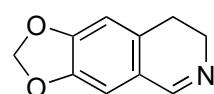


Problem Session (2)

2023.11.9. Shuji Toyama

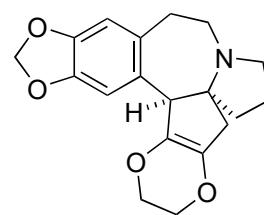
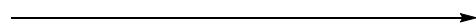
Please explain the reaction mechanisms.

1.

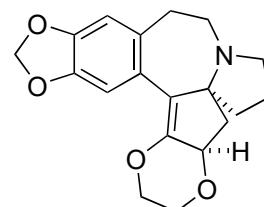


1-1

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

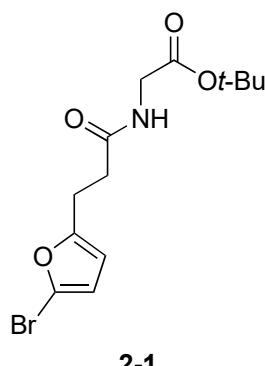


1-3
51% (racemic)

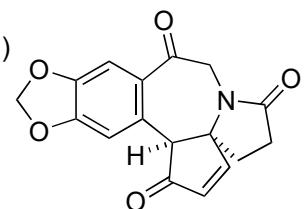


1-4
32% (racemic)

2.



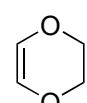
1. **2-2** (1.7 equiv), Pd₂(dba)₃ (2.5 mol%), DPEphos (10 mol%)
Cs₂CO₃ (4 equiv), MeCN, 60 °C
62% (*Z* isomer:*E* isomer = 84:16)
2. (CF₃CO)₂O (7.5 equiv), CF₃CO₂H (15 equiv), 60 °C, 30%



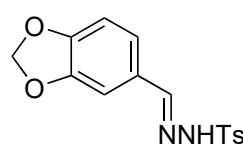
2-3
(racemic)



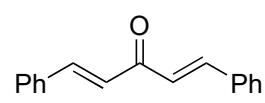
1-2



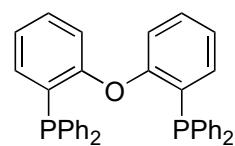
1,4-dioxene



2-2



dba



DPEphos

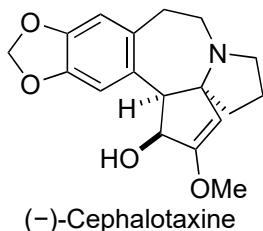
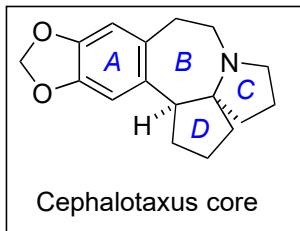
Problem Session (2) - Answer -

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_Shū_Nakamura

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

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

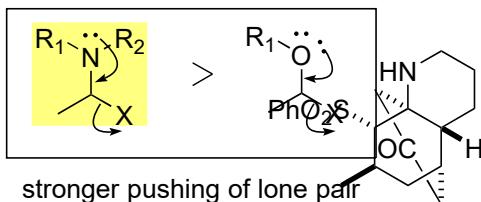
Sakai and Mori (*Org. Lett.* **2021**, *23*, 4391.) ⇒ Problem 1

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

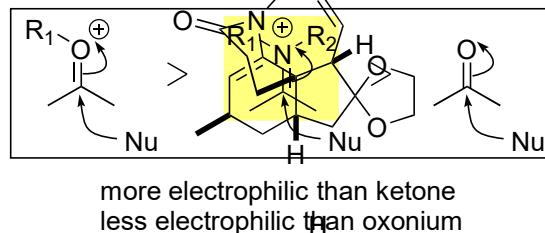
Yamaguchi (*Chem. Eur. J.* **2023**, e202302769.) ⇒ Problem 2

2. Comparison of nitrogen with oxygen

Amine



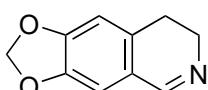
Iminium



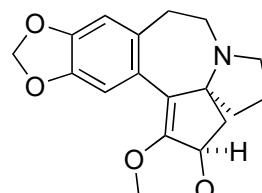
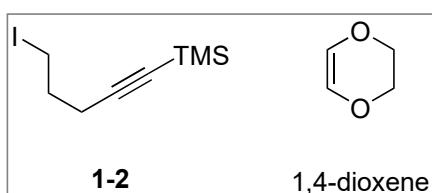
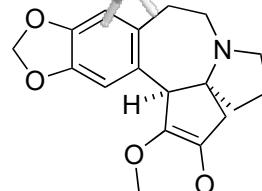
These properties of nitrogen are widely used for synthesis of natural products.

Answer

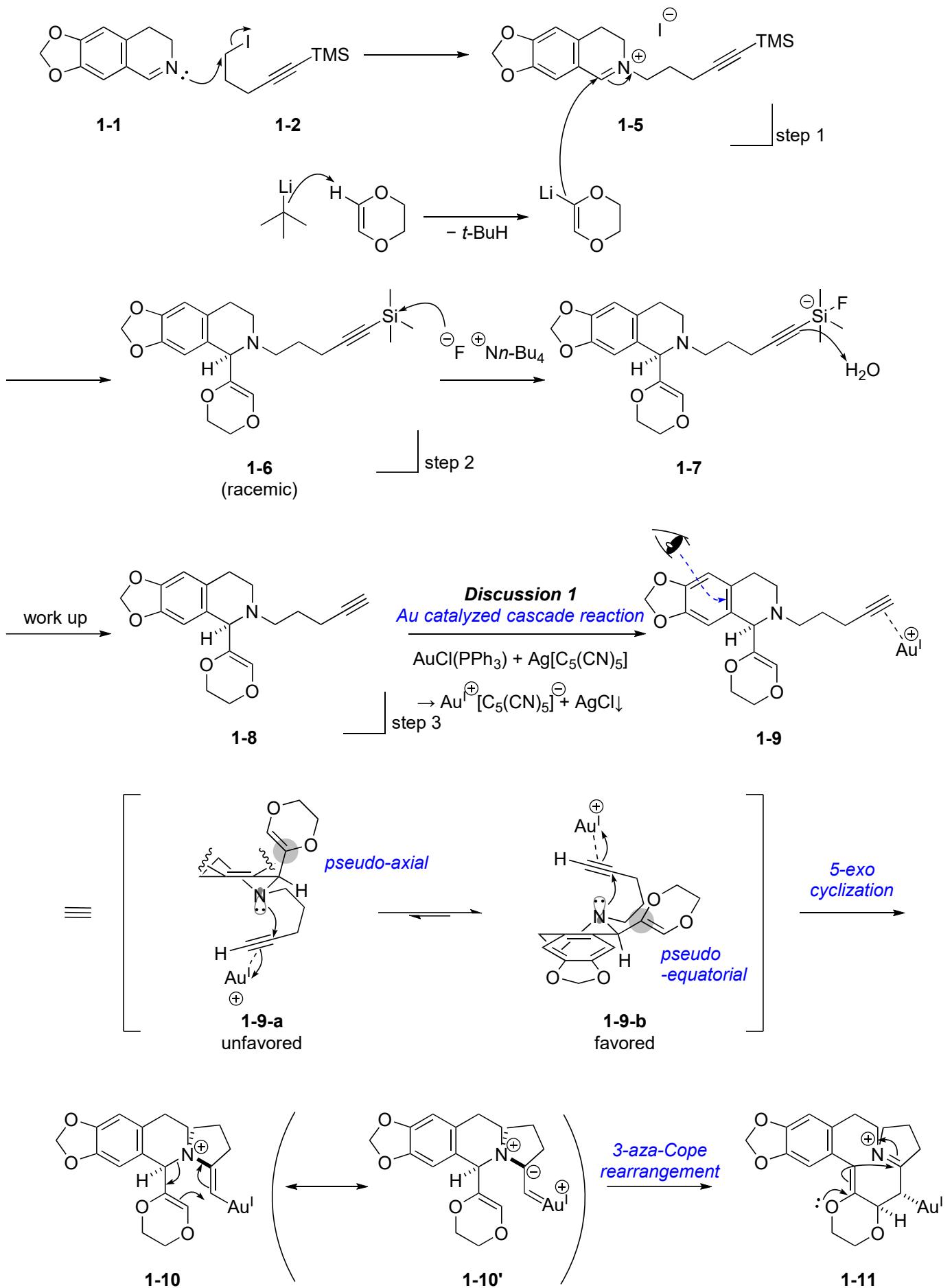
1.

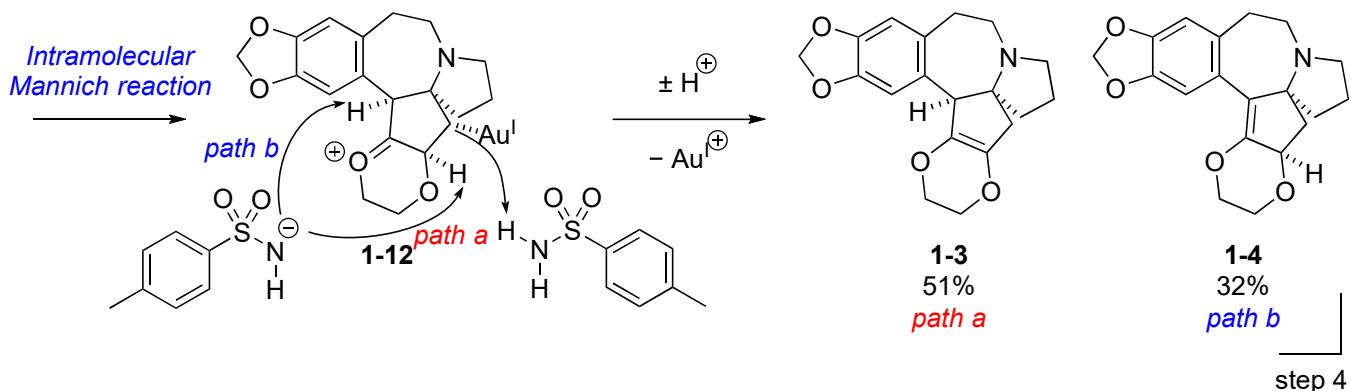


1. **1-2** (1.5 equiv), MeCN, 65 °C, 97%
2. 1,4-dioxene (1.5 equiv), *t*-BuLi (1.4 equiv), THF, -80 °C
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TsNH₂ (4 equiv), *t*-BuOH, 55 °C



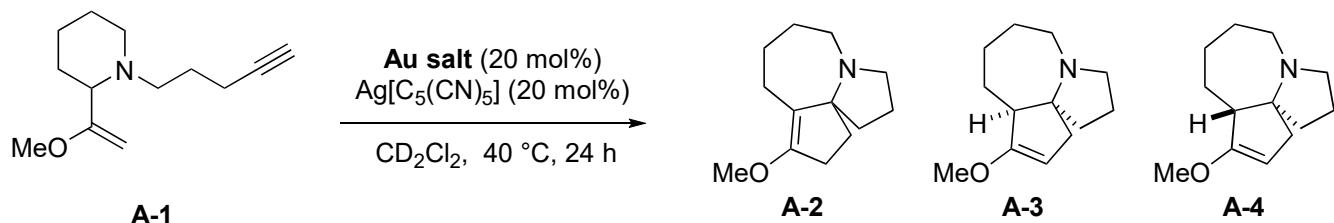
Sakai, T.; Okumura, C.; Futamura, M.; Noda, N.; Nagae, A.; Kitamoto, C.; Kamiya, M.; Mori, Y.
Org. Lett. **2021**, *23*, 4391.





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

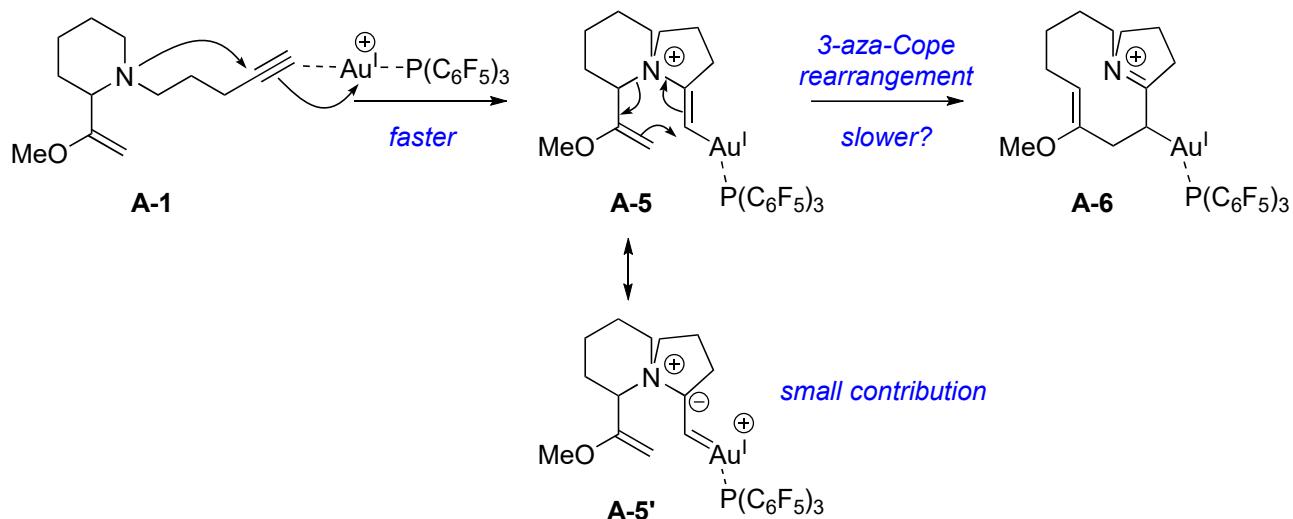
Discussion 1-1: Optimization of Au salt



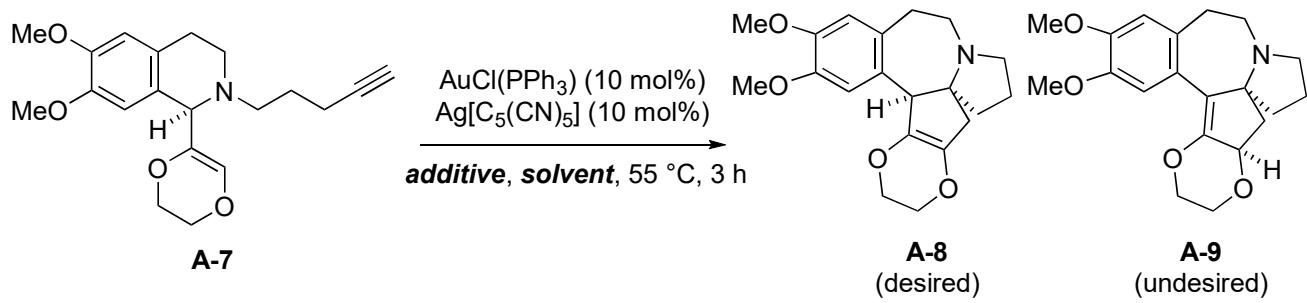
entry	Au salt	Total yield for A-2, A-3 and A-4 (%) ^a
1	$AuCl(PPh_3)$	86 (A-2:A-3:A-4 = 59:9:18)
2	$AuCl[P(C_6F_5)_3]$	19 (A-2:A-3:A-4 = 8:5:6)

^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

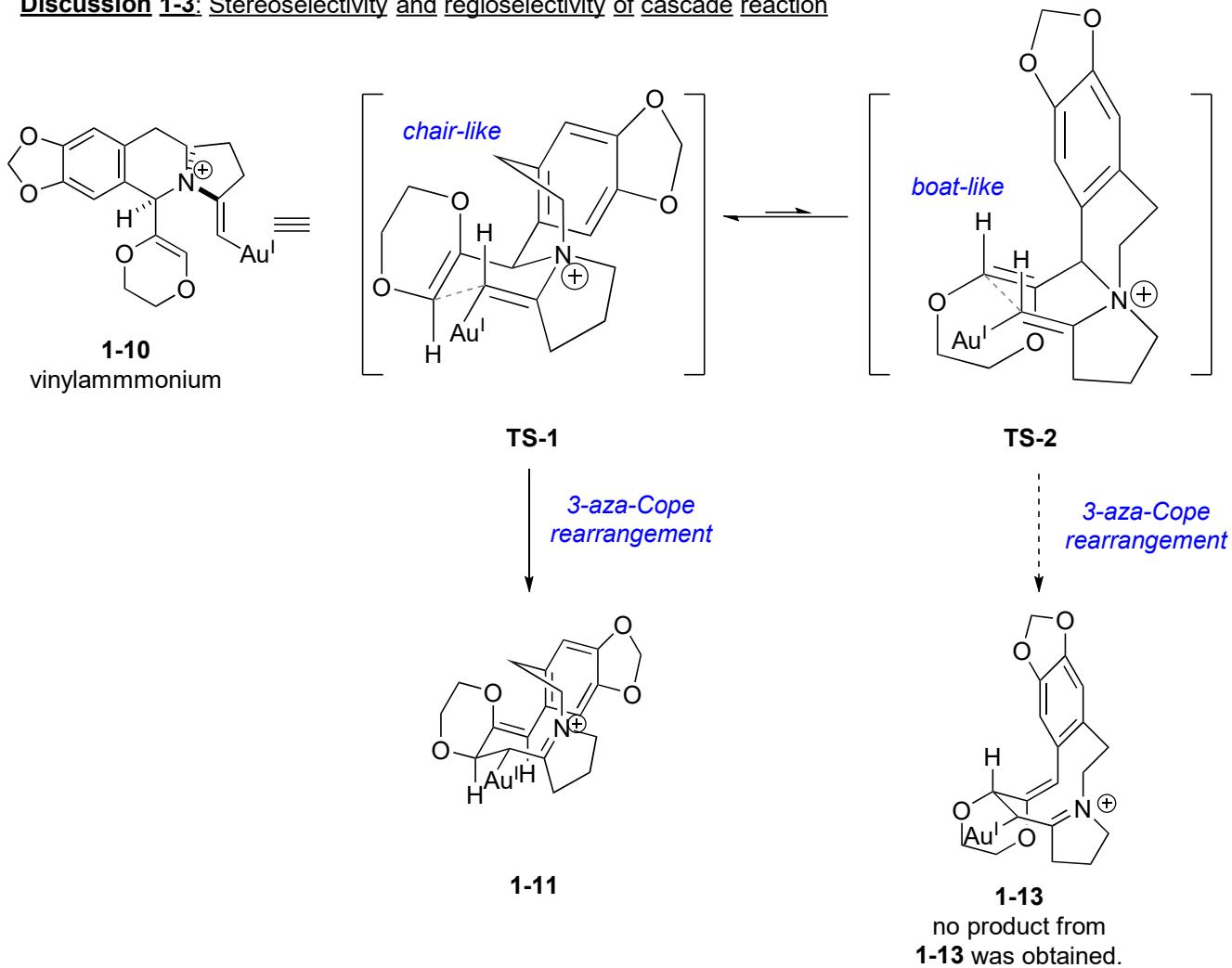


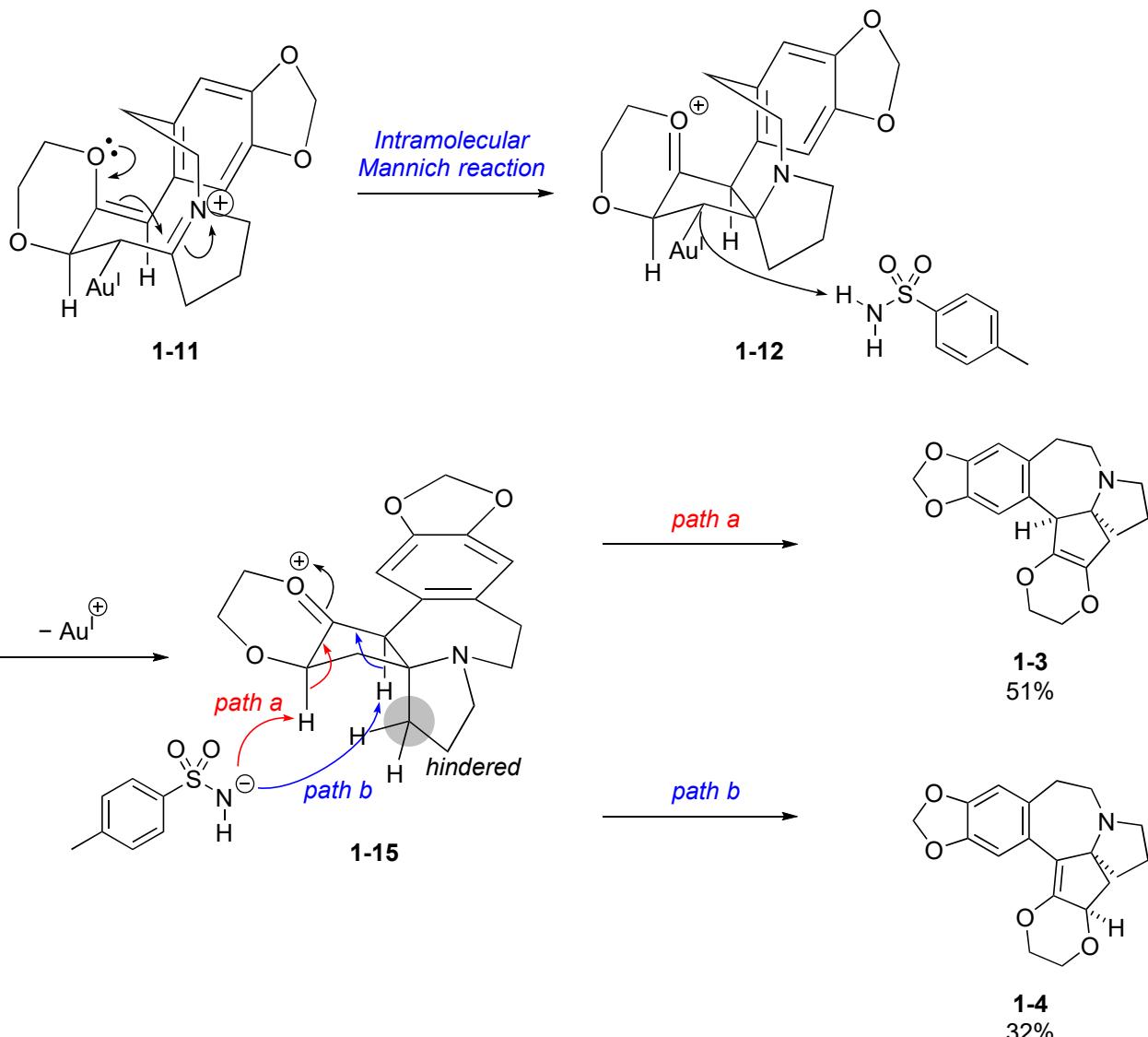
entry	solvent	additive	A-8 (%)^a	A-9 (%)^a	A-8/(A-8+A-9)	A-7 rcv. (%)^a
1	1,2-dichroloethane		26	38	0.41	
2	1,2-dichroloethane	PhCONH ₂ (pKa 16.0)	27	23	0.54	3
3	1,2-dichroloethane	TsNH ₂ (pKa 10.2)	40	24	0.63	4
4	1,2-dichroloethane	PhCO ₂ H (pKa 4.2)	16	33	0.33	4
5	<i>t</i> -BuOH (pKa 15.4)	TsNH ₂ (pKa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

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

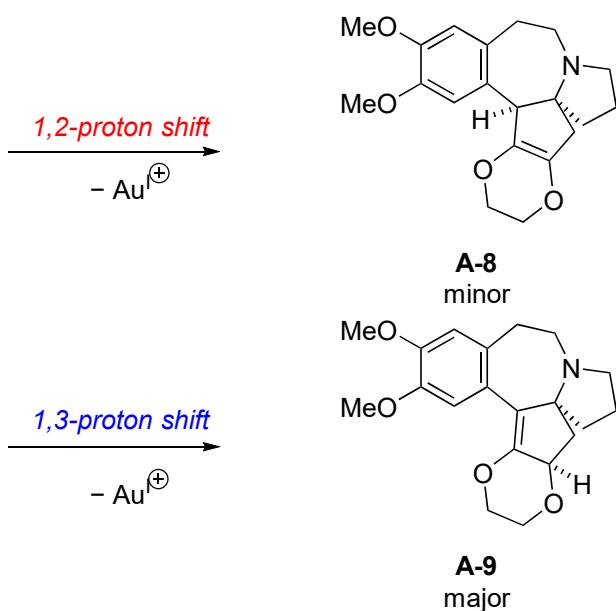
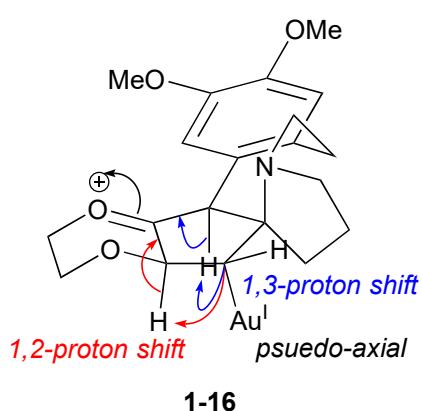
Proton source was important on this reaction. Aprotic solvent yielded undesired **A-9** as a major product (entry 1). Addition of weak acid was effective to improve the ratio of **A-8** (entries 2-4). Finally, *t*-BuOH and TsNH₂ condition showed the best result (entry 5).

Discussion 1-3: Stereoselectivity and regioselectivity of cascade reaction

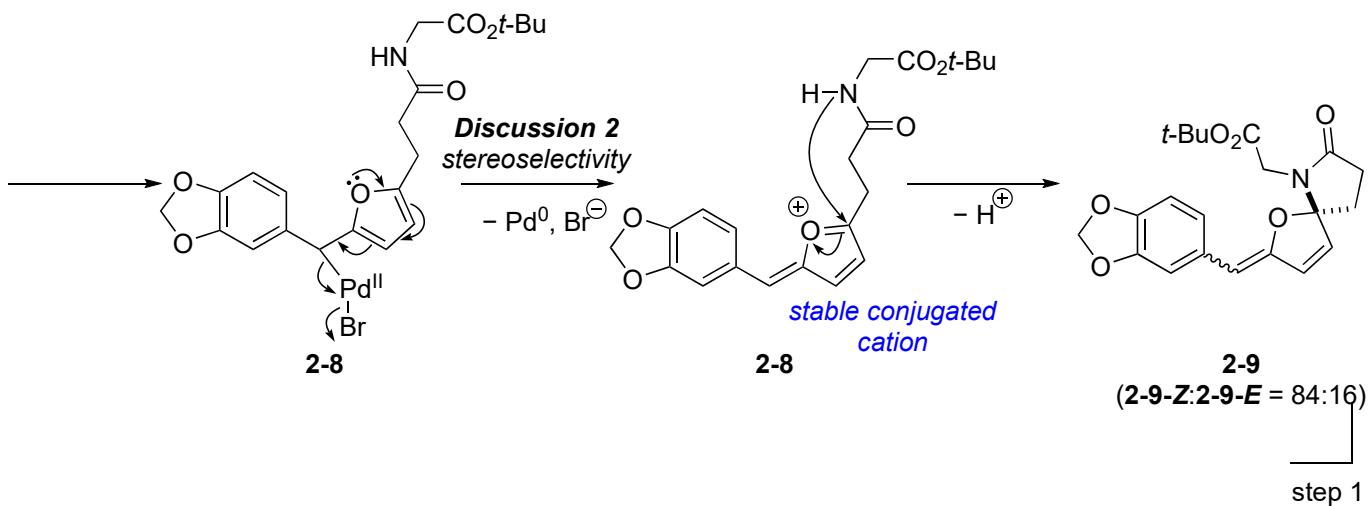
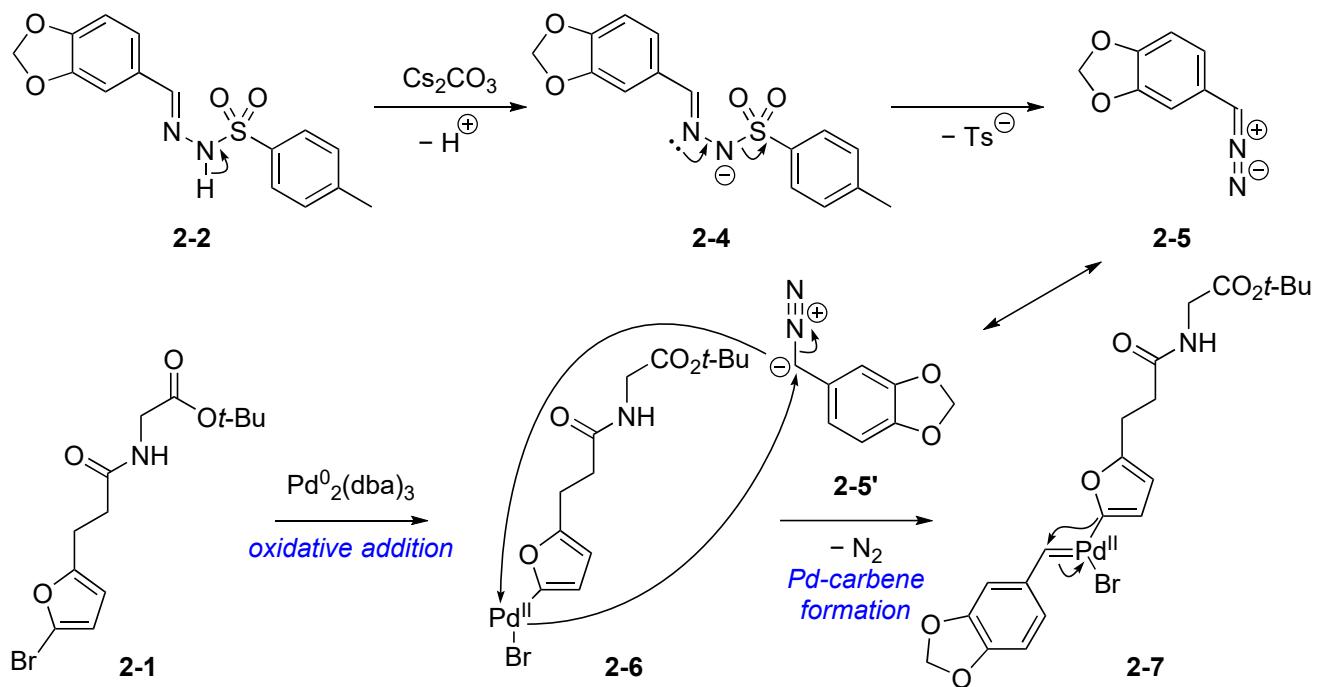
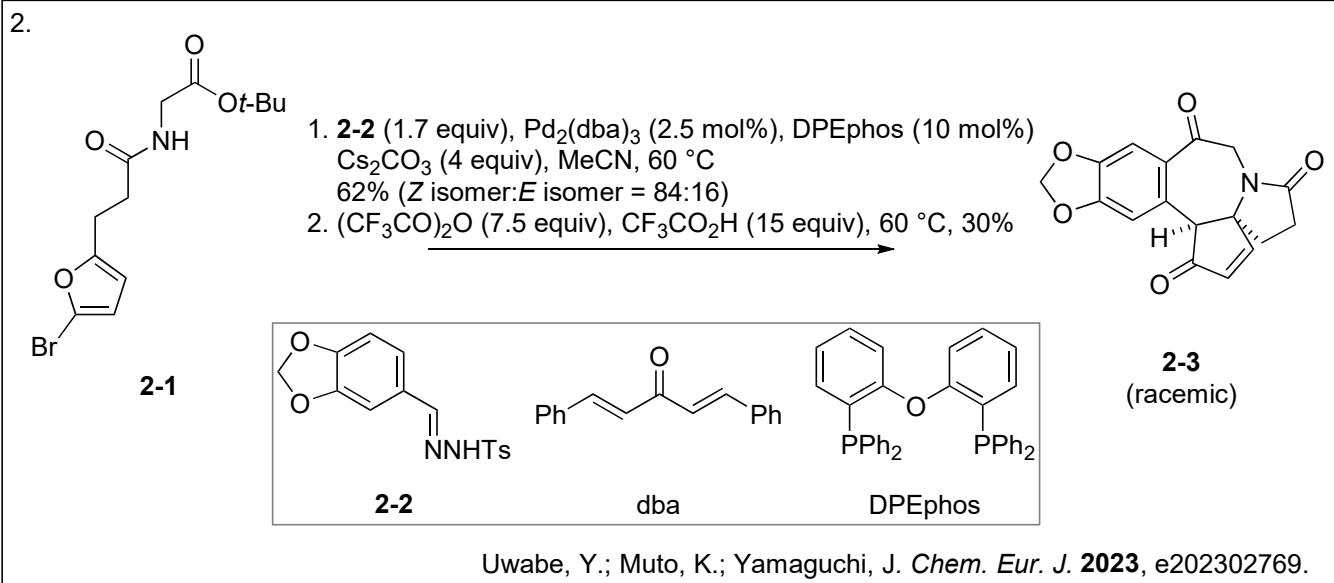


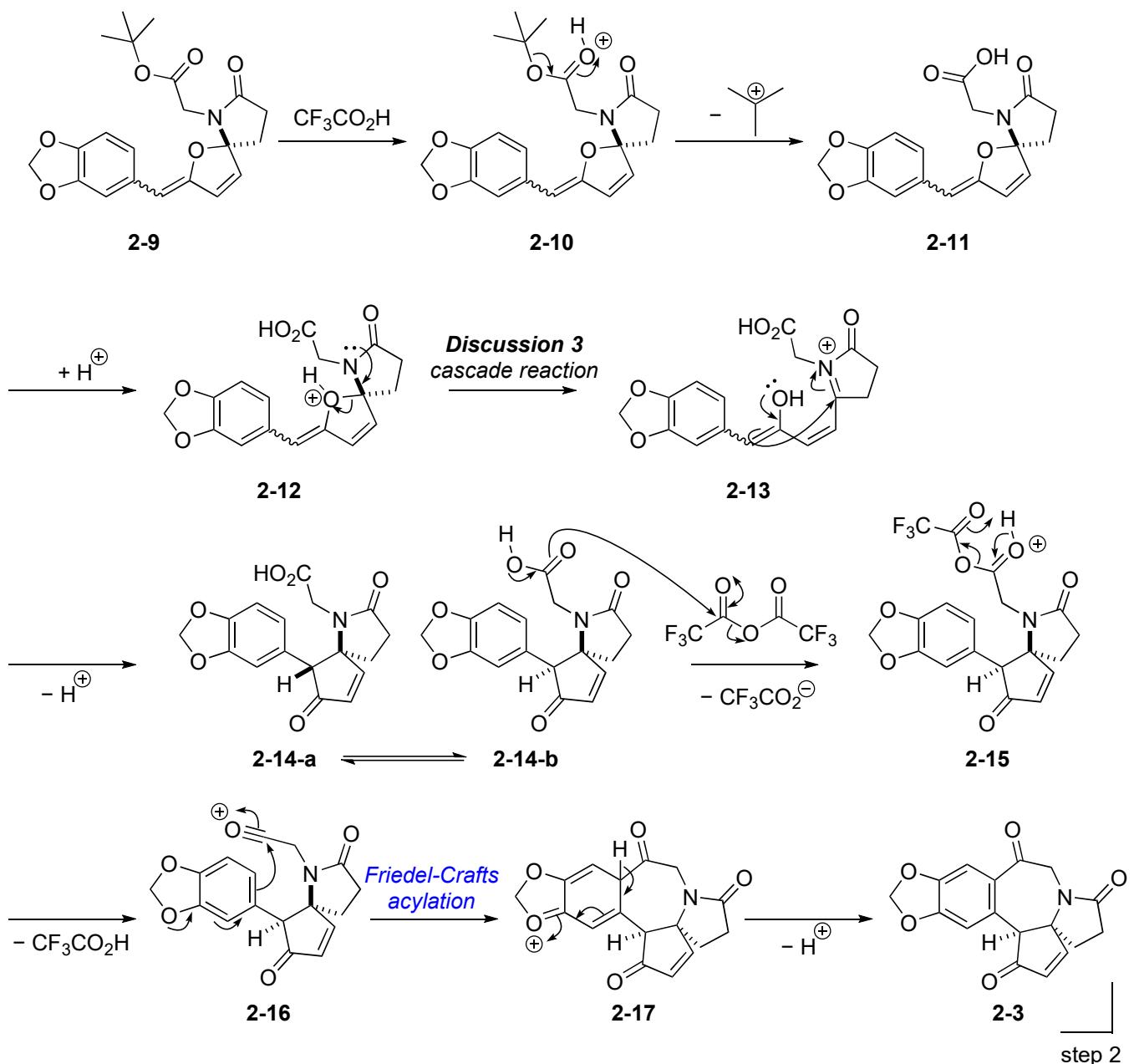


On aprotic condition of Discussion 1-2

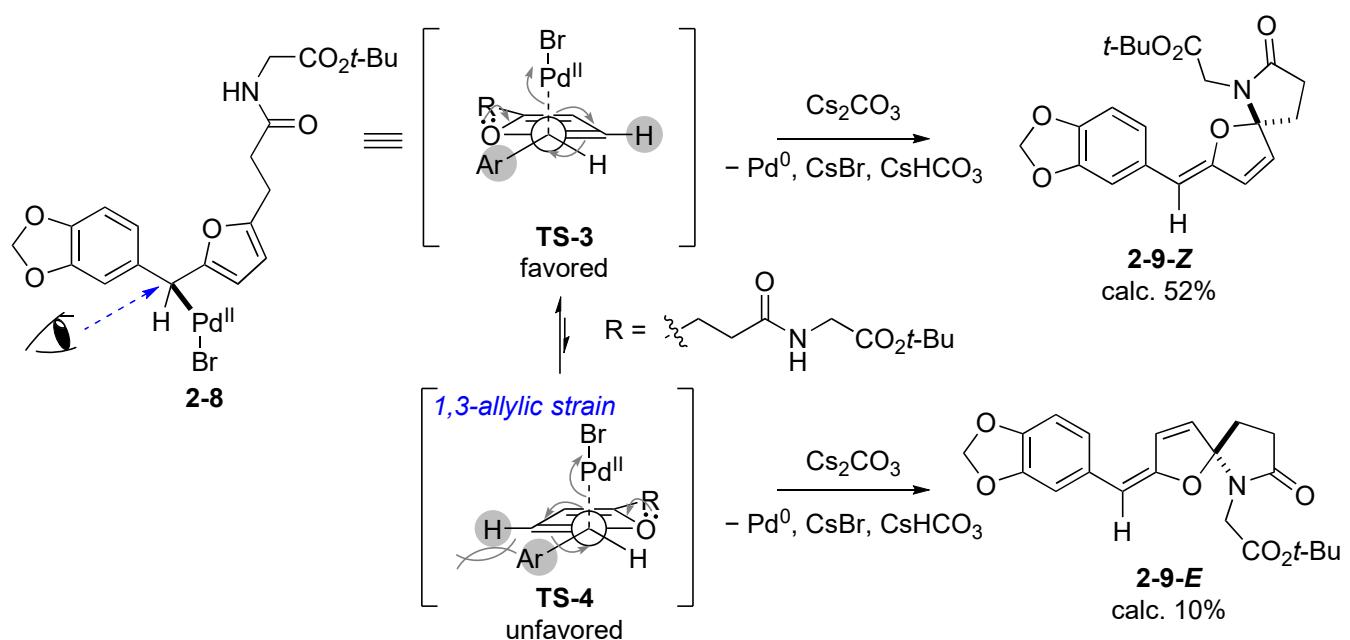


Both 1,2-proton shift and 1,3-proton shift are possible and conjugated olefin **A-9** is thermodynamically favored.
 → 1,3-proton shift may be impossible. Proton may be transferred by solvent (1,2-dichloroethane), tertiary amine of substrate, or slightly remained water.

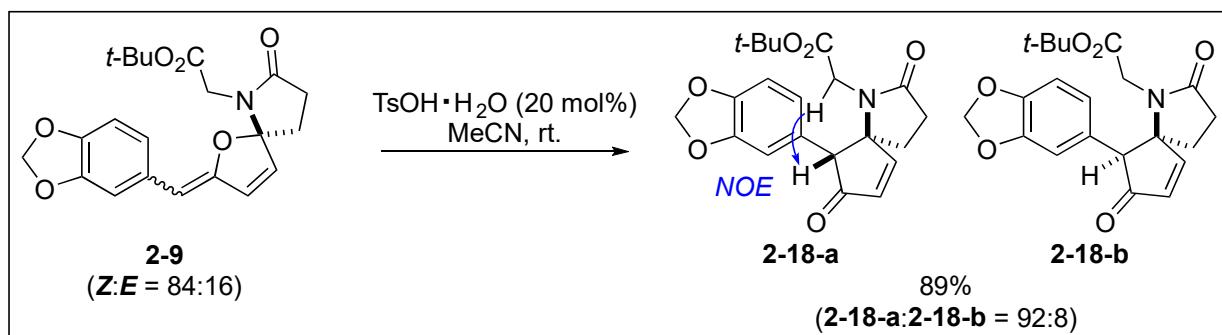




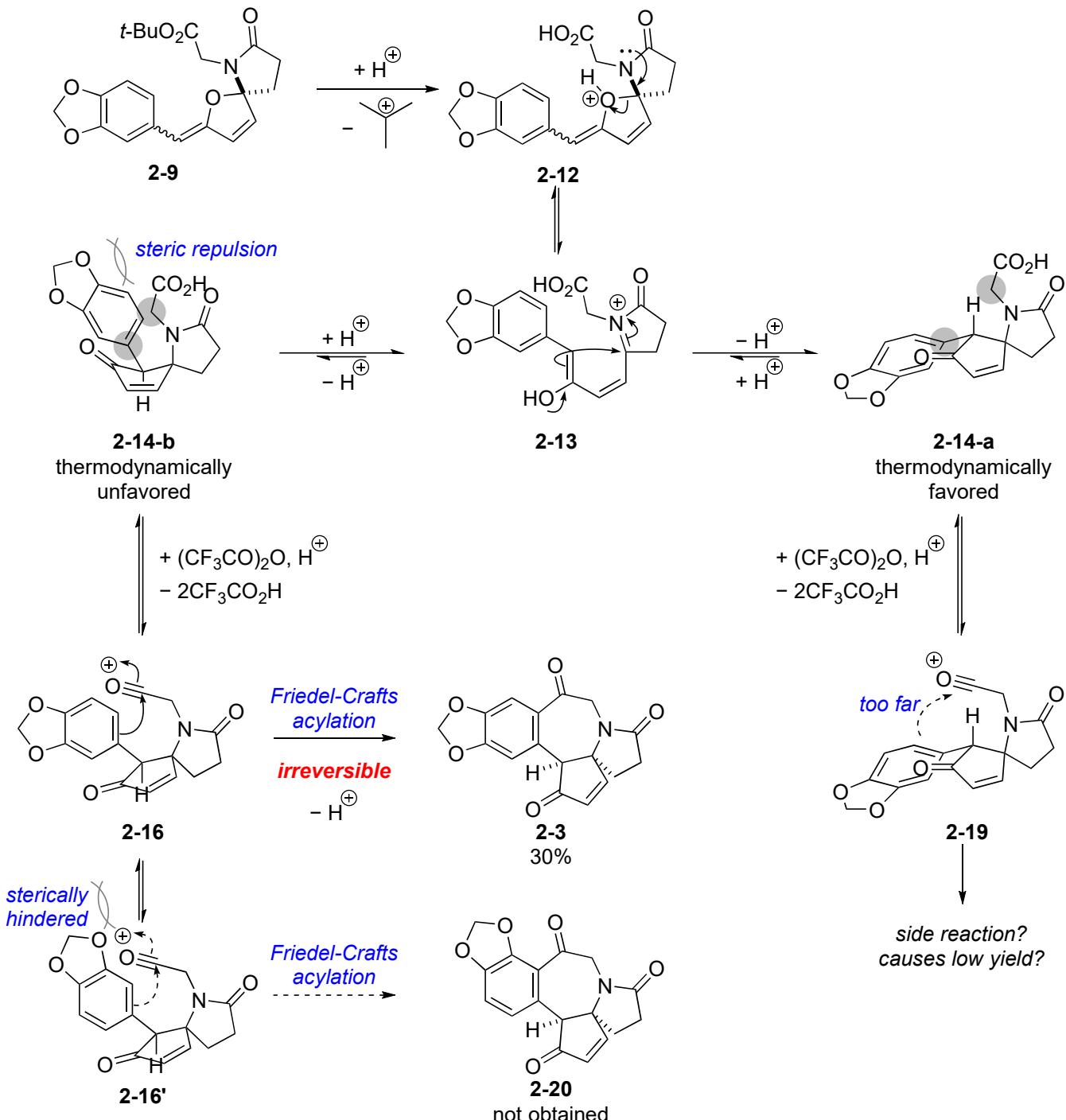
Discussion 2: Stereoselectivity of Pd-catalyzed dearomatic spirocyclization.



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**.