Problem Session (3) -Answer-

2021. 7. 3. Yuuki Watanabe

Topic: Total synthesis of welwitindolinones

0. Introduction

0-1. Isolation

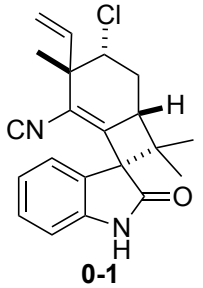
Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson,G. M. L.; Shaffer, S.; Smith,C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935.

0-2. Bioactivity

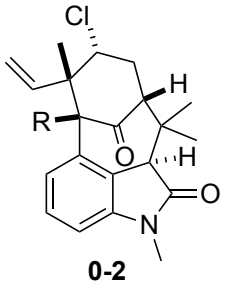
Reversing P-glycoprotein-mediated multidrug resistance in cancer cells
Smith, C. D.; Zilfou, J. T.; Stratmann, K.; Patterson, G. M. L.; Moore, R. E. *Mol. Pharmacol.* **1995**, *47*, 241.

0-3. total synthesis

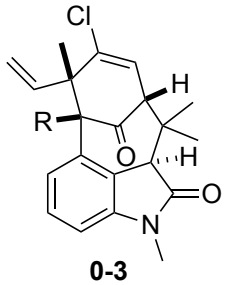
(+)-welwitindolinone A isonitrile: Baran (2005, 2007, 2008), Wood (2006, 2008, racemic)
(-)-*N*-Methylwelwitindolinone B isothiocyanate/isonitrile: Garg (2014), Rawal (2017)
(-)-*N*-Methylwelwitindolinone C isothiocyanate/isonitrile:
Rawal (2011), Garg (2011, 2012), Martin (2012), Hatakeyama (2015)
(+)-*N*-Methylwelwitindolinone D isonitrile: Rawal (2011, racemic), Garg (2013)



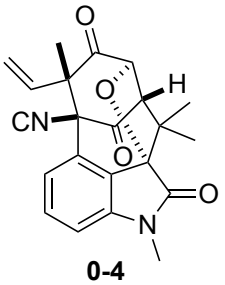
0-1
Welwitindolinone A isonitrile



0-2
***N*-Methylwelwitindolinone B**
R = NCS, R=NC



0-3
***N*-Methylwelwitindolinone C**
R = NCS, R=NC



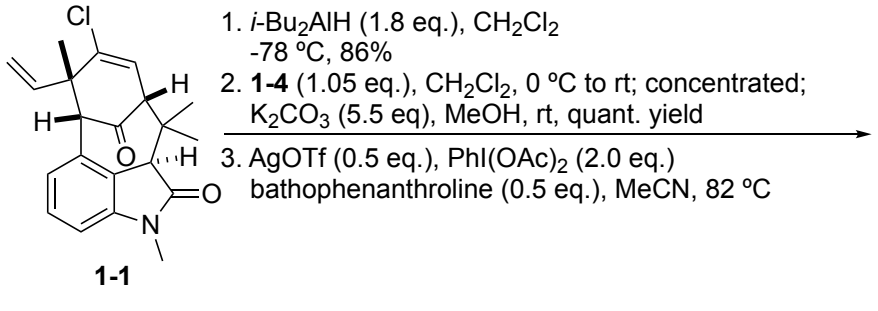
0-4
***N*-Methylwelwitindolinone D isonitrile**

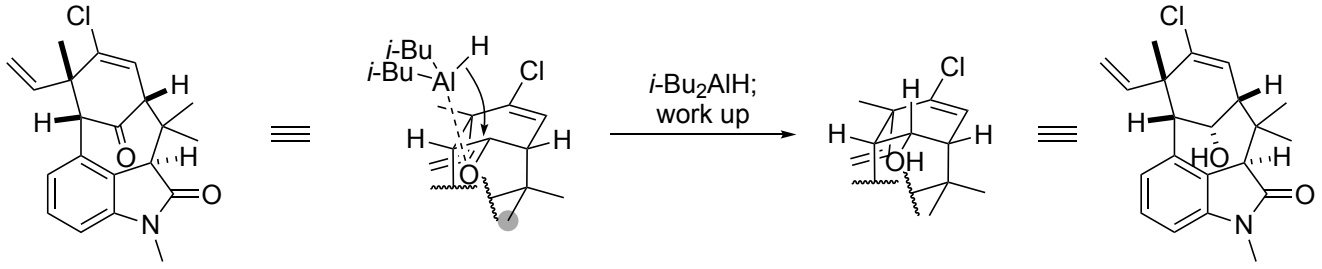
For details of welwitindolines, please see below documents.
-Total synthesis of welwitindolinone A isonitrile by Wood: 080913_PS_Yuuki_Amaoka, 140705_LS_Koichi_Hagiwara
-Overviews of synthetic study: 111022_LS_Naoto_Aoki

1. Answer of problem 1

Topic: Total synthesis of *N*-Methylwelwitindolinone C isothiocyanate by Garg (2011, 2012)
Huters, A. D.; Quasdorf, K. W.; Styduhar, E. D.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 15797.
Quasdorf, K. W.; Huters, A. D.; Lodewyk, M. W.; Tantillo, D. J.; Garg, N. K. *J. Am. Chem. Soc.* **2012**, *134*, 1396.

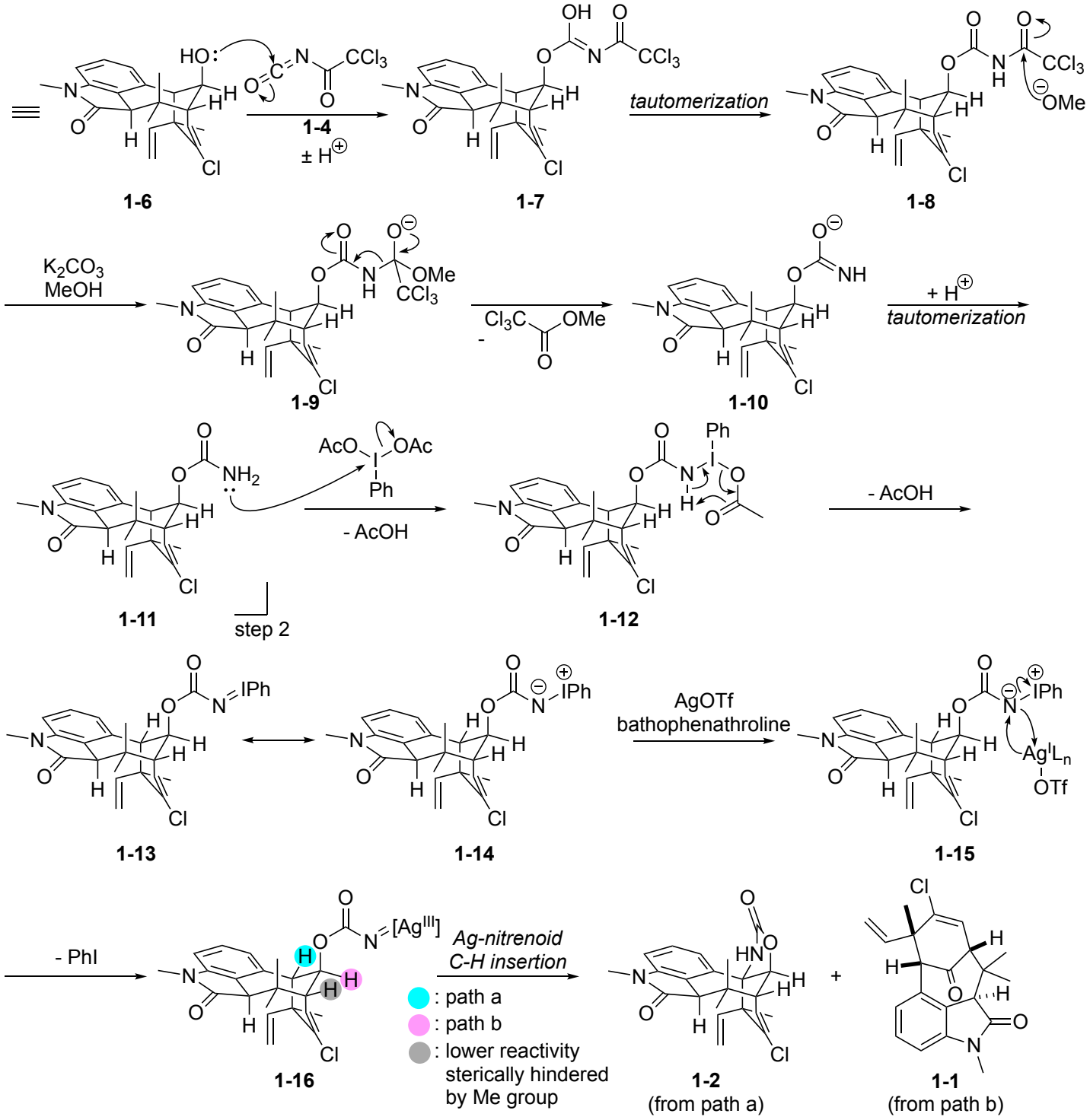
Problem 1:



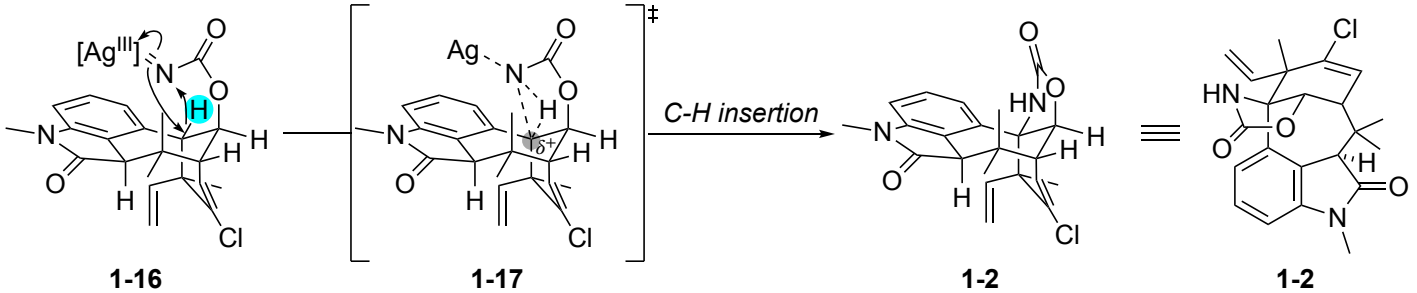


Indolinone moiety is omitted for clarity
●: sterically shielding
the α-face of ketone

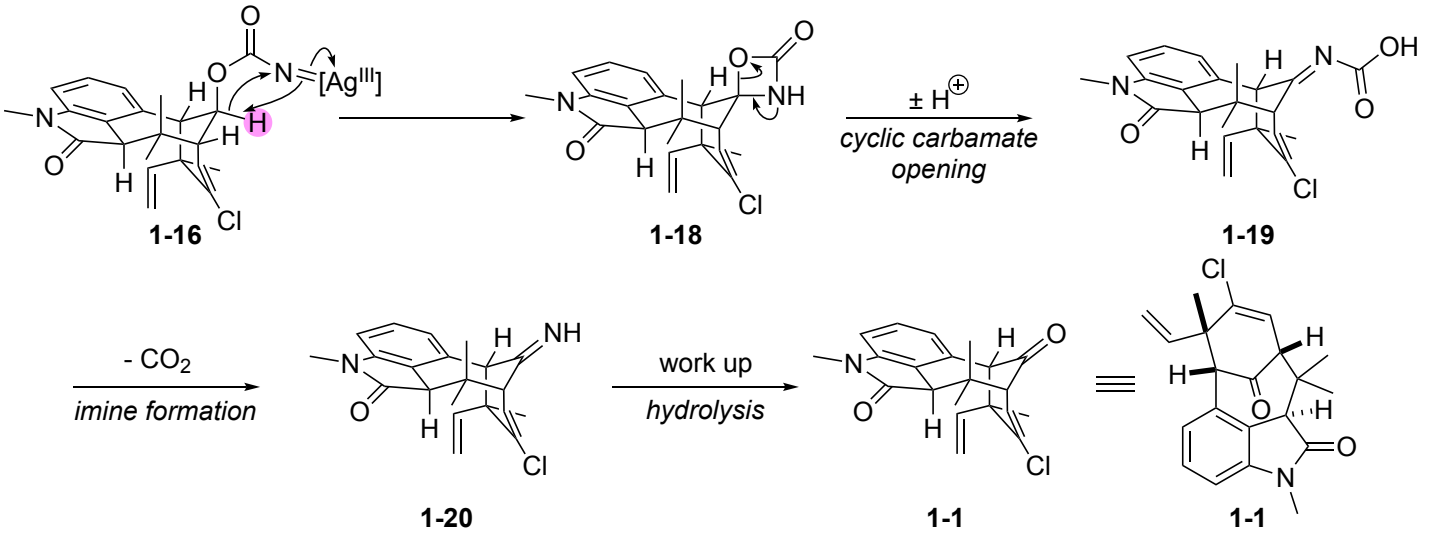
step 1

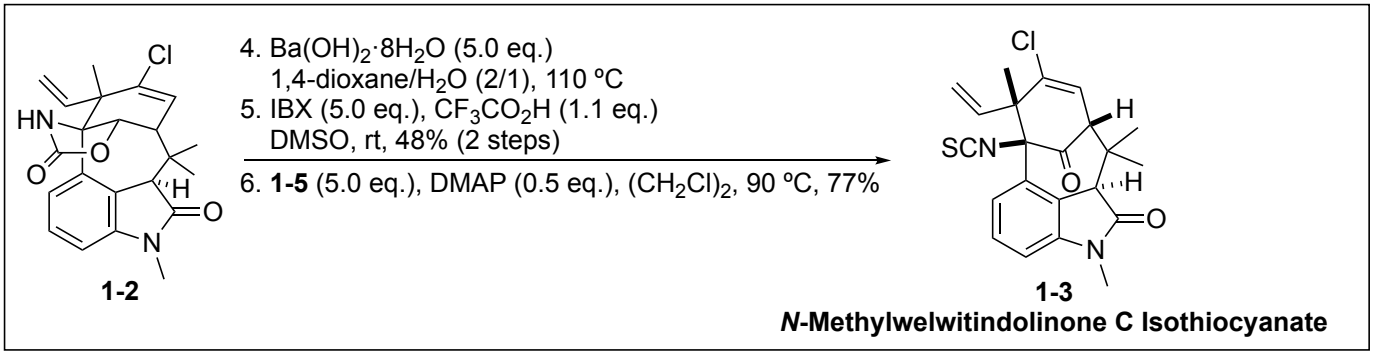


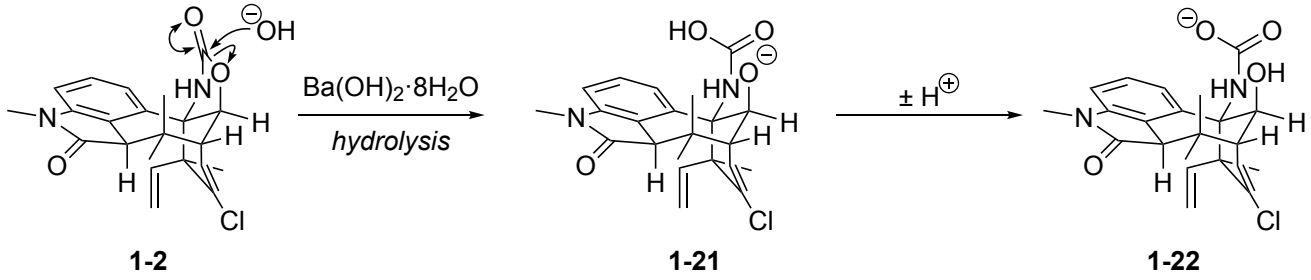
(i) path a (reacted with blue-highlighted hydrogen)

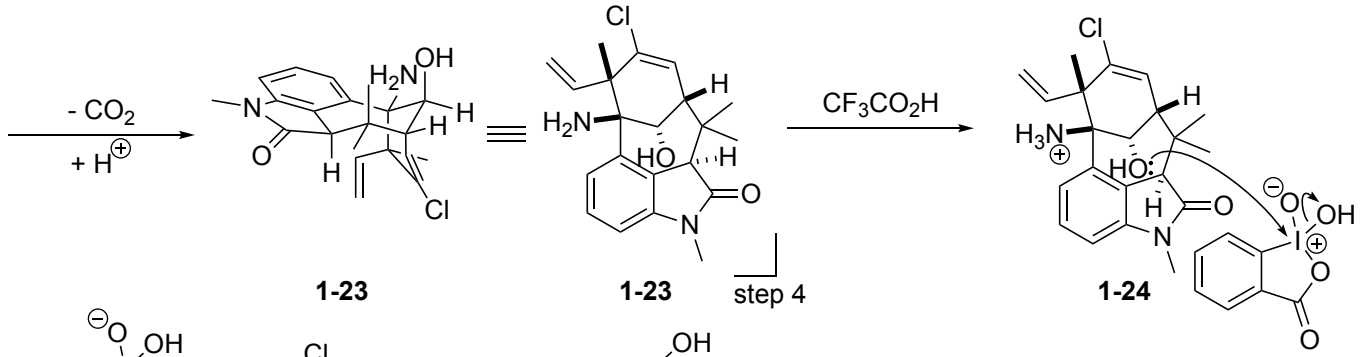


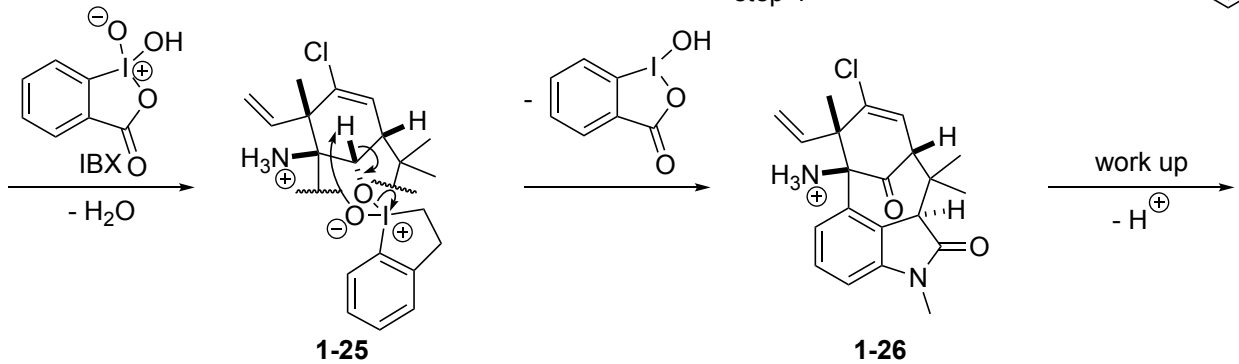
(ii) path b (reacted with pink-highlighted hydrogen)

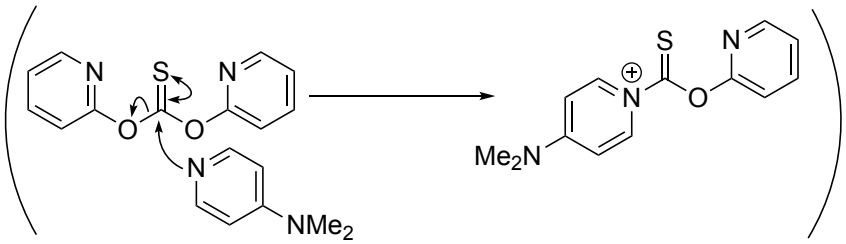


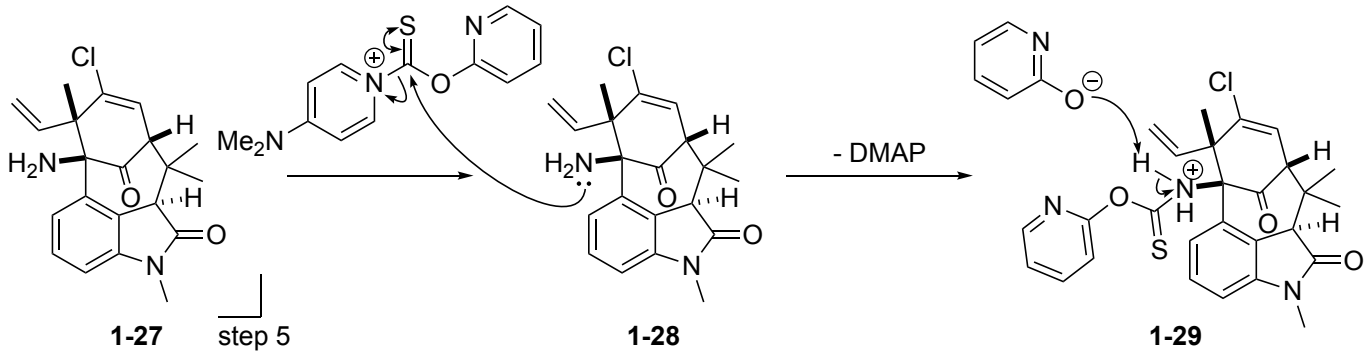




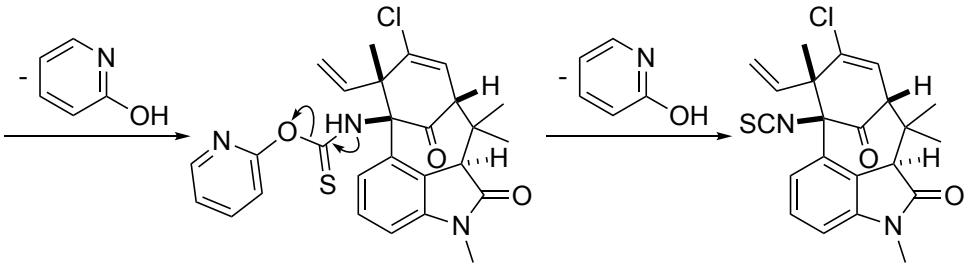






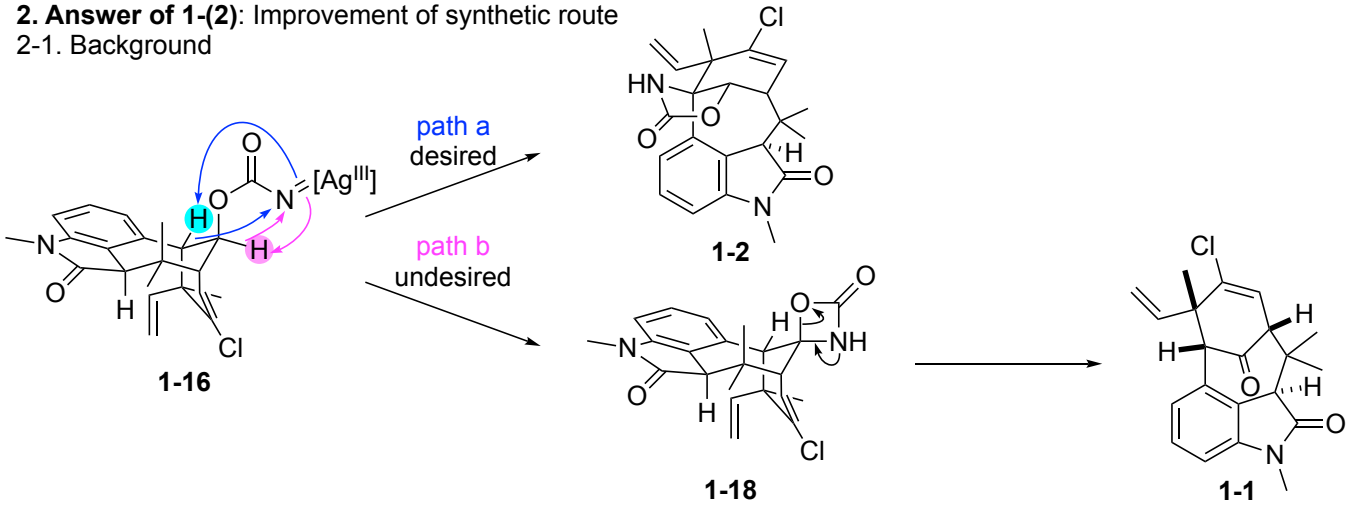


1-27 step 5 **1-28** - DMAP **1-29**



1-30 **1-3**
***N*-Methylwelwitindolinone C Isothiocyanate**

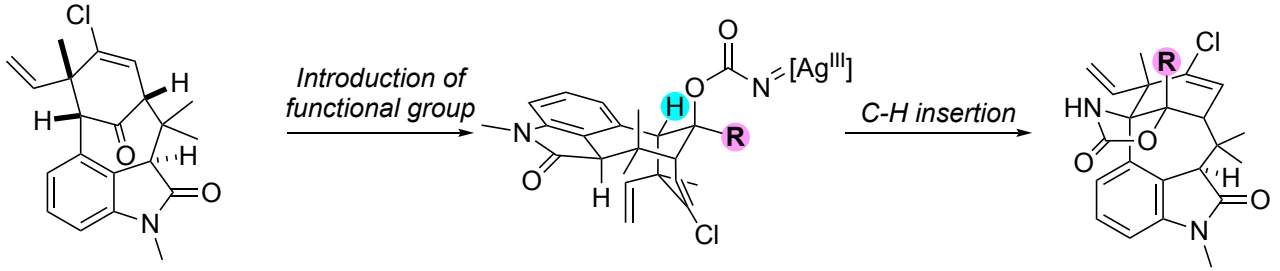
2. Answer of 1-(2): Improvement of synthetic route
2-1. Background



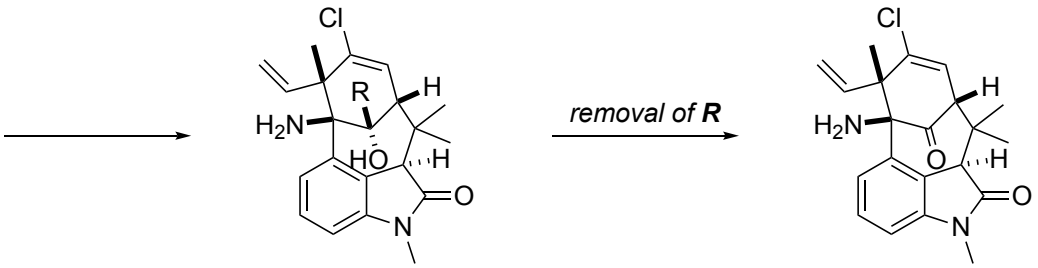
1-16 **1-2** **1-18** **1-1**

To subdue the generation of **1-1**, undesired path b must be supressed.

<Possible modification>



1-1 **1-16R** **1-2R**



1-23R **1-27**

The functional group **R** should have these features.
1. Nucleophilicity (enough to attack to ketone moiety)
2. Desorption ability or the ease of removal.

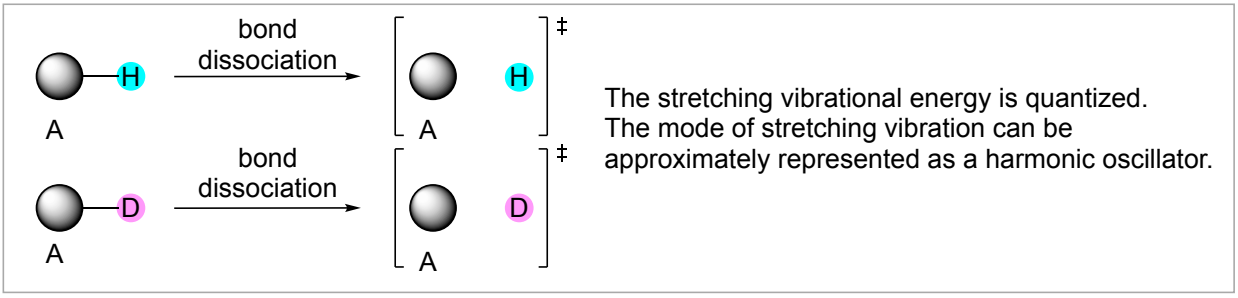
→ **Key**: Deuterium replacing as a protective group

2-2. Answer -application of kinetic isotope effect (KIE)-

2-2-1. Introduction of KIE

KIE: the change in the reaction rate of a chemical reaction when one of the atoms in the reactants is replaced by one of its isotopes. This change in reaction rate derivers from heavier isotopologues having lower vibrational frequencies compared to their lighter conterparts.

Especially for H/D substitution, most KIEs arise from the difference of zero-point energy (ZPE) between the reactants and the transition state assumuing that A-H/A-D bond dissociates completely at transition state.



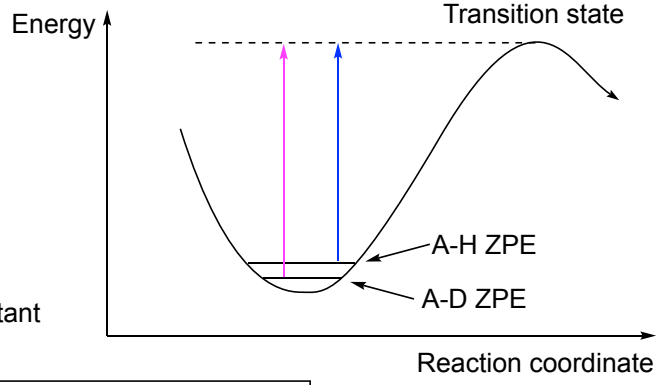
The stretching vibrational energy is quantized.
The mode of stretching vibration can be approximately represented as a harmonic oscillator.

The stretching vibrational energy can calculate with Schrödinger equation. The results are shown below. (B = H or D)

$$E_n = h\nu\left(n+\frac{1}{2}\right),\ \nu = \frac{1}{2\pi}\sqrt{\frac{k}{\mu}},\ \mu = \frac{m_A m_B}{m_A + m_B}$$

$$\therefore E_n = \frac{h}{2\pi}\sqrt{\frac{(m_A+m_B)k}{m_A m_B}}\left(n+\frac{1}{2}\right)$$

h: Plank constant, n: vibrational quantum number, k: force constant
μ: reduced mass, m_A, m_B: mass of each atom

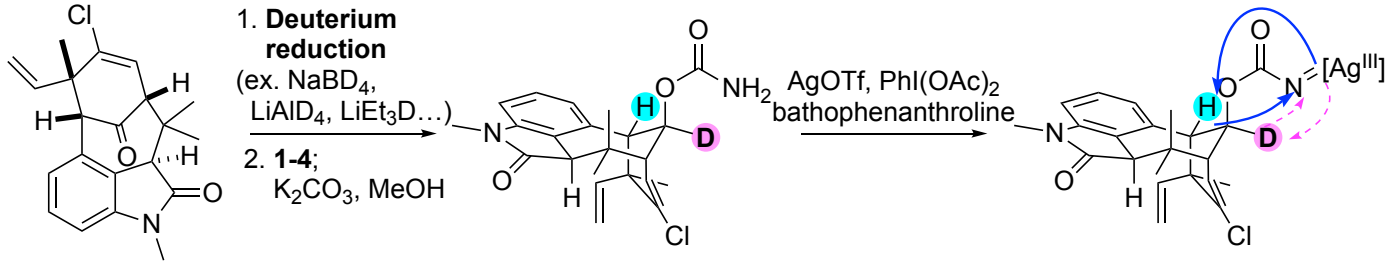


Assumuing that A is much heavier than H or D, the ZPE of A-H/A-D bonds can approximately calculate as

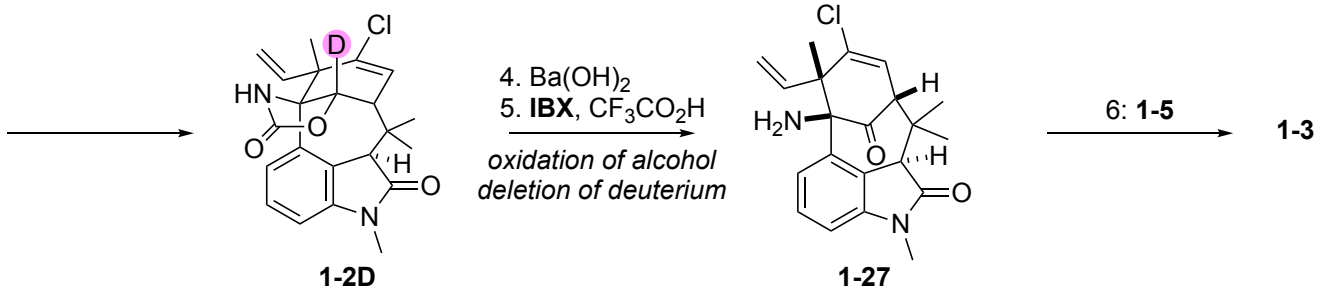
$$E_0^H \simeq \frac{h\sqrt{k}}{4\pi} \qquad E_0^D \simeq \frac{h\sqrt{2k}}{8\pi}$$

The ZPE of A-D bond is lower than that of A-H bond. It means that the energy for dissociating A-D bond is higher than A-H bond. Therefore, A-D bond is less reactive than A-H bond.

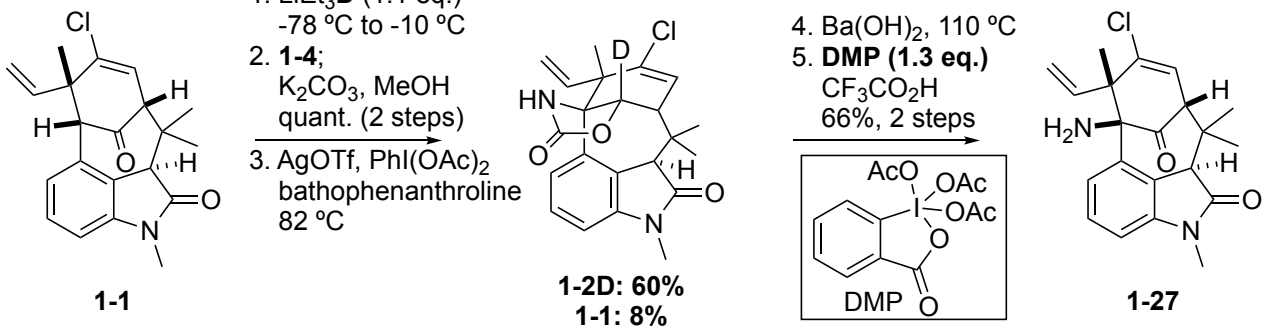
2-2-2. Answer in the problem



1-1 **1-11D** **1-16D**

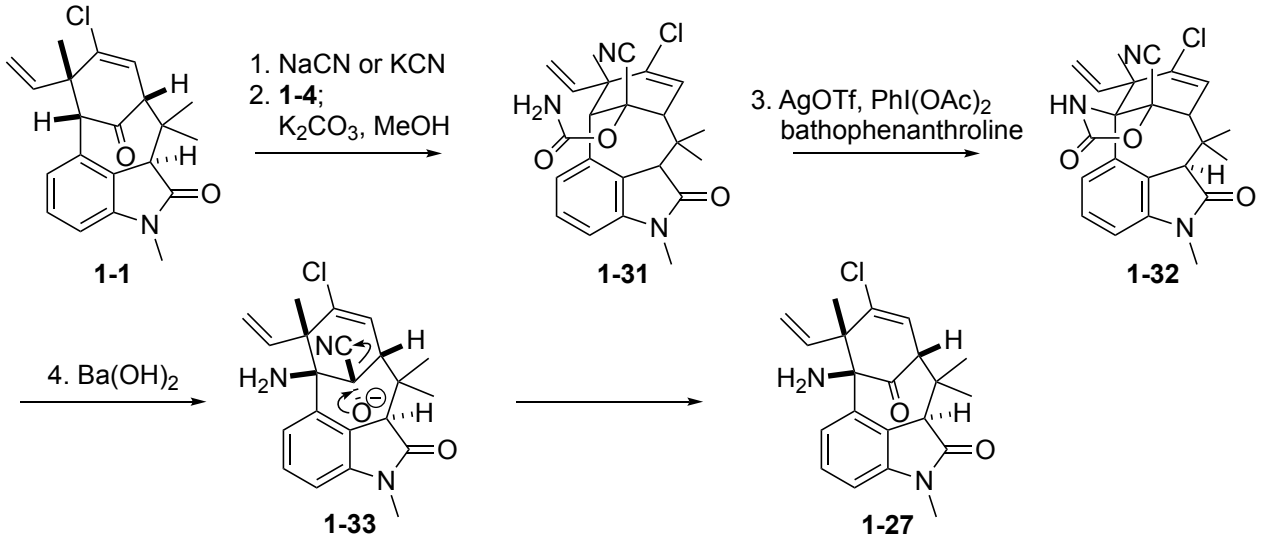


2-2-3. Garg's success



For other examples of the deuterium application in total syntheses;
Norzoanthamine (Tanino *et al*. *Science* **2004**, *305*, 495.): please see .131214_PS_Hiroyuki_Mutoh
Taxol (Baran *et al*. *J. Am. Chem. Soc*. **2020**, *142*, 10526.)

2-2-4. Possible another answer (utilization of CN)

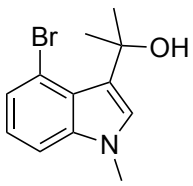


Nitrile moiety has both nucleophilicity and desorption ability. This synthetic plan is also applicable in this problem.

3. Answer of problem 2

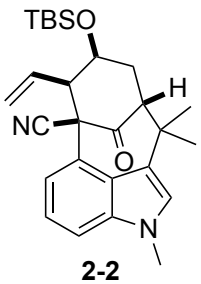
Topic: Total synthesis of *N*-Methylwelwitindolinone C isothiocyanate by Hatakeyama (2015)
Komine, K.; Nomura, Y.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2015**, *17*, 3918.

Problem 2:

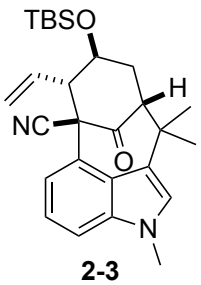


2-1

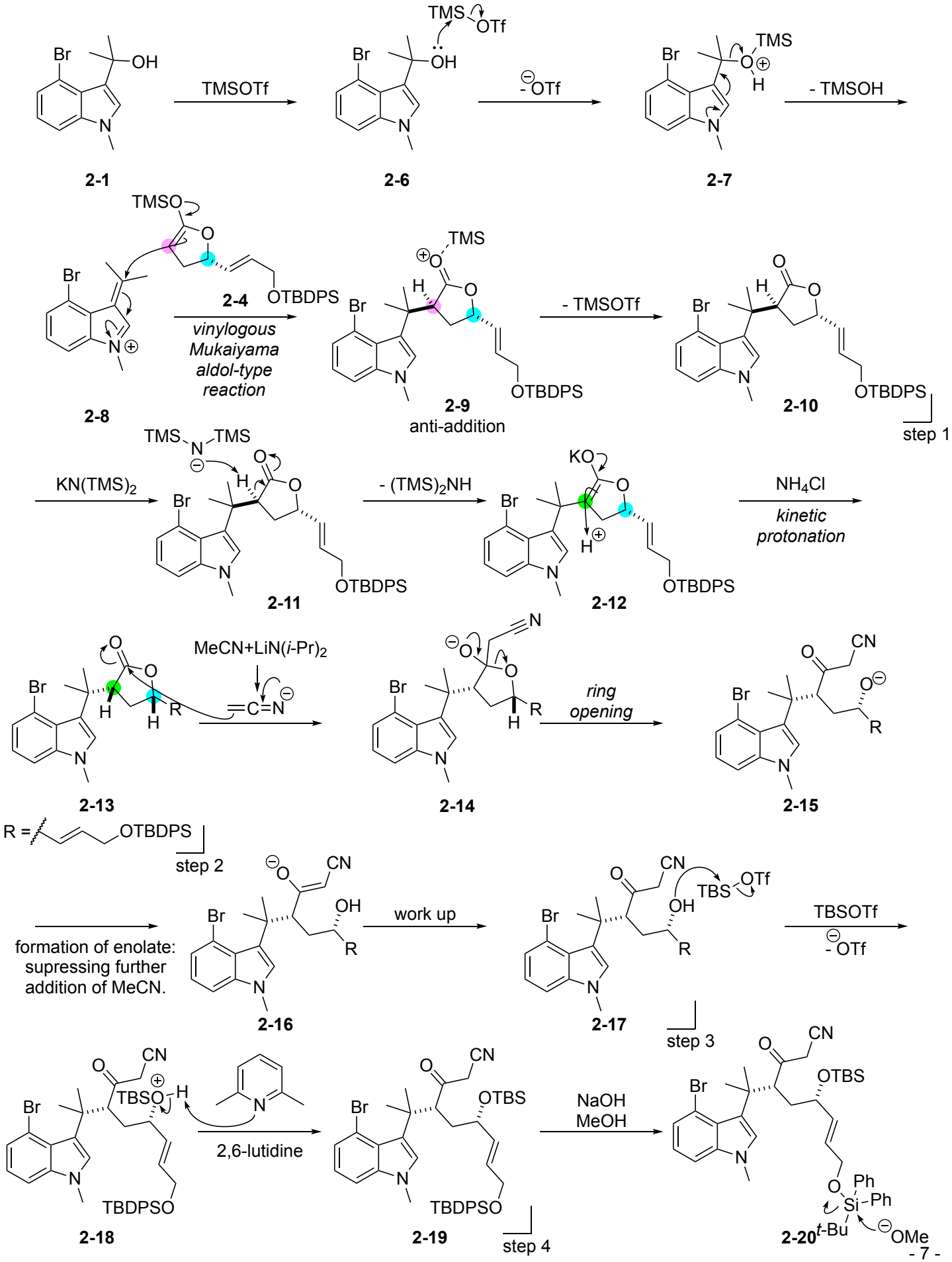
1. **2-4** (<3.0 eq.)[a)], TMSOTf (2.7 eq.), THF, -78 ºC, 82%
2. $KN(TMS)_2$ (3.0 eq.), DMF, rt;
   sat. NH_4Cl aq. at -78 ºC, 80%[b)]
3. MeCN (5.0 eq.), $LiN(i\text{-}Pr)_2$ (4.8 eq.), THF, -78 ºC[c)]
4. TBSOTf (4.0 eq.), 2,6-lutidine (5.0 eq.), CH_2Cl_2, 0 ºC
5. 10% NaOH in MeOH (calc. 24 eq.), 60 ºC, 84% (3 steps)
6. Ac_2O (6.0 eq.), Et_3N (12 eq.), DMAP (0.2 eq.)
   CH_2Cl_2, 0 ºC;
   DMAP (6.0 eq.), MeOH, 0 ºC to rt, 93%
7. $Pd_2(dba)_3$ (0.2 eq.), XPhos (0.8 eq.)
   t-BuOK (2.0 eq.), toluene, 110 ºC

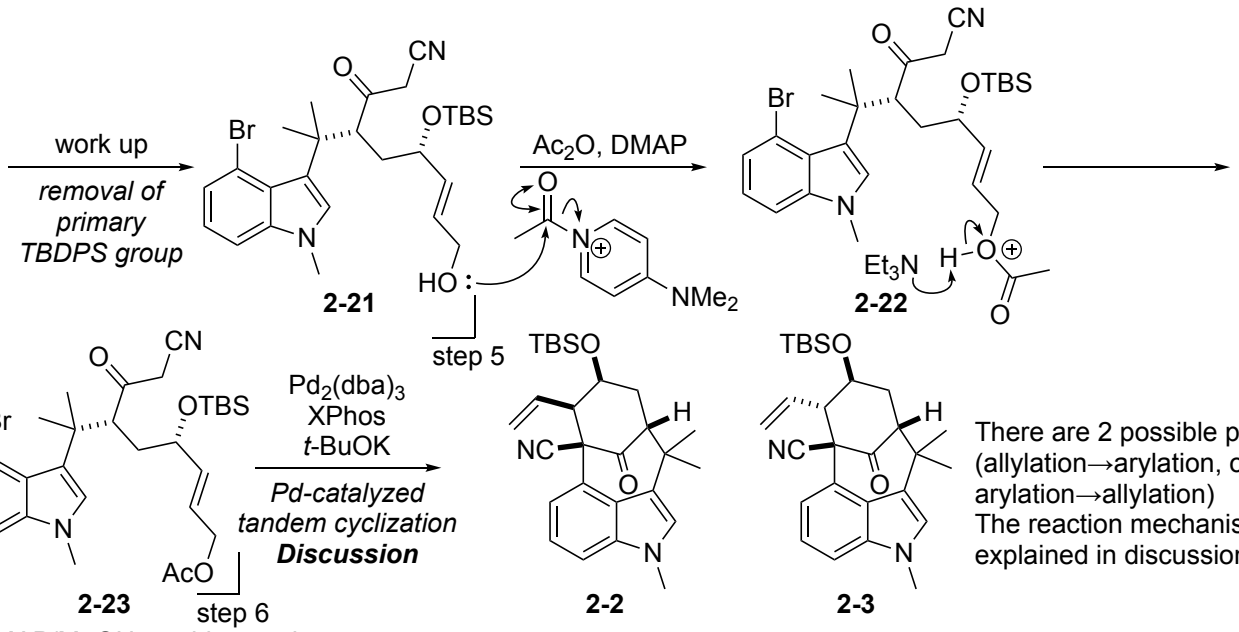


2-2
67%



2-3
33%

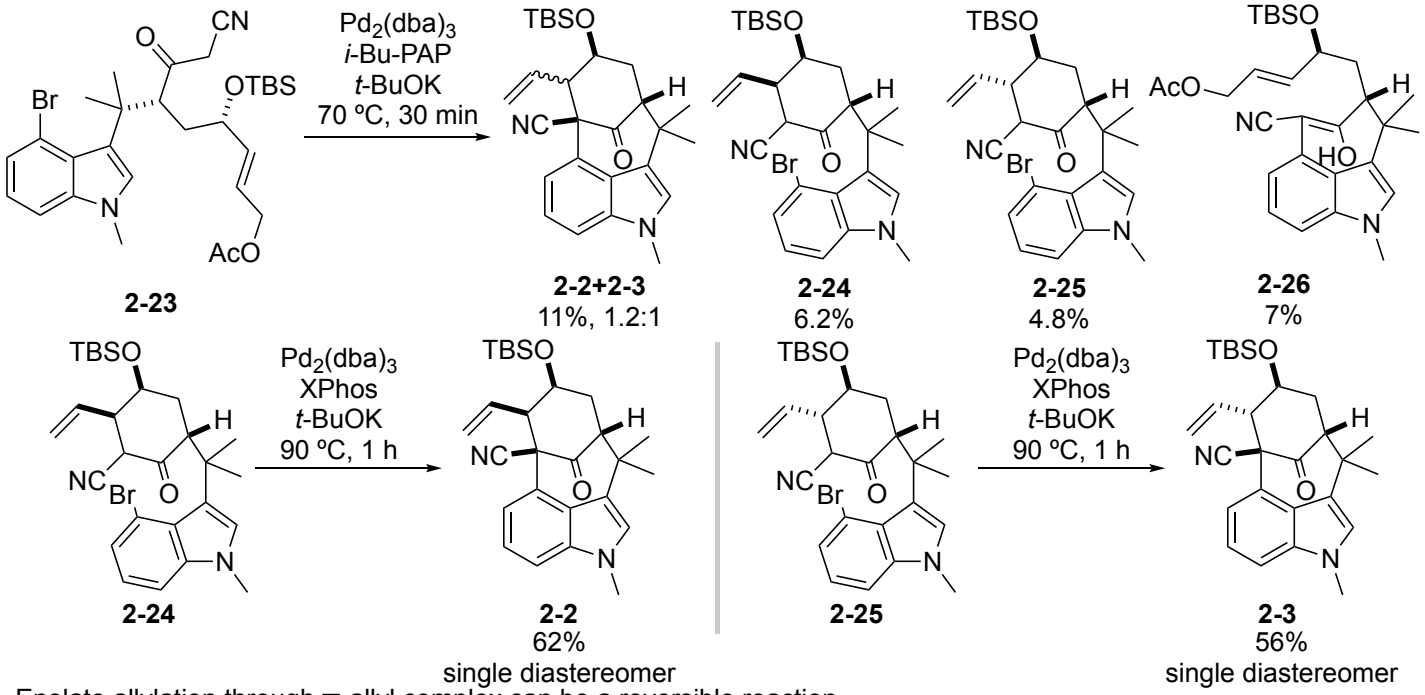

TMSOTf
- OTf
- TMSOH
2-1
2-6
2-7
2-4
OTBDPS
vinylogous Mukaiyama aldol-type reaction
2-8
2-9
anti-addition
- TMSOTf
2-10
step 1
KN(TMS)2
- (TMS)2NH
NH4Cl
kinetic protonation
2-11
2-12
MeCN+LiN(i-Pr)2
ring opening
2-13
2-14
2-15
R = OTBDPS
step 2
formation of enolate: supressing further addition of MeCN.
work up
2-16
TBSOTf
- OTf
2-17
step 3
2,6-lutidine
NaOH
MeOH
2-18
2-19
step 4
2-20
t-Bu
OMe



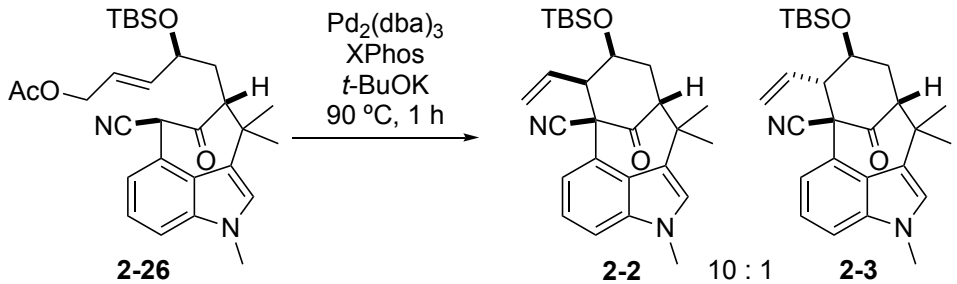
* DMAP/MeOH would quench the excess amount of Ac_2O.

4. Discussion

4-1. Experimental results



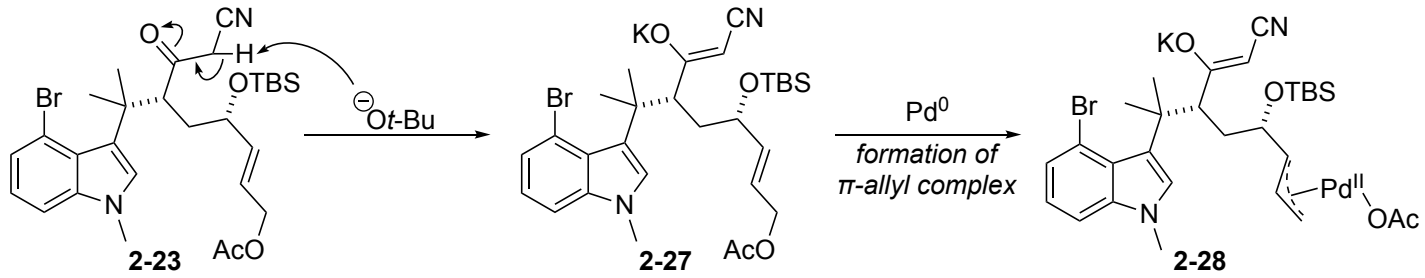
Enolate allylation through π-allyl complex can be a reversible reaction.
However, the reversible allylation will cause the epimerization at allylic position.
As a result, **2-2** and **2-3** would be obtained as a diastereo mixture from both **2-24** and **2-25**.
In this case, the results suggest that enolate allylation is irreversible. →This reaction is not thermodynamic control.

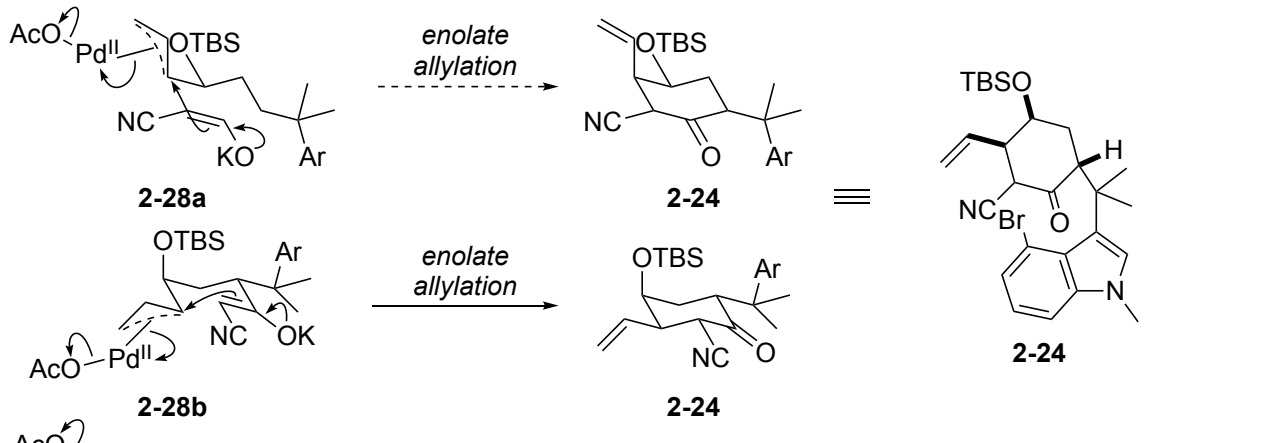


The over-all ratio of obtained **2-2** and **2-3** was 2:1. Considered the above results, allylation→arylation pathway (**2-23**→(**2-24**, **2-25**)→**2-2**, **2-3**) should be relatively dominant. But the reaction rate is almost the same.

4-2. Reaction mechanism

4-2-1. Allylation→arylation pathway

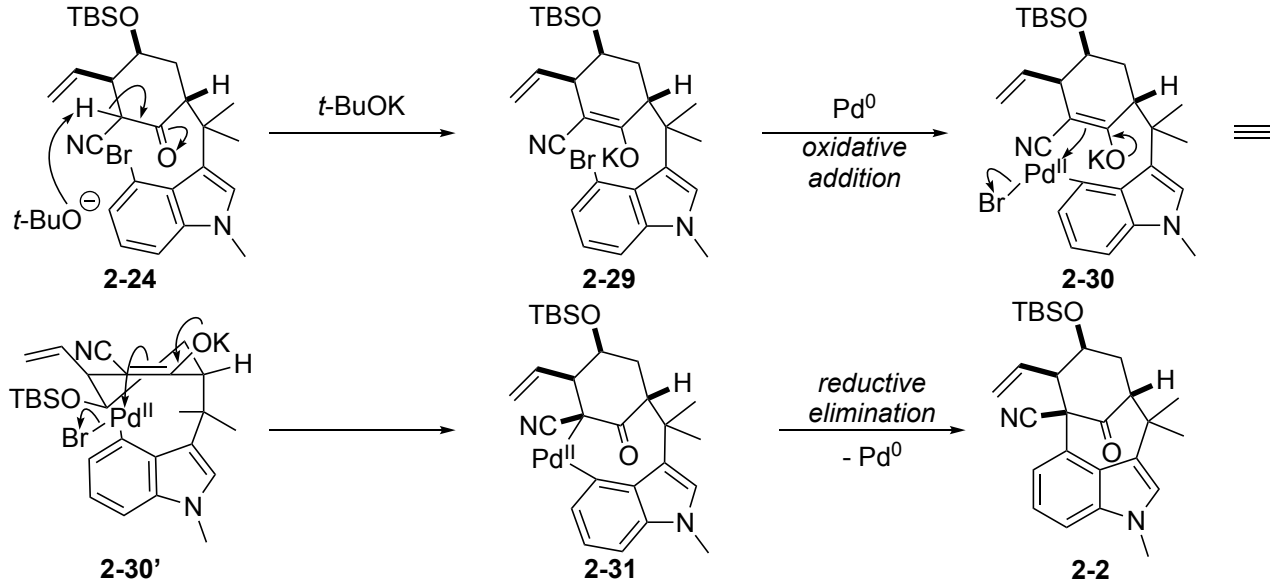


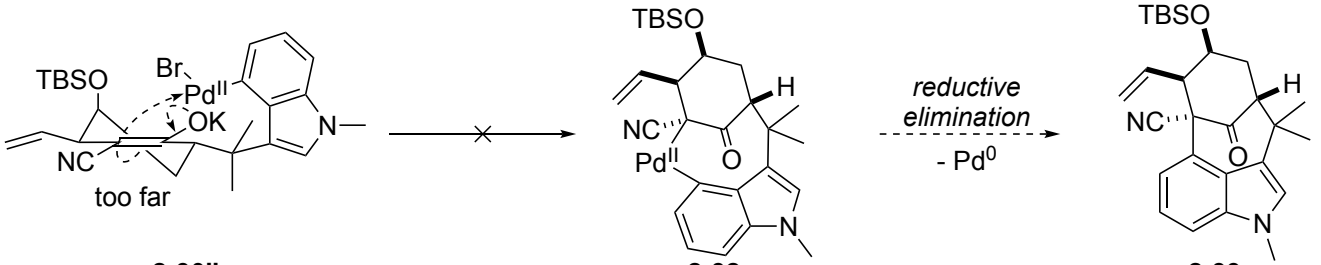


A values (kcal/mol)
OTMS: 0.74
$CH{=}CH_2$: 1.35
$CH(CH_3)_2$: 2.15

The most bulky dimethyl Ar group should be equatorial position.
Both boat formation (**2-28a** and **2-28c**) and chair formation (**2-28b** and **2-28d**) are conceivable.
Considering A-value and the bulkiness of π-allyl complex, **2-28b** and **2-28c** may be dominat pathway. Also, almost no stereoselectivity is observed.

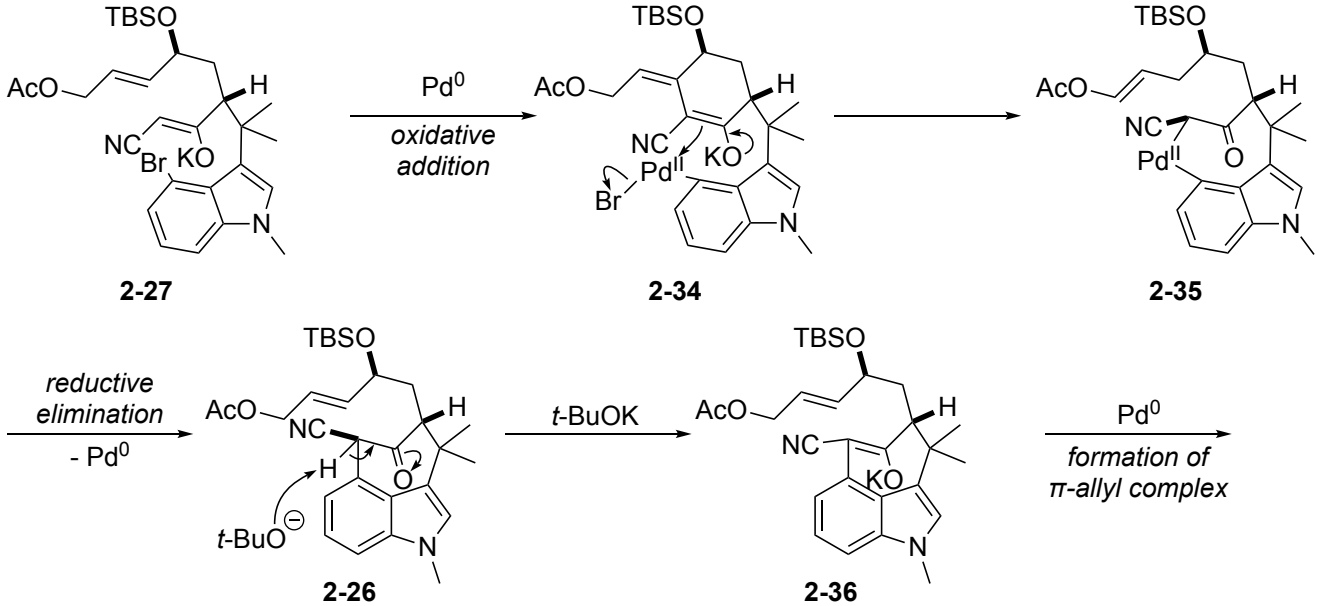
<Arylation of **2-24**>

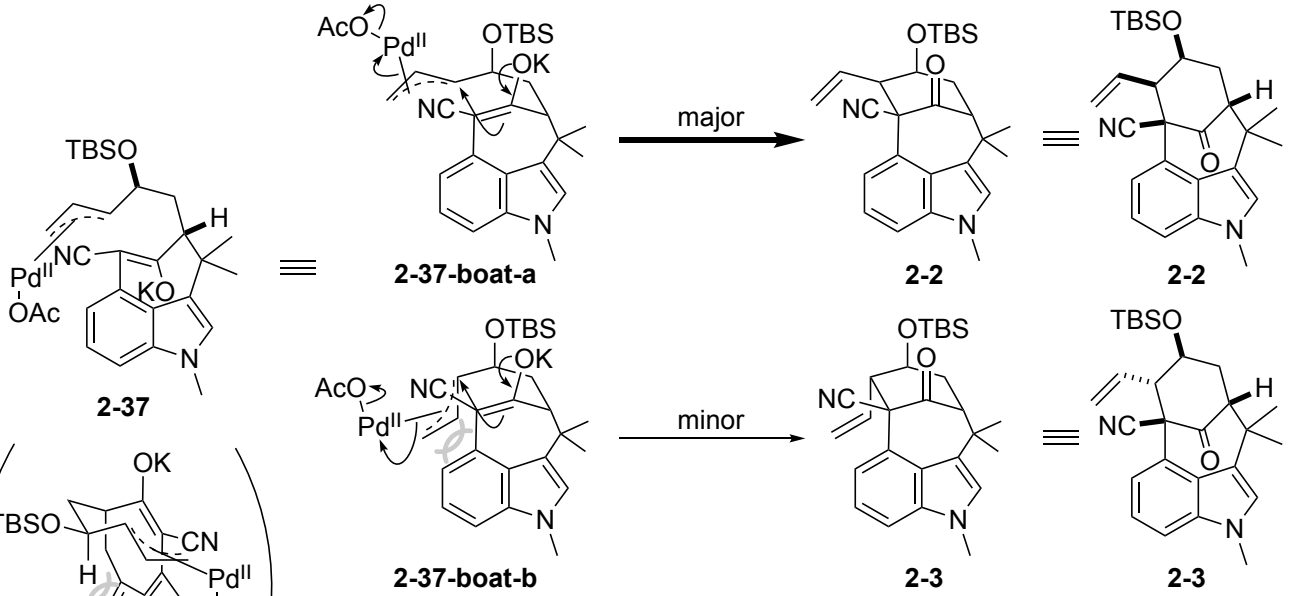


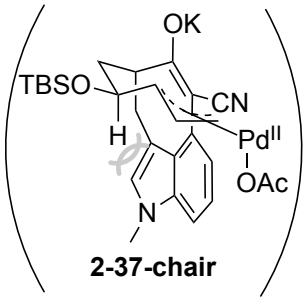


Arylation of **2-25** proceeds with the same manner and **2-3** is obtained.

4-2-2. Arylation→allylation pathway







2-37-chair has a strong transannular-type strain, while **2-37-boat** doesn't.
Although TBSO group locates on axial position,
diaxial strain would not affect strongly in this case.