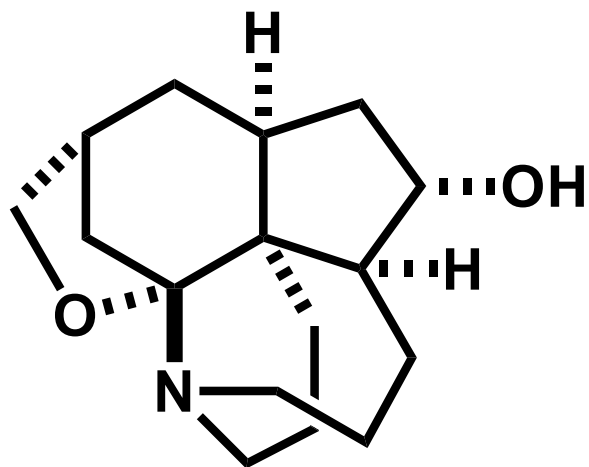


Total syntheses of Huperzine Q



Literature Seminer

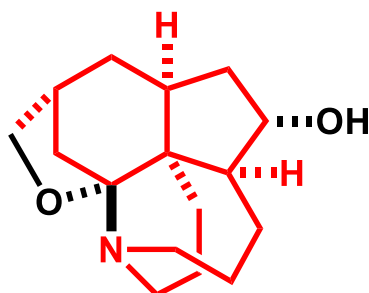
2017/09/16

Akira Tomiyama

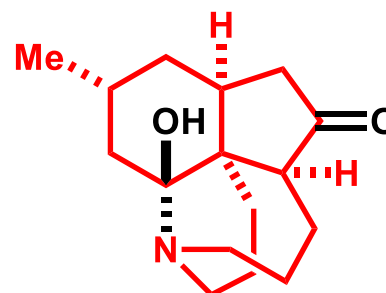
Contents

- 1. Introduction**
- 2. First total synthesis of Huperzine Q by Takayama**
- 3. Carbonyl-olefin metathesis strategy by Lei**
- 4. Main paper: DA and ring contraction strategy by Fukuyama**

Introduction: Huperzine Q



huperzine Q



fawcettimine

Isolation

from fern plant *Huperzia serrata* (*Lycopodium serratum*)

Zhu et al. *Helv. Chim. Acta* **2002**, 85, 1058.

Biological activity

not reported

(other *Lycopodium* Alkaloids: acetylcholine esterase inhibition, neurite outgrowth promotion)

Zhu et al. *Acta Pharmacol. Sin.* **1986**, 7, 507.

Hirasawa et al, *Heterocycles* **2006**, 68, 2357.

Structure

7/6/6/5/5 pentacycle

spiroaminal moiety

6 stereocenters, including a quaternary carbon

Total syntheses

Nakayama, A.; Kogure, N.; Kitajima, M.; Takayama, H. *Angew. Chem. Int. Ed.* **2011**, 50, 8025.

Hong, B.; Li, H.; Wu, J.; Zhang, J.; Lei, X. *Angew. Chem. Int. Ed.* **2015**, 54, 1011.

Tanimura, S.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2017**, 19, 3684.

Contents

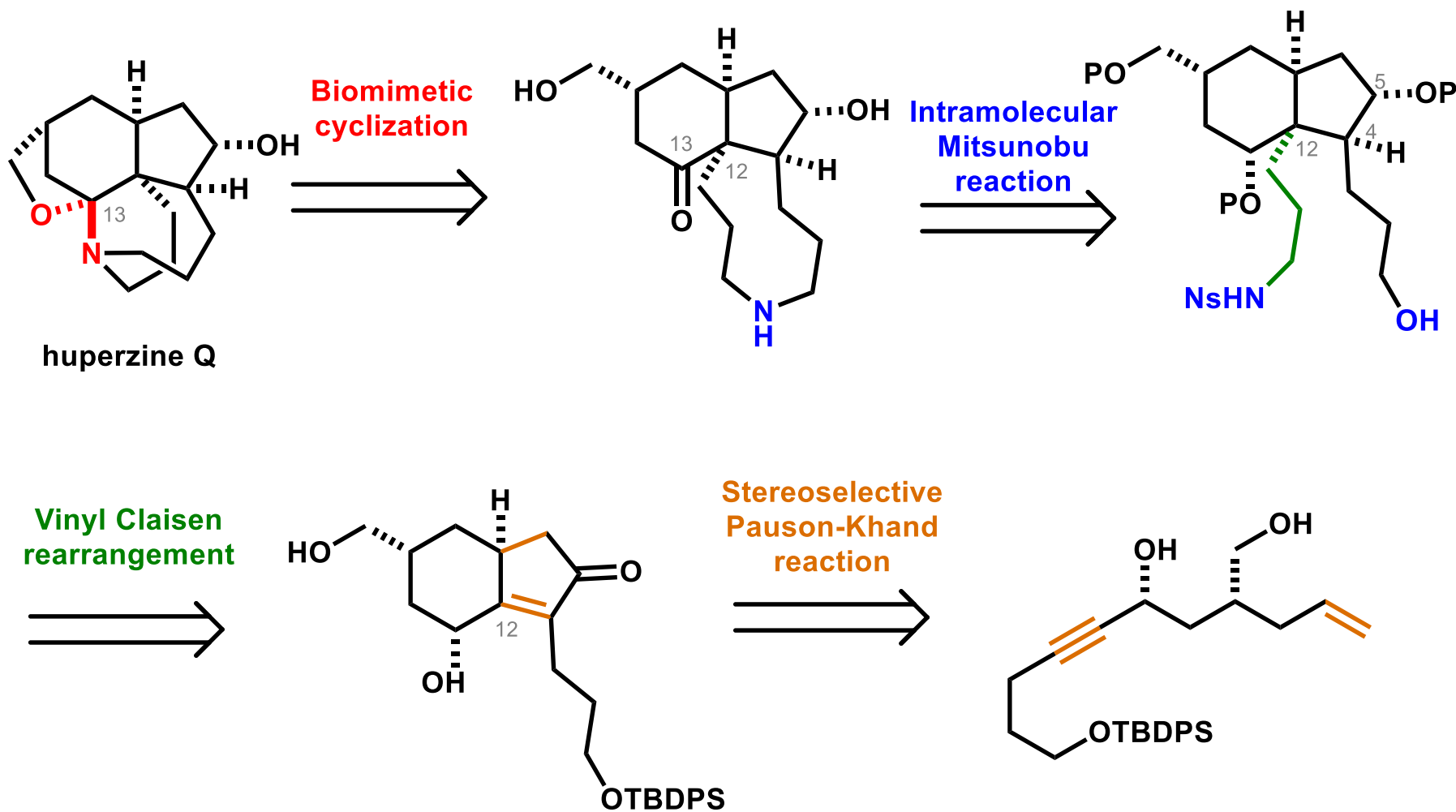
1. Introduction

2. First total synthesis of Huperzine Q by Takayama

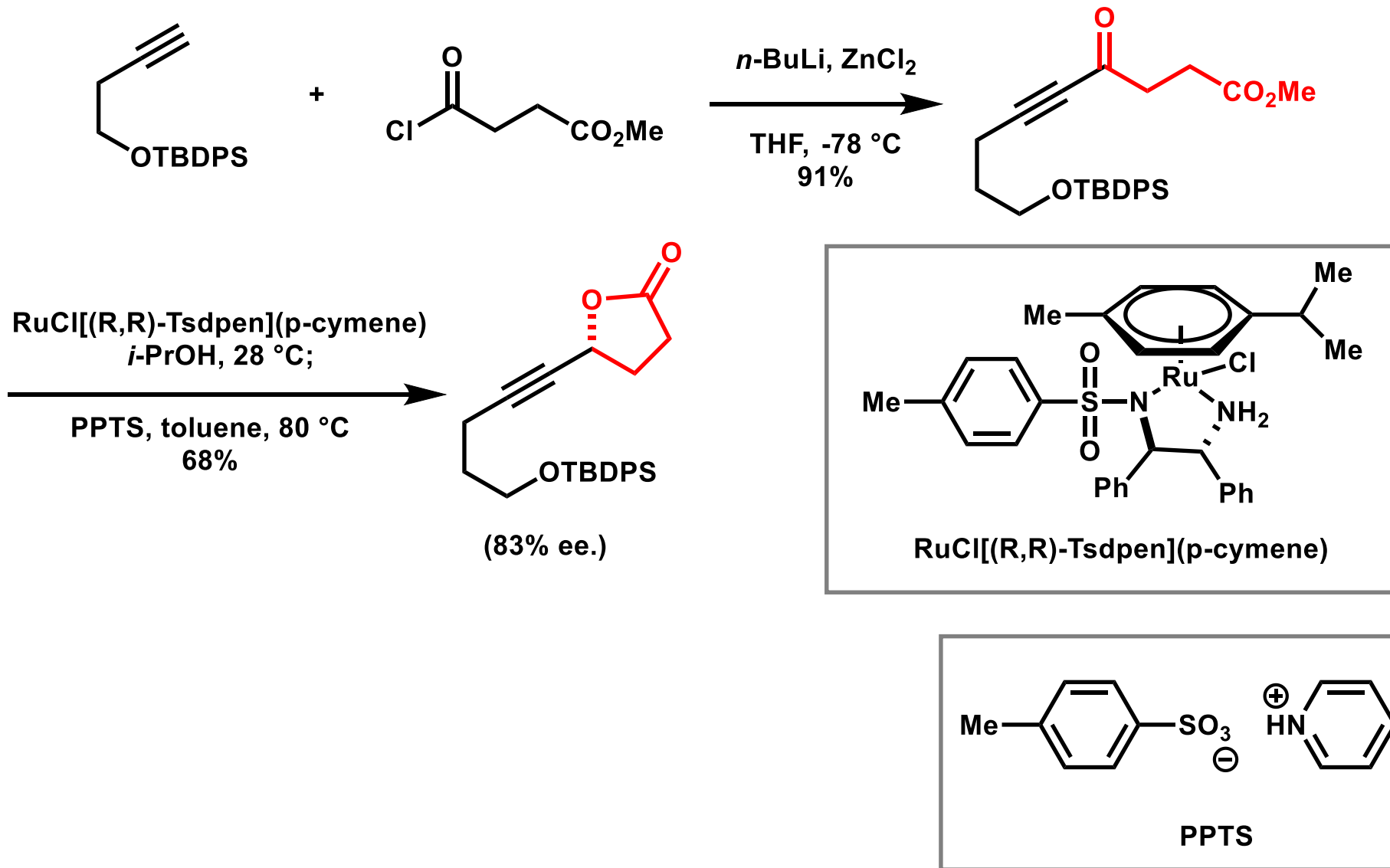
3. Carbonyl-olefin metathesis strategy by Lei

4. Main paper: DA and ring contraction strategy by Fukuyama

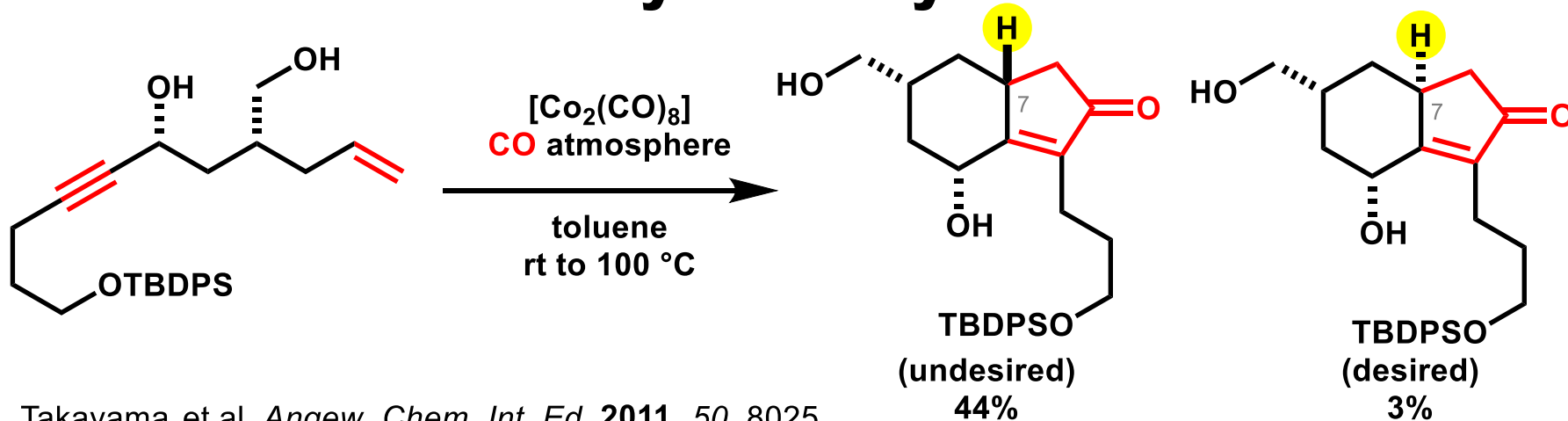
Takayama's Retrosynthesis



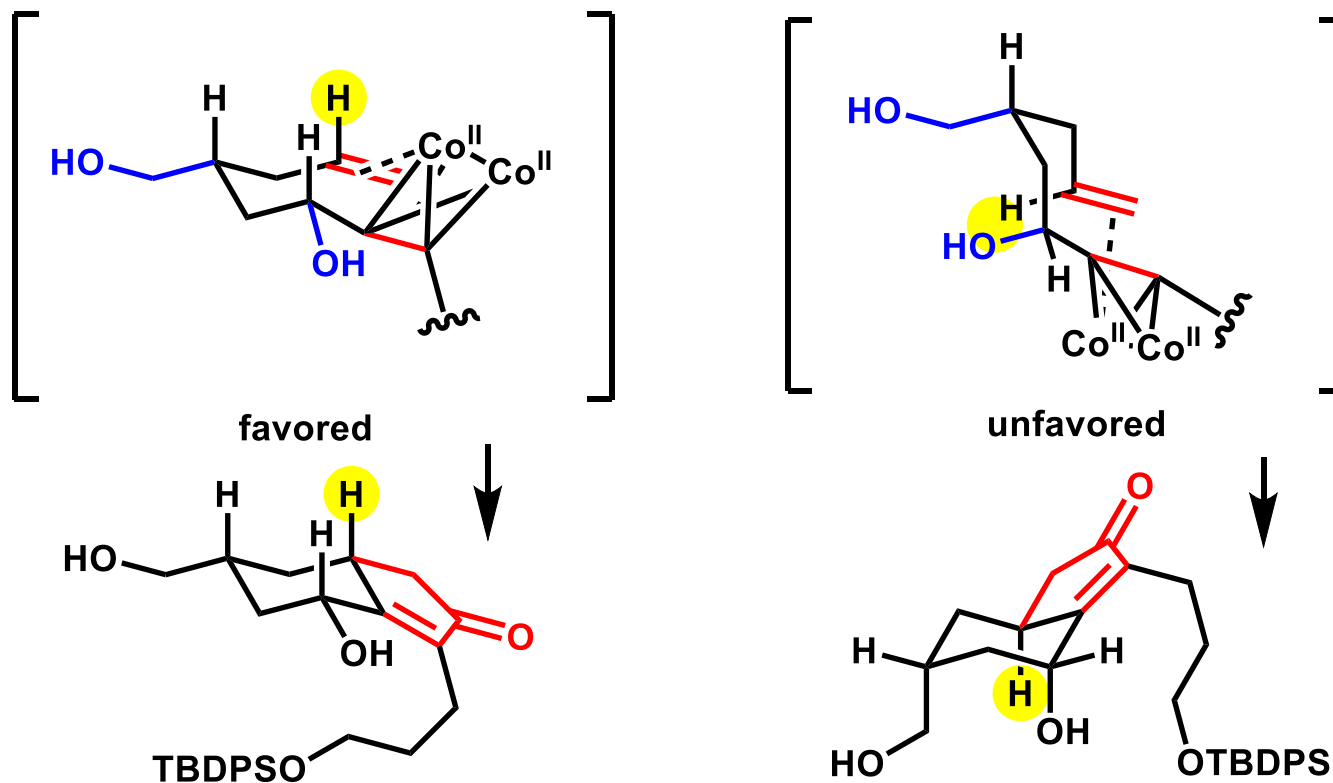
Takayama's synthesis



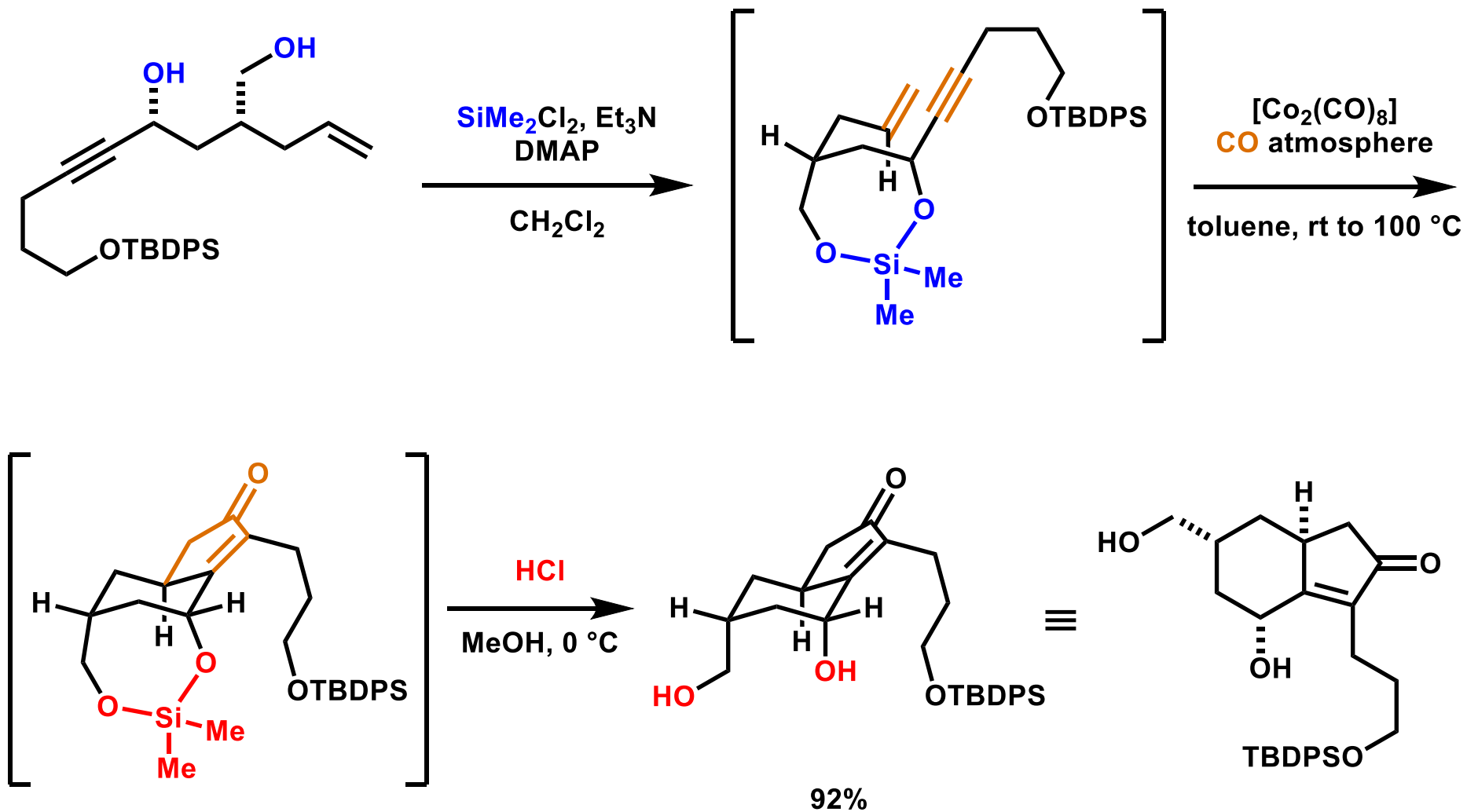
Takayama's synthesis



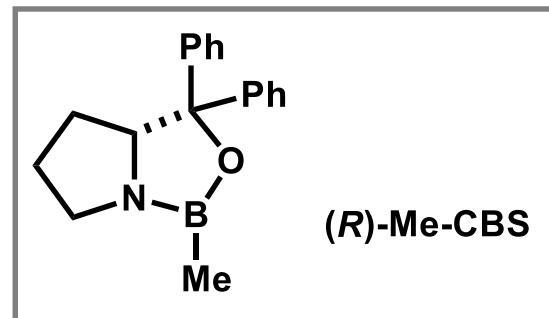
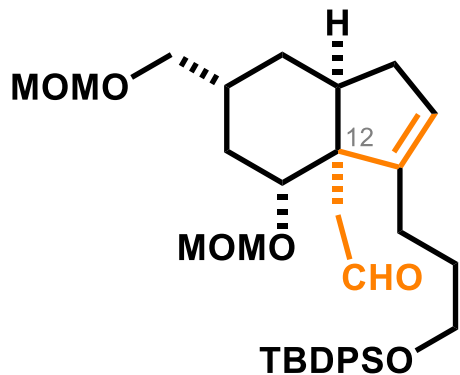
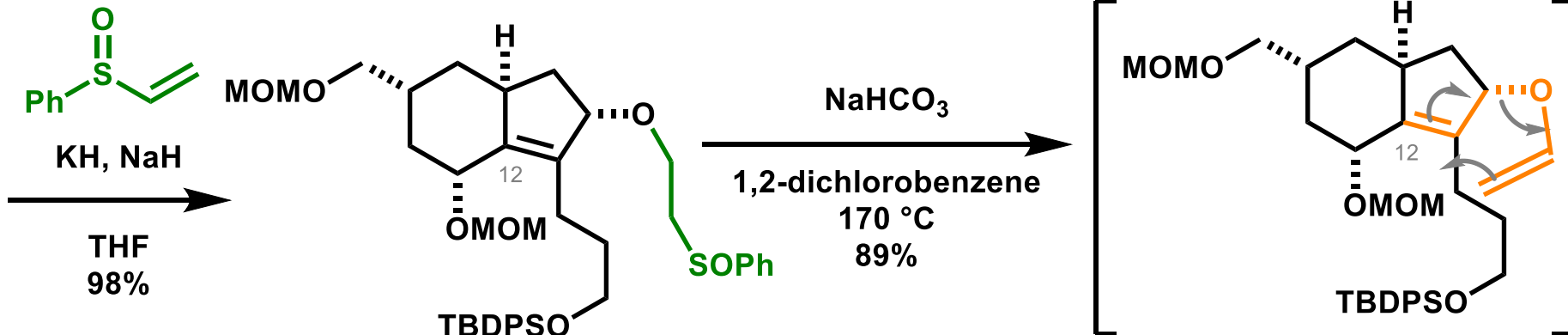
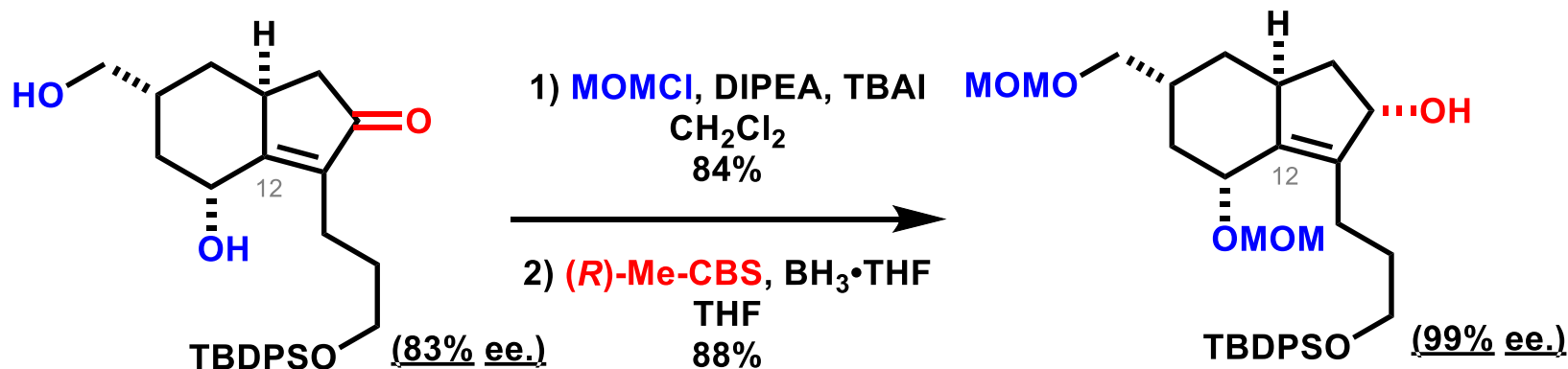
Takayama et al. *Angew. Chem. Int. Ed.* **2011**, *50*, 8025.



Takayama's synthesis

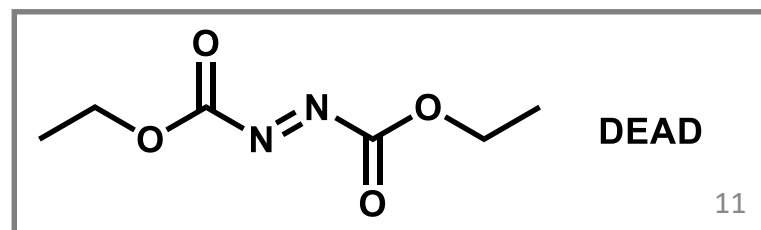
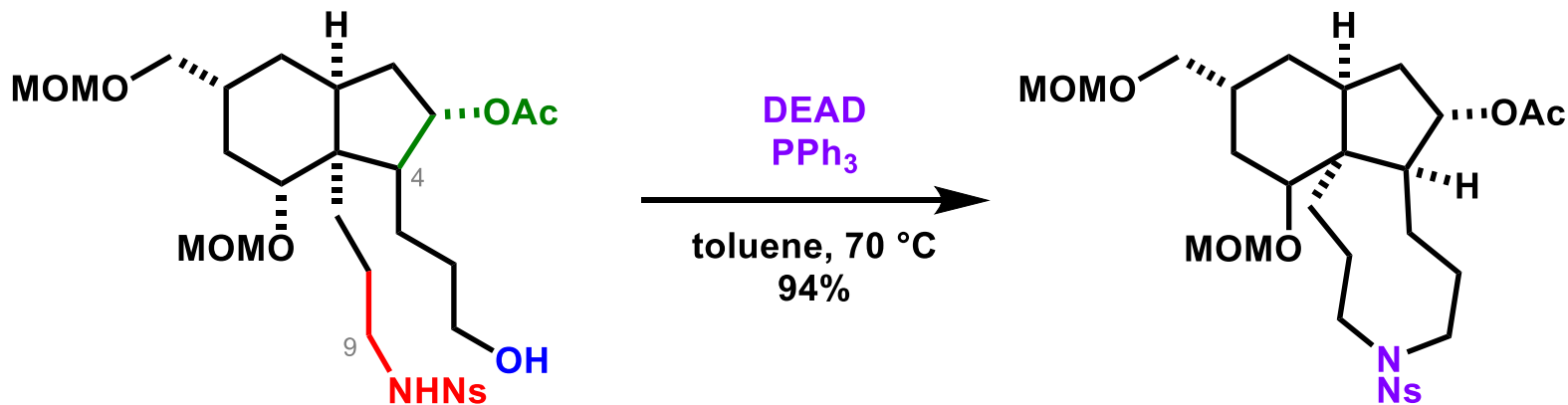
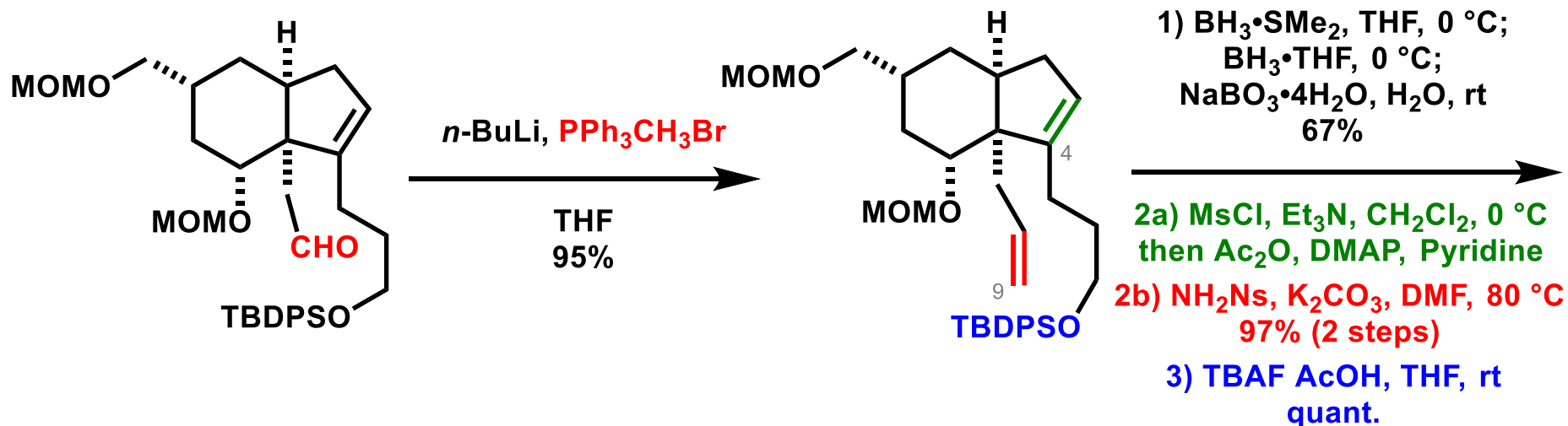


Takayama's synthesis

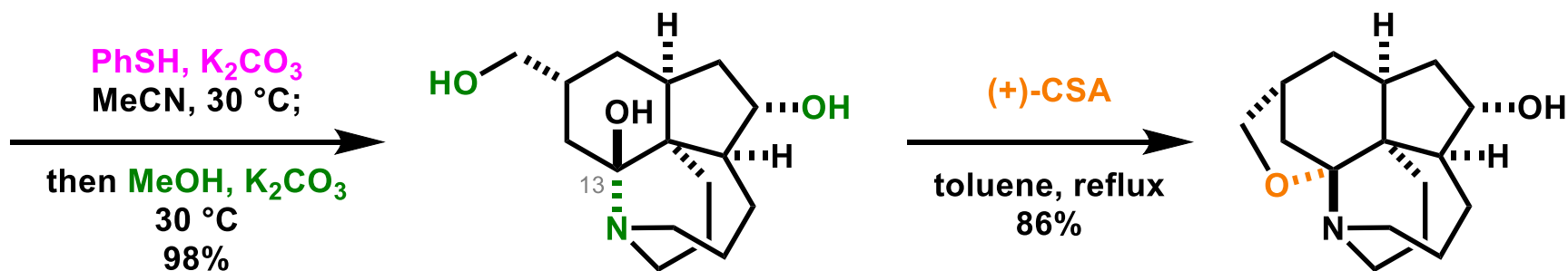
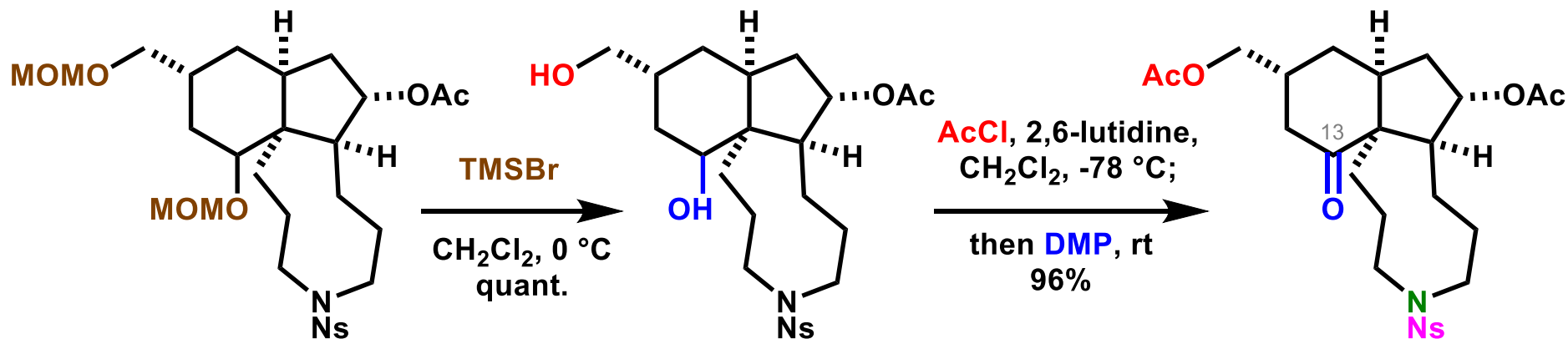


DIPEA = N,N-diisopropylethylamine
TBAI = Tetrabutylammonium iodide

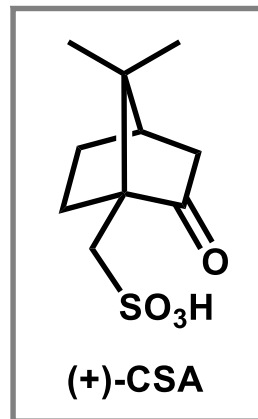
Takayama's synthesis



Takayama's synthesis

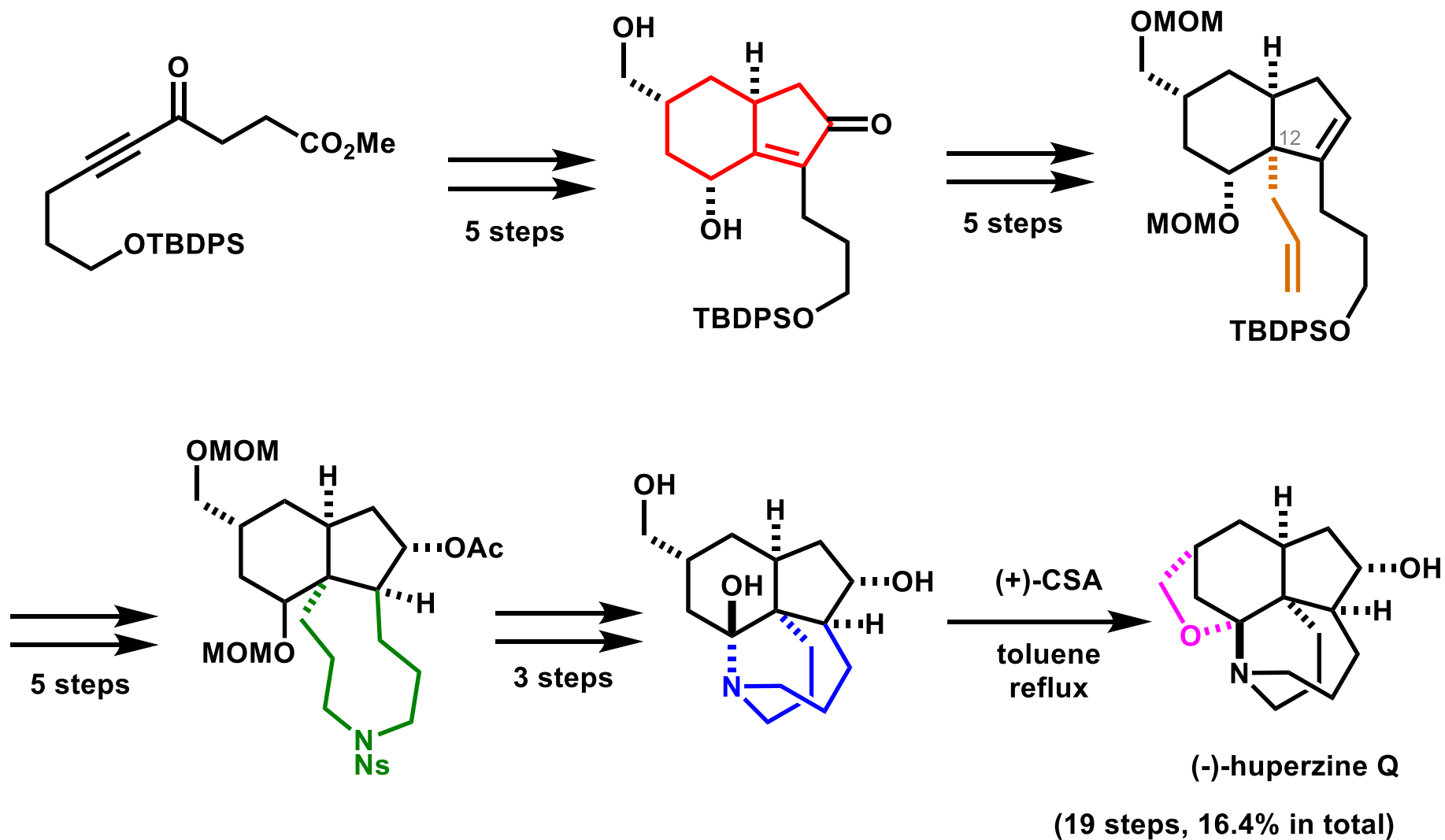


DMP = Dess-Martin periodinane



(-)-huperzine Q
(19 steps, 16.4% in total)

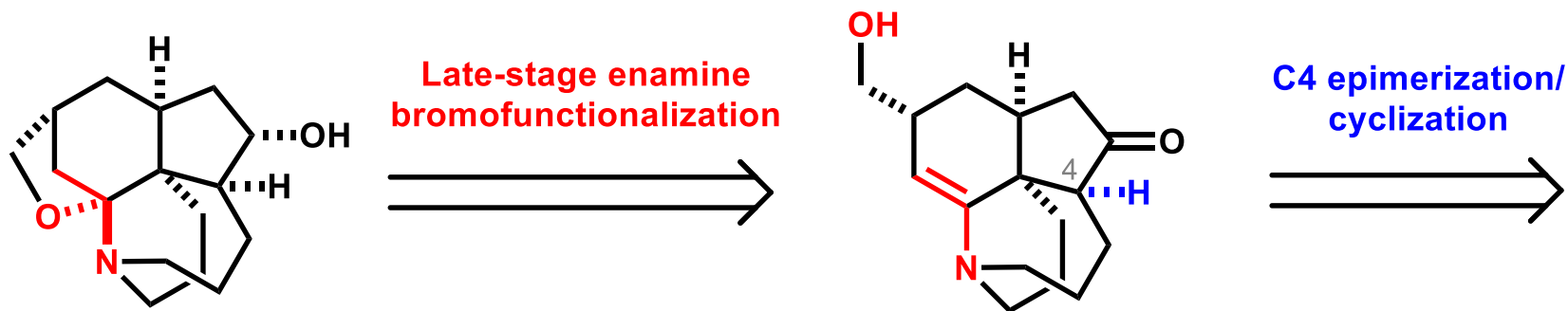
Takayama's synthesis



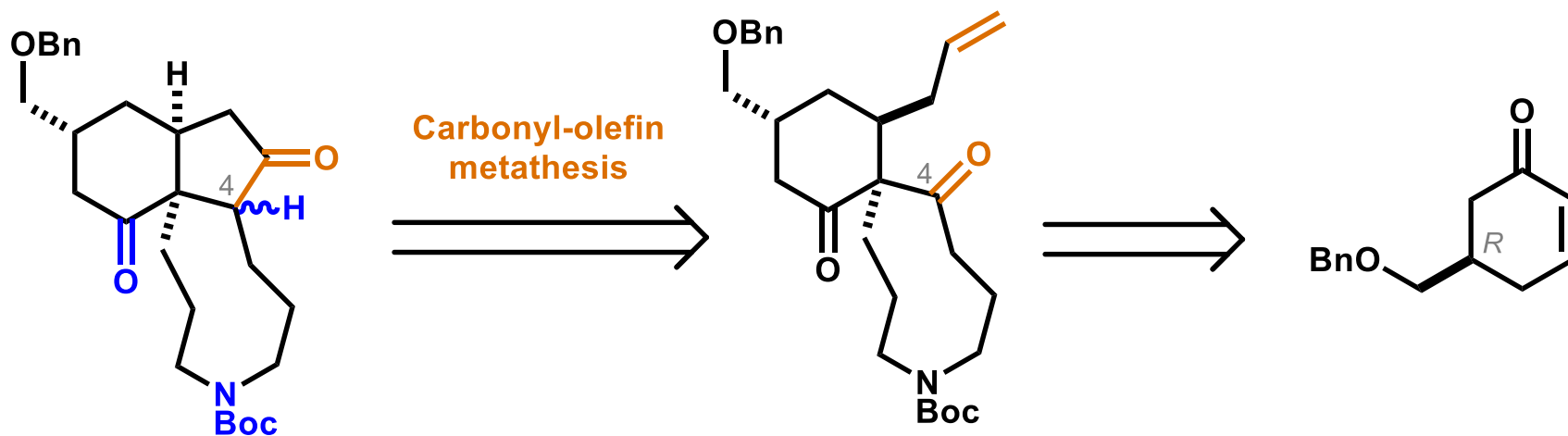
Contents

1. Introduction
2. First total synthesis of Huperzine Q by Takayama
- 3. Carbonyl-olefin metathesis strategy by Lei**
4. Main paper: DA and ring contraction strategy by Fukuyama

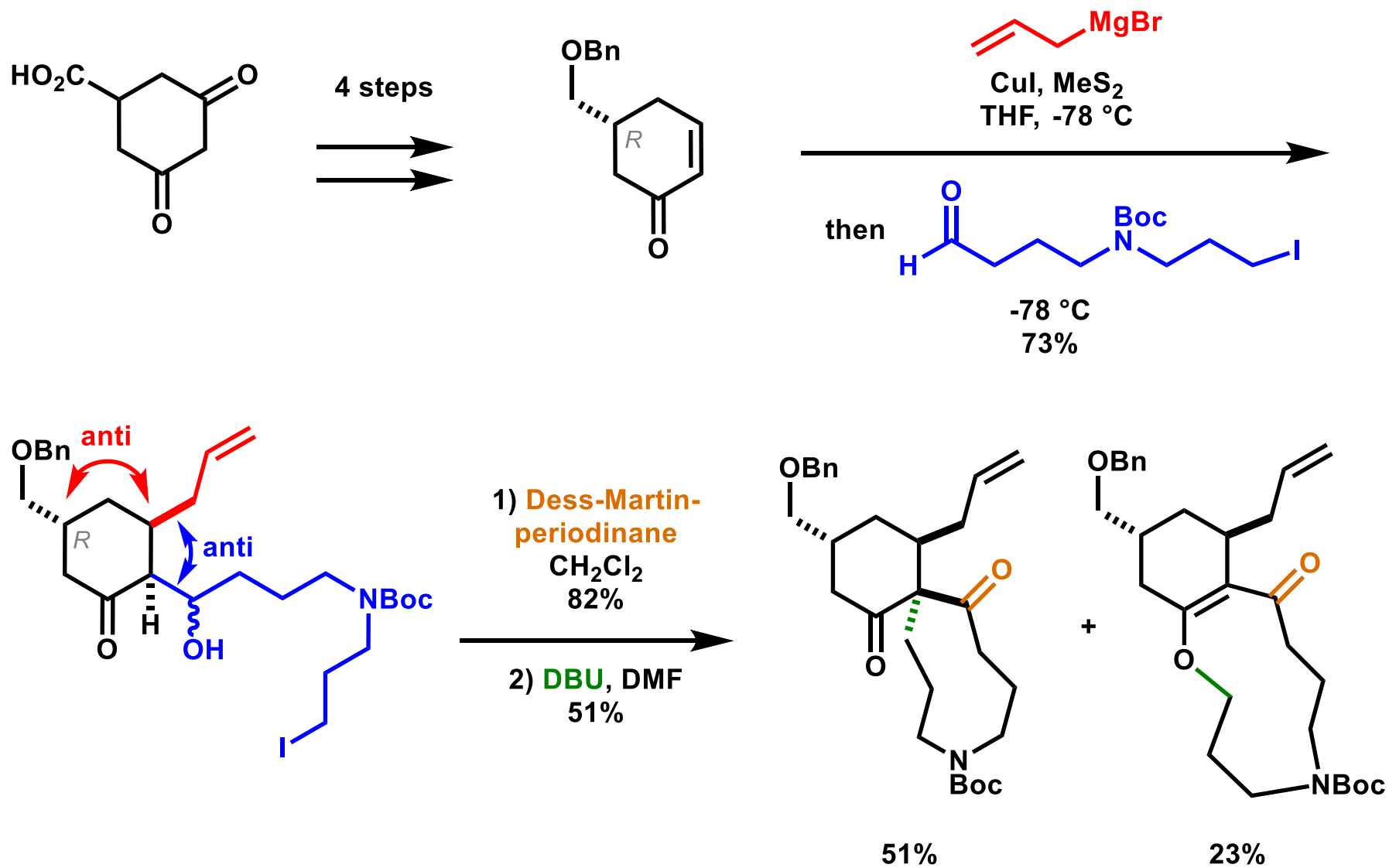
Lei's retrosynthesis



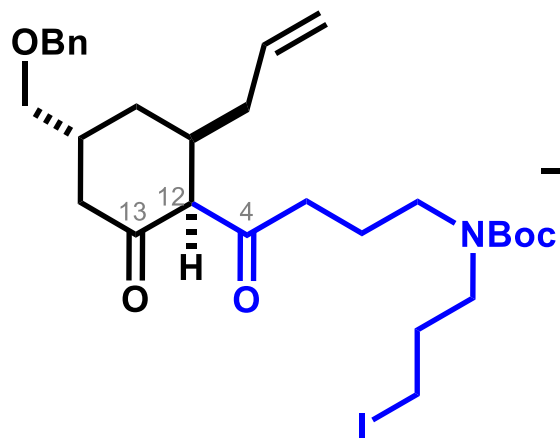
huperzine Q



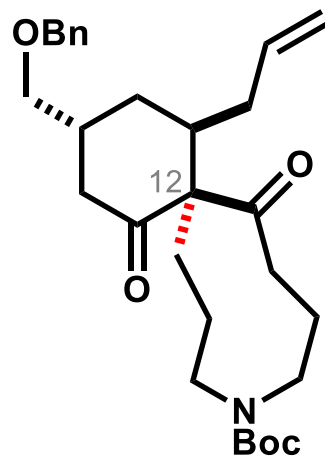
Lei's synthesis



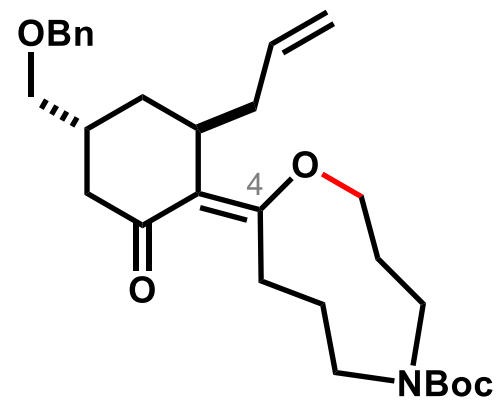
Lei's synthesis



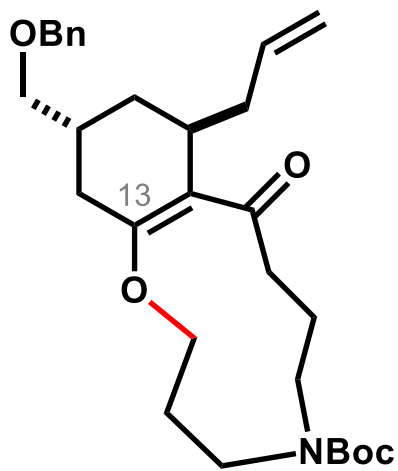
DBU



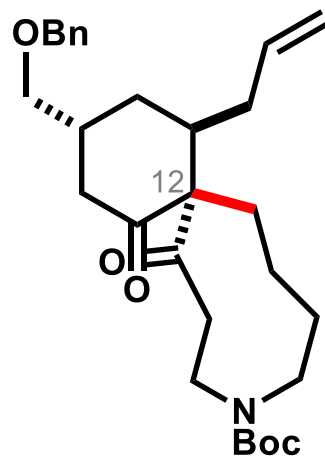
B (major)



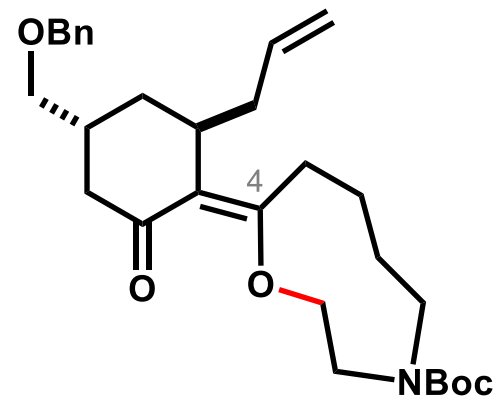
D (not detected)



A (minor)

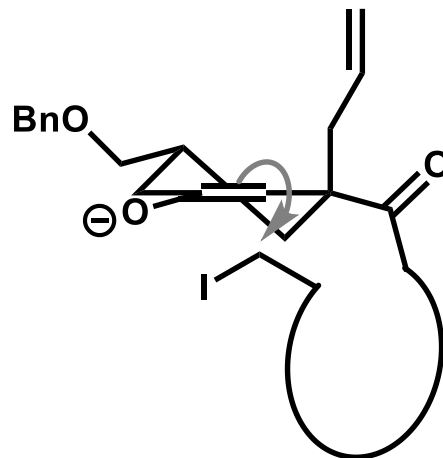
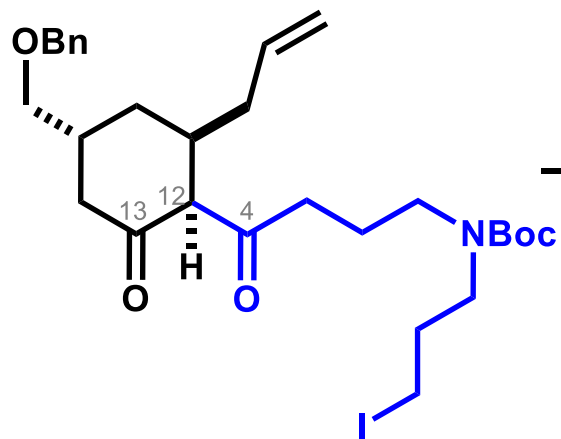


C (not detected)

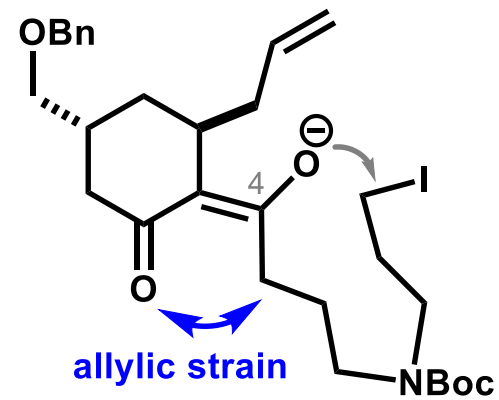


E (not detected)

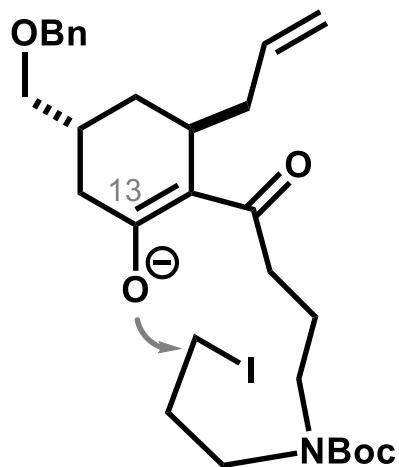
Lei's synthesis



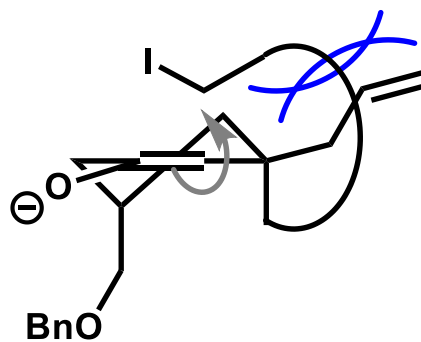
B (major)



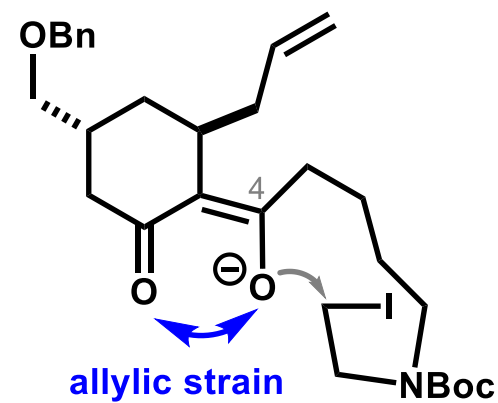
D (not detected)



A (minor)

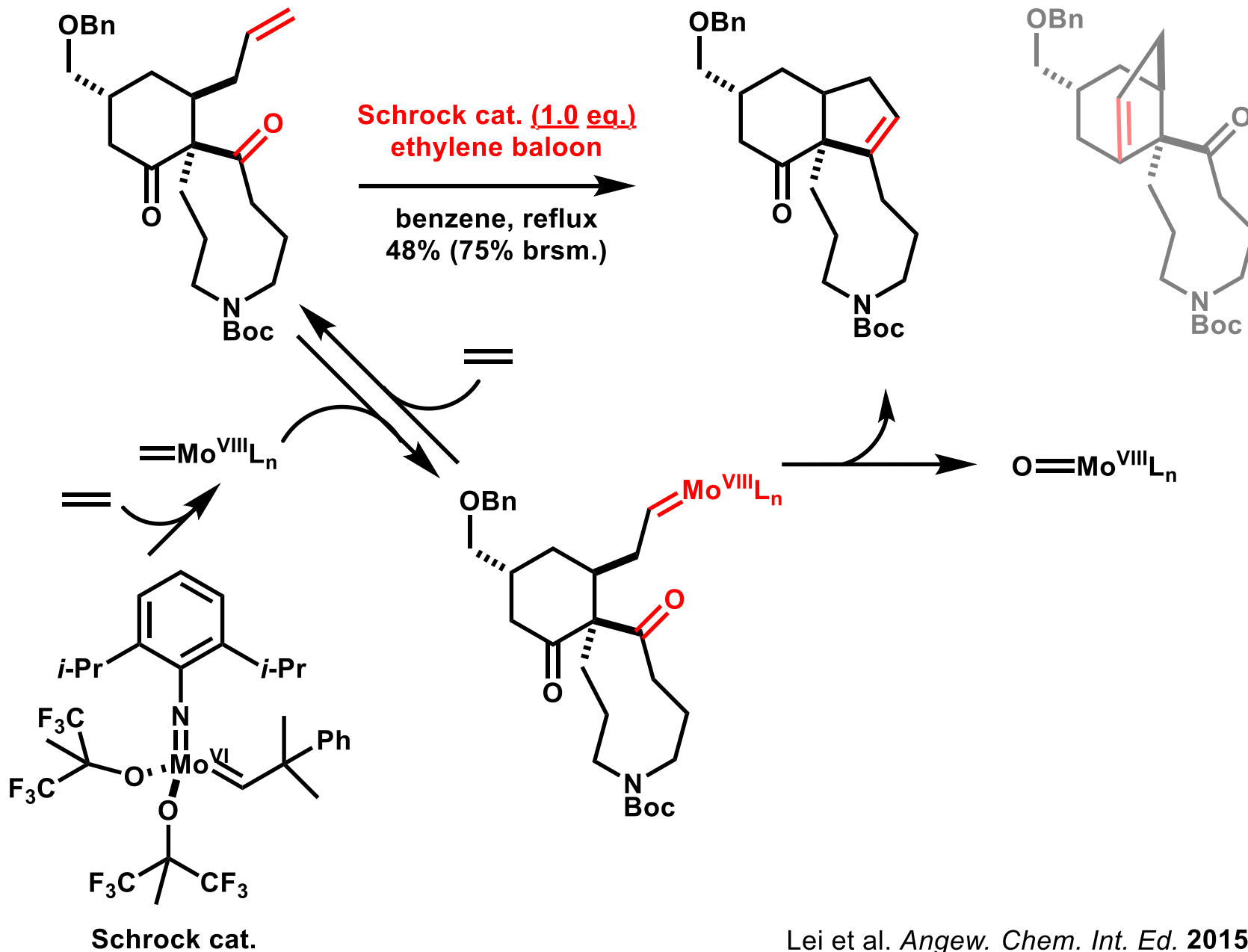


C (not detected)

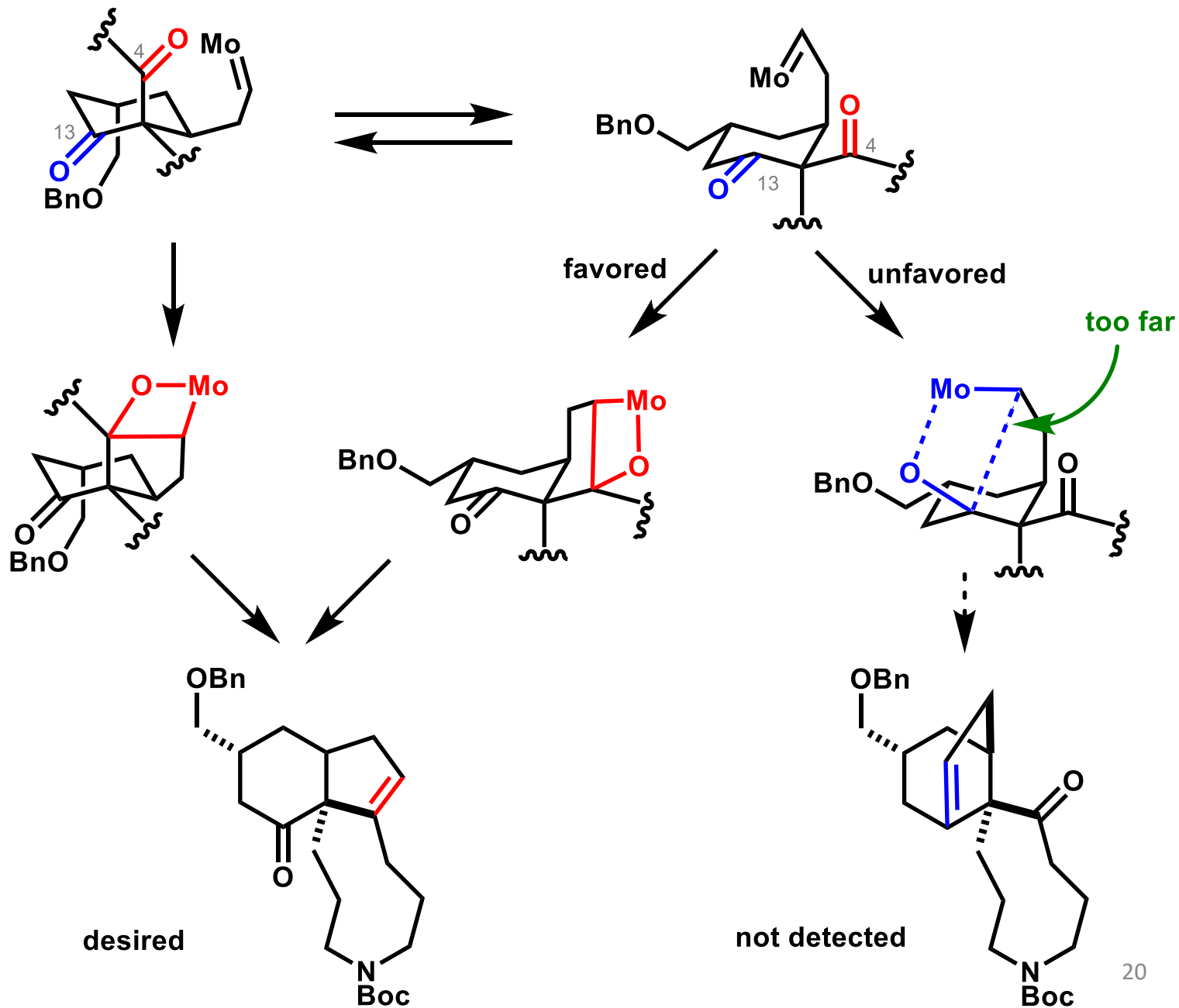


E (not detected)

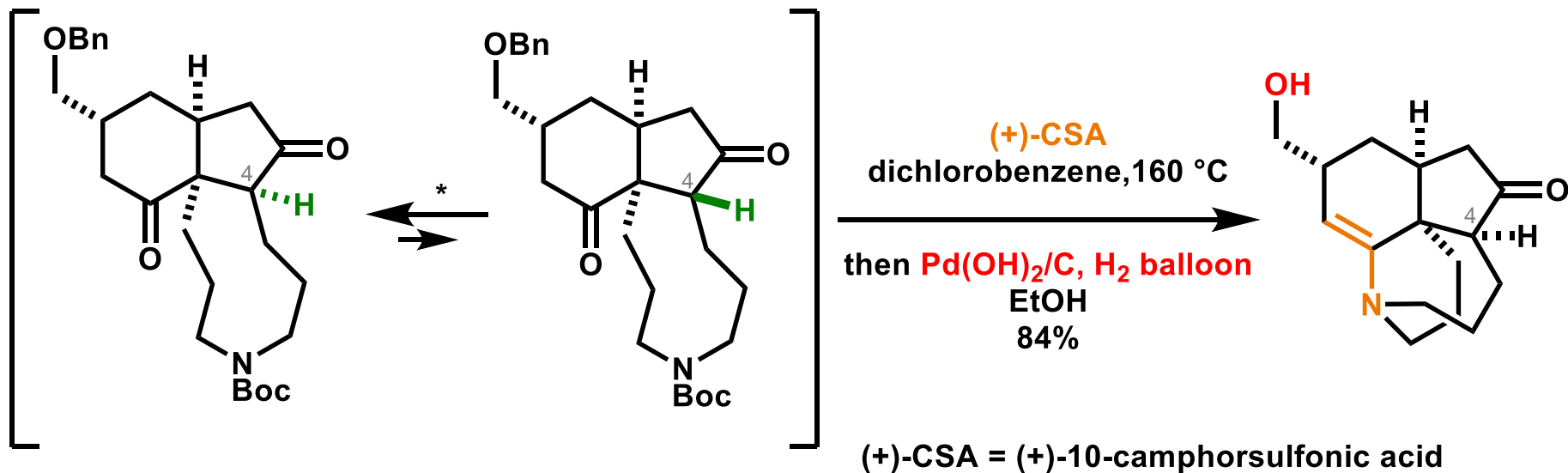
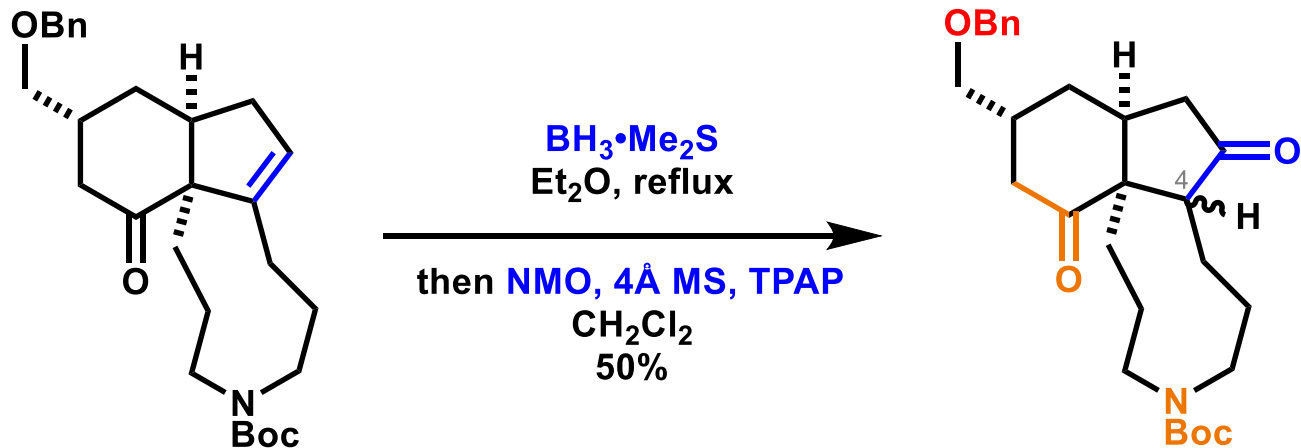
Lei's synthesis



Lei's synthesis



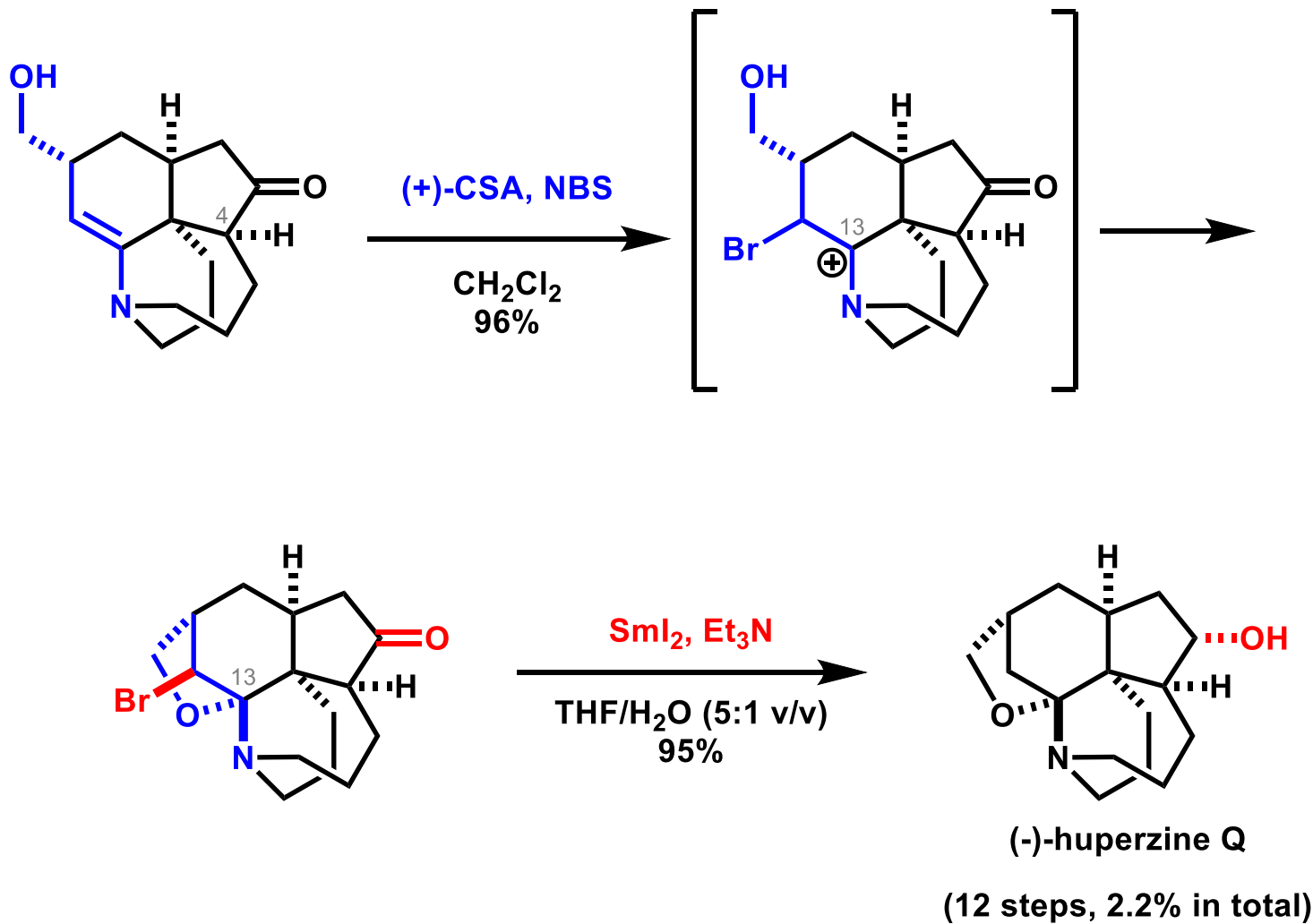
Lei's synthesis



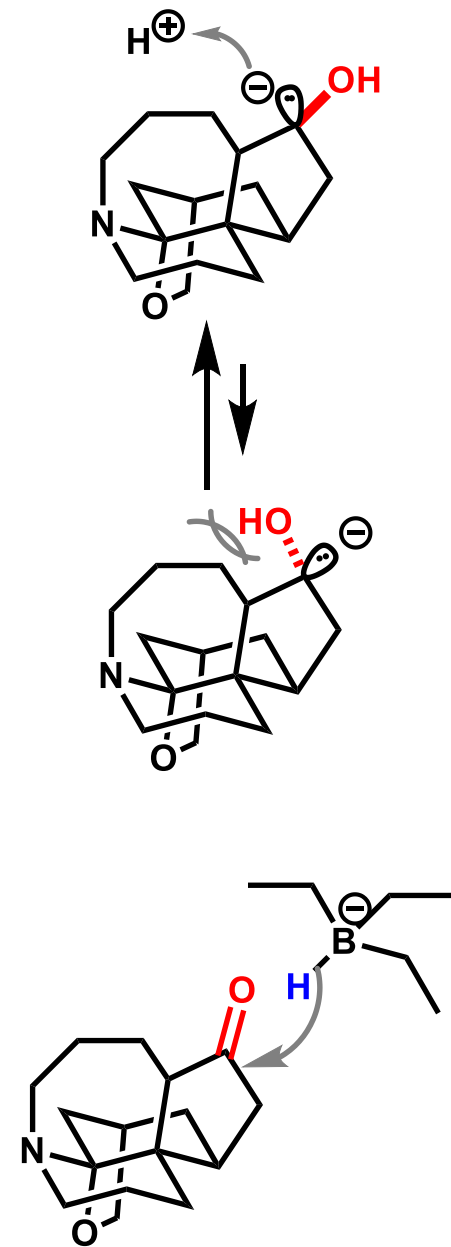
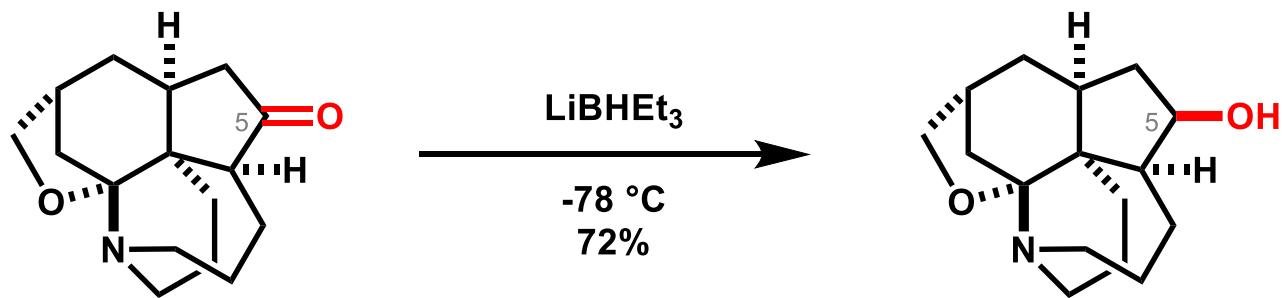
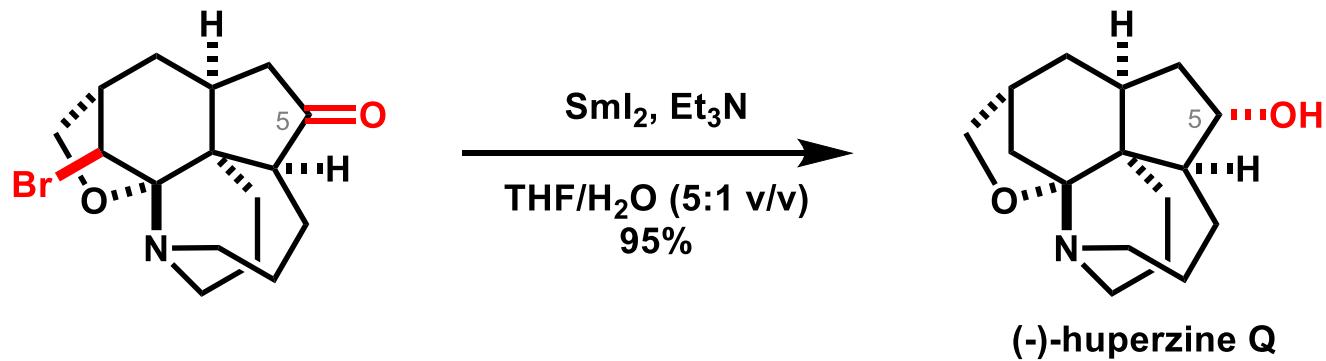
*Heathcock, C. H. et al. *J. Am. Chem. Soc.* **1986**, *108*, 5022

Lei et al. *Angew. Chem. Int. Ed.* **2015**, *54*, 1011.

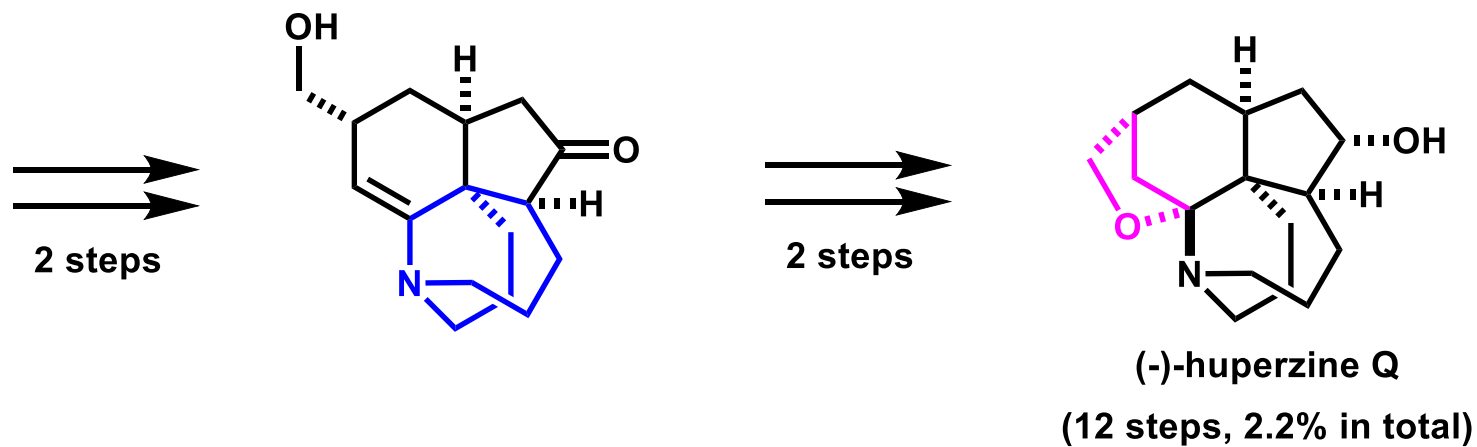
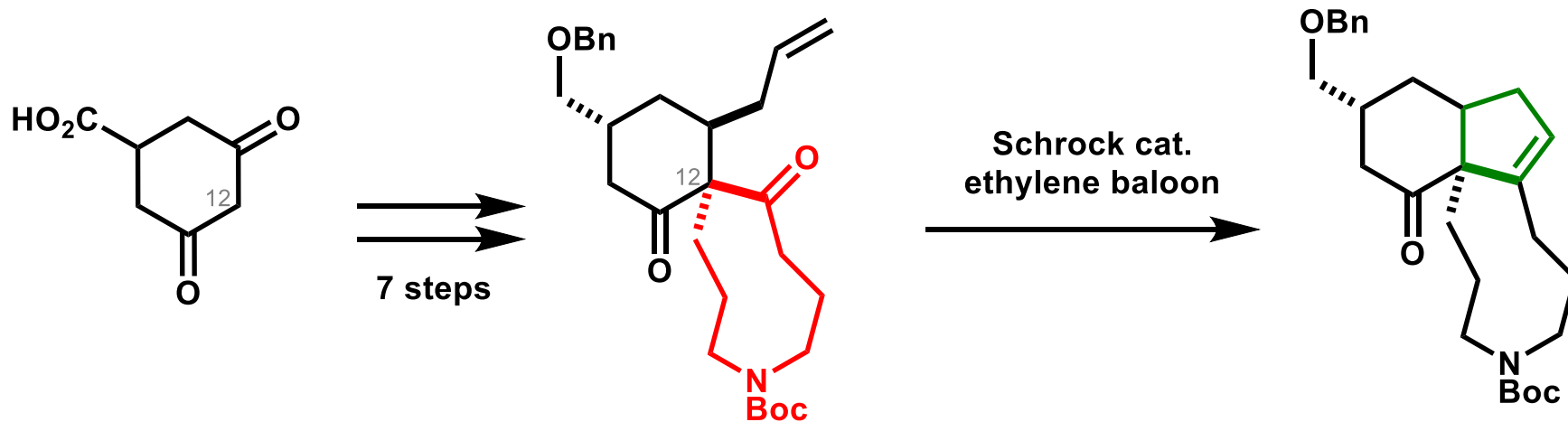
Lei's synthesis



Lei's synthesis



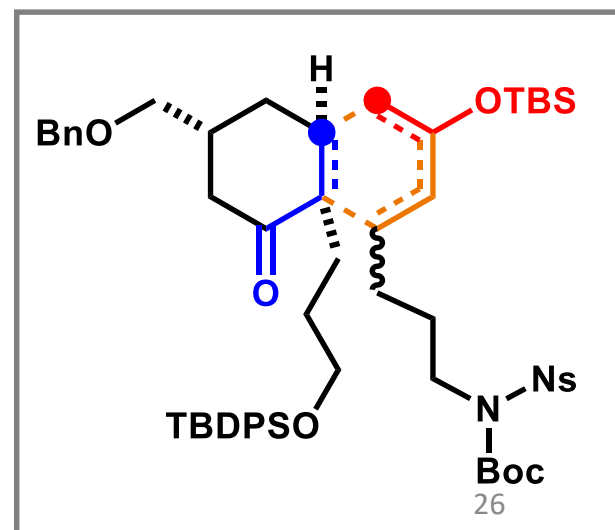
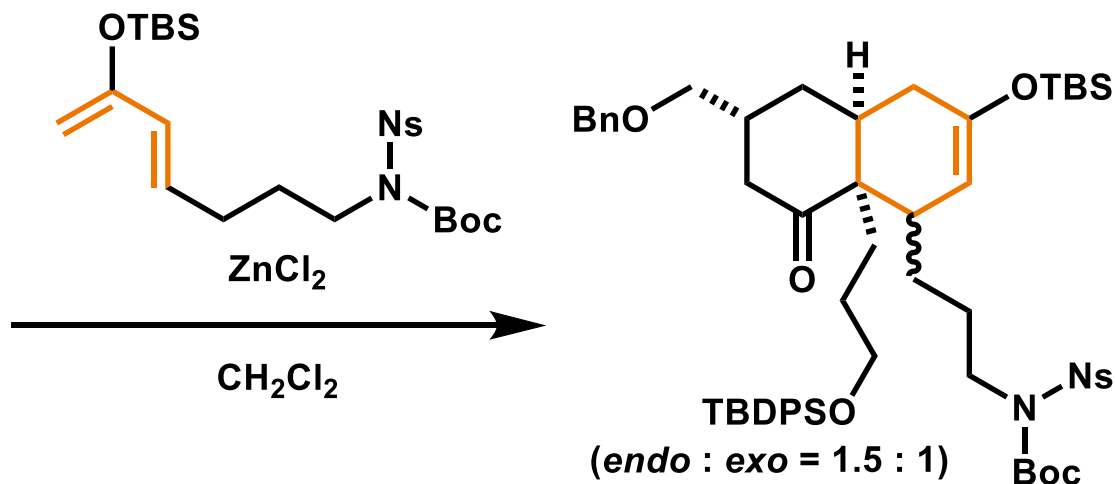
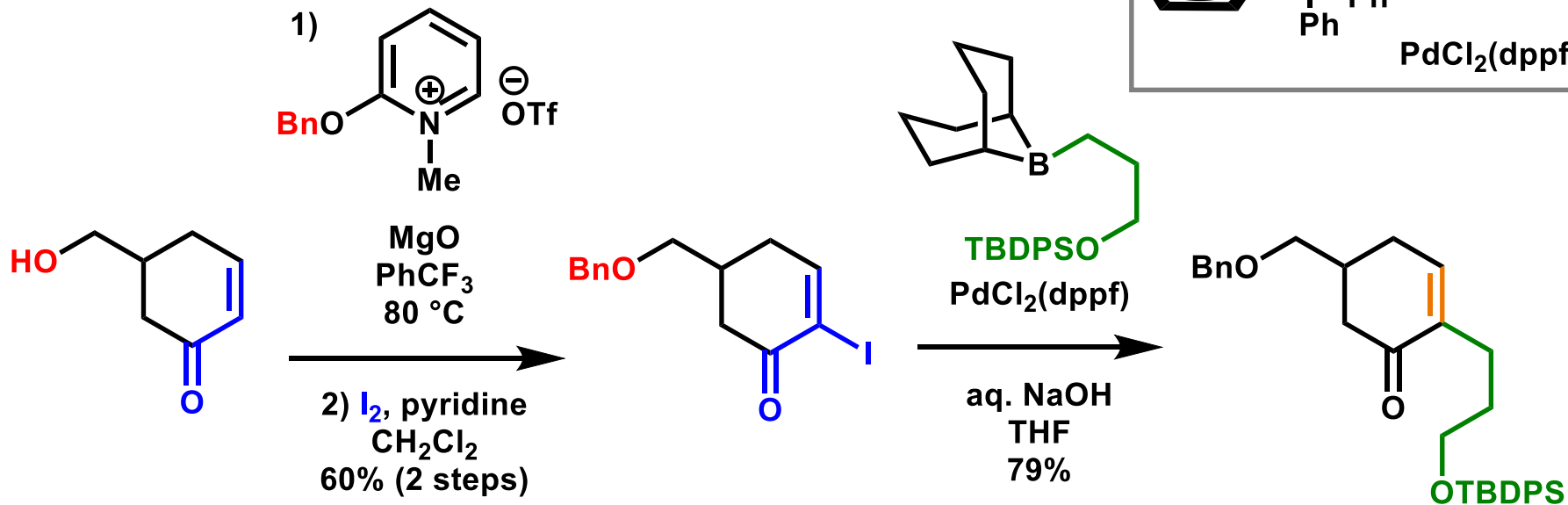
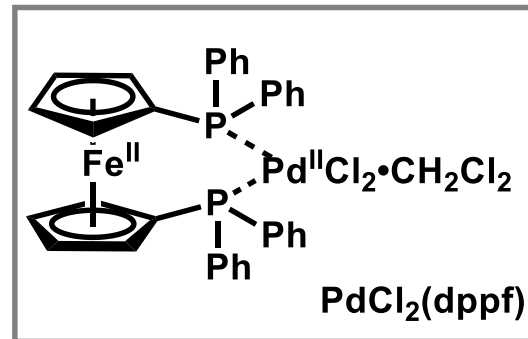
Lei's synthesis



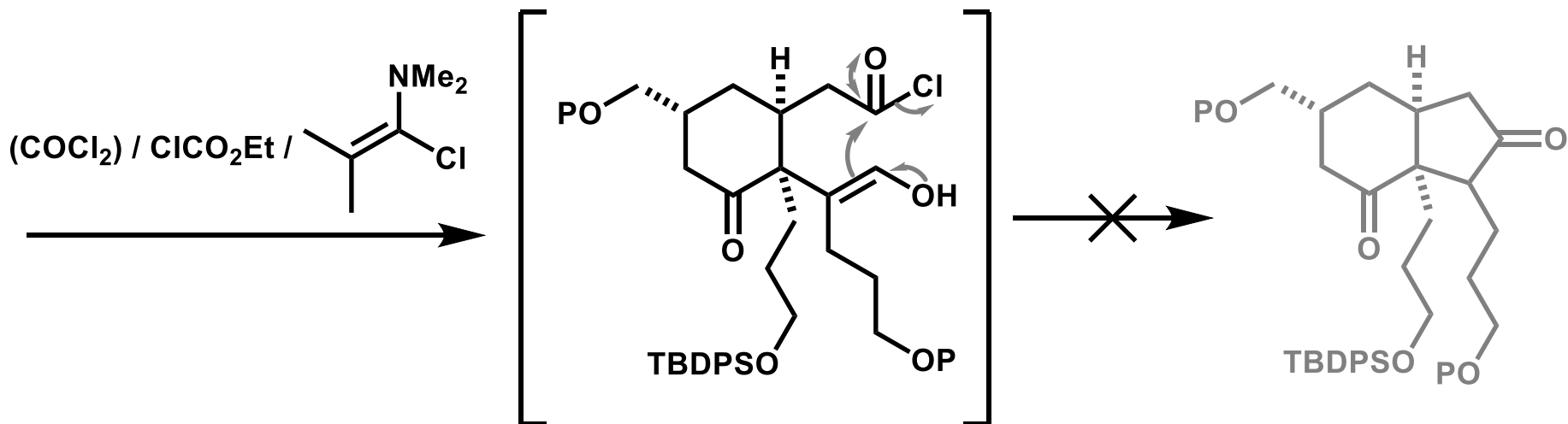
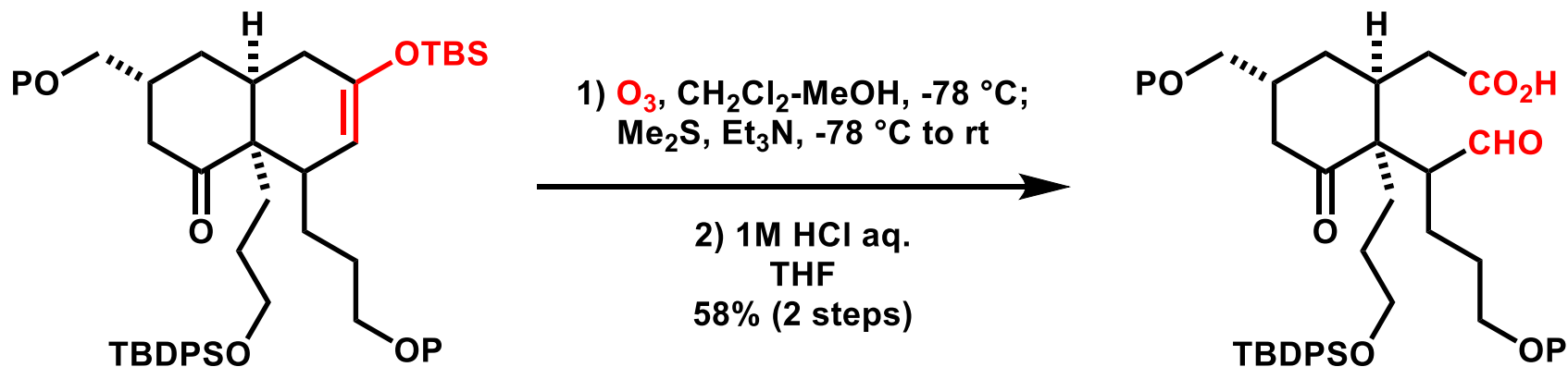
Contents

1. Introduction
2. First total synthesis of Huperzine Q by Takayama
3. Carbonyl-olefin metathesis strategy by Lei
- 4. Main paper: DA and ring contraction strategy by Fukuyama**

Fukuyama's synthesis



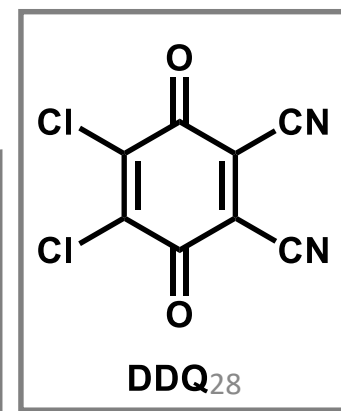
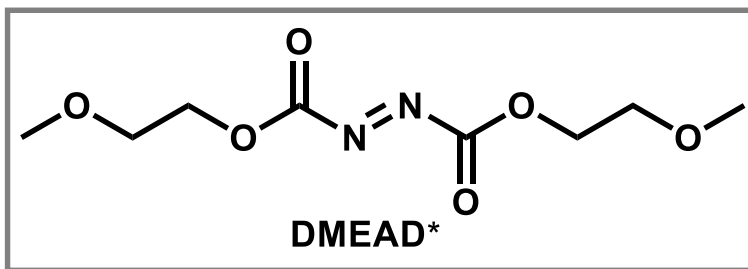
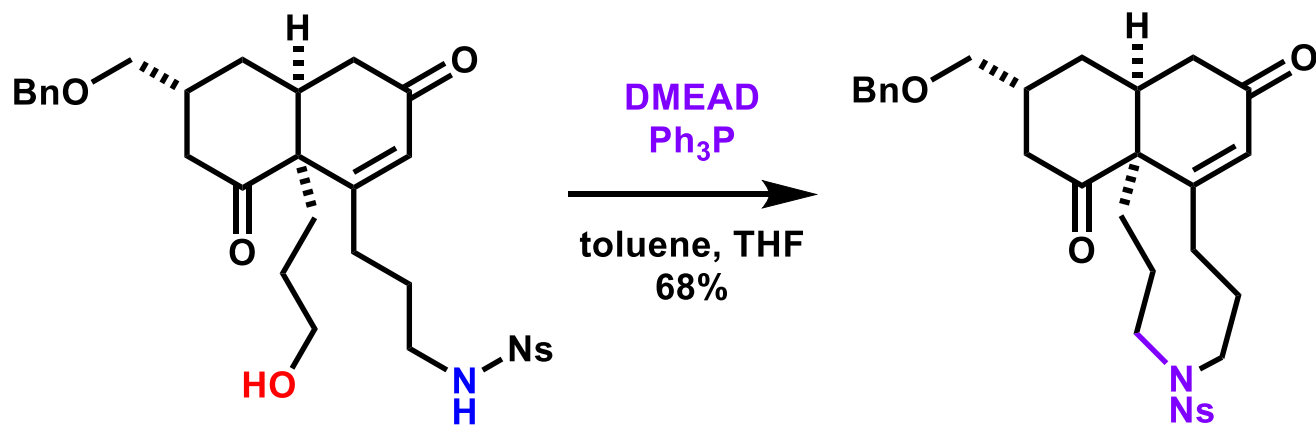
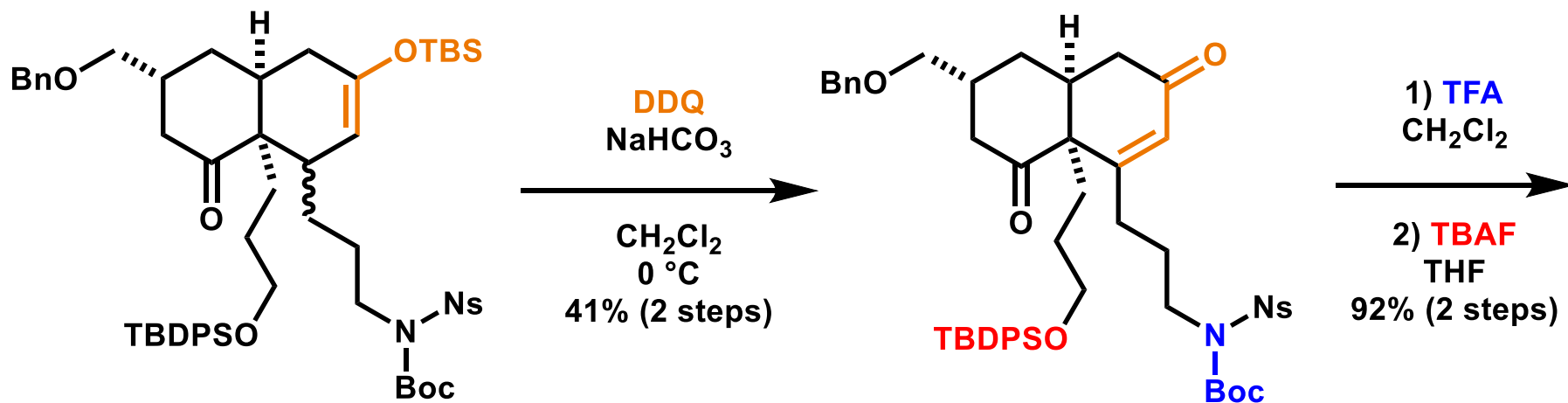
Fukuyama's synthesis



Inubushi et al. *Tetrahedron Lett.* **1979**, 20, 4307.

Tanimura. S. *Doctor thesis*, **2014**.

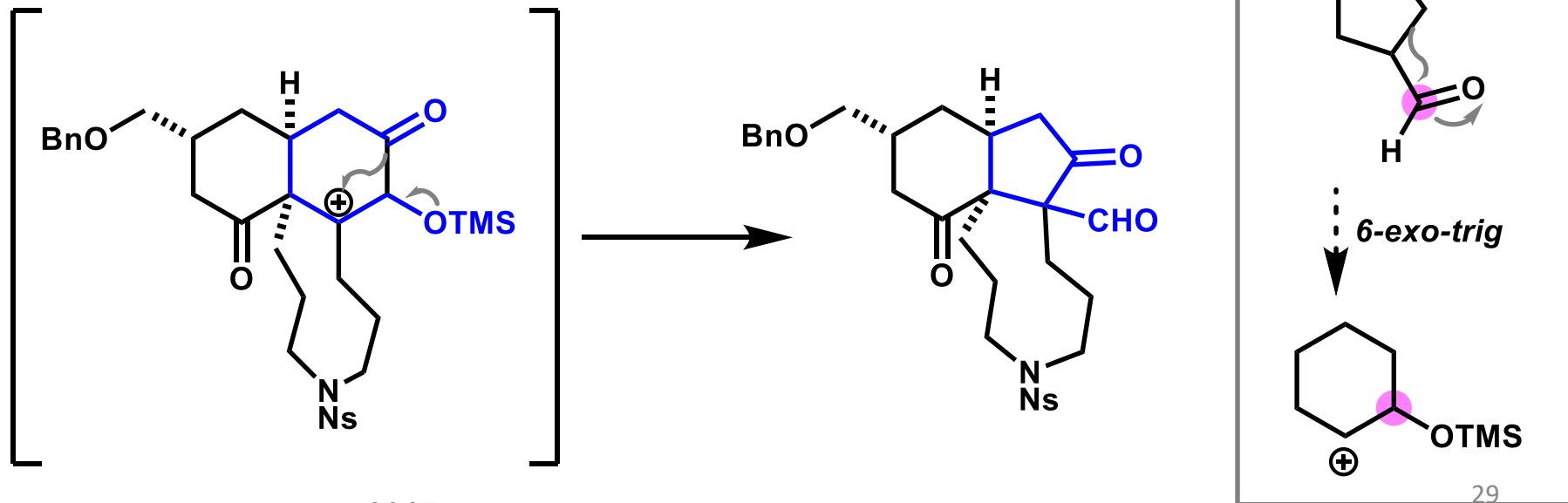
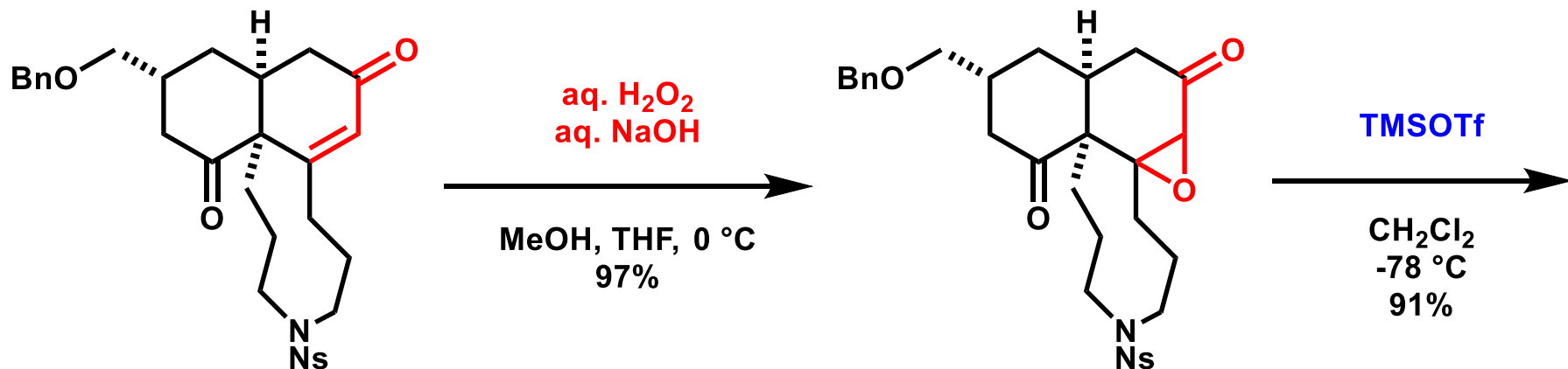
Fukuyama's synthesis



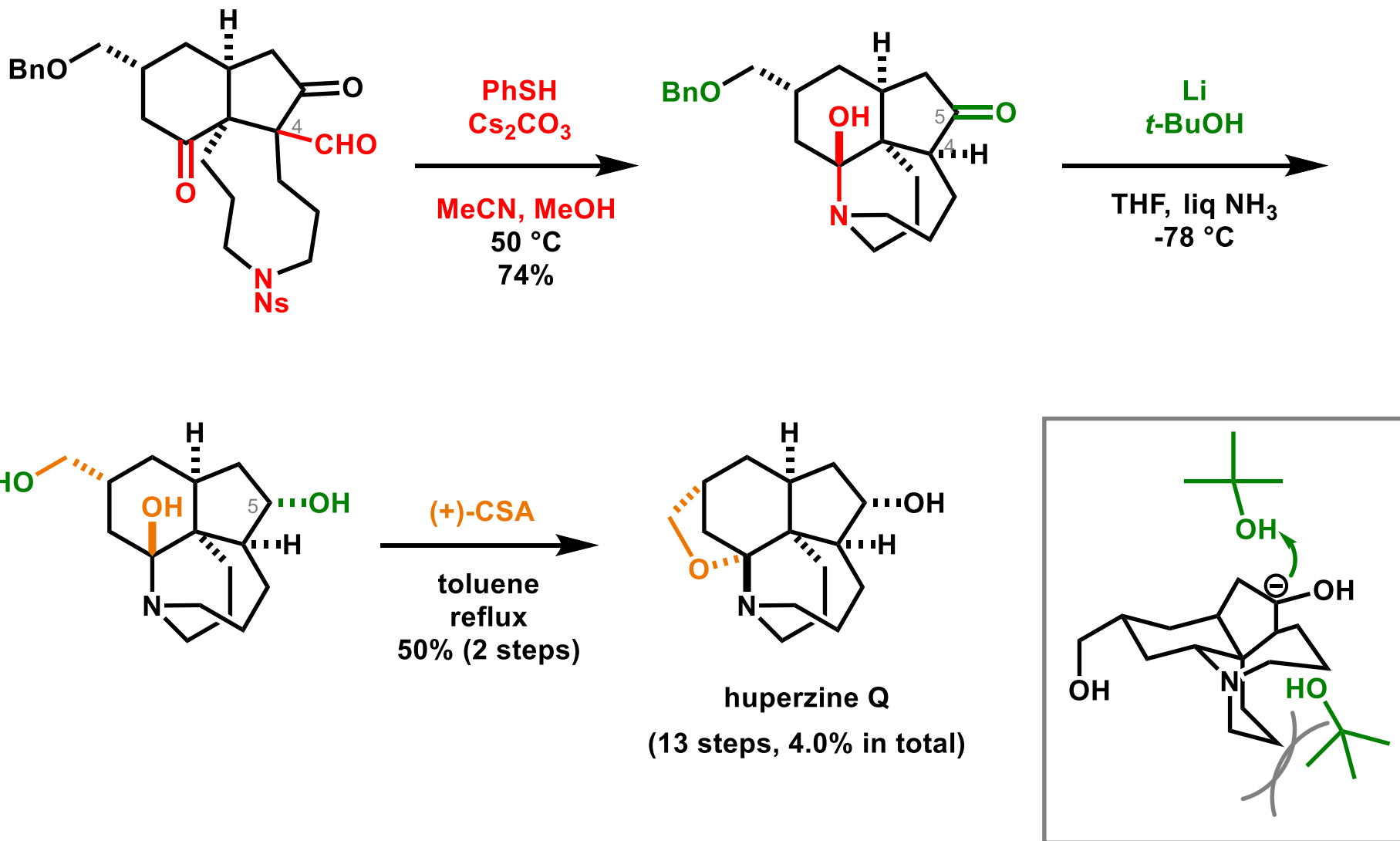
*Hagiya et al. *Tetrahedron* **2009**, *65*, 6109.

Fukuyama et al. *Org. Lett.* **2017**, *19*, 3684.

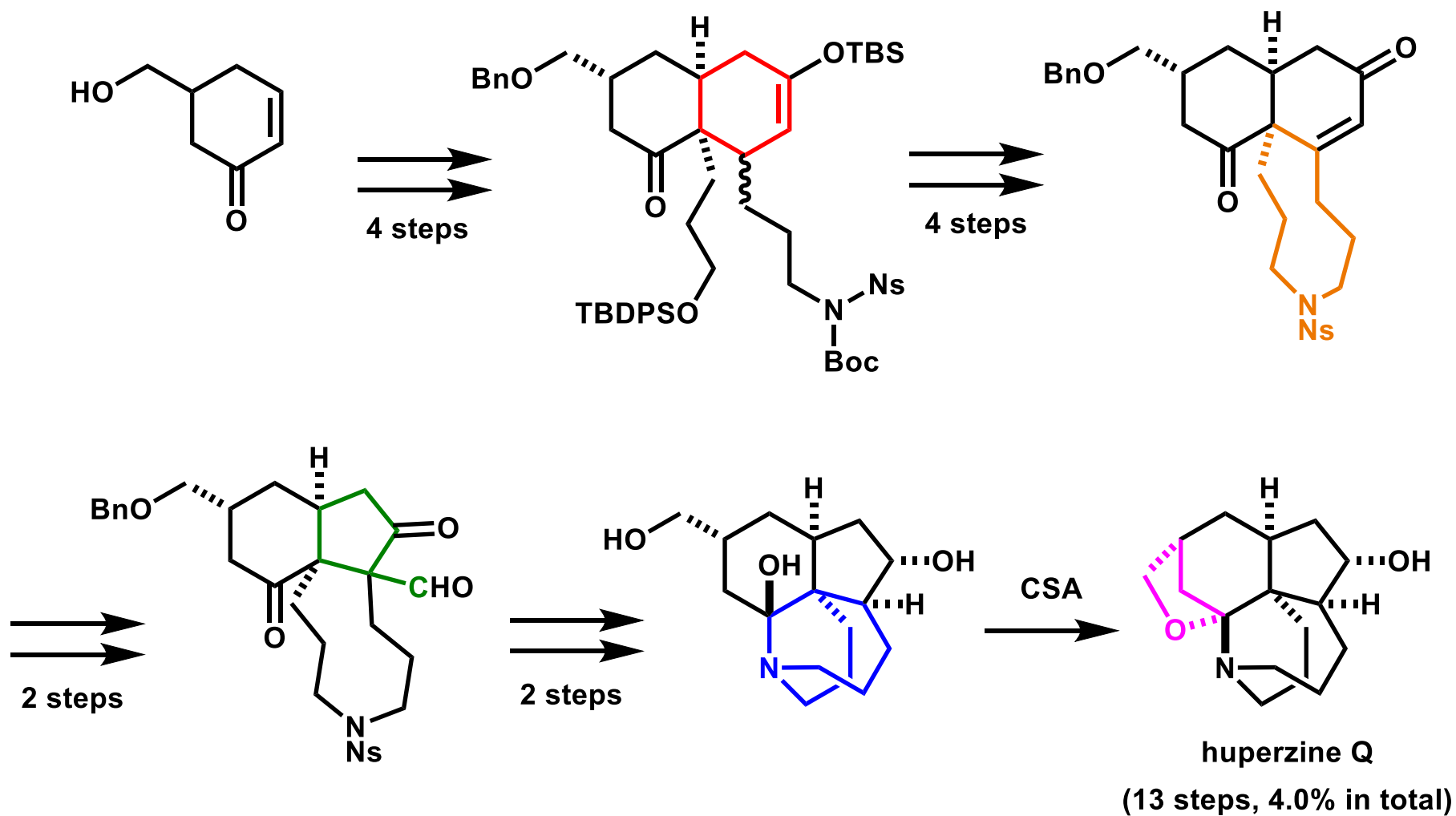
Fukuyama's synthesis



Fukuyama's synthesis

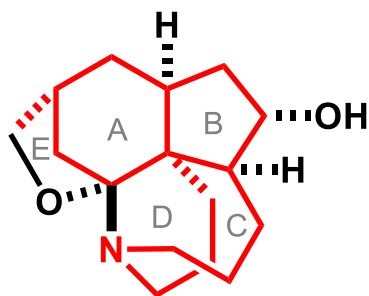


Fukuyama's synthesis

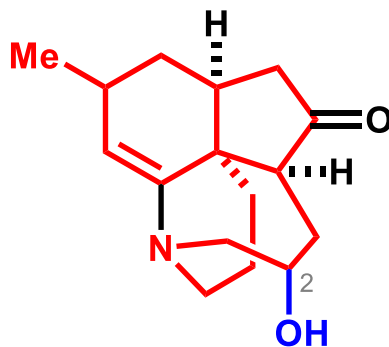


Summary

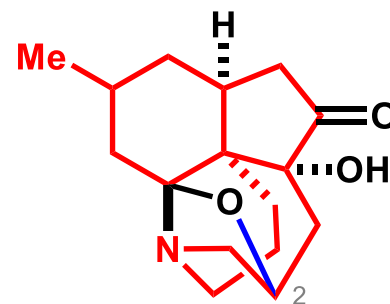
	steps	yield	stereochemistry	contraction of B-ring
Takayama's synthesis	19	16.4	asymmetry	Pauson-Khand
Lei's synthesis	12	2.2	asymmetry	carbonyl-olefin metathesis
Fukuyama's synthesis	13	4.0	racemate	Diels-Alder and ring-contraction



huperzine Q



huperzine I



huperzine S

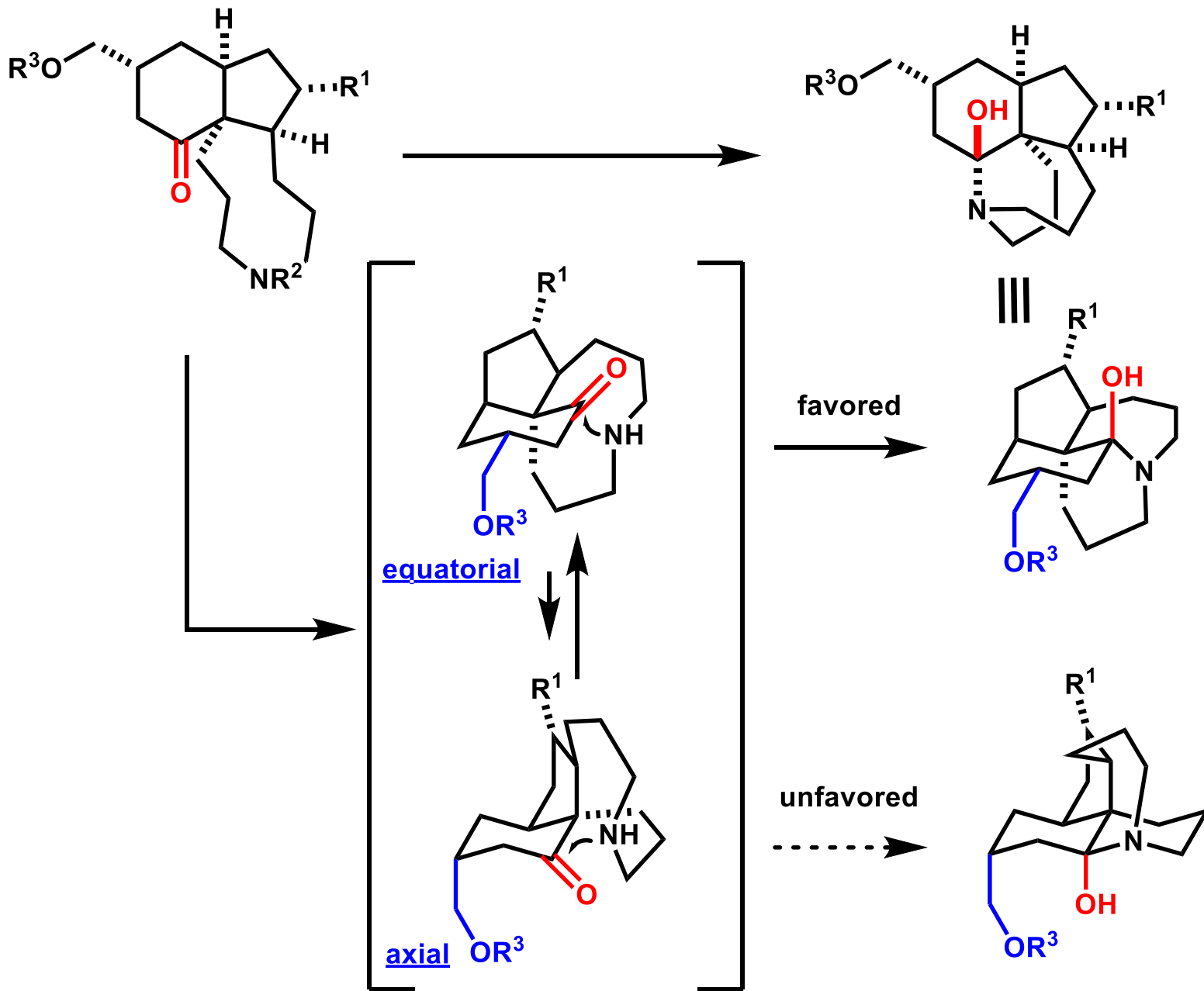
Takayama et al. *Angew. Chem. Int. Ed.* **2011**, *50*, 8025.

Lei et al. *Angew. Chem. Int. Ed.* **2015**, *54*, 1011.

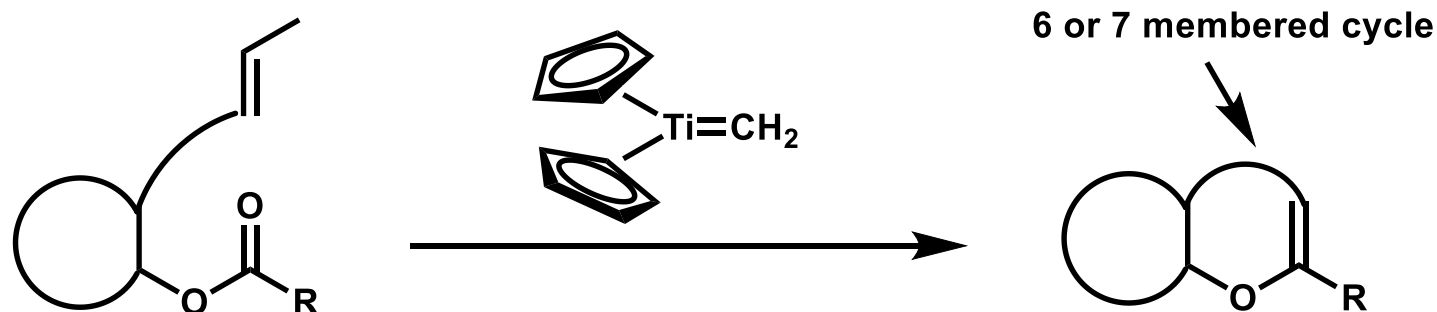
Fukuyama et al. *Org. Lett.* **2017**, *19*, 3684.

Appendix

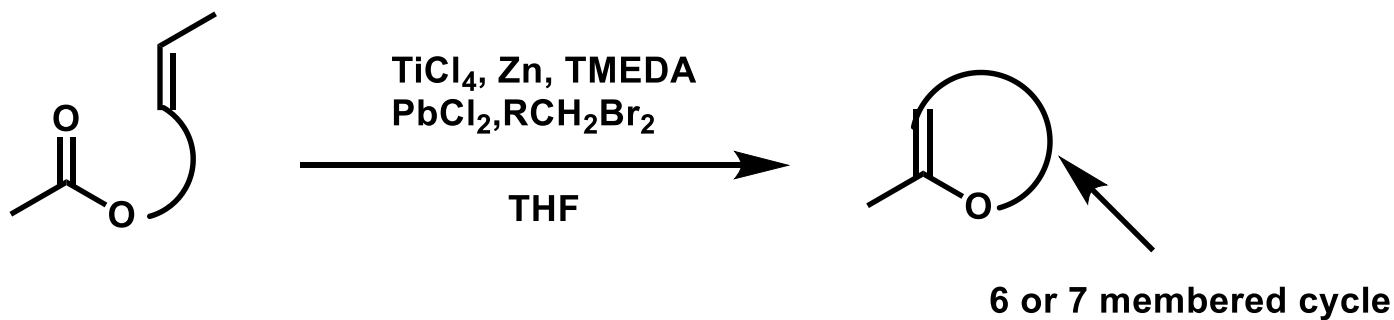
Stereoselectivity of hemiaminal



Another example of carbonyl olefin metathesis



K. C. Nicolaou, M. H. D. Postema, C. F. Claiborne, *J. Am. Chem. Soc.* **1996**, *118*, 1565.



K. Iyer, J. D. Rainier, *J. Am. Chem. Soc.* **2007**, *129*, 12604.