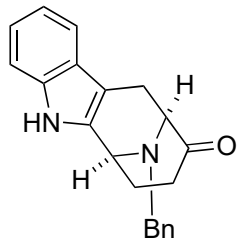
Problem Session (2)

20171209 Shimizu Shinsuke

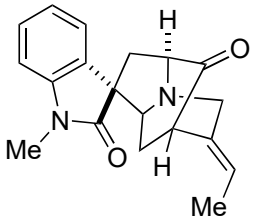
Please fill in the blank and provide following reaction mechanisms

Problem 1



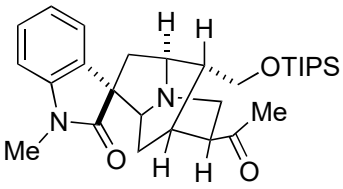
1-1

1. *t*-BuOCl, Et_3N, CH_2Cl_2, 0°C
   ; AcOH aq./MeOH, reflux (93%)
2. NaH, THF, 0 °C
   ; MeI, THF, 0 to rt (87%)
3. CAN, CH_3CN/H_2O, rt (60%)
4. **1-A**, *i*-Pr_2EtN, 55 °C (91%)
5. $Pd_2(dba)_3$ (40 mol%)
   $NaN(TMS)_2$, THF, rt (80%)



1-2

1-2 ⟶

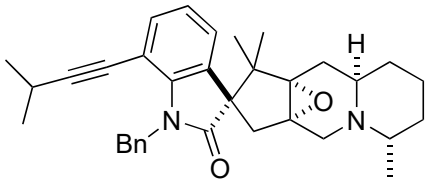


1-3
($C_{29}H_{44}N_2O_3Si$)

6. MeI, neat, 70 °C
   ; evp; $NaN(TMS)_2$ (2 eq), THF, rt (80%)
7. Na_2PdCl_4 (40 mol%), *t*-BuOOH (1.5 eq)
   dioxane/H_2O, 85 °C (65%)
8. ACE-Cl, $(ClCH_2)_2$, 85-90 °C
   ; evp; MeOH, reflux
   ; evp; NaOH aq., EtOAc, rt (80%)

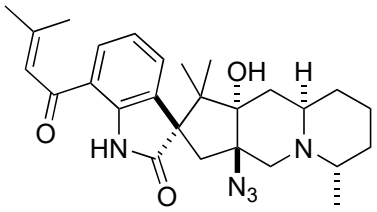
1-4
($C_{20}H_{22}N_2O_3$)

Problem 2



2-1

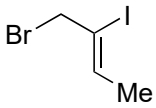
1. *t*-BuLi, O_2, THF, -78 °C
   ; Me_2S, NH_4Cl, rt (80%)
2. $MgCl_2$, NaN_3, CH_3CN
   60 °C, (42%)
3. $(PPh_3)AuNTf_2$ (1.1 eq)
   2-A (1.5 eq), THF, rt (73%)



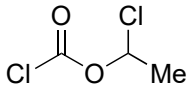
2-2

$(NH_4)_2Ce(NO_3)_6$

CAN



1-A



ACE-Cl

2-A

Problem Session (2) Answer

20171209 Shimizu Shinsuke

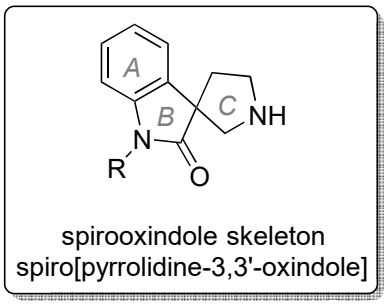
topic: Total synthesis of spirooxindole alkaloids

problem 1: **(+)-isoalstonisine**
Stephen, M. R.; Rahman, M. T.; Tiruveedhula, V. V. N. P. B.; Fonseca, G. O.; Deschamps, J. R.; Cook, J. M. *Chem. Eur. J.* **2017**, *23*, 15805.

isolation:
• from the ground leaves of the Malayan medicinal plant *Alstonia angustifolia var. latifolia* in 2000 by Kam et al. Kam, T.-S.; Choo, Y.-M. *Tetrahedron* **2000**, *56*, 6143.

structural feature:
• spirooxindole skeleton
• dihydropyrane moiety
• 8-azabicyclo[3.2.1]octane core

bioactivity:
not reported

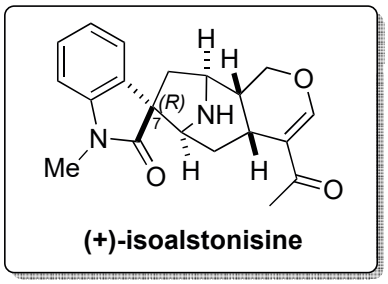


spirooxindole skeleton
spiro[pyrrolidine-3,3'-oxindole]

• construction of the skeleton -> see 170210_PS_Yuki_FUJIMOTO spirotryprostatin

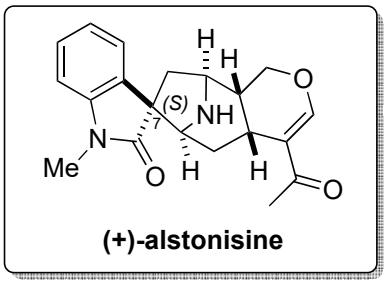
total synthesis:
(+)-isoalstonisine
• Stephen, M. R.; Rahman, M. T.; Tiruveedhula, V. V. N. P. B; Fonseca, G. O.; Deschamps, J. R.; Cook, J. M. *Chem. Eur. J.* **2017**, *23*, 15805.

(+)-alstonisine: stereoisomer of (+)-isoalstonisine at 7-position-> (7*S*)
• Wearing, X. Z.; Cook, J. M. *Org. Lett.* **2002**, *4*, 4237.
• Yang, J.; Wearing, X. Z.; Quesne, P. W. L.; Deschamps, J. R.; Cook, J. M. *J. Nat. Prod.* **2008**, *71*, 1431.
• Stephen, M. R.; Rahman, M. T.; Tiruveedhula, V. V. N. P. B; Fonseca, G. O.; Deschamps, J. R.; Cook, J. M. *Chem. Eur. J.* **2017,** *23,* 15805.



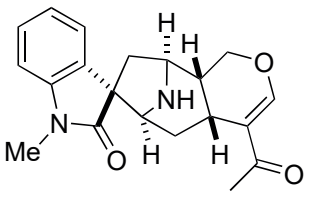
(+)-isoalstonisine

(target of **Problem 1**)



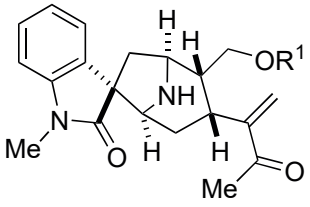
(+)-alstonisine

retrosynthetic analysis:
Stephen, M. R.; Rahman, M. T.; Tiruveedhula, V. V. N. P. B.; Fonseca, G. O.; Deschamps, J. R.; Cook, J. M. *Chem. Eur. J.* **2017**, *23*, 15805.



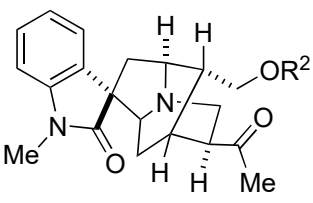
(+)-isoalstoniasine

Wacker oxi.



0-1

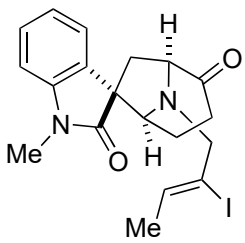
retro-Michael rxn.



0-2

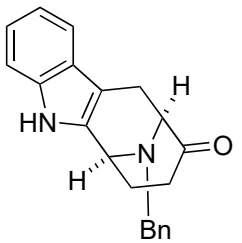
intramolecular-alkenylation

carbon extension

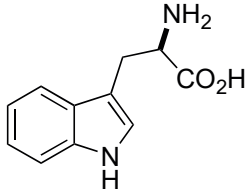


0-3

construction of spirooxindole

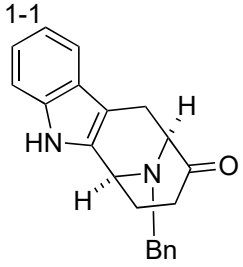


0-4 (**1-1**)



0-5
(D-tryptophan)

Problem 1-1



1-1

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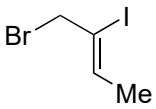
   $NaN(TMS)_2$, THF, rt (80%)

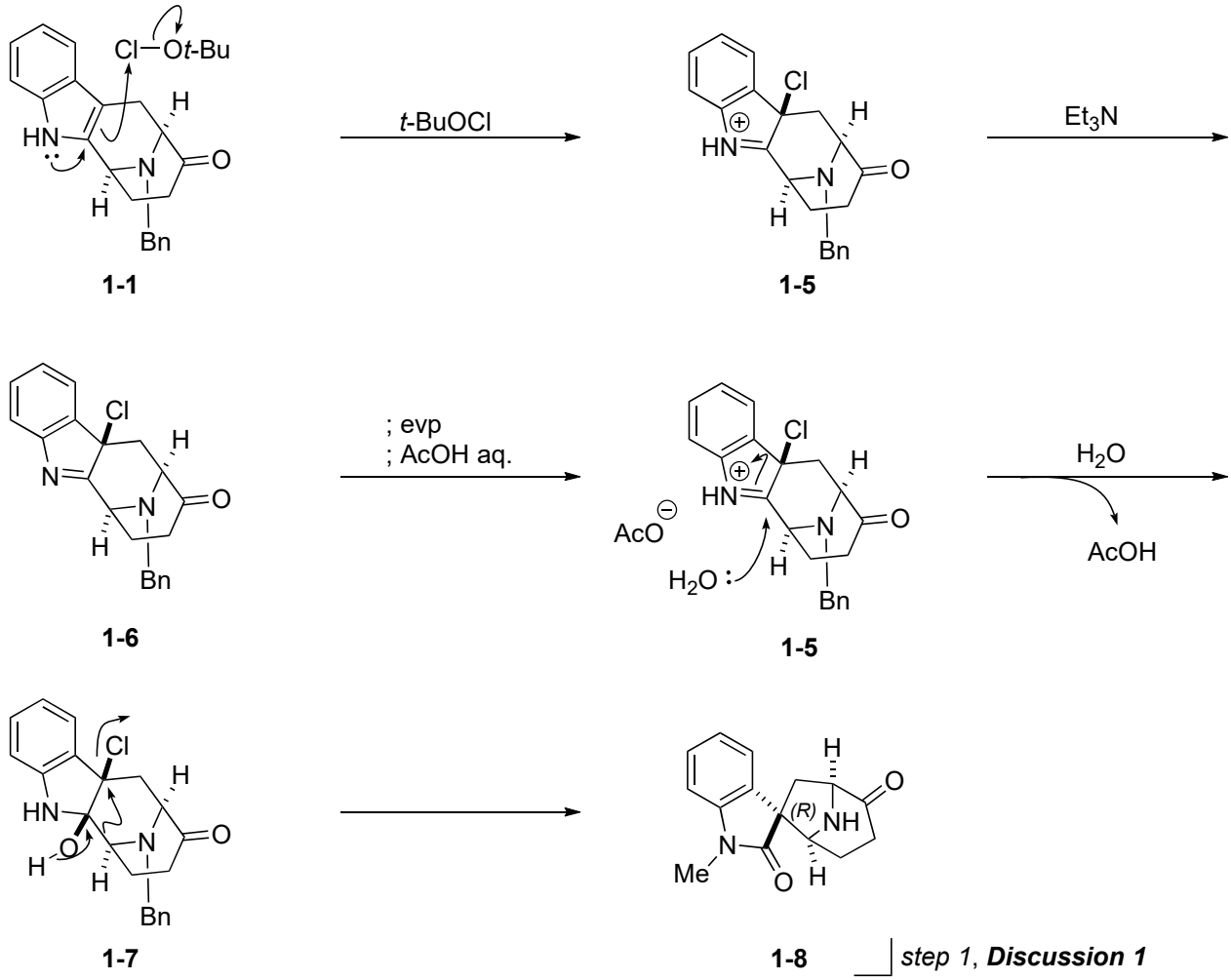
1-2



1-A

Stephen, M. R.; Rahman, M. T.; Tiruveedhula, V. V. N. P. B; Fonseca, G. O.; Deschamps, J. R.; Cook, J. M. *Chem. Eur. J.* **2017**, *23*, 15805.

Answer



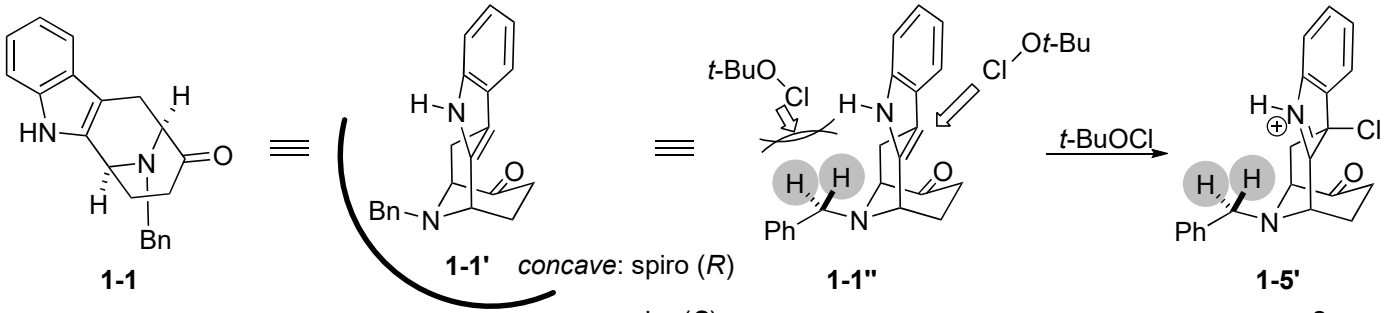
1-1 **1-5** **1-6** **1-5** **1-7** **1-8**

step 1, ***Discussion 1***

Discussion 1:

•stereoselectivity of *t*-BuOCl attack

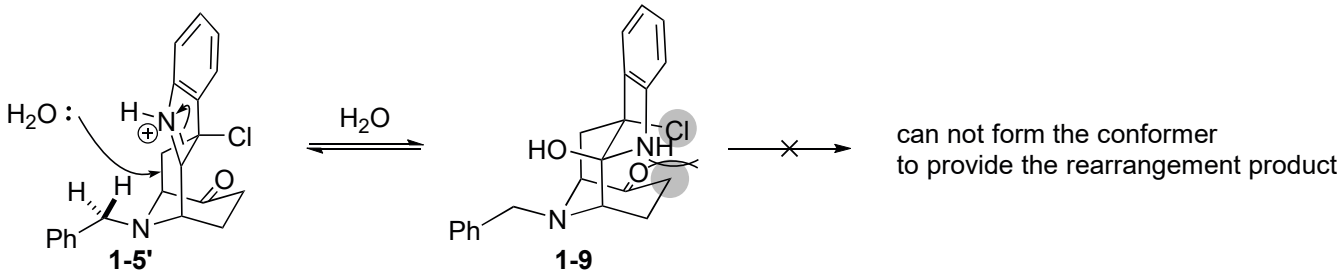
t-BuOCl: bulky reagent



1-1 **1-1'** *concave*: spiro (*R*) *convex*: spiro (*S*) **1-1''** **1-5'**

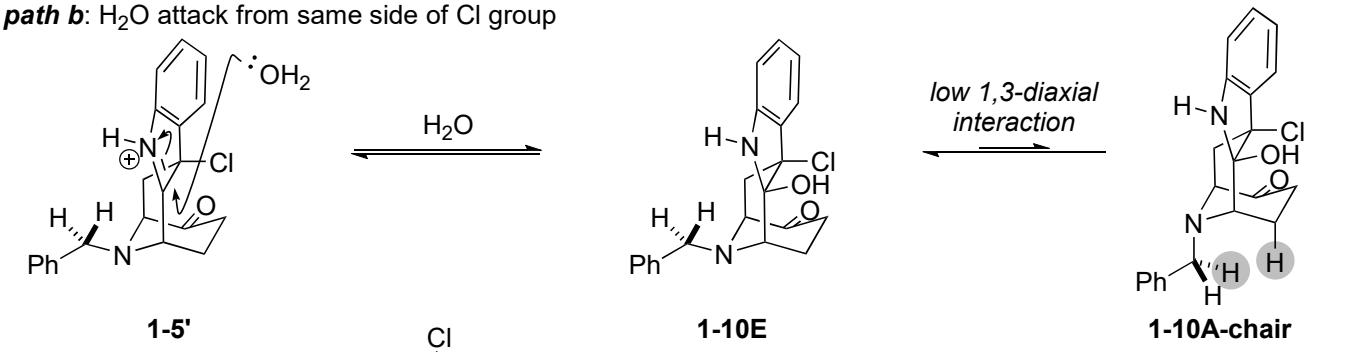
• stereoselectivity of H_2O attack

path a: H_2O attack from opposite side of Cl group

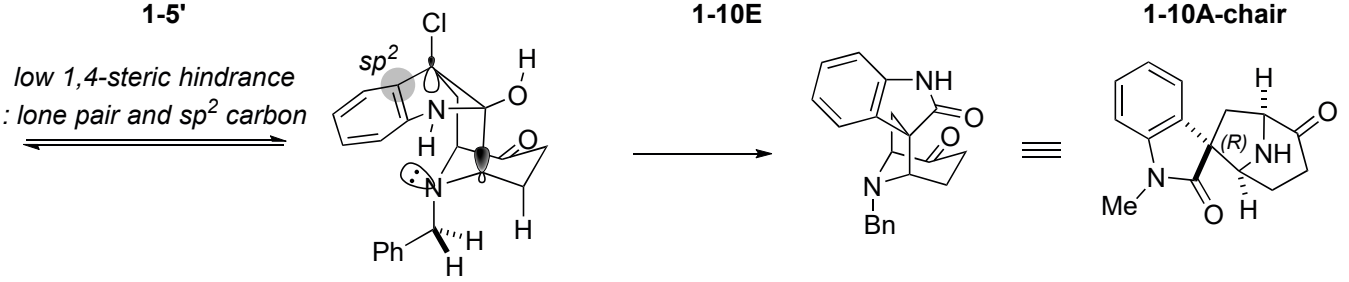


1-5' **1-9**

path b: H_2O attack from same side of Cl group

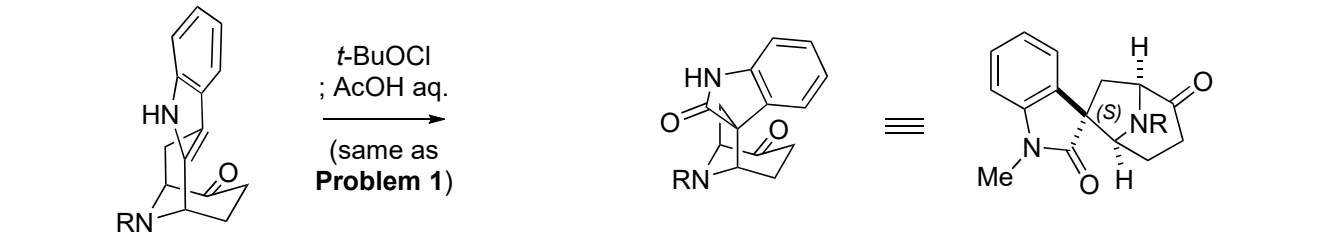


1-5' **1-10E** **1-10A-chair**



1-10A-boat 93% **1-8'** **1-8**

• Synthetic study of oxindole skeleton

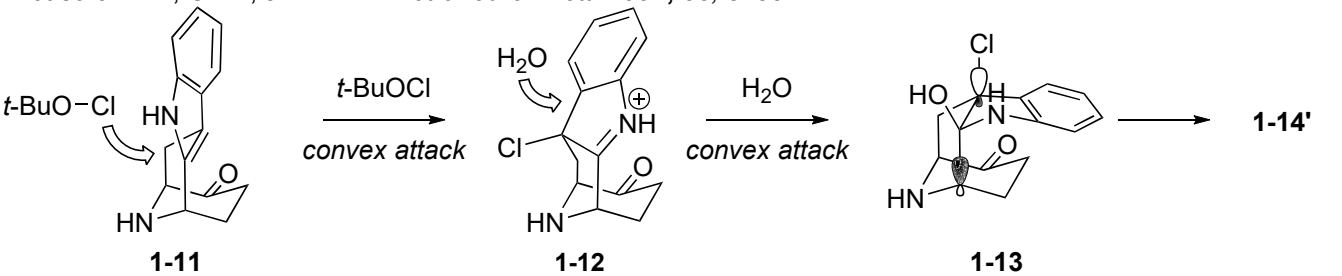


R=H: **1-11**
R=Bz: **1-15**

R=H: **1-14'** (80%)
R=Bz: **1-18'** (88%)

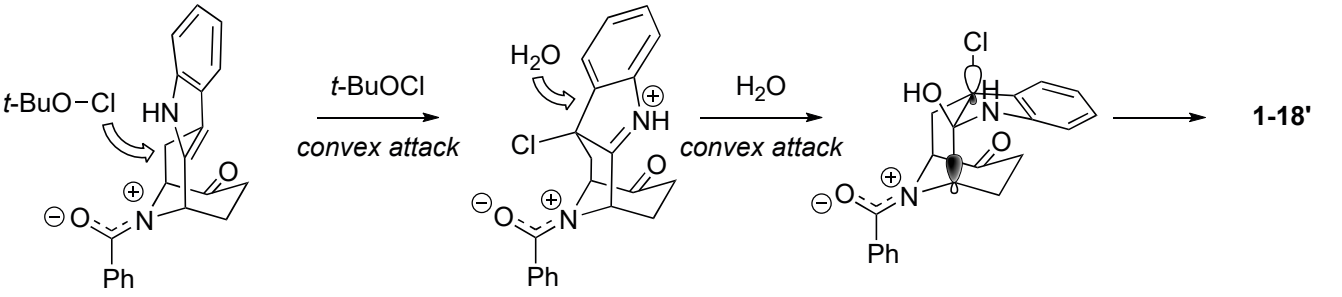
R=H: **1-14**
R=Bz: **1-18**

• *in case of N*-H; Cook, J. M. et al. *Tetrahedron Lett.* **1997,** *38,* 8799.



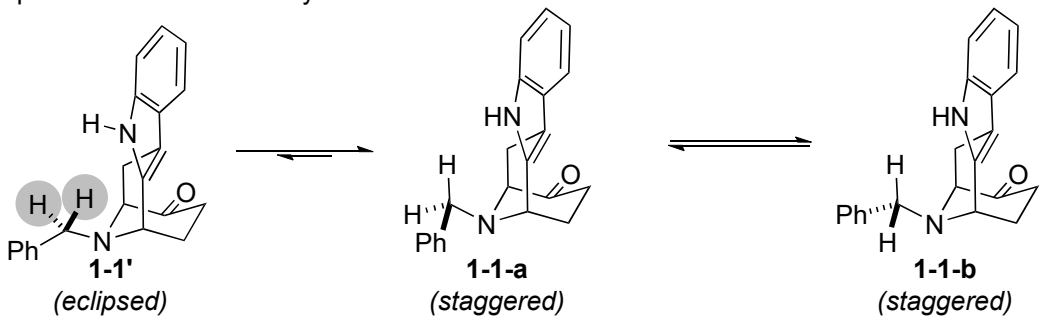
1-11 **1-12** **1-13** **1-14'**

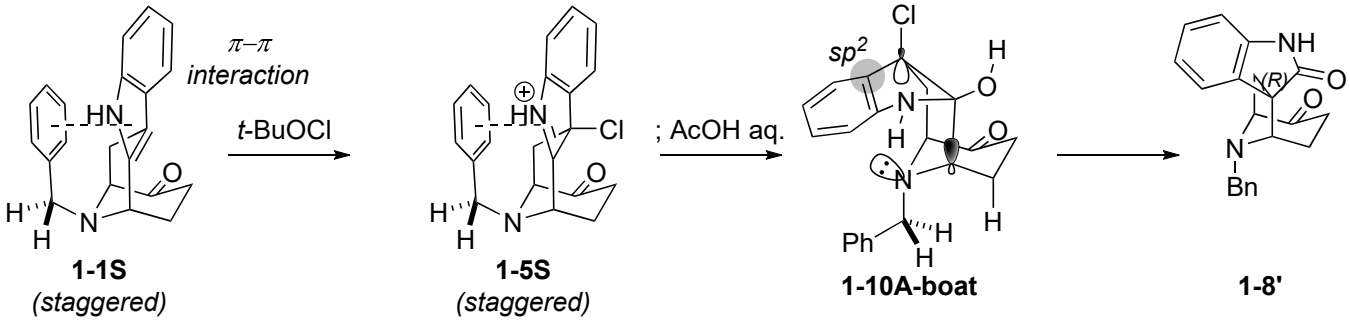
• *in case of N*-benzoyl; Cook, J. M. et al. *Heterocycles* **1989**, *29*, 519.

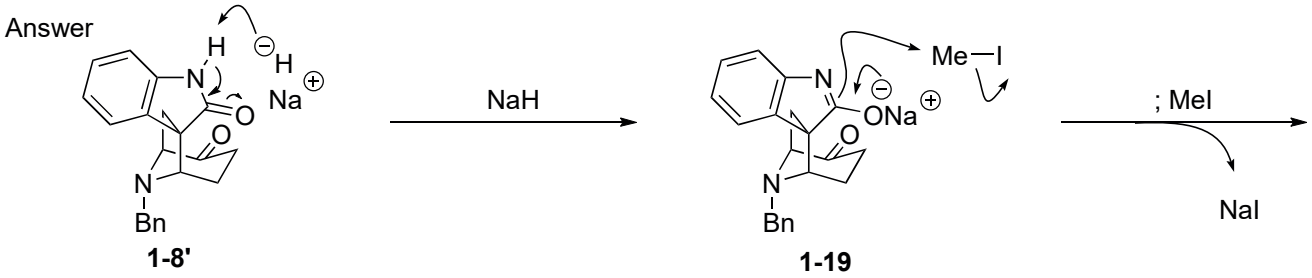


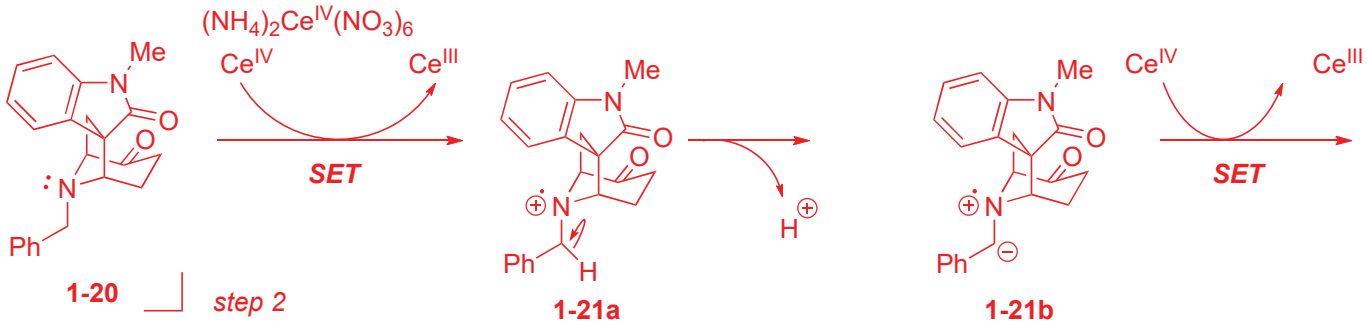
1-15 **1-16** **1-17** **1-18'**

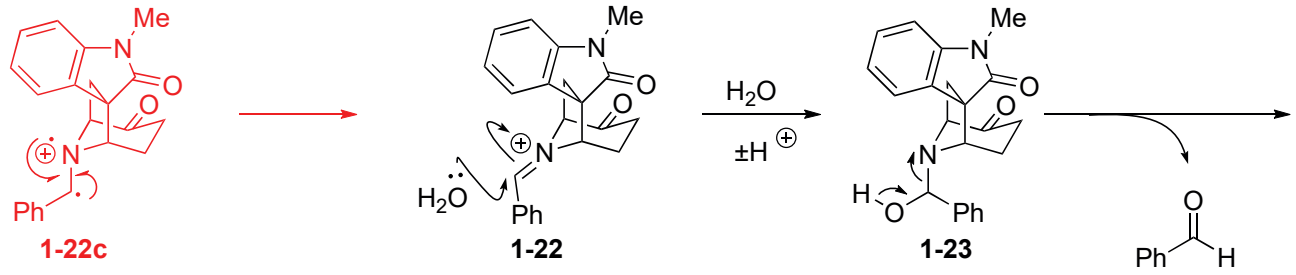
• my proposal for stereoselectivity

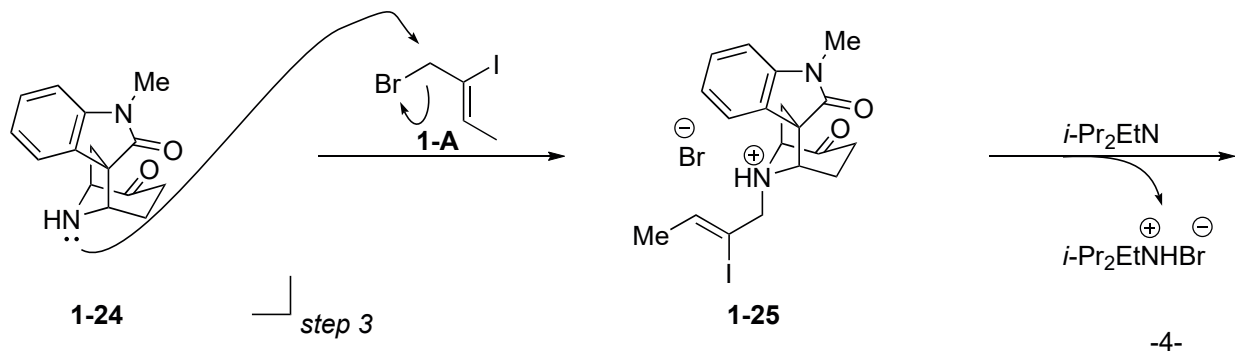


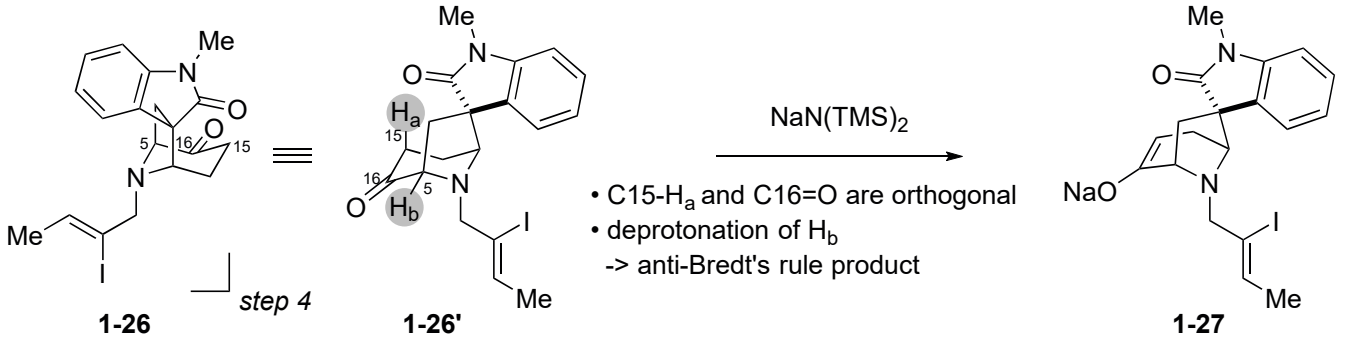


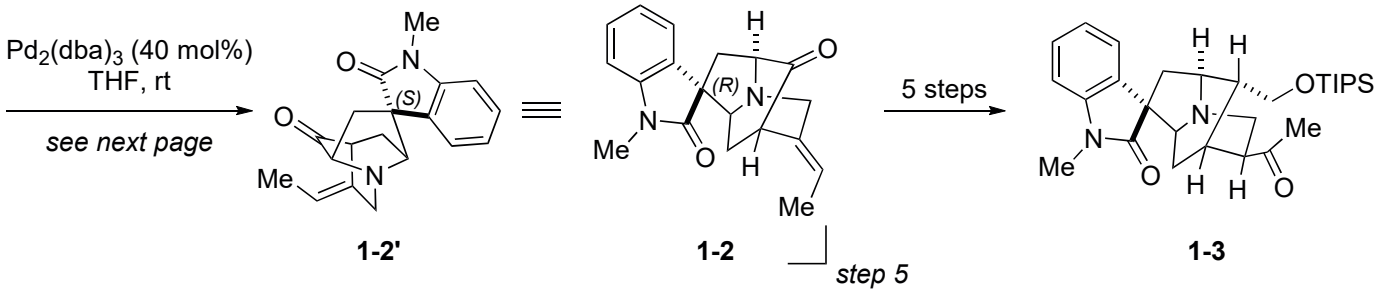


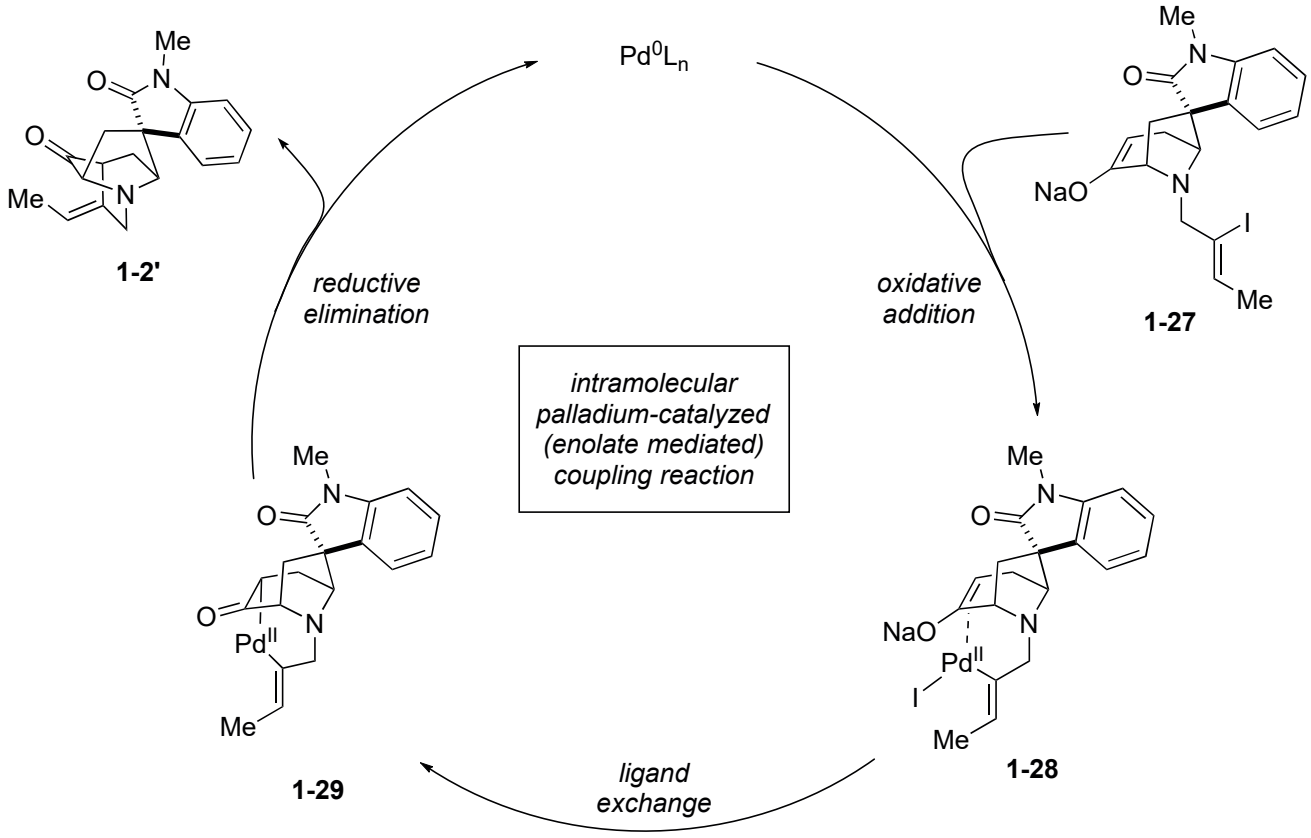




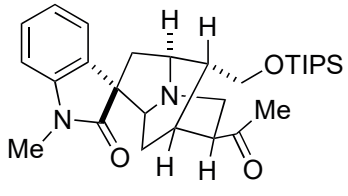








Problem 1-2



1-3
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7. Na_2PdCl_4 (40 mol%), *t*-BuOOH (1.5 eq)
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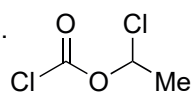
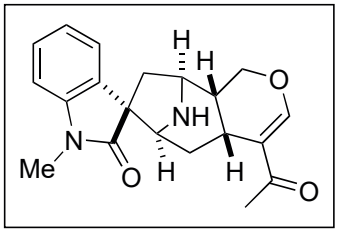
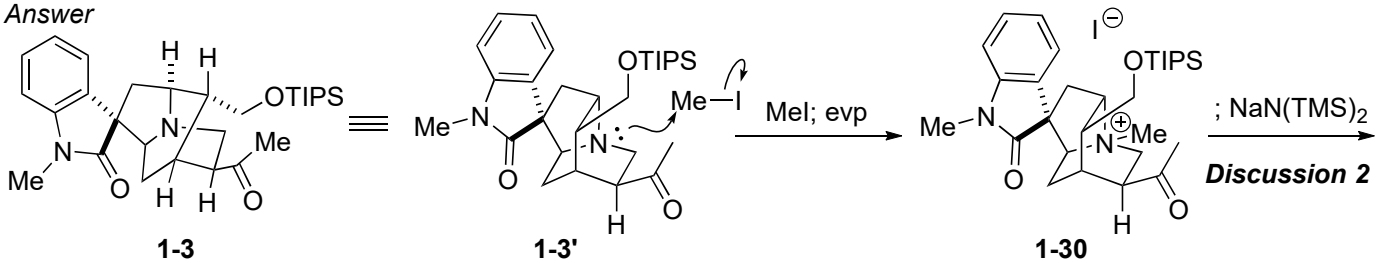
8.  (ACE-Cl)
$(ClCH_2)_2$, 85-90 °C
; evp; MeOH, reflux
; evp; NaOH aq., EtOAc, rt (80%)

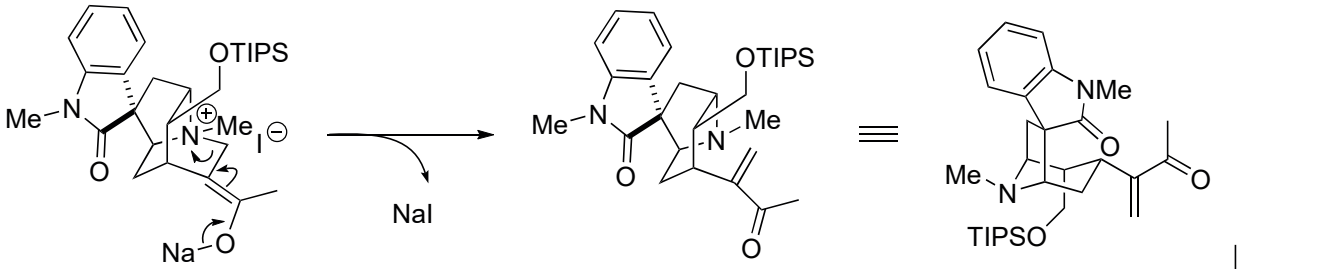


1-4
($C_{20}H_{22}N_2O_3$)

Answer



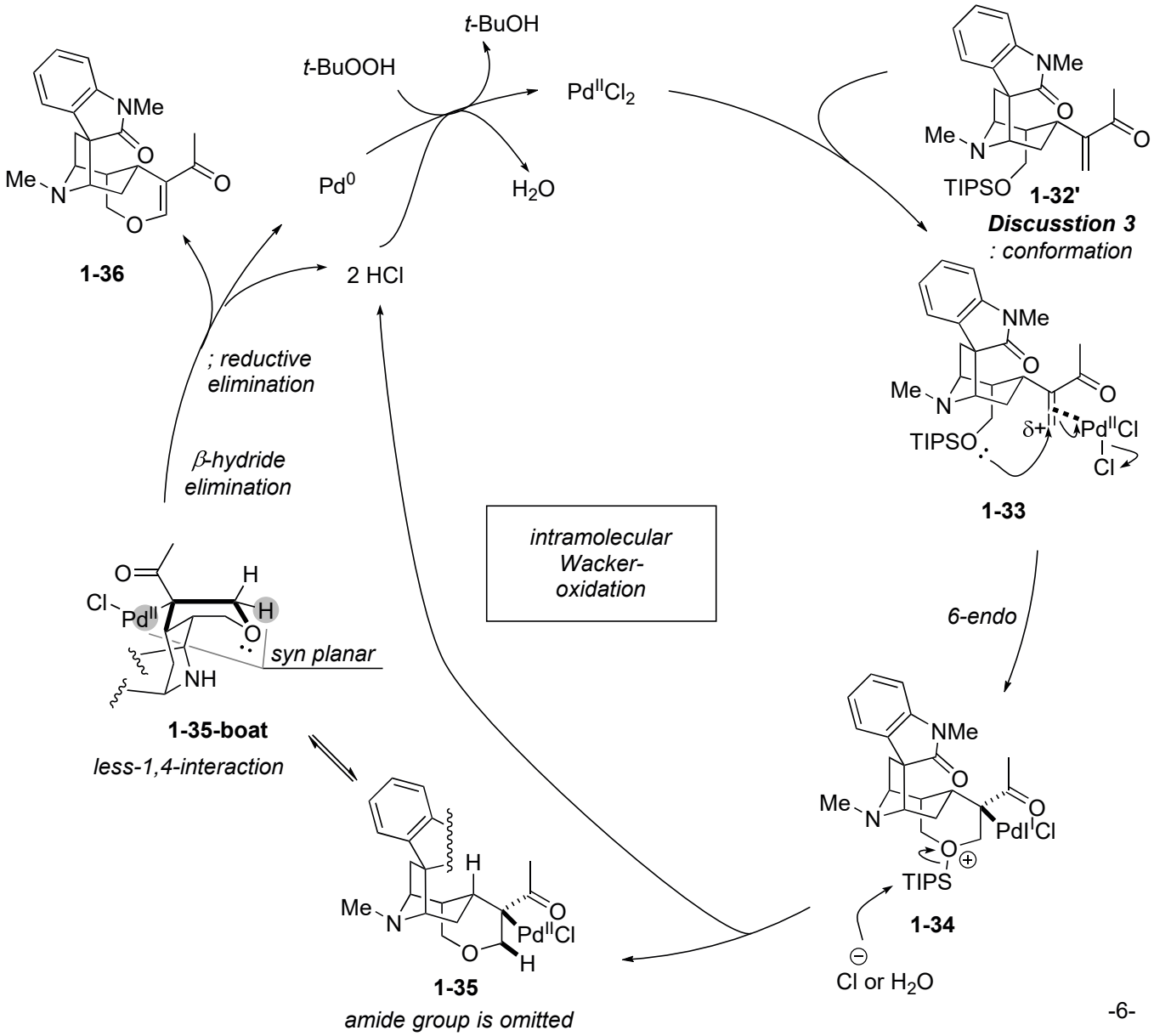
1-3 **1-3'** **1-30**



1-31 **1-32** **1-32'**

• Na_2PdCl_4 : $PdCl_2 + 2\ NaCl \xrightarrow{THF} Na_2PdCl_4$

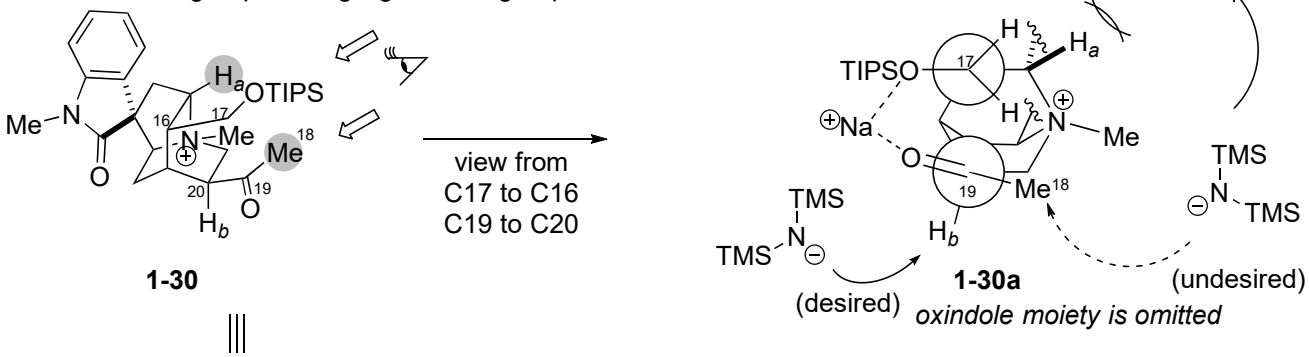
$PdCl_2$ is soluble in water. but, it is insoluble in most of the organic solvents.
Na_2PdCl_4 is used as a solubilized form of $PdCl_2$.
ref) Negishi, E. *John Wiley & Sons, Inc.* "Handbook of Organopalladium Chemistry for Organic Synthesis", **2003**



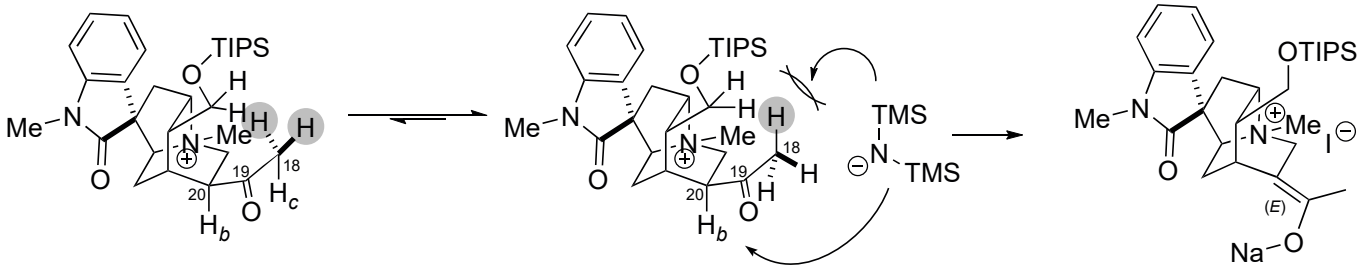
Discussion 2-1: formation of enolate and retro-Michael reaction

∅ stable conformation of **1-30**

- bulky OTIPS group is located on the opposite side of the highlighted H_a atom
- also, OTIPS group and highlighted Me group are far

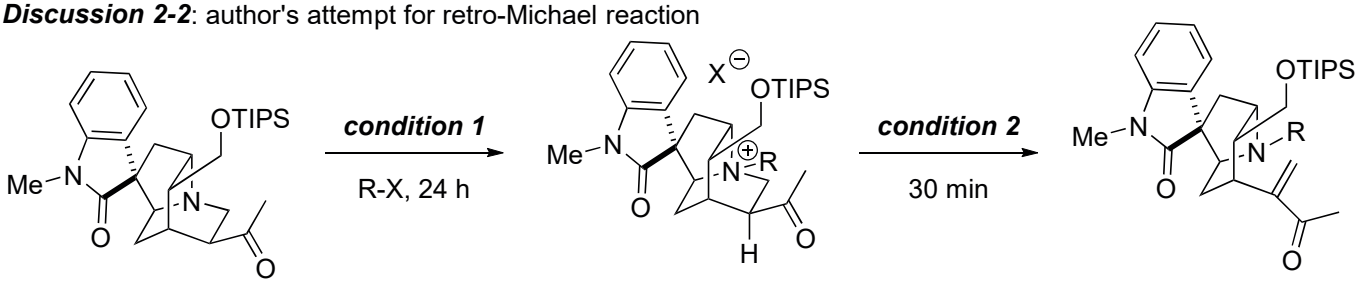


1-30 **1-30a**



1-30b **1-30c** **1-31*E***

Discussion 2-2: author's attempt for retro-Michael reaction

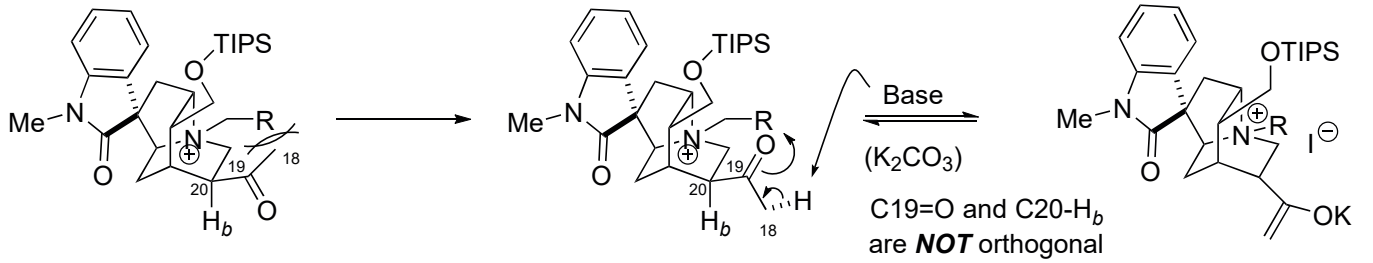


1-3' **1-30R** **1-32R**

table 1

entry	R-X	***condition 1***	***condition 2***	results
1	Bn-Br	$NaHCO_3$ MeOH, 64 °C	K_2CO_3 THF, 66 °C	decomp
2	Bn-Br	$NaHCO_3$, AgOTf MeOH, 64 °C	K_2CO_3 THF, 66 °C	decomp
3	allyl-Br	$NaHCO_3$, AgOTf neat, 70 °C	K_2CO_3 THF, 66 °C	decomp
4	Me-I	neat, 70 °C	*t*-BuOK THF, 23 °C	**1-32**: 30%
5	Me-I	neat, 70 °C	$NaN(TMS)_2$ THF, 23 °C	**1-32**: 80%

- my proposal for entries 1-3 of **table 1**



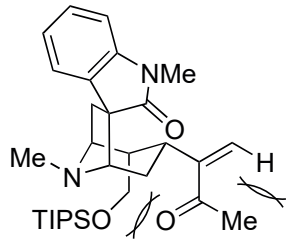
1-37: R=Ph
1-38: R=vinyl

1-39: R=Ph
1-40: R=vinyl

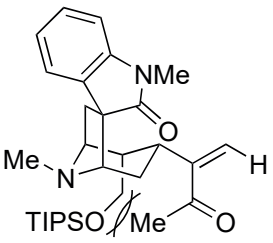
1-41: R=Ph
1-42: R=vinyl

Discusstion 3 *: stable conformation of* ***1-32'*** for intramolecular Wacker oxidation

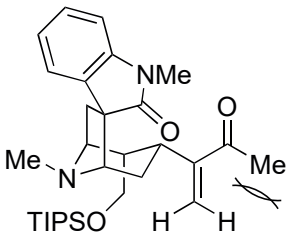
• direction of exo olefin



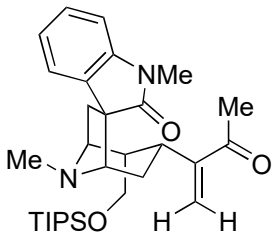
1-32a
disfavor



1-32b
disfavor

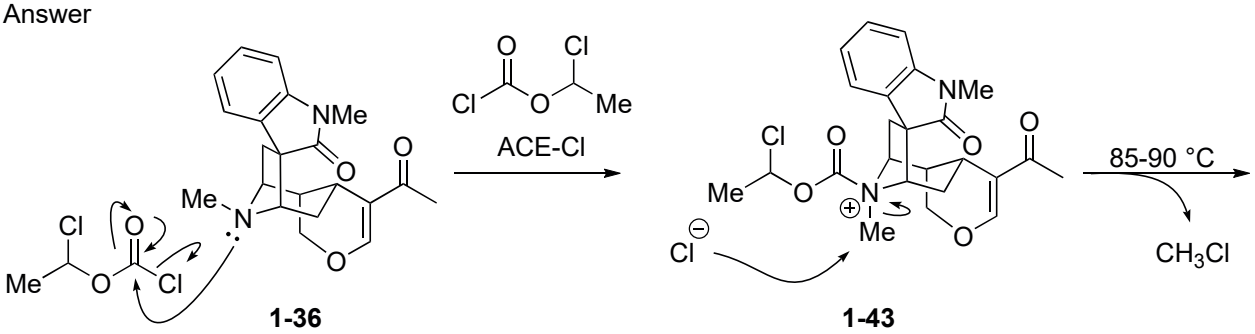


1-32c
disfavor

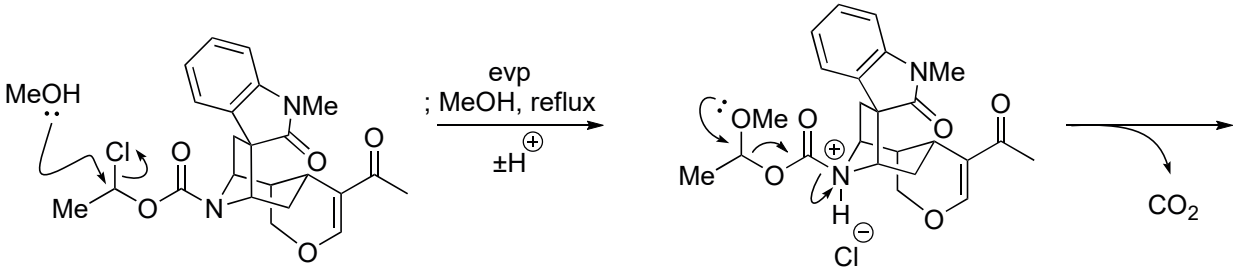


1-32d
favor

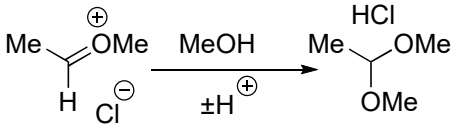
Answer

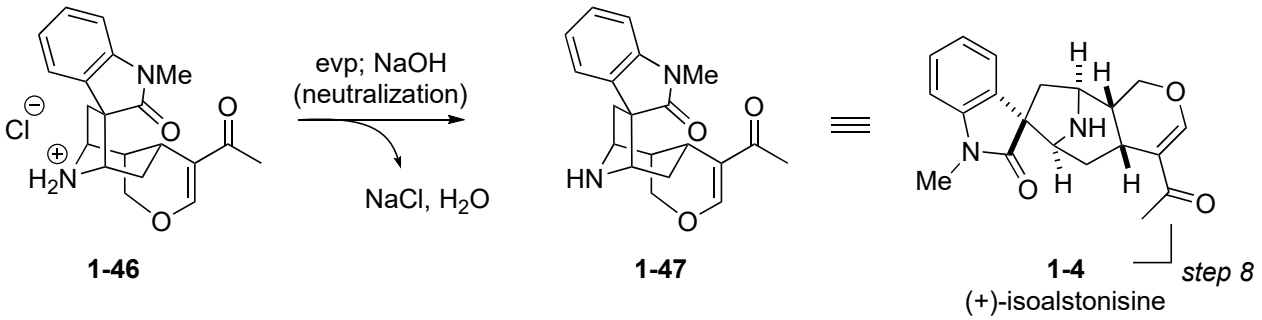


1-36 **1-43**



1-44 **1-45**





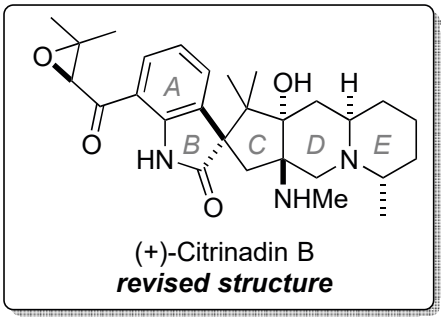
1-46 **1-47** **1-4**
(+)-isoalstonisine

step 8

problem 2: **(+)-Citrinadin B**
Kong, K.; Enquist. J. A.; McCallum, M. E.; Smith, G. M.; Matsumaru, T.; Menhaji-Klotz, E.; Wood, J. L. *J. Am. Chem.* **2013**, *135*, 10890.

isolation:
from Penicillium citrinum N059 in 2004 by Kobayashi
Tsuda, M.; Kasai, Y.; Komatsu, K.; Sone, T.; Tanaka, M.; Mikami, Y.; Kobayashi, J. *Org. Lett.* **2004**, *6*, 3087.

bioactivity:
modest cytotoxicity against murine leukemia L1210 cells
Tsuda, M.; Kasai, Y.; Komatsu, K.; Sone, T.; Tanaka, M.; Mikami, Y.; Kobayashi, *J. Org. Lett.* **2004**, *6*, 3087.



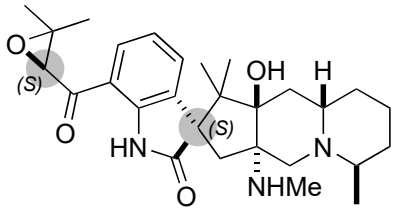
(+)-Citrinadin B
revised structure

structural feature:
• epoxyketone, spirooxindole, methyl piperidine moieties
• tricyclic core

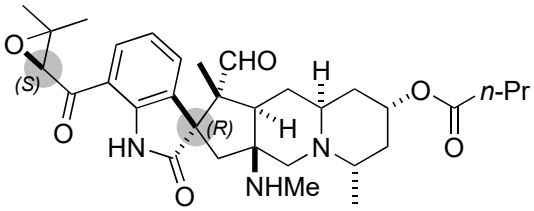
synthetic study:
• Pettersson, M.; Knueppel, D.; Martin, S. F. *Org. Lett.* **2007**, *9*, 4623.
• McIver, A. L.; Deiters, A. *Org. Lett.* **2010**, *12*, 1288.
• Guerrero, C. A.; Sorensen, E. J. *Org. Lett.* **2011**, *13*, 5164.

total synthesis:
• Kong, K.; Enquist. J. A.; McCallum, M. E.; Smith, G. M.; Matsumaru, T.; Menhaji-Klotz, E.; Wood, J. L. *J. Am. Chem.* **2013**, *135*, 10890. (***Problem 2***)
• Bian, Z.; Marvin, C. C.; Pettersson, M.; Martin, S. F. *J. Am. Chem.* **2014**, *136*, 14184.

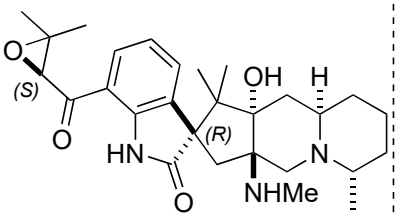
stereochemical revision:



(+)-Citrinadin B
***original structure*:**
1D and 2D NMR experiments, and CD studies



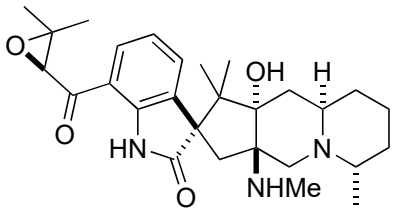
PF1270A
***original structure*:**
X-ray crystallographic analysis



(+)-Citrinadin B
***revised structure*:**
synthesized (**Problem 2**)

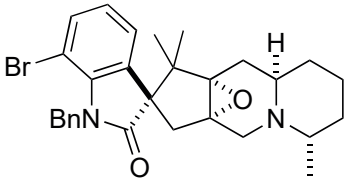
the difference in the assigned structures of citrinadin B and PF1270A is the relative stereochemistry of the α,β-epoxy ketone and the pentacyclic core.

retrosynthetic analysis:



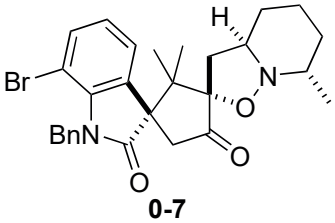
(+)-Citrinadin B

Sonogashira coupling
⟹
alkyne-oxidation
(**Problem 2**)



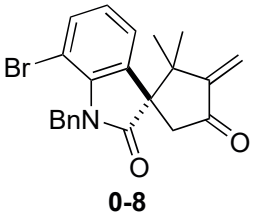
0-6

construction of tricyclic core
⟹

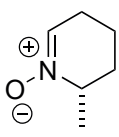


0-7

[3+2]-dipolar cycloaddition
⟹

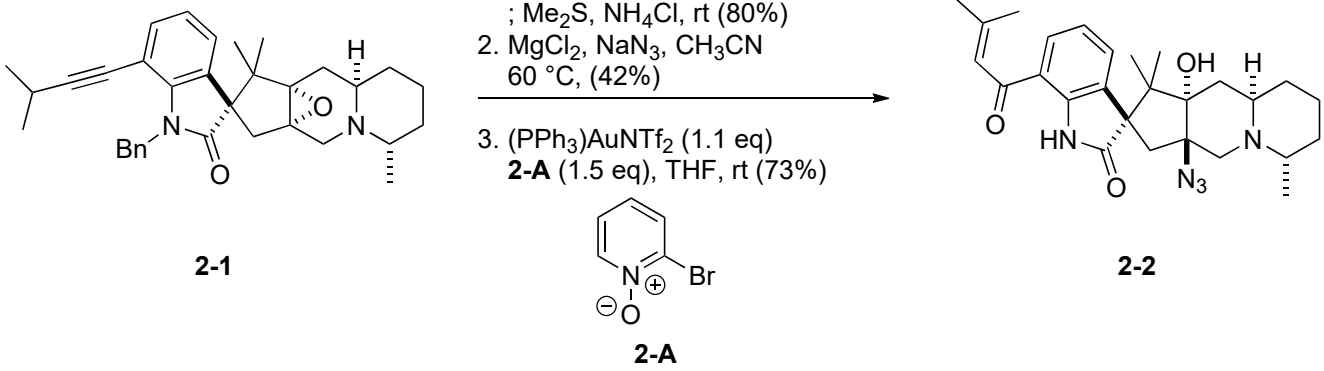


0-8



0-9

Problem 2

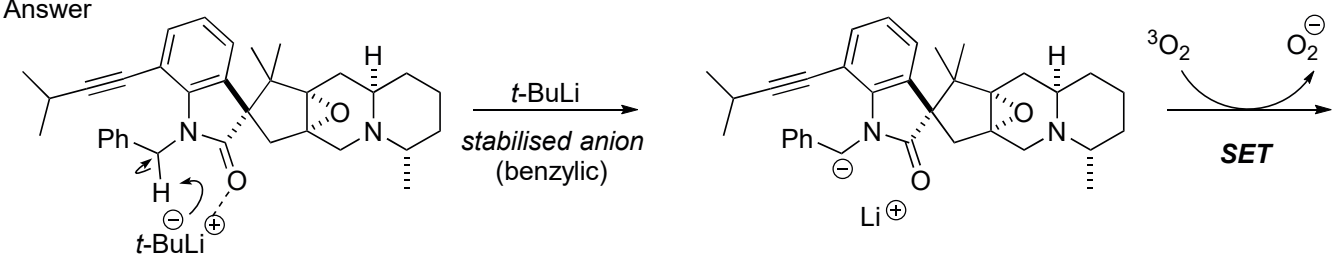


2-1 **2-2**

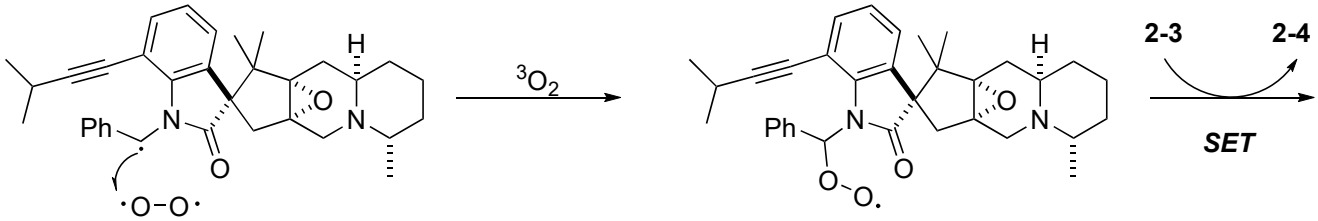
2-A

Kong, K.; Enquist. J. A.; McCallum, M. E.; Smith, G. M.; Matsumaru, T.; Menhaji-Klotz, E.; Wood, J. L. *J. Am. Chem.* **2013**, *135*, 10890.

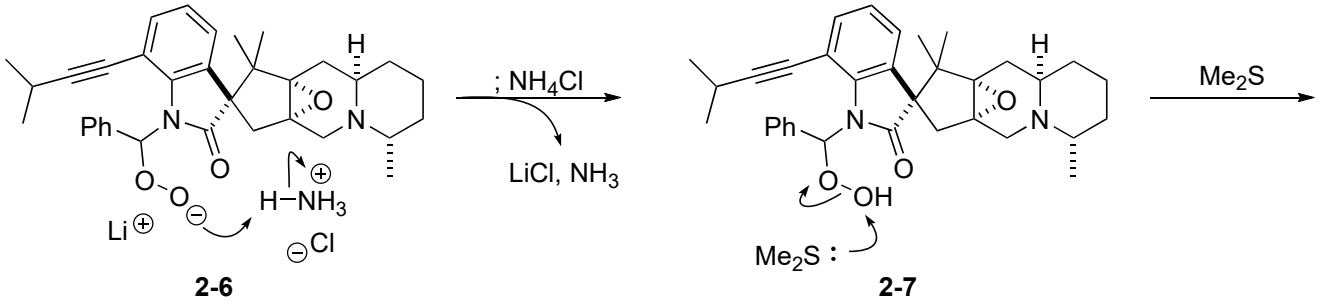
Answer



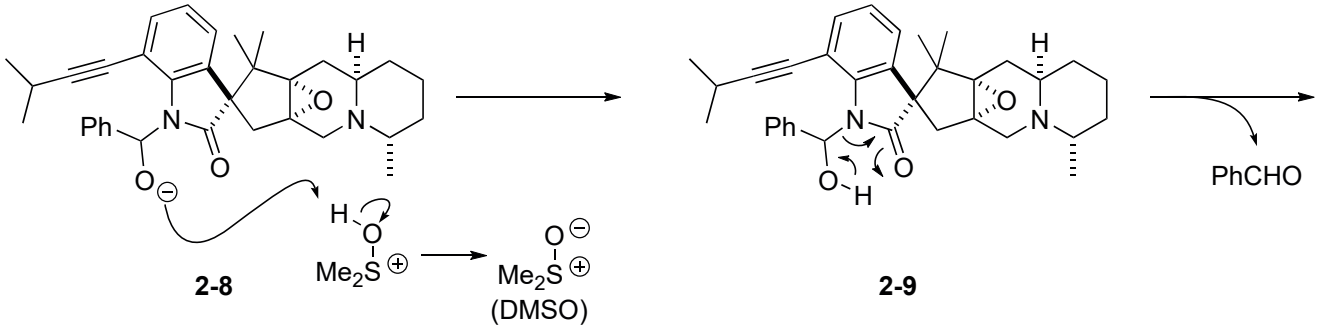
2-1 **2-3**



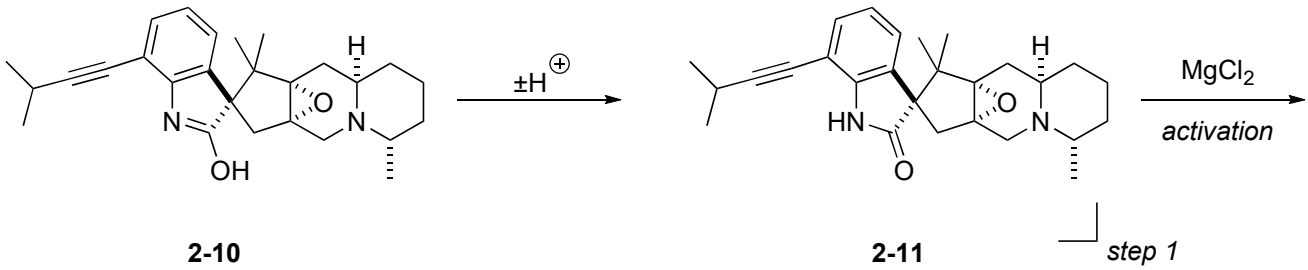
2-4 **2-5**



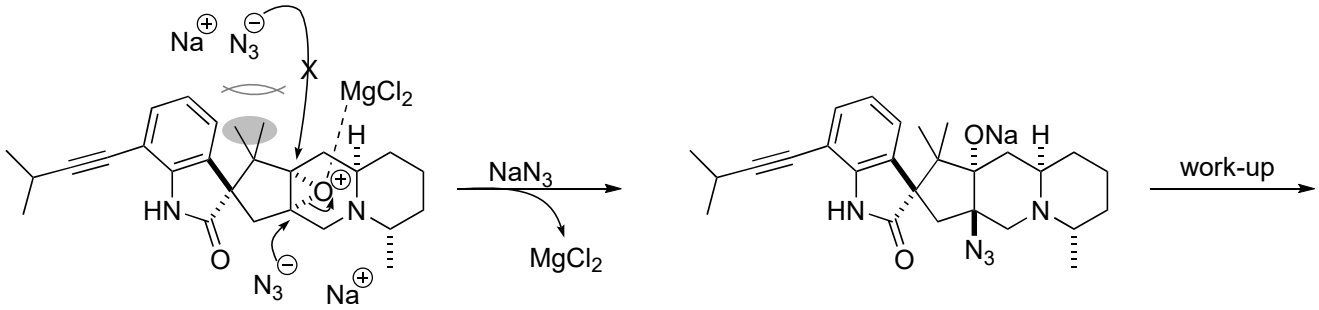
2-6 **2-7**



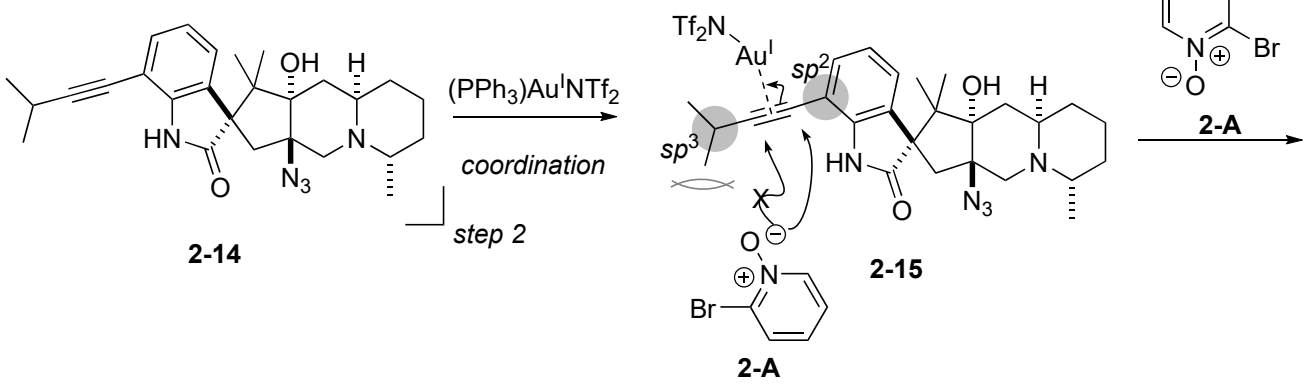
2-8 **2-9**



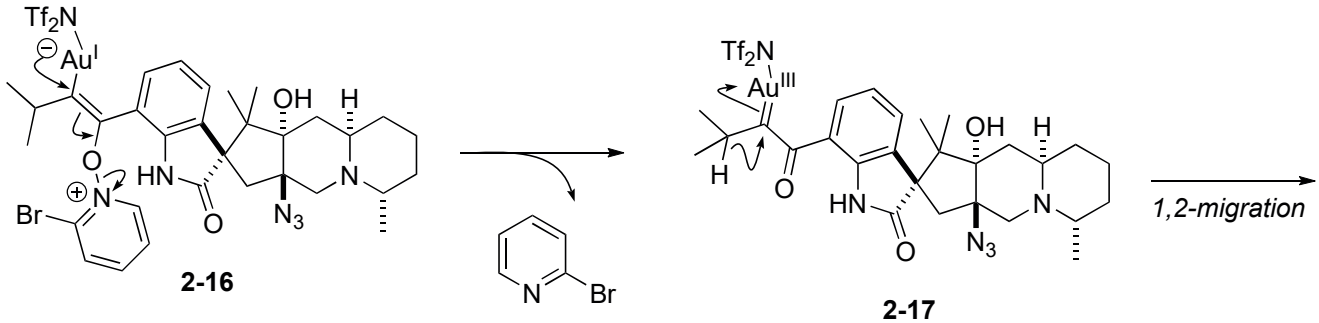
2-10 **2-11**



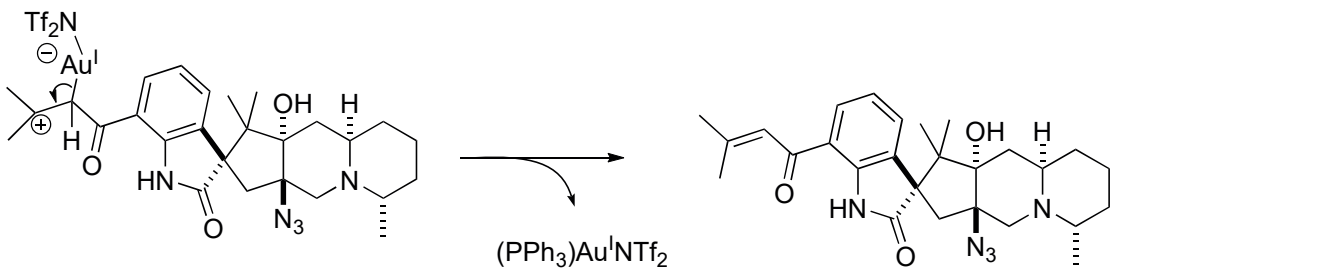
2-12 **2-13**



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



2-16 **2-17**



2-18 **2-19**