Cope-Type Hydroaminations of Alkenes and Alkynes

Yexenia E. Nieves-Quinones
Advisor: Dr. Daniel Singleton
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Hydroaminations of alkenes and alkynes is one of the simplest and most desired synthetic transformations. However, no general method to achieve this has been developed. This chemical transformation consists of the direct formation of a new C – N bond by addition of an amine to an unsaturated C – C bond. For many years, researchers have focused their attention into the development of new methods to accomplish this transformation to access the synthesis of nitrogen containing molecules. Acid and base catalyzed reactions have been used for this purpose. Also, transition metal catalysis has been used in order to activate unsaturated C – C bonds for this transformation. Nonetheless, the reactions that are tolerated by these methodologies are very limited and have low stereoselectivity. For the metal catalyzed reactions, high sensitivity to air and moisture has been observed. In order to overcome these limitations, many researchers continue to explore this area.

In 1976, House and co-workers made an interesting discovery; they observed that a classical reaction, known as the Cope elimination, had gone backwards. In the reaction shown in Figure 1, the formation of the pyrrolidine was the reverse of a Cope elimination, this is referred to as a Cope-type hydroamination. A Cope elimination reaction consists of the syn elimination of tertiary amine oxides to afford an alkene and a hydroxyl amine. The mechanism for this transformation has been well studied and is known to proceed via a concerted pathway with a cyclic 5-membered transition state (Figure 2). This new observation caught the attention of many scientists, who have studied toward the substrate scope, solvent and substituent effects, and also the mechanism for this reaction. The first proposed mechanism for this transformation, proposed by House, suggested that it proceeded via a radical pathway. Later, in the early 90’s, another mechanism was proposed suggesting that the reaction proceeded via a concerted, synchronous mechanism with a 5-membered transition state (Figure 2). This mechanism was based on results reported by Black, Doyle, Ciganek and Oppolzer.

Figure 1: First reported reverse Cope-elimination
After this discovery, a significant amount of studies have been done in order to understand the behavior of this transformation and develop applications for this technique. Recently, a series of competition experiments, and computational studies have being carried in order to understand how substitution, tether length, stability, and strain of the substrates can affect the products and the rate of the cyclization process. In this work, Holmes and Houk, demonstrated that the reactivity and major product of a reverse Cope-elimination can be affected by: the tether length and the substituents present on the distal carbon of the alkenes (Figure 3). Computational studies demonstrated that the conformation of the tether length in the transition state is the factor that determinates the major product for this transformation. Also, it was concluded that the reactions proceeds via a concerted 5-membered, planar transition state, rather than a radical pathway.

The increased interest in finding applications for this new approach lead Beauchemin and co-workers to develop a methodology that allowed them to perform intermolecular Cope-type hydroaminations. Recently, an extensive experimental and computational study by Beauchemin demonstrated that this transformation could also be used for intermolecular hydroaminations of alkenes and alkynes. In this work, they found that the reactivity of alkynes was higher than that of alkenes. The experimental results showed that the reactivity of the unsaturated compounds was highly dependent of their stability, and that solvents also affected the rate and yield for these reactions. Computational results demonstrated that the polarity of the solvent has a huge impact in the rate of the reaction and that the proton transfer step was, in fact, the rate limiting step for the alkenes hydroamination.

Extended studies also lead to the development of an aldehyde catalyzed intermolecular Cope-type hydroamination. In this work, Beauchemin and co-workers developed a catalyzed reaction that was described as partially intramolecular. Kinetic experiments were developed in order to determine the catalytic cycle for this process. Through these experiments it was
determined that the hydroamination is the rate-limiting step of the process; that there is a resting state for the catalyst, and also, that catalyst inhibition is a competitive process.

Due to some limitations presented by the Cope-type hydroamination methodologies discussed, another method was developed. Recently, hydrogen bonding directed Cope-type hydroamination was reported.\textsuperscript{14} It was seen that it lead to stereoselective reaction products and that milder reaction conditions could be used. Some experiments were developed in order to determine the charge distribution in the transition state for this process.

Development of new methods and applications for this reaction continues. The synthesis of ketonitriles,\textsuperscript{15} 3,5-disubstituted isoxazoles,\textsuperscript{16} 3,5-disubstituted pyrazoles,\textsuperscript{17} and some other compounds, using allenes\textsuperscript{15} and 1,3-dialkynes\textsuperscript{16,17} with this methodology has been recently reported. Also, the use of hydrazines for this transformation has been developed.\textsuperscript{18,19,20}

References: