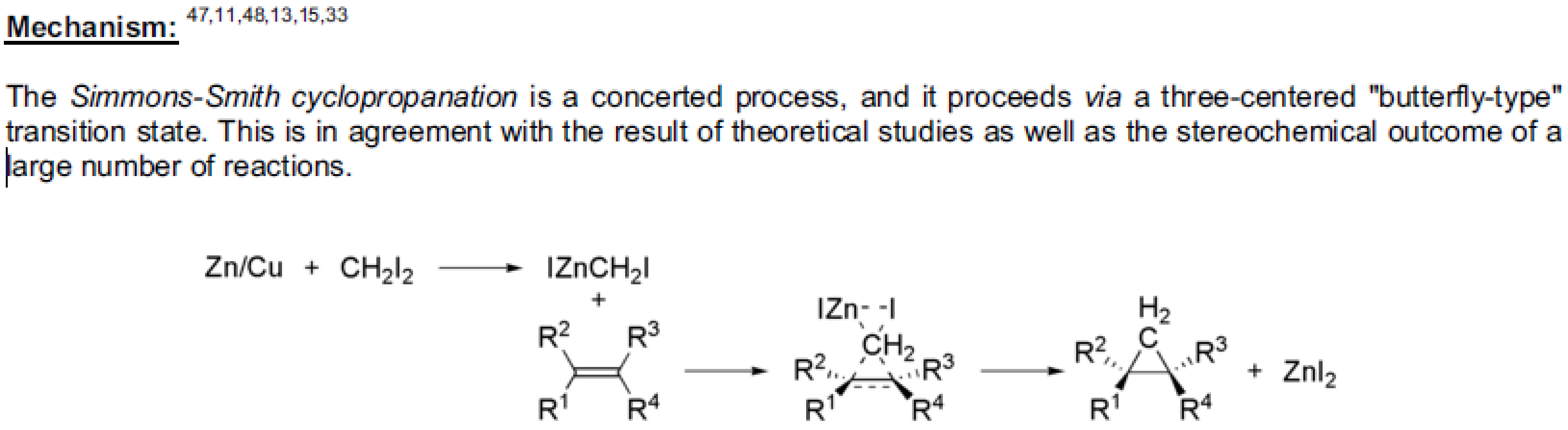
SIMMONS-SMITH CYCLOPROPANATION

In 1958, H.E. Simmons and R.D. Smith were the first to utilize diiodomethane (CH2I2) in the presence of zinc-copper couple (Zn-Cu) to convert unfunctionalized alkenes (e.g., cyclohexene, styrene) to cyclopropanes stereospecifically. This transformation proved to be general and has become the most powerful method of cyclopropane formation: it bears the name of its discoverers and is referred to as the Simmons-Smith cyclopropanation.



Mechanism: [47,11,48,13,15,33]

The *Simmons-Smith cyclopropanation* is a concerted process, and it proceeds *via* a three-centered "butterfly-type" transition state. This is in agreement with the result of theoretical studies as well as the stereochemical outcome of a large number of reactions.

$$Zn/Cu + CH_2I_2 \longrightarrow IZnCH_2I$$

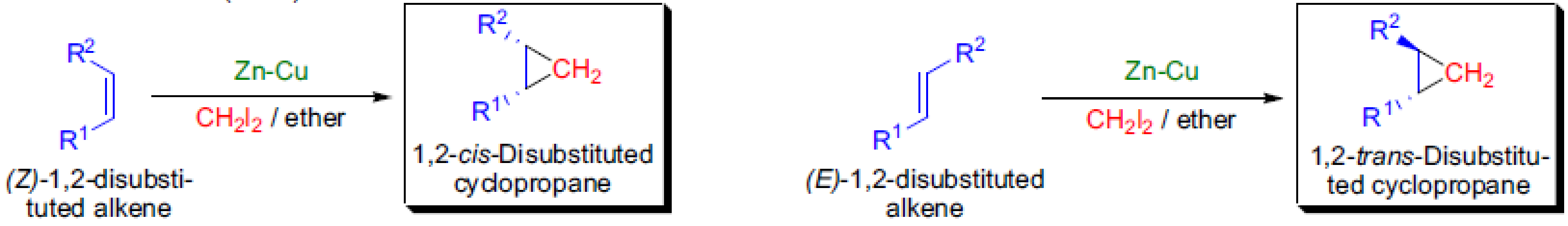
The most important features of the reaction are:

1) A wide range of alkenes can be used: simple alkenes, α,β-unsaturates ketones and aldehydes, electron rich alkenes (enol ethers, enamines, etc.);

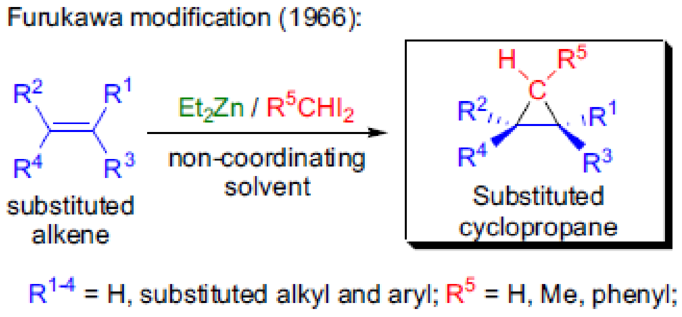
2) Due to the electrophilic nature of the reagent, the rate of cyclopropanation is faster with more electron rich alkenes. However, highly substituted alkenes may react slower due to the increased steric hindrance;

3) The cyclopropanation is stereospecific, so the stereochemical information in the alkene substrates is translated to the products;

Simmons & Smith (1958):



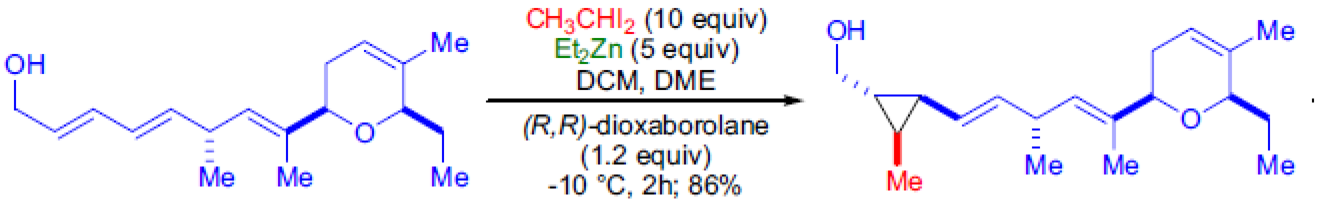
4) When a substituted methylene group is transferred to the alkene (R5≠H) a preference for *syn* stereochemistry is typically observed;


Furukawa modification (1966):

R^{1-4} = H, substituted alkyl and aryl; R^5 = H, Me, phenyl;

5) In case of chiral substrates, the cyclopropanation is highly diastereoselective and occurs from the less hindered face of the double bond;

6) When the alkene has functional groups containing heteroatoms (e.g., OH, OAc, OMe, OBn, NHR), a strong directing effect is observed and the delivery of the alkylidene occurs from the face of the double bond having the closer proximity of the functional group;



7) In cycloalkenols, the stereochemical outcome depends on the ring size: 5-, 6-, and 7-membered rings give rise to high cis-diastereoselectivity, while large ring cycloalkenols exhibit high levels of anti diastereoselectivity;

8) Usually no serious side reactions are observed (e.g., C-H insertion), and the reactionconditions are tolerant of most functional groups;

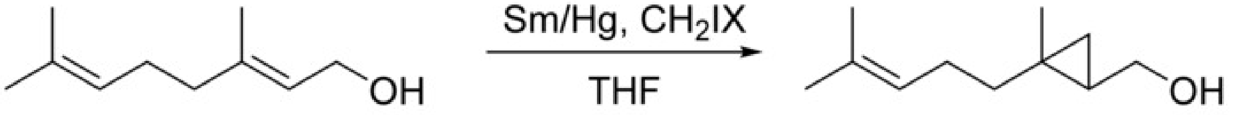
9) Non-coordinating solvents (e.g., DCM, DCE) are recommended, because the use of basic solvents decrease the rate of the reaction.

Today the preparation of the zinc-copper couple is more convenient (treatment of zinc powder with CuSO4 solution) than described in the original procedure. However, there have been several modifications to generate the active reagent:

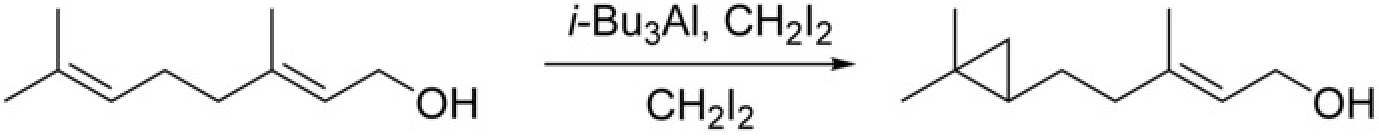
1) zinc-silver couple tends to give higher yields and shorter reaction times;

2) the use of diethylzinc with CH2I2 gives very reproducible results (Furukawa modification);

3) iodo- or chloromethylsamarium iodide (Sm/Hg/CH2I2) is the reagent of choice for the chemoselective cyclopropanation of allylic alcohols in the presence of other olefins (Molander modification);



4) dialkyl(iodomethyl)aluminum (i-Bu3Al/CH2I2) exclusively cyclopropanates unfunctionalized olefins in the presence of allylic alcohols.

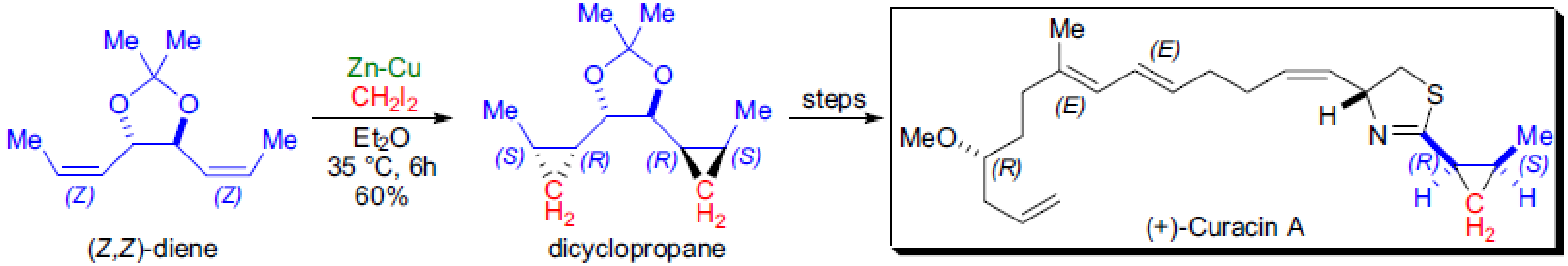


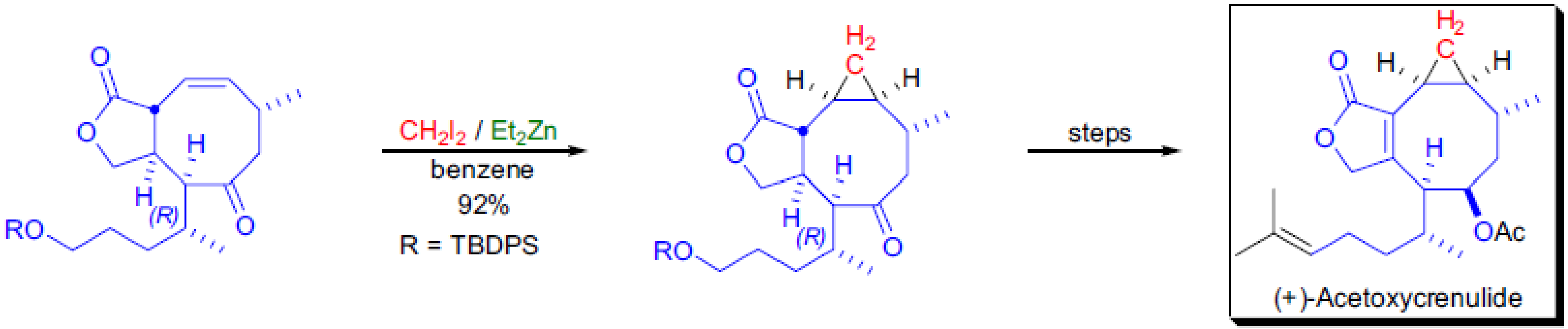
Asymmetric Simmons-Smith cyclopropanations can be achieved several different ways:

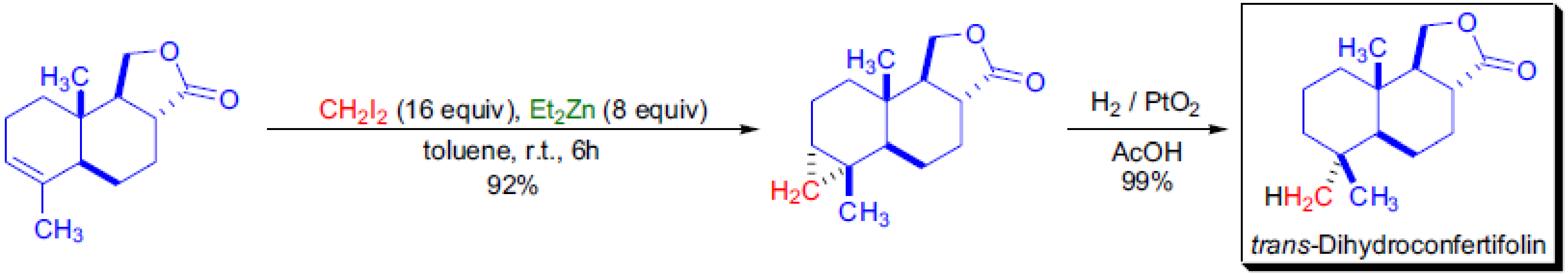
1) the use of cleavable chiral auxiliaries (e.g., chiral allylic ethers, acetals, boronates);

2) by the addition of stoichiometricamounts of chiral additives, such as dioxaborolane prepared from tetramethyltartaric acid diamide and butylboronic acid (Charette asymmetric modification). However, this method is only applicable to allylic alcohols;

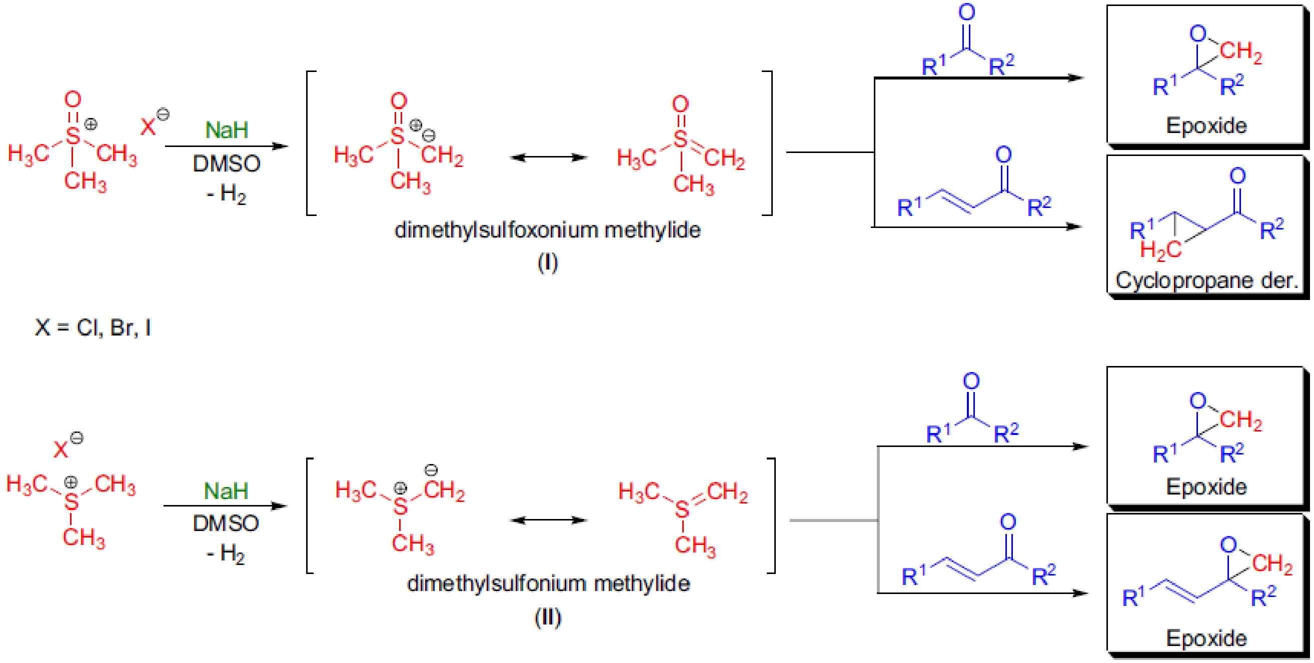
3) the use of chiral catalysts, such as the chiral disulfonamide ligand derived from trans-cyclohexanediamine, gives high ee's for allylic alcohols.


Me
Me
Me
Me
(Z)
(Z)
(Z,Z)-diene
Zn-Cu
CH_2I_2
Et_2O
35 °C, 6h
60%
dicyclopropane
(S)
(R)
(R)
(S)
steps
(+)-Curacin A
MeO
(E)
(E)
(R)
(S)

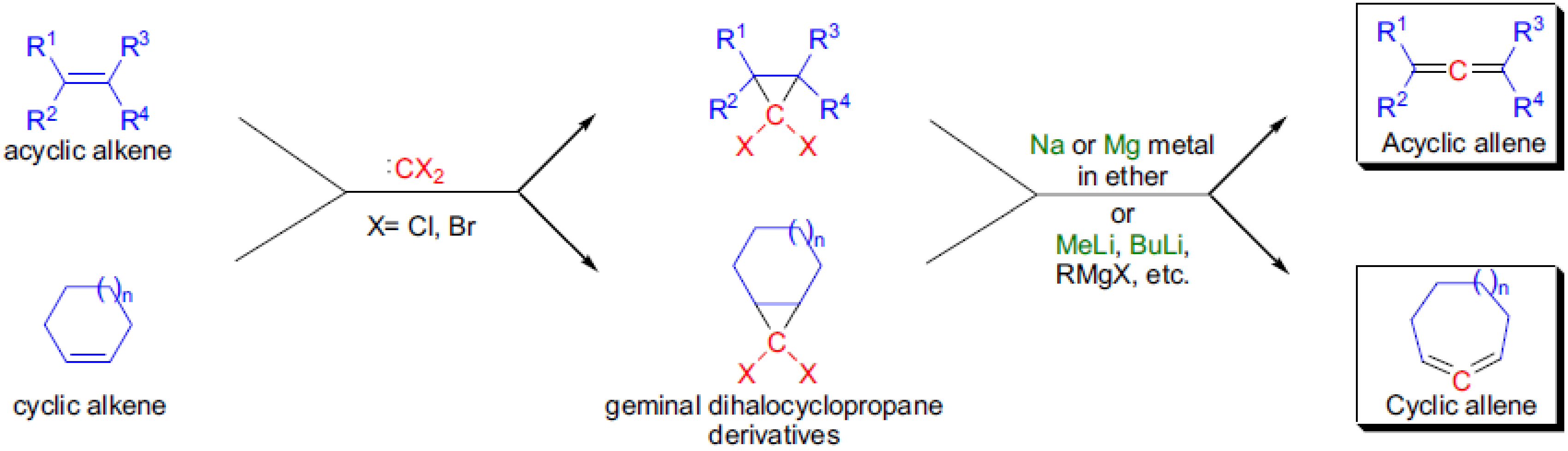

RO
(R)
CH_2I_2 / Et_2Zn
benzene
92%
R = TBDPS
steps
OAc
(+)-Acetoxycrenulide


H_3C
CH_3
CH_2I_2 (16 equiv), Et_2Zn (8 equiv)
toluene, r.t., 6h
92%
H_2C
H_2 / PtO_2
AcOH
99%
HH_2C
trans-Dihydroconfertifolin

COREY-CHAYKOVSKY EPOXIDATION AND CYCLOPROPANATION



DOERING-LAFLAMME ALLENE SYNTHESIS



acyclic alkene

cyclic alkene

$:CX_2$

X= Cl, Br

geminal dihalocyclopropane derivatives

Na or Mg metal in ether

or

MeLi, BuLi, RMgX, etc.

Acyclic allene

Cyclic allene