

Total Synthesis of (+)-Corymine

**2020.9.12. Literature Seminar
B4 Hibiki Asai**

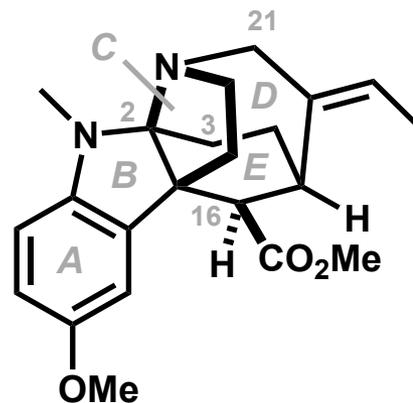
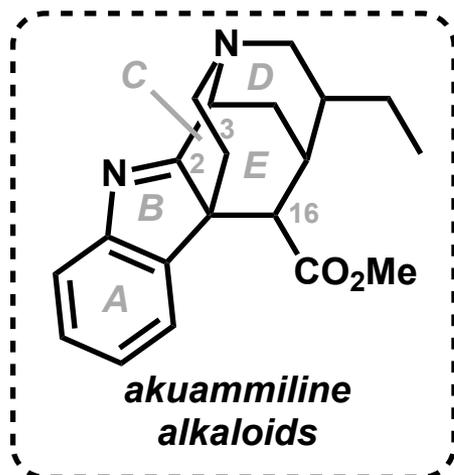
Contents

1. Introduction

2. Total synthesis of (-)-Vincorine (by MacMillan Group)

3. Total synthesis of (+)-Corymine (by Li Group)

Akuammiline Alkaloids



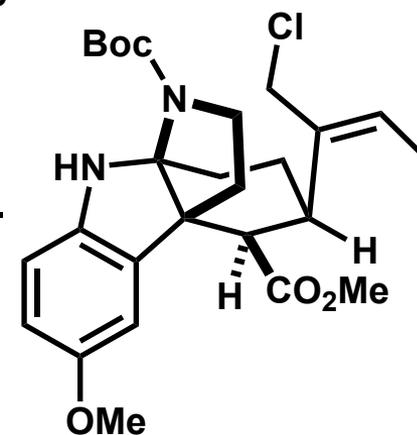
- (1) TMSOTf, 2,6-lutidine
CH₂Cl₂
- (2) K₂CO₃, KI
MeCN, 60 °C

construction of D-ring



- (3) HCHO, NaBH₃CN
MeCN, AcOH

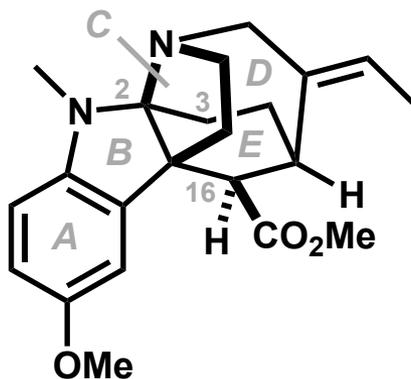
by Ma Group



- migration of C3-N bond to C2-N
- strained 7-membered azepanyl ring

- 1) Zi, W.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2012**, *134*, 4037.
- 2) Eckermann, R.; Gaich, T. *Synthesis* **2013**, *45*, 2813.

Vincorine and Corymine



(-)-vincorine

Isolation:

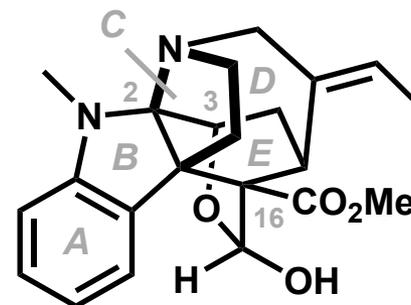
Vinca minor (1962) ¹⁾

Structural features:

pentacyclic caged structure
strained 7-membered azepanyl ring

Total synthesis:

Qin (2009 (35 steps, racemic)) ³⁾
Ma (2012 (18 steps, enantioselective)) ⁴⁾
MacMillan (2013 (9 steps, enantioselective)) ⁵⁾



(+)-corymine

Hunteria corymbosa (1962) ²⁾

hexacyclic caged structure
strained 7-membered azepanyl ring
C16 extra carbon

Li (2017 (21 steps, racemic),
2020 (11 steps, 99% ee)) ^{6) 7)}

1) Mokry, J.; Dubravkova, L.; Šefcovic, P. *Experientia* **1962**, *18*, 564.

2) Kiang, A. K.; Smith, G. F. *Proc. Chem. Soc.* **1962**, 298.

3) Zhang, M.; Huang, X.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6013.

4) Zi, W.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2012**, *134*, 4037.

5) Horning, B. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 6442.

6) Zhang, B.; Wang, X.; Cheng, C.; Sun, D.; Li, C. *Angew. Chem., Int. Ed.* **2017**, *56*, 7484

7) Zhang, B.; Wang, X.; Li, C. *J. Am. Chem. Soc.* **2020**, *142*, 3269.

8) Eckermann, R.; Gaich, T. *Synthesis* **2013**, *45*, 2813.

Introduction of Prof. MacMillan and Li



Prof. David W. C. MacMillan

1991 B.S. @ University of Glasgow

1996 Ph.D @ the University of California, Irvine (Prof. Larry E. Overman)

1996- Postdoctoral fellow

@ Harvard University (Prof. David A. Evans)

1998- @ the University of California, Berkeley

2000- @ the California Institute of Technology

2004- Professor @ the California Institute of Technology

2006- Professor @ Princeton University

2011- Distinguished professor @ Princeton University

Research topic: photoredox, organocatalysis, total synthesis



Prof. Chaozhong Li

1988 B.S @ University of Science and Technology of China

1993 Ph.D @ Shanghai Institute of Organic Chemistry

1993- Assistant Researcher @ Shanghai Institute of Organic Chemistry

1994- Postdoctoral fellow @ Iowa State University

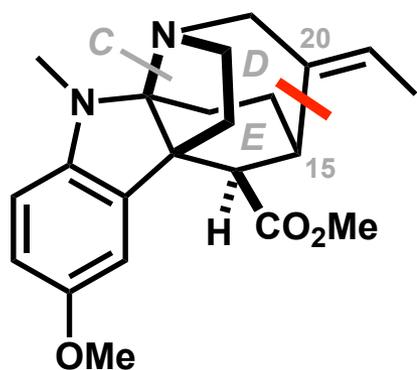
1999- Associate professor @ Shanghai Institute of Organic Chemistry

2000- Professor @ Shanghai Institute of Organic Chemistry

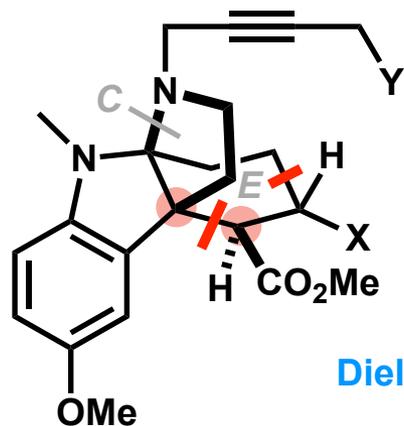
**Research topic: free radical chemistry, organofluorine chemistry,
organometallic chemistry, natural product synthesis**

Retrosynthetic Analysis

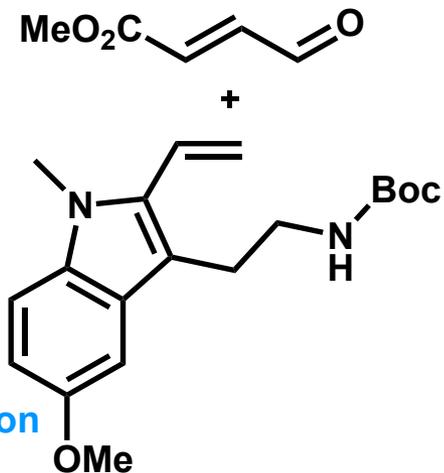
by MacMillan



7-membered
cyclization

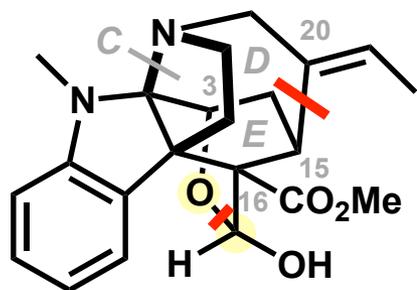


asymmetric
Diels-Alder reaction

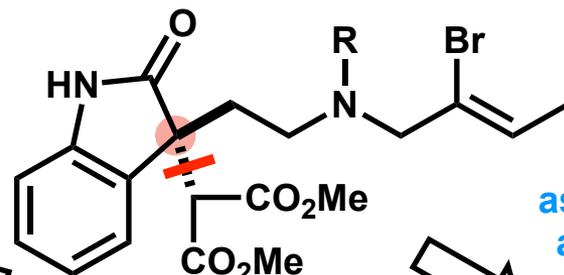
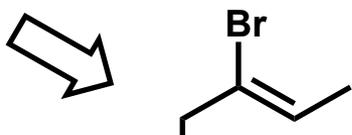


(-)-vincorine

; Hemiacetalization
7-membered
cyclization

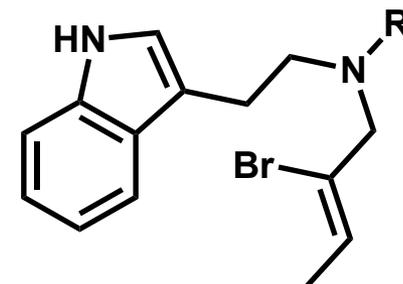
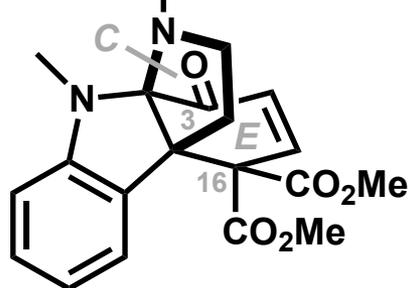


(+)-corymine



asymmetric
alkylation

by Li



- 1) Horning, B. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 6442.
- 2) Zhang, B.; Wang, X.; Li, C. *J. Am. Chem. Soc.* **2020**, *142*, 3269.

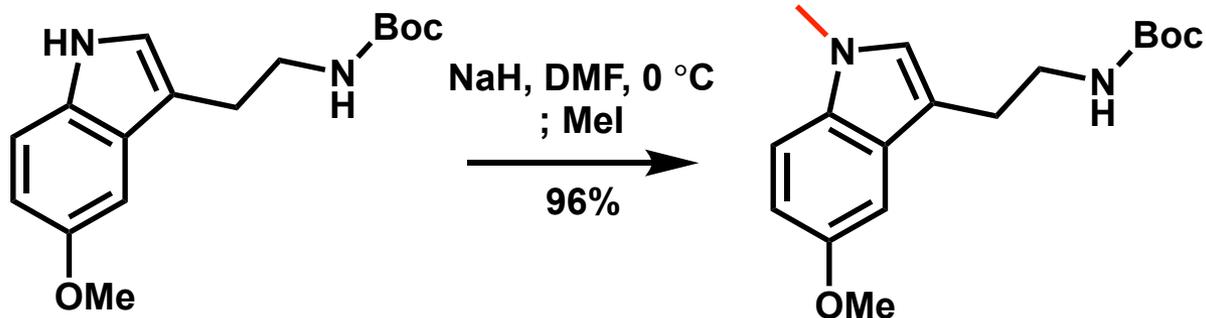
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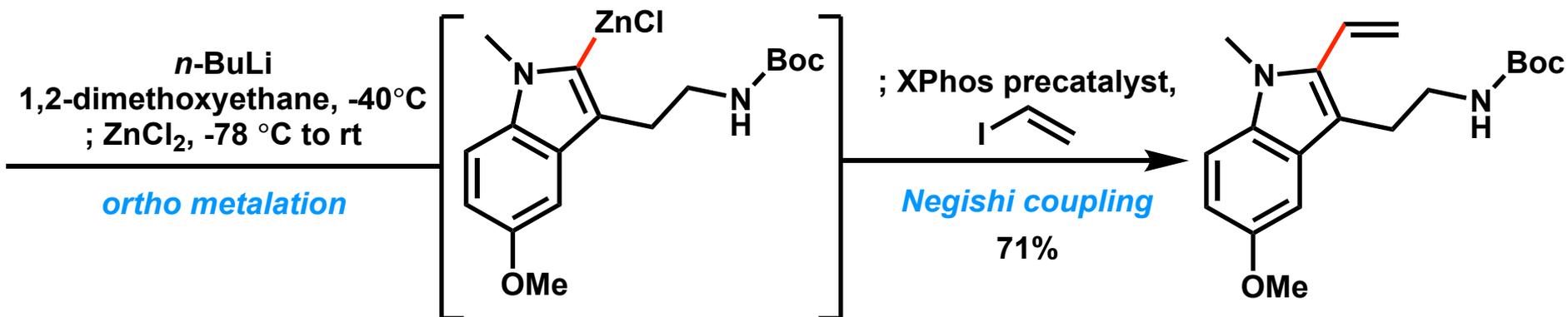
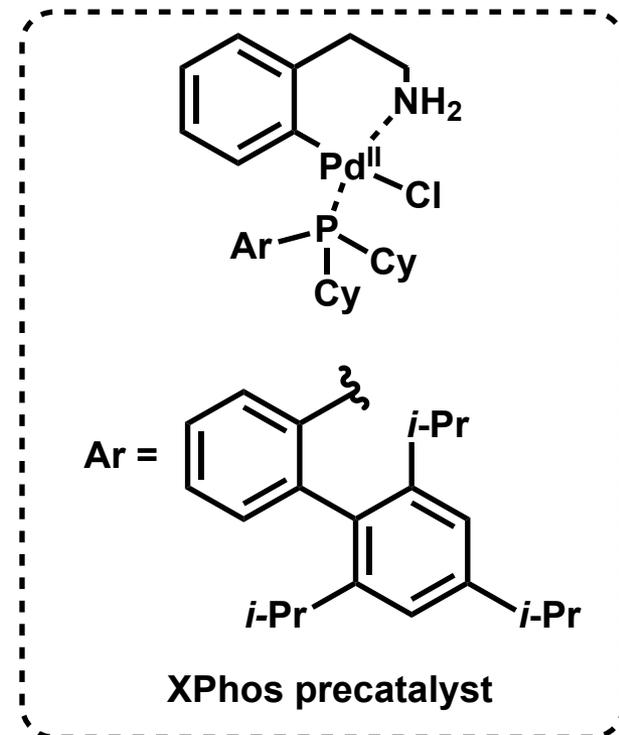
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(by MacMillan Group)**

**3. Total synthesis of (+)-Corymine
(by Li Group)**

Synthesis of Diene

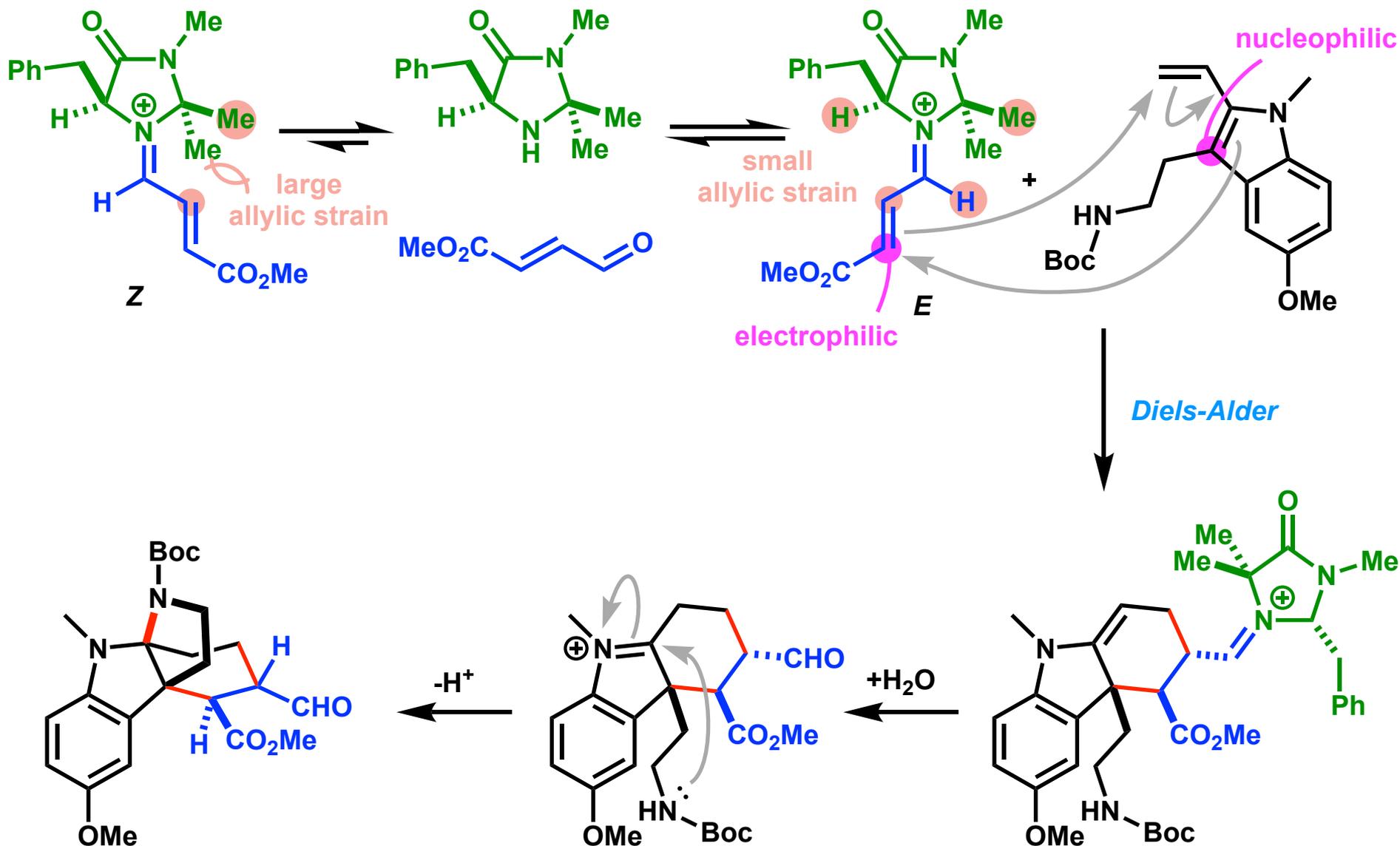


commercially available



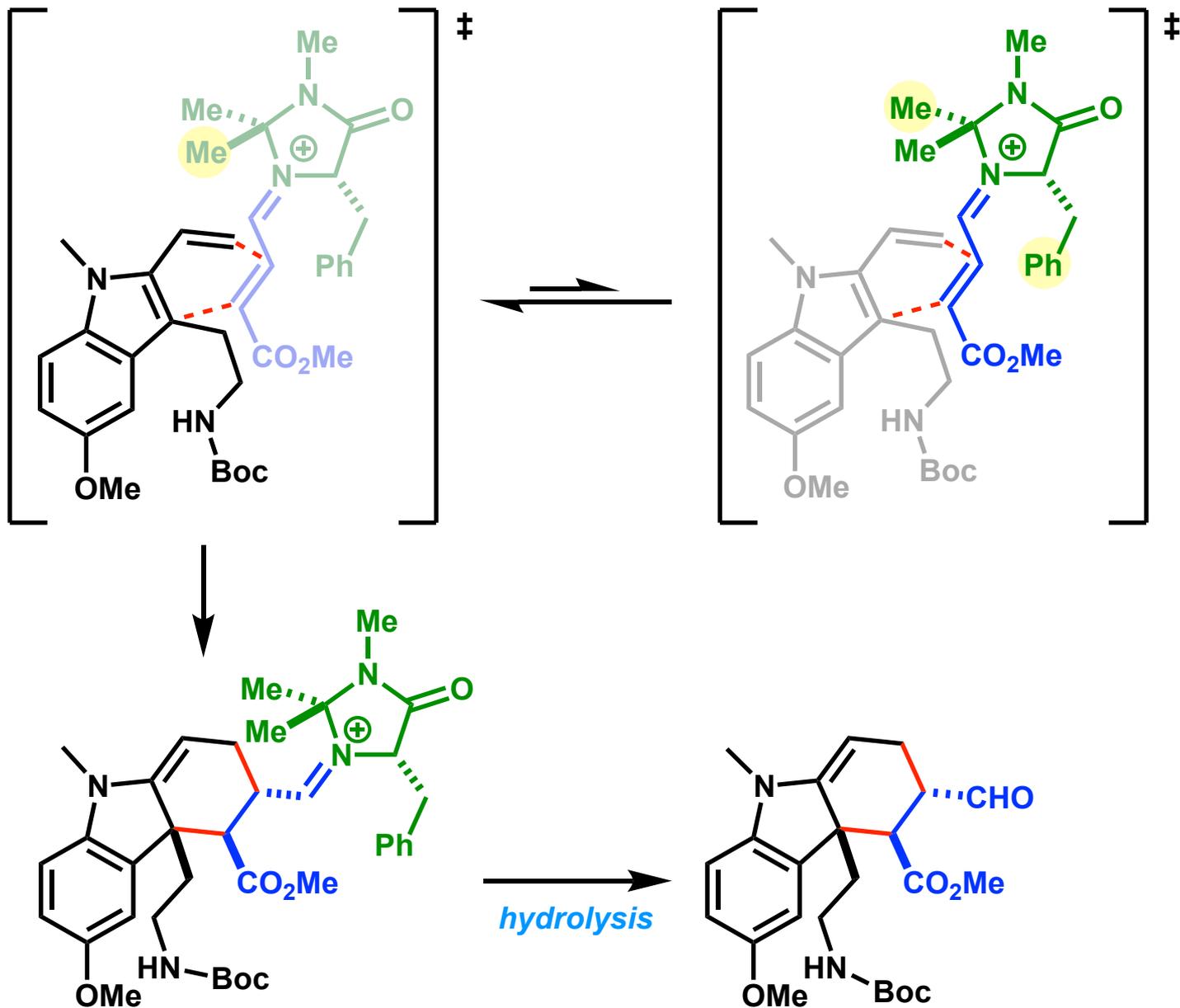
- 1) Horning, B. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 6442.
- 2) Biscoe, M. R.; Fros, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686.

Diels-Alder/Cyclization Cascade (II)



- 1) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.
- 2) Horning, B. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 6442.

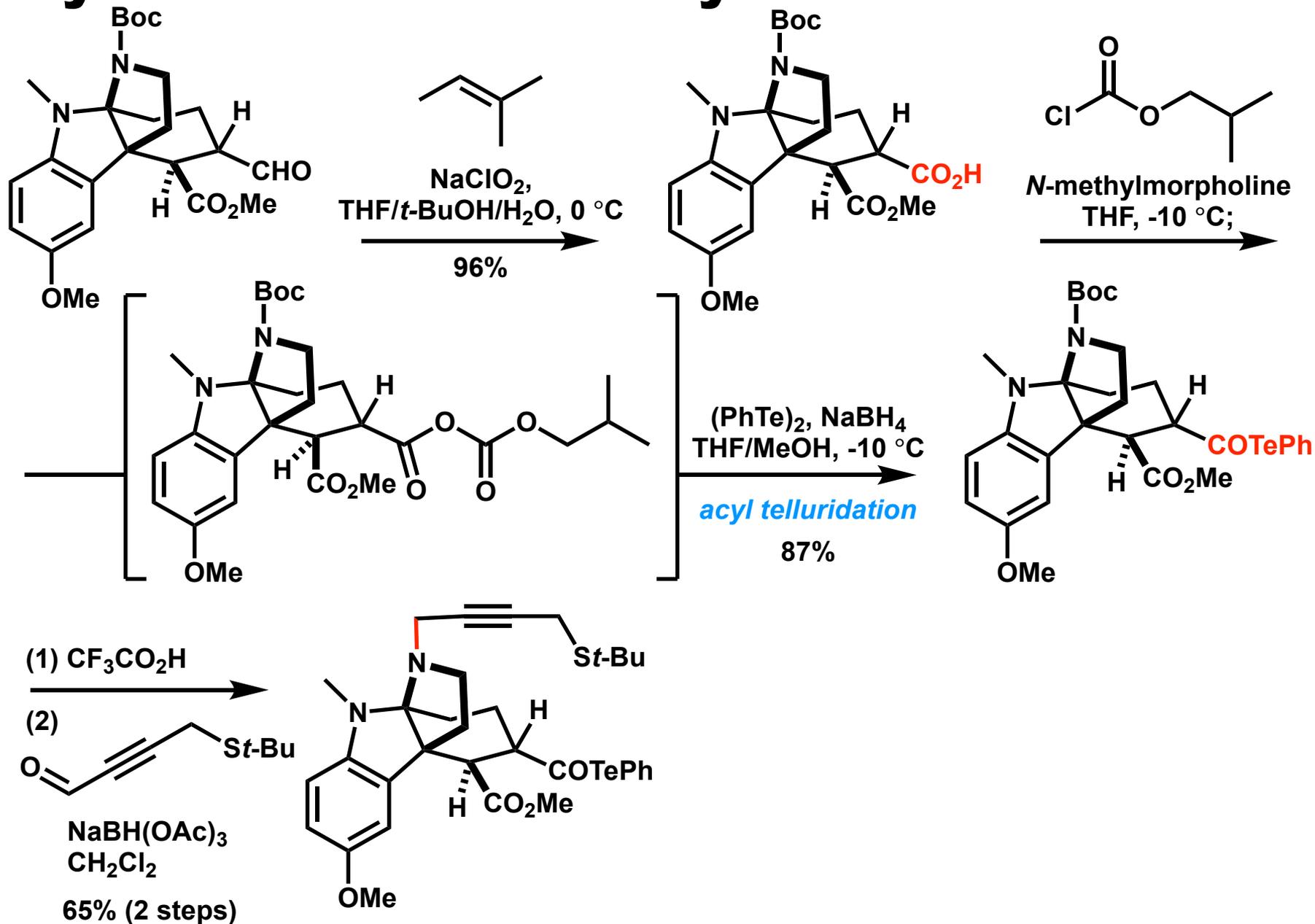
Enantioselectivity of Diels-Alder



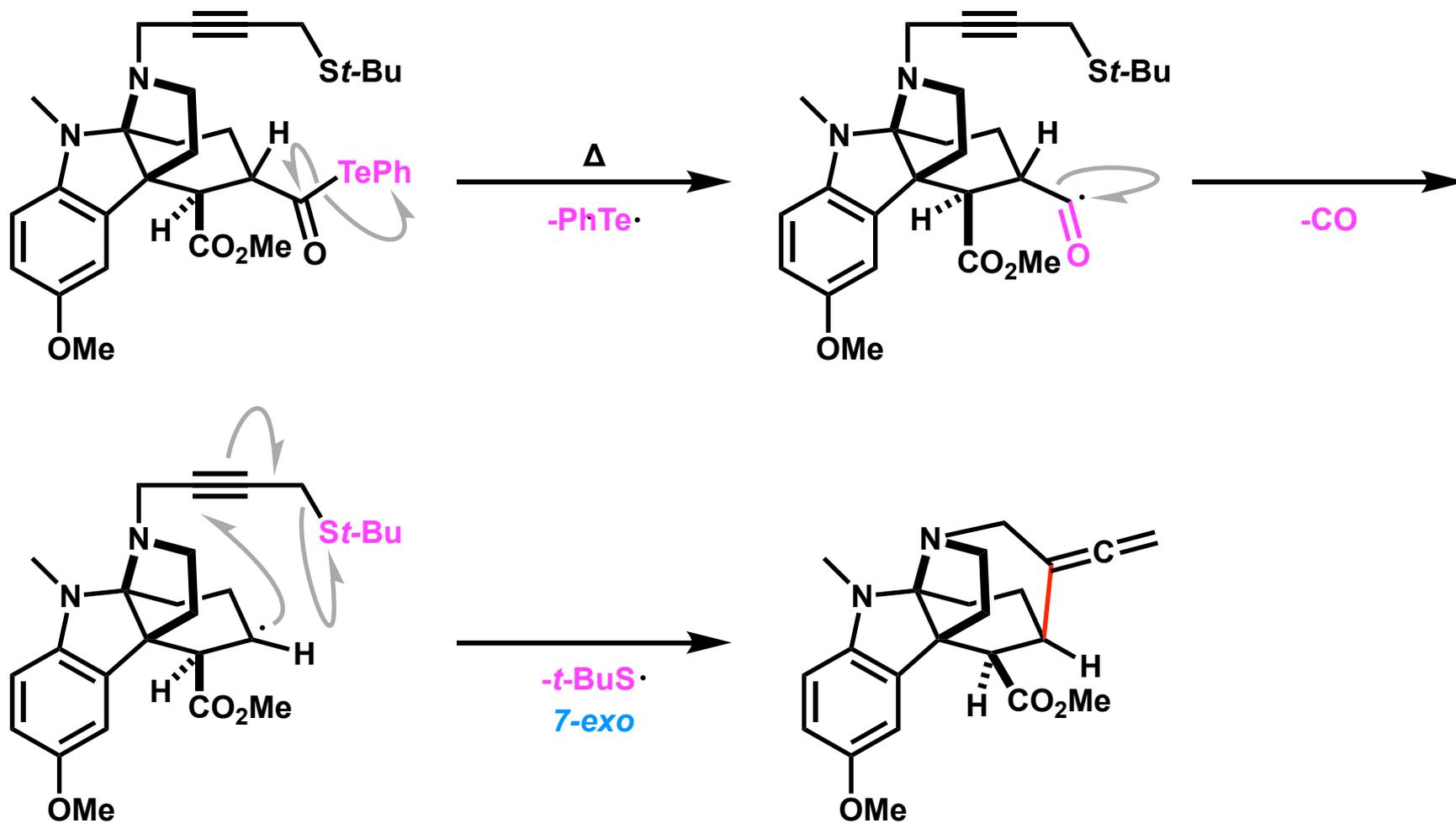
1) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.

2) Horning, B. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 6442.

Synthesis of Radical Cyclization Precursor

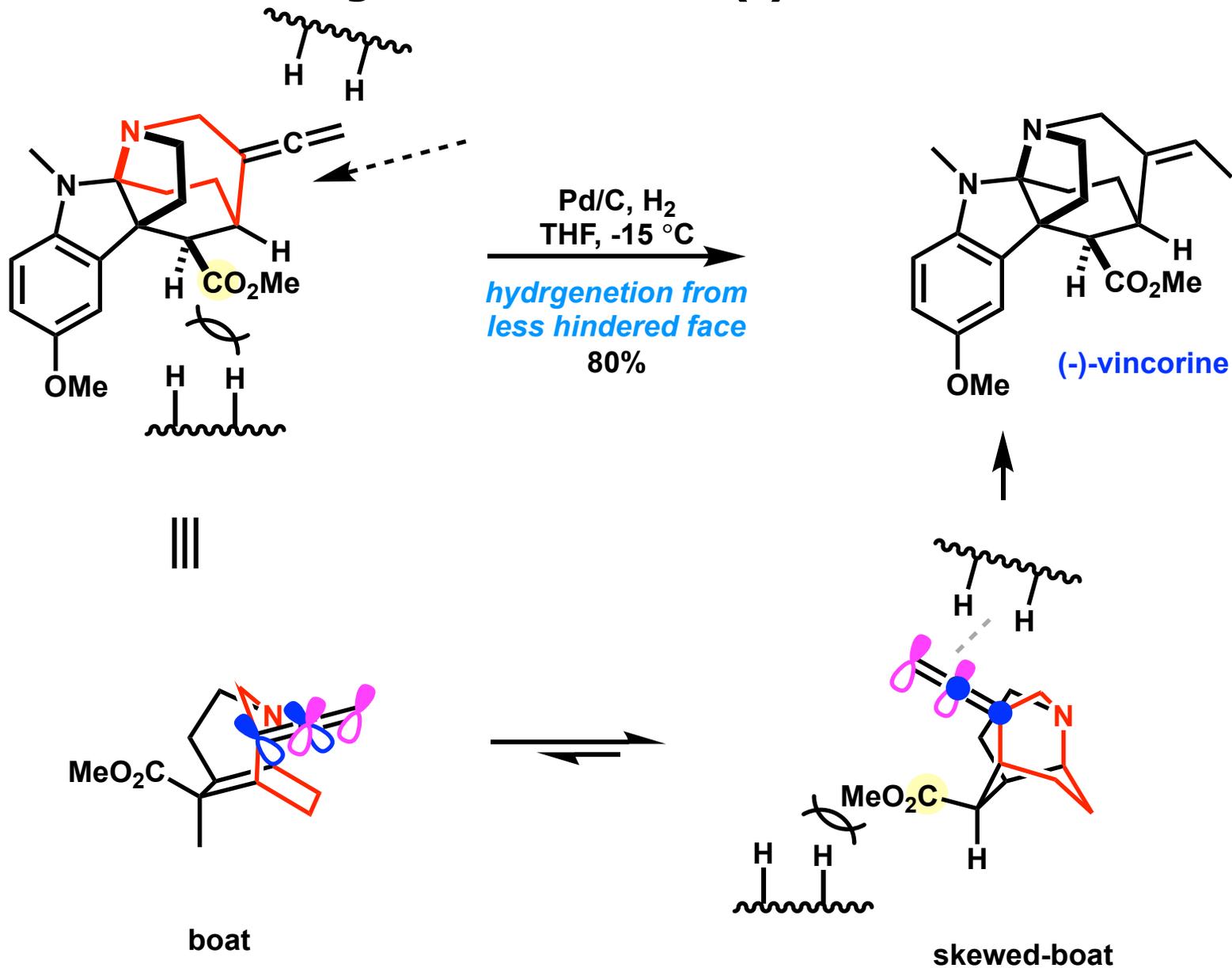


Radical Cyclization (II)

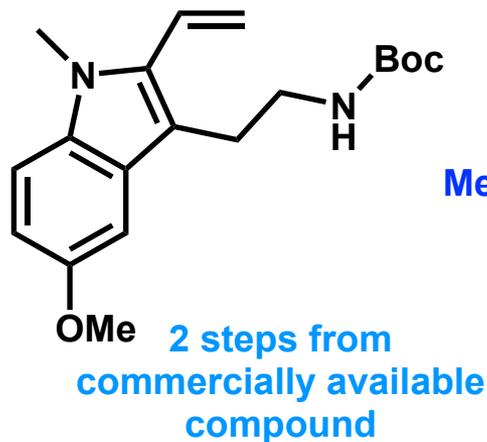


- 1) Horning, B. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 6442.
- 2) Chen, C.; Crich, D.; Papadatos, A. *J. Am. Chem. Soc.* **1992**, *114*, 8313.

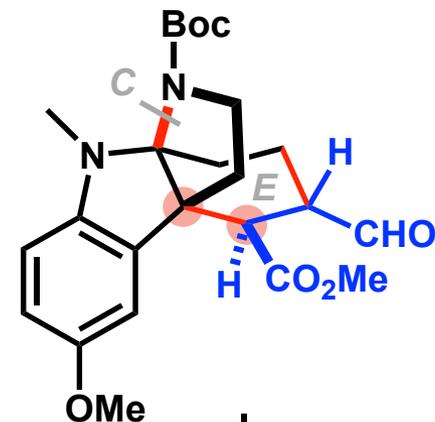
Total Synthesis of (-)-Vincorine



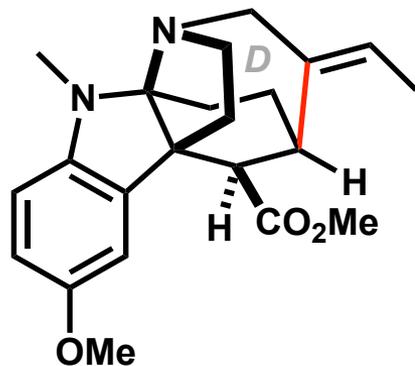
Short Summary



asymmetric
Diels-Alder reaction

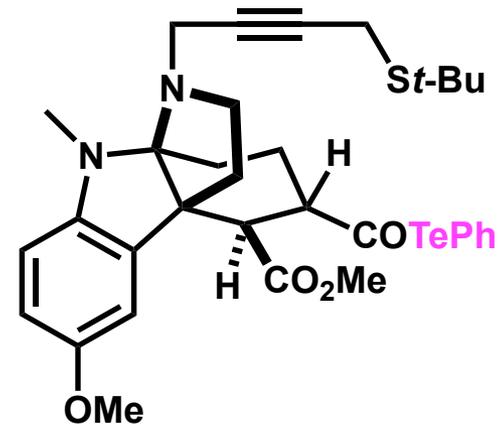


- 9 steps synthesis
- asymmetric Diels-Alder reaction
- radical cyclization using acyl telluride



(-)-vincorine

radical cyclization



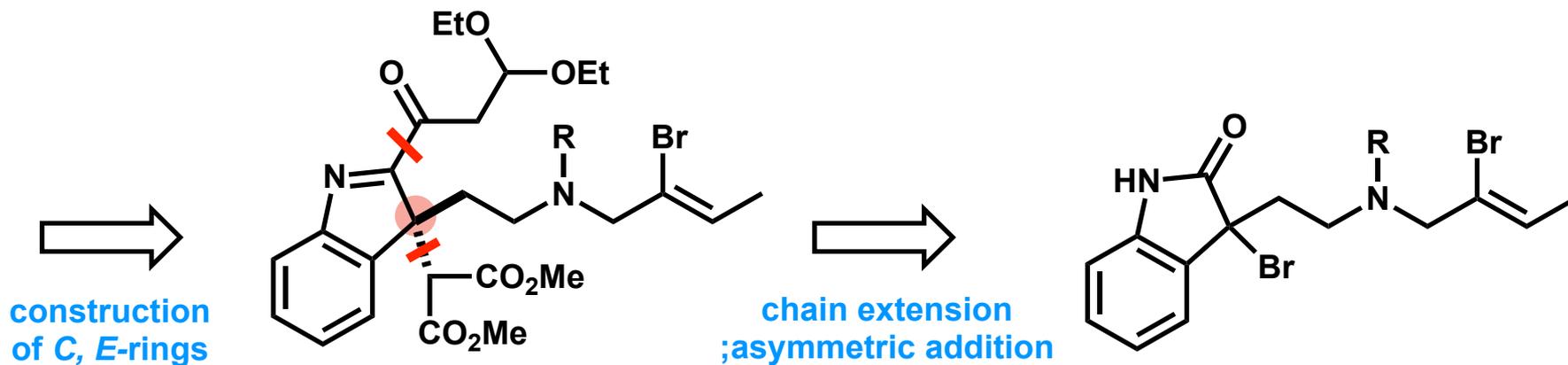
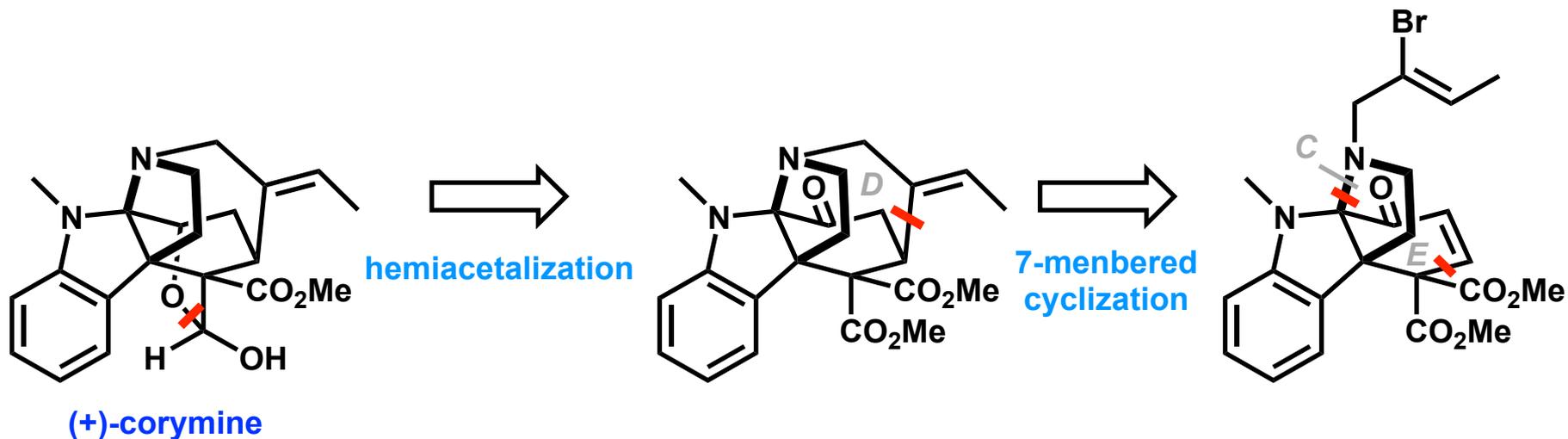
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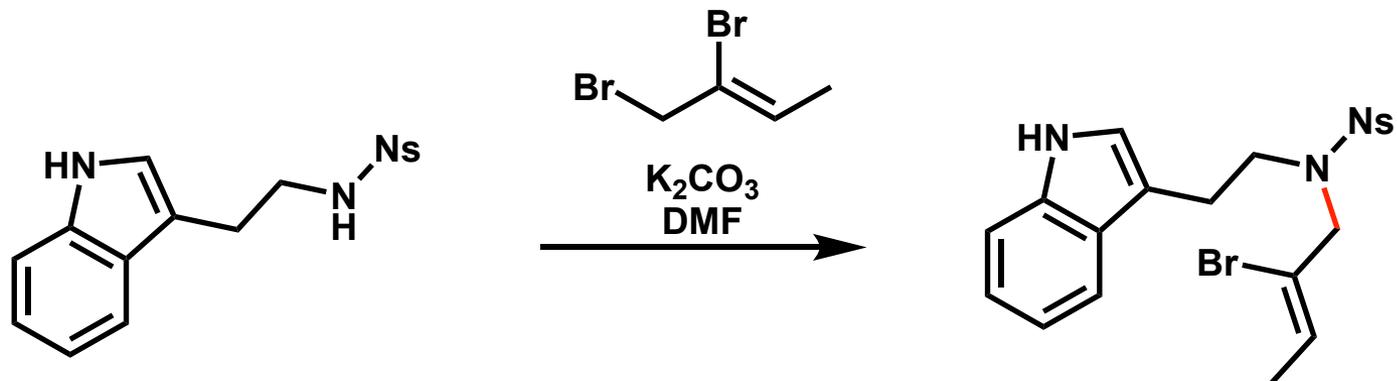
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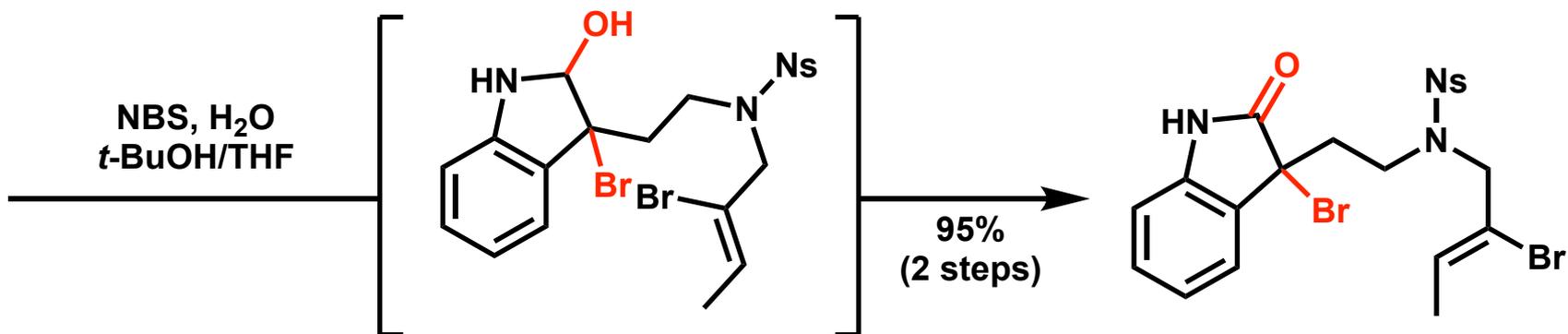
Retrosynthesis



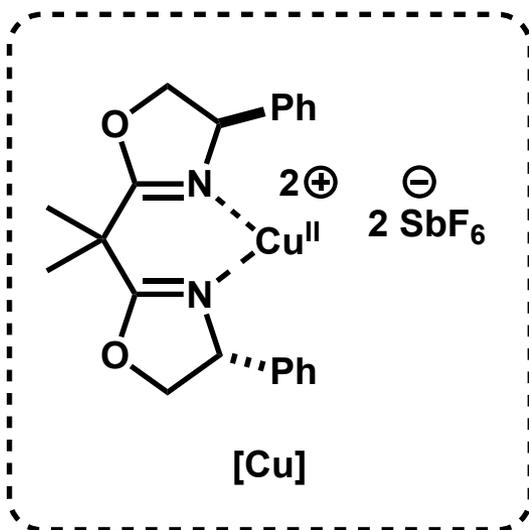
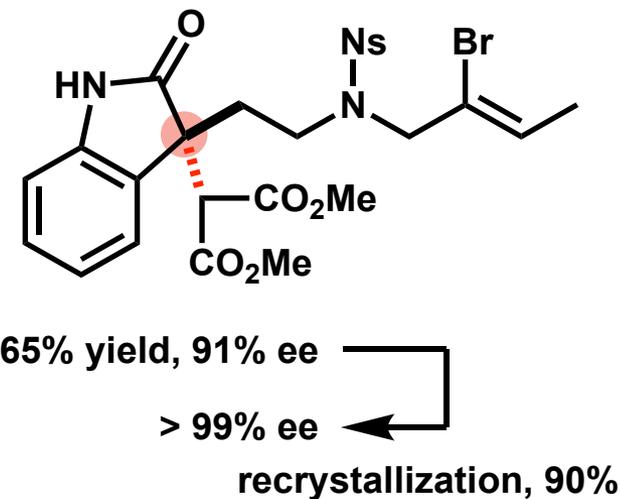
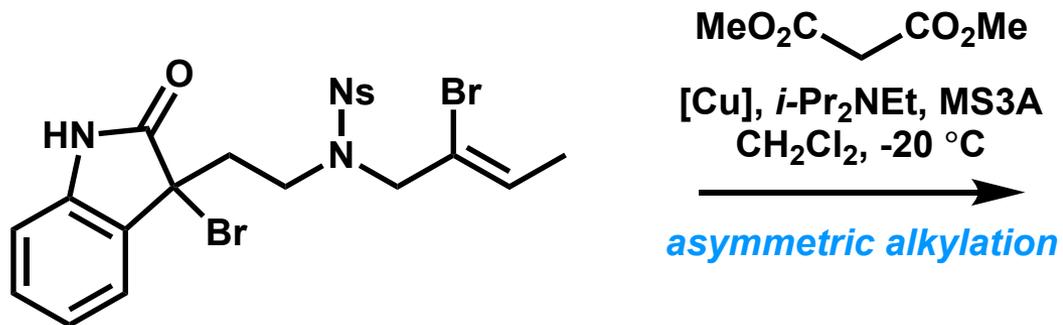
Synthesis of 3-bromooxindole



commercially available

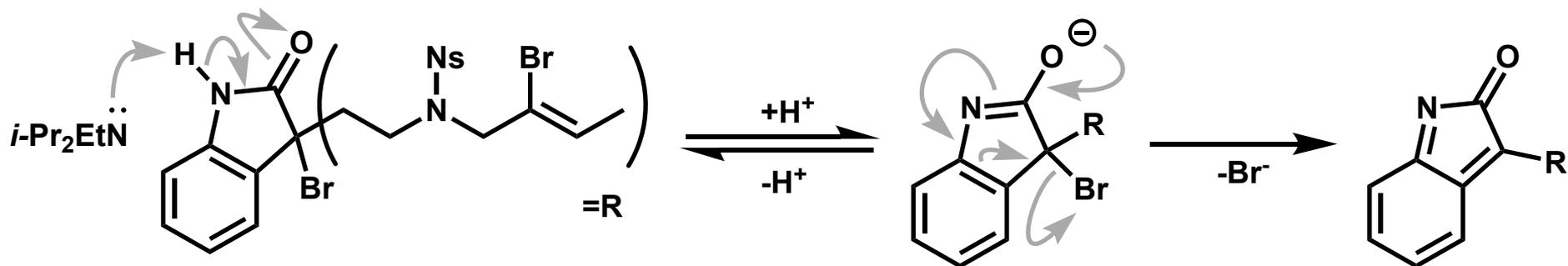
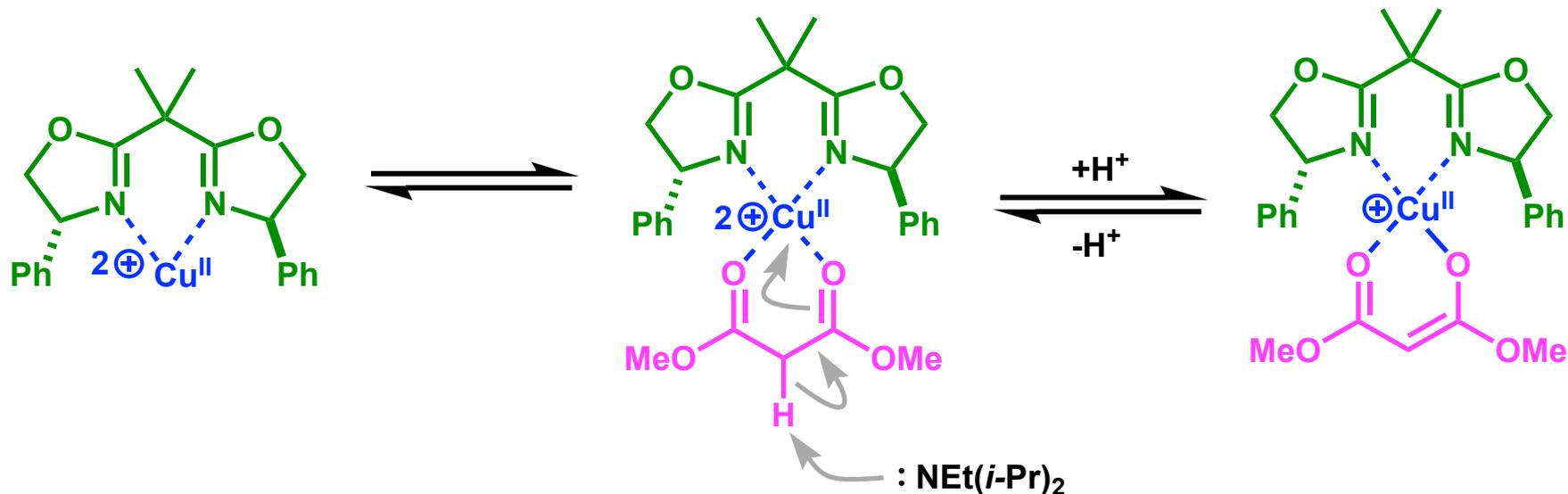


Cu-Catalyzed Enantioselective Alkylation



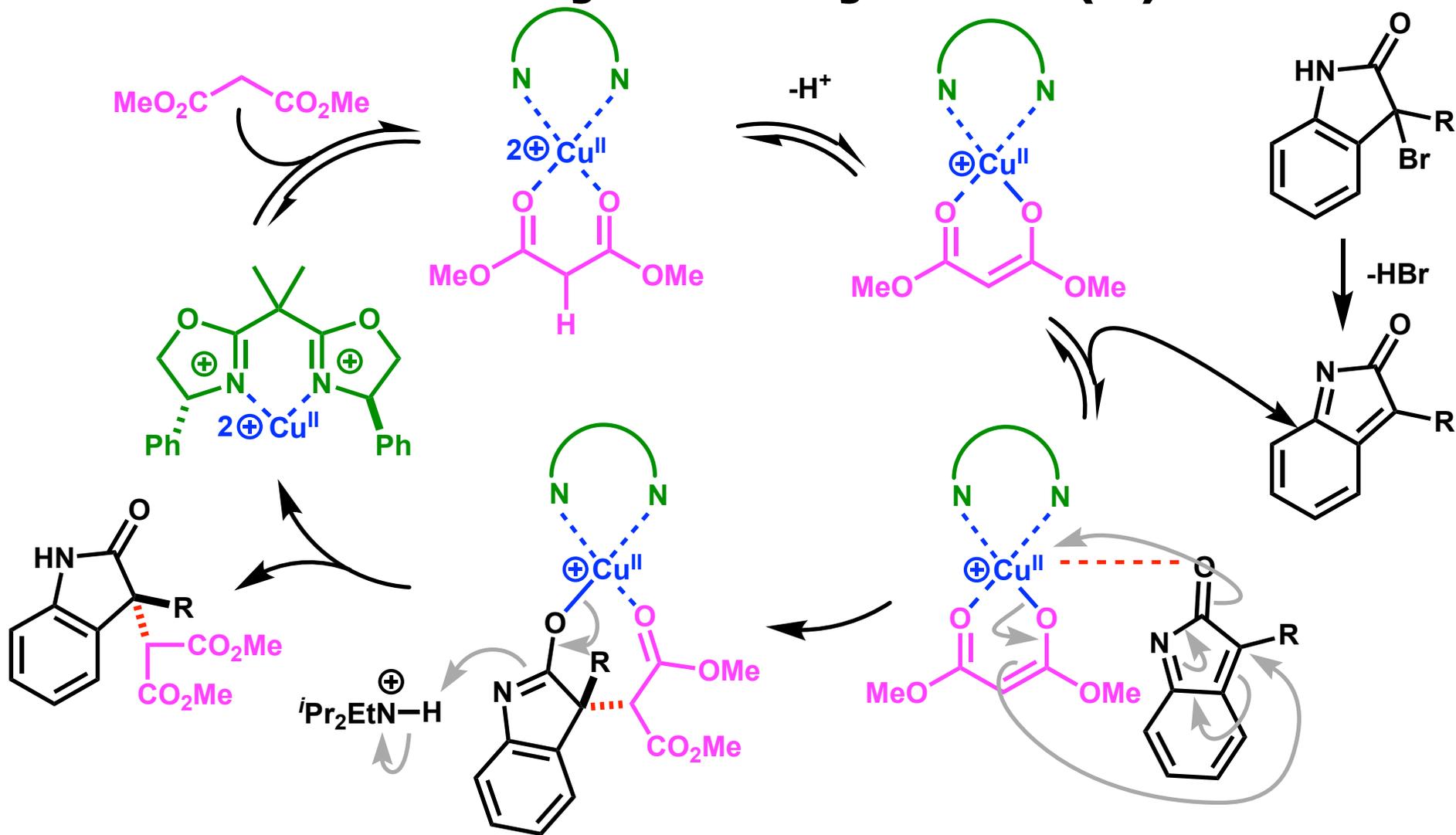
- 1) Zhang, B.; Wang, X.; Li, C. *J. Am. Chem. Soc.* **2020**, *142*, 3269.
- 2) Ma, S.; Han, X.; Krishnan, S.; Virgil, S. C.; Stolz, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8037.

Proposed Mechanism of Cu-Catalyzed Alkylation (I)



- 1) Zhang, B.; Wang, X.; Li, C. *J. Am. Chem. Soc.* **2020**, *142*, 3269.
- 2) Ma, S.; Han, X.; Krishnan, S.; Virgil, S. C.; Stolz, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8037.
- 3) D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger, J. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13097

Proposed Mechanism of Cu-Catalyzed Alkylation (II)

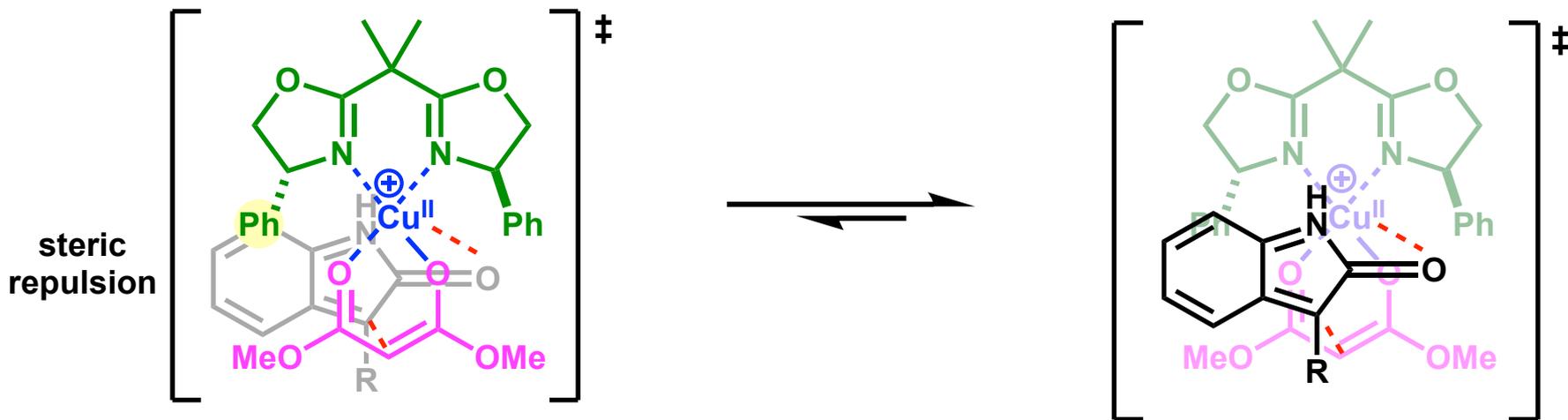
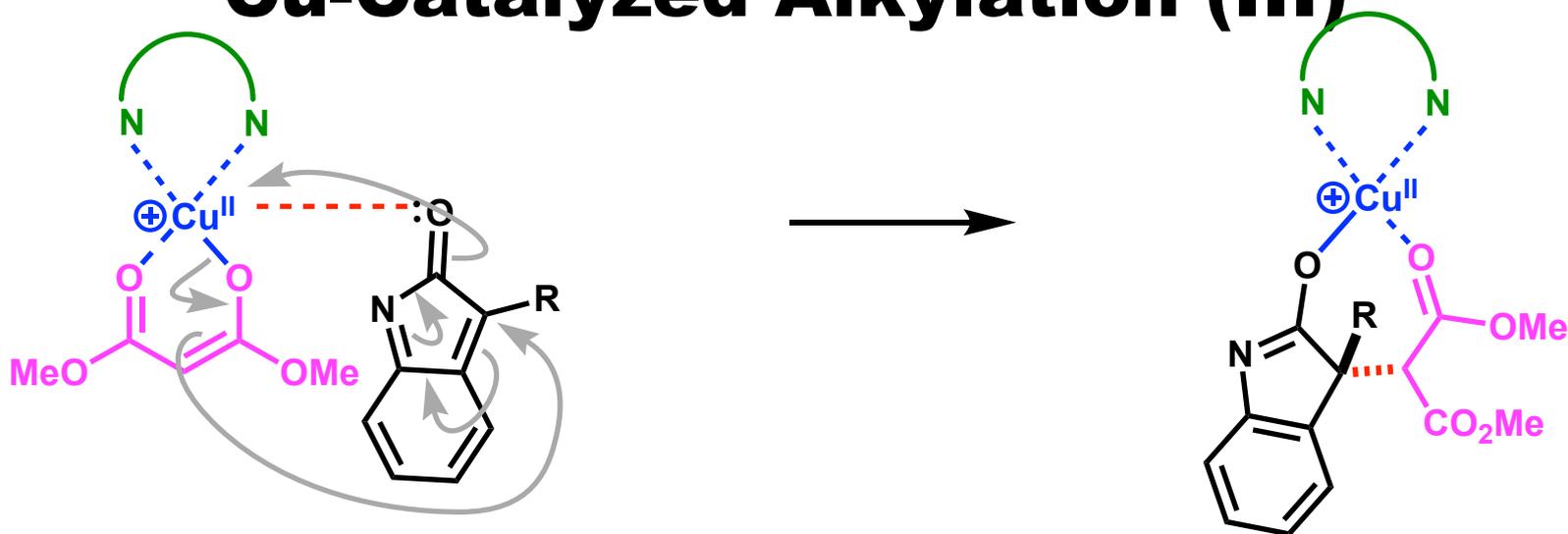


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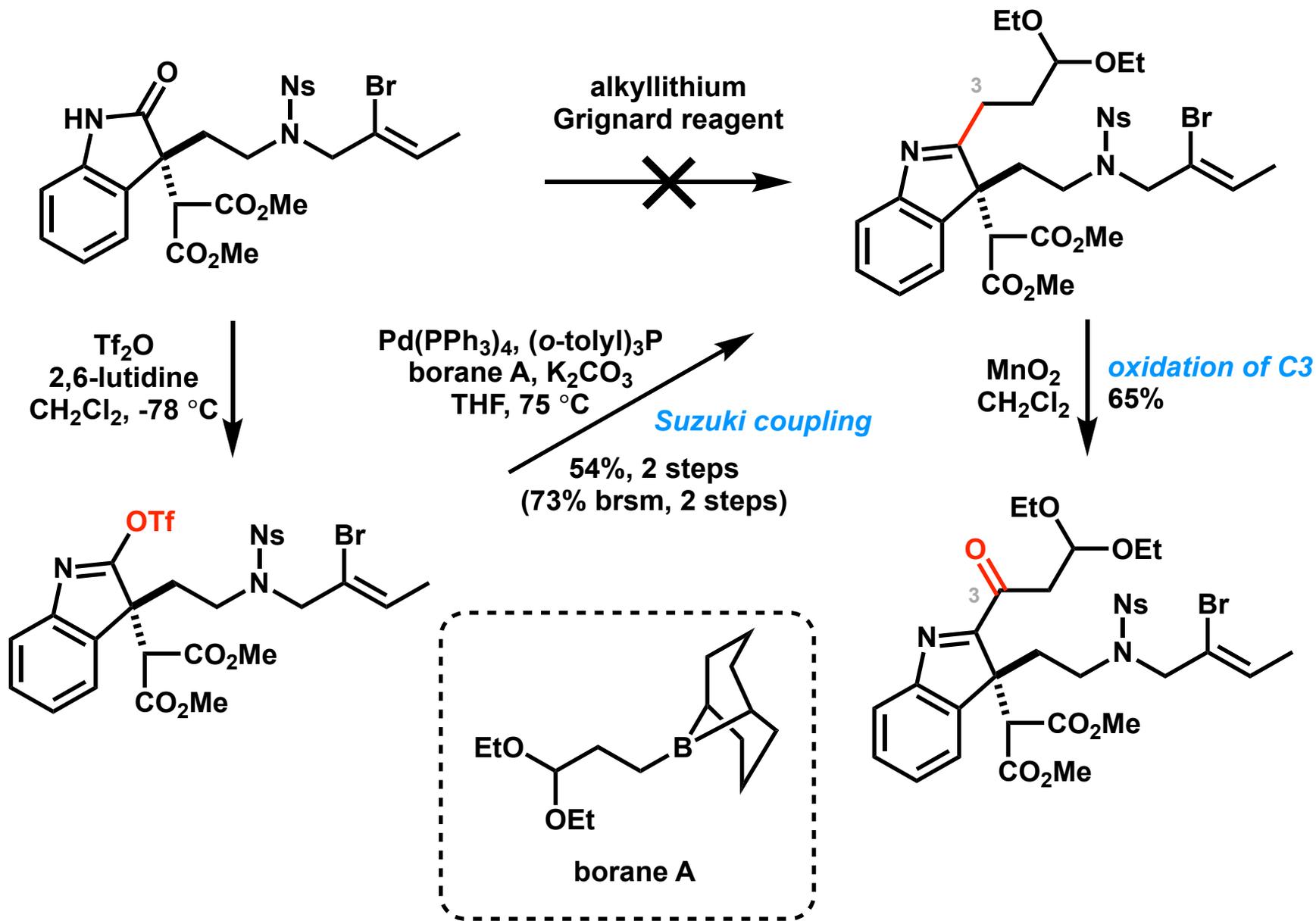
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Proposed Mechanism of Cu-Catalyzed Alkylation (III)

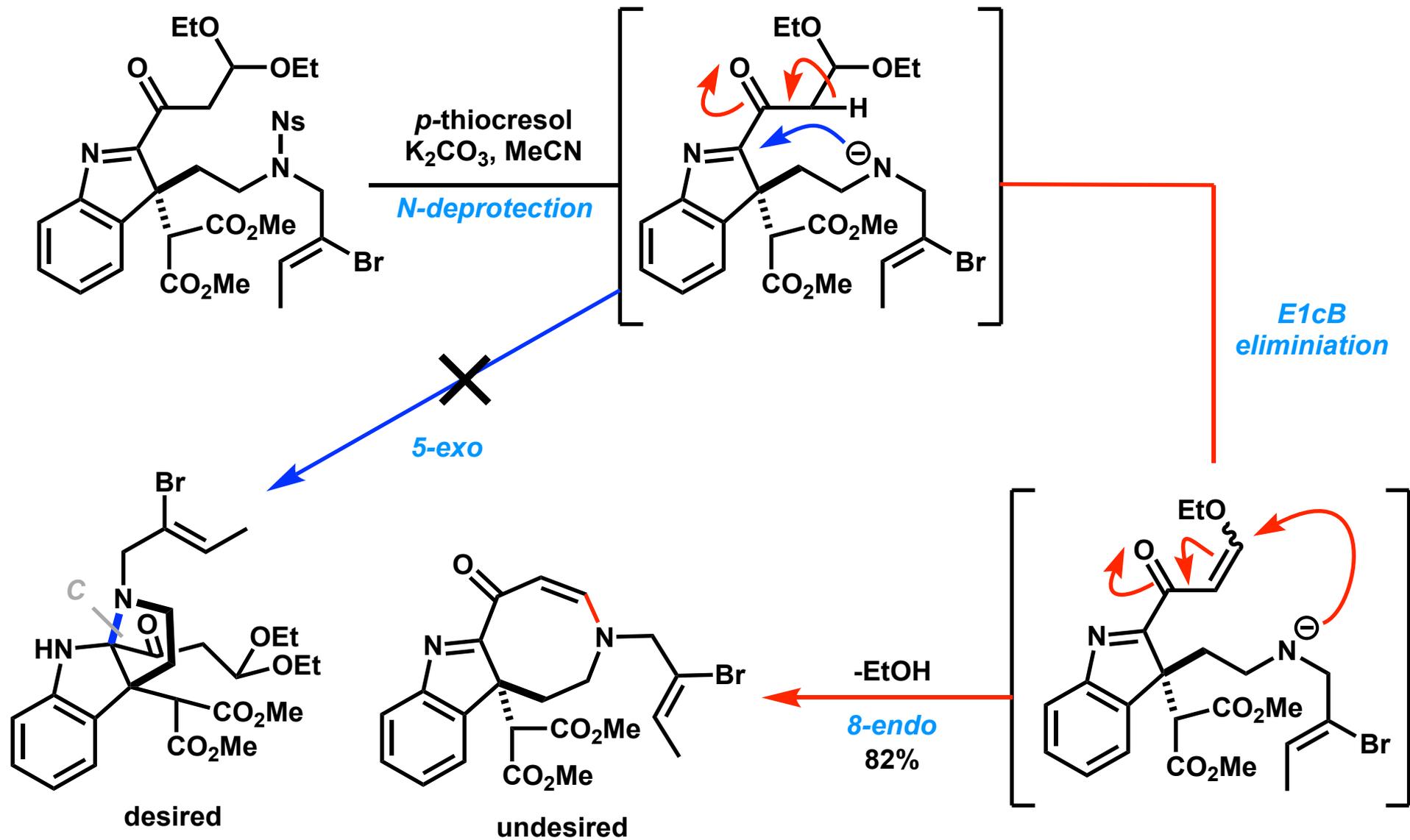


- 1) Zhang, B.; Wang, X.; Li, C. *J. Am. Chem. Soc.* **2020**, *142*, 3269.
- 2) Ma, S.; Han, X.; Krishnan, S.; Virgil, S. C.; Stolz, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8037.
- 3) D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger, J. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13097

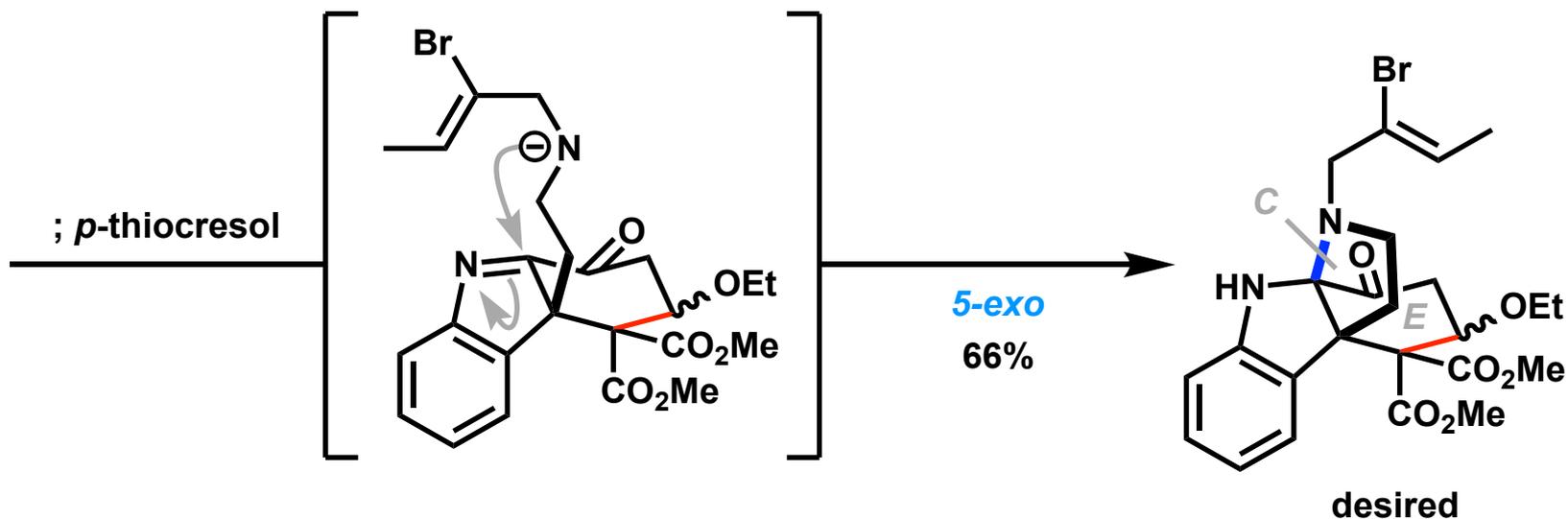
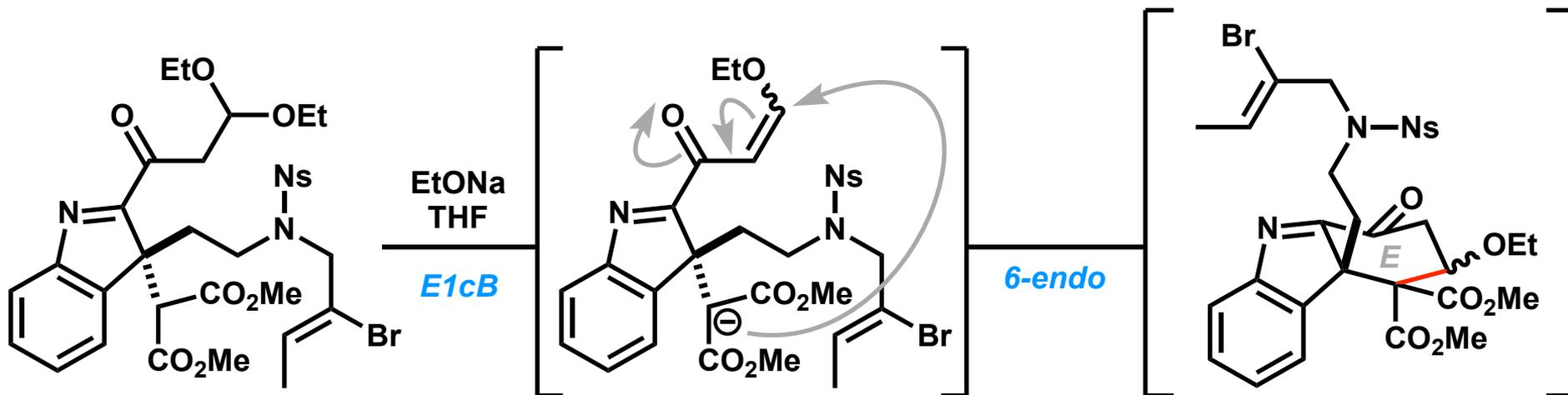
Installation of Alkyl Chain



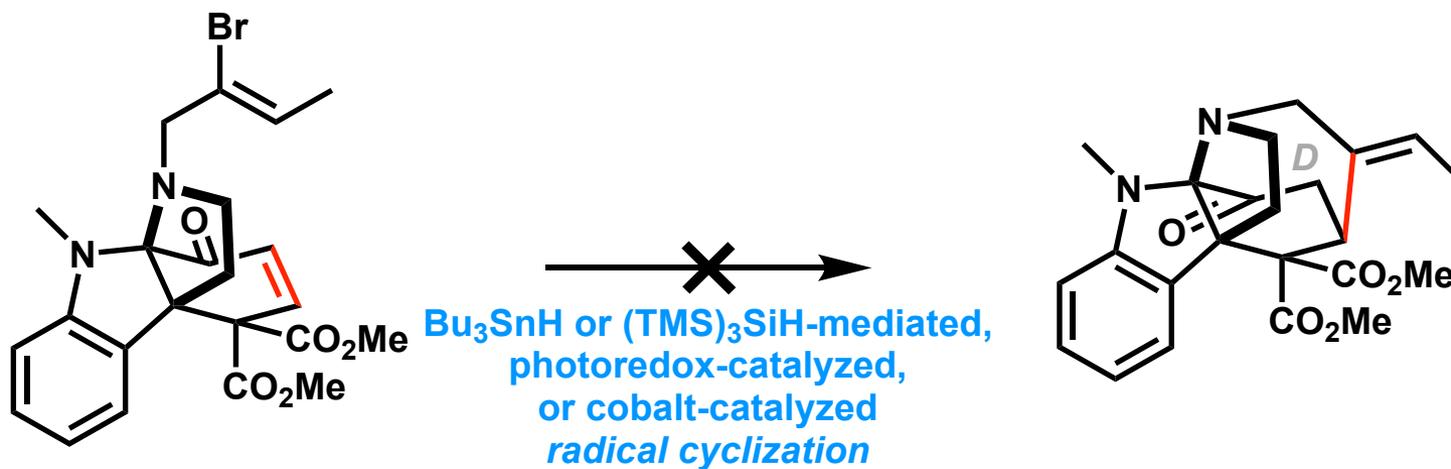
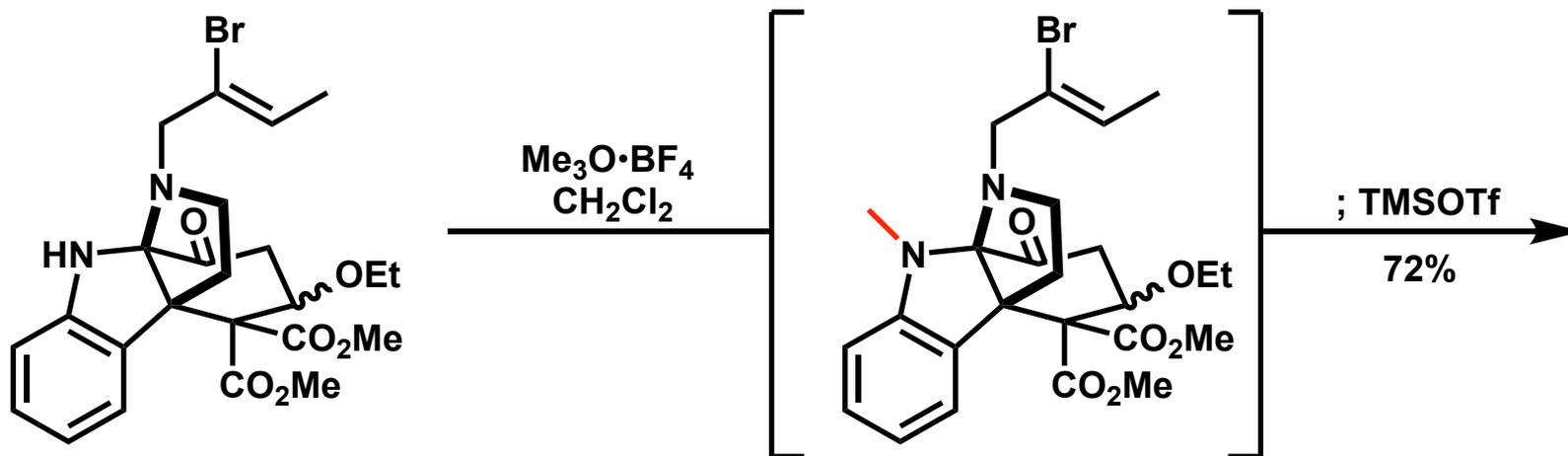
Attempted Construction of *C,E*-Rings



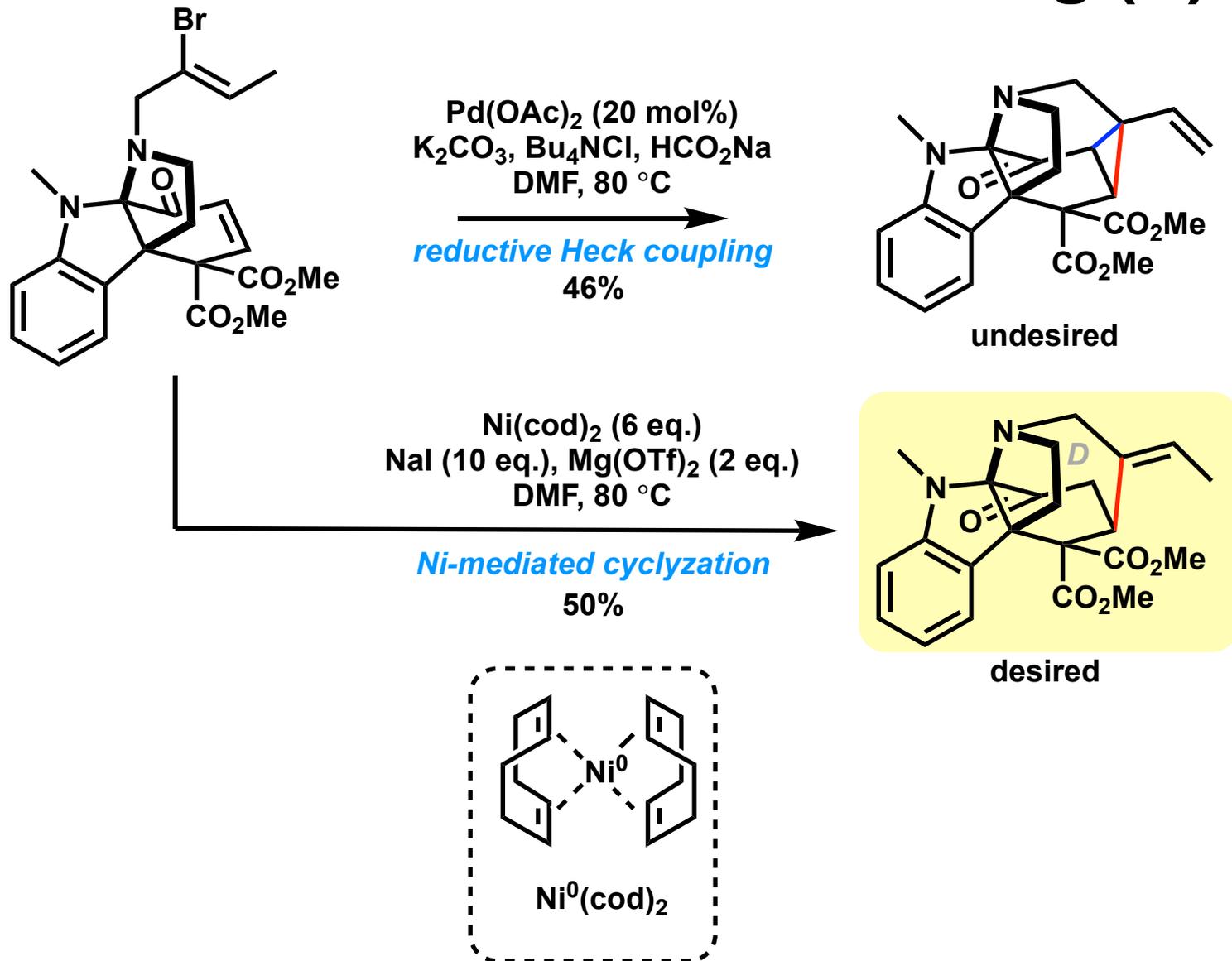
Construction of *C,E*-Rings (II)



Formation of 7-membered Ring (I)

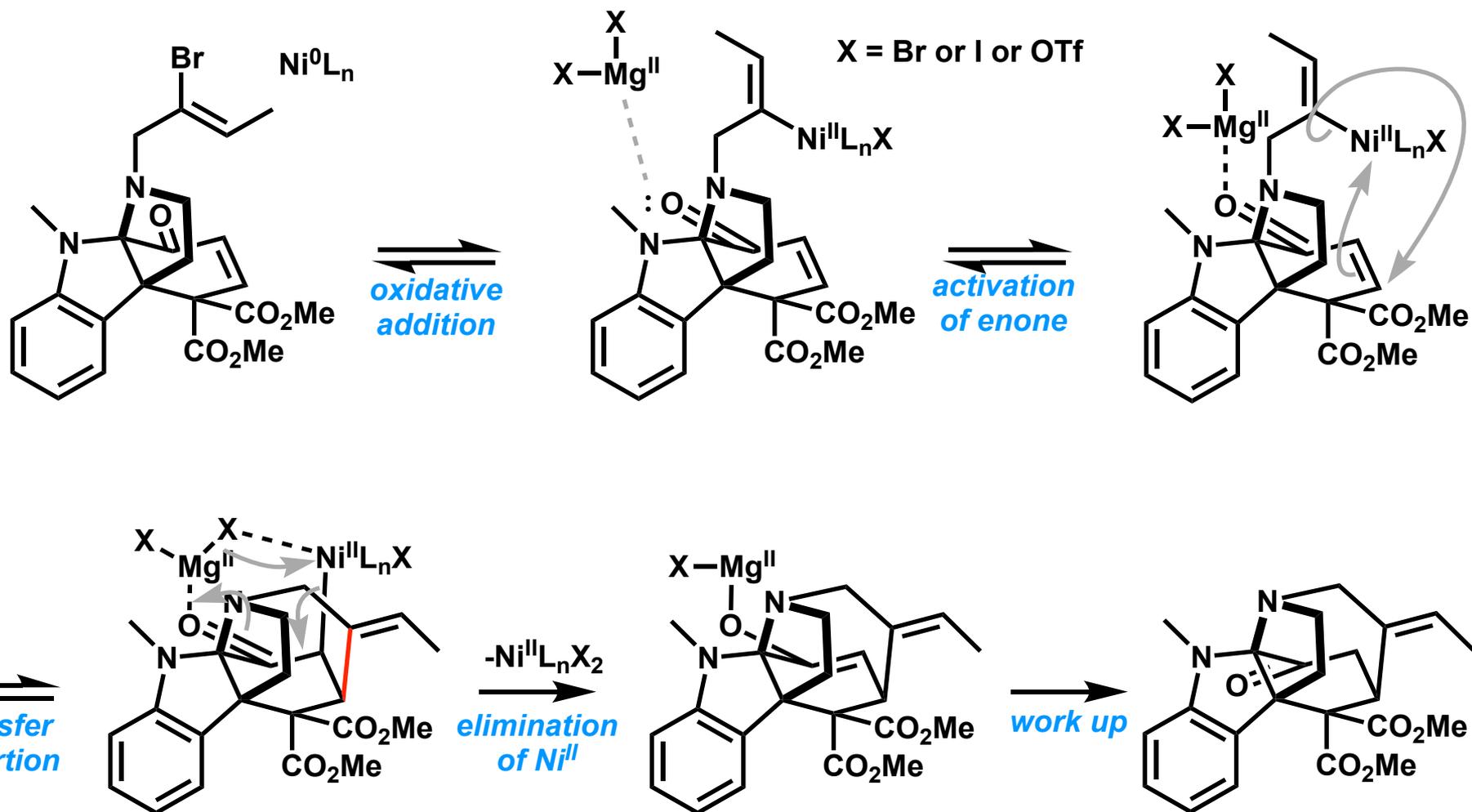


Formation of 7-membered Ring (II)



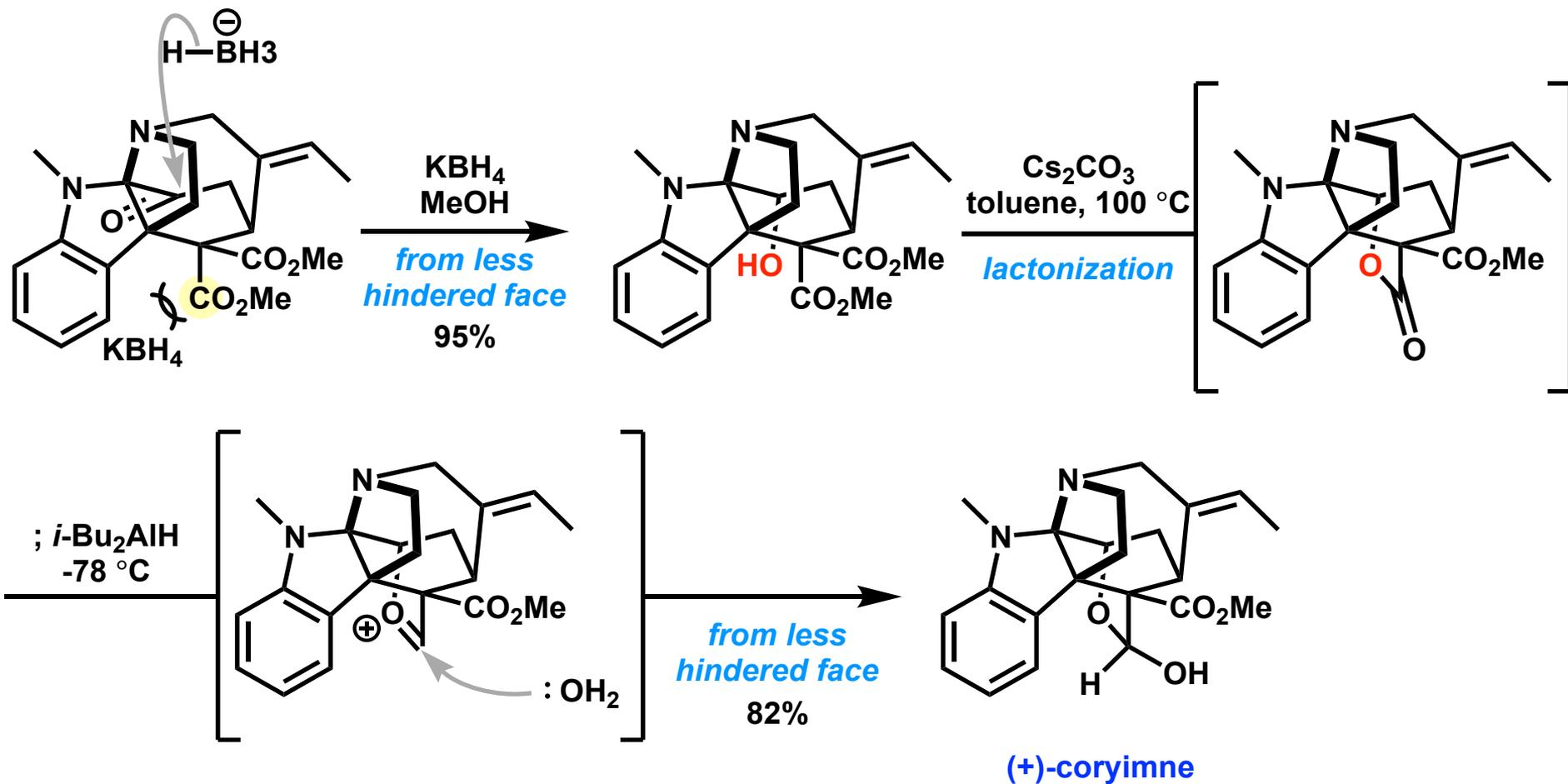
- 1) Zhang, B.; Wang, X.; Li, C. *J. Am. Chem. Soc.* **2020**, *142*, 3269.
- 2) Sole, D.; Cancho, Y.; Llebaria, A.; Moreto, J. M.; Delgado, A. *J. Am. Chem. Soc.* **1994**, *116*, 12133.
- 3) Nicolaou, K. C.; Roecker, A. J.; Follmann, M.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2107.
- 4) Okamura, H.; Mori, N.; Watanabe, H.; Takikawa, H. *Tetrahedron Lett.* **2018**, *59*, 4397.

Ni(cod)₂-Mediated Cyclization

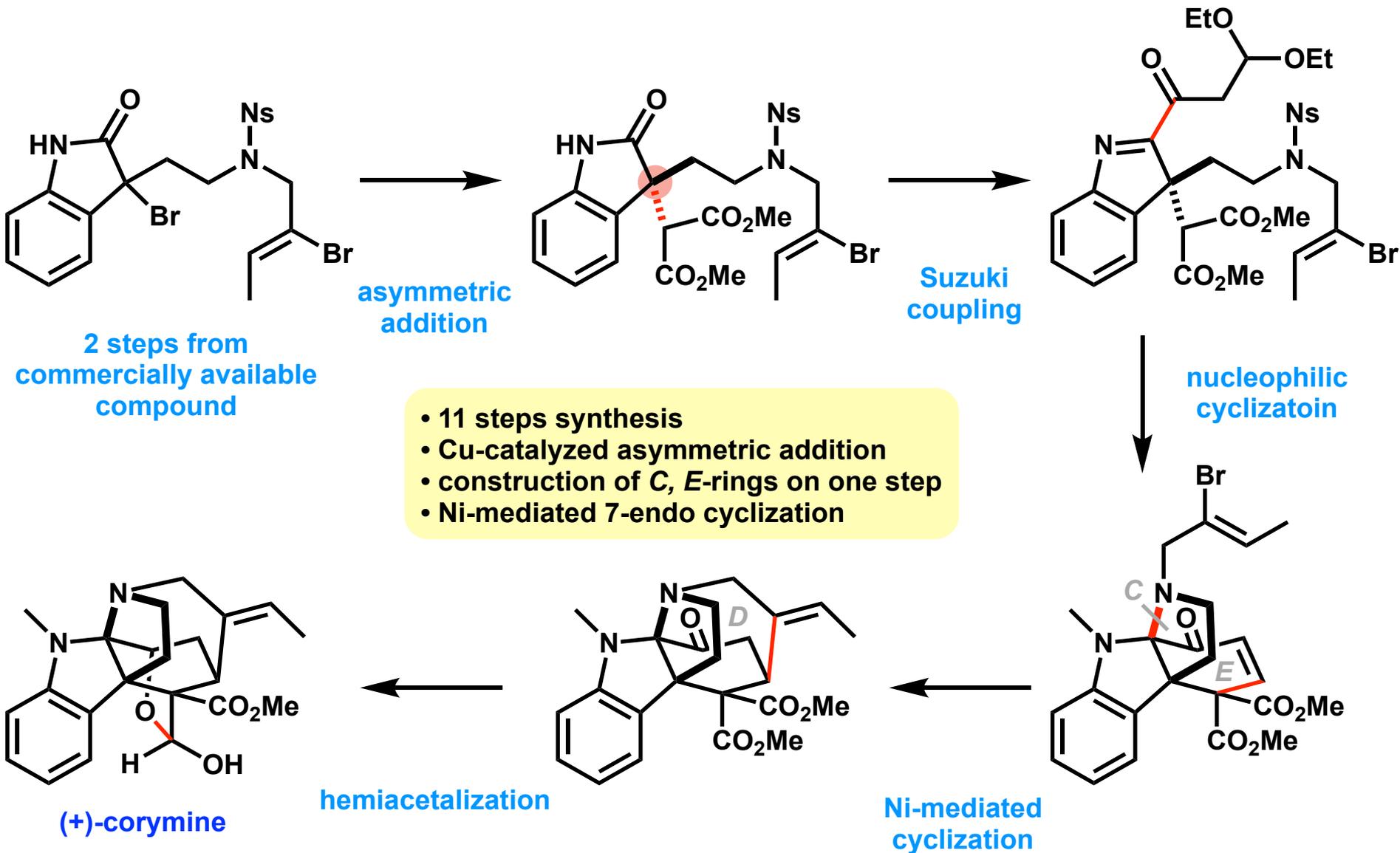


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- 3) Nicolaou, K. C.; Roecker, A. J.; Follmann, M.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2107.
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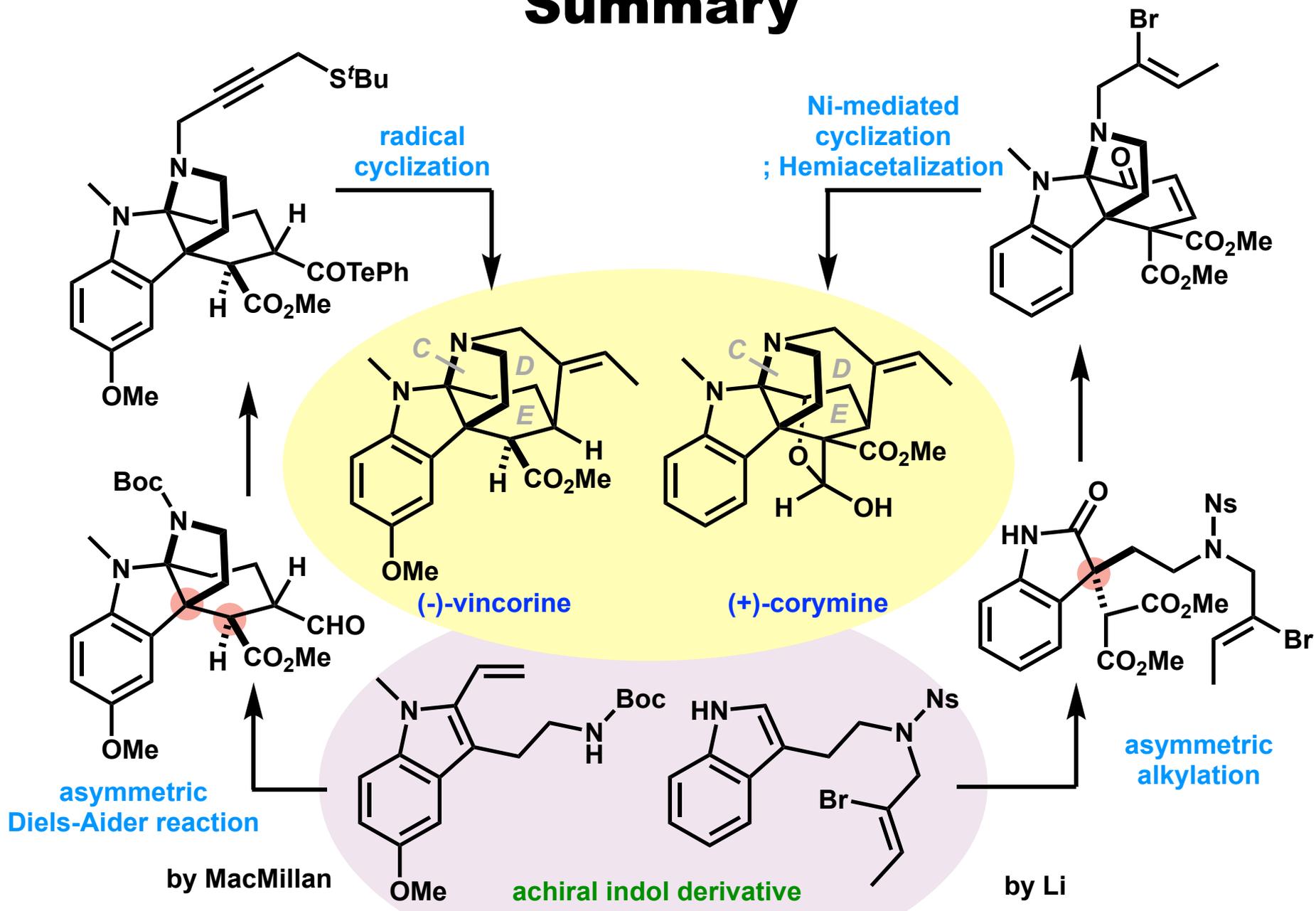
Total Synthesis of (+)-Corimine



Short Summary



Summary



1) Horning, B. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 6442.

2) Zhang, B.; Wang, X.; Li, C. *J. Am. Chem. Soc.* **2020**, *142*, 3269.