Total syntheses of Grayanoids

2024.1.27 Literature Seminar

B4 Yo Matsumoto

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Introduction of authors

Prof. Ming Yang

Career:
2008: B.S. @ Hubei University
2013: Ph.D. @ Lanzhou University (Prof. Yong-Qiang Tu)
2013-2015: Postdoc @ The Shanghai Institute of Organic Chemistry (Prof. Ang Li)
2015-2019: Postdoc @ The University of Chicago (Prof. Scott A. Snyder)
2019-Present: Professor @ Lanzhou University

Research Topics:
Total synthesis, Discovery of biosynthetic pathway, Medicinal chemistry

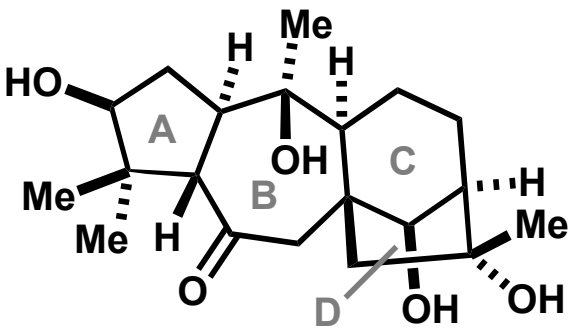
Prof. Yanxing Jia

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

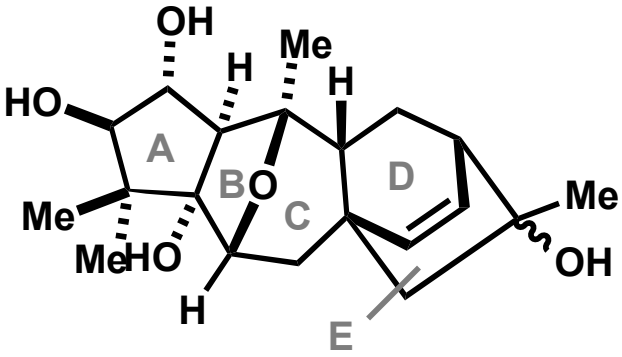
Research Topics:
Total synthesis, Synthetic medical chemistry, Development of synthetic methods

1) http://sklaoc.lzu.edu.cn/col_Professor/201903/F39F804AC68FBFF56F417B9A8EEB0D18.htm
2) http://www.jiayanxinggroup.com/Jia

Introduction of Grayanoids



principinol C



rhodomollin A (α-OH)
rhodomollin B (β-OH)

Isolation

rhododendron principis (2014, Hou group[1])

Structural feature

5/7/6/5 tetracyclic skeleton

Total synthesis

Jia group (2022)[2]

Isolation

rhododendron molle (2016, Yu group[3])

Bioactivity

Anti-influenza virus A/95-359 (rhodomollin B)[3]

Structural feature

5/7/6/6-fused ring system
oxa-bicyclo[3,2,1] core

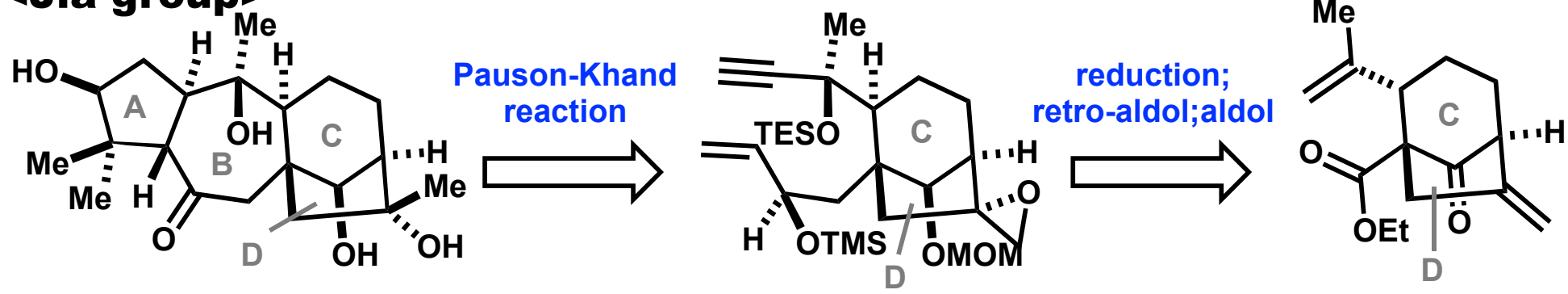
Total synthesis

Yang group (2023)[4]

1) *Tetrahydron Lett.* **2014**, *70*, 4317. 2) *J. Am. Chem. Soc.* **2022**, *144*, 20196. 3) *Sci. Rep.* **2016**, *6*, 36752.
4) *J. Am. Chem.* **2023**, *145*, 27160. 5) https://www.rhododendron.org/descriptionS_taxon.asp?ID=185
6) https://www.bg.s.u-tokyo.ac.jp/nikko-old/pra/rhododendron/renge_tutuji.html

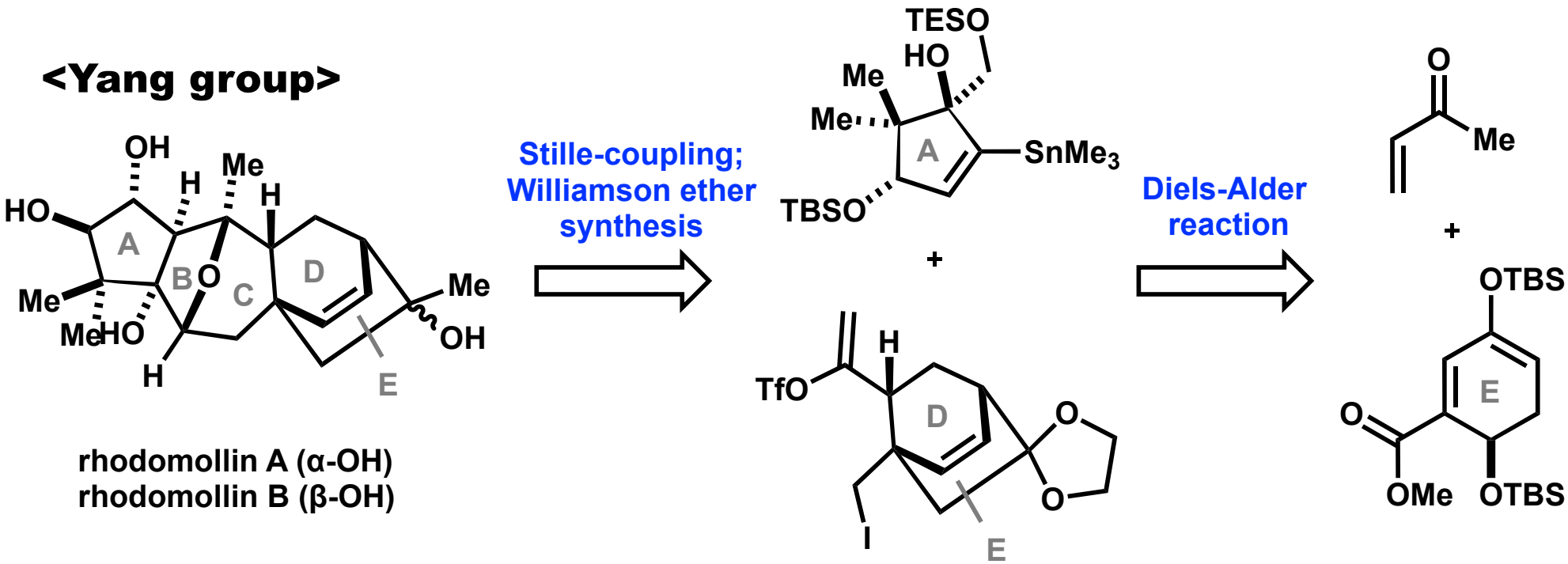
Retrosynthetic Analysis

<Jia group>



principinol C

<Yang group>

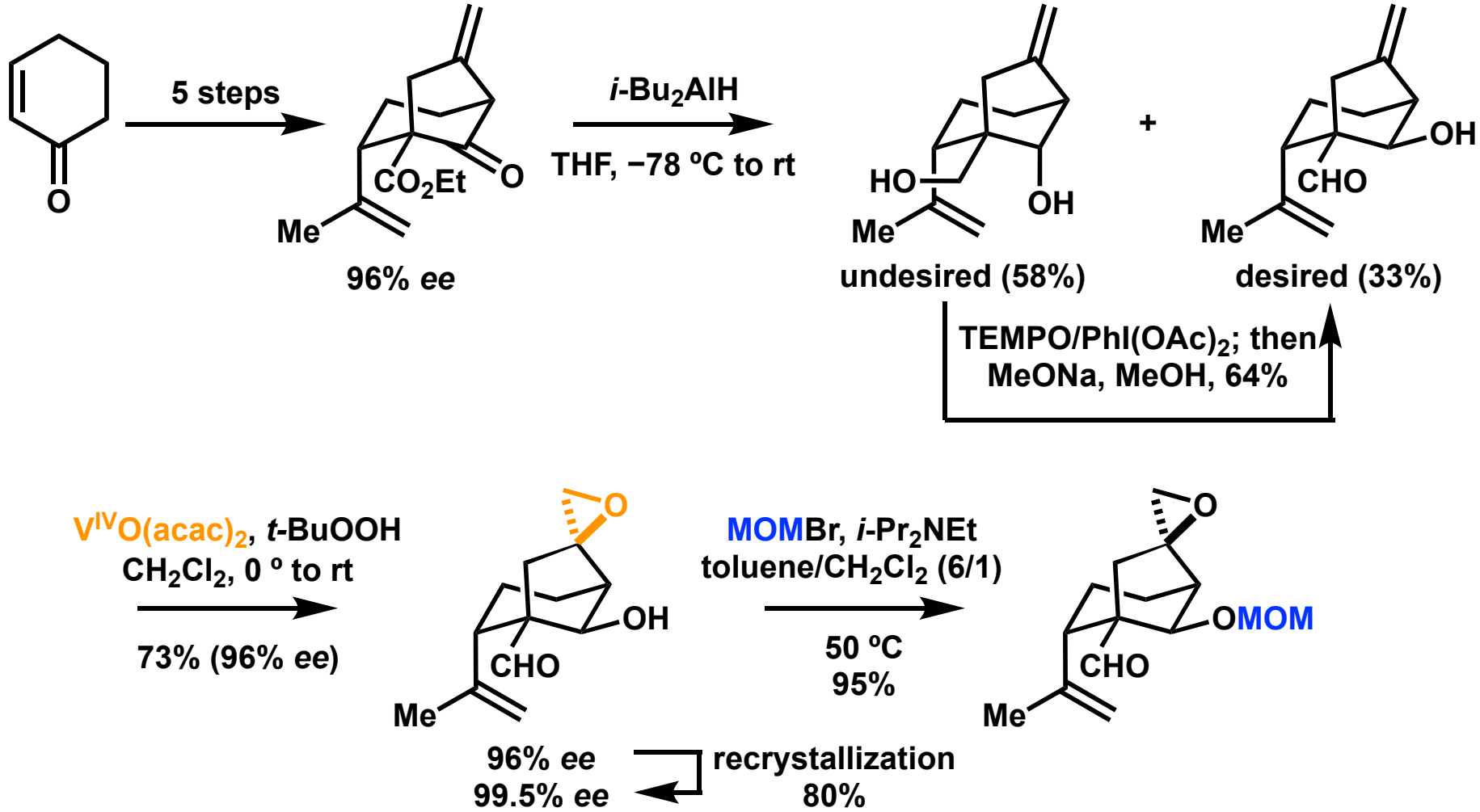


rhodomollin A (α-OH)
rhodomollin B (β-OH)

1) Ma, T.; Cheng, H.; Pitchakuntla, M.; Ma, W.; Jia, Y. *J. Am. Chem. Soc.* **2022**, *144*, 20196.
2) Zhao, W.; Zhang, D.; Wang, Y.; Yang, M. *J. Am. Chem. Soc.* **2023**, *145,* 27160.

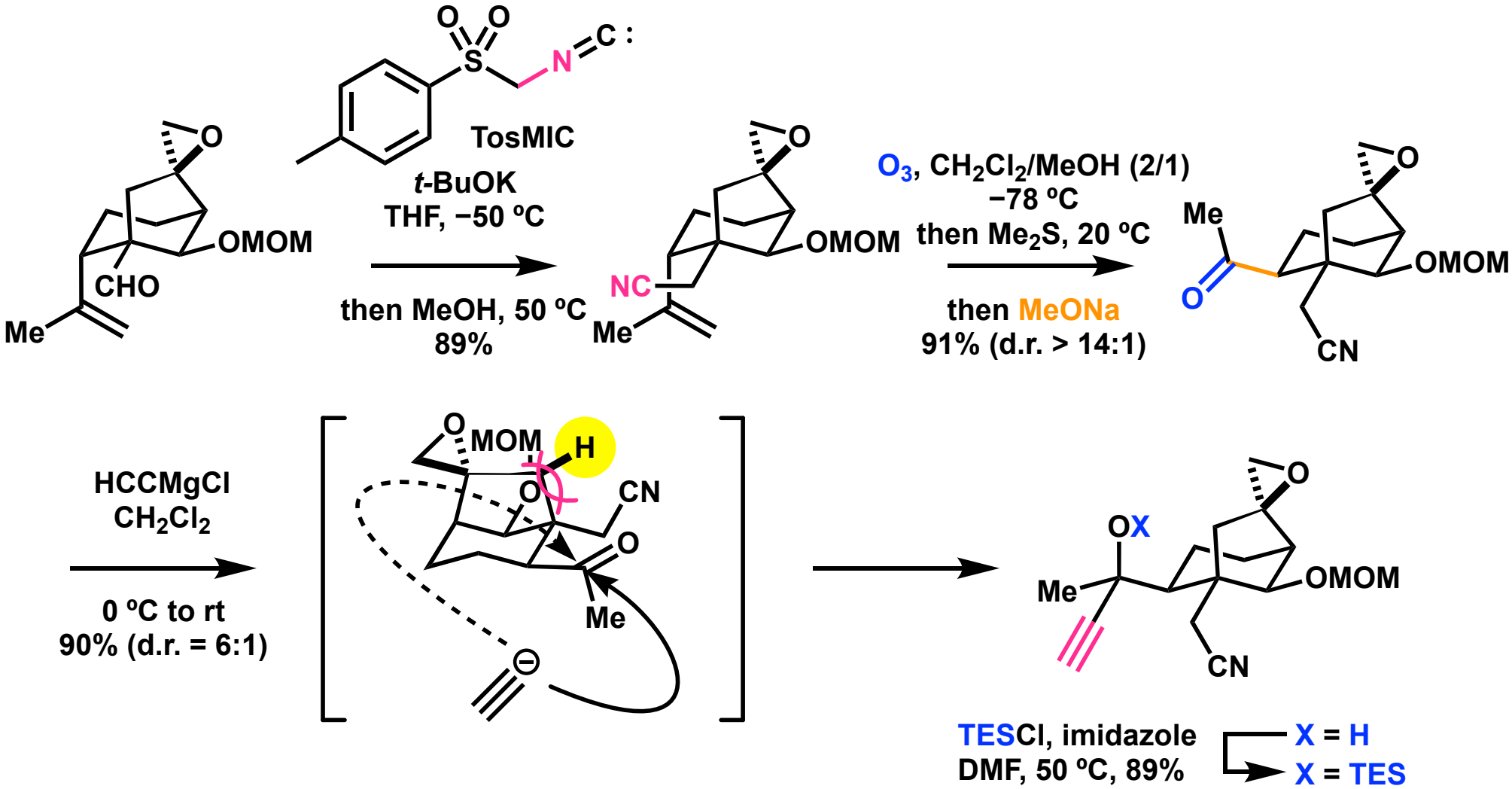
Contents

Syntheses of Tetracycle-1



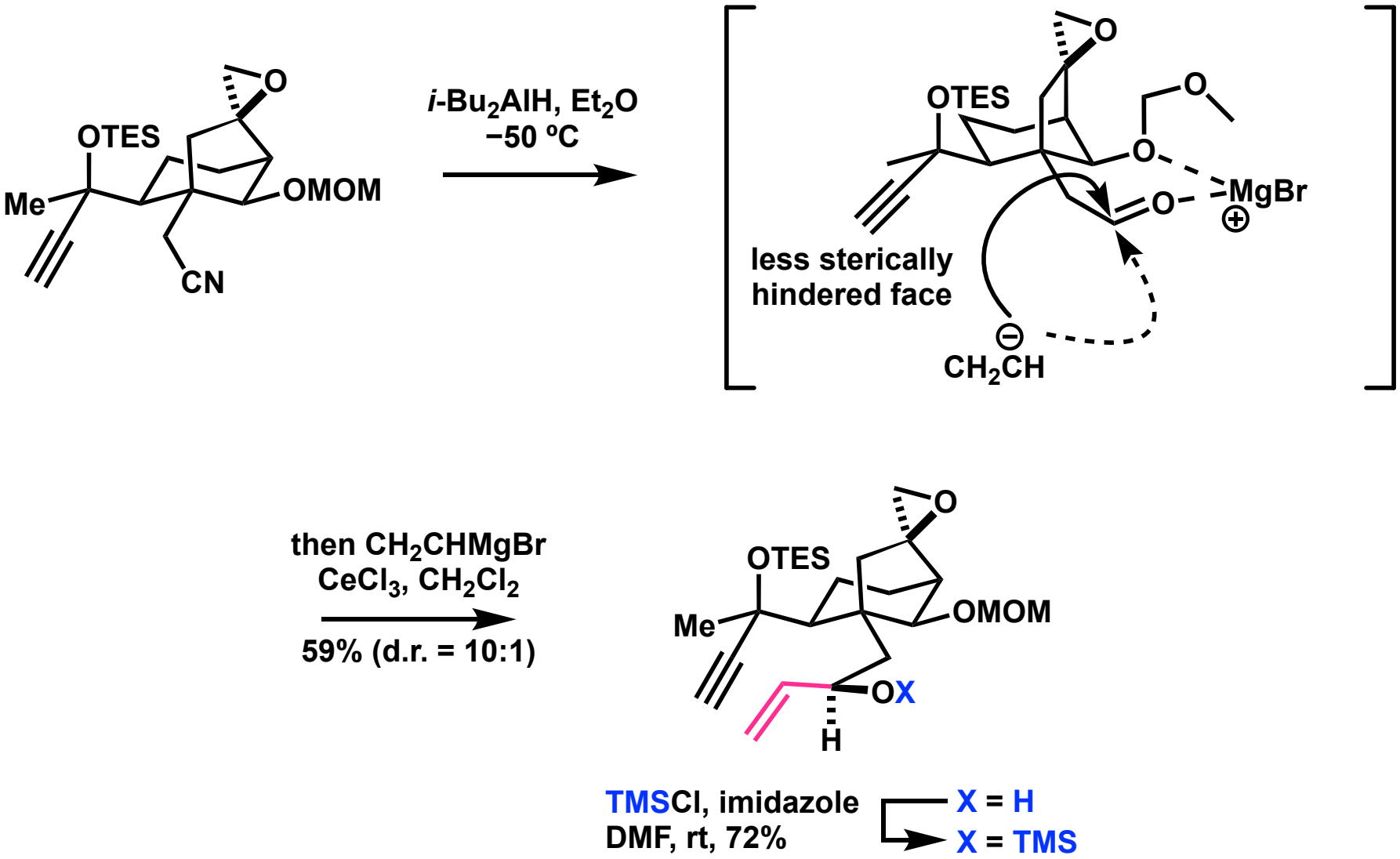
1) Ma, T.; Cheng, H.; Pitchakuntla, M.; Ma, W.; Jia, Y. *J. Am. Chem. Soc.* **2022**, *144*, 20196.

Syntheses of Tetracycle-2



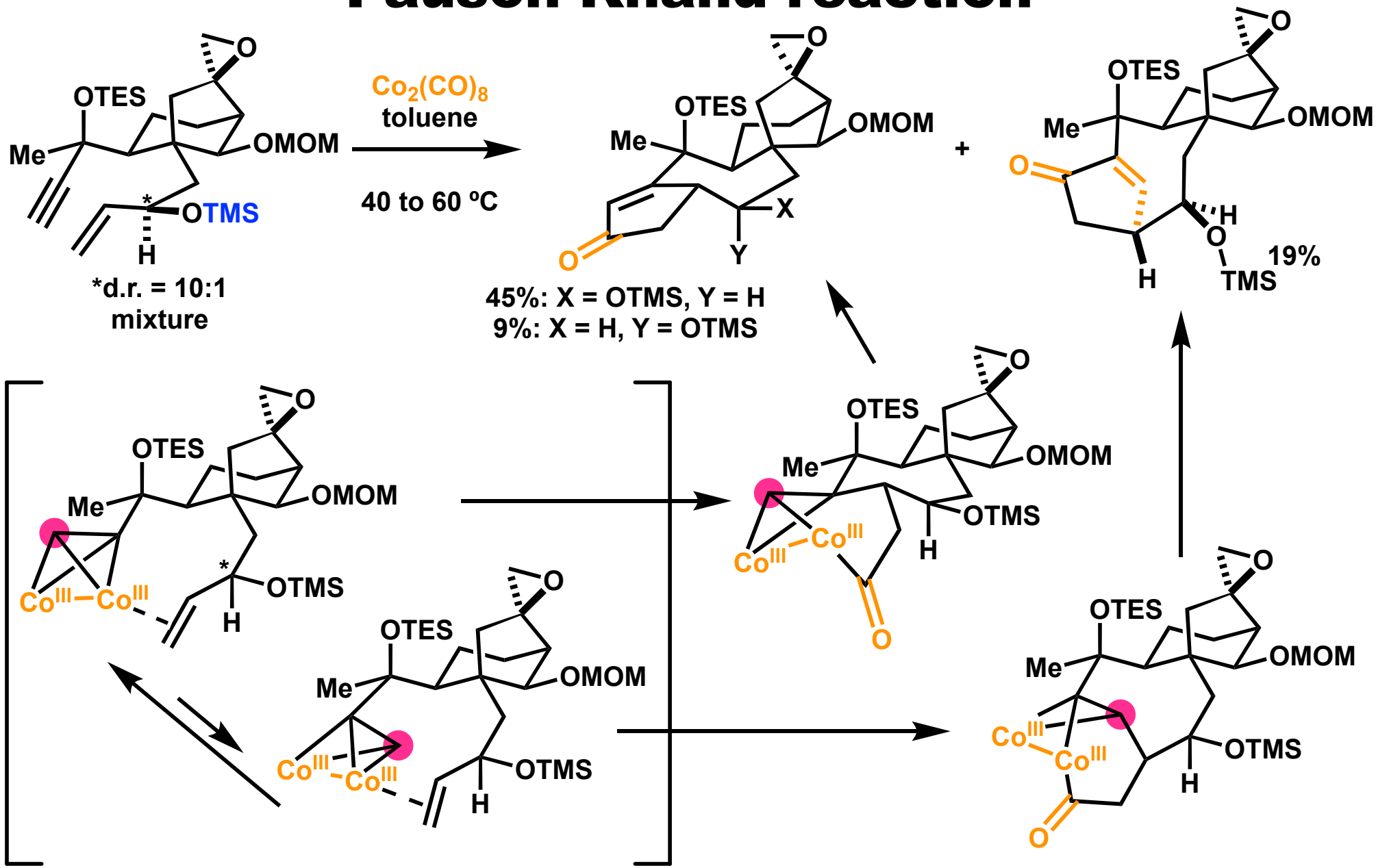
1) Ma, T.; Cheng, H.; Pitchakuntla, M.; Ma, W.; Jia, Y. *J. Am. Chem. Soc.* **2022**, *144*, 20196.

Syntheses of Tetracycle-3



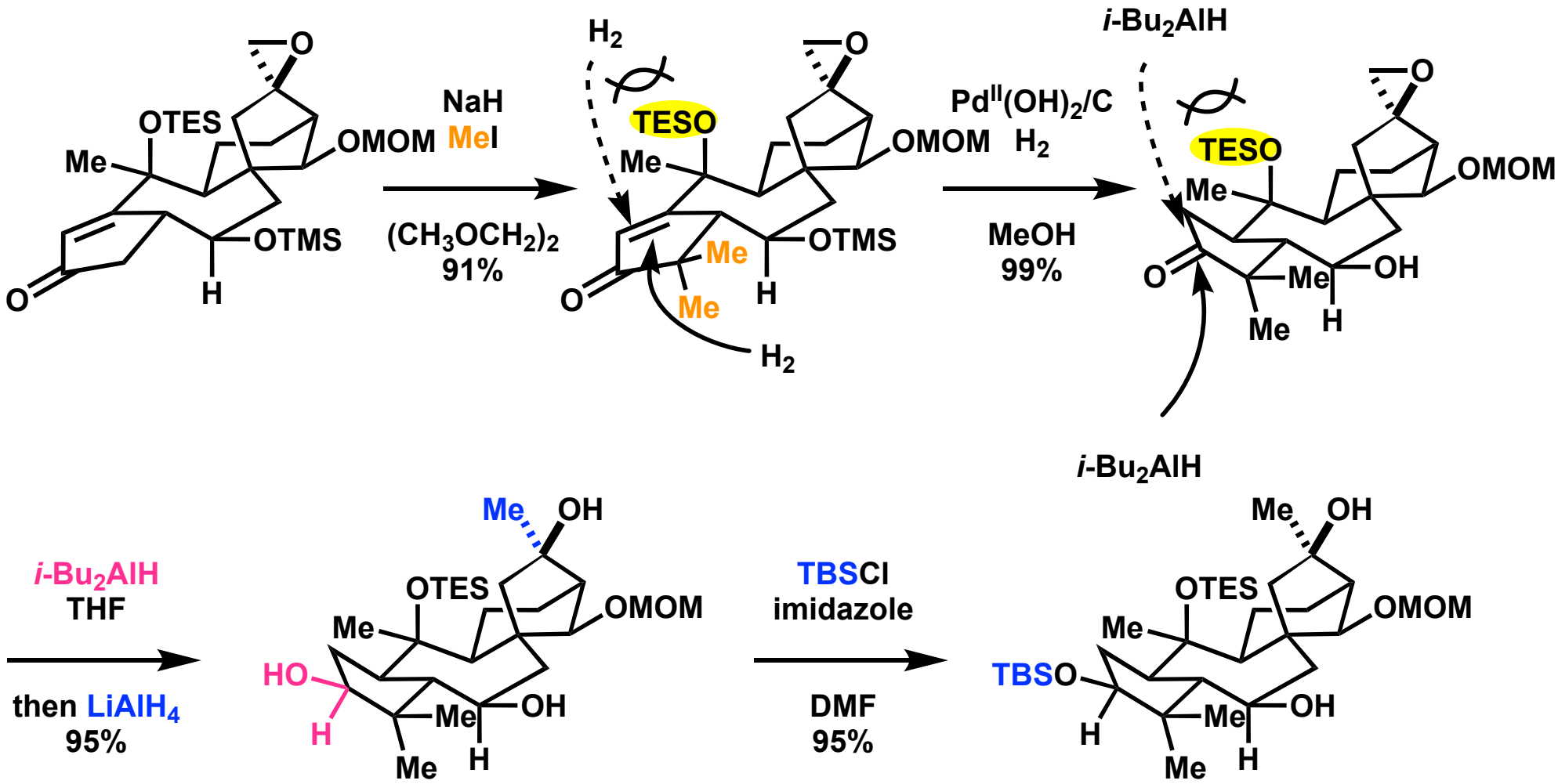
1) Ma, T.; Cheng, H.; Pitchakuntla, M.; Ma, W.; Jia, Y. *J. Am. Chem. Soc*. **2022**, *144*, 20196.

Pauson-Khand reaction



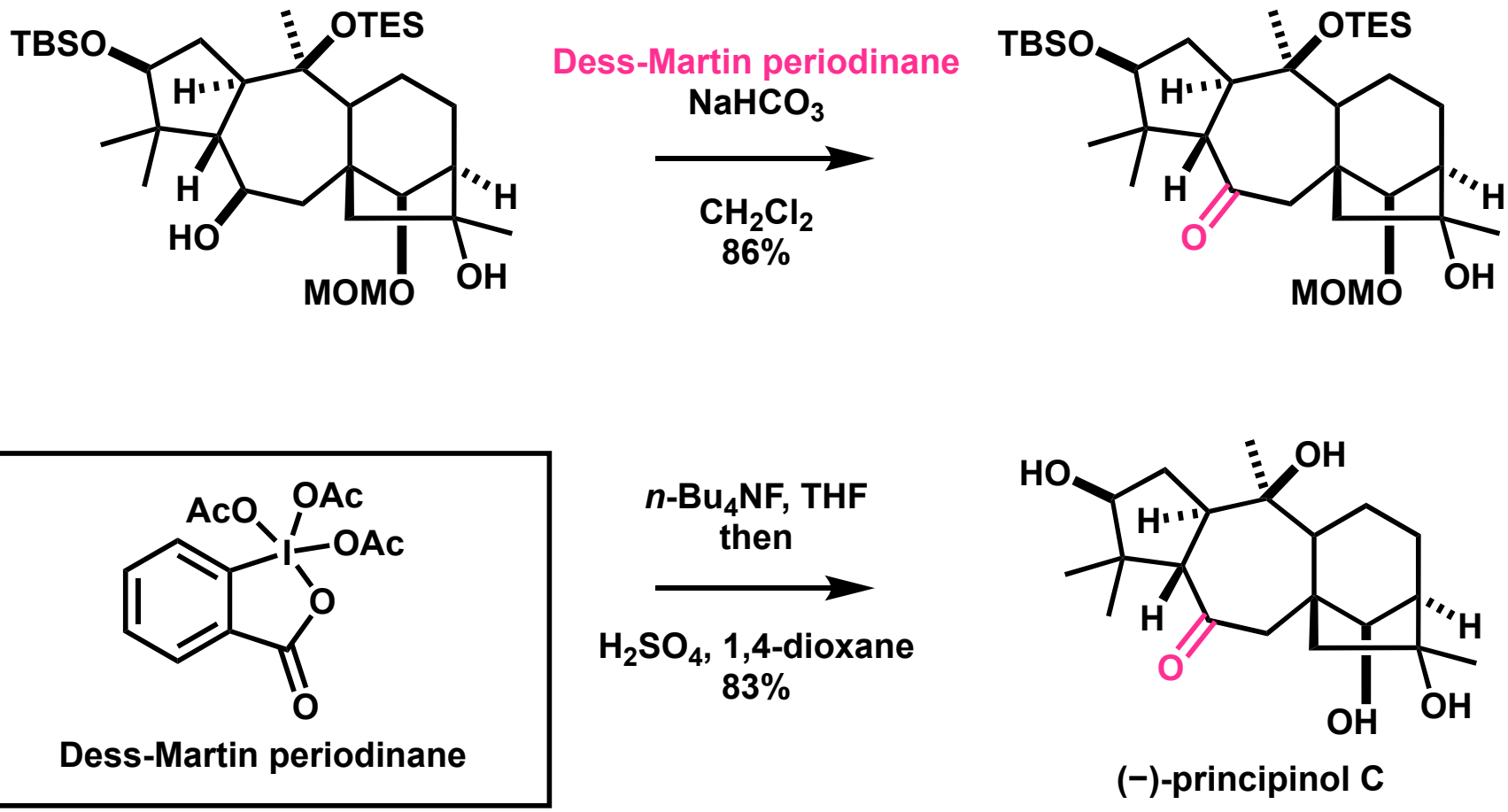
1) Ma, T.; Cheng, H.; Pitchakuntla, M.; Ma, W.; Jia, Y. *J. Am. Chem. Soc.* **2022**, *144*, 20196.

Syntheses of (−)-principinol C



1) Ma, T.; Cheng, H.; Pitchakuntla, M.; Ma, W.; Jia, Y. *J. Am. Chem. Soc.* **2022**, *144*, 20196.

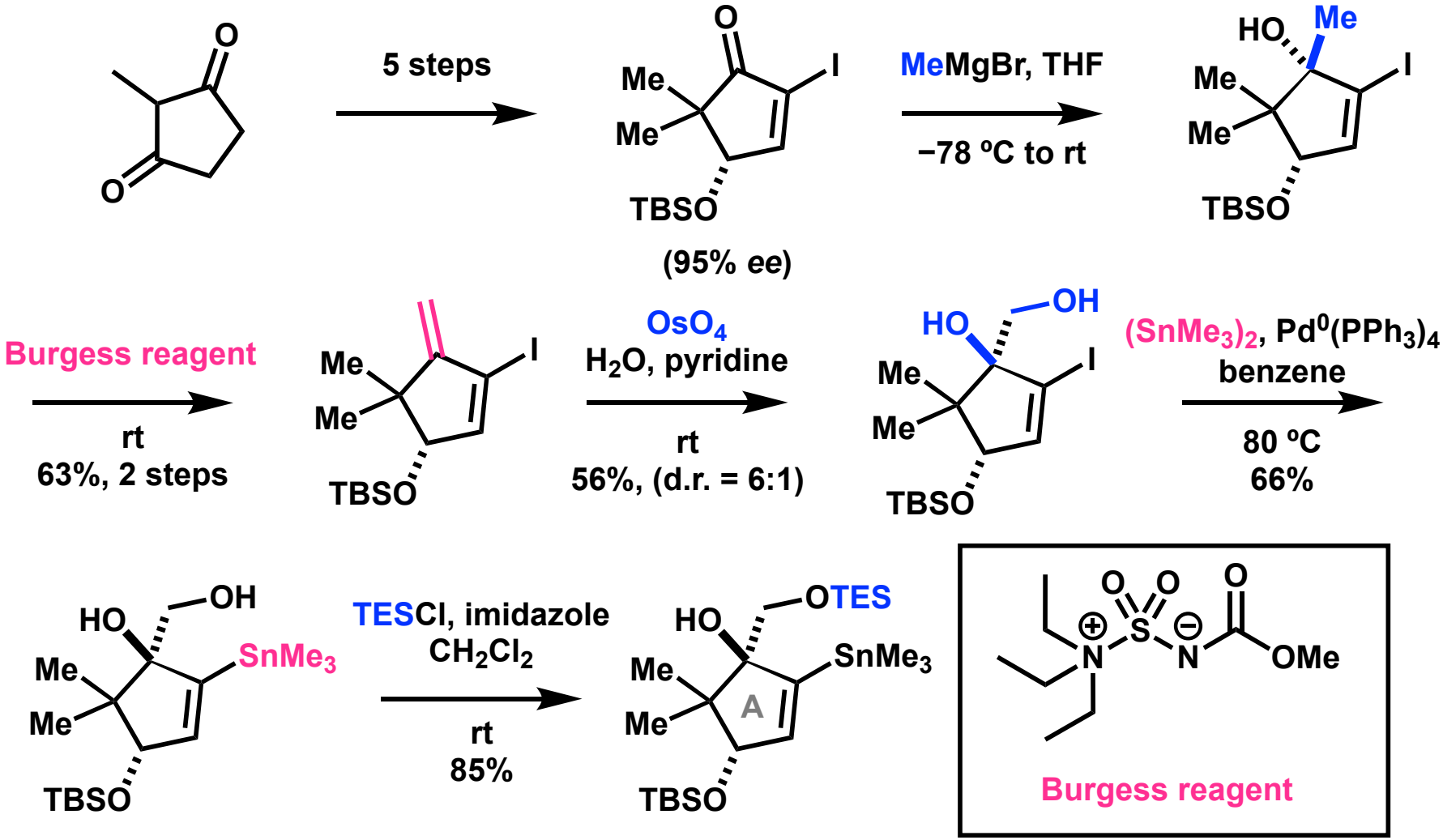
Syntheses of (−)-principinol C



1) Ma, T.; Cheng, H.; Pitchakuntla, M.; Ma, W.; Jia, Y. *J. Am. Chem. Soc.* **2022**, *144*, 20196.

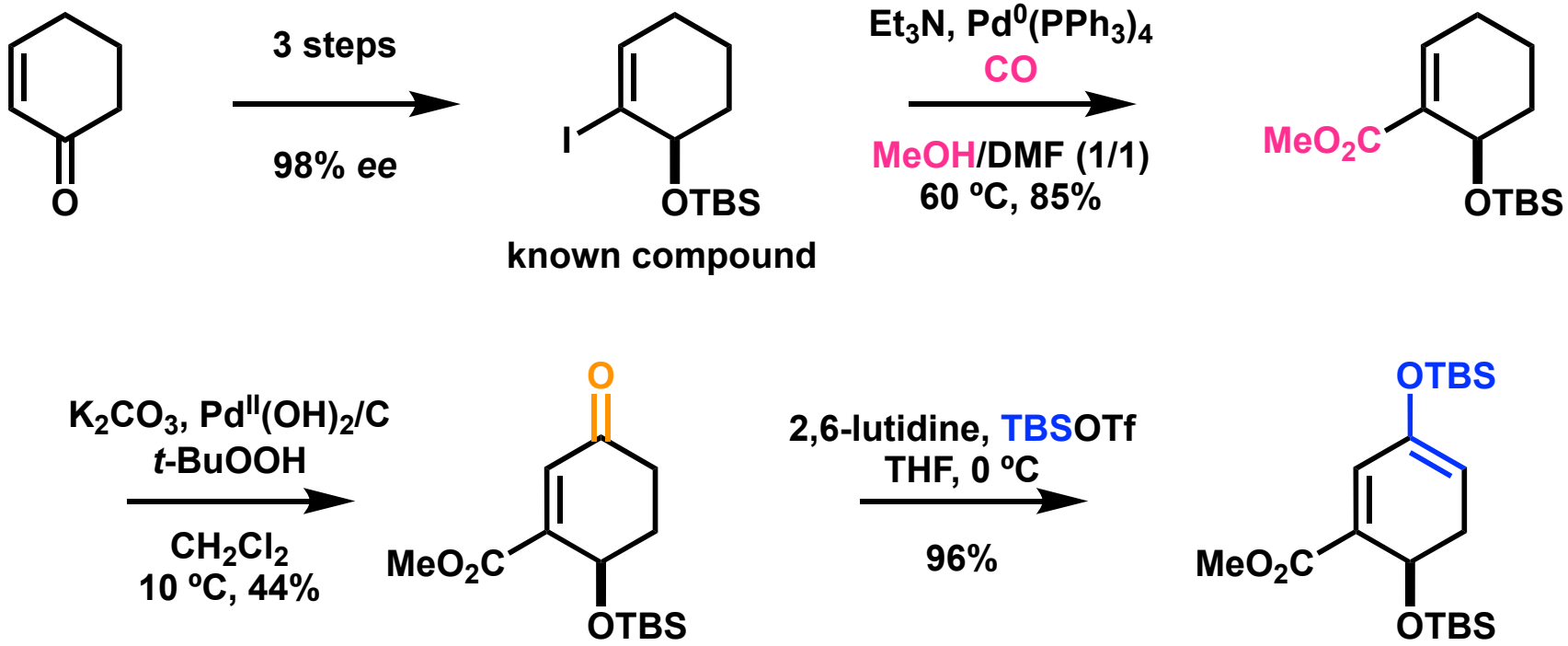
Contents

Syntheses of A-ring



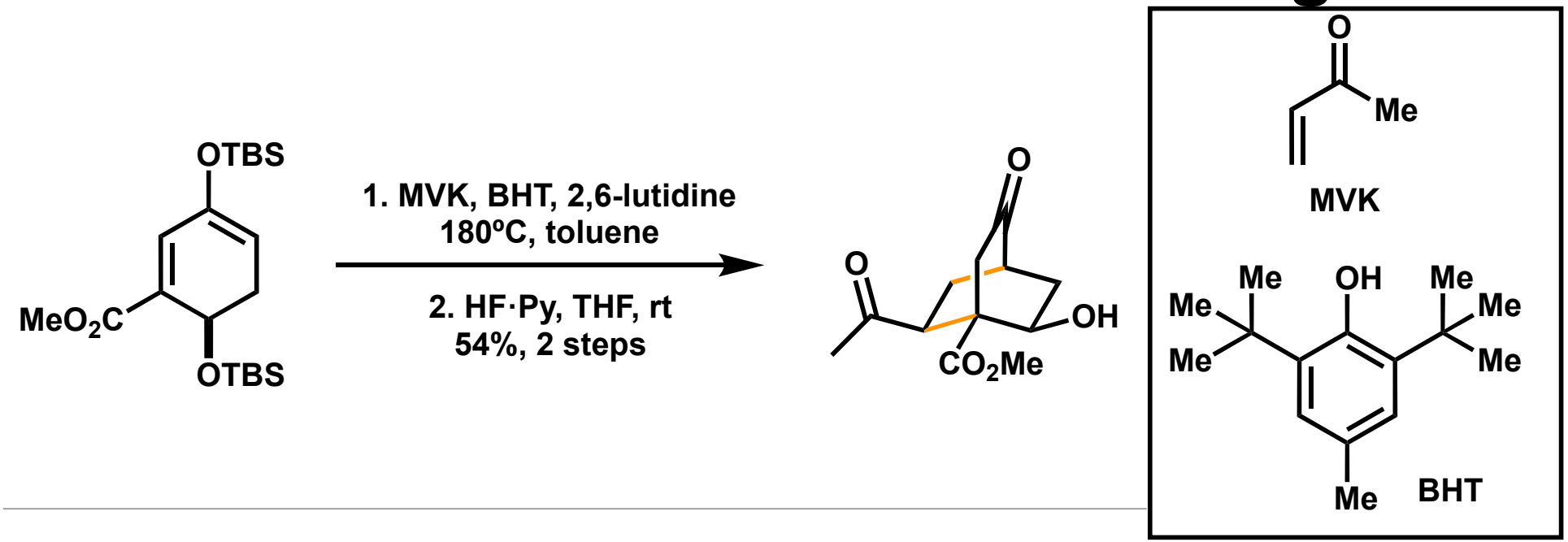
1) Zhao, W.; Zhang, D.; Wang, Y.; Yang, M. *J. Am. Chem. Soc.* **2023**, *145,* 27160.
2) Turlik, A.; Chen, Y.; Scruse, A. C.; Newhouse, T. M. *J. Am. Chem. Soc.* **2019**, *141*, 8088
3) Wang, Y.; Zhao, R.; Yang, M. *J. Am. Chem. Soc.* **2022**, *144*, 15033

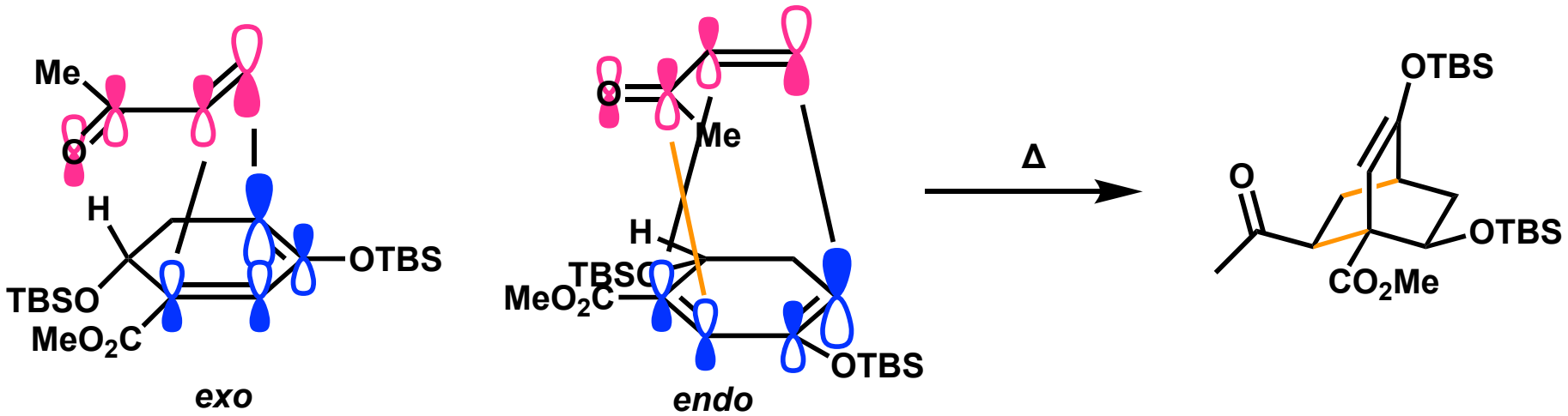
Syntheses of Silyl Enol Ether



1) Zhao, W.; Zhang, D.; Wang, Y.; Yang, M. *J. Am. Chem. Soc.* **2023**, *145,* 27160.

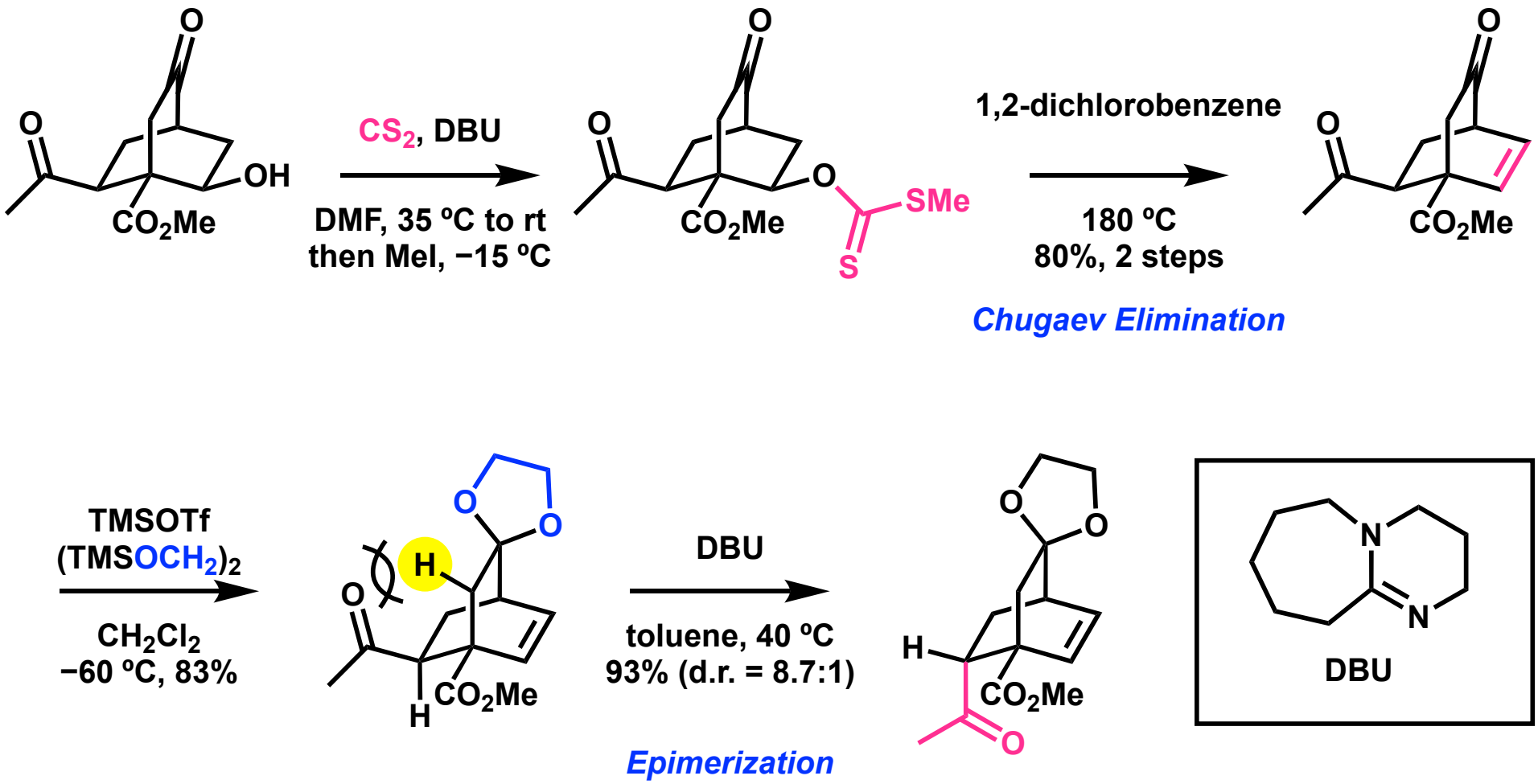
Diels-Alder reaction for DE-ring





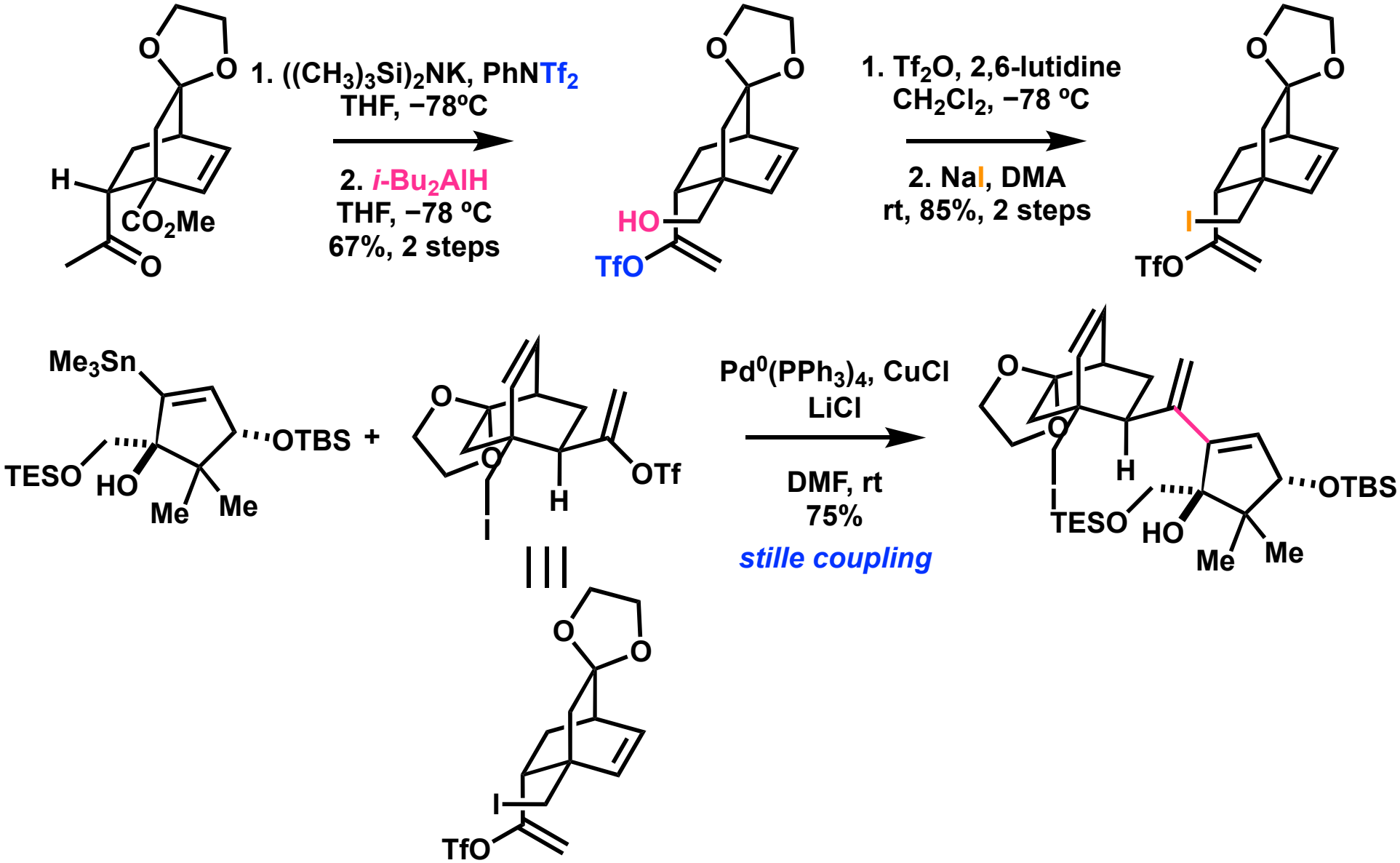
1) Zhao, W.; Zhang, D.; Wang, Y.; Yang, M. *J. Am. Chem. Soc.* **2023**, *145,* 27160.

Synthesis of DE-ring Fragment



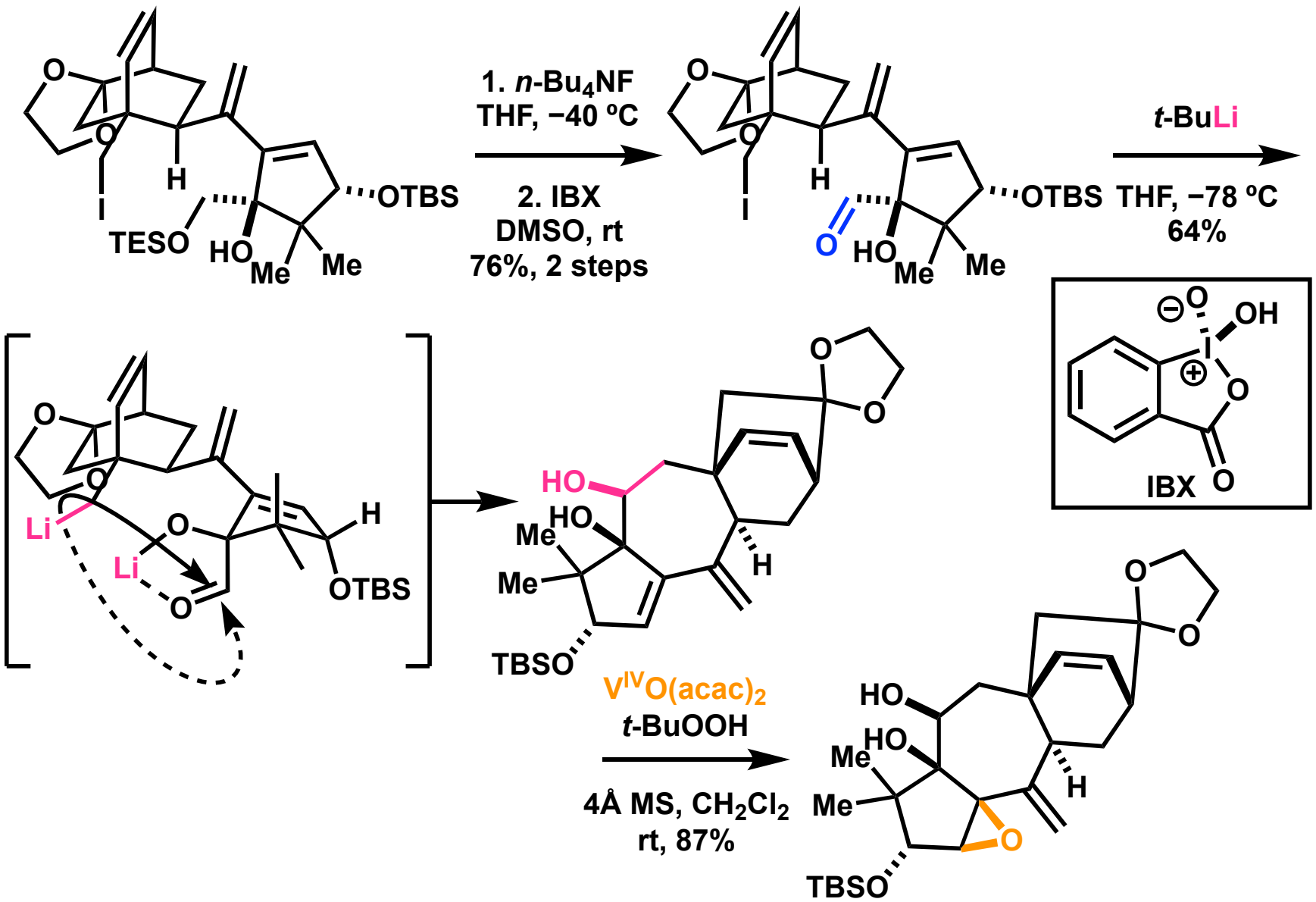
1) Zhao, W.; Zhang, D.; Wang, Y.; Yang, M. *J. Am. Chem. Soc.* **2023**, *145,* 27160.
2) Hwu, J. R.; Wetzel, J. M.; *J. Org. Chem.* **1985**, *50*, 3946.

Stille coupling



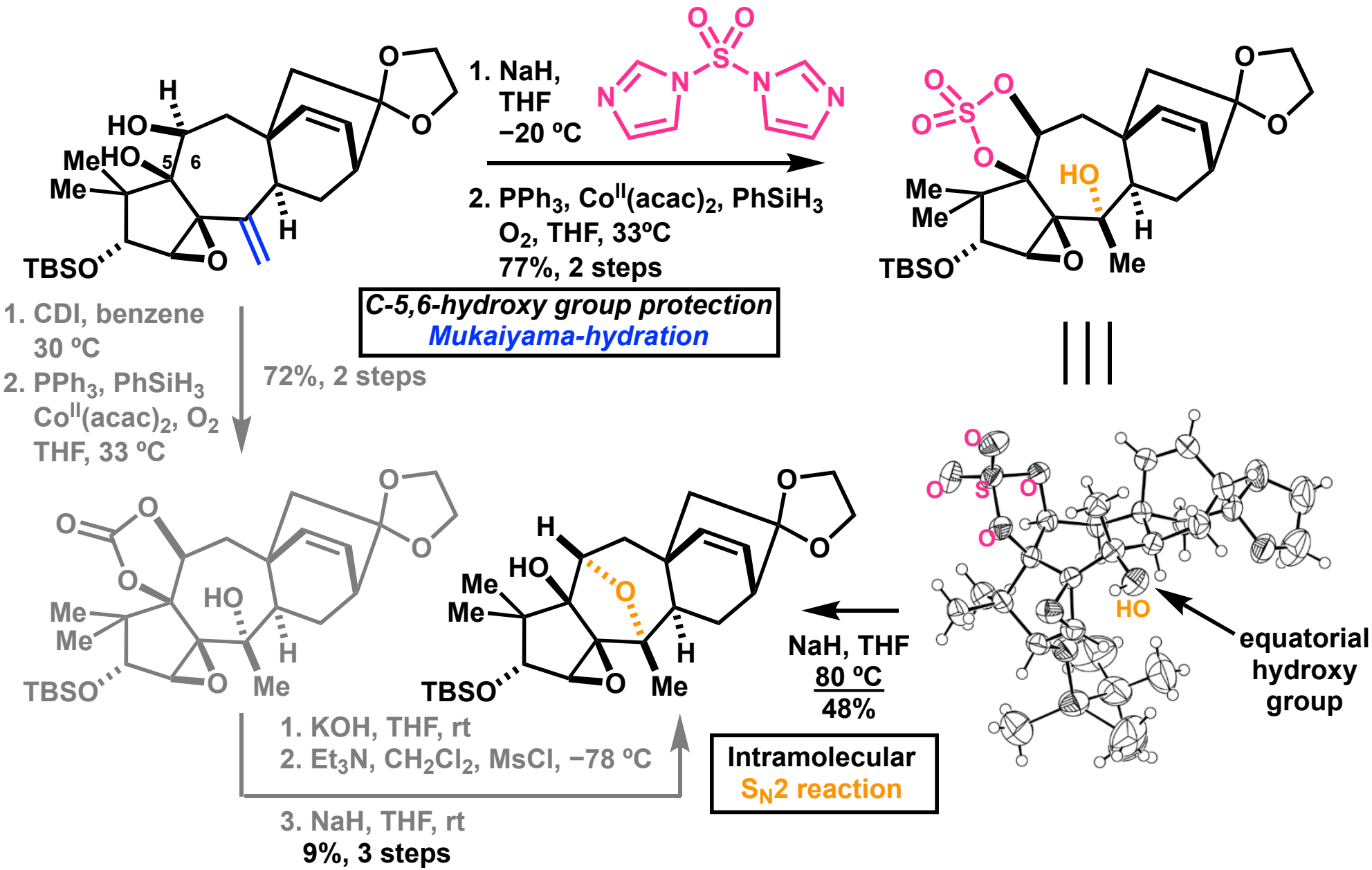
1) Zhao, W.; Zhang, D.; Wang, Y.; Yang, M. *J. Am. Chem. Soc.* **2023**, *145,* 27160.

Synthesis of Tetracyclic epoxide



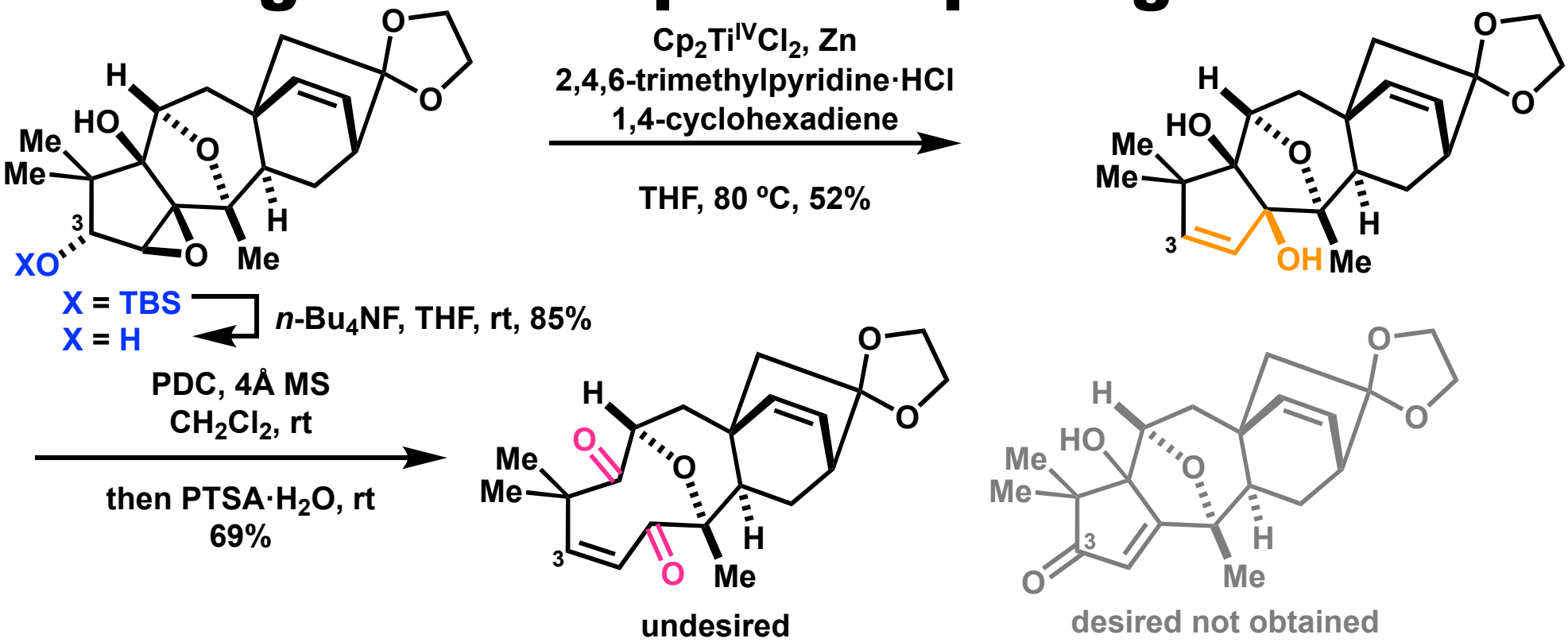
1) Zhao, W.; Zhang, D.; Wang, Y.; Yang, M. *J. Am. Chem. Soc.* **2023**, *145,* 27160.

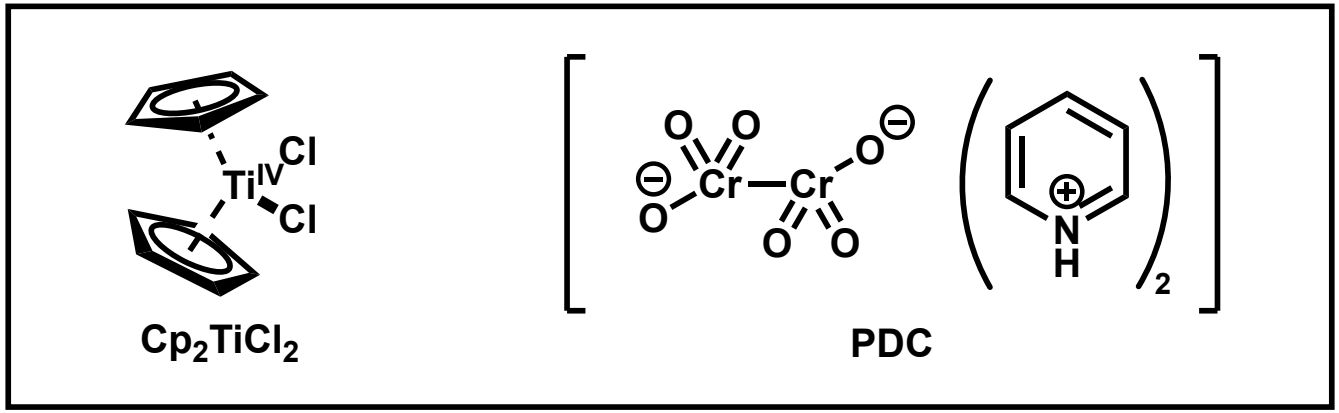
Construction of *oxa*-bicyclo[3,2,1] structure



1) Zhao, W.; Zhang, D.; Wang, Y.; Yang, M. *J. Am. Chem. Soc.* **2023**, *145,* 27160.

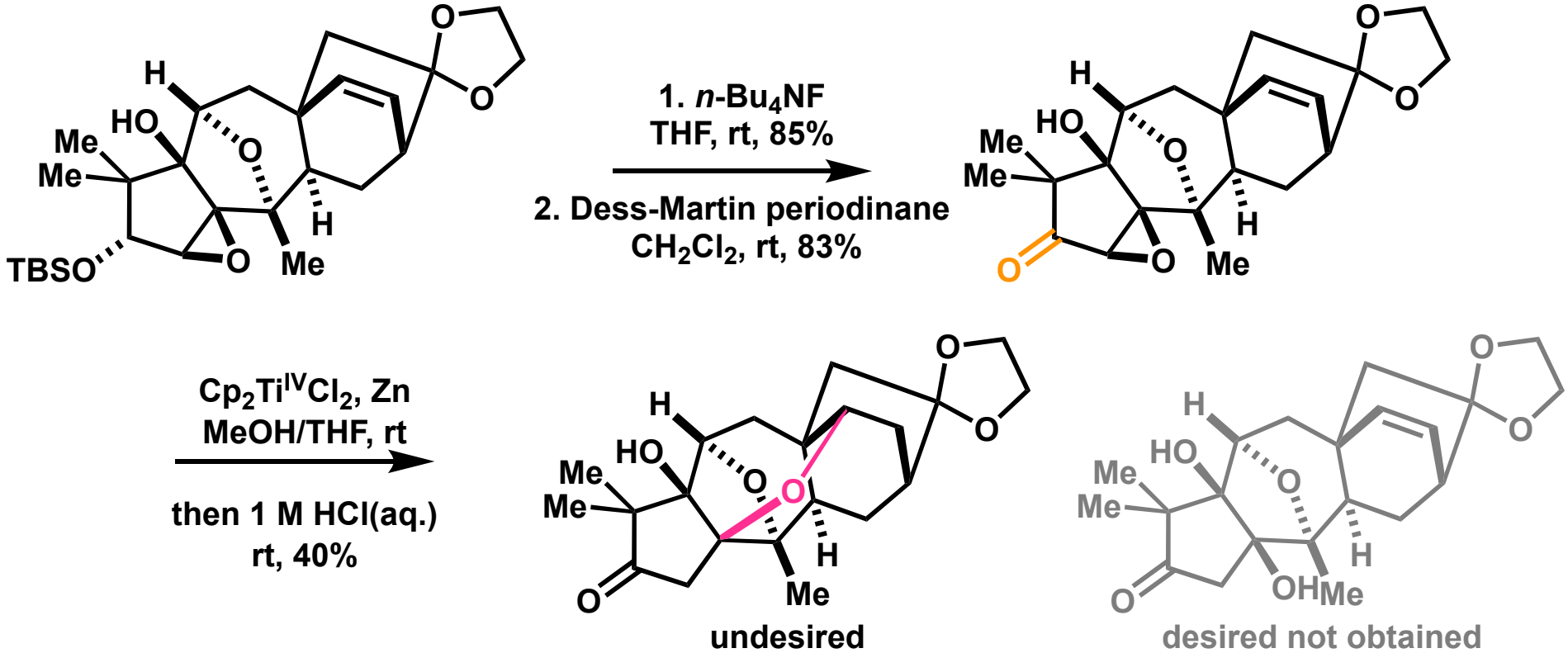
Investigation for Epoxide opening reaction-1

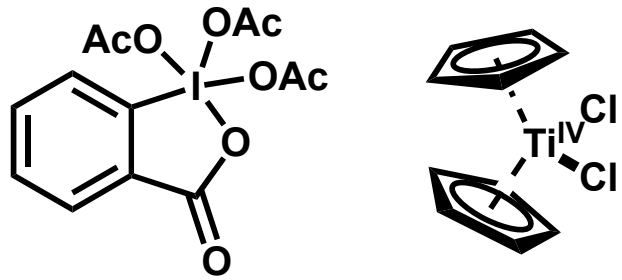




1) Zhao, W.; Zhang, D.; Wang, Y.; Yang, M. *J. Am. Chem. Soc.* **2023**, *145,* 27160.

Investigation for Epoxide opening reaction-2



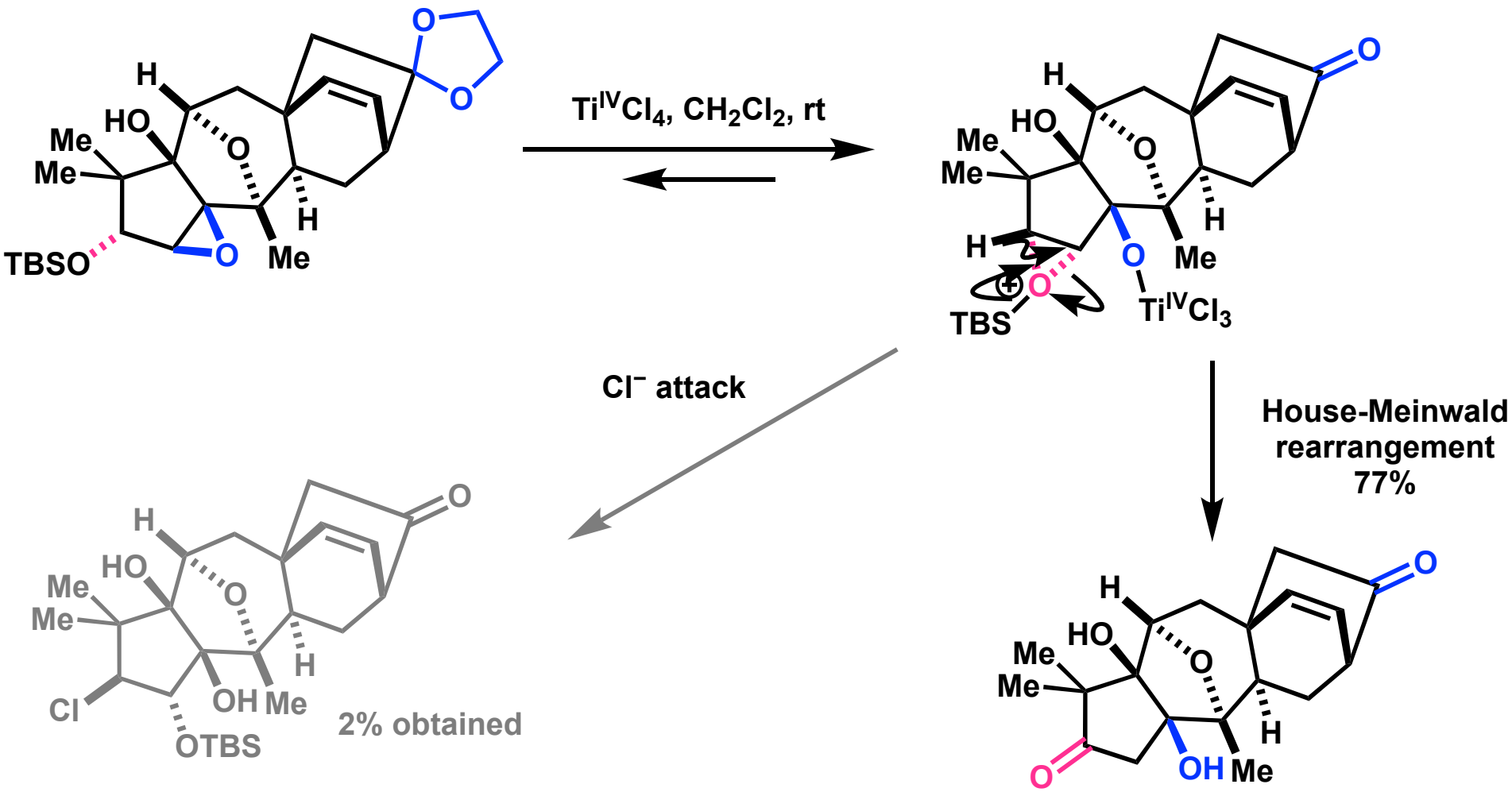


Dess-Martin periodinane

Cp_2TiCl_2

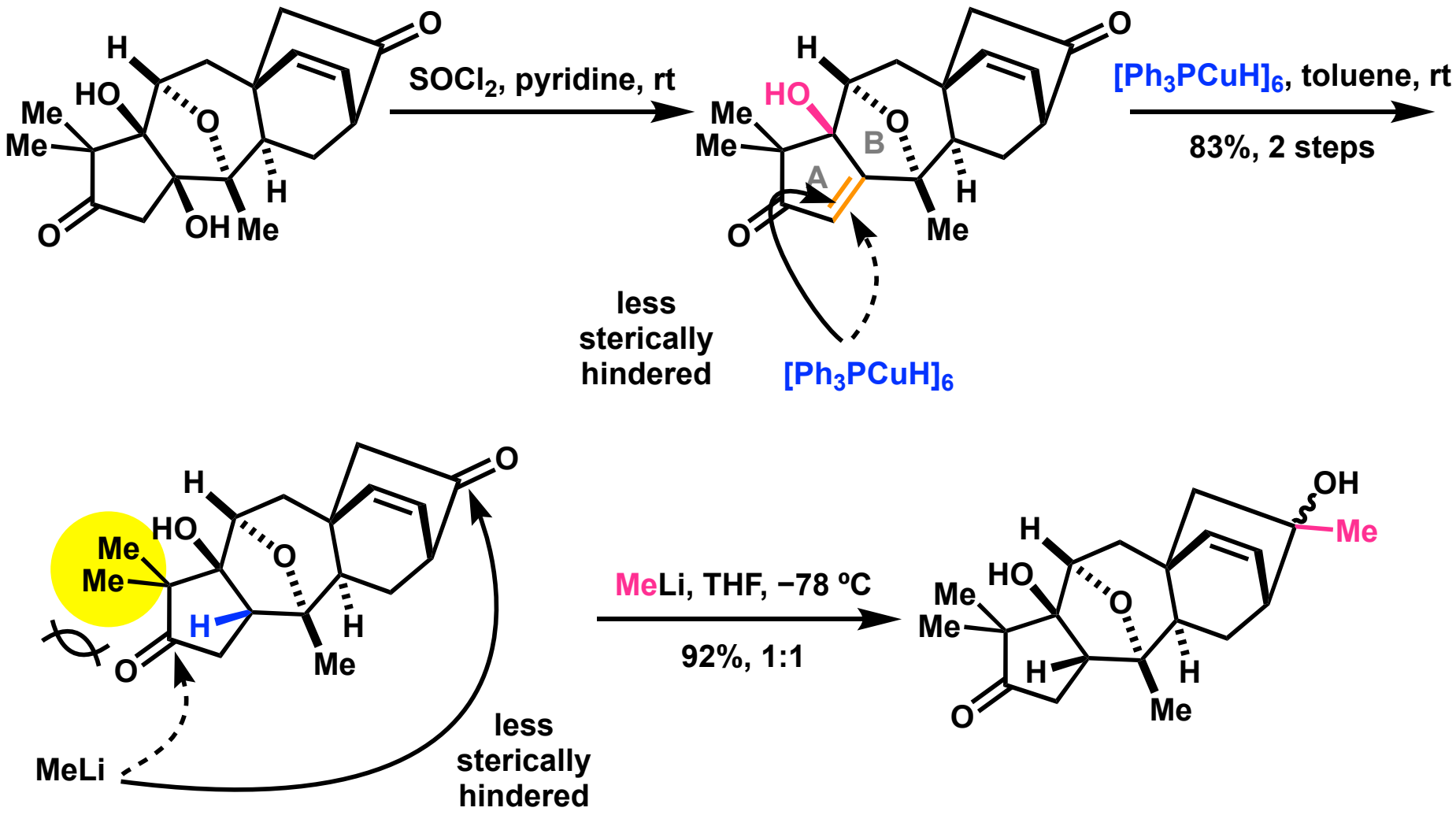
1) Zhao, W.; Zhang, D.; Wang, Y.; Yang, M. *J. Am. Chem. Soc.* **2023**, *145,* 27160.

$TiCl_4$ promoted Epoxide opening reaction



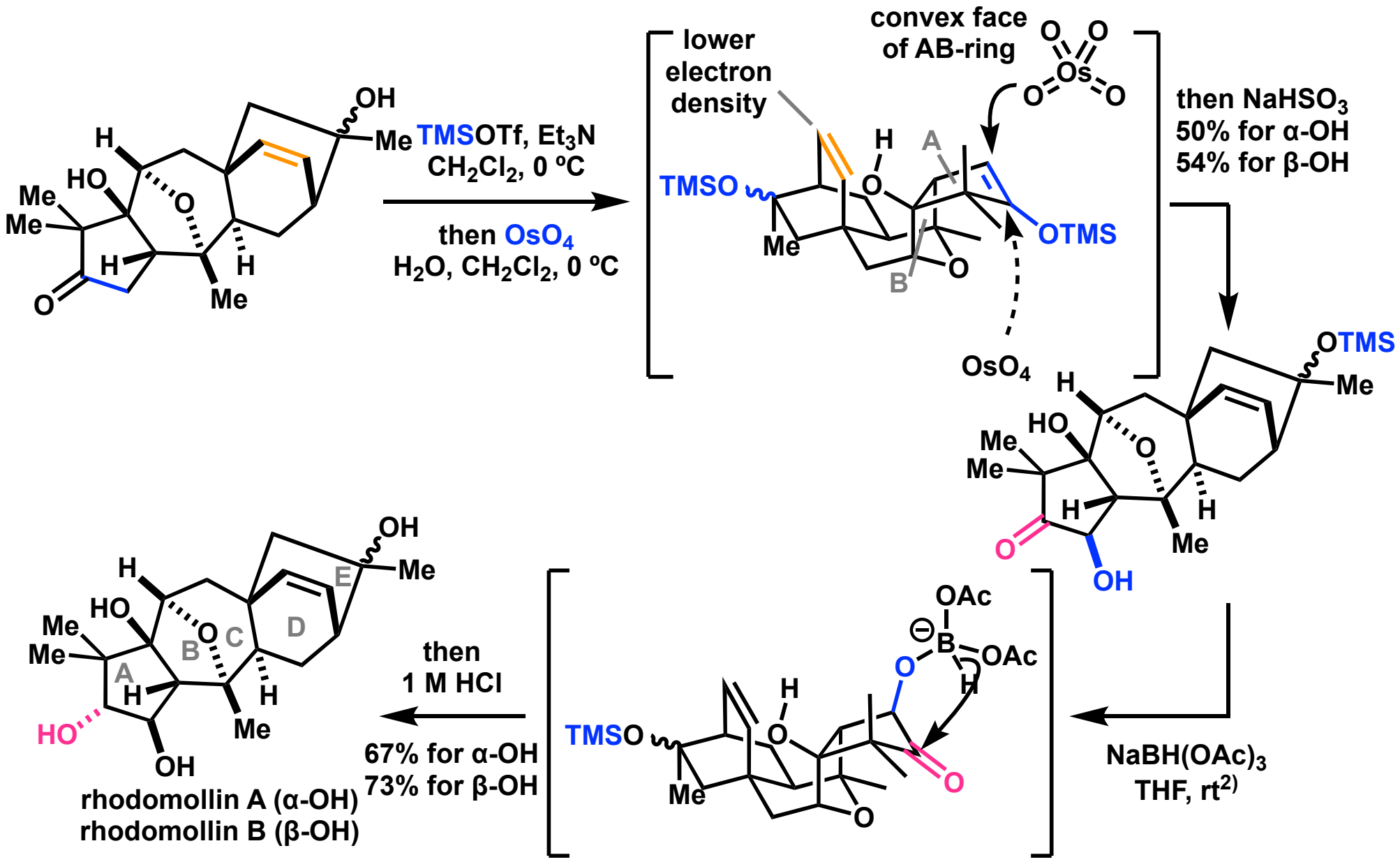
1) Zhao, W.; Zhang, D.; Wang, Y.; Yang, M. *J. Am. Chem. Soc.* **2023**, *145,* 27160.
2) He, F.; Feng, S.; Zhao, Y.; Shi, H.; Duan, X.; Li, H.; Xie, X.; She, X. *Angew. Chem. Int. Ed.* **2022**, *61*, No. e202205439

Syntheses of Rhodomollins



1) Zhao, W.; Zhang, D.; Wang, Y.; Yang, M. *J. Am. Chem. Soc.* **2023**, *145,* 27160

Synthesis of Rhodomollins

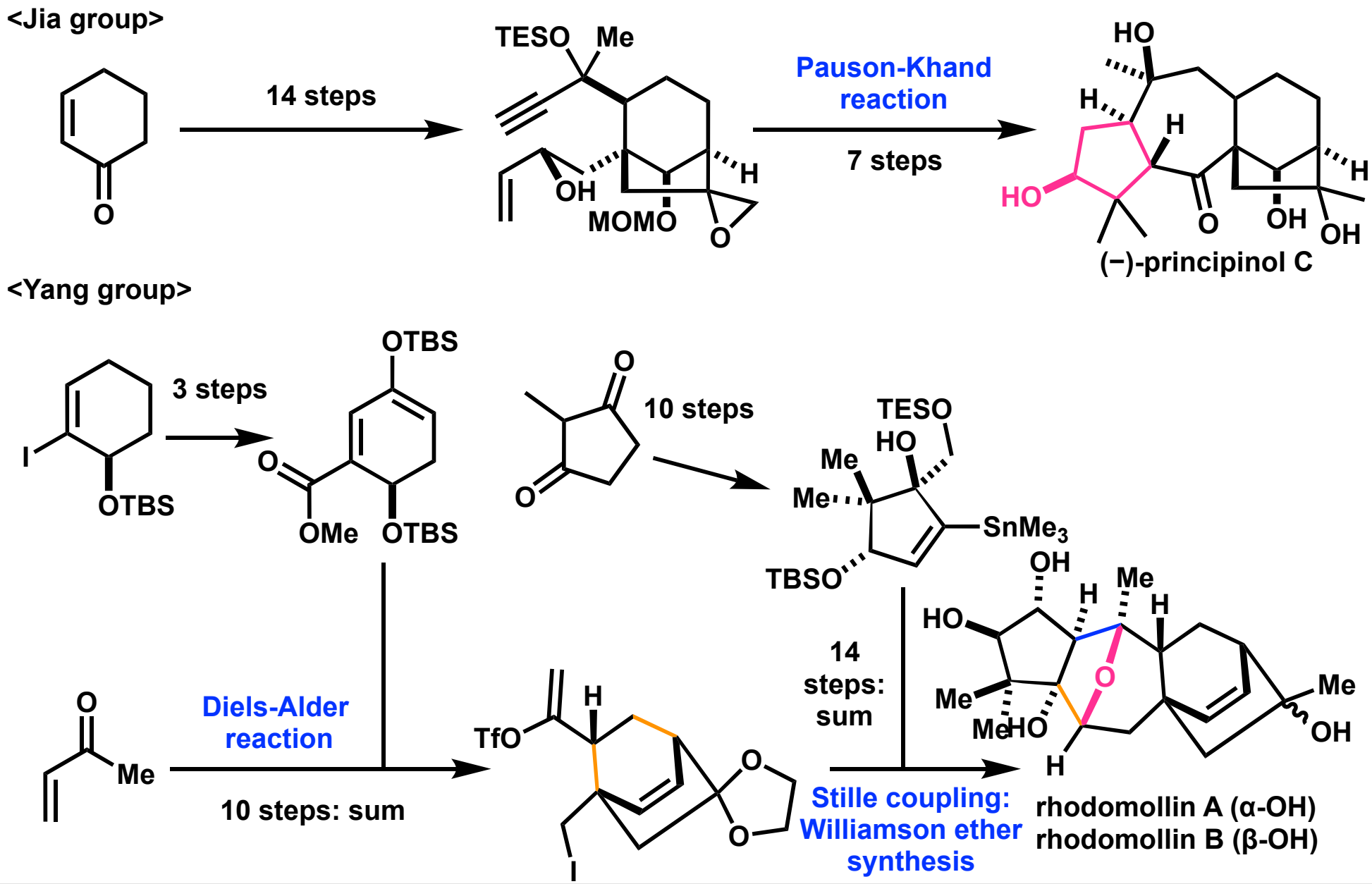


1) Zhao, W.; Zhang, D.; Wang, Y.; Yang, M. *J. Am. Chem. Soc.* **2023**, *145,* 27160

2) Watanabe, Y.; Morozumi, H.; Mutoh, H.; Hagiwara, K.; Inoue, M. *Angew. Chem. Int. Ed.* **2023**, *62,* e202309688

Contents

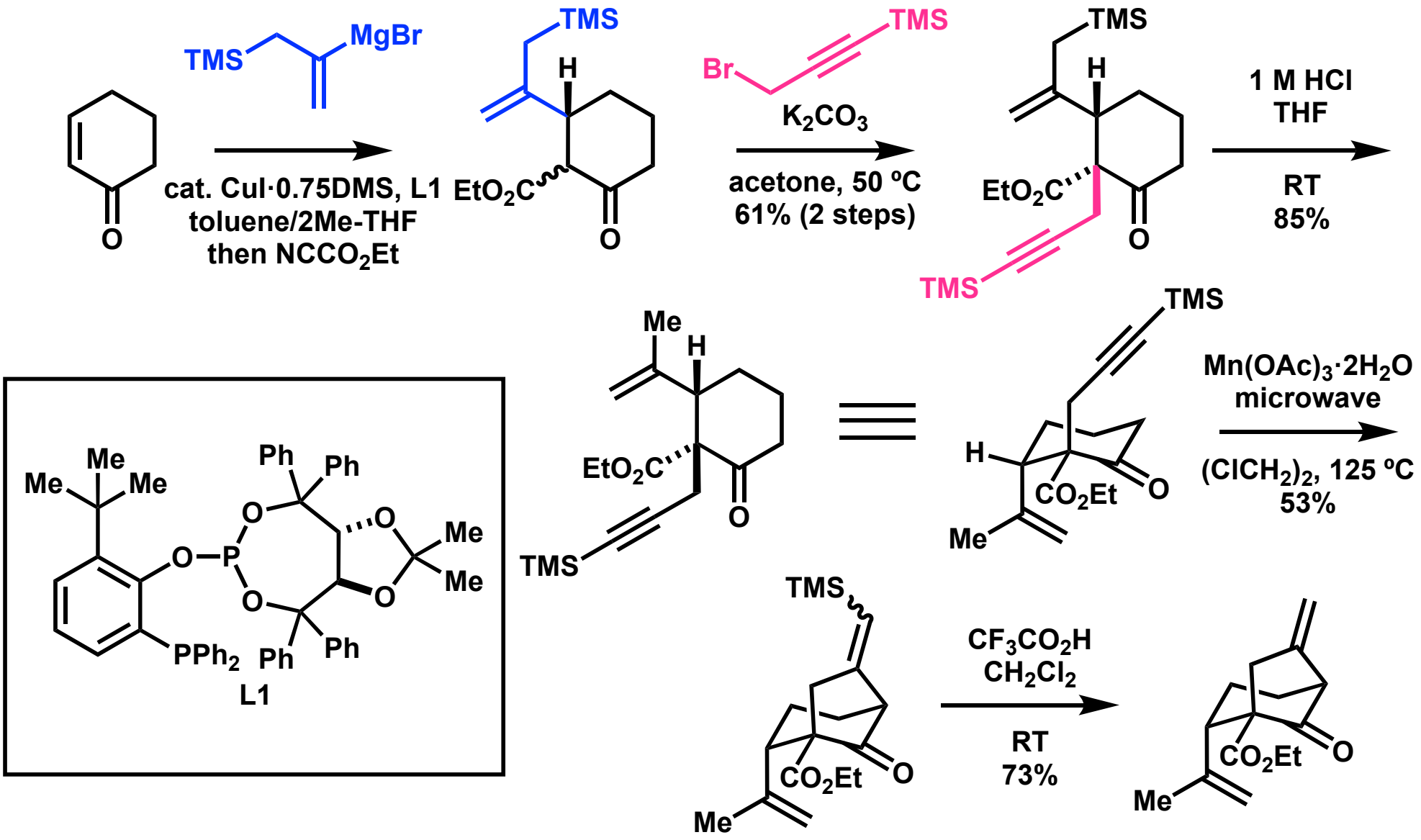
Summary



1) Ma, T.; Cheng, H.; Pitchakuntla, M.; Ma, W.; Jia, Y. *J. Am. Chem. Soc.* **2022**, *144*, 20196.

Appendix

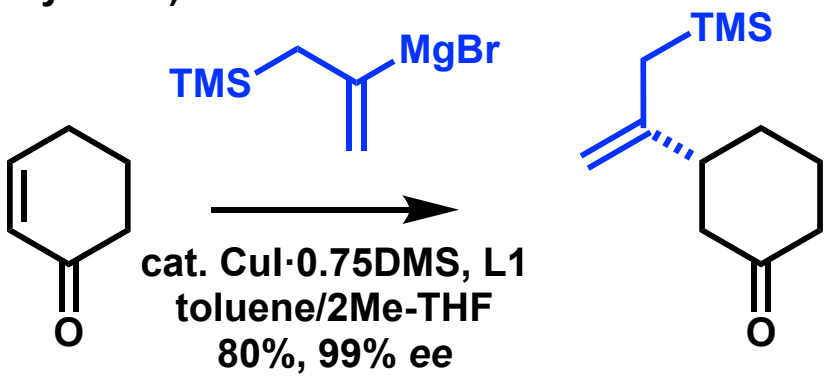
Syntheses of CD-ring

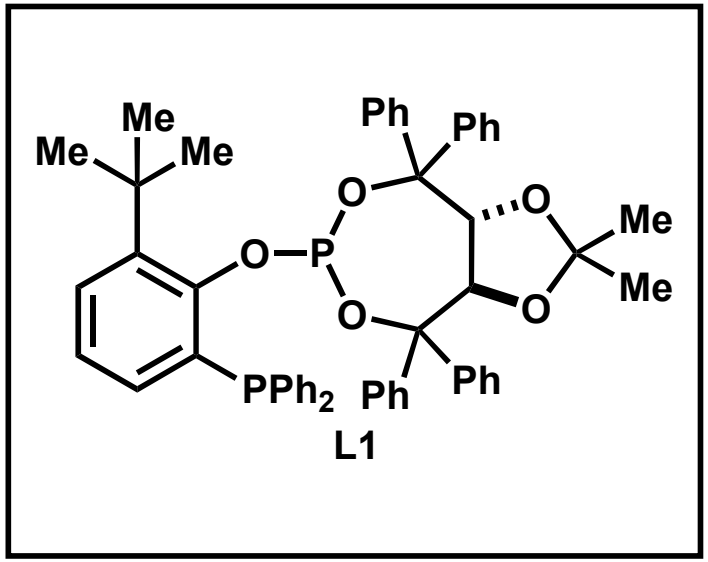


1) Guo, J.; Li, B.; Ma, W.; Pitchakuntla, M.; Jia, Y.; *Angew. Chem., Int. Ed.* **2020**, *59*, 15195

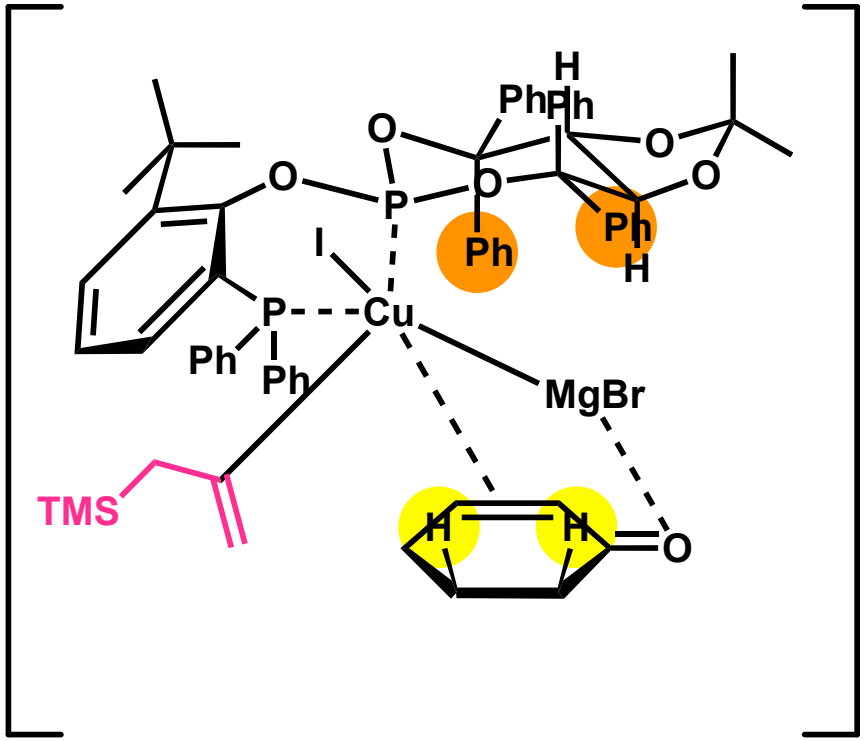
Enantio Selective 1,4-addition

baran (2016, maoecrystal V)[1)]



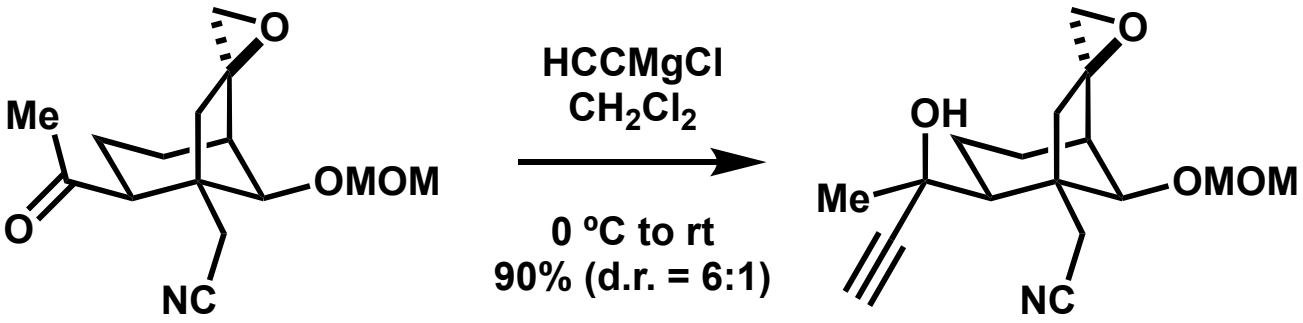


my opinion for selectivity



1) Cernijenko, A.; Risgaard, R.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 9425
2) Hayashi, M.; Matsumoto, R. *Tetrahedron Lett.* **2017**, *58*, 1793

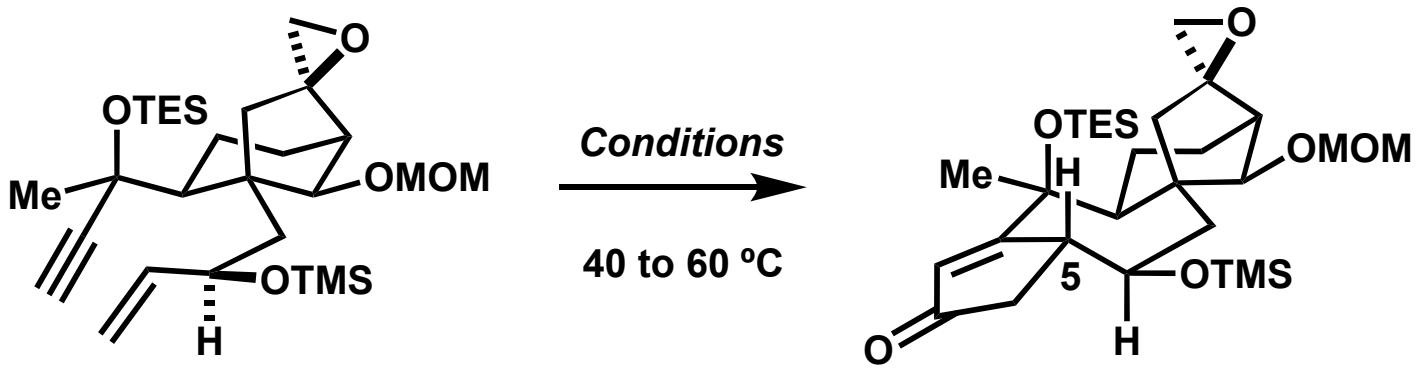
Optimization for Grignard Reaction



entry	conditions	yield (%)	d.r.
1	HCCMgBr (2.0 equiv), THF, 0 ºC to rt	73	1:3
2	TMSCCLi (2.0 equiv), THF, 0 ºC, then TBAF	51	1:4
3	Lithium acctylide ethylenediamine complex, THF, 0 ºC	-	-
4	HCCMgBr (2.0 equiv), toluene, 0 ºC to rt	71	4:1
5	HCCMgBr (2.0 equiv), CH_2Cl_2, 0 ºC to rt	69	6:1
6	HCCMgCl (2.0 equiv), toluene, 0 ºC to rt	93	4:1
7	HCCMgCl (2.0 equiv), CH_2Cl_2, 0 ºC to rt	91	6:1
8	HCCMgCl (2.0 equiv), Et_2O, 0 ºC to rt	49	2:1
9	HCCMgCl (2.0 equiv), MeTHF, 0 ºC to rt	49	1:3

1) Ma, T.; Cheng, H.; Pitchakuntla, M.; Ma, W.; Jia, Y. *J. Am. Chem. Soc.* **2022**, *144*, 20196

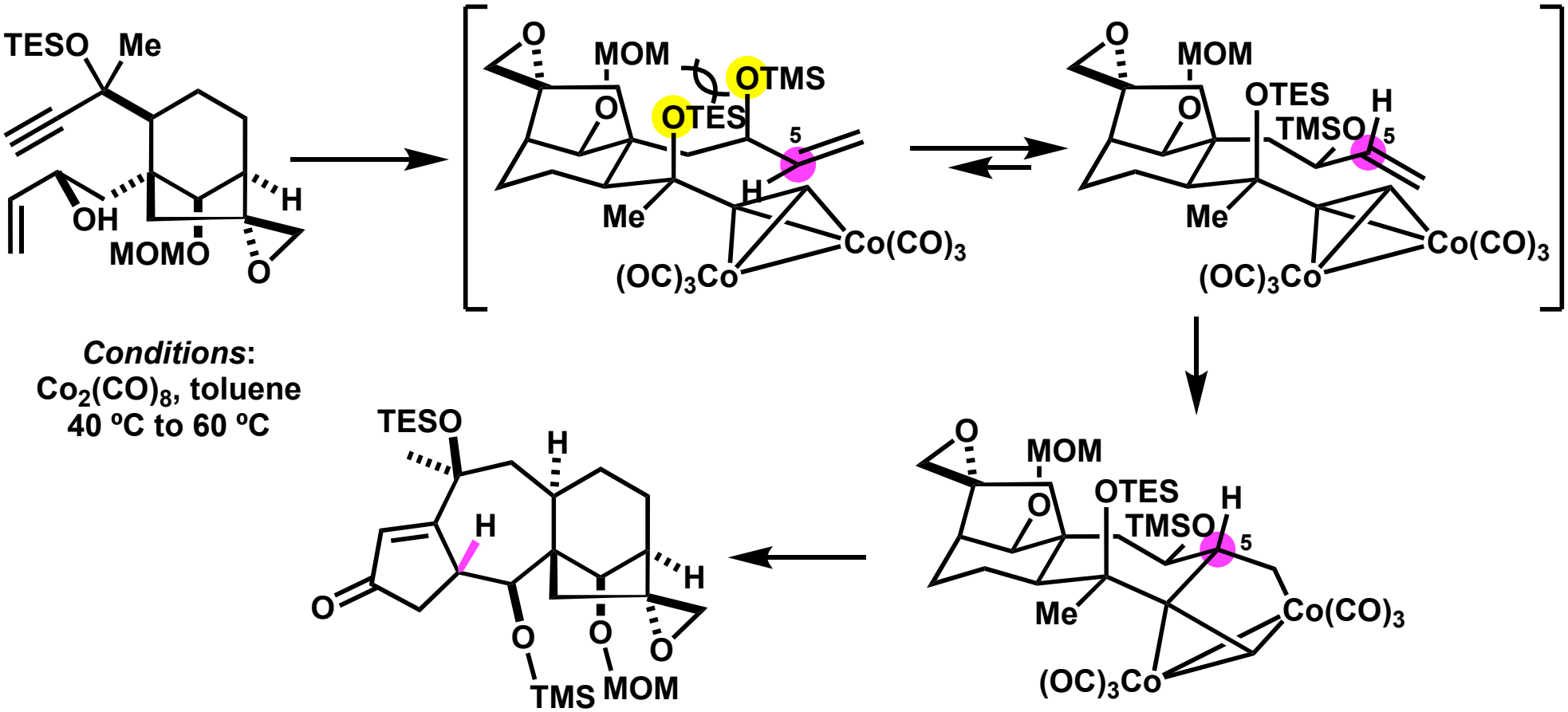
Optimization for Pauson-Khand reaction



entry	conditions	yield (%)
1	$Co_2(CO)_8$, toluene, 40 ºC	<5
2	$Co_2(CO)_8$, toluene, 40 ºC to 60 ºC	45
3	$Co_2(CO)_8$, toluene, 40 ºC to 110 ºC	21
4	$Co_2(CO)_8$, THF, 40 ºC to 60 ºC	20
5	$Co_2(CO)_8$, toluene, 40 ºC; then NMO, 60 ºC	-
6	$Co_2(CO)_8$, toluene, 40 ºC; then TMTU, rt	-
7	$Co_2(CO)_8$, toluene, 40 ºC; then TMAO, rt	-
8	$Co_2(CO)_8$, toluene, 40 ºC; then DMSO, rt	-
9	$[RhCl(CO)_2]_2$ (5 mol%), CO, toluene, rt to 90 ºC	C5-*epi*: 21%
10	$[RhCl(CO)_2]_2$ (5 mol%), CO, toluene, 110 ºC	-
11	$[RhCl(CO)_2]_2$ (1.5 mol%), CO, toluene, 110 ºC	-

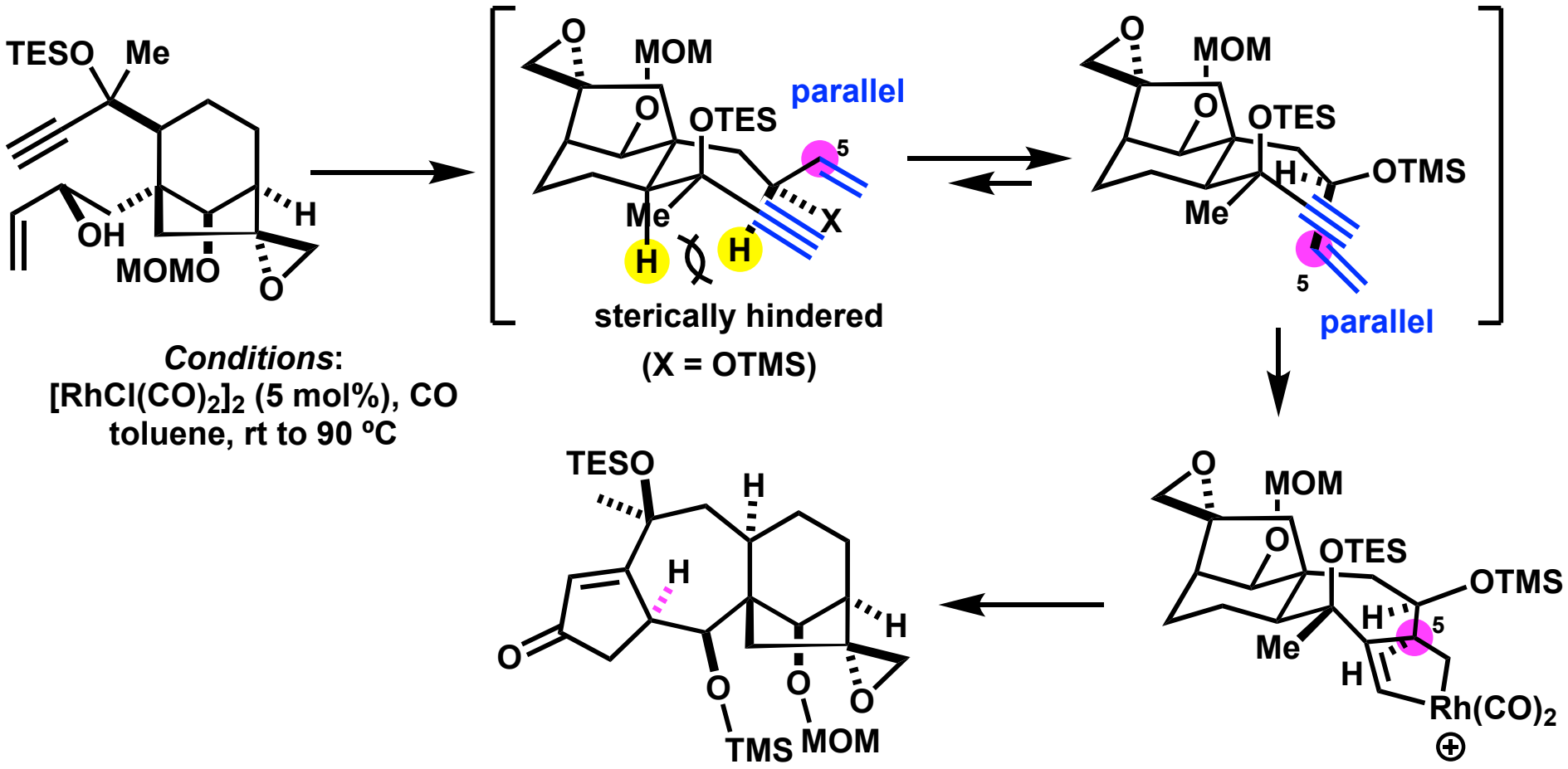
1) Ma, T.; Cheng, H.; Pitchakuntla, M.; Ma, W.; Jia, Y. *J. Am. Chem. Soc.* **2022**, *144*, 20196

Stereoselectivity of Pauson-Khand reaction with Cobalt



1) Ma, T.; Cheng, H.; Pitchakuntla, M.; Ma, W.; Jia, Y. *J. Am. Chem. Soc.* **2022**, *144*, 20196
2) Marco-Contelles, J.; De Opazo, E. *J. Carbohydr. Chem.* **2002**, *21*, 201

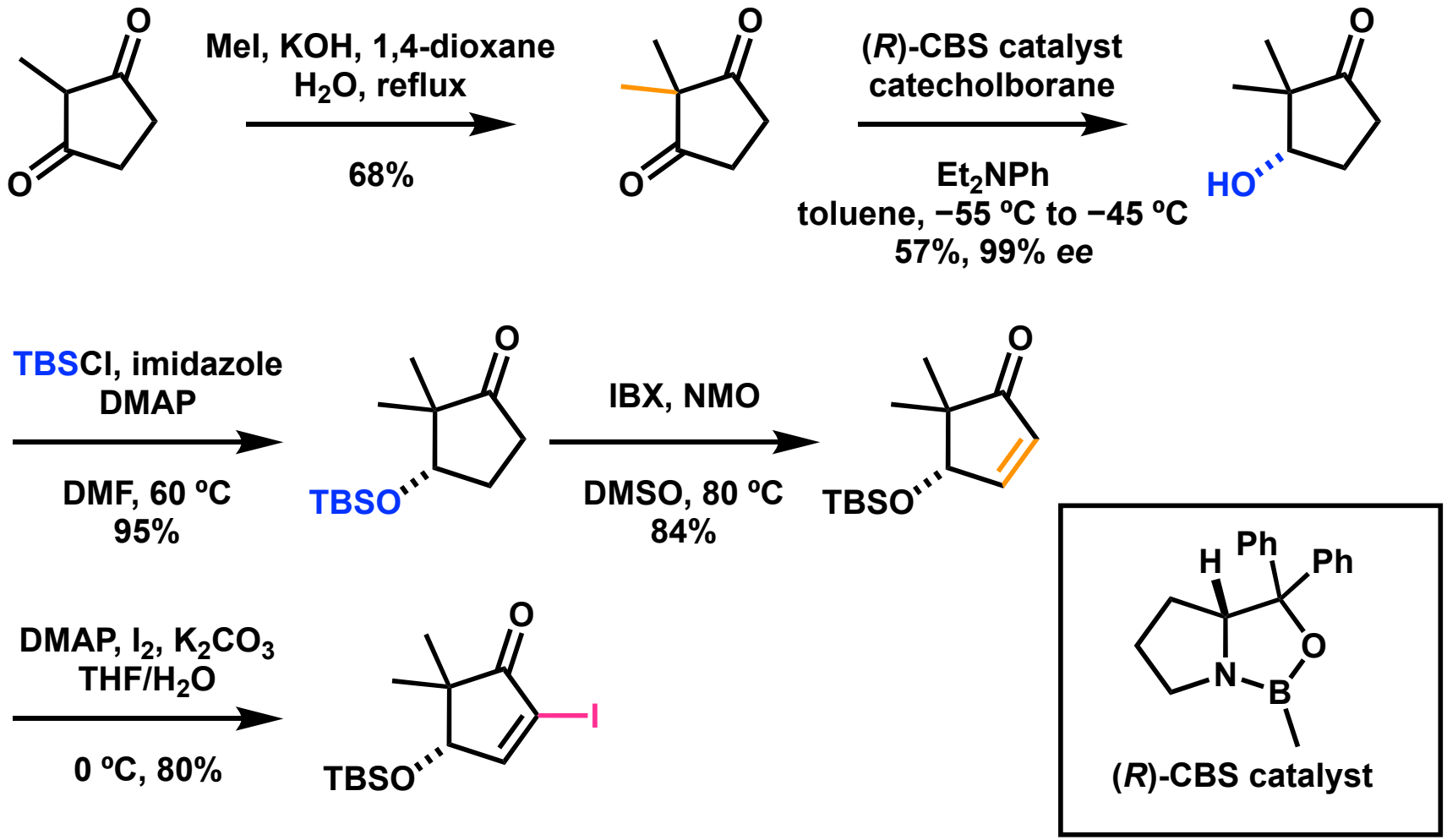
Stereoselectivity of Pauson-Khand-type reaction with Rhodium



Conditions:
$[RhCl(CO)_2]_2$ (5 mol%), CO
toluene, rt to 90 ºC

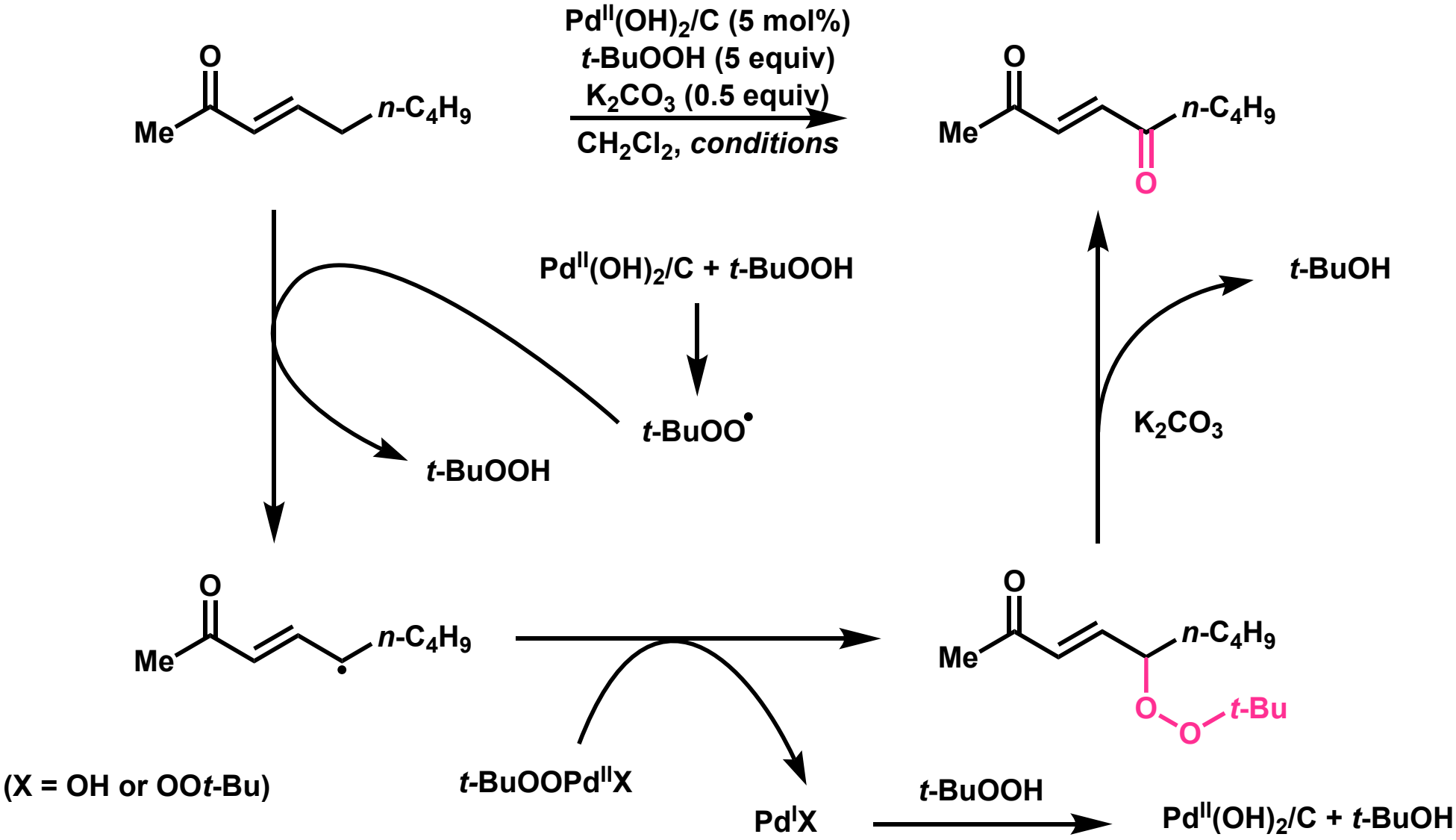
1) Ma, T.; Cheng, H.; Pitchakuntla, M.; Ma, W.; Jia, Y. *J. Am. Chem. Soc.* **2022**, *144*, 20196
2) Angew. *Chem. Int. Ed.* **2023**, *62*, e202300211 3) *J. Am. Chem. Soc.* **2011**, *133*, 7621

Preparation of A-ring-iodide



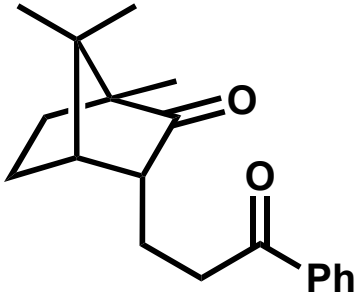
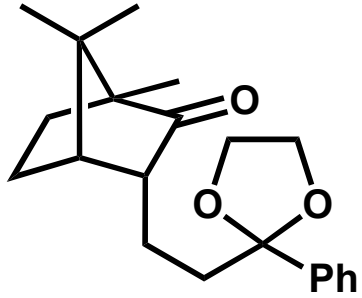
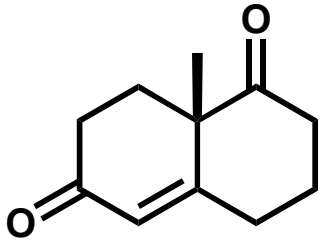
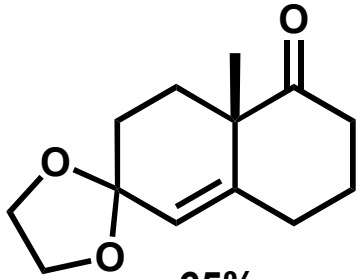
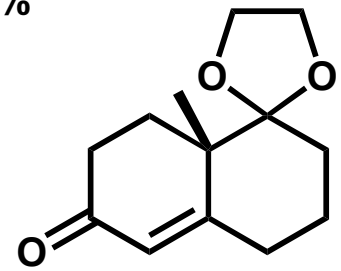
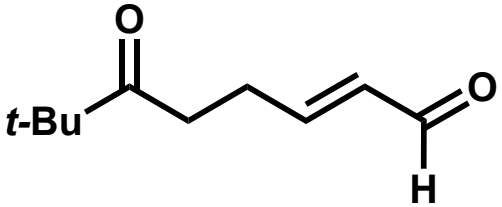
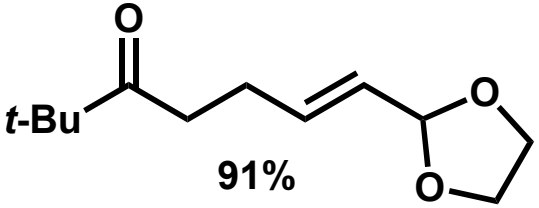
1) Turlik, A.; Chen, Y.; Scruse, A. C.; Newhouse, T. M. *J. Am. Chem. Soc.* **2019**, *141*, 8088
2) Wang, Y.; Zhao, R.; Yang, M. *J. Am. Chem. Soc.* **2022**, *144*, 15033

Oxidation of Enones to 1,4-Enediones



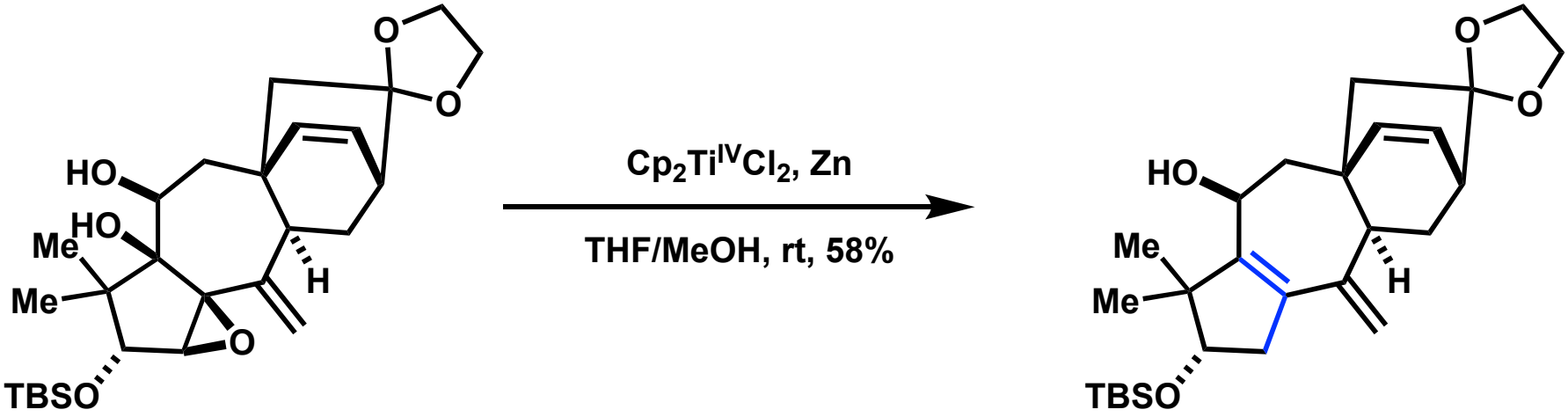
1) Yu, J-Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003,** *125*, 3232

Dioxolation with Trimethylsilyl Cationic Species

substrate	$(TMSCH_2)_2$ equiv	TMSOTf equiv	concentration (M) / CH_2Cl_2	time (h) / temp. (ºC)	products / isolated yield
	1.15	0.25	0.60	31/−45	 82%
	1.05	0.02	1.5	51/−78	 65%  detected diketal was also detected
	1.05	0.02	0.61	5/−78	 91%

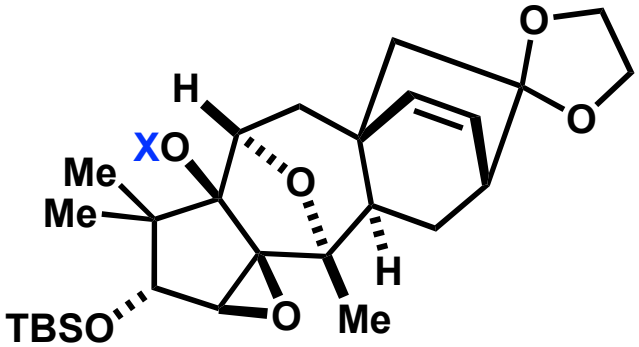
1) Hwu, J. R.; Wetzel, M. J. *J. Org. Chem.* **1985**, *50*, 3946

Epoxide Opening without *oxa*-bicyclo[3,2,1] core



1) Zhao, W.; Zhang, D.; Wang, Y.; Yang, M. *J. Am. Chem. Soc.* **2023**, *145,* 27160.

Investigation for Epoxide opening reaction-3

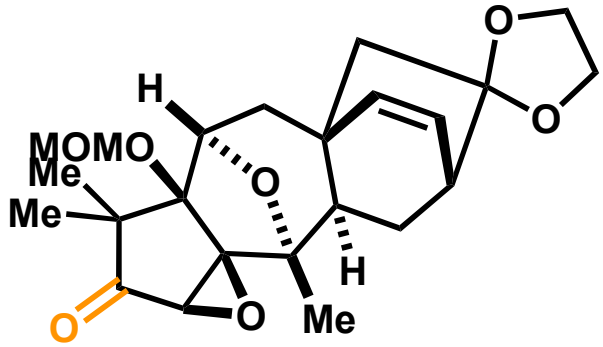


X = H
X = MOM

MOMBr, *i*-Pr_2NEt, *n*-Bu_4NI
THF, 80 ºC, 74%

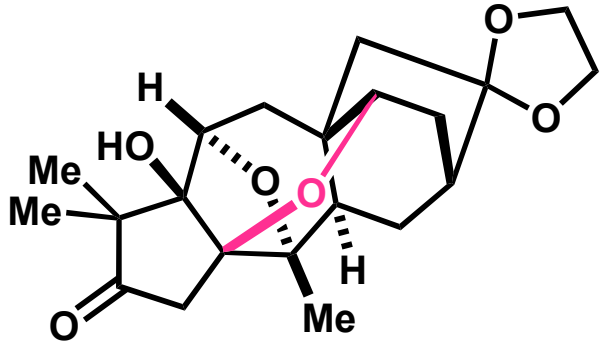
1. *n*-Bu_4NF, THF, rt
2. Dess-Martin periodinane

CH_2Cl_2, rt, 72% (2 steps)

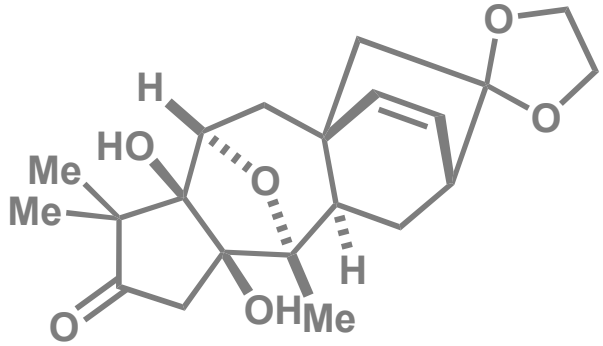


Cp_2TiCl_2, Zn
MeOH/THF, rt

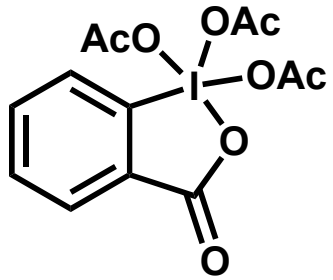
then PPTS(aq.)
rt, 38%



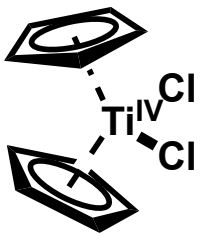
undesired



desired not obtained



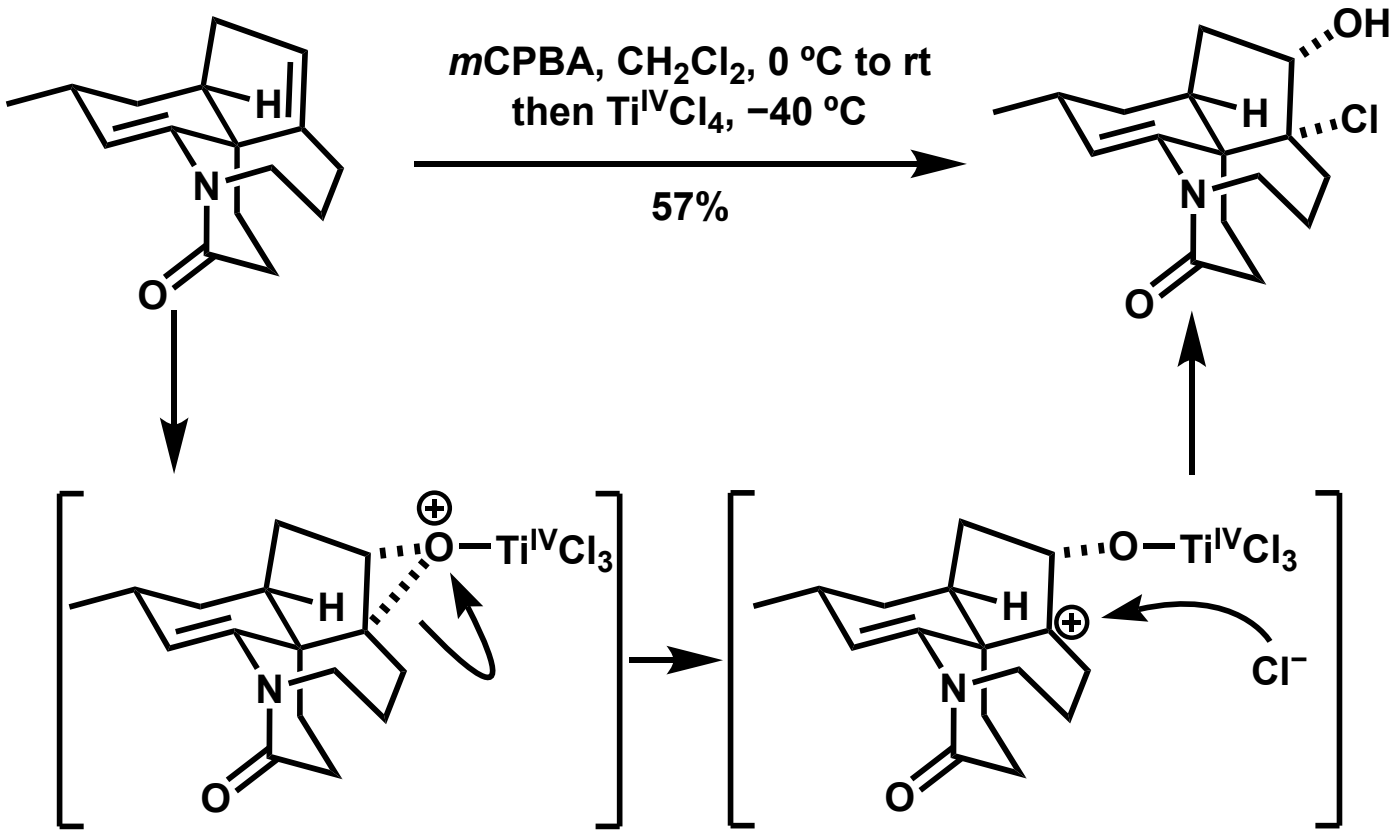
Dess-Martin periodinane



Cp_2TiCl_2

1) Zhao, W.; Zhang, D.; Wang, Y.; Yang, M. *J. Am. Chem. Soc.* **2023**, *145,* 27160.

Epoxide Opening with $TiCl_4$



1) He, F.; Feng, S.; Zhao, Y.; Shi, H.; Duan, X.; Li, H.; Xie, X.; She, X. *Angew. Chem. Int. Ed.* **2022**, *61*, No. e202205439