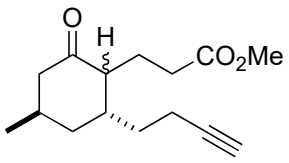
Problem Session (3)

2021.7.17. Shu Nakamura

Topic: *Lycopodium* alkaloids

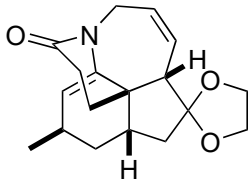
Please explain the reaction mechanism.

1.



1-1
(dr ~ 1:1)

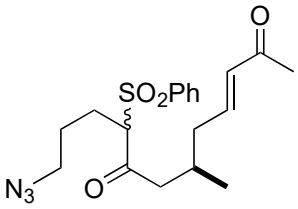
1. **1-2** (3.5 eq.), AcOH/toluene (2/5), reflux, 70%[a)]
2. $PtCl_2$ (10 mol%), toluene, 90 °C, 87%
3. SeO_2 (1 eq.), 1.4-dioxane, 85 °C, 54%
4. 1 M NaOH aq./CH_2Cl_2[b)], rt, 76%
5. ethylene glycol (6 eq.), PPTS (1 eq.), benzene, reflux, 87%
6. *m*-CPBA (3 eq.), CH_2Cl_2, -78 °C to rt, 98%
7. KOH·alumina (1000 wt%), CBr_2F_2 (13 eq.), *t*-BuOH/CH_2Cl_2 (7/3), -15 °C to rt, 46%



1-3

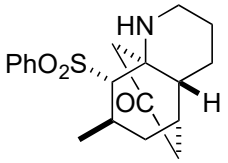
a) as a 10:1 mixture of enamide isomers
b) 5 drops of CH_2Cl_2 were added to NaOH aq. (20 mL)

2.

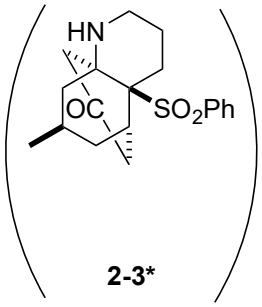


2-1
(as a mixture of diastereomers)

1. *i*-Pr_2NH (6 eq.), *i*-PrOH/CH_2Cl_2 (4/1), rt, 89%
2. PPh_3 (1 eq.), THF, reflux; concentrated; *i*-Pr_2NEt (6.25 eq.), TBSOTf (2.5 eq.), CH_2Cl_2, 0 °C, 82%
3. $Zn(OTf)_2$ (3 eq.), $(CH_2Cl)_2$, 96 °C, 54%

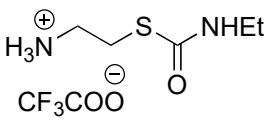


2-2

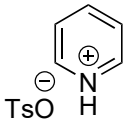


2-3*

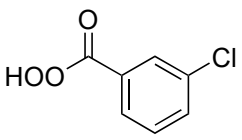
* Authors expected to obtain **2-3**.
However, only **2-2** was obtained, instead.



1-2



PPTS

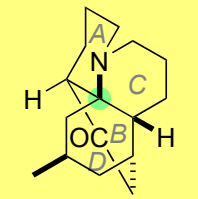


m-CPBA

Problem Session (3) -Answer- 2021.7.17. Shu Nakamura

Topic: Synthesis of *Lycopodium* alkaloids using Sulfur
- sulfonyl rearrangement -

Introduction:

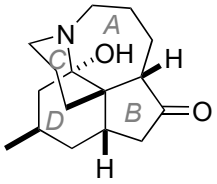


lycopodine
(AChE inhibitor)

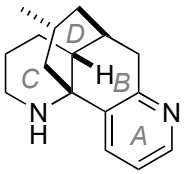
***Lycopodium* alkaloids:** isolated mainly from *Lycopodium* species

isolation
lycopodine (1881)
(Bödeker, K. *Liebigs Ann. Chem.*, **1881**, *208*, 363.)

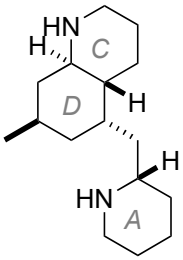
structural features:
tetracyclic ABCD ring system
-> commonly divided into 4 classes in respect of their structures
lycopodine class, fawcettimine class, lycodine class, phlegmarine class
tetrasubstituted carbon atom



fawcettimine



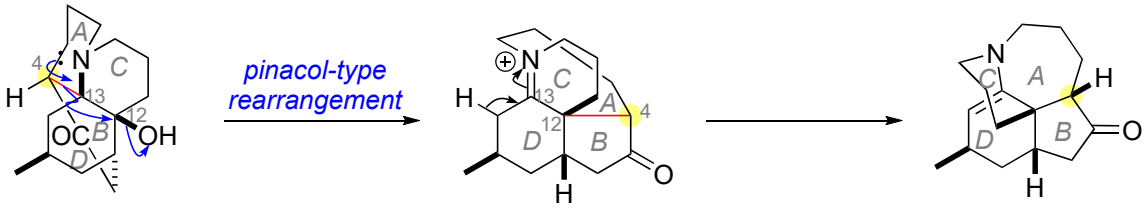
lycodine



phlegmarine

Lycopodium clavatum

Proposed biosynthetic pathway from lycopodine type to fawcettidine



lycodoline
(*lycopodine class*)

fawcettidine
(*fawcettimine class*)

For more information, see:
Siengalewicz, P.; Mulzer, J.; Rinner, U. In *The Alkaloids*; Knölker, H.-J.,Ed.; Academic Press: New York, 2013; Vol. 72, pp. 1-151.

1.

1. **1-2** (3.5 eq.), AcOH/toluene (2/5), reflux, 70%[a)]
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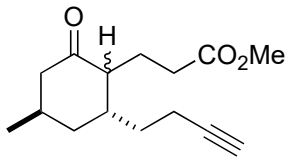
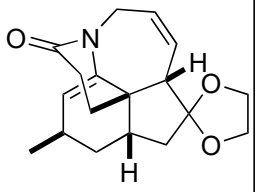


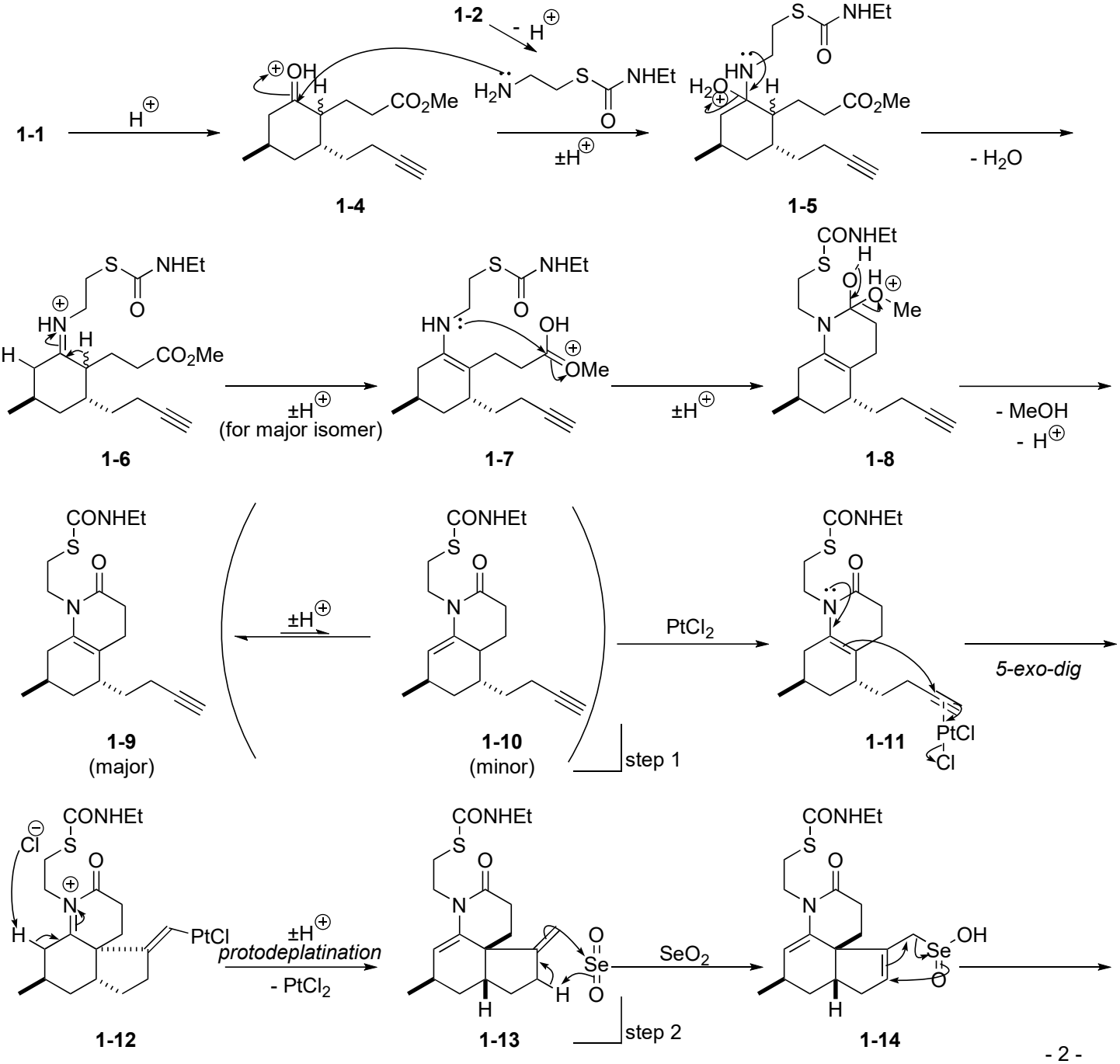
1-1
(dr ~ 1:1)

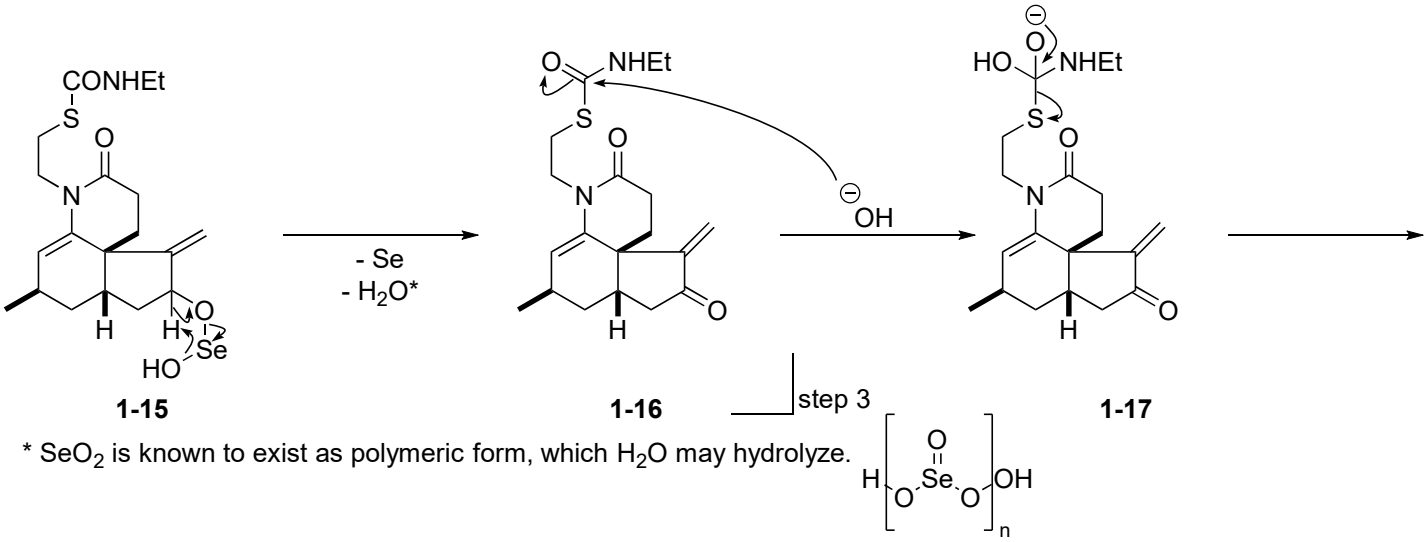


1-3

a) as a 10:1 mixture of enamide isomers
b) 5 drops of CH_2Cl_2 were added to NaOH aq. (20 mL)

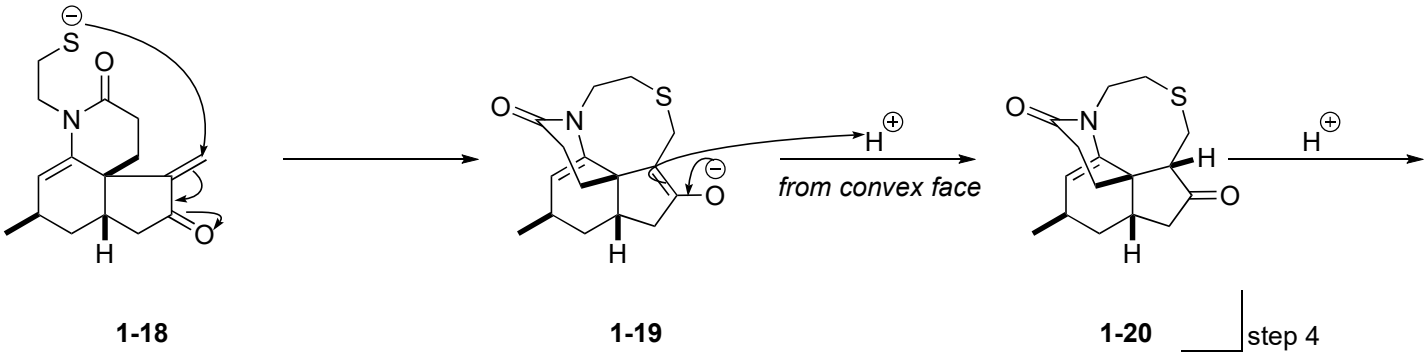
Kozak, J. A.: Dake, G. R. *Angew. Chem. Int. Ed.* **2008**, *47*, 4221.



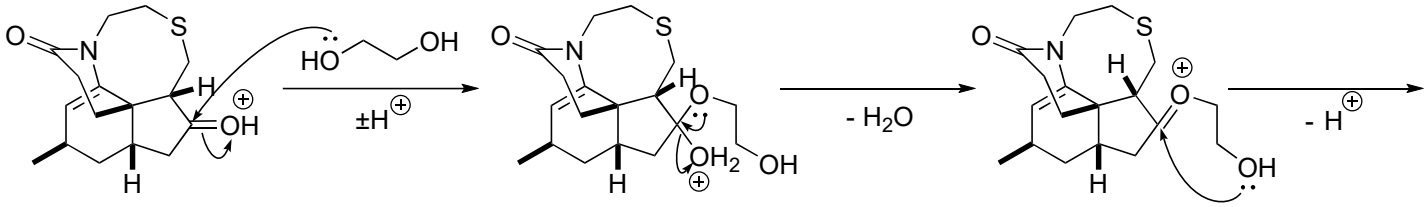


1-15 **1-16** **1-17**

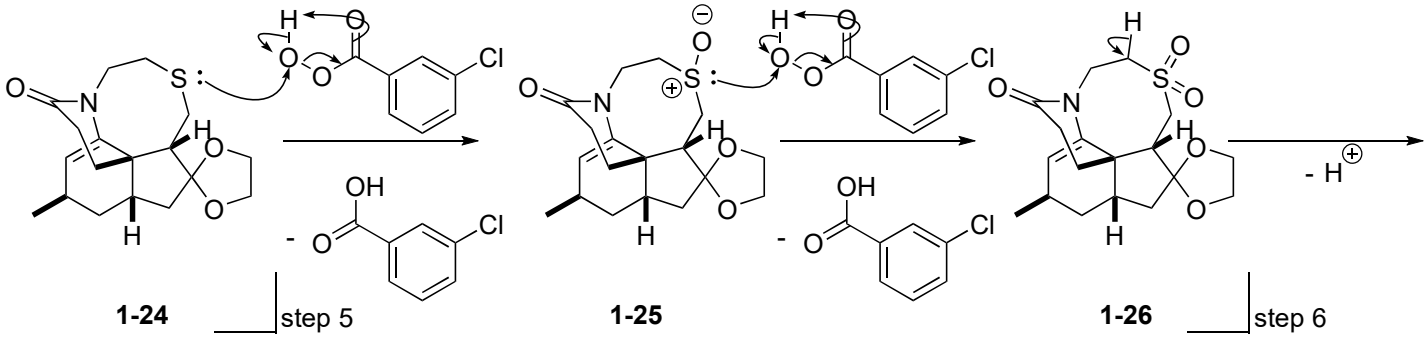
* SeO_2 is known to exist as polymeric form, which H_2O may hydrolyze.



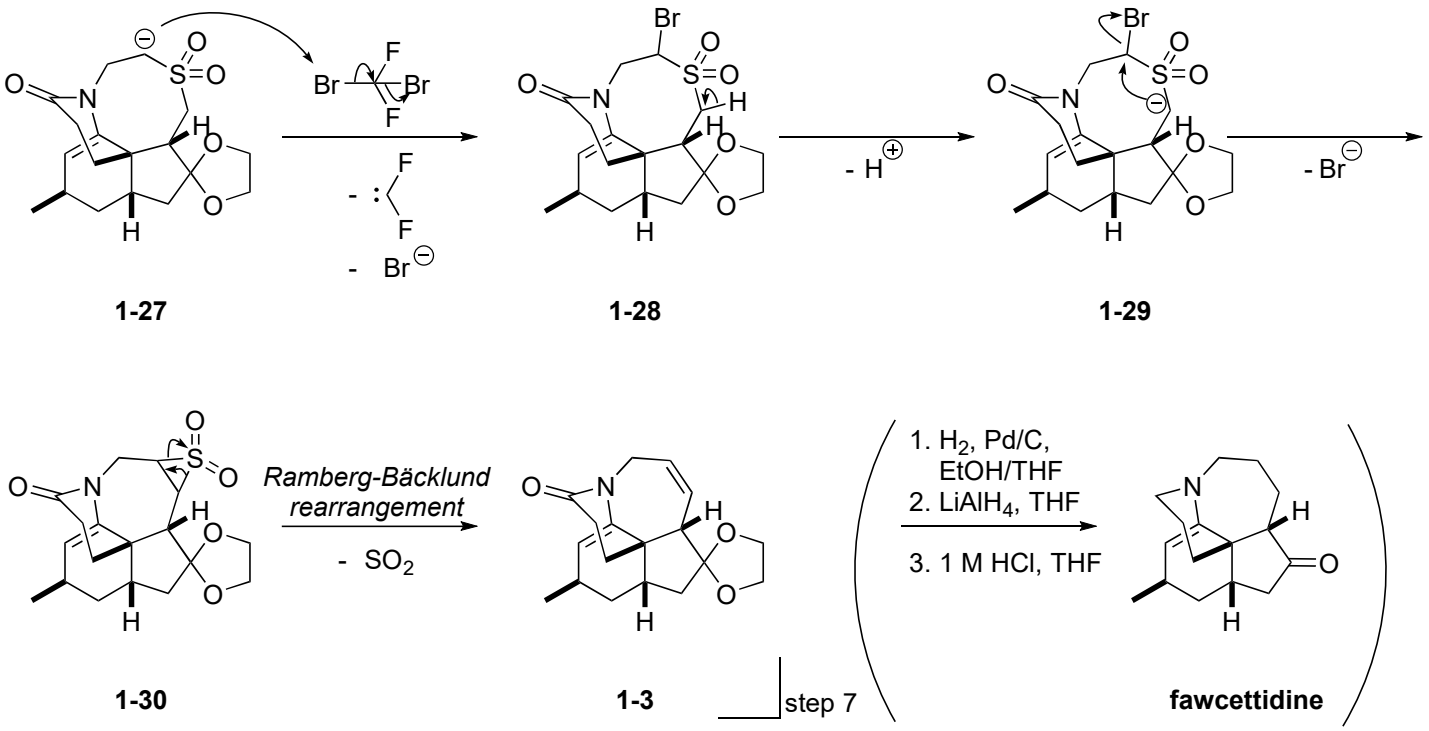
1-18 **1-19** **1-20**



1-21 **1-22** **1-23**

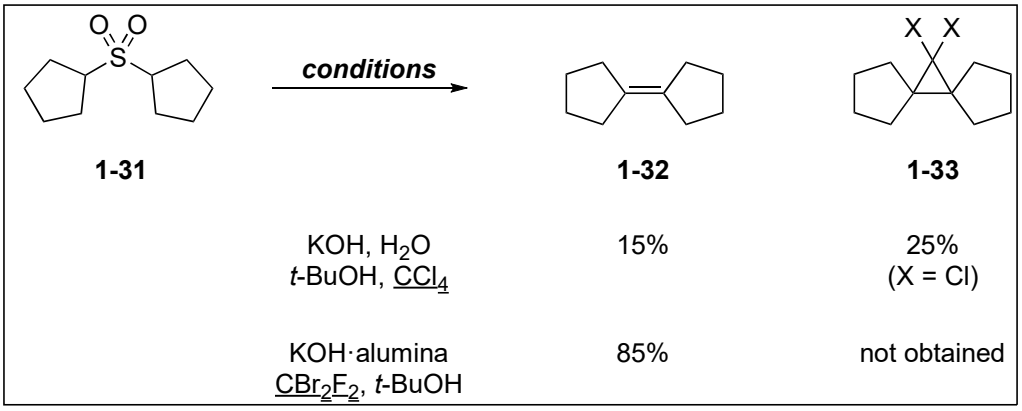


1-24 **1-25** **1-26**



Appendix: The use of CBr_2F_2 - stability of dihalocarbene -

In the one-pot procedure of Ramberg-Bäcklund rearrangement, a carbene adduct to generated olefin is sometimes obtained as a by-product.

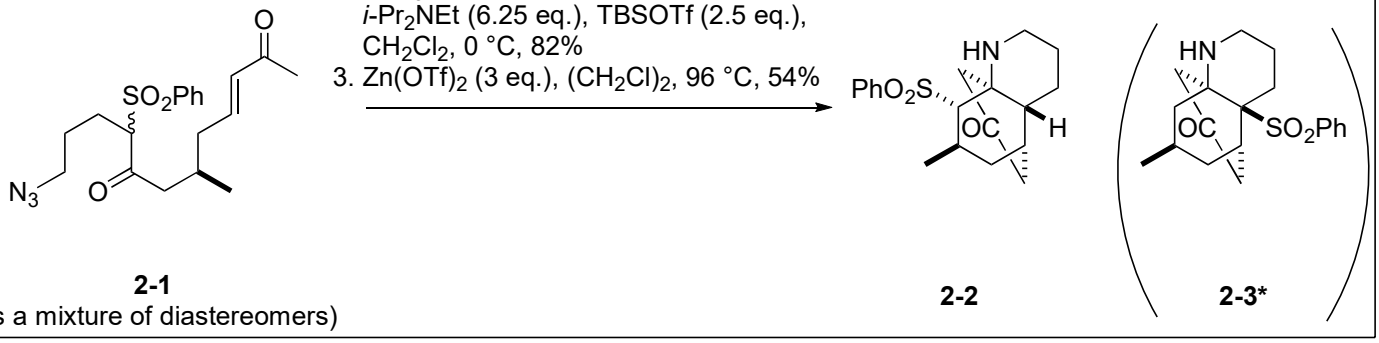


Meyers, C. Y.; Malte, A. M.; Matthew, W. S. *J. Am. Chem. Soc.* **1969**, *91*, 7510.
Chan, T.-L.; Fong, S.; Li, Y.; Man, T.-O.; Poon, C.-D. *J. Chem. Soc., Chem. Commun.* **1994**, 1771.

The larger overlap between $2p_{(C)}$ and $2p_{(F)}$ (than between $2p_{(C)}$ and $3p_{(Cl)}$) stabilizes difluorocarbene than dichlorocarbene.
Therefore, CBr_2F_2 is better halogen source for this Ramberg-Bäcklund rearrangement.

Also see: Moss, R. A. *Acc. Chem. Res.* **1980**, *13*, 58.

2.

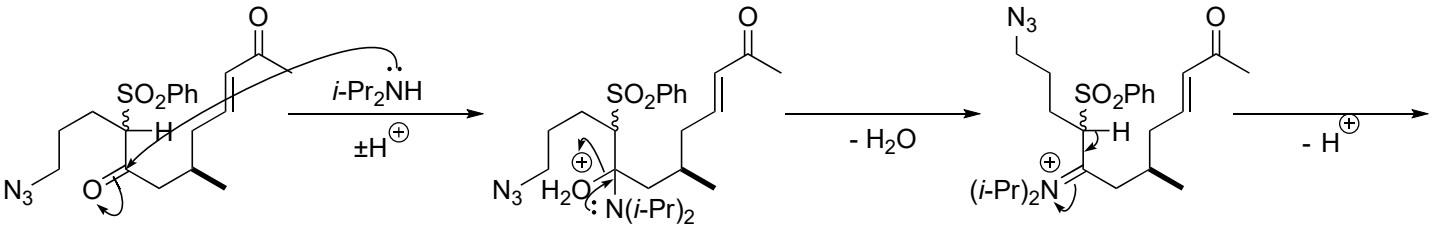


2-1
(as a mixture of diastereomers)

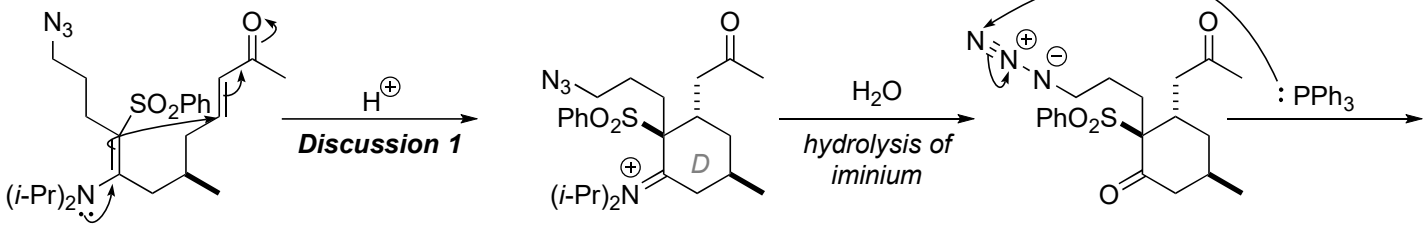
2-2

2-3*

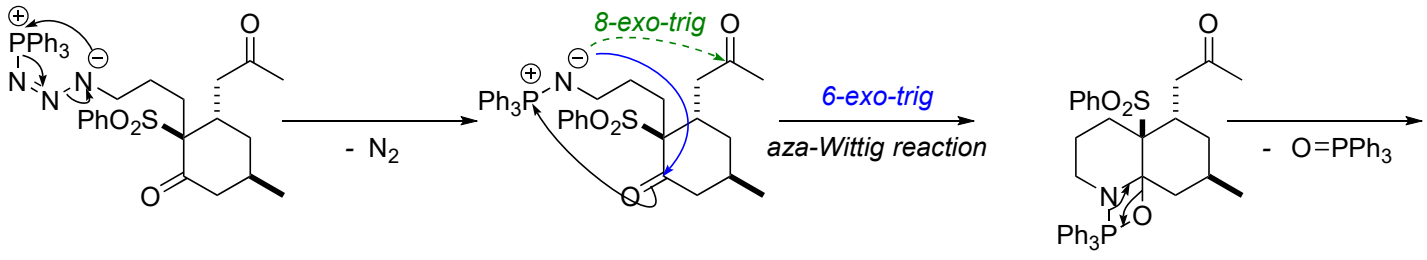
Yang, H.; Carter, R. G.; Zakharov, L. N. *J. Am. Chem. Soc.* **2008**, *130*, 9238.
Yang, H.; Carter, R. G. *J. Org. Chem.* **2010**, *75*, 4929.



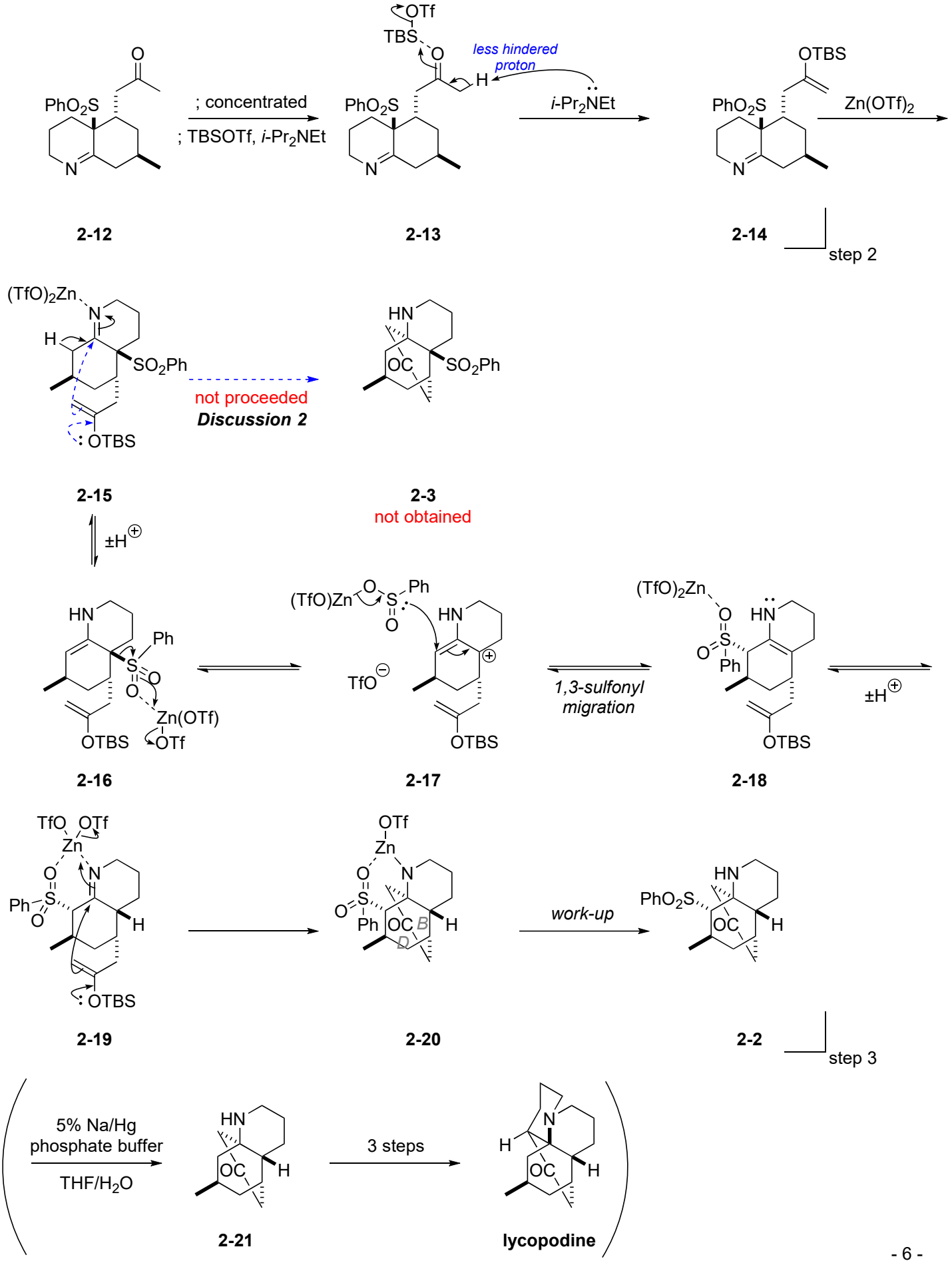
2-1 **2-4** **2-5**



2-6 **2-7** **2-8**



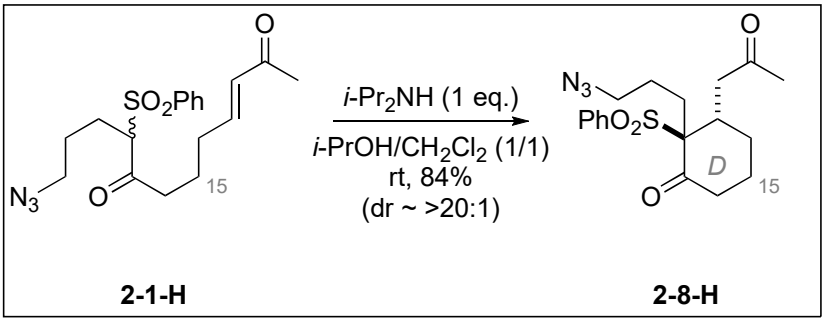
2-9 **2-10** **2-11**

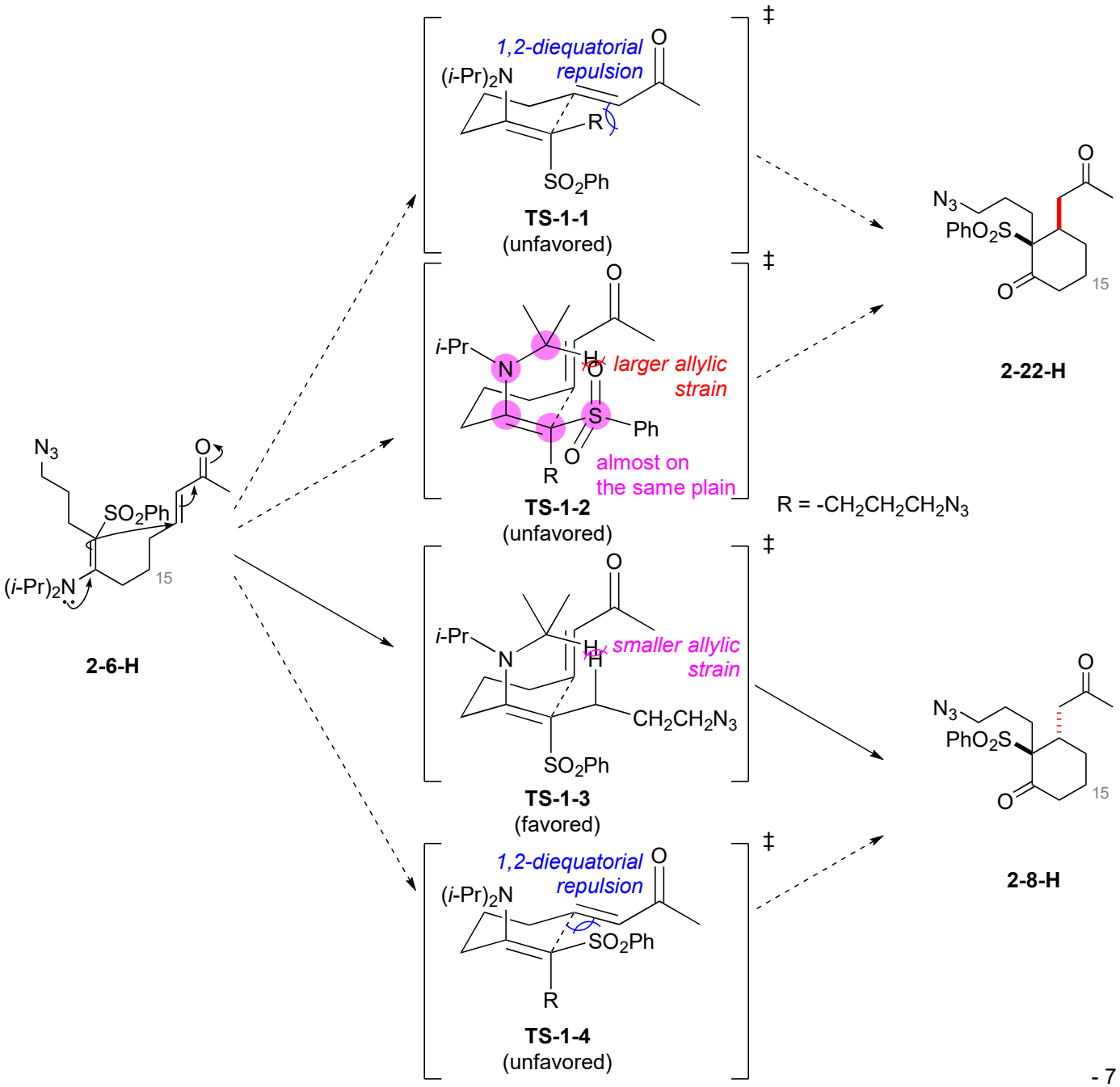

; concentrated
; TBSOTf, i-Pr2NEt
less hindered proton
i-Pr2NEt
Zn(OTf)2
2-12
2-13
2-14
step 2
not proceeded
Discussion 2
2-15
2-3
not obtained
±H
1,3-sulfonyl migration
±H
2-16
2-17
2-18
work-up
2-19
2-20
2-2
step 3
5% Na/Hg
phosphate buffer
THF/H2O
3 steps
2-21
lycopodine

Discussion:

1. Diastereo-selectivity of intramolecular Michael addition

When C15-desmethyl model substrate **2-1-H** was treated with the similar conditions, the same selectivity appeared. Therefore, C15-Me is omitted in this discussion.

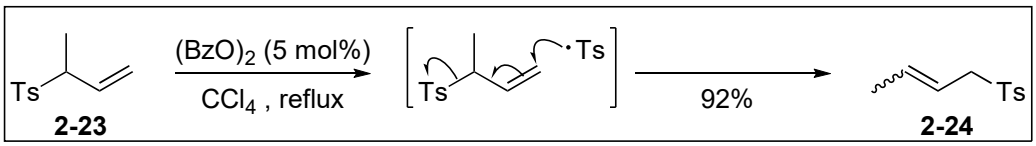




2. Tandem 1,3-sulfonyl migration, Mannich reaction

2-1. Mechanism of 1,3-sulfonyl migration

Radical mechanism is also known.

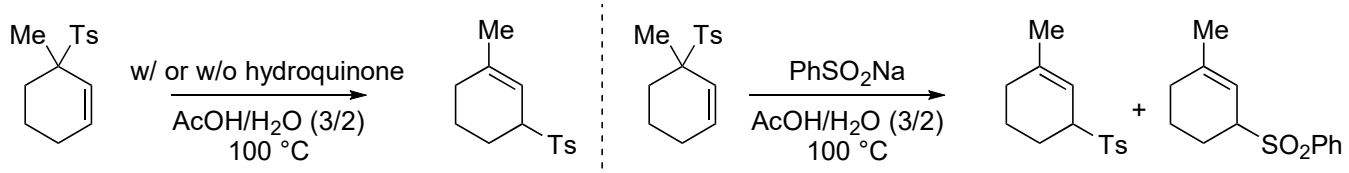


2-23 **2-24**

Knignt, D. J.; Lin, P.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 2707.

However, this rearrangement (via radical pathway) needs radical initiator (or *hv*) and is inhibited by radical quencher.

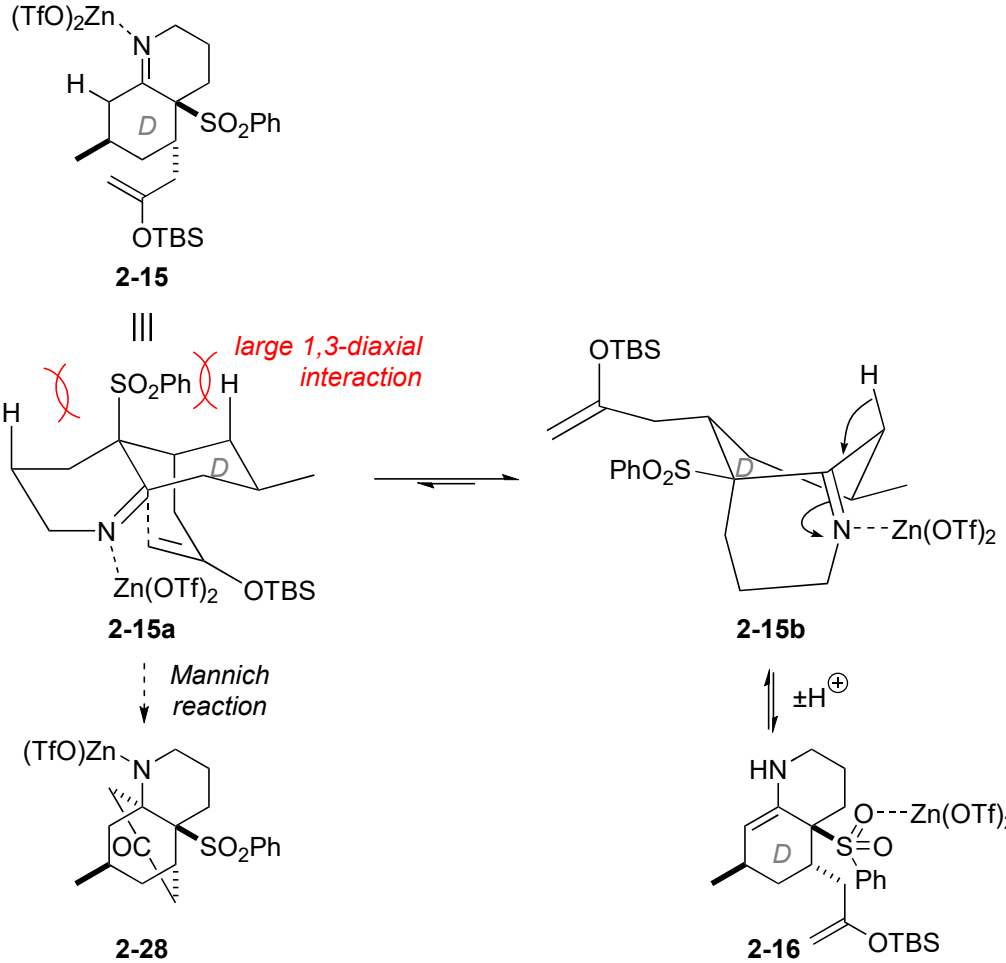
It is also known that acid promotes this migration, which is not inhibited by hydroquinone (radical quencher).

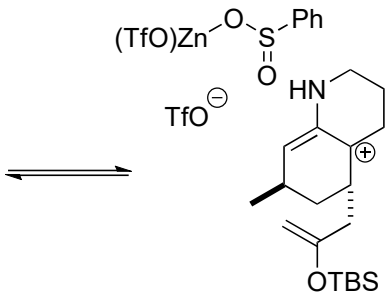


2-25 **2-26** **2-25** **2-26** **2-27**

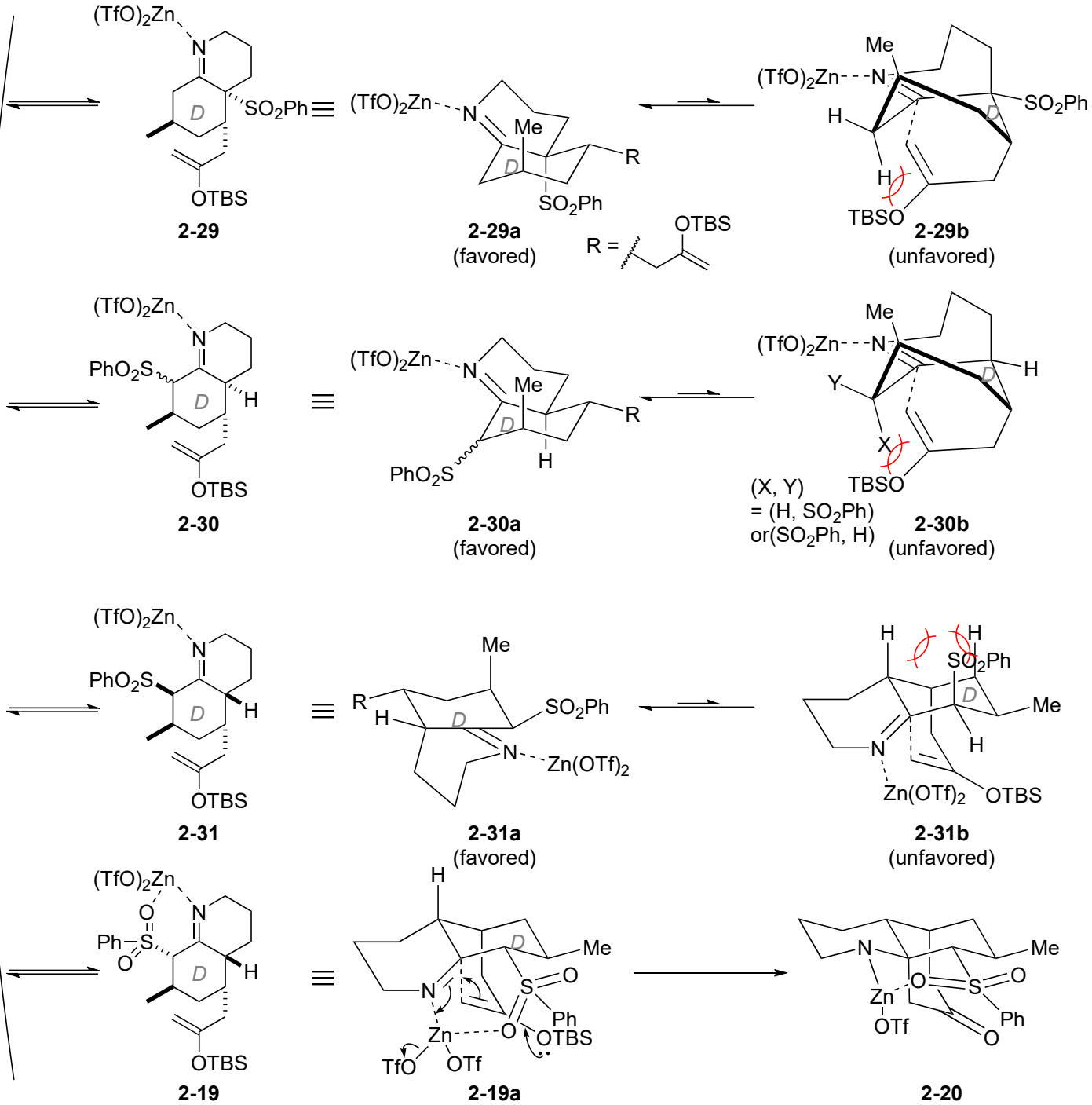
2-27 was also detected in the presence of $PhSO_2Na$.
-> Acidic conditions also initiate 1,3-sulfonyl migration via *ionic mechanism*.

2-2. Necessity of sulfonyl migration for Mannich reaction





2-17



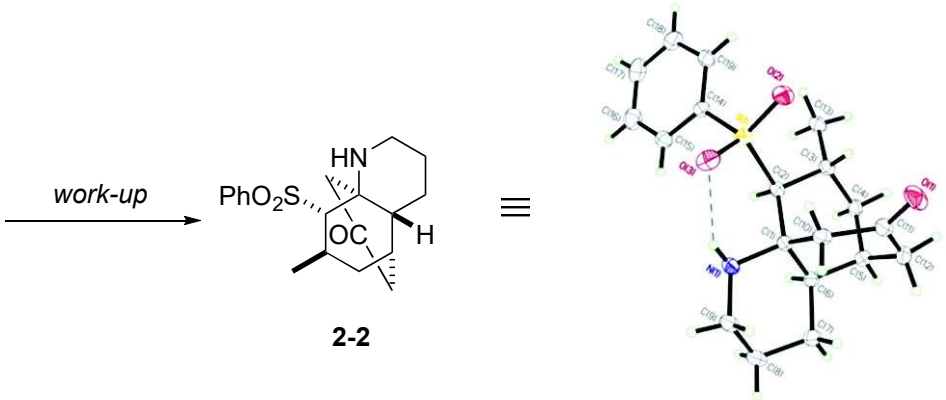
2-29 **2-29a** (favored) **2-29b** (unfavored)

2-30 **2-30a** (favored) **2-30b** (unfavored)

2-31 **2-31a** (favored) **2-31b** (unfavored)

2-19 **2-19a** **2-20**

Only **2-19** has a suitable conformer which has axial side chain R.
Therefore, Mannich cyclization proceeded via only **2-19a**.

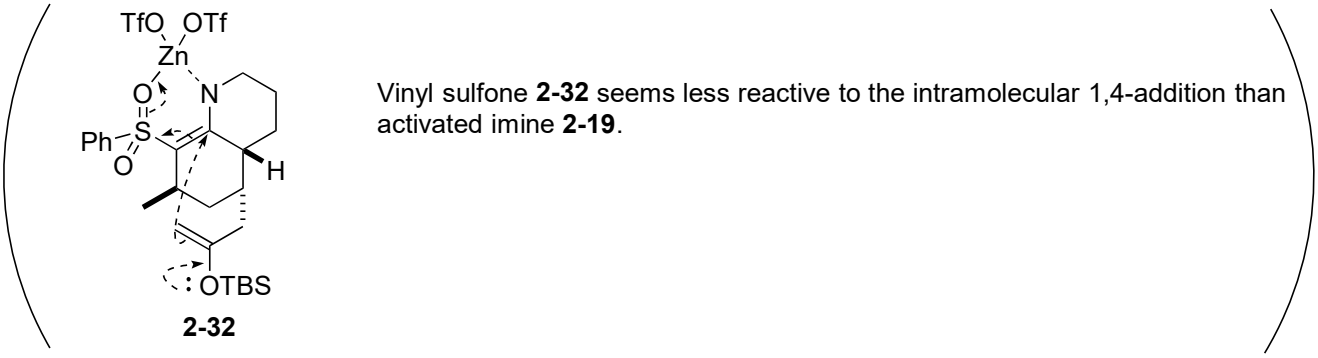


2-2

≡

(X-ray structure)

1,3-Sulfonyl migration occurred <u>before</u> Mannich cyclization to afford most preferable imine **2-19**.



2-32

Vinyl sulfone **2-32** seems less reactive to the intramolecular 1,4-addition than activated imine **2-19**.