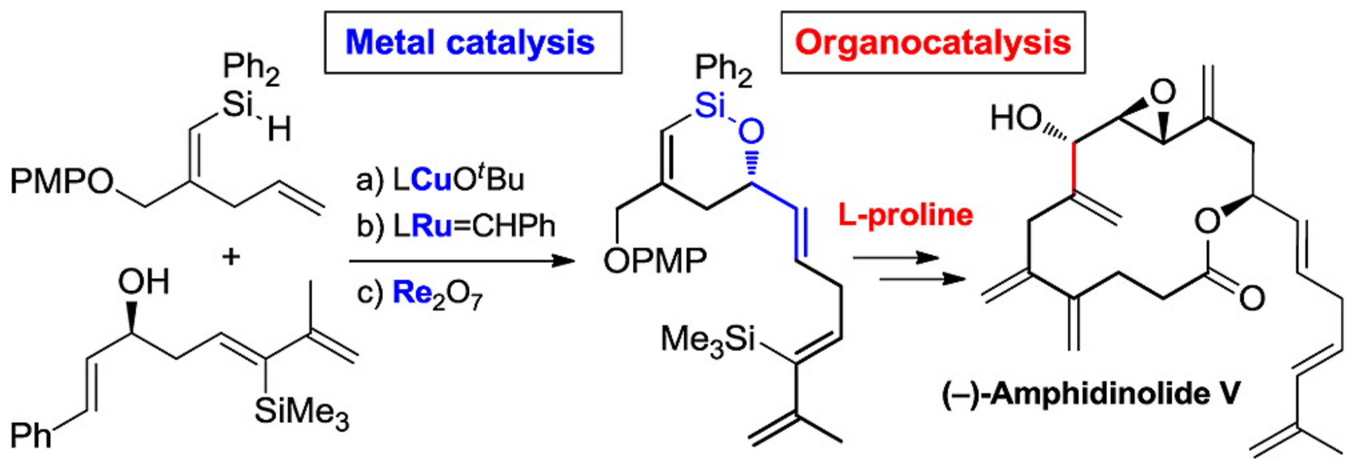
Asymmetric Total Synthesis of (−)-Amphidinolide V through Effective Combinations of Catalytic Transformations

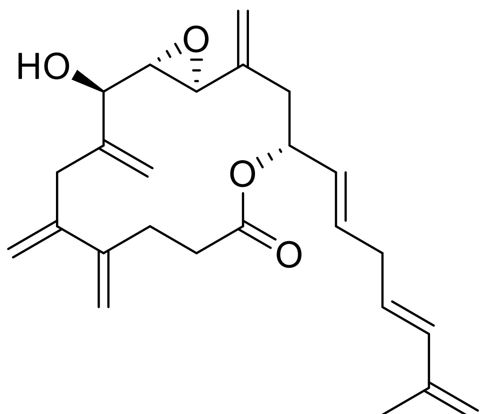
Ivan Volchkov and Daesung Lee. *J. Am. Chem. Soc.* **2013**, *135*, 5324−5327



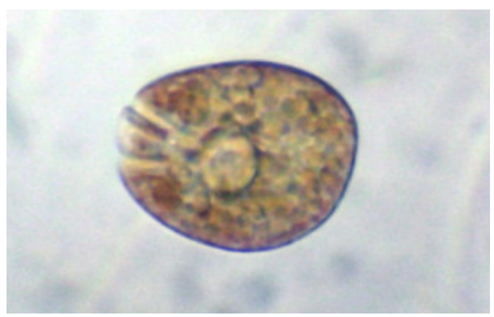
Liming Cao
Wipf Group Current Literature
4/20/2011

Amphidinolide V

- Amphidinolides: secondary metabolites from symbiotic dinoflagellates *Amphidinium sp.*
- (+)-Amphidinolide V: *Amphidinium* strain Y-15 with other 14 members
- Plankton: flatworm *Amphiscolops sp.* at Chatan beach, Okinawa
- Cytotoxicity: murine lymphoma L1210 (IC_{50}, 3.2 μg/mL) and human epidermoid carcinoma KB cells (IC_{50}, 7 μg/mL) in vitro



(+)-Amphidinolide V



Amphidinium sp.

flatworm *Amphiscolops sp.*

Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77
http://www.pirx.com/droplet/gallery/amphidinium.html
http://www.wetwebmedia.com/fltwmidfaq3.html

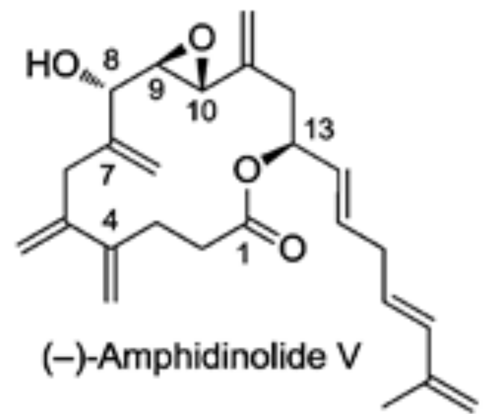
(-)-Amphidinolide V

Structure:

- 14-membered macrolactone
- A syn-epoxyalcohol subunit
- Three isolated and two vicinal exo-methylene groups
- An unsaturated side chain

Stereogenic centers:

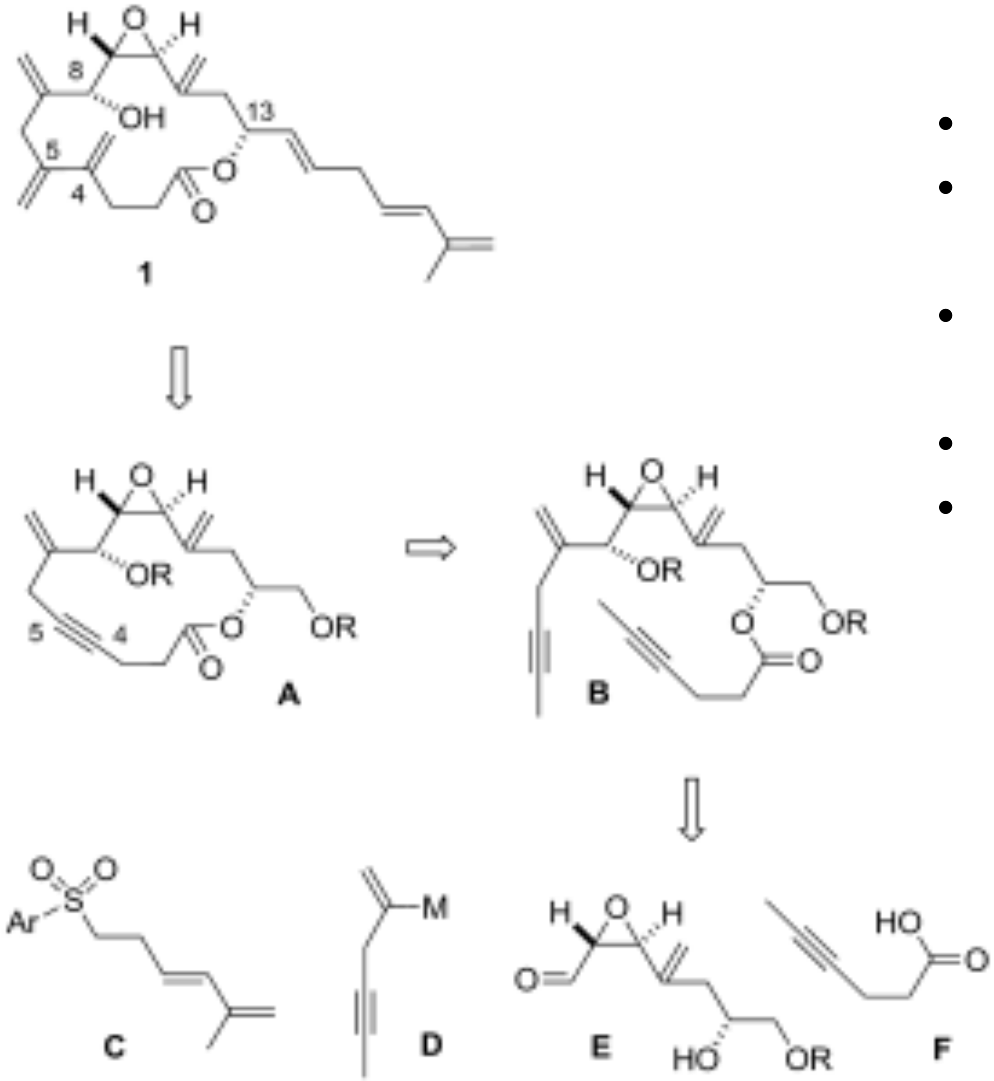
- ^{1}H-^{1}H coupling constants and NOESY data
- First total synthesis by Fürstner et al



(–)-Amphidinolide V

Volchkov, I.; Lee, D. *J. Am. Chem. Soc.* **2013**, *135*, 5324−5327
Kubota, T.; Tsuda, M.; Kobayashi, J. Tetrahedron Lett. **2000**, *41*, 713
Fürstner, A.; Larionov, O.; Flügge, S.Angew. Chem., Int. Ed. **2007**, *46*, 5545
Fürstner, A.; Flügge, S.; Larionov, O.; Takahashi, Y.; Kubota, T.; Kobayashi, J. J. Chem.-Eur. J. **2009**, *15*, 4011

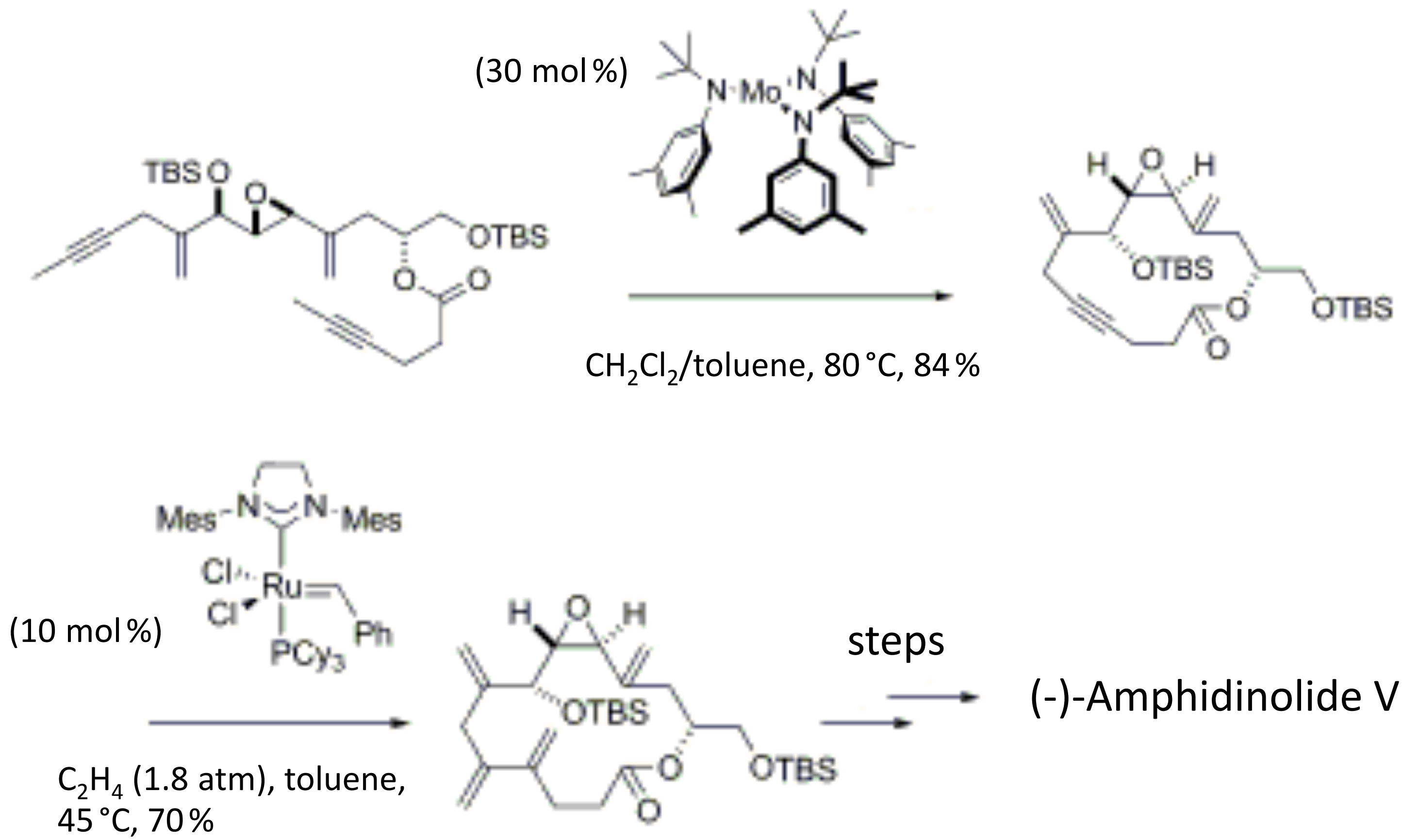
Fürstner retrosynthetic analysis of (-)-Amphidinolide V



- Ring-closing alkyne metathesis
- Enyne metathesis reaction with ethylene
- Stereoselective alkylation of epoxyaldehyde
- Julia olefination
- Esterification

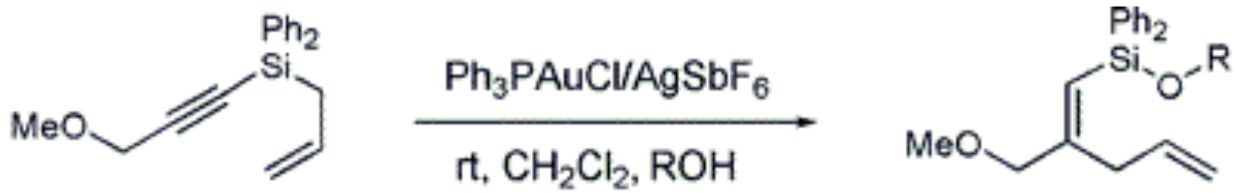
Fürstner, A.; Flügge, S.; Larionov, O.; Takahashi, Y.; Kubota, T.; Kobayashi, *J. Chem.–Eur. J.* **2009**, *15*, 4011

Key Steps in Fürstner's Synthesis

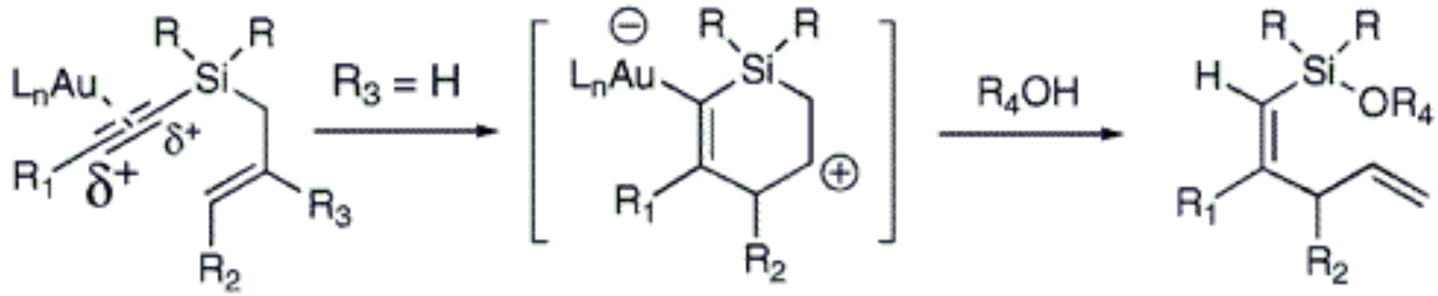


Fürstner, A.; Flügge, S.; Larionov, O.; Takahashi, Y.; Kubota, T.; Kobayashi, *J. Chem.−Eur. J.* **2009**, *15*, 4011

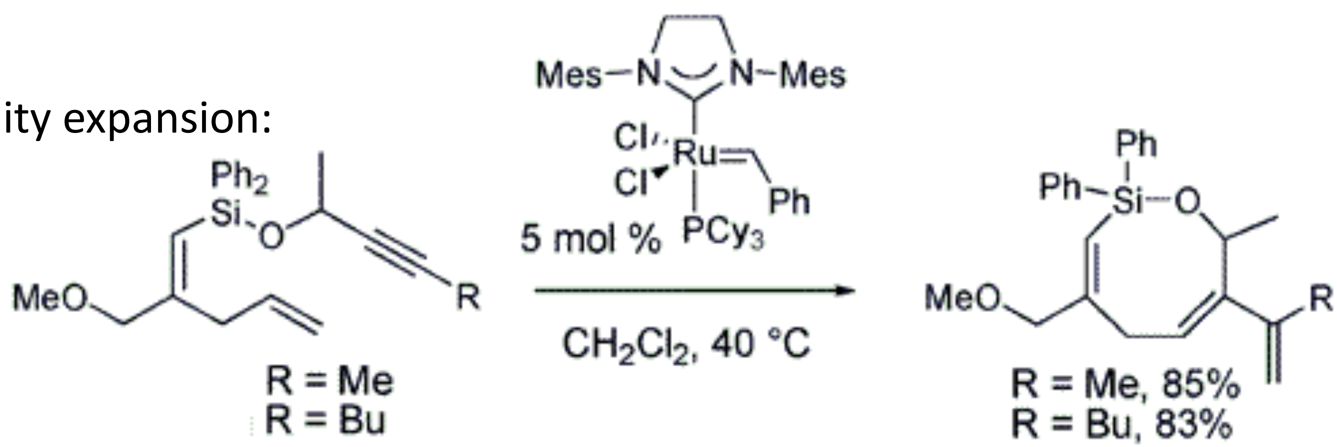
Intramolecular Allylation−Alcoholysis Catalyzed by Gold



Mechanism:

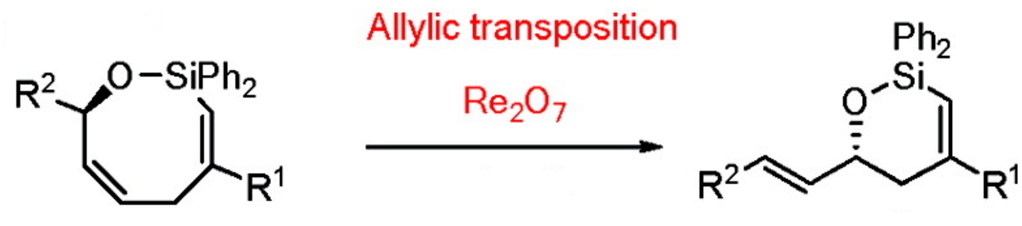


Utility expansion:

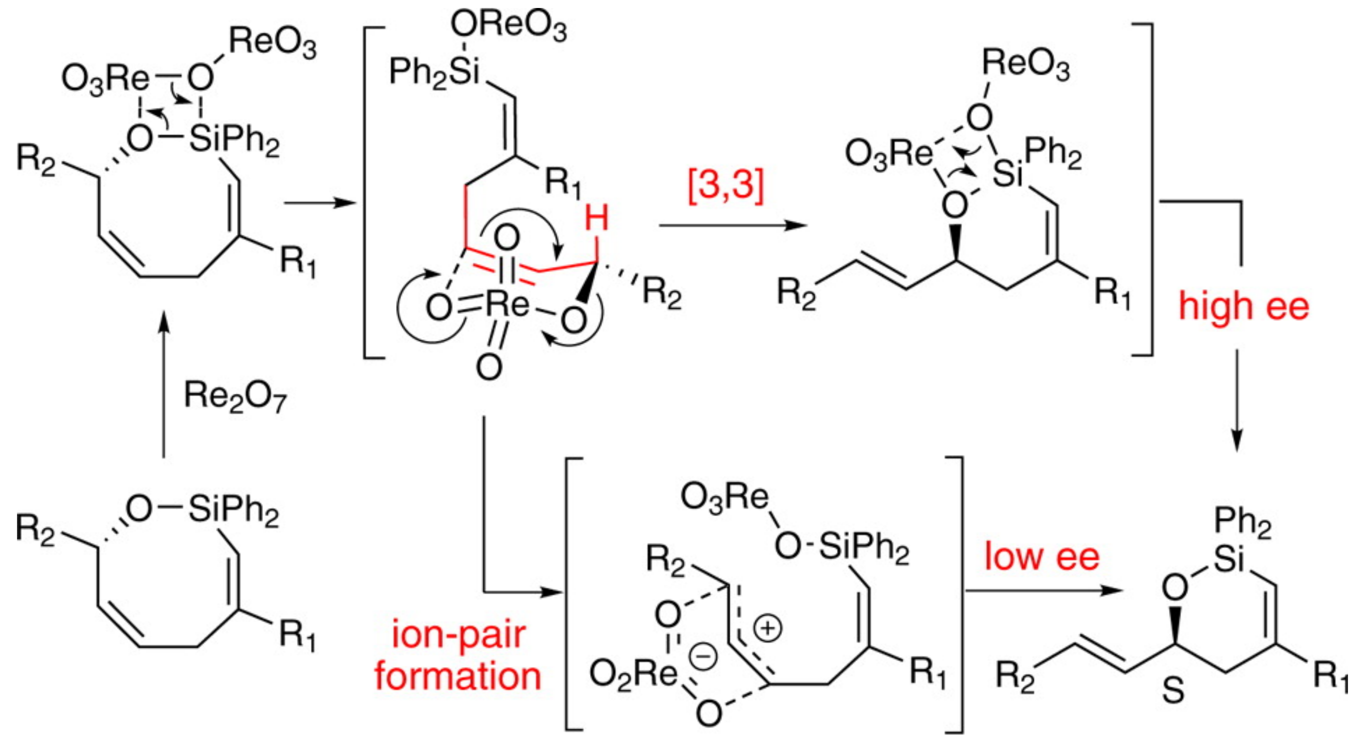


Park, S.; Lee, D. *J. Am. Chem. Soc*. **2006**, *128*, 10664–10665

Ring Contraction of Eight-Membered Siloxacycles

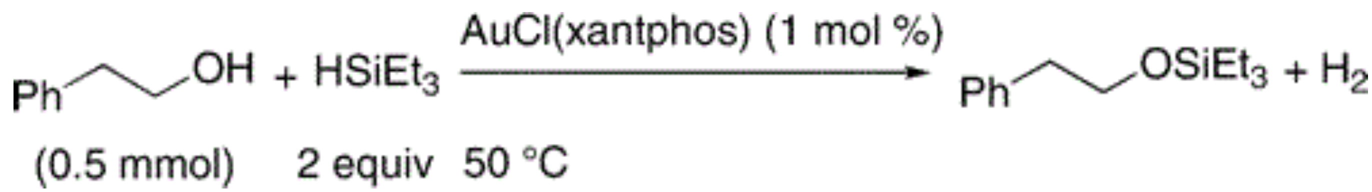


Mechanism:

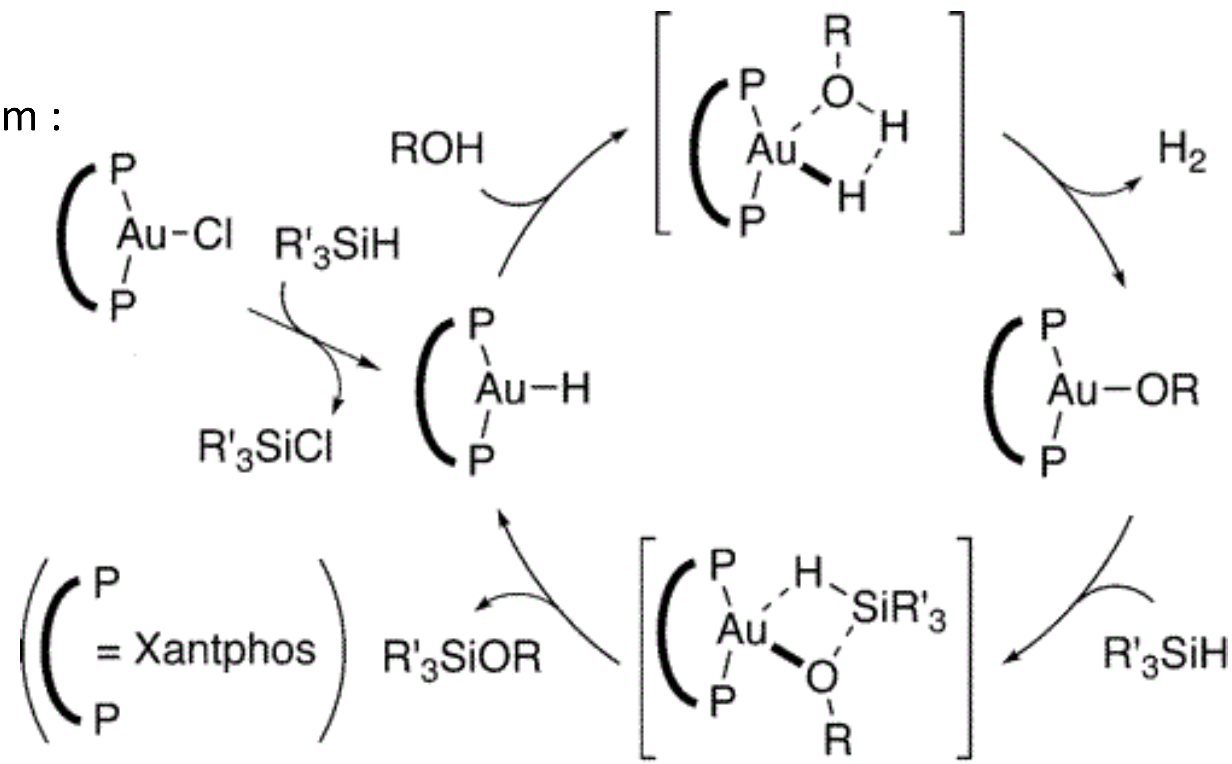


Volchkov, I.; Park, S.; Lee, D. *Org. Lett*. **2011,** *13*, 3530.

Au(I)-Xantphos-Catalyzed Dehydrogenative Silylation

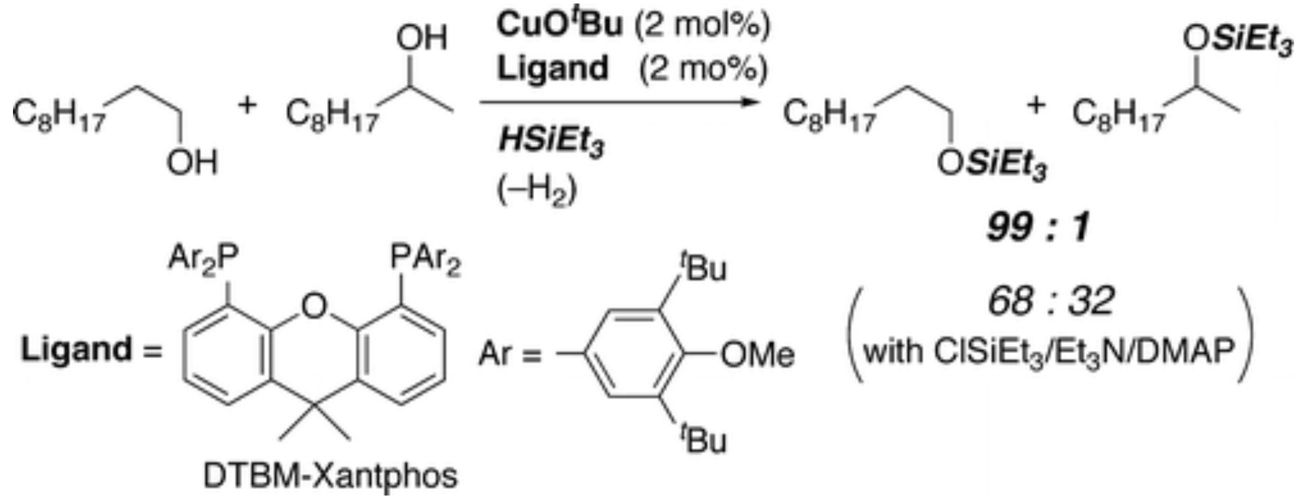


Mechanism :

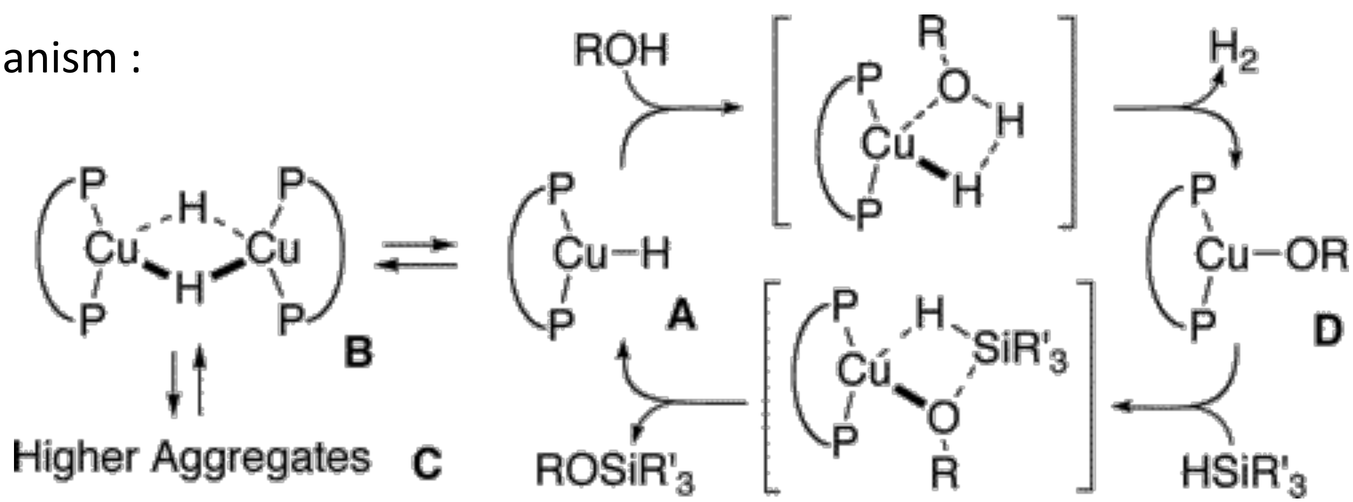


Ito, H.; Takagi, K.; Miyahara, T.; Sawamura, M. *Org. Lett.* 2005, 7, 3001

Versatile Dehydrogenative Alcohol Silylation Catalyzed by Cu(I)–Phosphine Complex



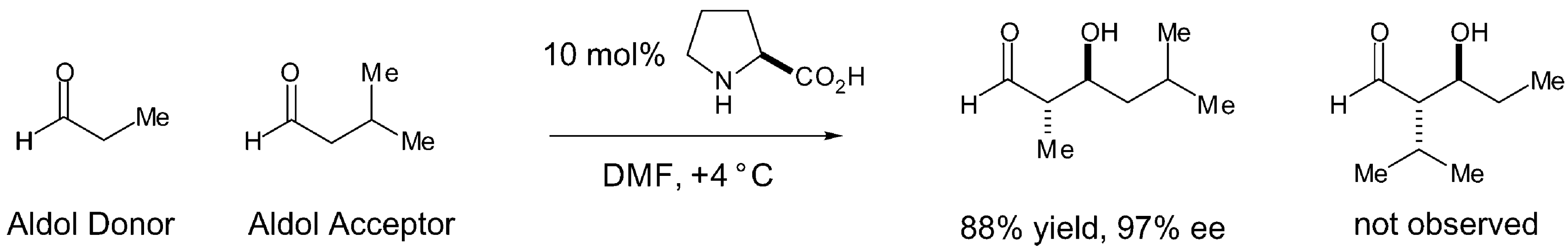
Mechanism :



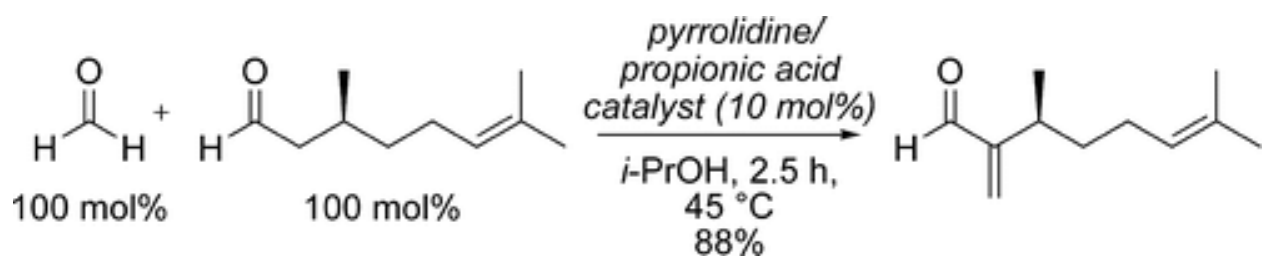
Ito, H.; Watanabe, A.; Sawamura, M. *Org. Lett.* 2005, 7, 1869

Cross-Aldol condesation of Nonequivalent Aldehydes

- The direct organocatalytic cross-aldol reaction of two nonequivalent aldehydes:



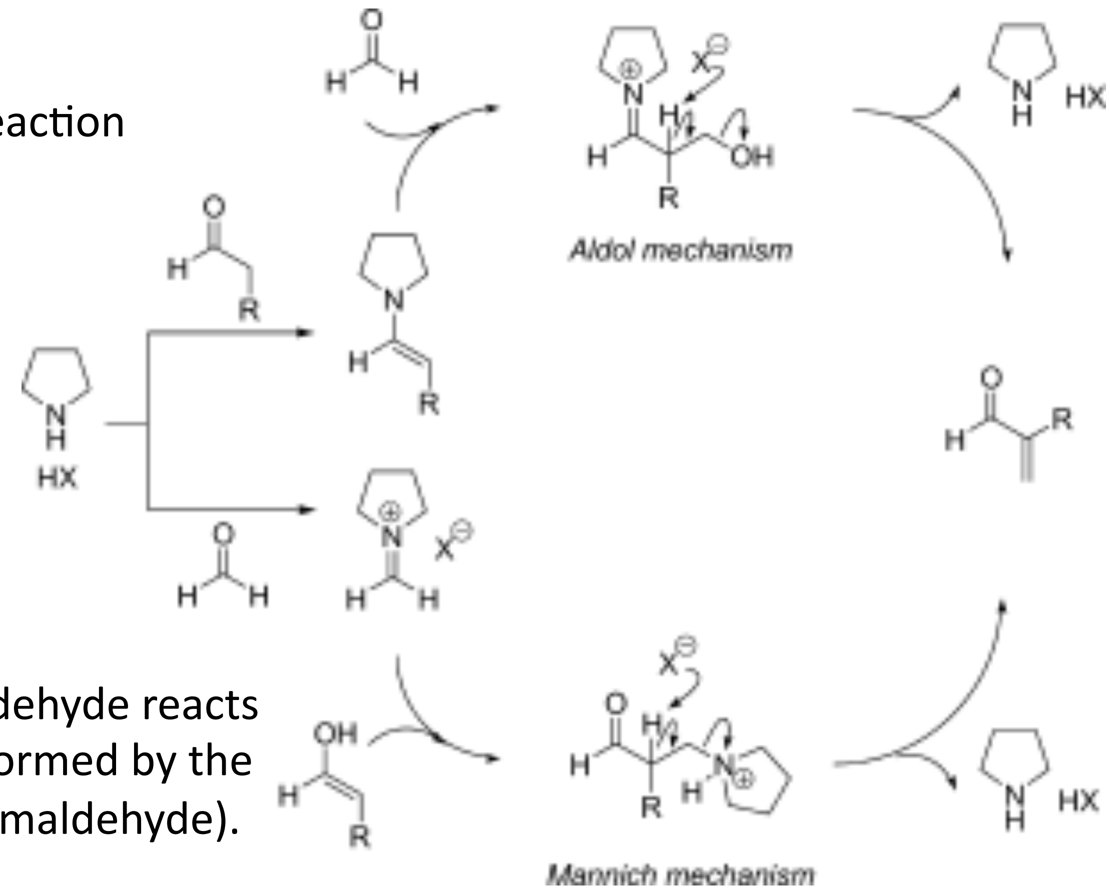
- The direct cross-condensation to form the corresponding α,β-unsaturated aldehyde:



Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798
Erkkilä, A.; Pihko, P. M. *J. Org. Chem*. **2006**, *71,* 2538

Possible mechanisms for the α-methylenation reaction

- Text book mechanisms:



- An enamine-catalyzed aldol reaction followed by an acid- or base-catalyzed elimination of the β-hydroxy group.

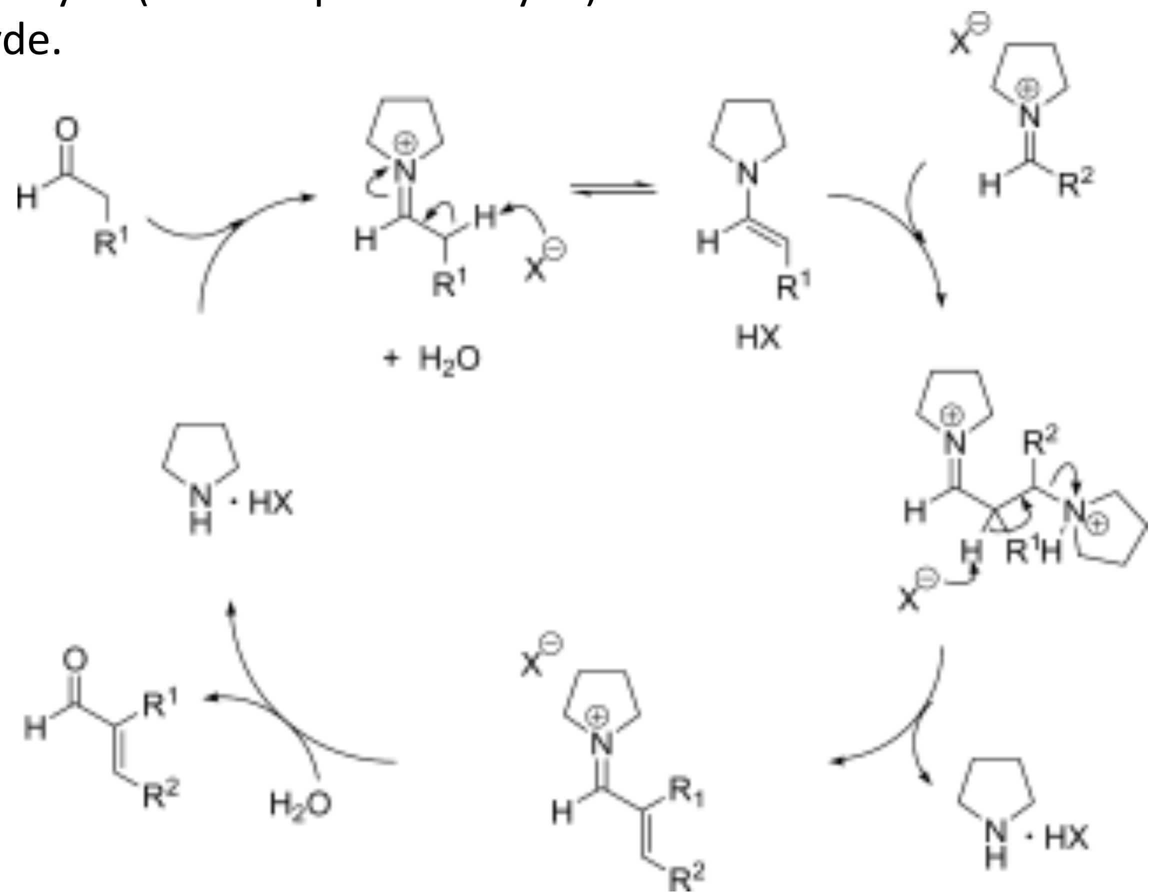
- The enol form of the donor aldehyde reacts with the iminium compound formed by the acceptor aldehyde (usually formaldehyde).

Erkkilä, A.; Pihko, P. M. *Eur. J. Org. Chem*. **2007,** 4205.

Double activation of the reaction components

Knoevenagel–Mannich-type mechanism :

- Iminium species of formaldehyde (the acceptor aldehyde) reacts with the enamine species of the donor aldehyde.
- Second-order dependence of the reaction rate on catalyst concentration

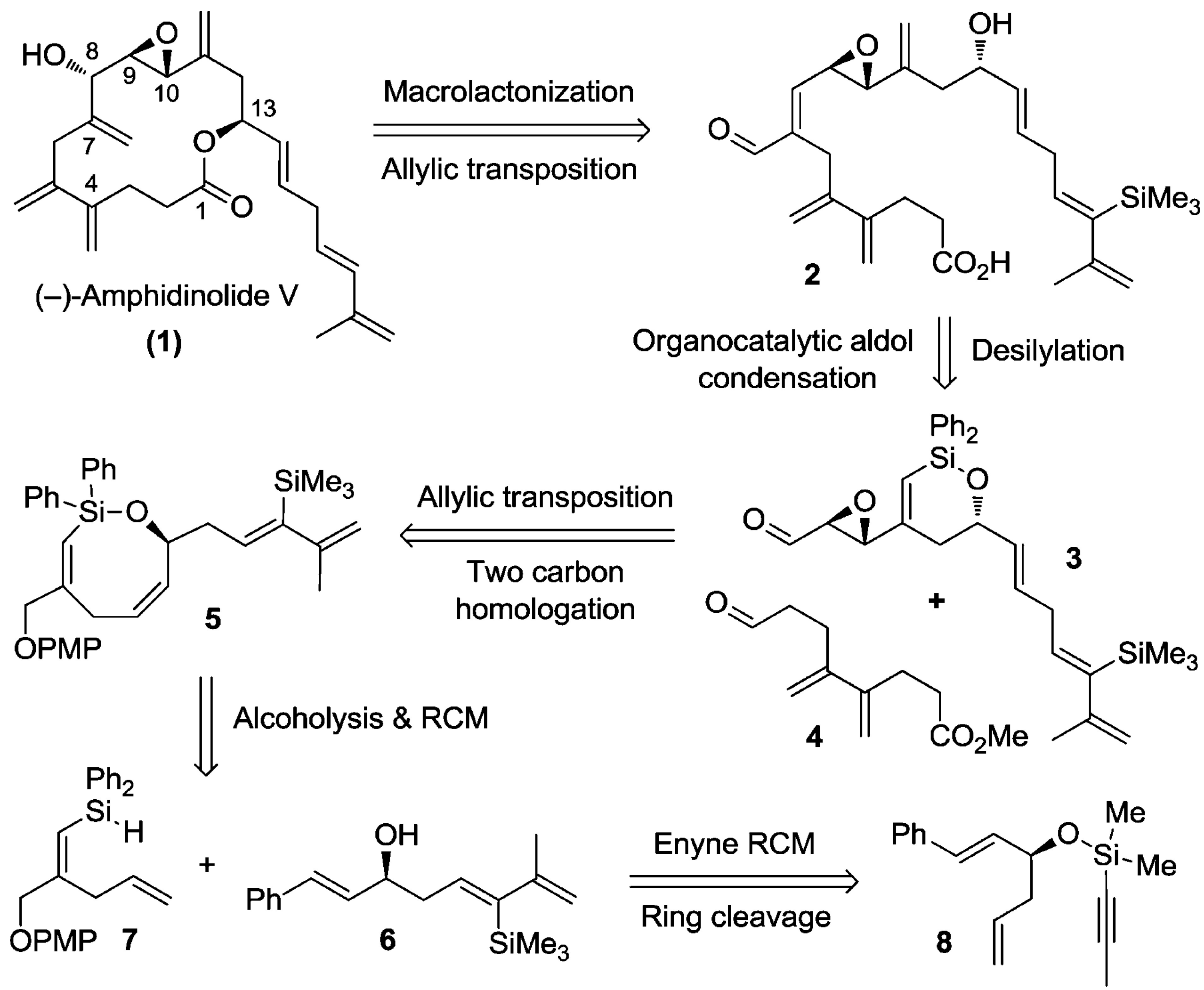


Erkkilä, A.; Pihko, P. M. *Eur. J. Org. Chem*. **2007,** 4205.

Retrosynthetic Analysis

Alkene moities:
enyne metathesis

- Transition metal-catalyzed reactions
- Proline-mediated cross-condensation



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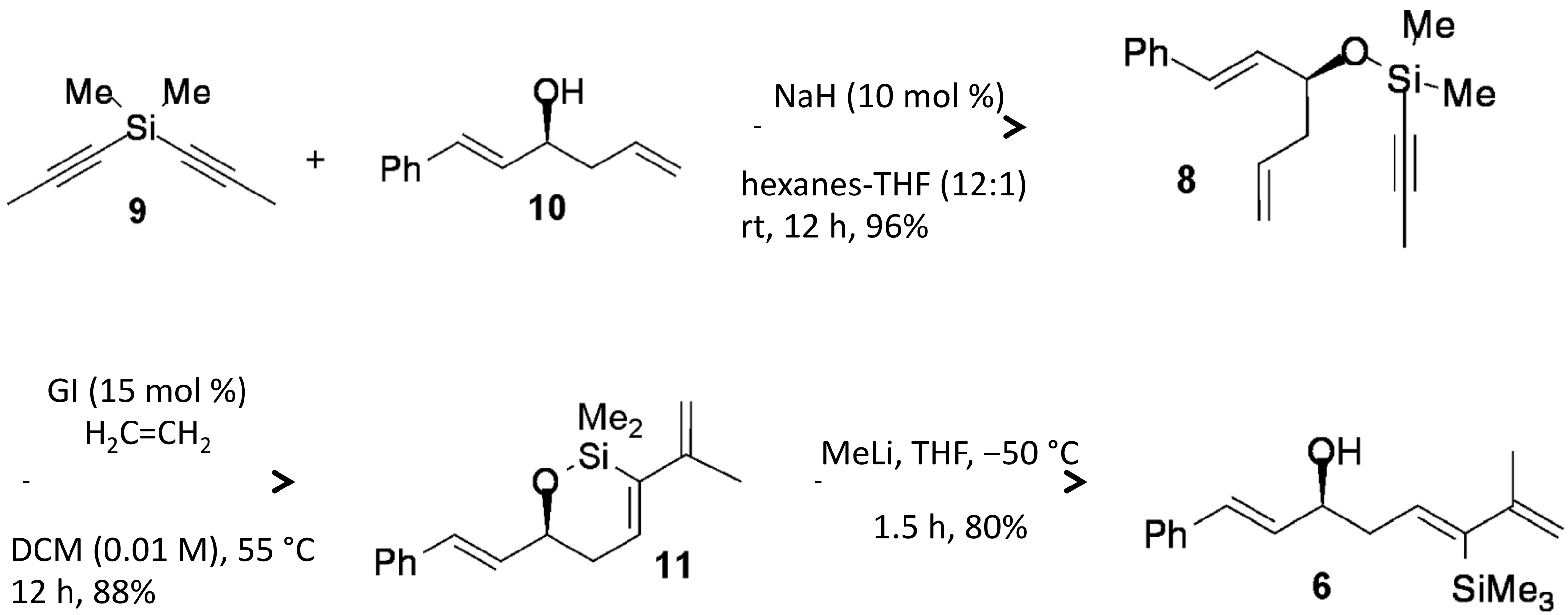
Substrate for Allylic Transposition Precursor



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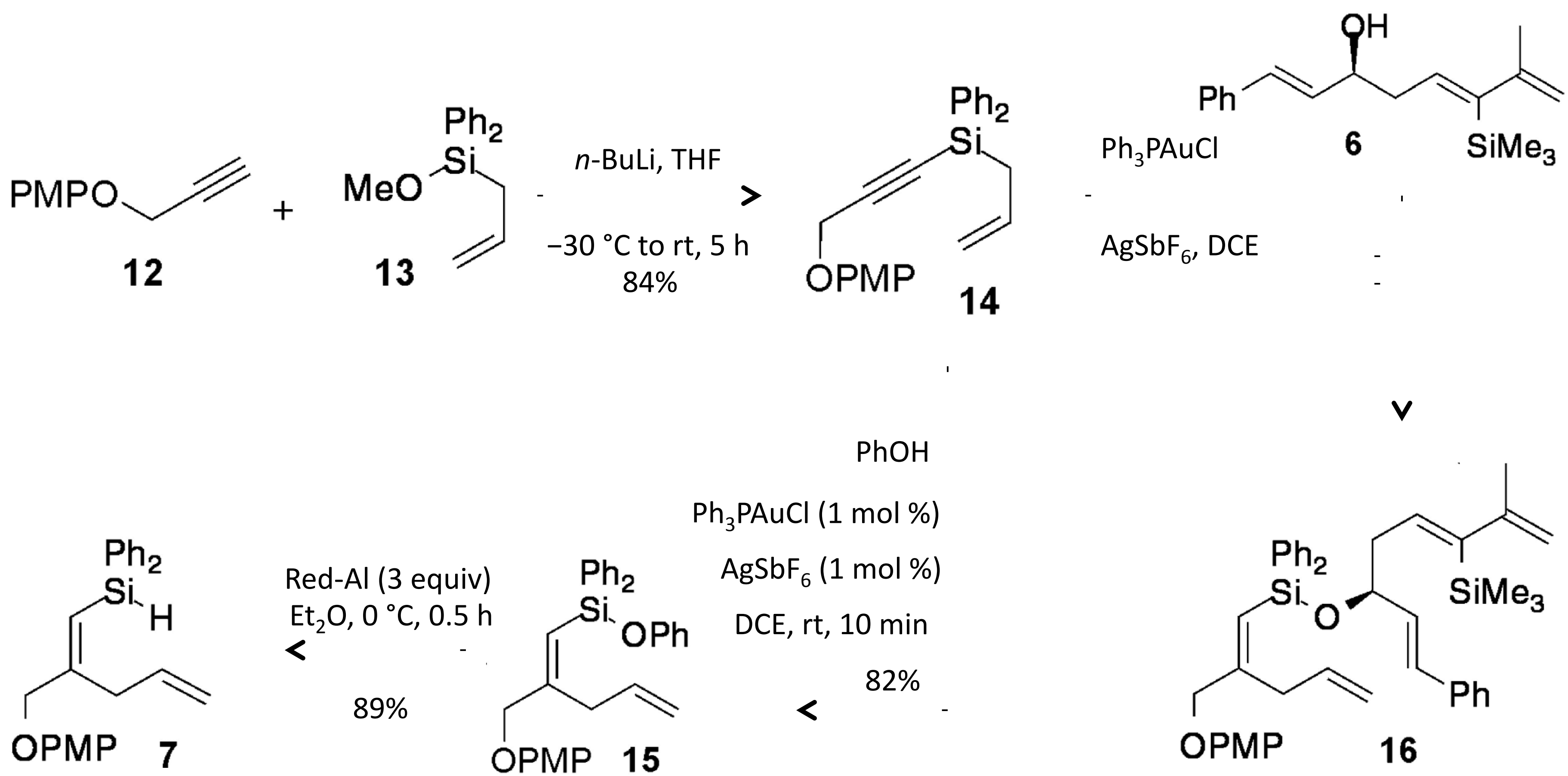

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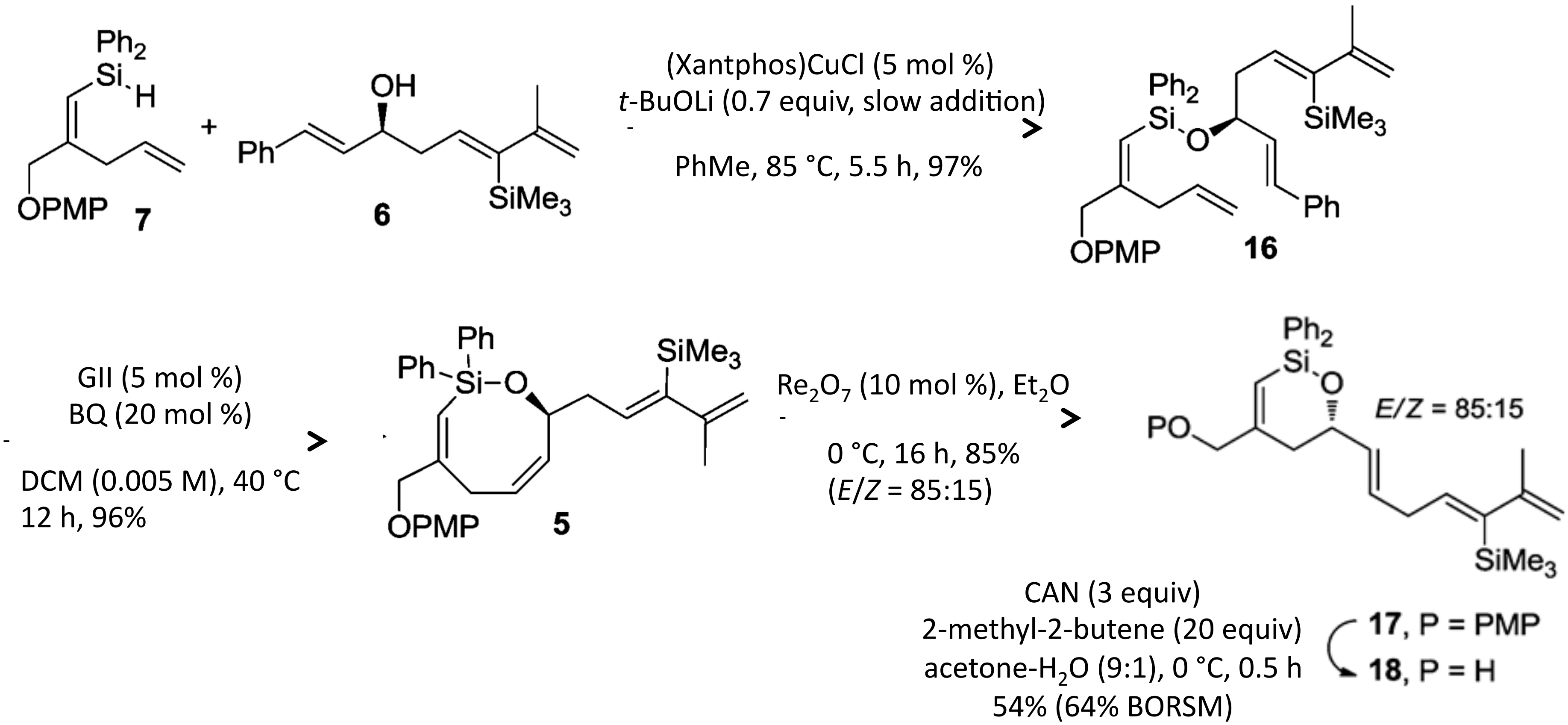
Preparation of Acceptor Aldehyde



Volchkov, I.; Lee, D. *J. Am. Chem. Soc.* **2013**, *135*, 5324–5327
Ito, H.; Takagi, K.; Miyahara, T.; Sawamura, M. *Org. Lett.* 2005, 7, 3001
Ito, H.; Watanabe, A.; Sawamura, M. *Org. Lett.* 2005, 7, 1869

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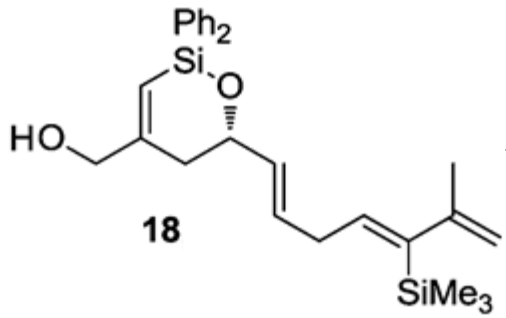
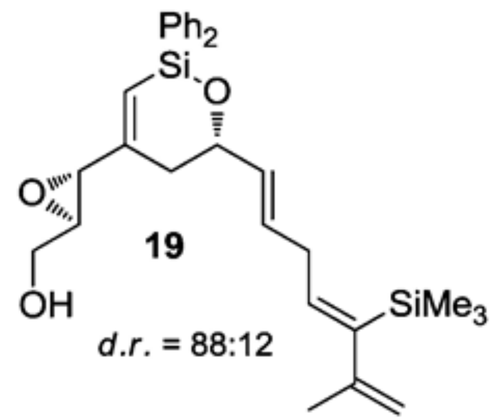


18

1. IBX, DMSO, rt, 1 h;
2. $(EtO)_2P(O)CH_2CO_2Et$, NaHMDS, THF, −78 °C to 0 °C, 3 h, 79% (2 steps)
3. DIBAL-H, THF, −50 °C, 1.5 h, 91%
4. Ti(*i*-PrO)$_4$ (10 mol %), (−)-d-DIPT (15 mol %) *t*-BuOOH, MS (4 Å), DCM, −20 °C, 12 h, dr = 88:12



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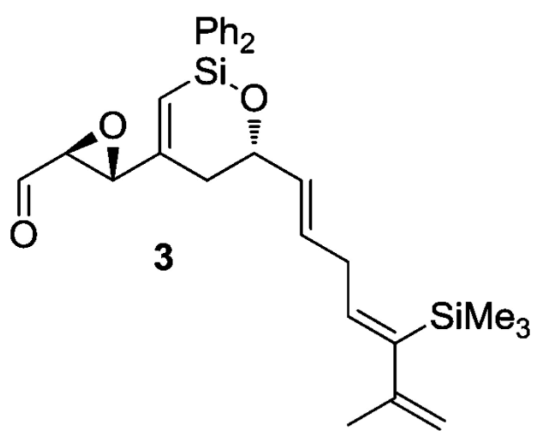
d.r. = 88:12

SO_3·Py, DMSO, Et_3N, DCM

10 °C, 3 h, 94% (2 steps)



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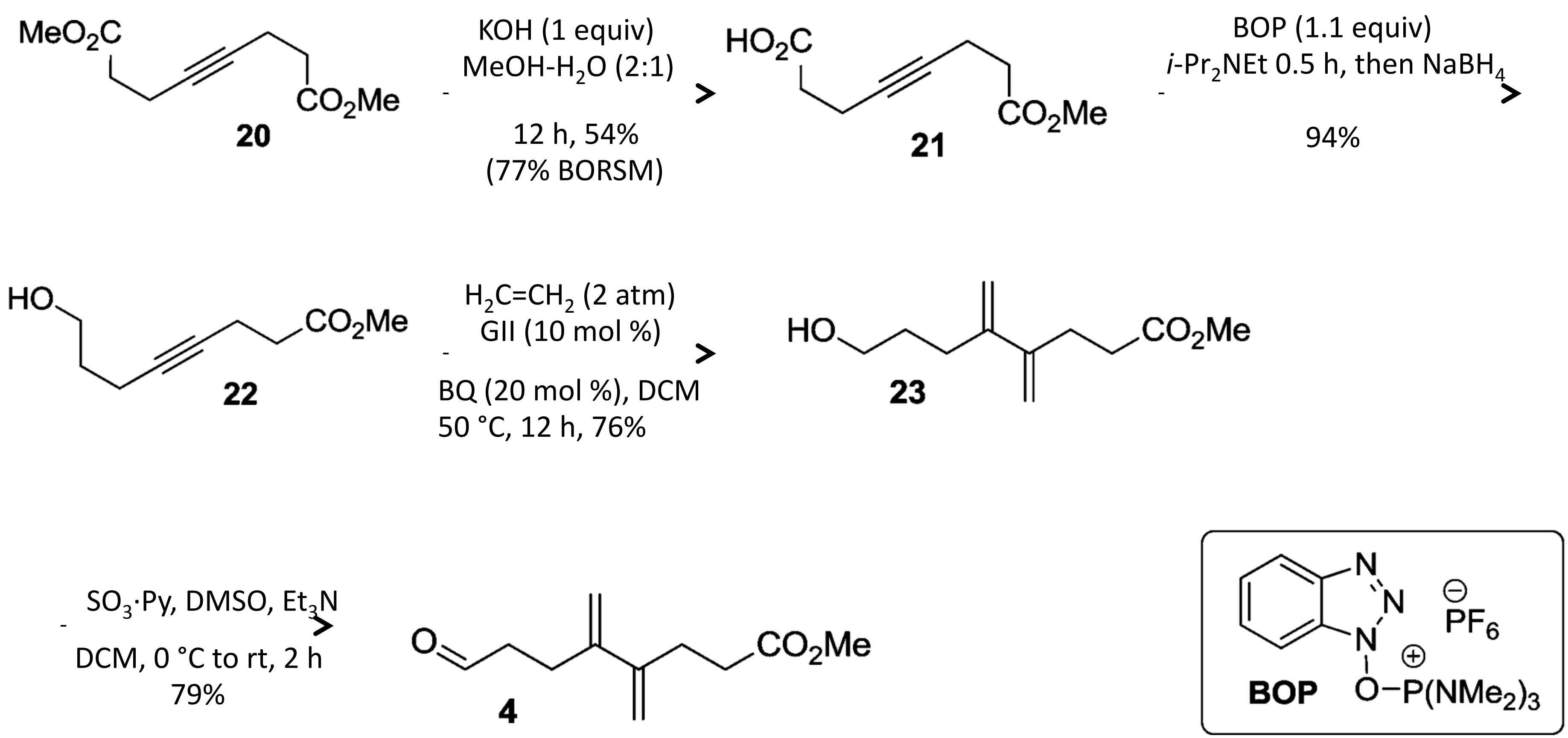
Preparation of Donor Aldehyde



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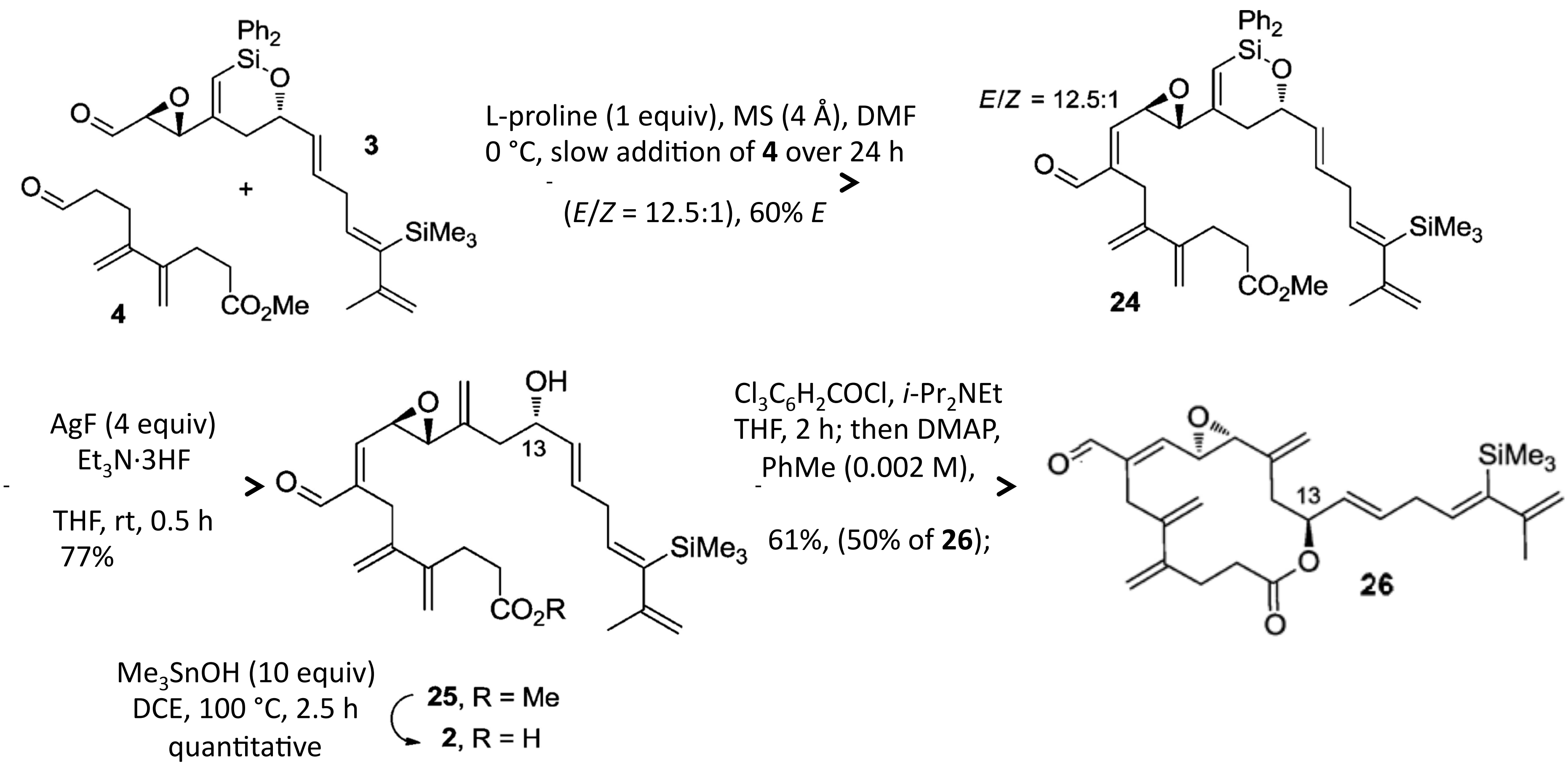
Cross-Aldol Condensation and Completion of the Synthesis



Volchkov, I.; Lee, D. *J. Am. Chem. Soc.* **2013**, *135*, 5324−5327

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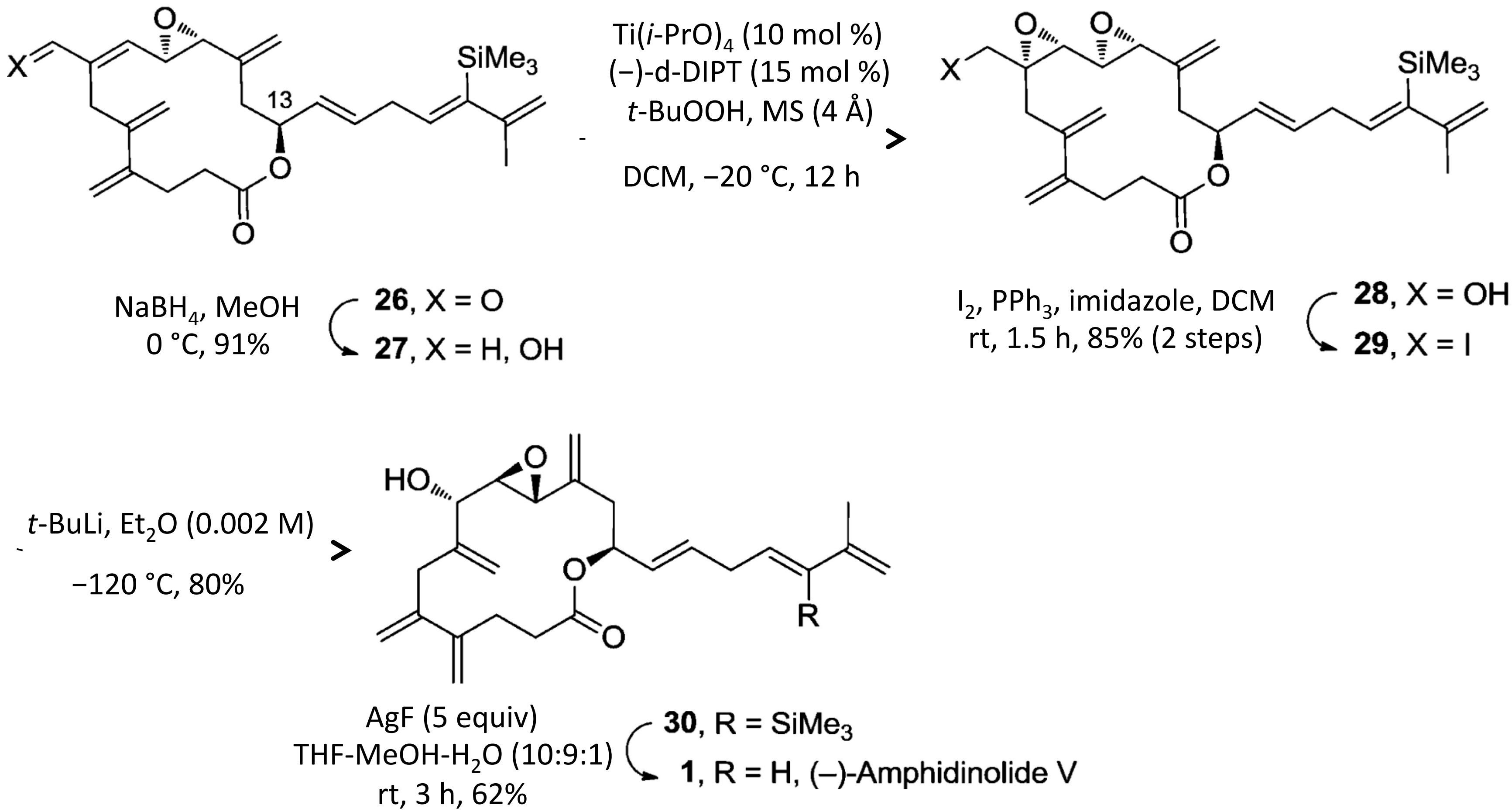

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Conclusion

- 22 steps (LLS) to (-)-amphidinolide with 3.3% overall yield
- Silicon-tethered ring-closing enyne and diene metathesis as well as the allylic transposition of silyl ethers for construction of 1,3- and 1.5-diene motifs
- Silicon tether as efficient protecting group
- Direct proline-mediated cross-aldol condensation of nonequivalent aldehydes

Volchkov, I.; Lee, D. *J. Am. Chem. Soc.* **2013**, *135*, 5324–5327