

Synthesis of Cyclopropanes

Topic Review

Key references:

- M. Ohkita, S. Nishida and T. Tsuji, in *PATAI'S Chemistry of Functional Groups*, John Wiley & Sons, Ltd, 2009.
- J.-i. Yoshida, *Synlett*, 2006, 515-526.
- W. A. Donaldson, *Tetrahedron*, 2001, **57**, 8589-8627.
- H. Lebel, J.-F. Marcoux, C. Molinaro and A. B. Charette, *Chem. Rev.*, 2003, **103**, 977-1050.
- D. Y. K. Chen, R. H. Powner and J.-A. Richard, *Chem. Soc. Rev.*, 2012, **41**, 4631-4642.

Gong Xu

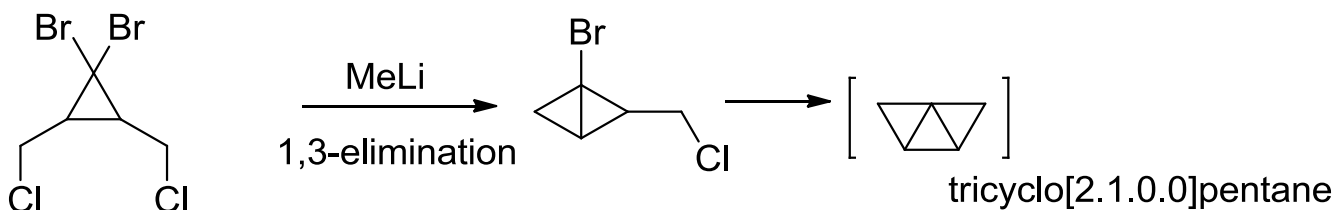
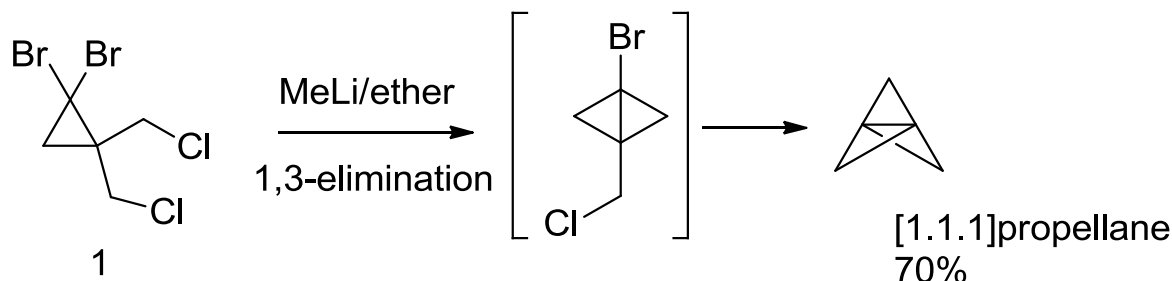
February 27, 2014

Contents

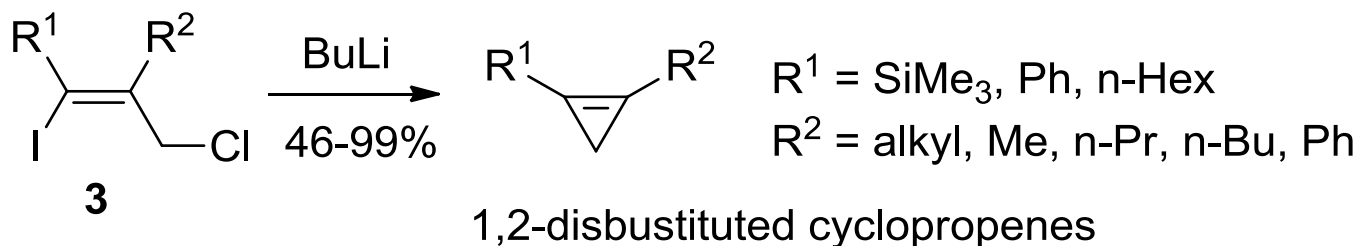
- I. Cyclopropanation *via* 1,3-bond formation
- II. Cyclopropanation of C-C multiple bonds with carbenes and carbenoids
- III. Cyclopropanation of Michael acceptors
- IV. Cyclopropanation of active methylene compounds
- V. Cyclopropane photochemistry

I. Cyclopropanation *via* 1,3-bond formation

- ❖ A. Reductive 1,3-elimination reaction of **alkyl dihalides** (classical methods, useful for the synthesis of highly strained polycyclic hydrocarbons)

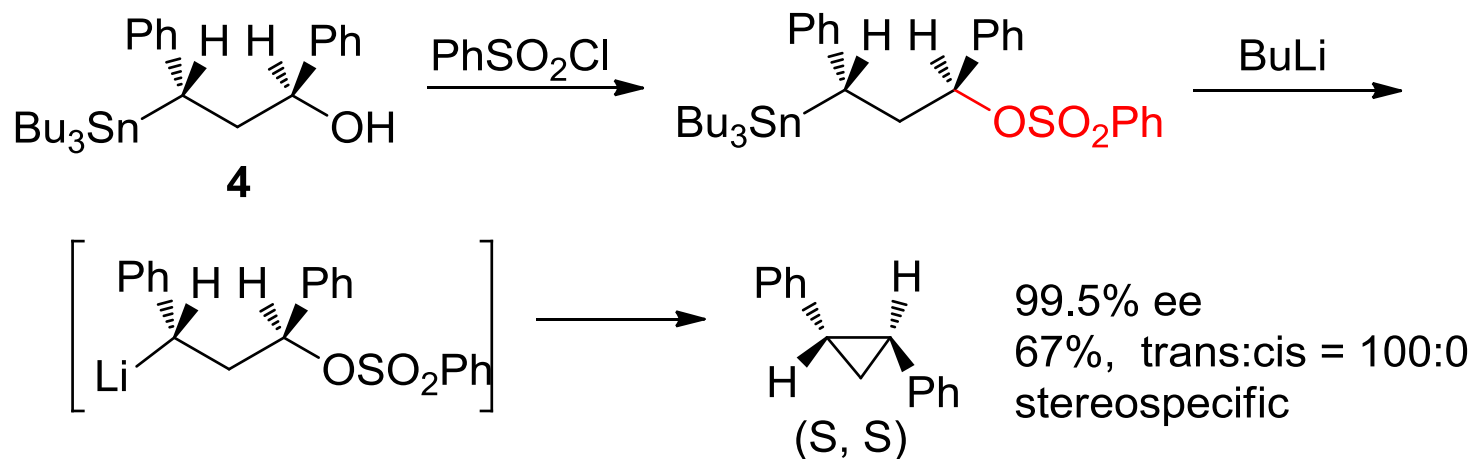


J. Am. Chem. Soc., 1993, 115 (23), 10653



T. Stoll and E.-i. Negishi,
Tetrahedron Lett., 1985,
26, 5671-5674

❖ B. 1,3-Elimination reaction of **alkyltin compounds with a leaving group at γ -position**

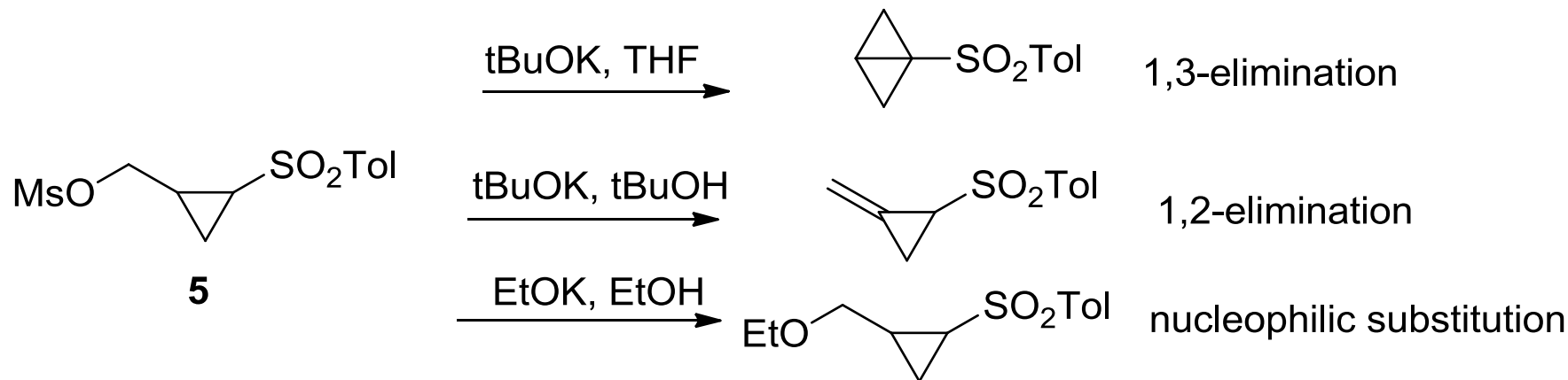


A. Krief and M. Hobe, *Tetrahedron Lett.*, 1992, 33, 6527-6528.

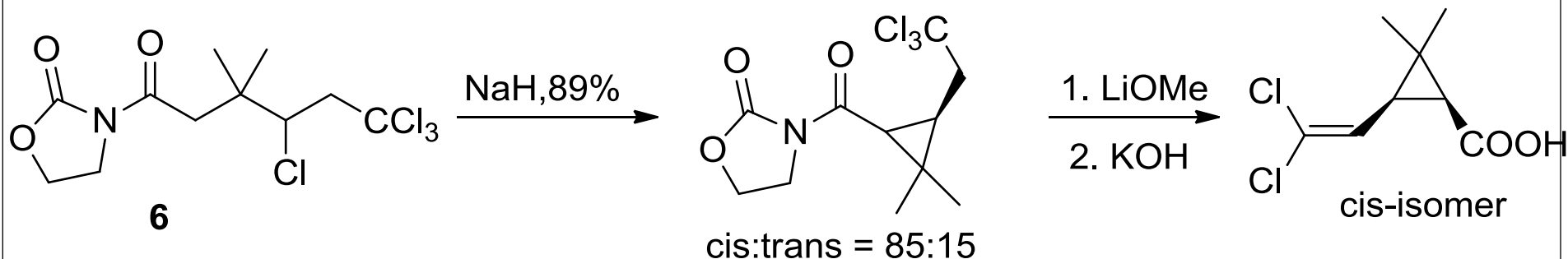
➤ **Mechanism:** initial transmetalation followed by the intramolecular nucleophilic substitution.

❖ C. 1,3-elimination of HX

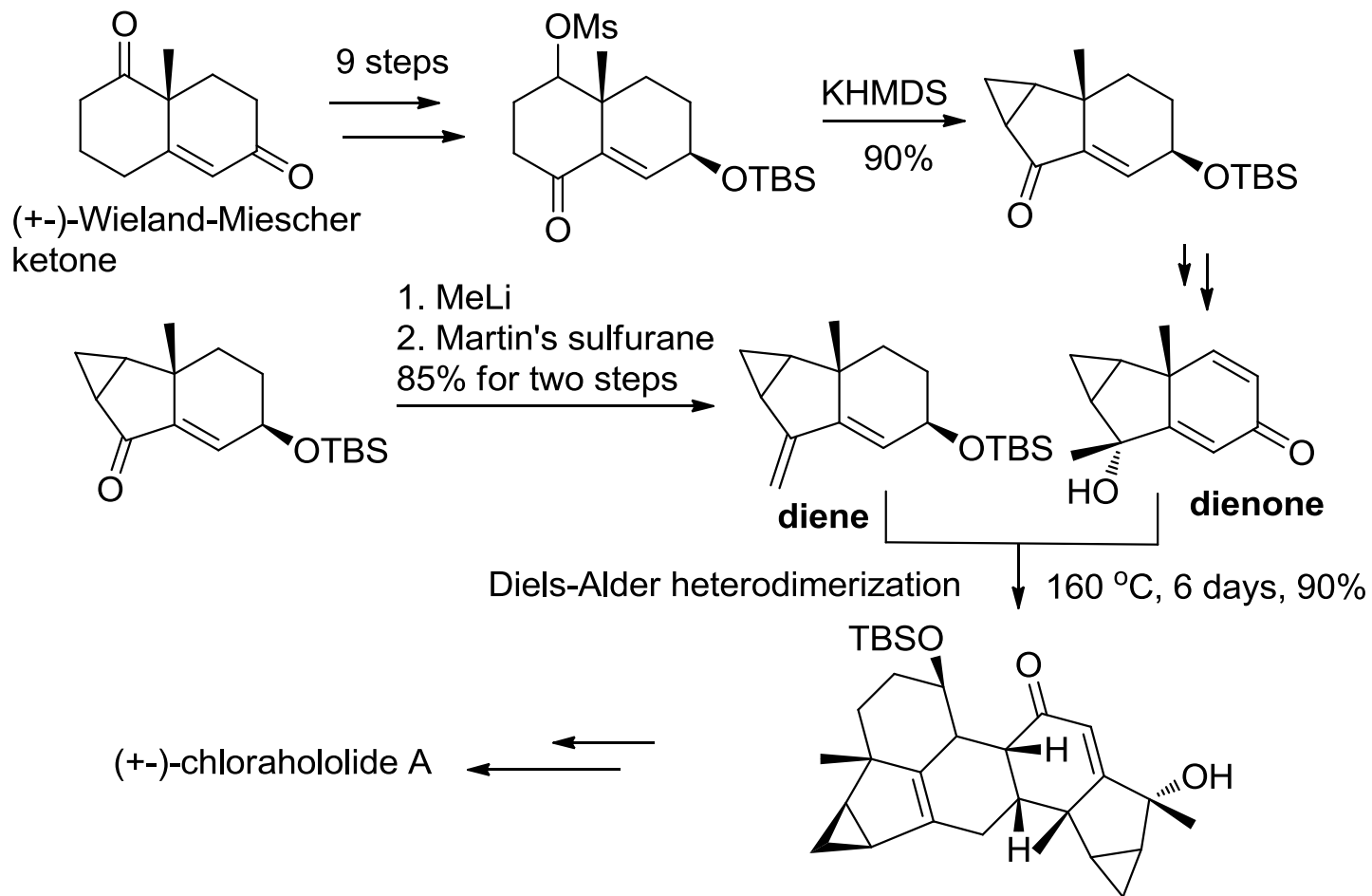
Active methylene and methine compounds bearing a leaving group on the γ -carbon atom can afford cyclopropane derivatives.



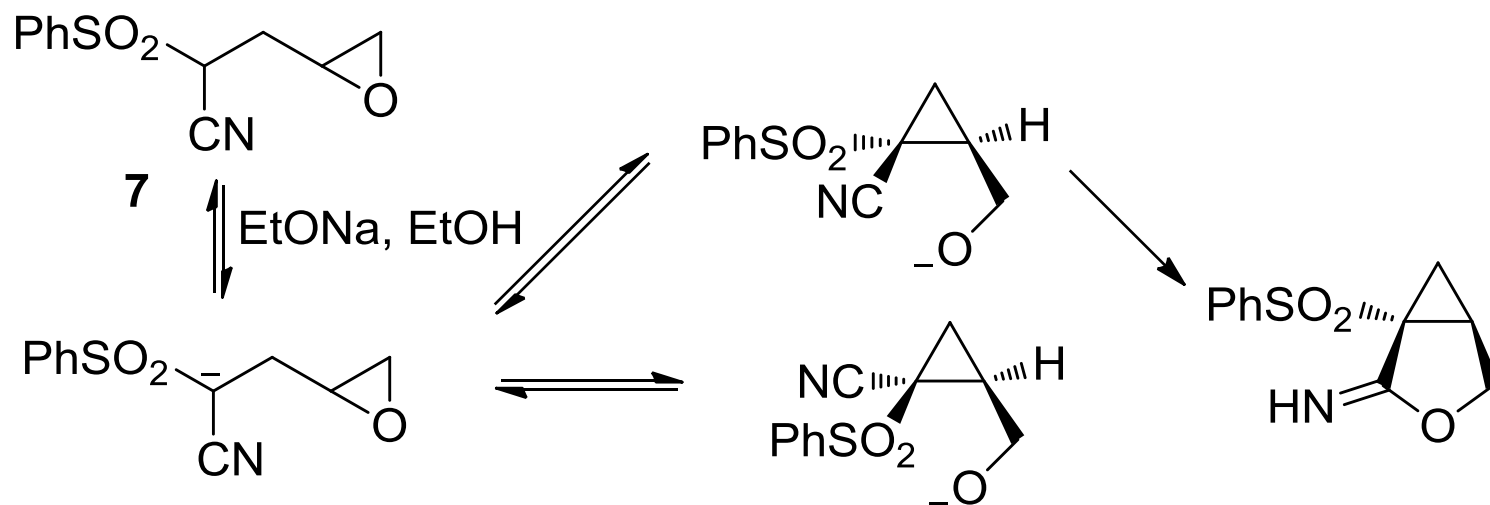
S. W. Roberts and C. J. M. Stirling, *J. Chem. Soc., Chem. Commun.*, 1991, 170-171



W. A. Kleschick, *J. Org. Chem.*, 1986, 51, 5429-5433.

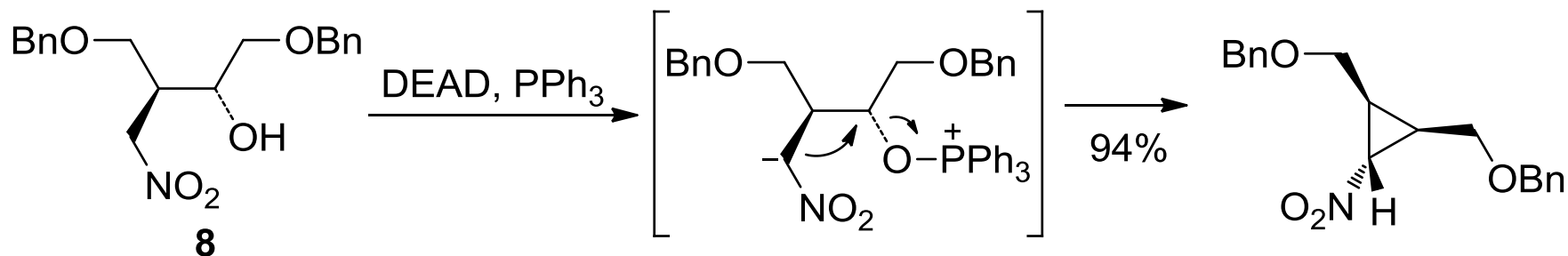


Synthesis towards to Chlorahololide A



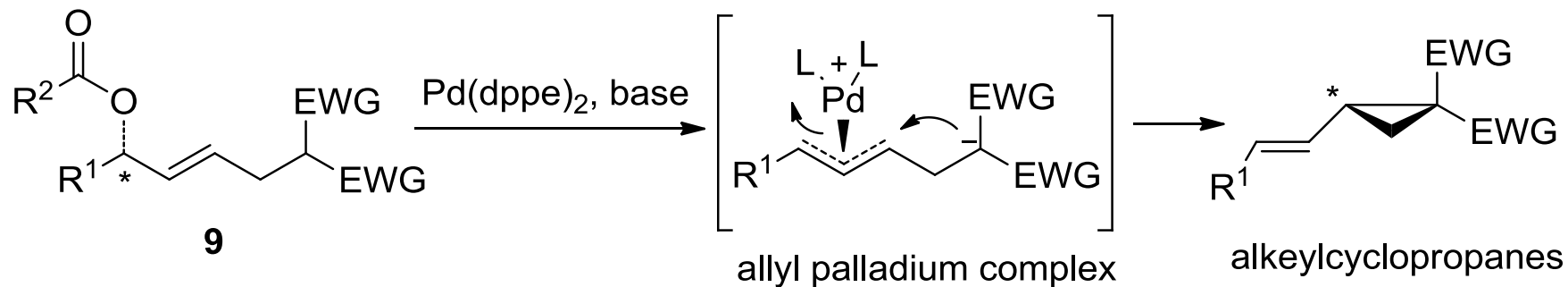
F. Benedetti, F. Berti and A. Risaliti,
Tetrahedron Lett., 1993, 34, 6443-6446.

Bicyclic imine

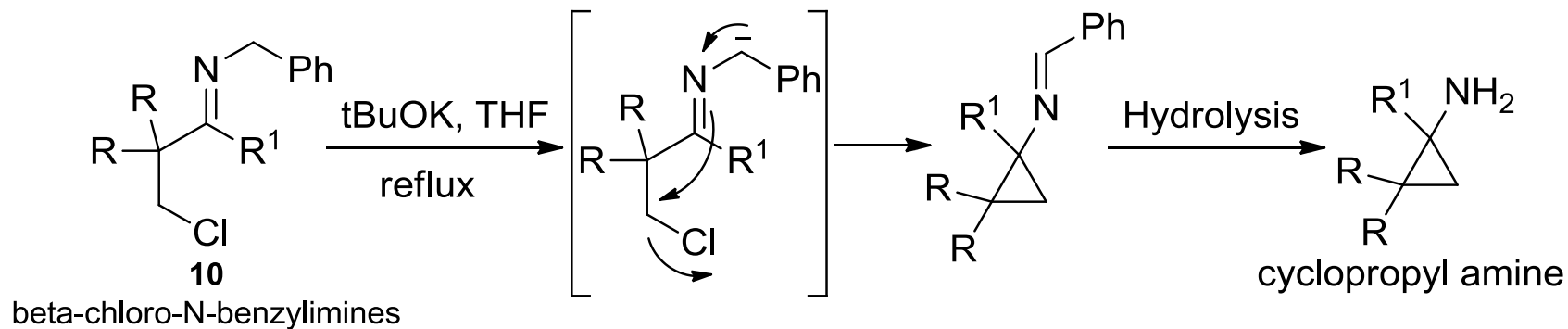


J. Yu, J. R. Falck and C. Mioskowski,
J. Org. Chem., 1992, 57, 3757-3759.

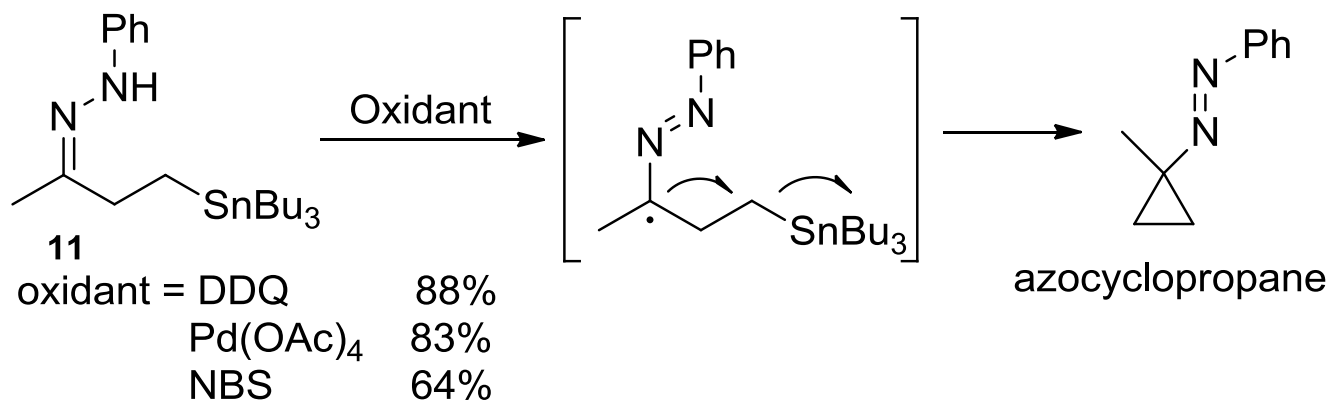
Nitrocyclopropane



F. Colobert and J.-P. Genet, *Tetrahedron Lett.*, 1985, 26, 2779-2782.

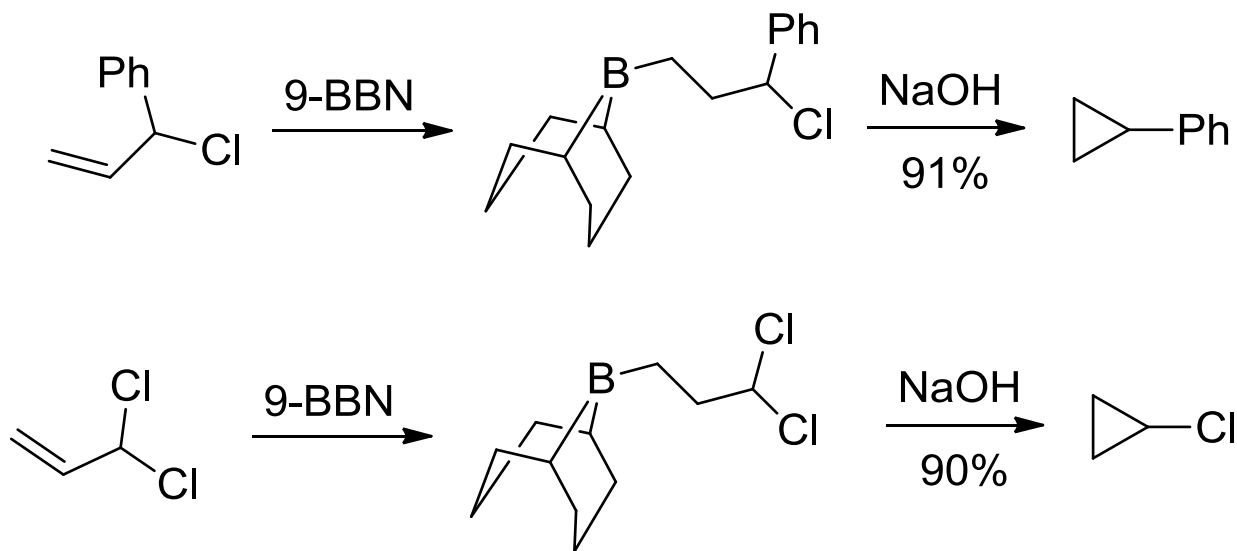
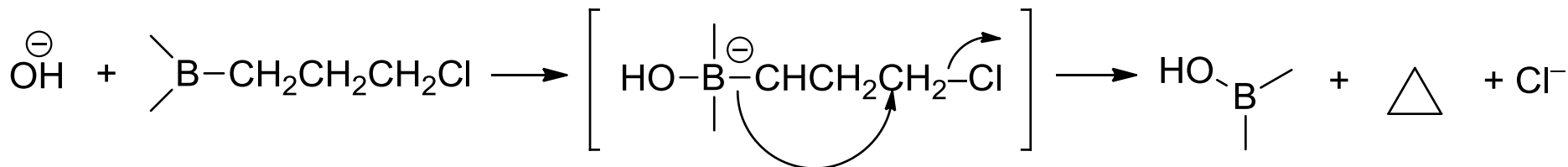
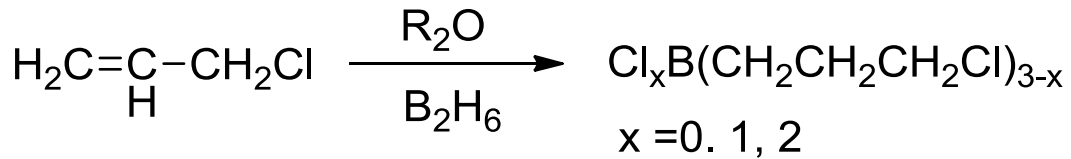


N. De Kimpe, P. Sulmon and N. Schamp, *Tetrahedron Lett*, 1989, **30**, 5029.



H. Nishiyama, H. Arai, Y. Kanai, H. Kawashima and K. Itoh, *Tetrahedron Lett*, 1986, 27, 361

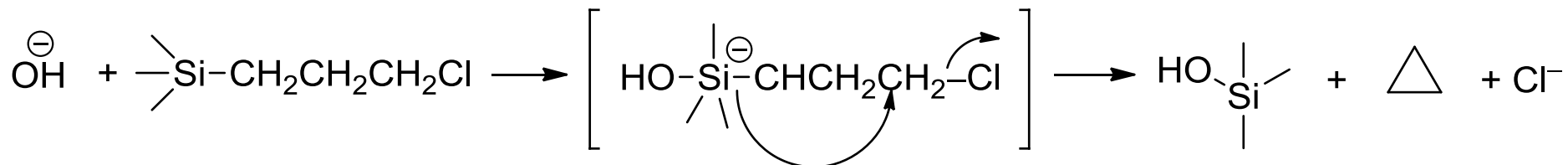
❖ D. γ -Elimination of haloalkylboranes



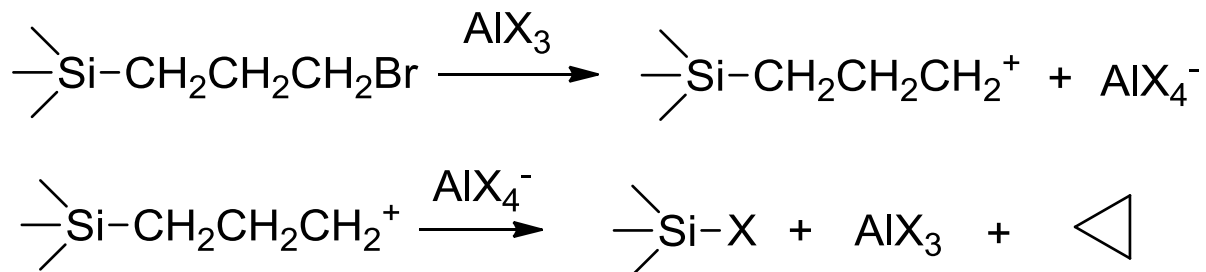
Hawthorne, M. F.; Dupont, J. A. *J. Am. Chem. Soc.* **1958**, *80*, 5830.

Brown, H. C.; Rhodes, S. P. *J. Am. Chem. Soc.* **1969**, *91*, 2149.

❖ E. γ -Elimination involving silicon

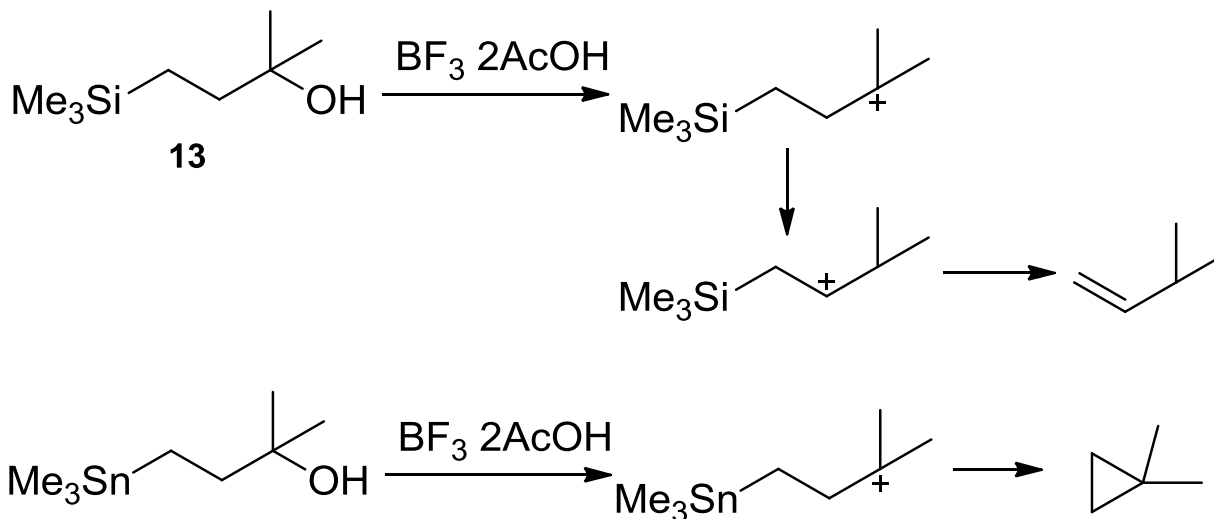
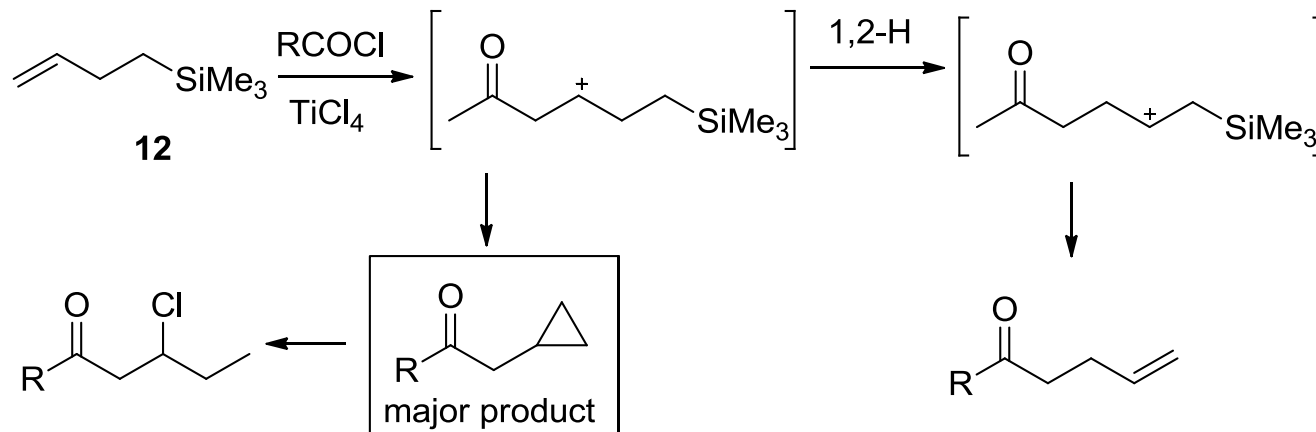


- The base coordinated with silicon and increased the carbanionic character of the silicon-carbon bond;
- **Nucleophilic attack on silicon** as the major driving force.



- Aluminum chloride to cause ionization of the carbon-halogen bond;
- The major driving force for these reactions comes from the ability of **electropositive silicon to release an electron-pair to electronically deficient carbon** within the molecule.

❖ F. γ -Elimination of Group 14 Elements involving γ -carbocation

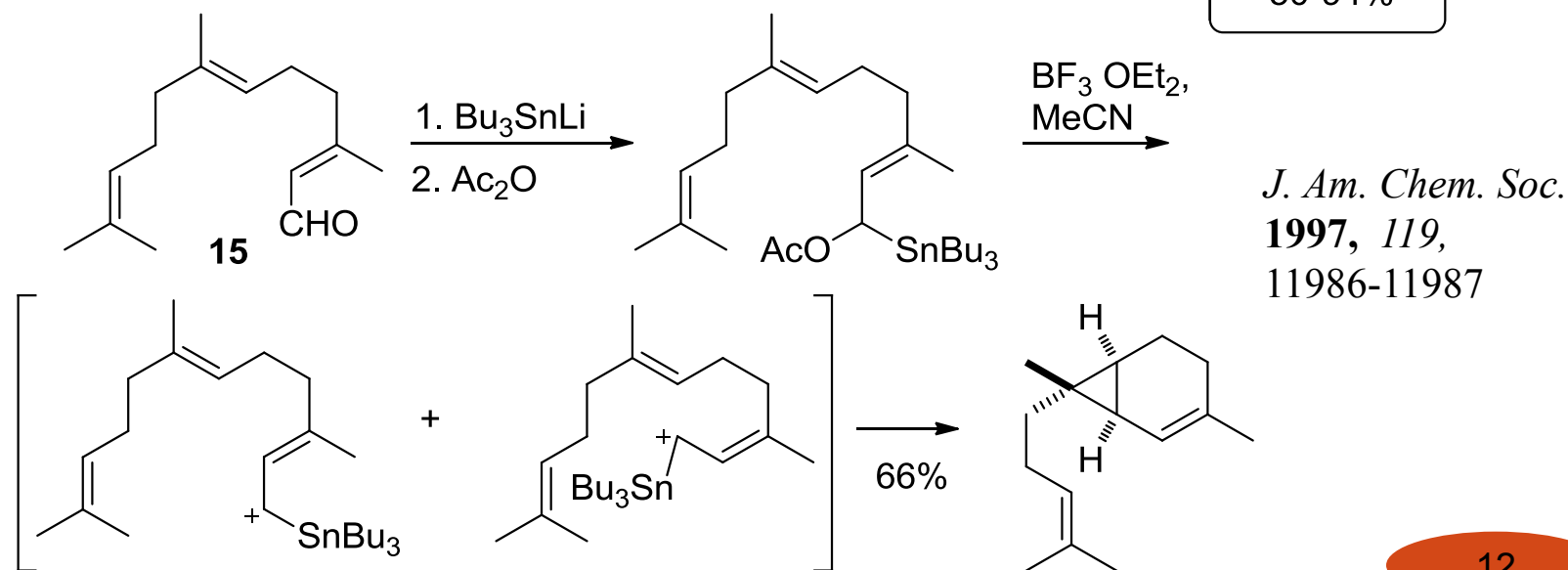
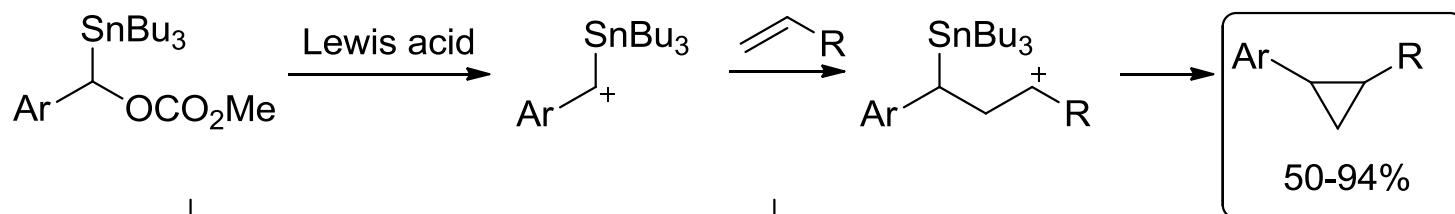
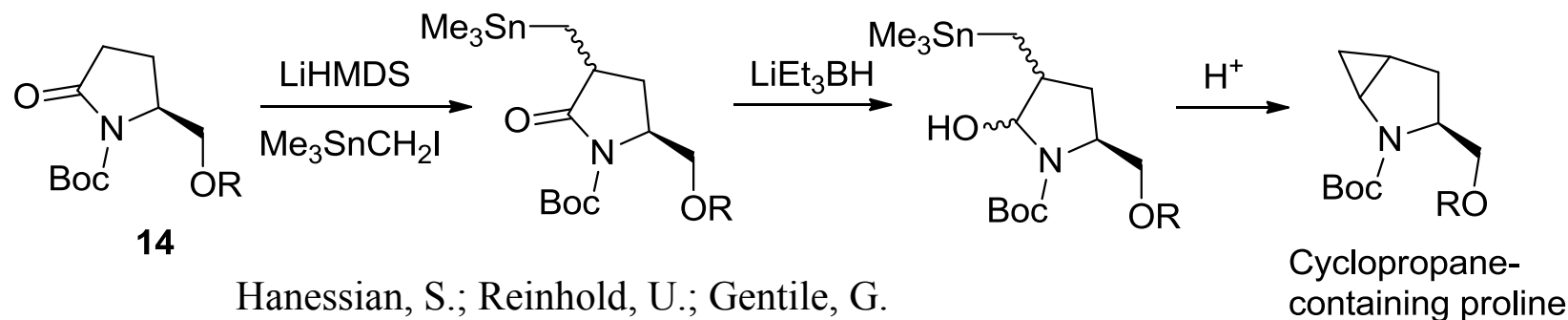


Molecular orbital consideration:
the energy level of C–Sn σ orbital is higher than that of C–Si σ orbital.

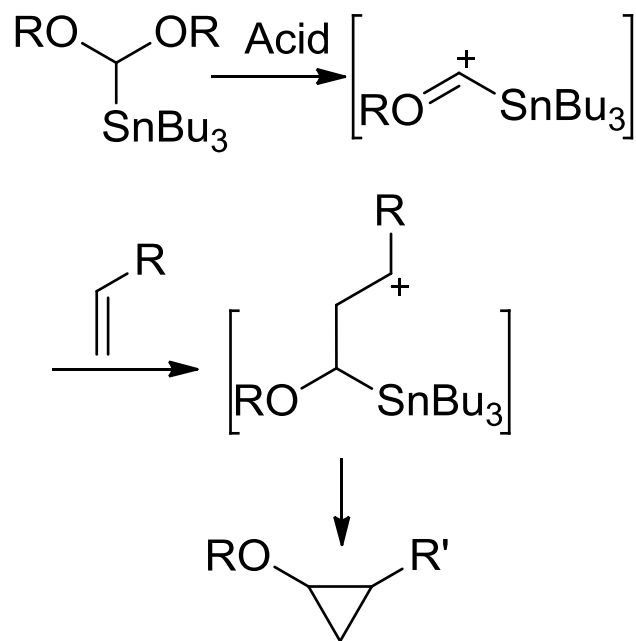
Fleming, I.; Patel, S. K. *Tetrahedron Lett.* 1981, 22, 2321.

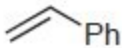

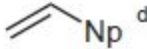

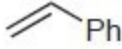

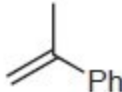


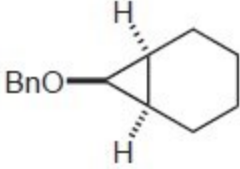

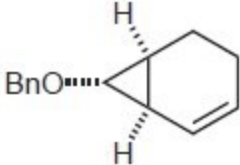
Fleming, I.; Urch, C. J. *Tetrahedron Lett.* 1983, 24, 4591

➤ Carbocationic cyclopropanation of alkenes using **tin**



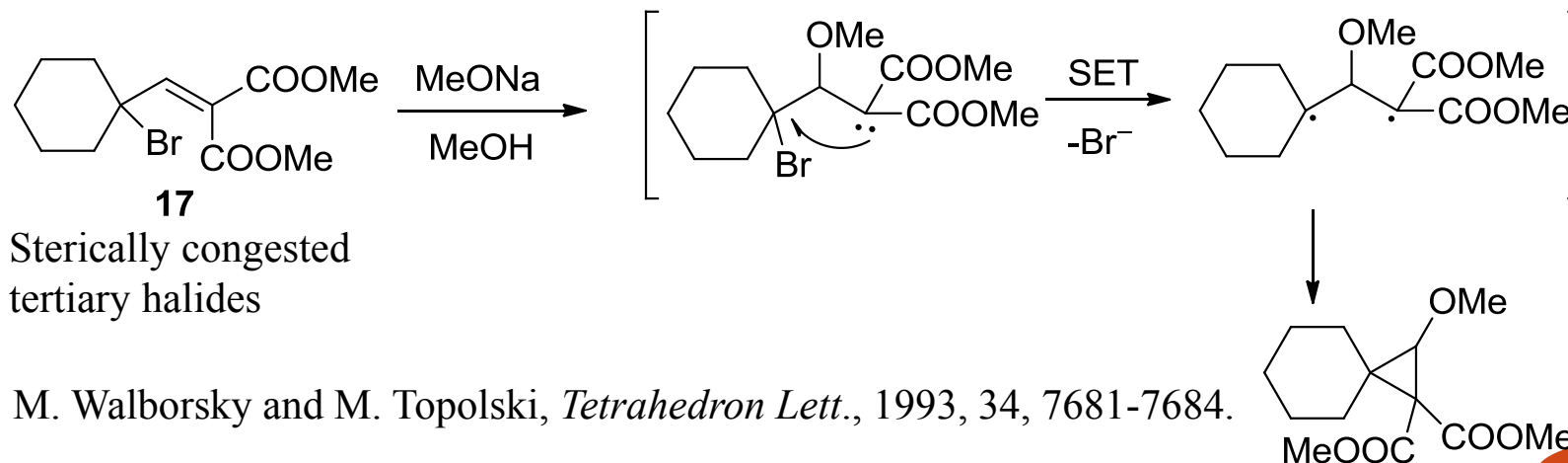
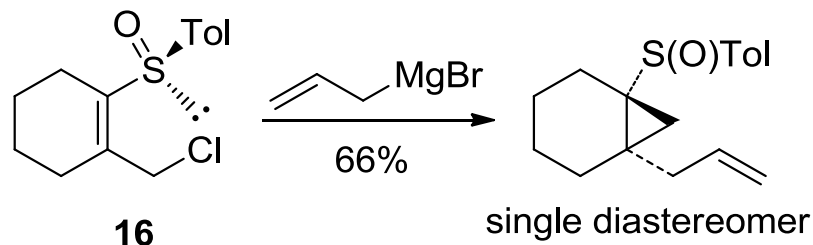
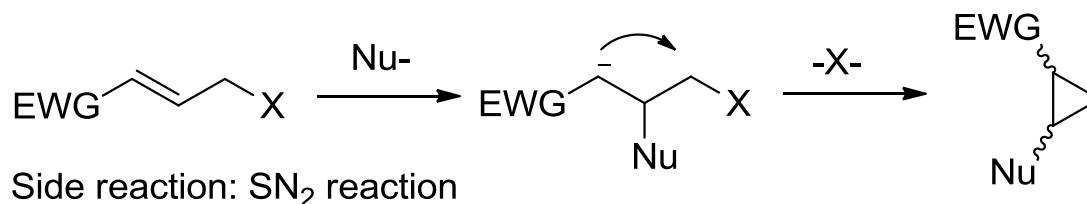
➤ Carbocationic cyclopropanation of alkenes using **tin-substituted acetals**



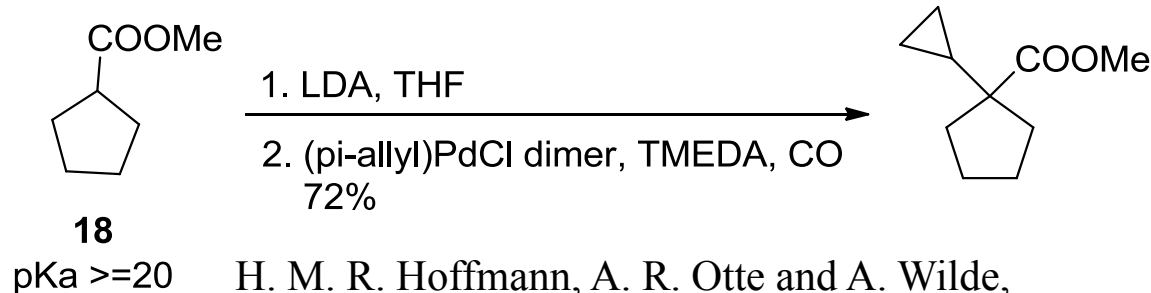
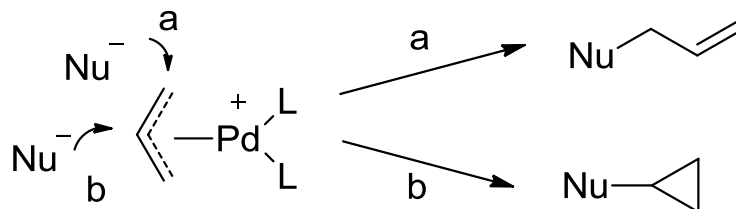
Acetal	Olefin	Product	Yield (%) ^b	<i>cis/trans</i> ^c or <i>endo/exo</i>
$\begin{array}{c} \text{EtO} \\ \\ \text{EtO}-\text{C}-\text{SnBu}_3 \\ \text{40a} \end{array}$			58	74:26
$\begin{array}{c} \text{BnO} \\ \\ \text{BnO}-\text{C}-\text{SnBu}_3 \\ \text{40b} \end{array}$			75	69:31
			89	74:26
			86	89:11
			74	65:35
			31	33:67

❖ G. Cyclization of allylic derivatives

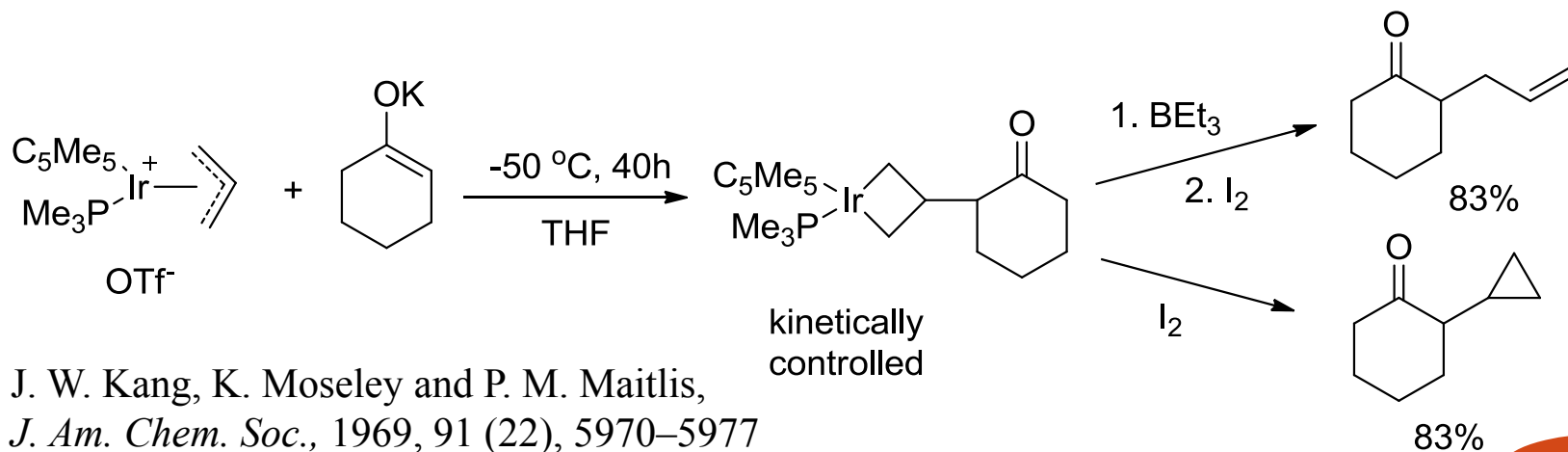
➤ γ -Substituted michael acceptors and nucleophiles



➤ Reactions involving a metal complex with π -allyl ligand

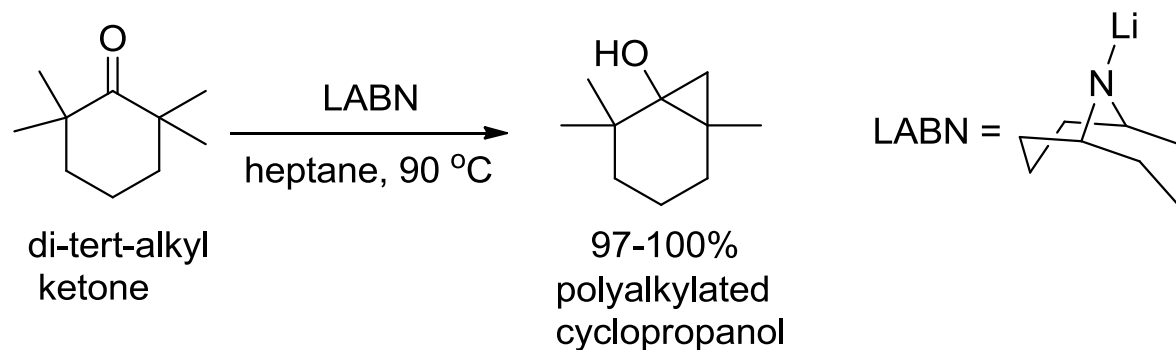
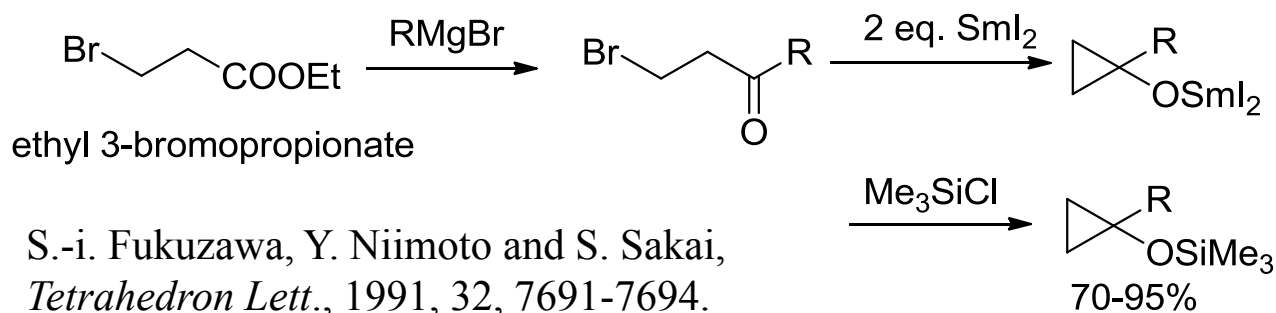
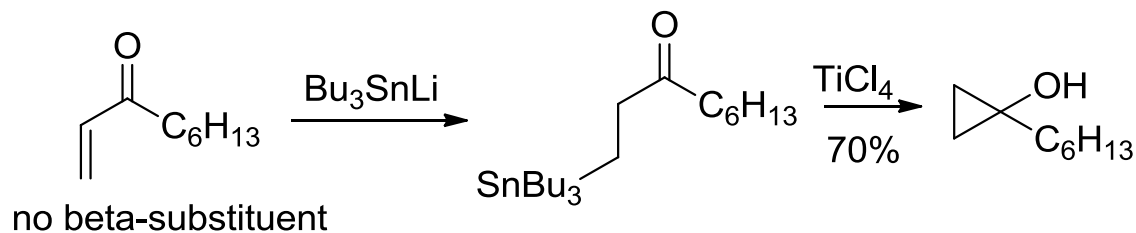


H. M. R. Hoffmann, A. R. Otte and A. Wilde,
Angew. Chem. Int. Ed. Engl. 1992, **31**, 234-236.



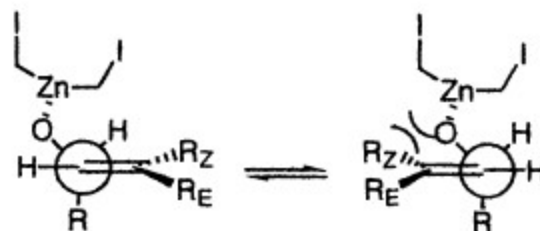
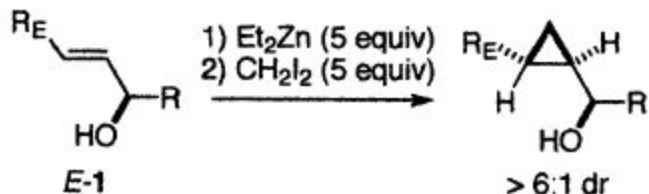
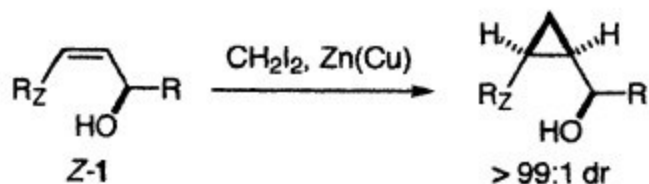
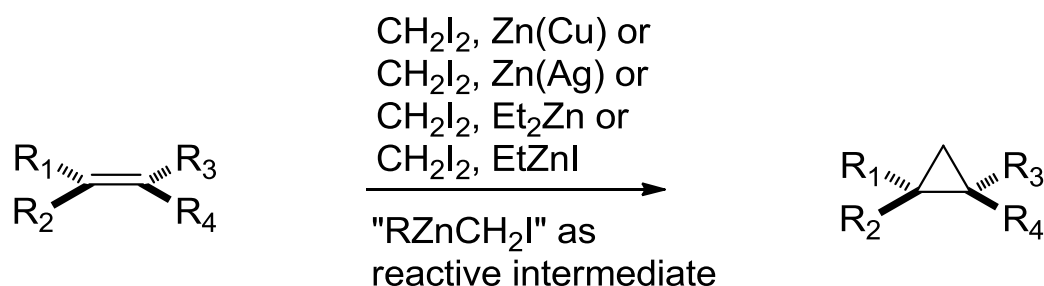
J. W. Kang, K. Moseley and P. M. Maitlis,
J. Am. Chem. Soc., 1969, 91 (22), 5970–5977

➤ H. **Cyclopropanols** from **carbonyl derivatives** via 1,3-bond formation between the carbonyl and C-beta carbons

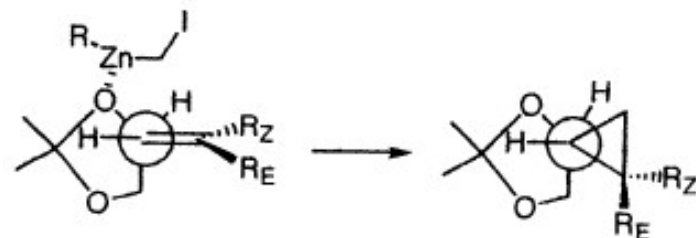
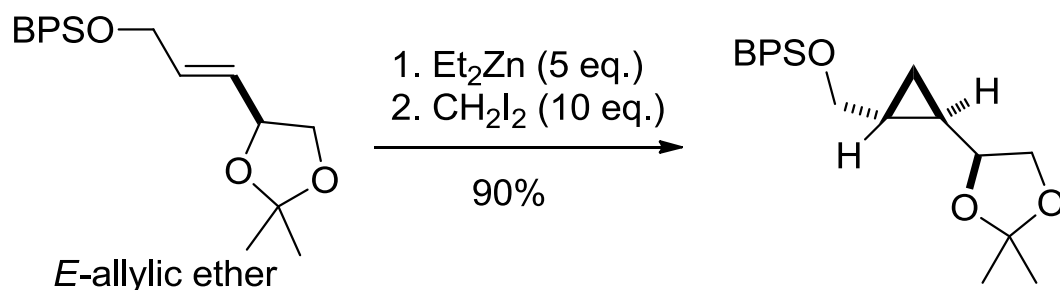
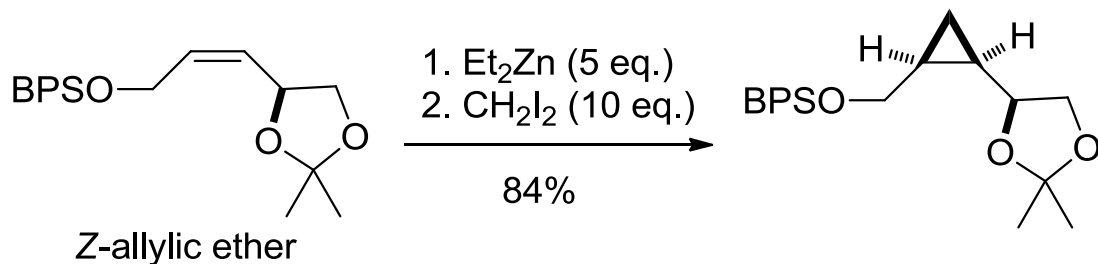


II. Cyclopropanation C-C multiple bonds with carbenes and carbenoids

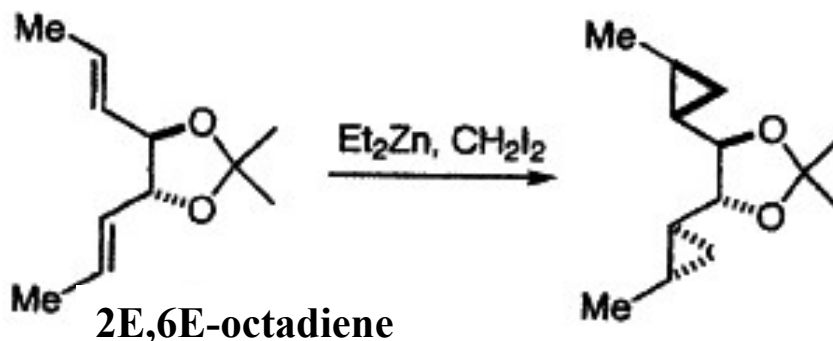
❖ A. Simmons-Smith cyclopropanation

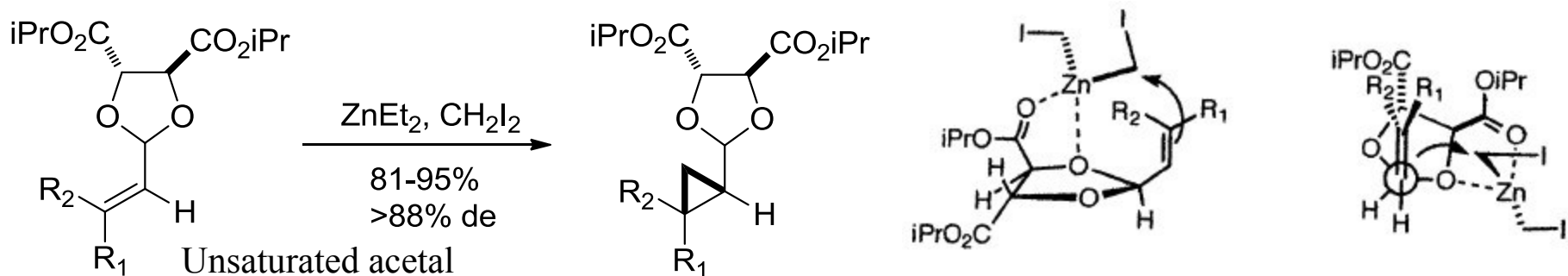


II. Cyclopropanation C-C multiple bonds with carbenes and carbenoids

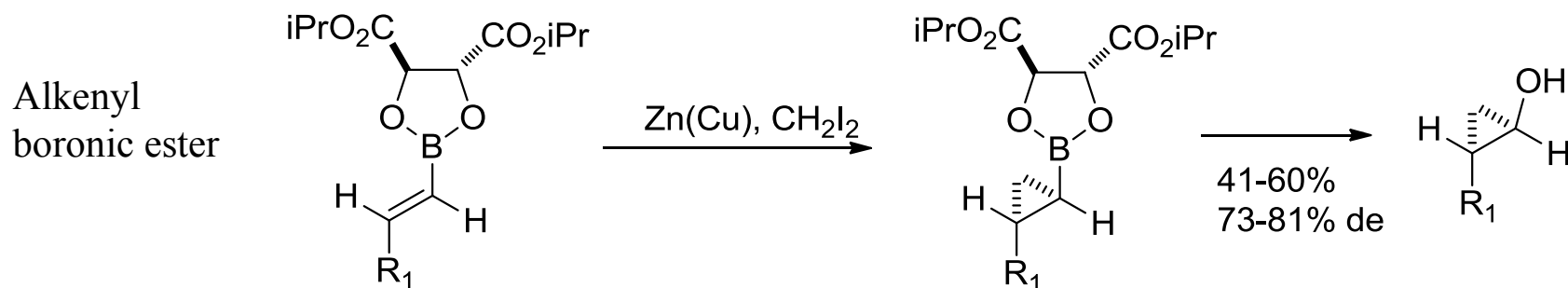


T. Morikawa, H. Sasaki, R. Hanai, A. Shibuya and T. Taguchi, *J. Org. Chem.*, 1994, 59, 97-103.

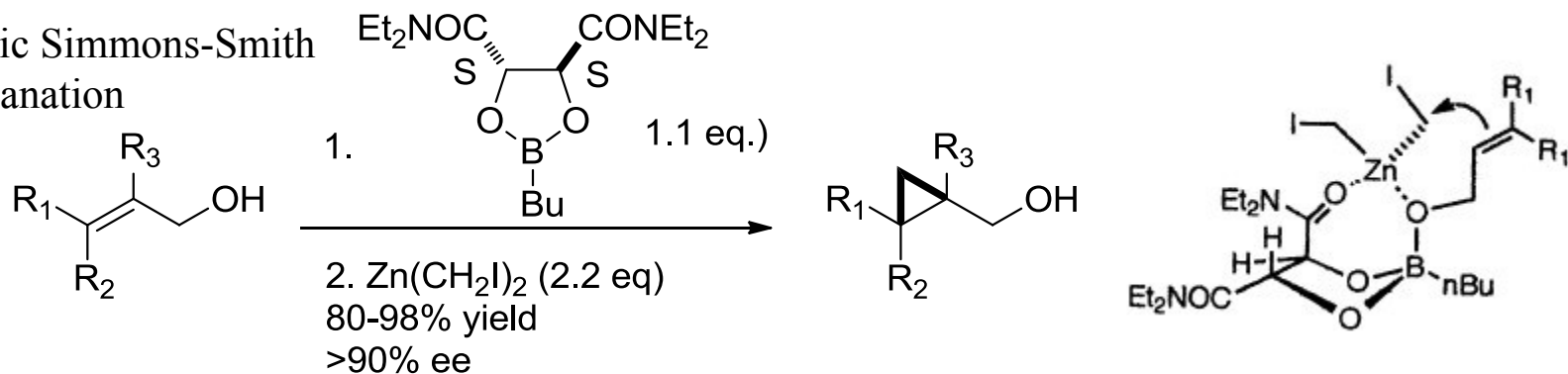




A. Mori, I. Arai, H. Yamamoto, H. Nakai and Y. Arai, *Tetrahedron*, 1986, 42, 6447-6458.



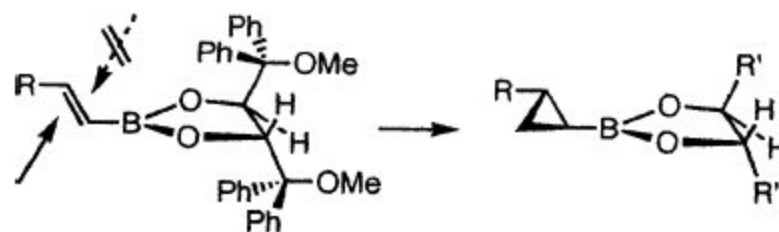
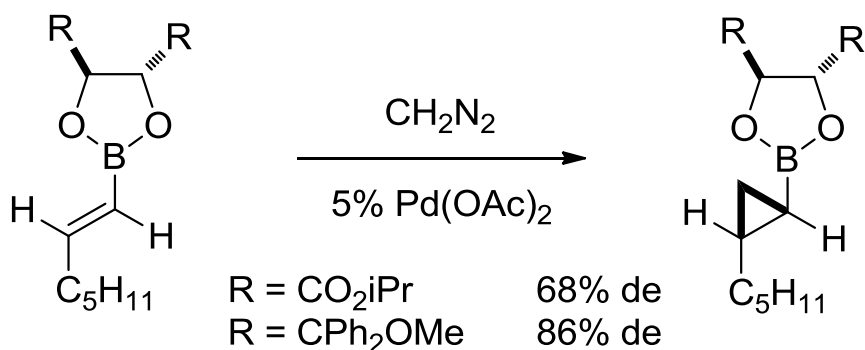
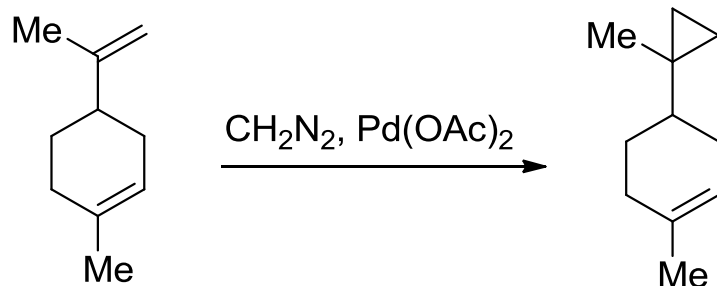
Asymmetric Simmons-Smith cyclopropanation



A. B. Charette and H. Juteau, *J. Am. Chem. Soc.*, 1994, 116, 2651-2652.

❖ B. Olefin cyclopropanation with diazomethane/palladium

“**Pd-carbene**” species as intermediate, only terminal olefins, 1,1-disubstituted, and 1,2-disubstituted olefins are reactive

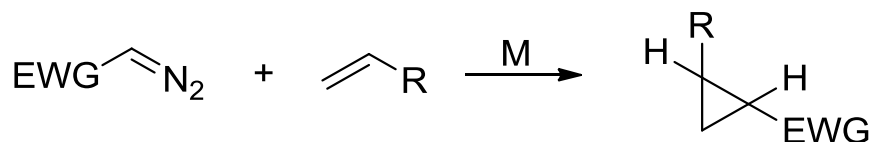


Less hindered direction

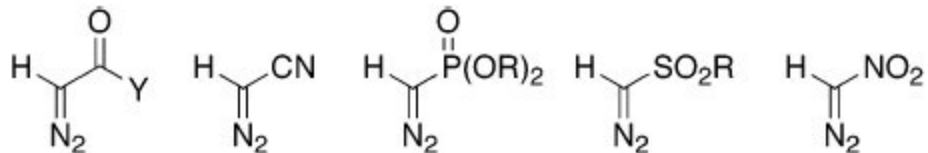
J. E. A. Luithle and J. Pietruszka, *J. Org. Chem.*, **1999**, 64, 8287-8297

J. Pietruszka and M. Widenmeyer, *Synlett*, 1997, **1997**, 977-979.

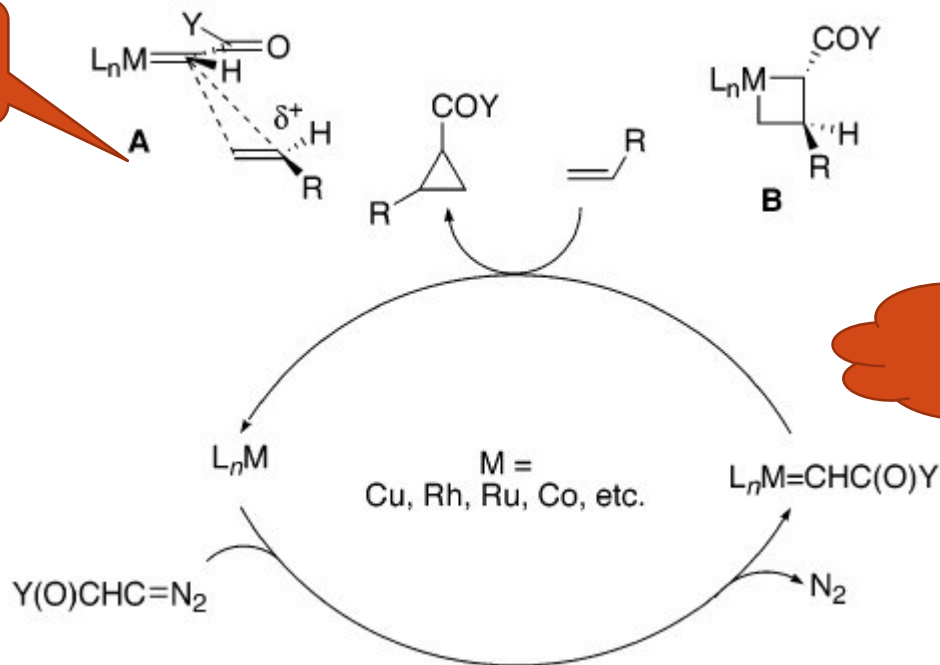
- ❖ C. Diazoalkanes bearing an Electron-Withdrawing group
 (metal catalysts derived from **Cu, Rh, Ru, Co**, Fe, Os, **Pd**, Pt, Cr have been reported to catalyze the diazo reagent decomposition.)

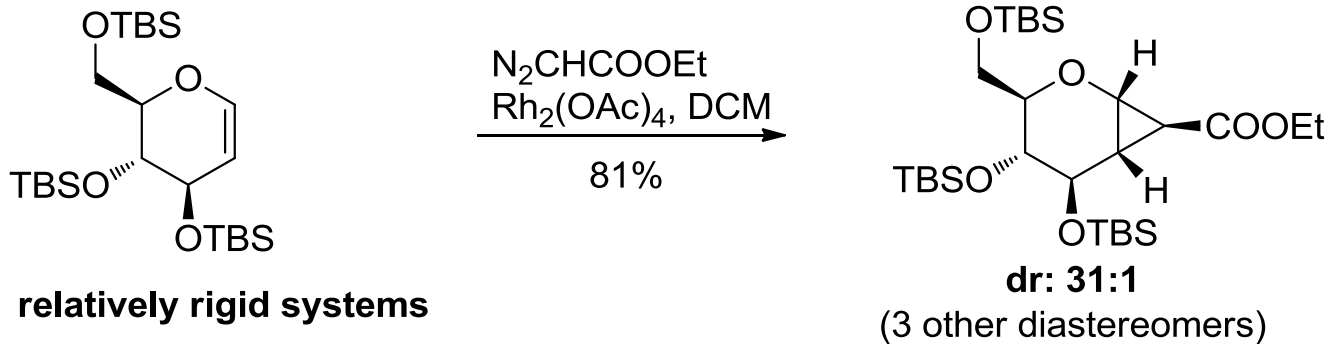
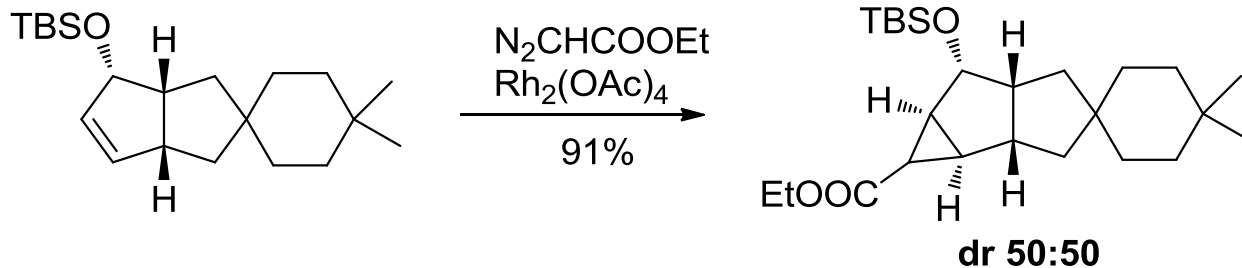


Most common diazo reagents



Favor the *trans* isomer

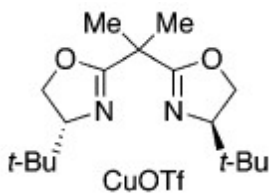
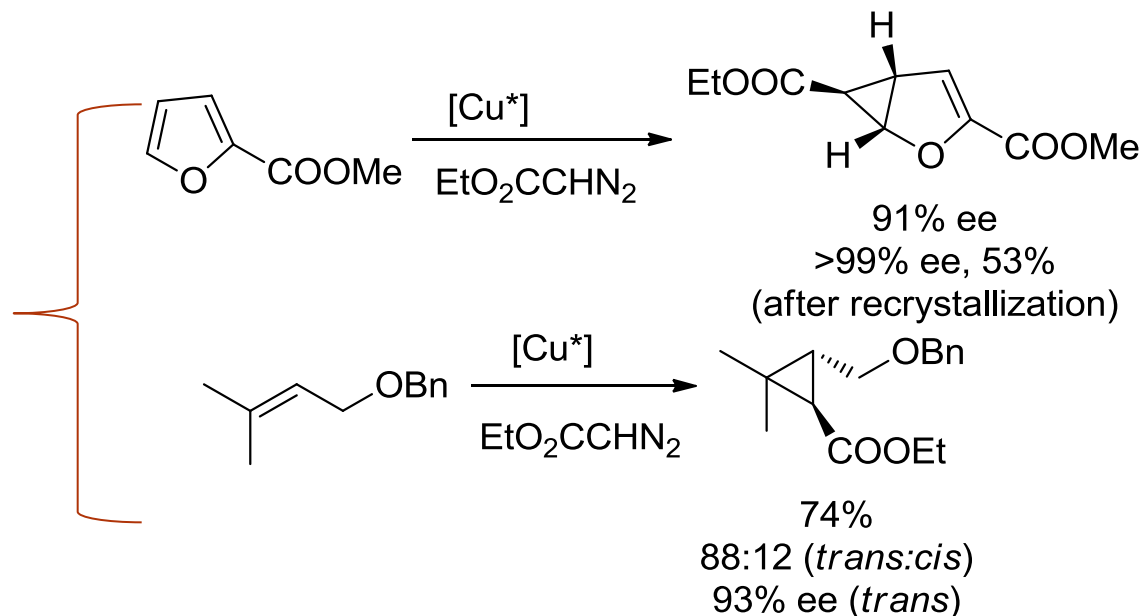




J. O. Hoberg and D. J. Claffey, *Tetrahedron Lett.*, 1996, **37**, 2533-2536.

relatively rigid systems

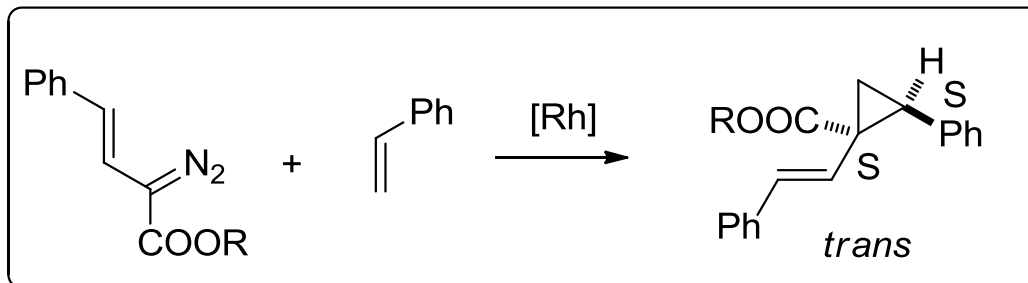
Enantioselective
copper-based
 intermolecular
 cyclopropanation



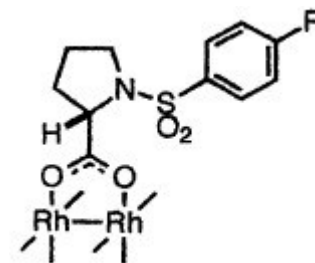
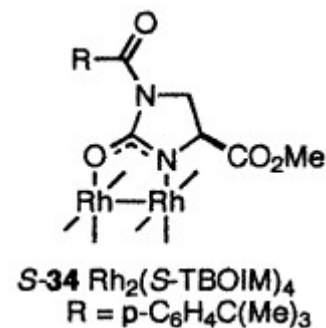
C. Böhm and O. Reiser, *Org. Lett.*, 2001, **3**, 1315-1318

N. Østergaard, J. F. Jensen and D. Tanner, *Tetrahedron*, 2001, **57**, 6083.

➤ Vinyldiazoester reagents in asymmetric catalysis.

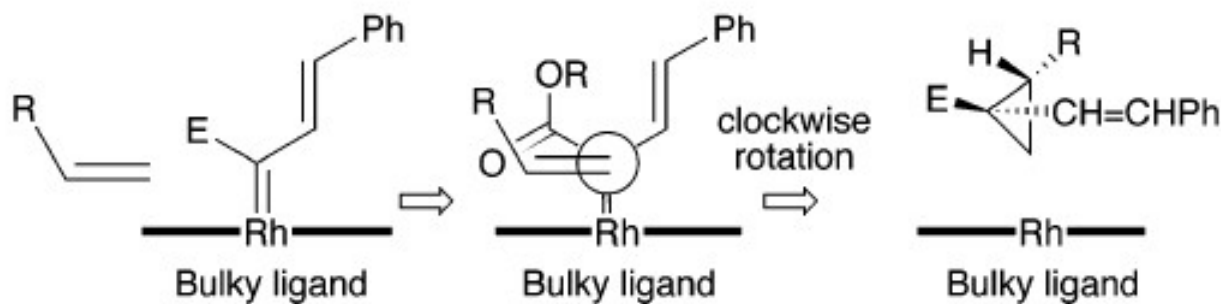


Me	$\text{Rh}_2(\text{OAc})_4$	94% (racemic)
Me	S-34, $\text{Rh}_2(\text{S-TBSP})_4$	63% (90%ee, S,S)
Me	S-38, $\text{Rh}_2(\text{S-DOSP})_4$	83% (92%ee, S,S)
(R)-pantolactone	$\text{Rh}_2(\text{O}_2\text{CC}_7\text{H}_{15})_4$	84% (97%de, R,R)



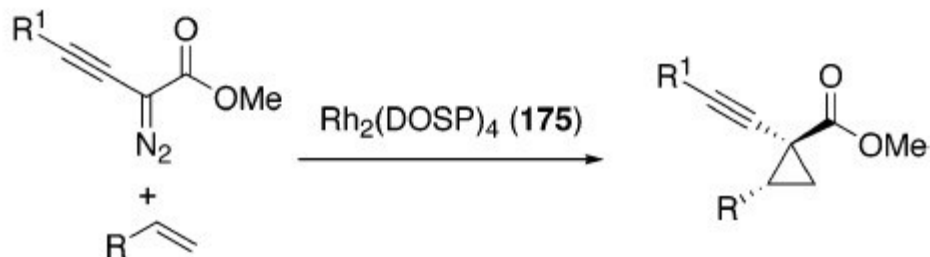
S-38 $\text{Rh}_2(\text{S-DOSP})_4$, R = C₁₂H₂₅

H. M. L. Davies, P. R. Bruzinski, D. H. Lake, N. Kong and M. J. Fall,
J. Am. Chem. Soc., 1996, 118, 6897-6907.



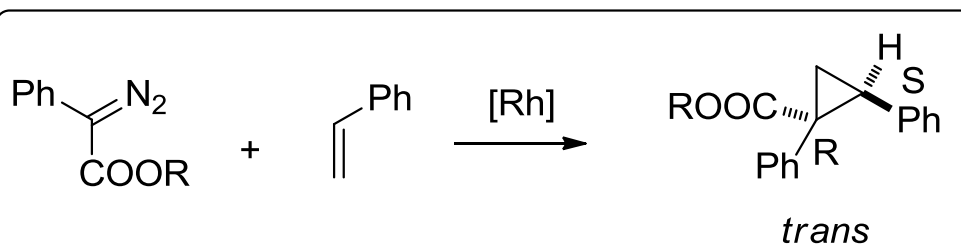
Diastereoselective rhodium-catalyzed cyclopropanation

➤ Ary- and alkynyldiazoester reagents in asymmetric catalysis.

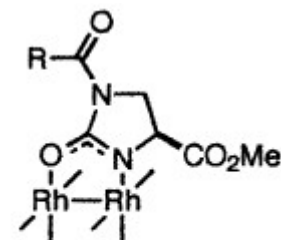


R ¹	R	yield (%)	dr	ee (%)
Ph	Ph	68	92:8	89
Et	Ph	91	99:1	56
TMS	Ph	84	94:6	65
Ph	OBu	66	>97:3	87
Ph	OAc	61	>97:3	95

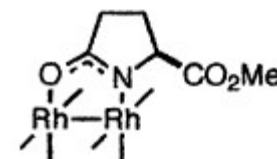
Same trends as those found with the vinyl-substituted reagents



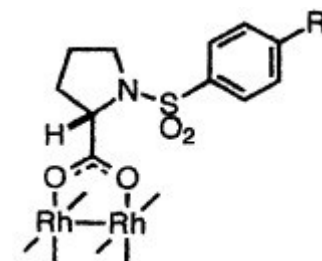
S-36, Rh₂[S-MEPY]₄ 27% (49%ee, 1*R*,2*S*)
 S-34, Rh₂(S-TBSP)₄ 90% (87%ee, 1*R*,2*S*)
 S-37, Rh₂(S-TBOIM)₄ 63% (77%ee, 1*R*,2*S*)



S-34 Rh₂(S-TBOIM)₄
R = p-C₆H₄C(Me)₃

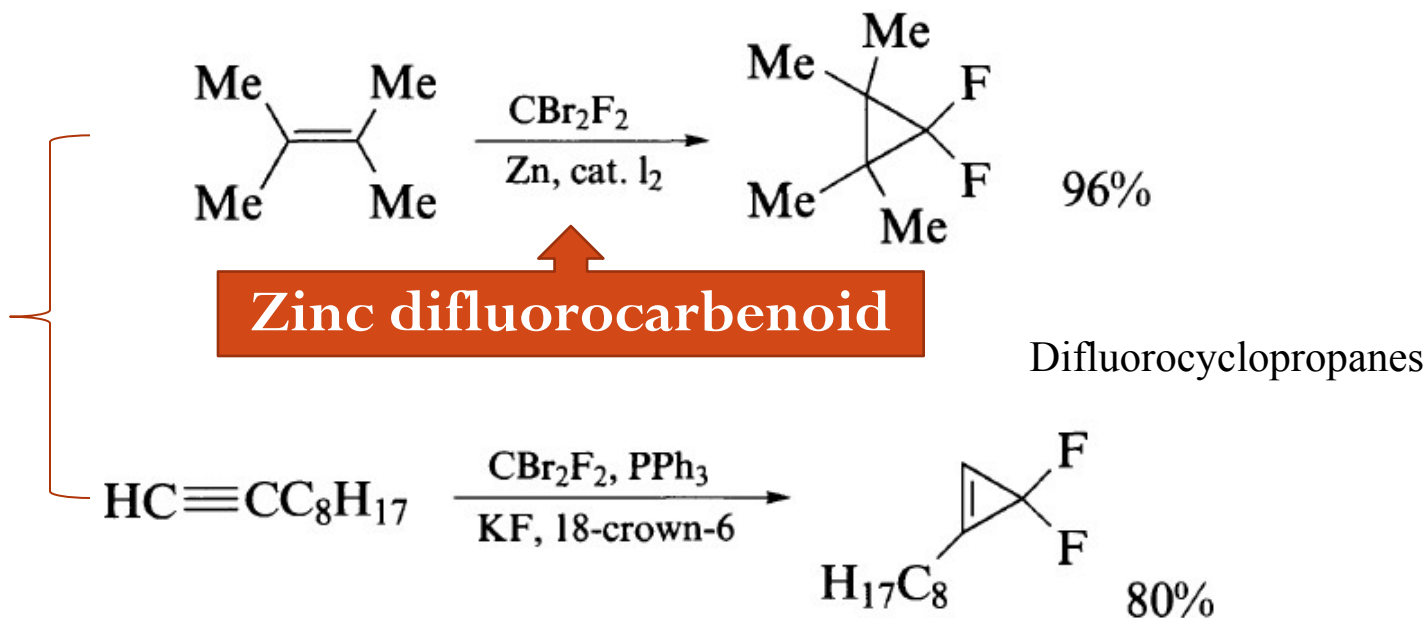


S-36 Rh₂(S-MEPY)₄

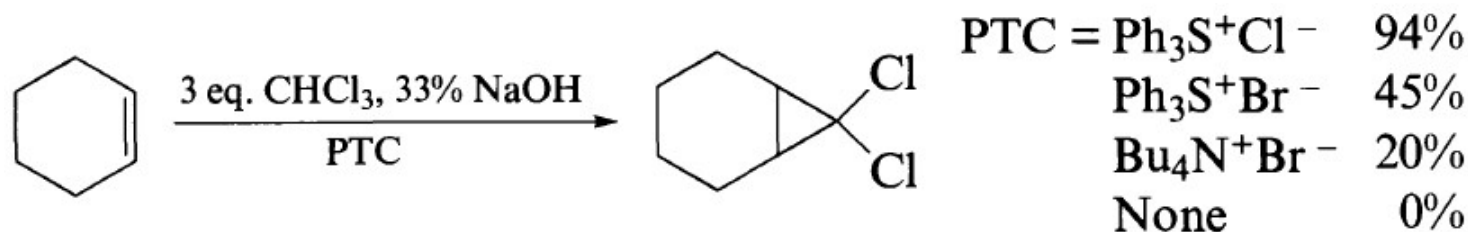


S-37 Rh₂(S-TBSP)₄, R = t-Bu
 175 R = C₁₂H₂₆ Rh₂[2S-DOSP]₄

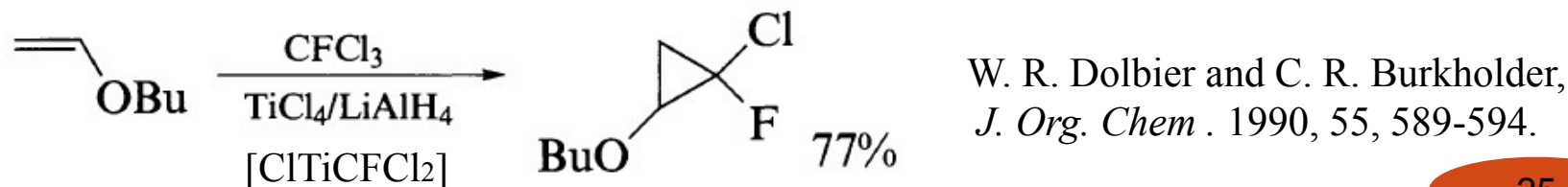
❖ D. Halocarbenes



Y. Bessard and M. Schlosser, *Tetrahedron*, 1991, **47**, 7323-7328.

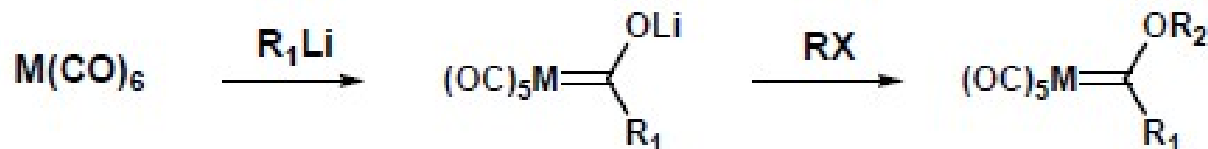


S. Kondo, Y. Takeda and K. Tsuda, *Synthesis*, 1989, **1989**, 862-864.

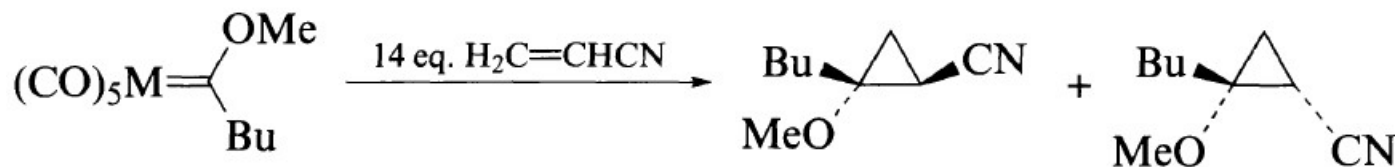


❖ E. Carbenes alpha-substituted with heteroatoms other than halogen

- Alkoxycarbene from Fischer carbene complex $[(\text{CO})_5\text{M}=\text{CR}_1(\text{OR}_2)]$; $\text{M} = \text{Cr}, \text{Mo}, \text{W}$; $\text{R}_1 = \text{alkyl, alkenyl and aryl}$

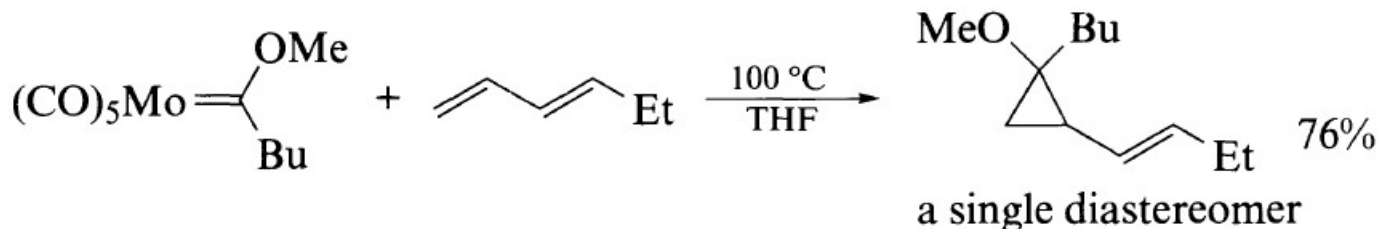


Electron-deficient alkenes

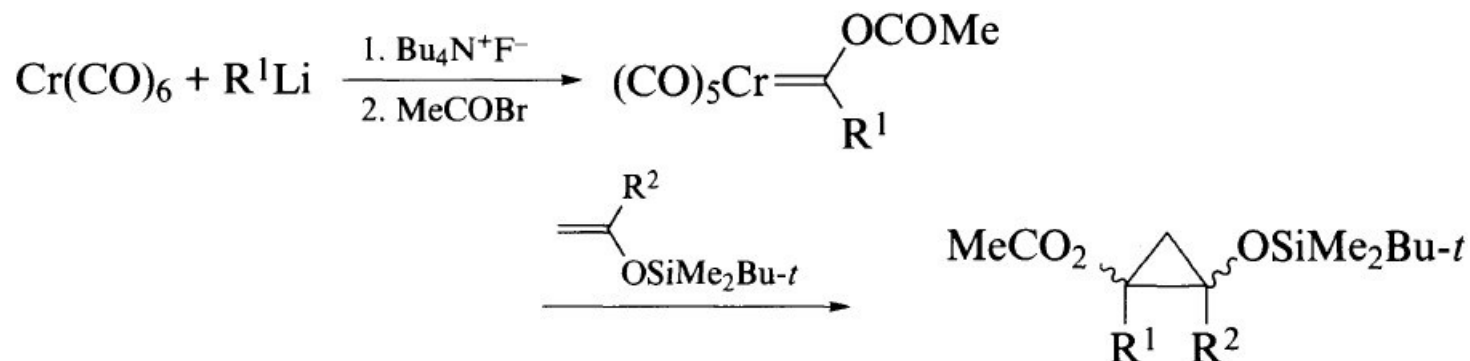


$\text{M} = \text{Mo}$ (THF / 65 °C / 1 h)	32%	23%
Cr (PhMe / 80 °C / 2.5 h)	26%	24%
W (PhMe / 110 °C / 5 h)	39%	30%

Conjugated alkenes



➤ The reactions of silyl enol ethers with acyloxycarbene-chromium complex

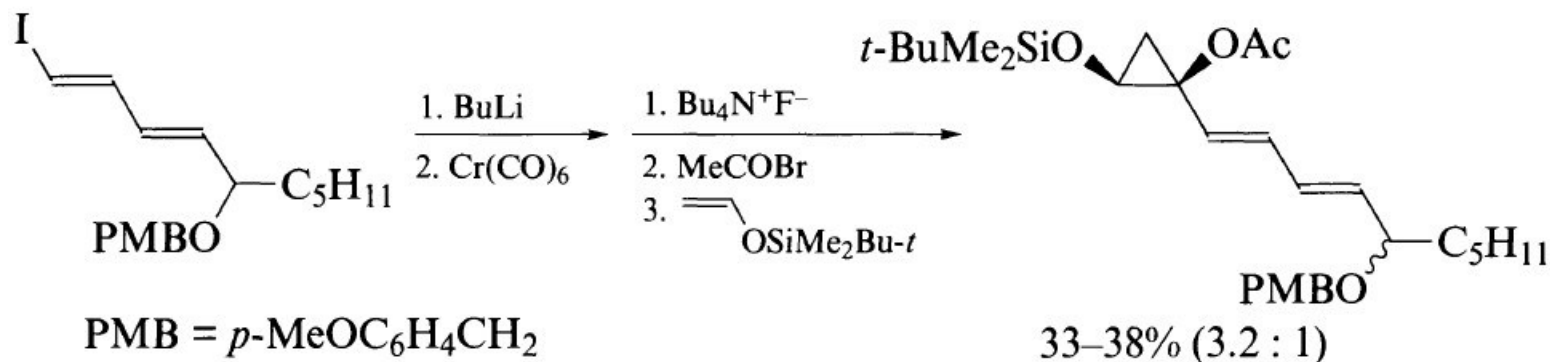


$\text{R}^1 = \text{Me}, \text{R}^2 = \text{Ph}$ 78%, (*E*) : (*Z*) = 1 : 1

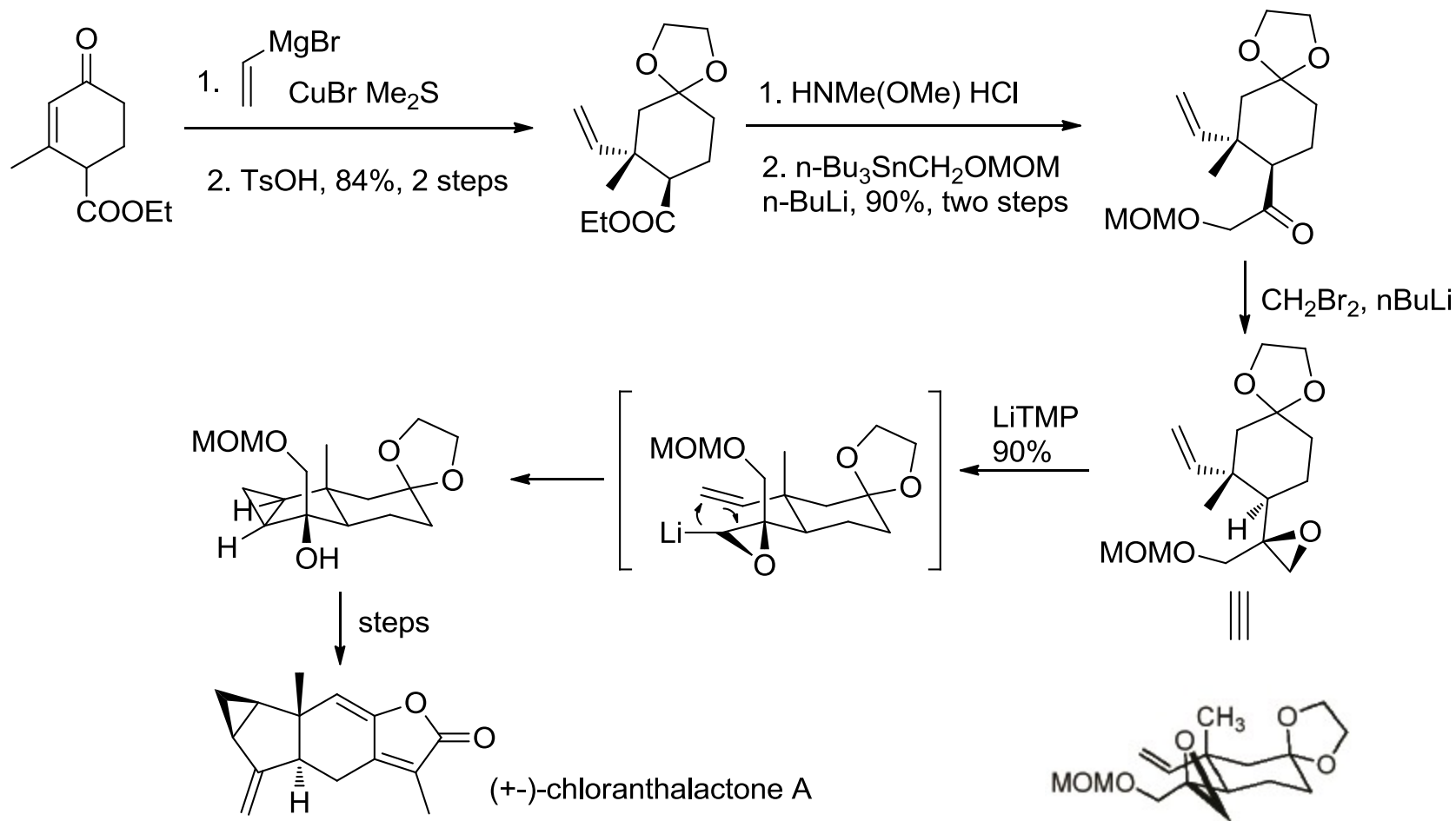
$\text{R}^1 = 1\text{-cyclohexenyl}, \text{R}^2 = \text{H}$ 48%, (*cis* only)

$\text{R}^1 = \text{Ph}, \text{R}^2 = \text{H}$ 61%, (*E*) : (*Z*) = 6.4 : 1

C. K. Murray, D. C. Yang and W. D. Wulff, *J. Am. Chem. Soc.*, 1990, 112, 5660-5662.

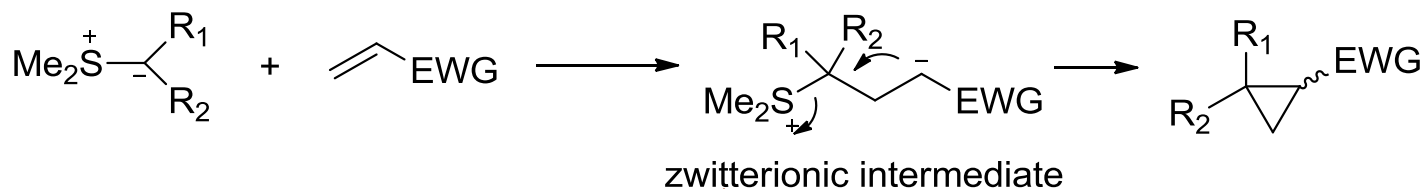


❖ F. Intramolecular cyclopropanation of lithiated epoxide

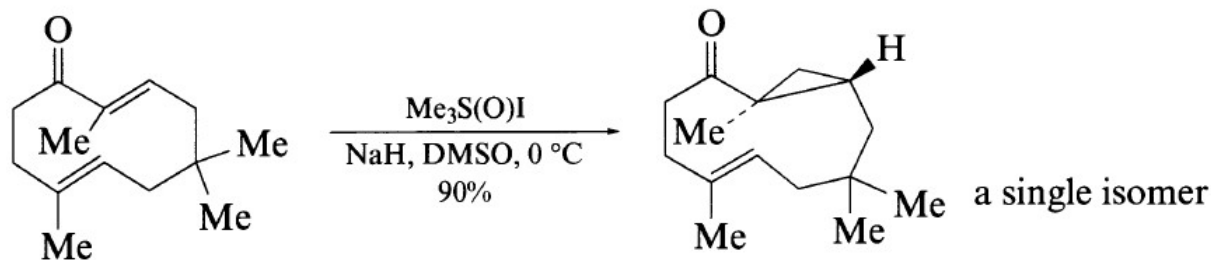


III. Cyclopropanation of Michael acceptors

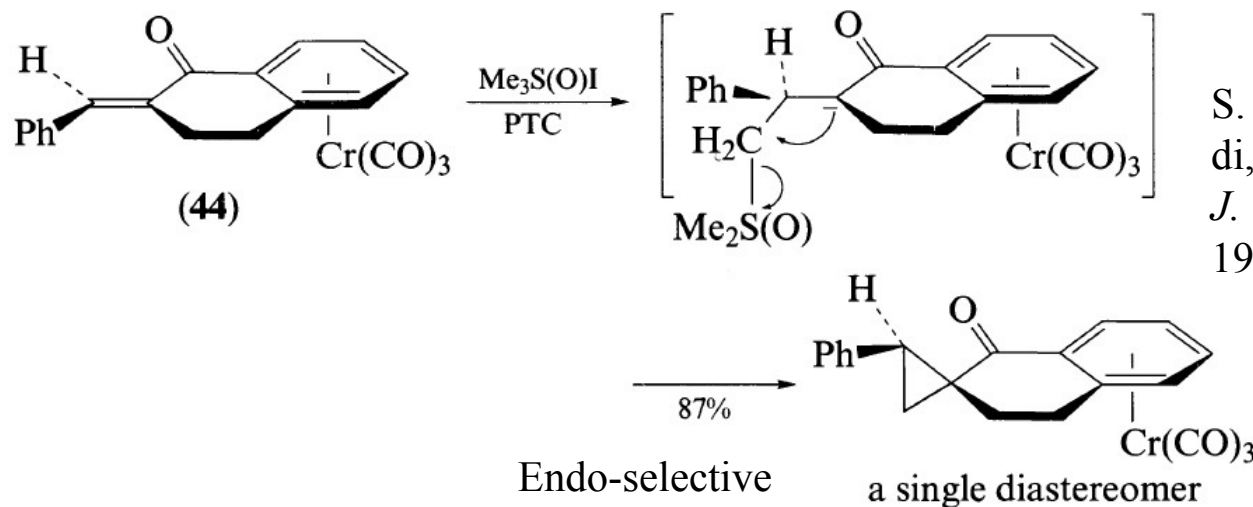
❖ With sulfur ylides



Generally cyclopropanation occurs on the less hindered side of double bond



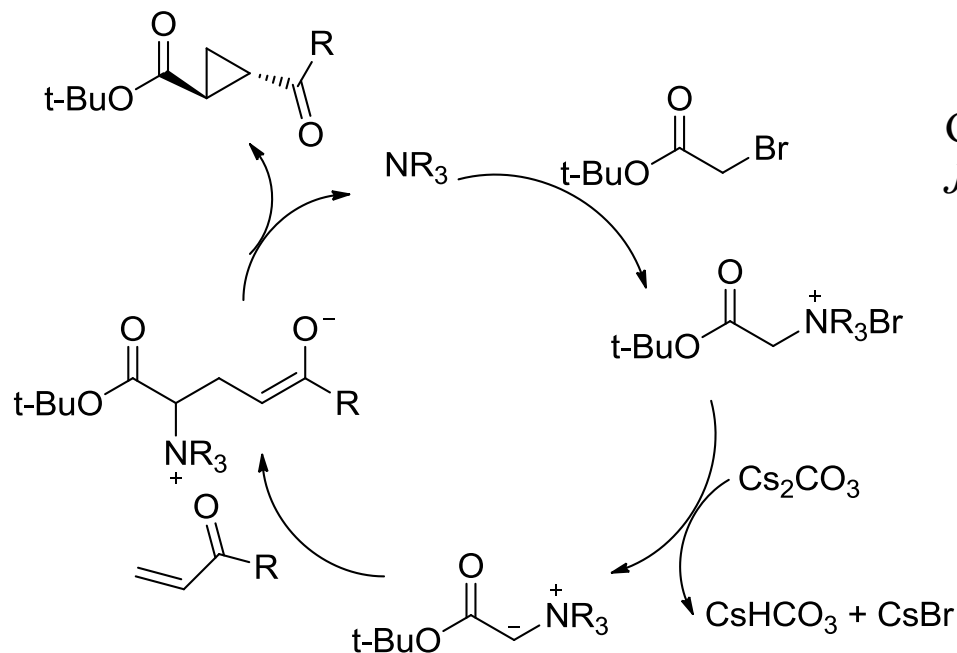
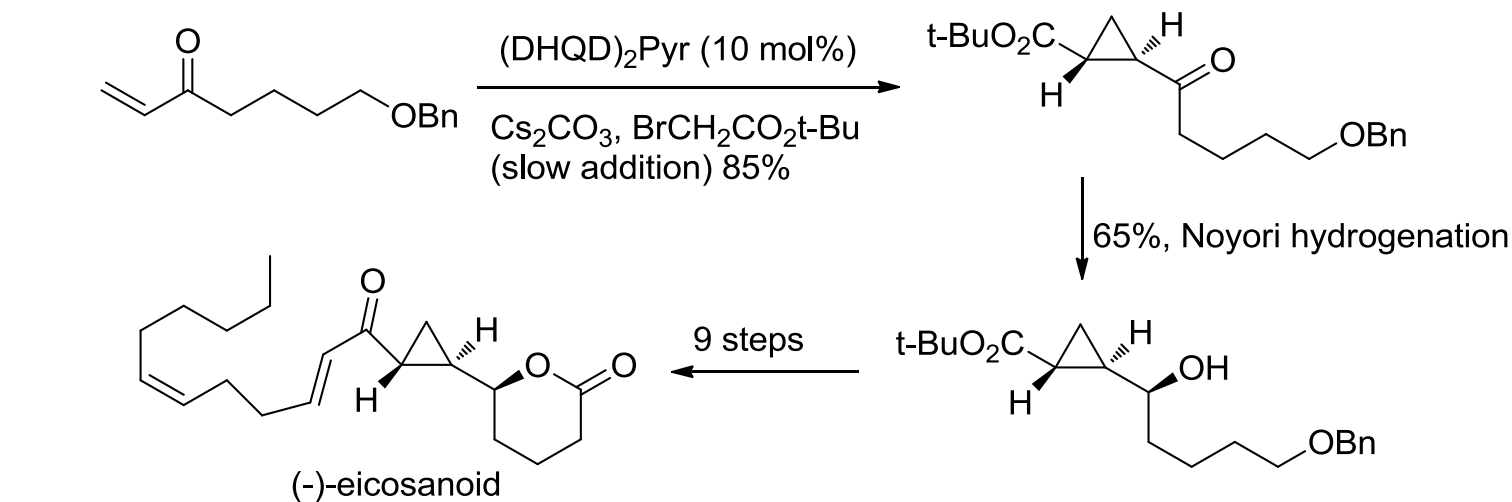
T. Takahashi, Y. Yamashita, T. Doi and J. Tsuji, *J. Org. Chem.*, 1989, 54, 4 273-4275.



S. Ganesh, K. M. Sathe, M. Nandi, P. Chakrabarti and A. Sarkar, *J. Chem. Soc., Chem. Commun.*, 1993, 224-226.

III. Cyclopropanation of Michael acceptors

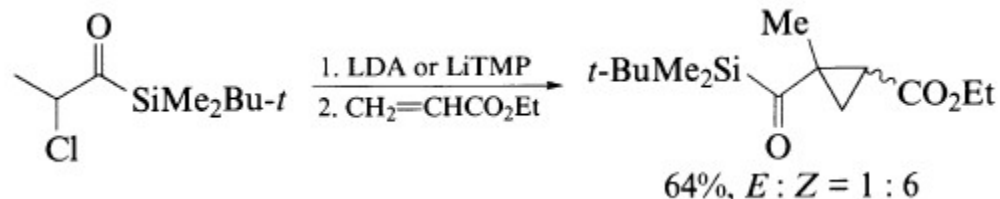
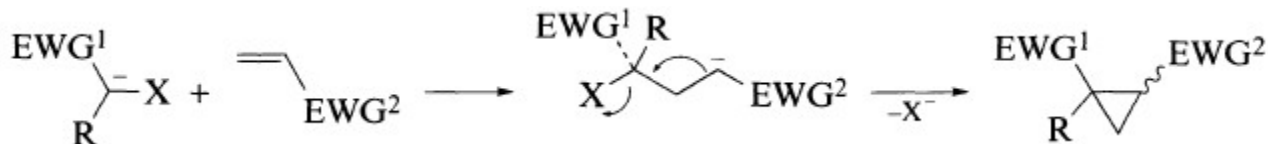
❖ With ammonium ylides



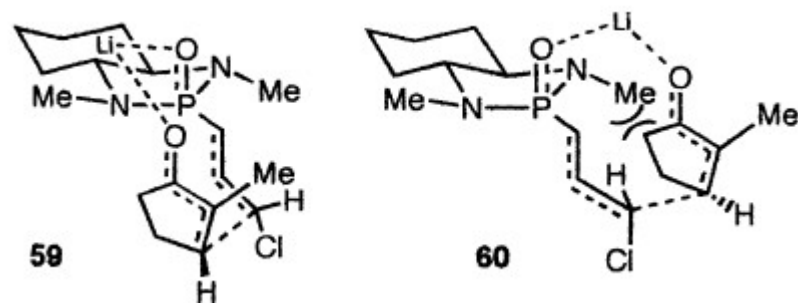
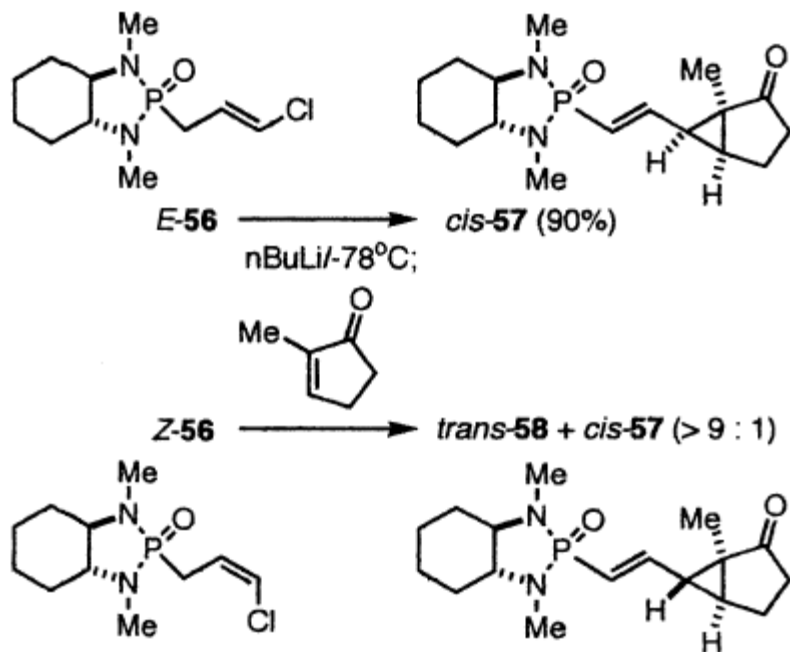
G. Kumaraswamy and M. Padmaja,
J. Org. Chem., 2008, 73, 5198–5201.

III. Cyclopropanation of Michael acceptors

❖ With alpha-halocarbanions and related species



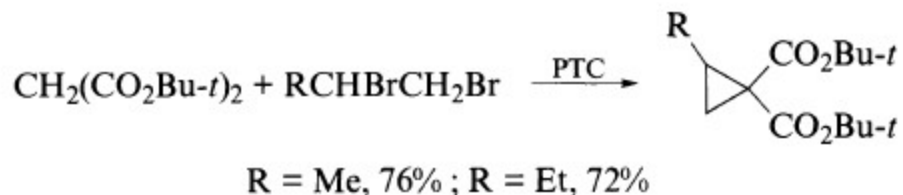
J. S. Nowick and R. L. Danheiser,
Tetrahedron, 1988, 44, 4113-4134.



S. Hanessian, D. Andreotti and A. Gomtsyan,
J. Am. Chem. Soc., 1995, 117, 10393-10394.

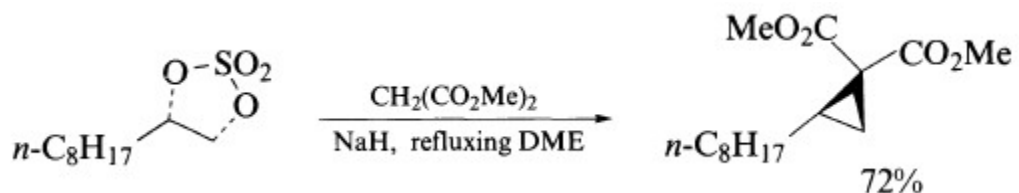
IV. Cyclopropanation of active methylene compounds

Dimethyl or diethyl malonate gave low yield



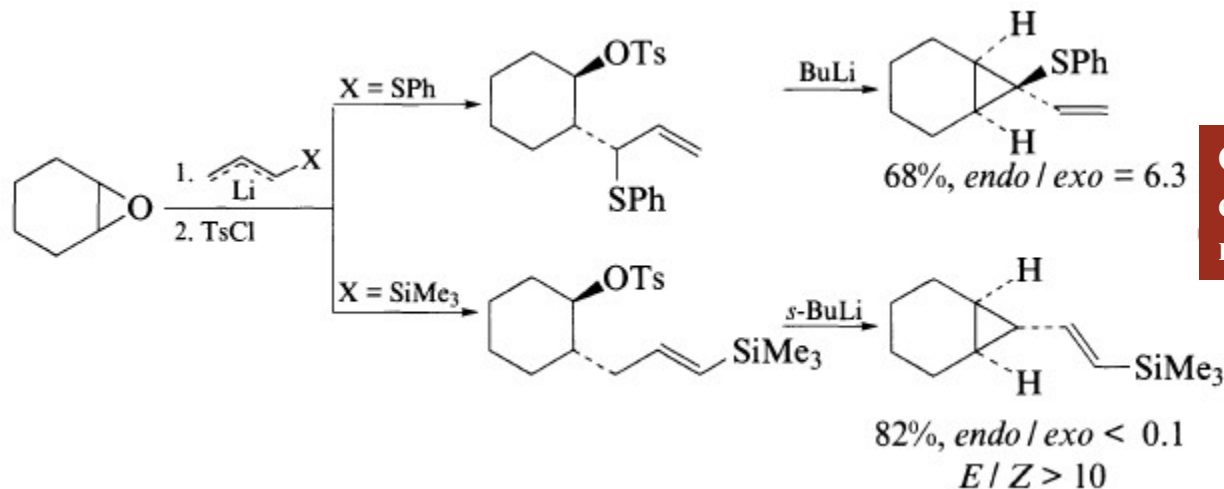
1,2-dihaloethane as reagents

J. E. Baldwin, R. M. Adlington and B. J. Rawlings, *Tetrahedron Lett.*, 1985, 26, 481-484.



Cyclic sulfates as reagents

Y. Gao and K. B. Sharpless, *J. Am. Chem. Soc.*, 1988, 110, 7538-7539.

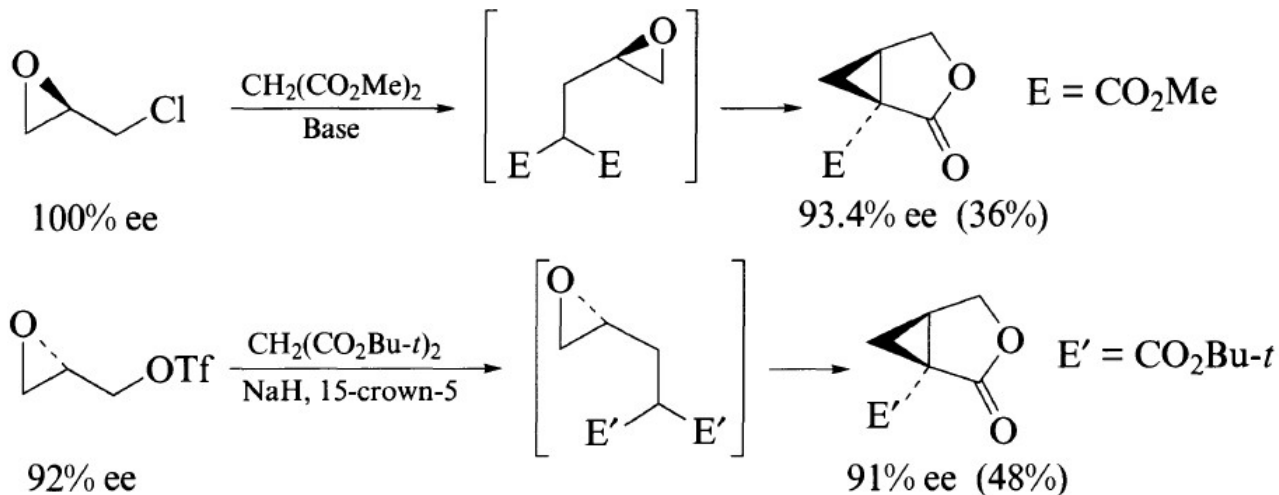


Oxiranes as cyclopropanation reagents

E. Schaumann, A. Kirschning and F. Narjes, *J. Org. Chem.*, 1991, 56, 717-723.

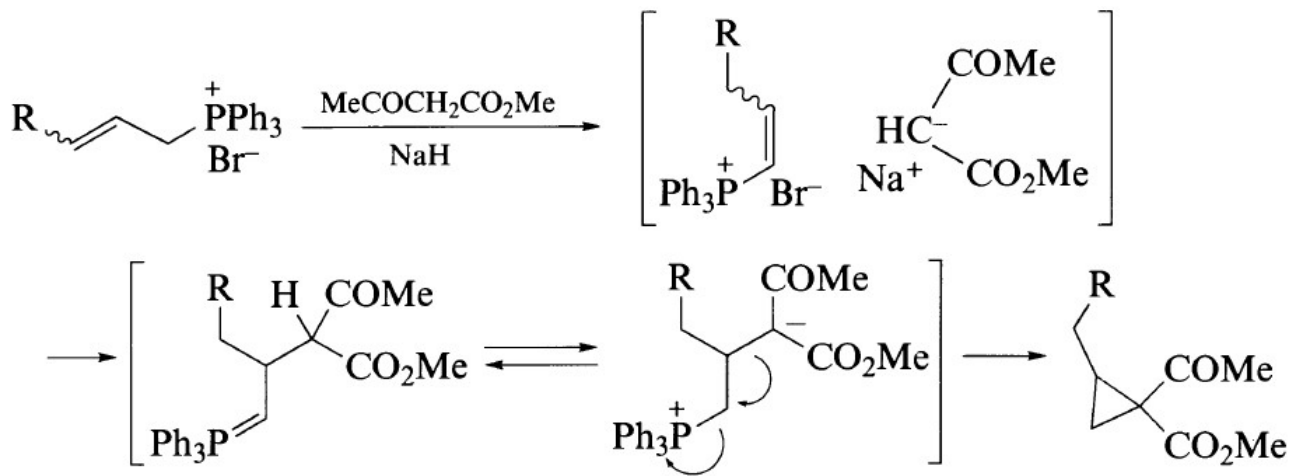
IV. Cyclopropanation of active methylene compounds

Tandem
cyclopropanation-
lactonization of
malonic ester



K. Burgess and K. K. Ho, *J. Org. Chem.*, 1992, 57, 5931-5936.

Michael acceptor
carrying a leaving
group at the alpha-
carbon atom



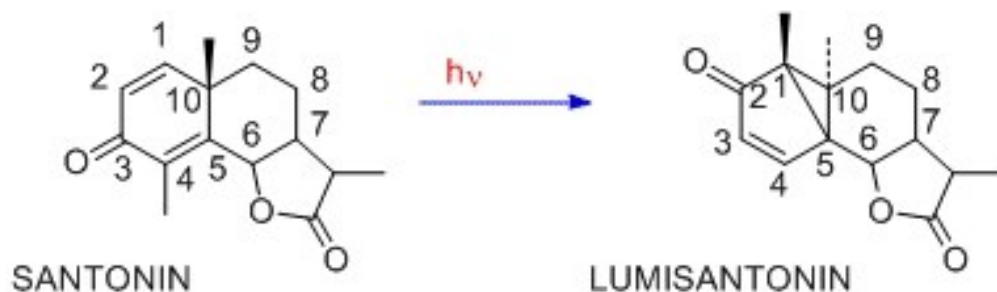
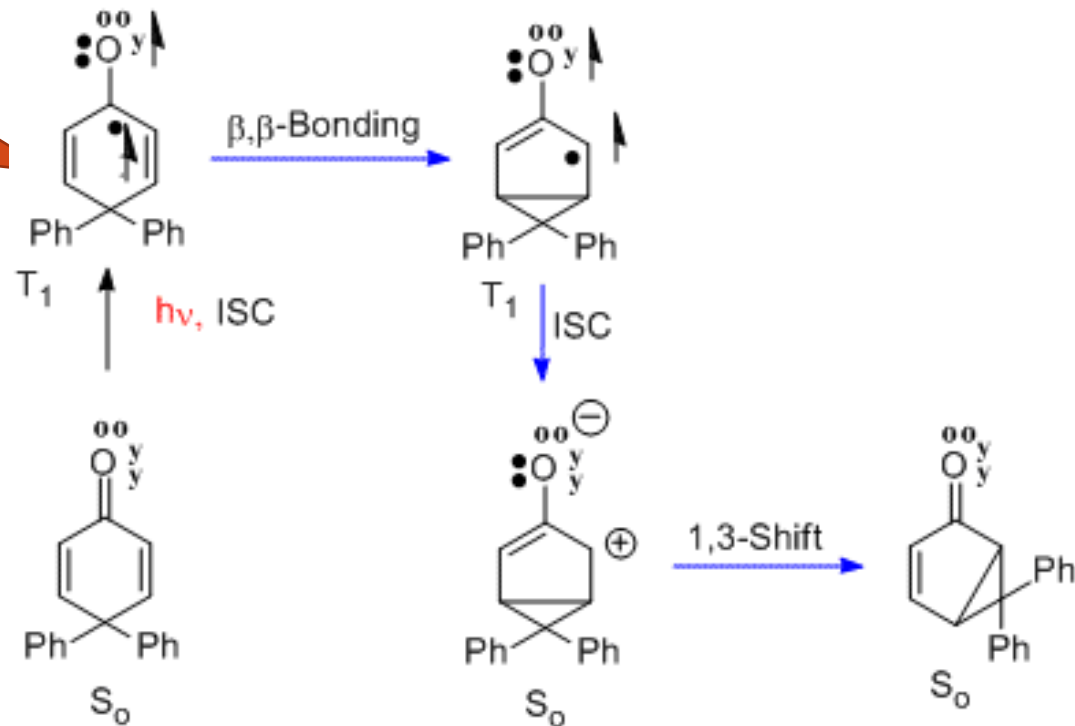
R = Et, 80% ; R = (CH₂)₂CH=CH₂, 85% (E) : (Z) = ca 3 : 7

D. Jacoby, J. P. Célérier, H. Petit and G. Lhommet, *Synthesis*, 1990, 1990, 301-304.

V. Cyclopropane Photochemistry

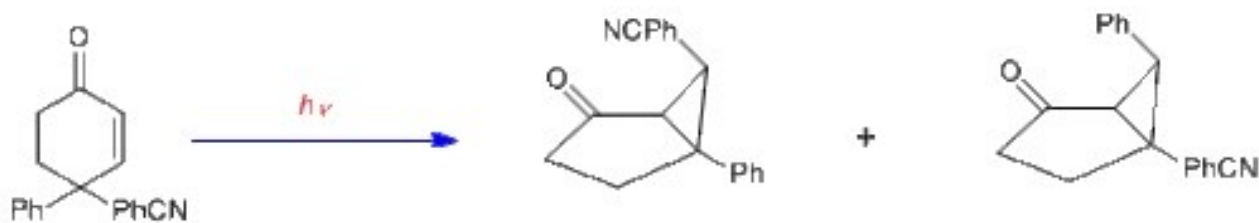
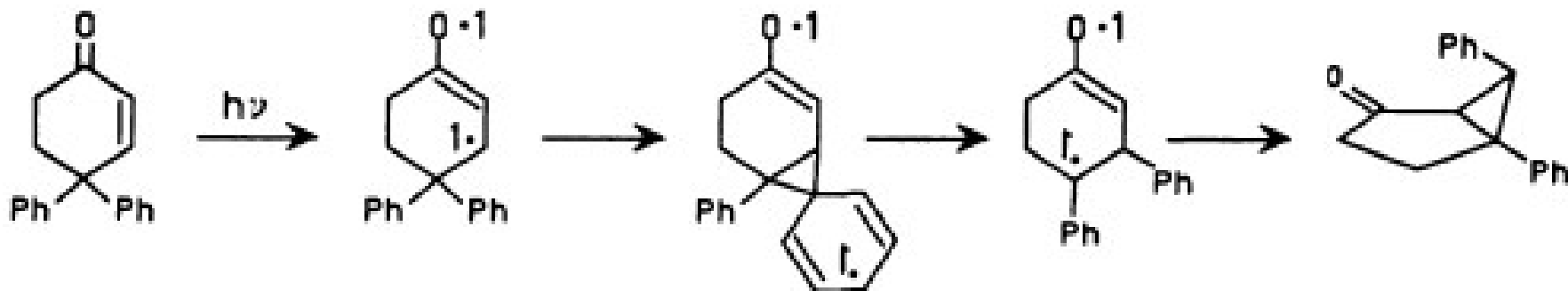
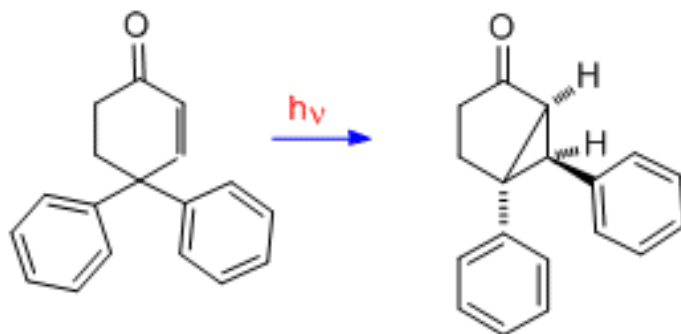
❖ Type-A Rearrangement of 2,5-Cyclohexadienones

n-pi*
triplet excited state



V. Cyclopropane Photochemistry

- ❖ Rearrangement of 4-Arylcyclohexenones (one double bond missing compared to 2,5-Cyclohexadienones)

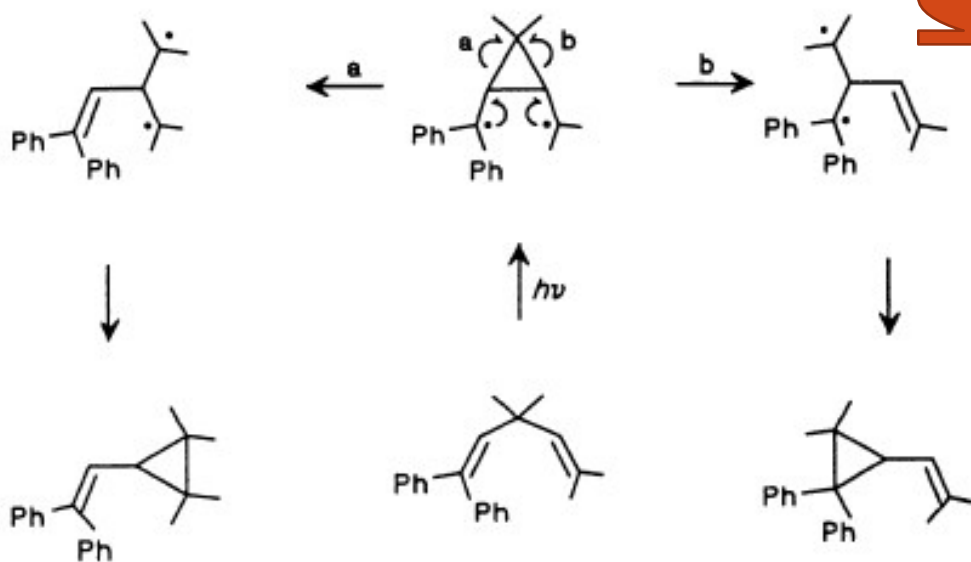
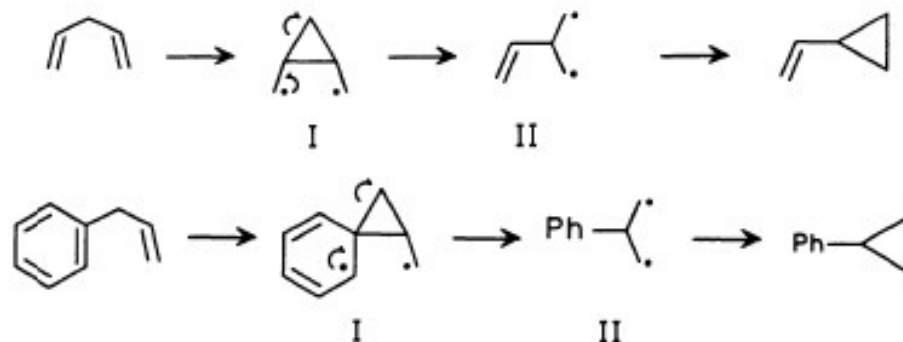


15 : 1

V. Cyclopropane Photochemistry

❖ The Di-pi-methane Rearrangement

Two π -systems separated by a saturated carbon atom (a 1,4-diene or an allyl-substituted aromatic ring) to form an ene- (or aryl-) substituted cyclopropane.



favored

The Pratt diene rearrangement (regioselectivity):

Less stabilized diradical center utilizes its odd-electron density to open the three-membered ring, which leads to the more stabilized Diradical II.

Thank You!