

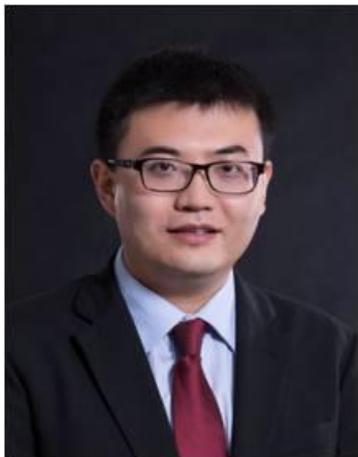
Total Syntheses of Calyciphylline A-Type Alkaloids

2022.10.1. Literature Seminar
B4 Shuji Toyama

Contents

- 1. Introduction**
- 2. Total synthesis of (-)-Daphniyunnine C
(by Li Group)**
- 3. Total synthesis of (-)-10-Deoxy-daphnipaxianine A,
(+)-Daphlogamine E and (+)-Calyciphylline R
(by Xu Group)**
- 4. Summary**

Introduction of Prof. Li and Xu



Prof. Ang Li

2004 B. S., @ Peking University (Prof. Yang)
2009 Ph.D., @ The Scripps Research Institute (Prof. Nicolaou)
2010 Research fellow @ Institute of Chemical and Engineering Science (Prof. Nicolaou)
2010- Professor @ Shanghai Institute of Organic Chemistry

Research topic: Total synthesis of structurally and biologically interesting natural products

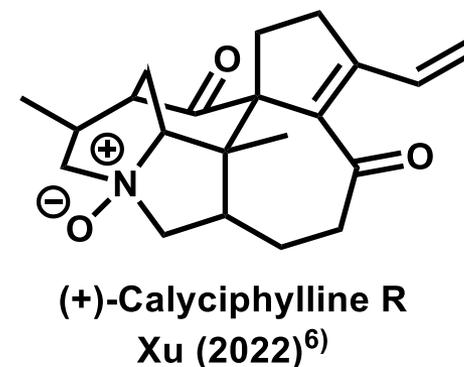
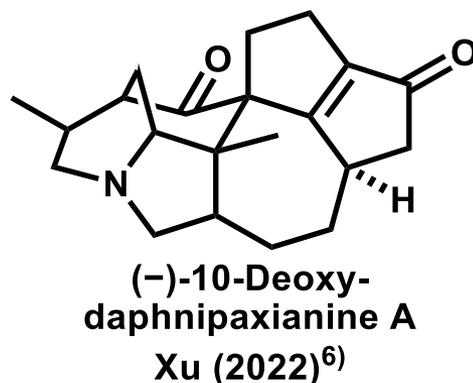
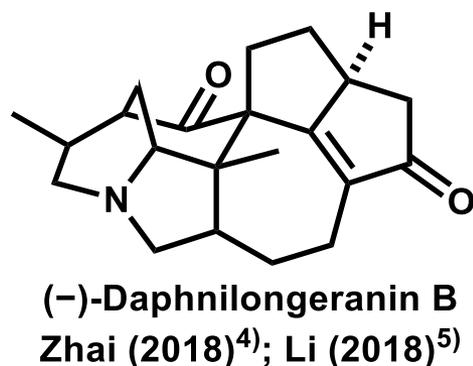
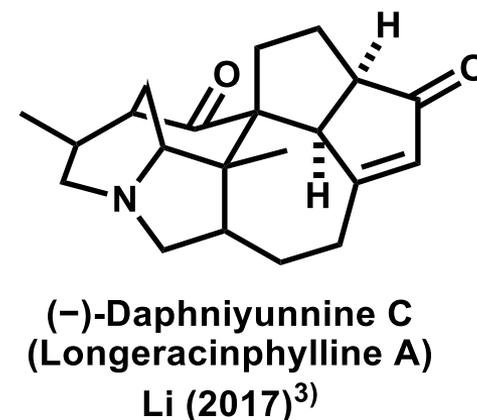
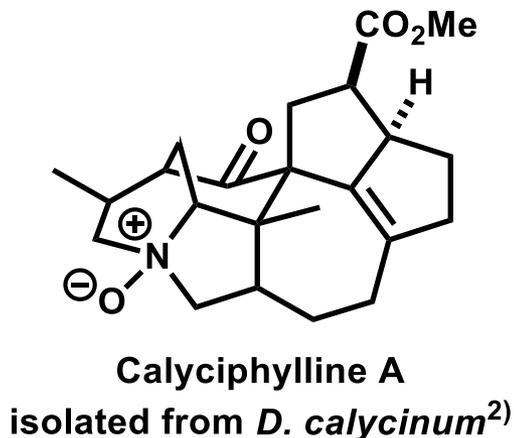
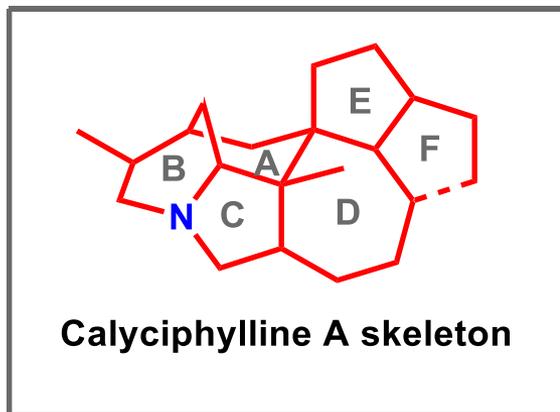


Prof. Jing Xu

2000 B. S., @ Nanchang University
2004 M. S., @ Tongji University
2009 Ph.D., @ Leipzig University (Prof. Zhang)
2009- Postdoctoral fellow @ University of California San Diego
2014- Assistant Professor @ Southern University of Science and Technology
2020- Professor @ Southern University of Science and Technology

Research topic: Total synthesis of complex caged natural products
Small molecule medicinal chemistry

Calyciphylline A-Type Alkaloids



- hexa-or-pentacyclic skeleton
- two consecutive quaternary carbons
- tertiary amine

1) Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936.

2) Morita, H.; Kobayashi, J. *Org. Lett.* **2003**, *5*, 2895.

3) Li, J.; Zhang, W.; Zhang, F.; Chen, Y.; Li, A. *J. Am. Chem. Soc.* **2017**, *139*, 14893.

4) Chen, X.; Zhang, H.-J.; Yang, X.; Lv, H.; Shao, X.; Tao, C.; Wang, H.; Cheng, B.; Li, Y.; Guo, J.; Zhang, J.; Zhai, H. *Angew. Chem., Int. Ed.* **2018**, *57*, 947.

5) Zhang, W. H.; Ding, M.; Li, J.; Guo, Z. C.; Lu, M.; Chen, Y.; Liu, L. C.; Shen, Y. H.; Li, A. *J. Am. Chem. Soc.* **2018**, *140*, 4227.

6) Zhang, Y.; Chen, Y.; Song, M.; Tan, B.; Jiang, Y.; Yan, C.; Jiang, Y.; Hu, X.; Zhang, C.; Chen, W.; Xu, J. *J. Am. Chem. Soc.* **2022**, *144*, 16042.

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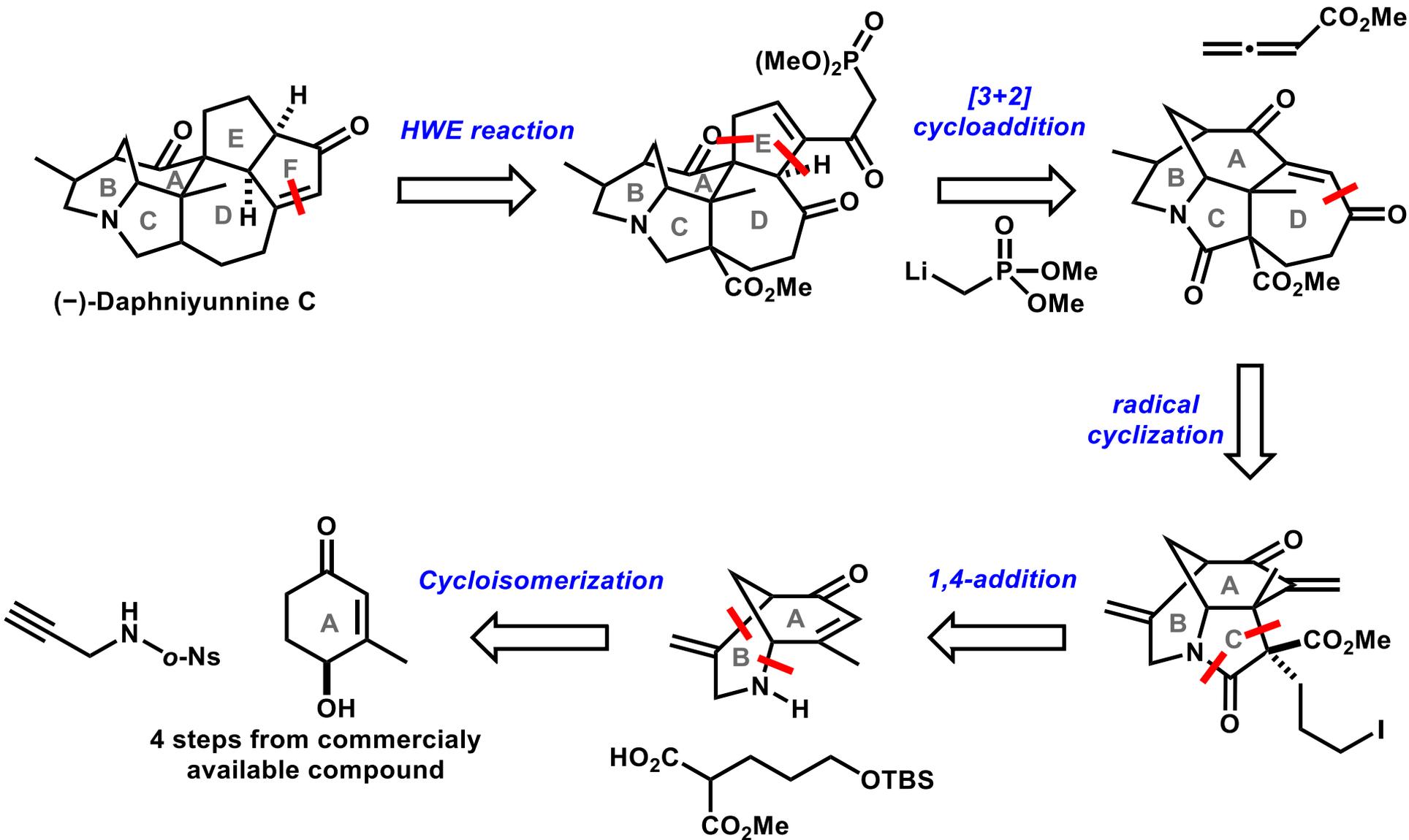
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(by Li Group)**

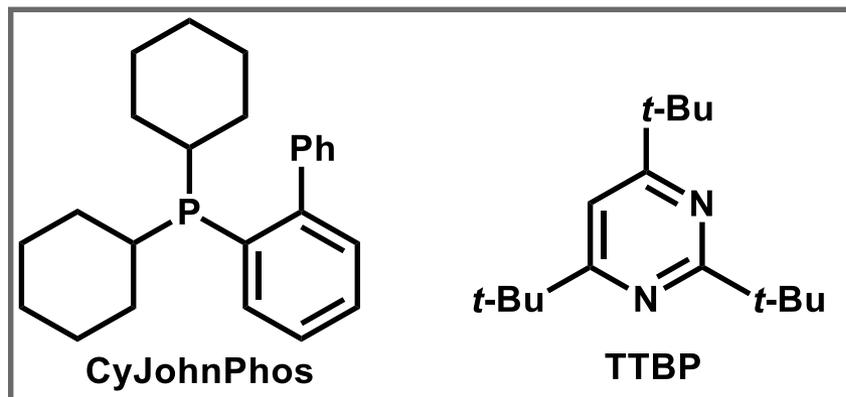
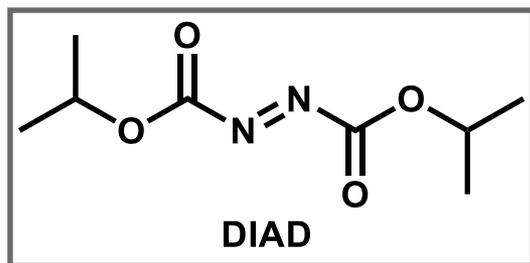
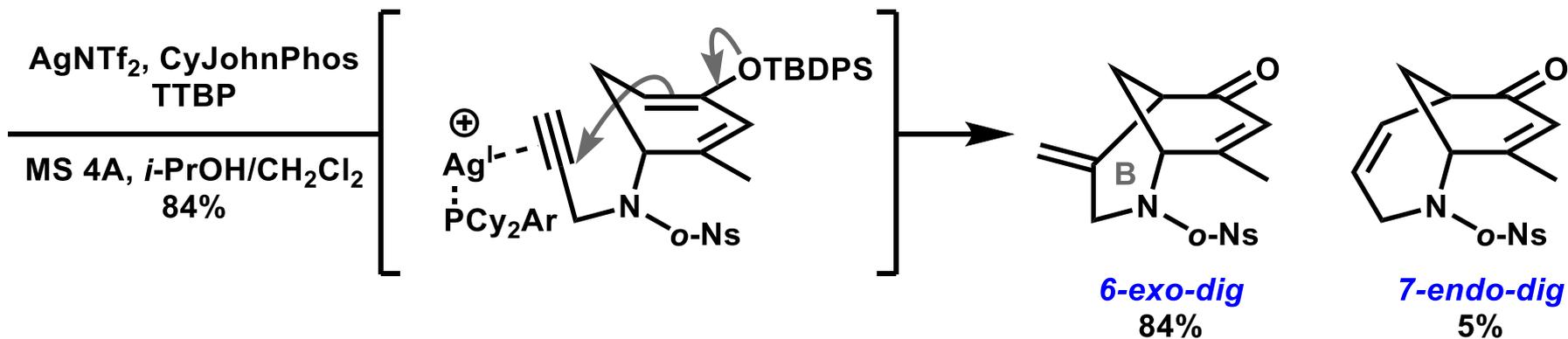
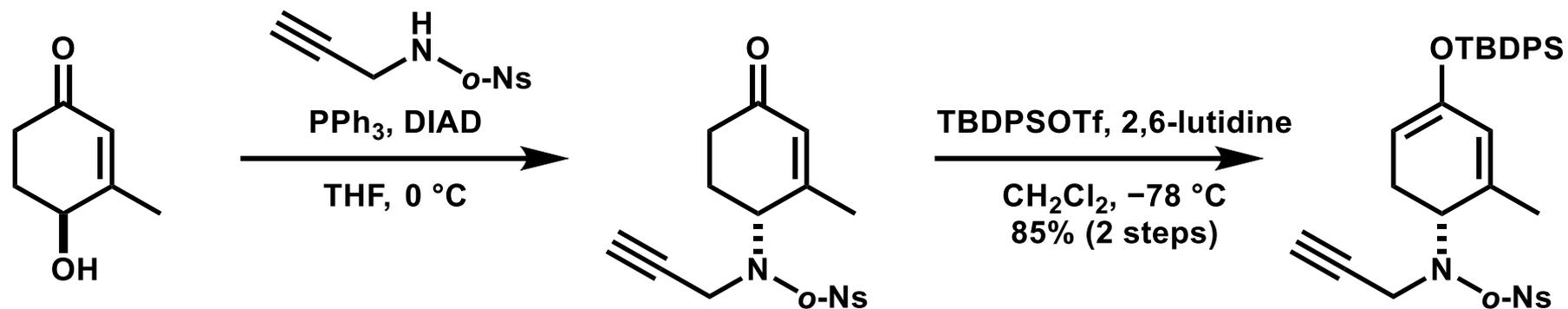
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4. Summary

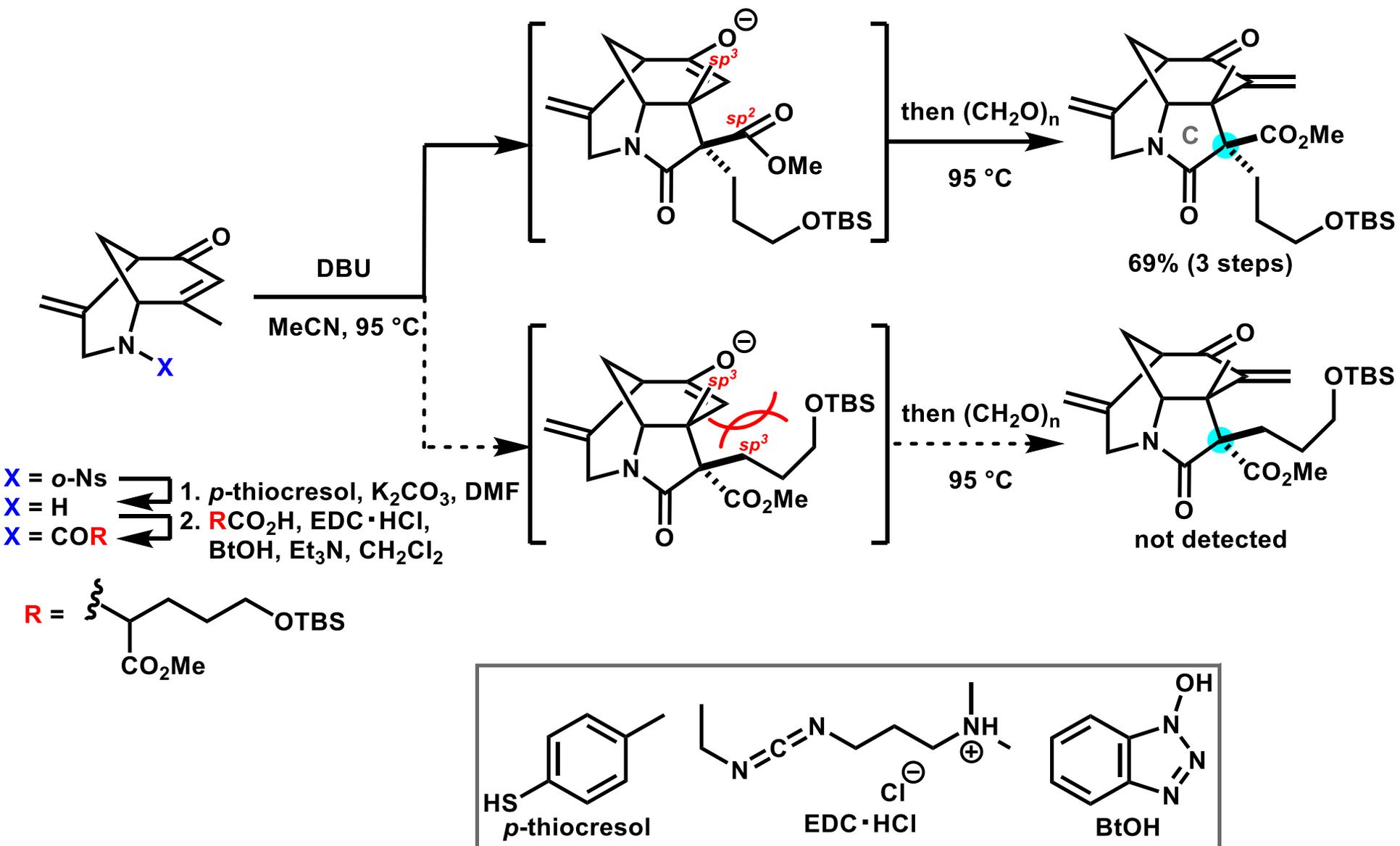
Retrosynthetic Analysis (by Li)



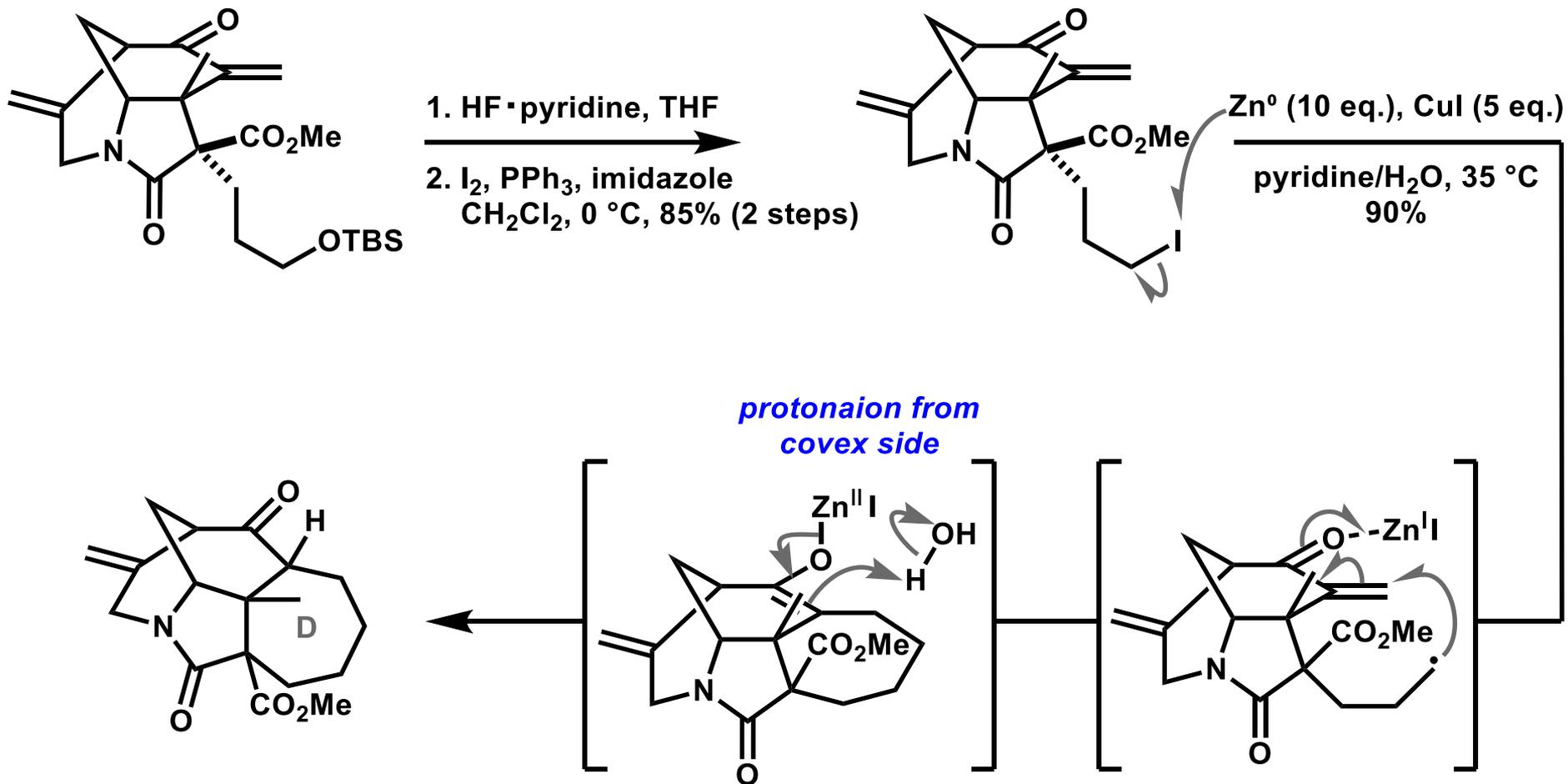
Construction of B-ring



Construction of C-ring

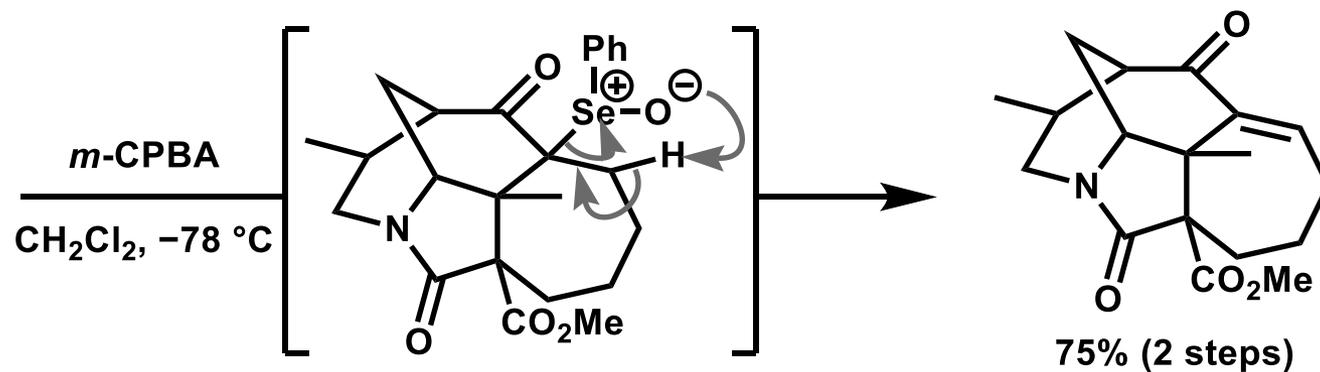
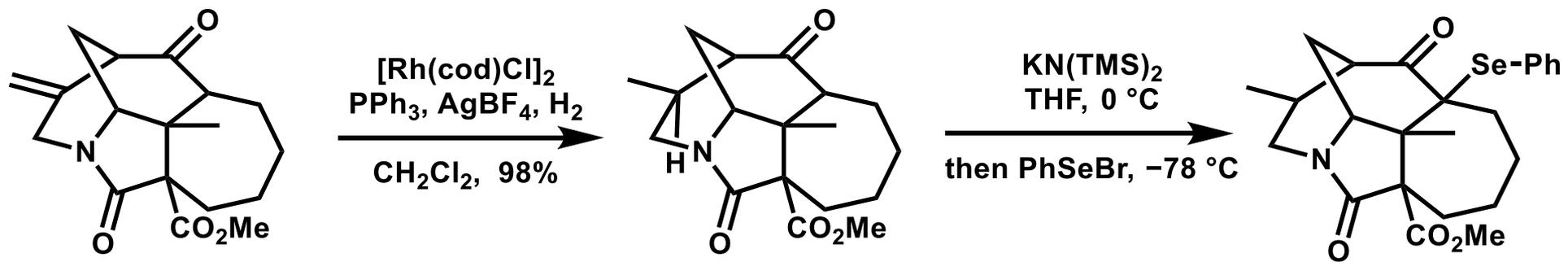


Construction of D-ring

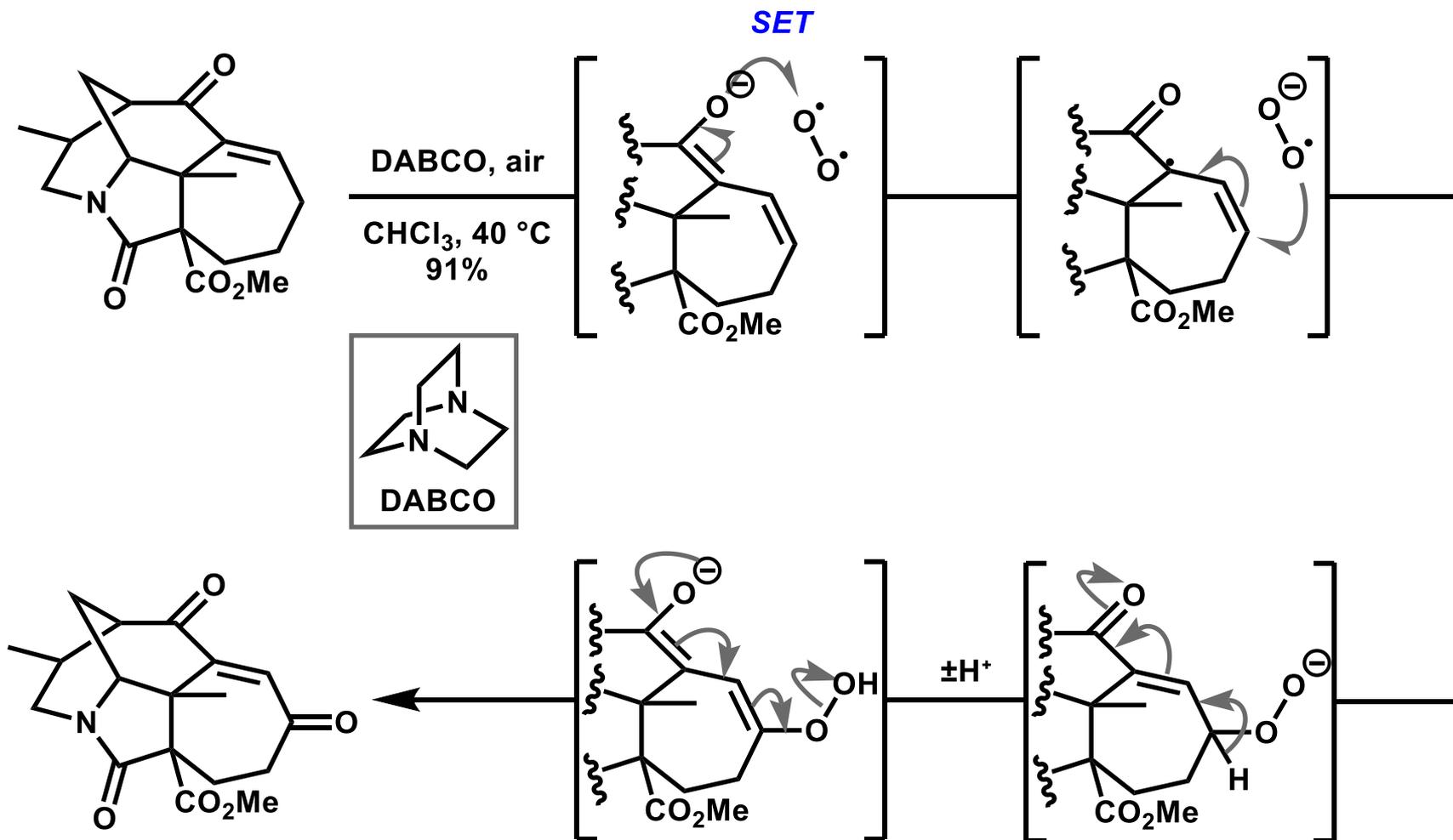


- 1) Li, J.; Zhang, W.; Zhang, F.; Chen, Y.; Li, A. *J. Am. Chem. Soc.* **2017**, *139*, 14893.
- 2) Petrier, C.; Dupuy, C.; Luche, J. L. *Tetra. Lett.* **1986**, *27*, 3149.

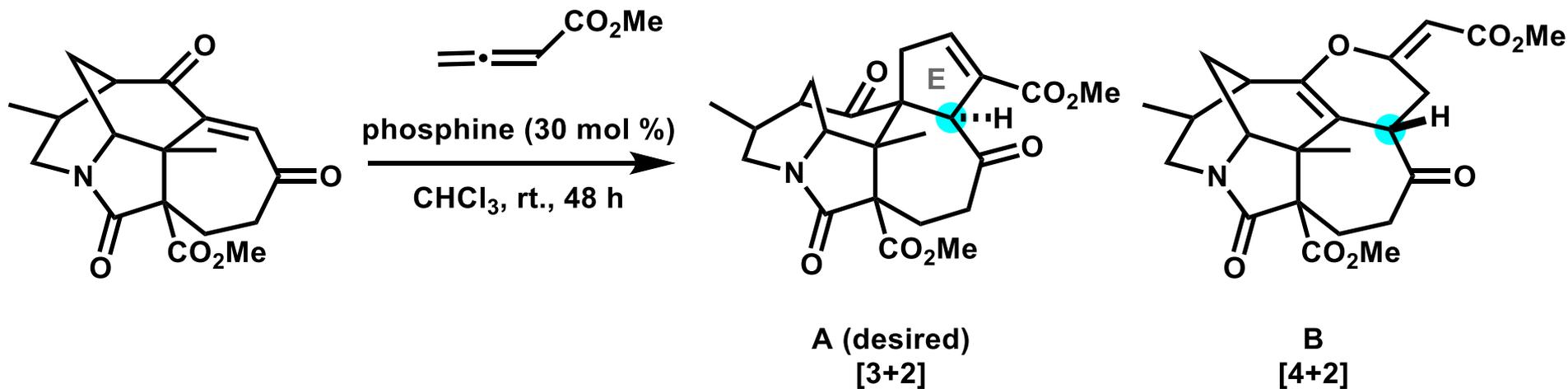
Conversion to enone



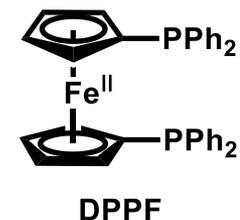
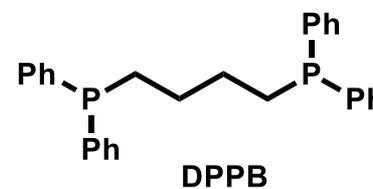
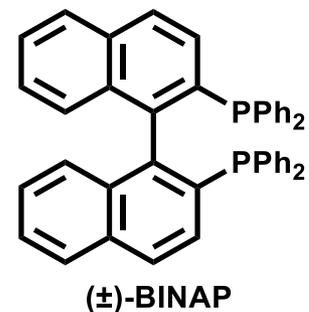
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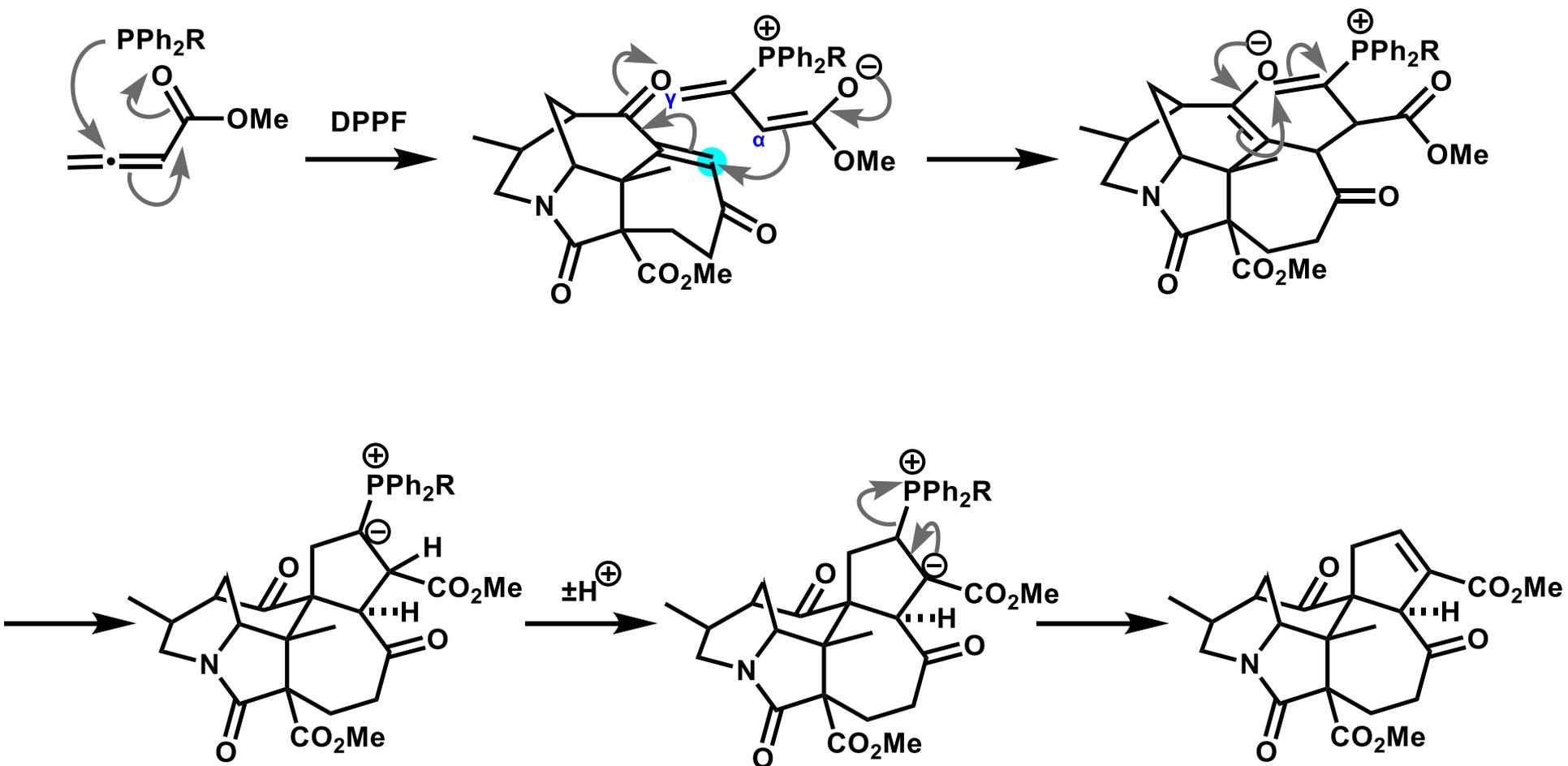
Optimization of [3+2] type cyclization



entry	phosphine	A (%)	B (%)
1	PPh ₃	31	40
2	P(4-F-Ph) ₃	35	38
3	PBu ₃	5	67
4	(±)-BINAP	15	23
5	DPPB	21	57
6	DPPF	45	22



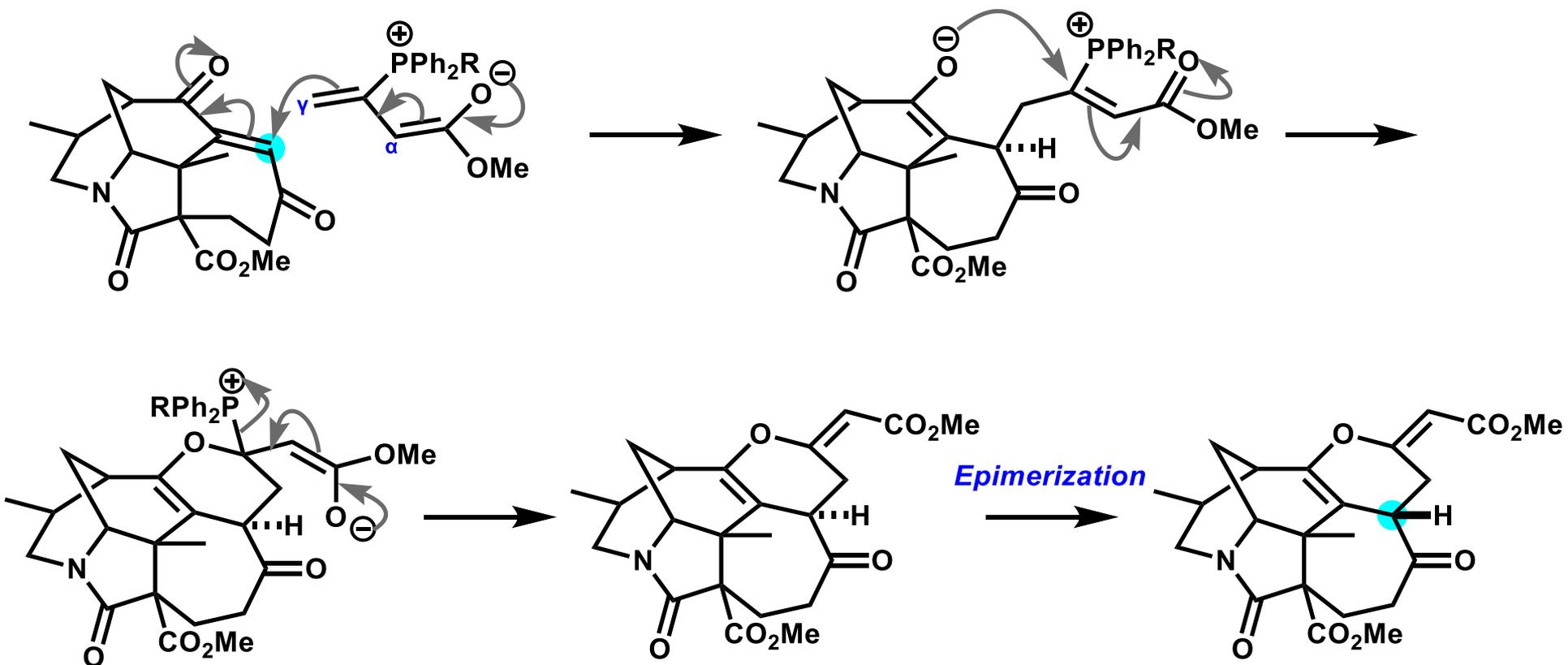
Proposed mechanism of [3+2] type cyclization



- 1) Li, J.; Zhang, W.; Zhang, F.; Chen, Y.; Li, A. *J. Am. Chem. Soc.* **2017**, *139*, 14893.
- 2) Liang, Y.; Liu, S.; Xia, Y.; Li, Y.; Yu, Z. X.; *Chem. Eur. J.* **2008**, *14*, 4361.

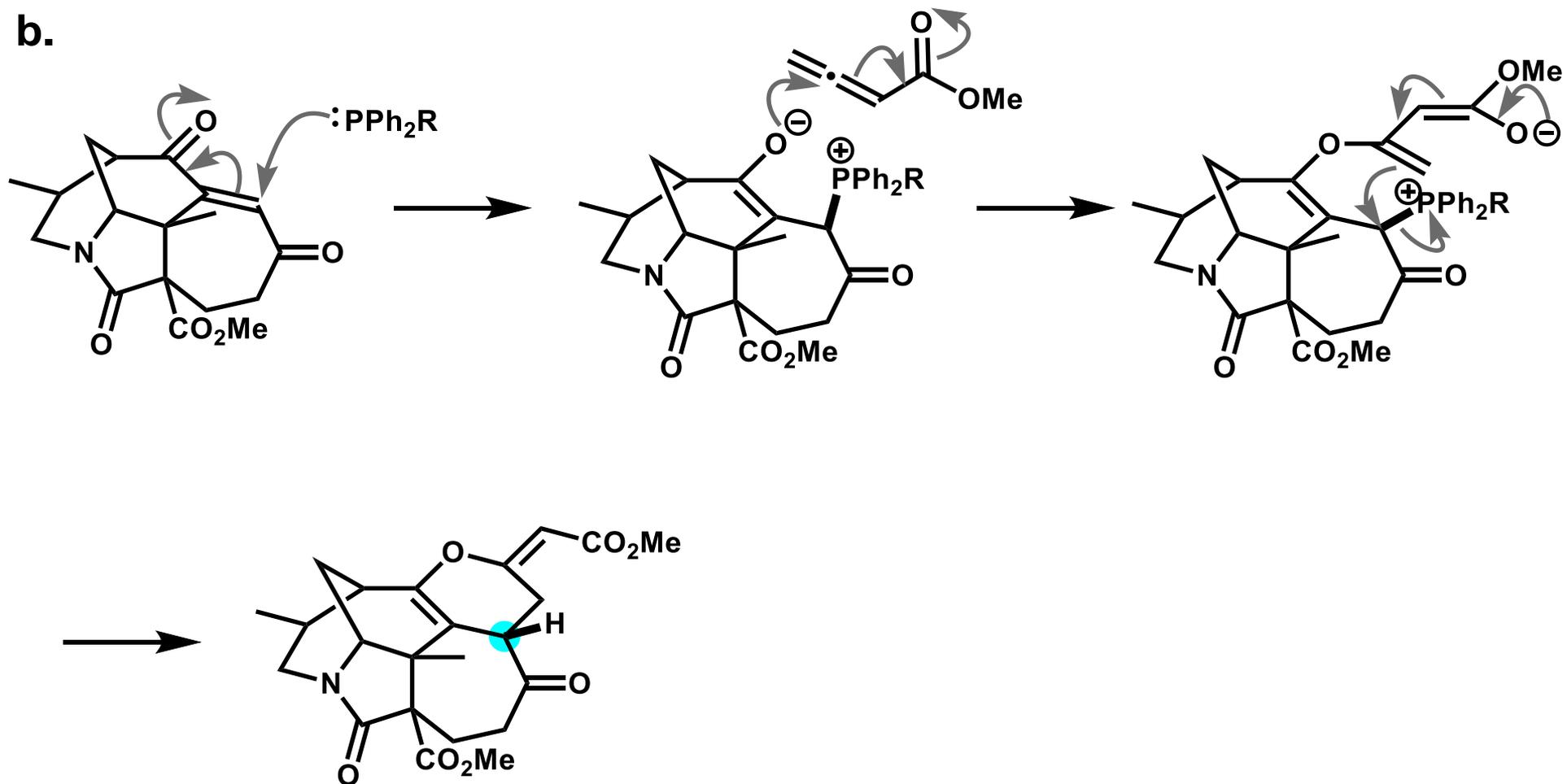
Proposed mechanism of [4+2] type cyclization

a.



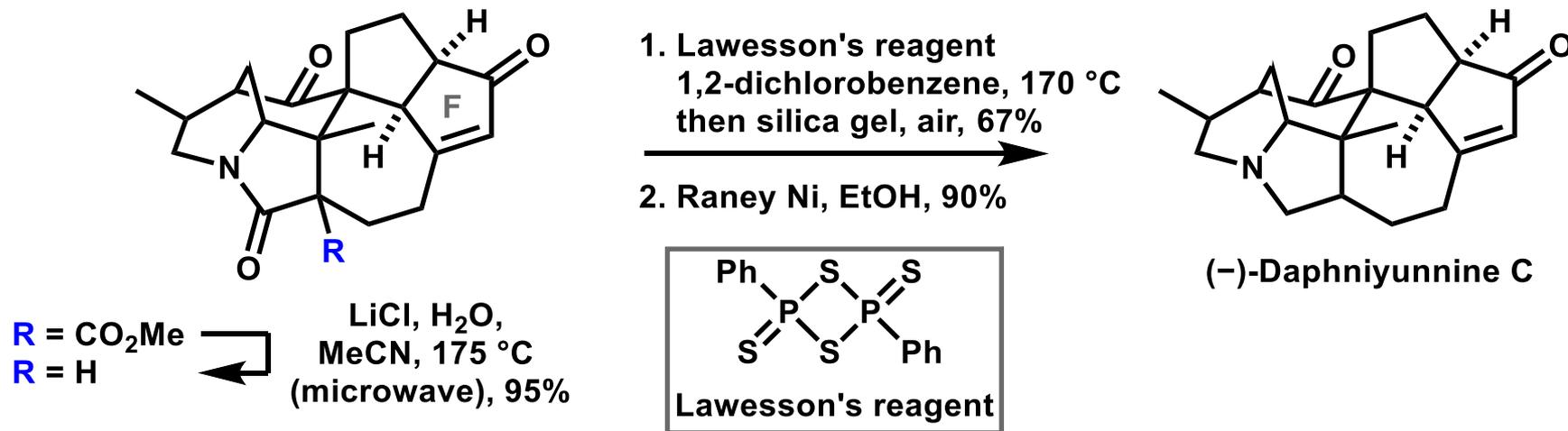
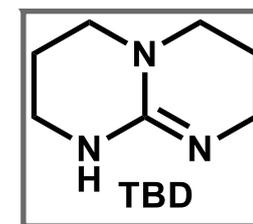
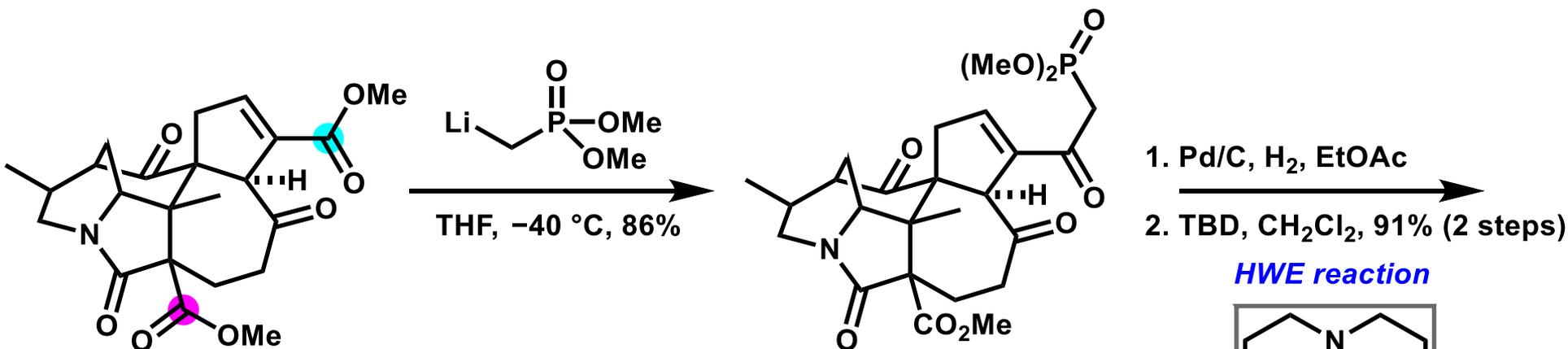
Proposed mechanism of [4+2] type cyclization

b.



Both mechanisms are possible.

Construction of F-ring



Contents

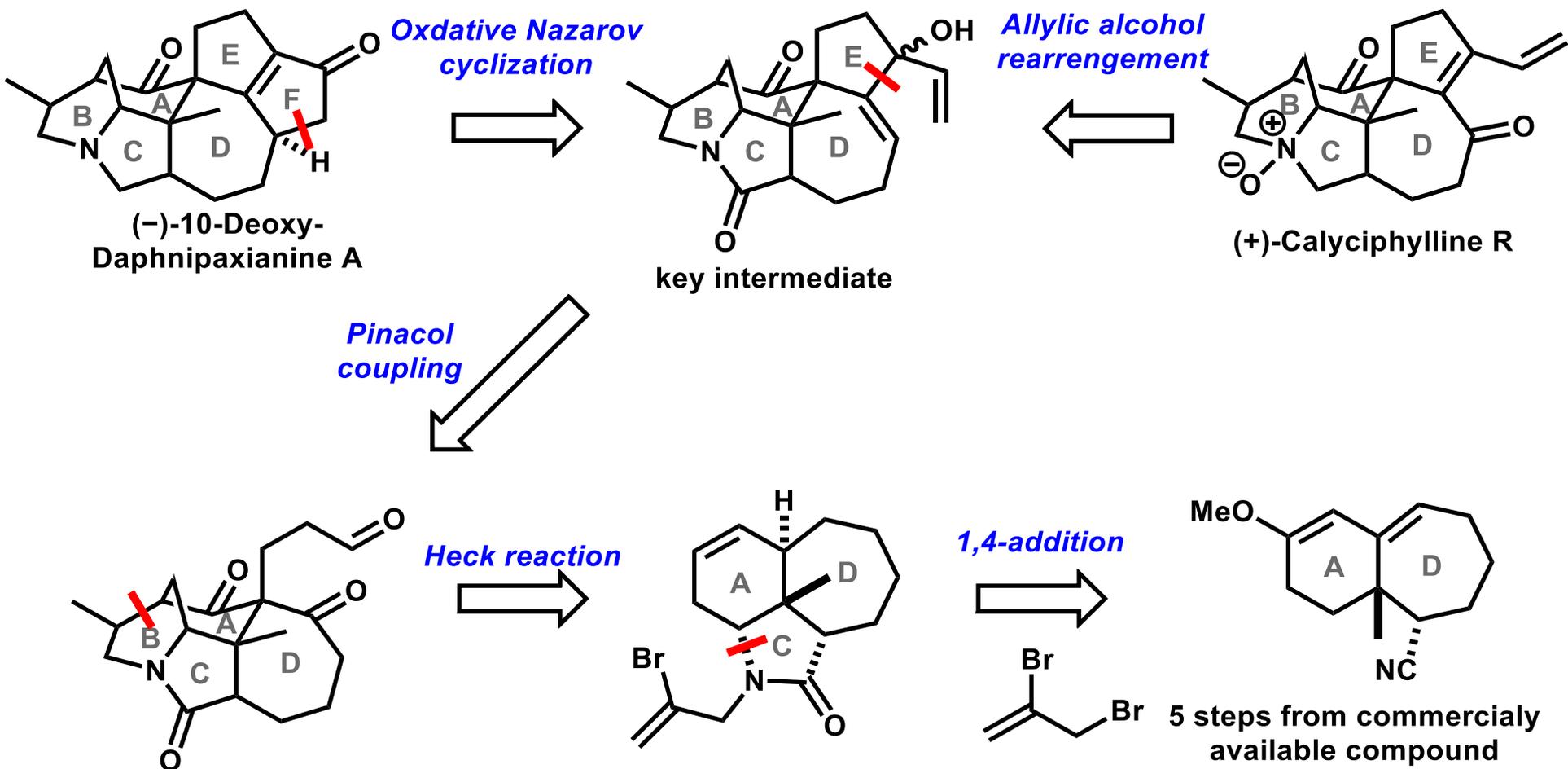
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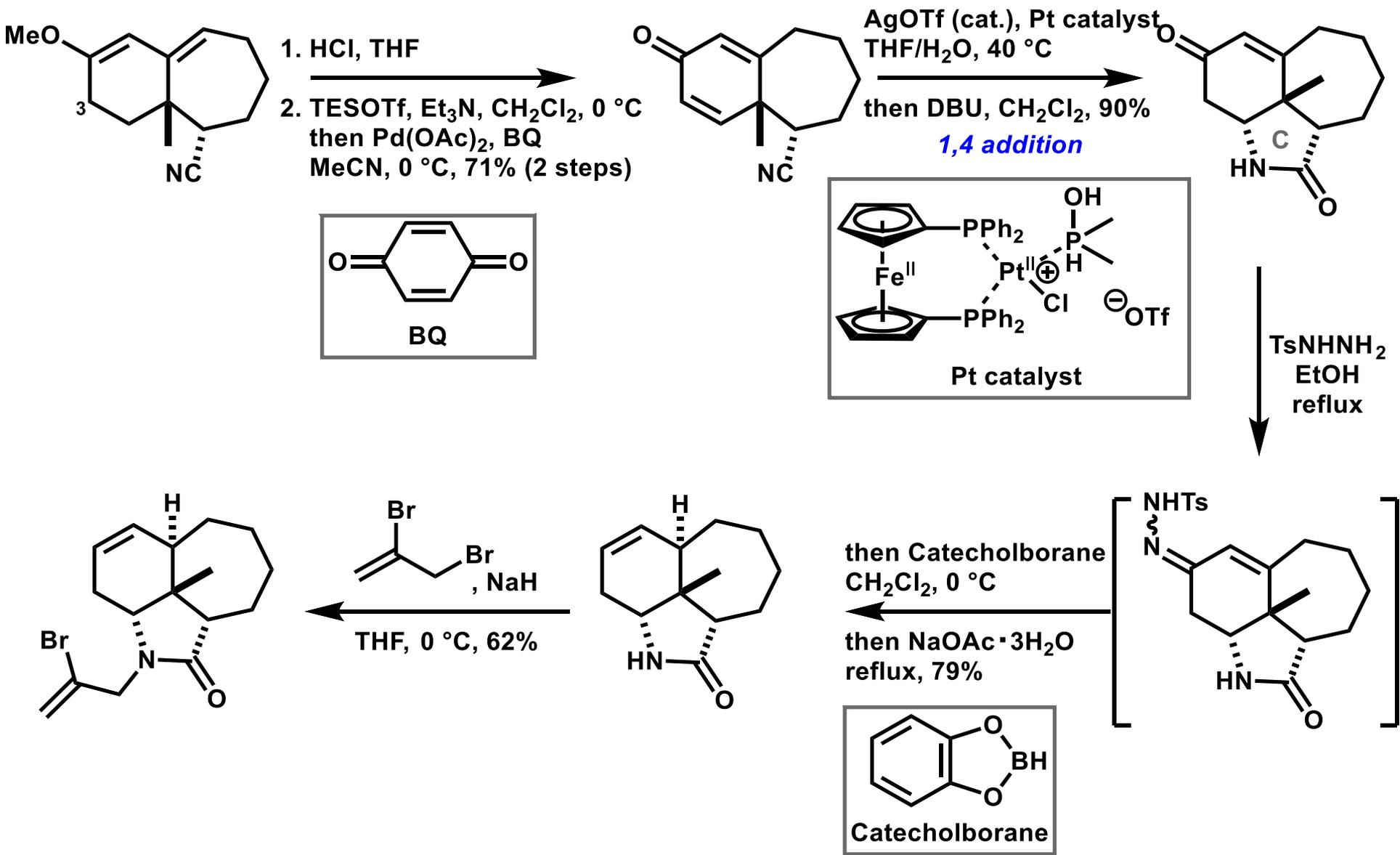
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(by Xu Group)**

4. Summary

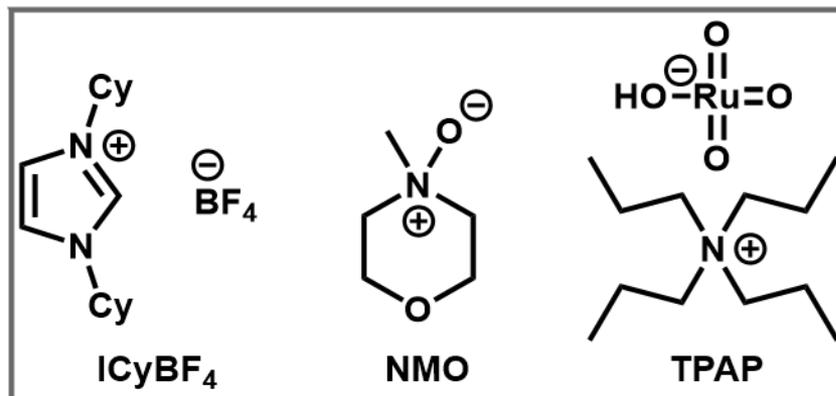
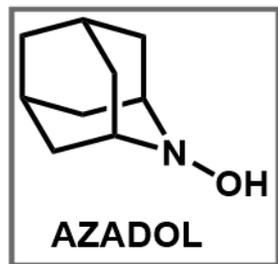
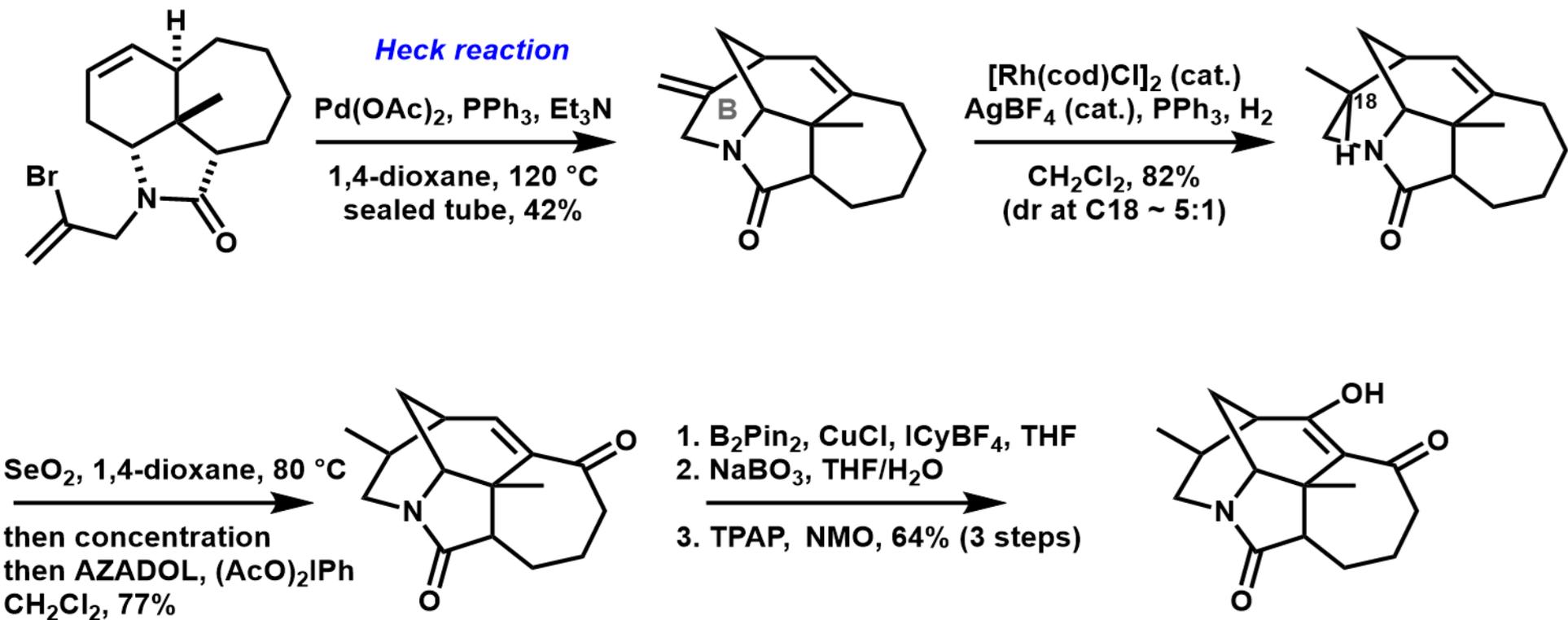
Retrosynthetic Analysis (by Xu)



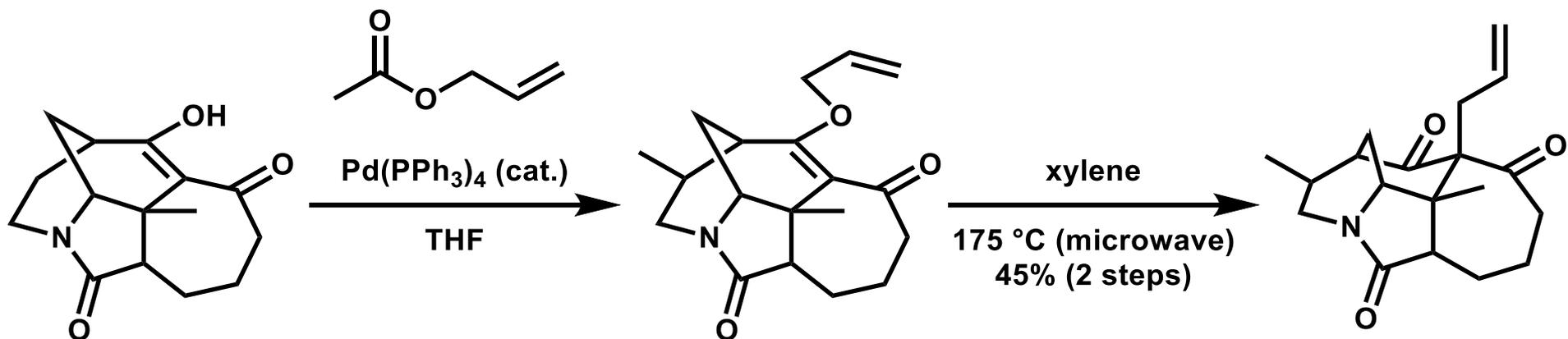
Construction of C-ring



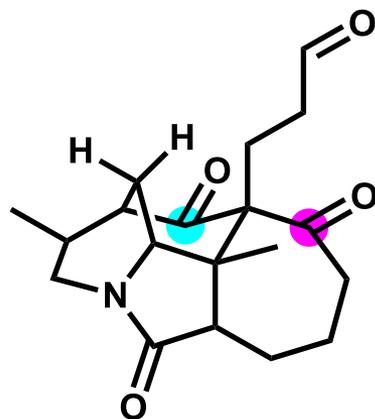
Construction of B-ring



Construction of E-ring

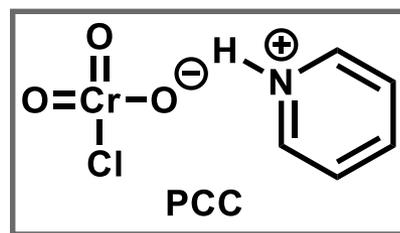
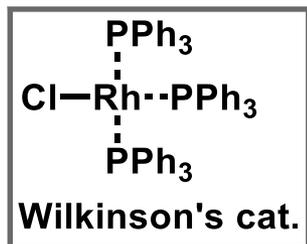
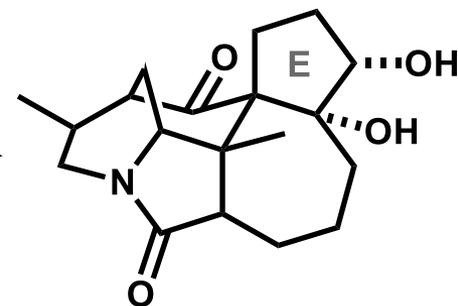


1. Wilkinson's cat.
Catecholborane, THF
then H_2O_2 , NaOH
2. PCC, NaOAc, CH_2Cl_2
61% (2 steps)

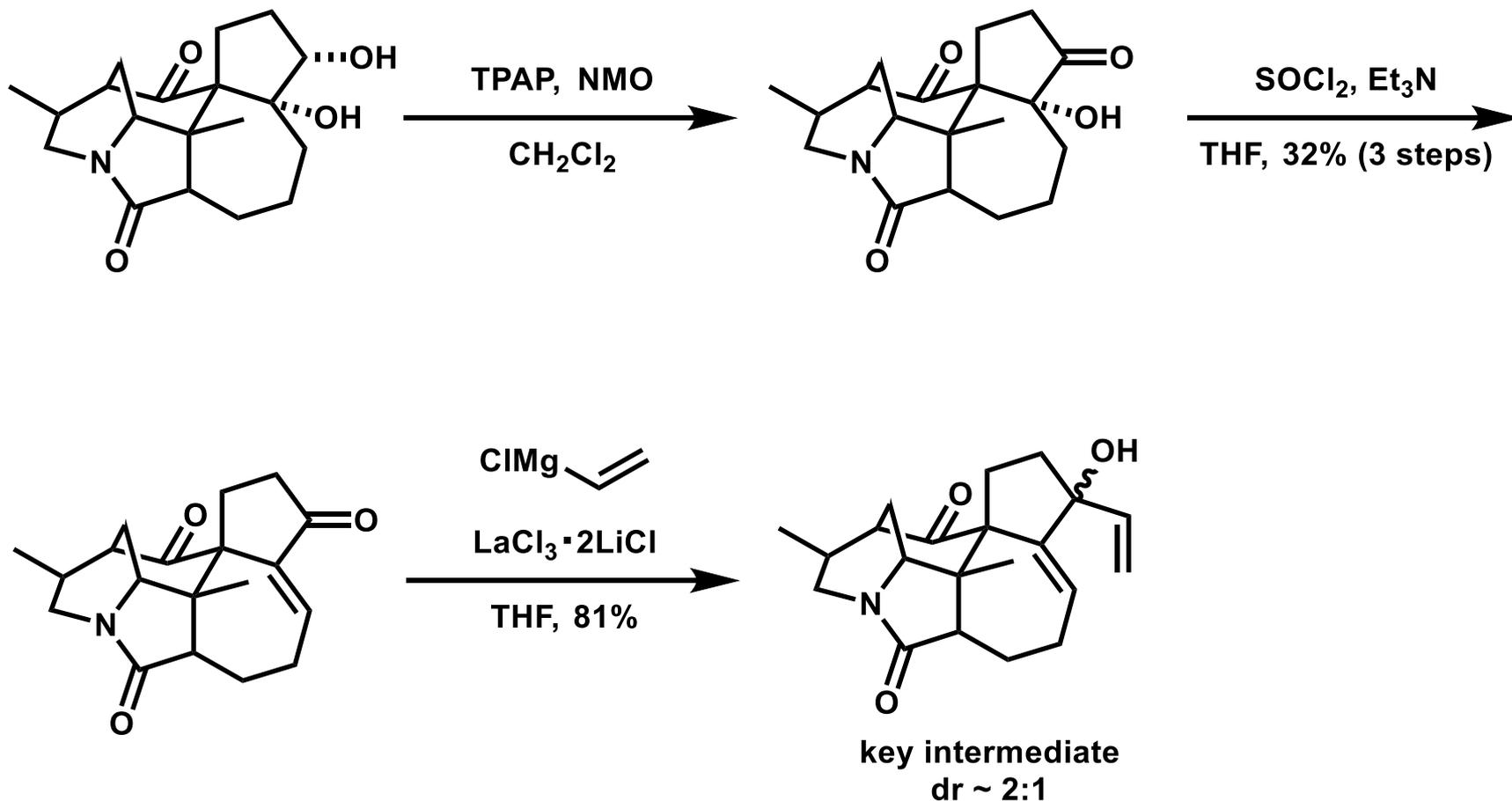


Pinacol coupling

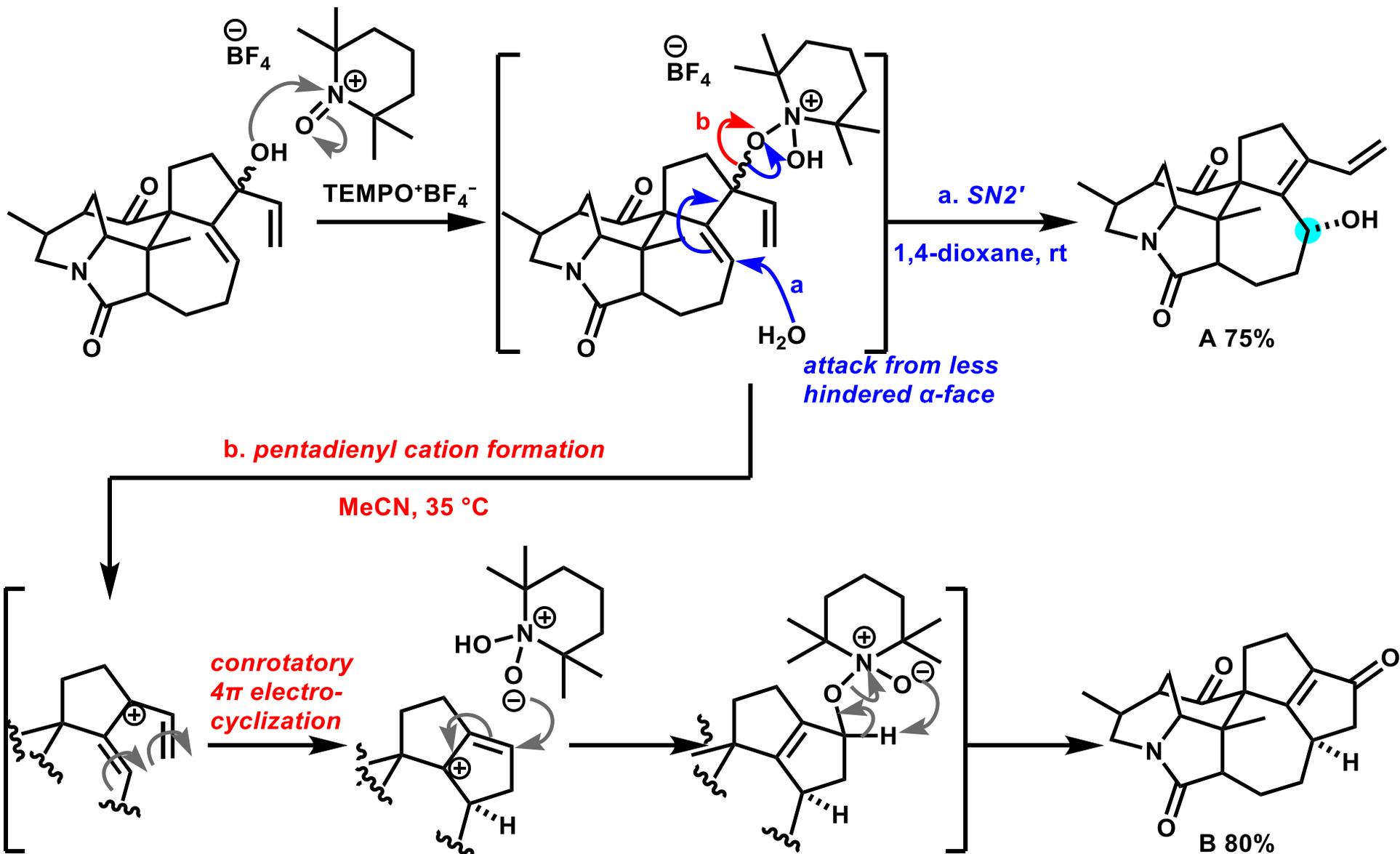
SmI_2 , THF



Synthesis of key intermediate

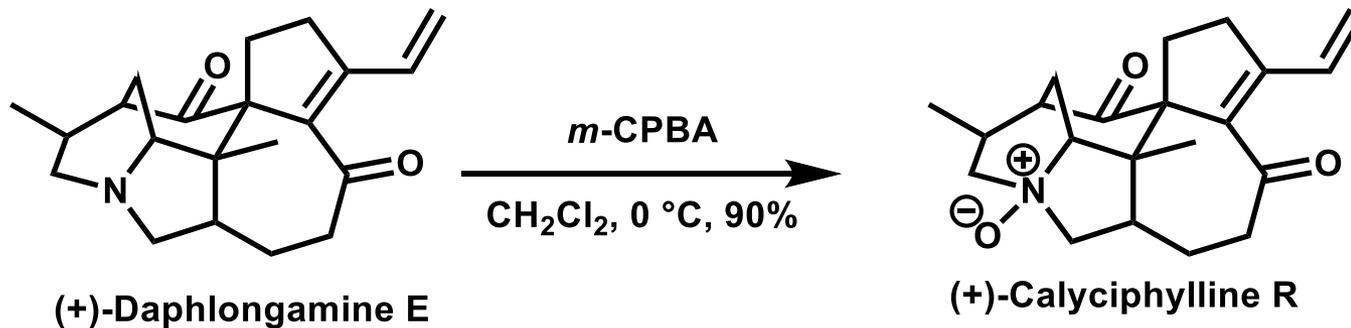
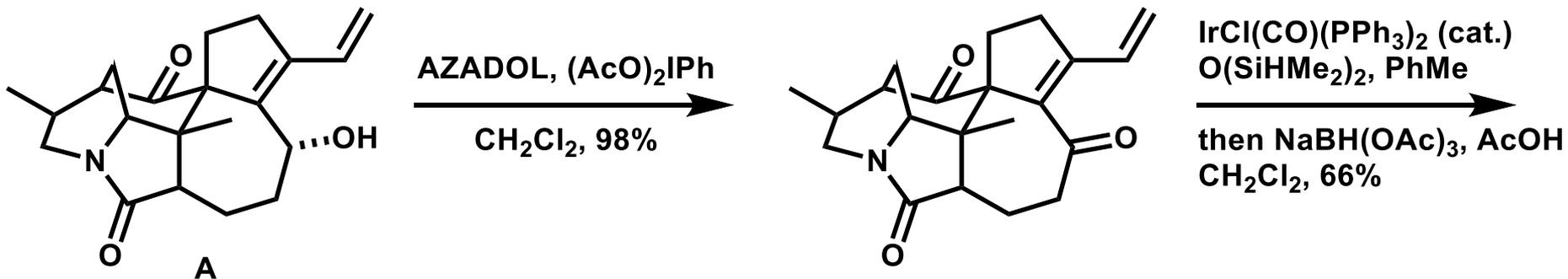


Proposed mechanism

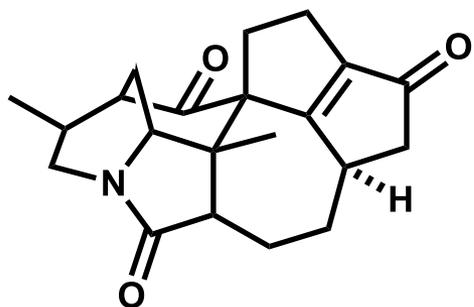


- 1) Zhang, Y.; Chen, Y.; Song, M.; Tan, B.; Jiang, Y.; Yan, C.; Jiang, Y.; Hu, X.; Zhang, C.; Chen, W.; Xu, J. *J. Am. Chem. Soc.* **2022**, *144*, 16042.
- 2) Shibuya, M.; Tomizawa, M.; Iwabuchi, Y. *J. Org. Chem.* **2008**, *73*, 4750.

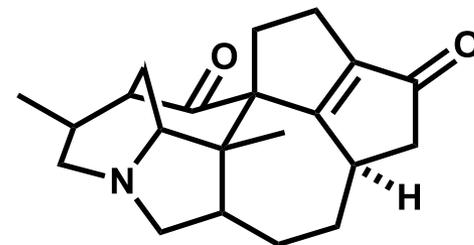
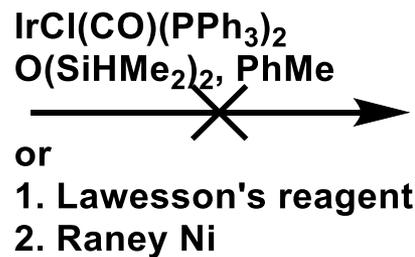
Selective amide reduction (1)



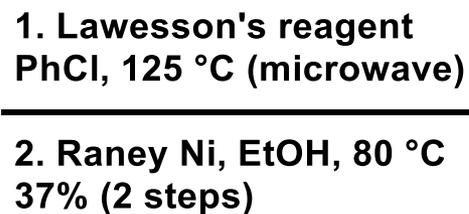
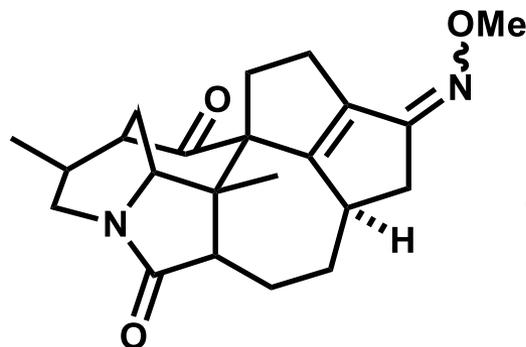
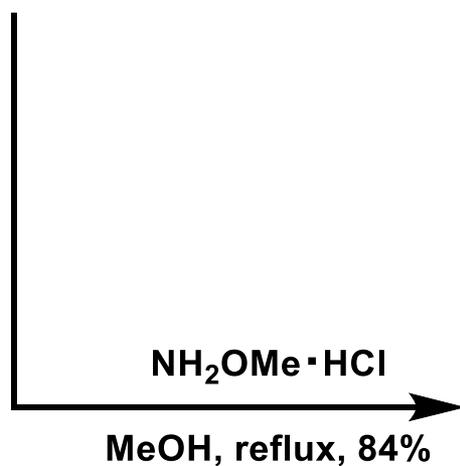
Selective amide reduction (2)



B



(-)-10-Deoxydaphnipaxianine A



Contents

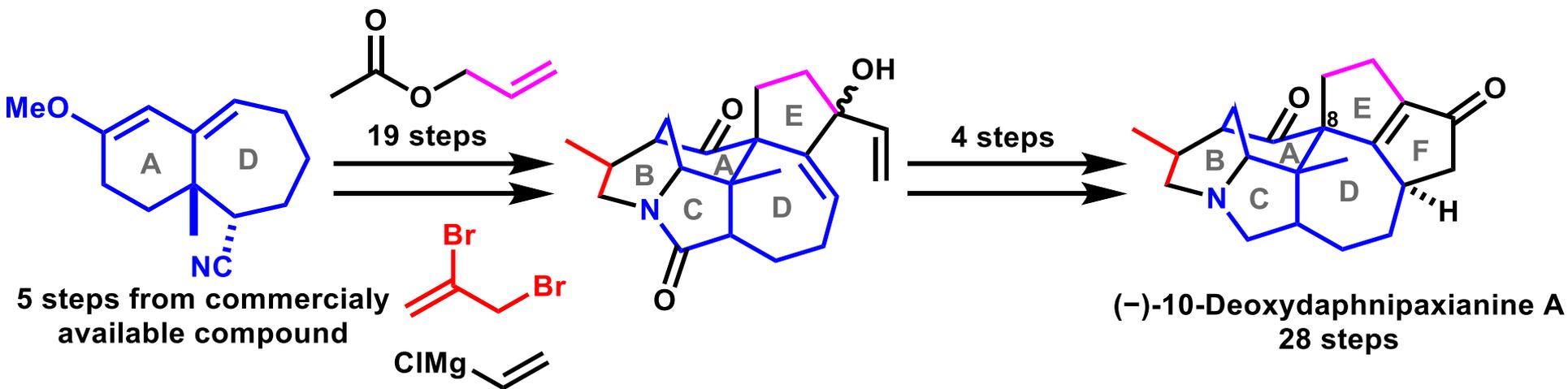
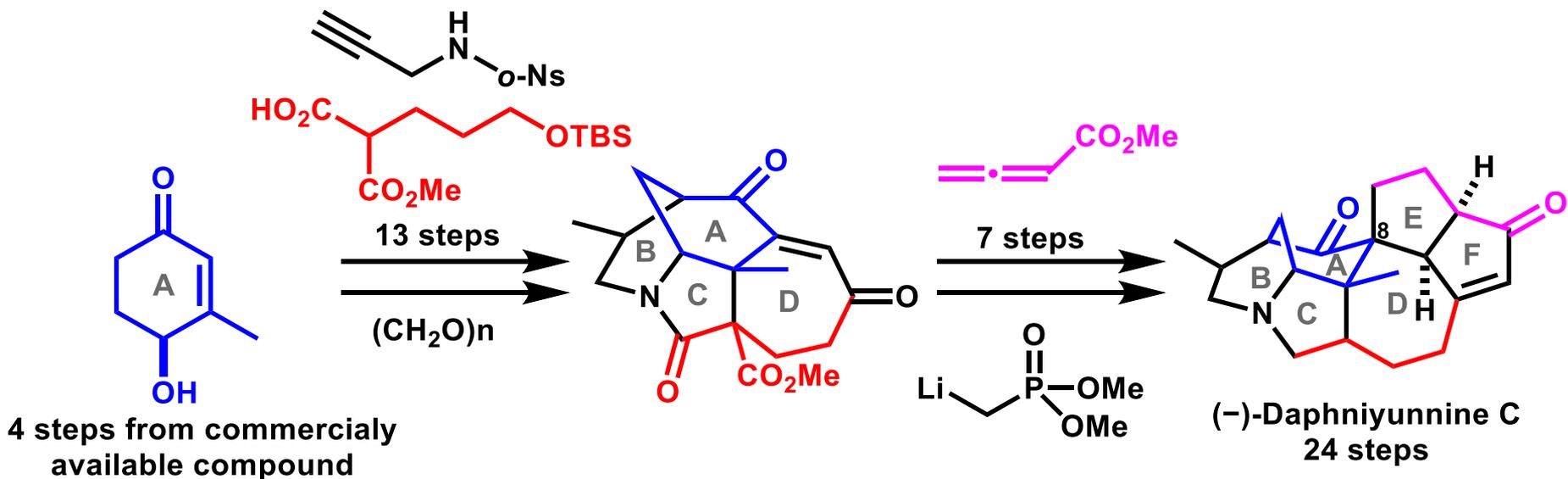
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4. Summary

Respective interesting approach

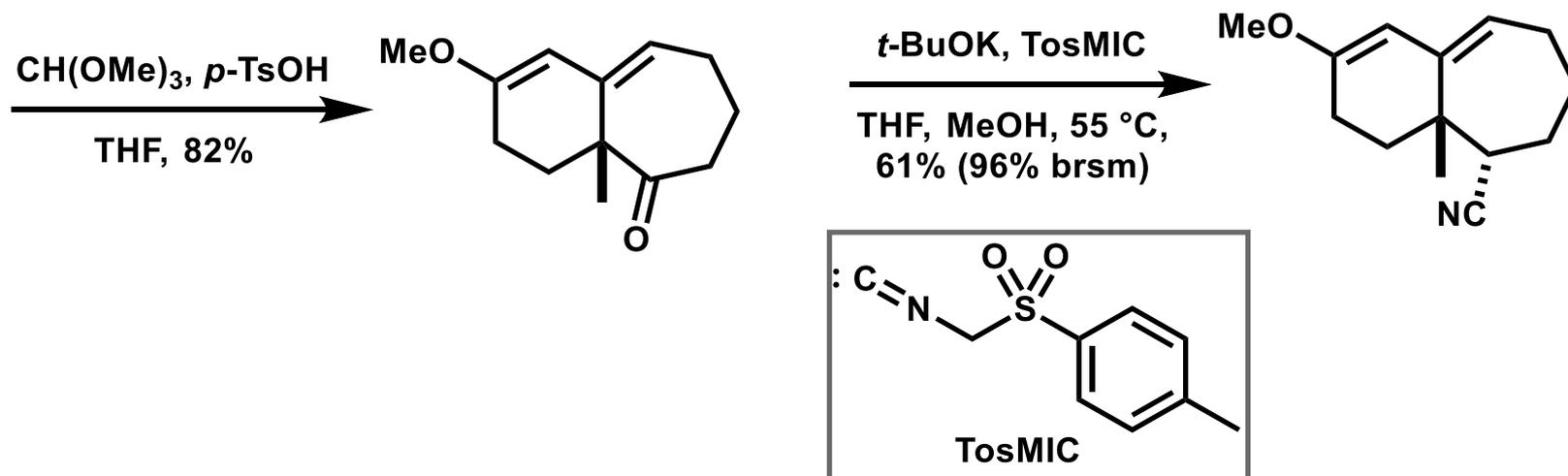
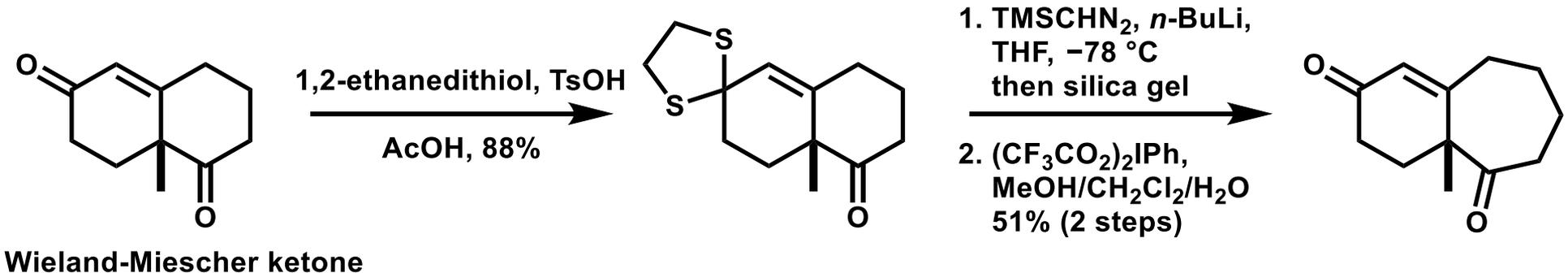


1) Li, J.; Zhang, W.; Zhang, F.; Chen, Y.; Li, A. *J. Am. Chem. Soc.* **2017**, *139*, 14893.

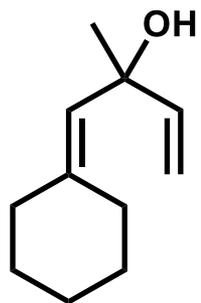
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Appendix

Preparation of bicyclic nitrile

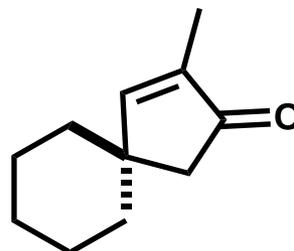


Examination of Oxidative Nazarov cyclization



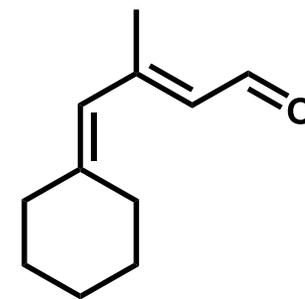
TEMPO⁺BF₄⁻, 1,4-dioxane, rt
4 h, 71%, A:B < 1:20

TEMPO⁺BF₄⁻, MeCN, 60 °C
30 min, 52%, A:B > 20:1
(rt 30 min, 38%, A:B = 3:1)

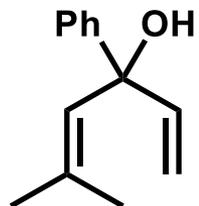


A

+

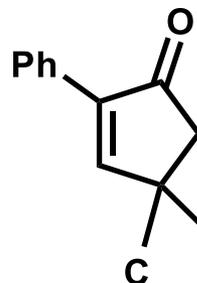


B



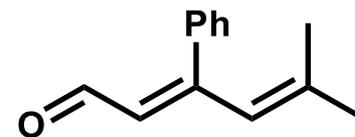
TEMPO⁺BF₄⁻, MeCN, rt
30 min, 49%, C:D = 1:1

TEMPO⁺BF₄⁻, MeCN, 60 °C
30 min, 71%, C:D > 20:1



C

+



D

Proposed mechanism of Ir cat. reduction

