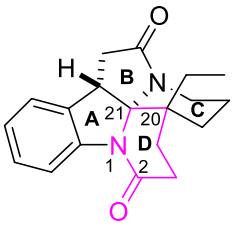
Problem Session (1) - Answer

2020/1/11 Takeuchi Aoi

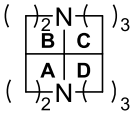
Topic: Total synthesis of leuconoxine alkaloid



leuconoxine

isolation
from *Leuconotis eugenifolius* (plants inhabiting Indonesia, and Malaysia)
by Abe and Yamauchi (1994)
Abe, F.; Yamauchi, T. *Phytochemistry,* **1994**, *35*, 169.

structural features
pentacyclic indole alkaloid
[5.5.6.6] diazafenestrane core
two contiguous quaternary stereogenic centers



biological activity not reported

total synthesis 7 reports so far

asymmetric: Zhu, Kawasaki, Gaich, and Wang

Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 19127.

Higuchi, K.; Suzuki, S.; Ueda, R.; Oshima, N.; Kobayashi, E.; Tayu, M.; Kawasaki, T. *Org. Lett.* **2015**, *17*, 154.

Pfaffenbach, M.; Gaich, T. *Chem. Eur. J.* **2015**, *21*, 6355.

Liu, Y.; Wang, H. *Chem. Commun.* **2019**, *55*, 3544

racemic: Tokuyama, Dai, and Liang

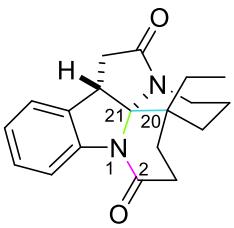
Umehara, A.; Ueda, H.; Tokuyama, H. *Org. Lett.* **2014**, *16*, 2526.

Yang, Y.; Bai, Y.; Sun, S.; Dai, M. *Org. Lett.* **2014**, *16*, 6216.

Li, Z.; Geng, Q.; Lv, Z.; Pritchett, B. P.; Baba, K.; Numajiri, Y.; Stoltz, B. M.; Liang, G. *Org. Chem. Front.* **2015**, *2*, 236

For details of Zhu's strategy, see also LS_Yuki_Matsui_140116.

strategy of construction of the δ-lactam skeleton



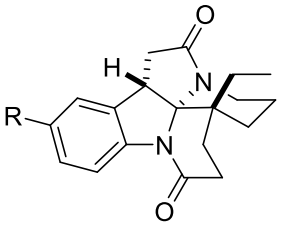
N1-C2 bond
amidation of ester
Zhu, Kawasaki, Liang

oxidative amidation of alcohol with indole NH
Gaich, Wang

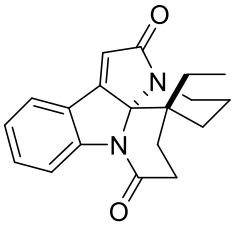
C20-C21 bond
Heck cross-coupling
Tokuyama

N1-C21 bond
transannular cyclization of an aryl amide with ketone
Dai → **Question 2**

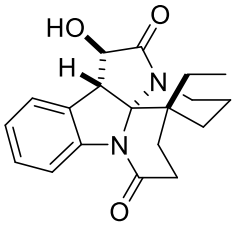
leuconoxine subfamily



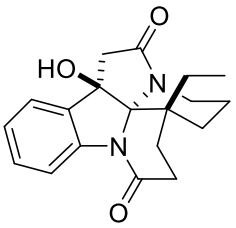
leuconoxine (R = H)
leuconodine C (R = OH)



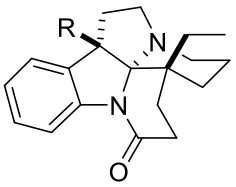
melodinine E



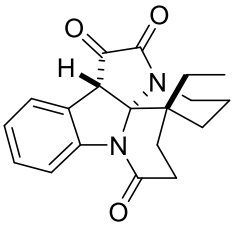
leuconodine A



leuconodine B



leuconodine D (R = H)
leuconodine E (R = OH)



leuconodine F

bioactivity

leuconodine B,D: moderate to weak cytotoxicity to KB cells

leuconodine E: moderate actitivity in reversing multidrug resistance in vincristine-resistant KB cells (IC_{50} = 9.34 μg/mL in 0.1 μg/mL vincristine)

Gan, C.-Y.; Low, Y.-Y.; Thomas, N. F.;Kam, T.-S. *J. Nat. Prod.* **2013**, *76*, 957.

total synthesis

melodinine E: Zhu(2013), Tokuyama(2014), Dai (2014), Wang (2019)
leuconodine A: Zhu (2015)
leuconodine B: Zhu(2013), Tokuyama(2014), Dai (2014)
leuconodine C: Zhu (2015)
leuconodine D: Dai (2016), Han (2019)
leuconodine E: Han (2019) ⟶ **Question 1**
leuconodine F: Zhu (2015)

Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 19127.
Umehara, A.; Ueda, H.; Tokuyama, H. *Org. Lett*. **2014**, *16*, 2526.
Yang, Y.; Bai, Y.; Sun, S.; Dai, M. *Org. Lett*. **2014**, *16*, 6216.
Liu, Y.; Wang, H. *Chem. Commun.* **2019**, *55*, 3544.
Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2015**, *137*, 6712.
Jing, Z.; Fu-She H. *J. Am. Chem. Soc.* **2019**, *84*, 13890.

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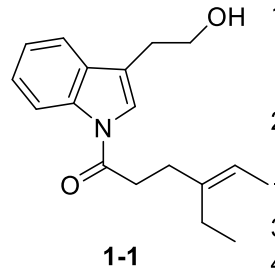
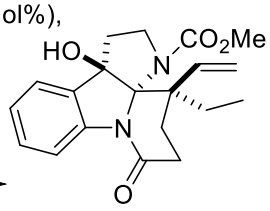
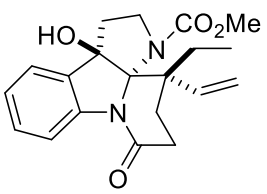


1-1

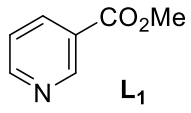
1. $Pd(OAc)_2$ (10 mol%), **L_1** (40 mol%), **L_2** (10 mol%), O_2 (balloon), *t*-$BuCO_2H$ (30 eq.), mesitylene, 95 °C, 88%
2. **L_3** (1.5 eq.), DEAD (2.0 eq.), Ph_3P (2.0 eq.), THF, rt.; then $NaHCO_3$ aq. quant.
3. PhSH (1.0 eq.), K_2CO_3 (3.0 eq.), DMF, rt, 85%
4. oxone (4.0 eq.), $NaHCO_3$ aq./acetone (1/1, 30 mM), 0°C; then HCl aq. 80%



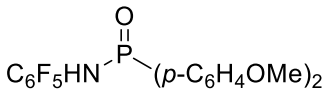
1-2 (dr = 1:1)



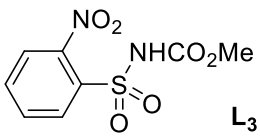
1-3



L_1



L_2



L_3

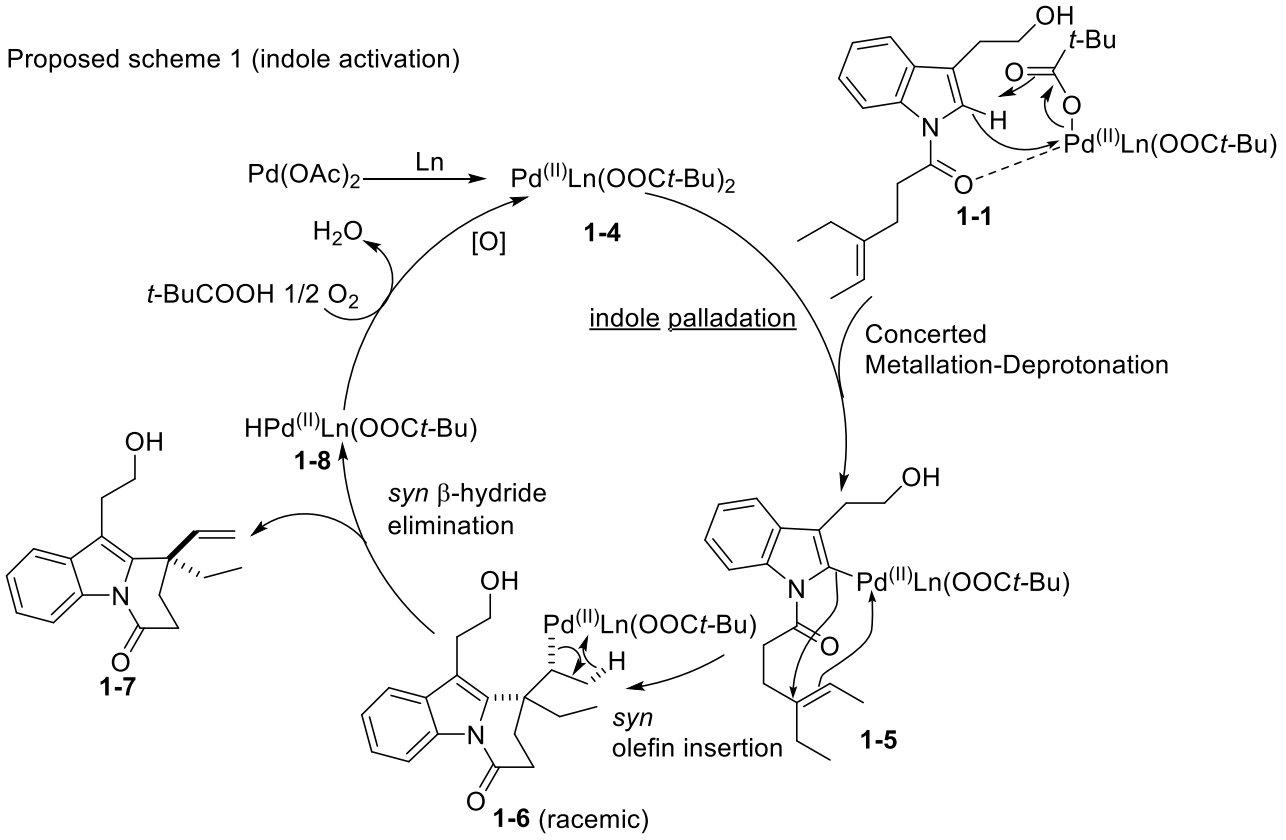
Jing, Z.; Fu-She H. *J. Org. Chem*. **2019**, *84*, 13890.

Step 1: oxidative Heck cross-coupling

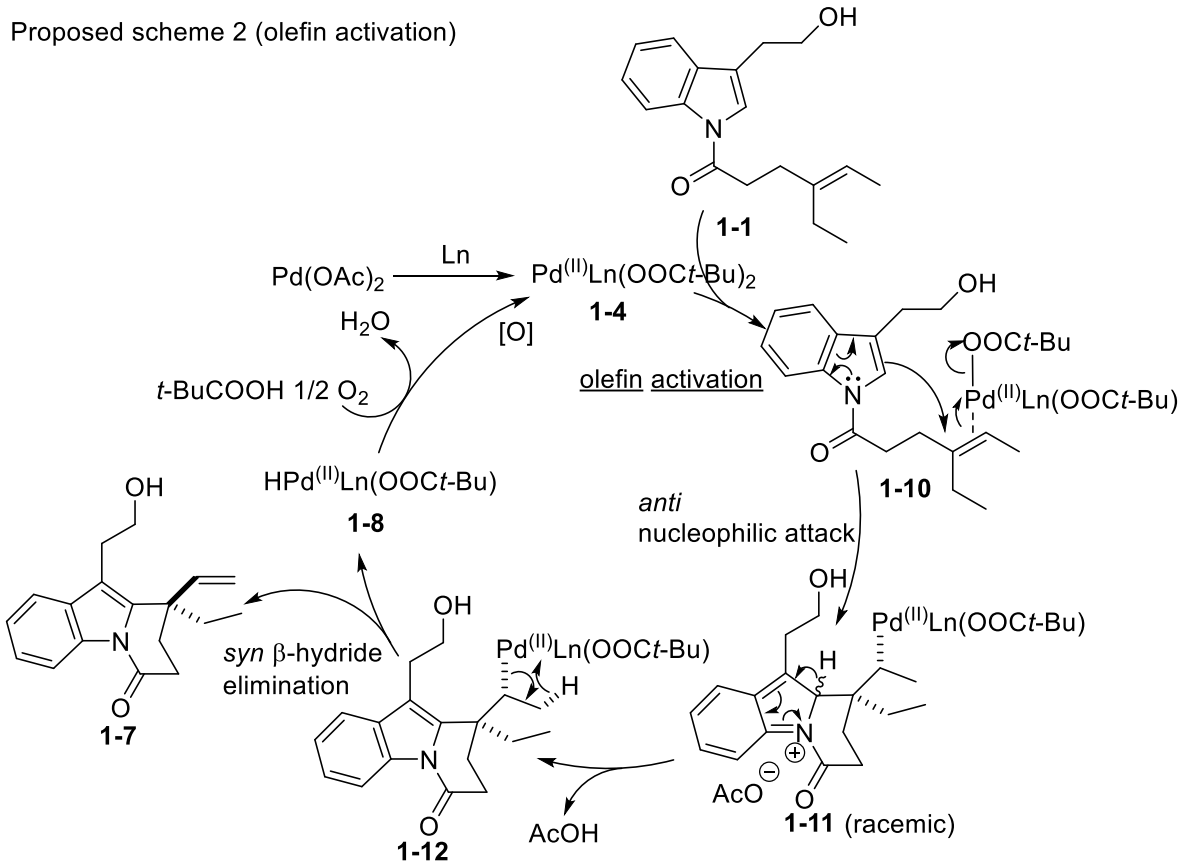
2 possible schemes are shown in the next page.

It is discussed which is a more likely pathway in ***discussion -1***.

Proposed scheme 1 (indole activation)

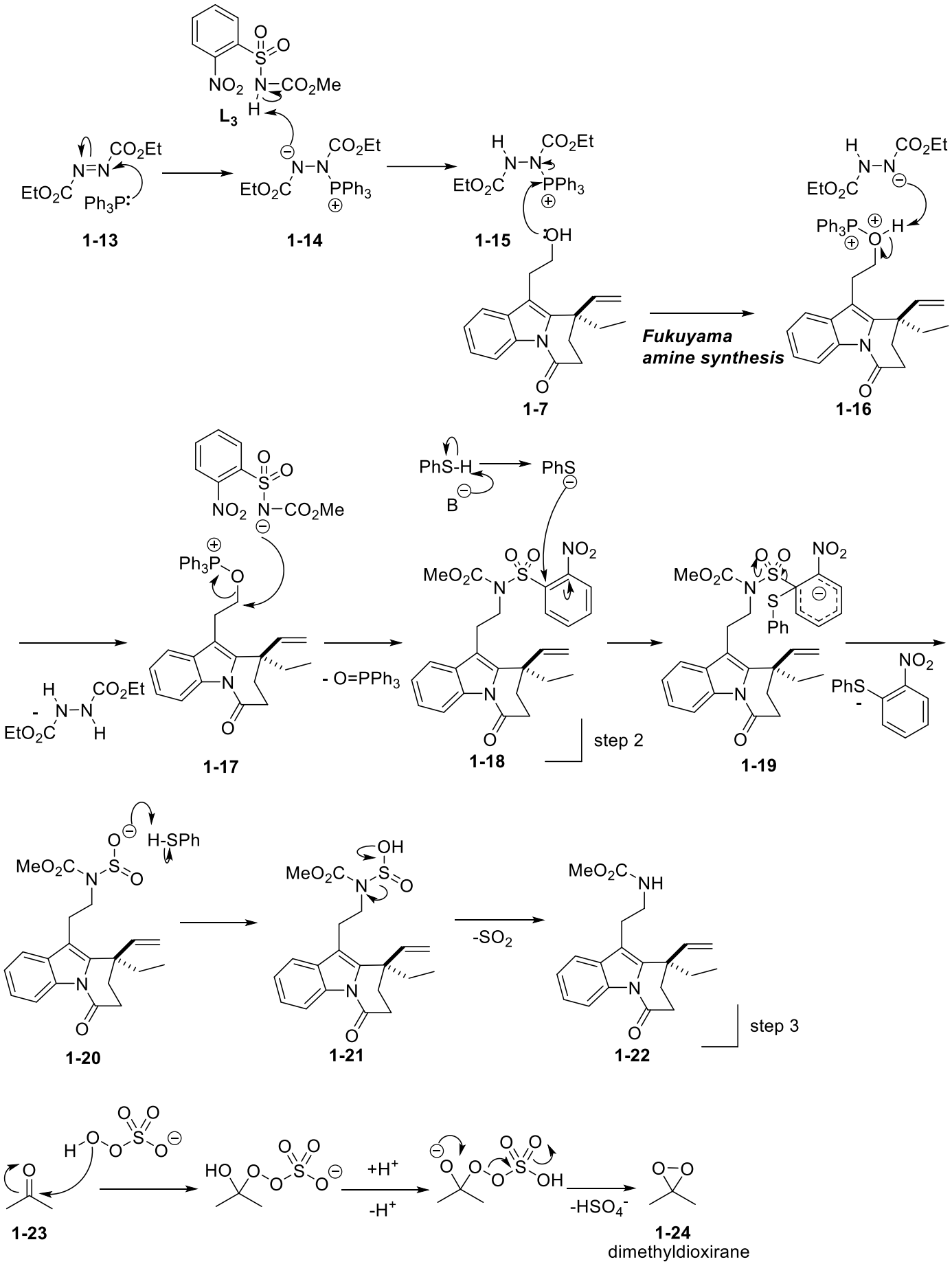


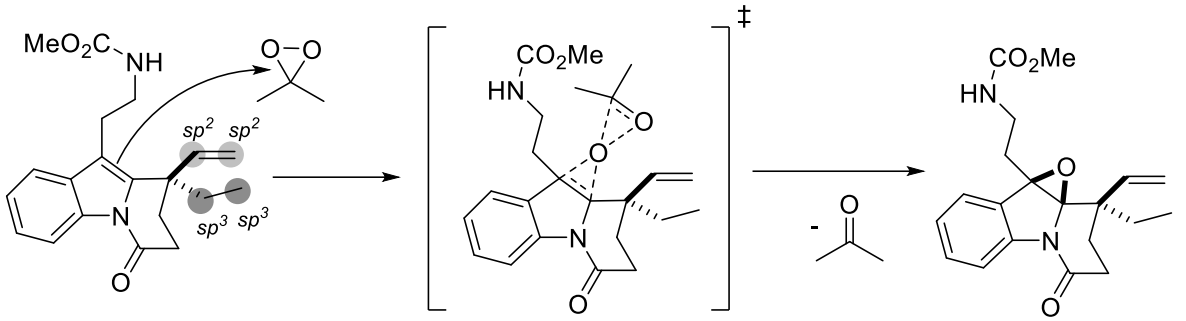
Proposed scheme 2 (olefin activation)

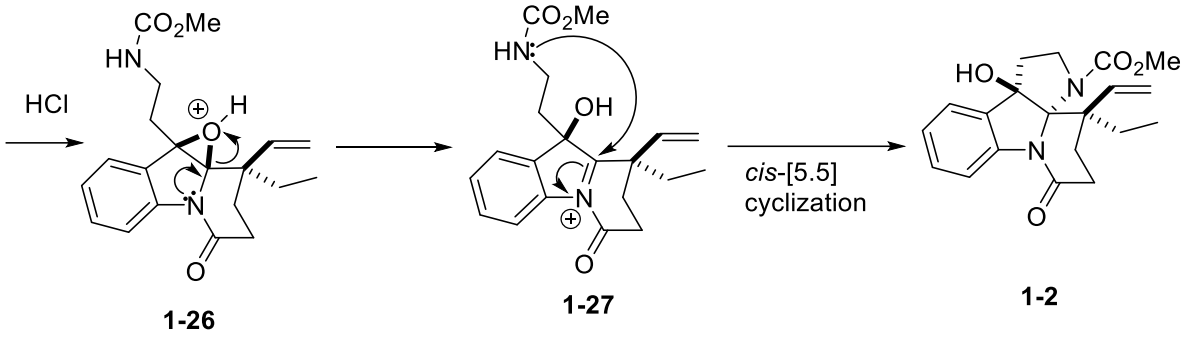


Ligand scopes by Stolz group revealed that oxidative cyclization to annulated indole occurred with pyridine as a ligand. The electronic properties of pyridine itself is not so suited that the catalytic center is sufficiently election-deficient for substrate activation. electronically altered pyridines: an electron−withdrawing carboxyl group at C3 (**L_1**) makes pyridines excellent ligands in these oxidative C–C bond formations.

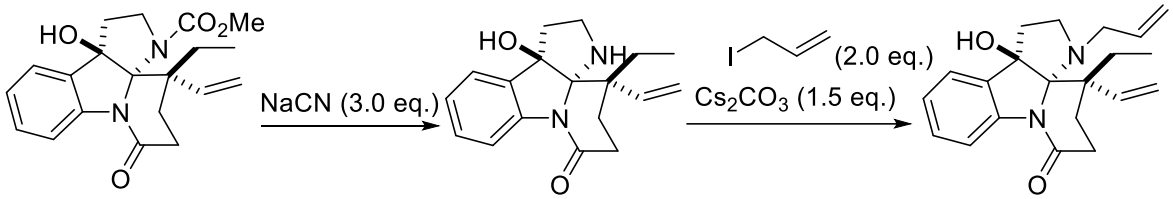
Ferreira, E.M.; Zhang, H.; Stoltz, B.M. *Tetrahedron*, **2008**, *64*, 5987-6001

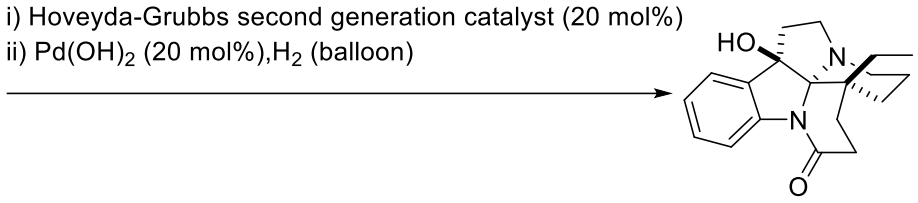

L3
1-13
1-14
1-15
1-7
Fukuyama
amine synthesis
1-16
1-17
- O=PPh3
1-18
step 2
1-19
1-20
1-21
-SO2
1-22
step 3
1-23
+H+
-H+
-HSO4-
1-24
dimethyldioxirane





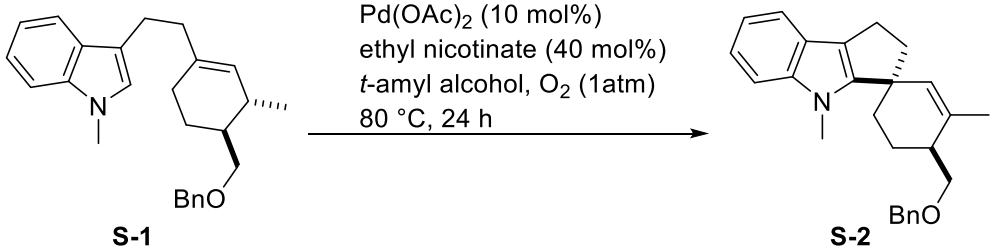
Leuconodine E was obtained from **1-3** in 4 steps.





Discussion-1 Determination of reacting mechanism of step 1.

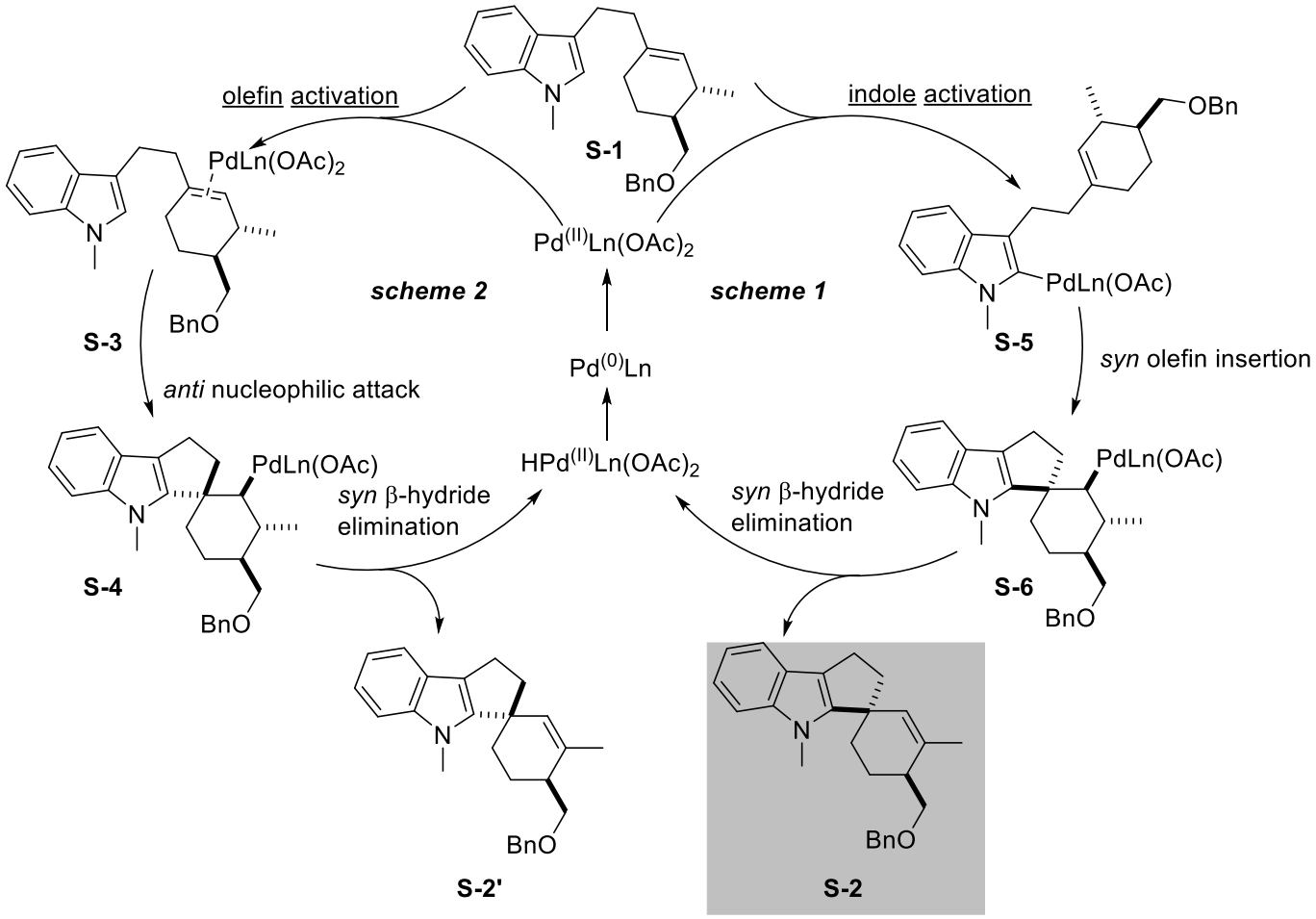
- In order to differentiate between 2 possible pathways, mechanistic probe **S-1** was designed by Stoltz team. **S-1** was subjected to indole annulation conditions and single diastereomer **S-2** was obtained.



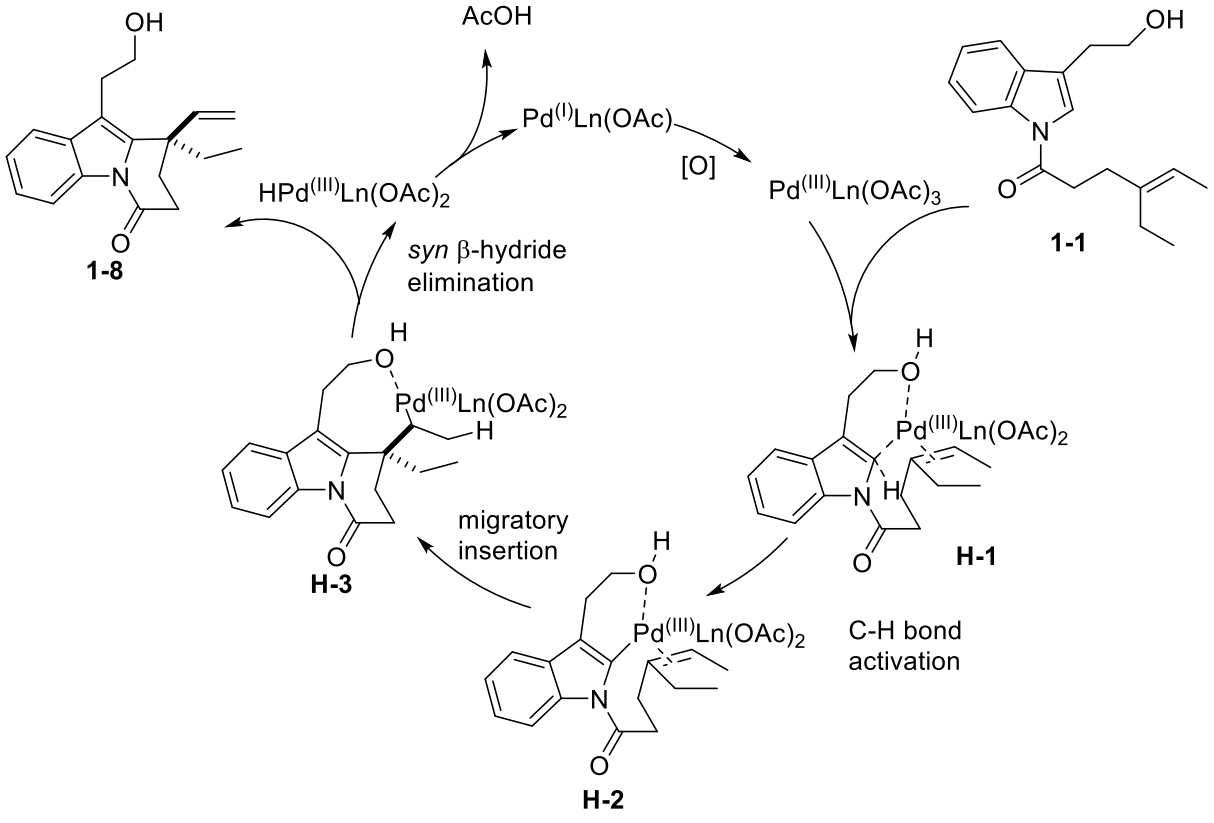
57% single diastereomer

Ferreira, E.M.; Zhang, H.; Stoltz, B.M. *Tetrahedron*, **2008**, *64*, 5987-6001

Chirality of the product **S-2** suggested indole annulation was proceeding in scheme 1. (see page 6)



■ Proposed scheme by Han



The author proposed Pd(I)/Pd(III) mechanism based on following experimental results;

1. Pd-containing species detection on HRMS under O_2 atmosphere revealed 4 strong peaks, which are assigned to Pd(III) or Pd(II) complexes. Considering Pd(II) complex mainly observed under Ar atmosphere, it is notable that Pd(II) species got oxidized to generate Pd(III) complex.

m/z	assigned species	Ar atmosphere
365.9951	$[Pd^{(III)}(MeCO_2^-)_2(t\text{-}BuCO_2^-)(H_2O)Na^+]$ (365.9901)	Not observed
385.0353	$[Pd^{(II)}(t\text{-}BuCO_2^-)\mathbf{L_1}(H_2O)Na^+]$ (385.0374)	strong
468.0598	$[Pd^{(III)}(MeCO_2^-)_2(t\text{-}BuCO_2^-)(t\text{-}BuCO_2H)(H_2O)Na^+]$(468.0582), $[Pd^{(II)}(t\text{-}BuCO_2^-)\mathbf{L_1}Na^+]$ (468.0609)	weak
481.0558	$[Pd^{(III)}(MeCO_2^-)_2(t\text{-}BuCO_2H)\ (H_2O)\mathbf{L_1}]$ (481.0559), $[Pd^{(II)}(t\text{-}BuCO_2^-)(\mathbf{L_1})_2]$ (481.0586)	weak

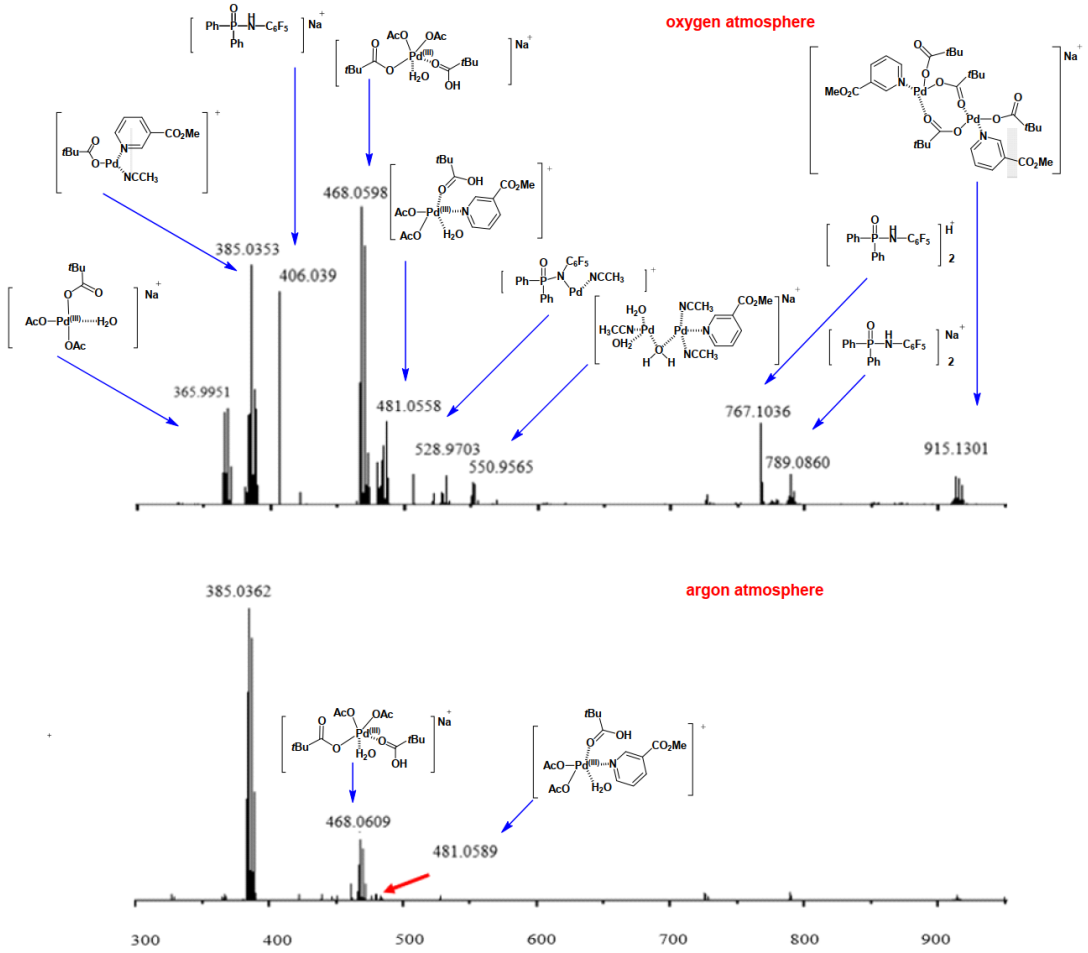


Figure 1. HRMS spectra for the reaction mixture under oxygen atmosphere (upper) and argon atmosphere (lower) after reacted at 130 °C for 1 h.

2. Reaction solution color changed from pale yellow to deep red-brown, which typically indicates the generation of $Pd^{(III)}$

Powers, D.; Ritter, T. *Nature Chem,* **2009**, *1*, 302–309

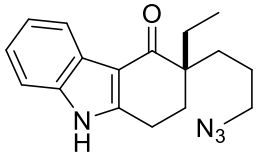
Powers, D. C.; Geibel, M. A. L.; Klein, J. E. M. N.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 17050– 17051

These information just implied the existence of Pd(III) complex, however, did not support Pd(III) complex behave as active species. As previously Pd(0)/Pd(II) cycle was reported for five-membered cyclization of indole, the reaction mechanism was proposed as above in this session.

Ferreira, E.M.; Zhang, H.; Stoltz, B.M. *Tetrahedron*, **2008**, *64*, 5987-6001

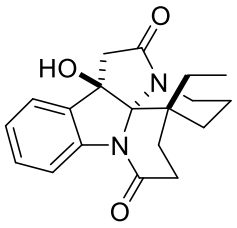
Kandukuri, S.R.; Schiffner, J.A.; Oestreich, M. *Angew. Chem. Int. Ed.*, **2012**, *51*,1265-1269

(2)



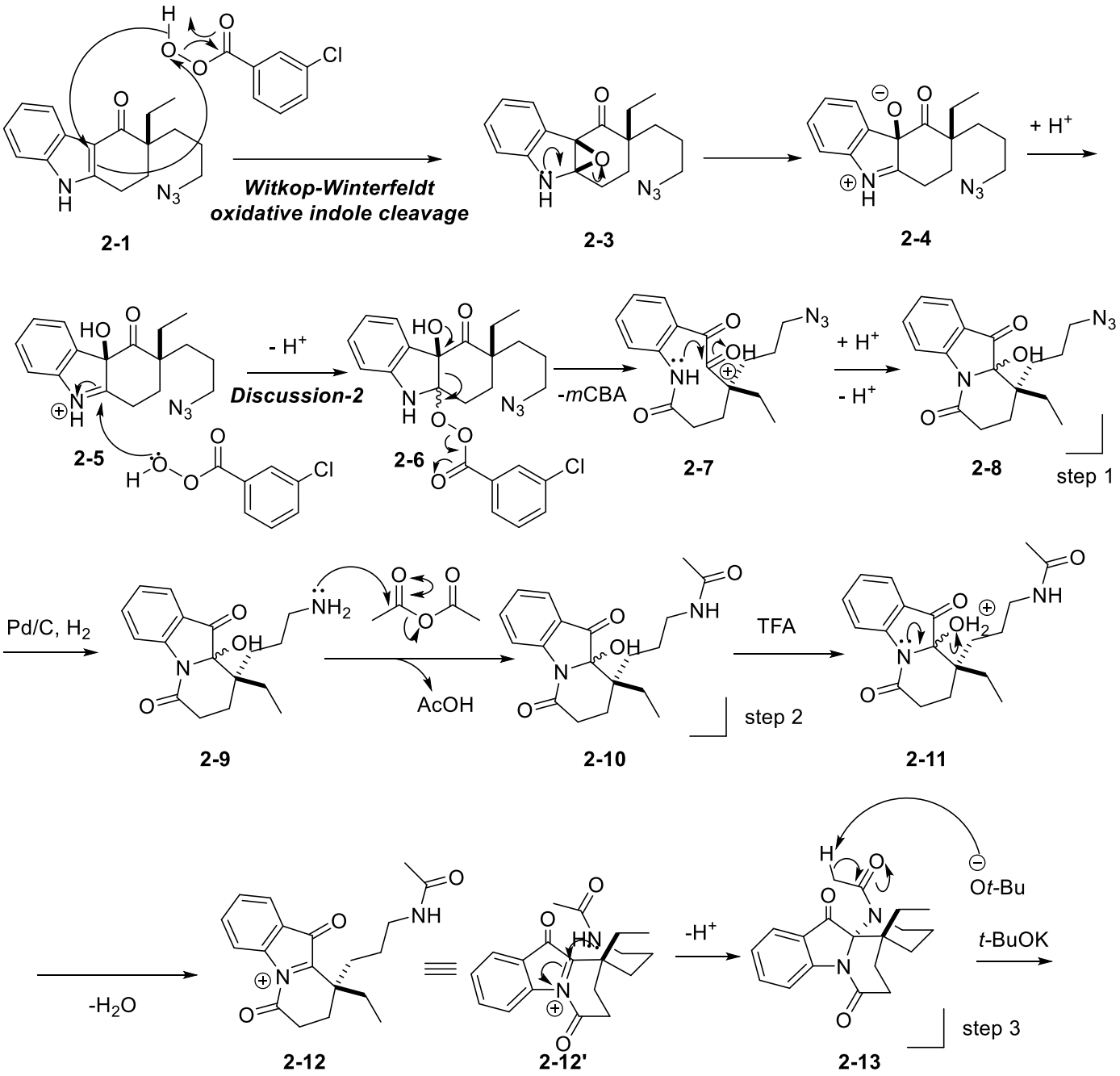
2-1

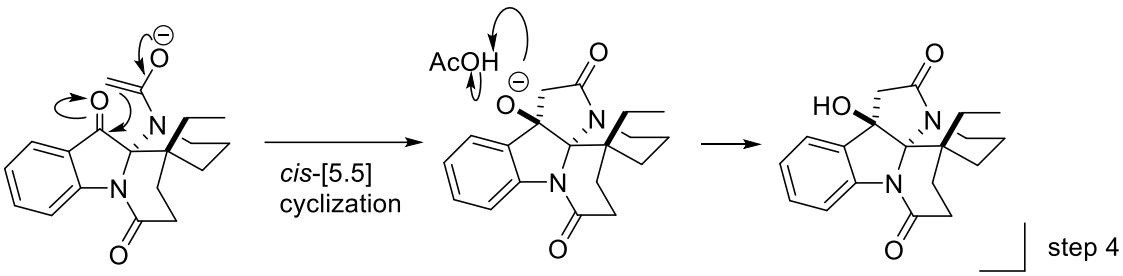
1. *m*CPBA (2.5 eq), $CHCl_3$, rt
2. Pd/C (10 mol%), H_2, Ac_2O (3.0 eq), NaOAc (5.0 eq), EtOAc, rt
3. TFA/CH_2Cl_2 (1/1, 0.1 M), rt, 30% over 3 steps
4. *t*-BuOK (7.1 eq), THF, -50 °C to -78 °C
   then AcOH (15 eq), -78 °C, 85%



2-2

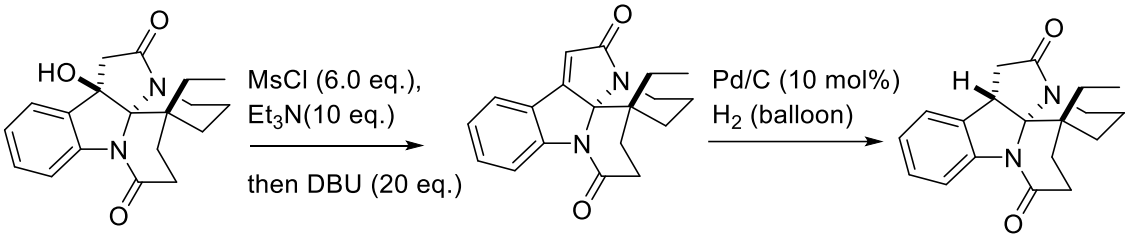
Yang, Y.; Bai, Y.; Sun, S.; Dai, M. *Org. Lett.* **2014**, *16*, 6216.





2-14 **2-15** **2-2**

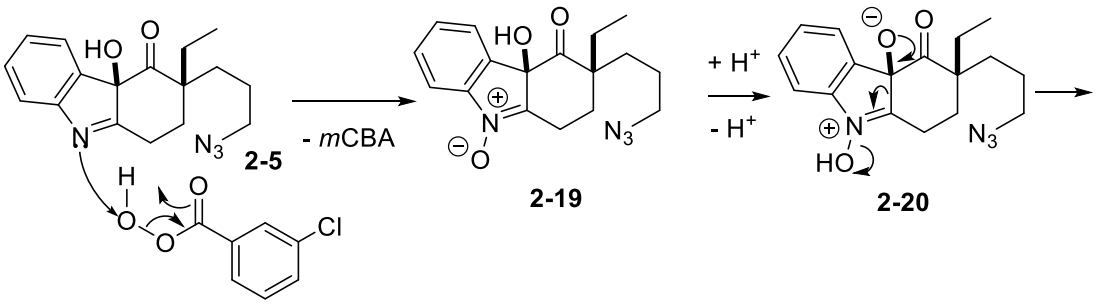
Leuconoxine was obtained from **2-2** in 2 steps. Detailed reaction mechanisms are introduced in LS_140116.



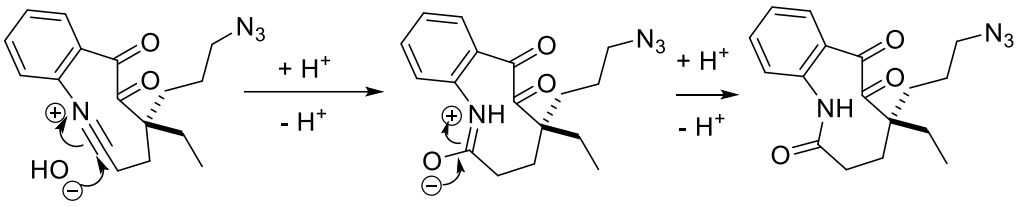
2-2 **2-18** **Leuconoxine**

Discussion-2

Oxidative indole cleavage (**2-5** to **2-7**) can be described in a mechanism via N-oxide.

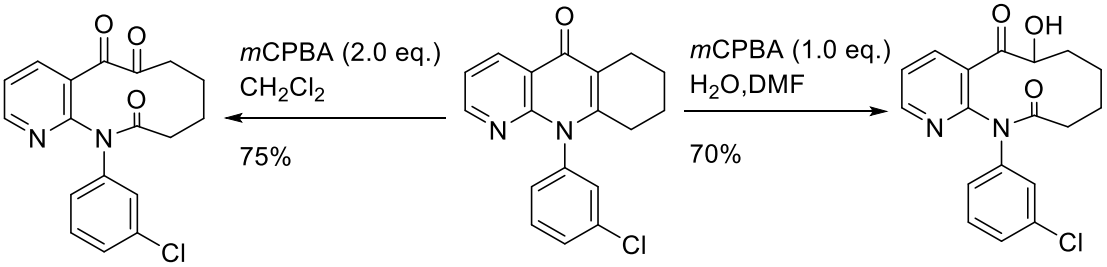


2-5 **2-19** **2-20**



2-21 **2-22** **2-7**

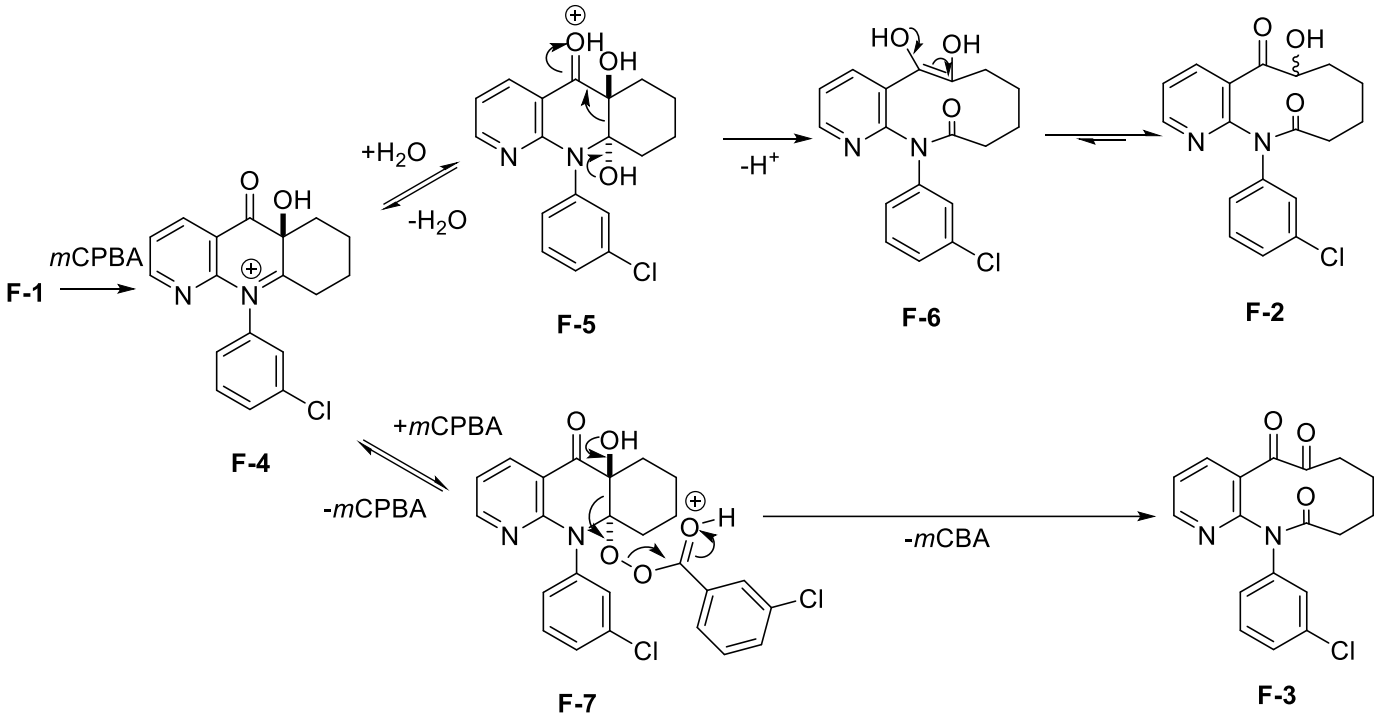
■ Oxidative cleavage of a tricyclic pyridone



F-3 **F-1** **F-2**

Friary, R.; Schwerdt, J. *Tetrahedron*, **1991**,*47*, 9981.

Proposed reaction mechanism



The cleavage from **F-4** to **F-2** or **F-3** got triggered with addition of nucleophile to the iminium ion. It is supposed oxidative indole cleavage (**2-5** to **2-7**) also proceeds in the similar mechanism.