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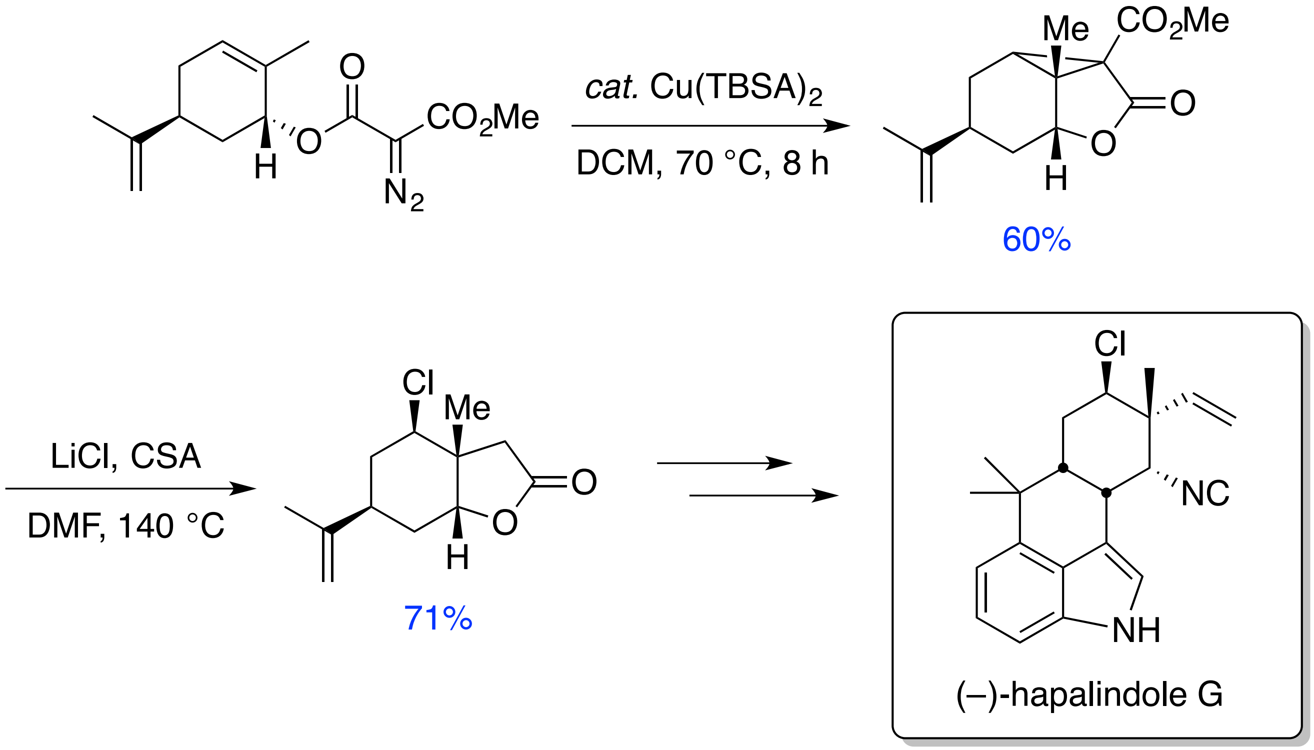
Renaud Group
Universität Bern

Topic Review
January 28th 2016

Intramolecular Cyclopropanations

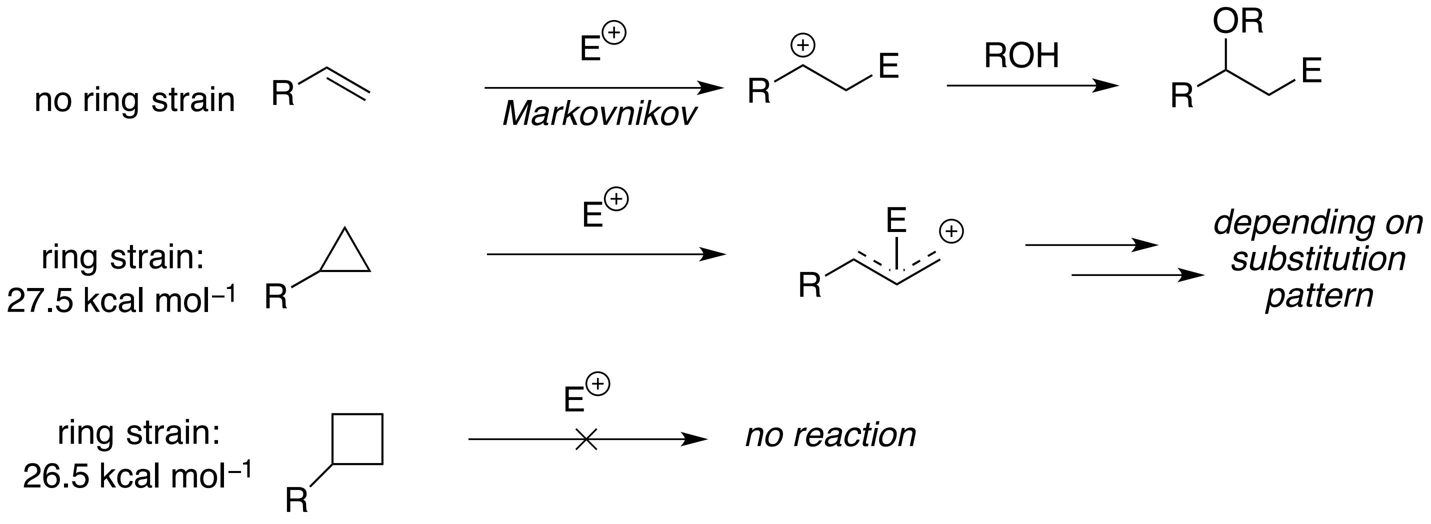


Example of utility of intramolecular cyclopropantions: Fukuyama, T.; Chen, X. *J. Am. Chem. Soc.* **1994**, *116*, 3125–3126.

A quick note on bonding

"Ring strain confers exceptional reactivity to the cyclopropane ring."
Chimia, **2009**, *63*, 162-167.
And many publications from a synthetic organic chemists concerning the synthesis and reactivity of cyclopropanes has a similar phrase!

How do you explain the following observation?

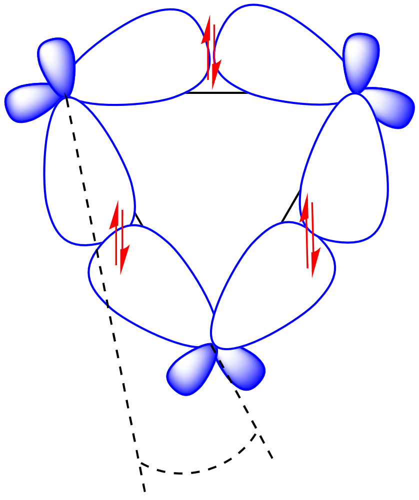


c.f. C–C bond dissociation energy is ~83-85 kcal mol^{-1}

Ring strain might provide a strong thermodynamic driving force for reaction but is doesn't explain the *reactivity*.
A suitable answer must therefore invoke bonding.

Problem: tightest angle between any AOs is 90° (e.g. orthogonal p-orbitals) but in cyclopropane we have to accomodate a bond angle of 60°

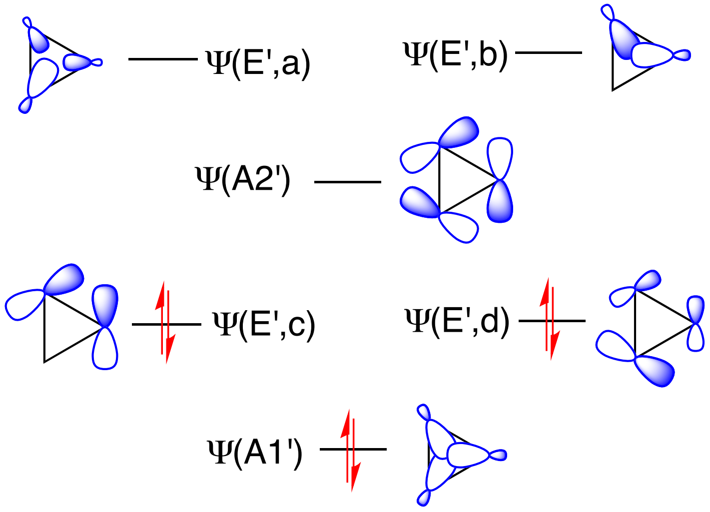
Pauling τ-bond treatment



22° and
~20% less effective overlap

Coulson-Moffit orbitals:
sp^3-hybridized C AOs orbitals

Hückel σ/π-bond treatment



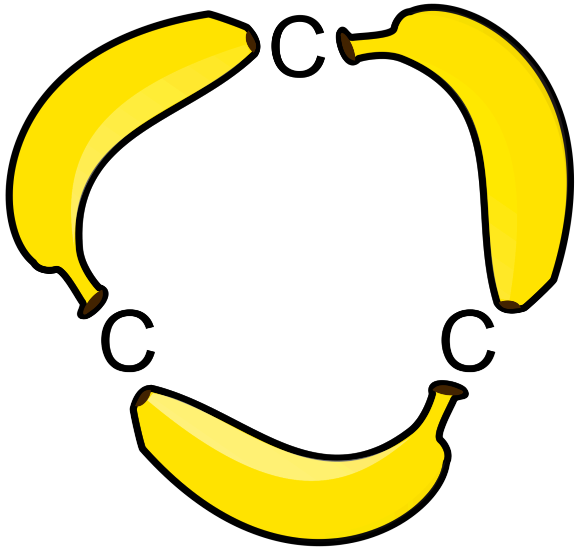
Walsh orbitals:
sp^2-hybridized C AOs

N.B.: This model is generally accepted (as is Hückel's approach to bonding) **but** it is likely wrong as it may not represent the ground state: Specifically, relative energies of Ψ(A2') with Ψ(E',a) and Ψ(E',b) are switched when valence AOs are used as the basis set instead of methylene and choosing methylene as basis set removes C–H bonds from MO picture See [Wiberg, K. B. *Acc. Chem. Res.* **1996**, *29*, 229–234] and [reference 17 therein]. Walsh orbitals work in other cases outside of cyclopropane.

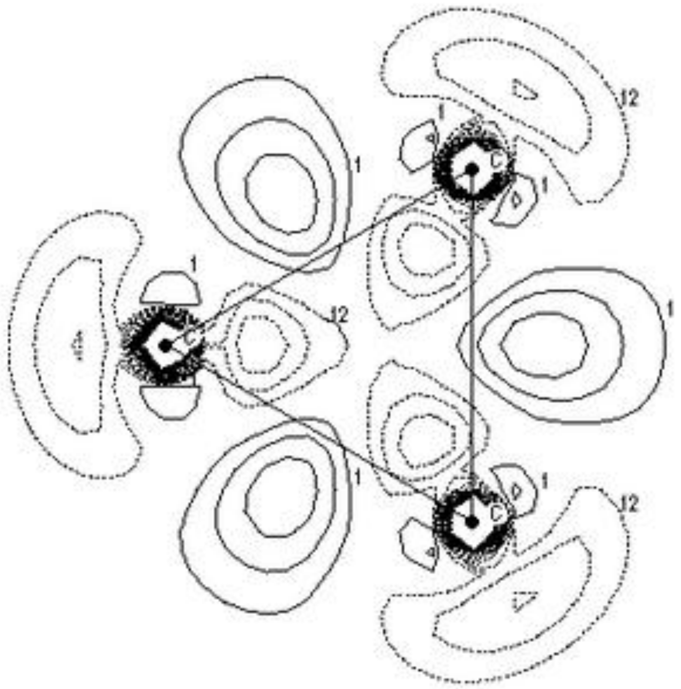
"the overall distribution of electrons [...] is exactly the same" [in the two models]. – Ian Fleming
At least theoretically and mathematically, and assuming that the basis sets are valid (interconvertible).

An excellent resource for Walsh's theory using methylene as basis set:
http://www.bluffton.edu/~bergerd/chem/walsh/derive.html, and references therein for the full story.

Banana Bond



X-ray diffraction of *cis*-1,2,3-tricyanocyclopropane: Hartman, A.; Hirshfeld, F. L. *Acta Crystallographica* **1966**, *20* (1), 80–82.



Cyclopropane Electron cloud

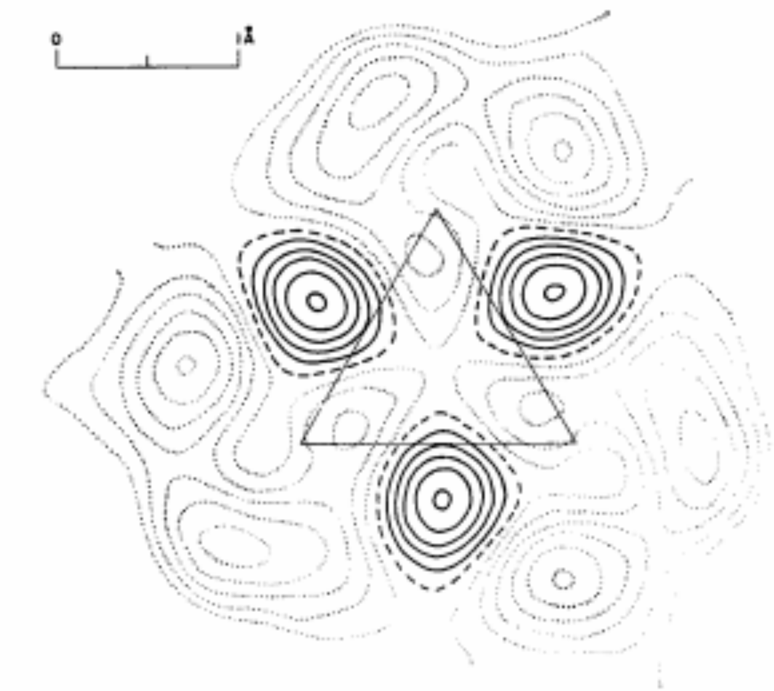
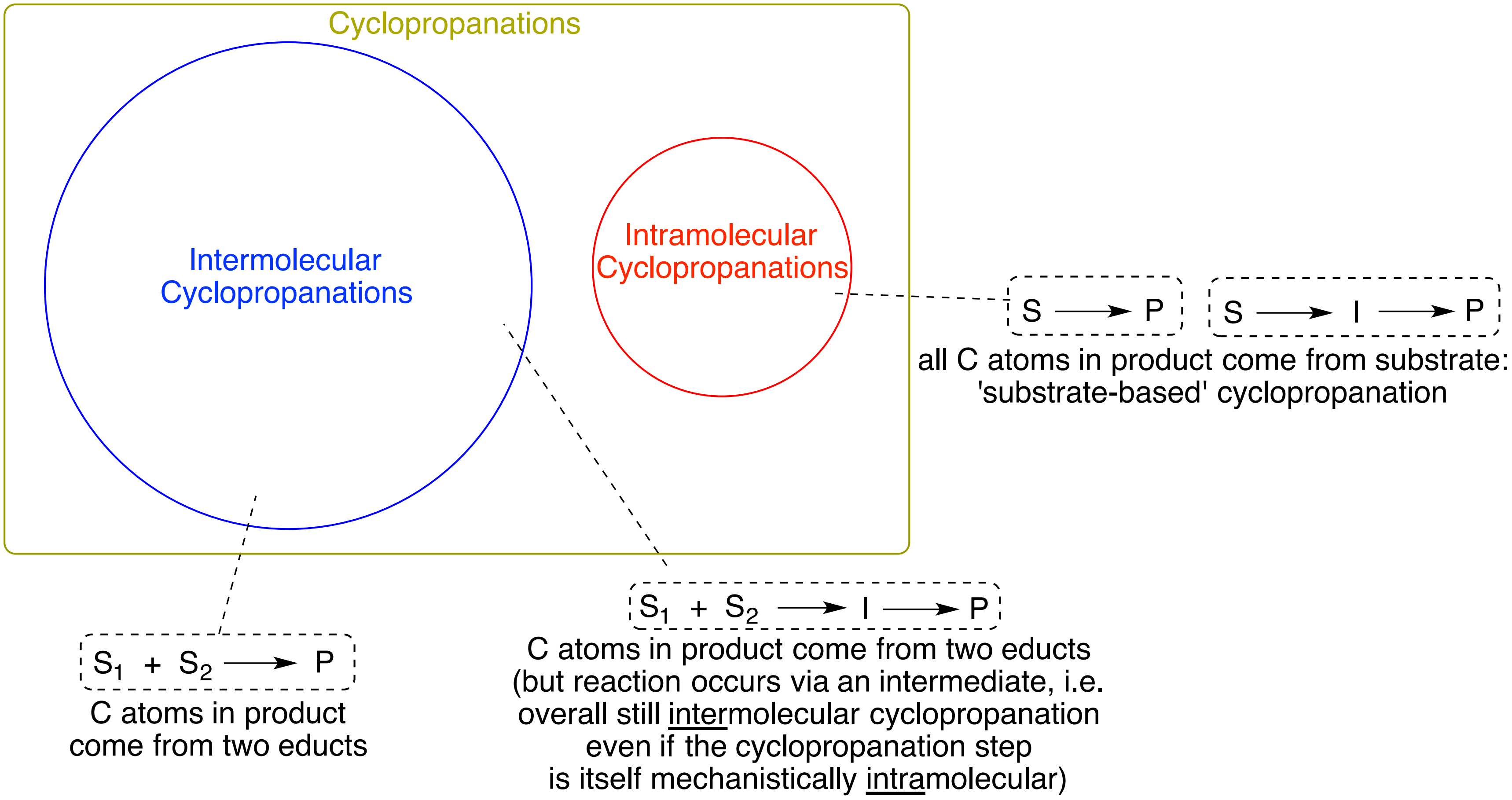


Fig. 2. Difference density in plane of cyclopropane ring. Contour interval 0·01 e.Å^{-3}, zero contour broken. Estimated standard deviation averages 0.017 e.Å^{-3}.

Classifications in a Venn diagram



Cyclopropanations

Intermolecular Cyclopropanations

Intramolecular Cyclopropanations

$S \longrightarrow P$ $S \longrightarrow I \longrightarrow P$

all C atoms in product come from substrate:
'substrate-based' cyclopropanation

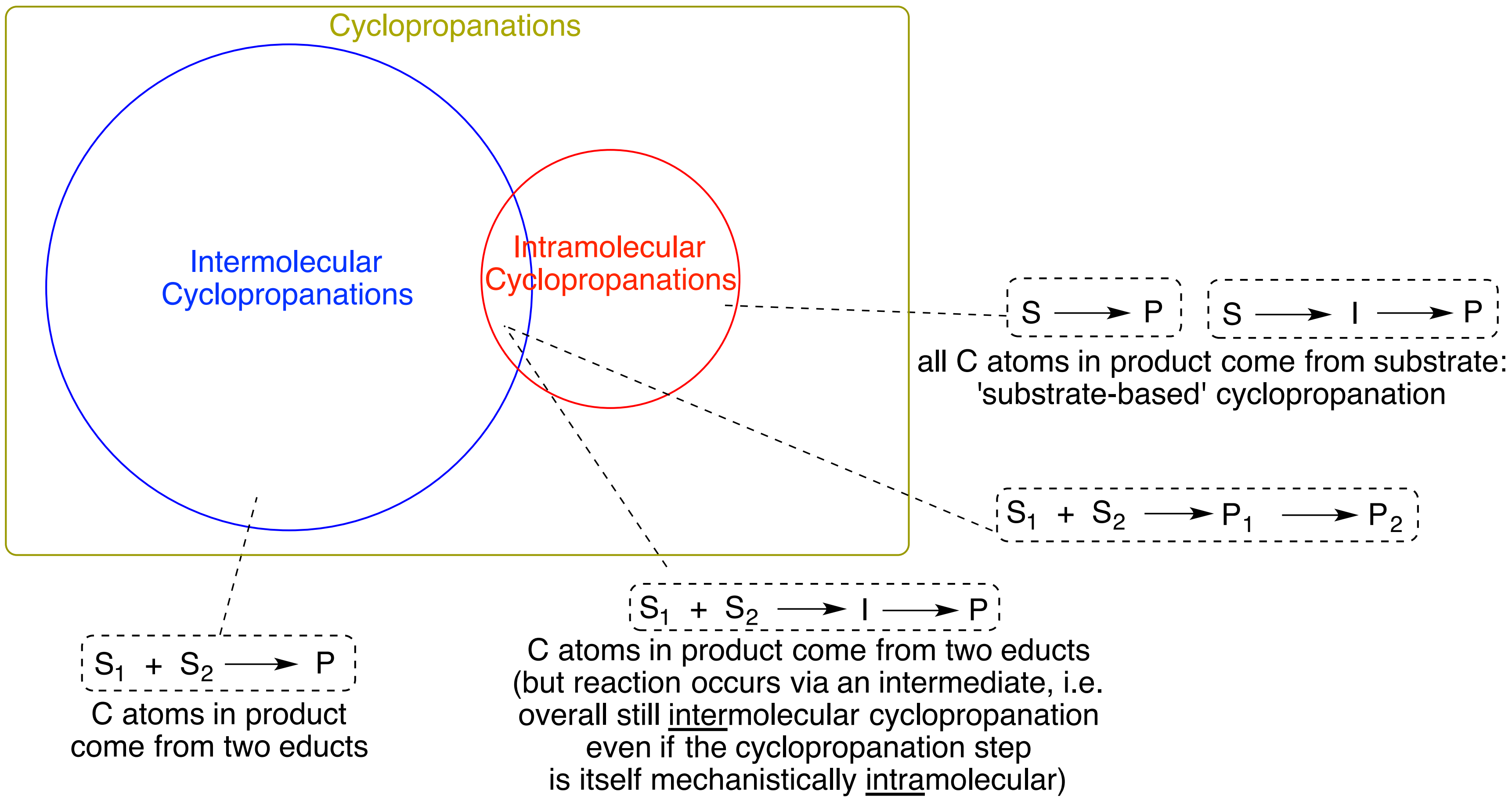
$S_1 + S_2 \longrightarrow P$

C atoms in product
come from two educts

$S_1 + S_2 \longrightarrow I \longrightarrow P$

C atoms in product come from two educts
(but reaction occurs via an intermediate, i.e.
overall still intermolecular cyclopropanation
even if the cyclopropanation step
is itself mechanistically intramolecular)

Classifications in a Venn diagram



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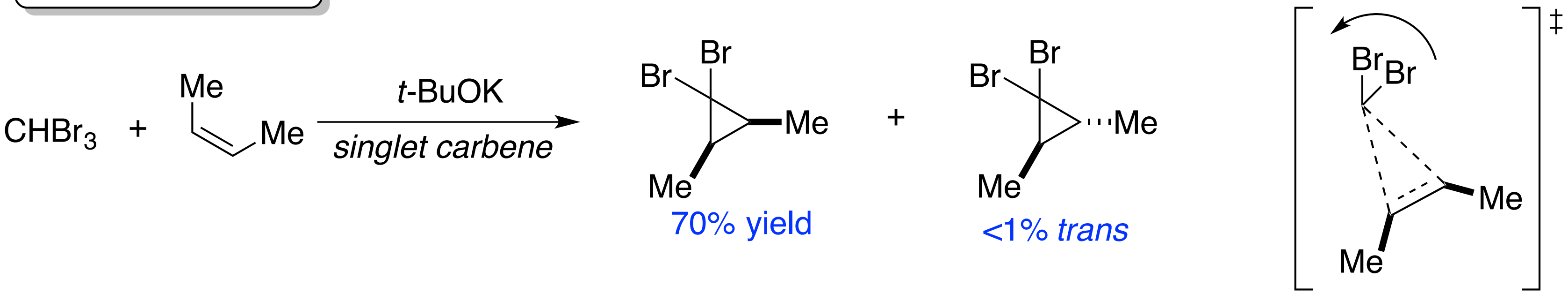
is itself mechanistically intramolecular)

Examples from free carbene chemistry

Intermolecular cyclopropanation example (no intermediate)

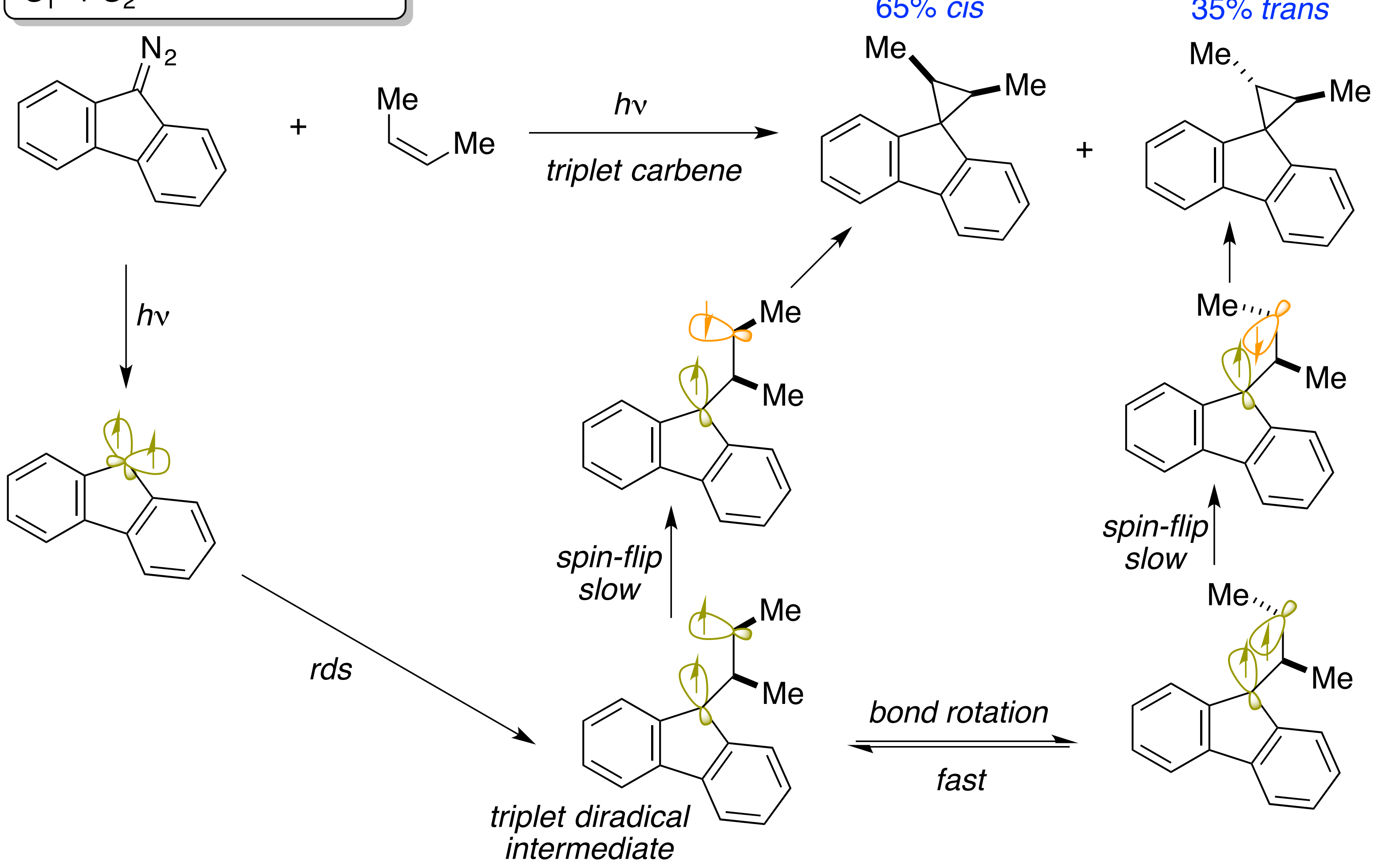
$S_1 + S_2 \longrightarrow P$



Examples from free carbene chemistry

Intermolecular cyclopropanation example (via an intermediate)

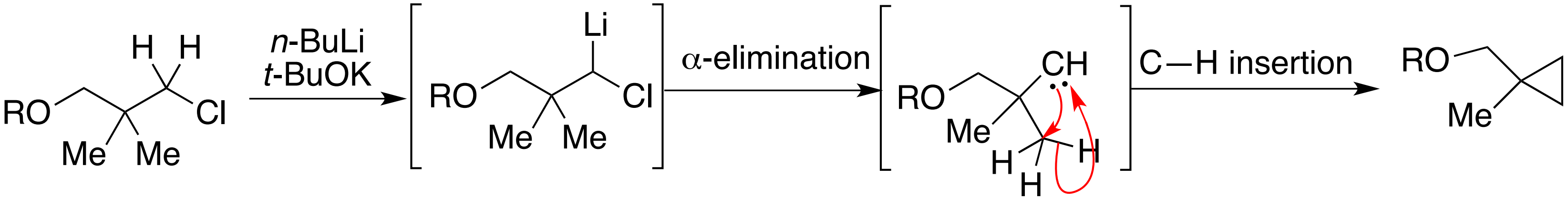
$S_1 + S_2 \longrightarrow I \longrightarrow P$



Examples from free carbene chemistry

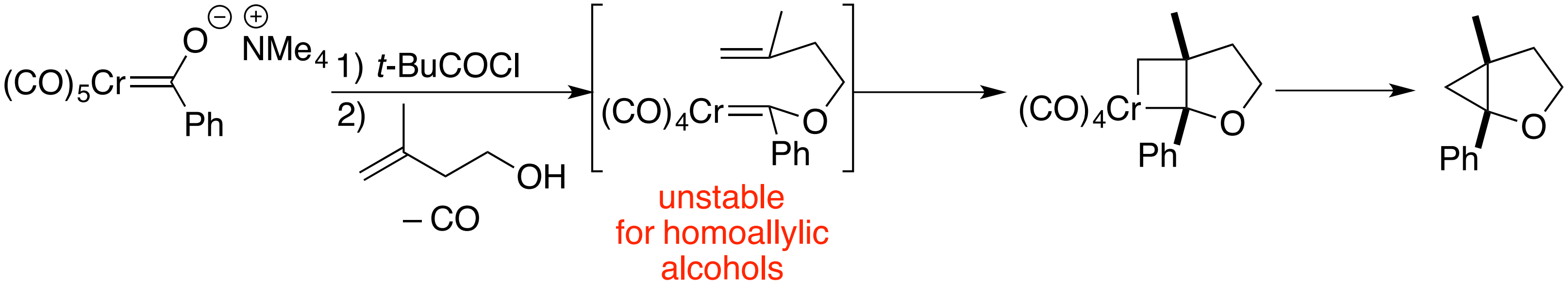
Intramolecular cyclopropanation example

S → P *or* S → I → P



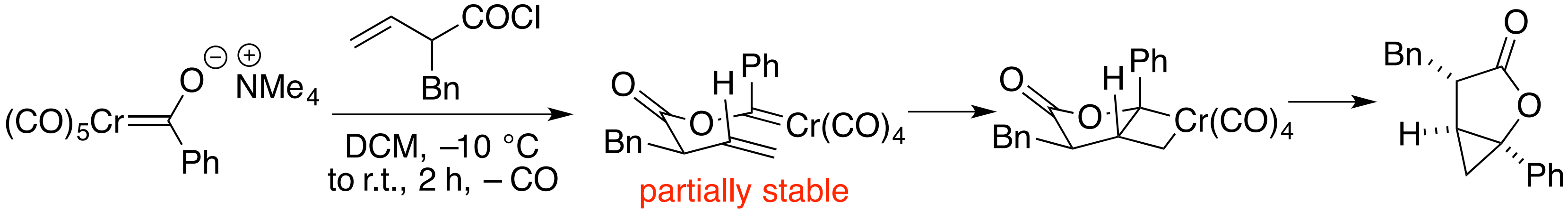
Ambiguous examples from free carbene chemistry and another, unambiguous (?), example

$S_1 + S_2 \longrightarrow I \longrightarrow P$



unstable
for homoallylic
alcohols

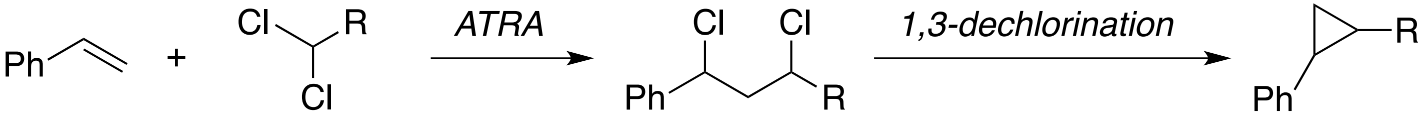
$S_1 + S_2 \longrightarrow P_1 \longrightarrow P_2$



partially stable

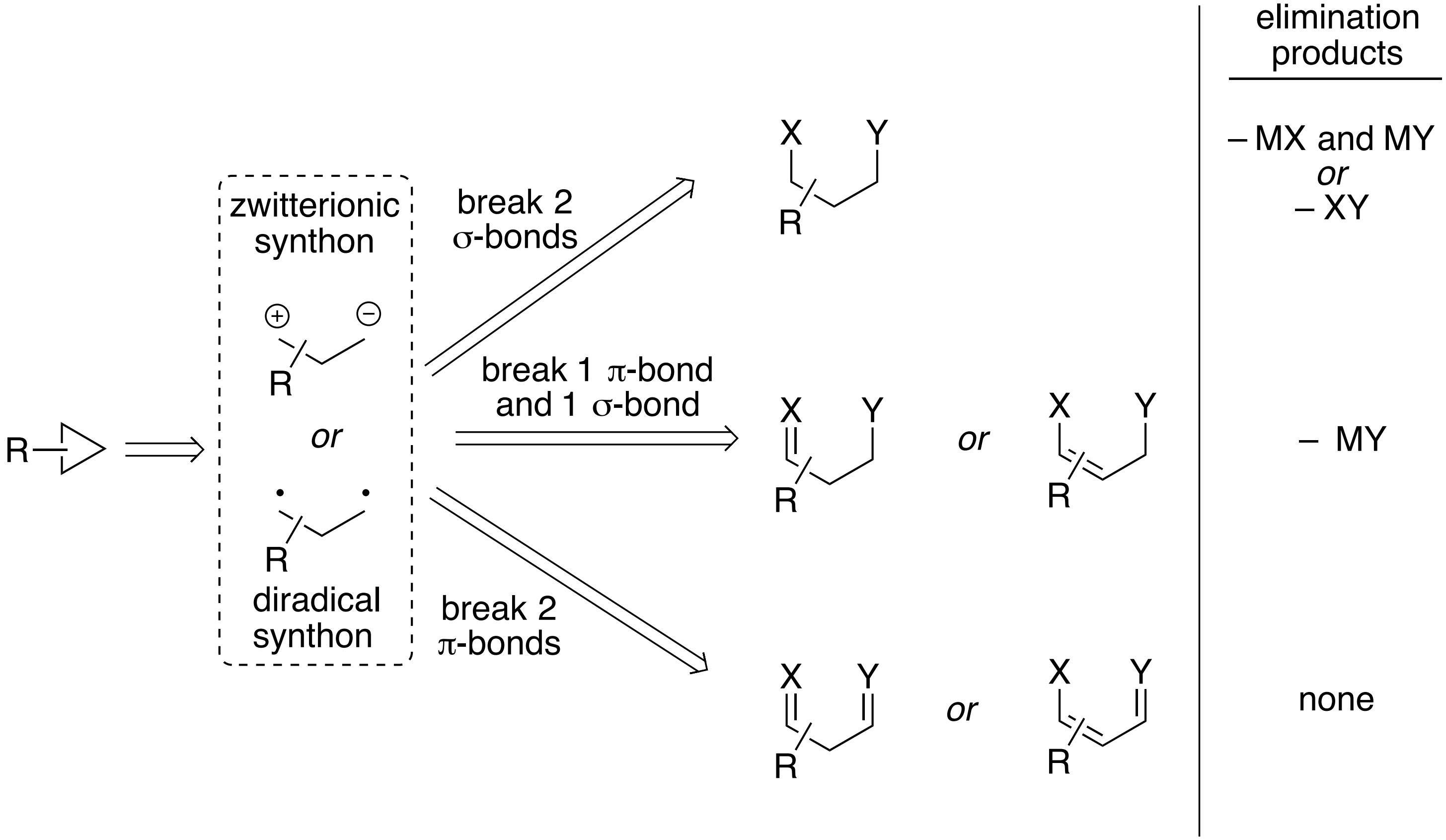
Intramolecular cyclopropanation example via an isolable first product arrived at from an intermolecular process

$S_1 + S_2 \longrightarrow P_1 \longrightarrow P_2$



Intramolecular cyclopropanation: 1,3-cyclization

cyclopropane cyclization occurs with formation of 1 C—C σ-bond



zwitterionic synthon

or

diradical synthon

break 2 σ-bonds

break 1 π-bond and 1 σ-bond

break 2 π-bonds

or

or

elimination products

– MX and MY
or
– XY

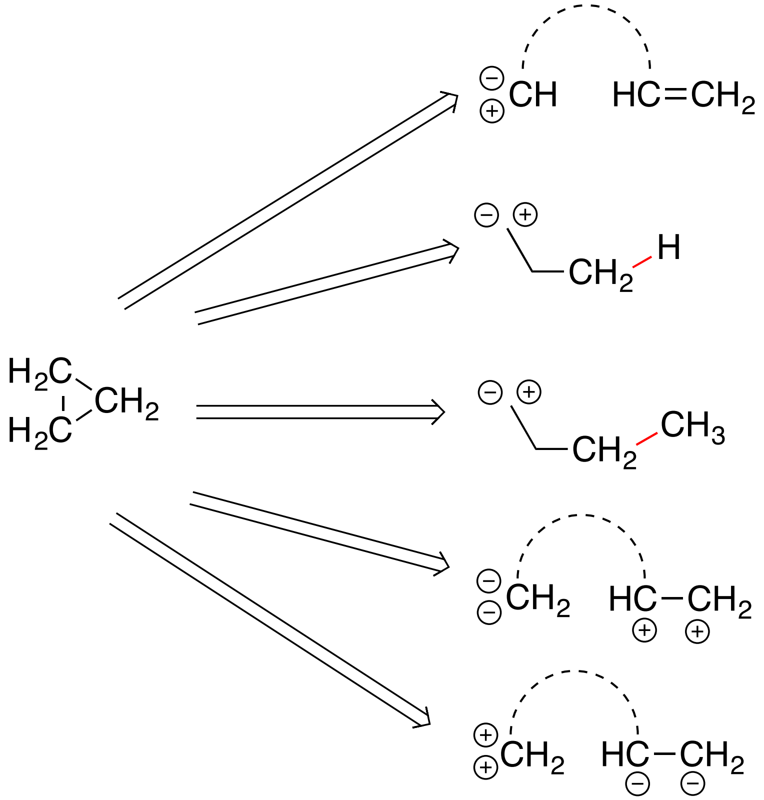
– MY

none

Kulinkovich, O. G. *Cyclopropanes in organic synthesis.* (Hoboken, New Jersey: Wiley, 2015), 57-58.

Intramolecular cyclopropanation: [2+1] and insertion reactions

cyclopropane cyclization occurs with formation of 2 C—C σ-bonds (except insertion reactions)



carbene add^n

carbene C—H inser^n

Chemoselectivity issuses (e.g. solvent)

carbene C—C inser^n

c.f. cyclobutane chemistry, other types difficult

1,1-carbodianion and 1,2-carbodication

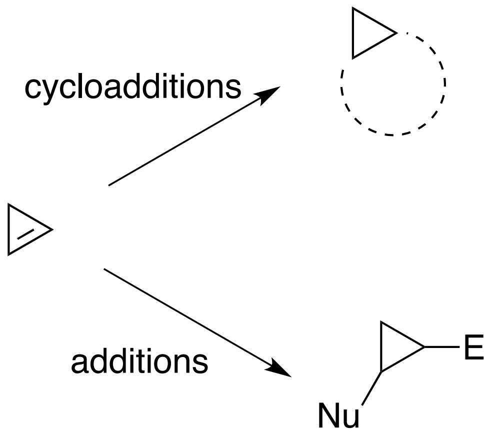
1,1-carbodication and 1,2-carbodianion

Mostly intermolecular

or involving recombination of respective radical-ion species

Kulinkovich, O. G. *Cyclopropanes in organic synthesis.* (Hoboken, New Jersey: Wiley, 2015), 65.

Cyclopropane formation from reactions to cyclopropene (without cyclopropane cyclization)

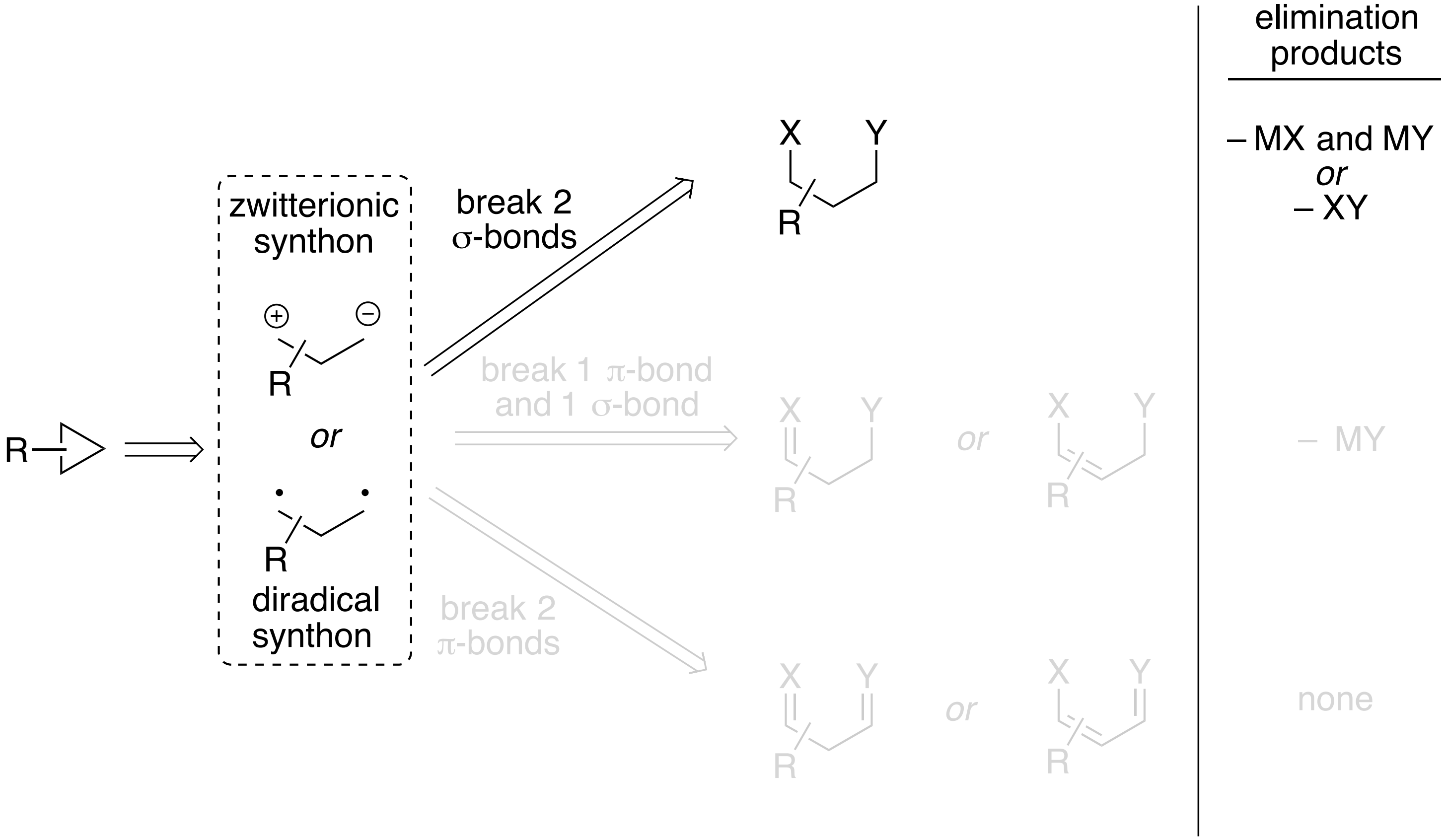


will not be covered in this topic review

For some information, however, on this topic see: Kulinkovich, O. G. *Cyclopropanes in organic synthesis.* (Hoboken, New Jersey: Wiley, 2015), 88-90.

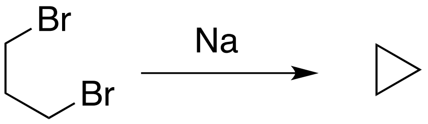
1,3-cyclizations by breaking 2 σ-bonds

cyclopropane cyclization occurs with formation of 1 C—C σ-bond



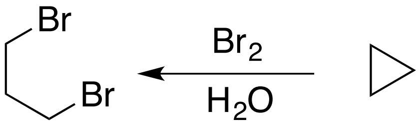
1,3-dehalogenation: dissolving metal

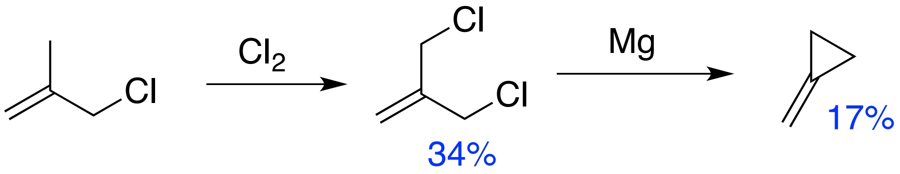
Often attributed as first
cyclopropane synthesis



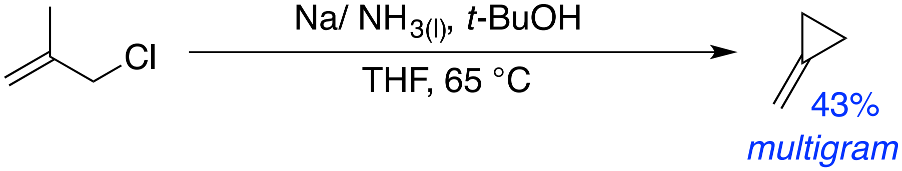
Freund, A. *J. Prakt. Chem.*, **1882**, *26*, 367–377.

Unique p-character of
bonding in cyclopropanes





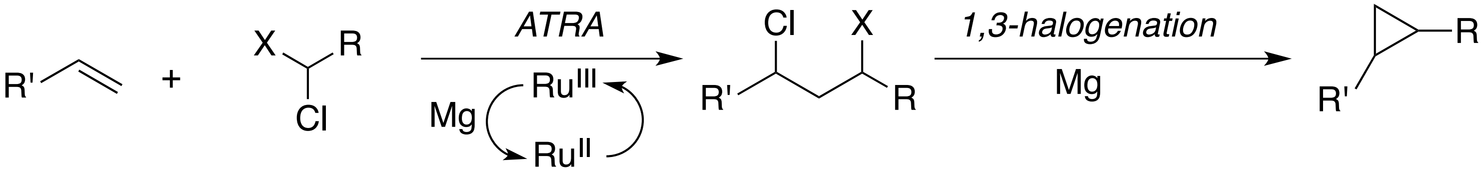
Gragson, J. T.; Greenlee, K. W.; Derfer, J. M.; Boord, C. E.
J. Am. Chem. Soc. **1953**, *75*, 3344–3347.

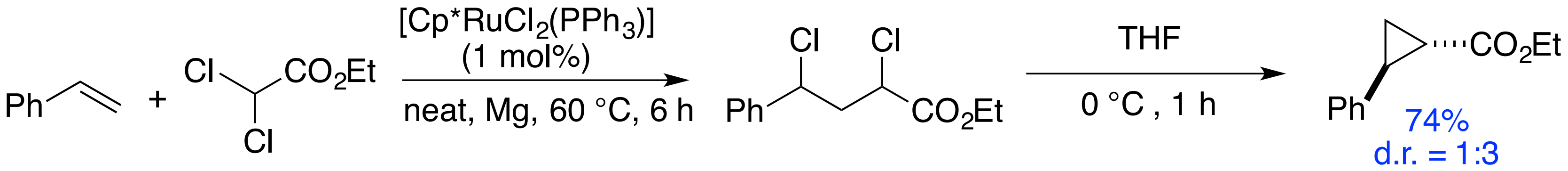


Salaun, J. R.; Champion, J.; Conia, J. M. *Org. Synth.* **1977**, *57*, 36.

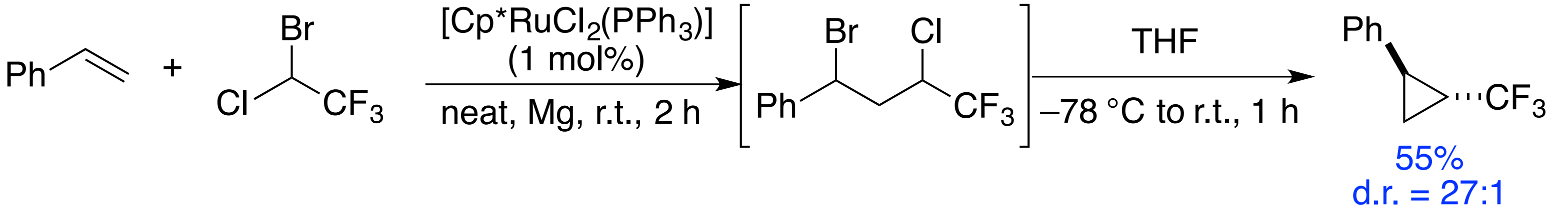
1,3-dehalogenation: dissolving metal

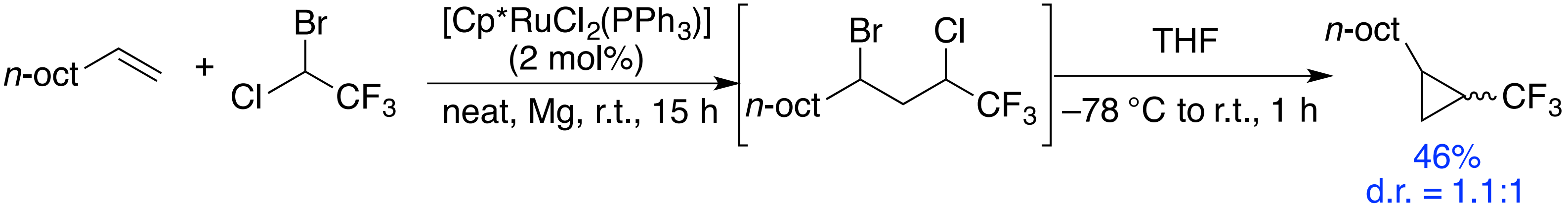
ruthenium-catalyzed Kharash ATRA/1,3-dehalogenation 1-pot sequence





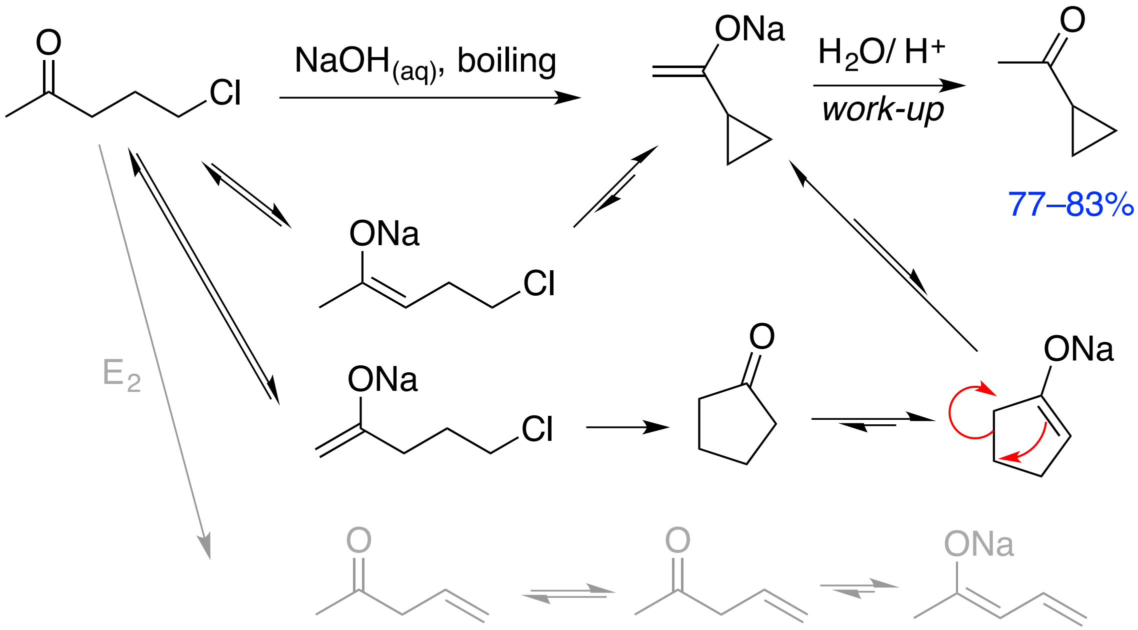
Thommes, K.; Kiefer, G.; Scopelliti, R.; Severin, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 8115–8119.





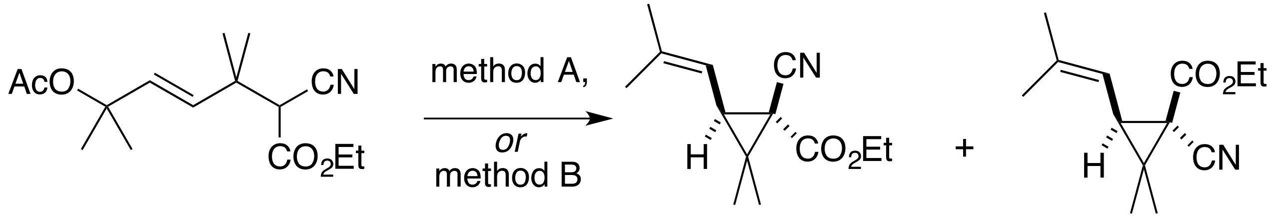
Risse, J.; Fernández-Zúmel, M. A.; Cudré, Y. *Org. Lett.* **2012**, *14*, 3060–3063.

elimination of HX



Cannon, G. W.; Ellis, R. C.; Leal, J. R. *Org. Synth.* **1951**, *31*, 74.

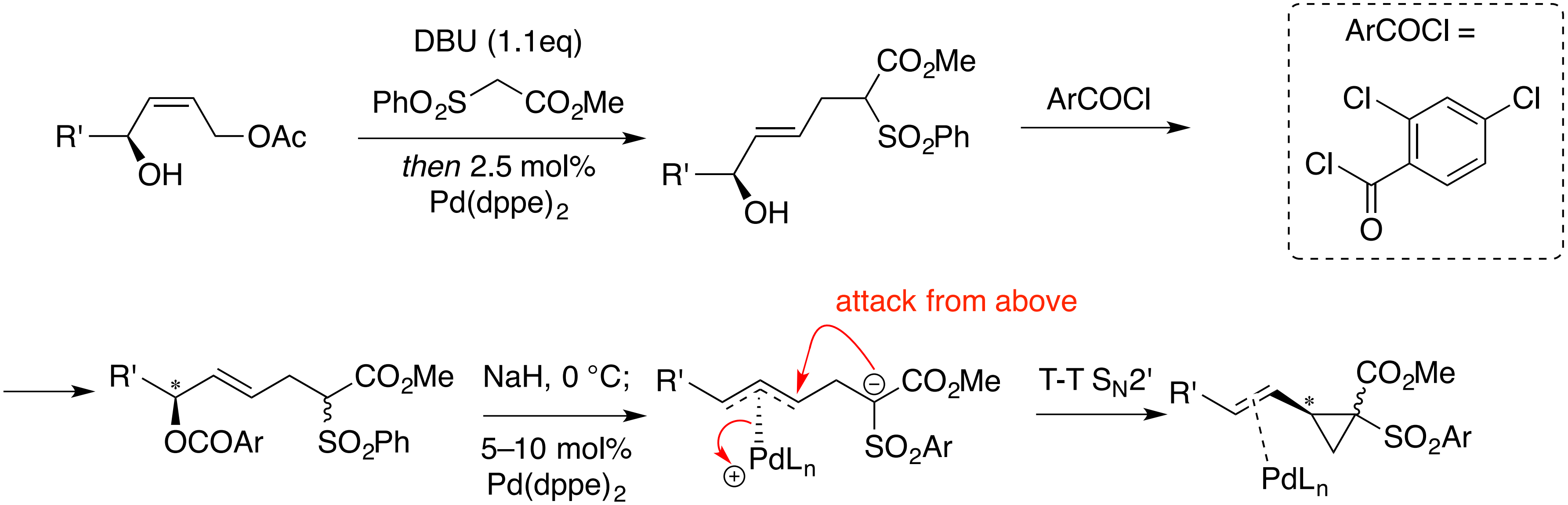
Double Tsuji-Trost by palladium-catalyzed allylation *and* palladium-catalyzed cyclopropanation



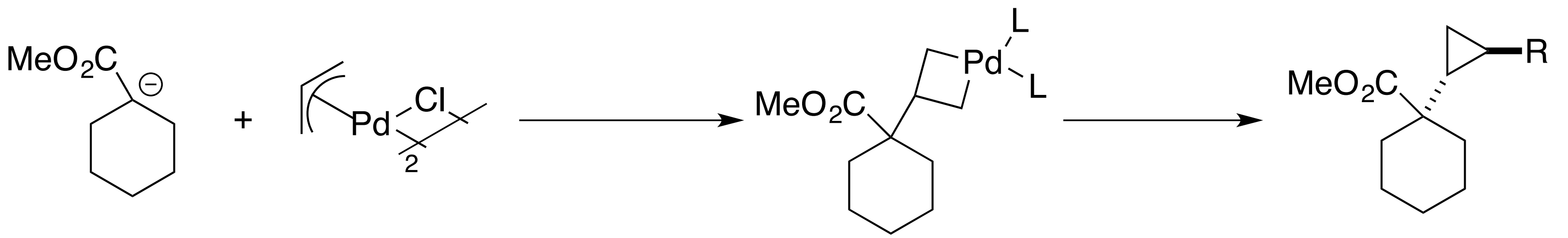
Genet, J.-P.; Piau, F. *J. Org. Chem.* **1981**, *46*, 2414–2417.

Method A: NaH only 0 °C then 65°C: d.r. = 1:1; Y = 75%
Method B: NaH, 0 °C then Pd^0 65°C : d.r. = 19:1; Y = 70%

- Tsuji-Trost type mechanism for first allylation and then second, except when no palladium used. For origin of this discovery: Colobert, F.; Genet, J.- P. *Tetrahedron Lett.* **1985**, *26*, 2779–2782 and reference [6] therein.

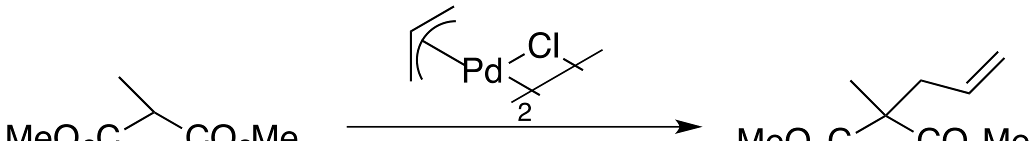


‘Regio-incorrect Tsuji-Trost’ leads to isolable palladocyclobutane



isolated and characterized:
Hoffmann, H. M. R.; Otte, A. R.; Wilde, A.; Menzer, S.; Williams, D. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 100–102.

R = H	70%
R = Me	78%
R= CO_2Me	37%



NEt_3, HMPA
THF, –78 °C

- Need appropiate enolate ester: Hegedus, L. S.; Darlington, W. H.; Russell, C. E. *J. Org. Chem.* **1980**, *45*, 5193–5196.

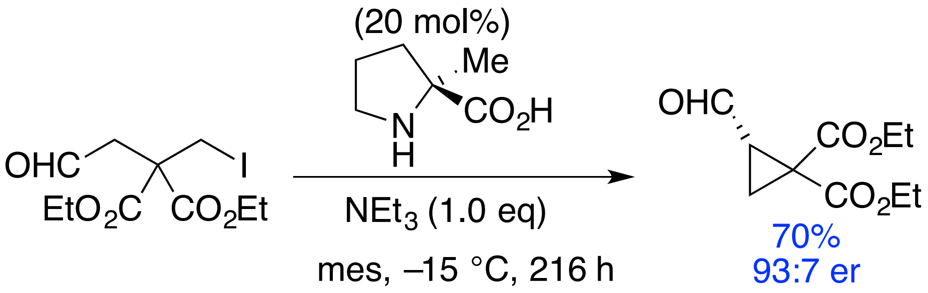
- Although Hückel calculations suggested attack at central carbon in π-allyl complex would be unfeasible [Curtis, M. D.; Eisenstein, O. *Organometallics* **1984**, *3*, 887–895], here it does occur.

- Nuc attack on η^3-allyl palladium complexes is explored further: Aranyos, A.; Szabó, K. J.; Castaño, A. M.; Bäckvall, J.-E. *Organometallics* **1997**, *16*, 1058–1064.

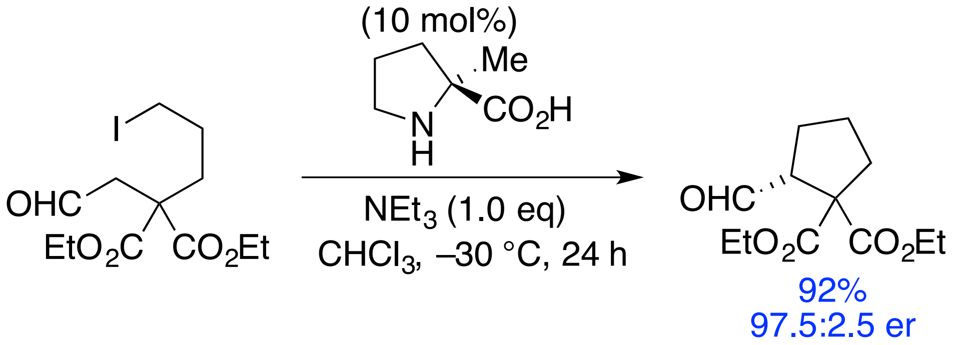
Hegedus, L. S.; Söderberg, B. C. G. *Transition metals in the synthesis of complex organic molecules, 3rd Ed.* (Sausalito, California: University Science Books, 2010), 28-29.

elimination of HX: enantioselective

Enantioselective (here with proline enamine organocatalysis)

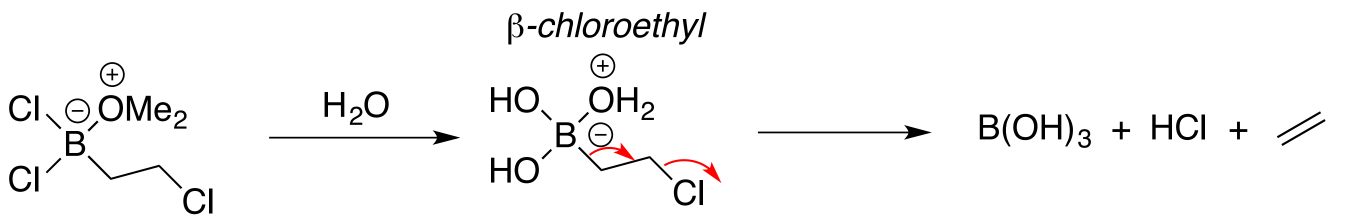


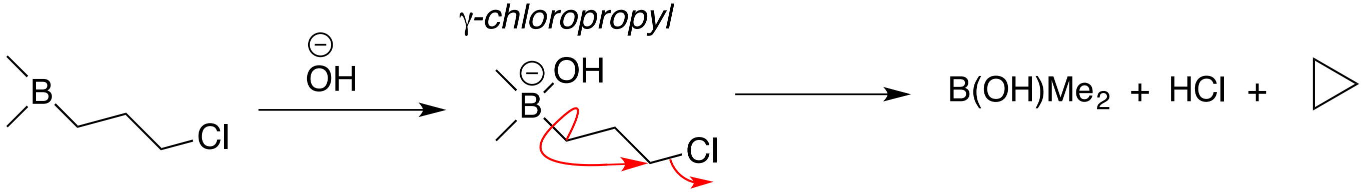
N.B.: - this was only example for cyclopropane, others were for cyclopentanes
- long reaction times, higher catalyst loading (c.f. 24 h with 10 mol%)



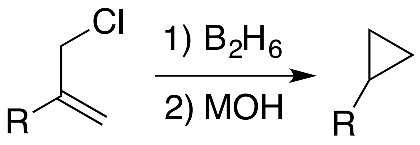
Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450–451.

γ-chloropropylborane-ate complex

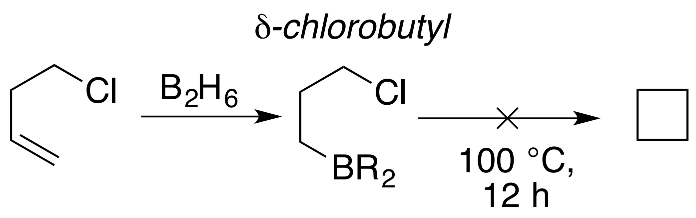




Discovery: Hawthorne, M. F.; Dupont, J. A. *J. Am. Chem. Soc.* **1958**, *80*, 5830–5832.

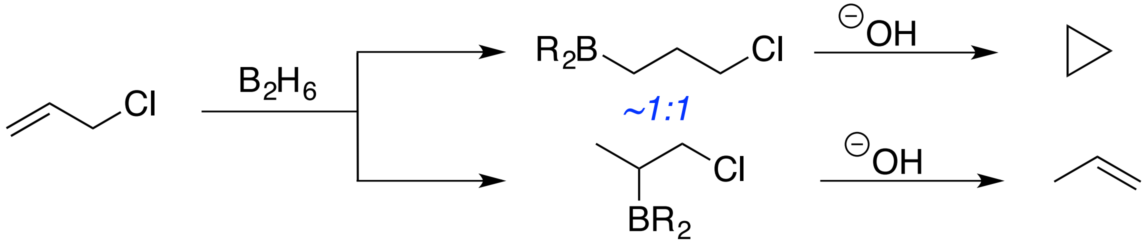


R	Y (%)
H	43
Me	71
n-propyl	61
Ph	55
Bn	45

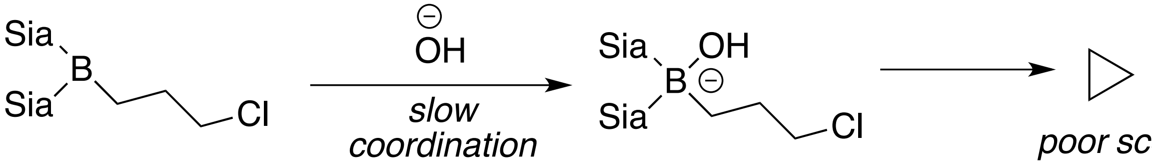


Hawthorne, M. F. *J. Am. Chem. Soc.* **1960**, *82*, 1886–1888.

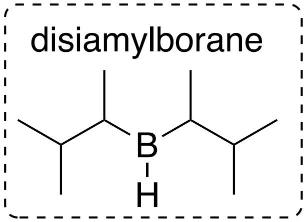
Problem: allylchloride powerfully directive (overides inherent selectivity of borane during hydroboration)

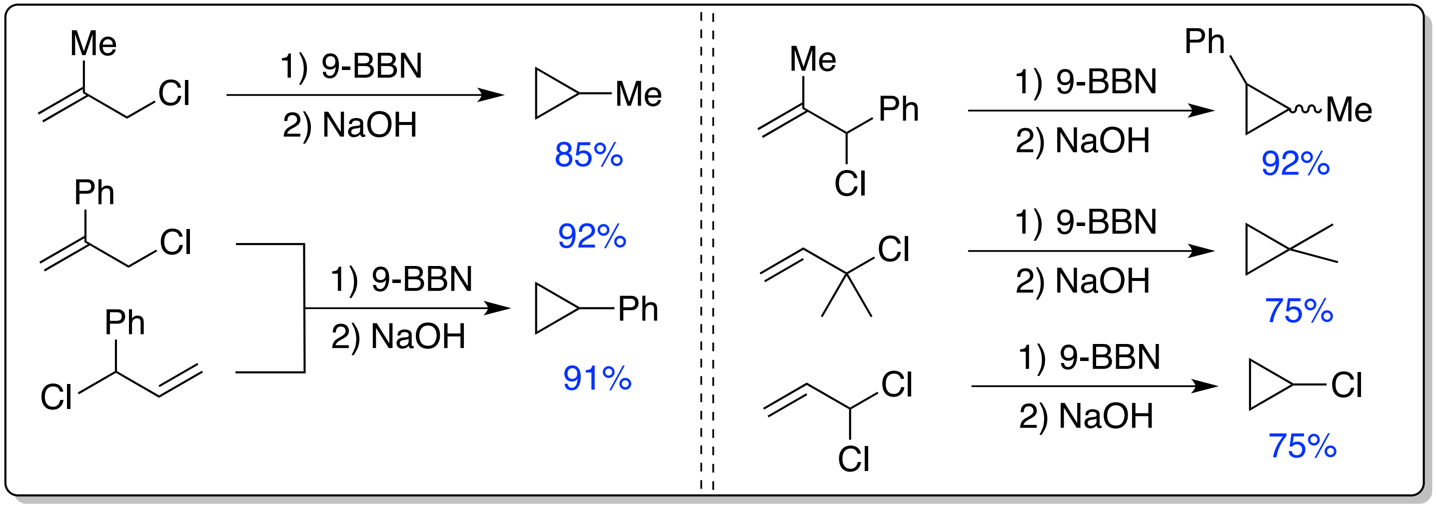


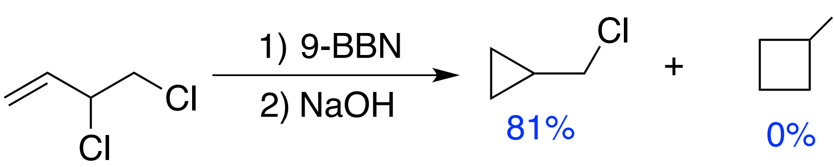
γ-chloropropylborane-ate complex



*poor scope,
side rxns when
chloride is reactive*





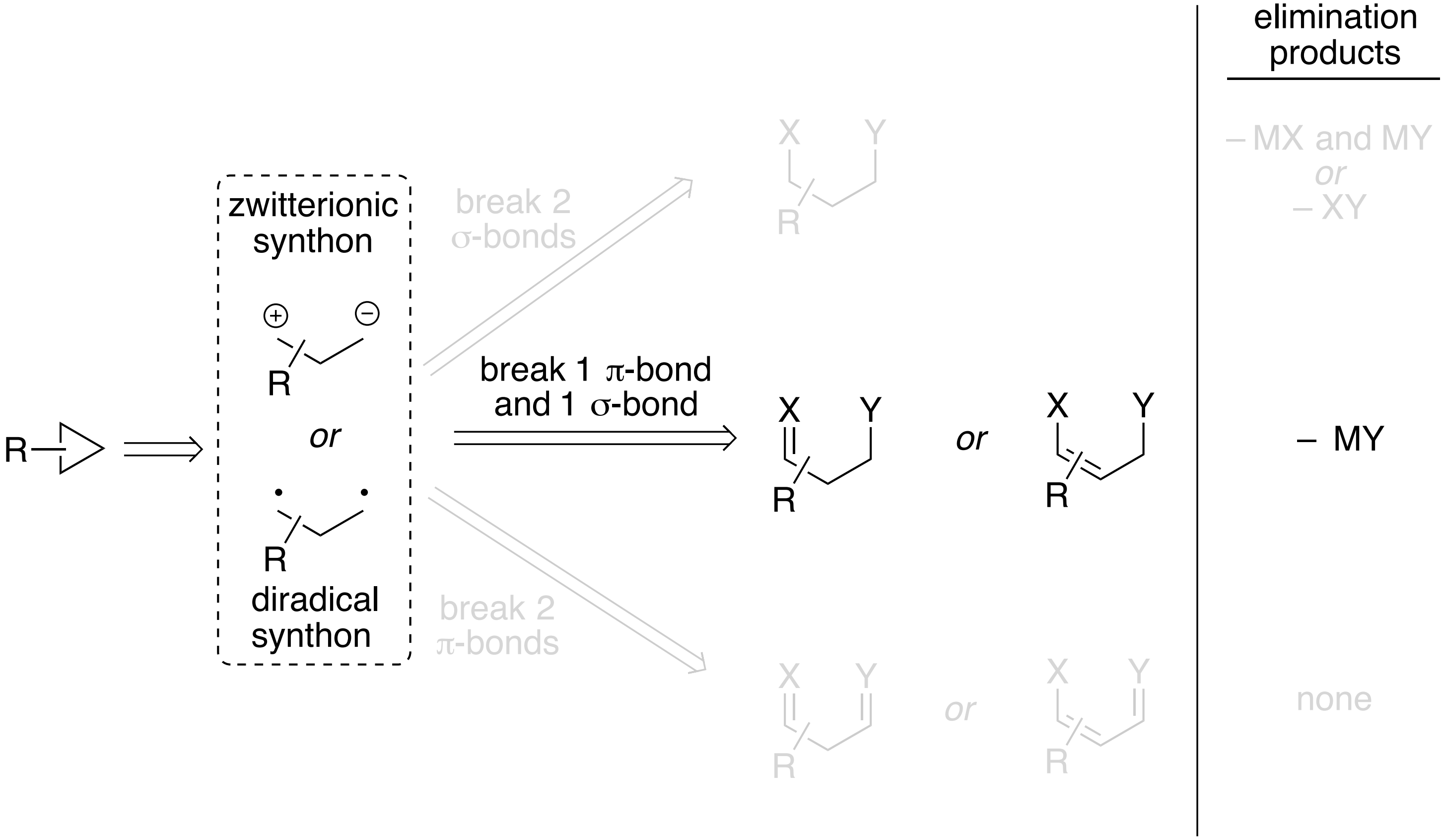


no cyclobutane

Brown, H. C.; Rhodes, S. P. *J. Am. Chem. Soc.* **1969**, *91* (8), 2149–2150.

1,3-cyclizations by breaking 1 σ-bond and 1 π-bond

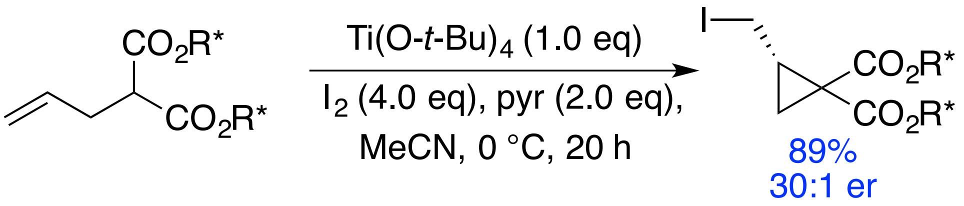
cyclopropane cyclization occurs with formation of 1 C—C σ-bond

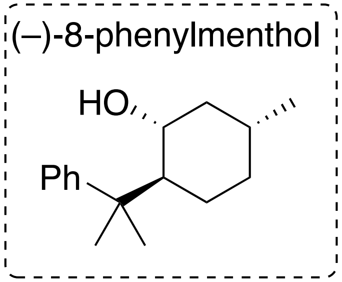


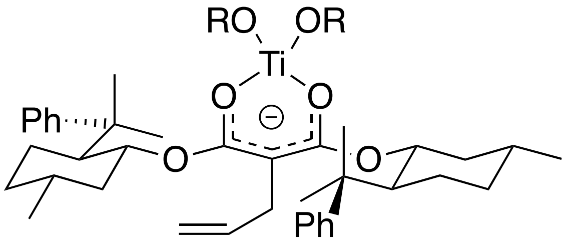
Diastereoselective with chiral aux

Diastereoselective (here with chiral auxilary)

R* = (–)-8-phenylmenthyl





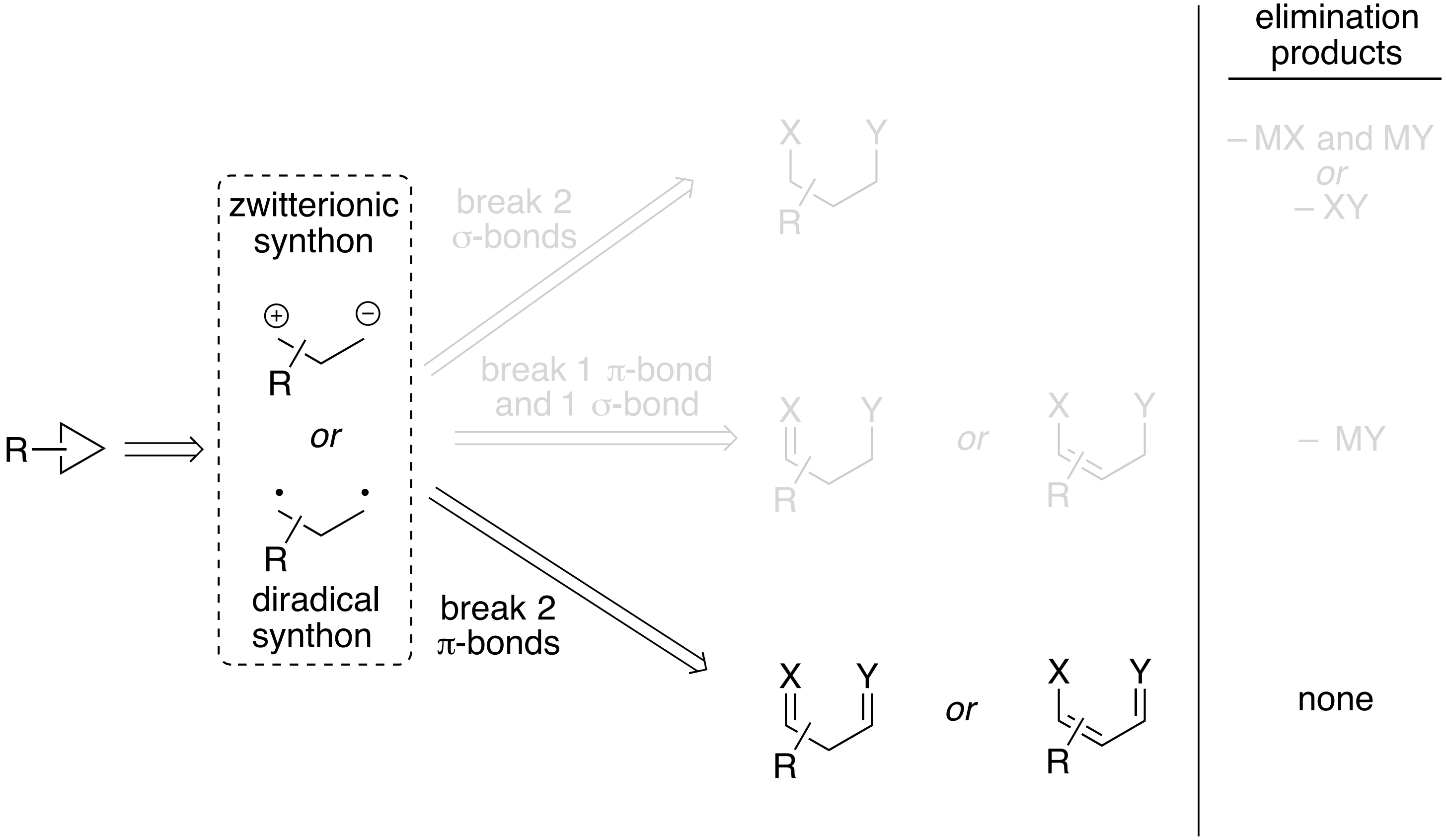


highly organized Ti-enolate leads to diastereoselective iodoination

Inoue, T.; Kitagawa, O.; Ochiai, O.; Taguchi, T. *Tetrahedron: Asymmetry* **1995**, *6*, 691–692.
Chiral titanium complex failed to induce enantioselectivity: Kitagawa, O.; Taguchi, T. *Synlett* **1999**, 1191–1199.

1,3-cyclizations by breaking 2 π-bonds

cyclopropane cyclization occurs with formation of 1 C—C σ-bond



zwitterionic synthon

or

diradical synthon

break 2 σ-bonds

break 1 π-bond and 1 σ-bond

break 2 π-bonds

or

or

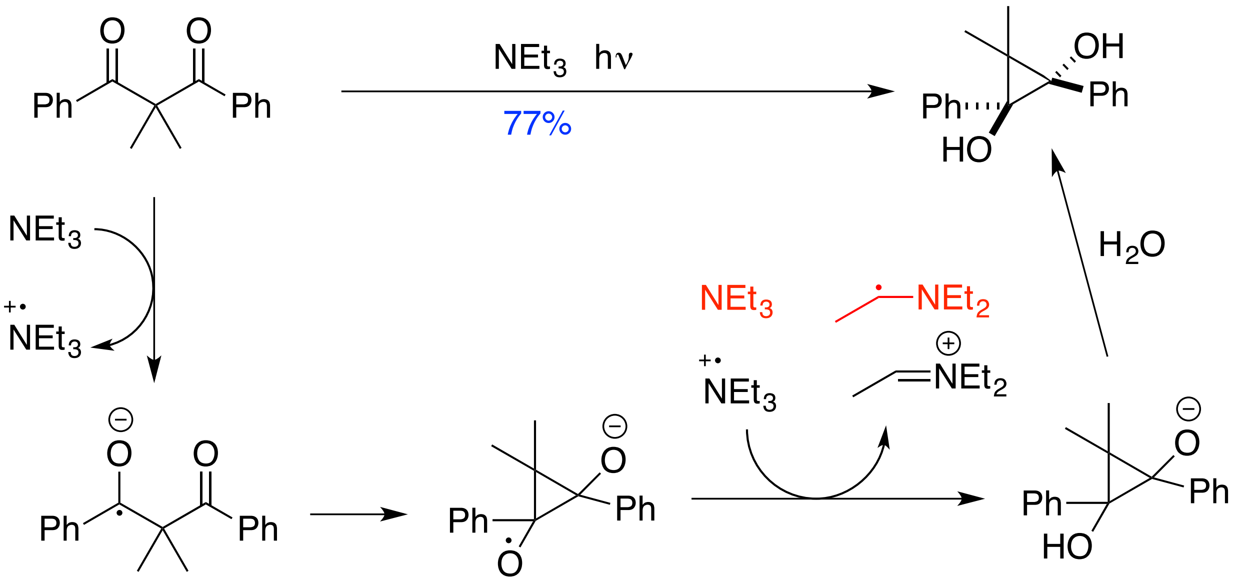
elimination products

– MX and MY
or
– XY

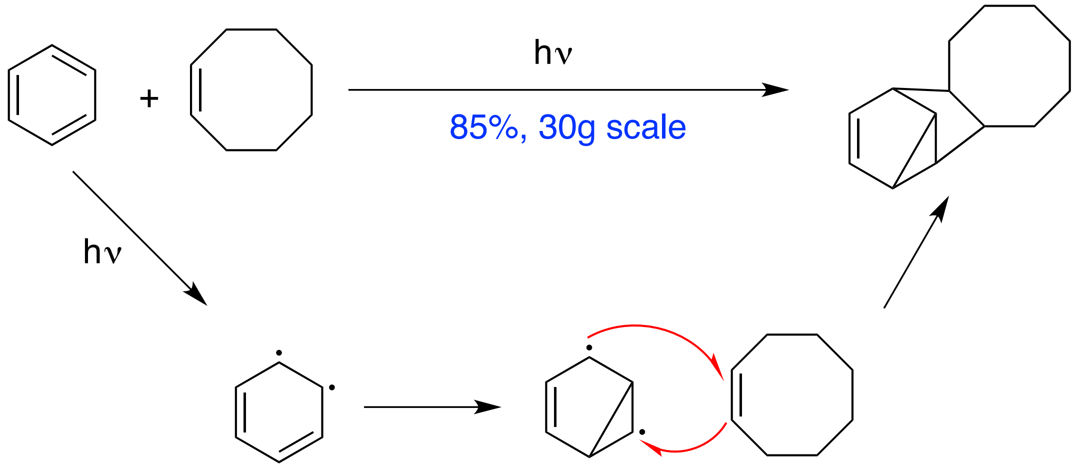
– MY

none

Photolysis of double bonds



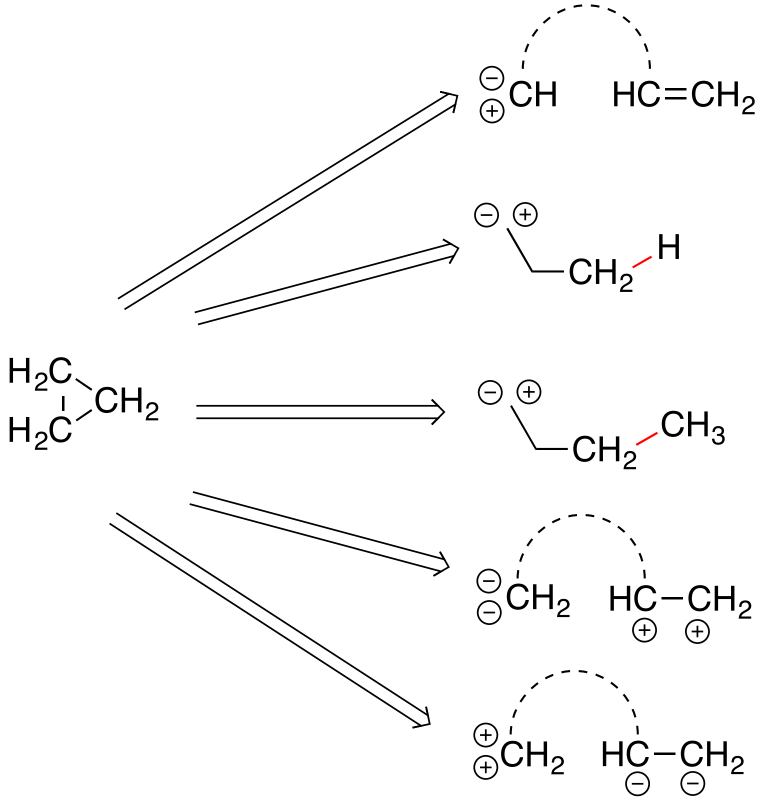
Hasegawa, E.; Katagi, H.; Nakagawa, D.; Horaguchi, T. *Tetrahedron Lett.* **1995**, *36*, 6915.



Wilzbach, K. E.; Kaplan, L. *J. Am. Chem. Soc.* **1966**, *88*, 2066–2067.

Intramolecular cyclopropanation: [2+1] and insertion reactions

cyclopropane cyclization occurs with formation of 2 C—C σ-bonds (except insertion reactions)



carbene add^n

carbene C—H inser^n

Chemoselectivity issuses (e.g. solvent)

carbene C—C inser^n

c.f. cyclobutane chemistry,
other types difficult

1,1-carbodianion and 1,2-carbodication

1,1-carbodication and 1,2-carbodianion

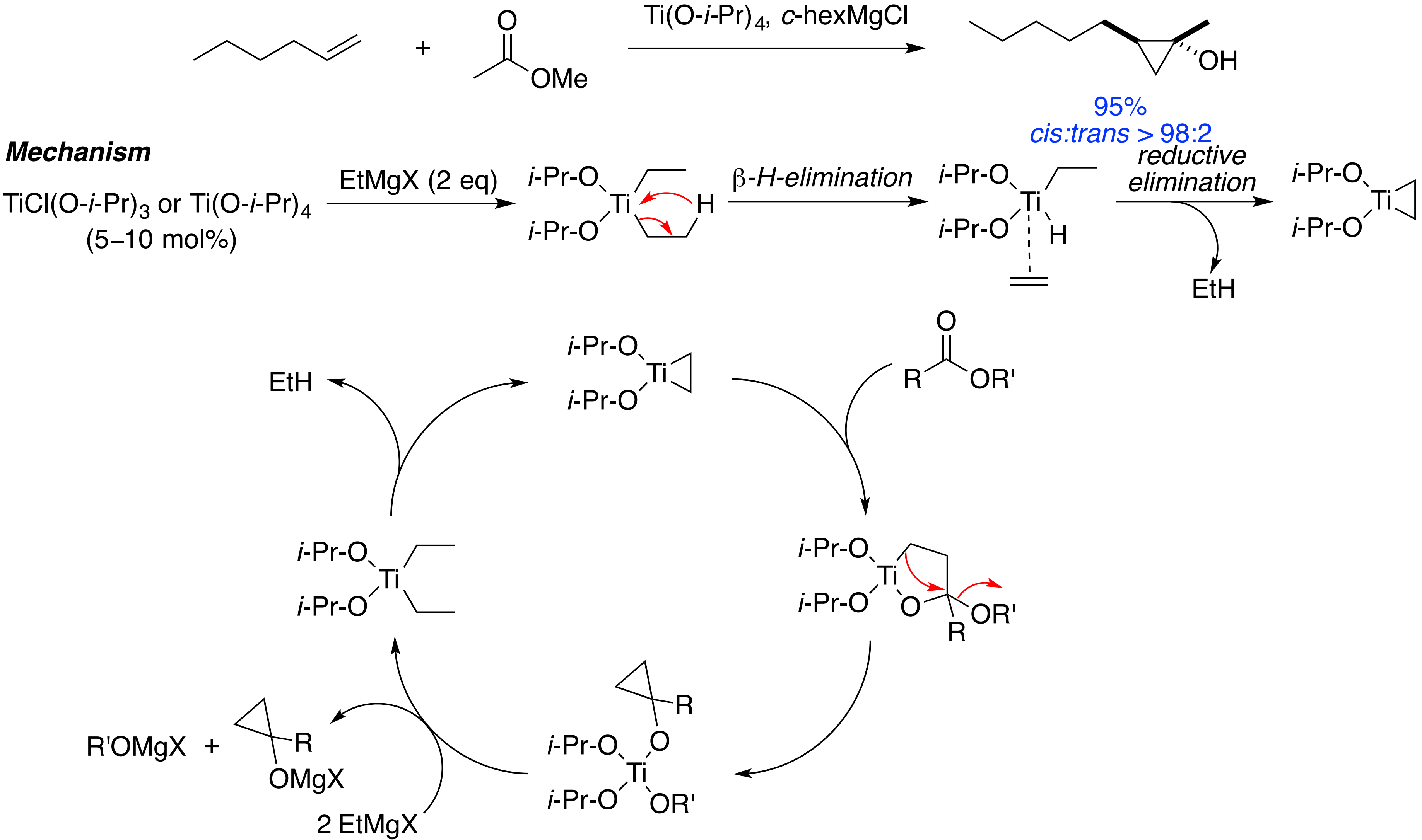
Mostly intermolecular

or involving recombination of respective radical-ion species

Kulinkovich, O. G. *Cyclopropanes in organic synthesis.* (Hoboken, New Jersey: Wiley, 2015), 65.

1,1-carbodication and 1,2-carbodianion

Kulinkovich-de Meijere hydroxycyclopropanation: intermolecular version and mechanism

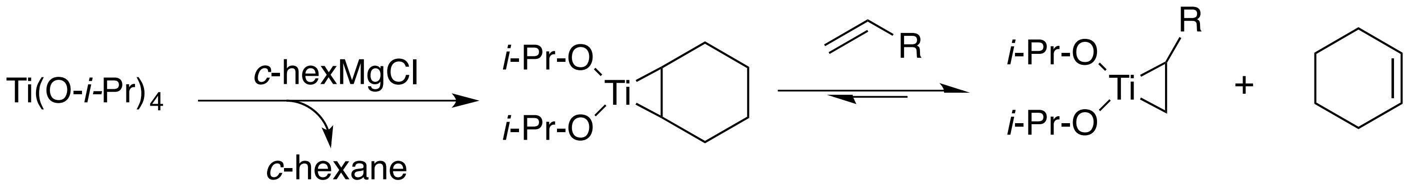


(a) For a review: Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789–2834. (b) For an important application to total synthesis: Kingsbury, J. S.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 13813–13815. (c) Hegedus, L. S.; Söderberg, B. C. G. *Transition metals in the synthesis of complex organic molecules, 3rd Ed.* (Sausalito, California: University Science Books, 2010), 142-143.

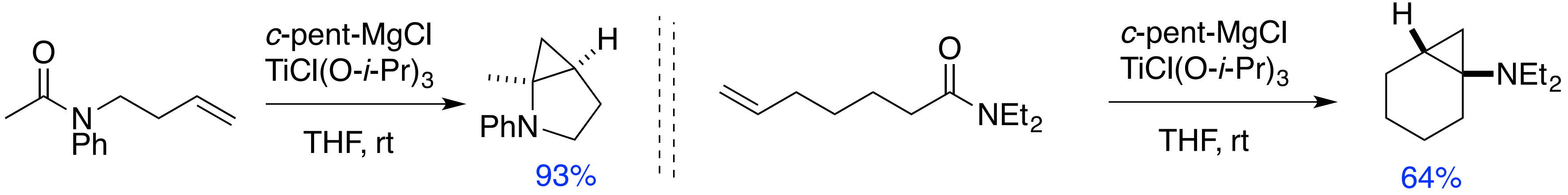
Kulinkovich-de Meijere reaction: intramolecular version and intelligent modification

A variation allows exhange of alkene component by exploiting the reversibility of the titanacyclopropane formation to increase substitution on the resulting cyclopropane. This also can open posibilities for intramolecular cyclopropanation: Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198–4199.

The exchange may be encouraged by choice of Grignard reagent:

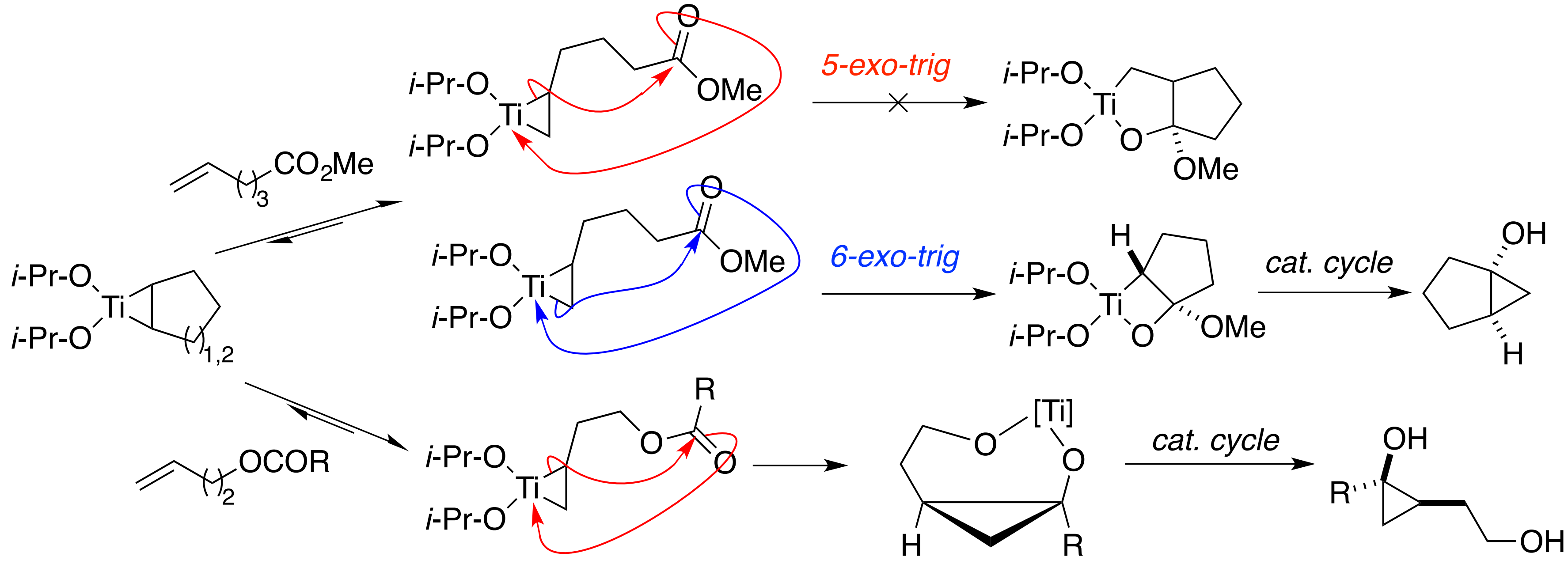


Analogously, intramolecular reaction of enamides to cyclopropylamines



Lee, J.; Cha, J. K. *J. Org. Chem.* **1997**, *62*, 1584–1585.

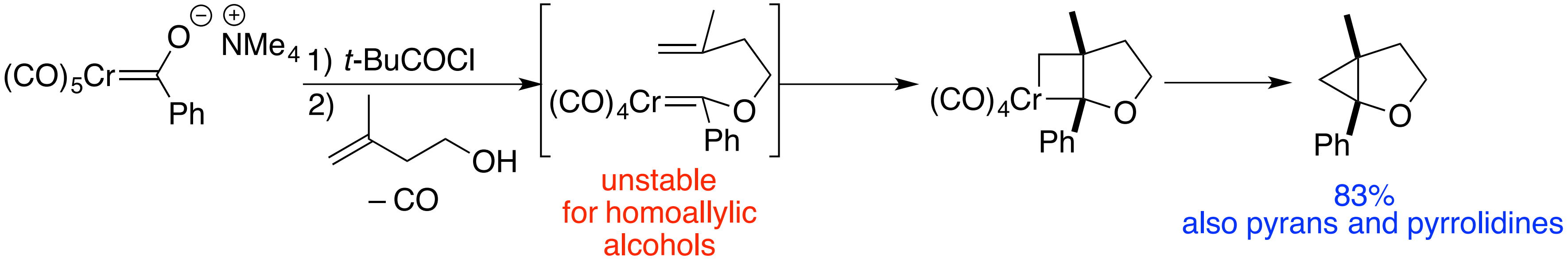
Kulinkovich-de Meijere reaction: intramolecular version and intelligent modification



See also: Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 6079–6082.

carbene [2+1] reactions (and 2 insertion examples)

Electrophilic group 6 Fischer carbenes

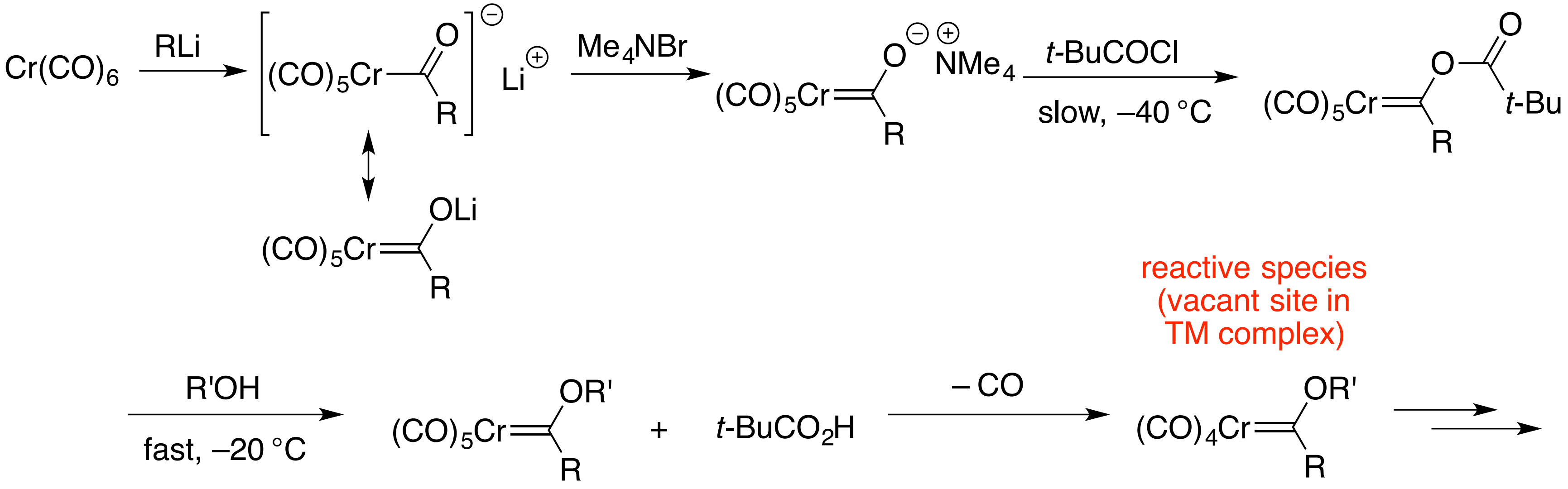


unstable
for homoallylic
alcohols

83%
also pyrans and pyrrolidines

Söderberg, B. C.; Hegedus, L. S. *Organometallics* **1990**, *9*, 3113–3121.

Facile synthesis of Fischer carbenes using gropu 6 metals



'mixed anhydride'

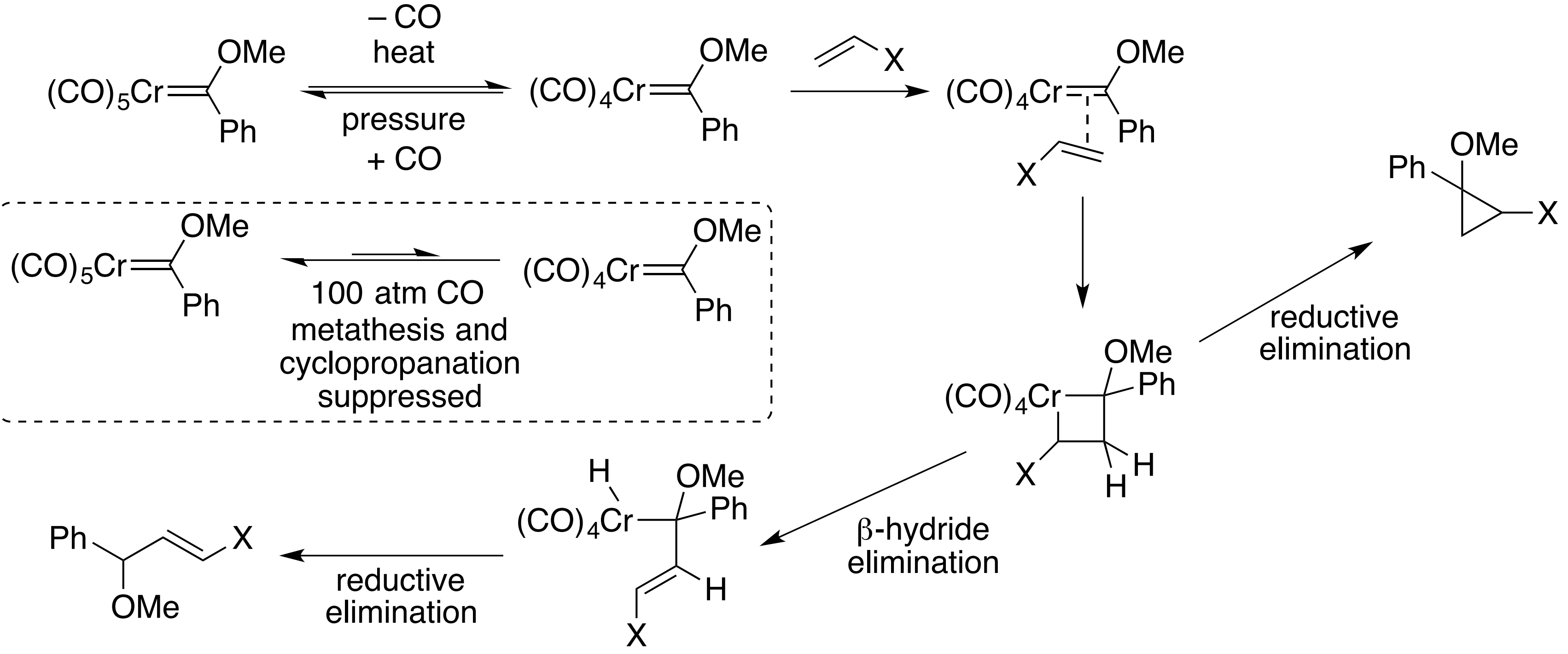
reactive species
(vacant site in
TM complex)

Semmelhack, M. F.; Bozell, J. J. *Tetrahedron Lett.* **1982**, *23*, 2931–2934.

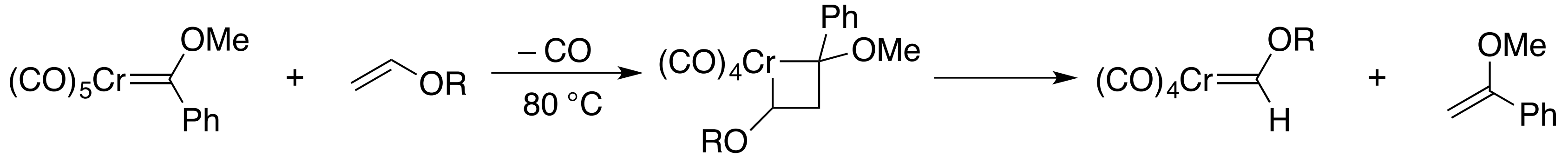
Hegedus, L. S.; Söderberg, B. C. G. *Transition metals in the synthesis of complex organic molecules, 3rd Ed.* (Sausalito, California: University Science Books, 2010), 196-199. See also 183-187 for background information on these complexes.

Electrophilic group 6 Fischer carbenes

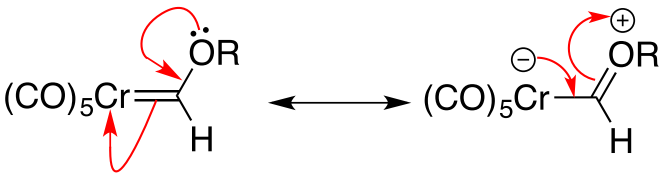
mechanism



evidence for metallacyclobutane: alkene metathesis



heteroatom-stabilized
chromium carbene



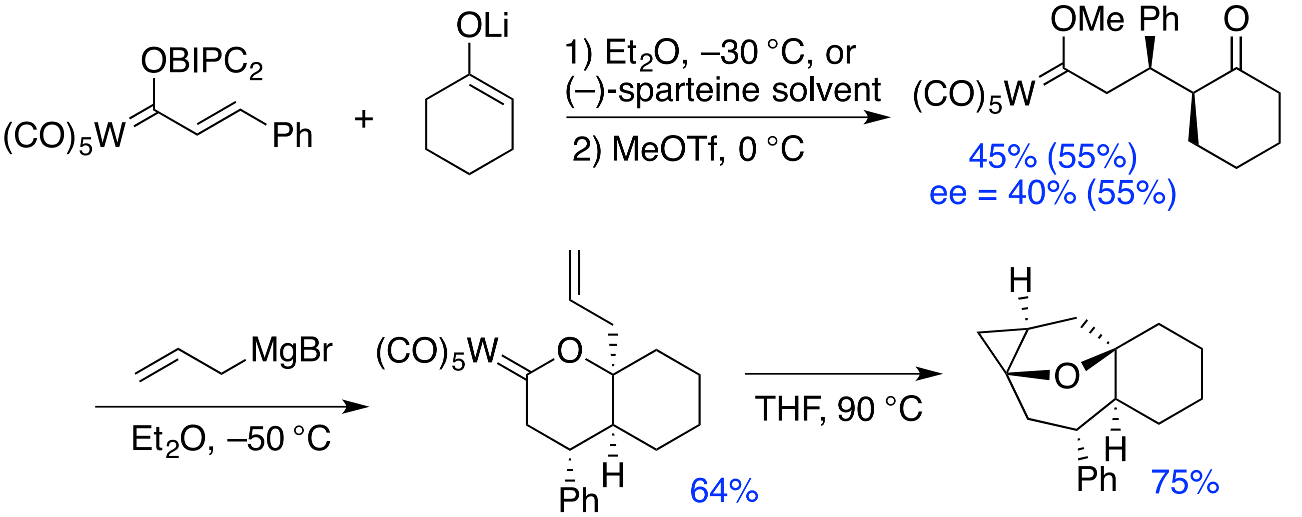
whereas:

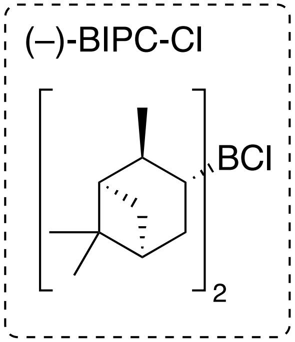
50–90%

Z = CO_2Me, $CONMe_2$, CN, P(O)(OMe)$_2$, SO_2Ph

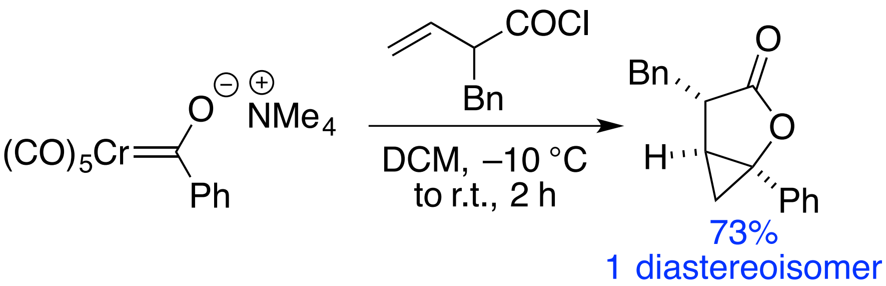
Electrophilic group 6 Fischer carbenes

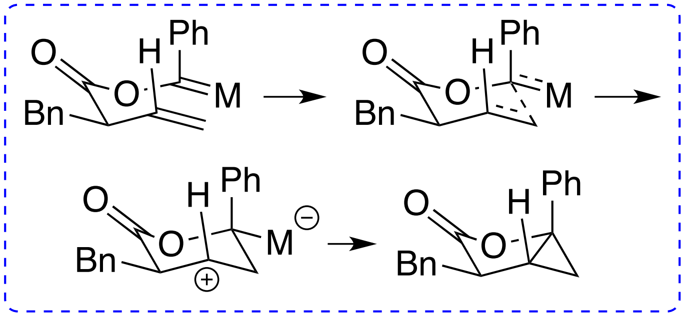
Diastereoselectivity from a leaving chiral auxilary. When alkene tethered in proximity may have metathesis.





Barluenga, J.; Diéguez, A.; Rodríguez, F.; Flórez, J.; Fañanás, F. J. *J. Am. Chem. Soc.* **2002**, *124*, 9056–9057.

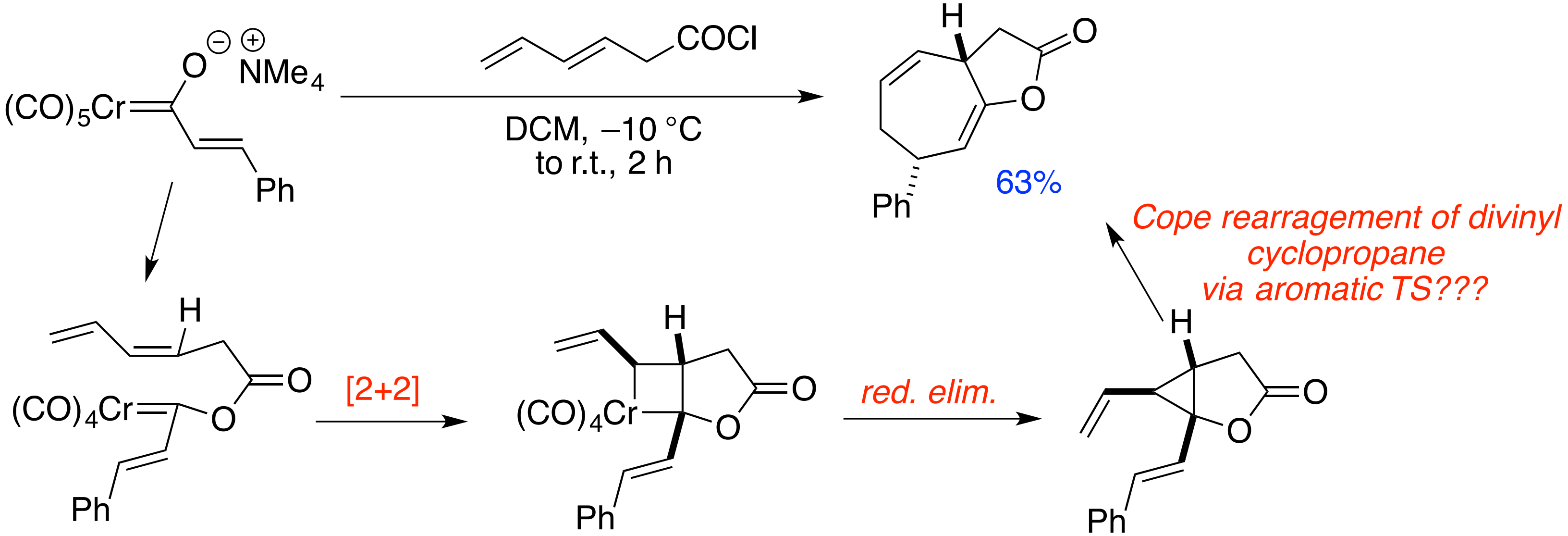




Barluenga, J.; Aznar, F.; Gutiérrez, I.; Martín, J. A. *Org. Lett.* **2002**, *4*, 2719–2722.

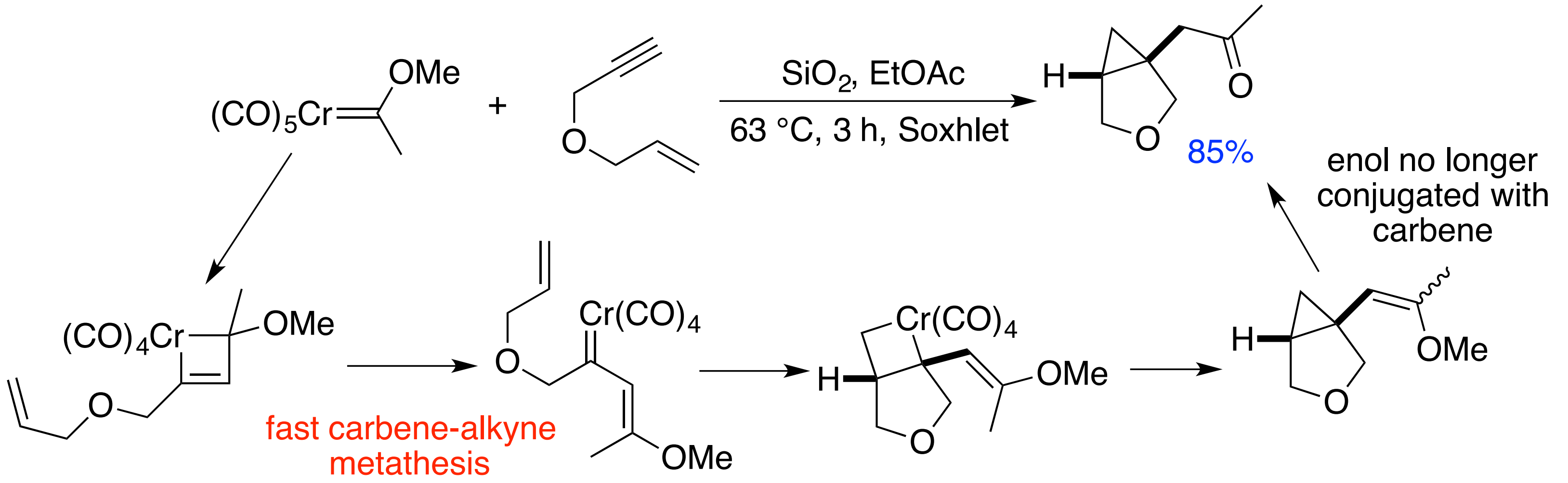
Electrophilic group 6 Fischer carbenes

not a cyclopropanation rxn, but via a cyclopropane intermediate



Cope rearrangement of divinyl cyclopropane via aromatic TS???

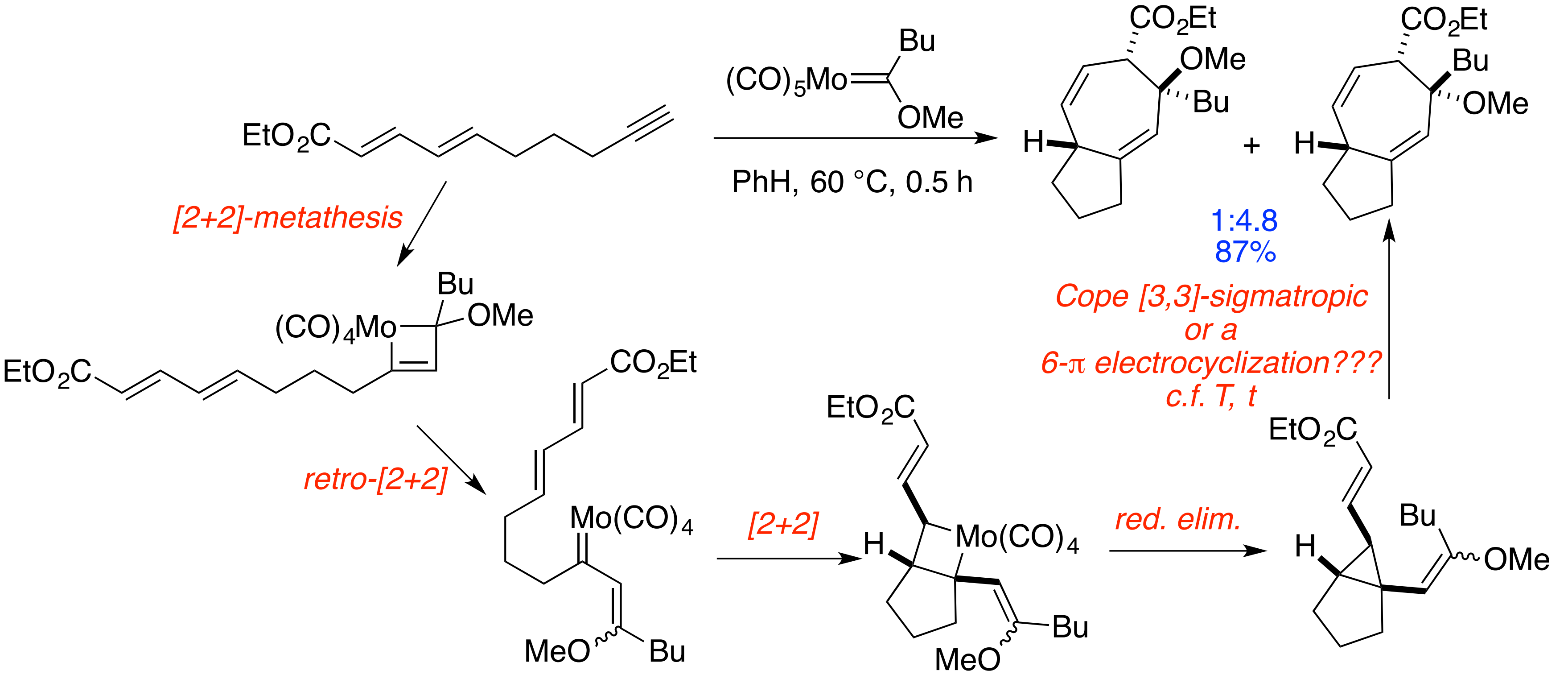
Barluenga, J.; Aznar, F.; Gutiérrez, I.; Martín, J. A. *Org. Lett.* **2002**, *4*, 2719–2722.



fast carbene-alkyne metathesis

enol no longer conjugated with carbene

Electrophilic group 6 Fischer carbenes

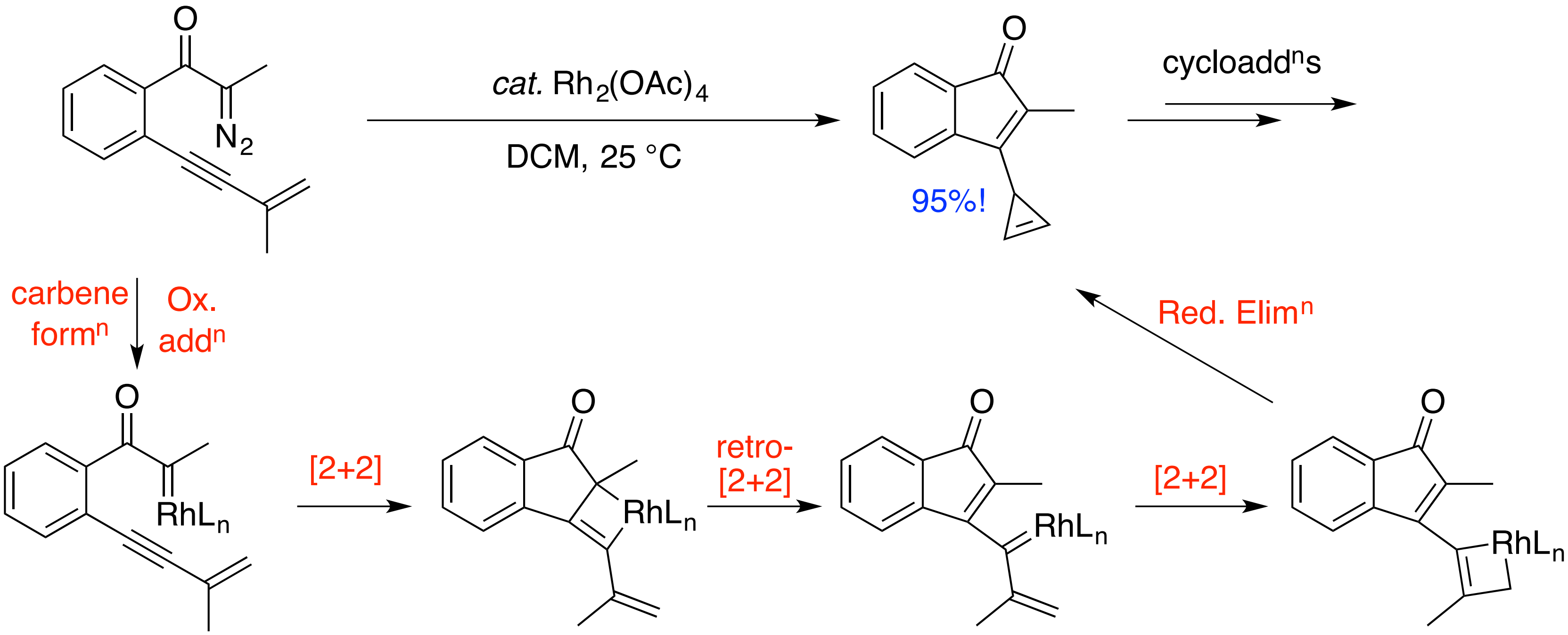


Harvey, D. F.; Lund, K. P. *J. Am. Chem. Soc.* **1991**, *113*, 5066–5068; Harvey, D. F.; Brown, M. F. *J. Org. Chem.* **1992**, *57*, 5559–5561. For examples with ene-yne, i.e. not diene where there is no Cope rearrangement: Harvey, D. F.; Lund, K. P.; Neil, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 8424–8434.

Rh- and Cu-carbenes with α-diazocarbonyl compounds: mechanism

Evidence for Cu- and Rh-bound carbenes from catalytic decomposition of α-diazocarbonyl compounds

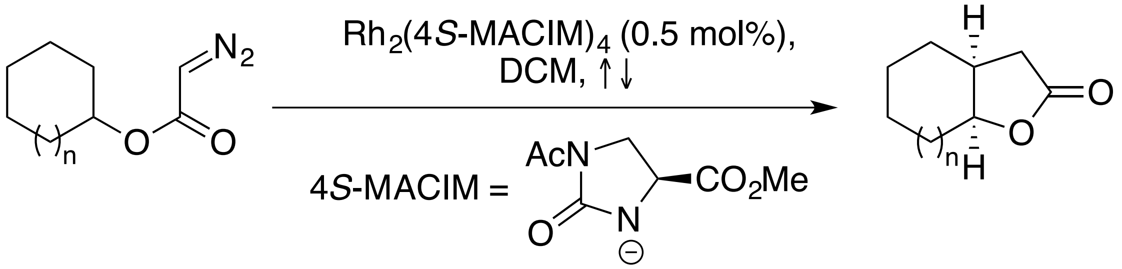
1) **metathesis**: highly efficient transformations that can be easily explained with metallacycobutane species and not by other types of carbenoid species



Padwa, A.; Austin, D. J.; Xu, S. L. *Tetrahedron Lett.* **1991**, *32*, 4103–4106; Hoye, T. R.; Dinsmore, C. J. *Tetrahedron Lett.* **1991**, 32, 3755–3758; Hoye, T. R.; Dinsmore, C. J. *J. Am. Chem. Soc.* **1991**, *113*, 4343–4345; Padwa, A.; Austin, D. J.; Xu, S. L. *J. Org. Chem.* **1992**, *57*, 1330–1331.

Rh- and Cu-carbenes with α-diazocarbonyl compounds: mechanism

2) **enantioselectivit**y: achiral substrates transformed into entioenriched products by catalytic quantities of enantiopure ligands and an appropiate metal

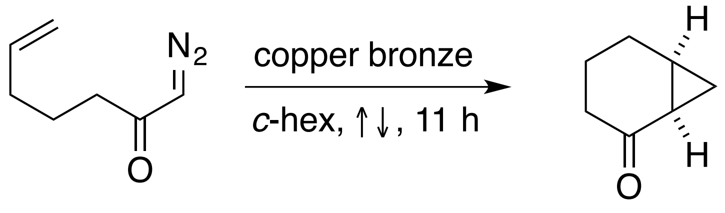


cis:trans = 99:1
ee = 96–97%
n = 1, 70%
n = 2, 75%
n = 3, 62%

Doyle, M. P.; Dyatkin, A. B.; Roos, G. H. P.; Canas, F.; Pierson, D. A.; van Basten, A.; Mueller, P.; Polleux, P.
J. Am. Chem. Soc. **1994**, *116*, 4507–4508.

therefore Cu- and Rh-catalyzed cyclopropanation likely to be via metallacyclobutanes arrived from metal-bound carbene complex, analagous to the group 6 Fischer carbenes

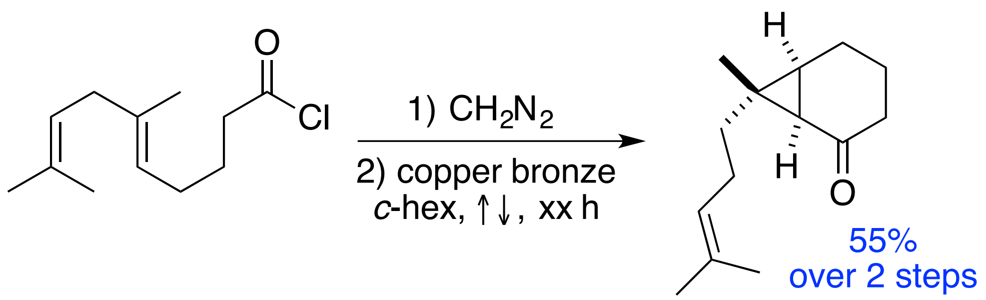
Rh- and Cu-carbenes with α-diazocarbonyl compounds: an evolution in complexity


bicyclo[4.1.0]heptane skeleton

copper bronze

c-hex, ↑↓, 11 h

JACS Stork 1961, 83, 4678

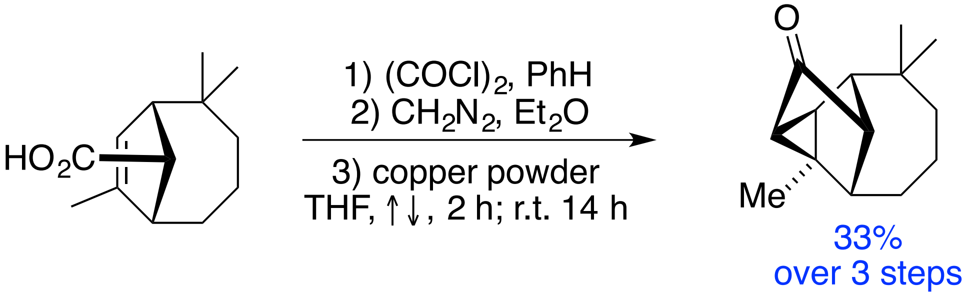

(±)-sirenin skeleton

1) CH_2N_2

2) copper bronze *c*-hex, ↑↓, xx h

55% over 2 steps

JACS Greico 1969, 91, 5660


1) $(COCl)_2$, PhH

2) CH_2N_2, Et_2O

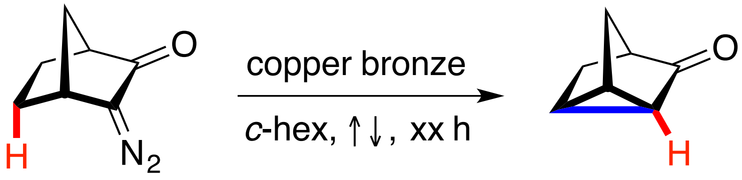
3) copper powder THF, ↑↓, 2 h; r.t. 14 h

33% over 3 steps

JOC Welch 1974, 39, 2665

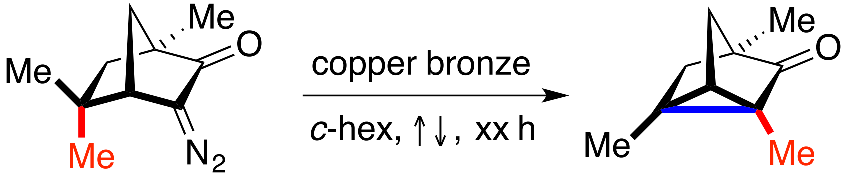
Rh- and Cu-carbenes with α-diazocarbonyl compounds: not just addition to π-bond

C-H Insertion



Tett Lett 1976 Nakata, 1515

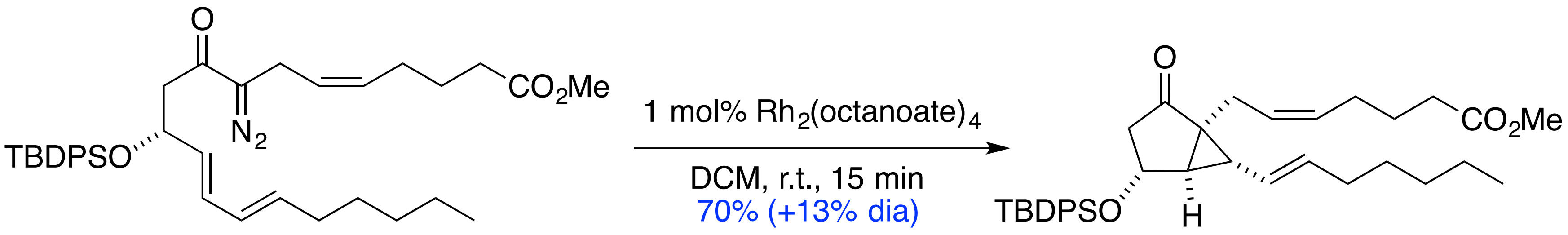
C-C insertion



JACS 1962 Danishefsky, 84, 879

Rh- and Cu-carbenes with α-diazocarbonyl compounds: examples

prostaglandins: diastereoselective (±)-8-*epi*-$PGF_{2\alpha}$

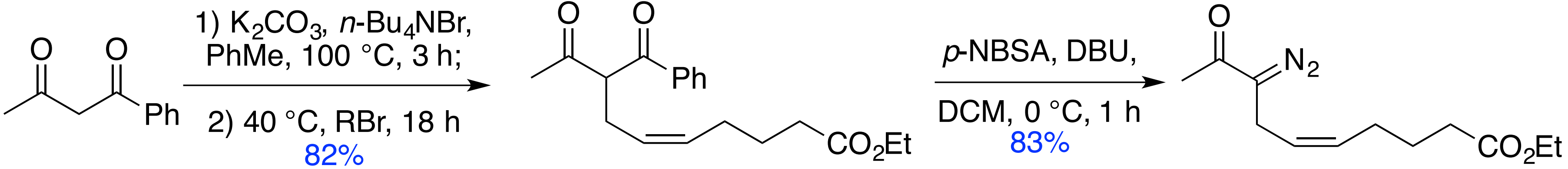


1 mol% $Rh_2(octanoate)_4$

DCM, r.t., 15 min

70% (+13% dia)

Taber, D. F.; Herr, R. J.; Gleave, D. M. *J. Org. Chem.* **1997**, *62*, 194–198.



1) K_2CO_3, *n*-Bu_4NBr, PhMe, 100 °C, 3 h;

2) 40 °C, RBr, 18 h

82%

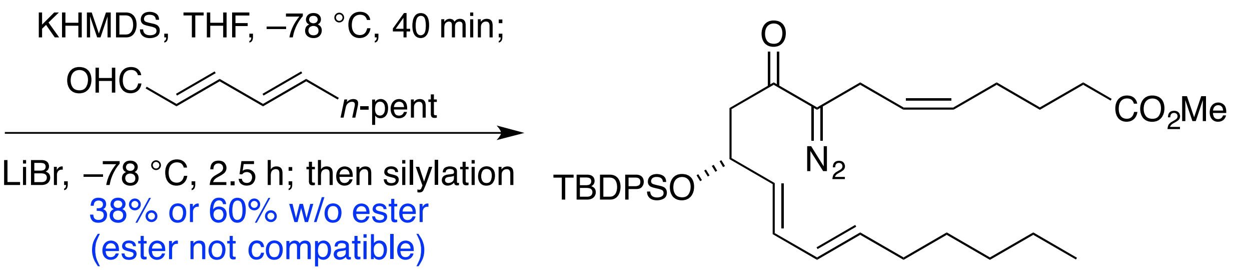
Regitz Diazo Transfer, RDT

p-NBSA, DBU,

DCM, 0 °C, 1 h

83%

Taber, D. F.; Gleave, D. M.; Herr, R. J.; Moody, K.; Hennessy, M. J. *J. Org. Chem.* **1995**, *60*, 2283–2285.



KHMDS, THF, –78 °C, 40 min;

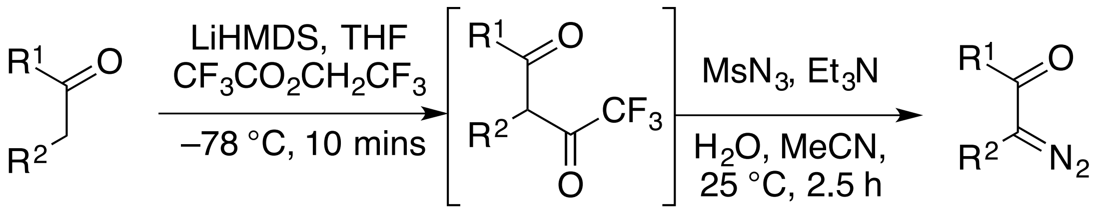
LiBr, –78 °C, 2.5 h; then silylation

38% or 60% w/o ester

(ester not compatible)

Rh- and Cu-carbenes with α-diazocarbonyl compounds: examples

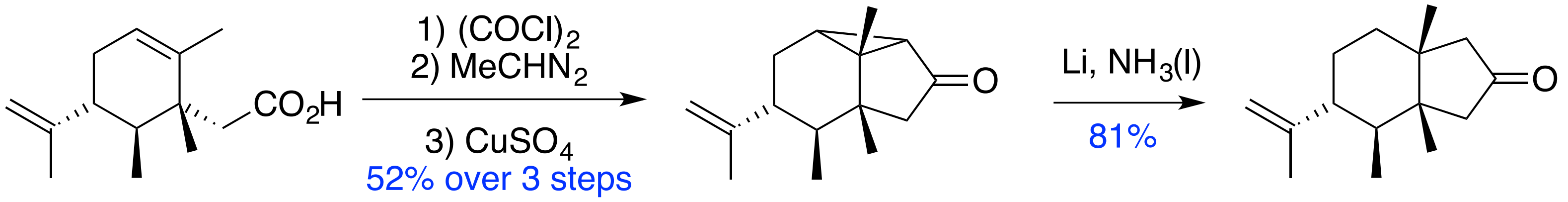
Improved synthesis of diazo-carbonyl compounds:



Danheiser, R. L.; Miller, R. F.;
Brisbois, R. G.; Park, S. Z.
J. Org. Chem. **1990**, *55*, 1959–1964.

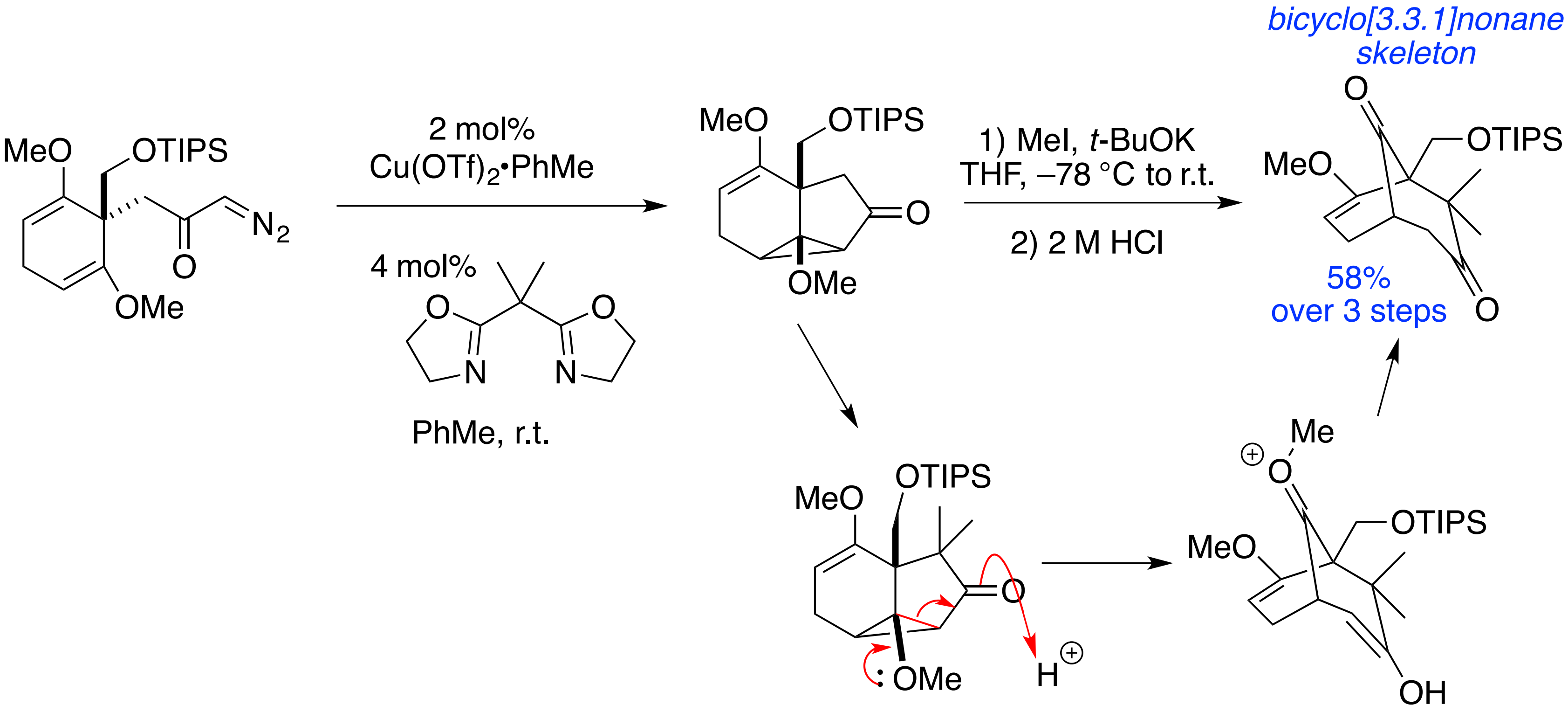
R^1, R^2 = alkyl, vinyl, aromatic, heteroaromatic; good to excellent yields

poly-fused polycycles



Srikrishna, A.; Vijaykumar, D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2583–2589.

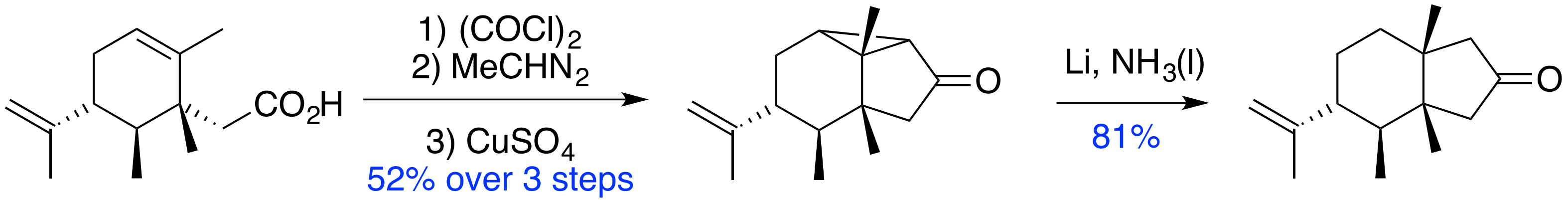
Rh- and Cu-carbenes with α-diazocarbonyl compounds: examples



Uwamori, M.; Nakada, M. *Tetrahedron Lett.* **2013**, *54*, 2022–2025.
Uwamori, M.; Saito, A.; Nakada, M. *J. Org. Chem.* **2012**, *77*, 5098–5107.

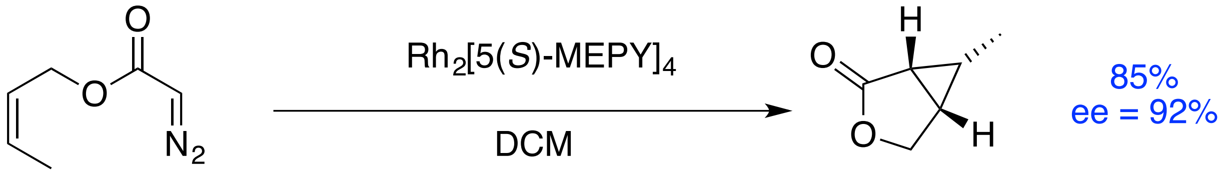
Rh- and Cu-carbenes with α-diazocarbonyl compounds: examples

poly-fused polycycles

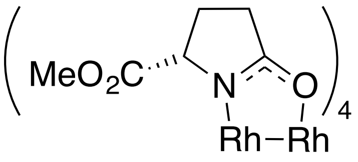


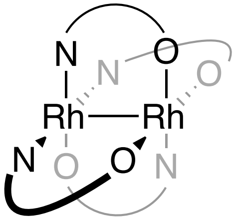
Srikrishna, A.; Vijaykumar, D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2583–2589.

enatioselective from simple achiral substrates



5(*S*)-MEPY =

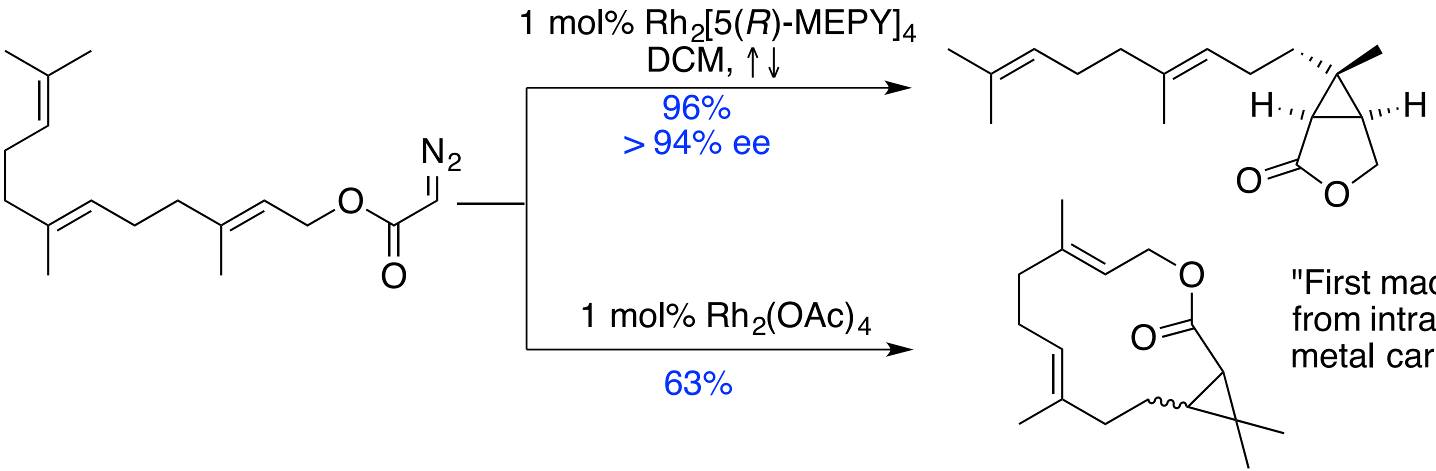




Hegedus, L. S.; Söderberg, B. C. G. *Transition metals in the synthesis of complex organic molecules, 3rd Ed.* (Sausalito, California: University Science Books, 2010), 216. See specifically references 143-145 for Chapter 6.

Rh- and Cu-carbenes with α-diazocarbonyl compounds: examples

catalyst effects regioselectivity for polyenes

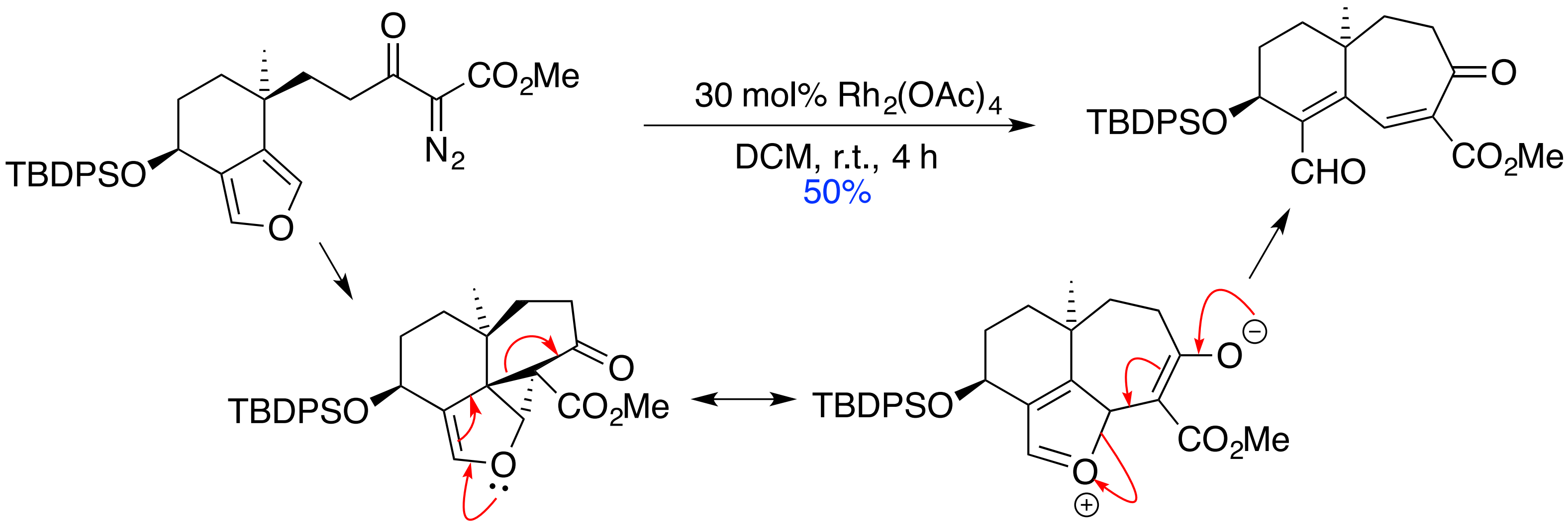


"First macrocylization from intramolecular metal carbene"

Rogers, D. H.; Yi, E. C.; Poulter, C. D. *J. Org. Chem.* **1995**, *60*, 941–945.
Doyle, M. P.; Protopopova, M. N.; Poulter, C. D.; Rogers, D. H. *J. Am. Chem. Soc.* **1995**, *117* , 7281–7282.
For a review of ligand effects: Padwa, A.; Austin, D. J. *Angew. Chem. Int. Ed.* **1994**, *33*, 1797–1815.

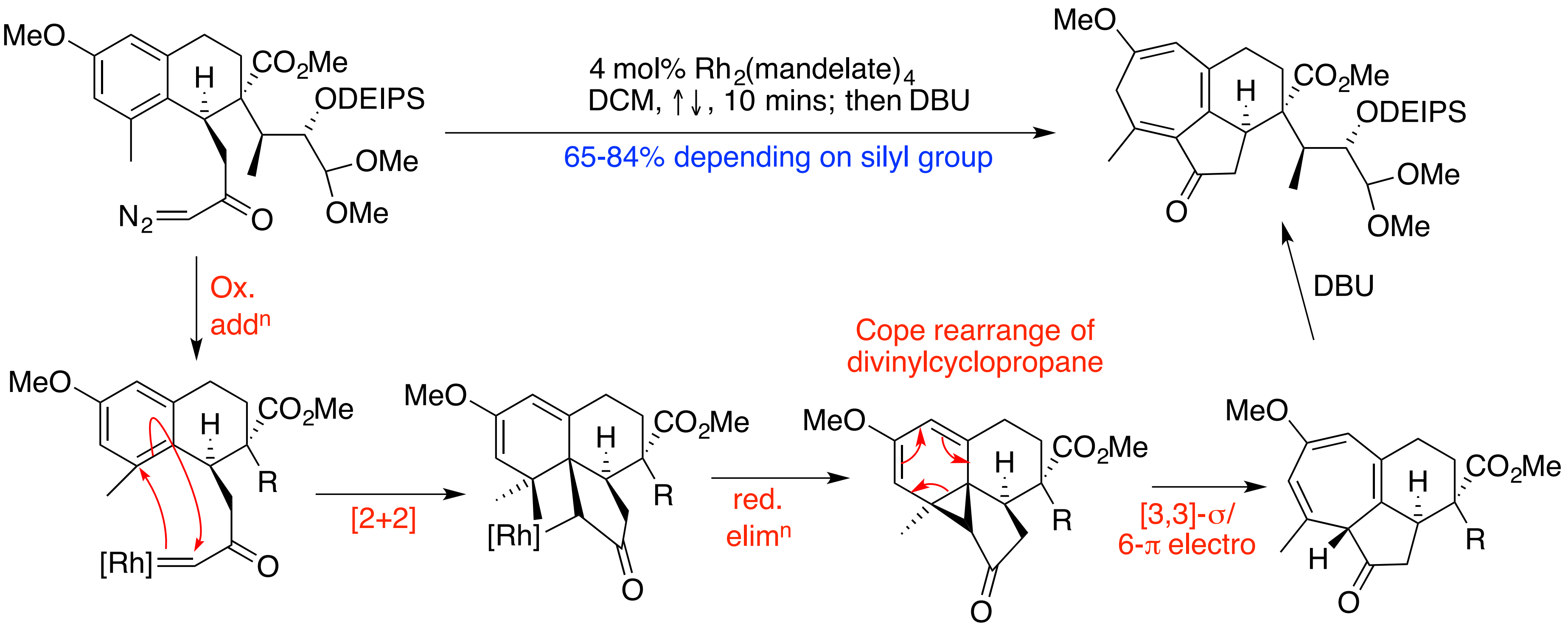
Rh- and Cu-carbenes with α-diazocarbonyl compounds: examples

may even have cyclopropanation with aromatics



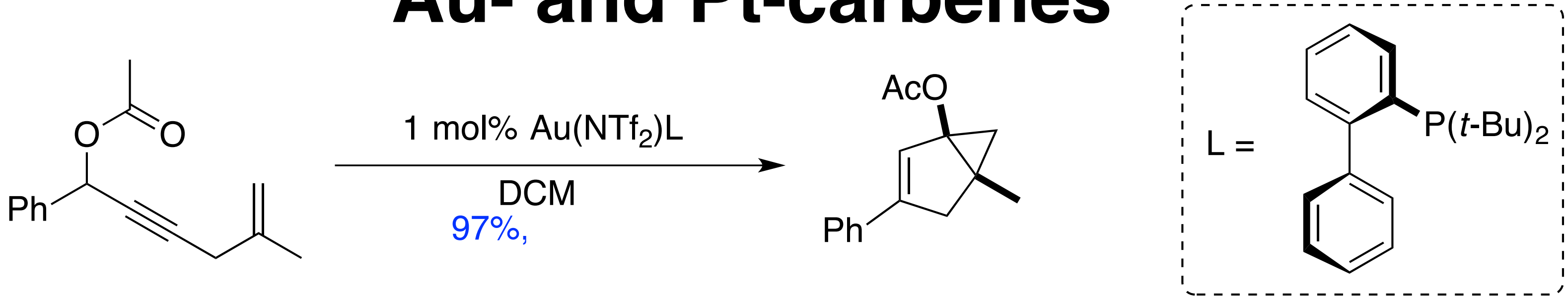
Hughes, C. C.; Kennedy-Smith, J. J.; Trauner, D. *Org. Lett.* **2003**, *5*, 4113–4115.

Rh- and Cu-carbenes with α-diazocarbonyl compounds: examples



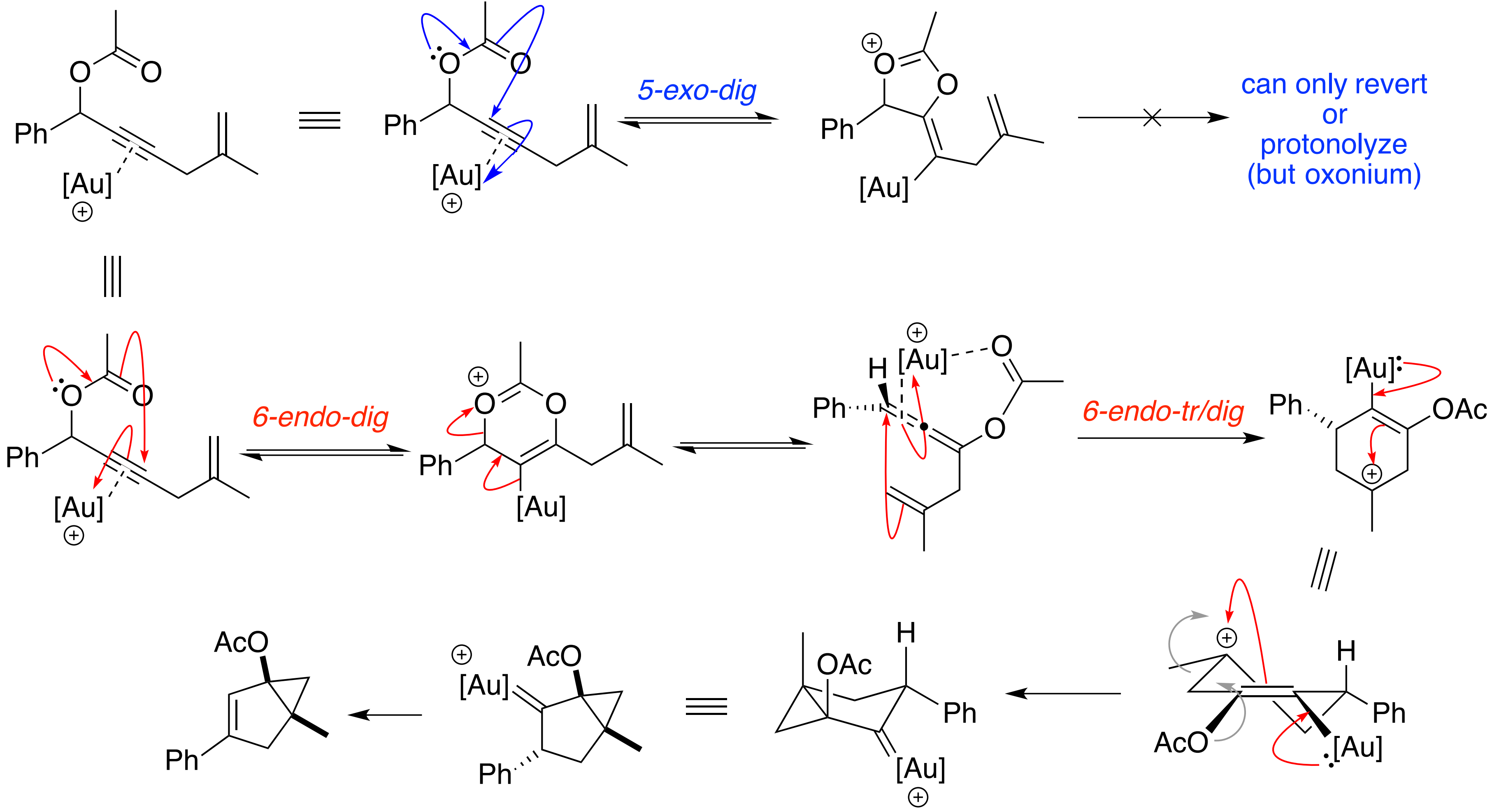
Frey, B.; Wells, A. P.; Rogers, D. H.; Mander, L. N. *J. Am. Chem. Soc.* **1998**, *120*, 1914–1915.
An improved synthesis: Zhang, H.; Appels, D. C.; Hockless, D.; Mander, L. N. *Tetrahedron Lett.* **1998**, *39*, 6577–6580.

Au- and Pt-carbenes

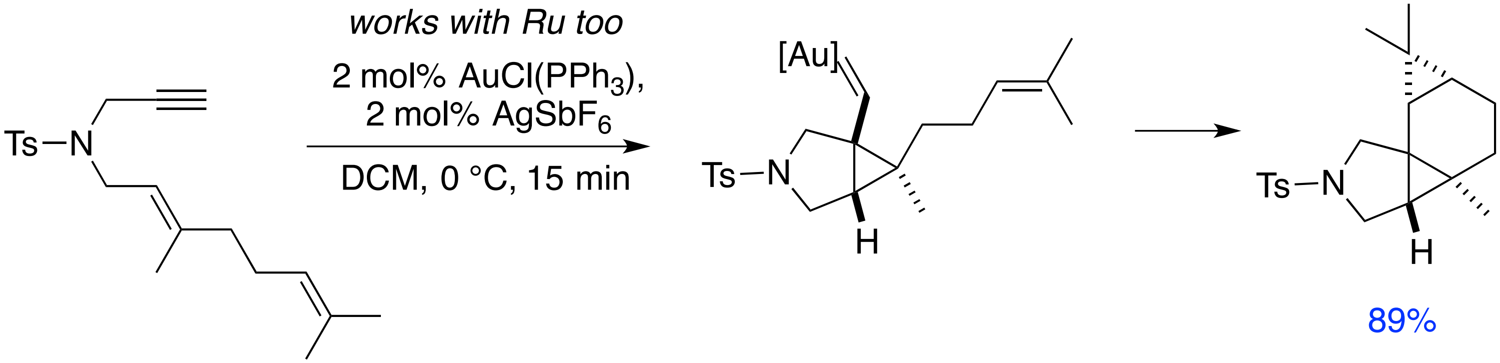


Buzas, A.; Gagosz, F. *J. Am. Chem. Soc.* **2006**, *128*, 12614–12615.

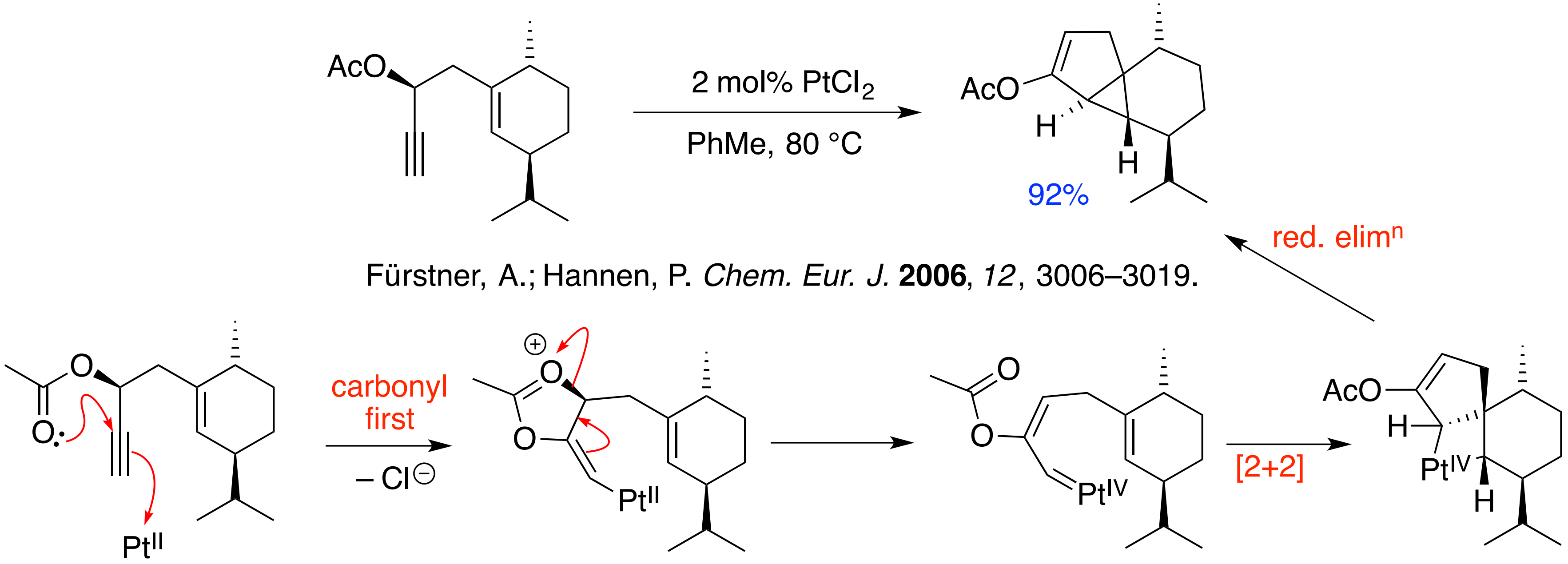
"large alkynophilic proton"



Au- and Pt-carbenes



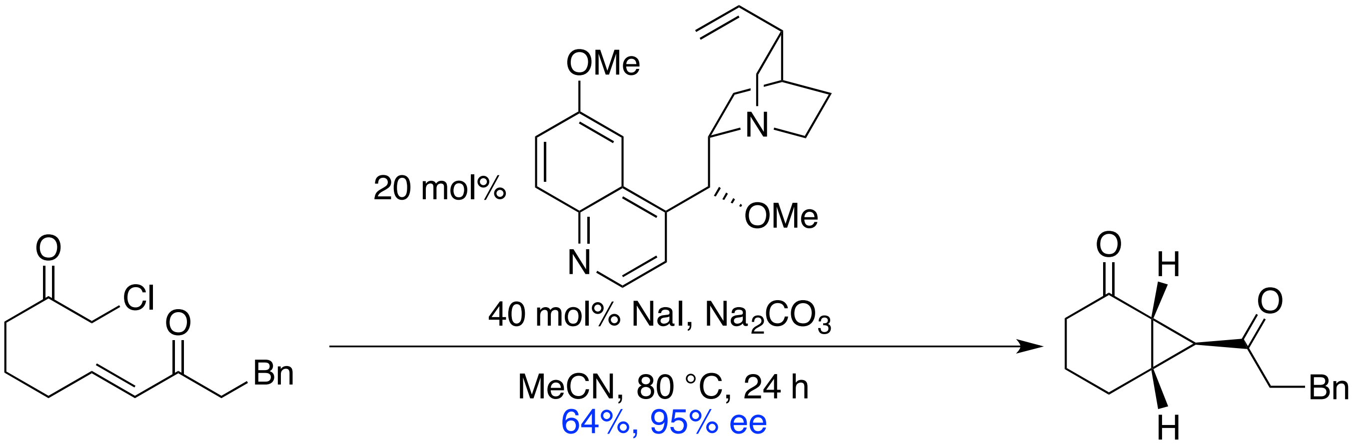
Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Jiménez Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1694–1702.

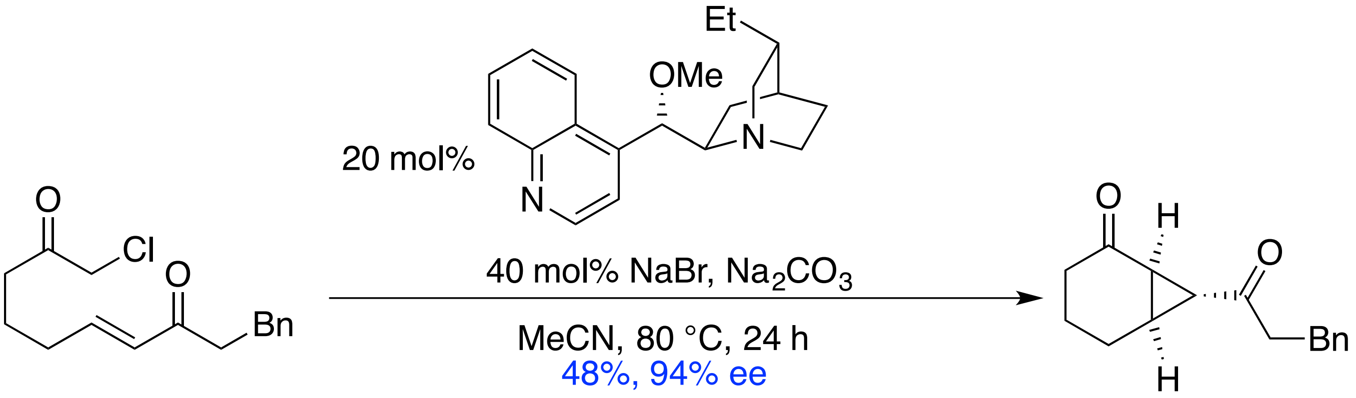


Fürstner, A.; Hannen, P. *Chem. Eur. J.* **2006**, *12*, 3006–3019.

Non-carbene [2+1] reactions

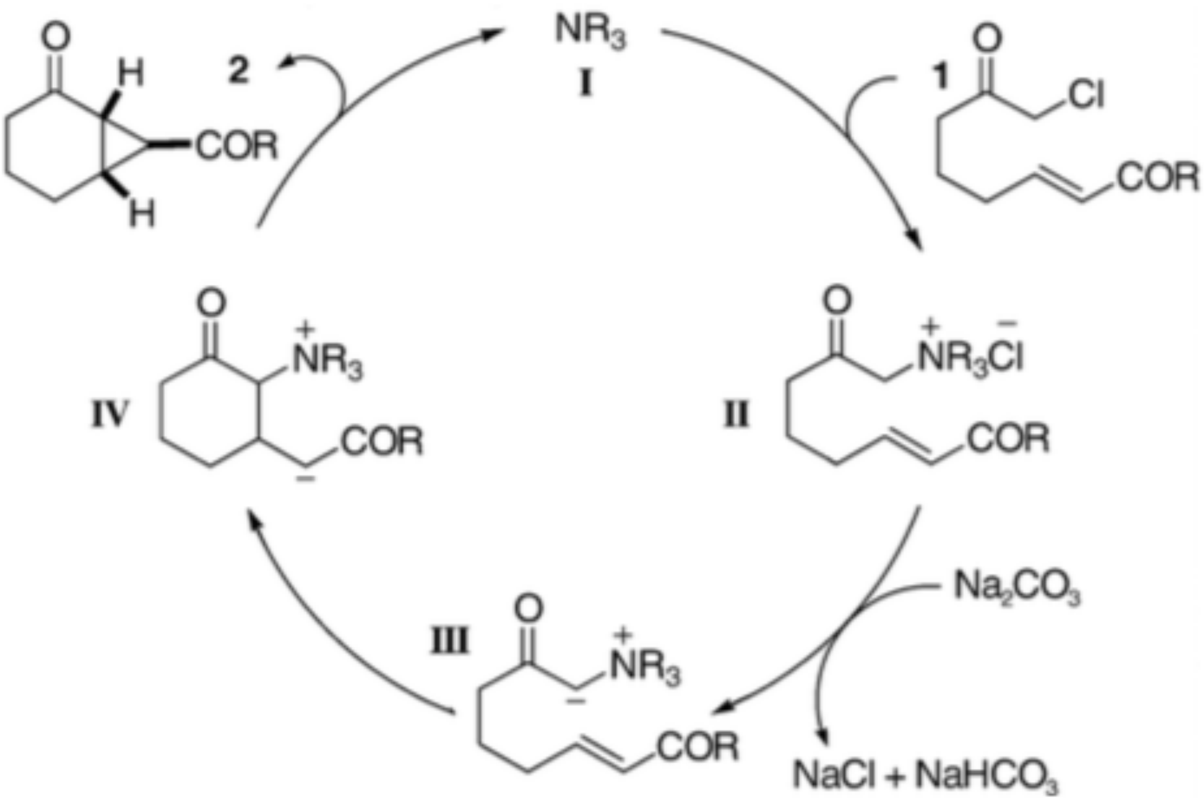
Organocatalyzed [2+1] additions





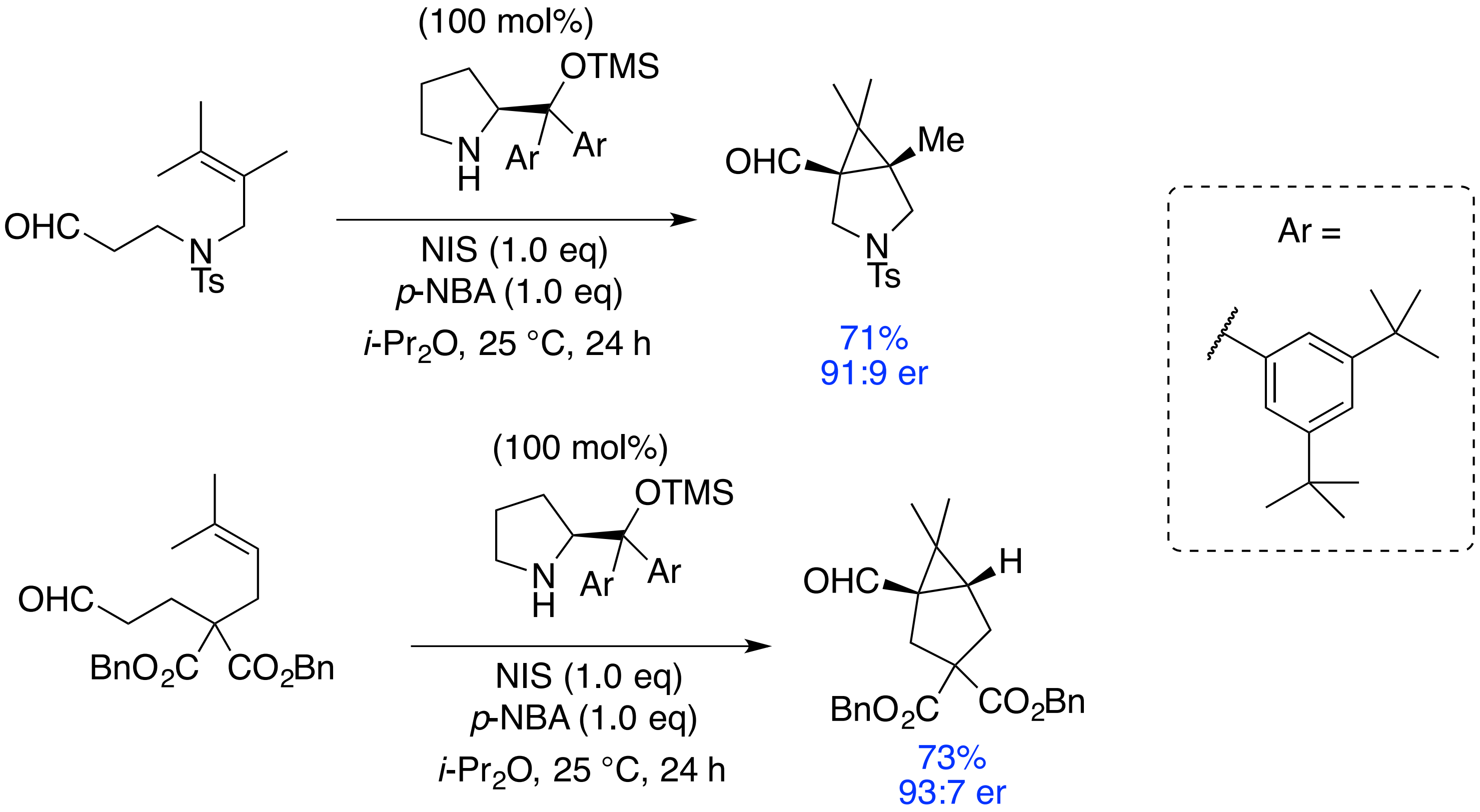
Bremeyer, N.; Smith, S. C.; Ley, S. V.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 2681–2684.

Organocatalyzed [2+1] additions



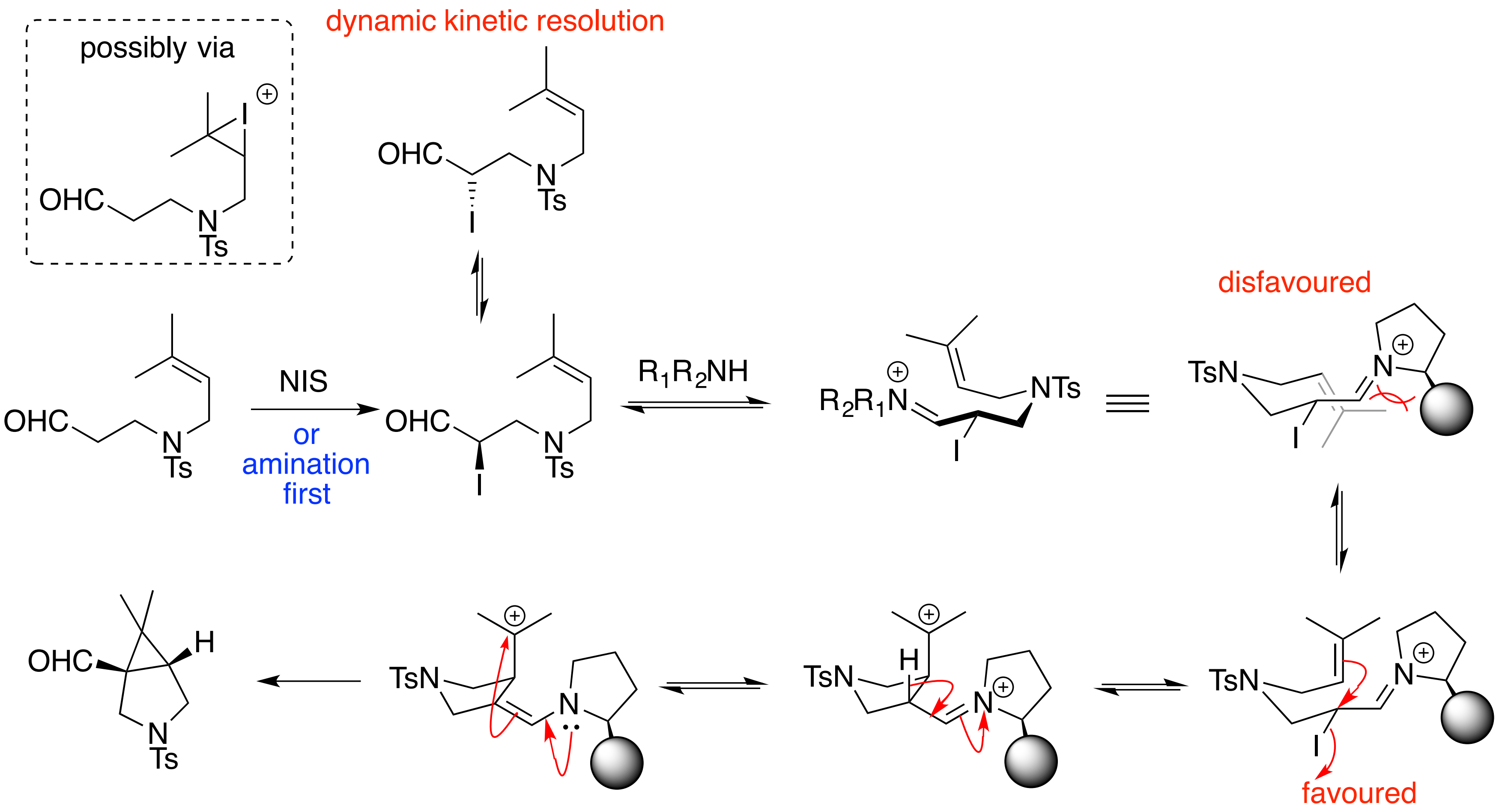
Scheme 1. Proposed catalytic cycle.

Organocatalyzed [2+1]-cyclization



Luo, C.; Wang, Z.; Huang, Y. *Nat. Commun.* **2015**, *6*, 10041.

Formally an enantioselective [2+1]-cyclization but really a 1,5- then 1,3-cyclization



Conclusions

Cycolpropanes exist as targets themselves or intermediates with interesting reactivity.

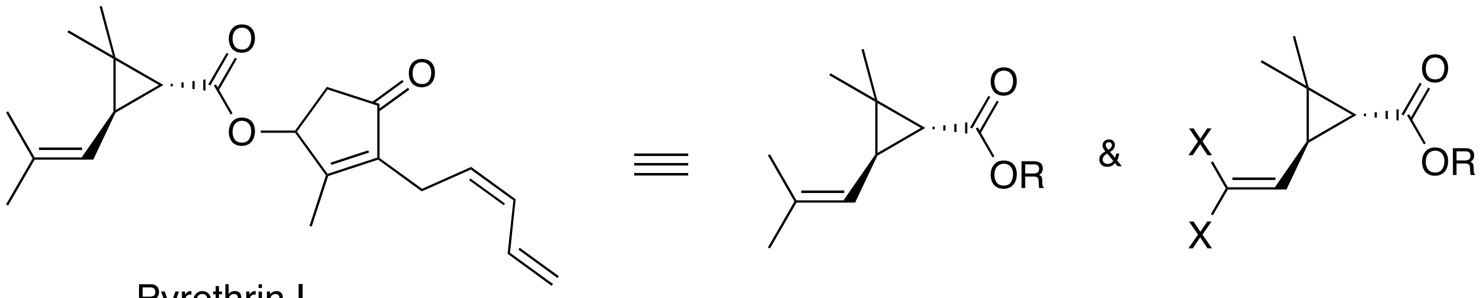
Logical breakdown of cyclopropanations into categories of synthons

1. **Make 1 C-C bond in cyclopropane i.e. 1,3-cylizations**
    1. **Break 2 σ-bonds (Wurtz, eliminate HX, etc.)**
    2. **Break 1 σ-bond and 1 π-bond (add to carbonyl, alkene, etc.)**
    3. **Break 2 π-bonds (excite π-bond)**
2. **Make 2 C-C bonds in cycopropane**
    1. **Carbene additions to π-bonds**
    2. **Carbene insertions in C-H or C-C bonds**
    3. **1,1-dication or 1,1-dianion and respective partner**

Carbene chemistry involoving α-diazocarbonyl compounds is a rich and fruitful field.

Thanks for your attention!

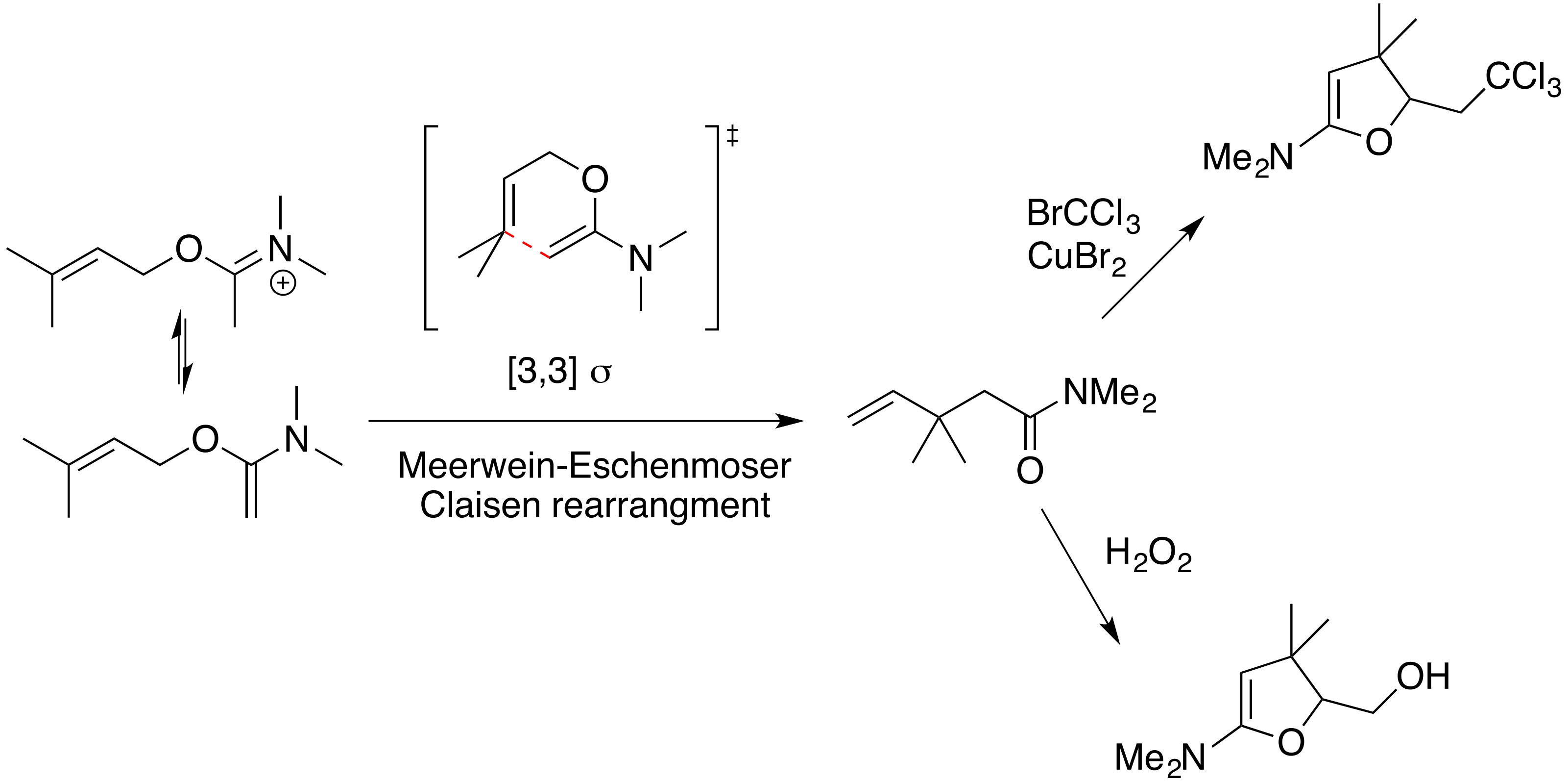
Reserve Slides

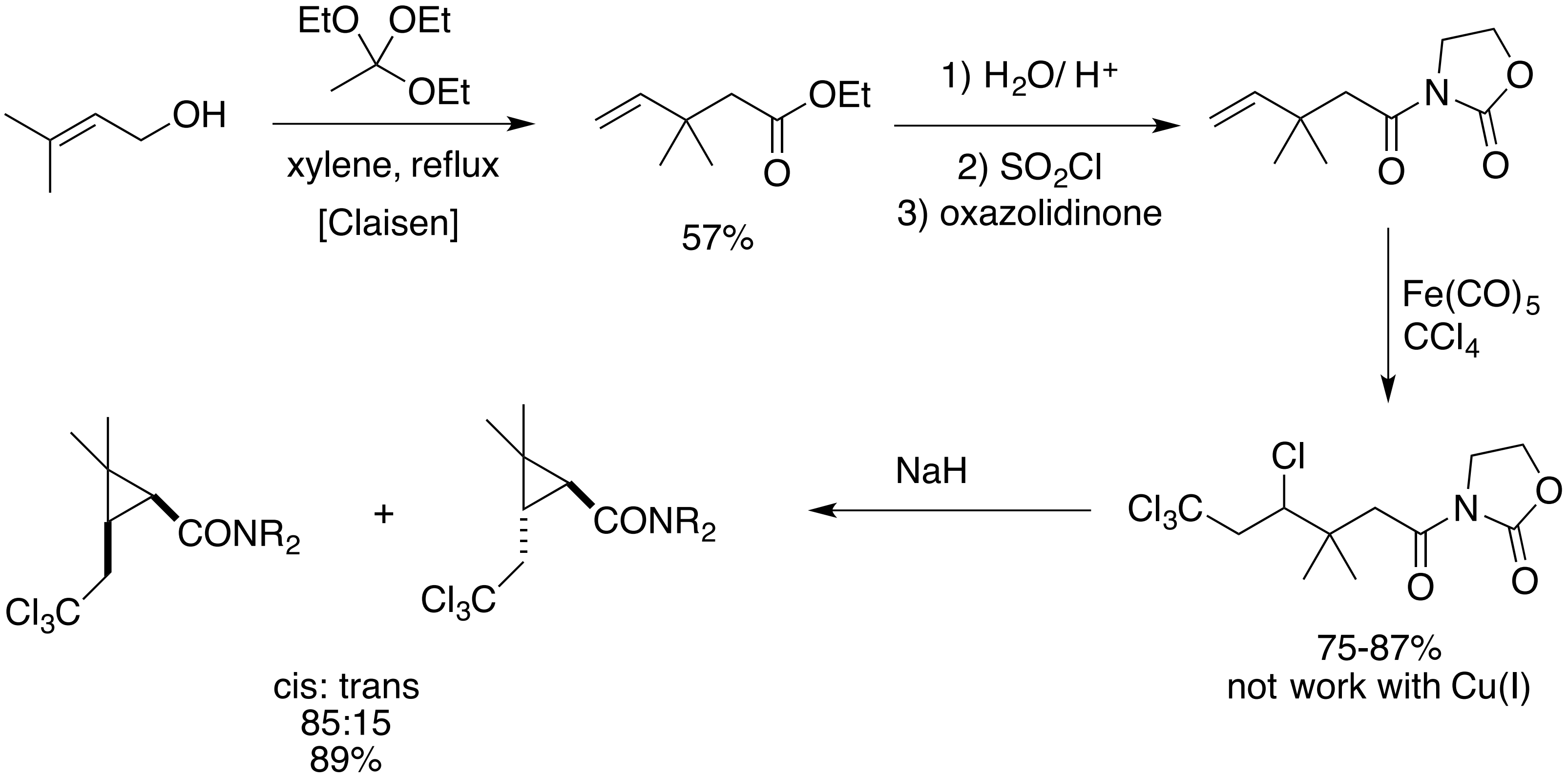


Pyrethrin I

X = Br, Cl

JOC, 1984, 49, 2682-2687
JOC, 1986, 51, 5429-5433



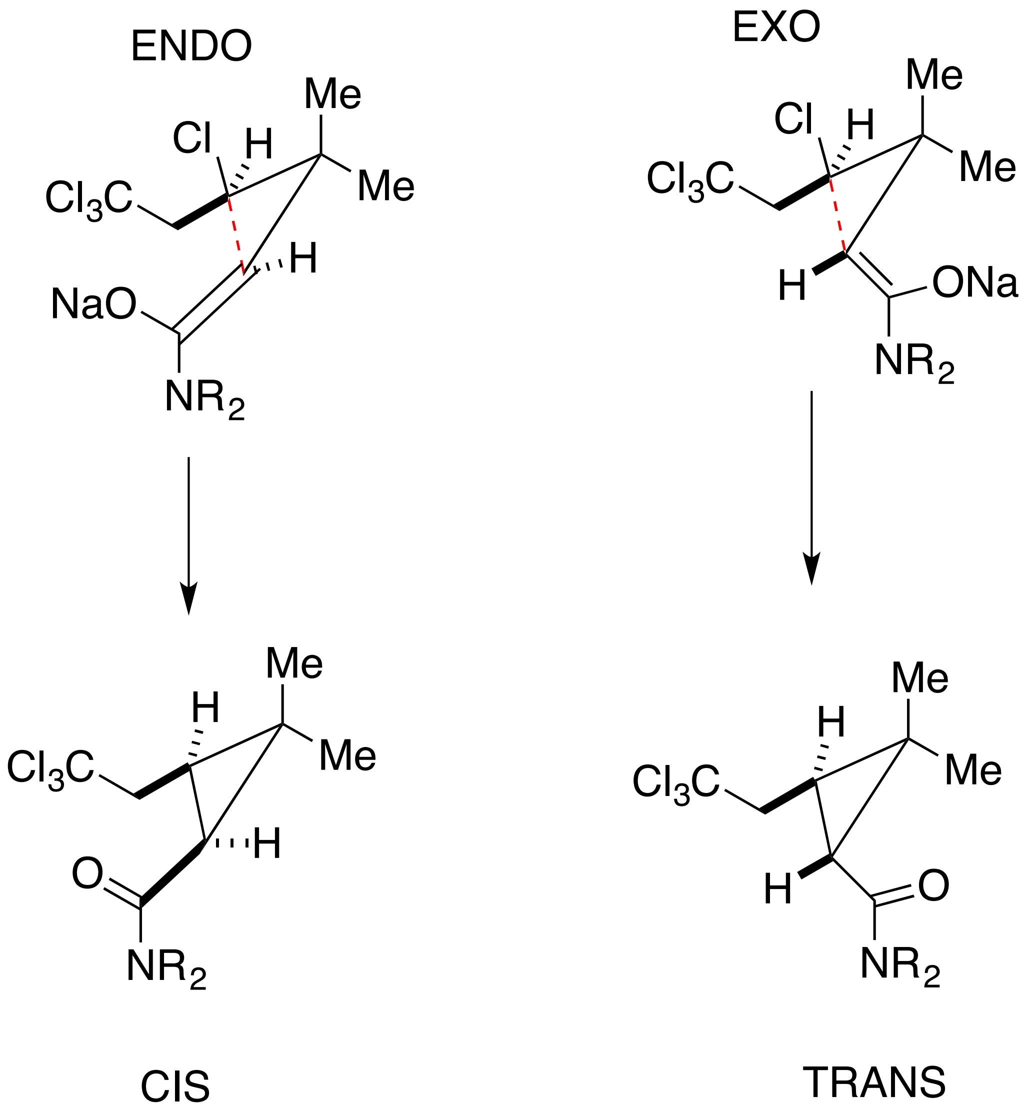


57%

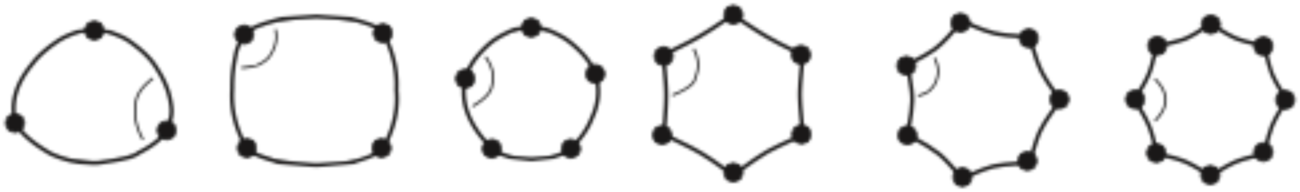
75-87%
not work with Cu(I)

cis: trans
85:15
89%

From cis-enolate



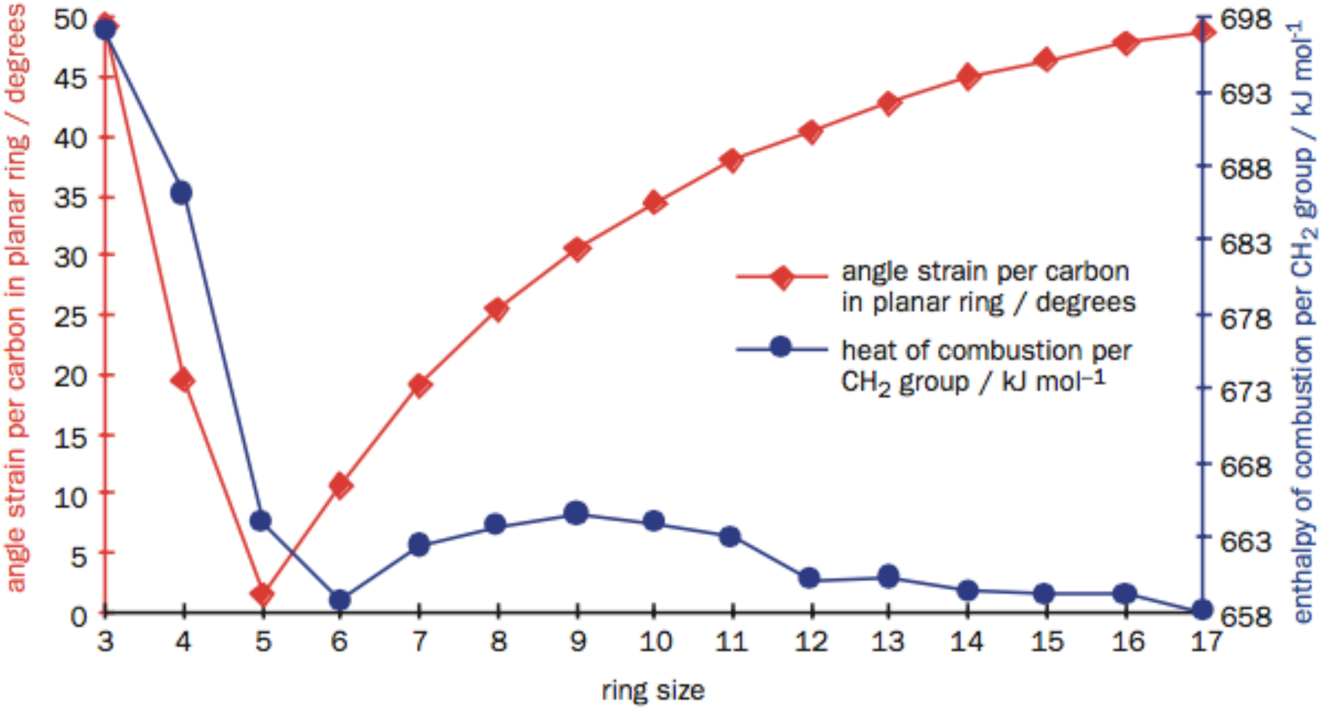
Reserve slide: assumption for planar rings



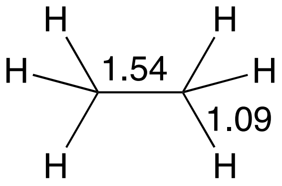
all internal angles 109.5°

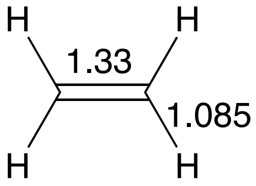
Number of atoms in ring	Internal angle in planar ring	109.5°— internal angle[a]
3	60°	49.5°
4	90°	19.5°
5	108°	1.5°
6	120°	–10.5°
7	128.5°	–19°
8	135°	–25.5°

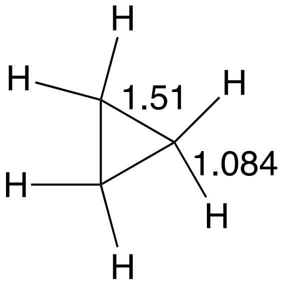
[a] A measure of strain per carbon atom.



Angles and Bonds

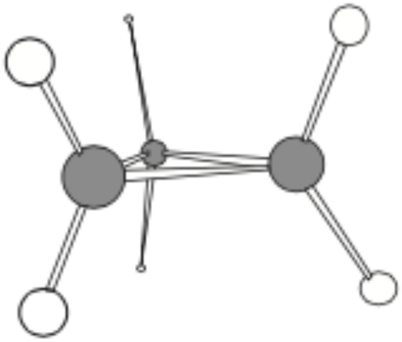

HCH = 109.5°
CCH = 111.2°


HCH = 117°
CCH = 121.5°

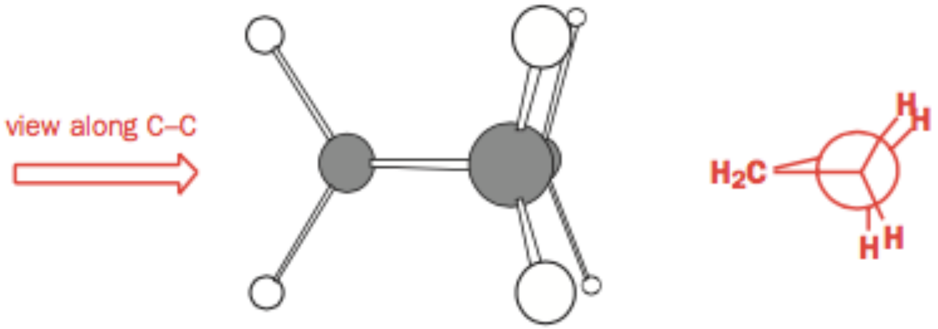

HCH = 114°
CCC = 60° (by def.)
CCH = 123°

Conformation: ring strain

Cyclopropane

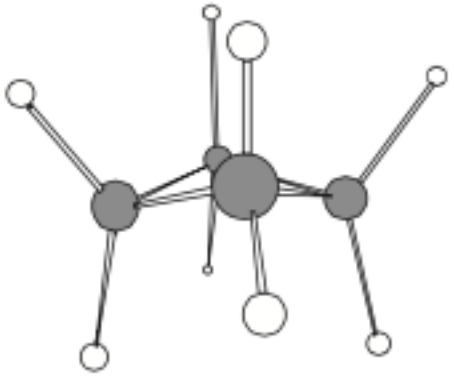


a side-on view of cyclopropane

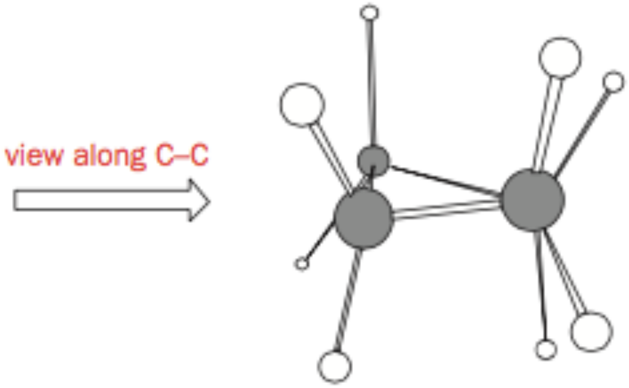


viewing cyclopropane (almost) along a C–C bond shows that all the C–H bonds are eclipsed

Cyclobutane

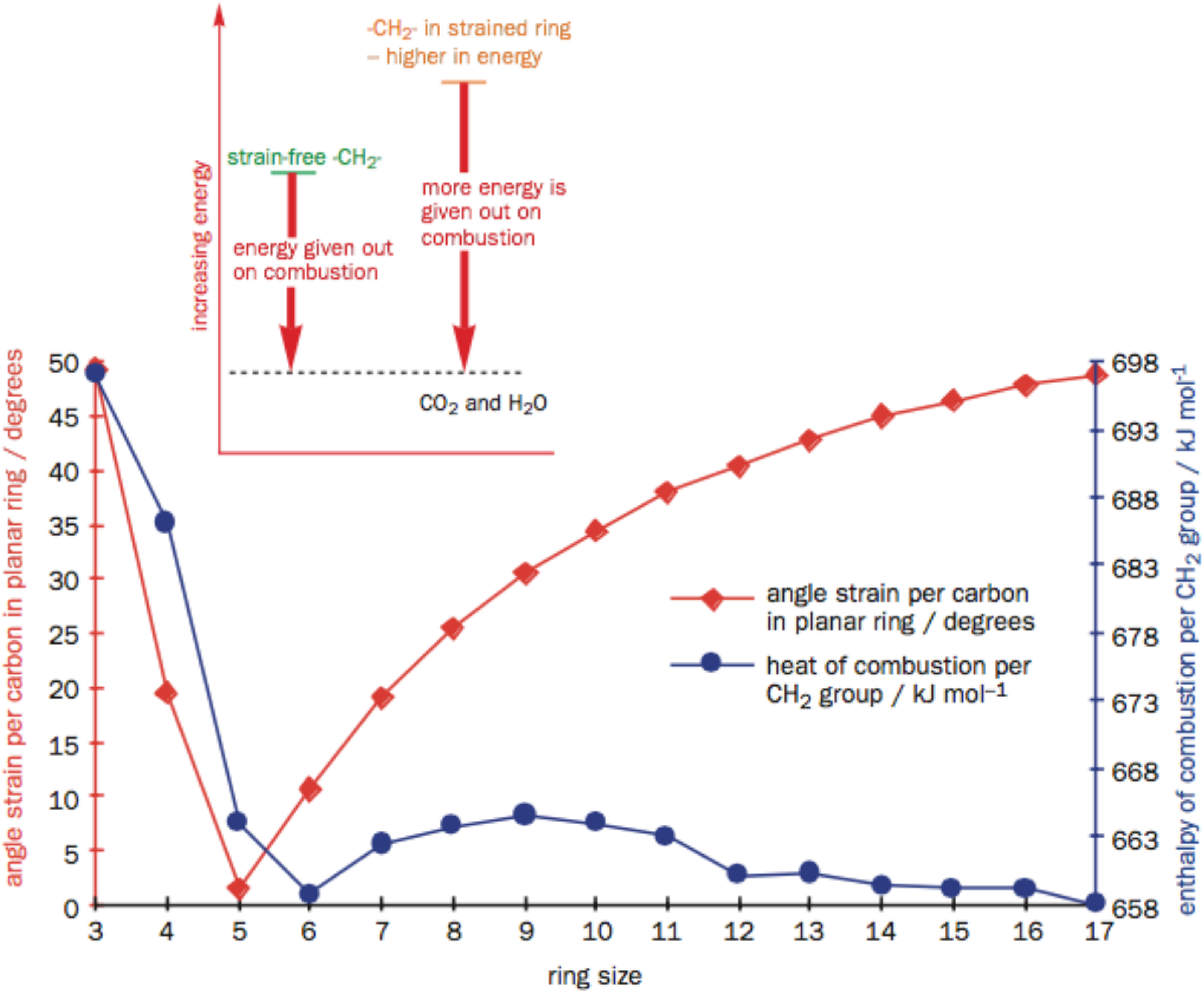


the puckered 'wing' conformation of cyclobutane



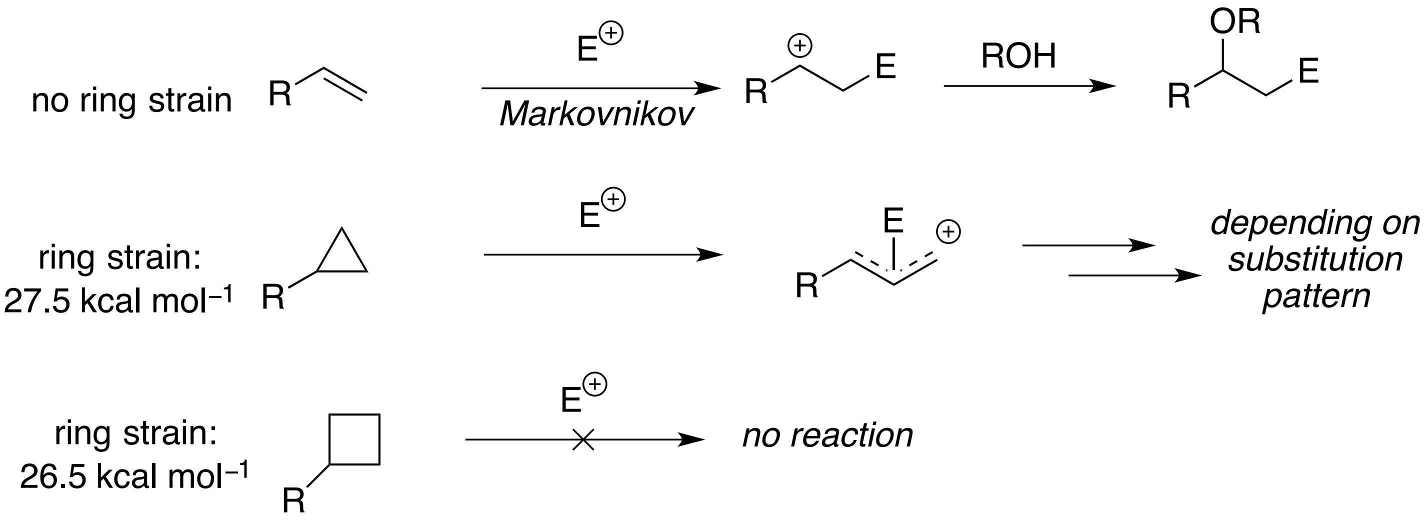
C–H bonds no longer fully eclipsed

Angular Strain and Gauche/ Eclipsing Strain
Pfitzer and … strain


-CH_2- in strained ring
– higher in energy
strain-free -CH_2-
more energy is given out on combustion
energy given out on combustion
increasing energy
CO_2 and H_2O
angle strain per carbon in planar ring / degrees
50
45
40
35
30
25
20
15
10
5
0
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
ring size
698
693
688
683
678
673
668
663
658
enthalpy of combustion per CH_2 group / kJ mol^{-1}
angle strain per carbon in planar ring / degrees
heat of combustion per CH_2 group / kJ mol^{-1}

How do you explain the following observation?

“Ring strain confers exceptional reactivity to the cyclopropane ring.”
De Simone, F; Waser, J. *Chimia*, **2009**, *63*, 162-167.

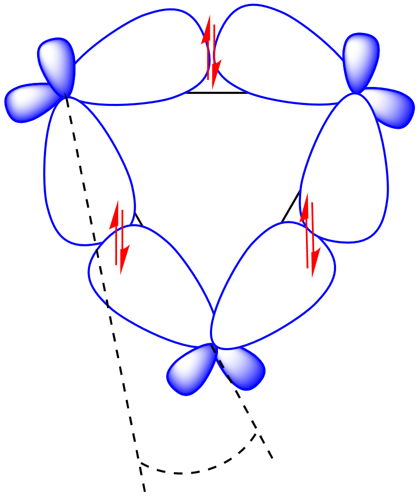


c.f. C–C bond dissociation energy is ~83-85 kcal mol^{-1}

Ring strain might provide a strong thermodynamic driving force
for reaction but is doesn’t explain the *reactivity*.
A suitable answer must therefore invoke bonding.

Problem: tightest angle between any AOs is 90° (e.g. orthogonal p-orbitals) but in cyclopropane we have to accomodate a bond angle of 60°

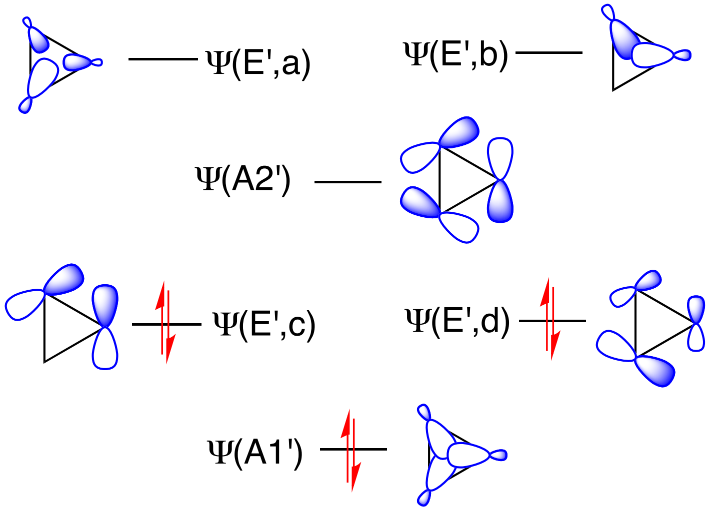
Pauling τ-bond treatment



22° and
~20% less effective overlap

Coulson-Moffit orbitals:
sp^3-hybridized C AOs orbitals

Hückel σ/π-bond treatment



Walsh orbitals:
sp^2-hybridized C AOs

N.B.: This model is generally accepted (as is Hückel's approach to bonding) **but** it is likely wrong as it may not represent the ground state: Specifically, relative energies of Ψ(A2') with Ψ(E',a) and Ψ(E',b) are switched when valence AOs are used as the basis set instead of methylene and choosing methylene as basis set removes C–H bonds from MO picture See [Wiberg, K. B. *Acc. Chem. Res.* **1996**, *29*, 229–234] and [reference 17 therein]. Walsh orbitals work in other cases outside of cyclopropane.

"the overall distribution of electrons [...] is exactly the same" [in the two models]. – Ian Fleming
At least theoretically and mathematically, and assuming that the basis sets are valid (interconvertible).

An excellent resource for Walsh's theory using methylene as basis set:
http://www.bluffton.edu/~bergerd/chem/walsh/derive.html, and references therein for the full story.

Applying Bent's rule

The H−C−H angle in cyclopropane is measured as 114 degrees. From this, and using Coulson's Theorem

$$1+\sqrt{\lambda^2}\cos(114)=0$$

where λ represents the amount of p-character in the AOs directed along the C−H bond in cyclopropane and can be deduced to be $sp^{2.46}$ hybridized. Now, using the equation

$$\frac{2}{1+\lambda_{\mathrm{C-H}}}+\frac{2}{1+\lambda_{\mathrm{C-C}}}=1$$

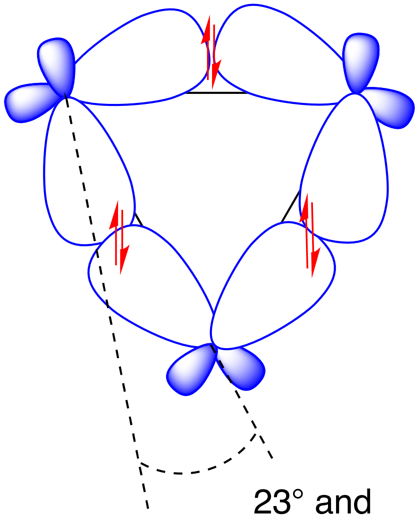
(which says that summing the s-character over all AOs at a given carbon must be total to 1) we find that $\lambda_{c-c} = 3.74$ so that the re-hybridized AOs directed along the C−C bond are $sp^{3.74}$ hybridized. We see that the C−C bonds in cyclopropane are very high in p-character (c.f. below for ethene). It is this high p-character that allows cyclopropane to behave in a similar fashion to an alkene in terms of stabilizing an adjacent charge or undergoing electrophilic substitution with bromine. Also tells us C−C−C interorbital angle of 105.5 degrees.

A similar treatment for ethene gives $sp^{2.20}$ for the AOs along the C−H bonds and $sp^{4.33}$ for along the C−C bonds (i.e. Pauling's 2 x τ-bonds as a point of comparison for cyclopropane). ((Or a single p-orbital and an $sp^{1.7}$ C−C directionalized "σ-bond" as in Hückel's treatment)).

http://chemistry.stackexchange.com/questions/10653/why-does-cyclopropane-give-bromine-water-test/10666#10666
And, https://en.wikipedia.org/wiki/Bent%27s_rule

Applying Bent’s rule

Coulson's theory and Bent's rule



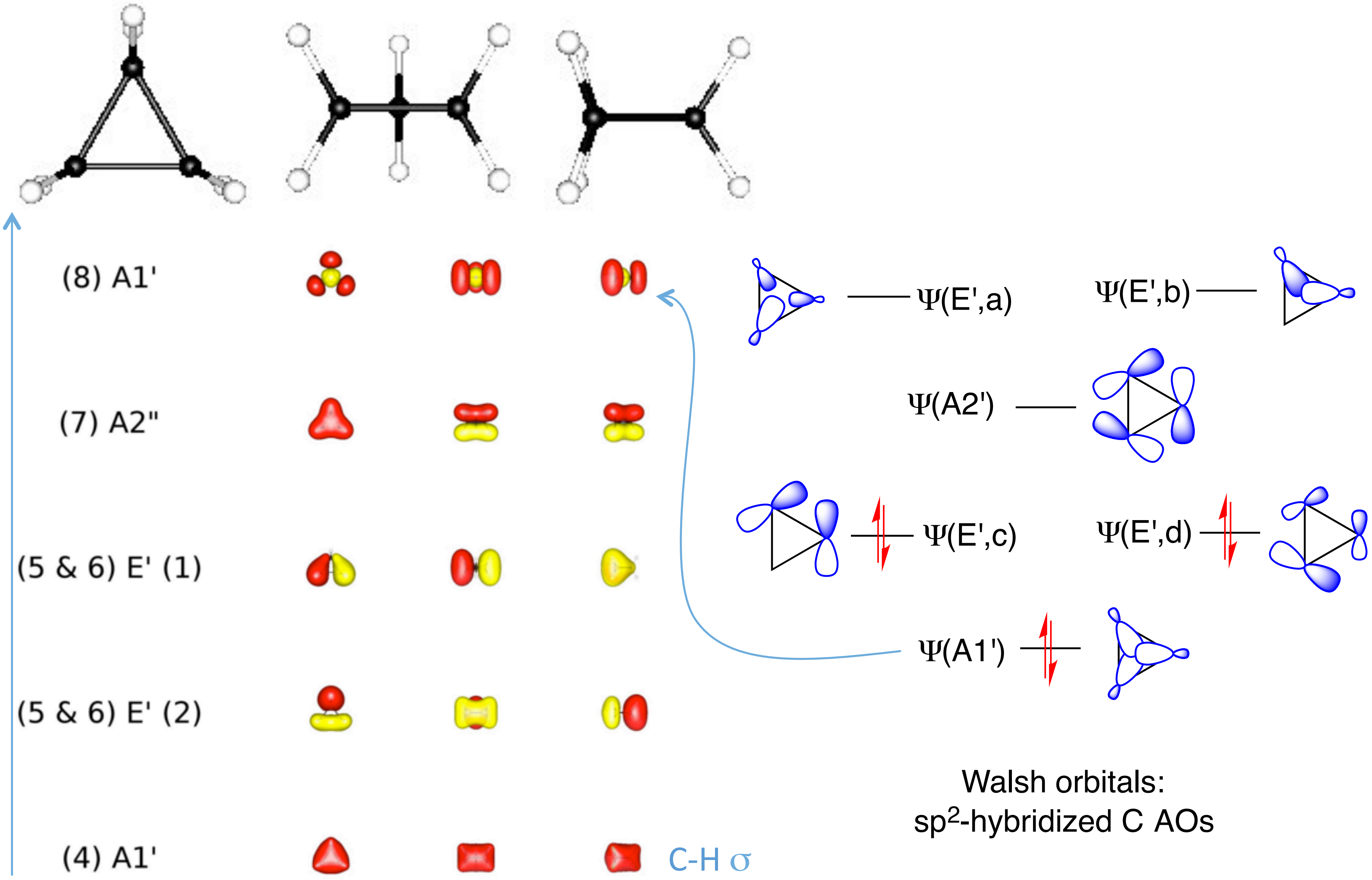
23° and interorbital angle is 105.5°

HCH angle	Hybridization of C AOs along C–H bond axis	Hybridization of C AOs associated with C–C bond	interorbital angle
114° (measured)	$sp^{2.46}$	$sp^{3.74}$	105.5° (deduced)
approximated as 120°	sp^2	sp^5	102° (deduced)

N.B.: for $sp^{3.74}$-hybridized C atom AOs associated with the C–C bonds we have assumed that the C atom AOs associated with the C–H bonds are fixed/ directionalized exactly along this axis.

sp^2 (C–C) and sp^5 (C–H) AOs have also been used with incorrect approximations, at least as incorrect as using sp^2-hybridized AOs in ethene, but this model does contain some physical significance as it qualitatively explains cyclopropane deformation density.

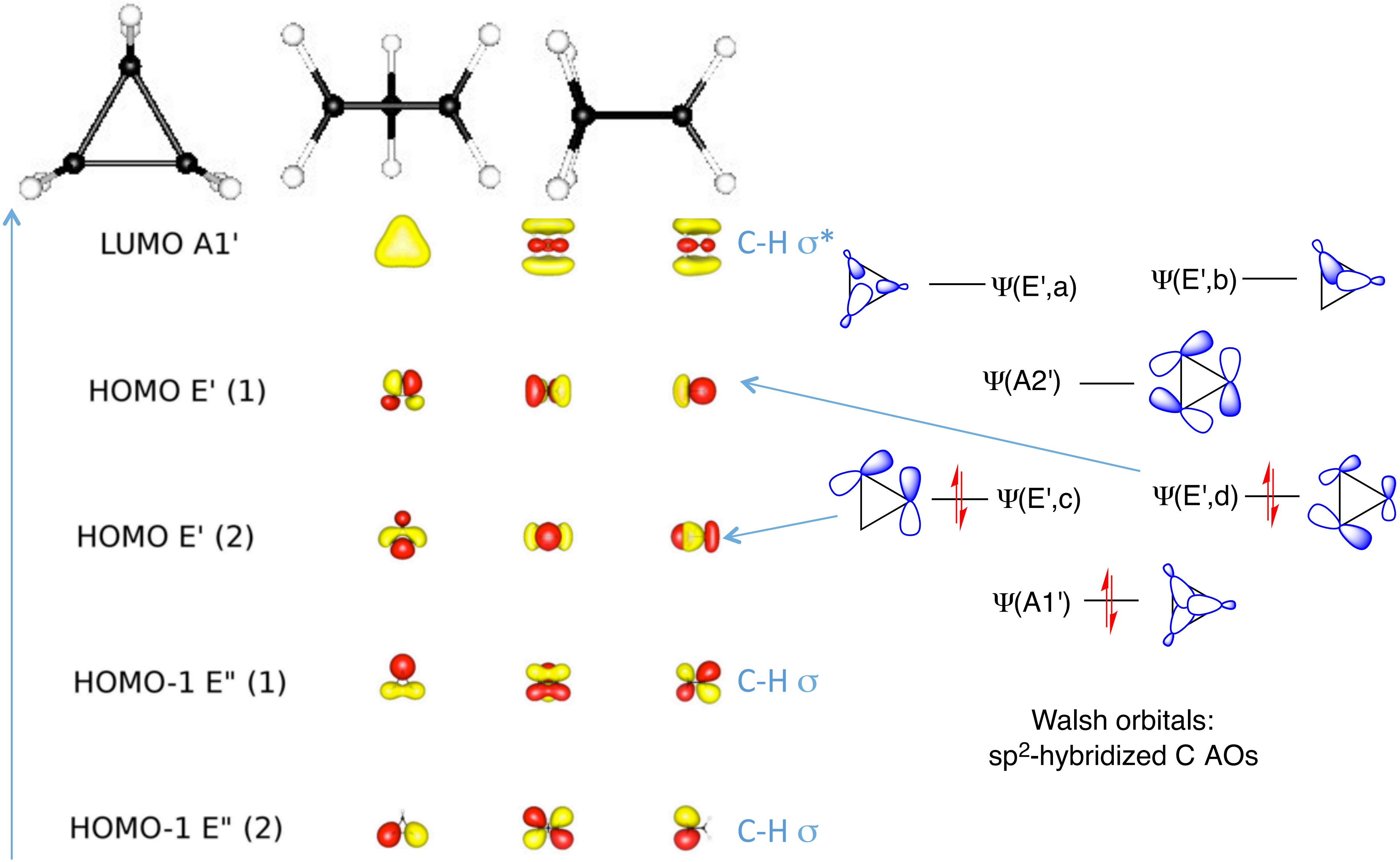
Bonding by use of number crunching



Walsh orbitals:
sp^2-hybridized C AOs

6 H atoms and 4 C atoms gives 18 valence AOs, and 18 MOs. All occupied (18 electrons) MOs and LUMO are depicted below. Calculation from valence orbitals, BP86/cc-PVTZ, D_{3h}.

Bonding by use of number crunching



LUMO A1' C-H σ^*

HOMO E' (1)

HOMO E' (2)

HOMO-1 E" (1) C-H σ

HOMO-1 E" (2) C-H σ

$\Psi(E',a)$

$\Psi(E',b)$

$\Psi(A2')$

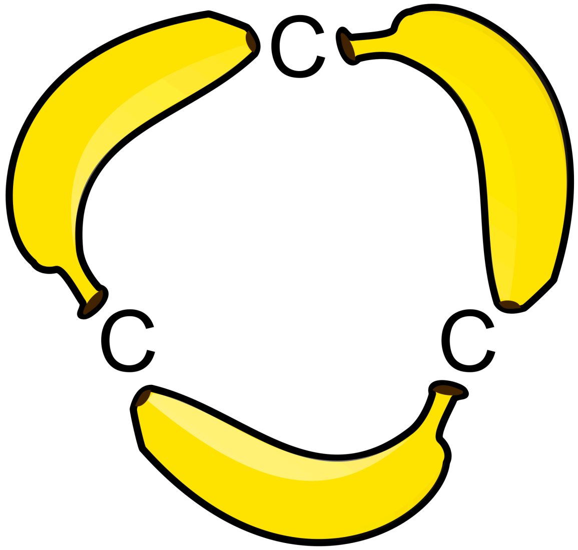
$\Psi(E',c)$

$\Psi(E',d)$

$\Psi(A1')$

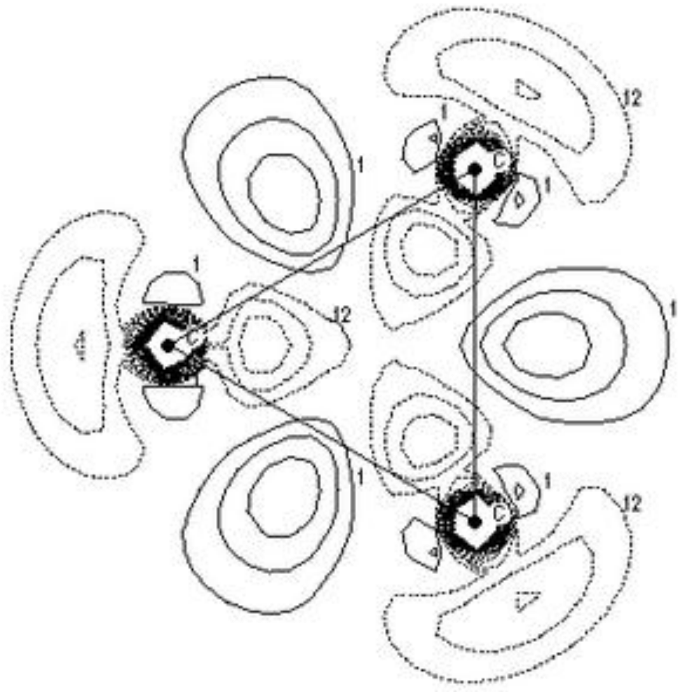
Walsh orbitals:
sp^2-hybridized C AOs

6 H atoms and 4 C atoms gives 18 valence AOs, and 18 MOs. All occupied (18 electrons) MOs and LUMO are depicted below. Calculation from valence orbitals, BP86/cc-PVTZ, D_{3h}.



Banana Bond

X-ray diffraction of *cis*-1,2,3-tricyanocyclopropane: Hartman, A.; Hirshfeld, F. L. *Acta Crystallographica* **1966**, *20* (1), 80–82.



Cyclopropane Electron cloud

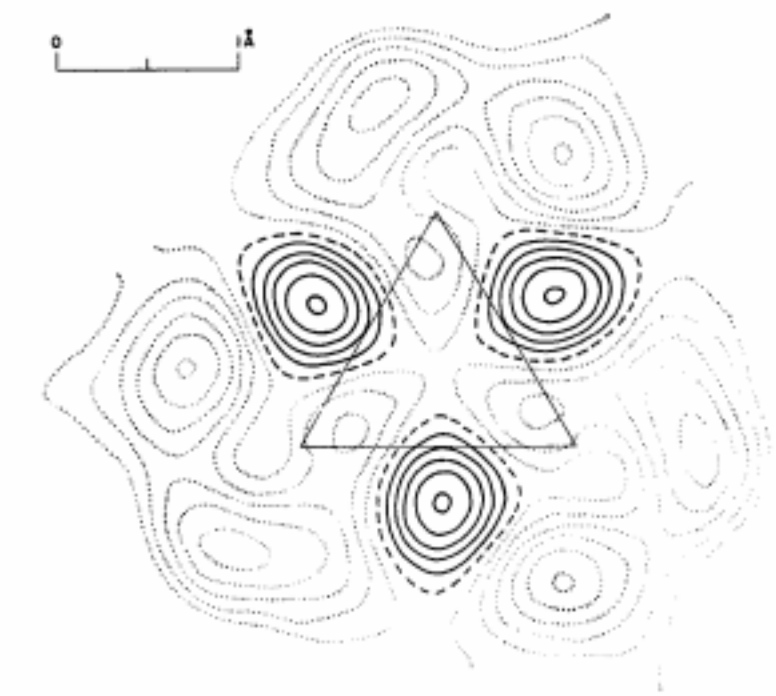
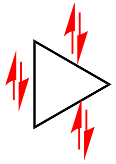
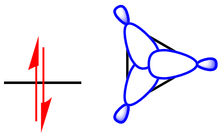
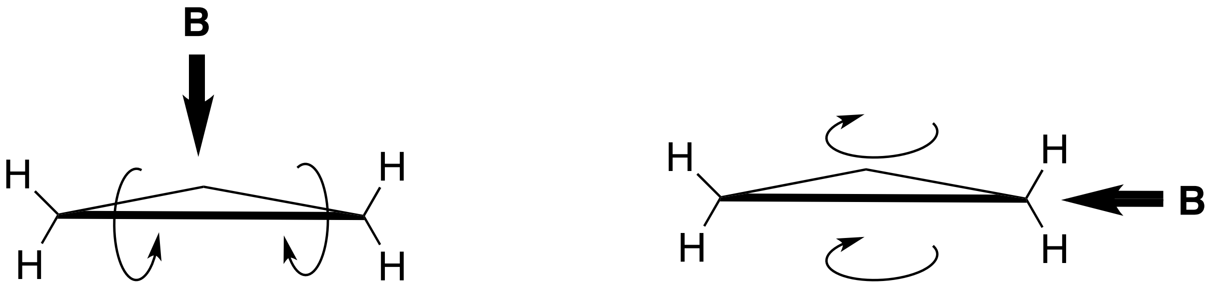


Fig. 2. Difference density in plane of cyclopropane ring. Contour interval 0·01 e.Å^{-3}, zero contour broken. Estimated standard deviation averages 0.017 e.Å^{-3}.

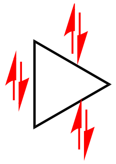
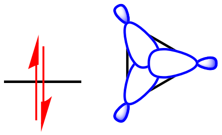
σ-aromaticity???

Dewar 1984		6 σ-electrons	4n + 2 (n=1)	aromatic
Cremer, Gauss 1986	 Ψ(A1') 3-centre, 2-electron bond	2 "surface" electrons	4n + 2 (n=0)	aromatic

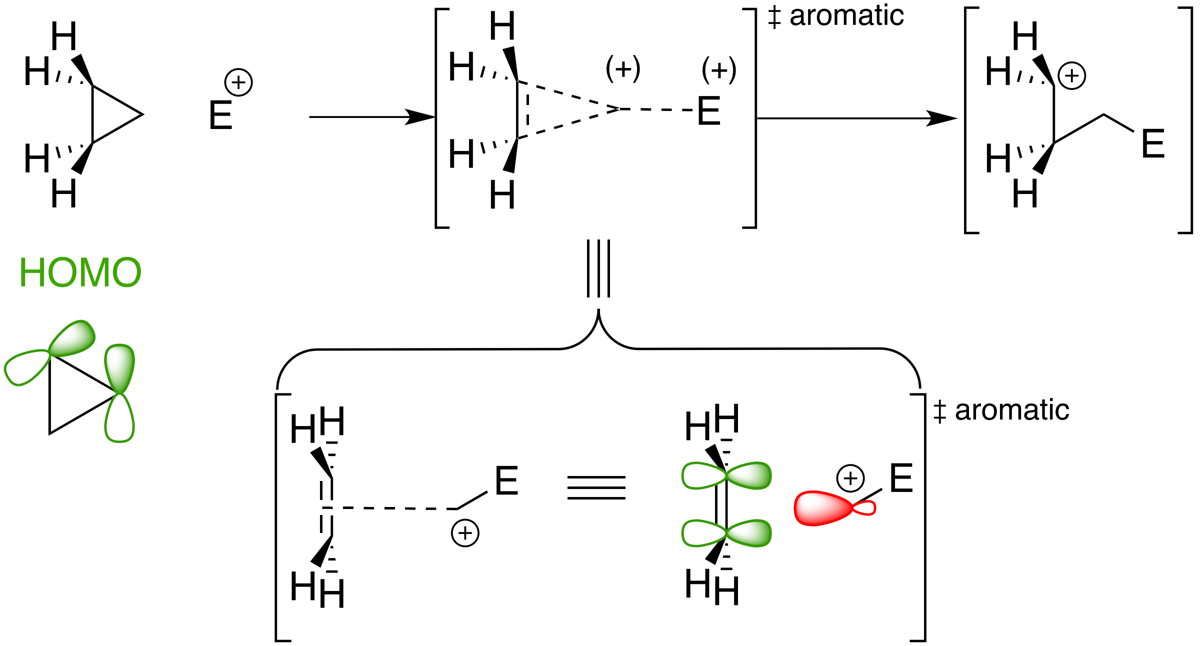


Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 669–682; Cremer, D.; Gauss, J. *J. Am. Chem. Soc.* **1986**, *108*, 7467–7477. For recent discrepancies of this theory: Carion, R.; Champagne, B.; Monaco, G.; Zanasi, R.; Pelloni, S.; Lazzeretti, P. *J. Chem. Theory Comput.* **2010**, *6*, 2002–2018; Pelloni, S.; Lazzeretti, P.; Zanasi, R. *J. Phys. Chem. A* **2007**, *111*, 8163–8169. Reviewed in: Wu, W.; Ma, B.; I-Chia Wu, J.; Schleyer, P. V. R.; Mo, Y. *Chem. Eur. J.* **2009**, *15*, 9730–9736.

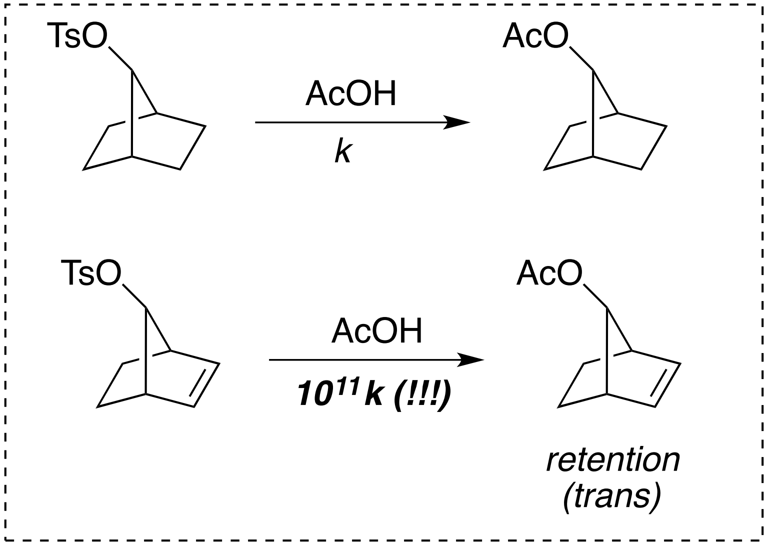
σ-aromaticity???

Dewar 1984		6 σ-electrons	4n + 2 (n=1)	aromatic
Cremer, Gauss 1986	 Ψ(A1')	2 "surface" electrons	4n + 2 (n=0)	aromatic

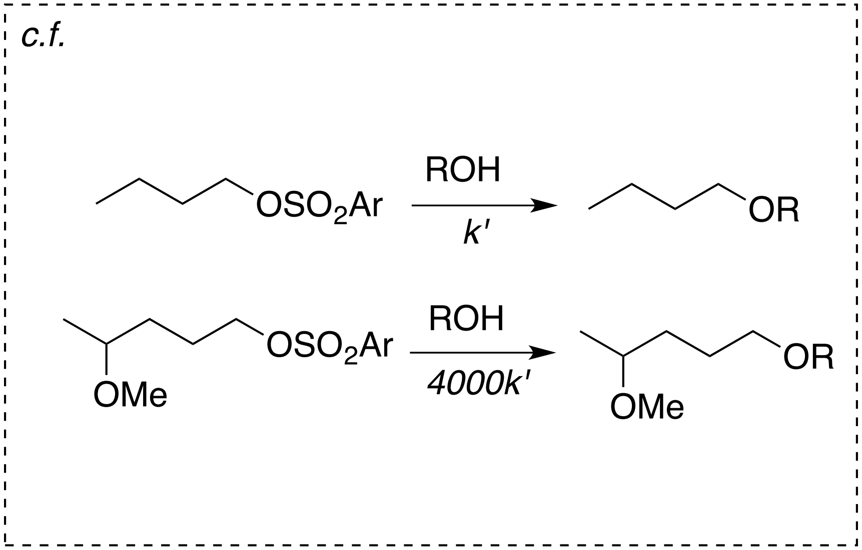
3-centre, 2-electron bond

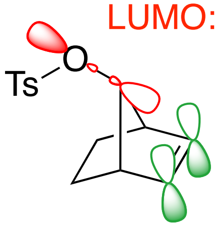


Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 669–682; Cremer, D.; Gauss, J. *J. Am. Chem. Soc.* **1986**, *108*, 7467–7477. For recent discrepancies of this theory: Carion, R.; Champagne, B.; Monaco, G.; Zanasi, R.; Pelloni, S.; Lazzeretti, P. *J. Chem. Theory Comput.* **2010**, *6*, 2002–2018; Pelloni, S.; Lazzeretti, P.; Zanasi, R. *J. Phys. Chem. A* **2007**, *111*, 8163–8169. Reviewed in: Wu, W.; Ma, B.; I-Chia Wu, J.; Schleyer, P. V. R.; Mo, Y. *Chem. Eur. J.* **2009**, *15*, 9730–9736.



retention
(trans)

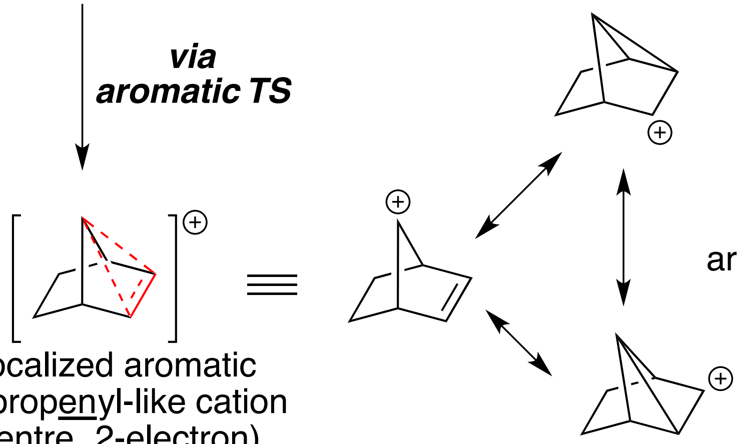




LUMO: empty C-O σ* orbital
0 electrons

HOMO: filled π orbital
2 electrons

4n + 2 electrons



delocalized aromatic
cyclopropenyl-like cation
(3-centre, 2-electron)

or...
α-cation to
aromatic cyclpropane

Reviews

- Discussions of bonding, reactivity, and reactions of cyclopropanes:

Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89* (1), 165–198; (b) Walsh, A. D. *Trans. Faraday Soc.* **1949**, *45*, 179–190; (c) de Meijere, A. *Angew. Chem. Int. Ed. Engl.* **1979**, *18* (11), 809–826; (d) Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43* (3), 804–818.

- Cyclopropanations:

(a) cation (bio-inspired): Taylor, R. E.; Engelhardt, F. C.; Schmitt, M. J. *Tetrahedron* **2003**, *59*, 5623–5634; (b) from terminal epoxides: M Hodgson, D.; Salik, S. *Curr. Org. Chem.* **2015**, *20* (1), 4–18; (c) stereoselective: Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103* (4), 977–1050; (d) asymmetric ylide: Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97* (6), 2341–2372.

- Biosynthesis and metabolism:

(a) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103* (4), 1625–1648;
(b) Thibodeaux, C. J.; Chang, W.-C.; Liu, H.-W. *Chem. Rev.* **2012**, *112* (3), 1681–1709.

- Books

- Misc: Gong's topic review (database: tr2014_02); Myers' Chem 115; various group meetings on other group's websites; chemistry stack exchange

Original desired structure

I. Physical considerations of cyclopropanes

II. Reactivity and basicity of cyclopropanes

III. Biosynthesis of cyclopropanes and metabolism
  ii. Enzyme approach
  iii. Rearrangement approach

IV. Prevalence of cyclopropanes
  i. In natural products and in drug discovery
  ii. In ring opening during total synthesis

V. Intramolecular cyclopropanations with applications
  i. 1,3-elimination-like
  ii. 1,3-coupling-like
  iii. Carbene or carbenoid additions to π-bonds