Total Synthesis of Myrioneurinol

2022.10.08 Literature Seminar
B4 Mizuki Sawada

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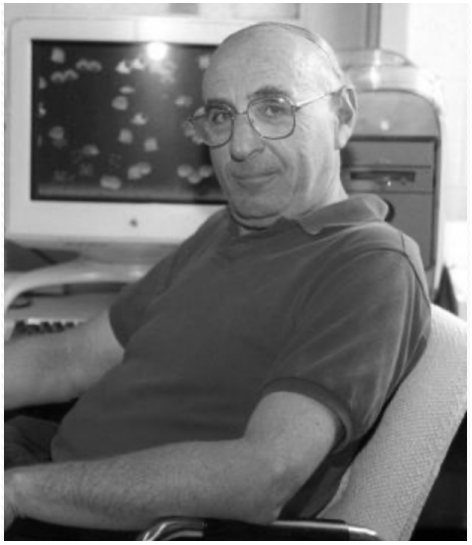
Introduction of Authors



Prof. Steven M. Weinreb[1)]

1963 A.B. @ Cornell University
1967 Ph.D. @ University of Rochester

Prof. Emeritus @ the Pennsylvania State University

Research Topic: synthesis of natural products; development of new synthetic methods; heterocyclic chemistry; pericyclic reactions and cycloadditions

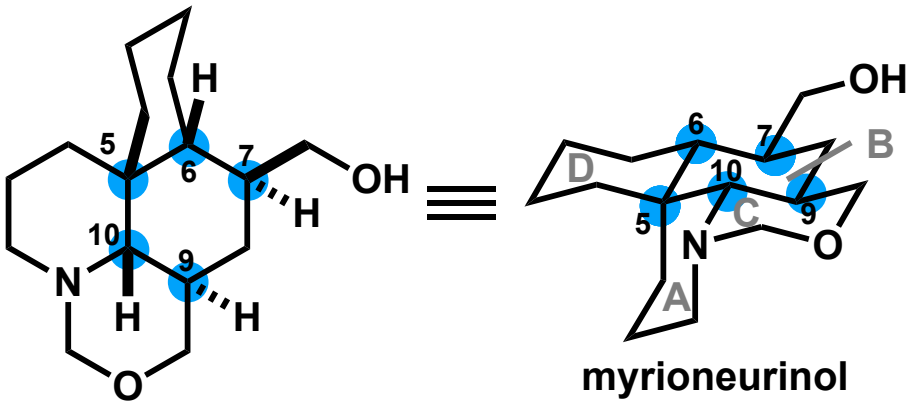
Assistant Prof. Myles Smith[2)]

2006 B.Sc. (Hons) @ the University of Cape Town
2015 Ph.D. @ Columbia University
2015- postdoctoral fellow
@ The Scripps Research Institute (Prof. Phil Baran)
and Stanford University (Associate Prof. Noah Burns)
2019- Assistant Professor
@ University of Texas Southwestern Medical Center

Research Topic: synthesis of complex molecules of medicinal value; development of novel platforms in asymmetric catalysis

1) https://science.psu.edu/chem/people/sxw8
2) https://labs.utsouthwestern.edu/node/12736

Introduction of Myrioneurinol



myrioneurinol

Isolation: from *Myrioneuron nutans* in 2007 by Bodo group[1)]

Structural features: tetracyclic skeleton of fused piperidine, oxazine and two cyclohexane
five stereogenic centers

Bioactivities: cytotoxicity (IC_{50} against KB cell: 26μg/mL)
antimararial activity (IC_{50}: 11 μg/mL)

Total synthesis: Weinreb group (2014, racemic)[2)]
Ma group (2022, racemic)[3)]
Smith group (2022, racemic and formal asymmetric)[4)]

1) Pham, V. C.; Jossang, A.; Sévenet, T.; Nguyen, V. H.; Bodo, B. *Tetrahedron.* **2007**, *63*, 11244.
2) (a) Nocket, A. J.; Weinreb, S. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 14162. (b) Nocket, A. J.; Feng, Y.; Weinreb, S. M. *J. Org. Chem*. **2015**, *80*, 1116.
3) Zhang, N.; Jiang, H.; Ma, Z. *Angew. Chem., Int. Ed.* **2022**, *61*, e202200085.
4) Aquilina, J. M.; Smith M. W. *J. Am. Chem. Soc.* **2022**, *144*, 11088.

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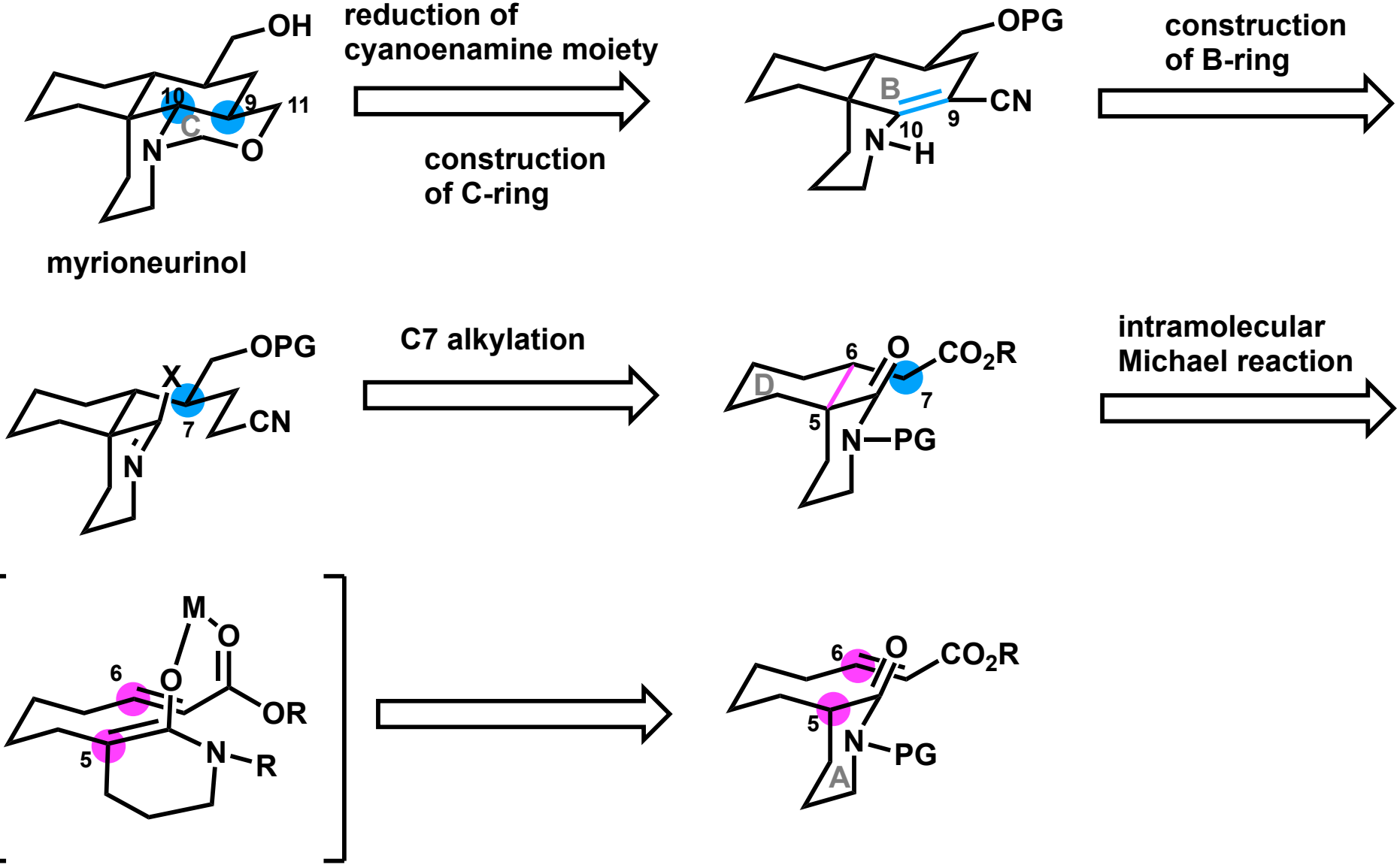
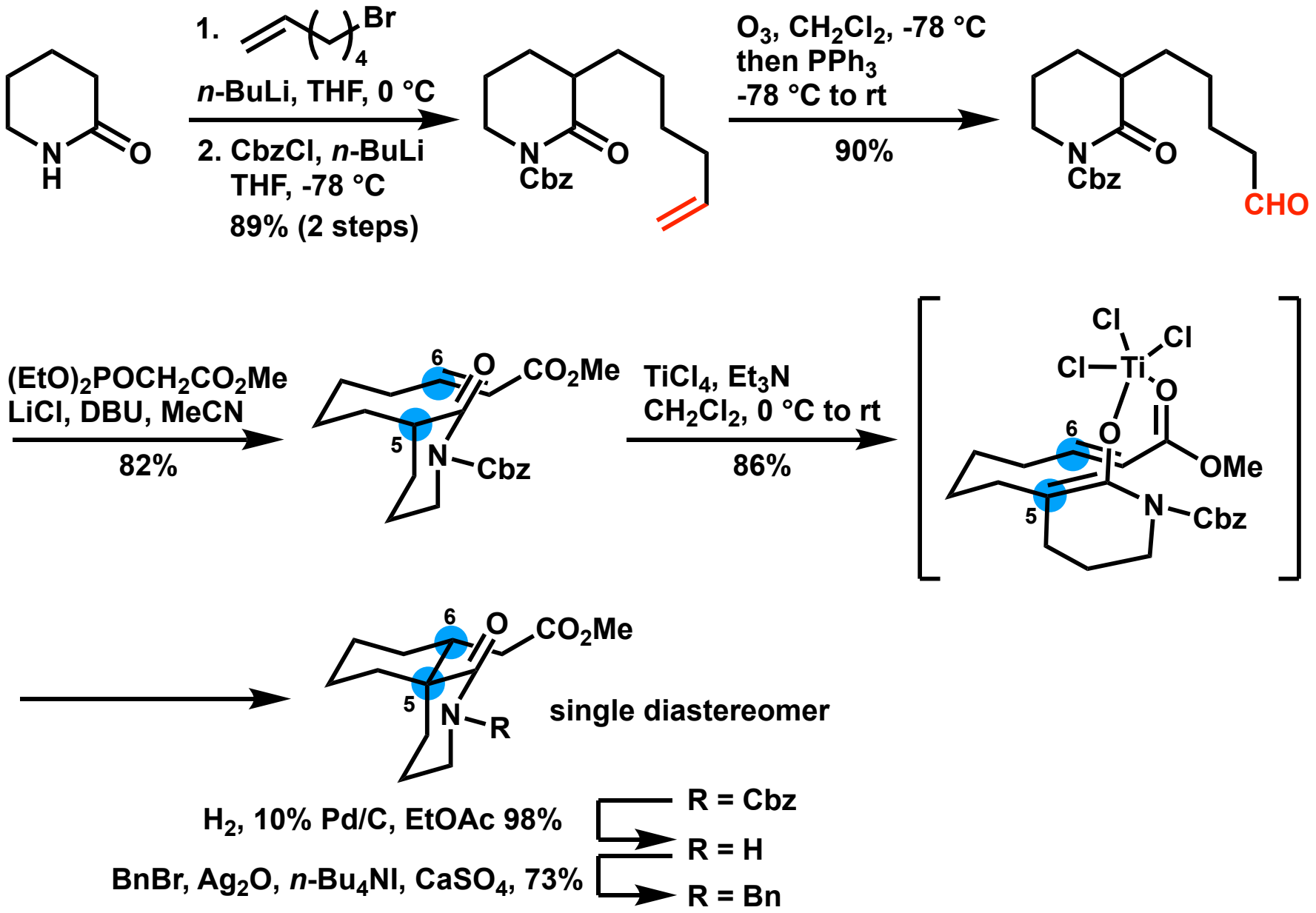
Retrosynthetic Analysis

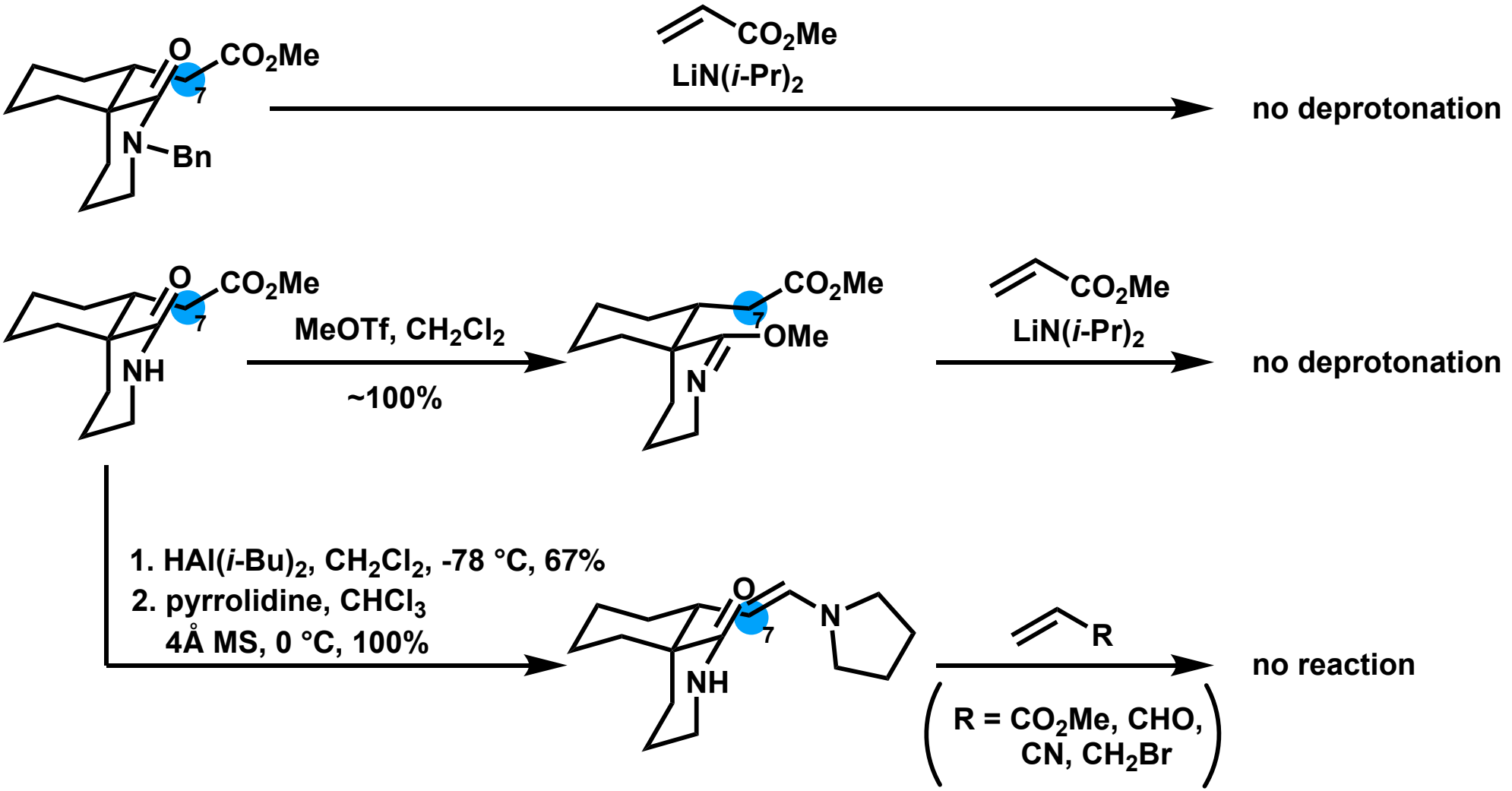
Initial retrosynthesis:



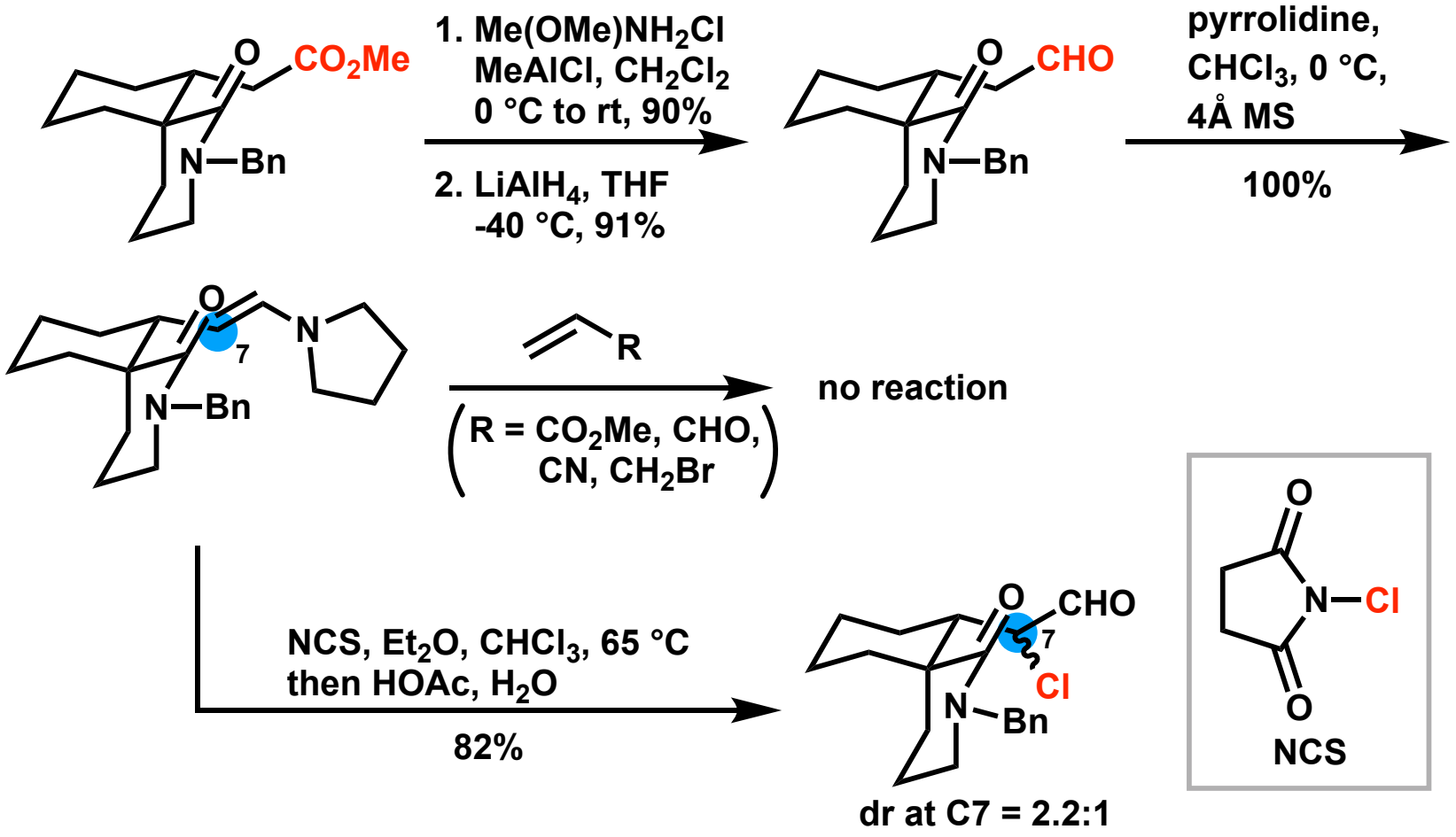
Formation of D-Ring via Intramolecular Michael Reaction



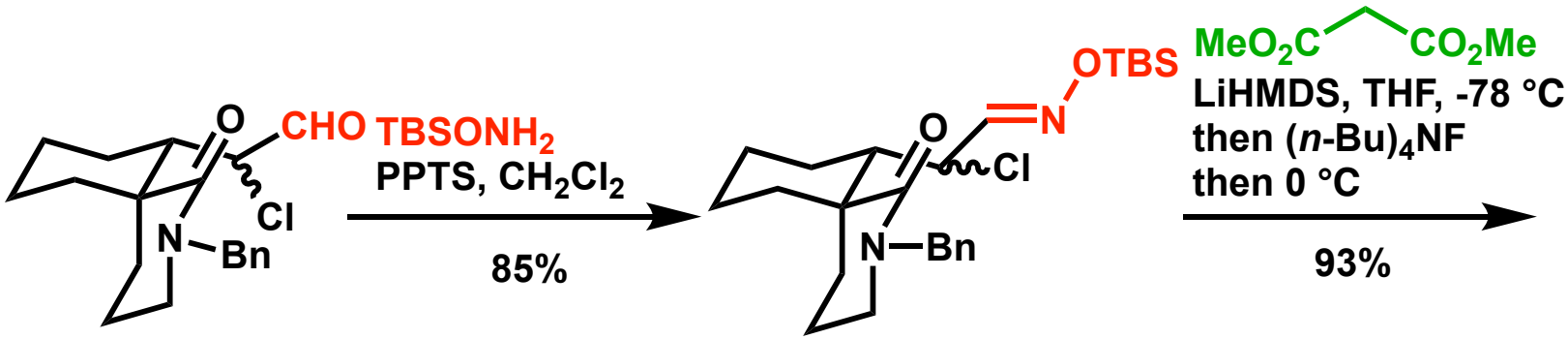
Attempted Alkylation at C7

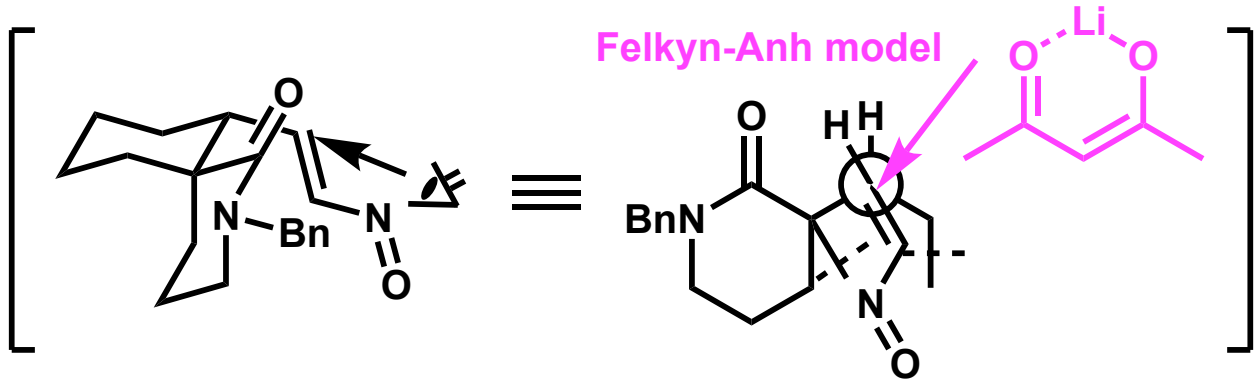


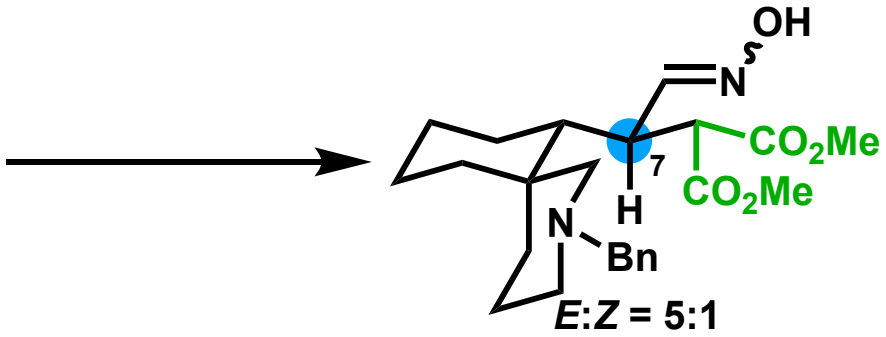
Chlorination at C7



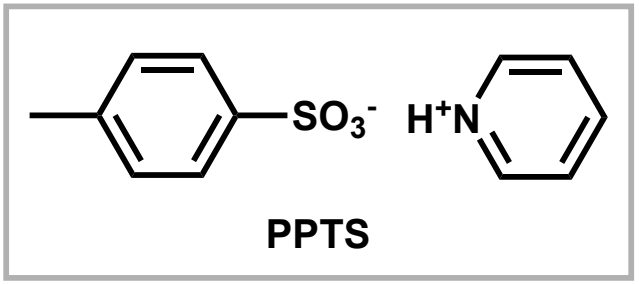
Diastereoselective Alkylation at C7



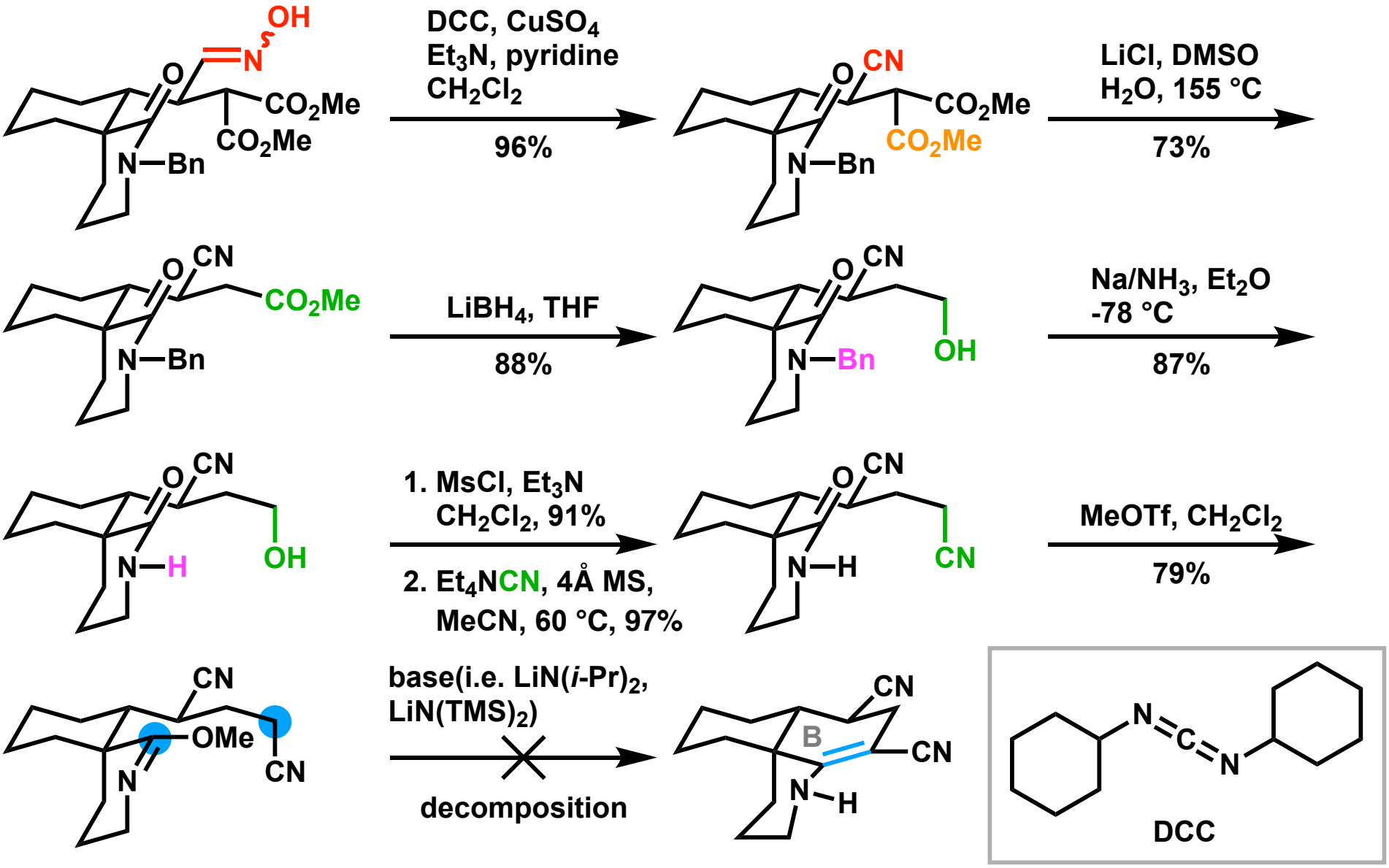




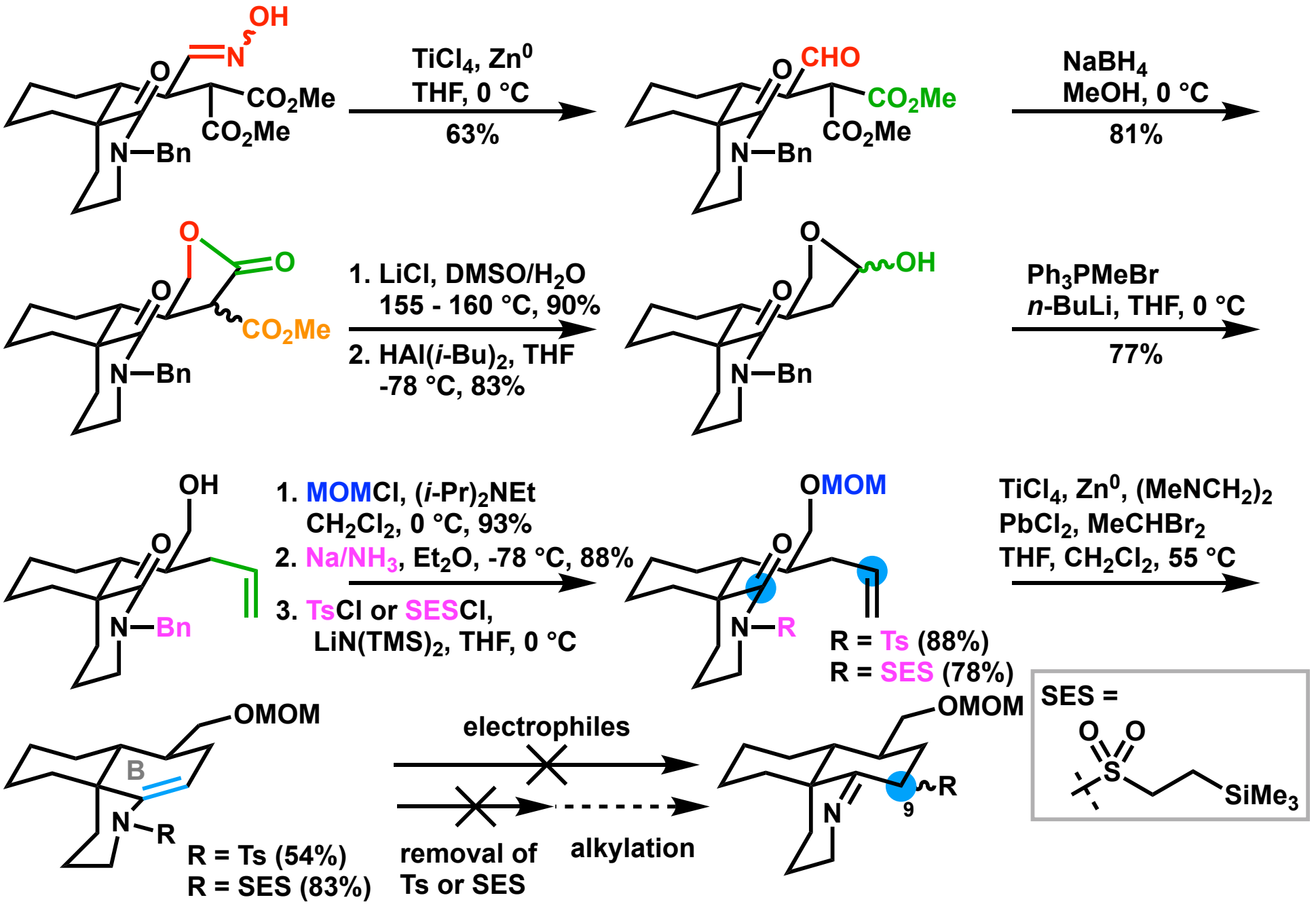
desired stereochemistry at C7



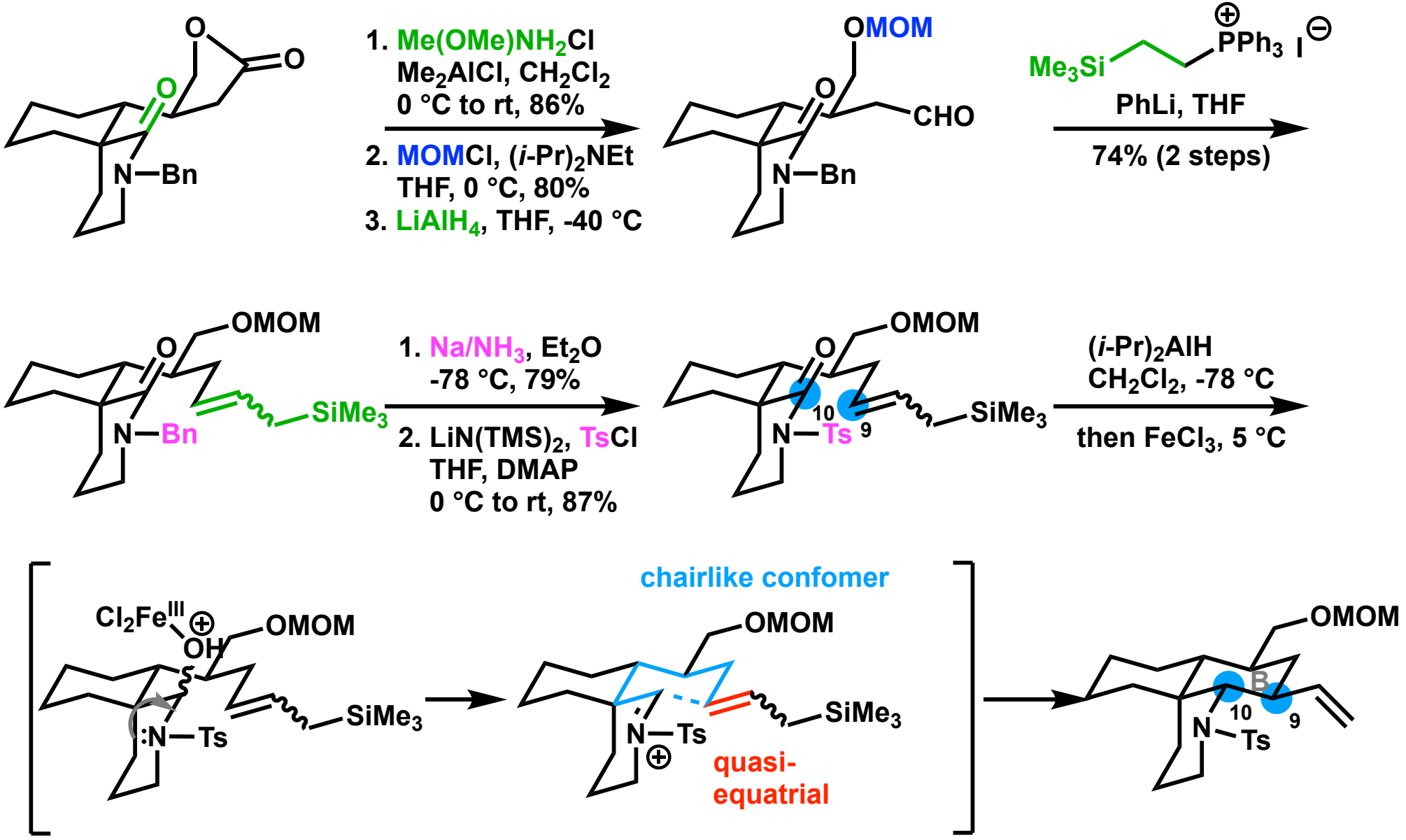
Attempted Formation of B-Ring



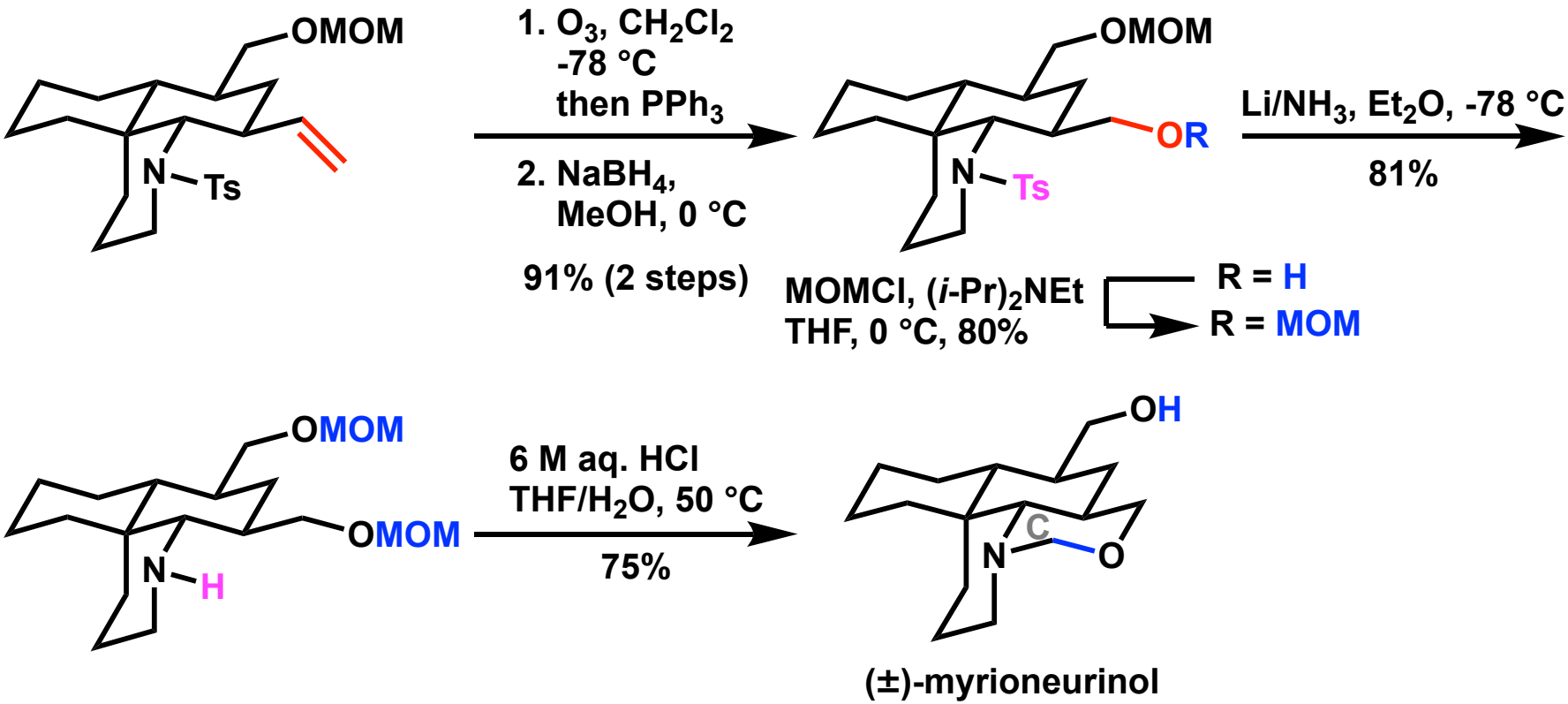
Attempted Formation of B-Ring



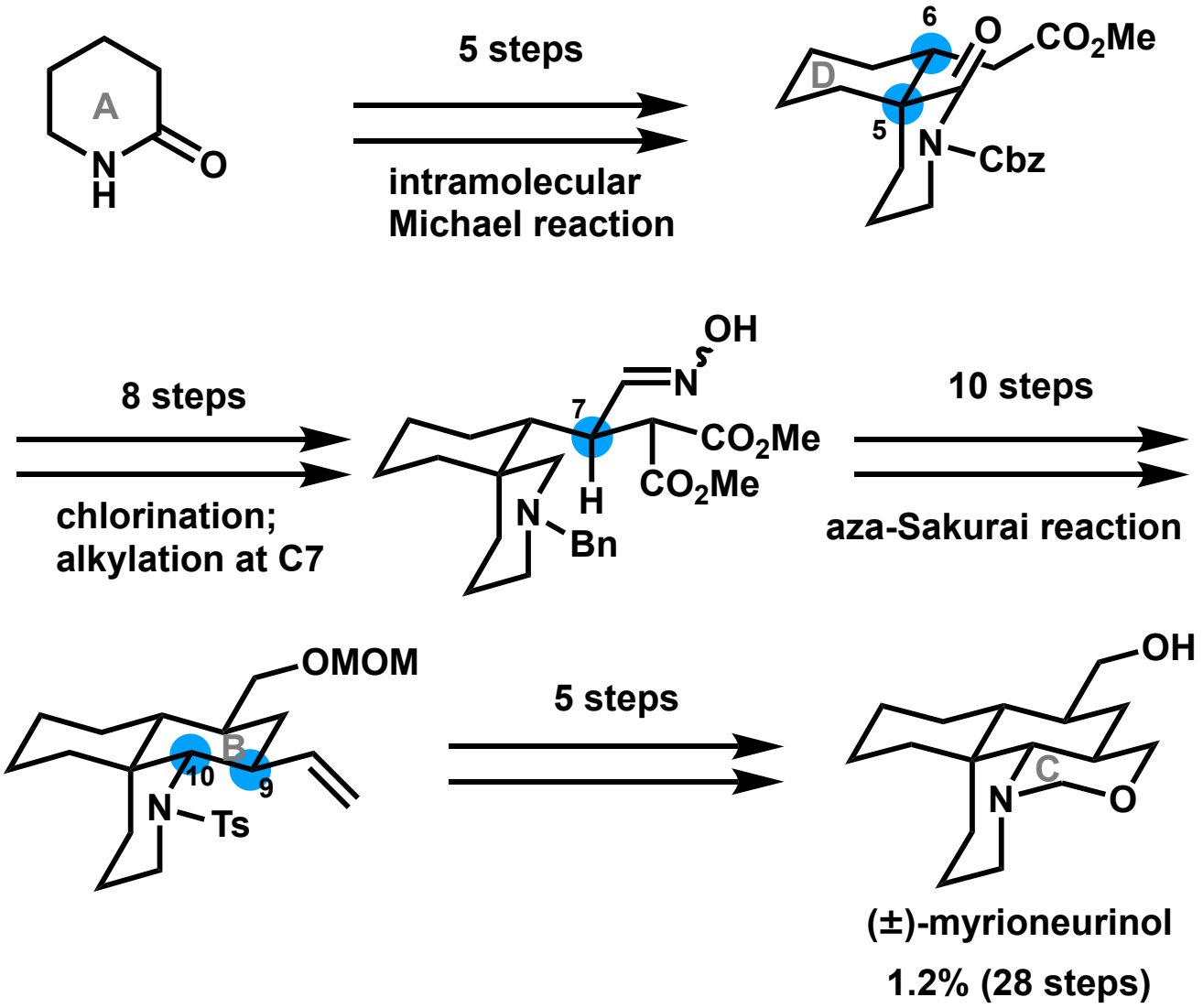
B-Ring Formation via Aza-Sakurai Reaction



Completion of Total Synthesis of (±)-Myrioneurinol



Short Summary



(±)-myrioneurinol

1.2% (28 steps)

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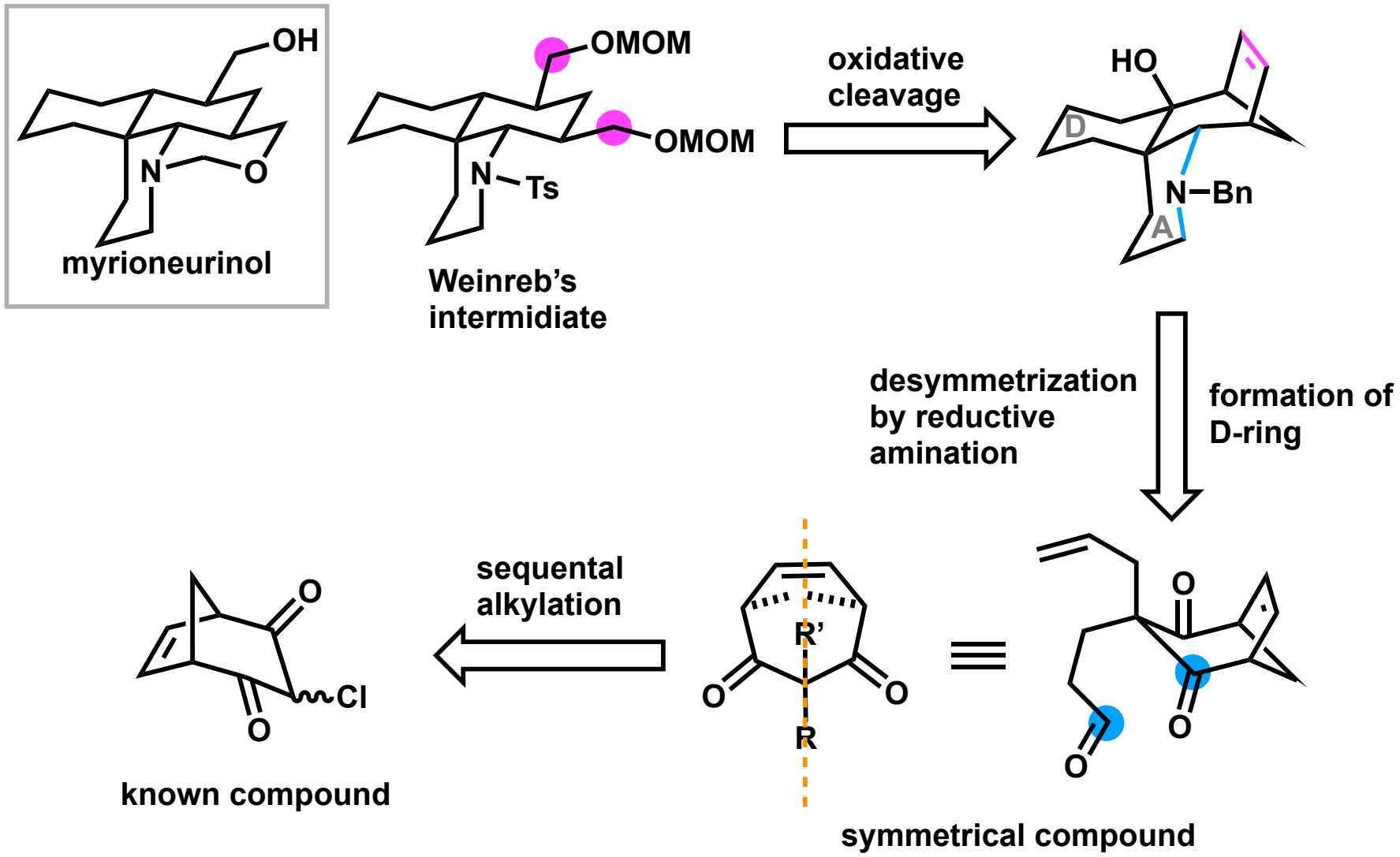
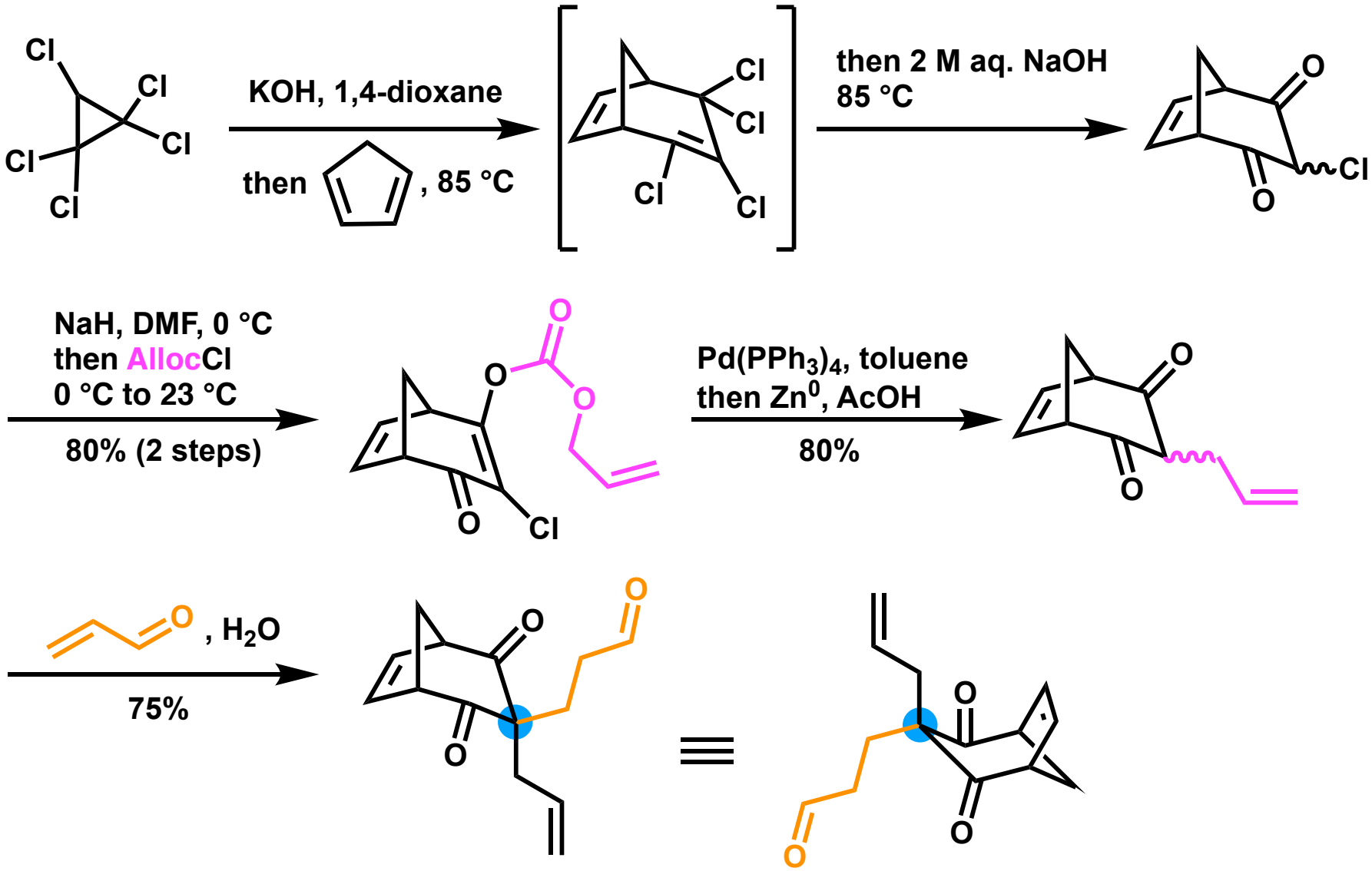
Retrosynthetic Analysis

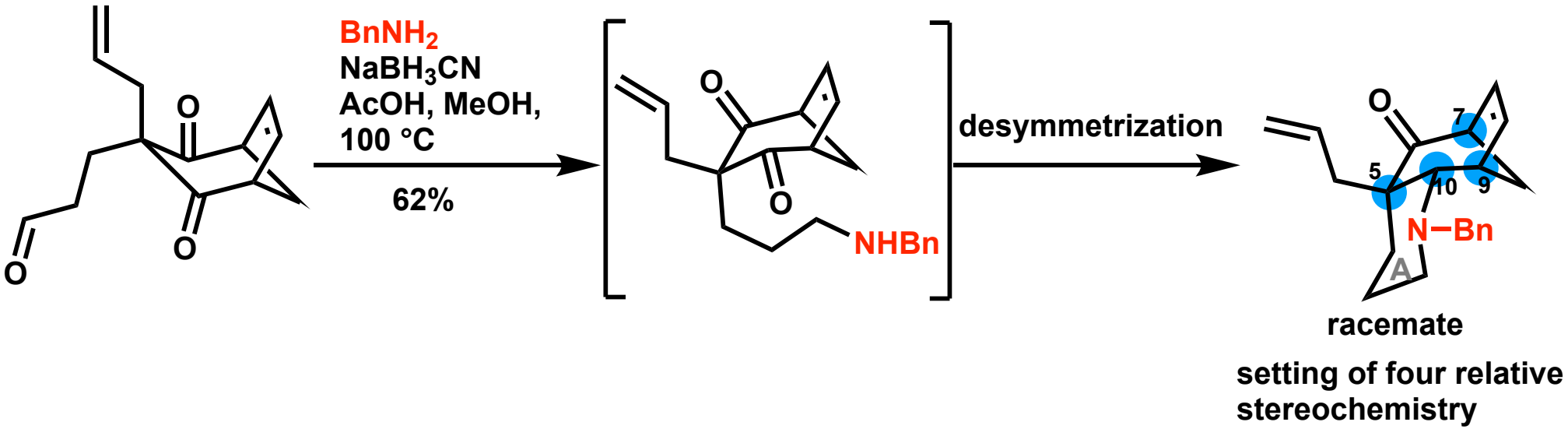


Synthesis of Symmetrical Compound

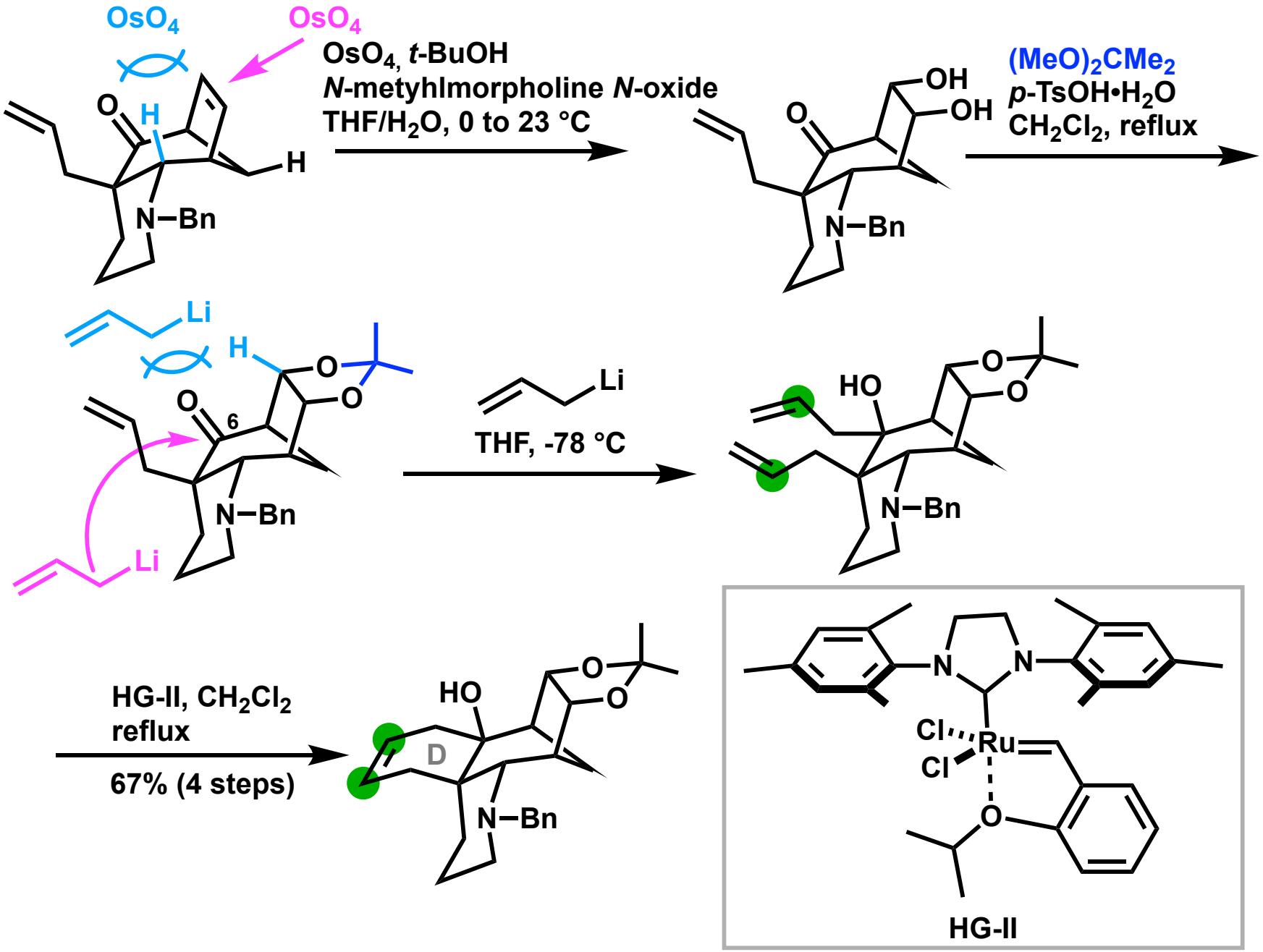


mixture of diastereomer
dr = 1.4:1

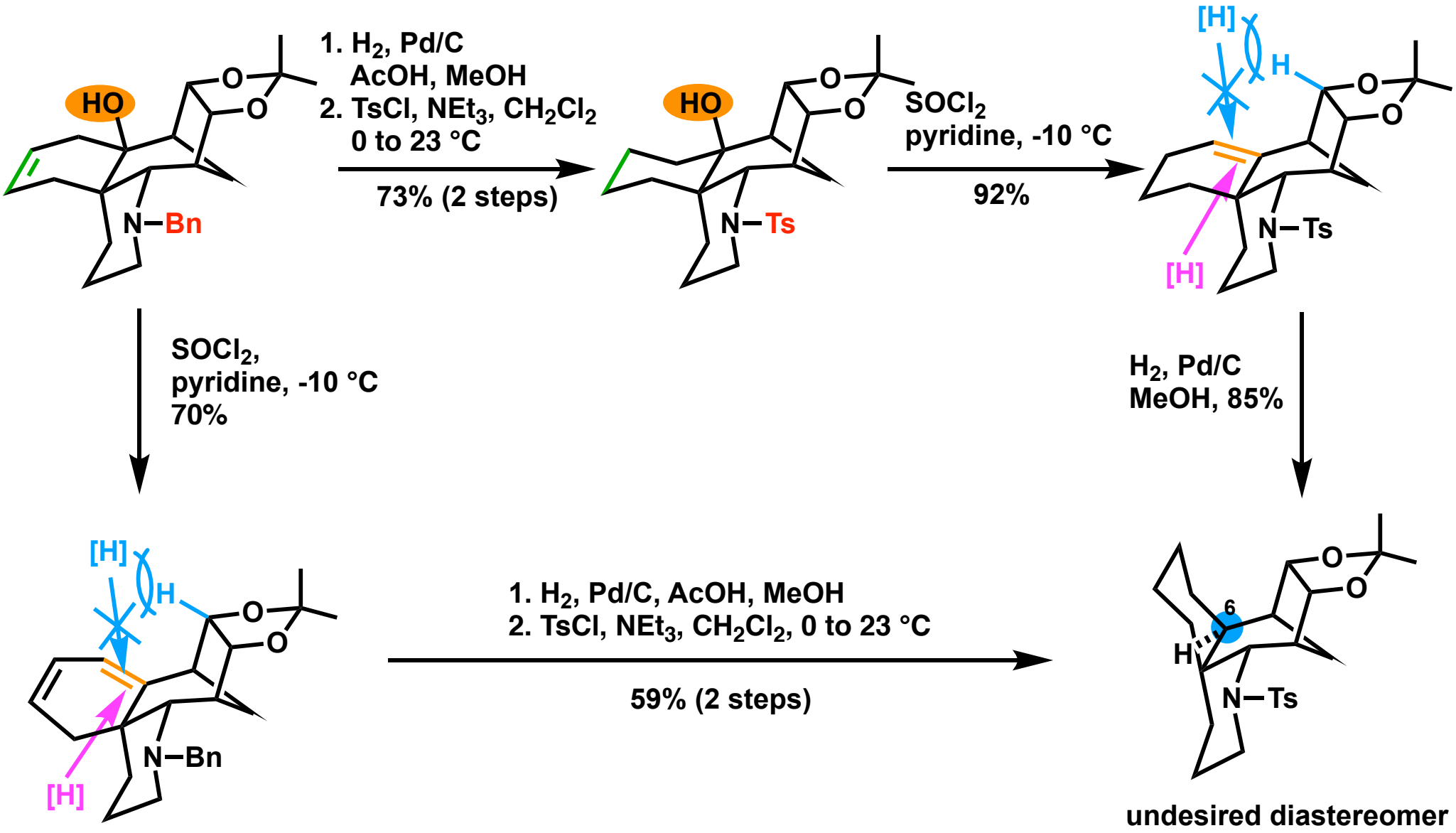
Desymmetrization by Reductive Amination



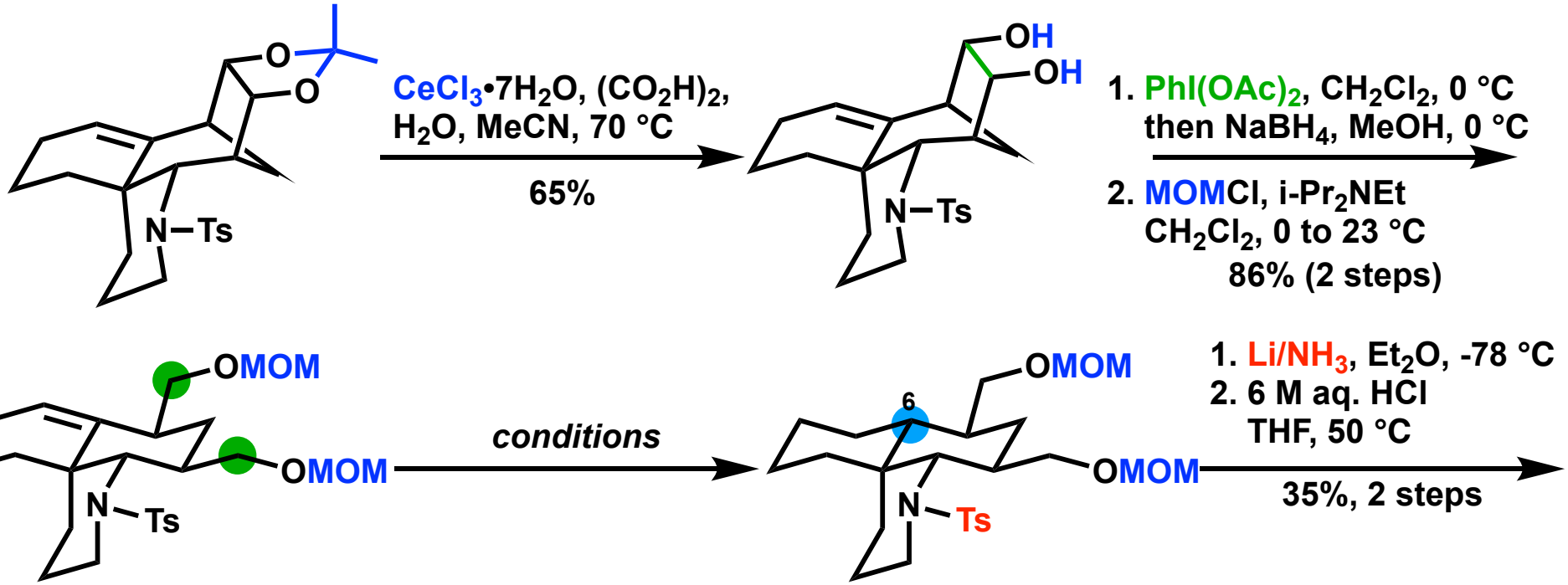
Construction of D-ring



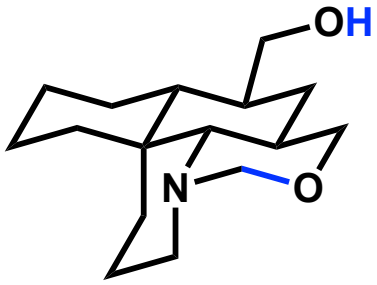
Attempted Removal of Tertiary Alcohol



Stereoselective Reduction of Olefin and Total Synthesis of (±)-Myrioneurinol



desired diastereomer
Weinreb's intermidiate

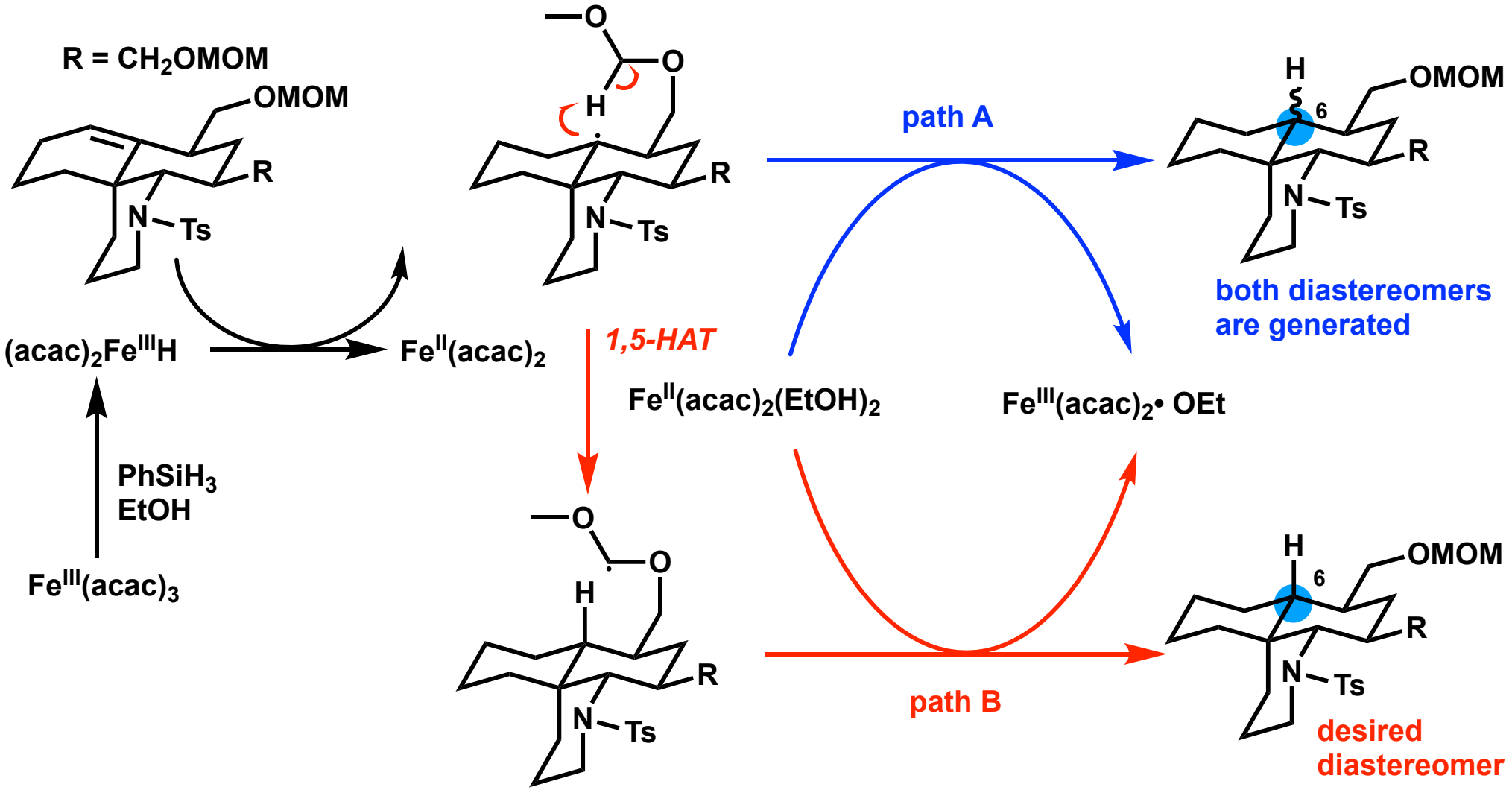


(±)-myrioneurinol

1.7% (18 steps)

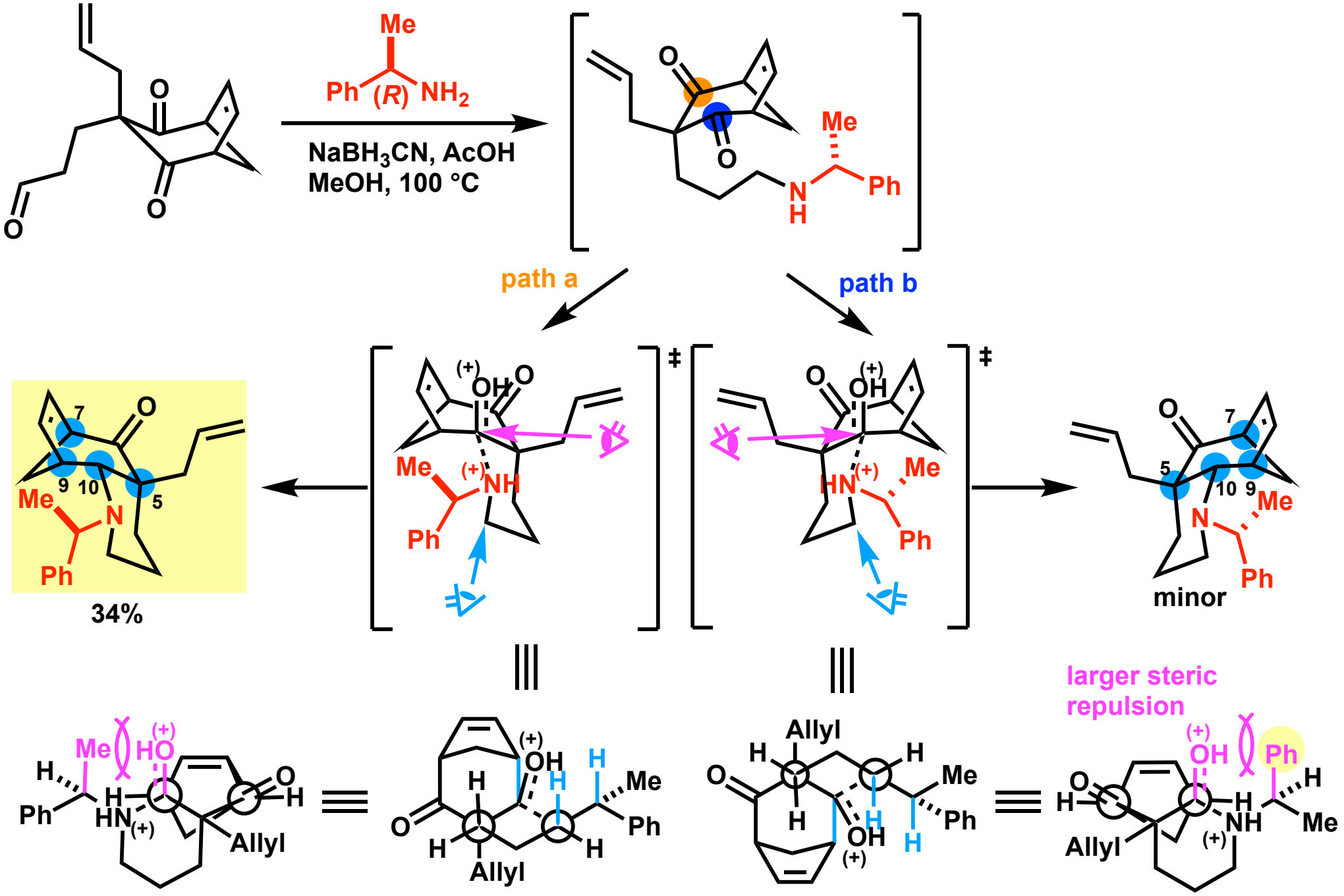
conditions	dr at C6	yield (%)
H_2, Pd/C, 23 °C	1.1:1	-
$Fe(acac)_3$, $PhSiH_3$, 60 °C	4:1	69
$Fe(acac)_3$, $PhSiH_3$, 40 °C	12:1	64

Proposed Mechanism of Fe-catalyzed Reduction

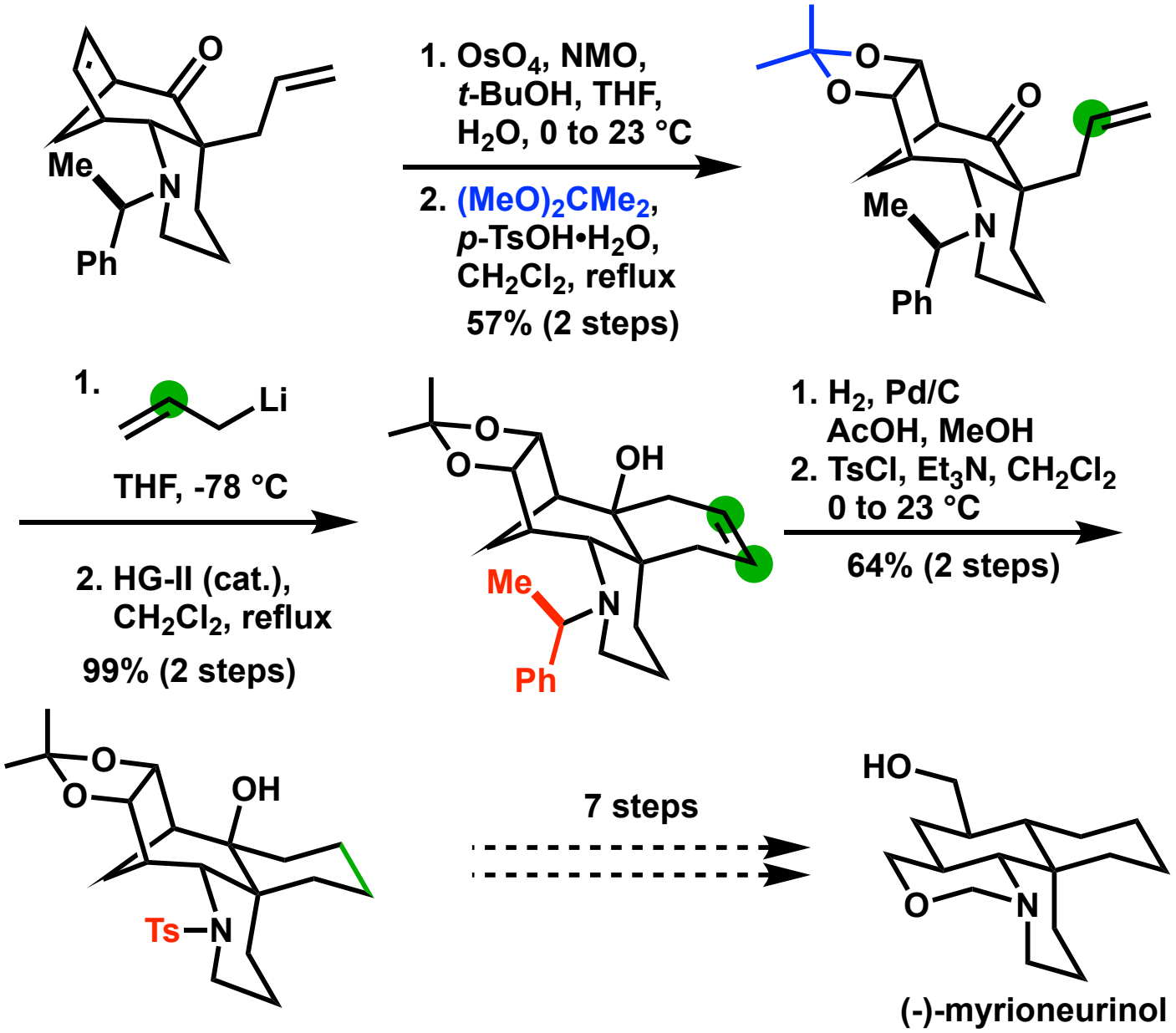


1) Lo, J. C.; Kim, D.; Pan, C.; Edwards, J. T.; Yabe, Y.; Gui, J.; Qin, T.; Gutierrez, S.; Giacoboni, J.; Smith, M. W.; Holland, P. L.; Baran, P. S. *J. Am. Chem. Soc.* **2017**, 139, 2484−2503.

Asymmetric Desymmetrization

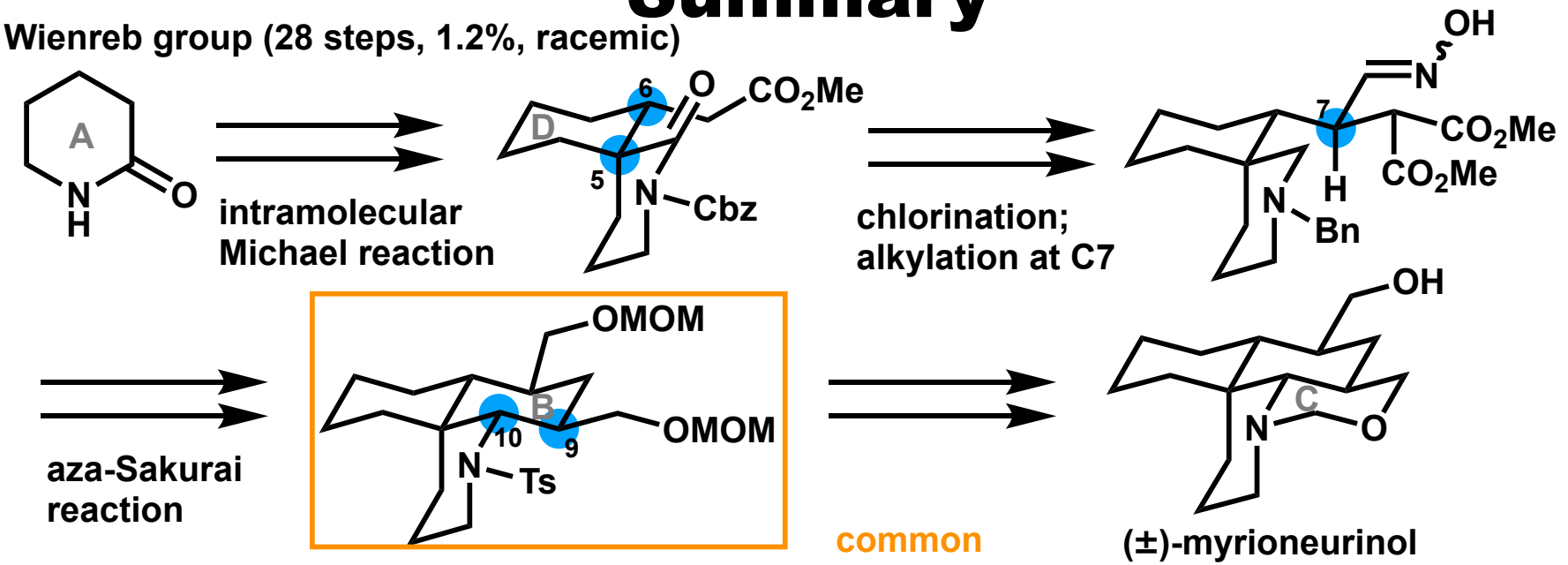


Formal Asymmetric Total Synthesis

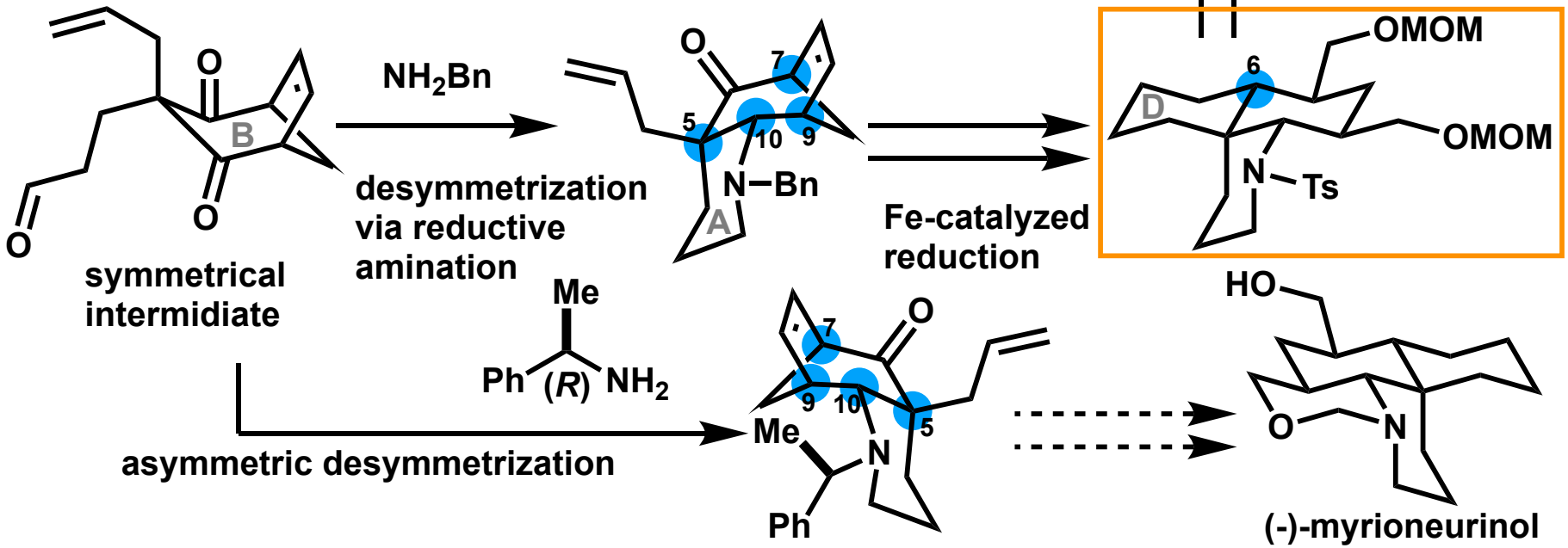


Summary

Wienreb group (28 steps, 1.2%, racemic)



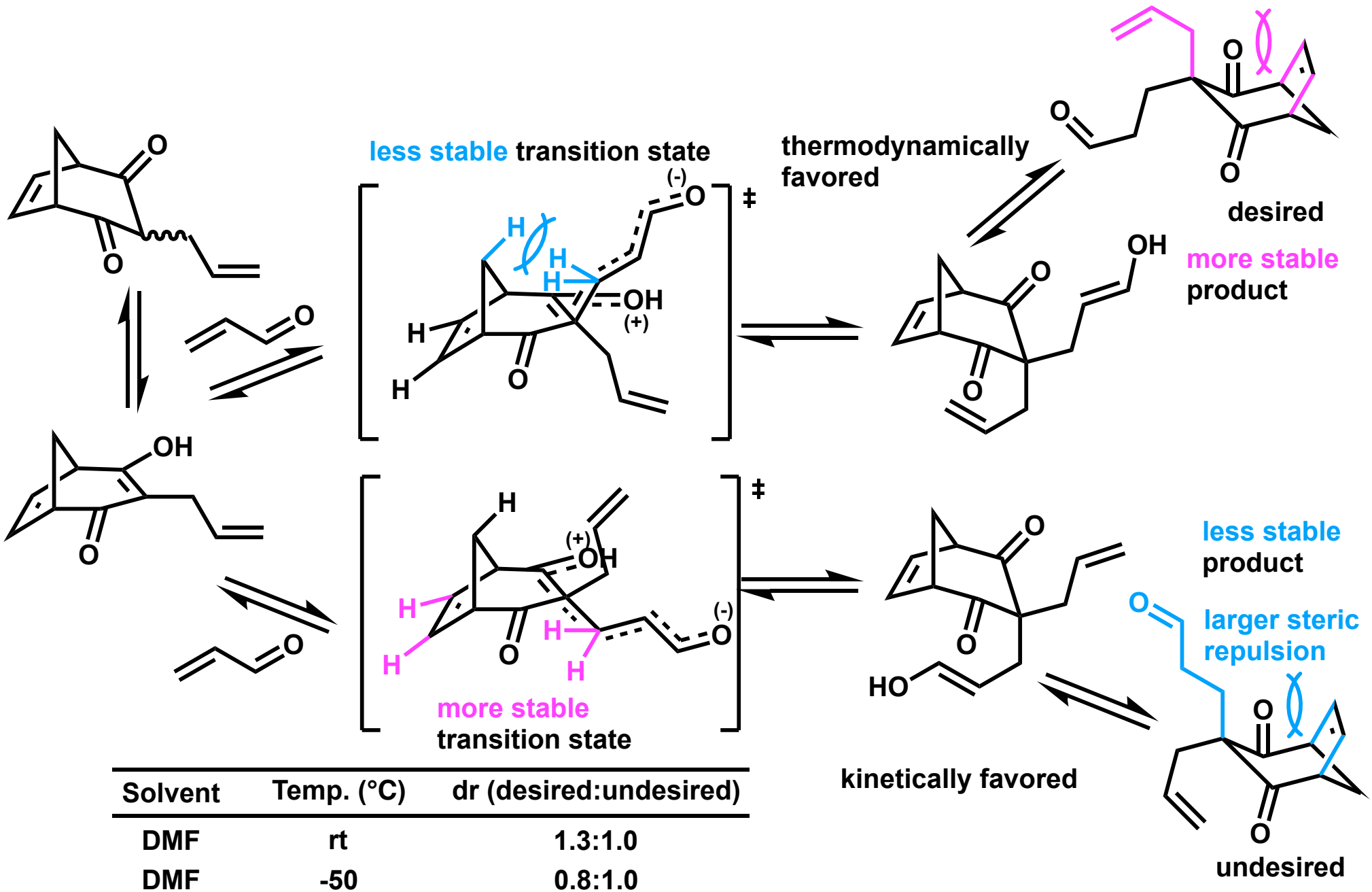
Smith group (18 steps, 1.7%, racemic)



formal asymmetric synthesis of (-)-myrioneurinol

Appendix

Stereoselectivity of Michael addition



Solvent	Temp. (°C)	dr (desired:undesired)
DMF	rt	1.3:1.0
DMF	-50	0.8:1.0