# Total Synthesis of (–)-Nahuoic Acid $C_i$ ($B_{ii}$)

Qi Liu, Yifan Deng, Amos B. Smith, III.*

University of Philadelphia, Pennsylvania

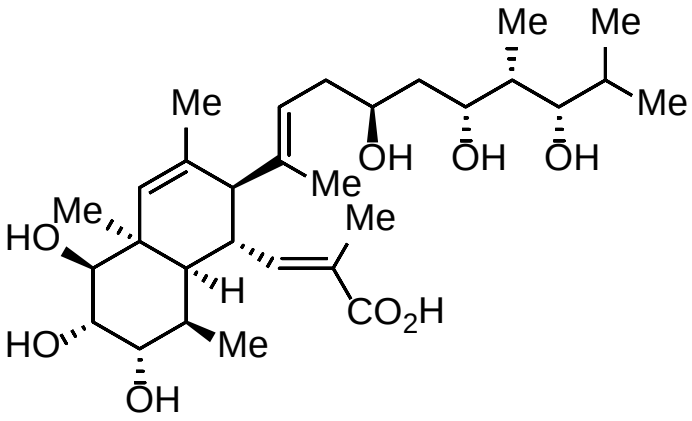
March 9, 2019

Presented by Chris Peruzzi

*J. Am. Chem. Soc.* **2017**, *139*, 13668

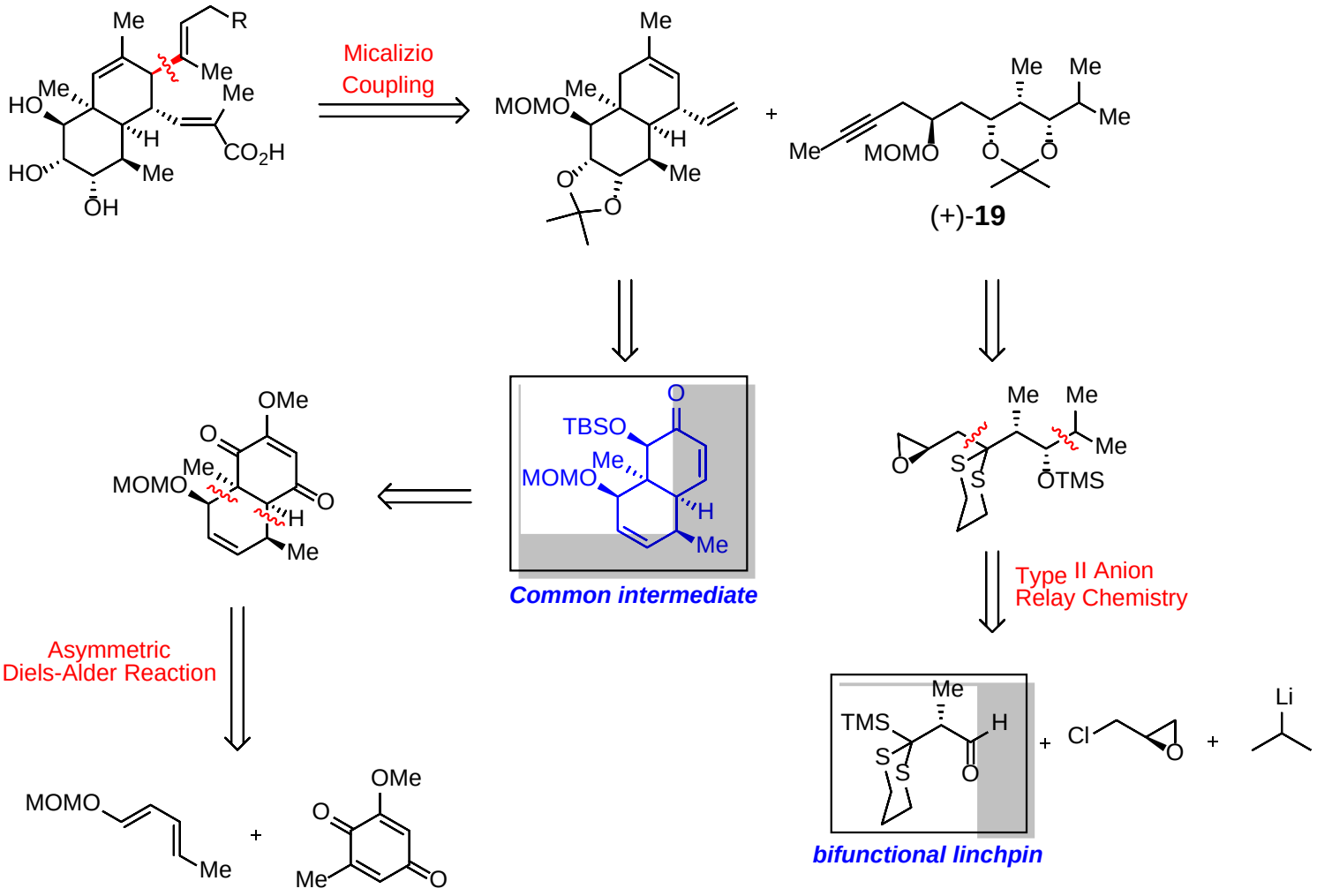
# Background

- Isolated from tropical marine sediment
- Nahuoic acid derivatives inhibit SETD8 enzyme, which is the epigenetic regulator of cell cycle progression
- Contain 8 contiguous stereocenters in a *cis*-decalin framework

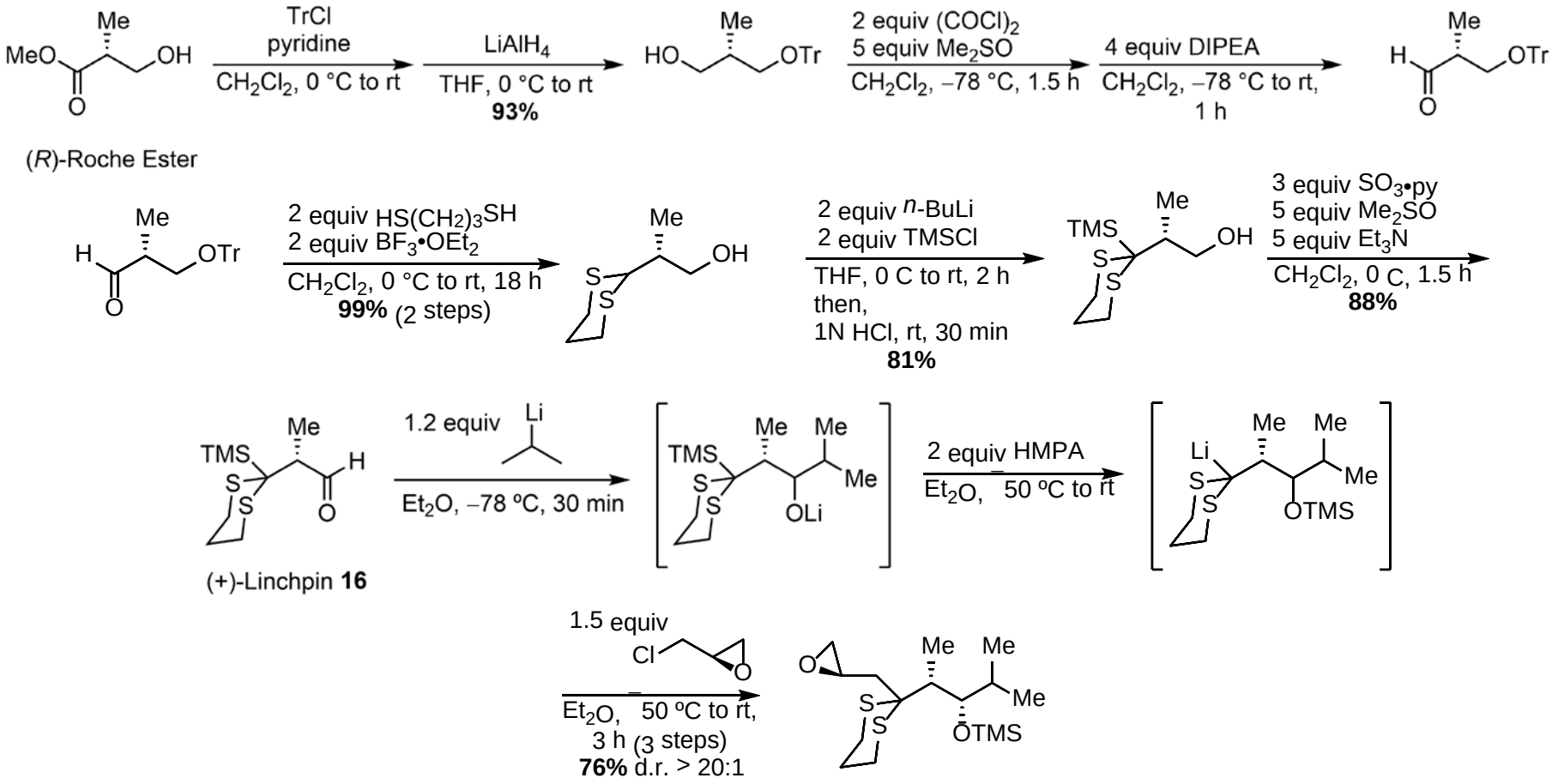



https://3c1703fe8d.site.internapcdn.net/newman/csz/news/800/2014/ancientreefs.jpg

# Synthetic Plan

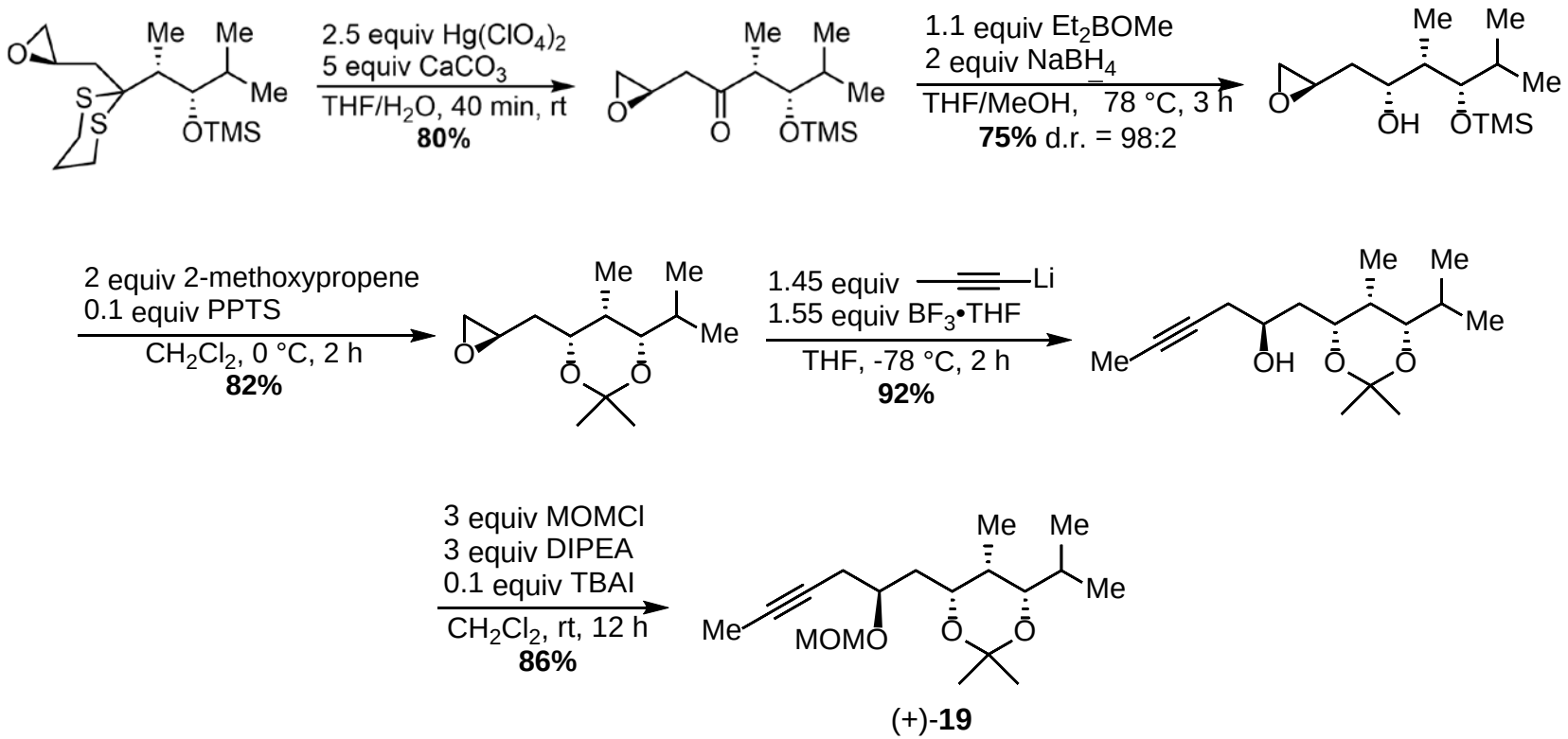


# Synthesis of Side Chain (+)-19



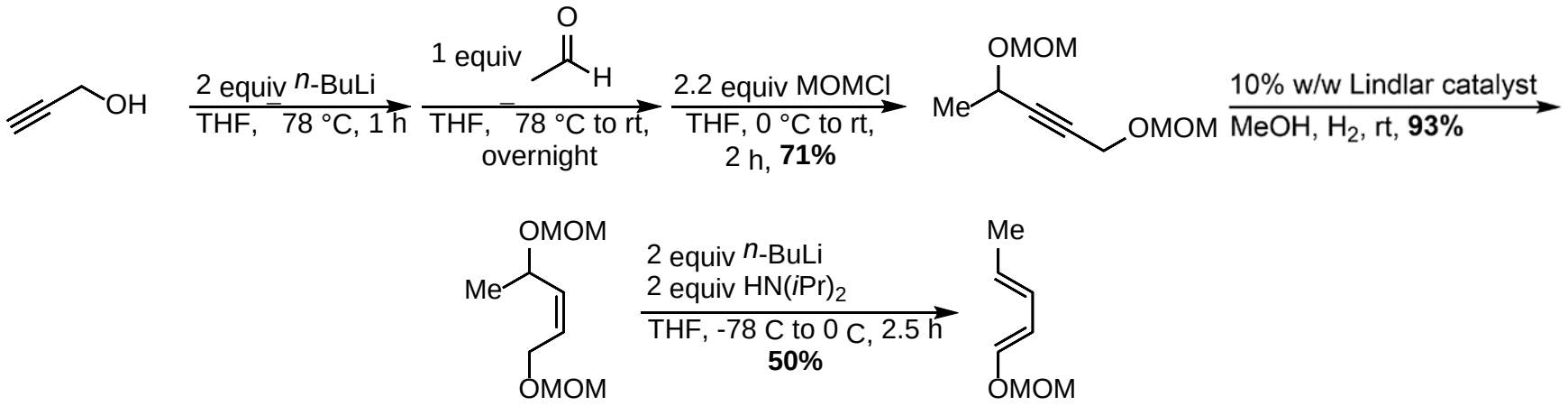

*Synlett*. **2005**, *4,* 655-657
*Chem. Eur. J.* **2009**, *15*, 2874.

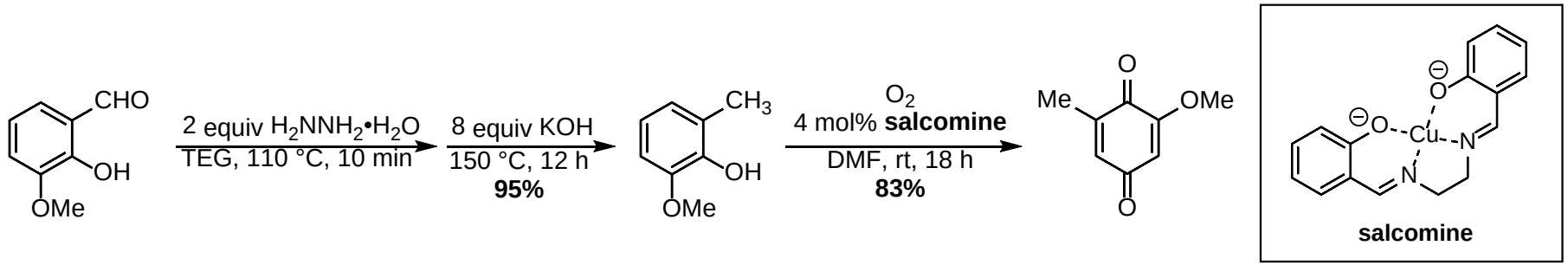
# Synthesis of Side Chain (+)-19




(+)-**19**

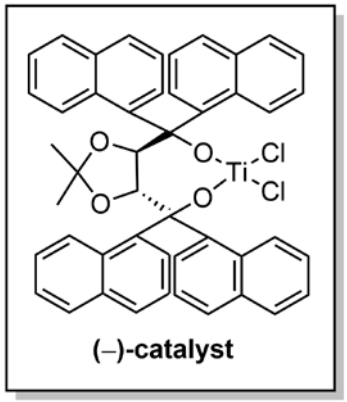
# Diels-Alder Synthons

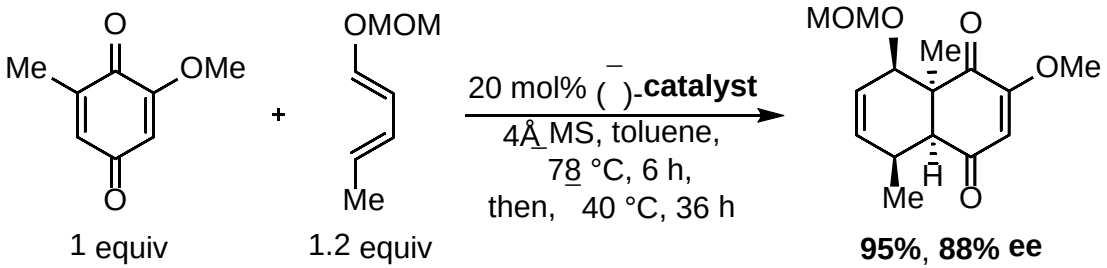



*J. Org. Chem.* **1987**, *52*, 4817
*Org. Lett.* **2015**, *17*, 2030

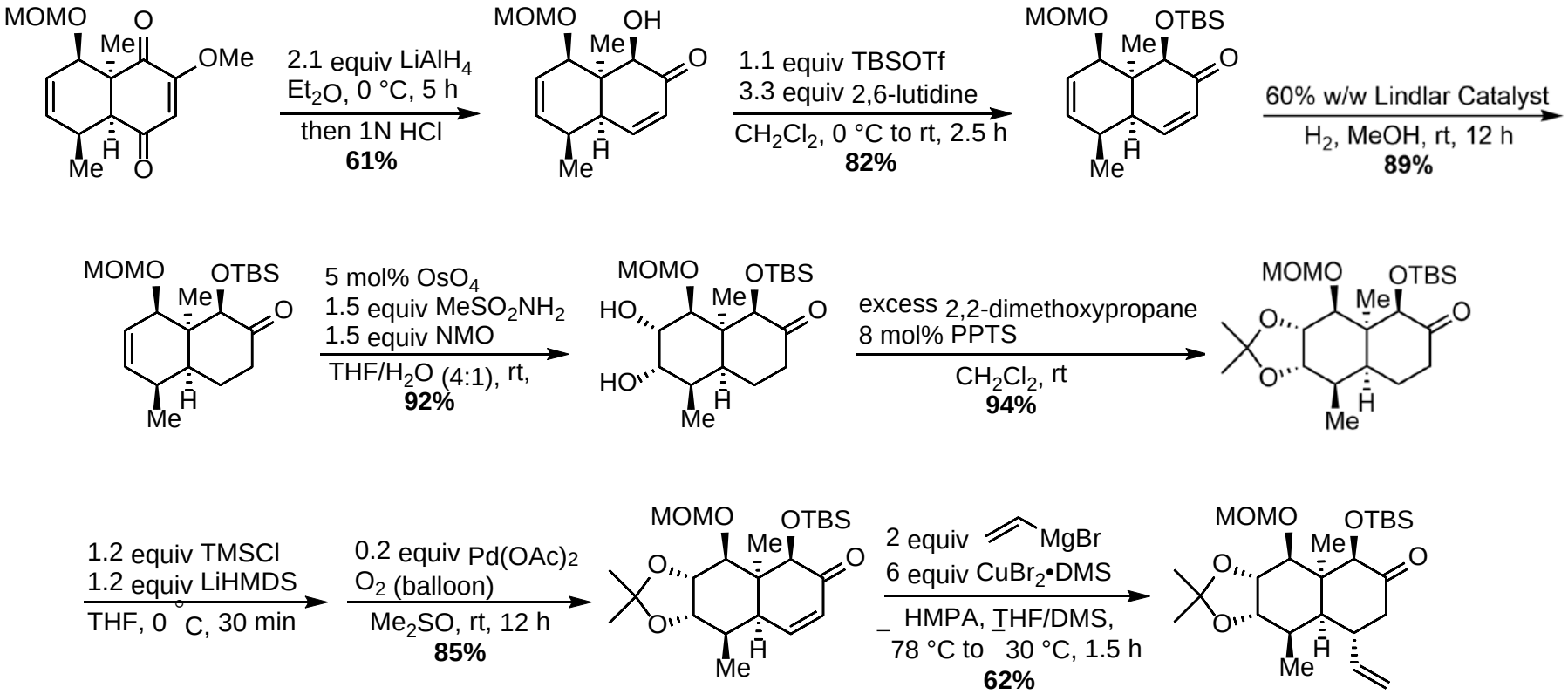
# Asymmetric Diels-Alder



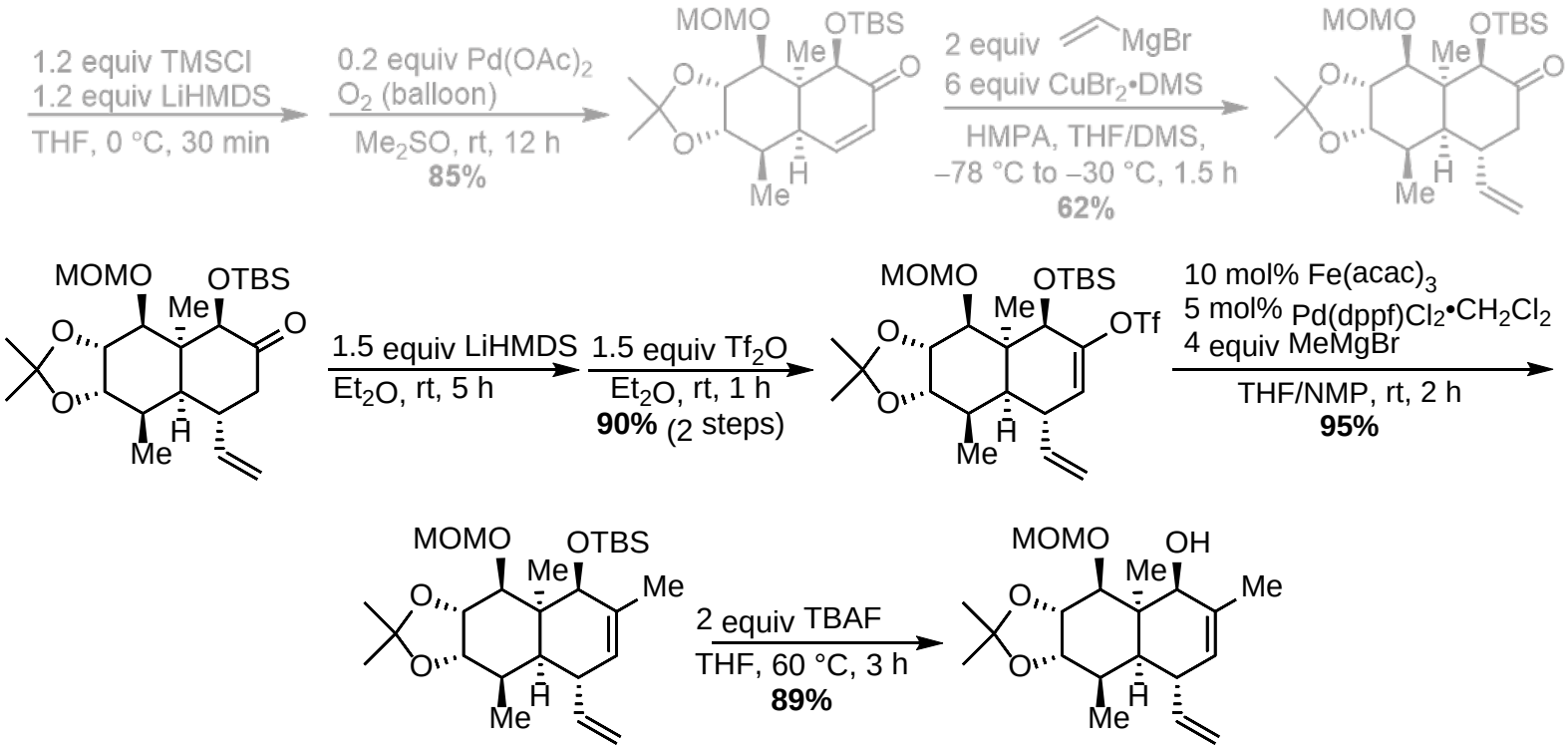




| Conditions | Results |
|---|---|
| Toluene/$CH_2Cl_2$, 120 °C, 48 h | 74%, racemic |
| 1 eq. **catalyst**, $CH_2Cl_2$, –40 °C, 24 h | 71%, 73% ee |
| 20 mol% **catalyst**, $CH_2Cl_2$, 0 °C to rt, 24 h | 25%, 55% ee |
| 20 mol% **catalyst**, $CH_2Cl_2$, –60 °C, 12 h | 80%, 71% ee |
| 20 mol% **catalyst**, toluene, –78 to –40 °C, 42 h | 95%, 88% ee |

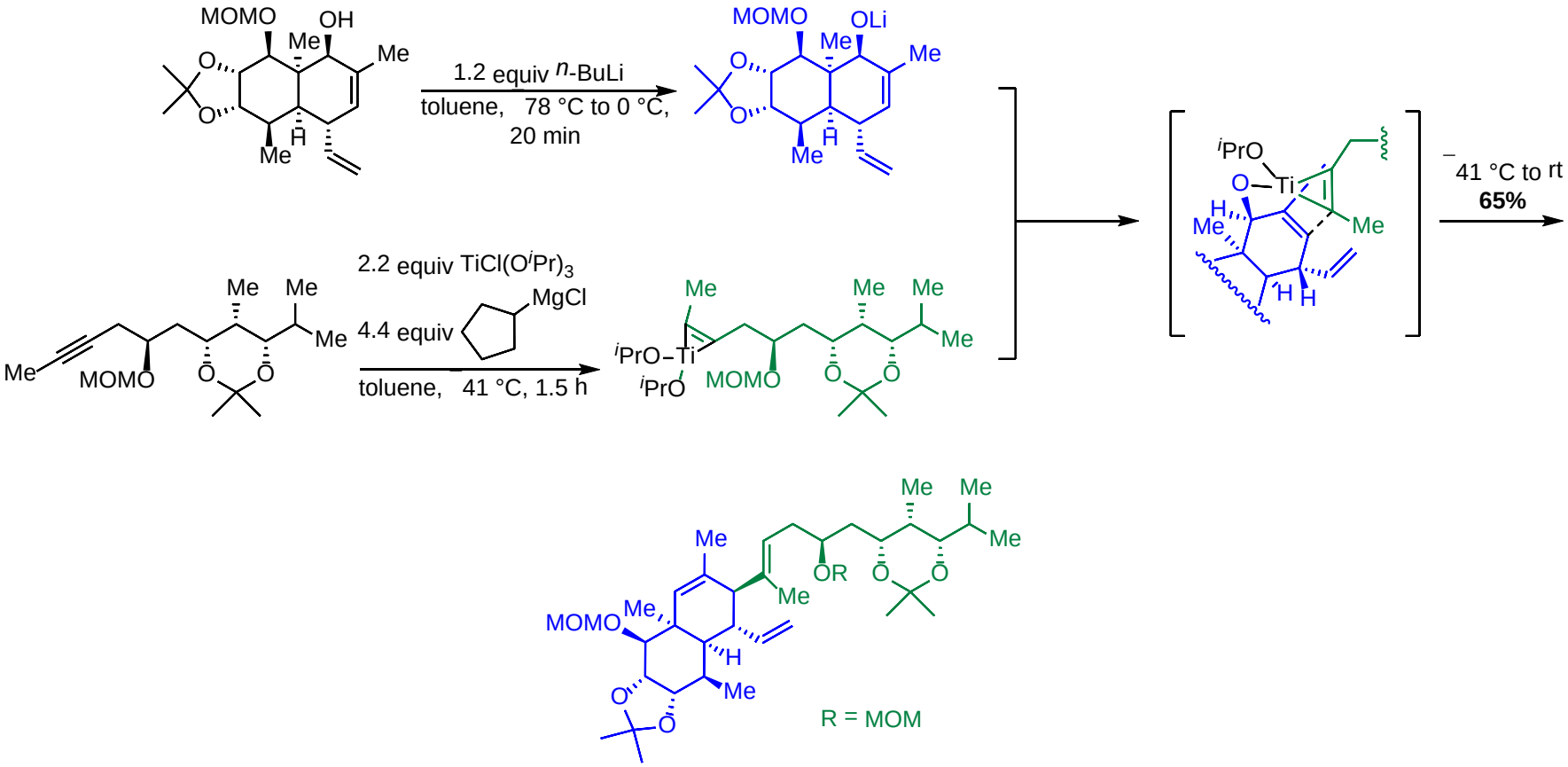
# Functionalization of Diels–Alder Adduct



# Functionalization of Diels–Alder Adduct

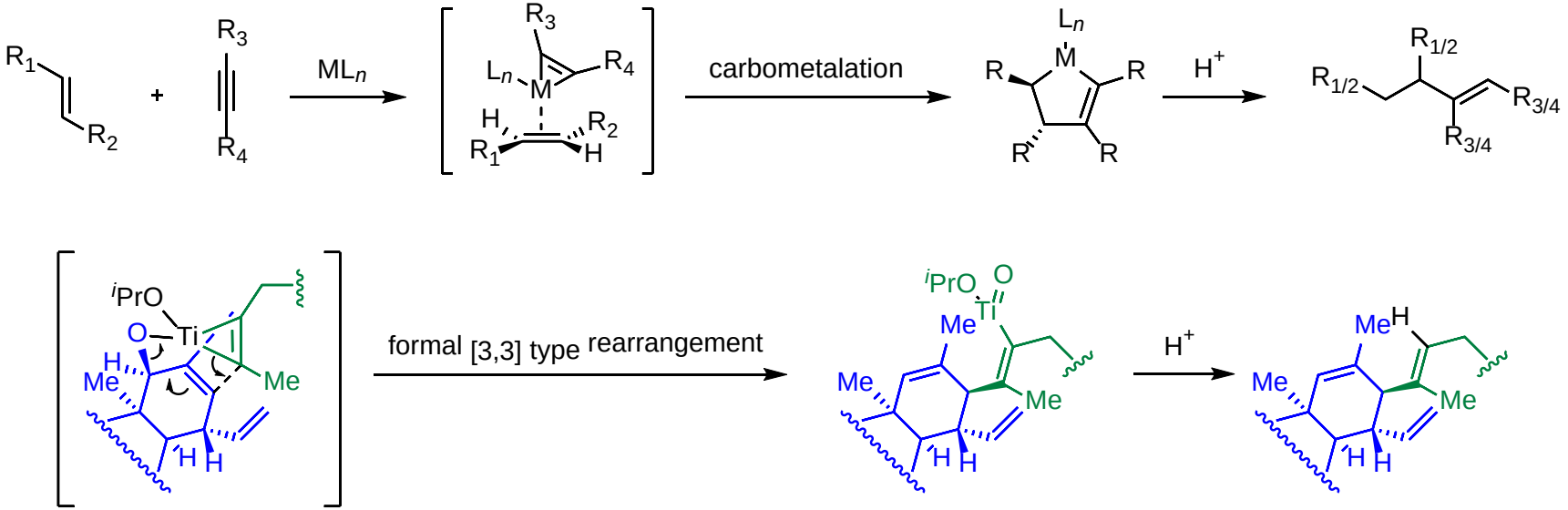


# Micalizio Coupling



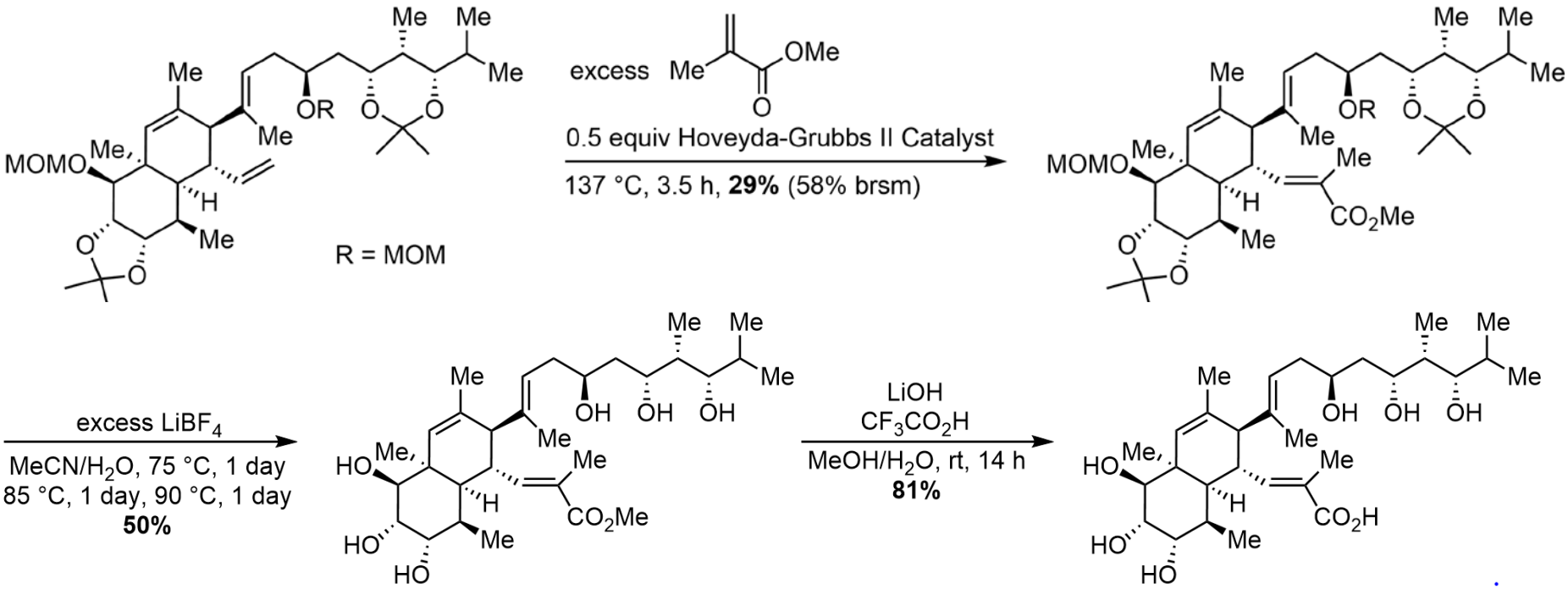
# Micalizio Alkene–Alkyne Coupling

General Reaction




*Angew. Chem., Int. Ed.* **2007**, *46*, 1440
*J. Am. Chem. Soc.* **2007**, *129*, 15112.
*Angew. Chem., Int. Ed.* **2012**, *51*, 5152.

# Endgame Strategy for Nahuoic Acid $C_i$




**Nahuoic Acid $C_i$**
**16 Steps**