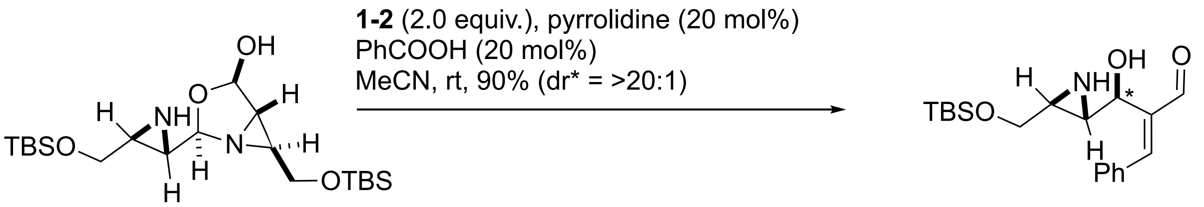
Problem Session (2)

2025/06/28 Ryo Nishikawa

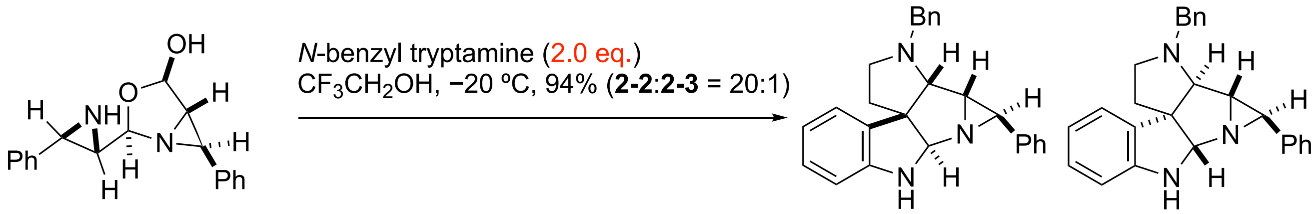
Please provide the reaction mechanism and stereoselectivity.

1



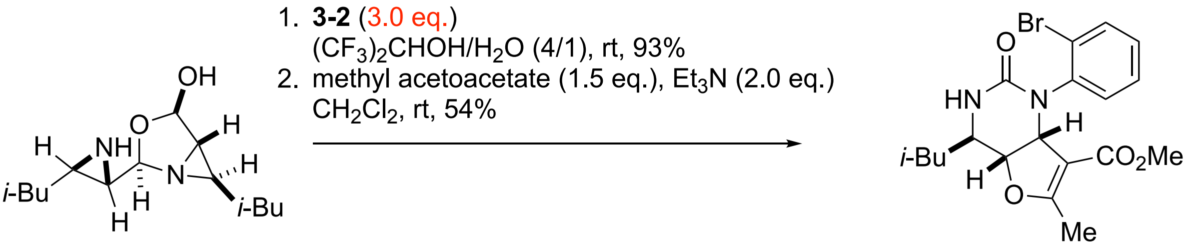
1-1 **1-3**

2

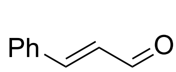


2-1 **2-2** **2-3**

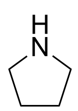
3



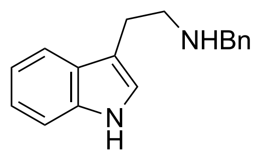
3-1 **3-3**



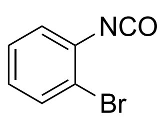
1-2



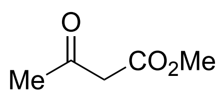
pyrrolidine



N-benzyl tryptamine



3-2



methyl acetoacetate

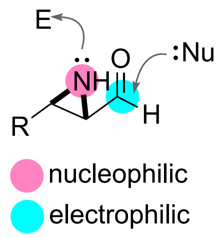
Problem Session (2) -Answer-

2025/06/28 Ryo Nishikawa

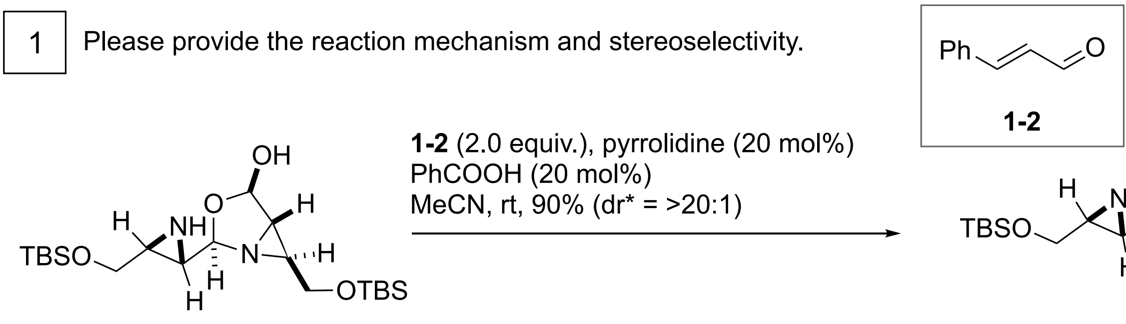
Topic: Amphoteric amino aldehyde

Introduction:

A compound that contains both nucleophilic and electrophilic sites within a single molecule is referred to as an amphoteric compound. Due to this characteristic, such compounds are considered valuable in multicomponent and tandem reactions. In this PS, I focused on the amphoteric compound that contains a nucleophilic aziridine moiety and an electrophilic aldehyde moiety within the same molecule, as shown on the right. It should be noted that all of the starting materials used in the problems are dimers of this amphoteric compound, because the amino aldehyde monomers are so unstable that they cannot be separated.

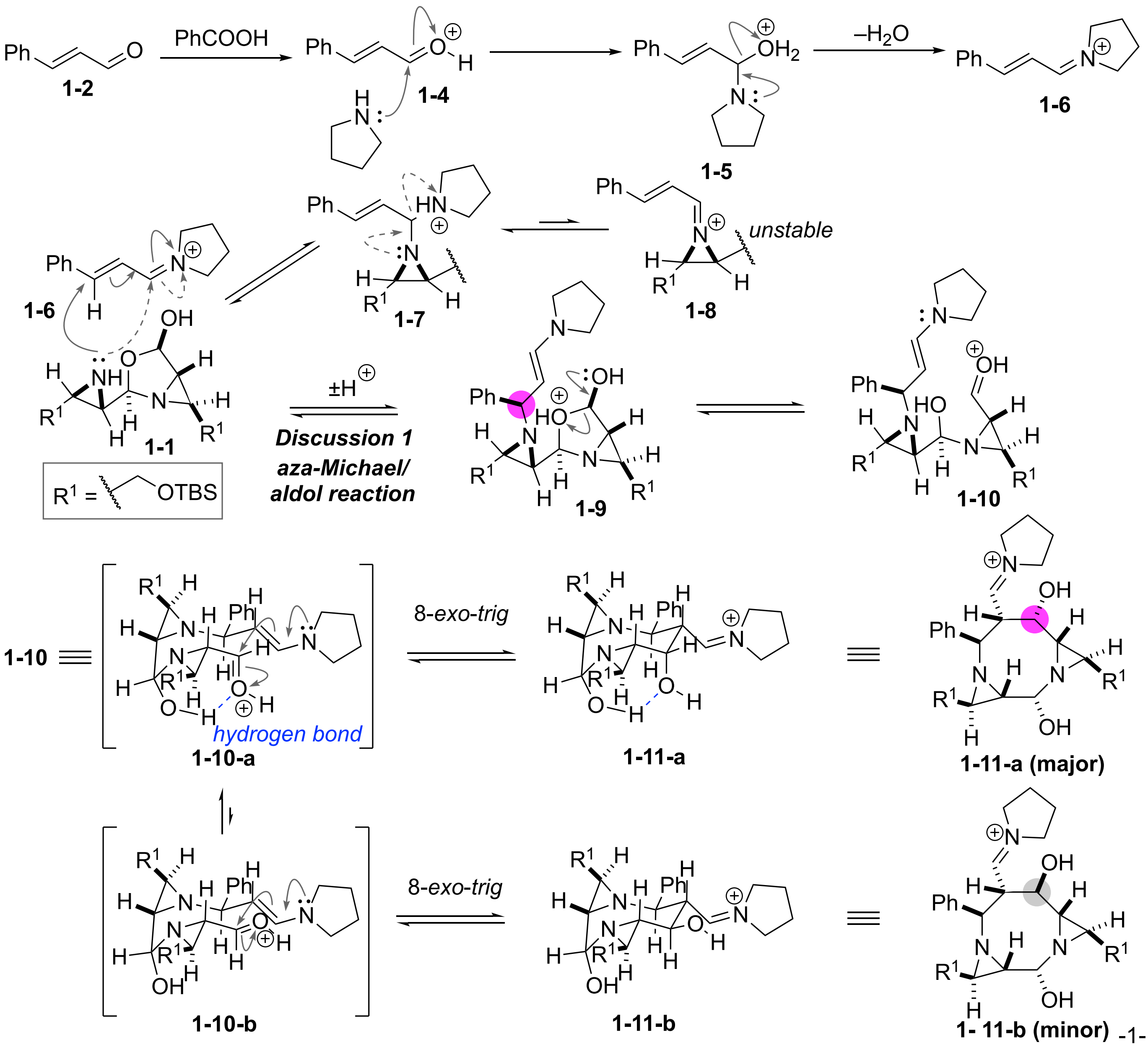


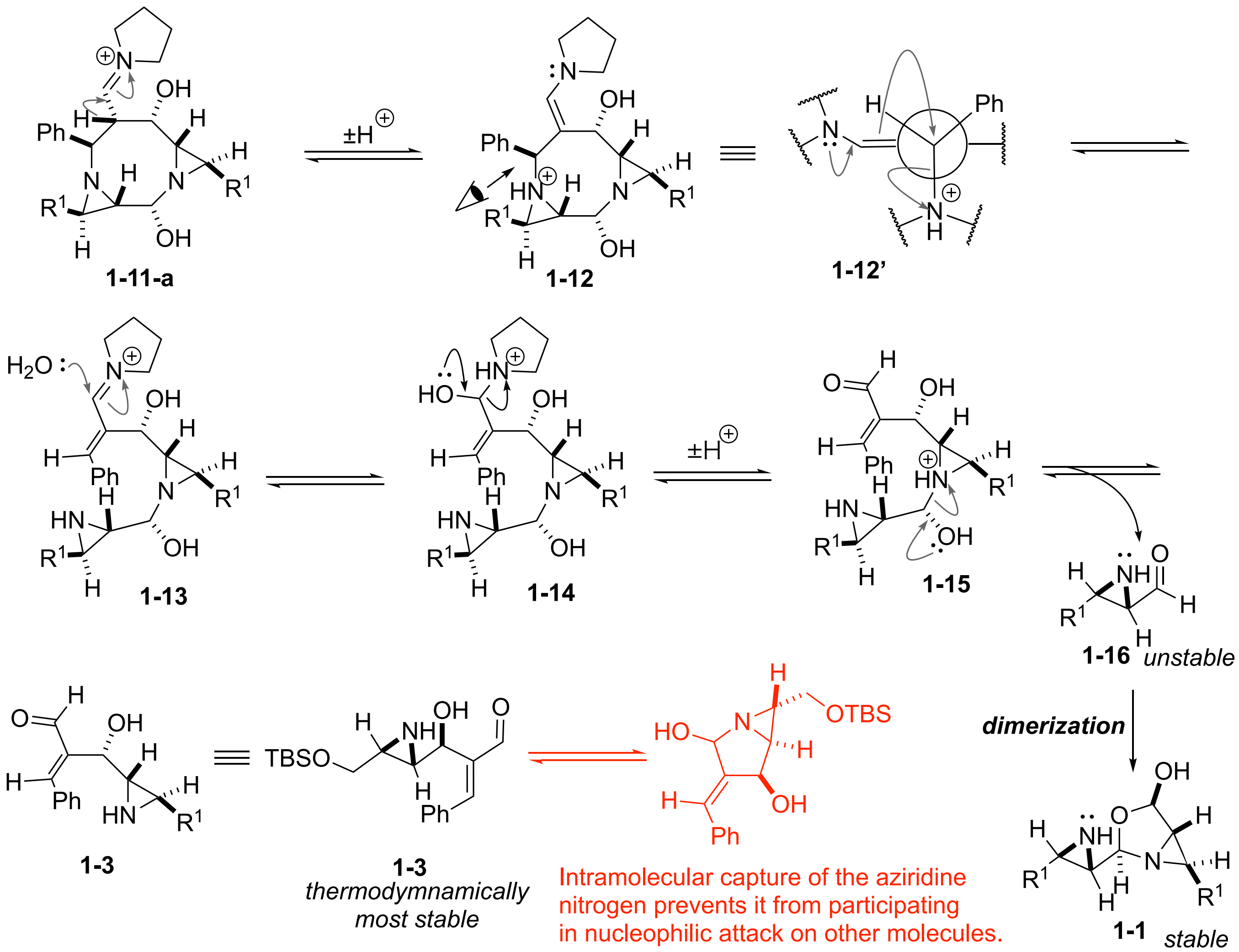
1 Please provide the reaction mechanism and stereoselectivity.



1-1 1-3

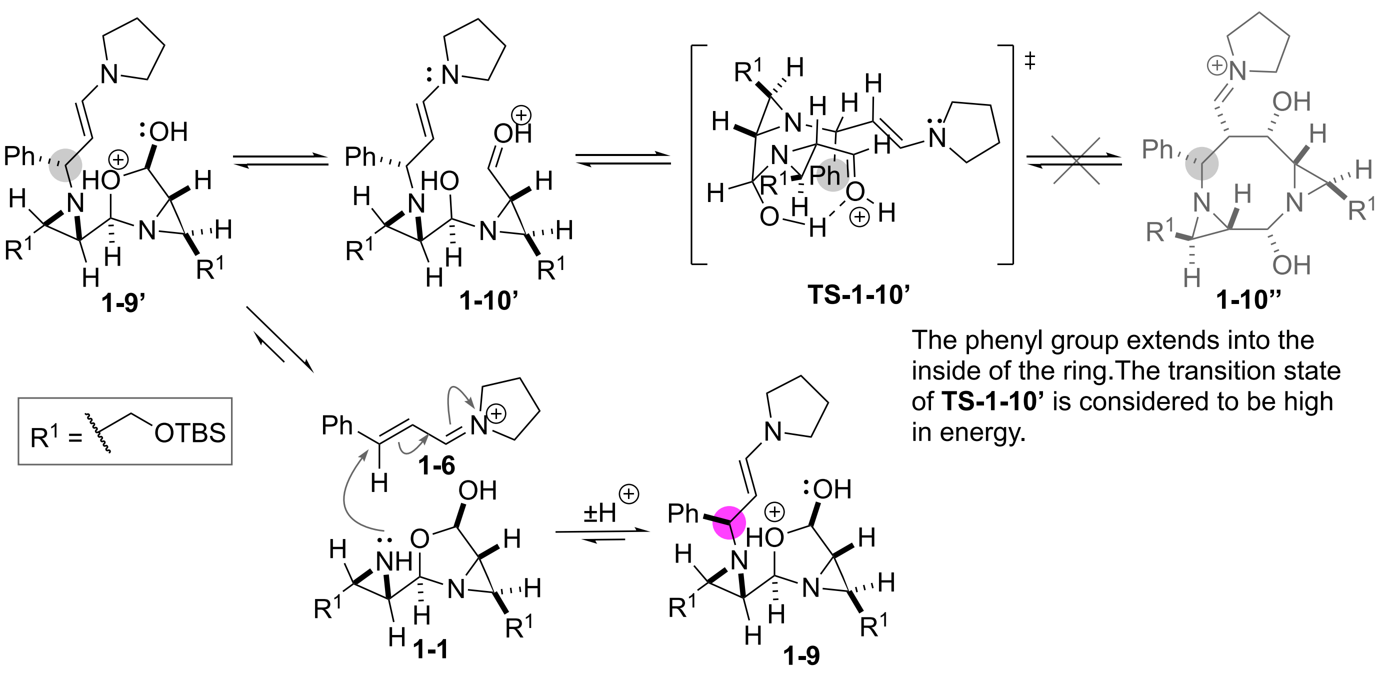
Hili, R.; Yudin, A. K. *J. Am. Chem. Soc.* **2009**, *131*, 16404.



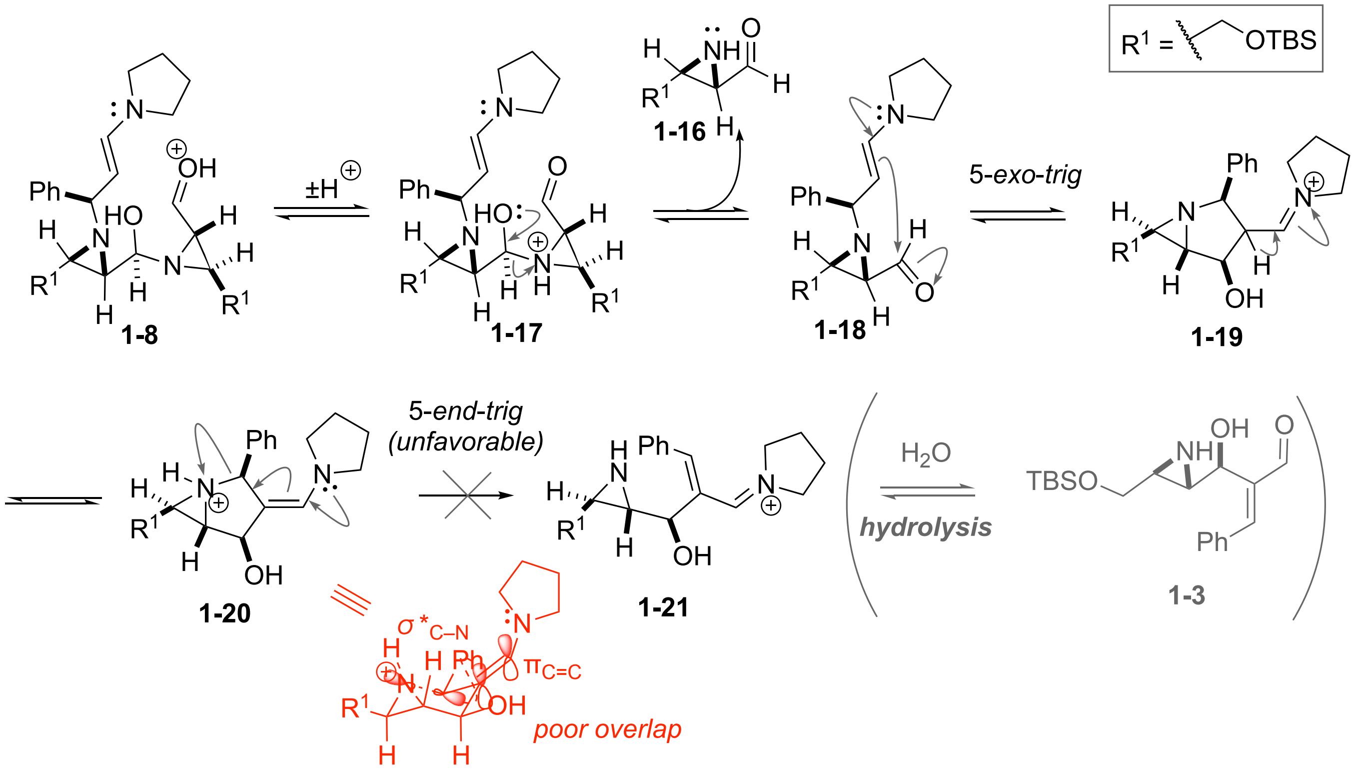


__Discussion 1: aza-Michael/aldol reaction__

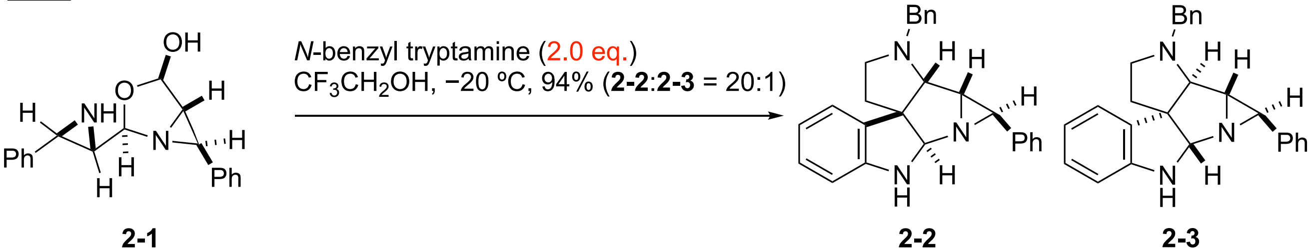
1-1. <u>stereoselectivity of Ph group (My proposal)</u>



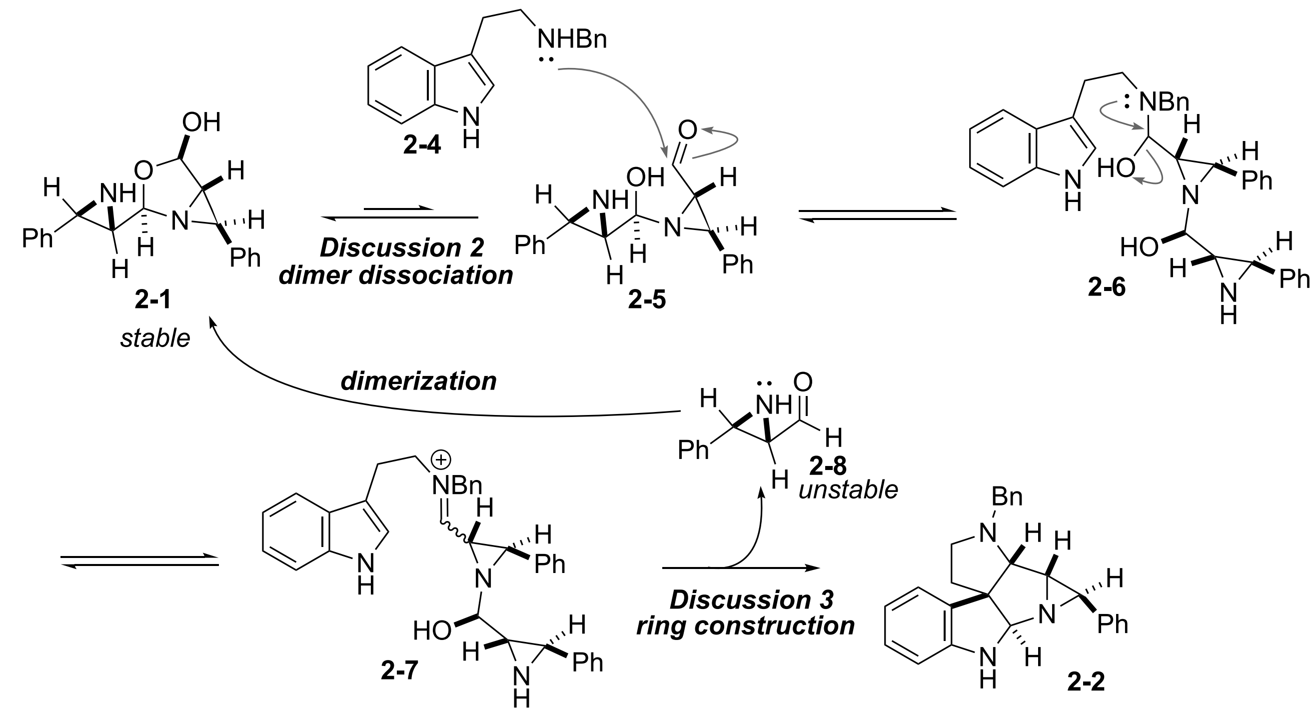
1-2. another possible passway: 5-*exo-trig*



2 Please provide the reaction mechanism and stereoselectivity.

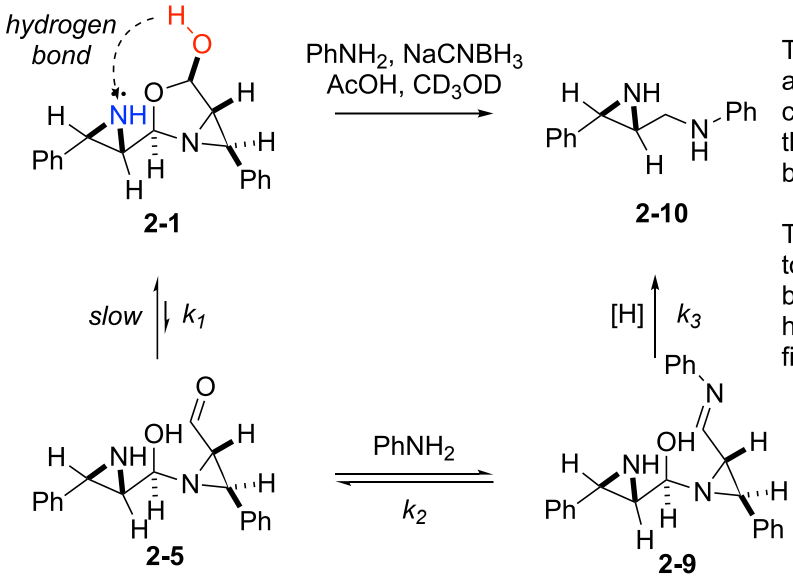


Hili, R.; Yudin, A. K. *J. Am. Chem. Soc.* **2006**, *128*, 14772.



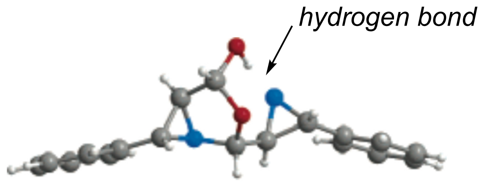
Discussion 2: dimer dissociation

2-1. Kinetic study on reductive amination



The fact that the reaction rate of the reductive amination was unaffected by changes in the concentrations of aniline or hydride suggests that neither k_2 nor k_3 is rate-determining but rather that k_1 is the rate-determining step.

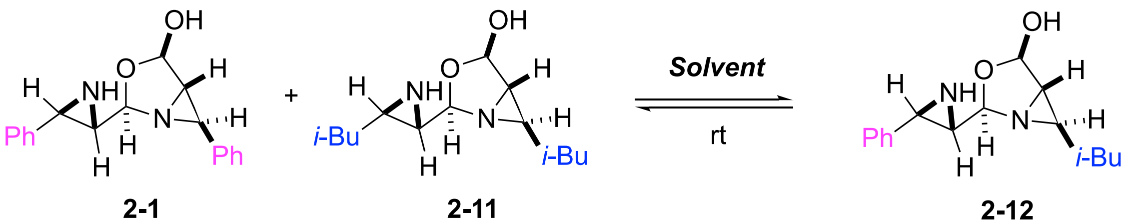
The slow dissociation of the hemiacetal is believed to be due to stabilization by hydrogen bonding between the 2-position aziridine moiety and the hydroxyl group of the hemiacetal, as shown in the figure below.



X-ray structure of **2-1**

2-2. Solvent effect of CF_3CH_2OH (TFE)

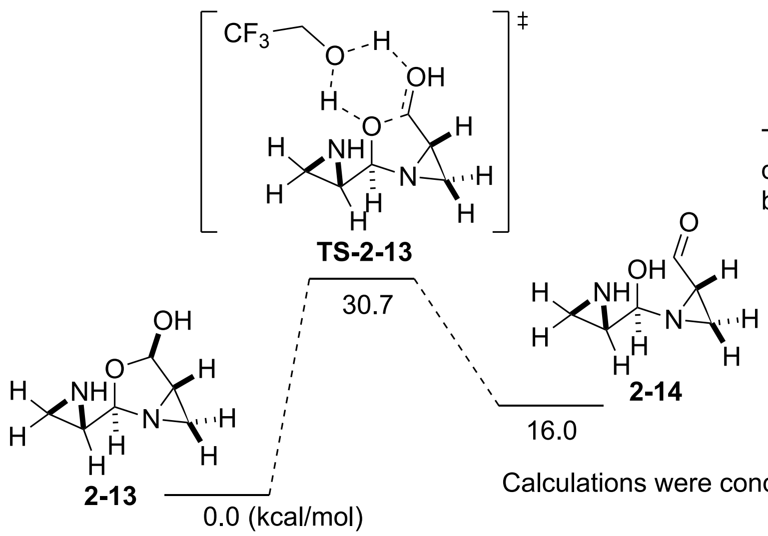
crossover experiment



CH_2Cl_2, MeOH, THF, MeCN, toluene: Small amounts of crossover product **2-12** were observed even after 1 h.
TFE: Generation of crossover product **2-12** was observed within 5 min.
→ It is considered that TFE promotes dimer dissociation and accelerates the reaction rate.

Assem, Naila.; Hili, Ryan.; He, Zhi.; Kasahara, T.; Inman, B. L.; Decker, S.; Yudin, A. K. J. Org. Chem. 2012, 77, 5613.

calculation



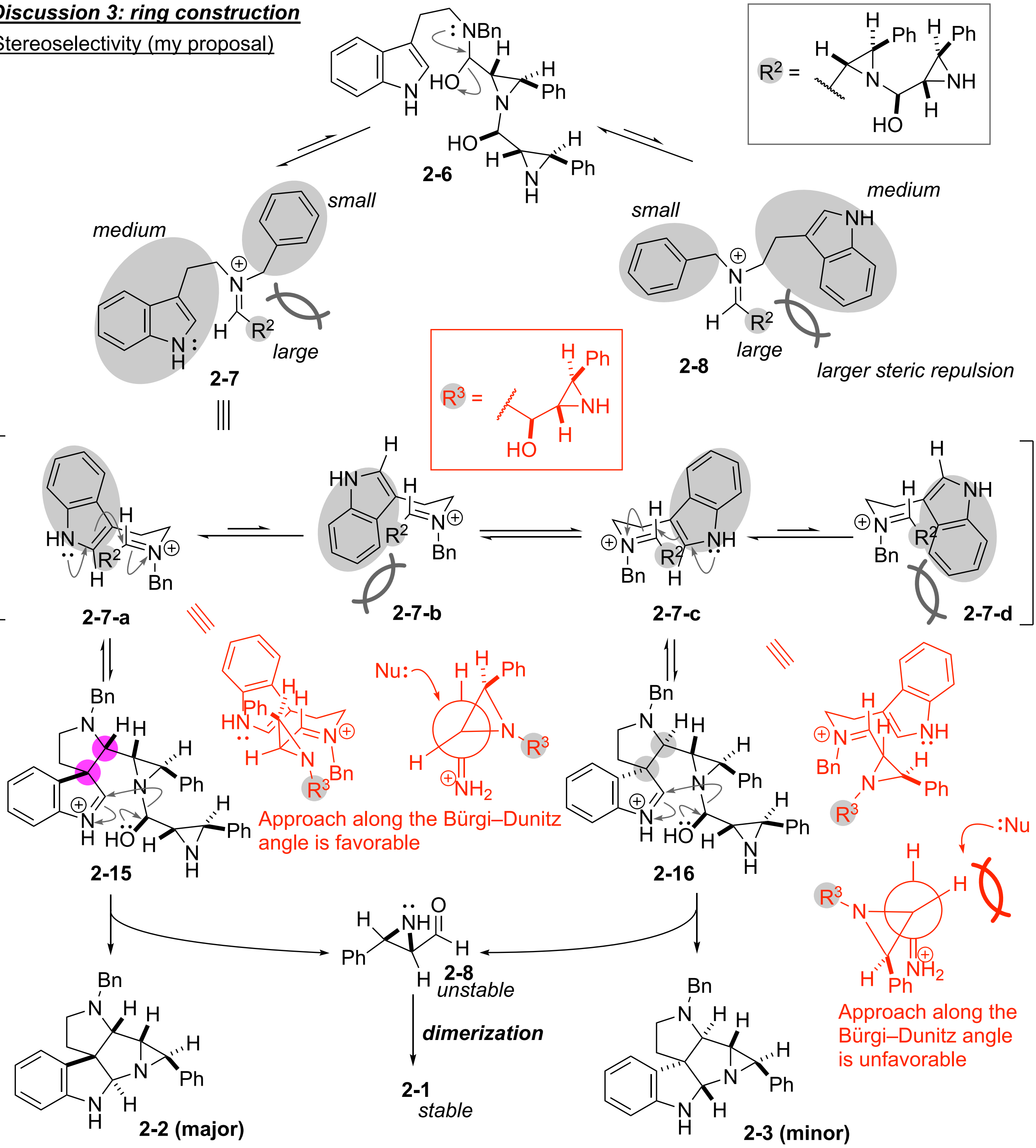
TFE is assumed to promote the dissociation of the dimer by disrupting the intramolecular hydrogen bonding in **2-13** and facilitating proton exchange.

Calculations were conducted at the MPWPW91/6-31G(d) level of theory.

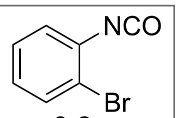
Belding, L.; Zaretsky, S.; Rotstein, B. H.; Yudin, A. K.; Dudding, T. J. Org. Chem. 2014, 79, 9465.

Discussion 3: ring construction

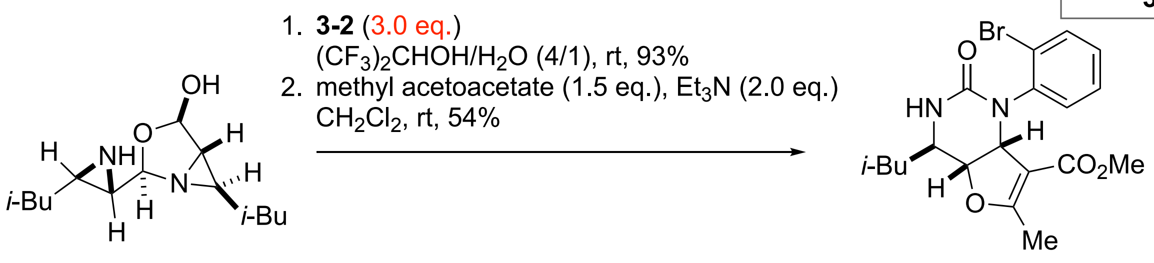
Stereoselectivity (my proposal)



3 Please provide the reaction mechanism and stereoselectivity.

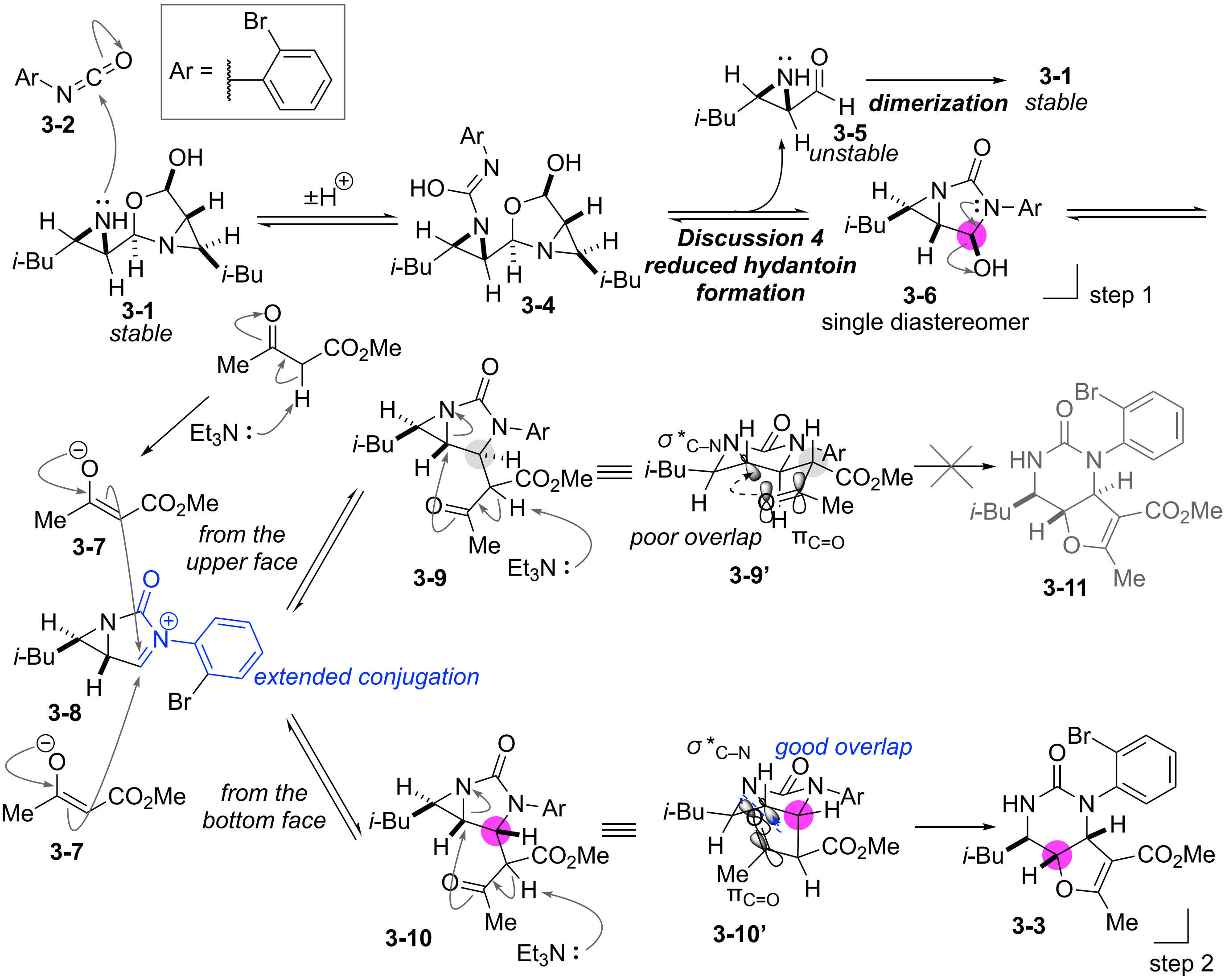


3-2



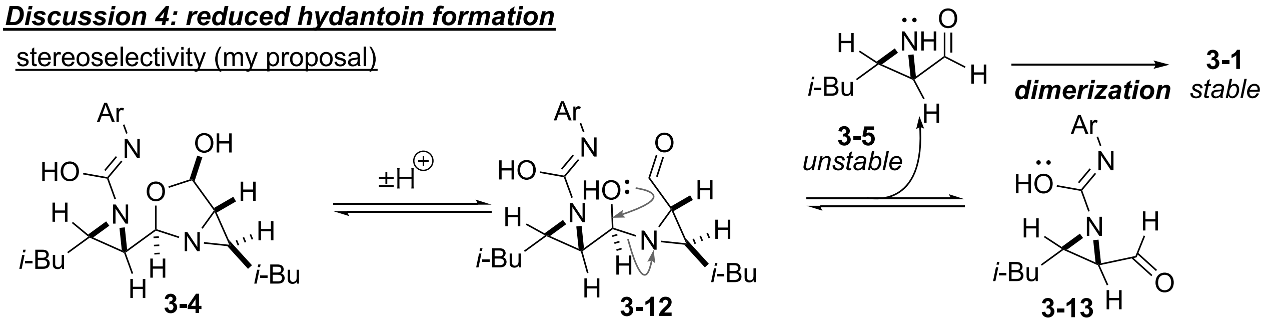
3-1 **3-3**

Cheung. L. L. W.; He, Z.; Decker, S. M.; Yudin, A. K. *Angew. Chem. Int. Ed.* **2011**, *50*, 11798.



Discussion 4: reduced hydantoin formation

stereoselectivity (my proposal)



$(CF_3)_2CHOH$ would be likely to promote dimer dissociation.