## Problem Session (3) -Answer-

2024/05/18 Yuyan Liang

**Topic:** Recent synthetic works by Qi's group.

-> quick construction of architecture of sarpagine alkaloids and spirooxidole alkaloids.

### 0. Introduction

0-1. Prof. Qi Xiangbin

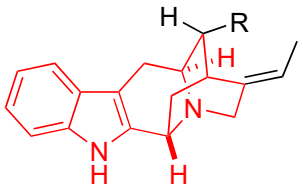
-2009: Ph.D UT Southwestern Medical Center, Dallas
2009-2013: Postdoctor University of Illinois Urbana-Champaign and medicinal chemistry research at UT Southwestern Medical Center.
2010- now: Director of chemistry center at NIBS (National Institute of Biological Science) Associate Investigator at Tsinghua Institute of Multidisciplinary Biomedical Research, Tsinghua University. Professor, East China Normal University

Research Area:
1. Novel synthetic methodology
2. Total synthesis of natural product

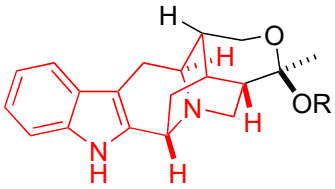
0-2. Total synthesis of natural products

0-2-1. Sarpagine alkaloids ----> **Problem 1**

isolation : from Apocynaceae plant
biological activity : anti-inflammatory, analgesic, anticancer, antiplasmodial activities.
structure feature : indole-fused 1-azabicyclo [2.2.2] octane (red color)
Representatives



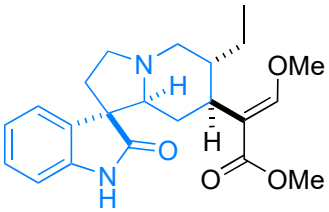
R = CHO, (+)-vellosimine
R = $CH_2OH$, (+)-normacusine B



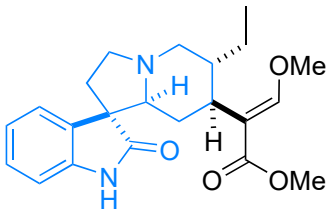
R = H, (-)-trinervine
R = Me, (-)-alstomutinine C

0-2-2. Spirooxindole alkaloids Rhynchophylline -----> **Problem 2**

isolation : from Uncaria rhynchophylla
biological activity : non-competitive NMDA antagonist and a calcium channel blocker.
structure feature : tetracyclic spiro[indolizidine-1,3'-oxindole] (blue color)

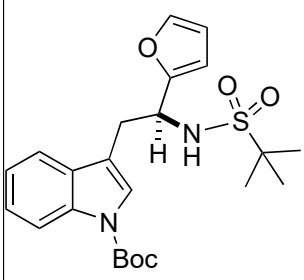


Rhynchophylline

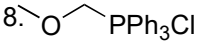


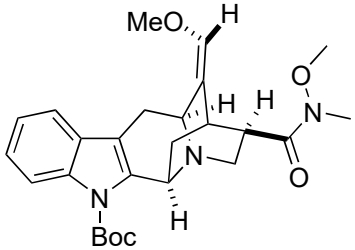
Isorhynchophylline

**Problem 1**



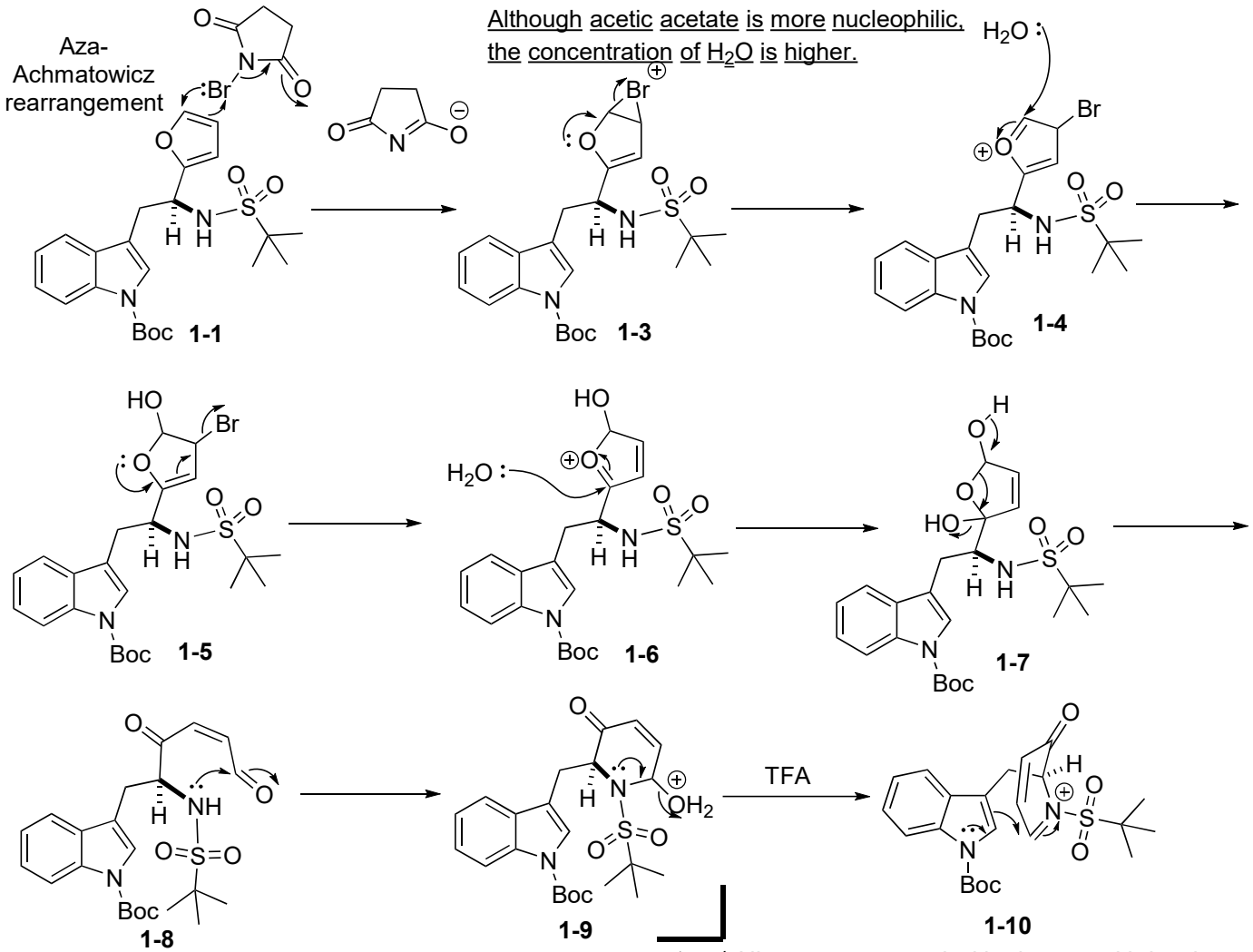
**1-1**

1. NBS (1.2 eq), $NaOAc{\cdot}3H_2O$ (3.0 eq)
   $MeCN:H_2O$ = 4:1, rt,;
2. TFA (1.5 eq), $CH_2Cl_2$, 0 °C, 80% (2 steps)
3. Pd/C, $H_2$, EtOAc, rt;
4. $AlCl_3$ (10.0 eq), anisole (6.0 eq), $CH_2Cl_2$, rt, 89% (2 steps)
5. acrylic Weinreb amide (5.0 eq), $Et_3N$ (2.0 eq), rt, 77%
6. $Boc_2O$ (1.2 eq), DMAP (0.2 eq), $CH_2Cl_2$, 96%
7. LiHMDS (2.5 eq), $I_2$ (1.2 eq), THF, -78 °C to rt, 61%
8.  (5.0 eq), *t*-BuOK (5.0 eq), THF, 0 °C to rt, 64%



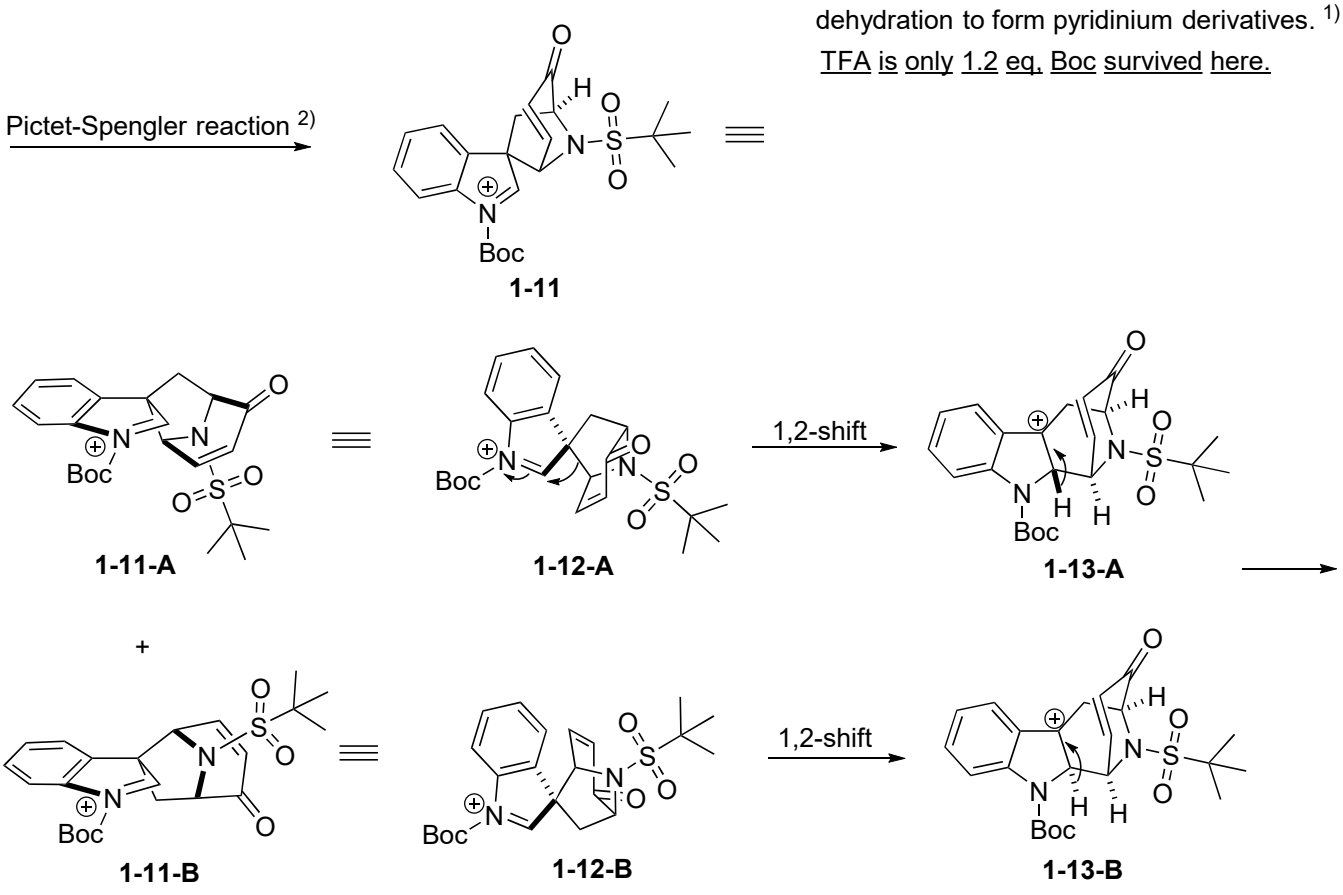
**1-2**

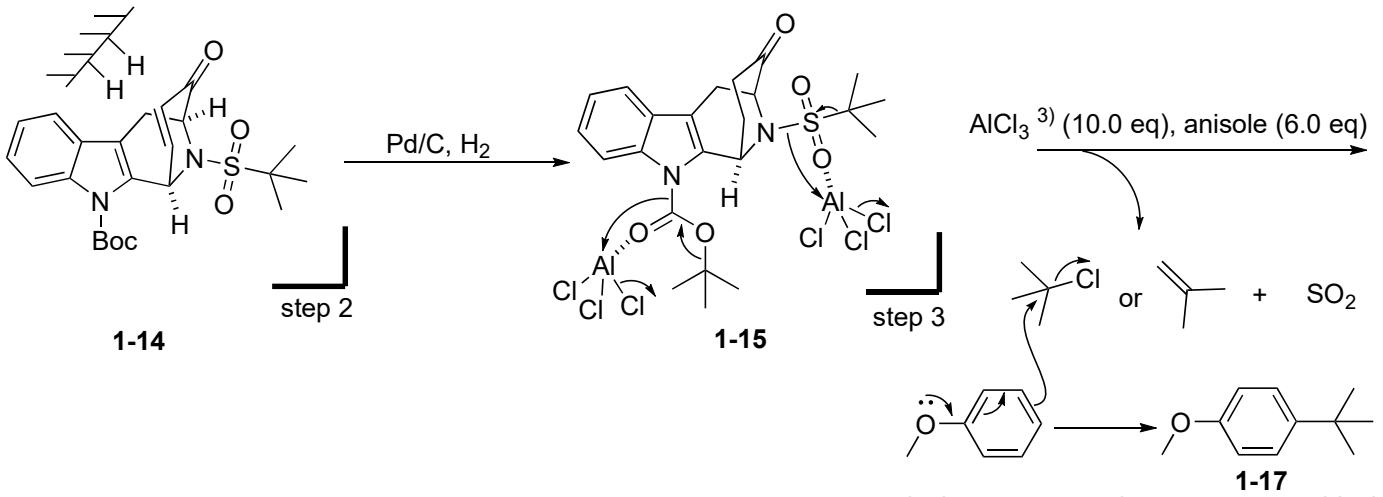
Zhang, Y.; Zhang, L.; Qi, X. B. *Angew. Chem. Int. Ed.* **2023**, *62*, e202304435



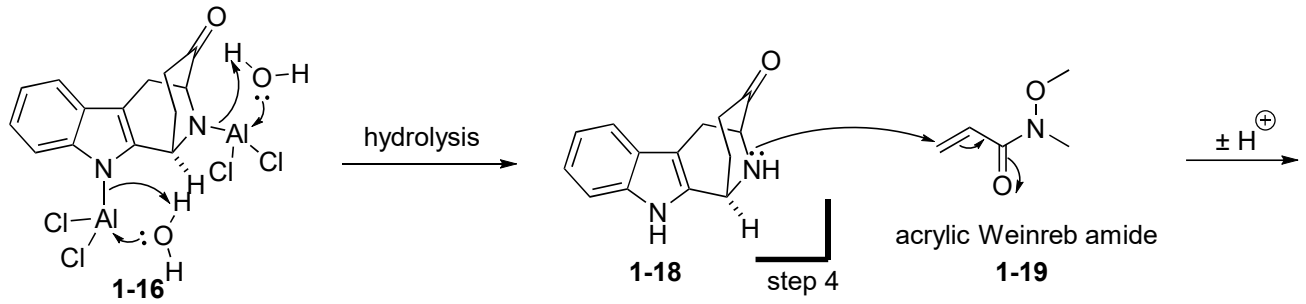

step 1 Nitrogen connected with electron-withdrawing group is stable and not prone to undergoing dehydration to form pyridinium derivatives. [1)]
TFA is only 1.2 eq, Boc survived here.

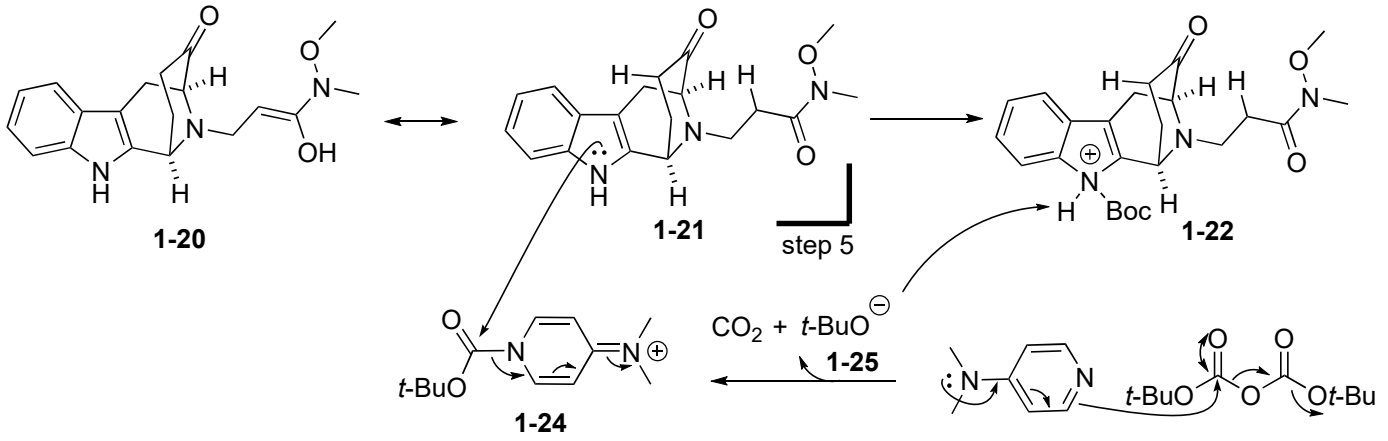
Pictet-Spengler reaction [2)]

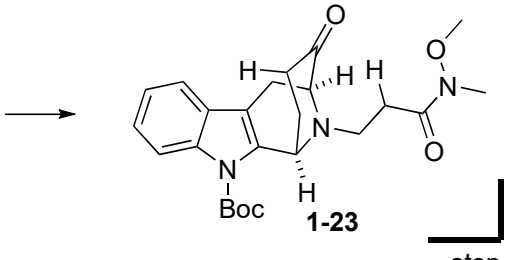


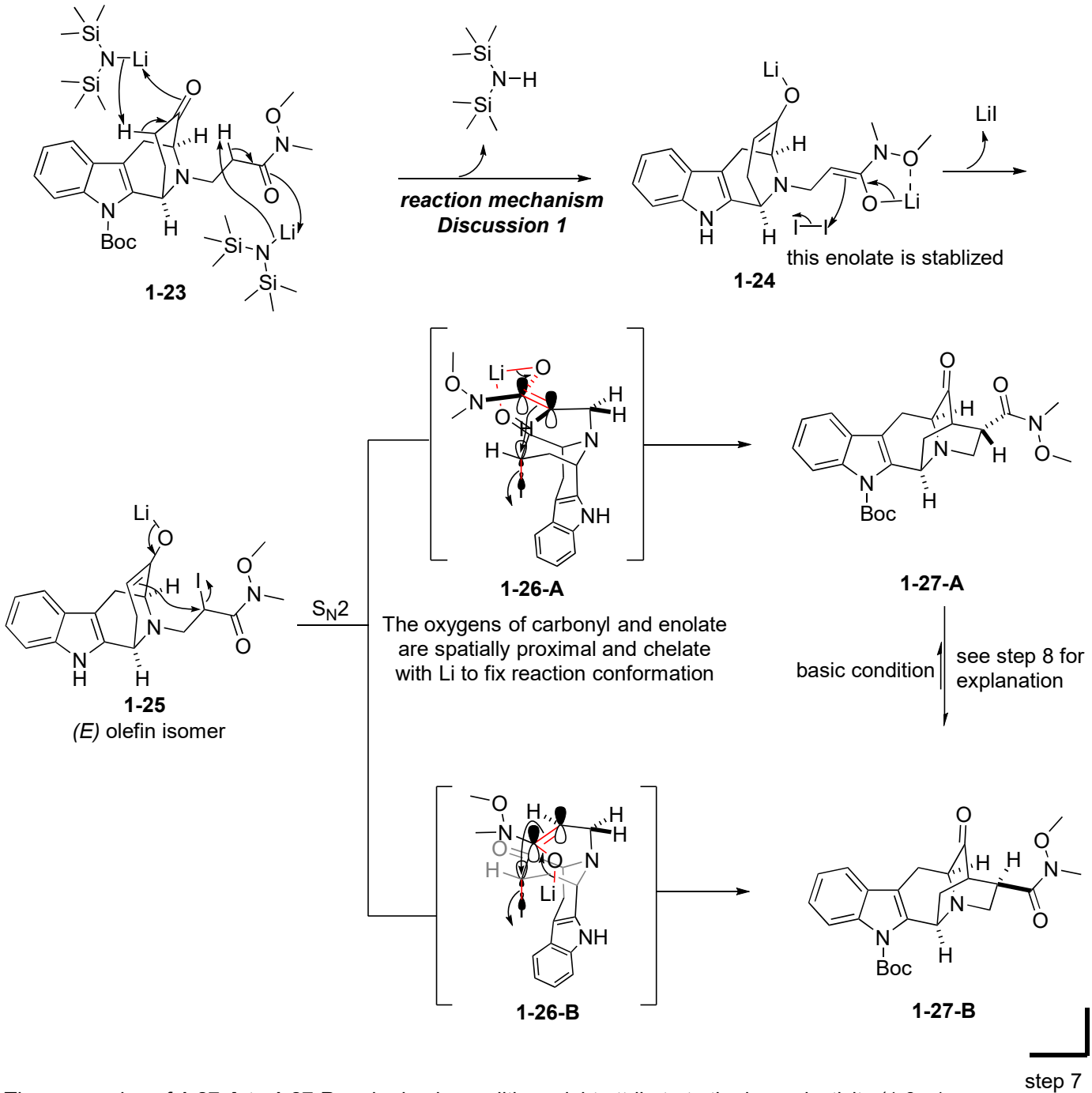



anisole acts as a cation scavenger to block the electrophilic substitution of indole aromatic ring.

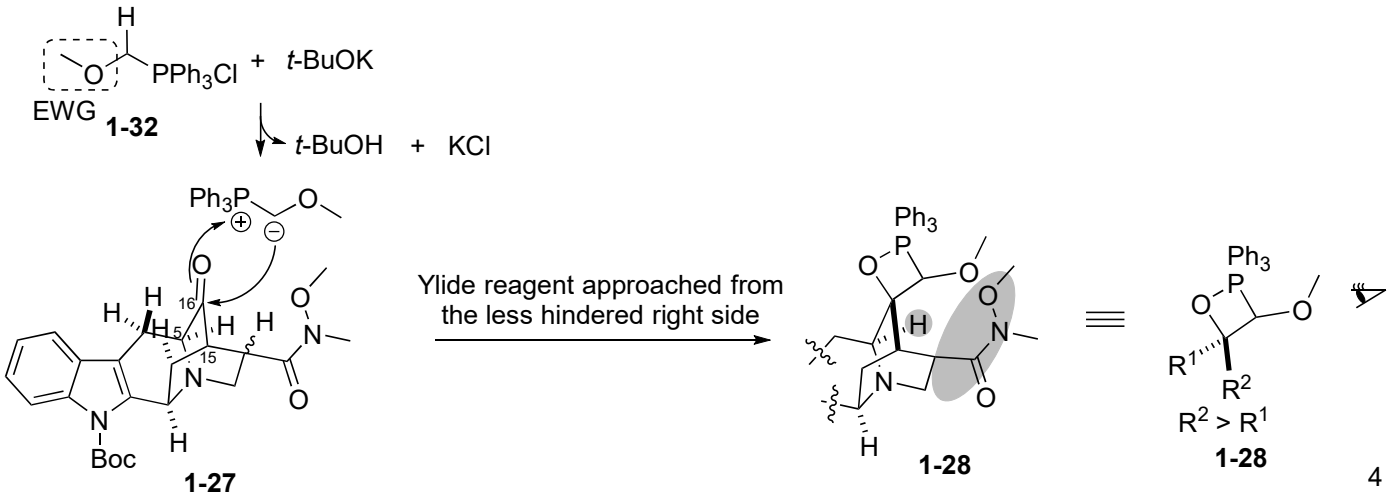


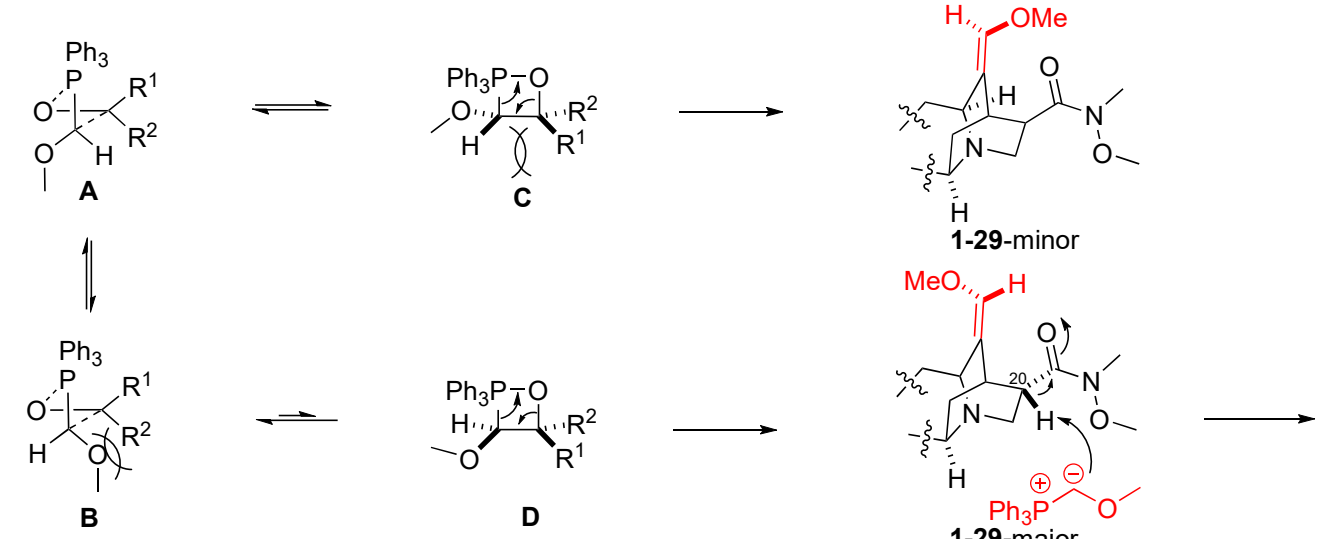



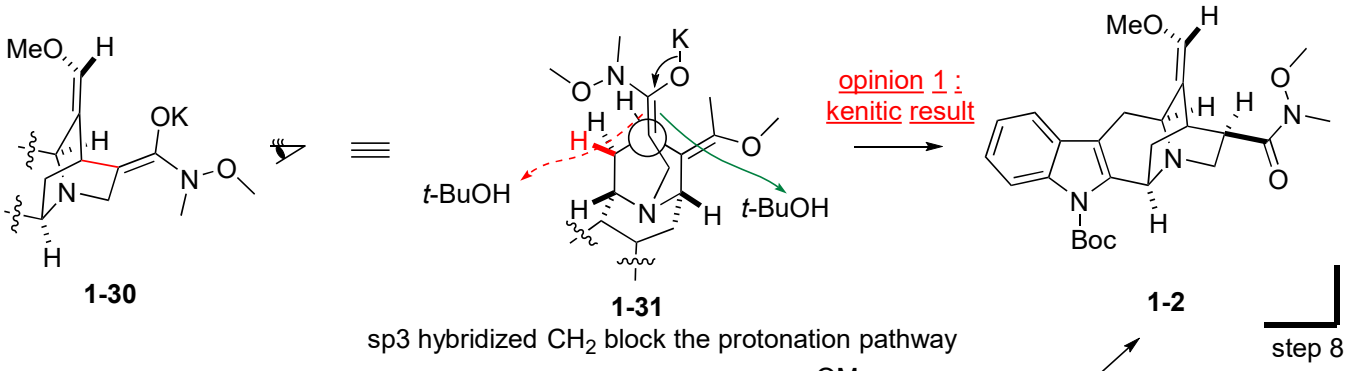



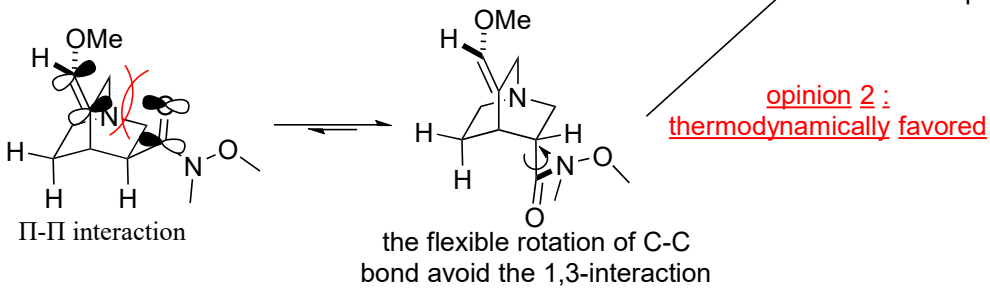



The conversion of **1-27-A** to **1-27-B** under basic condition might attribute to the low selectivity (1.6 : 1, it is not metioned which isomer is major). But as a matter of fact, the stereoselectivity in this step is inconsequential, because **1-27-A** will be isomized completely to **1-27-B** in next step.



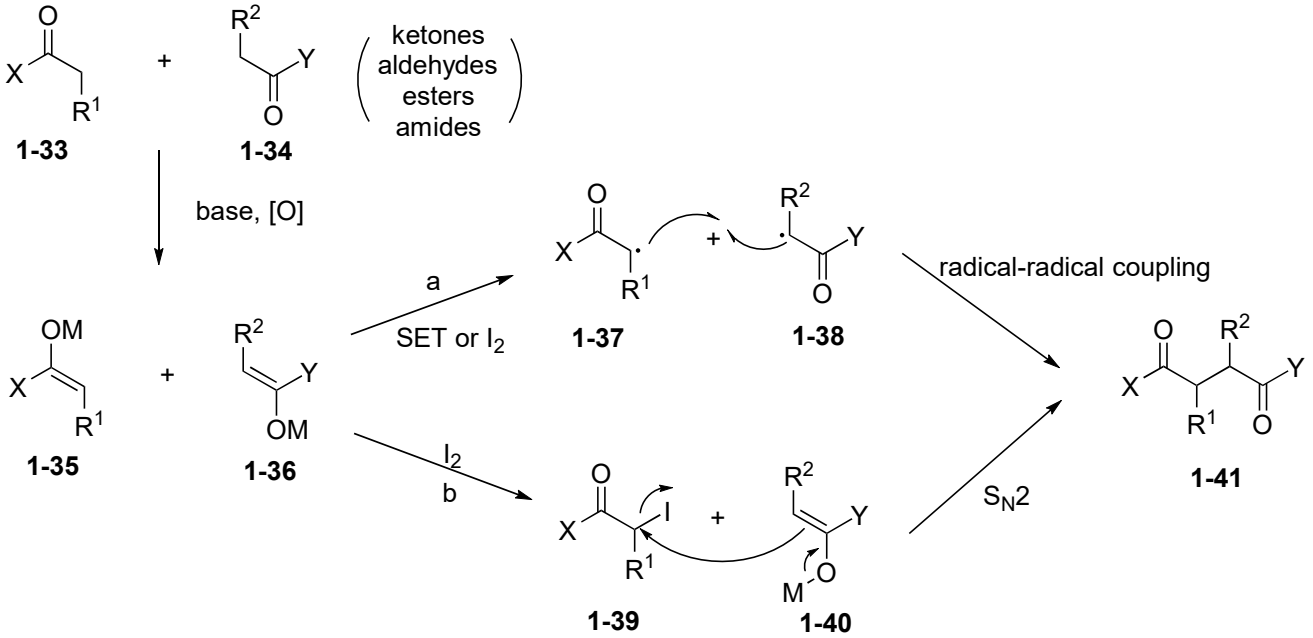


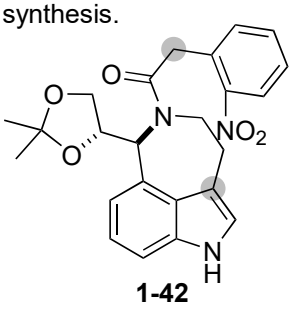

***Disscusion 1:*** Oxidative coupling reaction [4)]

1. Introduction of oxidative coupling reaction (intermolecular/intramolecular).
   ->C-C bond formation via oxidative coupling of enolate, enol derivatives, enamine



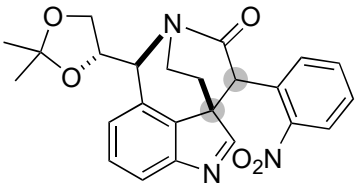
2. Examples for radical coupling mechanism.

The intramolecular oxidative coupling between enolates and indoles is also possible and applied to many total synthesis.



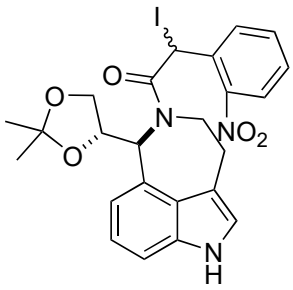
**1-42**

LiHMDS, THF, -78 °C to rt, 30 min;
$I_2$, -40 °C to rt, 73% brsm



**1-43**
desired

LiHMDS, THF, -78 °C, 30 min;
$I_2$, -78 °C to rt, 23%



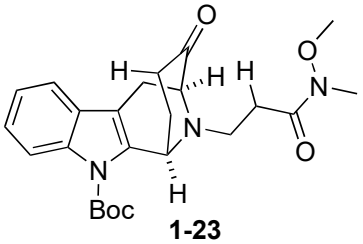
**1-44**

When $I_2$ was added at -78 °C, only iodation byproduct **1-44** was obtained as a single compound. However, when $I_2$ was added after elevating temperature to room temperature, no iodation byproduct **1-44** was observed but desired product **1-43** was provided in good yield. No further cyclization of **1-44** occurred, indicating that the reaction progress did not involve $S_N2$ reaction. Judging from the experimental result, the iodation is faster than oxidation of the corresponding anion to the radical at lower temperature. At higher temperature, the anion could be easier oxidized to radical.

Zuo, Z. W.; Ma, D. W. *Angew. Chem. Int. Ed.* **2011**, *50*, 12008.

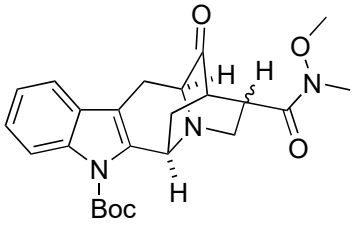
3. Evidence for $S_N2$ reaction mechanism in Problem 1, step 6.

Both intermolecular and intramolecular radical capture experiments rule out the radical pathway.

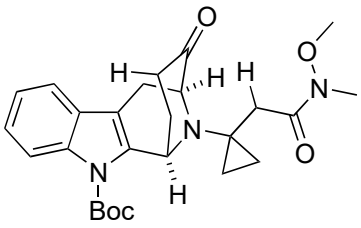


**1-23**

LiHMDS, $I_2$, TEMPO,
THF, -78 °C, 57%

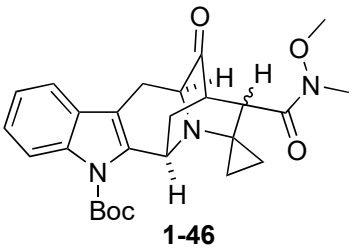


**1-27**

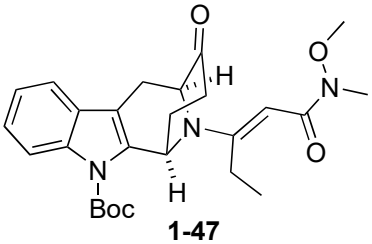


**1-45**

LiHMDS, $I_2$, THF
-78 °C, 23%

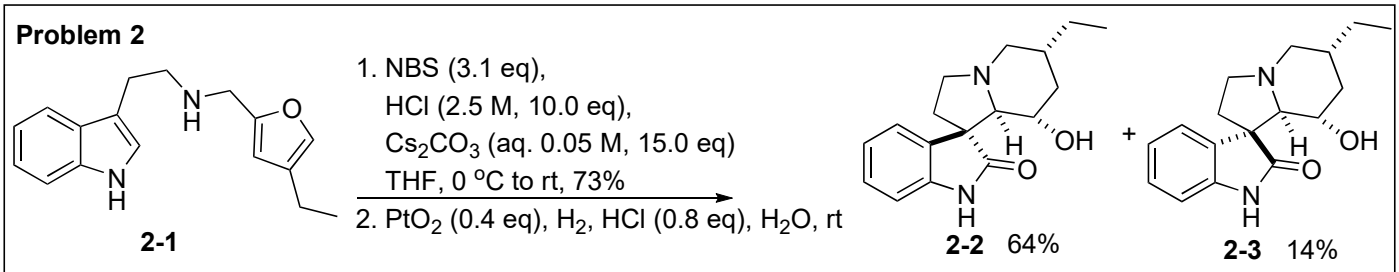


**1-46**

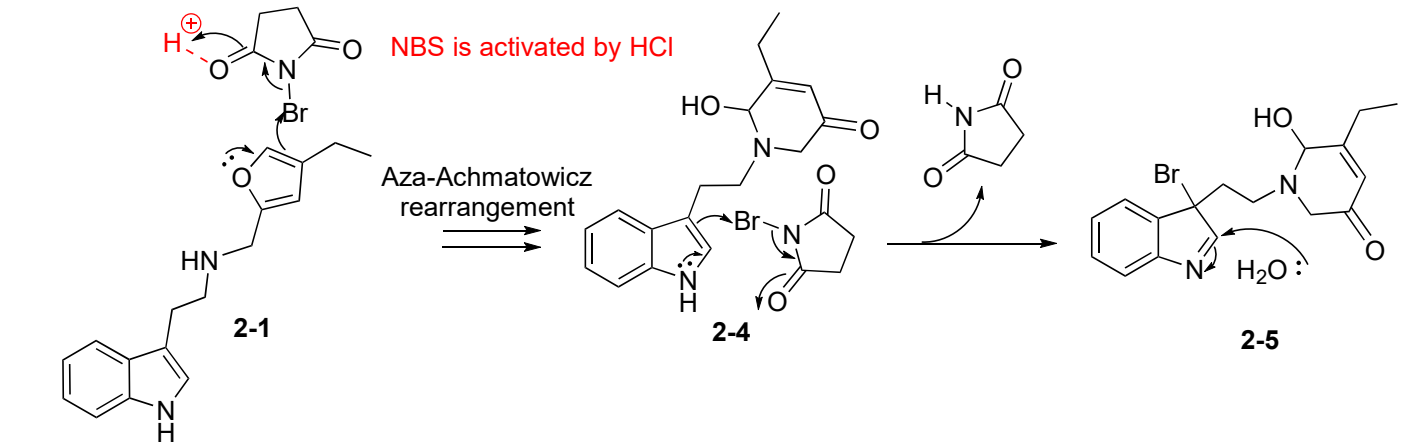


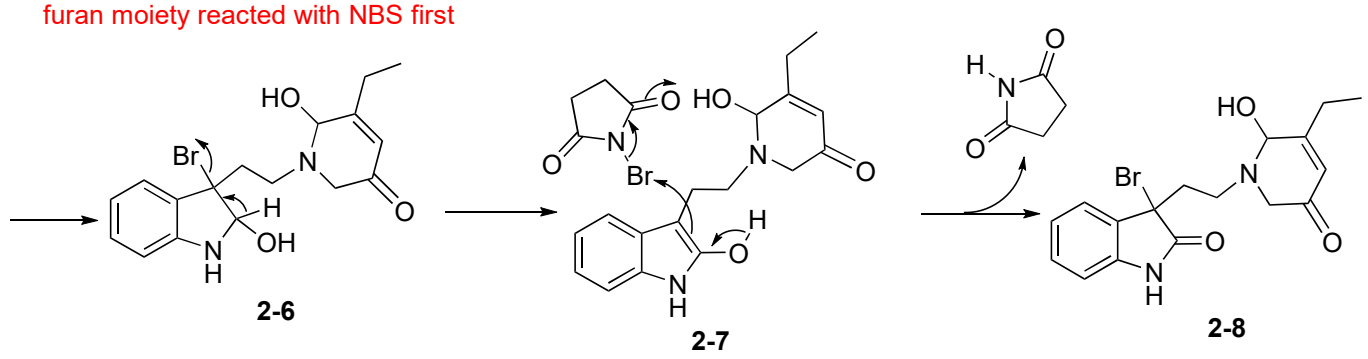
**1-47**
NOT detected

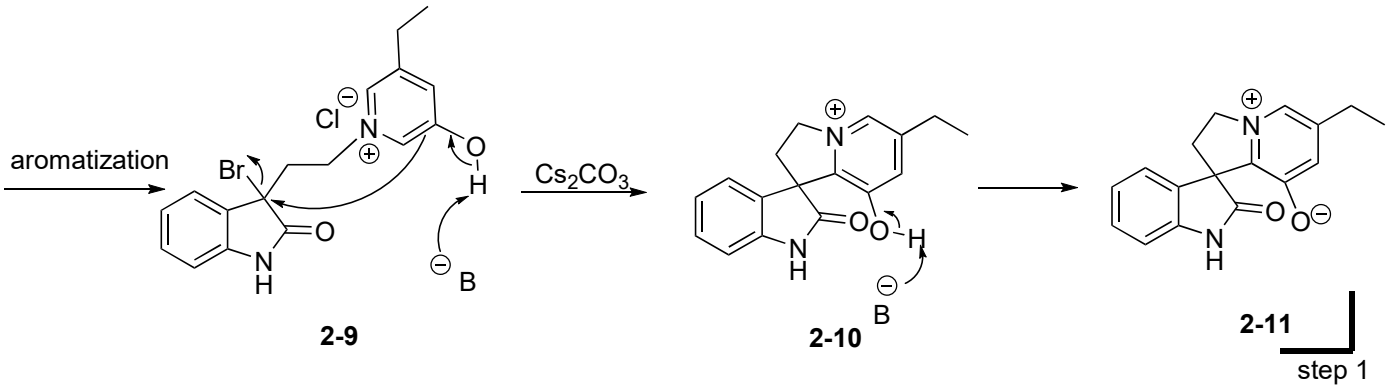
**Problem 2**

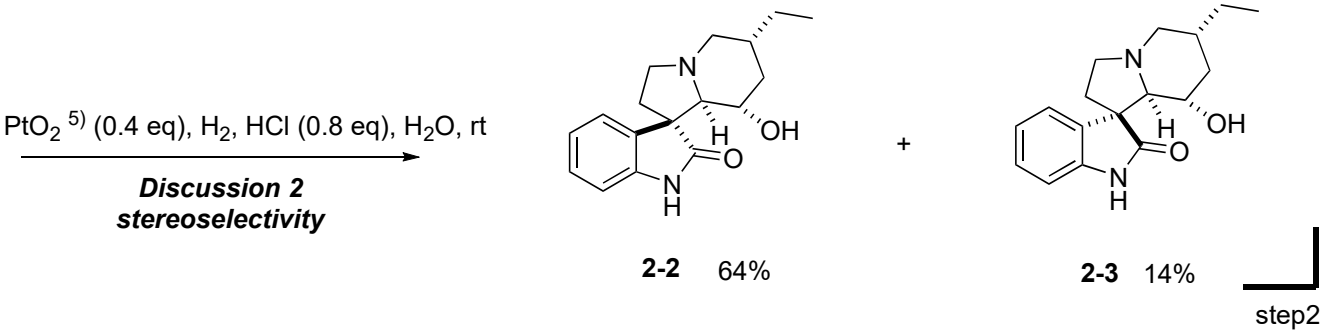



Wang, X.; Zhang, M. J.; Liu, X. L.; Lou, M. L.; Li, G.; Qi, X. B. *Org. Lett.* **2024**, *26*, 824

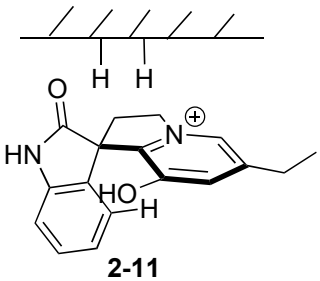


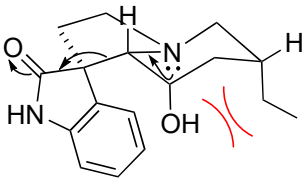
***Discussion2 :*** reaction pathway and stereoselectivity



**2-11**

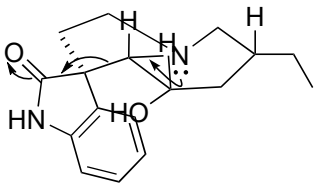
the two planar faces are almost orthogonal

hydrogenation from the Π face *anti* to pheny ring



**2-15**

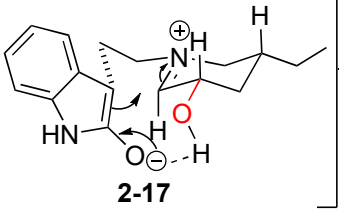
unstable 1,3-diaxial interaction



**2-16**

di-equatorial in boat-transition state

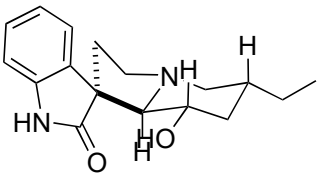
retro-Mannich / Mannich



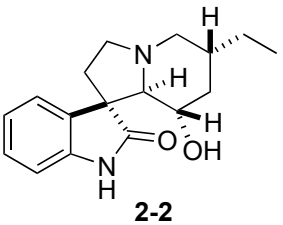
**2-17**

intramolecular hydrogen bond

fix reaction conformation

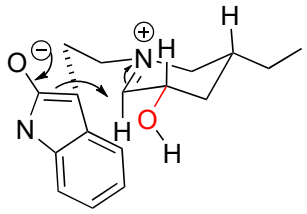


**2-2**



**2-2**

64%



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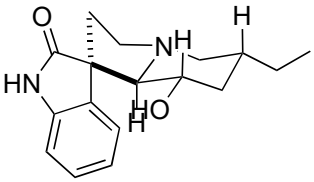

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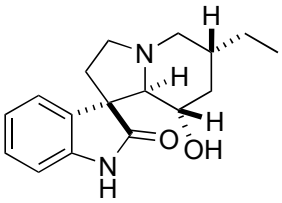

**2-3**

14%

**Reference**


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