

The chemistry and biology of cyclopropyl compounds

November 21, 2013

❖ Structure and reactivity

❖ Biology

❖ Chemistry

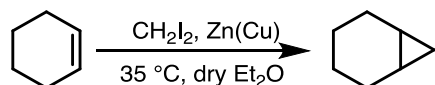
❖ Research Proposal

Brief history

First synthesis of cyclopropane

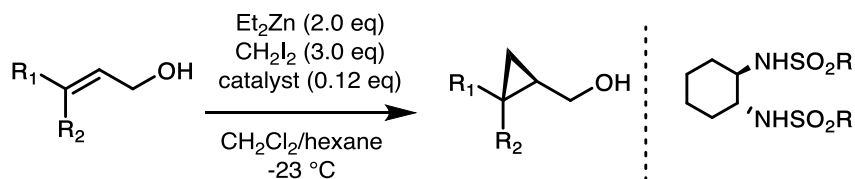


Simmons-Smith reaction



H. E. Simmons, R. D. Smith, *JACS*, **1958**, *80*, 5323

First catalytic, enantioselective S-S variant



Kobayashi *et al.*, *Tet. Lett.*, **1992**, *18*, 2575

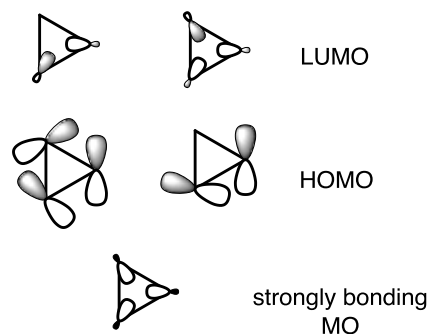
Cyclopropane is a colorless, sweet-smelling gas. It is flammable, but not more explosive than other alkanes.

Cyclopropane was used as an anesthetic: rapid, not unpleasant anesthesia. Prolonged anesthesia can lead to decreased blood pressure and cardiac dysrhythmia (“cyclopropane shock”)

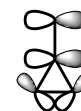
Structure and bonding

- Three carbons in the same plane. Bond angle 60°.
- C—C bonds are shorter than in alkanes (1.51 Å vs. 1.54 Å).
- H—C—H angle opened up (115 Å vs. 106 Å in propane)
- C—H bonds are more acidic (pKa=46, vs. 51 in propane)
- Significant rehybridization:
 - C—C bonds have more p character
 - C—H bonds have more s character
- Strain energy = 27.5 kcal/mol.

The following Walsh MO's can be drawn:



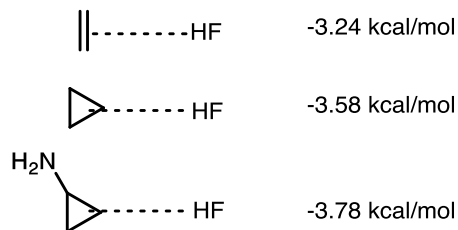
The cyclopropane ring can interact with adjacent p-orbitals.



Computational studies on cyclopropane structures

V. Bunge *et al.*, *Theor. Chem. Account*, **2007**, 118, 597

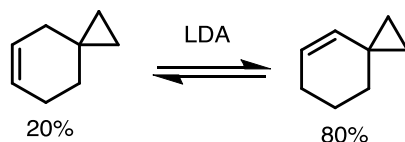
- Extra p character in C—C bonds: sp^x , $3.30 < x < 3.70$ (NBO analysis)
- Polar molecules can interact with cyclopropane and its derivatives in a manner that is similar to alkenes.
- The possible formation of unconventional hydrogen bond interactions may be essential in structure-activity studies of systems containing a cyclopropane ring.



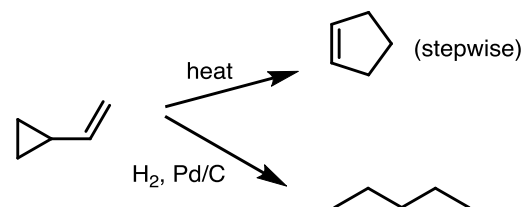
Reactivity of cyclopropanes

Review: *ACIE*, **1979**, 18, 809

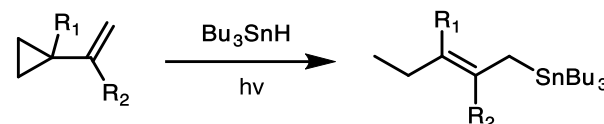
Conjugation with C=C double bonds



In many cases cyclopropanes behave similarly to alkenes



Adjacent radicals can open up cyclopropane rings – an important process for studying enzymatic reactions

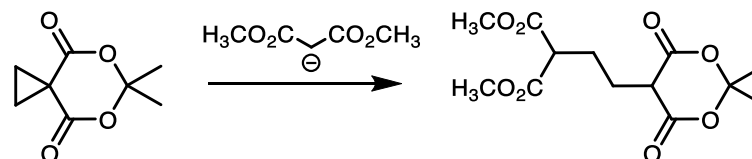


Adjacent carbocations are stabilized by cyclopropane ring



Solvolyzes 2.5×10^8 times faster

The “homologous Michael reaction”

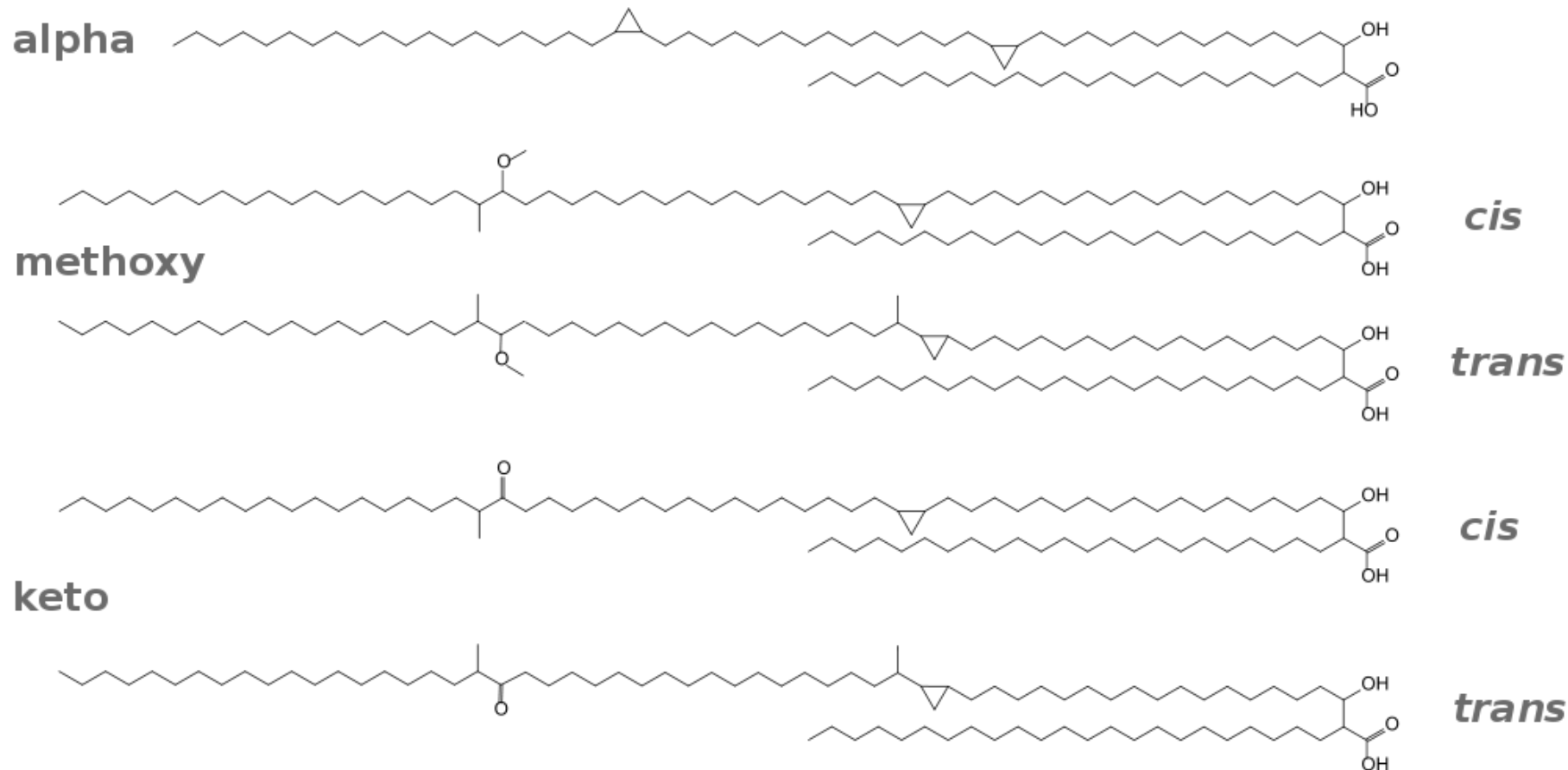


Cyclopropyl natural products

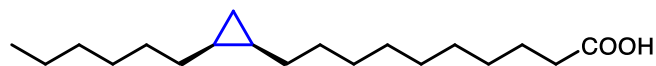
Approximately 4000 NP's containing cyclopropyl group

Lipids

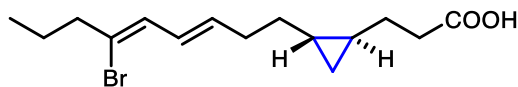
Mycolic acids are components of the cell wall of the bacterium *Mycobacterium tuberculosis*, the causative agent of tuberculosis.



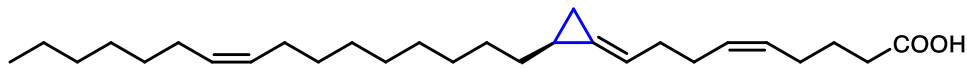
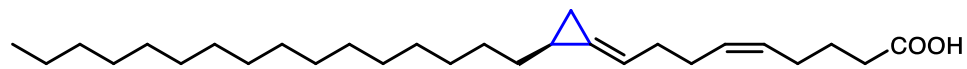
Other lipids



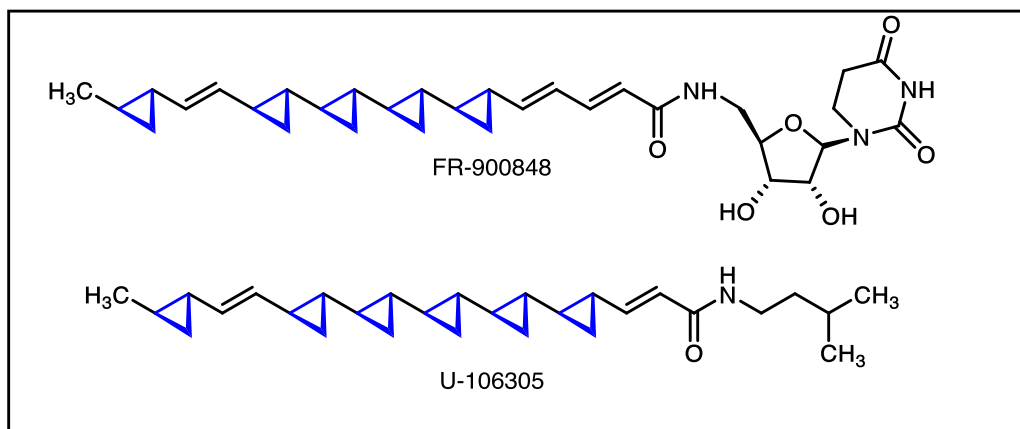
lactobacillic acid



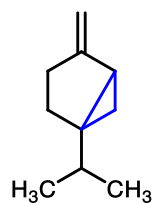
majusculoic acid



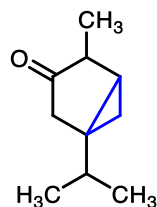
amphimic acids



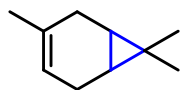
Monoterpenes



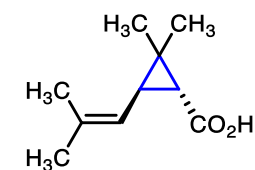
sabinene



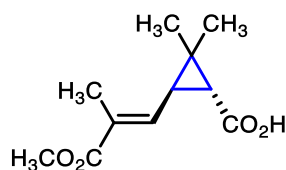
thujone



carene



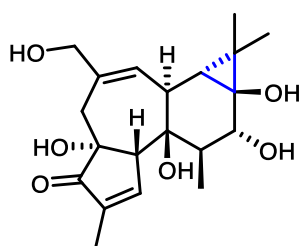
chrysanthemic acid



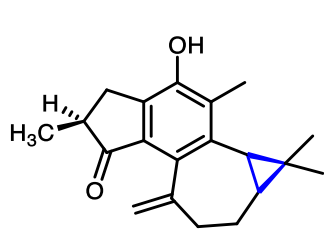
pyrethric acid

Pyretric acid derivatives are among the most widely used insecticides.

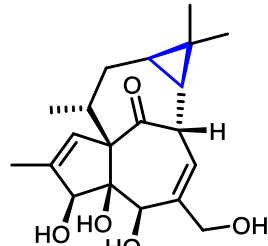
Diterpenes



phorbol

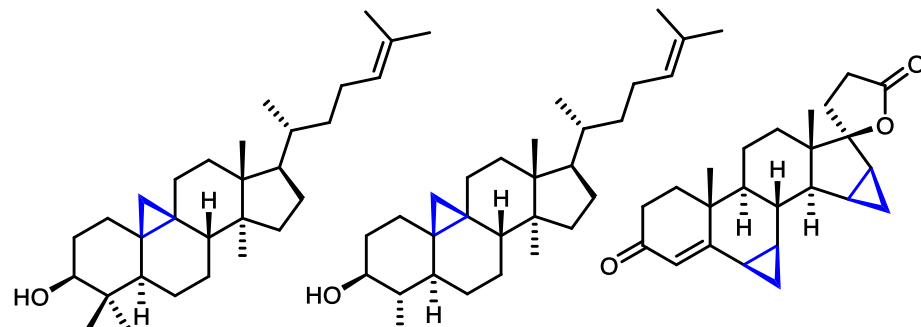


jatrophaolone A



ingenol

Steroids

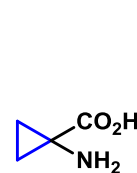
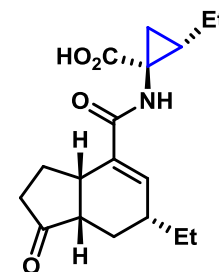
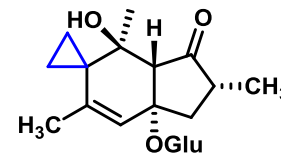
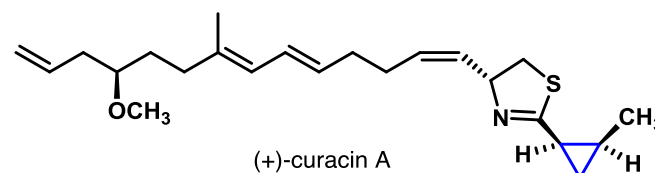


cycloartenol

cycloeucalenol

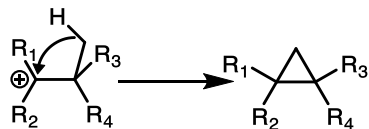
drospirenone

Misc. natural products

AAC
phytohormone
precursor(+)-coronatine
phytotoxin(+)-ptaquiloside
anticancer agent(+)-curacin A
antimitotic agent

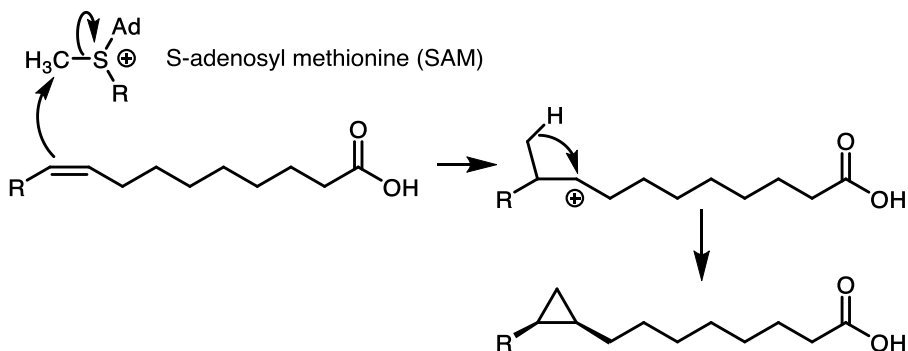
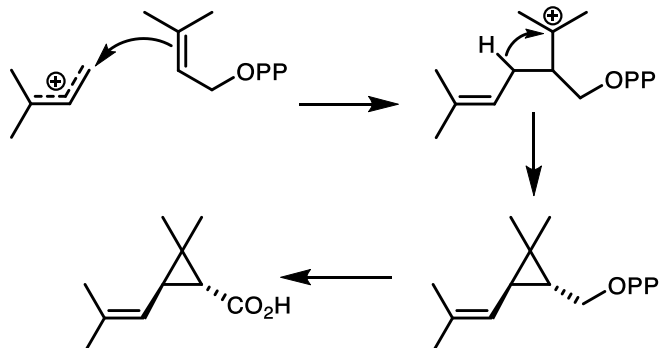
Biosynthesis

The most common mechanism for the biosynthesis of cyclopropane derivatives:

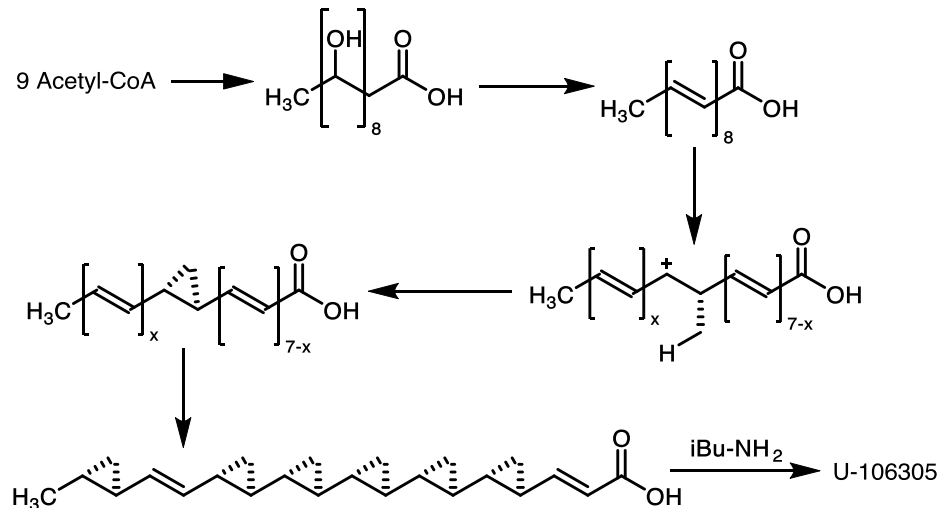


There are different ways in which carbocations are made.

- **Terpenes:** phosphates leave and thus a positive charge is generated on the carbon chain.
- **Lipids:** C=C double bond gets methylated (SAM) in the first step.

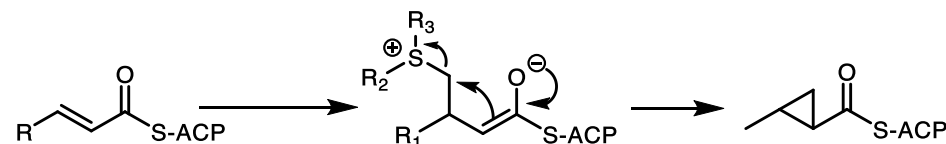


Biosynthesis of U-106305



Kuo *et al.*, *JACS*, **1995**, *117*, 10629

Alternatively, cyclopropanation via ylides:

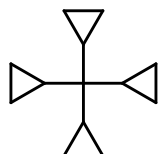
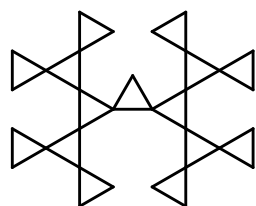
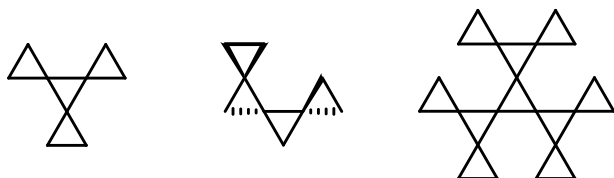


Barett *et al.*, *JACS*, **1997**, *119*, 8608

FR-900848 has an analogous biosynthesis. It was shown that the particular polyketide synthase has a cyclopropanase domain.

Chem. Commun., **2008**, 6016

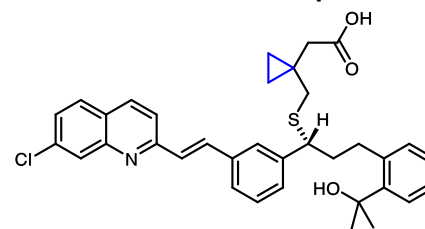
Artificial oligocyclopropanes



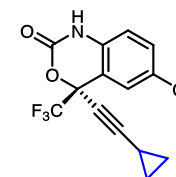
Review: *ACIE*, **2001**, *40*, 2251

Cyclopropane and pharma

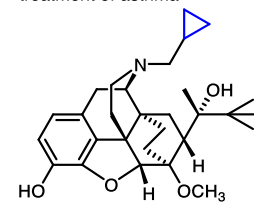
- There are >100 pharmaceutical agents containing a cyclopropyl group.
- 8 substances from the top 200 US bestselling drugs (2012)



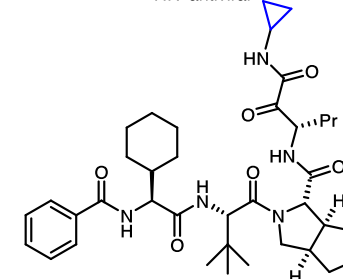
Singulair (#11)
treatment of asthma



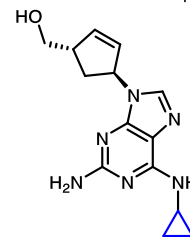
Efavirenz (#14 in Atrilpa)
HIV antirviral



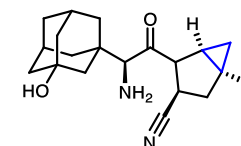
Buprenorphine (#34 in Suboxone)
treat opioid add.



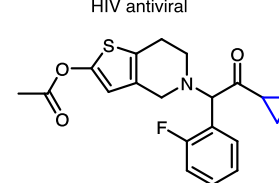
Incivek (#39)
antiviral



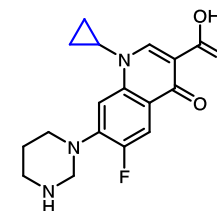
Abacavir (#130 in Epzicom)
HIV antiviral



Onglyza (#146)
Antidiabetic



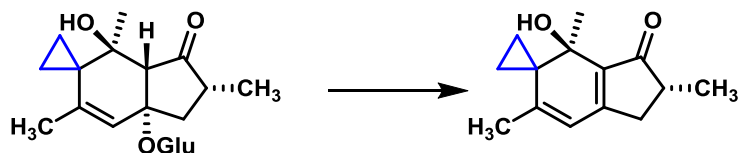
Effient (#184)
platelet aggregation inhib.



Ciprofloxacin (#195 in Ciprodex)
antibiotic

What do cyclopropanes do in living organisms?

- Large spectrum of biological activities: antibiotic, antiviral, antitumor, neurochemical activity.
- Several mechanisms through which they achieve activity: addition to cyclopropane bond, C—H oxidation, radical chemistry, two electron oxidations, nucleophilic substitution, electrophilic ring opening
- Geometric and conformational effects can also play a role.

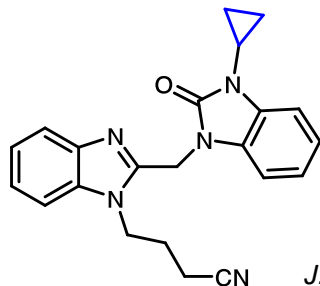


Under weakly alkaline conditions ptaquiloside is converted in to the unstable dienone, which forms covalent adducts with AA's, nucleosides and nucleotides (v. electrophilic cyclopropane).

Top. Curr. Chem., **2000**, 207, 1

Cyclopropane as alkyl bioisostere

- Similar size and electronical properties, usually improved metabolic stability.
- In the following example this was the most metabolically stable compound amongst a number of analogues.



J. Med. Chem., **2011**, 54, 2529

Biophysical properties

- *Mycobacterium tuberculosis* produces cyclopropanated lipids (see above).
- These lipids are thought to contribute to both drug resistance and survival in hostile environment by the formation of an impermeable asymmetric lipid bilayer.
- Bacteria with high proportion of cyclopropanated lipids are resistant to killing by hydrogen peroxide. Cyclopropanation = important in adaptation to oxidative stress.
- Increased stability to killing by freezing.
- Cyclopropanation contributes to the structural integrity of the cell wall complex. Cyclopropanated membranes enhance stability by suppressing segmental mobility of hydrocarbon chains, thus providing increased rigidity with respect to external shock.

J. Biol. Chem., **1995**, 270, 27292

PNAS, **1995**, 92, 6630

What is the role of ologicyclopropanes?

FR-900848: antifungal agent against *Aspergillus fumigatus*, essentially non-toxic

U-106305: potent inhibitor of cholesterol ester transfer protein (CETP), potential therapeutic application for coronary heart disease patients.

- Chemical protection against oxidative environments.
- Rigidifying membranes.
- Is there something else? Why do the bacteria need 5-6 cyclopropanes?
- These structures are known to have helical conformation. Does this play a role?

How can you make cyclopropanes?

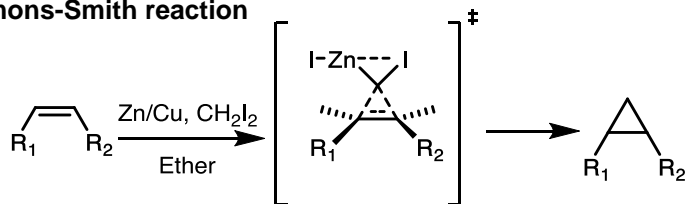
Super review: Charette *et al.*, *Chem. Rev.*, **2003**, 103, 977

There are three main ways:

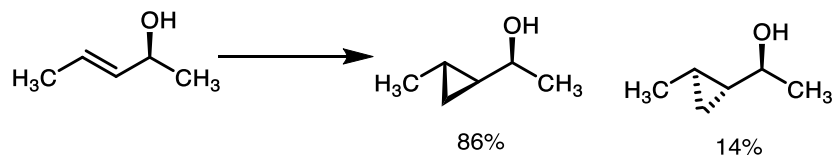
- 1) Halomethyl-metal mediated (Simmons-Smith)
- 2) Transition metal catalyzed decomposition of diazoalkanes
- 3) Michael initiated ring closure

1) Halomethyl-metal mediated cyclopropanation

Simmons-Smith reaction

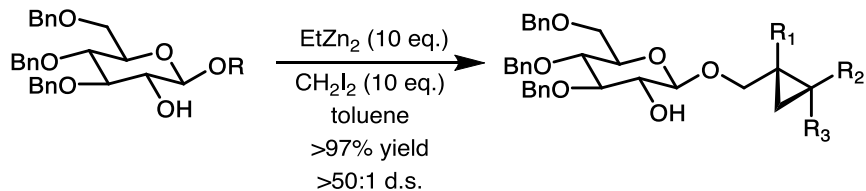


Alcohols and ethers can induce diastereoselectivity:



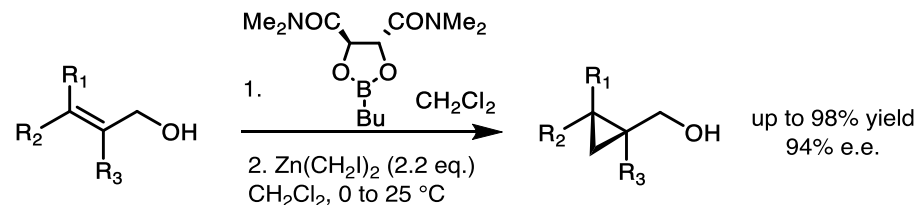
Charette *et al.*, *JOC*, **1995**, 60, 2966

Chiral auxiliaries can give rise to high selectivity



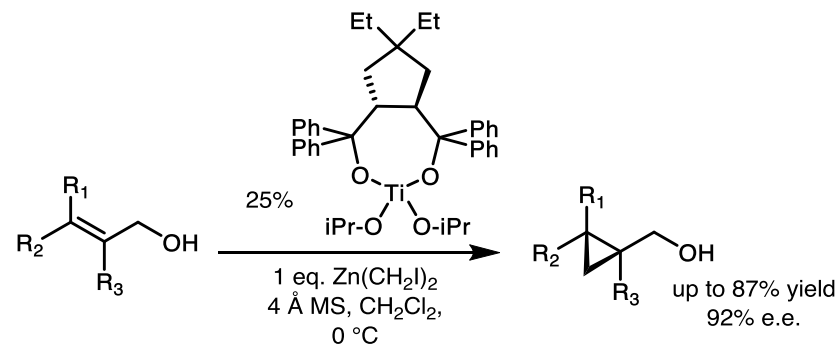
Charette *et al.*, *JACS*, **1991**, 113, 8166

The most common method is to use stoichiometric chiral ligand:



Charette *et al.*, *JACS*, **1994**, 116, 2651

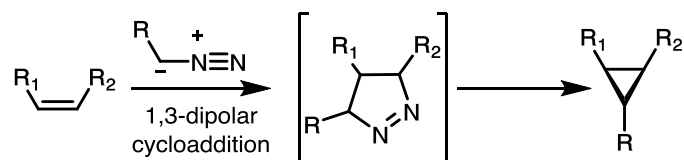
There are also catalytic enantioselective methods:



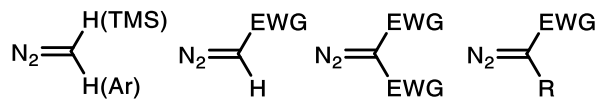
Charette *et al.*, *JACS*, **2001**, 123, 12168

The most reliable method is to use stoichiometric chiral ligand on allylic alcohols. (Charette cyclopropanation)

2) Transition metal catalyzed decomposition of diazoalkanes

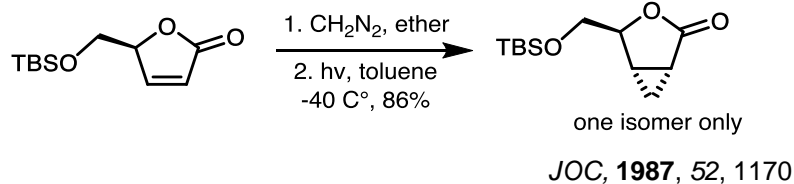


Diazoalkane precursors

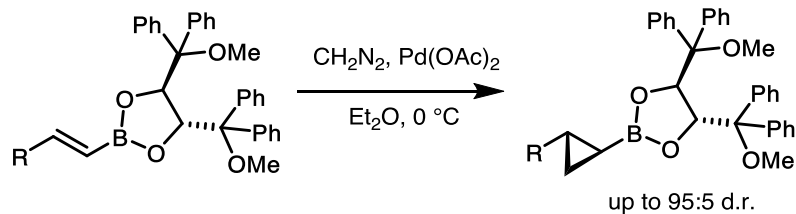


Most common metals used: Cu, Rh, Ru, Co, Fe, Os, Pd, Pt, Cr

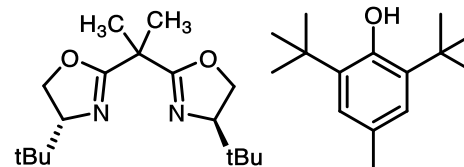
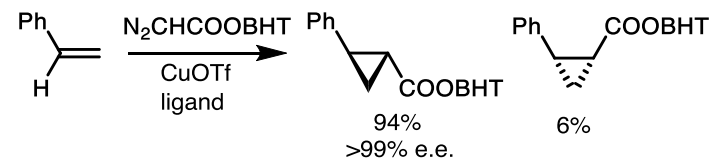
Relative diastereoselection



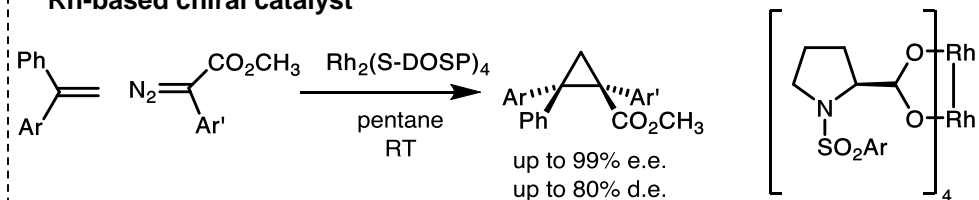
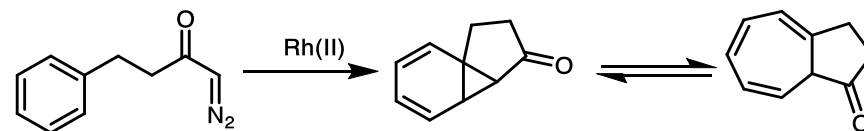
Chiral auxiliary

Pietruszka *et al.*, *Synlett*, **1997**, 977

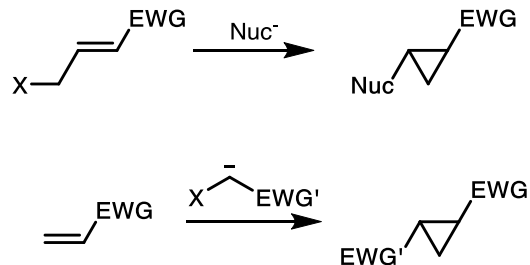
Cu-based chiral catalyst

D. A. Evans *et al.*, *JACS*, **1991**, 113, 726

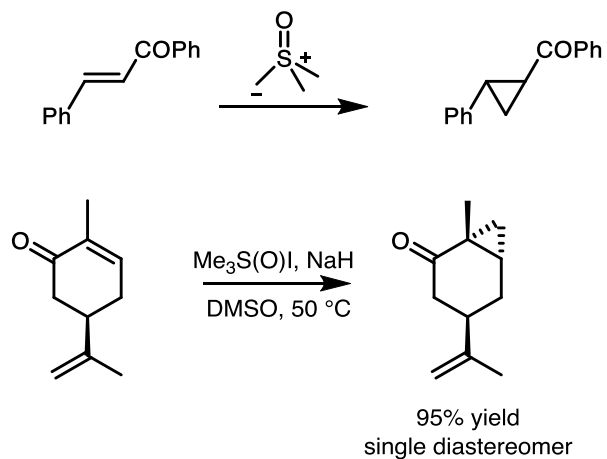
Rh-based chiral catalyst

H. M. L. Davies *et al.*, *Org. Lett.*, **2000**, 2, 823This method can be applied for intramolecular cyclopropanations:
Buchner reaction

3) Michael initiated ring closure

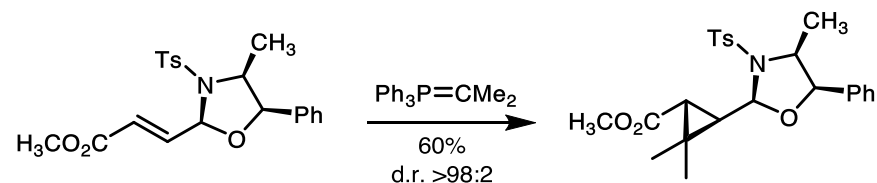


Corey-Chaykovsky reaction



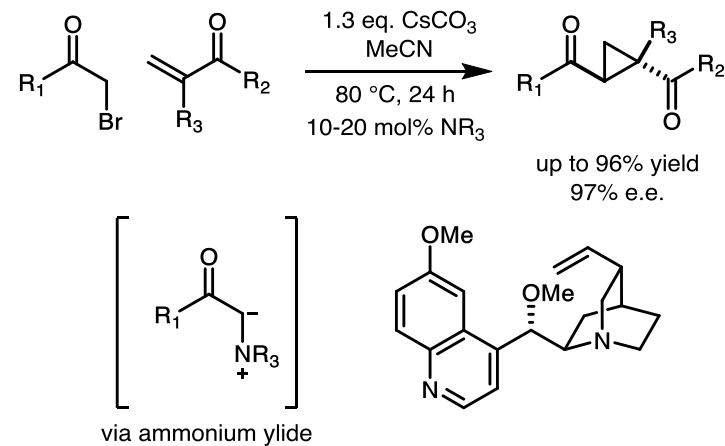
JACS, 1962, 84, 867

Chiral auxiliary



Tet. Lett., 1989, 30, 3733

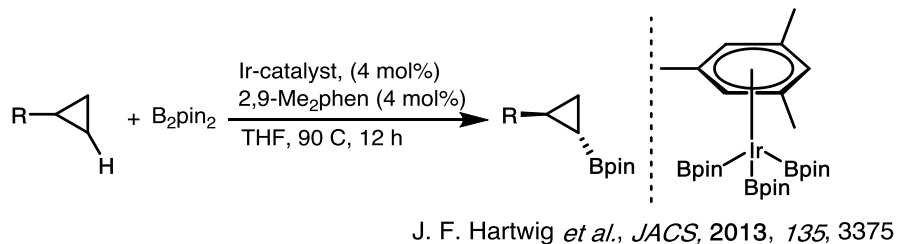
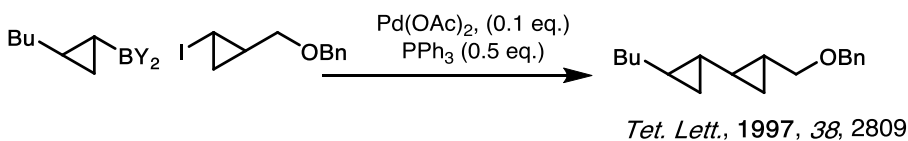
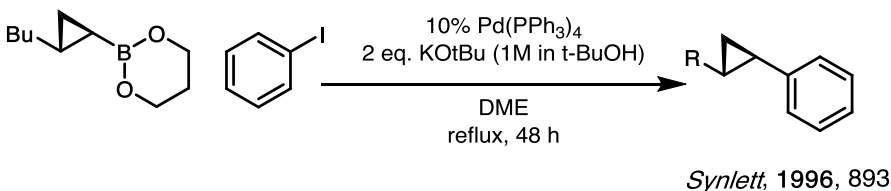
Chiral nucleophile

S. V. Ley, M. J. Gaunt *et al.*, ACIE, 2004, 116, 4741

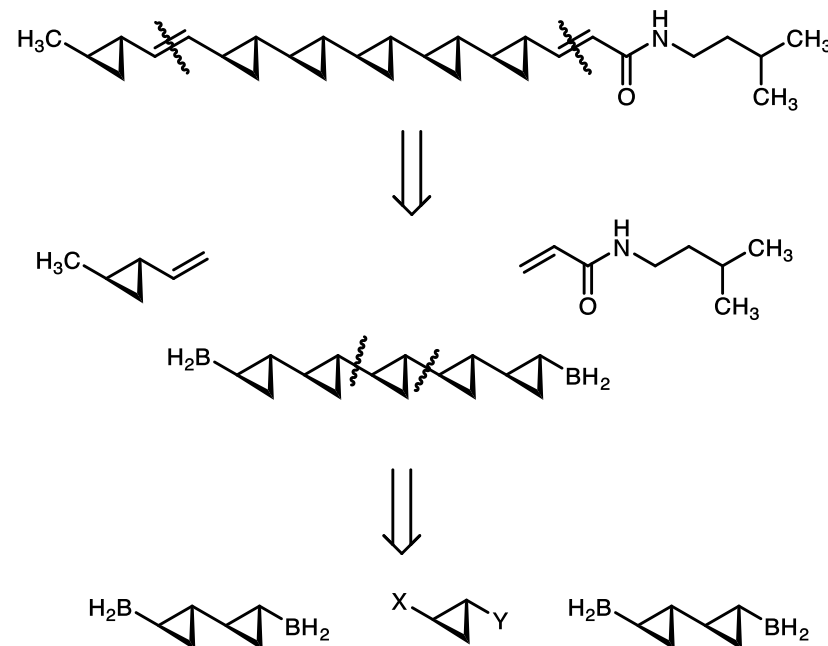
Great method, but can only access cyclopropanes with adjacent EWG's

- Previous syntheses used Charetté's cyclopropanation methodology on allylic alcohols.
- Cyclopropanation steps very effective.
- Building the carbon chain requires many extra steps (oxidation, olefination, reduction)
- A more efficient strategy would be to build the carbon chain a lot faster.
- Cross-coupling, especially Suzuki reactions could be very helpful

Prior work on cyclopropane cross-couplings



Planned retrosynthesis



- This is mostly based on cross-coupling methodologies.
- Probably boronic acid derivatives are the best choice – easiest to transform into other useful functionalities.