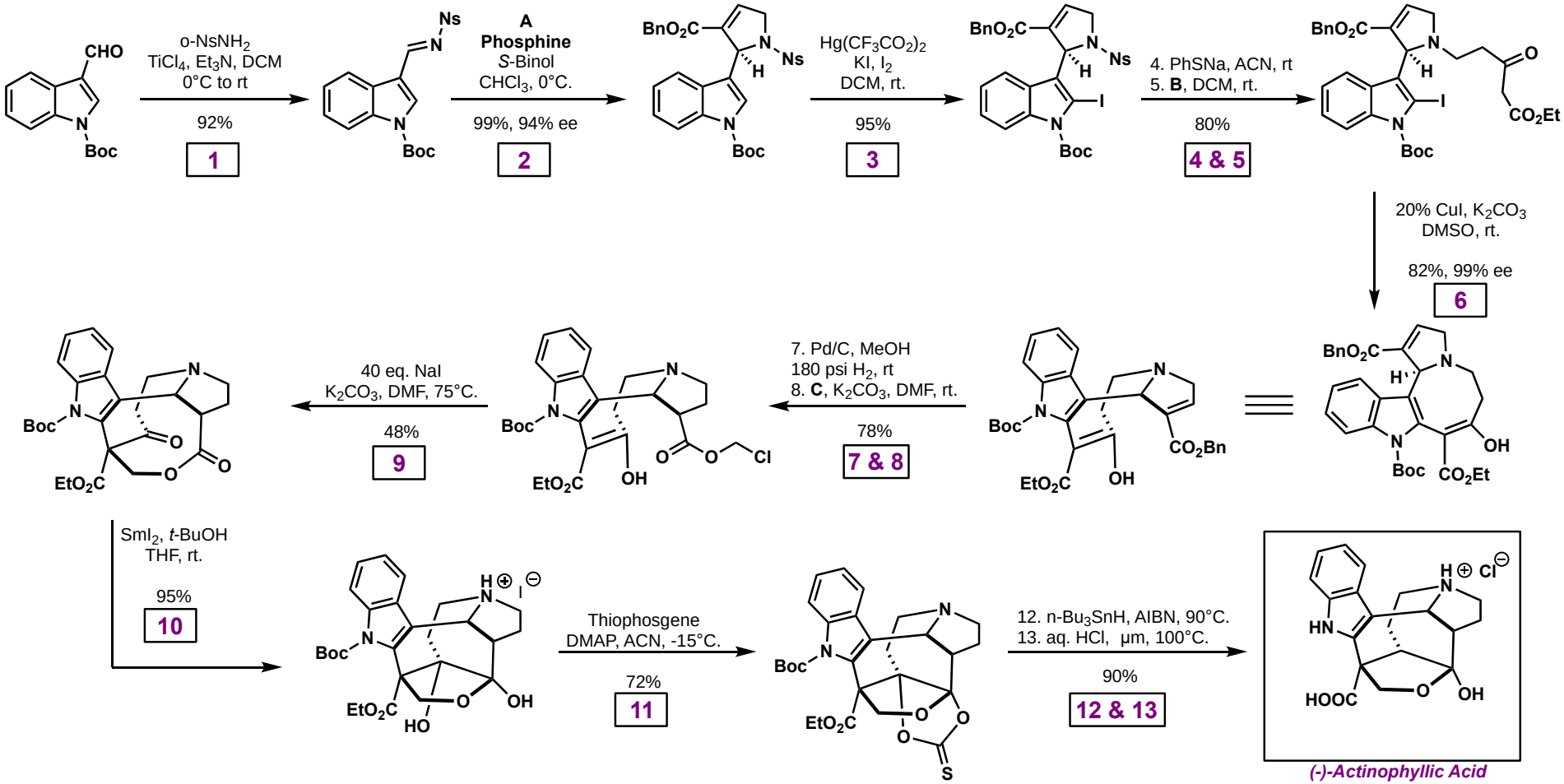
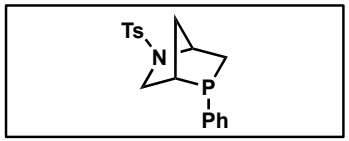
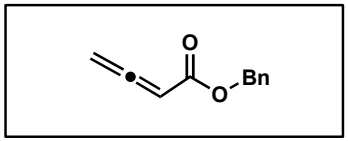
E132: Total Synthesis of (–)-Actinophyllic Acid

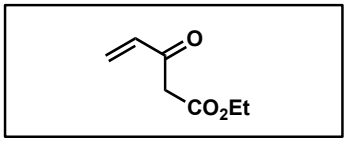




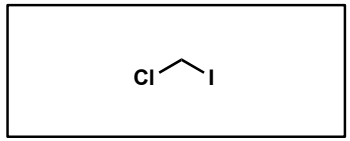
Phosphine



Compound A



Compound B



Compound C

[1] L. Cai, K. Zhang, O. Kwon *JACS* **2016**, *138*, 3298.
[2] Y. Kawamoto, F. Karube, T. Kobayashi, H. Ito *OL* **2020** *ASAP*.

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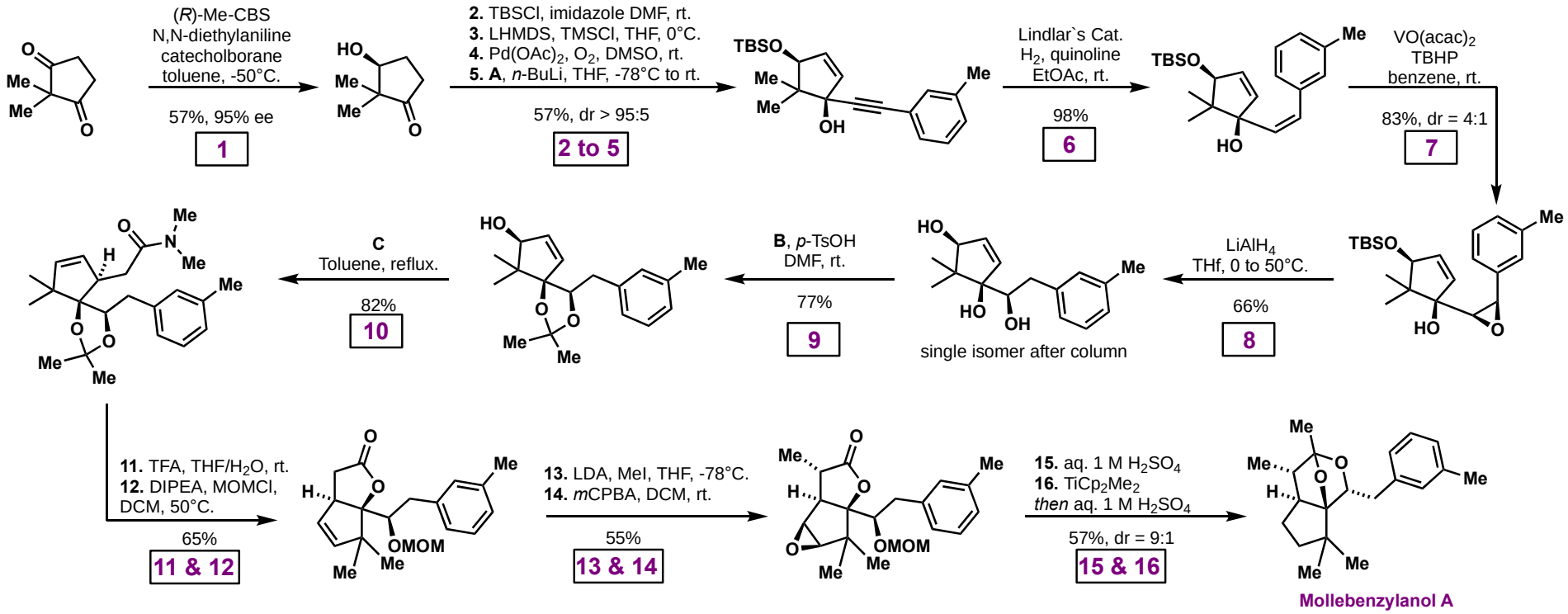
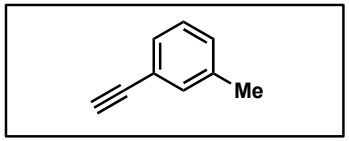
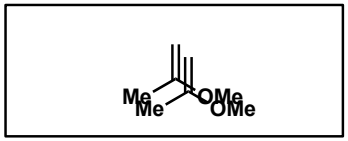
E132: Total Synthesis of Mollebenzylanol A

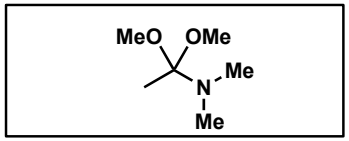




Compound A



Compound B



Compound C

[1] L. Cai, K. Zhang, O. Kwon *JACS* **2016**, *138*, 3298.
[2] Y. Kawamoto, F. Karube, T. Kobayashi, H. Ito *OL* **2020** *ASAP*.

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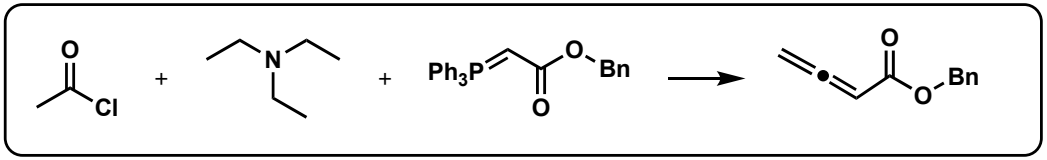
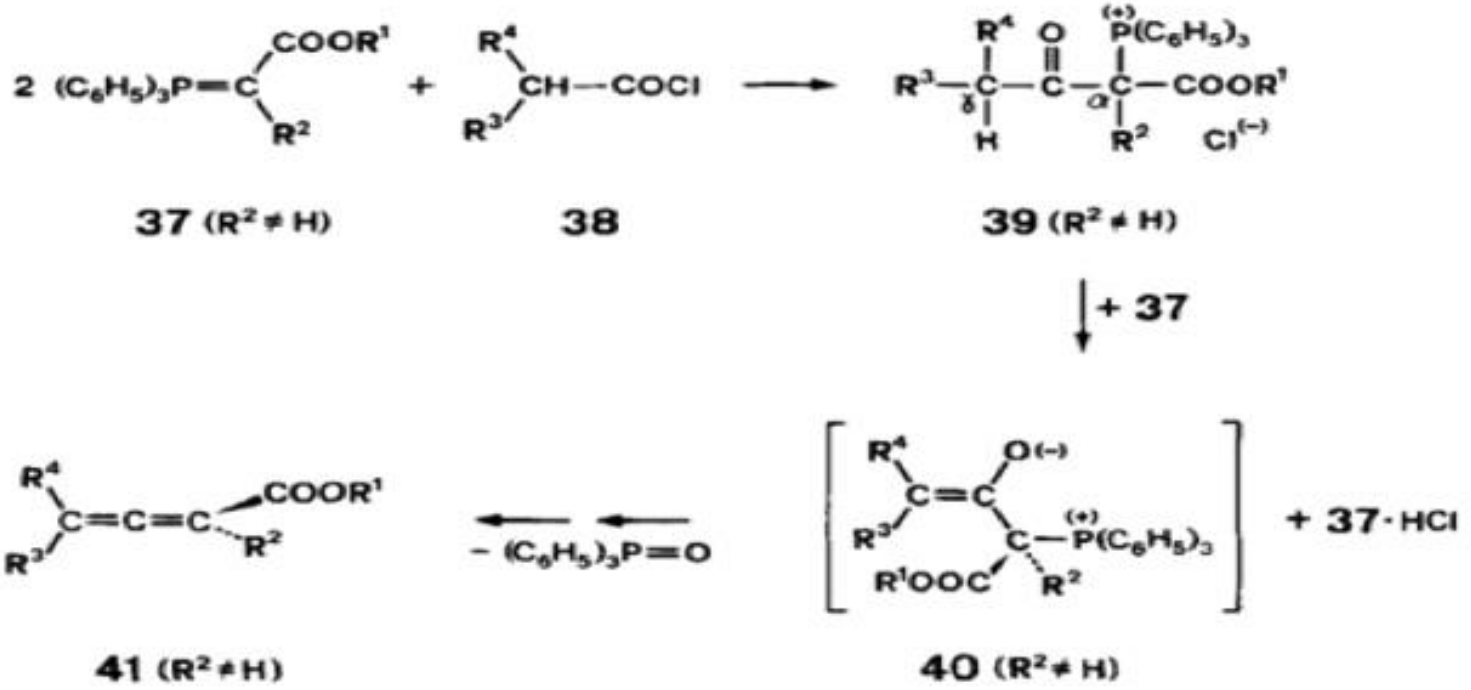
E132: Total Synthesis of (-)-Actinophyllic Acid Walkthrough

Compound A - How would you synthesize it?



Compound A - Mechanism

Schema 10[a])



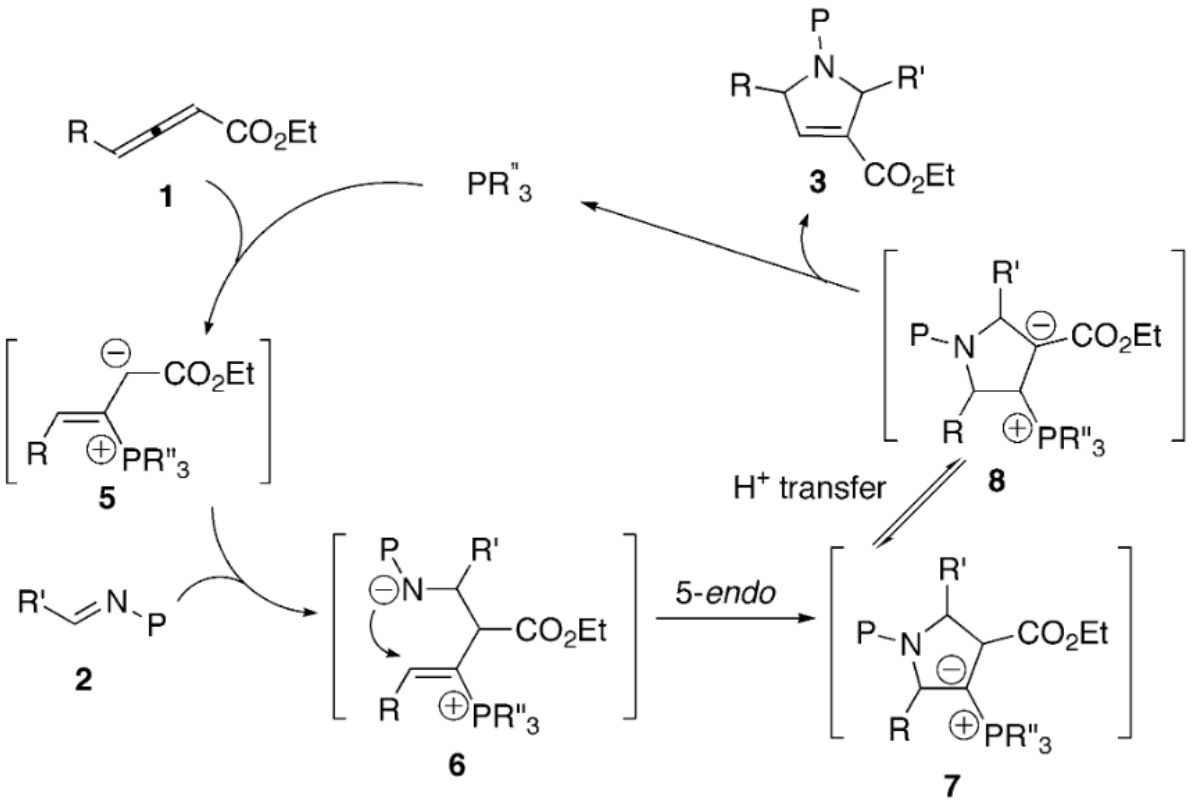
[a]) Die gezeichneten Formeln drücken keine bevorzugte Stereoselektivität aus.

[3] H.-J. Bestmann, H. Hartung *Chem. Ber.* **1966**, *99*, 1198.

E132: Total Synthesis of (-)-Actinophyllic Acid Walkthrough

Step 2 - Mechanism

- Lu`s [3+2] reaction
- zwitterionic intermediate **5** adds to imine **2**
- Intramolecular amide anion (**6**) addition to vinyl phosphonium
- Ylide **7** undergoes proton transfer, yielding intermediate **8**
- dissociation into 3-pyrroline **3** and phosphine catalyst



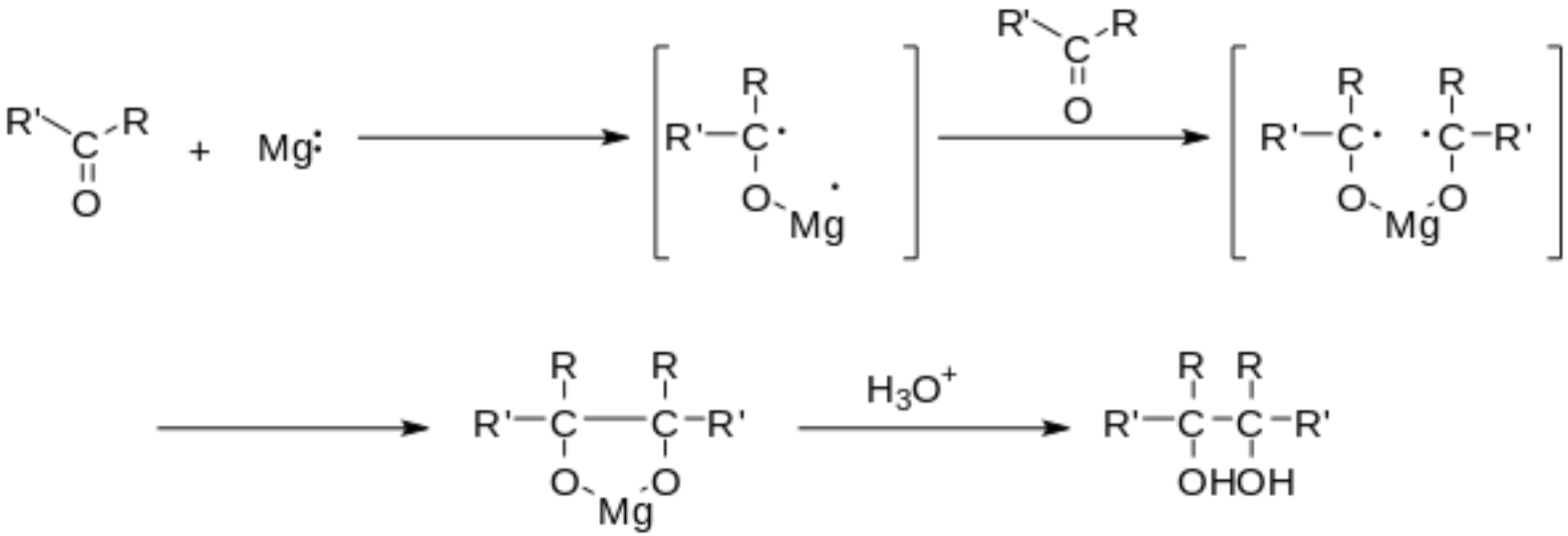
Scheme 1. Mechanistic rationale for the formation of pyrroline **3**.

[4] X.-F. Zhu, C. E. Henry, O. Kwon *Tetrahedron* **2005**, *61*, 6276.

E132: Total Synthesis of (-)-Actinophyllic Acid Walkthrough

Step 10 - Mechanism

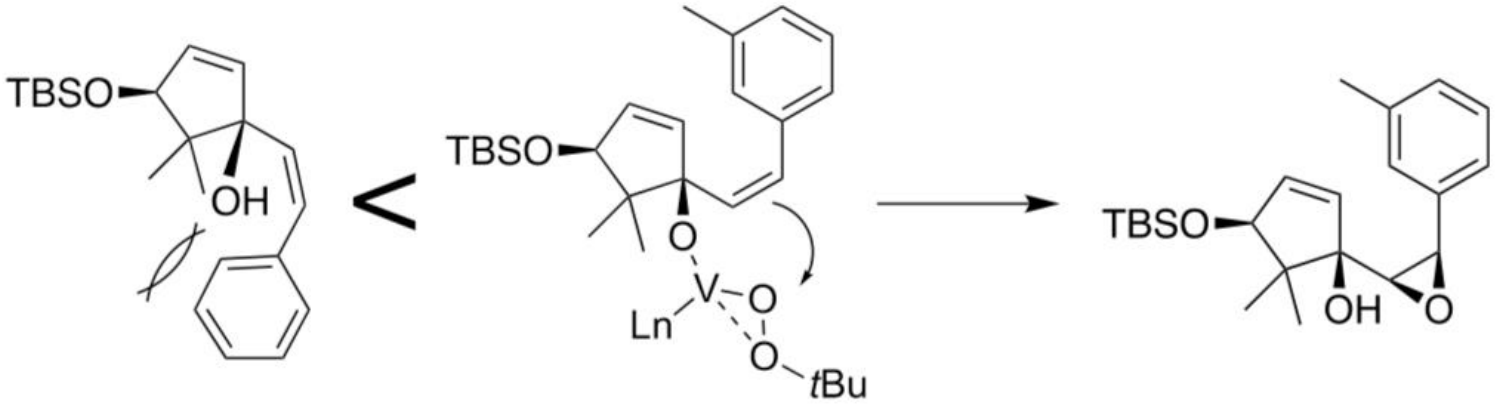
- Sm mediated Pinacol coupling
- one electron reduction of the carbonyl to Ketyl radical anion
- Two ketyl groups react in a coupling reaction
- Metal ususally assists with coordination to form a 5-membered cyclic compound
- cleavage of intermediate with water / acid



E132: Total Synthesis of Mollebenzylanol A Walkthrough

Step 7 - Stereochemistry

- Transition state **B** is more favorable than **A**
- avoiding steric repulsion (benzene <—> dimethyl group)
- $VO(acac)_2$ - TBHP complex approaches from the a face as the alcohol
- Regioselectivity : TBS is shielding the cyclopentene ring



A: disfavored **B**: favored

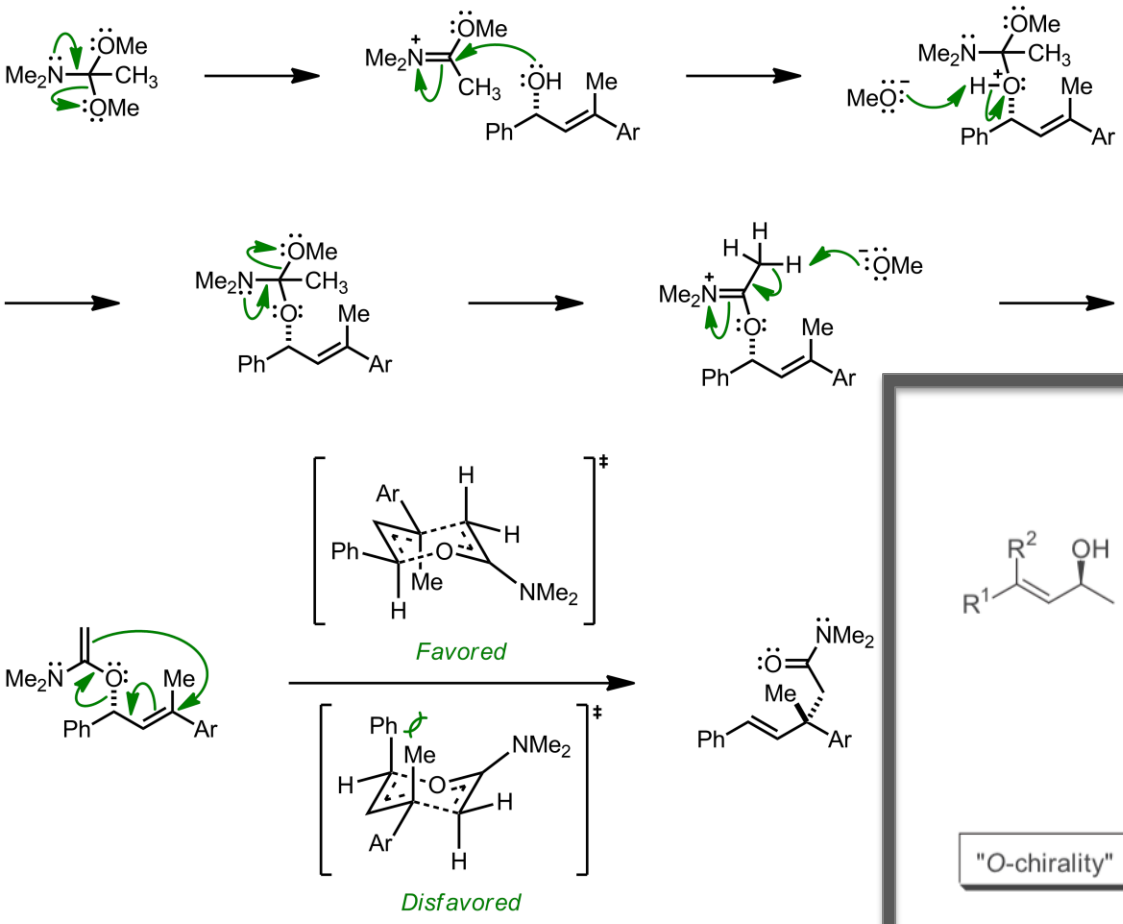
Figure 2. Selectivity of epoxidation.

[2] Y. Kawamoto, F. Karube, T. Kobayashi, H. Ito *OL* **2020** *ASAP*.

E132: Total Synthesis of Mollebenzylanol A Walkthrough

Step 10 - Mechanism

- Eschenmoser - Claisen rearrangement
- see schemes



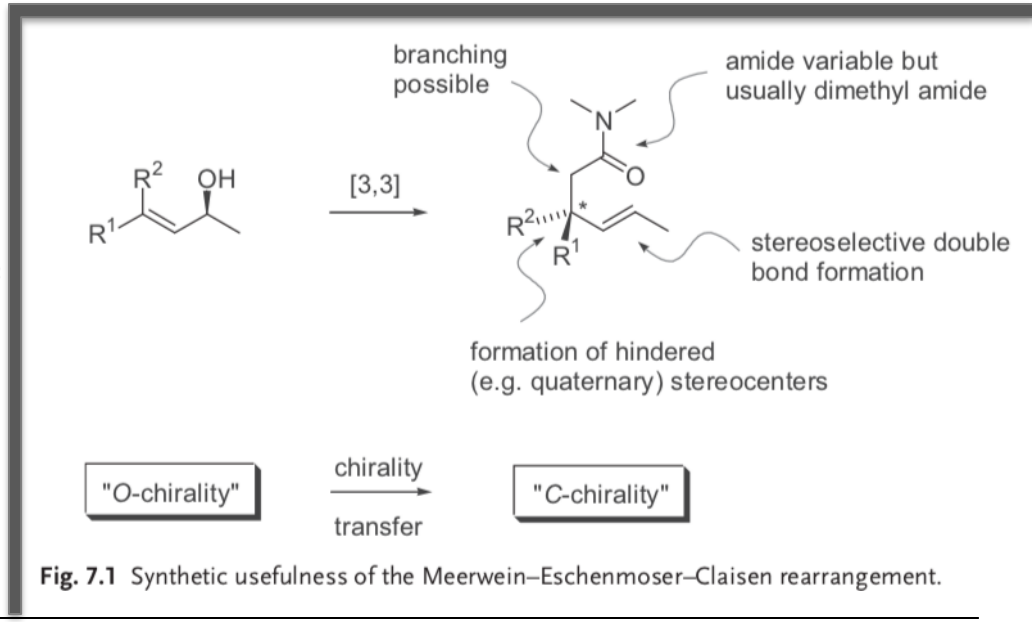


Fig. 7.1 Synthetic usefulness of the Meerwein–Eschenmoser–Claisen rearrangement.

[5] A. E. Wick, D. Felix, K. Steen, A. Eschenmoser *Helv. Chim. Acta* **1964** *47,* 2425.

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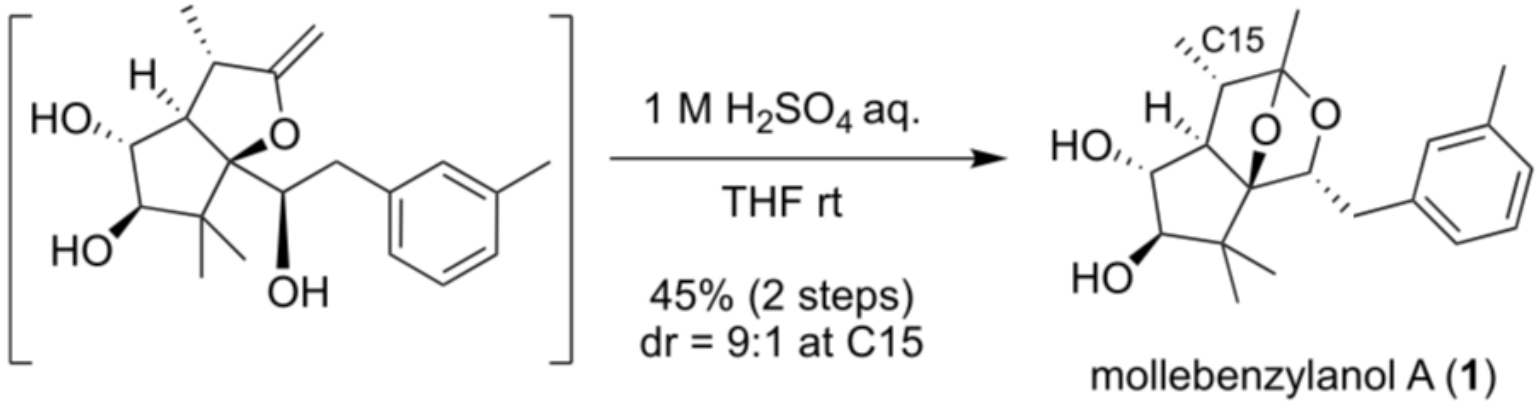
E132: Total Synthesis of Mollebenzylanol A Walkthrough

Step 16 - Intermediate & Mechanism

- Petasis reaction
- followed by acetalization
- Protonation of alkene followed by nucleophilic attack at carbocation



[5] A. E. Wick, D. Felix, K. Steen, A. Eschenmoser *Helv. Chim. Acta* **1964** *47,* 2425.
[2] Y. Kawamoto, F. Karube, T. Kobayashi, H. Ito *OL* **2020** *ASAP*.