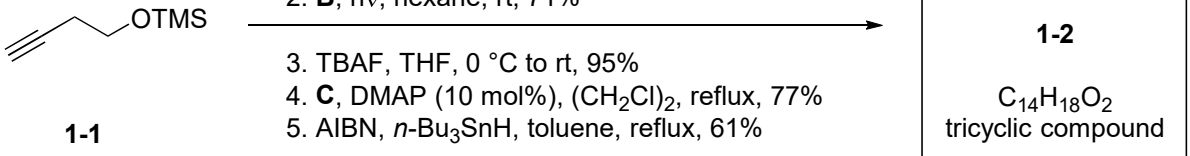
Problem Session (2)

2017.03.04. Yinghua Wang

Please fill in the blanks and provide each reaction mechanisms.

1



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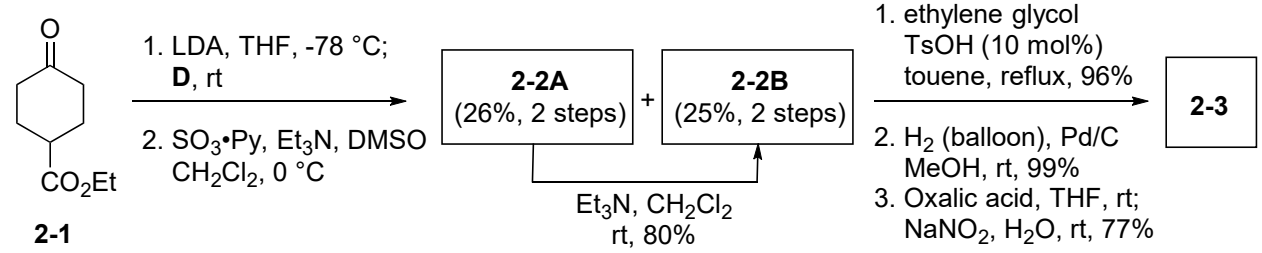
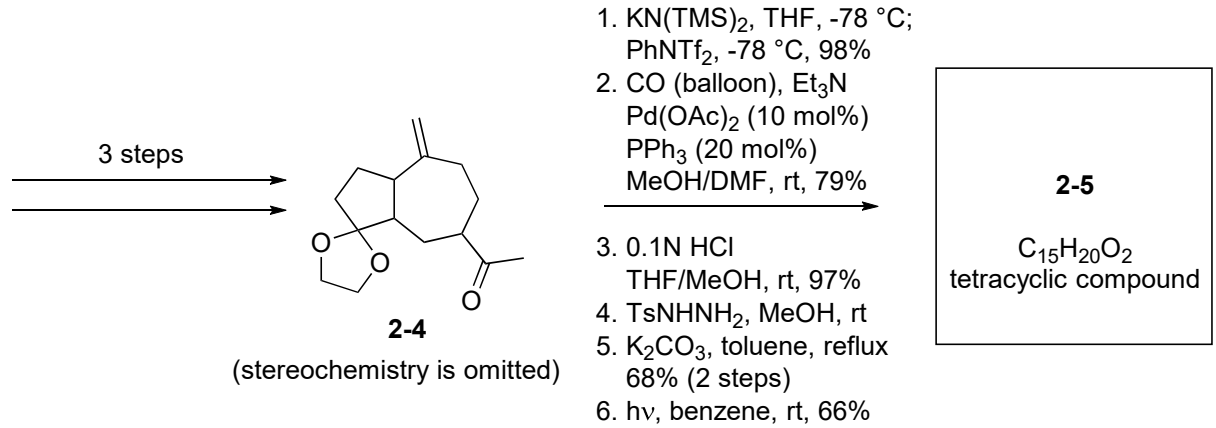
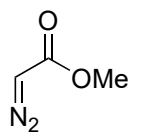
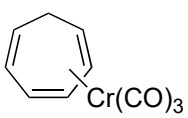


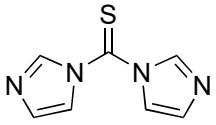




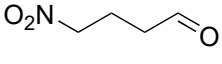
A



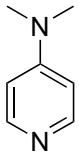
B



C



D



DMAP

AIBN

Problem Session (2) -Answer-

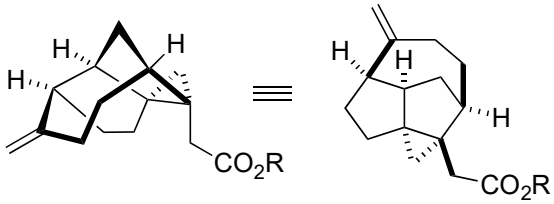
2017.03.04. Yinghua Wang

Topic: Total Synthesis of Echinopine A and B (also see Dr. Asaba's PS on Aug. 29, 2015.)

0. Introduction

0-1. Isolation

from air-dried roots of *E. spinosus*
Kiyota, H. *et. al*. *Org. Lett.* **2008**, *10*, 701.



R = H: **echinopine A** (**0-1**)
R = Me: **echinipine B** (**0-2**)

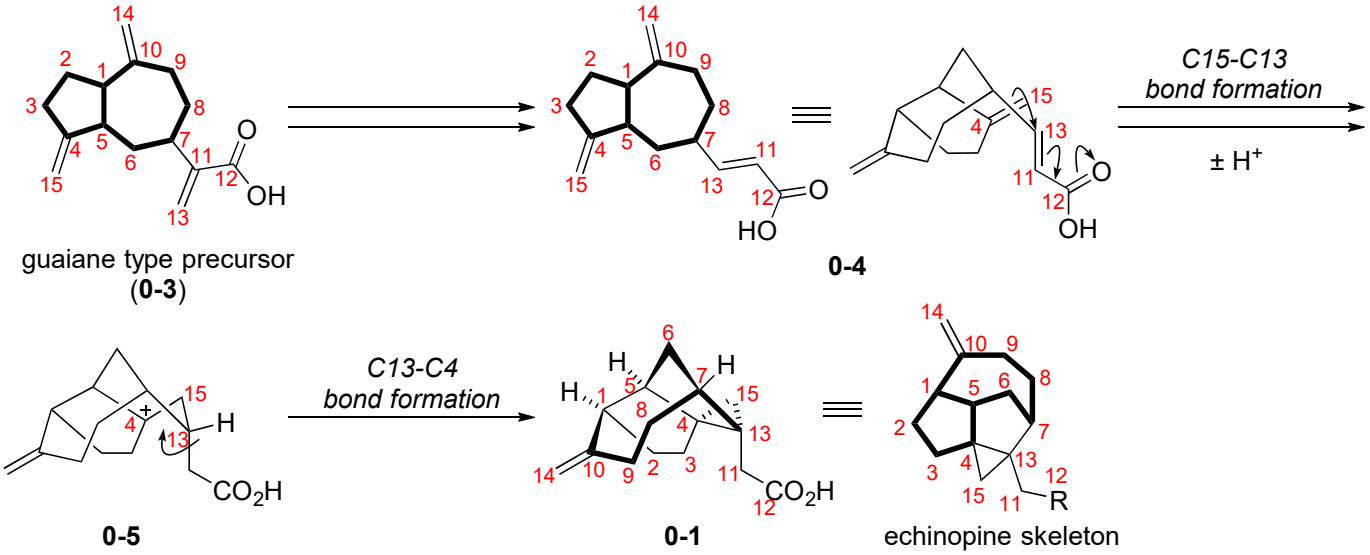
0-2. Biological activity

not reported

0-3. Structual feature

unique [3-5-5-7] tetracyclic skeleton
five contiguous stereocenters, including two quarternary carbons

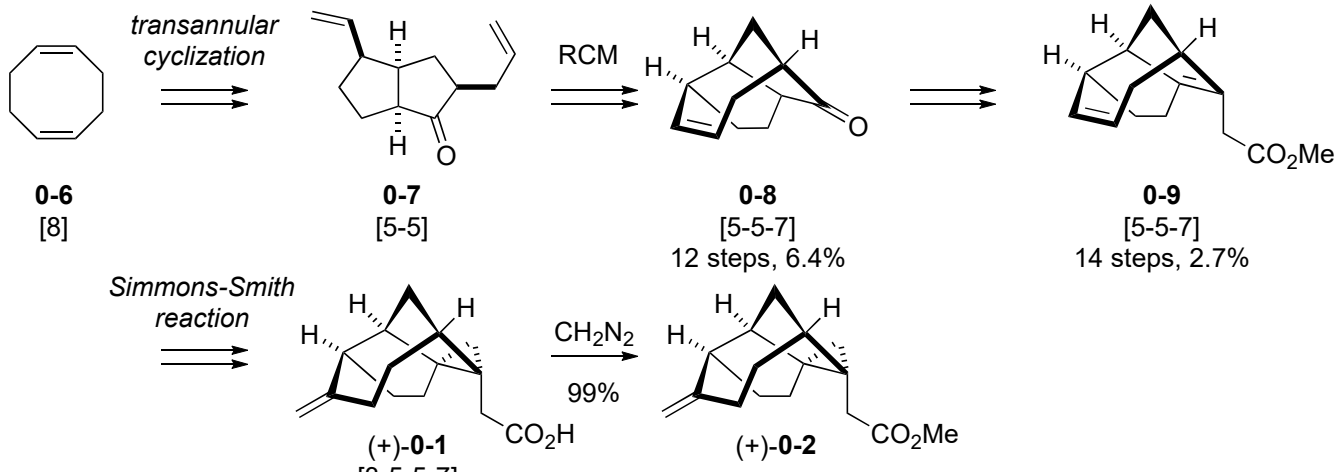
0-4. Proposed biosynthetic pathway for the echinopine skeleton



Dong, M.; Cong, B.; Yu, S.-H.; Sauriol, F.; Huo, C.-H.; Shi, Q.-W.; Gu, Y.-C.; Zamir, L. O.; Kiyota, H. *Org. Lett.* **2008**, *10*, 701.

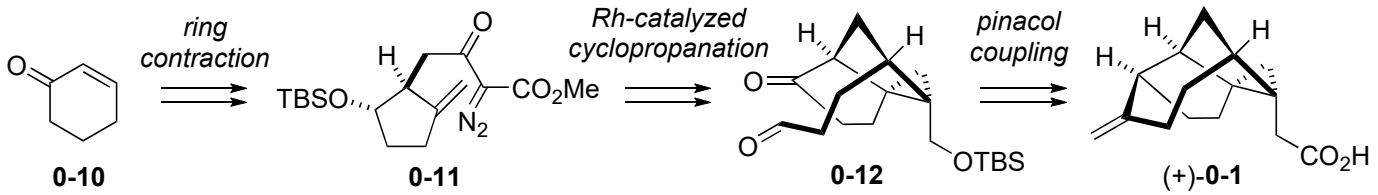
0-5. Total syntheses of echinopines

0-5-1. Magauer, Mulzer and Tiefenbacher's group (first total synthesis, asymmetric)



Magauer, T.; Mulzer, J.; Tiefenbacher, K. *Org. Lett.* **2009**, *11*, 5306.

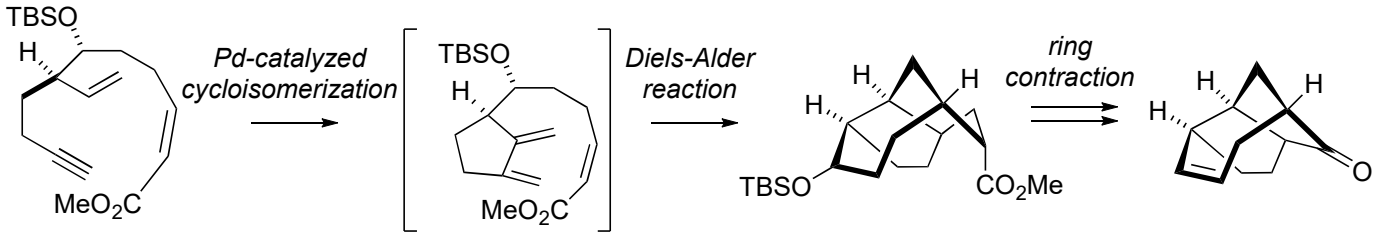
0-5-2. Nicolaou and Chen's group (1st generation, asymmetric)



0-10 [6] **0-11** [5] **0-12** [3-5-5] (+)-**0-1** [3-5-5-7]
0.79%, 37 steps

Nicolaou, K. C.; Ding, H.; Richard, J.-A.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2010**, *132*, 3815.

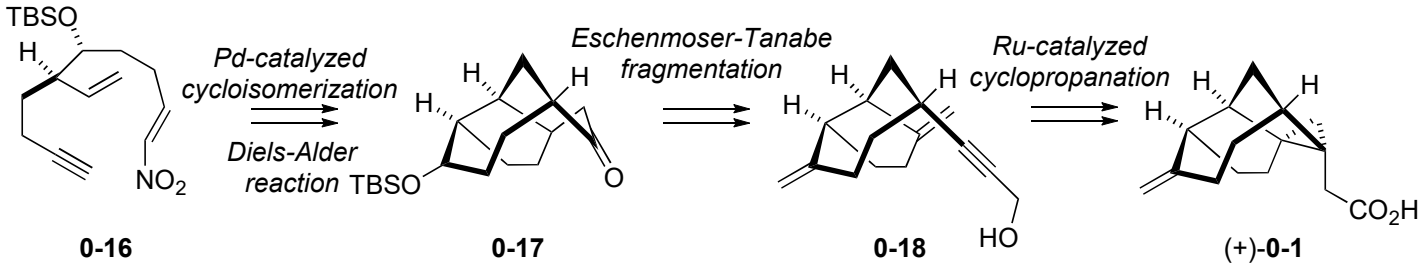
0-5-3. Chen's group (2nd generation, formal synthesis, asymmetric)



0-13 **0-14** [5] **0-15** [5-6-7] **0-8** [5-5-7]
25 steps, 6.1%

Peixoto, P. A.; Serverin, R.; Tseng, C.-C.; Chen, D. Y.-K. *Angew. Chem. Int. Ed.* **2011**, *50*, 3013.

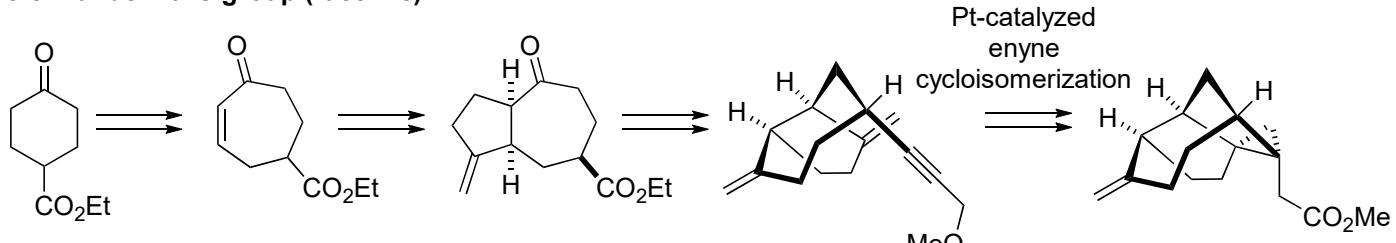
0-5-4. Chen's group (3rd generation, asymmetric)



0-16 **0-17** [5-6-7] **0-18** [5-7] (+)-**0-1** [3-5-5-7]
25 steps, 0.5%

Peixoto, P. A.; Richard, J.-A.; Serverin, R.; Chen, D. Y.-K. *Org. Lett.* **2011**, *13*, 5724.

0-5-5. Vanderwal's group (racemic)



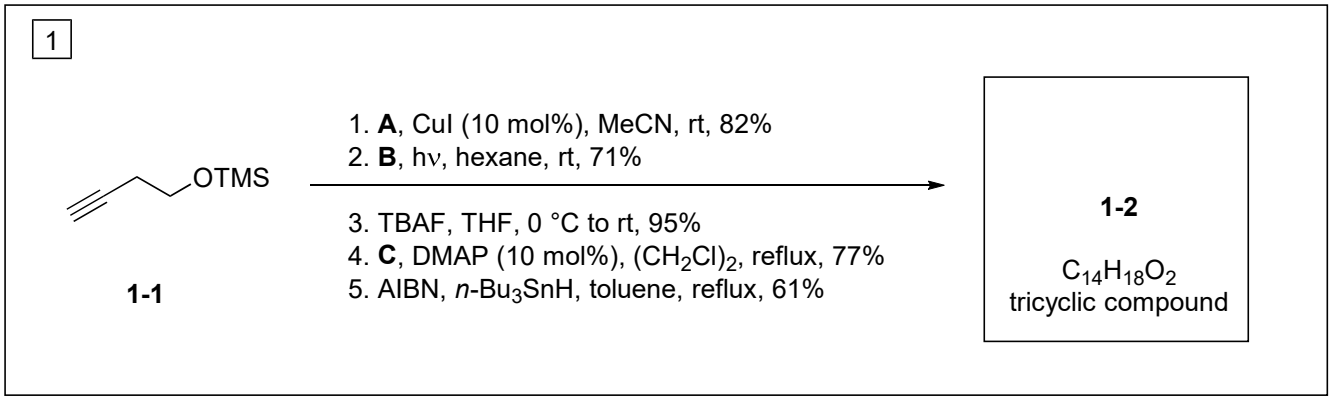
0-19 [6] **0-20** [7] **0-21** [5-7] **0-22** [5-7] (±)-**0-2** [3-5-5-7]
13 steps, 0.9%

Michels, T. D.; Dowling, M. S.; Vanderwal, C. D. *Angew. Chem. Int. Ed.* **2012**, *51*, 7572.
for more details of syntheses above, see Dr. Asaba's PS on Aug. 29, 2015.

0-5-6. Liang's group (racemic, Problem 2):
[6]→[6-6]→[5-7]→[5-5-5-7]→[3-5-5-7], 18 steps, 2.2%

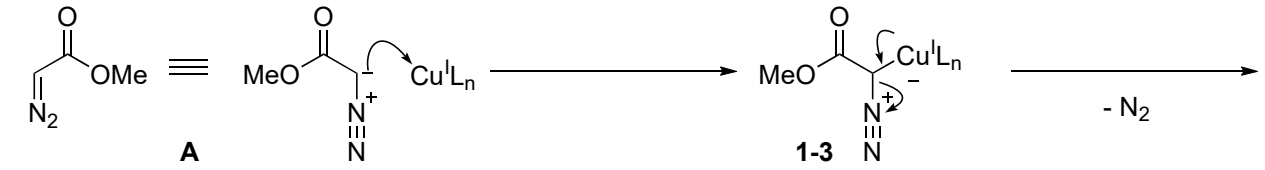
0-5-7. Rigby's group (racemic, formal synthesis, Problem 1):
[7]→[5-7]→[5-5-7]→[3-5-5-7], 5 steps, 26% to **0-9**

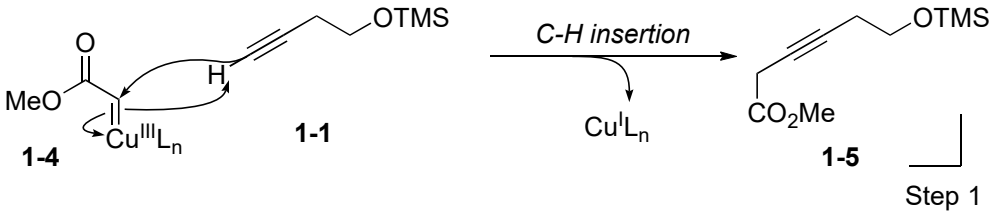
-Answer-



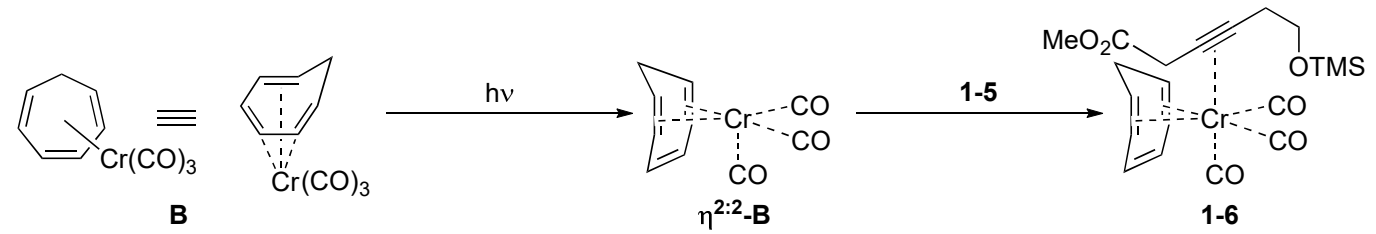
De, S.; Mirsa, S.; Rigby, J. H. *Org. Lett.* **2015**, *17*, 3230.

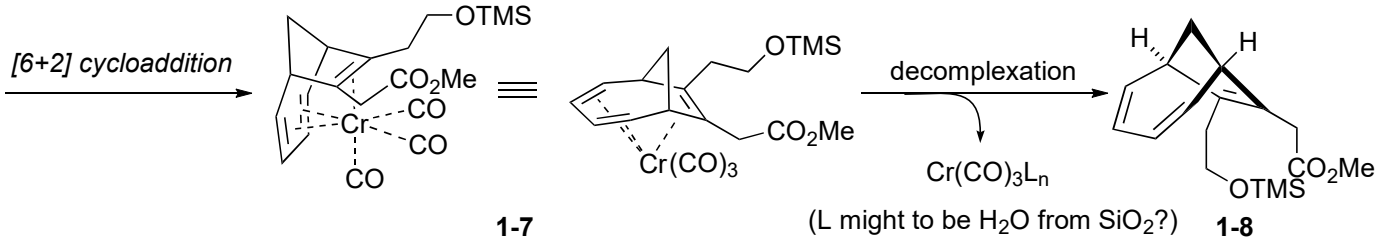
Step 1. Cu-mediated synthesis of 3-alkynoate (**Discussion 1**)



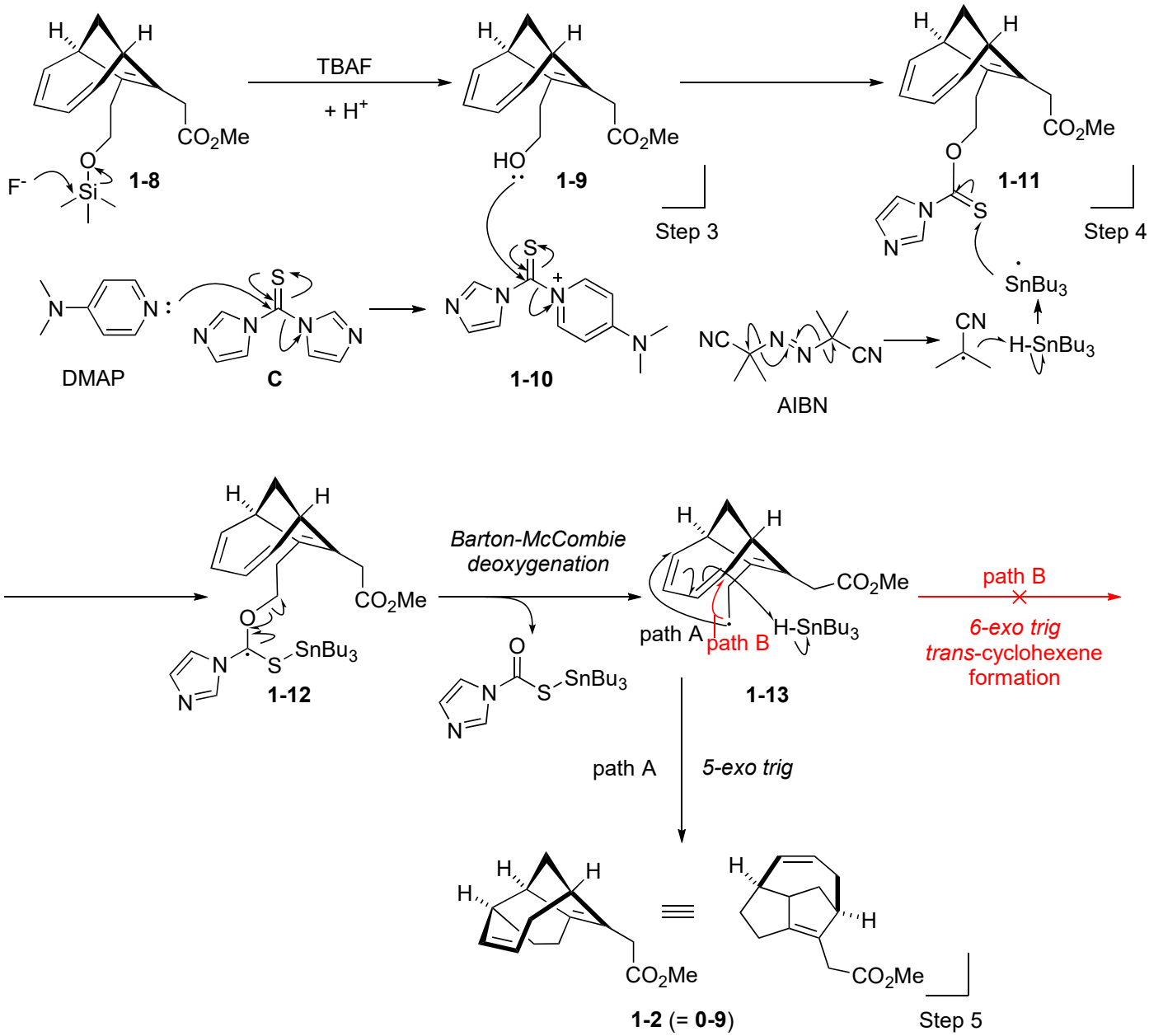


Step 2. Cr(0)-Promoted [6π+2π] cycloaddition: [7]→[5-7] (**Discussion 2**)



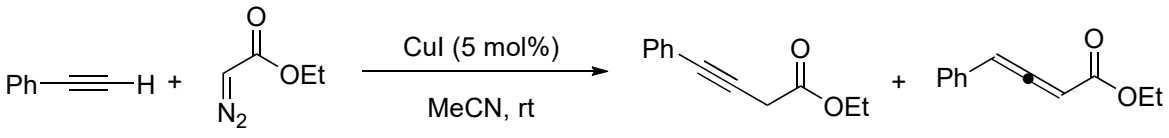


Step 3-5. Construction of [5,5,7] tricyclic core of echinopines: [5-7]→[5-5-7]



Discussion 1: Synthesis of 3-alkynoate

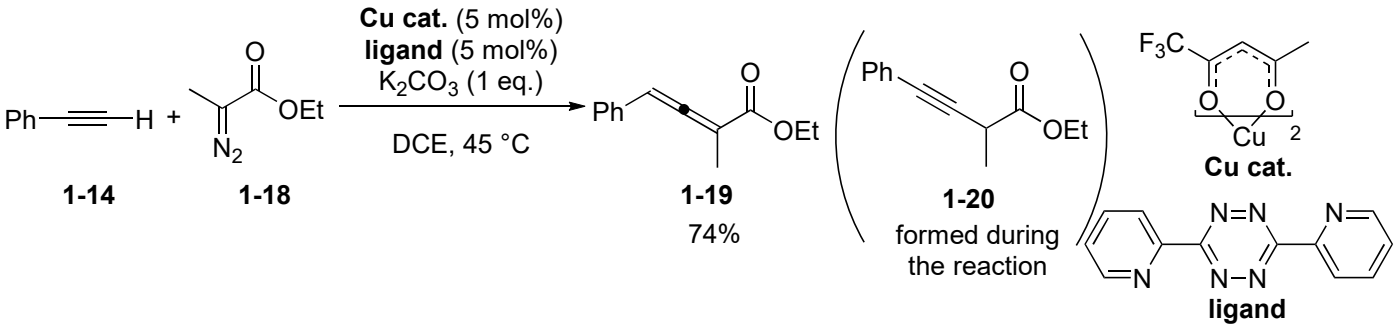
• CuI catalyzed C-H insertion



* no cyclopropene was observed.

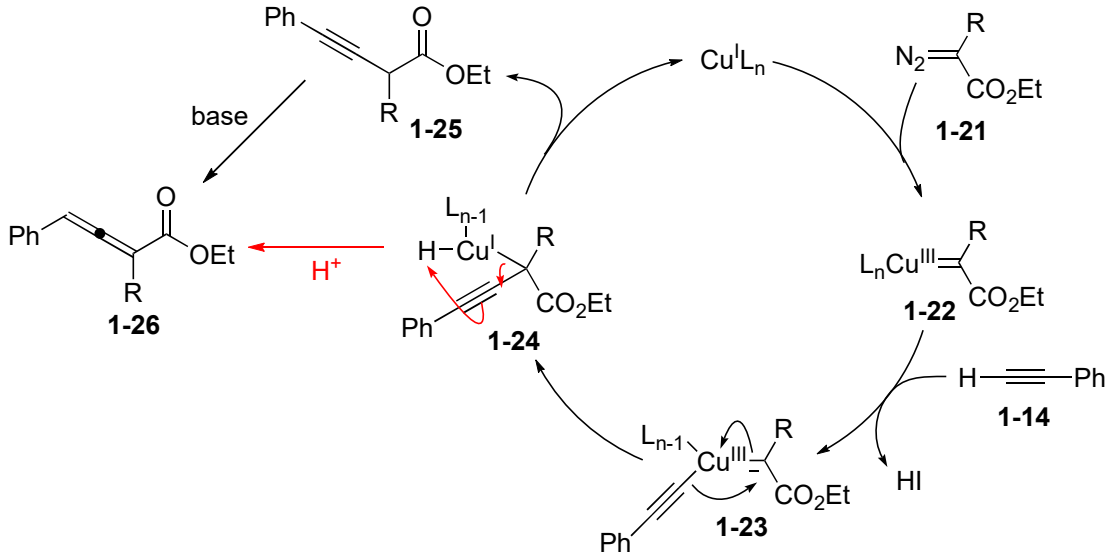
Suarez,A.; Fu, G. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 3580.

• Cu-catalyzed synthesis of allenoates



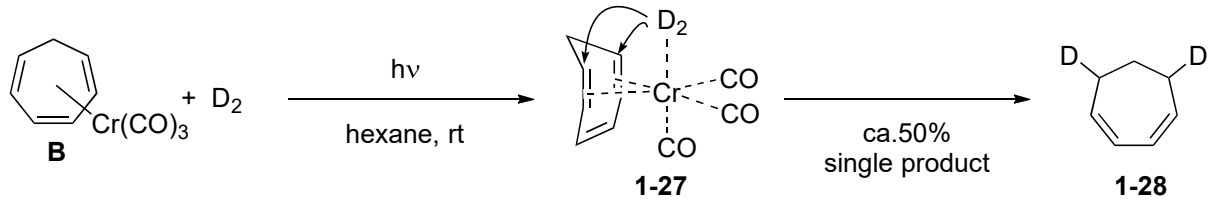
Hassink, M.; Liu, X.; Fox, J. M. *Org. Lett.* **2011**, *13*, 2388.

• proposed catalytic cycle



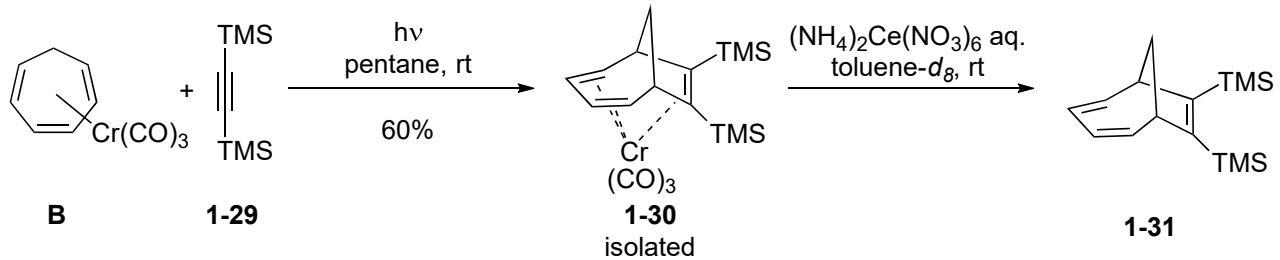
Discussion 2: Cr(0)-mediated intermolecular [6+2] cycloaddition
review: Rigby, J. H. *Acc. Chem. Res.* **1993**, *26*, 579.

• reansons for the reaction mechanism via $\eta^{2:2}$-Cr(0) species

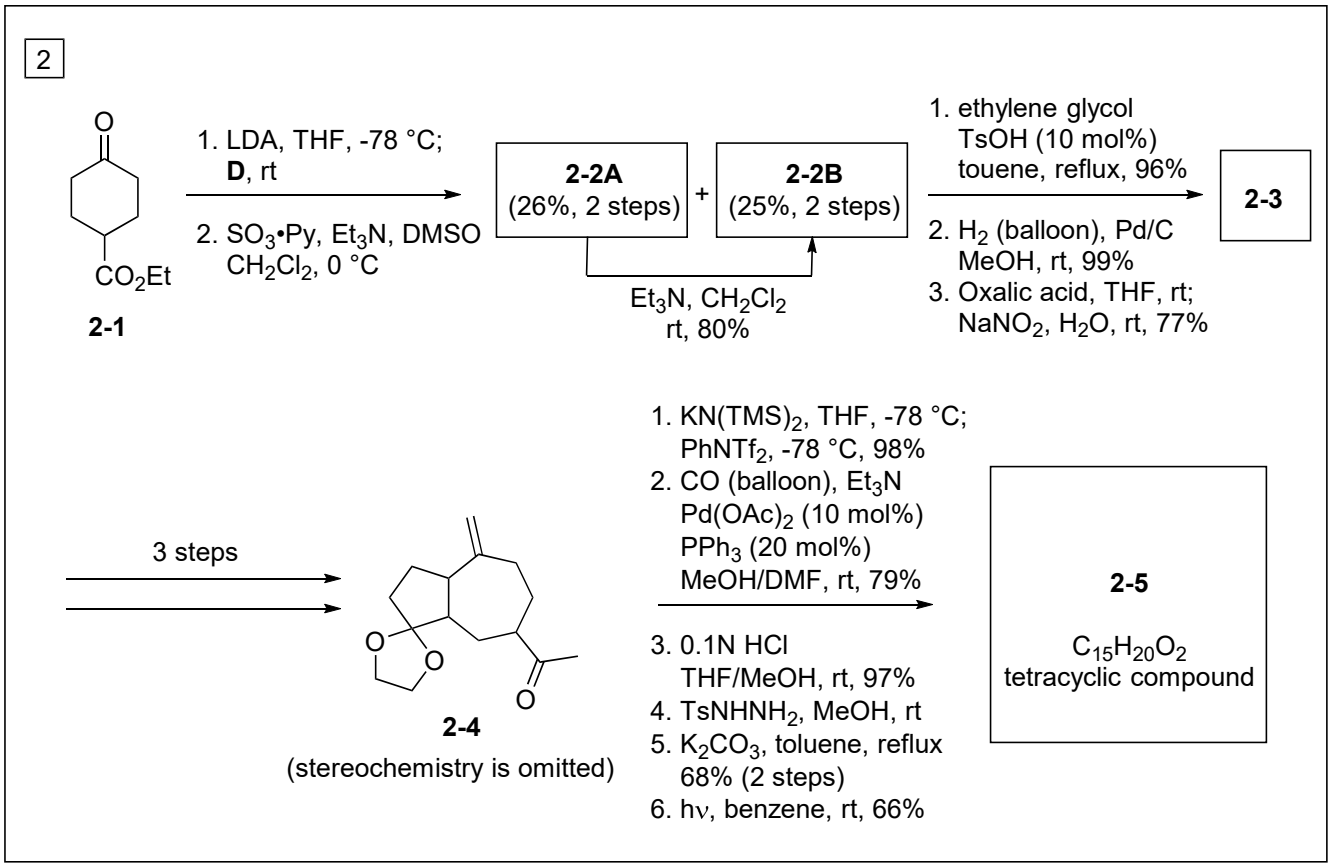


Fischler, I.; Grevels, F. H.; Leitich, J.; Ozkar, S. *Chem. Ber.* **1991**, *124*, 2857.

• existenece of $\eta^{4:2}$-Cr(0) complex as **1-7**



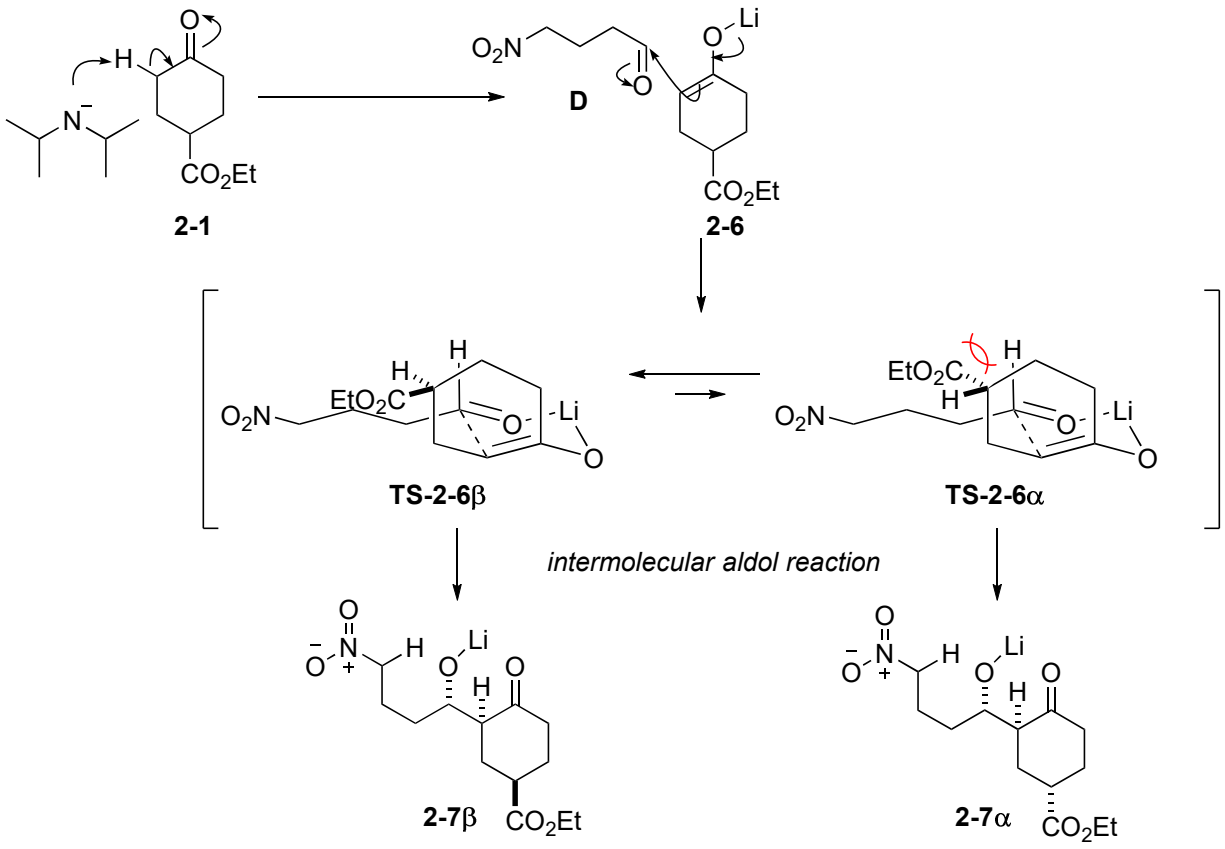
Fischler, I.; Grevels, F. H.; Leitich, J.; Ozkar, S. *Chem. Ber.* **1991**, *124*, 2857.

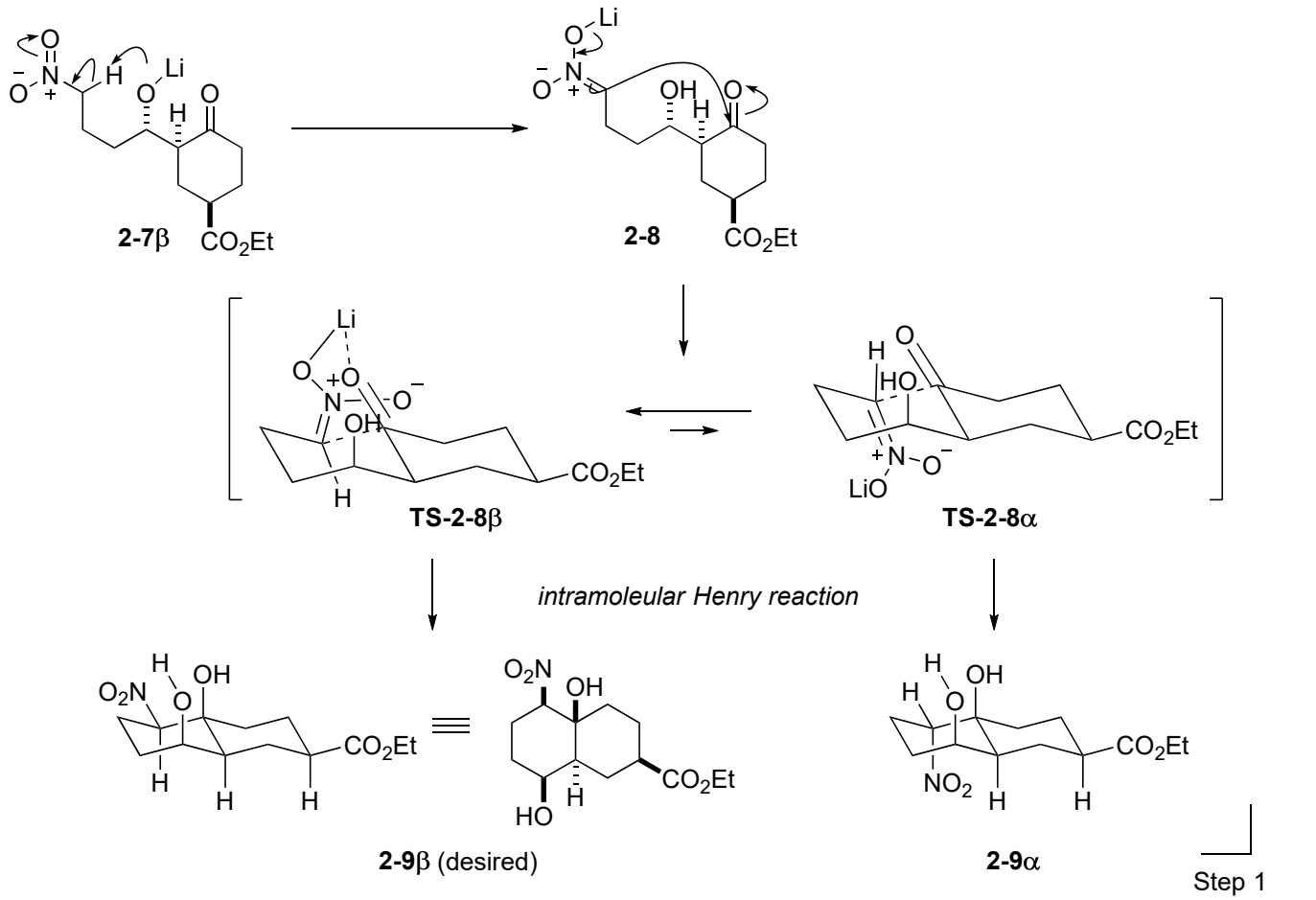


Xu, W.; Wu, S.; Zhou, L.; Liang, G. *Org. Lett.* **2013**, *15*, 1978.

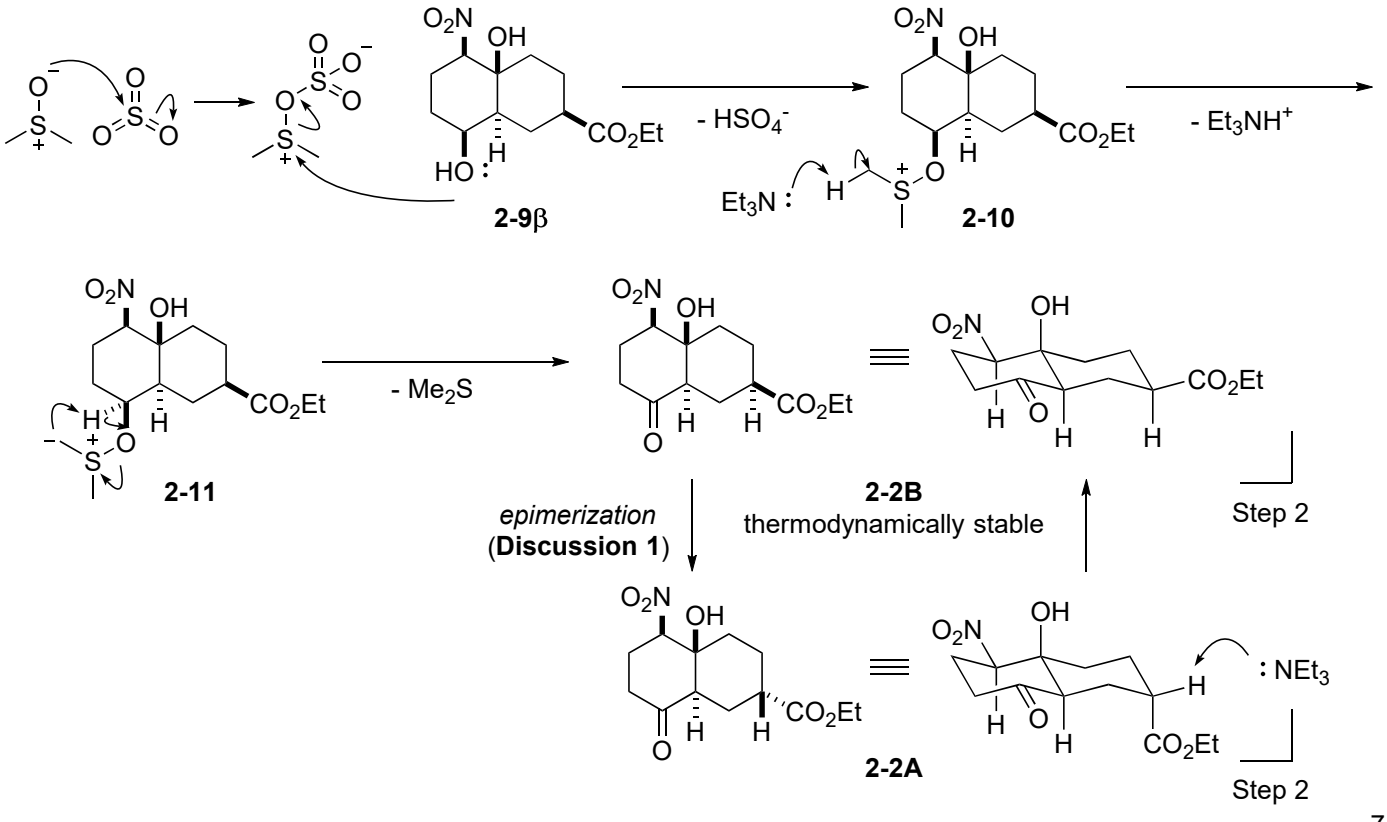
• Transformation from **2-1** to **2-2**: [6]→[6-6]

Step 1. Construction of *trans*-decalin ring via aldol-Henry cascade reaction



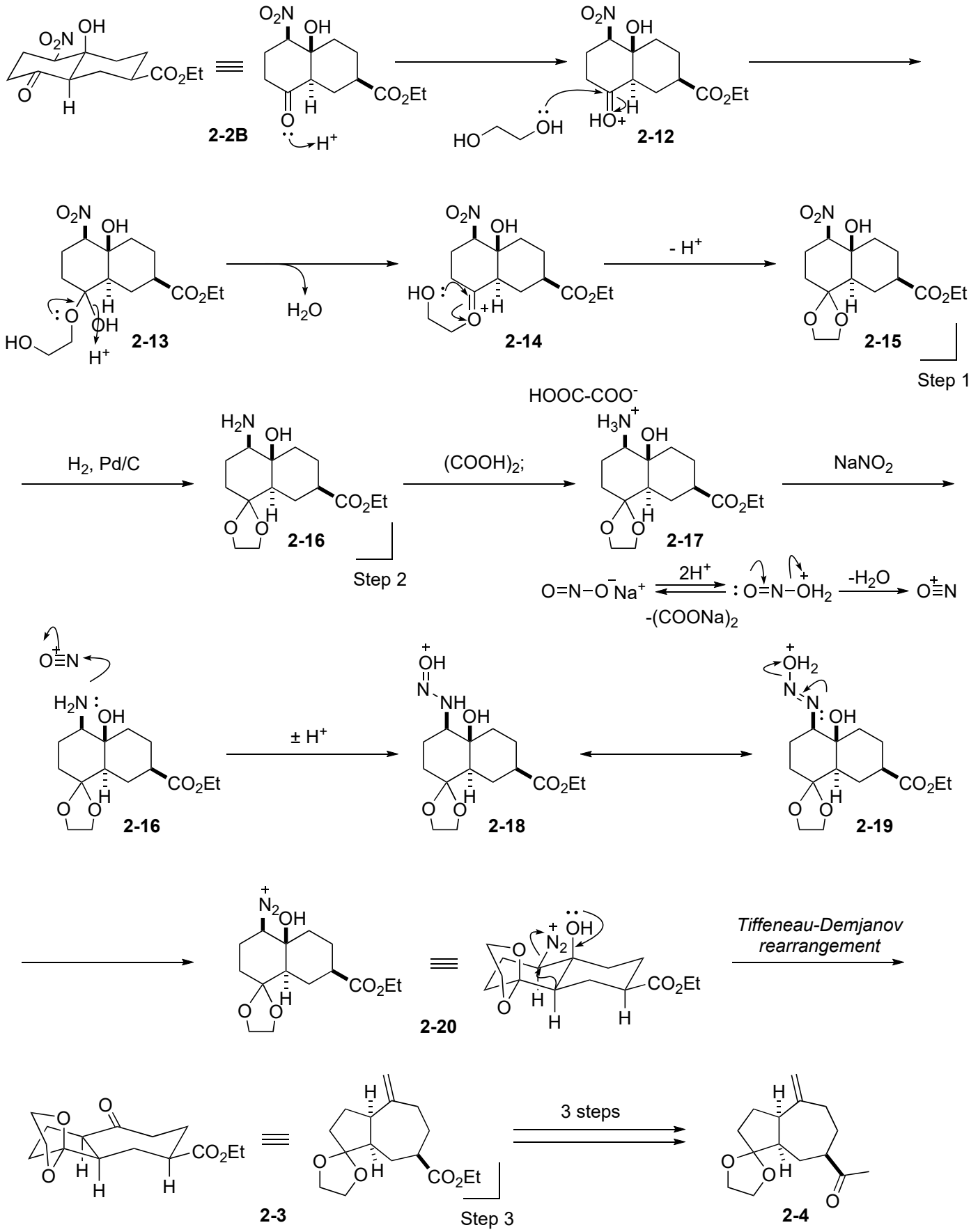


Step 2. Parikh-Doering Oxidation



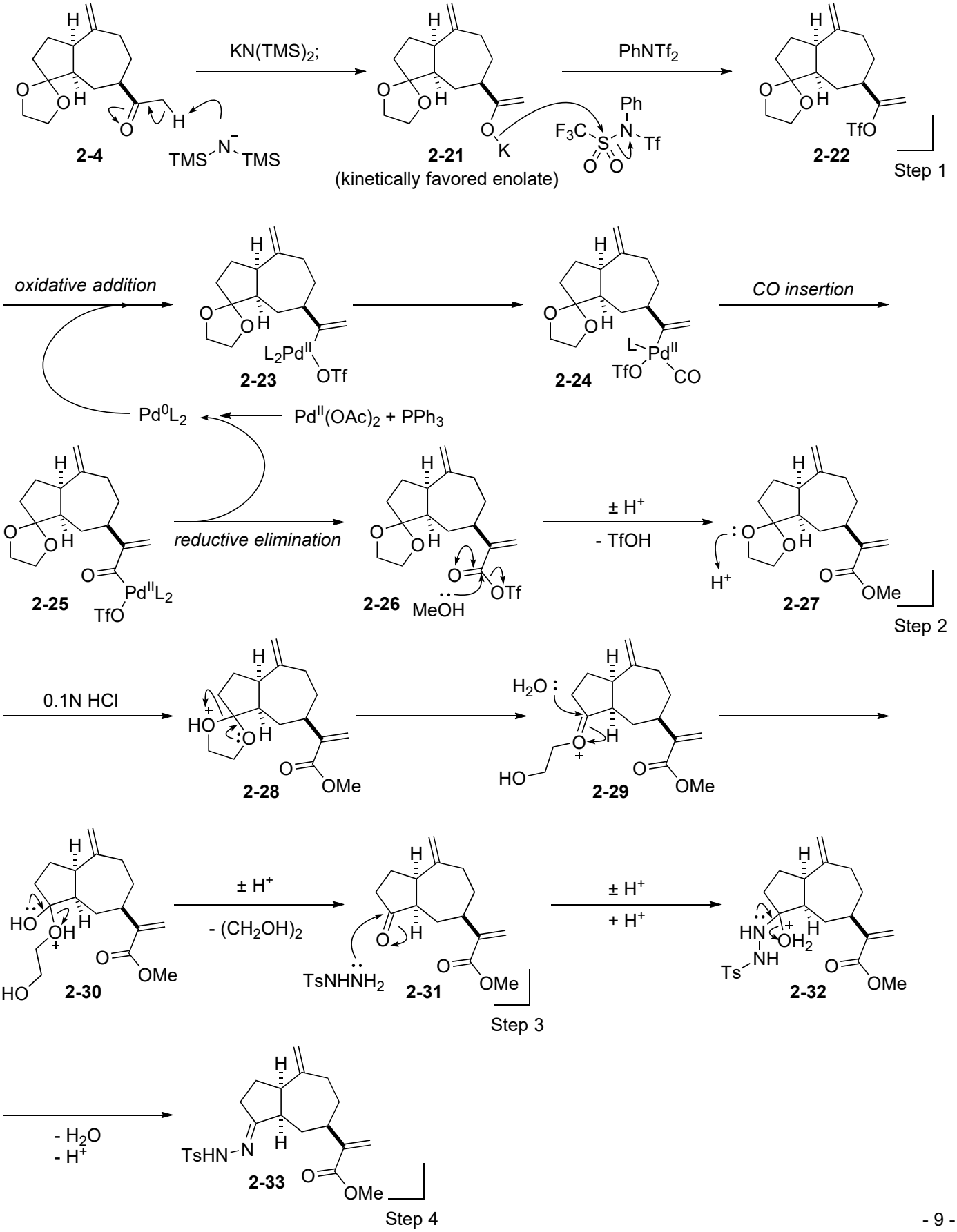
• Transformation from **2-2B** to **2-3**: [6-6]→[5-7]

Step1-3. Construction of cis-fused bicyclo [5.3.0] decane ring.

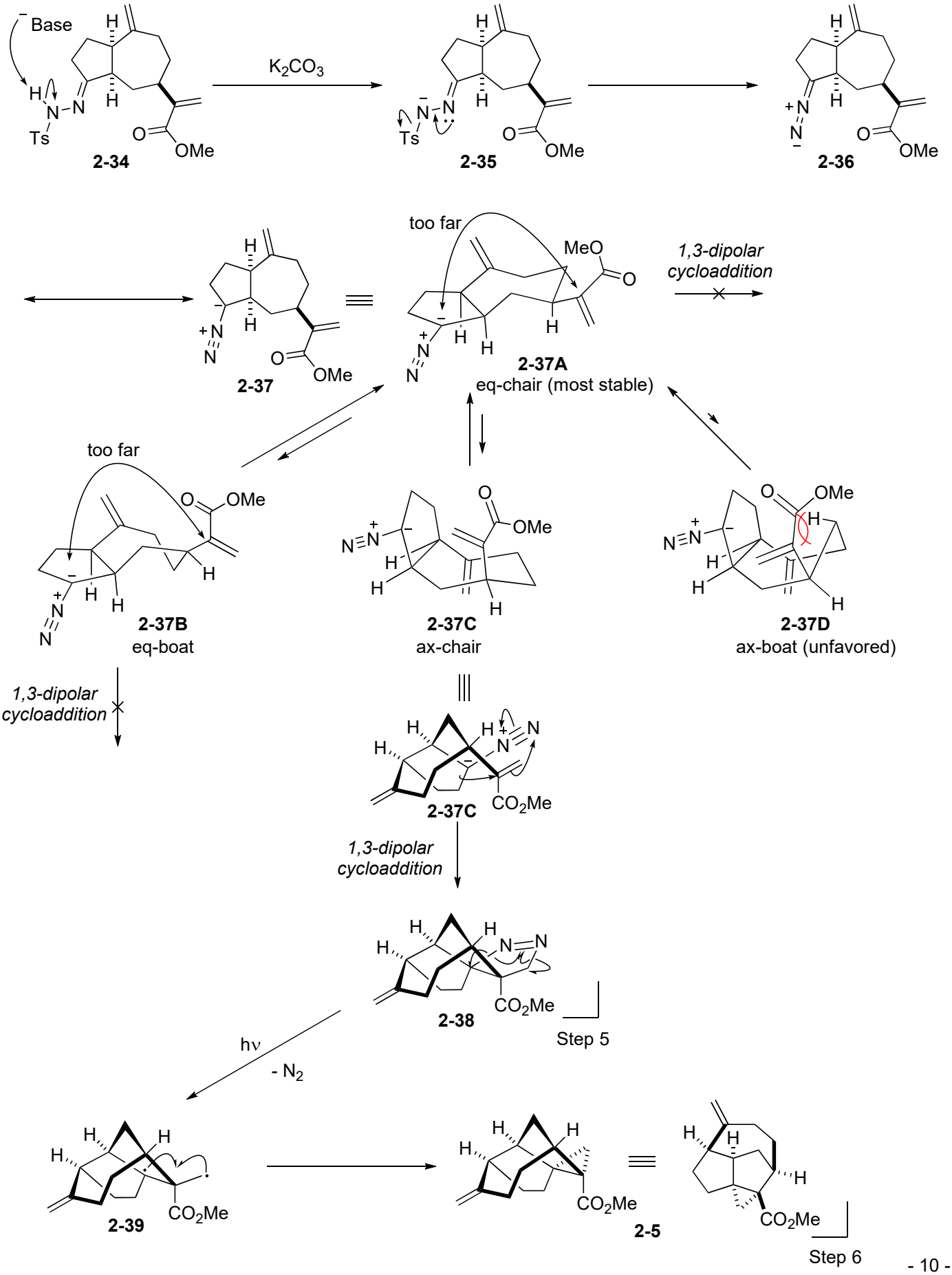


• Transformation from **2-4** to **2-5**: [5-7]→[3-5-5-7]

Step 1-4. Synthesis of precursor via Pd catalyzed carbonyation

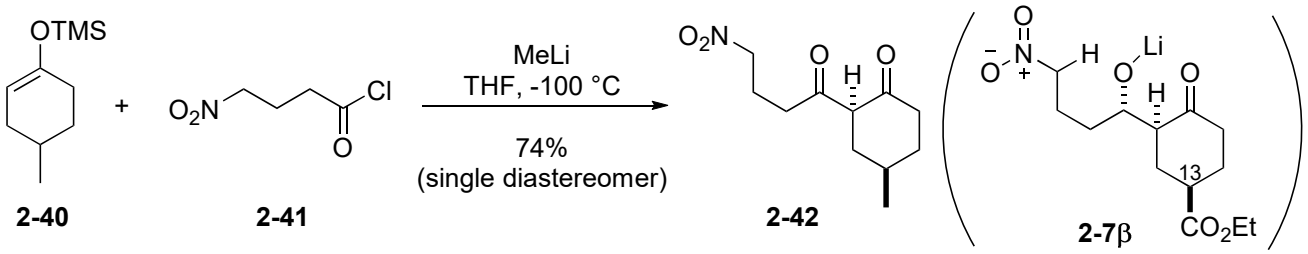


Step 5-6. Construction of echinopine core via intramolecular 1,3-dipolar cycloaddition



Discussion 1: When does the epimerization at C13 occur during construction of [6-6] structure?

• stereoselectivity of the first aldol reaction

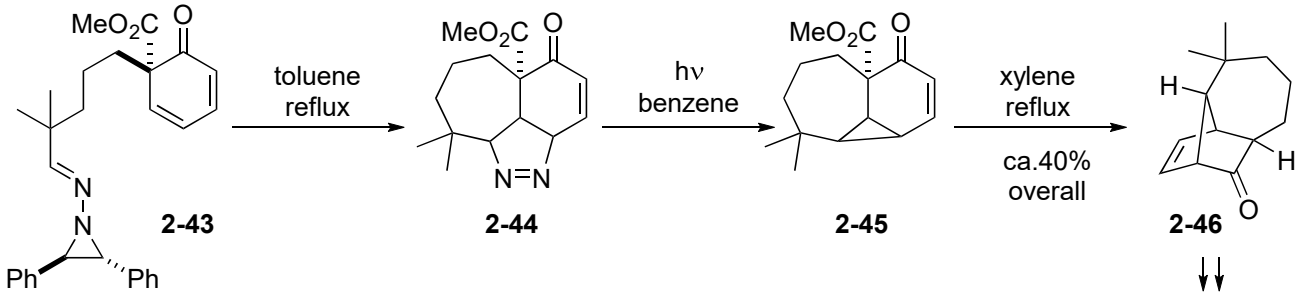


2-40 **2-41** **2-42** **2-7β**

Weller, T.; Seebach, D.; Davis, R. E.; Laird, B. B. *Helv. Chim. Acta*. **1981**, *64*, 736.

→ **2-7β** is proposed to be formed as a single diastereomer, so epimerization at C13 is ocuured by Et_3N in the following Parikh-Doering oxidation?

Discussion 2: Another example of intramolecular 1,3-dipolar cycloaddition in natural product synthesis



2-43 **2-44** **2-45** **2-46**

(-)-longifolene

Klunder, J. M.; Caron, M.; Uchiyama, M.; Sharpless, K. B. *J.Org. Chem.* **1985**, *50*, 915.