

Problem Session (2)

Topic: Total synthesis of tetrodotoxin

Introduction:

Biological activity:

·Analgesic effect by blocking the voltage-gated sodium channels (clinical trials are currently underway)

Structure:

·Tetracyclic skeleton with a tricyclic orthoester (a dioxadamantane core)

·Cyclic guanidine moiety

·Highly oxidized (8 oxygen atom per 11 carbon atom)

Total synthesis:

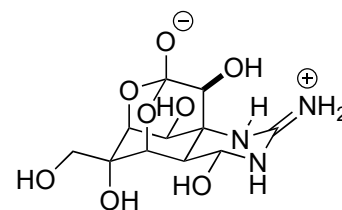
·First total synthesis of (±)-tetrodotoxin by Kishi's group in 1972

(*J. Am. Chem. Soc.* **1972**, *94*, 9217.)

·First asymmetric total synthesis by Isobe's group in 2003

(*J. Am. Chem. Soc.* **2003**, *125*, 8798.)

(More information: 130803_LS_Ken_MUKAI, 170930_LS_Takahiro_Watanabe)



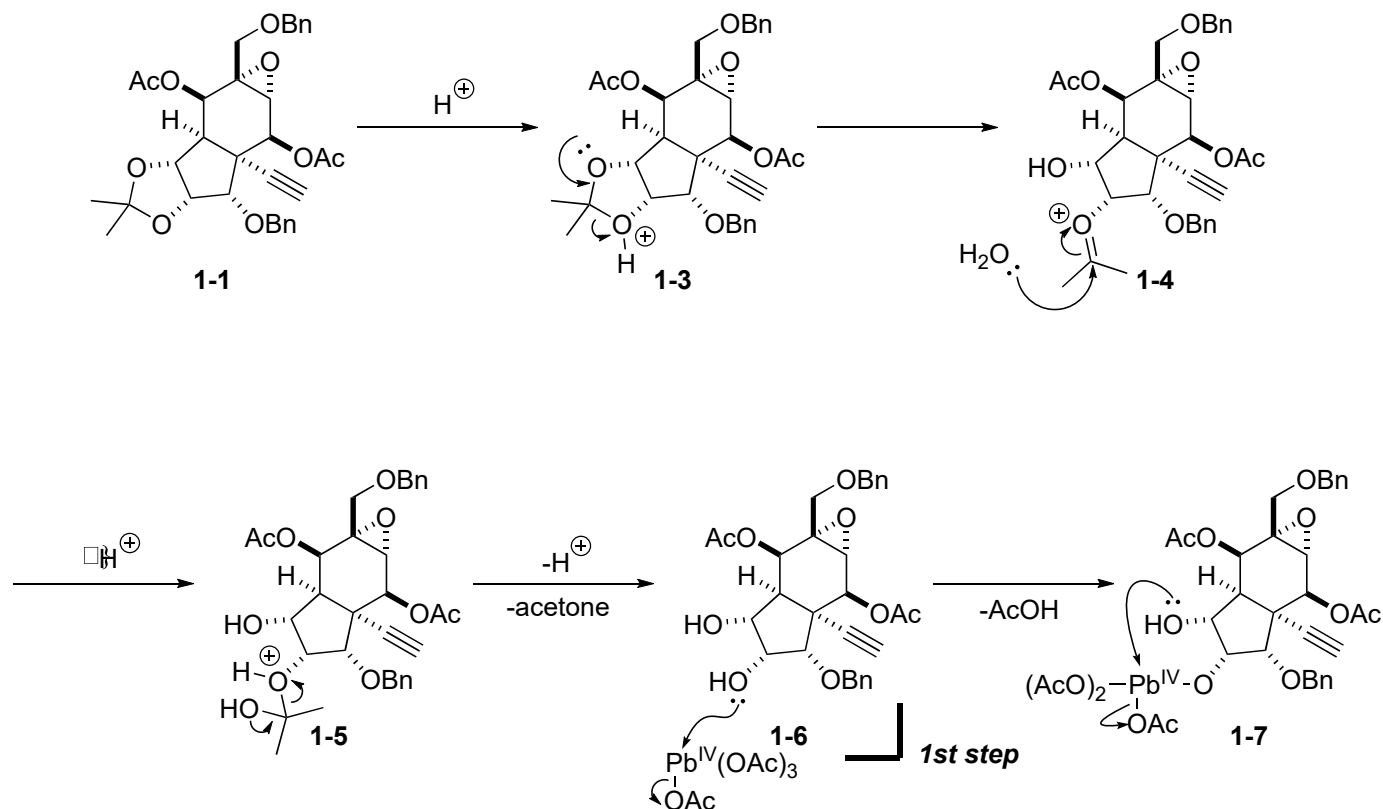
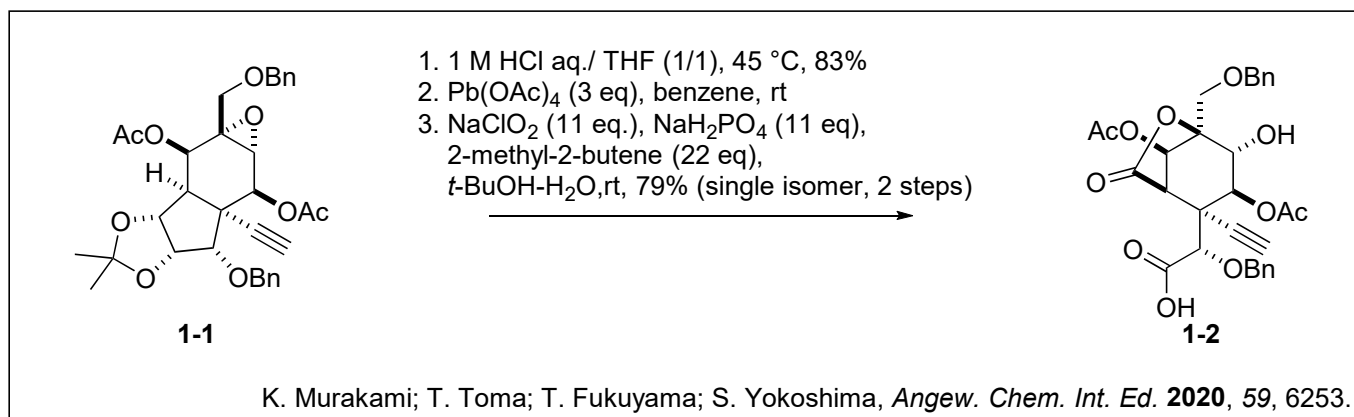
tetrodotoxin

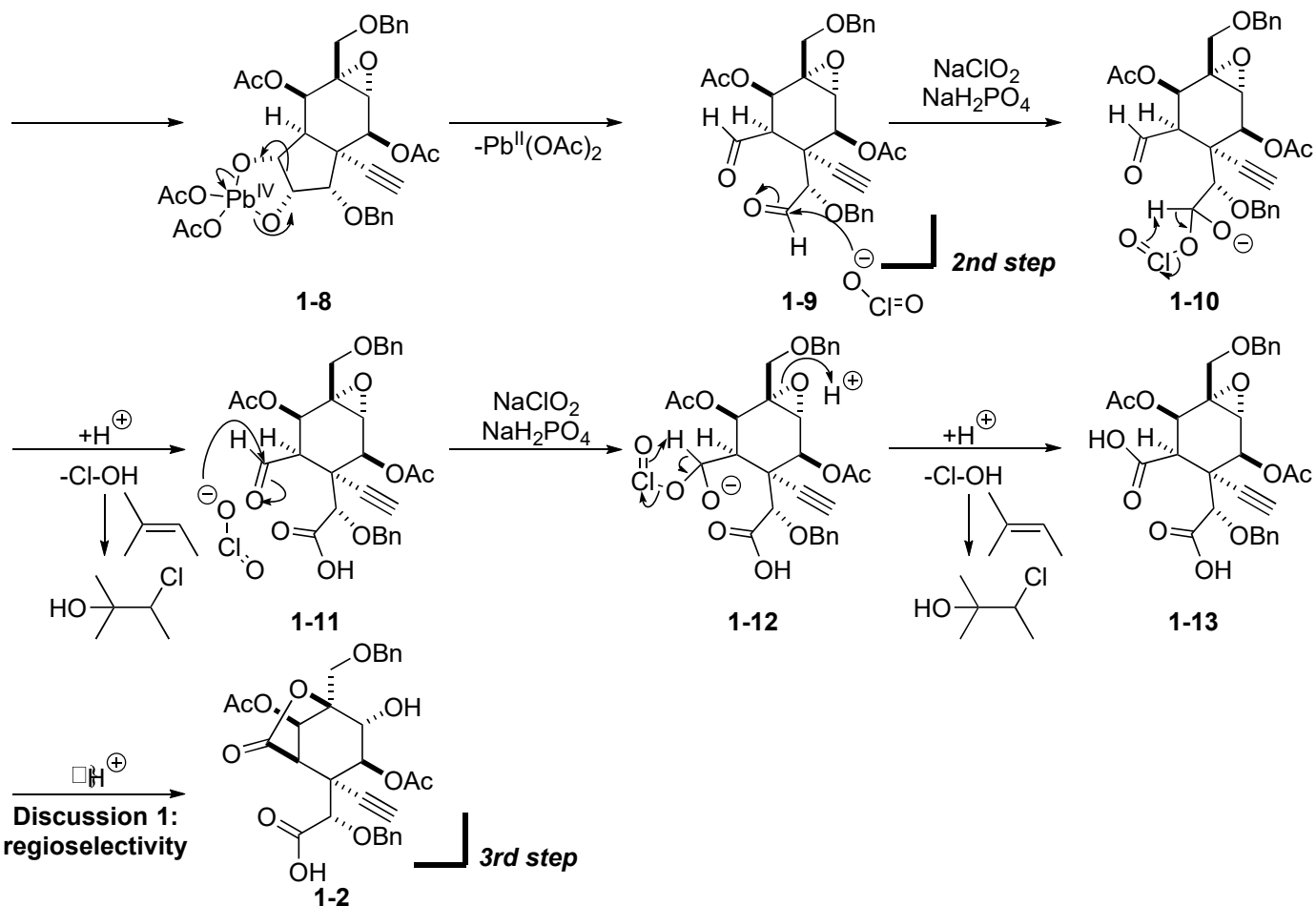
Chemical Formula: $C_{11}H_{17}N_3O_8$

Answer:

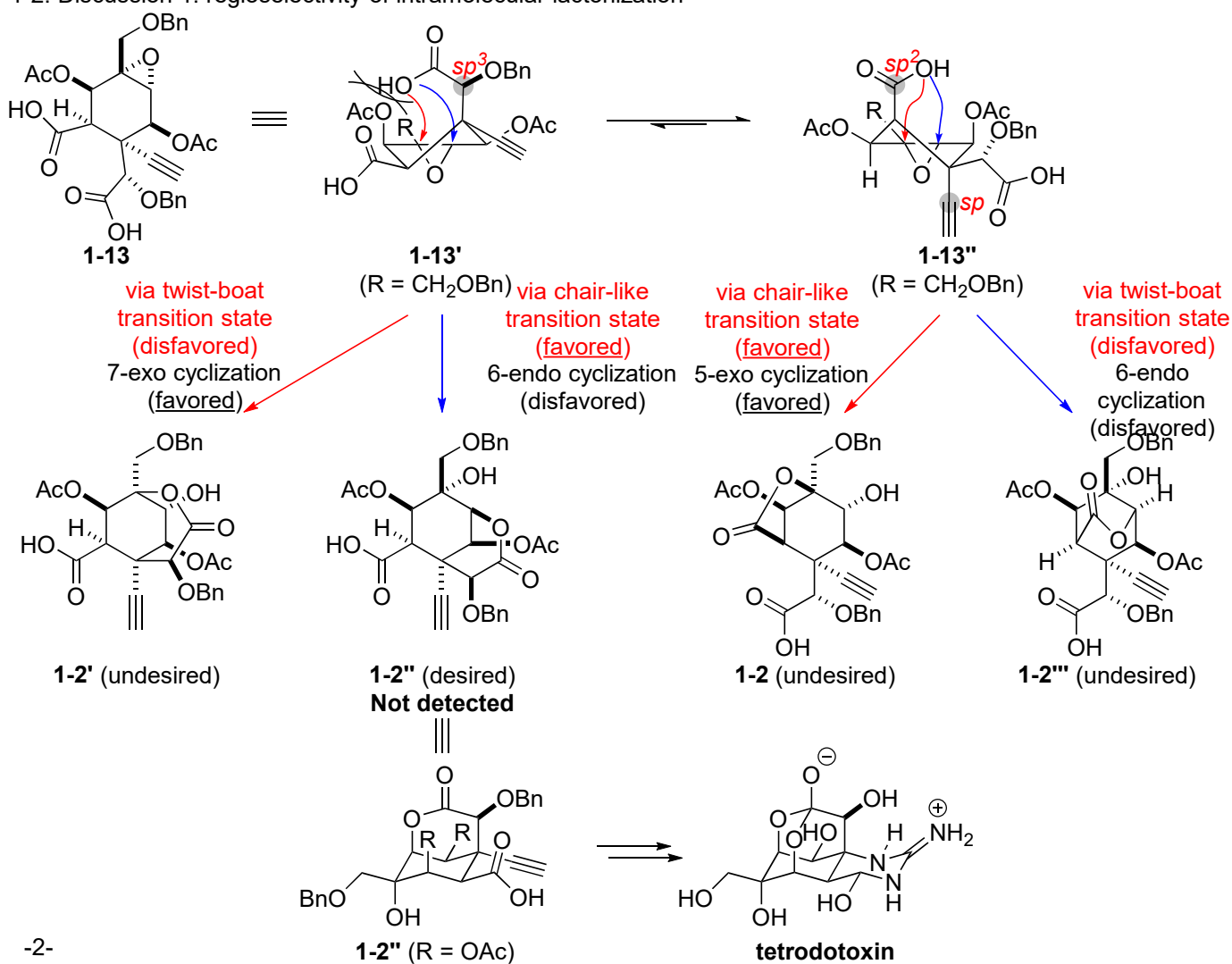
1. First plan for total synthesis of tetradotoxin

1-1. Reaction mechanism



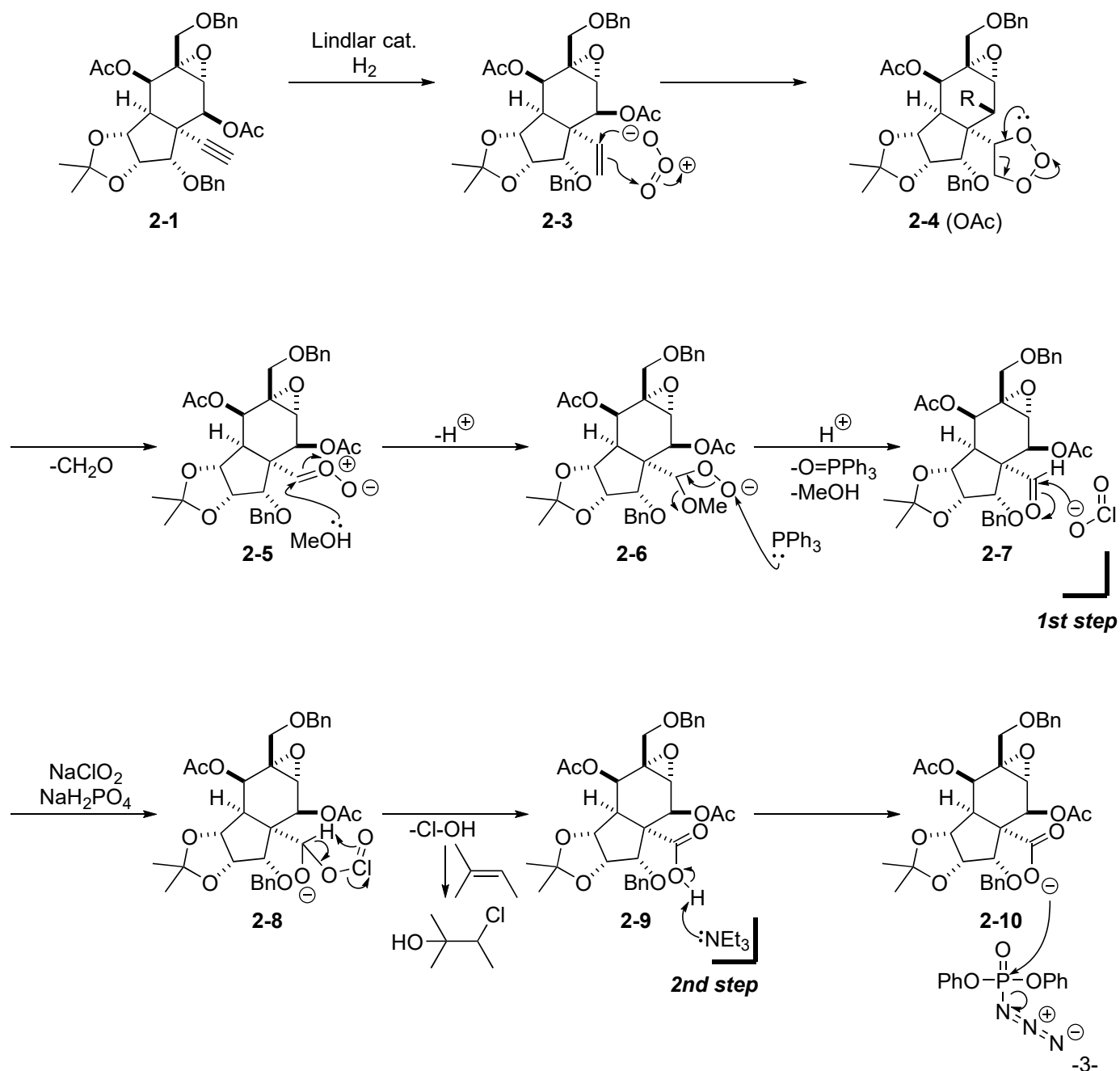
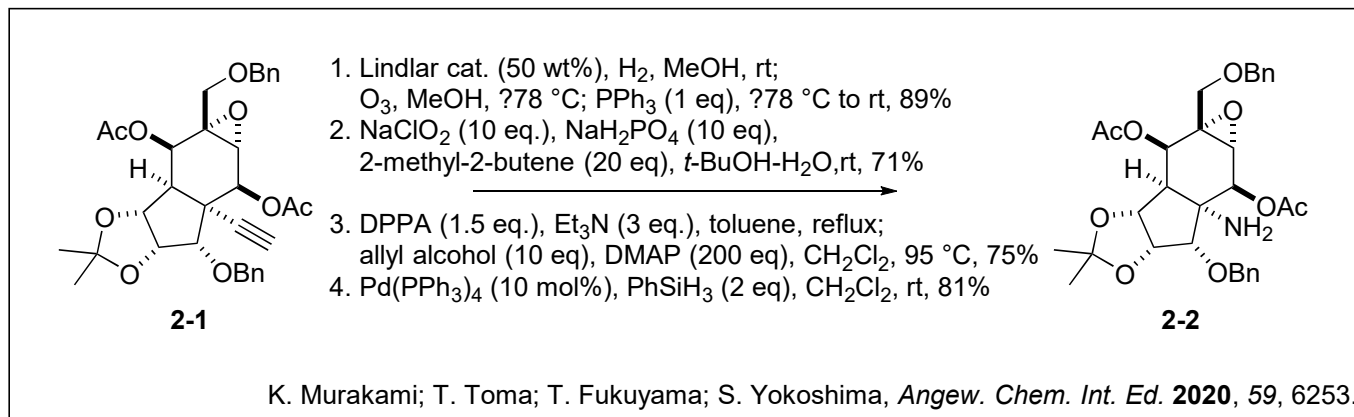


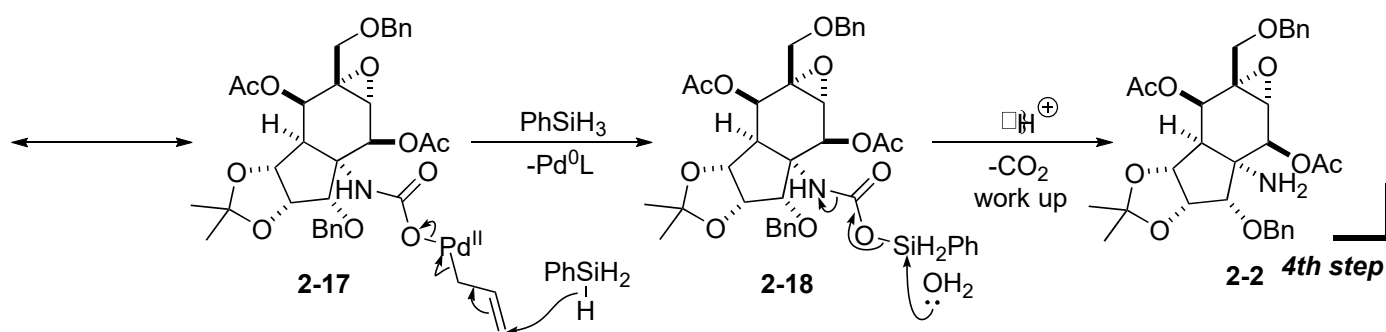
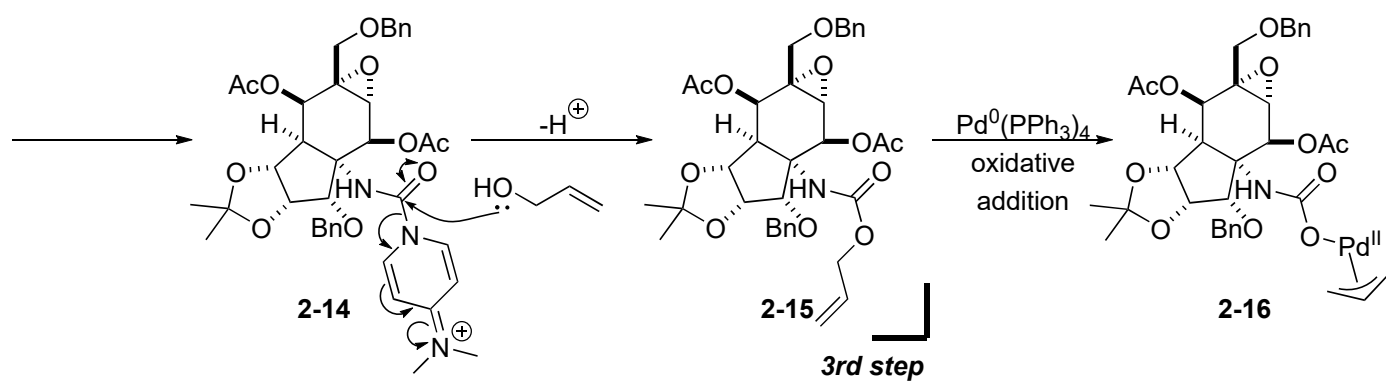
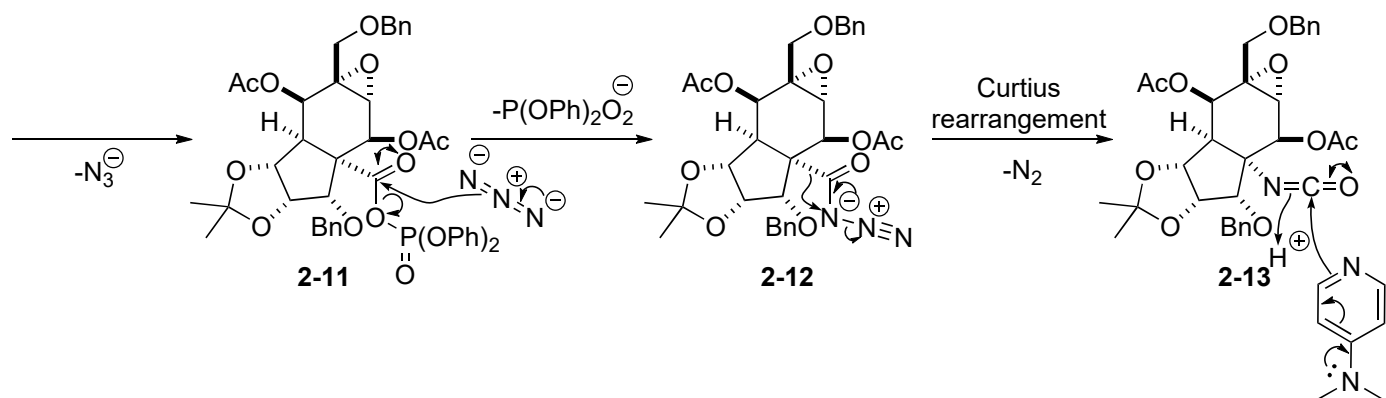
1-2. Discussion 1: regioselectivity of intramolecular lactonization



2. Second plan for total synthesis of tetrodotoxin

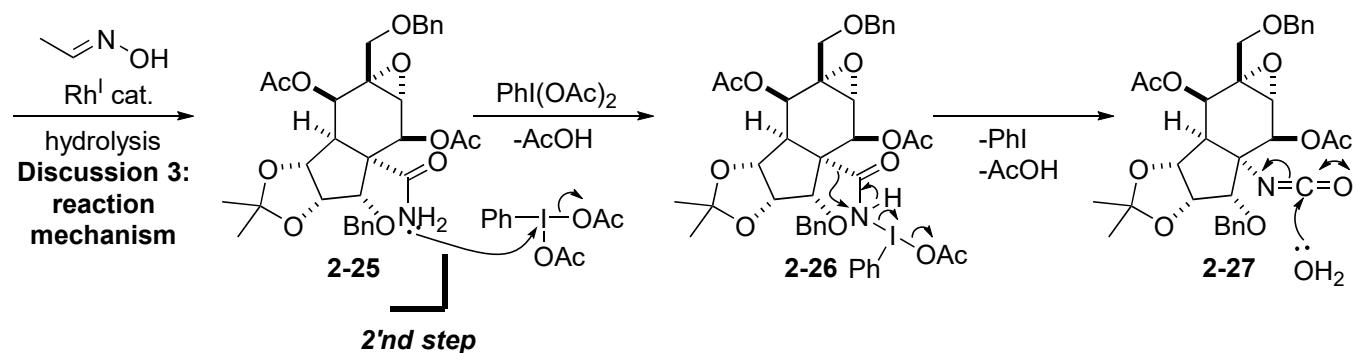
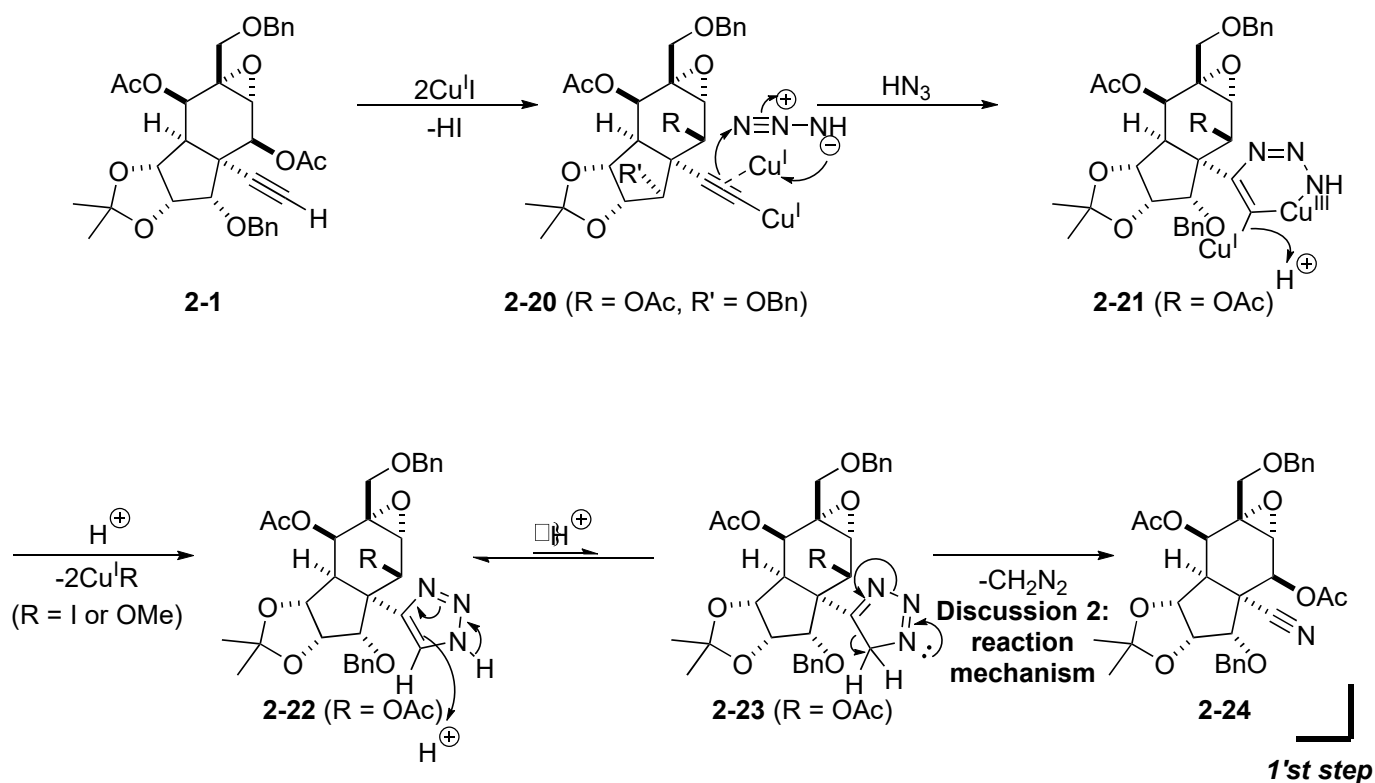
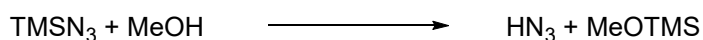
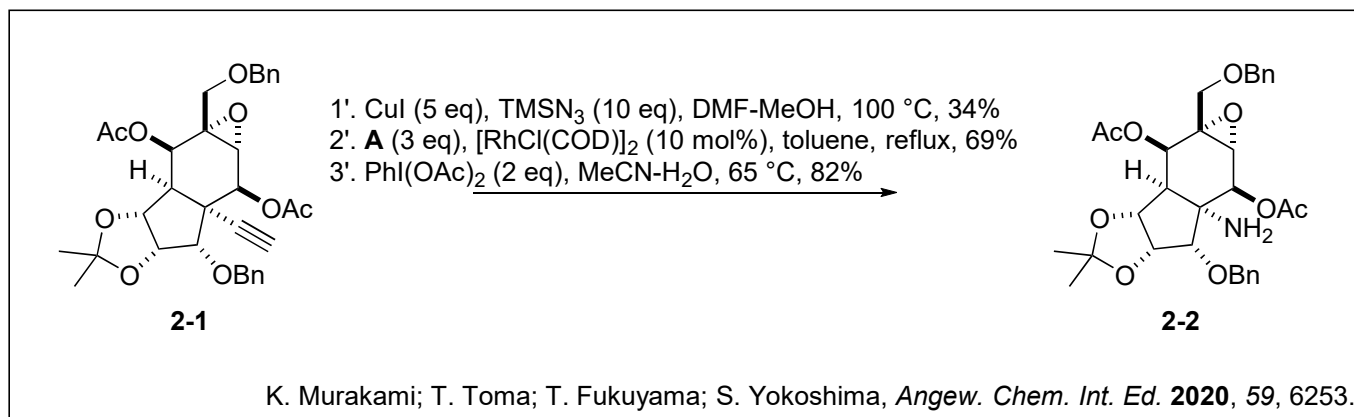
2-1. Reaction mechanism 1

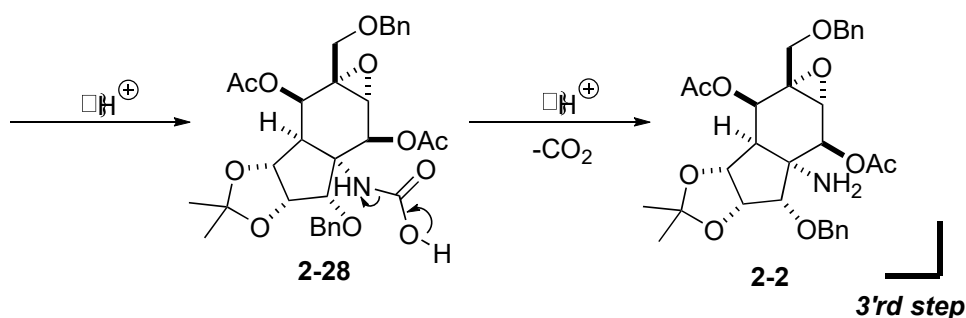




2. Second plan for total synthesis of tetrodotoxin

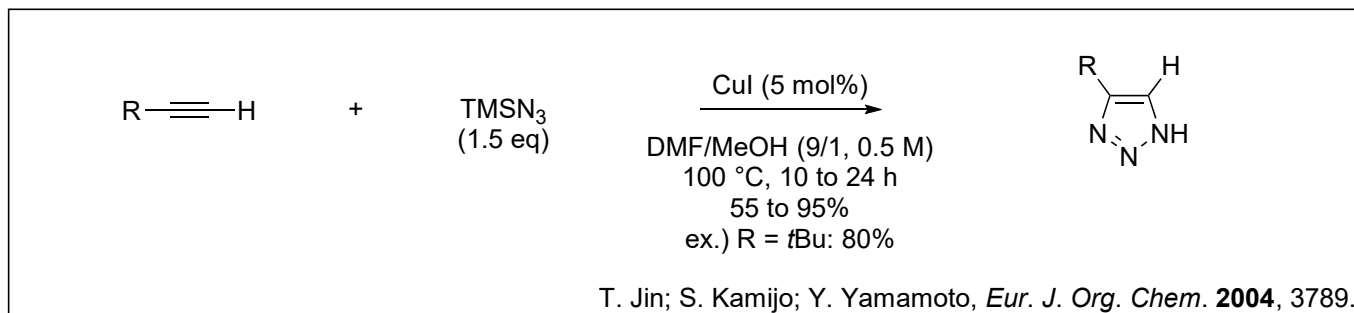
2-2. Reaction mechanism 2



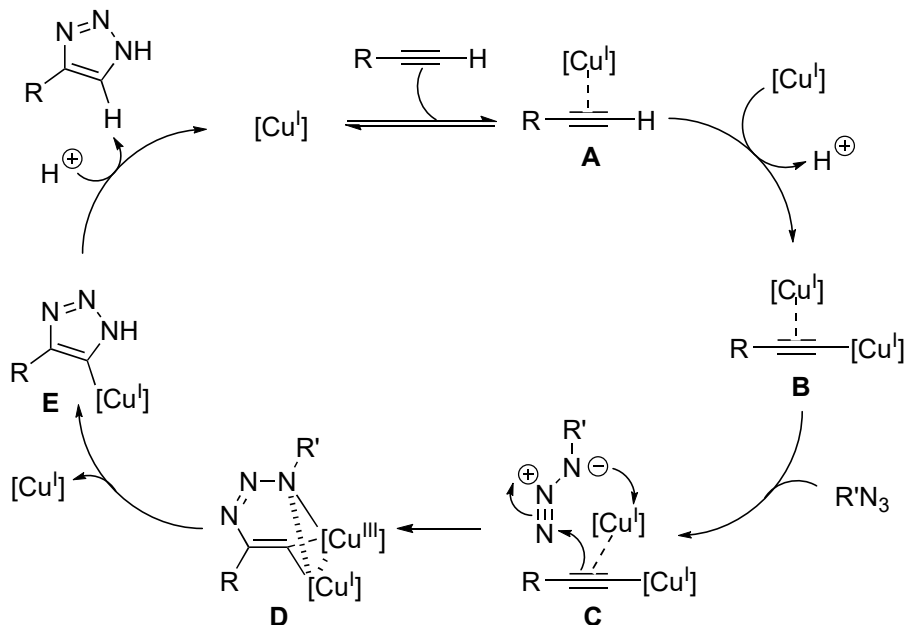


2-3. Discussion 2: Reaction mechanism of cyano formation from ethynyl group

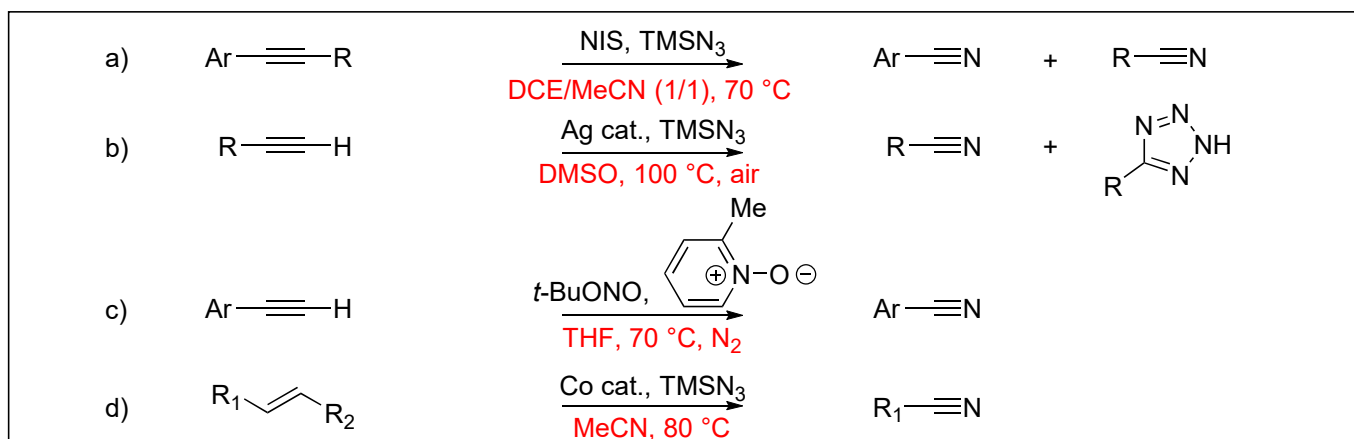
2-3-1. CuAAC (Cu^I -catalyzed azide-alkyne cycloaddition)¹⁾



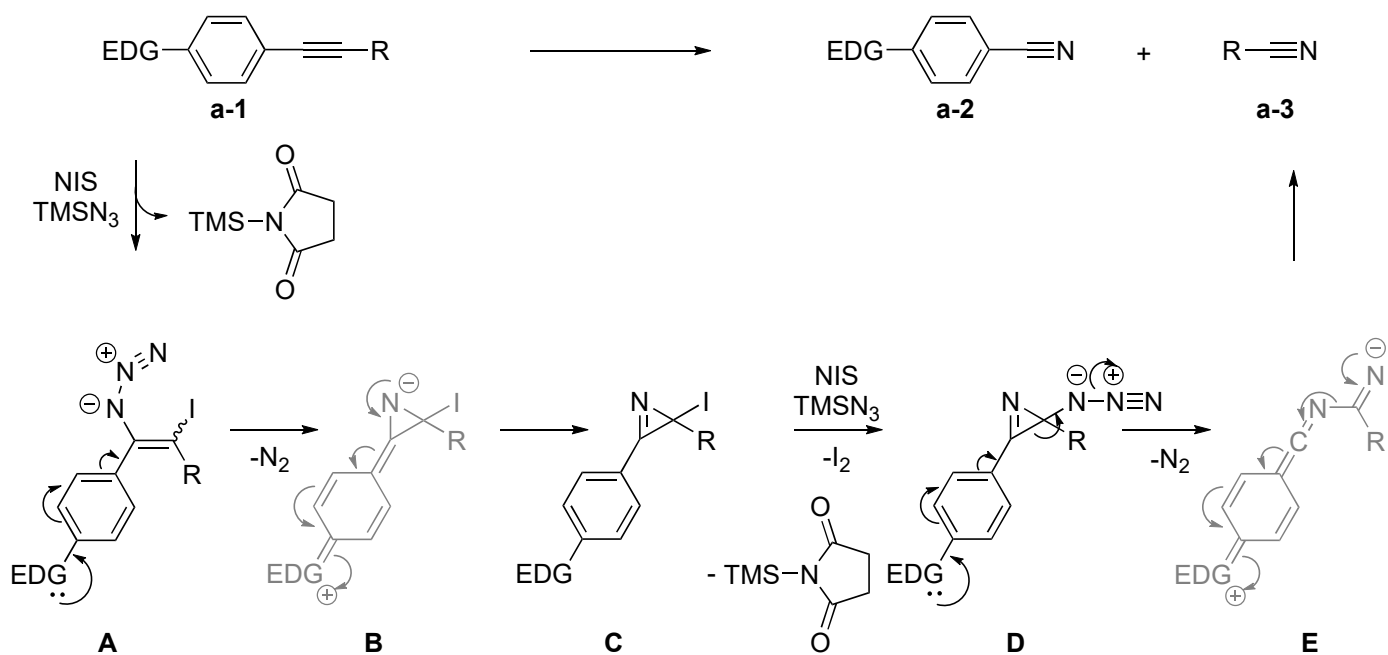
Proposed mechanism of CuAAC²⁾



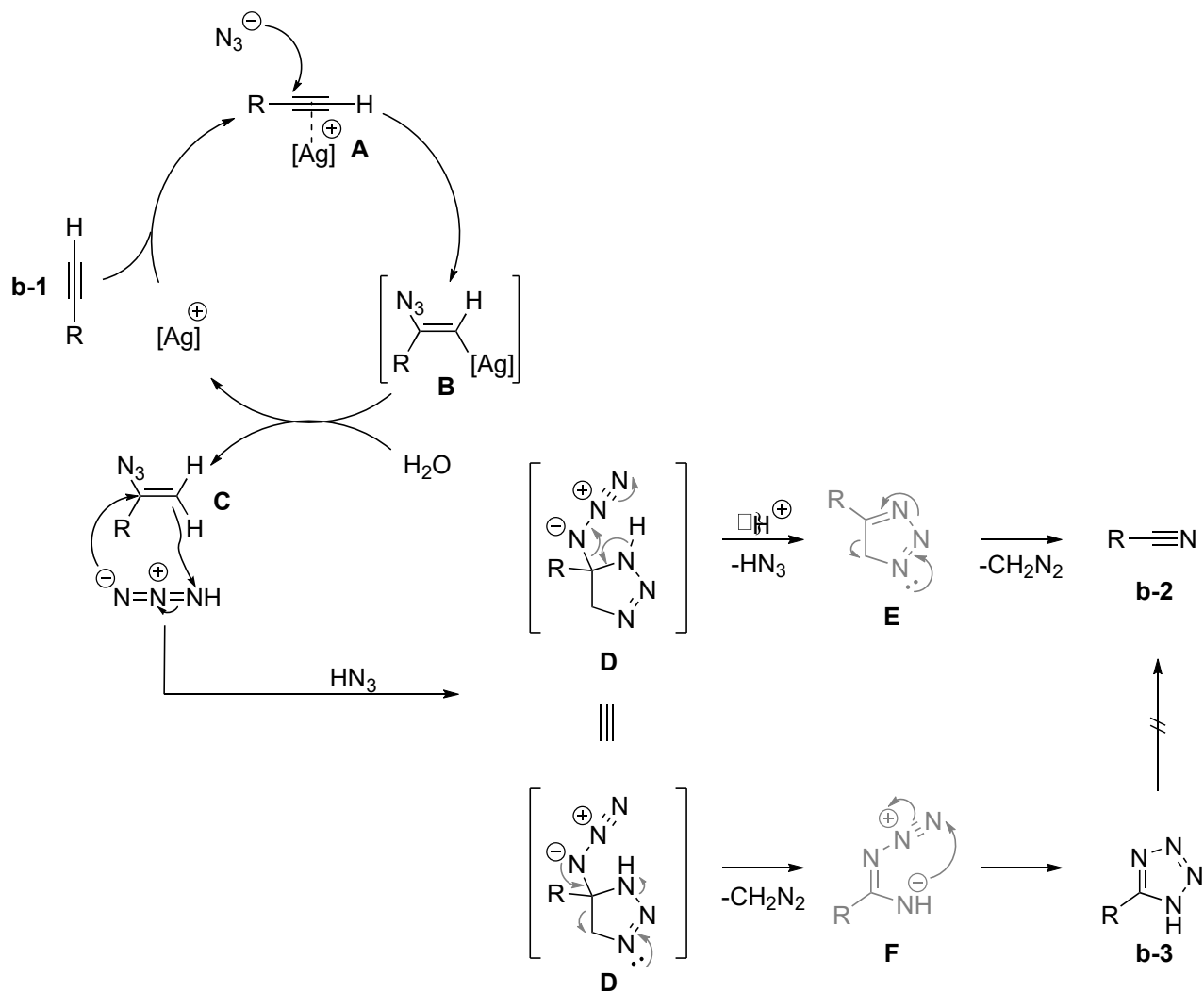
2-3-2. Cyano formation reaction under other reaction conditions



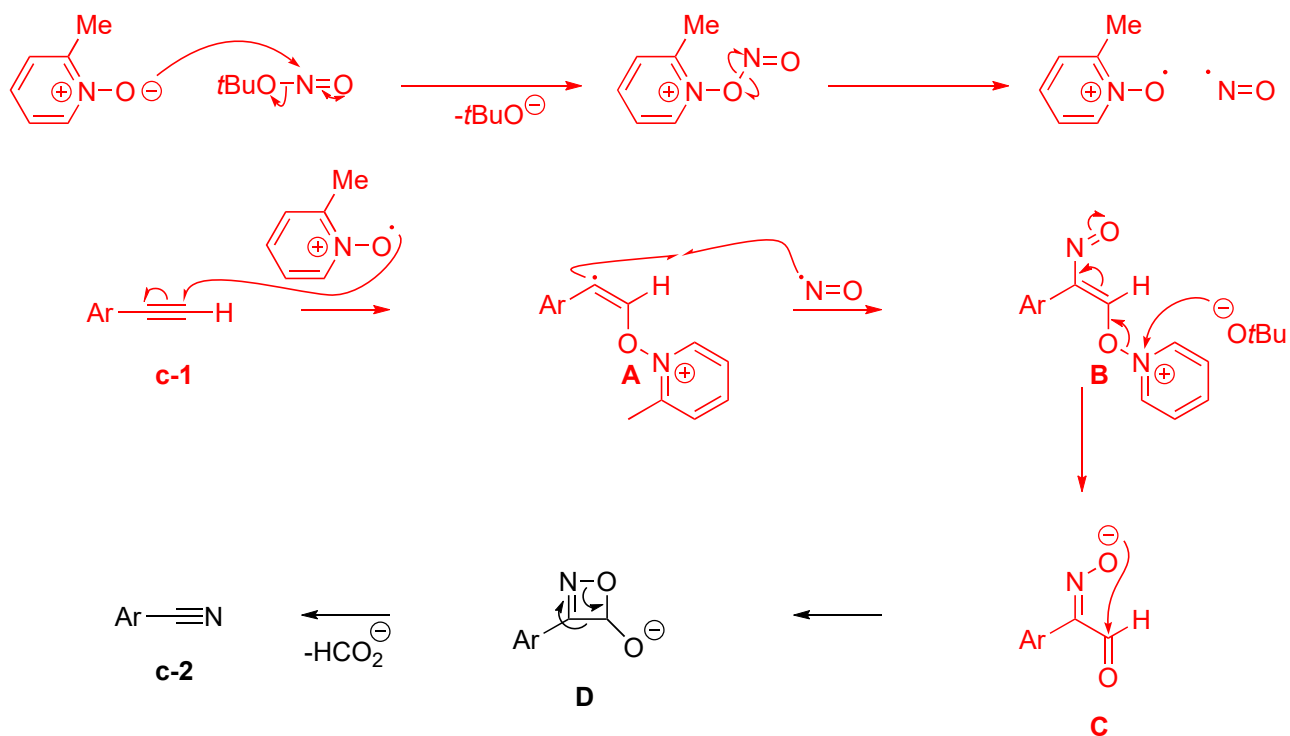
Proposed mechanism of reaction a) in journal³⁾



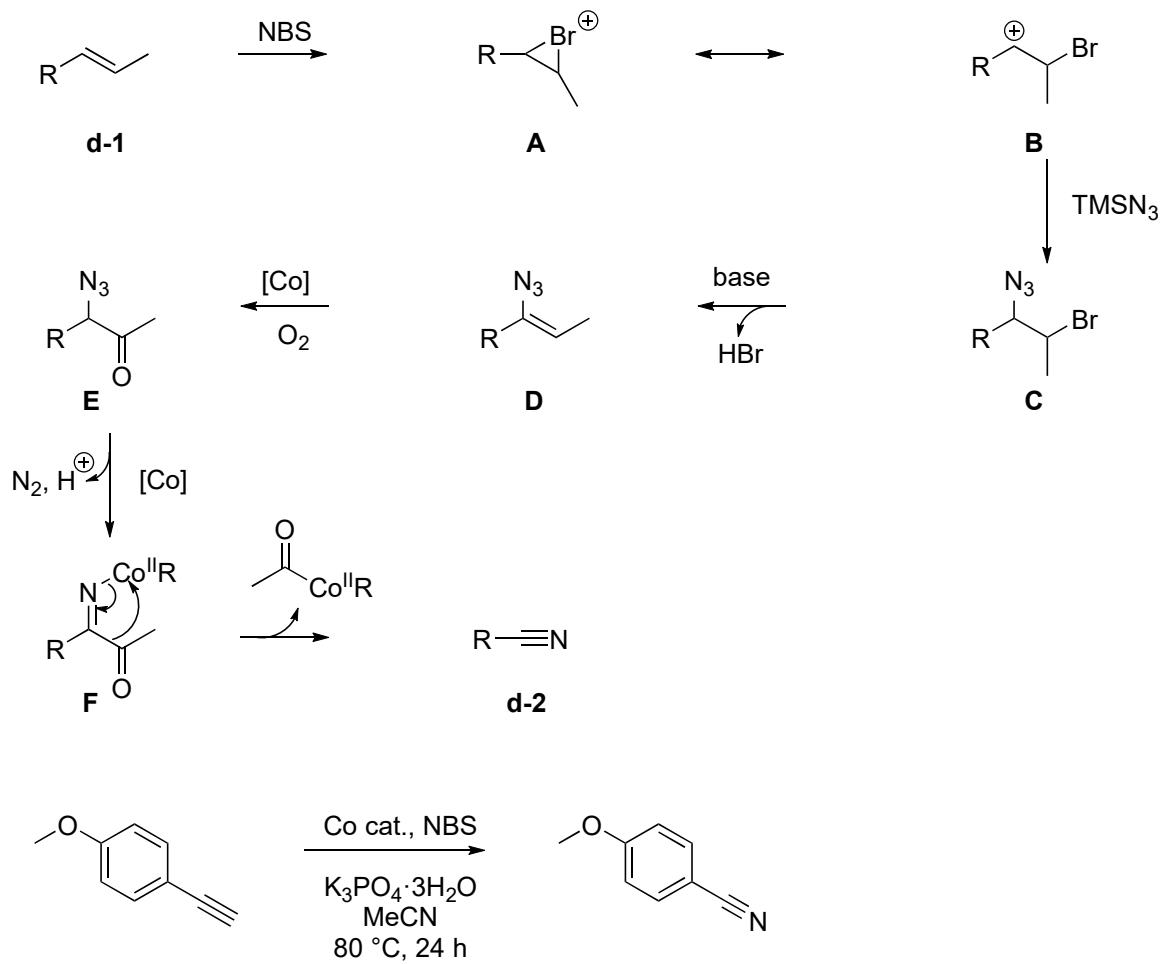
Proposed mechanism of reaction b) in journal⁴⁾



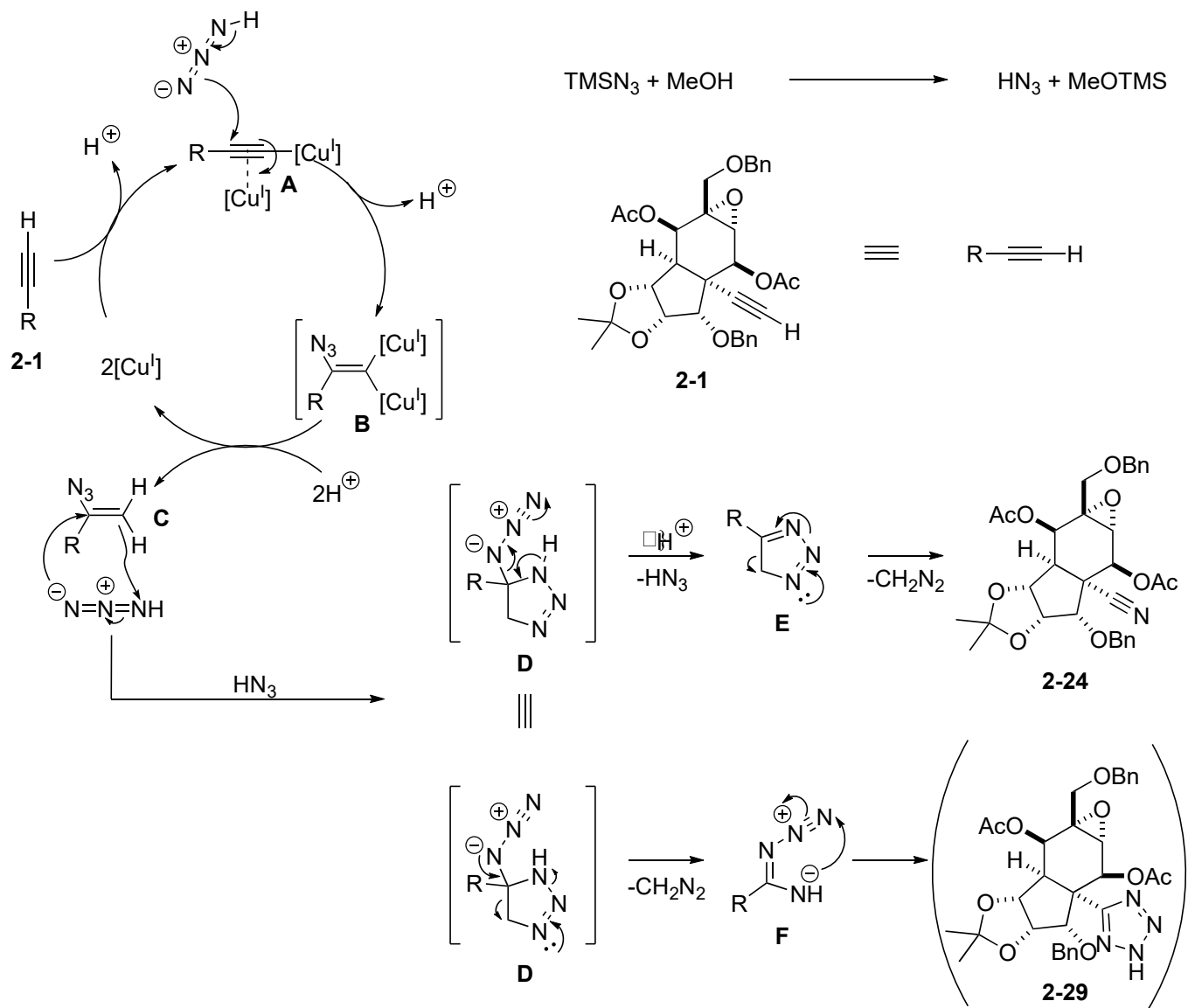
Proposed mechanism of reaction c)⁵⁾



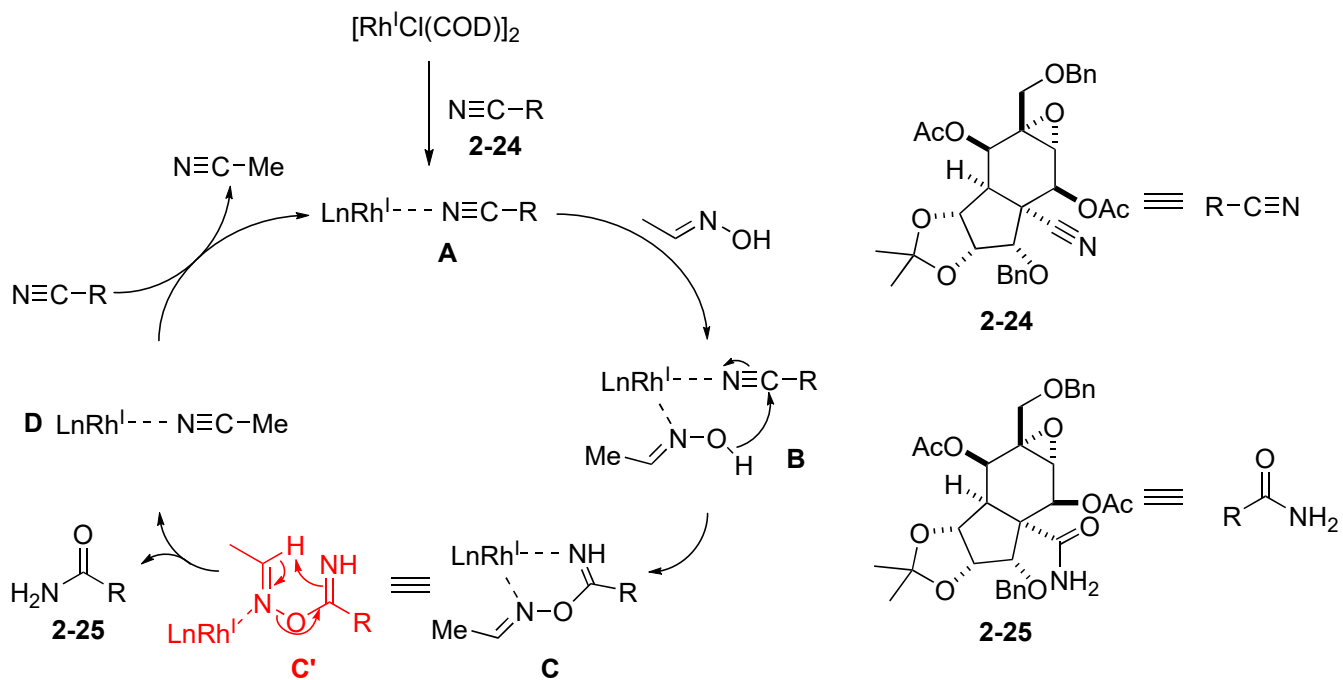
Proposed mechanism of reaction d) in journal⁶⁾



2-3-4. Another mechanism based on reaction b) (Cu was used as a Lewis acid)



2-4. Discussion 3: Proposed reaction mechanism for hydrolysis of nitrile⁷⁾



References:

- 1) T. Jin; S. Kamijo; Y. Yamamoto, *Eur. J. Org. Chem.* **2004**, 3789.
- 2) B. T. Worrell; J. A. Malik; V. V. Fokin, *Science* **2013**, *340*, 457.
- 3) N. Okamoto; M. Ishikura; R. Yanada, *Org. Lett.* **2013**, *15*, 2571.
- 4) T. Shen; T. Wang; C. Qin; N. Jiao, *Angew. Chem.* **2013**, *125*, 6809.
- 5) U. Dutta; D.W. Lupton; D. Maiti, *Org. Lett.* **2016**, *18*, 860.
- 6) S. Xu; T. Cai; Z. Yun, *Synlett* **2016**, *27*, 221.
- 7) J. Lee; M. Kim; S. Chang; H.-Y. Lee, *Org. Lett.* **2009**, *11*, 5598.