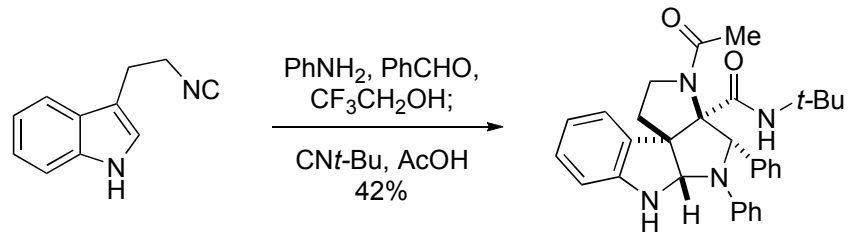
Problem session (3)

2016.12.17. Akinori Yamaguchi

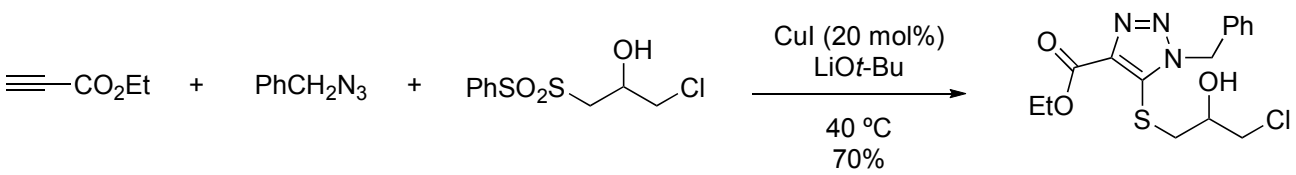
Please provide the reaction mechanisms and fill in the blank.

(1)



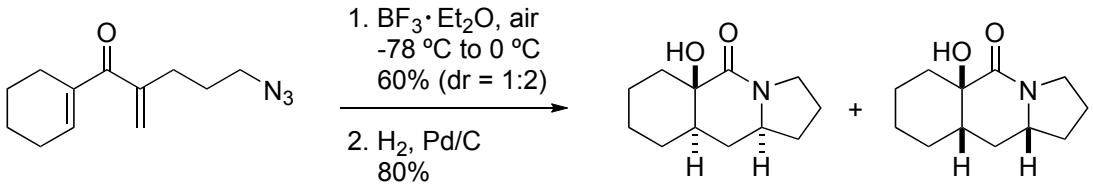
1-1 **1-2**

(2)



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

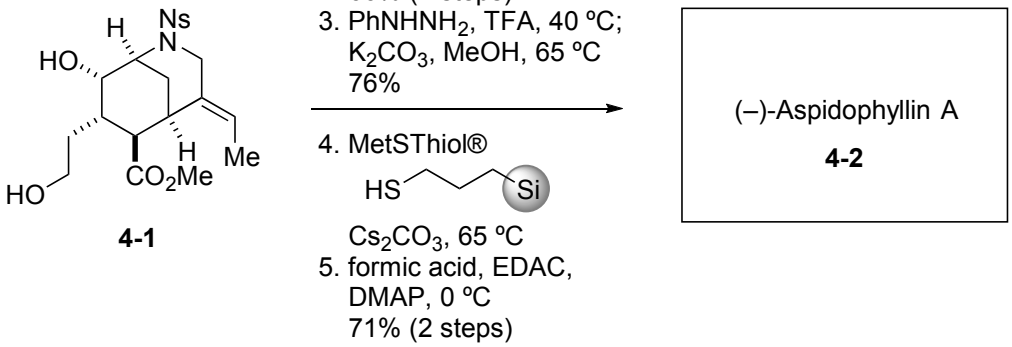
(3)



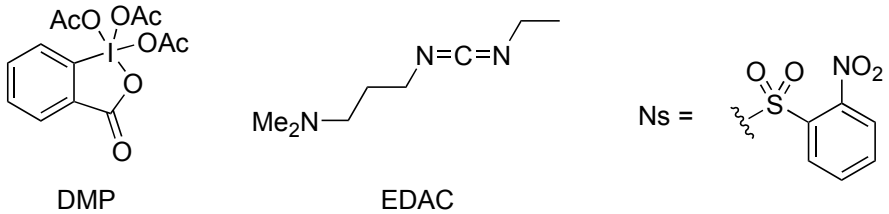
3-1 **3-2** **3-3**

3-2:**3-3** = 1:2

(4)



4-1



Problem Session (3): Answer

2016. 12. 17. Akinori Yamaguchi

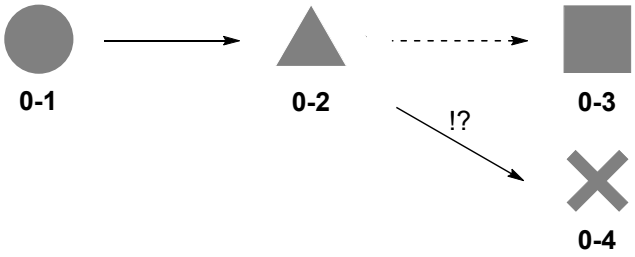
Topic: **"Interrupted" reaction**

<Introduction>

1. definition

"Interrupted" reaction	≡	Reaction that gives the product resulting from capture of the intermediate instead of the product seemingly estimated

2. general scheme of "Interrupted" reaction



(1)

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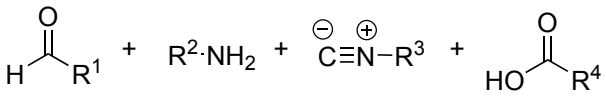
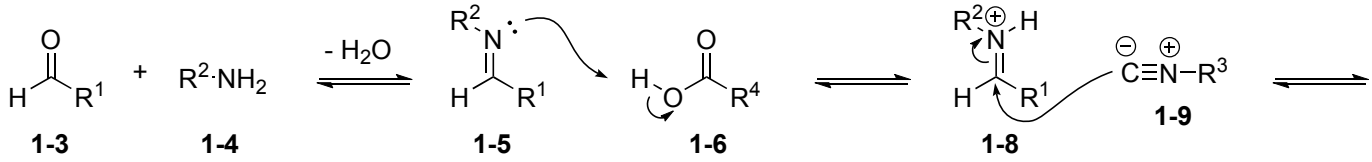
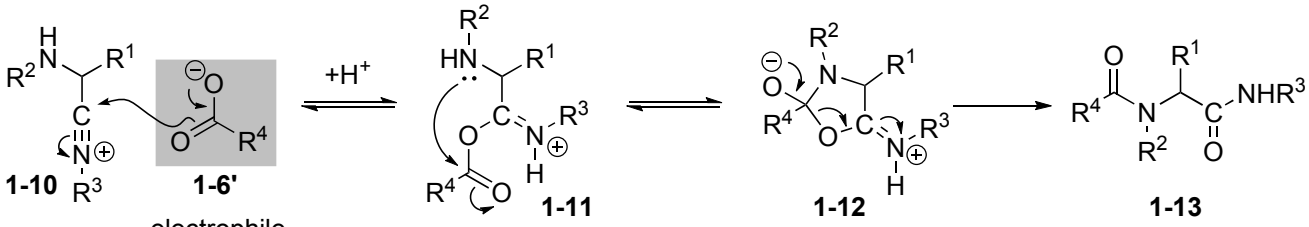
1. Interrupted Ugi reaction

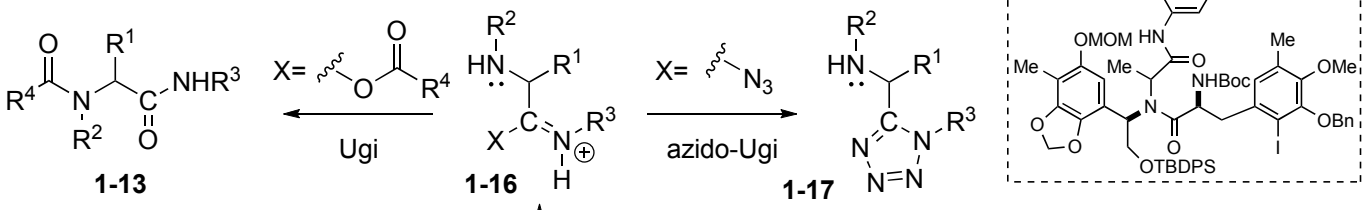
1-1. Classic Ugi reaction (a four-component coupling reaction)

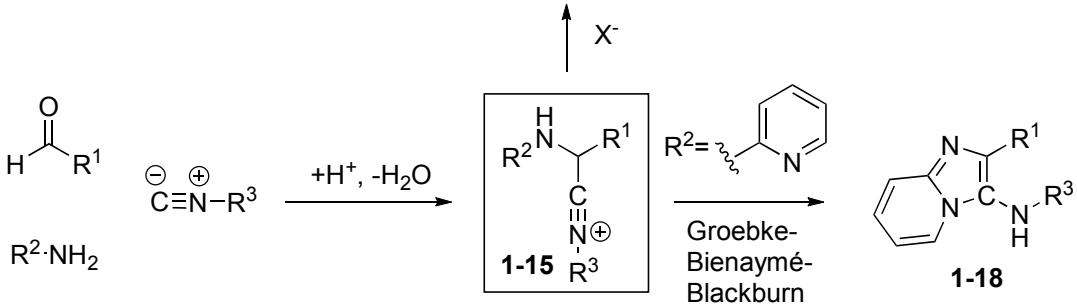


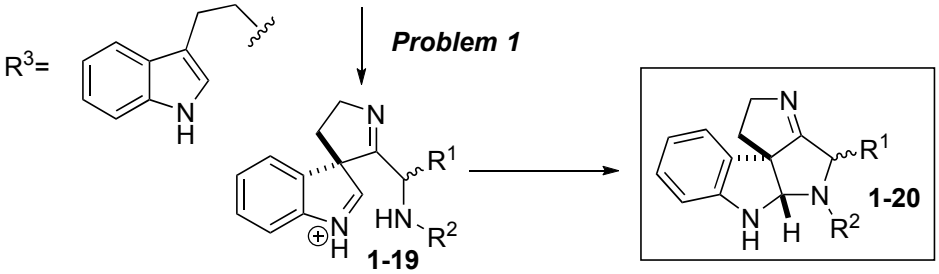




1-2. Variations of Ugi reaction

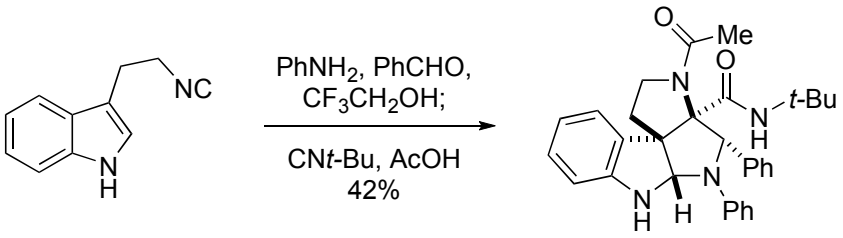






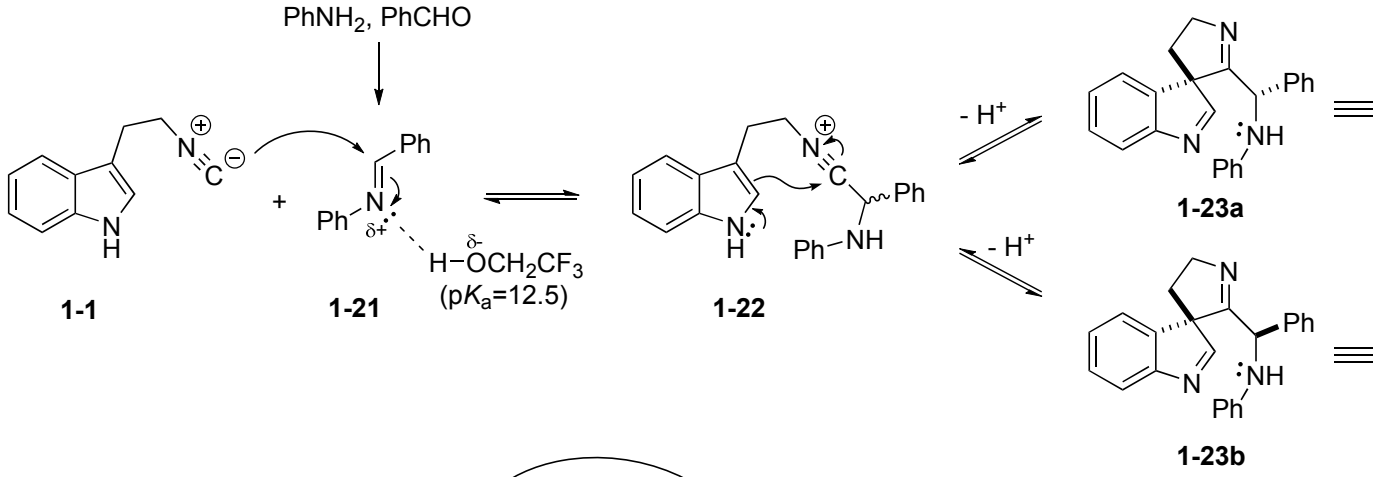
1-3. Reaction mechanism

(1)

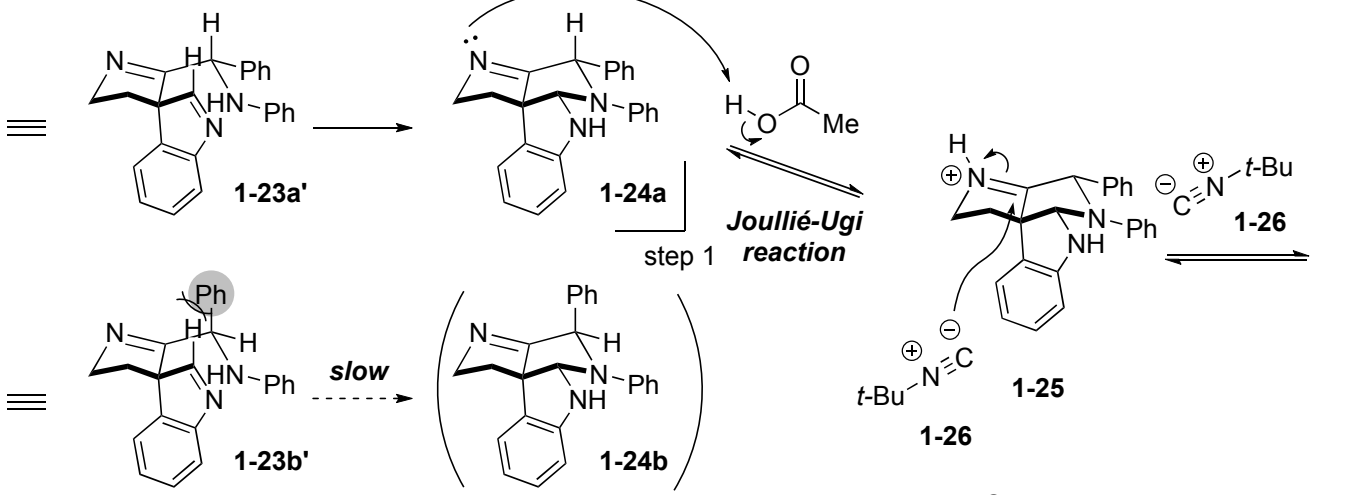


1-1 **1-2**

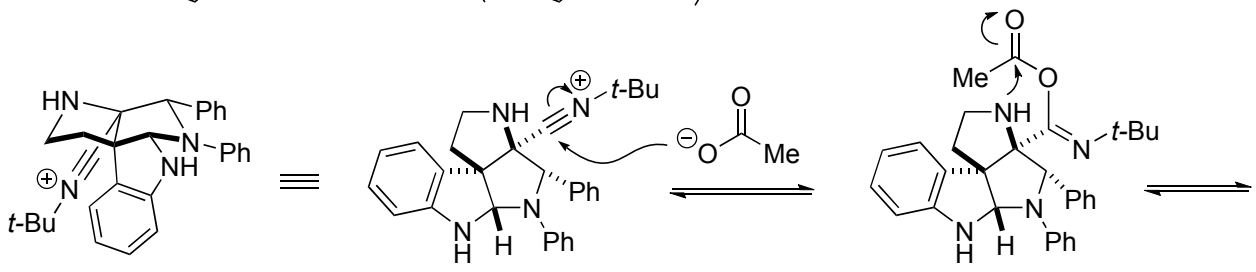
Ruijter, E. *et al. Chem. Commun.* **2016**, *52*, 12482.



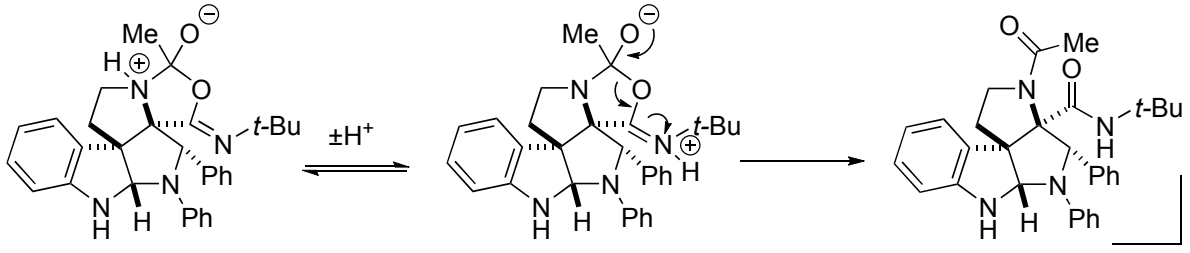
1-1 **1-21** **1-22** **1-23a** **1-23b**



1-23a' **1-24a** **1-23b'** **1-24b** **1-25** **1-26**



1-27 **1-27'** **1-28**

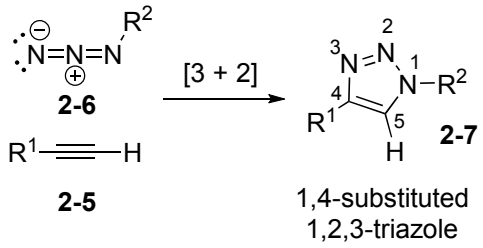


1-29 **1-30** **1-2**

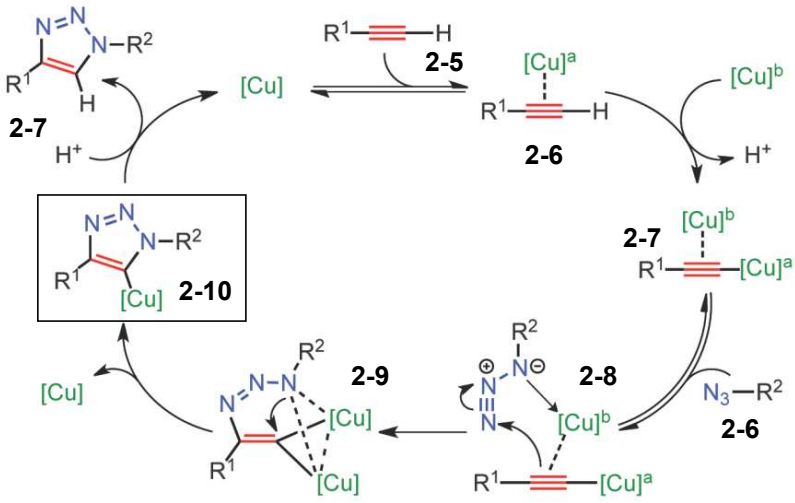
2. Interrupted Click reaction

2-1 Click reaction (Huisgen Cycloaddition)

· Azido-Alkyne Cycloaddition (AAC)



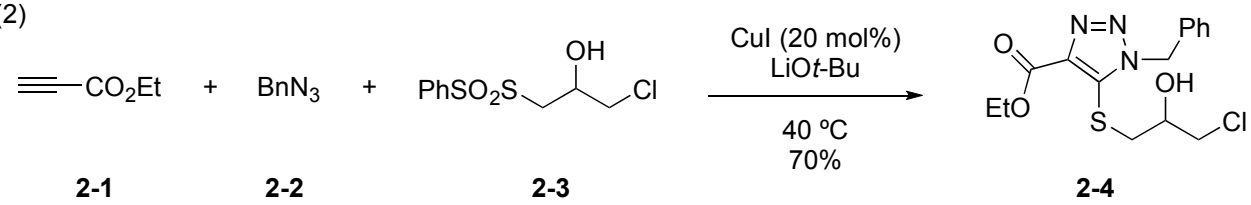
· Copper(I)-catalyzed Azido-Alkyne Cycloaddition (CuAAC)



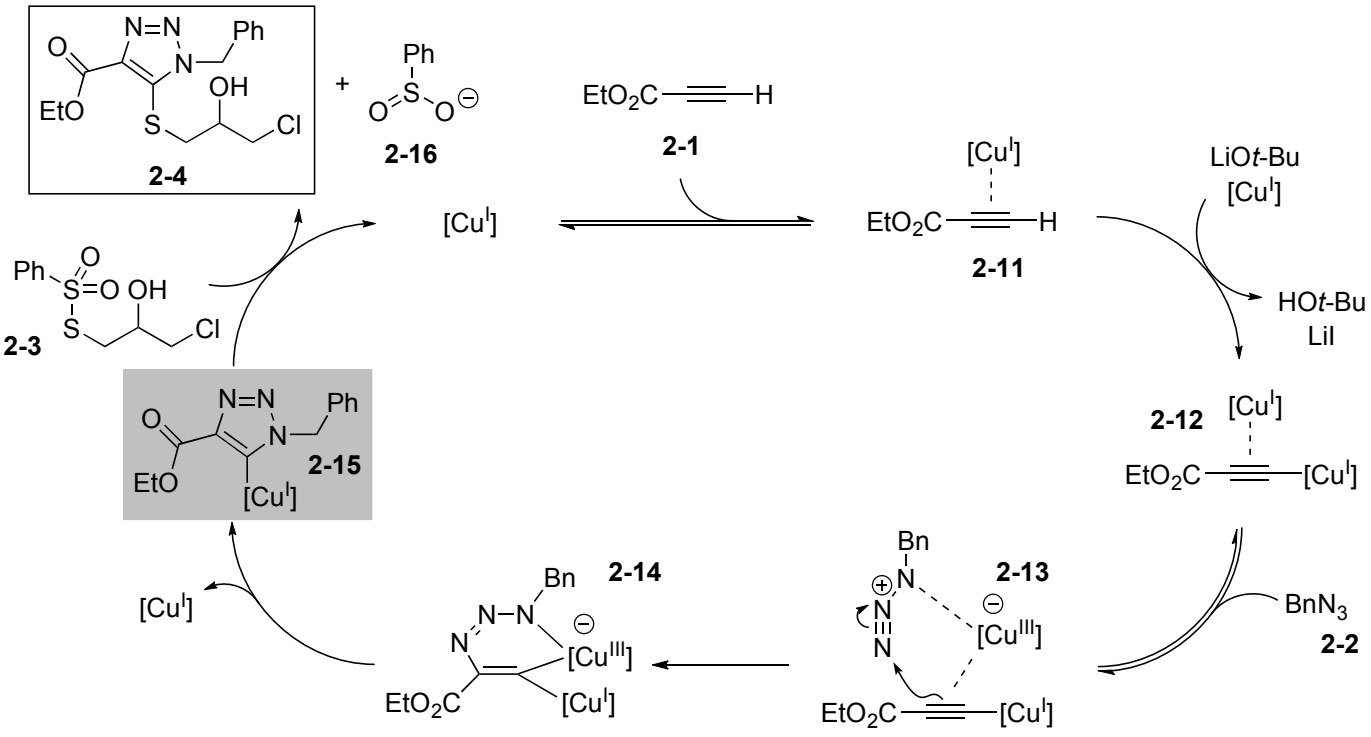
Fokin, V. V. *et al. Science* **2013**, *340*, 457.

2-2. Reaction mechanism

(2)



Xu, Z. *et al. Angew. Chem. Int. Ed.* **2016**, *55*, 649.



2-3. Design of electrophile **2-3**

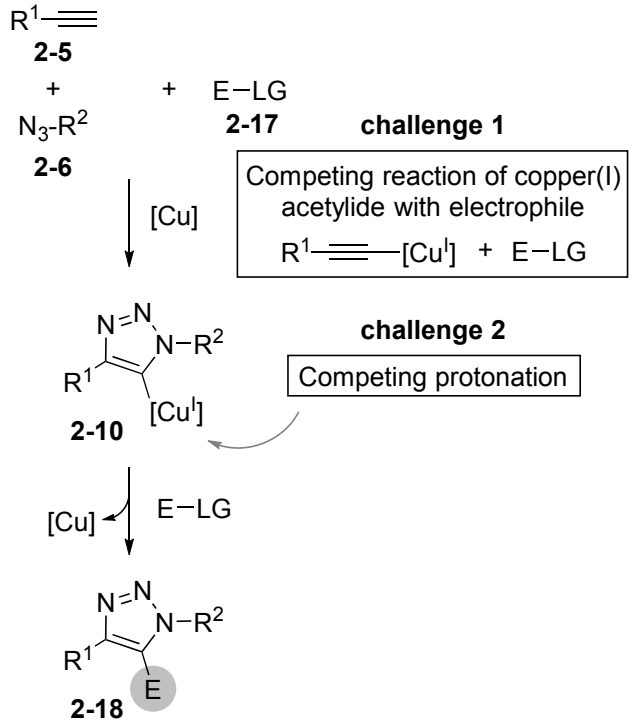
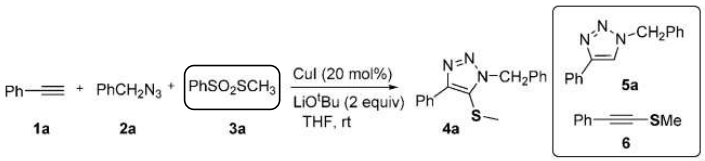
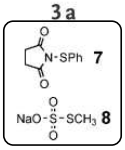


Table: Optimization of reaction conditions



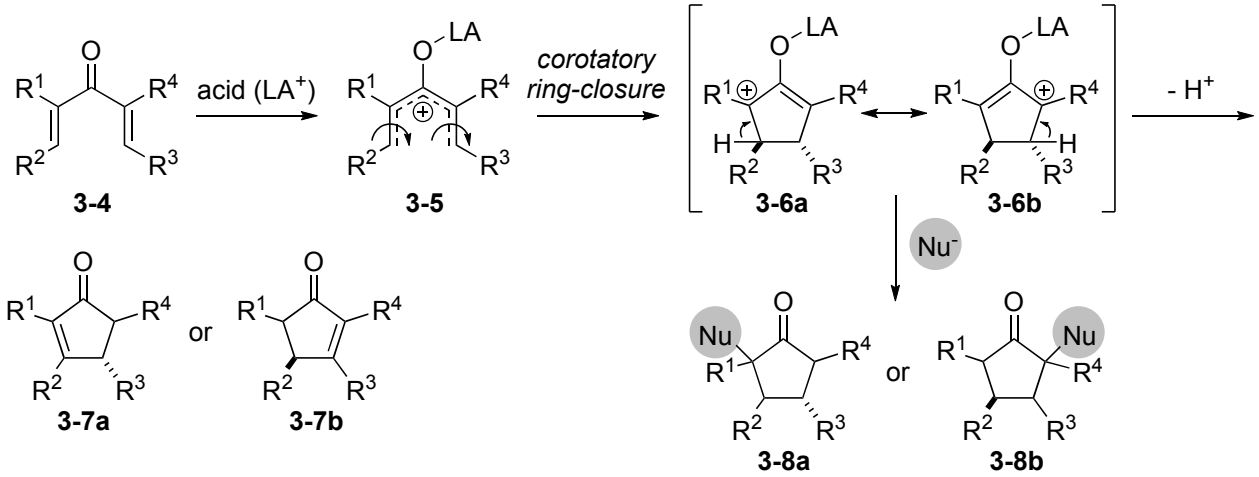
Entry	Base	Temp [°C]	Electrophile	Yield [%][b] 4a	5a
1	LiO^{t}Bu	25	**3a**	74	8
2	LiO^{t}Bu	25	 **7**	0[c]	66
3	LiO^{t}Bu	25	**8**	0	96
4	KO^{t}Bu	25	**3a**	< 5	64
5	NaOMe	25	**3a**	30	52
6	NaH	25	**3a**	25	56
7	K_2CO_3	25	**3a**	< 5	92
8	Et_3N	25	**3a**	< 5	94
9	LiO^{t}Bu	40	**3a**	81	5
10[d]	**LiO^{t}Bu**	**40**	**3a**	**95 (90)**	**trace**

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), **3a** (0.3 mmol), CuI (20 mol%), base (0.4 mmol), 4 Å molecular sieves (MS, 150 mg), THF (1 mL) was stirred at room temperature under N_2 atmosphere for

---

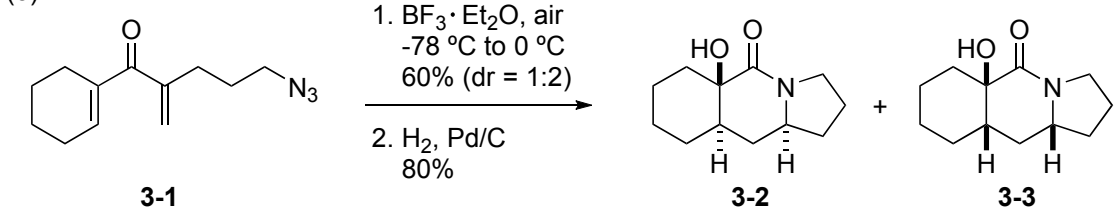
3. Interrupted Nazorov cyclization

3-1. Nazarov Cyclization



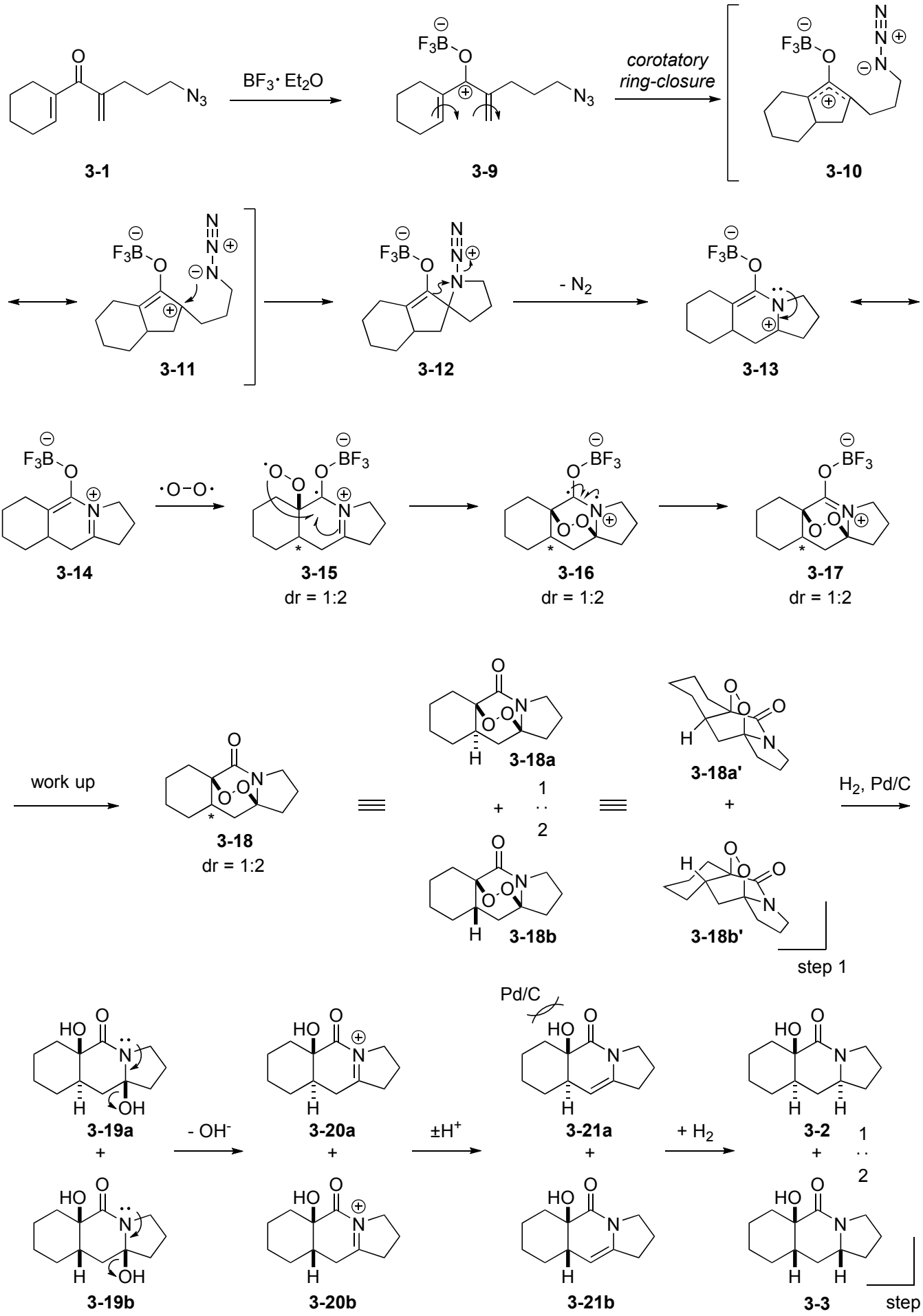
3-2. Reaction mechanism

(3)



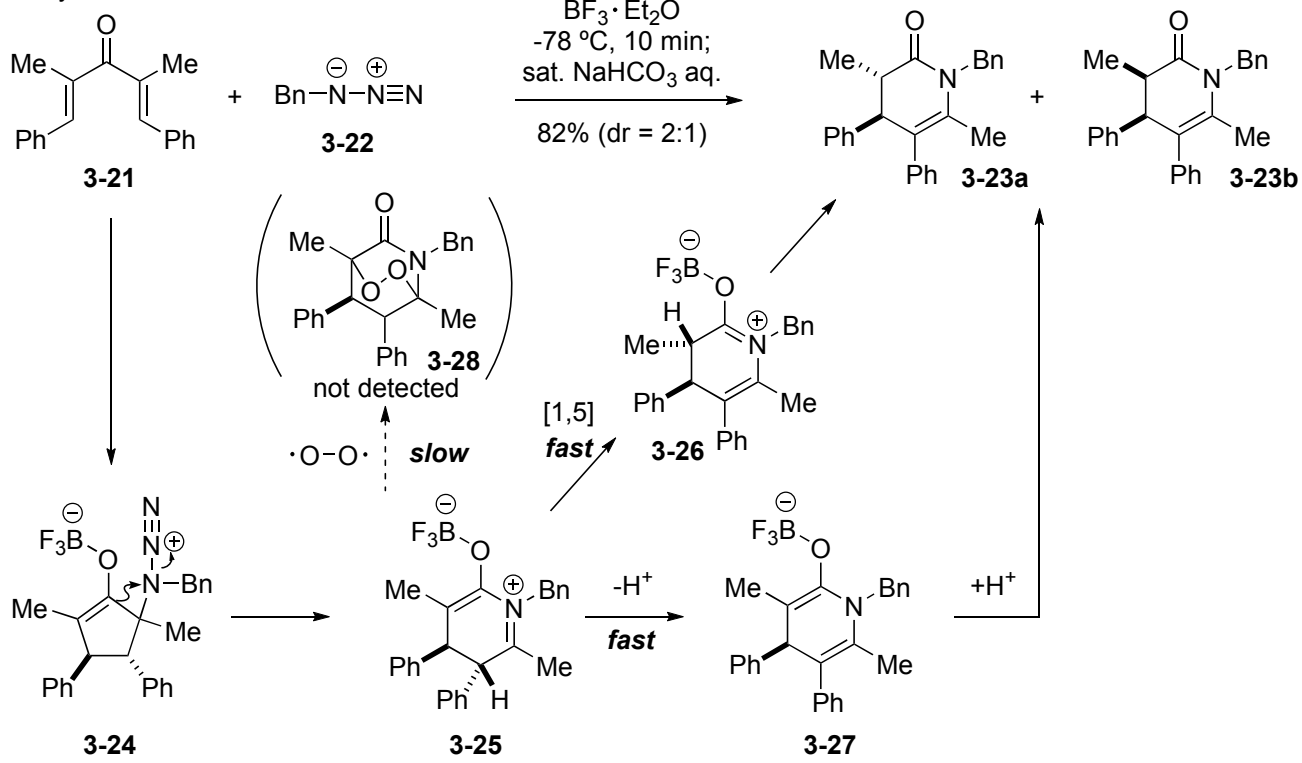
3-2:**3-3** = 1:2

West, F. G. *et al. Org. Lett.* **2007**, *9*, 703.

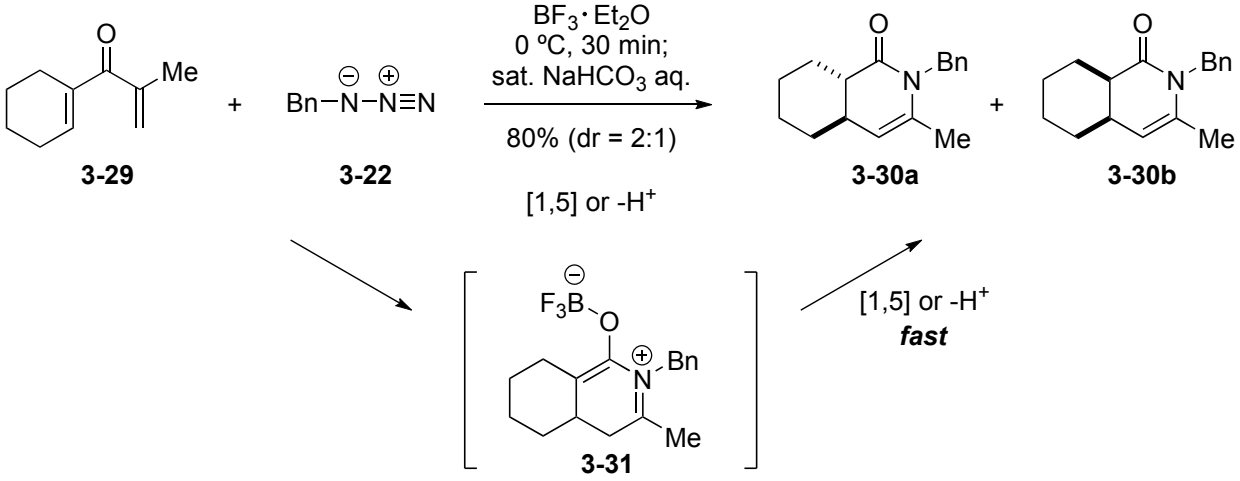

3-1
BF3· Et2O
3-9
corotatory
ring-closure
3-10
3-11
3-12
- N2
3-13
3-14
·O−O·
3-15
dr = 1:2
3-16
dr = 1:2
3-17
dr = 1:2
work up
3-18
dr = 1:2
3-18a
3-18b
3-18a'
3-18b'
H2, Pd/C
step 1
3-19a
3-19b
- OH-
3-20a
3-20b
±H+
Pd/C
3-21a
3-21b
+ H2
3-2
3-3
step 2

3-3. Reactivity of 1,4-dipole West, F. G. *et al. J. Am. Chem. Soc.* **2007**, *129*, 12019.

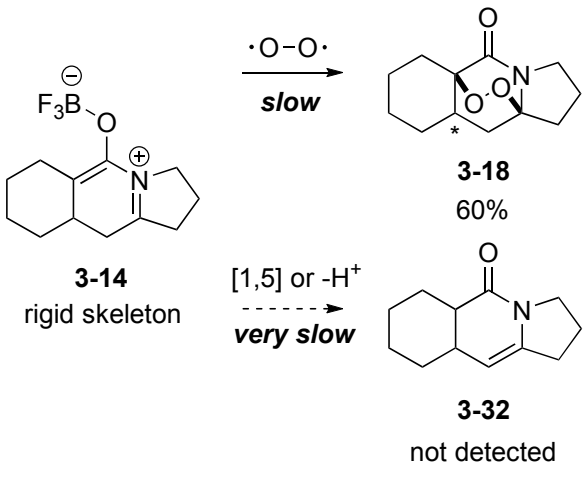
· Monocyclic betaine



· Bicyclic betaine

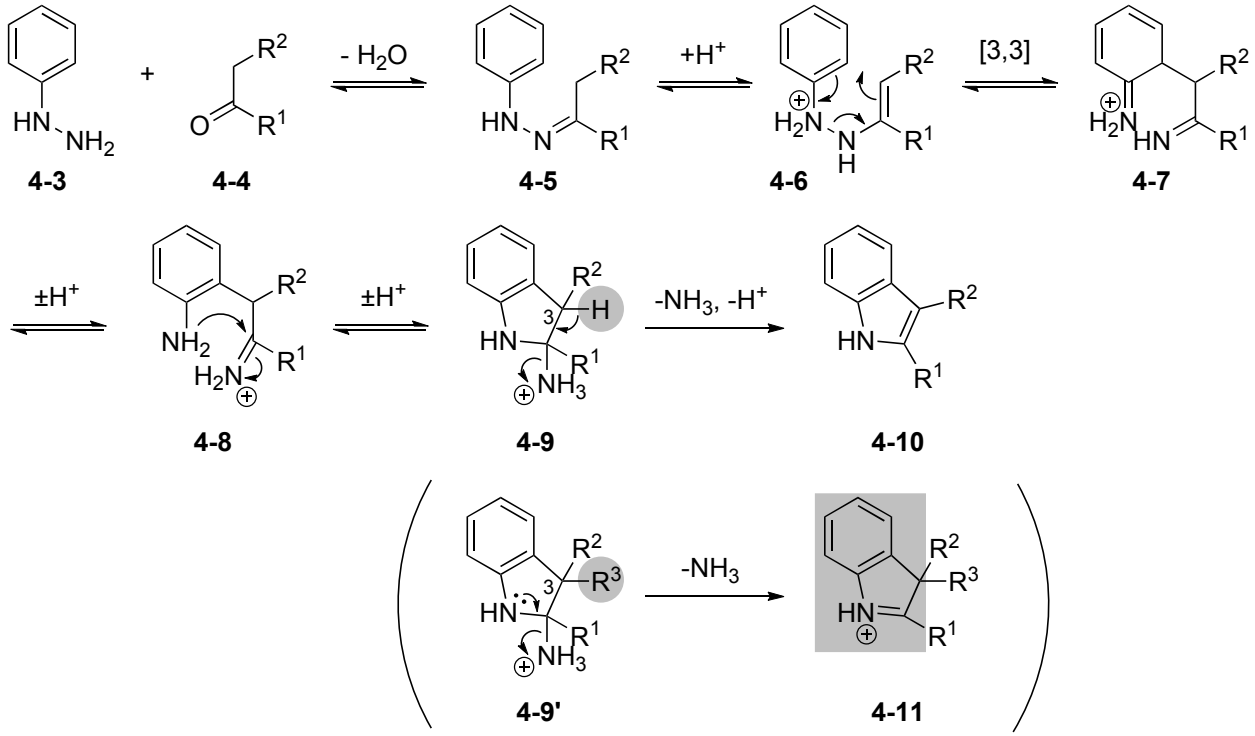


· Tricyclic betaine (**This problem**)



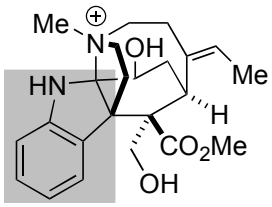
4. Interrupted Fischer indolization

4-1. Classic Fischer indolization

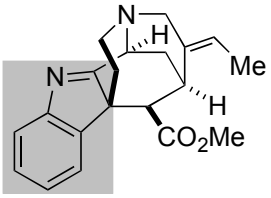


4-2. Akuammiline Alkaloid

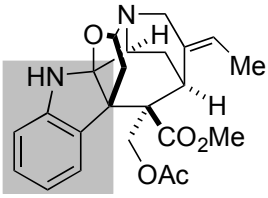
<Representatives>



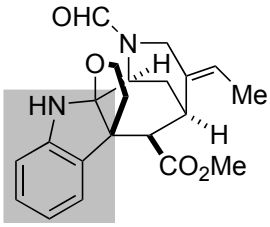
(–)-Echitamine (**4-12**)
(1875)
displays in vivo and
in vitro cytotoxicity



(+)-Strictamine (**4-13**)
(1966)
inhibits transcription factor
NF-κB



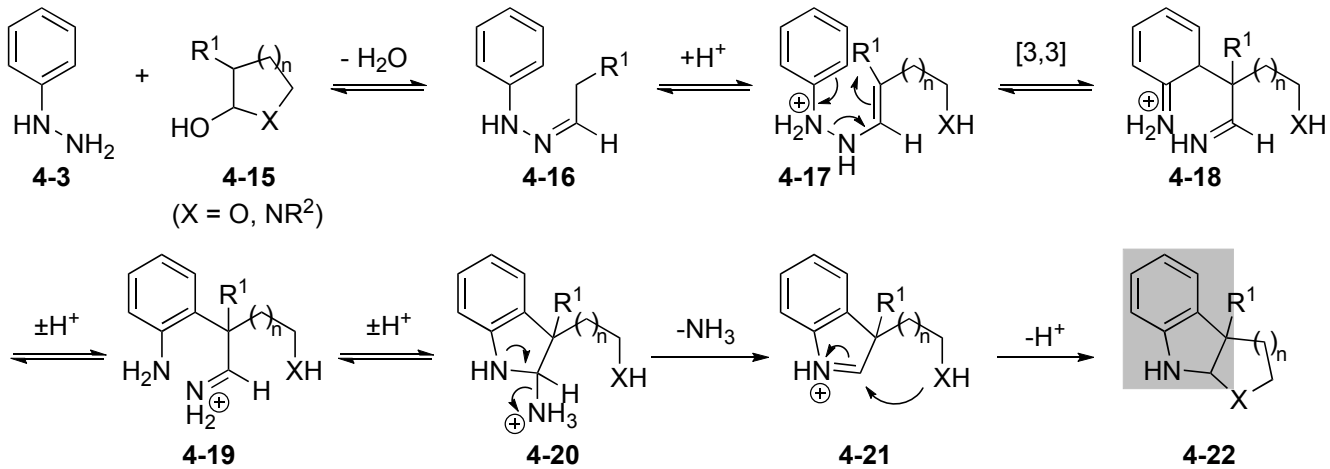
(+)-Picraline (**4-14**)
(1954)
derivatives inhibit
SGLT2 protein



(–)-Aspidophyllin A (**4-2**)
(2007)
reverses drug resistance
in cancer cells

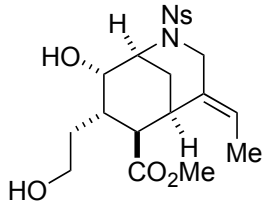
4-3. Interrupted Fischer indolization

Garg, N. K. *et al. J. Am. Chem. Soc.* **2011**, *133*, 5752.



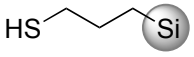
4-4. Reaction mechanism

(4)

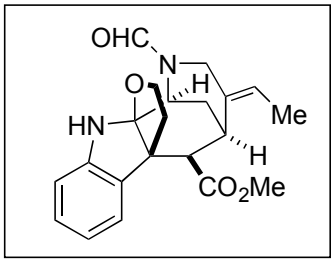


4-1

1. *p*-TsOH· H_2O, 80 ºC
2. DMP, 40 ºC
   66% (2 steps)
3. $PhNHNH_2$, TFA, 40 ºC;
   K_2CO_3, MeOH, 65 ºC
   76%
4. MetSThiol®

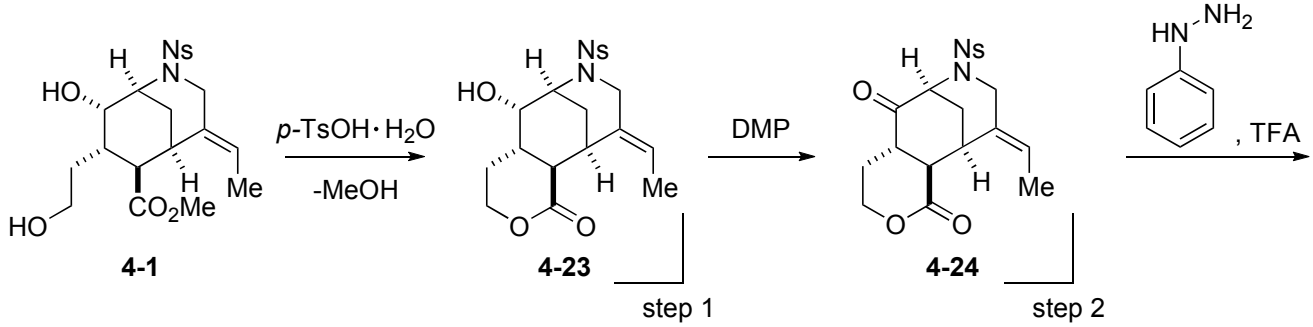


   Cs_2CO_3, 65 ºC
5. formic acid, EDAC,
   DMAPformic acid, EDAC,
   DMAP, 0 ºC
   71% (2 steps)

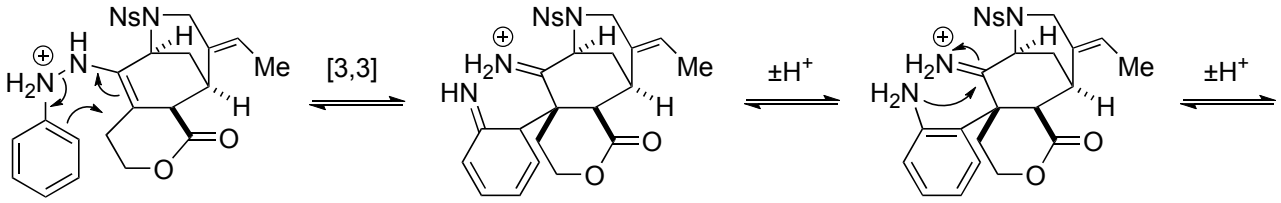


(–)-Aspidophyllin A
4-2

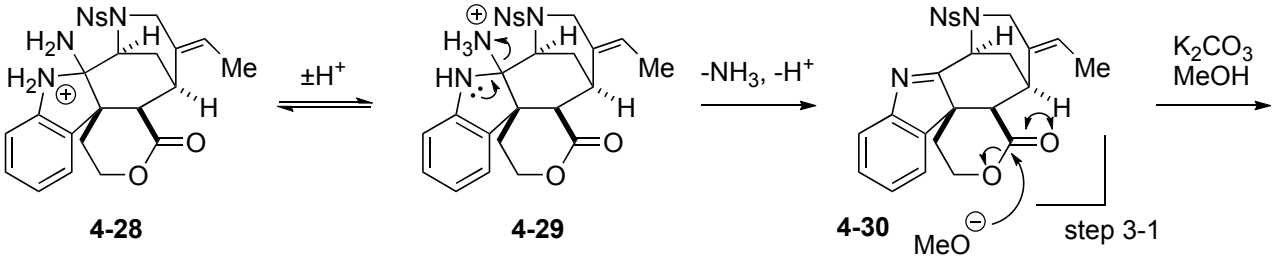
Garg, N. K. *et al. J. Am. Chem. Soc.* **2016**, *138*, 1162.



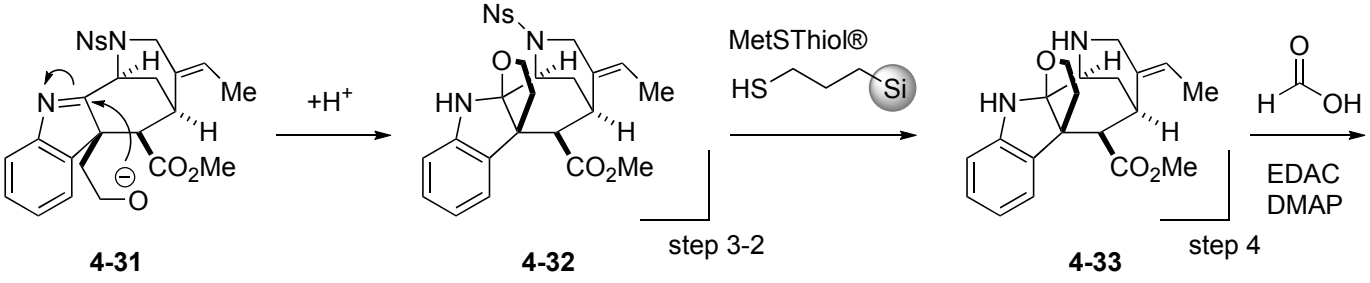
4-1 **4-23** **4-24**



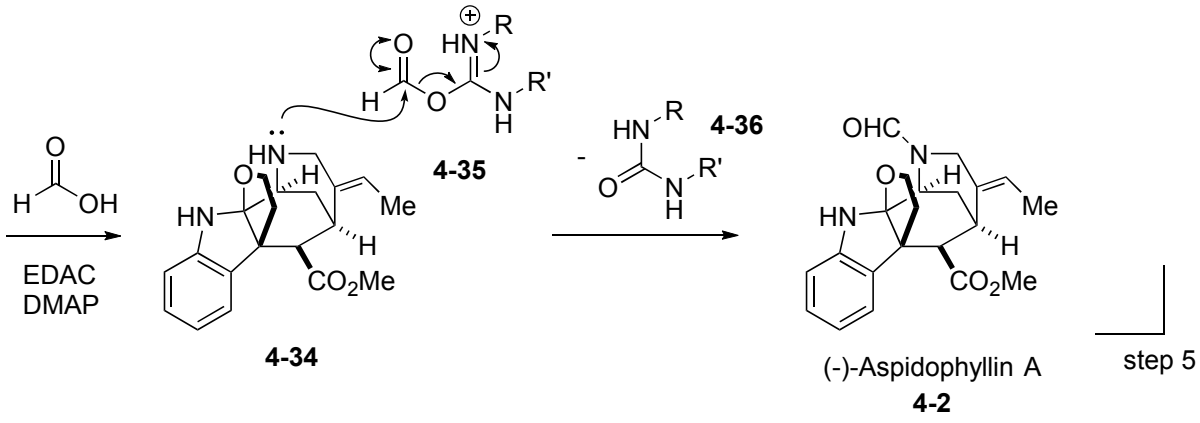
4-25 **4-26** **4-27**



4-28 **4-29** **4-30**

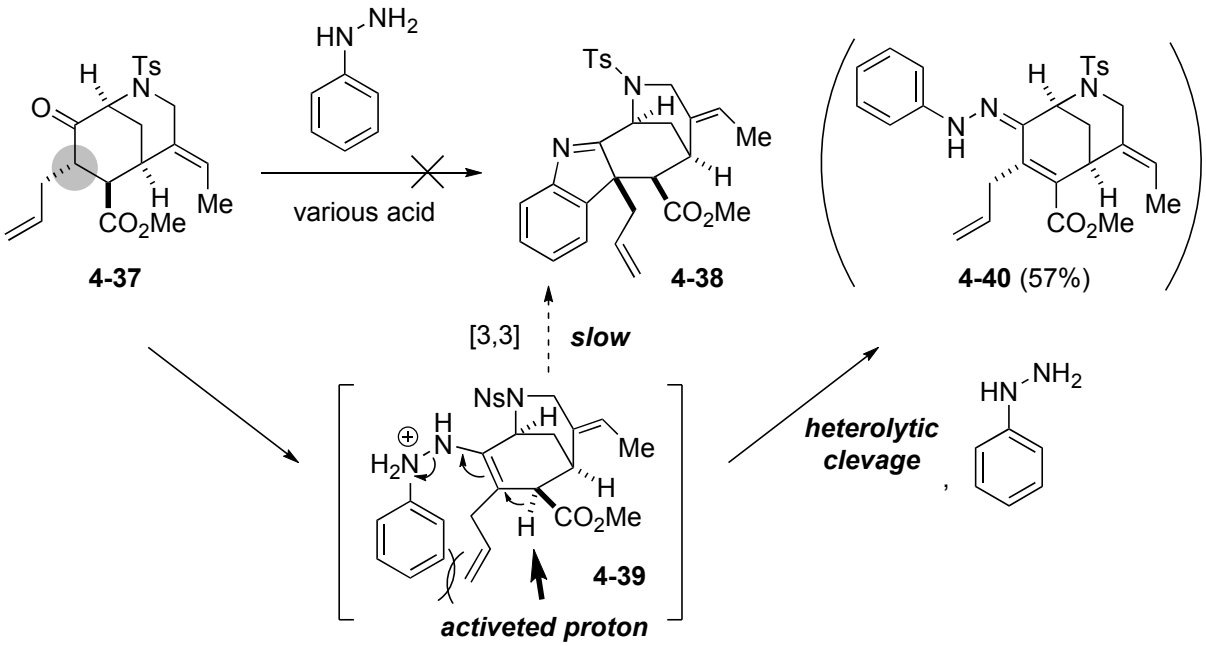


4-31 **4-32** **4-33**

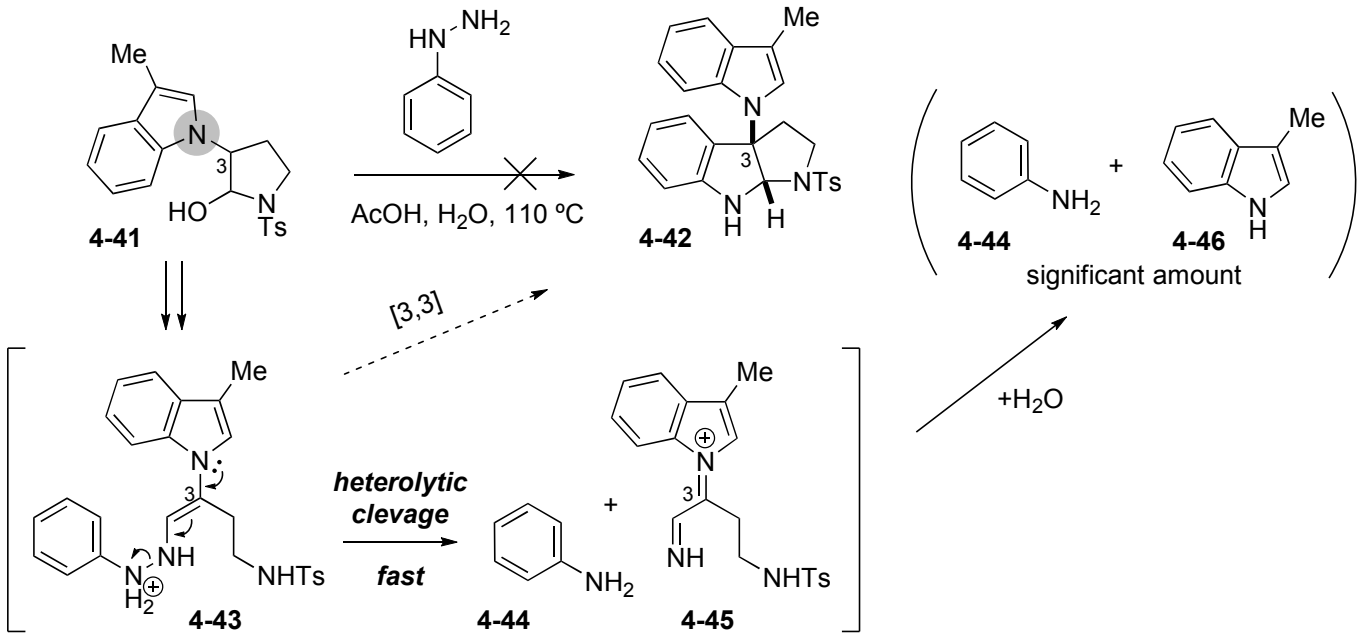


4-5. Examples of failed Fischer indolization

· α-hanging carbon chain and activated β-proton

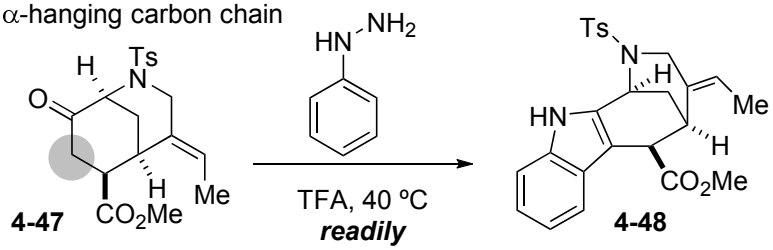


· 3-nitrogen substituent

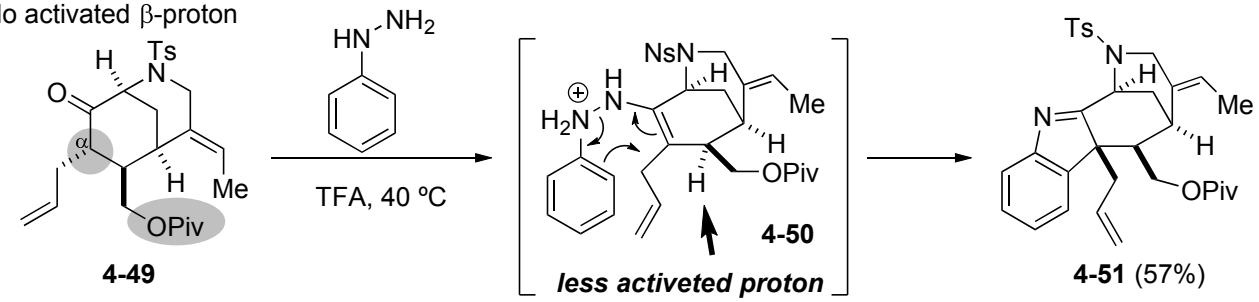


4-6. In what case does Fischer indolization success ?

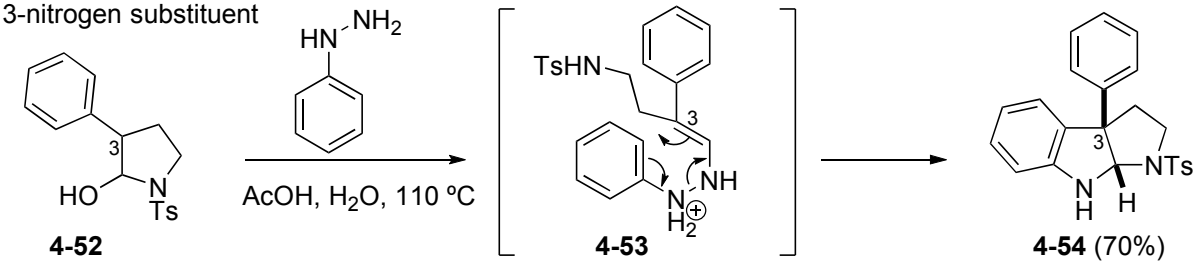
・No α-hanging carbon chain



・No activated β-proton



・No 3-nitrogen substituent



→ Slow [3,3]-sigmatropic rearrengement or weak N-N bond lead to heterolytic N-N bond clevage; in other words, lower yields or even failure to cyclize.

Energy profile (ΔG [ΔH], in kcal/mol) Garg, N. K. *et al. J. Am. Chem. Soc.* **2011**, *133*, 5752.

Table 2. Substituent Effects on the Free Energy (Enthalpy)[a] Profile [SCS-MP2/6-31G(d)(water)//MP2/6-31G(d)(water)]

Entry	Substituents	8a	9a	α-TS	8b	9b	β-TS
1	R_1: H, R_2: H	0.0 (0.0)	14.3 (14.1)	32.6 (30.3)	0.6 (0.3)	14.4 (14.3)	**31.1 (28.7)**[b]
2	R_1: CH_3, R_2: H	0.0 (0.0)	10.6 (10.3)	26.1 (23.9)	0.5 (0.4)	10.7 (10.7)	**24.7 (22.8)**[b]
3	R_1: CH_3, R_2: CH_3	0.2 (0.0)	9.3 (8.7)	**22.9 (20.3)**[b]	0.0 (0.0)	8.7 (7.7)	**22.3 (20.0)**[b]
4	R_1: Indolyl, R_2: CH_3	0.0 (0.0)	9.2 (8.8)	**18.0 (16.5)**[c]	2.2 (2.7)	9.0 (9.3)	21.2 (19.3)
5	R_1: CH_3, R_2: N(H)acetyl	0.0 (0.0)	7.5 (7.4)	**18.5 (17.7)**[c]	1.1 (1.5)	7.4 (8.5)	19.6 (17.9)

[a] Free energies (enthalpies in parentheses) in kcal/mol relative to the phenylhydrazone are given. [b] Favored transition state involves [3,3]-sigmatropic rearrangement. [c] Favored transition state leads to N−N bond cleavage products.

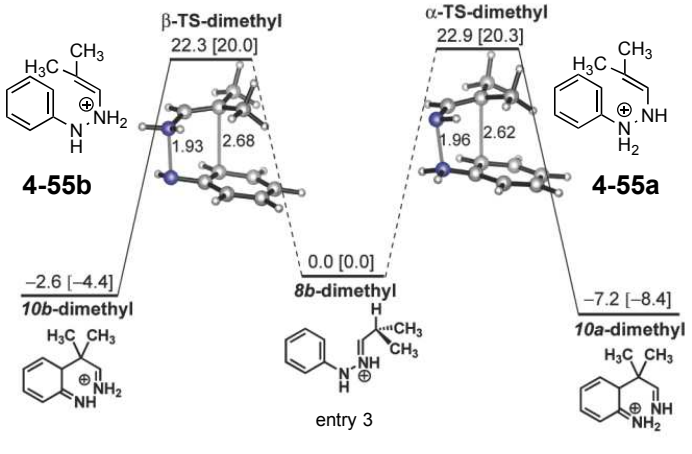


Figure 2. Energy profile (ΔG [ΔH], in kcal/mol) for the acid-promoted transformation of dimethyl-substituted hydrazone.

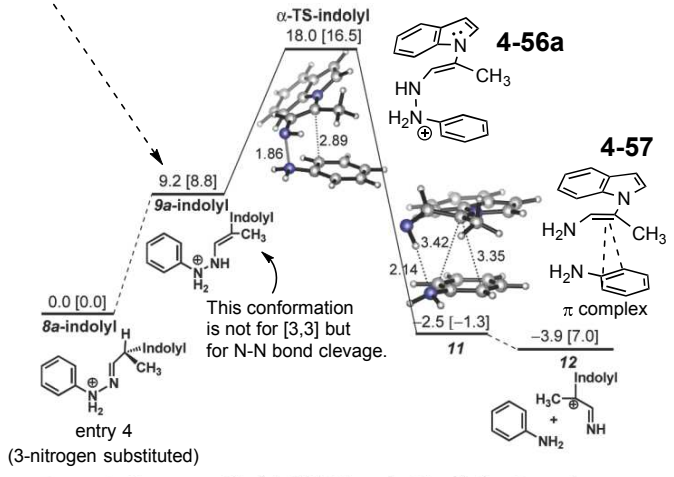


Figure 3. Energy profile (ΔG [ΔH], in kcal/mol) for the acid-promoted transformation of indolyl-substituted hydrazone.