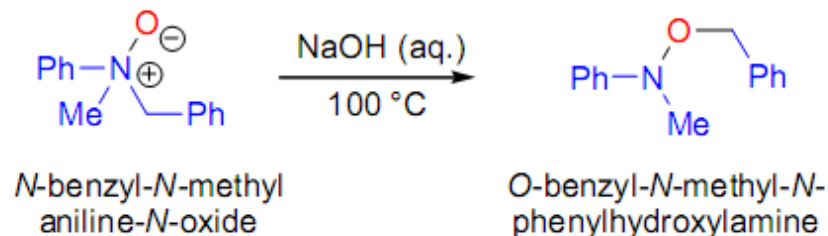


Meisenheimer rearrangement

Meisenheimer rearrangement

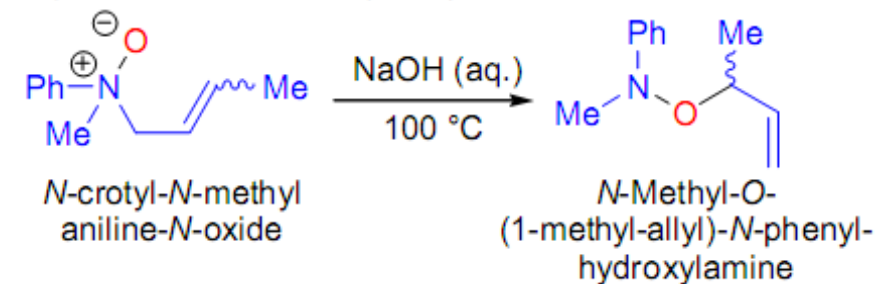
In 1919, J. Meisenheimer reported that upon heating in an aqueous sodium hydroxide solution, *N*-benzyl-*N*-methyl aniline-*N*-oxide underwent a facile isomerization to afford *O*-benzyl-*N*-methyl-*N*-phenyl hydroxylamine.

Meisenheimer (1919):



Three decades later, A.C. Cope and co-workers reinvestigated the rearrangement to explore its mechanism. They discovered that the isomerization of *N*-crotyl-*N*-methyl aniline *N*-oxide occurred with the inversion of the allylic system to give *N*-methyl-*O*-(1-methyl-allyl)-*N*-phenylhydroxylamine.

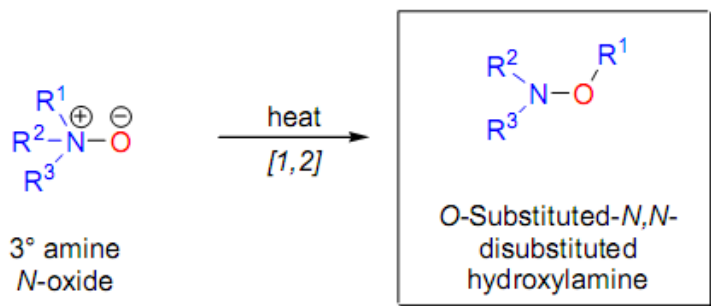
Cope and Kleinschmidt (1944):



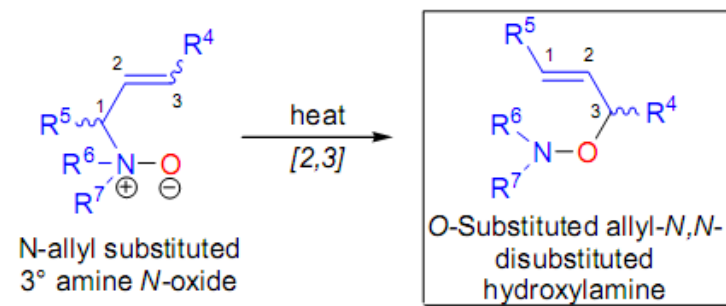
Meisenheimer rearrangement

The thermal rearrangement of certain tertiary amine N-oxides to the corresponding O-substituted-N,N-disubstituted hydroxylamines is known as the Meisenheimer rearrangement.

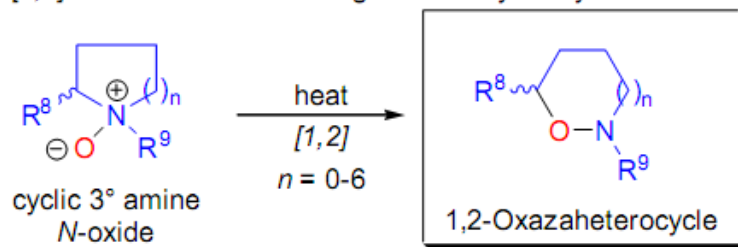
[1,2]-Meisenheimer rearrangement in acyclic systems:



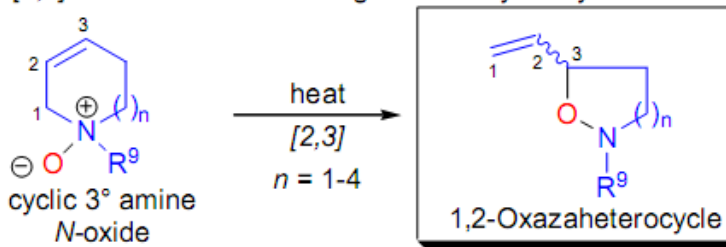
[2,3]-Meisenheimer rearrangement in acyclic systems:



[1,2]-Meisenheimer rearrangement in cyclic systems:

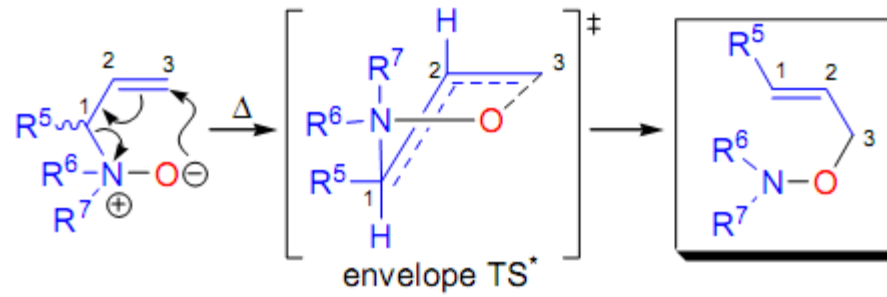
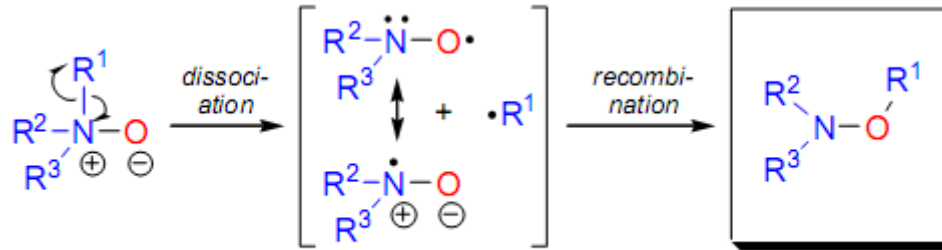


[2,3]-Meisenheimer rearrangement in cyclic systems:



$R^1 = \text{CH}_2\text{Ph}, \text{CHPh}_2, \text{CH}_2\text{Ar}, \text{allyl}; R^{2-3} = \text{alkyl with no } \beta\text{-hydrogen, aryl}; R^{4-5} = \text{H, alkyl, aryl}; R^{6-7} = \text{alkyl with no } \beta\text{-hydrogen, aryl}; R^8 = \text{alkenyl, aryl}; R^9 = \text{alkyl with no } \beta\text{-hydrogen}$

Mechanism:

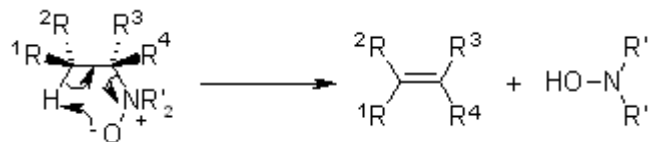


The general features of the reaction

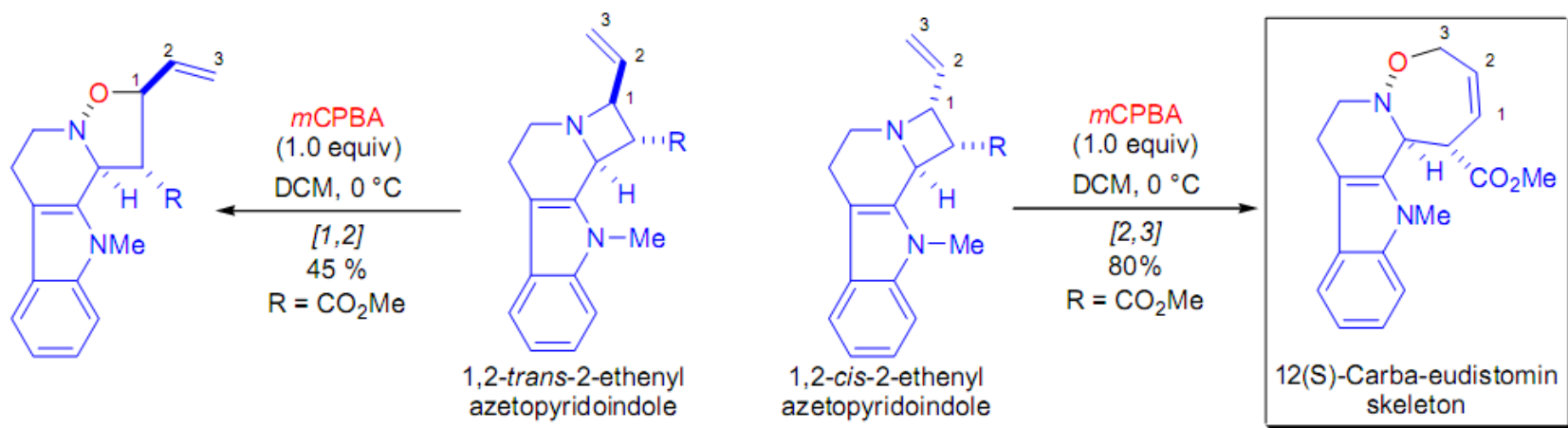
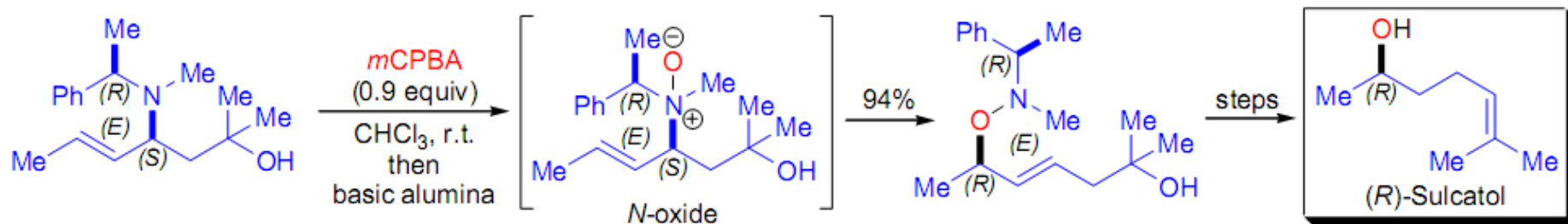
- 1) The rearrangement takes place in both open-chain and cyclic systems
- 2) The [1,2]- and [2,3]-shift of substituents are the two different modes of the transformation;
- 3) The [1,2]-shift occurs when one of the substituents is capable of stabilizing radicals (R1 = benzyl, diphenylmethyl, etc.)
- 4) The [2,3]-shift is common when one of the substituents is allylic
- 5) During the [1,2]-shift, the stereocenter on the migrating group suffers extensive racemization;

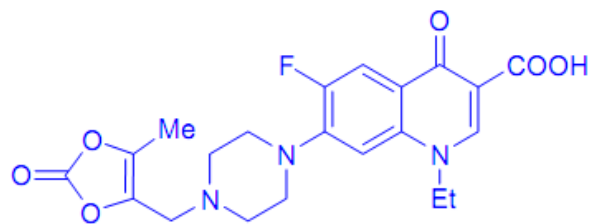
6) The [2,3]-shift usually takes place much faster than the [1,2]-shift and the transfer of chirality of the migrating group is possible

7) When any of the R₁, R₂ or R₃, R₄ are alkyl groups that have a hydrogen atom at their β-position, the Cope elimination becomes competitive

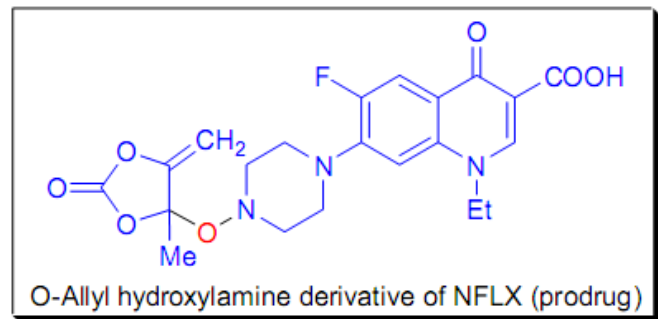
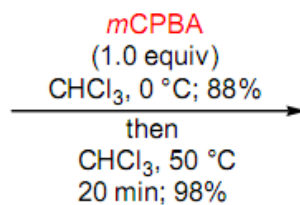


Synthetic Applications:

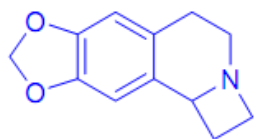




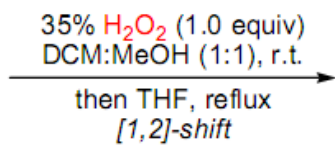
N-allyl derivative of NFLX (prodrug)



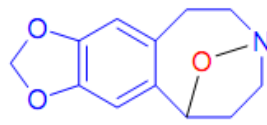
O-Allyl hydroxylamine derivative of NFLX (prodrug)



azetidione

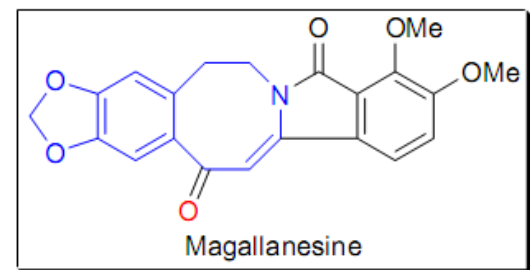


64%



azocine

steps



Magallanesine