Recent Developments in Aliphatic C–H Azidation of Complex Molecules

Reported by Martin Garcia Chavez 12/12/2017

Introduction: Organic azides are prevalent in organic synthesis, chemical biology, and the pharmaceutical industry.[1] This is primarily due to their ability to serve as versatile intermediates for rapid conversion to functional groups including amides, amines, and triazoles. As a result, many azidation reactions have been developed in order to access azides from various functional groups such as alkyl halides, epoxides, and alkenes.[1] Unfortunately, these methods often require harsh conditions that limit their utility in complex molecules. In order to alleviate these issues chemists have employed directed and non–directed C–H functionalization strategies as a way to functionalize unactivated C–H bonds. Directed methods have been successful in the formation of C–N bonds (and in the ultimate installation of a C–N_3 bond), but they require the pre-functionalization of the substrate, and a directing group that can be problematic to remove. Non–directed methods can introduce azides without the pre-functionalization of the substrate or a directing group, which is advantageous in the derivatization of complex molecules.

Manganese-Catalyzed Azidation: Groves and coworkers recently reported a manganese-catalyzed C–H azidation that is applicable to complex molecules. Utilizing aqueous sodium azide and two different manganese catalysts (Mn(TMP)Cl or Mn(salen)Cl) Groves selectively introduced an azide into secondary, tertiary, and benzylic C–H bonds.[2] Noteworthy is the successful application of this method to arteminisin, a sesquiterpene lactone **(Figure 1)**. Furthermore, the azidation of arteminisin was performed without destruction of the reactive *endo*-peroxide bridge highlighting the mild conditions of this method.

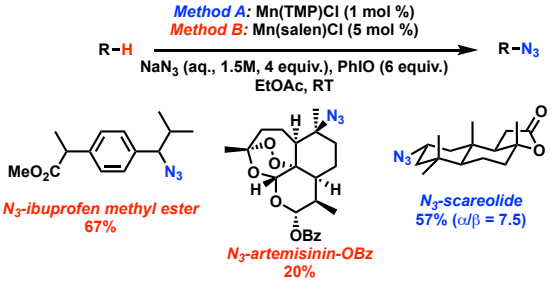

Figure 1. Successful Azidation of Complex Molecules.

Iron-Catalyzed Azidation: Concurrently, Hartwig and coworkers developed a complementary method for the azidation of tertiary C–H bonds in complex molecules. This method utilizes $Fe(OAc)_2$ as the catalyst along with a hypervalent iodine reagent and a tridentate PyBox ligand (**Figure 2**).[3] In addition to the mild conditions, this method provides two clear advantages over the manganese-catalyzed azidation: 1) the elimination

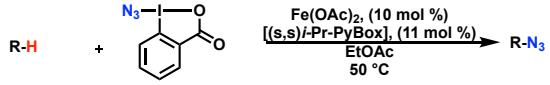

Figure 2. Iron-Catalyzed Azidation Conditions.

of the oxygenation byproducts that are observed in the Groves azidation method, and the ability to use lower catalyst loadings.[4] Hartwig and coworkers demonstrated the utility of this method utilizing the azide group as a precursor that can be converted into a variety of functional groups (**Figure 3**).[3] For example, the azide–alkyne Huisgen cycloaddition reaction allowed attachment of a fluorescent tag to a gibberellic acid derivative **(Figure 3)**. Also, a biotin tag was attached to a podocarpic acid derivative illustrating the possibility to use this method as a way to purify complex natural products along with their biological target. The ability to attach these two tags opens the possibility of being able to utilize this method in the identification of targets in biologically active molecules.

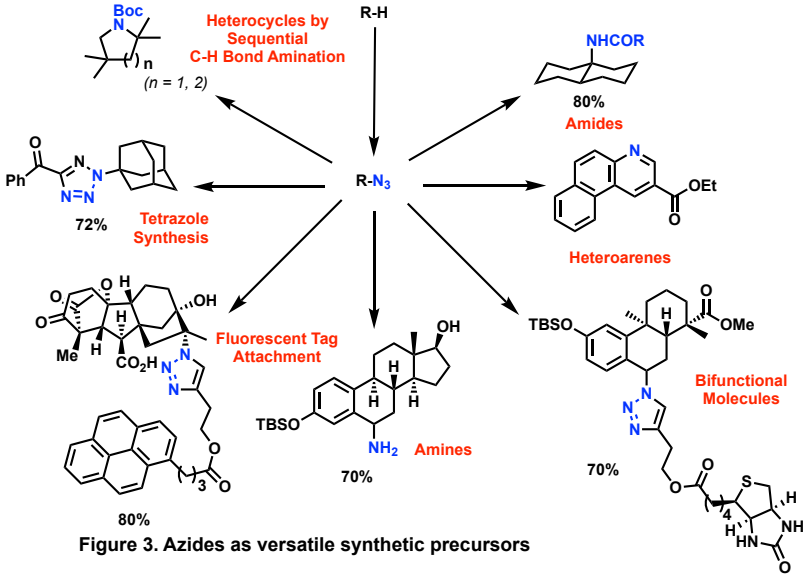

Figure 3. Azides as versatile synthetic precursors

<u>Iron-Catalyzed Trifluoromethylazidation</u>: Hartwig and coworkers also developed a method for the difunctionalization of olefins in complex natural products with CF_3 and azide groups. This method utilizes $Fe(OAc)_2$ as the catalyst along with a hypervalent iodine reagent, $TMSN_3$ and a tridentate PyBox ligand (**Figure 4**).[4] This method allows for the incorporation of two different groups that have the ability to modulate the bioactivity of complex molecules.

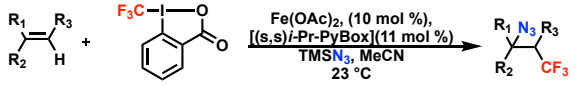

Figure 4. Iron-Catalyzed Trifluoromethylazidation Conditions.

<u>Conclusion:</u> The Groves and Hartwig groups are pioneers in the field of non–directed aliphatic C–H azidation. While certain advances in selectivity are needed, the application of this method as a way to install a point of attachment for further derivatization is particularly promising.

<u>References</u>: 1) Brase, S. *et al*. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188. 2) Huang, X. *et al*. *J. Am. Chem. Soc.* **2015**, *137*, 5300. 3) Sharma, A. *et al*. *Nature* **2015**, *517*, 600. 4) Kamirov, R.R. *et al*. *ACS Cent. Sci*. **2016**, *2*, 715.