

Total Synthesis of Altemicidin and SB-203207

**2021.10.9. Literature Seminar
B4 Jaejoong Han**

Contents

1. Introduction

**2. Total synthesis of (-)-Altemicidin
(by Kende Group)**

**3. Total synthesis of (+)-SB-203207
(by Fukuyama and Kan Group)**

**4. Total synthesis of Altemicidin (racemic)
(by Maimone Group)**

5. Summary

Contents

1. Introduction

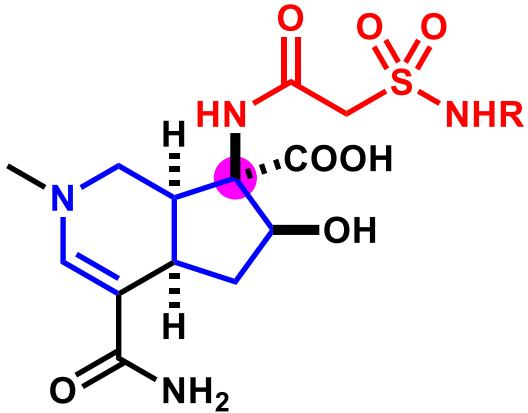
**2. Total synthesis of (-)-Altemicidin
(by Kende Group)**

**3. Total synthesis of (+)-SB-203207
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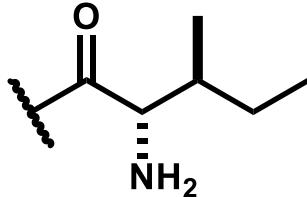
**4. Total synthesis of Altemicidin (racemic)
(by Maimone Group)**

5. Summary

(-)-Altemicidin and (+)-SB-203207



(-)-altemicidin : R = H
(+)-SB-203207 : R =



Isolation: Streptomyces sioyaensis SA-1758 (1989, (-)-altemicidin)¹⁾
Streptomyces NCIMB40513 (2000, (+)-SB-203207)²⁾

Structural features: *cis*-6,5 membered ring
sulfonamide, α -tertiary amine stereocenter

Biological activities: tRNA synthetase inhibitor²⁾, AMP mimic³⁾

Total syntheses:

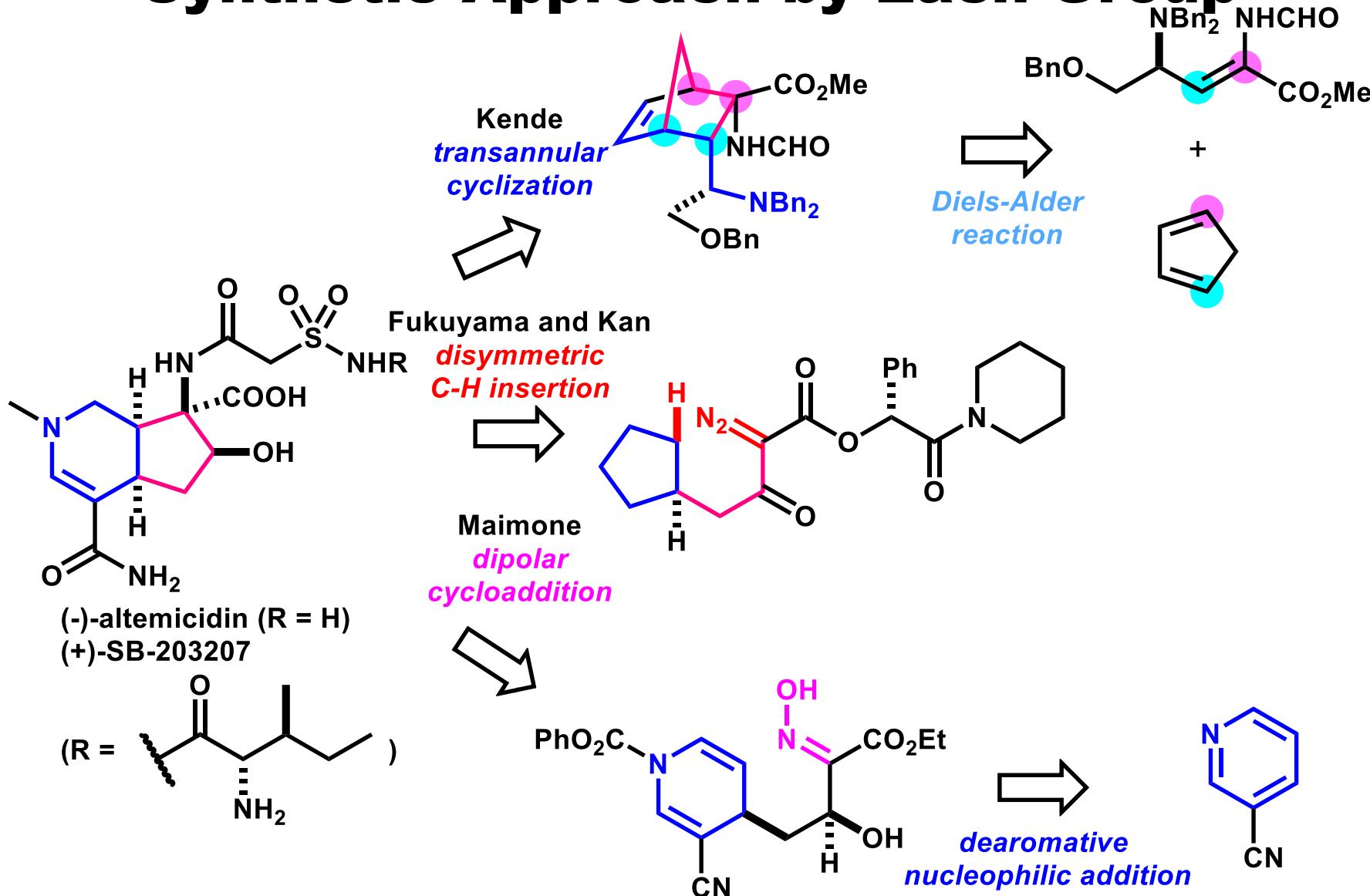
Kende (1995 (27 steps, (-)-altemicidin, asymmetric))⁴⁾

Fukuyama and Kan (2014 (32 steps, (+)-SB-203207, asymmetric))⁵⁾

Maimone (2021 (11 steps, (-)-altemicidin, racemic))⁶⁾

- 1) Takahashi, A.; Kurasawa, S.; Ikeda, D.; Okami, Y.; Takeuchi, T. *J. Antibiot.* **1989**, *42*, 1556.
- 2) Stefanska, A. L.; Cassels, R.; Ready, S. J.; Warr, S. R. *J. Antibiot.* **2000**, *53*, 357.
- 3) Banwell, M. G.; Crasto, C. F.; Easton, C. J.; Karoli, T.; March, D. R.; Nairn, M. R.; O'Hanlon, P. J.; Oldham, M. D.; Willis, A. C.; Yue, W. *Chem. Commun.* **2001**, *21*, 2210.
- 4) Kende, A. S.; Liu, K.; Jos Brands, K. M. *J. Am. Chem. Soc.* **1995**, *117*, 10597-10598.
- 5) Hirooka, Y.; Ikeuchi, K.; Kawamoto, Y.; Akao, Y.; Furuta, T.; Asakawa, T.; Inai, M.; Wakimoto, T.; Fukuyama, T.; Kan, T. *Org. Lett.* **2014**, *16*, 1646 -1649.
- 6) Harmange Magnani, C. S.; Maimone, T. J. *J. Am. Chem. Soc.* **2021**, *143*, 7935–7939.

Synthetic Approach by Each Group



1) Kende, A. S.; Liu, K.; Jos Brands, K. M. *J. Am. Chem. Soc.* **1995**, 117, 10597-10598.

2) Hirooka, Y.; Ikeuchi, K.; Kawamoto, Y.; Akao, Y.; Furuta, T.; Asakawa, T.; Inai, M.; Wakimoto, T.; Fukuyama, T.; Kan, T. *Org. Lett.* **2014**, 16, 1646-1649.

3) Harmange Magnani, C. S.; Maimone, T. J. *J. Am. Chem. Soc.* **2021**, 143, 7935–7939.

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5. Summary

Introduction of Prof. Kende

Prof. Andrew S. Kende (1932 - 2018)



1957 Ph.D @ Harvard University (Prof. Robert B. Woodward)

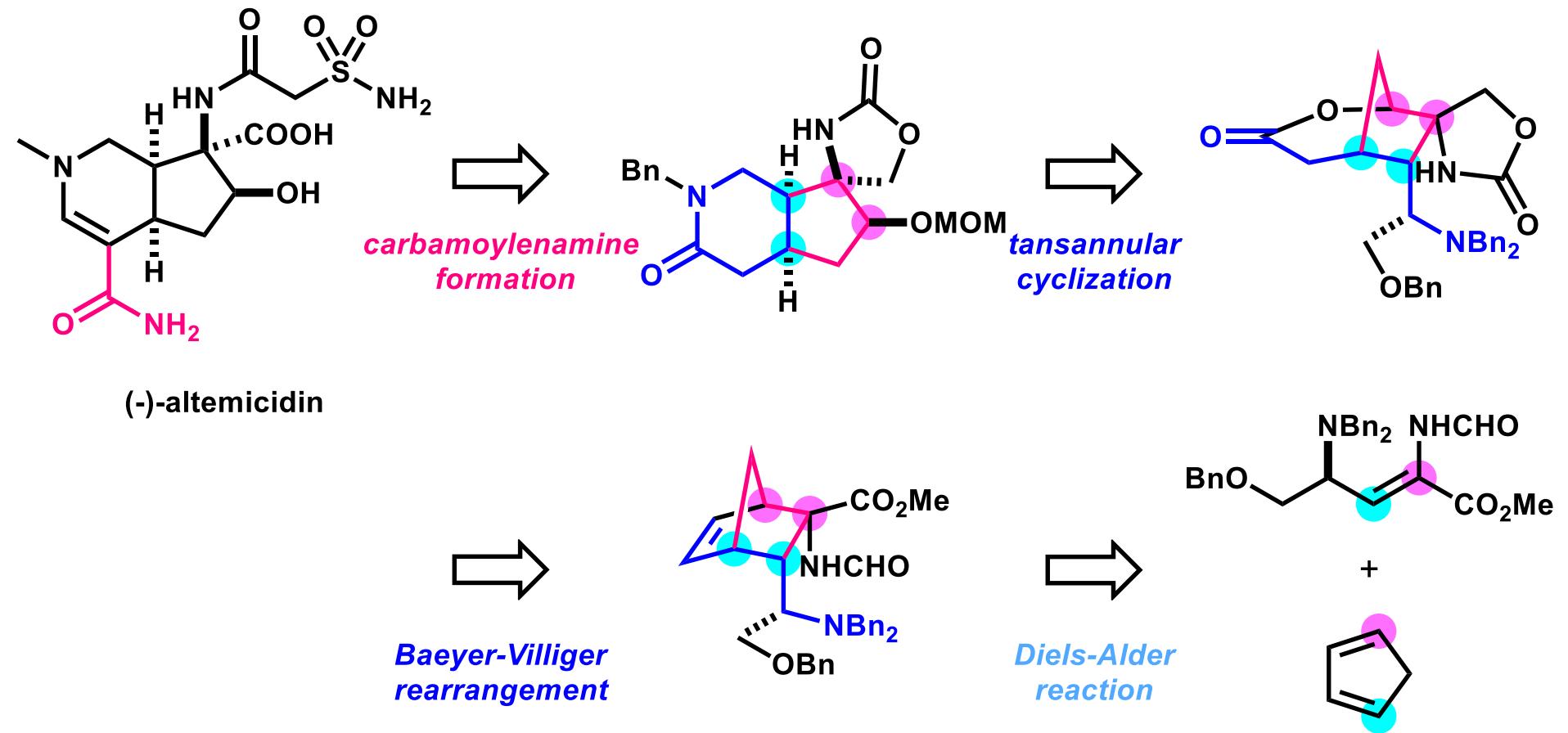
1957 Postdoctoral Fellow @ NRC-American Cancer Society

1968-1998 Professor @ University of Rochester

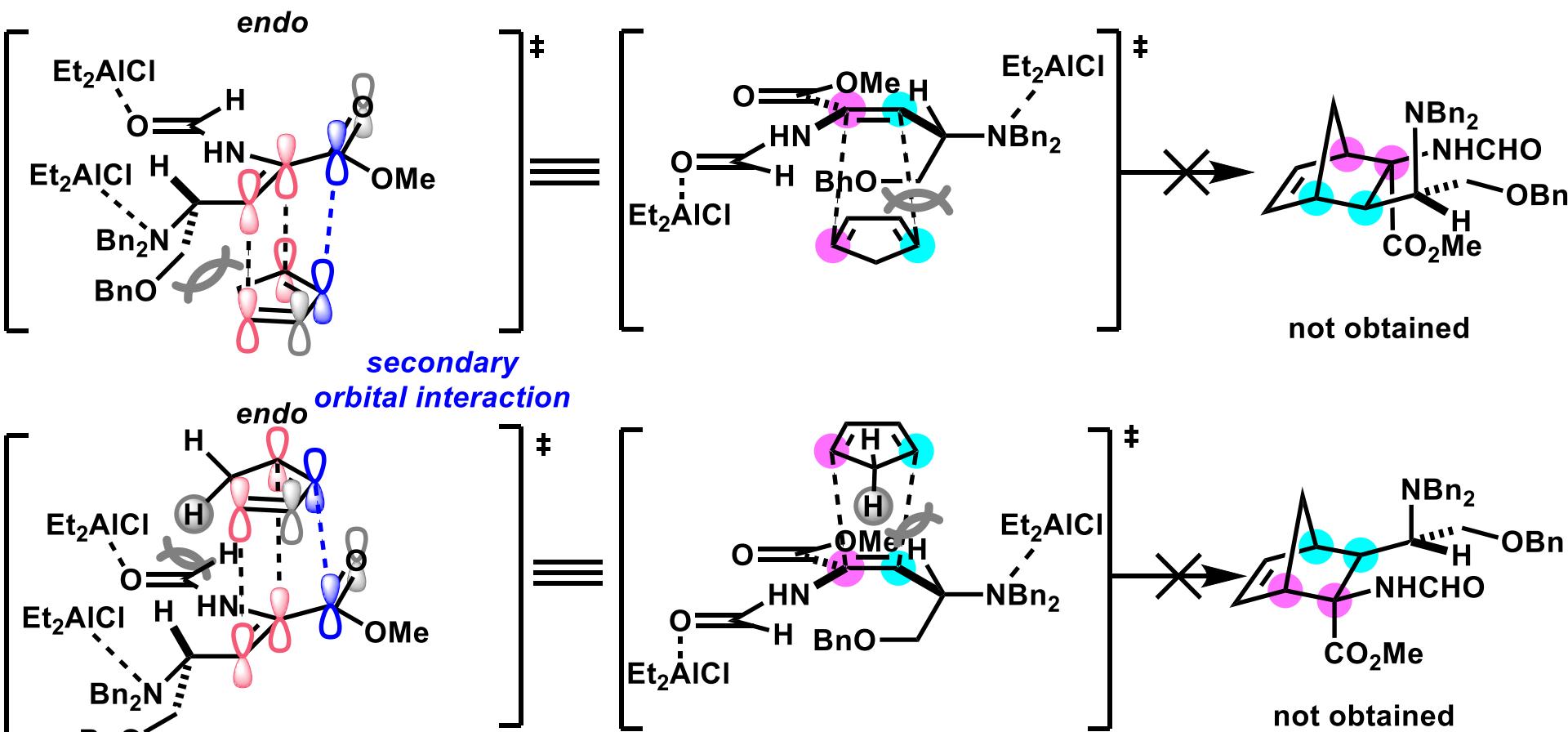
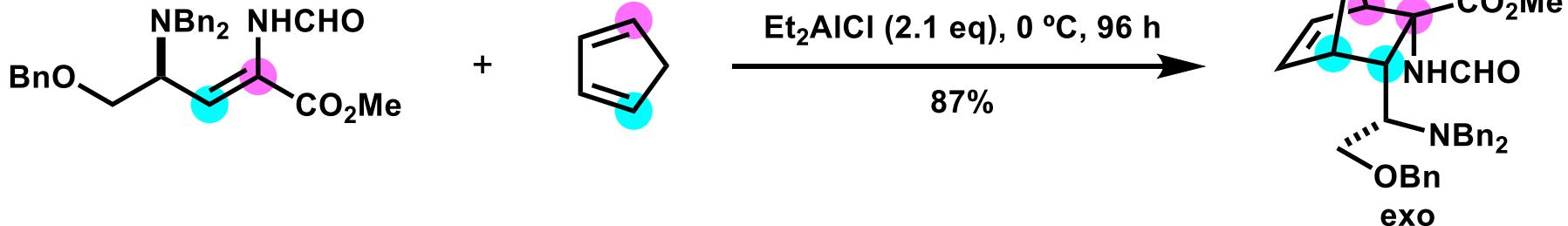
Research topics:

total synthesis, rearrangement reactions, chemistry of small rings,
biochemical studies of polyhalogenated xenobiotics and of bacterial
autoinducers

Retrosynthetic Analysis



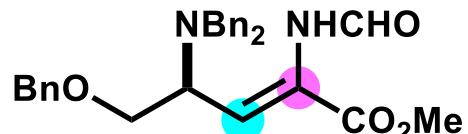
Stereoselectivity of Diels-Alder (1)



1) Kende, A. S.; Liu, K.; Jos Brands, K. M. *J. Am. Chem. Soc.* **1995**, 117, 10597-10598.

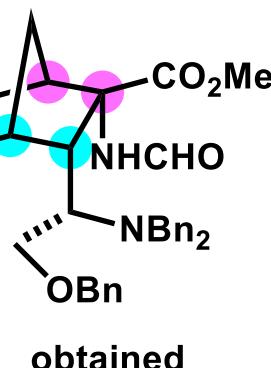
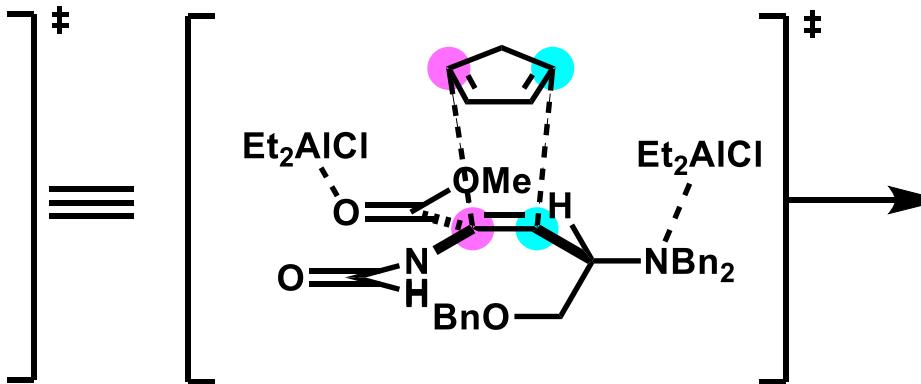
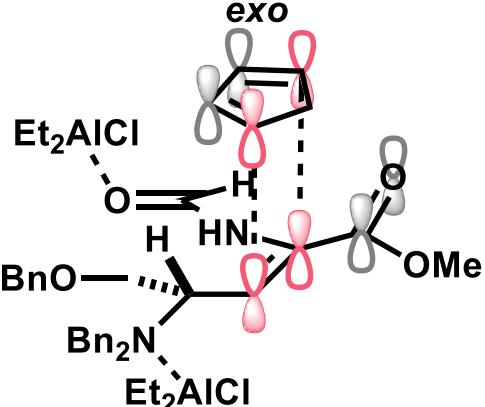
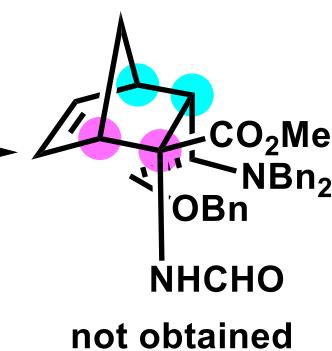
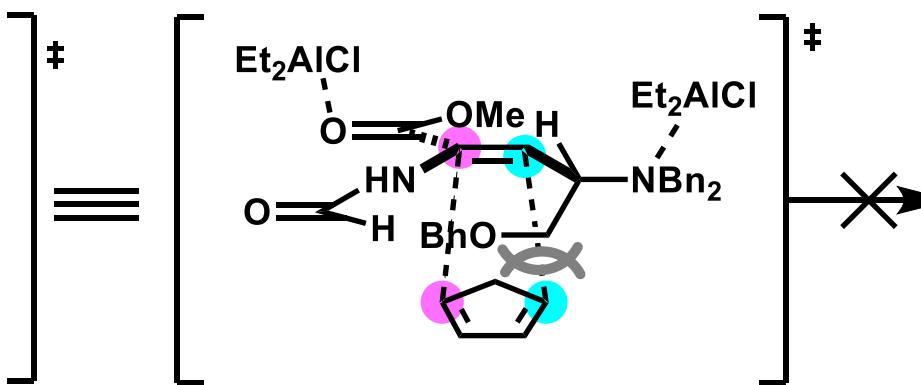
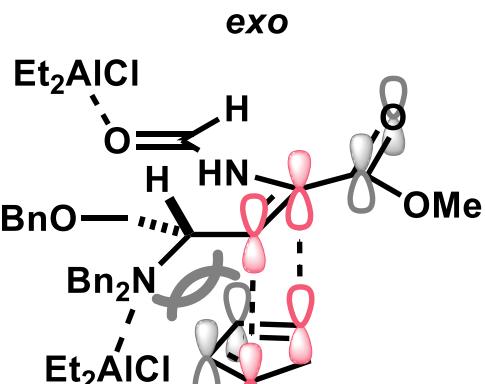
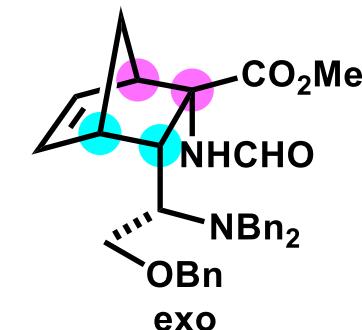
2) Reetz, T.; Kayser, F.; Harms, K. *Tetrahedron Lett.* **1992**, 33, 3453.

Stereoselectivity of Diels-Alder (2)

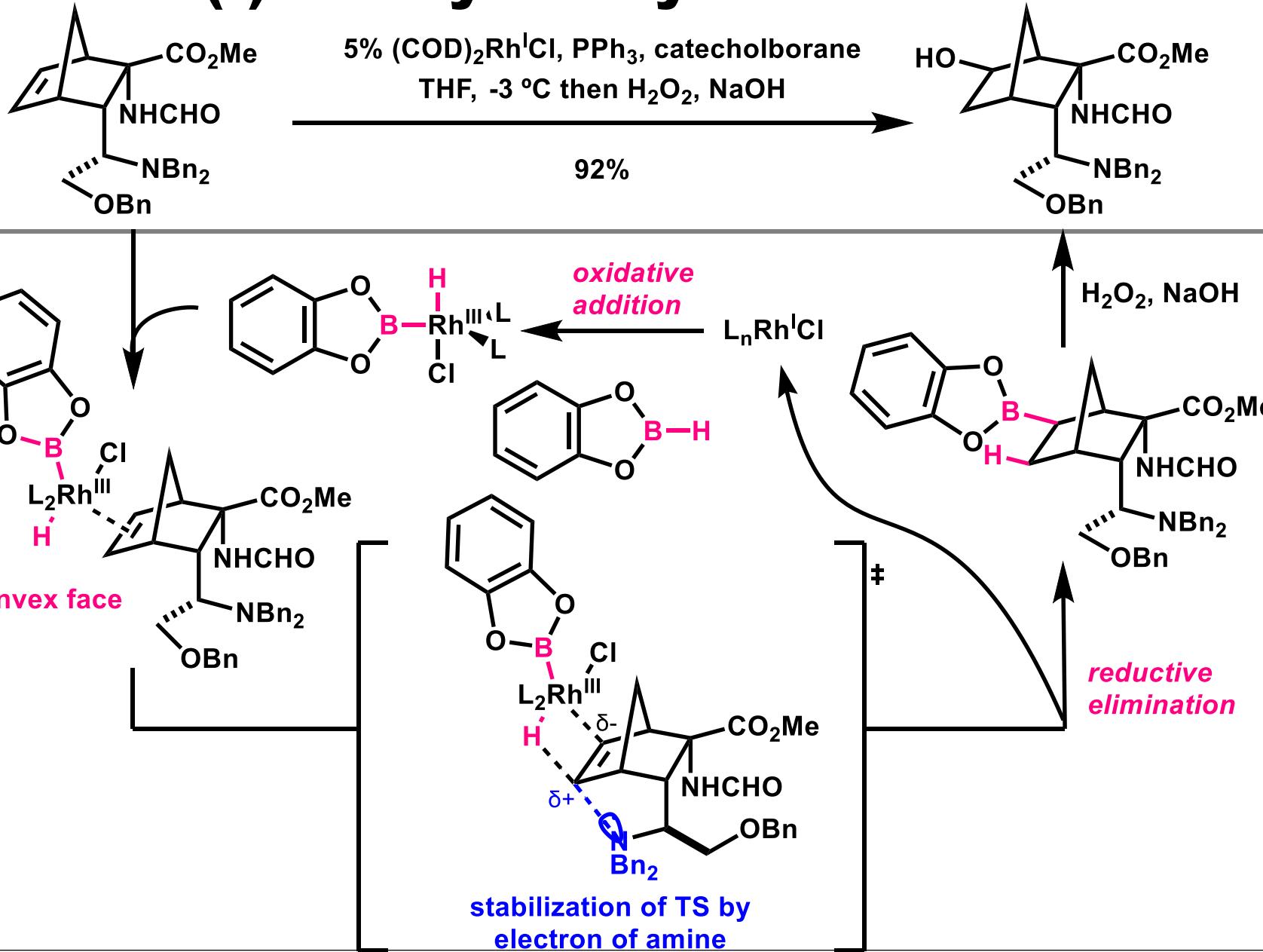


Et_2AlCl (2.1 eq), 0 °C, 96 h

87%



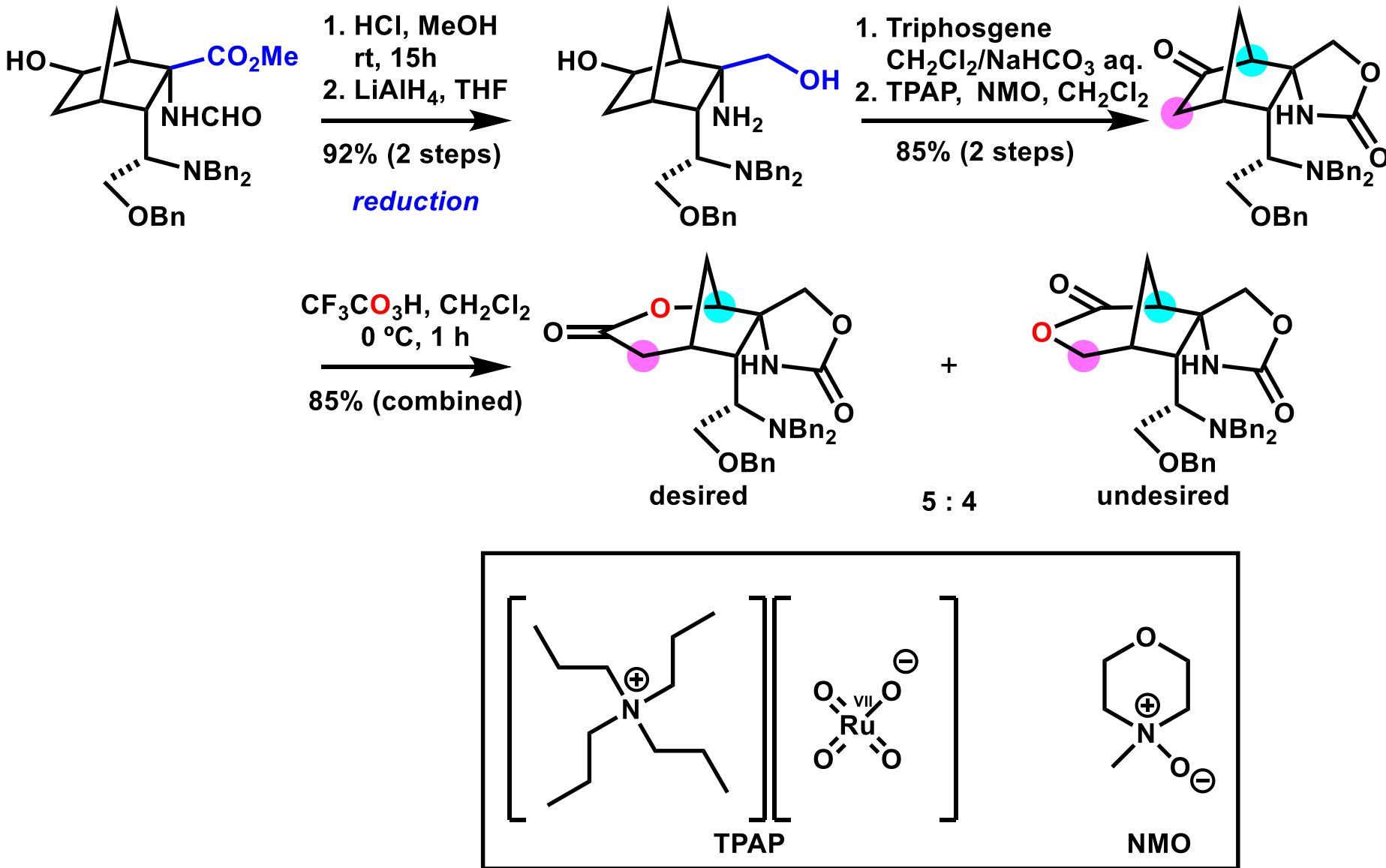
Rh(I)-Catalyzed Hydroboration



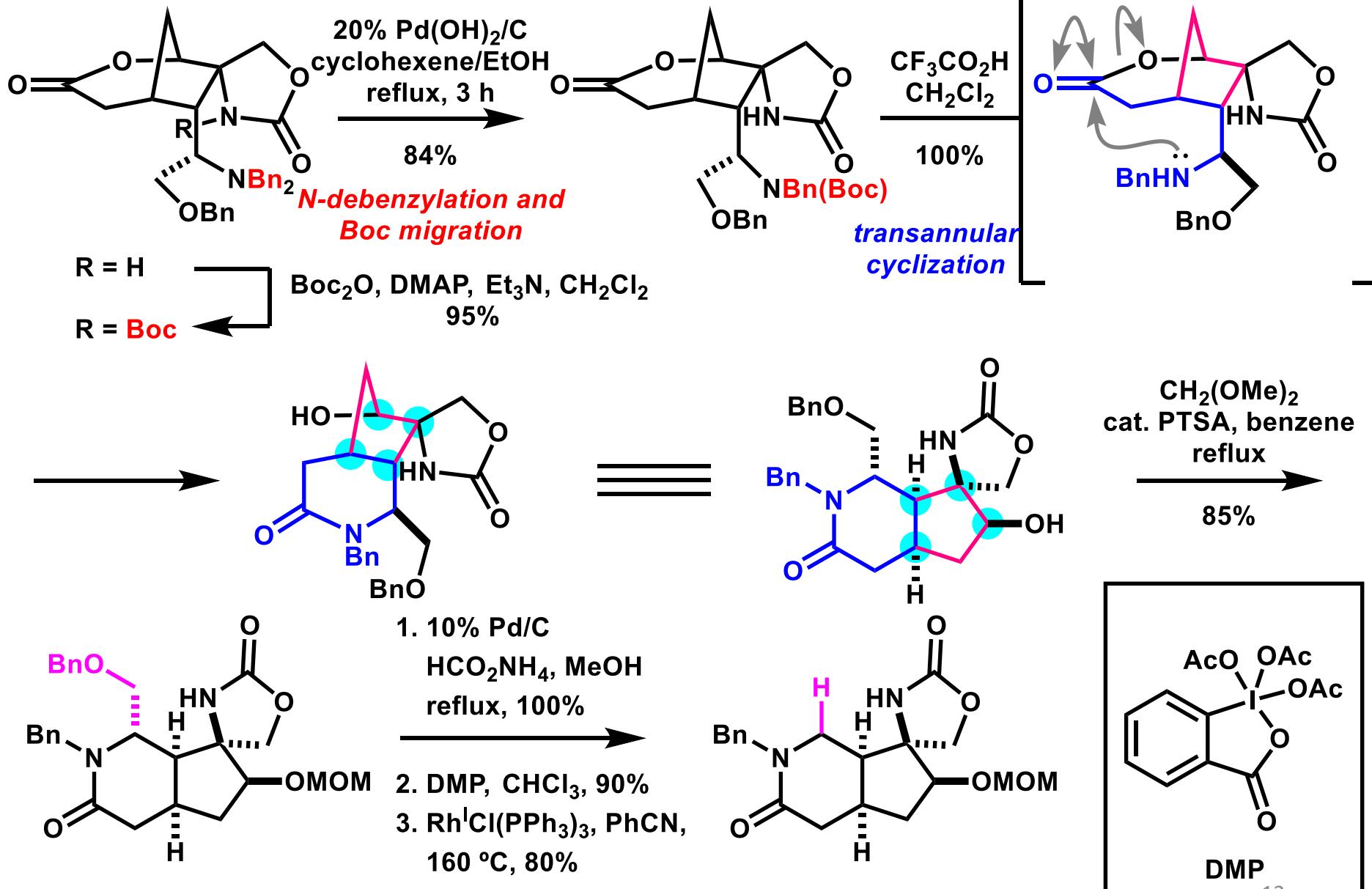
1) Kende, A. S.; Liu, K.; Jos Brands, K. M. *J. Am. Chem. Soc.* **1995**, 117, 10597-10598.

2) Brands, K. M. J.; Kende, A. S. *Tetrahedron Lett.* **1992**, 33, 5887.

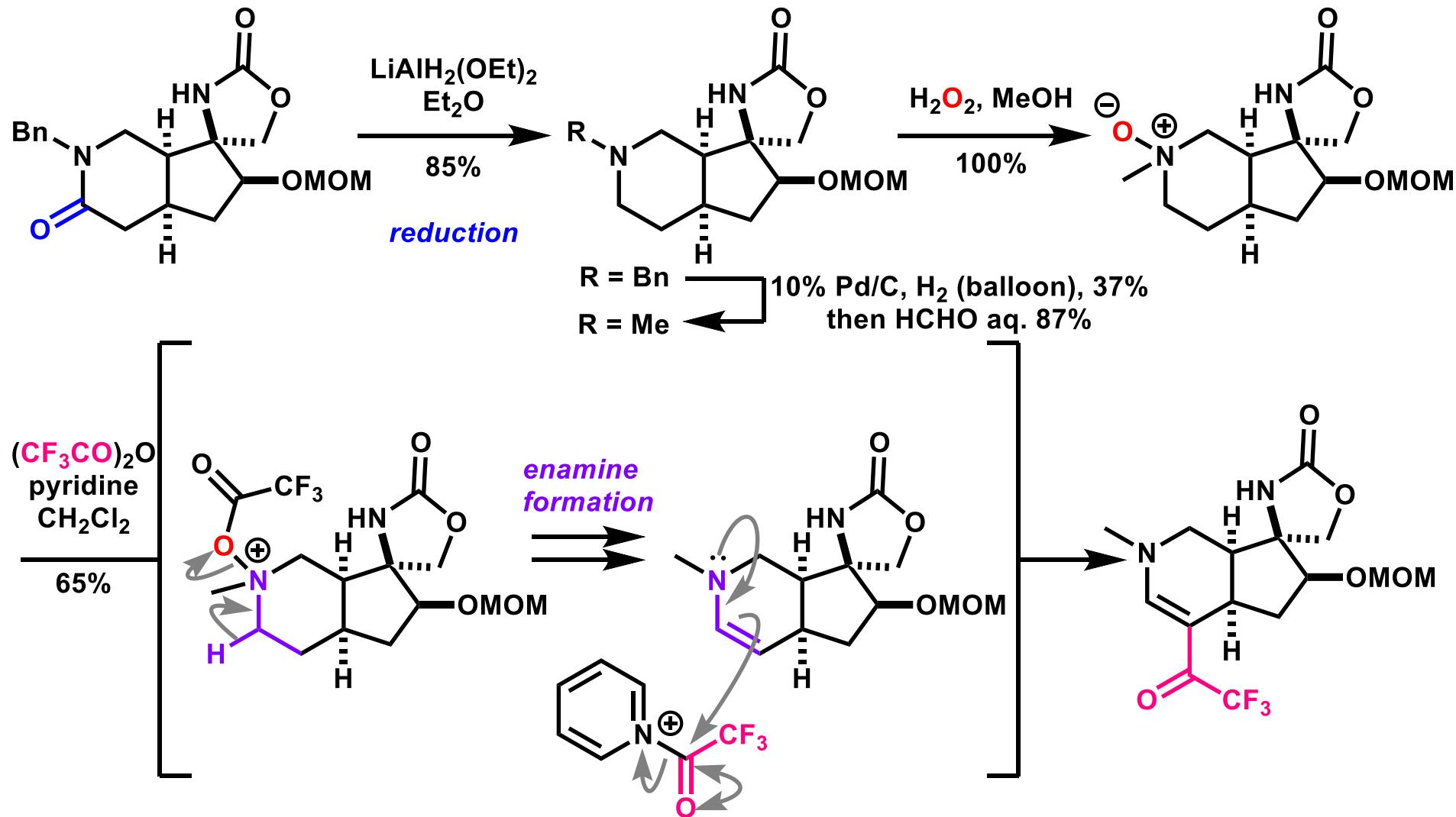
Construction of Oxazolidinone



Transannular Cyclization

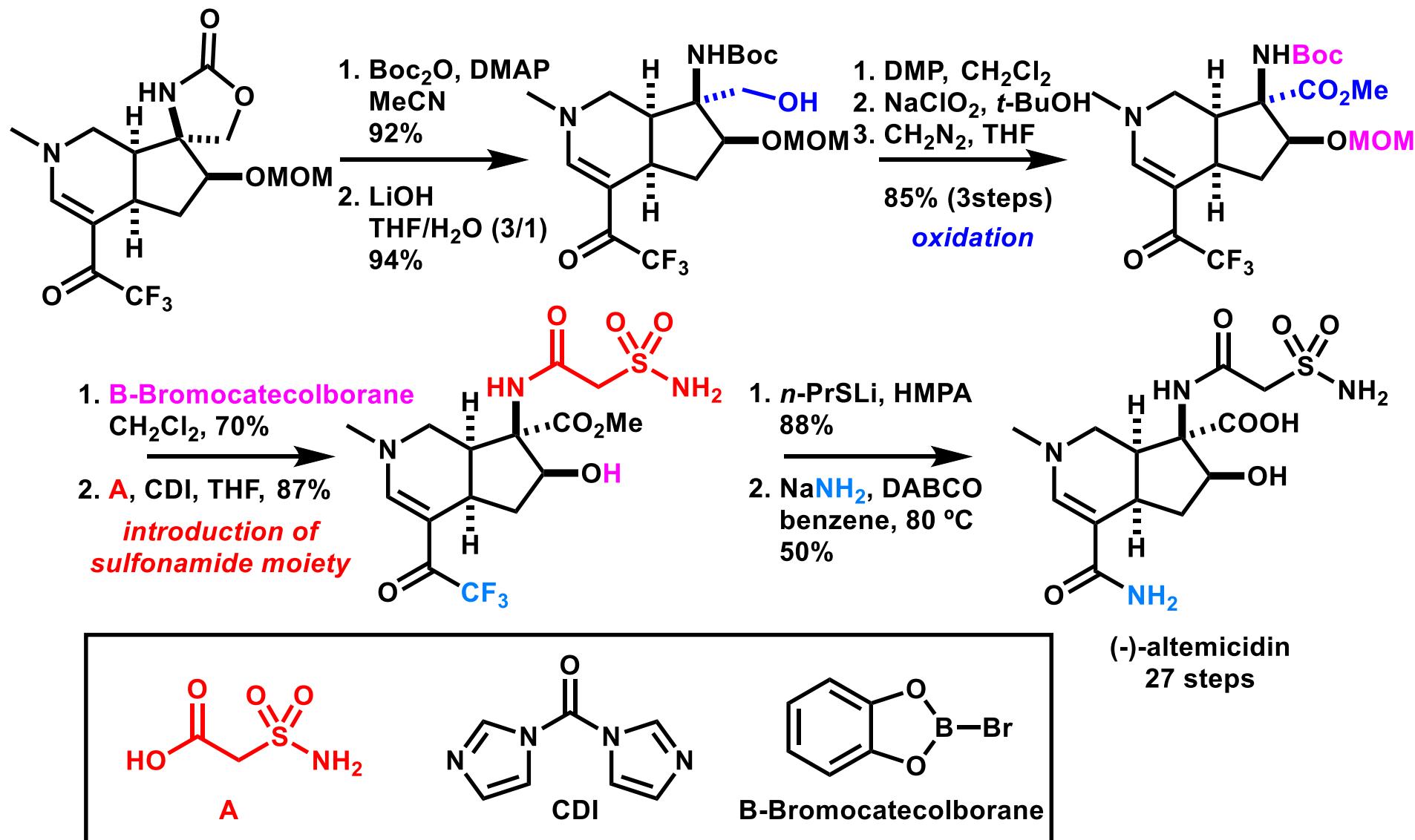


Construction of Terahydropyridine



- 1) Kende, A. S.; Liu, K.; Jos Brands, K. M. *J. Am. Chem. Soc.* **1995**, 117, 10597-10598.
 2) Grierson, D. *Org. React. (N.Y.)*, **1990**, 39, 85.

Total synthesis of (-)-Altemicidin



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5. Summary

Introduction of Prof. Fukuyama and Kan

Prof. Tohru Fukuyama (1948 -)



1971 B.S. @ Nagoya University
1977 Ph.D @ Harvard University (Prof. Yoshito Kishi)
1977- Postdoctoral fellow @ Harvard University (Prof. Yoshito Kishi)
1978- Assistant Professor @ Rice University
1982- Associate Professor @ Rice University
1988- Professor @ Rice University
1995- Professor @ The University of Tokyo
2012- Professor @ Nagoya University
2013- Specially Appointed Professor @ Nagoya University

Research topics: total synthesis of alkaloid compounds



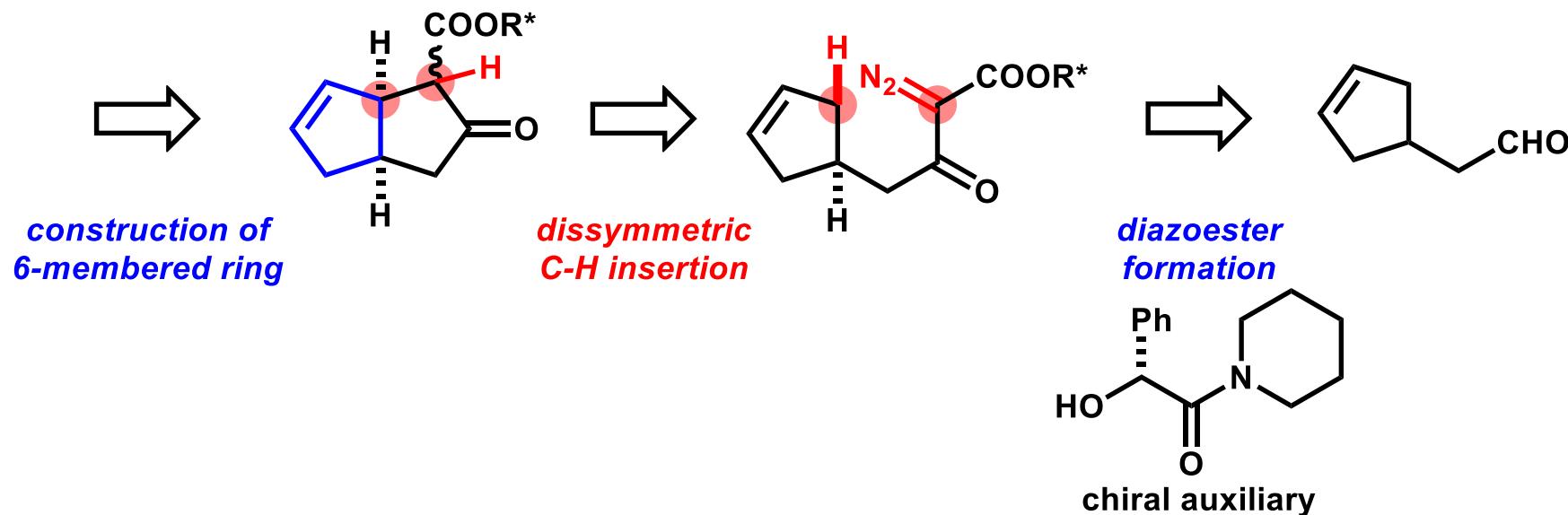
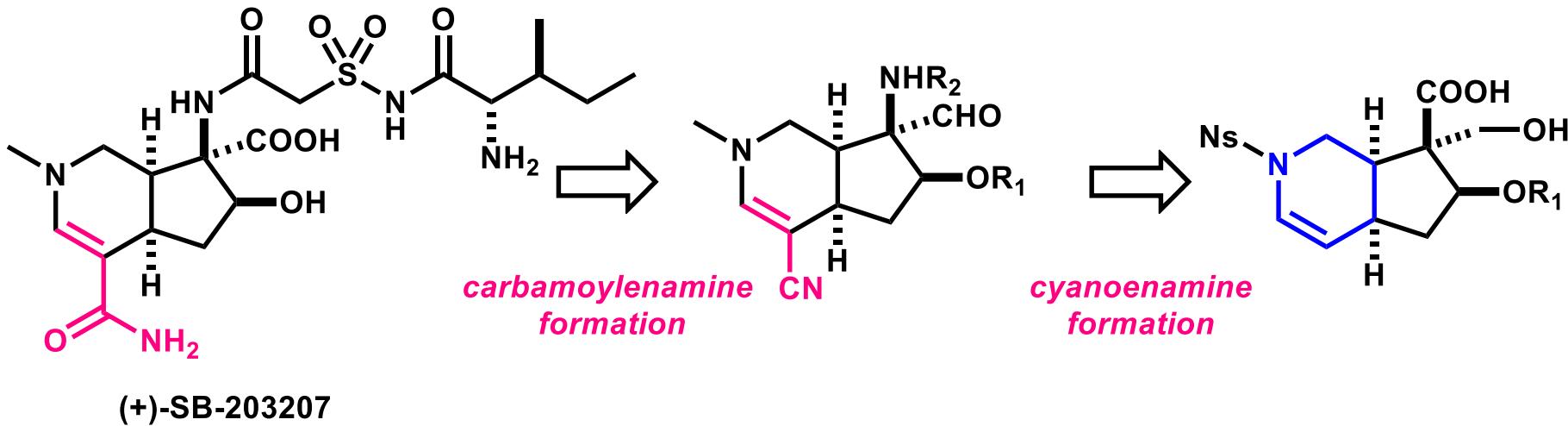
Prof. Toshiyuki Kan (1964 – 2021)

1987 B.S @ Hokkaido University
1993 Ph.D @ Hokkaido University
1993- Researcher @ Suntory Institute for Bioorganic Research
1996- Assistant Professor @ The University of Tokyo
2003- Associate Professor @ The University of Tokyo
2004- Professor @ Shizuoka University

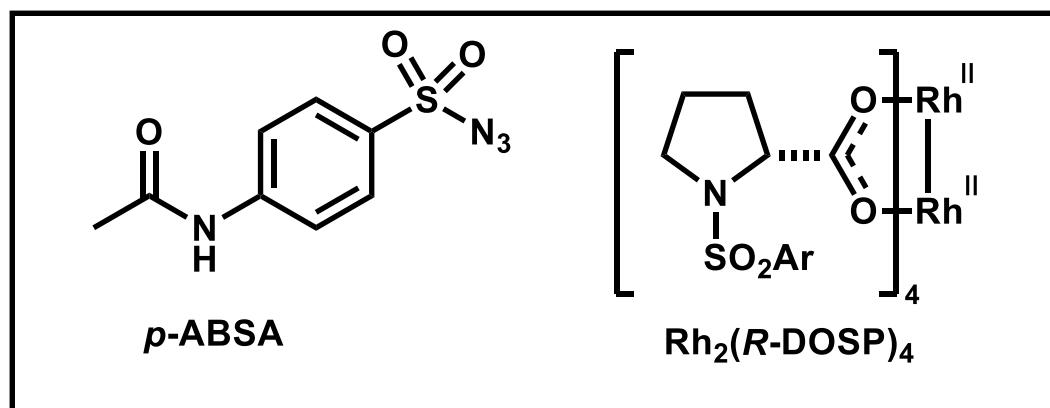
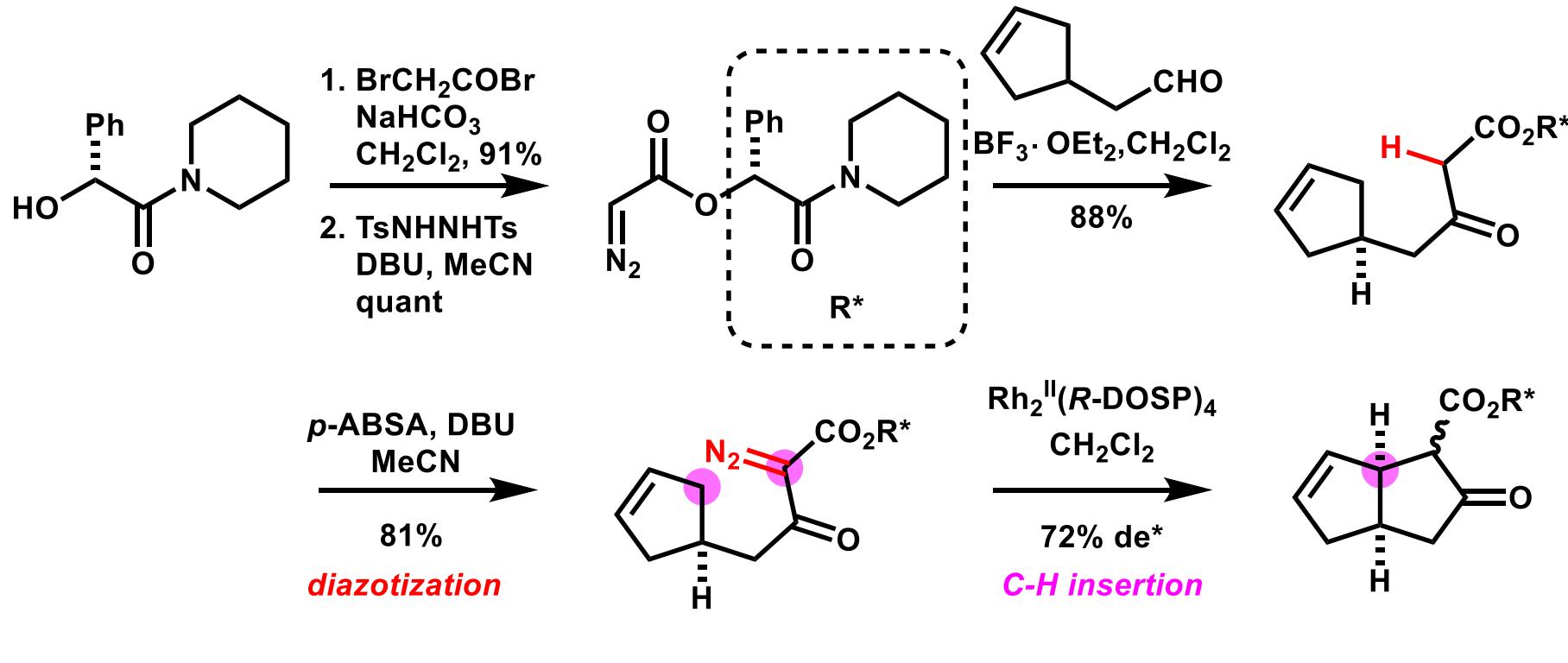
Research topics: total synthesis, organic chemistry, medical chemistry, chemical biology

- 1) http://www.ps.nagoya-u.ac.jp/lab_pages/natural_products/member_fukuyama.html
- 2) <https://www.us-yakuzo.jp/english/cv/knack/>

Retrosynthetic Analysis



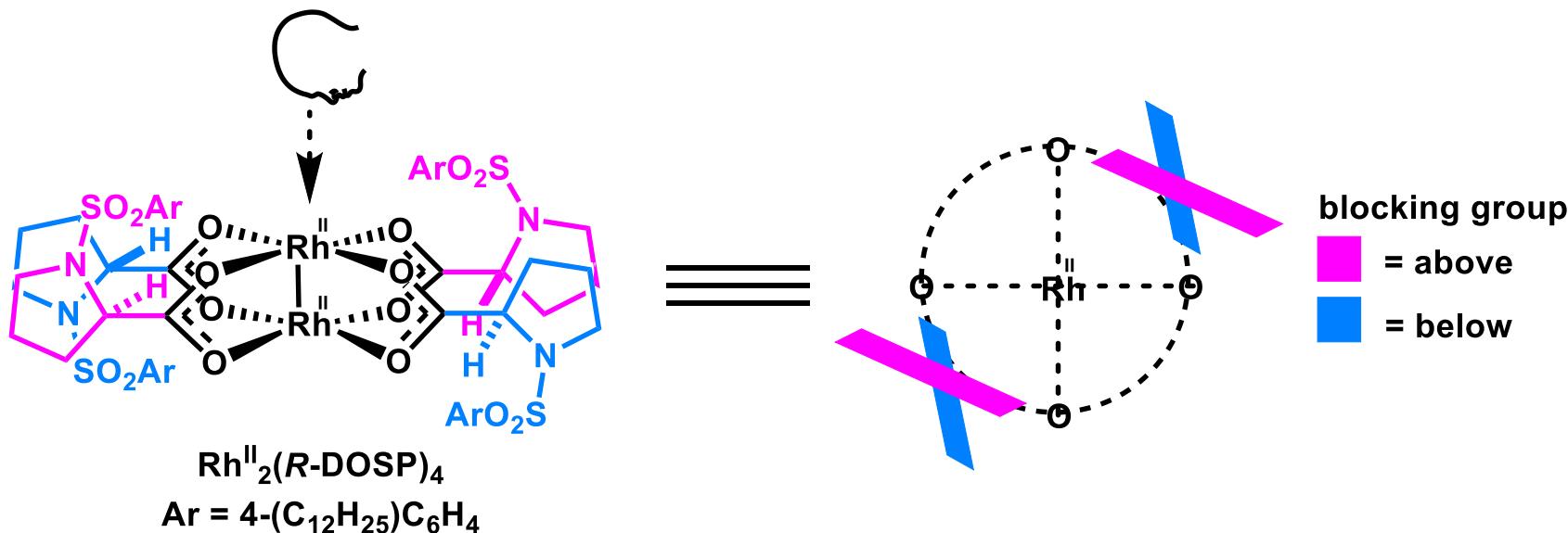
Construction of Bicyclic [3.3.0] Framework



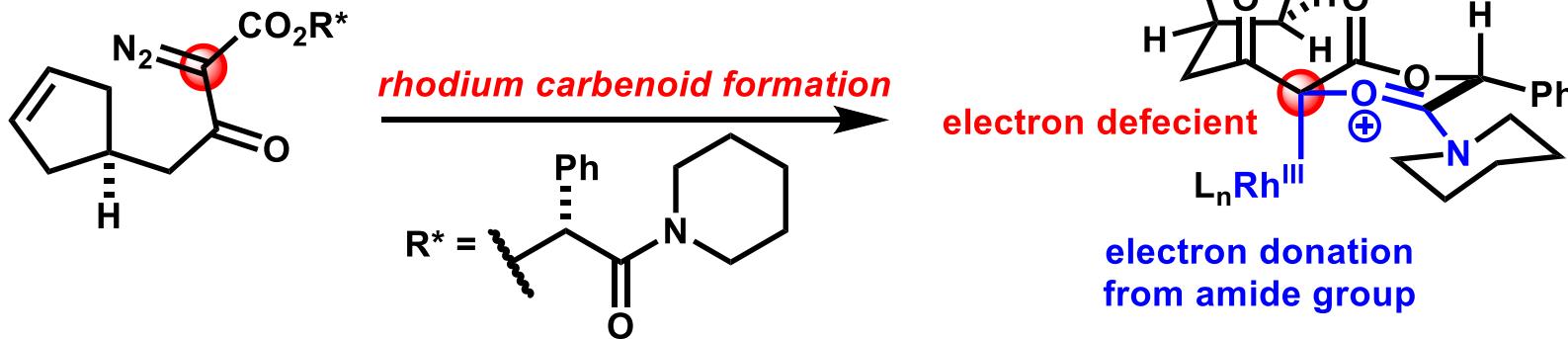
* diastereomeric excess was determined after 5 steps conversion

Dissymmetric C-H Insertion (1)

1. D₂ symmetric conformation of Rh^{II}₂(R-DOSP)₄



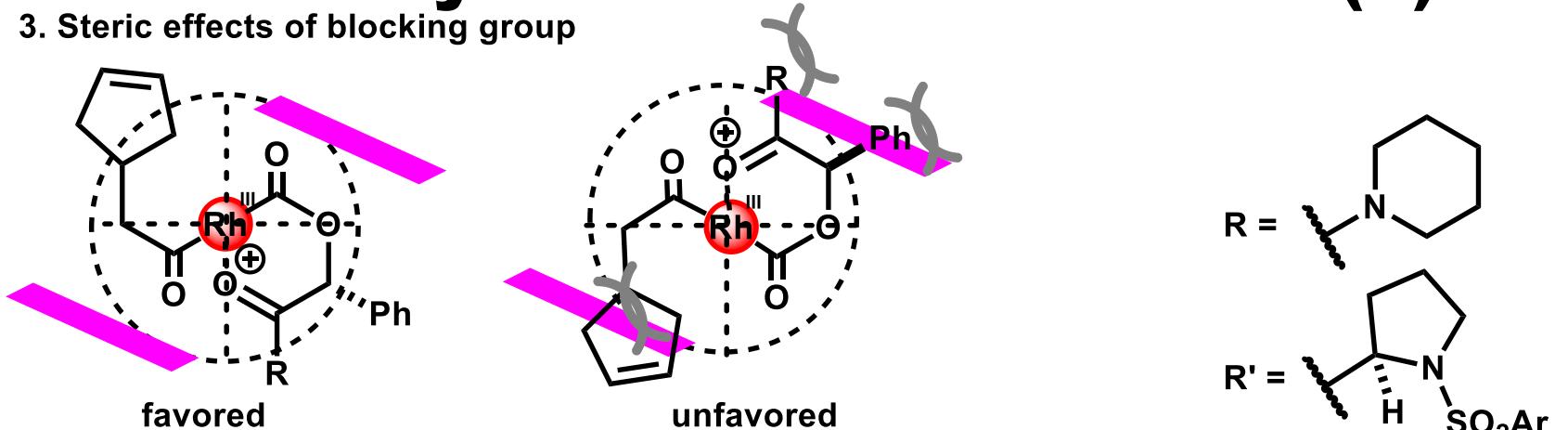
2. The role of a chiral auxiliary



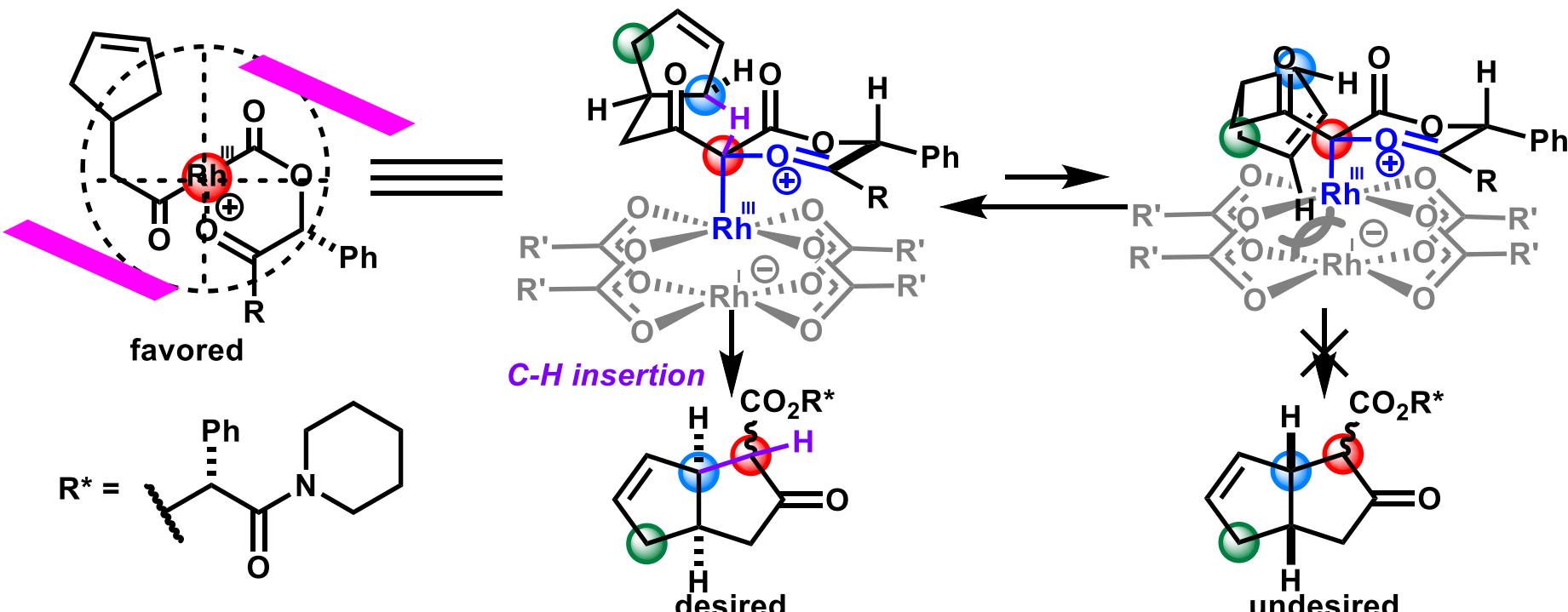
- 1) Hirooka, Y.; Ikeuchi, K.; Kawamoto, Y.; Akao, Y.; Furuta, T.; Asakawa, T.; Inai, M.; Wakimoto, T.; Fukuyama, T.; Kan, T. *Org. Lett.* **2014**, 16, 1646-1649.
2) Kan, T.; Inoue, T.; Kawamoto, Y.; Yonehara, M.; Fukuyama, T. *Synlett*, **2006**, 1583-1585.

Dissymmetric C-H Insertion (2)

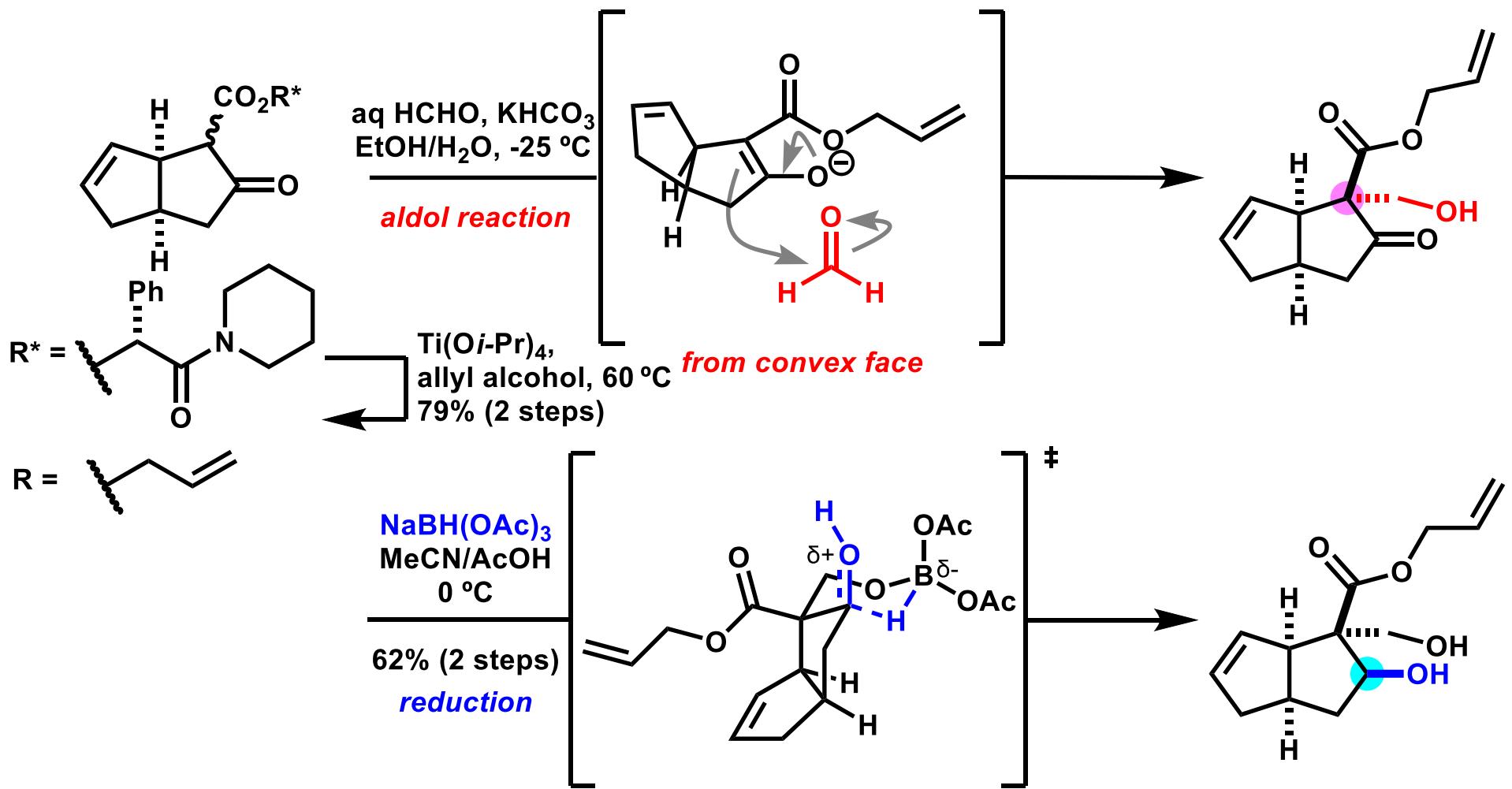
3. Steric effects of blocking group



4. Enantioselective C-H insertion

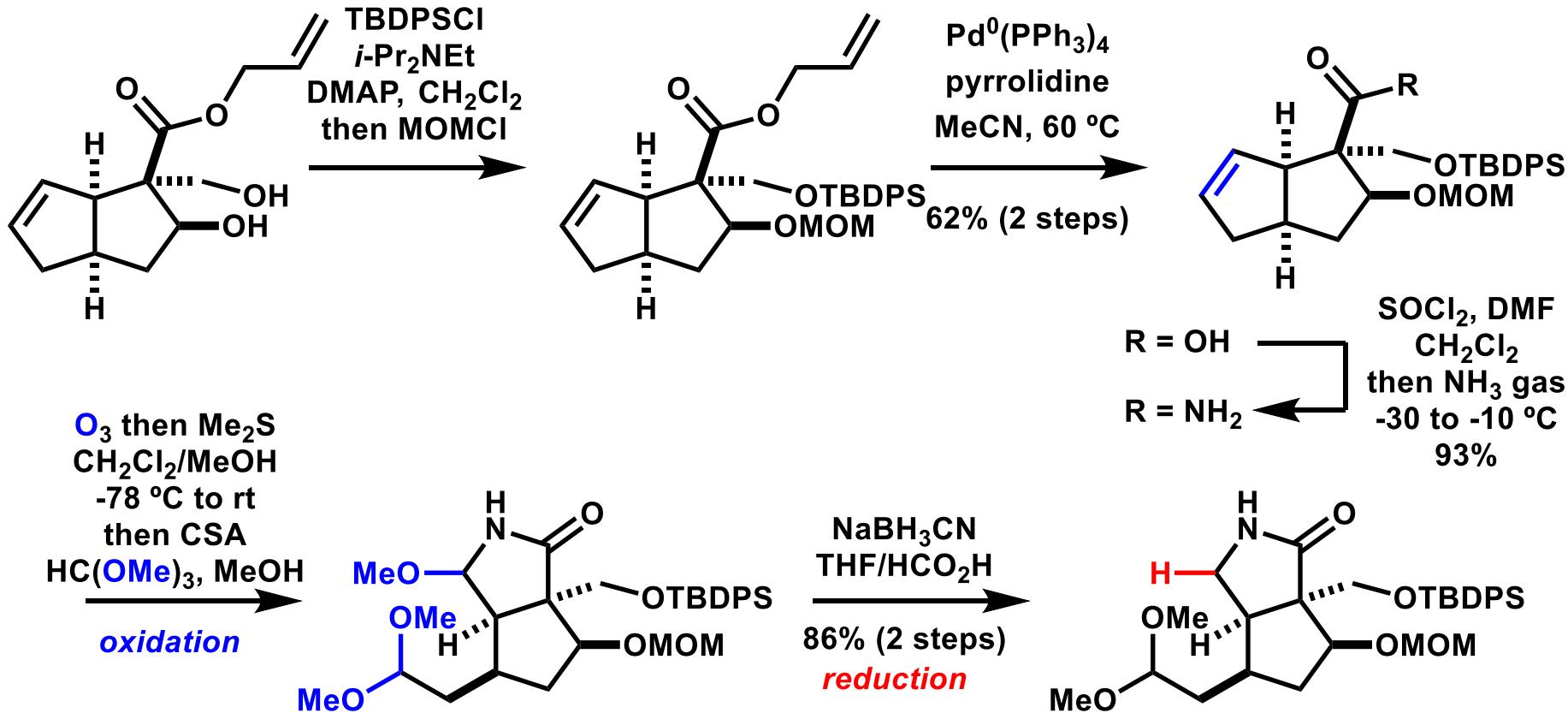


Stereoselective Reduction of Ketone



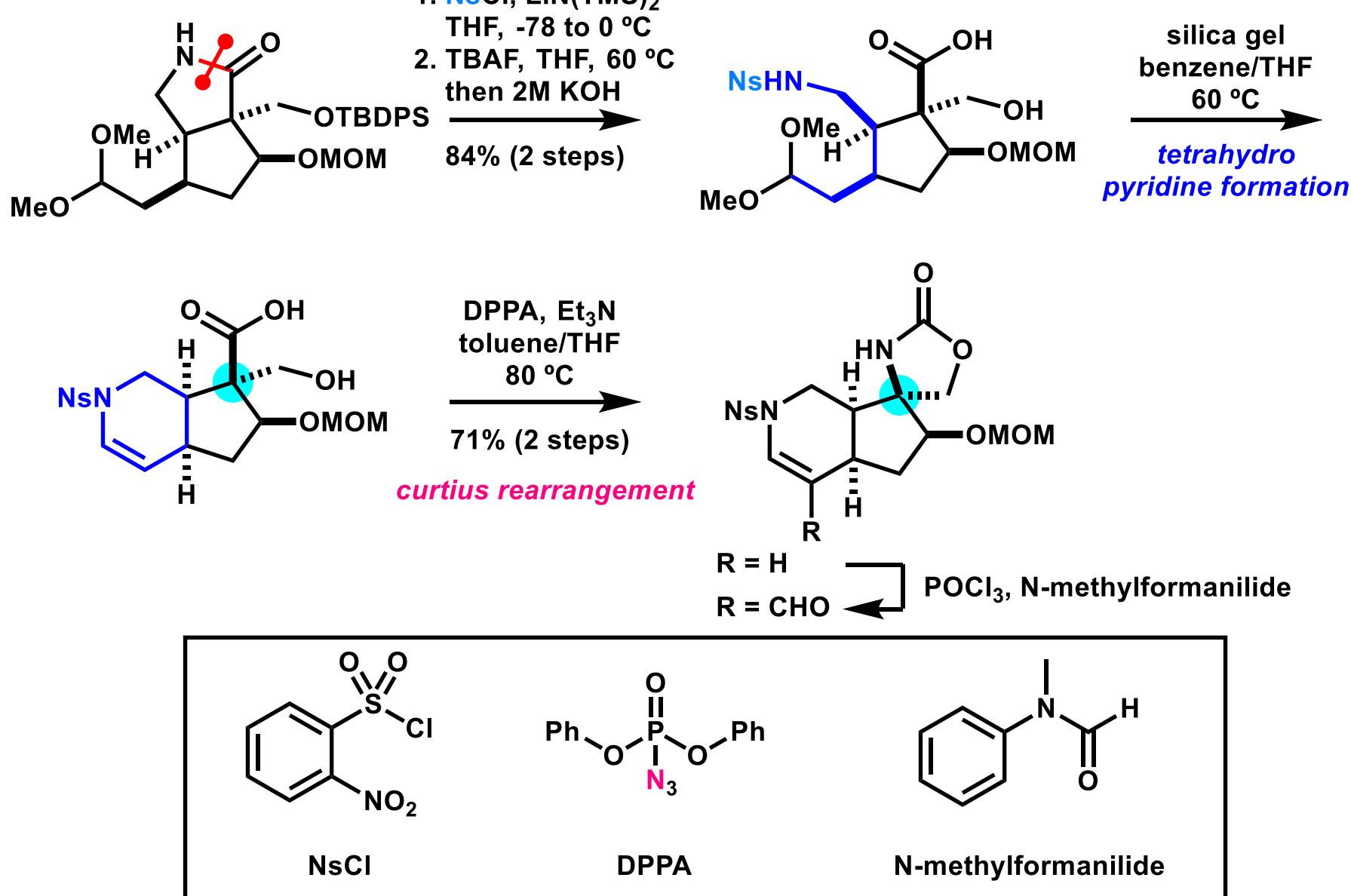
- 1) Hirooka, Y.; Ikeuchi, K.; Kawamoto, Y.; Akao, Y.; Furuta, T.; Asakawa, T.; Inai, M.; Wakimoto, T.; Fukuyama, T.; Kan, T. *Org. Lett.* **2014**, *16*, 1646-1649.

Cleavage of Cyclopentene

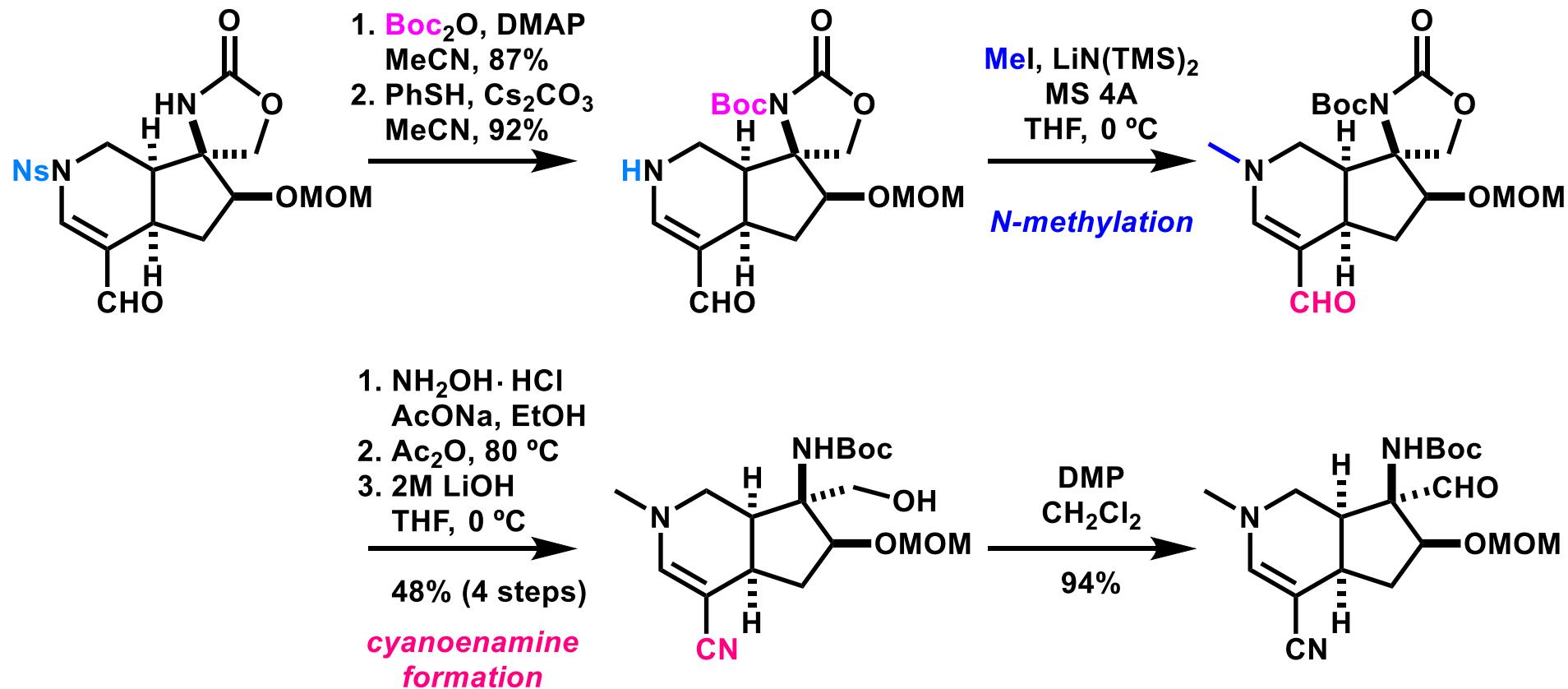


1) Hirooka, Y.; Ikeuchi, K.; Kawamoto, Y.; Akao, Y.; Furuta, T.; Asakawa, T.; Inai, M.; Wakimoto, T.; Fukuyama, T.; Kan, T. *Org. Lett.* **2014**, *16*, 1646-1649.

Construction of Tetrahydropyridine Moiety

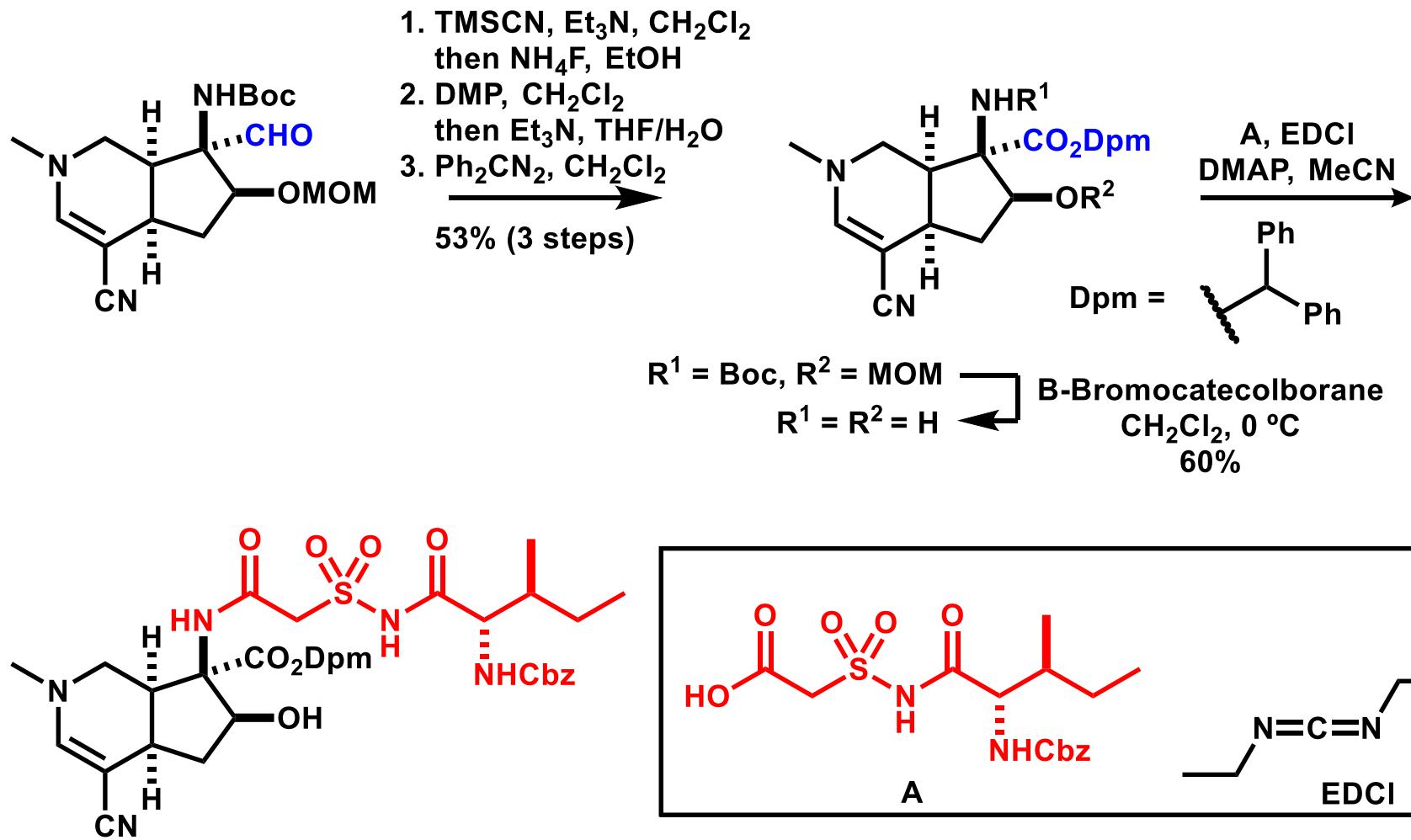


Formation of Cyanoenamine



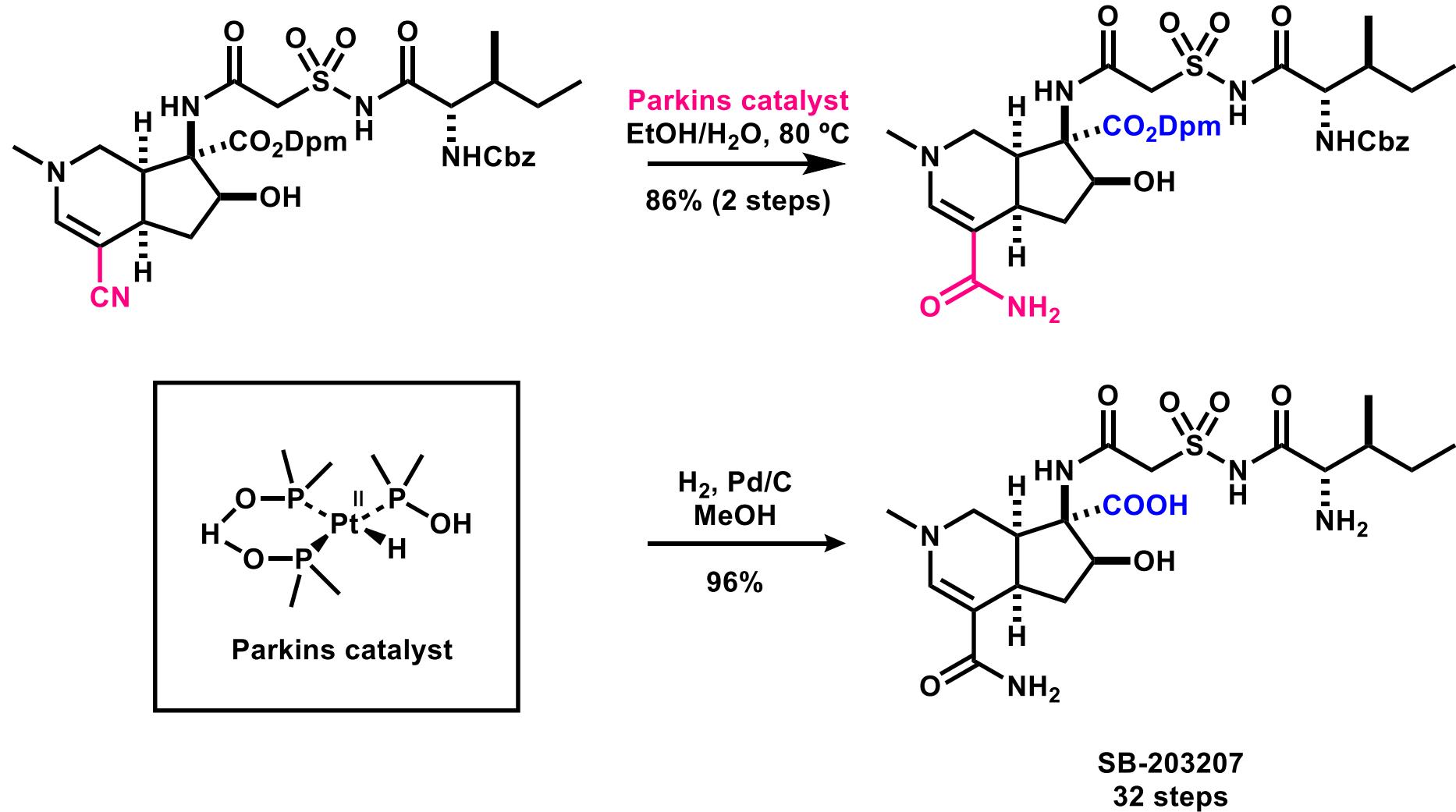
1) Hirooka, Y.; Ikeuchi, K.; Kawamoto, Y.; Akao, Y.; Furuta, T.; Asakawa, T.; Inai, M.; Wakimoto, T.; Fukuyama, T.; Kan, T. *Org. Lett.* **2014**, 16, 1646-1649.

Introduction of Sulfonamide Moiety



- 1) Hirooka, Y.; Ikeuchi, K.; Kawamoto, Y.; Akao, Y.; Furuta, T.; Asakawa, T.; Inai, M.; Wakimoto, T.; Fukuyama, T.; Kan, T. *Org. Lett.* **2014**, 16, 1646-1649.

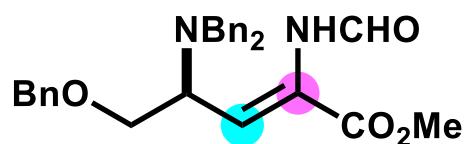
Total synthesis of (+)-SB-203207



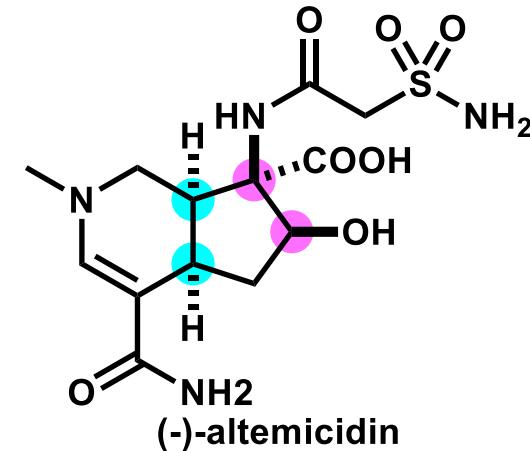
- 1) Hirooka, Y.; Ikeuchi, K.; Kawamoto, Y.; Akao, Y.; Furuta, T.; Asakawa, T.; Inai, M.; Wakimoto, T.; Fukuyama, T.; Kan, T. *Org. Lett.* **2014**, *16*, 1646-1649.
2) Ghaffar, T.; Parkins, A. W. *J. Mol. Catal. A* **2000**, *160*, 249.

Short Summary

Kende's Group

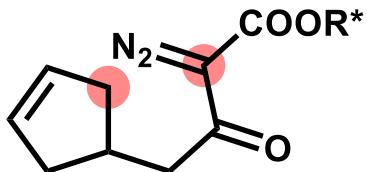


*stereoselective
Dielks-Alder reaction*

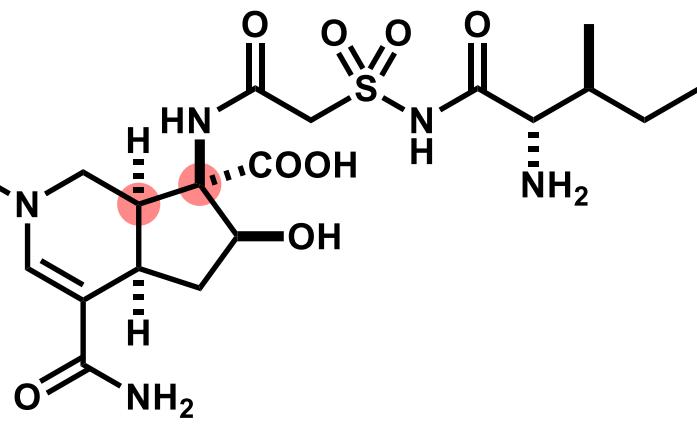
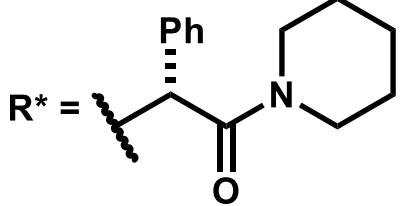
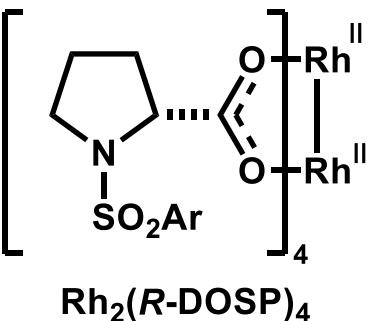


$(-)$ -altemicidin

Fukuyama and Kan's Group



dissymmetric C-H insertion



$(+)$ -SB-203207

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Introduction of Associate Prof. Maimone



Associate Prof. Thomas J. Maimone (1982)

2004 B.S @ University of California, Berkeley

2009 Ph.D @ The Scripps Research Institute, CA (Prof. Phil S. Baran)

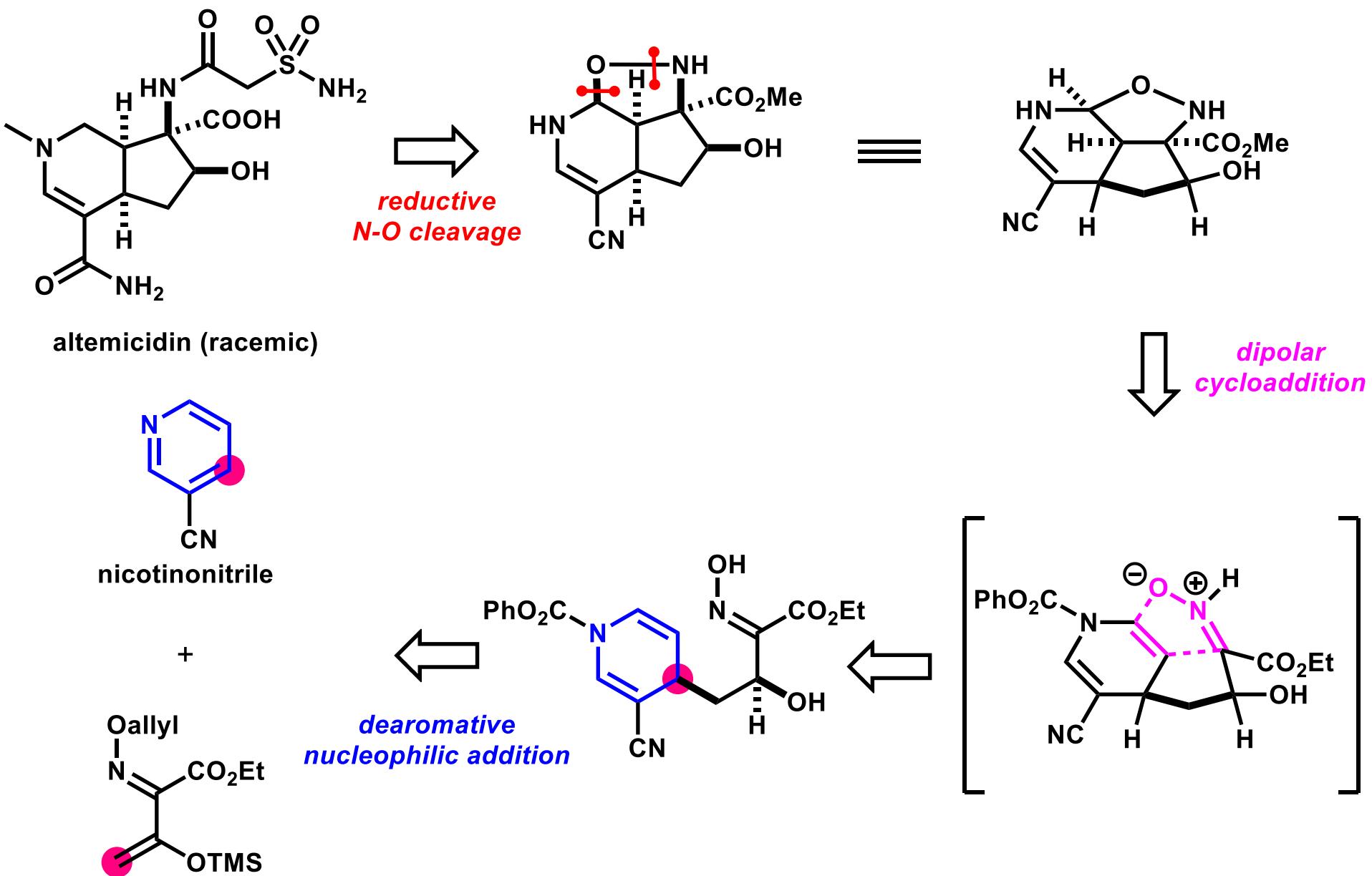
**2009- NIH Postdoctoral Fellow @ Massachusetts Institute of Technology
(Prof. Stephen L. Buchwald)**

2012- Assistance Professor @ University of California, Berkeley

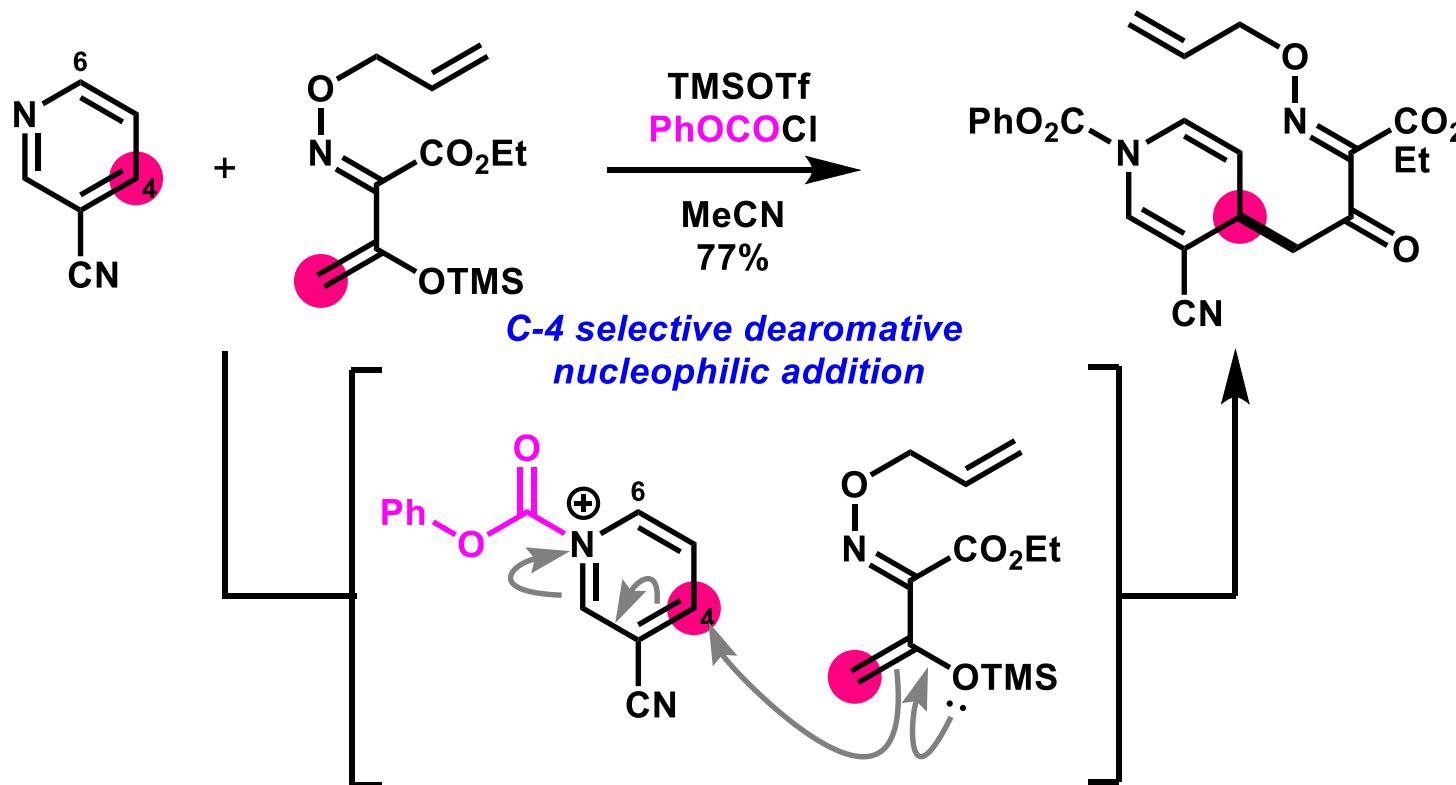
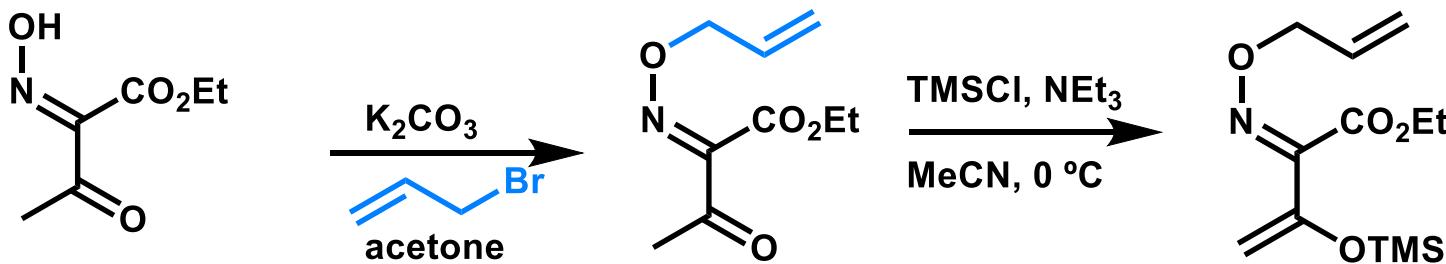
2018- Associate Professor @ University of California, Berkeley

Research topics: total synthesis of biologically active natural compounds

Retrosynthetic Analysis



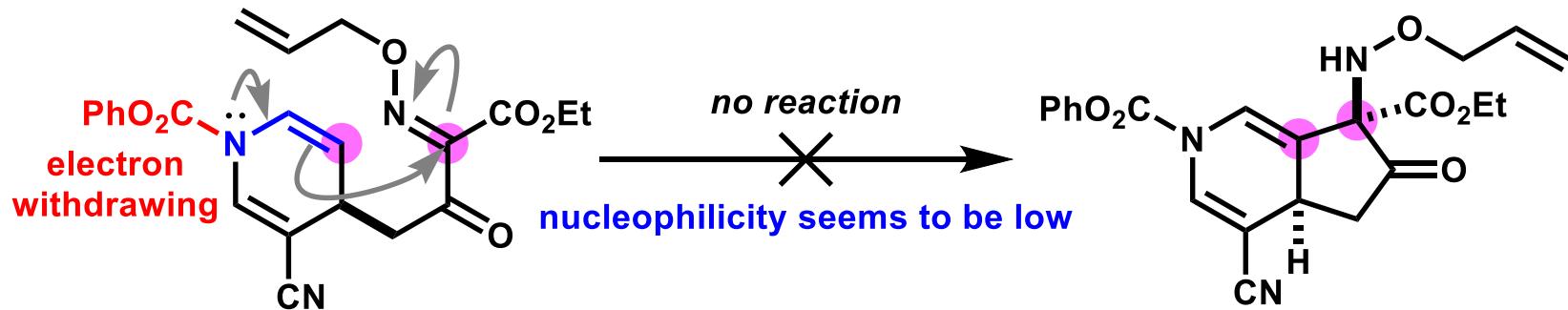
Dearomative Nucleophilic Addition



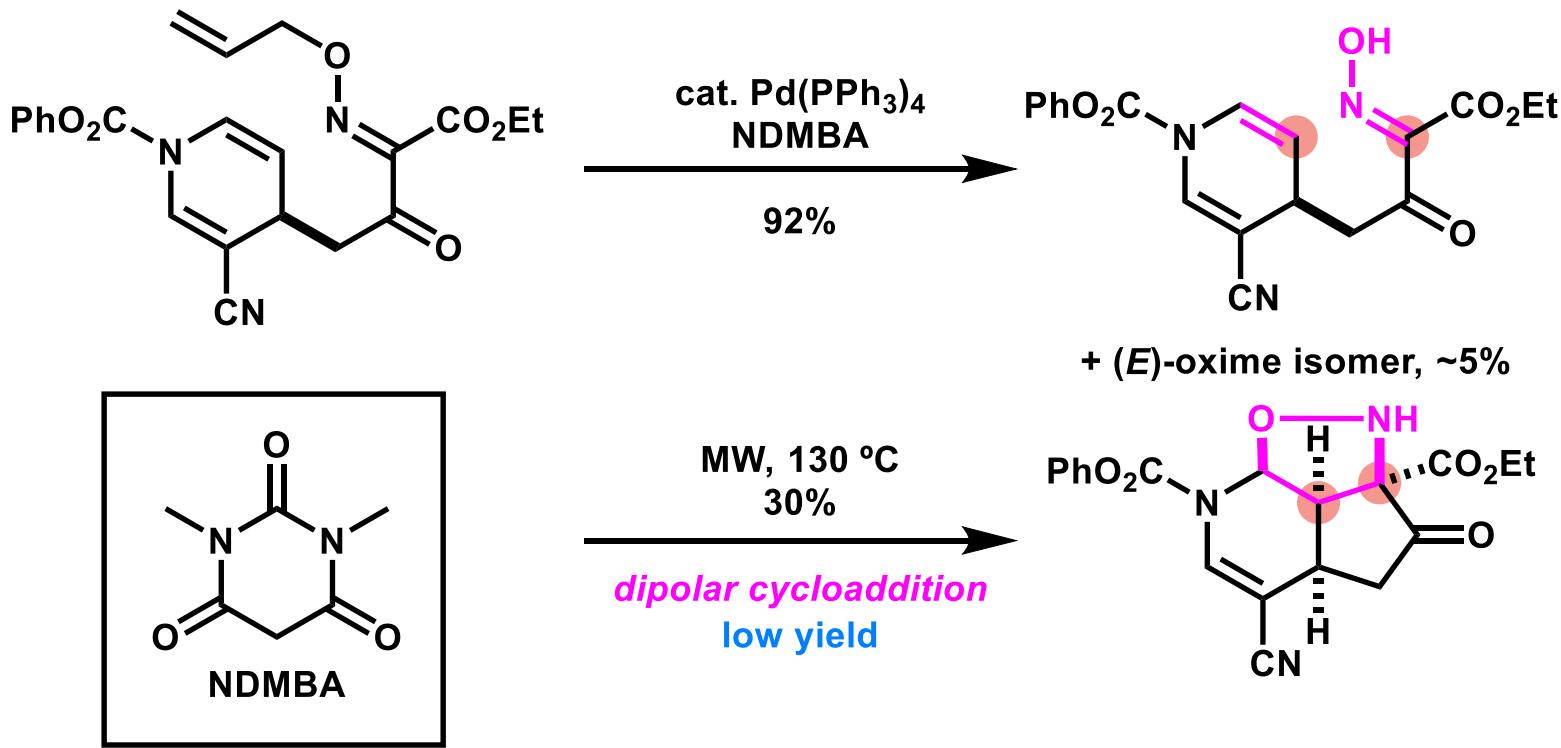
- 1) Harmange Magnani, C. S.; Maimone, T. J. *J. Am. Chem. Soc.* **2021**, 143, 7935–7939.
2) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, 112, 2642.

Attempts to Forge α -Amine Stereocenter

1. Nucleophilic attack by dihydropyridine

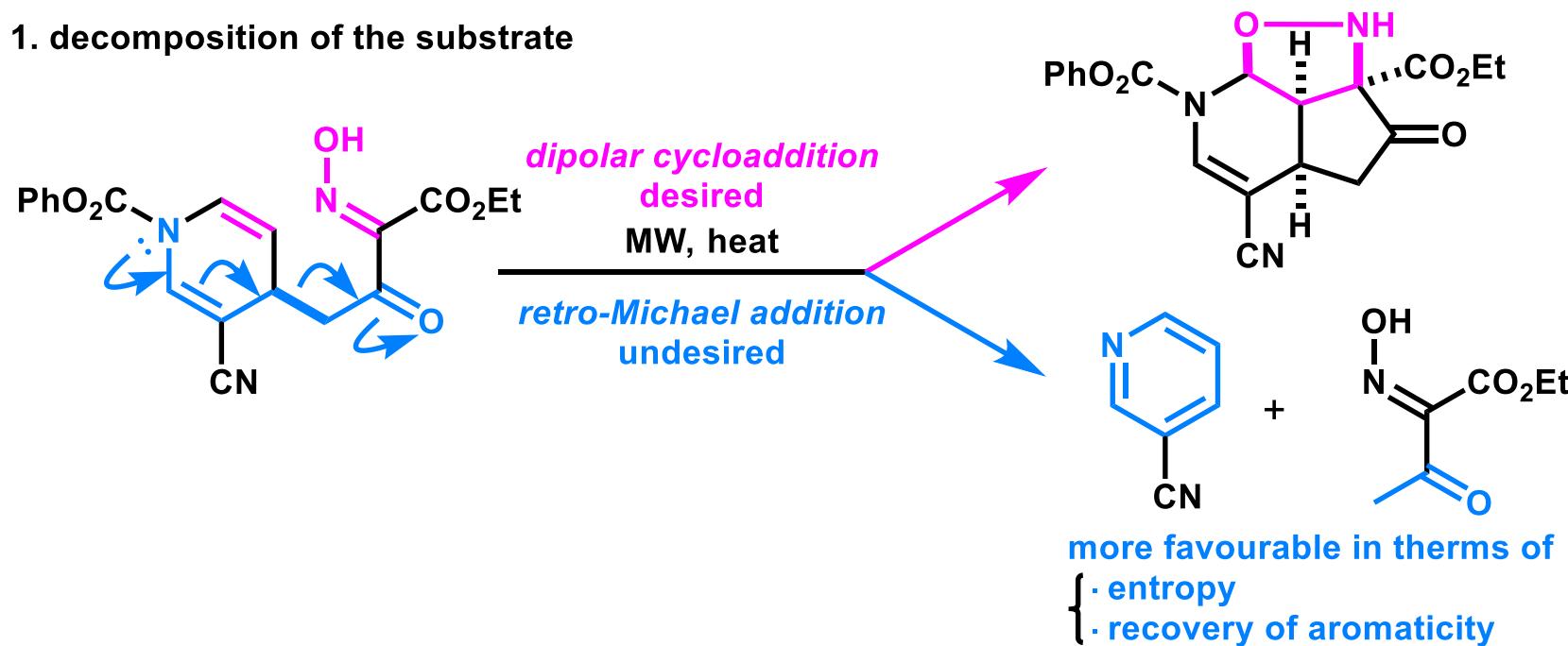


2. dipolar cycloaddition

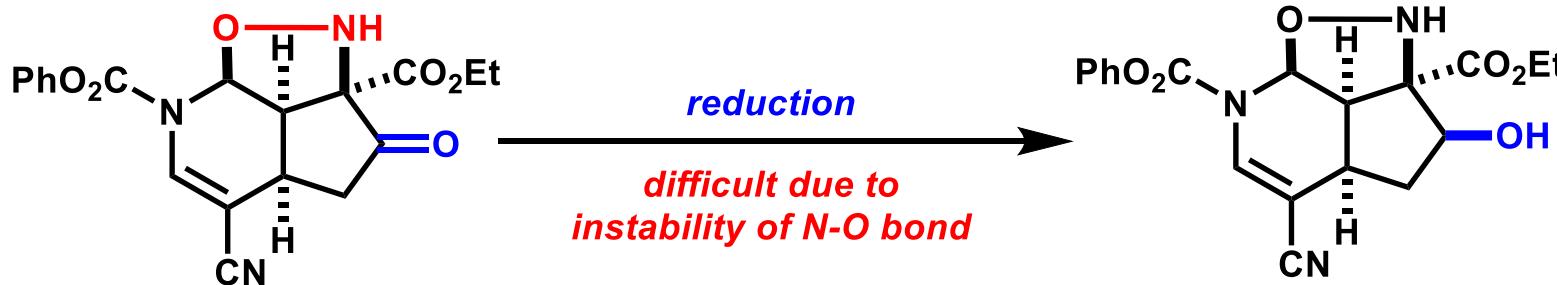


Promblems in Dipolar Cycloaddition

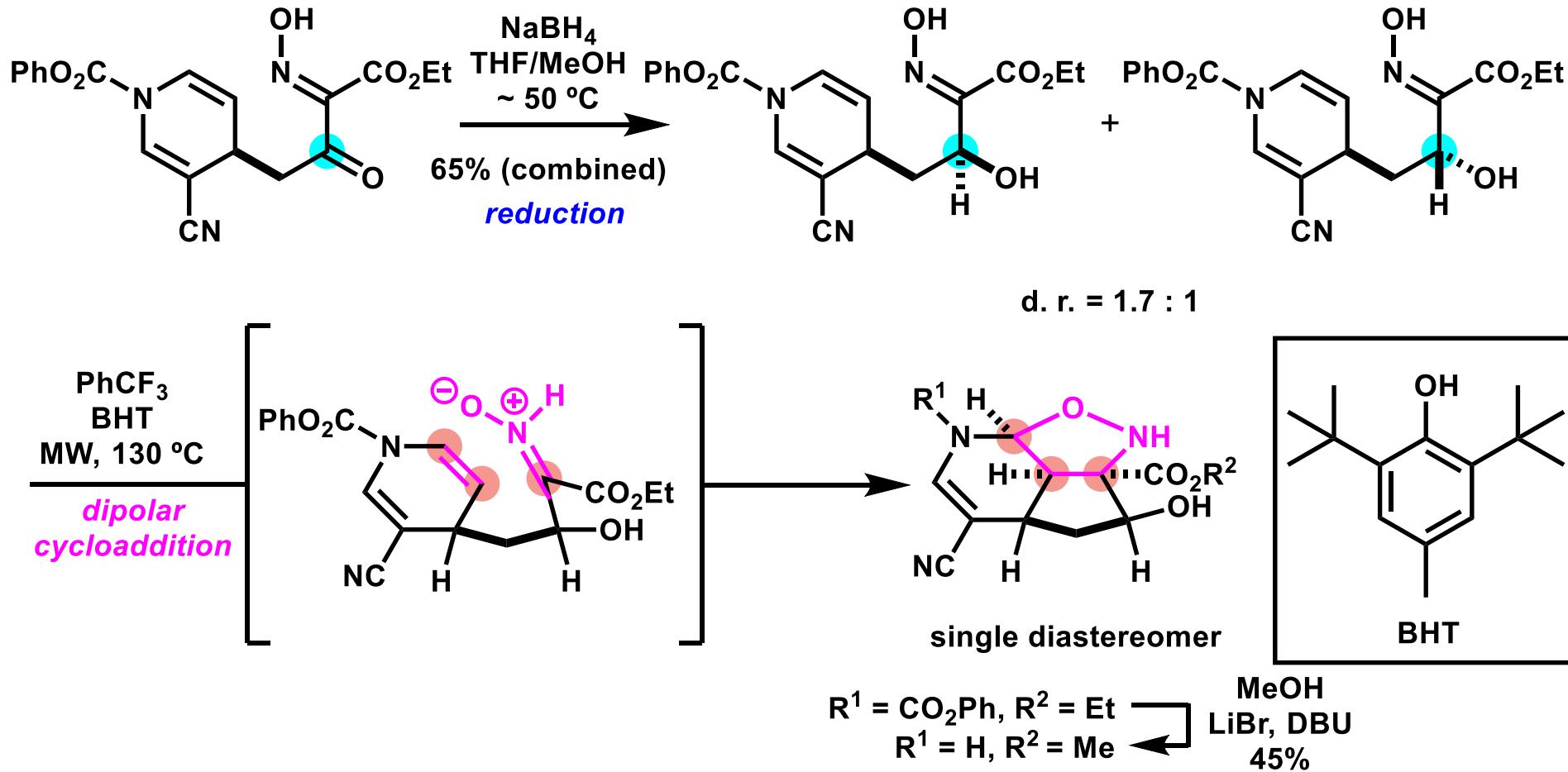
1. decomposition of the substrate



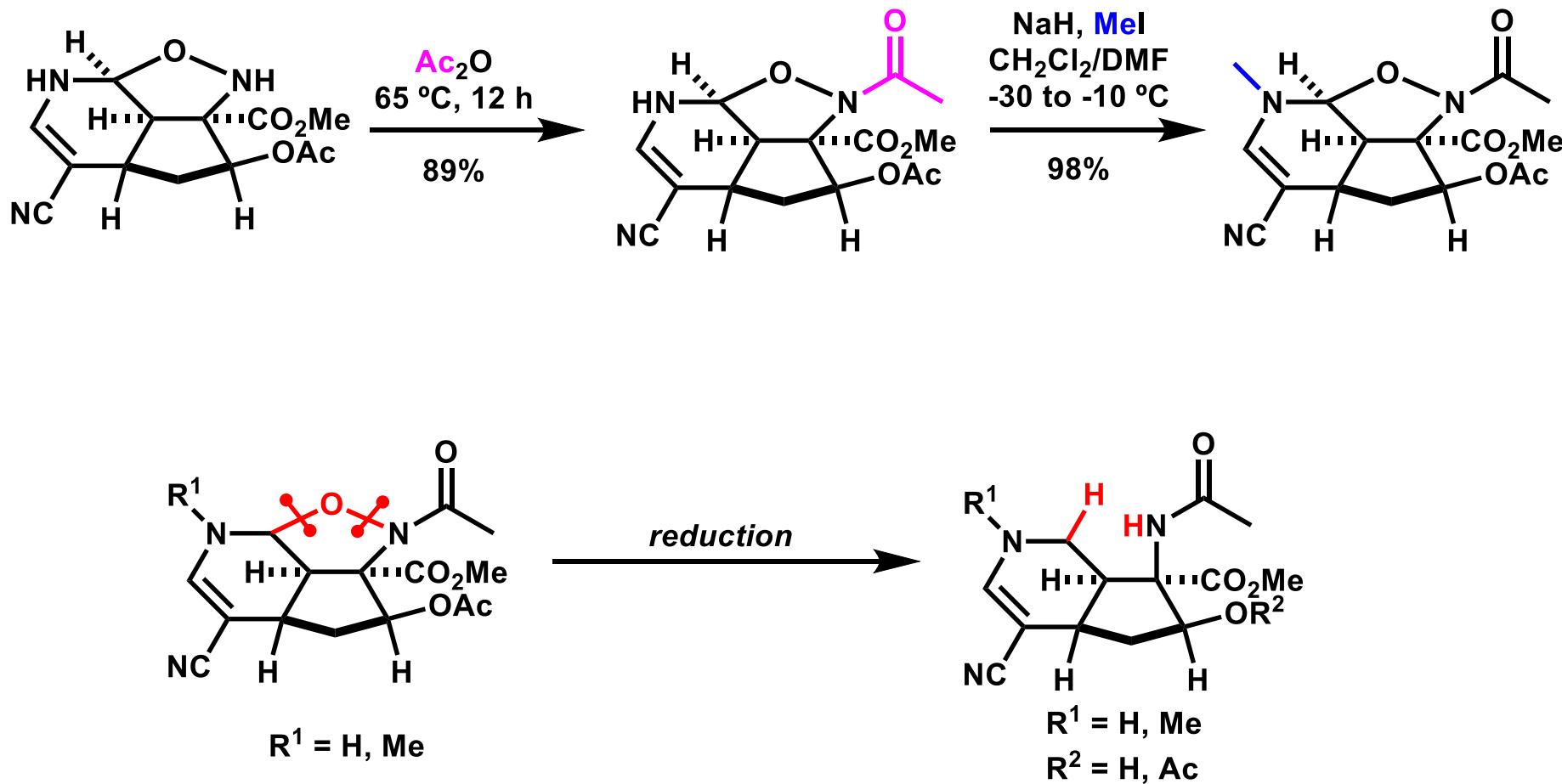
2. difficulty of reduction of ketone



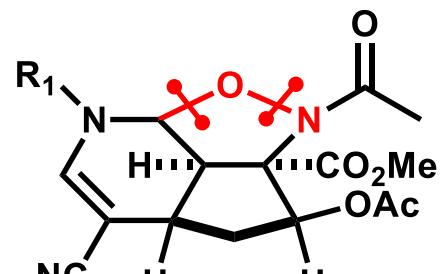
Successful Dipolar Cycloaddition



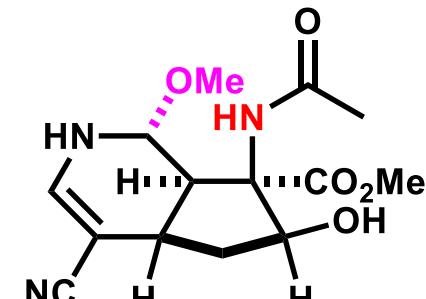
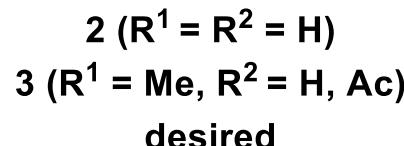
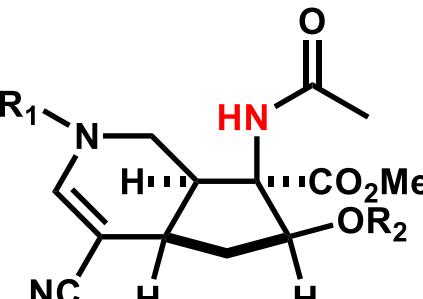
Reductive Cleavage of N-O and C-O bond (1)



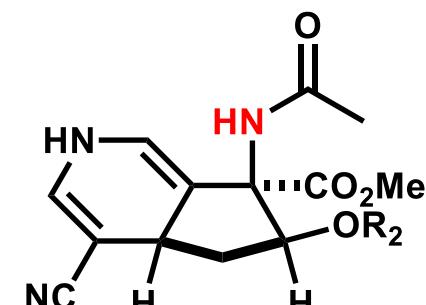
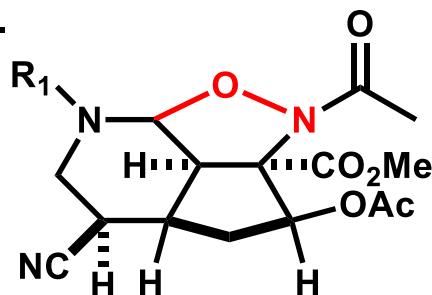
Reductive Cleavage of N-O and C-O bond (2)



conditions



R^1	<i>conditions</i>	product
H	$Sm^{II}I_2$ -THF, MeOH	4
H	10 % Pd/C, H_2 , MeOH	5
H^a	$Mo^0(CO)_6$, PhSiH ₃	2 : 6 (40%, 4:1)
H^a	$Mo^0(CO)_6$, NaBH ₃ CN	2 (5%), 1 (95%)
H^a	$Mo^0(CO)_3(MeCN)_3^b$, NaBH ₃ CN	2 : 6 (78%, 20:1)
Me ^a	$Mo^0(CO)_3(MeCN)_3^b$, NaBH ₃ CN	3 (82%)

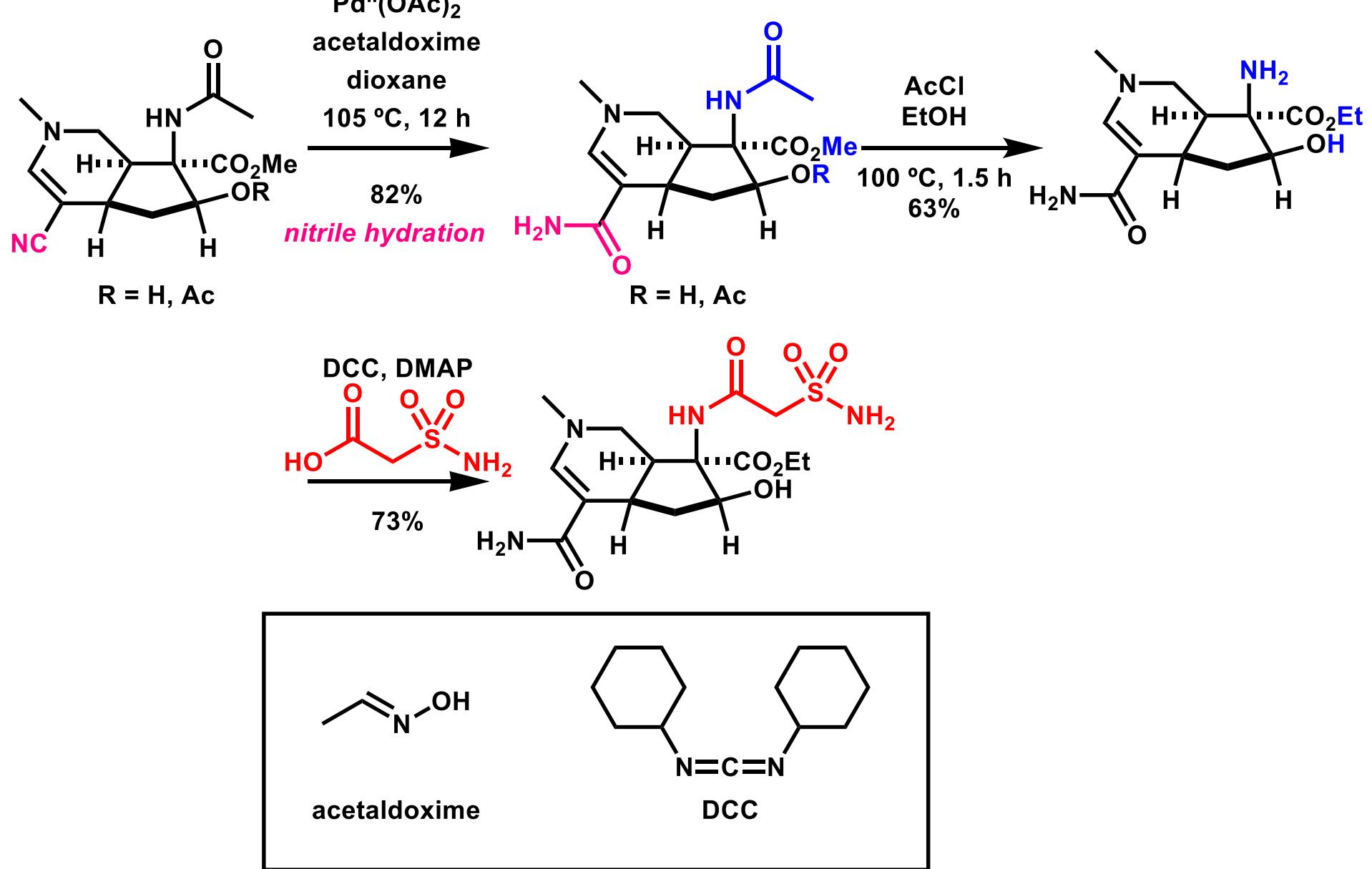


^a Reactions performed in MeCN at 85 °C with 1.0 eq. of Mo(0).

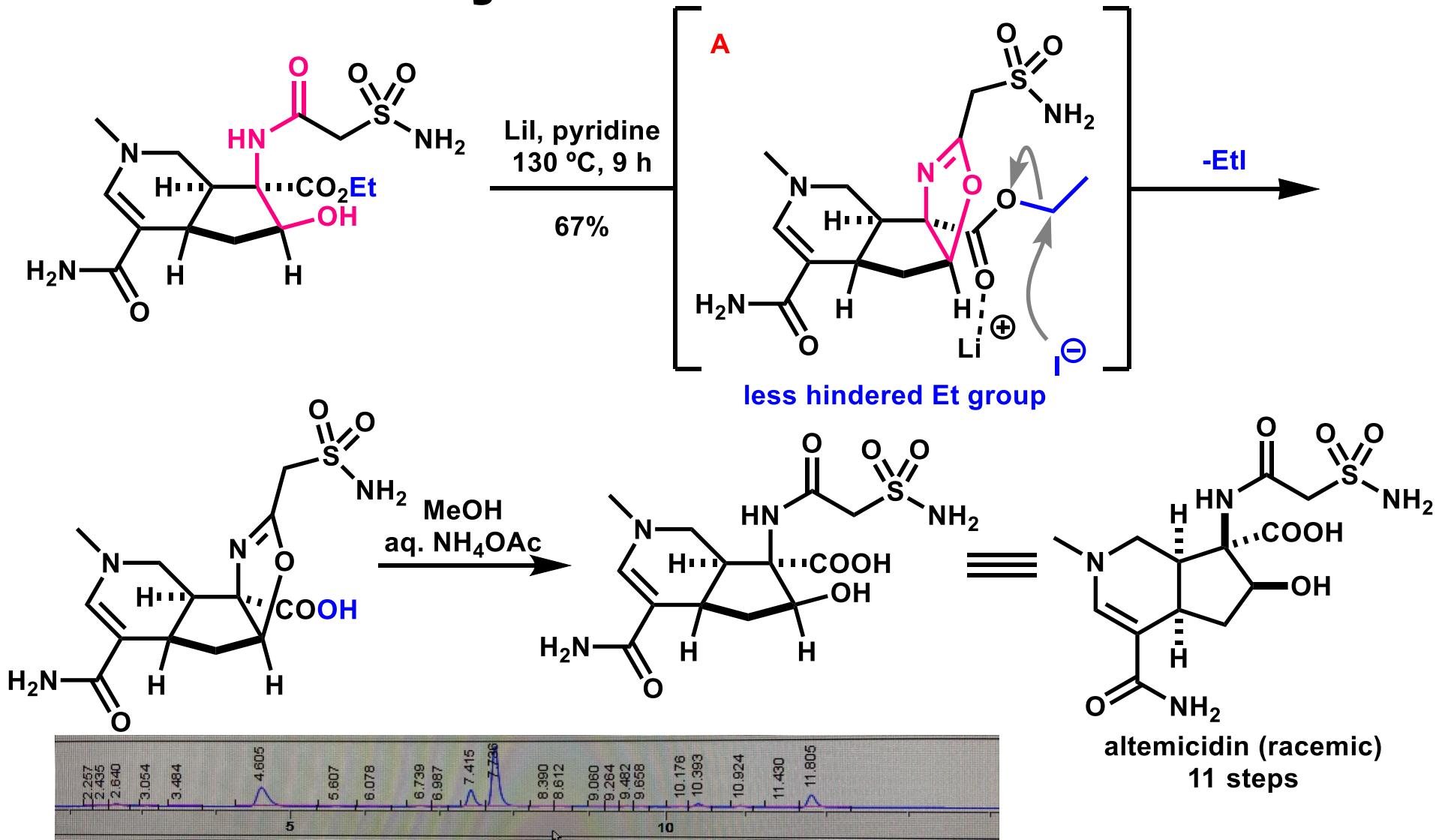
^b Prepared from $Mo^0(CO)_6$ in MeCN before the addition of 1.

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Introduction of Sulfonamide Moiety



Total synthesis of Altemicidin



Summary

