Total Synthesis of (-)-Conidiogenones and (+)-Aberrarone

Literature Seminar
2022. 10. 29

Manaka Matsumoto

Contents

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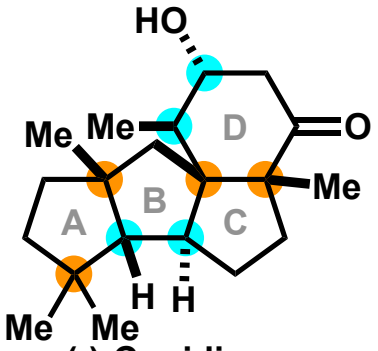
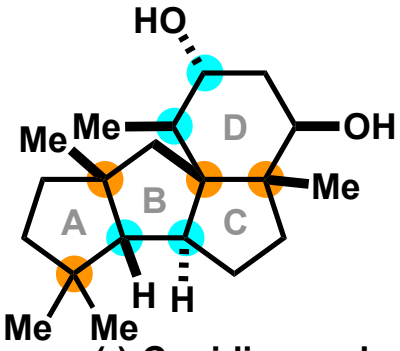
Conidiogenones



(-)-Conidiogenone



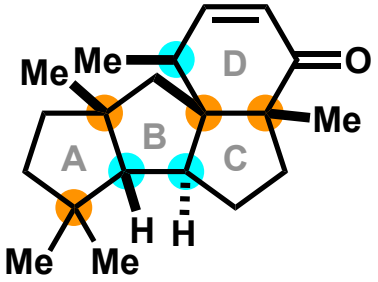
(-)-Conidiogenol

Isolation

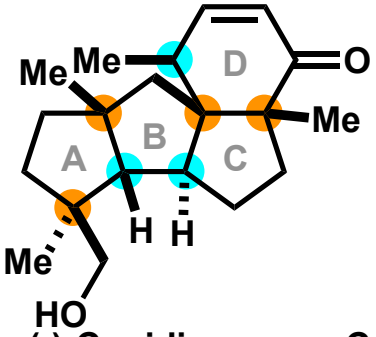
from the genis *Penicillium*

Conidiogenone and Conidiogenol (2002)[1)]

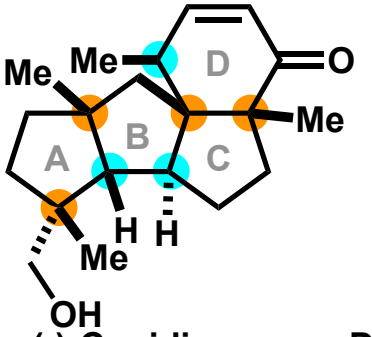
Conidiogenone B,C,D (2009)[2)]



(-)-Conidiogenone B



(-)-Conidiogenone C



(-)-Conidiogenone D

Biological activity

induction of conidiogenesis (Conidiogenone and Conidiogenol)[1)]

antibacterial activity (Conidiogenone B)[3)]

cytotoxicity (Cinidiogenone C)[2)]

Structural features

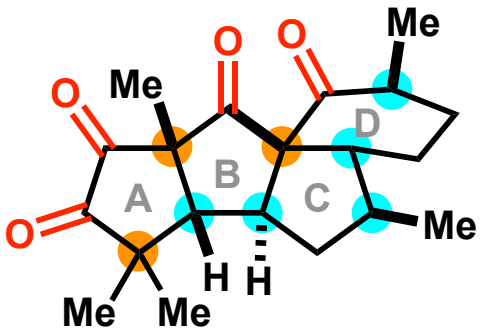
5-5-5-6 ring system, few functional groups, four quaternary carbons

Total synthesis

Tu (2016)[4)], Snyder (2019)[5)], Zhai (2020)[6)]

1) Roncal, T.; Cordobés, S.; Ugalge, U.; He, Y.; Sterner, O. *Tetrahedron Lett.* **2002**, *43*, 6799
2) Du, L.; Li, D.; Zhu, T.; Cai, S.; Wang, F.; Xiao, X.; Gu, Q. *Tetrahedron.* **2009**, *65*, 1033
3) Gao, S.; Li, X.; Zhang, Y.; Li, C.; Wang, B. *Chem.Biodivers.* **2011**, *8*, 1748
4) Hou, S.-H.; Tu, Y.-Q.; Wang, S.-H.; Xi, C.-C.; Zhang, F.-M.; Wang, S.-H.; Li, Y.-T.; Liu, L. *Angew. Chem., Int. Ed.* **2016**, *55*, 4456
5) Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. A. *Nature* **2019**, *569*, 703
6) Xu, B.; Xun, W.; Su, S.; Zhai, H. *Angew. Chem., Int. Ed.* **2020**, *59*, 16475

(+)-Aberrarone



(+)-Aberrarone

Isolation
from gorgonian coral *Pseudopterogorgia elisabethae* (2009)[1)]

Biological activity
anti malarial activity[1)]

Stractural features
5-5-5-6 ring system, four ketones, three quaternary carbons, seven stereogenic centers

Total synthesis
Carreira (2022)

Synthetic study
Ito (2015)[2)]

1) Rodríguez,I.; Rodríguez, A.D.; Zhao, H.; *J. Org. Chem.*, **2009**,*74*, 7581
2) Kobayashi, T.; Tokumoto, K.; Tsuchitani, Y.; Abe, H.; Ito, H. *Tetrahedron* **2015**, *71*, 5918

Introduction of Prof. Snyder and Prof. Carreira

Prof. Scott A. Snyder

1999 B. A., @ Williams College (Prof. Markgraf)
2004 Ph.D., @ The Scripps Research Institute (Prof. Nicolaou)
2004- Postdoctoral fellow @ Harvard University
2006- Assistant Professor @ Columbia University
2011- Associate Professor @ Columbia University
2013- Associate Professor @ The Scripps Research Institute
2015- Professor @ The University of Chicago

Research topic: Synthesis of complex natural products

Prof. Erick M. Carreira

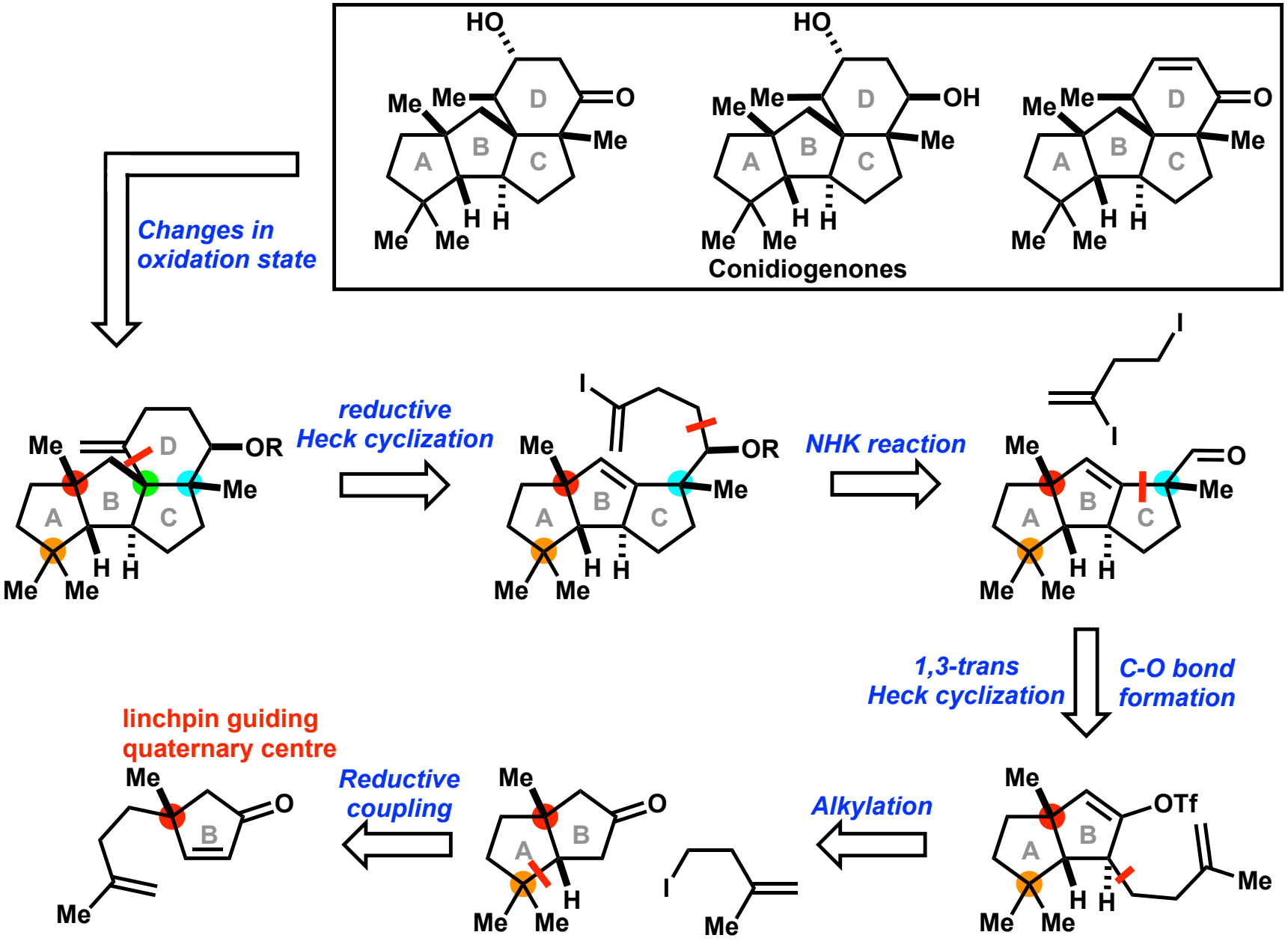
1984 B. S., @ University of Illinois at Urbana-Champaign (Prof. Denmark)
1990 Ph.D., @ Harvard University (Prof. Evans)
1990- Postdoctoral fellow @ California Institute of Technology
1992- Assistant Professor @ California Institute of Technology
1996- Associate Professor @ California Institute of Technology
1997- Professor @ California Institute of Technology
1998- Professor @ ETH Zürich

Research topic: Asymmetric synthesis of biologically active, stereo-chemically complex, natural products

1) https://snyder-group.uchicago.edu/sasnyder.html
2) https://carreira.ethz.ch/the-group/people/prof-dr-erick-m-carreira

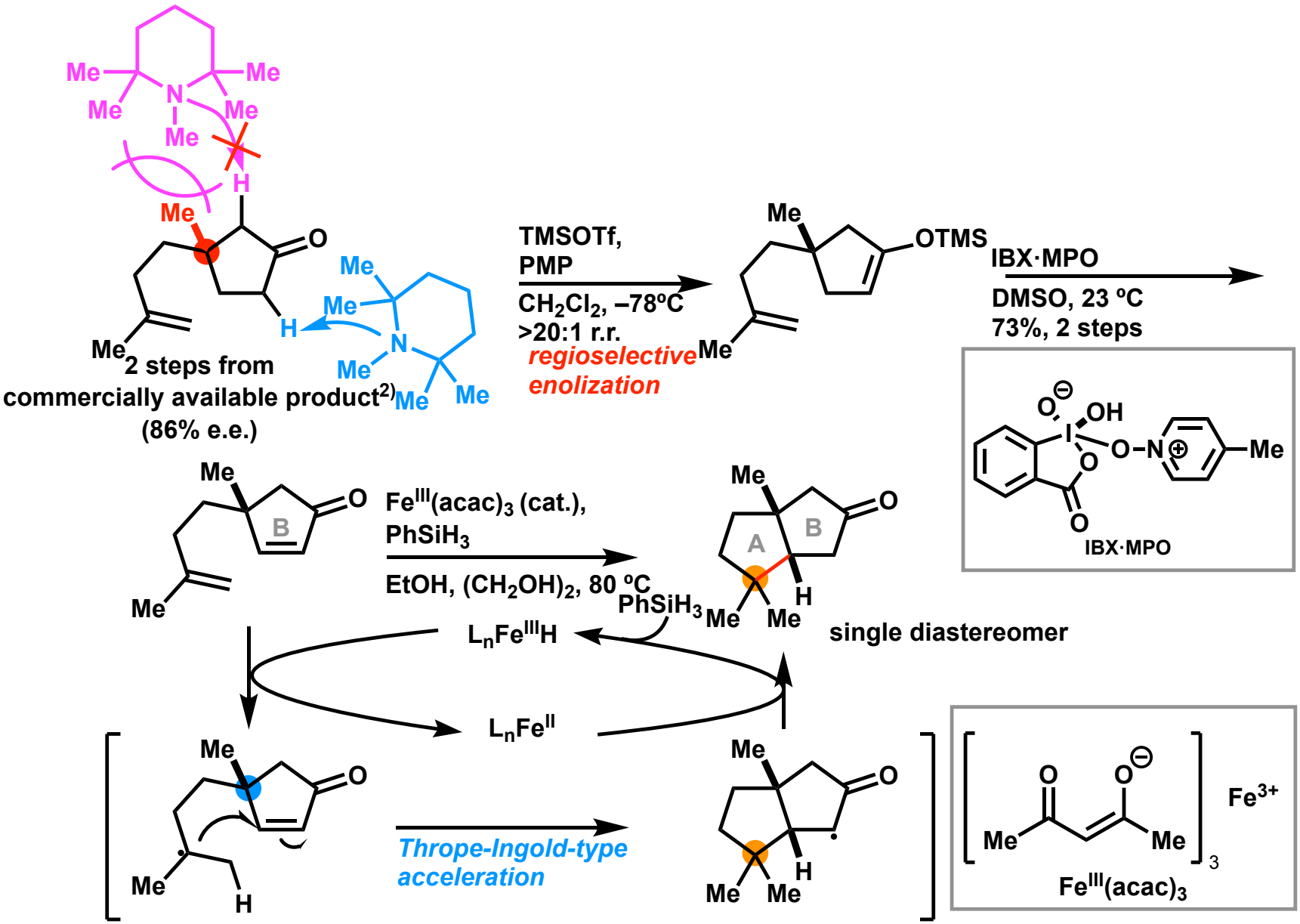
Contents

Retrosynthetic Analysis



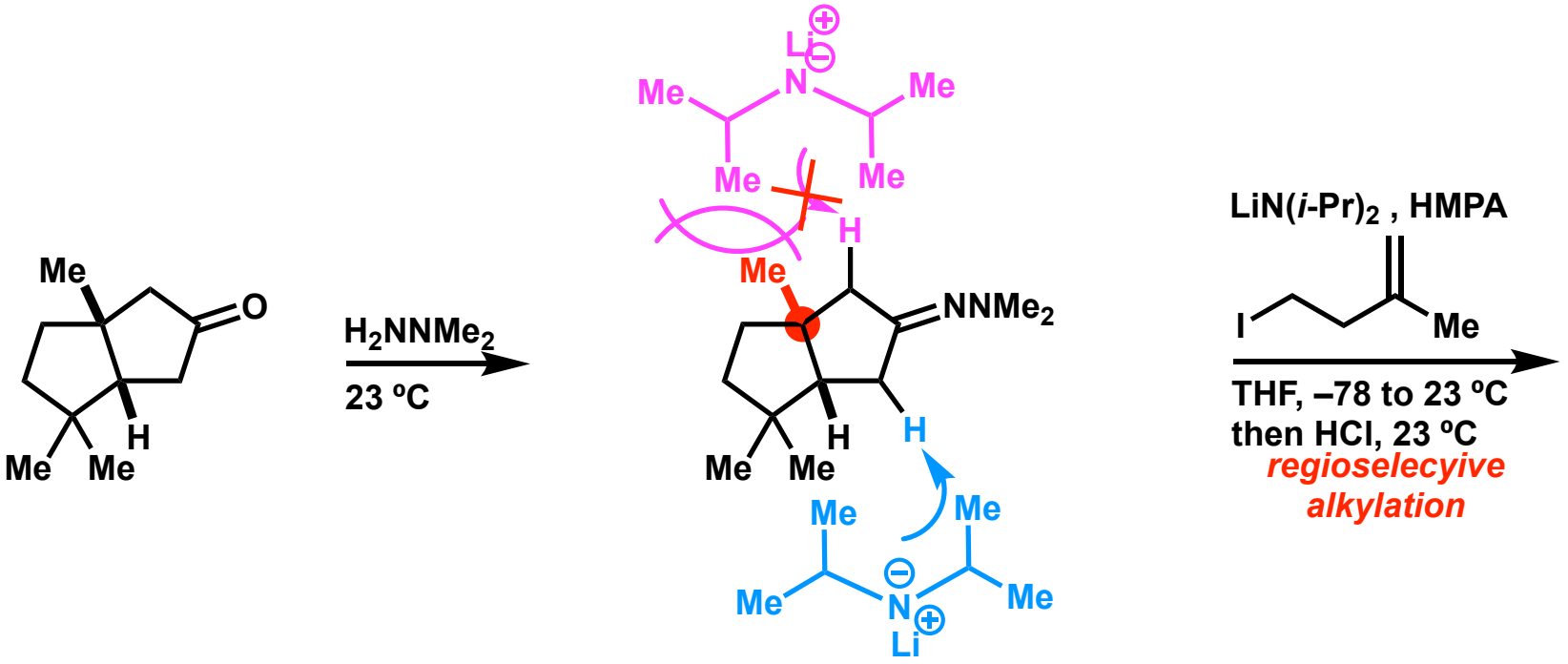
1) Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. A. *Nature* **2019**, *569*, 703

Construction of A-ring



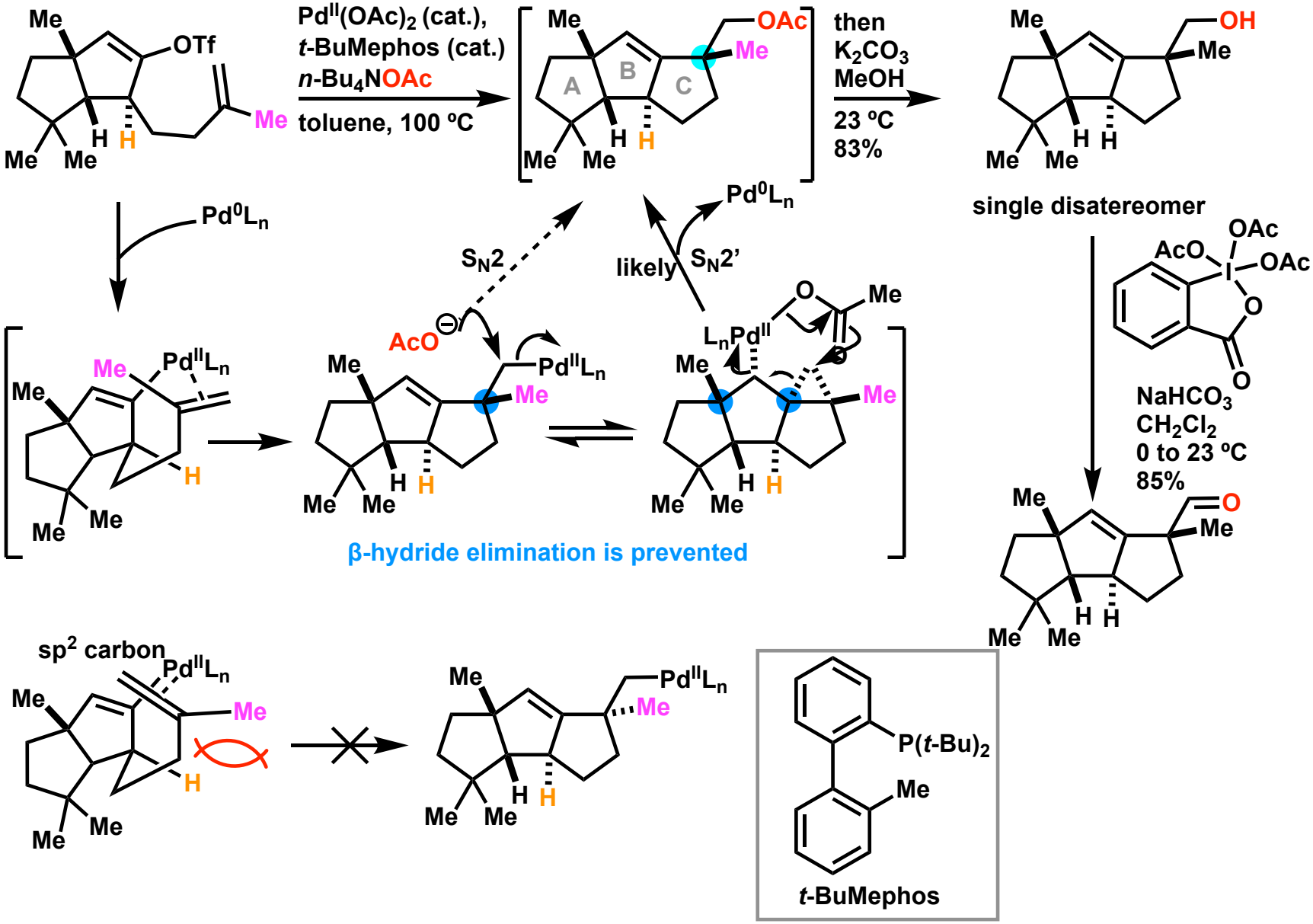
1) Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. A. *Nature* **2019**, *569*, 703
2) Brown, M. K. & Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**,*130*, 12904
3) Lo, J. C., Yabe, Y. & Baran, P. S. *J. Am. Chem. Soc.* **2014**,*136*, 1304

Regioselective Functionalization



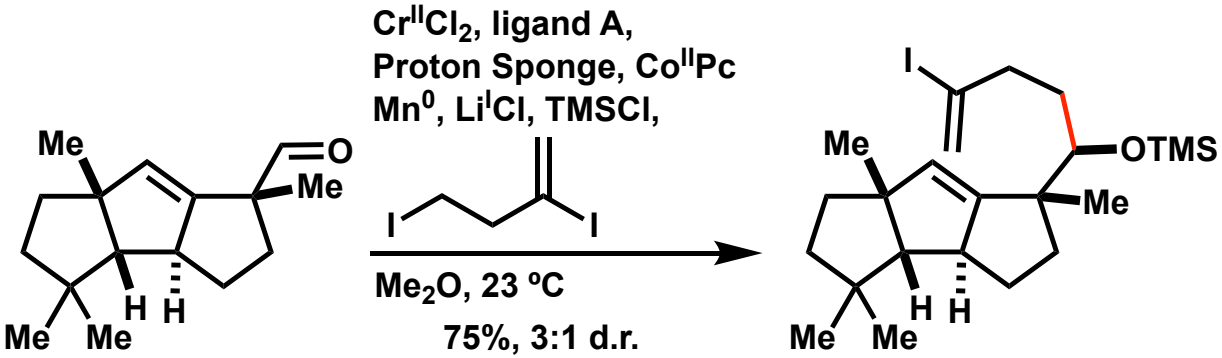
1) Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. A. *Nature* **2019**, *569*, 703

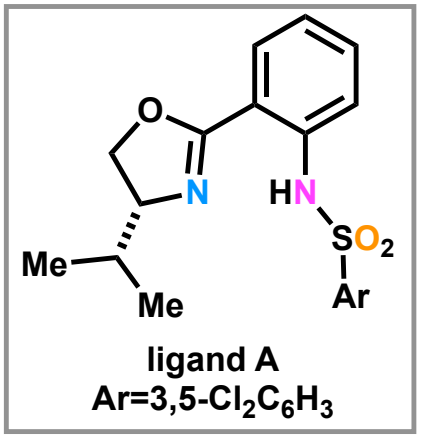
Pd-Catalysed Cascade

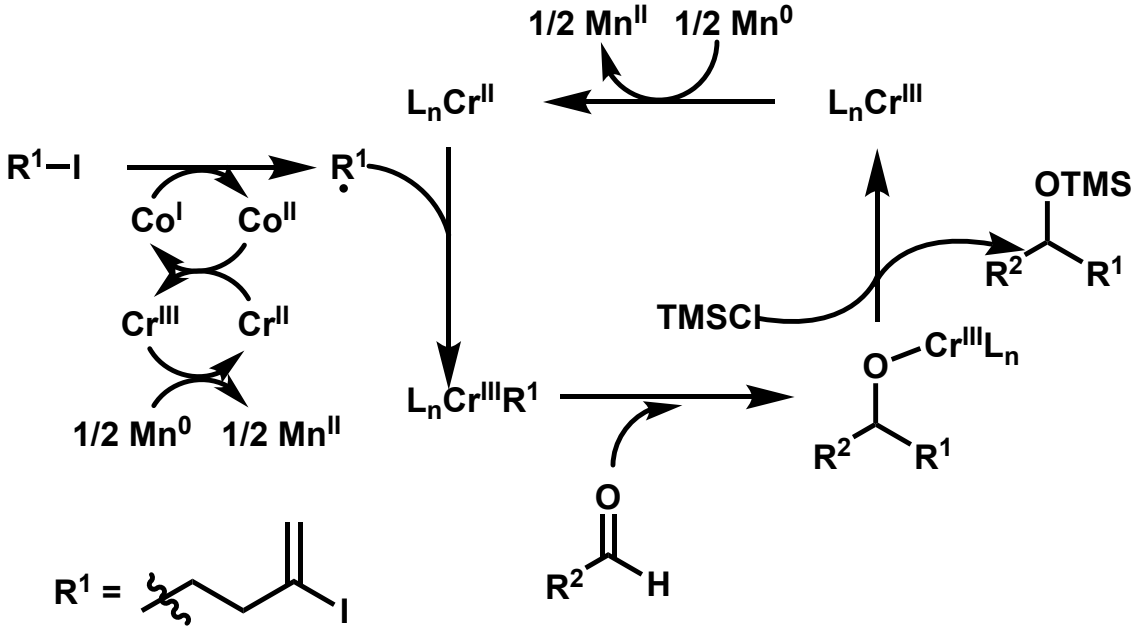


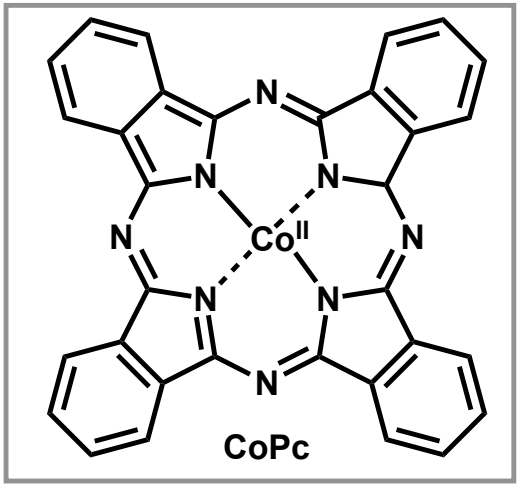
1) Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. A. *Nature* **2019**, *569*, 703
2) Yi, H.; Hu, P.; Snyder, S. A. *Angew. Chem., Int. Ed*. **2020**, 59, 2674

NHK Reaction



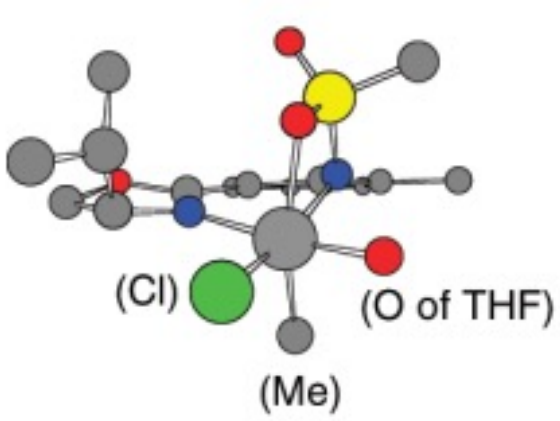




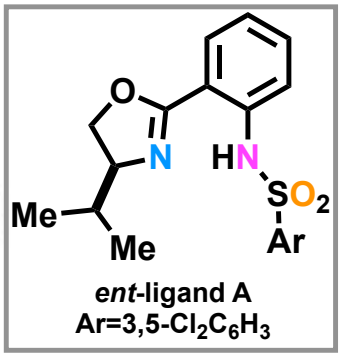


1) Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. A. *Nature* **2019**, *569*, 703
2) Guo, H.; Dong, C.-G.; Kim, D.-S.; Urabe, D.; Wang, J.; Kim, J. T.; Liu, X.; Sasaki, T.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131,* 15387

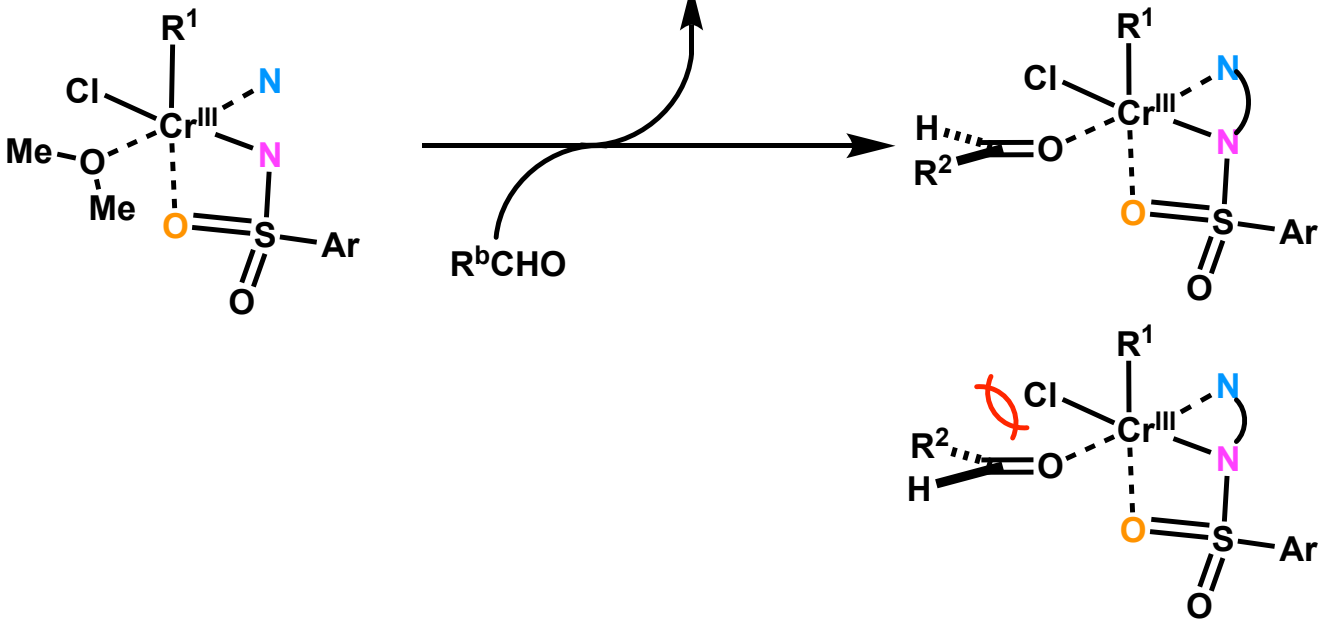
Stereoselectivity of NHK Reaction

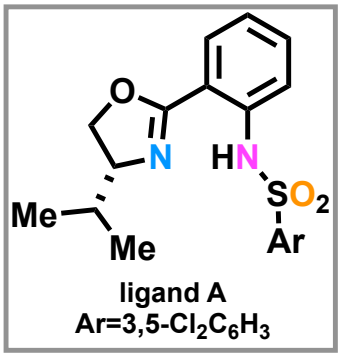


X-ray structure of
Cr^{III}(*ent*-ligand A)(Me)(Cl) complex



ent-ligand A
Ar=3,5-$Cl_2C_6H_3$

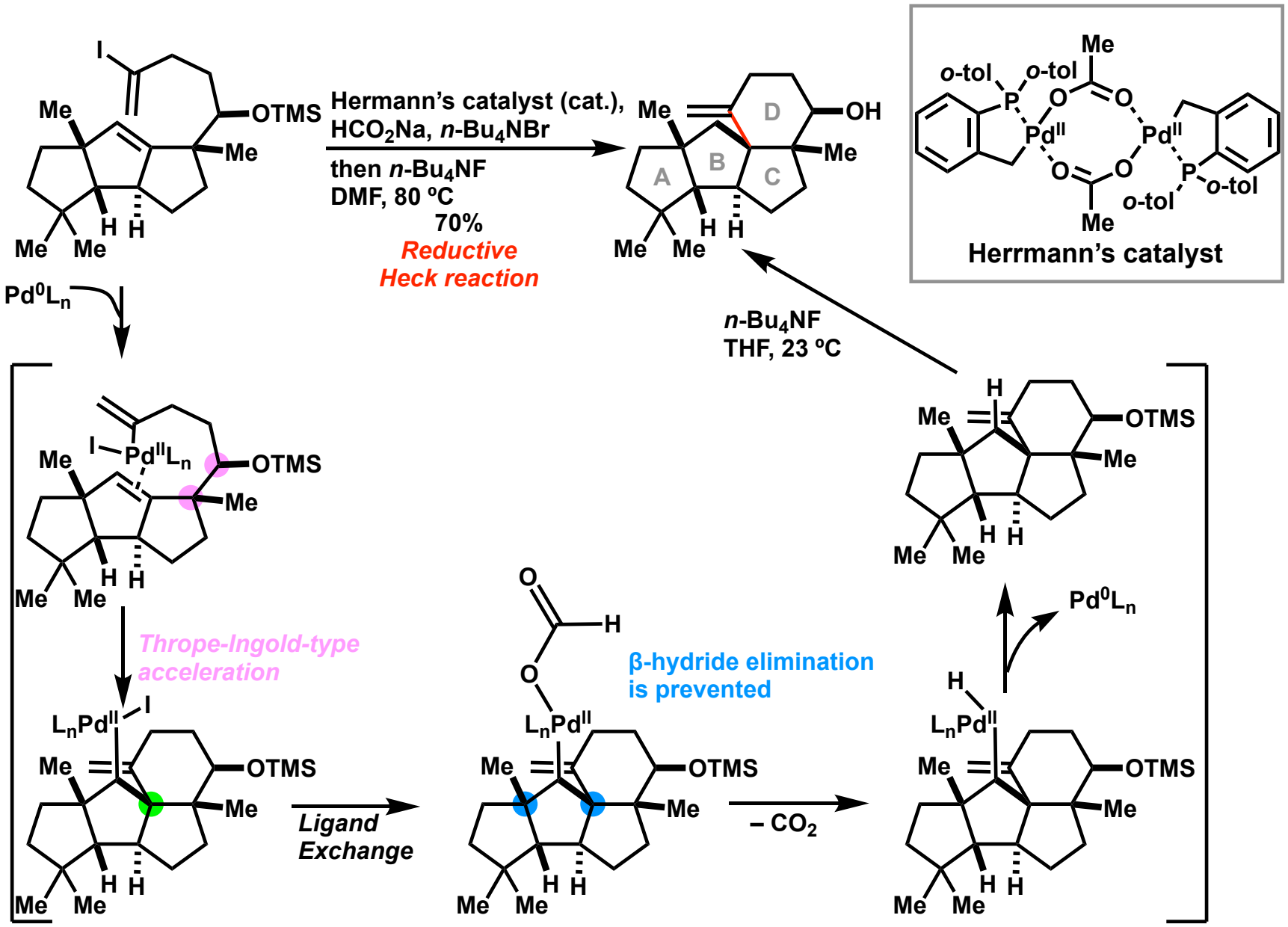




ligand A
Ar=3,5-$Cl_2C_6H_3$

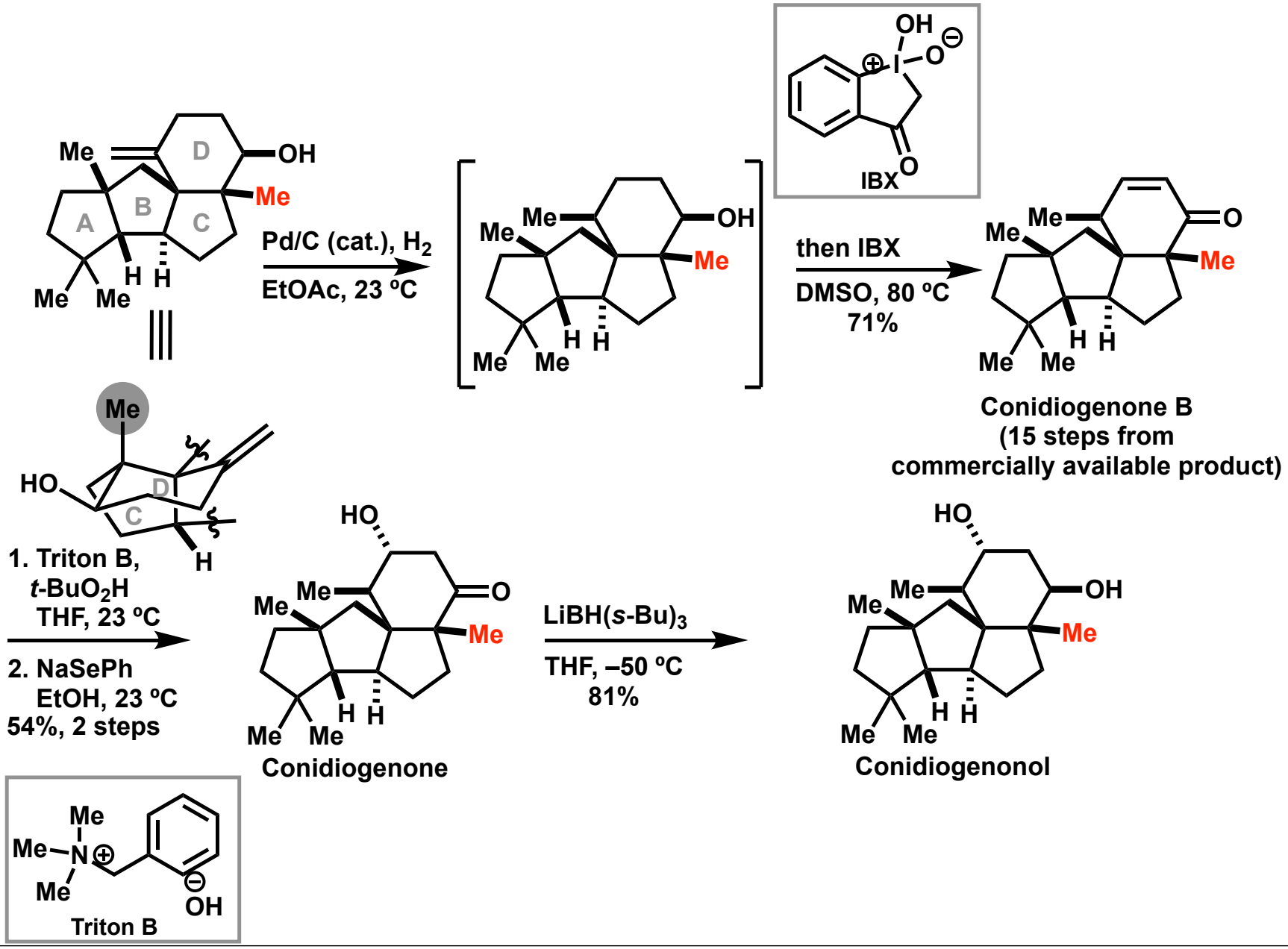
1) Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. A. *Nature* **2019**, *569*, 703
2) Guo, H.; Dong, C.-G.; Kim, D.-S.; Urabe, D.; Wang, J.; Kim, J. T.; Liu, X.; Sasaki, T.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, 15387

Reductive Heck Reaction



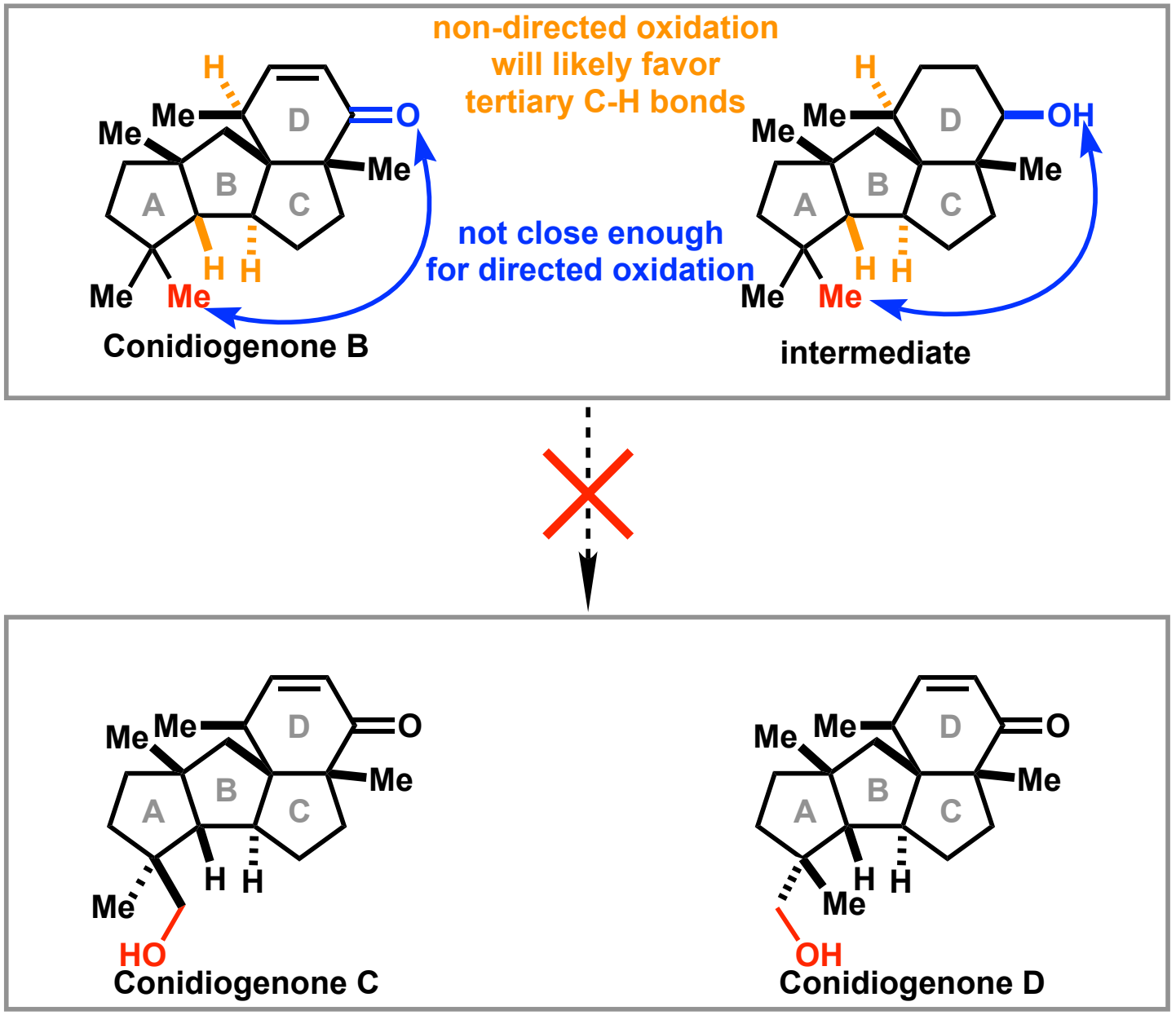
1) Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. A. *Nature*, **2019**, *569*, 703
2) Baran, P. S., Maimone, T. J. & Richter, J. M. *Nature*, **2007**, *446*, 404

Total Synthesis of Three Conidiogenones



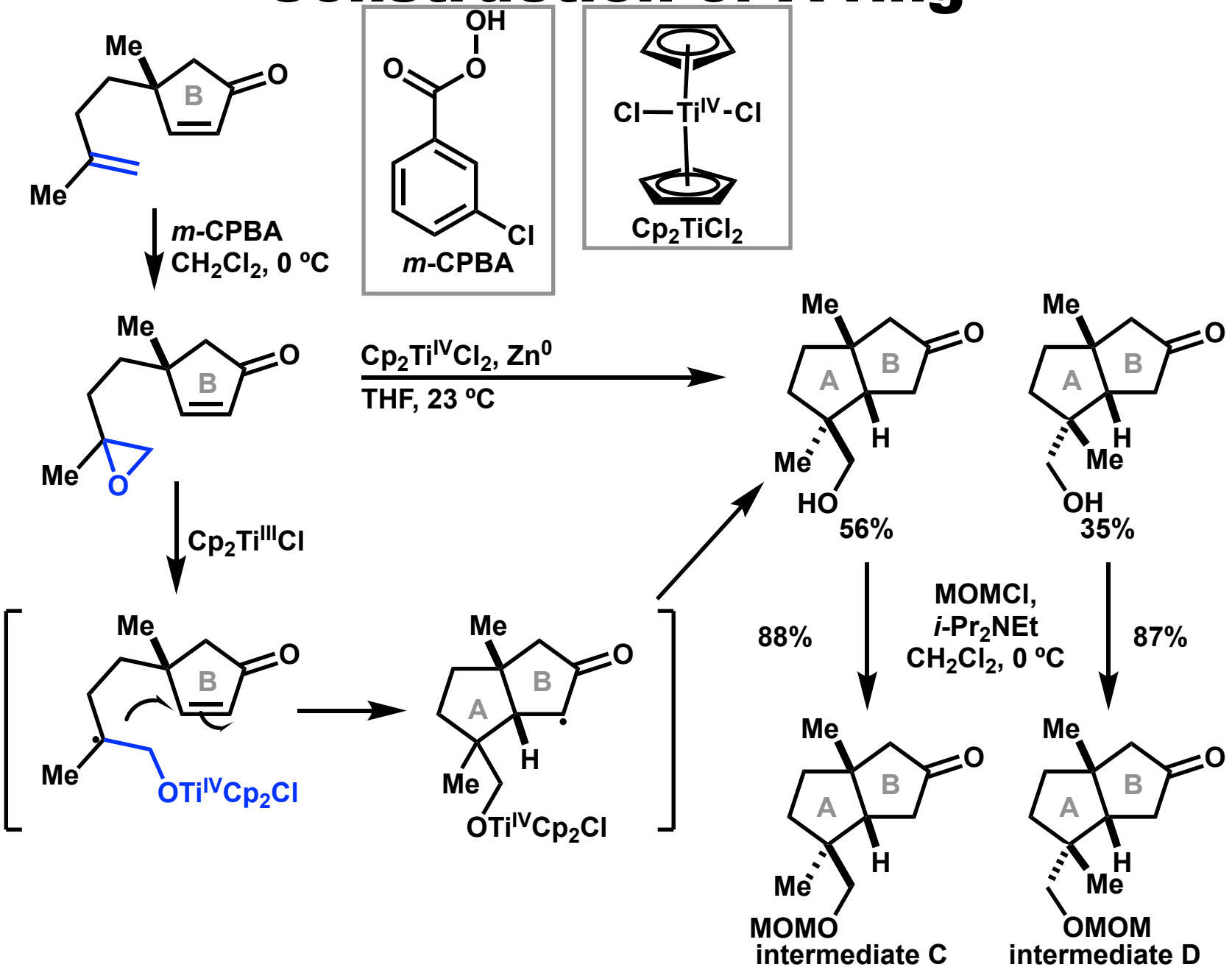
1) Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. A. *Nature* **2019**, *569*, 703

Synthesis of Conidiogenone C and D



1) Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. A. *Nature* **2019**, *569*, 703

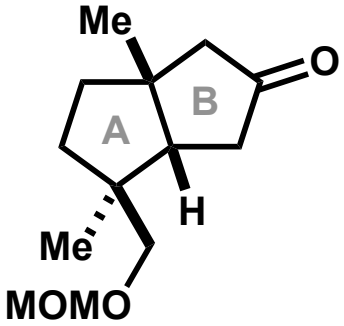
Construction of A-ring



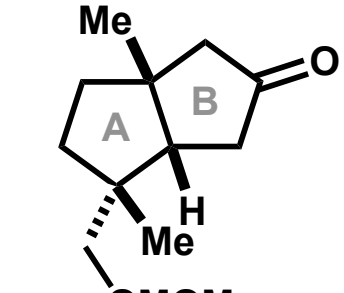
1) Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. A. *Nature* **2019**, *569*, 703

2) Rosales, A.; Rodriguez-Garcia, I.; Munoz-Bascon, J.; Roldan-Molina, E.; Padial, N. M.; Morales, L. P.; Garcia-Ocana, M.; Oltra, J. E. *Eur. J. Org. Chem.* **2015**, *2015*, 4567

Total Synthesis of Conidiogenone C and D



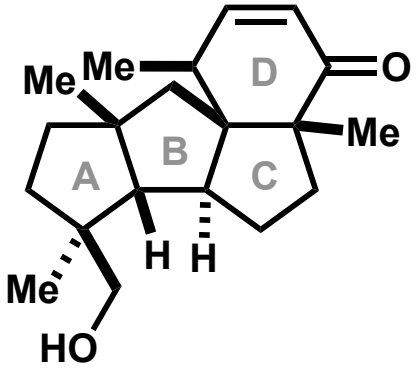
intermediate C



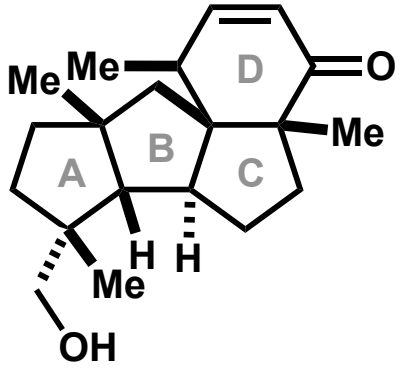
intermediate D

Construction of C and D ring in the similar way to the synthesis of Conidiogenone B

deprotection of MOM ether



Conidiogenone C
15 steps

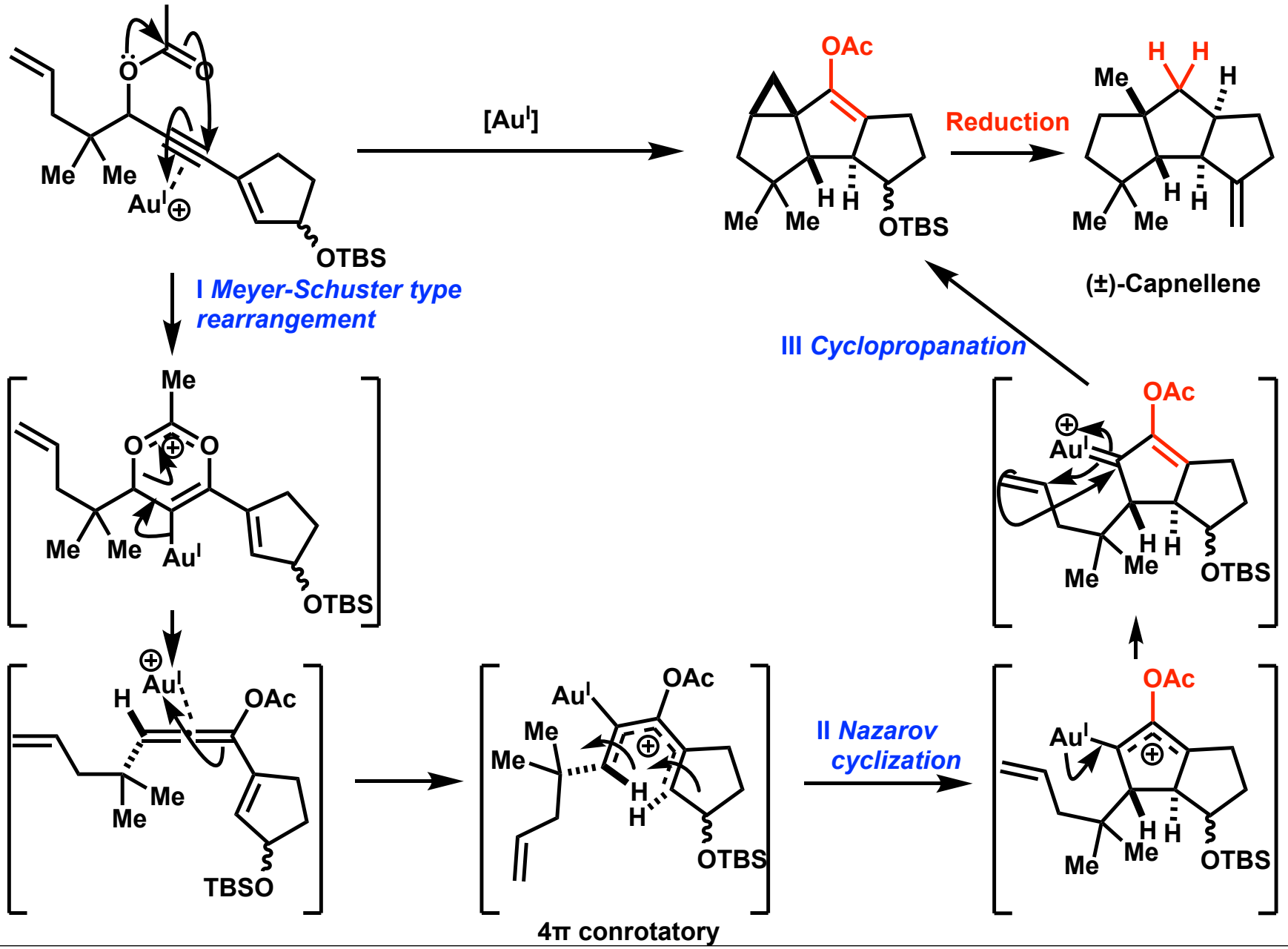


Conidiogenone D
15 steps

1) Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. A. *Nature* **2019**, *569*, 703

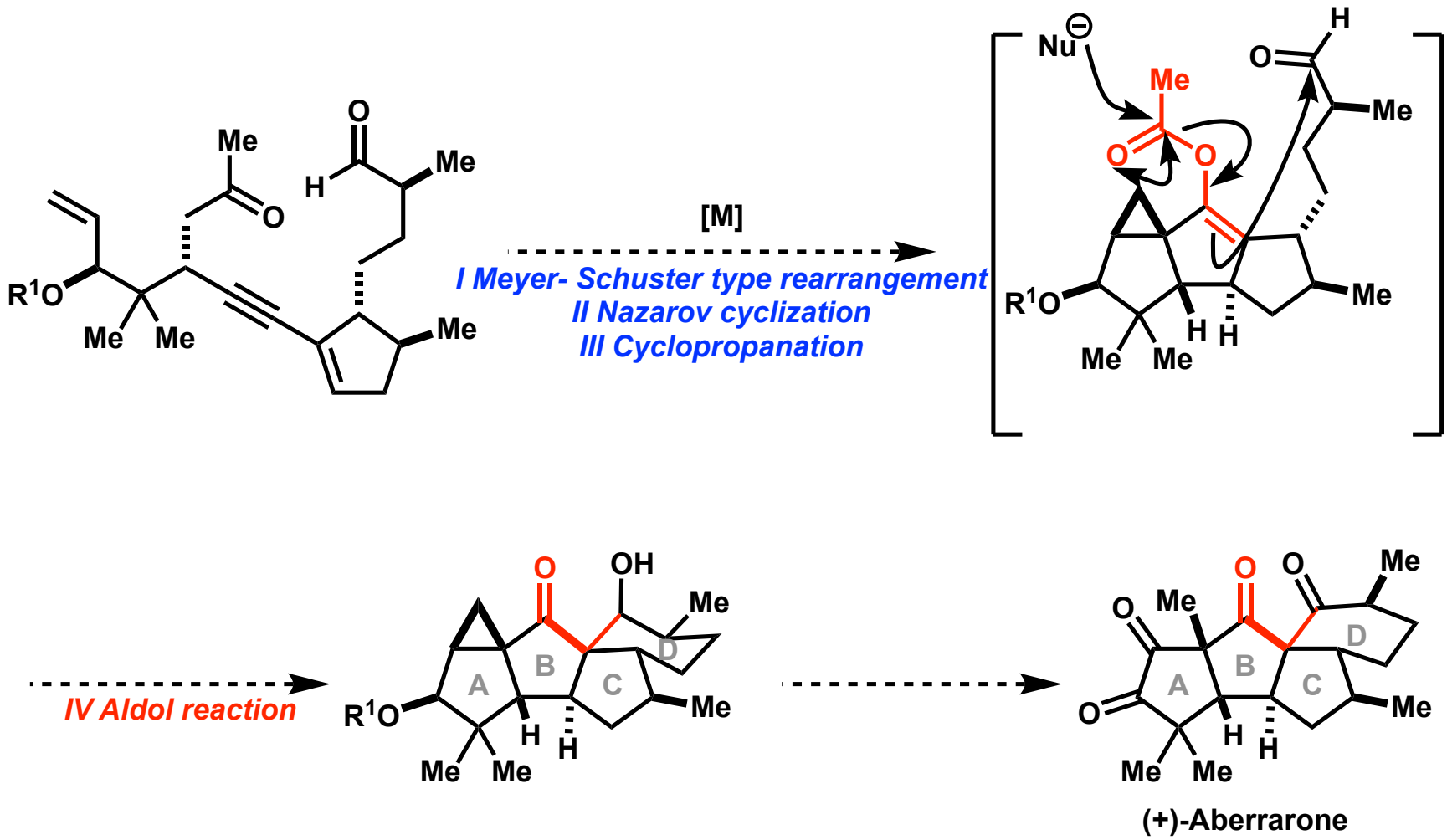
Contents

Prior Work by Malacria Group



1) Amberg, W.M.; Carreira, E.M. *J. Am. Chem. Soc.* **2022**, *144*, 15475
2) Lemière, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2009**, *131*, 2993

Key Synthetic Step of (+)-Aberrarone



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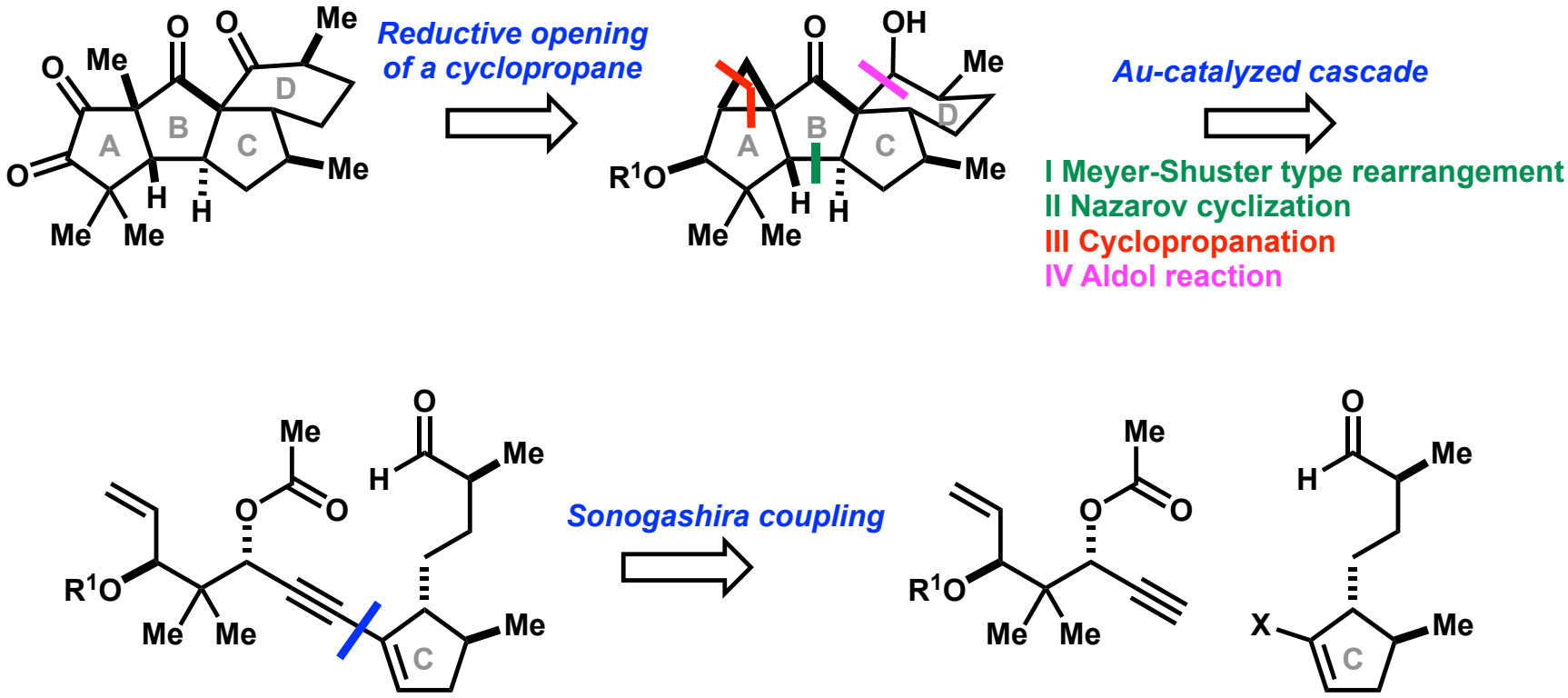
Retrosynthetic Analysis



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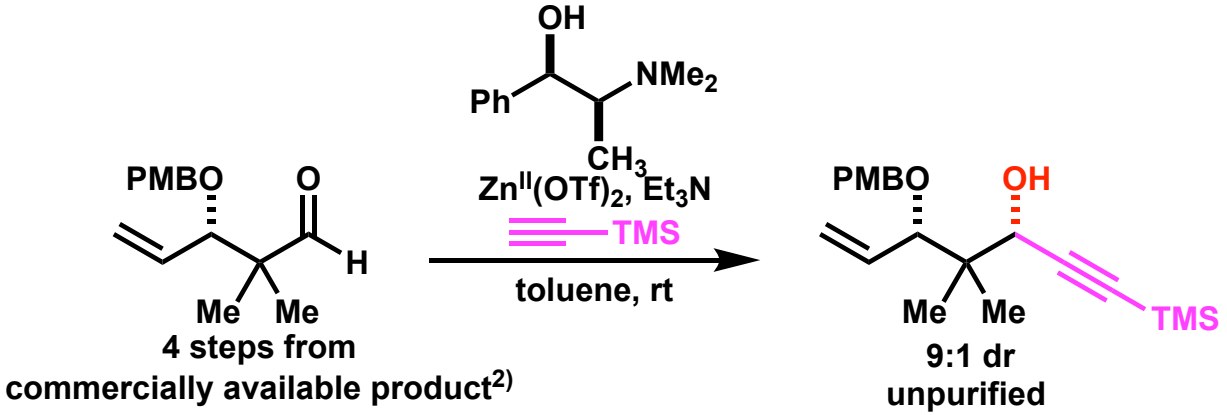
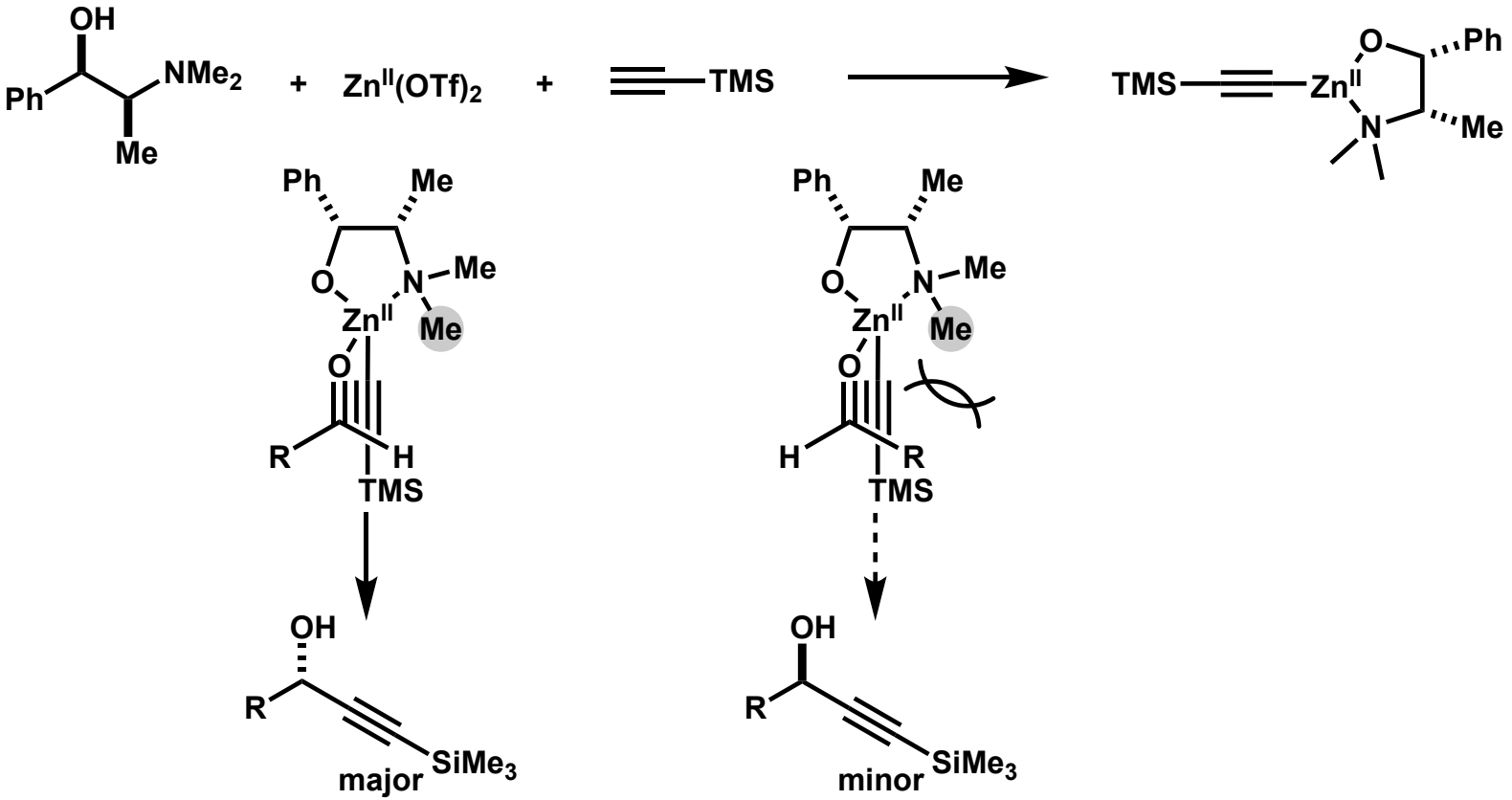
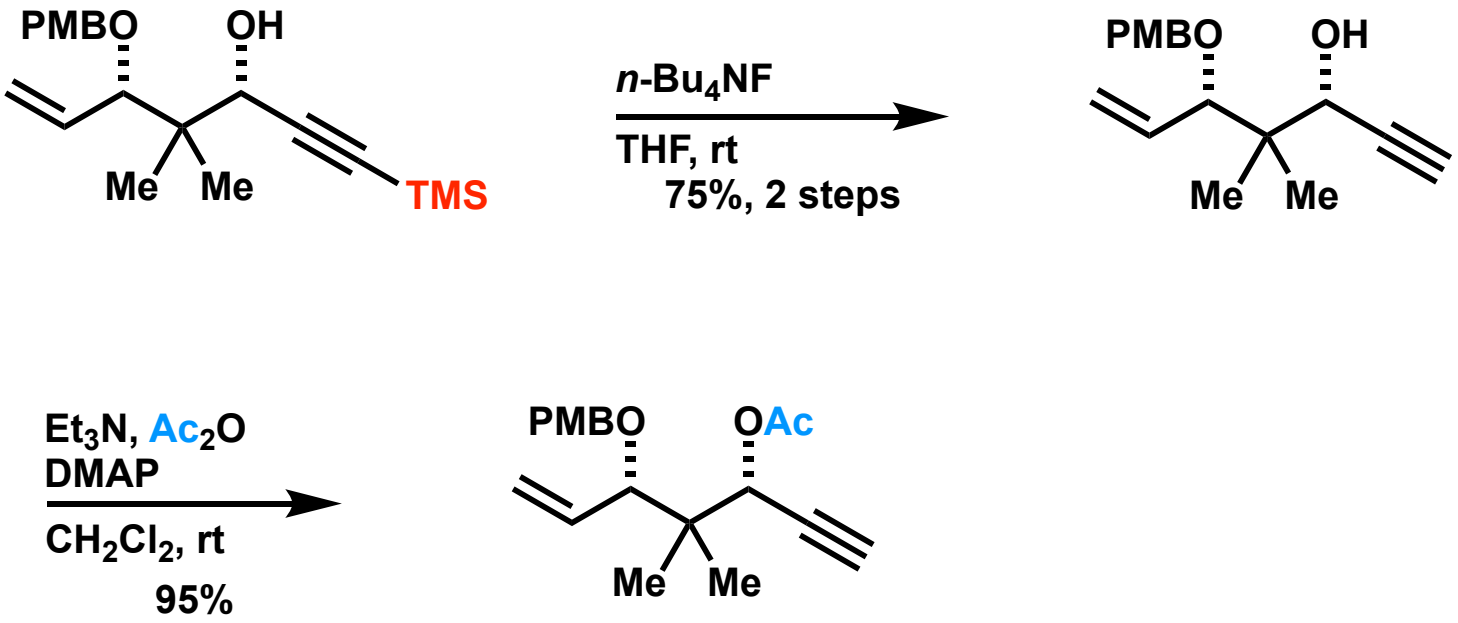
Synthesis of A-ring Fragment (1)





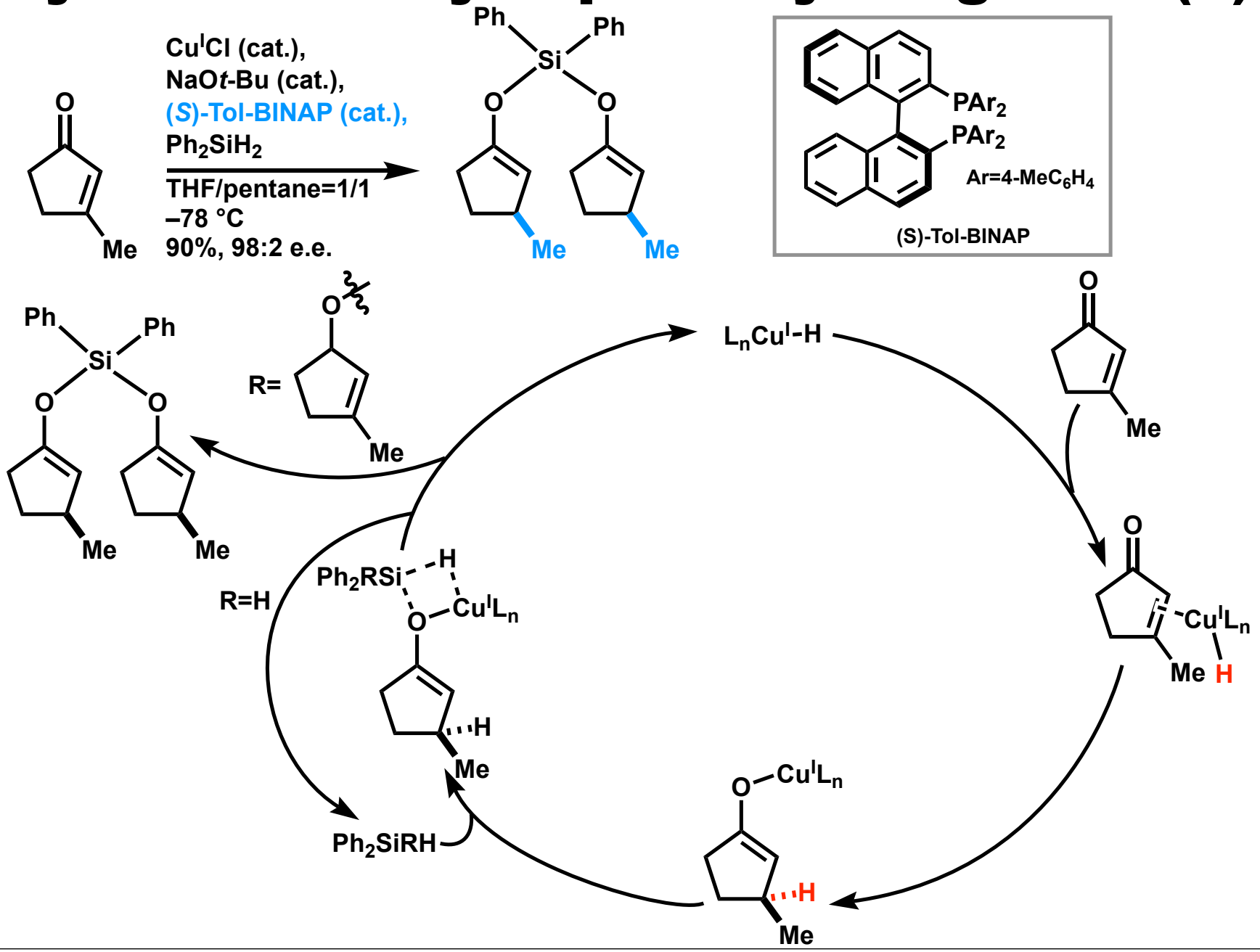
1) Amberg, W.M.; Carreira, E.M. *J. Am. Chem. Soc.* **2022**, *144*, 15475
2) Gill, D.; Taylor, N. H.; Thomas, E. J. *Tetrahedron* **2011**, *67*, 5034
3) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806
4) Asami, M.; Miyairi, N.; Sasahara, Y., Ichikawa, K.; Hosoda, N.; Ito, S. *Tetrahedron*, **2015**, *71,* 6796

Synthesis of A-ring Fragment (2)



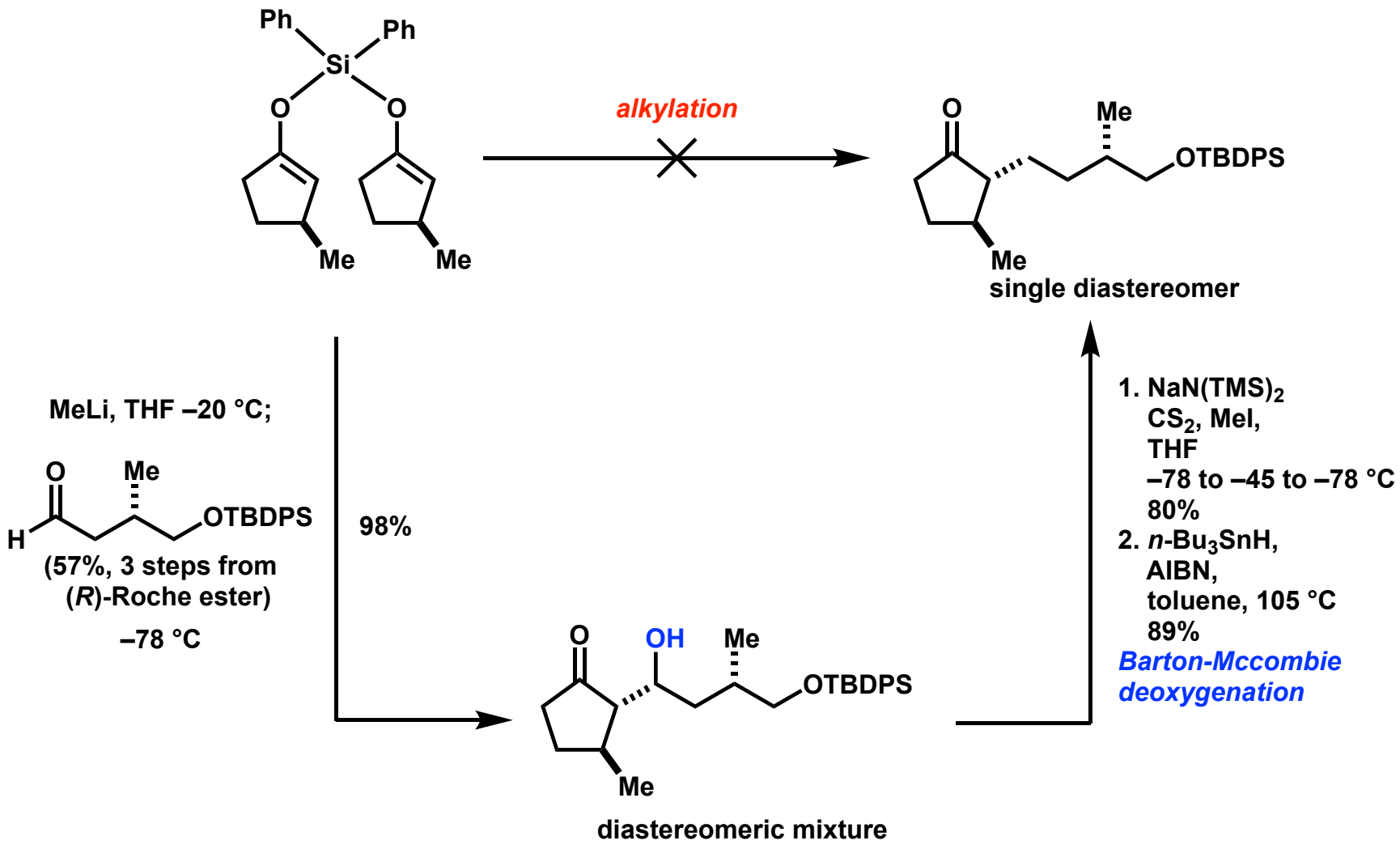
1) Amberg, W.M.; Carreira, E.M. *J. Am. Chem. Soc.* **2022**, *144*, 15475

Synthesis of cyclopentenyl fragment (1)



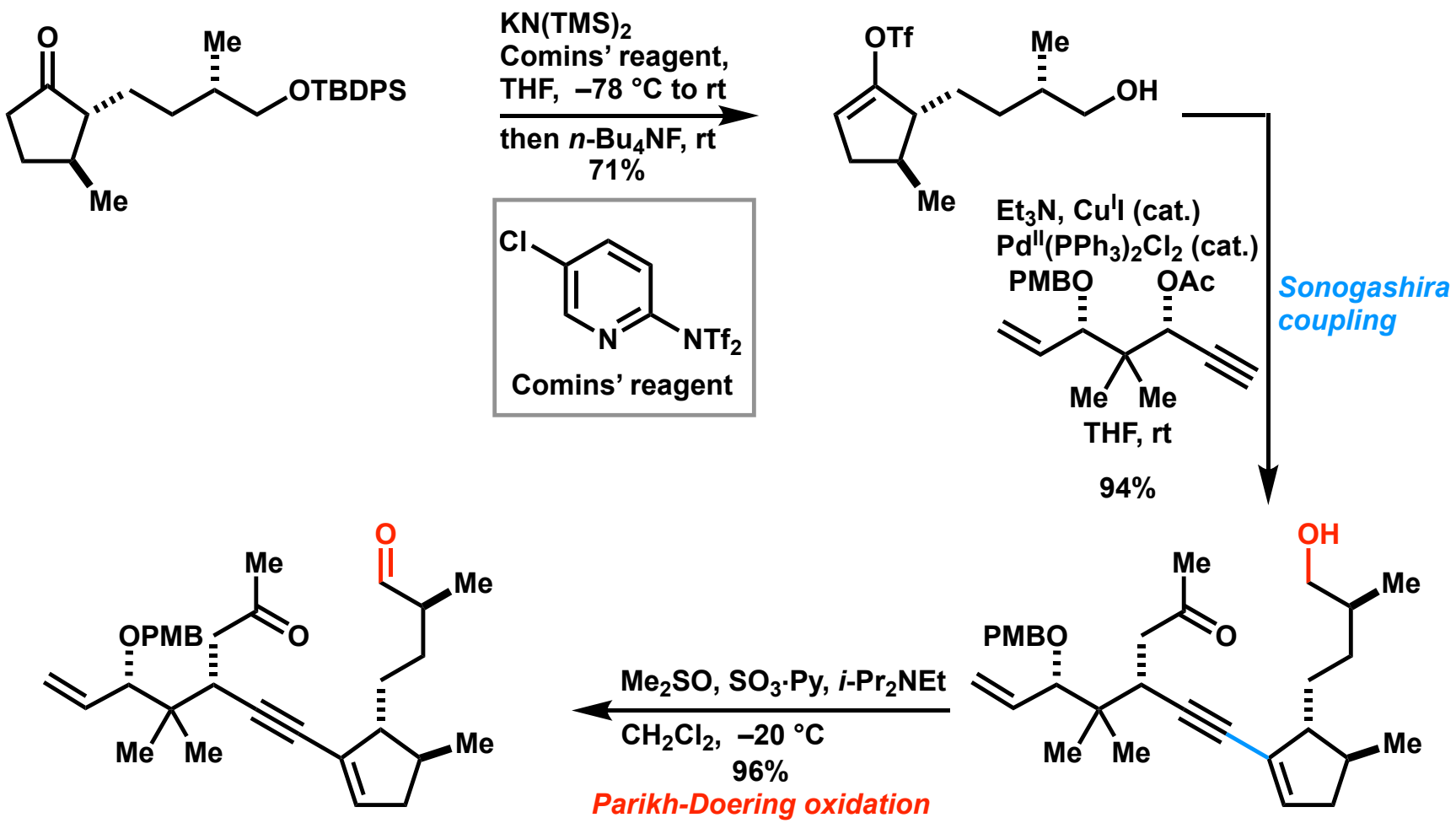
1) Amberg, W.M.; Carreira, E.M. *J. Am. Chem. Soc.* **2022**, *144*, 15475
2) Chae, J.; Yun, J.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 4809
3) Rendler, S.; Oestreich, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 498

Synthesis of cyclopentenyl fragment (2)



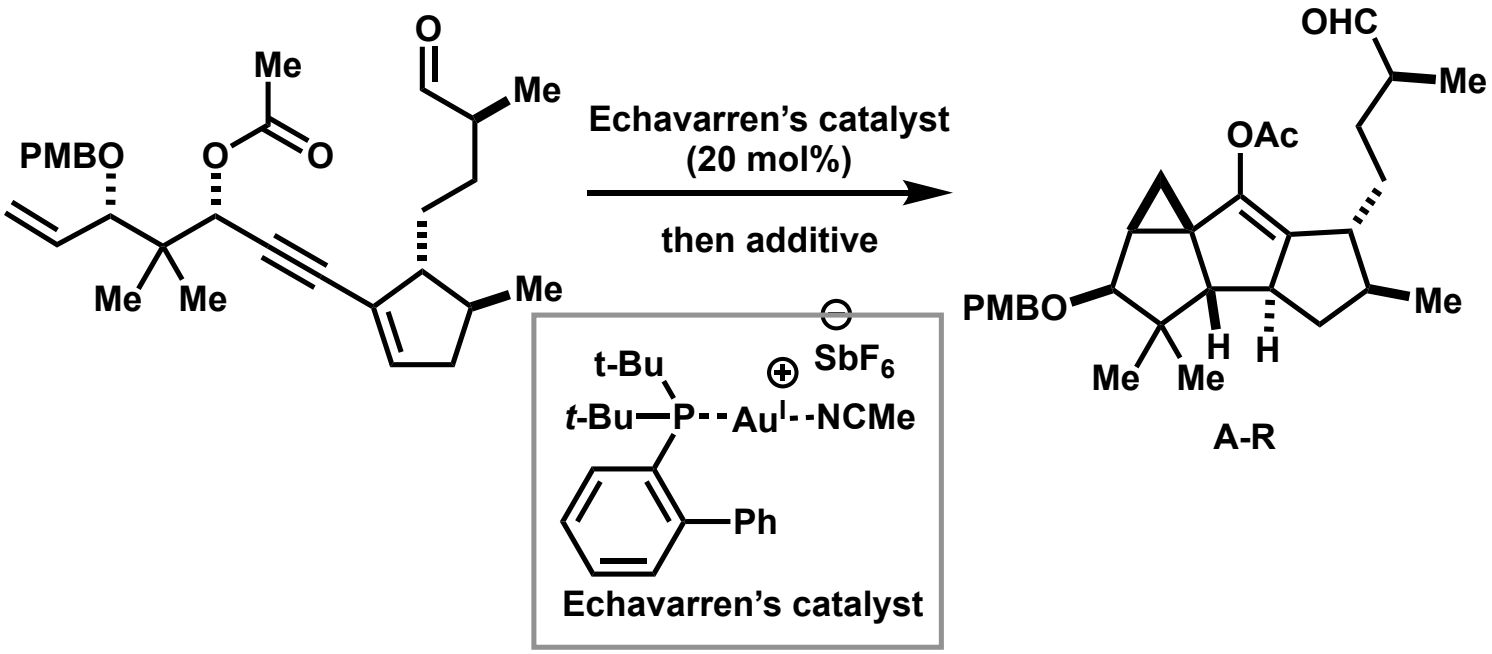
1) Amberg, W.M.; Carreira, E.M. *J. Am. Chem. Soc.* **2022**, *144*, 15475

Synthesis of cyclization precursor



1) Amberg, W.M.; Carreira, E.M. *J. Am. Chem. Soc.* **2022**, *144*, 15475

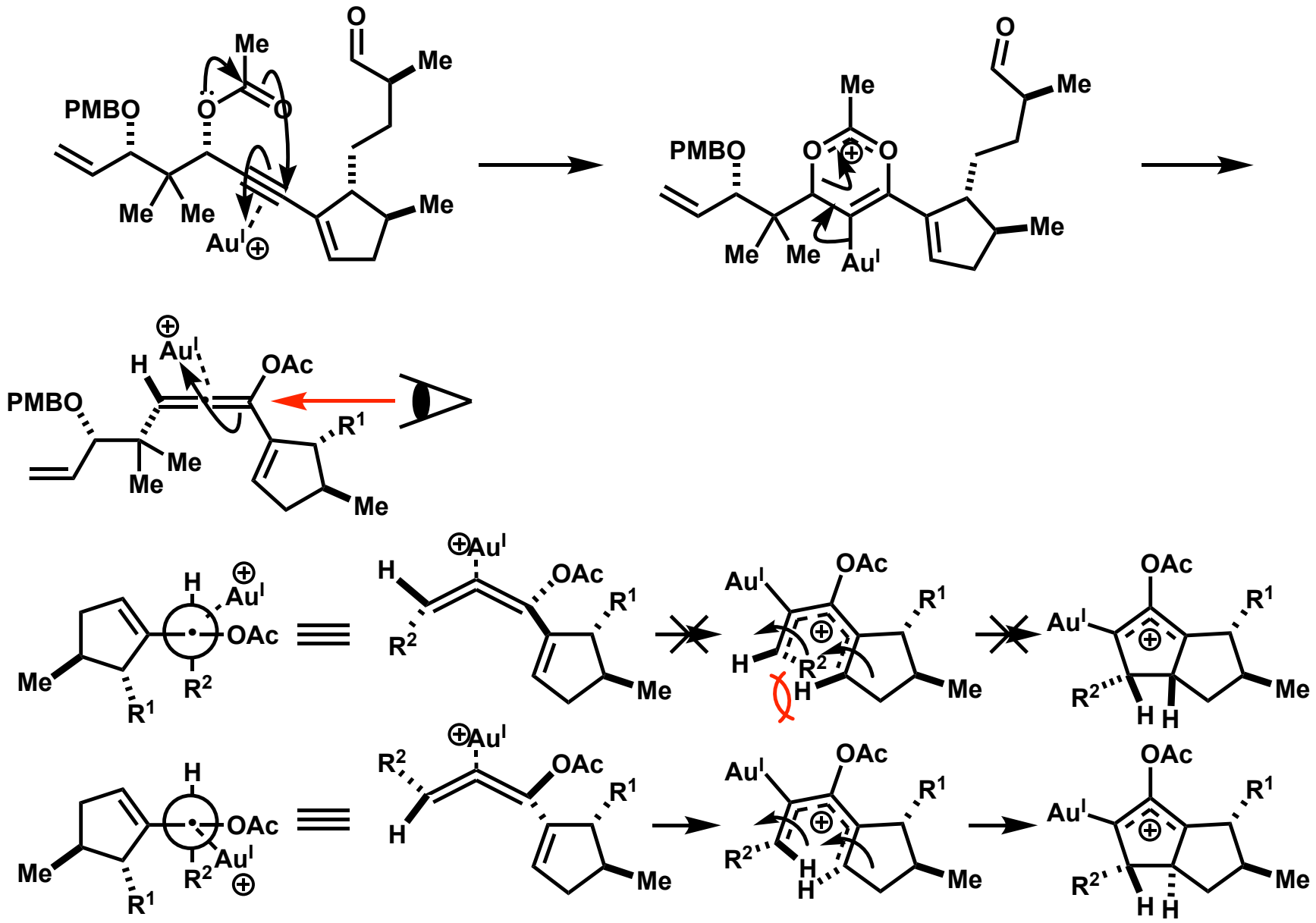
Investigation of cyclization cascade



entry	solvent	additive	temperature	time	Result
1	$THF/H_2O=500/1$	none	0 °C	12 h	recovery of starting material (95%)
2	CH_2Cl_2	none	0 °C	12 h	A-R (40%)
3	CH_2Cl_2	$TiCl_4$	−78 °C	1 min	decomposition

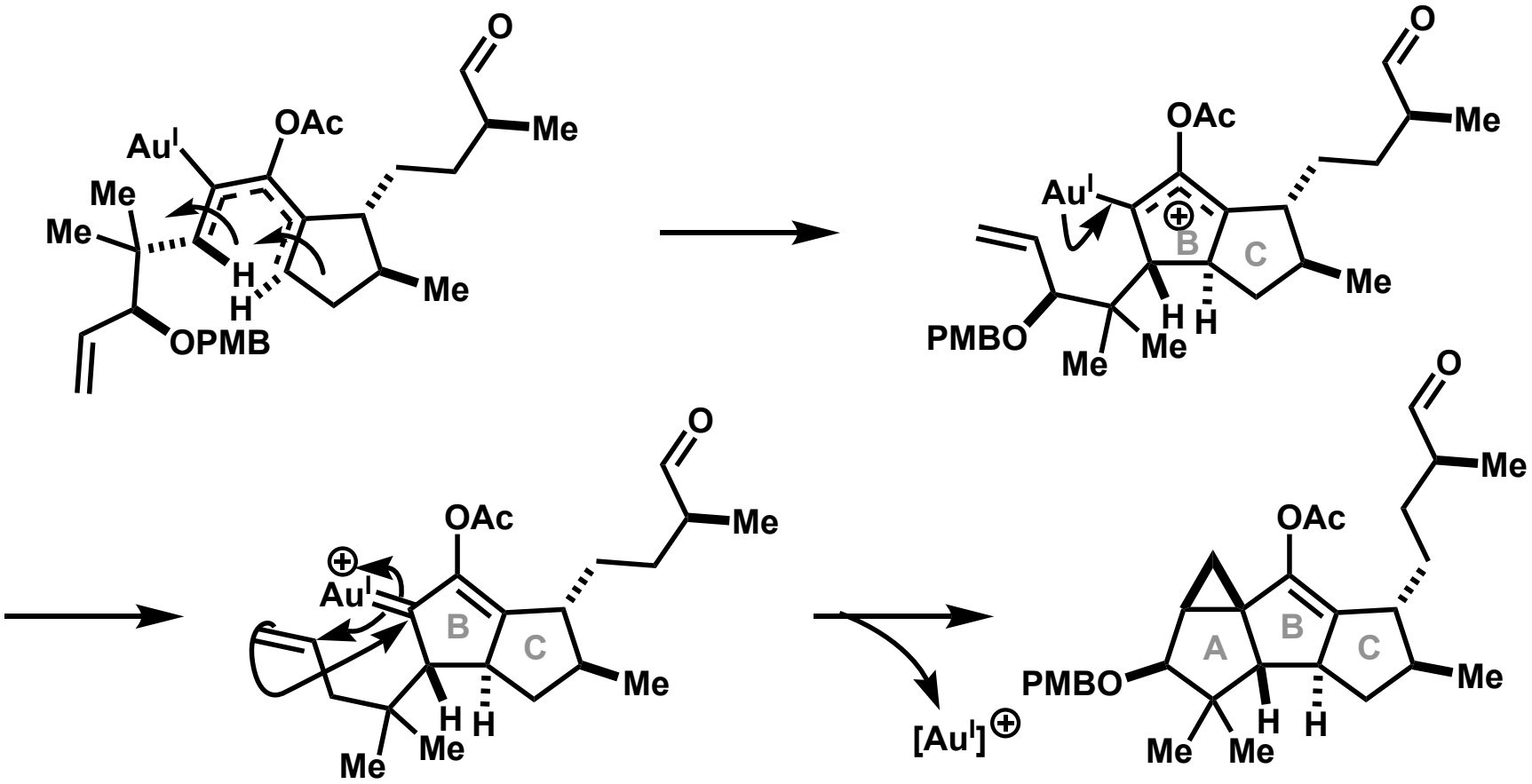
1) Amberg, W.M.; Carreira, E.M. *J. Am. Chem. Soc.* **2022**, *144*, 15475

Mechanism of Cyclization Cascade (1)



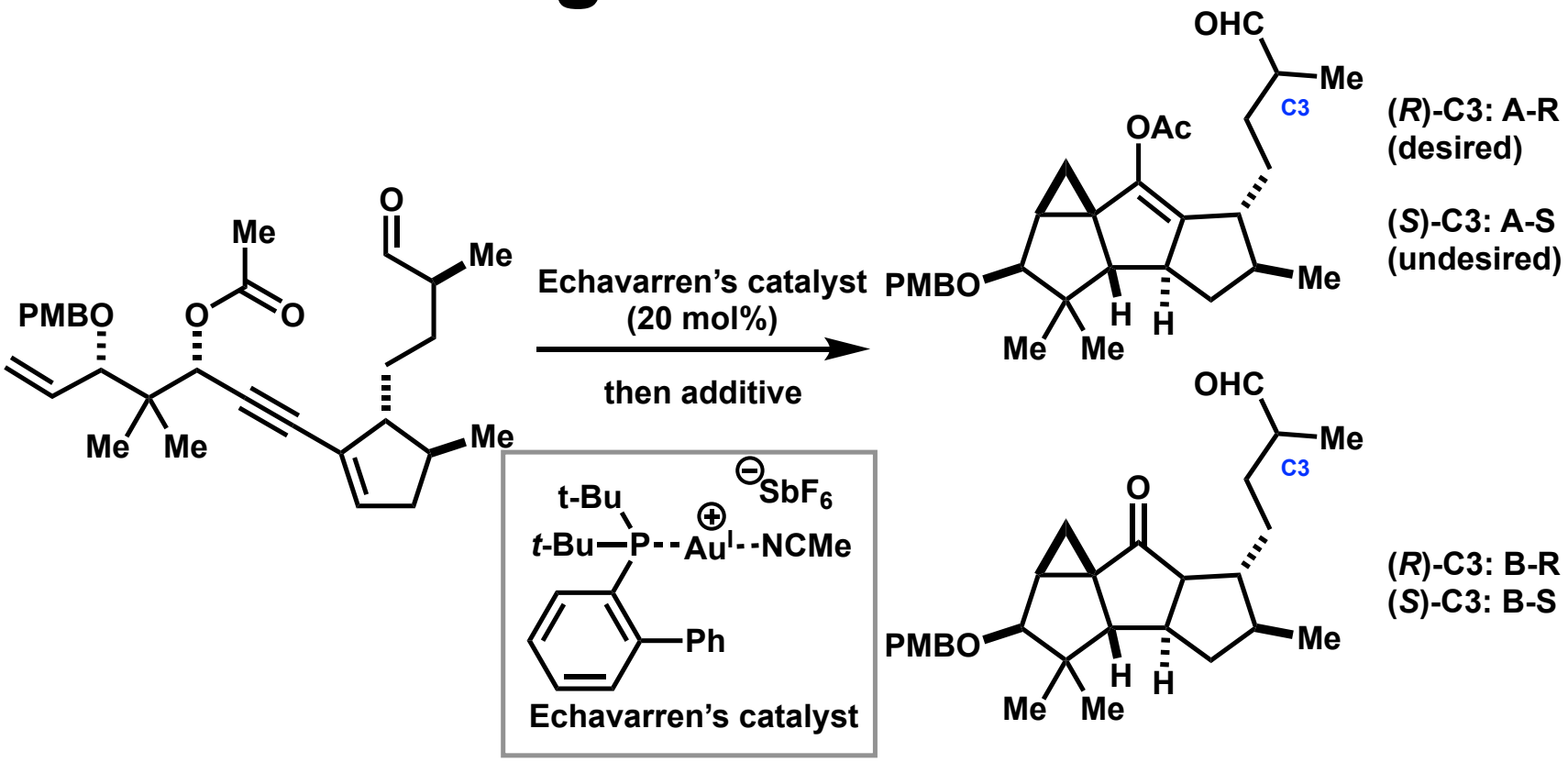
1) Amberg, W.M.; Carreira, E.M. *J. Am. Chem. Soc.* **2022**, *144*, 15475
2) Lemière, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2009**, *131*, 2993

Mechanism of cyclization(2)



1) Amberg, W.M.; Carreira, E.M. *J. Am. Chem. Soc.* **2022**, *144*, 15475
2) Lemière, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2009**, *131*, 2993

Investigation of additives

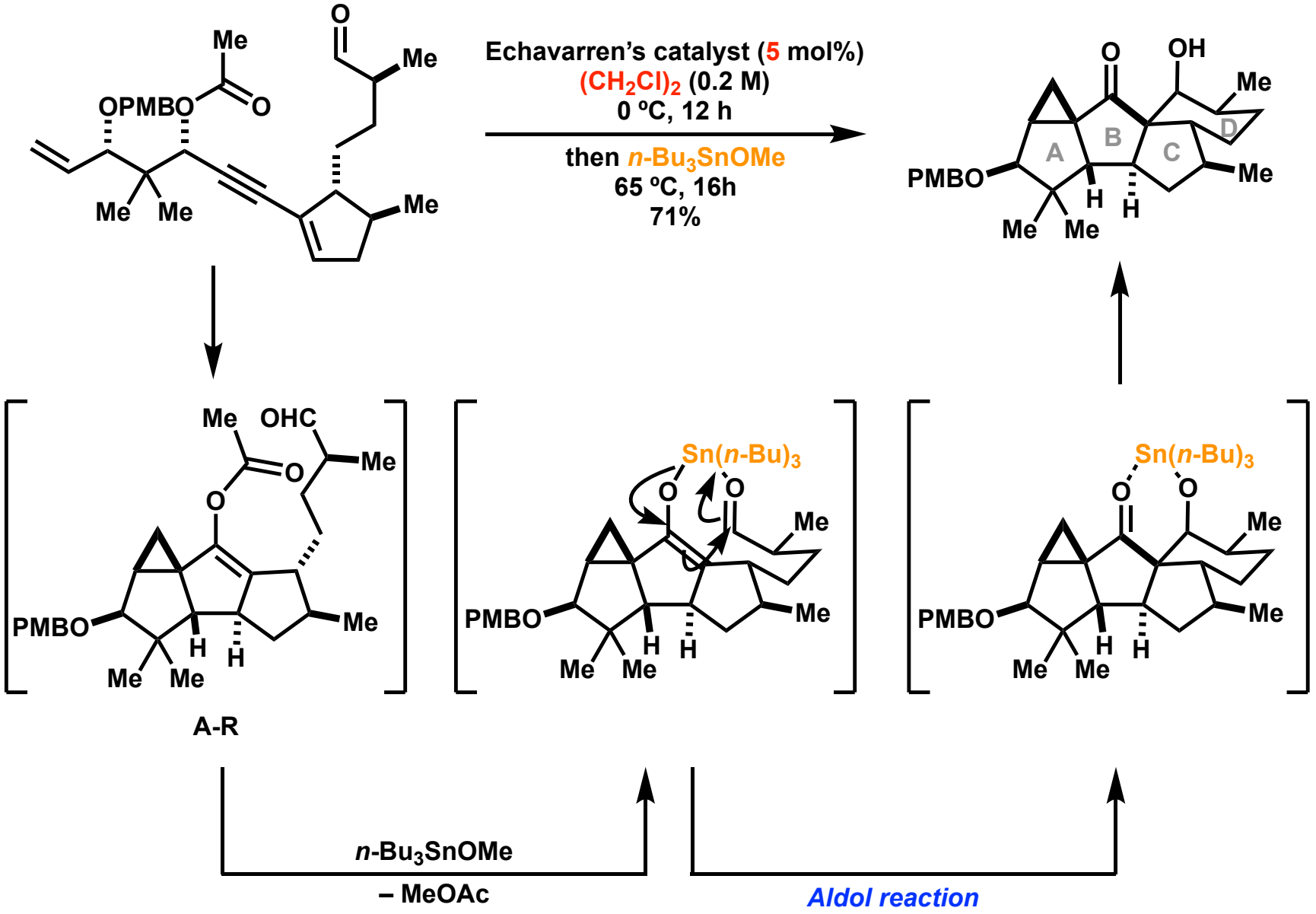


entry	solvent	additive	temperature	time	Result
4	CH_2Cl_2	NaOMe in MeOH	0-25 ºC	72 h	A-R:A-S (1:1)* , B-R:B-S (1:1)*
5	CH_2Cl_2	K_2CO_3 in MeOH	0-25 ºC	72 h	B-R:B-S (1:1)*
6	CH_2Cl_2	Et_2AlOEt	0 ºC	12 h	A-R:A-S (1:1)*
7	CH_2Cl_2	*n*-Bu_3SnOMe	0-25 ºC	12 h	A-R (43%)

* inseparable diastereomeric mixture

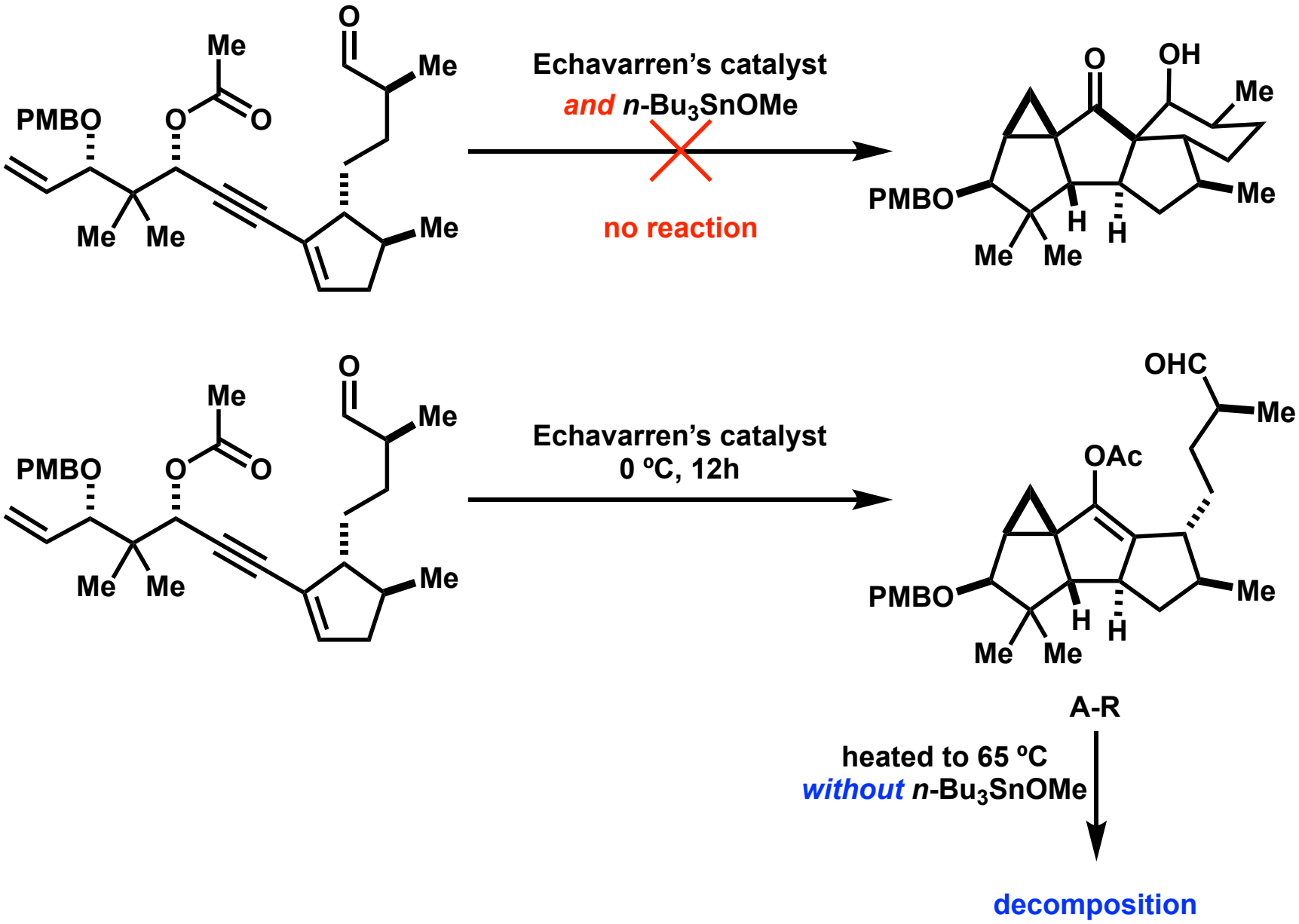
1) Amberg, W.M.; Carreira, E.M. *J. Am. Chem. Soc.* **2022**, *144*, 15475

Completion of key cyclization cascade



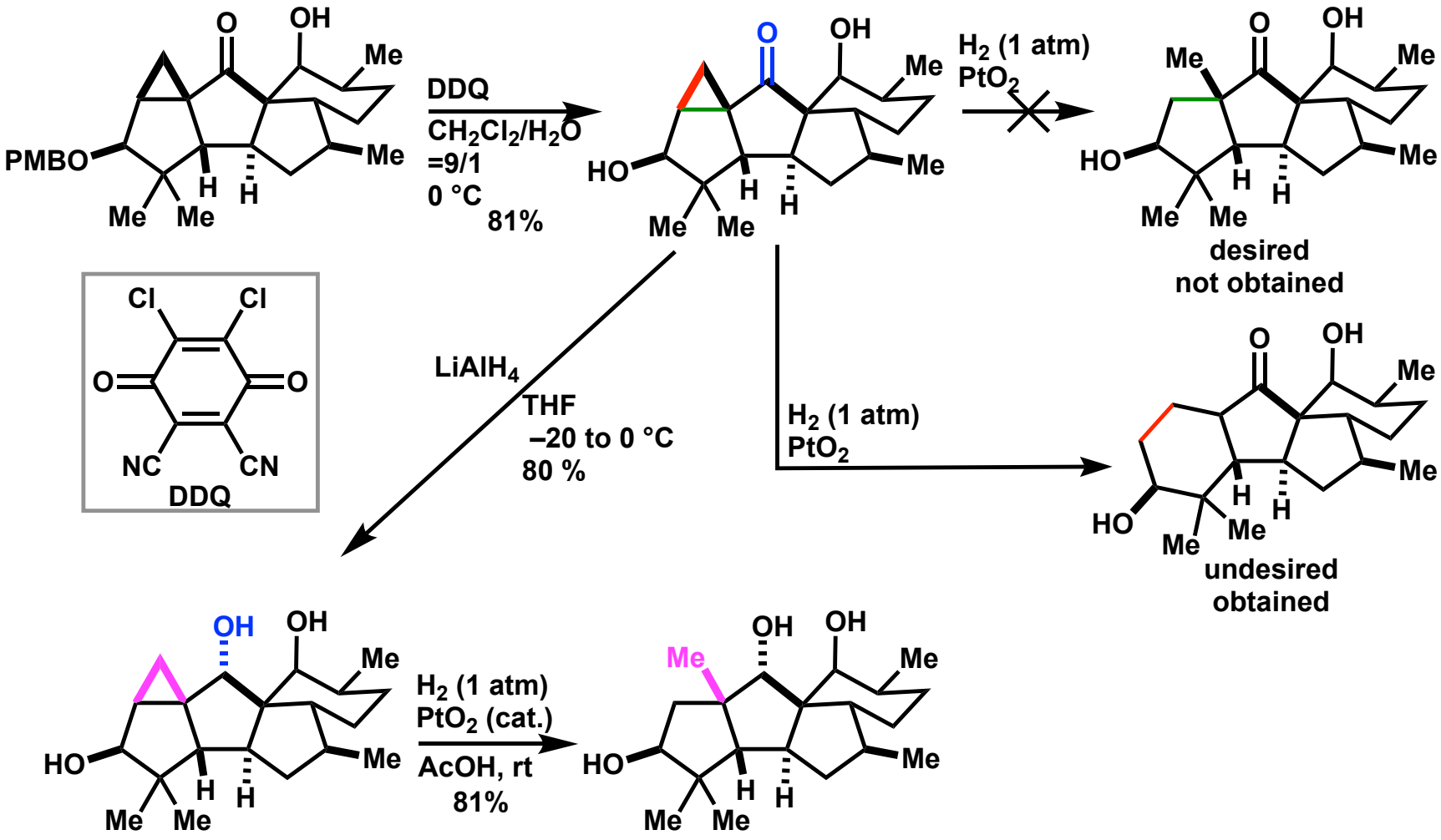
1) Amberg, W.M.; Carreira, E.M. *J. Am. Chem. Soc.* **2022**, *144*, 15475

Roles of n-Bu_3OMe



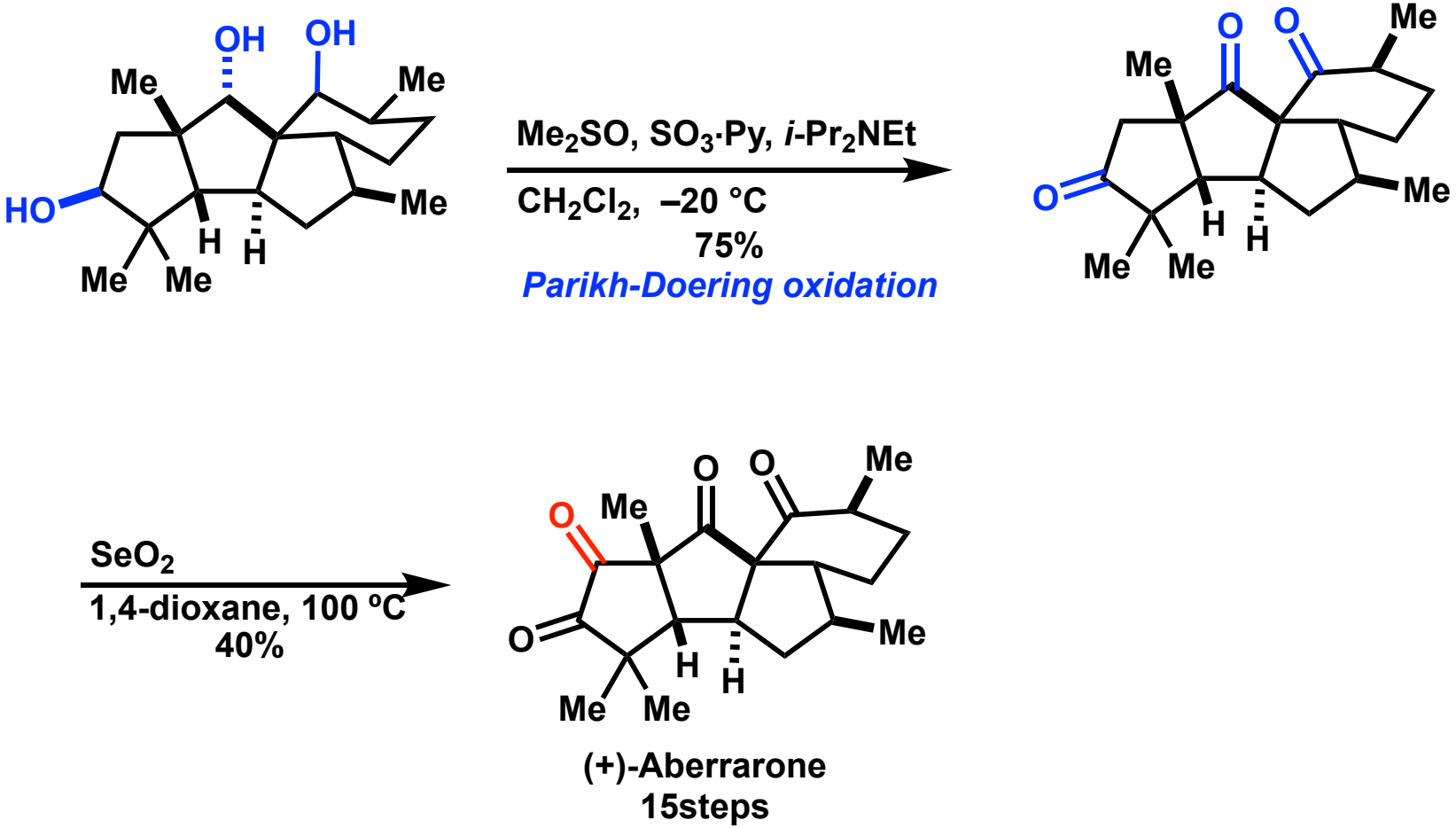
1) Amberg, W.M.; Carreira, E.M. *J. Am. Chem. Soc.* **2022**, *144*, 15475

Reductive opening of cyclopropane



1) Amberg, W.M.; Carreira, E.M. *J. Am. Chem. Soc.* **2022**, *144*, 15475

Total synthesis of (+)-Aberrarone



1) Amberg, W.M.; Carreira, E.M. *J. Am. Chem. Soc.* **2022**, *144*, 15475

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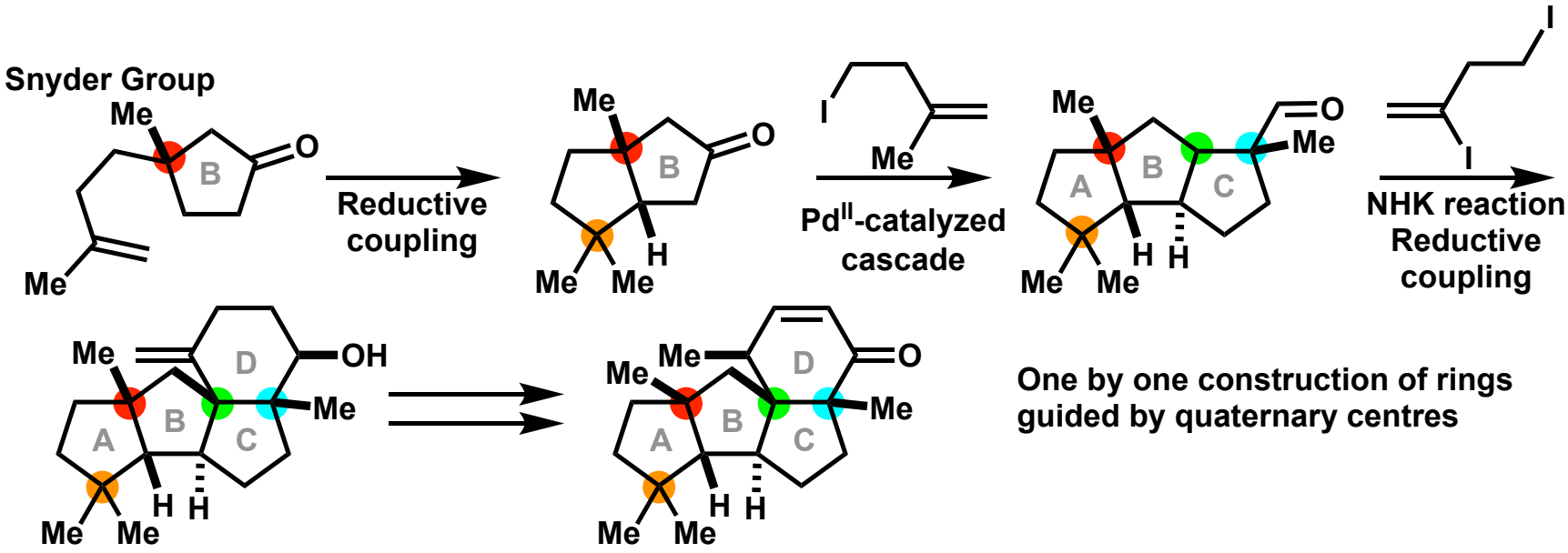
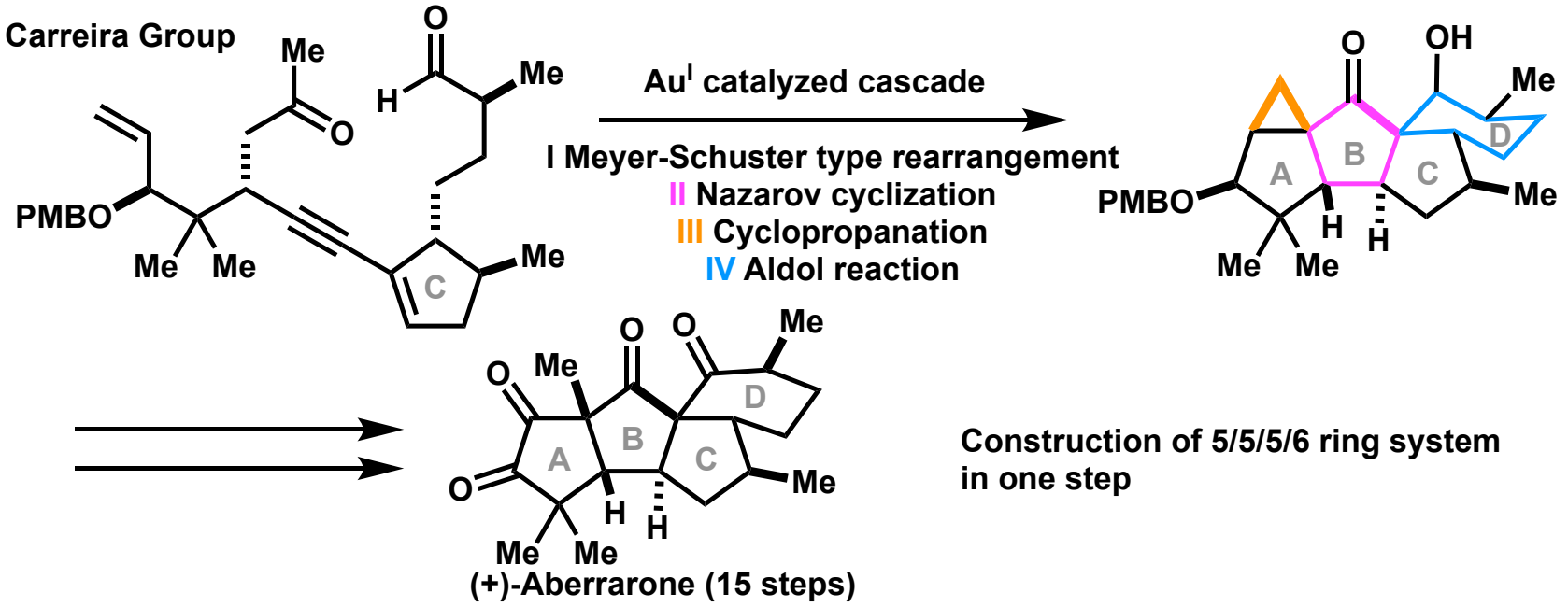
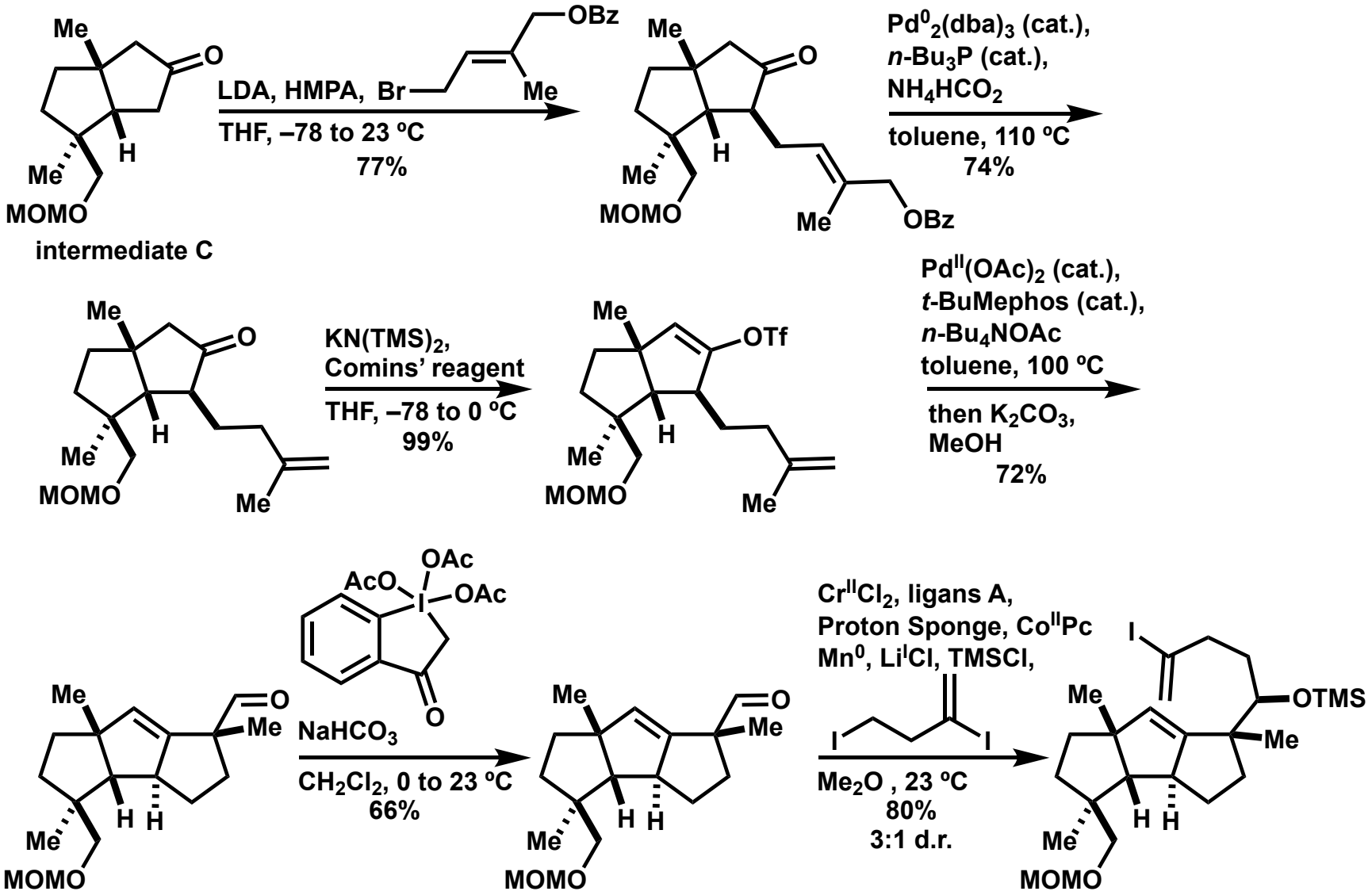
Summary


Snyder Group
Reductive coupling
Pd^{II}-catalyzed cascade
NHK reaction
Reductive coupling
One by one construction of rings guided by quaternary centres
Conidiogenone B (15 steps)


Carreira Group
Au^{I} catalyzed cascade
I Meyer-Schuster type rearrangement
II Nazarov cyclization
III Cyclopropanation
IV Aldol reaction
Construction of 5/5/5/6 ring system in one step
(+)-Aberrarone (15 steps)

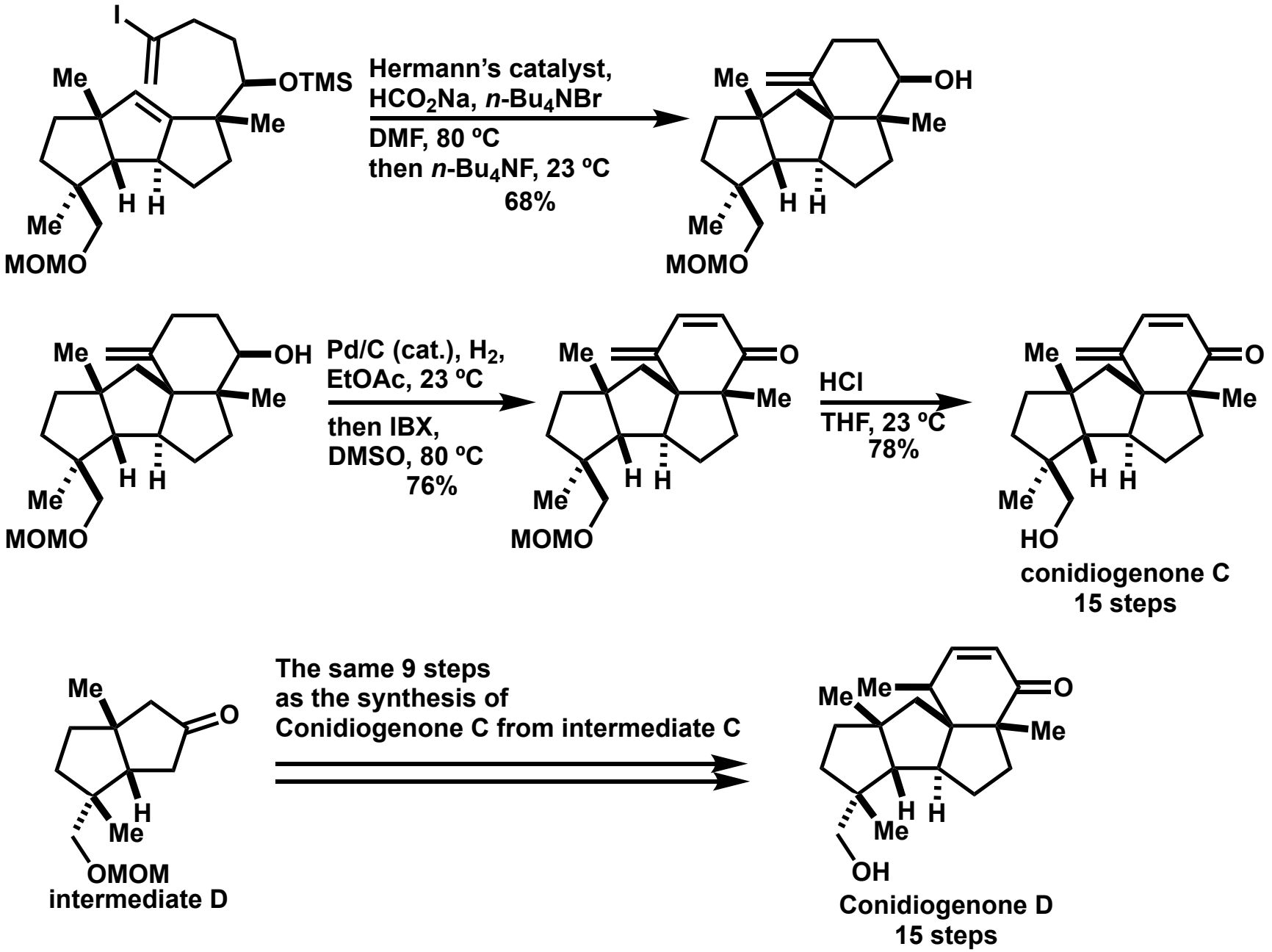
Appendix

Total Synthesis of Conidiogenone C and D (1)



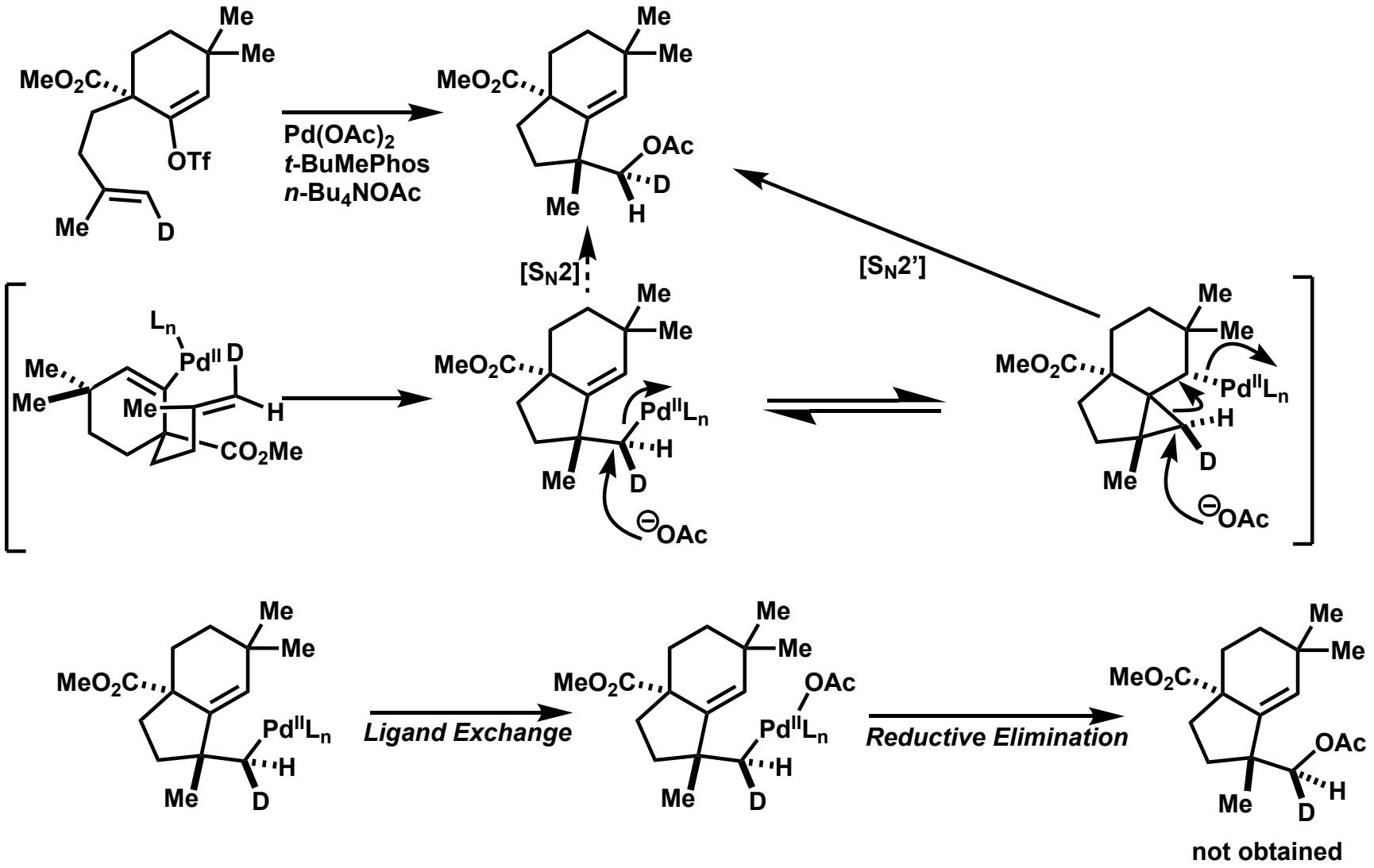
1) Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. A. *Nature* **2019**, *569*, 703

Total Synthesis of Conidiogenone C and D (2)



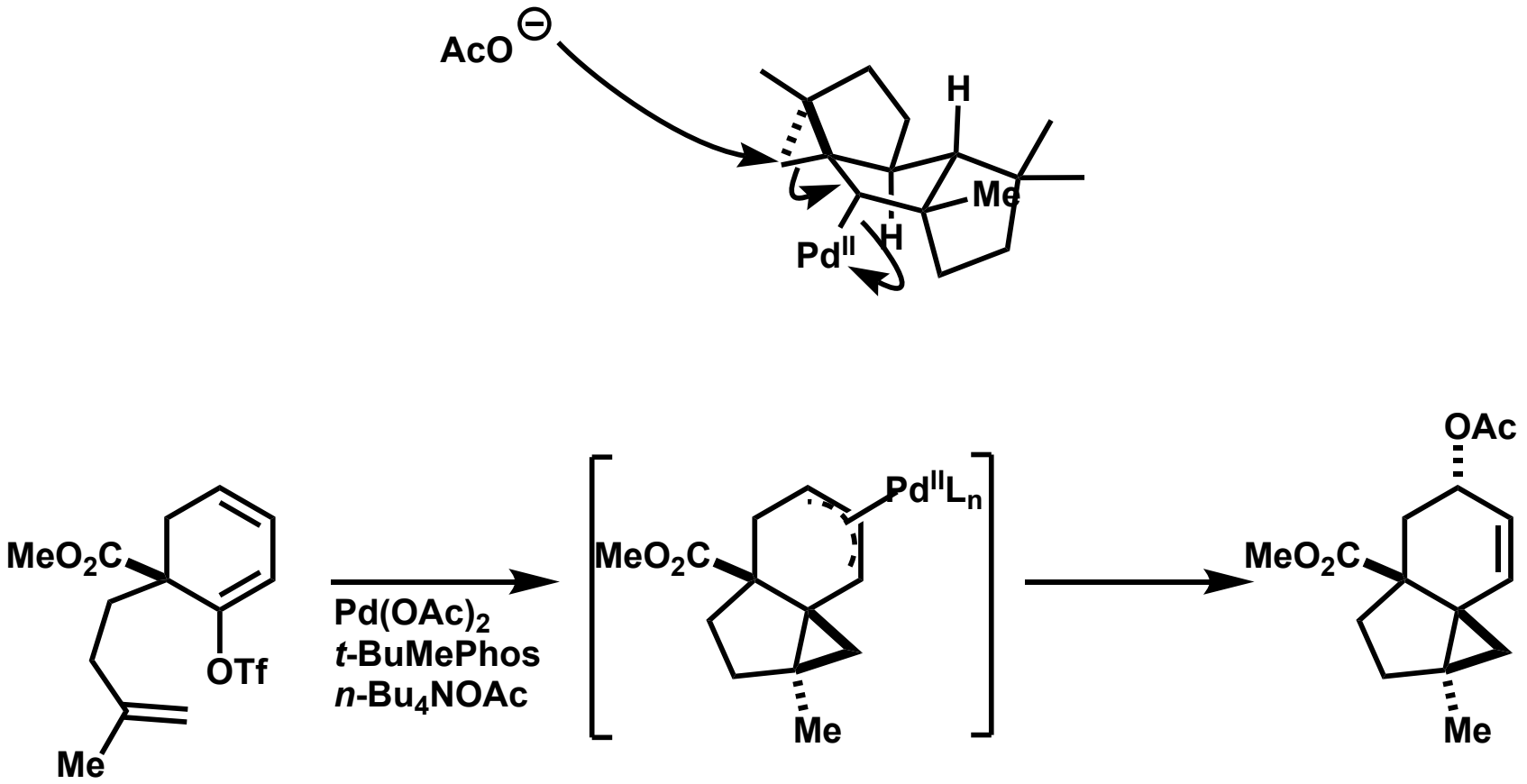
1) Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. A. *Nature* **2019**, *569*, 703

Mechanism of Pd^{II} catalyzed C-O bond formation (1)



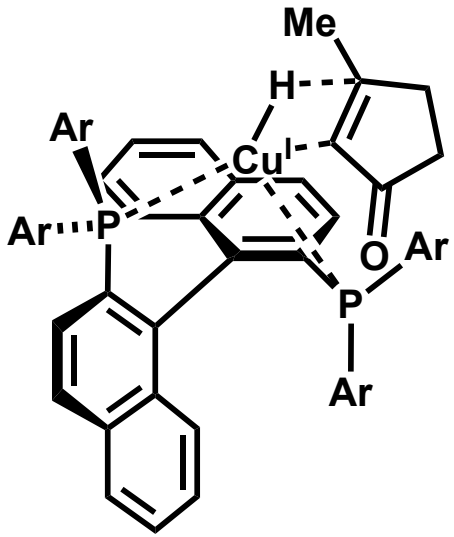
1) Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. A. *Nature* **2019**, *569*, 703
2) Yi, H.; Hu, P.; Snyder, S. A. *Angew. Chem., Int. Ed*. **2020**, 59, 2674

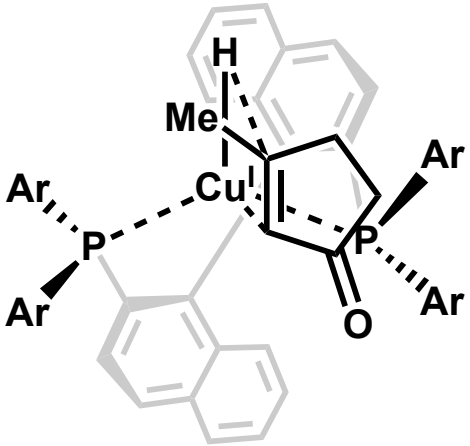
Mechanism of Pd^{II} catalyzed C-O bond formation (2)

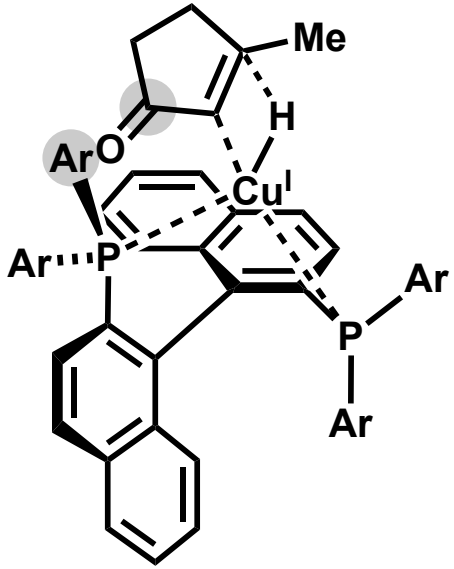


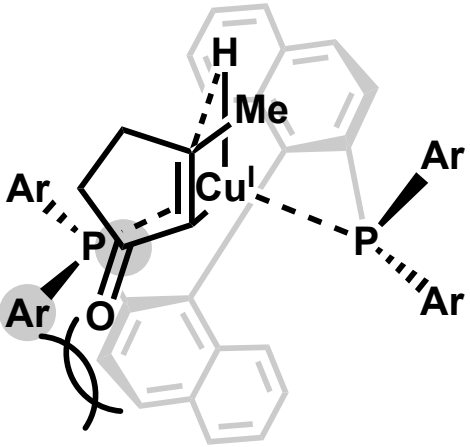
1) Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. A. *Nature* **2019**, *569*, 703
2) Yi, H.; Hu, P.; Snyder, S. A. *Angew. Chem., Int. Ed*. **2020**, 59, 2674

Enantioselectivity of Conjugate Reduction



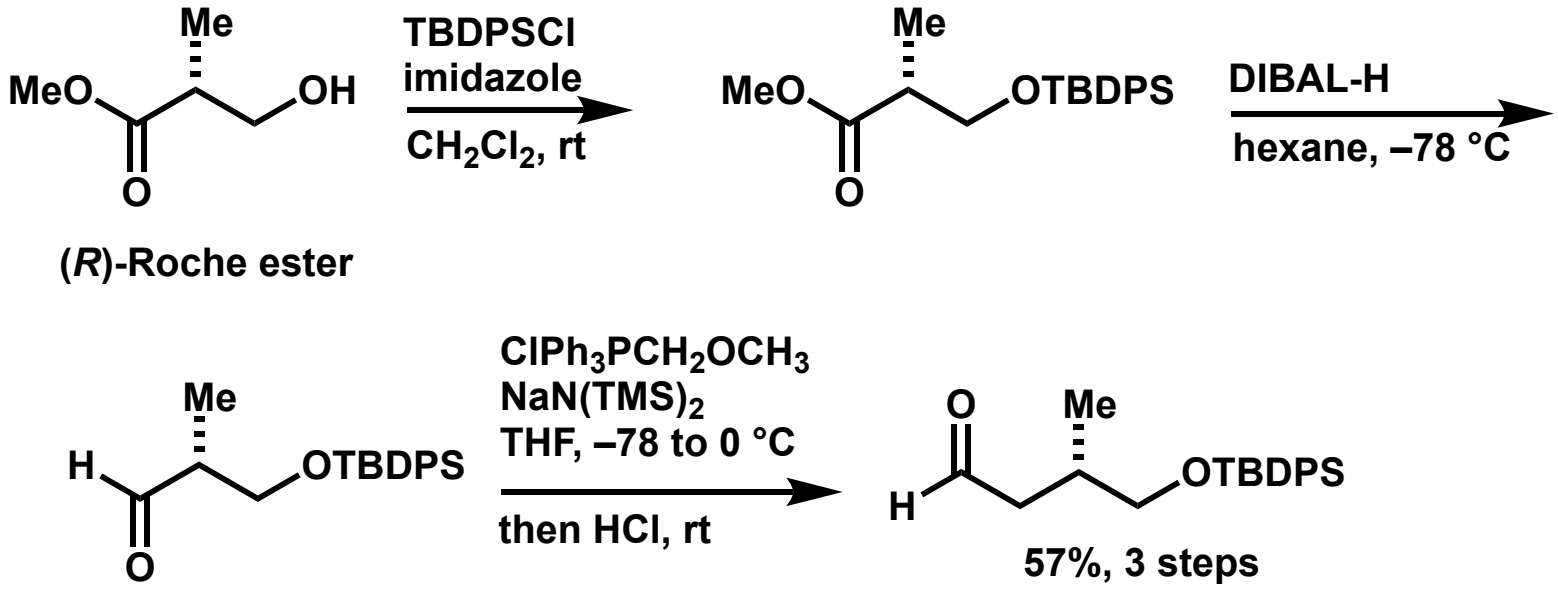






1) Amberg, W.M.; Carreira, E.M. *J. Am. Chem. Soc.* **2022**, *144,* 15475−15479
2) Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797

Preparation of a substrate from (*R*)-Roche ester



1) Amberg, W.M.; Carreira, E.M. *J. Am. Chem. Soc.* **2022**, *144*, 15475