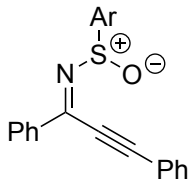
Problem Session (4)

Please provide the reaction mechanisms.

2024.1.6

Hibiki Asai

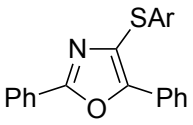
1 Ar = *p*-ClC_6H_4



1-1

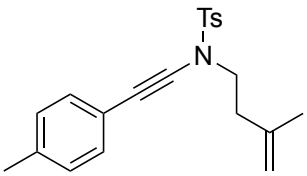
1. **1-A** (5 mol%), $(CH_2Cl)_2$, 80 ºC, 97%

2. imidazol (1 equiv), benzene, 30 ºC, 90%



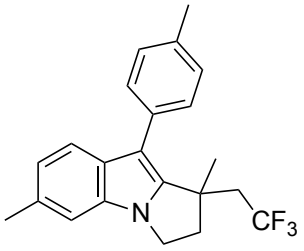
1-2

2

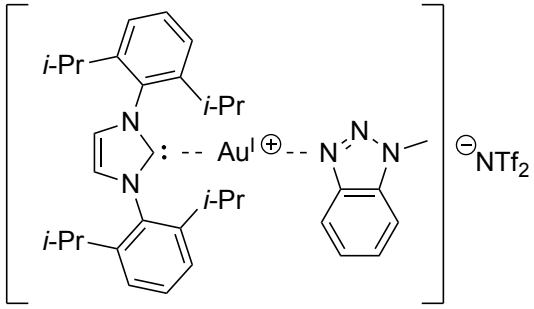


2-1

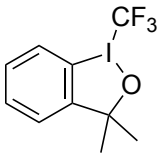
CuCl (20 mol%), **2-A** (1.2 equiv)
MeCN, 60 ºC, 63%



2-2



1-A



2-A

Tf: trifluoromethanesulfonyl
Ts: *p*-toluenesulfonyl

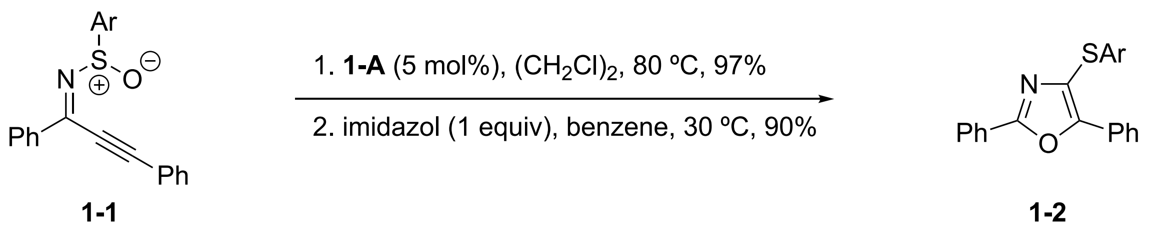
2024.1.6

Problem Session (4)

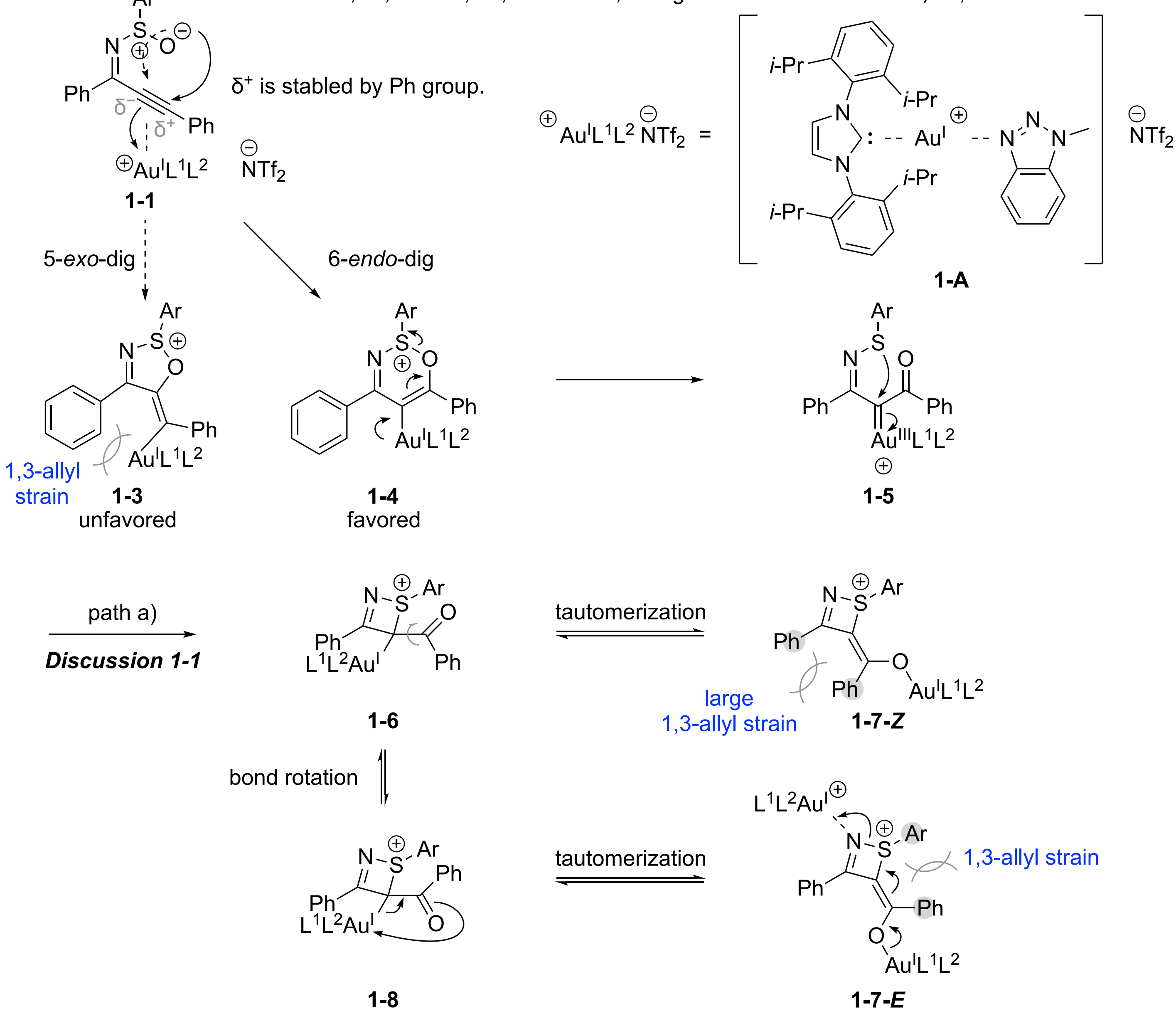
Topic: N-S bond

Hibiki Asai

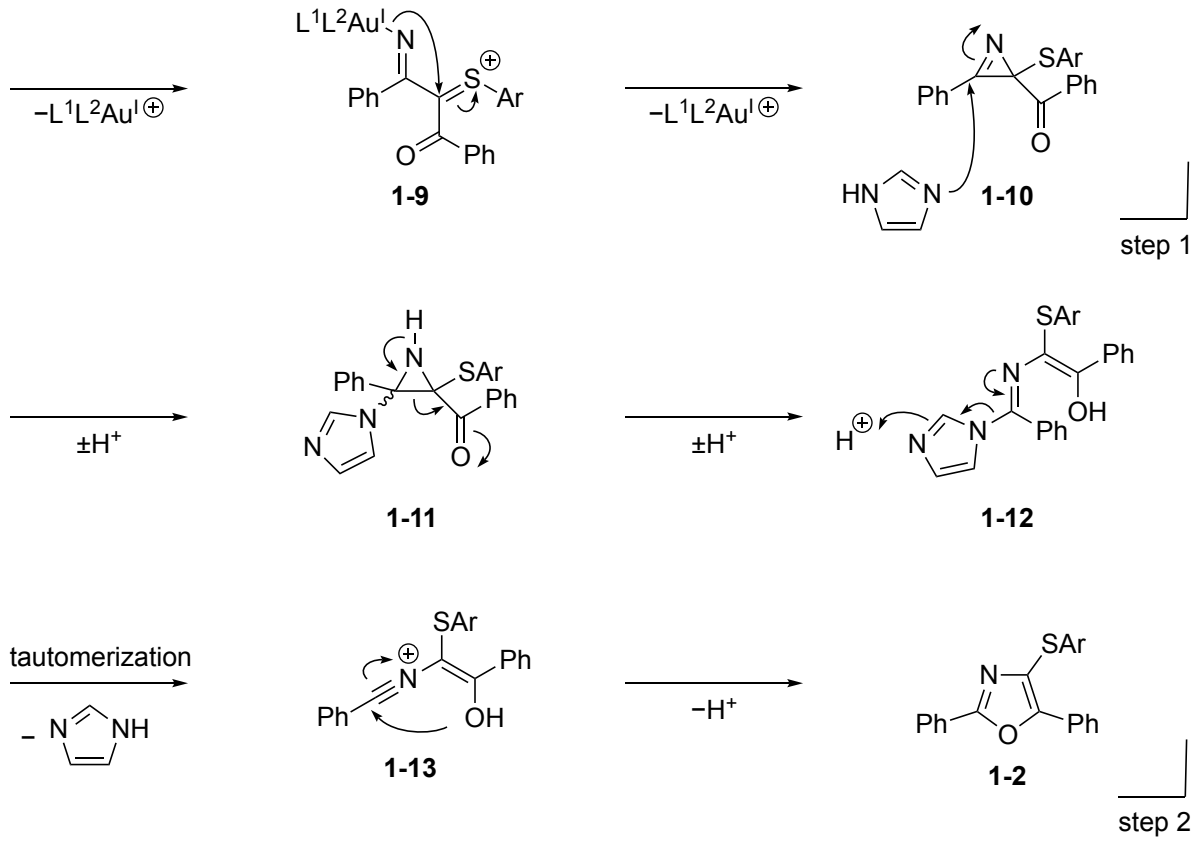
1 Ar = *p*-ClC$_6$H$_4$



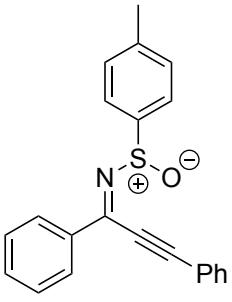
Tashiro, H.; Terada, M.; Nakamura, I. *Angew. Chem. Int. Ed.* **2021,** *60*, 12248–12252.



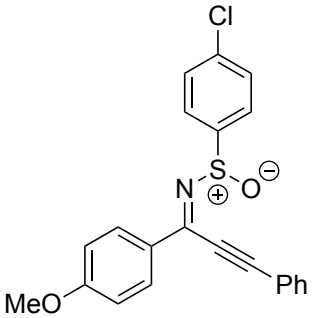
While it is thought that the difference energy between **1-7-*Z*** and **1-7-*E*** is small, and that the same product is obtained from both **1-7-*Z*** and **1-7-*E***, the following reaction mechanism was shown from **1-7-*E*** because probably **1-7-*Z*** is less stable due to large 1,3-allyl strain.



Discussion 1-1: Mechanism of cyclization and rearrangement
1) control experiment
a) crossover experiment

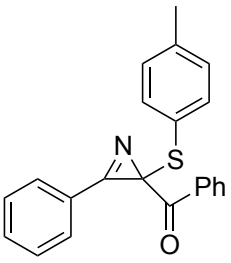


1-14 (0.10 mmol)

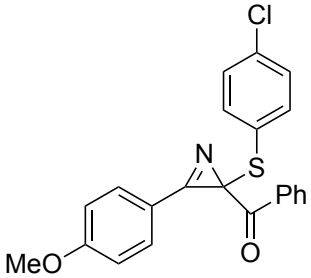


1-15 (0.10 mmol)

1-A (5 mol%)
$(CH_2Cl)_2$, 60 ºC

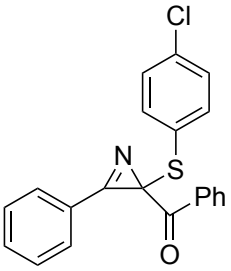


1-16 (0.066 mmol)

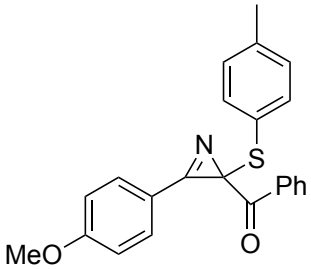


1-17 (0.054 mmol)

Crossover products were not detected on HRMS.
→N-S bond isn't cleavage until C-S bond is formed.



1-10 (not detected)



1-18 (not detected)

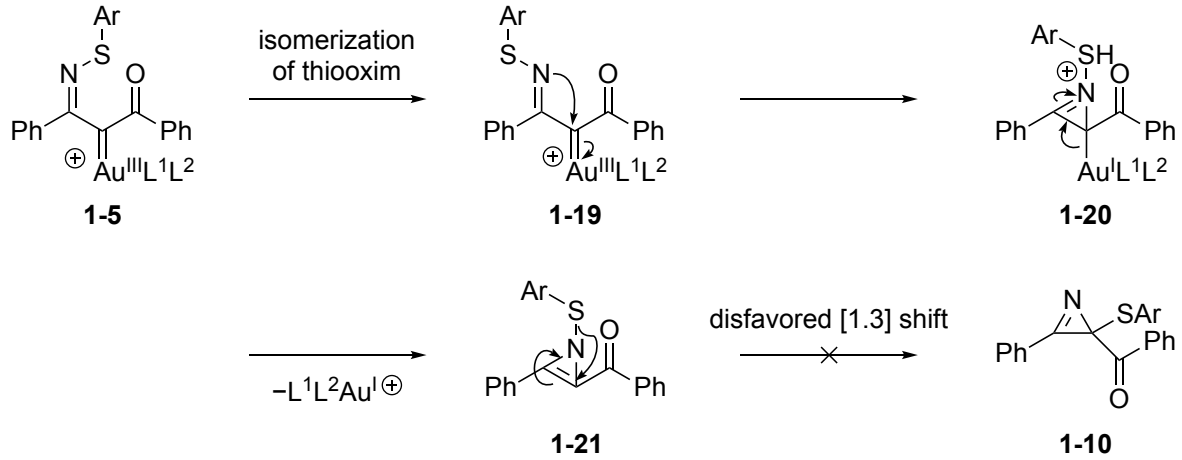
b) reaction of chiral substrate

1-14 (96% *ee)* **1-16** (4% *ee*)

Chirality on S atom didn't reflect on the product.
→S-O bond should be cleavaged before C-S bond formtion.

2) Other possible reaction pathes
path b) impossible path

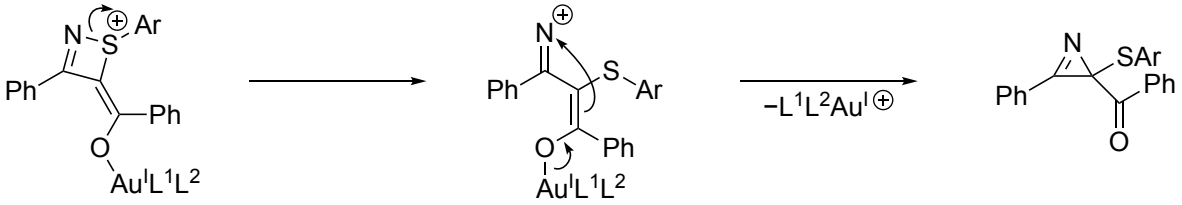
Ar = *p*-ClC_6H_4



1-5 **1-19** **1-20** **1-21** **1-10**

In path b, [1.3] shift of SAr is required, which is impossioble.

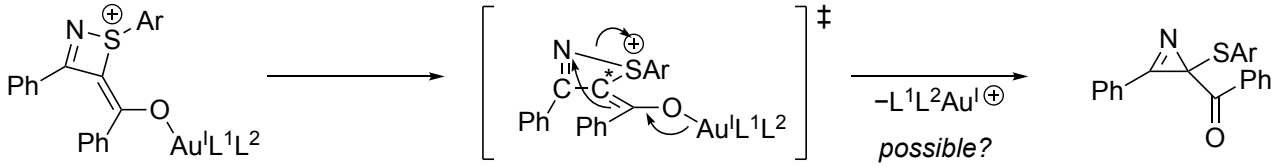
path c) another possible path



1-7-*E* **1-22** too unstable? **1-10**

In the ring openning of 4-membered ring on page 2 (**1-7-*E*** to **1-10**), 2 molecules of Au^I catalyst involve the reaction, which might be unplausible because the amount of Au^I catalyst is only 5 mol%. Therefore, **1-22** is considered as another intermediate of rearrangement.

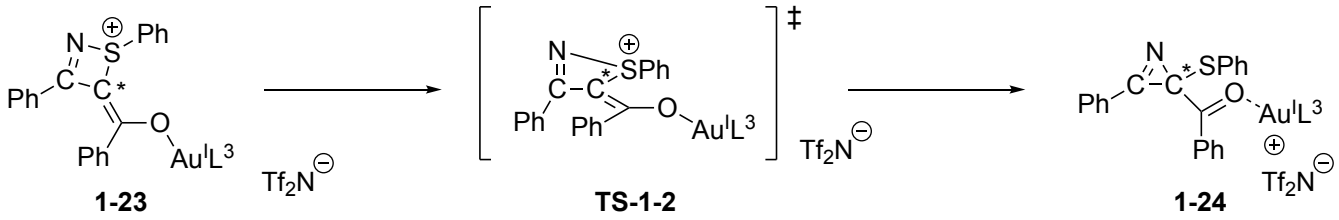
path d) author's proposed mechanism



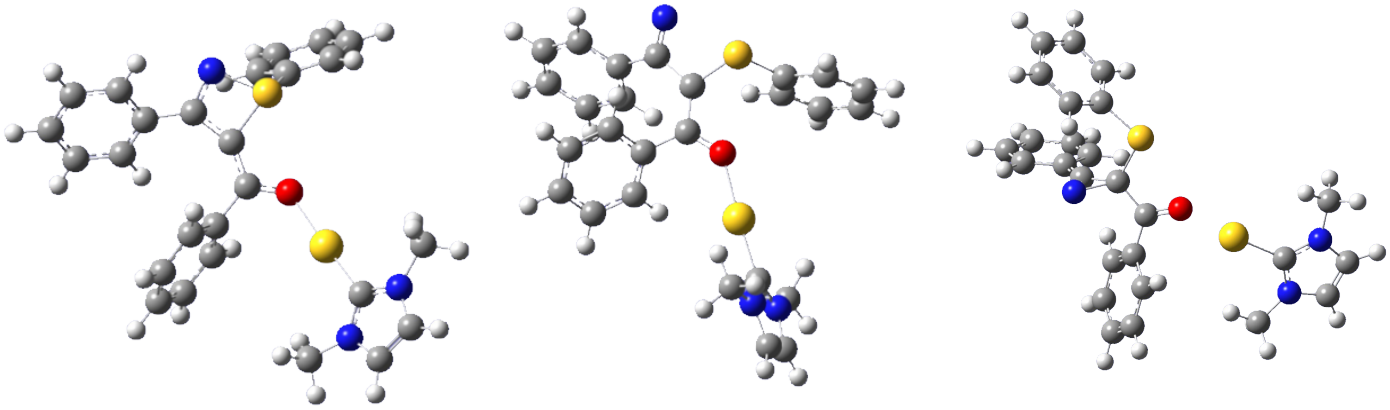
1-7-*Z* **TS-1-1** **1-10**

Author proposed concerted rearrangement according to the IRC analysis of rearrangement shown below.

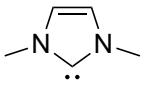
3) Calculation



1-23 **TS-1-2** **1-24**

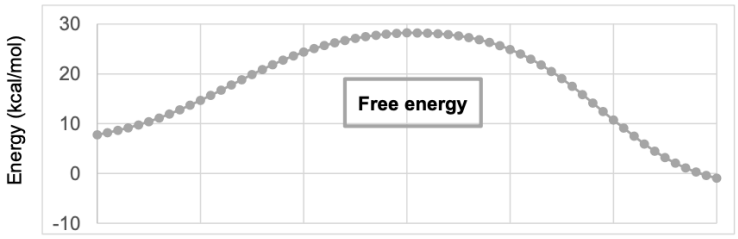


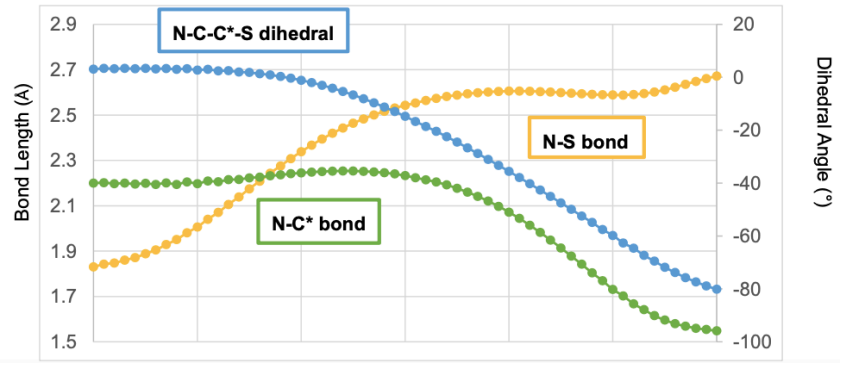
L^3 =



B3LYP/SDD for Au, 6-31+g(d, p) for others

intrinsic reaction coordinate (IRC) of rearrangement





Mulliken charge of the Au atom

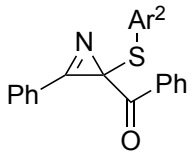
1-23	**TS-1-2**	**1-24**
0.305	0.060	0.356

Author argued that the four-membered ring became twisted when the N-S bond length was increased, which was followed by N-C* bond formation. Considerring Mulliken charge of the Au atom on **1-23**, **TS-1-2**, and **1-24**, Au atom acts as a Lewis acid to promote elonggation of the N-S bond.

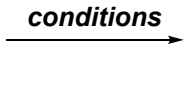
Judged from IRC calculation, N-S bond is almost cleavaged in **TS-1-2**. Therefore, this path d is S_N1-like S_N2 reaction on sp^2 N atom, which resembles path c.

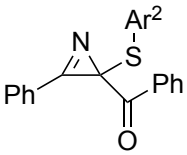
From the above, both path a and path d are plausible.

Discussion 1-2: Role of 1-methyl-1 H-benzotriazole

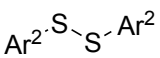


1-16



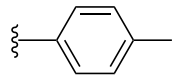


1-16



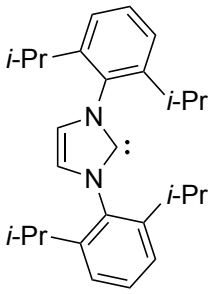
1-25

Ar^2 =

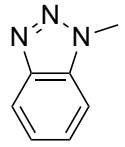


1	$(CH_2Cl)_2$, 80 ºC, 1 h	99% rcv.	-
2	$\underline{L^1}\underline{AuNTf_2}$ (5 mol%) $(CH_2Cl)_2$, 80 ºC, 1 h	66% rcv.	16%
3	$L^1\underline{L^2}AuNTf_2$ (5 mol%) $(CH_2Cl)_2$, 80 ºC, 1 h	98% rcv.	-

L^1 =

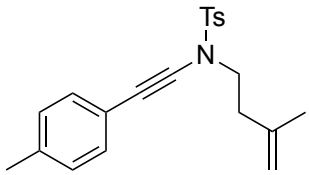


L^2 =



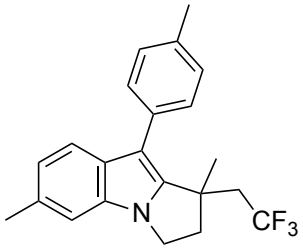
2H-azirine **1-16** seems to be decomposed by cationic gold catalyst L^1AuNTf_2 (entry 2). On the other hand, in the presence of ligand L^2, **1-16** is quantitively recovered (entry 3). Ligand L^2 is thought to coordinate with Au^I, and prevent the decomposition of **1-16** due to lowering the cationy of Au^I.

2



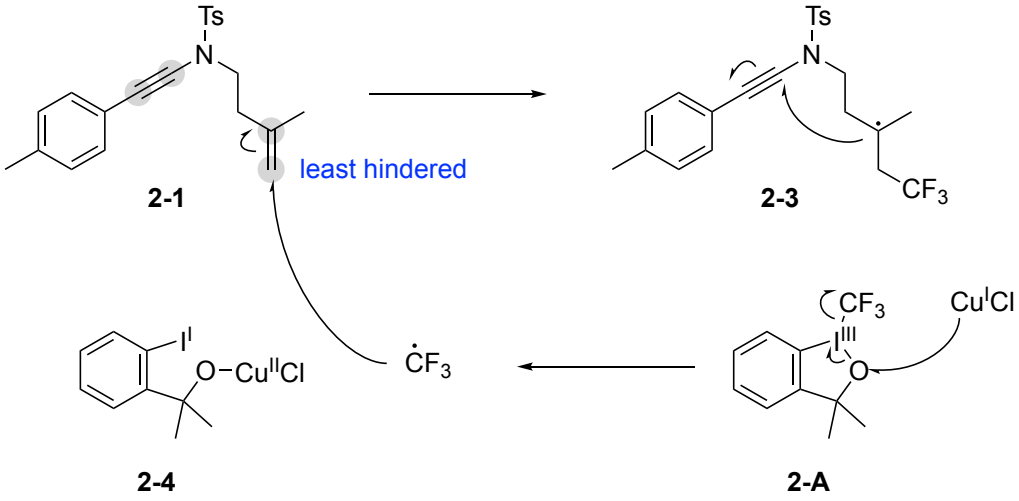
2-1

CuCl (20 mol%), **2-A** (1.2 equiv)
MeCN, 60 ºC, 63%

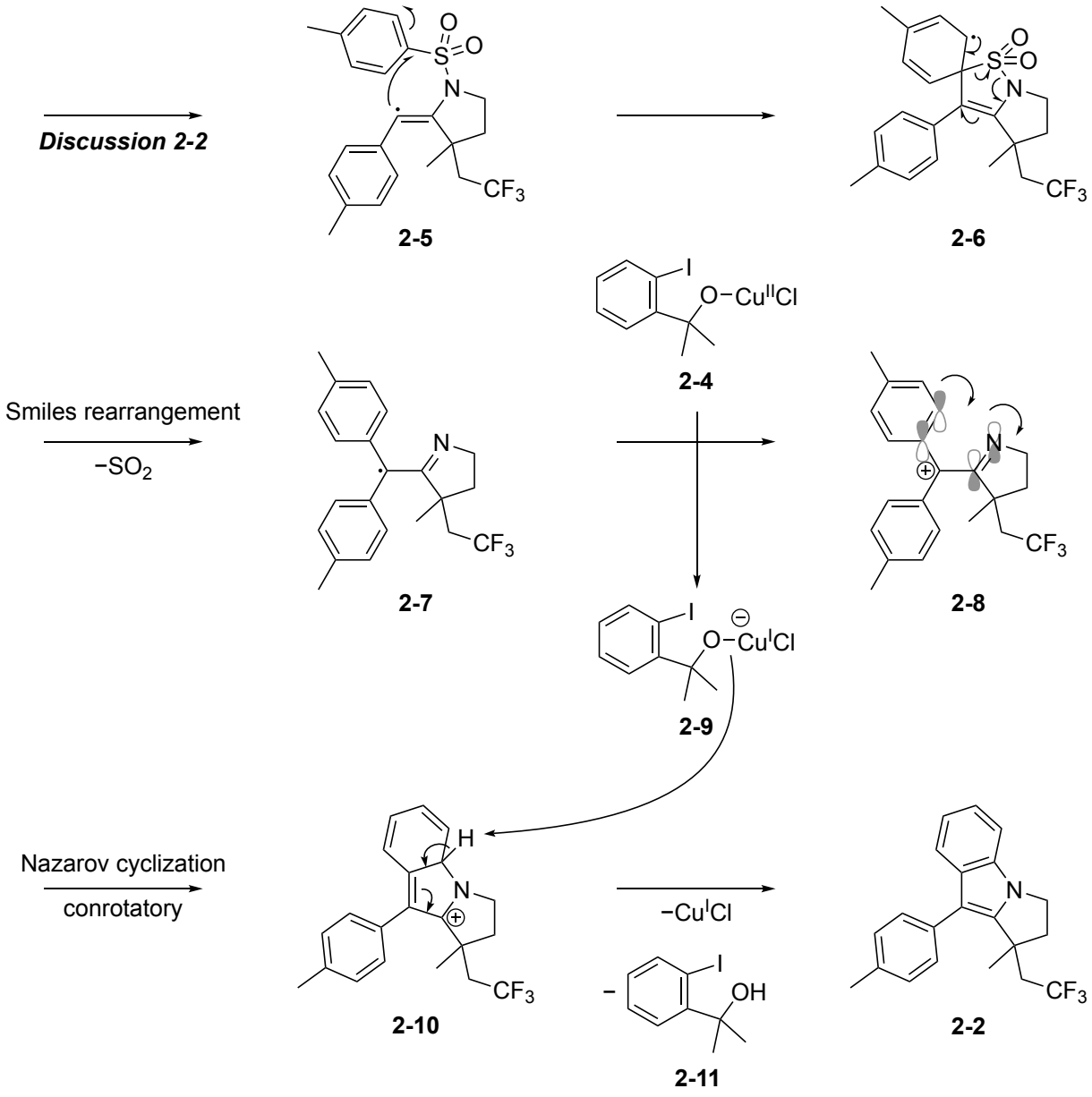


2-2

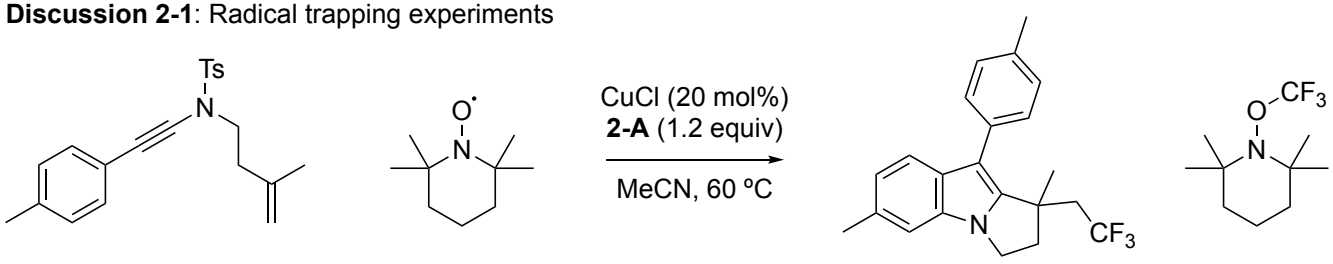
Li, S.; Wang, Y.; Wu, Z.; Shi, W.; Lei, Y.; Davies, P. W.; Shu, W. *Org. Lett.* **2021**, *23*, 7209–7214.



2-1 **2-3** **2-4** **2-A**



Discussion 2-1: Radical trapping experiments



2-1

2-12 (1 equiv)

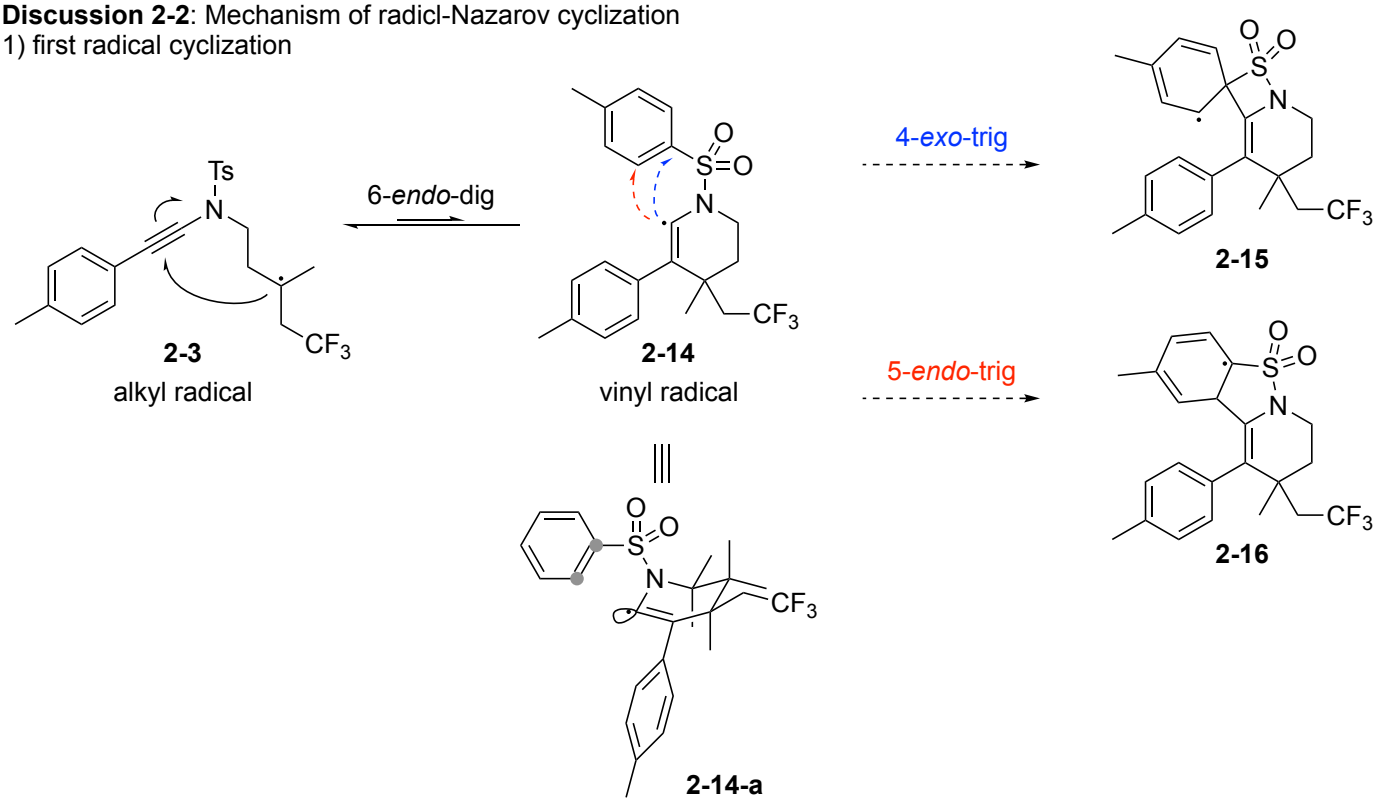
2-2 not observed

2-13 observed on ^{19}F NMR

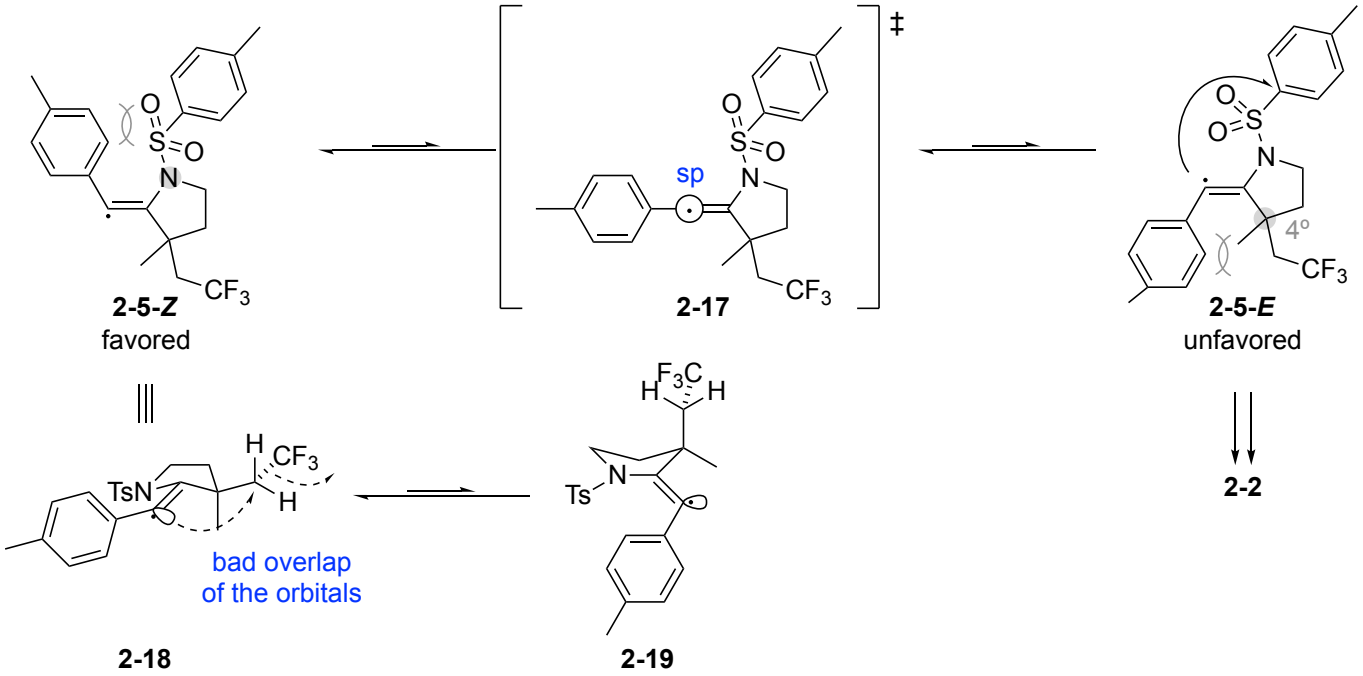
•CF_3 seems to participate in the reaction.

2-A

Discussion 2-2: Mechanism of radicl-Nazarov cyclization
1) first radical cyclization

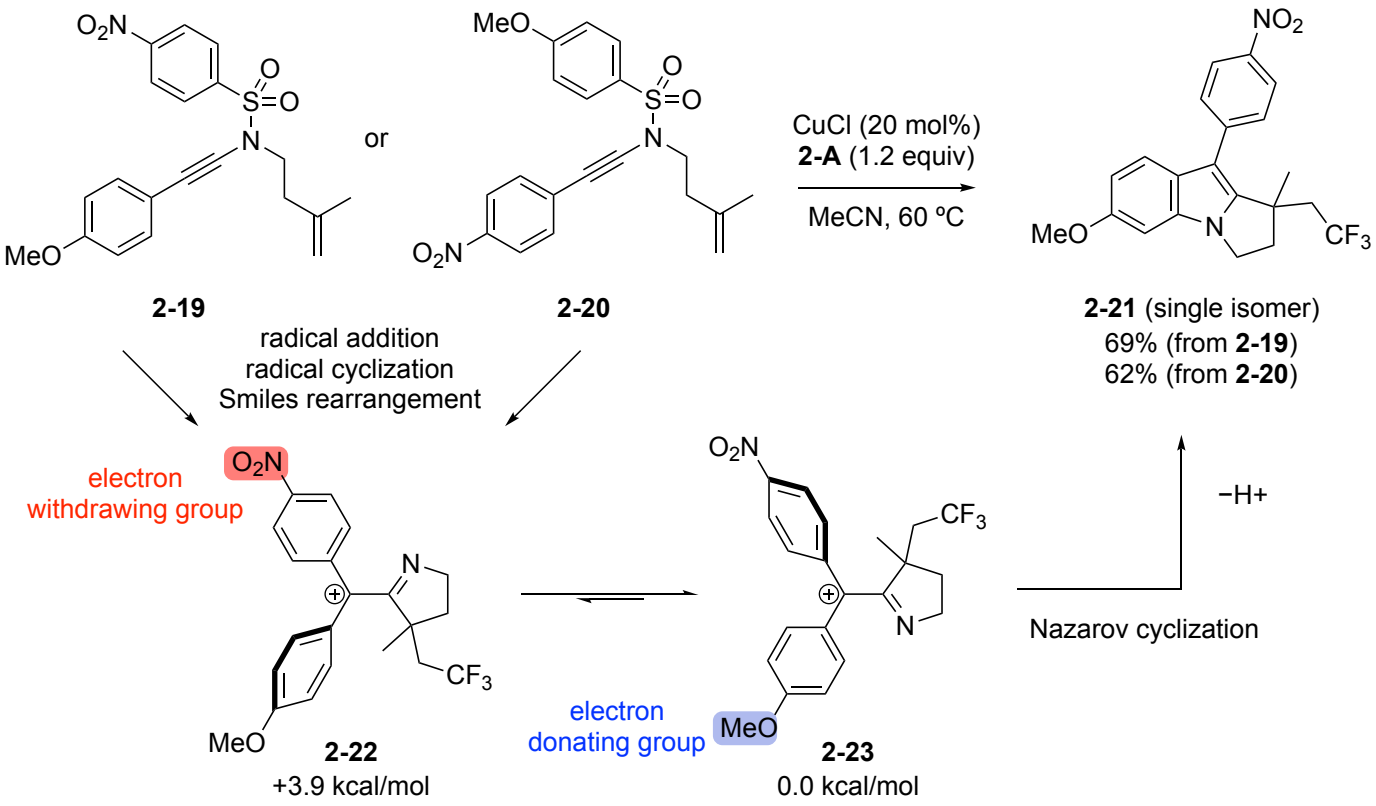


In the first cyclization from **2-3**, undesired 6-*endo* cyclized intermediate **2-14** might be generated. However, the second cyclization, in which vinyl radical of **2-14** attacks to Ts group,can't occur because of the bad overlap between the orbital of vinyl radical and that of aromatic ring. Therefore, unstable vinyl radical is thought to go back to more stable alkyl radical **2-3**.



About 5-*exo* cyclized product **2-5**, *E*-isomer is slightly unfavored because of large 1,3-allyl strain between aromatic ring and 4º carbon. On the other hand, the following second cyclization occur from only **2-5-*E***. From **2-5-*Z***, side reaction might occur in which $\bullet CF_3$ was rejected by vinyl radical to give 4-membered ring. However, this side reaction should be slow because ofthe bad overlap between the orbital of vinyl raical and that of σ* of C-CF_3, and thus **2-5-*Z*** is thought to be go back to **2-3**.

2) Nazarov cyclization



Indole **2-21** was obtained as a single isomer from both sulfonamide **2-19** and **2-20**, which suggets that common ation intermediate **2-23**, in which benzyl cation is stabled by electron rich aromatic ring, go through Nazarov cyclization.