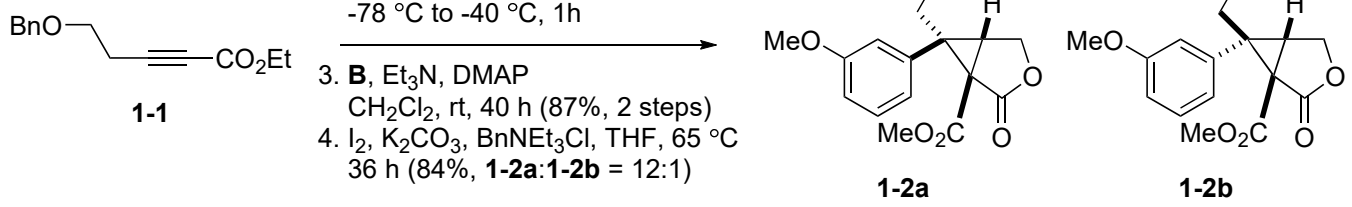
Problem Session (2)

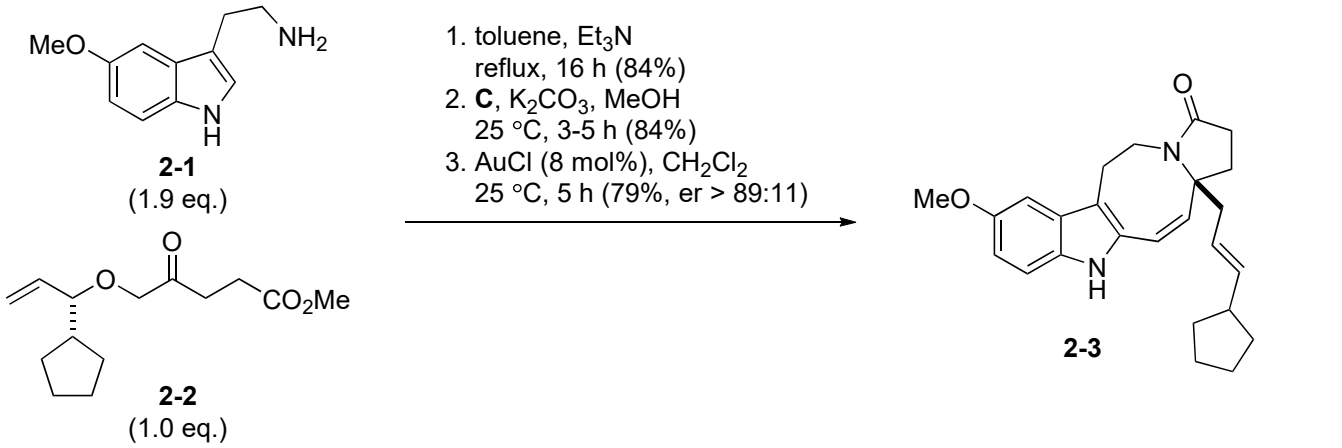
2017/6/17 Takumi Fukuda

Please provide the reasonable reaction mechanisms and explain the stereoselectivities.

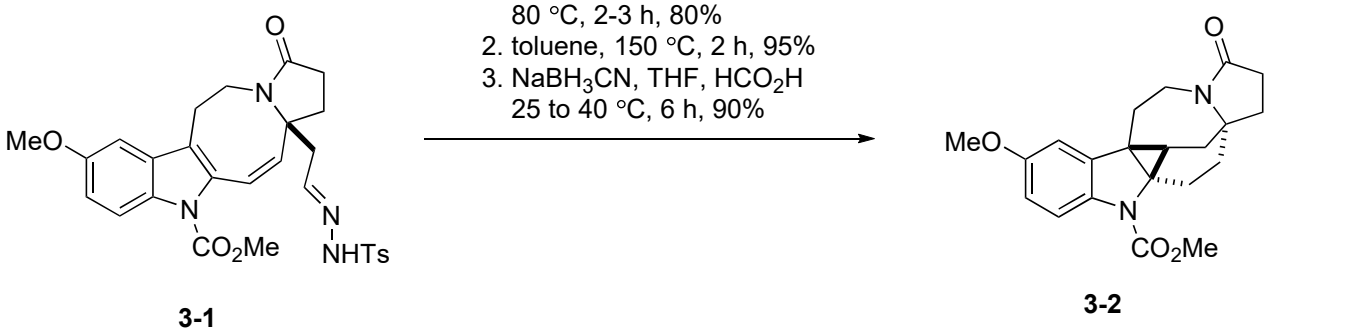
(1)

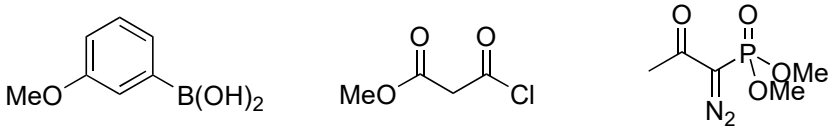


(2)



(3)



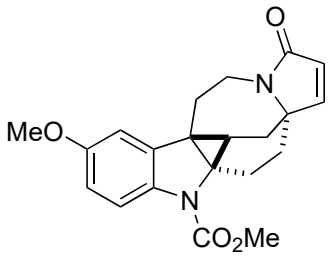


Problem Session (2) Answer

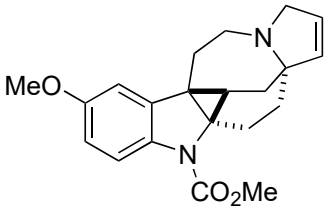
2017/6/17 Takumi Fukuda

Topic: total syntheses of Lundurines

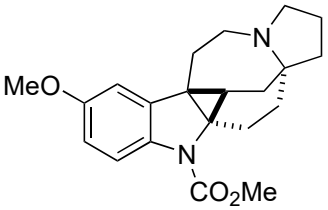
0. Introduction



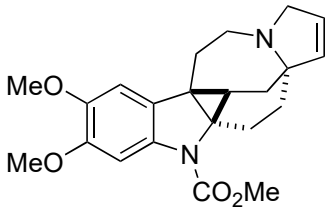
Lundurine A (**0-1**)



Lundurine B (**0-2**)



Lundurine C (**0-3**)



Lundurine D (**0-4**)

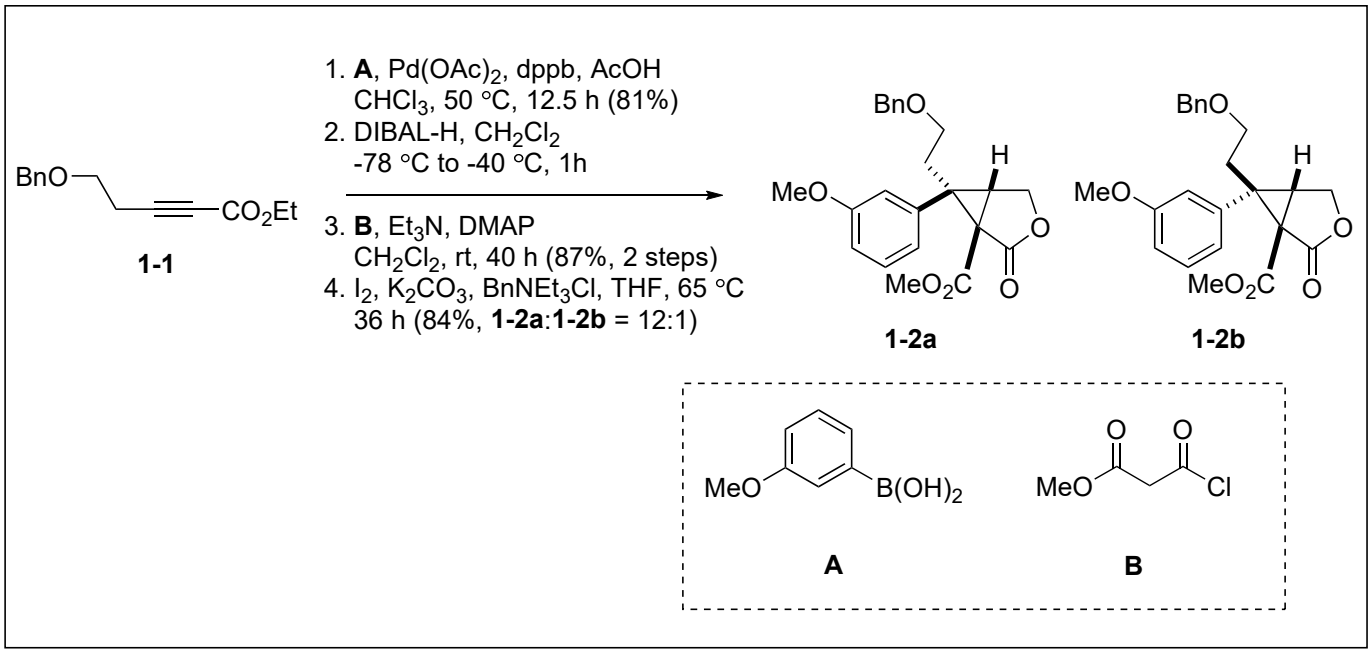
Isolation: from *Kospia tenius*
(Kam, T. S.; Yoganathan, K.; Chuah, C. H. *Tetrahedron Lett.* **1995**, *36*, 759.)
(Kam, T. S.; Lim, K. H.; Yoganathan, K.; Hayashi, M.; Komiyama, K. *Tetrahedron* **2004**, *60*, 10739.)

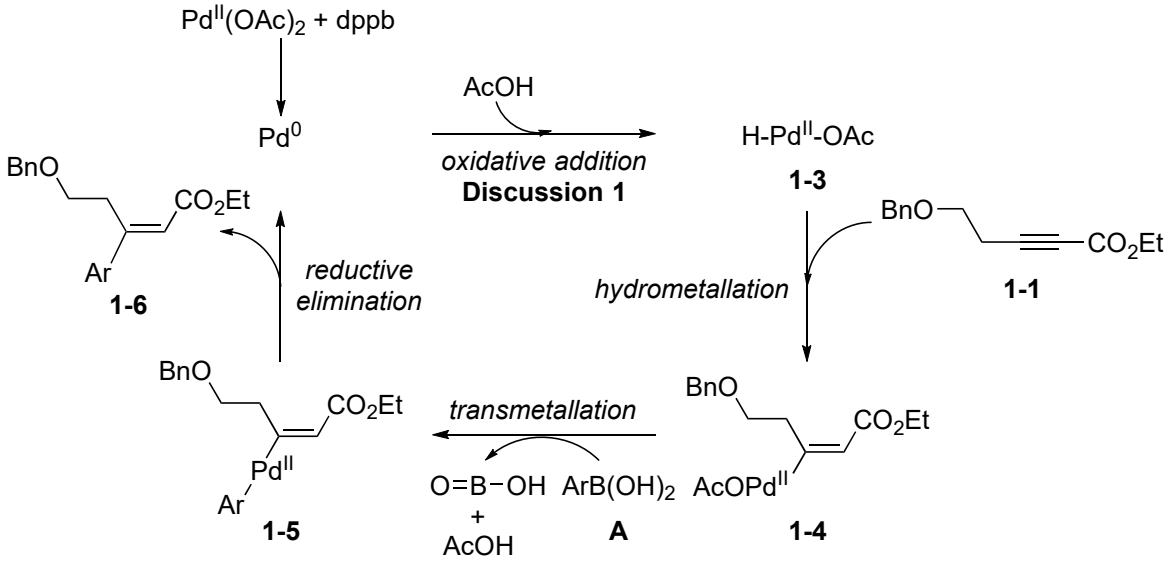
Pharmacological activity
Lundurine B and D: cytotoxicity against B16 melanoma cells and circumvention of drug-resistance in vincristine-resistant KB cells.
(Kam, T. S.; Lim, K. H.; Yoganathan, K.; Hayashi, M.; Komiyama, K. *Tetrahedron* **2004**, *60*, 10739.)

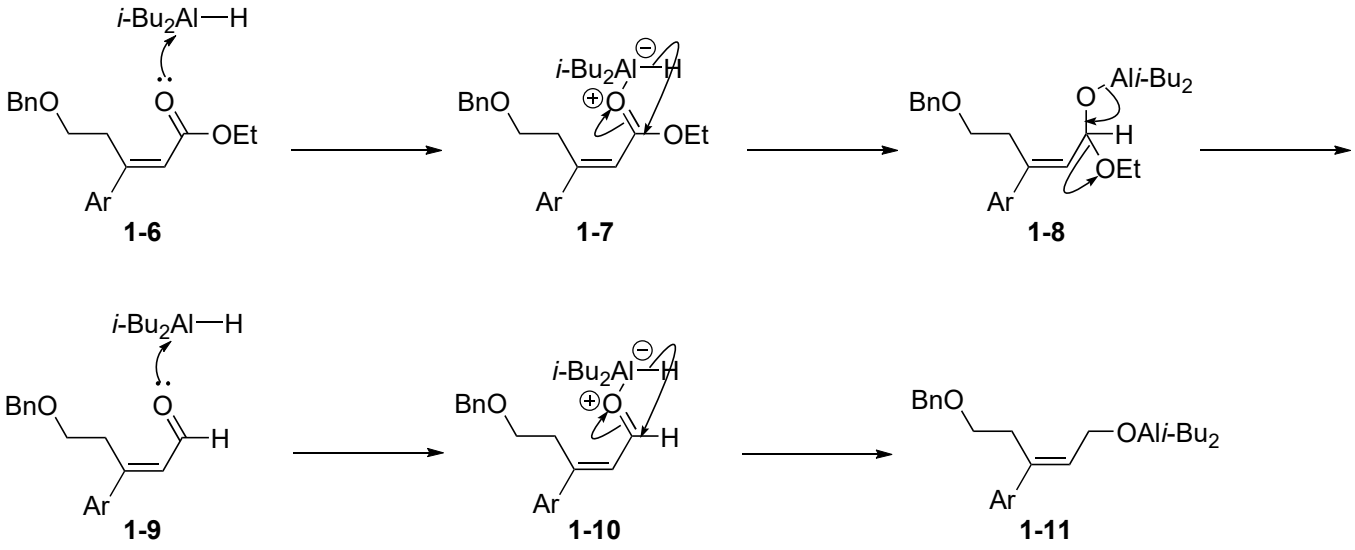
Stractural feature
indoline alkaloid
hexacyclic ring system
cyclopropane ring

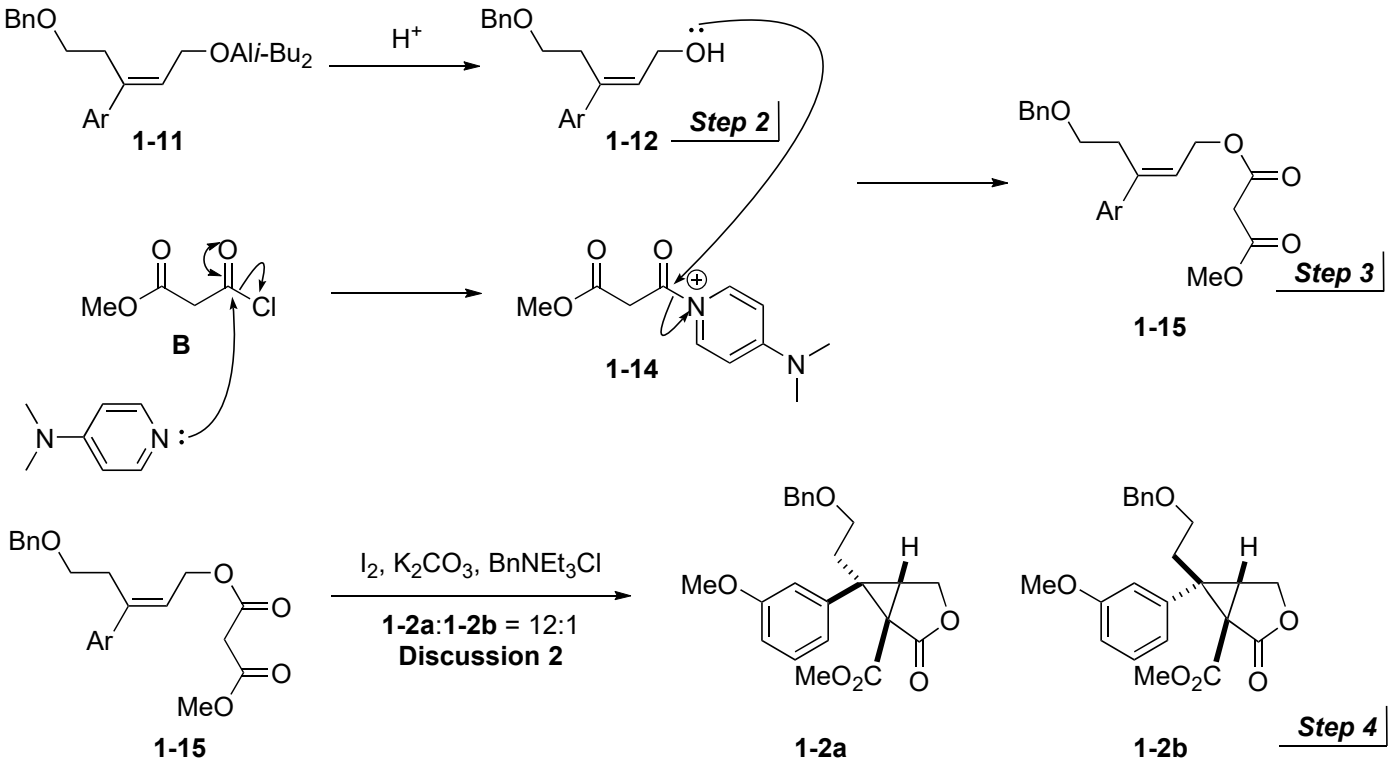
Total synthesis:
(±)-Lundurine B: Hoshi, M.; Kaneko, O.; Nakajima, M.; Arai, S.; Nishida, A. *Org. Lett*. **2014**, *16*, 768. (Problem 1)
(±)-Lundurine A and B: Arai, S.; Nakajima, M.; Nishida, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 5569.
(–)-Lundurine A: Jin, S.; Gong, J.; Qin, Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 2228.
(–)-Lundurine B: Nakajima, M.; Arai, S.; Nishida, A. *Chem. Asian J.* **2015**, *10*, 1065.
(–)-Lundurine A: Huang, H.X.; Jin, S.J.; Gong, J.; Zhang, D.; Song, H.; Qin, Y. *Chem. Eur. J*. **2015**, *21*, 13284.
(–)-Lundurine A-C: Kirillova, M. S.; Muratore, M. E.; Dorel, R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2016**, *138*. 3671. (Problem 2 and 3)

1-1. Reaction mechanism







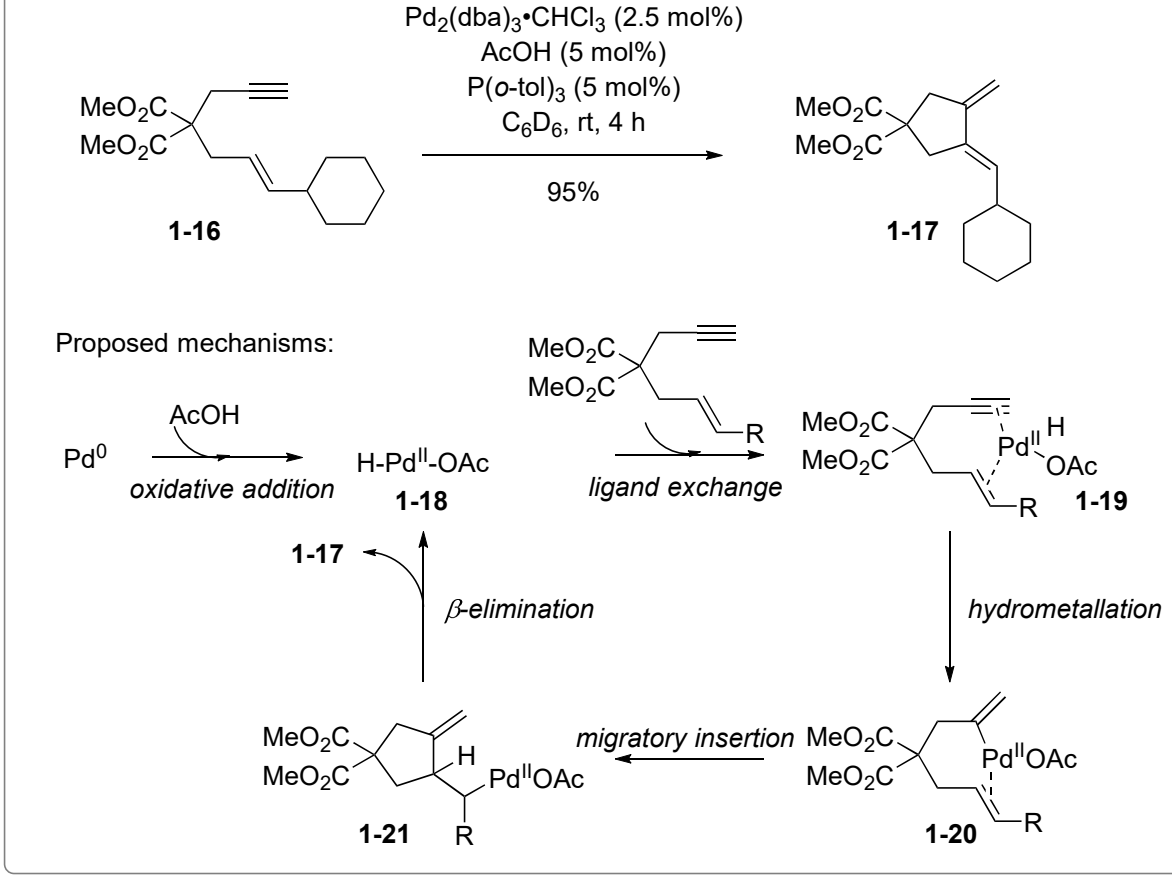


1. Discussion

1-1. Suzuki-Miyaura type cross-coupling

1-1-1.Oxidative addition of AcOH to Pd^0

Trost, B. M; Romero, D. N.; Rise, F. *J. Am. Chem. Soc.* **1994**, *116*, 4268.



1-1-2. transmetallation and reductive elimination

Amatore, C.; Jutand, A.; Duc, G. L. *Chem. Eur. J.* **2011**, *17*, 2492.
Study of the mechanism of the Suzuki-Miyaura reaction by DFT calculation, NMR experiment and cyclic voltammetry.

$$[(p\text{-CN-}C_6H_4)Pd^{II}BrL_2] + PhB(OH)_2 + OH^- + 2L \xrightarrow[\text{DMF, 25 °C}]{k_{obs}} p\text{-CN-}C_6H_4\text{-Ph} + [Pd^0L_3] + B(OH)_3 + Br^- + L \quad (1)$$

1.0 eq. β eq. α eq. L = PPh_3

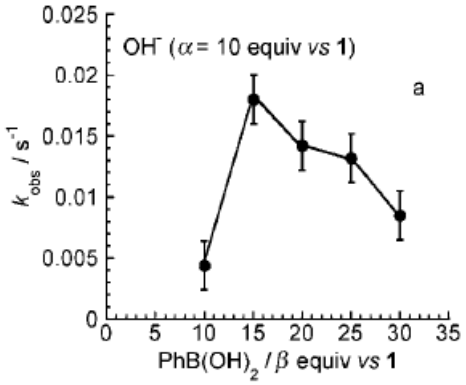


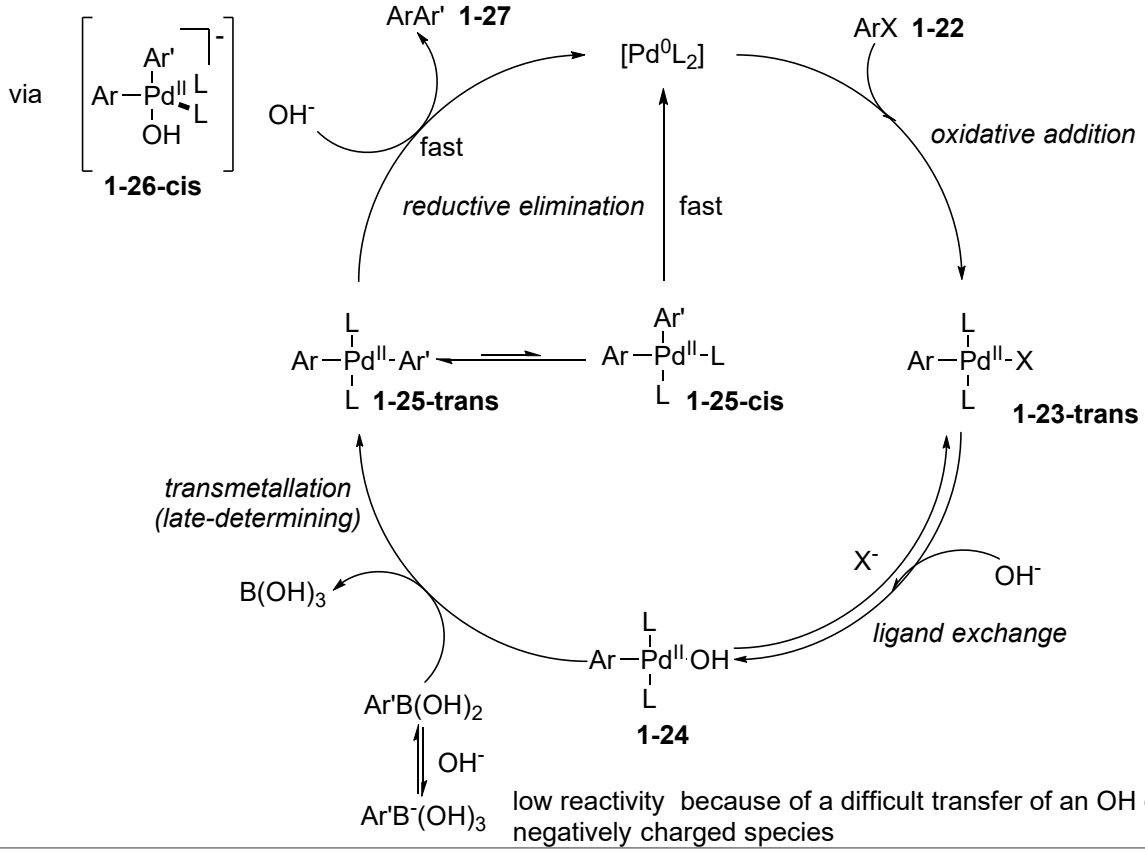
Figure.1

♦ k_{obs} was increased with the concetration of $PhB(OH)_2$ and decreased when the ratio of β/α became higher than 1.5. (bell-shaped curve.)

The role of base:

1. formation of $[ArPd(OH)(PPh_3)_2]$ as reactive species.
2. formation of unreactive $Ar'B^-(OH)_3$.
3. accerelate the reductive elimination step by reacction of OH^- with intermidiate trans-$[ArPdAr'(PPh_3)_2]$ complex.

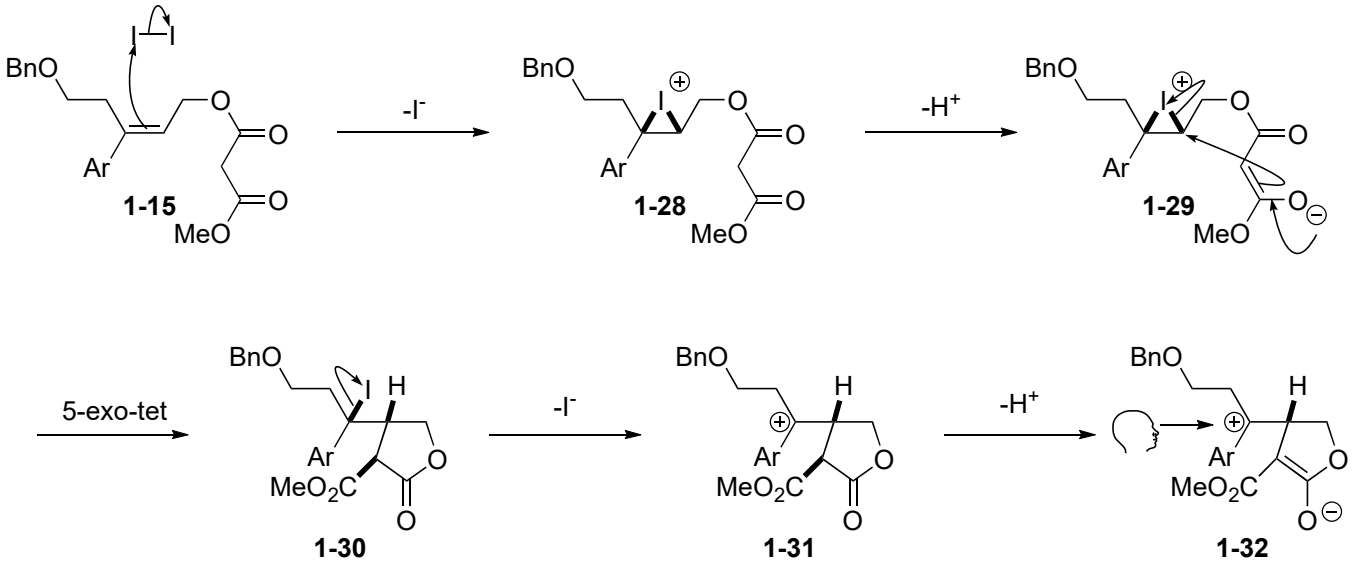
Proposed Mechanisms:

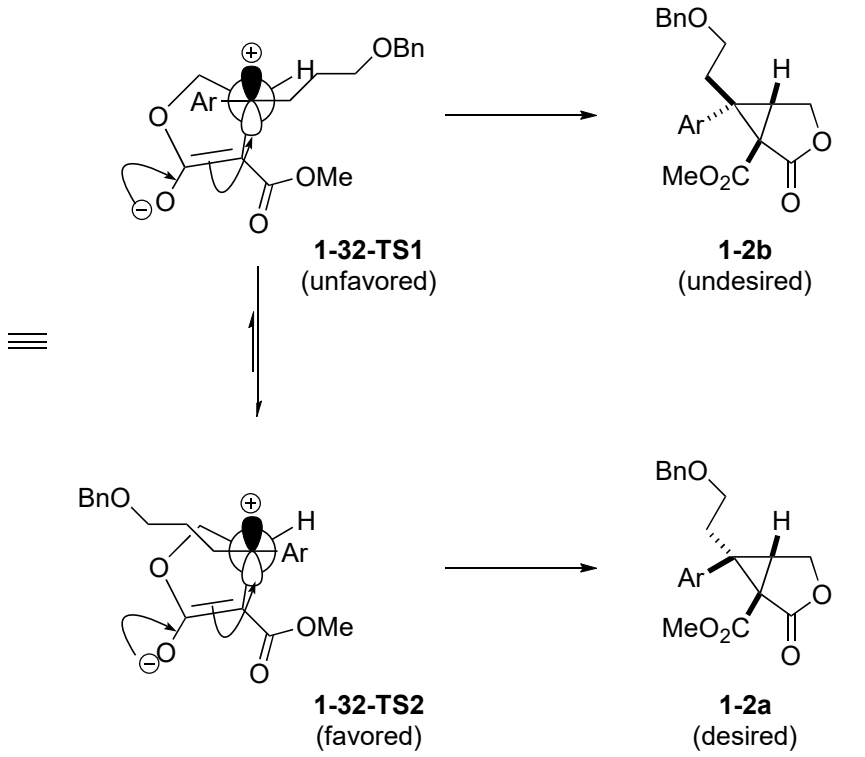


low reactivity because of a difficult transfer of an OH group to a negatively charged species

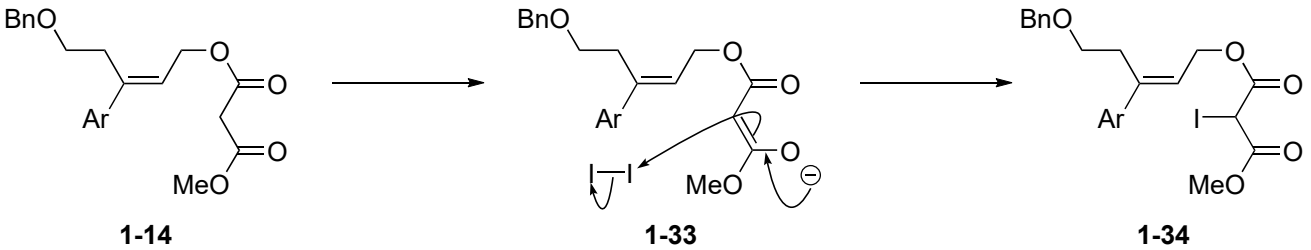
1-2. lactonization and cyclopropanation

1-2-1. olefin iodination path

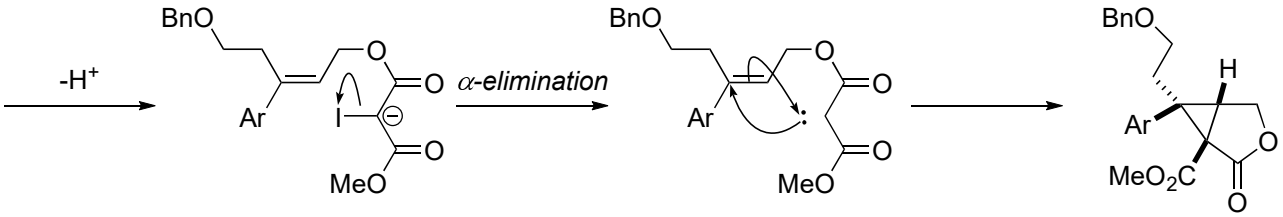




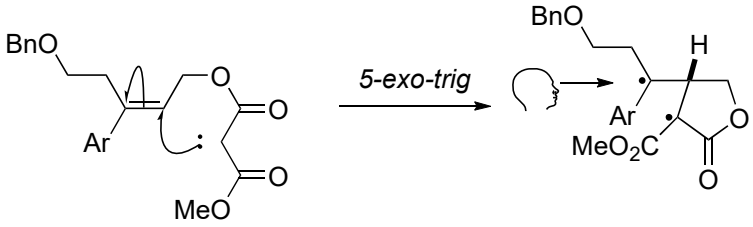
1-2-2. carbene path



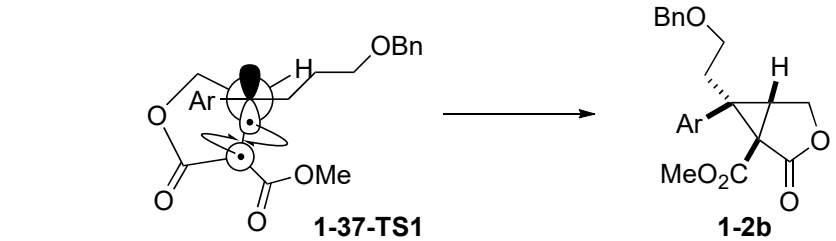
1-14 **1-33** **1-34**



1-35 **1-36** (singlet) **1-2a** only

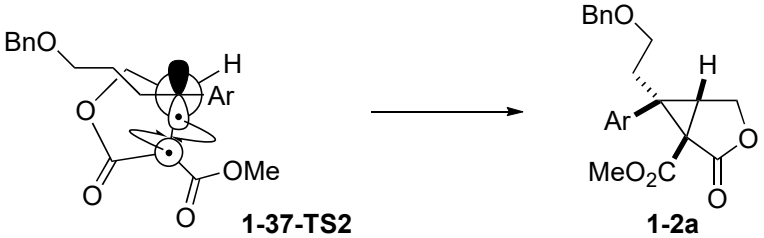


1-36 (triplet) **1-37**



1-37-TS1 (unfavored) **1-2b** (undesired)

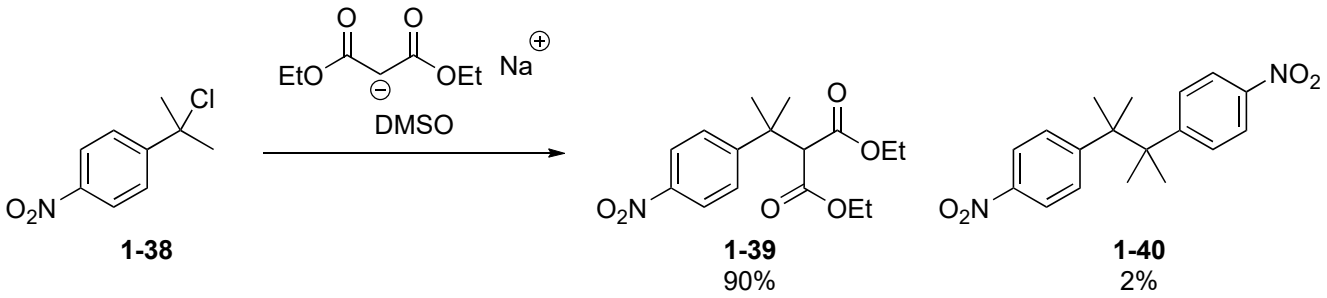
≡



1-37-TS2 (favored) **1-2a** (desired)

1-2-3. SET path

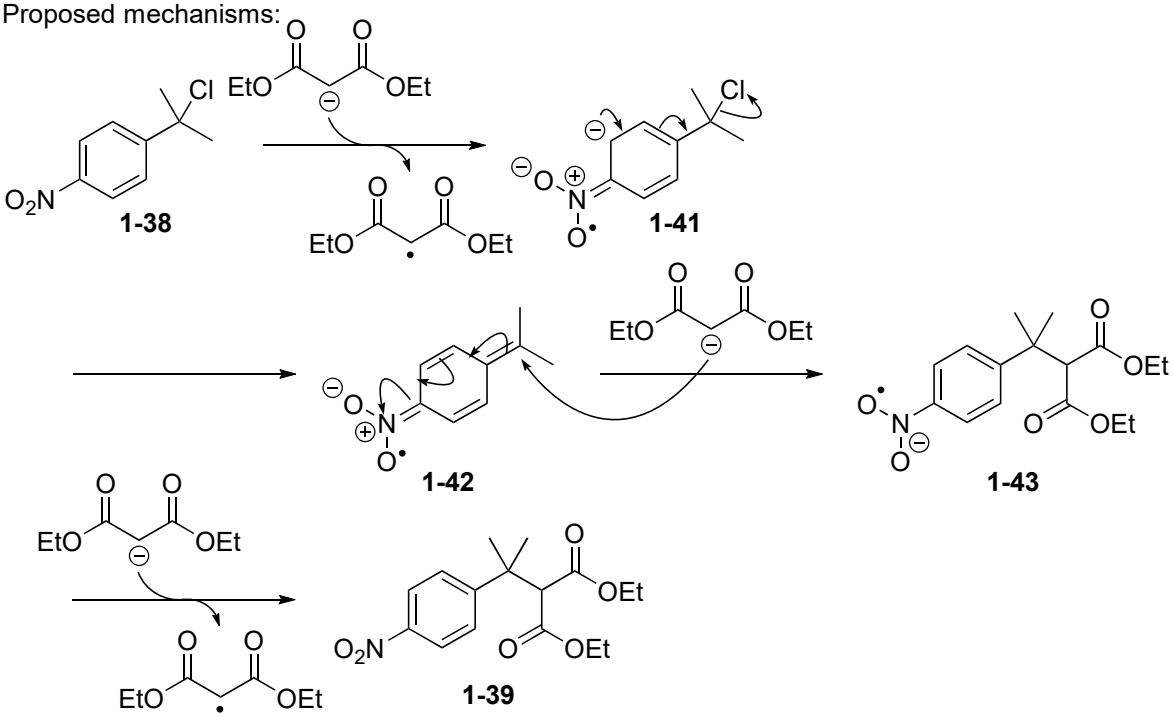
Kornblum, N. et al. *J. Am. Chem. Soc.* **1967**, *89*, 725.

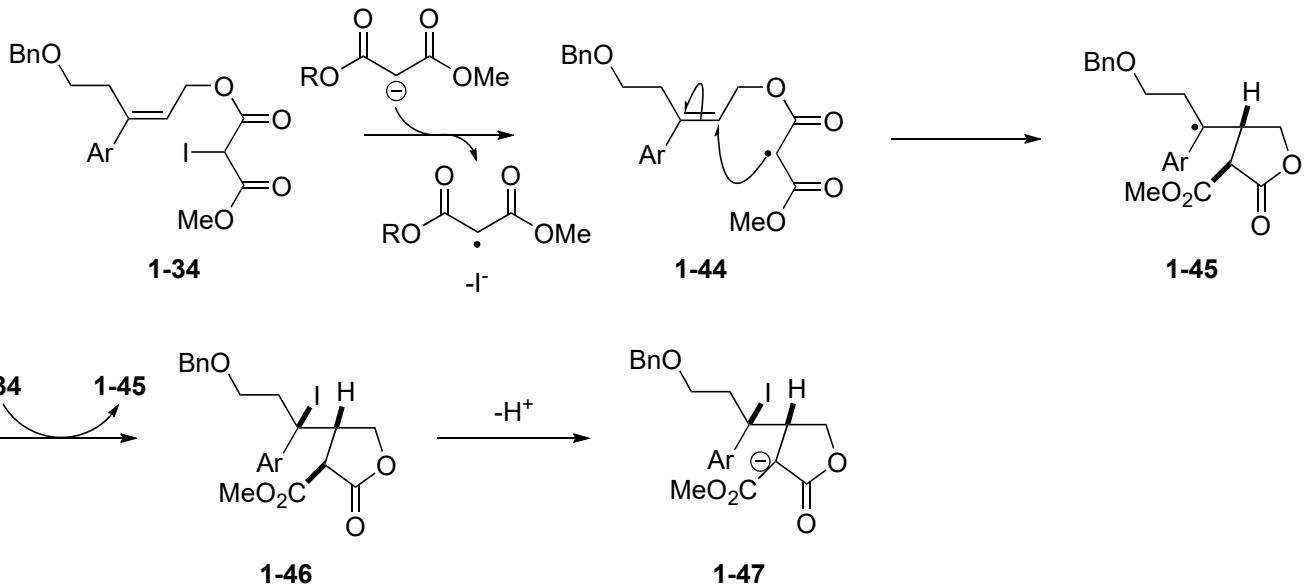


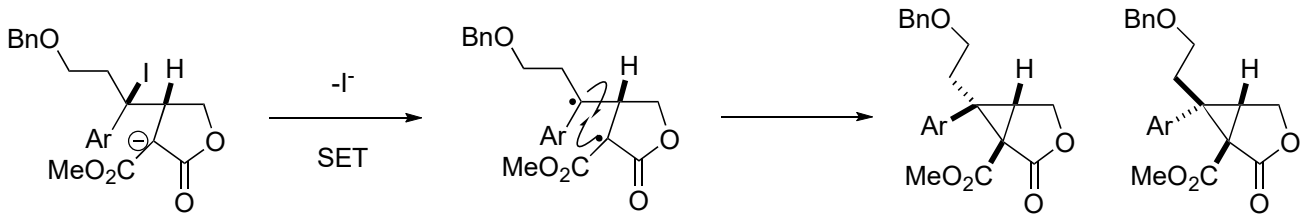
1-38 **1-39** 90% **1-40** 2%

Supporting data: Light speeds up the reaction, *p*-dinitrobenzene or oxygen retards the reaction.

Proposed mechanisms:







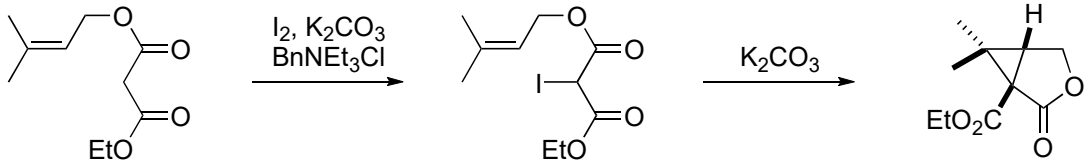
1-47 **1-37** **1-2a** **1-2b**

2. Experimental data

2-1. Intermediate (Toke, L. *et al. Tetrahedron Lett.* **1990**, 31, 7501.)

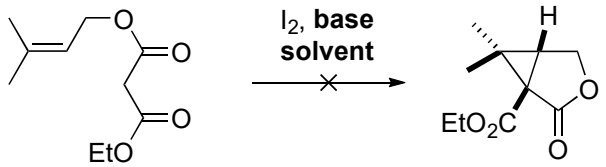
1-49 could be isolated if K_2CO_3 and $KHCO_3$ mixture were removed by filteration. In the absence of K_2CO_3 reaction stoped and restarted again if K_2CO_3 was added and heating continued.

→ Olefin iodonation path was rejected.



1-48 **1-49** **1-50**

2-2. Experiment with other bases (Toke, L. *et al. Tetrahedron* **1993**, 49, 5133.)



1-48 **1-50**

base: t-BuOK, MeONa, DBU, pyridine, KH
solvent: MeOH, toluene, DMSO

These bases were able to remove the proton from iodomalonic ester moiety.

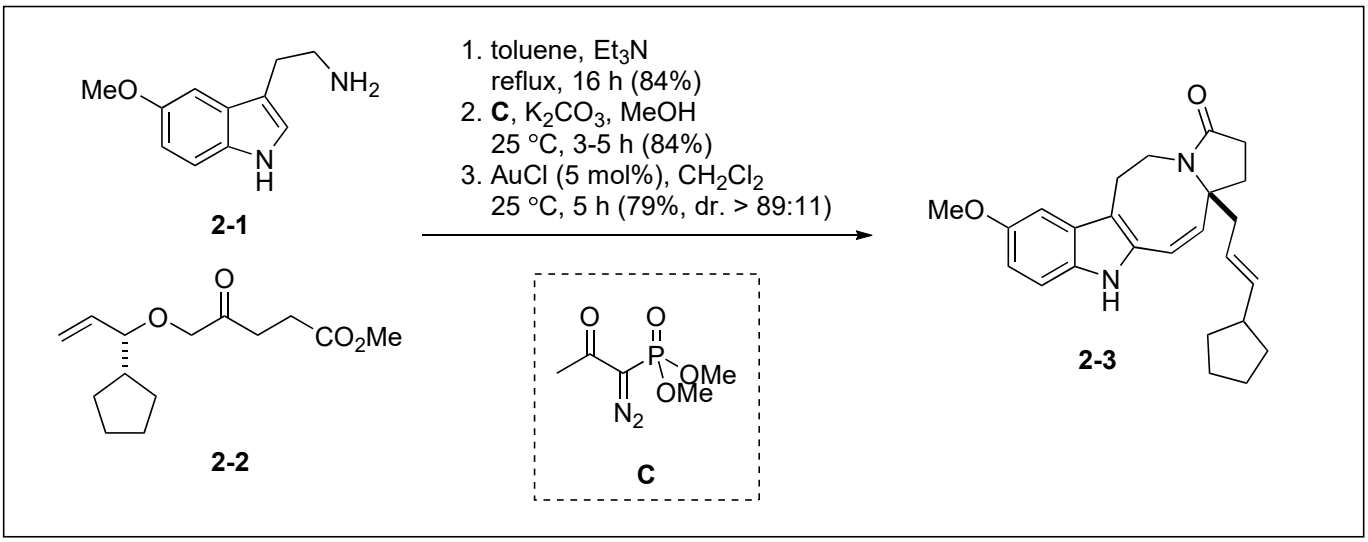
→ Carbene path was rejected.

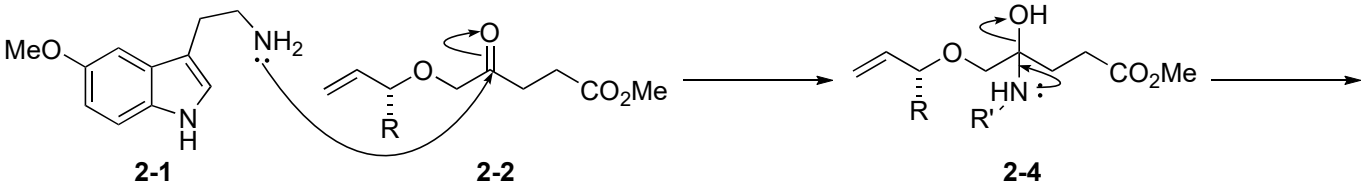
2-3. ESR experimant (Toke, L. *et al. Tetrahedron* **1993**, 49, 5133.)

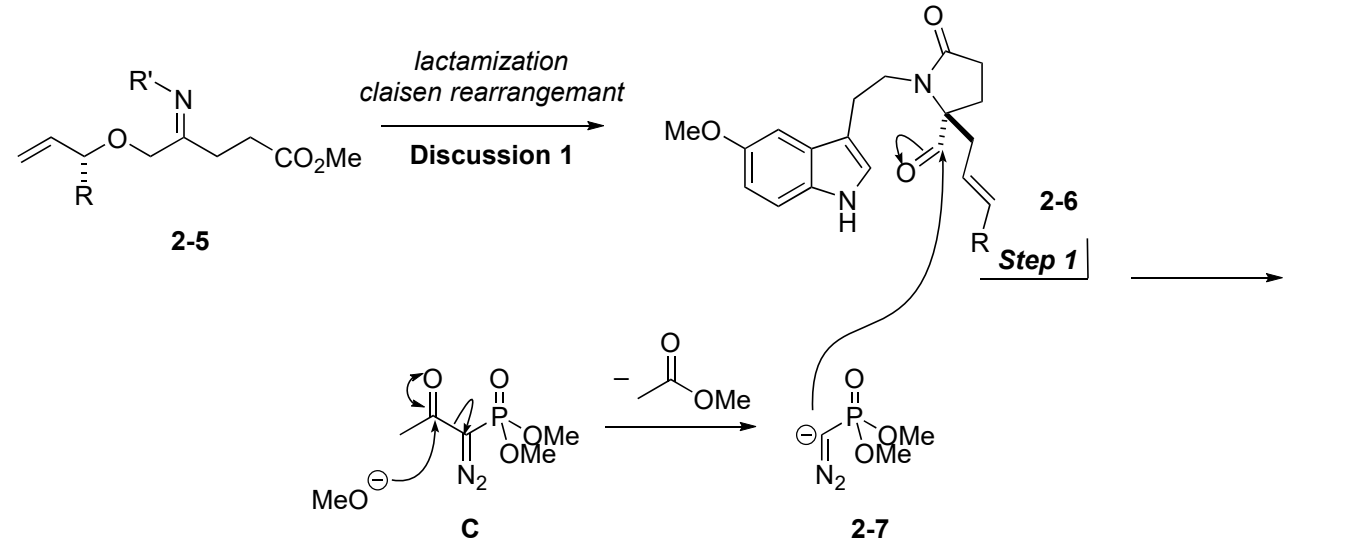
One or two different radicals were generated in this type of reaction.

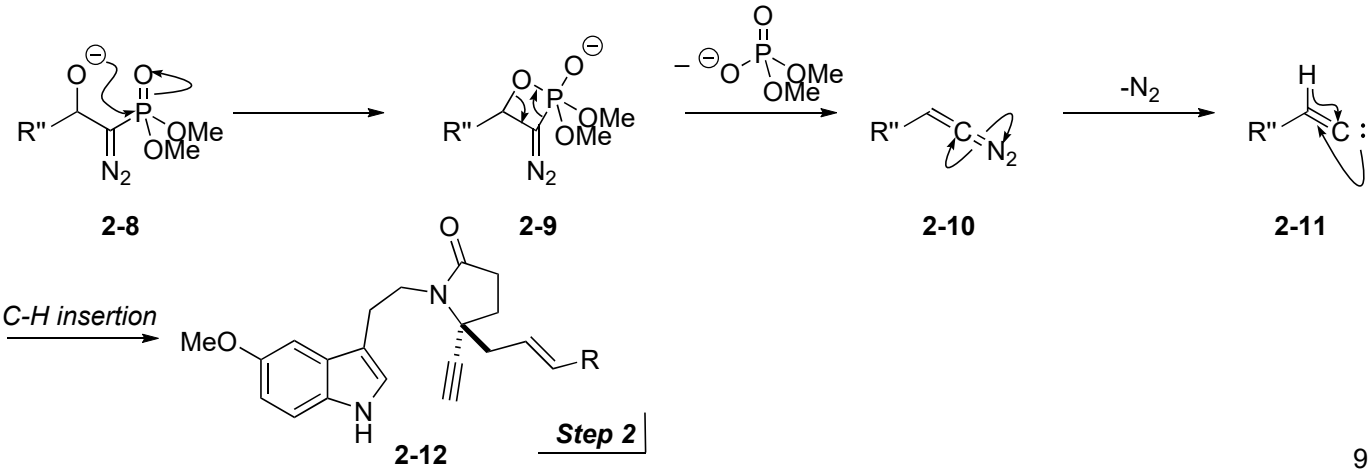
→ Olefin iodonation path and singlet carbene path were rejected.

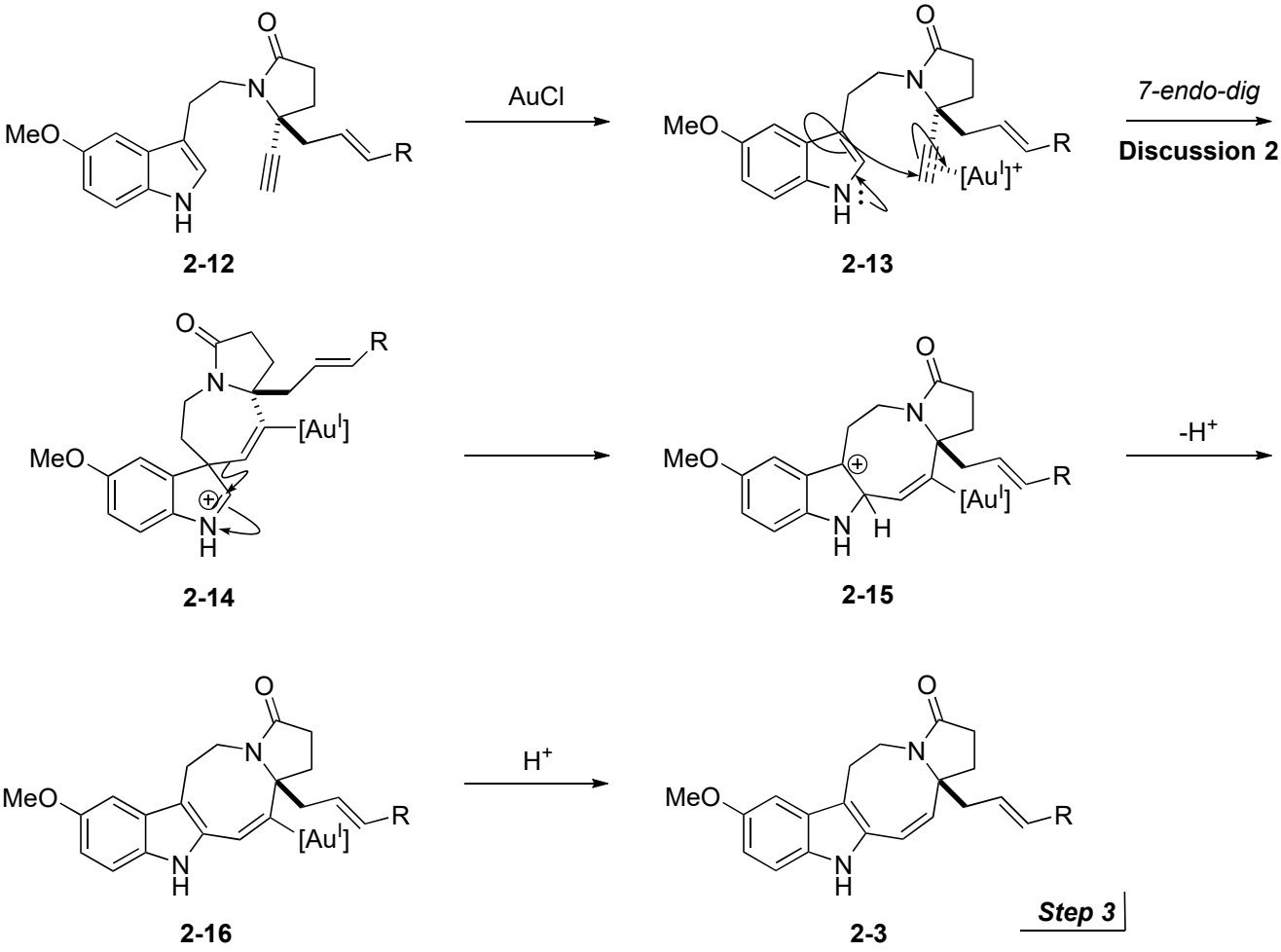
2-1. Reaction mechanism



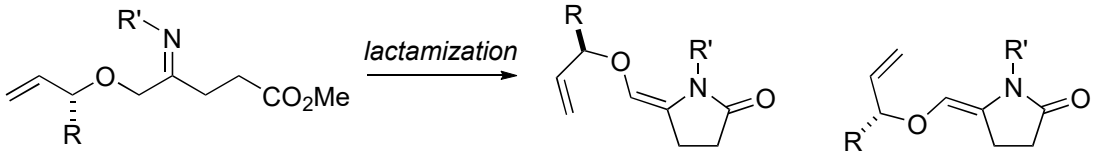




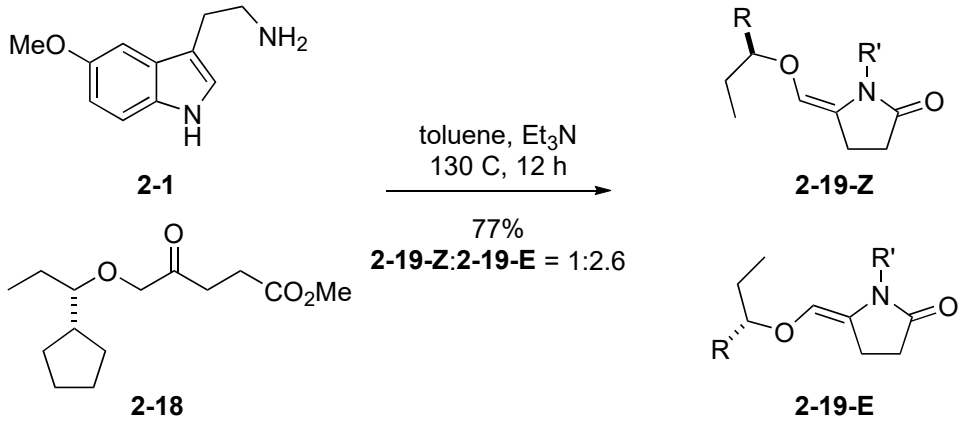


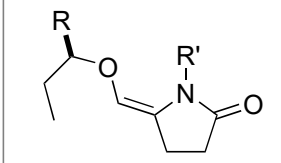


2. Discussion
2-1. Enantioselective Claisen rearrangement
2-1-1. Lactamization



Kirillova, M. S.; Muratore, M. E.; Dorel, R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2016**, *138*.

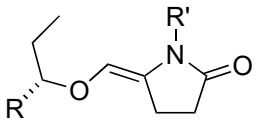




2-19-Z

toluene, Et_3N
MeOH, H_2O
100 °C, 16 h

no reaction
(single diastereomer)



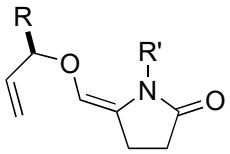
2-19-E

toluene, Et_3N
MeOH, H_2O
100 °C, 16 h

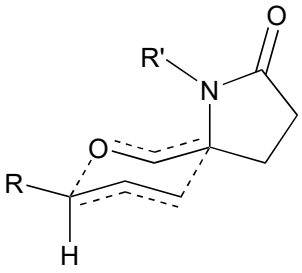
no reaction
(single diastereomer)

There was probably no equilibrium between **2-17-Z** and **2-17-E**.

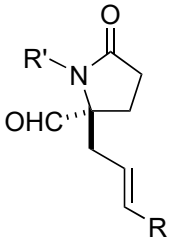
2-1-2. Claisen rearrangement



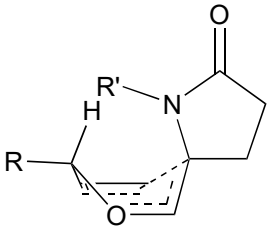
2-17-Z



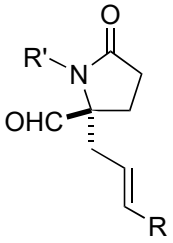
2-17-Z-TS$_{chair}$
(favored)



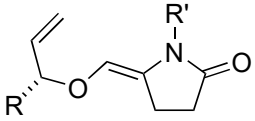
2-6
(desired)



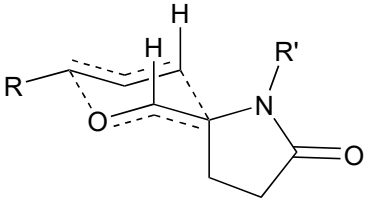
2-17-Z-TS$_{boat}$
(unfavored)



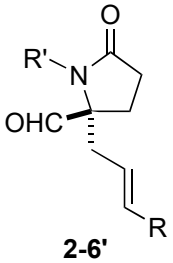
2-6'
(undesired)



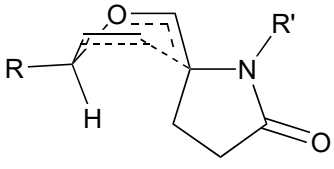
2-17-E



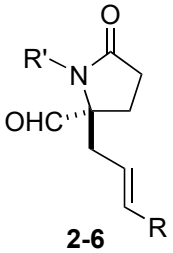
2-17-E-TS$_{chair}$
(unfavored)



2-6'
(undesired)



2-17-E-TS$_{boat}$
(favored)

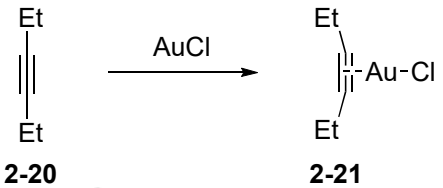


2-6
(desired)

2-2.gold(I)-catalyzed cyclization

Wu, J.; Kroll, P.; Dias, H. V. R. *Inorganic Chemistry*, **2009**, *48*, 423.

Alkyne-Au^{I} complex was isolated and X-ray analysis was conducted.



2-20 **2-21**

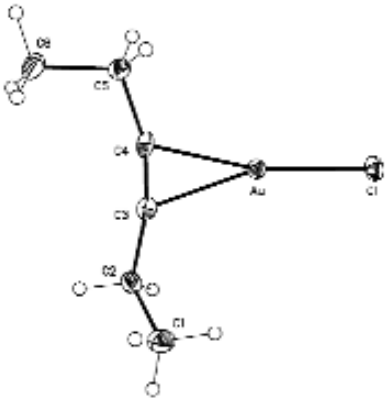
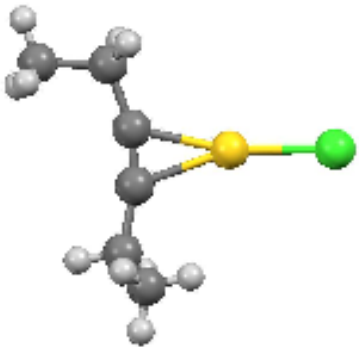


Figure 2. Molecular structure of Au(EtC≡CEt)Cl. Selected bond lengths (Å) and angles (deg): Au—C1 2.152(4), Au—C3 2.172(5), Au—Cl 2.2703(11), C1—C2 1.530(7), C2—C3 1.472(7), C3—C4 1.224(6), C4—C5 1.460(6), C5—C6 1.526(6); C1—Au—C3 32.88(17), C1—Au—Cl 167.13(13), C3—Au—Cl 159.99(12), C3—C2—C1 112.4(4), C4—C3—C2 166.9(5), C4—C3—Au 72.7(3), C2—C3—Au 120.3(3), C3—C4—C5 163.0(5), C3—C4—Au 74.4(3), C5—C1—Au 122.6(3), C4—C5—C6 111.6(4).



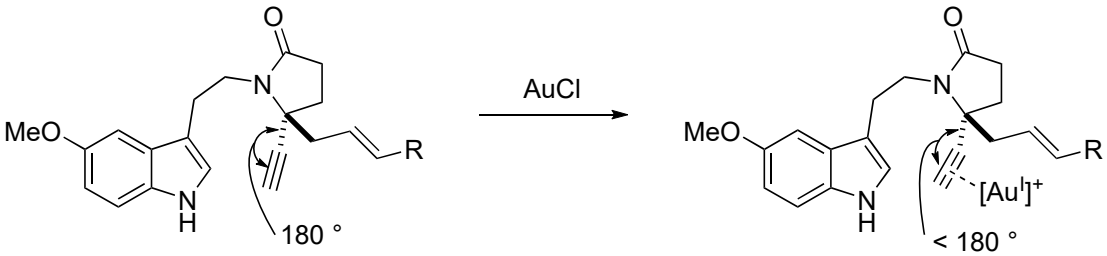
X-ray structure of **2-21**

Table 1. Selected Bond Lengths (Å) and Angles (deg) of Au(EtC≡CEt)Cl[a]

Parameter	experimental	computed
C3≡C4	1.224(6)	1.247
Au−C4	2.152(4)	2.206
Au−C3	2.172(5)	2.231
Au−Cl	2.2703(11)	2.304
C4−C3−C2	166.9(5)	165.7
C3−C4−C5	163.0(5)	163.0

[a] See Figure 2 for the atom numbering scheme. The calculated C≡C distance of free 3-hexyne is 1.215 Å.

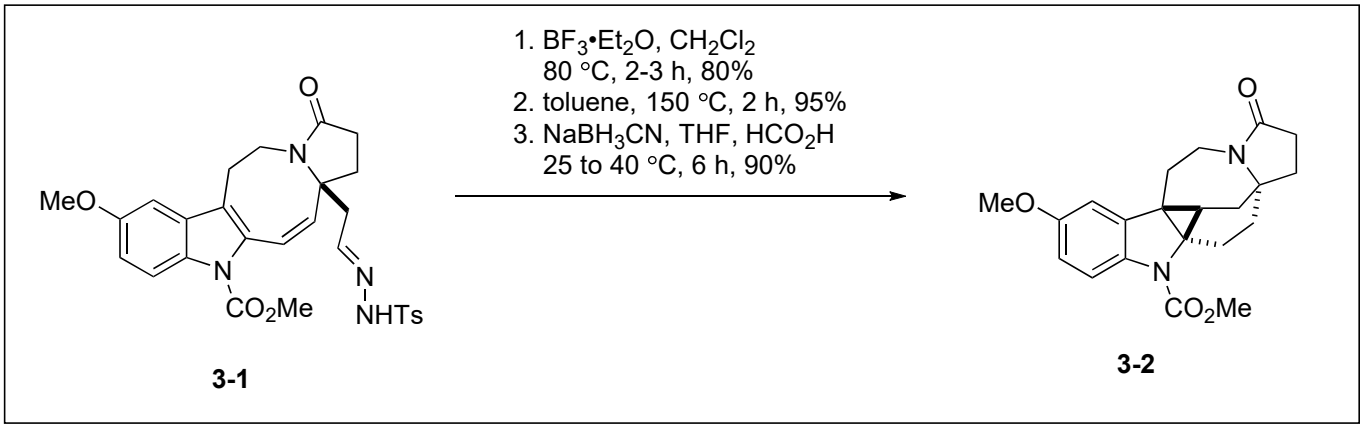
The average C≡C−C angle was 165.0 °, which indicates a significant deviation from linearity.



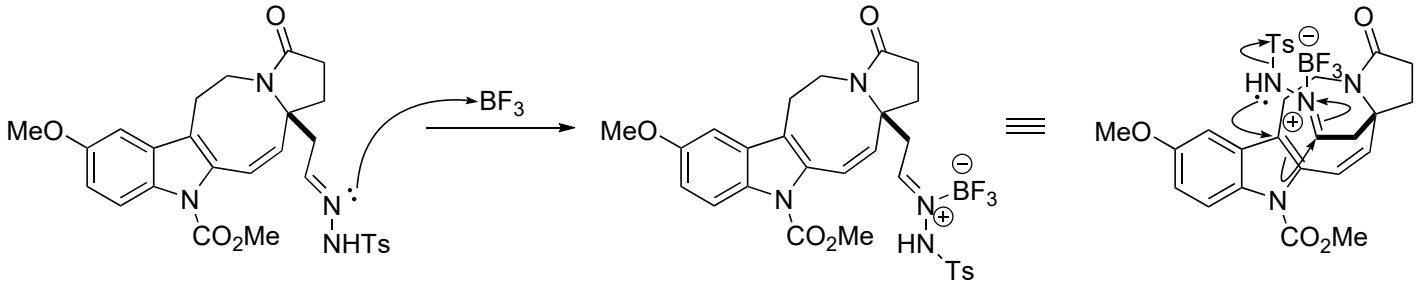
2-12 **2-13**

7-endo-dig cyclization was more favored.

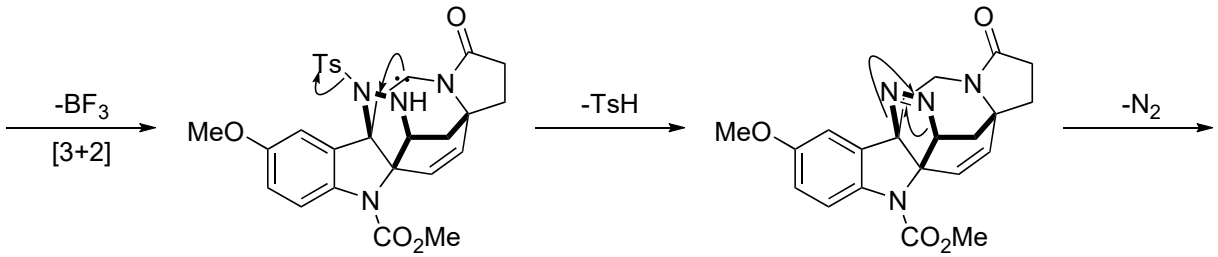
3. Reaction mechanism



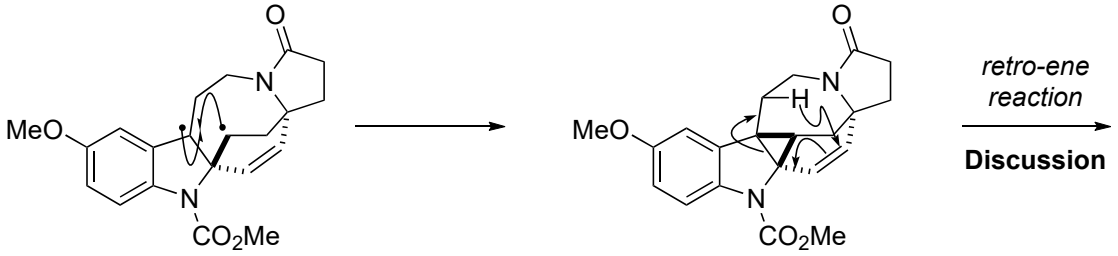
3-1 **3-2**



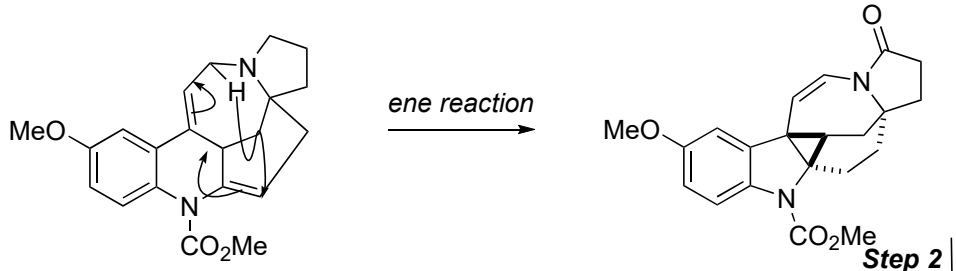
3-1 **3-3** **3-3**



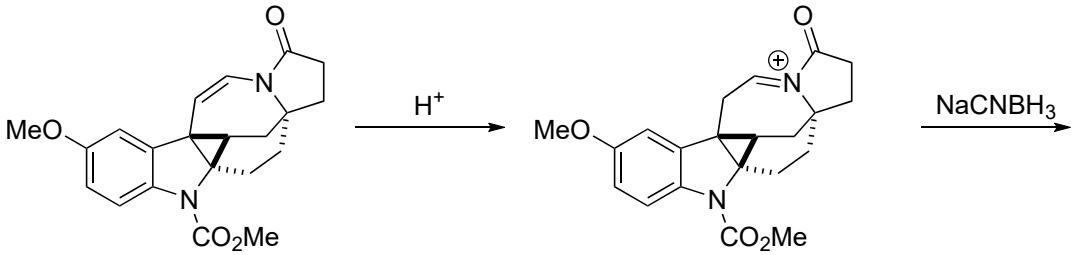
3-4 **3-5**



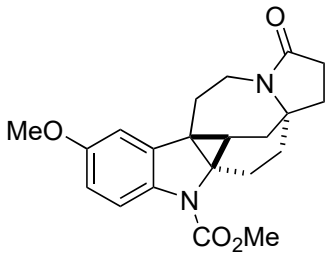
3-6 **3-7** ***Step 1***



3-8 **3-9** ***Step 2***

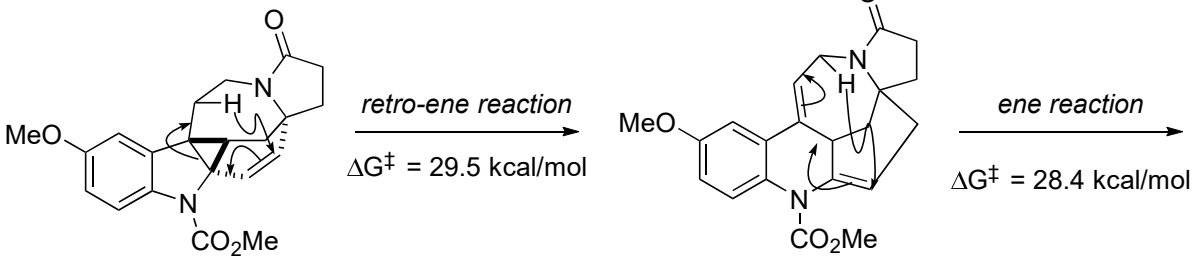


3-9 **3-10**

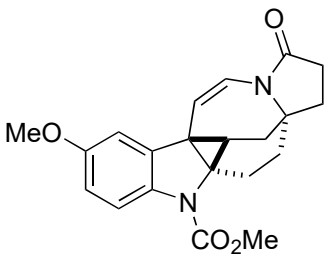


3-11 ***Step 3***

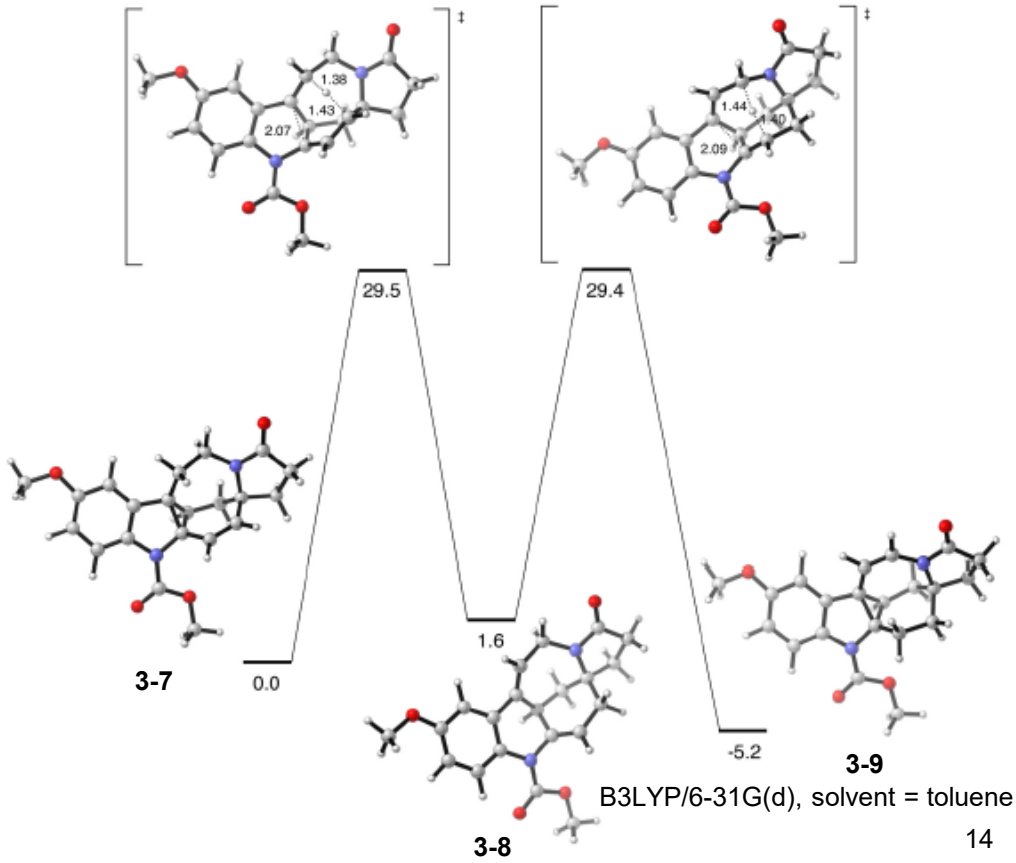
3. Discussion
3-1. Retro-ene/ene reaction
3-1-1. DFT calculation



3-7 **3-8**



3-9



B3LYP/6-31G(d), solvent = toluene