Selective Metal-Mediated C-C Bond Activation of Strain Compounds: Application to Challenging non-Natural Product Synthesis

For the last few decades, organic chemists have spent much effort in developing efficient methods for the stereoselective construction of carbon-carbon and carbon-heteroatom bonds. One of the many applications of these developed methods could be the synthesis of complex natural products, which remains one of the most exciting and daunting endeavors in organic chemistry. However, unconventional non-natural products such as A and B are similar to natural products syntheses; it requires not only a broad knowledge of chemistry but also inspiration, dedication, patience, innovative ideas, and creativity.

The research group of Professor Marek at the Technion-Israel Institute of Technology has been immersed in this endeavor for the past decade and is continually developing new strategies and methods to solve synthetic problems in an efficient and elegant way. However, some molecular frameworks are still extremely challenging to prepare in a practical and efficient way using our currently available chemical synthetic methods. This includes the preparation of chiral deuterated neopentane (A), which is a saturated hydrocarbon that represents the archetype of a molecule where the chirality is based on the dissymmetric mass distribution (hydrogen versus deuterium). The synthesis of such entity would underline the relationship between macroscopic chirality and the art of organic synthesis.\(^1\) To reach such small but sophisticated molecule, one has to address the leading question of the 21\(^{\text{st}}\) century in organic synthesis: “how to perform synthesis efficiently using the fewest number of steps and functional group interconversions”.\(^1\) While many approaches in synthesis have taken advantage of the synthetic tools that are available for C-C and C-heteroatom bond formation, distinctly missing from this list are the methods based on a combination of both C-H and C-C bond activations.\(^1\) We believe that the combination of C-H bond and selective C-C bond activations in a single-pot reaction could offer an unusual, yet effective, approach to the synthesis of complex molecular architecture. Our approach was
therefore aimed to eventually set the stage for eventual applications to complex molecule synthesis.

Similar to metal-catalyzed activation of C-H bond, the C-C bond activation is a subfield of chemical synthesis that is of current interest since it can lead to the design of new, selective and efficient processes utilizing hydrocarbons. Although the activation of C–C single bonds of strained rings (e.g., cyclopropanes) is a known process, stereoselective carbon-carbon bond activation using transition metal catalysts has only recently emerged as an efficient tool for the synthesis of valued-added products\(^2\).

In this context, during my Ph.D. thesis, I developed a new, elegant and efficient zirconocene-mediated methodology of ring opening reaction of three membered-rings of alkylidenecyclopropane under mild conditions through a unique combination of allylic C-H bond activation reaction followed by a selective C-C bond cleavage to give bismetallated allyl-alkyl zirconocene species that selectively react with two different electrophiles with high regio- and diastereoselectivity (Scheme 1).\(^1\)

Accordingly, I was heavily engaged in the elucidation of this intriguing reaction where an organometallic species “walk” -through allylic C–H bond activations- along the carbon chain of \(\omega\)-ene-cyclopropanes (cyclopropane species possessing a remote double bond) to finally activate the C-C bond to give the bifunctional nucleophilic species that is further derivatized with two different electrophiles (Scheme 2). This “magic” transformation could be used to prepare synthetically challenging all-carbon quaternary stereocenters in acyclic systems (this work has been published in *Nature*).\(^1\)
Finally, we have applied this strategy to the easy preparation of challenging enantiomerically enriched all-carbon stereogenic centers in acyclic systems such as the simplest enantiomerically enriched saturated hydrocarbons with a quaternary stereogenic center, the (2S)-4-ethyl-4-methyl octane B and (S)-[\(^2\)H\(^1\), \(^2\)H\(^2\), \(^2\)H\(^3\)]-neopentane A, which then was fully characterized by a unique D-NMR method using chiral liquid crystals and VCD spectroscopies (this work has been submitted to Science).\(^3\)

In the course of this research, we have also developed a simple and selective metal-catalyzed ring-expansion reaction of substituted alkylidenecyclopropanes into enantiomerically pure cyclobutene derivatives possessing quaternary stereogenic centers (Scheme 3).\(^4\)

Alkylidenecyclopropanes (ACPs), highly strained but stable molecules, have been extensively studied for many years. They are of synthetic interest due to the multiple possibilities for reaction of the three strained bonds in the cyclopropane ring and of the exocyclic double bond.
However, despite this growing interest, very few methods for the synthesis of optically active alkylidenecyclopropanes were developed. In this context, we have reported the preparation of enantiomerically pure ACPs 2 upon the copper – catalyzed addition of Grignard reagent to 1 as well as the preparation of heterosubstituted ACPs 3 and 4 from 1 through a [2, 3]- (path a) and [3, 3]-(path b) heteroatom sigmatropic rearrangement. For an easy preparation of enantiomerically pure alkylidenecyclopropanes 2, 3 and 4, one should start from enantiomerically pure cyclopropenylcarbinol 1. Therefore, we have also developed a kinetic resolution to obtain 1 in high enantiomeric excess (Scheme 4).

Scheme 4. Different reactions for the preparation of ACPs possessing a quaternary stereocenter.

In conclusion, during my PhD thesis, I could design a powerful approach to various enantiomerically pure alkylidenecyclopropane species that were successfully used to develop the combined allylic C-H and selective C-C bond activations. This approach, mediated by the presence of a unique organometallic species, could lead to the preparation of all-carbon quaternary stereocenters in acyclic systems. As an application of our strategy, the synthesis of (S)-$^{2}^{2}^{2}$H1, $^{2}$H2, $^{2}$H3]-neopentane A was achieved.

References:


