Development of radical based synthetic strategies for the total synthesis of natural products and Posttranslational modification of proteins.

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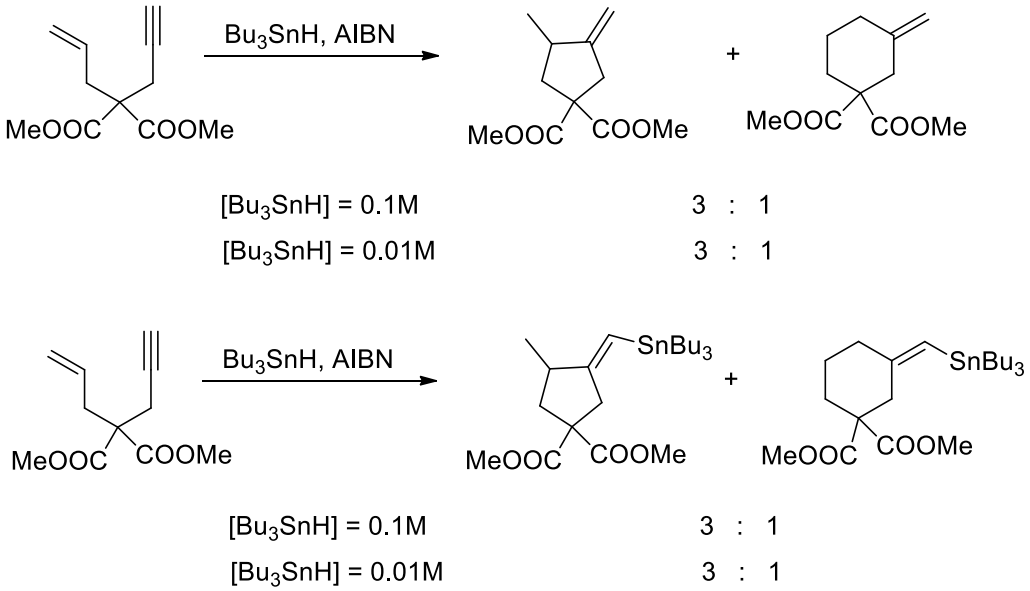
Though the "art" of organic synthesis was considered to have achieved the total synthesis of any given molecule, the goal of organic synthesis of the 20th century[1], organic synthesis in the 21st century faced new challenges as green chemistry became the main subject of chemical processes.[2] As the result, the "ideal synthesis" immerged as an important aim of organic synthesis,[3] and various guidelines and criteria including development of efficient synthetic strategies were introduced toward achieving a significant aspect of the ideal synthesis.[4] Toward this goal, various aspects of economy of the synthesis have become the measures of efficiency of synthetic routes to complex targets.[5] These objectives are also in accord with the principles of green chemistry.[6] Multistep reactions in one synthetic operation[7] are known as tandem, domino and cascade reactions. They satisfy the objectives of ideal synthesis and the principles of green chemistry. The reactions not only construct complex structures in a single operation but also eliminate isolation and purification steps of the intermediates. A reactive intermediate with good control of the reactivity could serve the purpose of these multistep reactions in one operation as the reactive intermediate could form another reactive intermediate after the first reaction. Free radical would be an ideal candidate since it is so reactive that often times it is difficult to control the reactivity of the free radical though it generates another reactive free radical after the reaction.

In this seminar, three utilities of radical intermediates in organic synthesis will be presented.

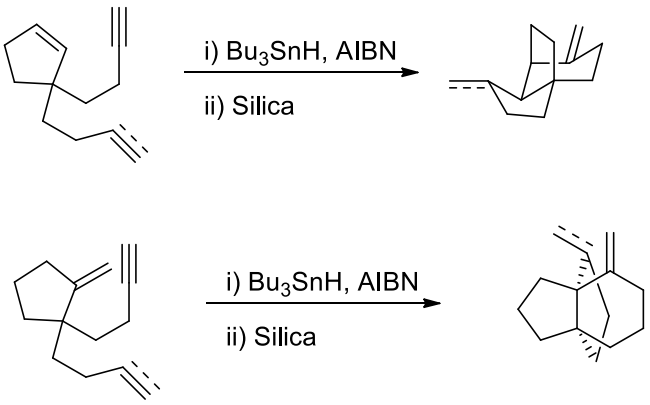
1. Tandem free radical cyclization-rearrangement of 1-hexen-5-yne system.

Free radical cyclization reaction of 1-hexen-5-yne system initiated by tin radical showed an unusual concentration dependent cyclization pattern through the cyclopropylmethyl radical intermediate (Scheme 1). The stabilization effect by the trialkyltin group for the cyclopropylmethyl radical intermediate greatly affects the rearrangement as the corresponding unsubstituted one does not provide enough stabilization for the rearrangement.



Scheme 1. Trialkyltin substitution promotes rearrangement.

Based on this observation by G. Stork,[8] tandem cyclization reactions of 1-hexen-5-yne system with extra butenyl chain were developed to produce various complex polycyclic structures depending on the connectivity of the butenyl chain (Scheme 2).



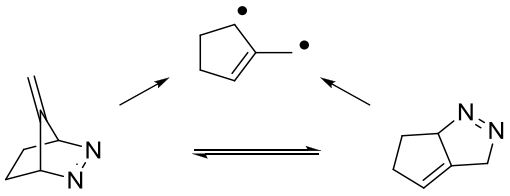
Scheme 2. Formation of polycyclic structures.

In this seminar, application of the free radical tandem cyclization reaction to the total syntheses of propellane natural products[9] and quadrane natural products[10] will be presented along with some of the mechanistical aspect of the tandem cyclization-rearrangement reaction will be discussed.

2. Tandem cycloaddtion reactions involving a diradical species, Trimethylenemethane.

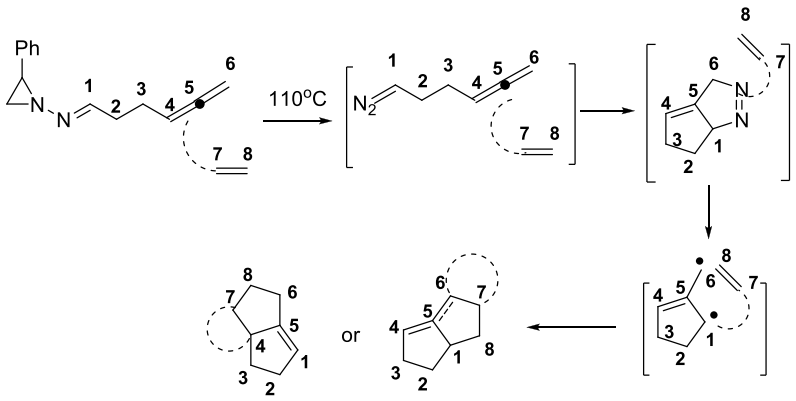
Diradical species represented by Trimethylenemethane(TMM) diyl can undergo more transformations than a single radical species. TMM can undergo [2+3]cycloaddition reaction with multiple bonds.

Methylene-2,3-diazabicyclo[2.2.1]hept-2-ene has been used as the stable precursor of the TMM diyl for physical organic chemistry studies. In those studies it was indicated that tetrahydrocyclopentapyrrazole also was a precursor for the TMM diyl as those two precursors could be in equilibrium and have the similar activation barrier to form the TMM diyl intermediate (Scheme 8).[11]



Scheme 3. Routes to methylcyclopentene TMM diyl.

Since tetrahydrocyclopentapyrazole can be obtained from the [2+3] cycloaddition reaction of allenes with diazo compound that can readily be generated from aziridinyl imines, a new tandem sequence for the TMM diyl [2+3] cycloaddition reaction was designed and executed from a precursor containing an aziridinyl imine, an allene and an olefin (Scheme 9).[12]



Scheme 4. A new tandem [2+3] cycloaddition reaction route via TMM diyls.

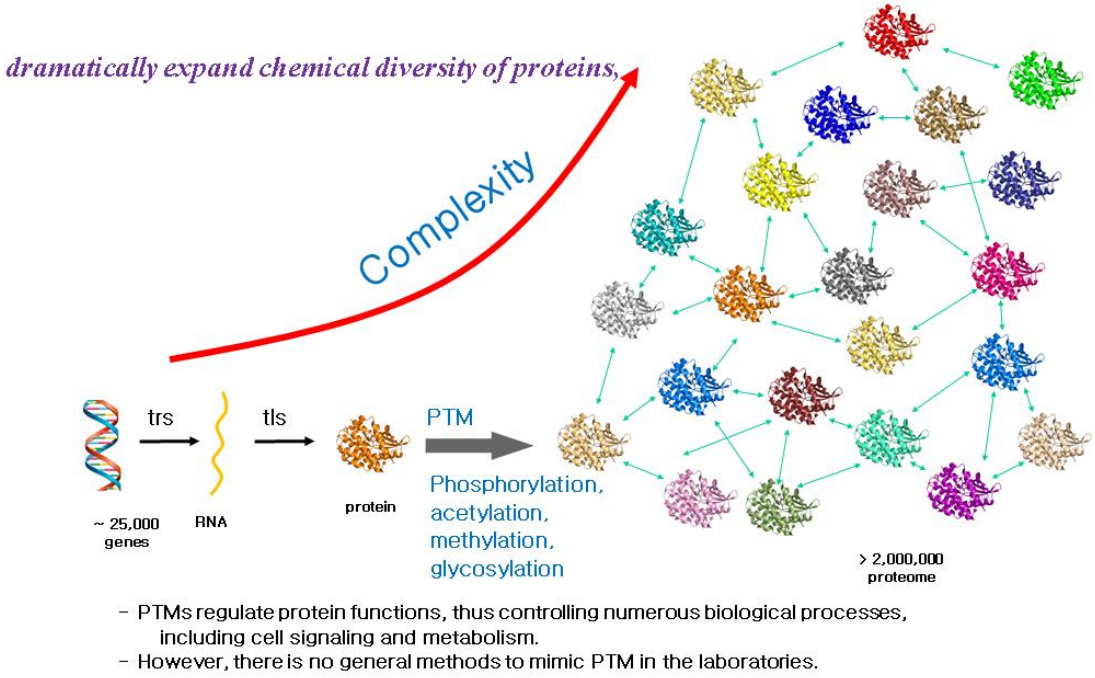
Linearly fused triquinanes and anglularly fused triquinanes were obtained from linear substrates through tandem cycloaddition reactions. This efficient tandem cycloaddition

reaction via TMM diyl intermediate was applied to the total synthesis of polyquinane natural products such as hirsutene, [13] panaginsene[14] and crinipellins.[15]

3. Radical C-C bond forming reaction in proteins.

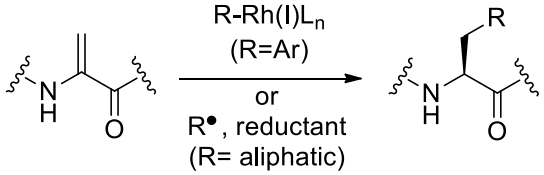
Another advantage of free radicals in addition to the high reactivity is the compatibility with water. Unlike other reactive intermediates, radicals do not react with water molecules and thus the radical reaction can be run in aqueous medium. That could allow development of organic reactions with proteins.

Development of C-C bond forming reaction with proteins is important in studying the posttranslational modification of proteins. Posttranslational modification of proteins expand the diversity of protein function (Scheme 5).[16]



Scheme 5. Posttranslational modification of proteins.

To mimic posttranslational modification of nature, we have devised a reaction protocol using radical C-C bond forming reaction using dehydroalanine as the common precursor (Scheme 6).



Scheme 6. Radical C-C bond forming reaction in water with Dha.

Development of the C-C bond forming reaction with dehydroalanine in water and application of the reaction to the modification of proteins will be presented.

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