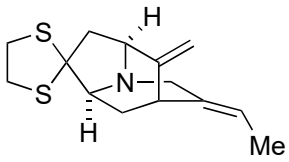
Problem Session (3)

20180526 Shimizu Shinsuke

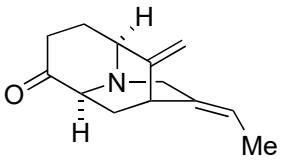
Please provide following reaction mechanisms

Problem 1



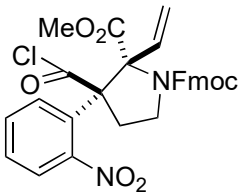
1-1

1. CF_3CO_2H, **1-1**, CH_2Cl_2 then, Me_3OBF_4, rt; $CuSO_4$, 0 °C to rt; NH_3, rt (74%)
2. *n*-BuLi, $TMSCHN_2$, Et_2O/THF, -78 °C then **1-1**; MeOH, silica gel, -78 °C to rt (88%)



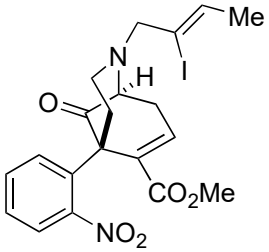
1-2

Problem 2



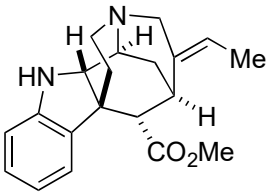
2-1

1. CH_2N_2, CaO, Et_2O, 23 °C (65%)
2. DBU, 23 °C, CH_2Cl_2/MeOH; CF_3CO_2H, CH_2Cl_2, -30 to 23 °C (54%)
3. **A**, AgOTf, CH_2Cl_2 proton sponge, 0 °C (42%)



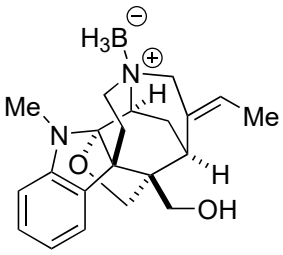
2-2

Problem 3

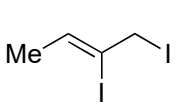


3-1

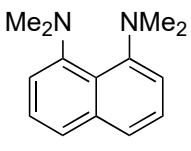
1. $LiBH_4$, THF, 60 °C (69%)
2. PCC, Celite®, CH_2Cl_2, 23 °C
3. Cs_2CO_3, $(CH_2O)_n$ (9 eq), THF 23 °C (43%, 2 steps)
4. MeI, Cs_2CO_3, MeOH 30 °C (45%, recovery: 33%)



3-2



A



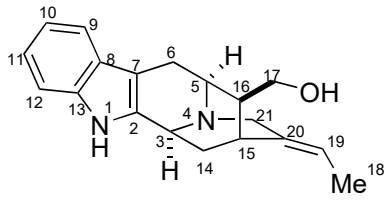
proton sponge

Problem Session (3) Answer

20180526 Shimizu Shinsuke

topic: Total synthesis of sarpagine alkaloid and akuammiline alkaloids

problem 1: **16-epinormacusine B** (**1-3**), sarpagine alkaloid
(Krüger, S.; Gaich, T. *Chem. Eur. J.* **2016**, 4893.)



16-epinormacusine B (**1-3**)

isolation:
from the leaves of *Ervatamia hirta* from Malaysia by Clivio et al. in 1991
(Clivio, P.; Richard, B.; Deverre, J.-R.; Sevenet, T.; Zeches, M.; Men-Oliver, L. L. *Phytochemistry* **1991**, *30*, 3785.)

bioactivity:
not reported (used in traditional medicine and poisoned arrows.)

total syntheses:
• Yu, J.; Liao, X.; Cook, J. M. *Org. Lett.* **2002**, *4*, 4681.
• Krüger, S.; Gaich, T. *Chem. Eur. J.* **2016**, 4893. (**problem 1**)

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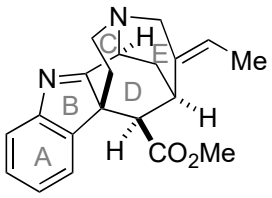
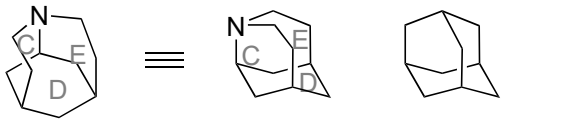
problem 2: **(±)-strictamine** (**2-3**), akuammiline alkakloid
(Echkermann, R.; Breunig, M. Gaich, T. *Chem. Commun.* **2016**, *52*, 11363.)



strictamine (**2-3**)

isolation:
from the plant of *Rhazya stricta* by Schnoes, et al. in 1966
(Schnoes, H. K.; Biemann, K.; Mokry, J.; Kompis, I.; Chatterjee, A.; Ganguli, G. *J. Org. Chem.* **1966**, *31*, 1641.)

bioactivity:
inhibitory effects of the nuclear factor-κB, which is involved in the regulation of gene expression in immune and inflammatory responses.
(Hou, Y.; Cao, X.; Wang, L.; Cheng, B.; Dong, L.; Luo, X.; Bai, G.; Gao, W. *J. Chromatogr. B* **2012**, *908*, 98.)



methanoquinolizidine (**0-1**) **0-1'** adamantane (**0-2**)

Structural feature:
very compact cage-like structure (methanoquinolizidine, **0-1**) reminischent of adamantane (**0-2**)

total syntheses:
• (+): Moreno, J.; Picazo, E.; Morrill, L. A. Smith, J. M. Garg, N. K. *J. Am. Chem. Soc.* **2016**,*138*, 1162.
• (±): Ren, W.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 3500.
• (±, formal) Nishiyama, D.; Ohara, A.; Chiba, H.; Kumagai, H.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2016**, *18*, 1670.
• (±): Echkermann, R.; Breunig, M. Gaich, T. *Chem. Commun.* **2016**, *52*, 11363. (**problem 2**)

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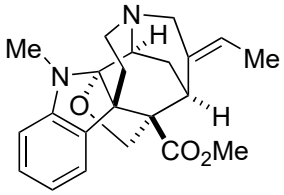
problem 3: **(–)-Ψ-akuammigine** (**3-3**), akuammiline alkaloid
(Picazo, E.; Morrill, L. A.; Susick, R.; Moreno, J.; Smith, J.; Garg, N. K. *J. Am. Chem. Soc.* ASAP)

isolation:
from the plant of *Picralima klaineana* by Henry in 1932
(Henry, T. A. *J. Chem. Soc.* **1932**, 2759.)



(–)-Ψ-akuammigine (**3-3**)

bioactivity:
activity as an anti-inflammatory agent
(Duwiejua, M.; Woode, E.; Obiri, D. D. *J. Ethnopharmacol.* **2002**, *81*, 73.)

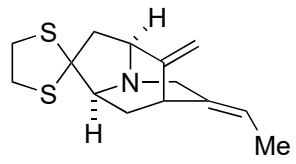
Structural feature:
most structurally complex of the methanoquinolizidine containing akuammiline alkaloids

total synthesis:
Picazo, E.; Morrill, L. A.; Susick, R.; Moreno, J.; Smith, J.; Garg, N. K. *J. Am. Chem. Soc.* ASAP. (**problem 3**)

indole alkaloid chemistry
see, 160625_PS_Eiji_Yoshida_Recent_total_synthesis_of_monoterpene_indole_alkaloids_answer

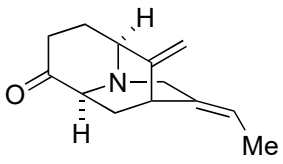
Answer 1

Problem 1



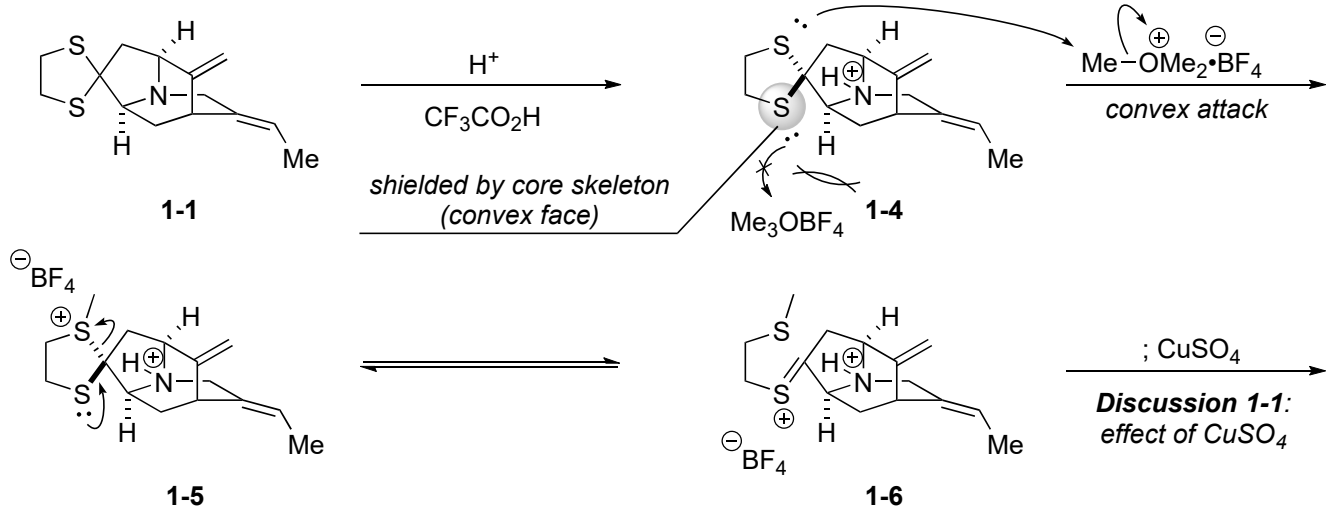
1. CF_3CO_2H, **1-1**, CH_2Cl_2 then, Me_3OBF_4, rt;
   3% $CuSO_4$ aq., 0 °C to rt; 25% NH_3 aq., rt (74%)

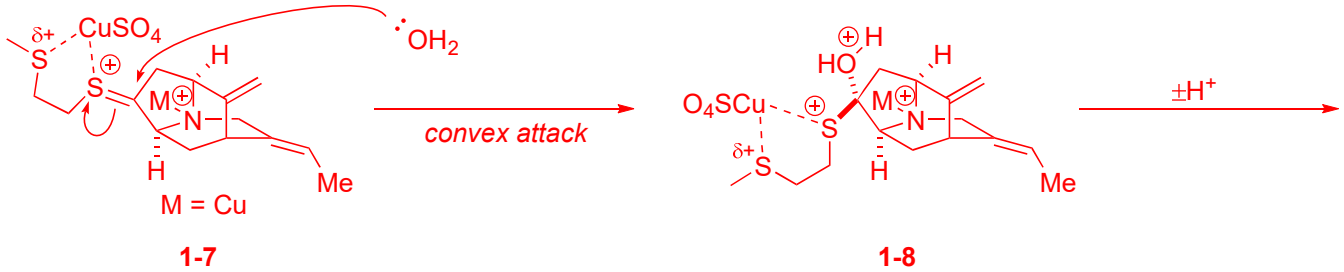
2. *n*-BuLi, $TMSCHN_2$, Et_2O/THF, -78 °C then **1-1**;
   MeOH, silica gel, -78 °C to rt (88%)

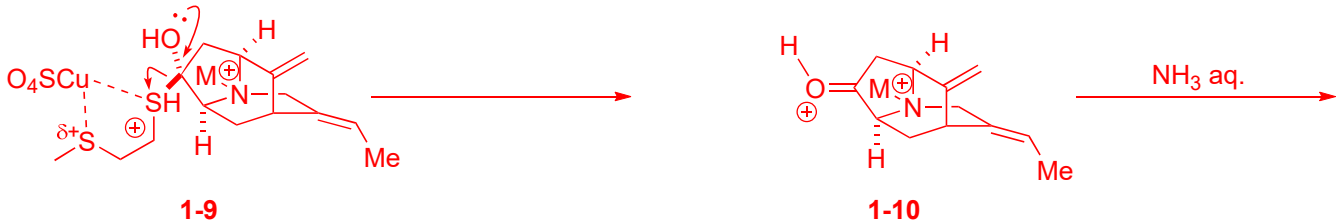


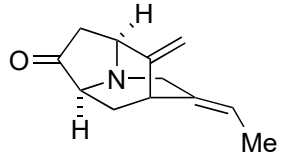
1-1 **1-2**

Krüger, S.; Gaich, T. *Chem. Eur. J.* **2017**, *23*, 15805.

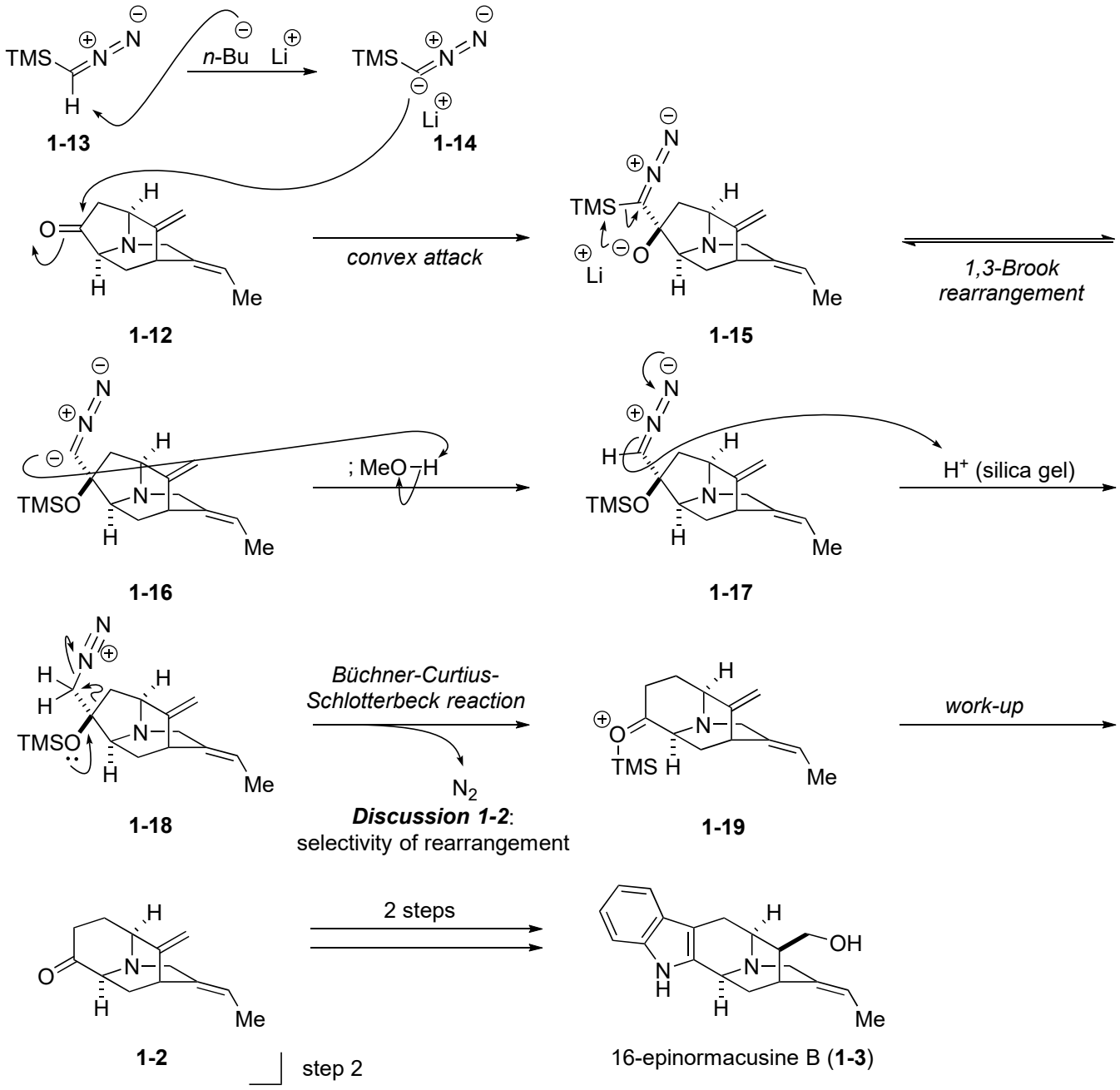






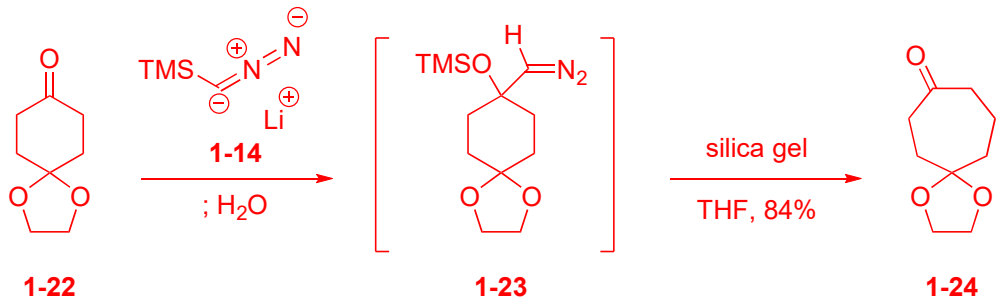


1-12 step 1



genaration of **1-16**

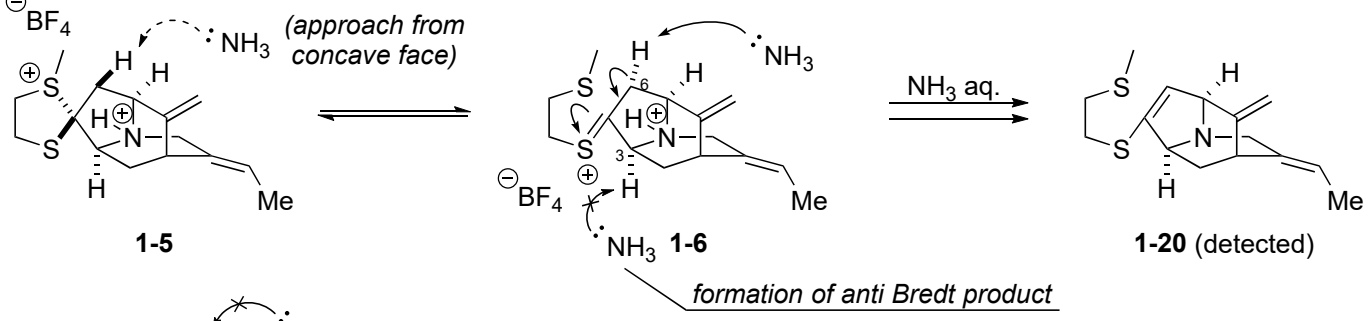
(Liu, H.; Sun, C.; Lee, N.-K.; Henry, R. F.; Lee, D. *Chem. Eur. J.* **2012**, *18*, 11889.)

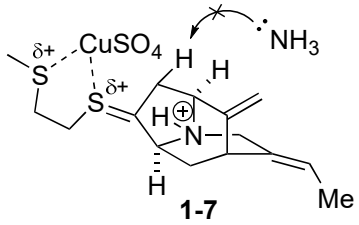


1-23 was generated by addition of **1-14** to **1-22**.
So, generation of **1-16** and **1-17** was depicted.

Discusstion 1-1: effect of $CuSO_4$

*when $CuSO_4$ was not employed, addition of NH_3 formed **1-20** (yield was not reported in the paper)*

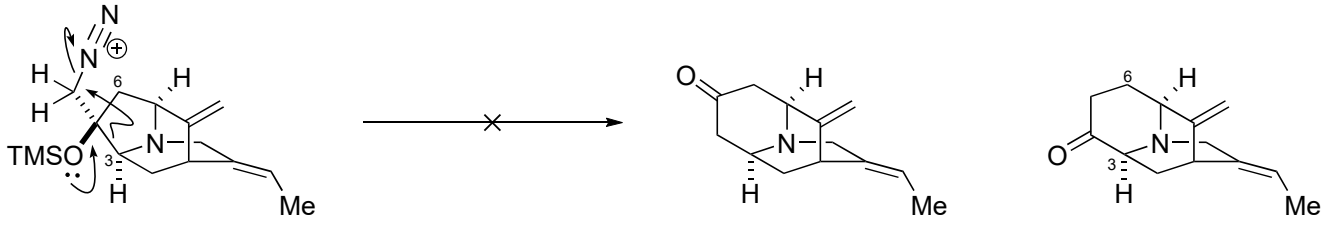




1-7

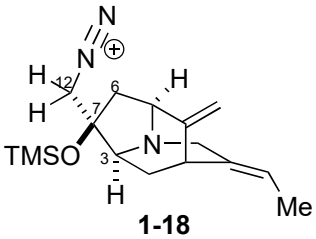
Formation of copper complex **1-7** delocalized positive charge of sulfur atom.
It resulted in the decreased acidity of the α-sulfenic proton of **1-7**.
So, deprotonation of **1-7** didn't occur in the presence of $CuSO_4$.

Discussion 1-2: setectivity of rearrangement

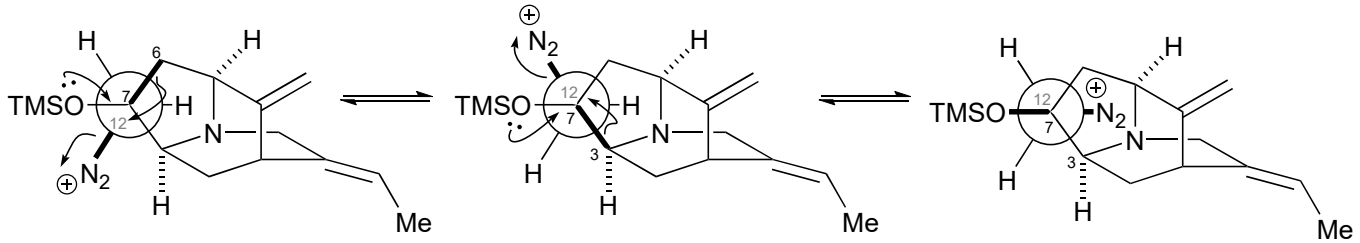


1-18 | **1-21** not formed | **1-2** formed

there are three possible conformers.
the rearrangement occured only when the conformation of **1-18** was **1-18a**.



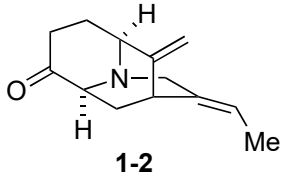
1-18



1-18a
parallel: C6-C7 and C12-N bonds

1-18b
parallel: C3-C7 and C12-N bonds

1-18c
parallel: O-C7 and C12-N bonds



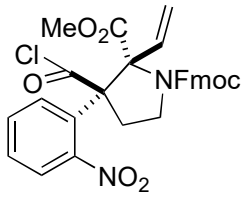
1-2

migration of C3 position carbon is an unfavorable pathway because of its rigidity.

no reaction

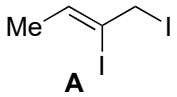
Answer 2

Problem 2

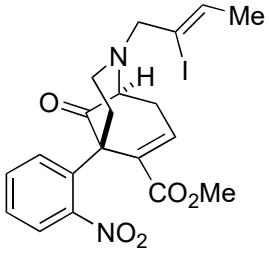


2-1

1. CH_2N_2, CaO, Et_2O, 23 °C (65%)
2. DBU, 23 °C, CH_2Cl_2/MeOH; CF_3CO_2H, CH_2Cl_2, -30 to 23 °C (54%)
3. **A**, AgOTf, CH_2Cl_2, proton sponge, 0 °C (42%)

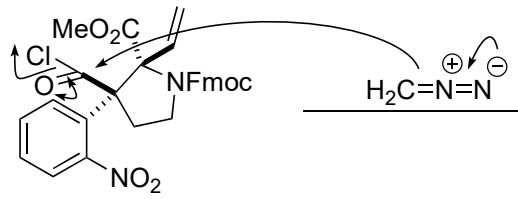


A

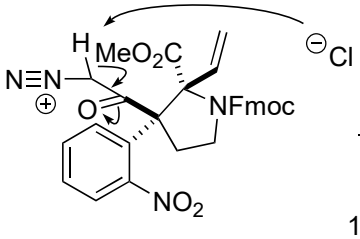


2-2

(Echkermann, R.; Breunig, M. Gaich, T. *Chem. Commun.* **2016**, *52*, 11363.)



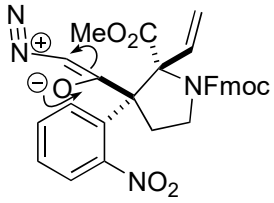
2-1



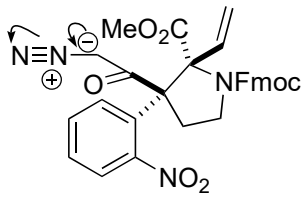
2-4

***Discussion 2**: CaO was used as a scavenger*

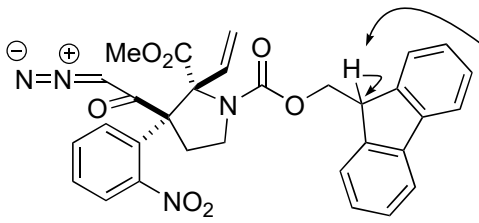
1/2 CaO → 1/2 $CaCl_2$, 1/2 H_2O



2-5

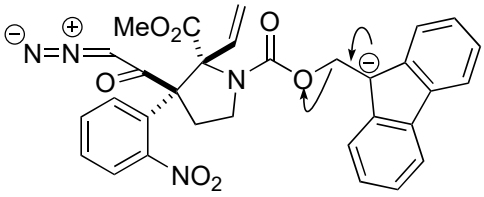


2-6

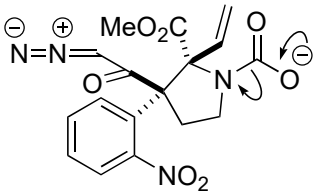


2-7

step 1

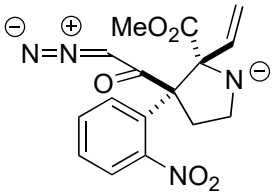


2-8



2-9

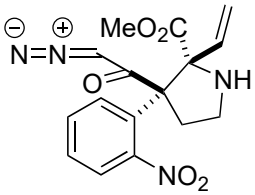
pKa carbamic acid: 3.9
DBU-H^+: 12
MeOH: 15.5



2-10

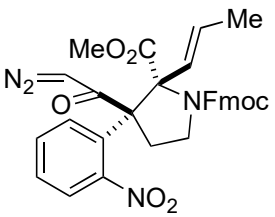
MeO−H

MeO^- / DBU-H^+ ⇌ MeOH / DBU



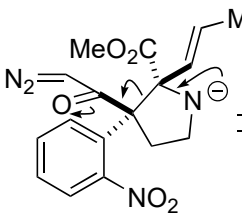
2-11

when 2nd step was conducted under aprotic condition (THF)
(Eckermann, R.; Breuning,M.; Gaich, T. *Chem. Eur. J.* **2017**, *23*, 3938.)

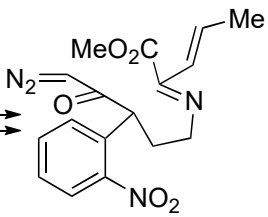


2-12

DBU, THF, 23 °C



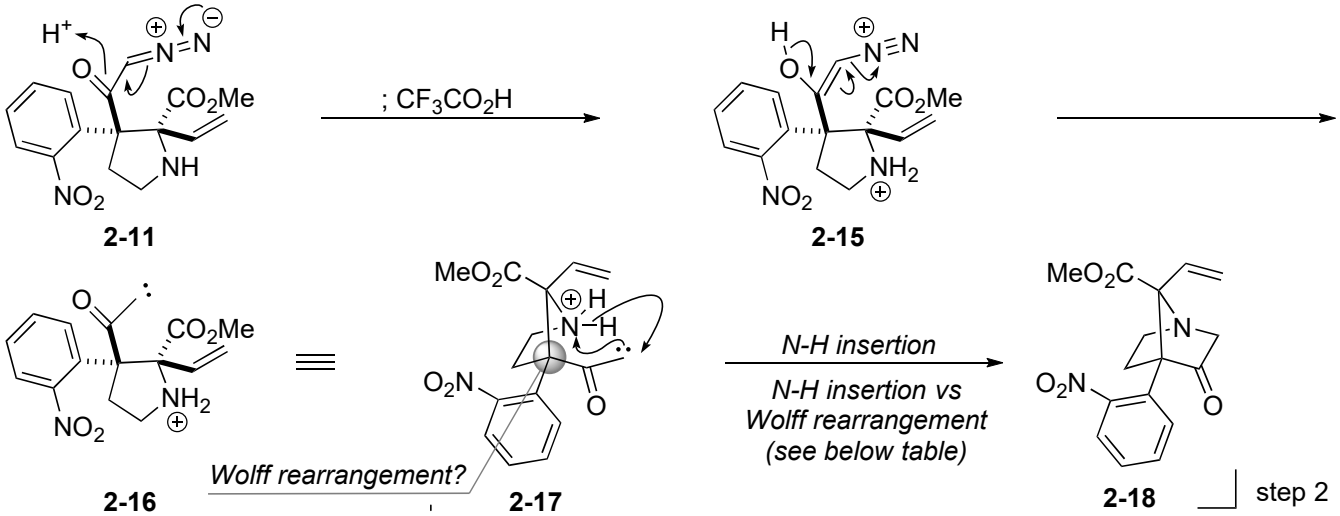
2-13

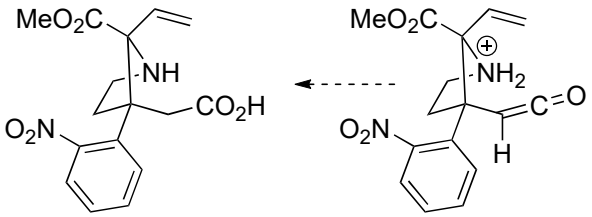


2-14 (isolated)

To prevent fragmentation of **2-10**, MeOH was used as a protic solvent.

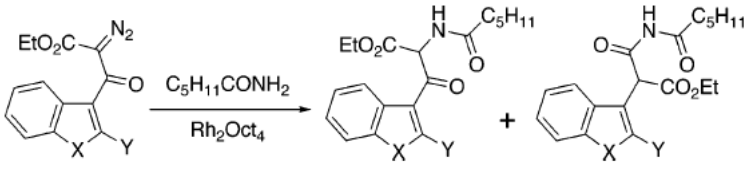
(a) auther proposal





In this table, when diazo **40** was used as a starting material, N-H insertion adduct **51** was obtained exclusively. Electron withdrawing group suppress the Wolff rearrangement.
(Davies, J. R.; Kane, P. D.; Moody, C. J.; Slawin, A. M. Z. *J. Org. Chem.* **2005**, *70*, 5840.)

TABLE 1. Competing N–H Insertion and Wolff Rearrangement in the Dirhodium Tetraoctanoate-Catalyzed Reactions of 3-Indolyl and 3-Benzothienyl Diazoketoesters

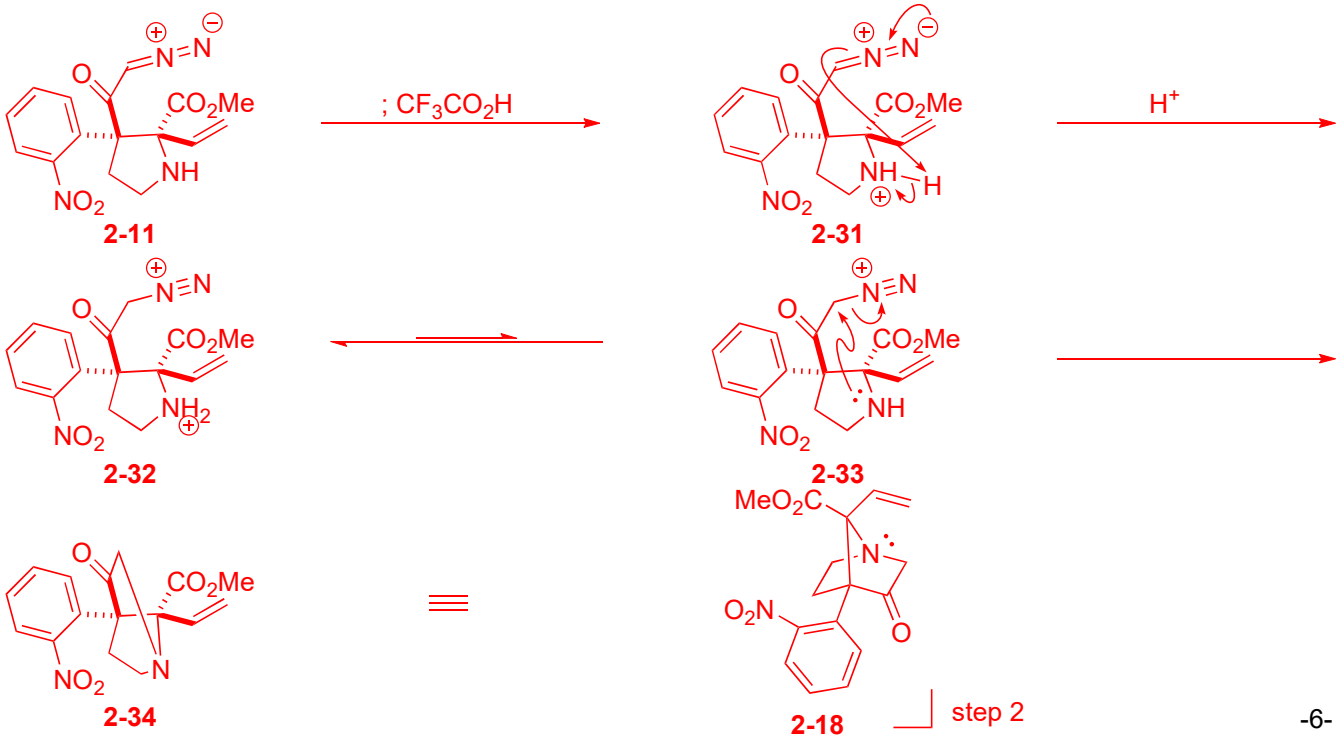


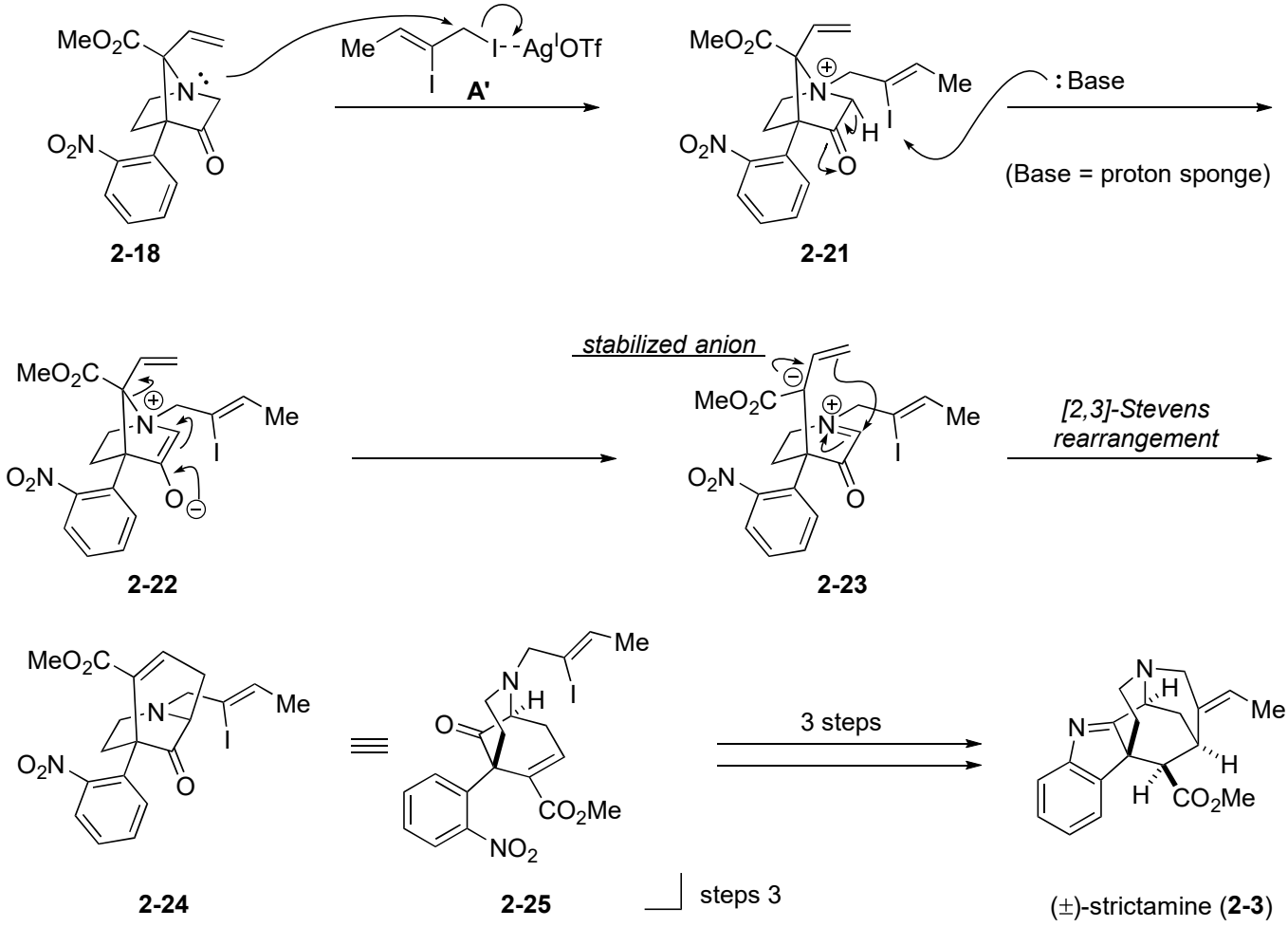
diazo	X	Y	N–H insertion	yield/%	Wolff	yield/%
25	NBoc	H	**26**	39	**27**	55
36	NBoc	Cl	**47**	47	**48**	38
38	NBs	H	**49**	52	**50**	23
40	NNs	H	**51**	52		0
44	NMe	H		0	**52**	81
42	S	H	**53**	38	**54**	30

Bs: brosyl; *p*-bromobenzenesulfonyl

N-H insertion of **2-17** occured prior to Wolff rearrangement because of electron withdrawing groups, CO_2Me and $ArNO_2$.

(b) our proposal





***Discussion 2**: effect of CaO in the presence of diazomethane*

Pace, V.; Verniest, G.; Sinisterra, J.-V.; Alcántara, . R.; Kimpe, N. D. *J. Org. Chem.* **2010**, *75*, 5760.

in this paper (*JOC*, **2010**, *75*, 5760.), screening of HX scavenger was investigated to form diazoketone **2-27**

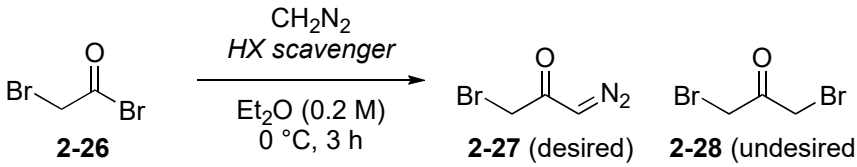


TABLE 1. Hydrohalic Acid Scavenger Effect in the Acylation of Diazomethane with Bromoacetyl Bromide

entry	CH_2N_2 (equiv)	HX scavenger (equiv)	yield of **6a** (%)
1	1.3	Et_3N (1.1)	complex mixture
2	1.3	Et_3N (0.7)	complex mixture
3	1.3	$NaHCO_3$ (1.1)	0[a]
4	1.3	$KHCO_3$ (1.1)	15[b]
5	1.3	K_2CO_3 (0.5)	52[c]
6	1.3	K_2CO_3 (1.1)	65[d]
7	1.3	K_2CO_3 (2.0)	39
8	0.7	CaO (0.7)	64
9	1.0	CaO (3.0)	100
10	1.0	CaO (6.0)	100

Reactions were carried out at 0°C during 3 h using 1.0 equiv of bromoacetyl bromide. [a]1,3-Dibromoacetone was recovered as the only reaction product in 34% yield. [b]28% of 1,3-dibromoacetone was detected via ^{1}H NMR. [c]36% of 1,3-dibromoacetone was detected via ^{1}H NMR. [d]15% of 1,3-dibromoacetone was detected via ^{1}H NMR.

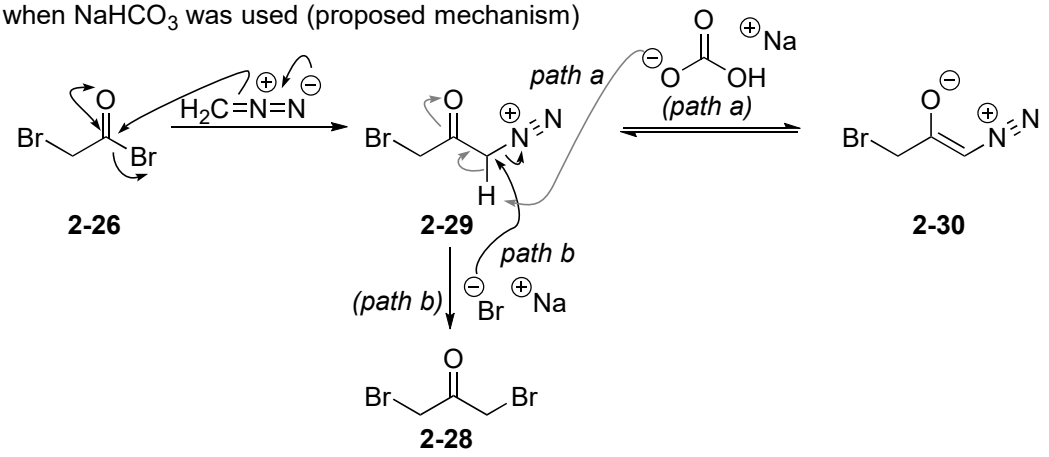
results...
$NaHCO_3$: only **2-28** was formed (34%)
$KHCO_3$: desired **2-27** was slightly obtained
CaO: **2-27** was obtained in quantitative yield.

table 2. solubility of each salt in Et_2O

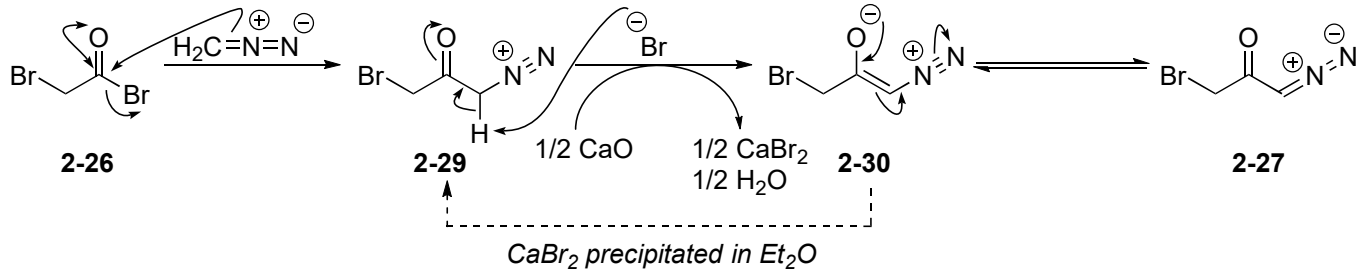
scavenger	solubility in Et_2O (g/100 g)
NaBr	0.08 (20 °C)
KBr	0.02 (15 °C)
$CaBr_2$	insoluble

(http://chemister.r./Database/properties-en.php?bdid=1&id=165, 23/05/2018)

when $NaHCO_3$ was used (proposed mechanism)



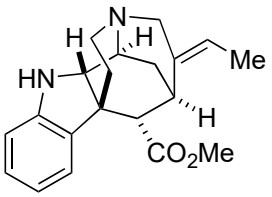
when CaO was used (proposed mechanism)



$CaBr_2$ precipitated in Et_2O

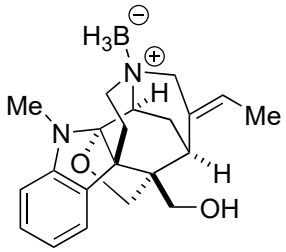
Answer 3

Problem 3



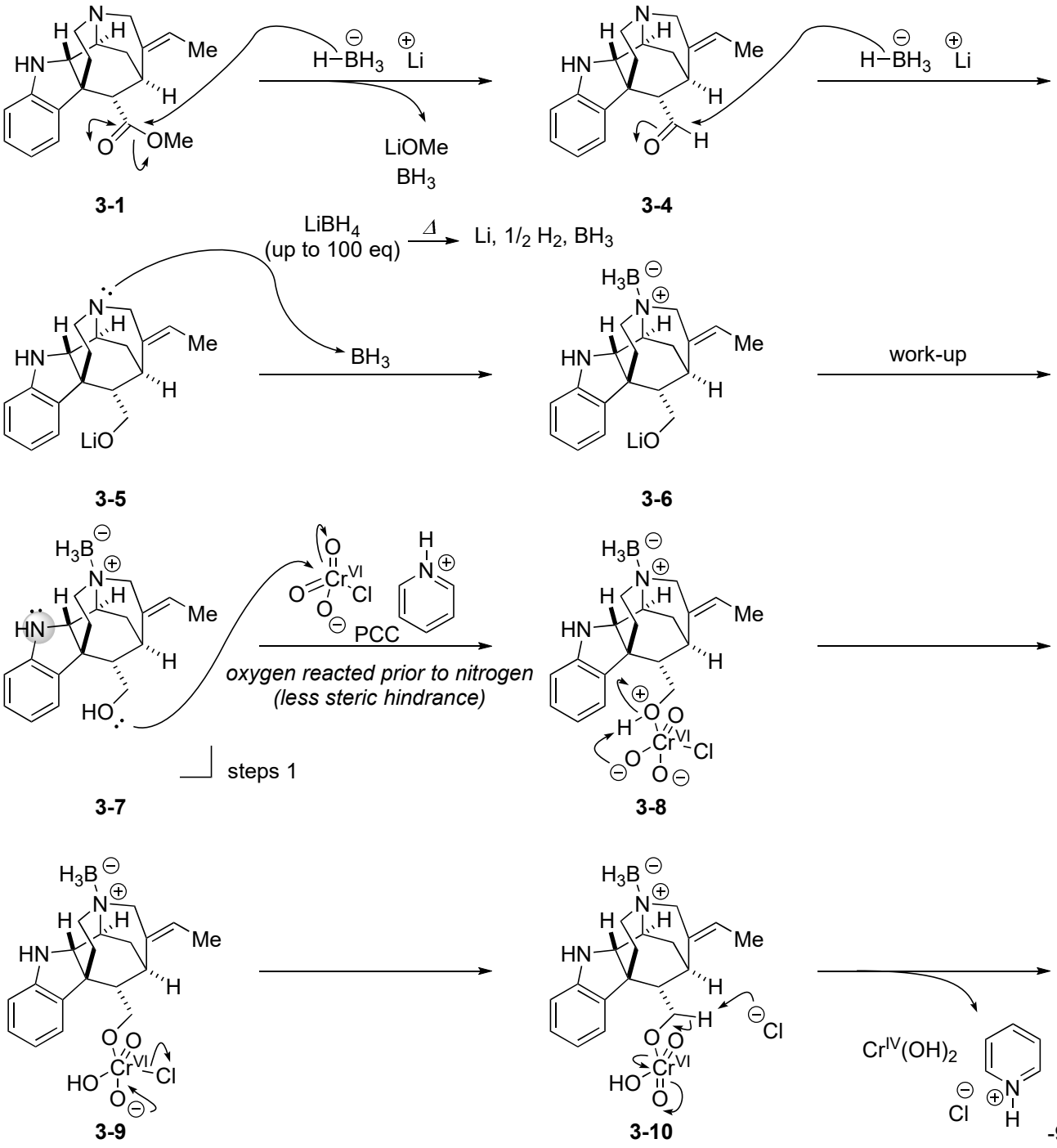
3-1

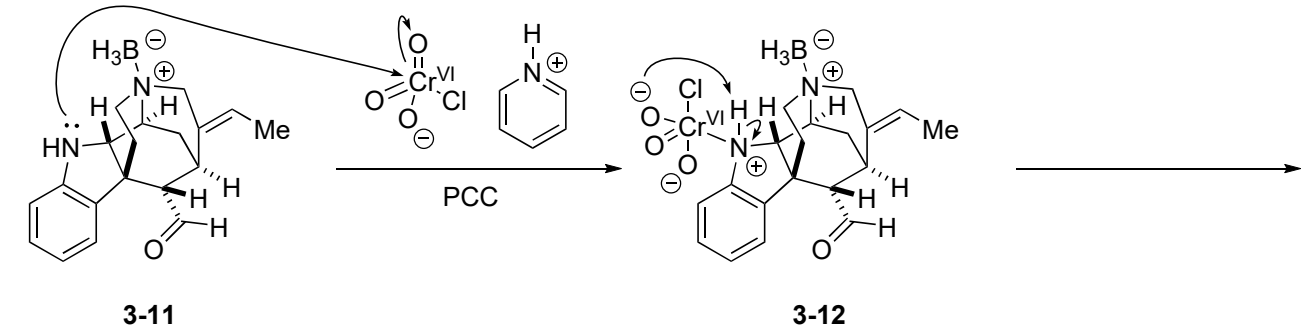
1. $LiBH_4$, THF, 60 °C (69%)
2. PCC, Celite®, CH_2Cl_2, 23 °C
3. Cs_2CO_3, $(CH_2O)_n$ (9 eq), THF
   23 °C (43%, 2 steps)
4. MeI, Cs_2CO_3, MeOH
   30 °C (45%, recovery: 33%)



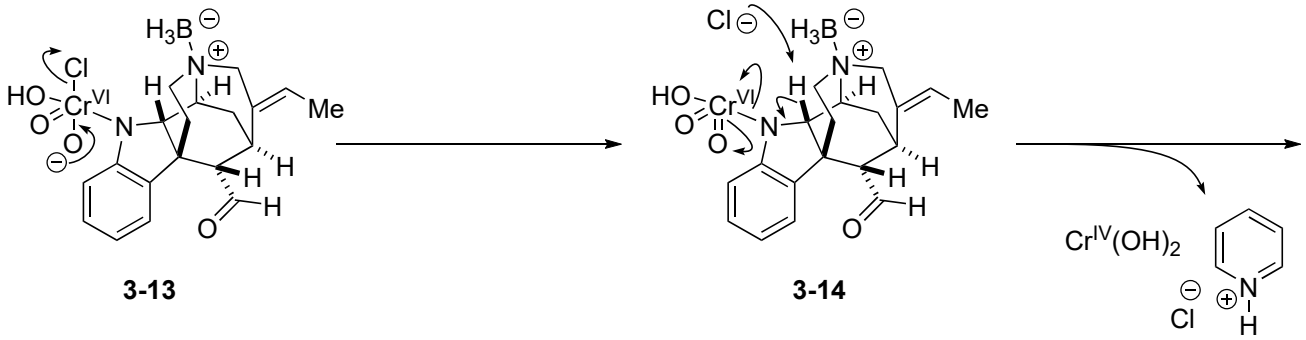
3-2

Picazo, E.; Morrill, L. A.; Susick, R.; Moreno, J.; Smith, J.; Garg, N. K. *J. Am. Chem. Soc.* ASAP.

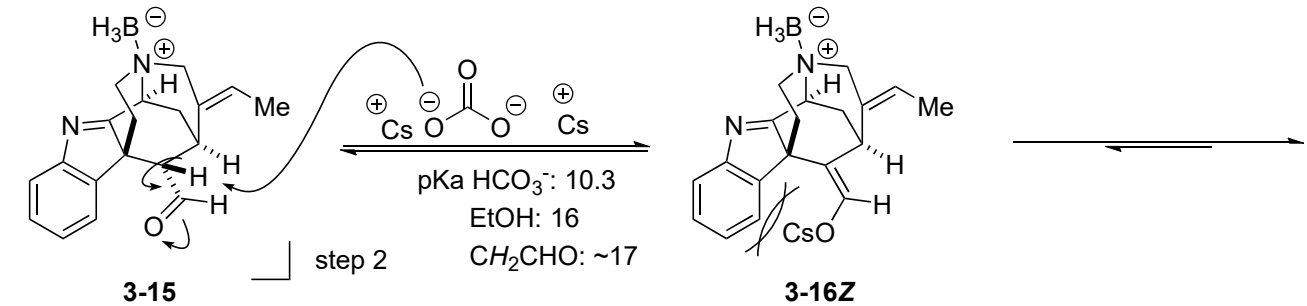




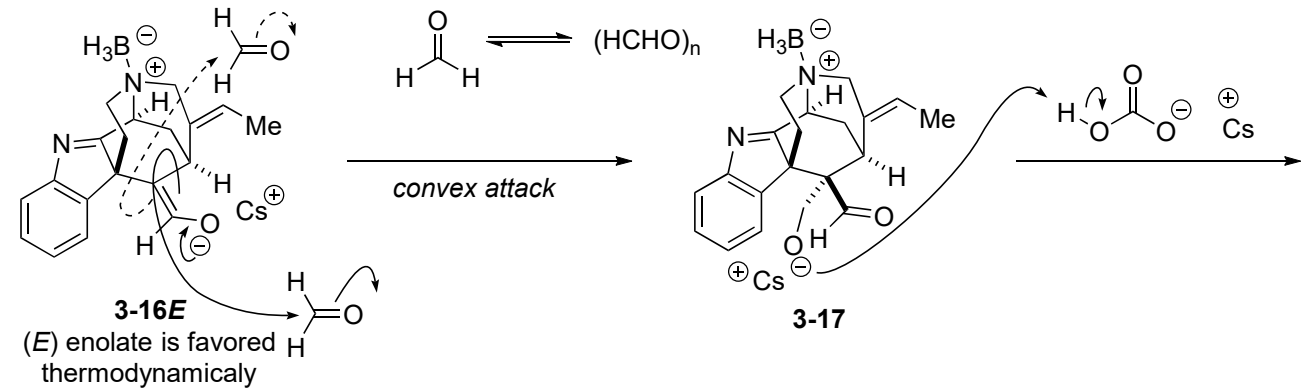
3-11 **3-12**



3-13 **3-14**

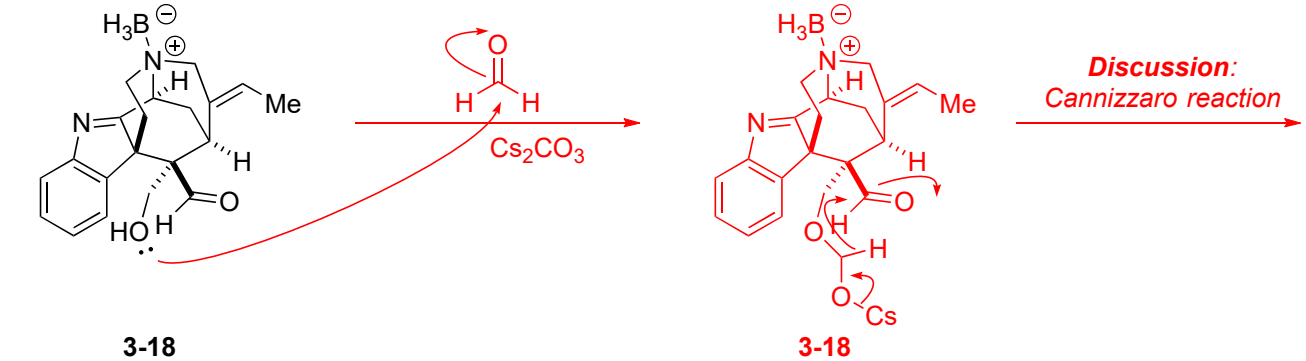


3-15 **3-16Z**



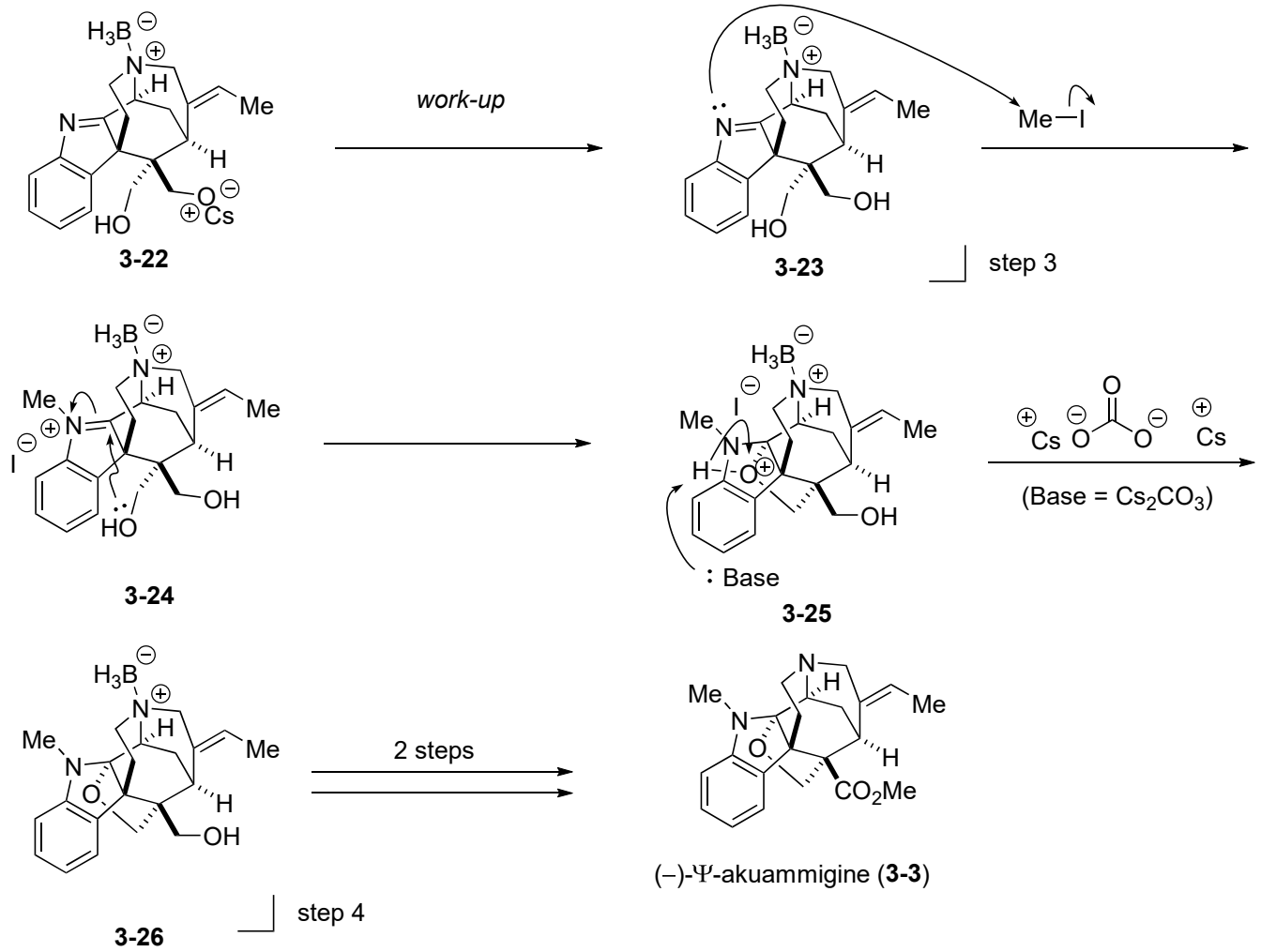
3-16*E*
(*E*) enolate is favored thermodynamicaly

3-17



3-18 **3-18**

Discussion:
Cannizzaro reaction



***Discussion**: Cannizzaro reaction*
(Picazo, E.; Morrill, L. A.; Susick, R.; Moreno, J.; Smith, J.; Garg, N. K. *J. Am. Chem. Soc.* ASAP.)