Synthesis and Reaction of Medium-sized Cyclic Alkyne Having Endocyclic Nitrogen Functionality at The Propargylic Position

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SYNTHESIS AND REACTIONS OF MEDIUM-SIZED CYCLIC ALKYNE HAVING ENDOCYCLIC NITROGEN FUNCTIONALITY AT THE PROPARGYLIC POSITION

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Summary

In this PhD project, novel cyclic alkene and alkynes having endocyclic heteroatoms were designed and synthesized. Particularly, cyclic alkynes having endocyclic nitrogen functionality at the propargylic position were synthesized with Nicholas reaction, and well studied their stereochemistry and reactivity. In the chapter 2, stereoselective multimodal transformations of planar chiral amide promoted by Lewis acid activation their heterofunctionality or *E*-alkene moiety were described to afford a variety of carbon central chiral molecules in stereospecific manner. BF_3•OEt_2 and $TiCl_4$ are efficient for activation of heteroatom prior to *E*-alkene and resulted in the ring opening and sacrificing the stereoselectivity during the transformation. In contrast, the Au(I), Bønsted acid, positive halogen preferentially activatied *E*-alkene moiety and resulted in poly cyclic amide in stereospecific manner.

In the Chapter 3, the medium-sized cyclic enyne having endocyclic nitrogen functionality at the allylic propargylic position was designed and synthesized by means of Nicholas cyclization as a key reaction. The nine-membered cobalt complex synthesized shows the dynamic planar chirality and their enantiomers could be separated by chiral HPLC. However, the nine-membered allylic propargylic nitrogen-embedded cyclic enyne has excessive reactivity and caused Cope rearrangement to afford undesired allene in excellent yield by removal of cobalt moiety. In sharp contrast, the expanded ten-membered allylic propargylic

nitrogen-embedded cyclic enyne were successfully synthesized and exhibited reasonable dynamic planar chirality.

In the chapter 4, double Nicholas reaction of 2-butyne-1,4-diol derived cobalt-complex, followed by removal of cobalt moiety were successfully developed for an efficient synthesis of cycloalkynes having endocyclic heterofunctionalities at the both of propargylic positions. The structural and spectroscopic analysis show the propargylic heteoatoms not only significant affect the structural feature of cycloalkyne, but also raise high reactivity of the alkyne moiety. The kinetic study reveals nitrogen or oxygen embedded cycloalkynes possess much higher reactivity than a reported cyclooctyne derivative along with the thermal stability. Finally, their diverse functionalization followed by the catalyst-free Huisgen-reaction are achieved, which supports their highly potential utility in the field of bioorganic chemistry as ligation tool.

In the chapter 5, stereochemical behavior and transformation with electrophilic addition reactions of cycloalkynes having endocyclic nitrogen functionality at the propargylic position were investigated. As a result, novel planar chiral cyclophyne was established and a variety of planar chiral *E*-cycloalkenes were synthesized based on the *anti*-selective halogenation reactions from nitrogen-embedded medium sized cyclic alkynes. Furthermore, novel ring contraction reactions by means of halogenation with AcOH, TsOH, $(PhO)_2POOH$ and so on were developed.

In summary, this PhD project achieved to develop new chemistry on the basis of unique reactivity and stereochemical behavior of medium-sized heterocyclic alkene and alkynes, in particular, having nitrogen functionality at propargylic position along with their facile synthetic method. It is expected that these results will be exploited and utilized in structural chemistry, synthetic chemistry and bioorganic chemistry.