The Chemical Adventures with Bicyclobutane

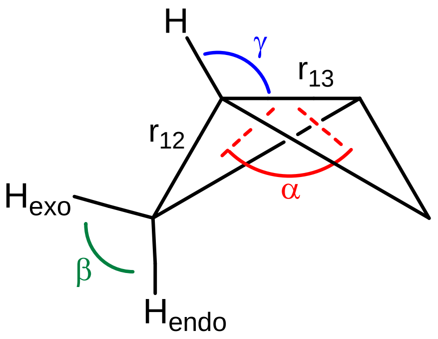
Maciej A. Walczak
Research Topic Seminar
February 12th, 2005

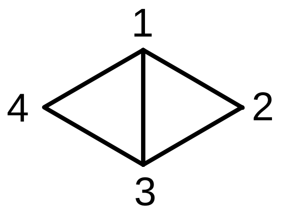
Outline

- Structural and Theoretical Aspects of Bicyclobutane
- Synthetic Routes to Bicyclobutane Skeleton
- Reactions of Bicyclobutanes
- Some Synthetic Applications of Bicyclobutanes

Leading Reviews:
Wiberg *Tetrahedron* 1965, 21, 2749
Hoz in *Chemistry of Cyclopropyl Group* (Rappoport, Ed.) 1987
Bishop *Chem. Rev.* 1976, 76, 461

Structure of Bicylobutane



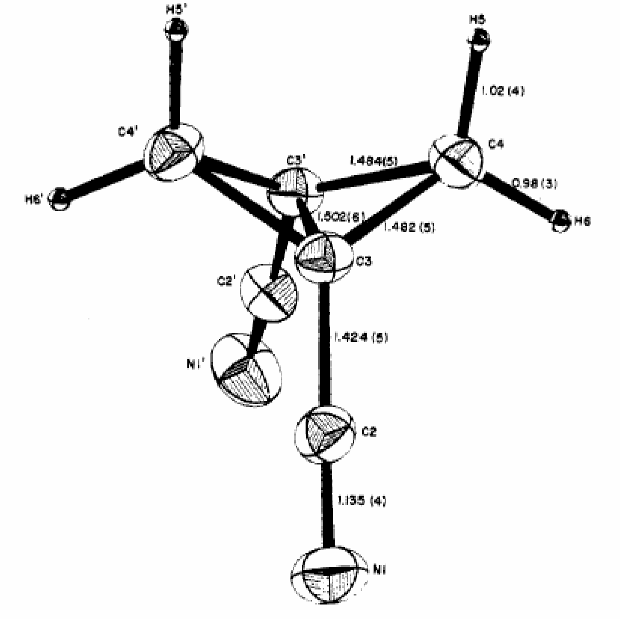


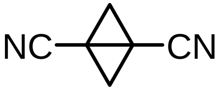
Method	α	β	γ	$C_1{-}C_2$	$C_1{-}C_3$	$C_1{-}H_1$	$C_2{-}H_{exo}$	$C_2{-}H_{endo}$
Vibrational Spectra[a]	126	118	163	1.53	1.54	1.08	1.08	1.08
NMR[b]	120.2	110.2	128.0	1.507	1.507	1.142	1.194	1.167
Electron Diffraction[b]	122.8	111.6	125.5	1.507	1.502	1.108	~1.106	~1.106
Microwave[c]	122.7	115.6	128.4	1.497	1.497	1.071	1.093	1.093

Angles are given in degrees and bond lengths in Ångstroms

[a] Haller, Srinivasan *J. Chem. Phys.* 1964, 41, 2745.
[b] Meiboon, Snyder *Acc. Chem. Res.* 1971, 4, 81.
[c] Harmony, Cox *J. Am. Chem. Soc.* 1966, 88, 5049 and Cox *et al. J. Chem. Phys.* 1969, 50, 1976.

X-ray Structure



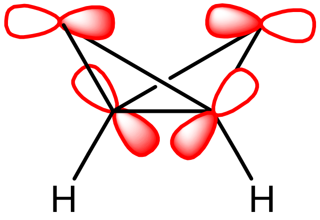


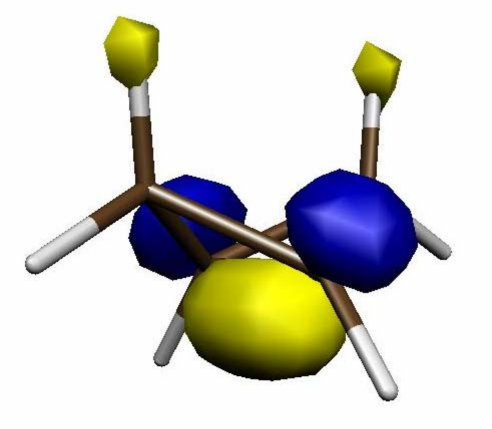
[a] Johnson, Schaefer *J. Org. Chem.* 1972, 37, 2762.

MO Treatment of Bicyclobutane

Walsh-type orbitals for bicyclobutane

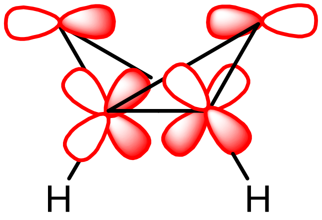
Ethylenic

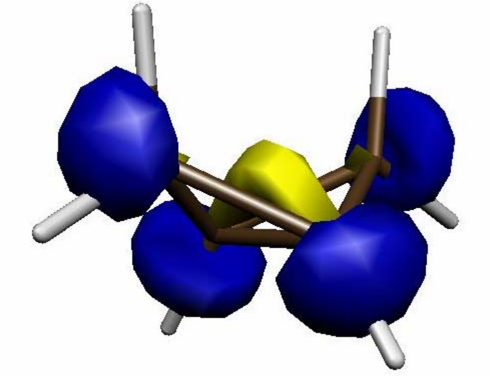




HOMO (-0.249 a.u.)

Acetylenic





LUMO (0.010 a.u.)

Pomerantz, Abrahamson
J. Am. Chem. Soc. 1966, 88, 3970

The Nature of the Central Bond

- *Ab initio* calculations show that 96% *p* character of central bond (compare cyclopropane, 86%)

Schulman, Newton *J. Am. Chem. Soc.* 1974, **96**, 6295

- $^1J_{CH}$ for C_1–H_1 is 205 Hz and that corresponds to 40% s character of the C–H bond hybrid

- $^1J_{CC}$ values for C_1–C_3 are exceptionally low (–5.4 to –17.5 Hz); using some approximations, Pomerantz calculated around 11% of *s* character for the central bond

Pomerantz, Hillenbrand *J. Am. Chem. Soc.* 1973, **95**, 5809

- Electron density of central bond is oriented outward (45° or 30.8°)

- Hückel calculations assign p-character to the central bond (p–σ and p–π ratio was estimated to 5:1)

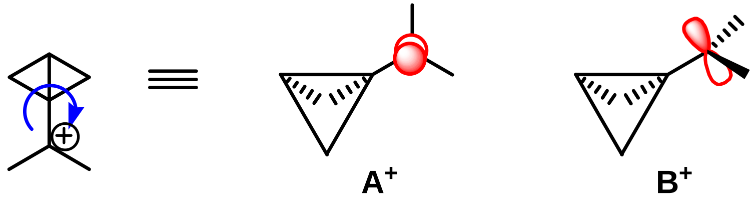
Schulman, Fisanick *J. Am. Chem. Soc.* 1970, **92**, 6653

- Unrestricted calculations (GVB/3-21G) assign ca. 4% of radical character

Schleyer *et al. J. Am. Chem. Soc.* 1986, **108**, 561

Interaction of C_1-C_3 bond with External Fragments – Theoretical Studies

- *Ab initio* calculations showed that conformer B^+ is 32 kcal·mol^{-1} more stable than A^+



- However, anion A^- is 0.12 kcal·mol^{-1} more stable than B^-

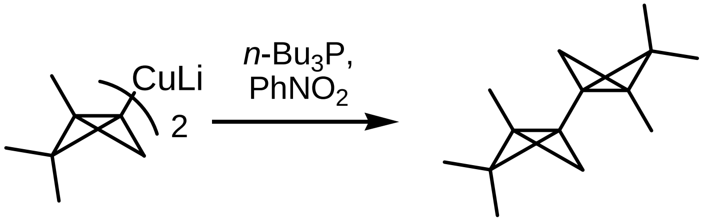
Greenberg A. *Tetrahedron Lett.* 1978, 3509

Theoretical studies revealed that lower stabilization energy is due to poor orbital overlap (structure B^-)

Hoz *et al. J. Mol. Str. (Theochem)* 1985, 121, 93

Experimental Evidence Π-Character of Central Bond

- Bicyclobutane dimer shows red shift in UV/VIS spectrum

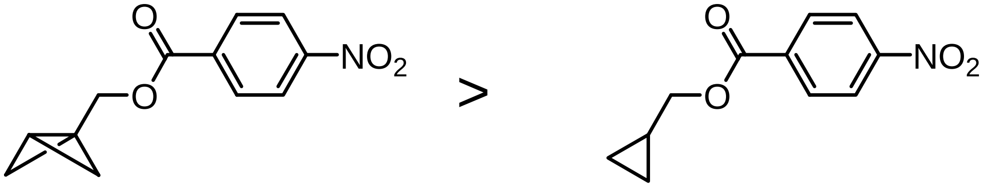


62%

λ_{max} = 190 nm

Moore, Costin *J. Am. Chem. Soc.* 1971, 93, 4910

- Solvolysis of benzoate ester is faster that in analogous cyclopropyl derivative



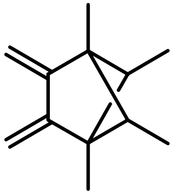
ca. 1000 times faster

Wiberg *et al. Tetrahedron* 1965, 21, 2749

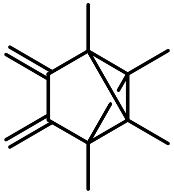
Further Evidence for Strong Π-Character of C_1-C_3 Bond

- Diels–Alder reaction of TCNE with A is faster than with B

A



20h, 55 °C

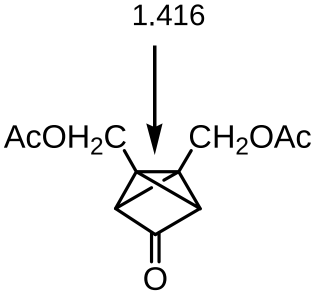


B

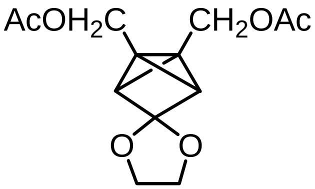
1 min, RT

Hogeveen, Capozzi *J. Am. Chem. Soc.* 1975, 97, 1479
Jorgensen, Borden *Tetrahedron Lett*. 1975, 223
Jorgensen *J. Am. Chem. Soc*. 1975, 97, 3082

- Central bond in C is shortened compared to similar compound D



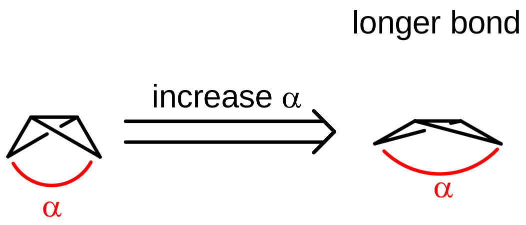
C



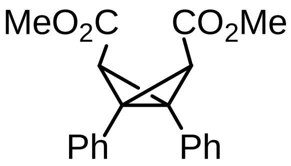
D

Dowd *et al. J. Org. Chem.* 1982, 47, 4240

Correlation Between Tilt Angle and Central Bond Length

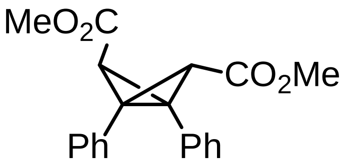


127.2°



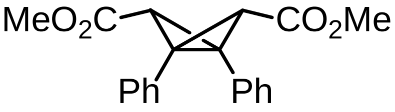
1.558 Å

121.2°



1.498 Å

113.4°

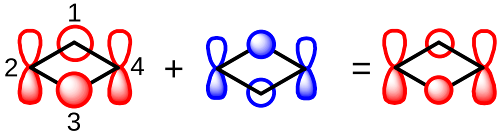


1.455 Å

Gassman *et al. J. Am. Chem. Soc.* 1983, 105, 5865

Origin of Coupling between r_{13} and a

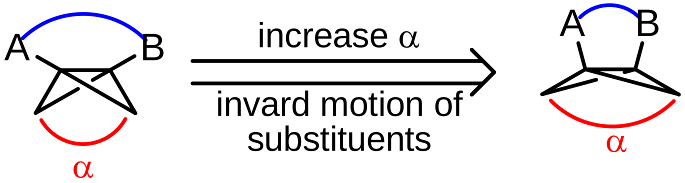
- Relation between r_{13} and a depends on coupling between occupied orbital with empty one



- In the puckered conformation, interactions between C_2 and C_4 are strengthened and C_1–C_3 weakened

Zil'berg *et al. Izv. Akad. Nauk* 1983, 2, 255

- Also, increasing α results in moving the bridging substituents inward



Strain in Small Rings

ΔH_f	12.73	6.78	-18.44	-29.50
SE	27.5	26.5	6.2	0.0

ΔH_f	**51.9**	37.7	9.09	29.9
SE	**63.9**	54.7	31.09	51.8
ΔSE	**8.9**	0.7	-2.61	-1.2

↑

large deviation from the additive scheme

ΔH_f = heat of formation

SE = strain enrgy

ΔSE = difference between experimental and calulated SE

all energies in kcal mol^{-1}

Wiberg in *Chemistry of Cyclopropyl Group* (Rappoport, Ed.) 1987

Strain in Cyclobutane

- Estimated Baeyer (ring) strain for cycboutane is 6.75 kcal mol^{-1}
- Dunitz-Shomaker hypothesis: non-bonded 1,3-carbon/carbon interactions destabilize cyclobutane ring - puckered conformation

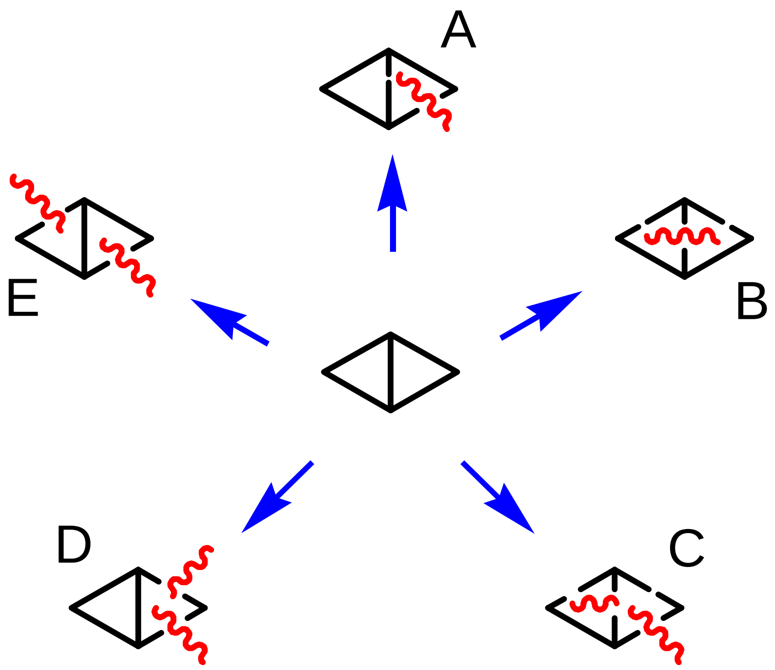
Dunitz, Shomaker *J. Phys. Chem.* 1952, 27, 1703

- DE$_{1,3}$ was calculated for planar and puckered cyclobutane conformers (CNDO/2)

DE$_{1,3}$ [kcal mol^{-1}]	33.5	29.7

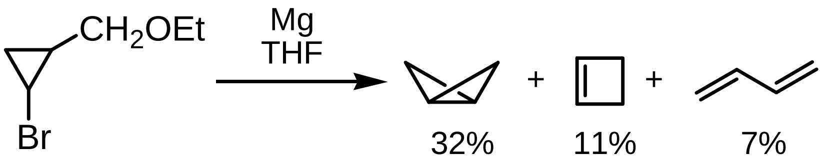
Bauld *et al. J. Am. Chem. Soc.* 1977, 99, 8140

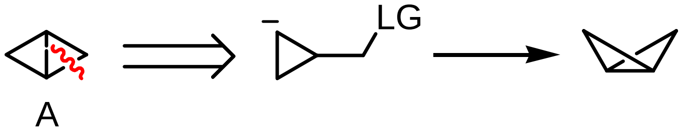
Synthetic Routes to Bicyclobutane Skeleton



Case A - Ionic Substitution

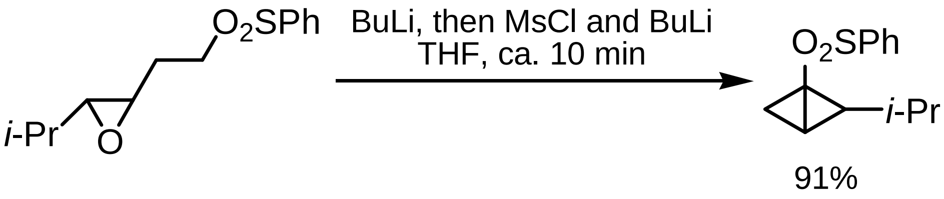
- Ionic substitution is one of the method to form side C–C bond





Abramova, Zotova *Izv. Akad. Nauk* 1979, 697

- Even as poor leaving groups as EtO⁻ can be displaced to form bicyclic ring

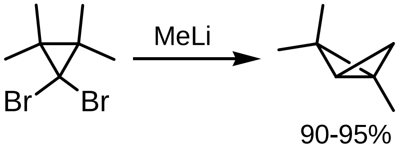


yields: 50-91%

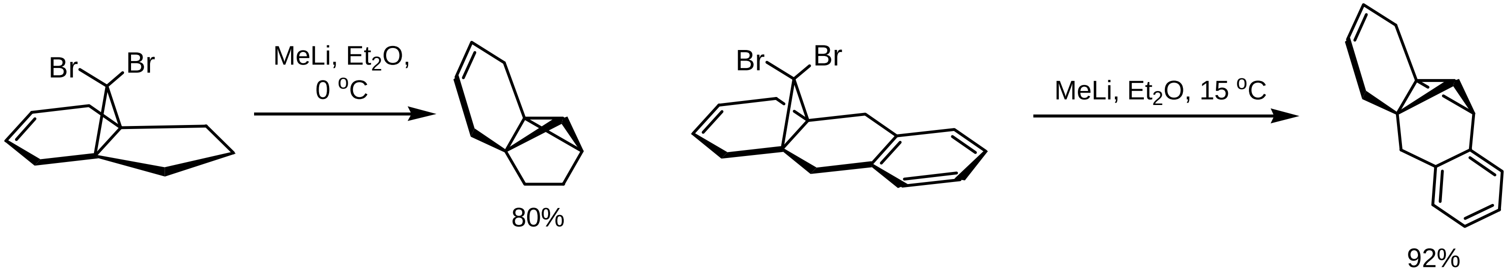
Gaoni *Tetrahedron Let.* 1981, 4339

Gaoni *J. Org. Chem.* 1982, 47, 2564

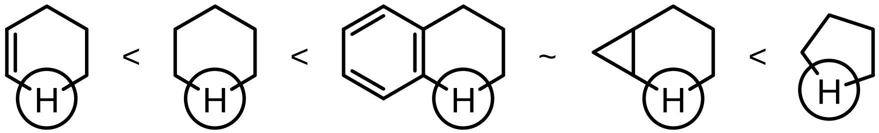
Case A – Carbene Insertion



Skattebøl *Tetrahedron Lett.* 1970, 2361
Moore *et al.* *Tetrahedron Lett.* 1970, 2365



Paquette *et al.* *J. Am. Chem. Soc.* 1980, **102**, 637

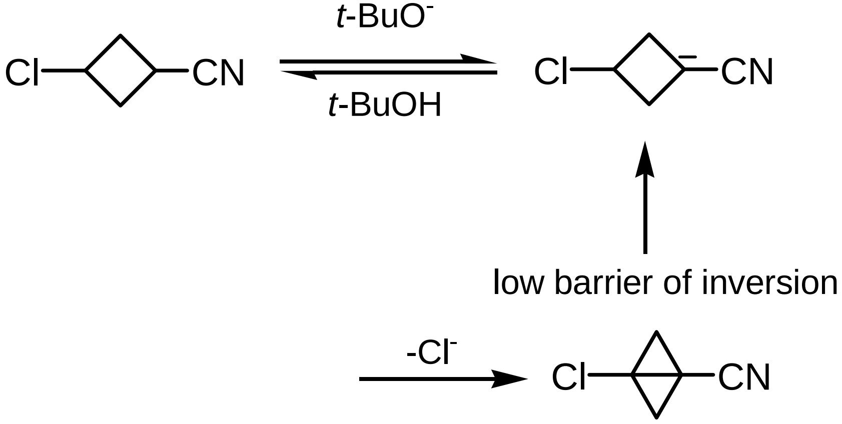


- Regiospecificity is determined by proximity of the cyclopropylidene to the C_α–H bond and nucleophilicity of the later

Approach B – Formation of Central Bond

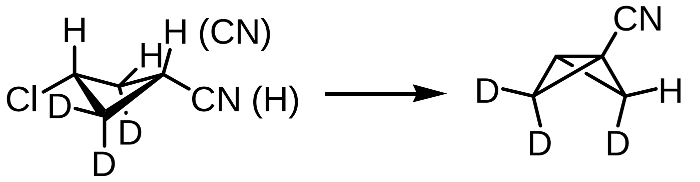
- Displacement across the ring is the main method for the synthesis of bicyclobutanes

Hoz *et al.*
J. Am. Chem. Soc. 1979, 101, 2475



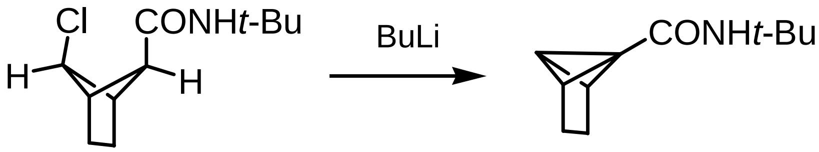
- Elimination of *cis*– and *trans*– substituted cyclobutanes leads to bicyclobutane ring

Hall *et al.*
J. Am. Chem. Soc. 1971, 93, 110



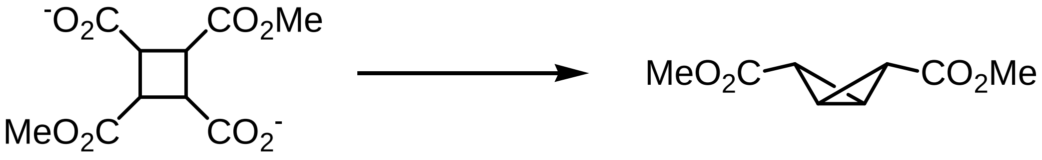
- 1,3-elimination is stereospecific. However, nuclefuge can be also expelled from the axial positon

Meinwald *et al.*
J. Am. Chem. Soc. 1963, 85, 1880



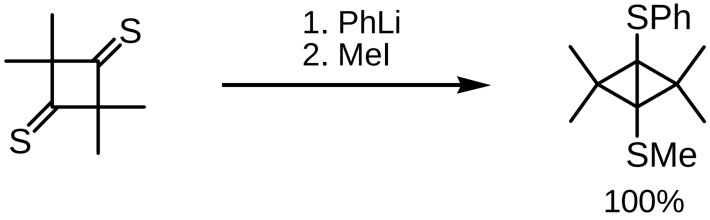
Approach B – Different Methods

- Electrolytic synthesis



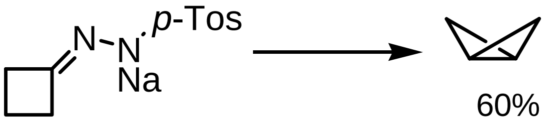
Rifi *J. Am. Chem. Soc.* 1967, 89, 4442

- Reductive coupling of tioketones



Gassman, Mullins *Tetrahedron Lett.* 1979, 46, 4457

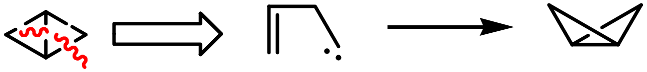
- Decomposition of diazonium salts



Bayless *et al. J. Am. Chem. Soc.* 1965, 87, 661

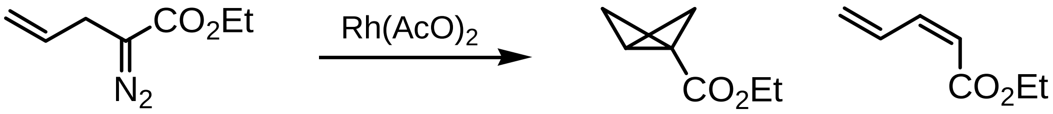
Route C

- Typical approach is addition of carbene generated from diazocompounds to double bond



C

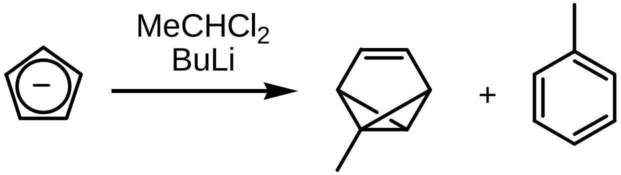
- Some examples:



51%

39%

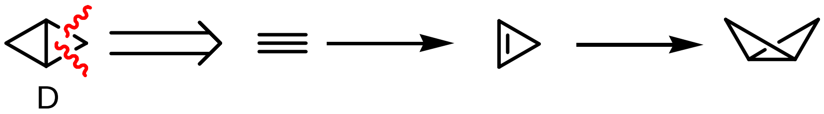
Ganem *Tetrahedron Lett.* 1981, 22, 4163
For similar approach, see also:
Lemal, Shim *Tetrahedron Lett.* 1964, 323;
Lemal *et al. J. Am. Chem. Soc.* 1963, 85, 2529



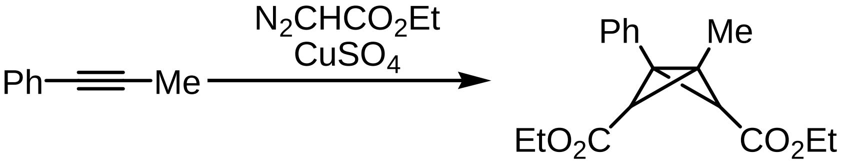
Christl *et al. Chem. Ber.* 1986, 119, 960

Approach D –
Simultaneous Formation of Cyclopropane Ring

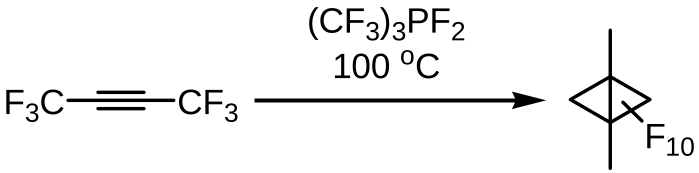
- Cyclopropene and alkynes are used to form bicyclobutane scaffold by reaction with Rh carbenoids



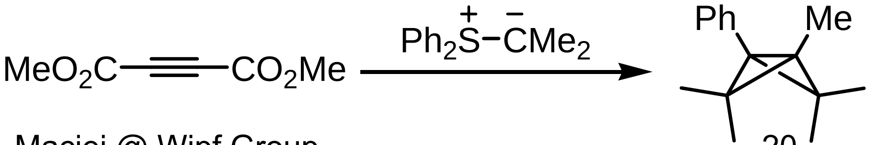
- Simple alkynes have been converted into symmetric bicyclobutanes



Dyakonov *Zh. Org. Khim.* 1961, 31, 3881



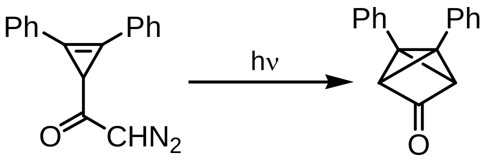
Mahler *J. Am. Chem. Soc.* 1962, 84, 4600



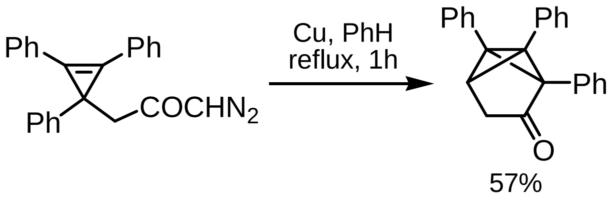
Corey *et al. J. Am. Chem. Soc.* 1967, 89, 3912

Carbene Addition to Cyclopropene

- Instramolecular closure of stabilized carbenes was used to construct strained tricyclic systems

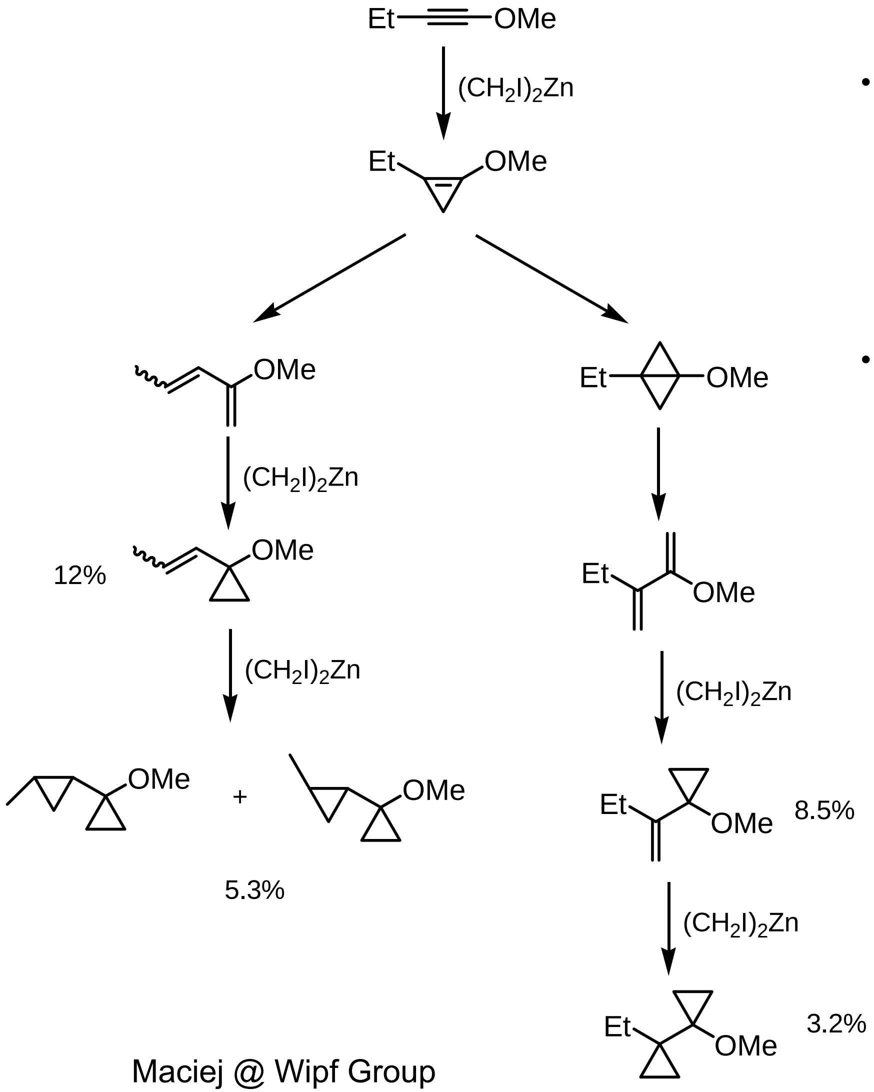


Masamune *J. Am. Chem. Soc*. 1964, **86**, 735



Small *J. Am. Chem. Soc*. 1964, **86**, 2091

Zinc Carbenoids – Reactions with Alkynes



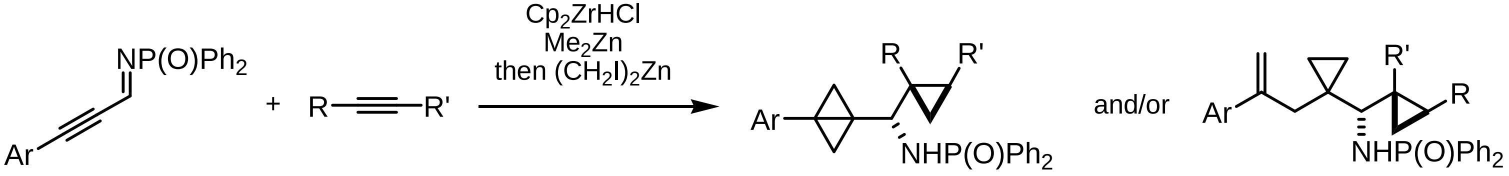
- Zinc carbenoids generated from metallic zinc and CH_2I_2 were shown to react with alkynes to give mixture of cyclopropanated products

- Bicyclobutane was postulated as the intermediate (not isolated)

Jautelat, Schwarz *Tetraherdon Lett.* 1966, 5101

Multicomponent Synthesis of Bicyclobutanes

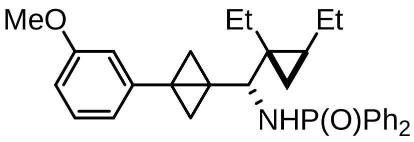
- Aditionof vinylzinc to N-diphenylphosphinyl imies followed by Simmons-Smith type cyclopropanation afforded bicyclobutane or β-cyclopropyl alkenes



R, R' cannot be H

R' = H

- Bicyclobutane were obtained for compounds possessing sterically more demanding groups



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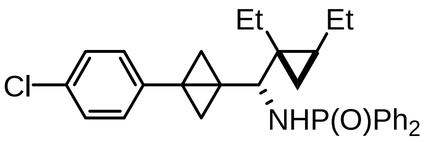

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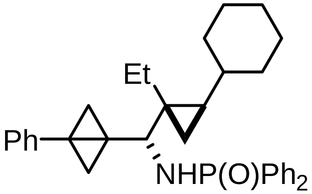

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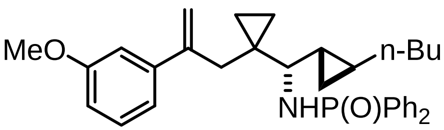
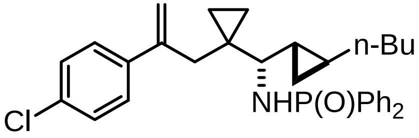
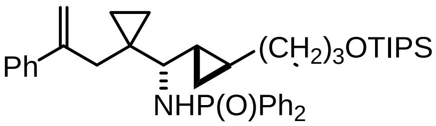


50%



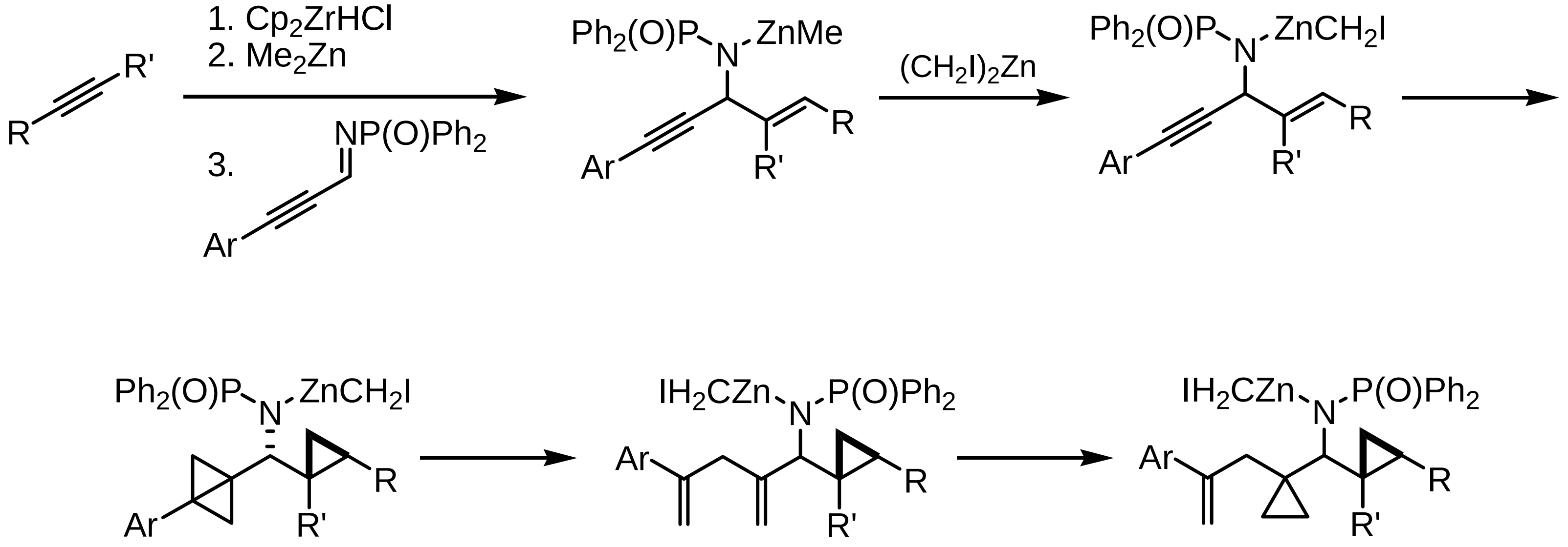
58%



66%

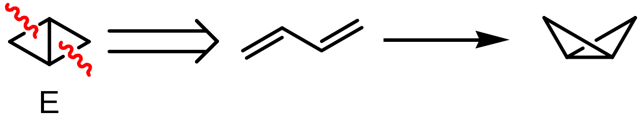
Wipf, Stephenson, Okumura *J. Am. Chem. Soc.* 2003, 125, 14694

Mechanistic Rationale

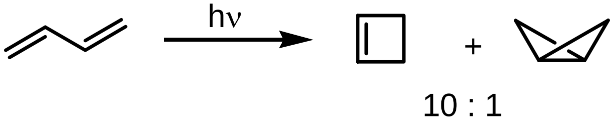


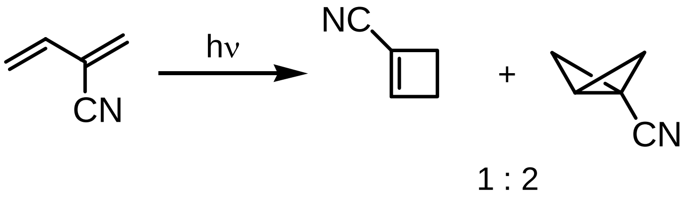
Route E

- Majority of these transformations involve photochemical activation of butadiene derivatives



- Ratio of cyclobutene and bicyclobutane depends on substitution of butadiene



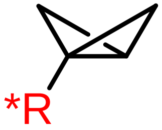


- Theoretical calculations show that optimal overlap is achieved when two unsaturated bonds are perpendicular

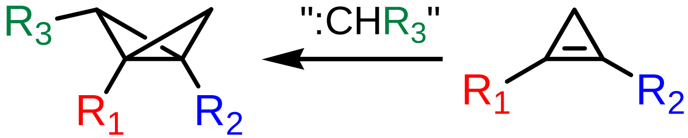
- Good yield is obtained from cyclic 1,3-diene that adopt *s-trans* conformation

Enantiomerically Pure Bicyclobutanes

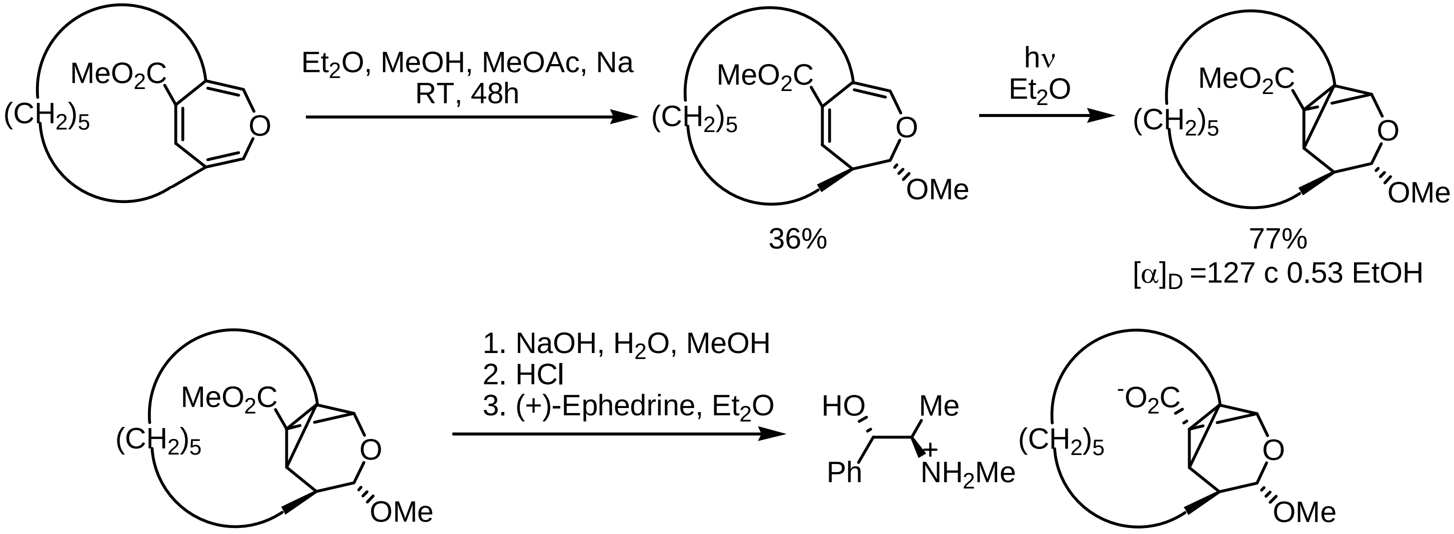
- Attachment of chiral unit



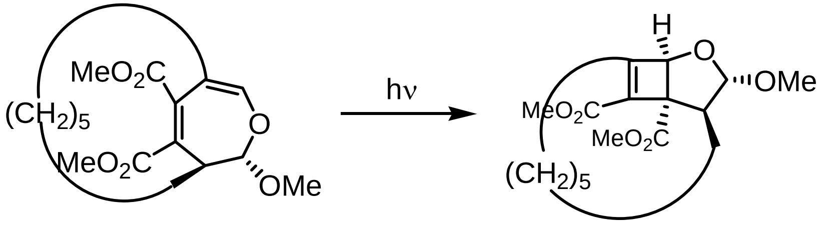
- Diastereoselective/enantioselective synthesis from prochiral substrates



Approach A – Internal Chirality



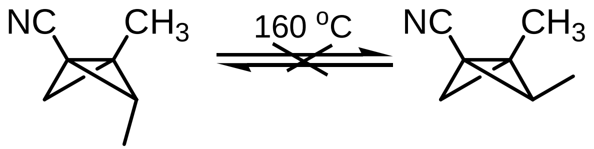
But, compare:



Tochtermann *et al. Liebigs Ann.* 1997, 1125

Inversion of Bicyclobutane

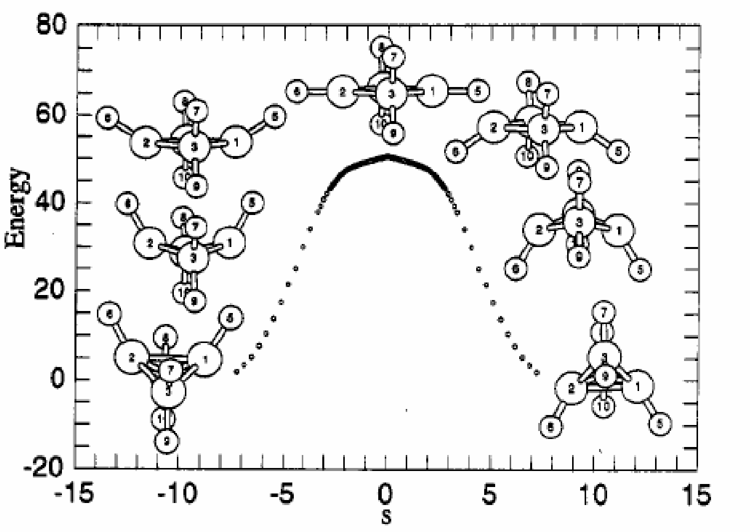
- Bicyclobutane ring usually doesn't undergo inversion

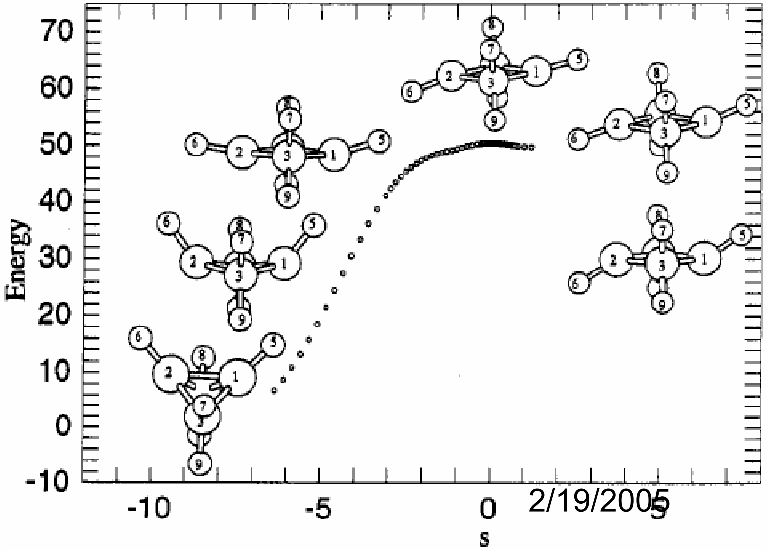


Cairncross, Blanchard
J. Am. Chem. Soc. 1966, 88, 496

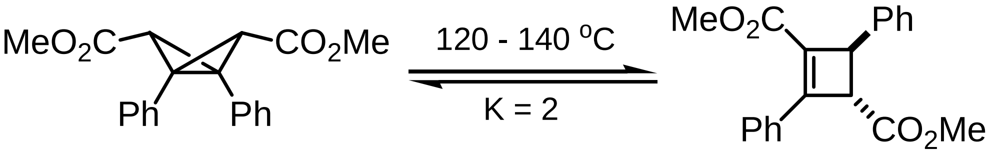
- Calculated barrier for interconversion of two isomeric bicyclobutanes is about 50 kcal mol^{-1}

Gordon *et al.*
J. Am. Chem. Soc. 1994,116, 9241
Politzer et al.
J. Am. Chem. Soc. 1987, 106, 4211



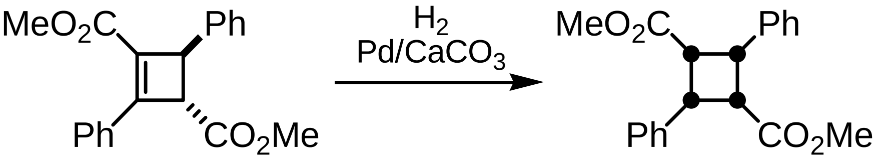


Thermal Isomerization – Revised Structure



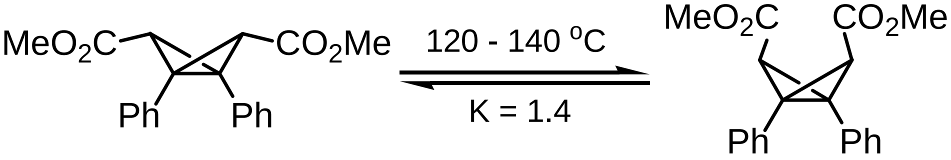
^{1}H (40MHz, $CHCl_3$) δ 8.1, 4.26, 3.67
ratio 1:3

A. D'yakonov *et al. Tetrahedron Lett.* **1966**, 1135



(?)

dimethyl η-truxillate



R. B. Woodward et al. *J. Am. Chem. Soc.* **1969**, 91, 4612

Reactions of Bicyclobutane

- Acid-Promoted Reactions

- Reactions of Bicyclobutane with Nucleophiles

- Reactions with Unsaturated Systems

- Thermal Reactions

- Bicyclobutane and Carbenes

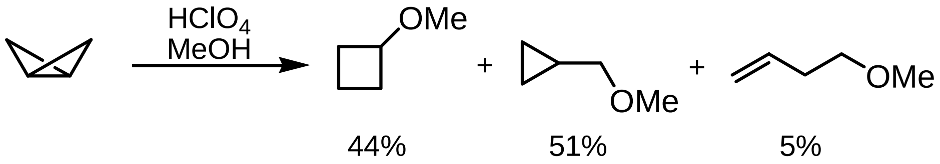
- Metal-Catalyzed Reactions

- Radical Reactions (Polymerization)
- Photochemical Reactions

Reactions with Electrophiles

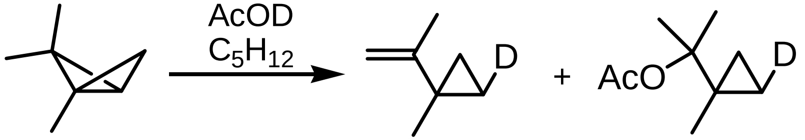
- At low pH (<4) bicyclobutane undergoes ring opening

Dauben *et al.*
J. Org. Chem. 1969, 34, 261



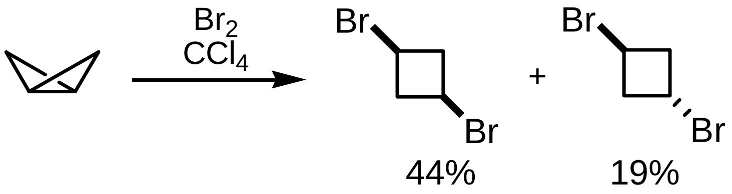
- Acid-catalyzed additions are stereospecific

Moore *et al.*
Tetrahedron Lett. 1970, 2365



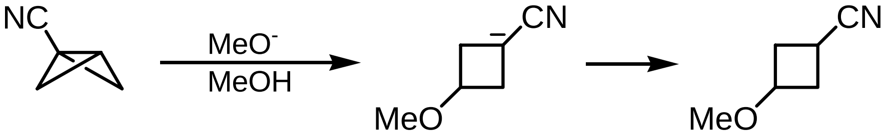
- Reactions with halogenes usually give mixture of *cis* and *trans* isomers

Wiberg
Tetrahedron 1965, 21, 2749

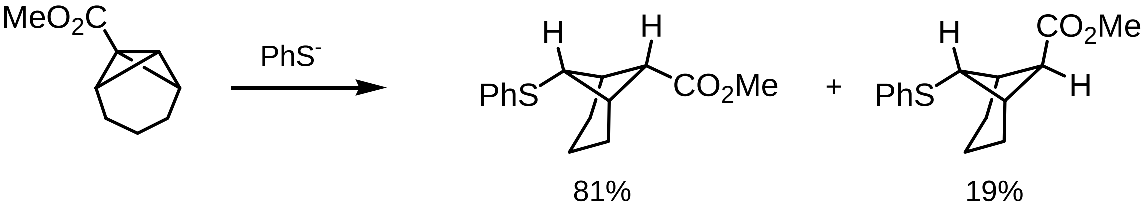


Mechanistic Aspects

- Bicyclobutanes substituted with electron-withdrawing groups undergo addition of nucleophiles
- Nucleophilic addition is believed to be a two-step process

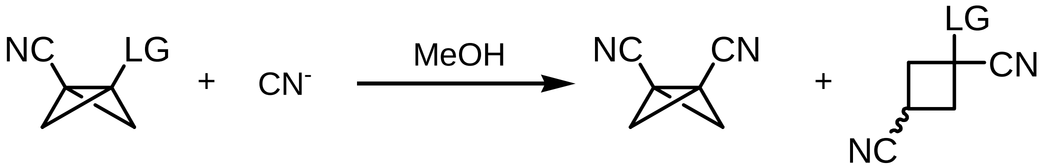


- Nucleophile approaches bicyclic ring from the *endo* side
- Stabilized carboanion can be protonated from both sides but cis protonation prevails



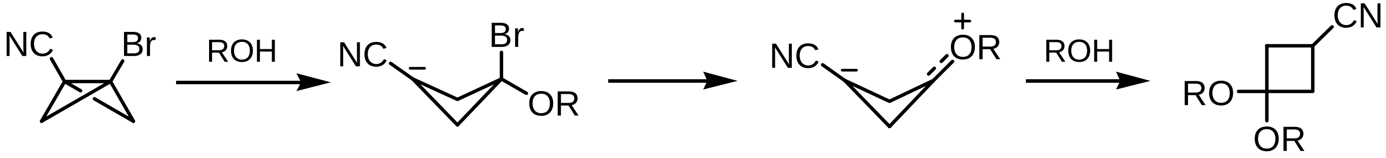
Addition-Elimination Across C_1-C_3 Bond

- In the presence of good leaving group, bicyclobutane can undergo addition–elimination reaction



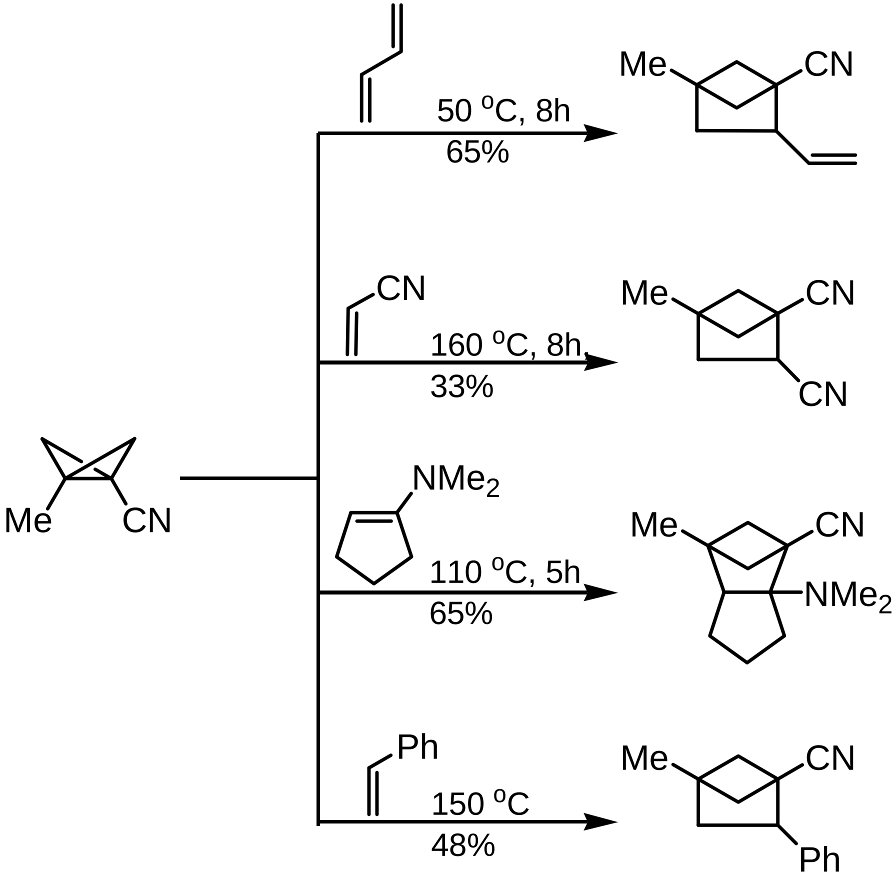
LG = Cl	17%	41%
LG = Br	60%	0%

- "Ionic bicyclobutanes" are the compounds that possess central covalent C_1–C_3 bond replaced by the ionic one



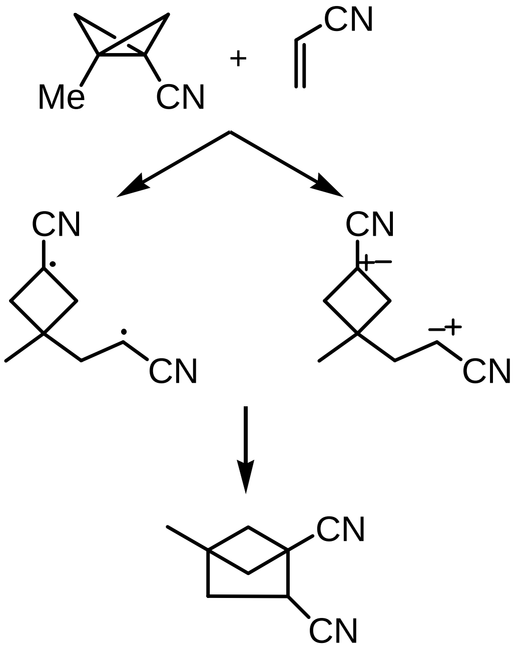
Reactions with Unsaturated Bonds

- C_1–C_3 bond may react with alkynes to afford tricyclo[1.1.2]hexanes



Mechanistic Speculations

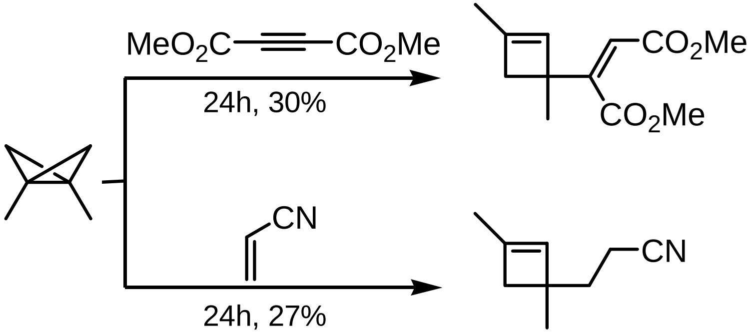
- Mechanism of these reactions may be ionic or radical
- Reactions with maleonitrile and fumaronitrile lead to mixture of *cis*/*trans* isomers
- Ethylene reacts with 1-cyano-3-methyl bicyclo[1.1.0]butane giving mixture of cycloadduct and “ene” product



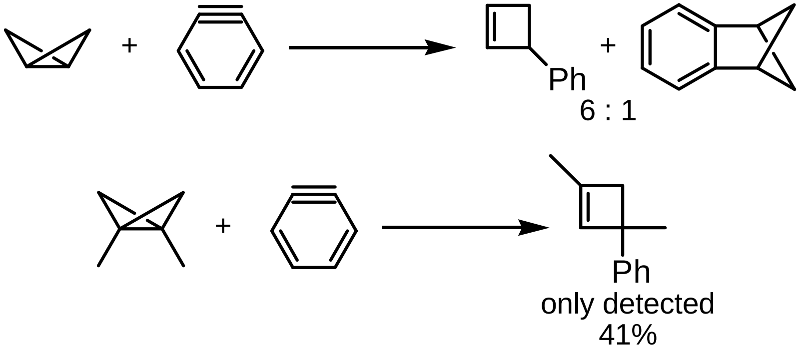
Cairncross, Blanchard *J. Am. Chem. Soc.* 1966, **88**, 496

“Ene”-type Reactions

- Electron-deficient alkynes, alkenes and ketones add to bicyclobutane in an “ene” fashion

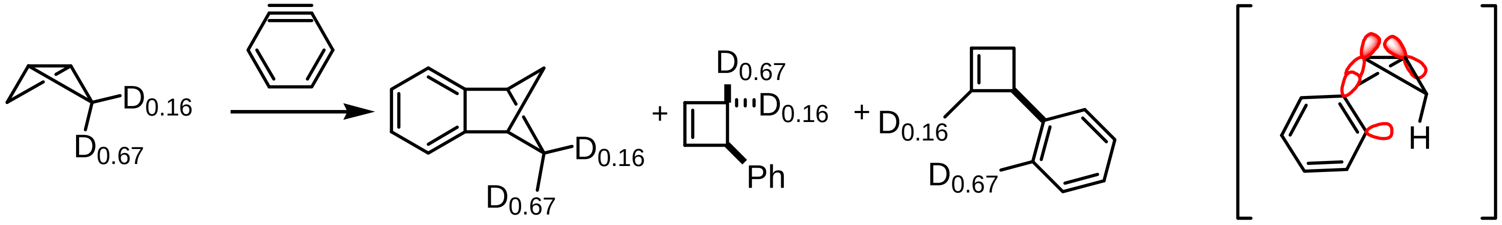


- Ratio of “ene’ vs. cycloaddition product is rationalized based on steric argument



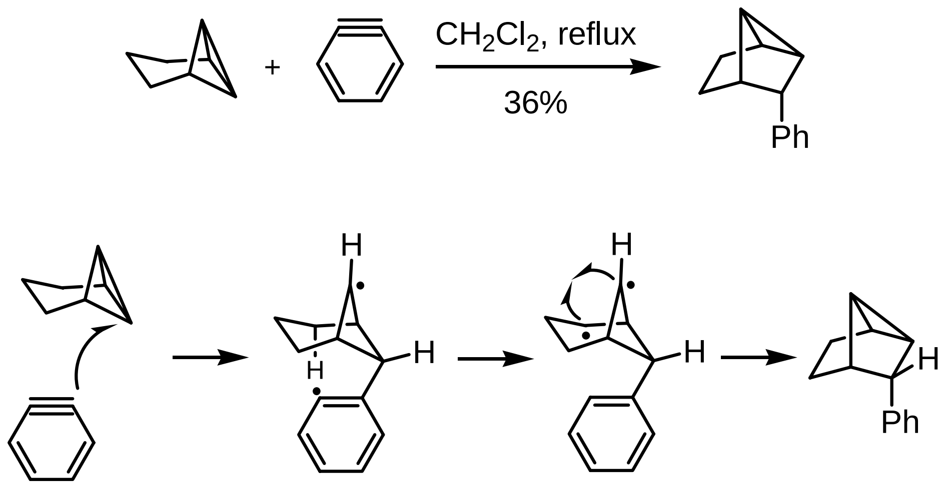
Pomerantz *et al. J. Am. Chem. Soc.* 1972, 94, 2752

- Alkene/alkyne approaches bicyclobutane from the rear side



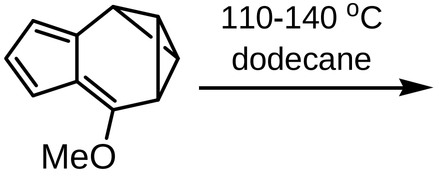
Pomerantz *et al. J. Am. Chem. Soc.* 1968, 90, 5040

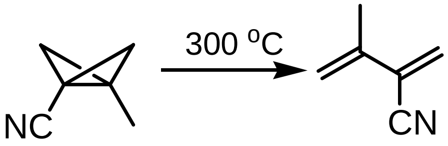
- In some cases radical mechanism is very likely



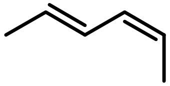
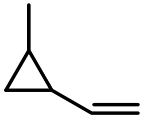
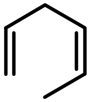
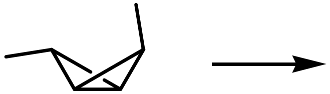
Gassman, Richmond *J. Am. Chem. Soc.* 1970, 92, 2090

Thermal Reactions





- Stereoselective opening of bicyclobutane has been rationalized in terms of $\sigma 2s+\sigma 2a$ conrotatory process

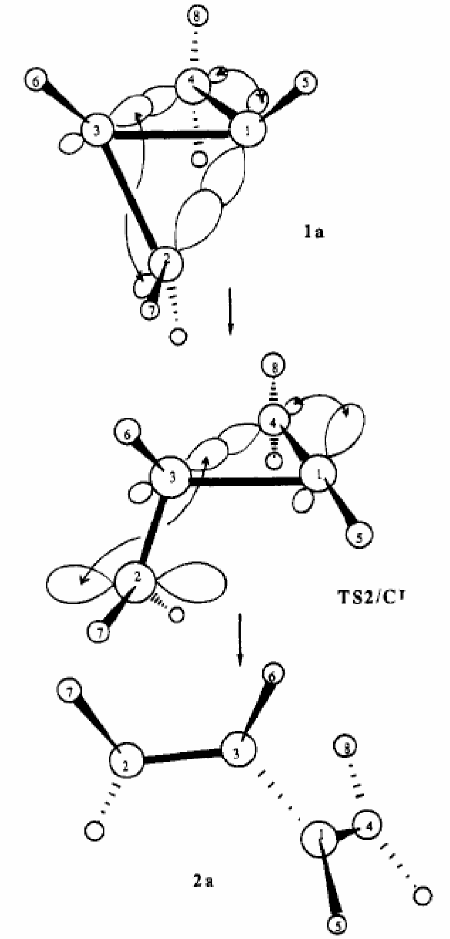
				
	3.9	93.2	2.9	-
	95	1.2	2.2	1.6

Closs, Pfeffer *J. Am. Chem. Soc.* 1968, 90, 2452

Theoretical Rationale

- Experimental activation energy (E_A) for opening is 40.6 kcal mol^{-1}
- E_A for concerted (symmetric) TS was calculated to 90 kcal mol^{-1} (However, for disrotatory TS, E_A = 97 kcal mol^{-1})
- Most likely mechanism is two-step process involving cyclopropylcarbinyl biradical; calculated E_A = 43.6 kcal mol^{-1}

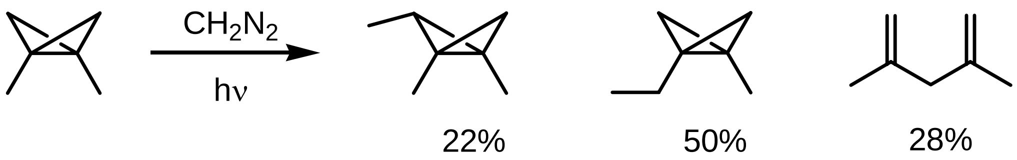
- High stereospecificity is achieved by slow conversion of "biradicaloids" compared to subsequent reactions



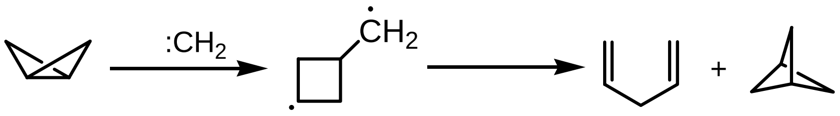
Dewar *J. Am. Chem. Soc.* 1975, 97, 2931
Shevlin *J. Am. Chem. Soc.* 1988, 110, 1666
Davis *J. Phys Chem. A* 2003, 107, 198

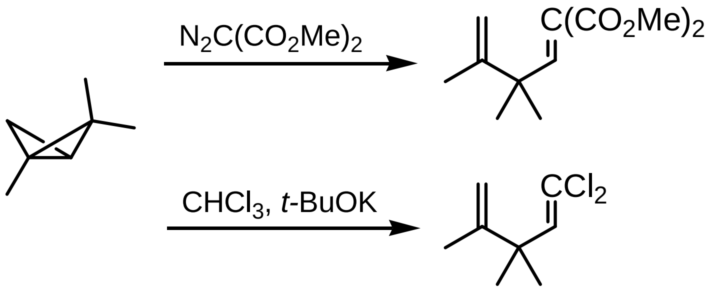
Bicyclobutane and Carbenes

- Bicyclobutane ring can react with carbenes to produce non-conjugated dienes but typical C-H insertion reaction can also occur



- Initially proposed mechanism of this transformation involved biradical intermediate but later investigations revealed that :CR_2 unit undergoes simultaneous insertion





Von E. Doering, Cobrun *Tetrahedron Lett.* 1965, 991

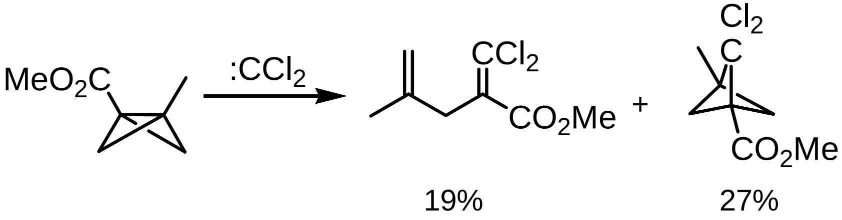
Jones *et al. Tetrahedron* 1985, 41, 1453

Jones, Mock *Tetrahedron Lett.* 1981, 3819

Bicyclobutane and Carbenes

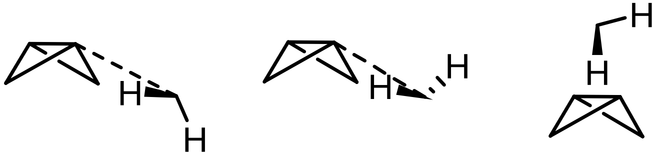
- Methylene may react with bicyclobutane to afford bicyclopentane

- However, high energy of isomerization (49.6 kcal mol^{-1}) argues against it's intermediacy in opening of bicyclobutane



Applequist, Wheeler *Tetrahedron Lett.* 1977, 3411

- Three transition states were located for singlet carbene attack on bicyclobutane



Transition Metal Promoted Rearrangements

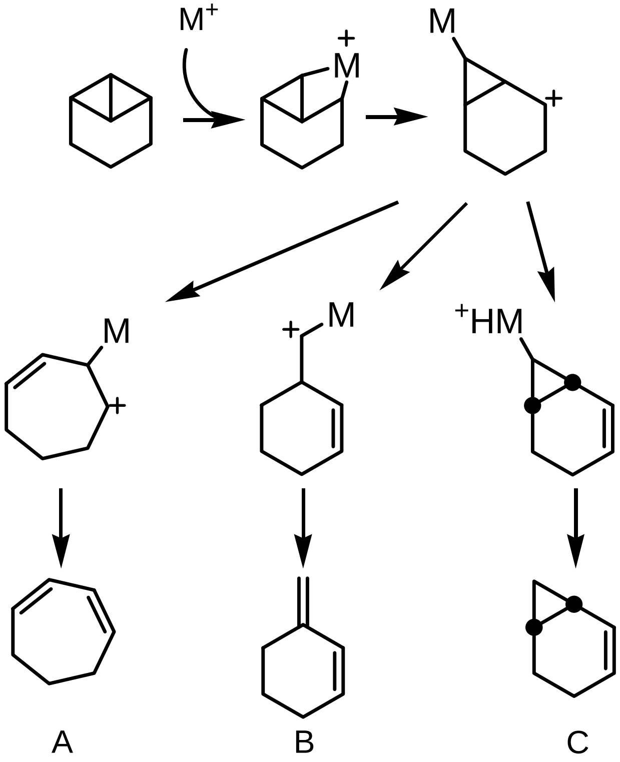
- “No class of transition metal catalyzed rearrangements has been the subject of more controversy than those of bicyclobutane.”

Bishop *Chem. Rev*. 1976, 76, 461

- Transition metals promote opening of bicyclobutane but not all reactions lead to the cleavage of the central bond
- Simple hydrocarbons and late TMs were studied (Rh, Ni, Pd, Ag)
- TM catalyzed reactions very often do not follow Woodward-Hoffmann rules

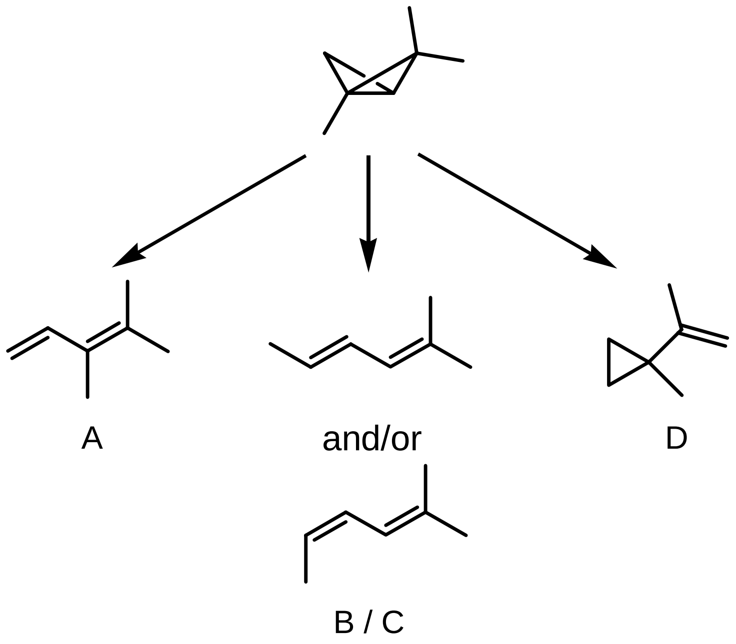
Model System 1

Catalyst	Mol %	% A	% B	% C
$AgBF_4$	0.45	100		
ZnI_2	6.5	88	11	
$HgBr_2$	9.0	85	8	
$[Rh(CO)_2Cl]_2$	4.0		98	
$[Ir(CO)_3Cl]_2$	5		91	
$[(CH_2CH_2)_2PdCl]_2$	1.2		94	
$(PhCN)_2PdCl_2$	5		69	
$[C_6F_5Cu]_4$	2		74	
$Ph_2Rh(CO)Cl$	5		92	5
$[Ru(CO)_3Cl_2]_2$	5		44	12



Model System 2

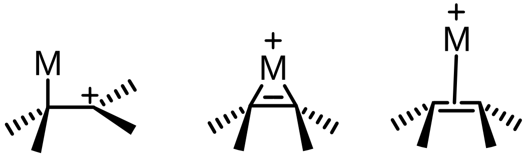
Catalyst	Mol %	% A	% B & C
$Rh(CO)[Ph_3P]_3I$	3.0	100	–
$PdCl_2(PhCN)_2$	0.2	20	80
$PdCl_2(Ph_3P)_2$	3.0	60	40
$PdCl_2(Ph_3P)_2$	0.3	100	–
$PdCl_2(Ph_3As)_2$	0.3	30	70
$PdCl_2(Ph_3As)_2$	1.5	60	40
$PdCl_2(Ph_3As)_2$	3.0	100	–
$PdCl_2(Py)_2$	0.3	15	85
$PdCl_2(Py)_2$	3.0	55	45
$PdCl_2(Py)_2$	6.0	55	45
$AgBF_4$	3.0	–	100



Bishop *Chem. Rev.* 1976, 76, 461

- Mode of the rearrangement depends on the metal used: Ag(I) and Rh(I) are at the opposite ends of the spectrum

- General mechanism would involve intermediacy of metallocarbonium ion or carbene complex

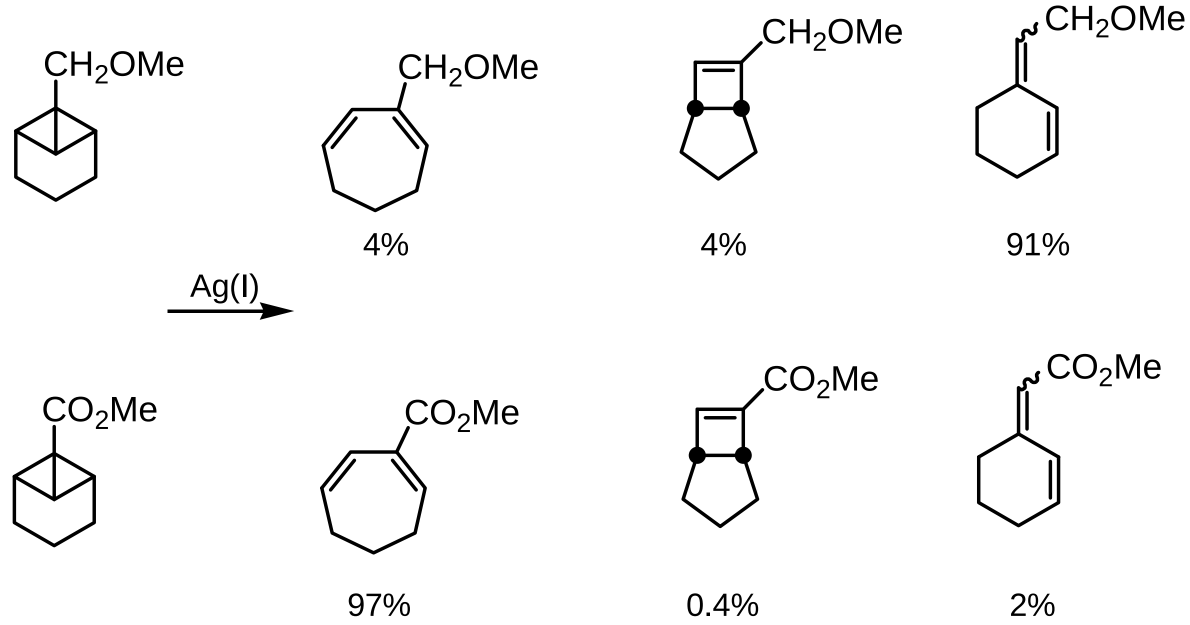


C=M(II) $\overset{+}{\mathrm{C}}\text{-}\overset{-}{\mathrm{M}}\mathrm{(I)}$ $\overset{-}{\mathrm{C}}\text{-}\overset{+}{\mathrm{M}}\mathrm{(III)}$

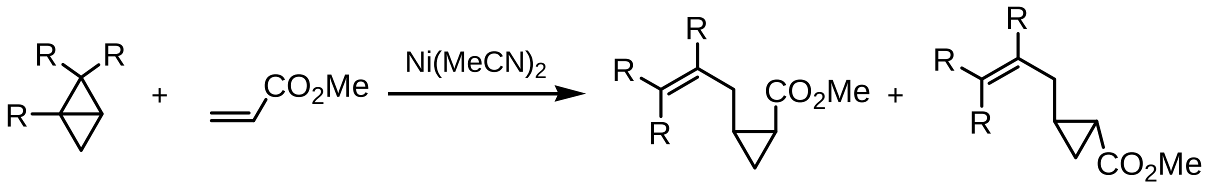
- Selectivity of the catalyst depends on relative stabilities of these two forms

- Reactivity patterns can be explained in terms of electron affinities and promotion energies of the metal

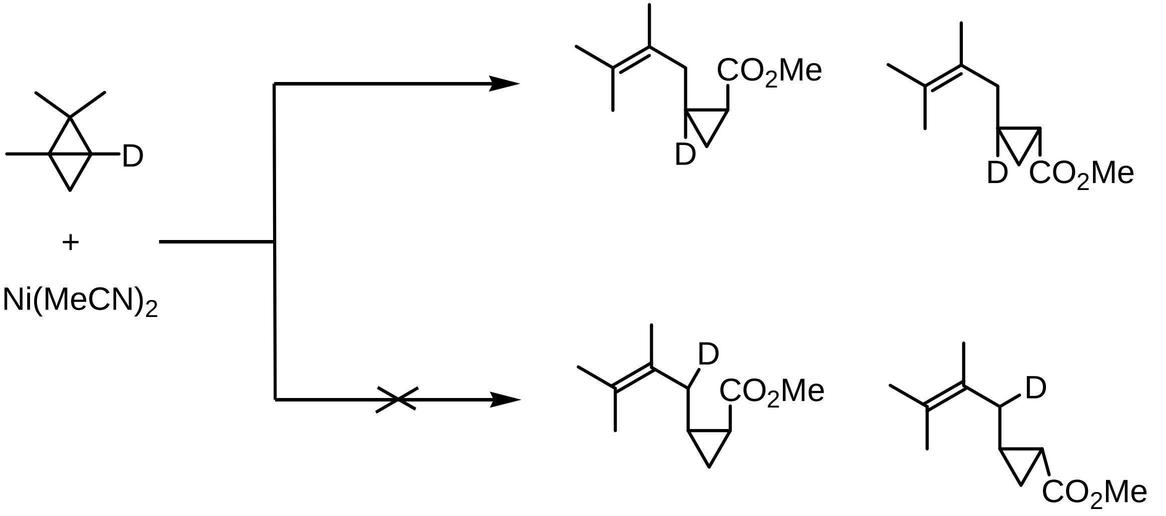
Ag(I)-Promoted Rearrangements



Ni(0)-Catalyzed Reactions of Bicyclo[1.1.0]butanes



R = H	ratio 65:35	yield quant.
R = Me	ratio 65:35	yield 70%

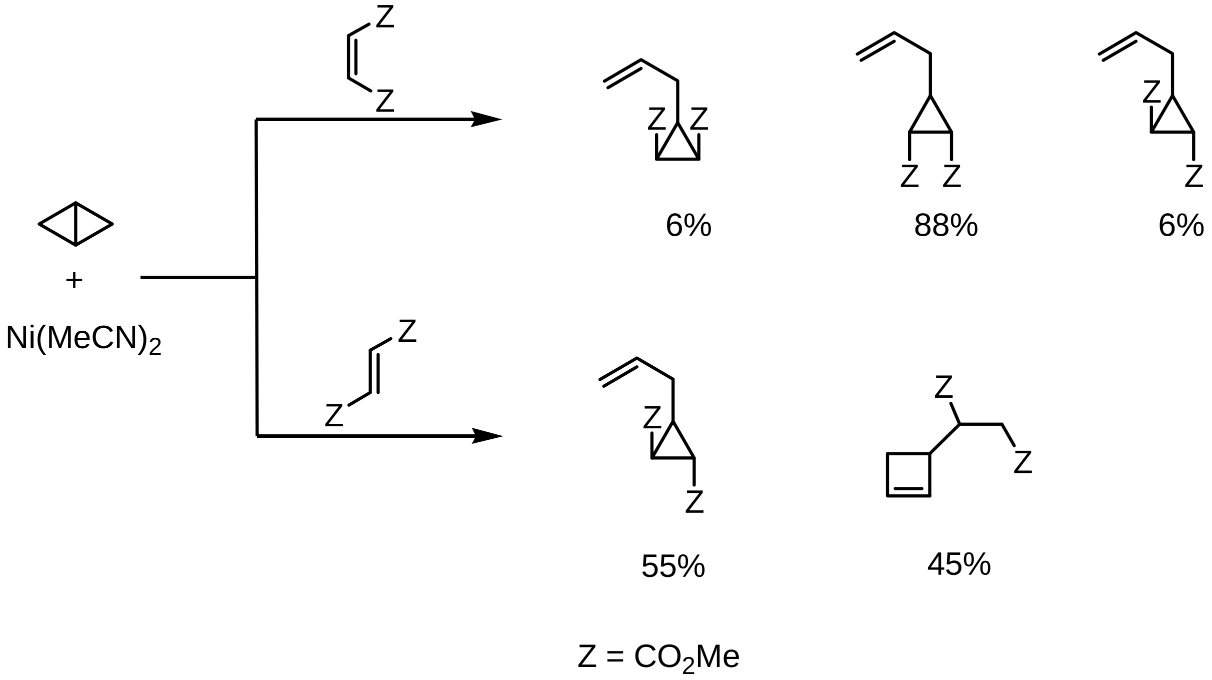


not observed, no H-shift

Noyori *et al. J. Am. Chem. Soc.* 1971, 93, 5894

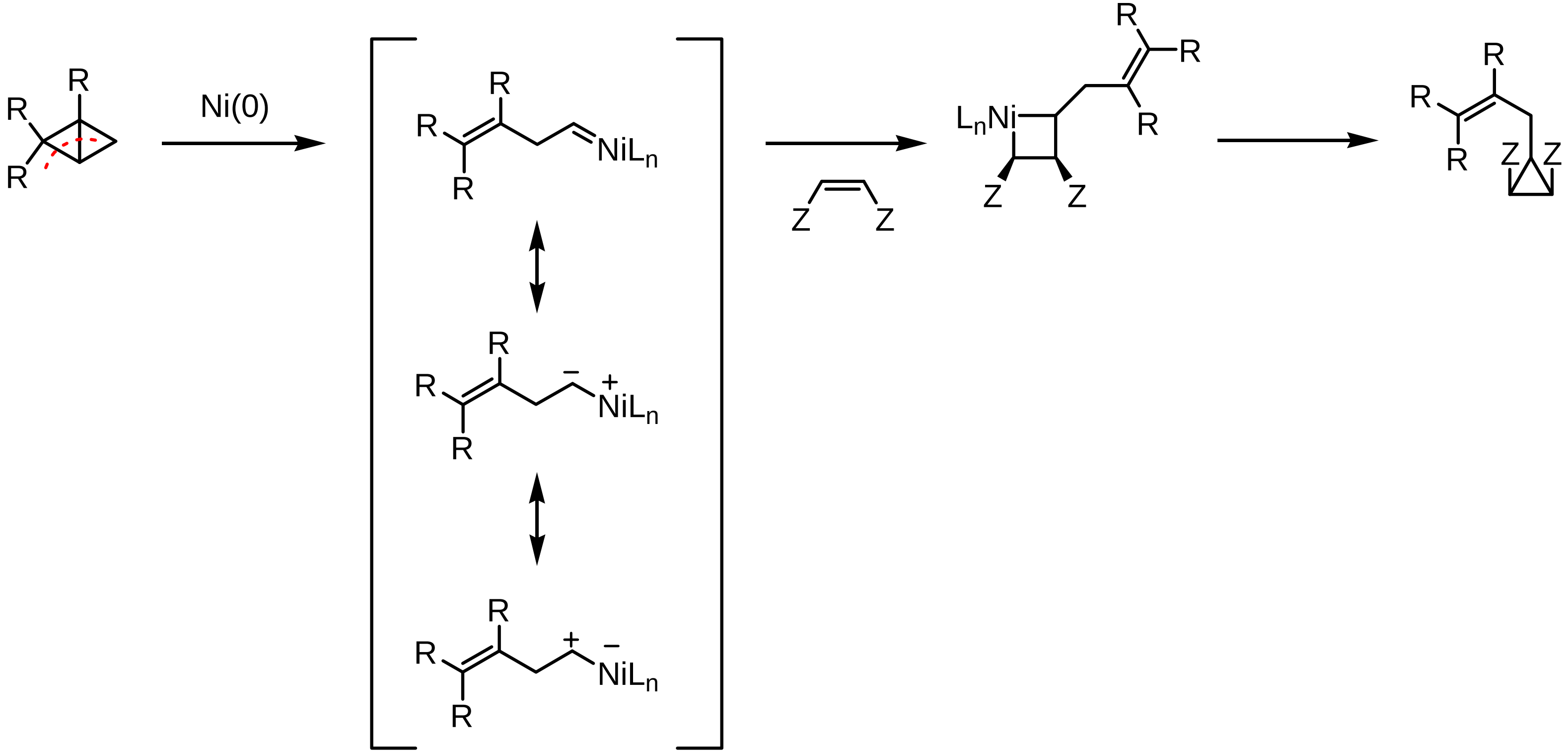
Stereospecificity on reactions of

- Reactions with methyl fumarate and maleate showed that Z-olefin react stereospecifically



Noyori *et al. J. Org. Chem.* 1981, 46, 2854

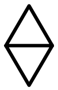
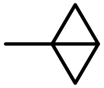
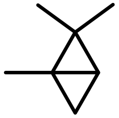
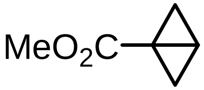
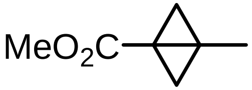
Mechanism of Ni(0)-Catalyzed Reactions of Bicyclobutanes



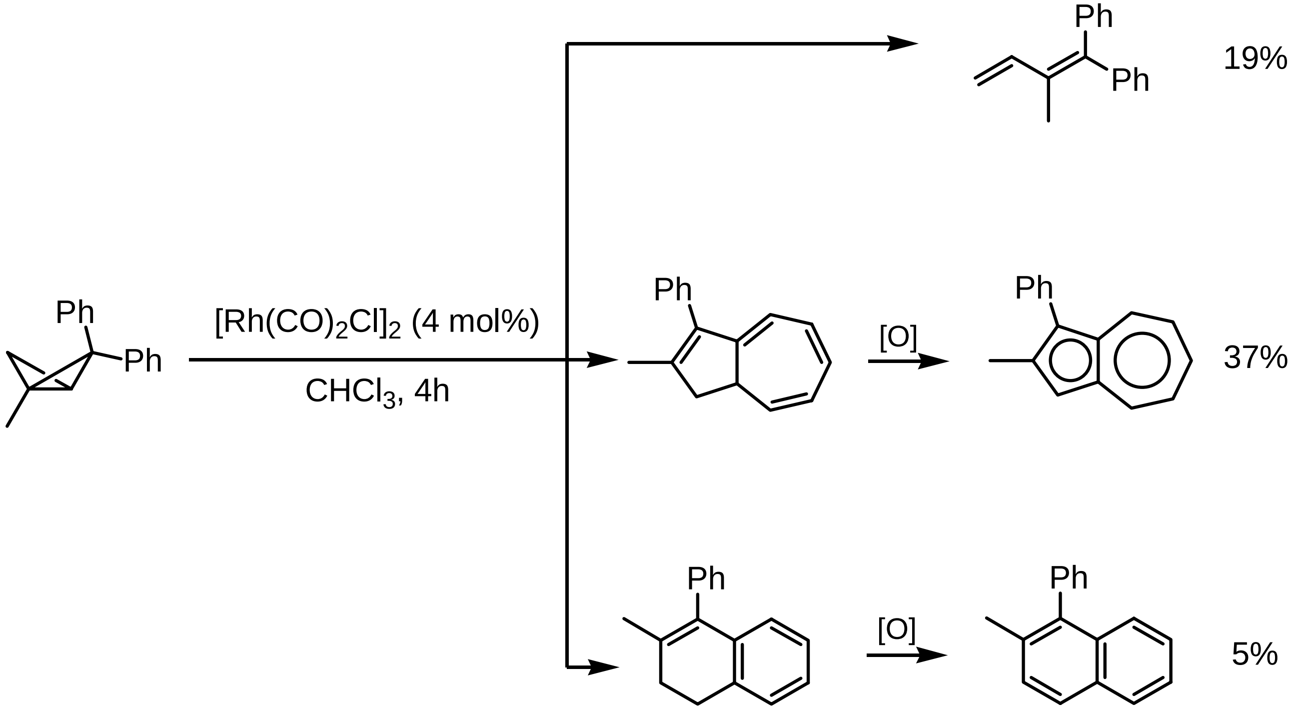
Noyori *Tetrahedron Lett.* 1973, 1691

Noyori *et al. Tetrahedron Lett.* 1974, 1749

Kinetic Data of $Ni(COD)_2$-Catalyzed Reactions of Bicyclobutanes with Methyl Acrylate

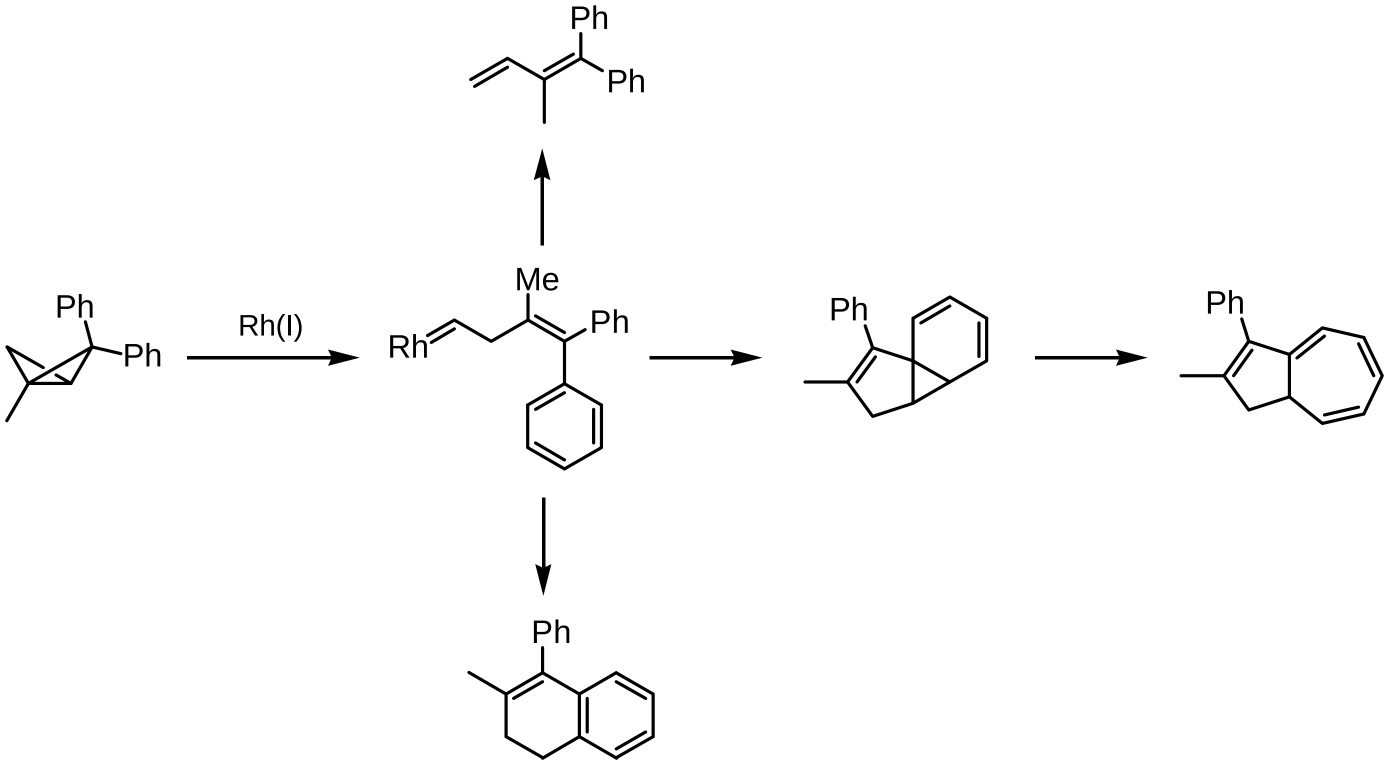
Bicyclobutane	*k*, $M^{-1} \cdot s^{-1}$	Relative Rate	Color of solution
	3.39×10^{-2}	1.0	yellow
	8.22×10^{-2}	2.4	yellow
	6.53×10^{-1}	19	yellow
	1.50×10^{-3}	0.04	dark orange
	1.12×10^{-3}	0.03	dark orange

Rh(I)-Catalyzed Insertion of Carbene into Benzene Ring



Gassman, Nakai *J. Am. Chem. Soc.* 1971, 93, 5897

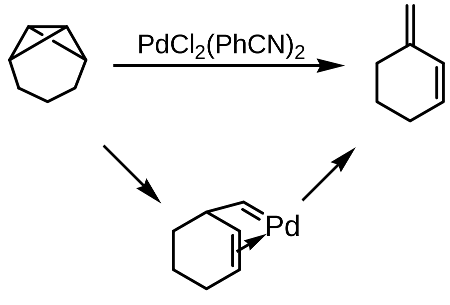
Mechnistic Rationale



Gassman, Nakai *J. Am. Chem. Soc.* 1971, 93, 5897

More Data on Bicyclobutane Rearangements

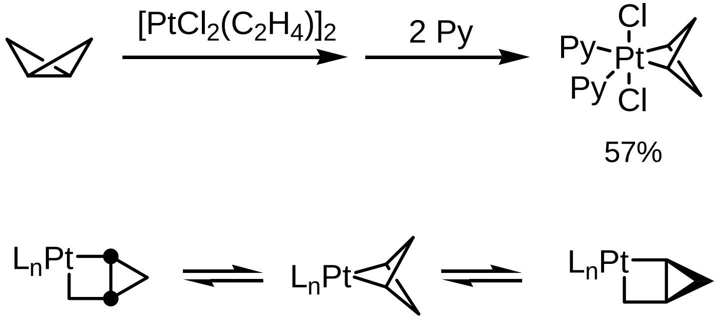
- Upon addition of $PdCl_2(PhCN)_2$ to tricyclo[4.1.0.0^{2,7}]heptane, ^1H NMR spectra showed new signals that were attributed to carbene A



observed by ^1H NMR

Dauben, Kielbania *J. Am. Chem. Soc.* 1972, 94, 3669

- Zeise’s salt react with bicyclobutane and stable Pt complex has been isolated and characterized by NMR



Takaya *et al. J. Am. Chem. Soc.* 1981, 103, 6257

Summary

- In spite of great synthetic and mechanistic efforts, chemistry of bicyclobutane still is unexplored area
- Available chemical tools allow synthesis of rather simple, achiral derivatives
- Bicyclobutane hasn't attracted much attention as a synthetic tool in construction of larger molecules
- Future developments in this field have to be directed towards reliable and well-behaved methods of synthesis