Skeletal Surgery: Recent Advances in Molecular Editing Methodologies

Reported by Danielle Loving April 12, 2022

Introduction

Molecular editing, defined as the insertion, deletion, and exchange of atoms, has emerged as a new, rapidly advancing field. While these types of transformations were reported in the 1800s,[1] renewed interest in this field arose due to pressure from pharmaceutical industry leaders wanting to accelerate drug discovery campaigns.[2] This class of transformations has the potential to provide both atomic tuning of bioactive molecules and alternative retrosynthetic planning. This literature seminar aims to highlight the advances in heavy atom manipulation methodologies and highlight their utility in the contexts of both complex molecule total synthesis and medicinal chemistry campaigns.

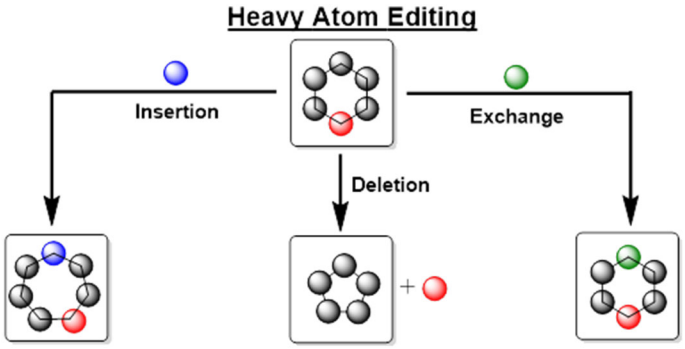

Figure 1: Heavy Atom Editing Classifications

Heavy Atom Insertion

Classical heavy atom insertion reactions, such as the Baeyer-Villiger oxidation, are widely utilized within synthetic chemistry. The development of new carbonyl-mediated carbon insertion methods and, more recently, expansion into non-carbonyl mediated transformations have been achieved. One highlighted example (Figure 2) involves the single carbon insertion into indoles and pyrroles to generate quinolines and pyridine rings.[3] Utilization of stable chlorodiazirines carbene precursors allows this method to occur under milder conditions, enabling derivatization of sensitive bioactive molecules. Furthermore, biocatalytic single carbon insertion into aziridines,[5] and single nitrogen insertion alkenes[6] have been developed, greatly expanding the suite of heavy atom insertion methodologies.

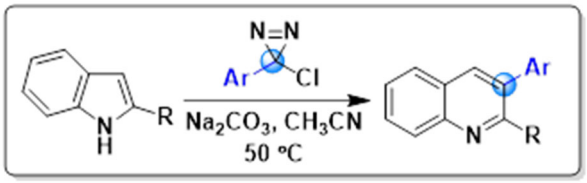

Figure 2: Single carbon insertion into indoles

Heavy Atom Deletion

The complete extrusion of a single atom was achieved in 1959 with the deletion of nitrogen from secondary amines to construct Csp^3-Csp^3 bonds.[7] However, poor functional group tolerance prevented widespread utilization of this reaction. The Levin laboratory overcame this shortcoming by utilizing anomeric amides to effectively remove a single nitrogen from secondary amines and construct Csp^3-Csp^3 bonds (Figure 3).[8] This strategy was utilized to enable skeletal remodeling of numerous cyclic and acyclic simple feedstock amines and complex bioactive compounds. Further heavy atom deletion methods have emerged, allowing for the deoxygenation of benzylic ethers[9] and single carbon deletion from N-heterocycles.[10]

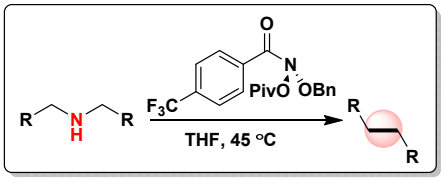

Figure 3: Nitrogen deletion of secondary amines

Heavy Atom Exchange

Synthetic strategies that perform single atom exchange within a limited number of steps were limited in the literature despite their potential to significantly accelerate the fine-tuning of lead pharmaceuticals and mechanism of action studies of bioactive molecules. To fill this gap, the Morofuji laboratory utilized a simple ring opening/closing sequence to afford the simple conversion of pyridine rings to anilines.[11] Additionally, by developing a novel nickel catalyzed decarbonylation of lactones, the carbon-to-oxygen conversion was developed via a three-step reaction sequence (Figure 4).[12]

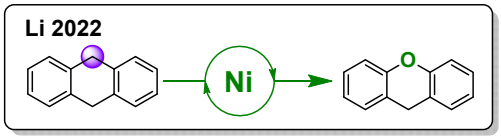

Figure 4: Carbon to oxygen exchange

References:

1. Baeyer, A. Villiger, V. *Ber.* **1899**, *32*, 3625
2. Blakemore, D. et al. *Nature.* **2018.** *10,* 383-394
3. Levin, M. et. al. *J. Am. Chem. Soc.* **2021**, *143* 11337– 11344
4. Arnold, F. *J. Am. Chem. Soc*. **2022**, *144*, 4739−4745
5. Cheng, X. et. al. *Nat. Comm.* **2022** 13 (425)
6. Hamm, K. *J. Am. Chem. Soc.* **1959**, *81*, 3294- 3297
7. Levin, M. et. al. *Nature* **2021**, *593*, 223-227
8. Shi, Z. et. al. *J. Am. Chem. Soc.* **2017***, 139,* 19, 6546–6549
9. Sarpong, R. et. al. *Nature* **2018**, *564,* 244-248
10. Morofuji, T. et. al. *Org. Lett* **2021**, *23,* 6126-6130
11. Li, J. et. al. *Chem. Sci.* **2022**, *13,* 1095-1100