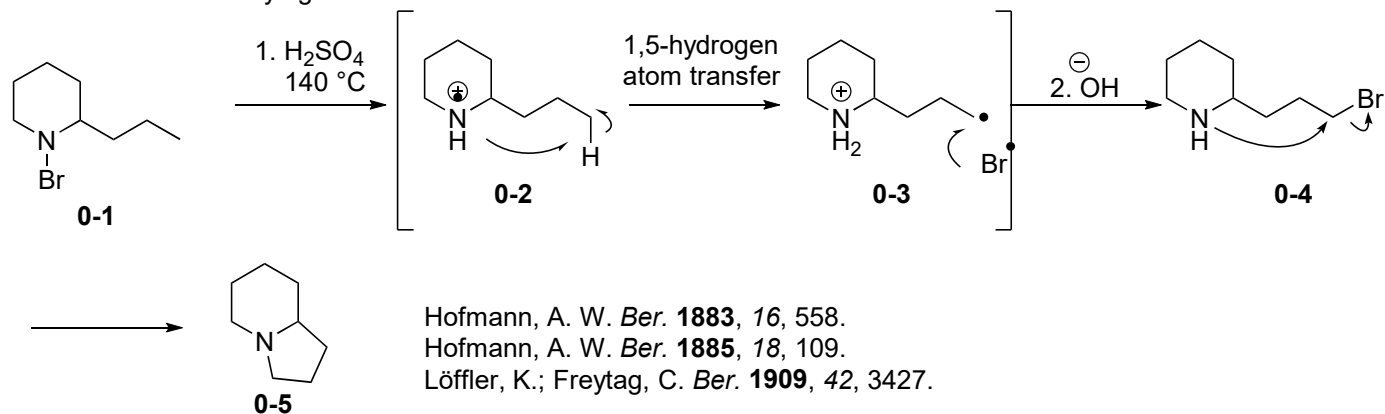


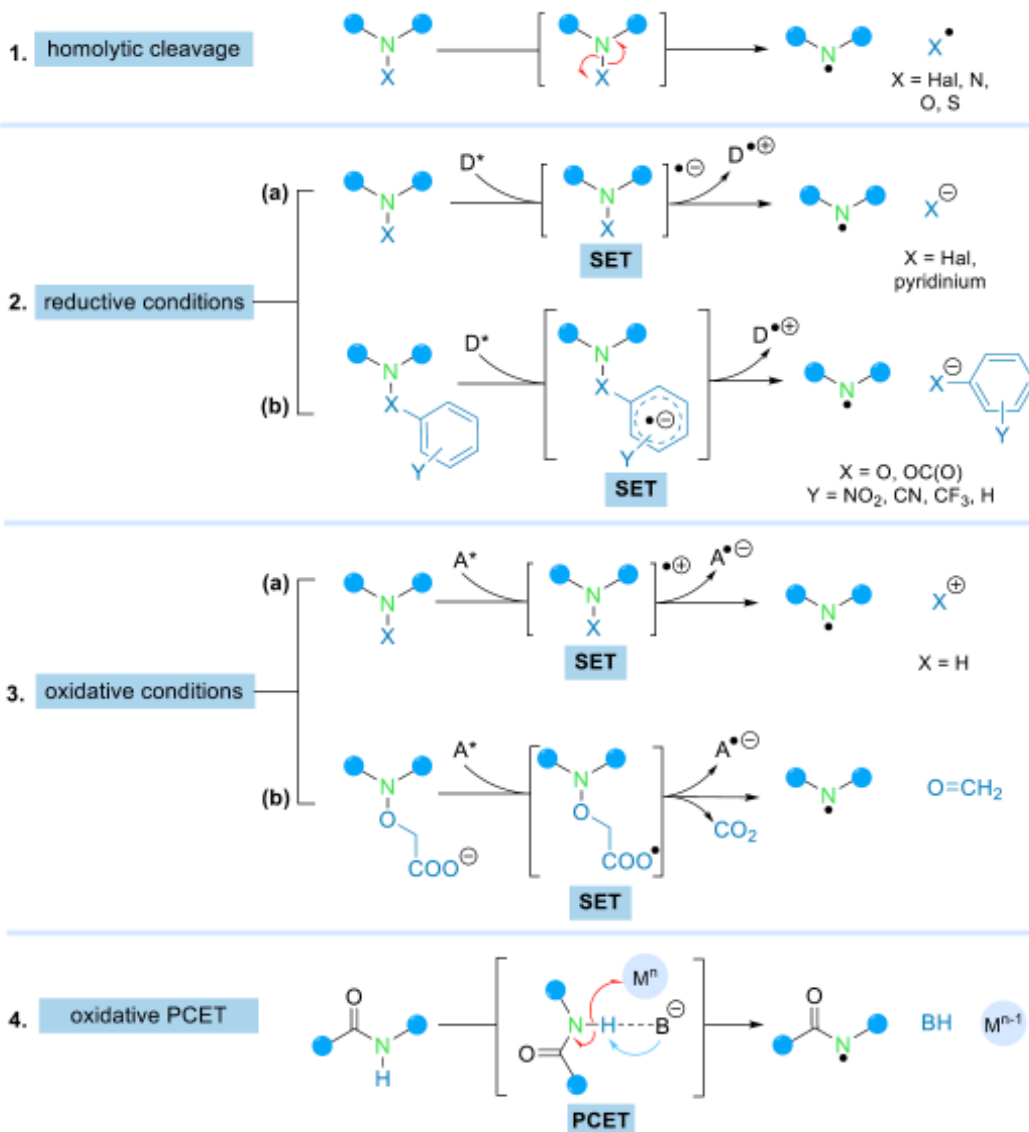
Topic: Reactions using nitrogen centered radical

- For recent reviews, see: Zard, A. Z. *Chem. Soc. Rev.* **2008**, 37, 1603.
Xiong, T.; Zhang, Q. *Chem. Soc. Rev.* **2016**, 45, 3069.
O'Neil, L. G.; Bower, J. F. *Angew. Chem. Int. Ed.* **2021**, 60, 25640.
Pratley, C.; Fenner, S.; Murphy, J. A. *Chem. Rev.* **2022**, 122, 8181.

- Early reaction of N-centered radical
Hofmann-Löffler-Freytag reaction



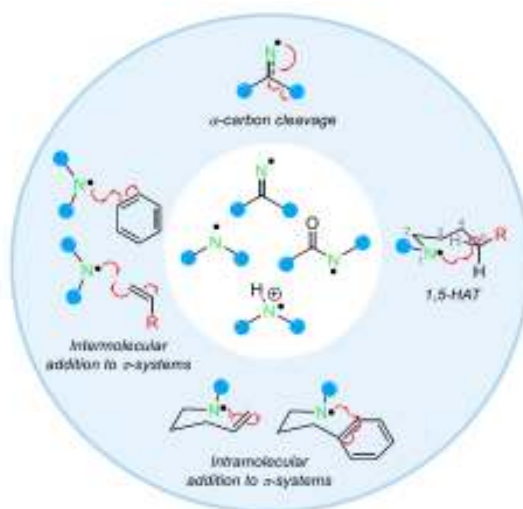
- Methods to generate N-centered radical



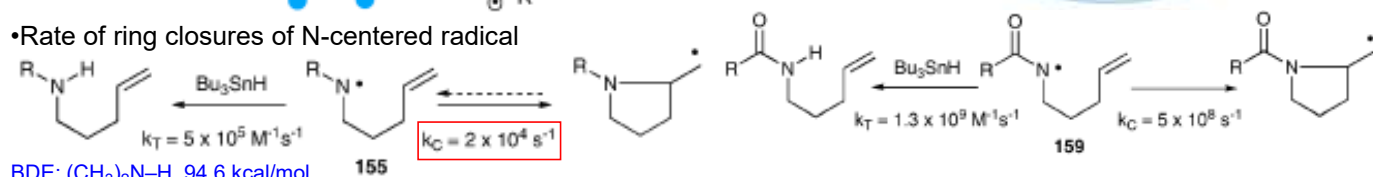
•Types of N-centered radical

•General reactivities of N-centered radical

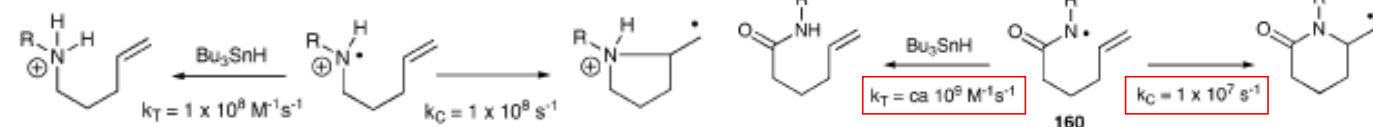
	Type	Structure	Orbital Structure	Configuration
"nucleophilic"	iminyl			σ
	aminyl			π
	amidyl			π
"electrophilic"	aminium			π



•Rate of ring closures of N-centered radical

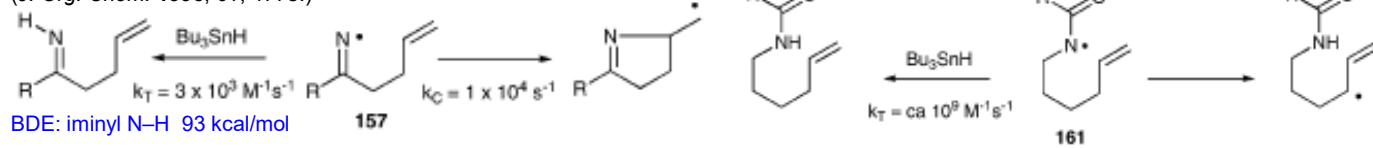


BDE: $(\text{CH}_3)_2\text{N-H}$ 94.6 kcal/mol

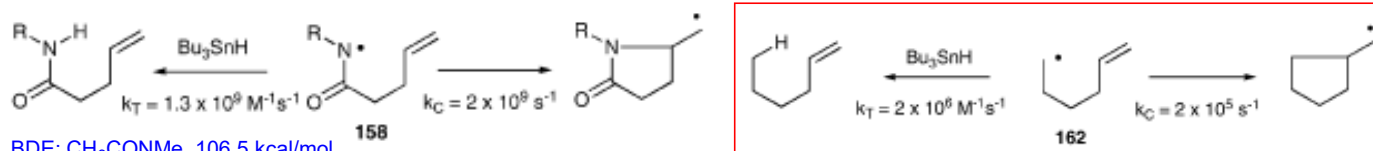


BDE: $(\text{CH}_3)_2\text{N}^+\text{H-H}$ 101.5 kcal/mol

(*J. Org. Chem.* **1996**, *61*, 4778.)



BDE: iminyl N-H 93 kcal/mol

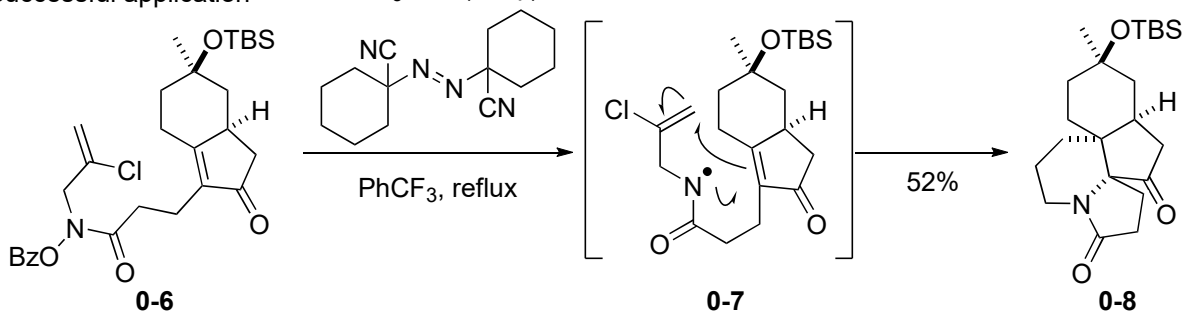


BDE: $\text{CH}_3\text{CONMe-H}$ 106.5 kcal/mol

Chem. Soc. Rev. **2008**, *37*, 1603.

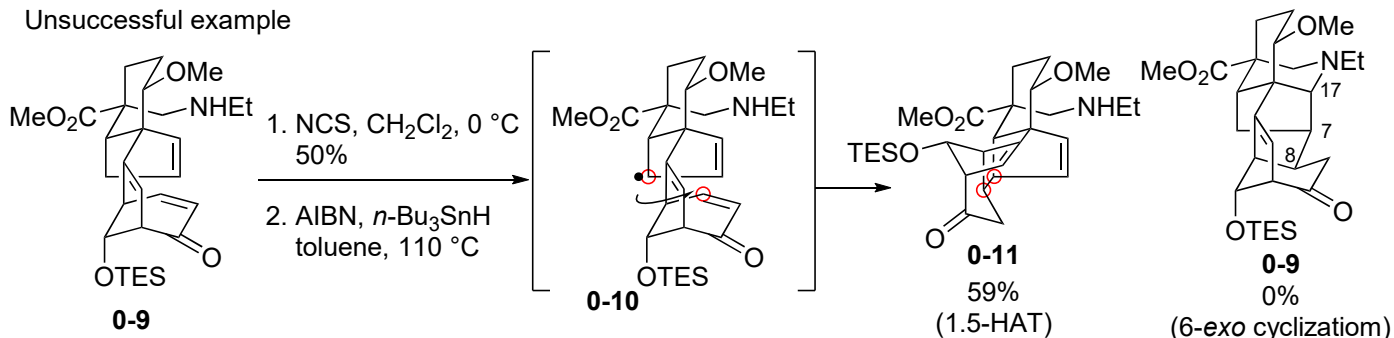
Successful application

n-Bu₃SnH (2 eq.)

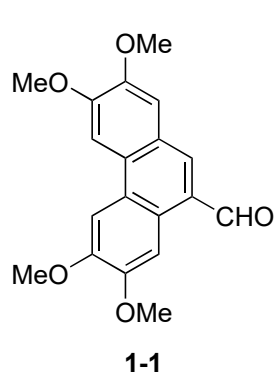


Zard, S. Z. et al. *Angew. Chem. Int. Ed.* **2002**, *41*, 1783. Zard, S. Z. et al. *Tetrahedron* **2008**, *64*, 4803.

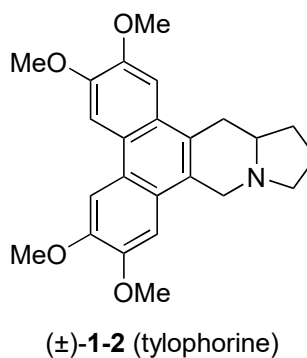
Unsuccessful example



(1) Please explain the reasonable reaction mechanisms.

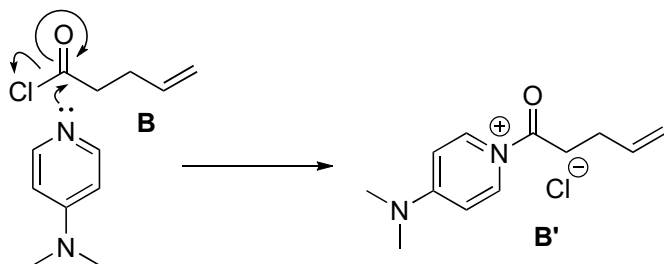
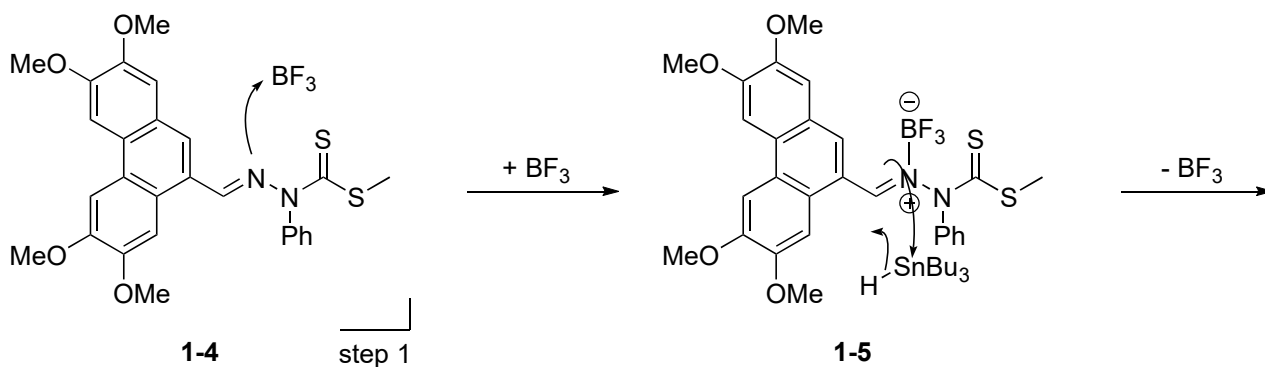
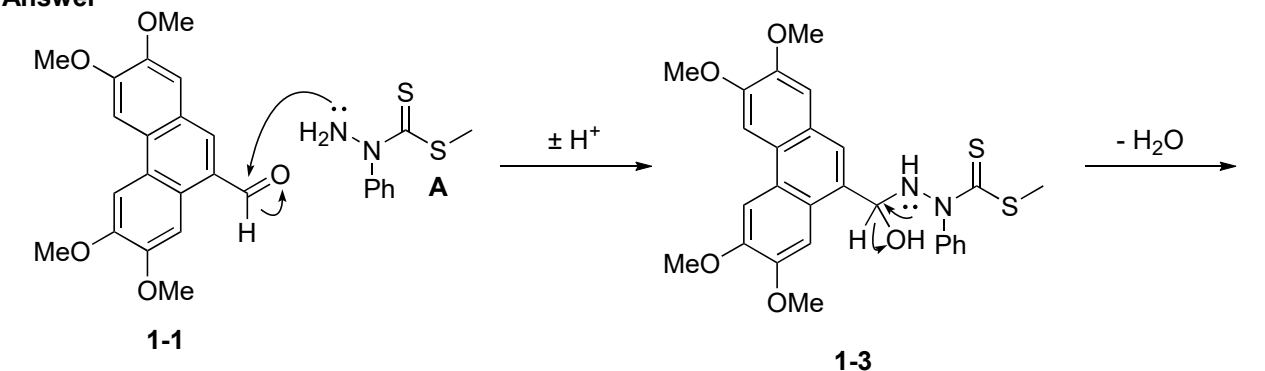


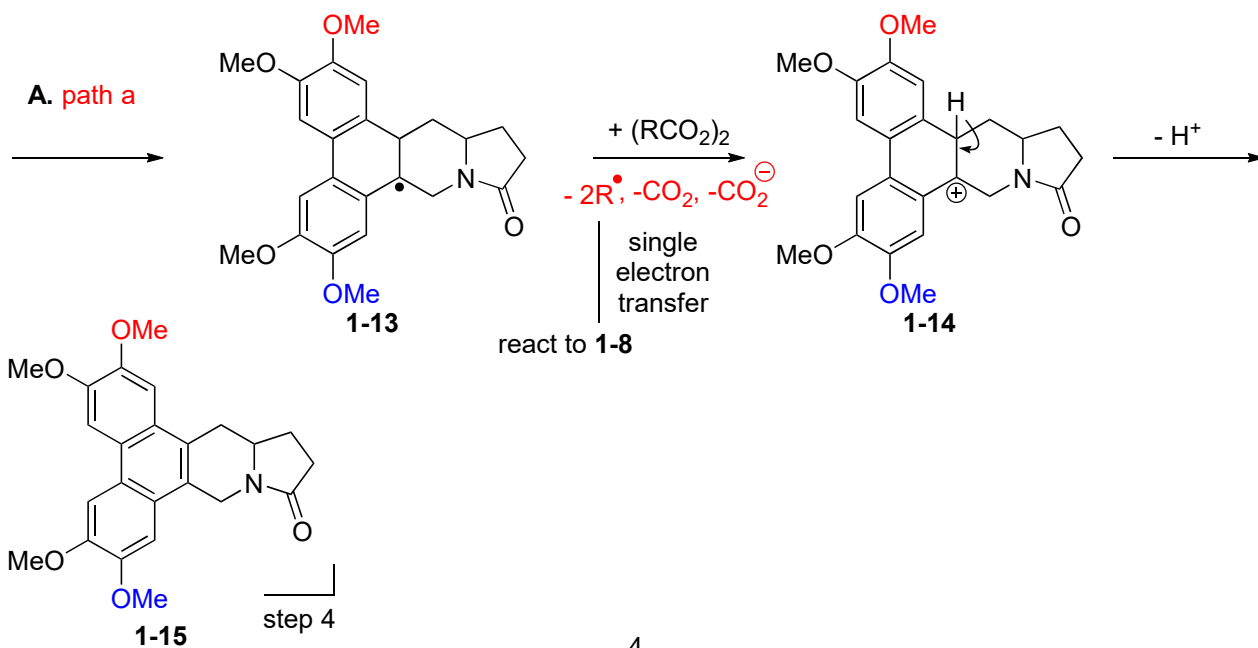
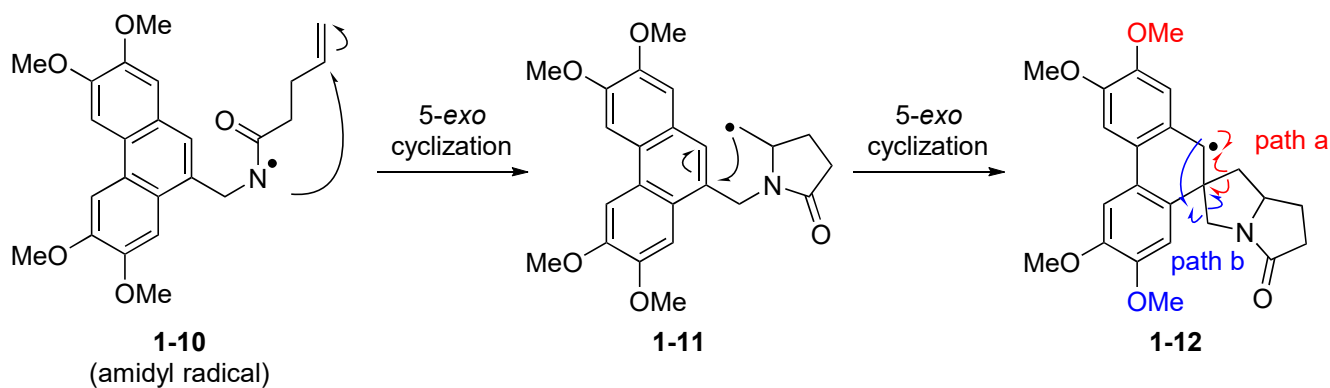
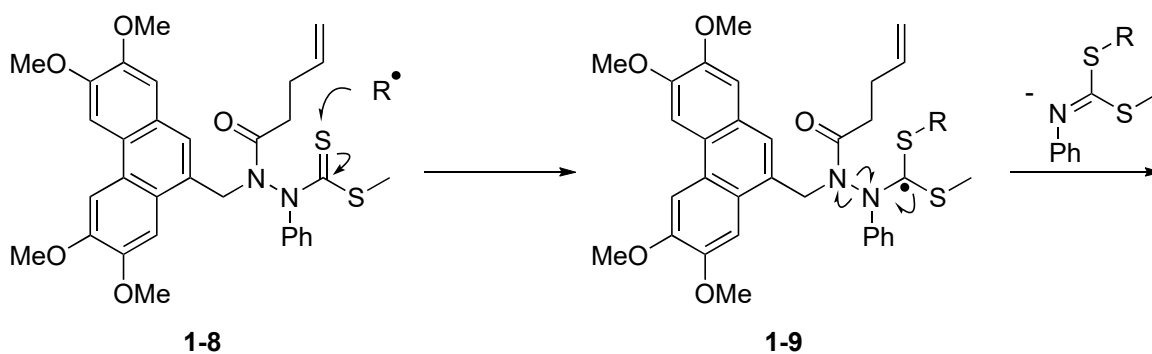
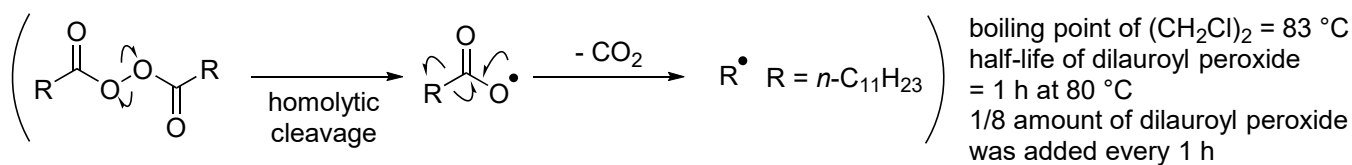
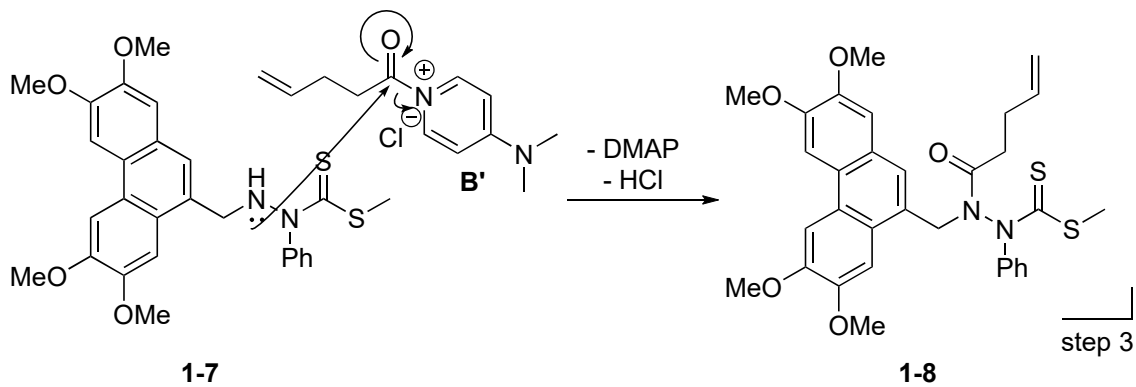
- A** (1.5 eq.), (CH₂Cl)₂, reflux, 97%
- n*-Bu₃SnH (1.5 eq.), BF₃·OEt₂ (1.5 eq.)
CH₂Cl₂, rt, 95%
- B** (5 eq.), DMAP (5 eq.)
toluene, reflux, 86%
- dilauroyl peroxide (2 eq.)
(CH₂Cl)₂, reflux, 66%
- LiAlH₄ (5 eq.), THF, reflux, 95%

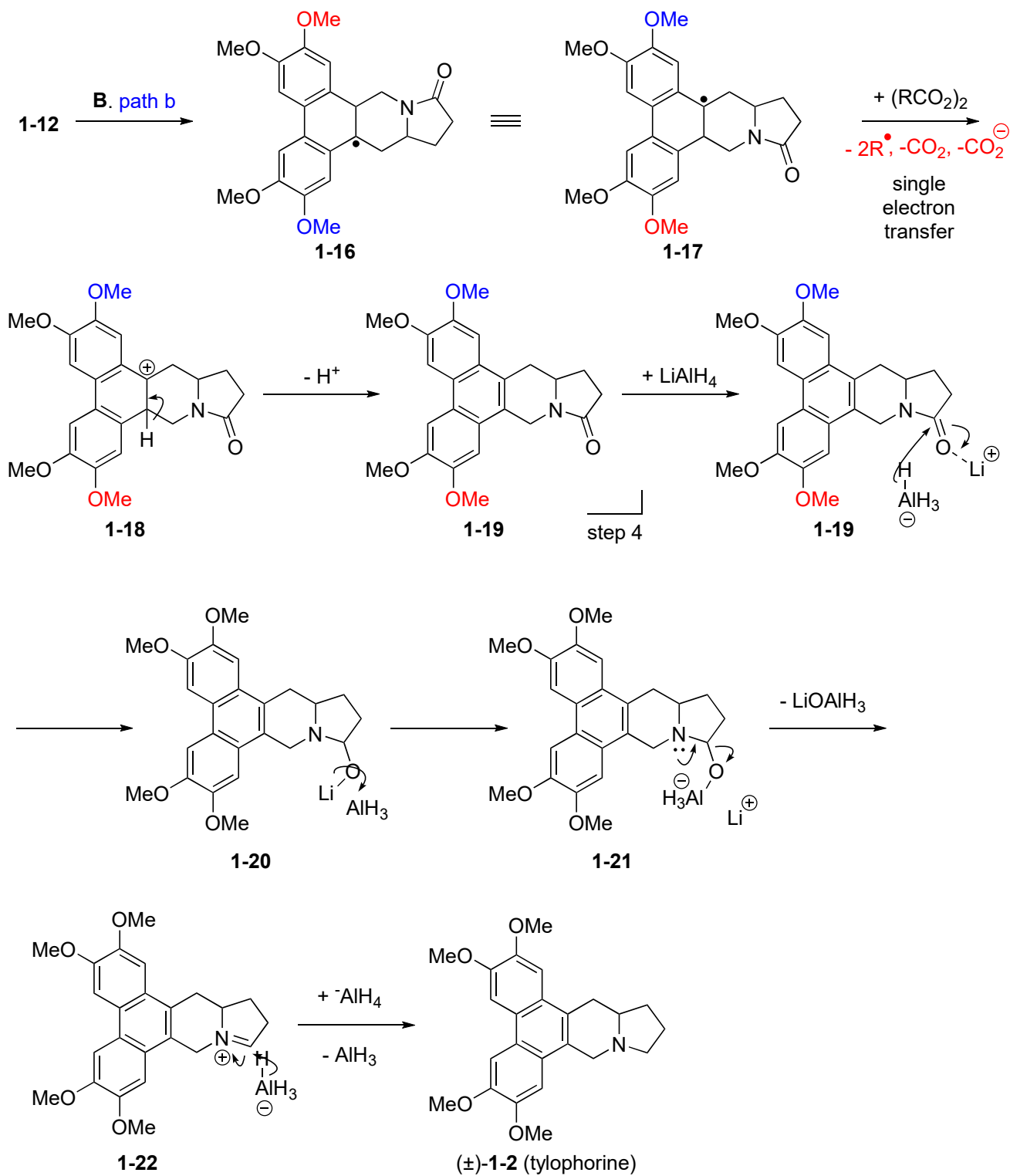


Han, G.; Liu, Y.; Wang, Q. *Org. Lett.* **2013**, *15*, 5334.

•Answer



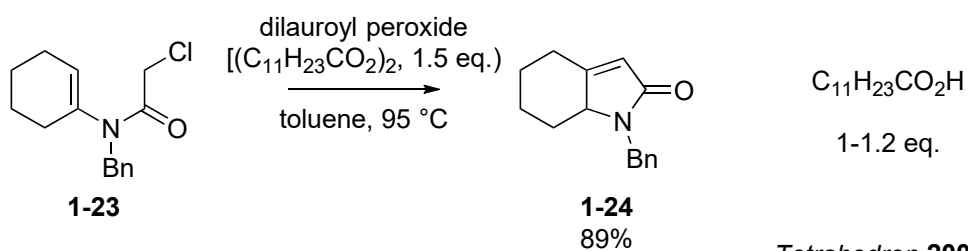




•Discussion 1

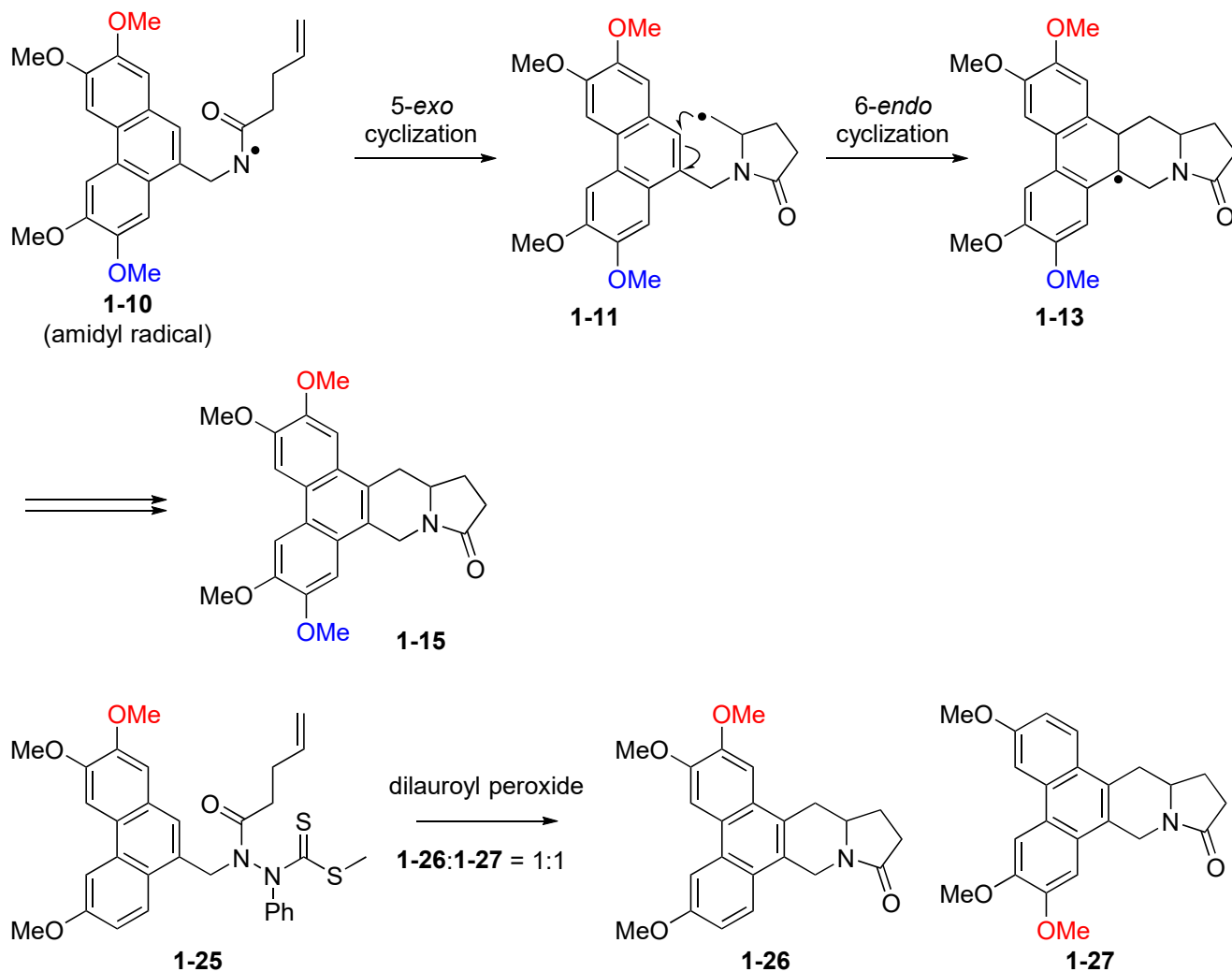
single electron transfer to peroxide
see page 9 for the detail

oxidative radical cyclization



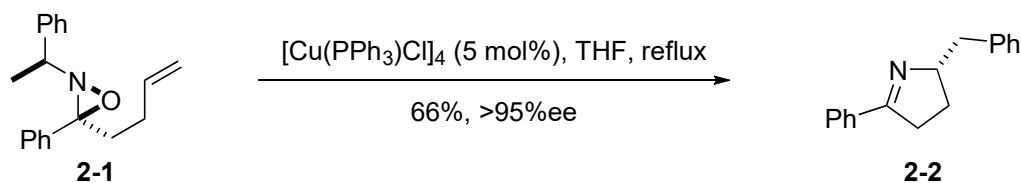
•Discussion 2

Alternative mechanism of cascade cyclization - 5-*exo*/6-*endo* cyclization-

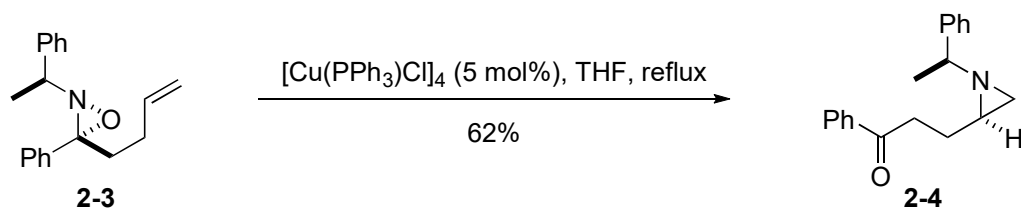


Since both **1-26** and **1-27** were obtained, the reaction mechanism should be 5-*exo*/5-*exo* cyclization.

(2) Please explain the reasonable reaction mechanisms and stereoselectivities.



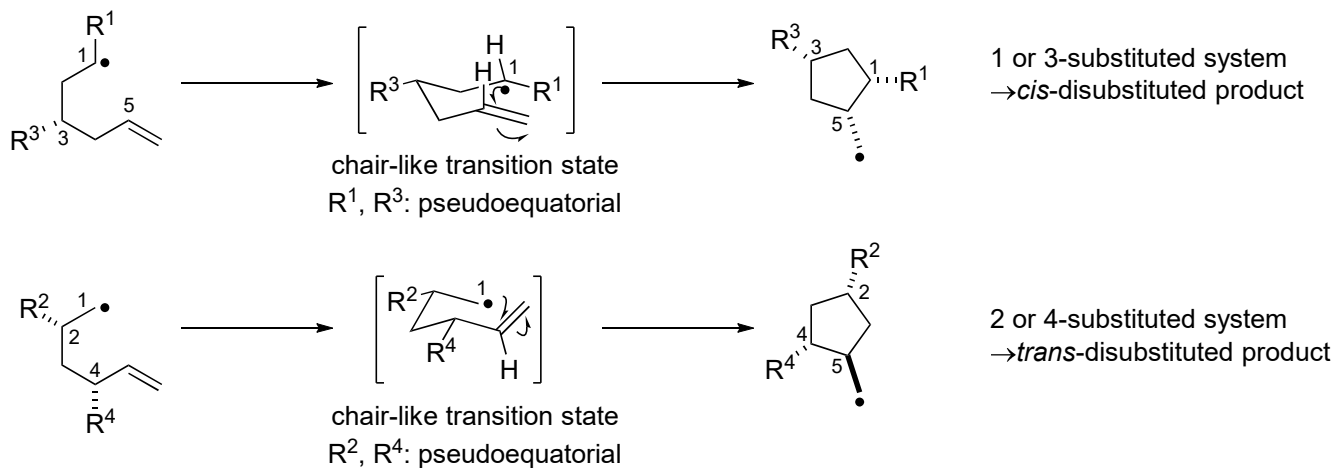
ee was not mentioned, but should be >95% ee



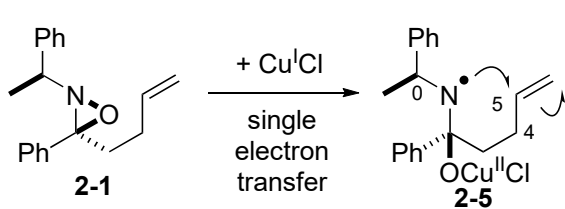
Aubé, J.; Peng, X.; Wang, Y.; Takusagawa, F. *J. Am. Chem. Soc.* **1992**, *114*, 5466.

prior to answer

Beckwith-Houk model for 5-exo radical cyclization

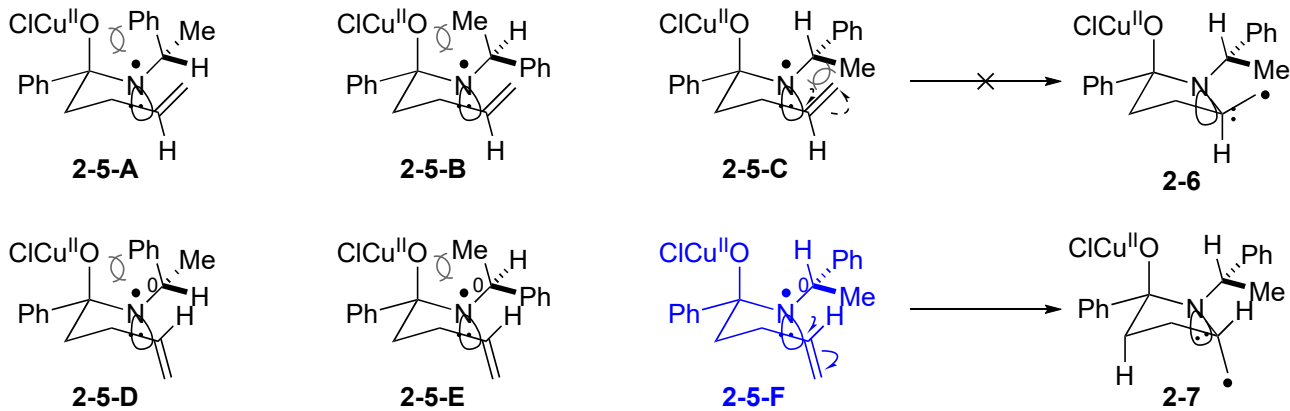
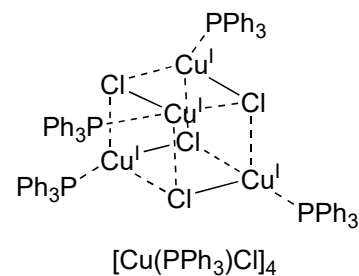


Answer



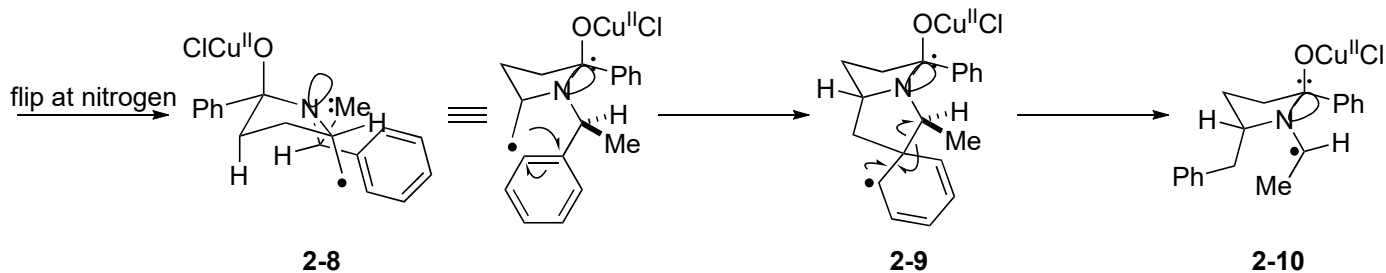
consider the rotation of C0-N bond and C4-C5 bond

A value
Ph: 3.0
OTMS: 0.74
Me: 1.70
C=CH: 0.41

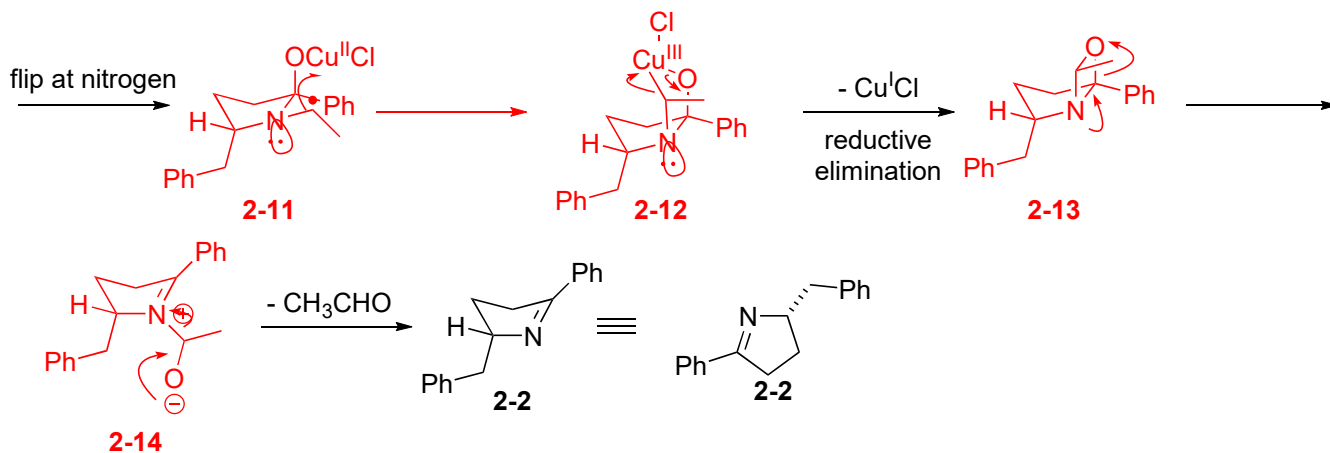


Considering the interaction between olefin and alkyl group on N, **2-5-A-2-5-C** should be less favorable than **2-5-D-2-5-F**.

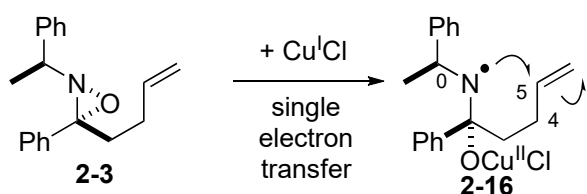
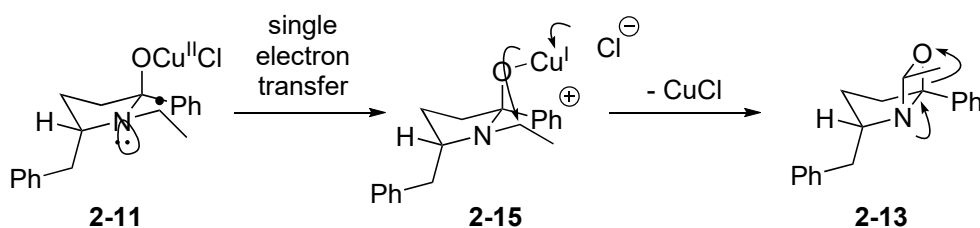
Considering the interaction between OCu and substituent of C0, **2-5-F** should be the most stable conformer.



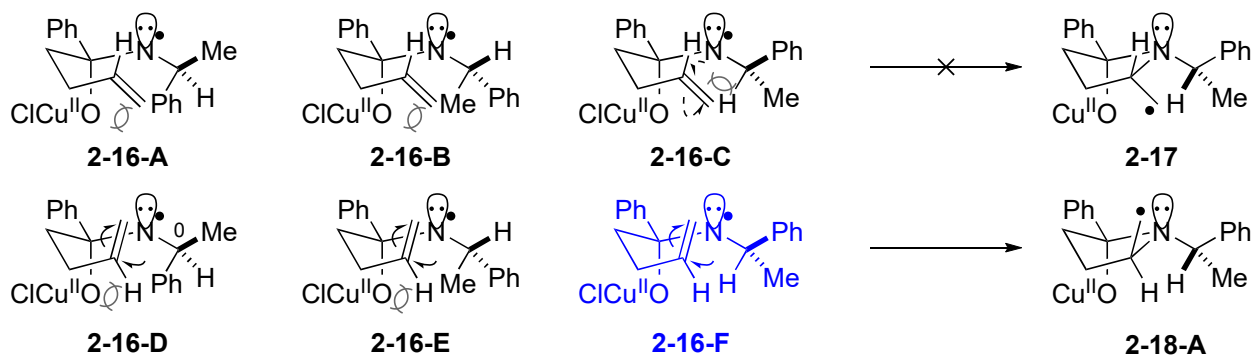
Ph migration would proceed through 5,5-*cis*-fused intermediate (**2-9**).
Thus flip at nitrogen was considered.



alternative pathway from 2-11 to 2-13

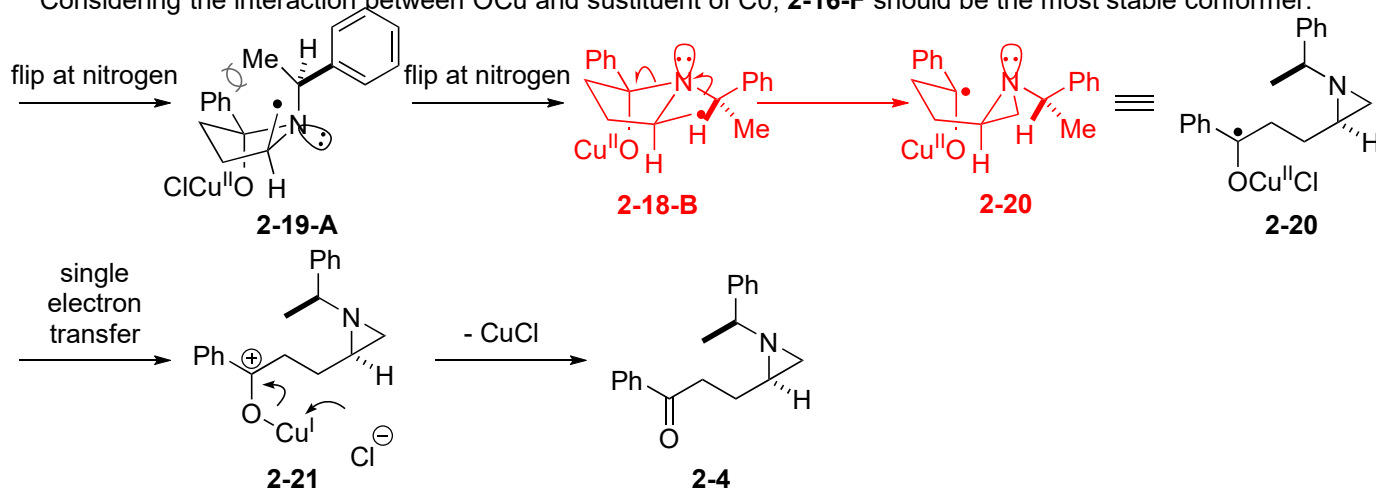


consider the rotation of C0-N bond and C4-C5 bond

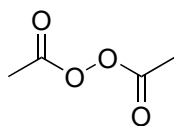


Considering the interaction between olefin and alkyl group on N, **2-16-A-2-16-C** should be less favorable than **2-16-D-2-16-F**.

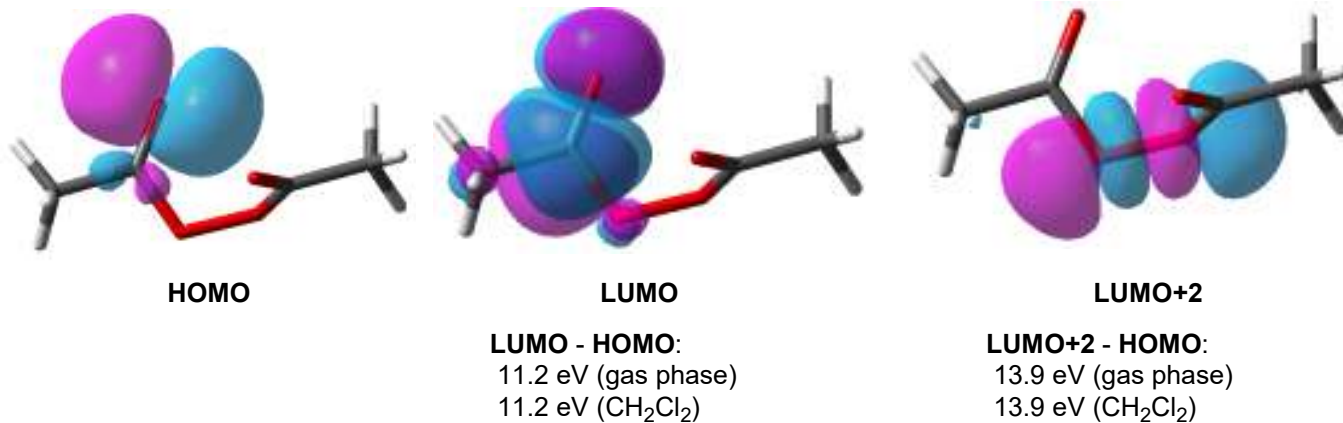
Considering the interaction between OCu and substituent of C0, **2-16-F** should be the most stable conformer.



calculation of alkyl peroxide (calculated by Dr. Fujino)

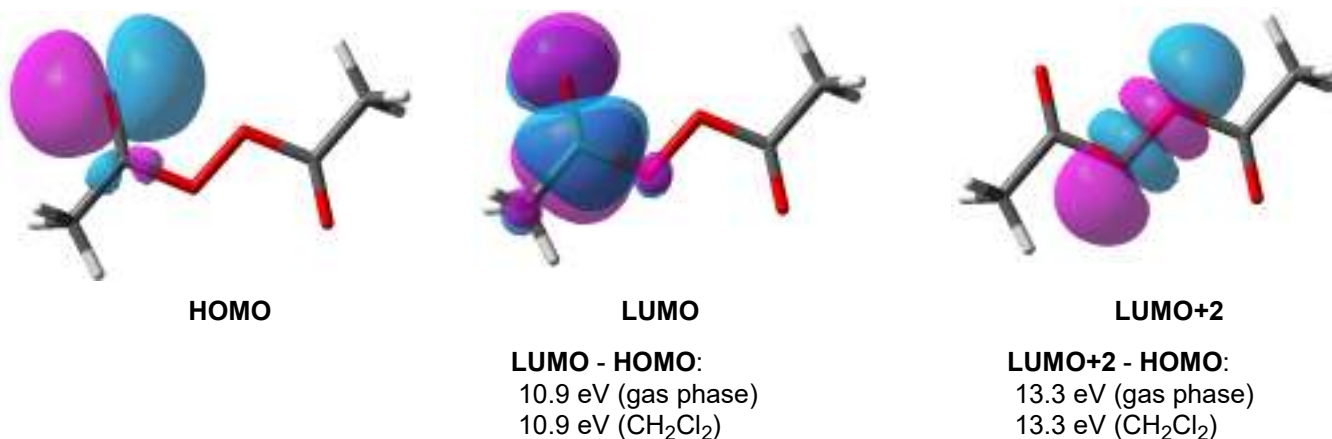


most stable conformer ($\Delta G = 0$ kcal/mol)

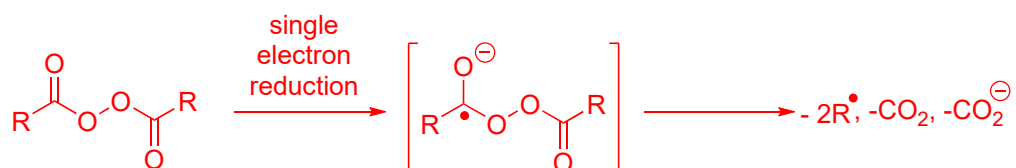


second stable conformer ($\Delta G = +5.08$ kcal/mol in gas phase, $+4.42$ kcal/mo in CH_2Cl_2)

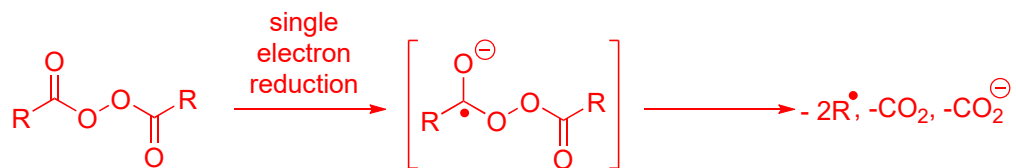
M06-2X/6-31+G(d) (gas phase) or M06-2X/6-31+G(d)/CPCM (CH_2Cl_2)

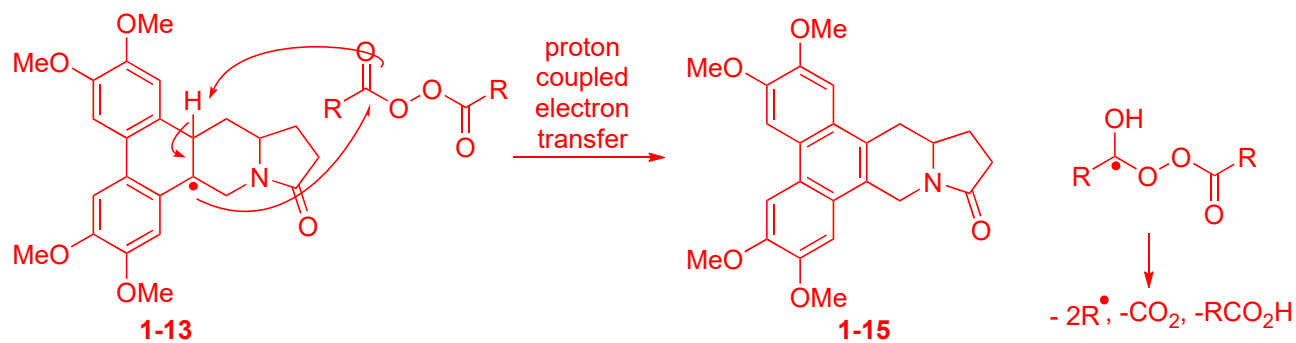


Judging from the calculation, single electron reduction should occur at $\text{C}=\text{O} \pi^*$ orbital.



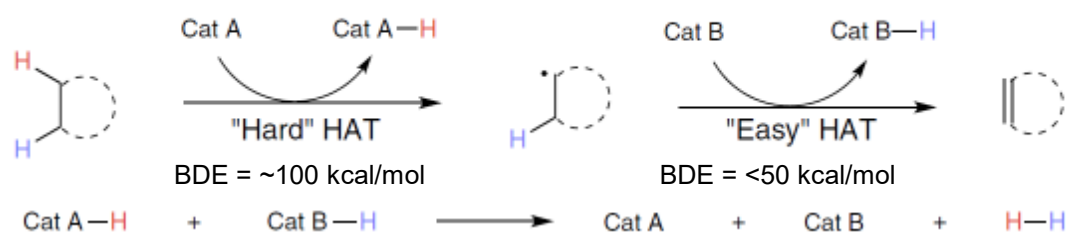
or directly provide R^\bullet in concerted mechanism





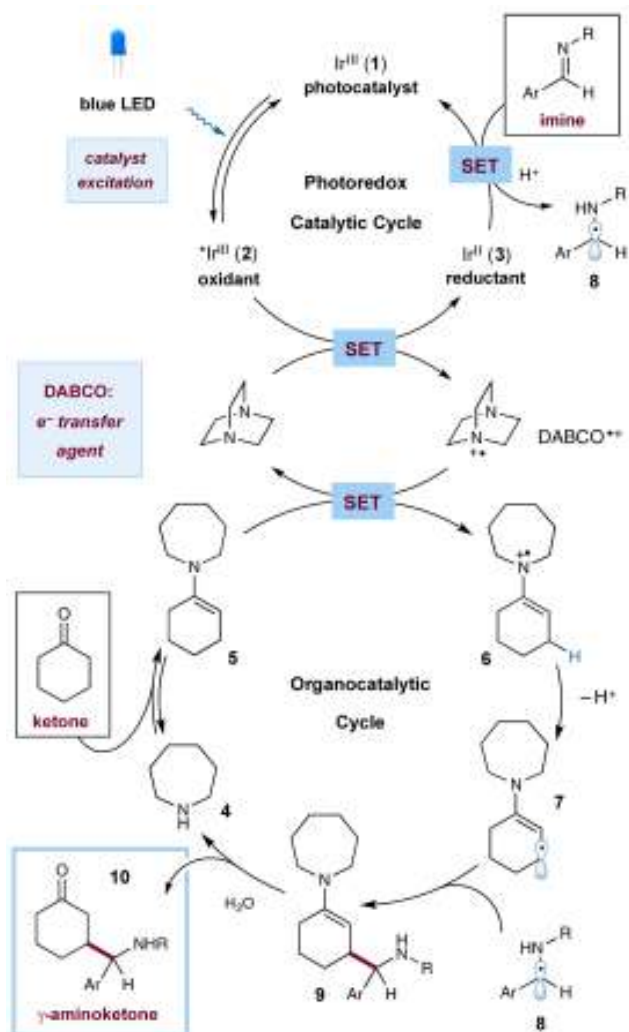
A radical lowers the bond dissociation energy of adjacent C-H

C Cooperative hydrogen atom transfer (cHAT)



West, J. G.; Huang, D. Sorensen, E. J. et al. *Nat. Commun.* **2015**, 6, 10093.

The acidity of C-H adjacent to radical cation or conjugated to radical cation is high.



Jeffrey, J. L.; Petronijevic, F. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, 137, 8404.