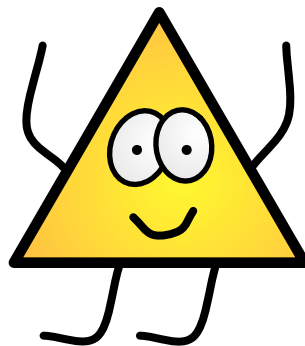
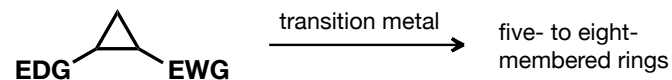
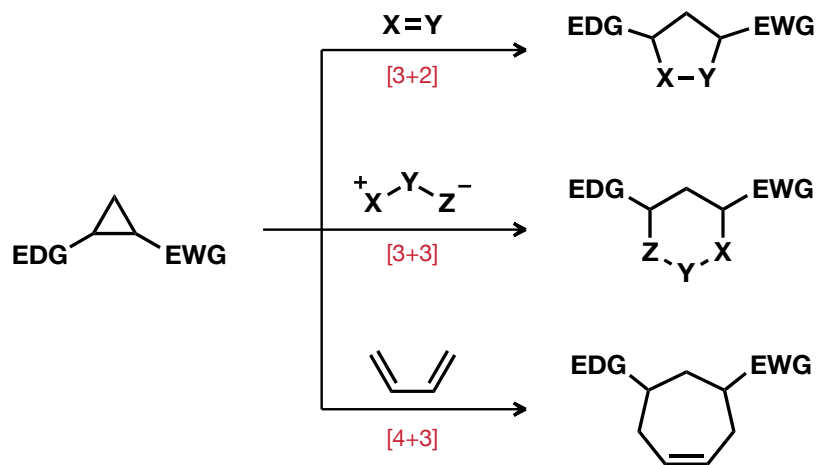

Cyclopropanes in Total Synthesis

Gaich-Group Seminar

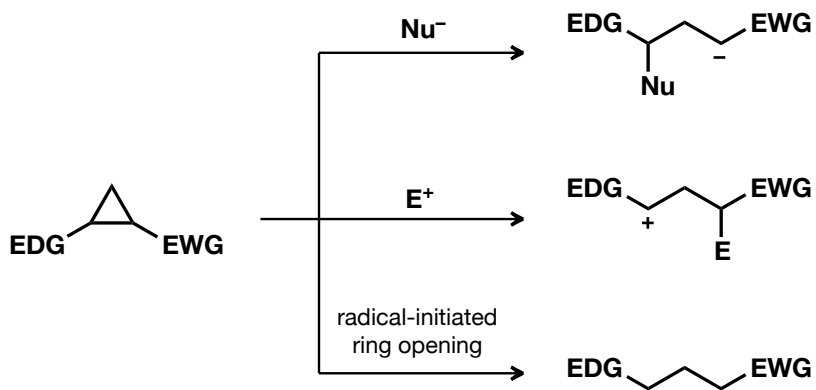
Erik Stempel
22.01.2013



formal cycloaddition strategies

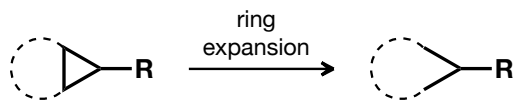
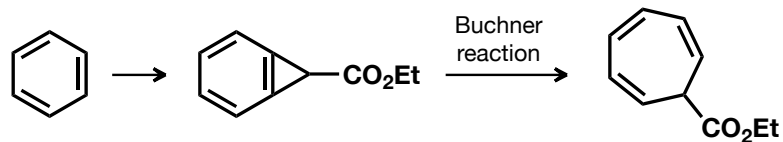


ring-opening strategies

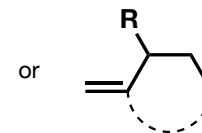
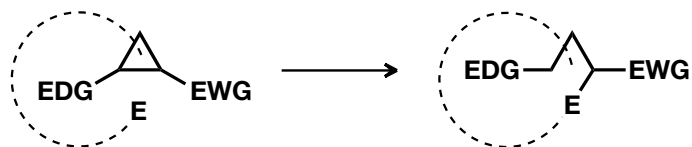
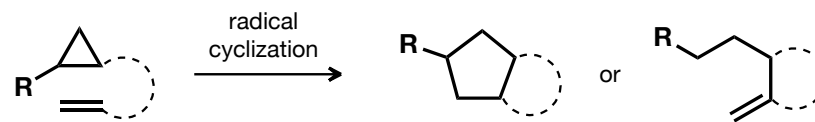
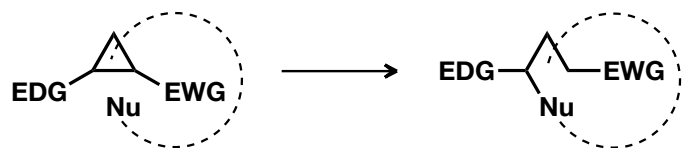


9

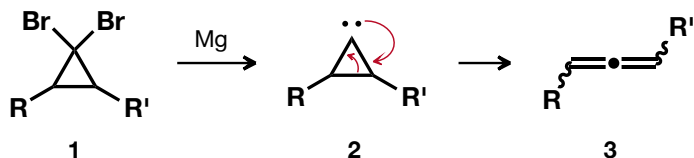
ring-opening strategies (*cont.*)



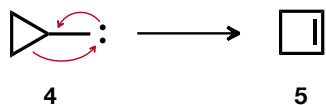
ring-opening-cyclization strategies



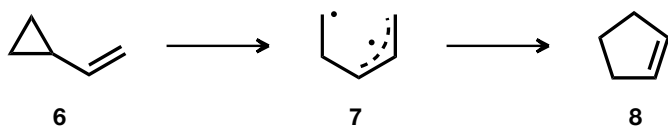
- Cyclopropyl Carbene Rearrangement (1958)



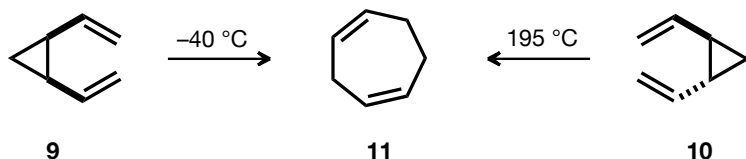
- Cyclopropylmethyl Carbene Rearr. (1960)



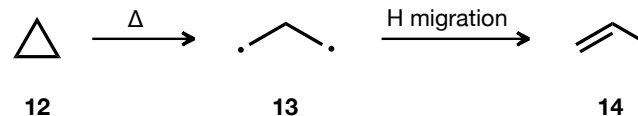
- Vinylcyclopropyl Rearr. (1960)



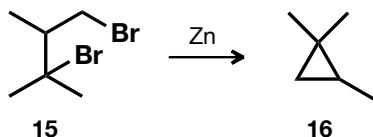
- Divinylcyclopropane Rearr. (1960)



- Thermal isomerization of cyclopropane (1922)

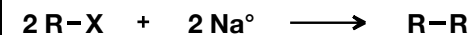


■ FREUND-GUSTAVSON Cyclopropane Synthesis

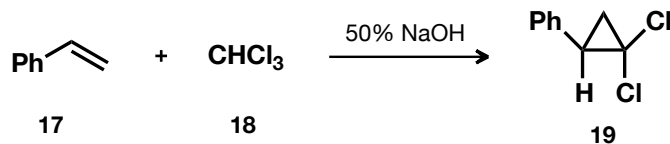


- Freund, A. *Monatsh.* **1882**, 3, 625.
- Gustavson, G. *J. Prakt. Chem.* **1887**, 36, 300.

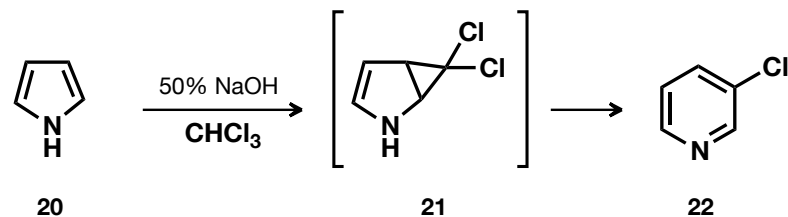
WURTZ Reaction



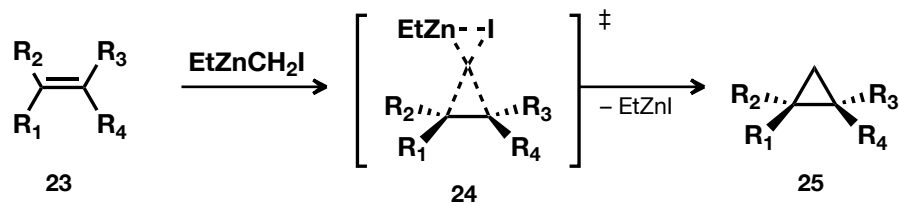
■ CIAMICIAN-DENNSTEDT Cyclopropanation



- Ciamician, G.; Dennstedt, N. *Chem. Ber.* **1881**, 14, 1153.



■ SIMMONS-SMITH Cyclopropanation

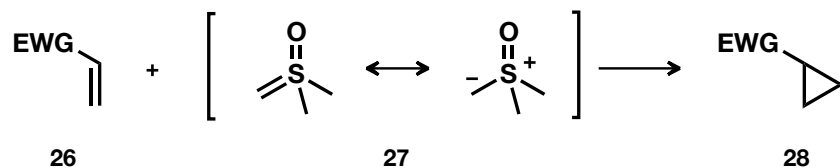


- Simmons, H.E.; Smith, R.D. *J. Am. Chem. Soc.* **1958**, 80, 5323
- Furukawa, J. *Tetrahedron* **1968**, 24, 53
- Simmons, H.E. *Org. React.* **1973**, 20, 1

MIRC

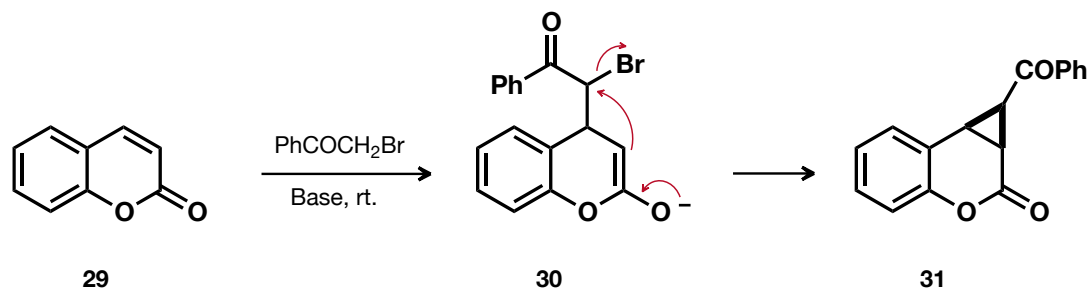
COREY-CHAYKOVSKY Cyclopropanation

- Johnson, A. J. *Am. Chem. Soc.* **1961**, *83*, 417.
- Corey, E.J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.



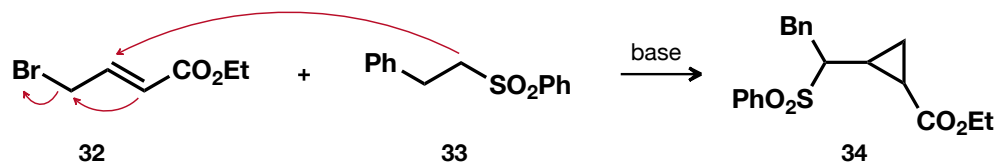
MOUSSERON-FRAISSE-McCOY Cyclopropanation

- Fraisse, J. *Bull. Soc. Chim. Fr.* **1957**, 986.
- McCoy, L.L. *J. Am. Chem. Soc.* **1958**, *80*, 6568.
- Mousseron, M. *Compt. Rendu.* **1959**, *248*, 887.

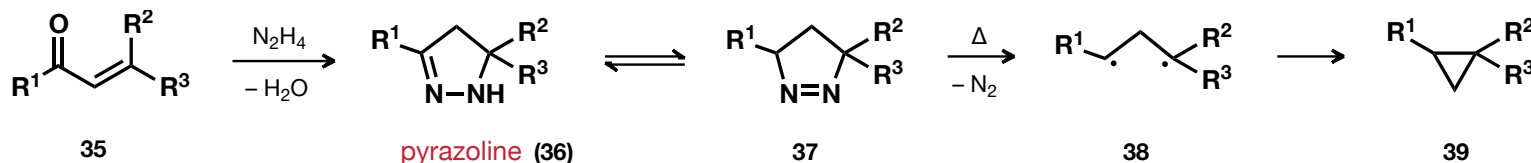


HASSNER-GHERA-LITTLE MIRC Reaction

- Ghera, E. *Tet. Lett.* **1979**, *20*, 4603.
- Little, R.D. *Tet. Lett.* **1980**, *21*, 2609.
- Hassner, A.; Ghera, E. *Tet. Lett.* **1990**, *31*, 3653.



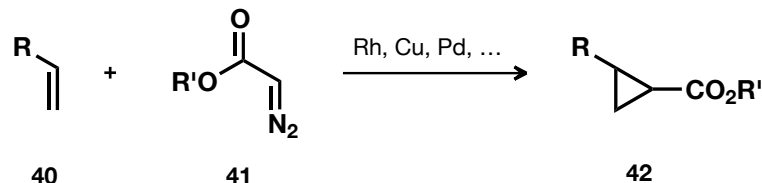
■ KISHNER Cyclopropane Synthesis



- Kishner, N. *J. Russ. Phys. Chem. Soc.* **1912**, *43*, 1132.

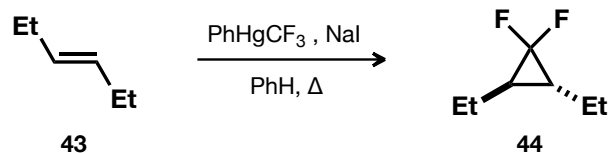
■ Carbenes

- Cyclopropanation *via* metal carbenes (metal-free = **PFAU-PLATTNER** Cyclopropanation)



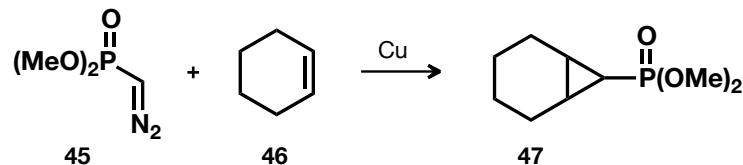
- Fischer, E.O. *Chem. Ber.* **1967**, *100*, 2445.
- Pfau, A.S.; Plattner, P.A. *Helv. Chim. Acta* **1939**, *22*, 202.

■ SEYFERTH Dihalocarbene Reagent



- Seyferth, D. *J. Am. Chem. Soc.* **1965**, *87*, 681.
- Seyferth, D. *J. Am. Chem. Soc.* **1967**, *89*, 959.

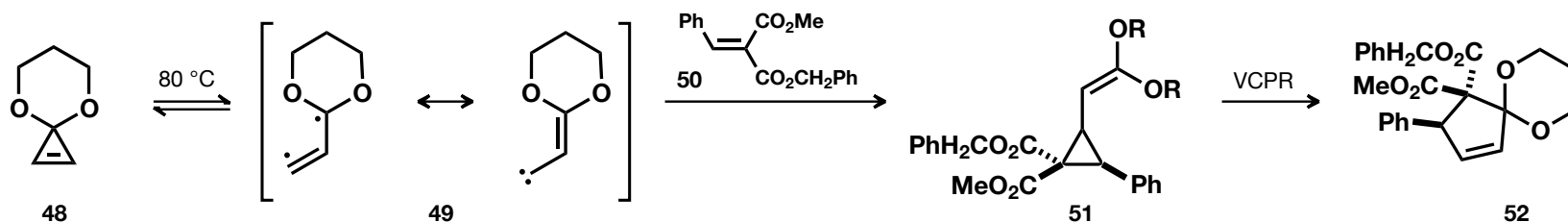
SEYFERTH-GILBERT Diazoalkane Reagent



- Seyferth, D. *J. Am. Chem. Soc.* **1967**, *89*, 4811.
- Seyferth, D. *J. Org. Chem.* **1971**, *36*, 128.

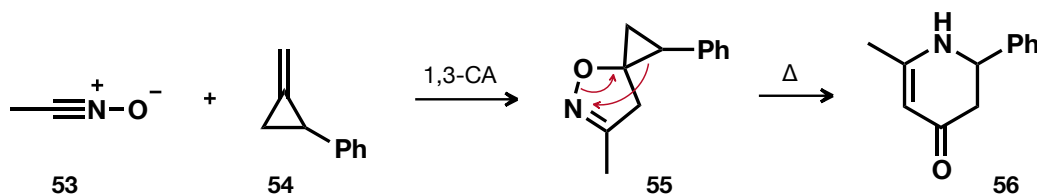
BOGER Thermal Cycloadditions

- Boger, D.L. *J. Am. Chem. Soc.* **1984**, *106*, 805.
- Boger, D.L. *Tet. Lett.* **1984**, *25*, 5611.

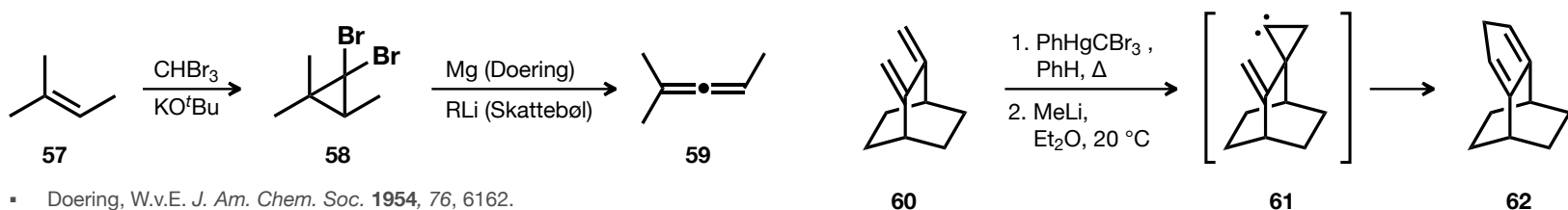


BRANDI-GUARNA Spirocyclopropane Rearr.

- Brandi, A.; Guarna, A. *J. Chem. Soc. Comm.* **1985**, 1518.
- Brandi, A.; Guarna, A. *Tet. Lett.* **1986**, *27*, 1727.
- Brandi, A.; Guarna, A. *J. Org. Chem.* **1988**, *53*, 2426.



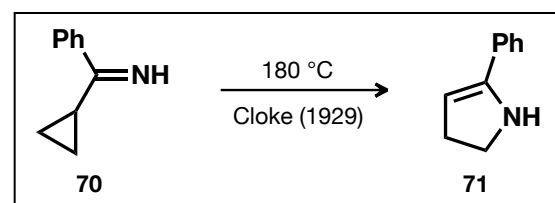
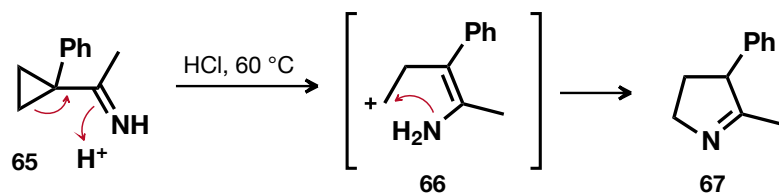
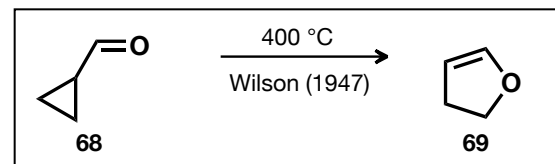
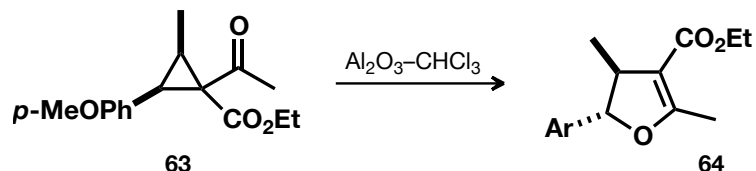
DOERING-LaFLAMME Allene Synthesis / SKATTEBØL Vinylhalocyclopropane Rearr.



- Doering, W.v.E. *J. Am. Chem. Soc.* **1954**, *76*, 6162.
- LaFlamme, P.M. *Tetrahedron* **1958**, *2*, 1975.
- Skattebøl, L. *Tet. Lett.* **1961**, *2*, 167.

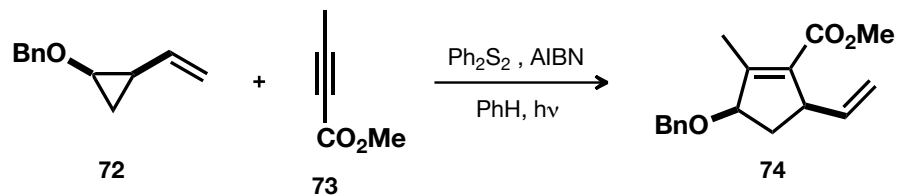
- VCPR = vinylcyclopropane rearrangement

■ CLOKE-WILSON Cyclopropyl Ketone Rearrangement

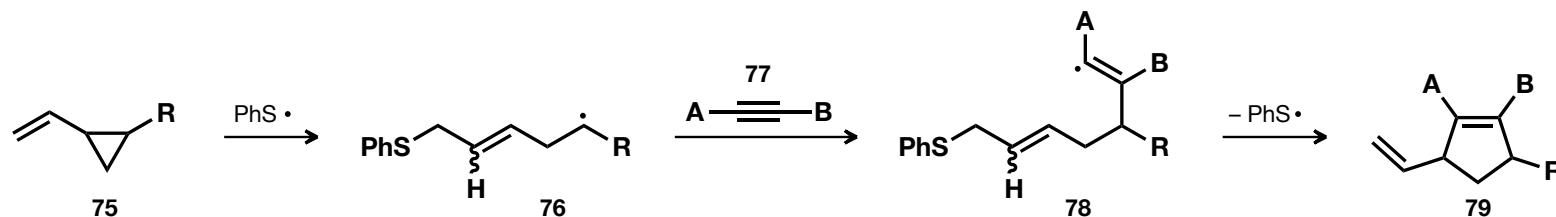


- Cloke, J.B. *J. Am. Chem. Soc.* **1929**, *51*, 1174.
- Wilson, C.L. *J. Am. Chem. Soc.* **1947**, *69*, 3002.

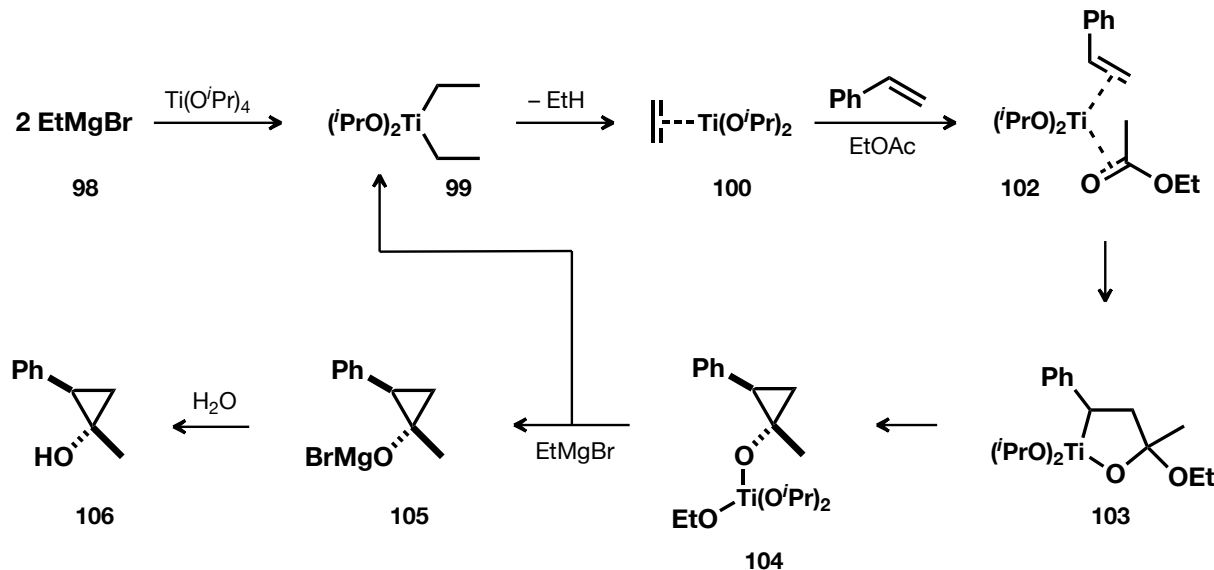
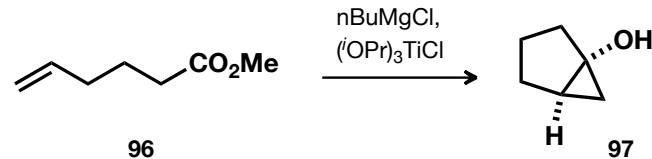
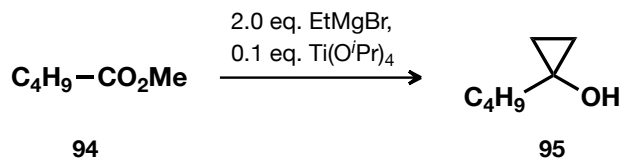
■ FELDMAN Vinylcyclopentane Synthesis



- Feldman, K.S. *J. Am. Chem. Soc.* **1986**, *108*, 1328.
- Feldman, K.S. *J. Am. Chem. Soc.* **1988**, *110*, 3300.
- Feldman, K.S. *J. Am. Chem. Soc.* **1989**, *111*, 4878.



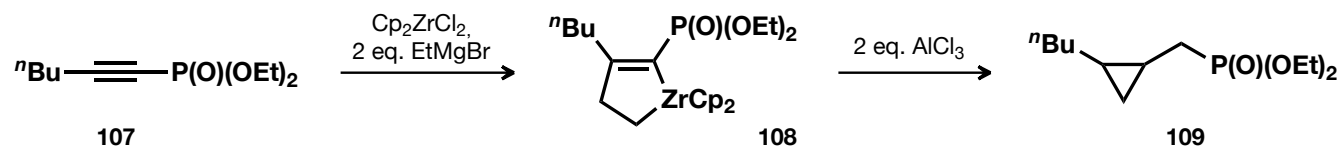
■ KULINKOVICH Hydroxycyclopropanation



- Kulinkovich, O.G. *Zh. Org. Khim.* **1989**, 25, 2245.
- Kulinkovich, O.G. *Synthesis* **1991**, 234.
- Kulinkovich, O.G. *Mendeleev Comm.* **1993**, 230.

■ SREBNIK-QUNTAR Cyclopropyl Phosphonates

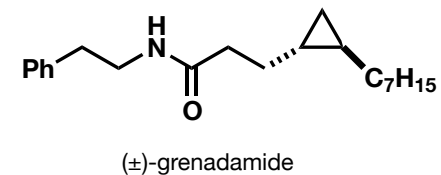
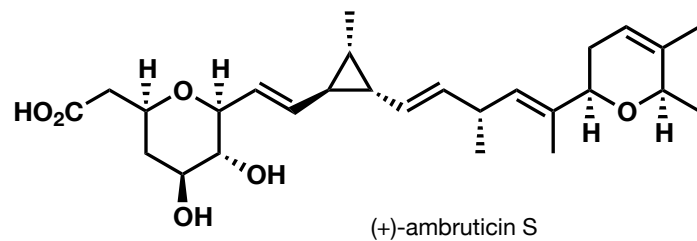
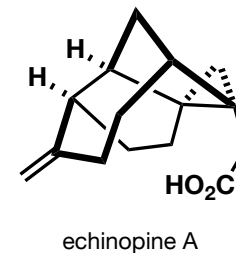
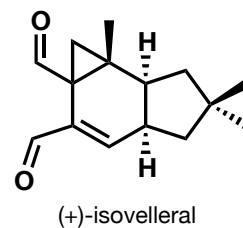
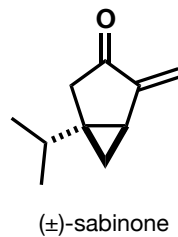
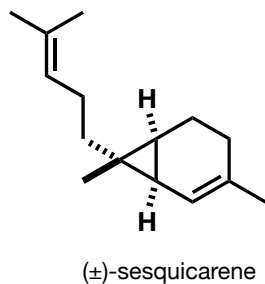
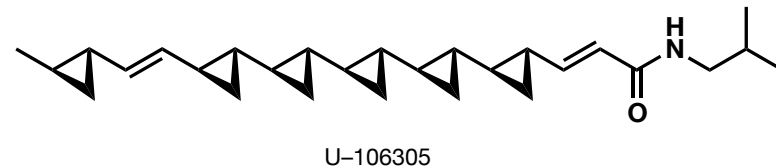
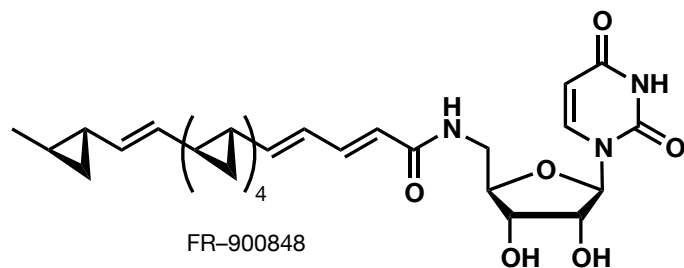
- Quntar, A.; Srebnik, M. *J. Organomet. Chem.* **2005**, 690, 2504.
- Quntar, A.; Srebnik, M. *J. Org. Chem.* **2006**, 71, 730.
- Srebnik, M.; Quntar, A. *Org. Prepar. Proced. Int.* **2008**, 40, 505.



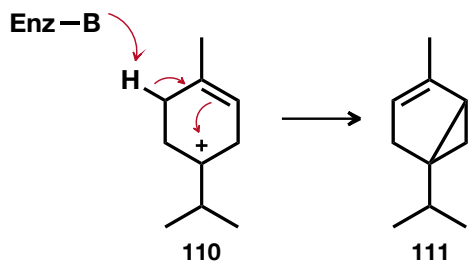
Cyclopropane Containing Natural Products

Gaich-Group Seminar
Erik Stempel

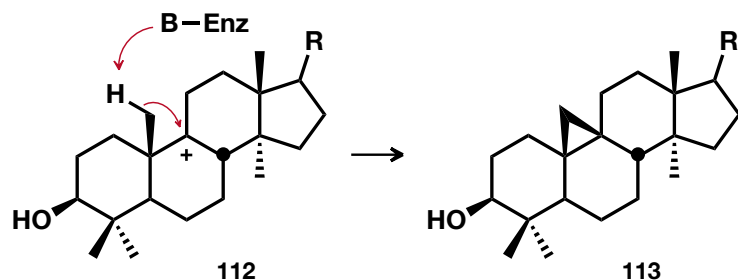
Nat. Prod.



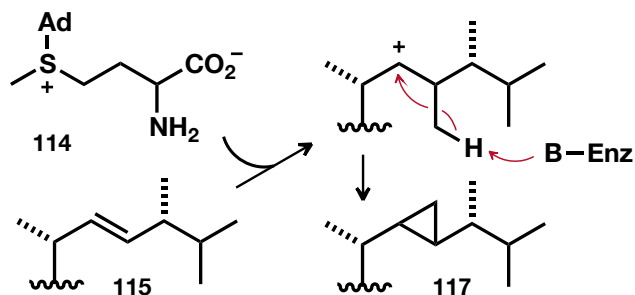
- Homoallyl cation ring closure.



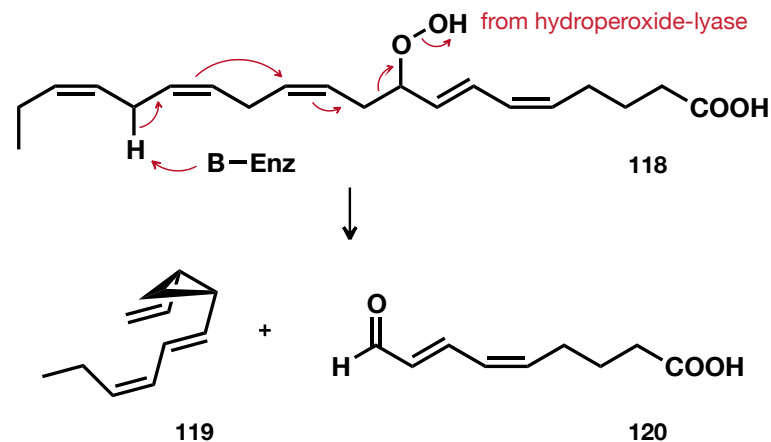
- Reaction of a cation with an enzyme-activated α -methyl group.



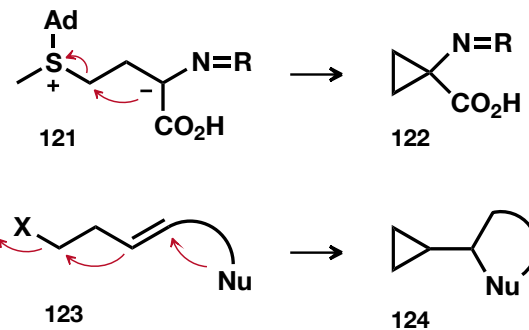
- Methyl transfer from SAM.



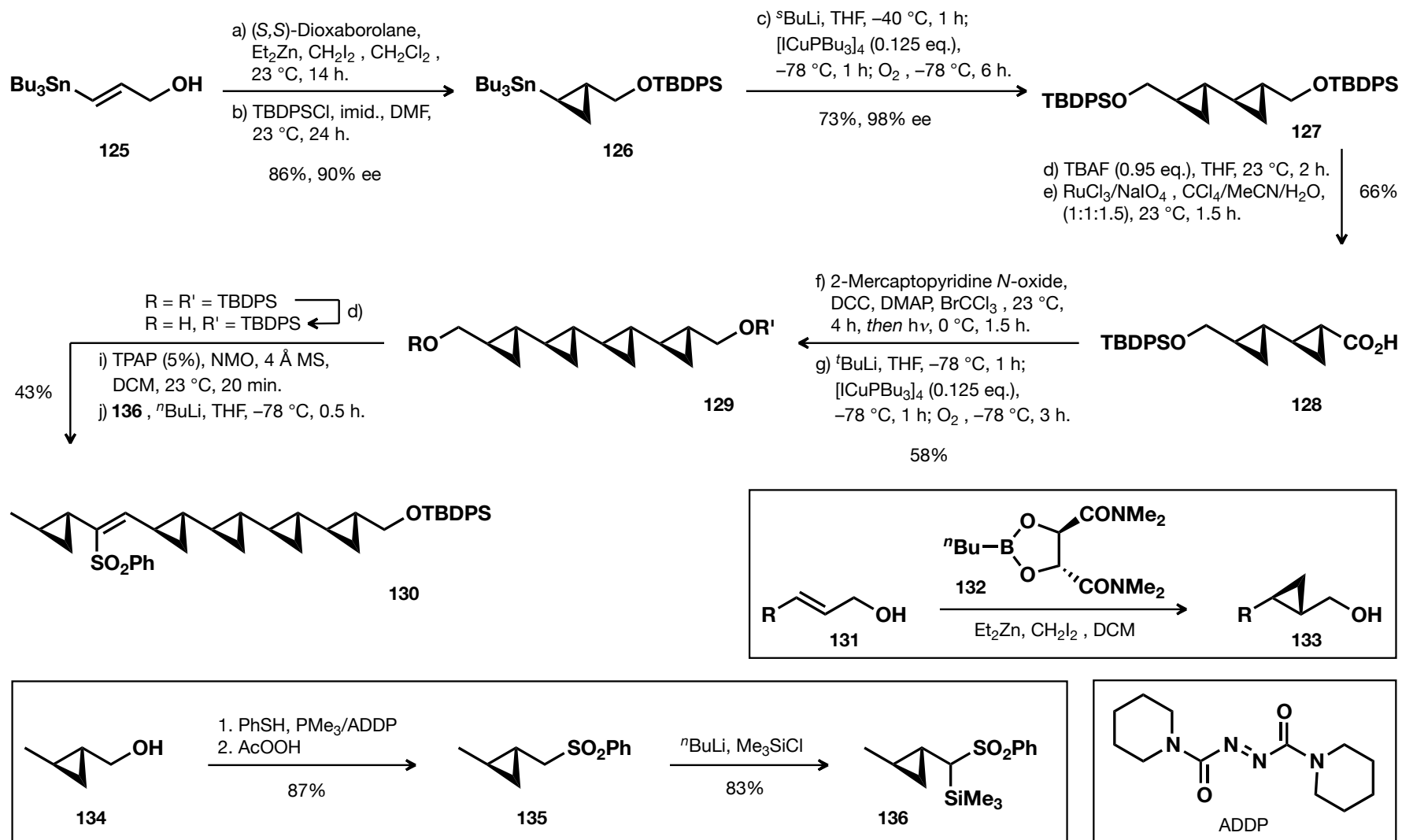
- Reaction with a homoconjugated double-bond (also *via* radicals).

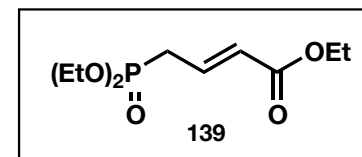
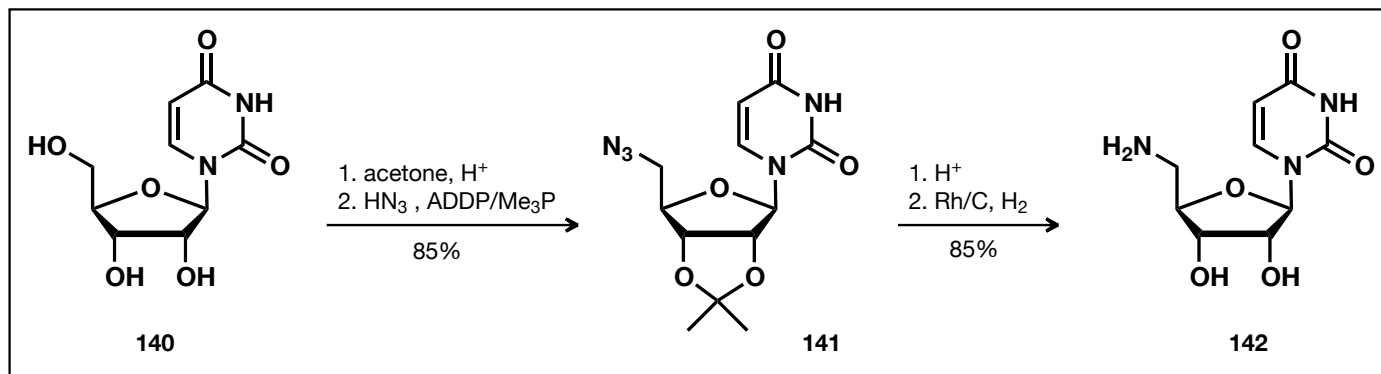
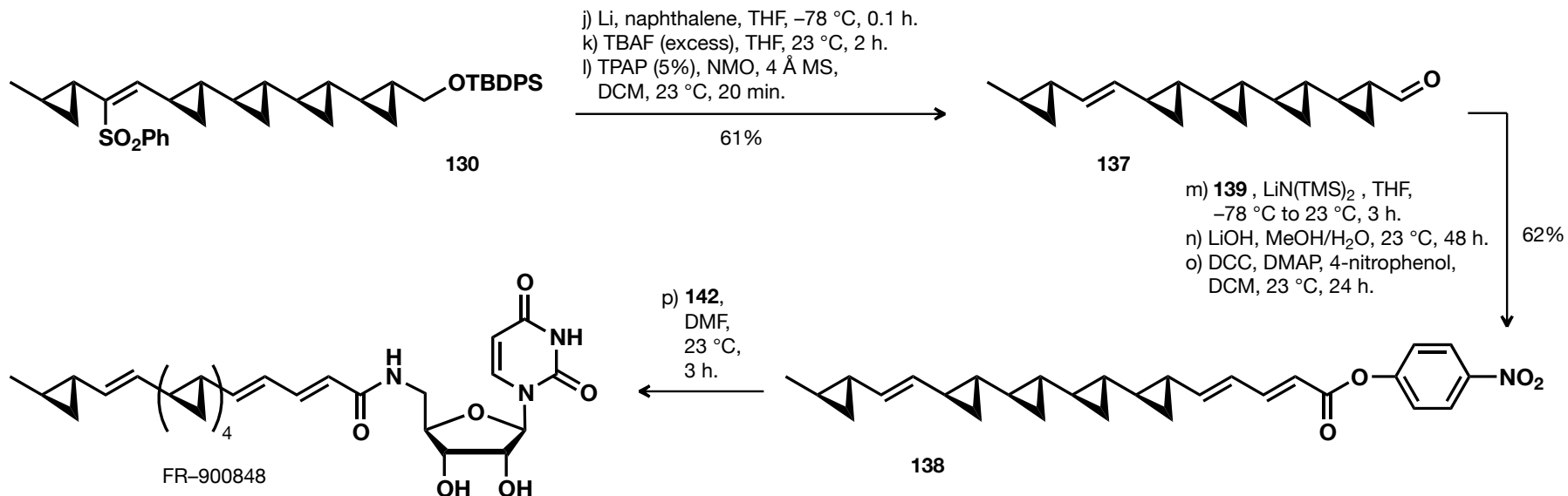


- Internal nucleophilic substitution (S_Ni)

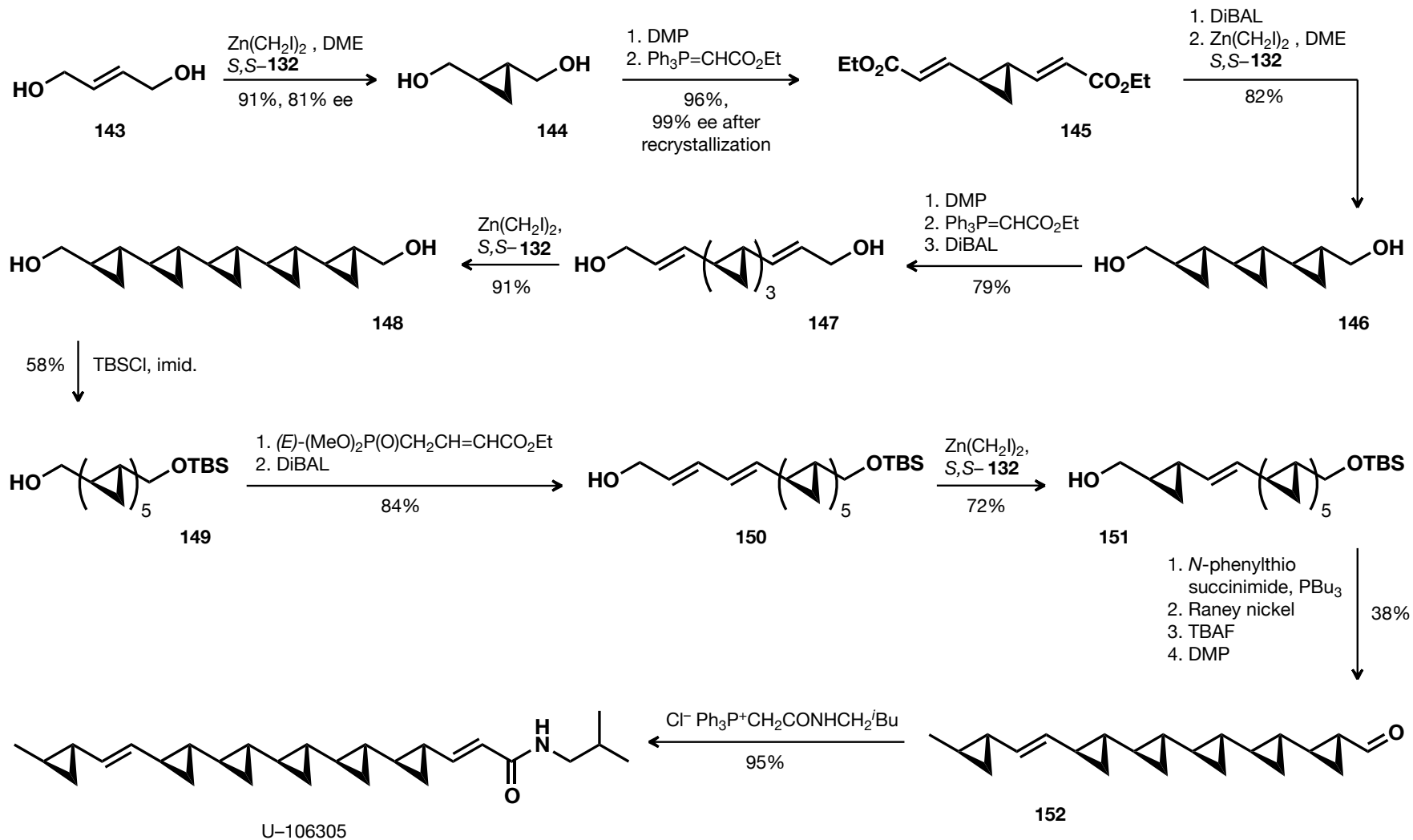


- several more



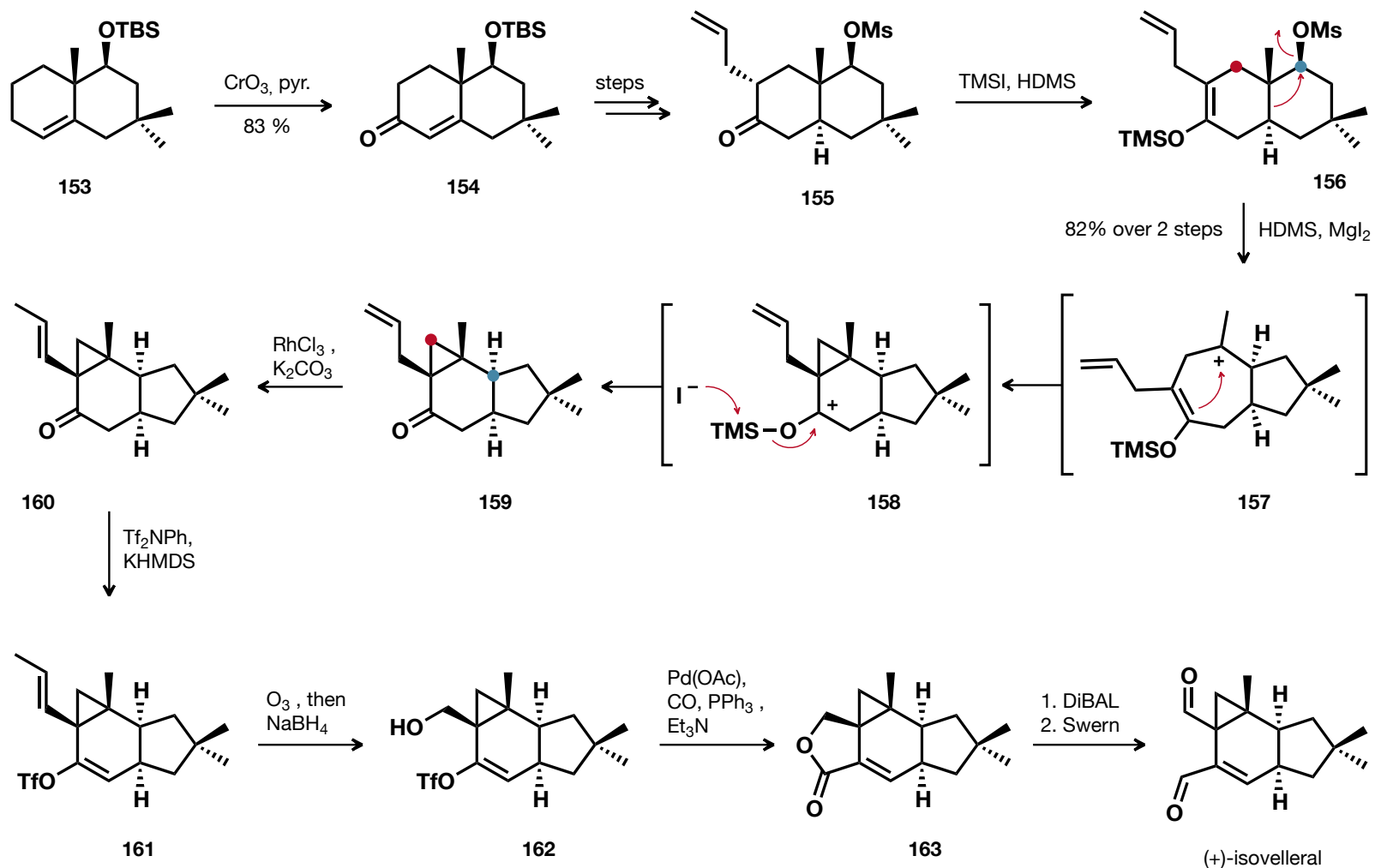


- Key features:
 - Charette–Juteau asymmetric cyclopropanation
 - Dimerization strategy
 - Horeau amplification principle



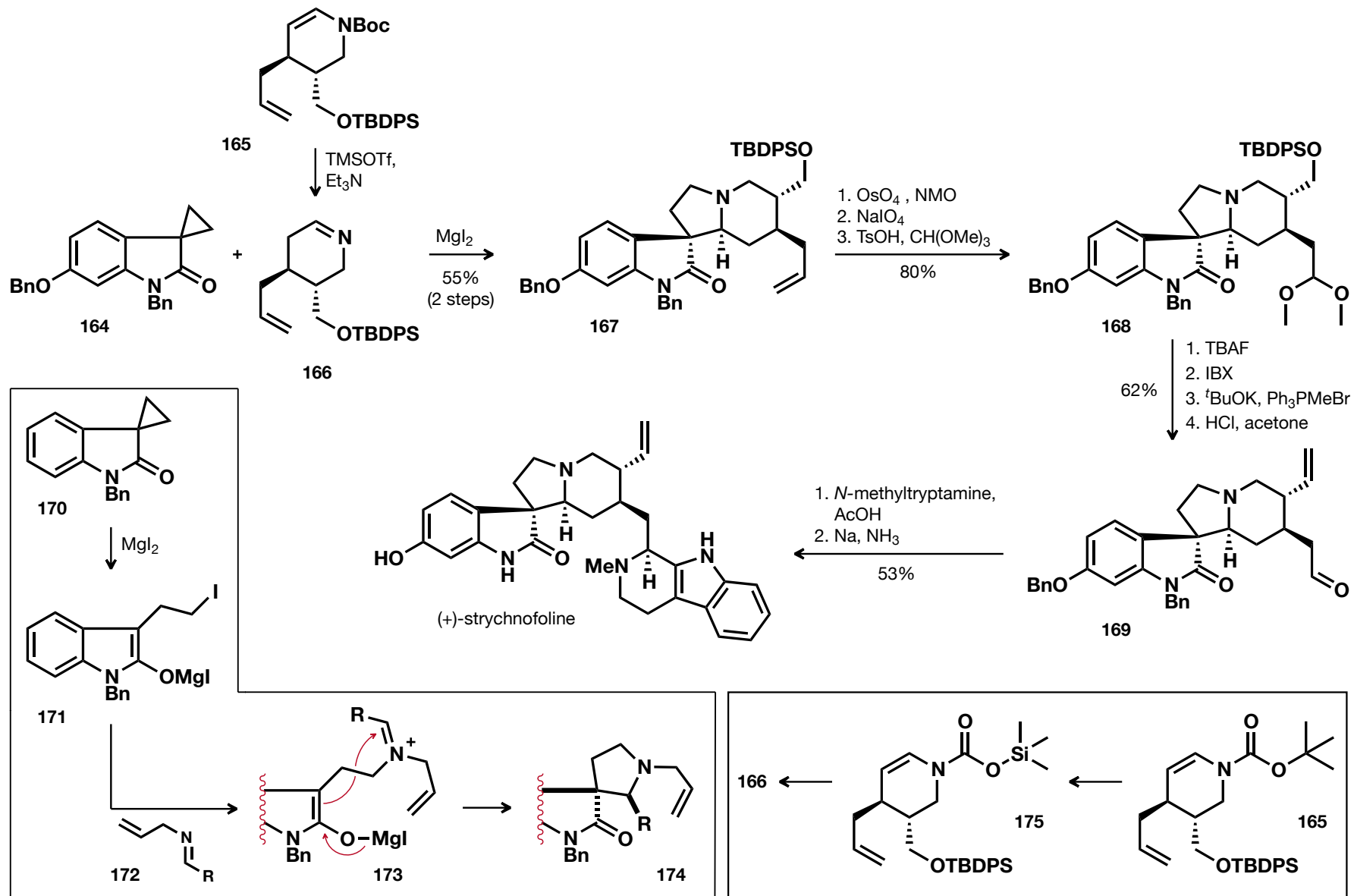
■ Key feature: Charette–Juteau asymmetric cyclopropanation

(+)-Isovelleral (de Groot, 2001)

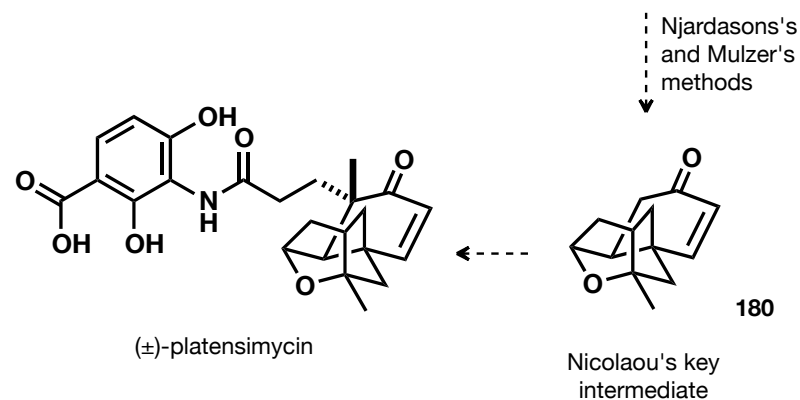
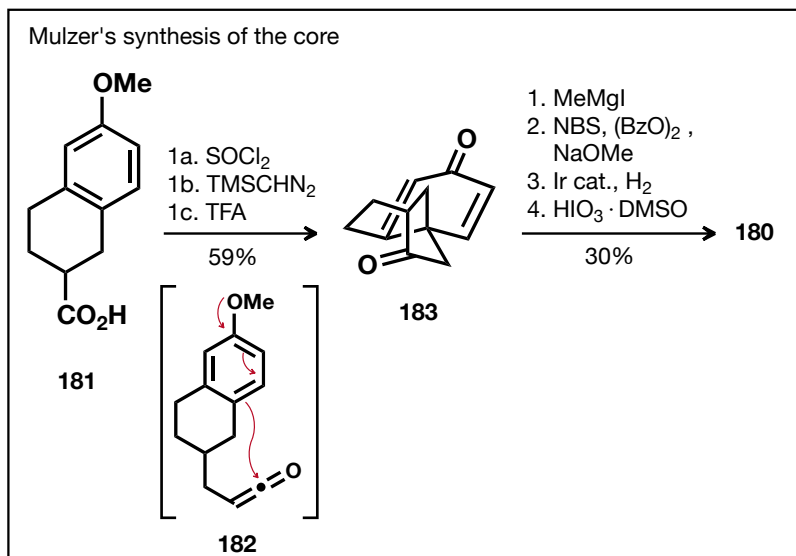
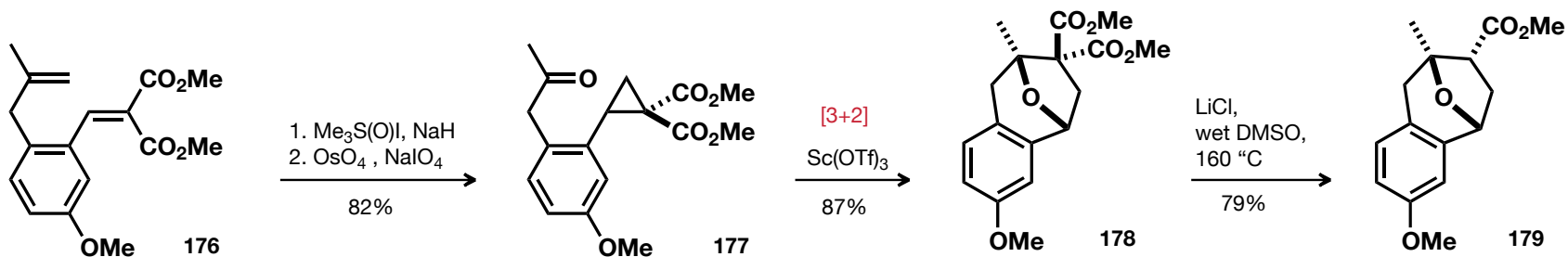


- Key step: magnesium mediated tandem rearrangement-cyclopropanation reaction

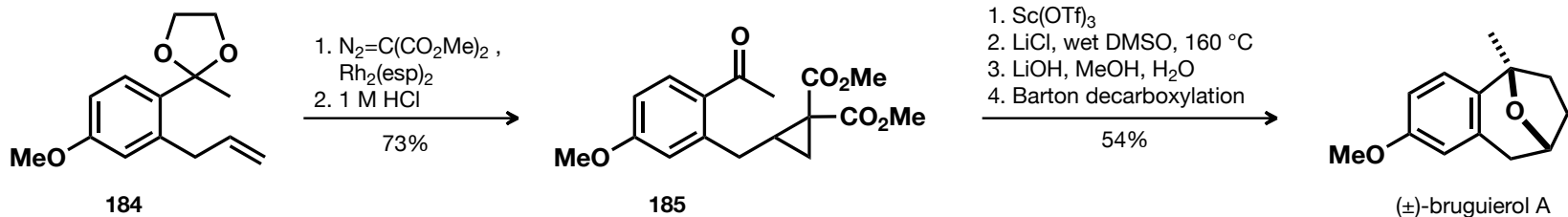
(+)-Strychnofoline (Carreira, 2006)



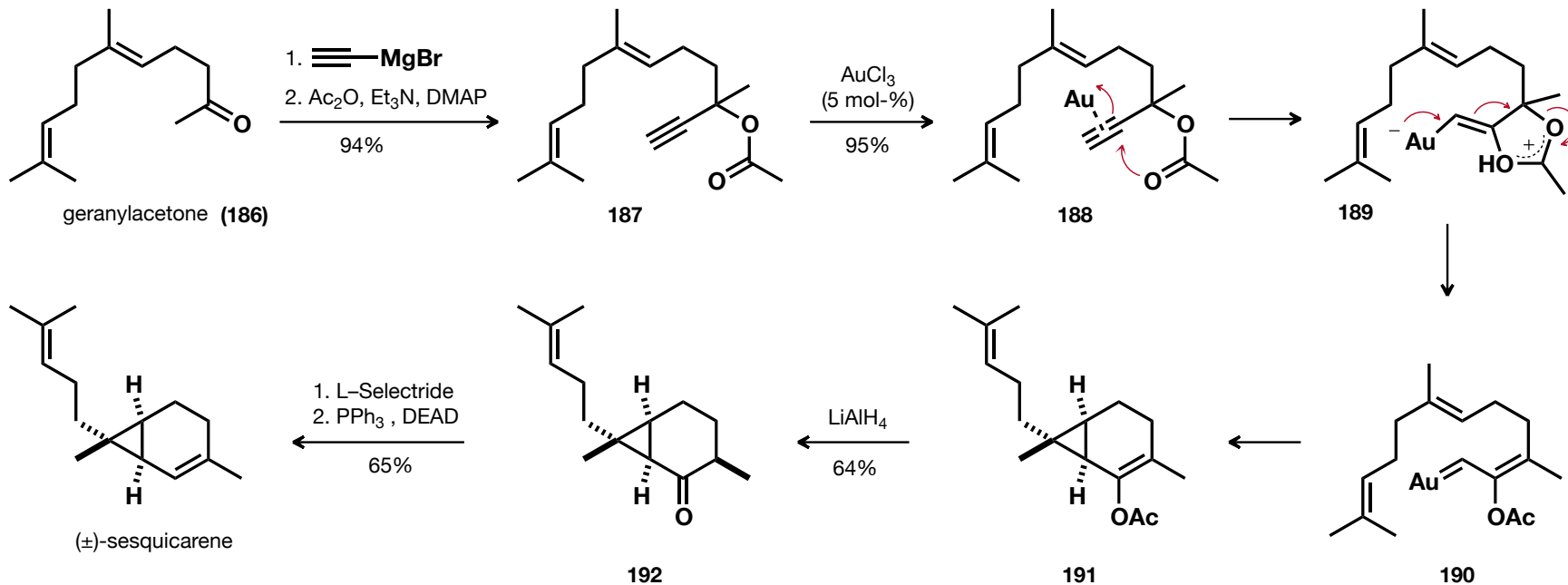
Examples for [3+2] Cycloaddition



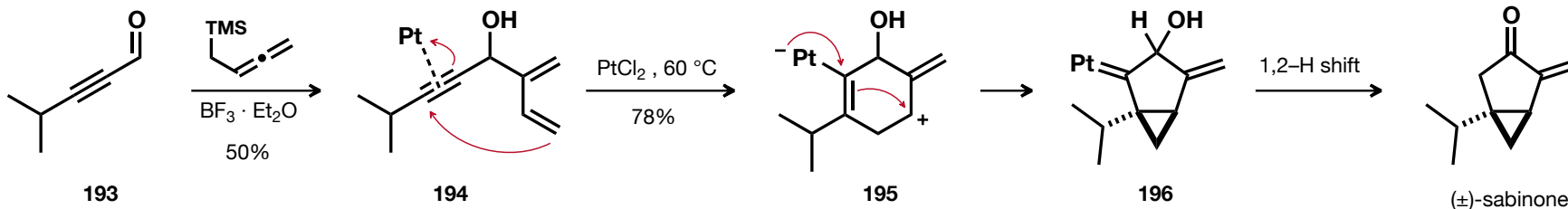
- Key features: formal [3+2] cycloaddition of a cyclopropane with a ketone



- (±)-Sesquicarene (Fürstner, 2004)
 - Key feature: Au-catalyzed cycloisomerization



- (±)-Sabinone (Fürstner, 2004)

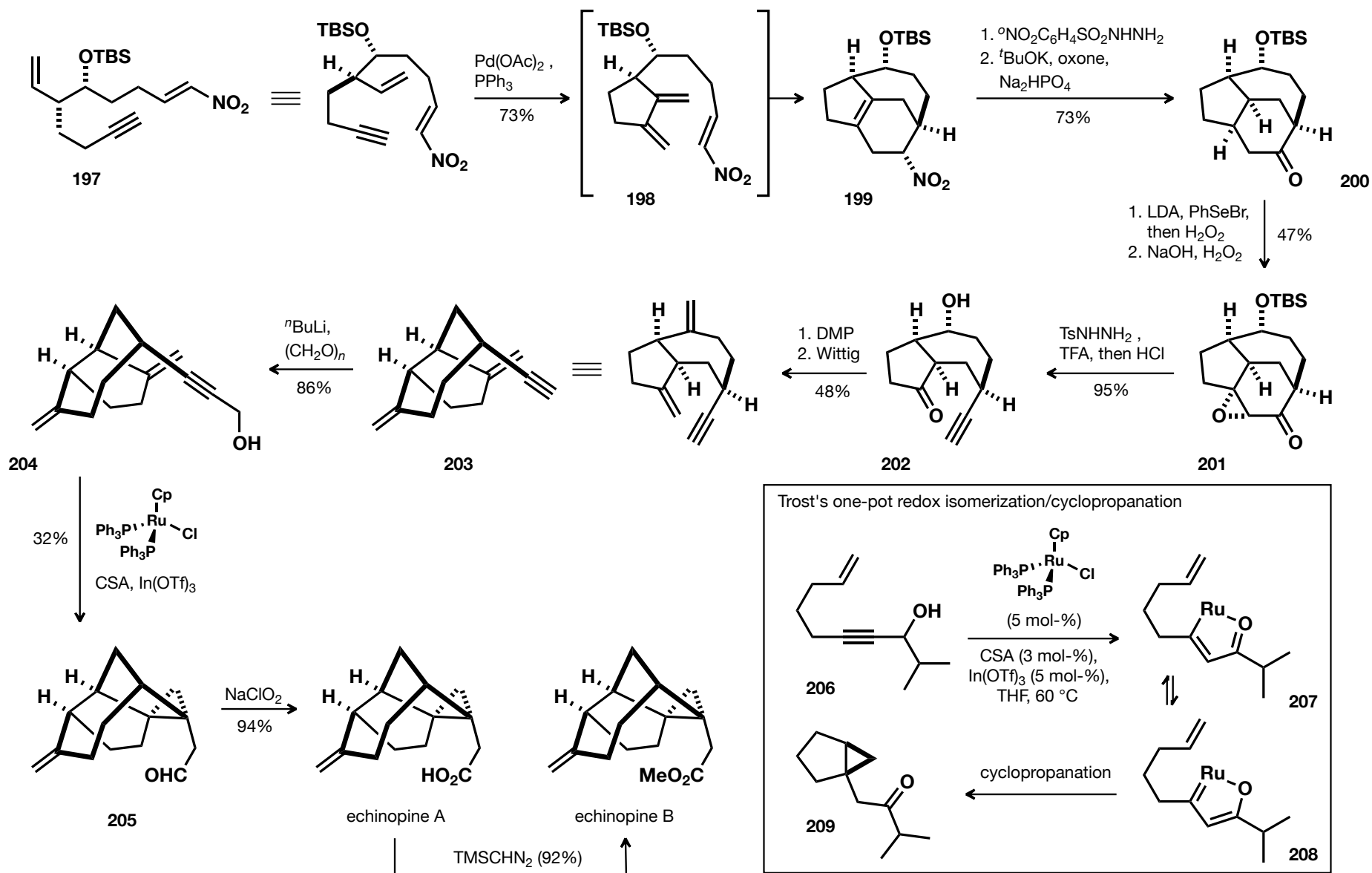


- Fürstner, A. *Chem. Commun.* **2004**, 2546.
- Fürstner, A. *J. Am Chem. Soc.* **2004**, 126, 8654.

Echinopines A and B (Chen, 2011)

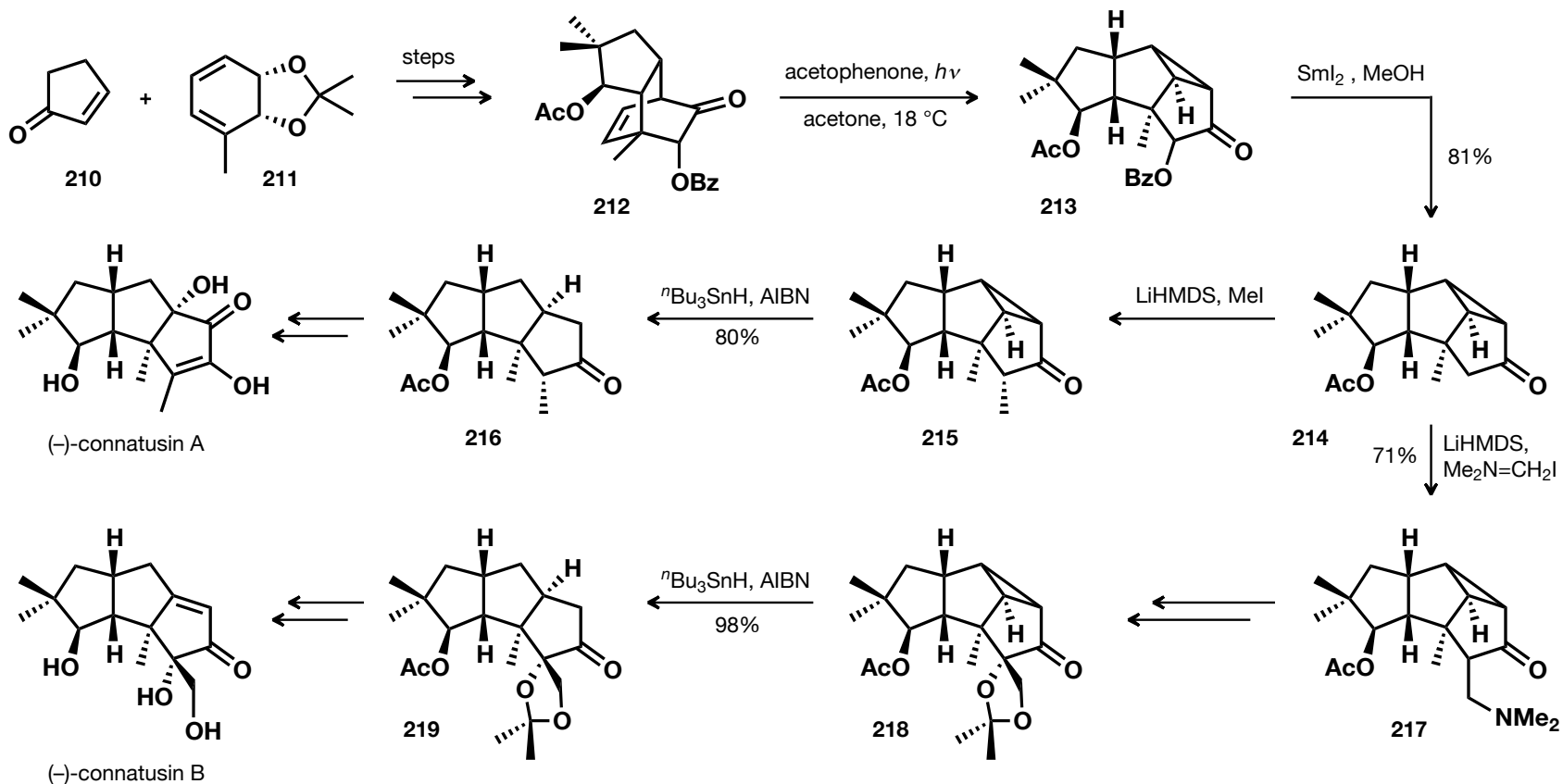
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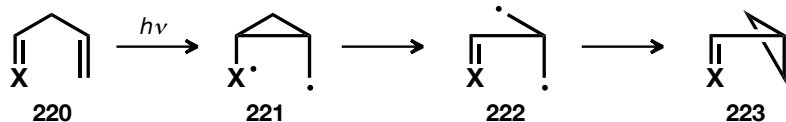


- Chen, Y.-K. *Org. Lett.* **2011**, *13*, 5724.
- Trost, B. M. *J. Am. Chem. Soc.* **2011**, *133*, 4766.

(-)-Connatusin A and B (Banwell, 2011)

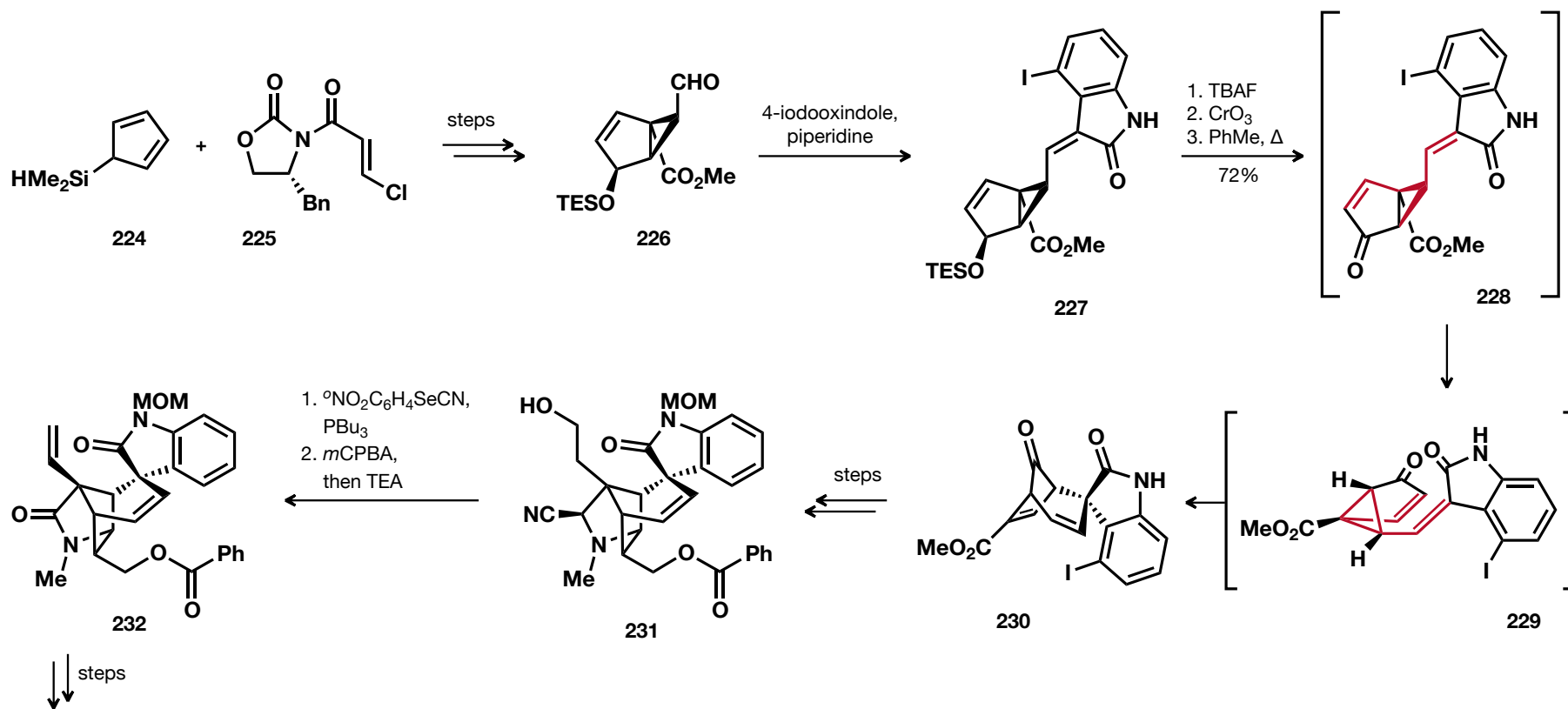


Di- π -methane rearrangement (X = CH₂) / Oxa-di- π -methane rearrangement (X = O)

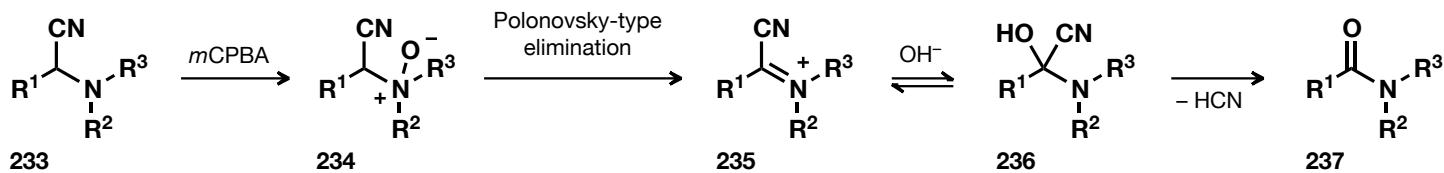


- Key features: oxa-di- π -methane rearrangement for the formation of a cyclopropane ring + reductive ring-opening process.

(+)-Gelsemine (Fukuyama, 1997)



Tandem Grieco elimination – conversion of α -aminonitriles to amides



(+)-gelsemine

- Fukuyama, T. *Pure & Appl. Chem* **1997**, 69, 501.
- Fukuyama, T. *Angew. Chem. Int. Ed.* **2000**, 39, 4073.
- Fukuyama, T. *Chem. Lett.* **2002**, 31, a 122.

Thanks for your attention.

Questions?
