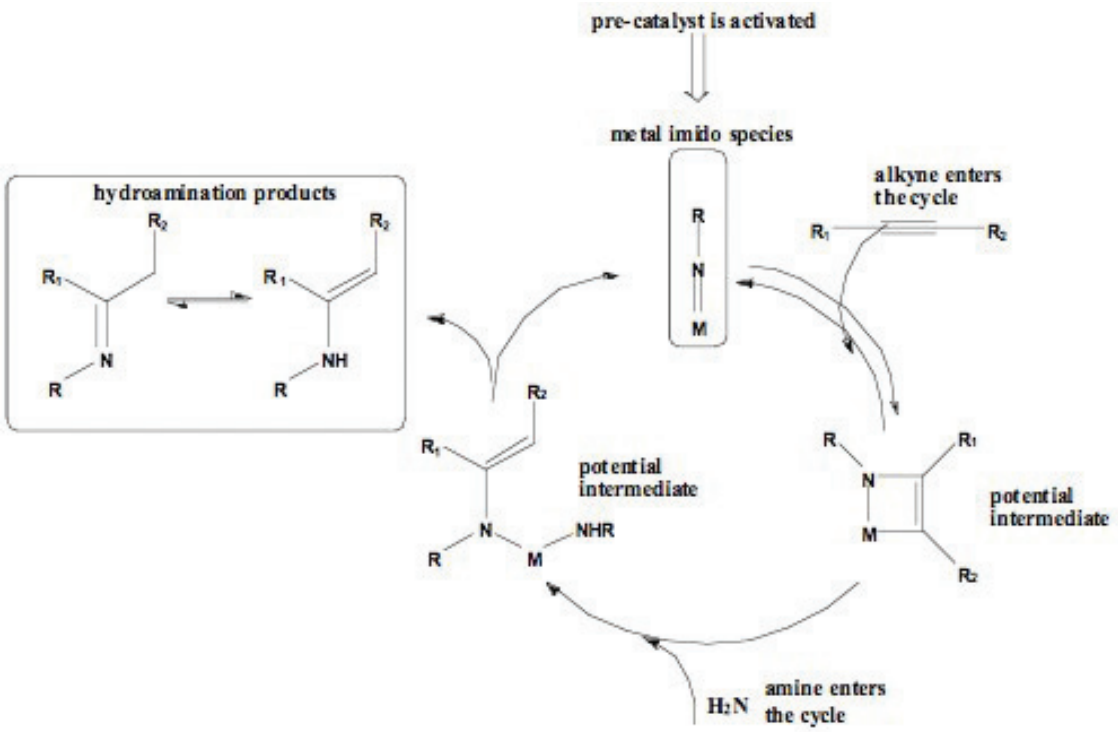


Figure 2 (A general scheme for a [2+2] catalytic hydroamination cycle)

A number of key studies by the groups of Bergman, Beller, Hartwig, Odom and many others have established some of the critical parameters that must be present in order for the above and related titanium catalysts to perform hydroamination reactions.[4] This in turn enables researchers such as us to better understand and design our catalytic reactions. The use of titanium aryloxide as coupling catalysts for alkenes and alkynes was the focus of Professor Waratuke's graduate work[5] and has grown into studying their application towards hydroamination reactions. In a hydroamination reaction, an amine and an unsaturated hydrocarbon are coupled in a specific manner such that a nitrogen of the amine adds to one carbon and a hydrogen of the amine adds to another carbon of the pi bond of the hydrocarbon. In several seminal papers by Bergman, a key imido intermediate, kinetic studies, and support for a [2 + 2] cycloaddition catalytic cycle was presented and is shown below in Figure 2

Results and Discussion

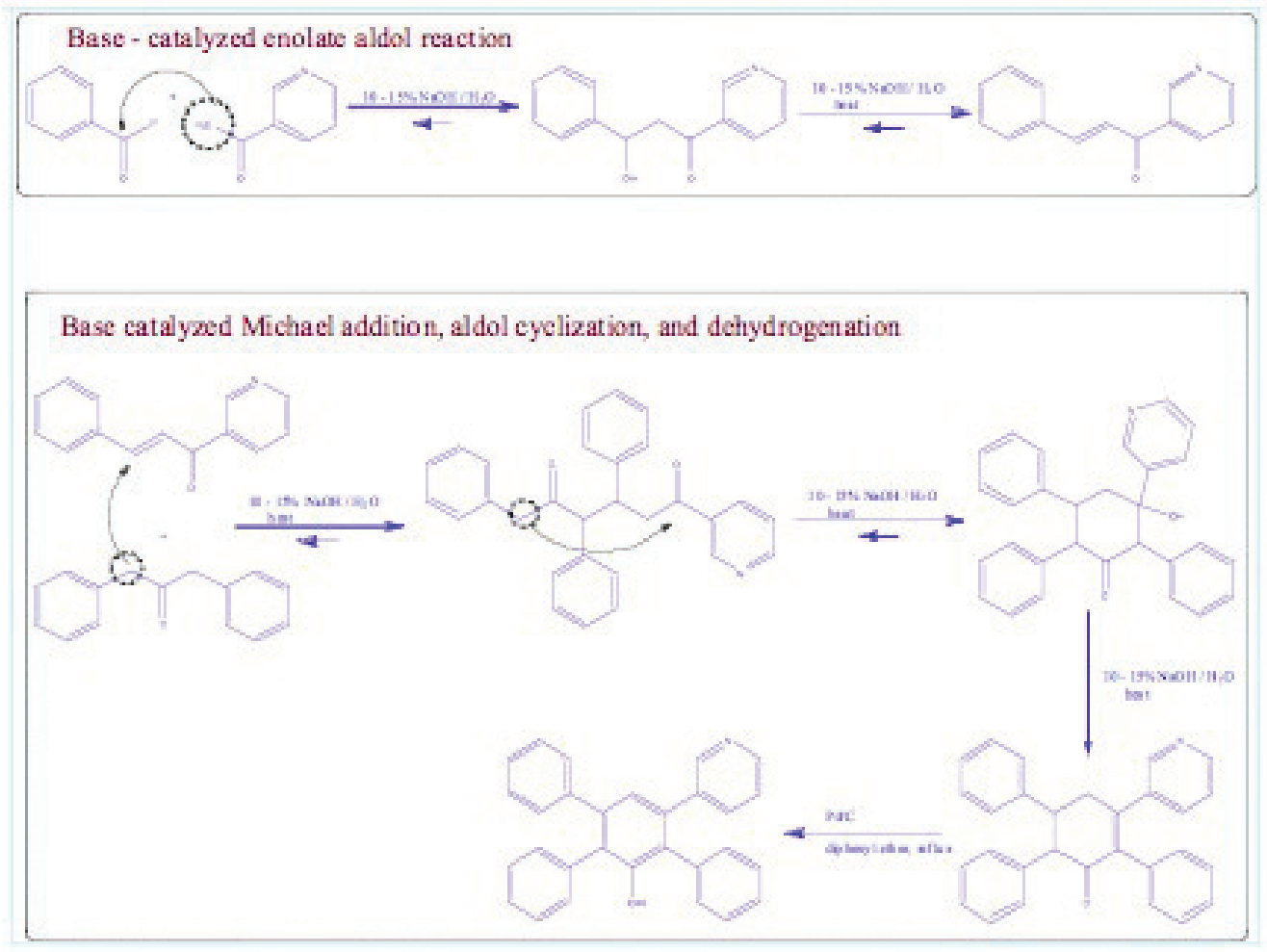
My initial research in the group has been based on making phenols and similar organic compounds (salens and tripodal amines) using standard organic laboratory methods and spectral analysis. This has enabled me to explore the novel synthesis phenol molecules with substituents that have a basic nitrogen functionality. A sterically demanding phenol with a bidentate ability would alter both the overall sterics and electronics of the catalyst and its ability to perform a wide-range of catalysis of organic compounds. There is precedence in the literature for related cyclopentadienyl and indenyl ligands with pendant amine groups.[6] I have been focused on a group of four modified phenol targets each of which share a synthetic approach that is based upon the synthesis of 2,3,5,6-tetraphenylphenol from the literature.[7] The overall synthesis involves aldol condensations and michael addition reactions that are taught in the sophomore organic course and are ubiquitous throughout the organic chemistry literature. An aldol condensation is an organic reaction where an enolate ion reacts with a carbonyl compound to form a β-hydroxyaldehyde or β-hydroxyketone followed by dehydration to a conjugated enone. The result of an aldol condensation is the production of a more complex alpha,beta-unsaturated carbonyl. During this reaction, water is eliminated upon treatment of two

equivalents of a carbonyl with acid or base. A michael addition is the nucleophilic addition of a carbanion to an alpha, beta unsaturated carbonyl compound. This is known as a conjugate addition and is one of the most useful methods for the mild formation of C-C bonds. Having the optimal base concentration and heat conditions will drive the reaction forward. The dilute moderate base NaOH is used with mild heat. In my current project the synthetic mechanism involves a series of steps which are all in equilibrium. By using the optimal base concentration, and isolating the reaction products, the overall reaction synthesis can be pushed forward. In this section, I will present the reaction methodology, analysis data, and the experimentals for these bidentate phenols

Phenoxide Synthesis

In general this reaction begins with an aldol condensation to generate an alpha, beta-unsaturated ketone. The next step involves a base catalyzed michael addition followed by an intra-molecular aldol reaction and base catalyzed dehydration to generate the next intermediate product. This is all done in the same reaction vessel under the same conditions (dilute sodium ethoxide base, ethanol, and heat). Finally, a dehydrogenation in diphenyl ether at elevated temperature using Pd/C is used to generate the substituted phenol. This was performed using 4 different ketones with the goal of generating 4 different bidentate phenoxides. The overall reaction scheme is represented in Figure 3.

Figure 3 (General phenoxide synthesis scheme)



Due to the likely presence of equilibrium species and lack of purification in the early reaction stages, I have had to be resourceful to move these reactions forward for the 4 modified phenols. The procedure used for my experiments was adapted from the text *Introduction to Organic laboratory technique, experiments 41 and 42*. This is the laboratory book used in our current organic Lab courses. The experiment was modified by scaling up forty times and using a variable ketone reagent. This phase of my project is on-going and if completely successful will be incorporated into the catalytic work. The details of the phenoxide synthesis can be found in the contained experimental section.

The catalytic portion of my research project and senior thesis is centered on developing a titanium phenoxide catalyst that will best facilitate the intra-molecular hydroamination reaction in figure 4. There are a range of titanium based catalysts that have been reported in the literature to be effective for these types of aminoalkene substrates.[8]

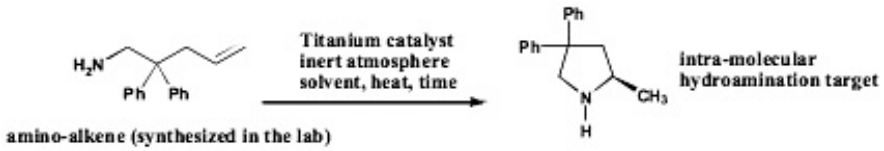


Figure 4 (example of an intra-molecular hydroamination)

The reaction above requires a great deal of preparation and lab work. The aminoalkene reagent and others under consideration require synthesis, the hydroamination reaction protocols must be established, and the product isolation and characterization must take place. I have just completed the synthesis of the 2,2-diphenyl-4-penten-1-amine and will be commencing catalysis studies shortly. The synthesis and spectral data can be found in the experimental section.

Experimental

(For specific spectra data or information please contact Steve Waratuke at swaratuke@bridgew.edu)

The chemical reagents: benzaldehyde, acetophenone, 3-aminoacetophenone, 4-aminoacetophenone, 3-acetylpyridine, and 4-acetylpyridine, as well as ethanol, ether and sodium hydroxide solutions, were purchased from commercial supplies. A solvent purification system was used to store the solvents THF and toluene in a pure form and under reduced pressure. These solvents were further distilled before their use in the reactions. N-butyl lithium solution was purchased as a 1.0 M solution in hexanes. The solutions containing the crude products were concentrated down by the use of a rotor vacuum pump and under reduced pressure. A 400 MHz NMR spectrometer was used to produce ^{1}H and ^{13}C spectra. Most moisture sensitive reactions were performed in a MBraun dry box and/or under a positive argon flow, using a dual vacuum/inert gas line.

Phenoxide constructed of acetophenone and benzaldehyde

Benzaldehyde (6 g, 57 mmol), acetophenone (6.59 mL, 57 mmol) and 32 mL of 95% ethanol were combined in a 250 mL round bottom flask and stirred for 30 minutes. Then 4 mL of a 0.6% w/v NaOH was added to the reaction mixture. A color change was observed from transparent to yellow upon the addition of the base. The reaction mixture was then allowed to sit at room temperature for 15 minutes and 5 mL of ice water added to the vessel. The precipitate formed was filtered by Hirsch funnel filtration techniques, resulting in a crude product yield of 11.09 g. This crude "chalcone-like" compound was put on the Schlenk line overnight to evaporate any residual water. After 24 hours or drying, the mass of the dried product was determined to be 8.86 g. The compound was characterized by Infrared spectroscopy (IR) and Nuclear Magnetic Resonance spectroscopy (NMR).

The next synthetic step involved the preparation of an α,β-unsaturated ketone by the reaction of the previously synthesized "chalcone-like" product with 1,3-diphenylacetone (8.078 g, 38 mmol) in a 250 mL conical flask. 20 mL of absolute ethanol (200 proof) and 10mL of a 2M NaOH solution were then added into the vessel and allowed to gently boil for 15 minutes. The reaction mixture was subsequently refluxed for two hours producing a dark green liquid and a white suspension at the bottom of the flask. After utilizing various crystallization techniques, the total product obtained weighed 15.01 g. However, this product still contained impurities such as carbonates and hydroxides from the original use of NaOH as a catalyst. Acetone was used as a suitable solvent for the extraction of these inorganic impurities. Upon centrifugation, the supernatant was poured off and concentrated by using a rotary evaporator. The mass of the solid purified product was 14.48 g , with a melting point range from 153 °C – 154.3 °C.

Phenoxide constructed of 3-aminoacetophenone and 4-aminoacetophenone and benzaldehyde

benzaldehyde (6 g, 57 mmol), 4-aminoacetophenone (7.7 g, 57 mmol) and 32 mL of 95% ethanol were combined in a 250 mL round bottom flask and stirred for 30 minutes. 4 mL of a 0.6% w/v NaOH was added and the reaction mixture turned slowly from light yellow to a dark red solution (this color change varies with each ketone). Then 10 mL of ice water was added and the crude "chalcone-like" product precipitate was collected by Hirsch filtration to yield 11.65 g of crude chalcone-like product. The α,β-unsaturated chalcone-like product (8.67 g, 38.8 mmol) is then reacted with 1,3-diphenylacetone (8.16 g, 38.8 mmol) in 20 mL of a 200 proof ethanol solution and 10 mL of 2M NaOH. The mixture was then refluxed for 2 hours during which the color becomes a dark green with a solid suspension. Water is then added to increase the amount of crude solid and a series of extractions are done using ethanol and methylene chloride which yields a green powder (0.84 g, 2 mmol) this has been characterized by ^{1}H and ^{13}C NMR.

Phenoxide constructed of 3-acetylpyridine and 4-acetylpyridine and benzaldehyde

Benzaldehyde (6 g, 57 mmol), 4-acetyl pyridine (2.72 mL, 24 mmol) and 32 mL of 95% ethanol were combined in a 250mL round bottom flask and stirred for 30 minutes using a micro spatula. 4 mL of a 0.6% w/v NaOH was added and the reaction mixture turned from yellow into a bright orange liquid. 5 mL of ice water was added into the flask and a cloudy light green precipitate was formed. The crude product was filtered using a Hirsch funnel and the compound had a mass of 11.31 g. This "muddy" chalcone was stored overnight in the refrigerator to facilitate crystallization. The reaction mixture was refluxed for two hours and allowed to cool at room temperature. Instead of a fine crystalline compound, an oily sticky compound was precipitated. Several attempts using extraction solvents such as methylene chloride and other crystallization techniques like the rotary evaporator were unsuccessful. My mentor and I resorted to using a column. A dry product was finally obtained and the mass was determined to be 4.12 g. This was a very low percent yield but was sufficient to continue with the next synthetic step which was reacting this compound with 1,3-diphenylacetone (4.70 g, 22 mmol). 50 mL of absolute ethanol and 2.5 mL of a 2.2 M NaOH were added and the reaction mixture was allowed to reflux for 2 hours then left to cool. The purified product from 3-acetylpyridine (2.986 g, 84% yield) and from 4-acetylpyridine (2.71 g, 76% yield) were extracted by Hirsch filtration and the mass was determined as 1.96 g. This compound was characterized by IR and NMR.

Synthesis of 2,2-diphenyl-4-penetenenitrile

The experiment was scaled down a fourth from the literatures in (Marks, J. Am. Chem. Soc. 2003, 14773). N-butyl lithium (16 mL of a 1.6 M solution in hexanes, 26 mmol) and THF (30 mL) at -78°C under Argon atmosphere were charged into a 250mL Schlenk flask. Distilled diisopropylamine (3.5 mL, 26 mmol) was slowly added to the mixture and stirred for a half hour at -78°C and in a dry ice and acetone bath. Diphenylacetonitrile (4.7 g, 24.5 mmol) was then added and the mixture allowed to warm to 0°C while stirring for an hour. Allyl bromide (4.3 mL, 25 mmol) was then added and the mixture stirred for three hours at room temperature. 25 mL of distilled water was used to quench the reaction and then the resulting phases were separated. Solutions of Et_2O (2 x 25 mL), water (25 mL), saturated aqueous NH_4Cl (2 x 25 mL) and brine (25 mL), were used to wash the organic layer. The final solution was dried over $MgSO_4$, and then filtered by Hirsch funnel technique. The resulting solution was concentrated down under reduced pressure. A crude yellow product of was obtained 2,2-diphenyl-4-penetenenitrile (9.57 g, 41 mmol, 89% yield). This crude product was characterized using a 400 MHz NMR spectrometer to obtain the ^{1}H and ^{13}C spectra. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.7 – 7.3 (m, 10H), 5.8 – 5.6 (m, 1H), 5.2 – 4.9 (d, 2H), 4.0 – 3.7 (d, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 139.6, 131.7, 129.1, 128.7, 127.8, 126.93, 121.85, 120.30, 77.00, 51.61, 43.8 .

Synthesis of 2,2-diphenyl-4-penetene-1-amine

The experiment was scaled down a fourth from the literatures in (Marks, J. *Am. Chem. Soc.* **2003**, *14773).* To a stirred mixture of $LiAlH_4$ (0.4 g, 10 mmol) in Et_2O (20 mL) at 0° C under argon was gradually added a solution of 2,2-diphenyl-4-pentenitrile (9.57 g, 41 mmol) in diethyl ether (Et_2O). The reaction was allowed to warm to room temperature and stirred for five hours. Et_2O (25 mL) was used to dilute the mixture and sequential addition of water (0.5 ml), 15% $NaOH_{(aq)}$ (0.4 ml) and water (2 ml) were used to quench the reaction. The filtrate was dried over anhydrous Na_2SO_4 and the precipitate was filtered off by Hirsch funnel filtration. The resulting solution was concentrated using a rotor vacuum pump. The crude amine (4.72 g, 83% yield) had a characteristic fish-like smell and was colorless oil. A proton and carbon-13 NMR analysis were done for characterization of the product. The NMR solvent used was chloroform-D. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4-7.29 (m, 4H), 7.23-7.10 (m, 6H), 5.48-5.07 (m, 2H), 4.96(d, 1H), 3.37 (s, 2H), 2.06-2.62 (d, 2H), 1.26 (s, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 144.6, 134.1, 128.18, 128.04, 77.31, 77.00, 76.67.

Discussion

The four different precursors to the phenoxide ligands have been successfully synthesized. However, the purity of the products is compromised in the later steps of the synthesis. This has led to the need to use new extraction techniques in order to obtain fine crystals of the desired product. The presence of some impurities is uttered by the formation of an oily suspension. These rudimentary mixtures were obtained in a crude oily form but were however purified by the use of a separating funnel and appropriate solvents such as ethanol and methylene chloride. Hence, my mentor and I have been working on ways to extract the product from these inorganic impurities related to conditions, likely by-products, and reversibility of the overall reaction. We also plan to evaluate other methods of performing the last synthetic step to achieve the aromatic phenols. Subsequently, once the synthesis of these modified phenols has been finished, we intend to react them with titanium tetrachloride in reducing conditions, to generate novel titanium compounds. Future studies would include exploring the catalytic abilities of these new compounds. The intra-molecular hydroamination work that I have begun to work on has proceeded smoothly as I have been able to prepare the aminoalkene 2,2-diphenyl-4-penten-1-amine to serve as a catalytic substrate. I intend to catalyze the cyclization of this aminoalkene using titanium aryl oxides and expand this reaction to consider a range of amino alkenes and phenoxide ligands (off the shelf and novel) catalyzed hydroaminations including intra-molecular hydroamination reactions of amino-alkenes. These catalytic products are of particular interest as they can contain 5 and 6 membered rings that when cyclized by intra-molecular hydroamination have a specific regio- and stereo-selective formation. This enables the clean formation of desirable reaction products and is a highly desirable method sought by the fine chemical and pharmaceutical drug synthesis industries as well as many chemists studying fundamental reaction chemistry.

Acknowledgement

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