Total synthesis of Phainanoid A

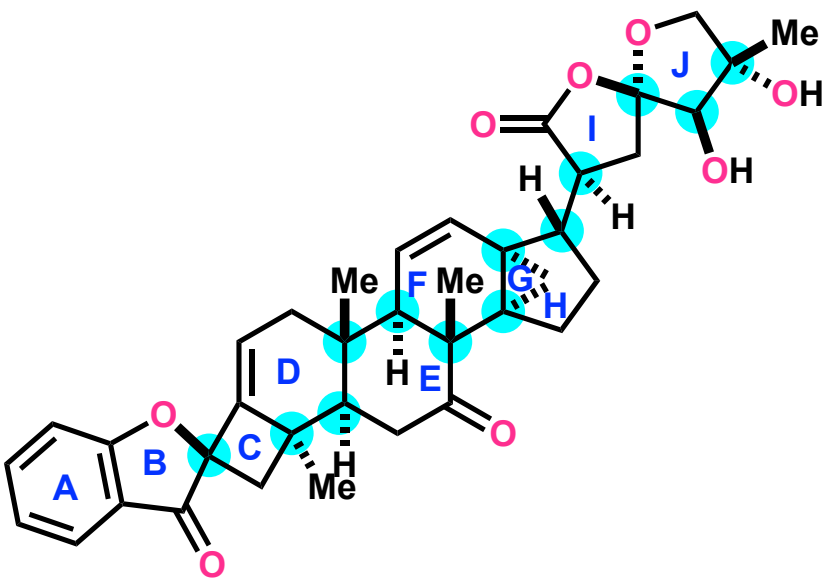
2024.10.19 Literature Seminar

B4 Dan Matsubara

Contents

Contents

Phainanoid A

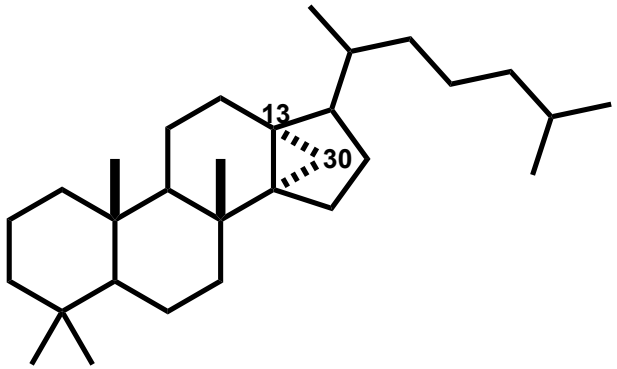


Isolation
from *Paranephelium hainanensis*[1)]

Biological activity
1. cytotoxicity against various cancer cell lines
2. potent immunosuppressive activity against induced proliferation of T and B lymphocytes

Total synthesis
racemic : Dong (2021)[2)]
asymmetric : Dong (2023)[3)]

Structual features
- **13,30-cyclodammarane-type triterpenoids**
- **benzofuranone based 4,5-spirocycle (A/B/C rings)**
- **13 stereocenters with 5 quaternary carbons (D/E/F rings)**
- **[4.3.1] propellane (F/G/H rings)**
- **5,5-oxaspirolactone (I/J rings)**



13, 30-cyclodammarane

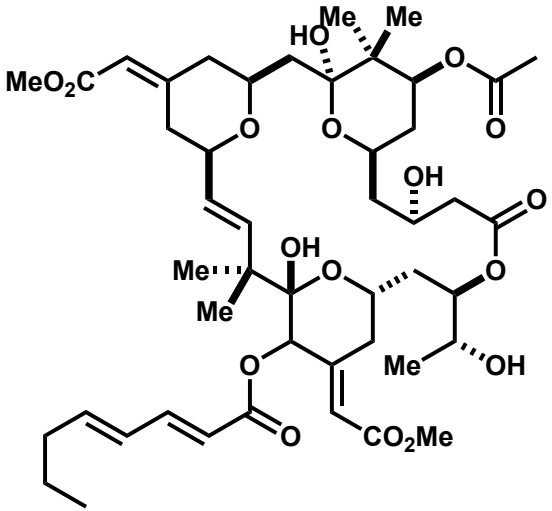
1) Fan, Y.; Zhang, H.; Zhou, Y.; Liu, H.; Tang, W.; Zhou, B.; Zuo, J.; Yue, *J. Am. Chem. Soc.* **2014,** *137,* 138.
2) Xie, J.; Liu, X.; Zhang, N.; Choi, S.; Dong, G. *J. Am. Chem. Soc.* **2021,** *143*, 19311.
3) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

Introduction of Prof. Dong

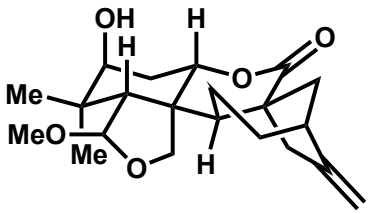
Prof. Guangbin Dong

1999-2003 B.S. @Peking University (Prof. Zhen Yang and Prof. Jiahua Chen)
2004-2009 Ph.D @Stanford University (Prof. Barry M. Trost)
2009-2011 Postdoc. @California Institute of Technology (Prof. Robert H. Grubbs)
2011-2016 Assistant Professor @University of Texas at Austin
2016 Professor @University of Texas at Austin
2016- Professor @University of Chicago

Research topics: C-H, C-C bond activation,Total synthesis



bryostatin 1

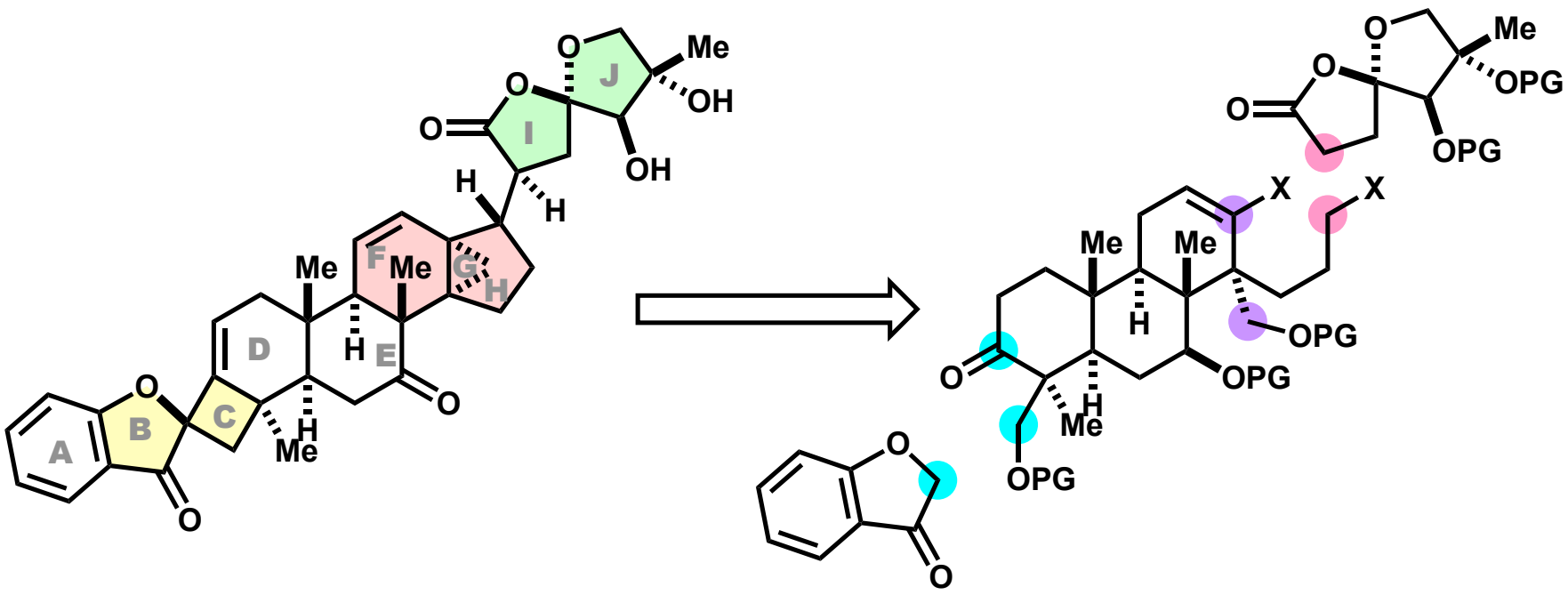


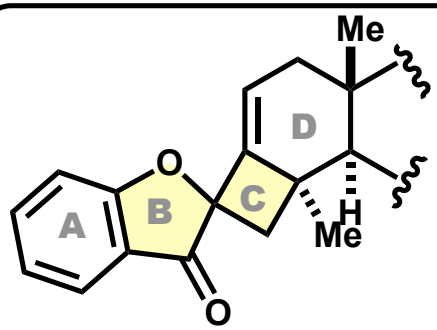
enmein

1 https://chemistry.uchicago.edu/faculty/guangbin-dong

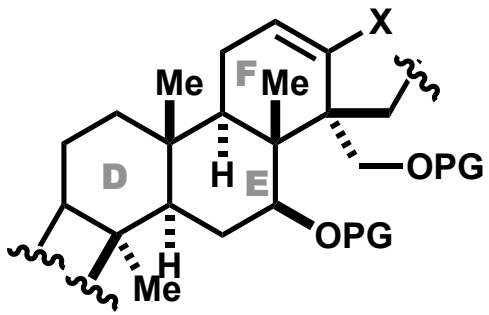
Contents

Synthetic Approach

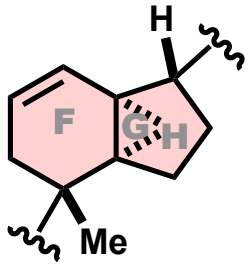




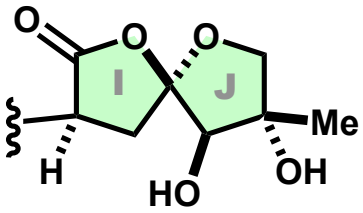
4,5-spirocycle



D/E/F core



[4. 3. 1] propellane

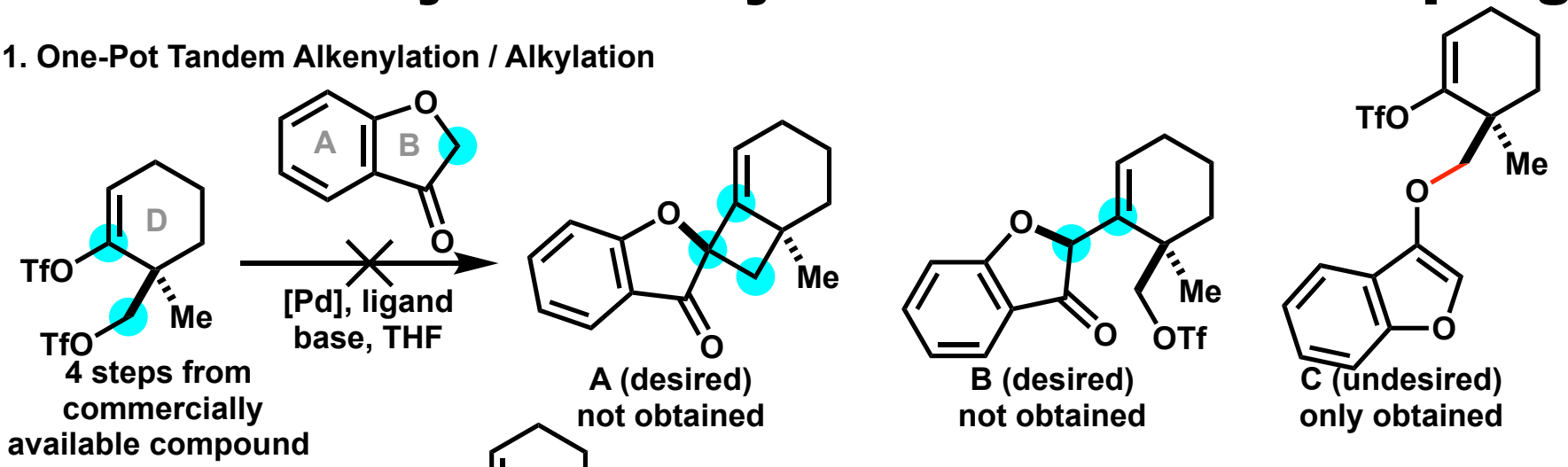


5,5-oxaspirolactone

1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

Tandem Alkenylation/Alkylation and Cross Coupling

1. One-Pot Tandem Alkenylation / Alkylation



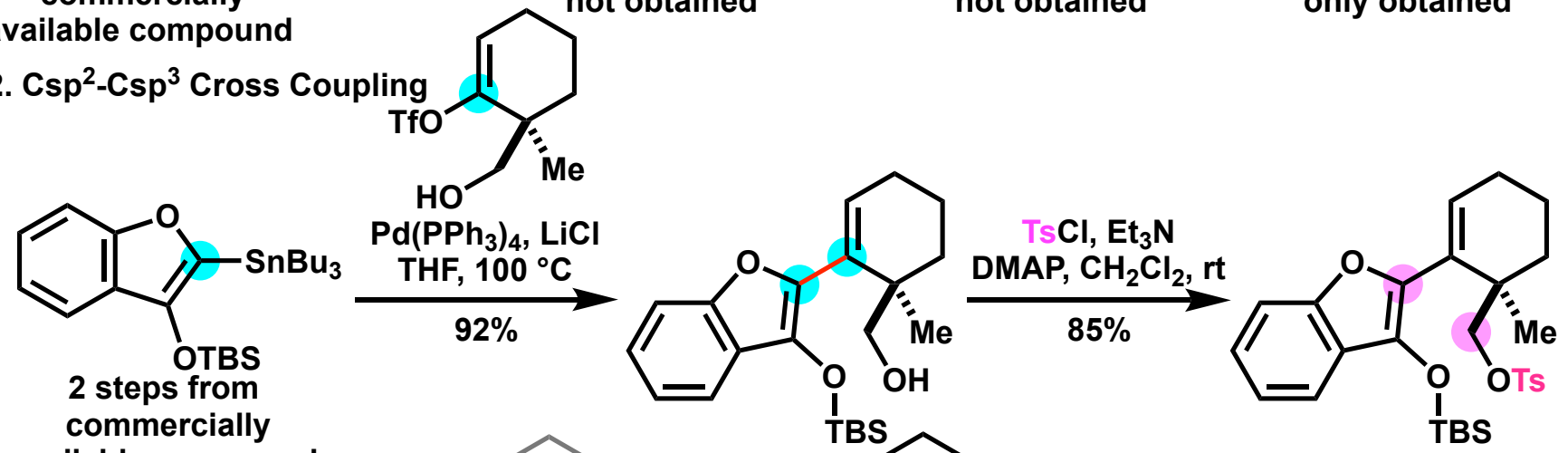
4 steps from commercially available compound

A (desired) not obtained

B (desired) not obtained

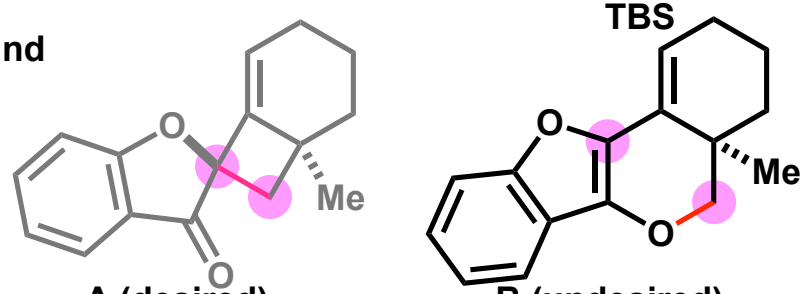
C (undesired) only obtained

2. Csp^2-Csp^3 Cross Coupling



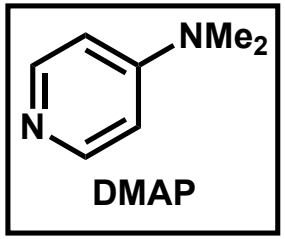
2 steps from commercially available compound

n-Bu_4NF
THF, 0 °C



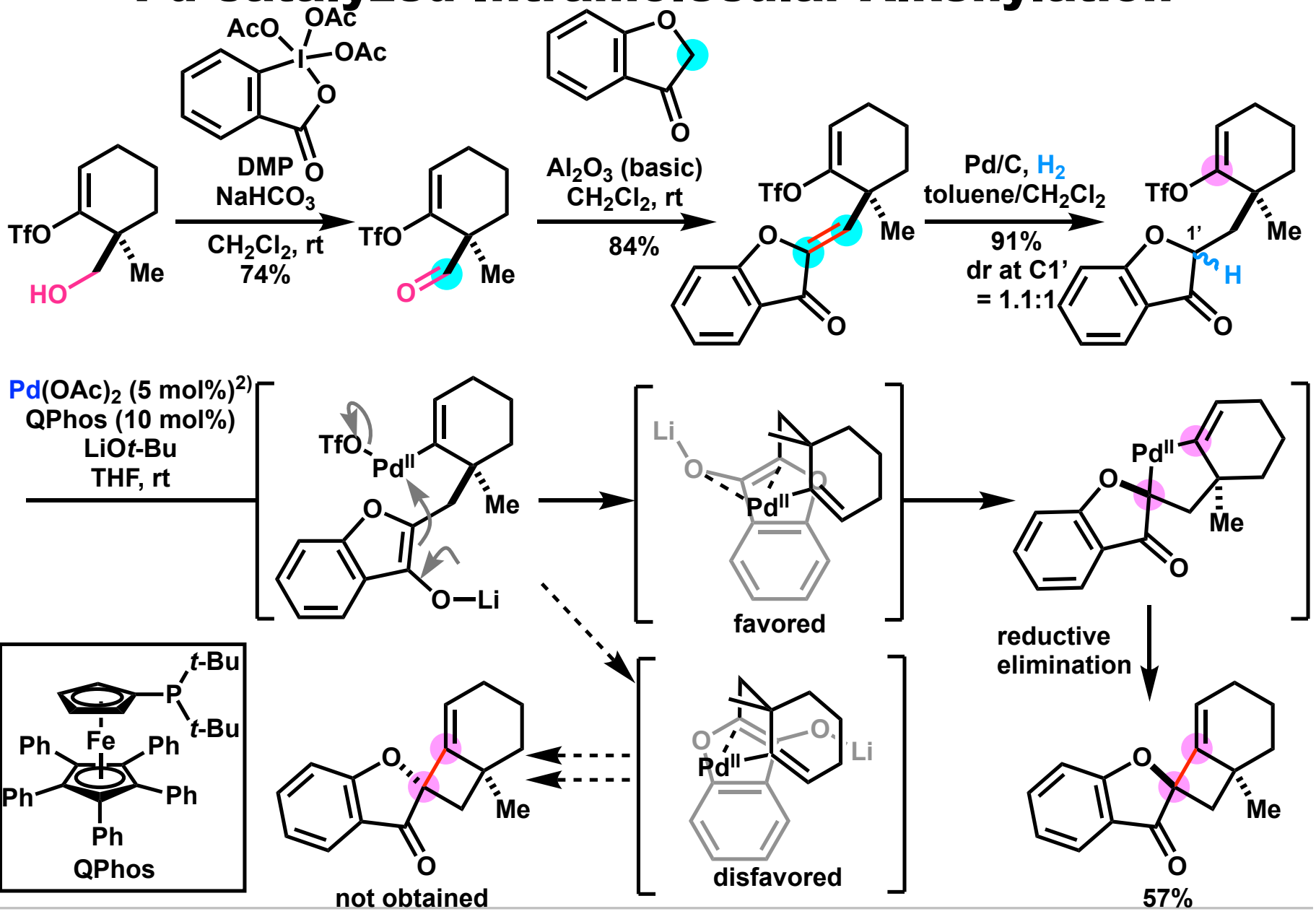
A (desired) not obtained

B (undesired) 67%



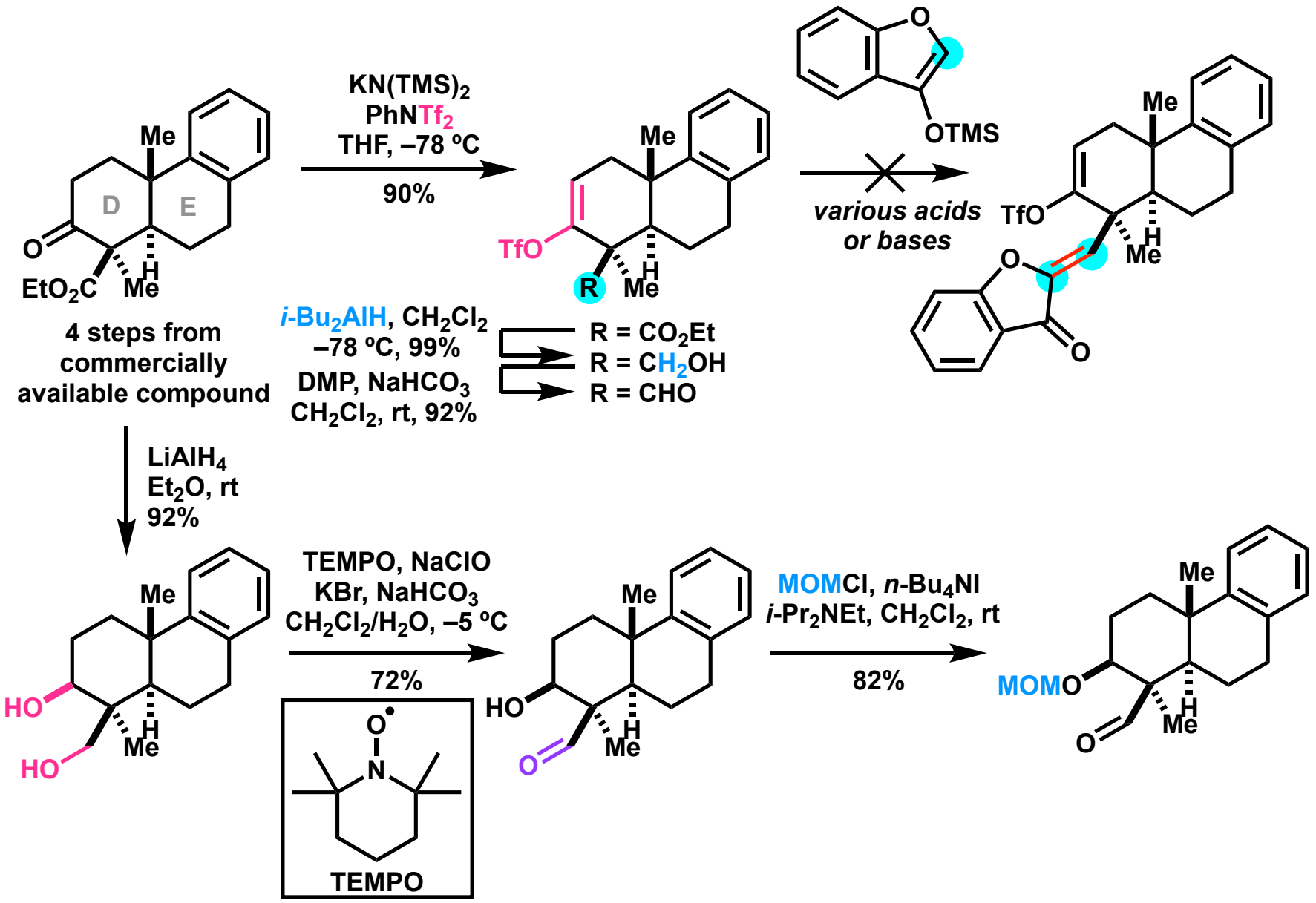
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828..

Pd-catalyzed Intramolecular Alkenylation



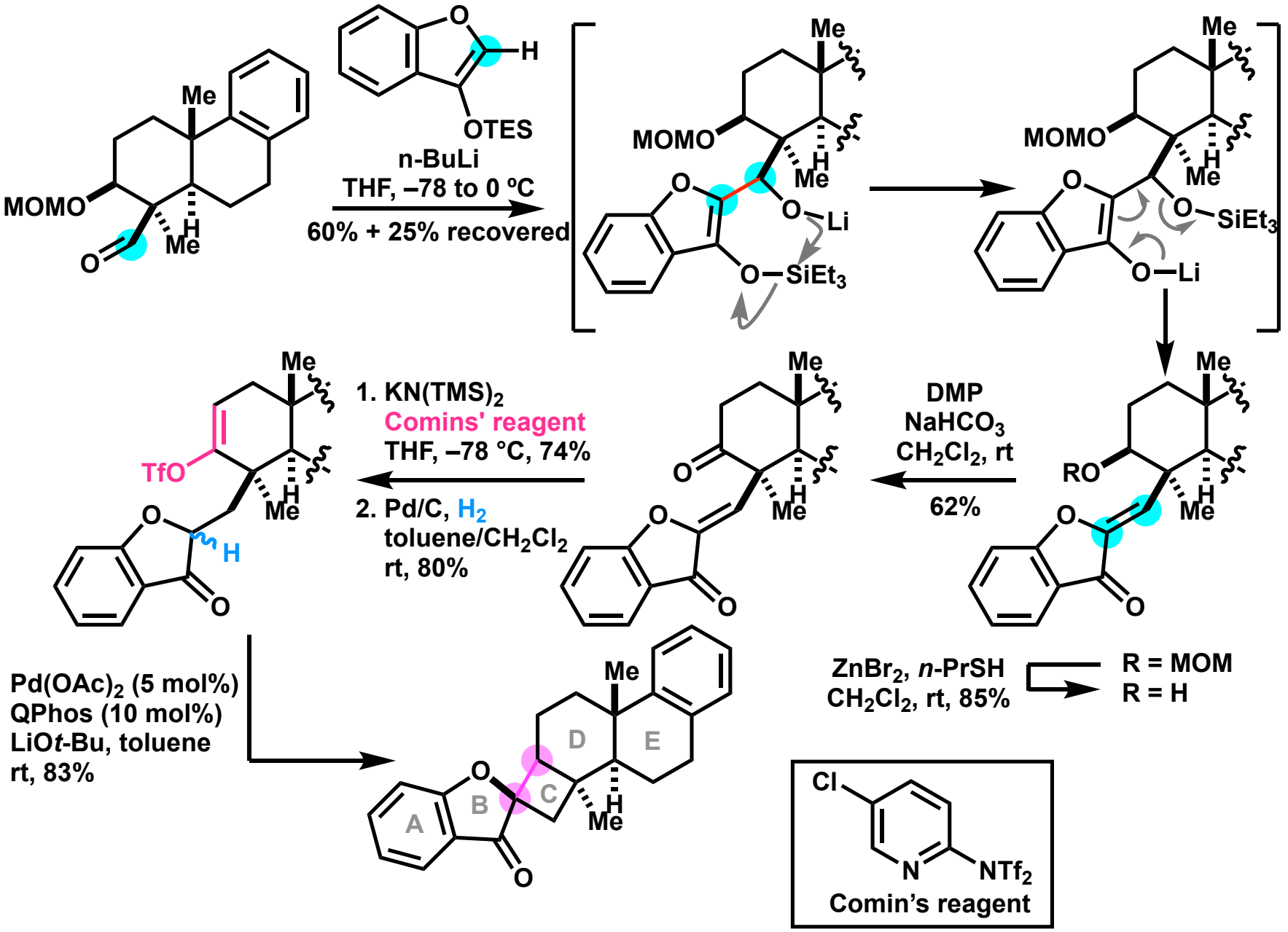
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.
2) Xie, J.; Wang, J.; Dong, G. *Org. Lett.* **2017,** *19*, 3017.

Attempts to Introduce A/B-Rings



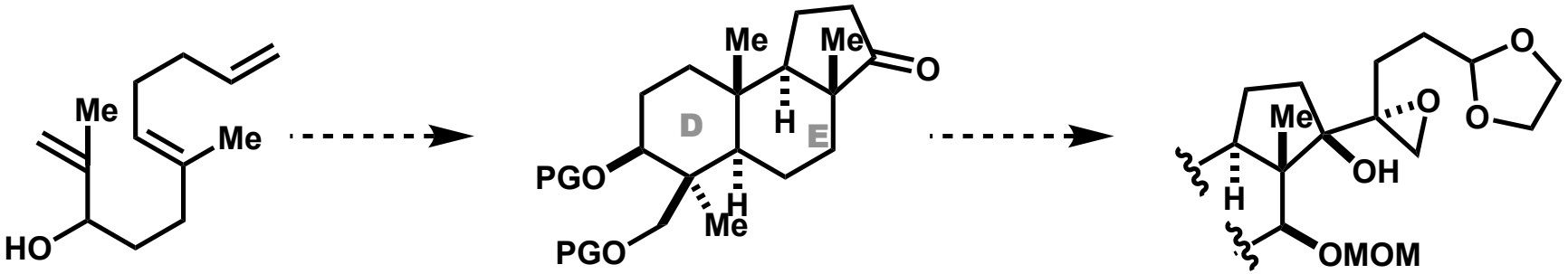
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

Construction of A/B/C/D/E Model Substrate

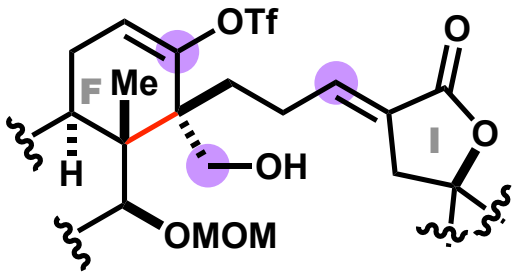


1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

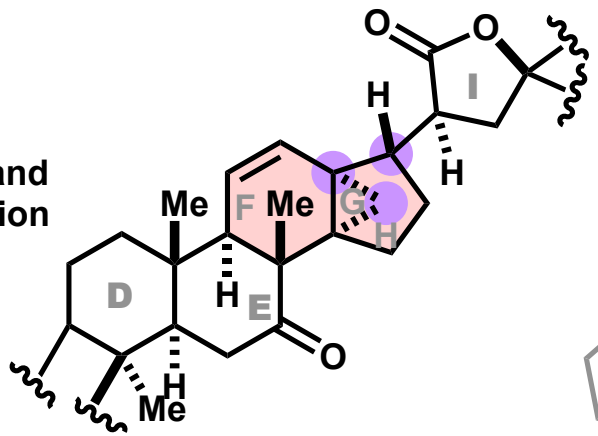
Synthetic Approach Toward D/E/F/G/H-Rings



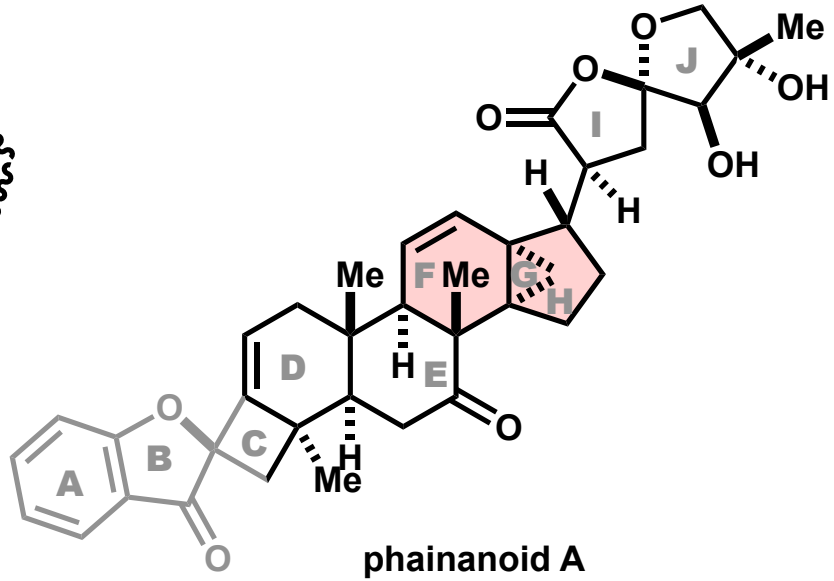
1. Semipinacol type Ring Expansion



2. Heck Cyclization and Homoallylic elimination



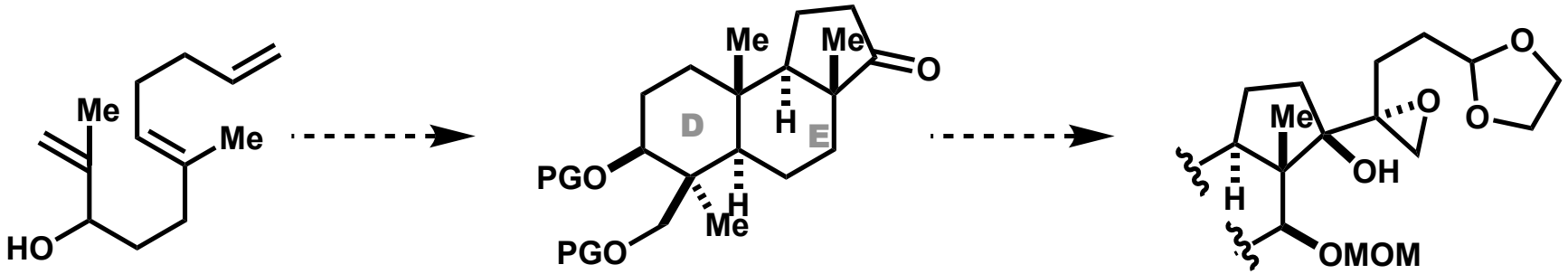
D/E/F core + [4. 3. 1] propellane



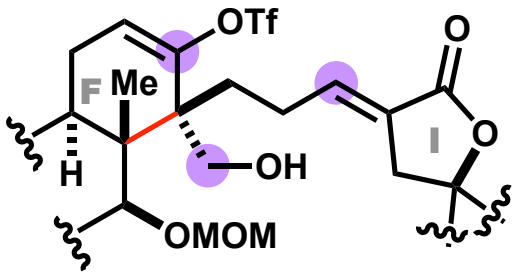
phainanoid A

1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

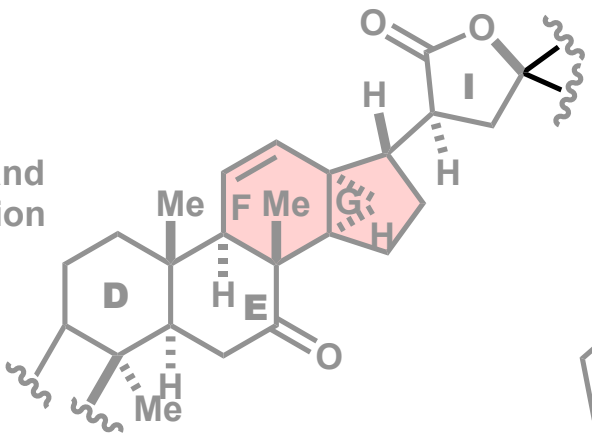
Synthetic Approach Toward D/E/F-Rings



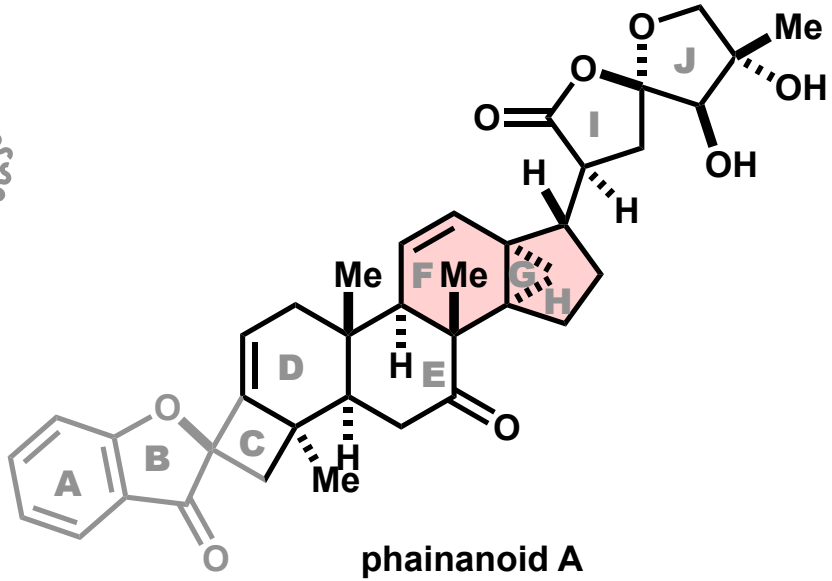
1. Semipinacol type Ring Expansion



2. Heck Cyclization and Homoallylic elimination



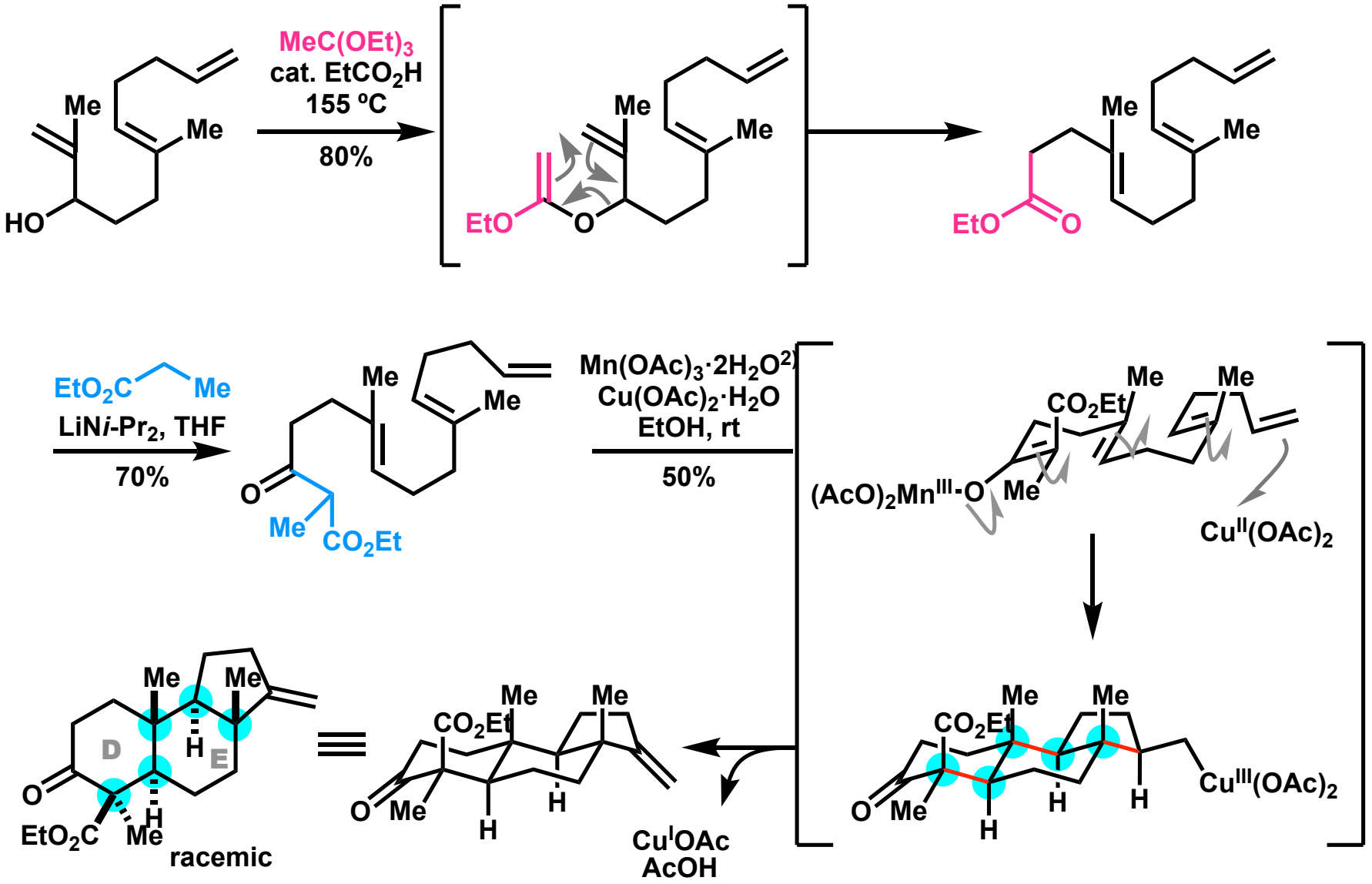
D/E/F core + [4. 3. 1] propellane



phainanoid A

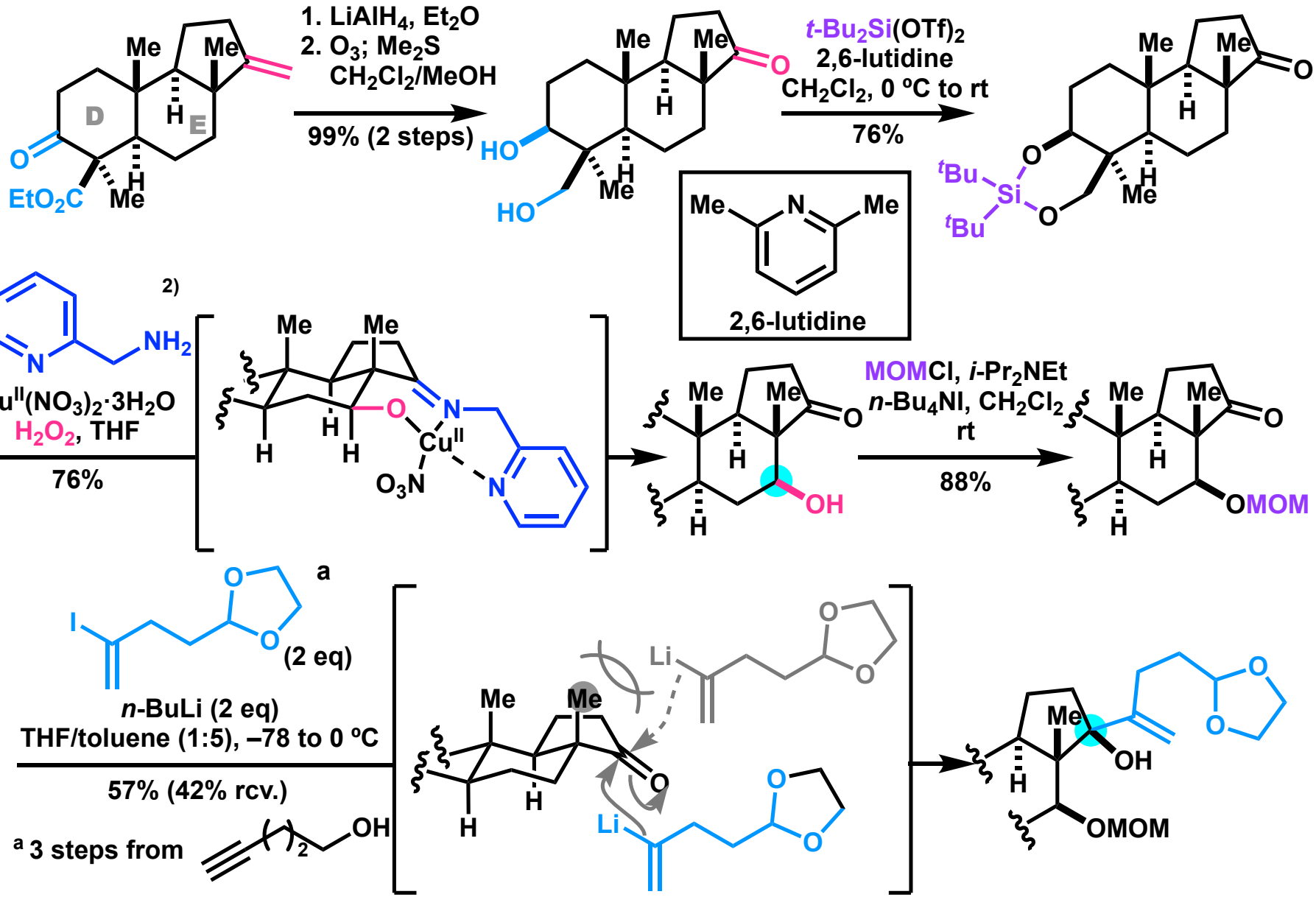
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

Oxidative Radical Polyene Cyclization



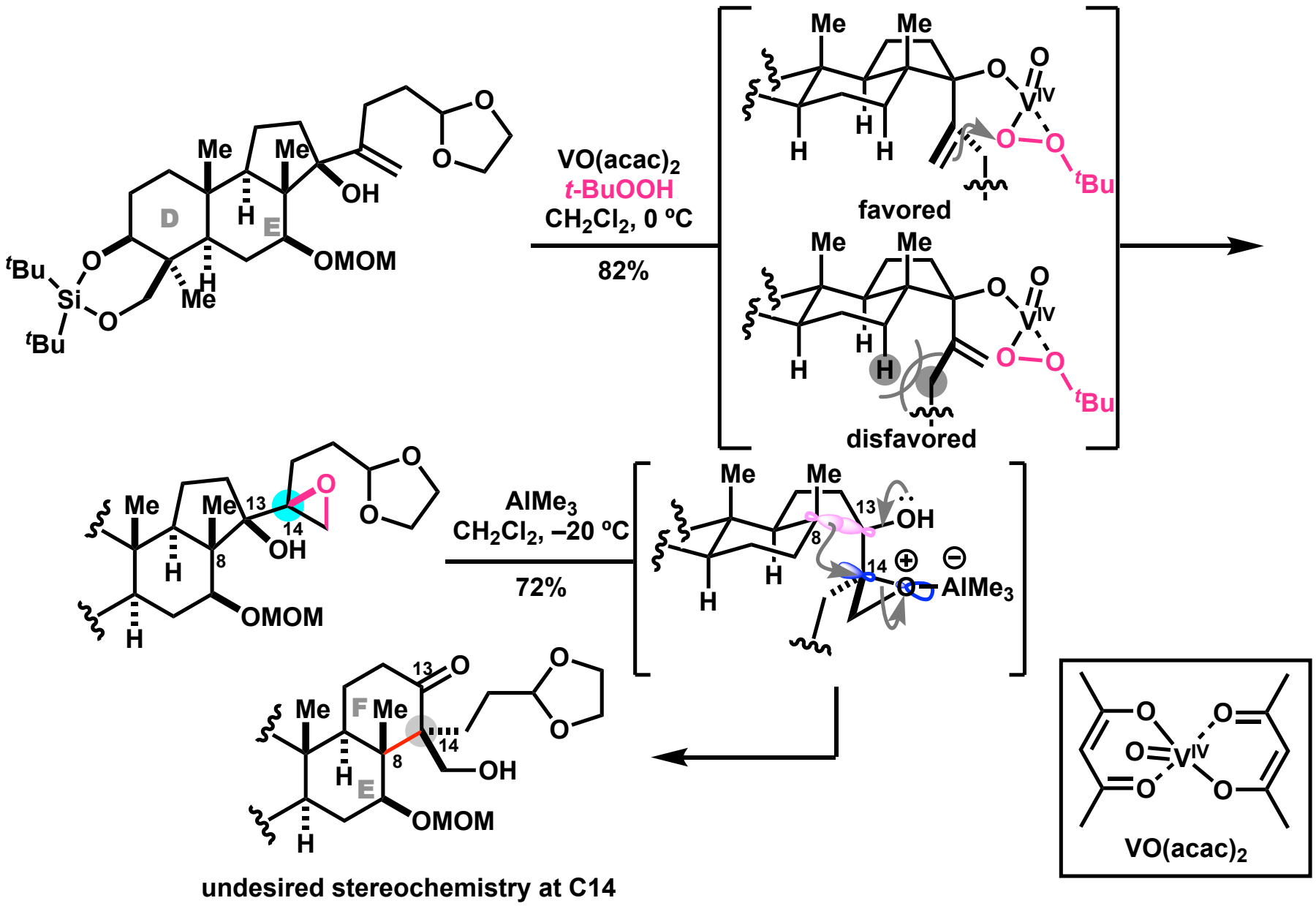
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.
2) Snider, B. *Chem. Rev.* **1996,** *96,* 339.

C-H Oxidation at C7 and Stereoselective 1,2-addition



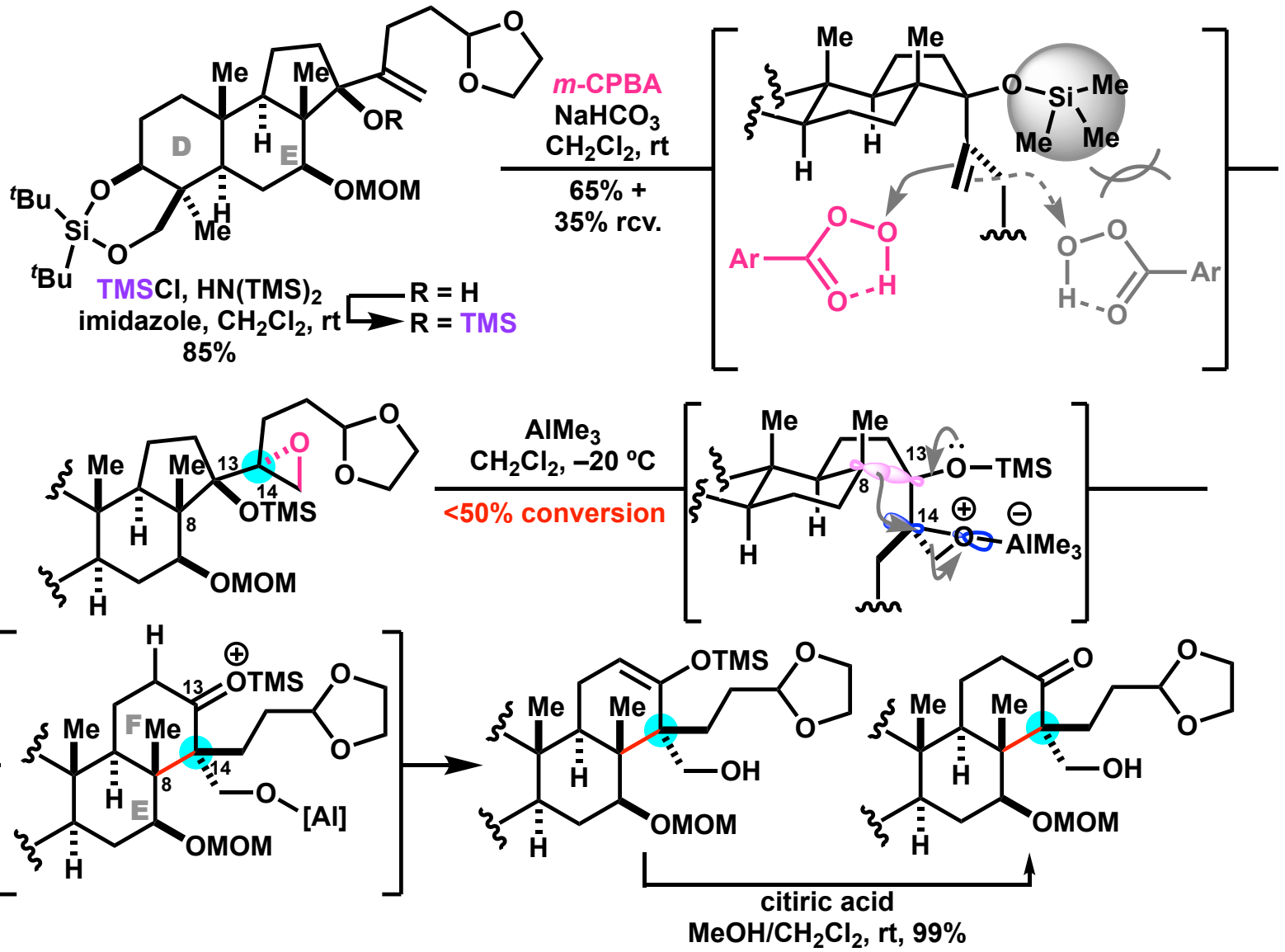
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.
2) Trammell, R.; See, Y.; Herrmann, A.; Xie, N.; Diaz, D.; Siegler, M.; Baran, P.; Garcia-Bosch, I. *J. Org. Chem. Soc.* **2017.** *82*, 7887

Undesired Stereochemistry at C14



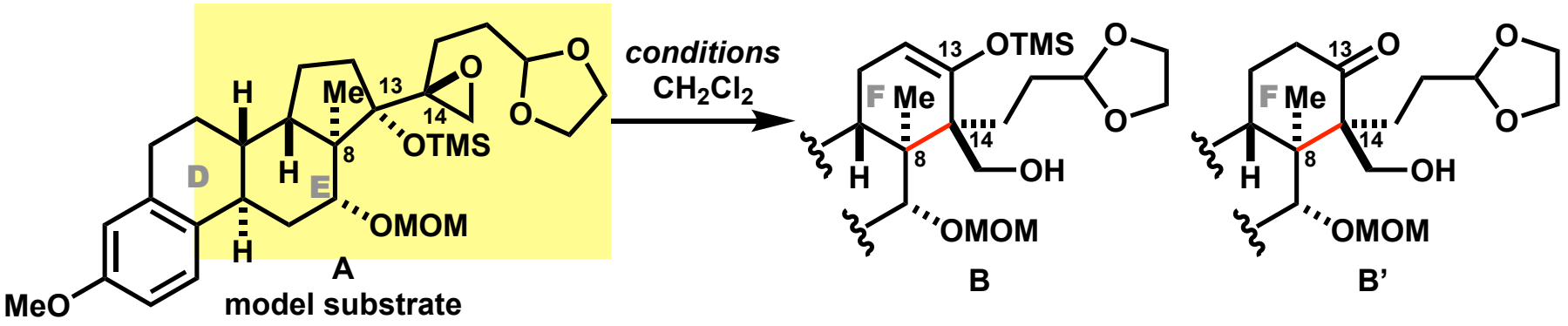
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

Desired Stereochemistry at C14

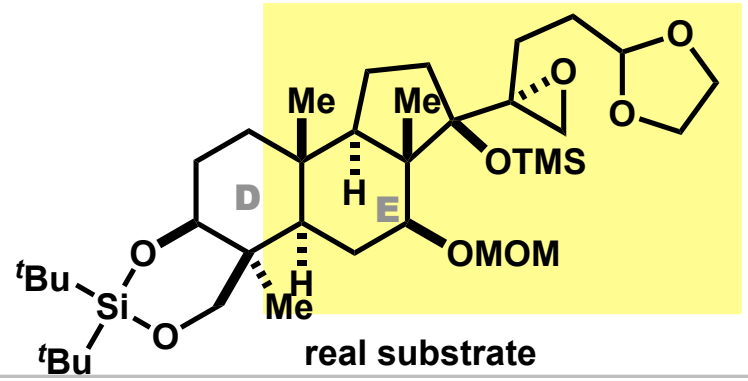


1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

Optimization of Semi Pinacol Rearrangement

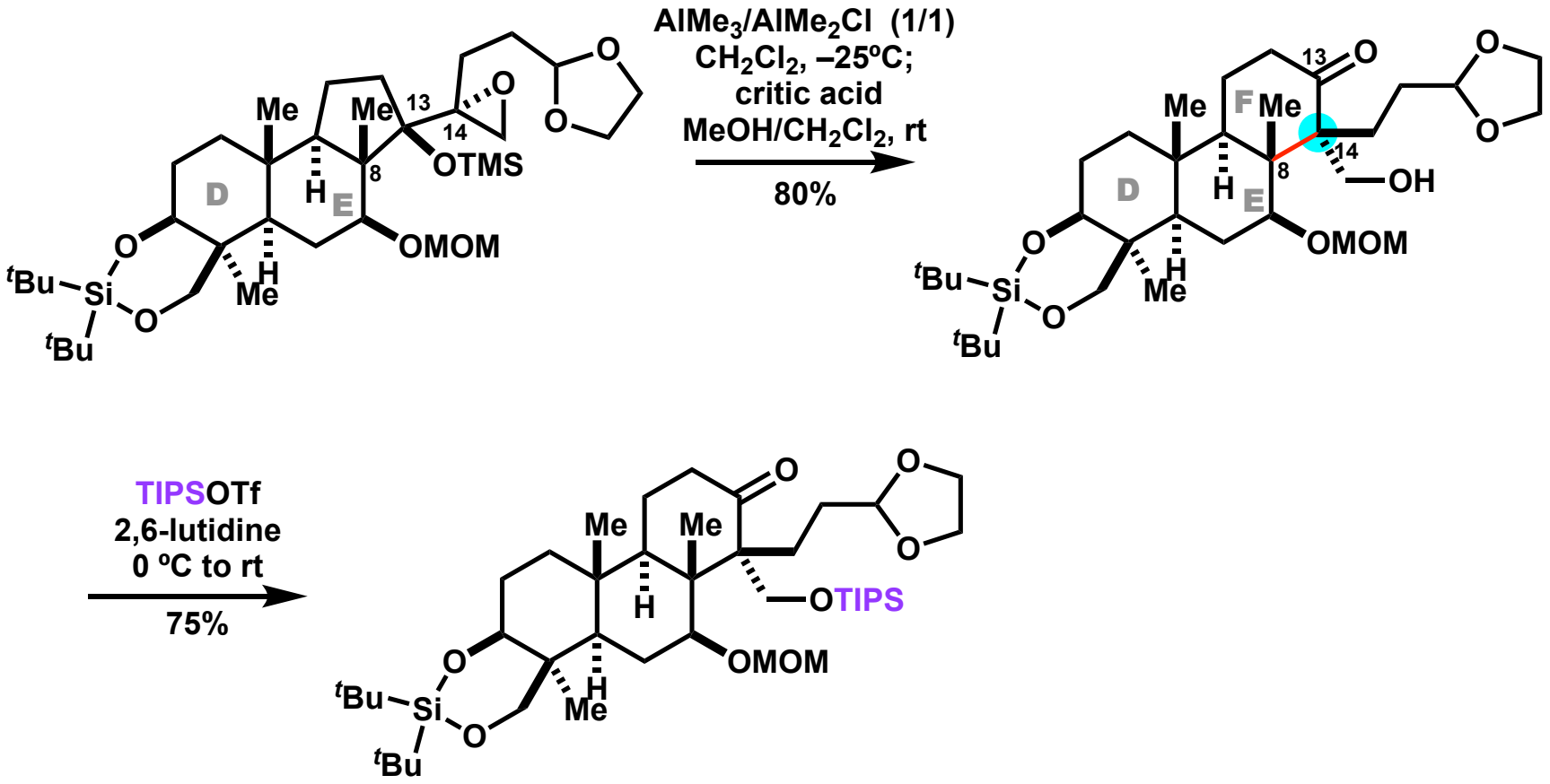


entry	Lewis acid (equiv)	additive	*T*/°C	B+B' (B:B')	rcv. A
1	$AlMe_3$ (6.0)	none	–10	47% (1:1.2)	39%
2	$AlMe_2Cl$ (1.0)	none	–78	0%	0%
3	TMSOTf (1.0)	2,6-lutidine	–78	0%	>90%
4	$Sc(OTf)_3$ (0.5)	none	0	0%	0%
5	$BF_3{\cdot}Et_2O$	none	–78	0%	0%
6	1:1 $AlMe_3$/$AlMe_2Cl$ (total [Al]: 2.0)	none	–10	76% (1:1.2)	0%



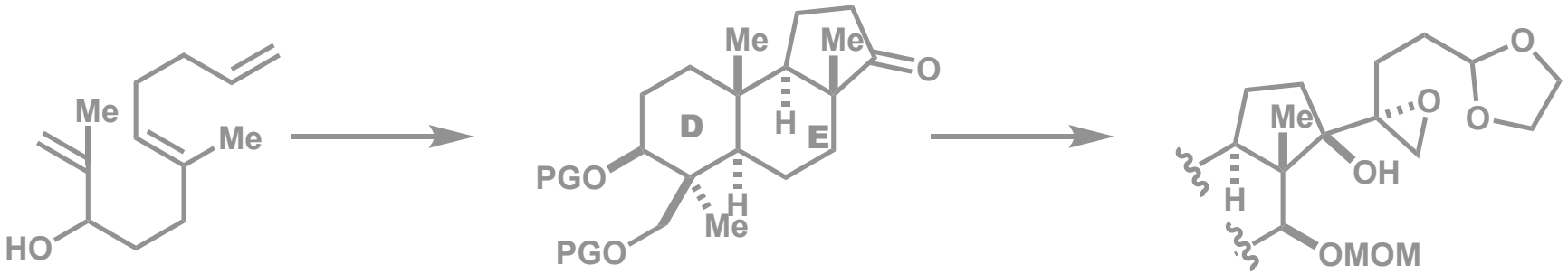
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

Completion of Construction of F-Ring

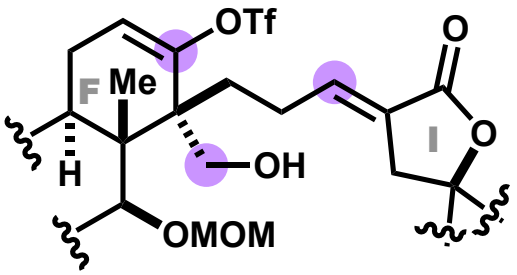


1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

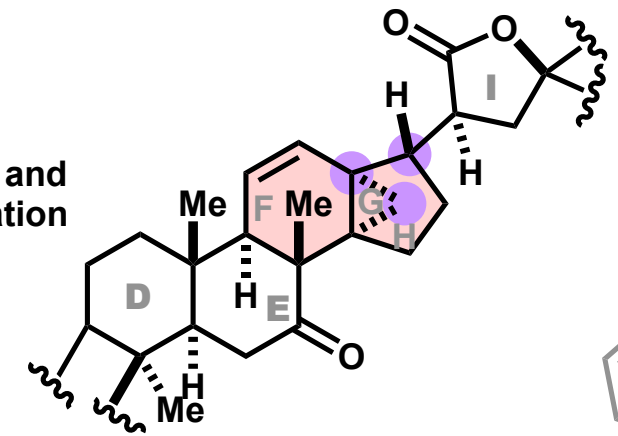
Synthetic Approach Toward F/G/H-Rings



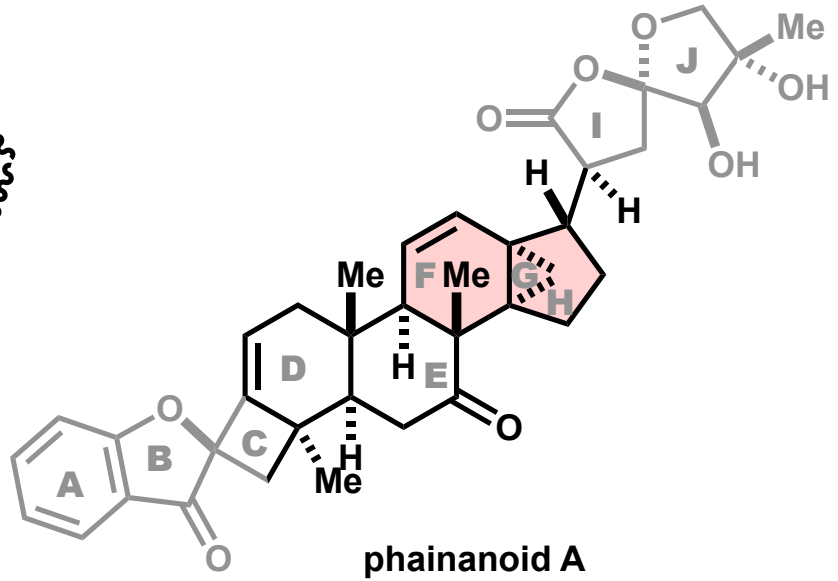
1. Semipinacol type Ring Expansion



2. Heck Cyclization and Homoallylic elimination



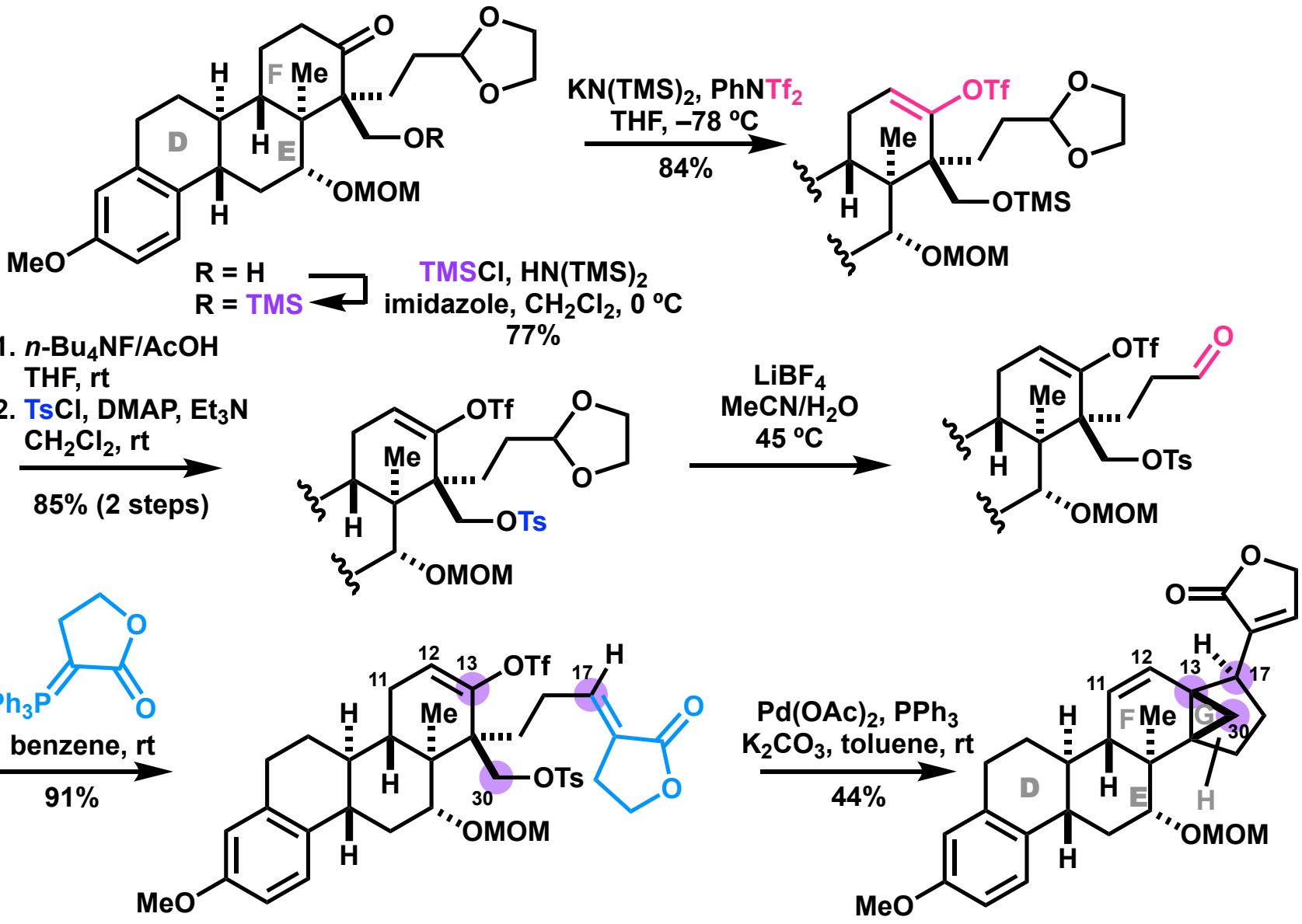
D/E/F core + [4. 3. 1] propellane



phainanoid A

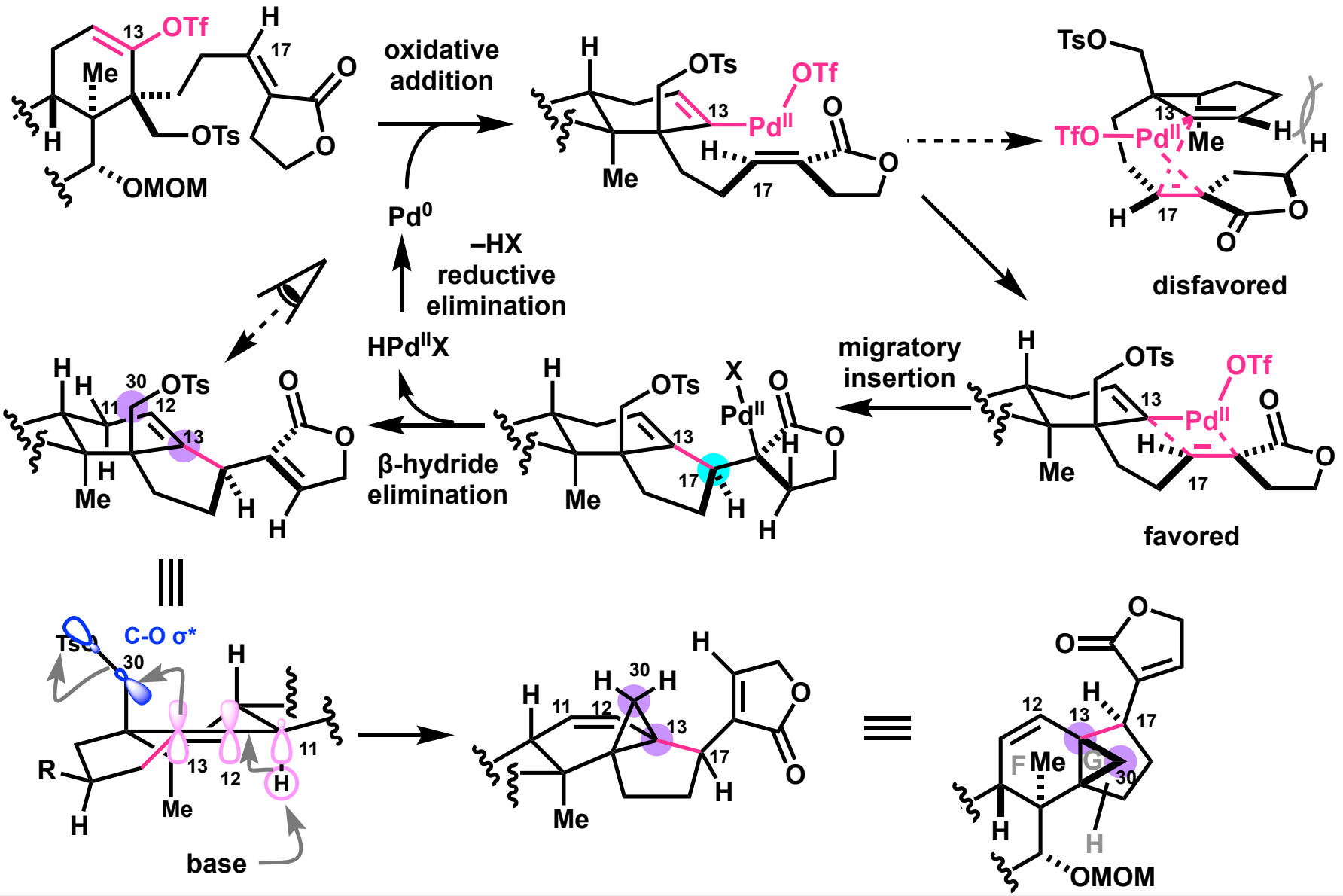
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

Tandem Heck Cyclization and Homoallylic Elimination



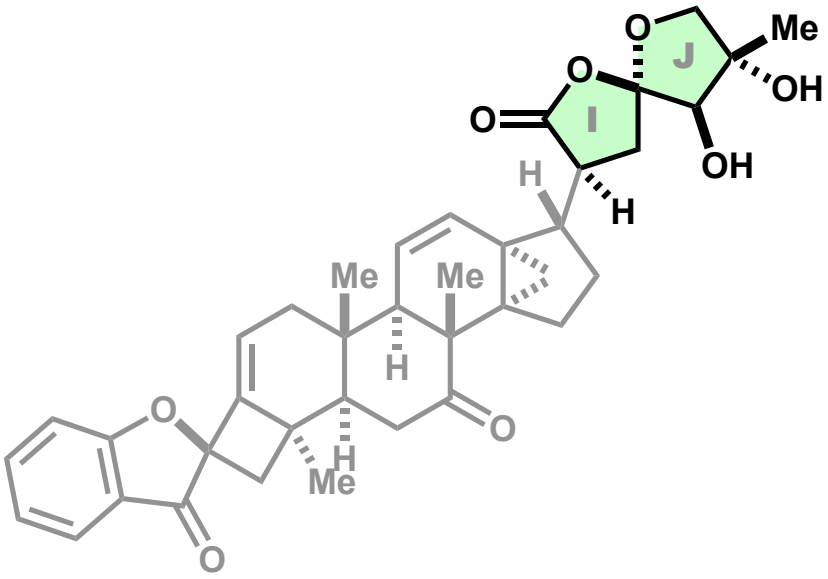
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

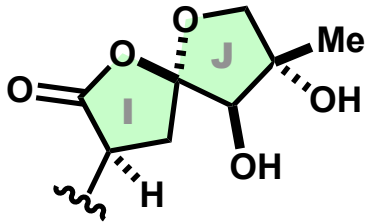
Reaction Mechanism : Pd-catalyzed Tandem Heck Cyclization and Cyclopropane Formation



1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

Construction of I/J-Rings

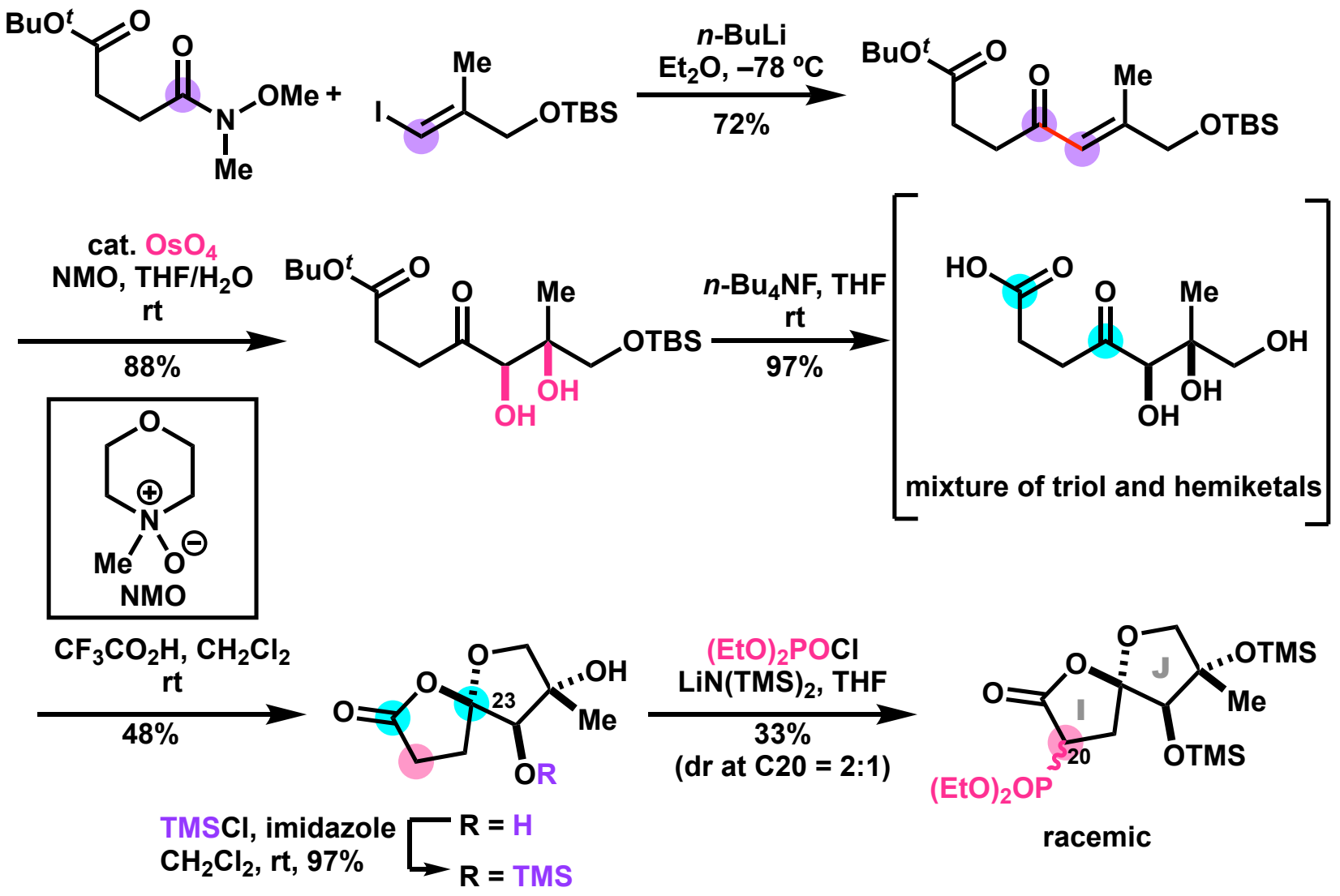




5,5-oxaspirolactone

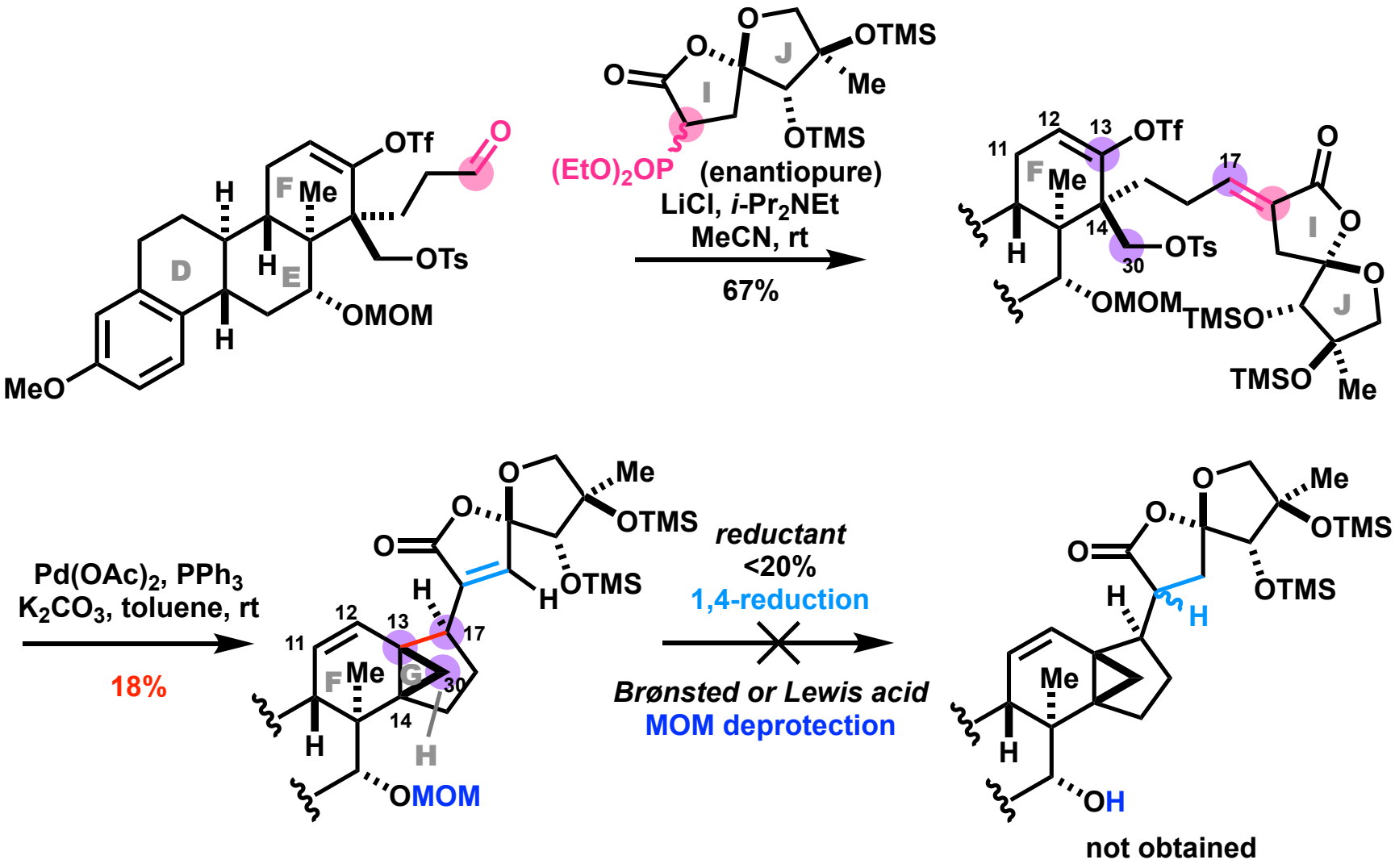
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

Construction of I/J-Rings



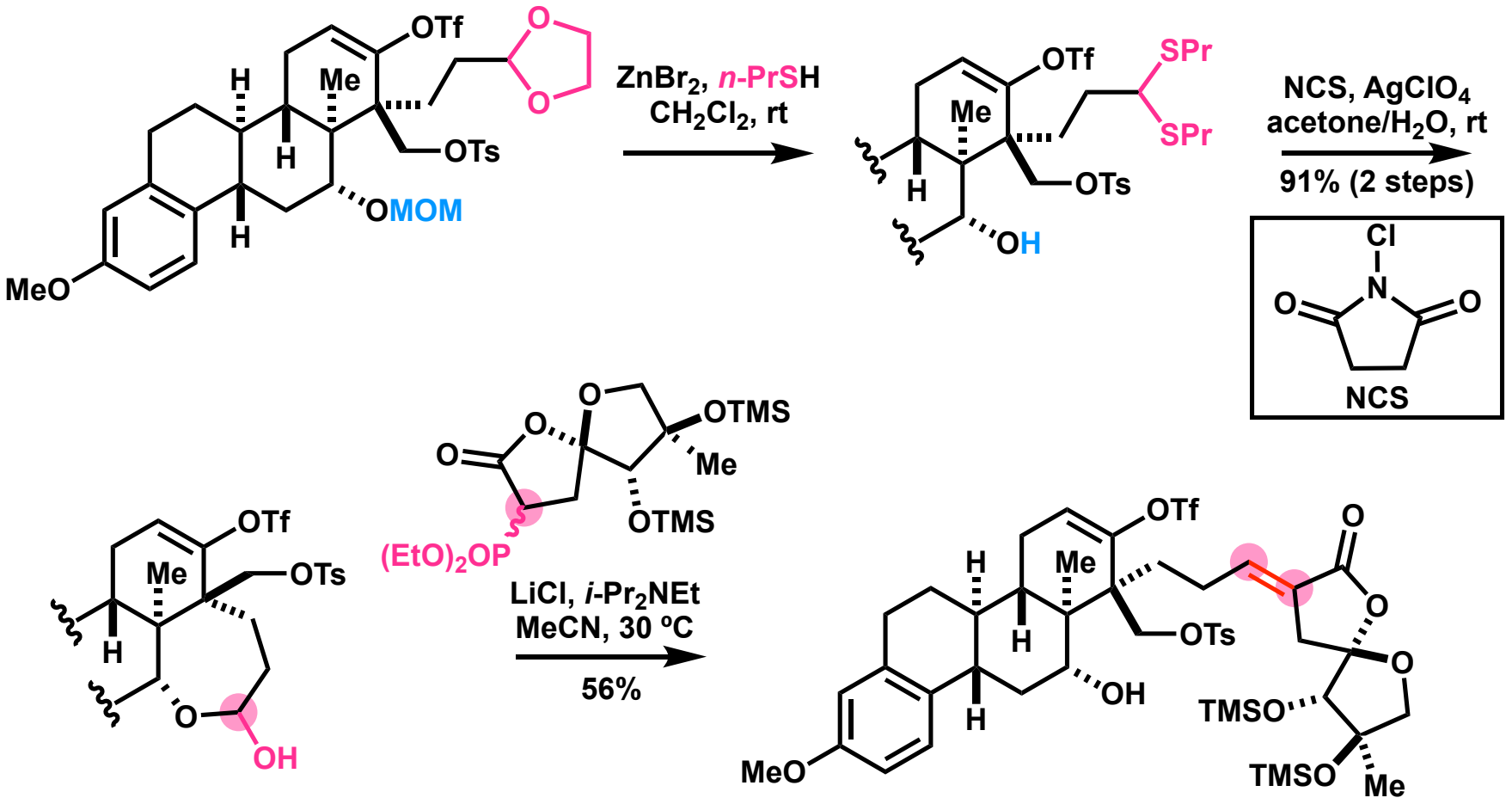
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

Attempts to Construct F/G/H-Rings by Pd-catalyzed Heck Cyclization



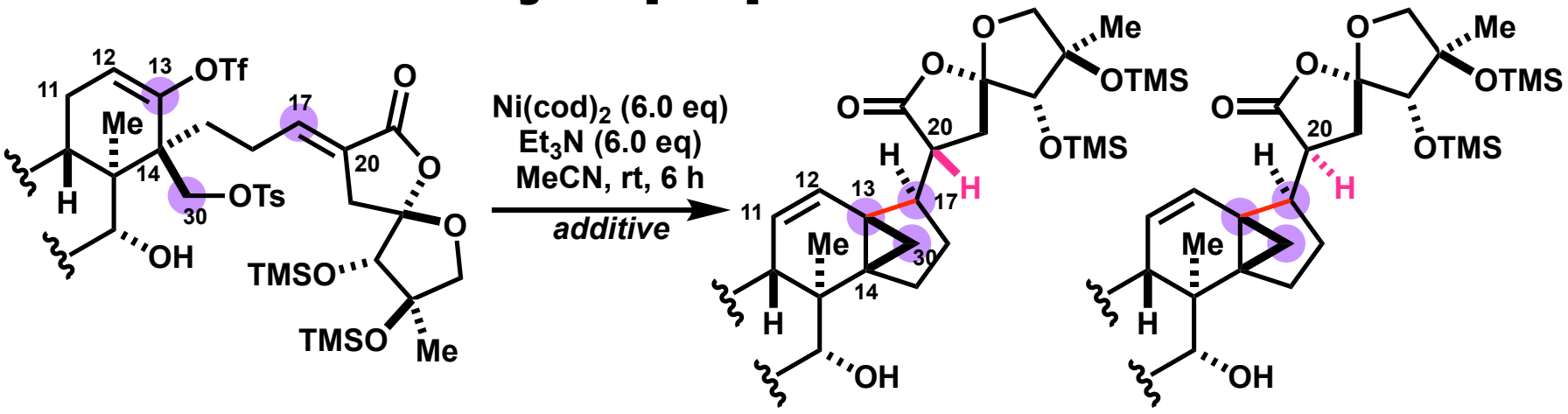
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

MOM Deprotection and HWE Olefination

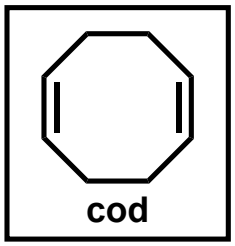


1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

Ni-Mediated Reductive Heck Cyclization and Cyclopropane Formation

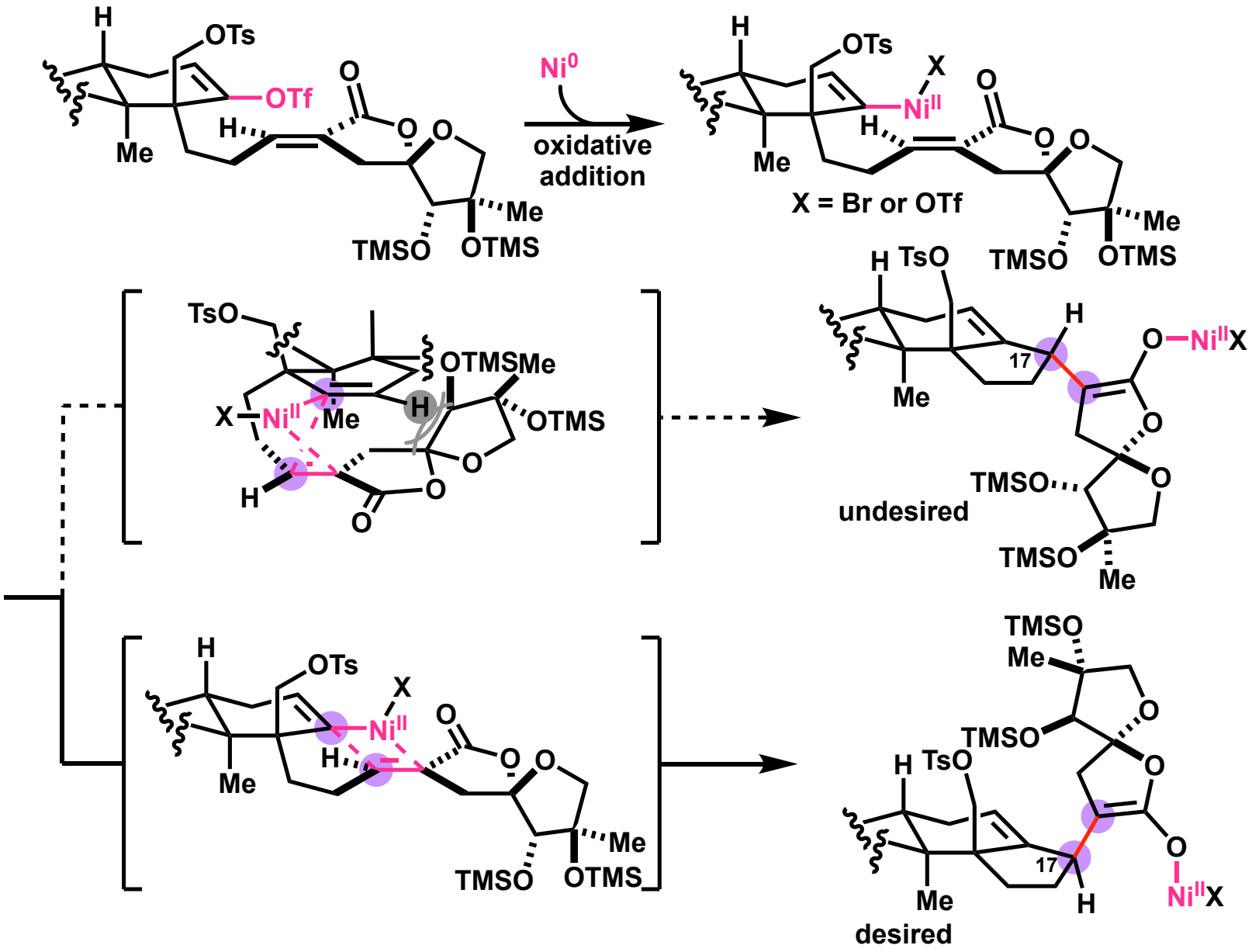


additive	B+B'	B:B'
—	<50%	1:2
LiBr (20 eq)	69%	9:1



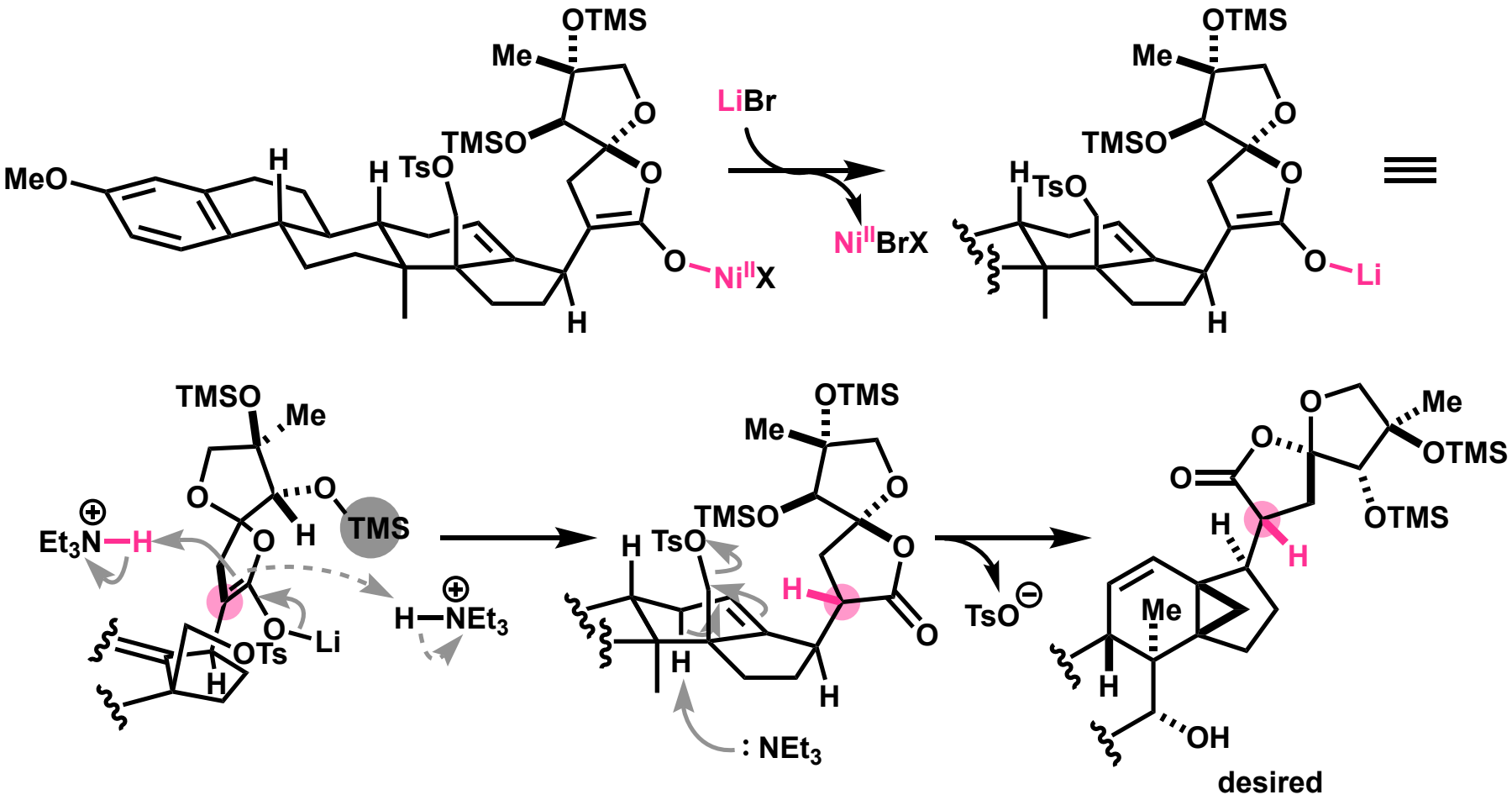
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.
2) Hofstra, J.; Poremba, K.; Shimozono, A.; Reisman, S. *Angew. Chem. Int. Ed.* **2019,** *58*, 14901

Plausible Mechanism: Reductive Heck Cyclization



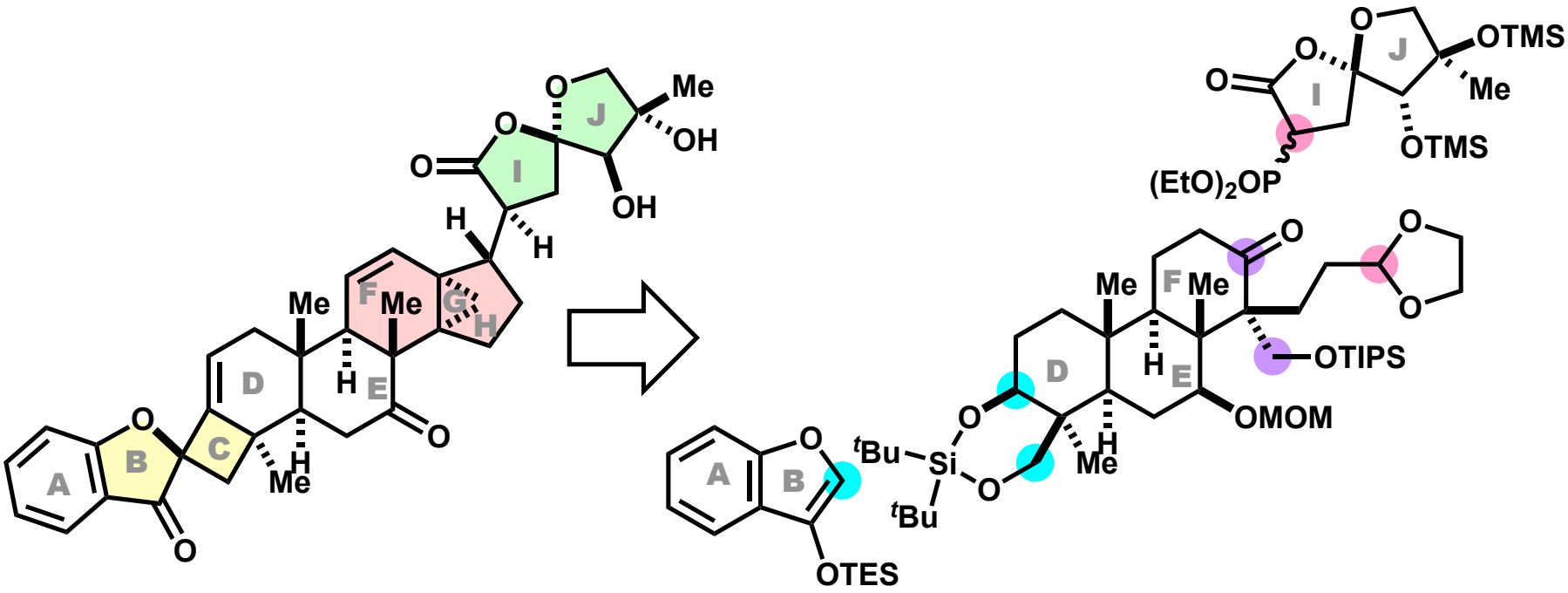
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

Plausible Mechanism: Protonation and Cyclopropane Fromation



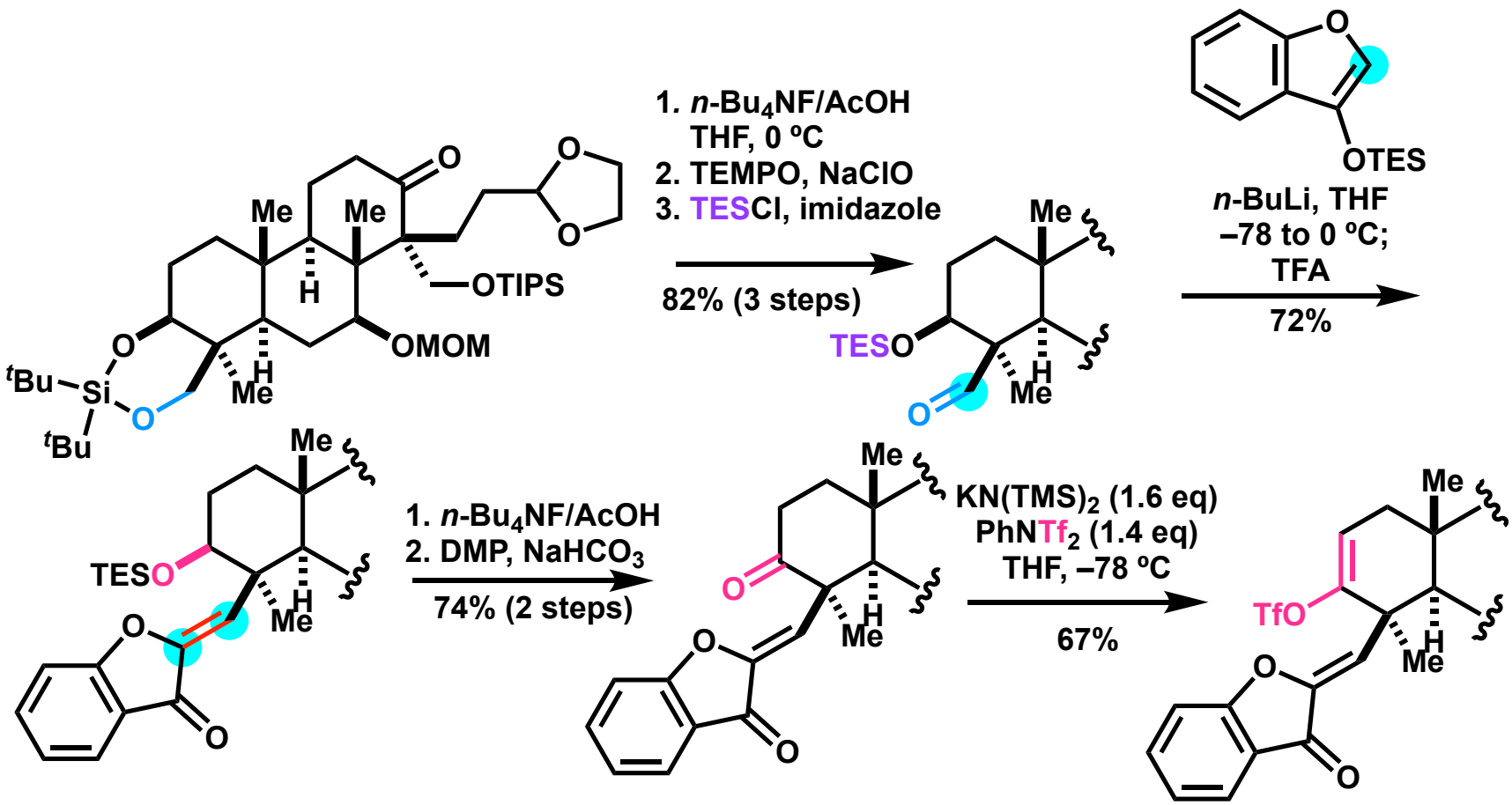
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

Bidirectional Total Synthesis



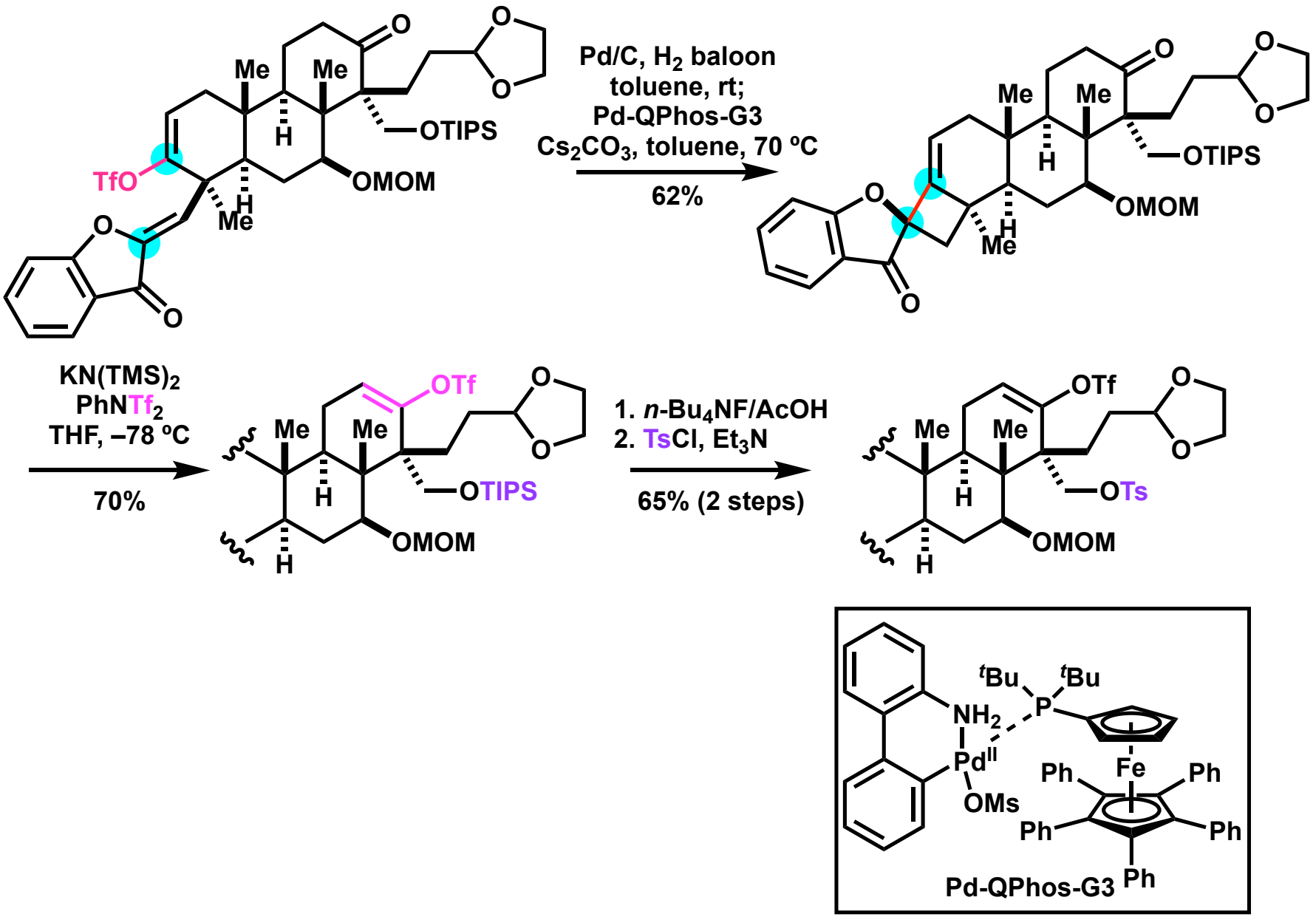
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

Synthesis of Precursor of 4,5-spirocycle



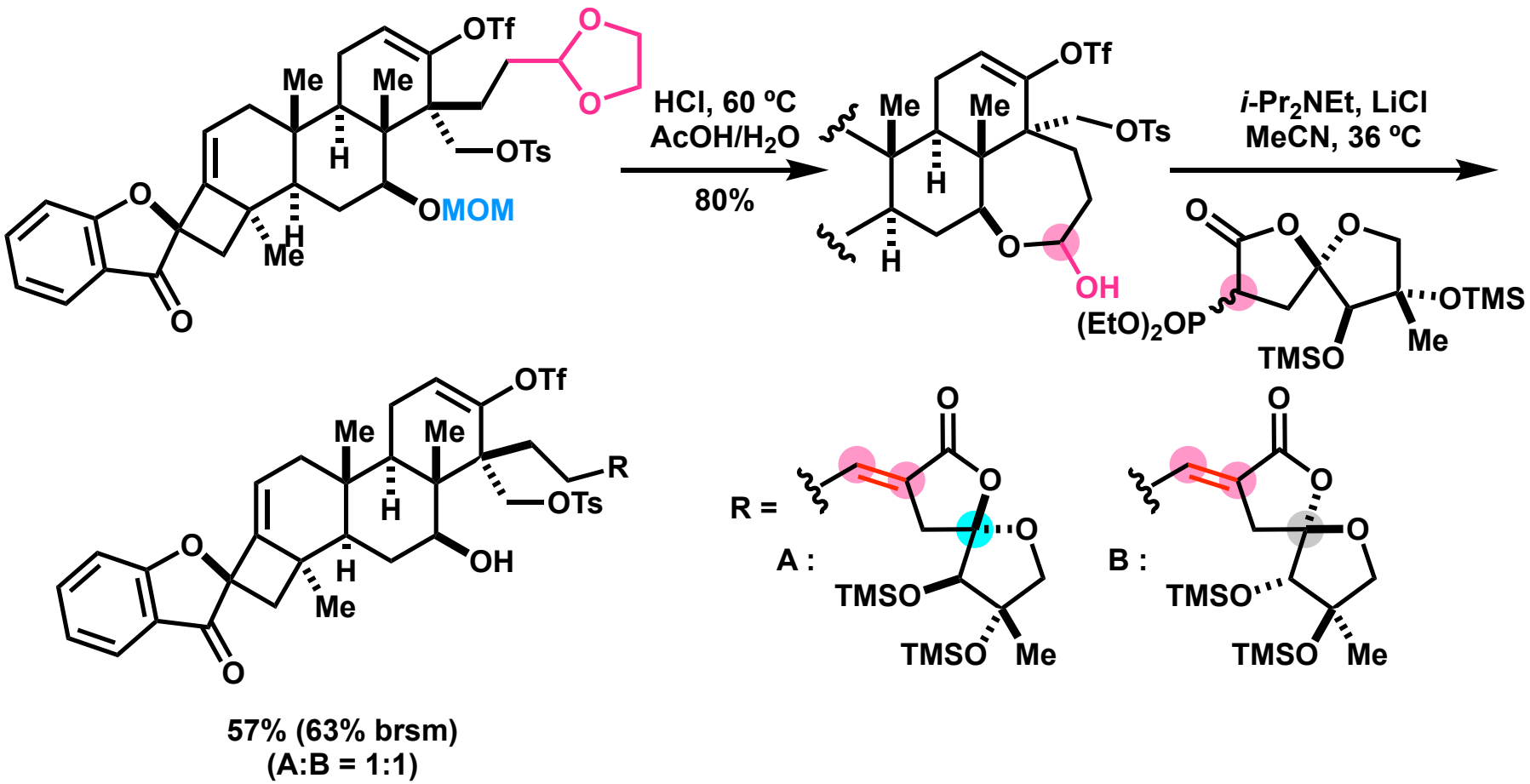
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

Construction of 4,5-spirocycle



1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

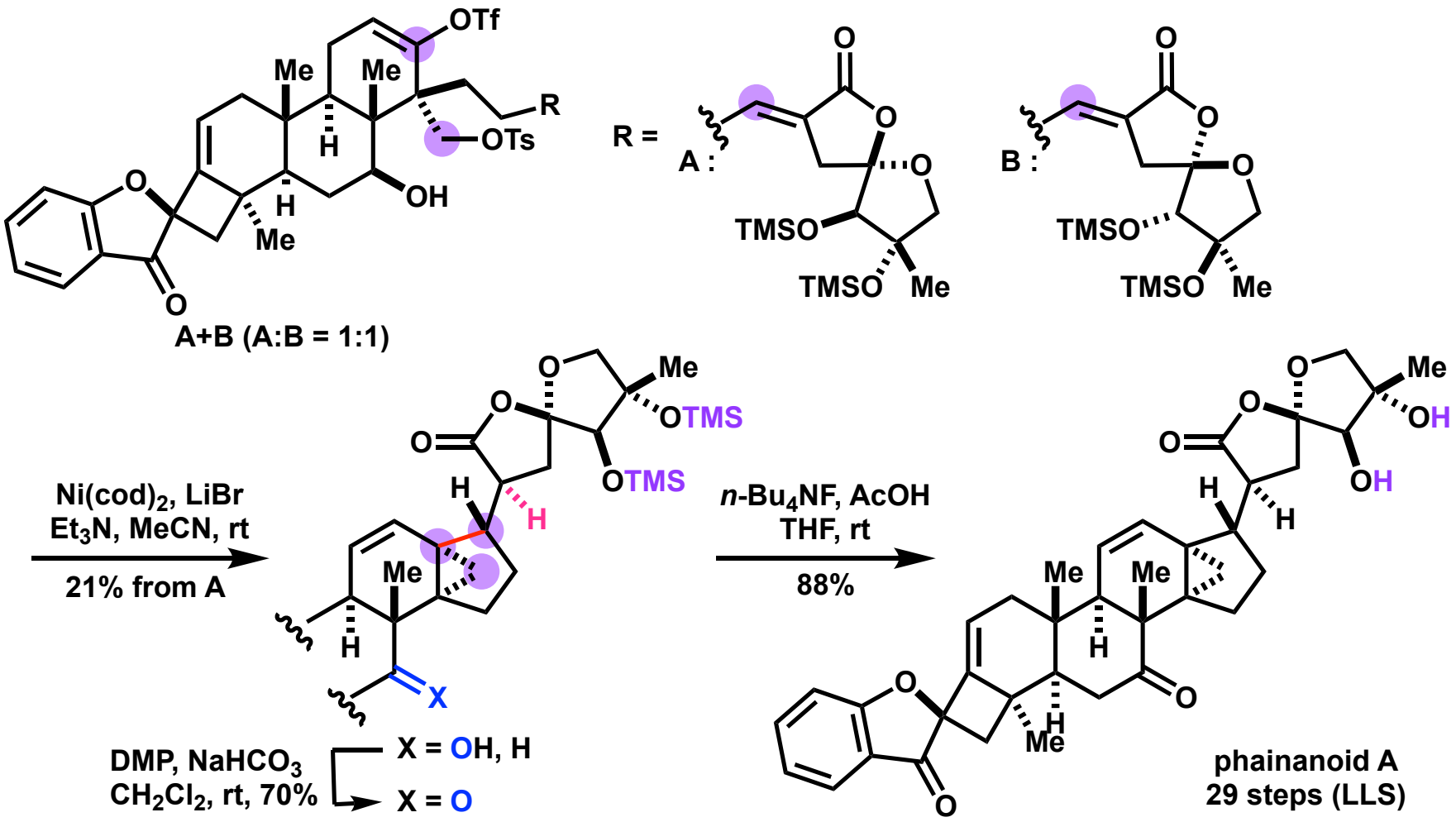
Preparation for Reductive Heck Cyclization



57% (63% brsm)
(A:B = 1:1)

1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

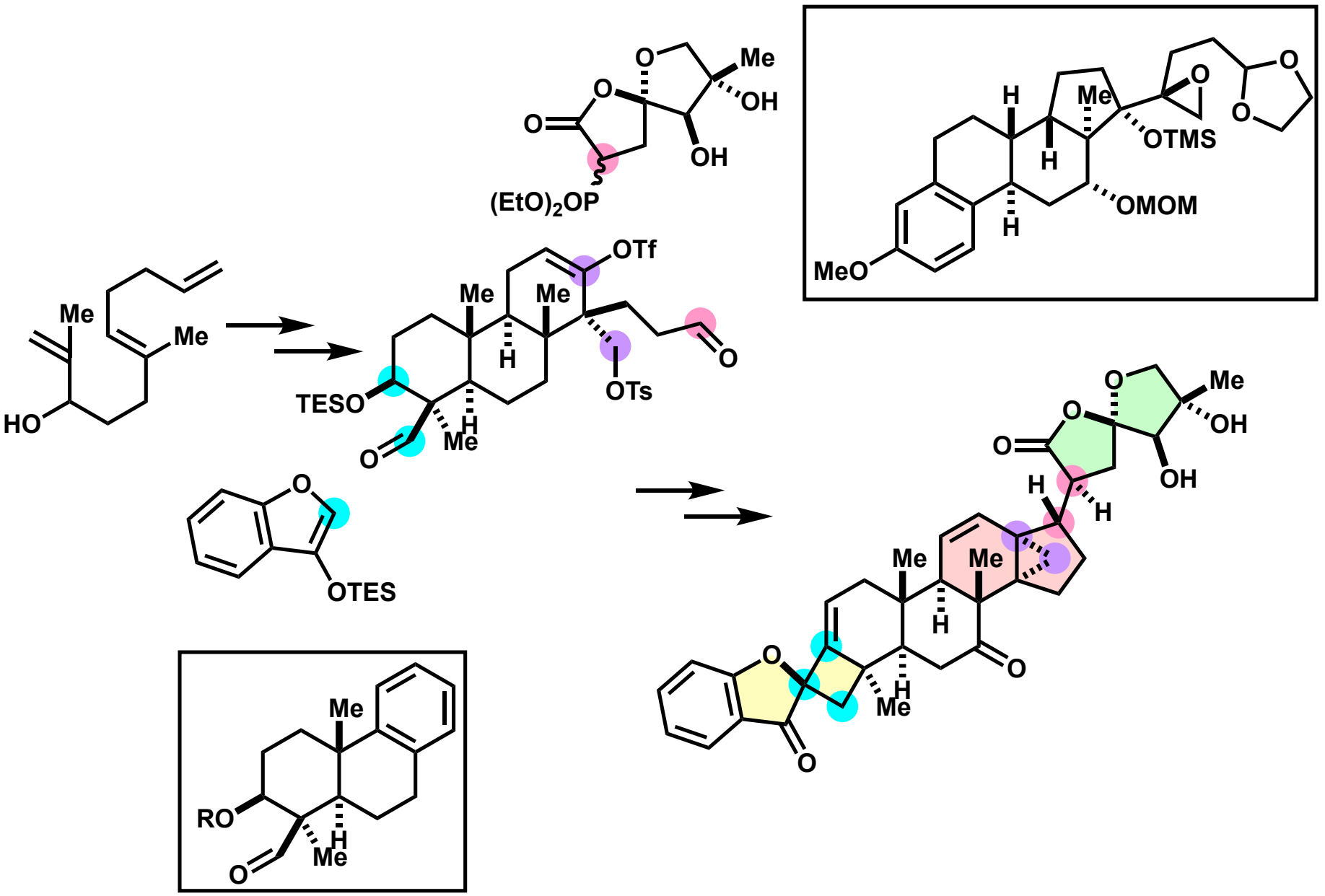
Total Synthesis of Phainanoid A (Racemic)



1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

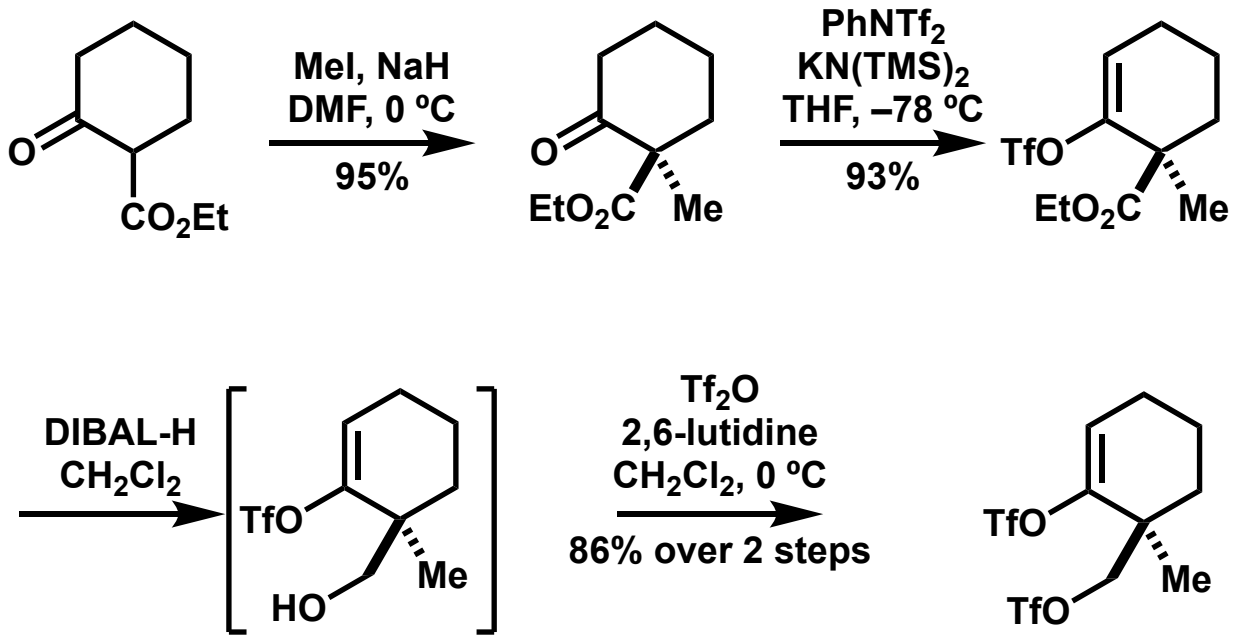
Contents

Summary

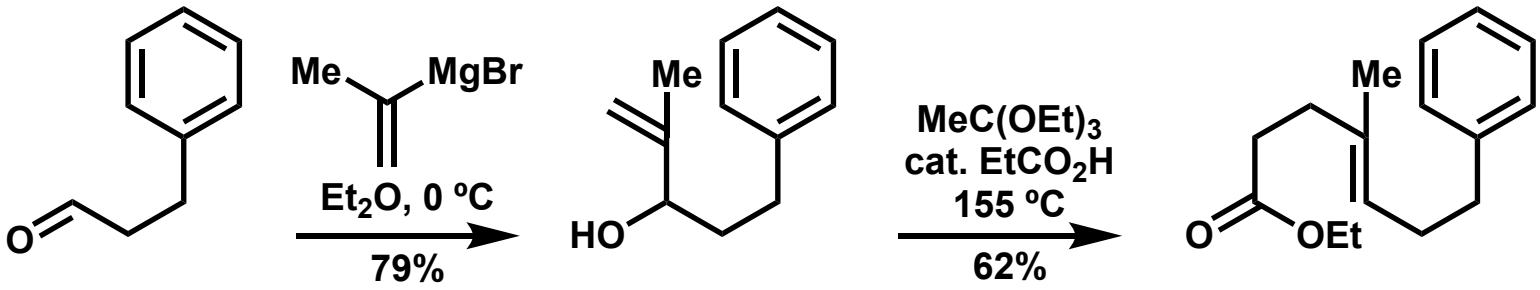


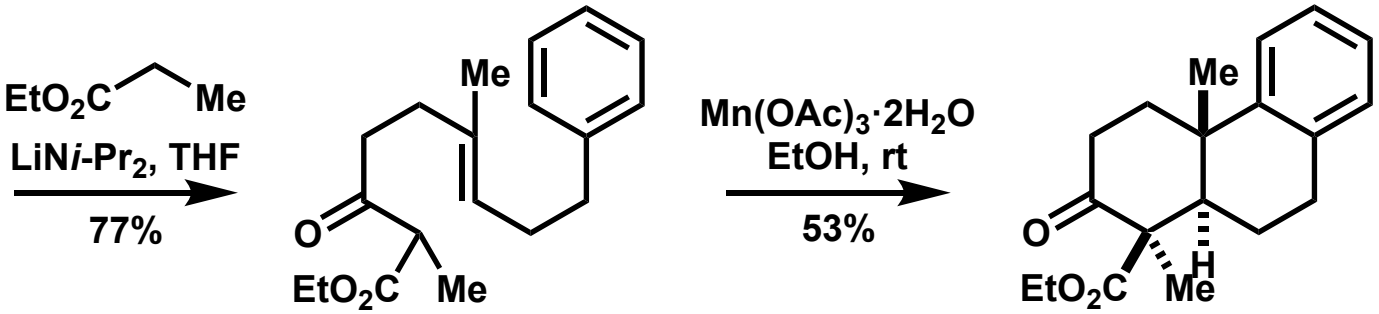
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.

Appendix

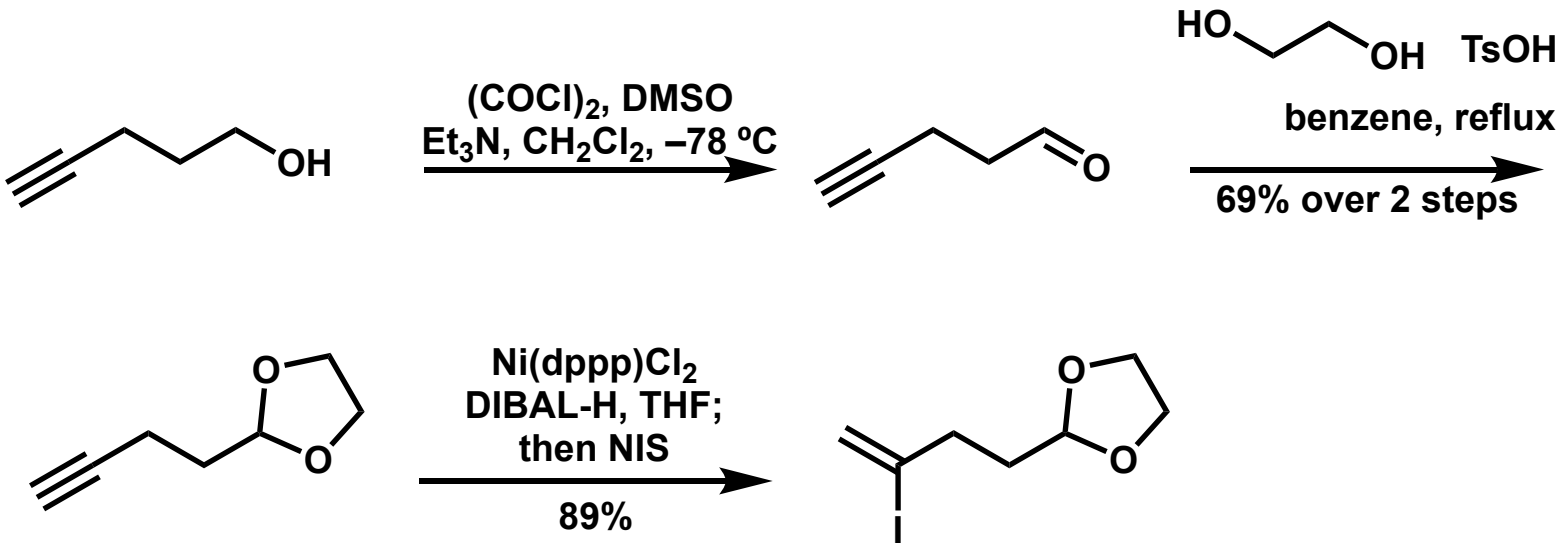


1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828

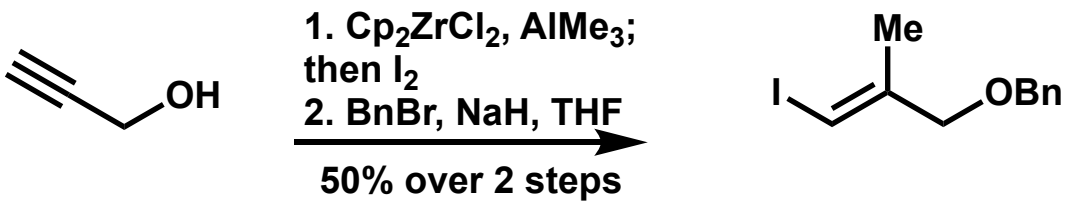




1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828

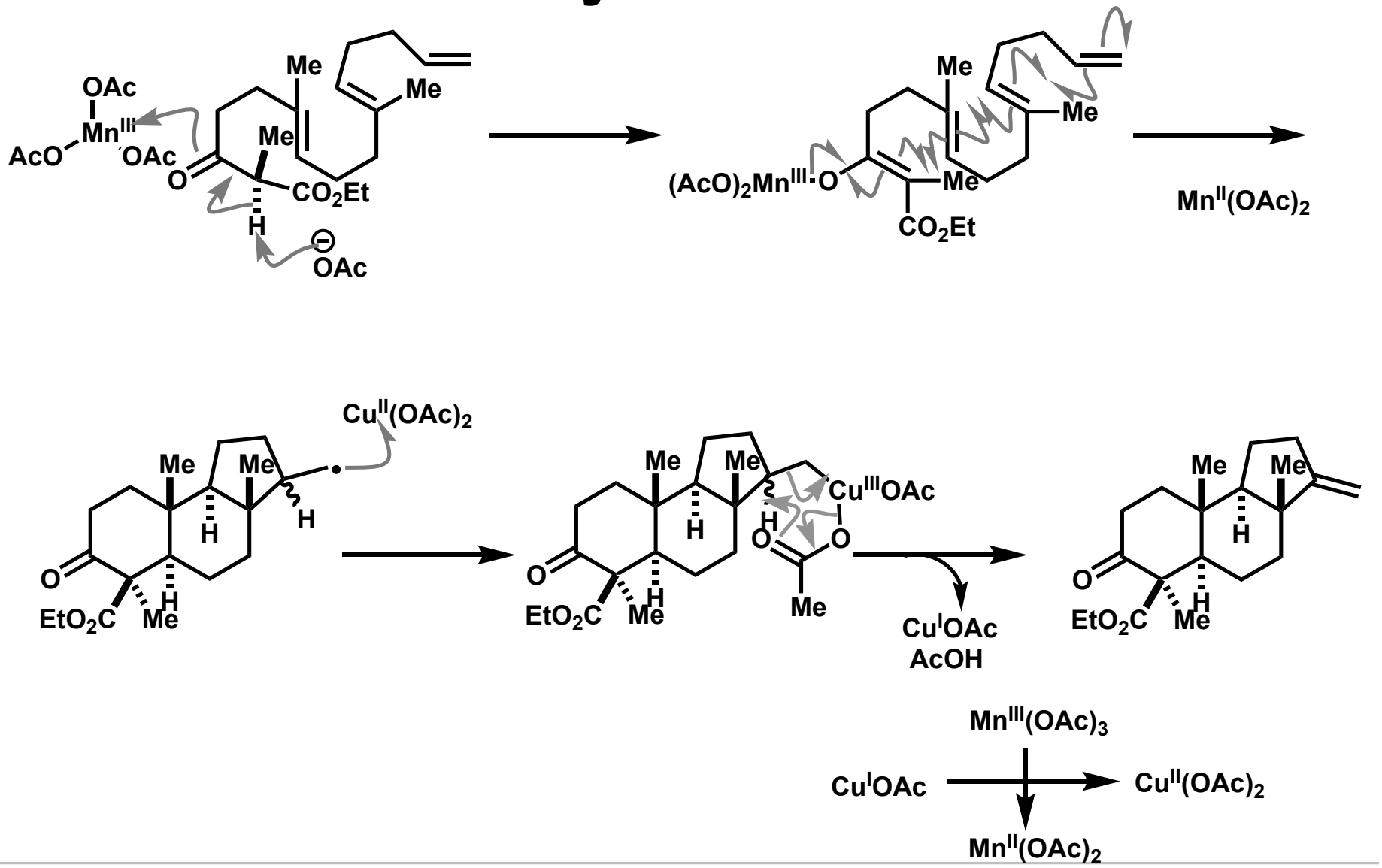


1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828



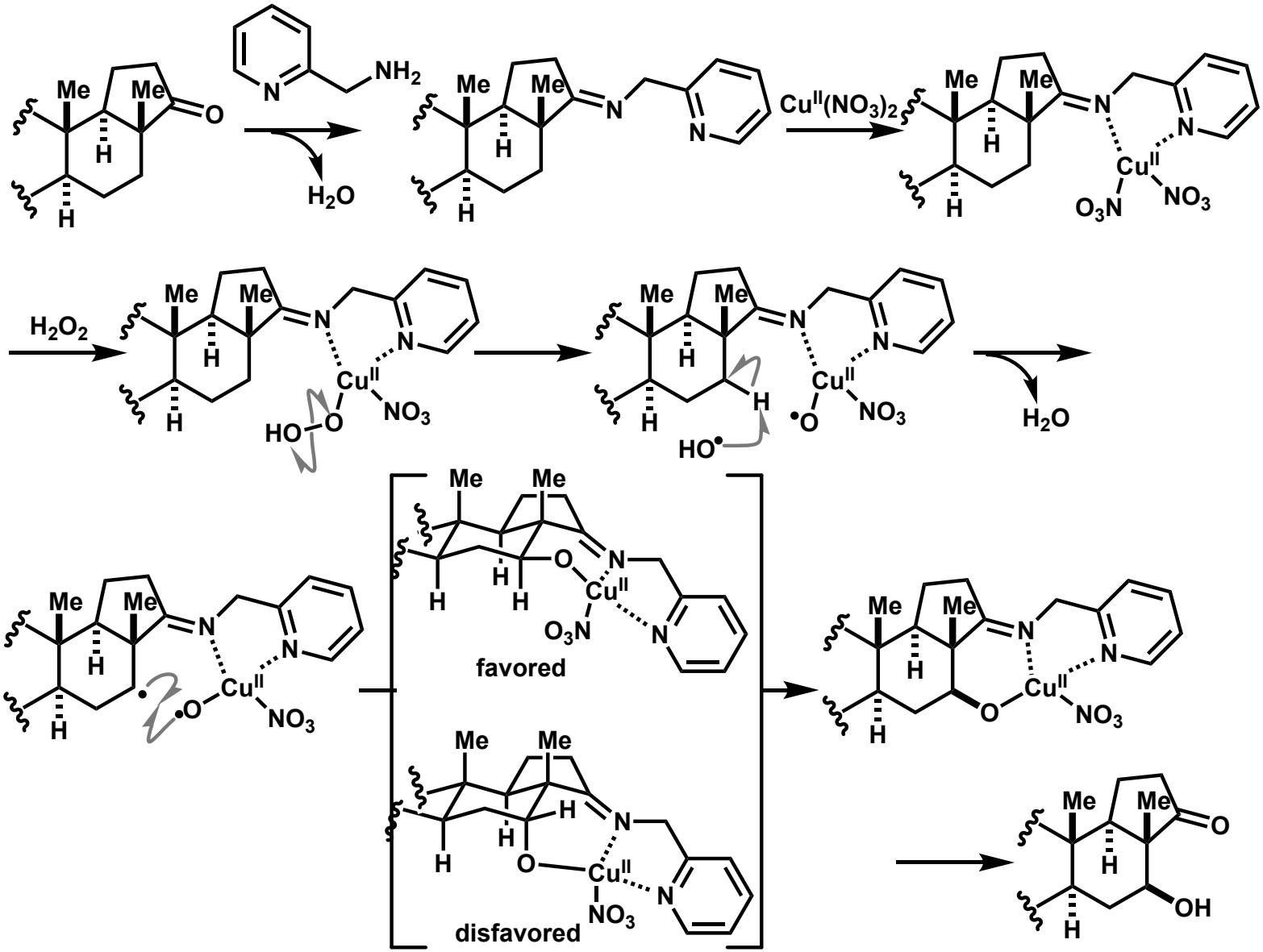
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828

Reaction mechanism of oxidative radical polyene cyclization

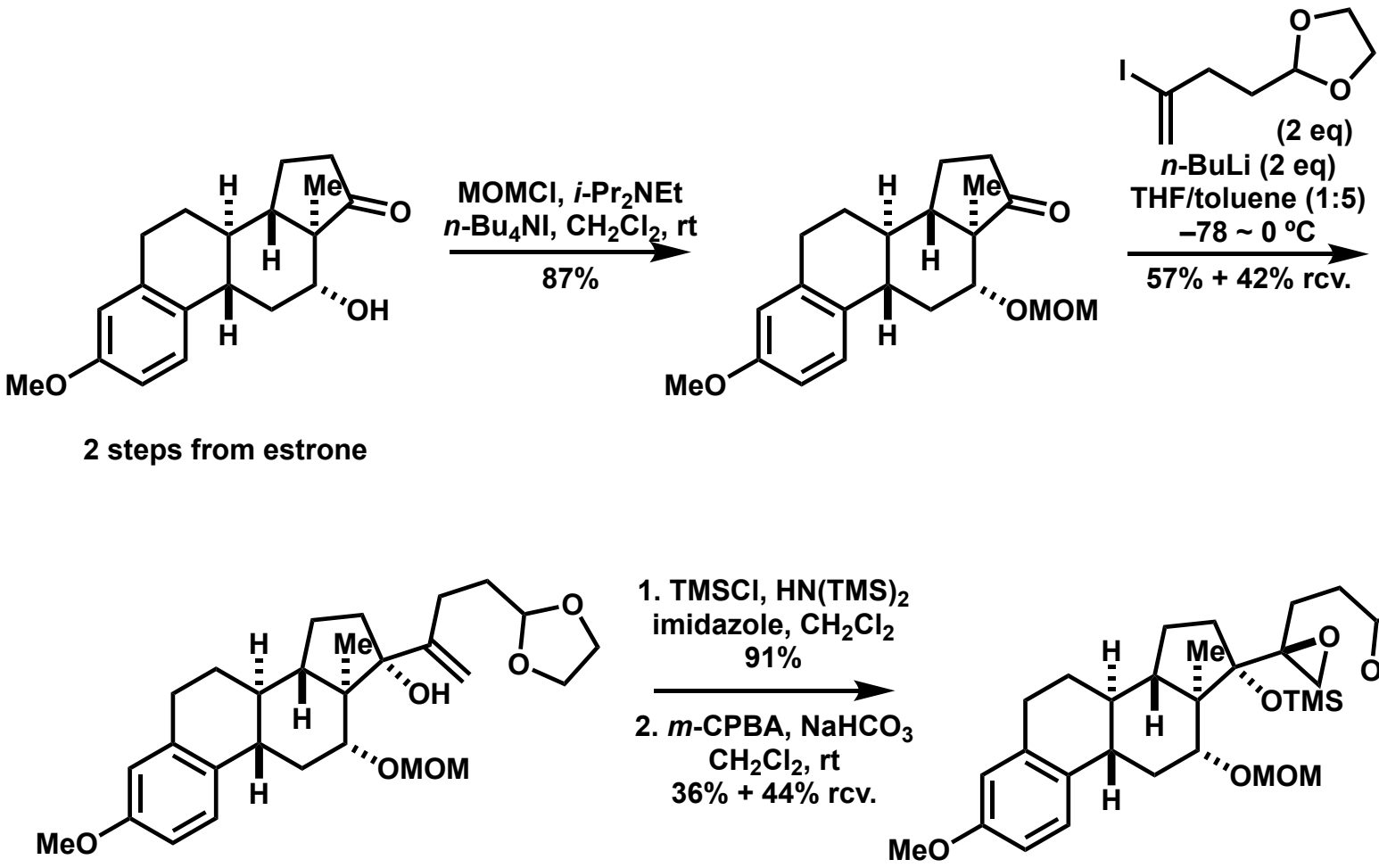


1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828
2) Snider, B. *Chem. Rev.* **1996,** *96,* 339.

Reaction mechanism of C-H oxidation

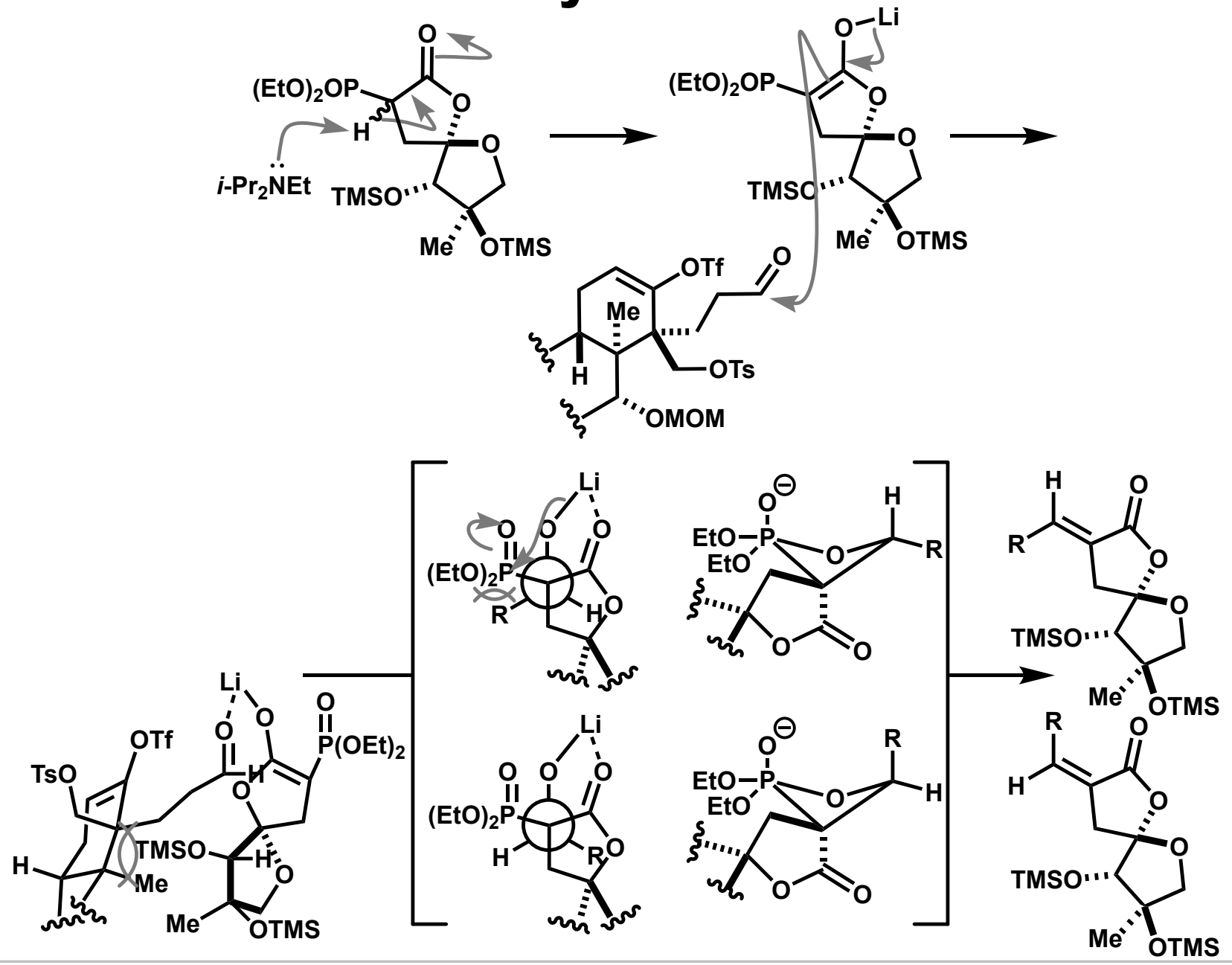


1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.
2) Trammell, R.; See, Y.; Herrmann, A.; Xie, N.; Diaz, D.; Siegler, M.; Baran, P.; Garcia-Bosch, I. *J. Org. Chem. Soc.* **2017,** *82,* 7887



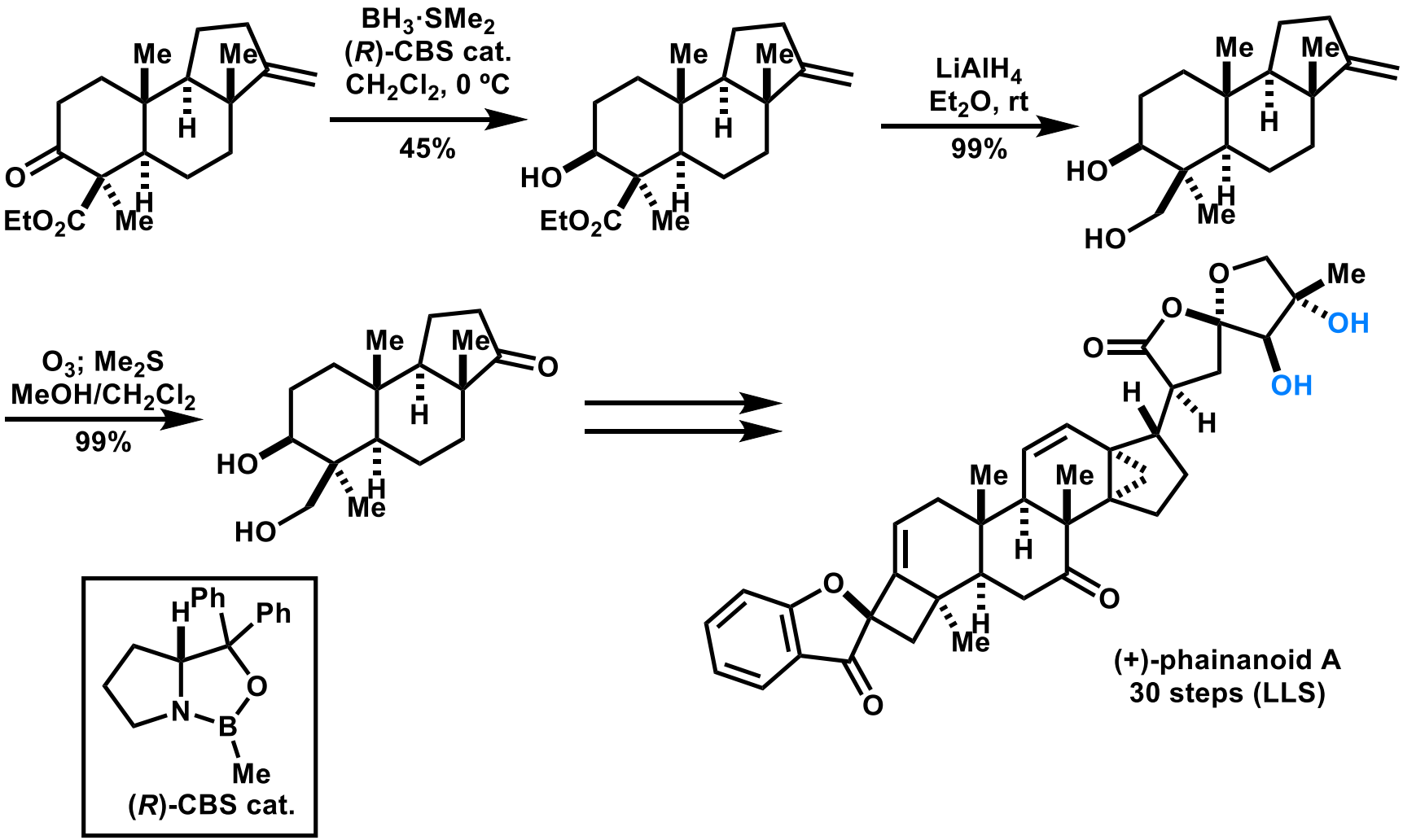
1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828

Stereoselectivity of HWE olefination



1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828

Assymmetric Total Synthesis of Phainanoid A



1) Xie, J.; Zeng, Z.; Liu, X.; Zhang, N.; Choi, S.; He, C.; Dong, G. *J. Am. Chem. Soc.* **2023,** *145*, 4828.