Total synthesis of Phomarol using a biomimetic S_N2' cyclization

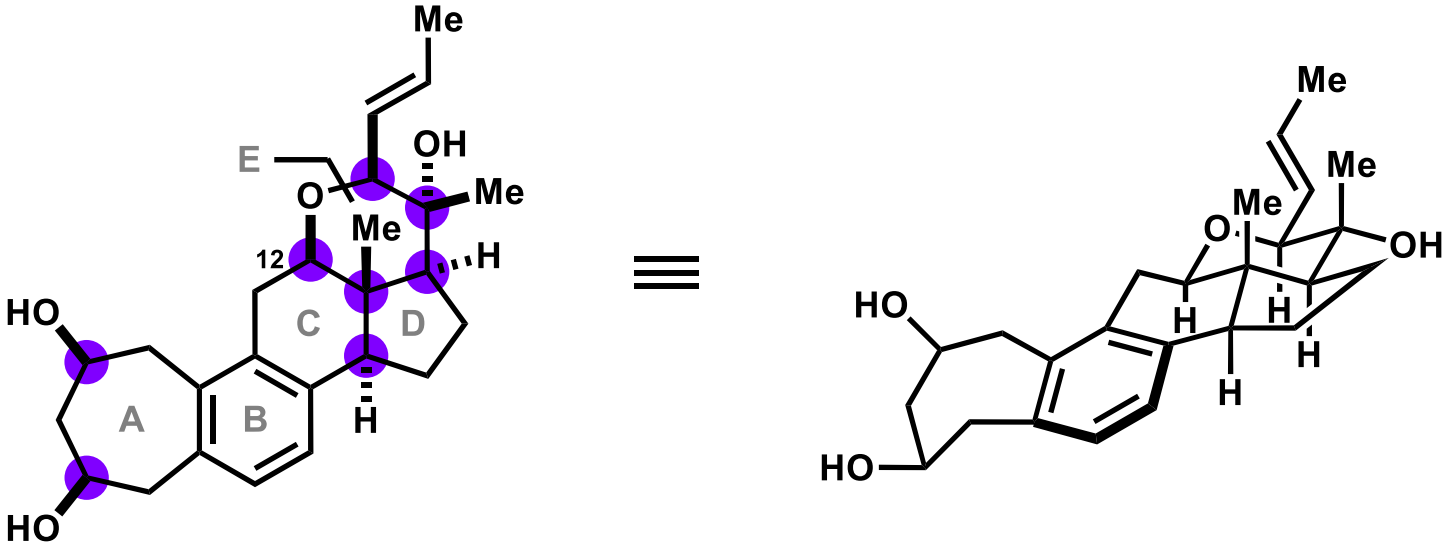
2023.6.17

D1 Yutaro Yamada

Contents

Contents

Phomarol



Isolation: from J08NF7 (fungal strain) of *Nemopilema nomurai* (jellyfish)[1)]

Biological activity: No biological activity reported.

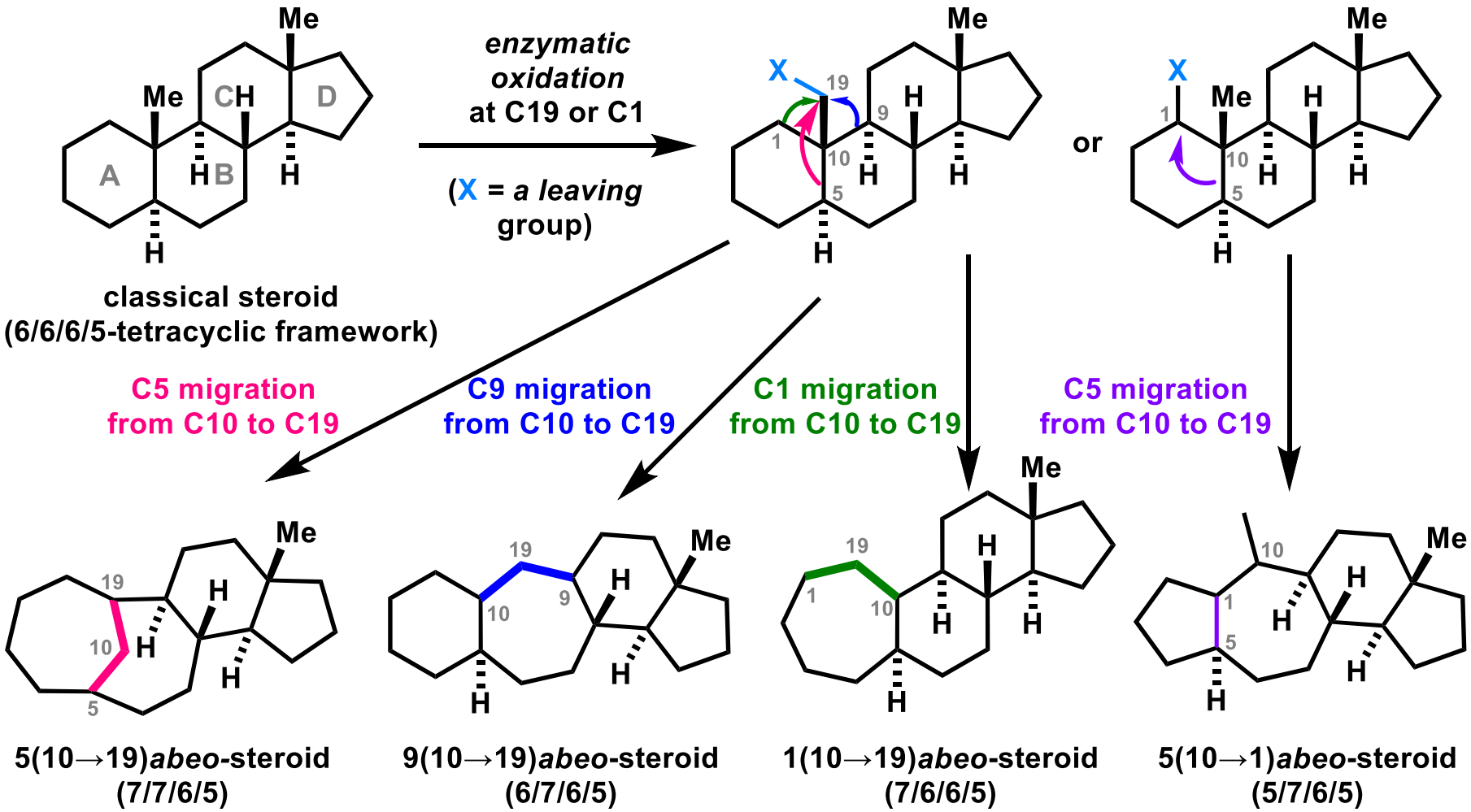
Structural features: 7/6/6/5/6-pentacyclic framework (C25 steroid), C12 oxidation, 8 stereocenters, cycloheptene-1,3-diol motif, aromatic B ring, densely functionalized tetrahydropyran ring (TPR)

Total synthesis of Phomarol

asymmetric: Li (2021)[2)], Gui (2023)[3)]

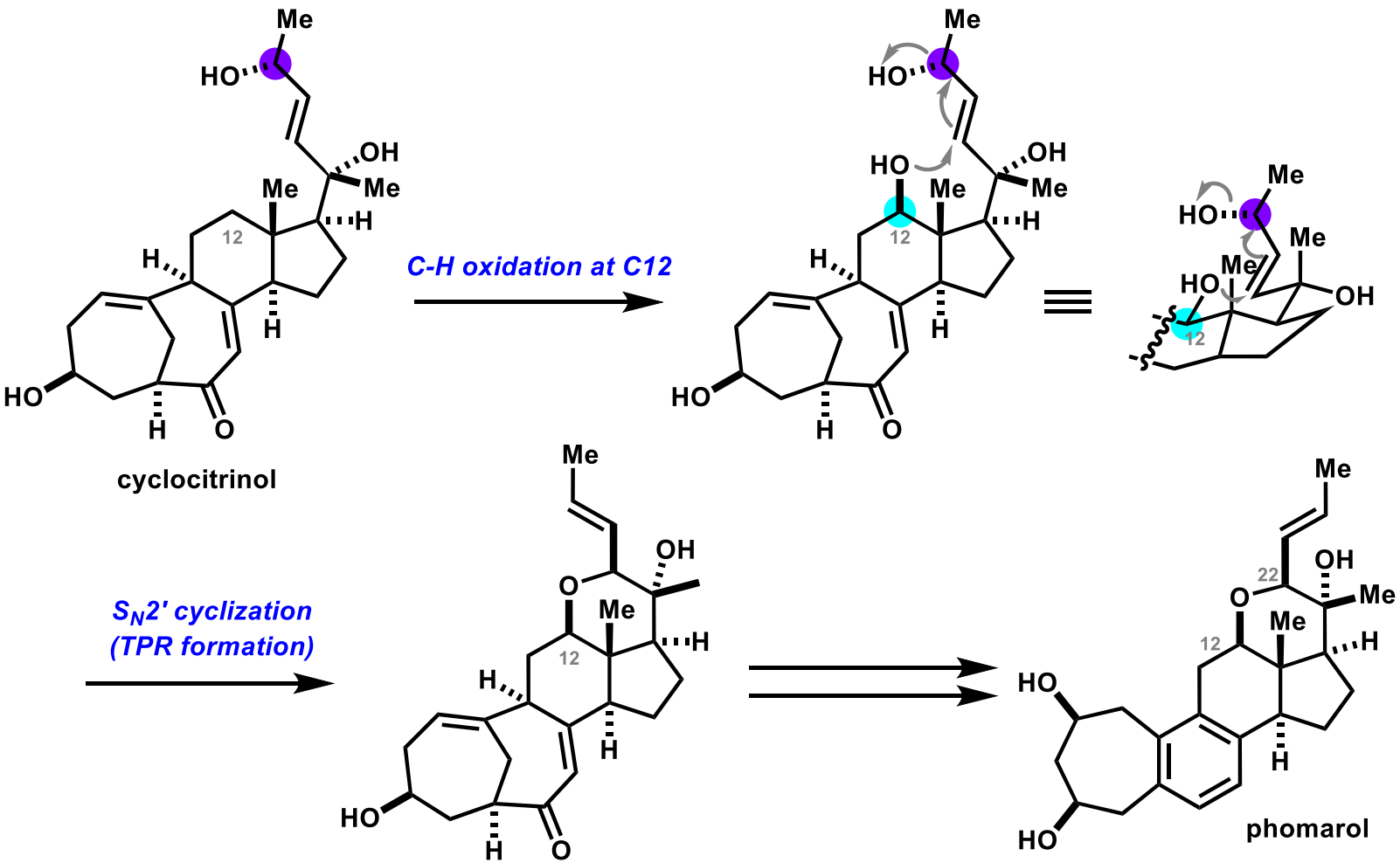
1) Kim. E. L.; Li. J. L.; Hong. J.; Yoon. W. D.; Kim. H. S.; Liu. Y.; Wei. X.; Jung. J. H., *Tetrahedron Letters*, **2016**, *57*, 2803.
2) Fan. J. H.; Wang. J. J.; Li. F.; Wang. G.; Guo. Q.; Chung. L. W.; Li. C. C., *CCS Chem.* **2021**, *3*, 348.
3) Wang. X.; Huang. G.; Wang. Y.; Gui. J., *J. Am. Chem. Soc.* **2023**, *145,* 9354.

Biosynthetic pathway (core skeleton)



1) Wang. Y.; Tian. H.; Gui. J., *J. Am. Chem. Soc.* **2021**, *143*, 19576.
2) Wang. X.; Huang. G.; Wang. Y.; Gui. J., *J. Am. Chem. Soc.* **2023**, *145*, 9354.

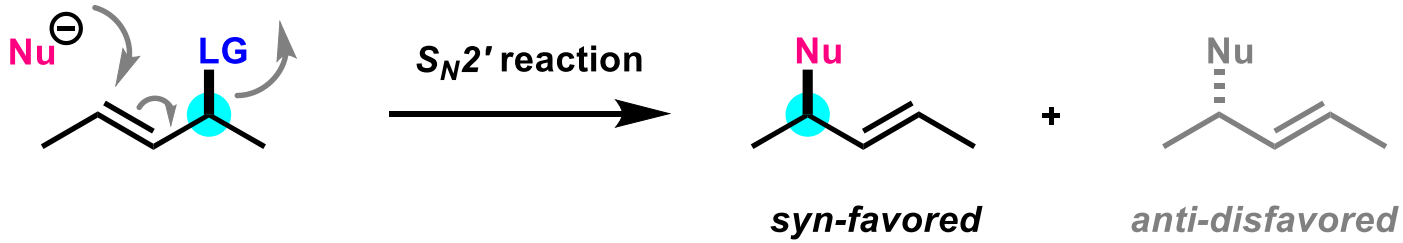
Biosynthetic pathway (side chain)



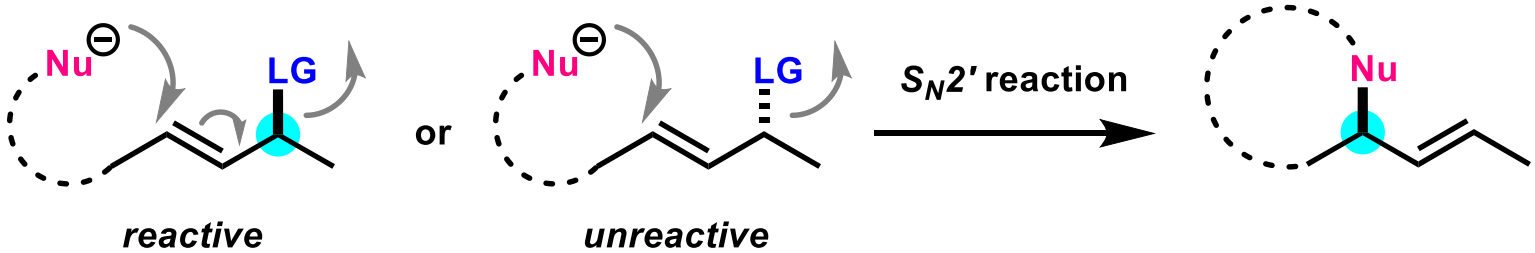
1) Kim. E. L.; Li. J. L.; Hong. J.; Yoon. W. D.; Kim. H. S.; Liu. Y.; Wei. X.; Jung. J. H., *Tetrahedron Letters*, **2016**, *57*, 2803.
2) Wang. X.; Huang. G.; Wang. Y.; Gui. J., *J. Am. Chem. Soc.* **2023**, *145,* 9354.

S_N2' reaction

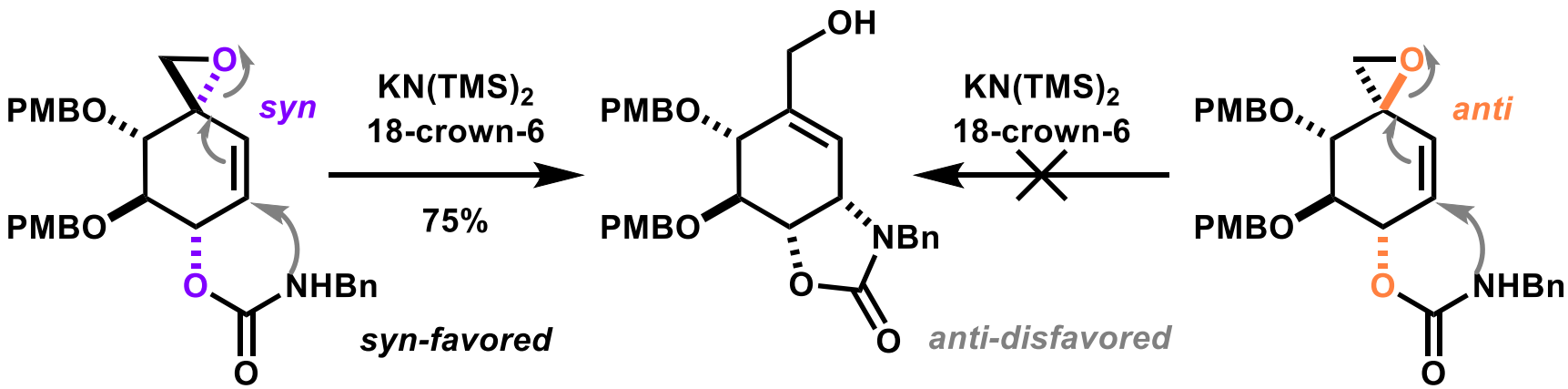
intermolecular S_N2' reaction



intramolecular S_N2' reaction

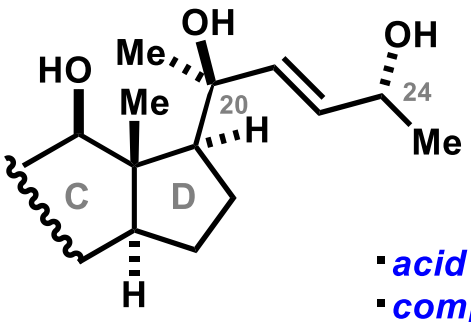


elucidation of the sterospecificity of the S_N2' reaction

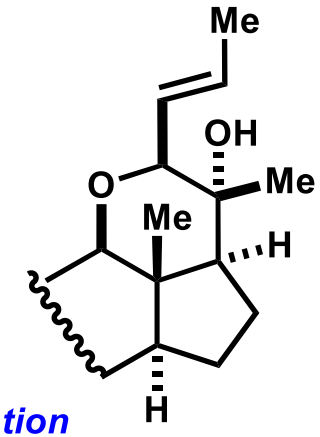


1) Kyo Park. T.; Danishefsky. S. J., *Tetrahedron Lett.* **1994**, *35*, 2667.
2) Wang. X.; Huang. G.; Wang. Y.; Gui. J., *J. Am. Chem. Soc.* **2023**, *145*, 9354.

Challenging points



biomimetic S_N2' cyclization

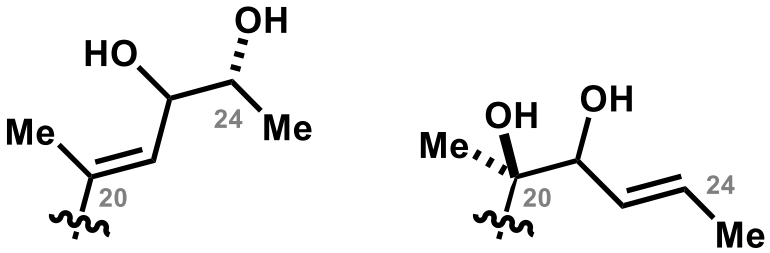


- *acid lability*
- *competition with vinyl epoxide formation*
- *undefined stereoelectronic preference*
- *unknown synthetic feasibility*

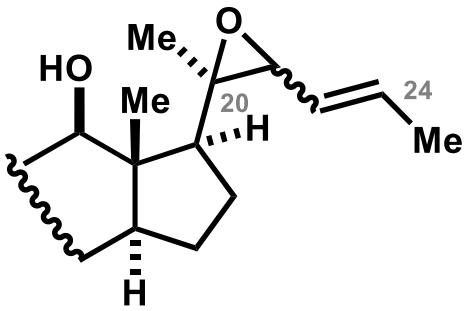
possible side products

dehydration

1,3-rearrangements



vinyl epoxide formation



1) Wang. Y.; Ju. W.; Tian. H.; Sun. S.; Li. X.; Tian. W.; Gui. J., *J. Am. Chem. Soc.* **2019**, *141*, 5021.
2) Wang. X.; Huang. G.; Wang. Y.; Gui. J., *J. Am. Chem. Soc.* **2023**, *145,* 9354.

Introduction of Prof. Li and Prof. Gui

Prof. Chuang Chuang Li[1)]

2001 B.S. @China Agricultural University (Prof. Dao-quan Wang)
2006 Ph.D. @Peking University (Prof. Zhen Yang)
2006- Postdoctoral associate
2008 @The Scripps Research Institute (Prof. Phil S. Baran)
2008- Associate Professor @Peking University
2014- Research Professor @Southern University of Science and Technology
2018- Full Professor @ Southern University of Science and Technology

Research interests:
development of novel synthetic methodology, chemical biology and total synthesis of biologically active and structurally interesting natural products

Prof. Jinghan Gui[2)]

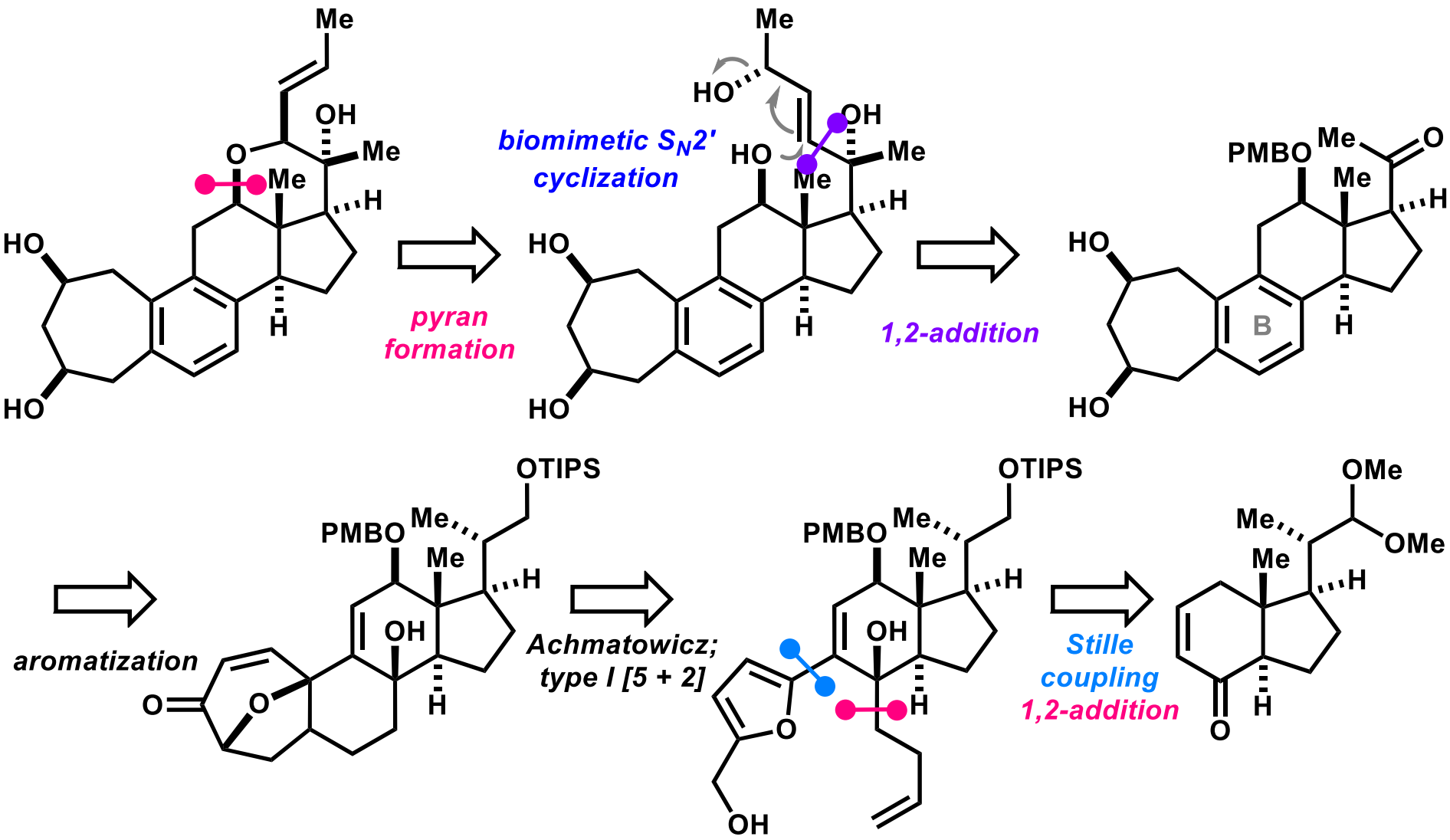
2007 B.S. @Anhui Normal University (Prof. Yimin Hu)
2012 Ph.D. @Shanghai Institute of Organic Chemistry (Prof. Weisheng Tian)
2012- Research Assistant @Shanghai Institute of Organic Chemistry
2013- Postdoctoral Associate
2016 @The Scripps Research Institute (Prof. Phil S. Baran)
2016- Professor @Shanghai Institute of Organic Chemistry

Research interests:
explore bioinspired strategic transformations, development of novel synthetic methodology

1) https://www.x-mol.com/groups/li-chuangchuang
2) http://guigroup.sioc.ac.cn/gui_group/prof.html

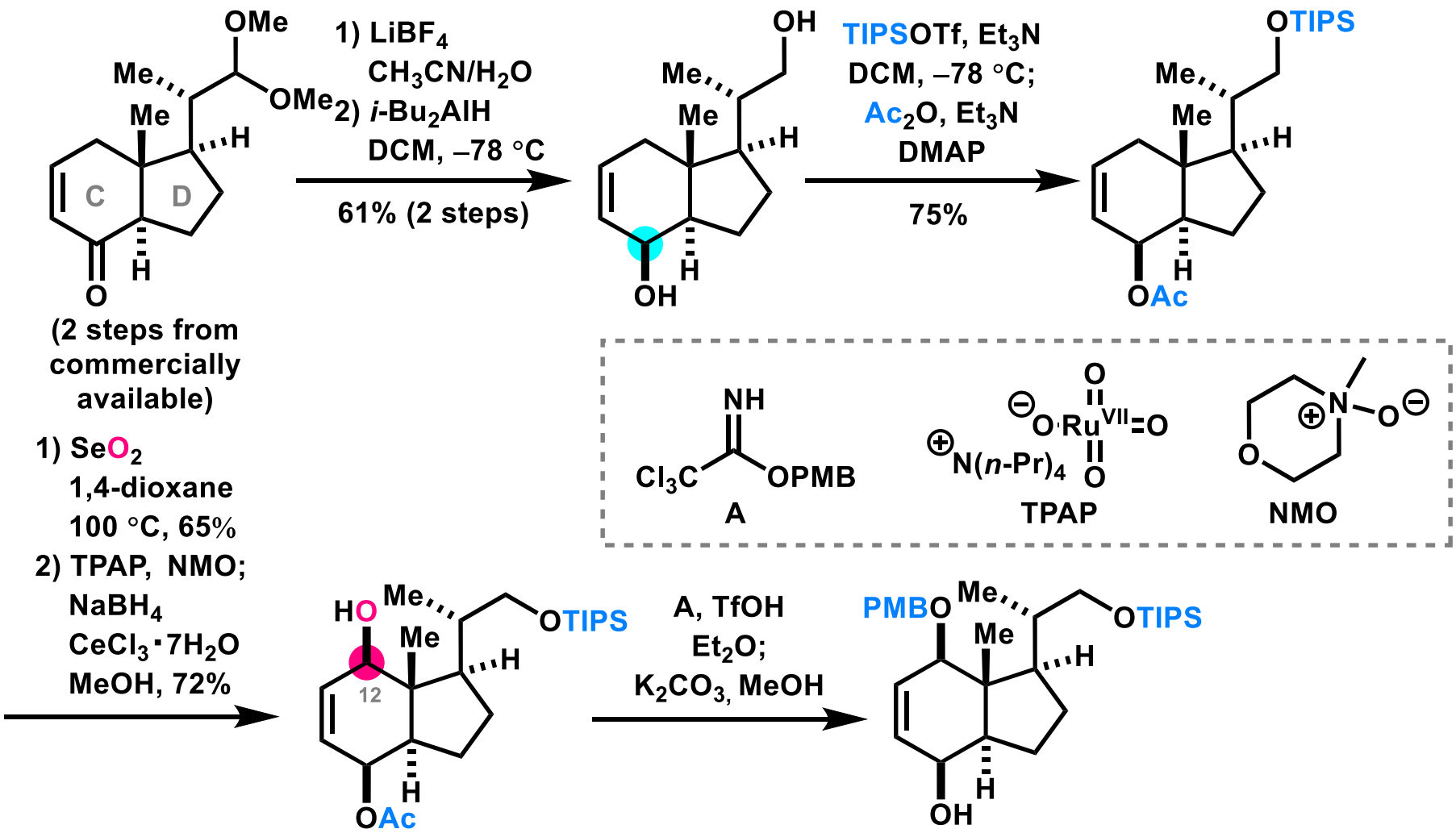
Contents

Retrosynthetic analysis



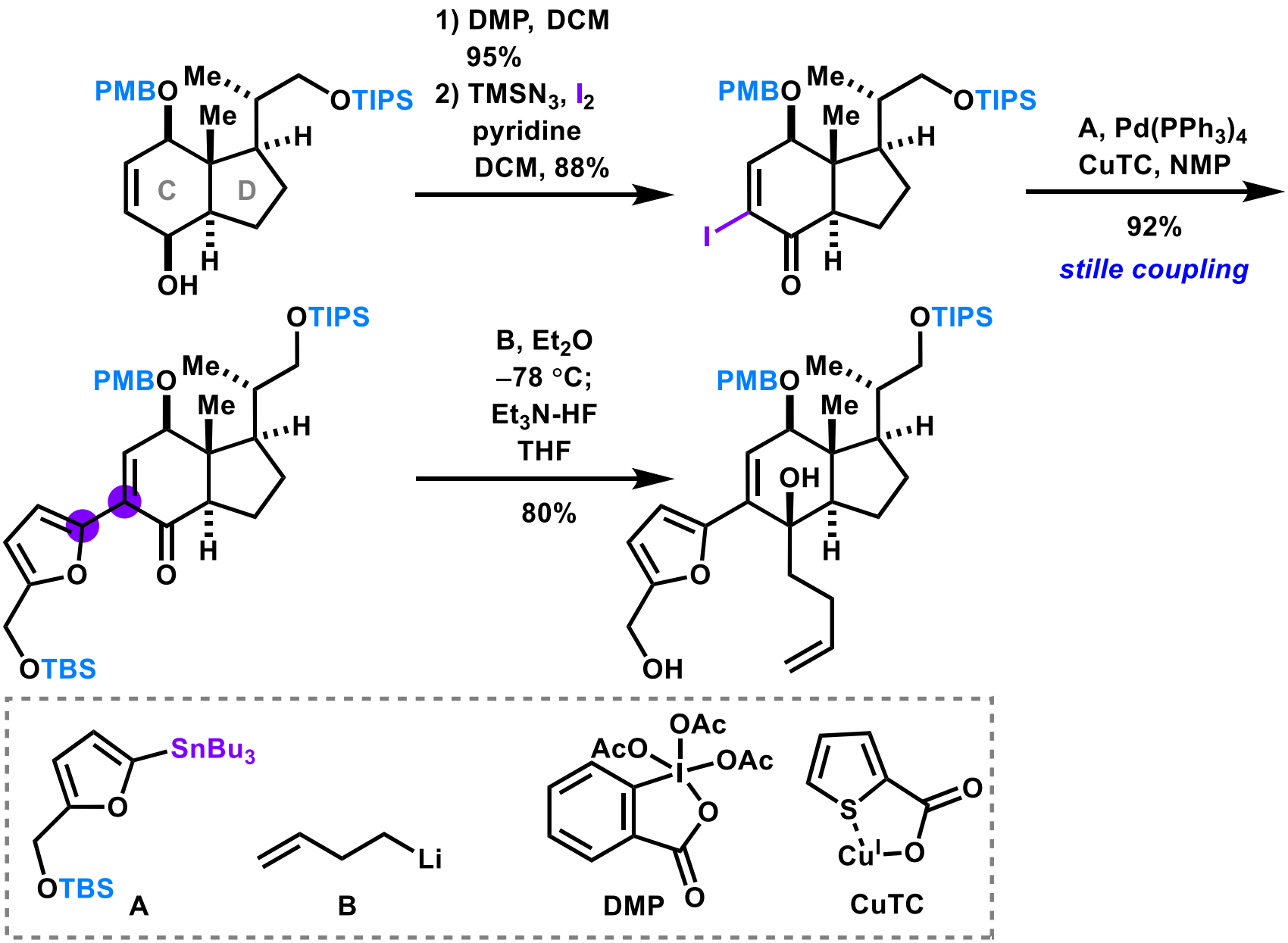
1) Fan. J. H.; Wang. J. J.; Li. F.; Wang. G.; Guo. Q.; Chung. L. W.; Li. C. C., *CCS Chem.* **2021**, *3*, 348.

C-H oxidation at C12



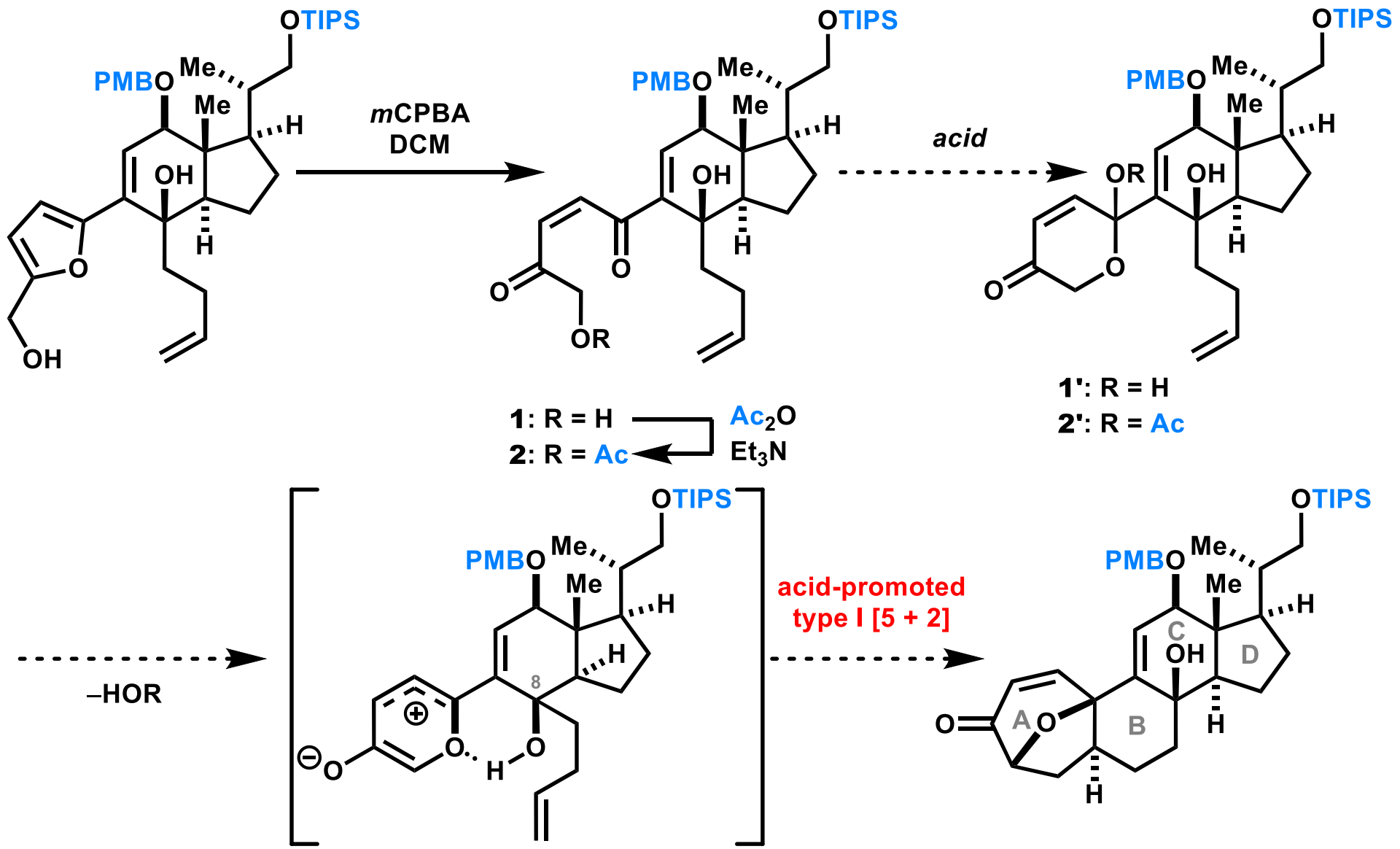
1) Fan. J. H.; Wang. J. J.; Li. F.; Wang. G.; Guo. Q.; Chung. L. W.; Li. C. C., *CCS Chem.* **2021**, *3*, 348.

Synthesis of furfuryl alcohol for [5+2] cycloaddition



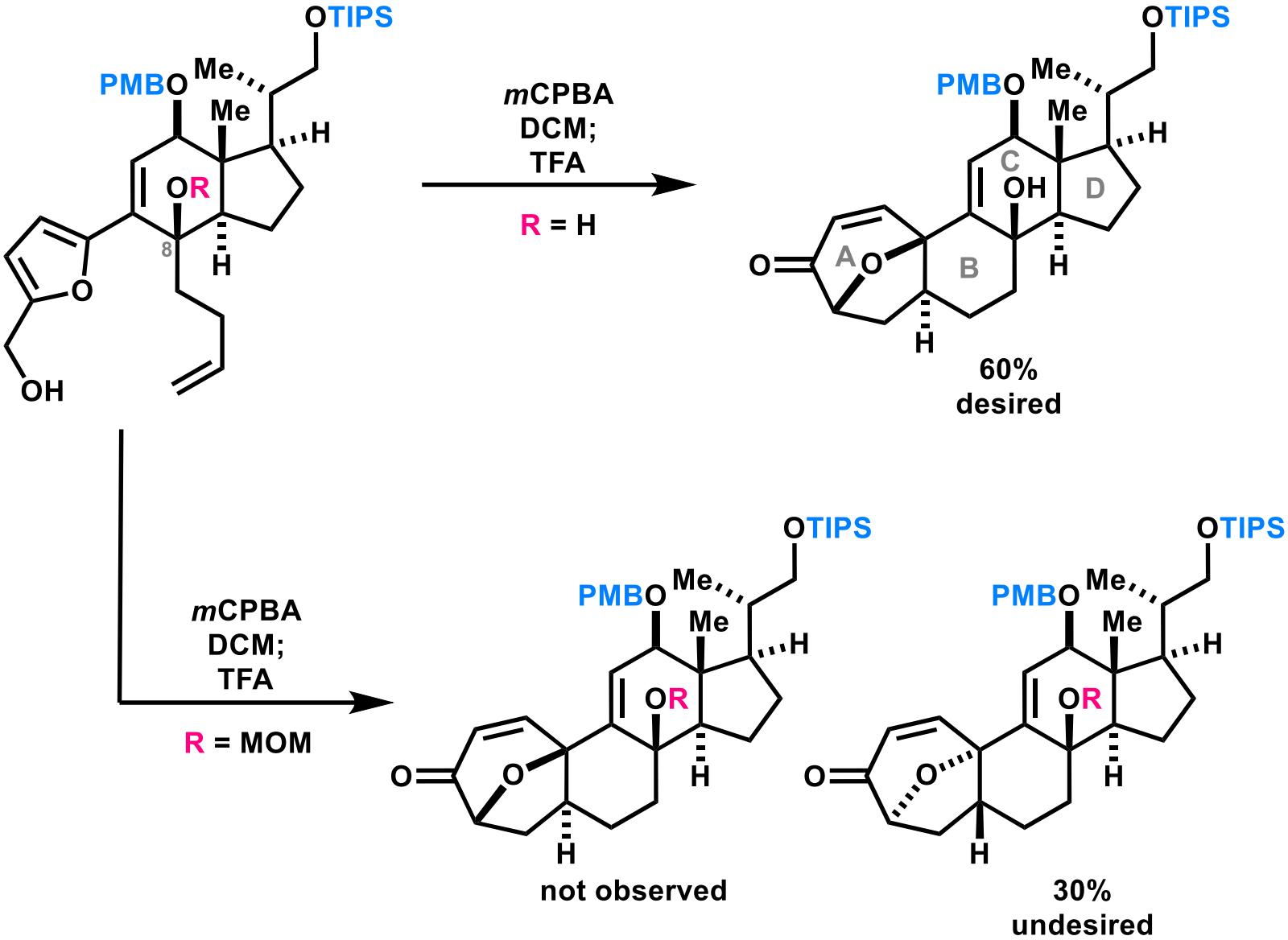
1) Fan. J. H.; Wang. J. J.; Li. F.; Wang. G.; Guo. Q.; Chung. L. W.; Li. C. C., *CCS Chem.* **2021**, *3*, 348.

Plan of [5+2] cycloaddition



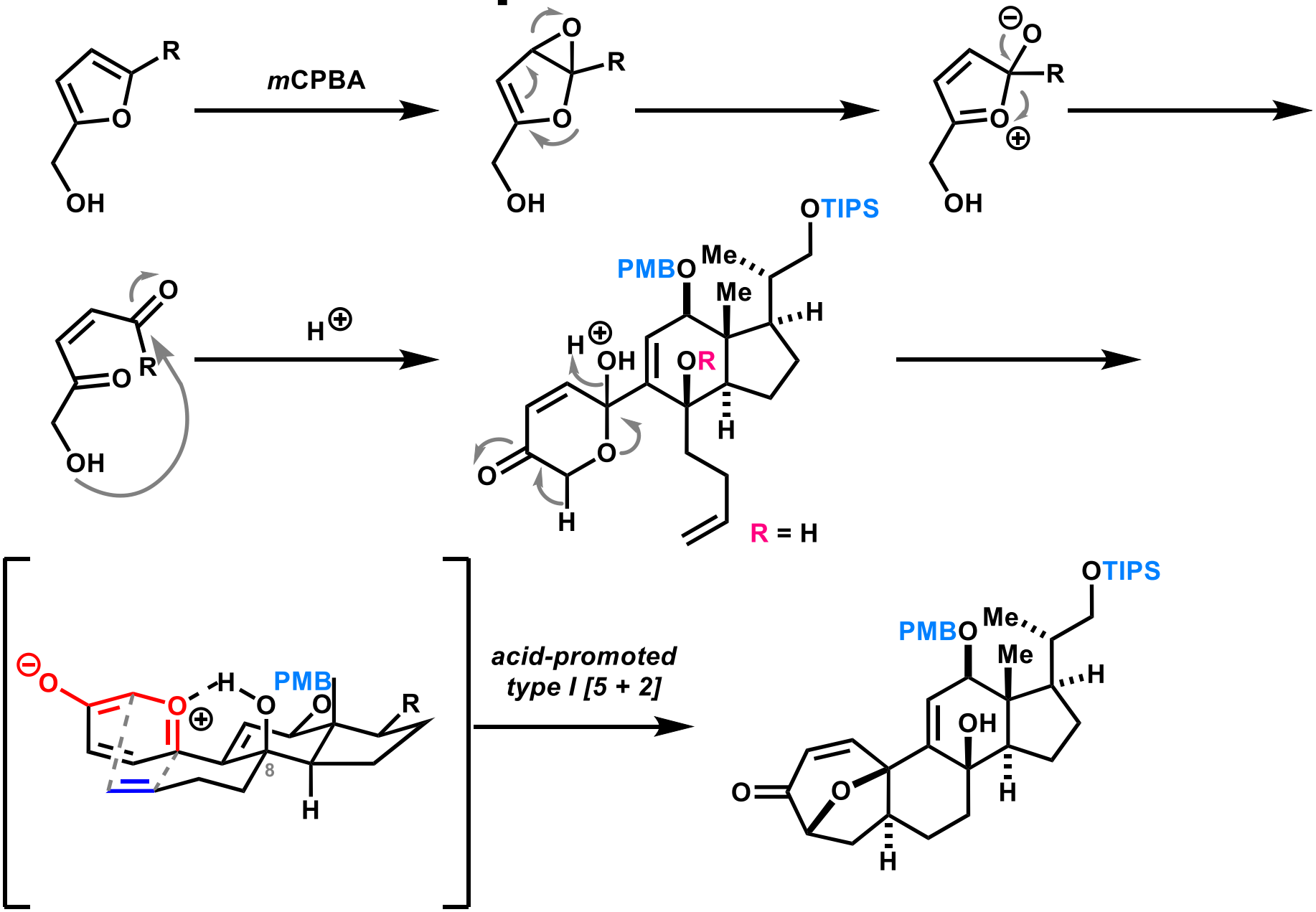
1) Fan. J. H.; Wang. J. J.; Li. F.; Wang. G.; Guo. Q.; Chung. L. W.; Li. C. C., *CCS Chem.* **2021**, *3*, 348.

[5+2] Cycloaddition



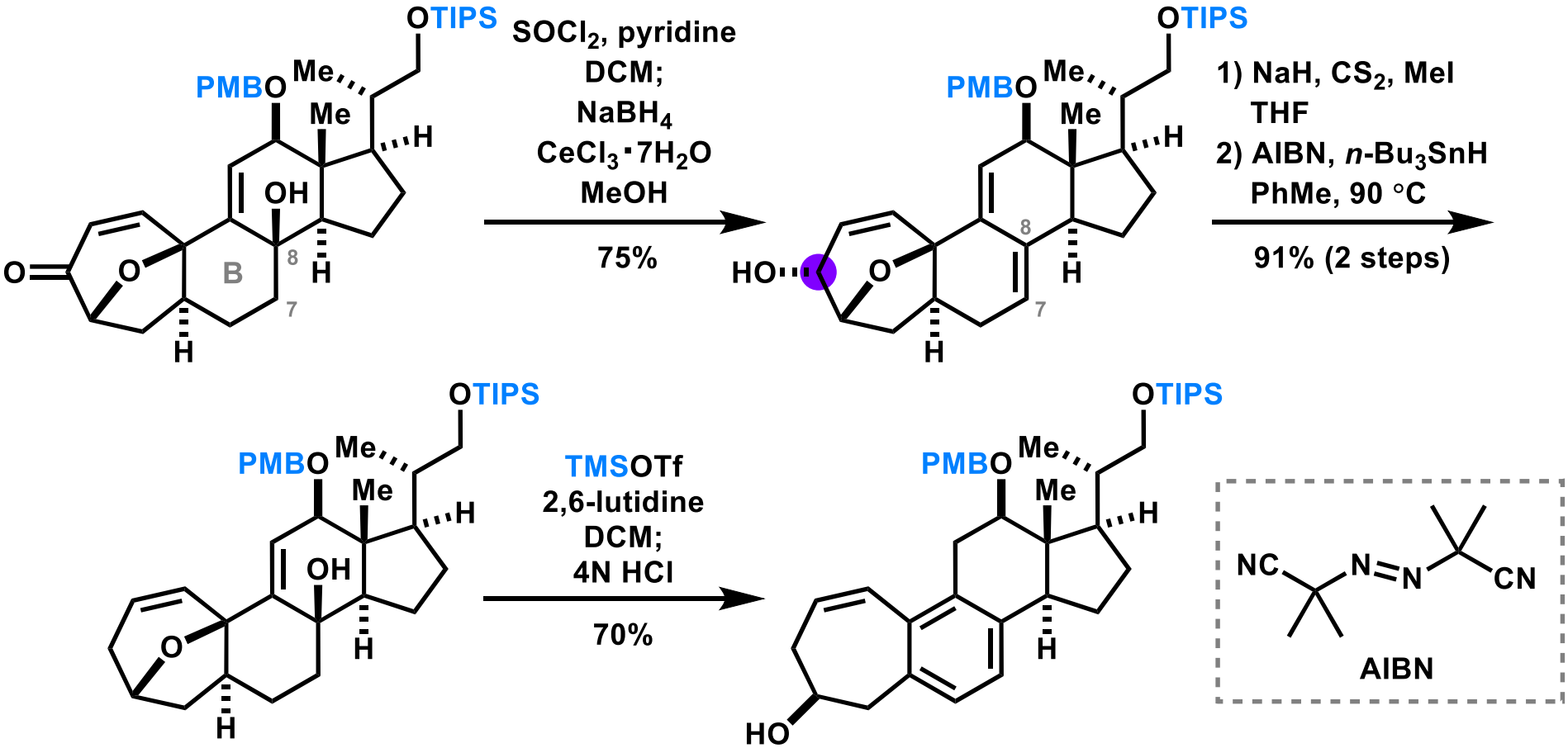
1) Fan. J. H.; Wang. J. J.; Li. F.; Wang. G.; Guo. Q.; Chung. L. W.; Li. C. C., *CCS Chem.* **2021**, *3*, 348.

Proposed mechanism



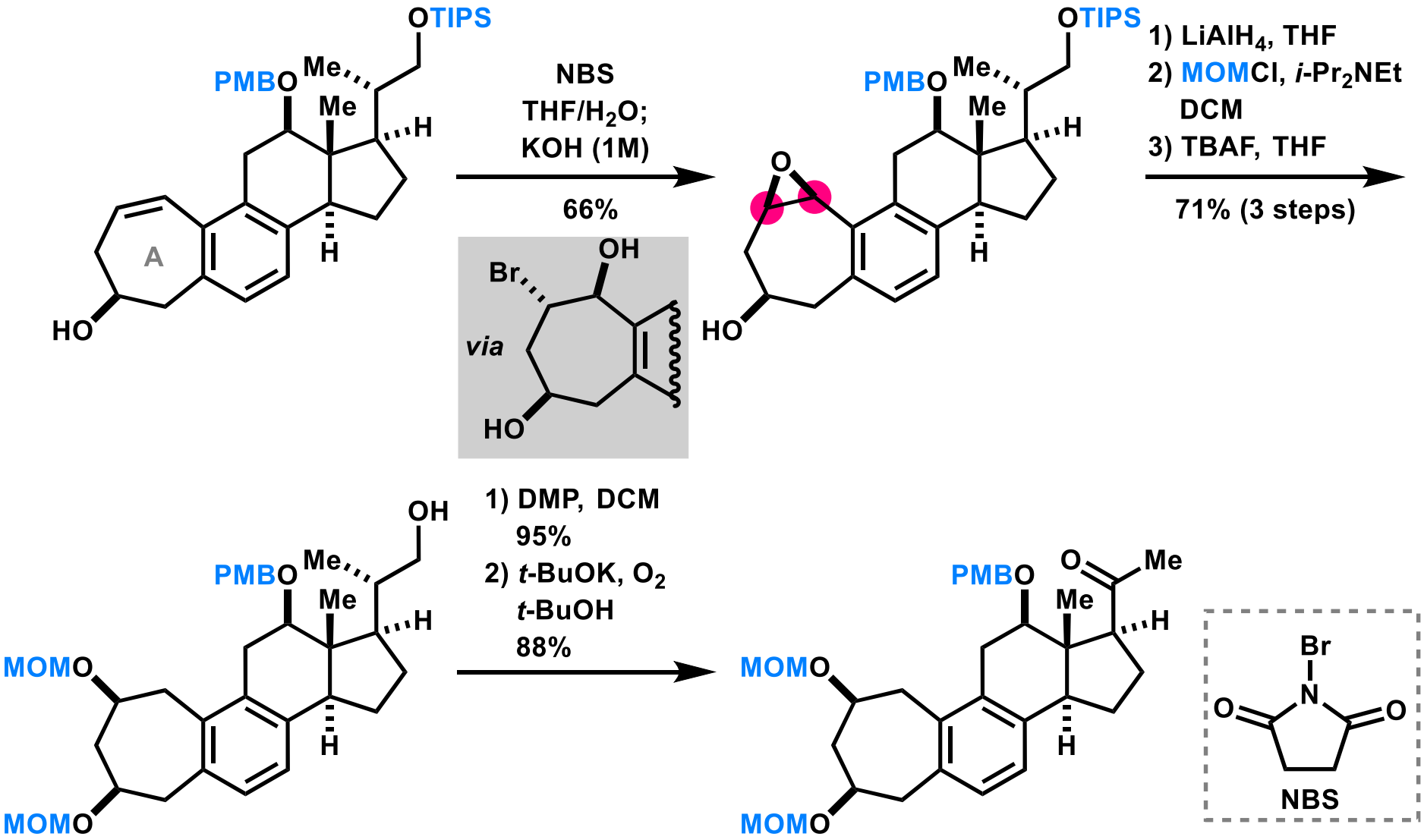
1) Fan. J. H.; Wang. J. J.; Li. F.; Wang. G.; Guo. Q.; Chung. L. W.; Li. C. C., *CCS Chem.* **2021**, *3*, 348.

Synthesis of 7/6/6/5-framework for TPR formation (1)



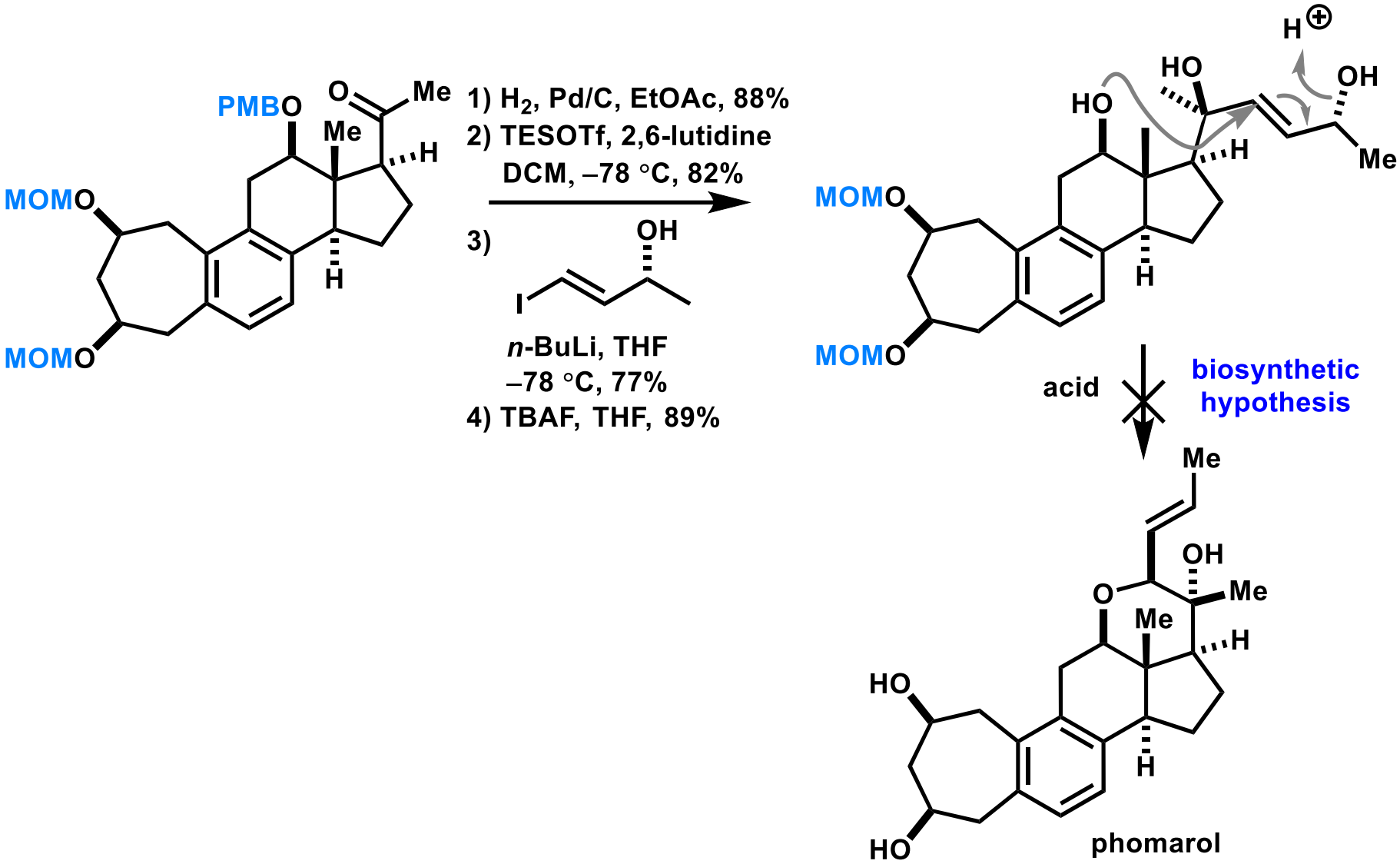
1) Fan. J. H.; Wang. J. J.; Li. F.; Wang. G.; Guo. Q.; Chung. L. W.; Li. C. C., *CCS Chem.* **2021**, *3*, 348.

Synthesis of 7/6/6/5-framework for TPR formation (2)



1) Fan. J. H.; Wang. J. J.; Li. F.; Wang. G.; Guo. Q.; Chung. L. W.; Li. C. C., *CCS Chem.* **2021**, *3*, 348.

Total synthesis of phomarol



1) Fan. J. H.; Wang. J. J.; Li. F.; Wang. G.; Guo. Q.; Chung. L. W.; Li. C. C., *CCS Chem.* **2021**, *3*, 348.

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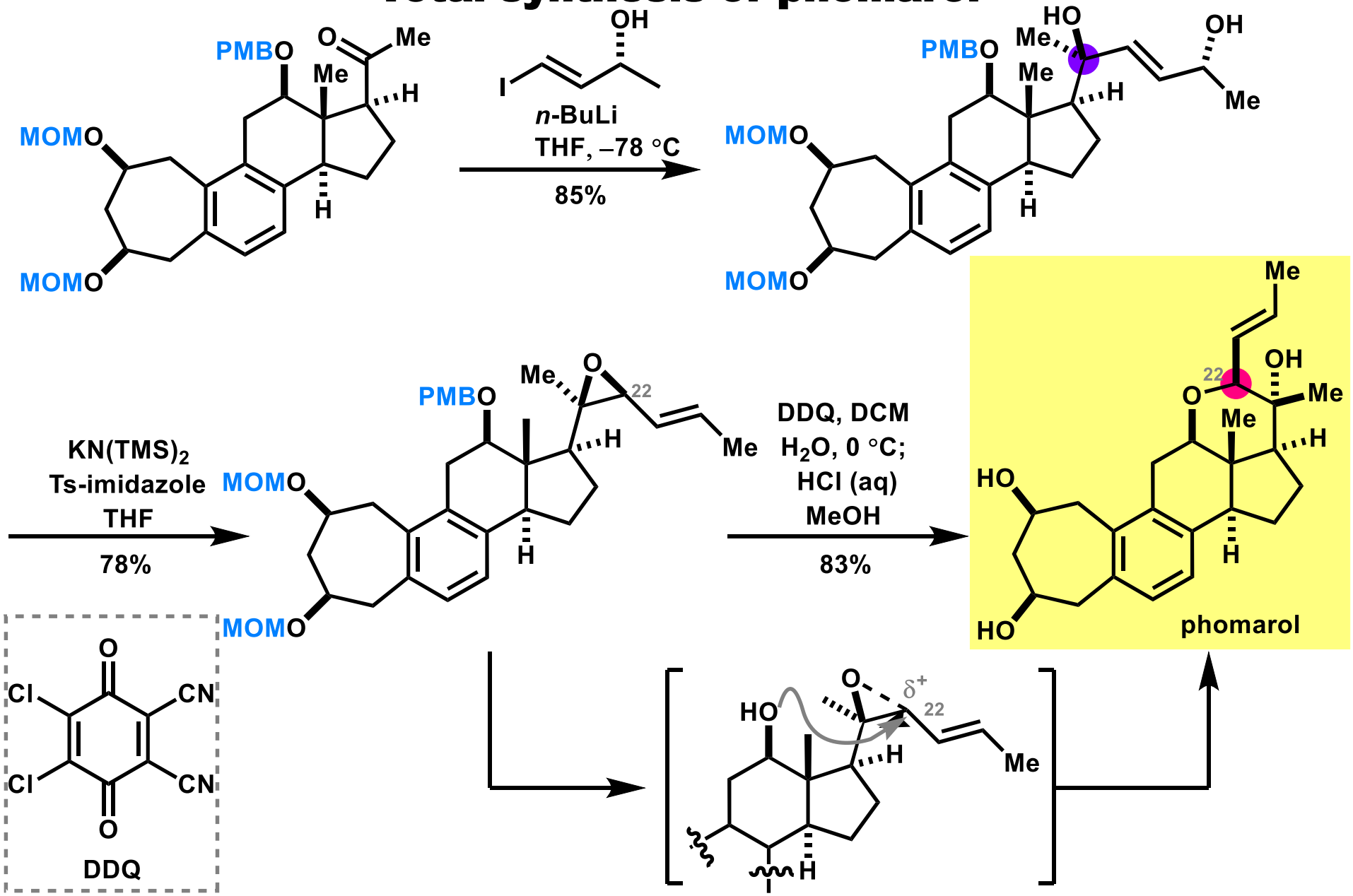

1) Fan. J. H.; Wang. J. J.; Li. F.; Wang. G.; Guo. Q.; Chung. L. W.; Li. C. C., *CCS Chem.* **2021**, *3*, 348.

Contents

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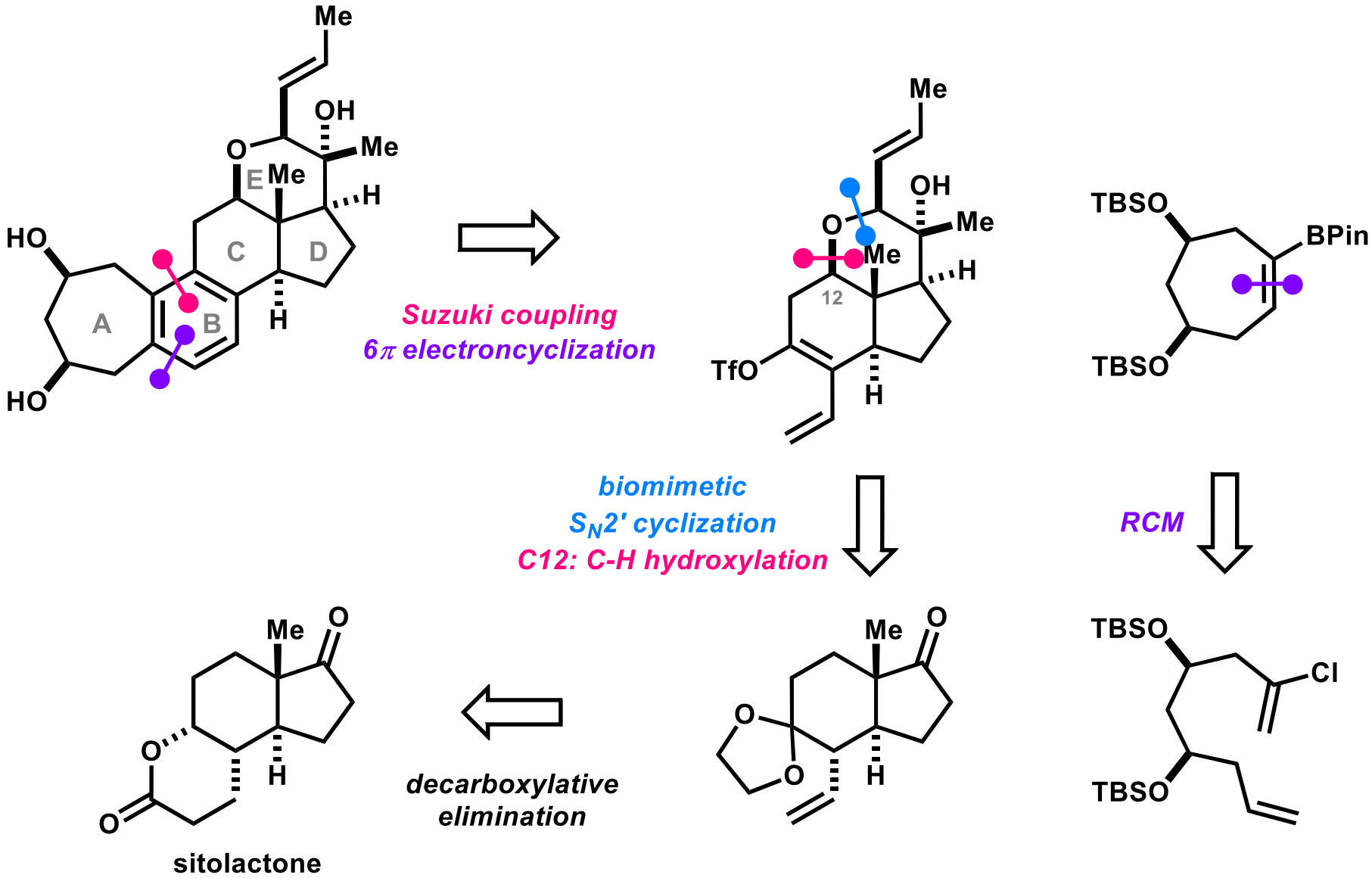
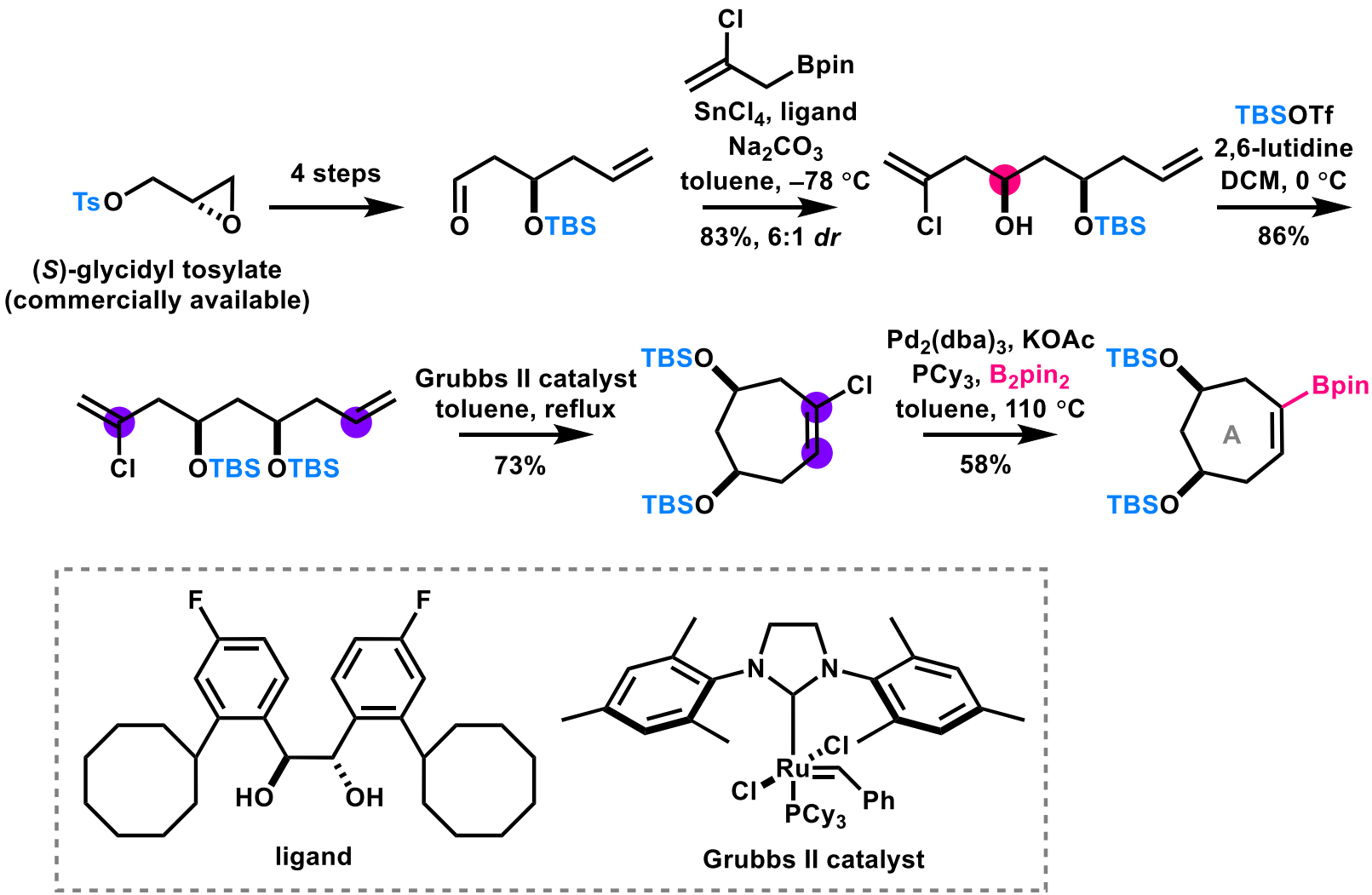


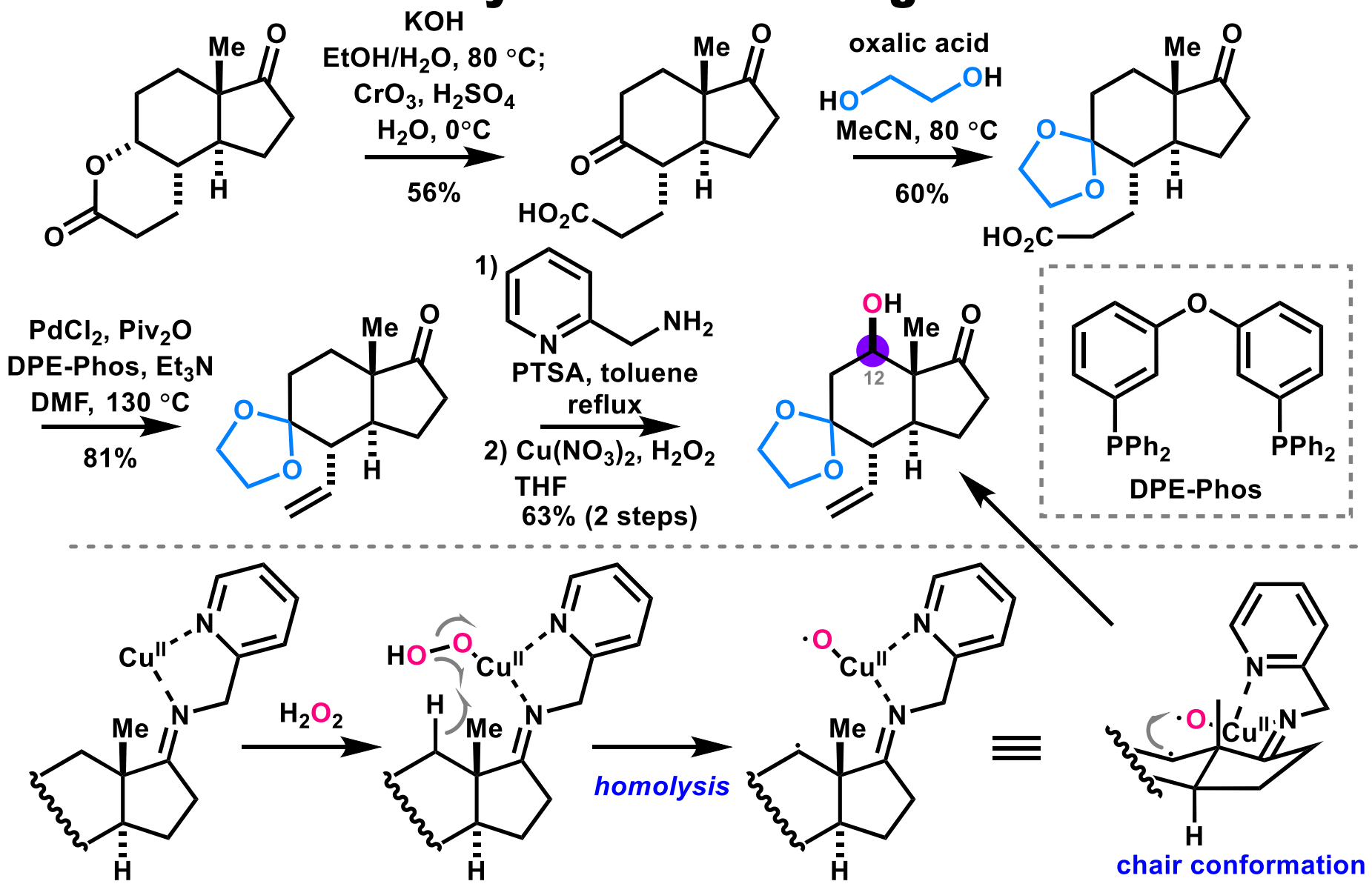
1) Wang. X.; Huang. G.; Wang. Y.; Gui. J., *J. Am. Chem. Soc.* **2023**, *145*, 9354.

Synthesis of A ring



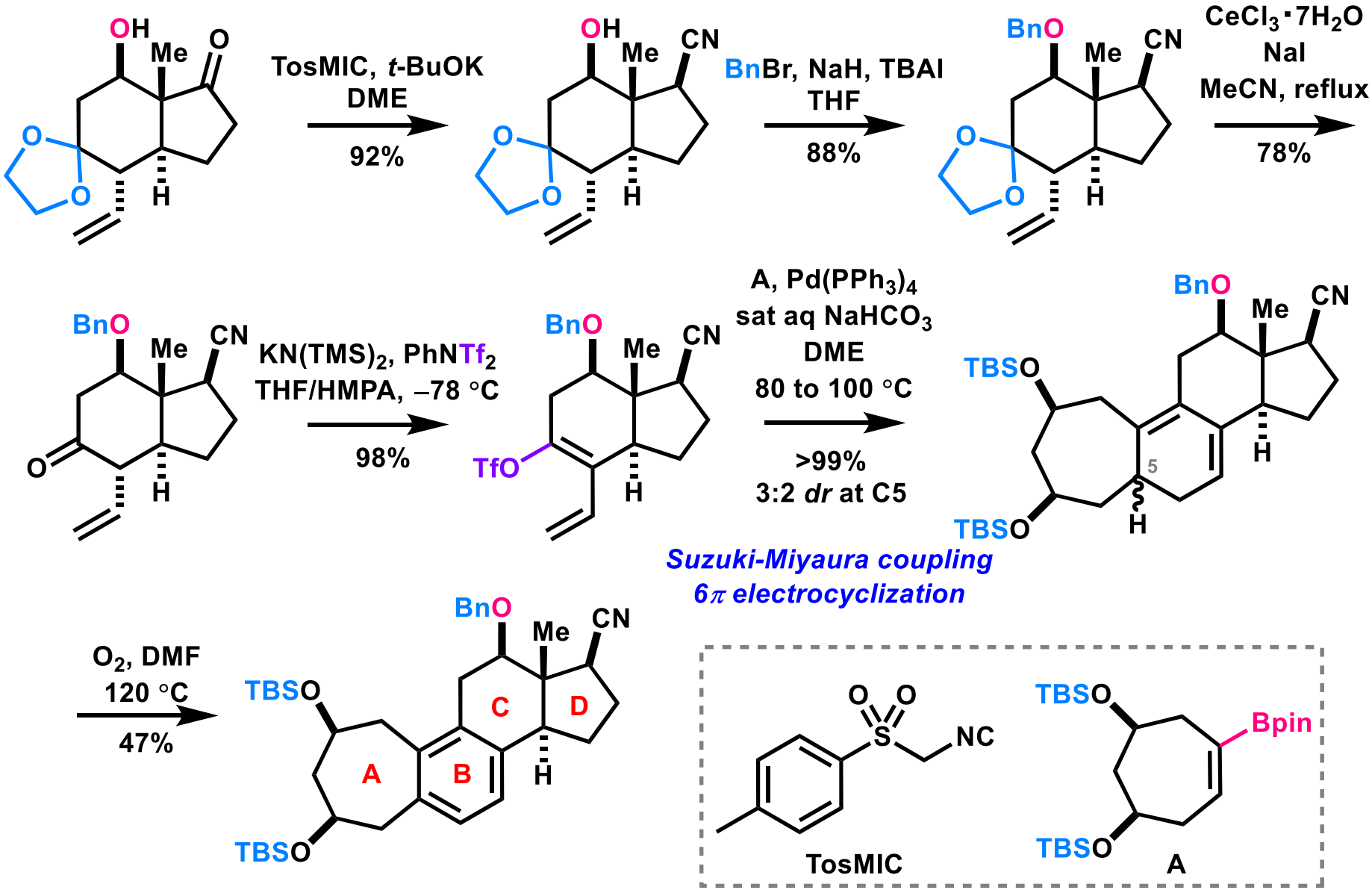
1) Wang. X.; Huang. G.; Wang. Y.; Gui. J., *J. Am. Chem. Soc.* **2023**, *145*, 9354.

Synthesis of CD ring



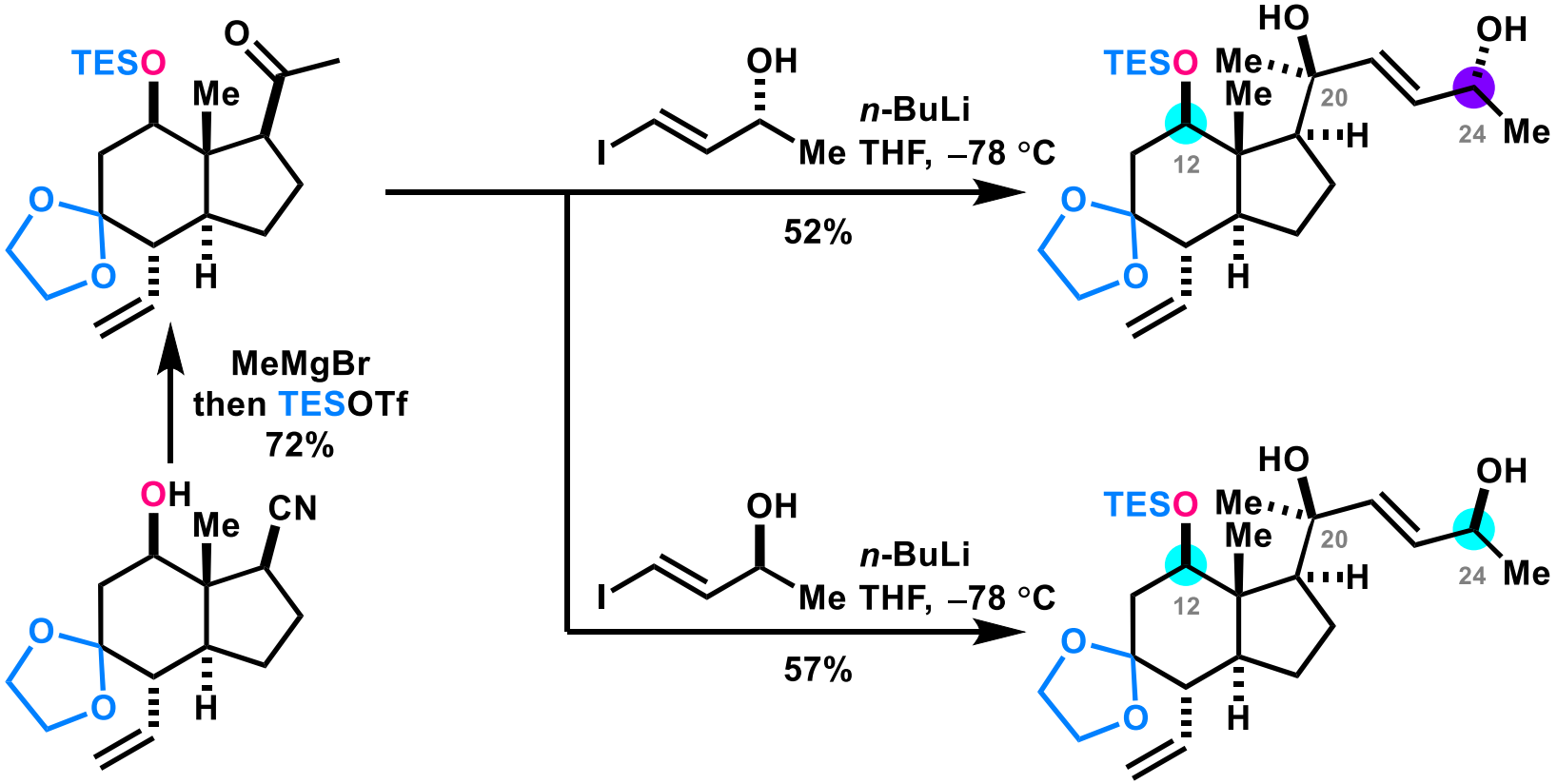
1) Wang. X.; Huang. G.; Wang. Y.; Gui. J., *J. Am. Chem. Soc.* **2023**, *145*, 9354.
2) Trammell. R.; See. Y. Y.; Herrmann. A. T.; Xie. N.; Díaz. D. E.; Siegler. M. A.; Baran. P. S.; Garcia-Bosch. G., *J. Org. Chem.* **2017**, *82*, 7887.

B ring formation



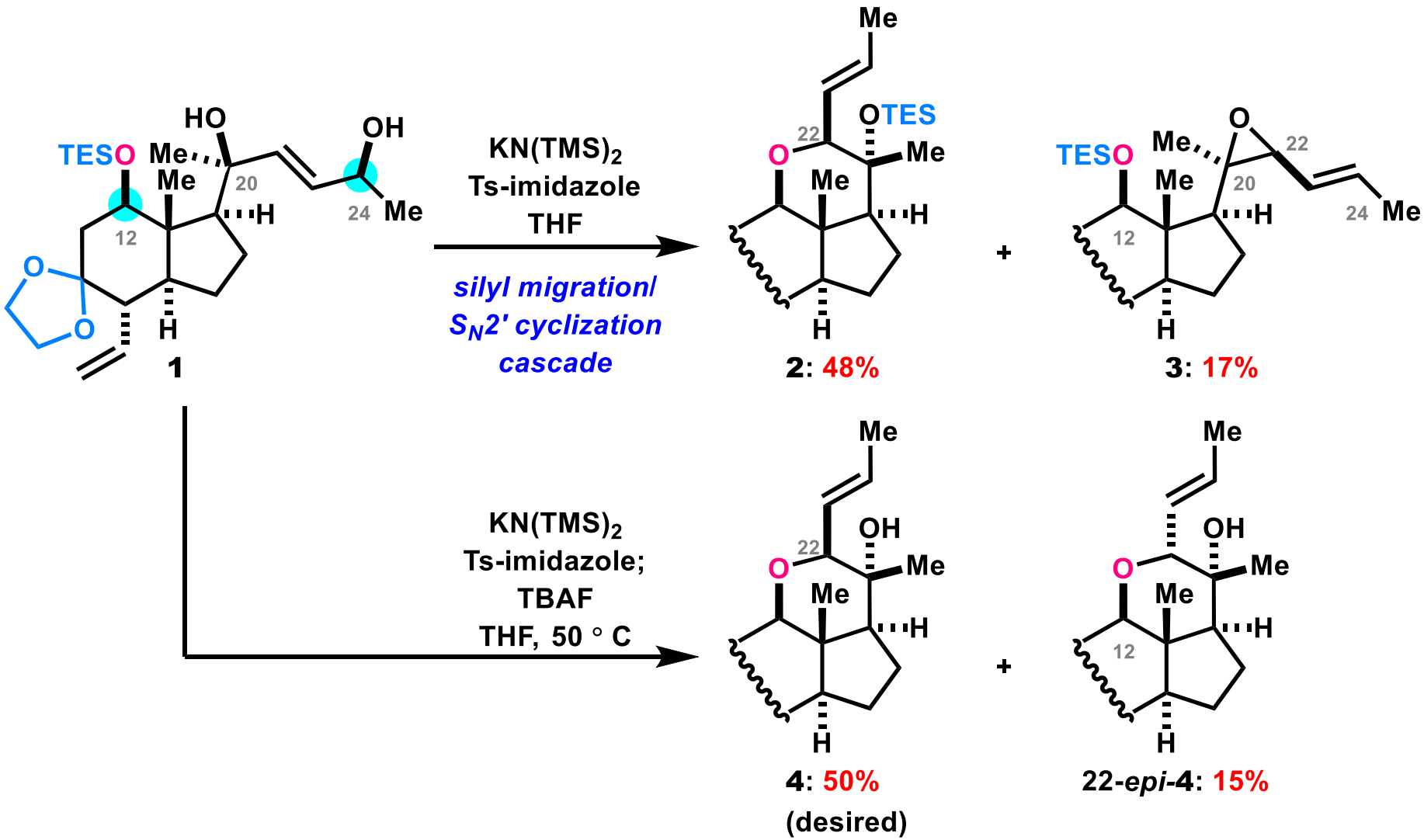
1) Wang. X.; Huang. G.; Wang. Y.; Gui. J., *J. Am. Chem. Soc.* **2023**, *145*, 9354.

Preparation of S_N2' reaction



1) Wang. X.; Huang. G.; Wang. Y.; Gui. J., *J. Am. Chem. Soc.* **2023**, *145*, 9354.

Controlled experiments for TPR formation (1)



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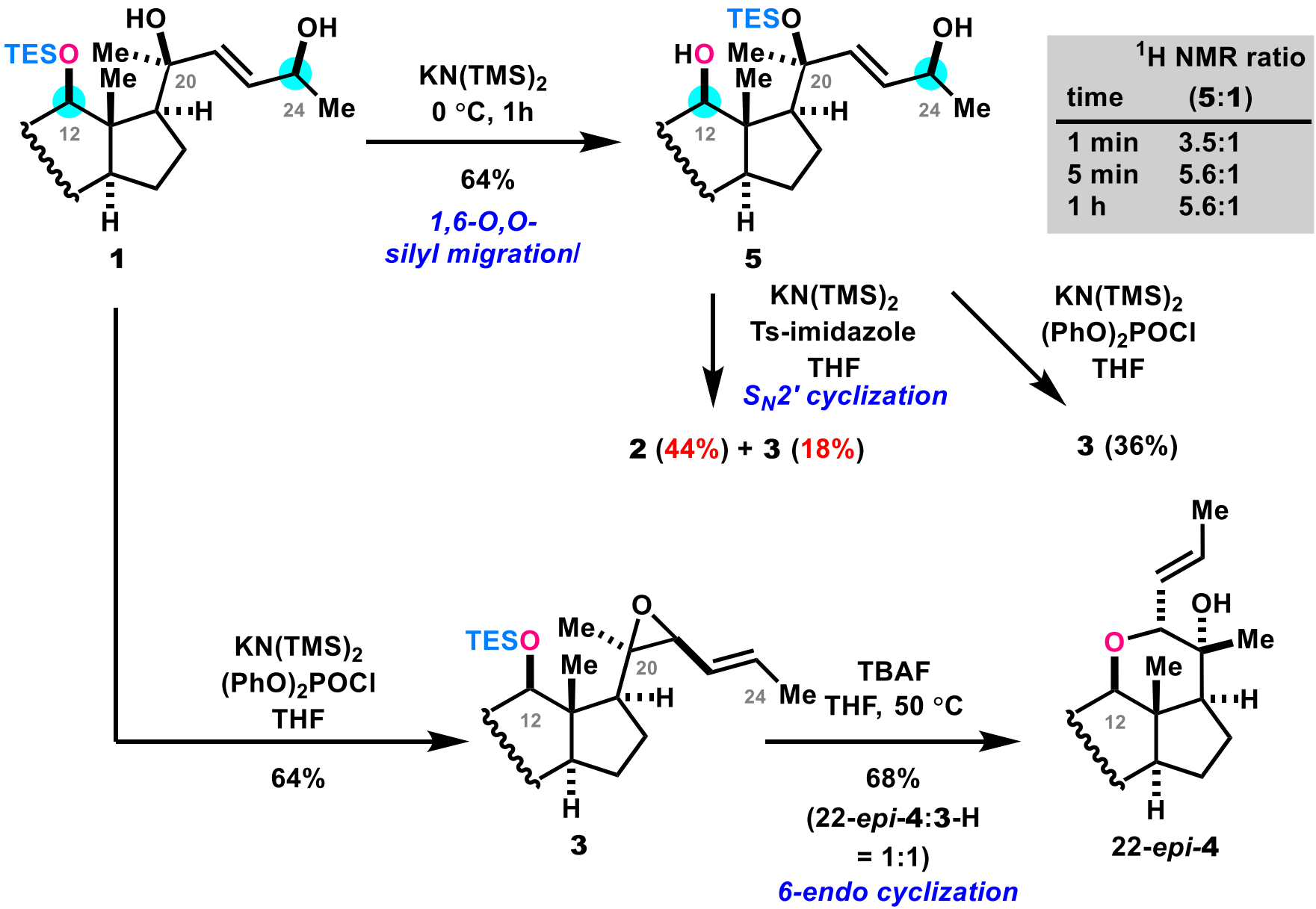
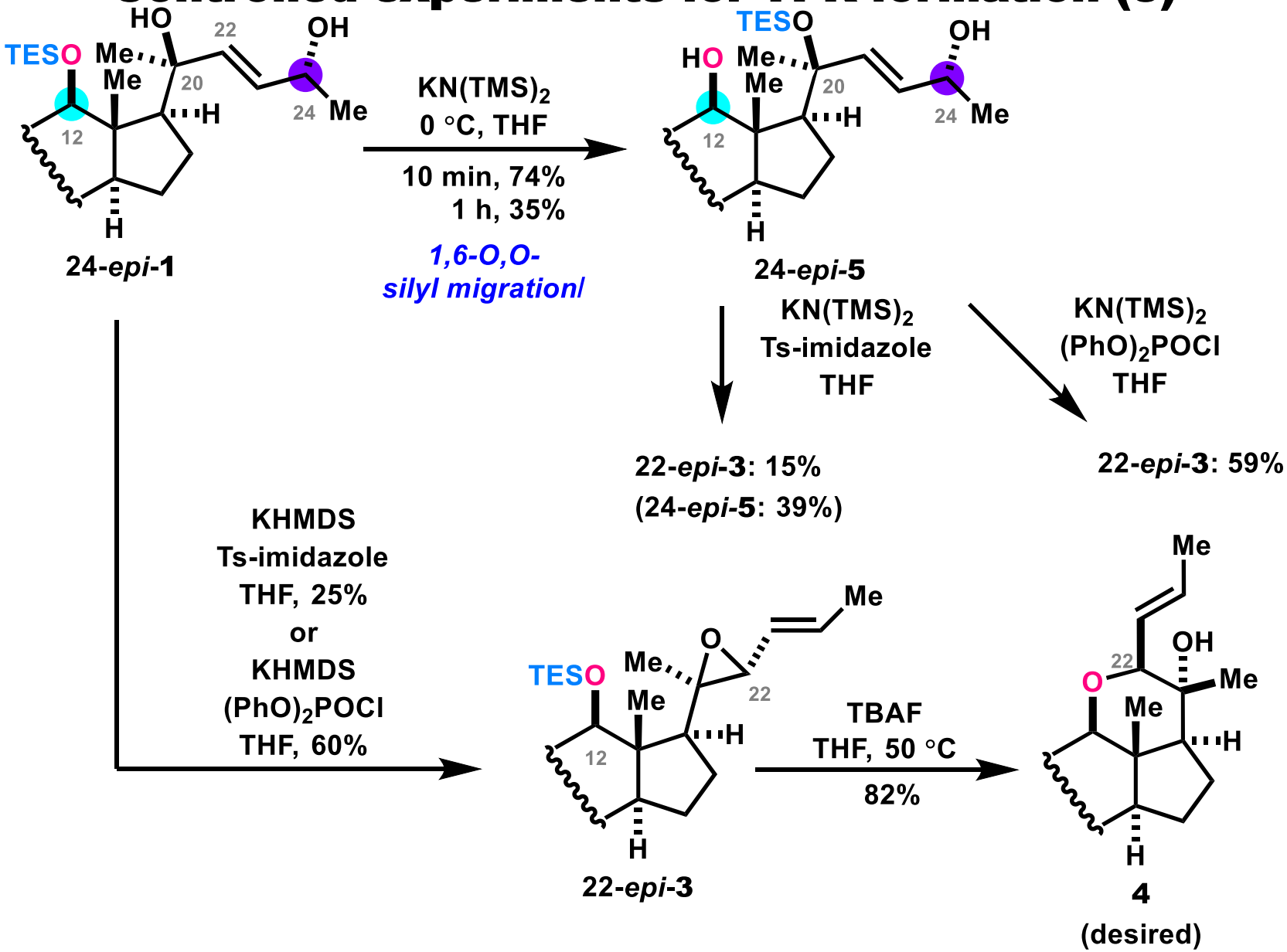
Controlled experiments for TPR formation (2)



time	^{1}H NMR ratio (5:1)
1 min	3.5:1
5 min	5.6:1
1 h	5.6:1

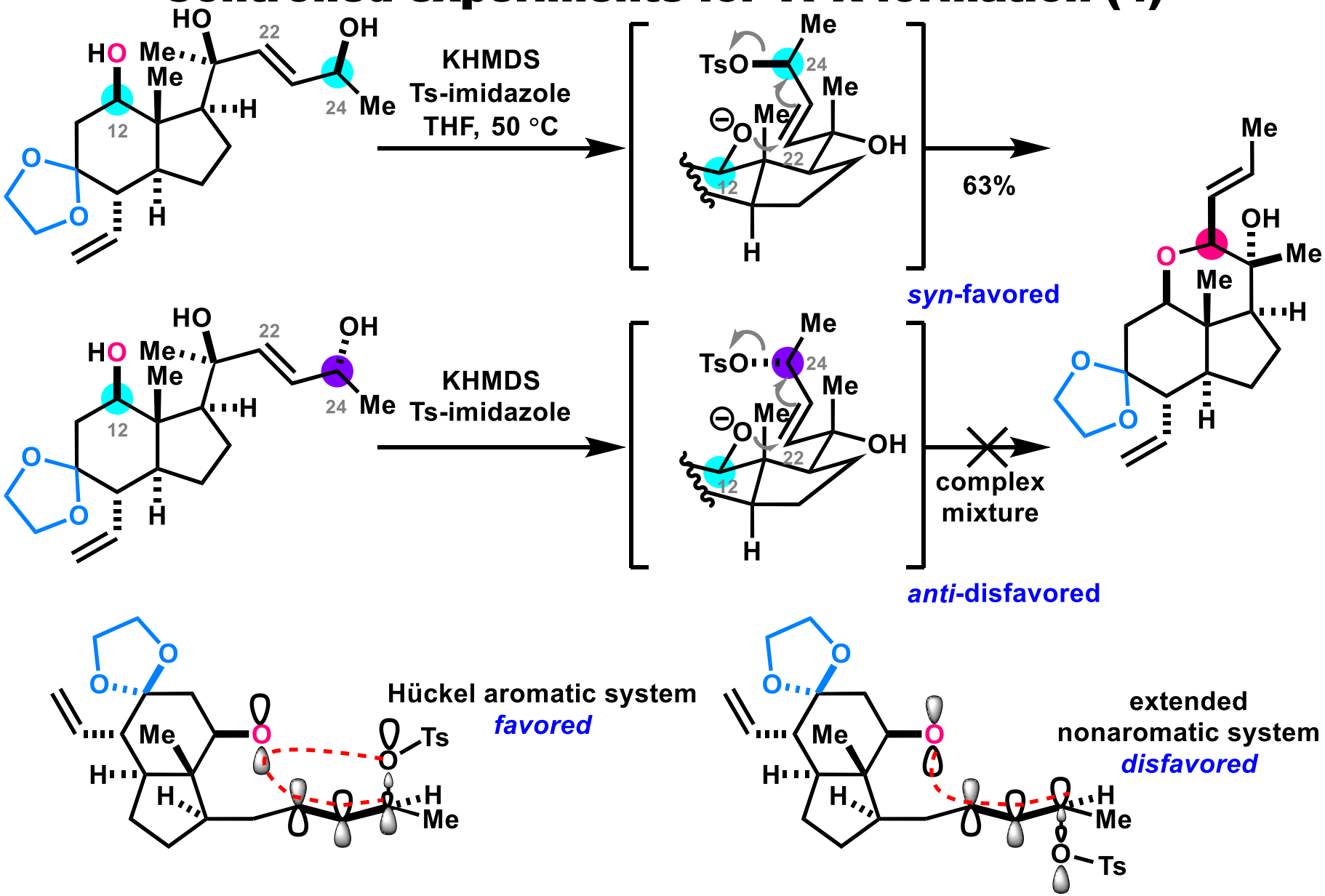
1) Wang. X.; Huang. G.; Wang. Y.; Gui. J., *J. Am. Chem. Soc.* **2023**, *145*, 9354.

Controlled experiments for TPR formation (3)



1) Wang. X.; Huang. G.; Wang. Y.; Gui. J., *J. Am. Chem. Soc.* **2023**, *145*, 9354.

Controlled experiments for TPR formation (4)



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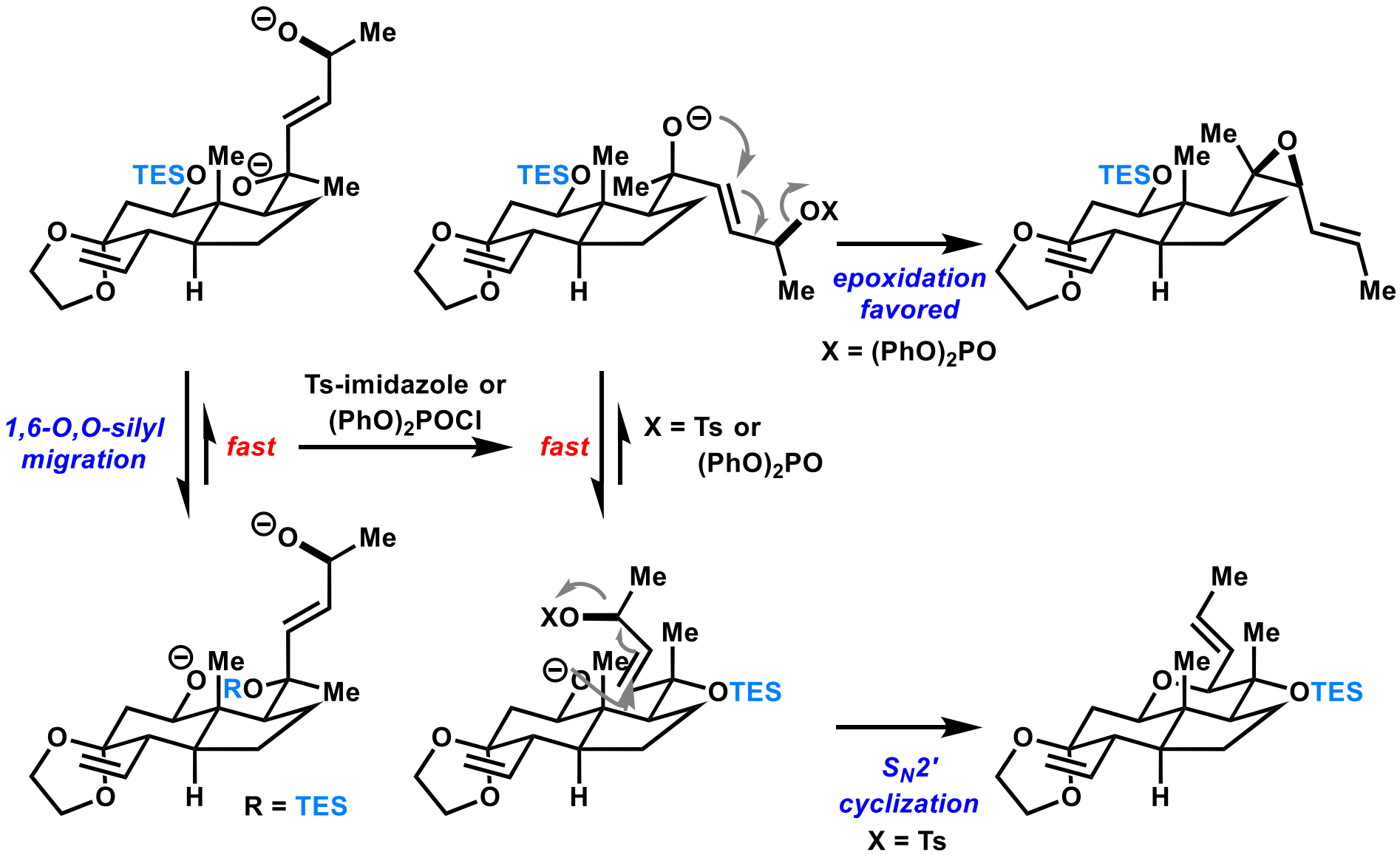
Proposed mechanism for tetrahydropyran formation (1)



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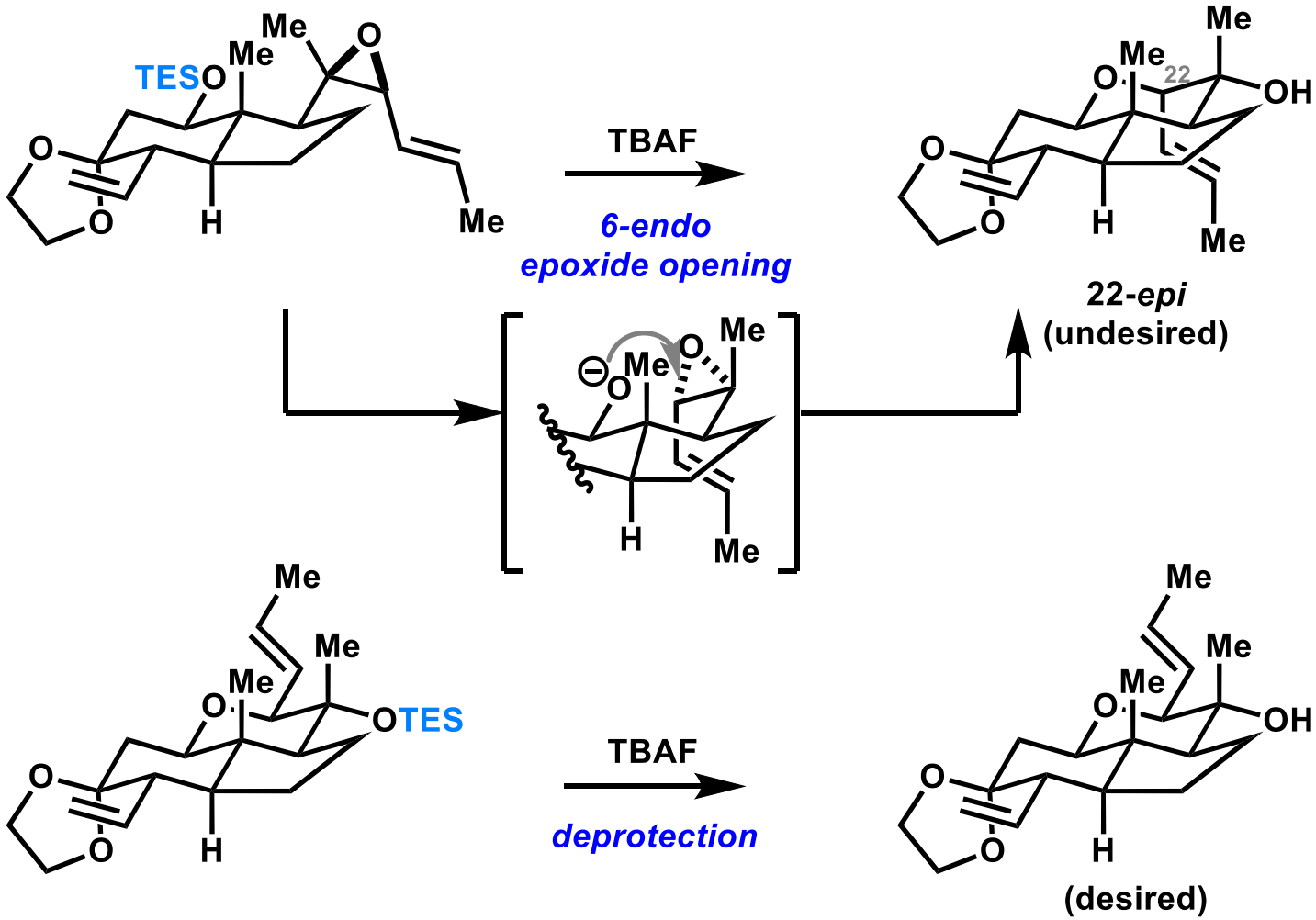
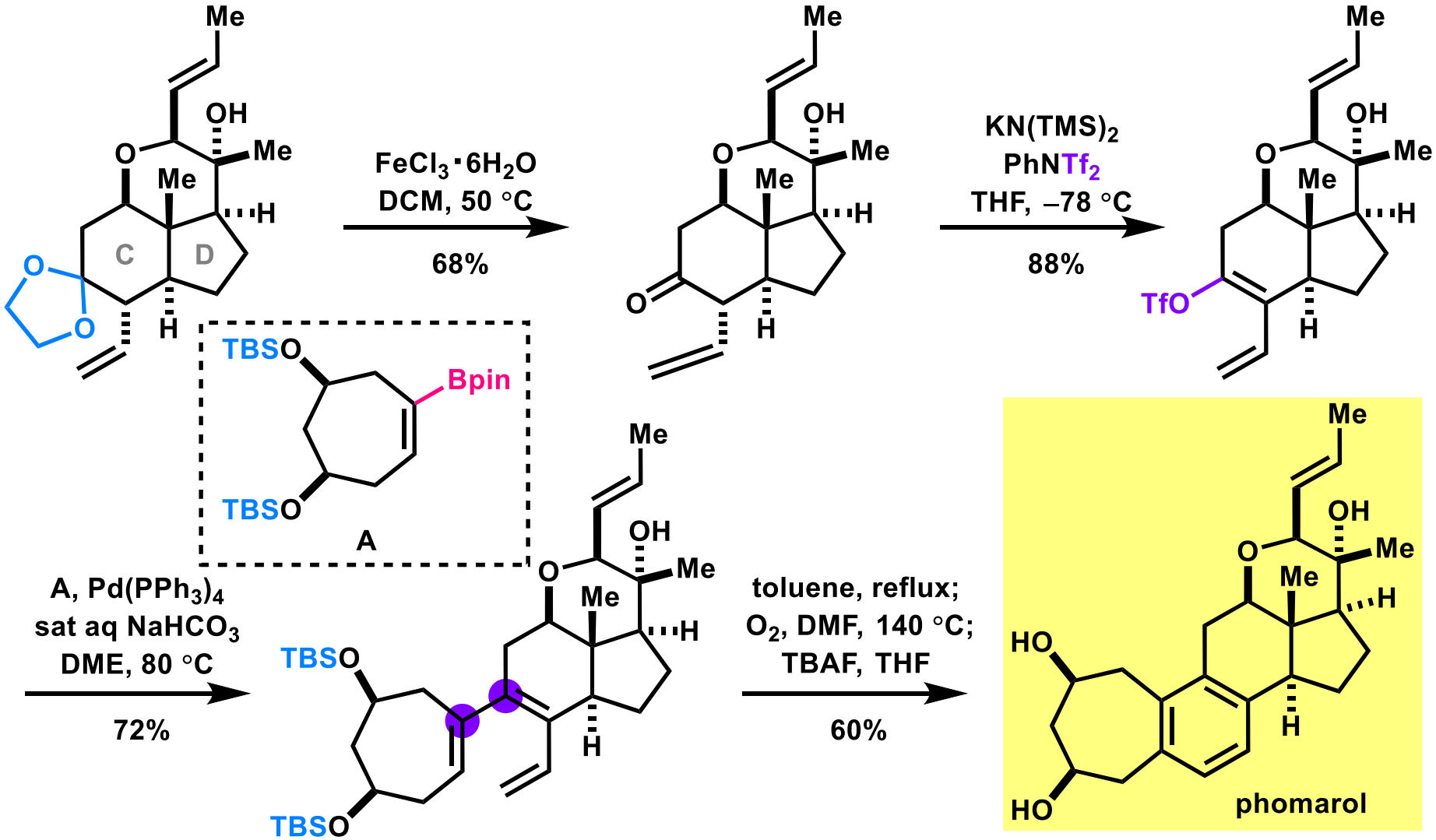
Proposed mechanism for tetrahydropyran formation (2)



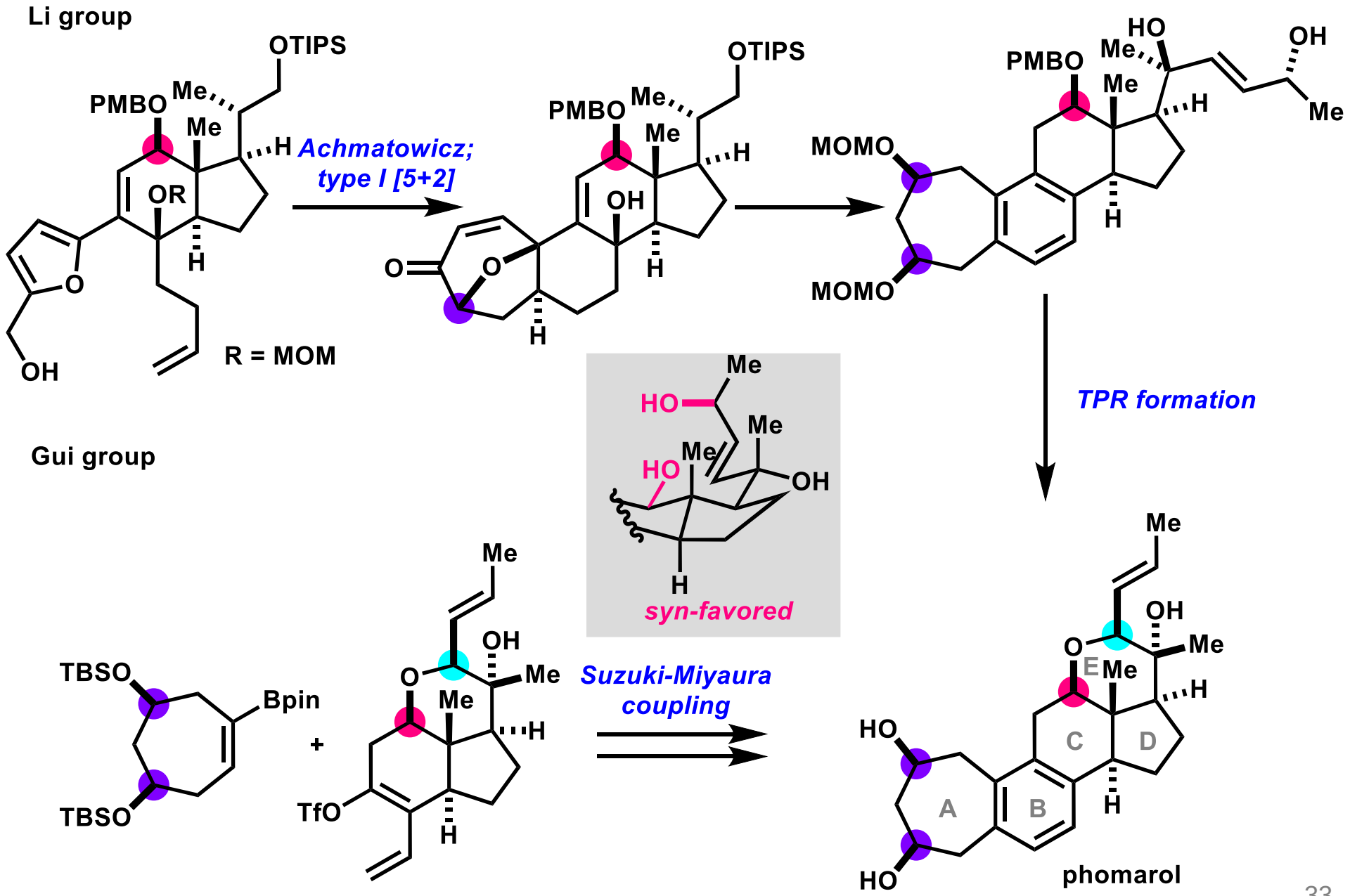
1) Wang. X.; Huang. G.; Wang. Y.; Gui. J., *J. Am. Chem. Soc.* **2023**, *145*, 9354.

Total synthesis of phomarol



1) Wang. X.; Huang. G.; Wang. Y.; Gui. J., *J. Am. Chem. Soc.* **2023**, *145*, 9354.

Summary


Li group
OTIPS
PMBO
Me
Me
H
OR
H
O
OH
R = MOM
Achmatowicz;
type I [5+2]
OTIPS
PMBO
Me
Me
H
OH
O
O
H
MOMO
MOMO
HO
Me
PMBO
Me
H
OH
Me
H
TPR formation
Me
HO
Me
Me
HO
OH
H
syn-favored
Gui group
TBSO
Bpin
TBSO
+
Me
OH
O
Me
Me
H
TfO
H
Suzuki-Miyaura
coupling
Me
OH
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E
Me
Me
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C
D
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B
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HO
phomarol