HETERO DIELS-ALDER CYCLOADDITION

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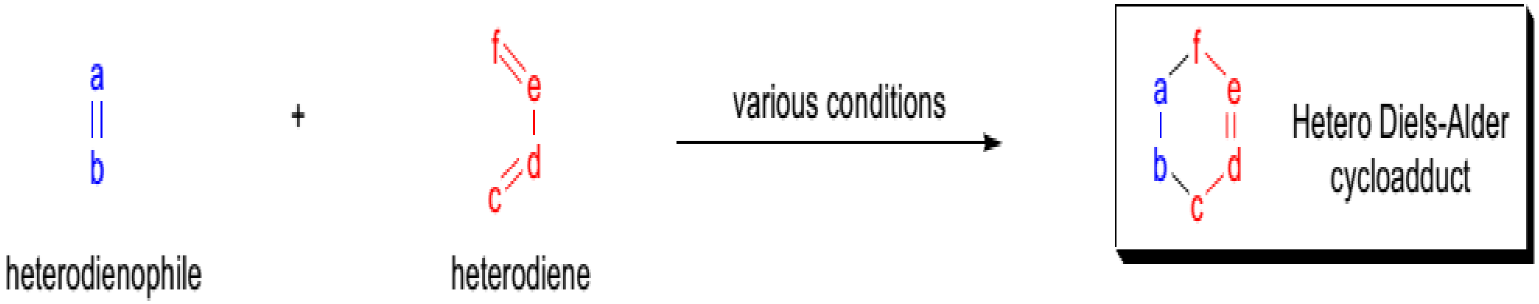
The [4π + 2π] cyclization of a diene and a dienophile to form a cyclohexene derivative is known as the Diels-Alder cycloaddition (D-A cycloaddition), but if one or more of the atoms in either component is other than carbon, then the reaction is referred to as the hetero D-A cycloaddition (HDA). The first example of an imine participating as a heterodienophile was reported by K. Alder in 1943.1 Since this initial report, the utilization of the HDA reaction in the synthesis of heterocyclic compounds has become pervasive.

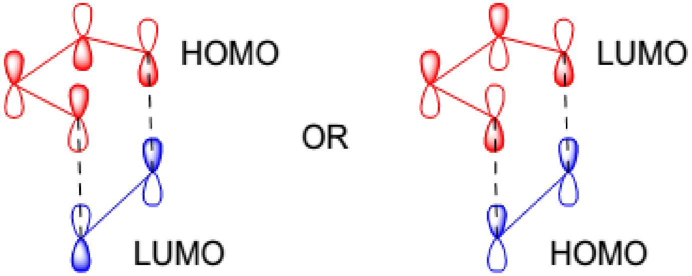


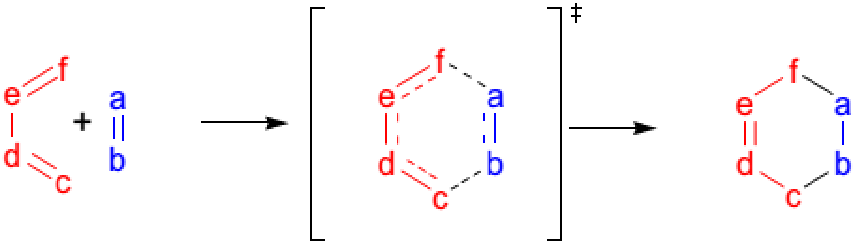
The general features of these reactions are:

1) High levels of regio- and diastereocontrol are observed and the outcome of the reaction can be predicted to the same extent as in the case of the all-carbon D-A reaction;
2) when the diene component does not contain a heteroatom and the heterodienophile is electron-deficient because of the heteroatom(s), the cycloaddition proceeds as a normal electron-demand D-A reaction (diene HOMO interacts with the LUMO of the heterodienophile);
3) when the diene contains one or more heteroatoms and/or electron-withdrawing substituents, it becomes electron-deficient, and therefore an electron-rich dienophile is needed and the reaction proceeds as an inverse electron-demand D-A reaction (heterodiene LUMO interacts with the HOMO of the dienophile);
4) when the heterodiene is substituted with one or more strongly electron-donating groups, the electron-deficient nature of the diene can be reversed and a normal electron-demand hetero D-A reaction can take place with a suitably electron-deficient dienophile;
5) HAD reactions can be catalyzed by Lewis acids, usually exhibiting higher regio- and stereoselectivities than uncatalyzed processes
6) by using a chiral auxiliary or catalyst the asymmetric HDA reaction can be realized.

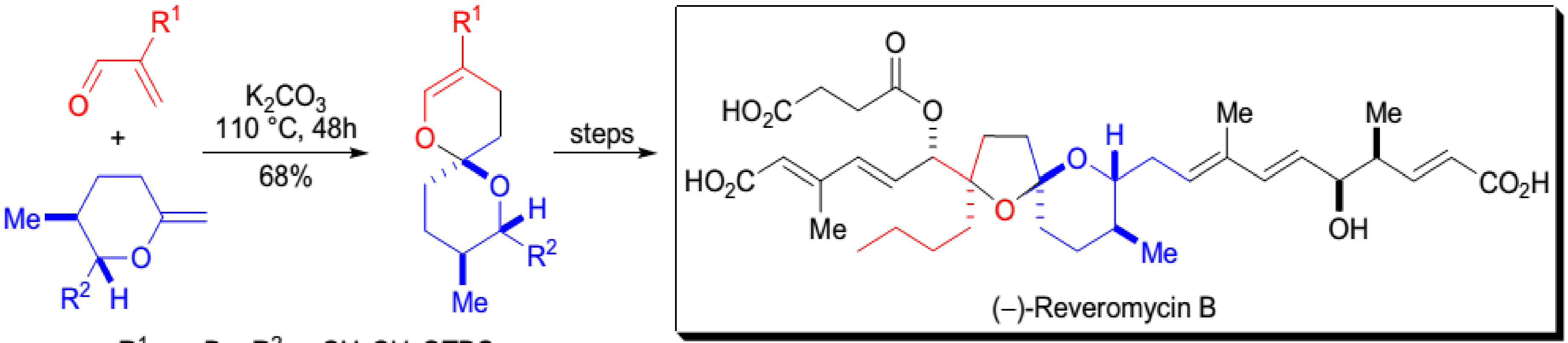
- Mechanism:

  Mechanistically the all-carbon Diels-Alder reaction is generally considered a concerted, pericyclic reaction with an aromatic transition state, but there is also evidence for a stepwise (diradical or diion) process. For HDA reactions, theoretical studies revealed that the transition states are usually concerted, but less symmetrical. Depending on the reaction conditions and the number and type of substituents on the reactants, the HDA reaction can become stepwise, exhibiting a polar transition state.



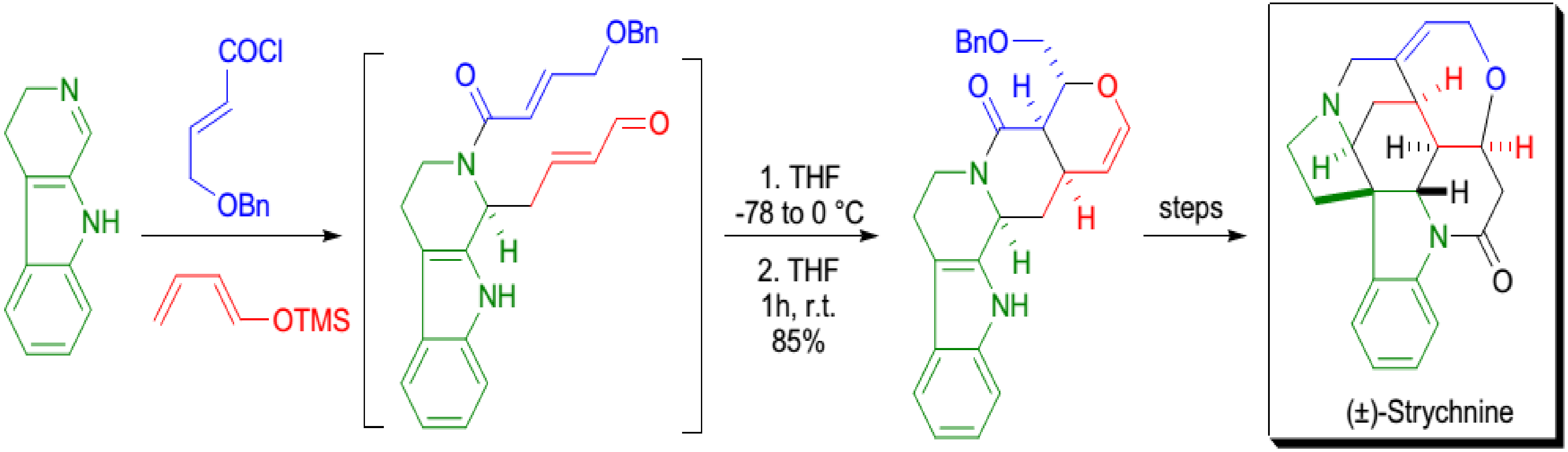


- Synthetic Applications:
  The enantioselective total synthesis of the epidermal growth factor inhibitor (–)-reveromycin B was completed by M.A. Rizzacasa and co-workers.70 The key step to assemble the 6,6-spiroketal moiety was the HDA reaction between an α,β unsaturated aldehyde (butylacrolein) and an enantiopure methylene pyran. The desired 6,6-spiroketal was obtained as a single enantiomer after heating the neat reactants in the absence of solvents at 110 ° C for 2 days.



R^1 = *n*-Bu; R^2 = CH_2CH_2OTBS

- In the laboratory of S.F. Martin, a biomimetic approach toward the total synthesis of (±)-strychnine was developed by using tandem vinylogous Mannich addition and HDA reaction to construct the pentacyclic heteroyohimboid core of the natural product.71 The commercially available 4,9-dihydro-3H-β-carboline was first converted to the corresponding N-acylium ion and then reacted with 1-trimethylsilyloxybutadiene in a vinylogous Mannich reaction. The resulting cycloaddition precursor readily underwent the expected HDA reaction in 85% yield.



- C.H. Swindell and co-workers enantioselectively prepared the Taxol A-ring side chain by using a thermal inverse electron-demand HDA reaction as the key step.73 The (Z)-ketene acetal was attached to a chiral auxiliary and reacted with the N-benzoylaldimine to give the desired dihydrooxazine in 75% yield with good diastereoselectivity.