HOFMANN ELIMINATION

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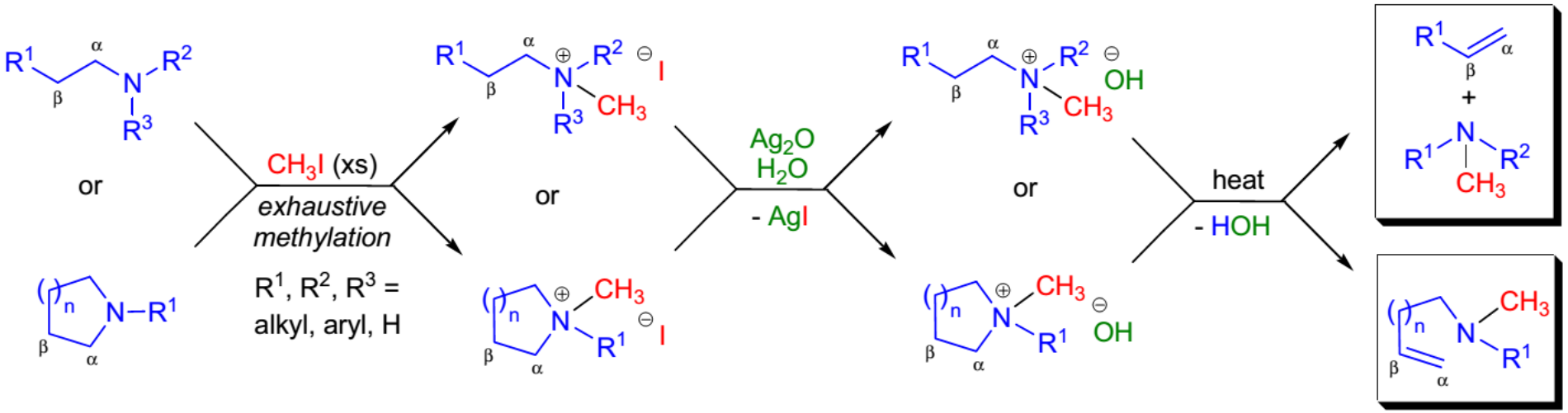
In 1851, A.W. Hofmann discovered that when trimethylpropylammonium hydroxide is heated, it decomposes to form a tertiary amine (trimethylamine), an olefin (propene), and water.Widespread use of this transformation did not occur until 1881, when Hofmann applied this method to the study of the structure of piperidines and nitrogencontaining natural products.The pyrolytic degradation of quaternary ammonium hydroxides to give a tertiary amine, an olefin and water is known as the Hofmann elimination.



The process involves three steps:

1) exhaustive methylation of the primary, secondary or tertiary amine with excess methyl iodide to yield the corresponding quaternary ammonium iodide;

2) treatment with silver oxide and water (the iodide counterion is exchanged with hydroxide ion)

3) the aqueous or alcoholic solution of the quaternary ammonium hydroxide is concentrated under reduced pressure and heated between 100-200 ° C to bring about the elimination.

•Mechanism:

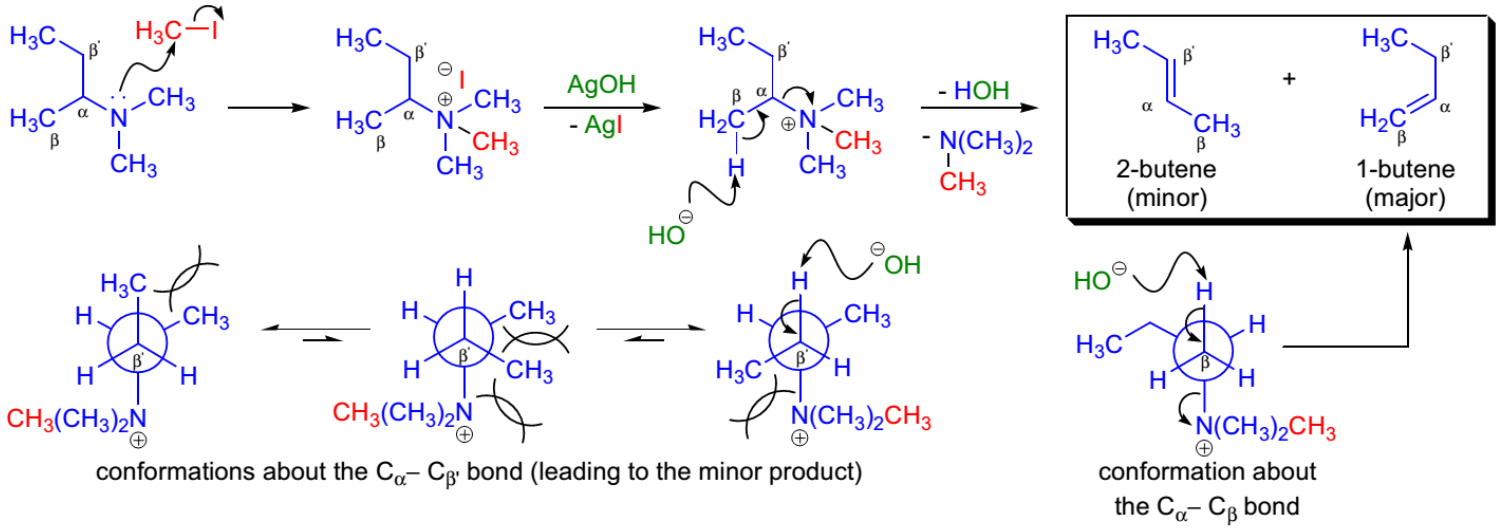
Generally the mechanism of the Hofmann elimination is E2, and it is an anti elimination (the leaving groups have to be trans-diaxial/antiperiplanar). However, in the case of certain substrates, the mechanism can be shifted in the carbanionic E1cb direction when the trans elimination process is unfavorable and the compounds contain sufficiently acidic allylic or benzylic β-hydrogen atoms. In acyclic substrates, the elimination gives rise to the least substituted alkene (Hofmann product). There are three factors which play a role in determining the outcome of the elimination:

1) the extent to which the double bond is developed in the transition state;

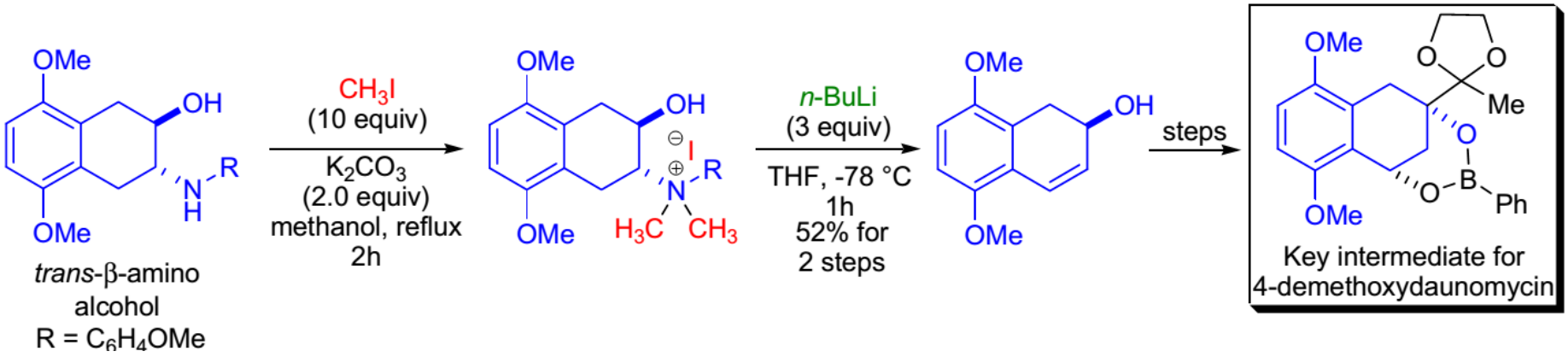
2) the acidity of the β-hydrogen atom

3)the influence of steric interactions in the transition state (this is the most widely accepted argument).

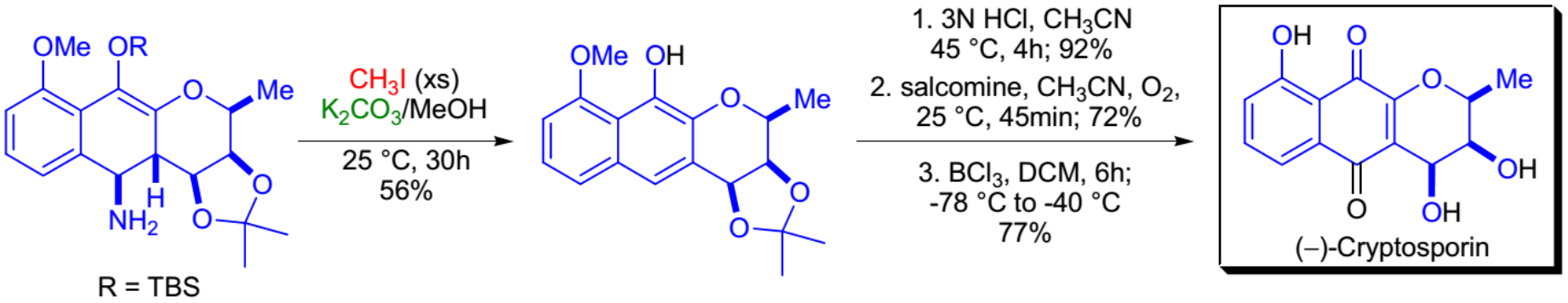
In cycloalkyl ammonium salts, the most important factor in the elimination process is the availability of the trans β-hydrogen atoms. When both the β and β' trans hydrogens atoms are available in cyclic substrates, the elimination gives the most substituted alkene (Saytzeff's rule).



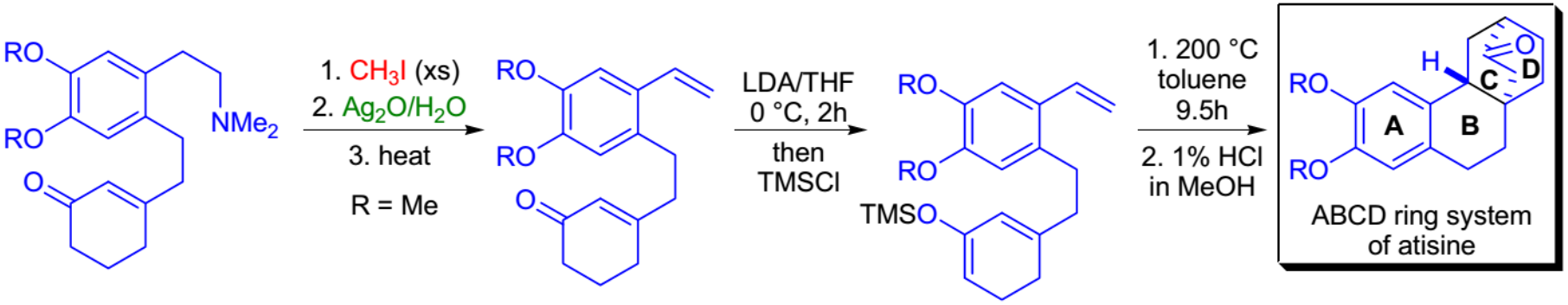
The enantioselective formal total synthesis of 4-demethoxydaunomycin was accomplished in the laboratory of M.Shibasaki. The key intermediate was prepared from an enantiomerically enriched trans-β-amino alcohol, which was first exhaustively methylated to the corresponding quaternary ammonium salt. This salt was then treated with excess n-BuLi to afford the desired allylic alcohol in moderate yield.



During the total synthesis of fungal metabolite (–)-cryptosporin, R.W. Franck and co-workers developed an efficient method for the regiospecific synthesis of naturally occurring naphtho[2,3-b]pyrano- and [2,3-b]furanoquinones using the Bradscher cycloaddition as the key step. The Hofmann elimination of a primary amine located at the benzylic position, was carried out in the last steps of the synthesis. Interestingly, exhaustive methylation of the primary amine with excess MeI in MeOH/K2CO3 resulted in spontaneous elimination of the quaternary ammonium salt at room temperature.



The ABCD ring system of the diterpene alkaloid atisine was constructed by T. Kametani et al using an intramolecular Diels-Alder cycloaddition reaction as the key step. The dienophile was obtained by the traditional Hofmann degradation of the corresponding dimethylamino precursor. The diene was prepared by the kinetic enolization of the cyclohexenone system with LDA.



In the laboratory of D.S. Watt, the enantioselective total synthesis of (+)-picrasin B was achieved from (–)-WielandMiescher ketone. At the early stages of the synthetic effort, an exocyclic double bond was introduced in a two-step procedure by first alkylating the bicyclic conjugated TMS enol ether with Eschenmoser’s salt at the γ-position, followed by Hofmann elimination of the dimethylamino group.