

Total Syntheses of Grayanane Diterpenoids

**2022.11.12. Literature Seminar
B4 Masahiro Toyoda**

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1. Introduction

**2. Total synthesis of Principinol D
(by Newhouse Group)**

**3. Total synthesis of Mollanol A
(by Yang Group)**

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2. Total synthesis of Principinol D (by Newhouse Group)

3. Total synthesis of Mollanol A (by Yang Group)

Introduction of Prof. Newhouse and Yang



Prof. Timothy R. Newhouse

2005 B.A., @ Colby College (Prof. D. M. Thamattoor)
2010 Ph.D., @ The Scripps Research Institute (Prof. P. S. Baran)
2013 Postdoctoral fellow @ Harvard University (Prof. E.J. Corey)
2018- Professor @ Yale University

Research topic: Total synthesis of complex natural products with potential applications to neuroscience

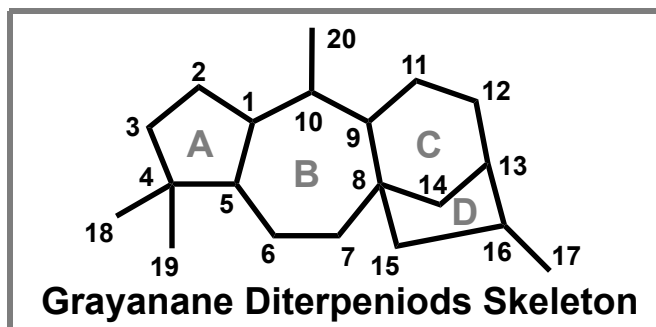


Prof. Ming Yang

2008 B.S., @ Hubei University
2013 Ph.D., @ Lanzhou University (Prof. Y.-Q. Tu)
2015 Postdoctoral fellow @ Shanghai Institute of Organic Chemistry (Prof. A. Li)
2018 Postdoctoral fellow @ The University of Chicago (Prof. S. A. Snyder)
2019- Professor @ Lanzhou University

Research topic: Total synthesis of complex natural products

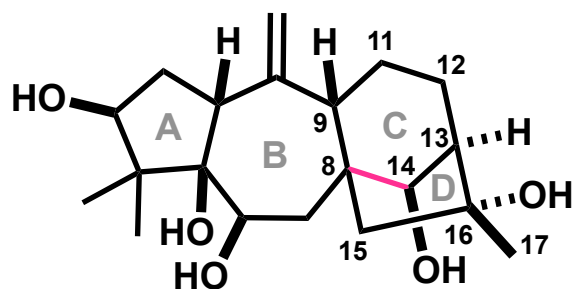
Grayanane Diterpenoids



Structural features:

- highly oxidized tetracyclic framework
- bicyclo[3.2.1] octane ring system

Principinol D



Isolation:

Rhododendron principis (2014)

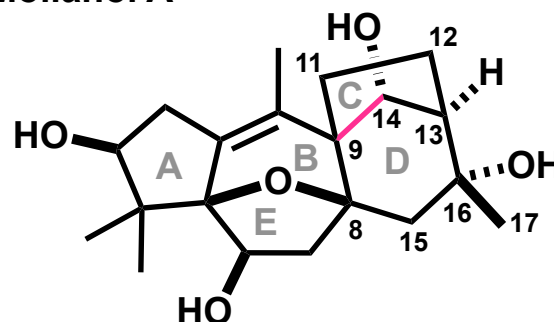
Biological activities:

inhibition on protein tyrosine phosphatase 1B (PTP1B) in vitro

Total syntheses:

Newhouse (2019, (+)-Principinol D, 19 steps)

Mollanol A



Isolation:

Rhododendron molle (2014)

Biological activities:

transcriptional activation effects on the *Xbp1* upstream promoters

Total syntheses:

Yang (2022, (+)-Mollanol A, 15 steps)

1) Liu, C.-C.; Lei, C.; Zhong, Y.; Gao, L.-X.; Li, J.-Y.; Yu, M.-H. *Tetrahedron*. **2014**, *70*, 4317.

2) Aneta, T.; Yifeng, C.; Anthony, C. S.; Timothy, R. N. *J. Am. Chem. Soc.* **2019**, *141*, 8088.

3) Yuran, W.; Rong, Z.; Ming, Y. *J. Am. Chem. Soc.* **2022**, *144*, 15033.

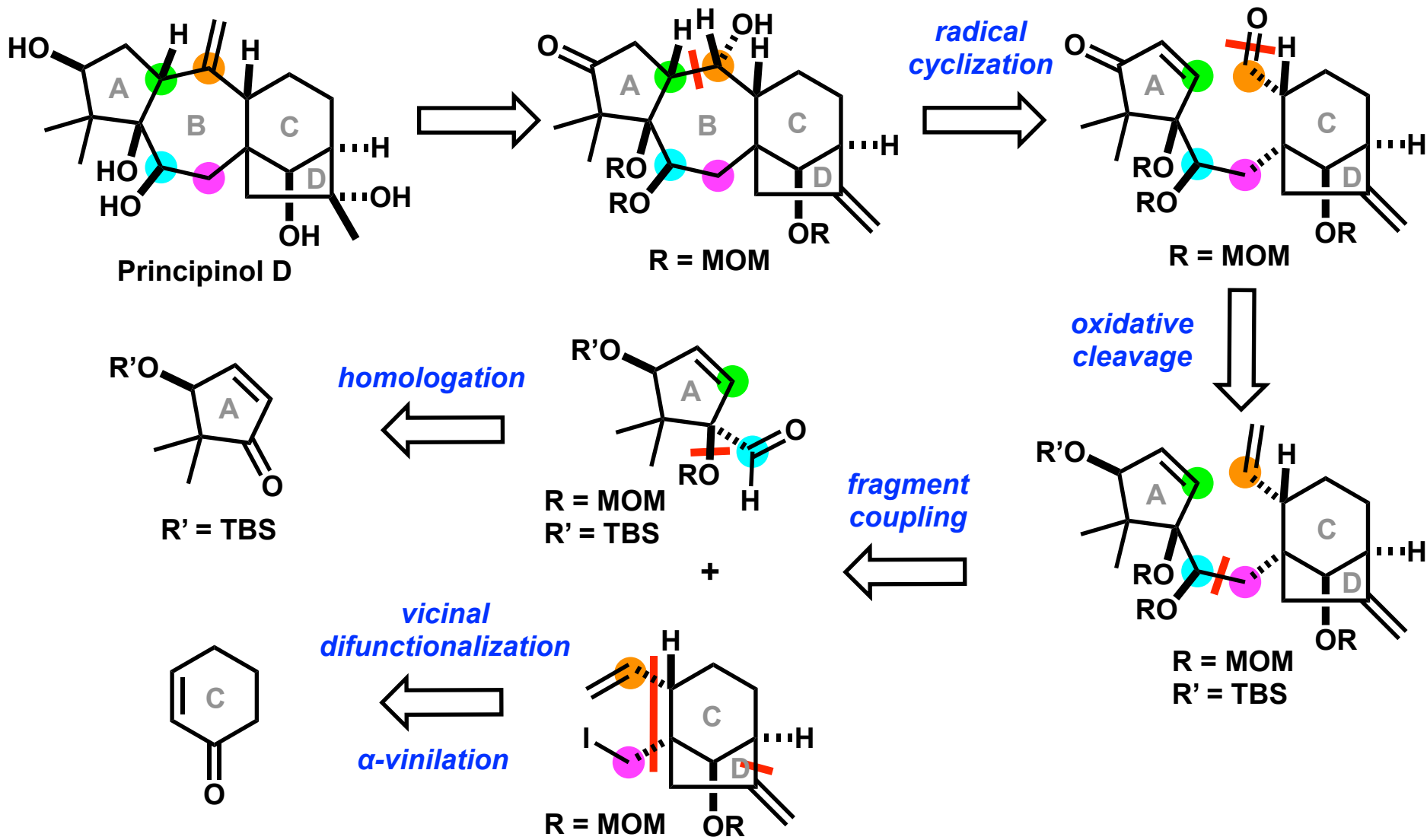
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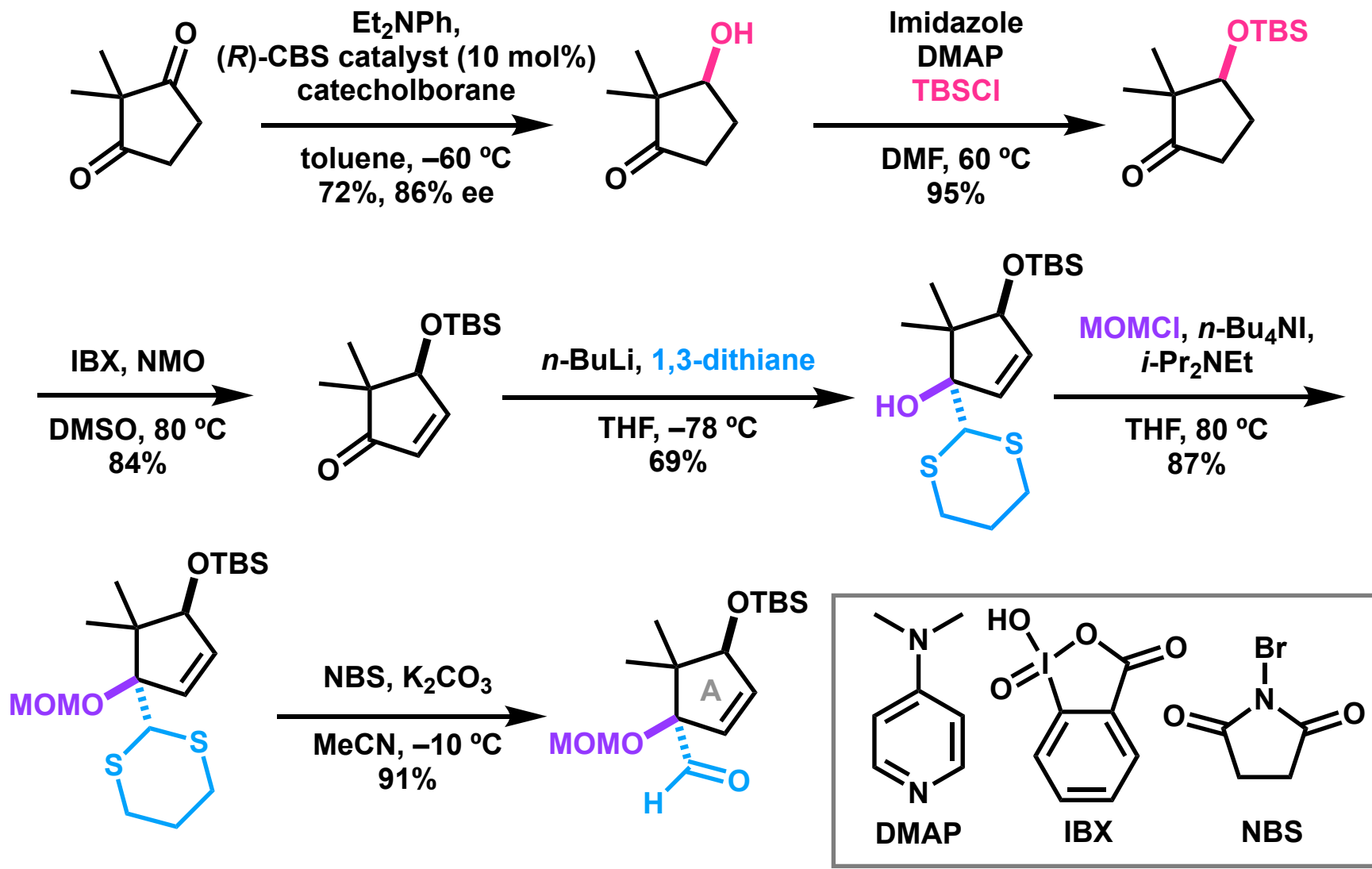
**2. Total synthesis of Principinol D
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**3. Total synthesis of Mollanol A
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Retrosynthetic Analysis (by Newhouse)

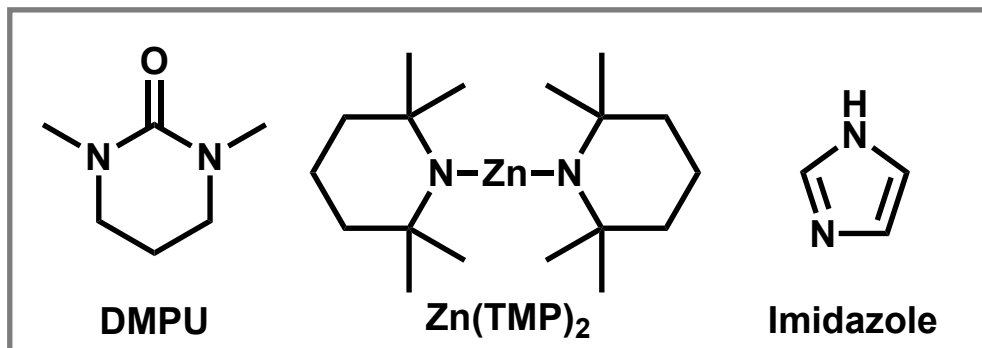
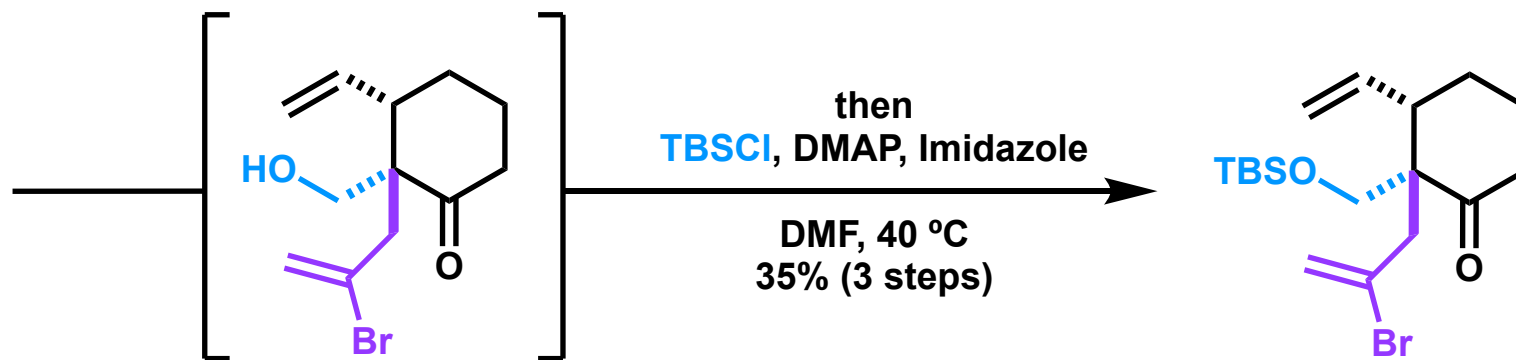
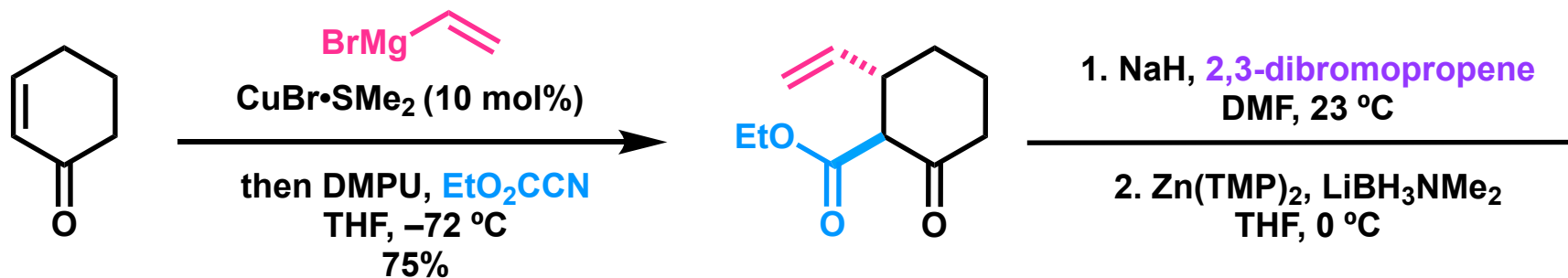


Construction of A-ring

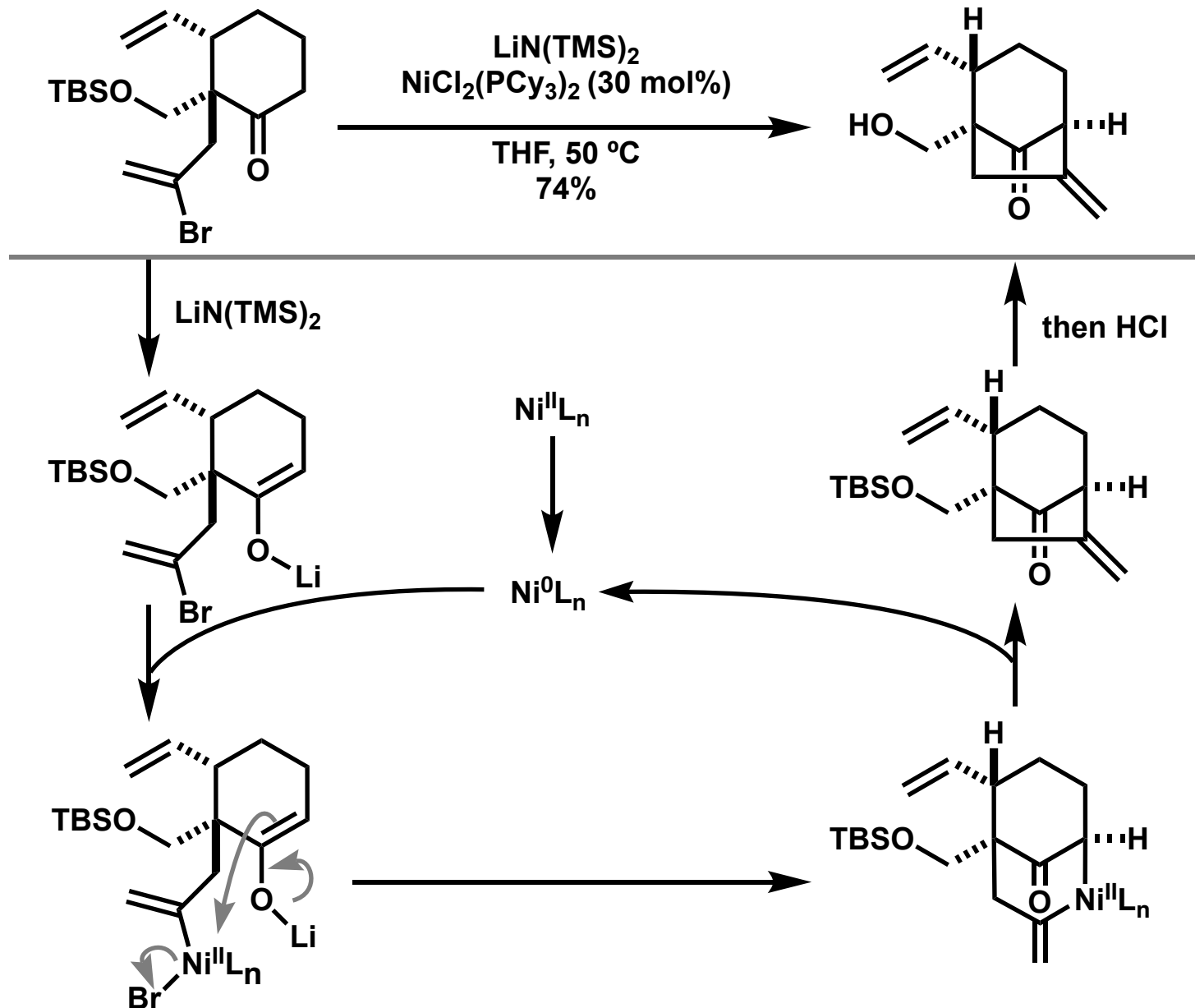


1) Aneta, T.; Yifeng, C.; Anthony, C. S.; Timothy, R. N. *J. Am. Chem. Soc.* **2019**, *141*, 8088.

Chemoselective Reduction of Ketoester

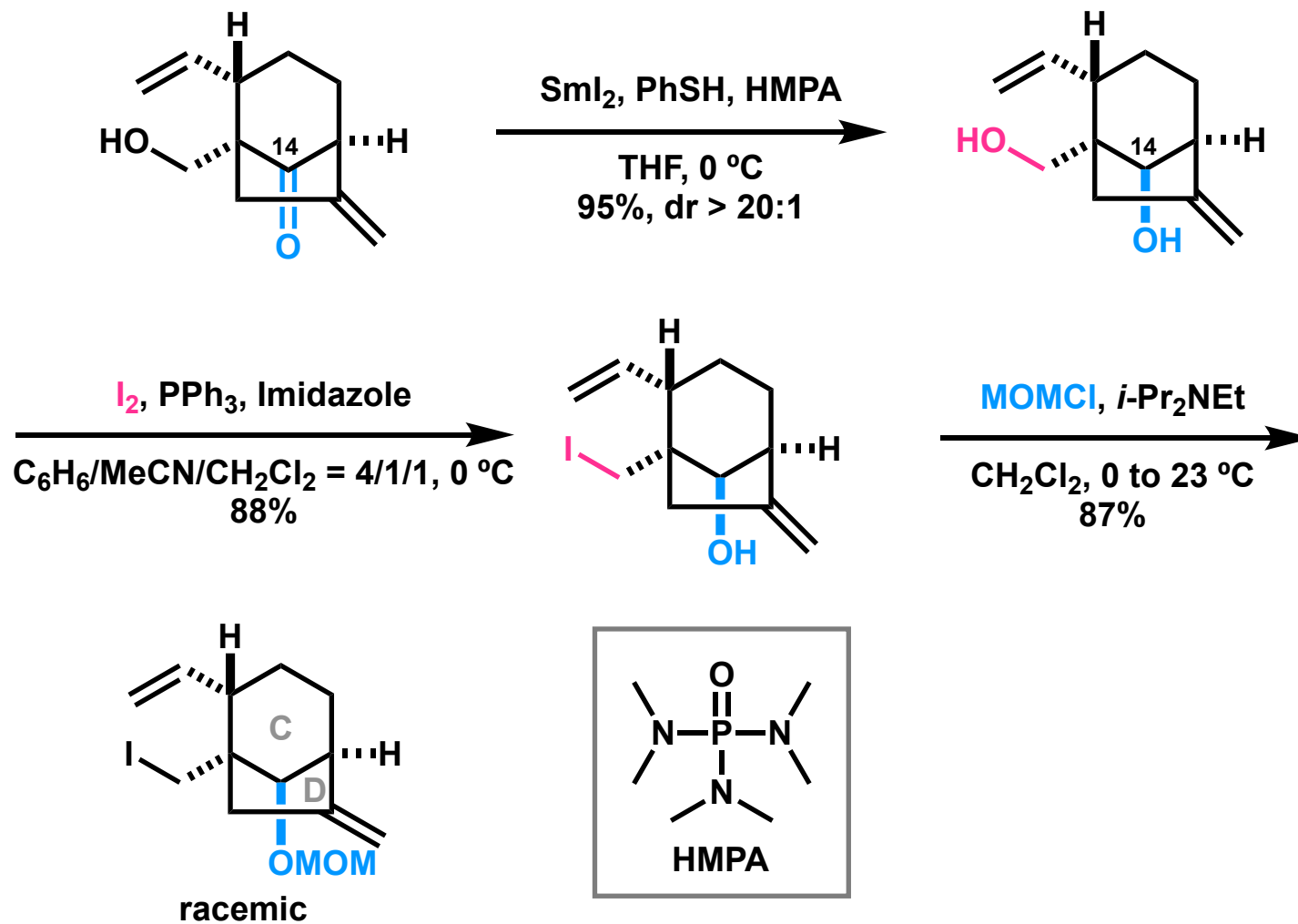


Ni-catalyzed α -vinylation Reaction

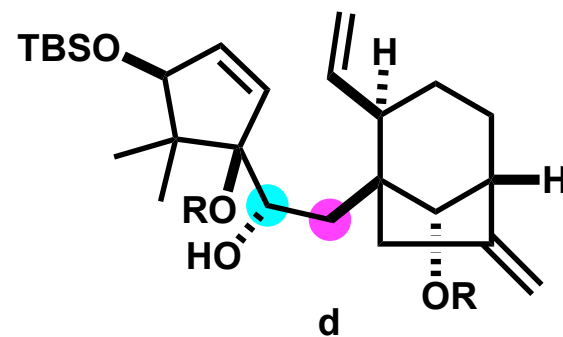
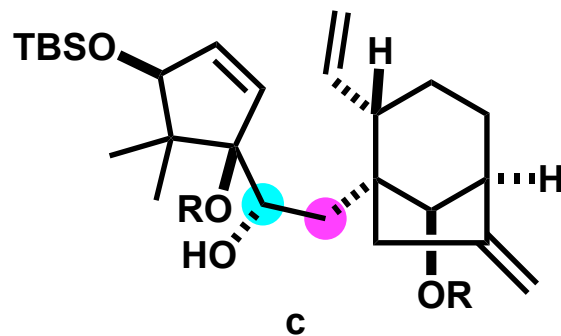
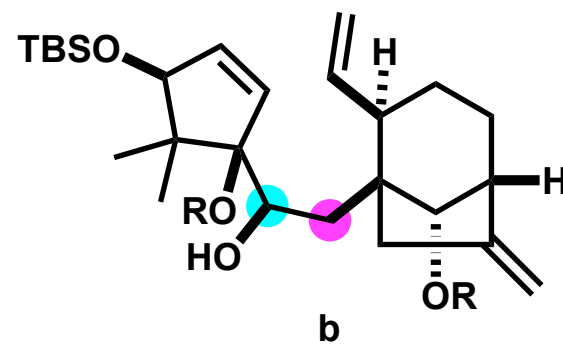
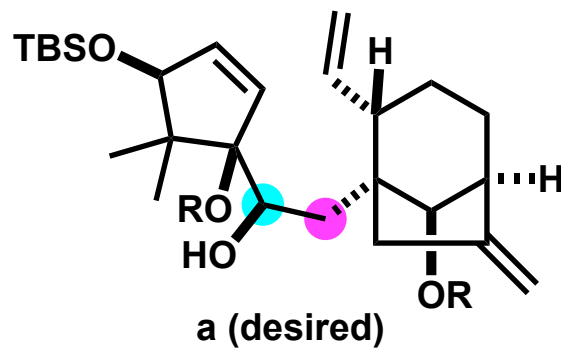
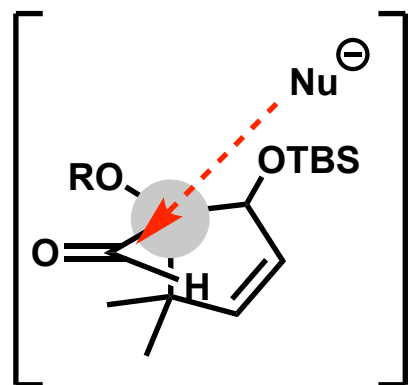
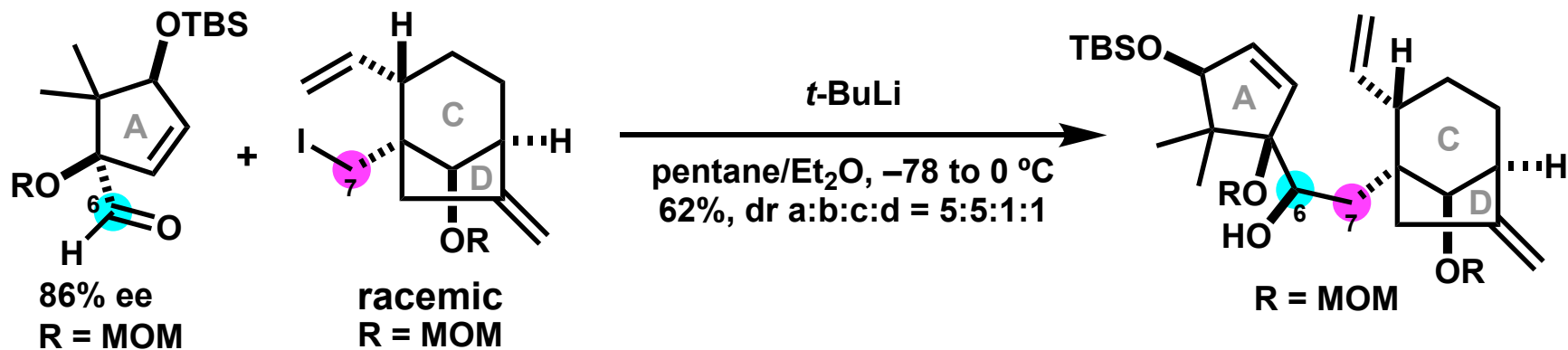


- 1) Aneta, T.; Yifeng, C.; Anthony, C. S.; Timothy, R. N. *J. Am. Chem. Soc.* **2019**, *141*, 8088.
- 2) Ankner, T.; Cosner, C. C.; Helquist, P. *Chem. Eur. J.* **2013**, *19*, 1858.

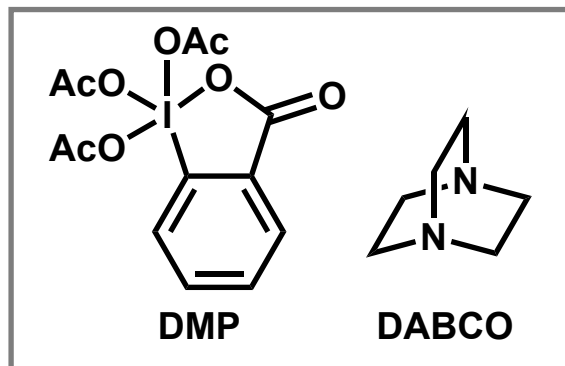
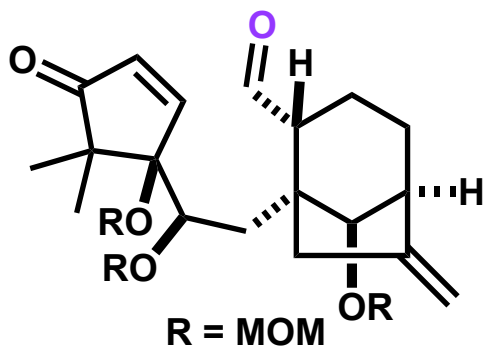
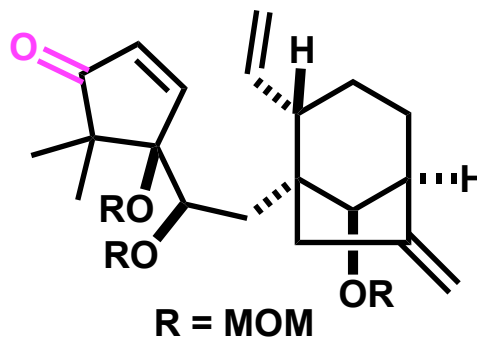
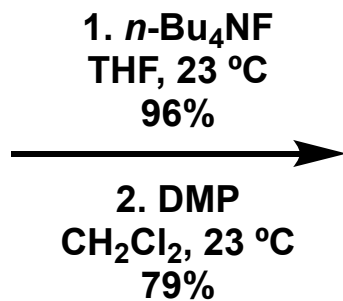
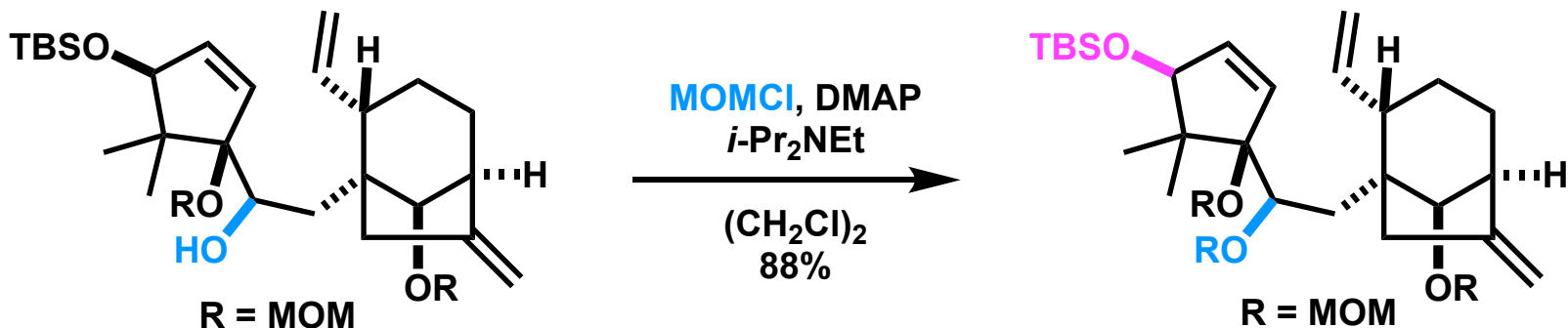
Construction of C/D-ring



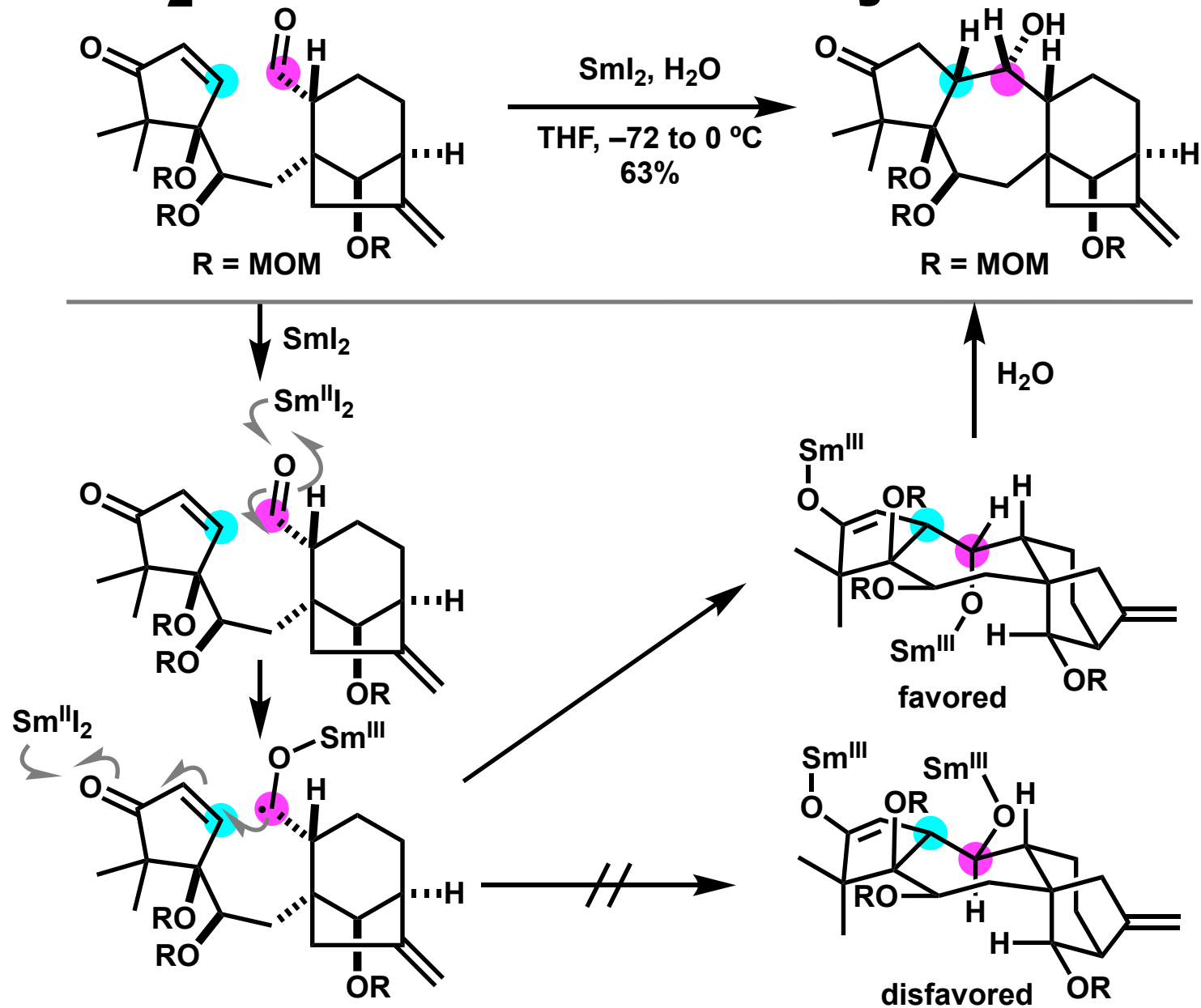
Fragment Coupling between A and C/D-ring



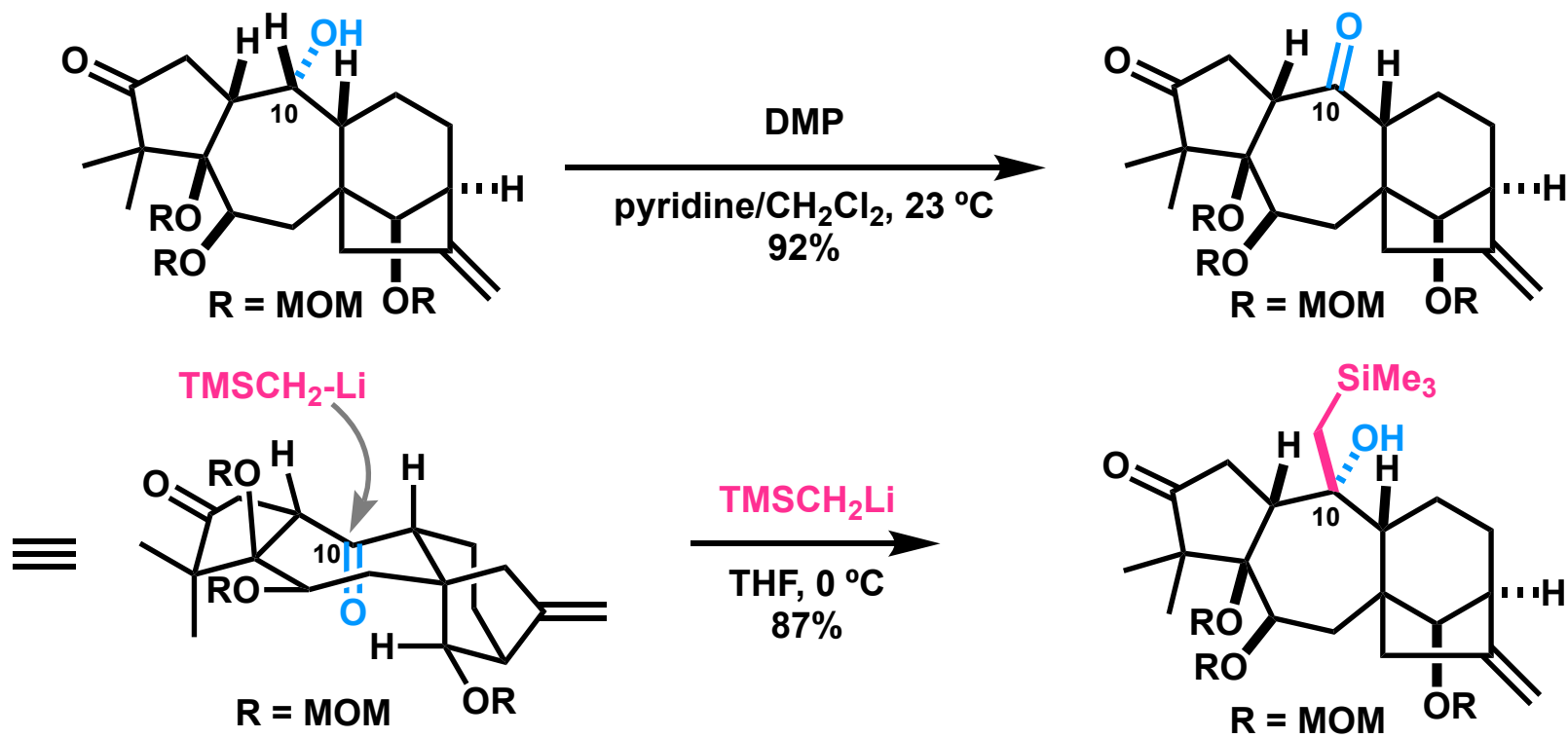
Preparation for Seven-membered Ring



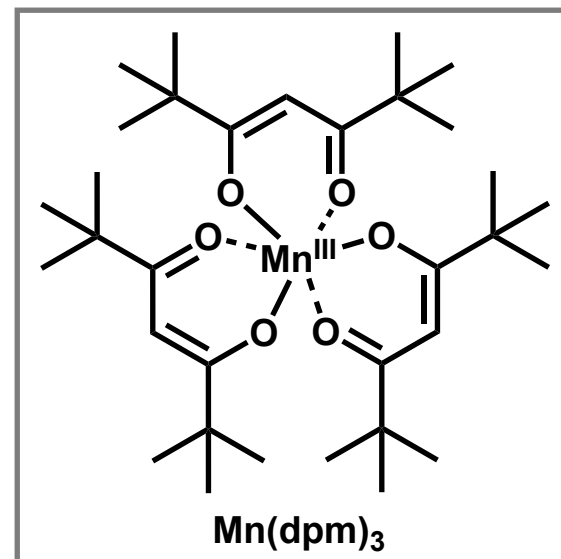
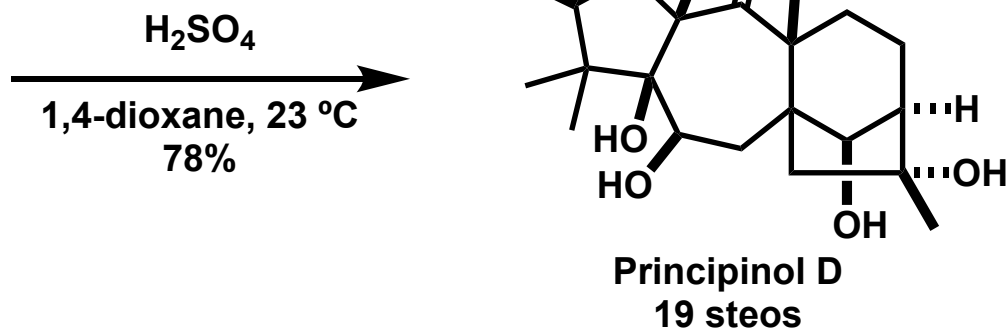
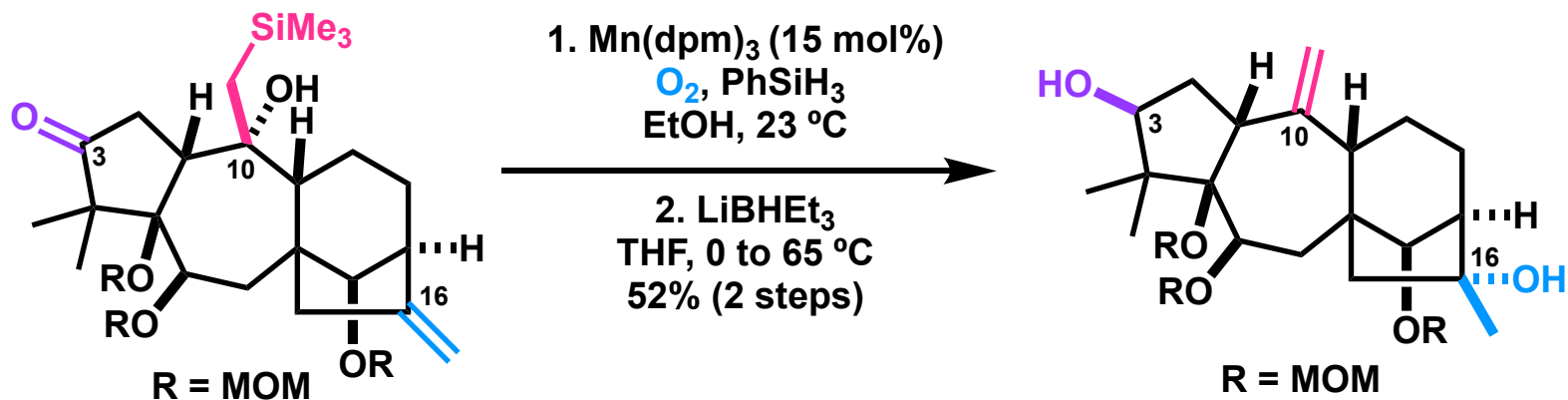
Sml₂-mediated Radical Cyclization



Total Synthesis of Principinol D



Total Synthesis of Principinol D



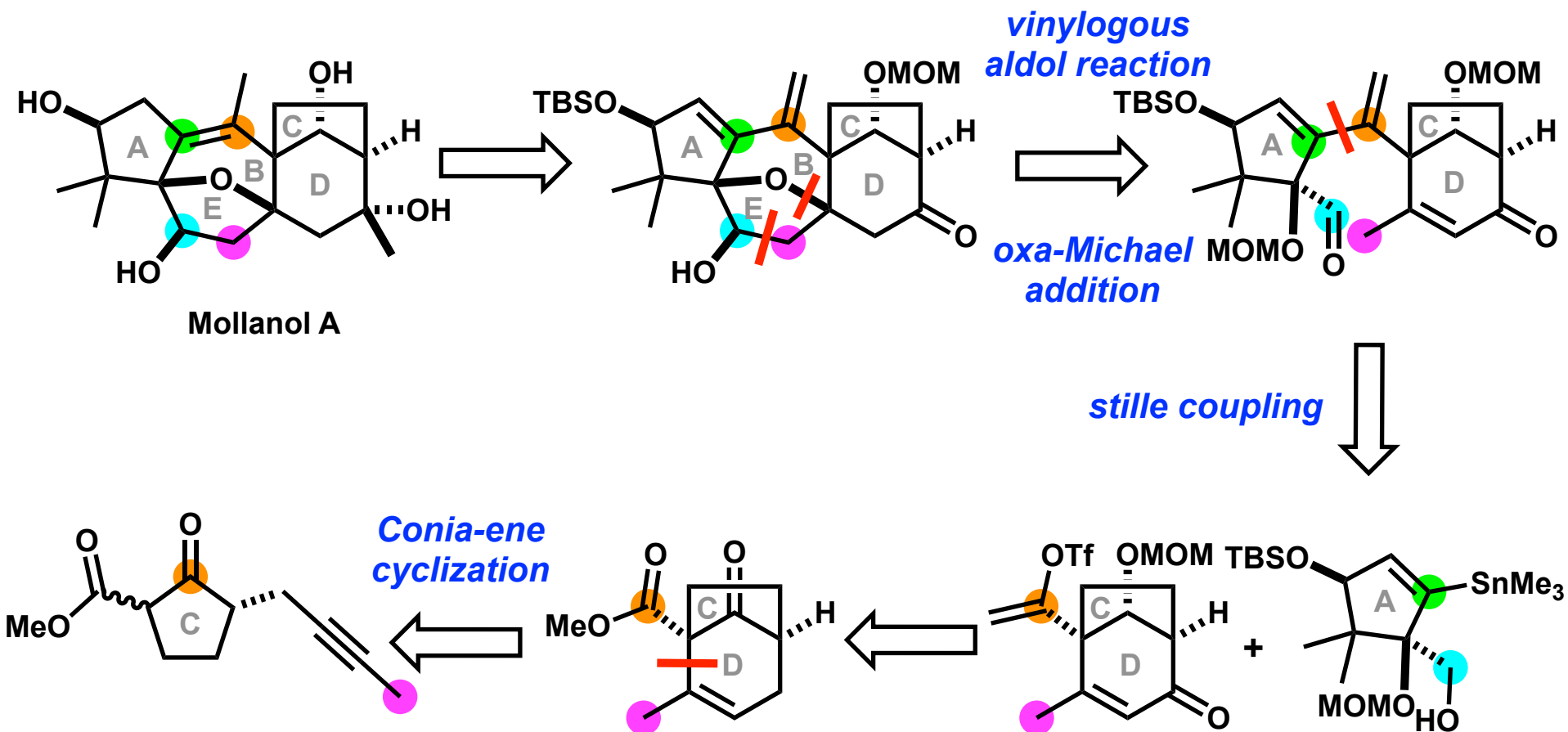
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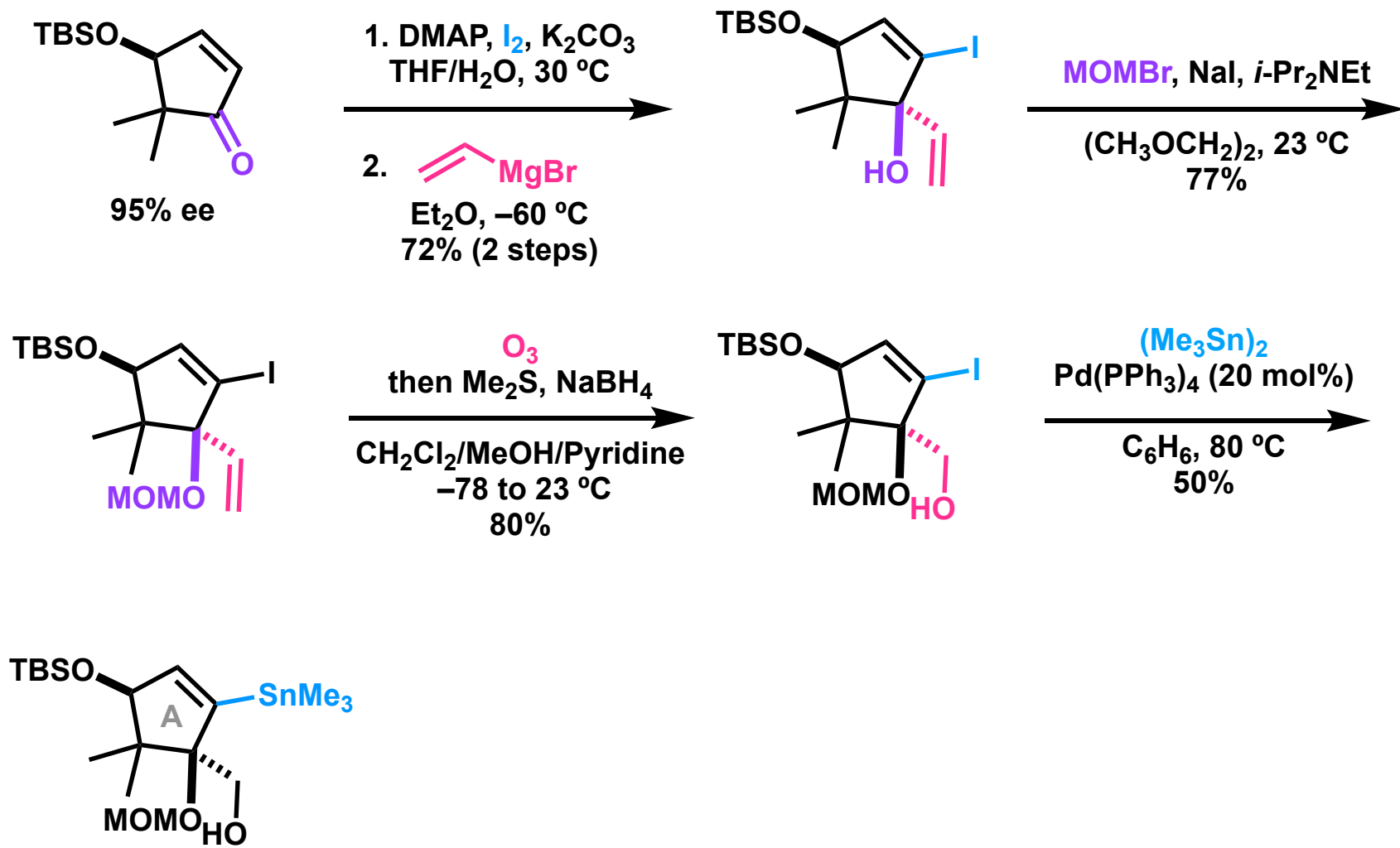
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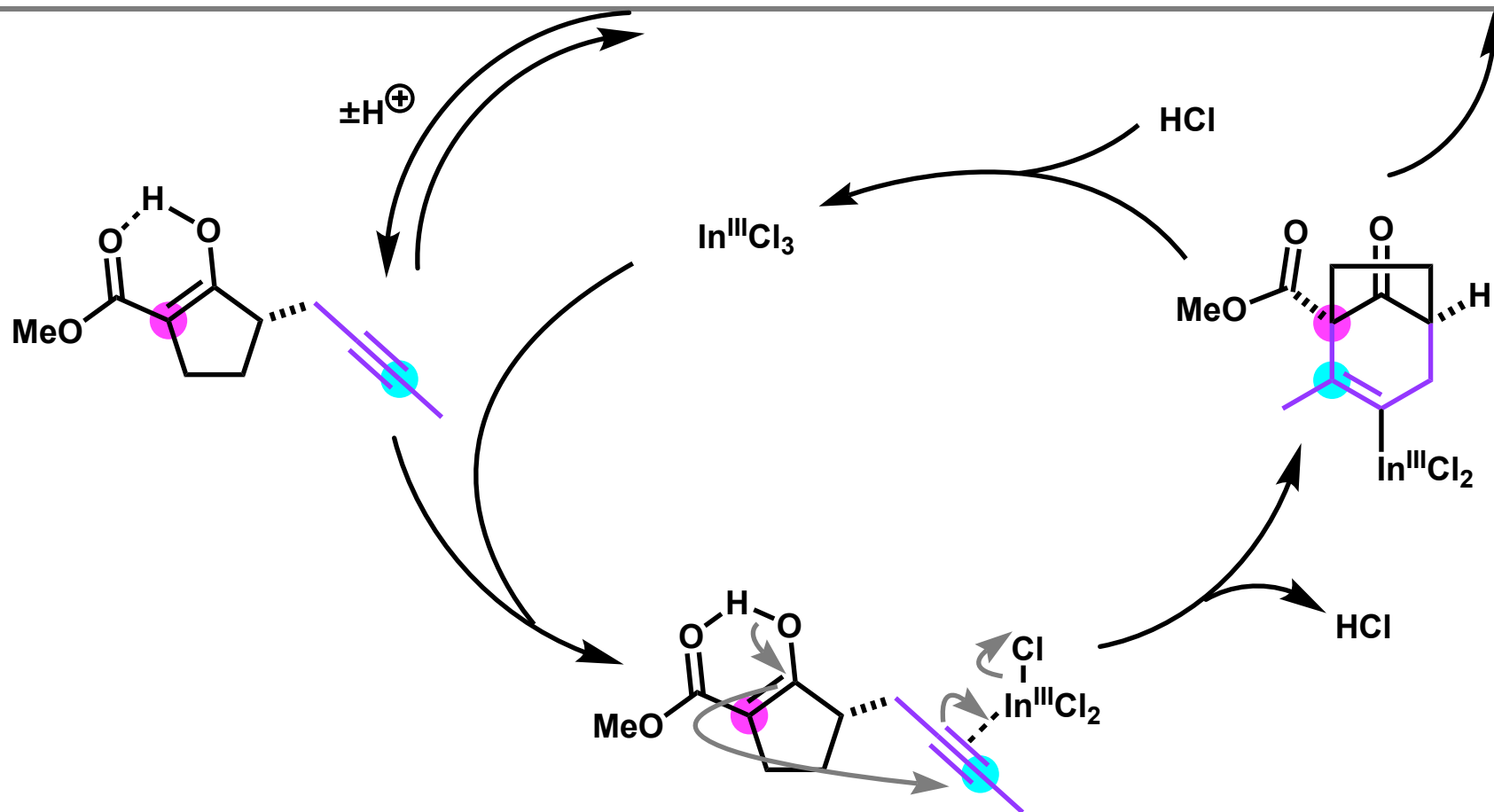
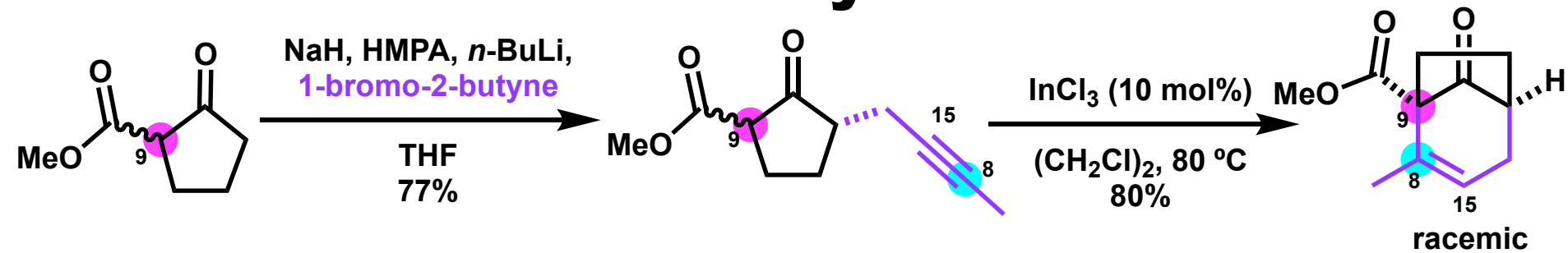


Construction of A-ring

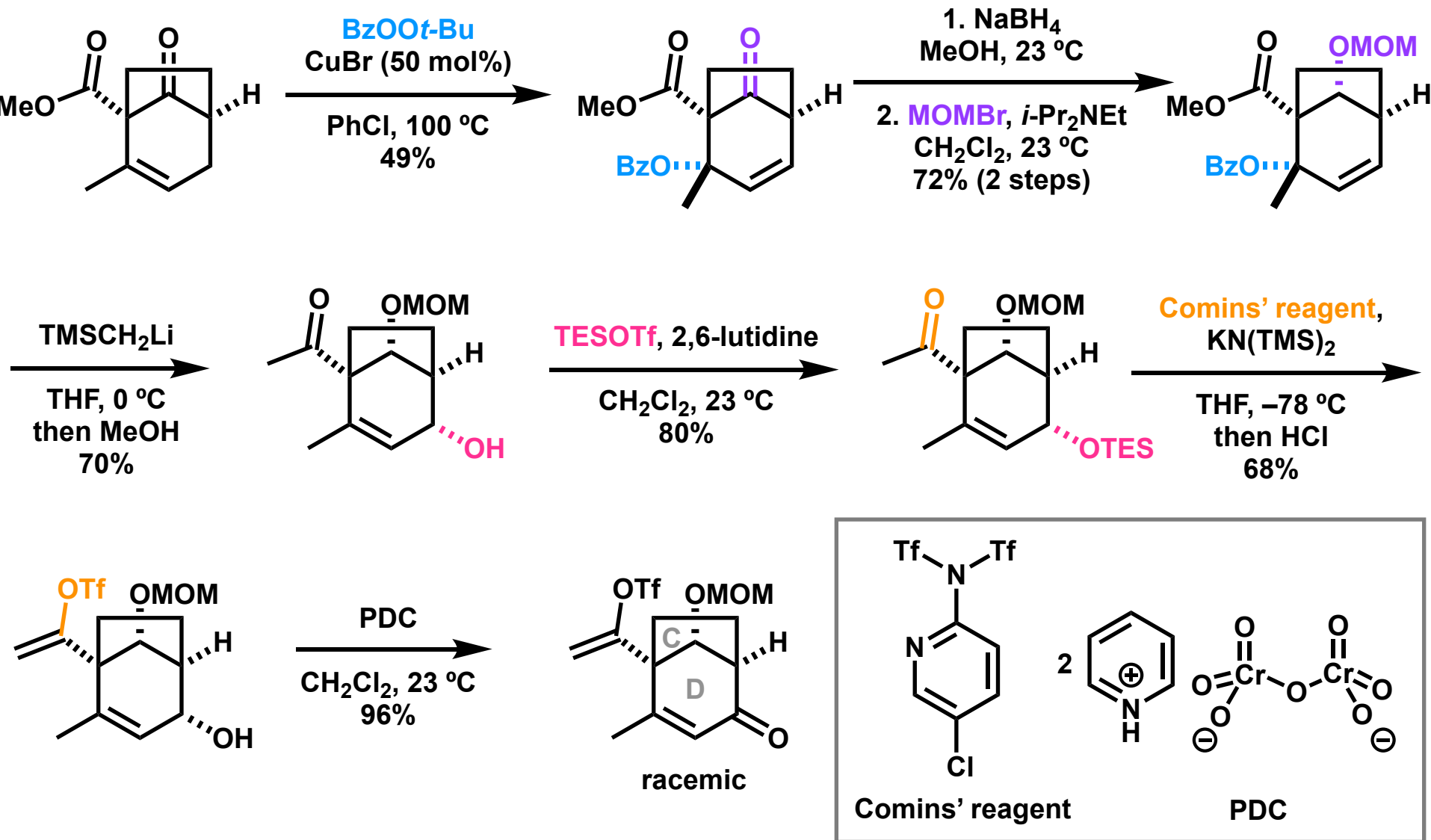


1) Yuran, W.; Rong, Z.; Ming, Y. *J. Am. Chem. Soc.* **2022**, *144*, 15033.

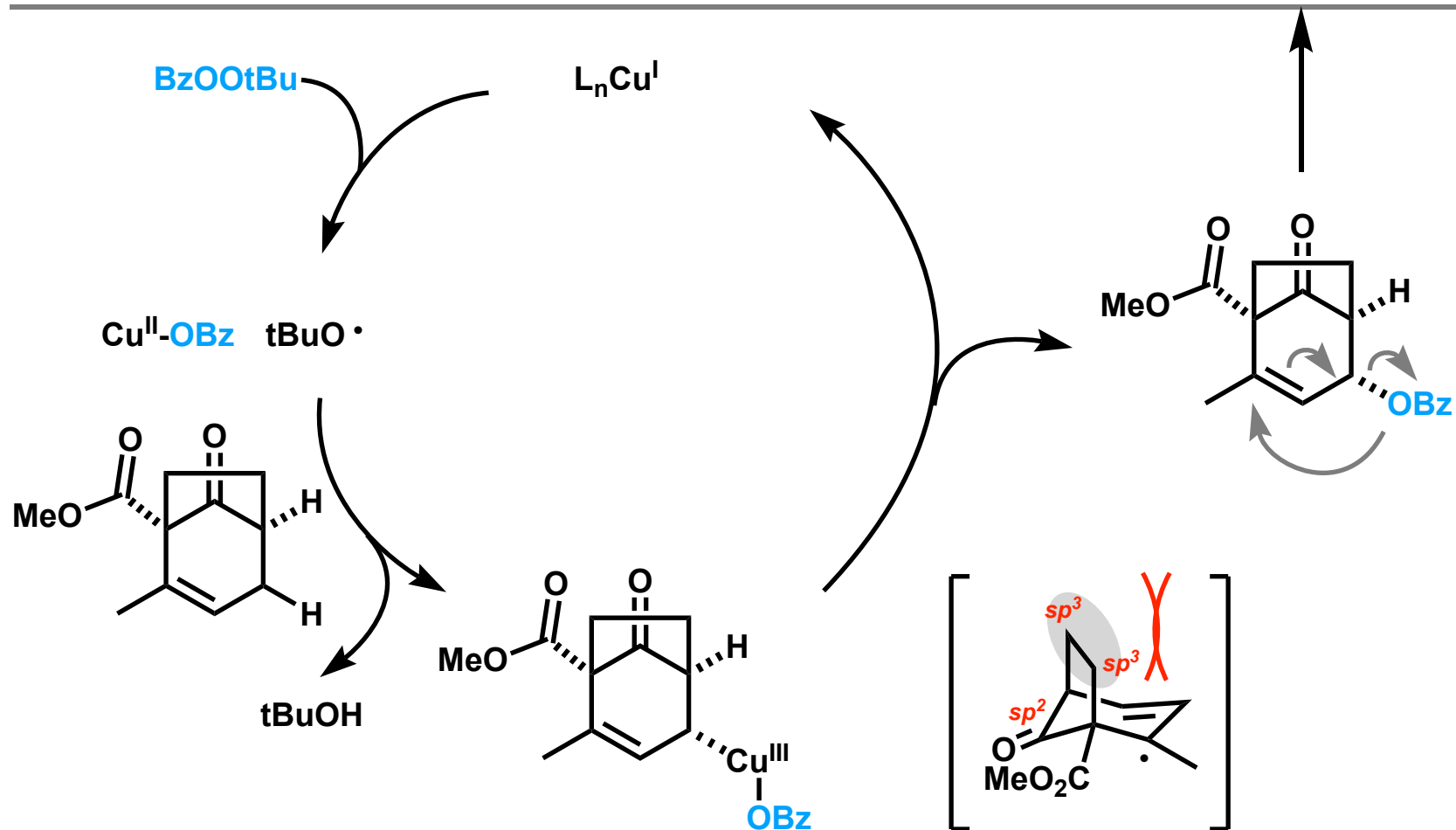
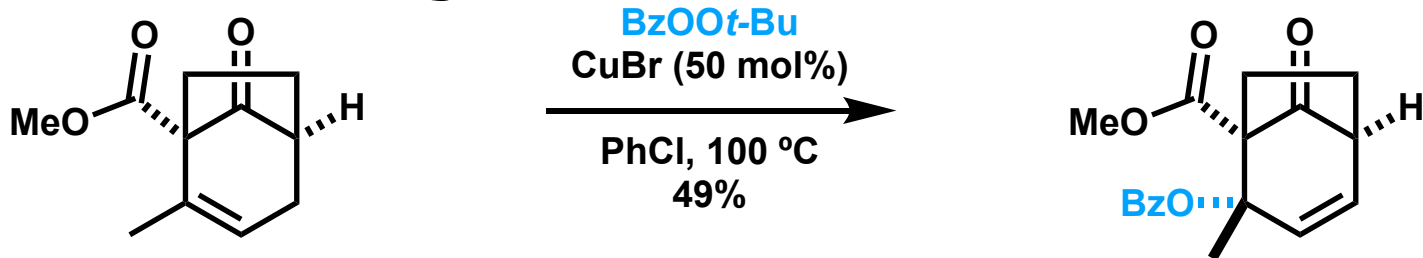
Conia-ene Cyclization



Construction of C/D-ring

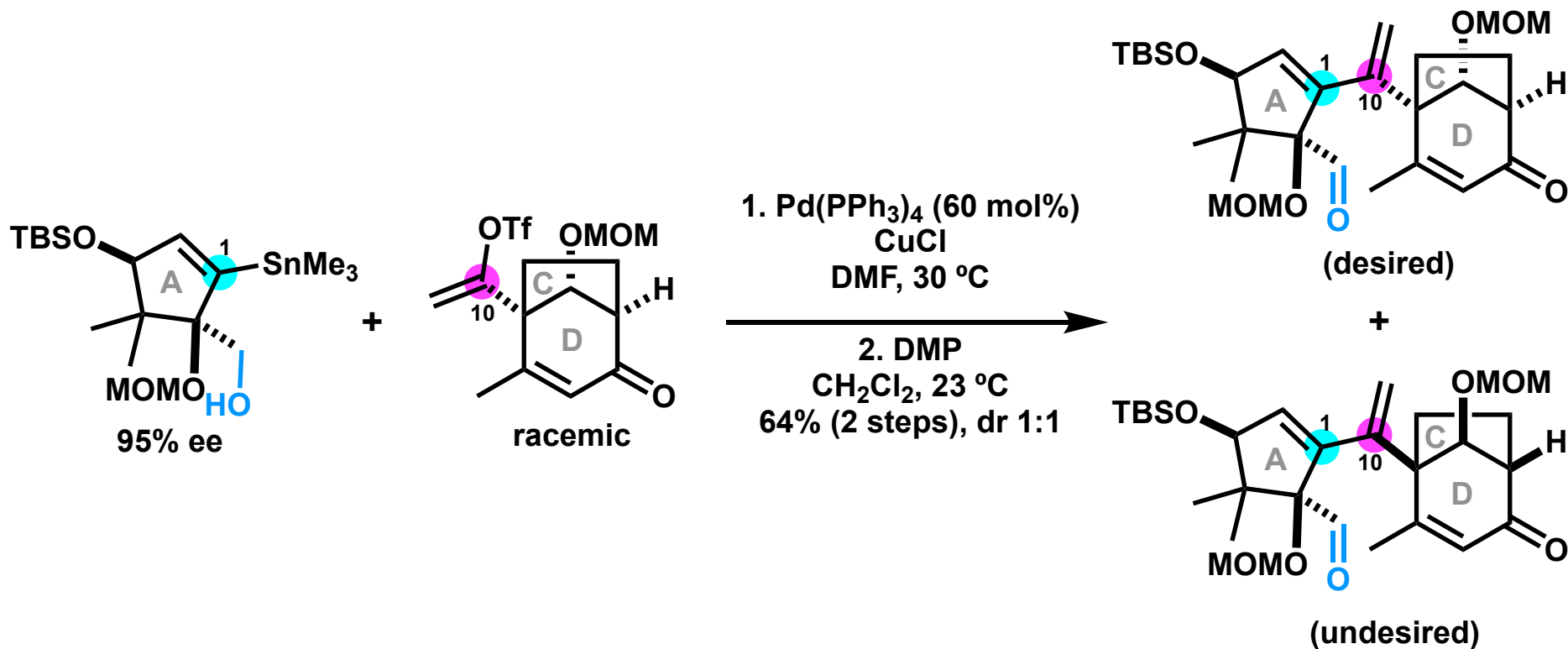


Allylic Oxidation

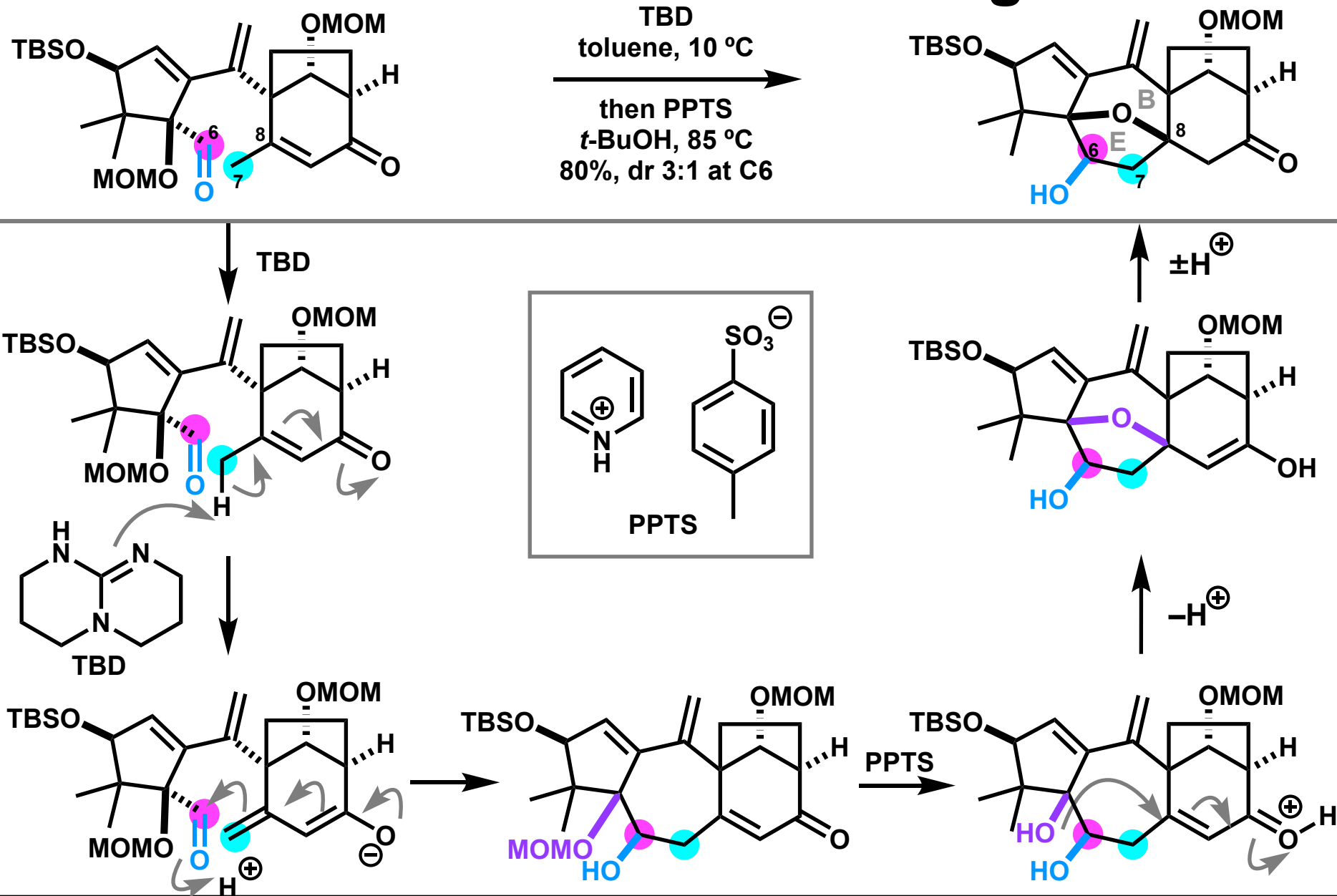


- 1) Yuran, W.; Rong, Z.; Ming, Y. *J. Am. Chem. Soc.* **2022**, *144*, 15033.
- 2) Kharasch, M. S.; Sosnovsky, G.; Yang, N. C. *J. Am. Chem. Soc.* **1959**, *81*, 5819.

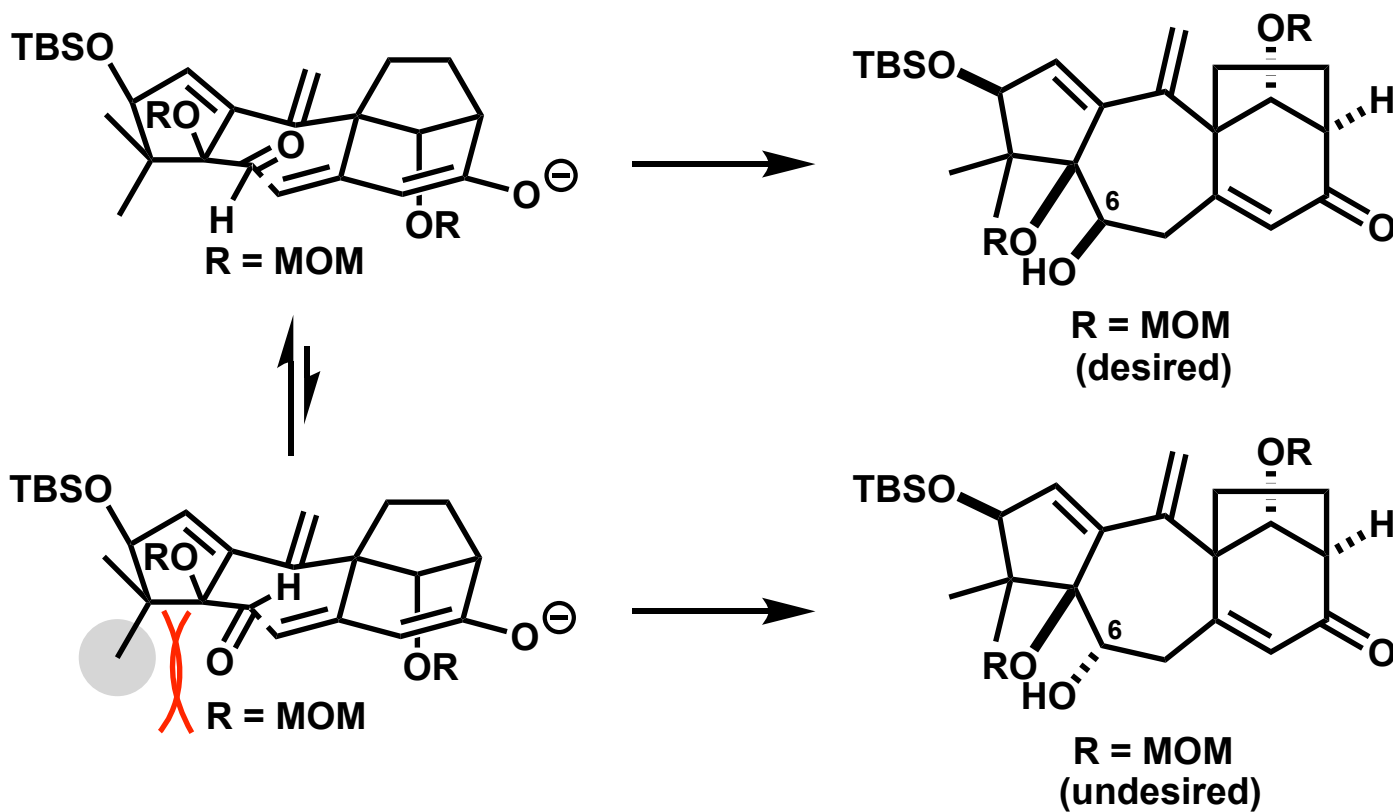
Stille Coupling between A and C/D-ring



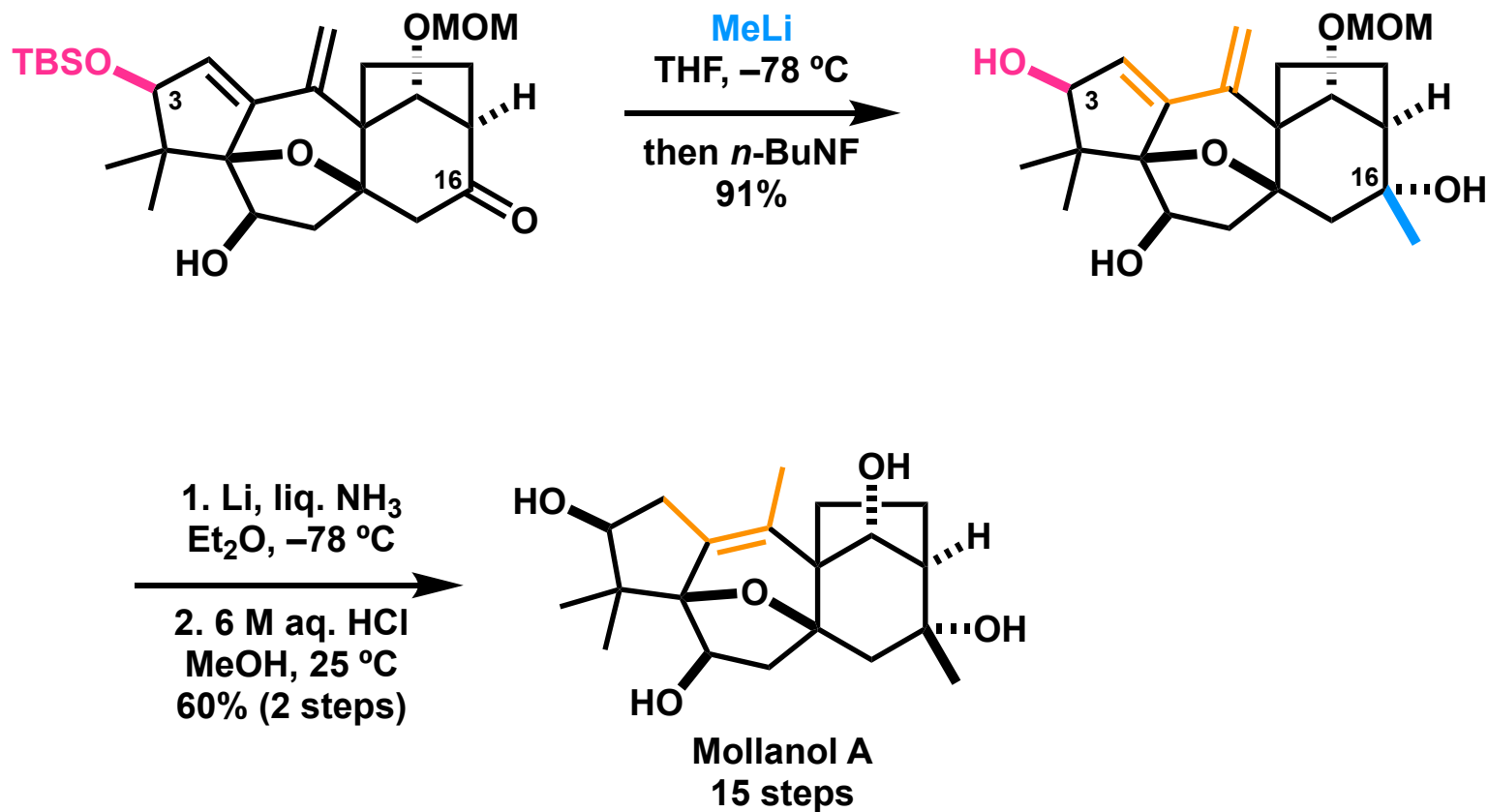
Construction of B/E-ring



Stereochemistry of Vinylogous Aldol Reaction

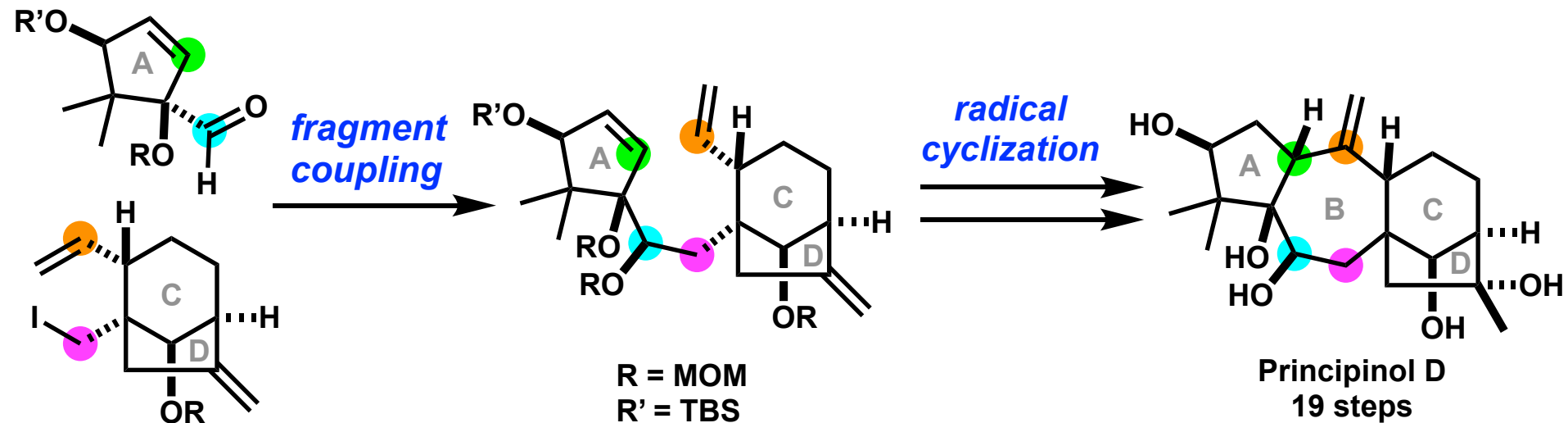


Total Synthesis of Mollanol A

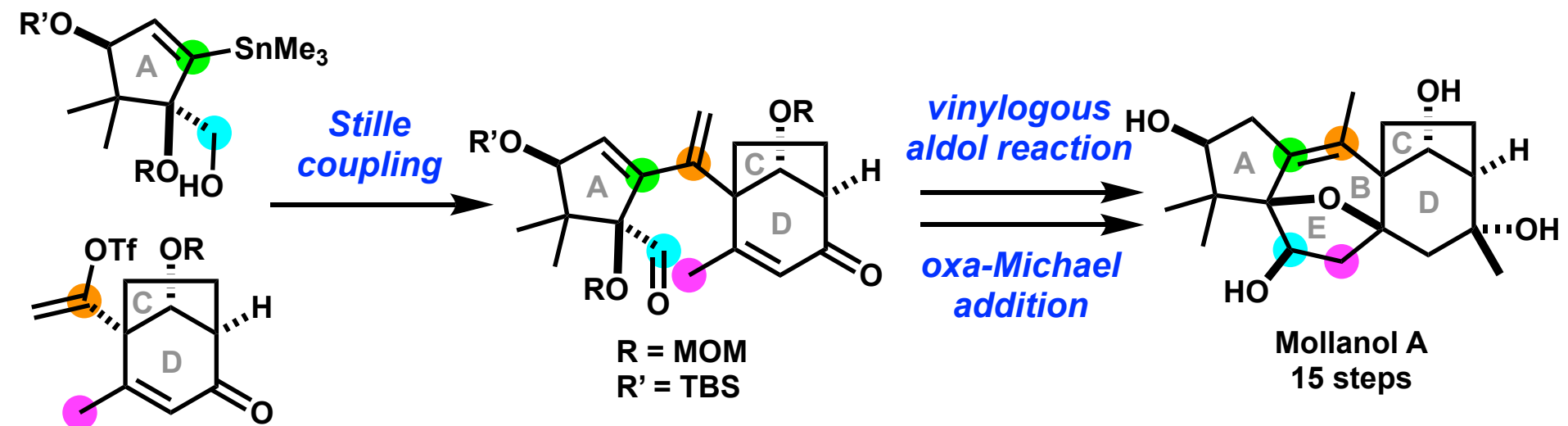


Summary

Newhouse



Yang



- 1) Aneta, T.; Yifeng, C.; Anthony, C. S.; Timothy, R. N. *J. Am. Chem. Soc.* **2019**, *141*, 8088.
- 2) Yuran, W.; Rong, Z.; Ming, Y. *J. Am. Chem. Soc.* **2022**, *144*, 15033.