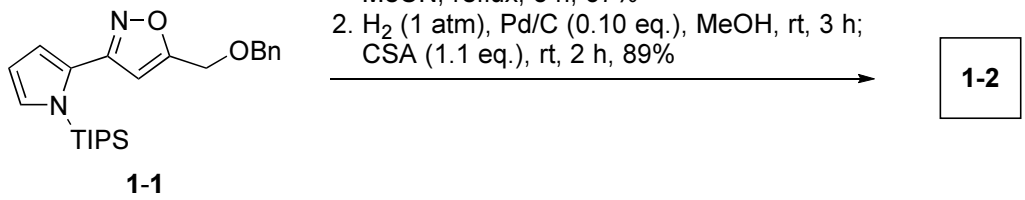
Problem Session

Mar. 5, 2016 Hiroaki Itoh

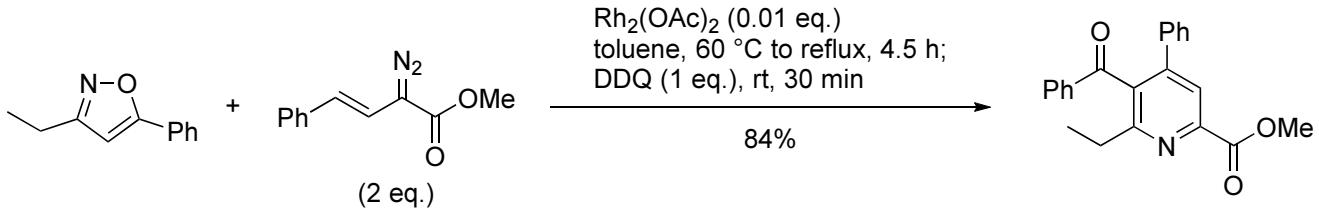
Please fill in the blank and explain reaction mechanisms.

1.



1-1

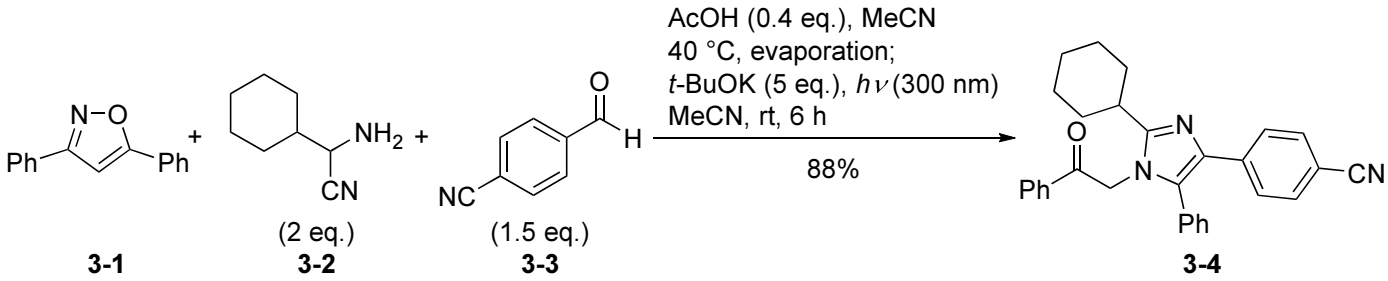
2.



(2 eq.)

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

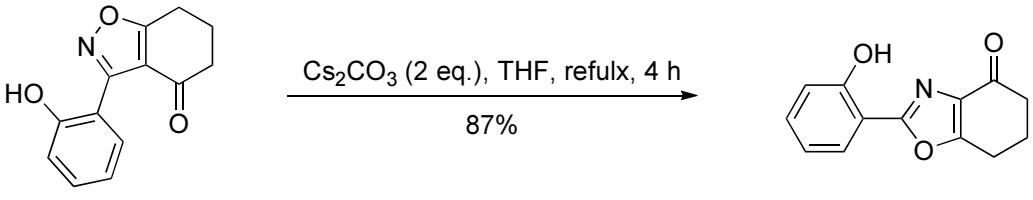
3.



(2 eq.) (1.5 eq.)

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

4.



4-1 **4-2**

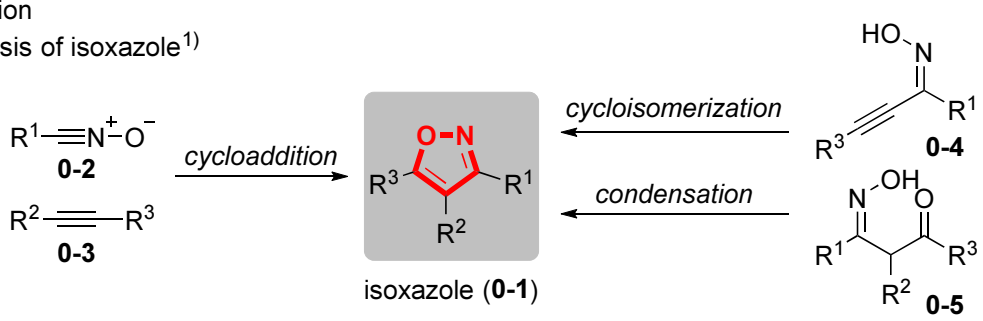
Problem Session -Answer

Mar. 5, 2016 Hiroaki Itoh

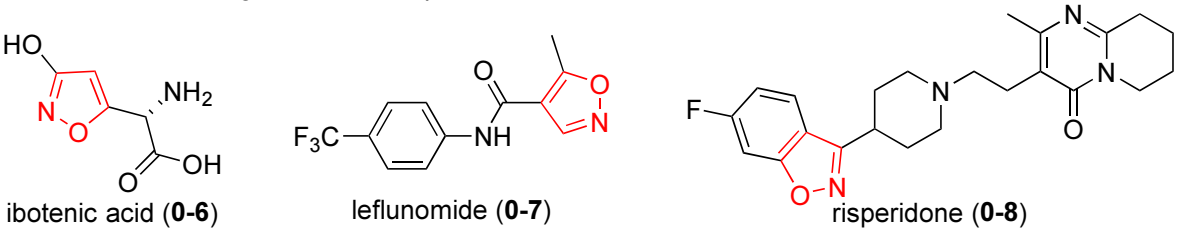
Transformation of isoxazoles

0. Introduction

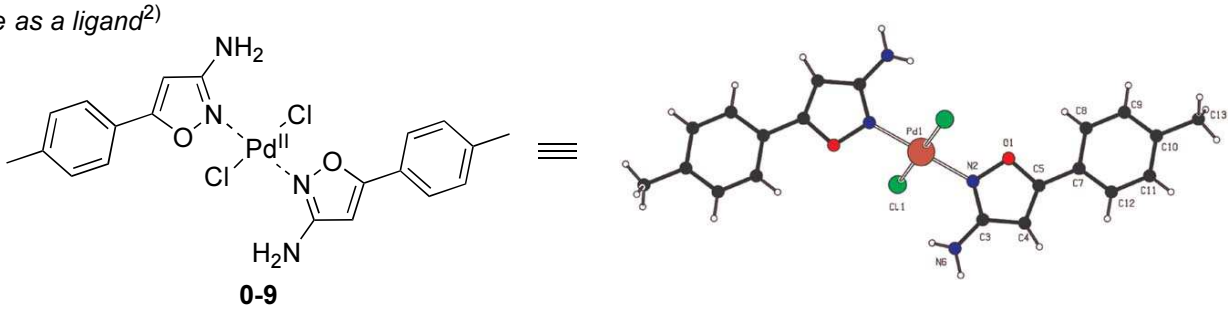
0-1. Synthesis of isoxazole[1)]



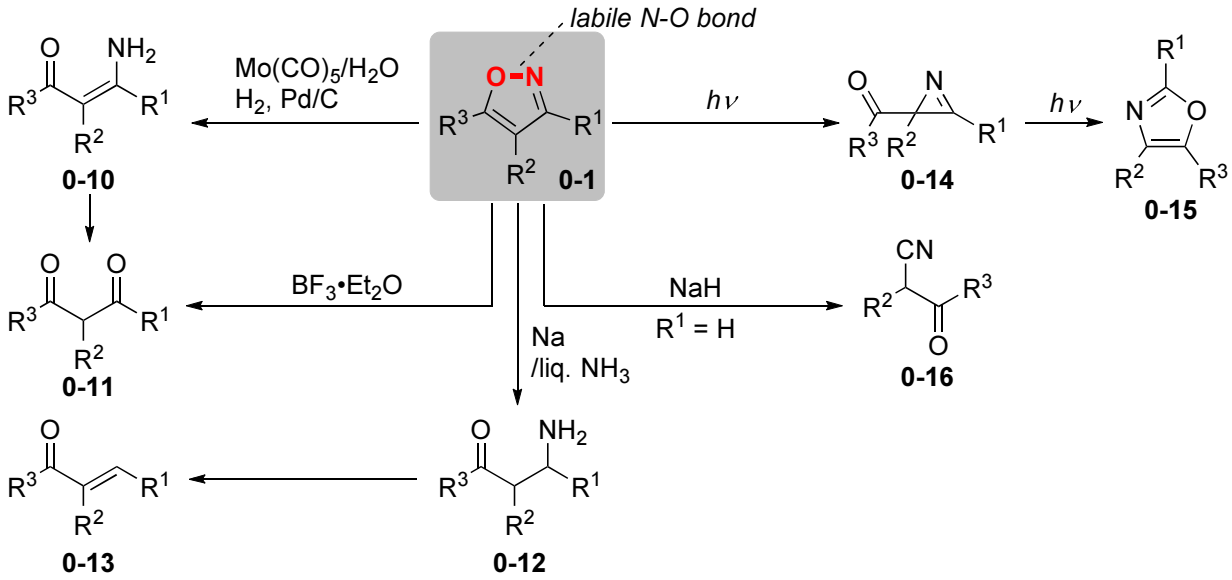
Examples of isoxazole containing bioactive compounds



Isoxazole as a ligand[2)]



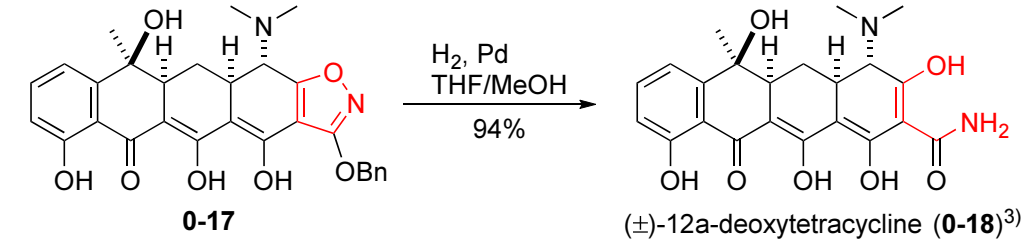
0-2. Basic transformation of isoxazoles[1)]



1) For reviews, see: (a) Hu, F.; Szostak, M. *Adv. Synth. Catal.* **2015**, *357*, 2583. (b) Shipman, M. *Contemp. Org. Synth.*, **1995**, 2, 1. (c) Baraldi, P.G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simon, D. *Synthesis* **1987**, 857.

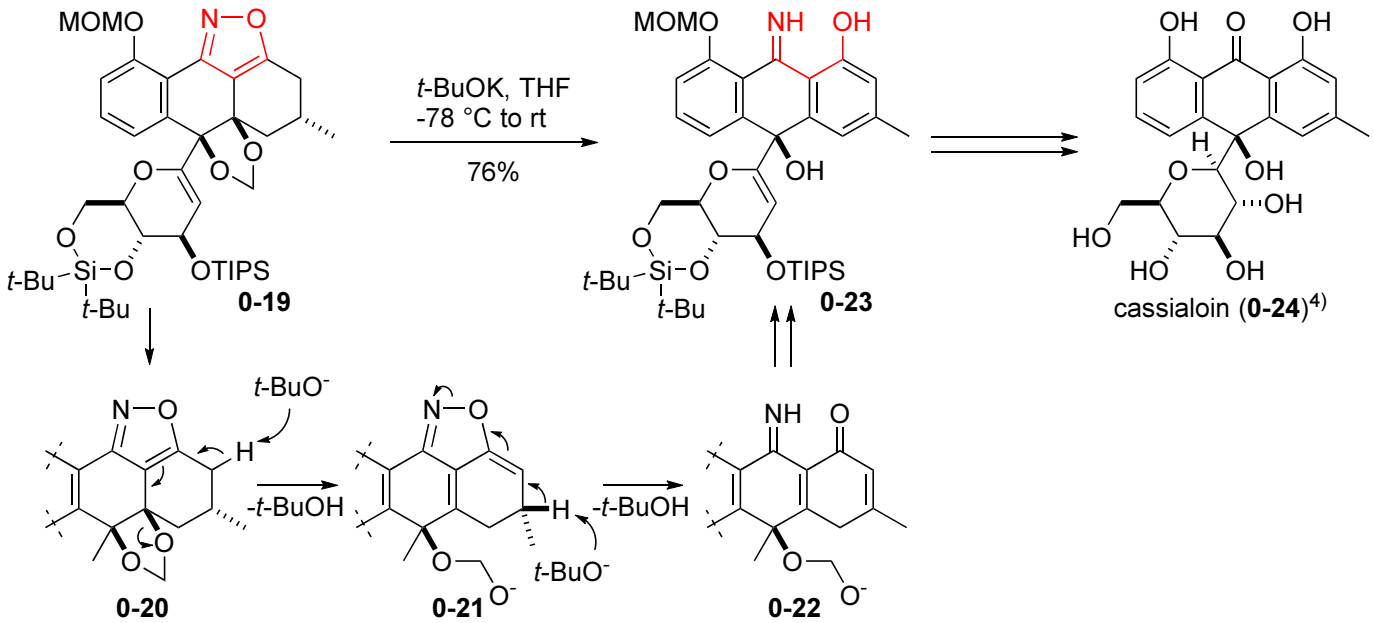
2) Potkin, V.I.; Bumagin, N. A.; Petkevich, S. K.; Lyakhov, A. S.; Rudakov, D. A.; Livantsov, M. V.; Golantsov, N. E. *Synthesis* **2012**, *44*, 151.

0-3. Selected synthetic application



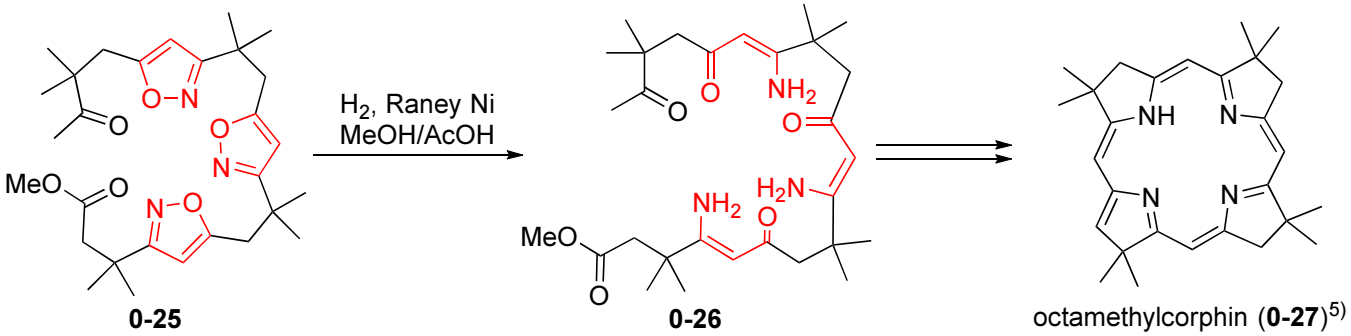
0-17

(±)-12a-deoxytetracycline (**0-18**)[3]



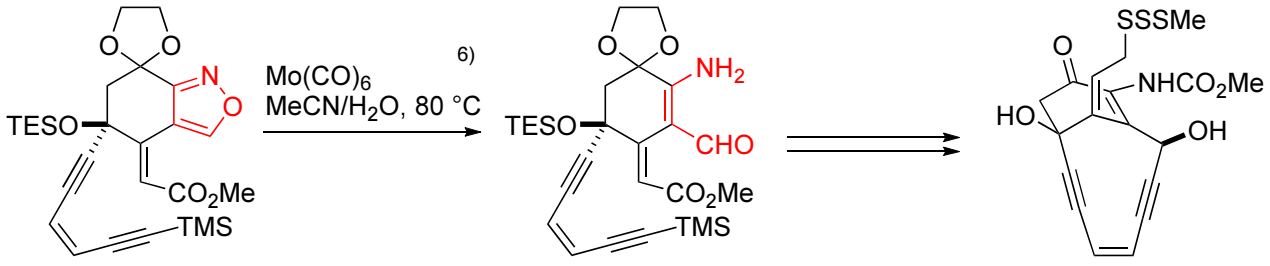
0-19 **0-20** **0-21** **0-22** **0-23**

cassialoin (**0-24**)[4]



0-25 **0-26**

octamethylcorphin (**0-27**)[5]

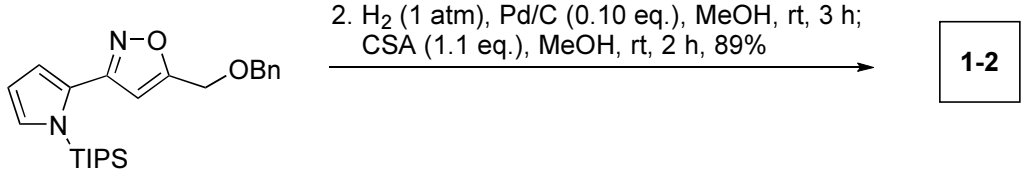


0-28 **0-29**

calicheamicinone (**0-30**)[7]

3) Stork, G.; La Clair, J. J.; Spargo, P.; Nargund, R. P.; Totah N. *J. Am. Chem. Soc.* **1996**, *118*, 5304.
4) Koyama, Y.; Yamaguchi, R.; Suzuki, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 1084.
5) Stevens, R. V.; Christensen, C. G.; Cory, R. M.; Thorsett, E. *J. Am. Chem. Soc.* **1975**, *97*, 5940.
6) (a) Nitta, M.; Kobayashi, T. *J. Chem. Soc., Chem. Commun.* **1982**, 877. (b) Nitta, M.; Kobayashi, T. *J. Chem. Soc. Perkin Trans. 1* **1985**, 1401.
7) Smith, A. L.; Hwang, C.-K.; Pitsinos, E.; Scarlato, G. R.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1992**, *114*, 3134.

1.

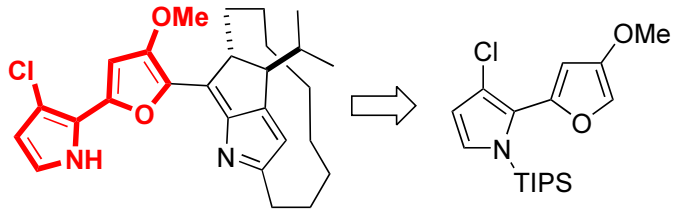


1-1

Frederich, J. H.; Matsui, J. K.; Chang, R. O.; Harran, P.G. *Tetrahedron Lett.* **2013**, *54*, 2645.
Frederich, J. H.; Harran, P. G. *J. Am. Chem. Soc.* **2013**, *135*, 3788.

1-1. Background

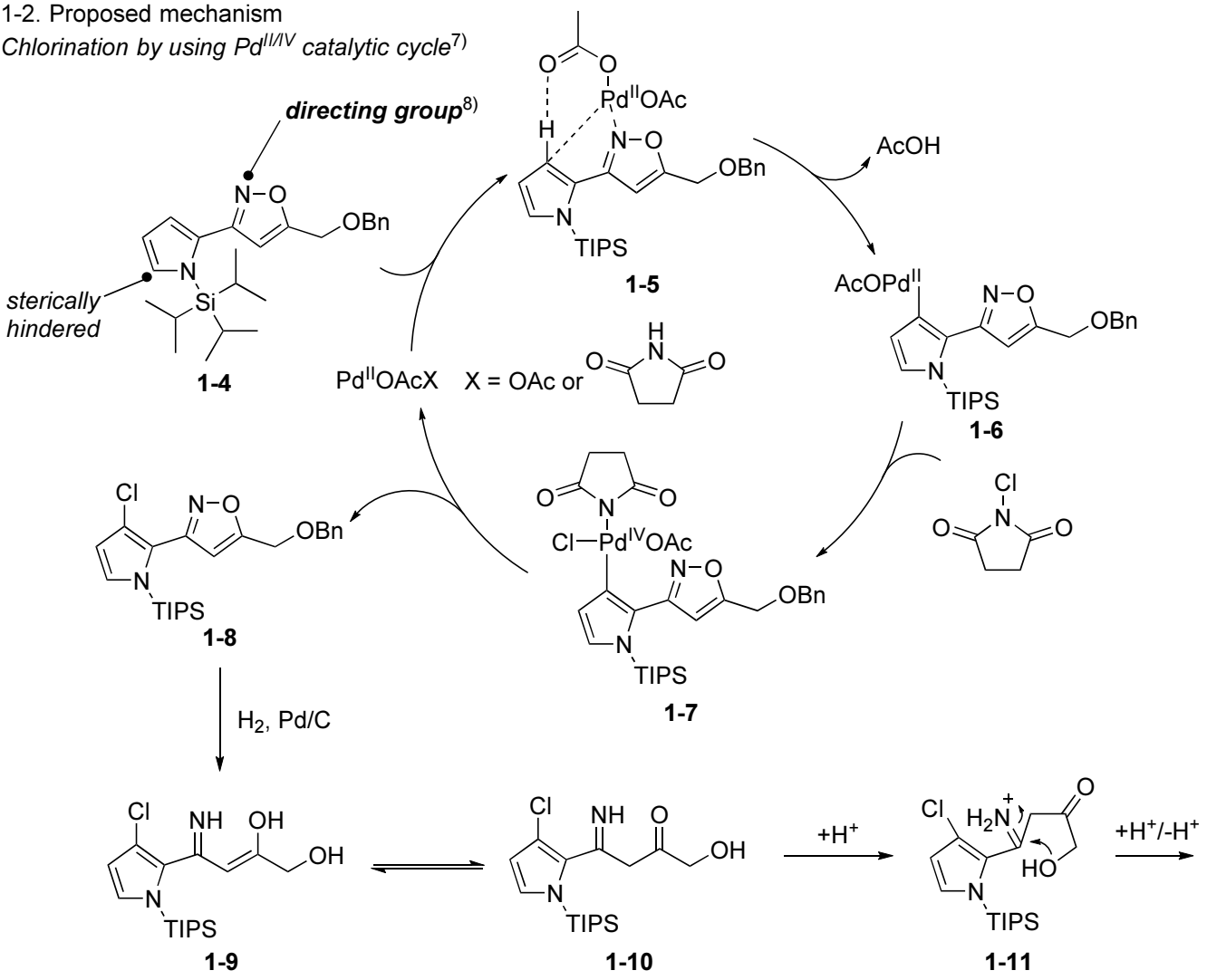
compound **1-2**: building block of roseophilin in the total synthesis by Harran et al.



(+)-roseophilin (**1-3**) **1-2**

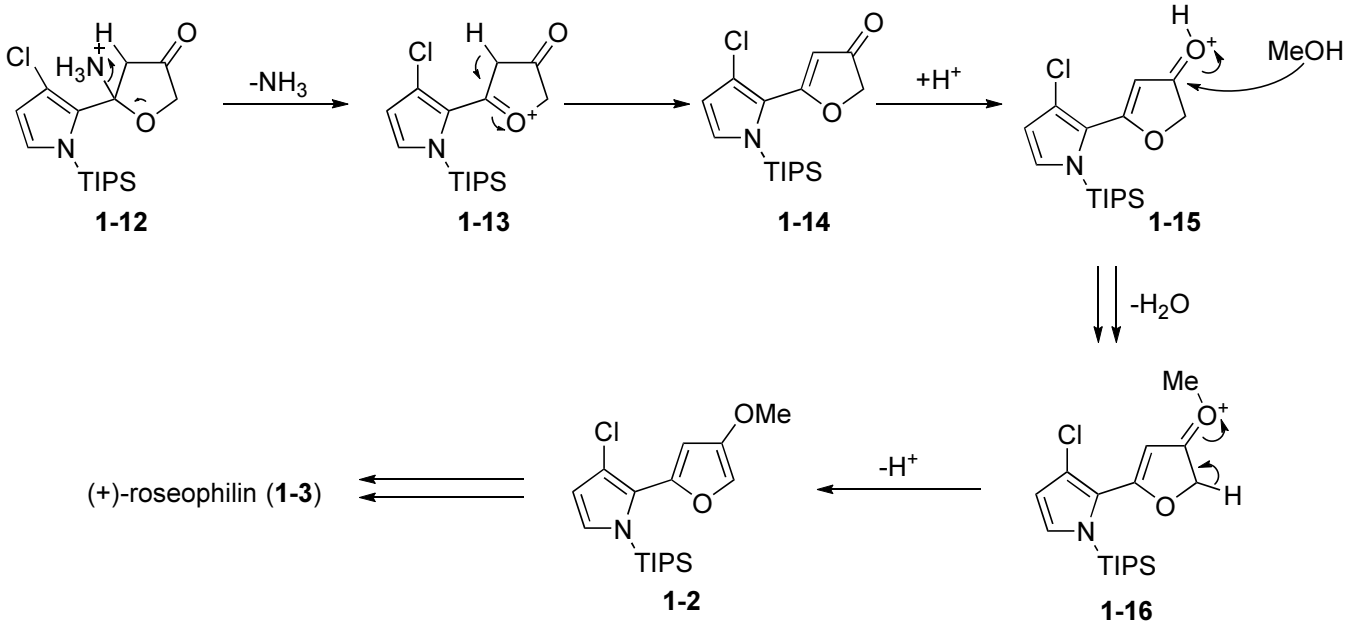
1-2. Proposed mechanism

Chlorination by using $Pd^{II/IV}$ catalytic cycle[7)]

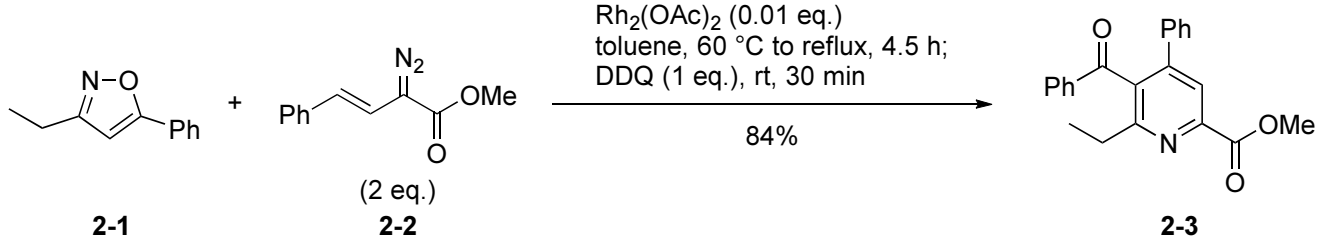


7) (a) Whitfiled, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142. (b) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 11483.

8) related Pd-catalyzed halogenation using directing group (CN):Du, B.; Jiang, X.; Sun, P. *J. Org. Chem.* **2013**, *78*, 2786.

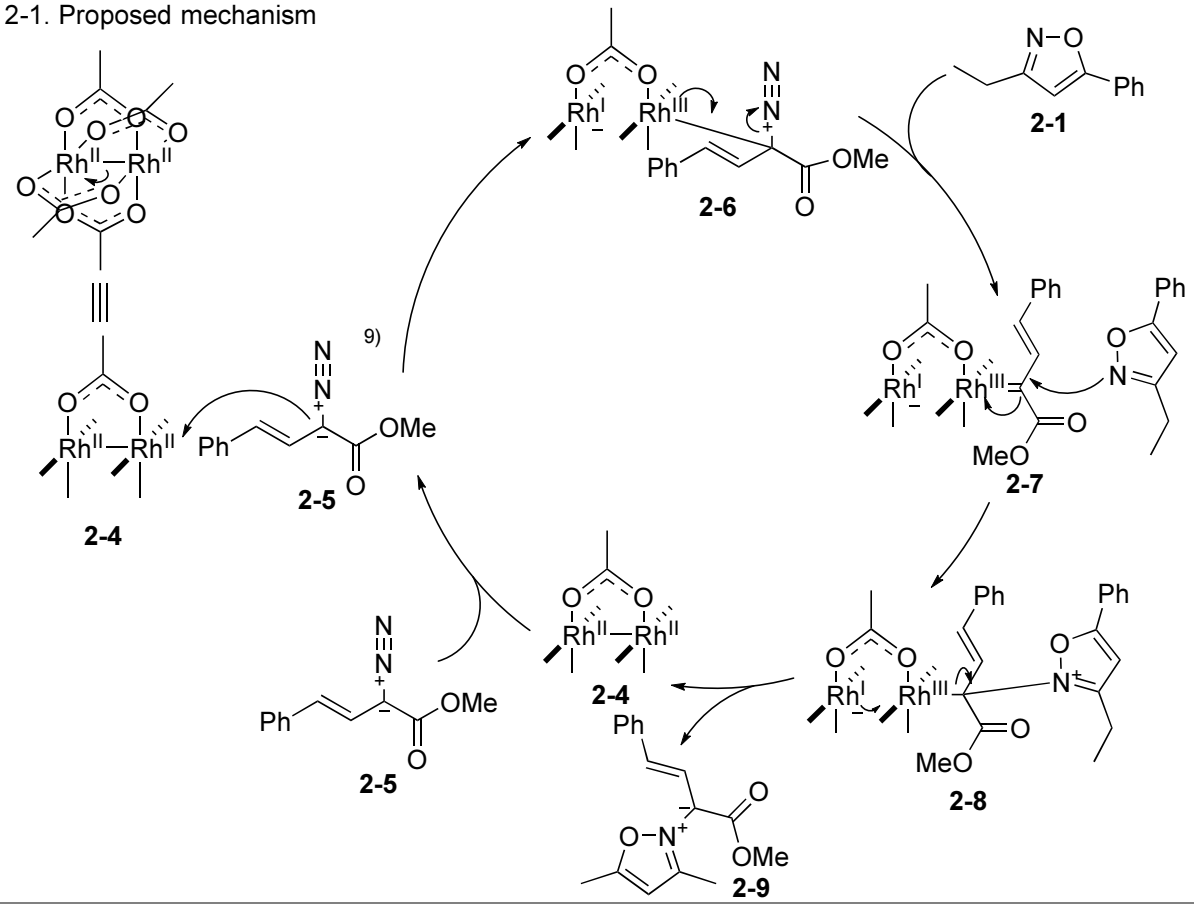


2.

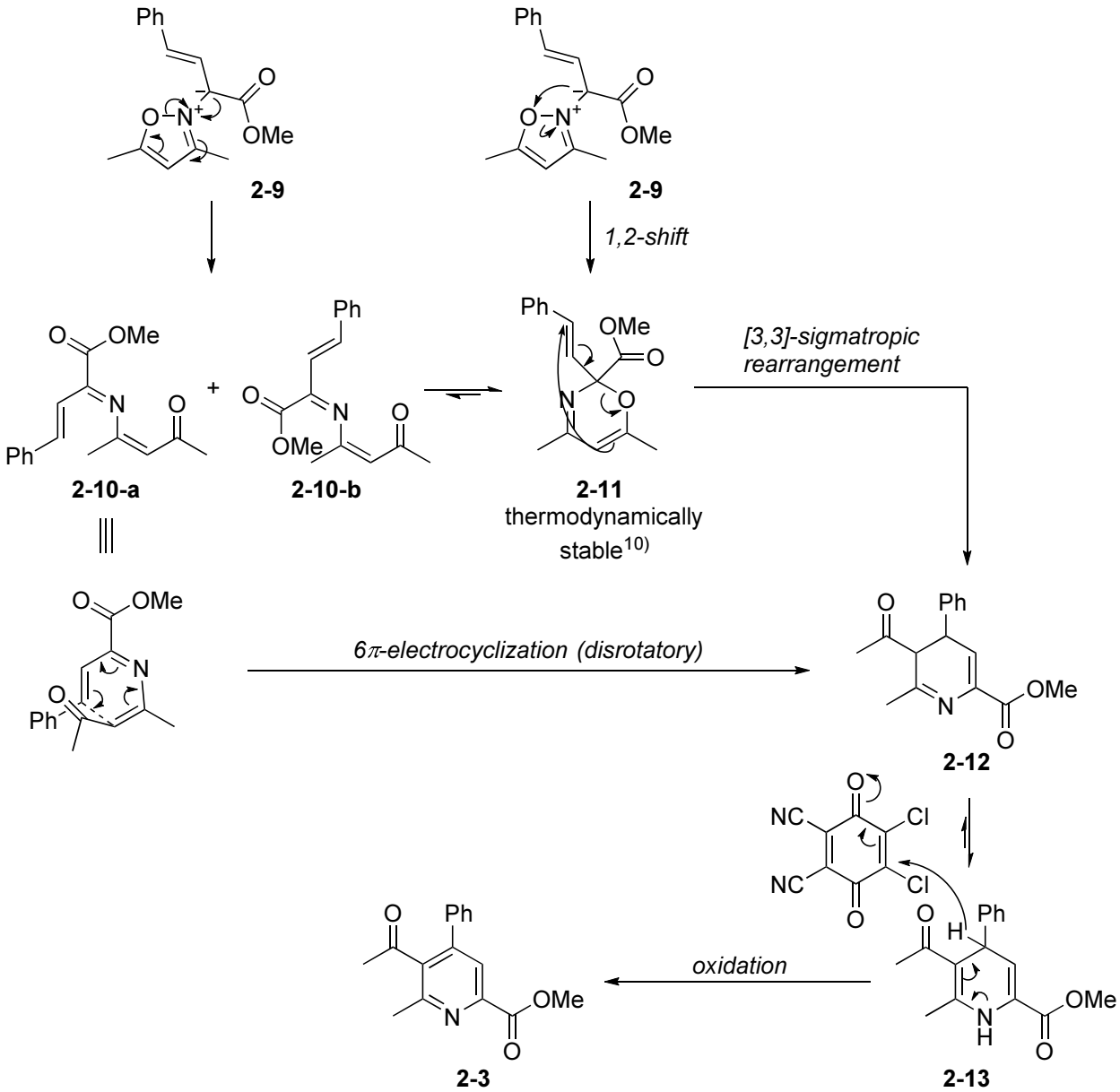


Manning, J. R.; Davies, H. W. *J. Am. Chem. Soc.* **2008**, *130*, 8602.

2-1. Proposed mechanism

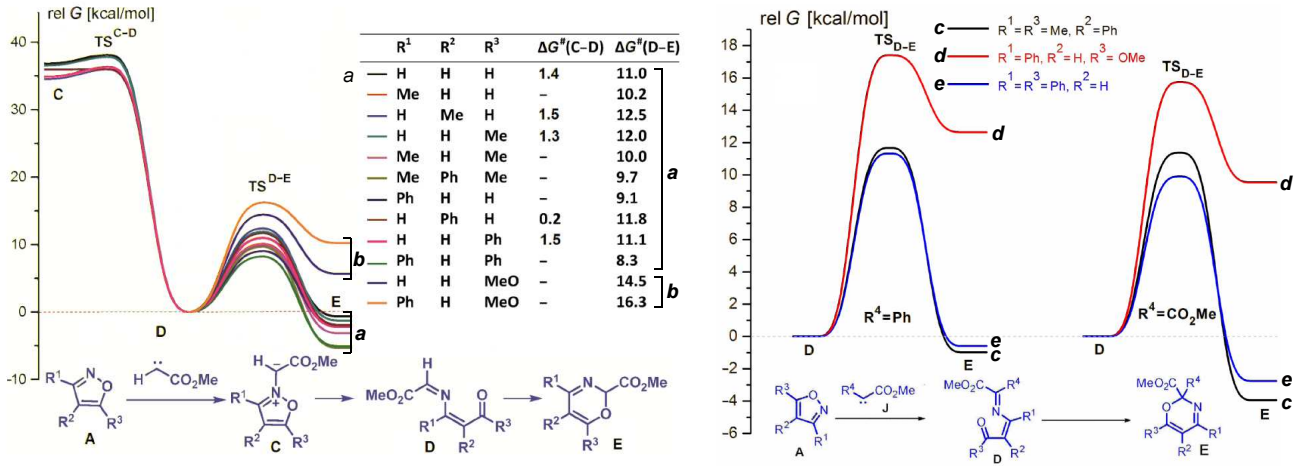


9) Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 7181.



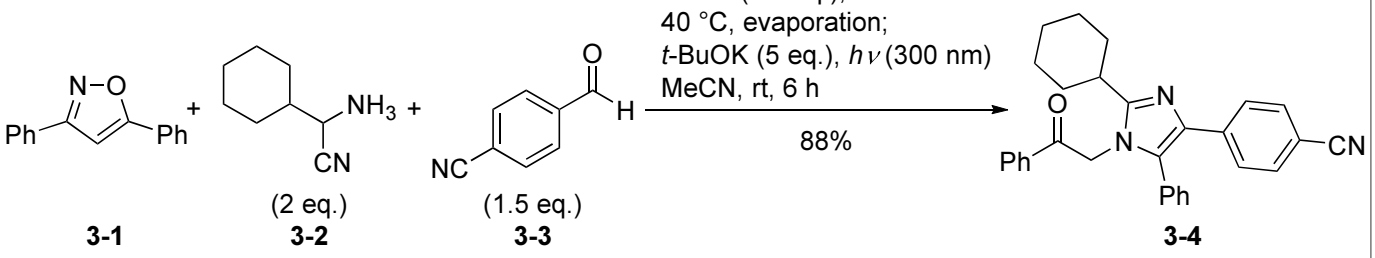
2-2. DFT calculation[10b)]

DFT B3LYP/6-31G(d), 298 K, CH_2Cl_2 (PCM)



10) (a) equilibrium between 3-imino-2-en-1-one and oxazine species can be affected by substituents of imino carbon: Kashima, K.; Tsuda, Y.; Imada, S.; Nishio, T. *J. Chem. Soc. Perkin Trans. 1* **1980**, 1866. (b) Khlebnikov, A. F.; Novikov, M. S.; Gorbunova, Y. G.; Galenko, E. E.; Mikhailov, K. I.; Pakalnis, V. V.; Avdontceva, M. S.; *Beilstein J. Org. Chem.* **2014**, *10*, 1896.

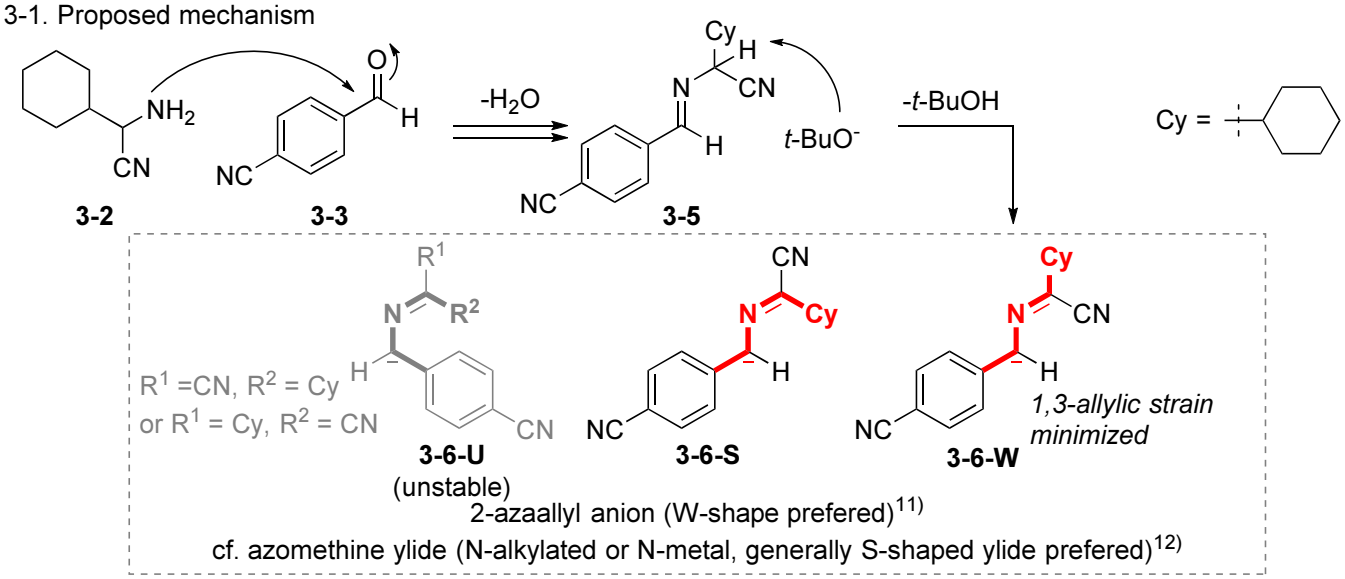
3.



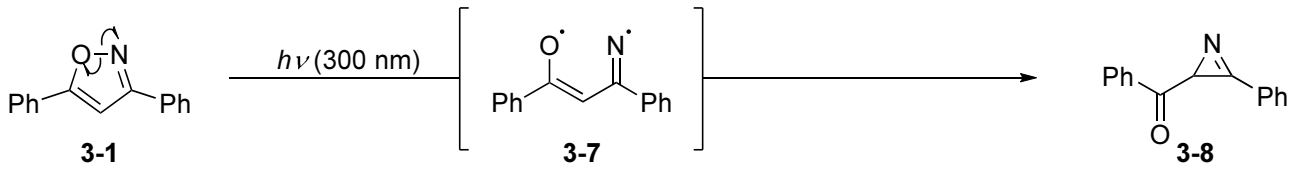
3-1 **3-2** **3-3** **3-4**

Pusch, S.; Opatz, T. *Org. Lett.* **2014**, *16*, 5430.

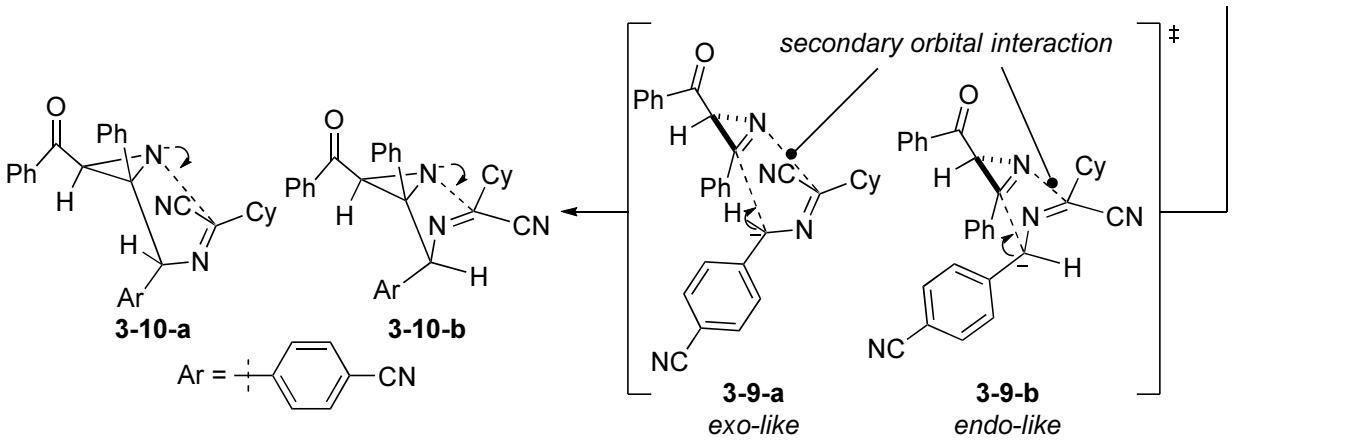
3-1. Proposed mechanism



3-2 **3-3** **3-5** **3-6-U** (unstable) **3-6-S** **3-6-W**



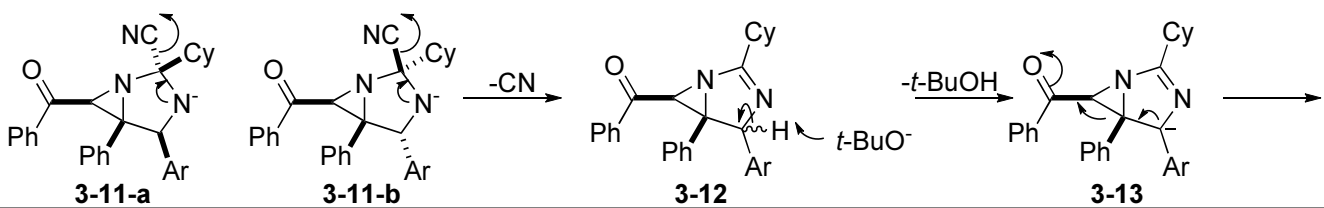
3-1 **3-7** **3-8**



3-10-a **3-10-b** **3-9-a** *exo-like* **3-9-b** *endo-like*

*cycloaddition of 2-azaallyl anion: "borderline" of stepwise/concerted*11a)

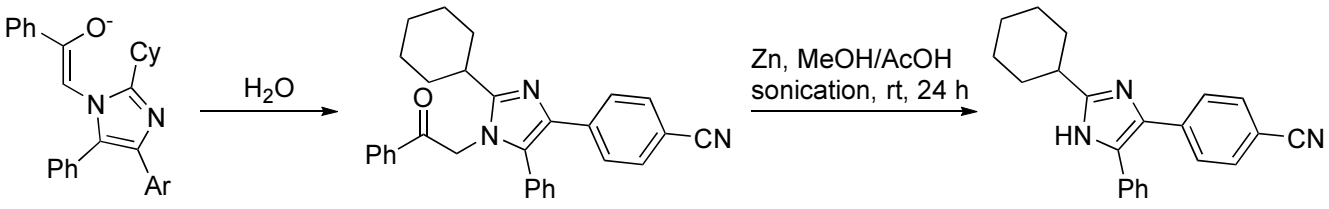
5-endo-trig (disfavored according to Baldwin's rules, "aborted" [2,3]-sigmatropic shift)



3-11-a **3-11-b** **3-12** **3-13**

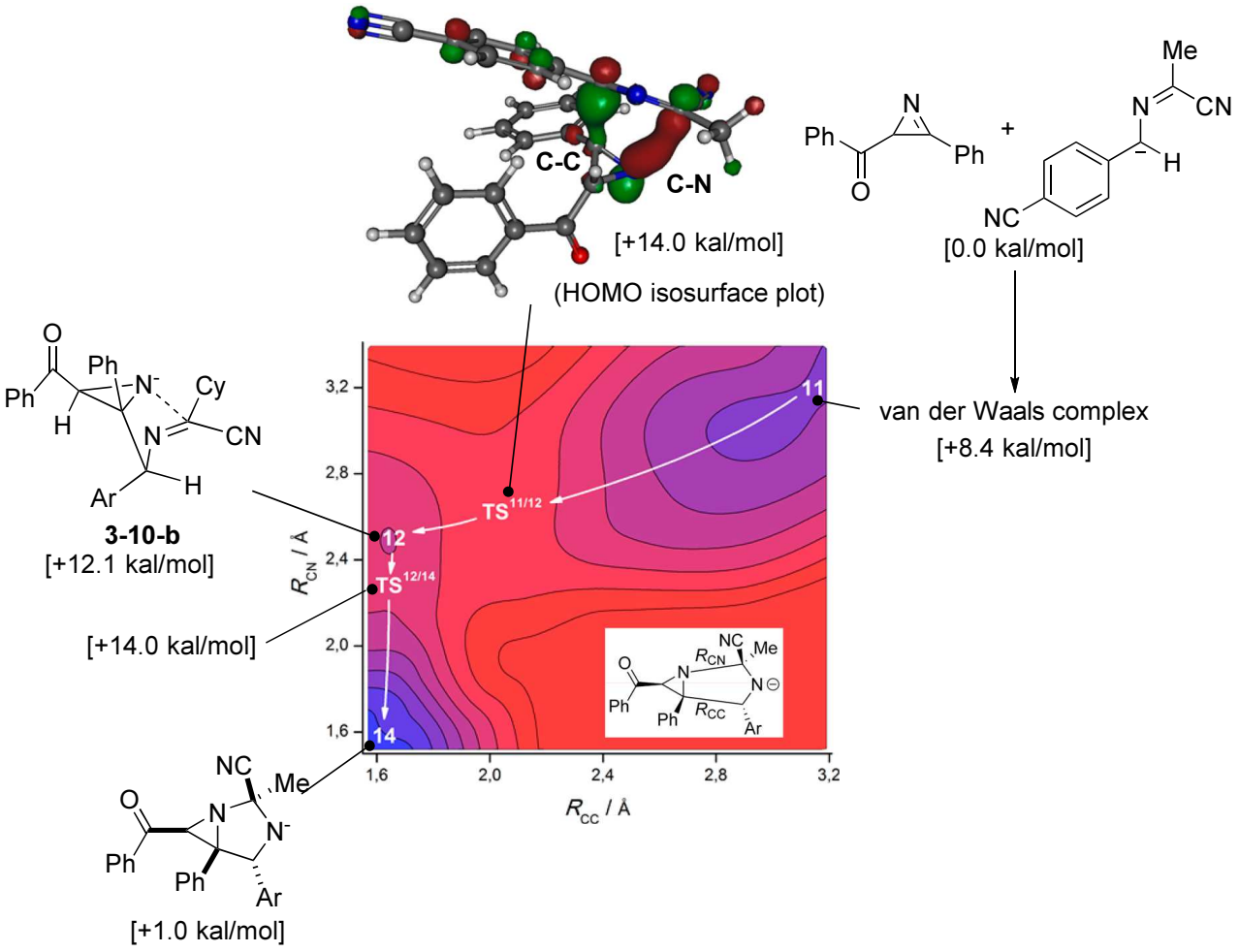
11) (a) Pearson, W. H.; Stoy, P. *Synlett* **2003**, 903. (b) Kauffmann, T.; Habersaat, K.; Köppelmann, E. *Angew. Chem., Int. Ed.* **1972**, *11*, 291.

12) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765.

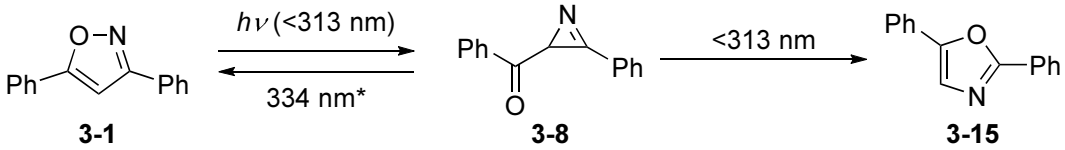


3-14 **3-4** **3-4'**

3-2. DFT calculation
(ORCA program package, PW6B95/ma-def2-SVP, 298 K)



3-3. Photoisomerization of isoxazole to oxazole[13)]

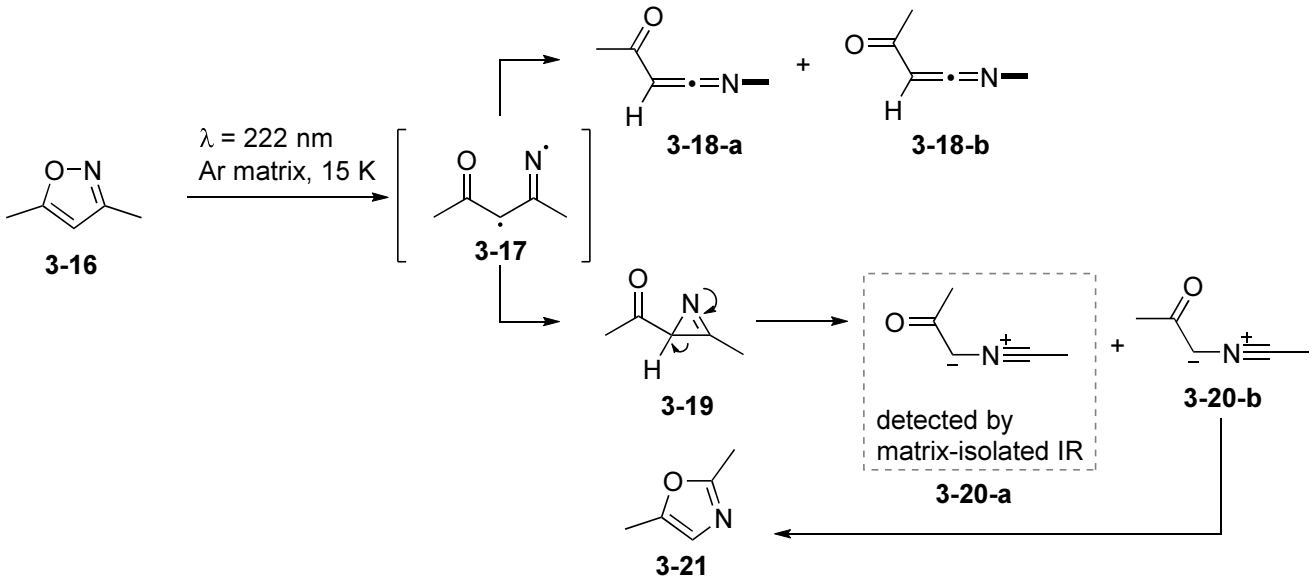


3-1 **3-8** **3-15**

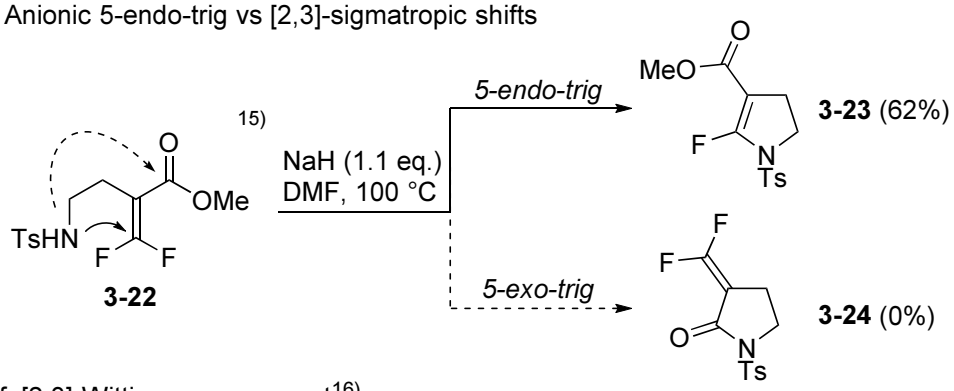
*isoxazole UV absorption drops off between 313 and 334 nm

13) Singh, B.; Ullman, E. F. *J. Am. Chem. Soc.* **1967**, *89*, 6911.

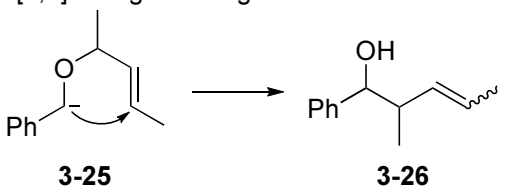
3-4. Matrix-isolated IR analysis of oxazole-isoxazole photoisomerization[14)]



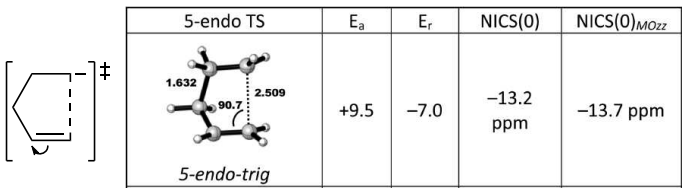
3-5. Anionic 5-endo-trig vs [2,3]-sigmatropic shifts



cf. [2,3]-Wittig rearrangement[16)]



17)

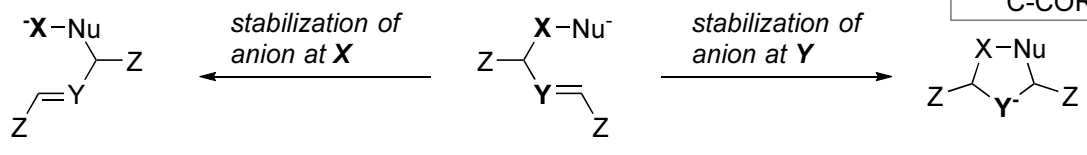


geometry: M05-2X/6-31+G**
NICS[18)]: PW91/IGLOIII

Electronic effect

electronegativity
Y = N
conjugation with EWG
Y = C-NO_2
C-SO_2R
C-COR

(kcal/mol) (kcal/mol)



[2,3]-Wittig rearrangements

Nu = CR_2, NR, O
X = CR_2, NR, O
Z = F, NR_2, OR

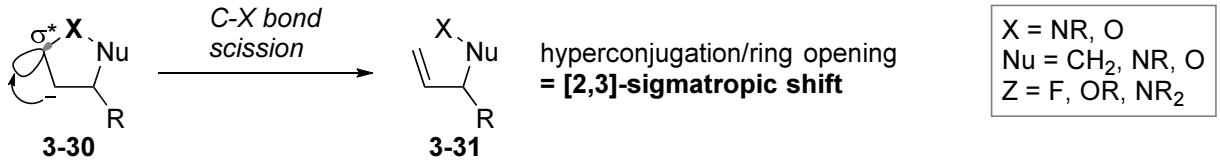
5-endo-trig
(disfavored according to Baldwin's rules)

"aborted" pericyclic reactions[17)]

14) Nune, C. M.; Reva, I.; Fausto, R. *J. Org. Chem.* **2013**, *78*, 10657.
15) Ichikawa, J.; Fujiwara, M.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun.* **2000**, 1887.
16) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.
17) Gilmore, K.; Manoharan, M.; Wu, J. I.; Schleyer, P. v. R.; Alabugin, I. V. *J. Am. Chem. Soc.* **2012**, *134*, 10584.
18) For a review, see: Chen, Z.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. R. *Chem. Rev.* **2005**, *105*, 3842.

Hyperconjugative stabilization

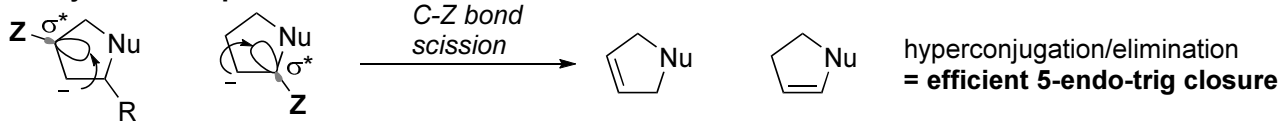
X = endocyclic σ-acceptor



3-30 **3-31**

n(C) to σ*(C-X)

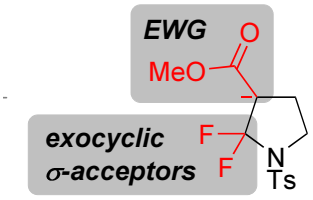
Z = exocyclic σ-acceptor



3-32-a **3-32-b** **3-33-a** **3-33-b**

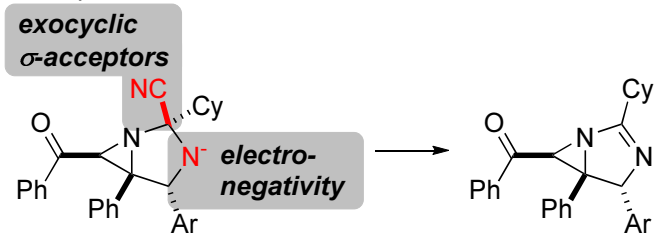
n(C) to σ*(C-Z)

Case1: ref 15



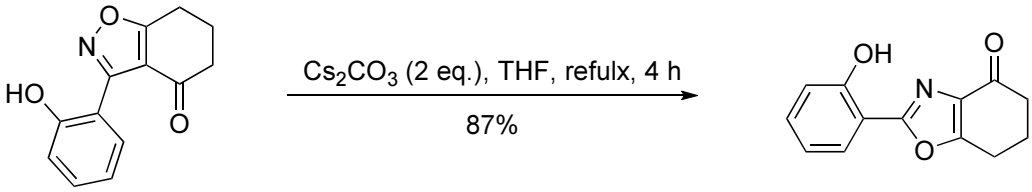
3-34 **3-23**

Case 2: problem 3



3-11-b **3-35**

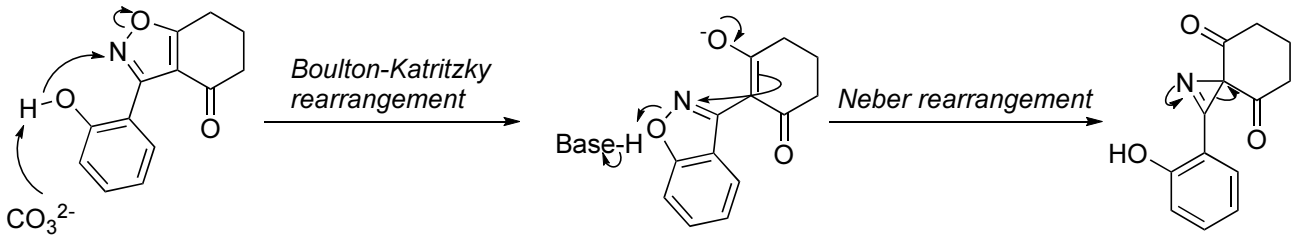
4.



4-1 **4-2**

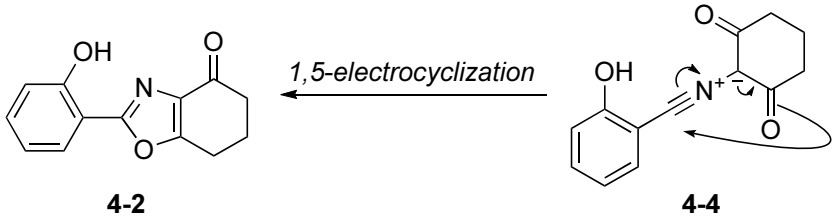
Jones, R. C. F.; Chatterley, A.; Marty, R.; Owton, W. M.; Elsegood, M. R. J. *Chem. Commun.* **2015**, *51*, 1112.

4-1. Proposed mechanism



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

general transformation from isoxazole to azirine:
photoreaction[13, 14] or pyrolysis[19]



4-2 **4-4**

19) Nunes, C. M.; Reva, I.; Pinho e Melo, T. M. V. D.; Fausto, R.; Šolomek, T.; Bally, T. *J. Am. Chem. Soc.* **2011**, *133*, 18911.