

2007

## Hydromination of Alkynes, Enynes, and Dienes Using Titanium Catalysts

Taryn Palluccio

Follow this and additional works at: [https://vc.bridgew.edu/undergrad\\_rev](https://vc.bridgew.edu/undergrad_rev)



Part of the [Organic Chemistry Commons](#)

### Recommended Citation

Palluccio, Taryn (2007). Hydromination of Alkynes, Enynes, and Dienes Using Titanium Catalysts. *Undergraduate Review*, 3, 32-35.  
Available at: [https://vc.bridgew.edu/undergrad\\_rev/vol3/iss1/8](https://vc.bridgew.edu/undergrad_rev/vol3/iss1/8)

This item is available as part of Virtual Commons, the open-access institutional repository of Bridgewater State University, Bridgewater, Massachusetts.  
Copyright © 2007 Taryn Palluccio

# Hydromination of Alkynes, Enynes, and Dienes Using Titanium Catalysts

**TARYN PALLUCCIO**

Taryn Palluccio, from Weymouth, is a senior majoring in chemistry. This project began as volunteer work last year and continued in the summer of 2006 as an Adrian Tinsley Program Summer Grant Project. She and her mentor, Dr. Stephen Waratuke, will continue this work in upcoming semesters and they will present this project at an American Chemical Society conference in Chicago in March 2007. Taryn plans to go on to graduate school.

## Abstract

**H**ydroamination reactions involve the addition of an amine to an alkene or alkyne and are often performed in the presence of a catalyst. The nature of the catalyst can control the selectivity and efficiency of these reactions. A range of catalytic methods exist for achieving hydroaminations. These include late transition metals and even organic catalysts.<sup>a</sup> Early transition metals, including titanium and zirconium, are known to be very active compounds to catalyze organic reactions.<sup>b</sup> As compared with previously successful organometallic catalysts, titanium is less expensive, less toxic, and widely available.

Amines are of much importance due to the many uses of these compounds. They are present in vitamins, medicines, and proteins, and are utilized by the pharmaceutical, agricultural, and textile industries. Synthesis of certain amines can often be difficult, time consuming, and costly. A more efficient and reliable method for creating such compounds would benefit the scientific community.<sup>c</sup> Learning about the reaction mechanisms and catalytic cycle involved in hydroamination can open doors for new chemistry endeavors. The design of new ligands on the catalysts can further improve syntheses and add to the understanding that scientists have about this type of chemistry.

In recent years it has been increasingly significant to synthesize organic molecules, such as amines, in a stereo and regio- specific manner. This means that only one out of several possible products is selectively made. These products often have very different chemical reactivity and pharmacological properties. The winners of the 2005 Nobel Prize in chemistry were awarded for their efforts in this field.<sup>d</sup>

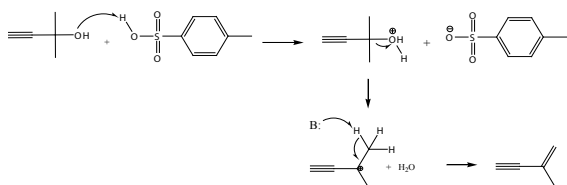
## Results and Discussion

### Catalytic Work

Two titanium aryl oxide catalysts have been synthesized according to literature procedures and used in hydroamination reactions. The aryl oxide type catalysts can be made in high yields by treating a toluene solution of the respective phenol with 0.5 equivalents of  $\text{Ti(IV)Cl}_4$ . The mixture is allowed to stir for 24 hours followed by removal of the toluene solvent by vacuum. The catalysts are moisture sensitive and thus require the use of dry atmosphere techniques.

The structure and geometry of the catalyst are significant in determining its reactivity; the bulky aromatic ligands provide electronic stability for the titanium center and sterically, they create a pocket at the chlorine atoms which is the active sight for catalysis.

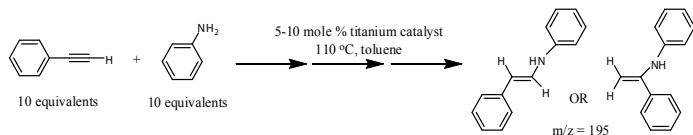
These pre-catalyst species are activated with 2 equivalents of n-butyl lithium. Both chloride ligands get replaced by butanes and reductive elimination forms an unstable titanacyclopropane intermediate. When the amine is added, the ring comes apart and forms a titanium bisamido species which converts to a 16 electron imido complex. This complex is thought to be essential for the hydroamination reaction (Scheme 1).



Scheme 1

### Enyne Synthesis

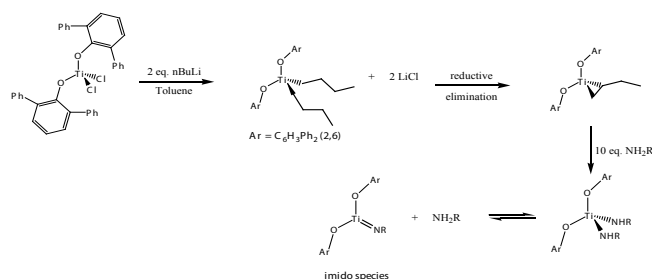
2-methyl-1-buten-3-yne was synthesized according to the literature. The first step involves protonation of the hydroxyl group of 2-methyl 3-butyne-2-ol to make it a better leaving group. This is followed by an E1 reaction where  $\text{H}_2\text{O}$  leaves and a stable tertiary carbocation is formed; a base in solution abstracts a  $\beta$ -hydrogen atom and the lone pair of electrons moves down to form the alkene bond (Scheme 2). My findings were consistent with the literature.



Scheme 2

### The Hydroamination Reactions

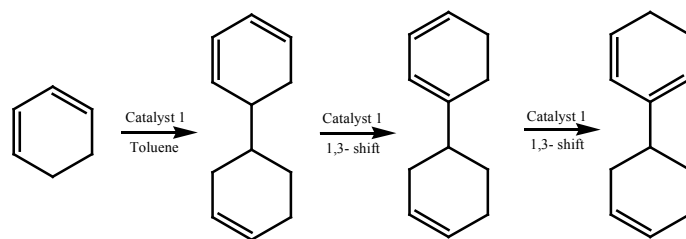
My initial work focused on optimization of alkyne and enyne hydroamination reactions. Variations have been incorporated such as reaction temperature, reagent addition order, and catalyst selection. An example of the standard hydroamination is given below (Scheme 3). Based on the success of the hydroaminations of phenylacetylene and 1-ethynylcyclohexene with aniline, I extended my focus to 2-methyl-1-buten-3-yne as a potential hydroamination substrate, which was not successful. These reactions were monitored using gas chromatography. The product retention times occur at approximately 19 minutes and appear over time as the starting materials are consumed.



Scheme 3

### Catalytic Reactions with 1, 3- cyclohexadiene

The dimerization of 1, 3- cyclohexadiene using  $\text{Ti}(\text{OC}_6\text{H}_3\text{Ph}_2-2,6)_2$  as catalyst occurs quickly at room temperature (Scheme 4). This reaction was monitored by gas chromatography; samples were taken at reaction start, 1.5 hours, and 3 hours. The data shows complete consumption of the diene starting material and the presumed product peak after only 1.5 hours. The product peak has a retention time of approximately 14 minutes.



Scheme 4

A related effort in the laboratory is to probe the relationship between previously observed diene dimerization reactions and potential diene hydroamination reactions. I have begun to explore diene hydroaminations using aryl oxide titanium catalysts. I hope to better understand how subtle changes in the reaction conditions and catalyst might enable a change from no observable reaction to predominantly diene dimerization or to the novel titanium catalyzed diene hydroamination.

Investigation into the hydroamination of 1, 3-cyclohexadiene with aniline reveals no formation of hydroamination products and barely any formation of dimerization products when aniline is added prior to the diene. We observe that these reactions do not compete and we are currently interested in the nature of the presumed inactive metallacycle species.

### Conclusions

The hydroaminations of phenylacetylene and 1-ethynylcyclohexene and the dimerization of 1, 3-cyclohexadiene have been optimized. The hydroamination of 2-methyl-1-buten-3-yne was not as

successful. Due to its extreme volatility, 2-methyl-1-buten-3-yne must be purified and used immediately upon synthesis. I will investigate the use of other enyne substrates and introduce other amine compounds. Isolation of the pure amine and imine products is ongoing. Several techniques were explored but to no avail. Although the literature procedure was followed, I did not have success with the methodology and intend to re-visit this work. Mass spectroscopy will be available in the near future for product characterization.

A promising area of this research is incorporating ligand variations on titanium. I have successfully synthesized and utilized two titanium aryl oxide catalysts. I intend to investigate the use of a third titanium metallacycle species which can be activated without *n*-butyl lithium. This species, if successful, will eliminate any role that *n*-butyl lithium may have on the hydroamination reaction. Insight from this work will allow me to further explore the use of titanium catalysts to hydroaminate alkene and diene compounds.

## Experimental

**General Methods:** All reactions were performed under an argon atmosphere using an MBraun dry box or a dual manifold vacuum/inert gas line. Phenylacetylene, 1-ethynylcyclohexene, and 1, 3-cyclohexadiene were purchased from commercial sources and were flushed with argon and stored over molecular sieves prior to use. Aniline and toluene were distilled under argon and stored over molecular sieves before use. Titanium (IV) chloride was purchased as a 1.0 M solution in toluene and *n*-butyl lithium as a 1.6 M solution in hexanes. The titanium catalysts and 2-methyl-1-buten-3-yne were synthesized according to literature procedures. All hydroamination reactions were monitored by gas chromatography on a Hewlett-Packard 6890 Series gas chromatograph using mesitylene as an internal standard.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR were recorded on a JEOL ECX 400 MHz spectrometer.

**Synthesis of 2-methyl-1-buten-3-yne:** Acetic anhydride (44.43 ml, 0.47 mol), *p*-toluenesulfonic acid monohydrate (3.2 g, 0.017 mol), and a stir bar were added to a 100 ml round bottom flask. The reaction mixture was stirred and cooled in an ice bath followed by slow addition of 3-methyl-1-butyne-2-ol (27.4 ml, 0.28 mol). The initial colorless mixture turns green; it is stirred for several hours and allowed to warm to room temperature. The volatile enyne is distilled from the reaction mixture and shaken with 15 ml of a cold NaOH solution. The organic layer is collected and dried over  $\text{MgSO}_4$ . Short path distillation was performed to afford the pure enyne (colorless oil, 16.1 %, 2.98 g, b.p.  $32^\circ\text{C}$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 5.394 (1 H, d), 5.301 (1 H, d), 2.876 (1 H, s), 1.908 (3 H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 125.97, 123.55, 84.97, 76.2, 23.3.

**Synthesis of  $\text{Ti}(\text{OC}_6\text{H}_3\text{Ph}_2\text{-2,6})_2\text{Cl}_2$ :** In the dry box, a 100 ml Schlenk flask was loaded with 2,6- diphenylphenol (2.5 g, 10.15 mmol), toluene (15 ml), and a stir bar. The flask was sealed, removed from the dry box, and attached to an argon line.  $\text{TiCl}_4$  (5.075 ml, 5.075 mmol) was syringed into the flask, which turns the mixture a deep red color. The mixture was stirred under argon for 24 hours followed by evacuation of the toluene solvent. The product was a dark red crystalline solid obtained in a 98.6% yield (3.05 g).

**Synthesis of  $\text{Ti}(\text{OC}_6\text{HPh}_4\text{-2,3,5,6})_2\text{Cl}_2$ :** In the dry box, a 100 ml Schlenk flask was loaded with 2,3,5,6- tetraphenylphenol (0.558 g, 1.4 mmol), toluene (10 ml), and a stir bar. The flask was sealed, removed from the dry box, and attached to an argon line.  $\text{TiCl}_4$  (0.70 ml, 0.7 mmol) was syringed into the flask, which turns the mixture a deep red color. The mixture was stirred under argon for 24 hours followed by evacuation of the toluene solvent. The product was a red-orange solid obtained in a 104% yield (0.666 g). The excess yield is likely due to unreacted phenol starting material.

**Procedure for the Dimerization Reaction of 1, 3-cyclohexadiene:** In a 20 ml reaction vial  $\text{Ti}(\text{OC}_6\text{H}_3\text{Ph}_2\text{-2,6})_2\text{Cl}_2$  (0.15 g, 0.246 mmol) was dissolved in 5 ml toluene. 2.1 equivalents of *n*- butyl lithium (0.323 ml, 0.517 mmol) were added to activate the catalyst which turns the initial red solution to black. After waiting two minutes, 50 equivalents of 1, 3-cyclohexadiene (1.174 ml, 12.3 mmol) were added to the vial. The vial was capped and allowed to stir at room temperature in the dry box. Samples were taken at reaction start, 1.5 hours, and 3 hours. Reaction progress was monitored by gas chromatography.

**General Procedure for Hydroamination Reactions:** Either aryl oxide catalyst (1 mmol) is dissolved in toluene (10-15 ml) and activated with 2 equivalents of *n*-butyl lithium. A solution of the alkyne or enyne (10 mmol), aniline (10 mmol), and mesitylene (5 mmol) was added to the activated catalyst. The reaction mixtures were stirred in a  $110^\circ\text{C}$  oil bath for 24 hours. The reactions were sampled at reaction start and end time and injected into the GC for analysis.

**Isolation Techniques:** Most of the crude hydroamination reactions were followed up with reduction of the imine species by sodium cyanoborohydride to yield the amine product. This is a standard method from the literature, but still requires refinement of the techniques. TLC was performed on these mixtures with various solvent mixtures including hexanes, methylene chloride, and ethyl acetate. Analysis of TLC bands by GC showed components in the retention time range of the products. The remaining reactions were filtered through silica gel and distilled under reduced pressure in an attempt to isolate the imine species initially formed in the catalytic reactions.

## Acknowledgements

I would like to thank the Adrian Tinsley Program for Undergraduate Research for funding this project and my mentor, Dr. Stephen Waratuke for his help and encouragement.

---

## Endnotes

### a

a) T.E. Muller, M. Beller; Chem. Rev. 1998, 98, 675. b) F.J. Sardina, H. Rapoport; Chem. Rev. 1996, 96, 1825. c) H.U. Blaser; Chem. Rev. 1992, 92, 935. d) J. Louie, M.S. Driver, B.C. Hamann, J.F. Hartwig; J. Org. Chem. 1997, 62, 1268. e) L.S. Hegedus, B.M. in Trost, I. Fleming; Compr. Org. Synth. 1991, 4, 551. f) C.G. Harthung, A. Tillack, H. Trauthwein, M. Beller; J. Org. Chem. 2001, 66, 6339

### b

a) P.J. Walsh, A.M. Barranger, R.G. Bergman; J. Am. Chem. Soc. 1992, 114, 1708. b) Haak, E.; Bytsovskov, I.; S. Doye; Angew. Chemie. Int. Ed. 1999, 38, 22, 3389. c) C. Lorber, R. Choukroun, L. Vendier; Organomet. 2004, 23, 1845. d) J.S. Johnson; R.G. Bergman; J. Am. Chem. Soc. 2001, 123, 2923. e) C. Cao, Y. Shi, A.L. Odom; J. Am. Chem. Soc. 2003, 125, 2880. f) Y. Shi, C. Cao, A.L. Odom; Inorg. Chem. 2004, 43, 1, 275. g) Y. Li, Y. Shi, A.L. Odom; J. Am. Chem. Soc. 2004, 126, 1794

### c

a) S. A. Lawrence; Amines: Synthesis, Properties and Applications. Cambridge University Press, Cambridge, UK 2004, (0-521-78284-8). b) A. Ricci; Modern Amination Methods. Wiley-VCH, Weinheim, 2000, (3-527-29976-9)

### d

a) Chemical & Engineering News: Cover story – Olefin Metathesis, December 23, 2002, Vol. 80, Num. 51. b) K. C. Nicolaou, S. A. Snyder; Classics in Total Synthesis II, VHC, Weinheim, 2003. c) W.S. Knowles and M.J. Sabacky, Chem. Commun., 1445 (1968). d) Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi and R. Noyori, J. Am. Chem. Soc. 102, 7932 (1980). e) T. Katsuki and K.B. Sharpless, J. Am. Chem. Soc. 102, 5974 (1980).