

Asymmetric Total Synthesis of Norzoanthamine

**2022_06_18
Literature session
D1 Yuyan Liang**

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2. Seminal Research

2.1 Total Synthesis of Norzoanthamine

(By Miyashita Group, 2004)

2.2 Total Synthesis of (-)-Norzoanthamine

(By Kobayashi Group, 2009)

3. Asymmetric Total Synthesis of Norzoanthamine

(By Gao Group, 2021)

4. Summary

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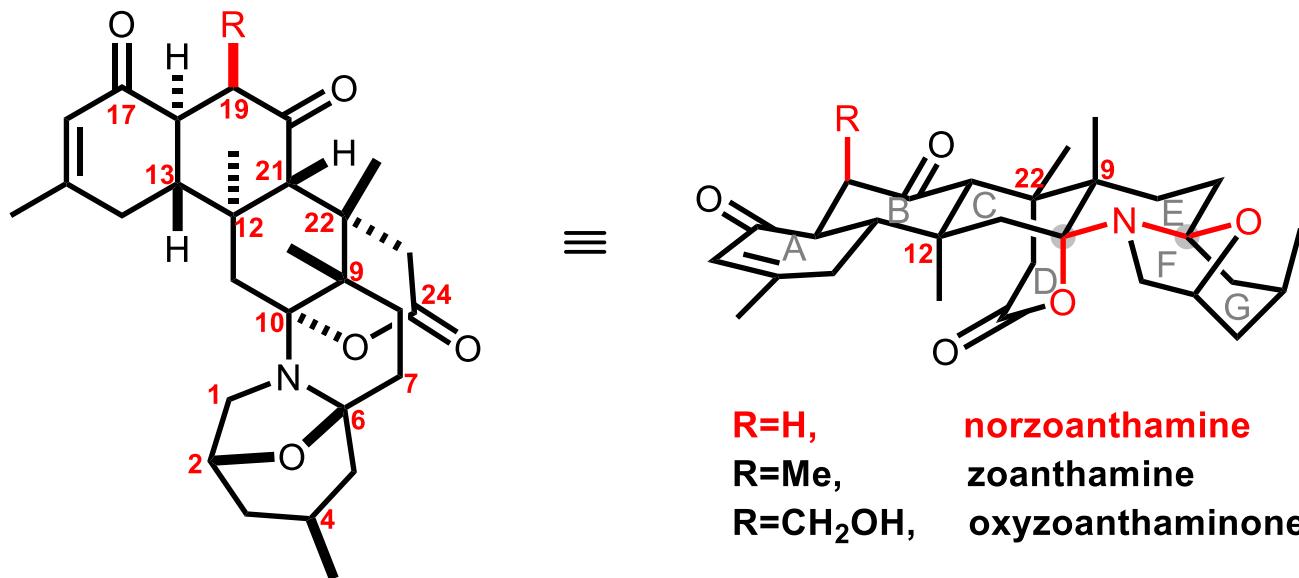
2.2 Total Synthesis of (-)-Norzoanthamine
(By Kobayashi Group, 2009)

3. Asymmetric Total Synthesis of Norzoanthamine

(By Gao Group, 2021)

4. Summary

Marine Alkaloid——Norzoanthamine



Isolation

from a Zoanthus species off the Ayamaru coast
of the Amami Islands south of Japan.
(1995, Uemura et al.)

Structural features

a trans-decaline motif in the AB rings;
a stereochemically dense C ring;
a bisaminal skeleton in the DEFG ring moiety.

Biological activity

suppress the loss of bone weight and strength in
ovariectomized mice;
a promising candidate for an antiosteoporotic drug.

Asymmetric Total Synthesis of Nozoanthamine:

Miyashita Group (2004)²⁾

Kobayashi Group (2009)²⁾

Gao Group (2021)

1) Fukuzawa, S.; Hayashi, Y.; Uemura, D.; Nagatsu, A.; Yamada, K.; Ijuin, Y. *Heterocycl. Commun.* **1995**, 1, 207.

2) 131214_PS_Hiroyuki_MUTOH_Total_Synthesis_of_Norzoanthamine

Overview of Strategies toward Synthetic Challenges

1) Stereoselective synthesis of the trans-anti-trans-fused ABC carbon skeleton

Miyashita Group

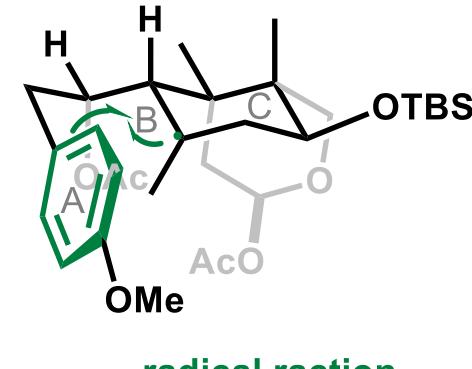
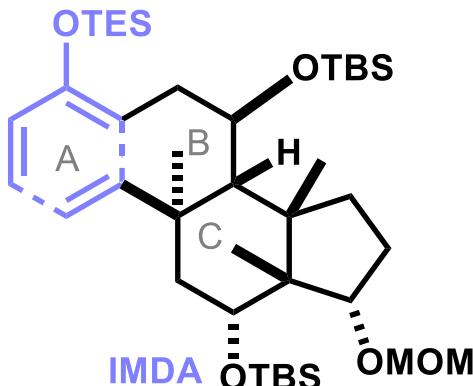
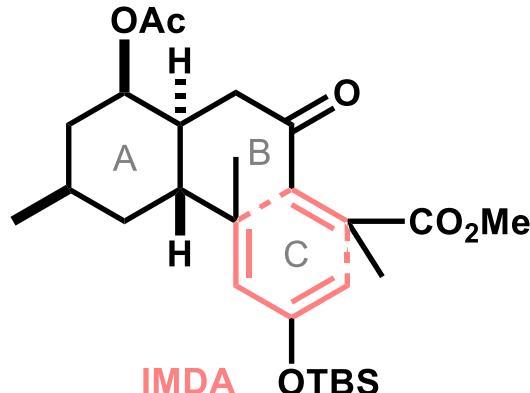
Kobayashi Group

Gao Group

intramolecular Diels-Alder (IMDA) (C ring)

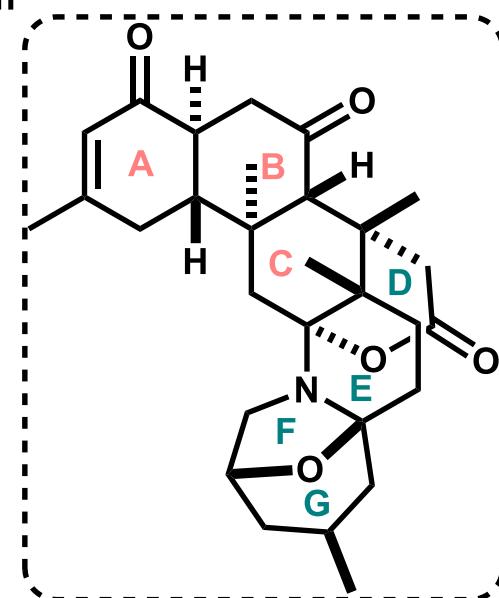
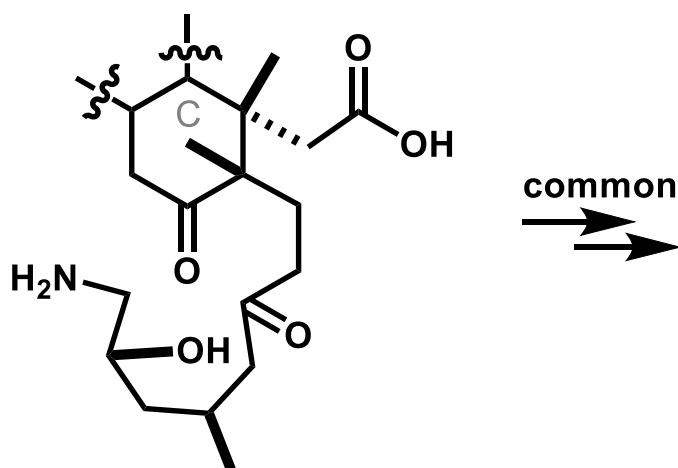
intramolecular Diels-Alder (IMDA) (A ring)

radical reactions

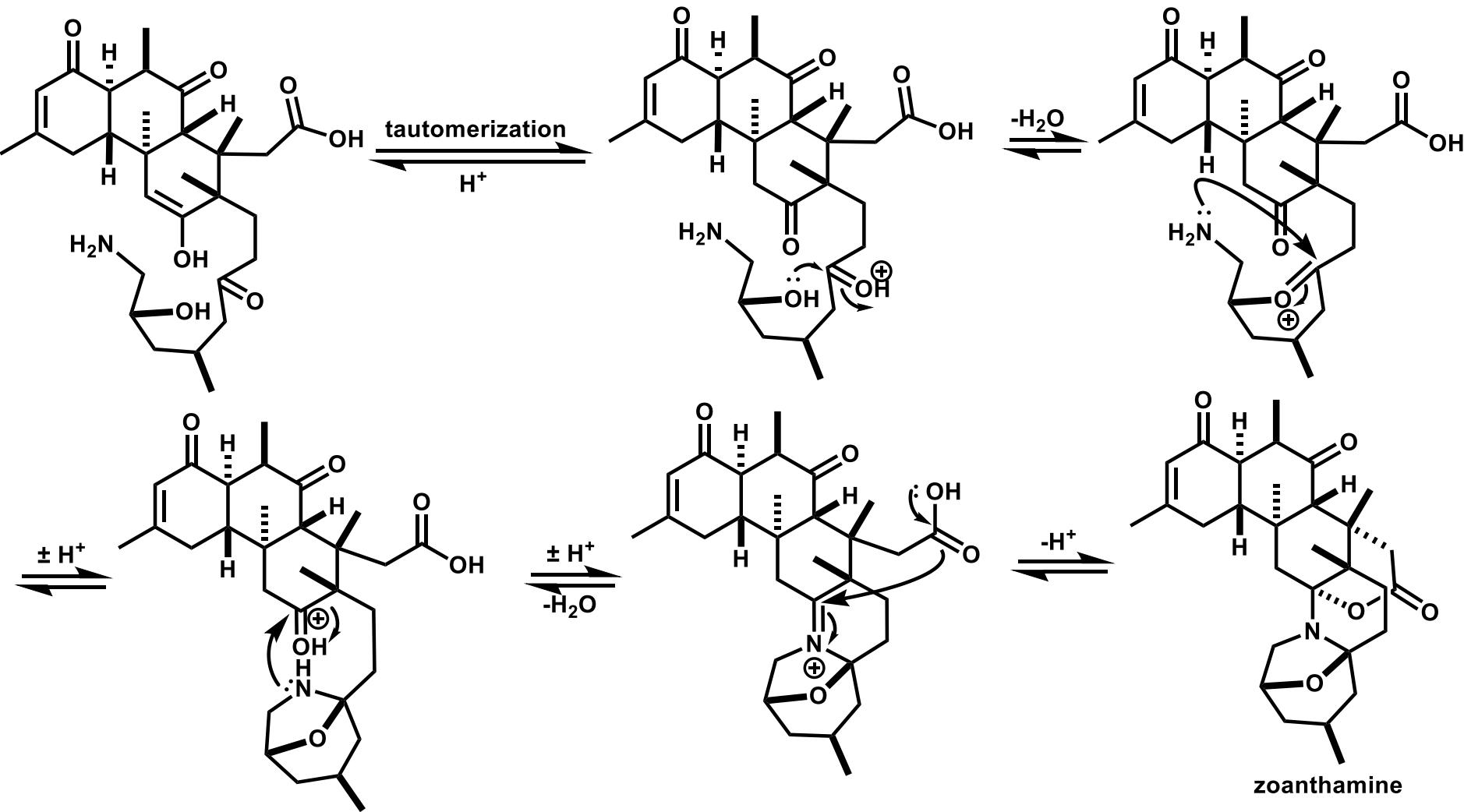


2) construction of bisaminal(DEFG ring) skeleton

late stage bioinspired bisaminal cyclization



Biosynthesis



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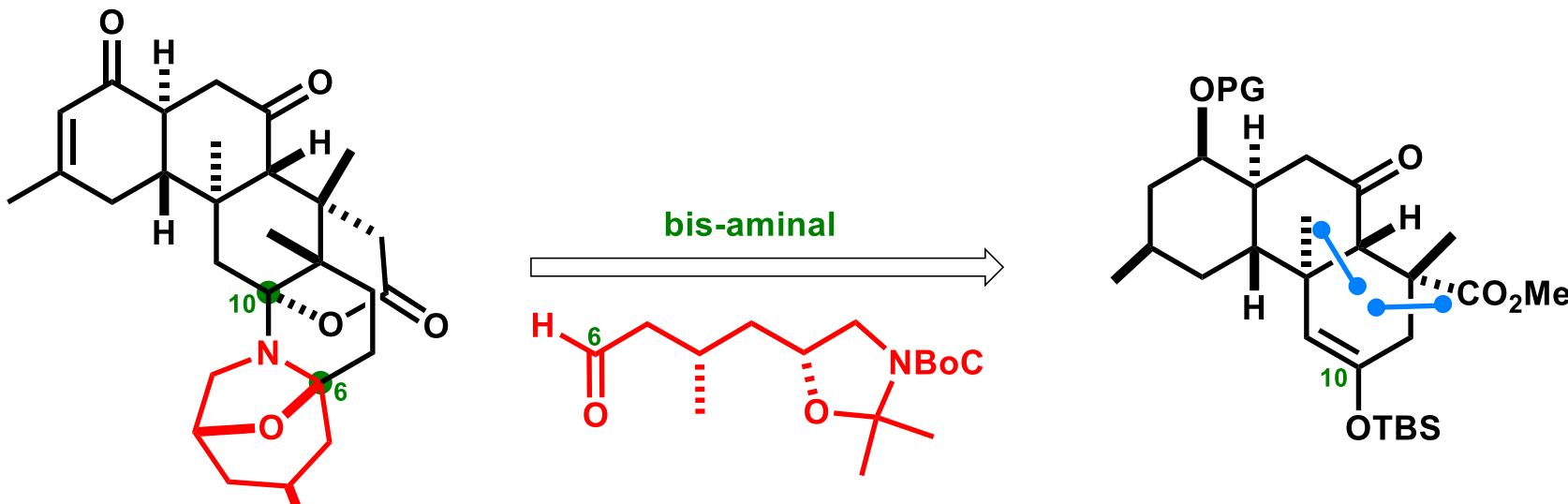
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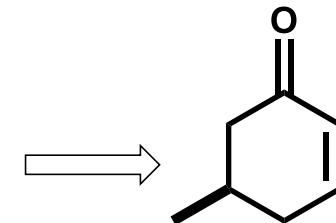
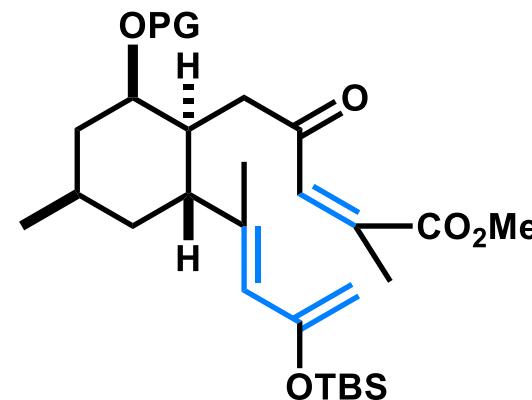
4. Summary

Retrosynthesis

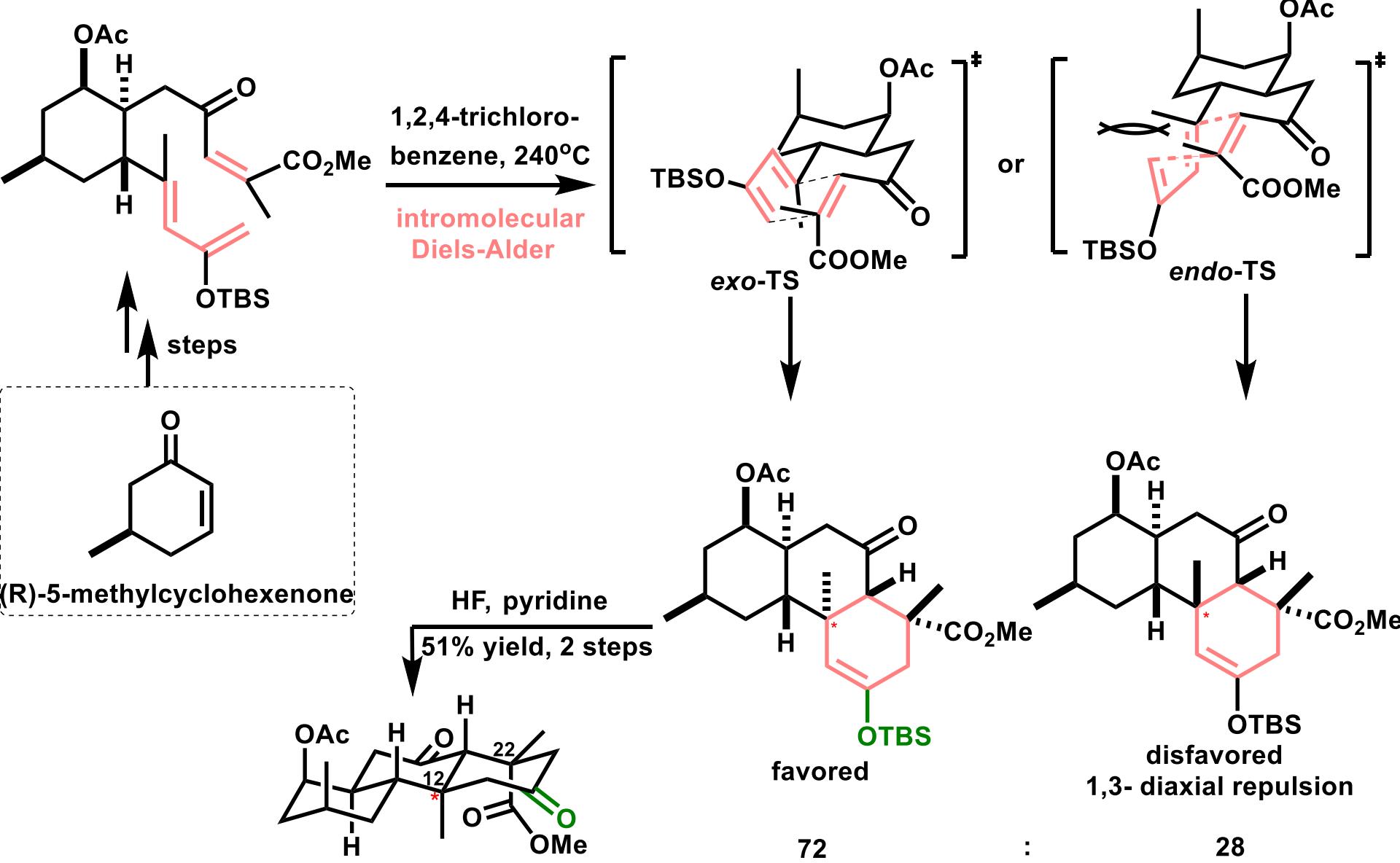


Norzoanthamine

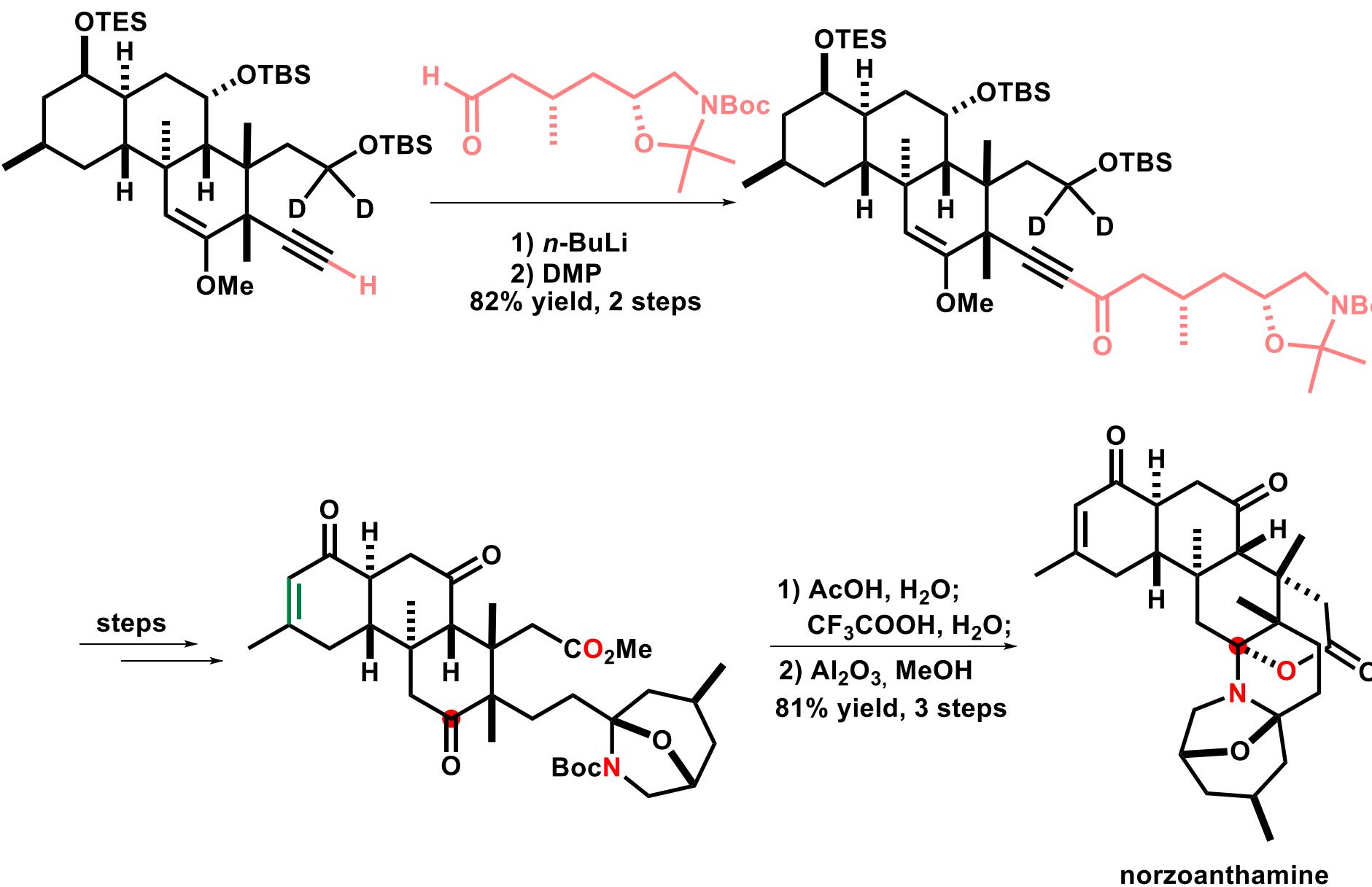
intramolecular Diels-Alder Reaction



Diastereoselectivity of IMDA Reaction



Construction of bisaminal skeleton in the DEFG ring



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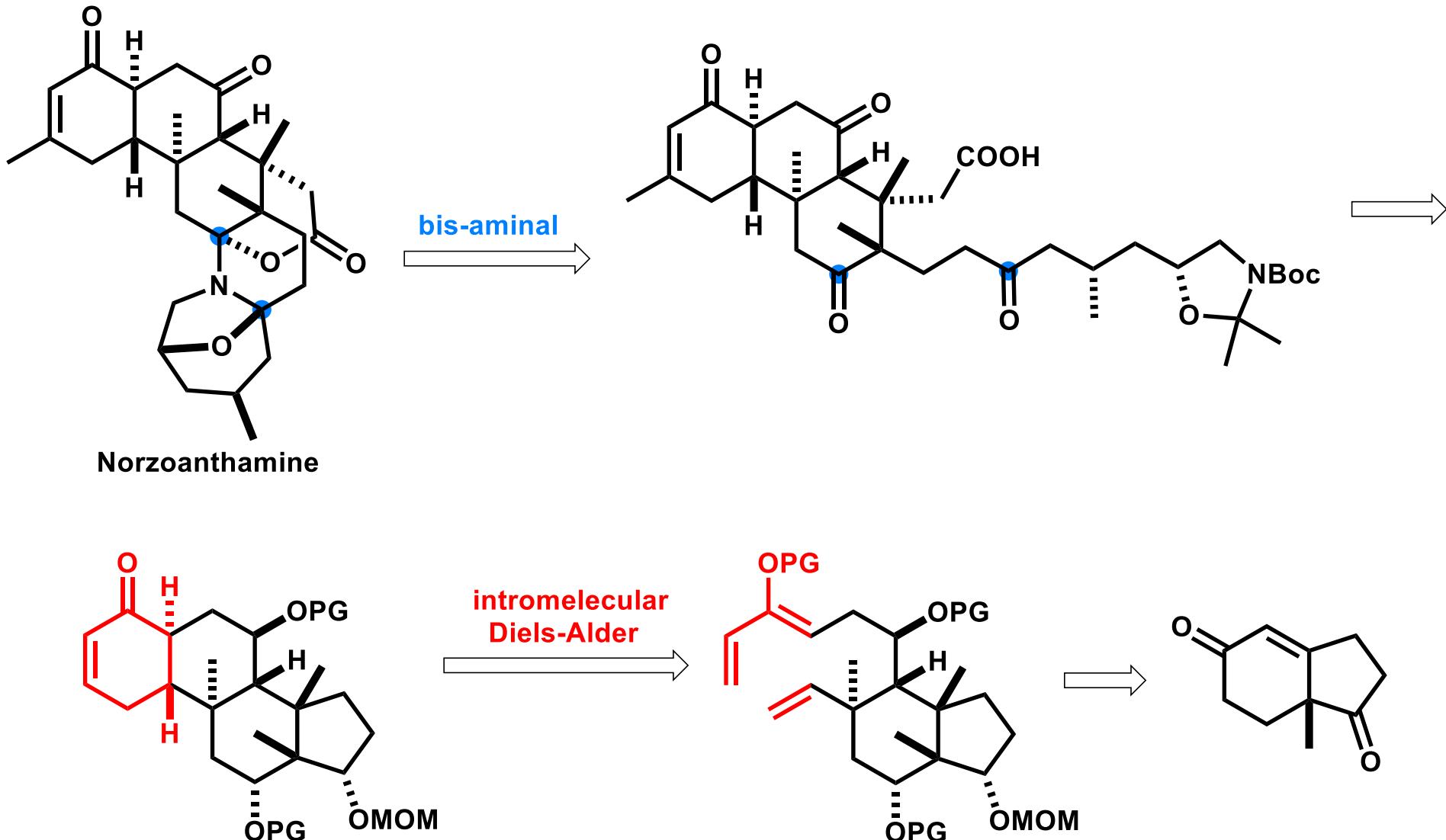
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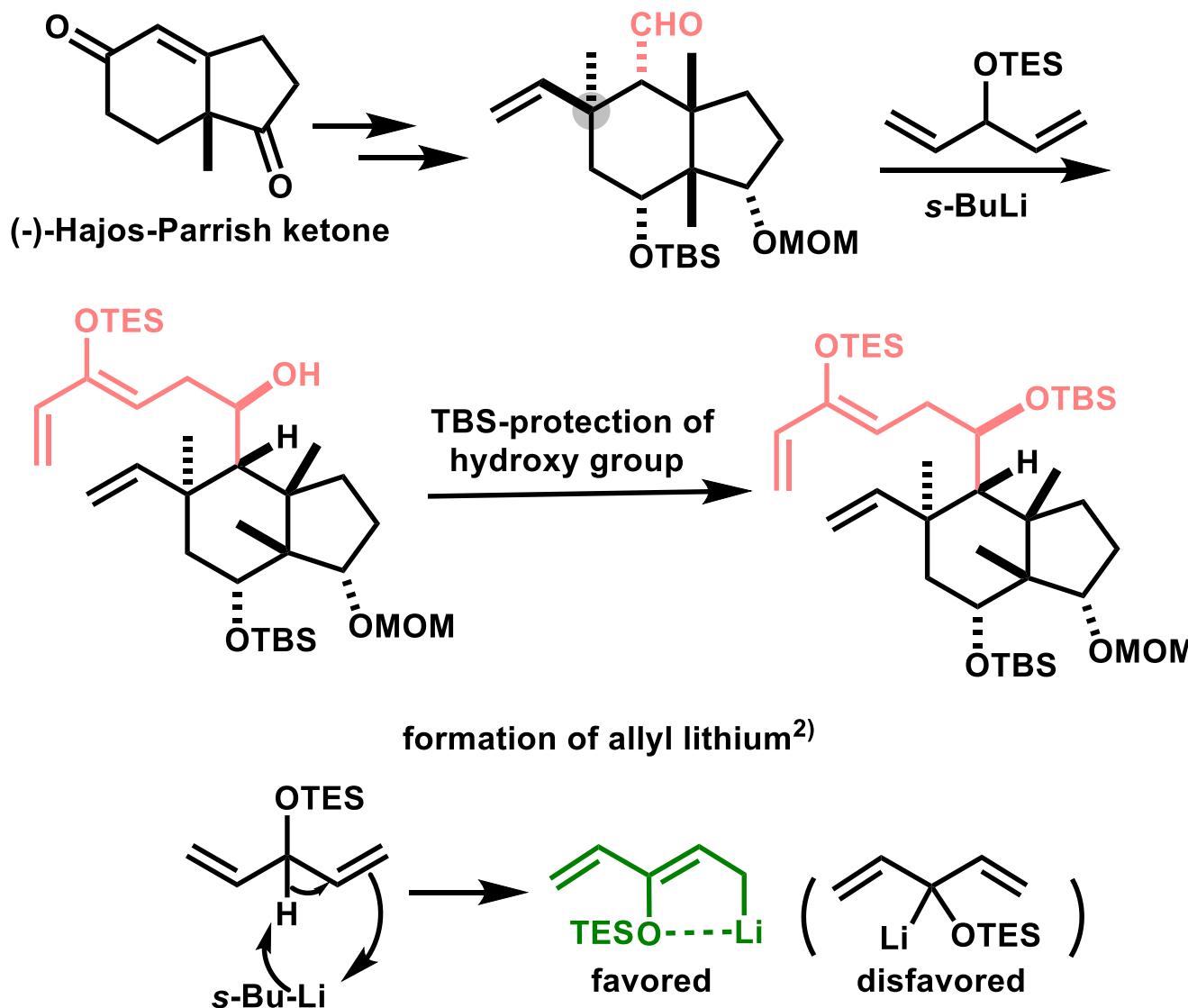
3. Asymmetric Total Synthesis of Norzoanthamine
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Retrosynthesis



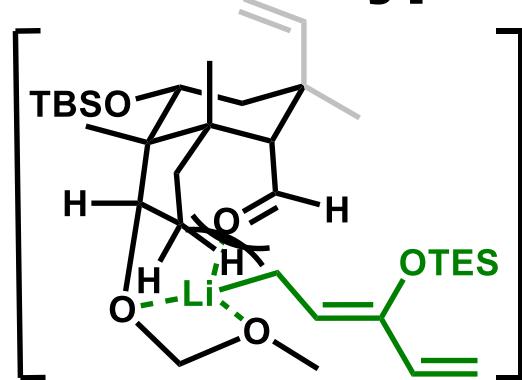
Construction of precursor—triene



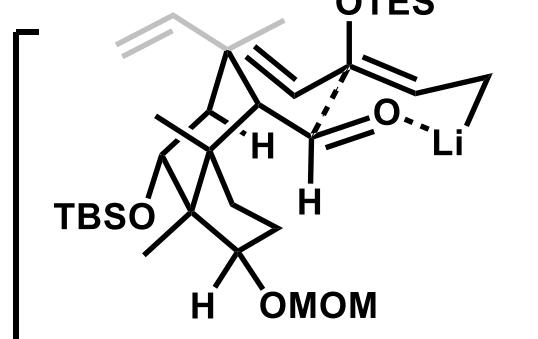
1) Murata, Y.; Yamashita, D.; Kitahara, K.; Minasako, Y.; Nakazaki, A.; Kobayashi, S. *Angew. Chem. Int. Ed.* 2009, 48, 1400

2) W. Clark Still; T. L. Macdonald. *J. Org. Chem.* 1976, 41, 3620

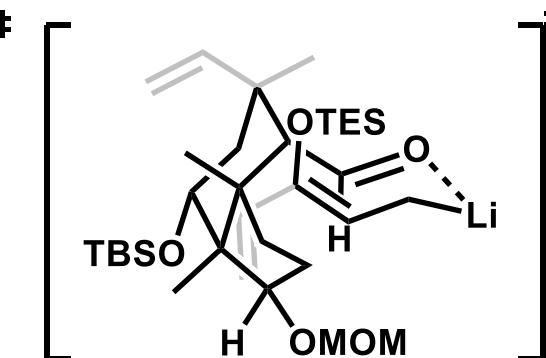
hypothesis of stereoselectivity



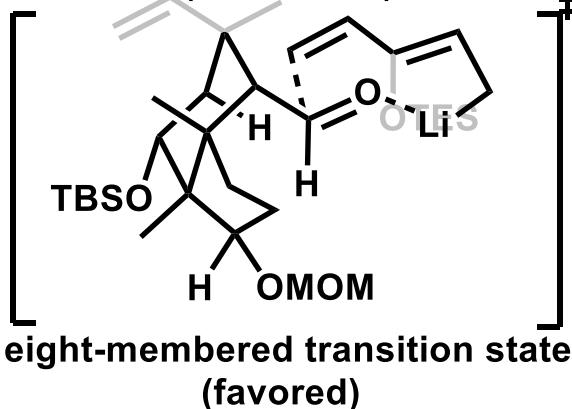
large steric repulsion between
aldehyde oxygen and hydrogen
on cyclopentane (disfavored)



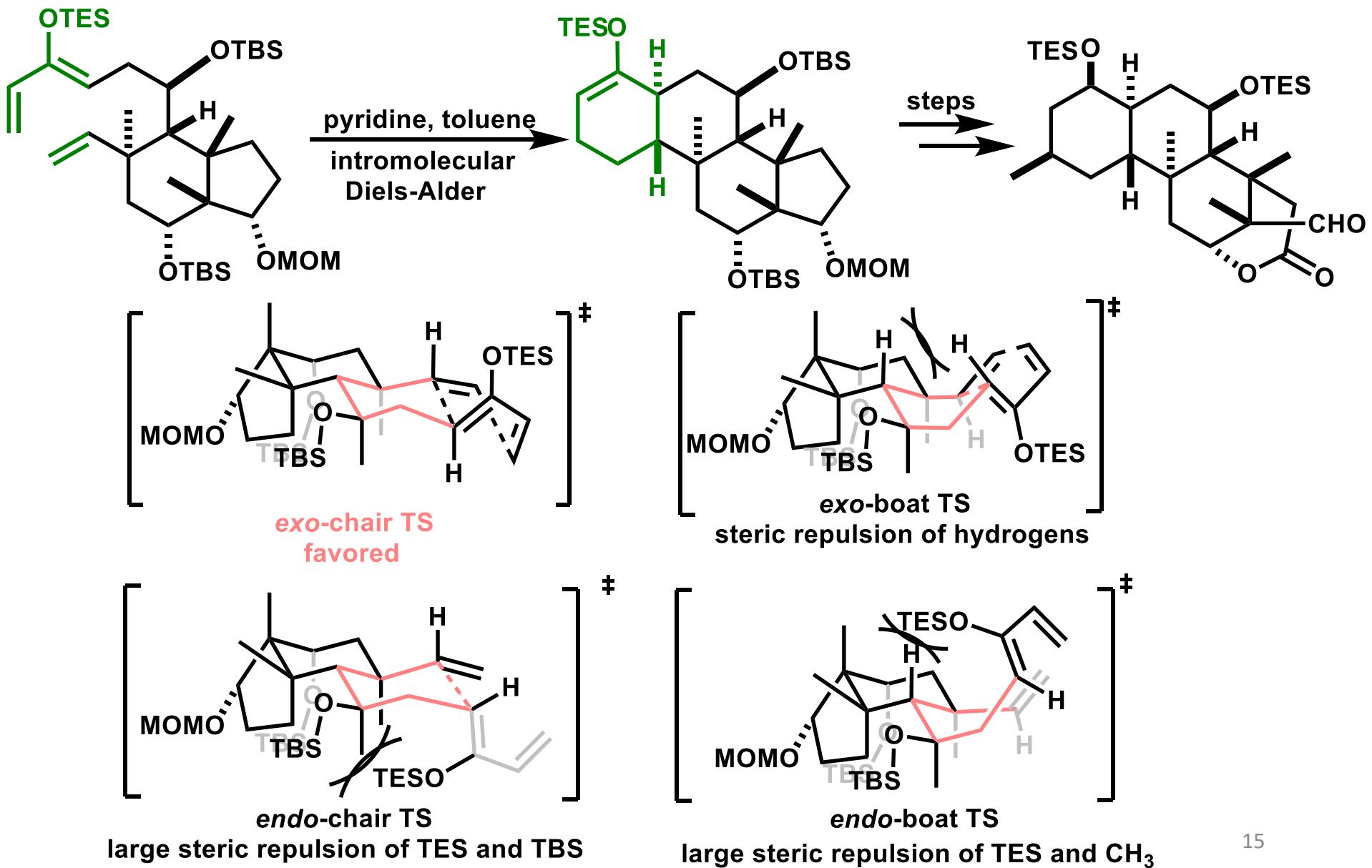
six-membered transition state
large steric hindrance on the react site
(disfavored)



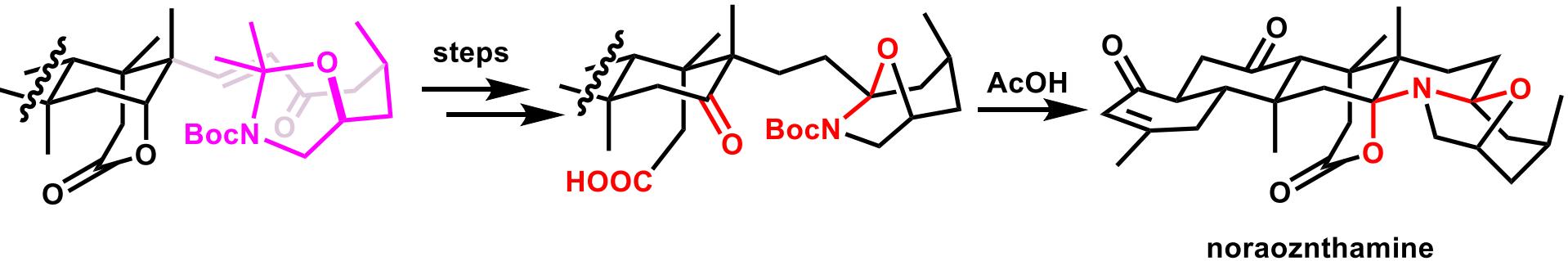
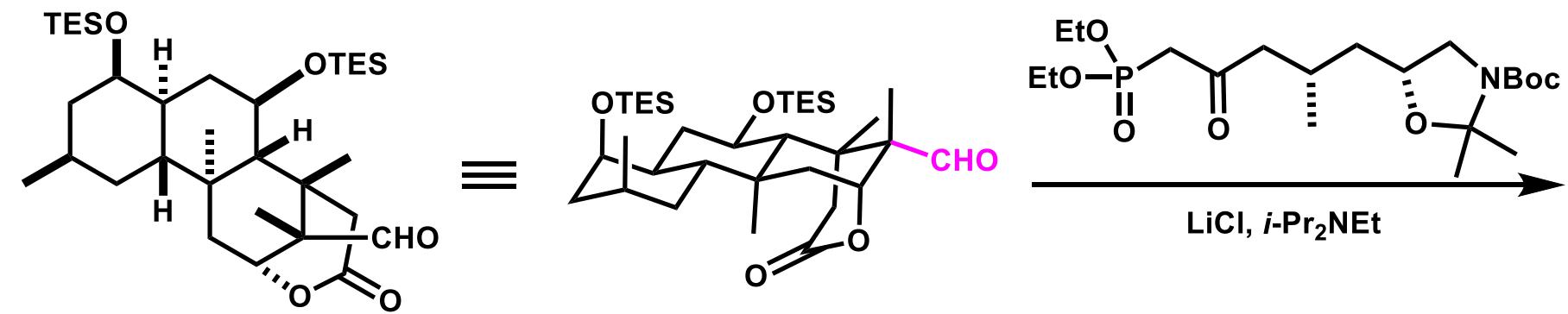
large steric repulsion exist if allyl
lithium species access the aldehyde
from concave face of bicyclic core
(disfavored)



Stereoselectivity of Intramolecular Diels-Alder Reaction



Construction of bisaminal skeleton in the DEFG ring



1) Yamashita, D.; Murata, Y.; Hikage, N.; Takao, K.-I.; Nakazaki, A.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2009**, 48, 1404.

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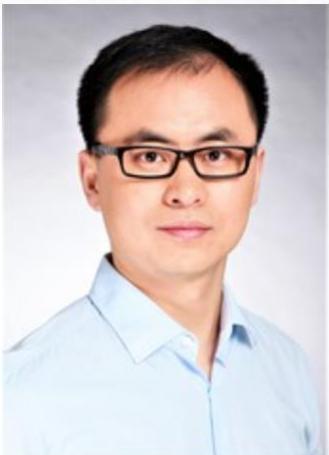
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Professor Gao Shuanhu

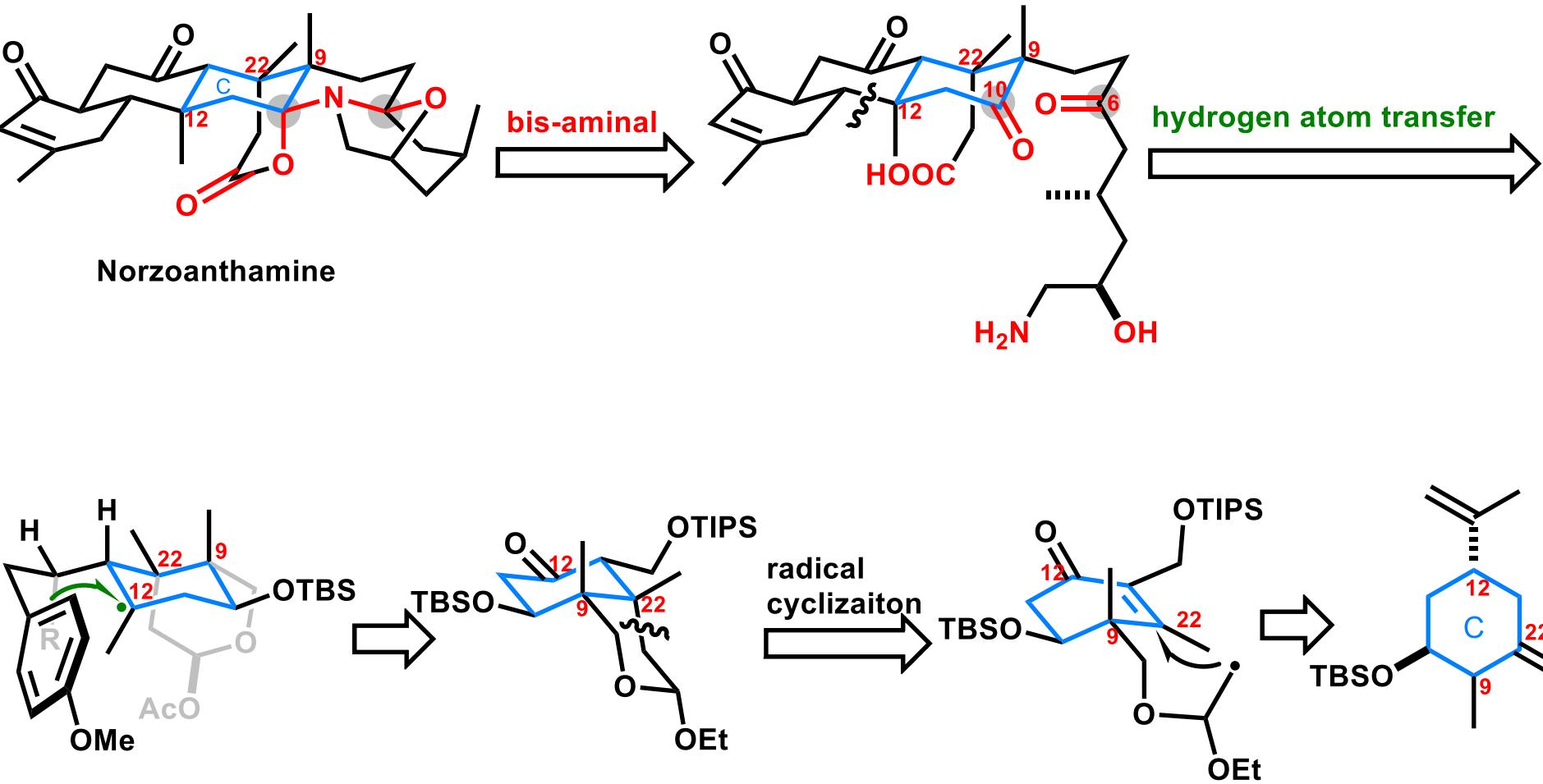


**1997-2001: B.S. Lanzhou University
2001-2006: Ph.D Lanzhou University (Supervisor: Prof. Yongqiang Tu)
2006-2010: Postdoctoral Department of Biochemistry, UT Southwestern Medical Center at Dallas
2010-present Professor, East China Normal University**

Research Topic:

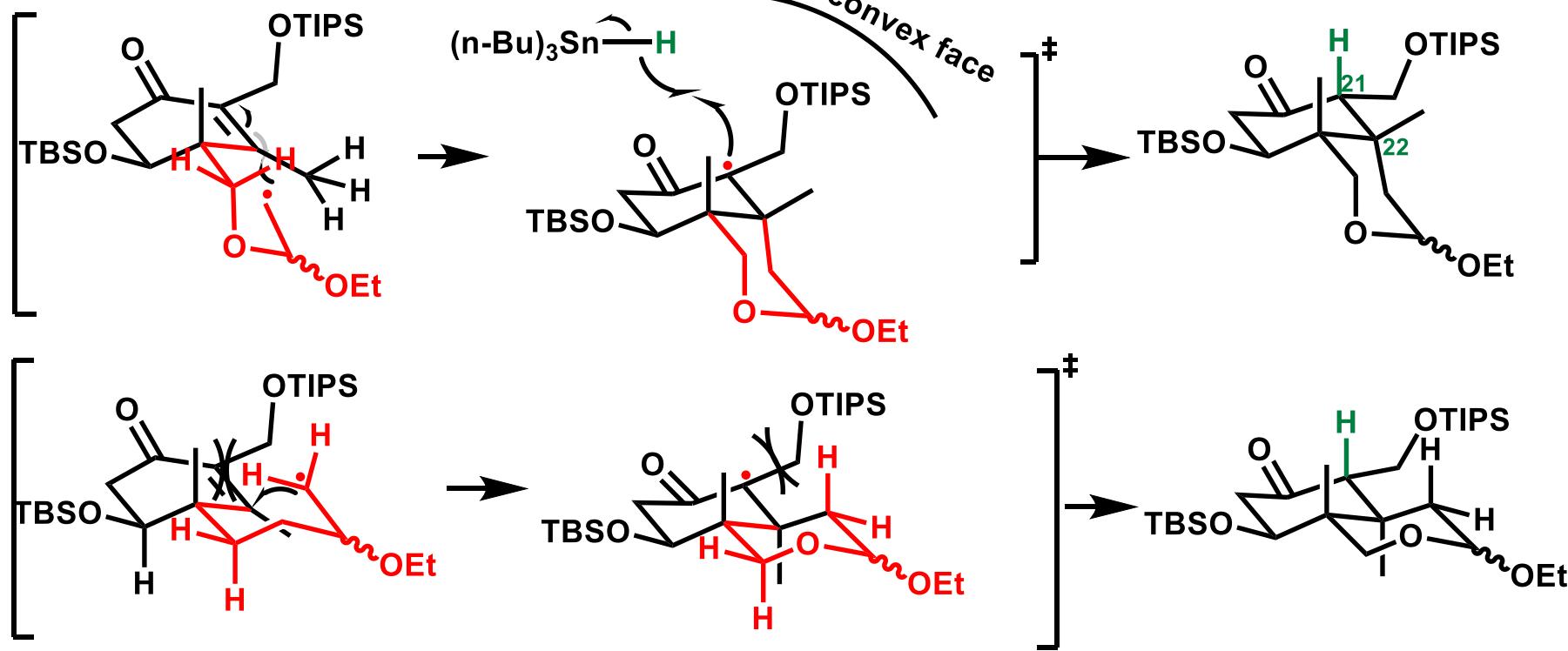
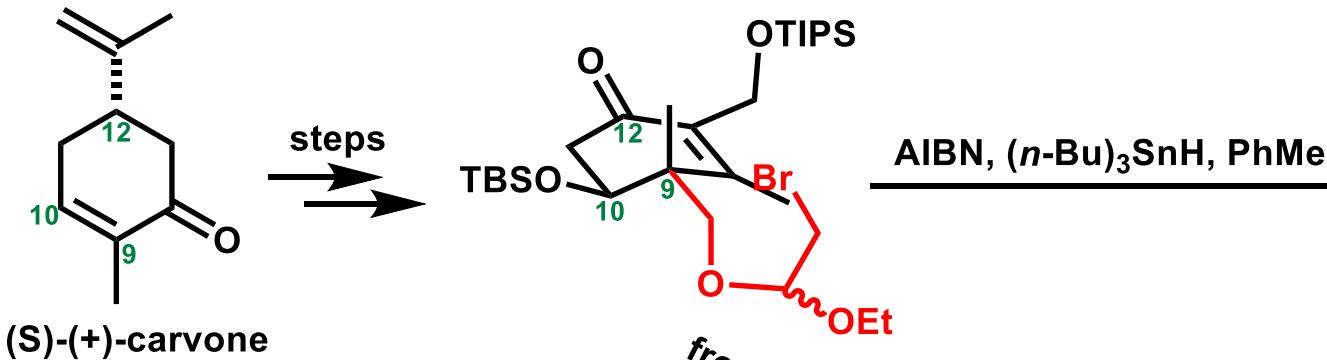
- 1) Bioactive natural products synthesis**
- 2) Useful synthetic methodology**
- 3) Medicinal chemistry and chemical biology**

Retrosynthesis



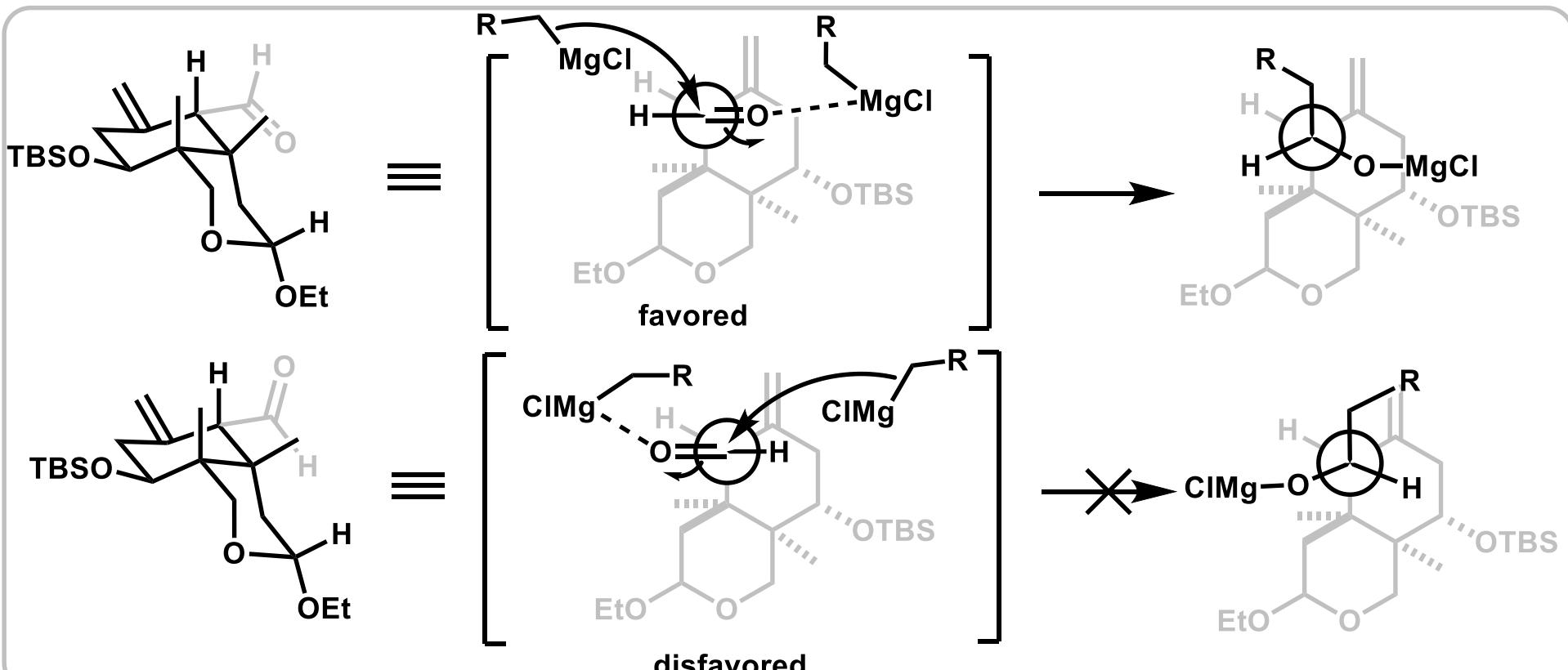
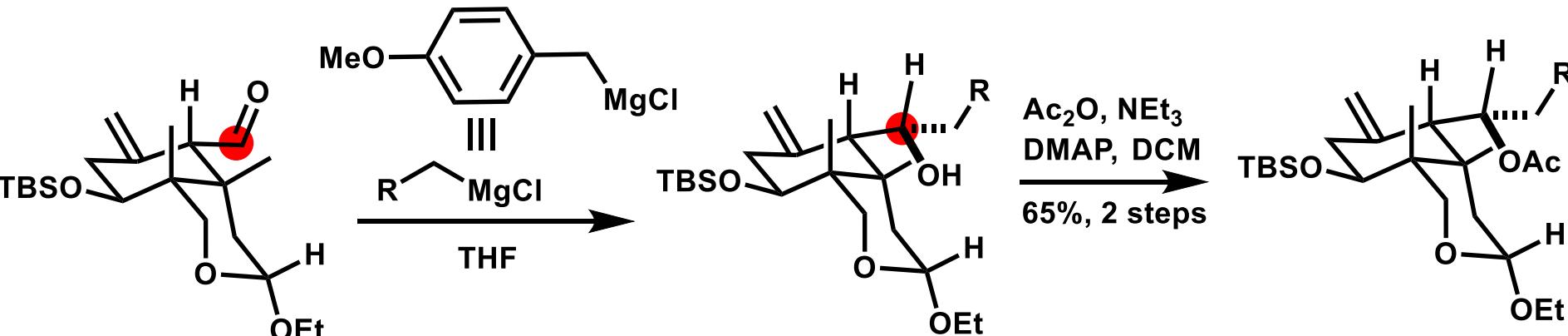
1) Zhengyuan Xin, Hui Wang, Haibing He, Xiaoli Zhao, and Shuanhu Gao. *Angew. Chem. Int. Ed.* **2021**, *60*, DOI: 10.1002/anie.202102643.

Decoration of C-ring Stereochemistry

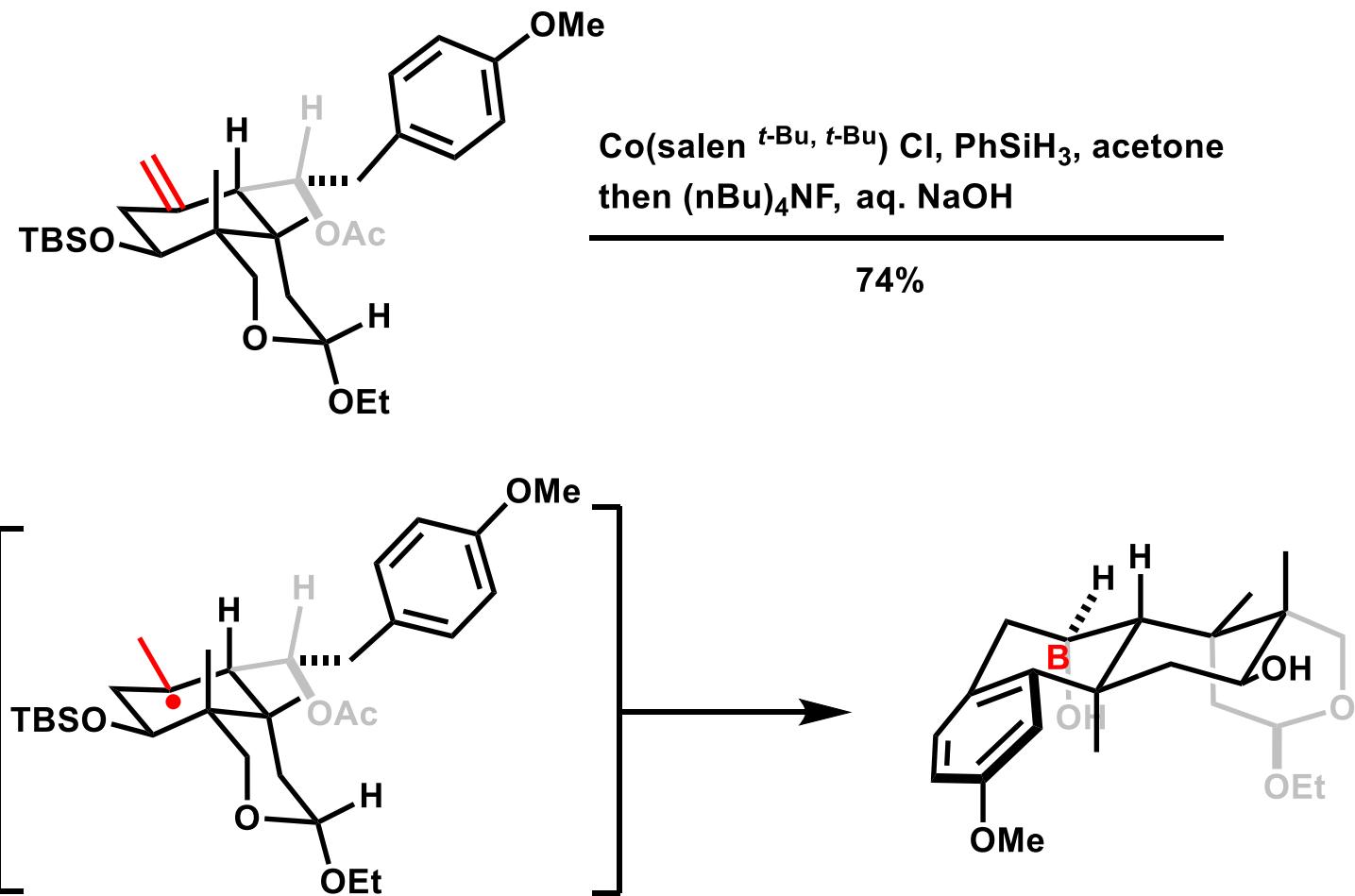


- 1) Zhengyuan Xin, Hui Wang, Haibing He, Xiaoli Zhao, and Shuanhu Gao. *Angew. Chem. Int. Ed.* 2021, 60, DOI: 10.1002/anie.202102643.
- 2) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* 1982, 104, 5564.

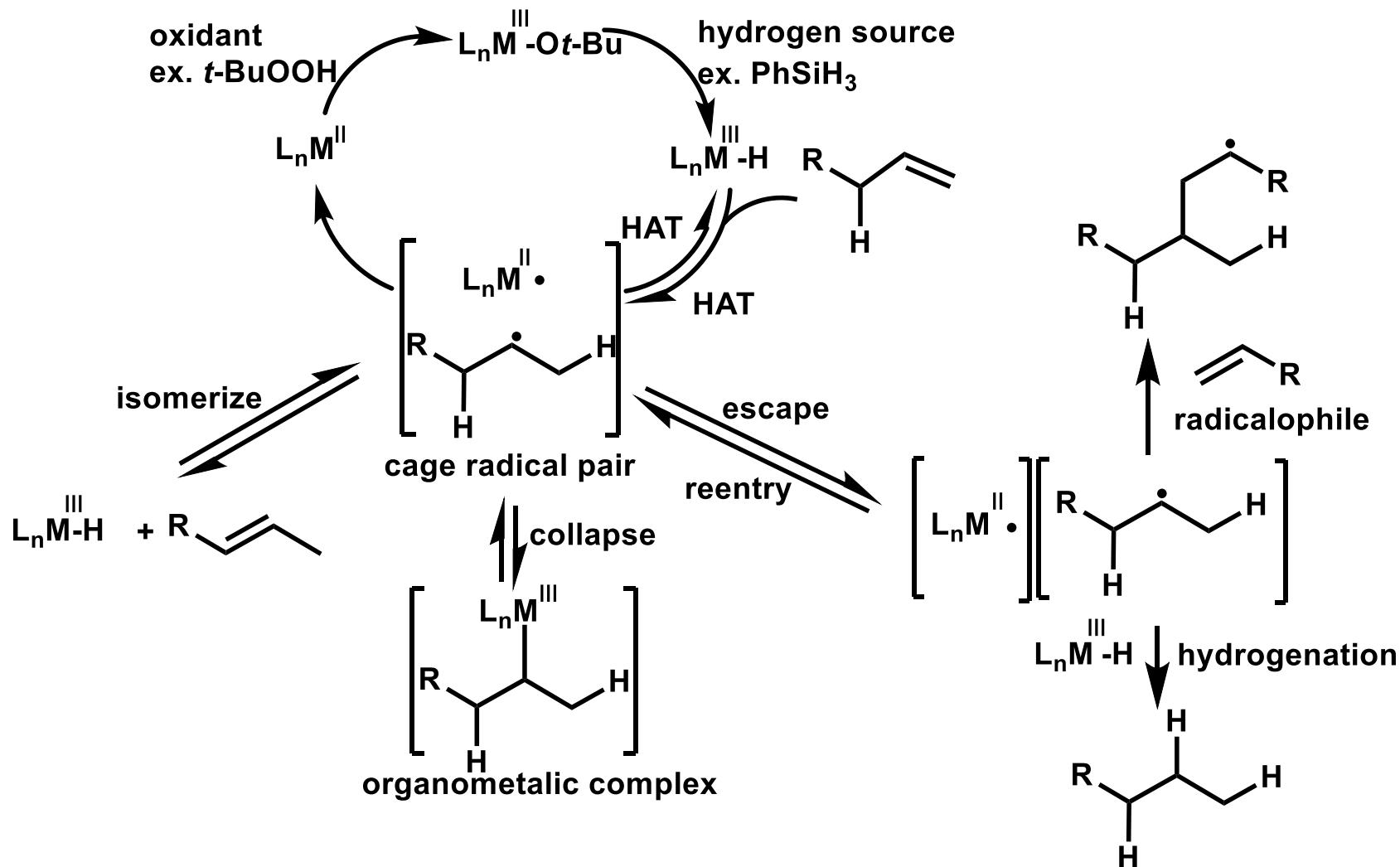
Diastereoselective Installation of Side Chain



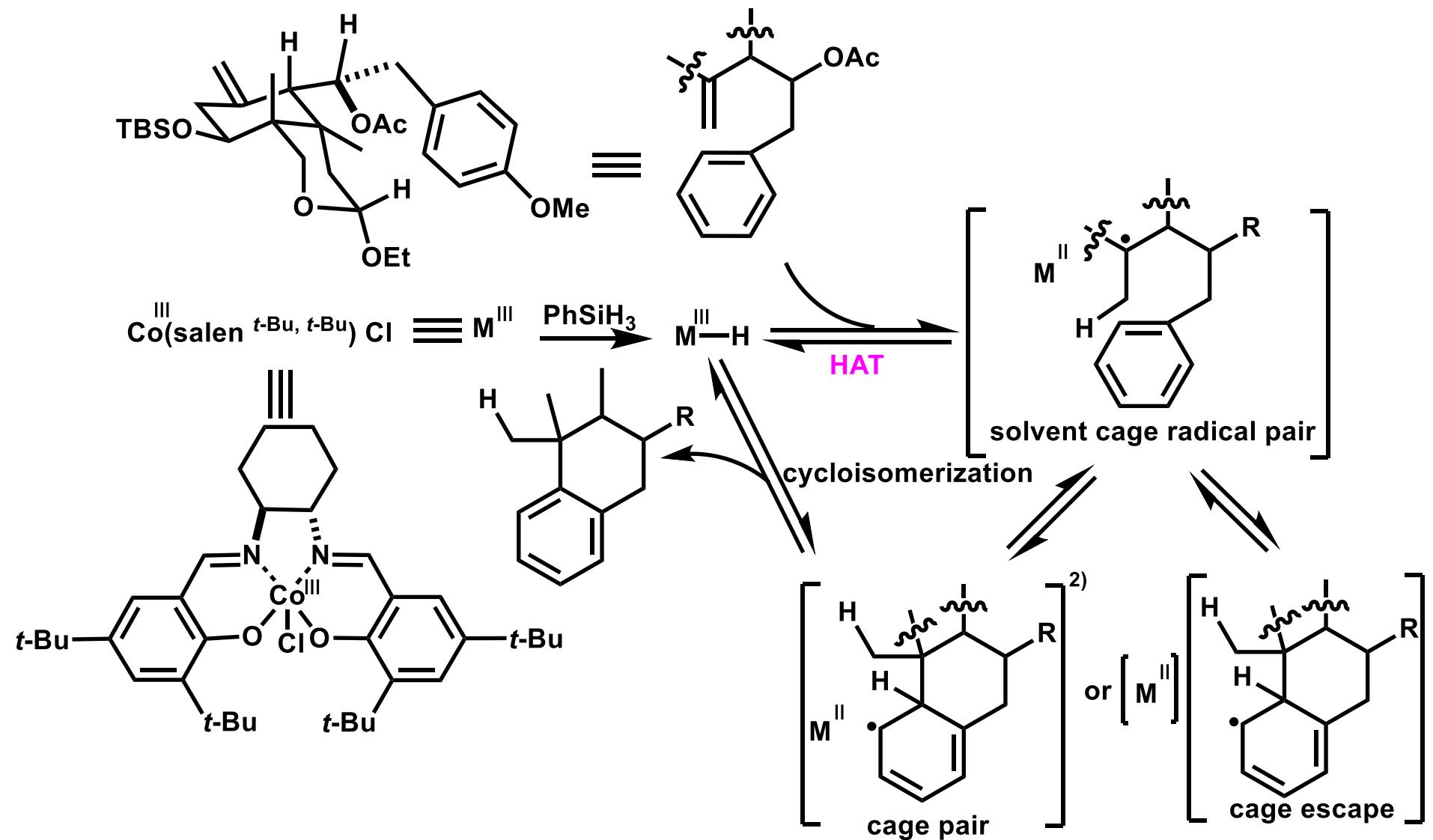
Construction of B ring——Hydrogen Atom Transfer



Metal Hydride Hydrogen Atom Transfer Reaction

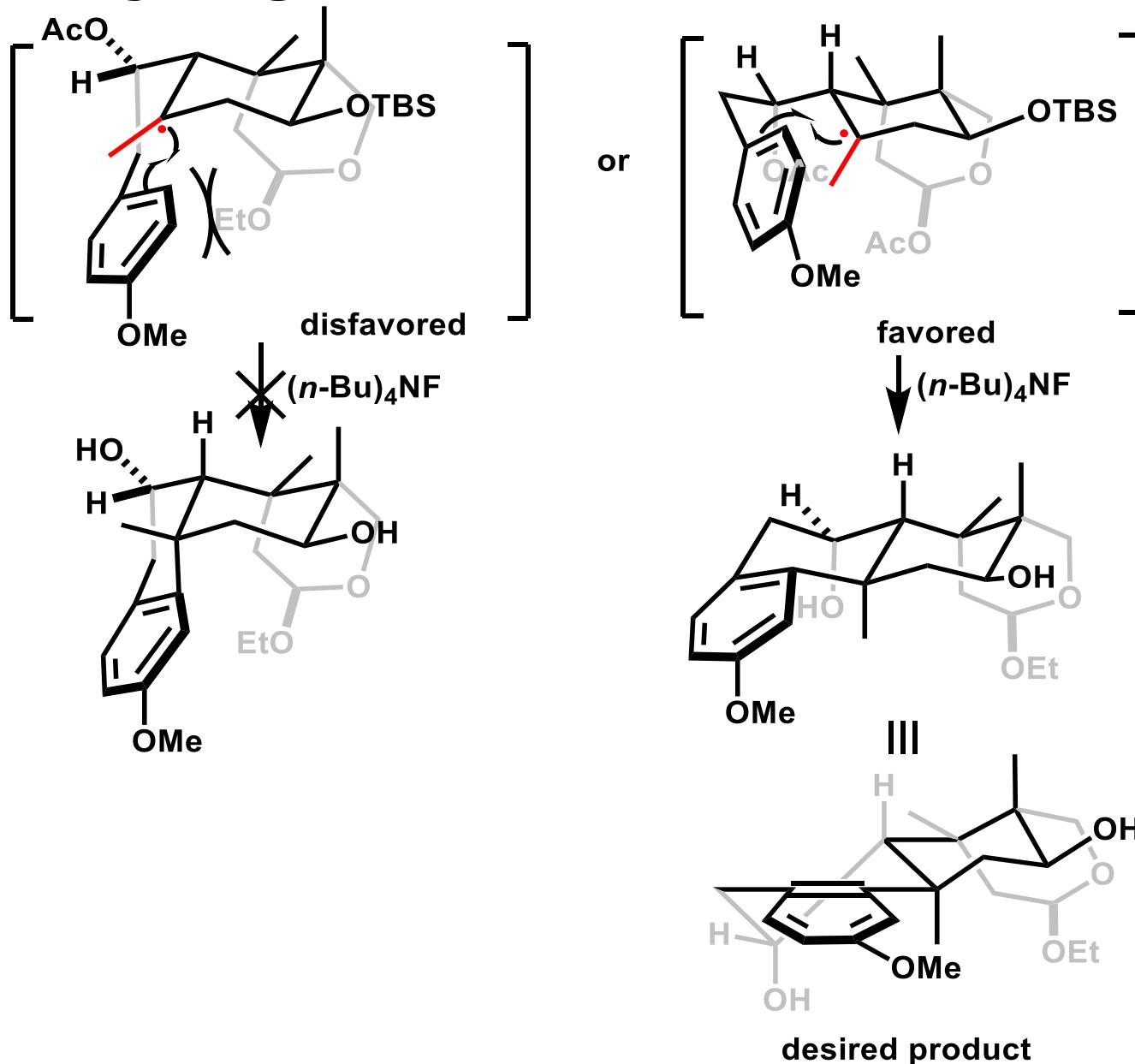


1) Sophia L. Shevick, Conner V. Wilson, Simona Kotesova, Dongyoung Kim, Patrick L. Holland, Ryan A. Shenvi. *Chem. Sci.*, **2020**, *11*, 12401.

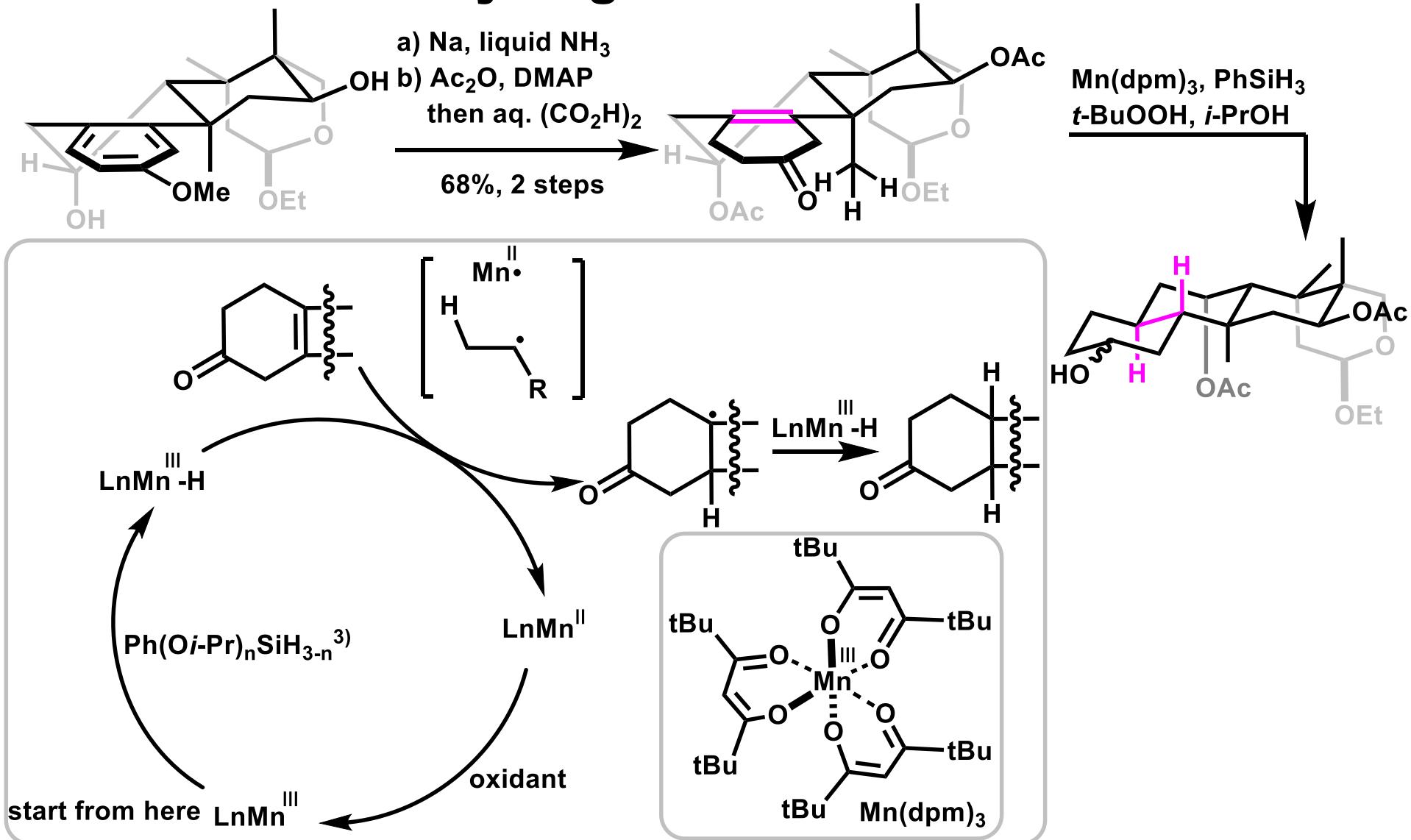


- 1) Sophia L. Shevick, Conner V. Wilson, Simona Kotesova, Dongyoung Kim, Patrick L. Holland, Ryan A. Shenvi. *Chem. Sci.*, **2020**, *11*, 12401.
- 2) Please refer to pendent slide

Stereoselectivity of Co-catalyzed Hydrogen Atom Transfer reaction



HAT Hydrogenation Reaction

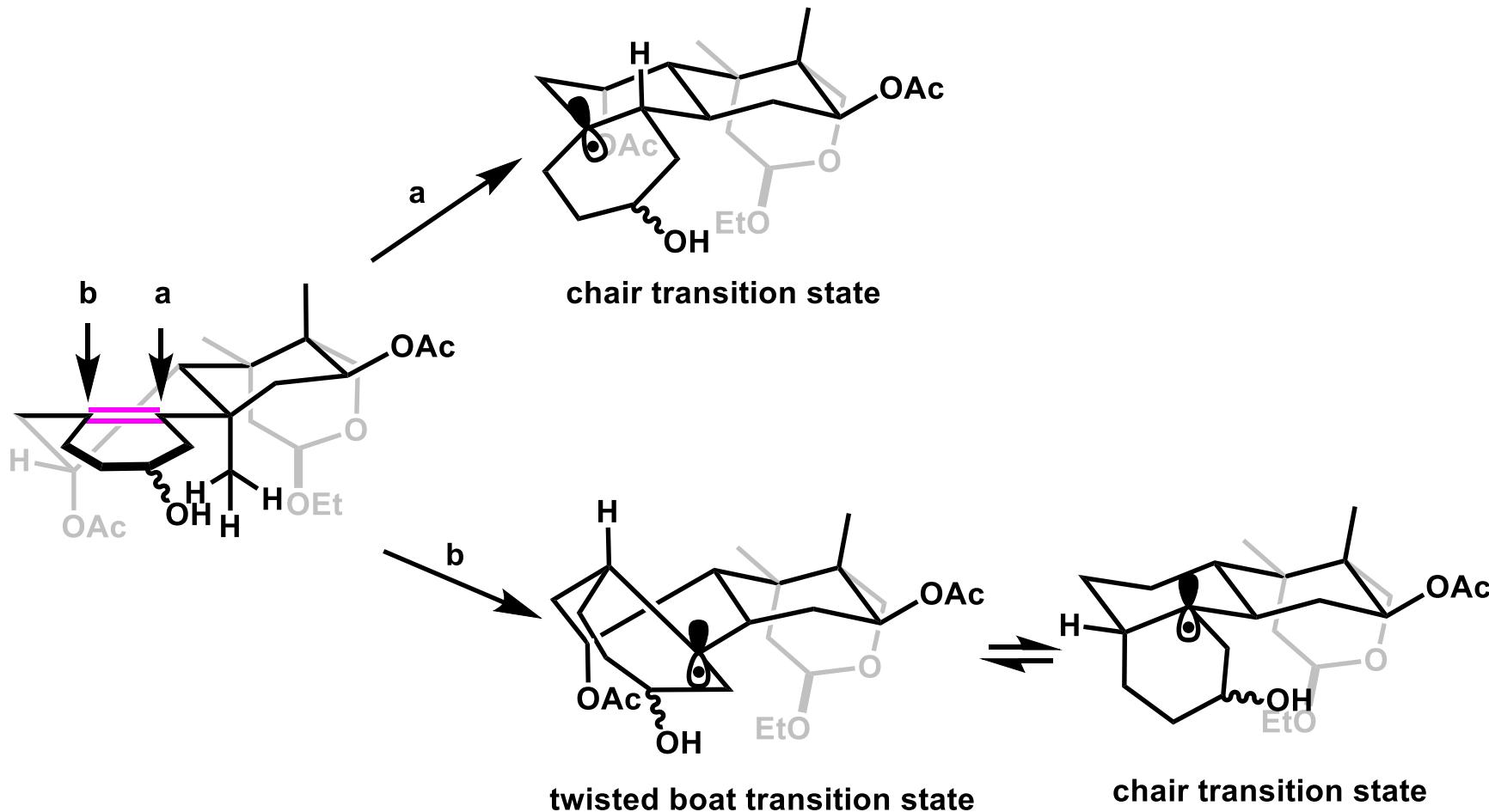


1) Zhengyuan Xin, Hui Wang, Haibing He, Xiaoli Zhao, and Shuanhu Gao. *Angew. Chem. Int. Ed.* **2021**, *60*, DOI: 10.1002/anie.202102643.

2) Steven W. M. Crossley, Carla Obradors, Ruben M. Martinez, Ryan A. Shenvi. *Chem. Rev.* **2016**, *116*, 8912.

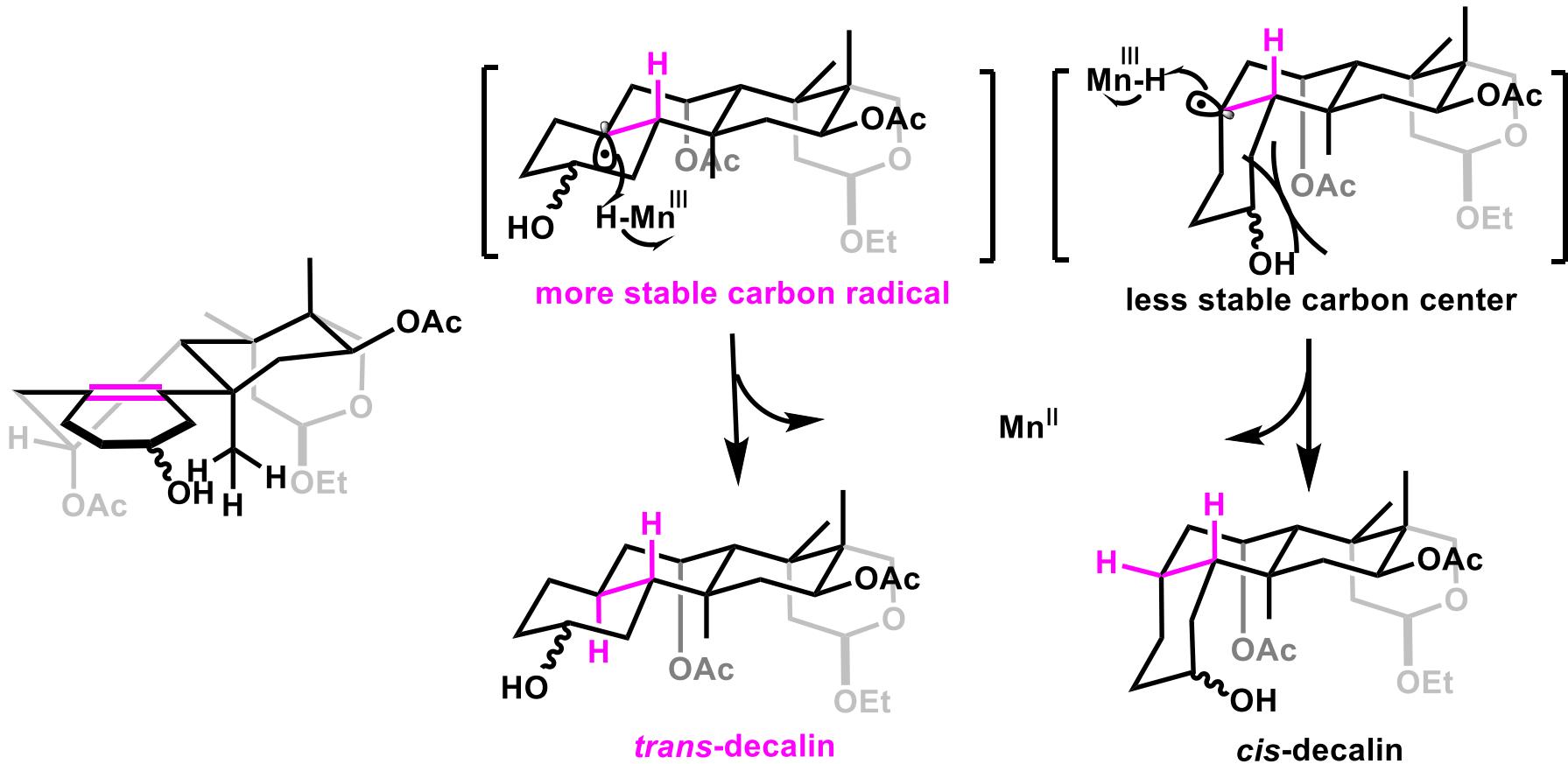
3) Carla Obradors; Ruben M. Martinez; Ryan A. Shenvi. *J. Am. Chem. Soc.* **2016**, *138*, 4962.

Stereoselectivity of HAT reaction



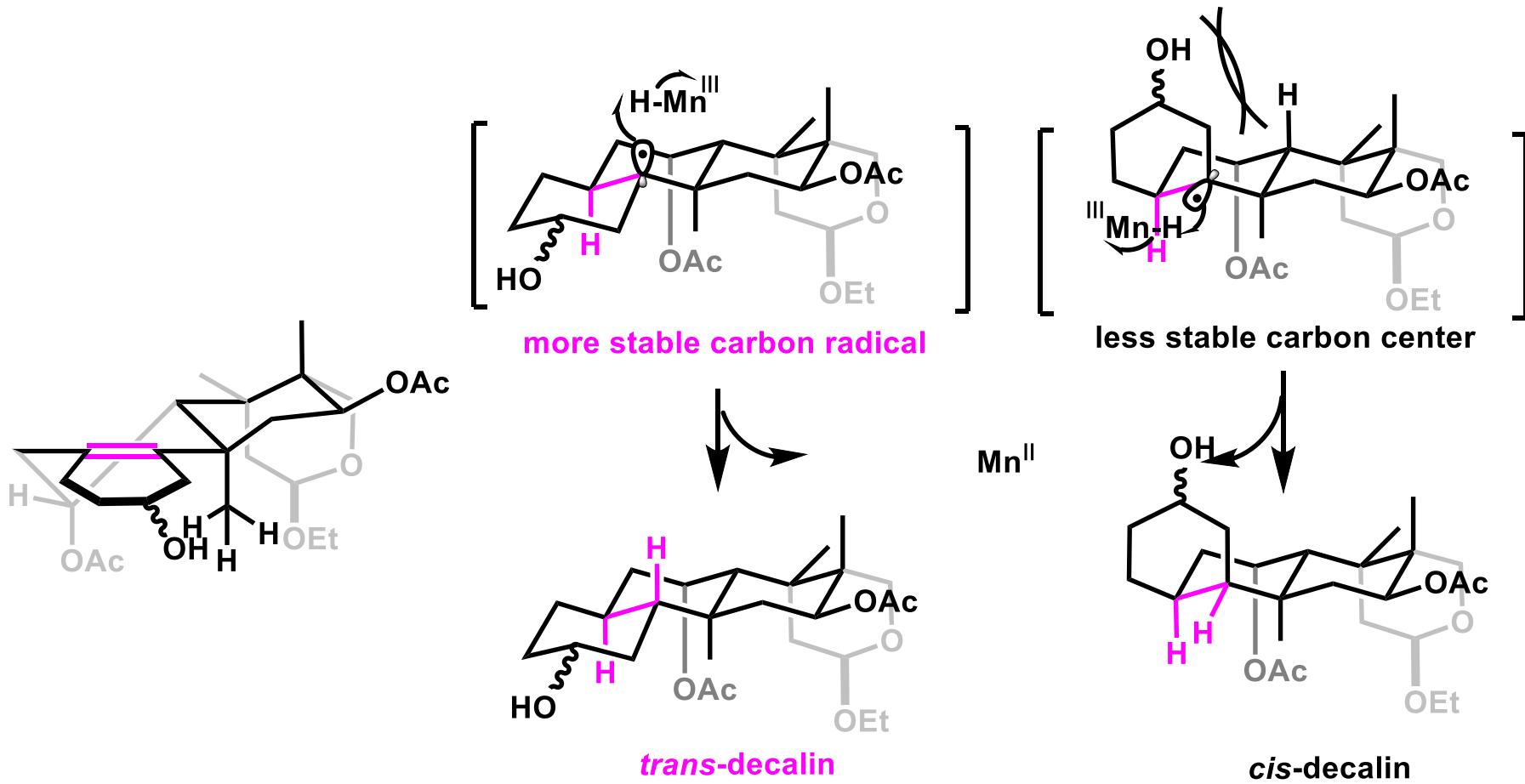
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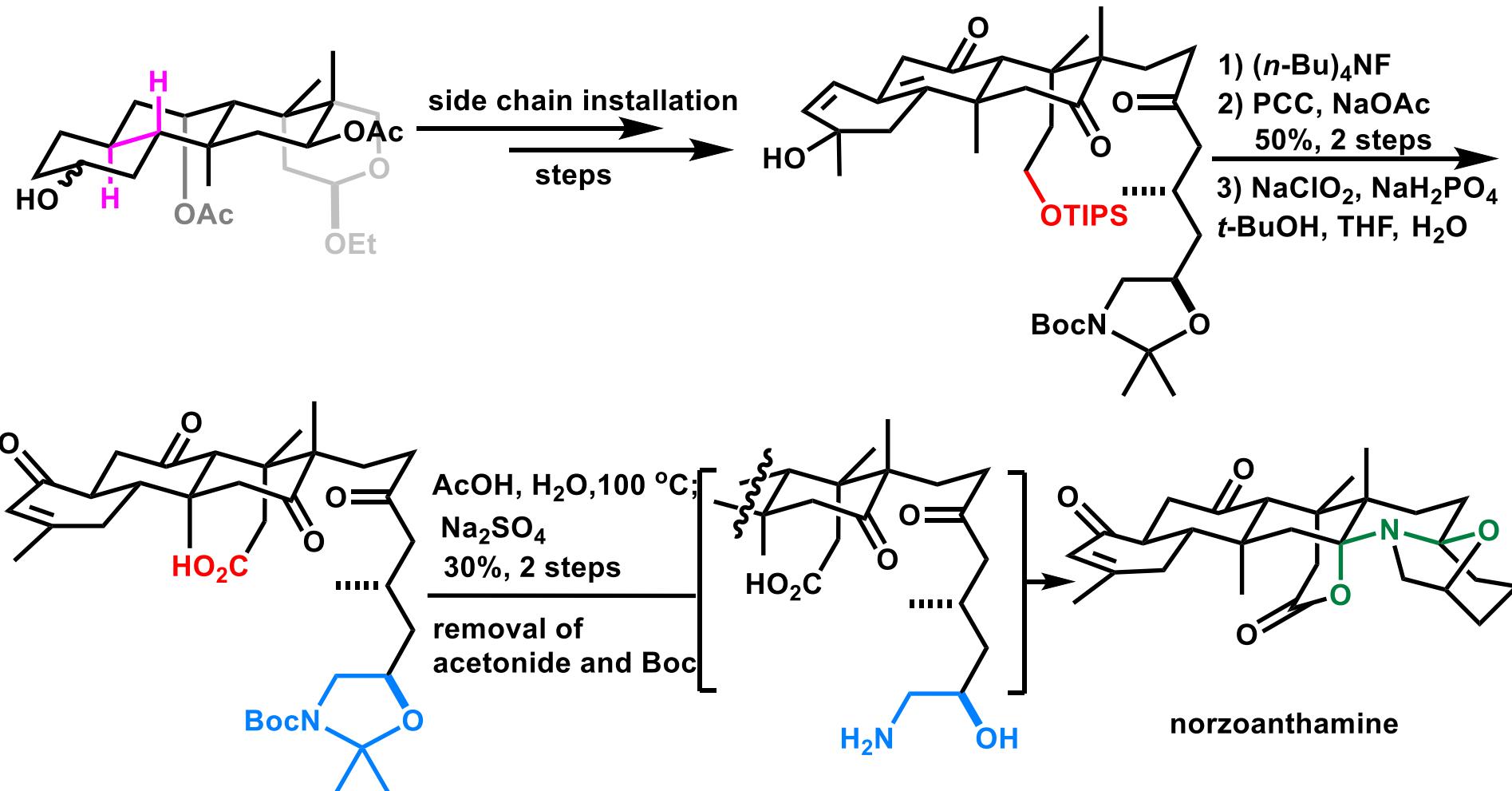
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Total Synthesis of Norzoanthamine



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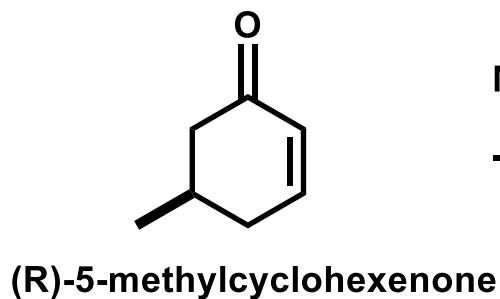
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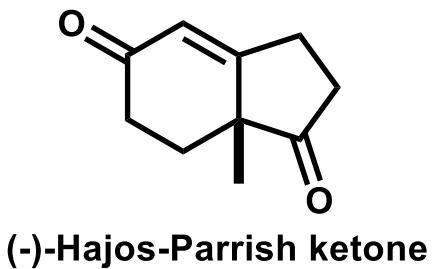
(By Gao Group, 2021)

4. Summary

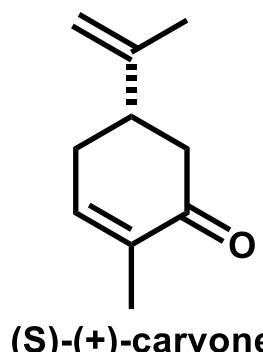
Summary



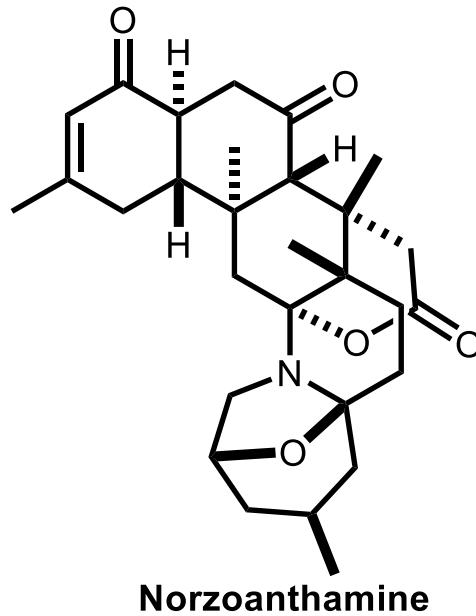
Miyashita Group
2004, 41 steps



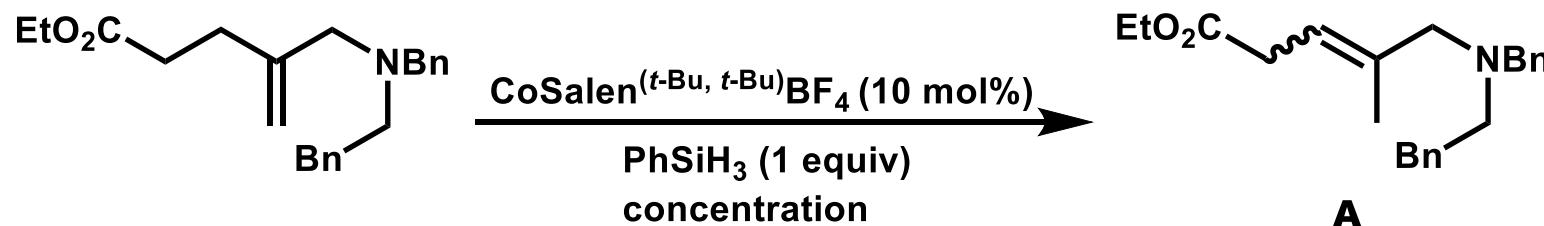
Kobayashi Group
2009, 47 steps



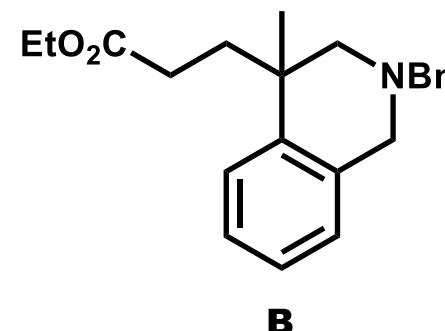
Gao Group
2021, 36 steps



High reaction dilutions favors cycloisomerized product



Concentration	A : B
100mM	1.2 : 1.0
10mM	0.34 : 1.0
1mM	trace : 1.0



if isomerization and cycloisomerization took place exclusively from the primary geminate radical pair, then the ratio of isomerization to cycloisomerization would be constant; thus the cage escape reaction of cycloisomerization could not be excluded.

1) Jeishla L. M. Matos; Samantha A. Green; Yuge Chun; Vuong Q. Dang; Russell G. Dushin; Paul Richardson; Jason S. Chen; David W. Piotrpwski; Brian M. Paegel; Ryan A. Shenvi. *Angew. Chem. Int. Ed.* **2020**, 59, 12998.