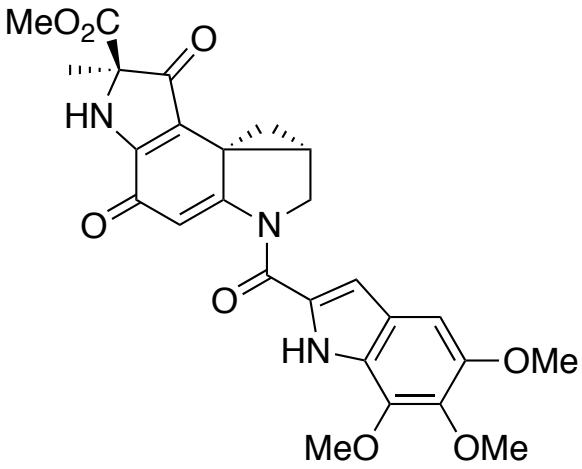
Cyclopropane-Containing Natural Products

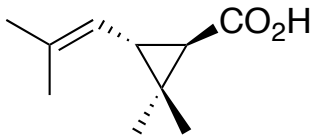
Olivier Wagnières

EPFL, 2.09.2012

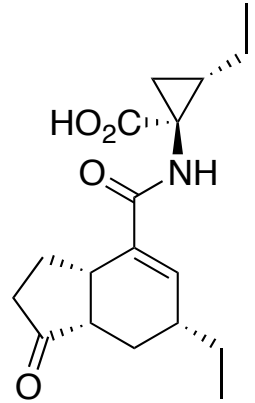
Exemples of Natural products



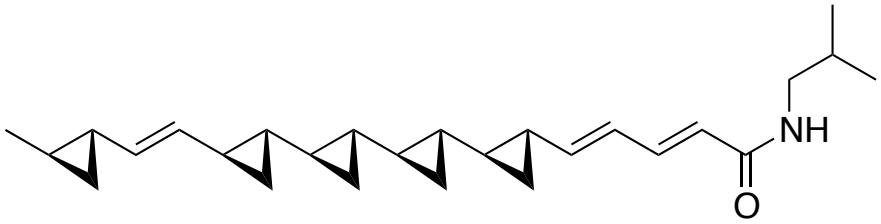
(+)-duocarmycin A



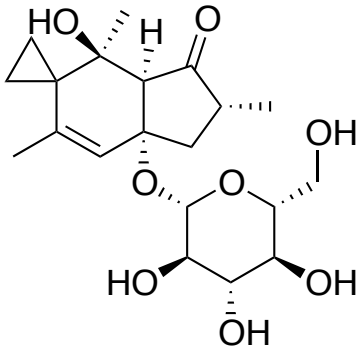
(+)-*trans*-chrysanthermic acid



(+)-coronatine



(-)-U-106305



(+)-ptaquiloside

Chen D. Y.-K., *et* al., Chem. Soc. Rev*., 2012, **41**, 4631-4642*

Utility of cyclopropyl group

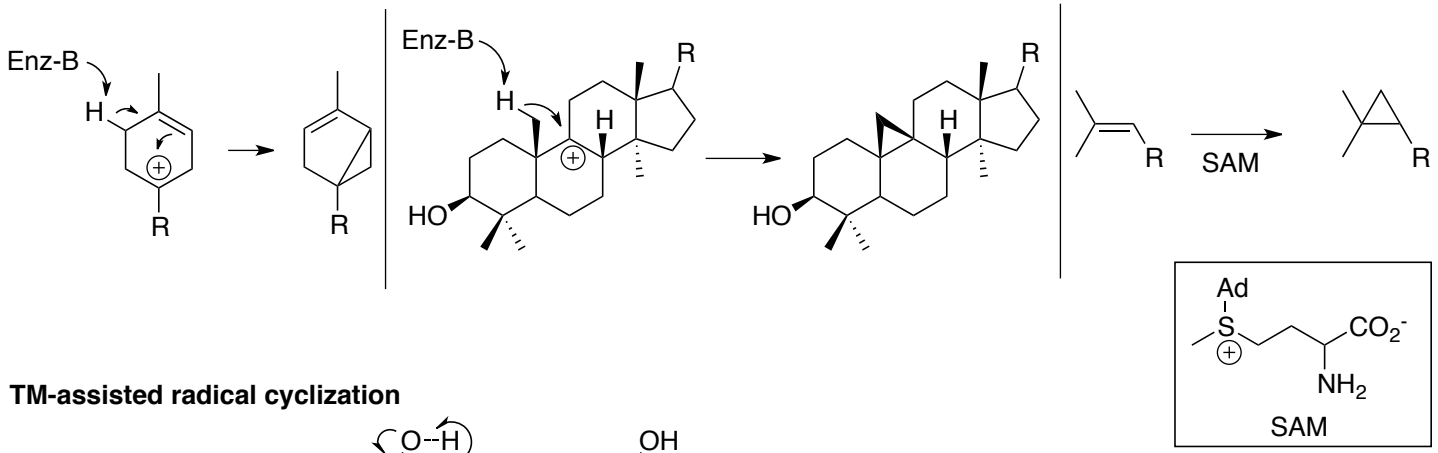
- If it is stable:
  - Lipophilic group with orientation and position that differ from related open-chain moiety;
  - Rigid structure, unique structural and electronical properties (sp^2 likeness, “banana-shaped” bond).

- If more labile, Energy source (~27 $kcal \cdot mol^{-1}$ cyclic strain):
  - High-Energy intermediate in metabolism;
  - Storage molecule to release energy-rich compounds;
  - To provide driving force and ensure irreversibility in inhibition mechanism.

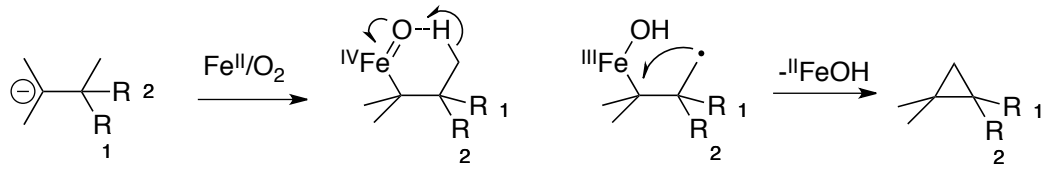
Wessjohann L. A., *et al., Chem. Rev.*, 2003, **103**(4), 1625-1647

Biosyntheses of cyclopropyl group

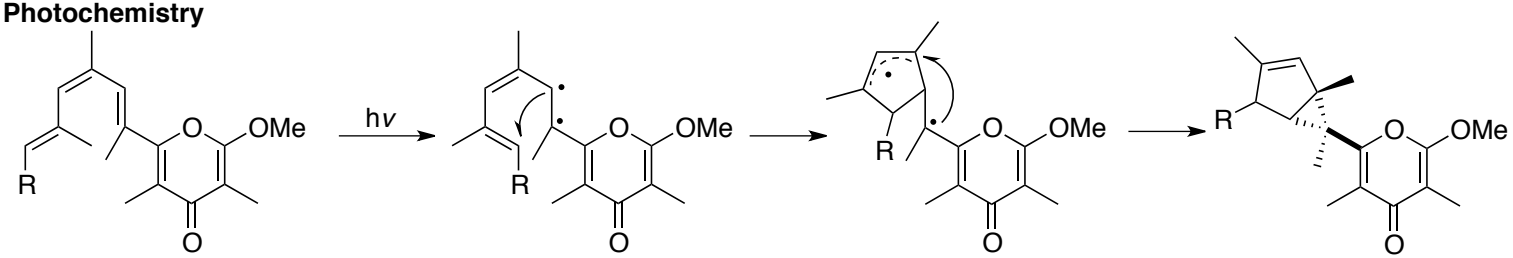
Rearrangement *via* cationic intermediate



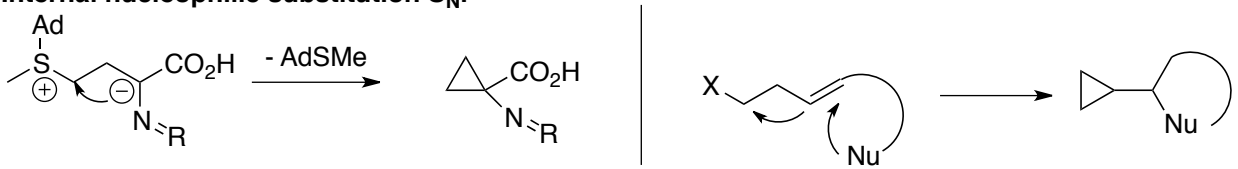
TM-assisted radical cyclization



Photochemistry

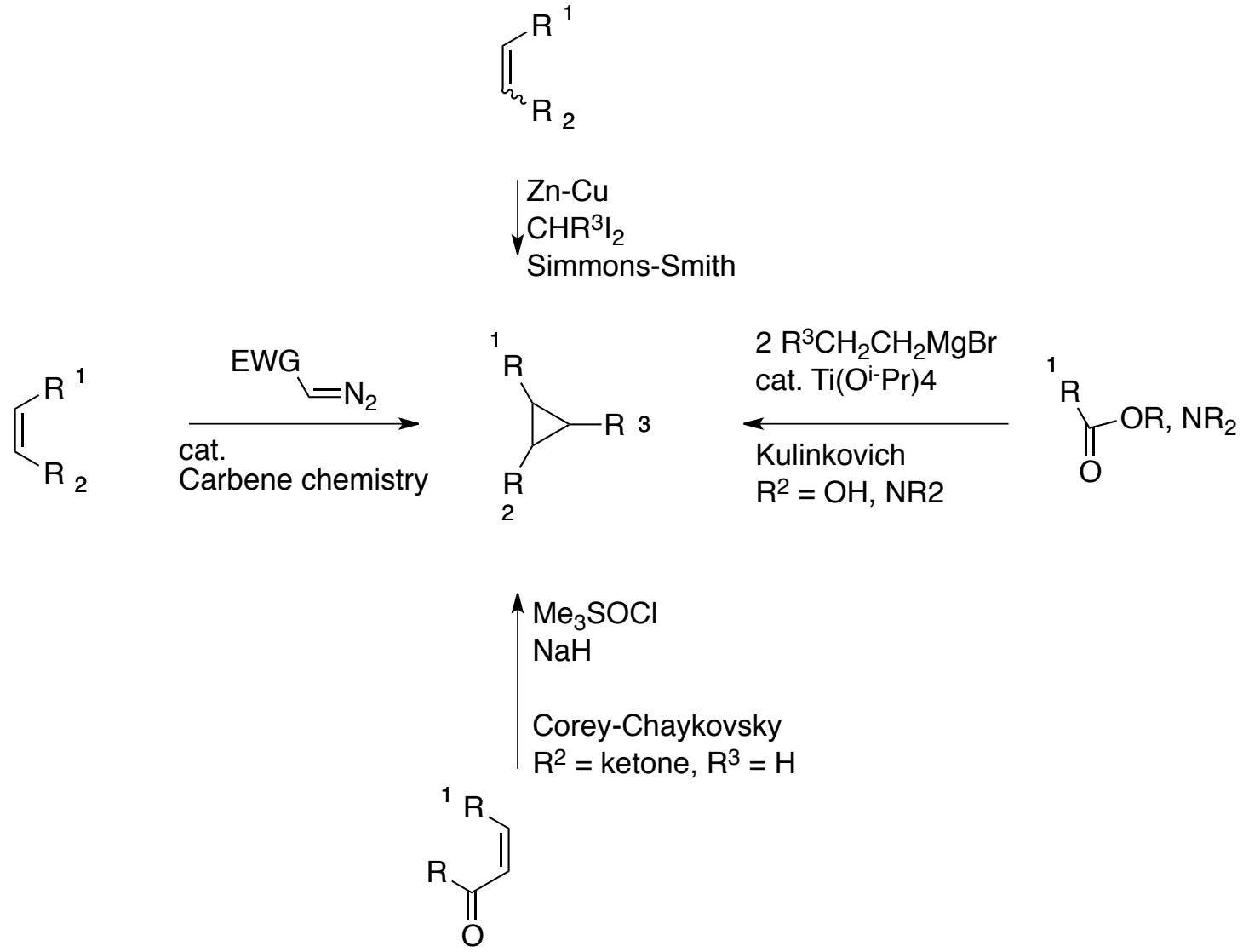


Internal nucleophilic substitution S_Ni



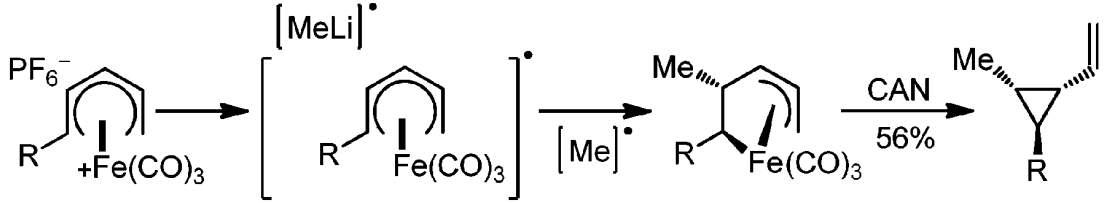
Wessjohann L. A., *et al., Chem. Rev.*, 2003, **103**(4), 1625-1647

Other syntheses (I)



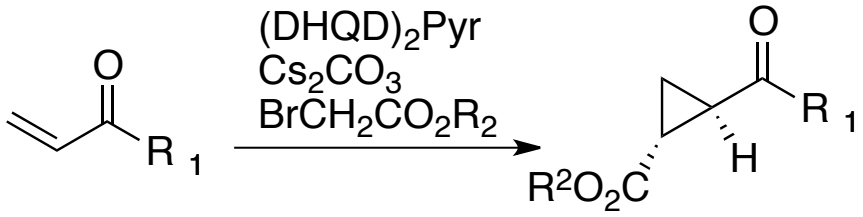
Other syntheses (II)

- Fe-mediated formation of cyclopropane



- LiTMP-triggered carbenoid insertion

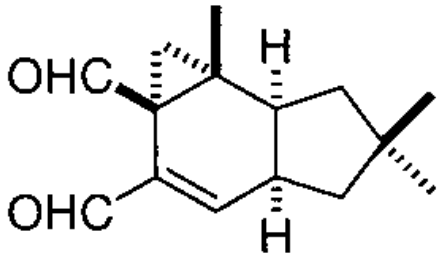
- Organocatalytic asymmetric cyclopropanation



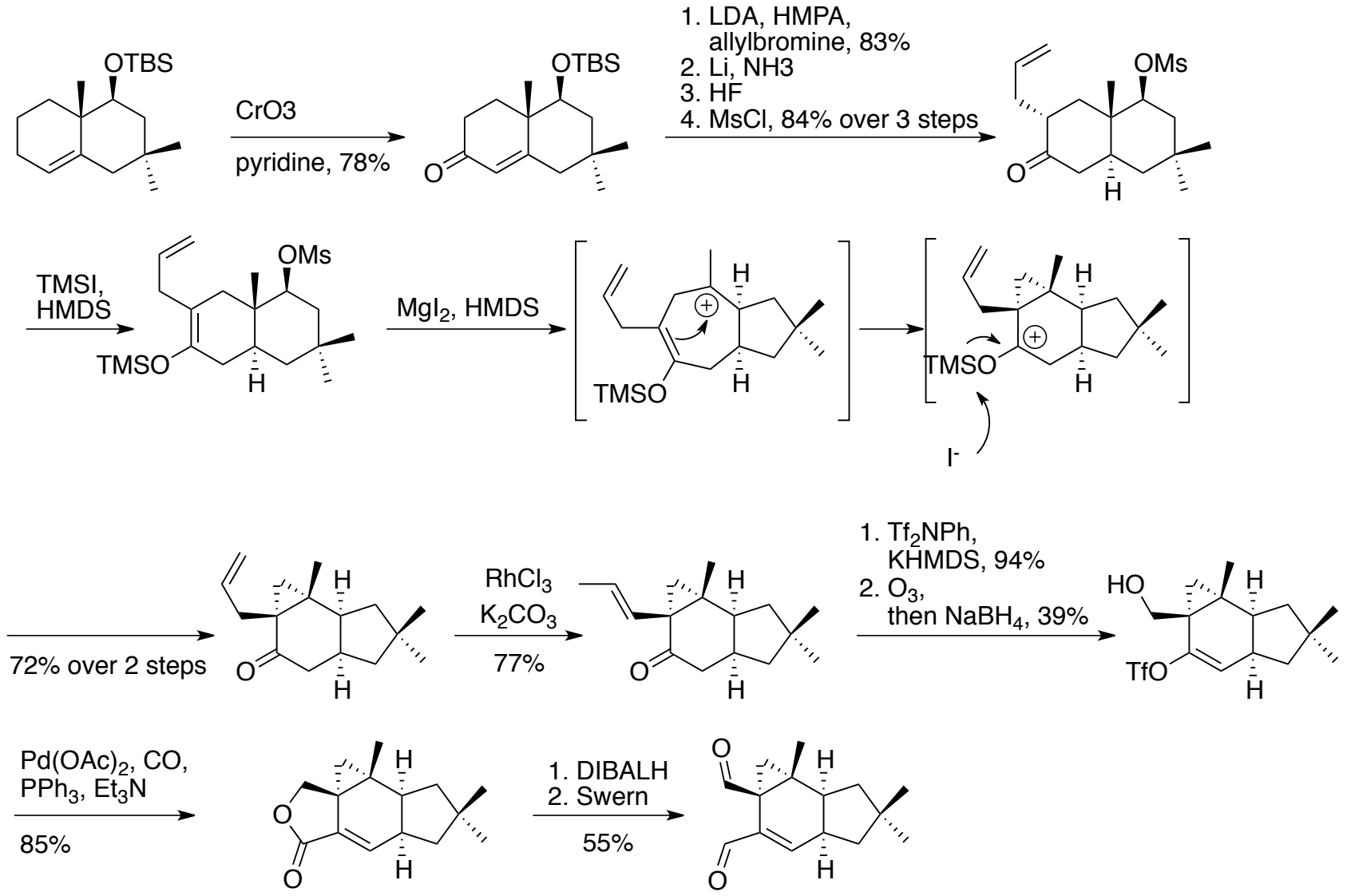
Chen D. Y.-K., *et* al., Chem. Soc. Rev*., 2012, **41**, 4631-4642*

Groot's synthesis of (+)-Isovelleral

- Isolated from *Lactarius* in 1995
- Familly shows antifungal and antibacterial activities
- Synthesis by A. de Groot in 2001
- Cyclopropane by solvolytic rearrangement



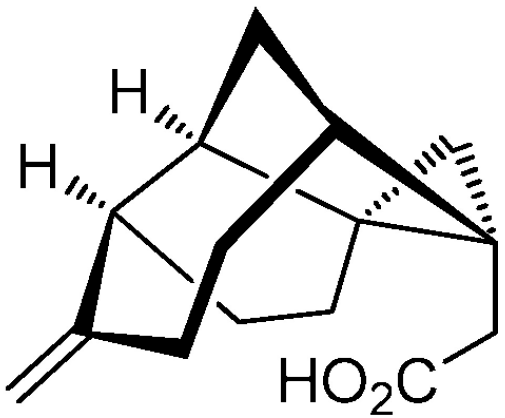
Synthesis of (+)-Isovelleral



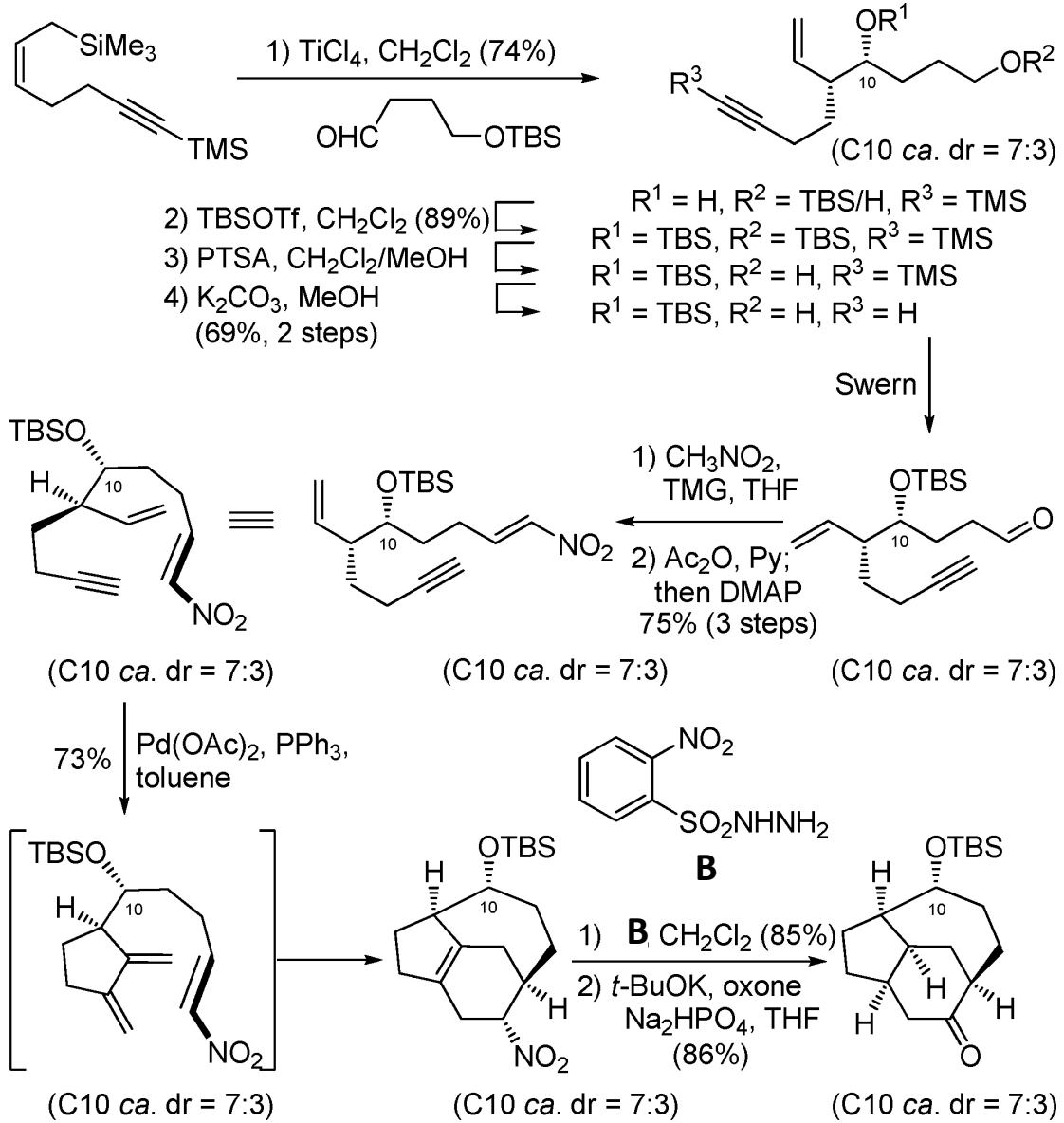
Groot A. *et al., J. Org. Chem.*, 2001, **66**, 2350-2357

Chen's synthesis of (±)-echinopine A and B

- Extracted in 2008 from *Echinops spinosus*
- Unique [3/5/5/7] ring system framework
- Synthesis by Chen's group in 2011
- Use of Trost's cyclopropanation of olefin with propargyl-alcohol

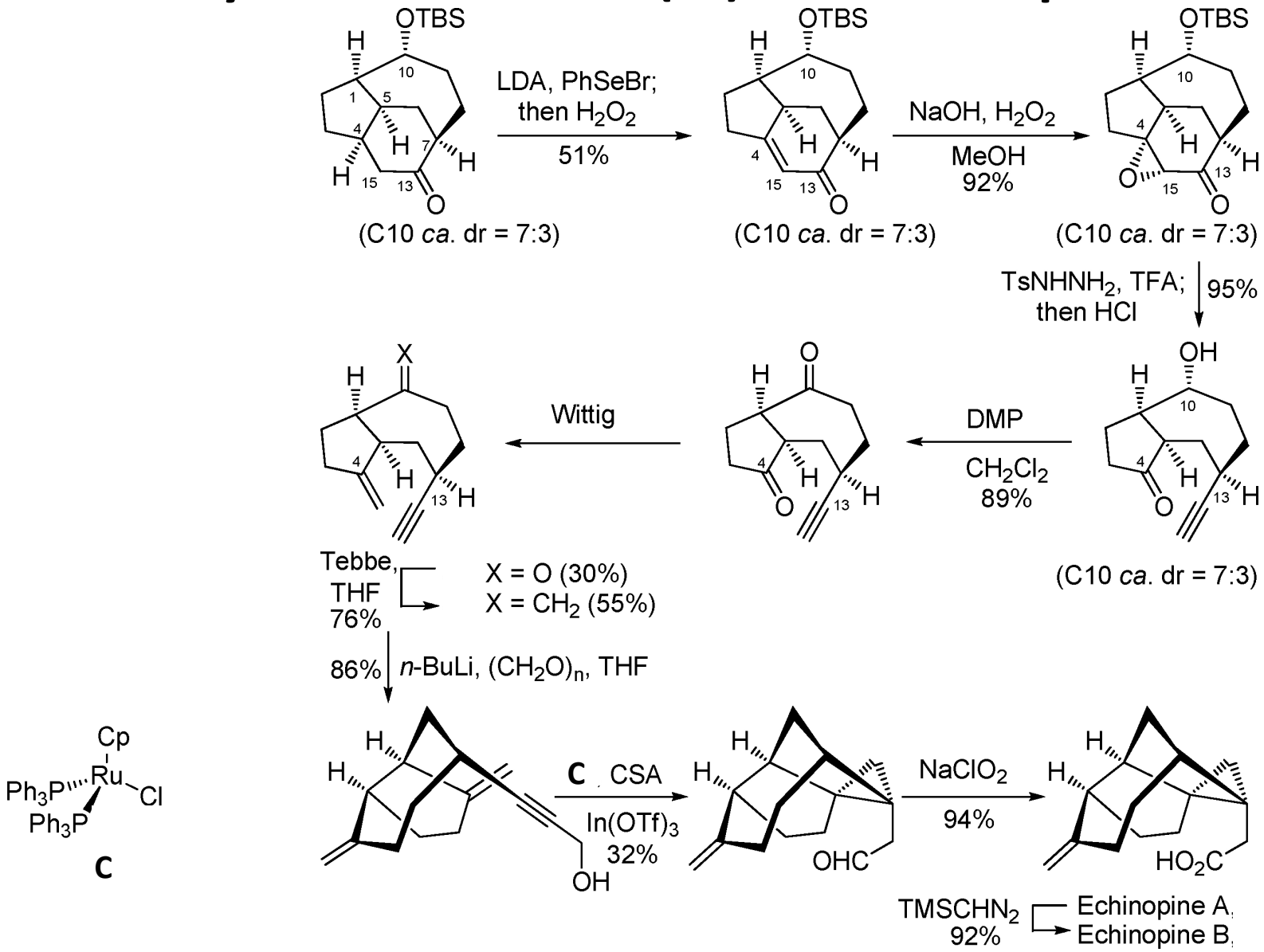


Synthesis of (±)-echinopines (I)



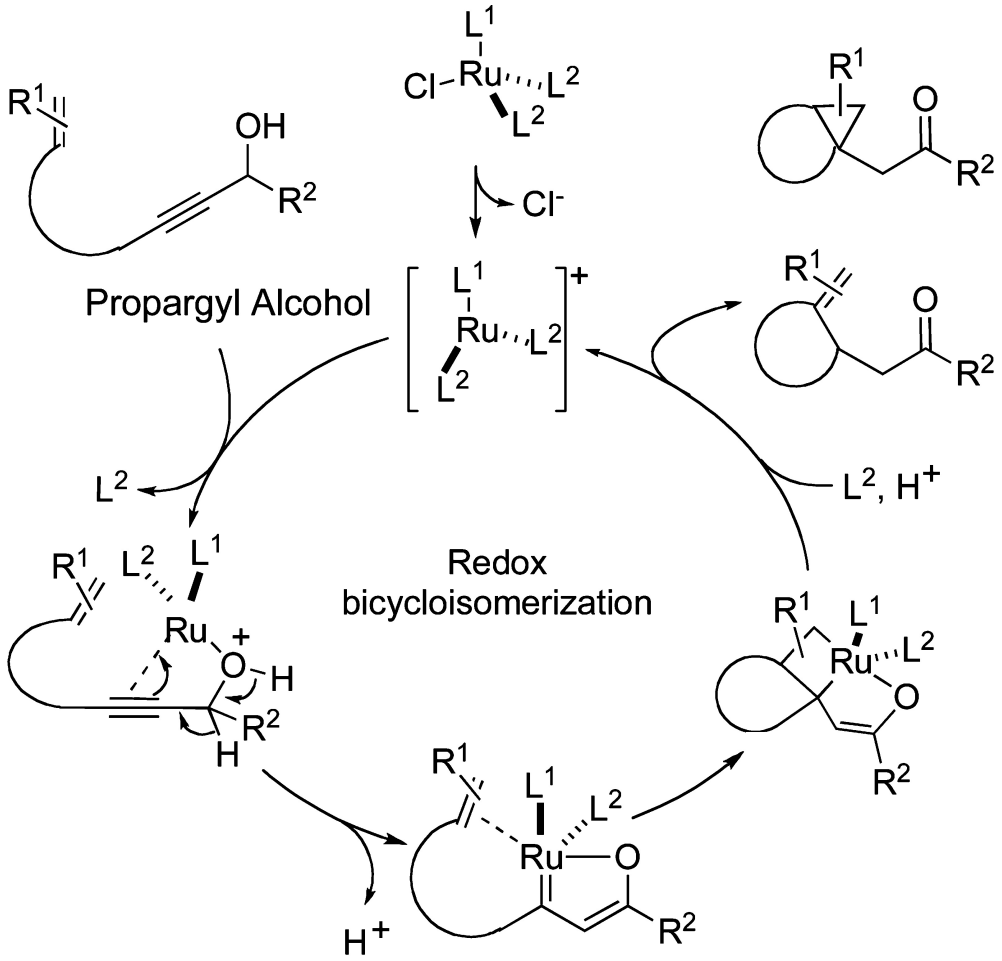
Chen D. Y.-K. *et al., Org. Lett.*, 2011, **13**, 5724-5727

Synthesis of (±)-echinopines (II)



Chen D. Y.-K. *et al., Org. Lett.*, 2011, **13**, 5724-5727

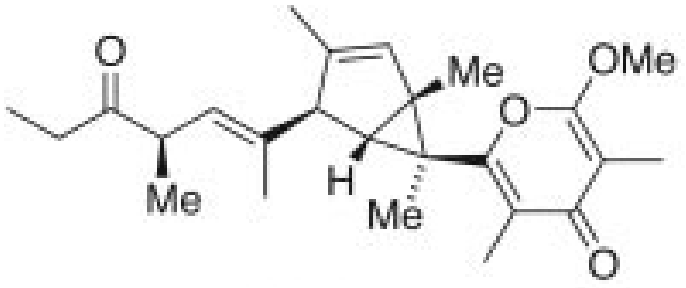
Cyclopropane-formation Mechanism



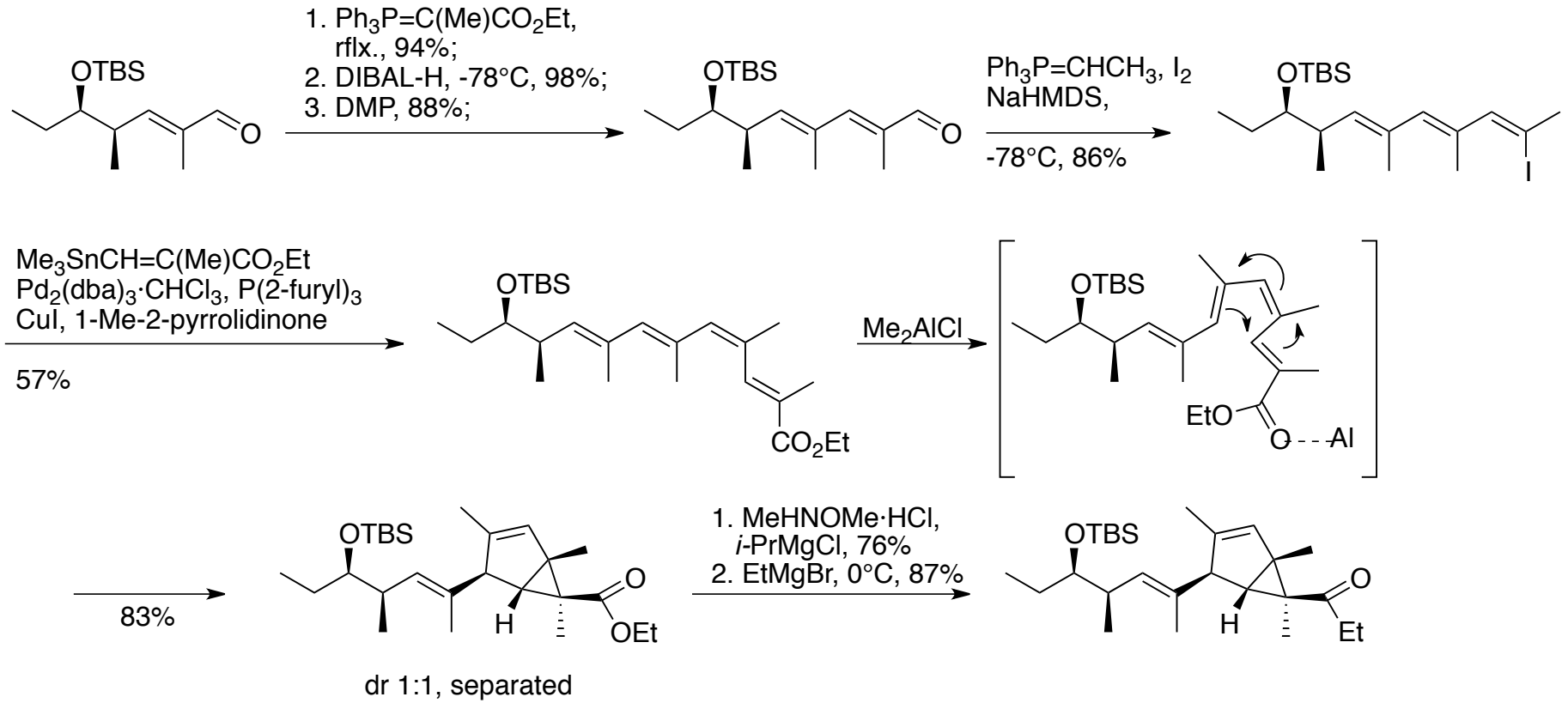
Trost B. M. *et al., J. Am. Chem. Soc.,* 2011, **133**(13), 4766–4769

Trauner's synthesis of (-)-crispatene

- Isolated in 1981 from mollusc *Elysia crispata*
- Numerous biosynthetic studies (photochemistry)
- Cyclopropane formed by cycloaddition

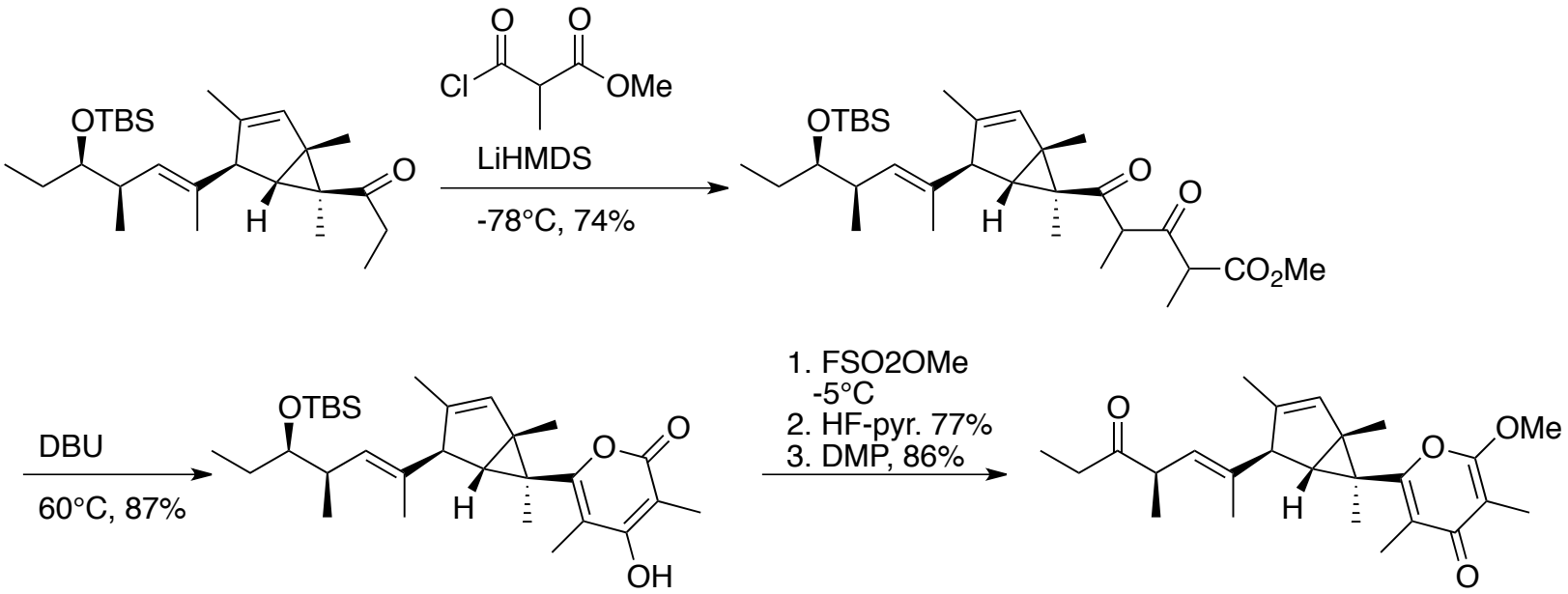


Synthesis of (-)-crispatene (I)



Trauner D. *et al., Proc. Natl. Acad. Sci. U. S. A.,* 2004, **101**, 12019-12023

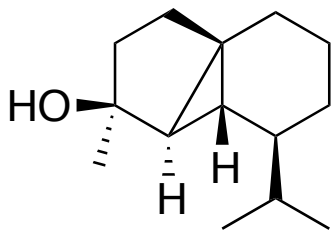
Synthesis of (-)-crispatene (II)



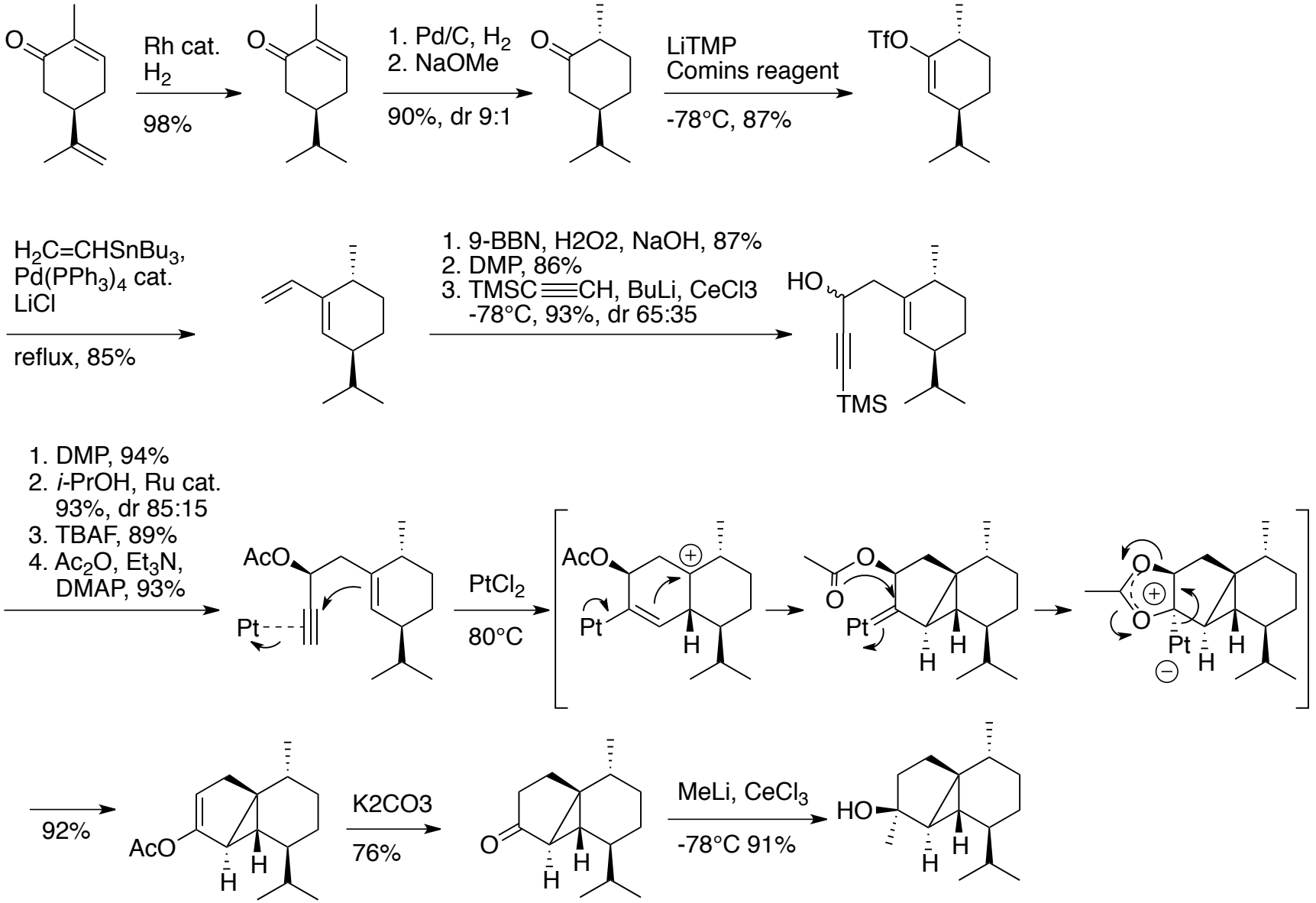
Trauner D. *et al., Proc. Natl. Acad. Sci. U. S. A.,* 2004, **101**, 12019-12023

Fürstner's synthesis of (-)-Cubebol

- Isolated in 1952 from cubeb oil
- Used in food chemistry
- Numerous total synthesis
- Fürstner used a Pt-catalyzed rearrangement to reach it in 2006



Synthesis of (-)-Cubebol



Fürstner A. *et al., Chem. Eur. J.*, 2006, **12**, 3006-3019