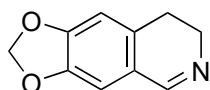


Problem Session (2)

2023.11.9. Shuji Toyama

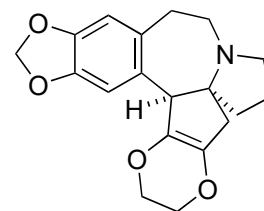
Please explain the reaction mechanisms.

1.

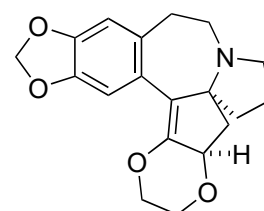


1-1

1. **1-2** (1.5 equiv), MeCN, 65 °C, 97%
2. 1,4-dioxene (1.5 equiv), *t*-BuLi (1.4 equiv), THF, -80 °C
3. TBAF (1.03 equiv), THF, 0 °C, 91% (2 steps)
4. AuCl(PPh₃) (2 mol%), Ag[C₅(CN)₅] (2 mol%)
TsNH₂ (4 equiv), *t*-BuOH, 55 °C

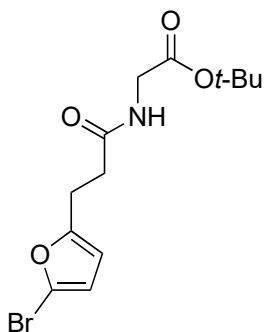


1-3
51% (racemic)



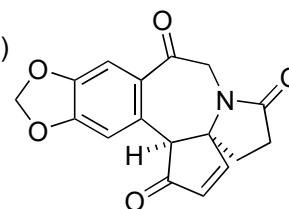
1-4
32% (racemic)

2.



2-1

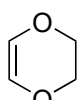
1. **2-2** (1.7 equiv), Pd₂(dba)₃ (2.5 mol%), DPEphos (10 mol%)
Cs₂CO₃ (4 equiv), MeCN, 60 °C
62% (Z isomer:E isomer = 84:16)
2. (CF₃CO)₂O (7.5 equiv), CF₃CO₂H (15 equiv), 60 °C, 30%



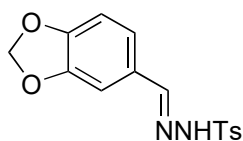
2-3
(racemic)



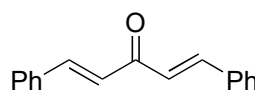
1-2



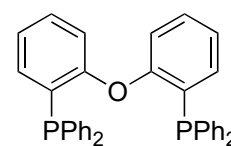
1,4-dioxene



2-2



dba



DPEphos

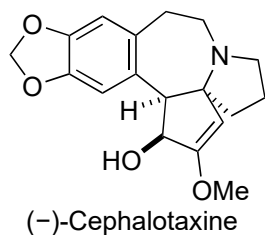
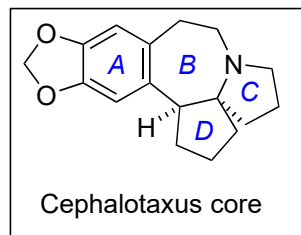
Problem Session (2) - Answer -

2023.11.9. Shuji Toyama

Topic: Total synthesis of Cephalotaxus alkaloids - cascade reaction via iminium

Introduction

1. Cephalotaxus alkaloids



Isolation: Cephalotaxus genus
Biological activities: antileukemic, antitumor
Structural features: spiro ring system, tertiary amine
Total syntheses: >30 examples

Weinreb (*J. Am. Chem. Soc.* **1972**, *94*, 7172.)

Semmelhack (*J. Am. Chem. Soc.* **1972**, *94*, 8629.)

Li (*Org. Lett.* **2011**, *13*, 3538.) ⇒ 200125_PS_Shu_Nakamura

Beaudry (*Angew. Chem. Int. Ed.* **2019**, *58*, 6752.) ⇒ 200125_PS_Shu_Nakamura

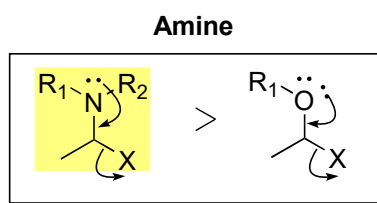
Kim (*Angew. Chem. Int. Ed.* **2021**, *60*, 12060.) ⇒ 230506_PS_Wentao_Wang

Sakai and Mori (*Org. Lett.* **2021**, *23*, 4391.) ⇒ Problem 1

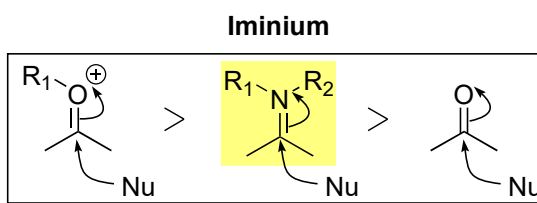
Fan (*J. Am. Chem. Soc.* **2023**, *145*, 9233.) ⇒ 230506_PS_Wentao_Wang

Yamaguchi (*Chem. Eur. J.* **2023**, e202302769.) ⇒ Problem 2

2. Comparison of nitrogen with oxygen



stronger pushing of lone pair

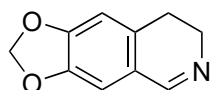


more electrophilic than ketone
less electrophilic than oxonium

These properties of nitrogen are widely used for synthesis of natural products.

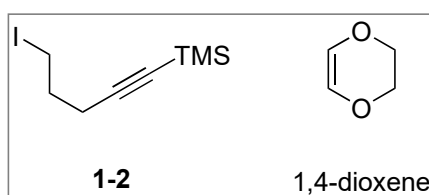
Answer

1.



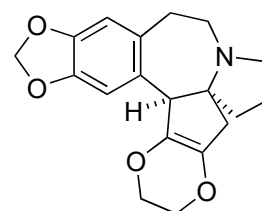
1-1

- 1-2 (1.5 equiv), MeCN, 65 °C, 97%
- 1,4-dioxene (1.5 equiv), *t*-BuLi (1.4 equiv), THF, -80 °C
- TBAF (1.03 equiv), THF, 0 °C, 91% (2 steps)
- AuCl(PPh₃) (2 mol%), Ag[C₅(CN)₅] (2 mol%)
TsNH₂ (4 equiv), *t*-BuOH, 55 °C



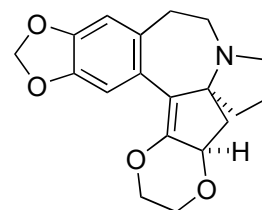
1-2

1,4-dioxene



1-3

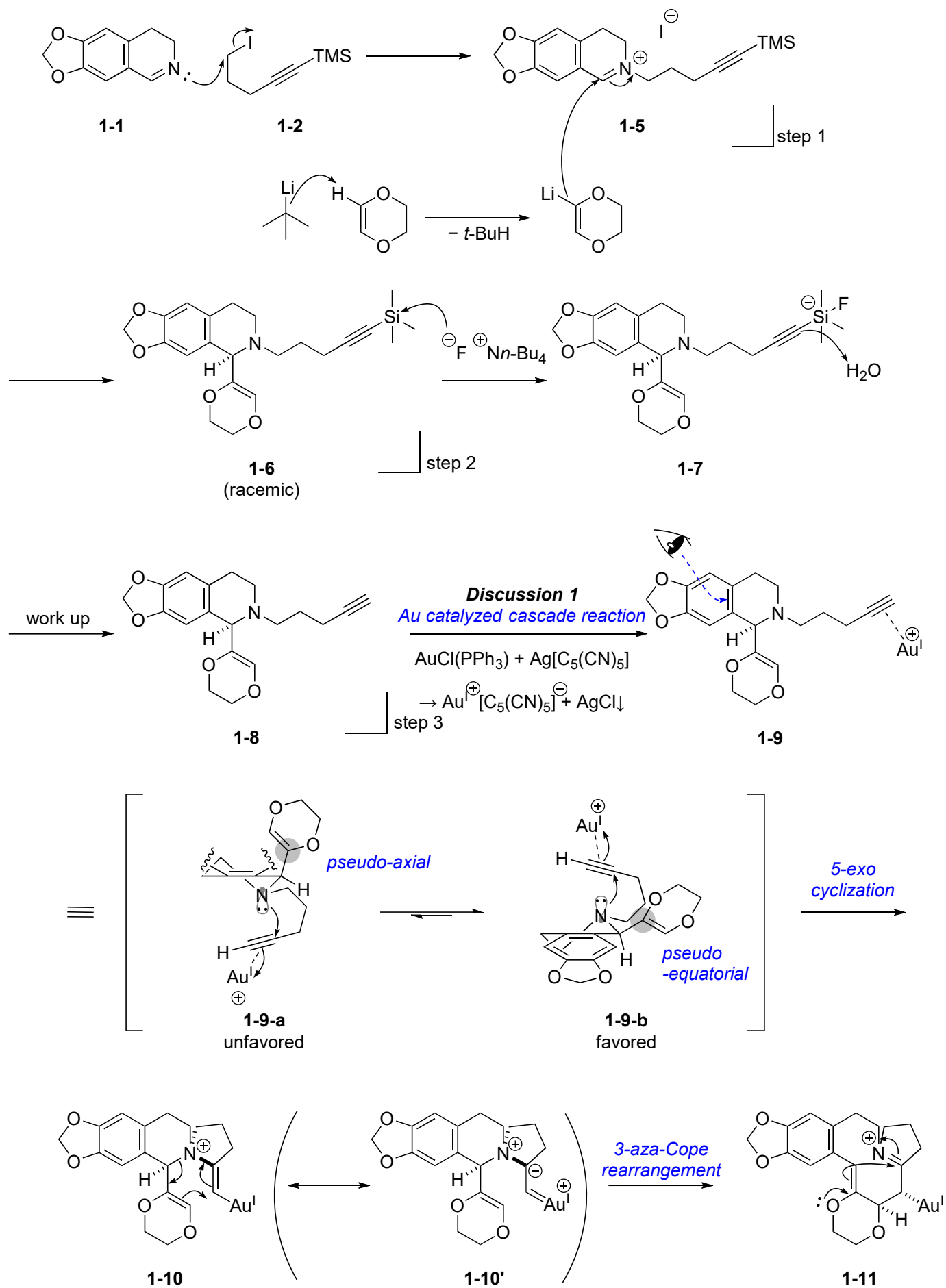
51% (racemic)

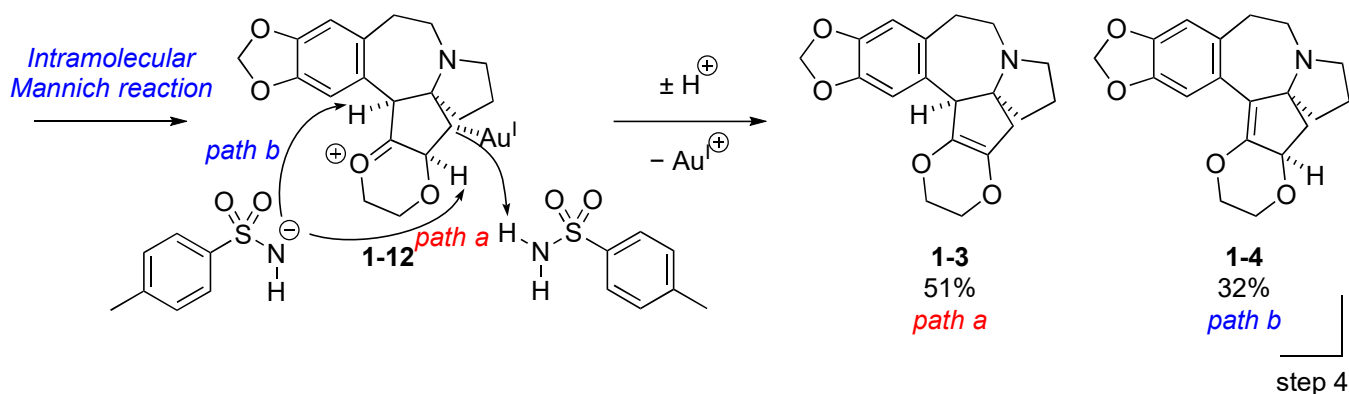


1-4

32% (racemic)

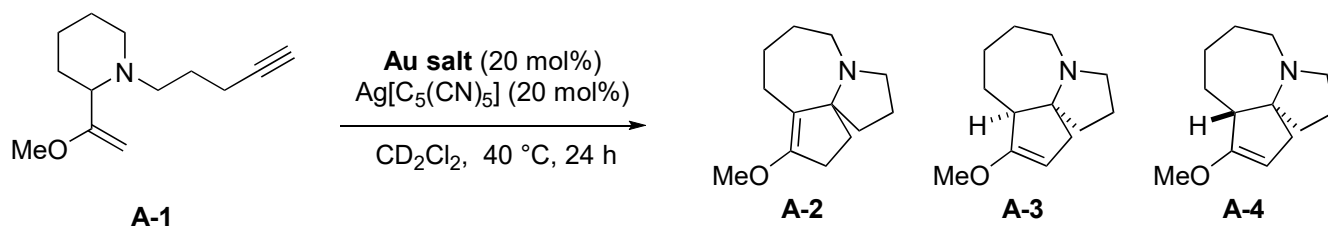
Sakai, T.; Okumura, C.; Futamura, M.; Noda, N.; Nagae, A.; Kitamoto, C.; Kamiya, M.; Mori, Y.
Org. Lett. **2021**, *23*, 4391.





Discussion 1: Au catalyzed cyclization and 3-aza-Cope/Mannich reaction

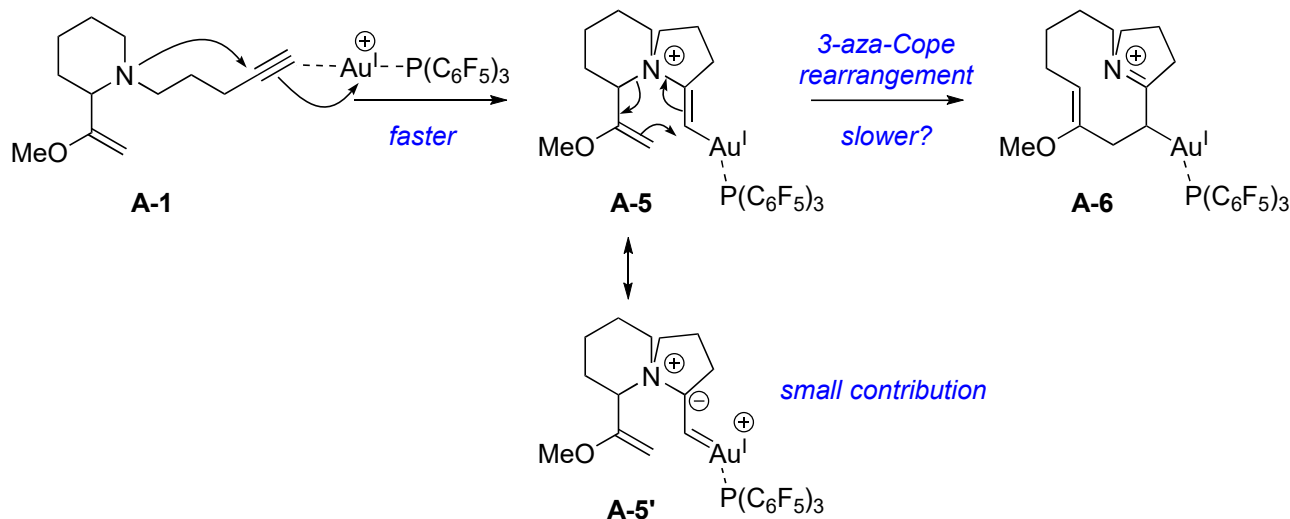
Discussion 1-1: Optimization of Au salt



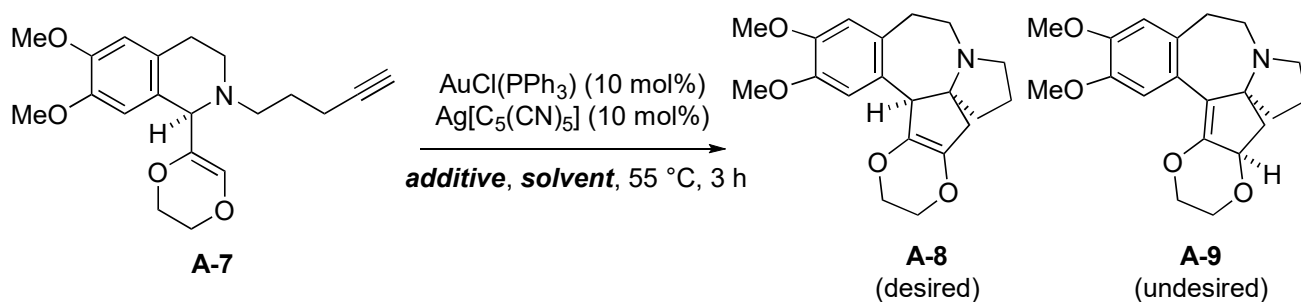
entry	Au salt	Total yield for A-2 , A-3 and A-4 (% ^a)
1	AuCl(PPh ₃)	86 (A-2:A-3:A-4 = 59:9:18)
2	AuCl[P(C ₆ F ₅) ₃]	19 (A-2:A-3:A-4 = 8:5:6)

^a NMR yield. 1,2-dichloroethane was used as an internal standard.

Very low total yield was observed when electron deficient phosphine ligand was used in entry 2. The first step, 5-exo-cyclization, should be faster when Au was electron deficient. I thought the second step, 3-aza-Cope rearrangement, got slower because of weak electron pushing from Au(I).



Discussion 1-2: Optimization of reaction condition

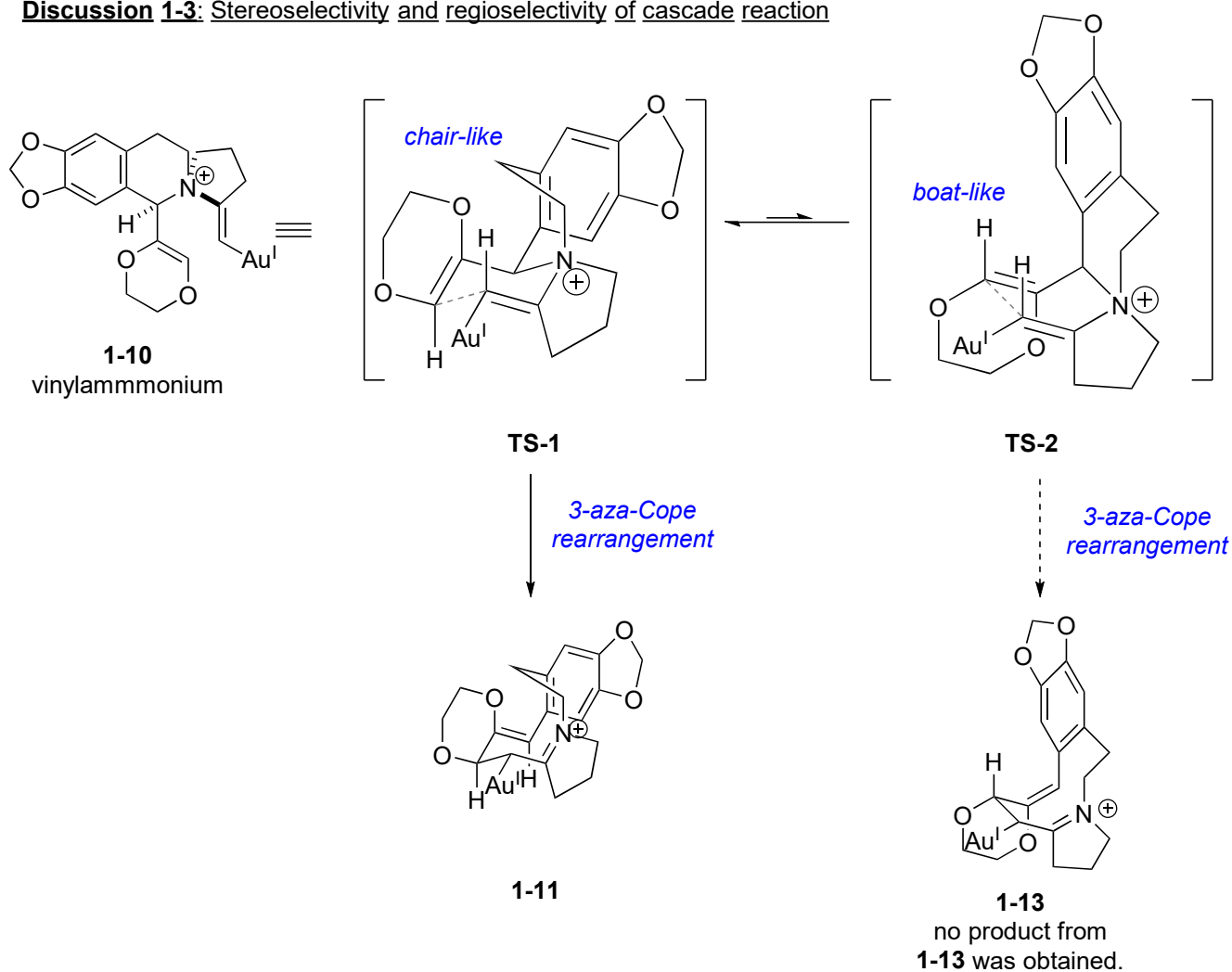


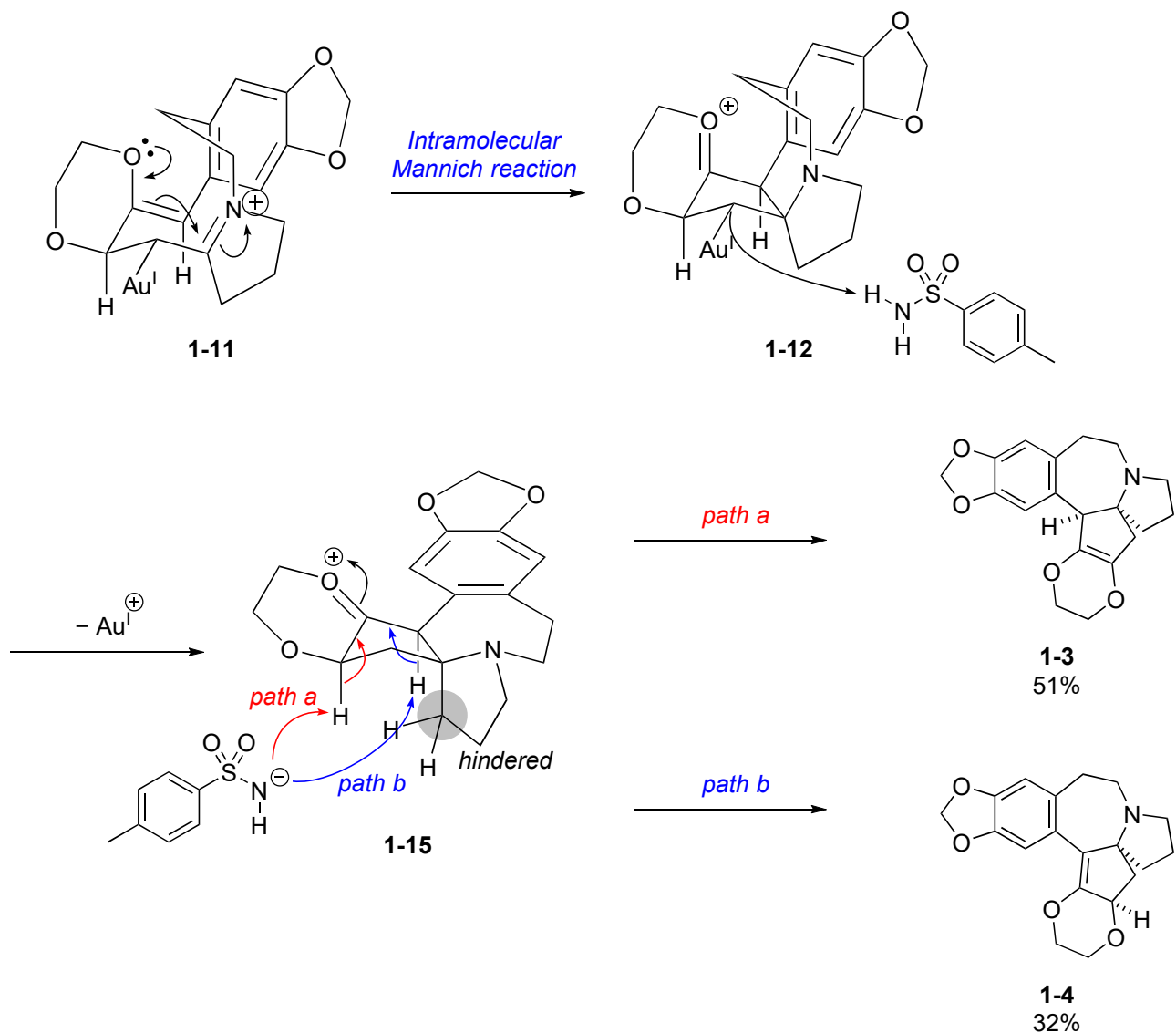
entry	solvent	additive	A-8 (% ^a)	A-9 (% ^a)	A-8/(A-8+A-9)	A-7 rcv. (% ^a)
1	1,2-dichloroethane		26	38	0.41	
2	1,2-dichloroethane	PhCONH ₂ (pKa 16.0)	27	23	0.54	3
3	1,2-dichloroethane	TsNH ₂ (pKa 10.2)	40	24	0.63	4
4	1,2-dichloroethane	PhCO ₂ H (pKa 4.2)	16	33	0.33	4
5	<i>t</i> -BuOH (pKa 15.4)	TsNH ₂ (pKa 10.2)	44	24	0.65	3

^a NMR yield. Ph₃CH was used as an internal standard.

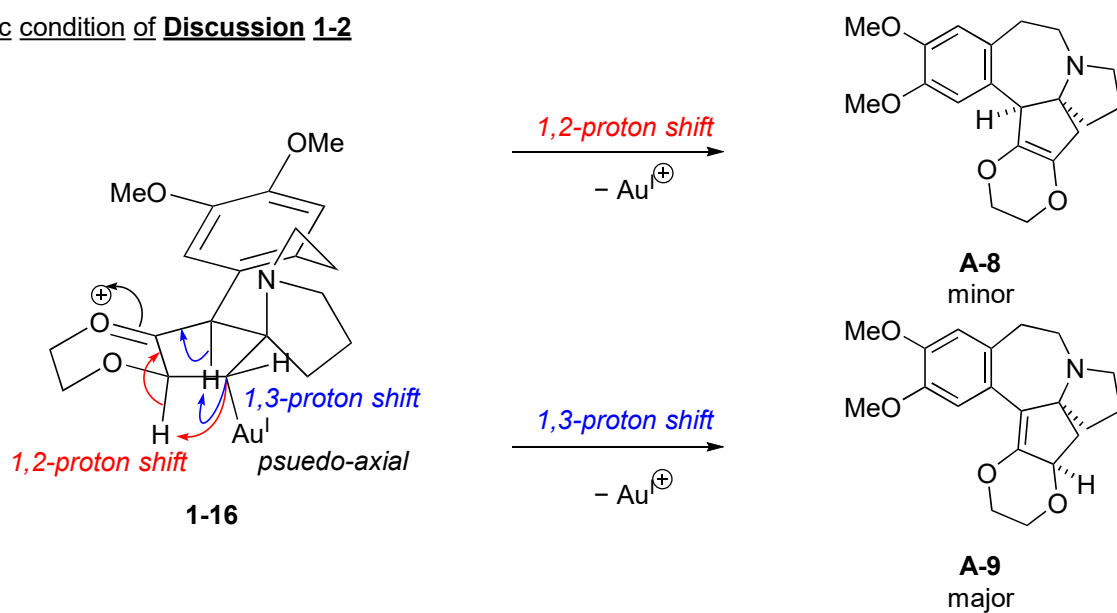
Proton source was important on this reaction. Aprotic solvent yielded undesired **A-9** as a major product (entry 1). Addition of weak acid was effective to improve the ratio of **A-8** (entries 2-4). Finally, *t*-BuOH and TsNH₂ condition showed the best result (entry 5).

Discussion 1-3: Stereoselectivity and regioselectivity of cascade reaction



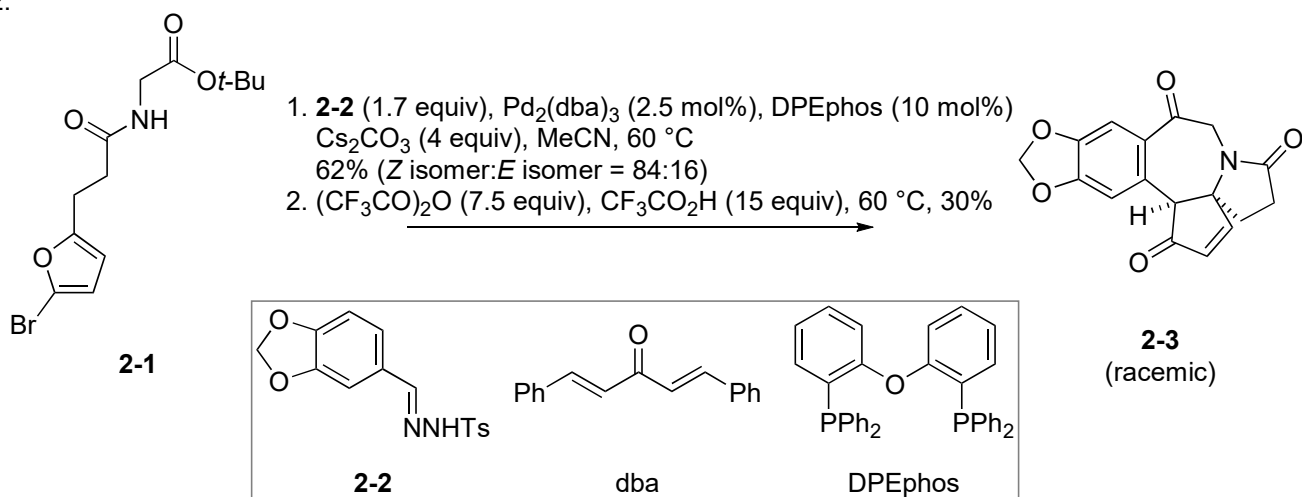
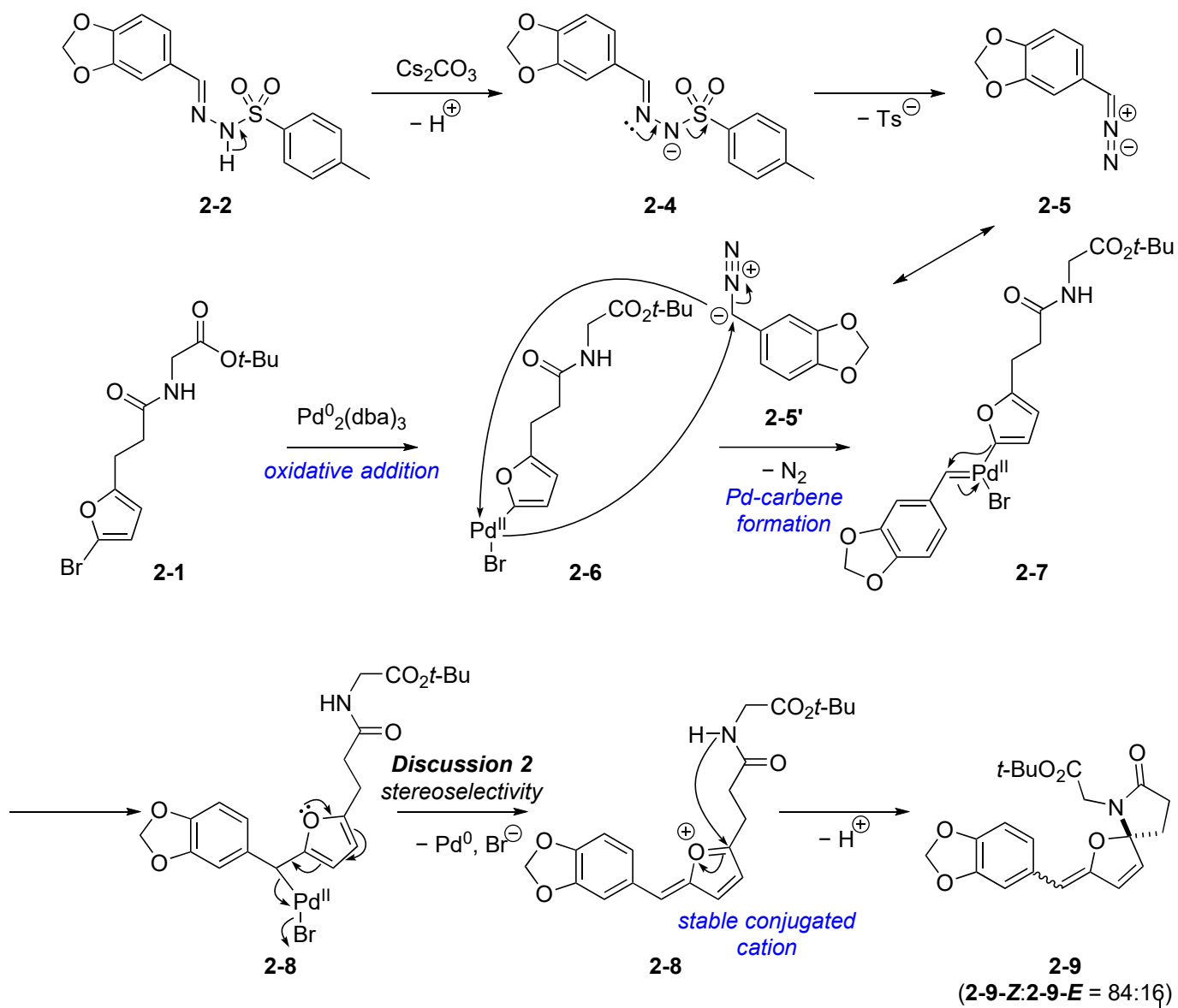


On aprotic condition of **Discussion 1-2**

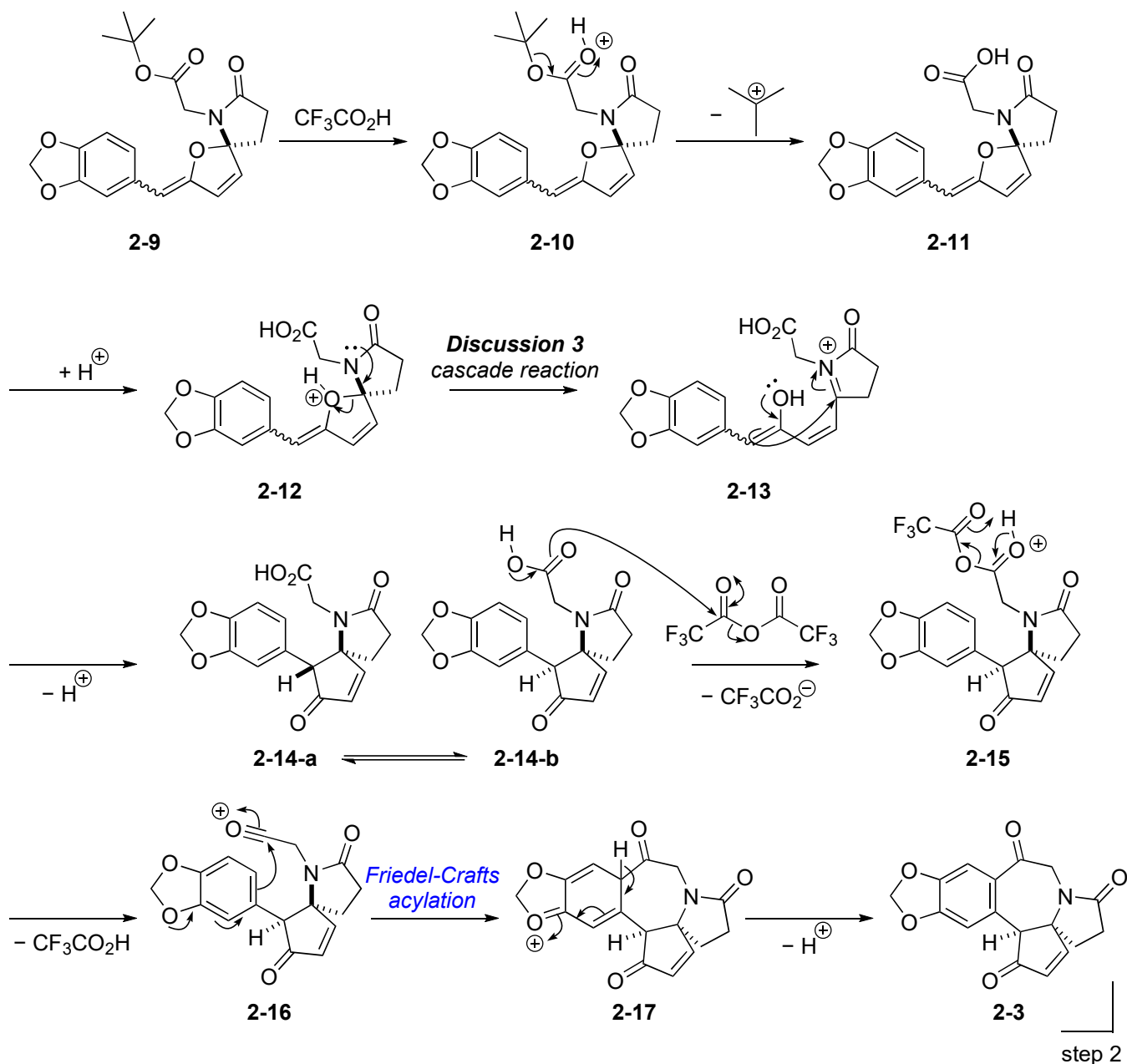


Both 1,2-proton shift and 1,3-proton shift are possible and conjugated olefin **A-9** is thermodynamically favored.
 → 1,3-proton shift may be impossible. Proton may be transferred by solvent (1,2-dichloroethane), tertiary amine of substrate, or slightly remained water.

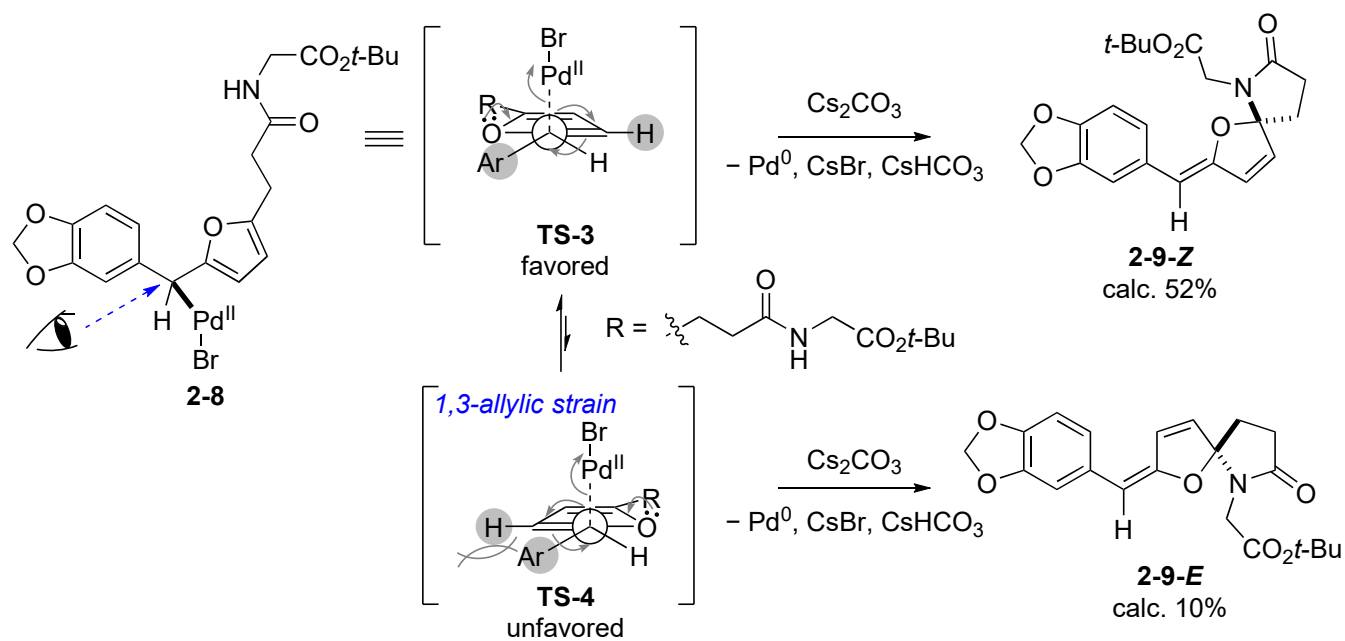
2.

Uwabe, Y.; Muto, K.; Yamaguchi, J. *Chem. Eur. J.* **2023**, e202302769.

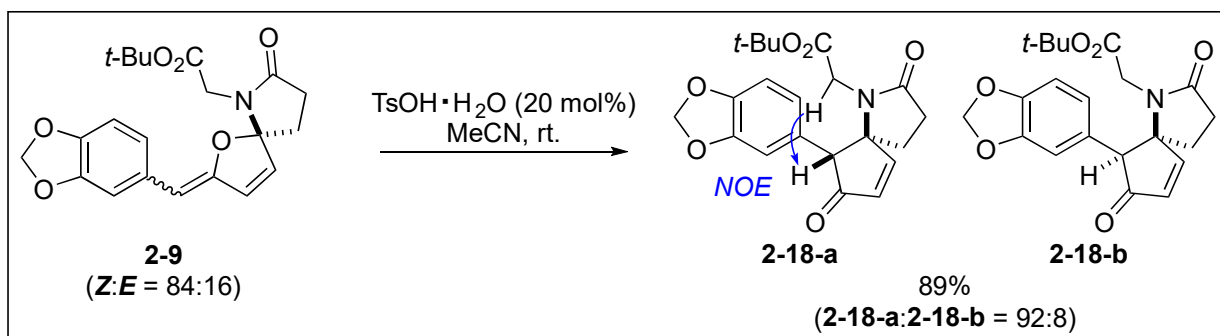
step 1



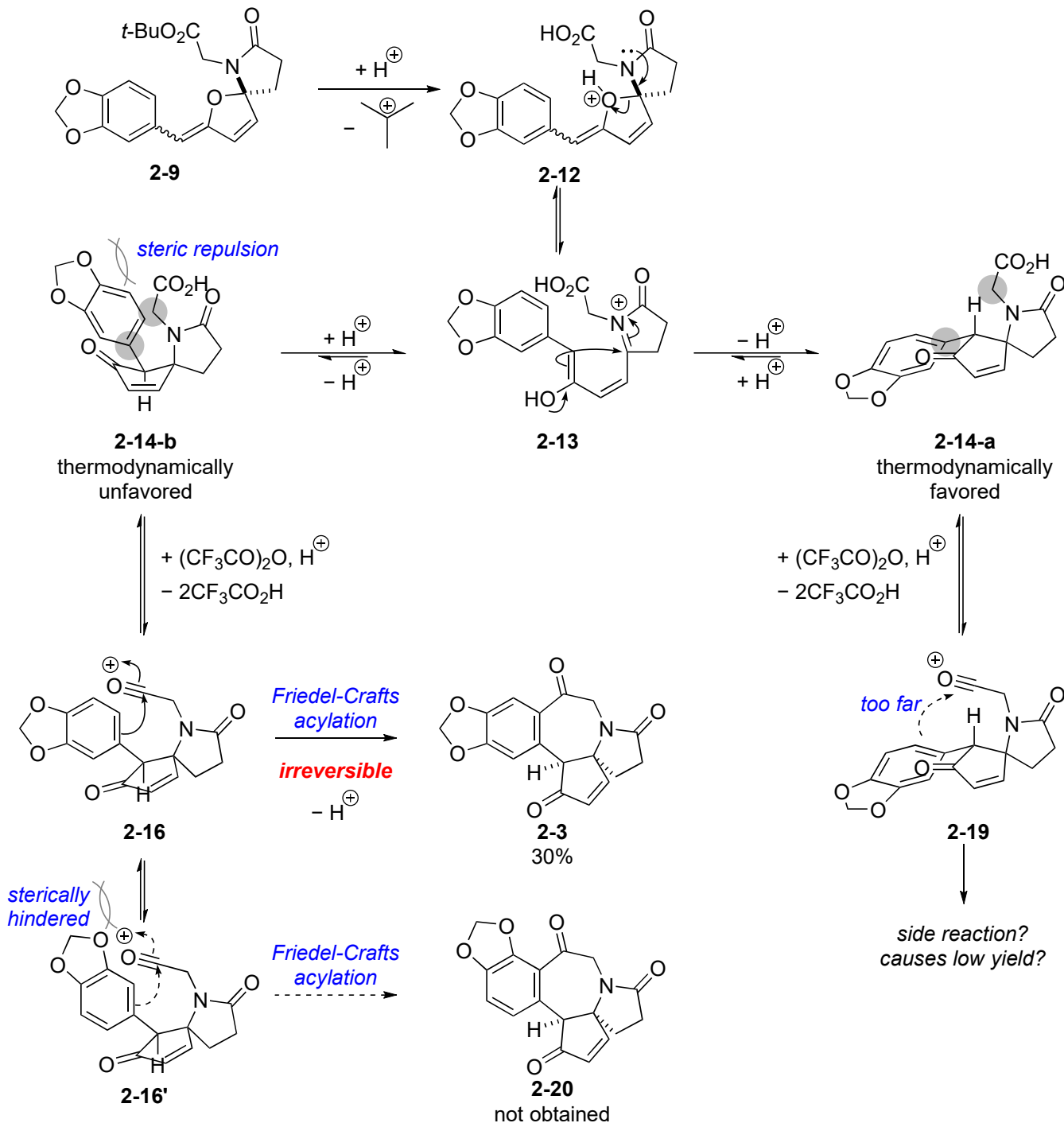
Discussion 2: Stereoselectivity of Pd-catalyzed dearomative spirocyclization.



Discussion 3: Aminal cleavage, Mannich reaction and Friedel-Crafts-acylation



Intermediate **2-18-a** was obtained as a major diastereomer on the above condition. **2-18-a** seems to be thermodynamically favored.



Aminal cleavage and intramolecular Mannich reaction should be reversible and the population of **2-14-b** should be smaller than that of **2-14-a**. However, after generating asylium cation **2-16**, intramolecular Friedel-Crafts acylation immediately proceed, which is irreversible. Therefore, desired product **2-3** was obtained. The low yield may be attributed to side reaction from thermodynamically favored **2-14-a**.