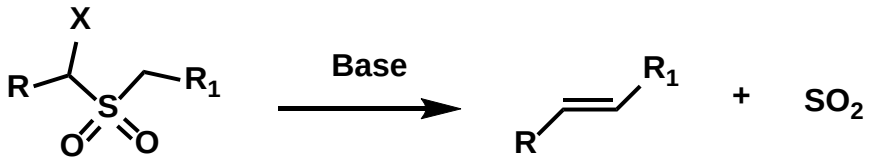
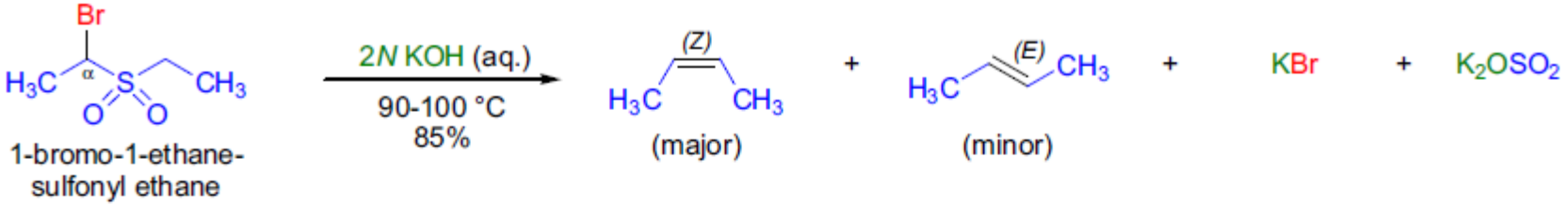
Ramberg–Bäcklund rearrangement

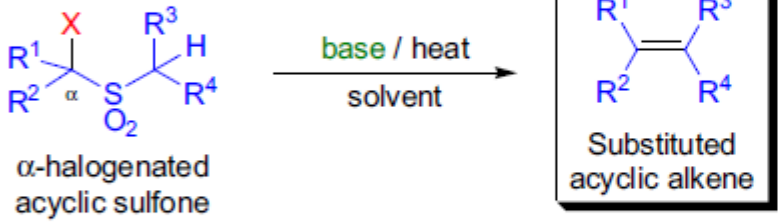
In 1940, L. Ramberg–B. Bäcklund described an interesting reaction in which 1-bromo-1-ethanesulfonyl ethane (an α-bromo sulfone) was predominantly converted to (Z)-2-butene when treated with a boiling aqueous KOH solution. There was no work published on this transformation until the early 1950s, when F.G. Bordwell and coworkers conducted a thorough kinetic investigation and elucidated the reaction mechanism. The base-induced rearrangement of α-halogenated sulfones via episulfone intermediates to produce alkenes is referred to as the L. , Ramberg–Bäcklund rearrangement.



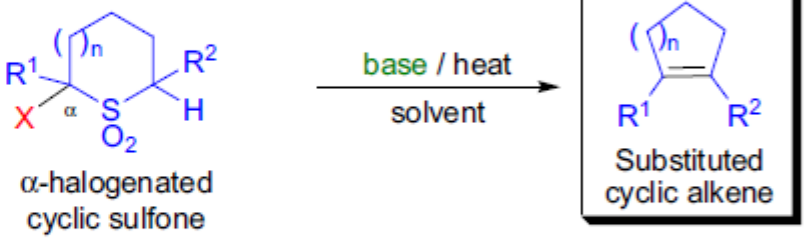
Ramberg and Bäcklund (1940):



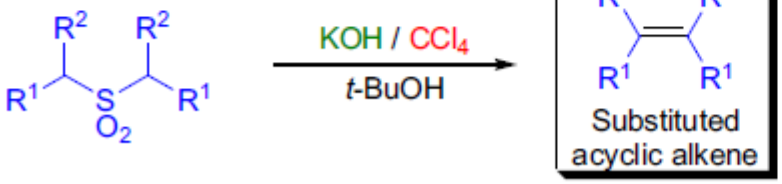
Rearrangement in acyclic systems:



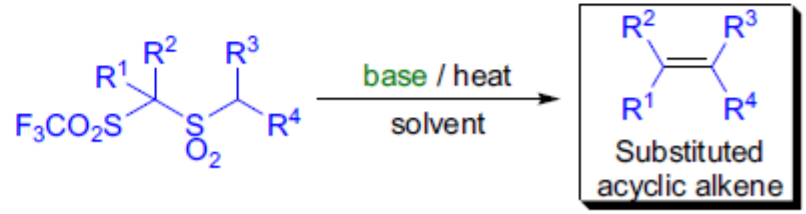
Rearrangement in cyclic systems (ring-contraction):



Meyers modification (*in situ* halogenation):



Hendrickson modification (triflinate leaving group):



$R^{1\text{-}4}$ = H, alkyl, aryl, heteroaryl, CO_2R; n = 0-12; X = Cl, Br, I, OTs; base: KOH, NaOH, KO*t*-Bu; solvent: THF, *t*-BuOH/DCM

1. The precursor halogenated sulfones can be easily prepared by the halogenation of the corresponding sulfones and the sulfones themselves are usually prepared by the oxidation of sulfides.

2. The reaction is well-suited for the preparation of 1,1- or 1,2-di, tri-, and tetrasubstituted alkenes.

3. The position of the newly formed double bond is unambiguous and under the reaction conditions no double bond migration takes place.

4. Both acyclic and cyclic substrates can be used and the reaction is especially useful for the preparation of strained cycloalkenes *via* ring-contraction.

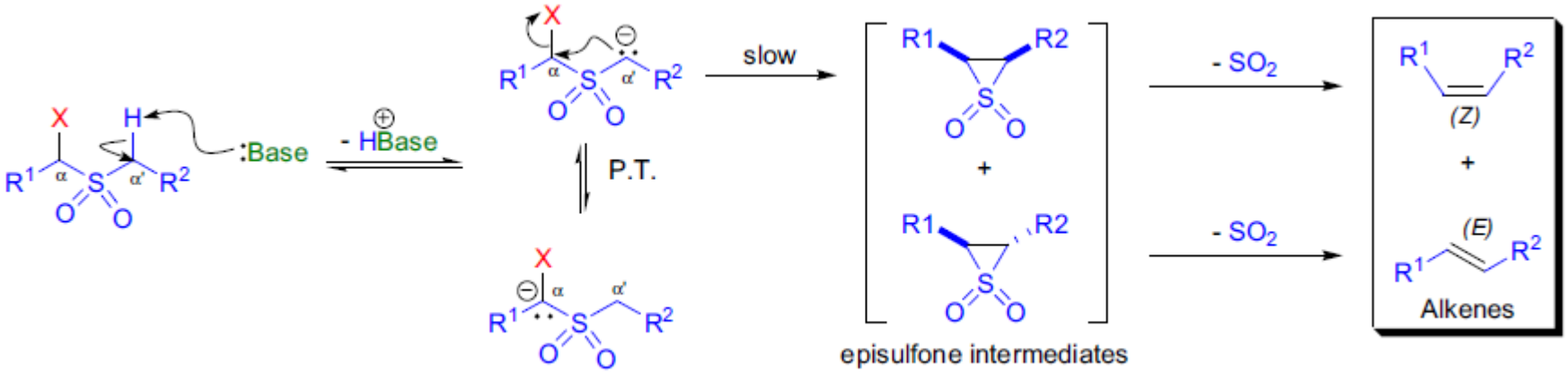
5. The stereochemical outcome of the rearrangement depends on both the base and the solvent, but the temperature is not decisive.

6. Aqueous base (e.g., KOH) favors the formation of (Z)-alkenes but strong bases in aprotic solvents (e.g., KO*t*-Bu/DMSO) predominantly give rise to (*E*)-alkenes.

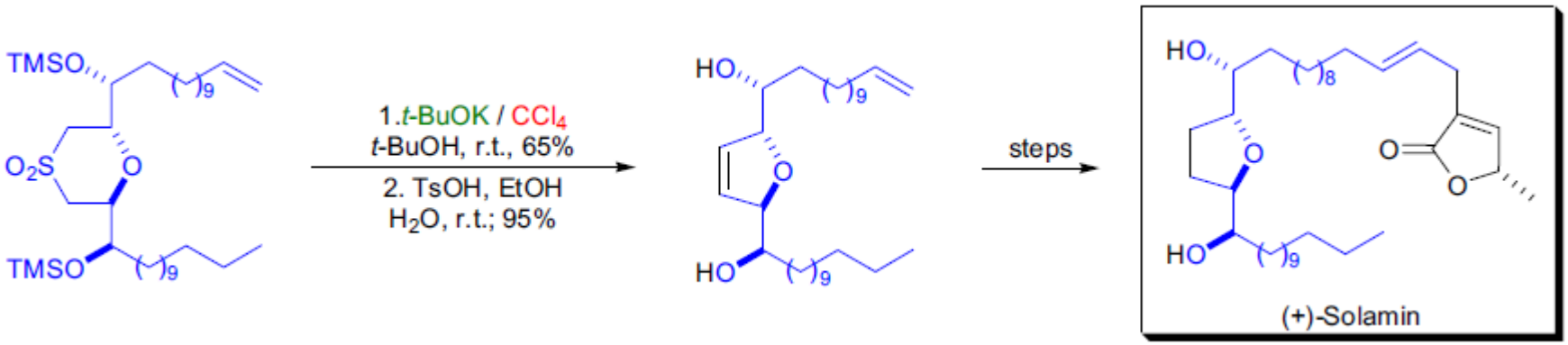
7. Base-sensitive functional groups need to be protected.

The mechanistic details of the rearrangement were investigated in detail predominantly by the research groups of F.G. Bordwell and L.A. Paquette who established that the transformation consists of three distinct steps:3

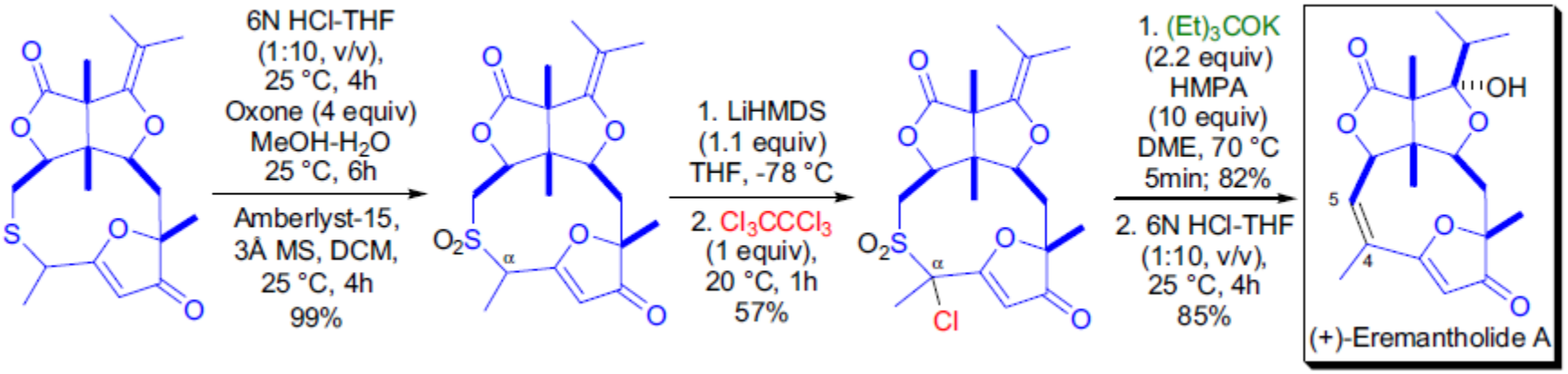
1. The first step of the process is the deprotonation of the sulfone at the á- or á'-position, which undergoes rapid equilibration;
2. Only the carbanion at the á'-position results in an intramolecular displacement reaction (SN*i* attack) on the carbon bearing the X group to give the reactive intermediate episulfones (thiirane 1,1-dioxides), which are generally formed as mixtures of *cis*- and *trans* stereoisomers (slow step);
3. The final step is the loss of SO2 either thermally or under base catalysis to give a mixture of alkene stereoisomers. The overall stereochemical outcome of the reaction is determined in the second step.



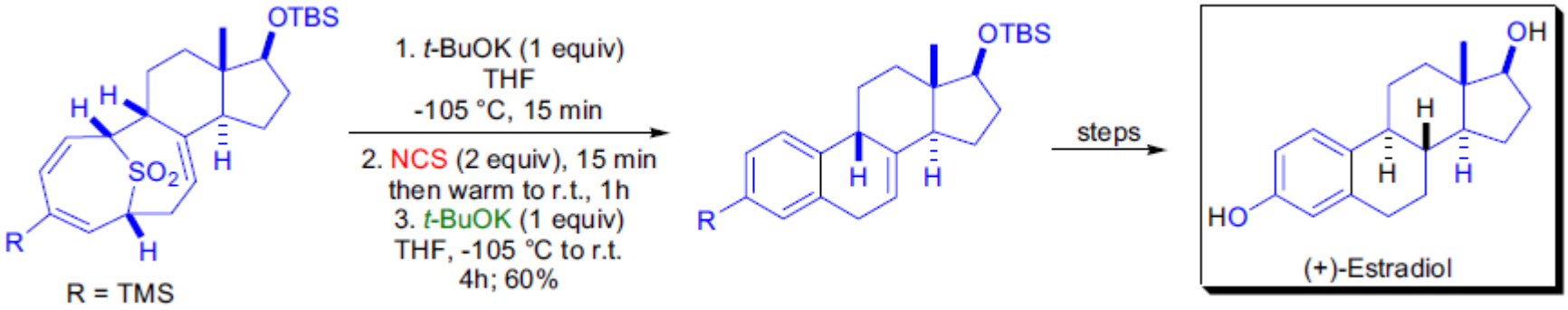
A concise convergent synthetic strategy was developed by B.M. Trost and co-workers for the synthesis of acetogenins, a class of compounds with a wide breadth of biological activity. The authors chose (+)-solamin as thetarget to demonstrate the utility of their strategy, which relied on the Meyers modification of the Ramberg-Bäcklund rearrangement as the key step. As the chlorination of the sulfone failed, the in situ chlorination-rearrangement was attempted and led to the successful conversion of the oxasulfone precursor to the desired 2,5-dihydrofuran core.



In the laboratory of R.K. Boeckman, the total synthesis of (+)-eremantholide A was accomplished using the Ramberg- Bäcklund rearrangementfor the crucial ring-contraction step at the end of the synthetic sequence. The ninemembered macrocyclic core of the natural product is highly strained since the C4-C5 double bond is twisted 88° out of the plane of the 3(2H)-furanone ring. The ring-contraction precursor 10-membered macrocyclic sulfide was sequentially treated with 6N HCl, Oxone and Amberlyst 15 resin to afford the corresponding sulfone. The chlorination of this sulfone took place exclusively at the more substituted α-position, and upon treatment with a strong base, the rearrangement yielded the desired product in good yield.



A novel benzannulation strategy featuring a [6+4] cycloaddition followed by Ramberg-Bäcklund *rearrangement* was employed for the total synthesis of (+)-estradiol by J.H. Rigby et al. The higher-order cycloaddition took place between a seven-membered TMS-substituted η6-thiepin 1,1-dioxide (CO)3Cr-complex and a highly substituted diene to afford directly the bicyclic sulfone rearrangement precursor. The ring-contraction was induced by the sequential treatment with *t*-BuOK and *N*-chlorosuccinimide at very low temperatures followed by the addition of another equivalent of the base.



The Ramberg- Bäcklund *rearrangement* was the key step in the total synthesis of the marine alkaloid manzamine Cby D.I. MaGee and E.J. Beck.35 The azacycloundecene ring was stereoselectively formed by exposing the α-chloro sulfone to a strong base. The use of weaker bases either resulted in no reaction or gave rise to mixtures of (*E*)- and(*Z*)-alkenes.