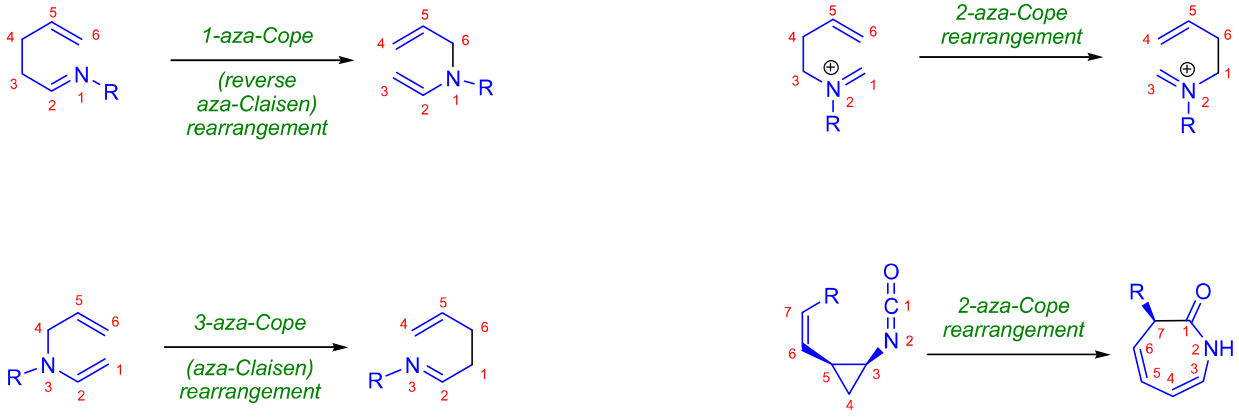
AZA-COPE REARRANGEMENT

(References are on page 538)

Importance:

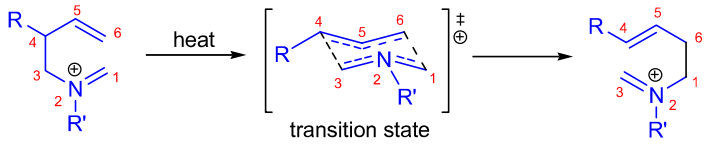
[*Seminal Publications*[1-3]*; Reviews*[4-6]*; Modifications & Improvements*[7-28]*; Theoretical Studies*[18,21,29]]

When 1,5-dienes are heated, they isomerize *via* a *[3,3]-sigmatropic rearrangement* known as the *Cope rearrangement*. The rearrangement of *N*-substituted 1,5-dienes is called the *aza-Cope rearrangement*. This reaction has many variants, namely *1-aza*-, *2-aza*-, *3-aza*- and *1,3-*, *2,3*-, *2,5*-, *3,4- diaza-Cope rearrangements*.[7,8] The *3-aza-Cope rearrangement* is also known as the *aza-Claisen rearrangement*. The rearrangement of *cis*-2-vinylcyclopropyl isocyanates to 1-azacyclohepta-4,6-dien-2-ones (*2-aza-divinylcyclopropane rearrangement*) is analogous to the well-known and highly stereospecific *cis-divinylcyclopropane rearrangement*. It is well established that the presence of an oxygen atom adjacent to the π-bond accelerates the *Cope rearrangement*. When there is a group attached to C3 or C4 with which the newly formed double bond can conjugate, the reaction takes place at a lower temperature than in the unsubstituted case. As with all *[3,3]-sigmatropic rearrangements*, the activation energies are significantly lowered when the starting diene is charged.



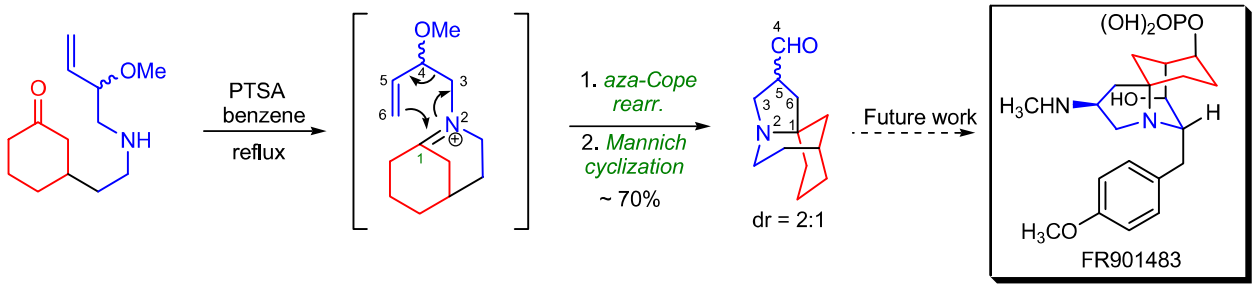
Mechanism:[30-35,18,36,21,37,38,29]

The *aza-Cope rearrangement* is a concerted process, and it usually takes place *via* a chairlike transition state where the substituents are arranged in a quasi-equatorial position. (*See more detail in Cope rearrangement.*)



Synthetic Applications:

The *tandem cationic aza-Cope rearrangement* followed by a *Mannich cyclization* was applied in the synthesis of the novel tricyclic core structure of the powerful immunosupressant FR901483 in the laboratory of K. Brummond.[39] Their approach was the first synthetic example in which this tandem reaction passes through a bridgehead iminium ion.



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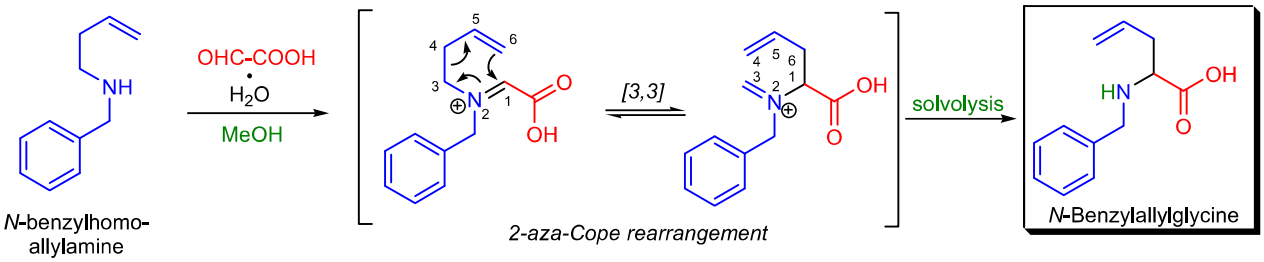
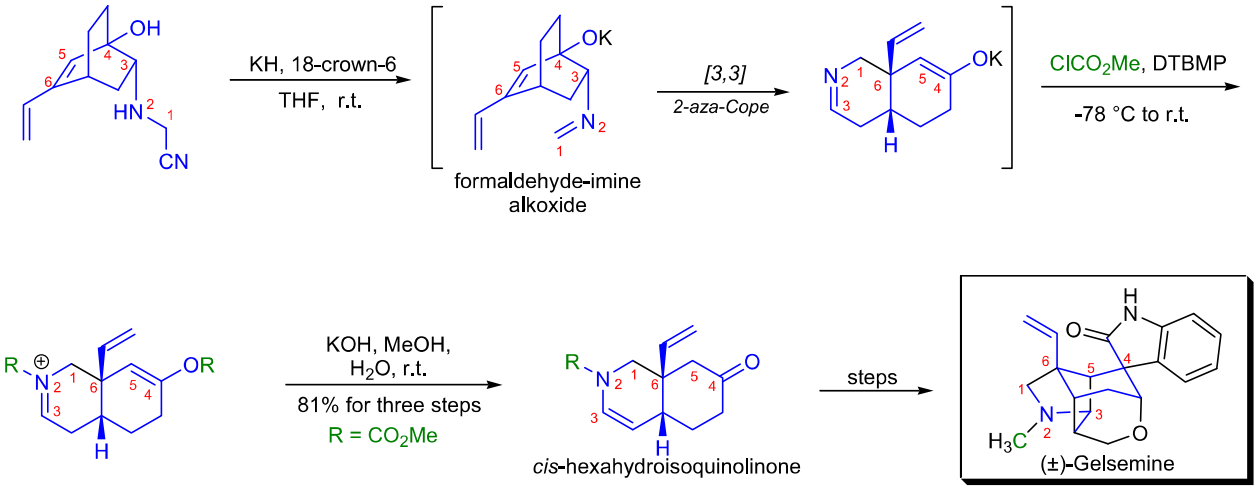
Synthetic Applications:

D.J. Bennett et al. developed a facile synthesis of *N*-benzylallylglycine based on a *tandem 2-aza-Cope/iminium ion solvolysis reaction*.[40] *N*-Benzylallylglycine can be prepared in good yield through a one-pot reaction of *N*-benzylhomoallylamine with glyoxylic acid monohydrate in methanol.



L.E. Overman and co-workers accomplished a total synthesis of (±)-gelsemine by a sequence where the key strategic steps are a sequential anionic 2-*aza-Cope rearrangement* and *Mannich cyclization*, an *intramolecular Heck reaction*, and a *complex base-promoted molecular reorganization* to generate the hexacyclic ring system.[41] The exposure of the bicyclic substrate to potassium hydride in the presence of 18-crown-6 initiated the anionic aza-Cope rearrangement of the bicyclic formaldehyde-imine alkoxide. The rearrangement product was quenched with excess methyl chloroformate then was treated with base to afford the desired *cis*-hexahydroisoquinolinone.



During the enantioselective total syntheses of (–)- and (+)-strychnine and the Wieland-Gumlich aldehyde, L.E. Overman and co-workers used the tandem *aza-Cope rearrangement/Mannich reaction* as a key step.[42] This central *aza-Cope/Mannich reorganization* step proceeded in 98% yield.