

Total Synthesis of (-)-Epicoccin G and (-)-Rostratin A

2020.9.19 Literature Seminar

B4 Wataru Shigematsu

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1. Introduction

2. Total Synthesis of (-)-Epicoccin G by Nicolaou's Group (2011)

3. Total Synthesis of (-)-Epicoccin G and (-)-Rostratin A by Baudoin's Group (2019) (main paper)

4. Summary

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Introduction of Prof. Baudoin

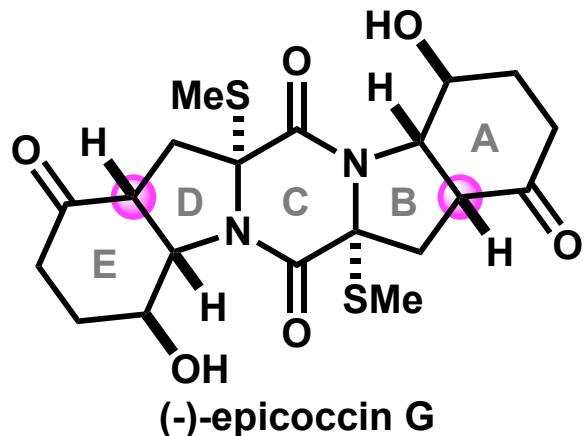


1995 B.S. @ National Graduate School of Chemistry, Paris
1999 Ph.D @ Collège de France (Prof. Jean-Marie Lehn)
1999 Postdoctoral @ Scripps Research Institute (Prof. K. C. Nicolaou)
1999 Group leader @ Institut de Chimie des Substances Naturelles
2006 Professor @ Claude Bernard University Lyon 1
2015 Professor @ The University of Basel

Research Topics

- Intermolecular C-H activation**
- Migratory cross-couplings involving metal chain or ring-walking**

(-)-Epicoccin G and (-)-Rostratin A

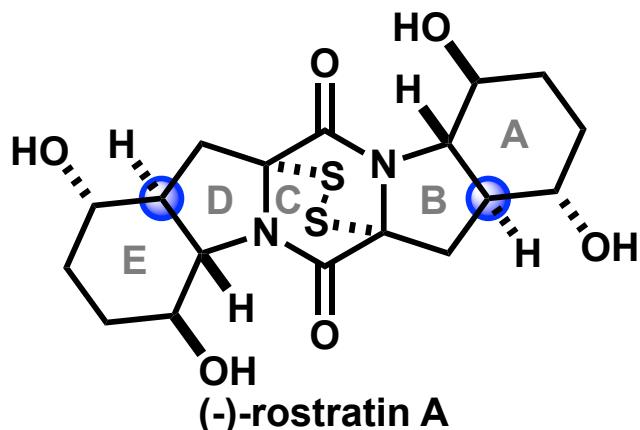


Isolation: *Epicoccum nigrum*

Biological activity: anti-HIV-1 activity in C8166 cells

Structural features: C_2 symmetry, cis,cis ring junction

Total synthesis: Nicolaou (2011), Baudoin (2019)



Isolation: *Exserohilum rostratum*

Biological activity: cytotoxicity against human colon carcinoma HTC-116

Structural features: C_2 symmetry, trans,trans ring junction, disulfide

Total synthesis: Baudoin (2019)

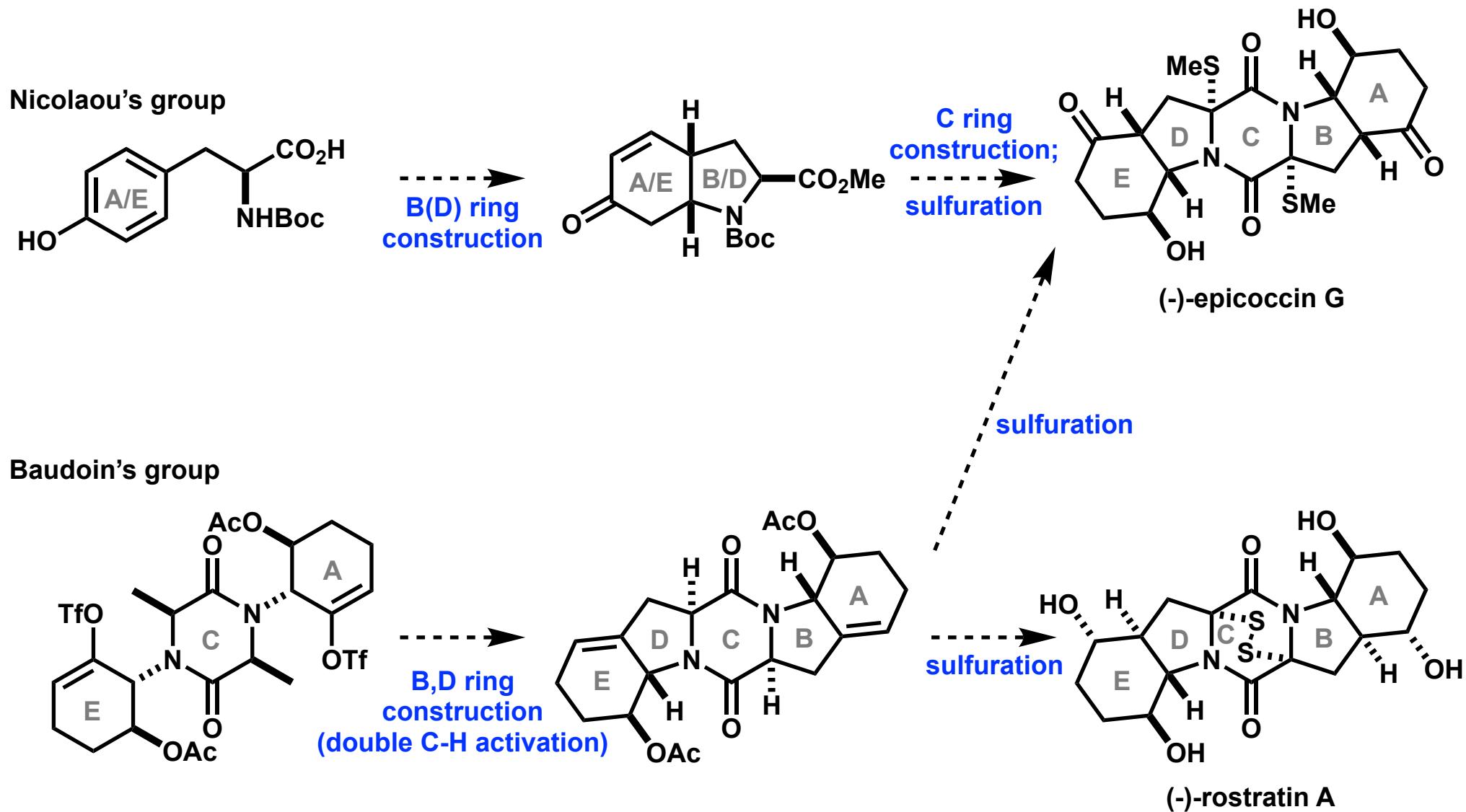
1) Guo, H.; Sun, B.; Gao, H.; Chen, X.; Liu, S.; Yao, X.; Liu, X.; Che, Y. *J. Nat. Prod.* **2009**, 72, 2115

2) Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun, Y.-P.; Sarlah, D. *J. Am. Chem. Soc.* **2011**, 133, 8150

3) Thesmar, P.; Baudoin, O. *J. Am. Chem. Soc.* **2019**, 141, 15779

4) Tan, R. X.; Jensen, P. R.; Williams, P. G.; Fenical, W. *J. Nat. Prod.* **2004**, 67, 1374

Synthetic Route of Both Group



- 1) Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun, Y.-P.; Sarlah, D. *J. Am. Chem. Soc.* **2011**, *133*, 8150
- 2) Thesmar, P.; Baudoin, O. *J. Am. Chem. Soc.* **2019**, *141*, 15779

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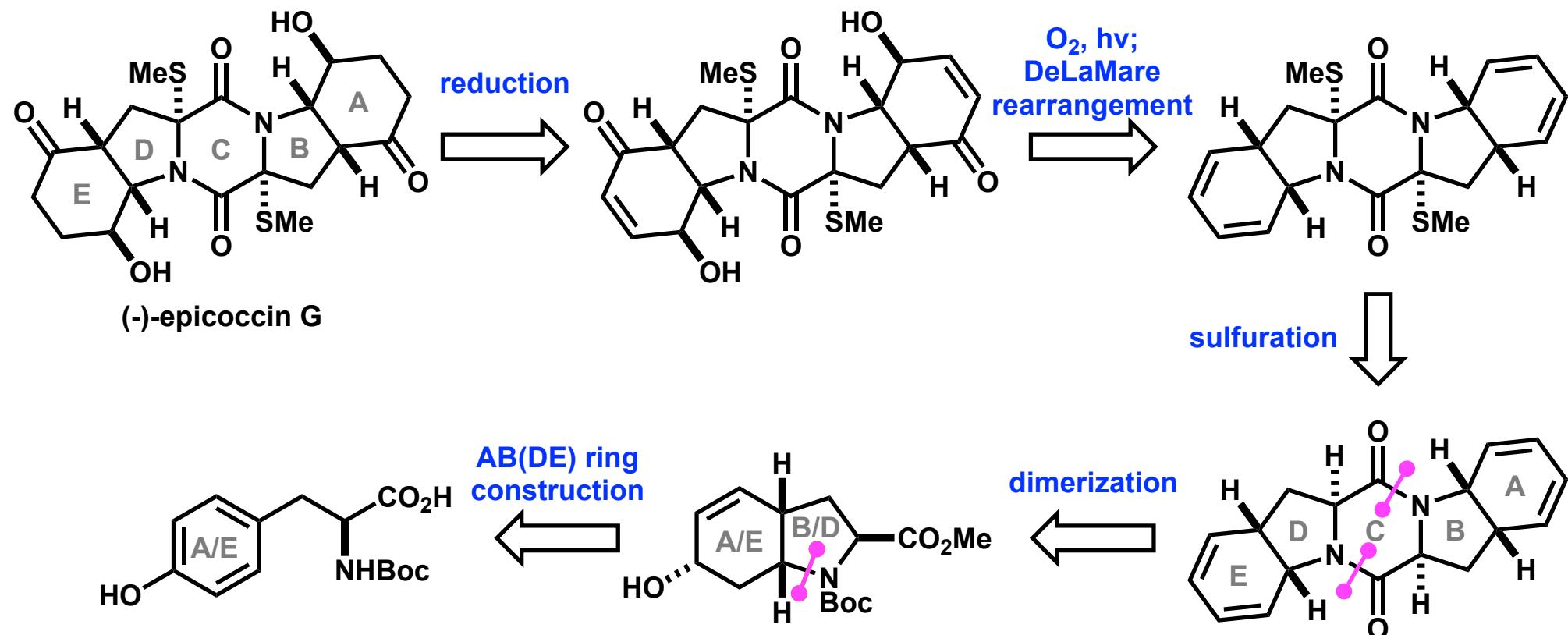
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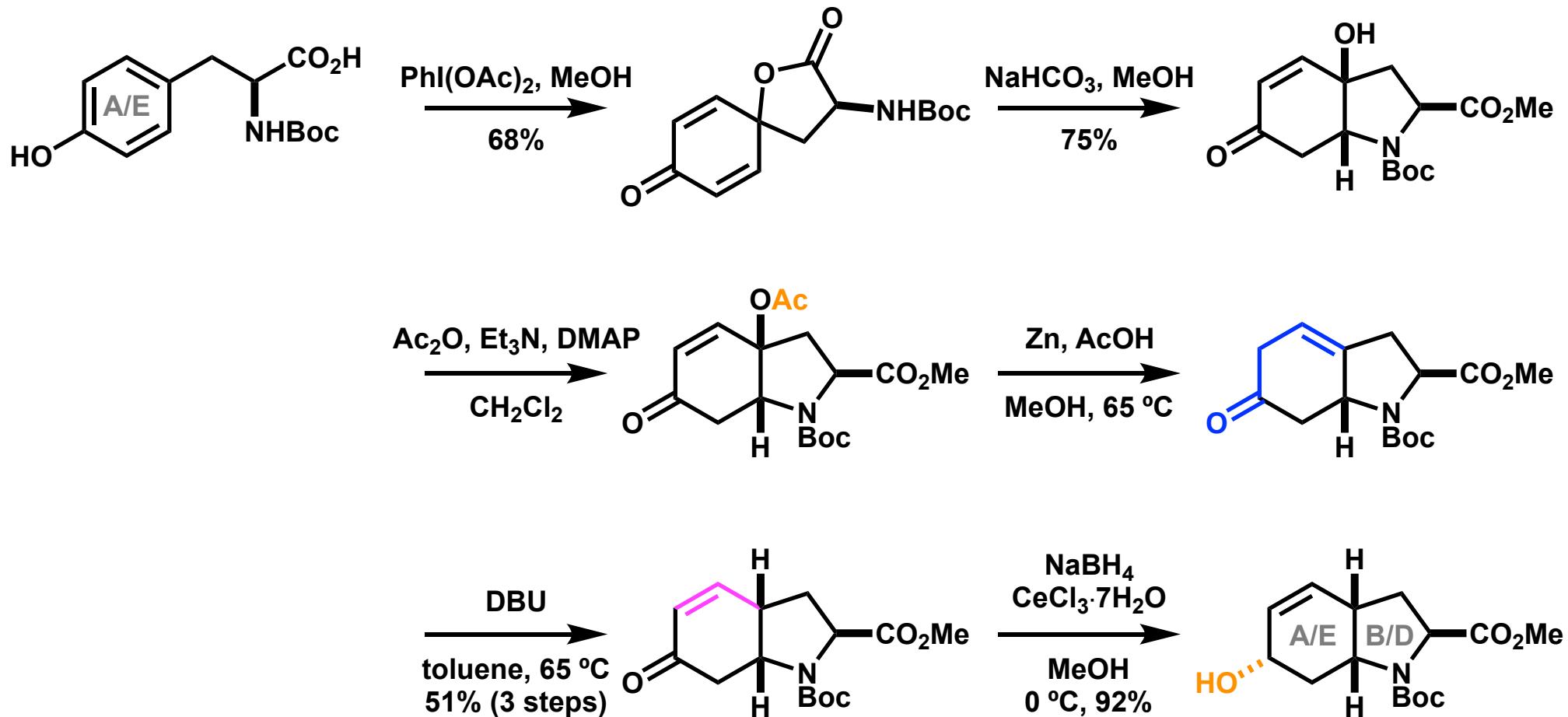
4. Summary

Retrosynthetic Analysis (Nicolaou's Group)



- 1) Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun, Y.-P.; Sarlah, D. *J. Am. Chem. Soc.* **2011**, 133, 8150
2) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, 33, 5477

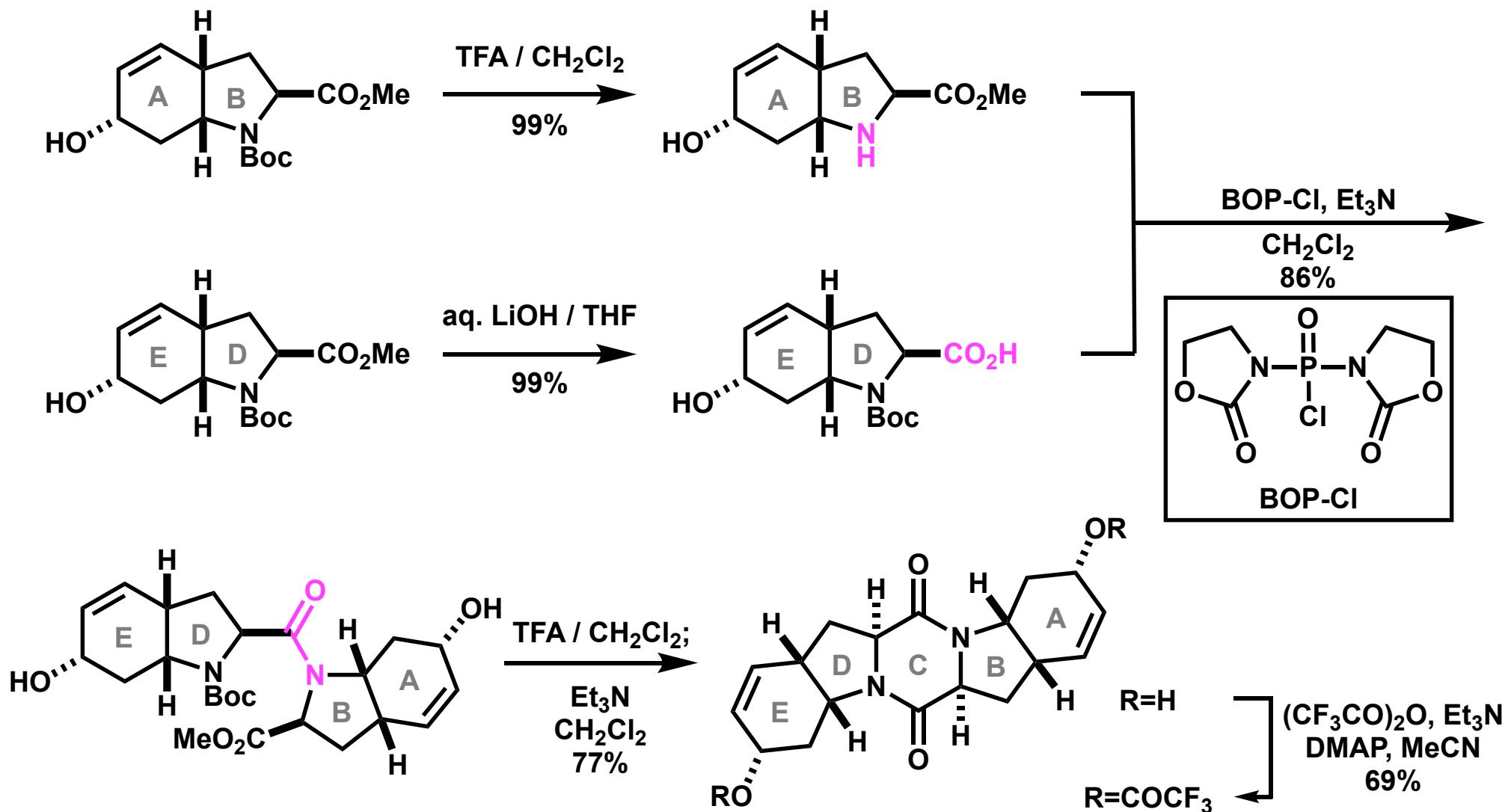
Synthesis of AB(DE) Ring



1) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, 33, 5477

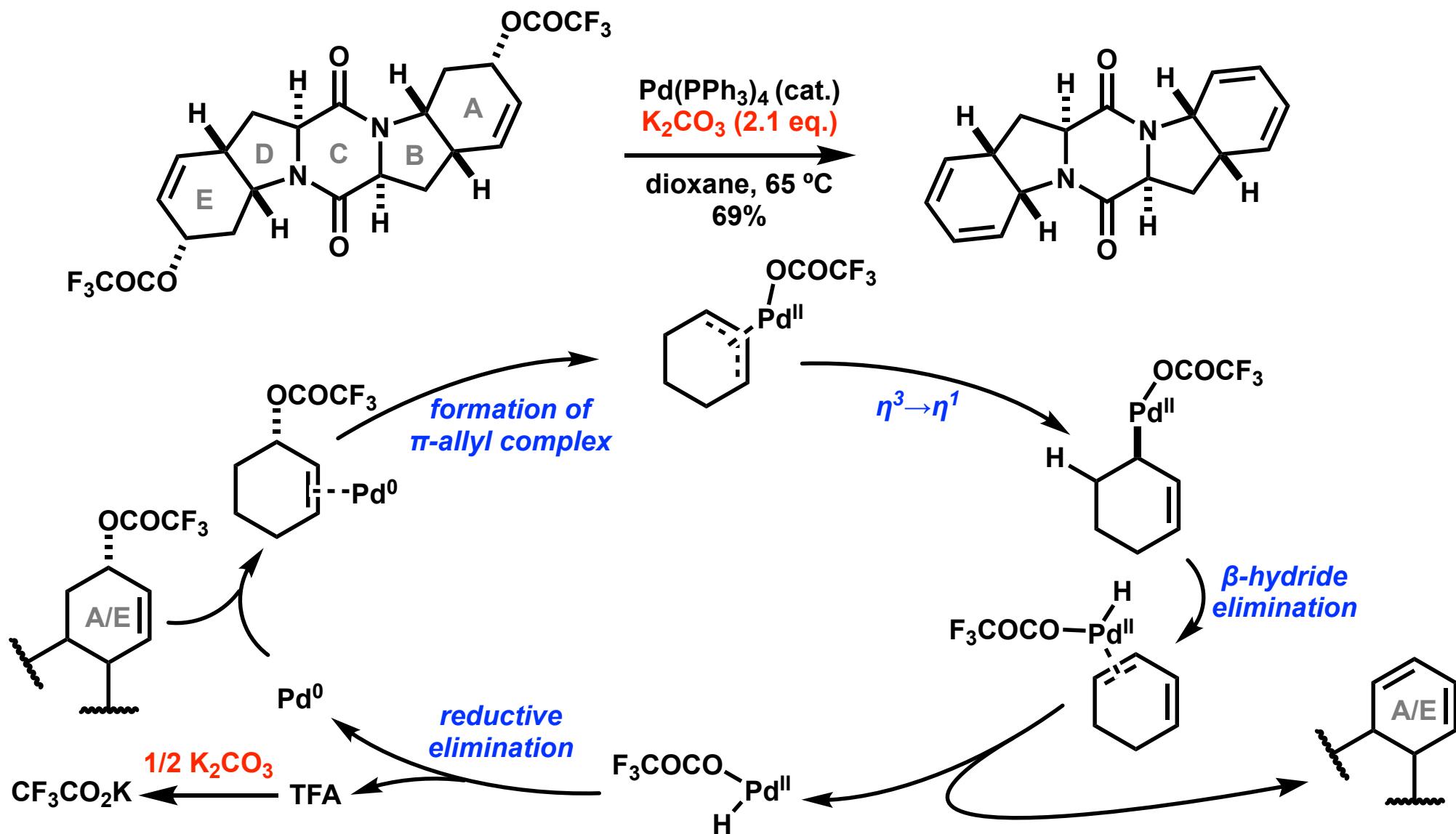
2) Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun, Y.-P.; Sarlah, D. *J. Am. Chem. Soc.* **2011**, 133, 8150

Dimerization



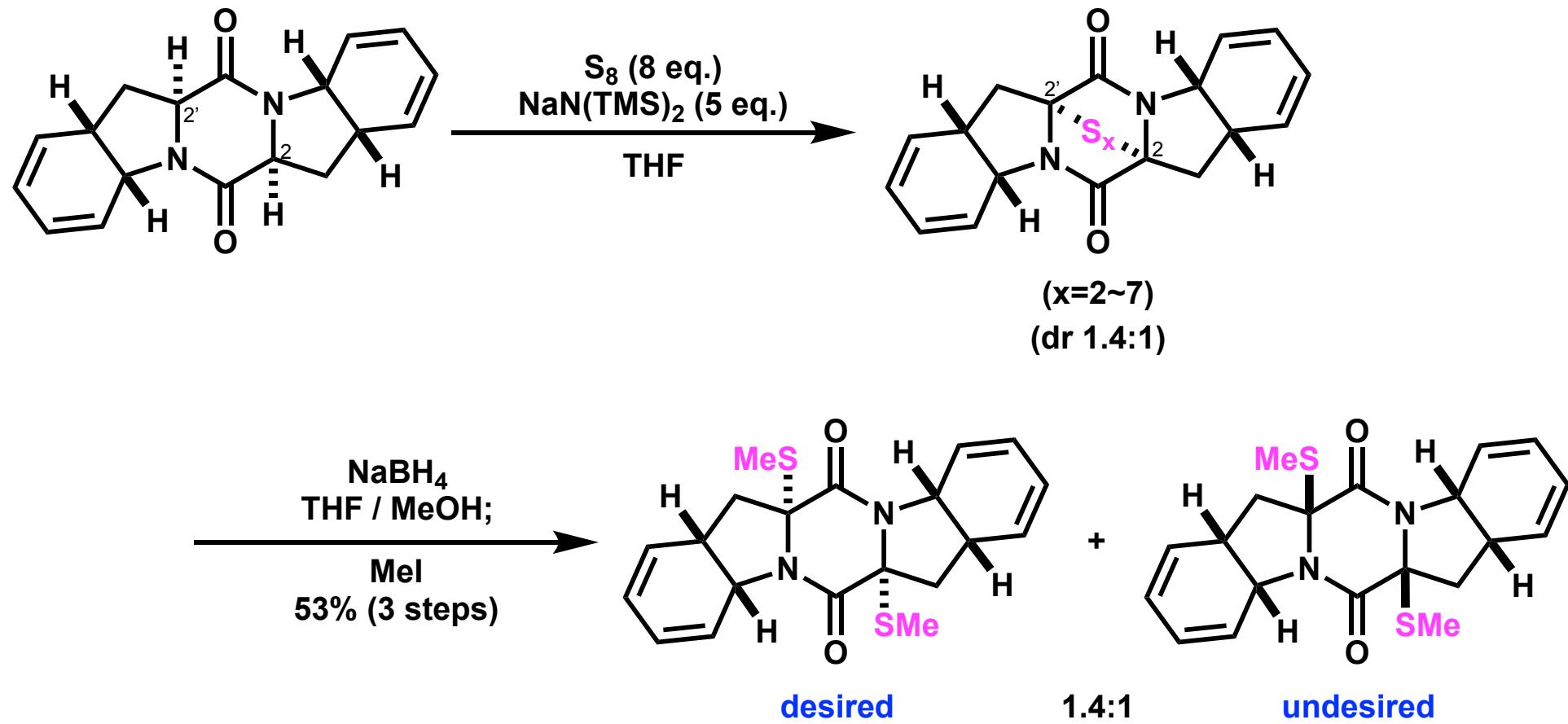
1) Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun, Y.-P.; Sarlah, D. *J. Am. Chem. Soc.* 2011, 133, 8150

Pd Catalyzed Diacylation



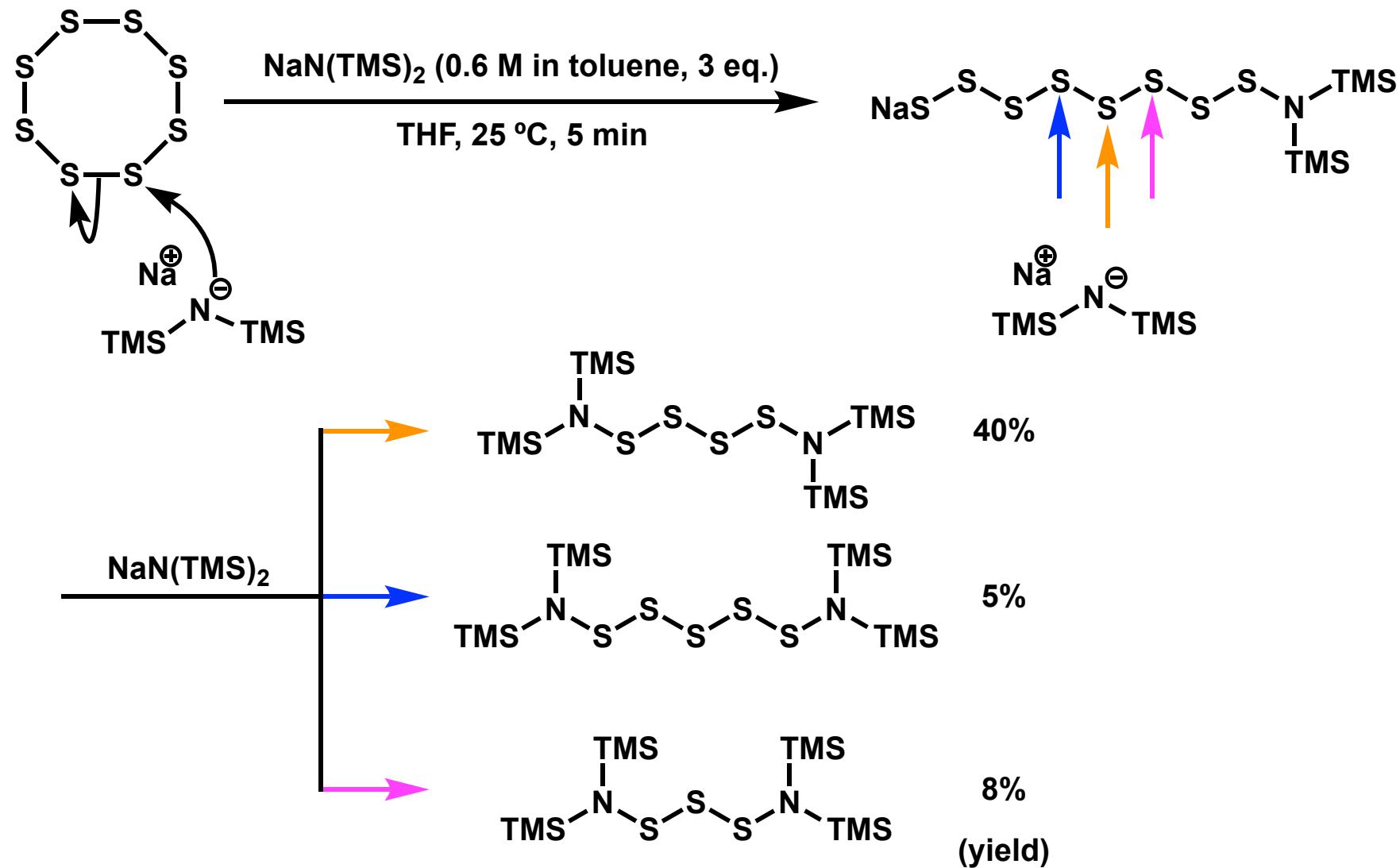
1) Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun, Y.-P.; Sarlah, D. *J. Am. Chem. Soc.* 2011, 133, 8150

Sulfuration



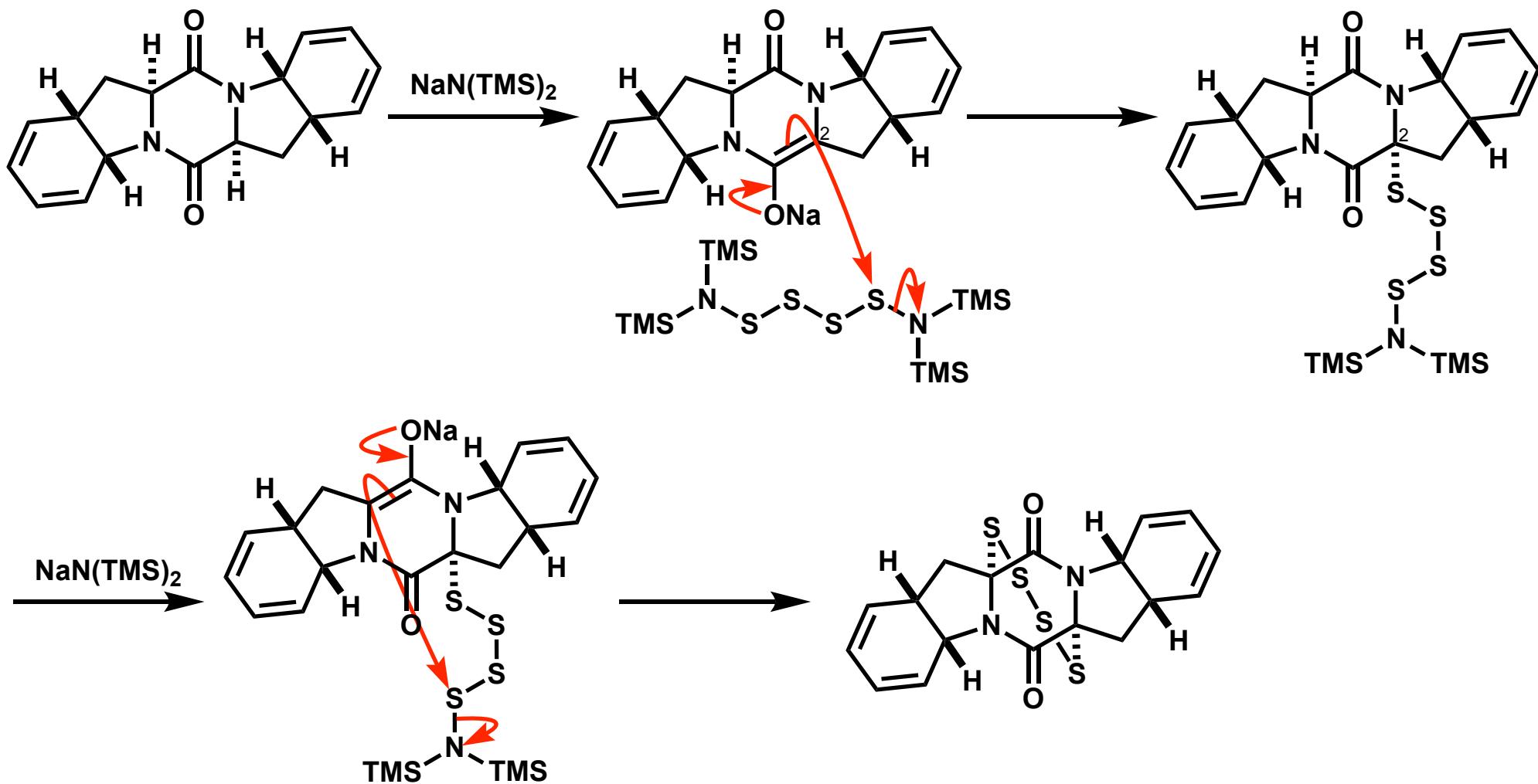
1) Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun, Y.-P.; Sarlah, D. *J. Am. Chem. Soc.* 2011, 133, 8150

Mechanism of Sulfuration (1)



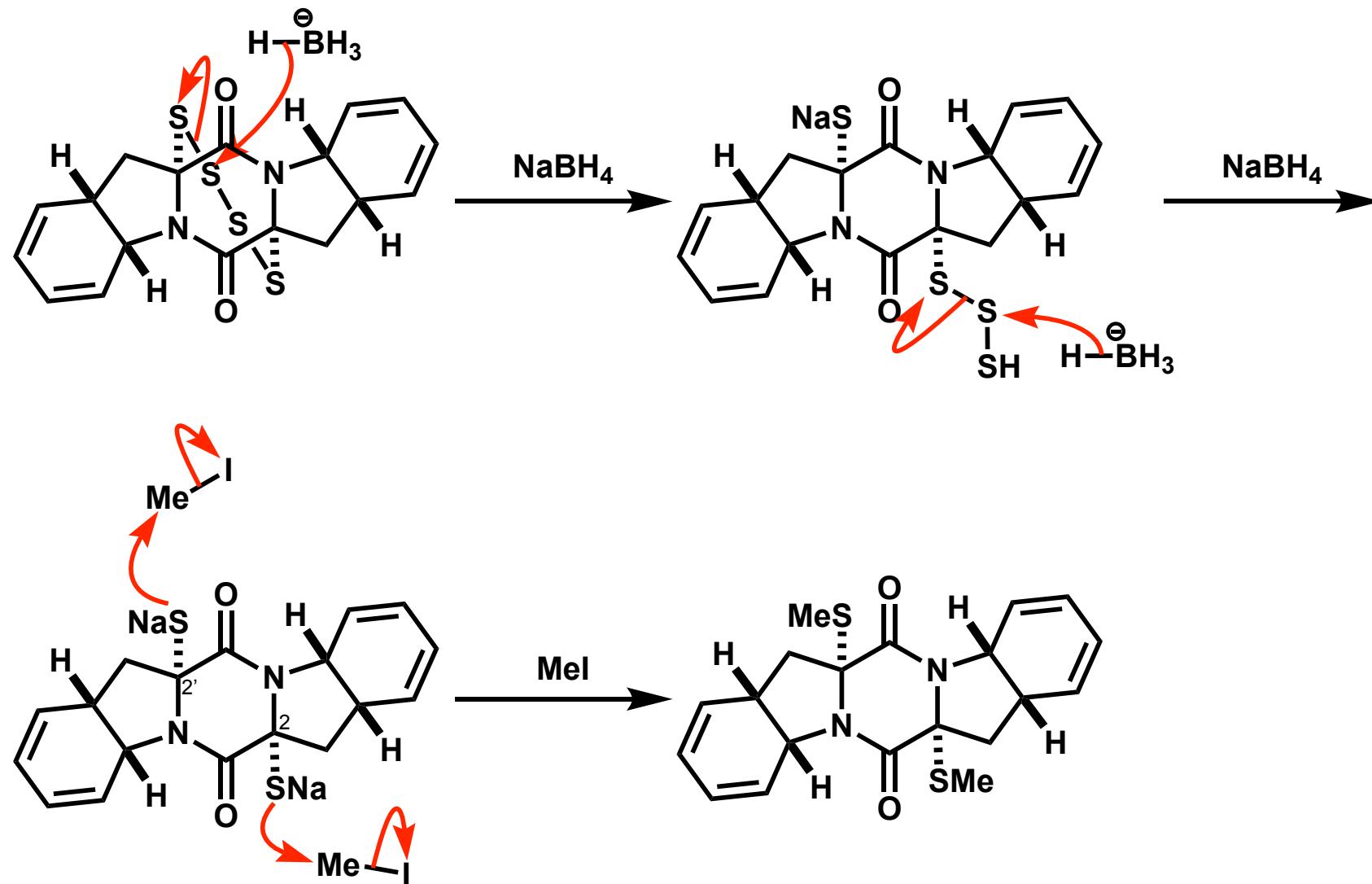
1) Nicolaou, K. C.; Lu, M.; Totokotsopoulos, S.; Heretsch, P.; Giguère, D.; Sun, Y.-P.; Sarlah, D.; Nguyen, T. H.; Wolf, I. C.; Smee, D. F.; Day, C. W.; Bopp, S.; Winzeler, E. A. *J. Am. Chem. Soc.* **2012**, *134*, 17320

Mechanism of Sulfuration (2)



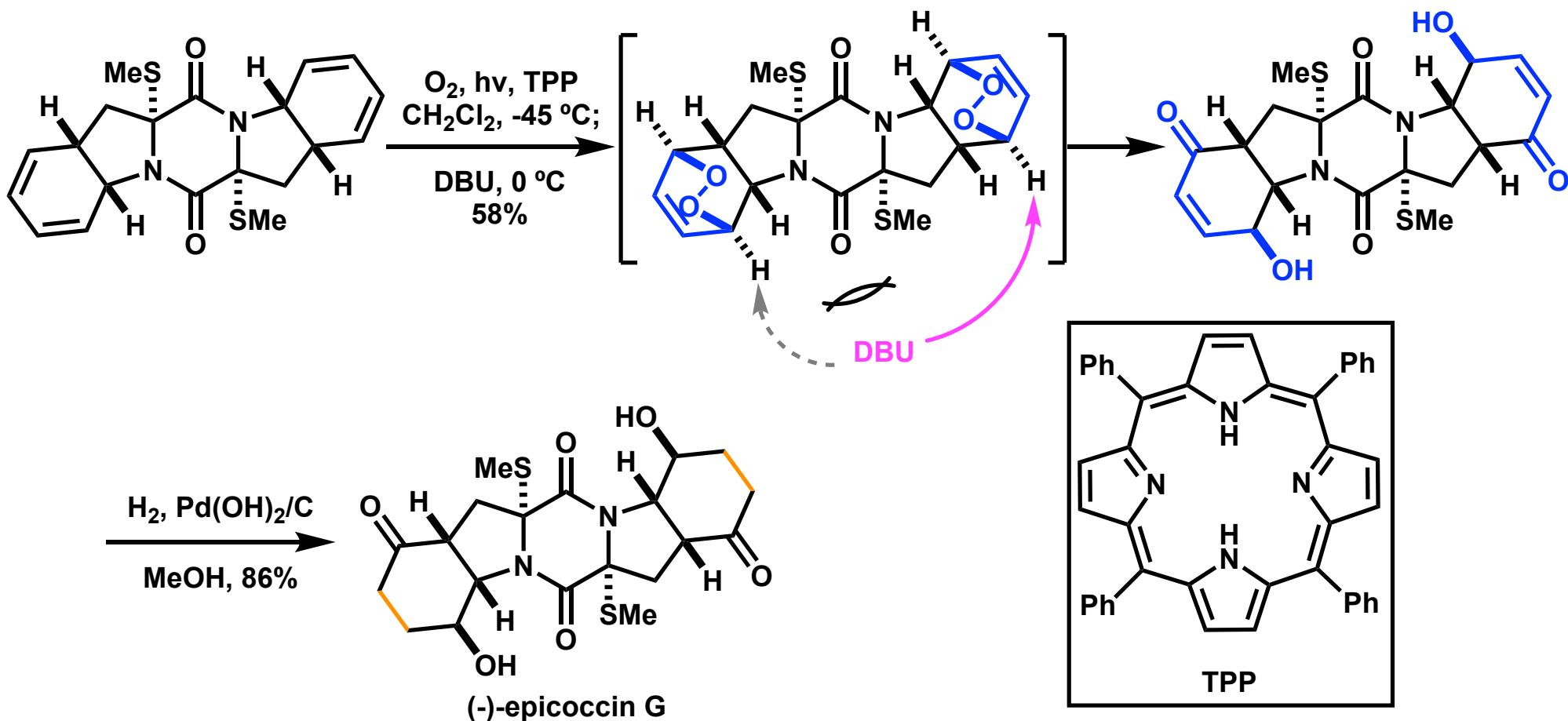
1) Nicolaou, K. C.; Lu, M.; Totokotsopoulos, S.; Heretsch, P.; Giguère, D.; Sun, Y.-P.; Sarlah, D.; Nguyen, T. H.; Wolf, I. C.; Smee, D. F.; Day, C. W.; Bopp, S.; Winzeler, E. A. *J. Am. Chem. Soc.* **2012**, *134*, 17320

Mechanism of Sulfuration (3)



1) Nicolaou, K. C.; Lu, M.; Totokotsopoulos, S.; Heretsch, P.; Giguère, D.; Sun, Y.-P.; Sarlah, D.; Nguyen, T. H.; Wolf, I. C.; Smee, D. F.; Day, C. W.; Bopp, S.; Winzeler, E. A. *J. Am. Chem. Soc.* **2012**, *134*, 17320

Total Synthesis of (-)-Epicoccin G



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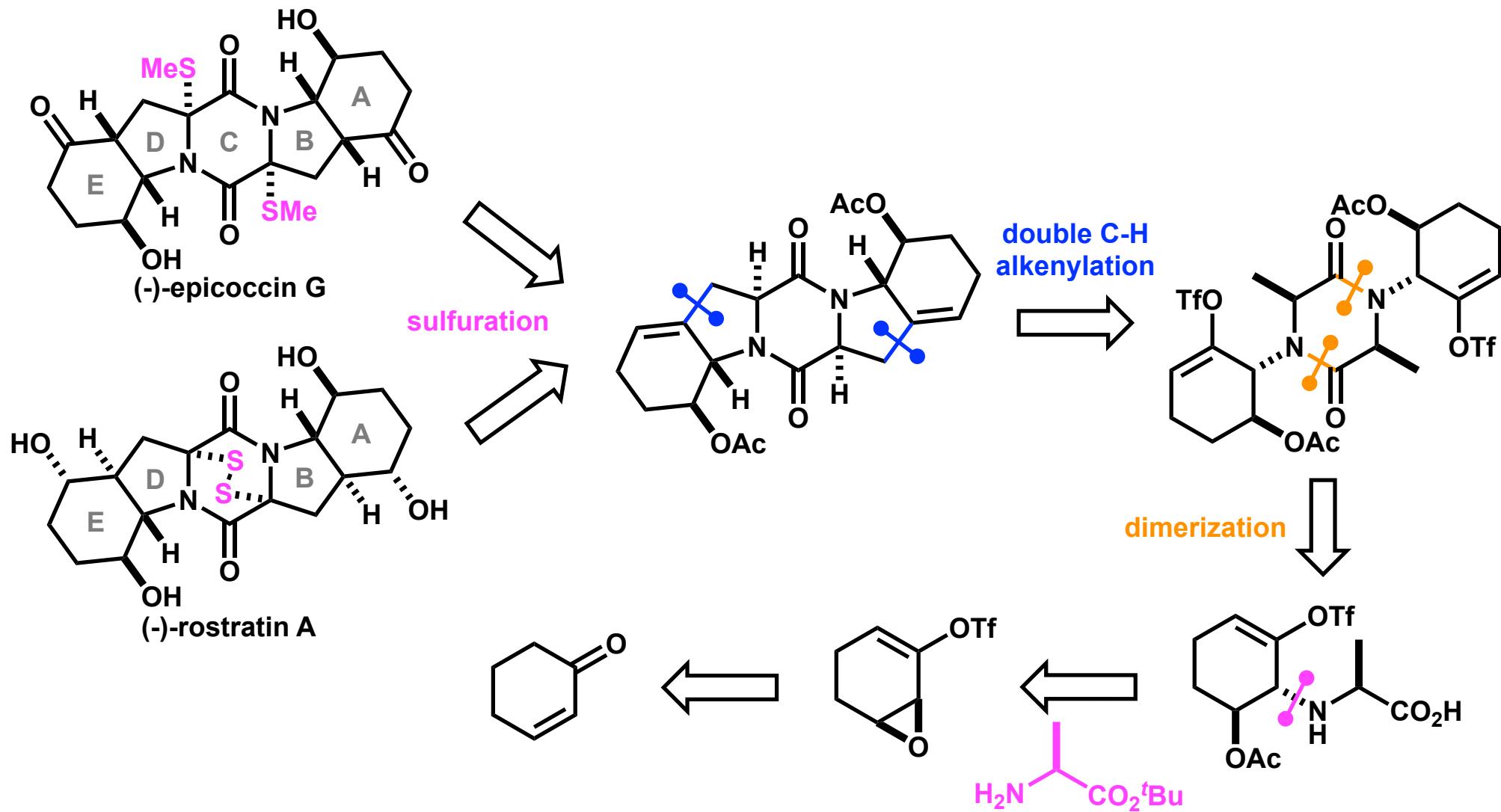
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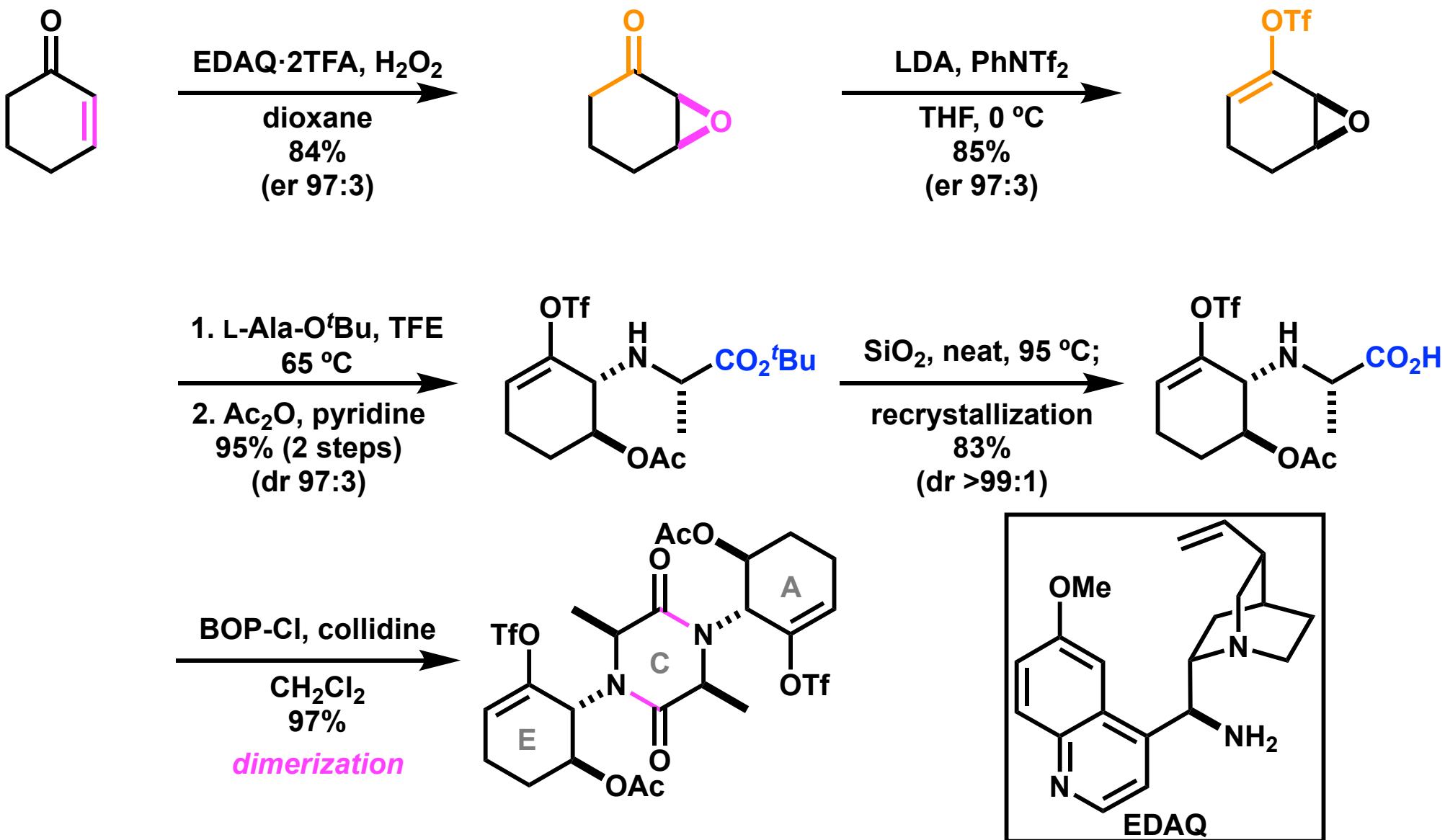
3. Total Synthesis of (-)-Epicoccin G and (-)-Rostratin A by Baudoin's Group (2019) (main paper)

4. Summary

Retrosynthetic Analysis (Baudoin's Group)



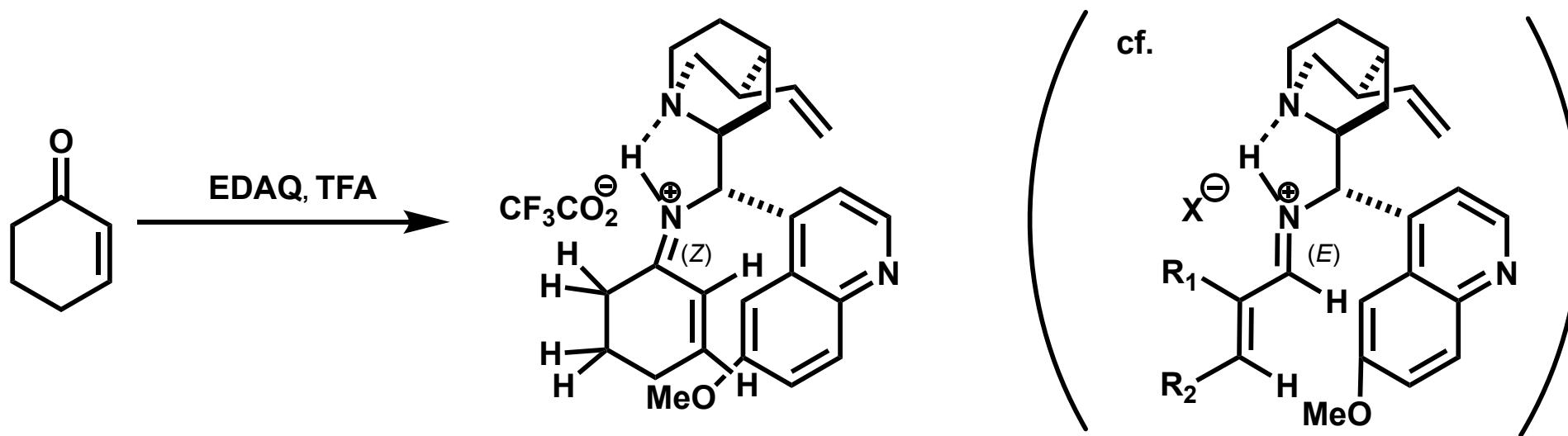
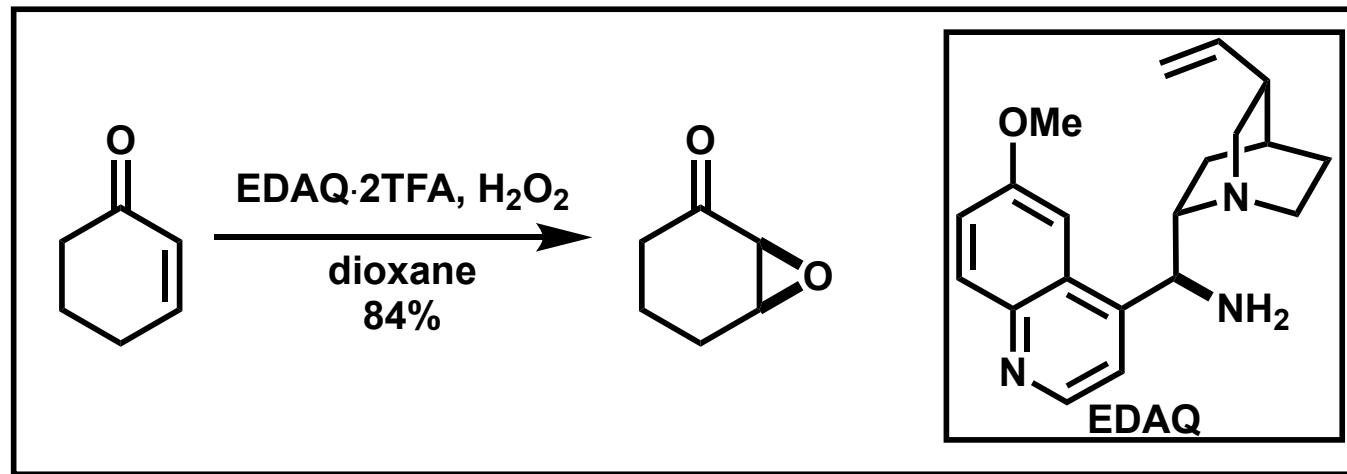
Construction of ACE Ring



1) Thesmar, P.; Baudoin, O. *J. Am. Chem. Soc.* **2019**, *141*, 15779

2) Lifchits, O.; Mahlau, M.; Reisinger, C. M.; Lee, A.; Farès, C.; Polyak, I.; Gopakumar, G.; Thiel, W.; List, B. *J. Am. Chem. Soc.* **2013**, *135*, 6677

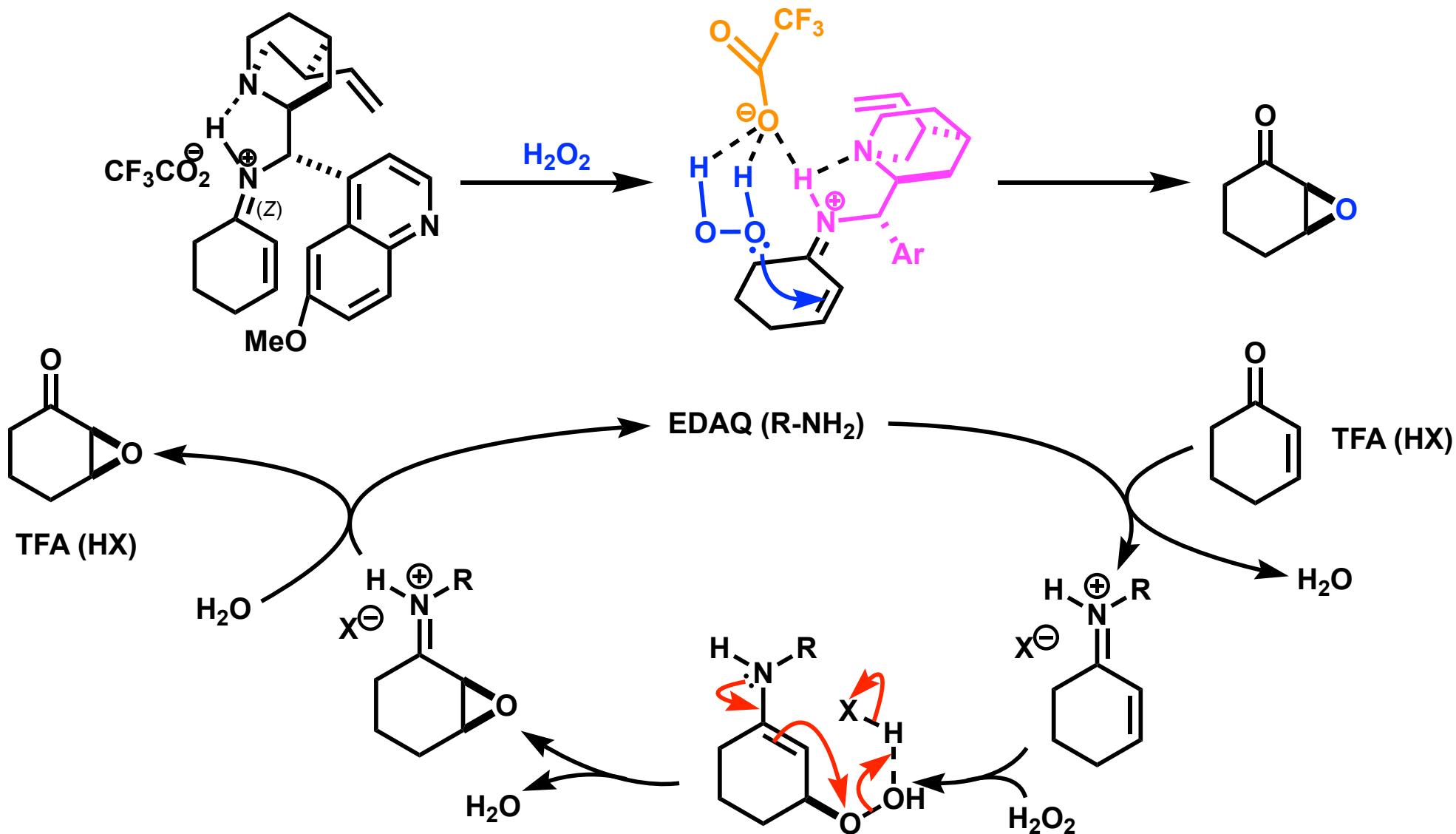
Proposed Reaction Mechanism of Epoxidation (1)



1) Thesmar, P.; Baudoin, O. *J. Am. Chem. Soc.* **2019**, *141*, 15779

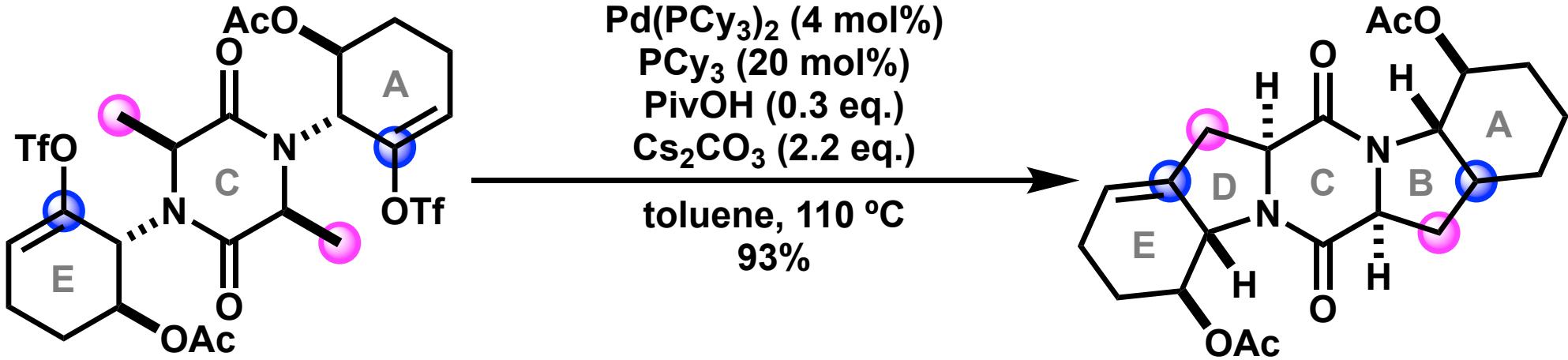
2) Lifchits, O.; Mahlau, M.; Reisinger, C. M.; Lee, A.; Farès, C.; Polyak, I.; Gopakumar, G.; Thiel, W.; List, B. *J. Am. Chem. Soc.* **2013**, *135*, 6677

Proposed Reaction Mechanism of Epoxidation (2)



1) Lifchits, O.; Mahlau, M.; Reisinger, C. M.; Lee, A.; Farès, C.; Polyak, I.; Gopakumar, G.; Thiel, W.; List, B. *J. Am. Chem. Soc.* **2013**, *135*, 6677

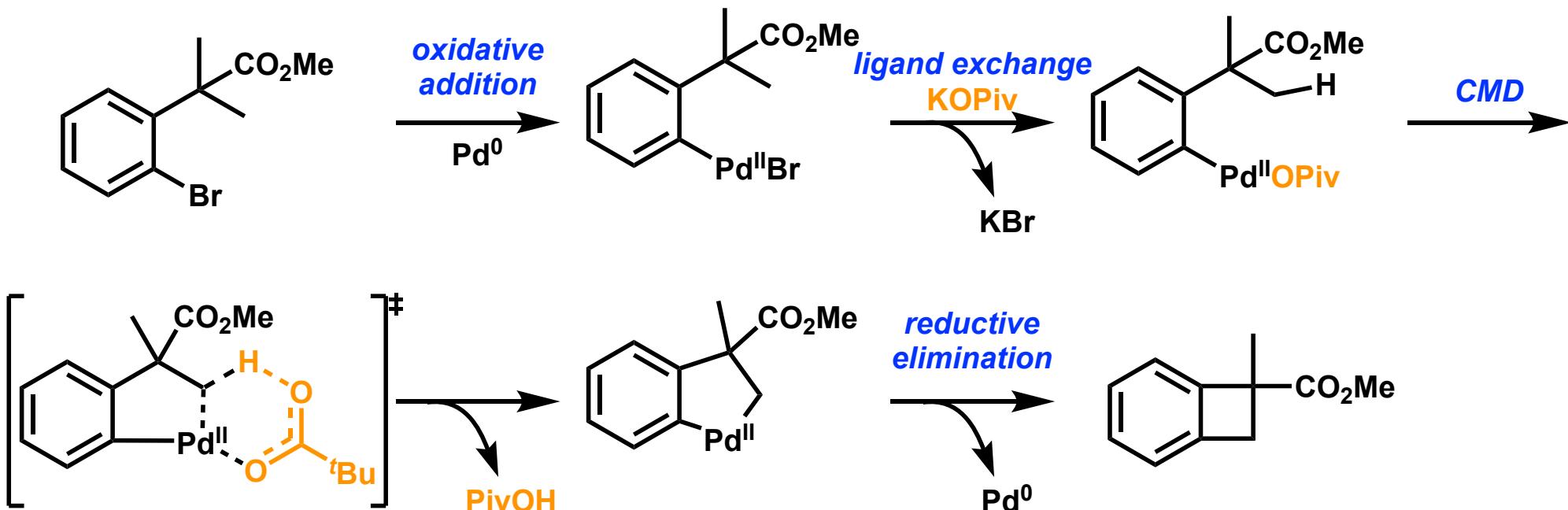
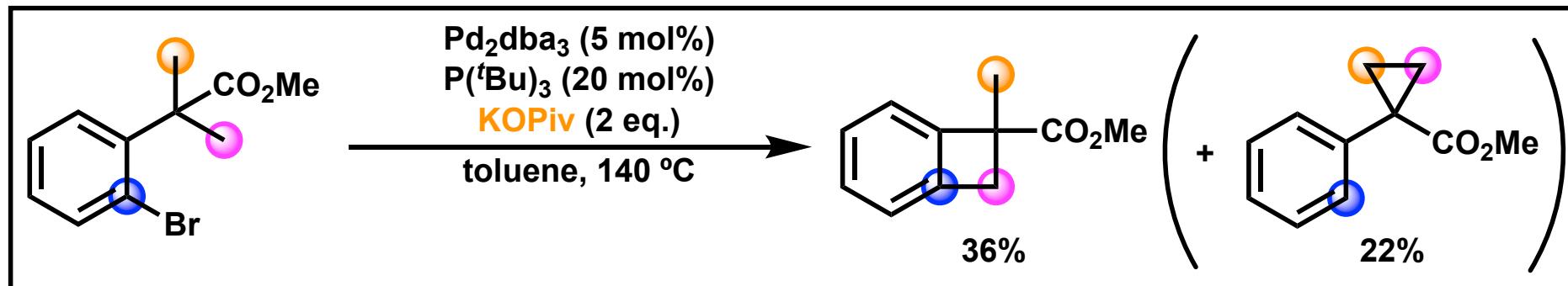
C(sp³)-H Activation



● ... C(sp³)-H activation

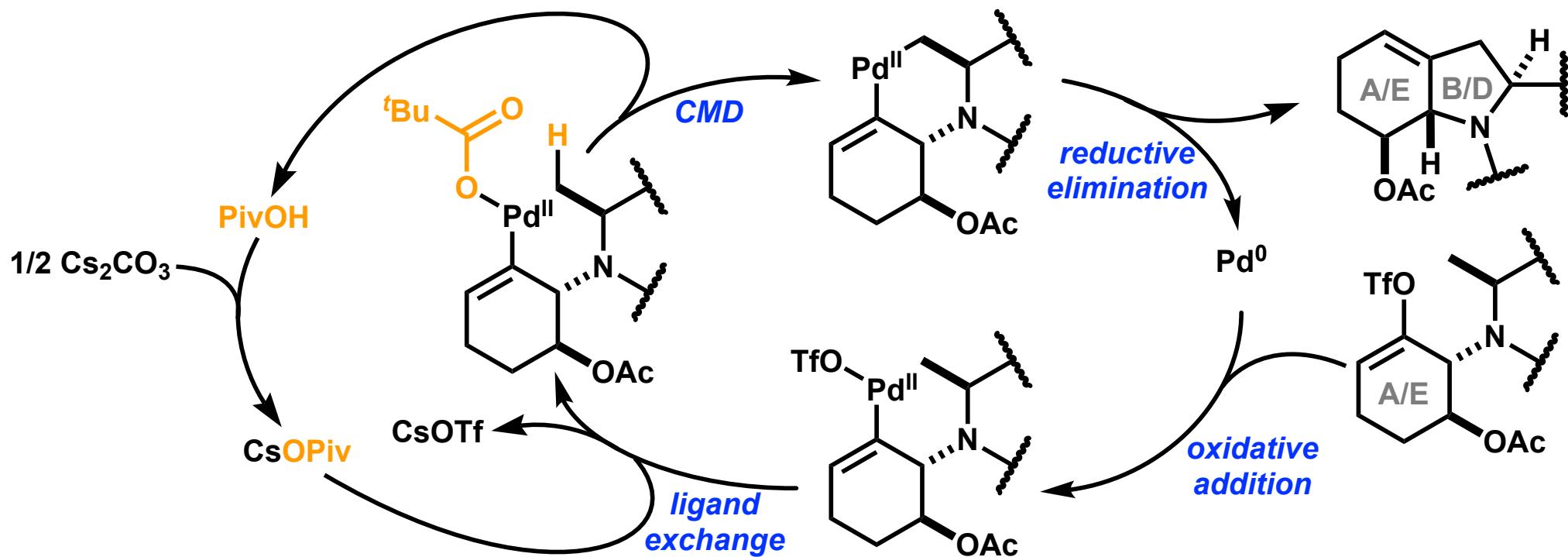
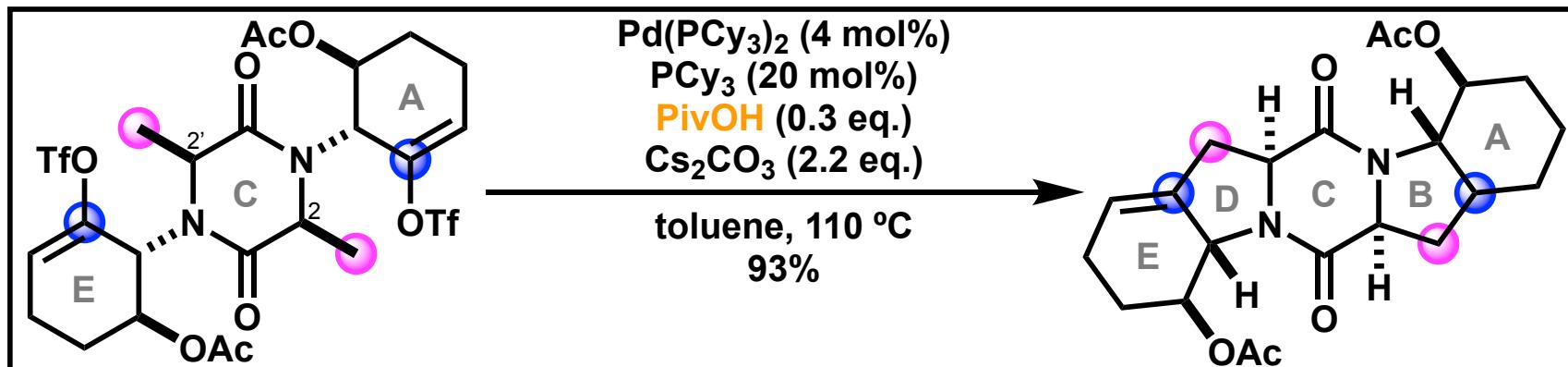
B,D ring construction

Another Example of C(sp³)-H Activation



1) Clemenceau, A.; Thesmar, P.; Gicquel, M.; Flohic, A. L.; Baudoin, O.
J. Am. Chem. Soc. **2020**, 142, 15355

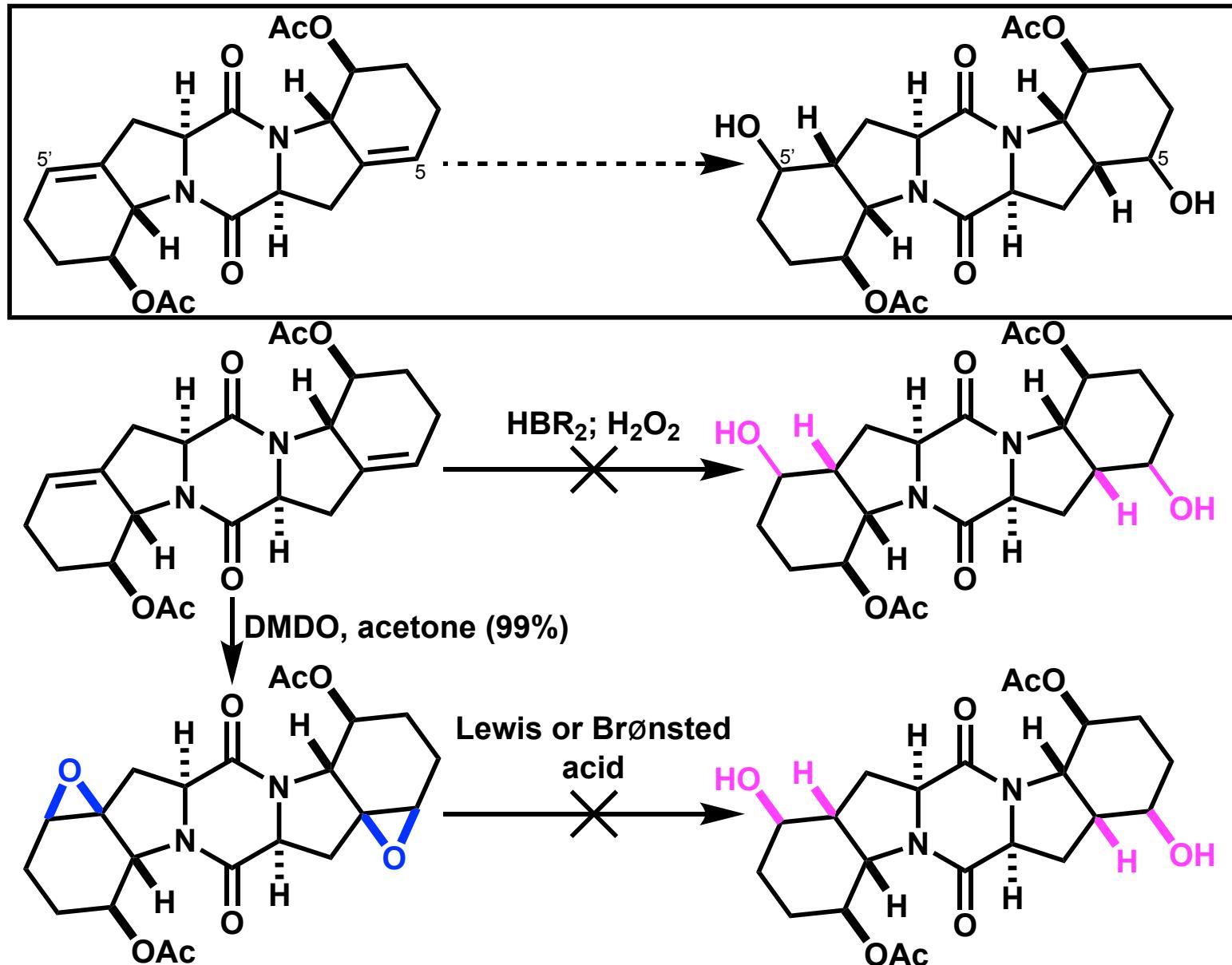
Proposed of Reaction Mechanism



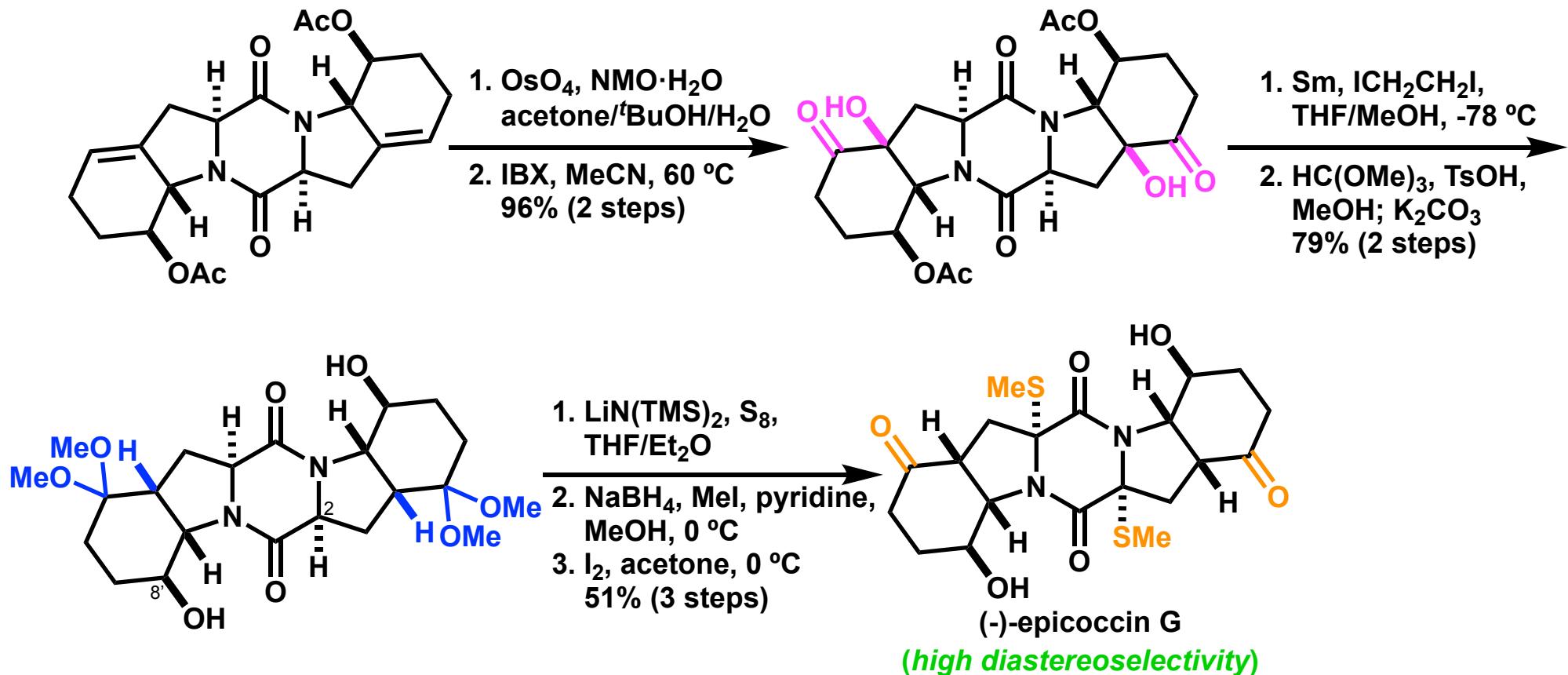
1) Thesmar, P.; Baudoin, O. *J. Am. Chem. Soc.* **2019**, *141*, 15779

2) Clemenceau, A.; Thesmar, P.; Gicquel, M.; Flohic, A. L.; Baudoin, O. *J. Am. Chem. Soc.* **2020**, *142*, 15355

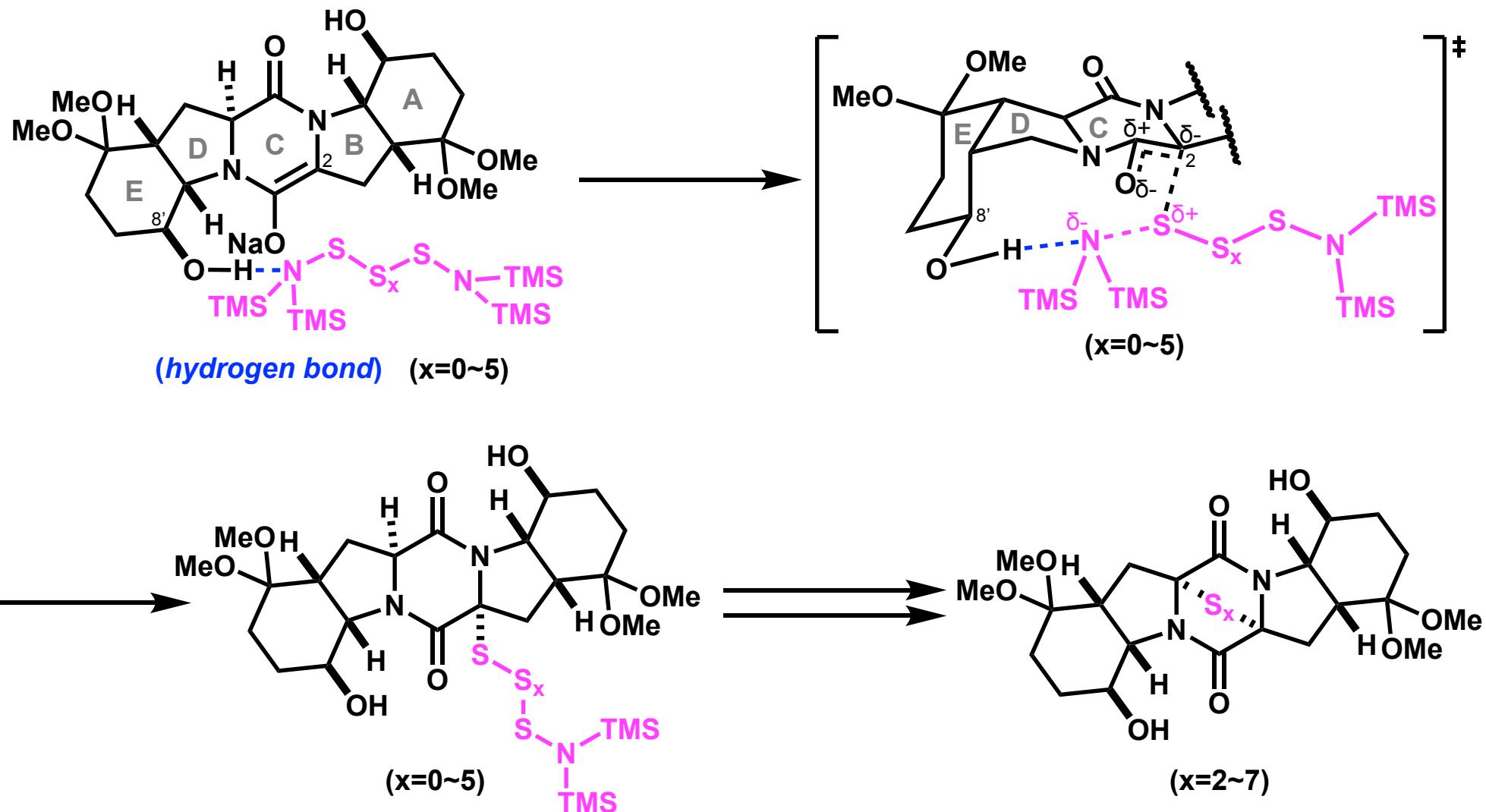
Failure of Hydration



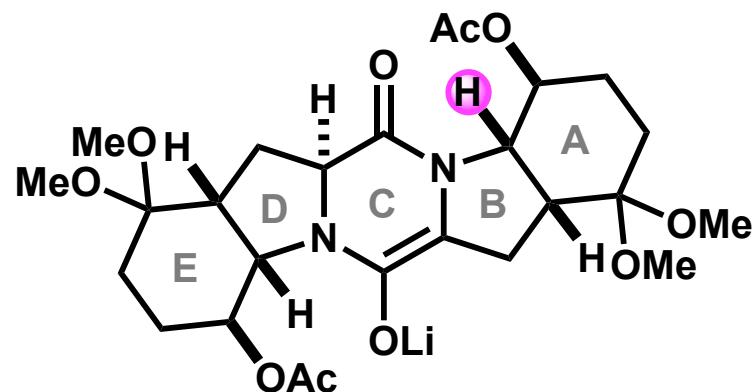
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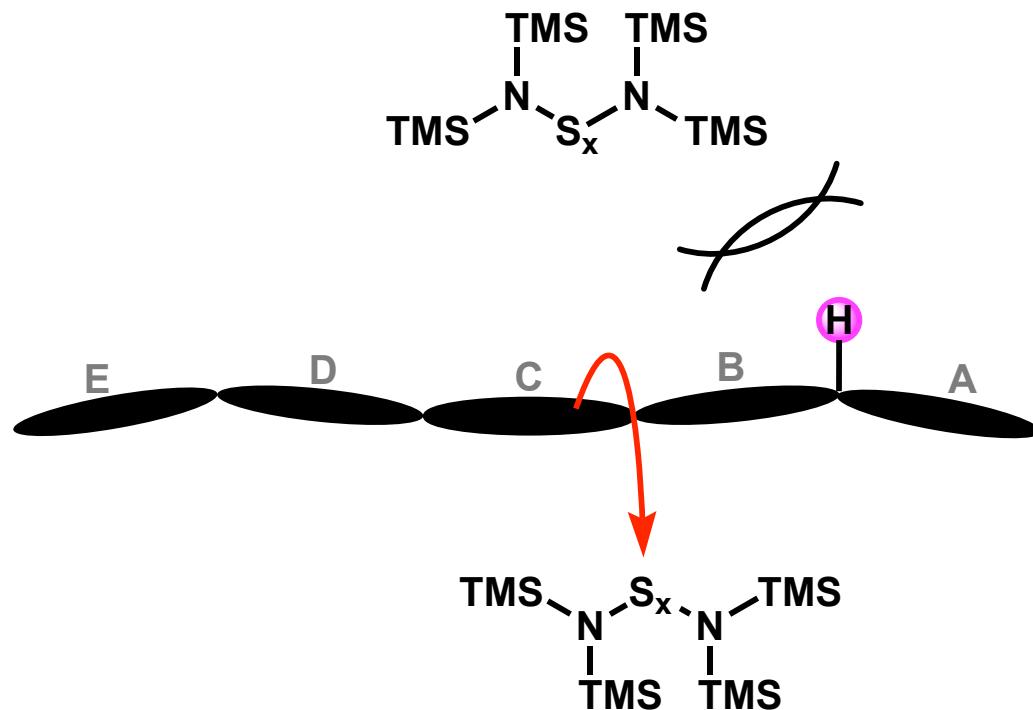
Diastereoselective Sulfuration (My Proposal)



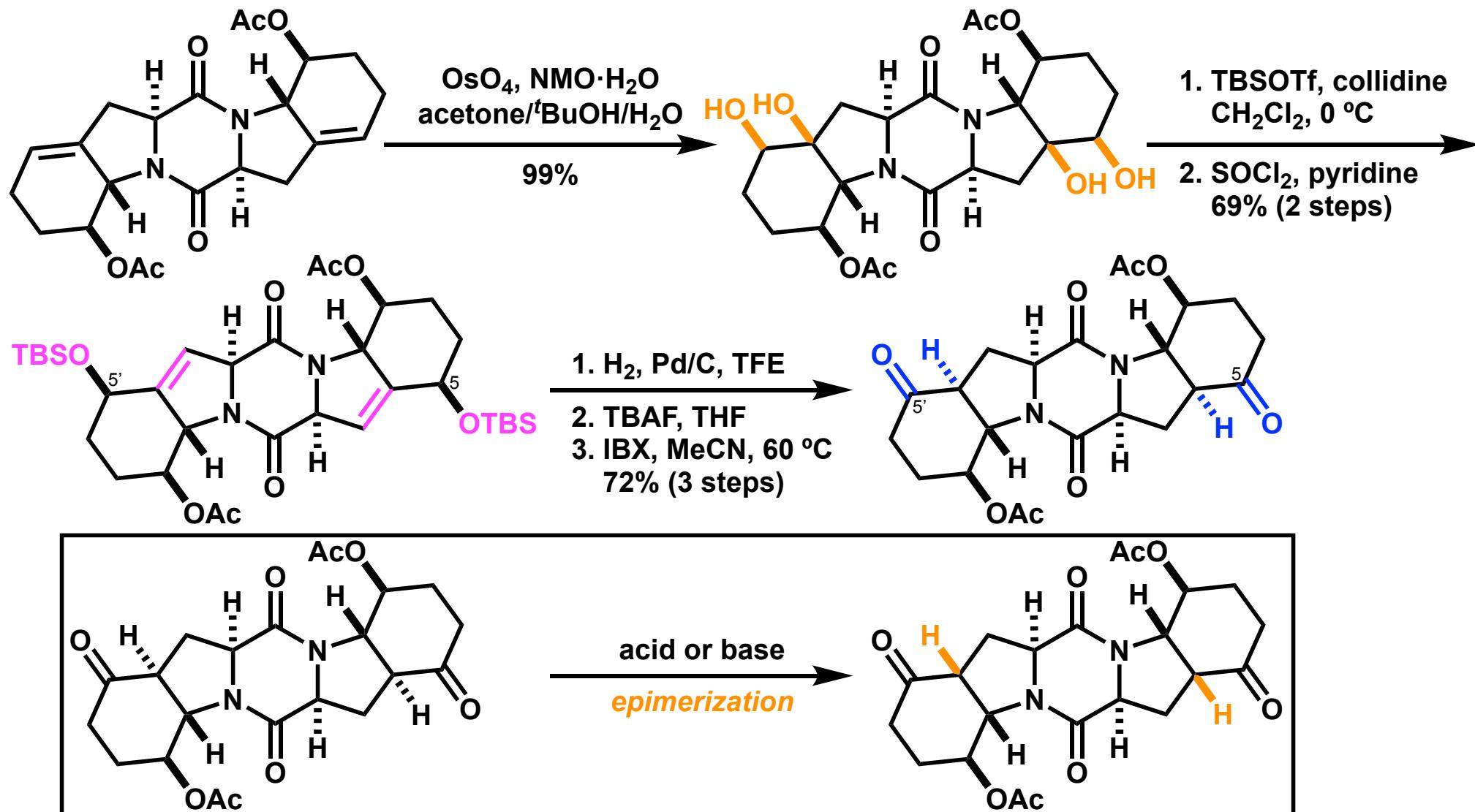
Diastereoselective Sulfuration (Prof. Inoue's Proposal)



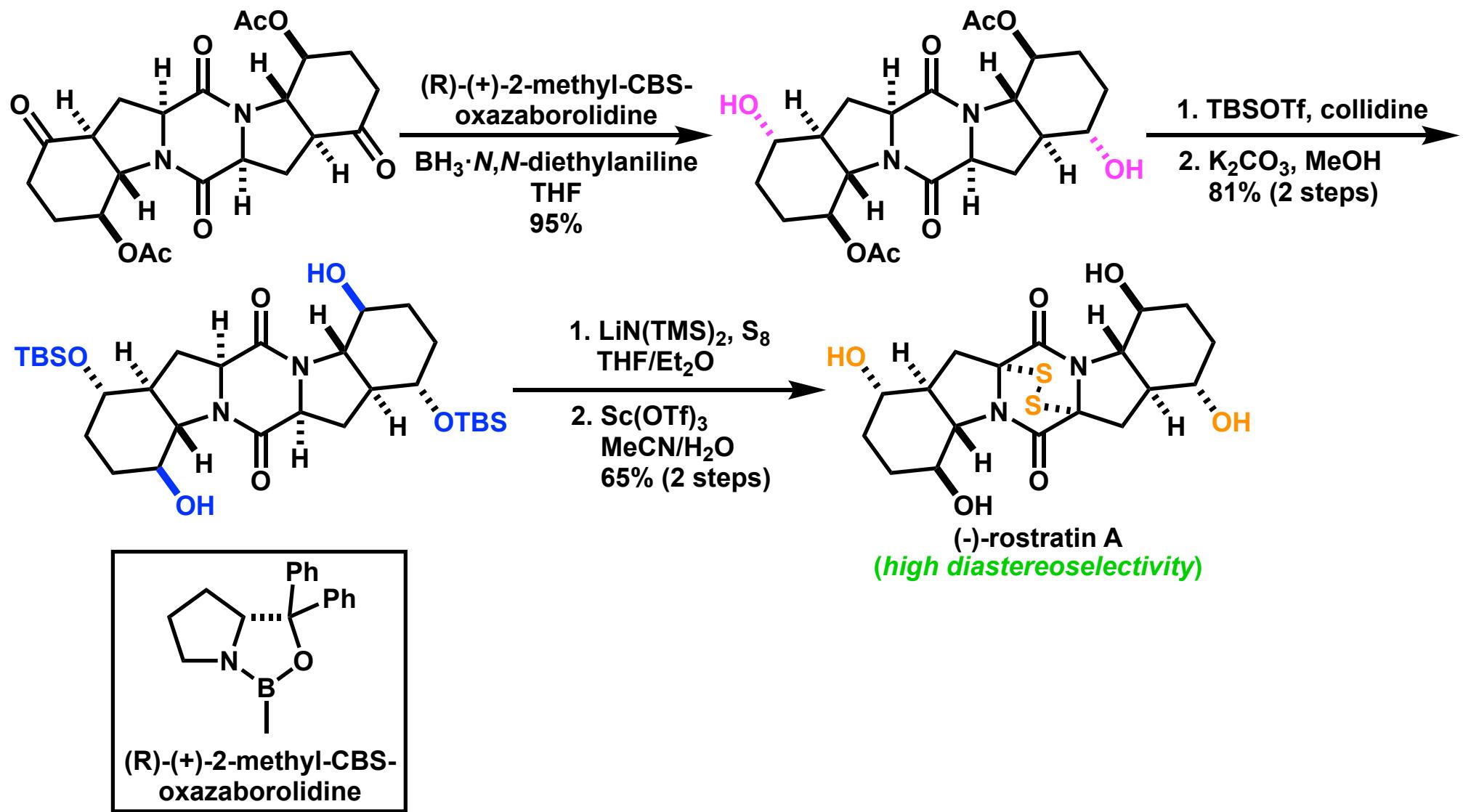
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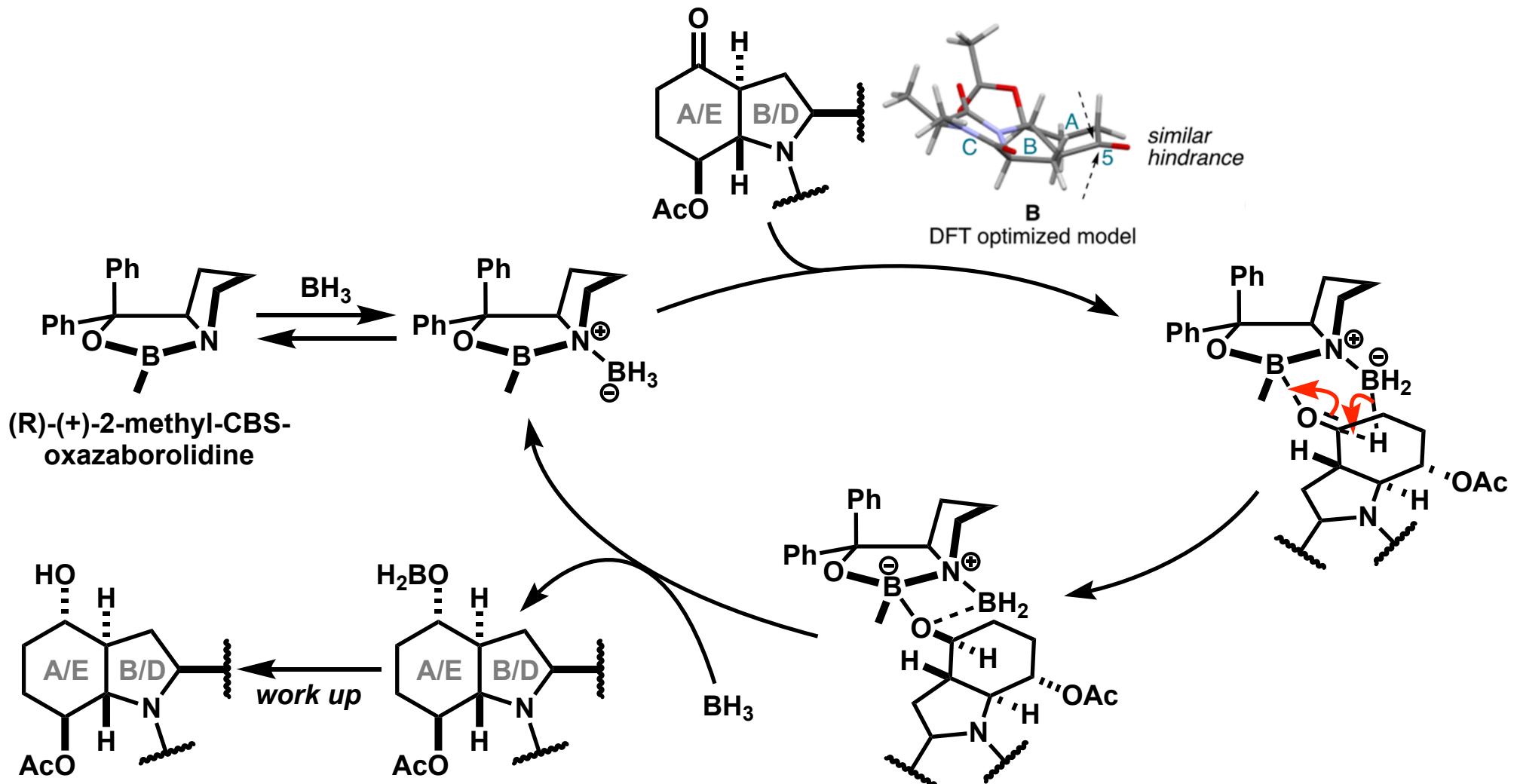
Installation of trans,trans Ring Junction of (-)-Rostratin A



Total Synthesis of (-)-Rostratin A



Diastereoselective Reduction

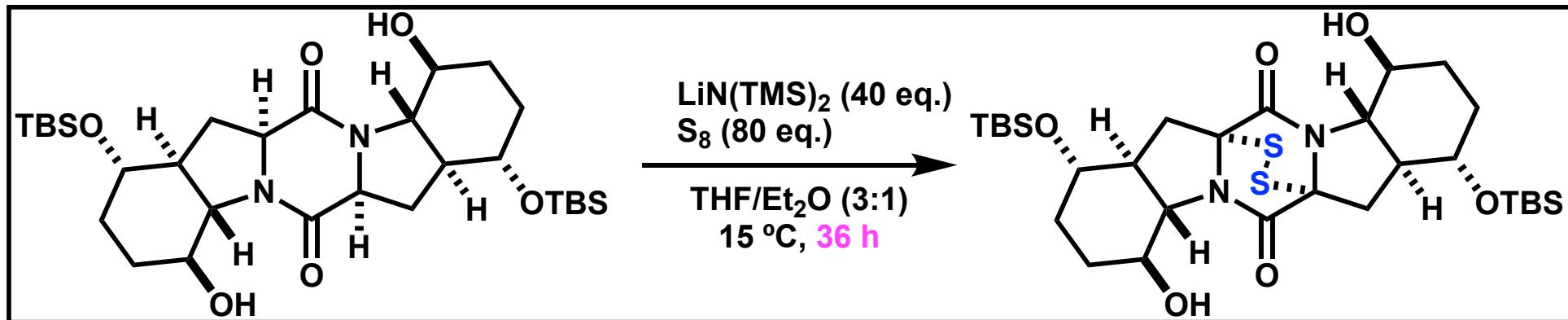


1) Thesmar, P.; Baudoin, O. *J. Am. Chem. Soc.* **2019**, *141*, 15779

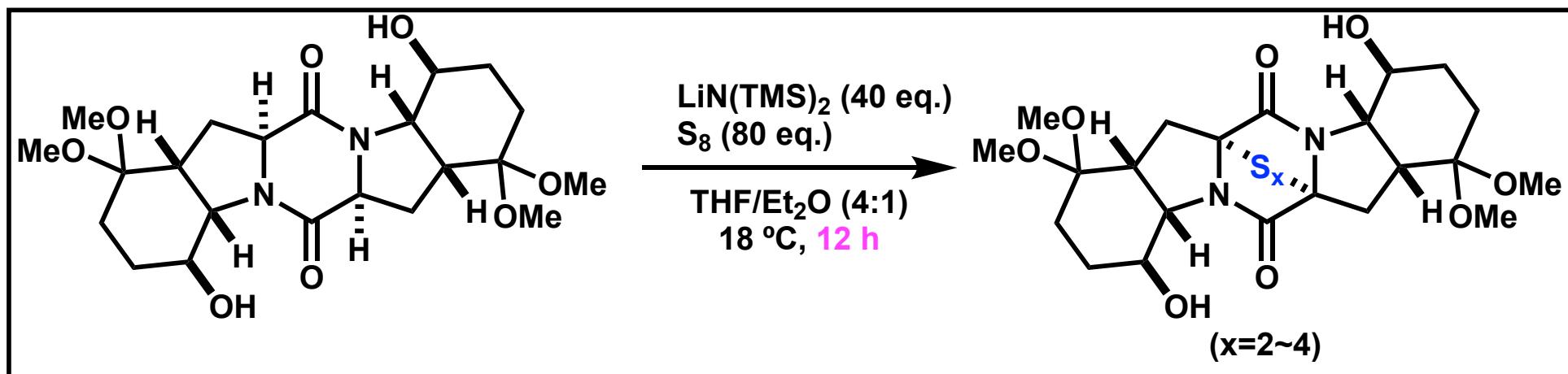
2) Jones, D. K.; Liotta, D. C.; Shinkai, I.; Mathre, D. J. *J. Org. Chem.* **1993**, *58*, 799

Disulfidation (1)

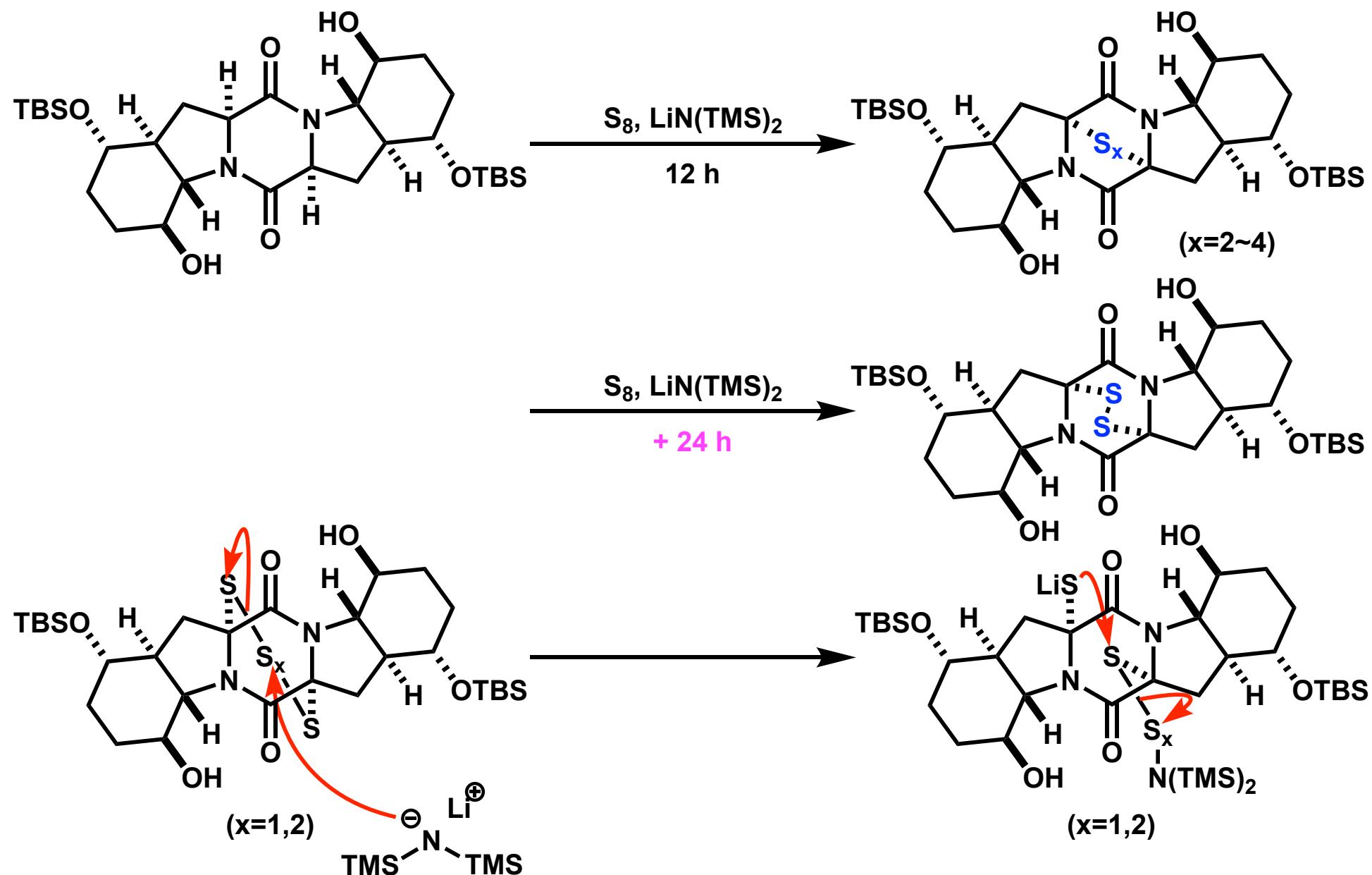
for (-)-rostratin A



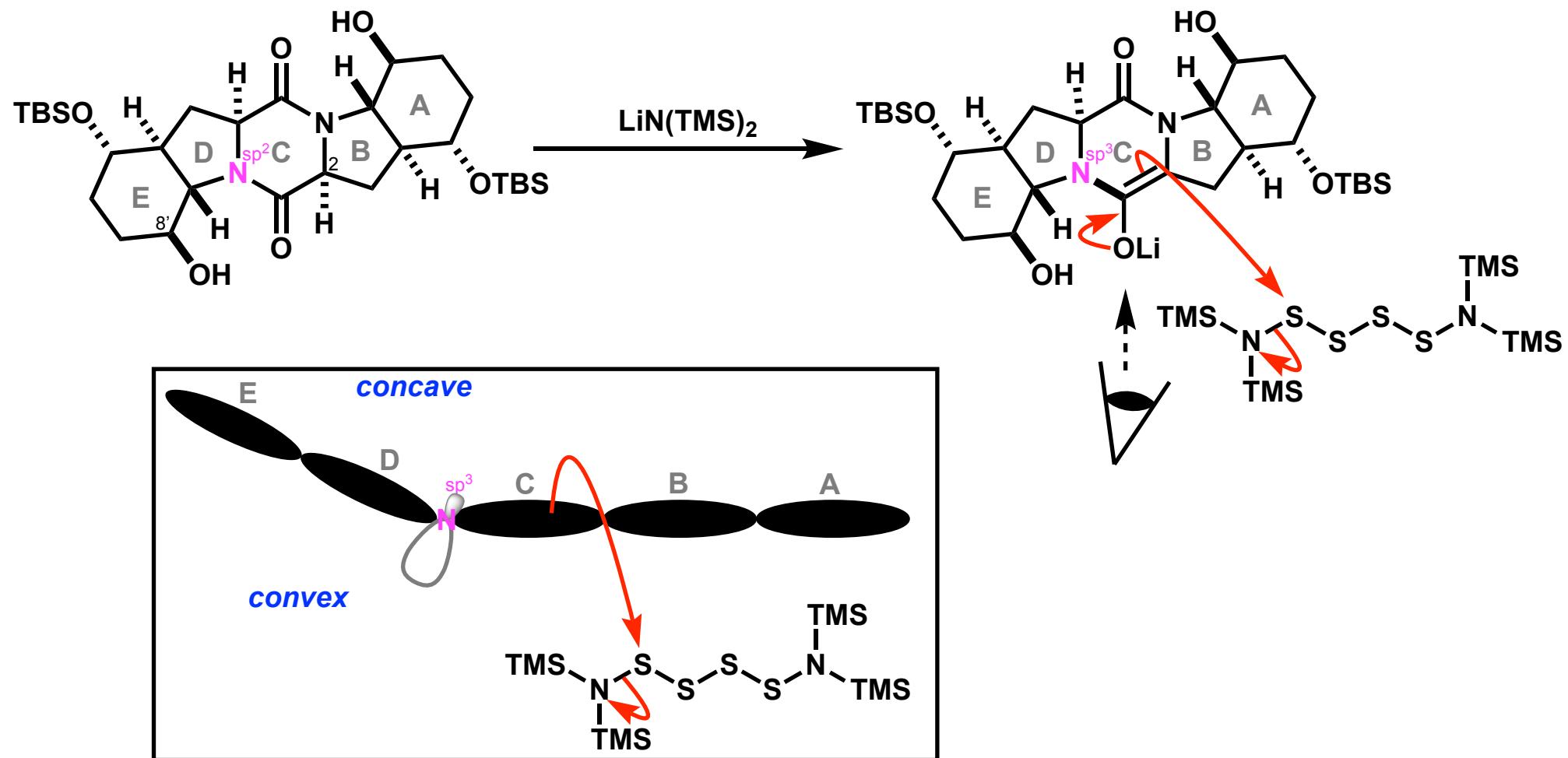
for (-)-epicoccin G



Disulfidation (2)



Diastereoselective Sulfuration for (-)-Rostratin A



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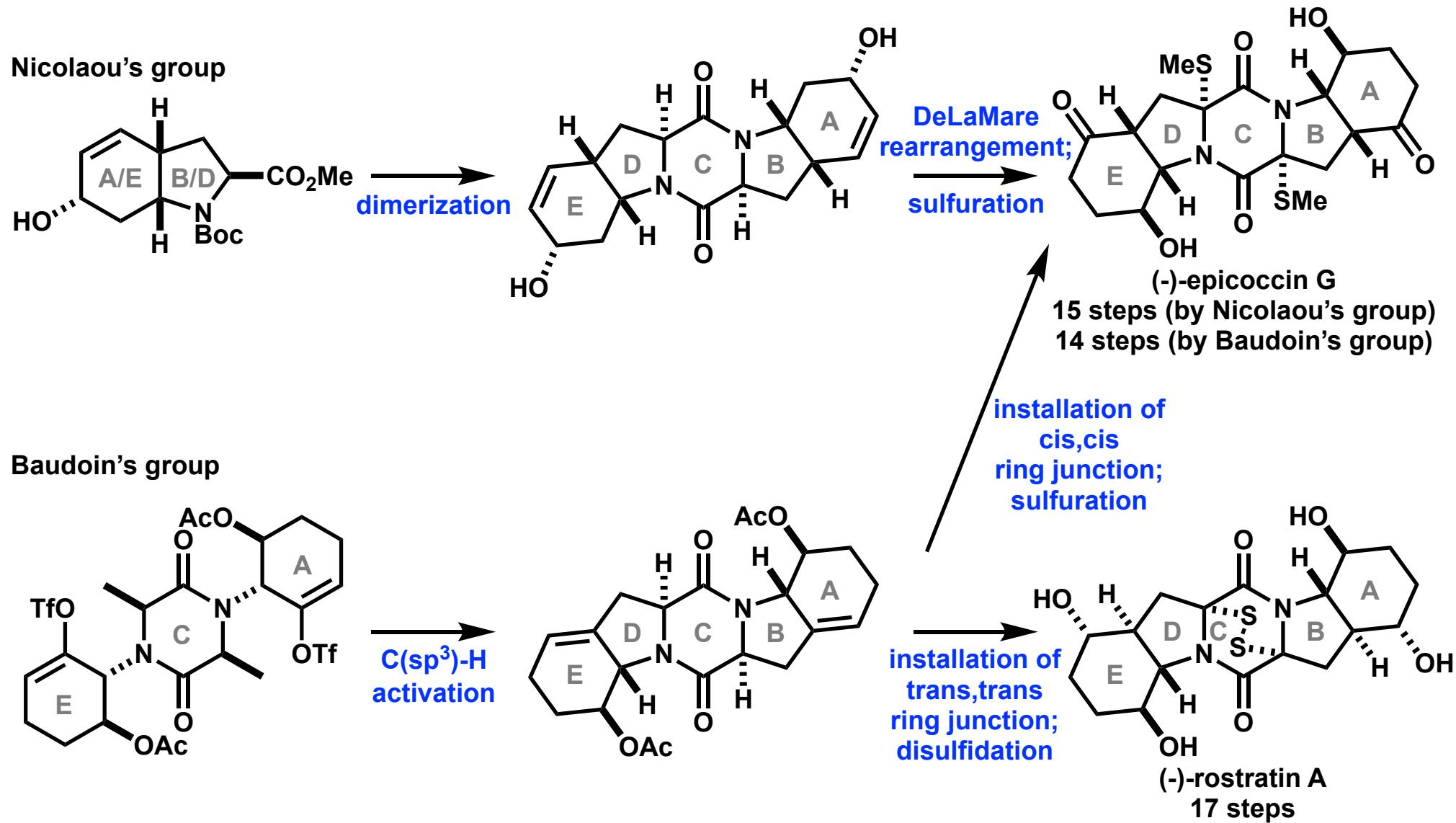
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- 1) Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun, Y.-P.; Sarlah, D. *J. Am. Chem. Soc.* **2011**, *133*, 8150
- 2) Thesmar, P.; Baudoin, O. *J. Am. Chem. Soc.* **2019**, *141*, 15779