Total Synthesis of (+)-Kalmanol

2024.10.26 Literature Seminar
B4 Ryo Nishikawa

Contents

1. Introduction

2. Synthetic study of (+)-Kalmanol
   (by Paquette Group, 1996)

3. Total synthesis of (+)-Kalmanol
   (by Jia Group, 2024)

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Introduction of Prof. Paquette and Prof. Jia

Prof. Leo A. Paquette

Career:
1956 B.S. @ Holy Cross College
1959 Ph.D. @ Massachusetts Institute of Technology (Prof. Norman A. Nelson)
1959-1963 Research Associate @ The Upjohn Company
1963-1969 Chemistry Faculty @ The Ohio State University
1969-2019 Full Professor @ The Ohio State University

Research Topics:
Synthesis of novel hydrocarcons, Total synthesis, Development of synthetic methods

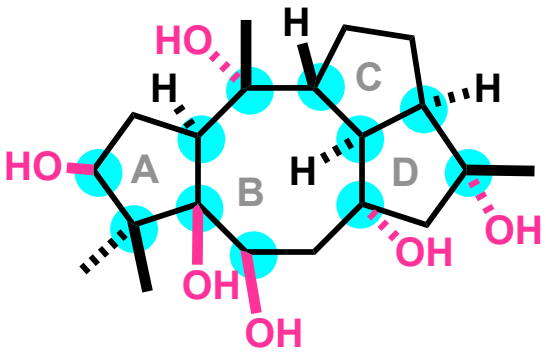
Prof. Yanxing Jia

Career:
1997 B.S. @ Lanzhou University
2002 Ph.D. @ Lanzhou University (Prof. Yongqiang Tu)
2002-2007 Postdoc @ Centre National de la Recherche Scientifique (Prof. Jieping Zhu)
2007-2011 Associate Professor @ Peking University
2011-Present Professor @ Peking University

Research Topics:
Total synthesis, Synthetic medical chemistry, Development of synthetic methods

1) https://www.organicreactions.org/board_members/deceased_members/leo_a-_paquette/
2) http://www.jiayanxinggroup.com/Jia

(+)-Kalmanol



(+)-kalmanol

Isolation:

from the leaves of *Kalmia angustifolia* L.[1)]

Biological activities:

Inhibition on voltage-gated sodium channel $Na_V1.4$.[2)]

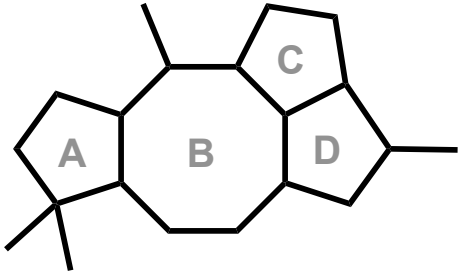
Total synthesis of (+)-kalmanol:

Luo (2023)[3)] (231007_PS_Yo_Matsumoto)

Jia (2024, 2024)[2), 4)]

Structual features:

- **5/8/5/5 tetracyclic kalmane skelton**
- **11 contiguous stereocenters**
- **Highly oxidative decoration**

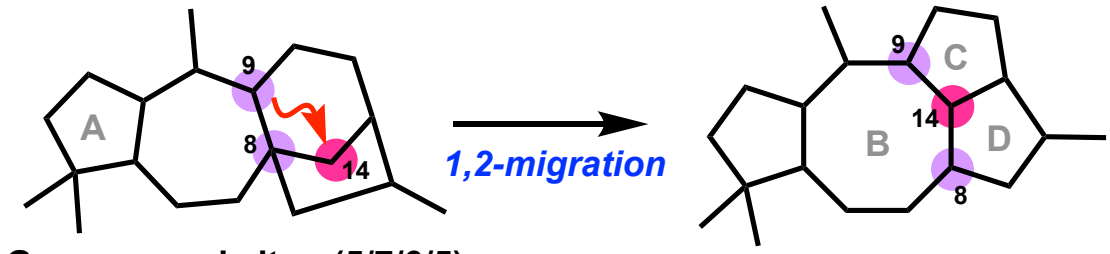


kalmane skelton

1) J. W. Bruke, R. W. Doskotch, C. Z. Ni, J. Clardy., *J. Am. Chem. Soc.* **1989**, 111, 5831.
2) Ma T, Ma Y, Li B, Jia Y., *Angew Chem Int Ed Engl.* **2024**, *63* ,e202407215.
3) L. Kong, H. Yu, M. Deng, F. Wu, S. Chen, T. Luo, J. Org. Chem. **2023**, *88*, 6017.
4) H. Cheng, T. Ma, X. Liu, Y. Jia, *CCS Chem.* 2024, Just Accepted. DOI: 10.31635/ccschem.024.202303731.

Strategies for Kalmane 5/8/5/5 Skelton

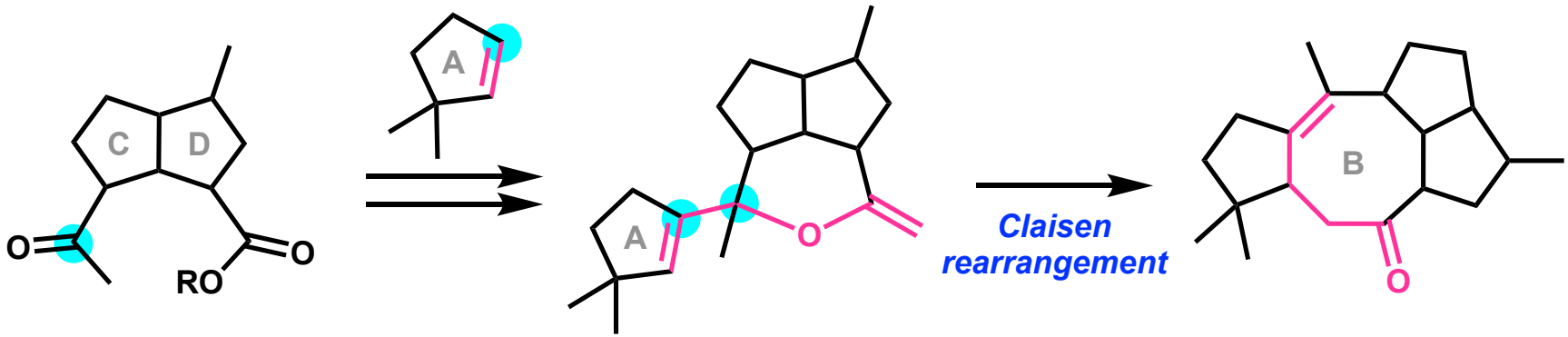
Strategy 1 : Biomimetic 1,2-migration



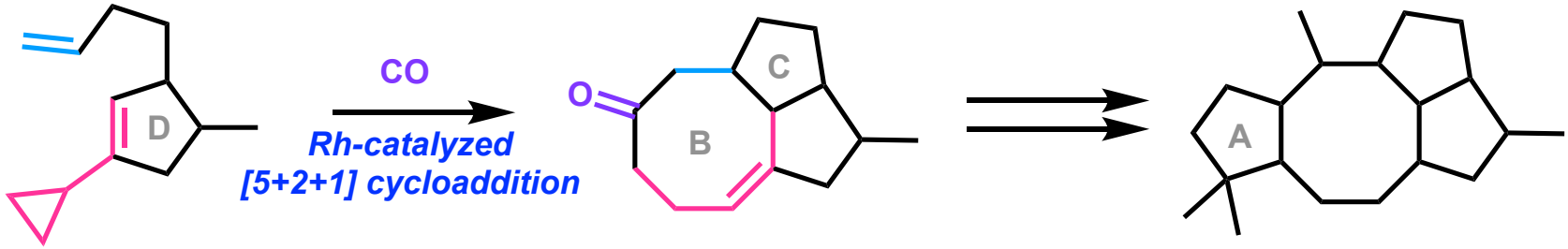
Grayanane skelton (5/7/6/5)

· Luo group (2023)[1)]
· Jia group (2024)[2)]

Strategy 2 : Claisen rearrangement ring expansion[3)]

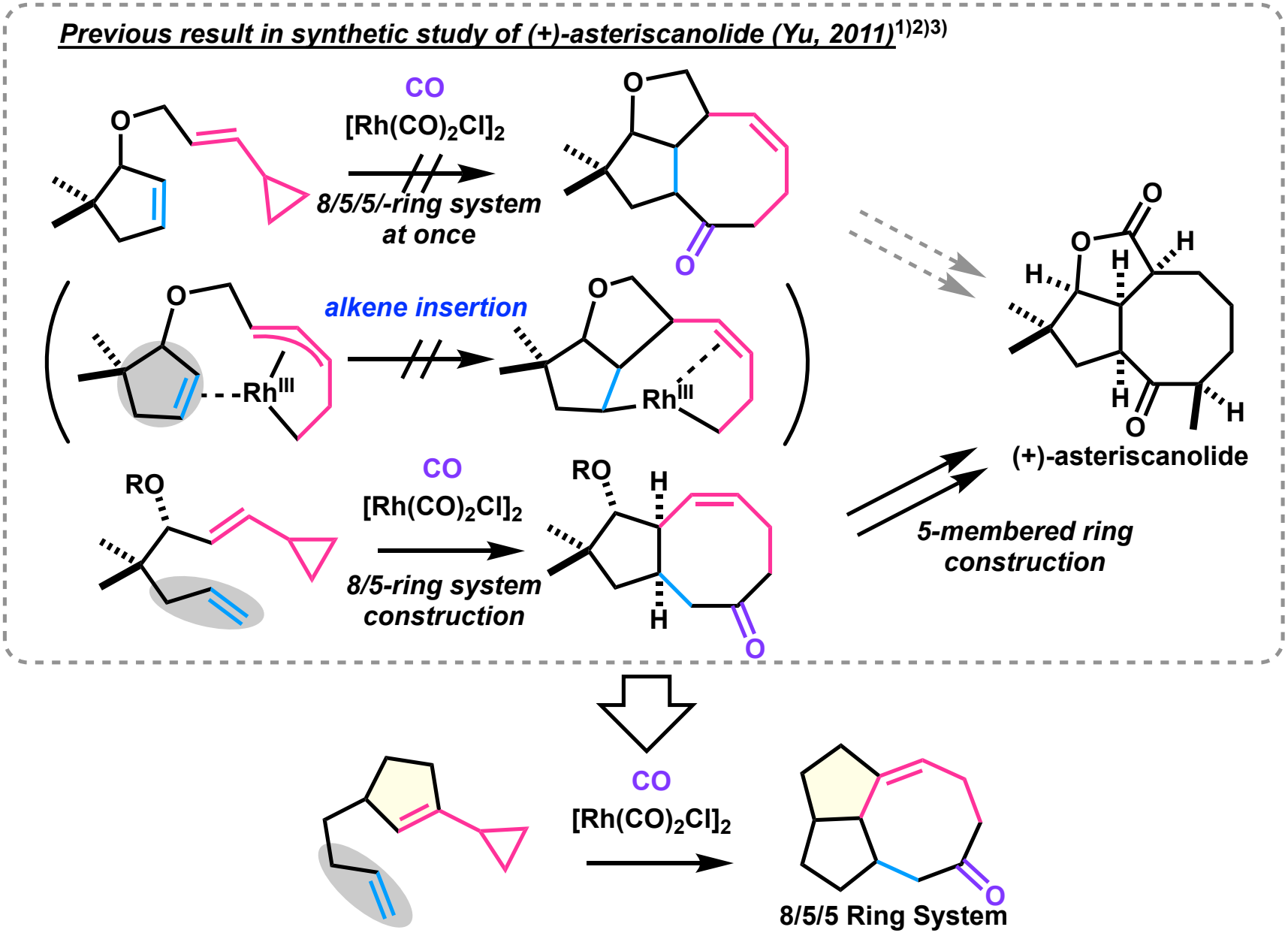


Strategy 3 : Rh-catalyzed [5+2+1] cycloaddition[4)]



1) L. Kong, H. Yu, M. Deng, F. Wu, S. Chen, T. Luo, J. Org. Chem. **2023**, *88*, 6017.
2) H. Cheng, T. Ma, X. Liu, Y. Jia, *CCS Chem.* **2024**, Just Accepted. DOI: **10.31635/ccschem.024.202303731**.
3) S. Borrelly, L. A. Paquette, *J. Am. Chem. Soc.* **1996**, *118*, 727.
4) Ma T, Ma Y, Li B, Jia Y., *Angew Chem Int Ed Engl.* **2024**, *63* ,e202407215.

Background of Key Reaction



1) L.-N. Wang, Z. Huang, Z.-X. Yu, *Org. Lett.* **2023**, *25*, 1732.
2) Y. Liang, X. Jiang, X.-F. Fu, S. Ye, T. Wang, J. Yuan, Y. Wang, Z.-X. Yu, *Chem. Asian J.* **2012**, *7*, 593.
3) Y. Liang, X. Jiang, Z.-X. Yu, *Chem. Commun.* **2011**, *47*, 6659.
4) Ma T, Ma Y, Li B, Jia Y., *Angew Chem Int Ed Engl.* **2024**, *63* ,e202407215.

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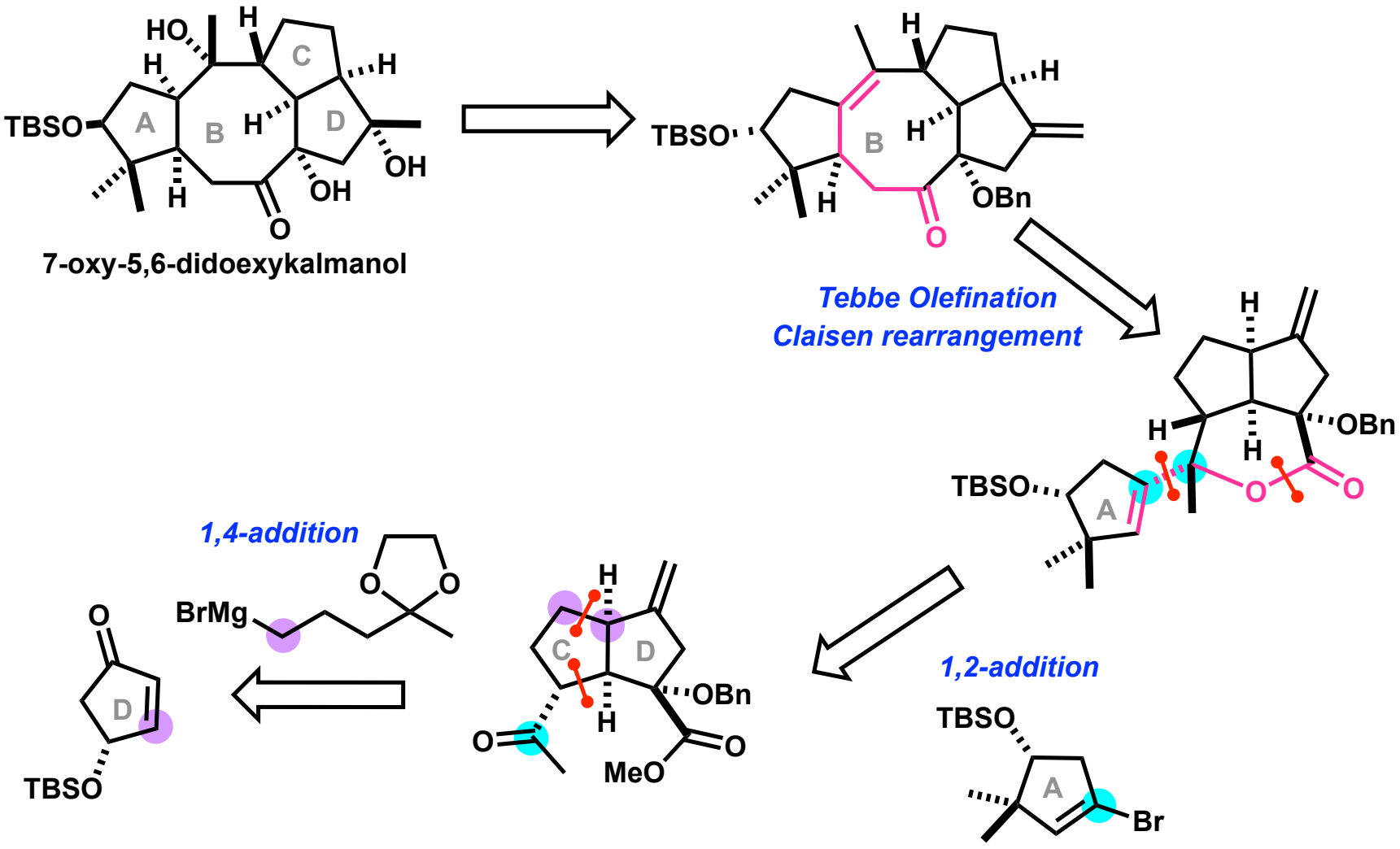
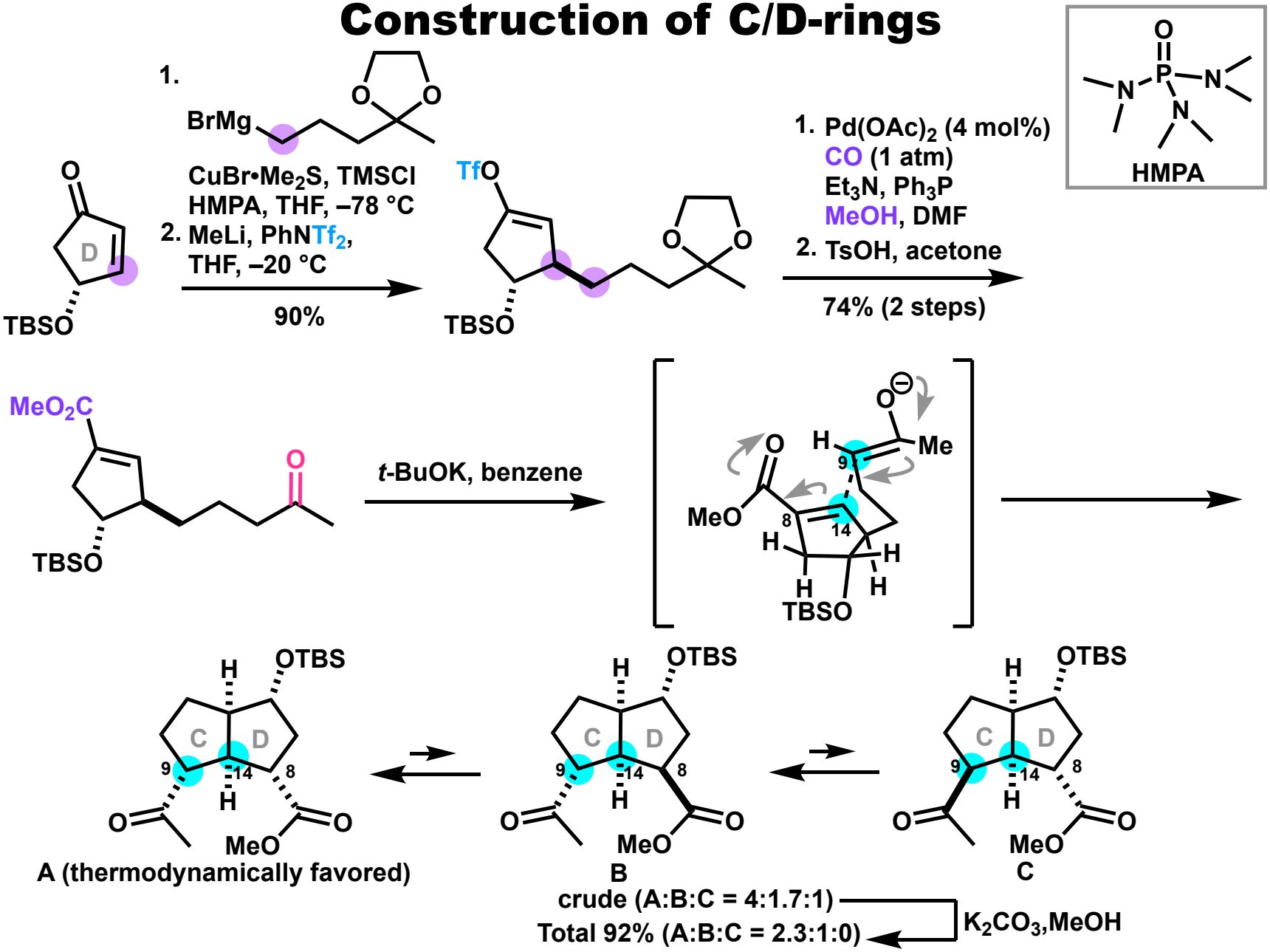
Retrosynthetic Analysis of 7-oxy-5,6-dideoxykalmanol



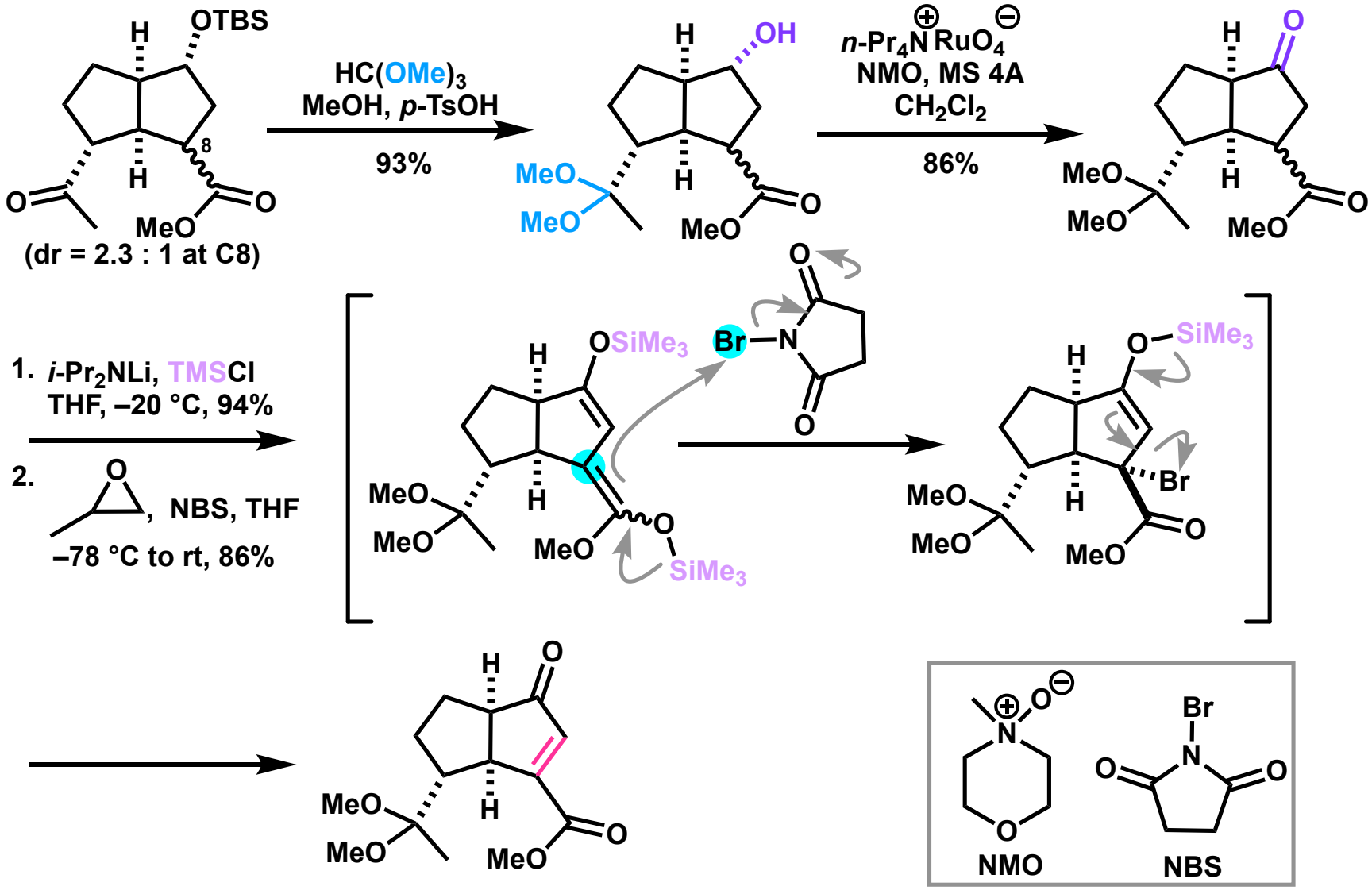
1) S. Borrelly, L. A. Paquette, *J. Am. Chem. Soc.* **1996**, *118*, 727.

Construction of C/D-rings



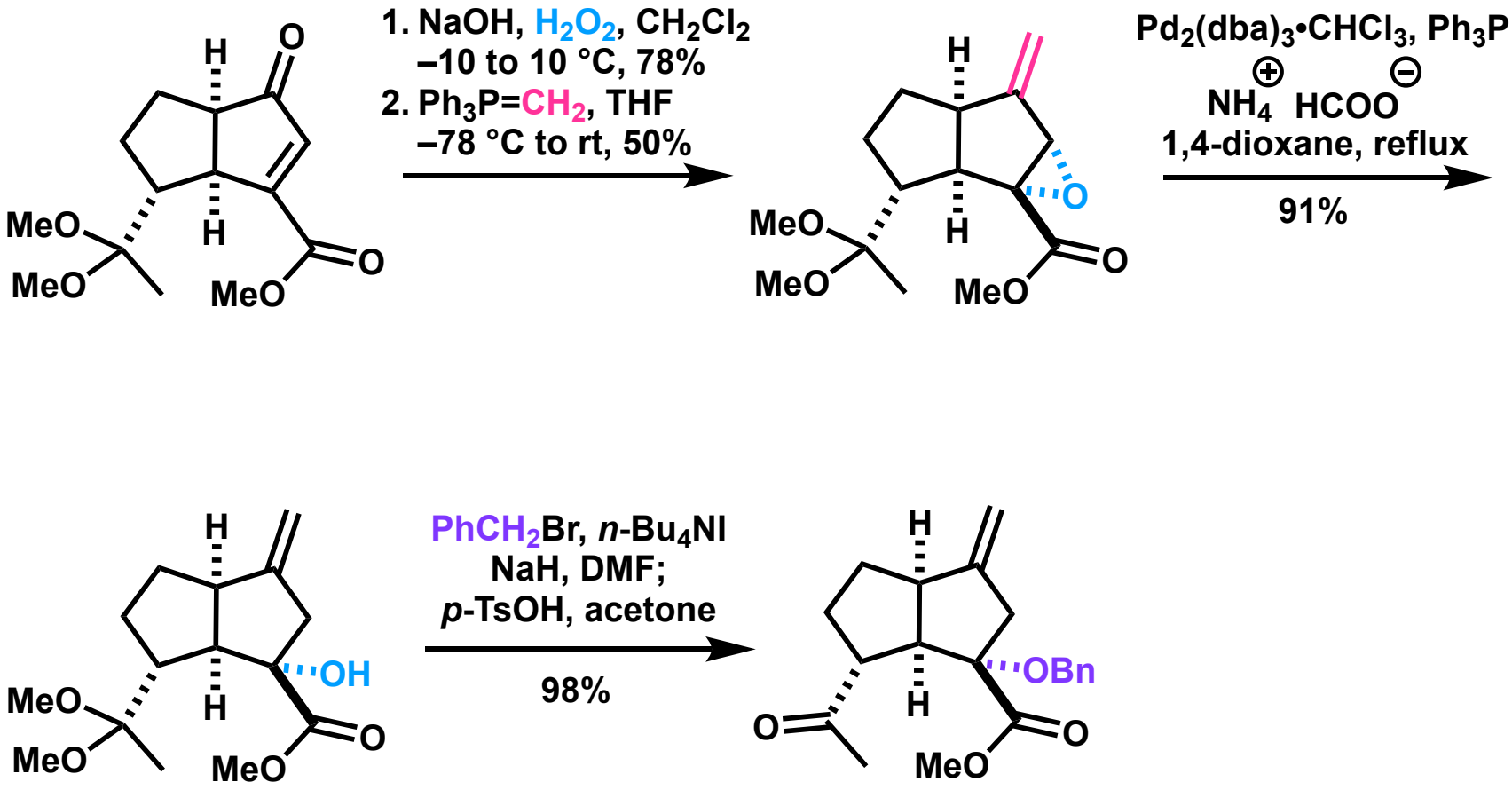
1) S. Borrelly, L. A. Paquette, *J. Am. Chem. Soc.* **1996**, *118*, 727.

Functionalization of C/D-rings (1)



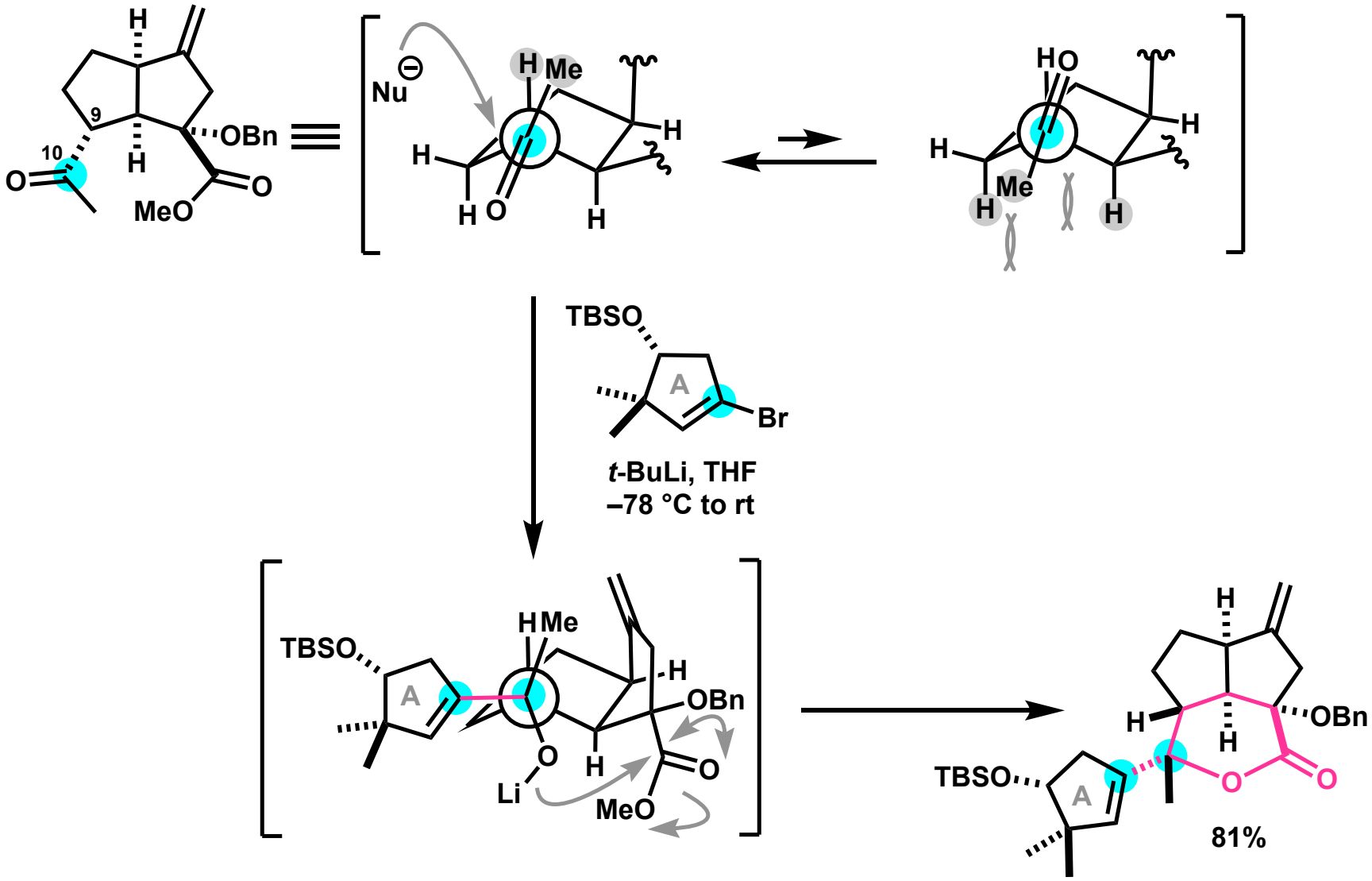
1) S. Borrelly, L. A. Paquette, *J. Am. Chem. Soc.* **1996**, *118*, 727.

Functionalization of C/D-rings (2)



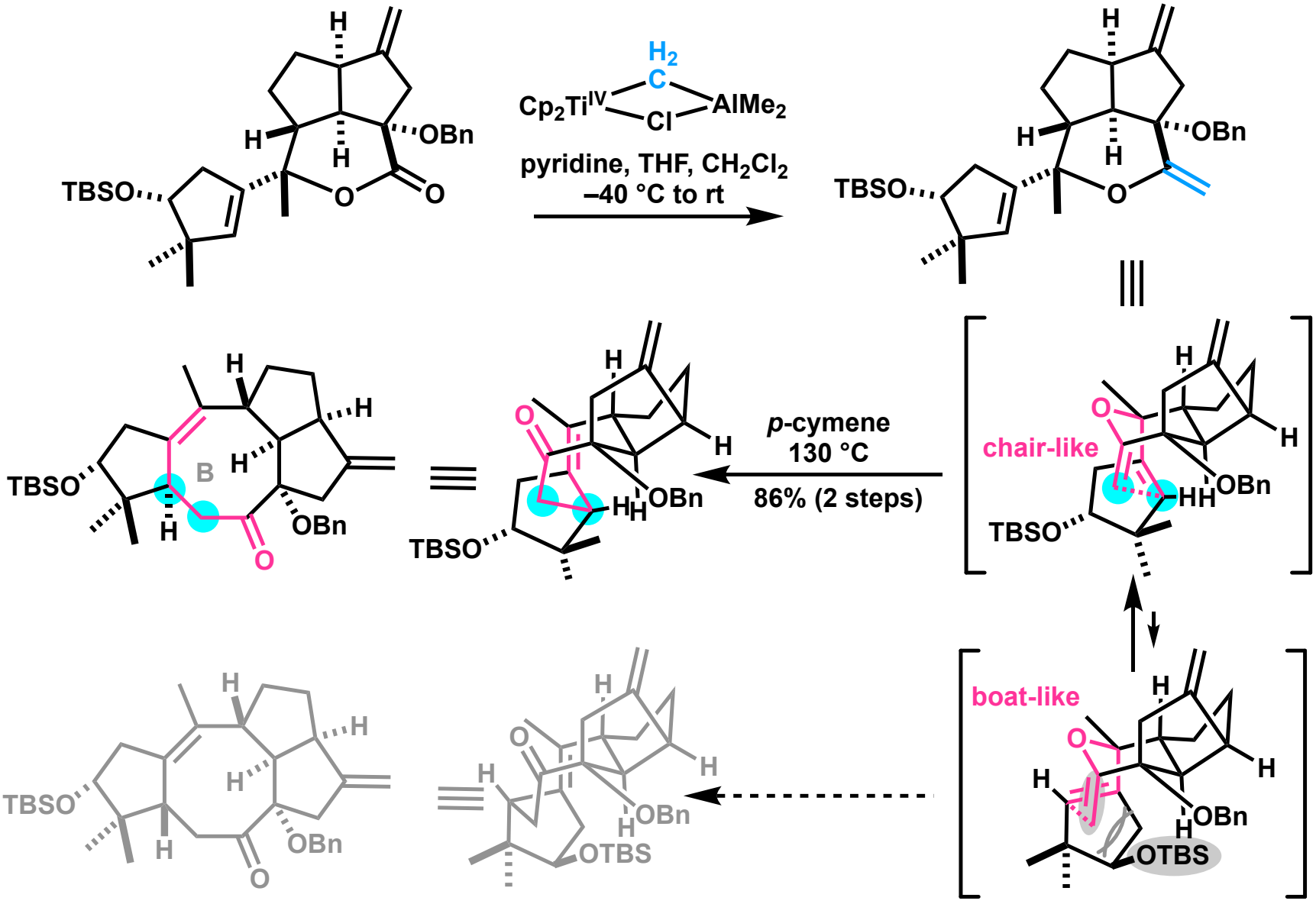
1) S. Borrelly, L. A. Paquette, *J. Am. Chem. Soc.* **1996**, *118*, 727.

Stereoselective 1,2-addition of A-ring Fragment



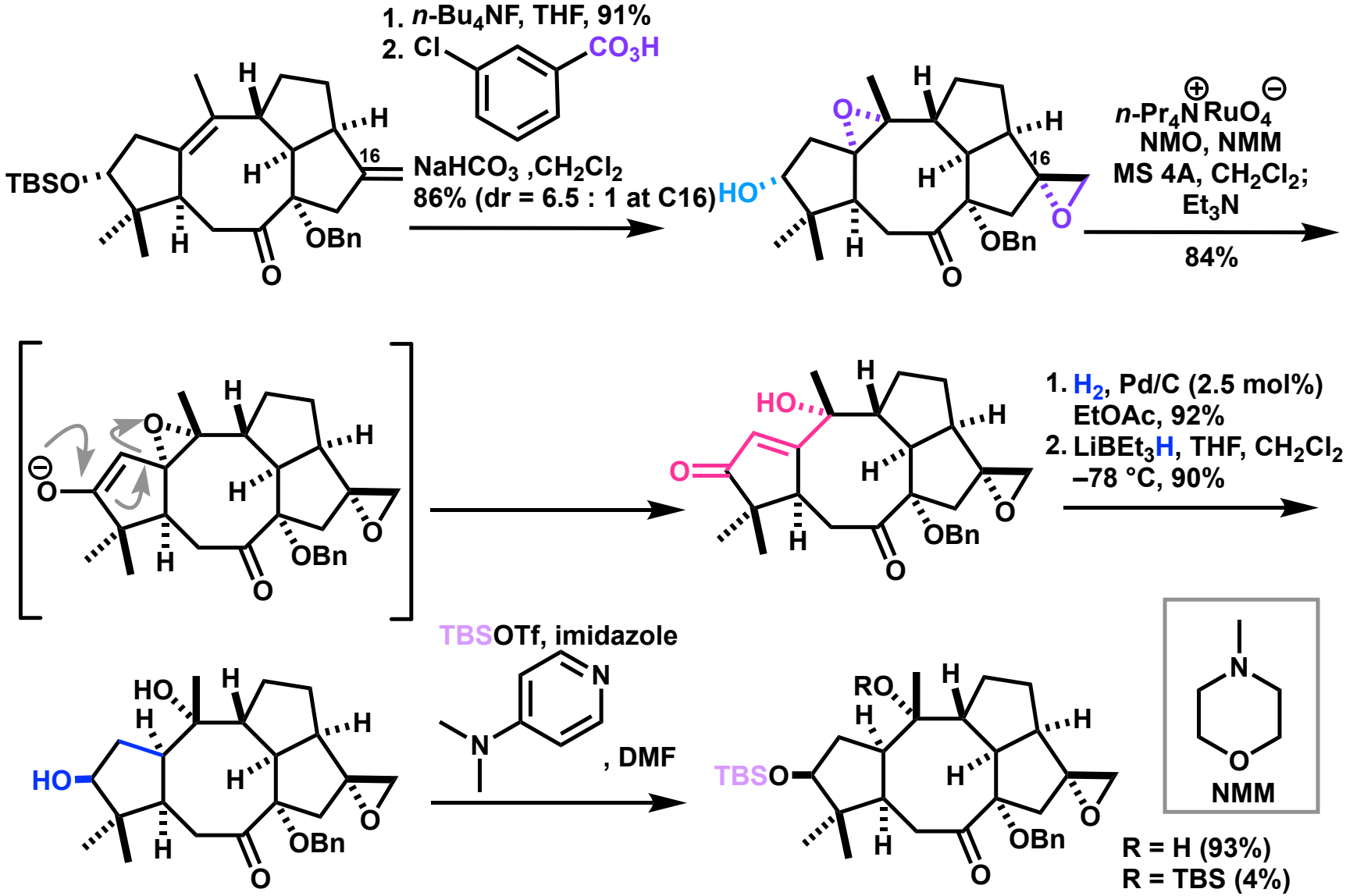
1) S. Borrelly, L. A. Paquette, *J. Am. Chem. Soc.* **1996**, *118*, 727.

Tebbe Olefination and Claisen Ring Expansion



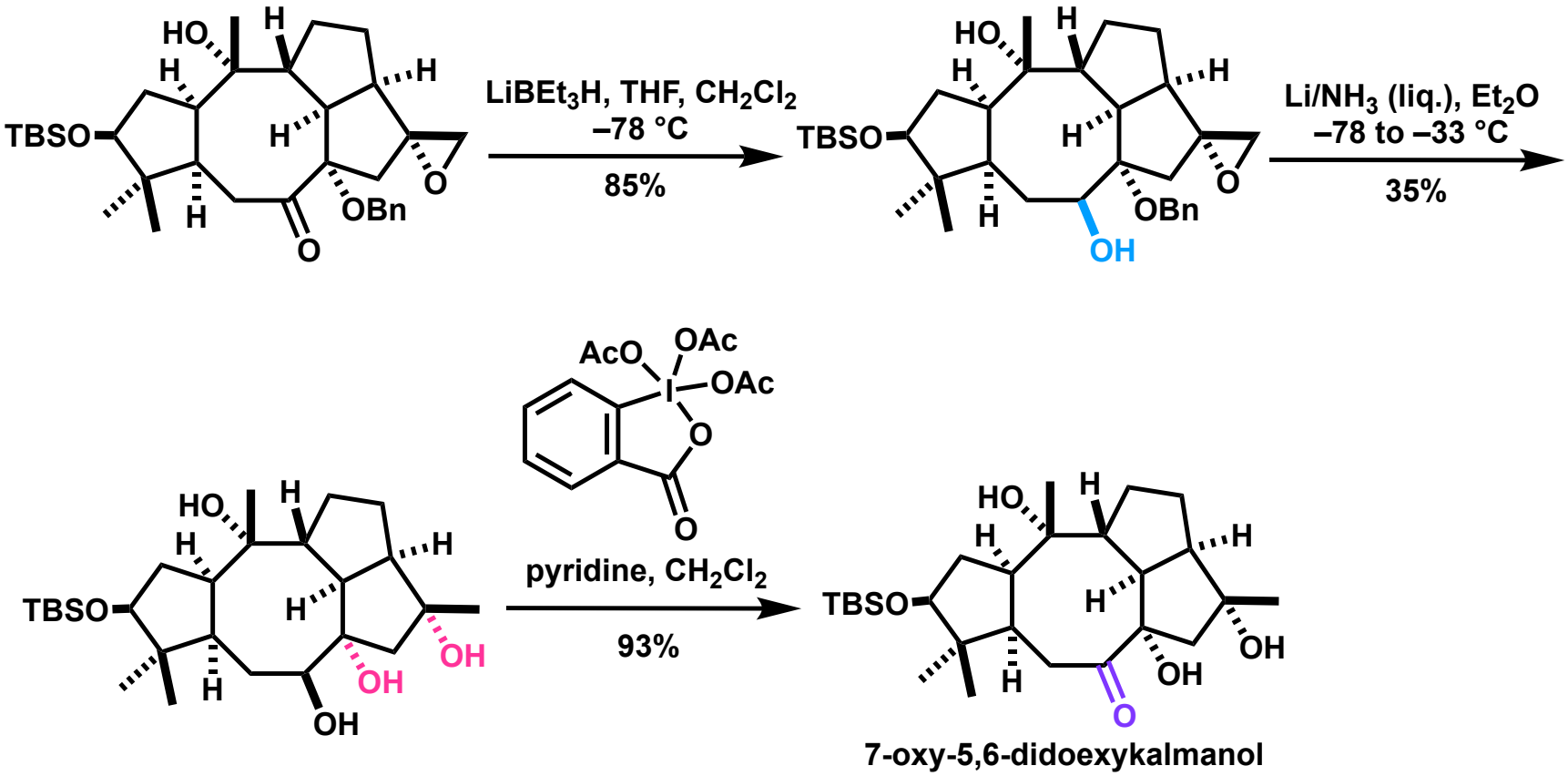
1) S. Borrelly, L. A. Paquette, *J. Am. Chem. Soc.* **1996**, *118*, 727.

Functionalization of Backbone (1)



1) S. Borrelly, L. A. Paquette, *J. Am. Chem. Soc.* **1996**, *118*, 727.

Functionalization of Backbone (2)



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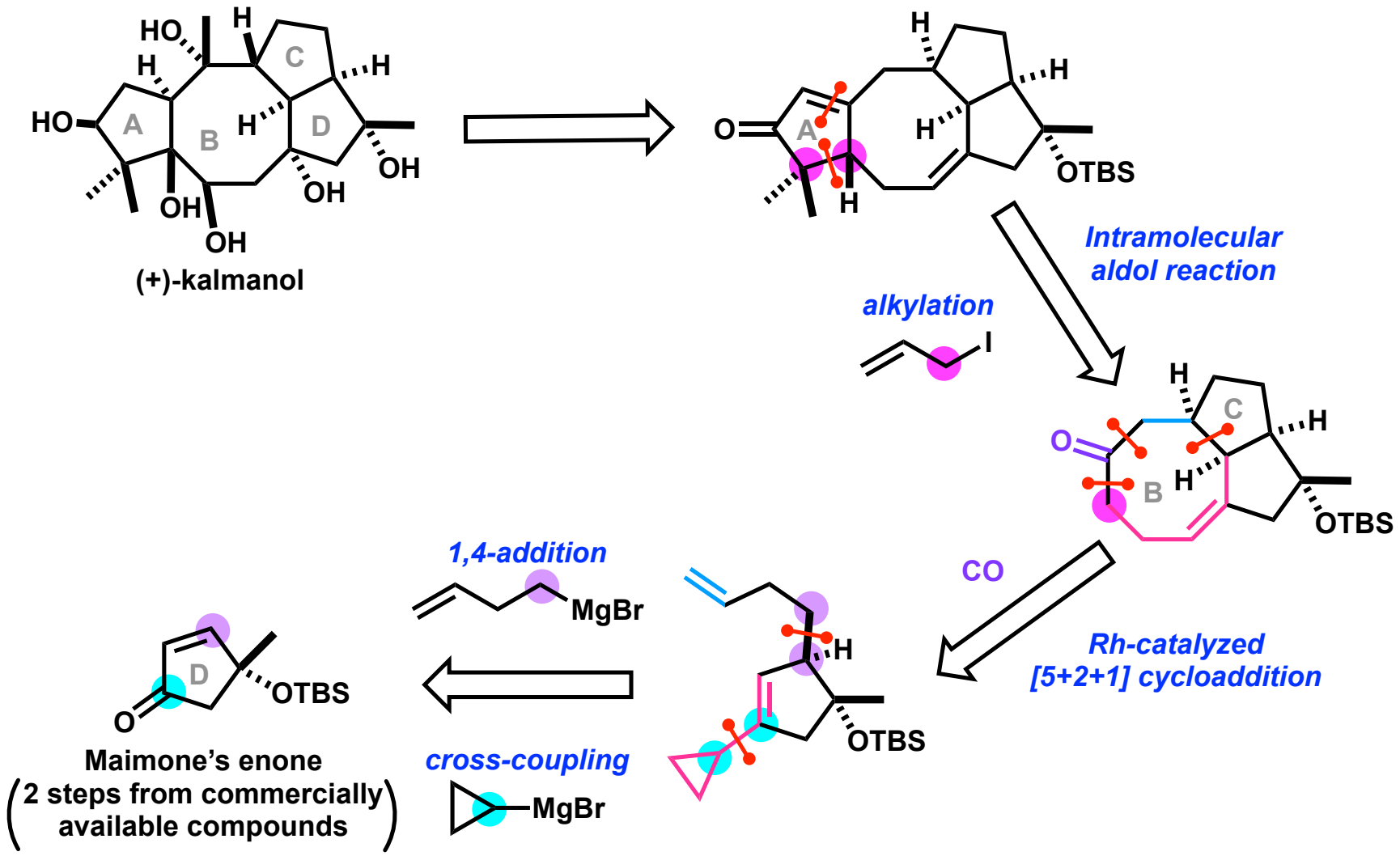
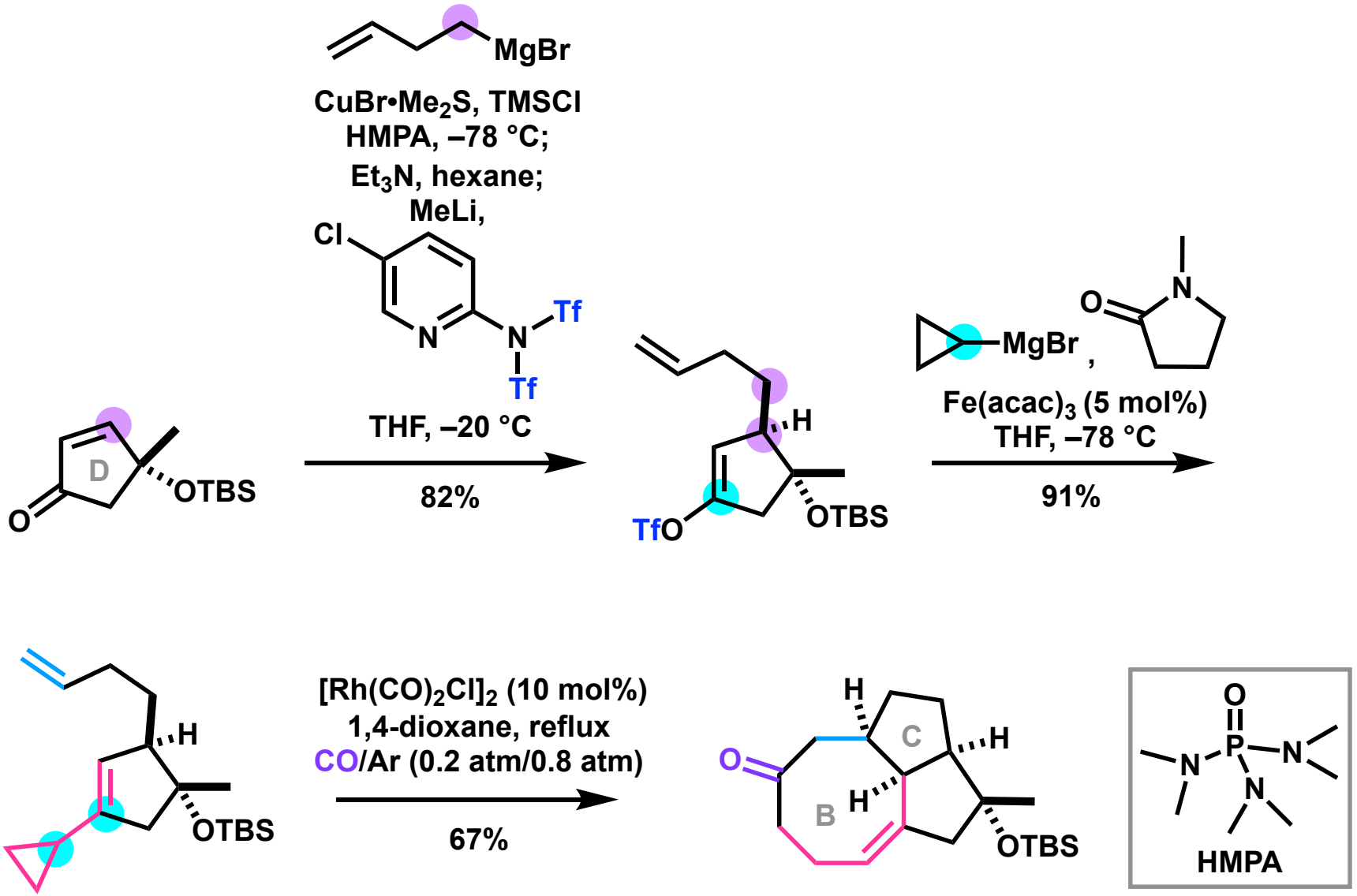


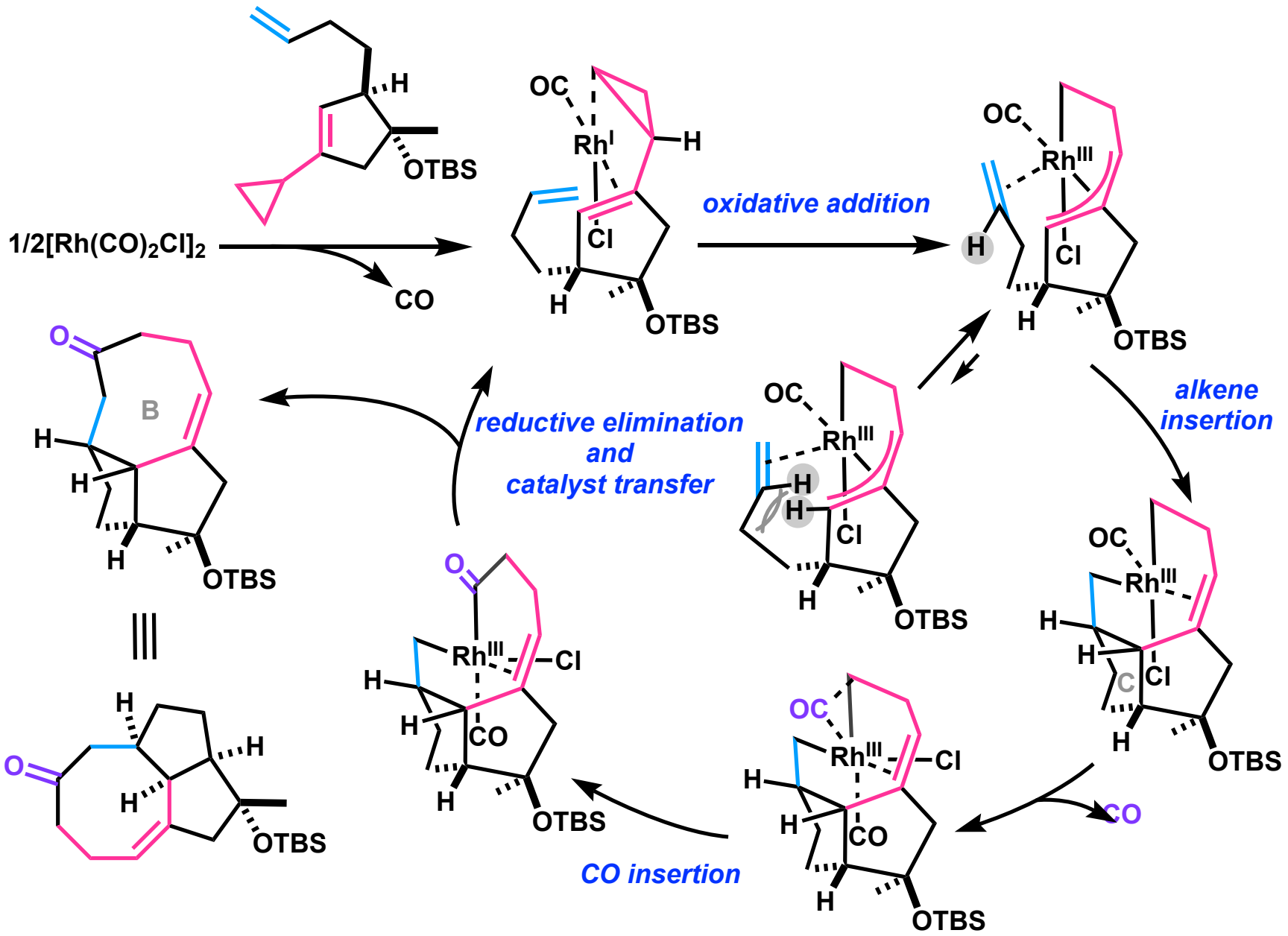
1) Ma T, Ma Y, Li B, Jia Y., *Angew Chem Int Ed Engl.* **2024**, *63* ,e202407215.

Construction of B/C-rings



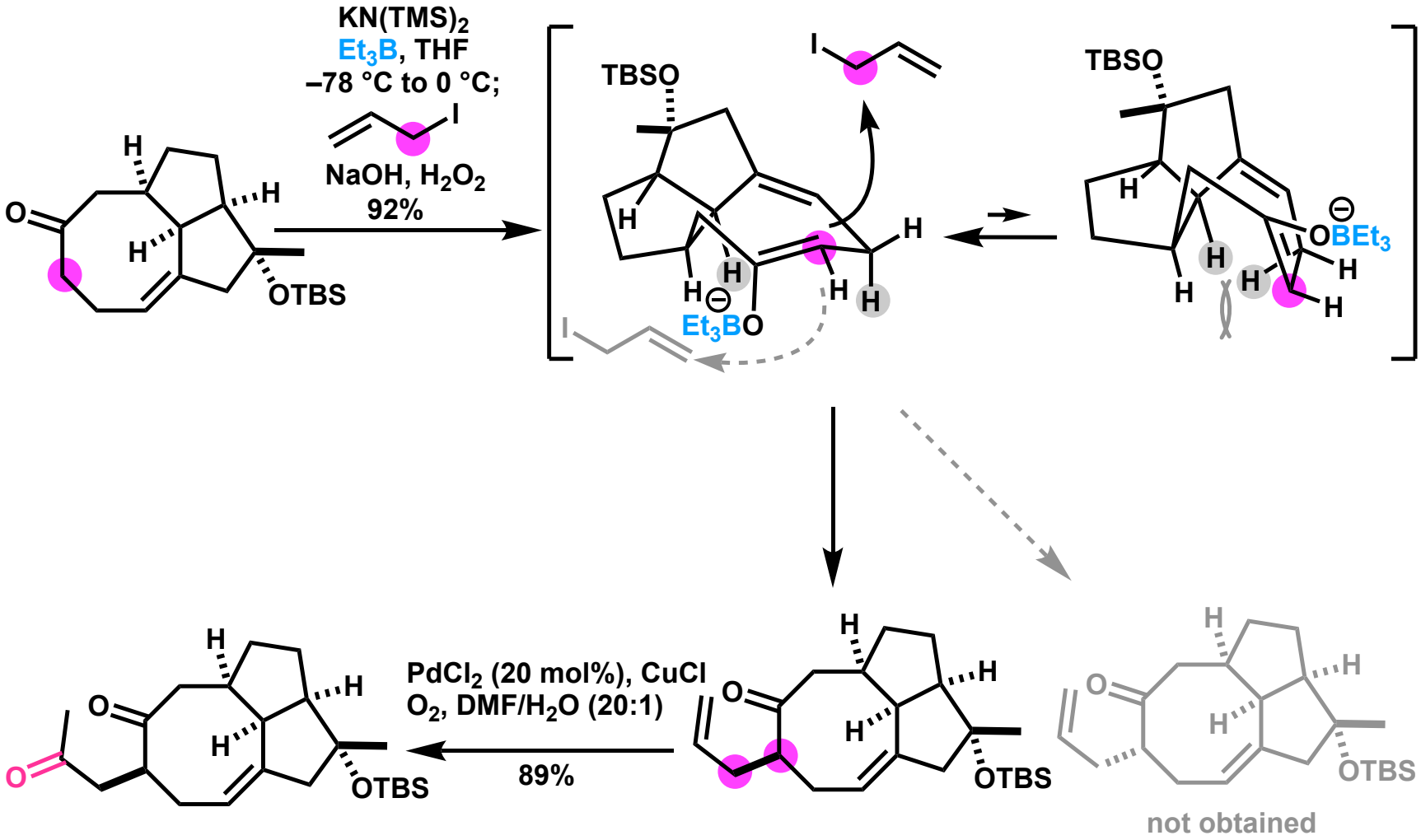
1) Ma T, Ma Y, Li B, Jia Y., *Angew Chem Int Ed Engl.* **2024**, *63* ,e202407215.

Rh-catalyzed [5+2+1] Cycloaddition



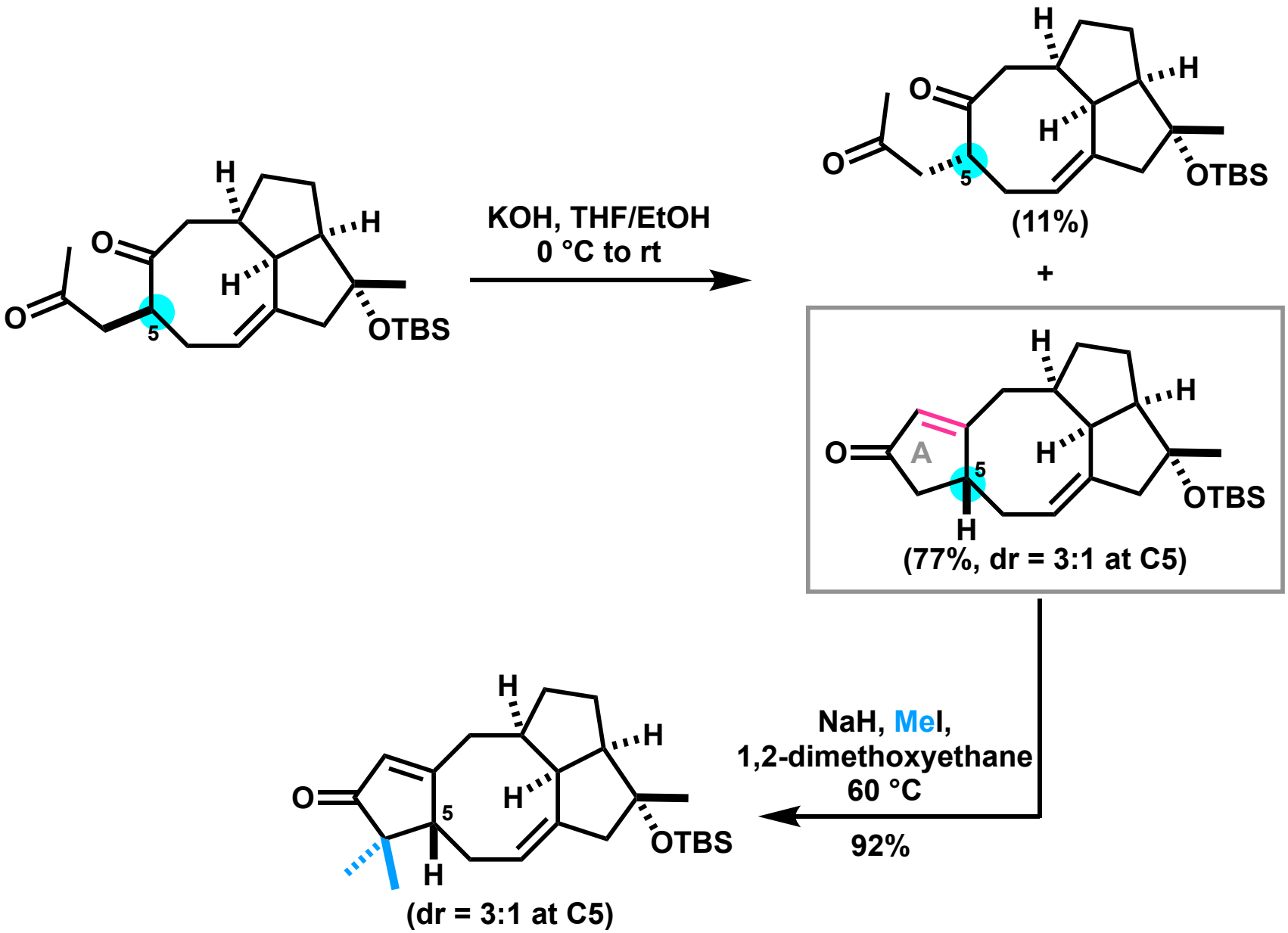
1) Ma T, Ma Y, Li B, Jia Y., *Angew Chem Int Ed Engl.* **2024**, *63* ,e202407215.
2) Y. Wang, W. Liao, Y. Wang, L. Jiao, Z.-X. Yu, *J. Am. Chem. Soc.* **2022**, *144*, 2624.

Construction of A-ring (1)



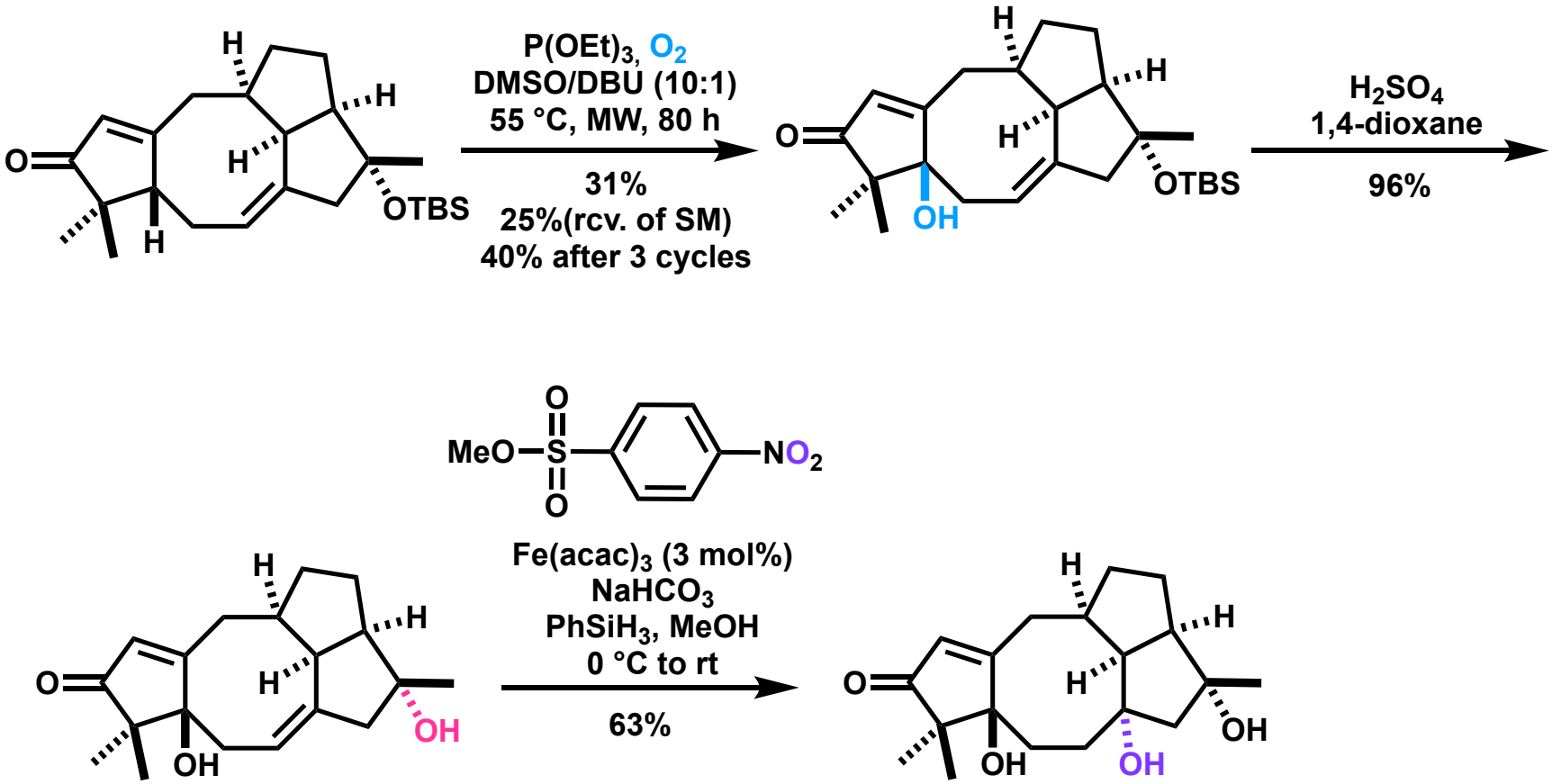
1) Ma T, Ma Y, Li B, Jia Y., *Angew Chem Int Ed Engl.* **2024**, *63* ,e202407215.

Construction of A-ring (2)



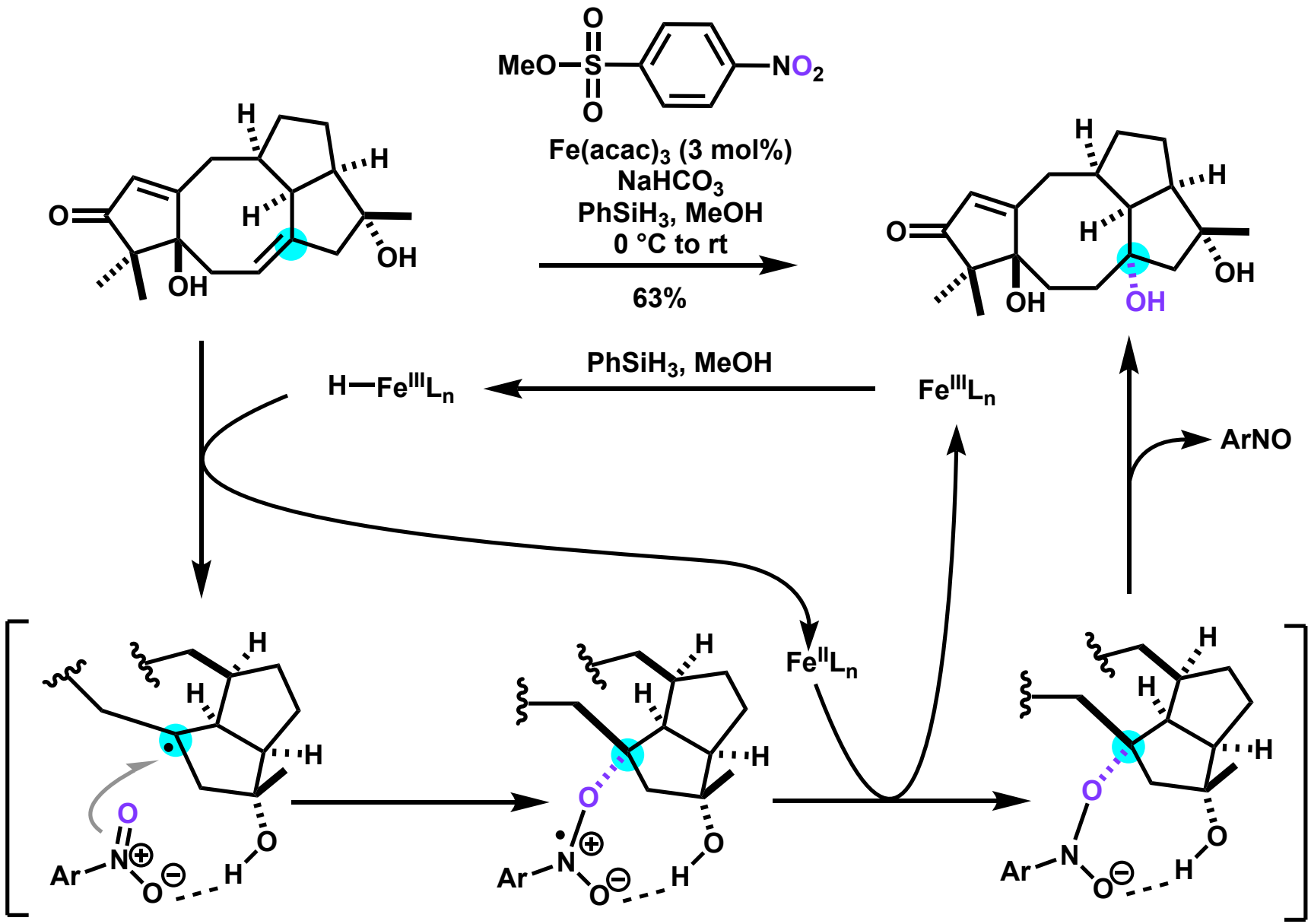
1) Ma T, Ma Y, Li B, Jia Y., *Angew Chem Int Ed Engl.* **2024**, *63* ,e202407215.

Synthesis of Triol



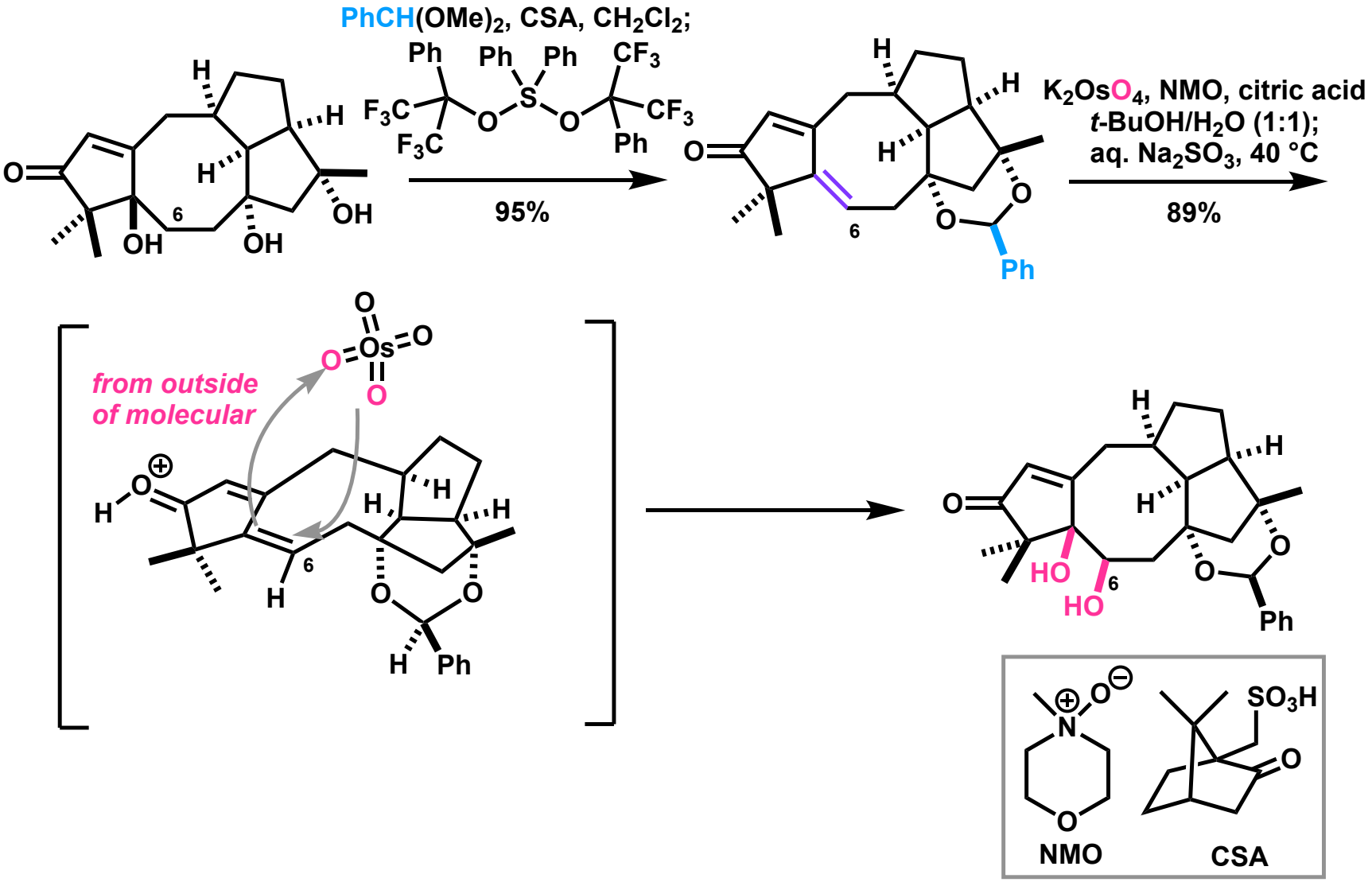
1) Ma T, Ma Y, Li B, Jia Y., *Angew Chem Int Ed Engl.* **2024**, *63* ,e202407215.

Mukaiyama Hydroxylation Using *p*-NsOMe



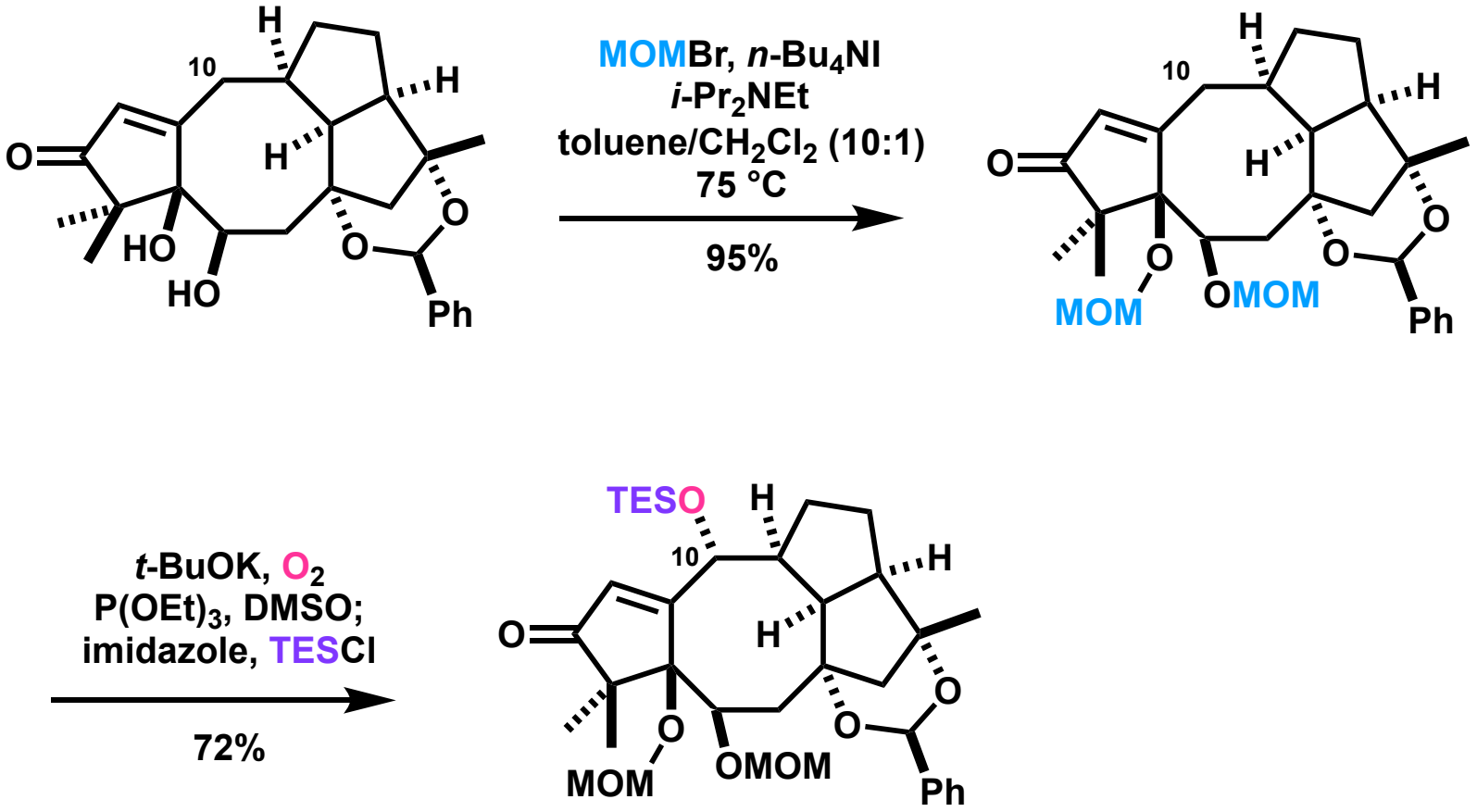
1) Ma T, Ma Y, Li B, Jia Y., *Angew Chem Int Ed Engl.* **2024**, *63* ,e202407215.
2) A. Bhunia, K. Bergander, C. G. Daniliuc, A. Studer, *Angew. Chem. Int. Ed.* **2021**, *60*, 8313.

Hydroxylation at C6



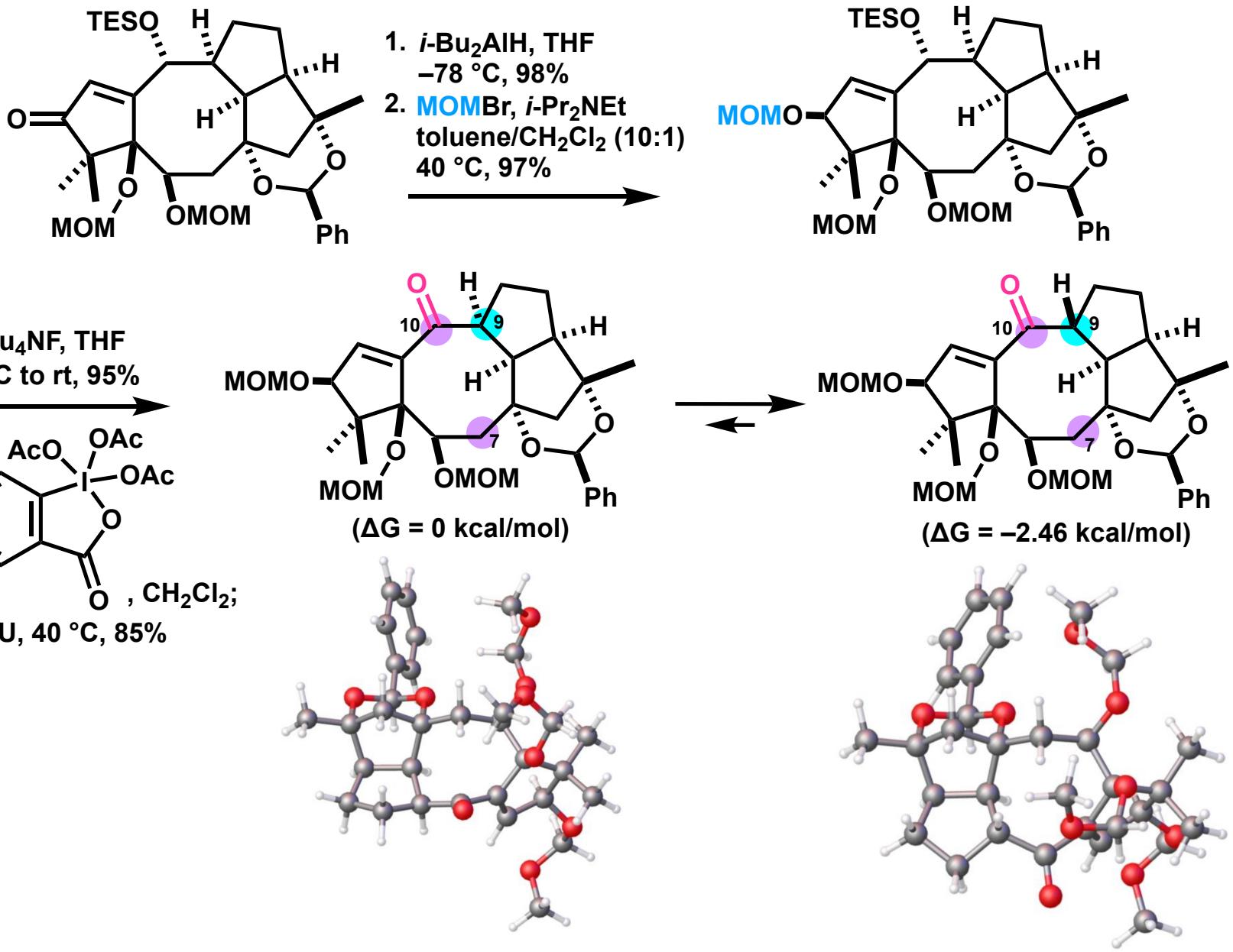
1) Ma T, Ma Y, Li B, Jia Y., *Angew Chem Int Ed Engl.* **2024**, *63* ,e202407215.
2) Aqeel A. Hussein, Nadhir N. A. Jafar, Yumiao Ma., *J. Org. Chem.* **2024**, *89*, 6892.

Hydroxylation at C10



1) Ma T, Ma Y, Li B, Jia Y., *Angew Chem Int Ed Engl.* **2024**, *63* ,e202407215.

Functionalization of Backbone (1)



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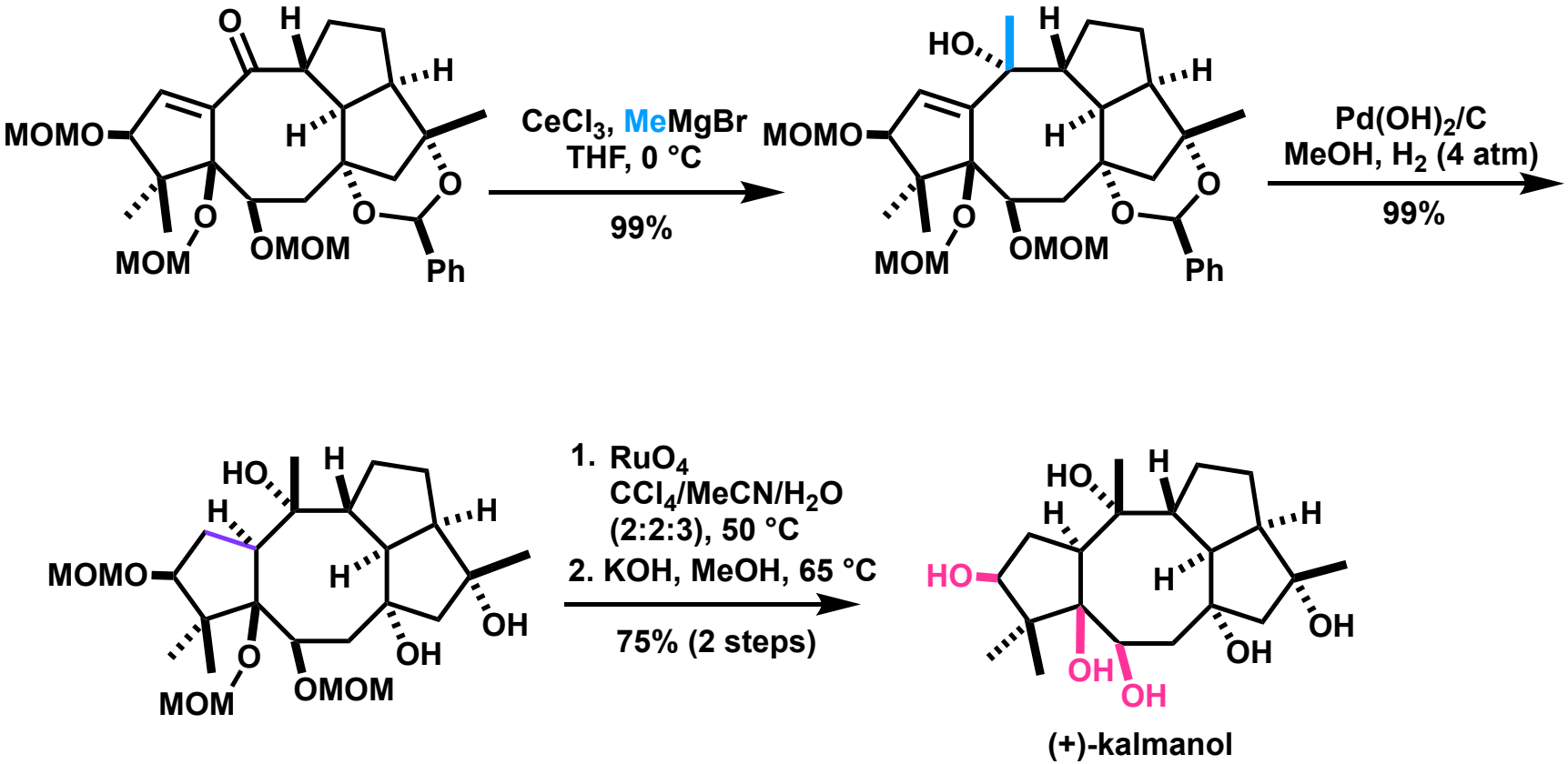
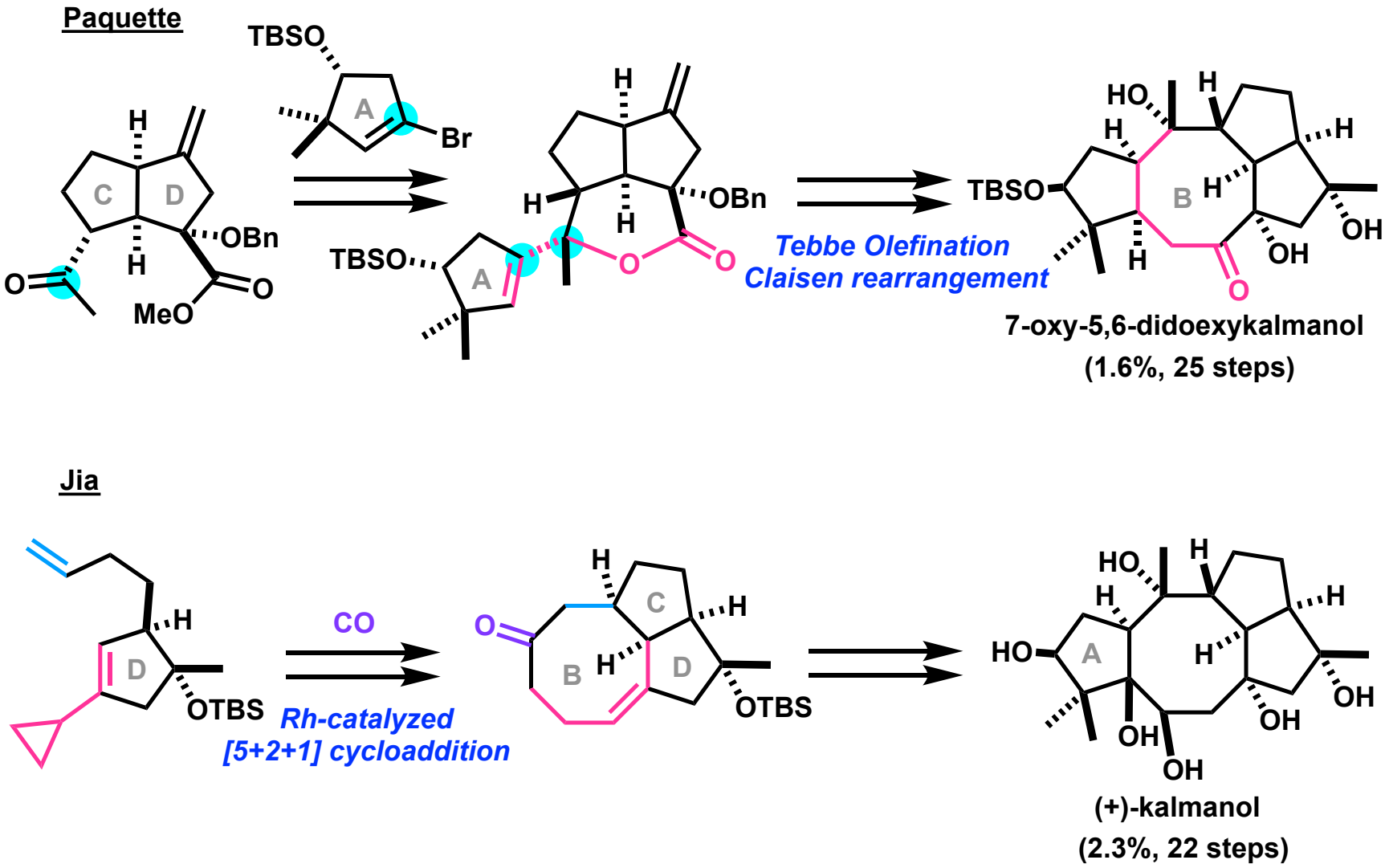
Functionalization of Backbone (2)



1) Ma T, Ma Y, Li B, Jia Y., *Angew Chem Int Ed Engl.* **2024**, *63* ,e202407215.

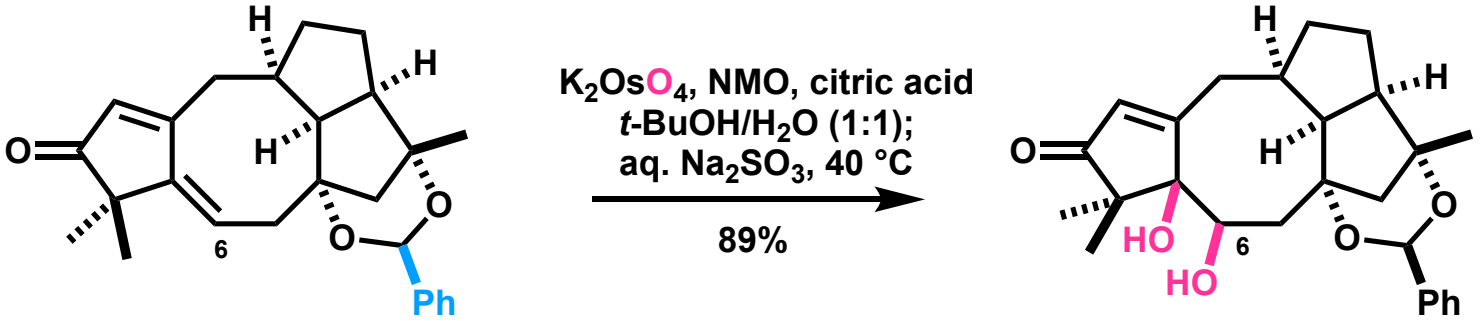
Summary

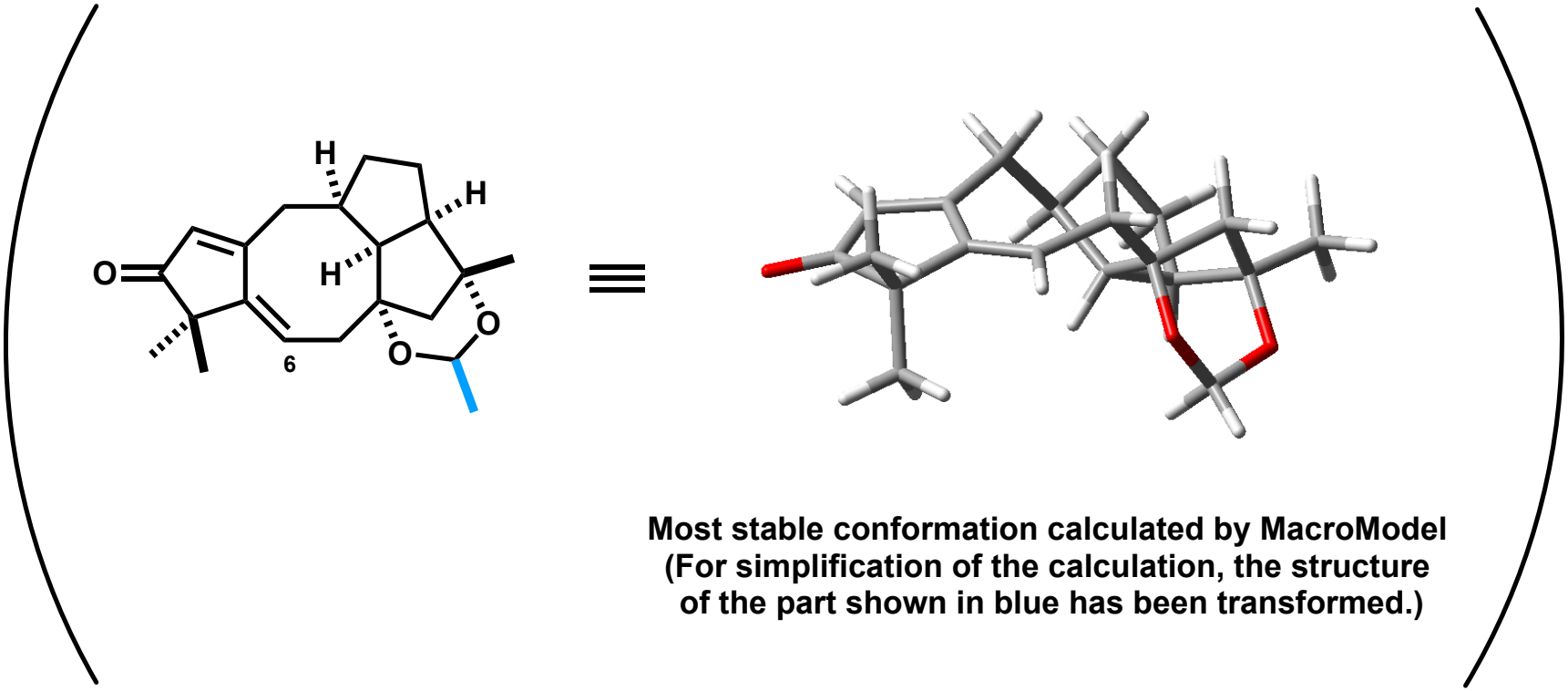


1) S. Borrelly, L. A. Paquette, *J. Am. Chem. Soc.* **1996**, *118*, 727.
2) Ma T, Ma Y, Li B, Jia Y., *Angew Chem Int Ed Engl.* **2024**, *63* ,e202407215.

Appendix

Stereoselectivity of Hydroxylation at C6





Most stable conformation calculated by MacroModel (For simplification of the calculation, the structure of the part shown in blue has been transformed.)

1) Ma T, Ma Y, Li B, Jia Y., *Angew Chem Int Ed Engl.* **2024**, *63* ,e202407215.
2) Aqeel A. Hussein, Nadhir N. A. Jafar, Yumiao Ma., *J. Org. Chem.* **2024**, *89*, 6892.