SECTION 3

Antiperiplanar Hypothesis

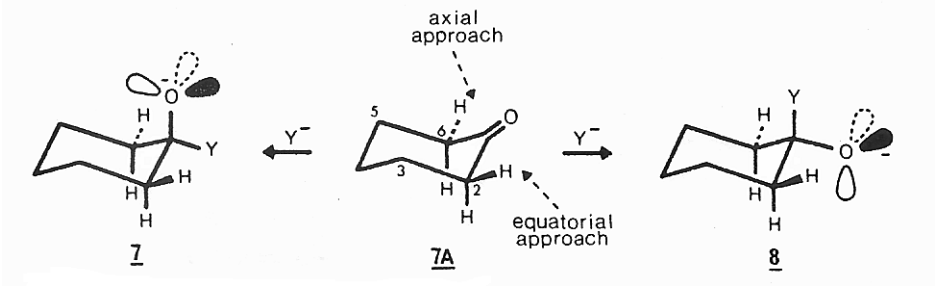
and Reactions at Unsaturated Systems

(2018)

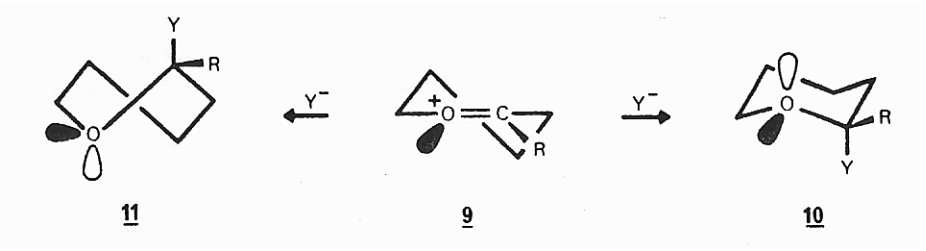
Reaction on Sp_2 Type Unsaturated System

In cyclic ketone, both processes lead to a chair but

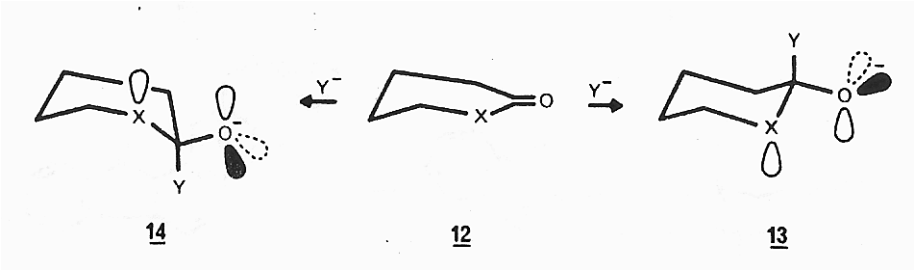
we will see that C–H and C–C hyperconjugation play an important role.



The situation is different when the carbonyl group is part of a ring as in oxocarbenium ion 9 where formation of 10 will be always favored.

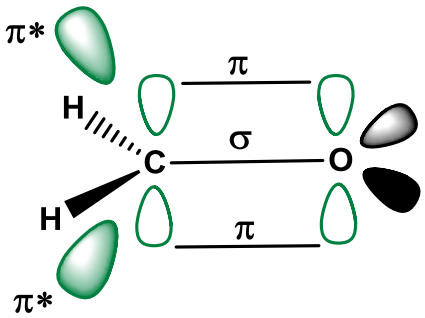


A situation similar with 12 (lactones and lactams) occurs favoring 13.



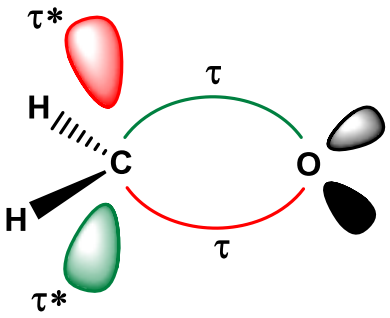
α-π vs τ Bonds in Carbonyl Group and Antibonding Orbitals

σ–π



The two antibonding orbitals π* correspond to a single orbital

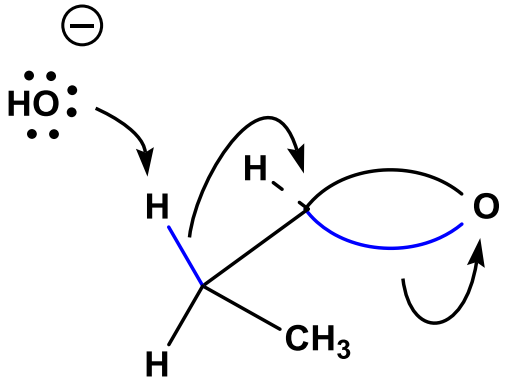
τ



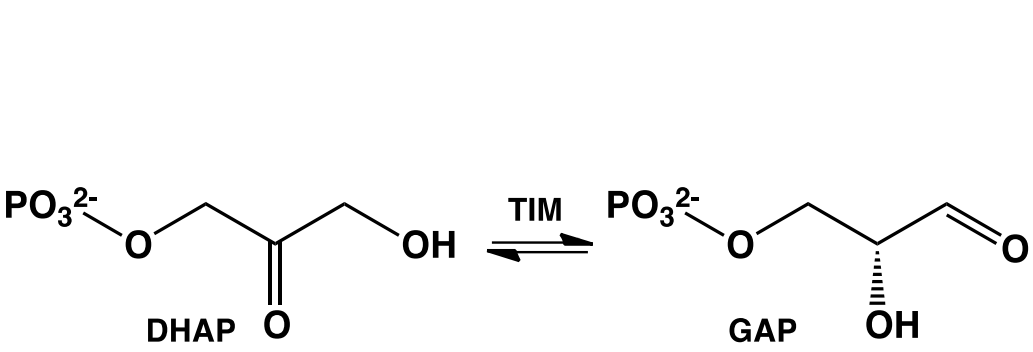
The two antibondiding orbitals τ* correspond to two different orbitals and confer tetrahedral character to carbonyl group

Base-Catalyzed Enolization of Carbonyl Groups

Molecular Modeling

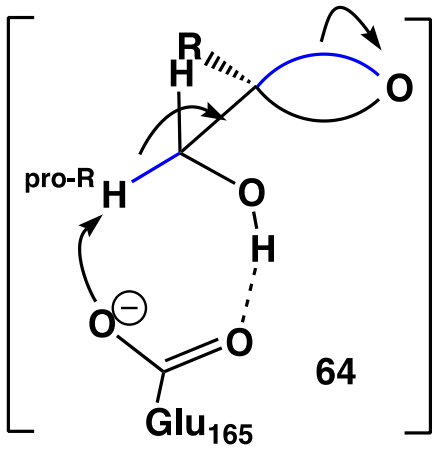


With Enzyme: catalysis by triosephosphate isomerase



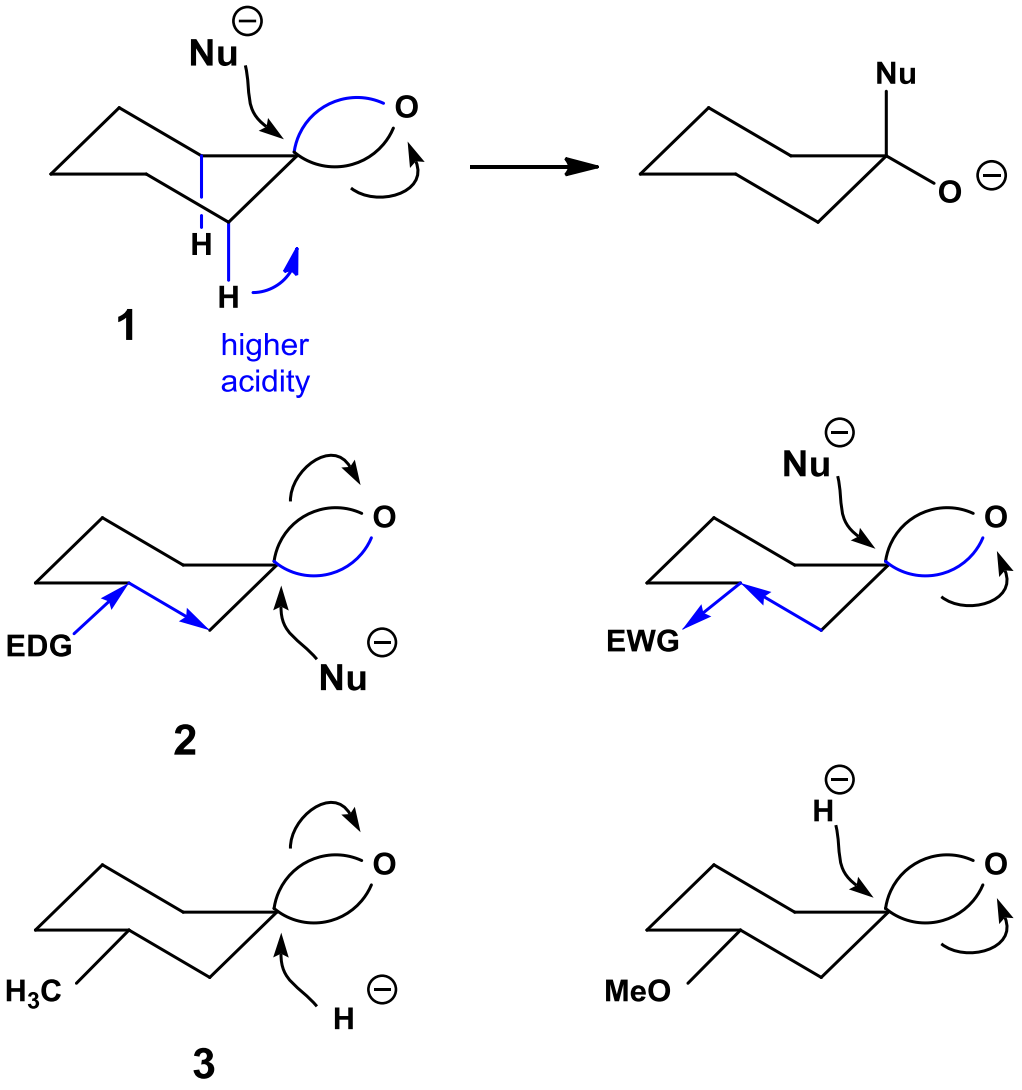
dihydroxyacetone phosphate

glyceraldehyde phosphate



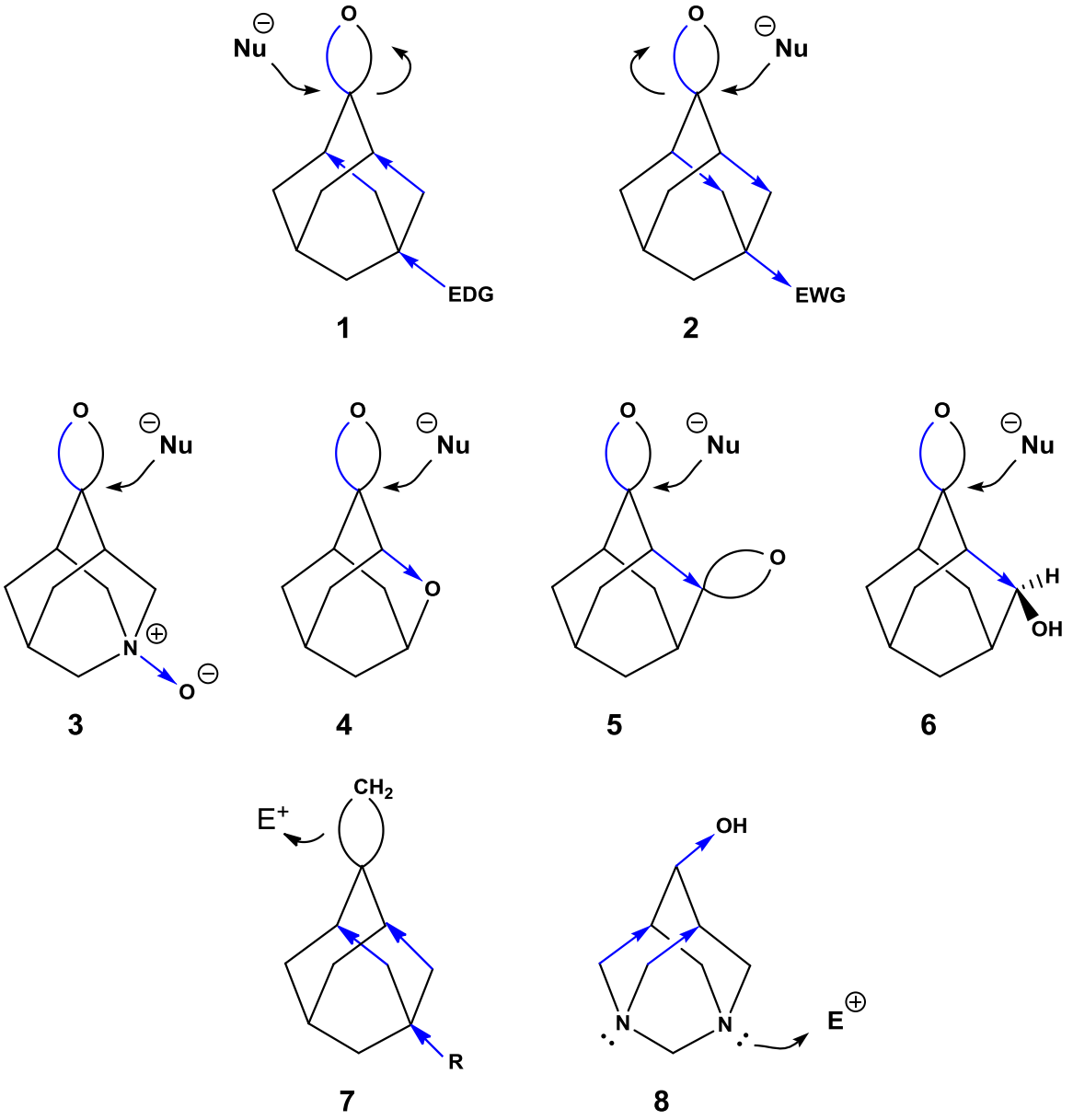
G. Jogl, S. Rozovsky, A. E. McDermott, L. Tong,
Proc. Natl. Acad. Sci., 2003, *100*, 50.

Nucleophilic Addition on Ketone and Hyperconjugation



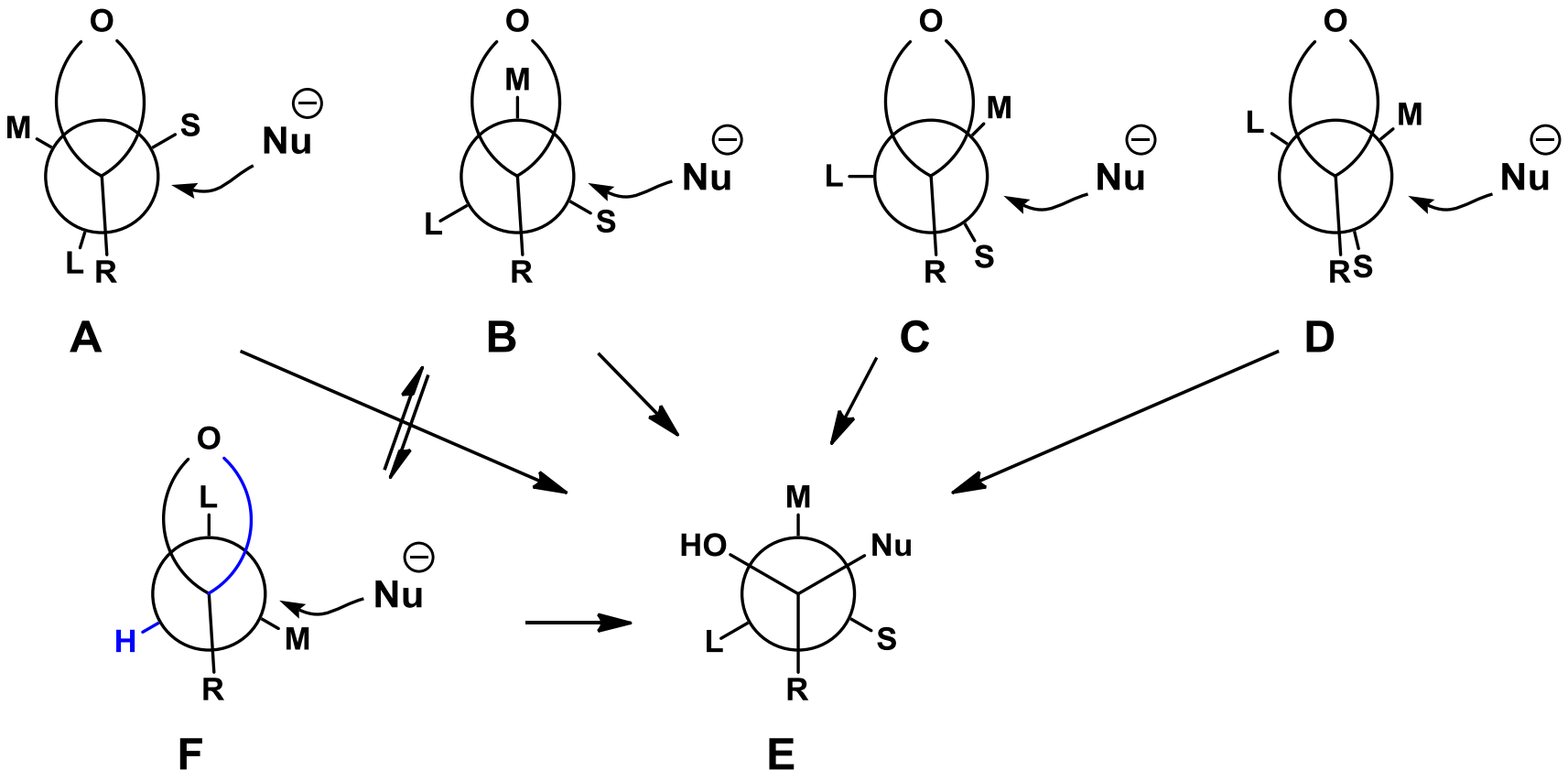
A. S. Cieplak, B. D. Tait, C. R. Johnson, *J. Am. Chem. Soc.*, 1989, *111*, 8447.

Nucleophilic Addition on Adamantanone - Cieplak Effect

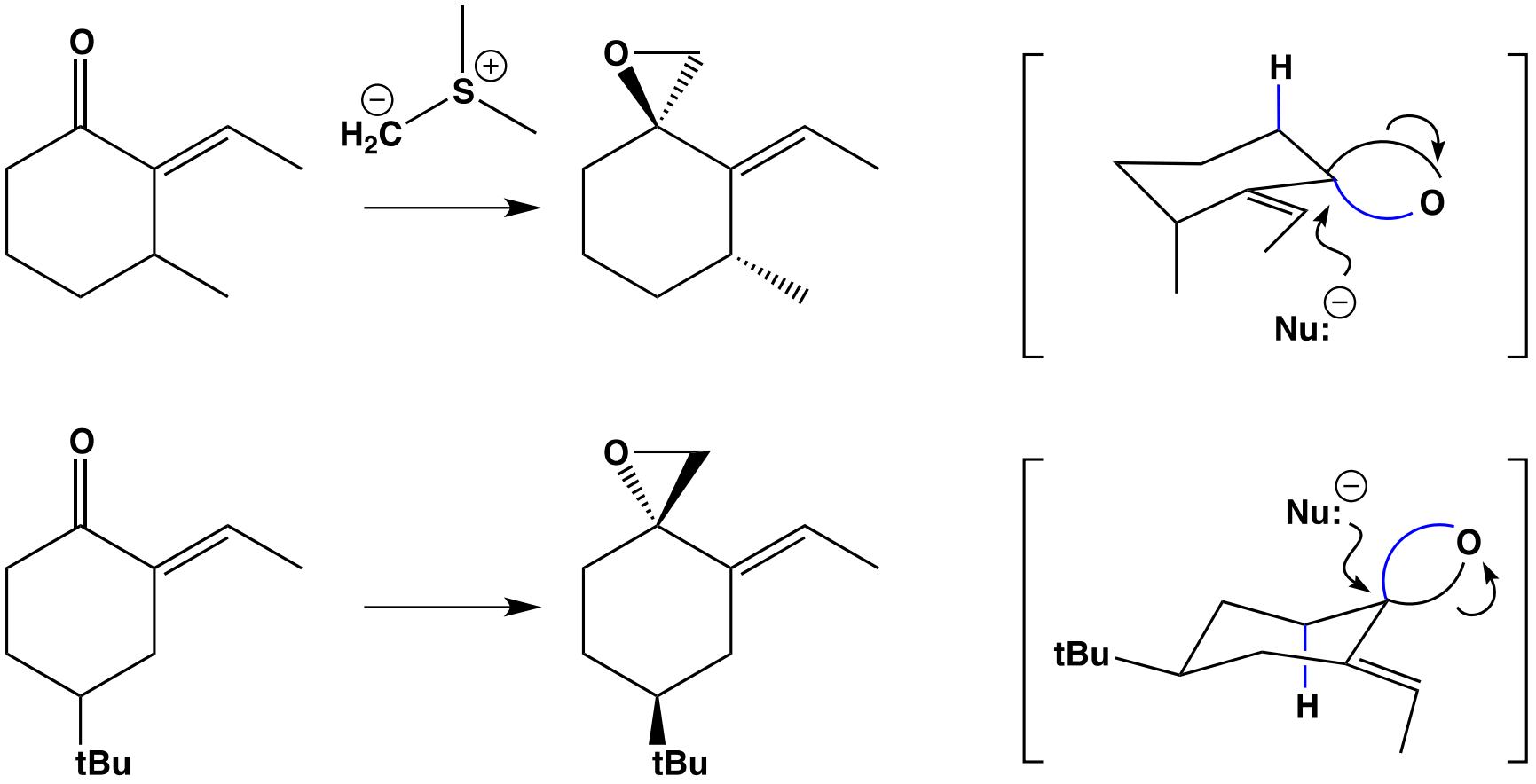


M. Kaselj, W. S. Chung, W. J. le Noble, *Chem. Rev.*, 1999, *99*, 1387.

Cram (A), Karabatsos (B), Felkin-Ahn (C), Wintner (D)

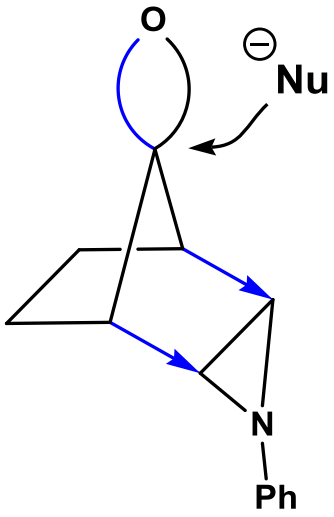


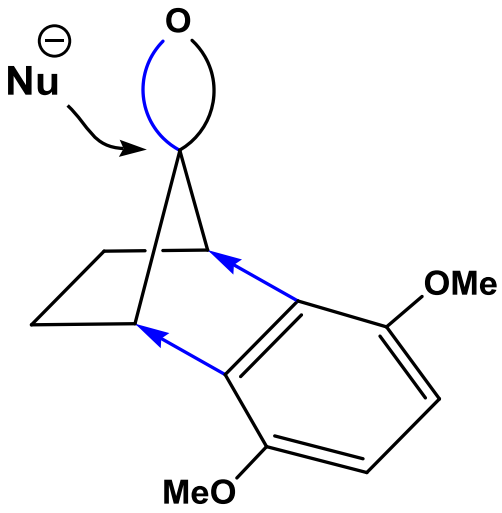
Nucleophilic Addition to Exomethylene Cyclohexanones

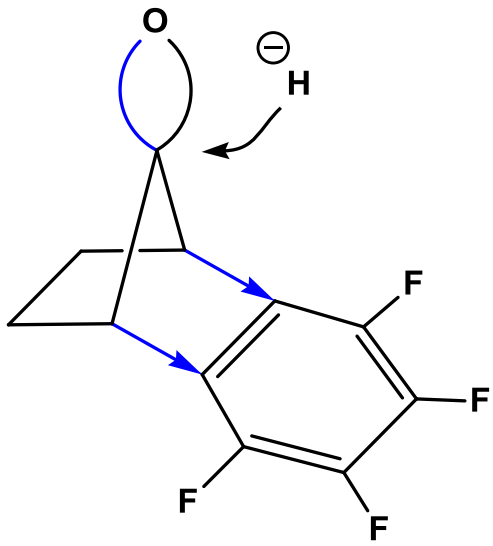


F. E. Ziegler, M. A. Cady, *J. Org. Chem.,* 1981, *46*, 122.

Nucleophilic Addition to Norbornenone

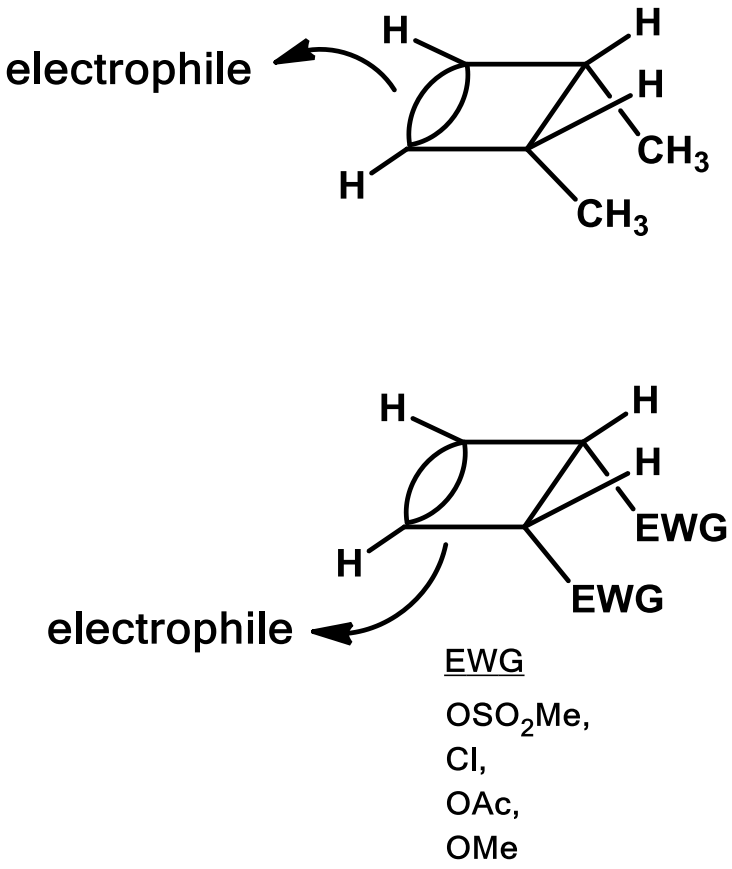






M. Kaselj, W. S. Chung, W. J. le Noble, *Chem. Rev.,* 1999, *99*, 1387.

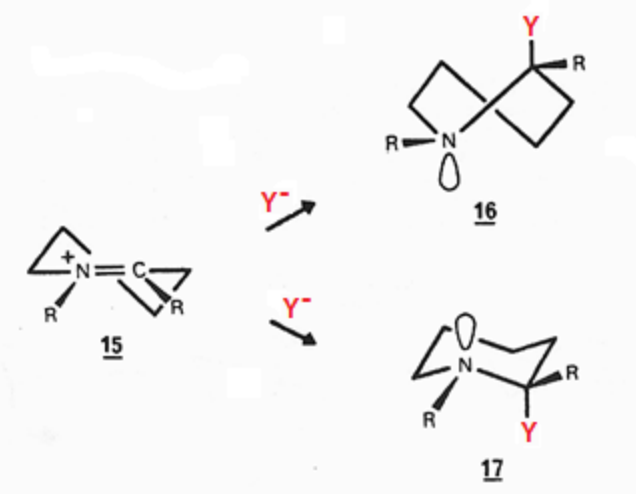
Electrophilic Addition on Cyclobutene



M. Kaselj, W. S. Chung, W. J. le Noble, *Chem. Rev.,* 1999, *99*, 1387.

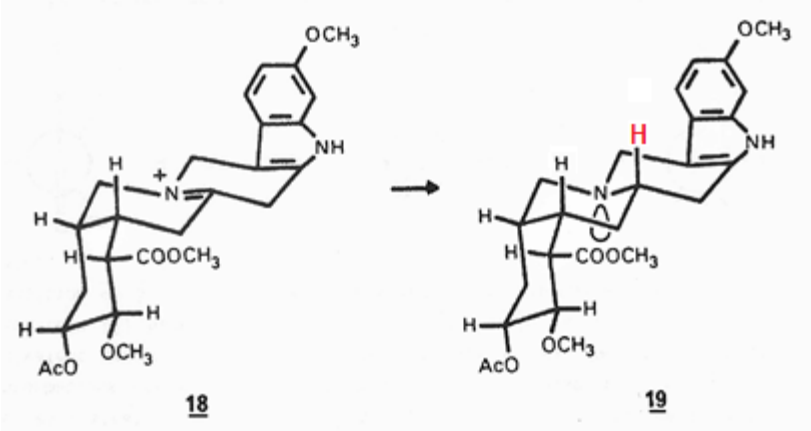
Stereoelectronic Control in Iminium Salts

Formation of 17 is highly favored.



E. TOROMANOFF.
Bull. Soc. Chim. Fr
1966, 3357.

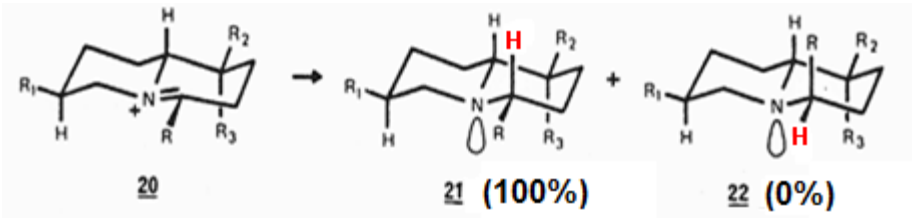
As in the Woodward total synthesis of Reserpine.



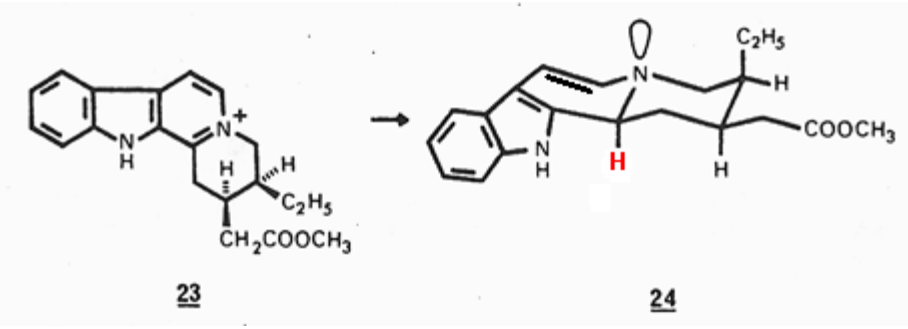
R.B. WOODWARD *et al.* *Tetrahedron* 1958, *2,* 1.

Other Examples of Iminium Salts

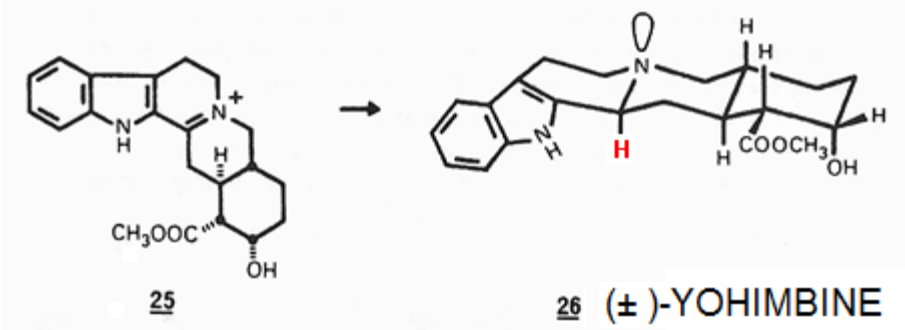
Borohydride reductions:



F. BOHLMANN et al.
Chem. Ber.
1963, *96,* 1792.

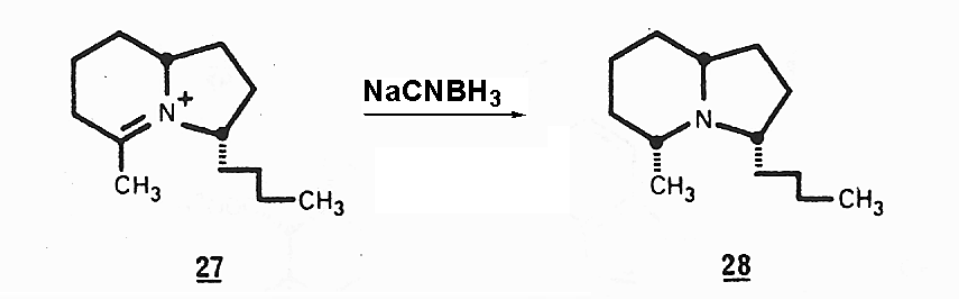


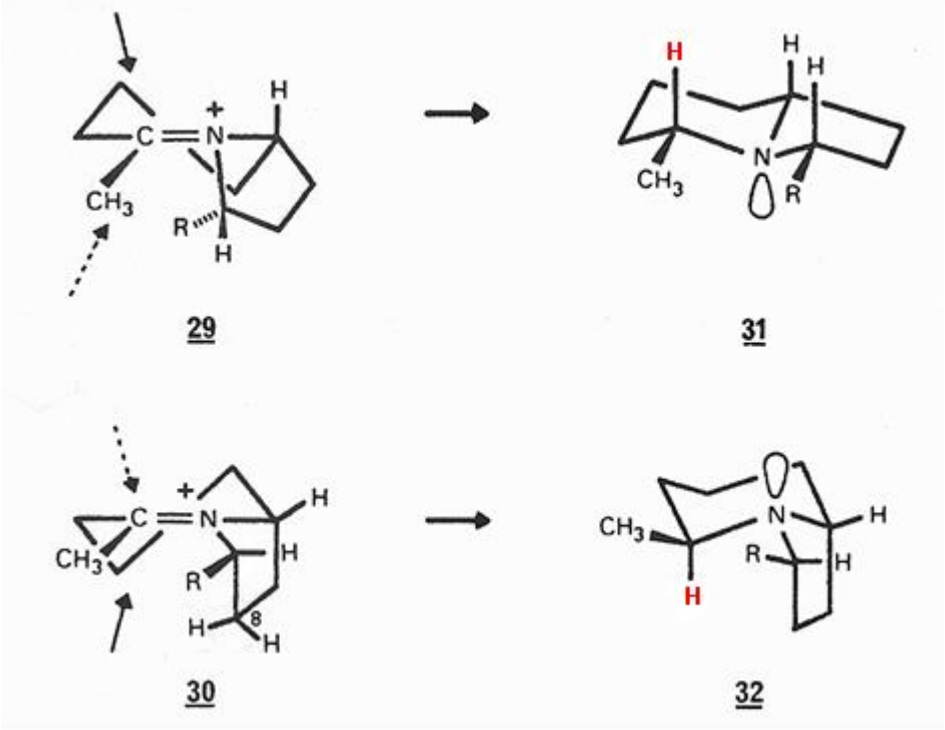
E. WENKERT et al.
Chem. Ber.
1967, *89,* 6741.



G. STORK et al.
J. Am. Chem. Soc.
1972, *94,* 5109.

More on Iminium Salts





There are 4 possible pathways in the reduction of 27. Two requires boat-like TS (dotted lines in 29 and 30).

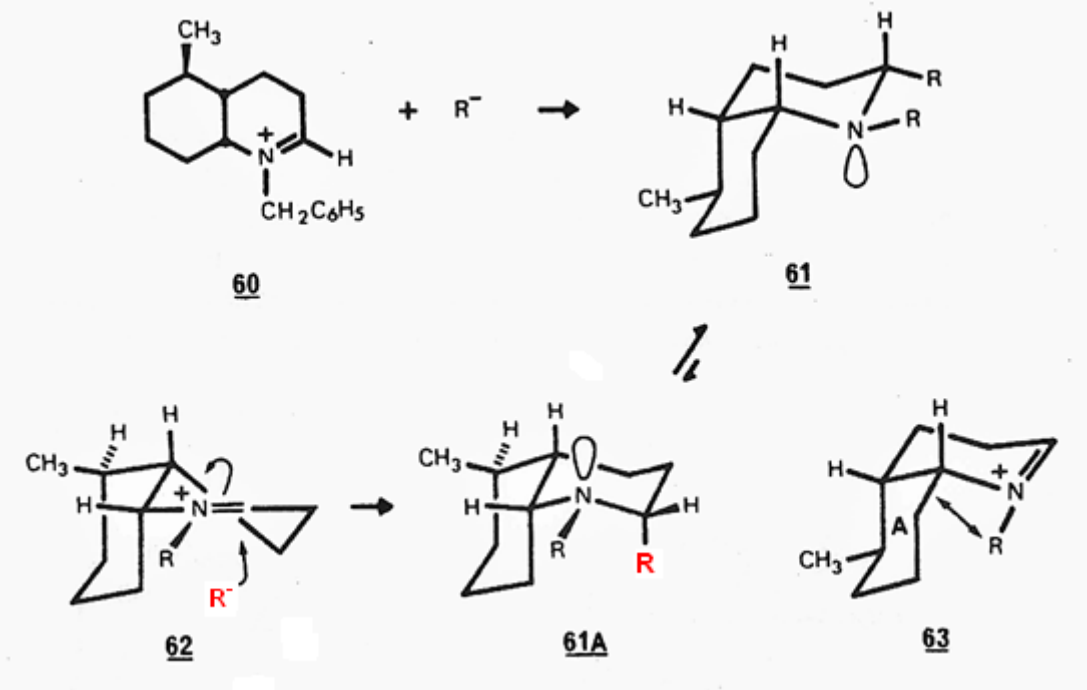
Of the two possible chair-like TS (solid arrow in 29 and 30), 30 suffers from severe steric interactions.

Thus, the process 29 to 31 is observed.

R.V. STEVENS *et al. J. Chem. Soc., Chem. Commun.* 1982, 102-103.

Strong SE Controlled Despite Severe Steric Effects

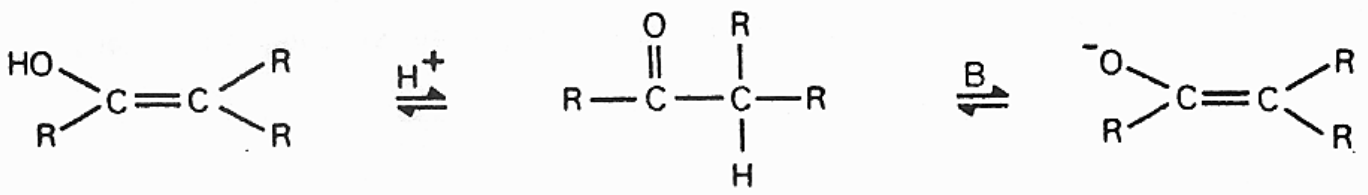
Organolithium and Grignard reagents add to iminium 60 from the more sterically congested α face yielding 61.



Conformation 63 was eliminated because of a strong $A^{1,2}$ steric interaction between the N-alkyl group and ring A.

L.E. OVERMAN *et al.* *J. Am. Chem. Soc.* 1980, *102,* 1454.

Enolization of Carbonyl Group



439 **438** **440**

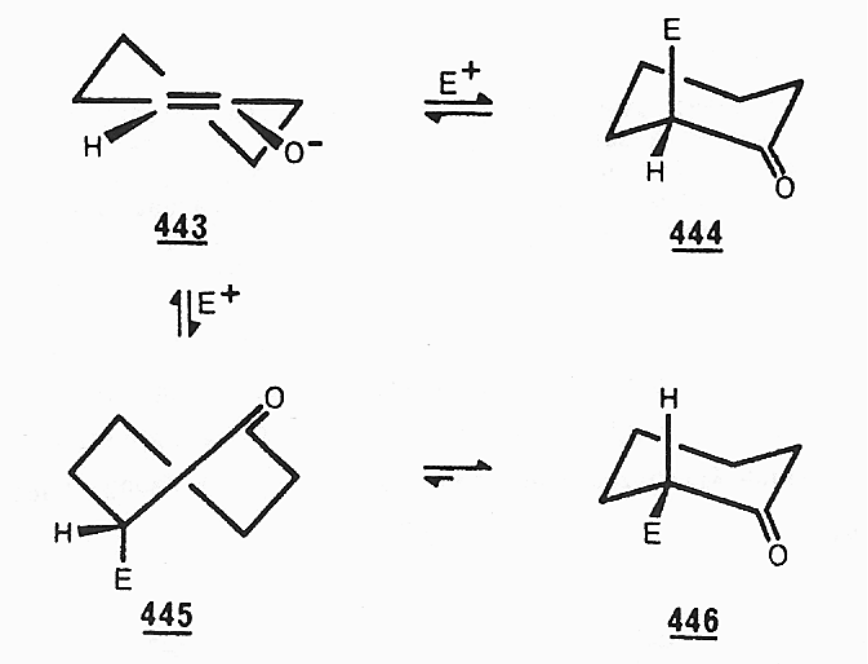
As early as 1953, Corey (123) observed that the kinetically controlled bromination of ketosteroids always gives the epimer in which bromide is "polar" (i.e. axial) and in 1954 (124), he proposed that these results can be explained on the following theoretical basis:

> "Ketonization of an enol and the reverse reaction, enolization of a ketone proceed through the same transition state and hence the same geometrical requirements for maximum opportunity for bond formation between the sp^3 + p-orbital made available by the leaving hydrogen and the p-orbital of the carbonyl carbon."

> "In the case of a cyclohexanone this implies that in enolization a "polar" (i.e. axial) α-hydrogen is lost in preference to an equatorial α-hydrogen (cf. 441 ⇌ 442). Furthermore, it follows that in the ketonization of an enolized cyclohexanone (e.g. by bromination or protonation) the incoming substituent should adopt preferentially the polar (axial) orientation."

COREY, E.J. ***Experientia*** **1953, 9, 329.;** ***J. Am. Chem. Soc.*** **1954,** ***76,*** **175; 1956,** ***78,*** **6229.**

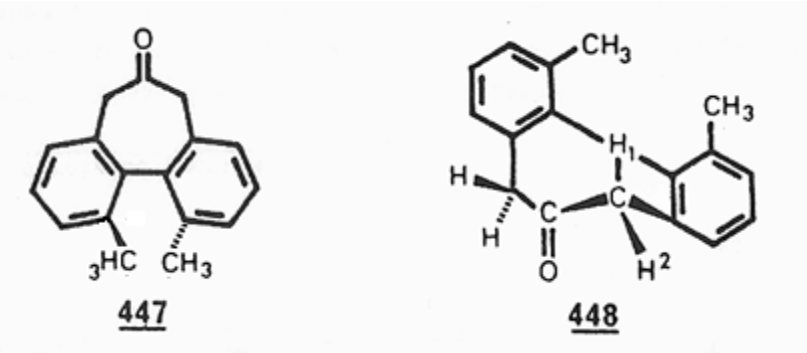
Stereochemistry of the Enolization Process



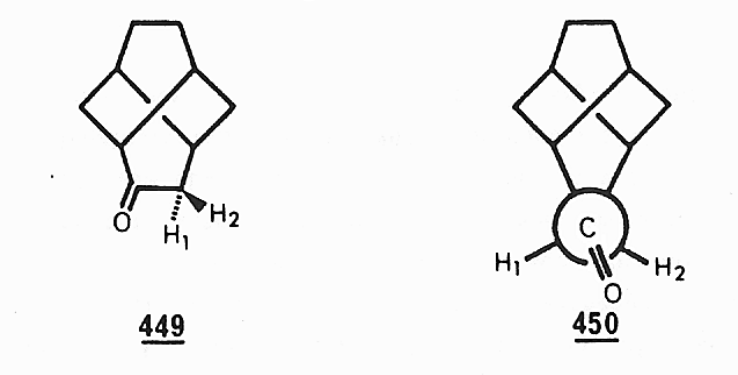
Toromanoff and Valls proposed that if stereoelectronic effects are an important parameter, the cyclohexanone enolate should react by two different pathways, one involving a chair-like transition state (443 to 444) and the other a boat-like transition state (443 to 445 to 446). Thus, both of these reactions proceed by perpendicular attack of the electrophile. Their energy difference results from the difference in strain between the chair (444) and the twist-boat (445) forms.

VALLS, J., TOROMANOFF, E. ***Bull. Soc. Chim. France*** **1961, 758.**

Experimental Evidence for S.E. in Enolization of Ketone



rate of exchange of H_1 / H_2 = 73 / 1 (CH_3ONa, CH_3OD)

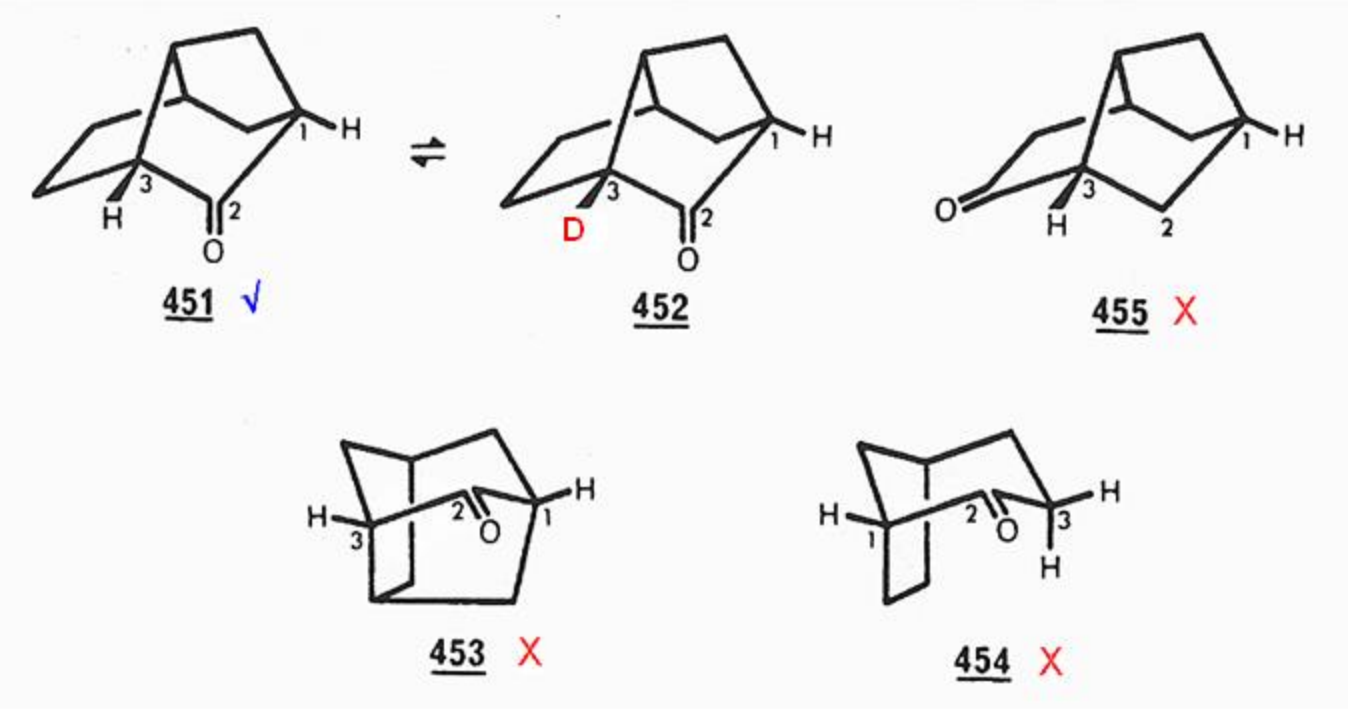


in 449, rate of exchange for H_1 / H_2 = 280 / 1

FRASER, R.R. *et al*. *J. Am. Chem. Soc.* 1976, *54,* 3809; 1978, *100*, 657.

H/D Exchange of Tricyclic Ketone

only 451 undergoes H/D exchange (CH_3ONa, CH_3OD, 25°C)



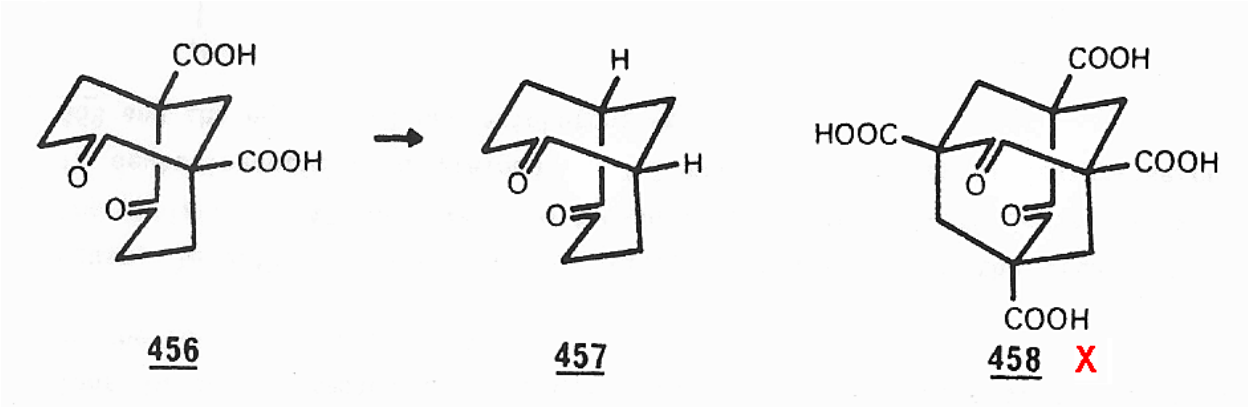
only 451 exists in a boat form,

as a result, the bridgehead C_3-H is appropriatly aligned to overlap with the π orbital of the carbonyl group

NICKON *et al*. *J. Am. Chem. Soc.* 1975, *93,* 904.

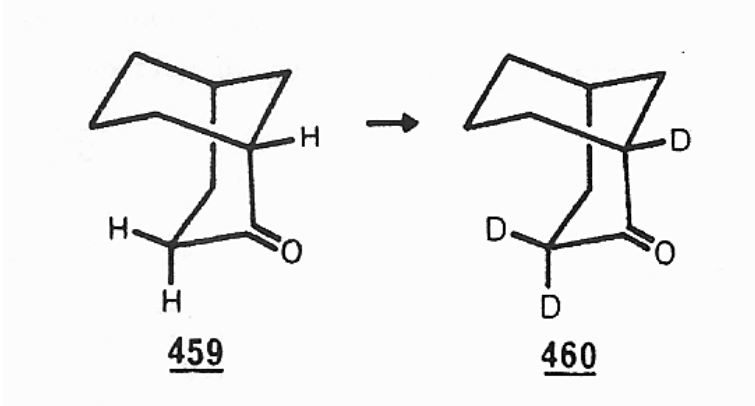
Decarboxylation of α-Keto Acid

456 undergoes decarboxylation, contrary to 458



456 457 458 X

This is in accord with deuterium incorporation in 459



459 460

MEERWEIN, H. *et al*. *Ann. Chem.* 1913, *398*, 196.

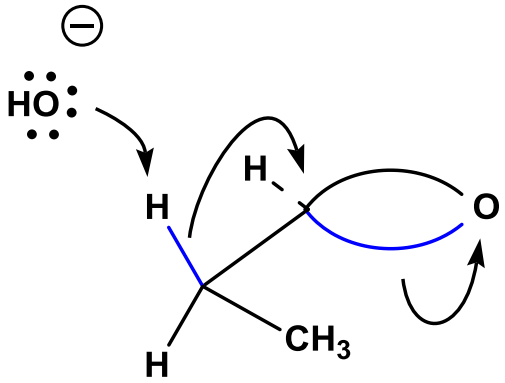
BOOTGER, O. *Chem. Ber.* 1937, *70B,* 314.

These compounds can undergo enolization because the cyclohexane can take a boat conformation.

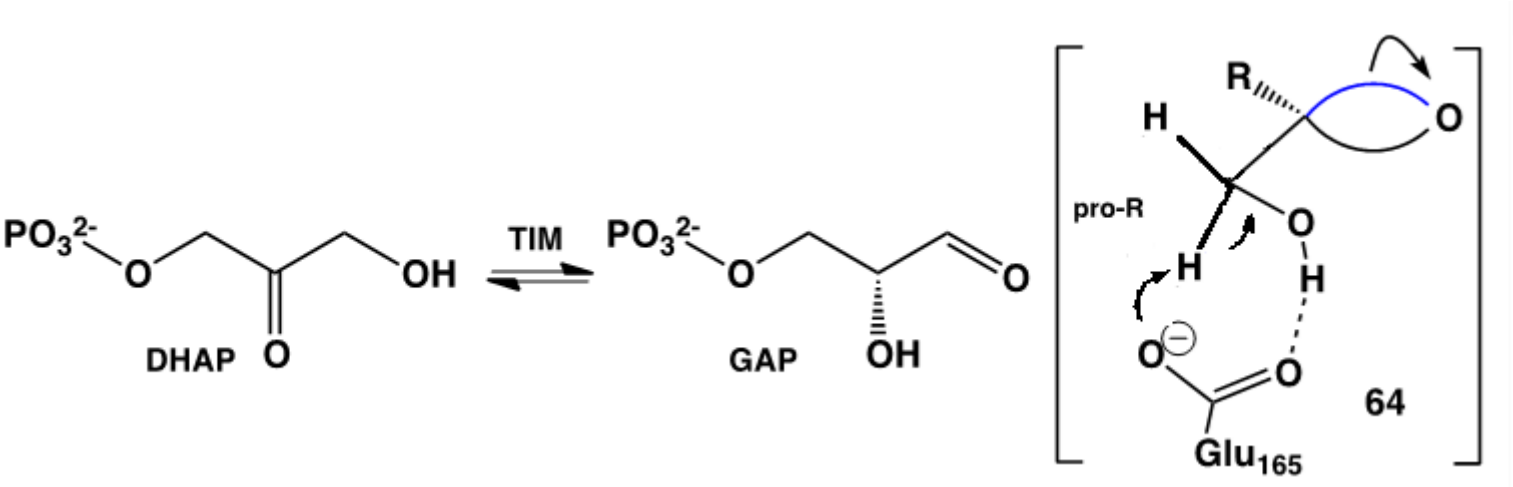
SCHAEFER and CLARK. *J. Org. Chem. Soc.* 1965, *30,* 1337.

Base-Catalyzed Enolization of Carbonyl Groups

Molecular Modeling

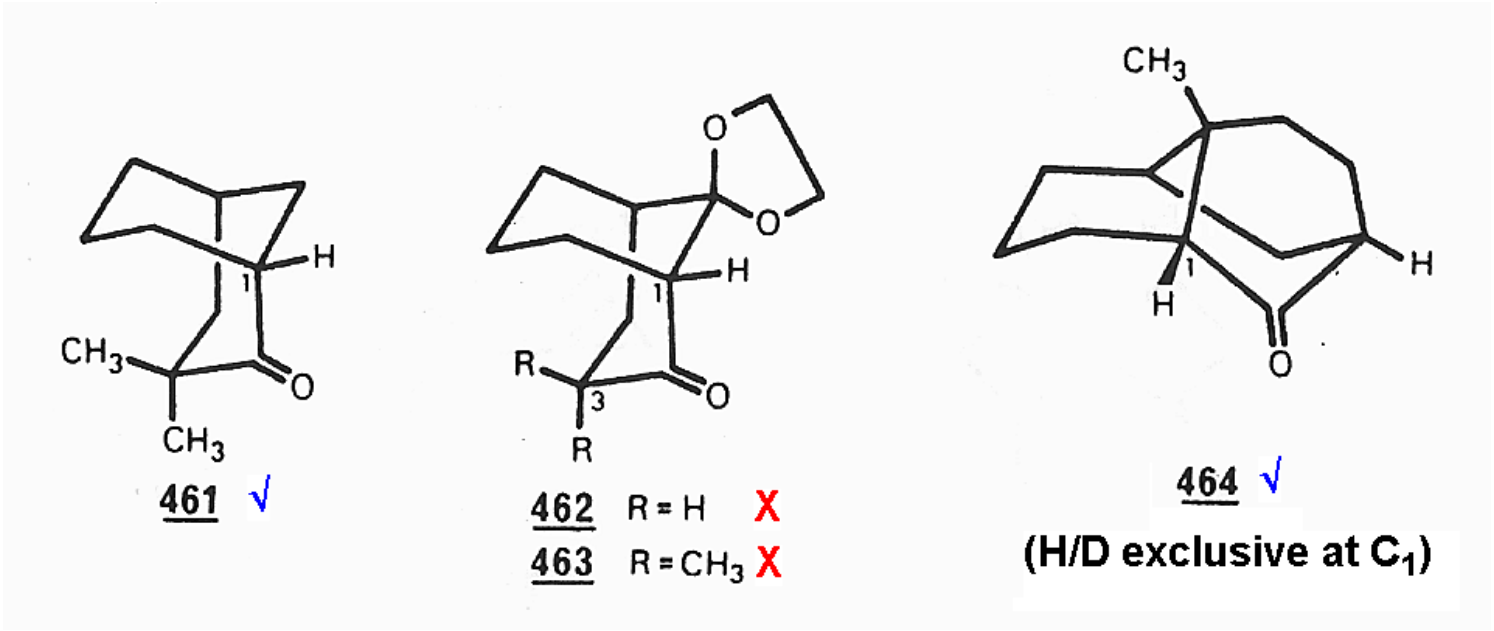


With Enzyme: catalysis by triosephosphate isomerase



G. Jogl, S. Rozovsky, A. E. McDermott, L. Tong,
Proc. Natl. Acad. Sci., 2003, *100*, 50.

More About H/D Exchange

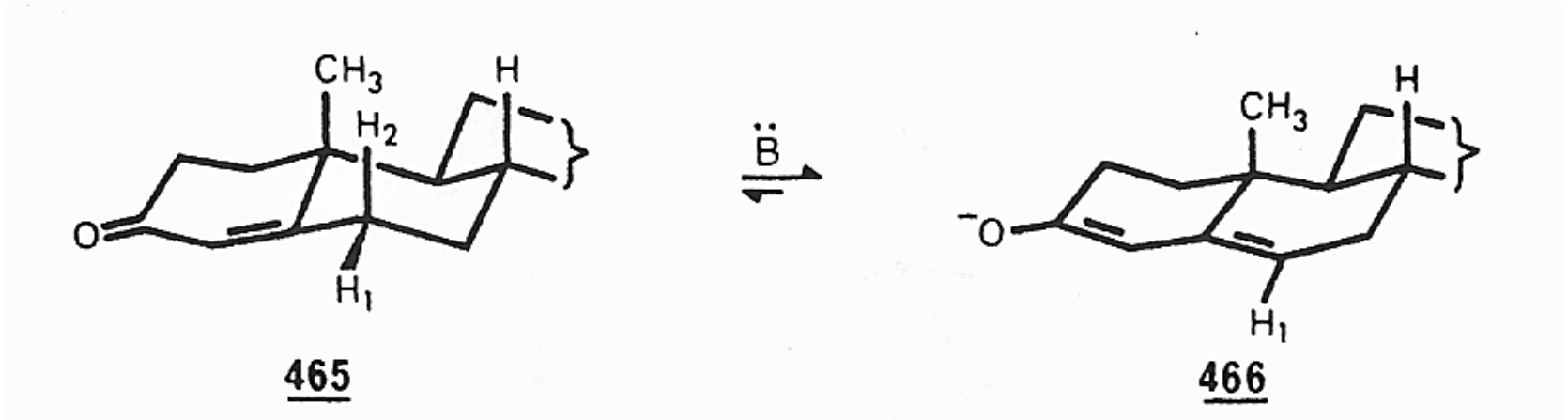


Conclusion:

a boat cyclohexane conformation is needed for H/D exchange

YAMADA *et al*. *Bull. Chem. Soc. Jpn* 1979, *52,* 186.

Selective Exchange of Axial-H at C_6 in Steroid



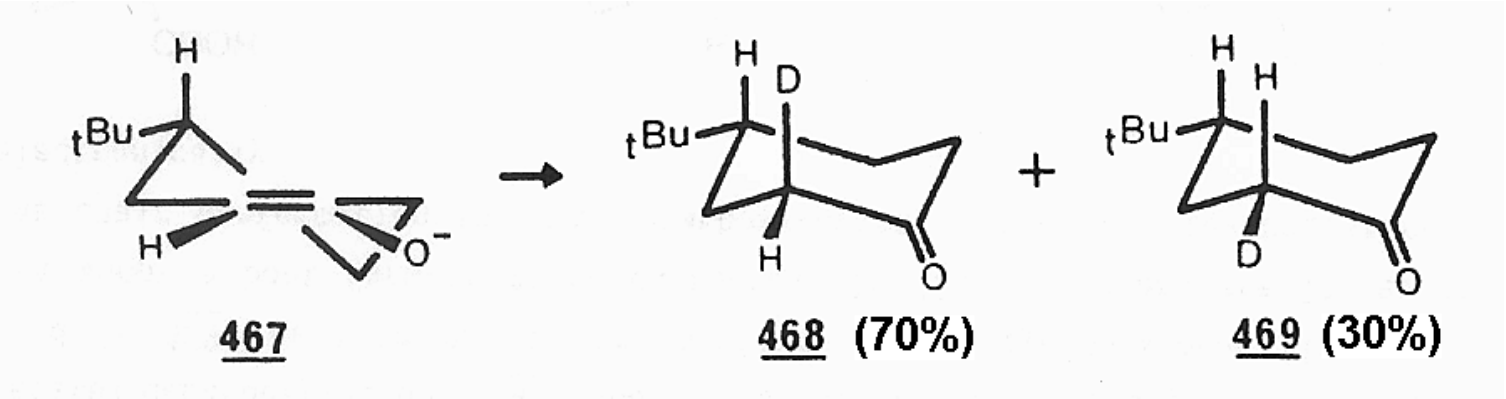
465 **466**

rate of H/D exchange at C_6 is 53 in favor of H_2

RINGOLD *et al*. *J. Am. Chem. Soc.* 1966, *88,* 1332.

Reaction of Enolate with Electrophiles

(Position of Transition State in Reaction of Enolates)



Axial protonation is not strongly favored. **They concluded that in practice this type of experiment is complicated by the fact that protonation of an enolate anion can occur either at the carbon (to give 468 or 469) or at at the oxygen atom (to yield the enol). Further reaction of the enol with aqueous acid also yields the two possible ketones 468 and 469. Furthermore, since the protonation steps of this strongly basic anion (either at C or O) are difusion-controlled, it is possible that the transition state geometries for both reactions resemble the geometry of the enolate anion, so the energy difference between the direction of attack on the enolate is small.**

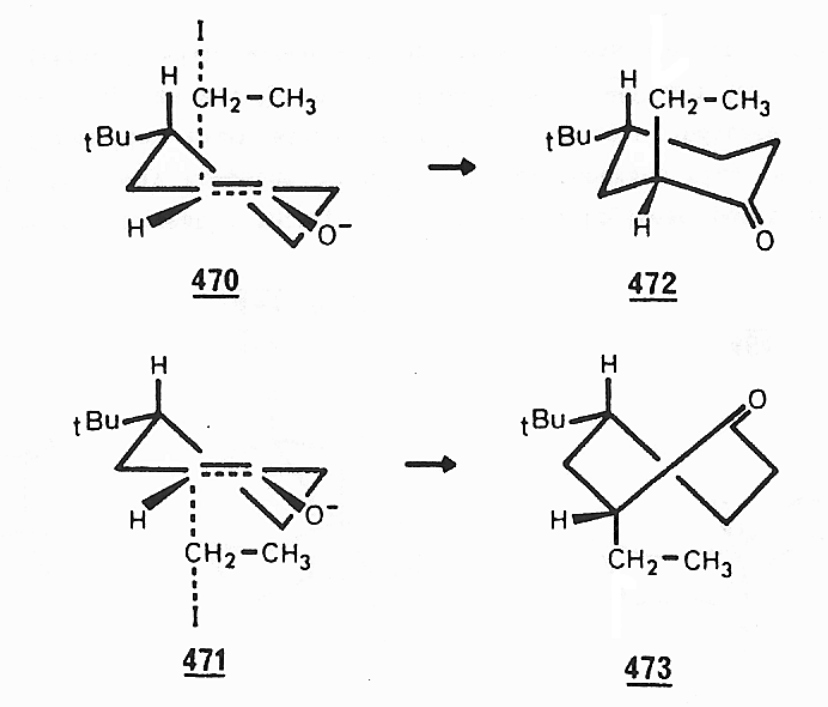
HOUSE *et al*. *J. Org. Chem.* 1968, *33*, 935.

Stereochemistry of Alkylation of Enolate

Alkylation of the enolate of *t*-butyl-cyclohexanone with triethyloxonium fluoroborate yielded a mixture of O-alkyl product and approximately equal amounts of the isomeric 2-ethyl-4-*t*-butyl cyclohexanones.

A similar mixture of C-alkylated product was obtained using ethyl iodide.

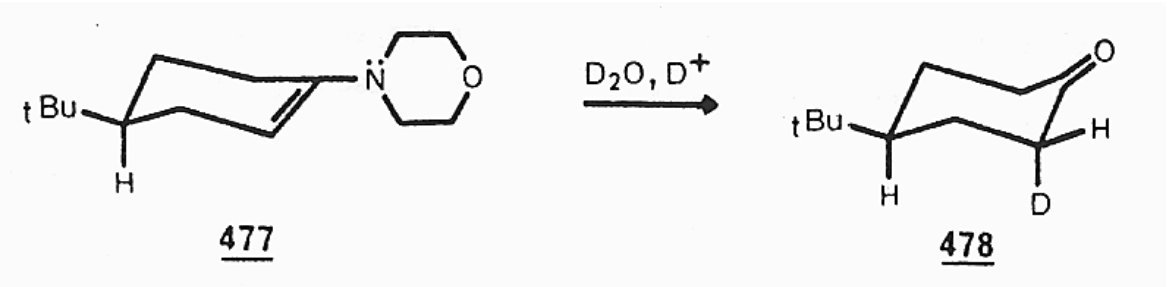
For this reason, they proposed that the corresponding transition state are early resembling the geometry of the enolate (*cf.* 470).



More Control on Protonation of Enamine

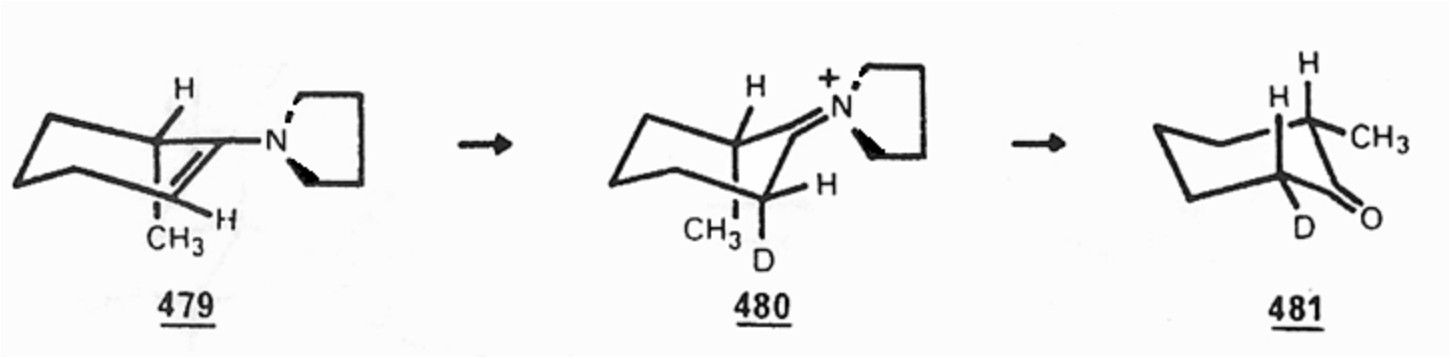
Enamine being less reactive than enolates.

TS should be less early leading to more stereoselective reaction on axial position.



477 478

SCHAEFER, J.P. *et al*. *Tetrahedron Lett.* 1965, 1801.

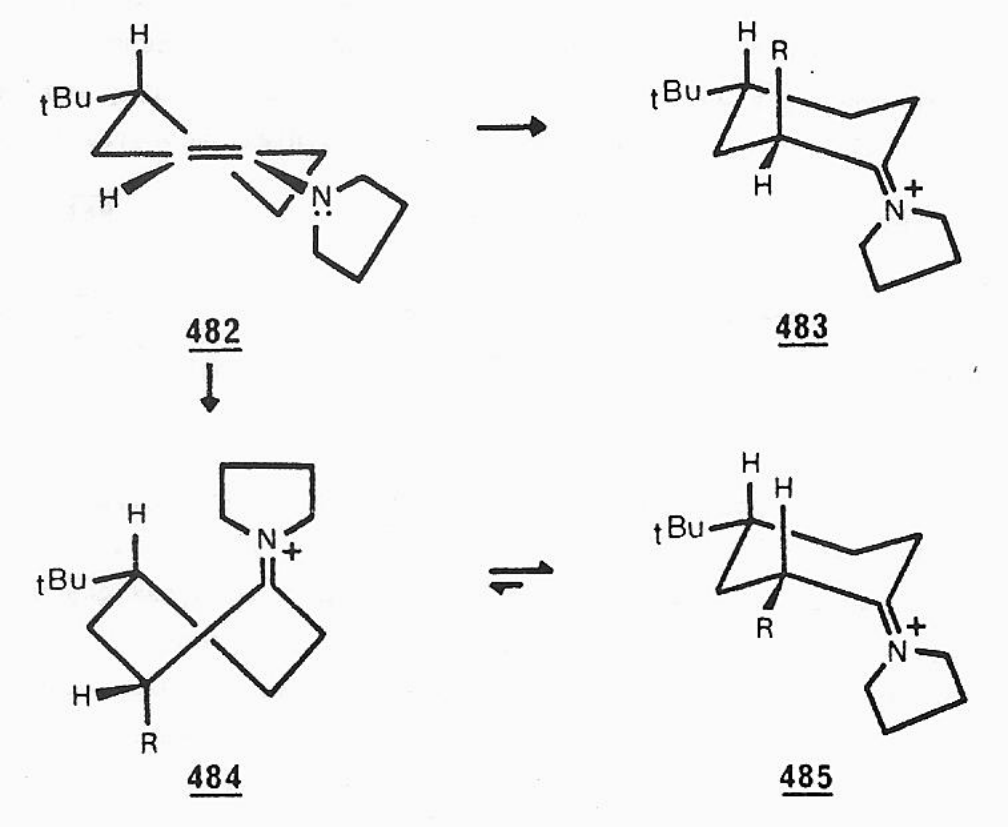


479 480 481

only

JOHNSON *et al*. *Tetrahedron Lett.* 1965, 4027.

Alkylation of Enamine is Also Highly Stereoselective

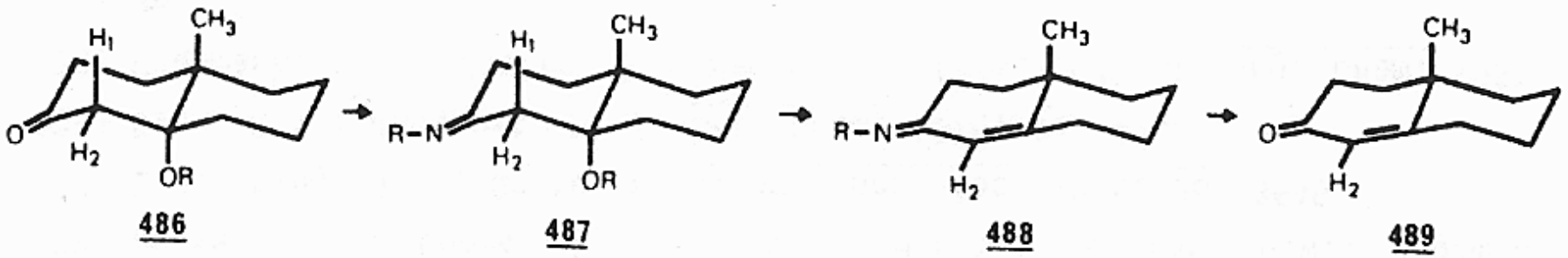


Alkylation proceeds mainly to give 483

[R = CH_3 (70%), $CH_3CH_2CH_2$ (90%) and CH_2=CH-CH_2 (93%)]

WOLFF, R.E. *et al*. *Bull. Chem. Soc. France* 1965, 2472.

S.E. Control in α-Deprotonation of Iminium Ion



using appropriate deuterium labeling, H_1 in 487 is preferentially removed

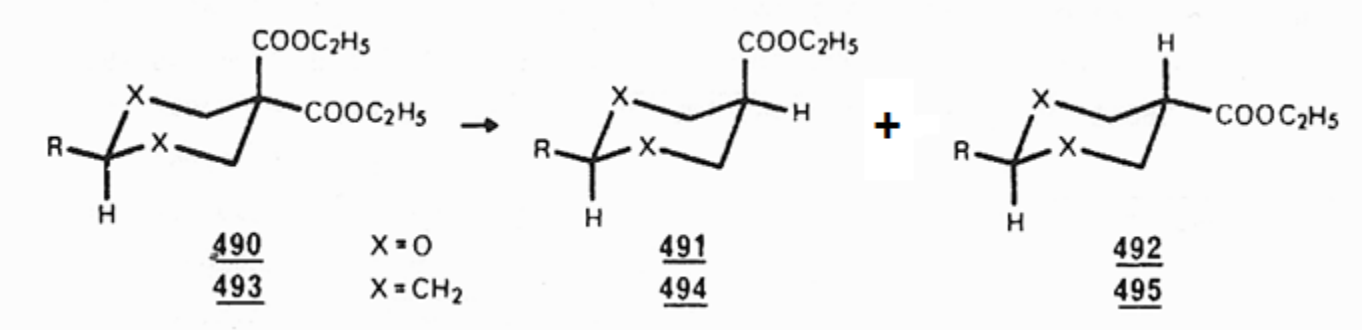
(OR = OH (factor of 18) OR = CH_3COO (factor of 110))

using hydroxide ion, H_1 in 486 is preferentially abstracted

(factor of 130) en route to yield 489

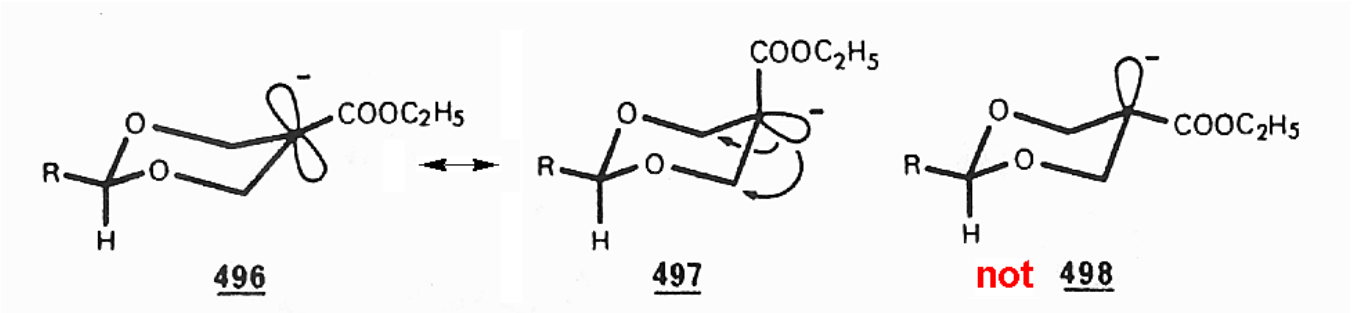
SPENCER, T.A. ***J. Chem. Soc., Chem. Commun.*** **1978, 49.**

Decarboxylation of C_5 Malonate in 1,3-Dioxane



heating 490 (X = O) at 150°C (NaCl, wet DMSO)
gave preferentially 491 (9:1 ratio)
on the other hand, 493 gave a 1:1 mixture of 494 and 495

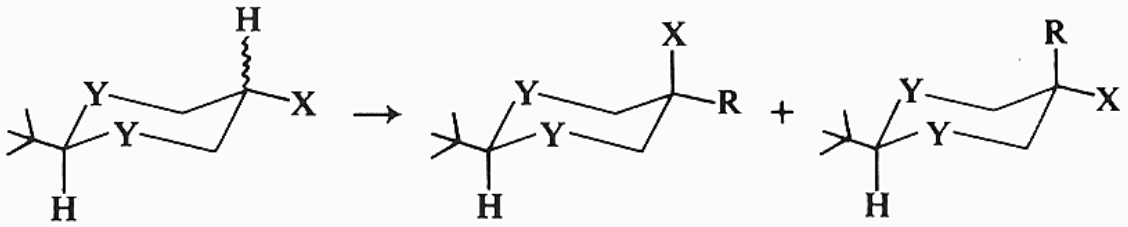
Explanation:



BANKS, H.D. *J. Org. Chem.* 1981, *46*, 1743.

Stereoselective Alkylation of Functional Groups at C_5 of 1,3-Dioxanes

TABLE 1. Alkylation of 2-*tert*-butyl-5-X-1,3-dioxanes



29 ("equatorial") **30** ("axial")

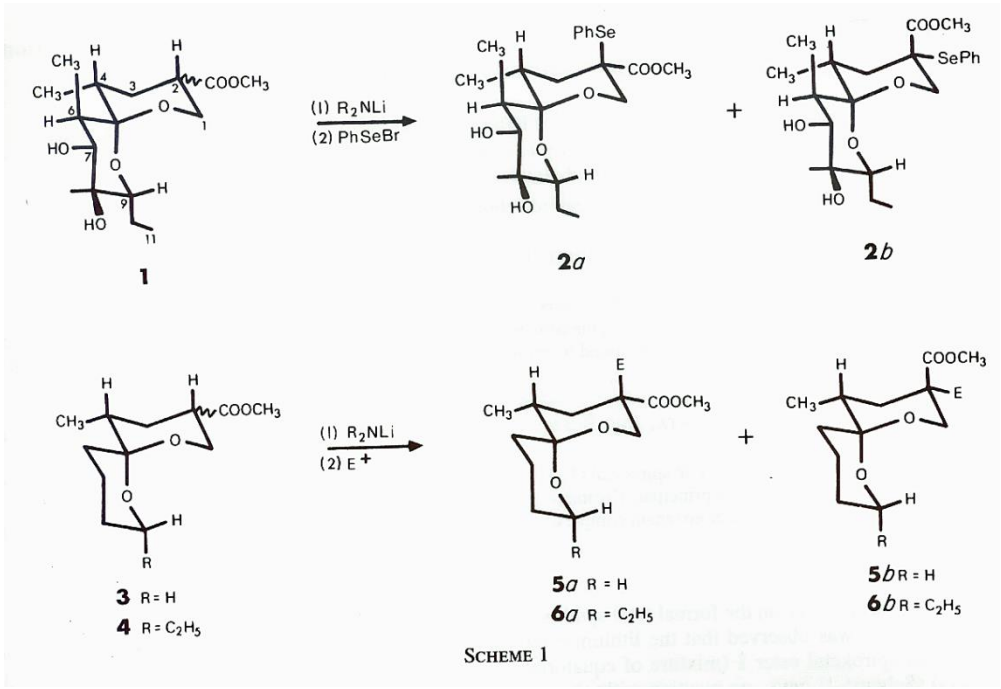
Starting material				Product ratio	
X	Y	Conditions	R—Y	equat./axial	Yield
$COOCH_3$	O	LDA, THF, −78°C	CH_3—I	98:2	70
		LDA, DME, −78°C	CH_2=CH—CH_2Br	>95:5	66
$COOCH_3$	CH_2	LDA, THF, −75°C	CH_3I	84:16	94.5

DESLONGCHAMPS, P. *et al*. *Can. J. Chem.* 1986, *64*, 1788.

Addition of Electrophiles on Ester Enolate Containing an Oxygen in the β-Position

TABLE 1. Addition of electrophilic reagents on ester enolates having an oxygen atom in the β-position

Substrate	Electrophilic reagent	Yield (%)	Isomers 2*a–b*, 5*a–b*, or 6*a–b*	
			Axial	Equatorial
3	PhSeBr	69	10	90
	CH_3I	90	14	86
4	PhSeBr	77	12	88
	O_2	85	15	85
	I_2	95	13	87
	CH_3I	99	11	89
	$(CH_3S)_2$	99	<1	>99
	$(PhS)_2$	95	<1	>99
1	PhSeBr	92	12	88



SCHEME 1

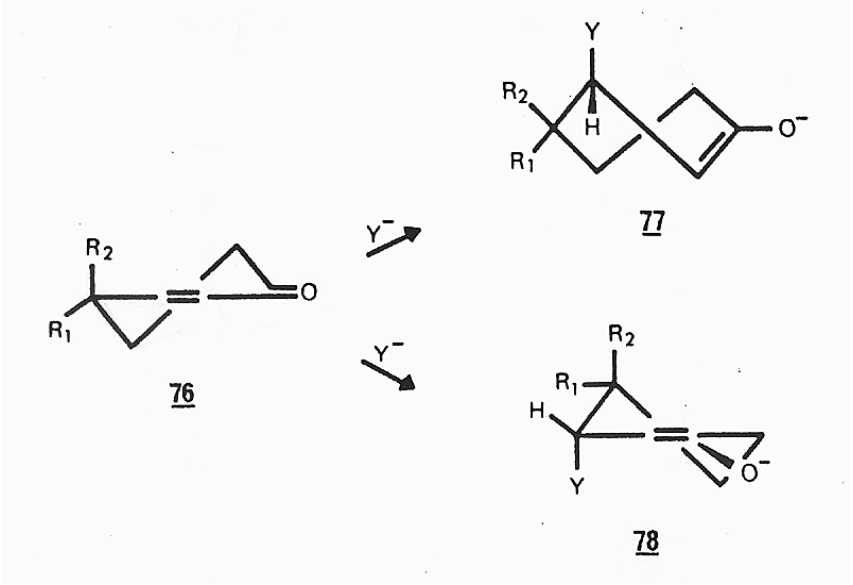
DESLONGCHAMPS, P. *et al*. *Can. J. Chem.* 1986, *64*, 1781-1787.

1,4-Addition in α,β-Unaturated Ketone

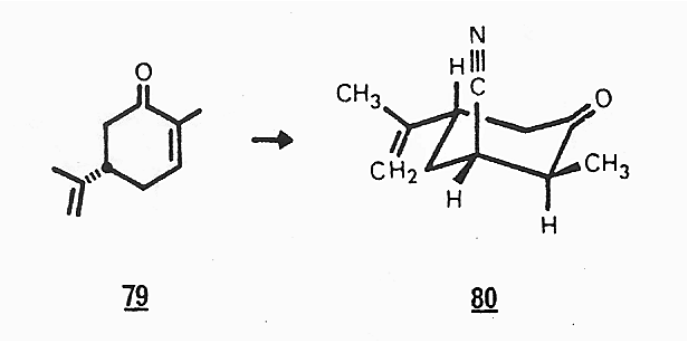
Intermediate 78 is preferred.

TOROMANOFF.

***Bull. Soc. Chim. Fr.* 1962, 708.**



One example with the conjugate addition of HCN.

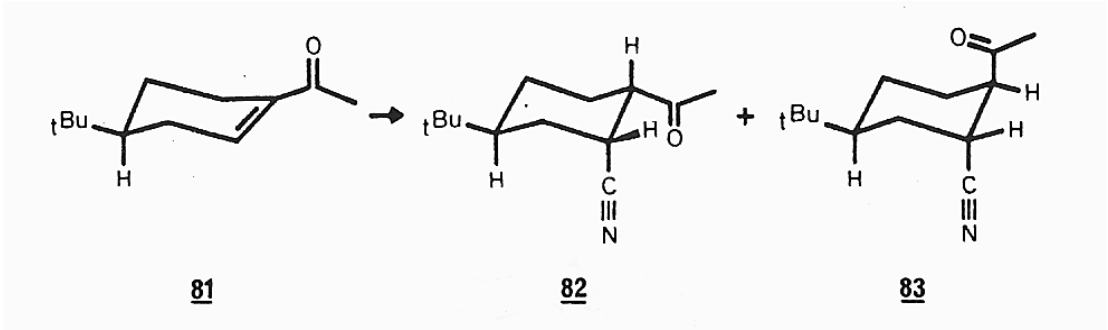


Compound 80 is the major product.

DJERASSI *et al.* *J. Org. Chem.* 1963, *28,* 1632.

Other Examples of HCN 1,4-Addition

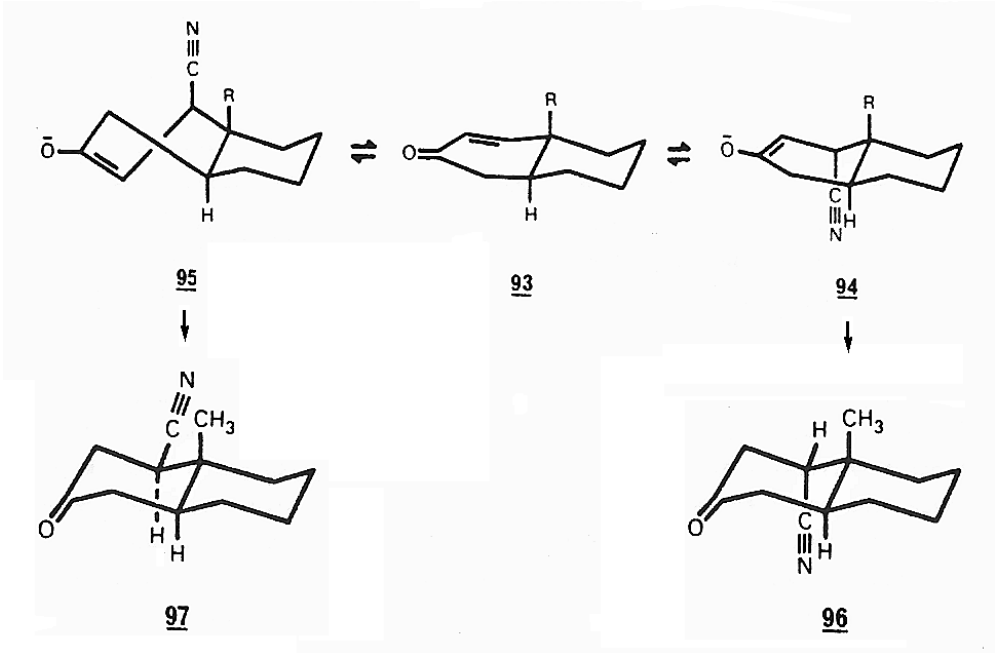
Compound 81 gives a mixture of 82 and 83 via a chair-like TS.



81 82 83

ALEXANDER et al.

***J. Chem. Soc., Perkin Trans 2,* 1972, 1601.**

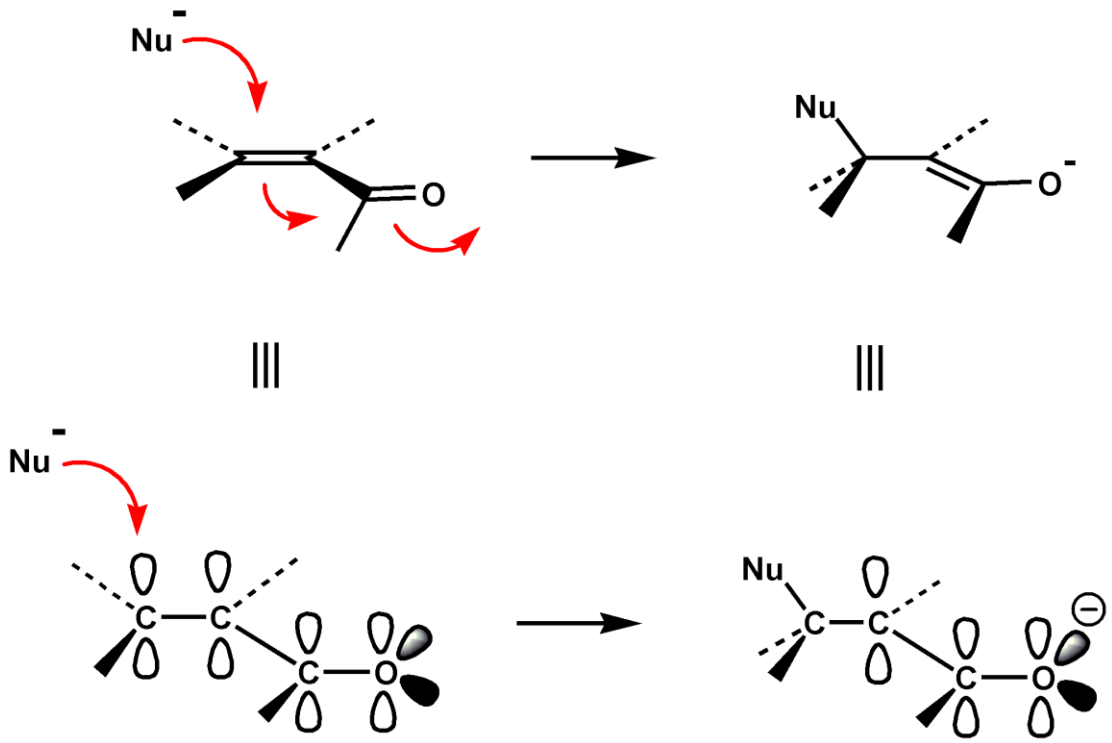


Compound 93 (R=H or CH_3) gave under strickly kinetically controlled conditions only the axial nitrile isomer 96;

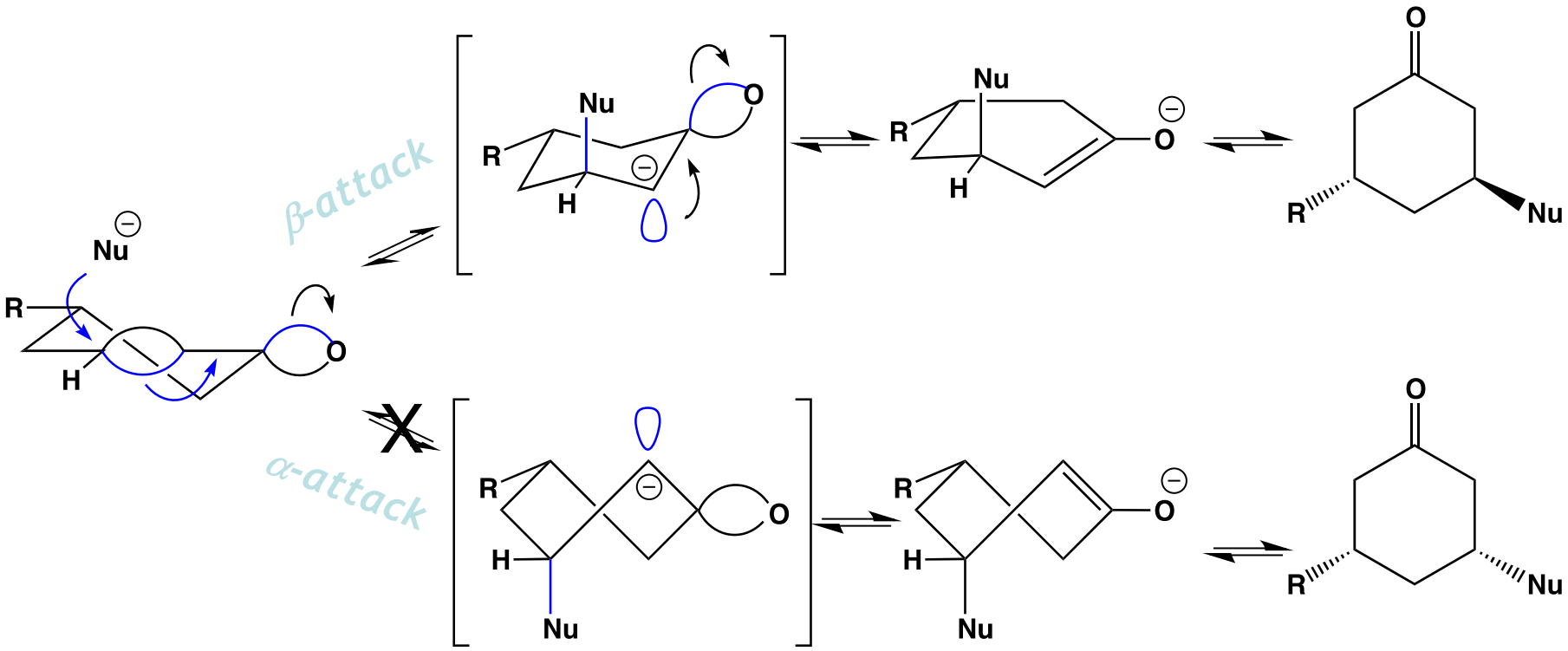
a result of an attack on the α face of 93 forming 94.

C. AGAMI *et al.* *Tetrahedron* 1981, *37,* 903.

Michael addition on enone (Stereoelectronic parameter)

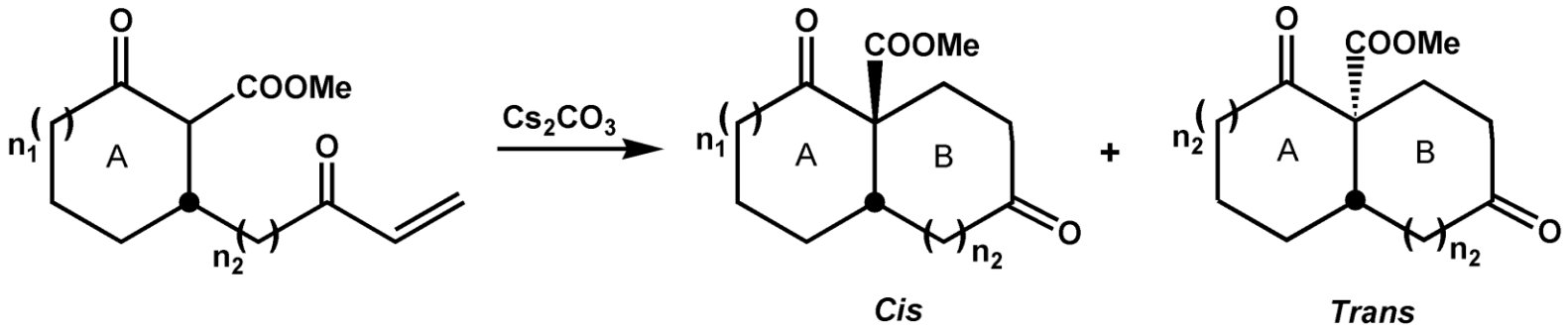


Conjugate Addition - Cyclohexenones



Intramolecular Michael Addition of β-Ketoester as a Function of Ring Size

RÉSUMÉ



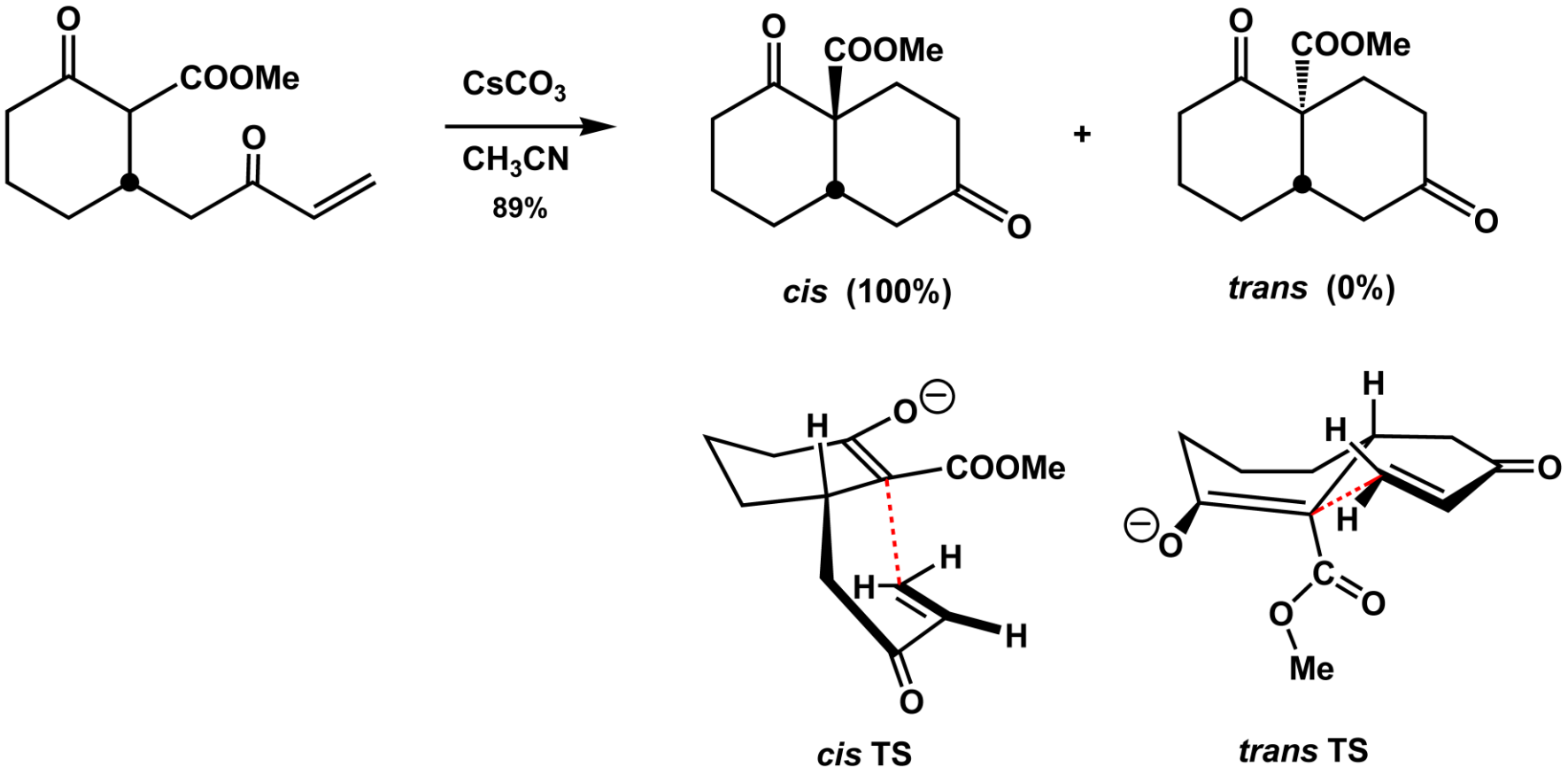
Cis *Trans*

Ring A	Ring B	Ratio *C/T*	Yield
5	5	-	0
6	5	-	0
5	6	1:0	70
6	6	1:0	89
5	7	1:0	88
6	7	5:1	60
5	8	1:0	15
6	8	1:1	20

G. BERTHIAUME
J.-F. LAVALLÉE
P. DESLONGCHAMPS

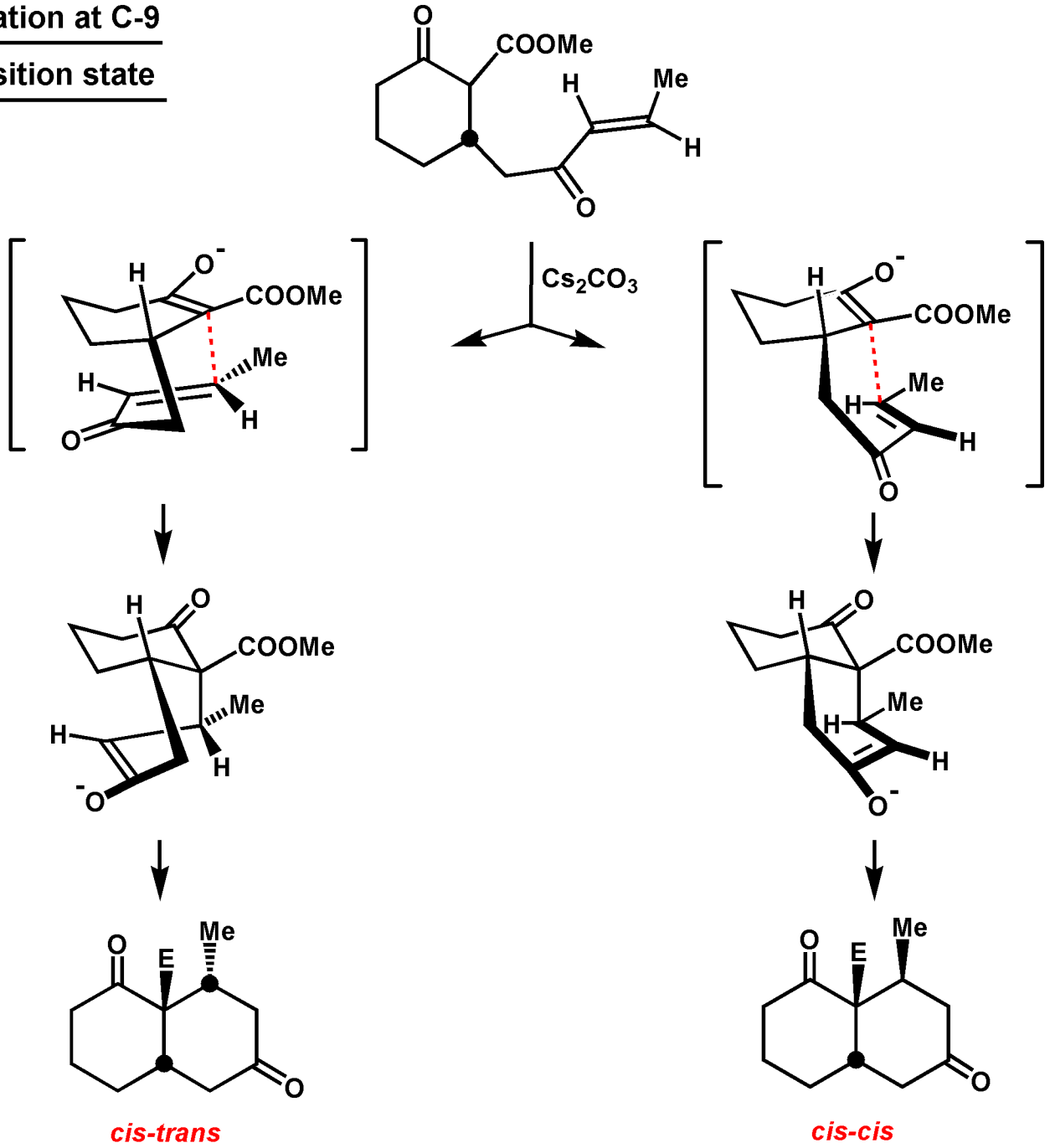
Tetrahedron Lett. *27*, 5451 (1986)

INTRAMOLECULAR MICHAEL ADDITION OF A CYCLIC β-KETOESTER

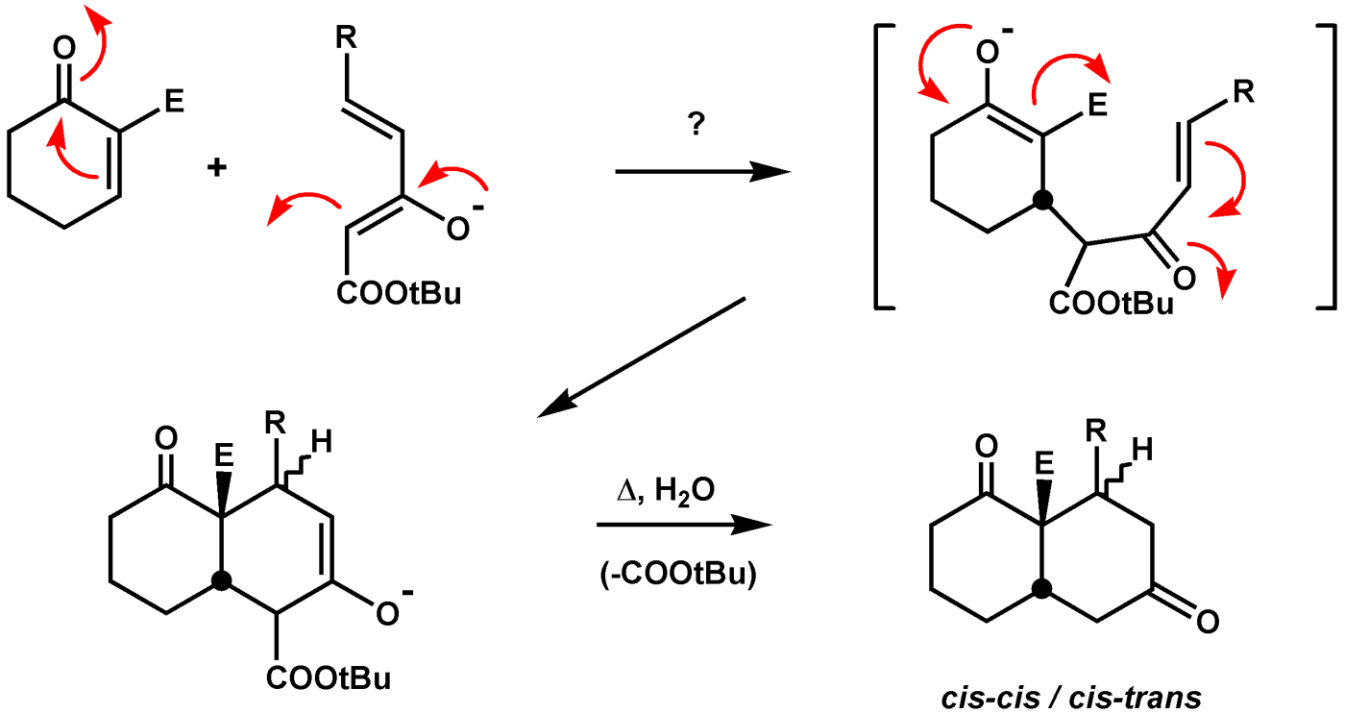


G. Berthiaume, J.-F. Lavallée, P. Deslongchamps.
Tetrahedron Lett. (1986), *27,* 5451.

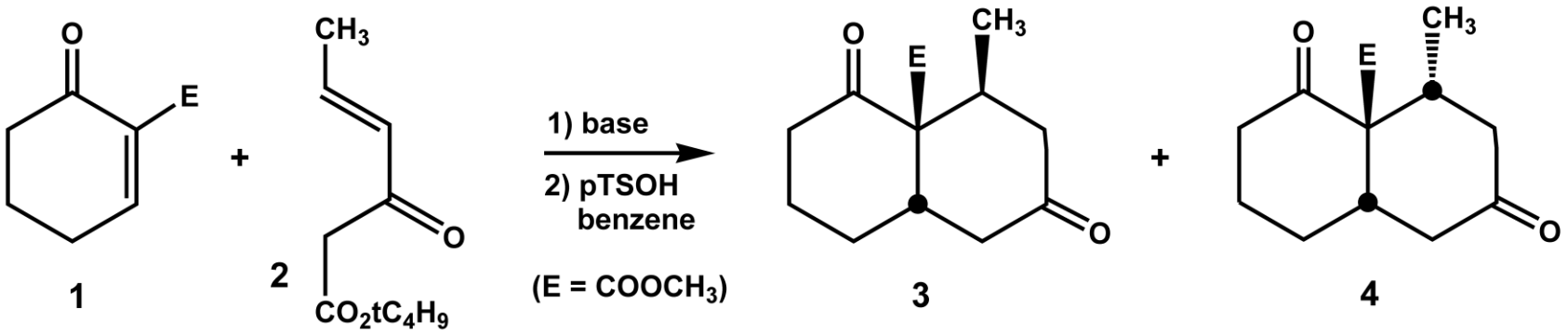
Configuration at C-9 and transition state



How about an intermolecular situation?



STEREOSELECTIVE INTERMOLECULAR ANIONIC CYCLIZATION

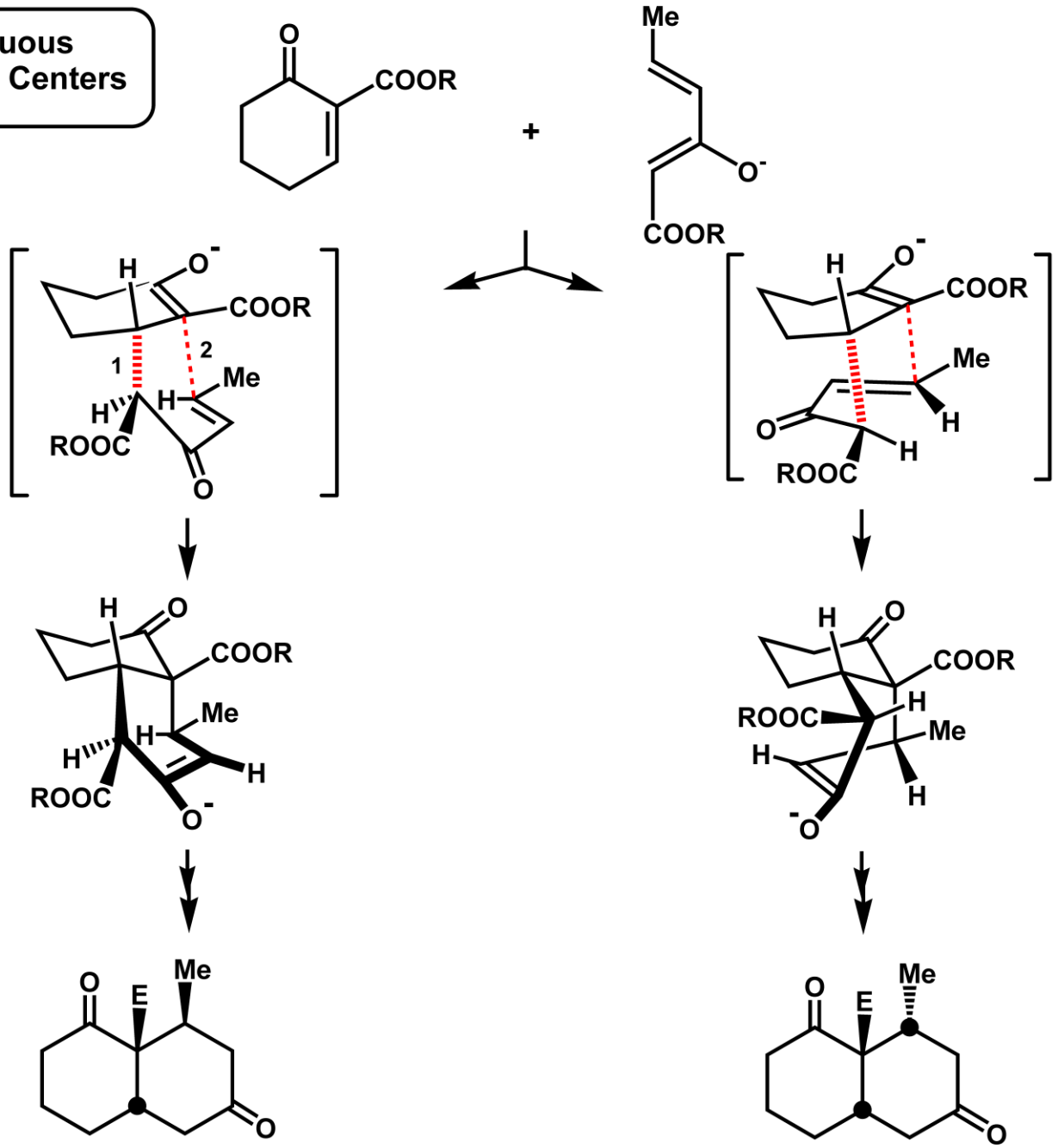


Entry	Base/Solvent	Ratio
		3 : 4
1	Cs_2CO_3 / DMF	54 : 46
2	KH / CH_3CN	50 : 50
3	Cs_2CO_3 / CH_3CN	75 : 25
4	Cs_2CO_3 / C_6H_6	95 : 5
5	Cs_2CO_3 / $CHCl_3$	>99 : 1

J.-F. LAVALLÉE, P. DESLONGCHAMPS.

Tetrahedron Lett. *29*, 5117 (1988).

3 Contiguous Stereogenic Centers

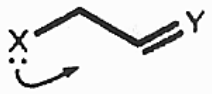


cis-cis (major isomer)

(E = COOMe)

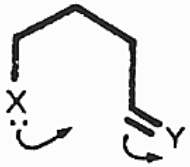
cis-trans

Baldwin Rules for Closure in Trigonal Systems

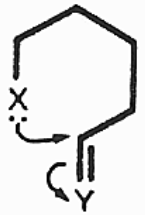


152 √

153 √



154 √

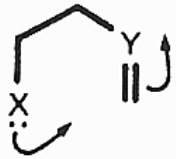


155 √

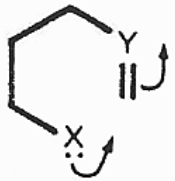
156 √

157 X

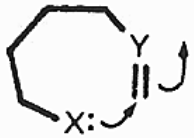
158 X



159 X



160 √

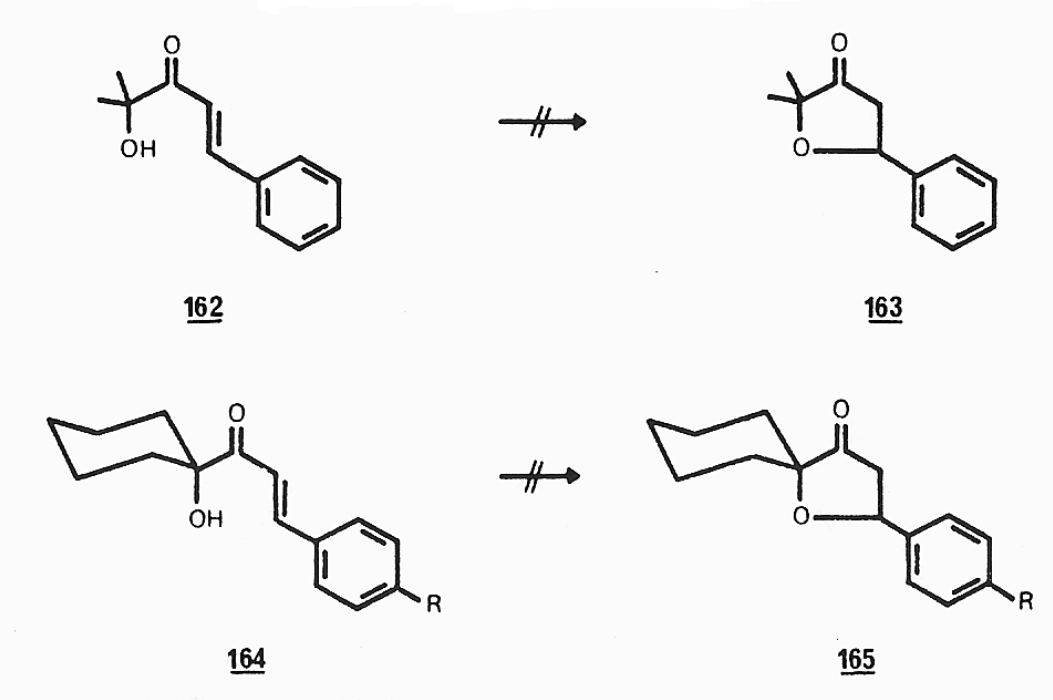


161 √

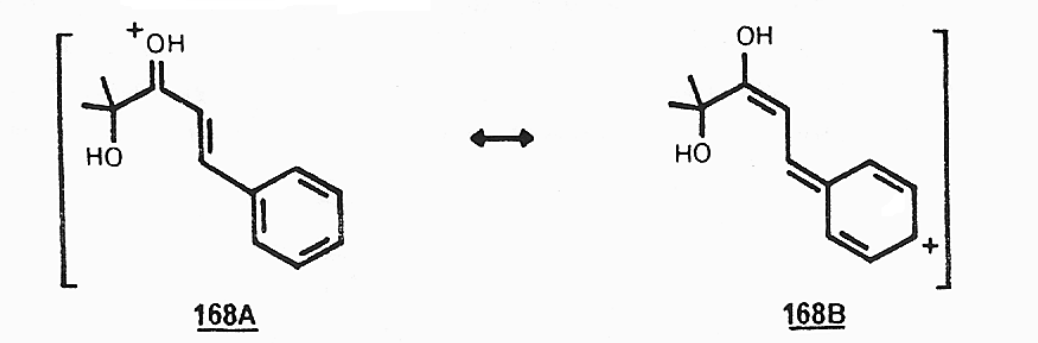
Examples of Forbidden Intramolecular Michael

No reaction with CH_3ONa/CH_3OH

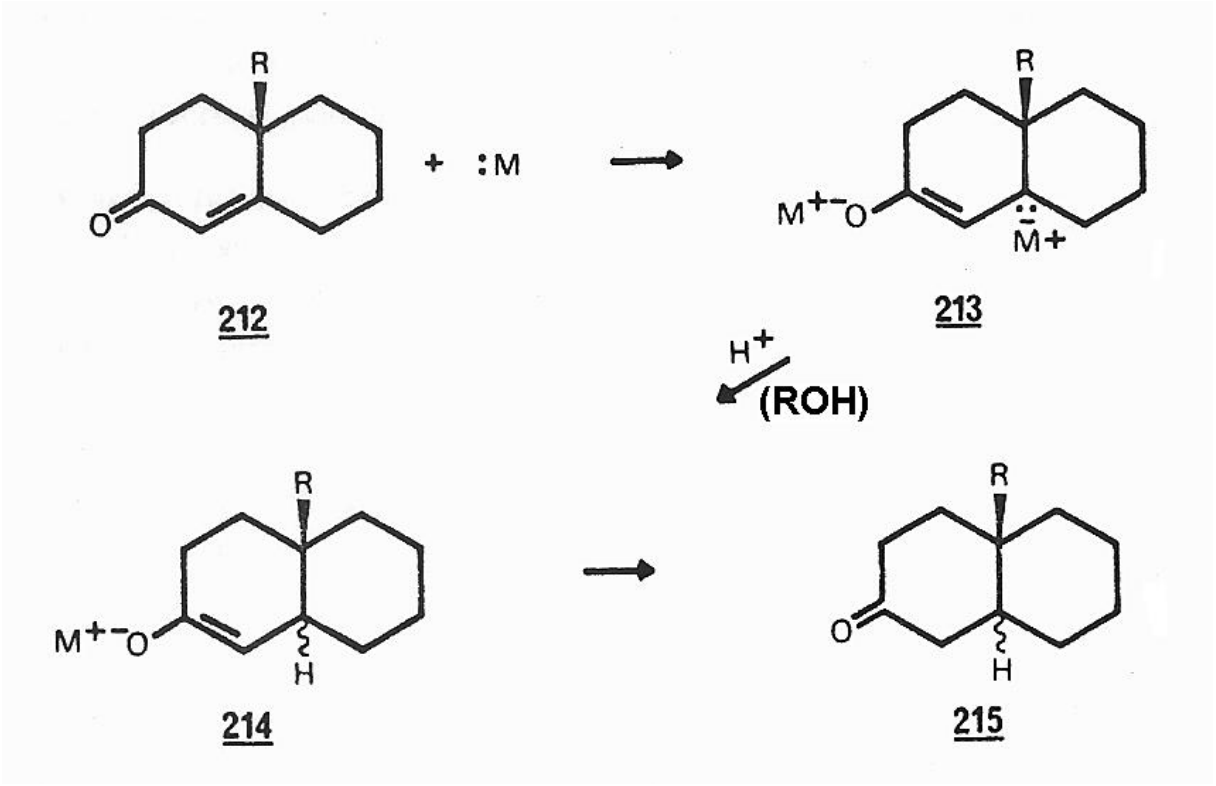
But takes place in acidic conditions



Due to



Reduction of Unsaturated Ketone with Metal / NH_3

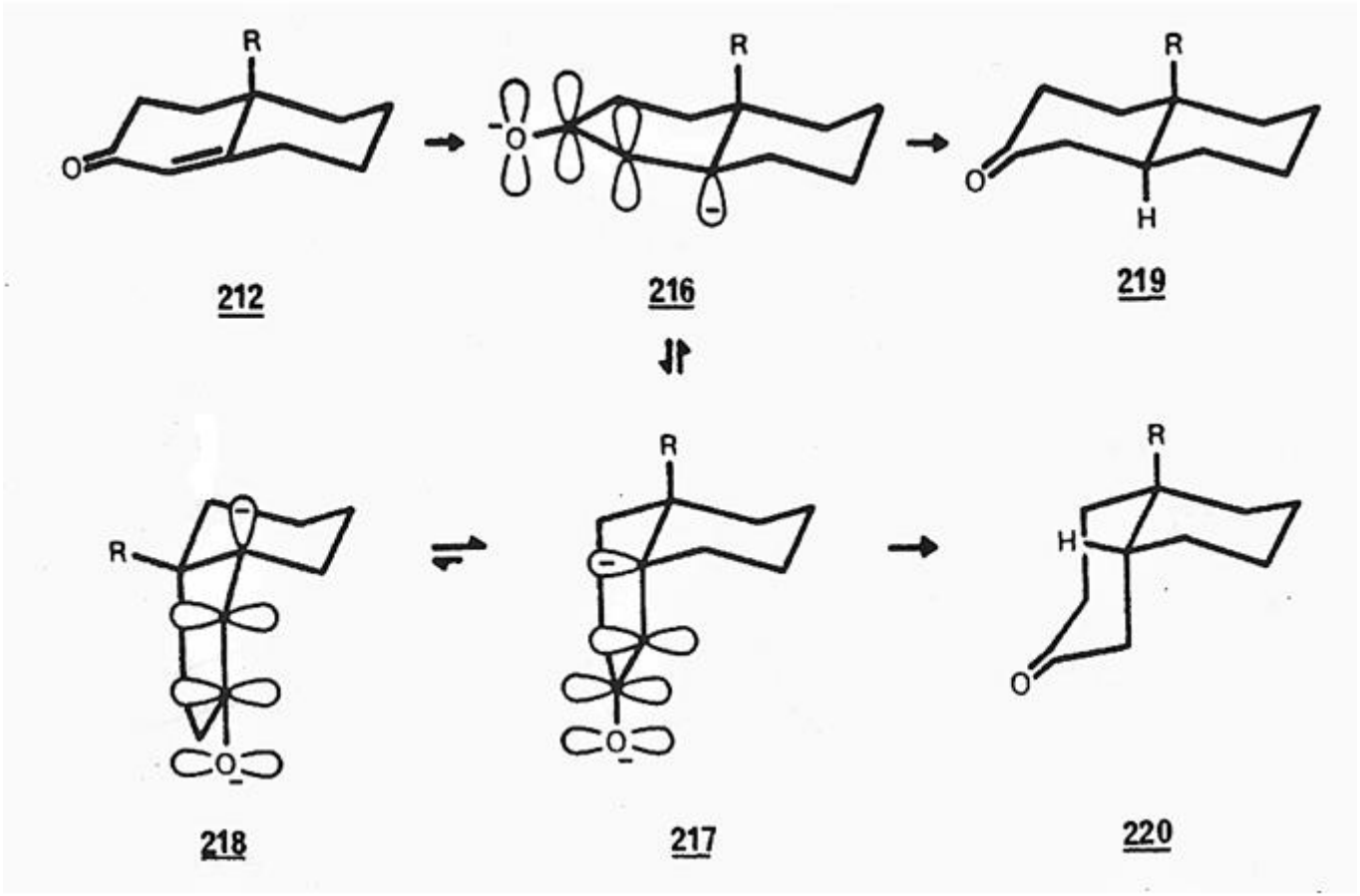


Metals: Li, Na, K, Ca, etc

G. STORK *et al. J. Am. Chem. Soc.* 1960, *82,* 1512; 1964, *86,* 1761.

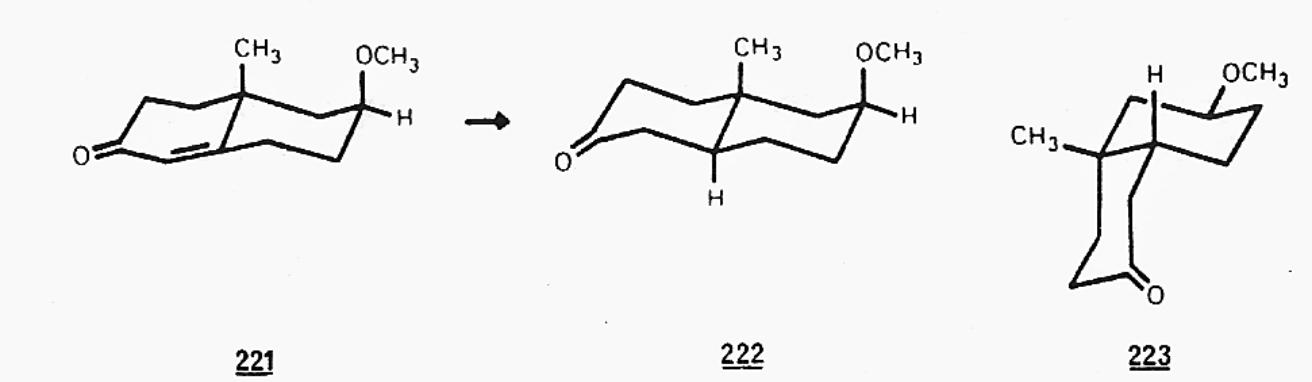
Stereoelectronic Effects and

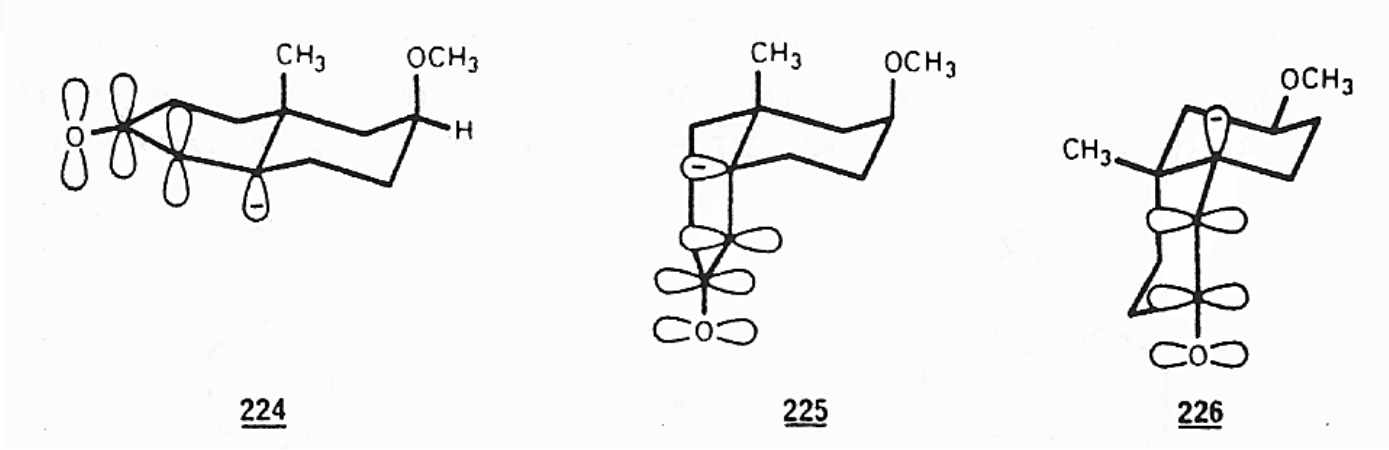
Chemical Reduction of Bicyclic Unsaturated Ketone



Reduction of Bicyclic Unsaturated Ketone with Li / NH_3 / EtOH

…gave only 222 even if it is less stable (~2 kcal/mol) than 223





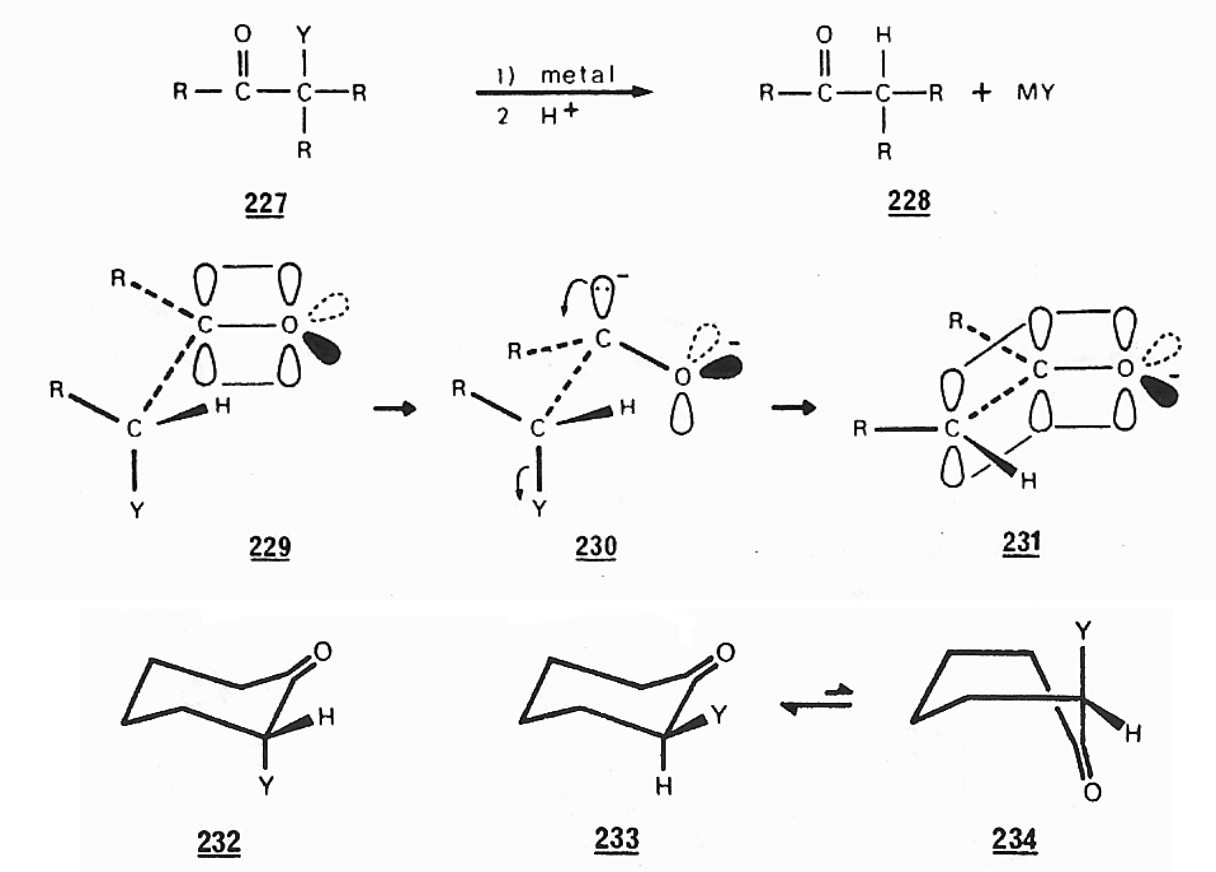
Because: **226 is electronically destabilized**

224 and 225 are both electronically stabilized but 225 is sterically disfavored

G. STORK *et al.* *J. Am. Chem. Soc.* 1960, *82,* 1512; 1964, *86,* 1761.

Hydrogenolysis of a Leaving Group α to Ketone

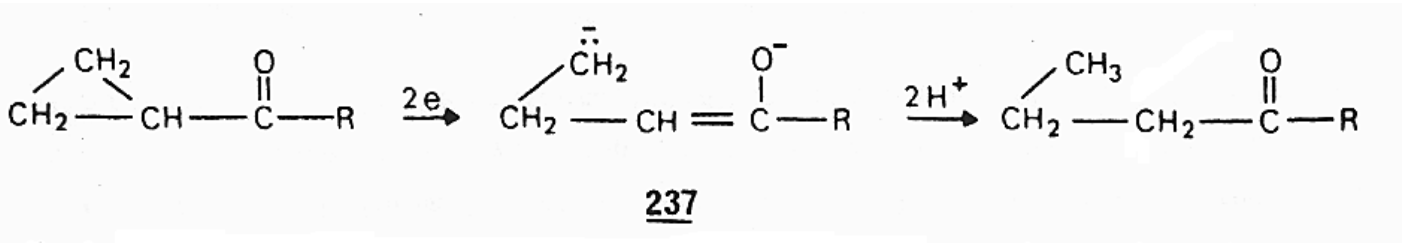
As a consequence, cyclohexanones with axial α substituents must be reduced more readily than analogous compounds with equatorial substituents, especially when the two compounds are essentially conformationally rigid.



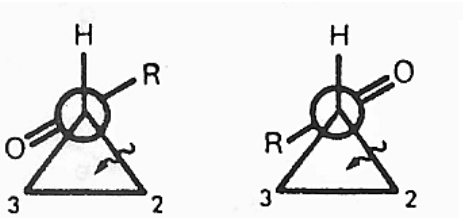
H.O. HOUSE. « Modern Synthetic Reactions »; 2nd Ed.,; W.A. Benjamin Inc.: Menlo Park, California, 1972; pp. 158-160.

C. DJERASSI. « Steroid Reactions »; Holden-Day Inc.: San Francisco, 1963; pp. 319-322.

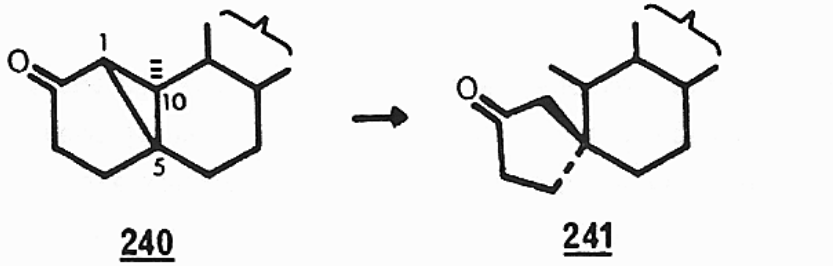
Chemical Reduction of Cyclopropyl Ketone with Li / NH_3



237



238 239



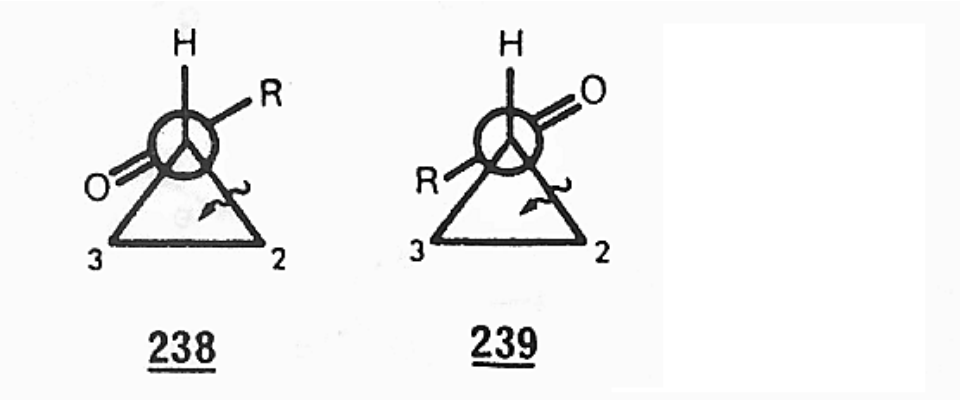
240 241

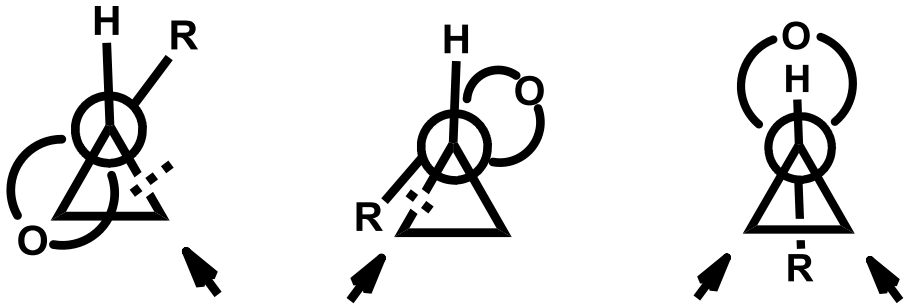
242 243

W.S. JOHNSON *et al.* *Tetrahedron Lett.* 1968, 2829.

W.G. DAUBEN *et al.* *J. Org. Chem.* 1966, *31,* 3794.

Tau bond and Cyclopropyl Ketone

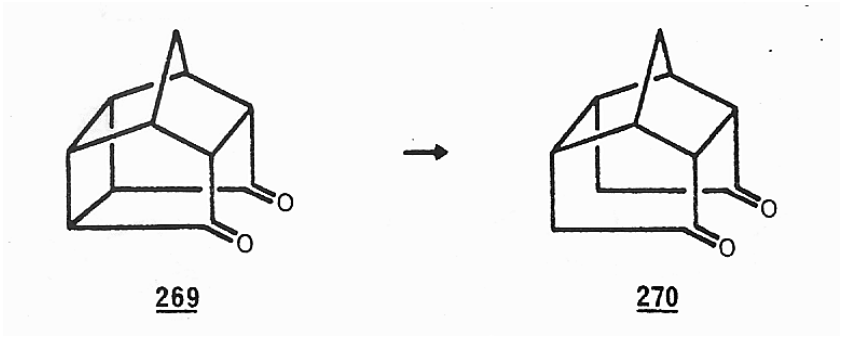




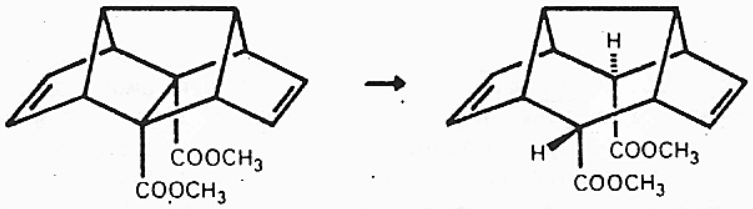
238
(staggered)

239
(eclipsed)

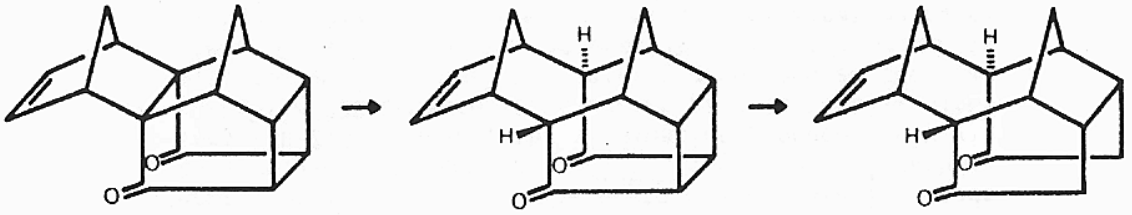
In Chemical Reduction, Two Carbonyl Groups are of Great Help



269 270



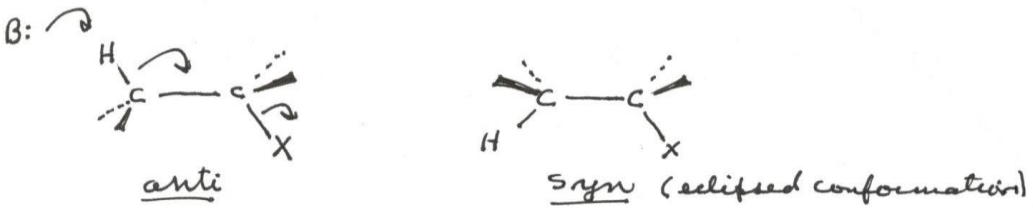
271 272



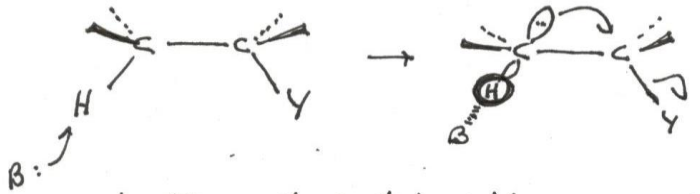
273 274 275

L.A. PAQUETTE *et al. J. Am. Chem. Soc.* 1978, *100,* 1600, 5845; 1981, *103,* 226.

Double Bond Formation – SYN and ANTI elimination



SYN elimination can take place via a double inversion mechanism.



respecting the antiperiplanar orientation.

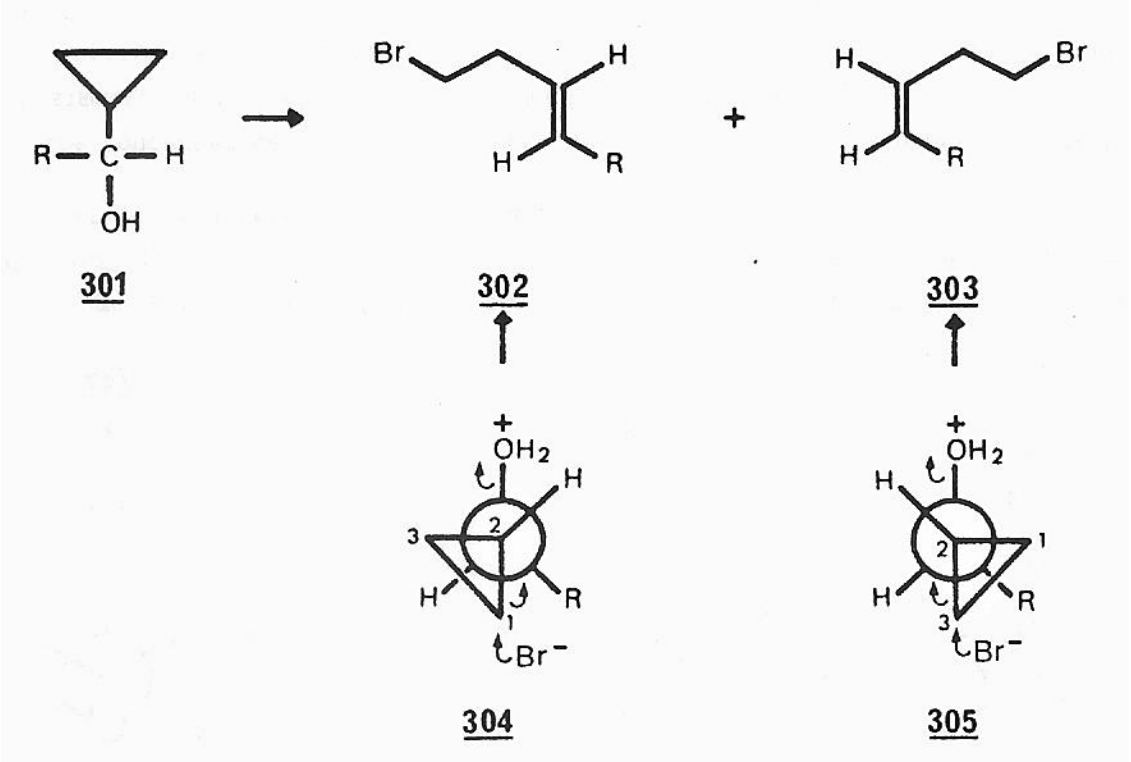
1) BORTSCH R.A., ZAVADA J. Chem. Rev. 1980, 80, 453

2) J. SICHER angew. Chem. int. Ed. Engl 1972, 11, 200

3) R.D. Bach, R C. Badger, T. J. Lang. J. A. C. S. 1979, 101, 2845

Julia Method of Homoallylic Bromides

by cleavage of cyclopropyl carbinols



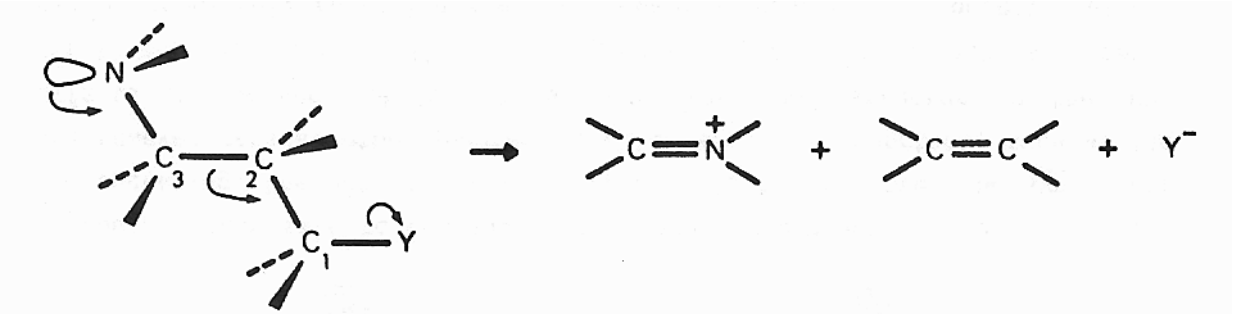
302 is obtained with 90-95% stereoselectivities

via 304 which is sterically favored

JULIA, M. *et al*. *Bull. Soc. Chim. France* 1960, 1072; 1961, 1849.

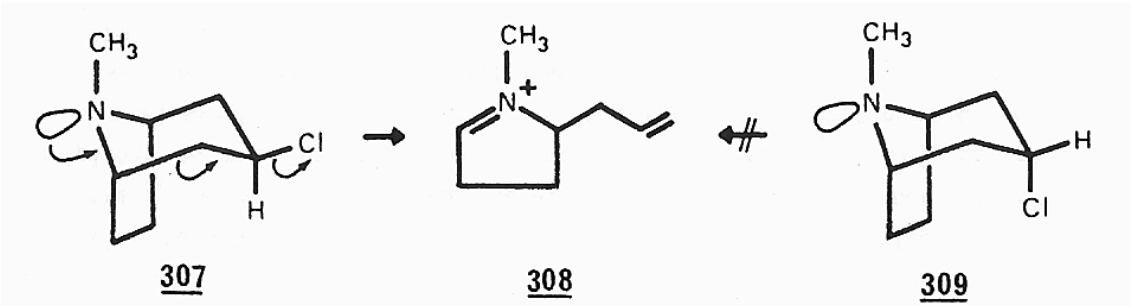
See also JOHNSON, W.S. *J. Am. Chem. Soc*. 1968, *90,* 2882.

1,4-Elimination Reaction

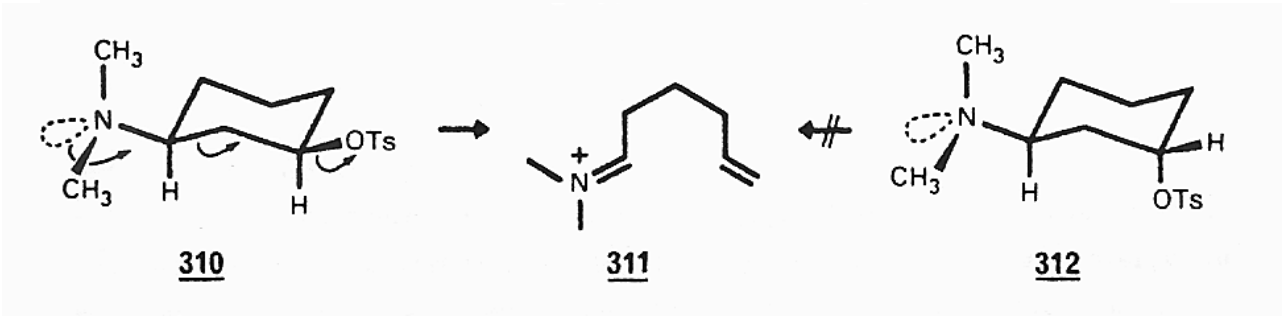


306

Some examples…



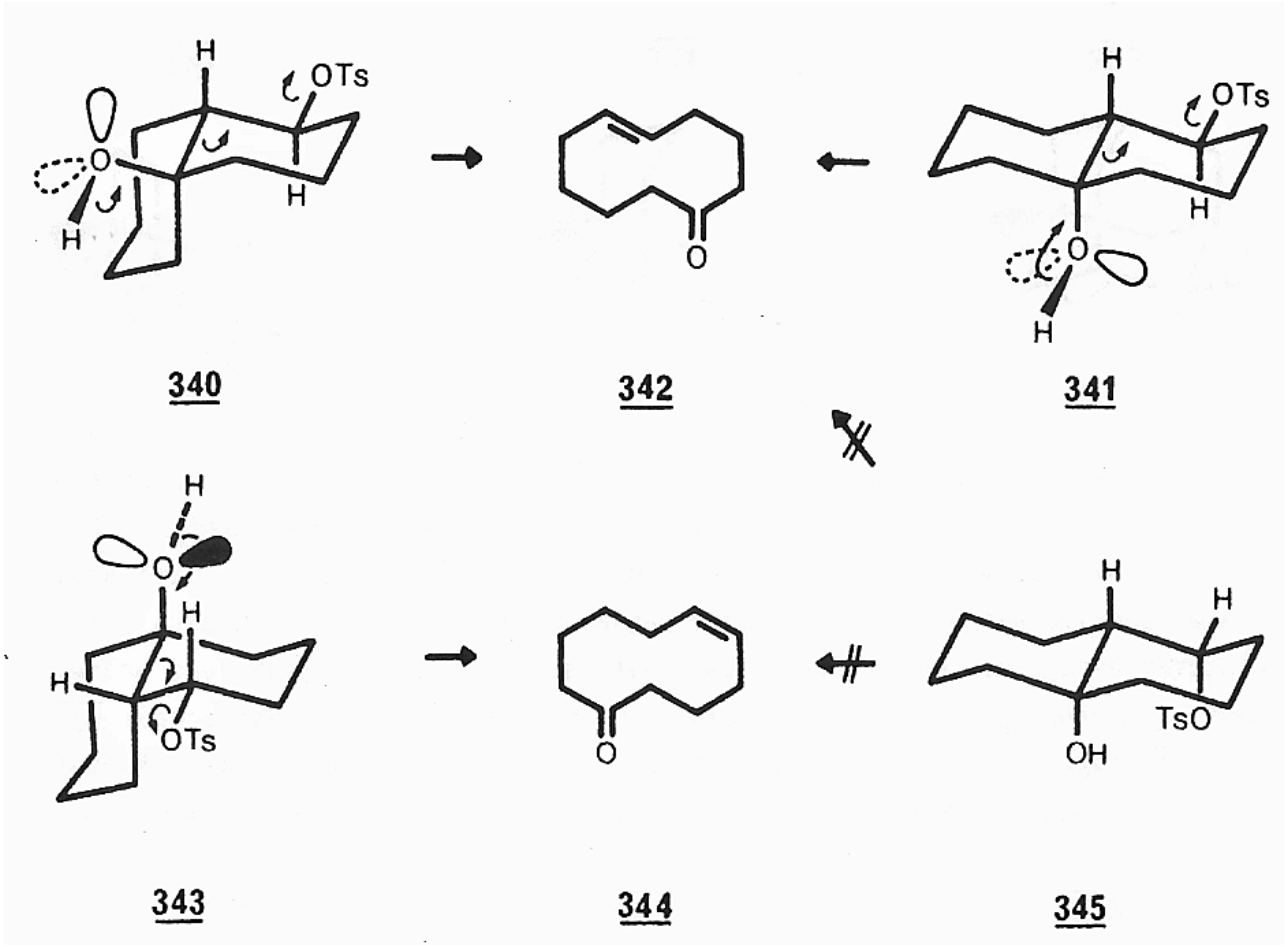
307 308 309



310 311 312

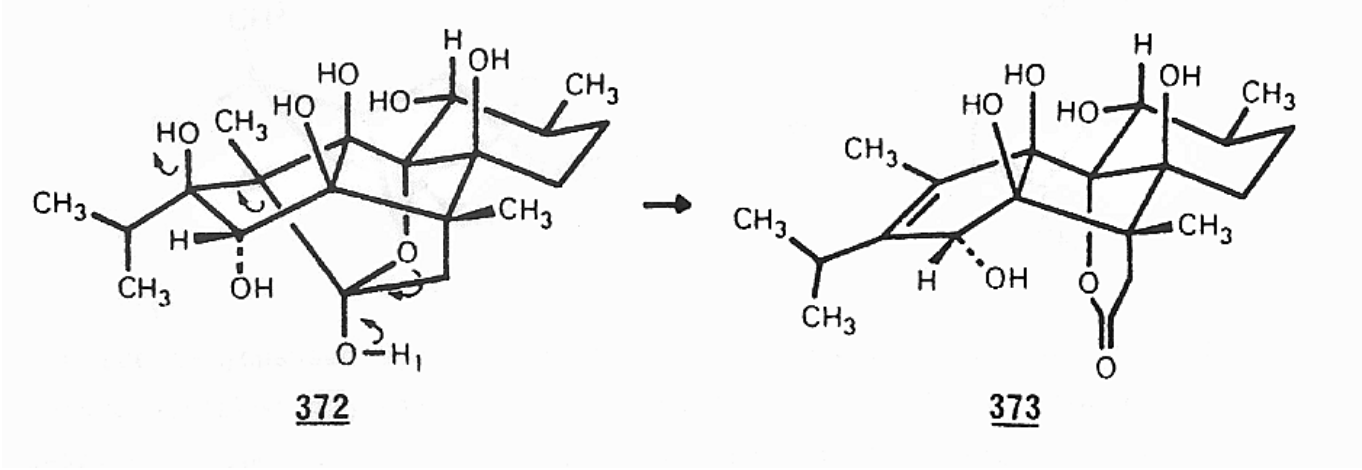
GROB, C.A. *et al.* *Angew. Chem. Int. Ed.* 1969, *8,* 535.

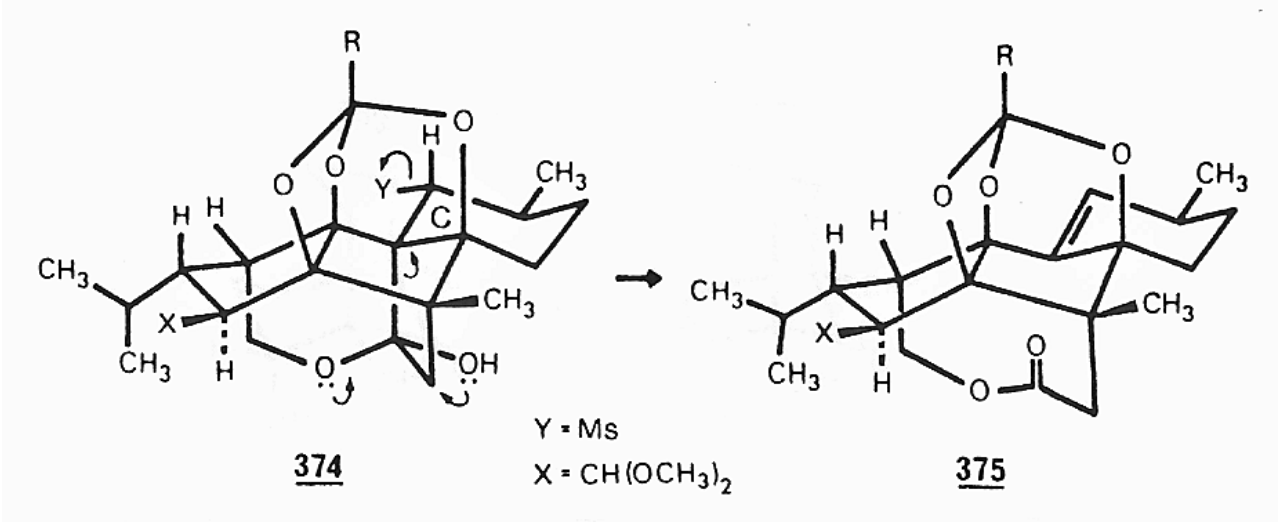
Other Examples of 1,4-Elimination



WHARTON *et al. J. Org. Chem.* 1965, *30,* 3254.

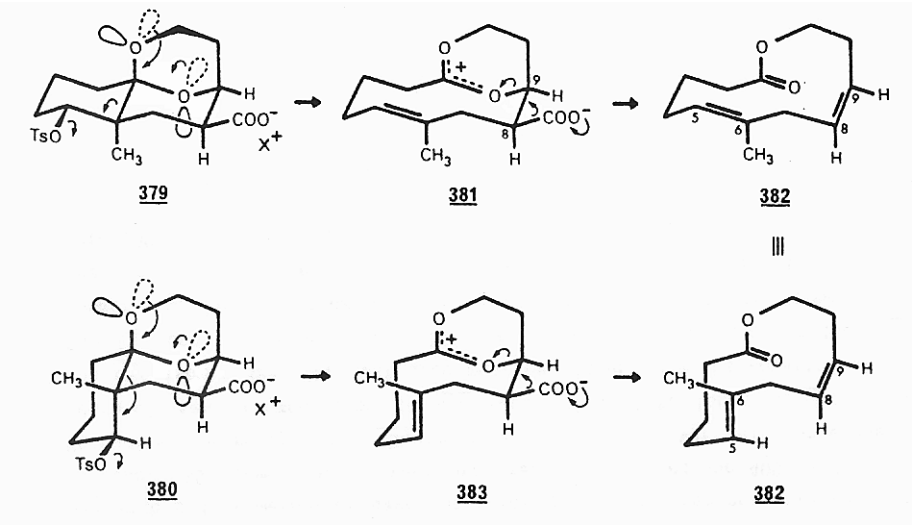
1,4-Elimination in Ryanodol

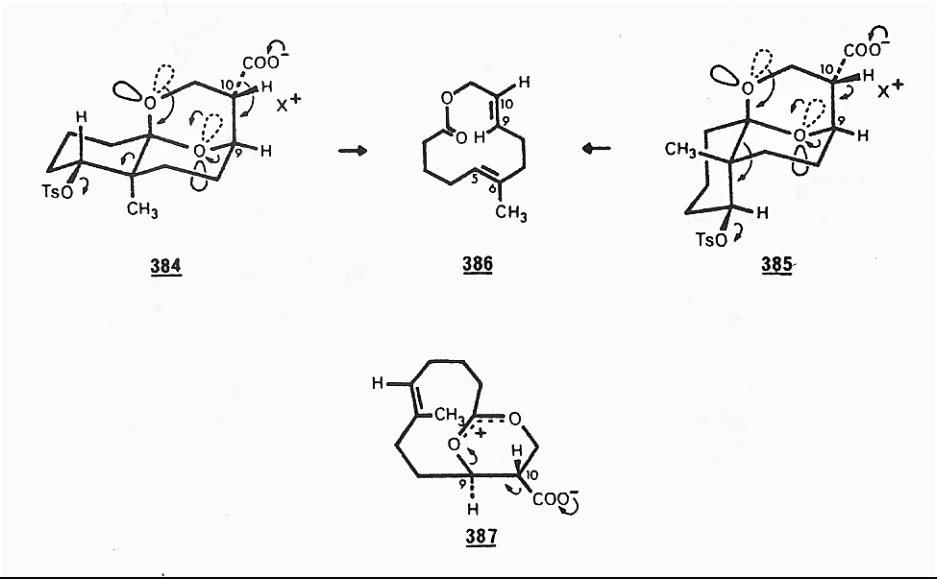




DESLONGCHAMPS *et al. Can. J. Chem.* 1979, *57,* 3348.

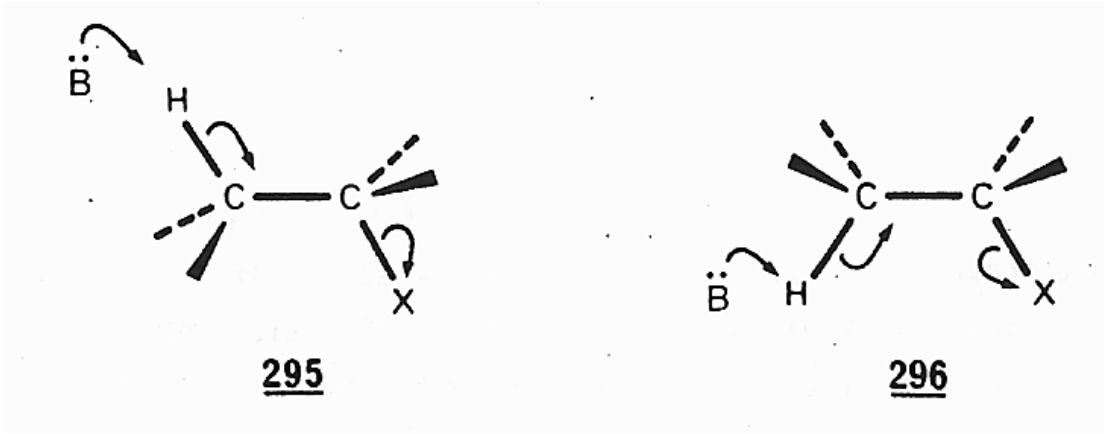
1,4-Elimination by Solvolysis





ESCHENMOSER, A. ***et al. Angew. Chem. Int. Ed. Engl.*** **1979, *18,* 634, 636.**

Double-bond Formation via a Concerted Mechanism (E2)



295 296

In conformationally mobile systems, both *syn* and *anti* eliminations are theoretically possible. The *anti* elimination should be favored electronically over the *syn* elimination because the electron pair of the C-H bond is antiperiplanar to the leaving group.

It would appear safe to conclude that where stereoelectronic effects alone are operating, the *anti* elimination process is favored over the syn. There are however several other parameters which are also important, such as the effects of the nucleophile, the solvent, the alkyl structure of the substrate and the nature of the leaving groups. Any of these variables is capable of completly reversing the stereochemical course of a concerted elimination reaction.

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