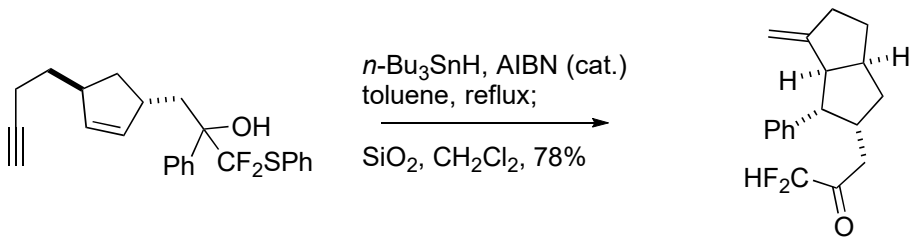
Problem Session 6

2017/10/14 Satoshi Hashimoto

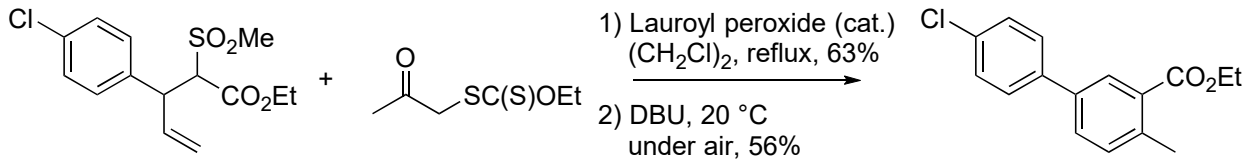
Please provide the reaction mechanisms.

1.



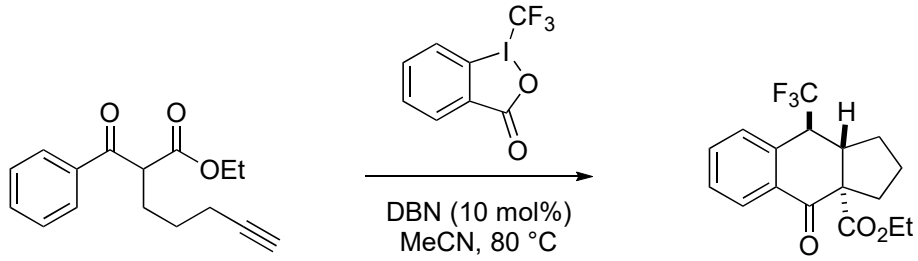
1-1 **1-2**

2.



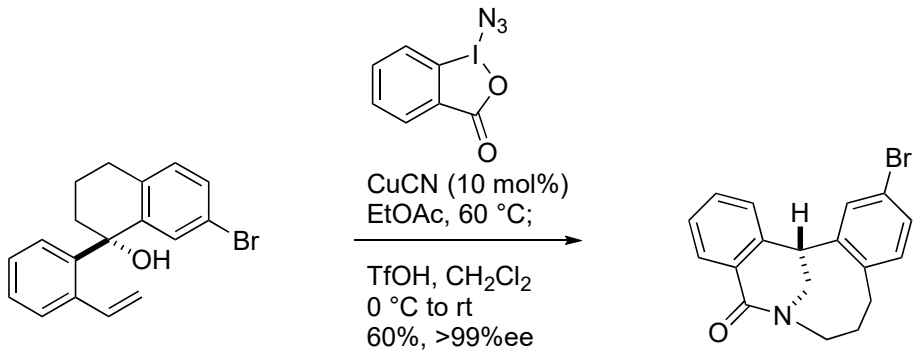
2-1 **2-2** **2-3**

3.

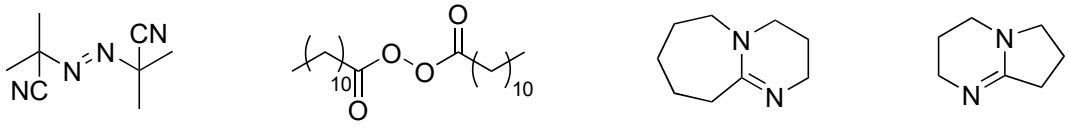


3-1 **3-2**

4.



4-1 **4-2**

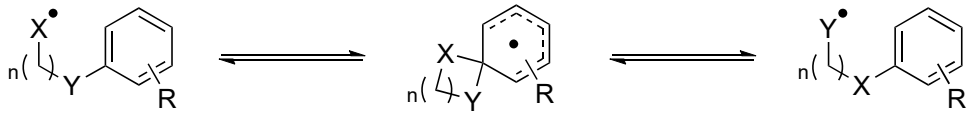


AIBN Lauroyl peroxide DBU DBN

Problem Session (6) Answer

2017/10/14 Satoshi Hashimoto

Radical aryl migration reactions:



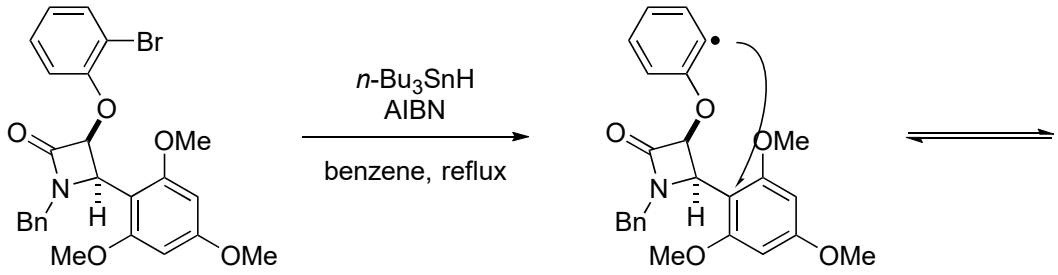
0-1 **0-2** **0-3**

n = 0-3
X = C, N, O, Si, P, S, Ge, etc.
Y = C, N, O, Si, P, S, Ge, etc.

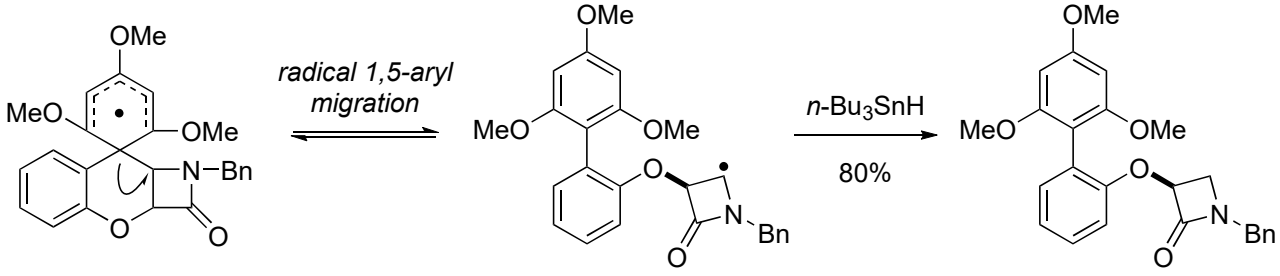
For reveiws:
Studer, A.; Bossart, M. *Tetrahedron* **2001**, *57*, 9649.
Chen, Z.-M.; Zhang, X.-M.; Tu, Y.-Q. *Chem. Soc. Rev.* **2015**, *44*, 5220.

• **Radical 1,2-aryl migration → Problem 2.** • **1,4-aryl migration → Problem 1,4.**

• **Radical 1,5-aryl migration** (example)



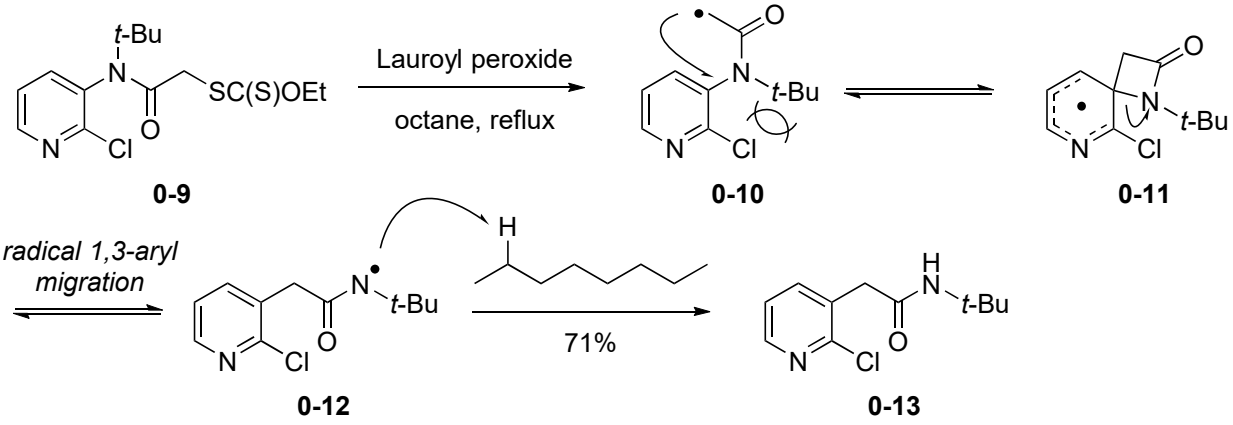
0-4 **0-5**



0-6 **0-7** **0-8**

Alcaide, B.; Rodríguez-Vicente, A. *Tetrahedron Lett.* **1998**, *39*, 6589.

• **Radical 1,3-aryl migration** (example)

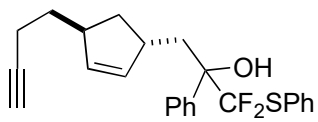


0-9 **0-10** **0-11**

0-12 **0-13**

Bacque, E.; Qacemi, M. E.; Zard, S. Z. *Org. Lett.* **2005**, *7*, 3817.

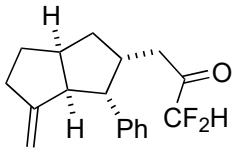
1.



1-1

n-Bu_3SnH (1 eq.)
AIBN (cat.)
toluene, reflux;

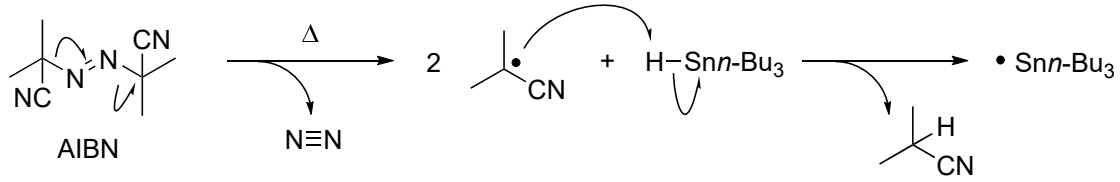
SiO_2, CH_2Cl_2, 78%



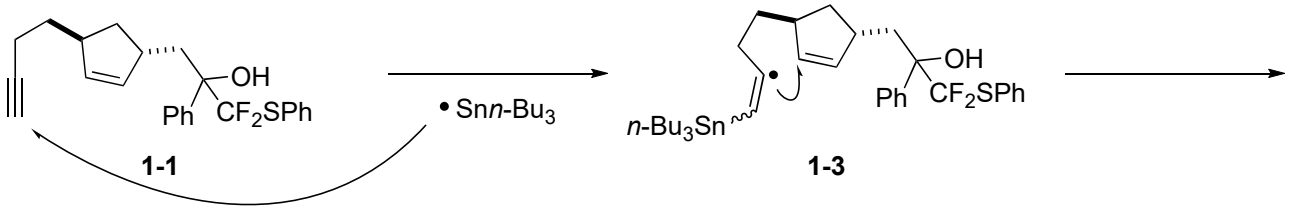
1-2

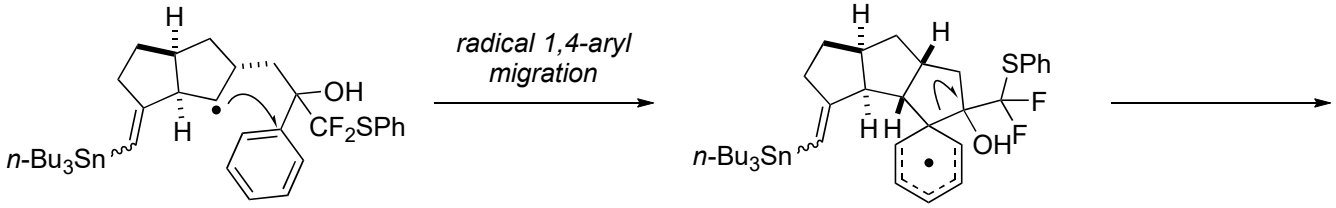
Answer: Pohmakotr, M. *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 2212.

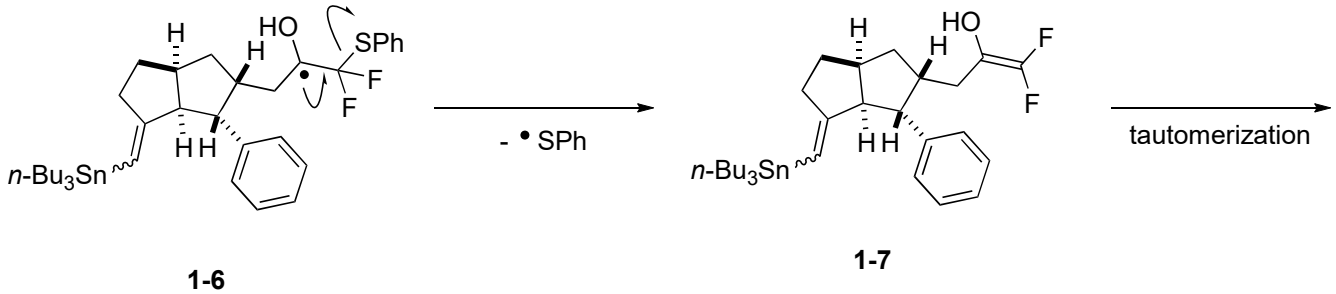
Initiation

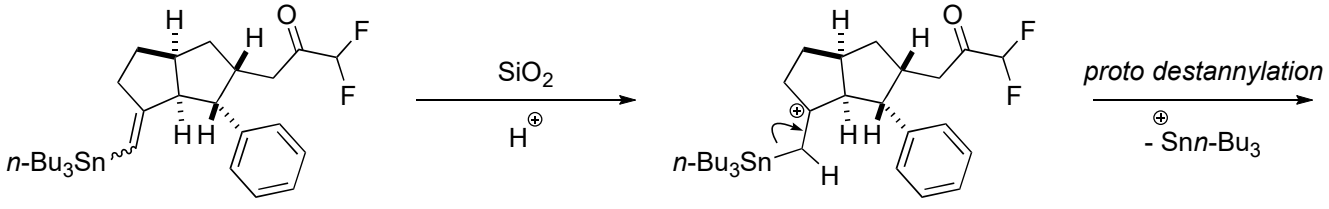


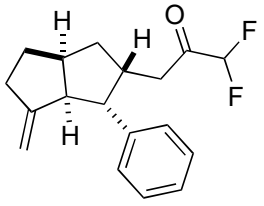
Propagation





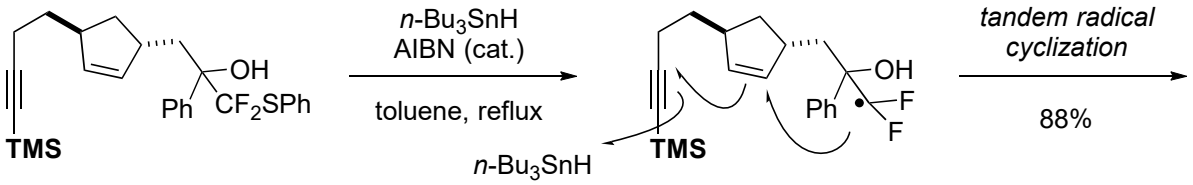




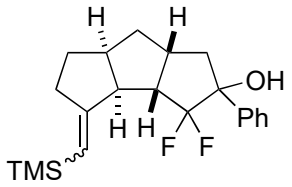


1-2

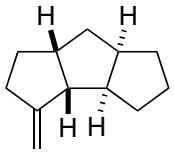
cf.



1-10 **1-11**



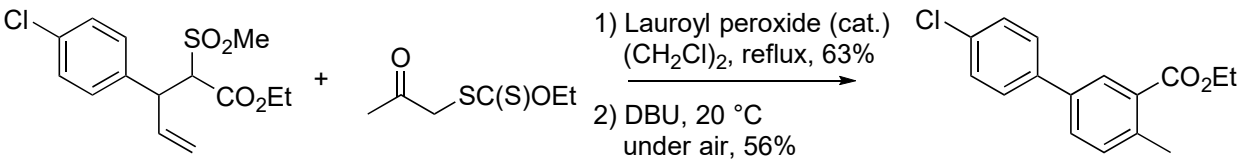
1-12



Triquinane skeleton

Pohmakotr, M. *et al. J. Org. Chem.* **2015**, *80*, 816.

2.

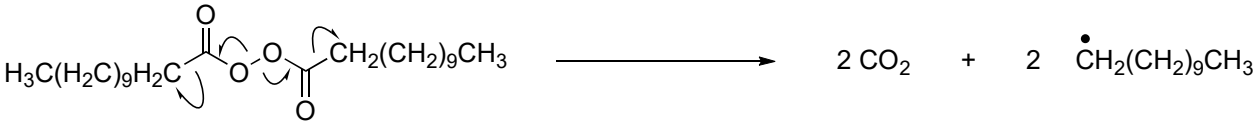


2-1 **2-2** **2-3**

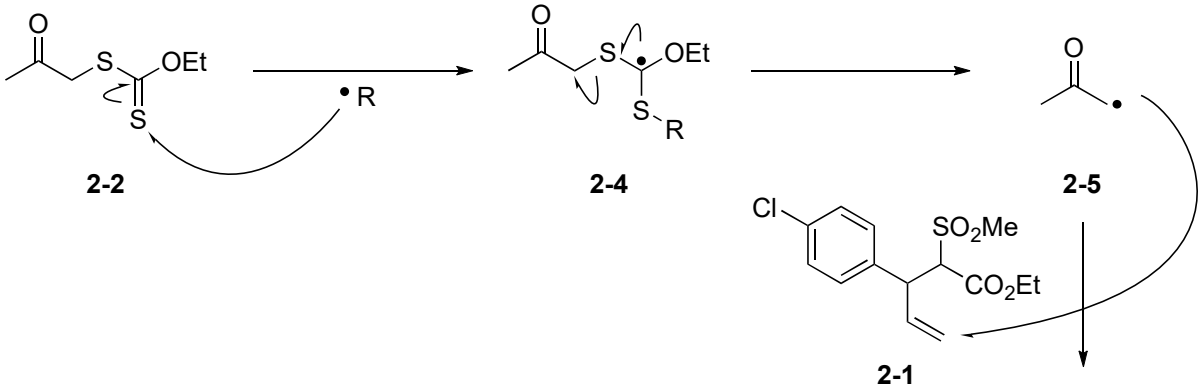
Quiclet-Sire, B.; Revol, G.; Zard, S. Z. *Org. Lett.* **2009**, *11*, 2832.

Answer:

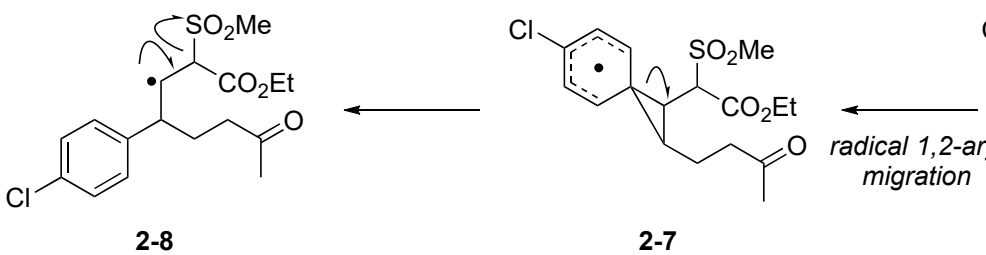
Initiation



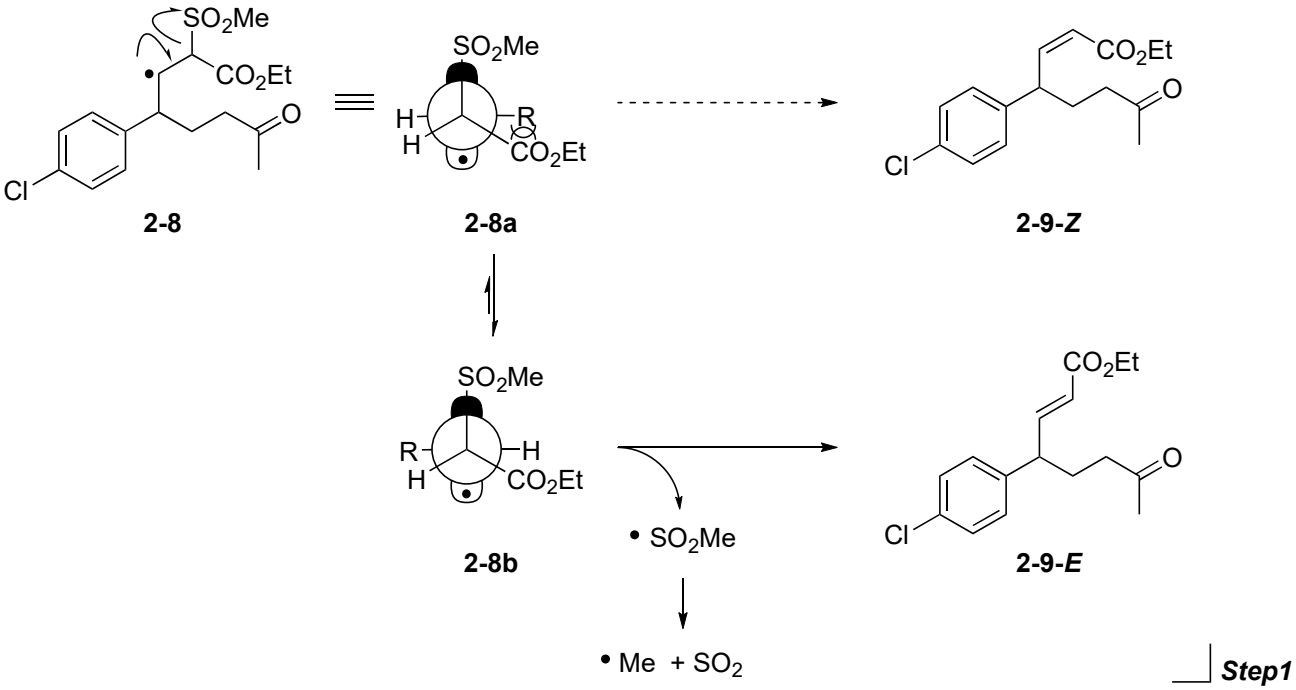
Propagation

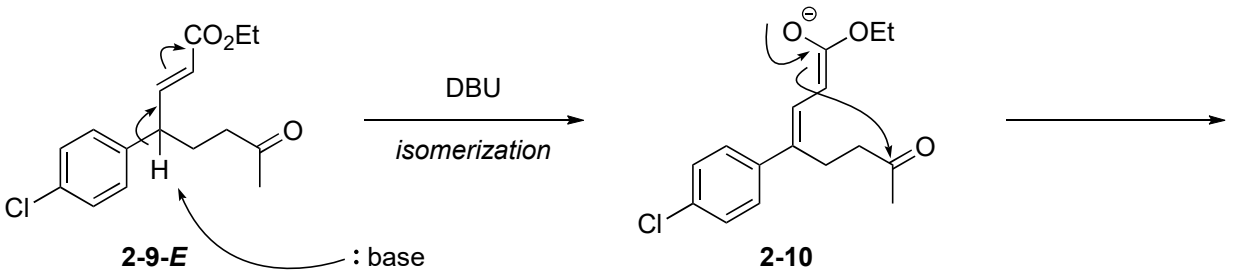


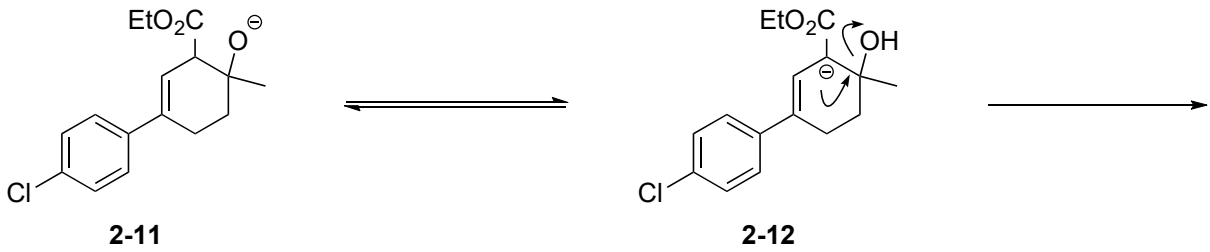
2-2 **2-4** **2-5** **2-1**

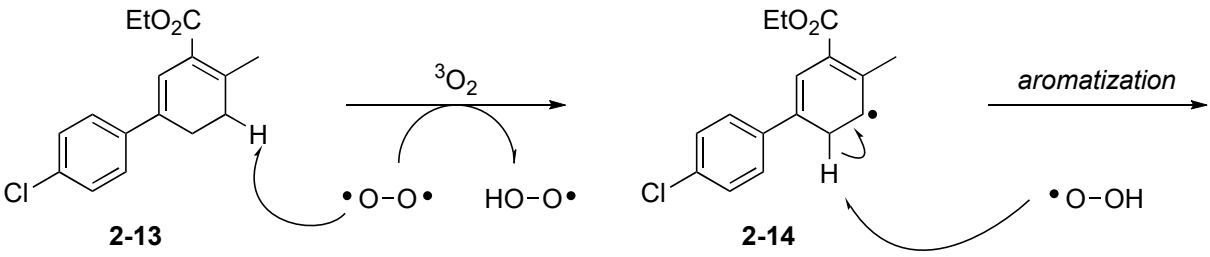


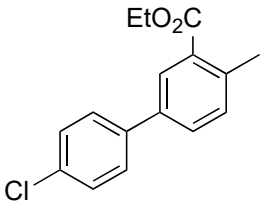
2-8 **2-7** **2-6**


SO2Me
CO2Et
O
Cl
2-8
SO2Me
H
H
R
CO2Et
2-8a
CO2Et
O
Cl
2-9-Z
SO2Me
R
H
H
CO2Et
2-8b
• SO2Me
• Me + SO2
CO2Et
O
Cl
2-9-E
Step1

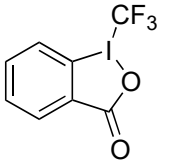

CO2Et
O
H
Cl
2-9-E
: base
DBU
isomerization
O
OEt
O
Cl
2-10


EtO2C
O
Cl
2-11
EtO2C
OH
Cl
2-12

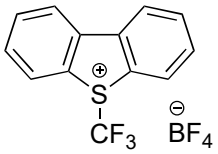

EtO2C
H
Cl
2-13
3O2
• O–O •
HO–O •
EtO2C
H
Cl
2-14
aromatization
• O–OH


EtO2C
Cl
2-3
Step2

Trifluoromethylating reagent



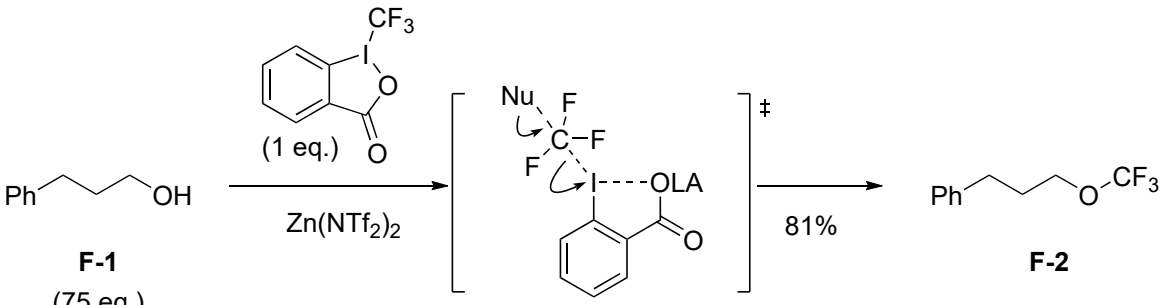
Togni's reagent



Umemoto's reagent

For recent review:
Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650.

• Acid promoted trifluoromethylation

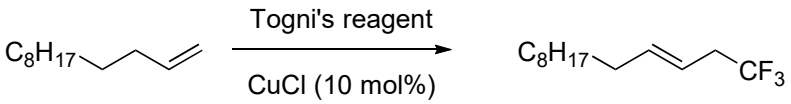


F-1
(75 eq.)

F-2

Togni, A. *et al. Angew. Chem. Int. Ed.* **2009**, *48*, 4332.
111117_LS_Koichi_Murai: recent advances in trifluoromethylation

• Radical-based trifluoromethylation

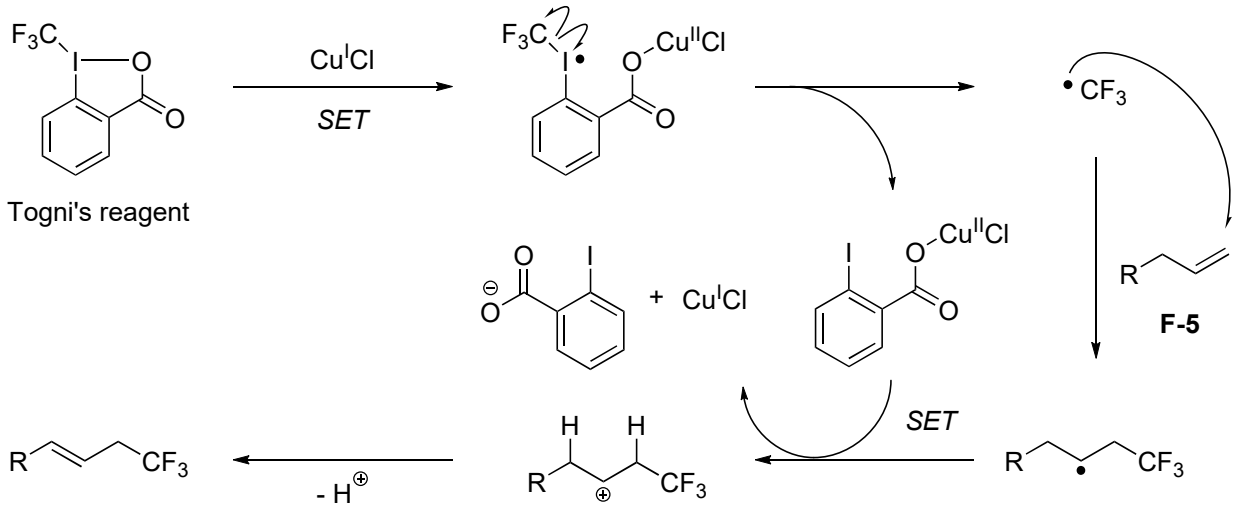


F-3

F-4

Wang, J. *et al. J. Am. Chem. Soc.* **2011**, *133*, 16410.

Proposed reaction mechanism:



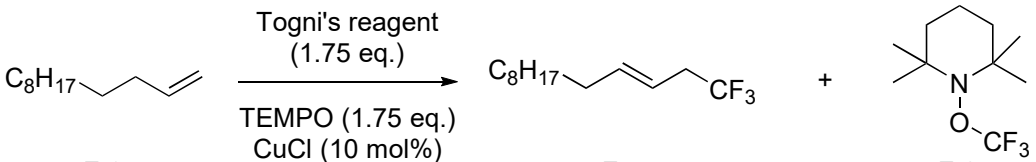
F-8
stable pdt.

F-7

F-6

F-5

Capture of CF_3 radical by TEMPO

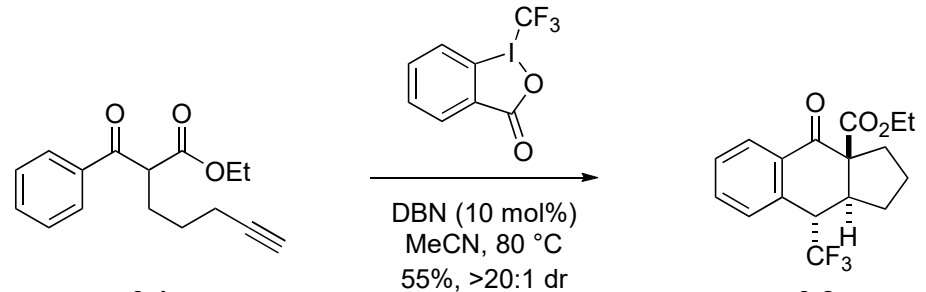


F-3

F-4
1% GC yield

F-9
79% yield

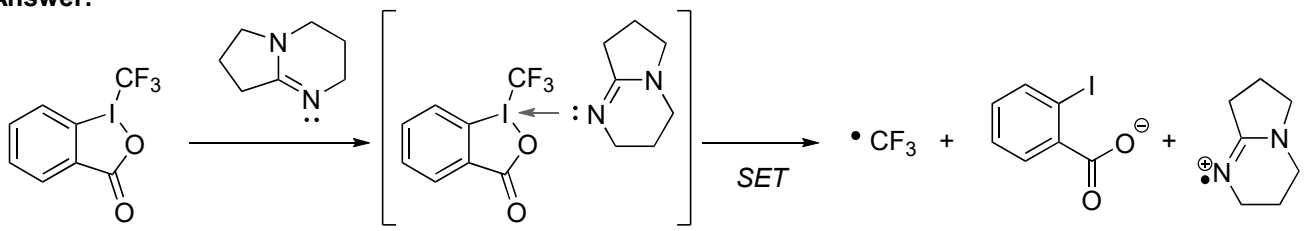
3.



3-1 **3-2**

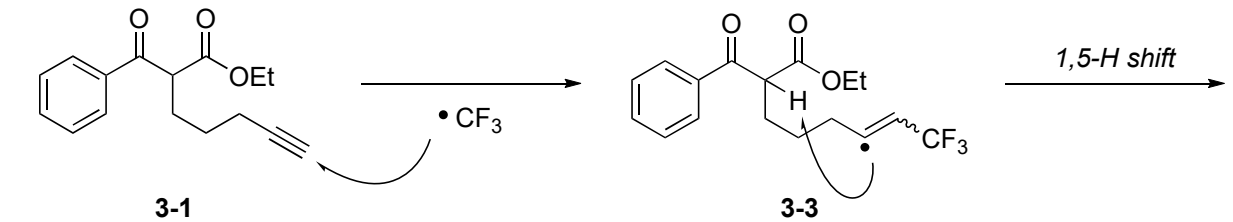
Huang, L.; Ye, L.; Li, X.-H.; Li, Z.-L.; Lin, J.-S.; Liu, X.-Y. *Org. Lett.* **2016**, *18*, 5284.

Answer:

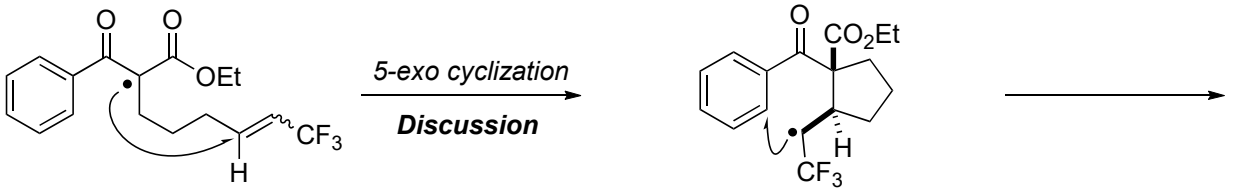


CT complex

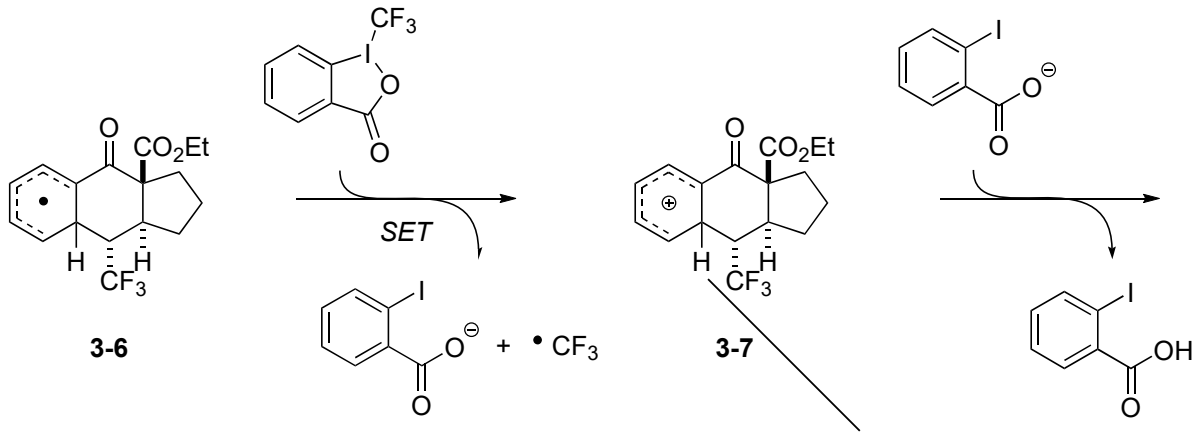
Cheng, Y.; Yu, S. *Org. Lett*. **2016**, *18*, 2962.



3-1 **3-3**



3-4 **3-5**



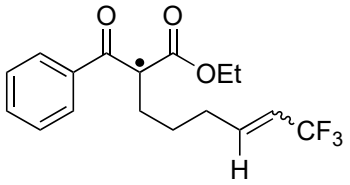
3-6 **3-7**

cyclohexadienyl cation: pKa -24.3 (aqueous media)

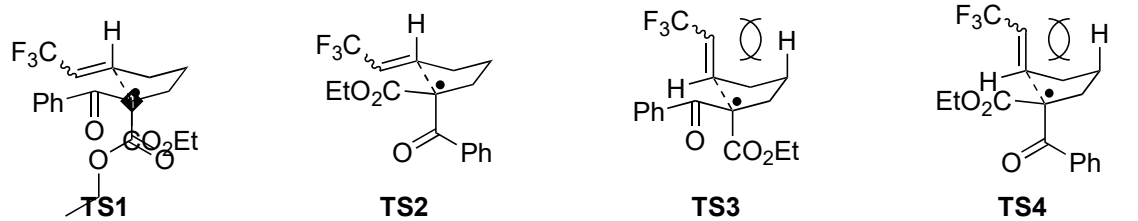
3-2

Comment:
DBN$^{\oplus}_{\bullet}$ might also serve SET reaction from **3-6** to **3-7**.
However, regenerated DBN would be consumed to deprotonate *o*-iodobenzoic acid.
So I proposed SET between **3-7** and Togni's reagent.

Discussion: Proposed mechanism of the stereoselectivity

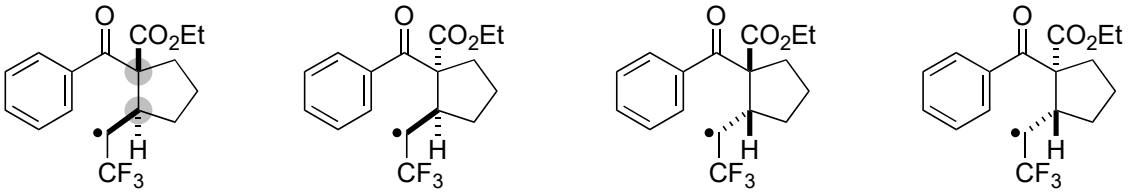


3-1 (stabilized by carbonyl groups)



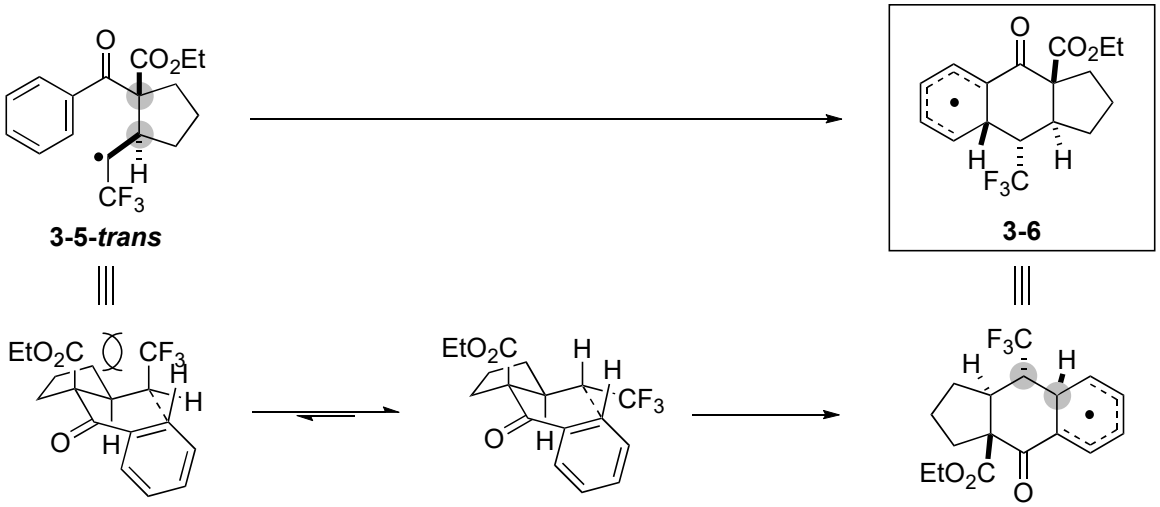
TS1 **TS2** **TS3** **TS4**

reversible



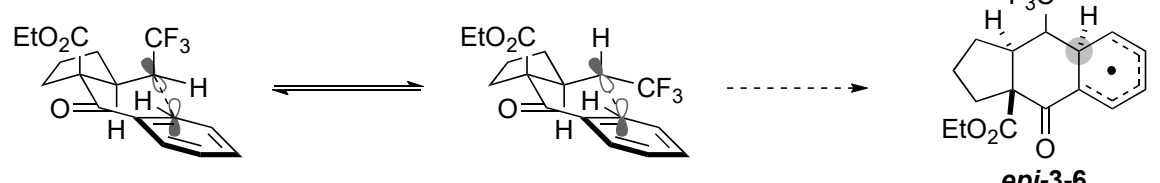
3-5-*trans* **3-5-*cis*** ***ent*-3-5-*cis*** ***ent*-3-5-*trans***

from 3-5-*trans*:



3-5-*trans* **3-6**

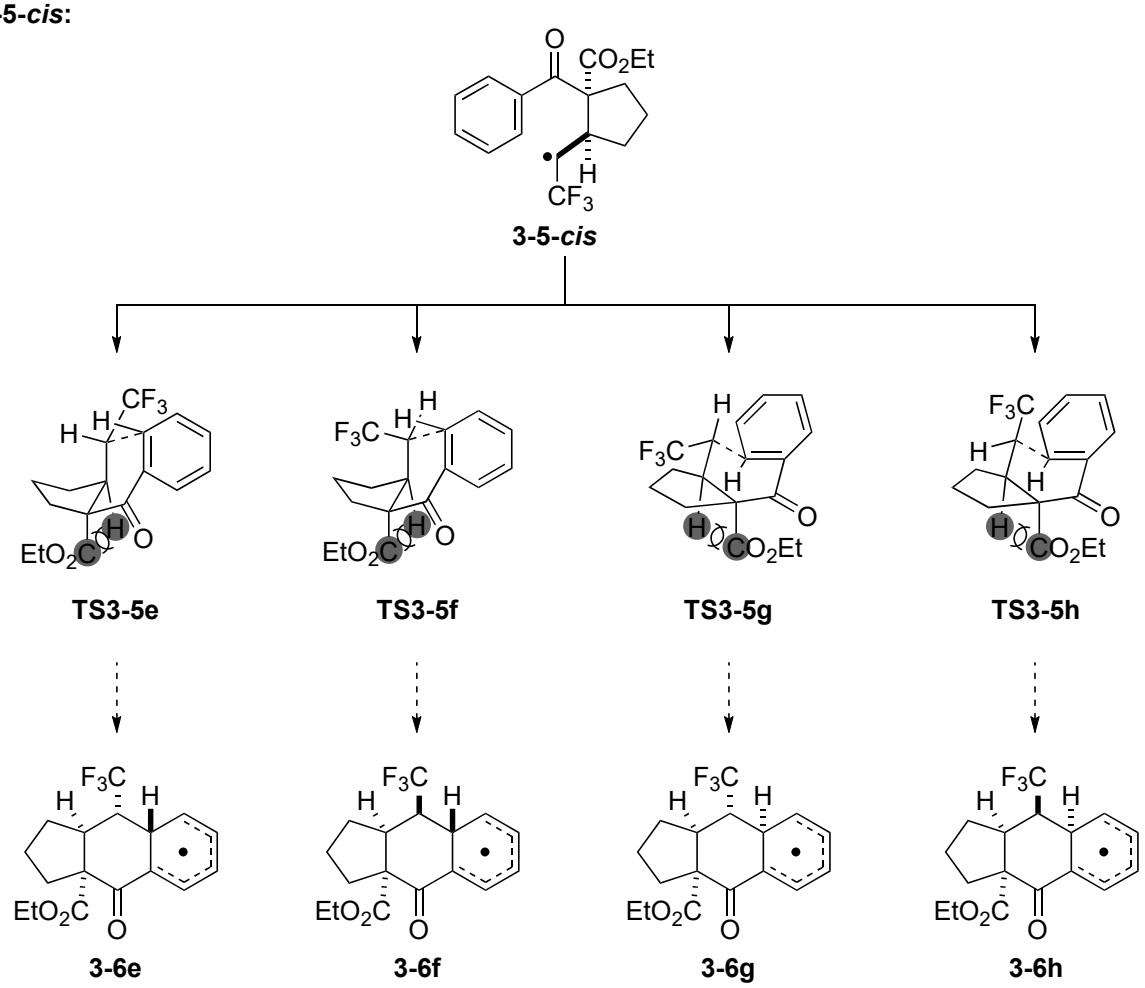
TS3-5a *disfavored* **TS3-5b** *favored* **3-6**



***epi*-3-6**

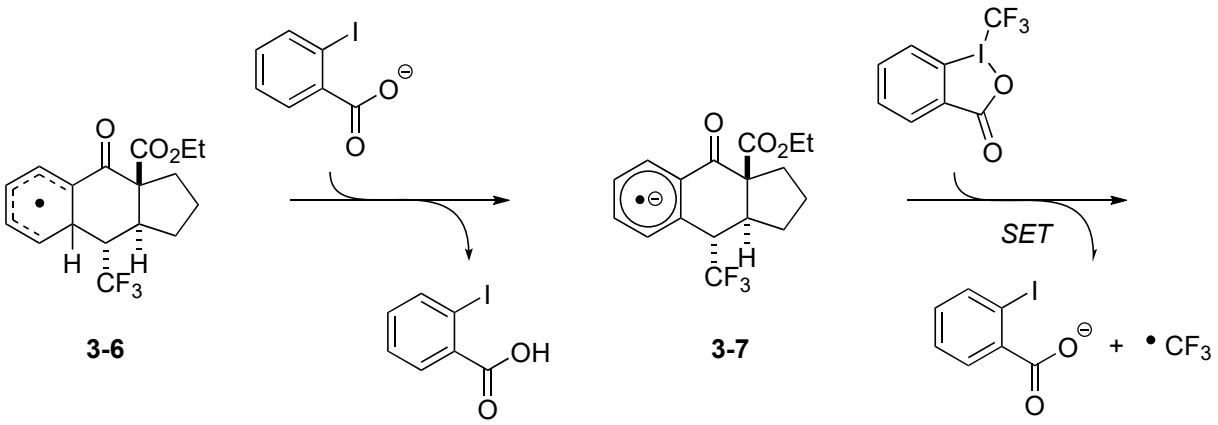
TS3-5c *bad orbital intaraction* **TS3-5d** *bad orbital intaraction*

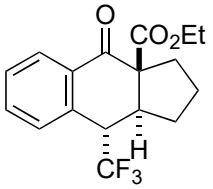
from 3-5-*cis*:



disfavored 1,2-interaction between highlighted H atom and CO_2Et group.

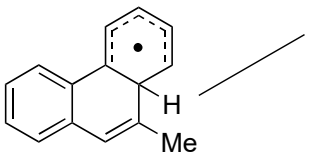
Other possible mechanism from **3-6** to **3-7:**





3-2

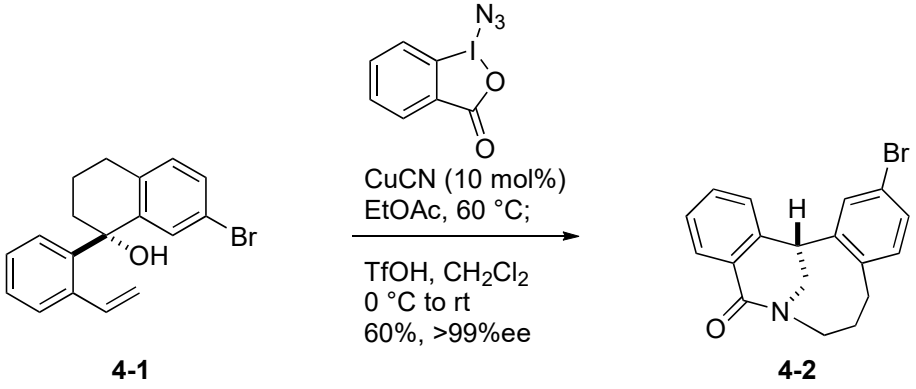
cf. predicted pKa value of related compound



o-iodobenzoic acid (exp.) pKa = 2.85 (in aqueous solution)

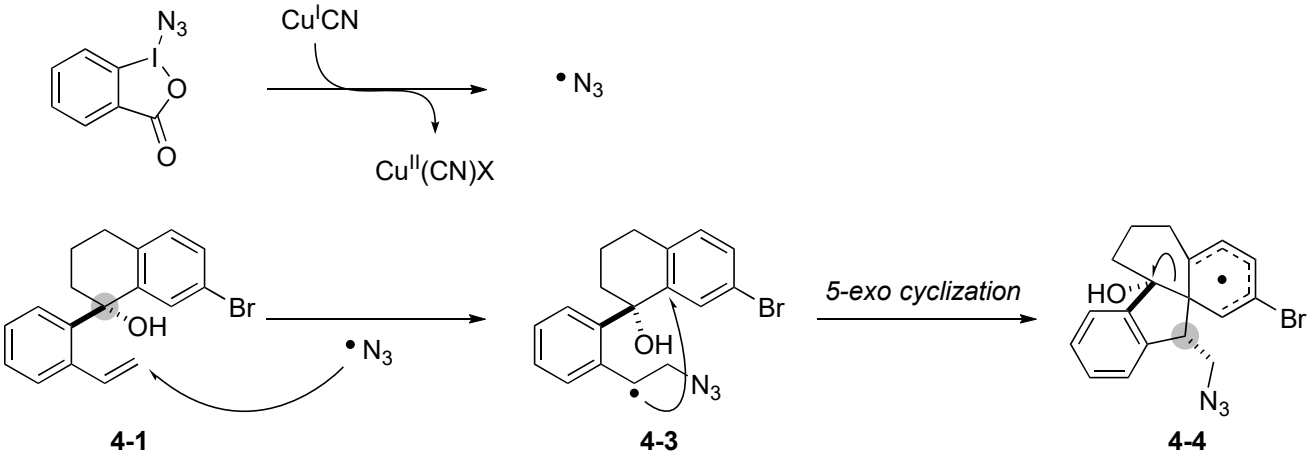
Studer, A. *et al. Angew. Chem. Int. Ed*. **2013**, *52*, 10792.

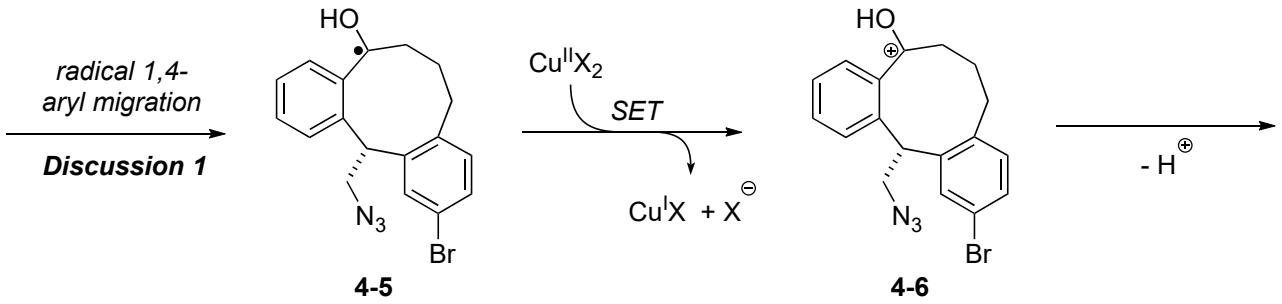
4.

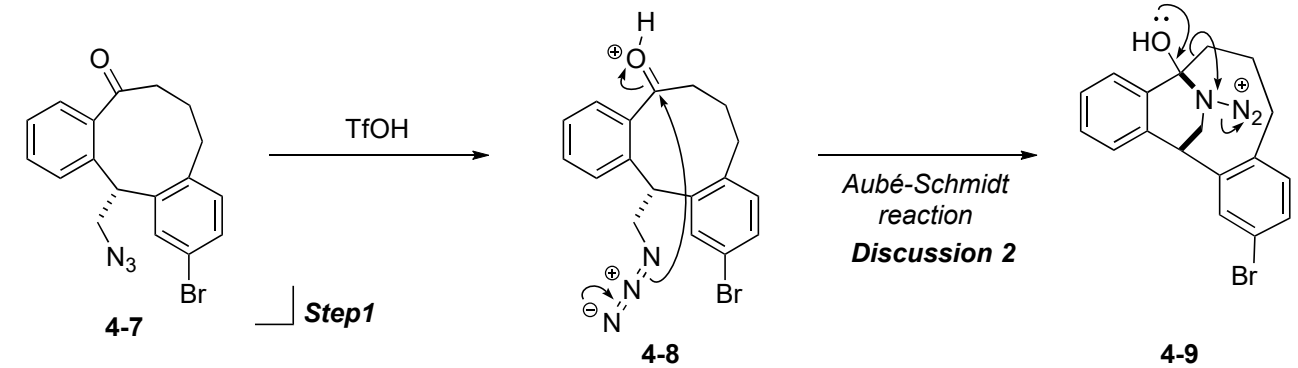


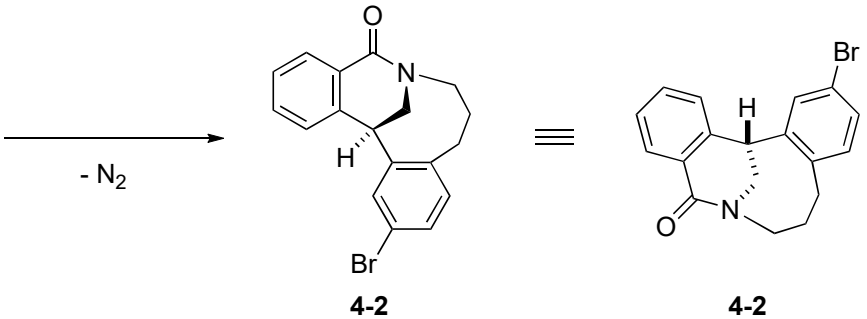
4-1 **4-2**

Answer: Liu, X.-Y. *et al. Nat. Commun.* **2016**, *7*, 13852.

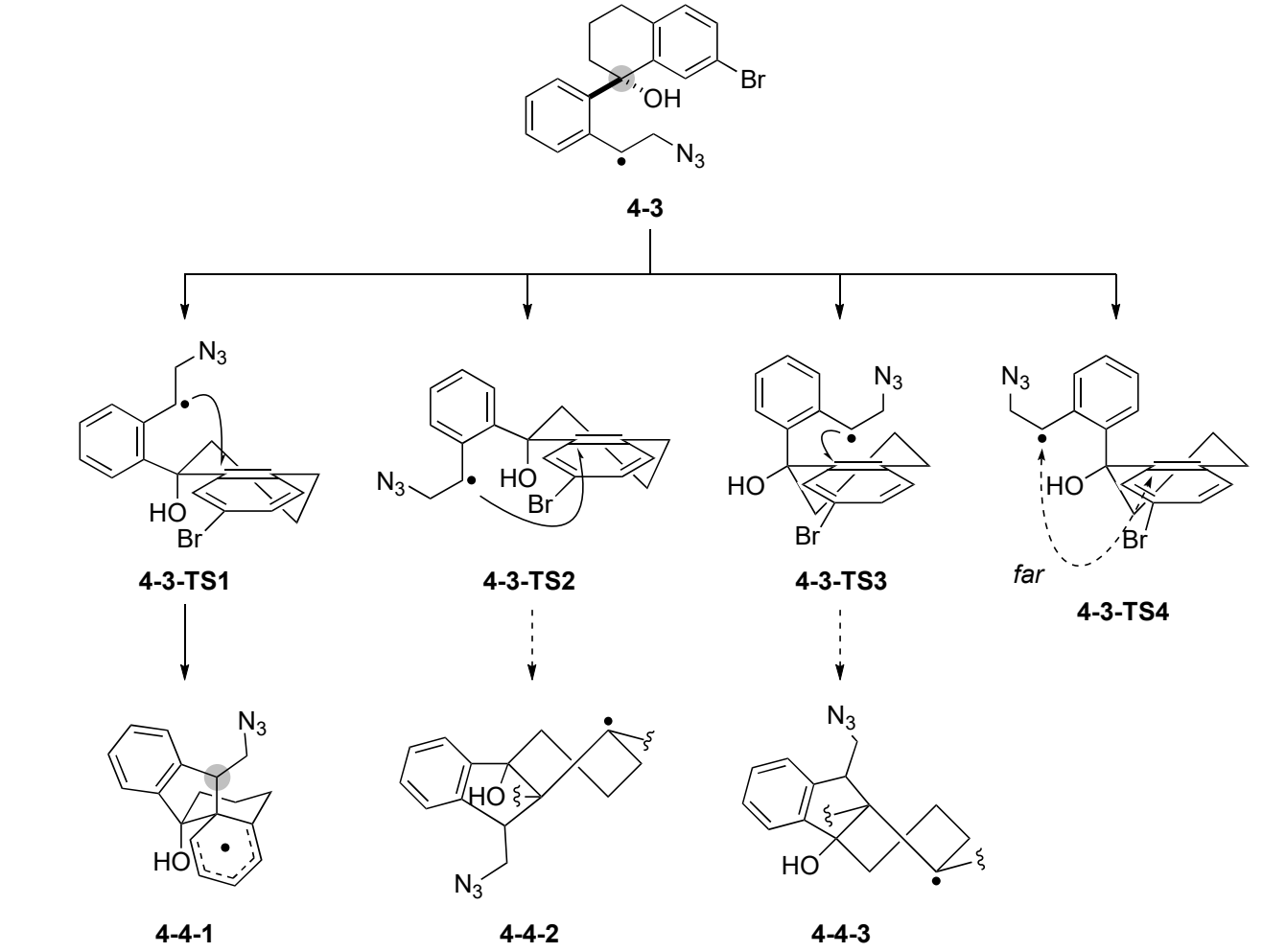


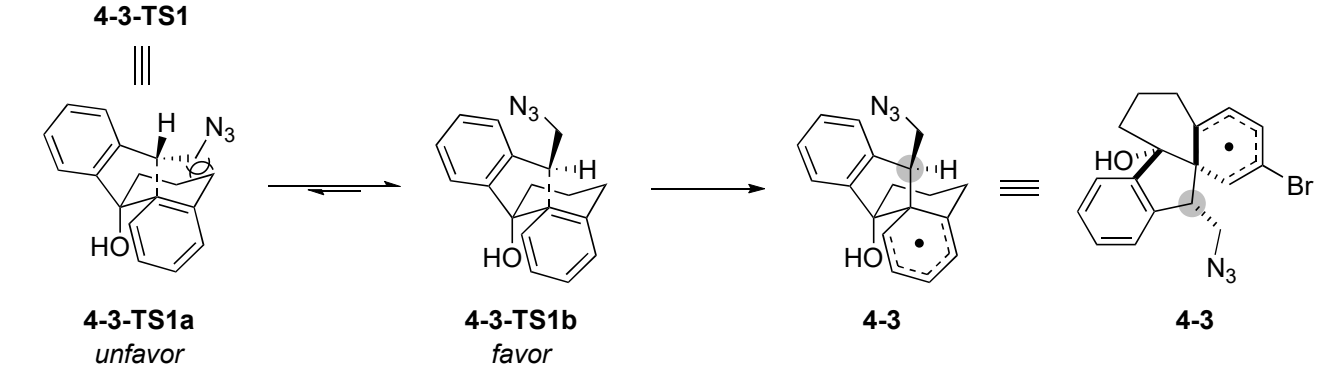






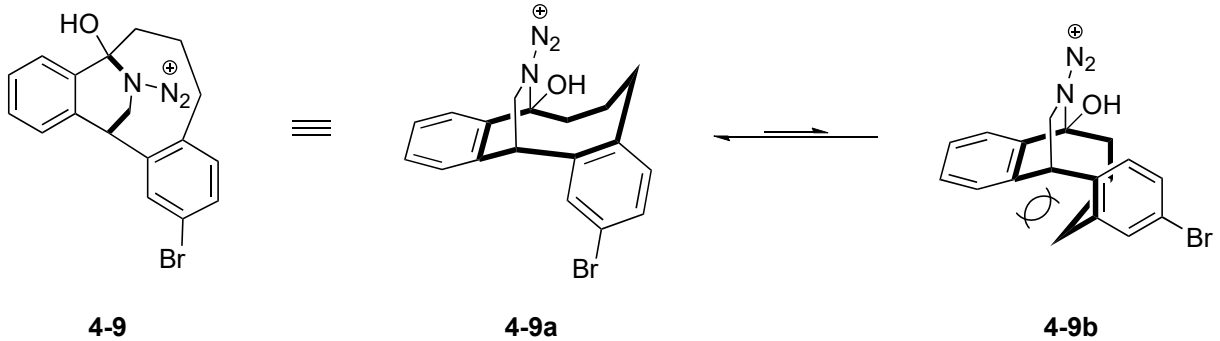
***Discussion 1*:** Proposed mechanism of chirality transfer



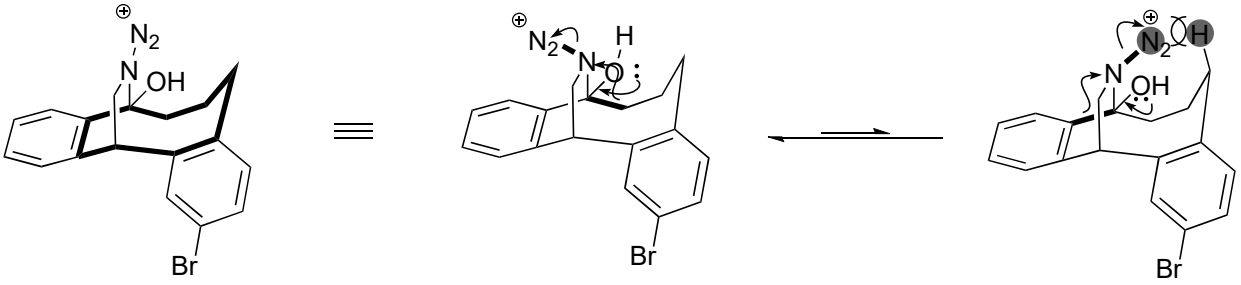


***Discussion 2*:** Regioselectivity of Aubé-Schmidt reaction

1. Conformation of 9-membered ring

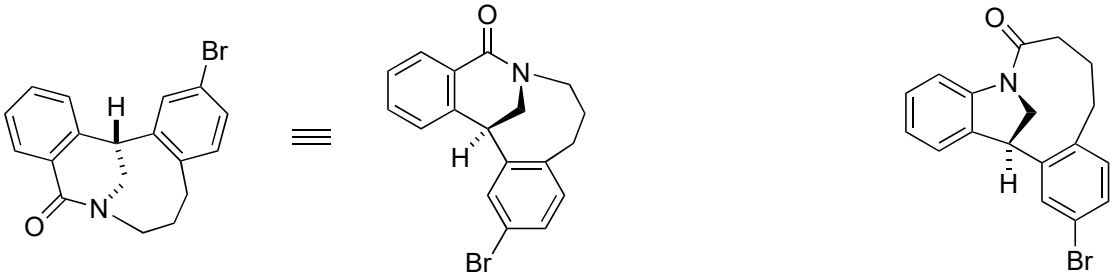


2. Migration of anti-periplaner C-C bond



4-9a **4-9aa** **4-9ab**

migration of anti-periplaner C-C bond



4-2 **4-2** **4-10**

not isolated