BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024, Tamil Nadu, India

Programme: M.Sc., Chemistry

Course Title: ORGANIC CHEMISTRY - I

Course Code: CHE611CC

UNIT V: Molecular Rearrangements

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Syllabus

First Semester –Organic Chemistry I

UNIT V – 5

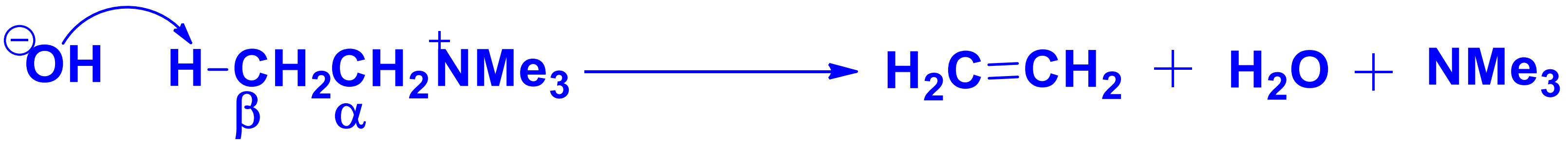
Molecular Rearrangements

Carbocation rearrangements – Migratory aptitude and memory effect – 1,2-Shifts

1. Wagner-Meerwein – Rearrangements involving electron–deficient species: 2. Wolff – 3. Lossen – 4. Schmidt – 5. Baeyer-Villiger – 6. Stevens – 7. Favorski – 8. Sommelet-Hauser – 9. Demyanov – 10. Pummerer – 11. Von-Richter – 12. Dienone-phenol rearrangements.

6. Stevens Rearrangement

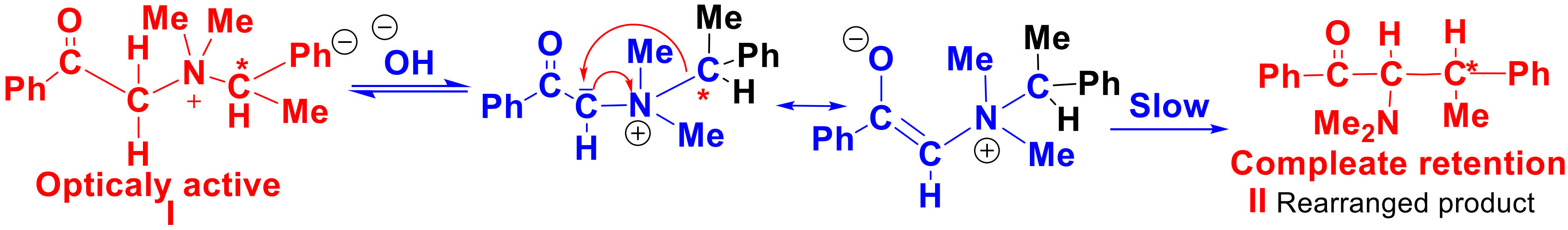
Quaternary ammonium ions, which contain β-H atom, undergo E-2 (Hoffmann) elimination with a base. Proceeding through carbanion - nitrogen to carbon migration.



$$^{\ominus}OH \quad \underset{\beta}{H-CH_2}\underset{\alpha}{CH_2}\overset{+}{N}Me_3 \longrightarrow H_2C{=}CH_2 + H_2O + NMe_3$$

If none of alkyl group posses β-H atom, similar as in the case of a ketone which has a β-carbonyl group, an α-H is removed by base to give an ylide (a species in which adjacent atoms bear formal opposite charges). The roll of the carbonyl group is to assist the formation of ylide by stabilizing a –ve charge.

Mechanism:

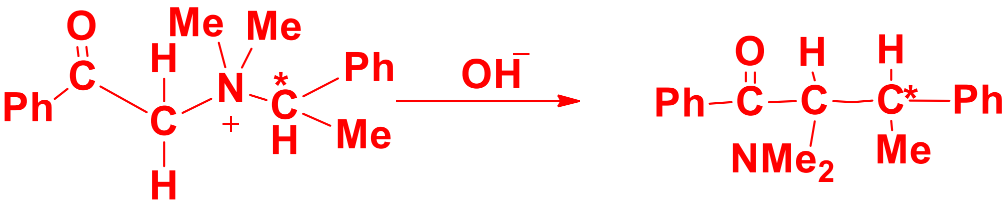


Evidences for Stevens Rearrangement

1) Proceeds through ion or related species. Nitrogen to carbon migration.

2) This rearrangement does not proceed readily when the benzoyl group is replaced by phenol or alkyl group. These being relatively ineffective in stabilizing the hydrogens on adjacent methylene group.

3) Although the reaction is accelerated by a base, limit is reached when slightly more than one equivalent is added, which points, virtually all of the substrate has been converted to conjugate base (ylide).



Opticaly active

I

Compleate retention

II

4) When the rearrangement is carried out on the optically active ammonium ions it gives (I). The α-phenyl ethyl group migrates with retention of configuration indicating that the new C-C bond formed and old C-N bond breaks on the same side of carbon.

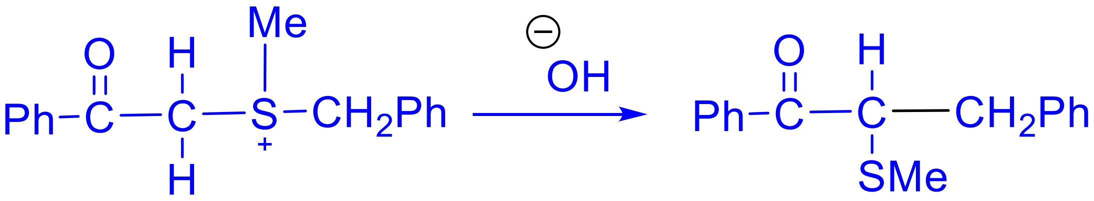
Evidences for Stevens Rearrangement

6) Crossover experiment & C14 labeled experiment shows that this reaction is intramolecular.

7) Most common migrating group are allyl, benzhydryl, 9-fluorenyl, 3-phenylpropargyl and phenacyl.

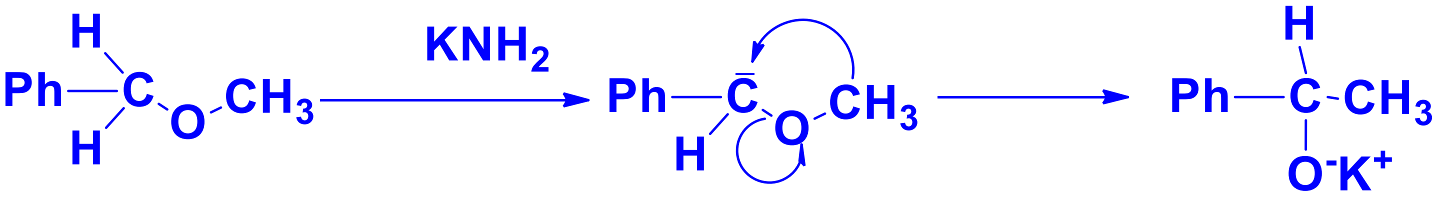
8) Strong bases like sodamide, phenyl lithium can also be used depending upon the substrate.

9) Similar rearrangements have been observed with sulphonium salt under sufficiently drastic conditions.

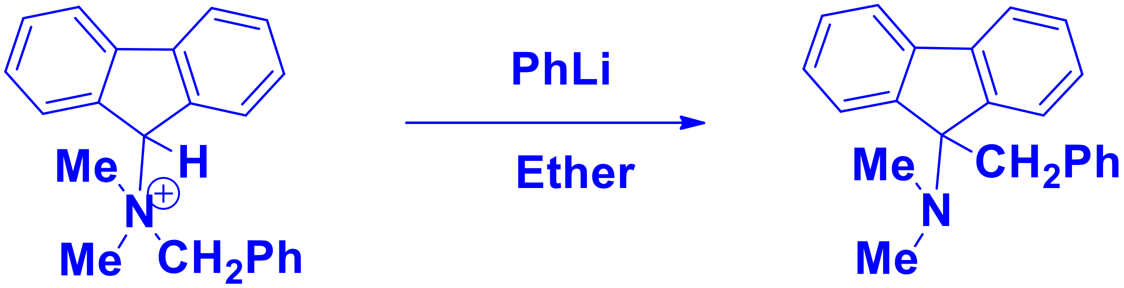


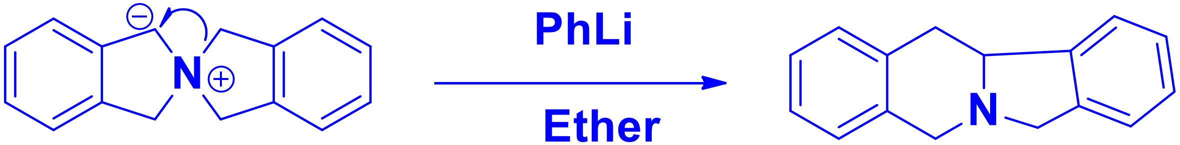
9) Similar rearrangement has been observed in benzyl or allyl ether under sufficiently drastic condition.

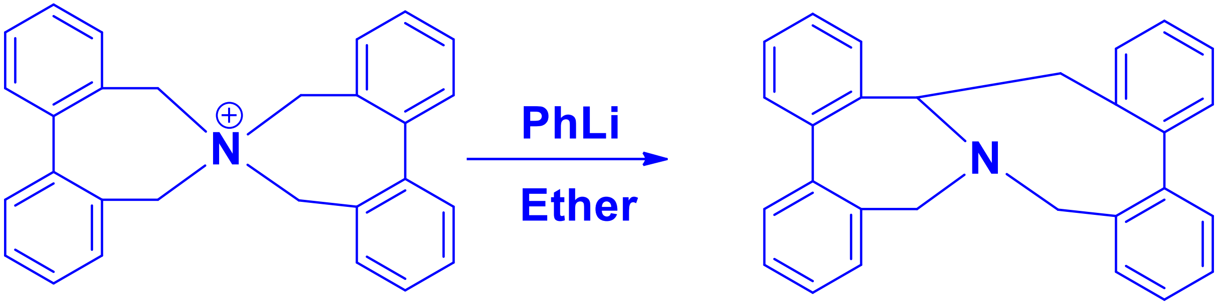
Wittig rearrangement is oxygen equivalent of Stevens Rearrangement



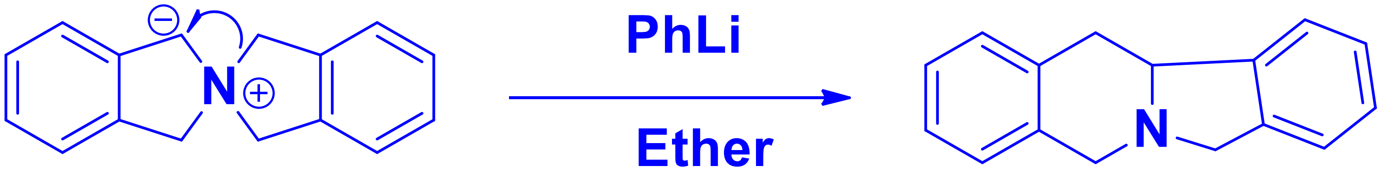
Examples for Stevens Rearrangement

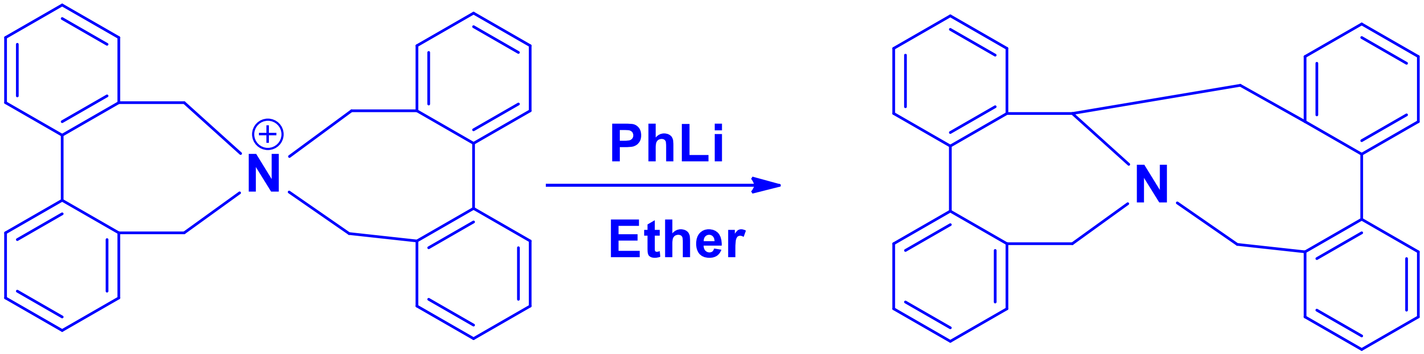


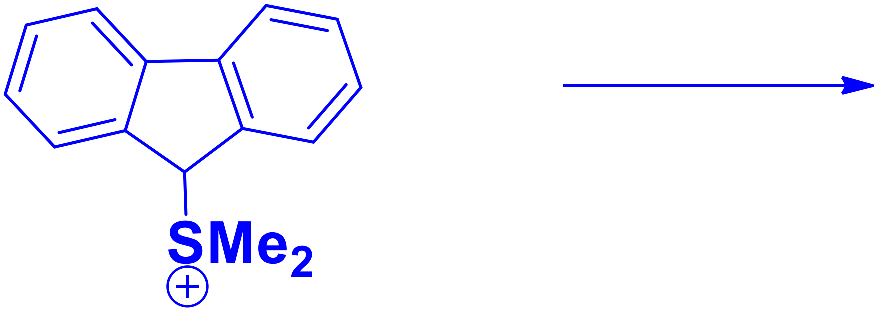


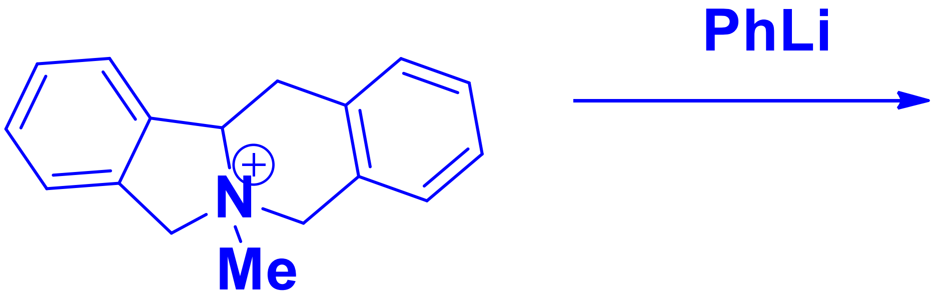


Examples for Stevens Rearrangement



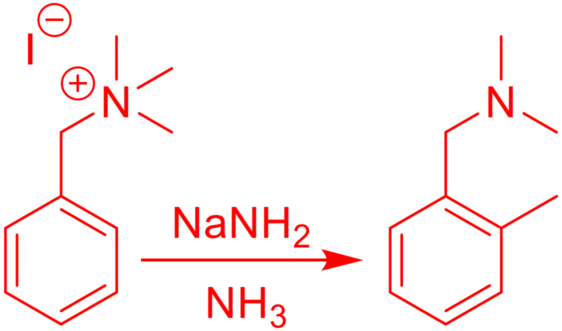






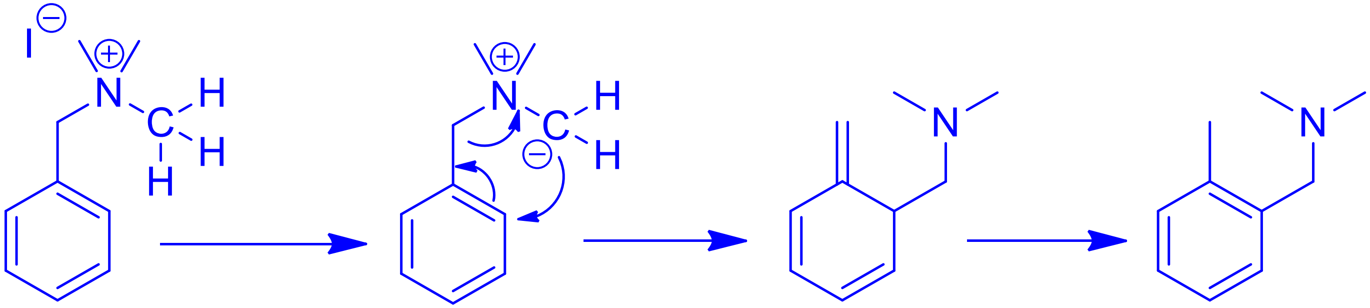
8. Sommelet-Hauser rearrangement

- **The Sommelet–Hauser rearrangement (named after M. Sommelet and Charles R. Hauser) is a rearrangement reaction of certain benzyl quaternary ammonium salts.**
- **The reagent is sodium amide or another alkali metal amide and the reaction product a N-dialkyl benzyl amine with a new alkyl group in the aromatic ortho position.**



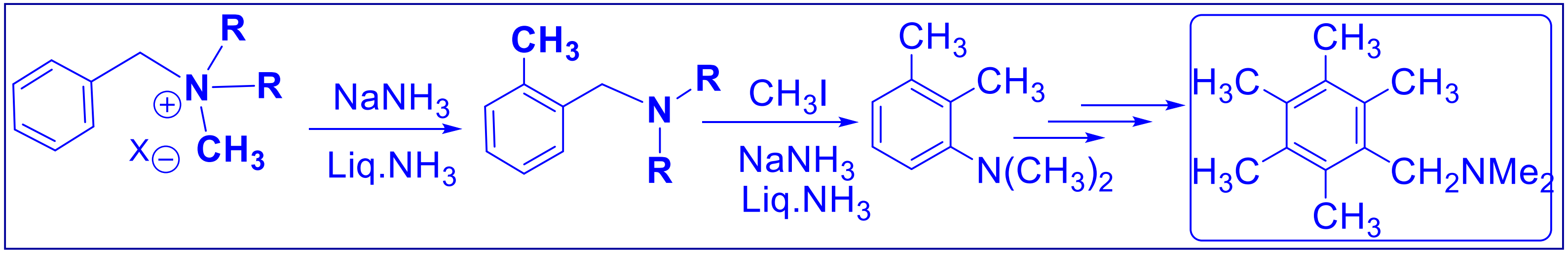
Mechanism

- **The benzylic methylene proton is acidic and deprotonation takes place to the ylide. The second step is a 2,3-sigmatropic rearrangement.**

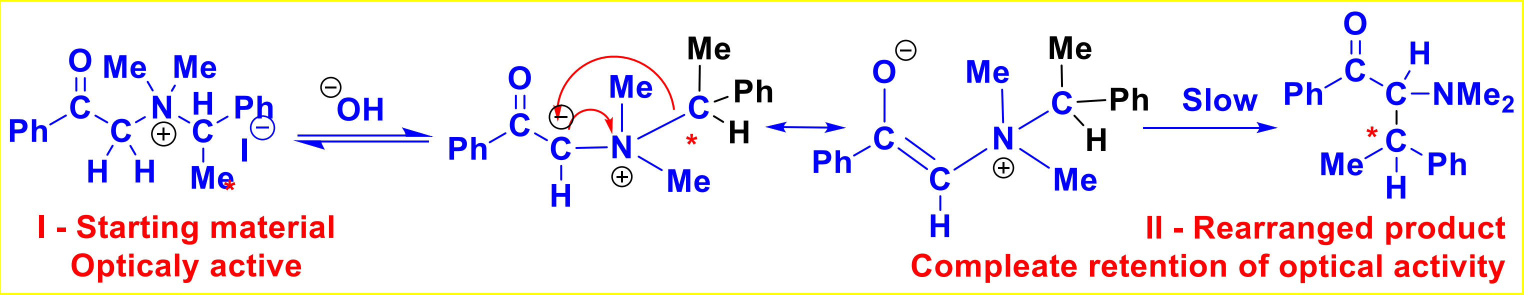


8. Sommelet-Hauser rearrangement

- Benzyl quaternary ammonium salt when treated with alkali metal amide undergoes rearrangement called Sommlet Houser rearrangement.
- Since the product is benzyl tertiary amine it can be further alkylated and the product again subjected to rearrangement this process may be continued around the ring until ortho position blocked we get poly alkylated benzene.
- In the absence of β-carbonyl group, the α -hydrogen is too weakly acidic for hydroxide ion induced rearrangement.



6. Stevens Rearrangement

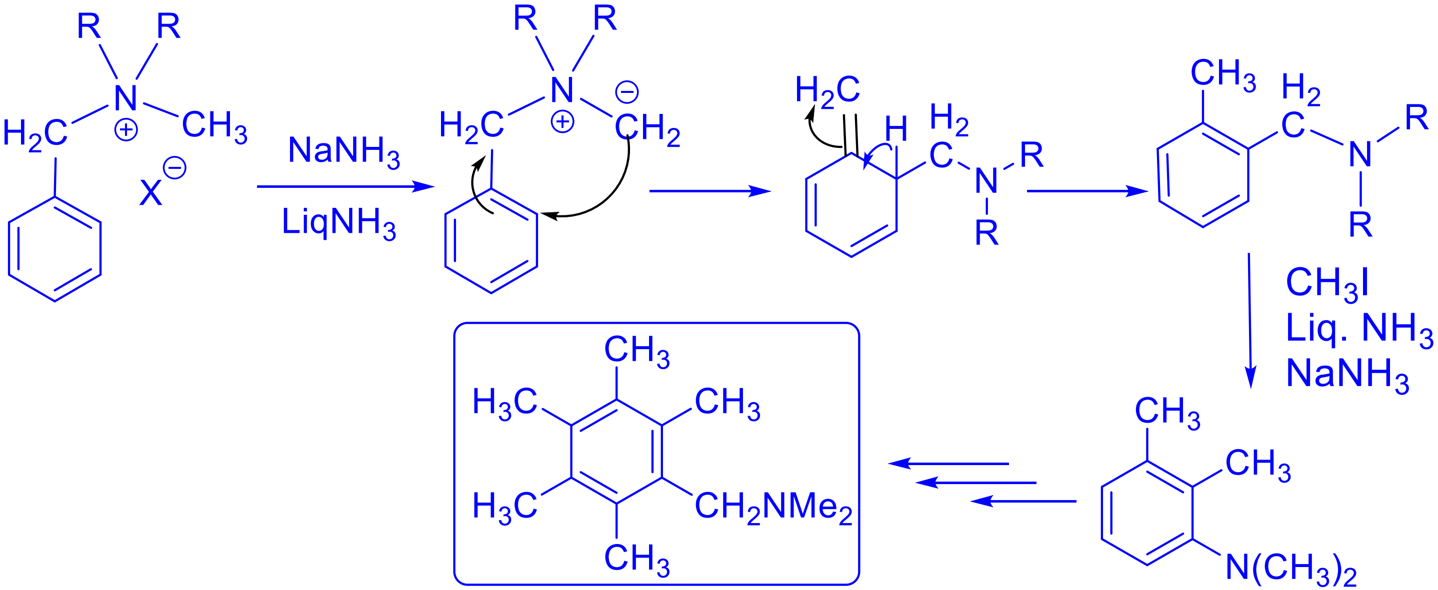


I - Starting material
Opticaly active

II - Rearranged product
Compleate retention of optical activity

- Thus, a strong base, such as amide ion in liquid ammonia, is to be used, for the rearrangement takes a different course.
- instead of [1,2] shift (Steven's rearrangement), a [3,2]-sigmatropic rearrangement takes place which is called Sommelet- Hauser rearrangement.

8. Machanism - Sommelet-Hauser rearrangement……

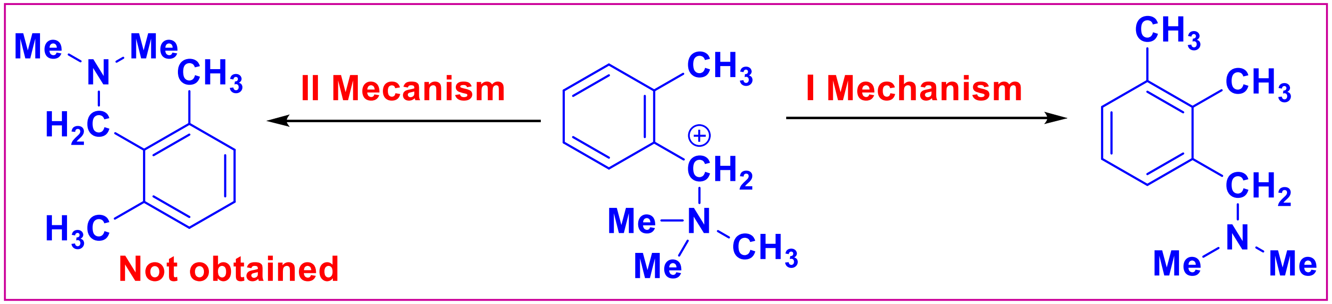


- Benzyl trimethyl amine labled with C^{14} at a position of benzyl group gave a product labled in ring methyl group as predicted by first mechanism and not in methyl methylene as required by second mechanism. The reaction is often carried out with 3 methyl groups on nitrogen.

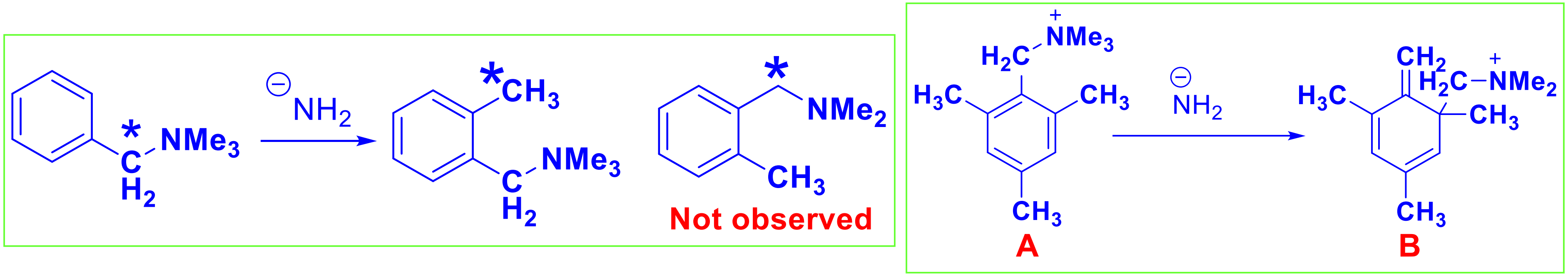
- The benzyl H is more acidic & it is one which first loses proton to give <u>I.</u> However, <u>II</u> which is present in smaller amount is the species undergo rearrangement shifting equation in its favour this mechanism is called SNi mechanism.

8. Sommelet-Hauser rearrangement…………

- Another mechanism which might be proposed is the one in which the methyl group actually breaks away from N and then attaches itself to the ring. Isotopic labeling studies showed that second mechanism is not operating.

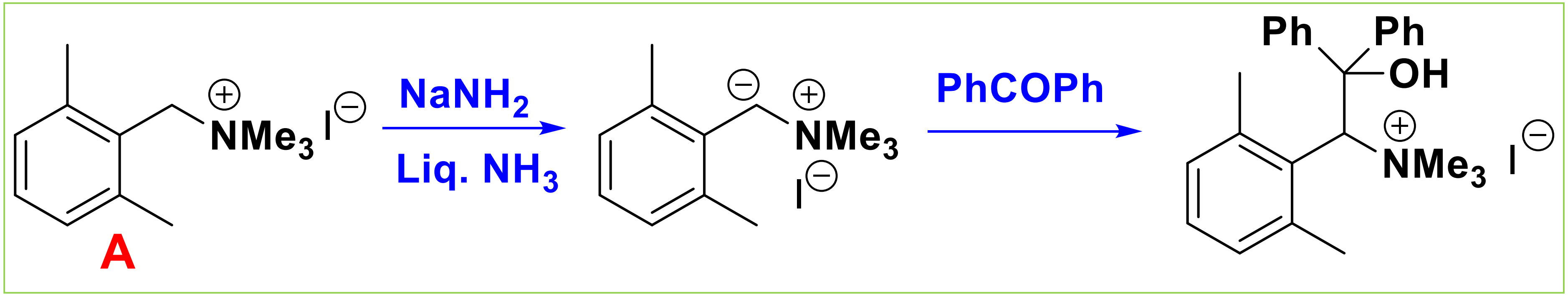


- Benzyl tri methyl amine labeled with C^{14} α-position of benzyl group gave product labeled in ring methyl group as predicted by first mechanism and not methylene as required by second mechanism.

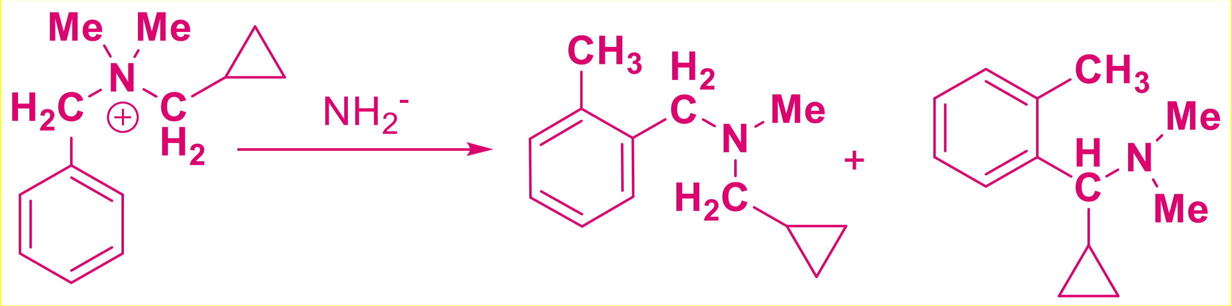


8. Sommelet-Hauser rearrangement…………

- Since A is substituted in both ortho position it could not give normal rearrangement product but first step of mechanism occurred. Another evidence.

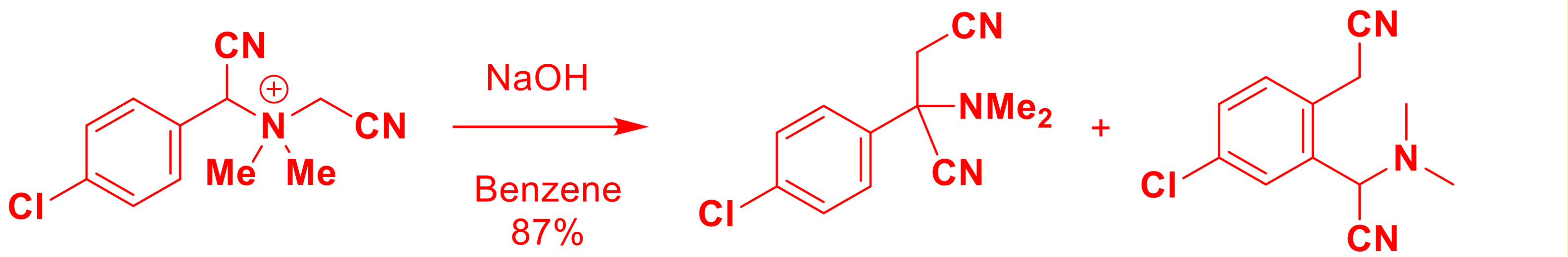


- When three groups attached to nitrogen are same competing products are obtained.



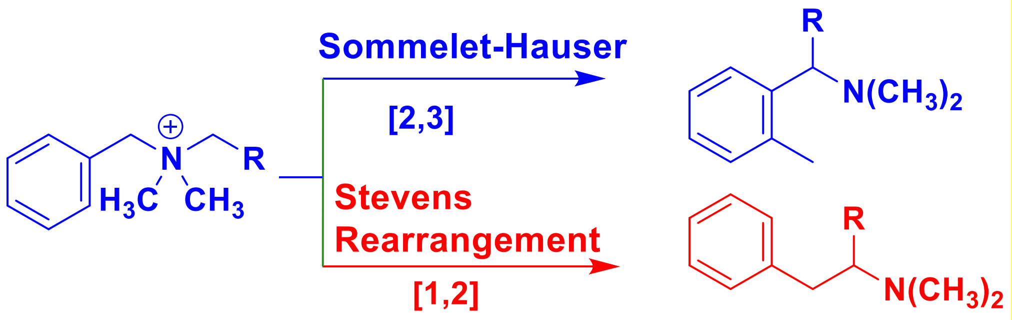
8. Sommelet-Hauser rearrangement………… Examples

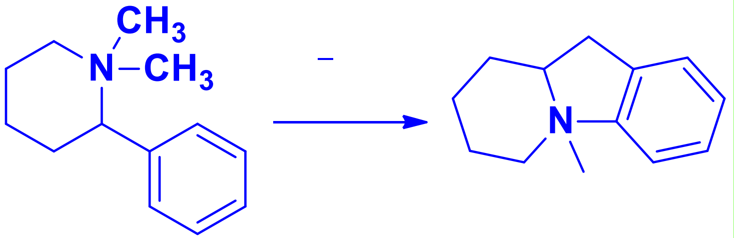
- ❖ **In any case, Stevens rearrangement is a competing process. There can be competition between Stevens and Sommelet-Hauser rearrangement mechanisms.**



Stevens rearrangement product

Sommelet-Hauser rearrangement product

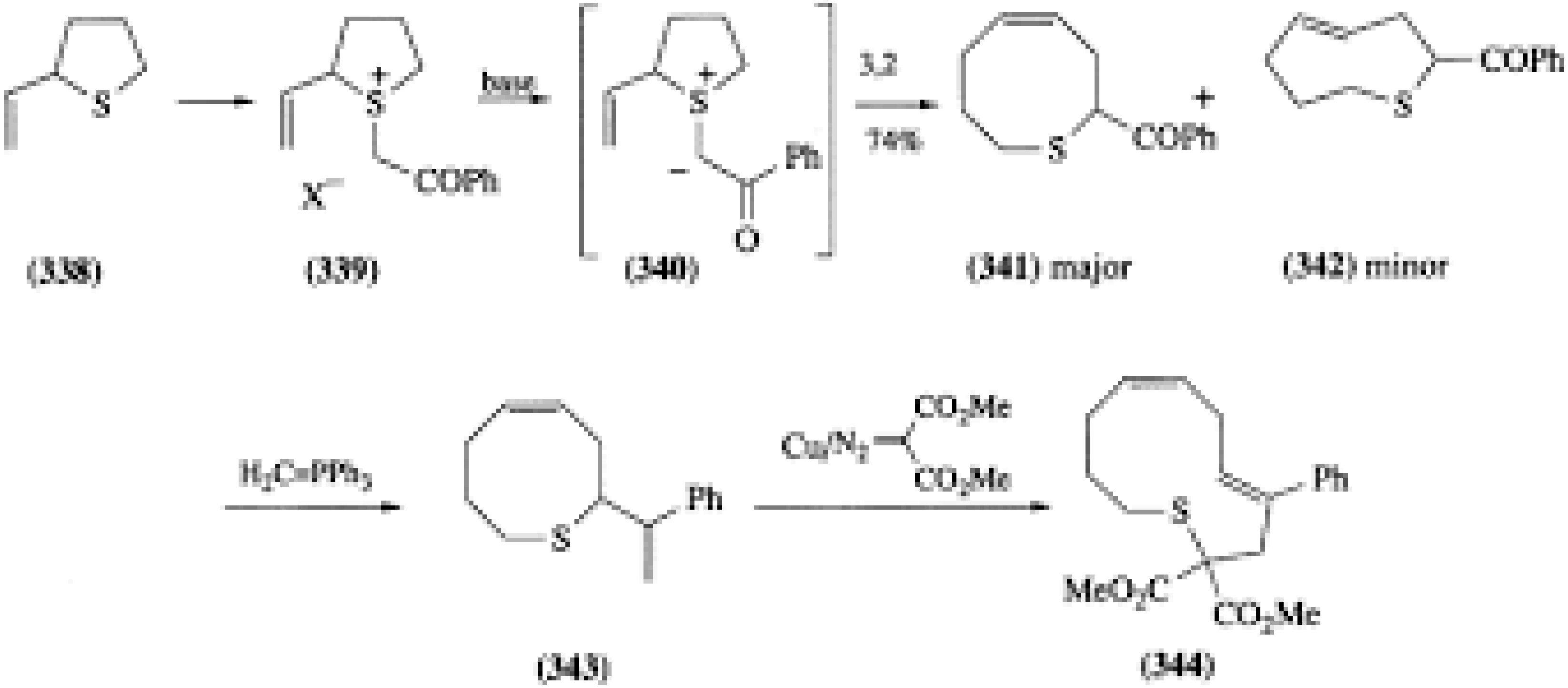


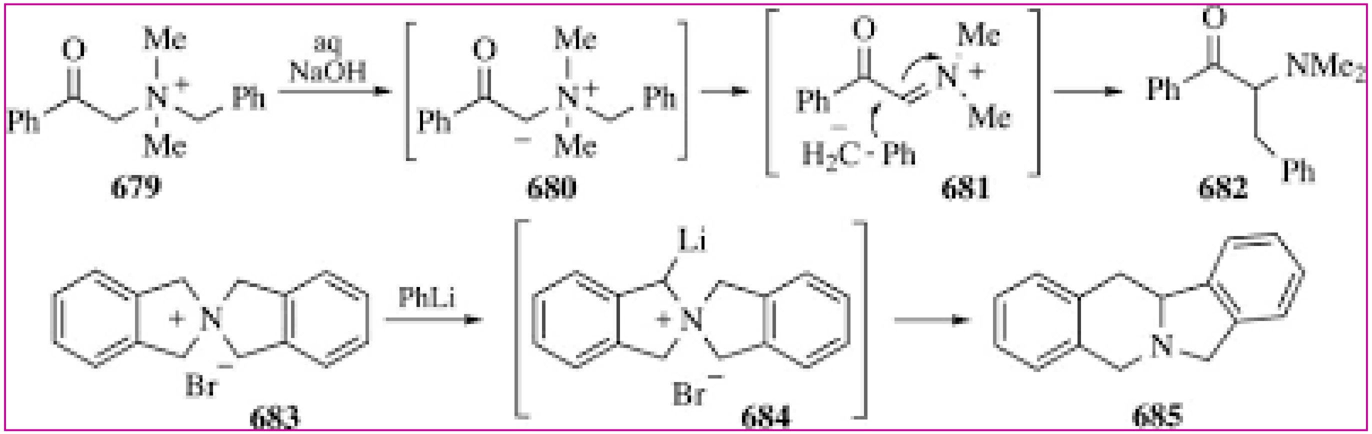


1,1dimethyl-2-phynyl piperidinium ion

J.Org.Chem, **1991**, 56, 6933

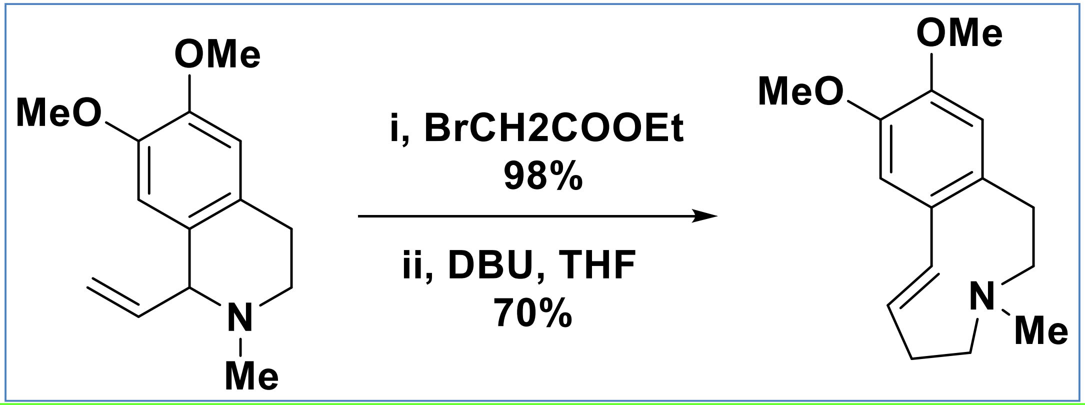
8. Sommelet-Hauser rearrangement…………



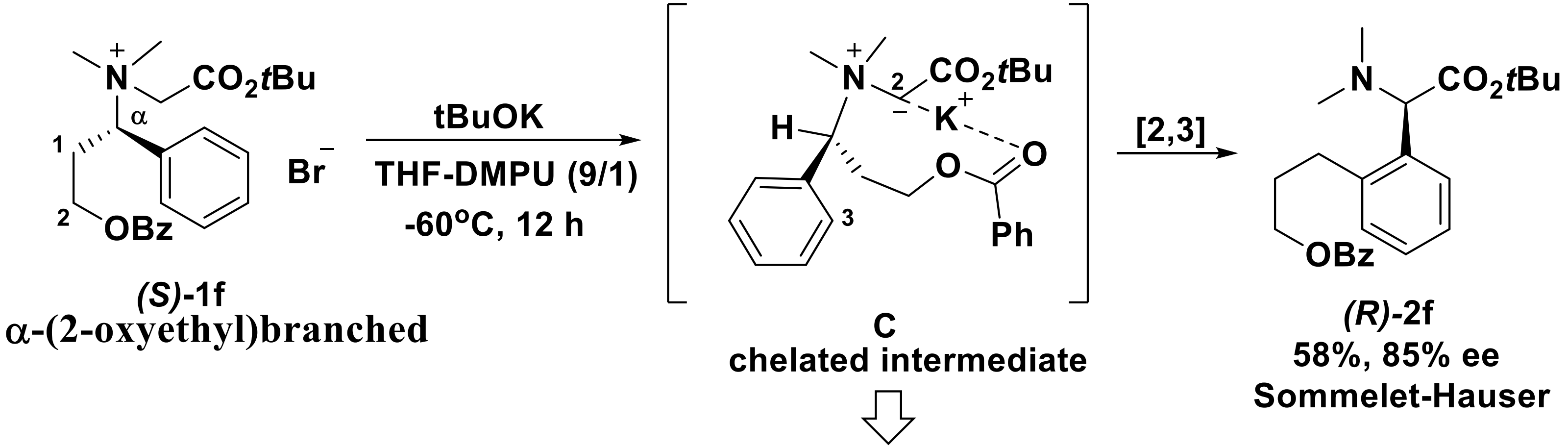


8. Sommelet-Hauser rearrangement………..

Example – 1



Example – 2



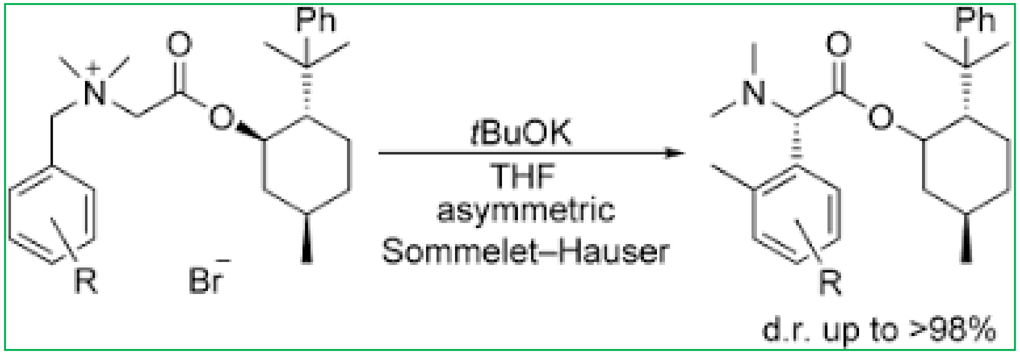
(S)-1f
α-(2-oxyethyl)branched

C
chelated intermediate

(R)-2f
58%, 85% ee
Sommelet-Hauser

Enhancement of dearomative [2,3] sigmatropic rearrangement

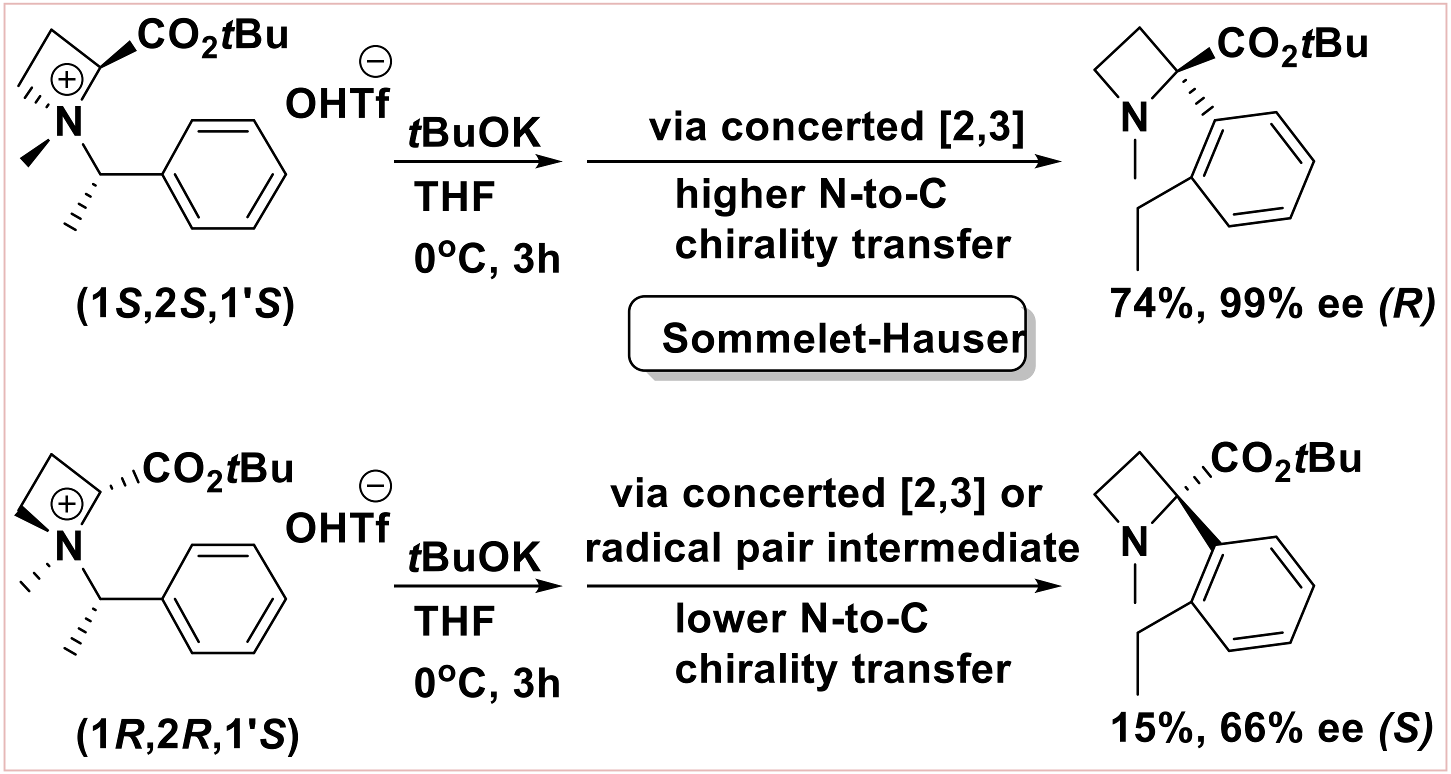
Example – 3

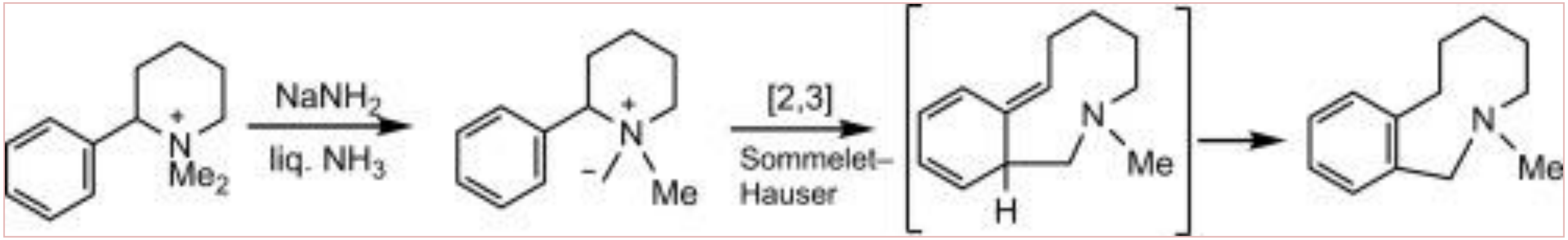


D.O. Tymoshenko, in Comprehensive Heterocyclic Chemistry III, 2008

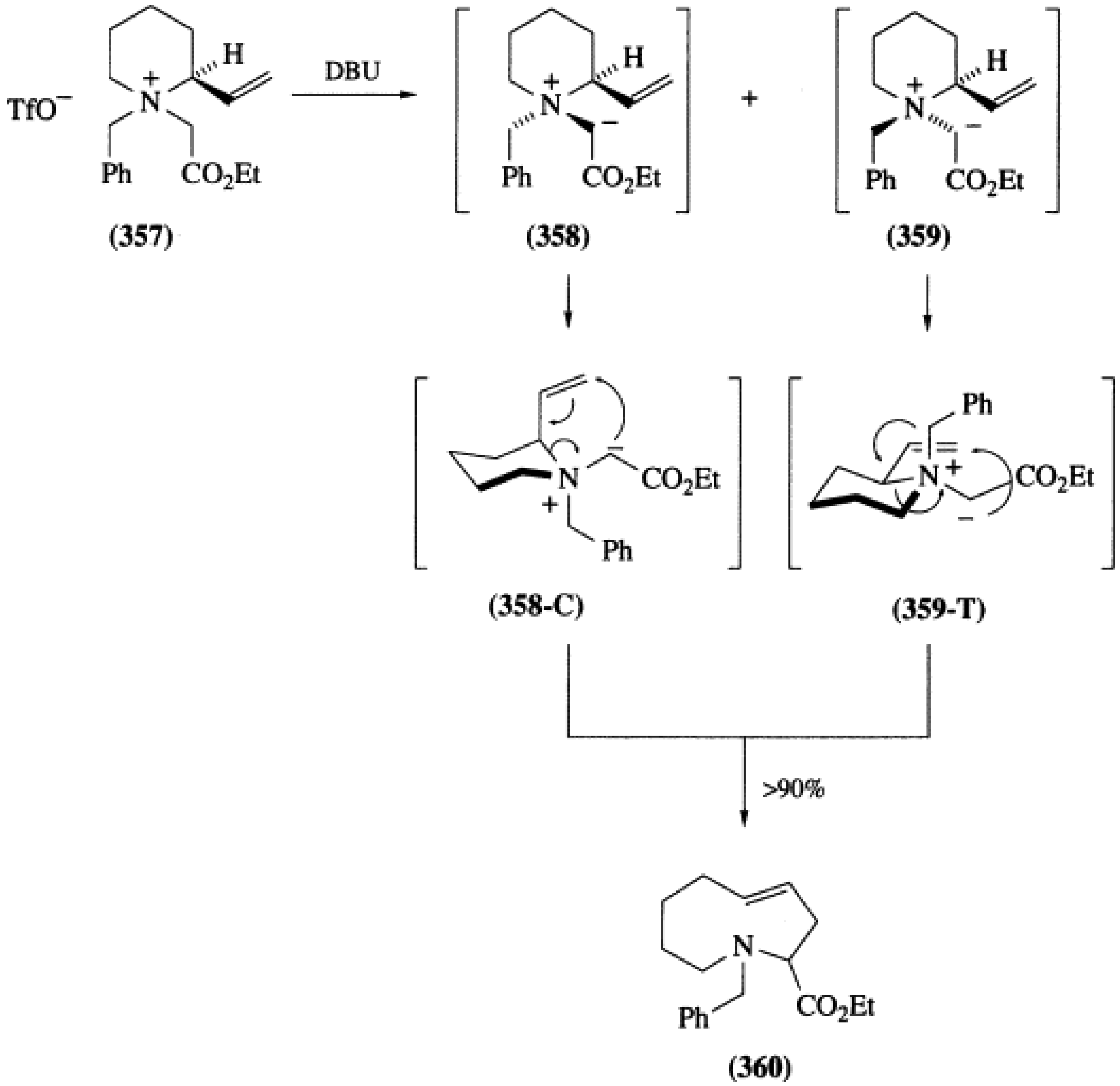
8. Sommelet-Hauser rearrangement………..

Example – 4



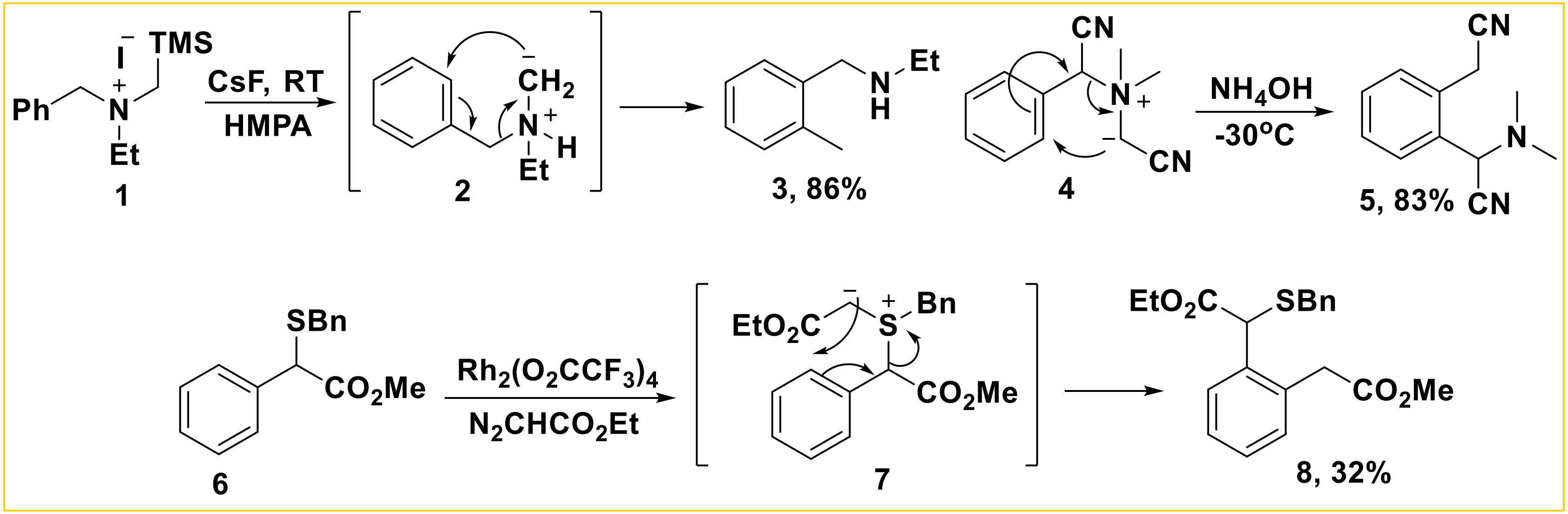


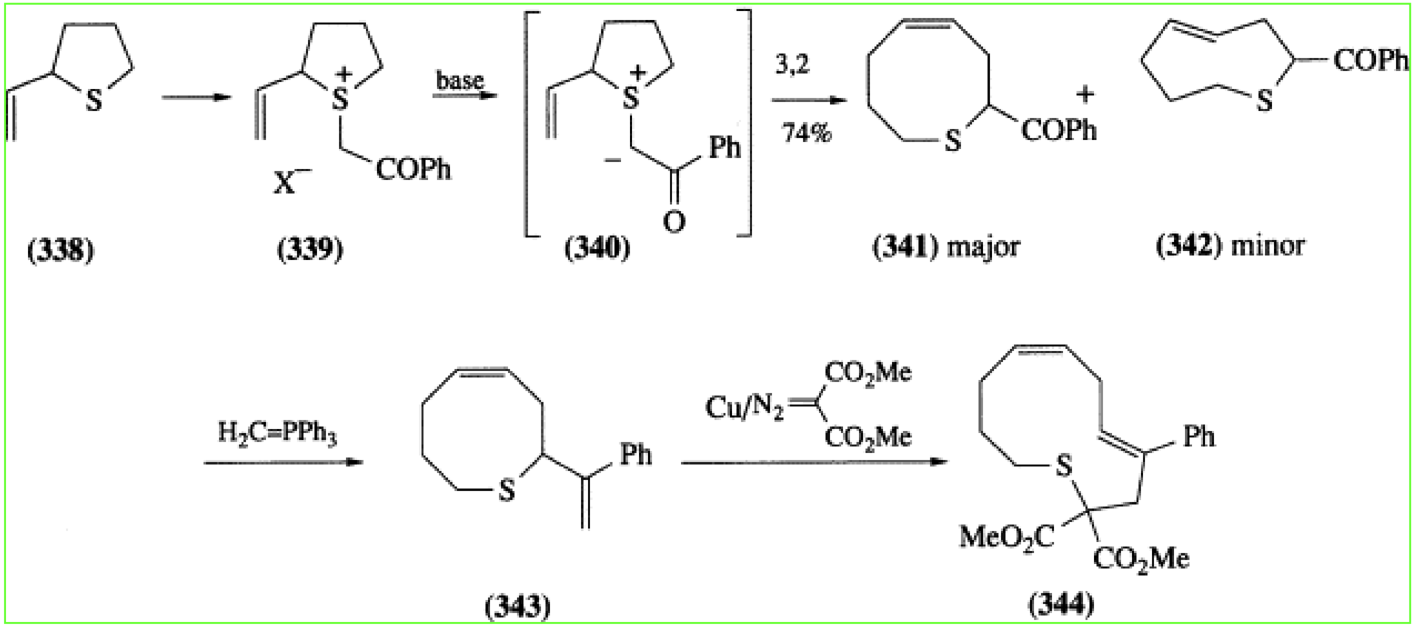
8. Sommelet-Hauser rearrangement………..



D.O. Tymoshenko, in Comprehensive Heterocyclic Chemistry III, 2008
https://www.sciencedirect.com/topics/chemistry/sommelet-hauser-rearrangement

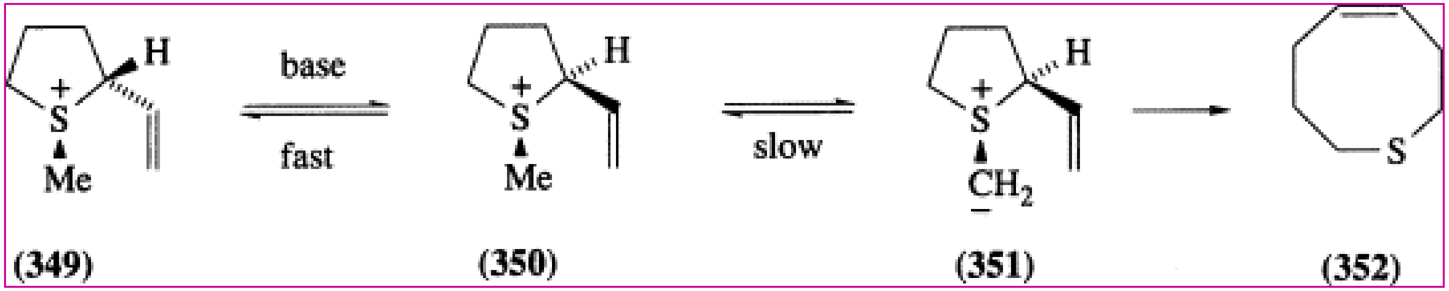
8. Sommelet-Hauser rearrangement…………

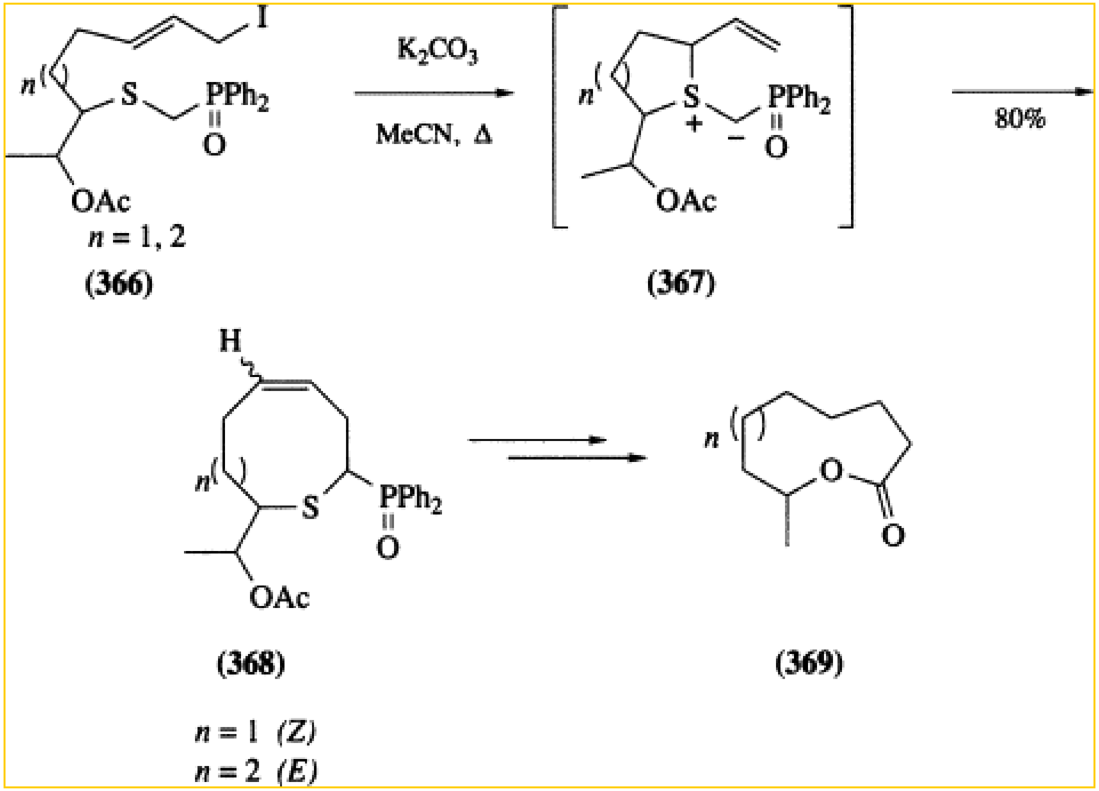




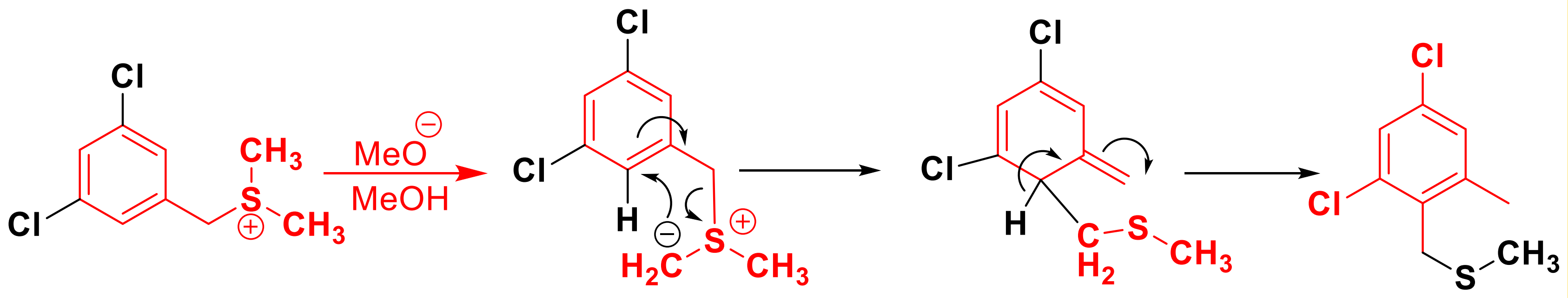
D.O. Tymoshenko, in Comprehensive Heterocyclic Chemistry III, 2008

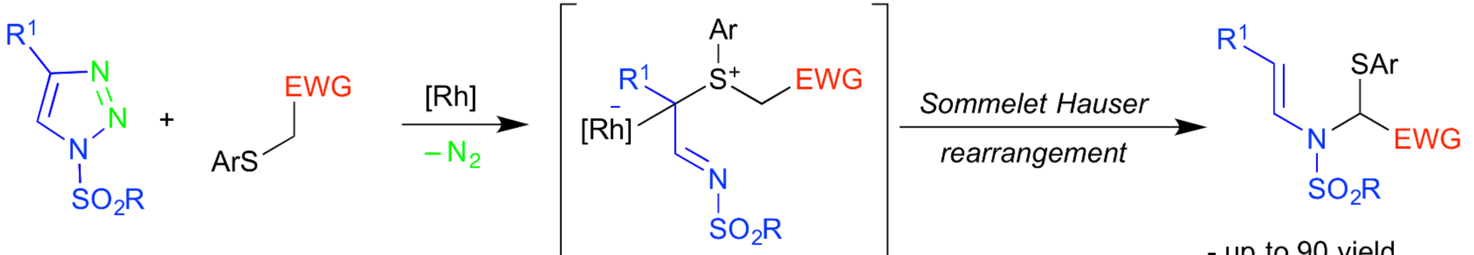
8. Sommelet-Hauser rearrangement………..





D.O. Tymoshenko, in Comprehensive Heterocyclic Chemistry III, 2008

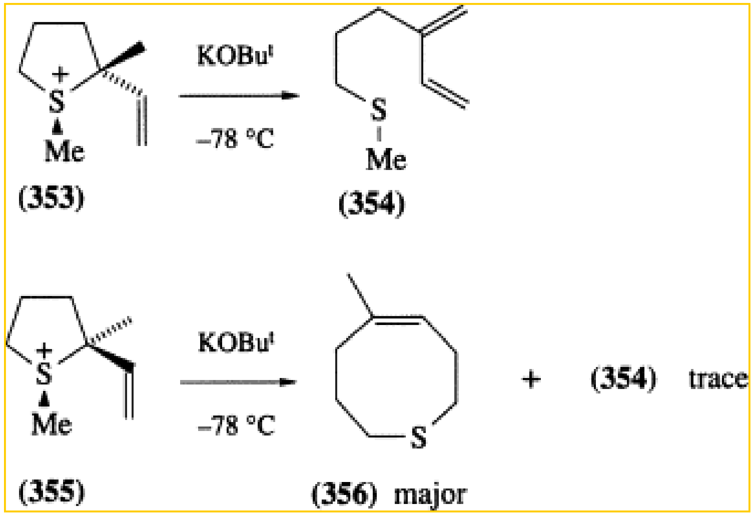




EWG = CO_2R, COR
$CONEt_2$

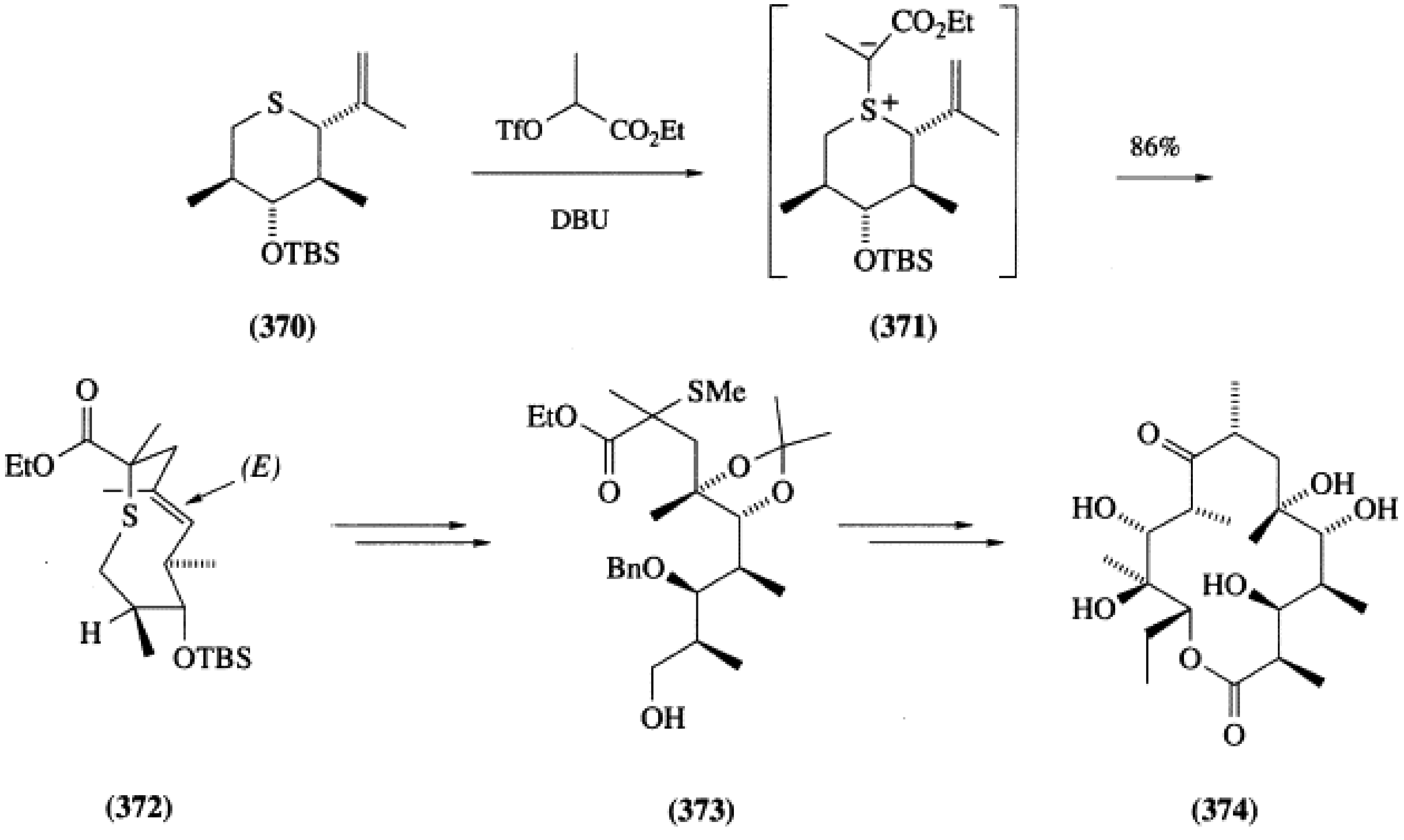
in-situ generated
S-ylide

- up to 90 yield
- 33 examples
- Excellent FG tolerance
- Highly selectivity



Tetrahedron letter, **1983**, 24, 2071

8. Sommelet-Hauser rearrangement………..



(370) (371)

(372) (373) (374)

Erythronolide A

D.O. Tymoshenko, in Comprehensive Heterocyclic Chemistry III, 2008

8. Sommelet-Hauser rearrangement…………

References

1. D.O. Tymoshenko, in Comprehensive Heterocyclic Chemistry III, 2008
https://www.sciencedirect.com/topics/chemistry/sommelet-hauser-rearrangement
2. M. Sommelet, Compt. Rend. 205, 56 (**1937**).
3. Rearrangements of Benzyltrimethylammonium Ion and Related Quaternary Ammonium Ions by Sodium Amide Involving Migration into the Ring Simon W. Kantor, Charles R. Hauser J. Am. Chem. Soc., **1951**, 73 (9), pp 4122–4131
doi:10.1021/ja01153a022
4. March, Jerry (**1985**), *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (3rd ed.), New York: Wiley, ISBN 0-471-85472-7
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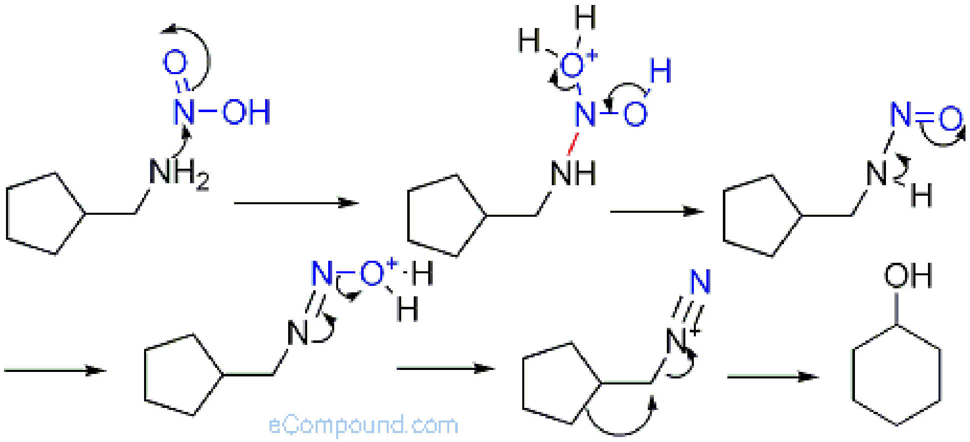
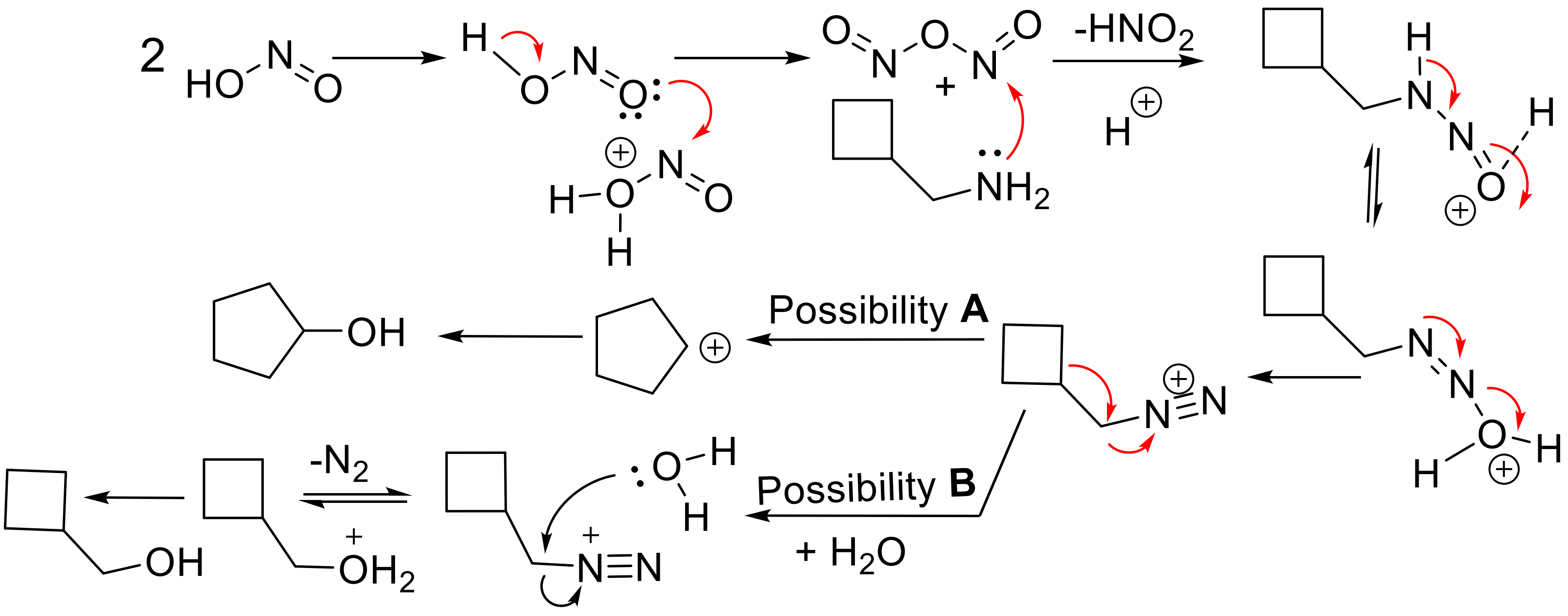
9. Demjanov rearrangement



- **The Tiffeneau-Demjanov rearrangement is a carbocation rearrangement of primary amines with nitrous acid to give rearranged alcohols.**
- **It involves substitution by an OH group with a possible ring expansion by one carbon.**
- **Often, the Demjanov rearrangement is followed by deprotonation to produce a cyclic ketone, an incredibly useful molecule for further reactions such as various nucleophilic attacks.**
- **The starting ring can be between four and eight carbons, appears to be useful in preparation of five, six, and seven membered rings, and to be less valuable for the preparation of smaller or larger rings.**
- **Yields decrease as initial ring size increases.**

9. Demjanov Rearrangement……Mechanism



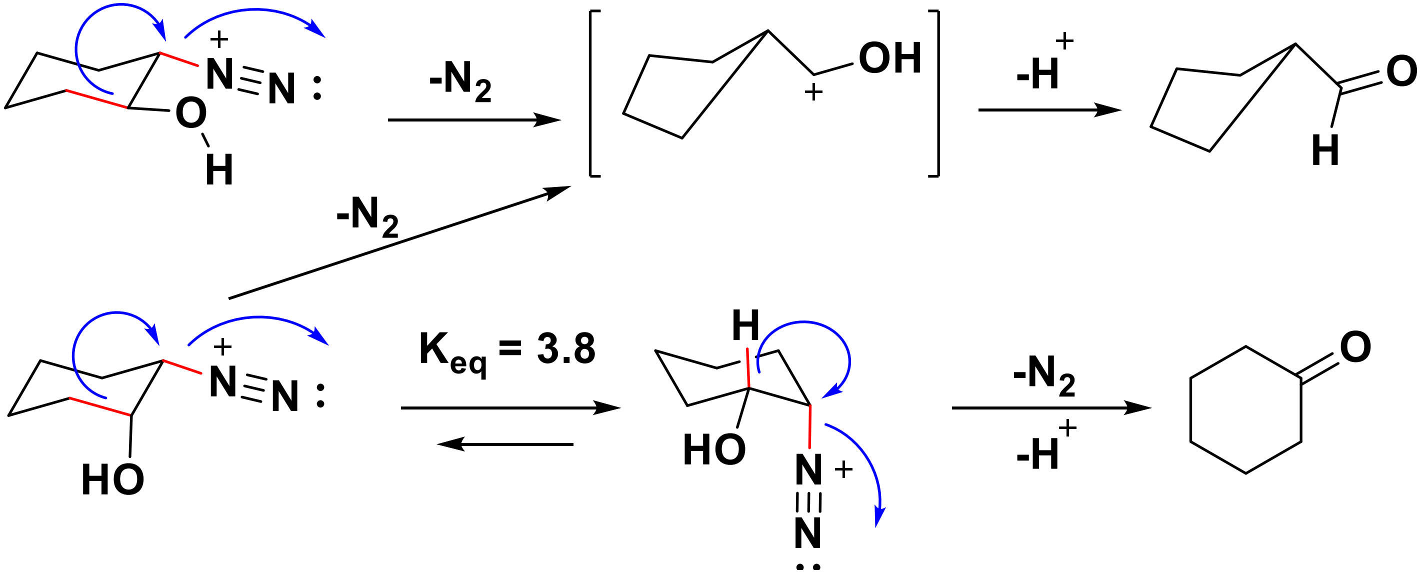
✓ The mechanism begins with the reaction of two nitrous acid molecules to produce nitrogen trioxide. This is then reacted with the NH_2 molecule attached to the four membered ring.

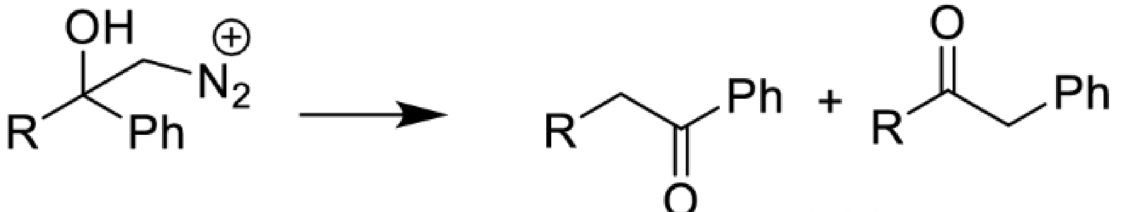
✓ At this point, two possibilities occur.

✓ In possibility A, the four membered ring expands to produce a charged five membered ring, thus expelling the nitrogen gas.

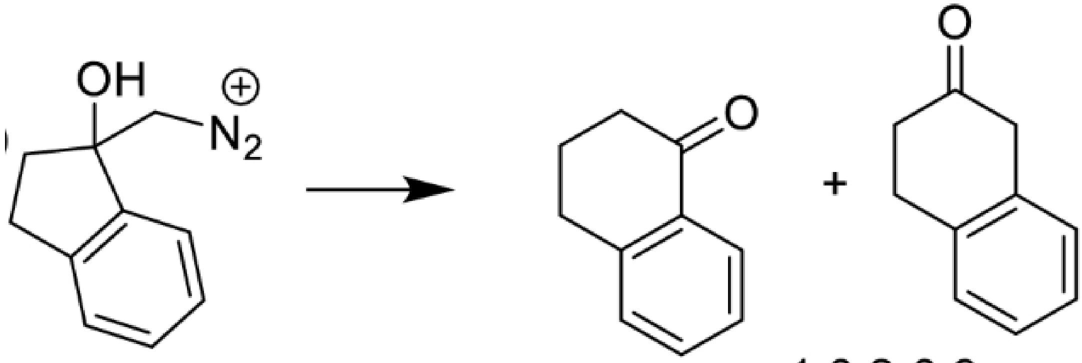
✓ Under the possibility B one can expect unrearranged alcohol formation

9. Demjanov Rearrangement……Examples





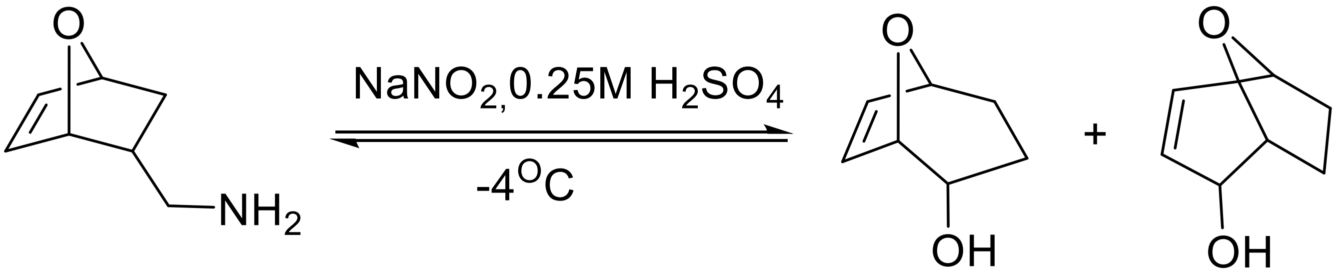
1:30

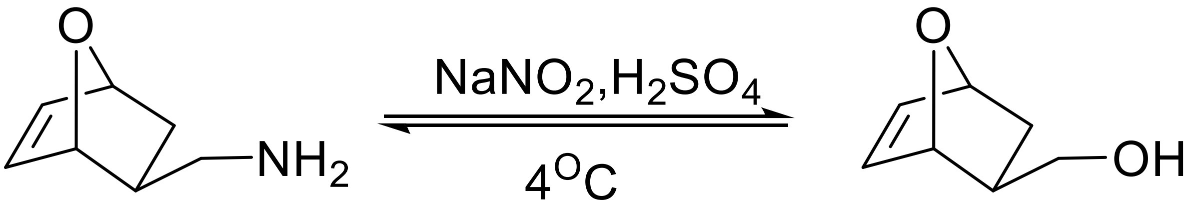


1:0.2-0.9

9. Demjanov rearrangement ……. Example

- It has been shown that the Demjanov reaction is susceptible to regioselectivity.

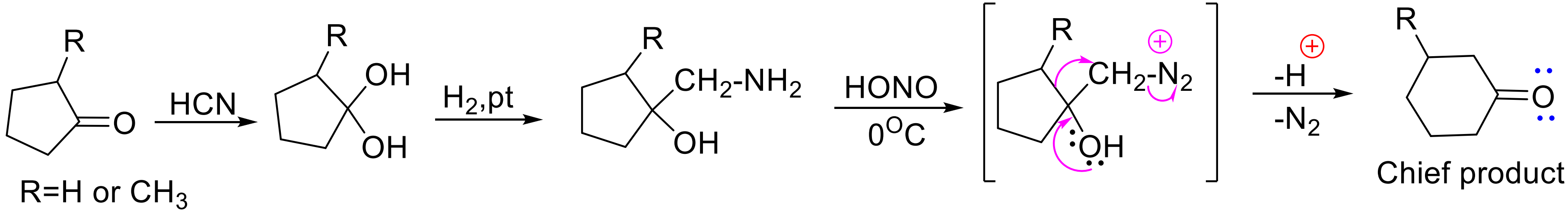


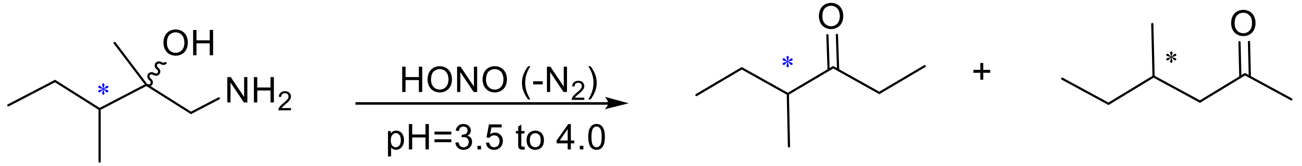


- When an exo methylamine underwent Demjanov nitrous acid deamination, ring enlargement was not produced.
- However, when the endo methylamine underwent the same conditions, a mixture of rearranged alcohols were produced.

9. Demjanov rearrangement ……. Example

- **If R = CH_3, the 2º-alkyl group shifts preferentially, the chief product being 3-methylcyclohexanone; the 2-methyl isomer is a minor product. The second reaction is informative because it demonstrates that the chiral 2º-butyl group moves with retention of configuration.**





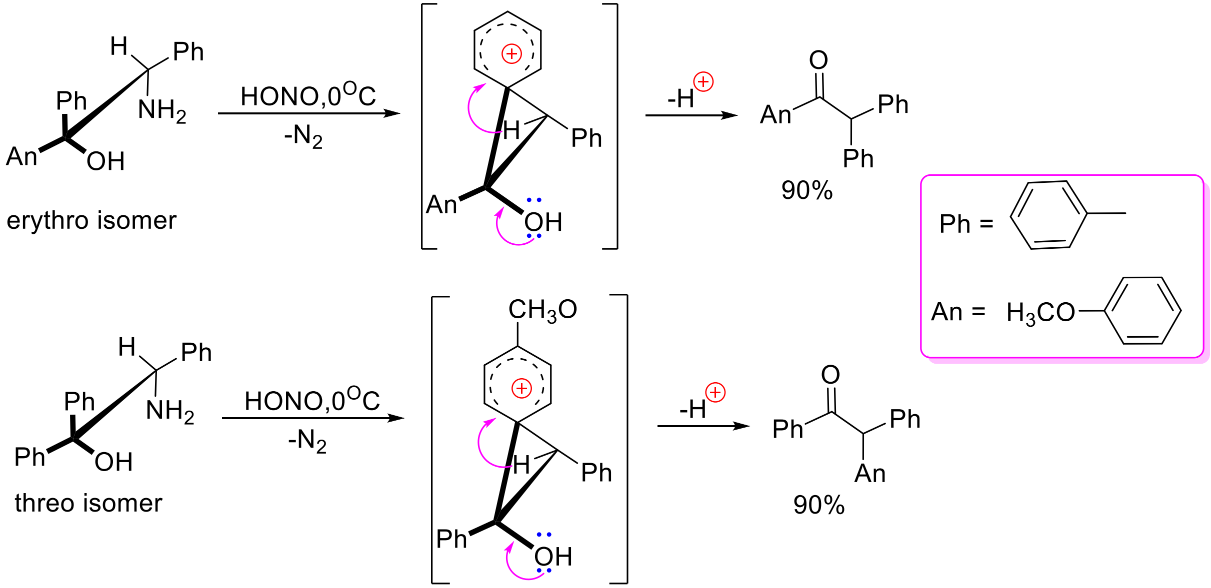
(3R)-1-amino-2,3-dimethyl-2-pentanol
(mixture of diastereomers)

(4R)-4-methyl-3-hexanone
(1,2-methyl shift)

4-methyl-2-hexanone
(1,2-sec-butyl shift,87% R)

9 Demjanov rearrangement ……. Example

❖ The third example illustrates the importance of substrate configuration on the course of rearrangement. The initial stage of an aryl group shift to an adjacent carbocation site may be viewed as an intramolecular electrophilic substitution of the Friedel-Crafts type.

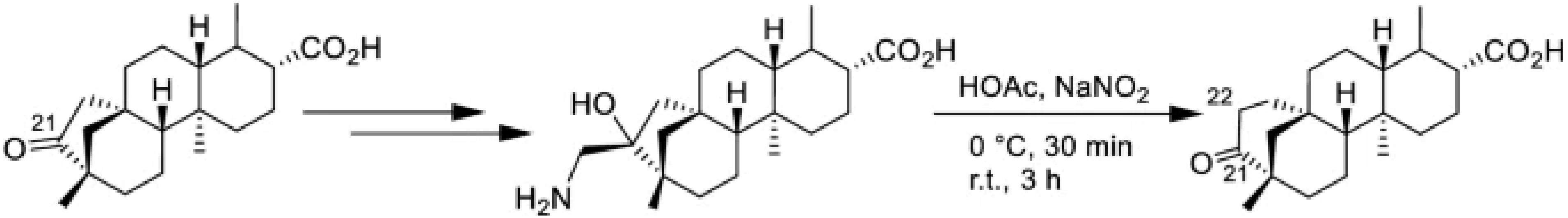


❖ Aryl ring approach from the side opposite to the departing nitrogen of the diazonium ion generates a phenonium ion intermediate (shown in brackets above), the structure of which is similar to a benzenonium ion.

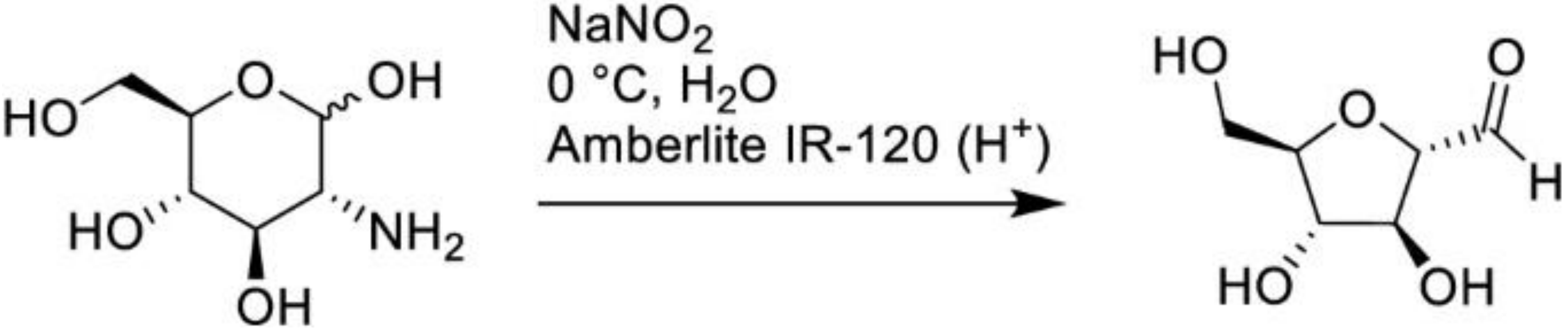
❖ In these two examples, diastereomeric reactants lead preferentially to diastereomeric intermediates, even though the anisyl group has a much greater migratory aptitude than phenyl. Electron pair donation by the hydroxyl substituent then acts to open the three-membered ring of these intermediates, yielding the ketone products.

9 Demjanov rearrangement ……. Example

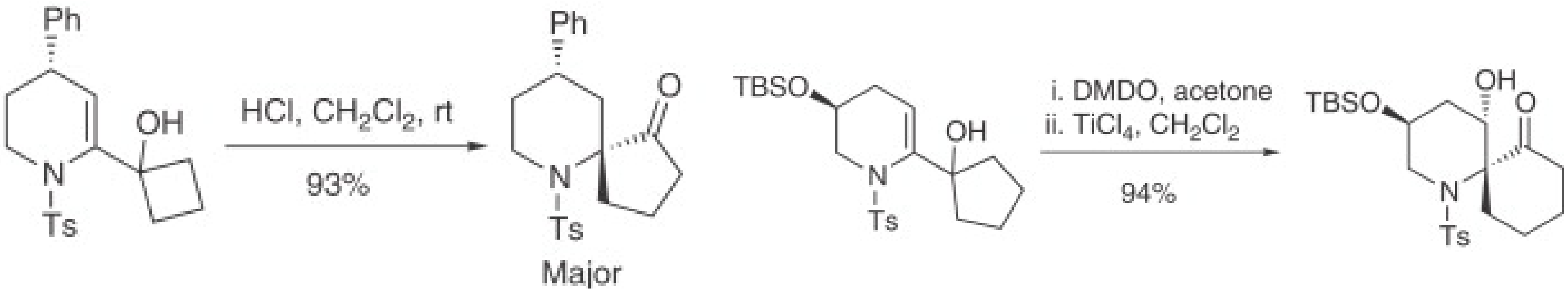
- ✓ **In the frame of the synthesis of the natural product (–)-isosteviol**



- ✓ **Contraction of six-membered ring to a five-membered ring**



9. Demjanov Rearrangement……



- **TD rearrangement provides a simple and selective method for homologation process. It has several advantages compared to other homologation reactions, such as applicability over a wide range of different educts, retention of the configuration, high yield, any unwanted side reactions and high selectivity of the product.**
- **Uses: The Demjanov rearrangement is extremely useful in producing a 1-carbon ring enlargement in four, five or six membered rings. Ring enlargements are incredibly useful in synthesizing mechanically useful molecules.**
- **Problems: This rearrangement also leads to a substituted, but not expanded, byproduct. Thus it can be difficult to isolate the two products and acquire the desired yield. Also, stereoisomers are produced depending on the direction of addition of the water molecule and other molecules may be produced depending on rearrangements.**

9 Demjanov rearrangement ……. Example

References

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6. Fattori, D; Henry, S; Vogel, P.*Tetrahedron*.**1993**, *49*, 1649.
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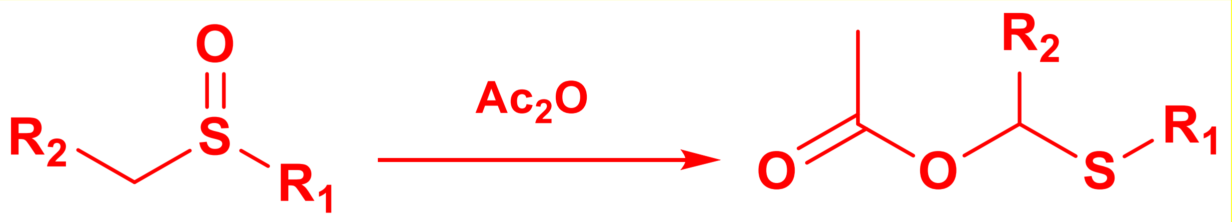
11. Jones, J.B.; Price, P. *Tetrahedron*.**1973**, *29*, 1941.
12. Stern, A.G.; Nickon, A. *J. Org. Chem.***1992**,*57*, 5432.
13. **The synthetic versatility of the Tiffeneau–Demjanov chemistry in homologation tactics, S.M. Kohlbacher, V-S Lonasz, L. Lelo, V. Pace *Monatshefte für Chemie - Chemical Monthly*, 150, 2011–2019, 2019.**

10. Pummerer rearrangement

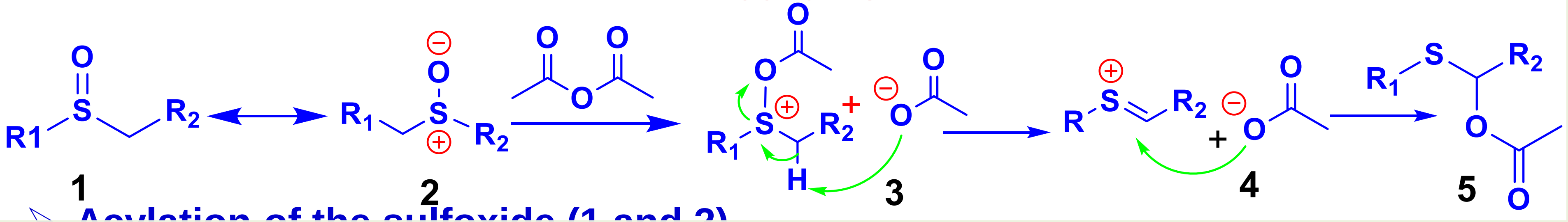
❖ Under Pummerer rearrangement an alkyl sulfoxide rearranges to an α-acyloxy–thioether in the presence of acetic anhydride. In this reaction, sulfur is reduced while adjacent carbon is oxidized.



❖ The usage of α-acyl sulfoxides and Lewis acids, such as $TiCl_4$ and $SnCl_4$.

❖ The reaction to proceed at lower temperatures (0 °C).

Mechanism:



➢ Acylation of the sulfoxide (1 and 2).

➢ Compound 3 undergoes elimination to produce the thionium ion 4.

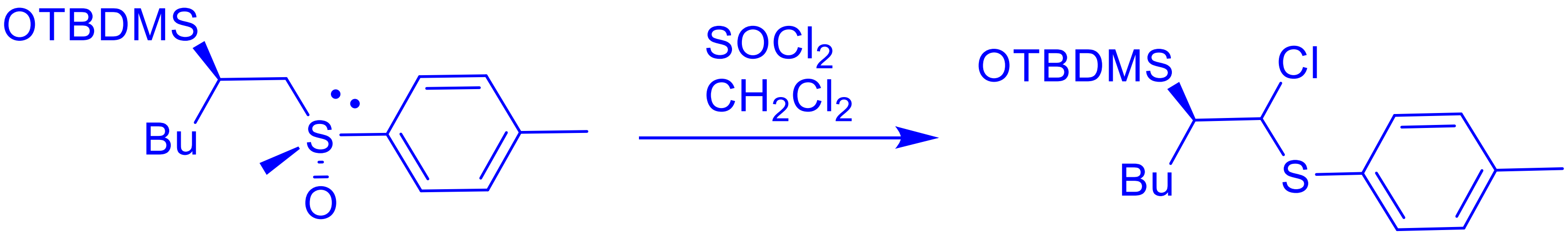
➢ Acetate adds to the sulfonium ion to give the final product 5.

❖ Common activators besides acetic anhydride are trifluoroacetic anhydride and trifluoromethanesulfonic anhydride.

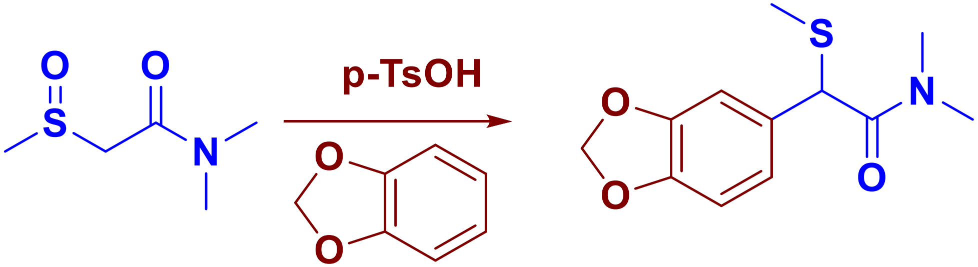
❖ Common nucleophiles besides acetates are arenes, alkenes, amides, halides and phenols.

Variations:

- The thionium ion can be trapped by both intramolecular and intermolecular nucleophiles forming carbon-carbon bonds and carbon-heteroatom bonds.
- For example, thionyl chloride can be used to generate and trap the sulfonium ion

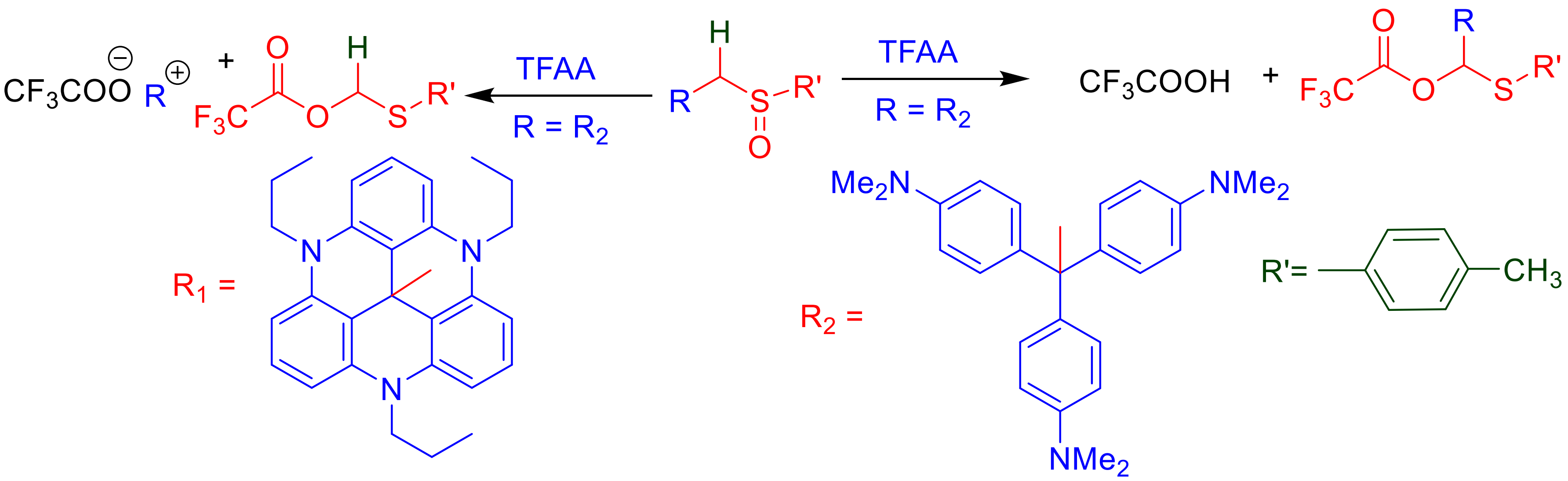


- Nucleophiles such as veratrole can also be used.



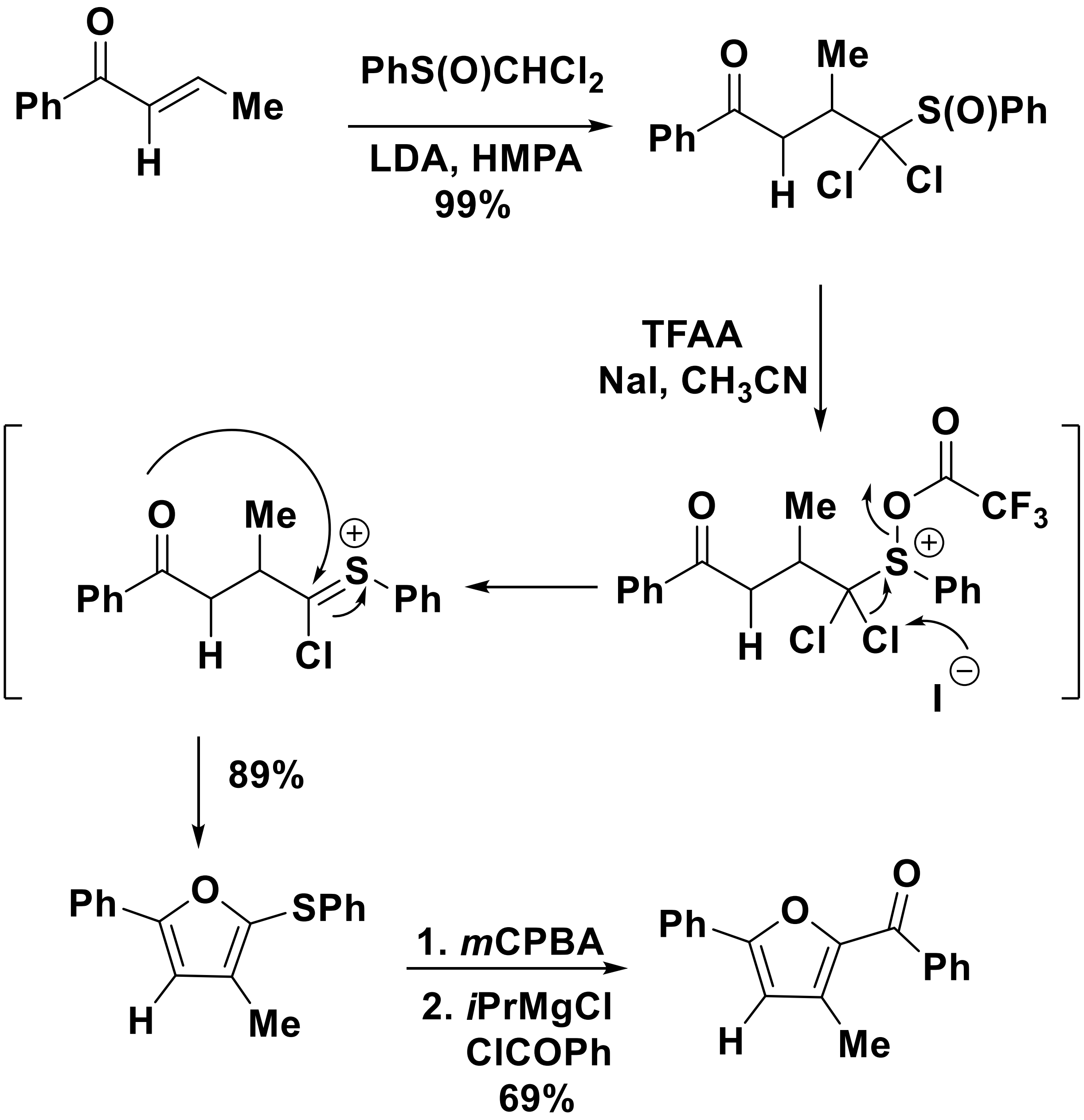
Pummerer fragmentation

- The α-organic residue can form a very good leaving group this group and not the α-hydrogen atom will eliminate in the intermediate step in a Pummerer fragmentation.
- This reaction type is demonstrated below with a set of sulfoxides and trifluoroacetic anhydride (TFAA)

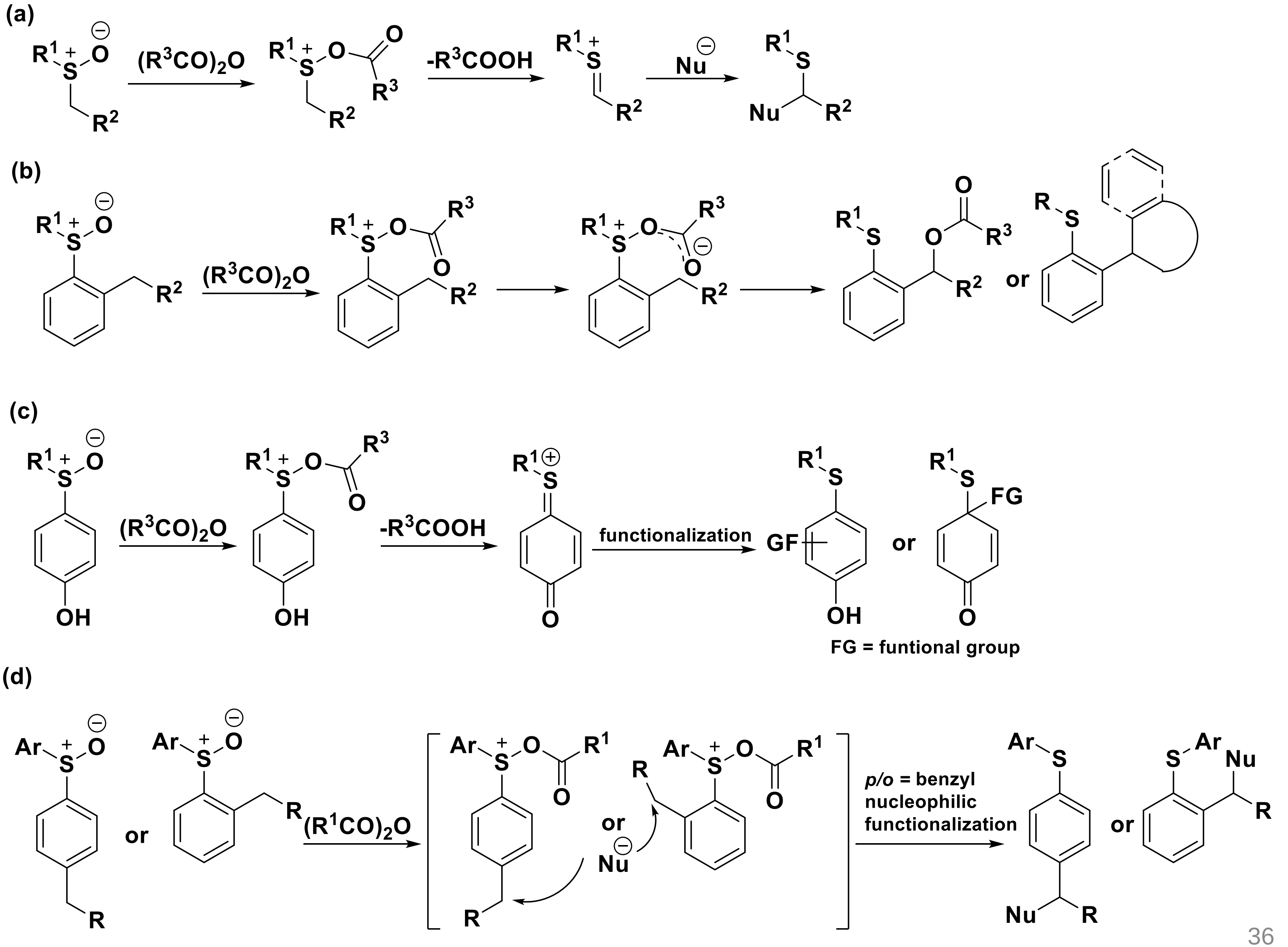


- In the reaction on the left, organic group is methyl violet and the carbocation has moderate pKa = 9.4 leading to a classical Pummerer rearrangement.
- The reaction on the left is a fragmentation because the leaving group with pKa+ = 23.7 is particularly stable.

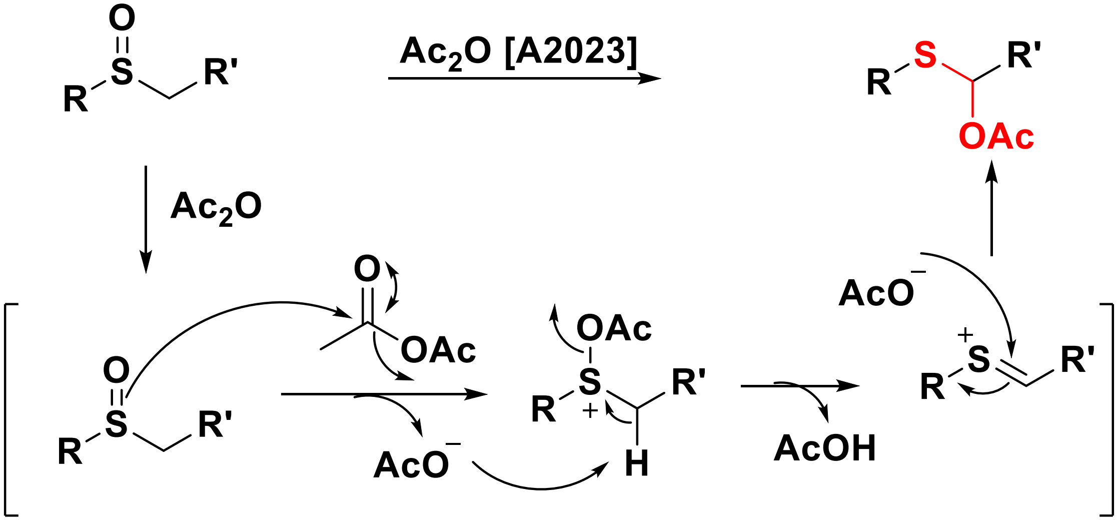
Example – 1


PhS(O)CHCl$_2$
LDA, HMPA
99%
TFAA
NaI, CH$_3$CN
89%
1. *m*CPBA
2. *i*PrMgCl
ClCOPh
69%

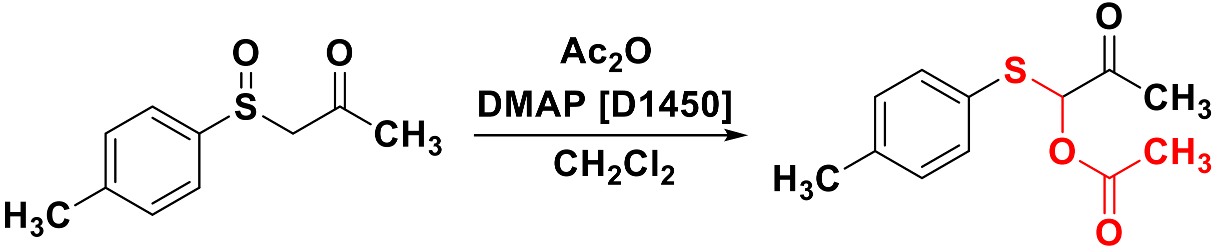
Example – 2

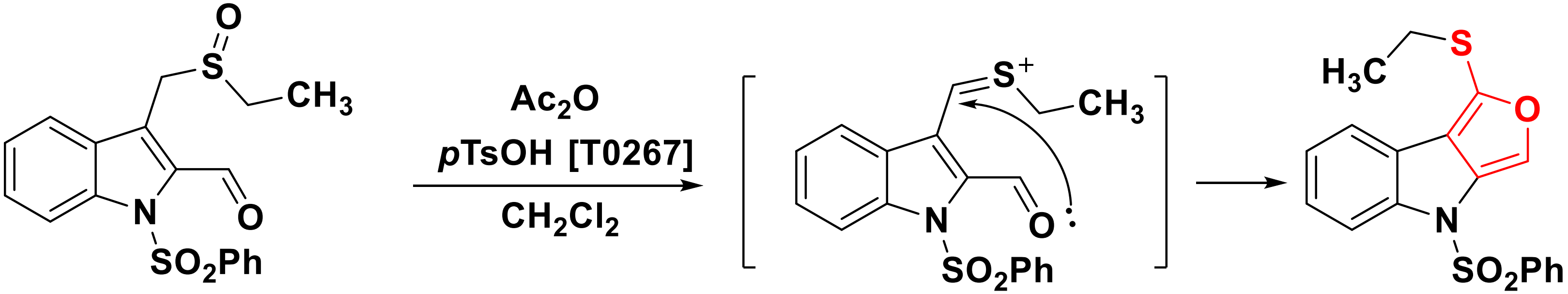

(a)
(R³CO)₂O
-R³COOH
Nu
(b)
(R³CO)₂O
or
(c)
(R³CO)₂O
-R³COOH
functionalization
or
FG = funtional group
(d)
or
(R¹CO)₂O
or
Nu
p/o = benzyl nucleophilic functionalization
or

General Pummerer Reaarangement and Mechanism



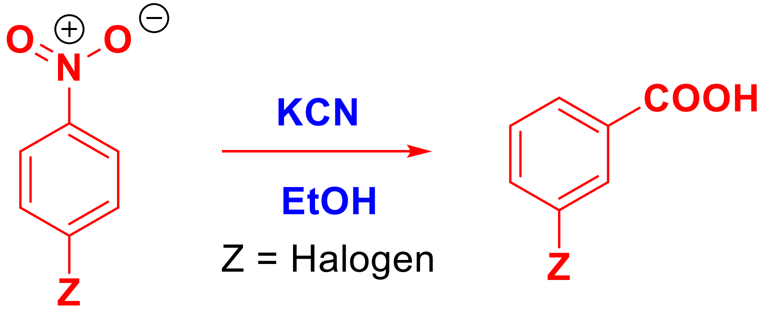
Selected Examples





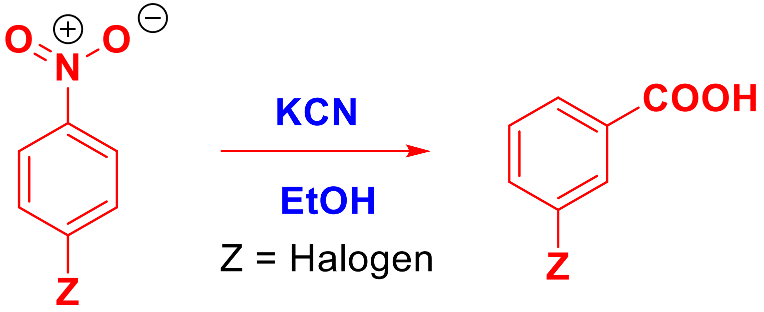
11. Von Richter Rearrangement

- **Hydro-de-nitro-cine-substitution**
- **The chemical reaction of aromatic nitro compounds with potassium cyanide giving carboxylation ortho to the position of the former nitro group is called Von Richter Rearrangement.**



- **The reaction is named after Victor von Richter. Carboxylation of para- or meta-substituted aromatic nitro compounds with cyanate takes place at 120-270°.**
- **The carboxyl group enters with cine substitution in a position ortho to the eliminated nitro group**
- **At one time it was believed that a nitrile, ArCN, was an intermediate, since cyanide is the reagent and nitriles are hydrolyzable to carboxylic acids under the reaction conditions.**

11. Von Richter Rearrangement

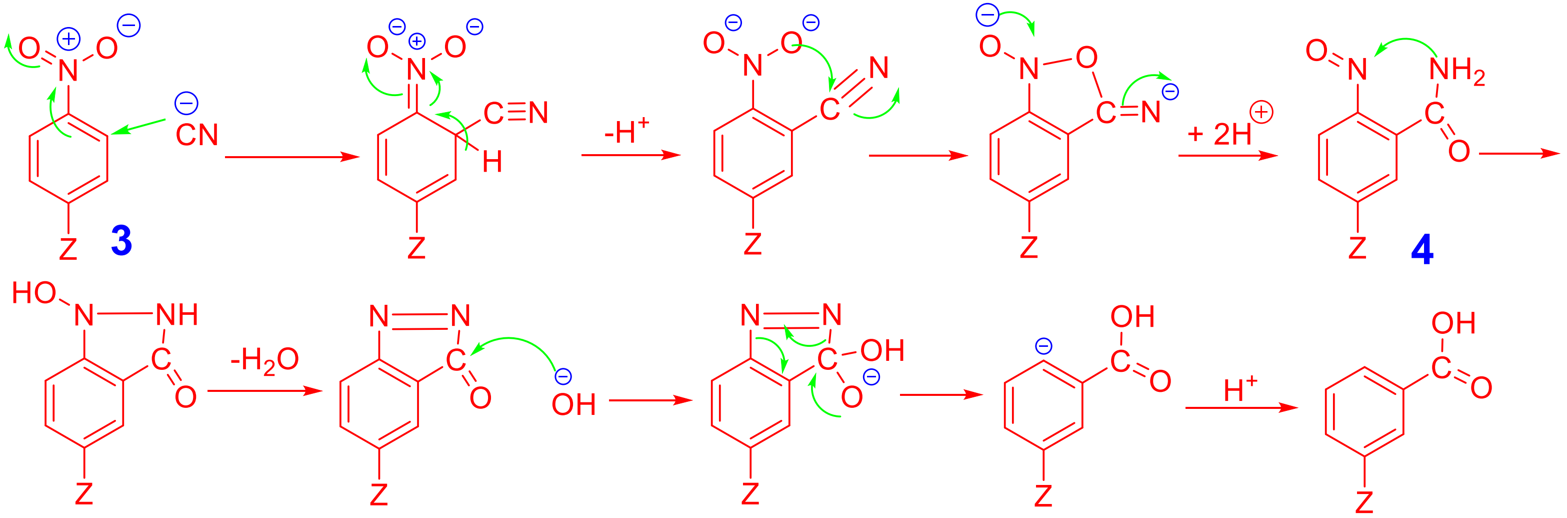


- However, a remarkable series of results proved this belief to be an error. Bunnett and Rauhut demonstrated that a-naphthyl cyanide is not hydrolysable to a-naphthoic acid under conditions at which b-nitronaphthalene undergoes the von Richter rearrangement to give a-naphthoic acid. This proved that the nitrile cannot be an intermediate.
- It was subsequently demonstrated that N_2 is a major product of the reaction.
- It had previously been assumed that all the nitrogen in the reaction was converted to ammonia, which would be compatible with a nitrile intermediate, since ammonia is a hydrolysis product of nitriles.
- At the same time it was shown that NO_2 is not a major product. The discovery of nitrogen indicated that a nitrogen–nitrogen bond must be formed during the course of the reaction. A mechanism in accord with all the facts was proposed by Rosenblum.

11. Von Richter Rearrangement…….

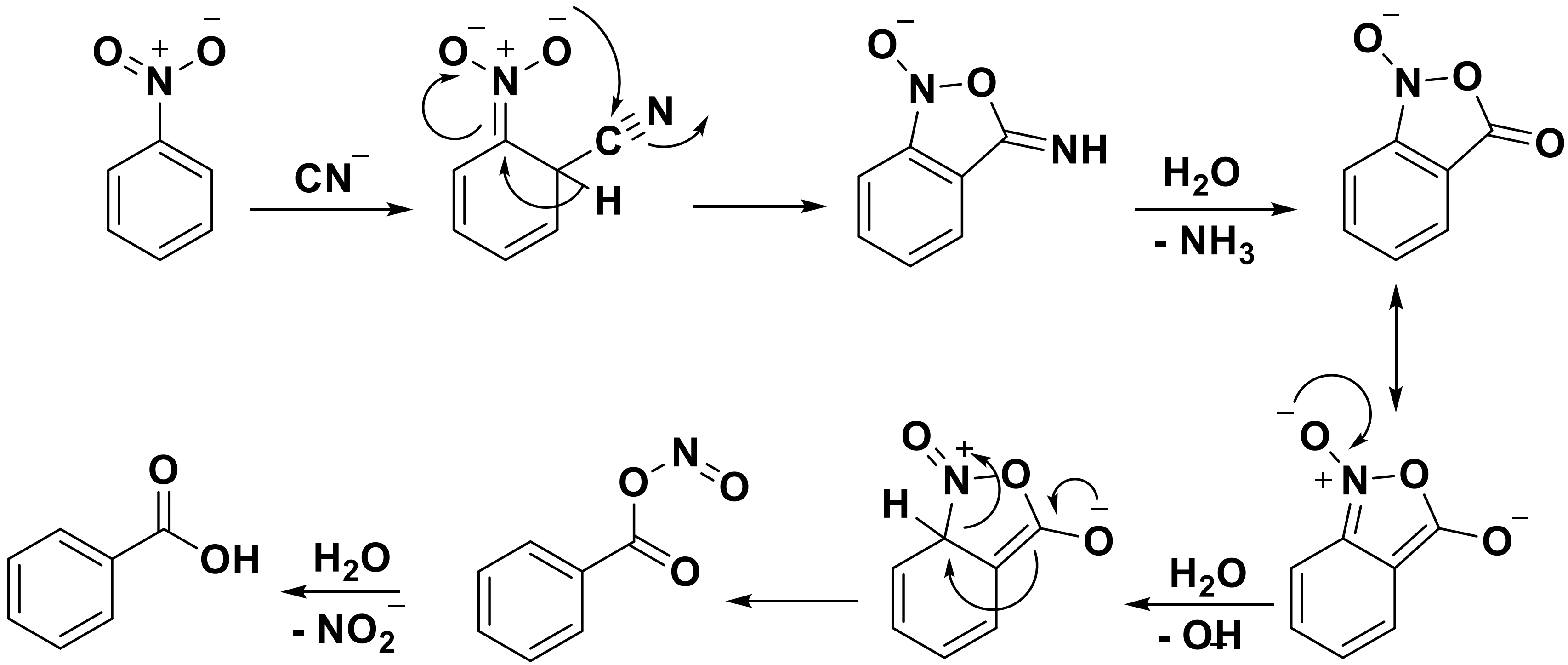
- ❖ As with other nucleophilic aromatic substitutions, the reaction gives best results when electron-withdrawing groups are in ortho and para positions, but yields are low, usually <20% and never >50%.

Mechanism

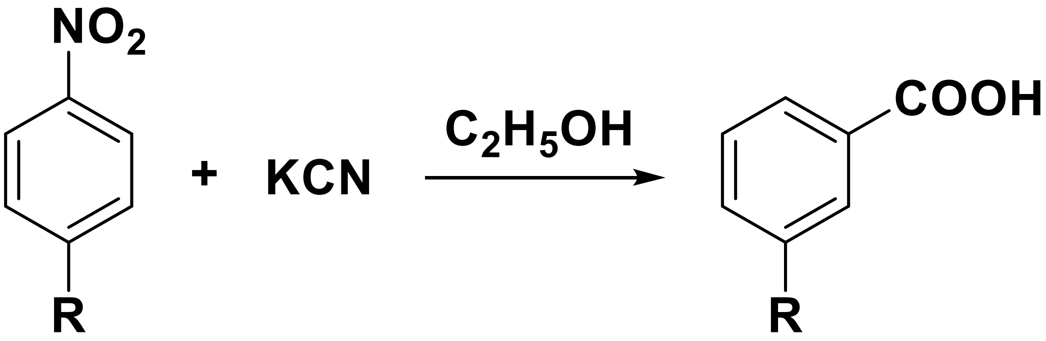


- ➢ Note that 3 is a stable compound; hence it should be possible to prepare it independently and to subject it to the conditions of the von Richter rearrangement. This was done and the correct products are obtained.
- ➢ Further evidence is that when 4 (Z = Cl or Br) was treated with cyanide in $H_2{}^{18}O$, half of the oxygen in the product was labeled, showing that one of the oxygens of the carboxyl group came from the nitro group and one from the solvent, as required by this mechanism.

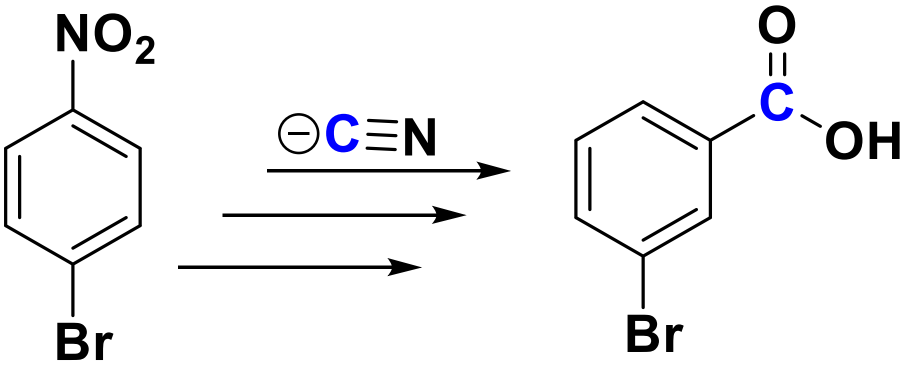
Example – 1



Example – 2

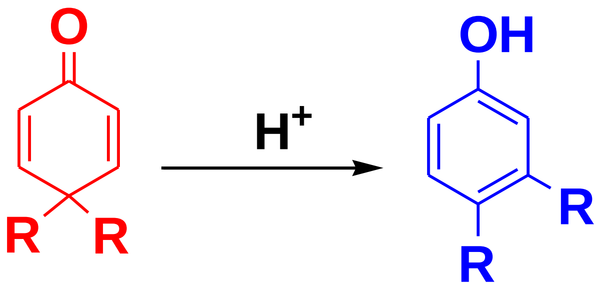


Example – 3



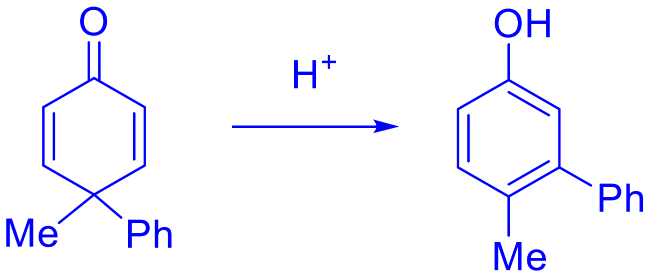
12. Dienone Phenol Rearrangement

- Compound in which a cyclohexadienone having two alkyl groups in the 4th position, upon acid treatment, undergoes migration of one of these groups to a position allylic to the carbonium ion generated by protonation of oxygen.
- Driving force in the overall reaction is the creation of aromatic system.

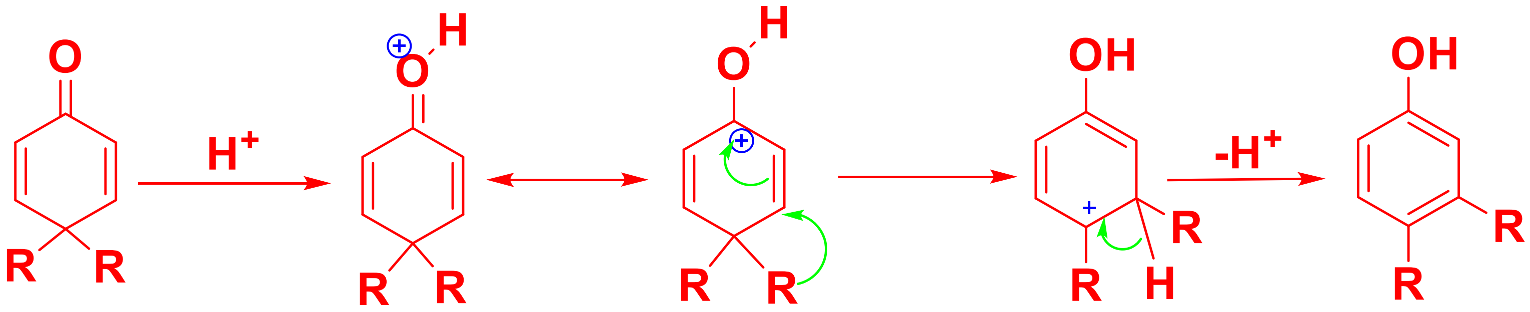


Dienone
quinonid form

Phenol
(benzenoid form)



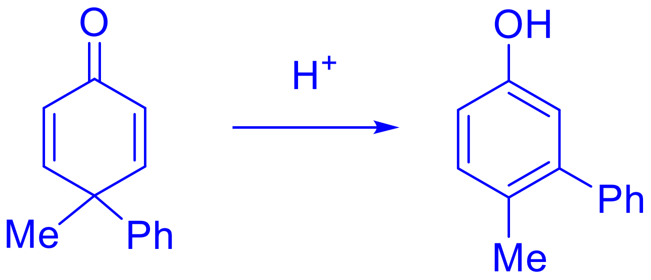
Mechanism:



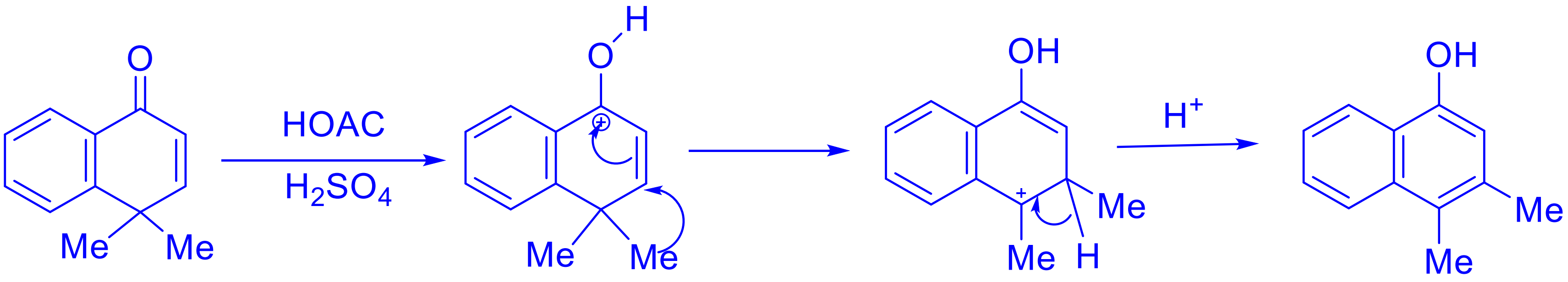
Migratory aptitude: Aryl > Alkyl > H

12. Dienone Phenol Rearrangement………..

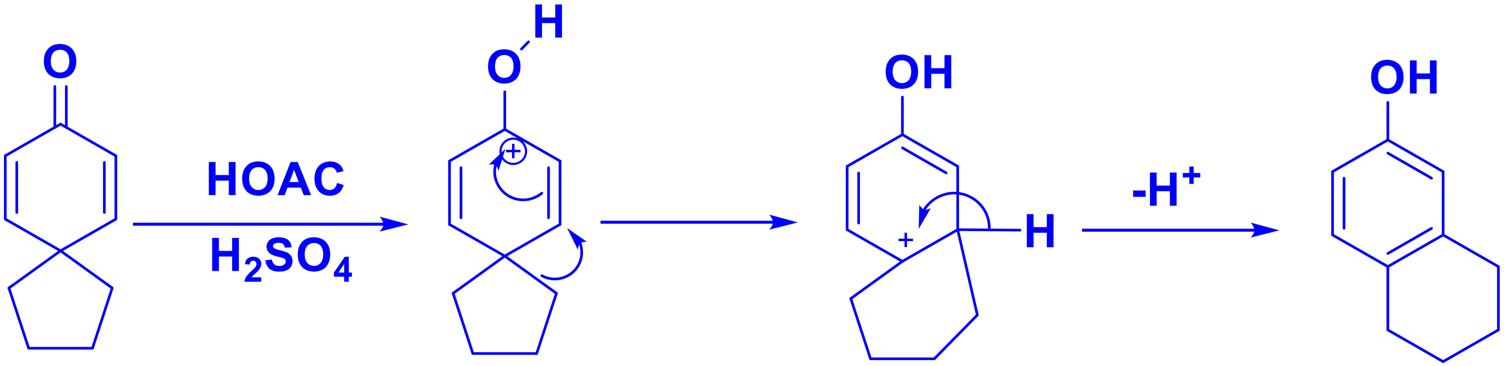
Example-1



Example-2



Example-3

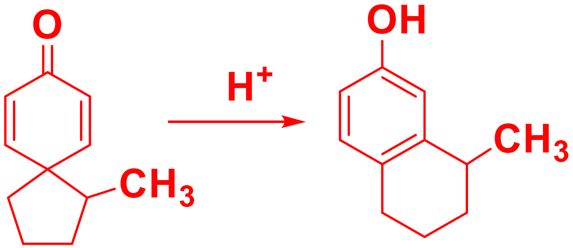


In this reaction the migratory aptitude is in the following order :

3^0 C-Center > 2^0 C-Center > 1^0 C-center

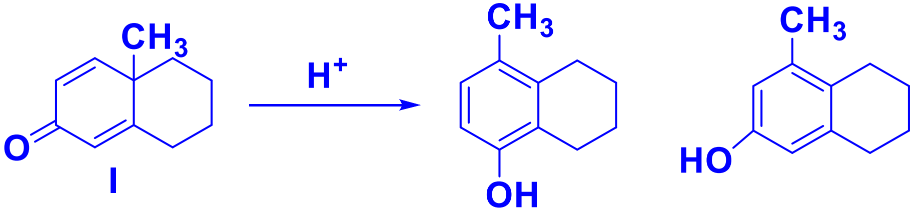
12. Dienone Phenol Rearrangement……………

Example-4



Example- 5

Dienone with angular methyl group (R at ring junction)

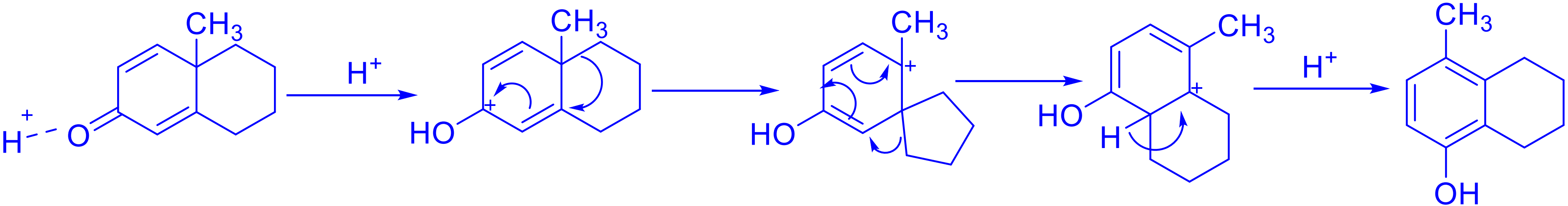


II, Observed

III, Not Oserved

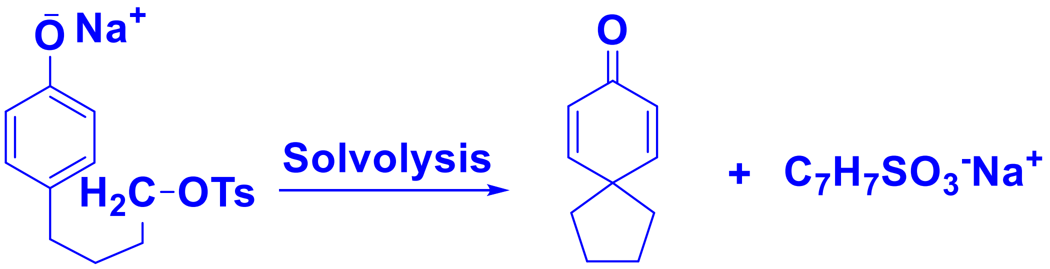
- Compound I on treatment with acid gives only the compound II and not III.
- The absence of compound III in the reaction mixture shows that, the compound I might have followed a different mechanism.

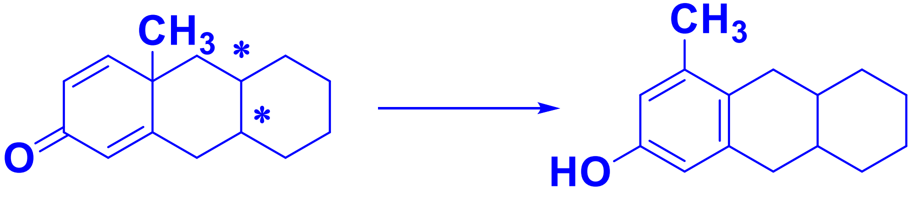
Mechanism



12. Dienone Phenol Rearrangement……………

Evidences

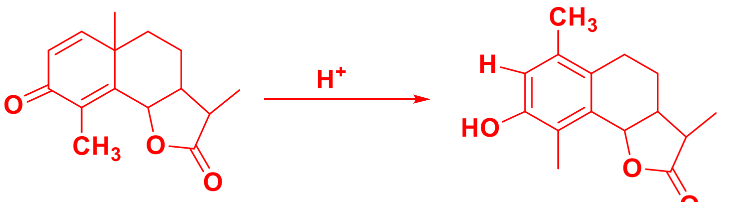




Optically active

Optically inactive

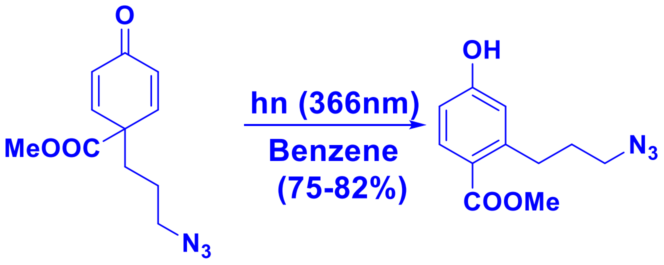
Synthetic applications- Synthesis of highly substituted phenols



Santonin

Desmotroposantonin

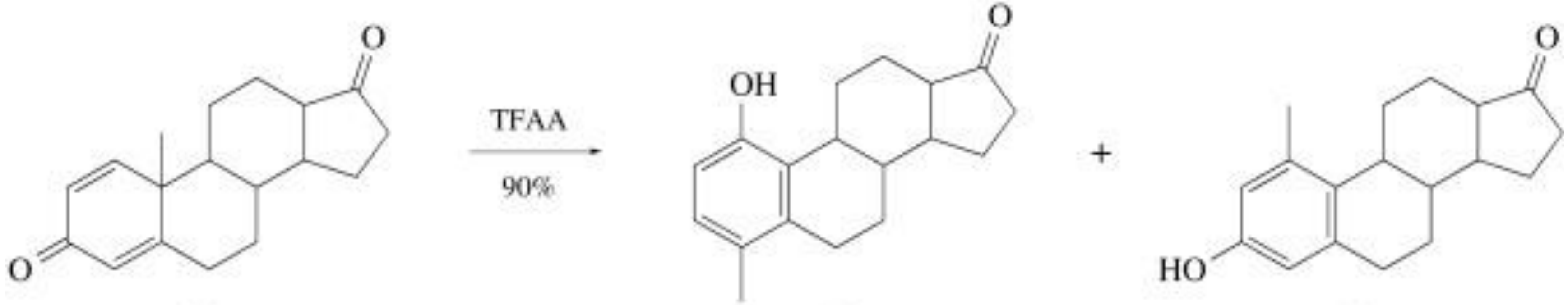
J.Chem.Soc (1930),1110-1115
Originally Carried out by A.Androcci in 1893



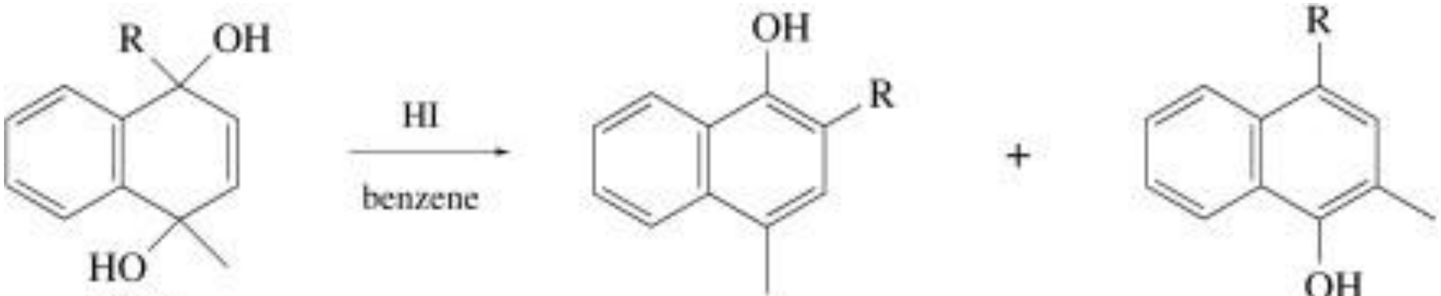
A.G.Shultz et.al
Organic Letters(2001),3,1177,1180

12. Dienone Phenol Rearrangement…………….

Example



(90) (91) 89 : 11 (92)

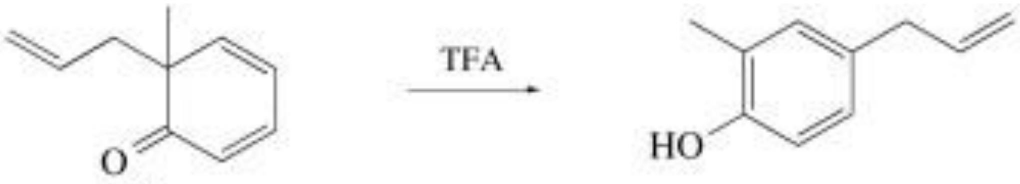


(93)

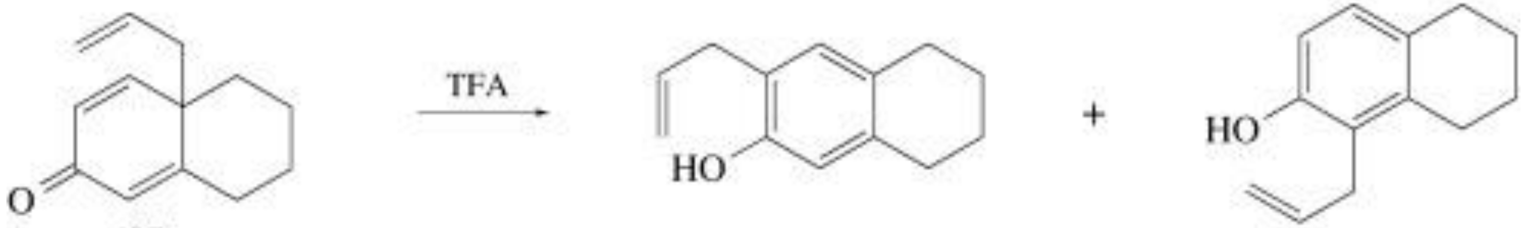
R		*Yield(%)*
Bu^n	83 : 17	50
Bu^s	86 : 14	95
Ph	97 : 3	77

https://www.sciencedirect.com/topics/chemistry/dienone-phenol-rearrangement

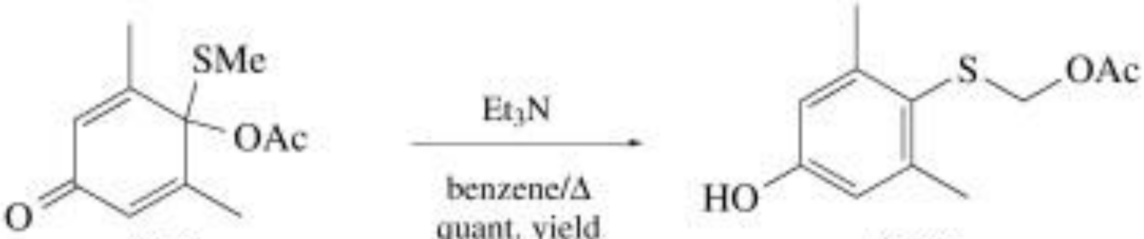
12. Dienone Phenol Rearrangement…………….



(96)



(97)



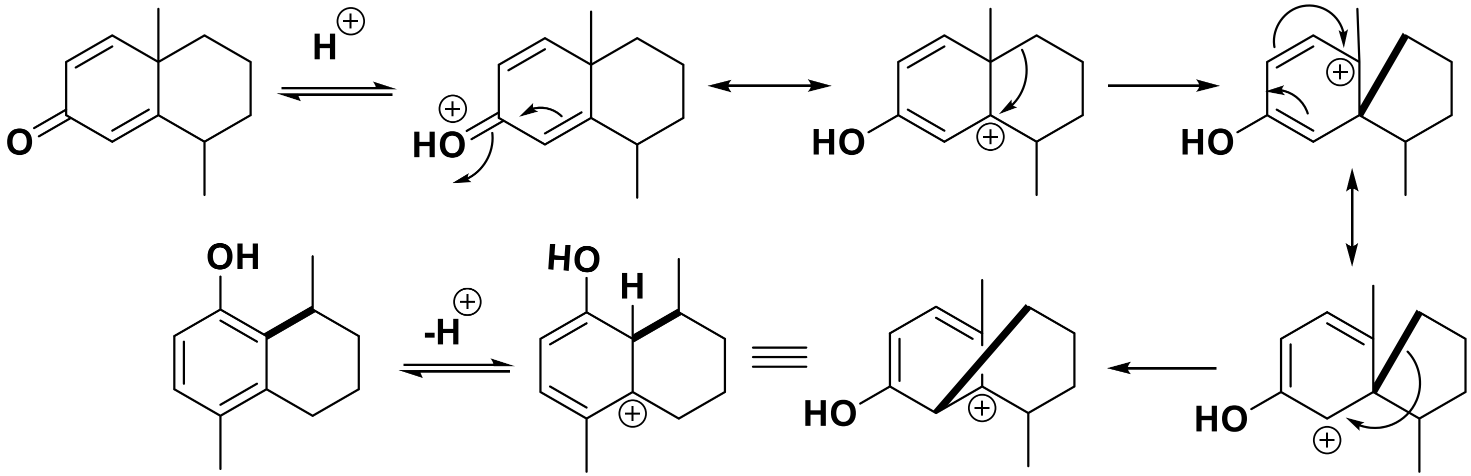
(99) (100)

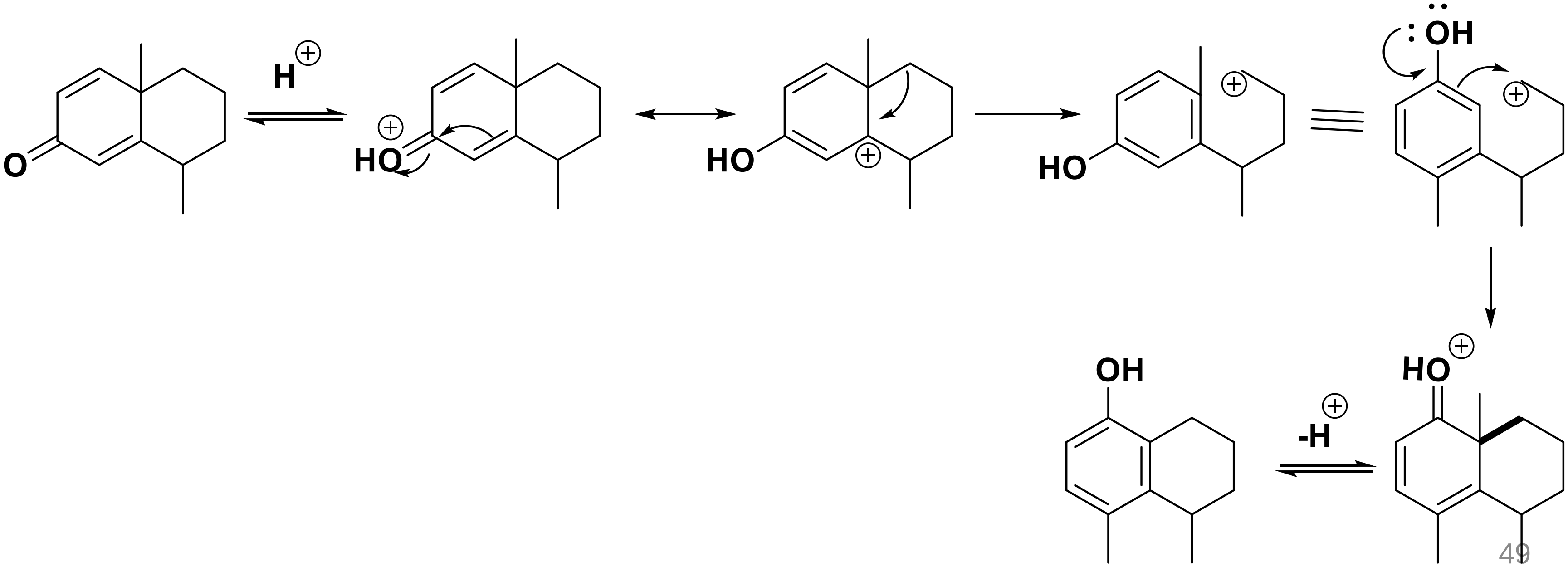
(94) (95)

R = Me, Et, Ph

12. Dienone Phenol Rearrangement…………….

Example






Thank You!