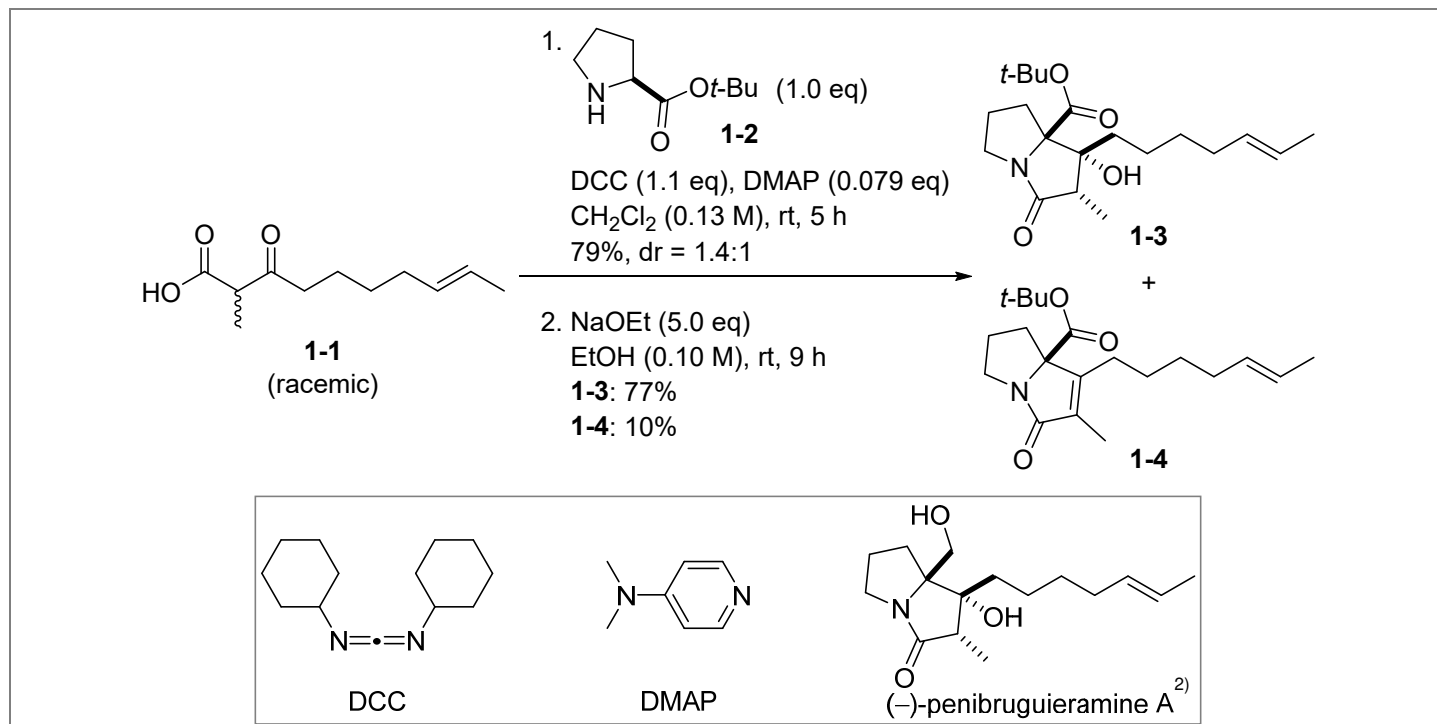
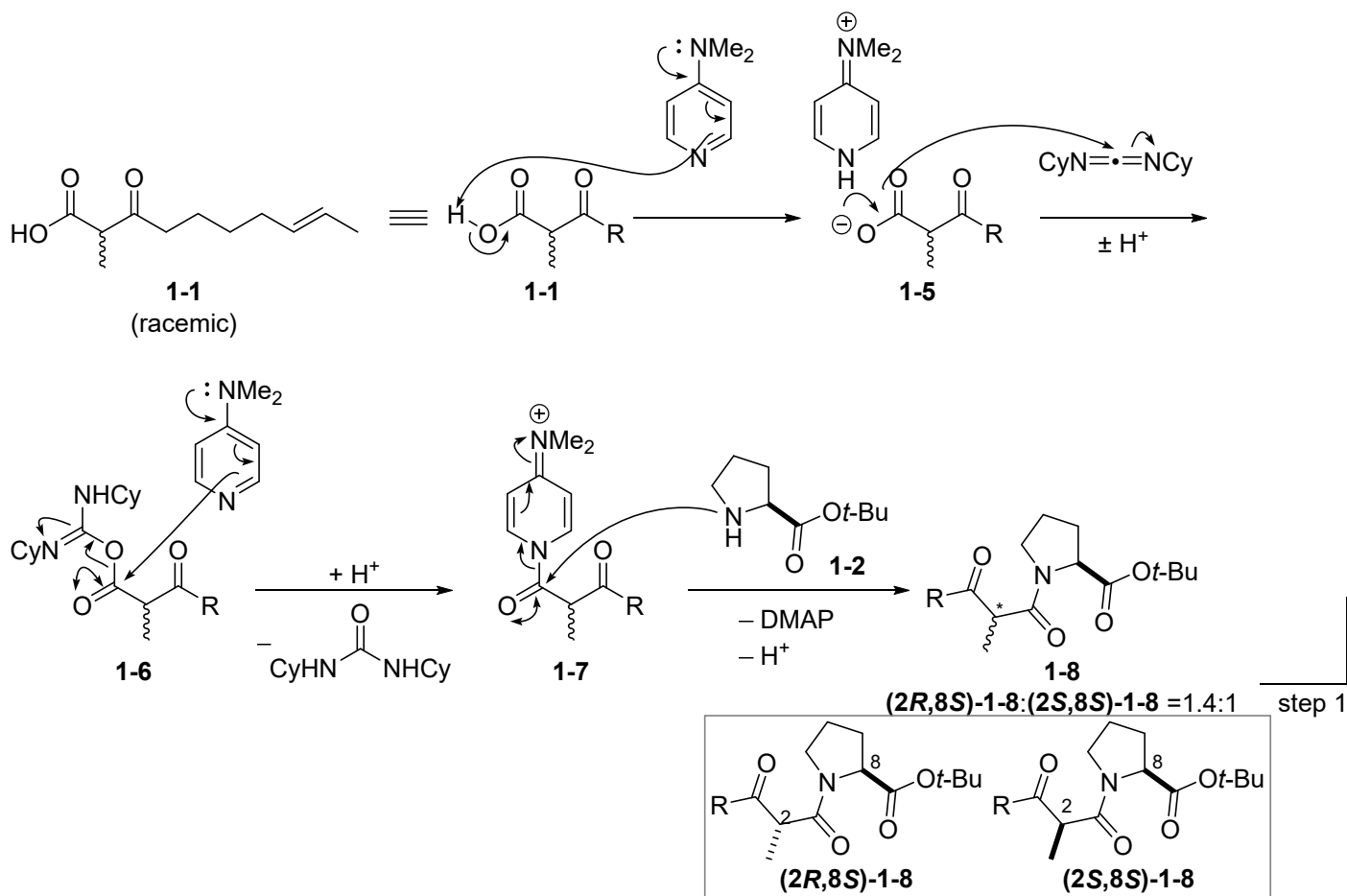


1. Total synthesis of (-)-penibrugueramine A by Prof. Kim group<sup>1)</sup>



1.1. Proposed reaction mechanisms

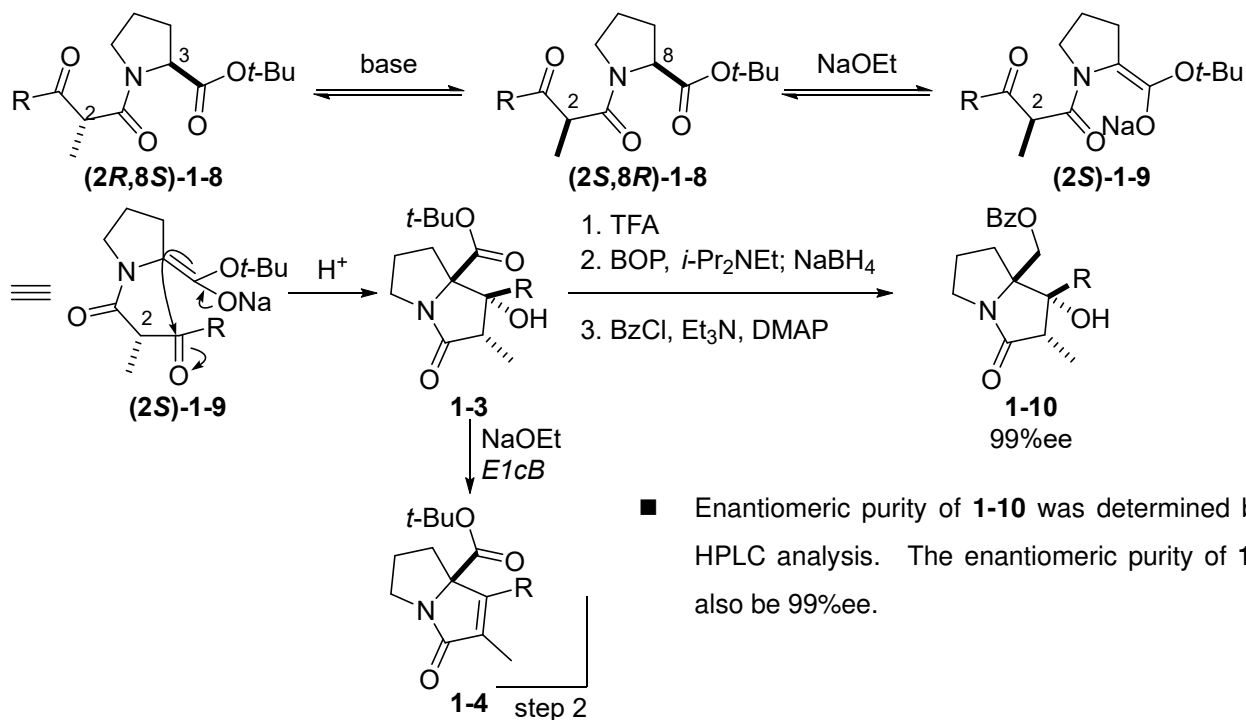
1.1.1. Condensation



<sup>1)</sup> Kim, J. H.; Lee, S.; Kim, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 10875.

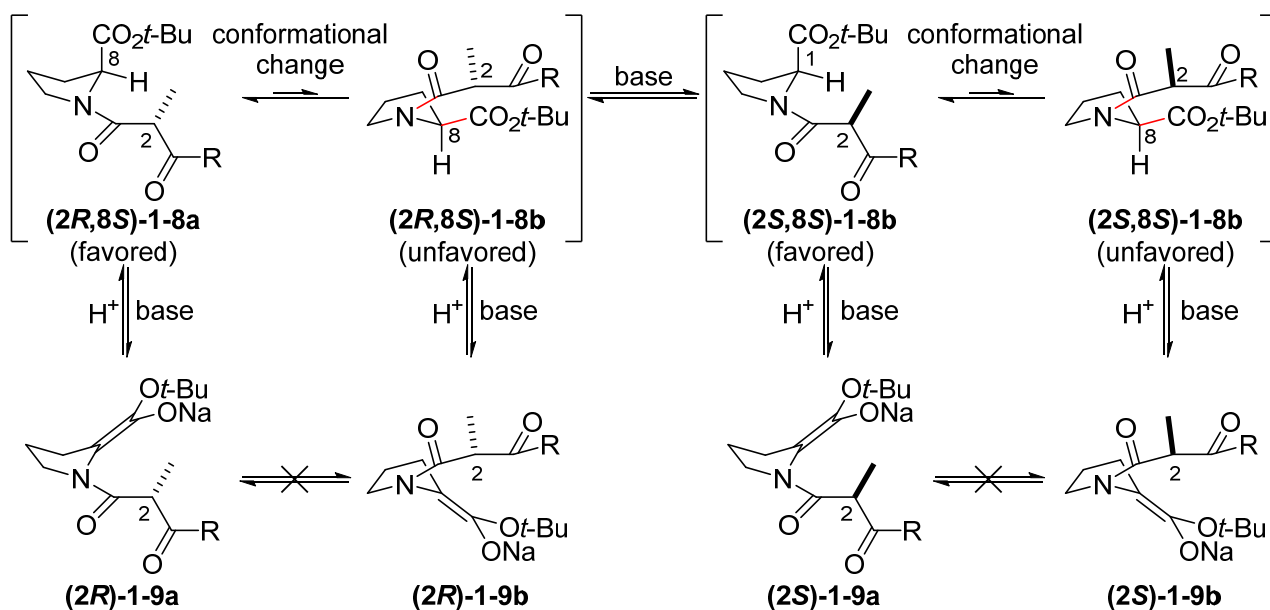
<sup>2)</sup> Zhou, Z.-F.; Kurtán, T.; Yang, X.-H.; Mándi, A.; Geng, M.-Y.; Ye, B.-P.; Tagliatella-Scafati, O.; Guo, Y.-W. *Org. Lett.* **2014**, *16*, 1390.

### 1.1.2. Intramolecular aldol reaction



- Enantiomeric purity of **1-10** was determined by chiral HPLC analysis. The enantiomeric purity of **1-3** must also be 99% ee.

### 1.2. Rationale for the stereoselectivity

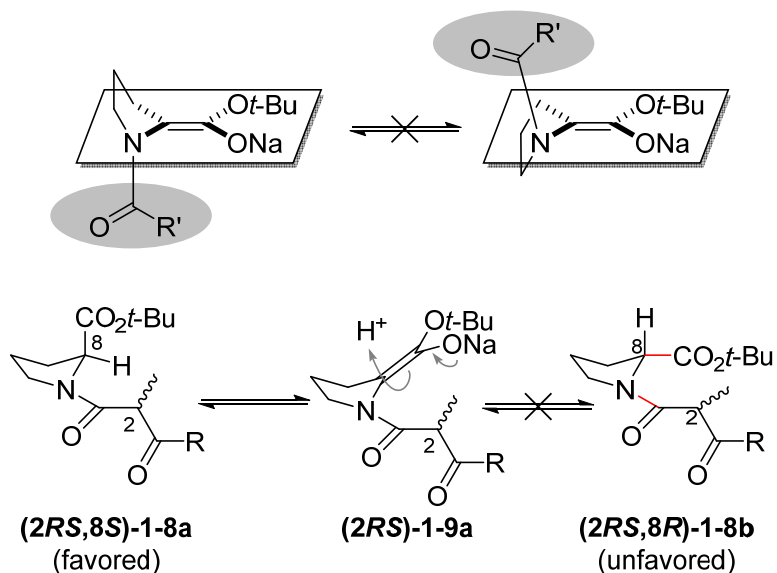


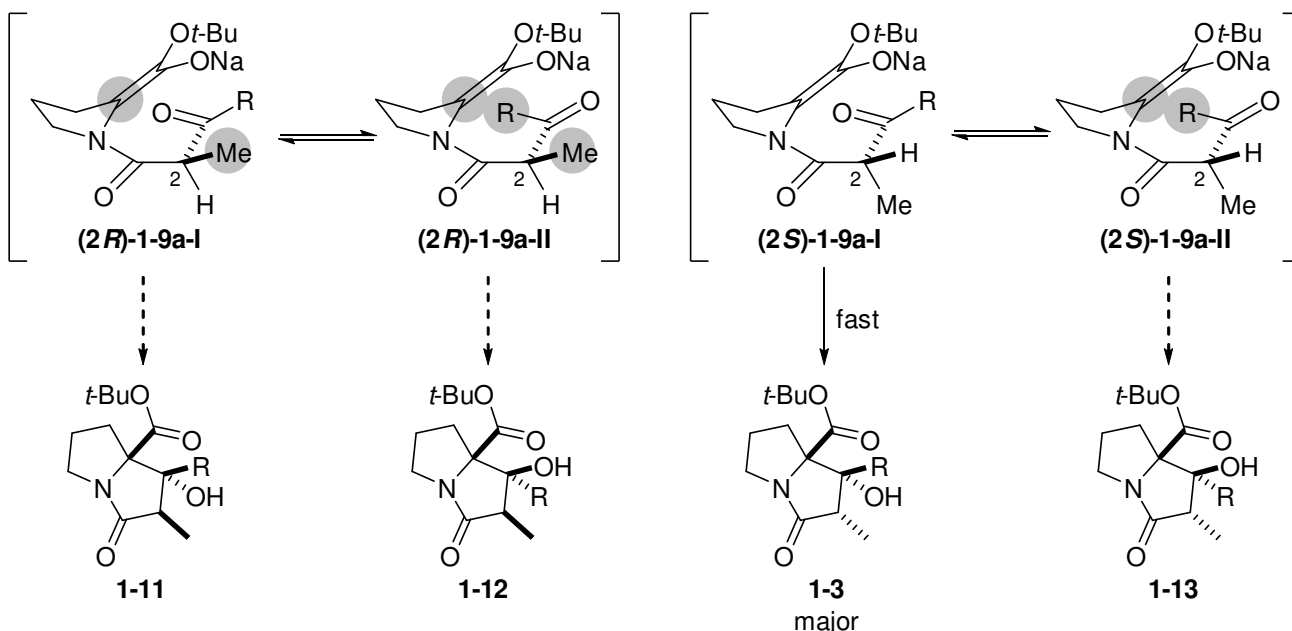
- (2R,8S)-1-8b** and **(2S,8S)-1-8b** would be unfavored due to the large 1,2-interaction.

- Considering the existence of a large *N*-acyl group, conformational change between **(2R)-1-9a** and **(2R)-1-9b**, and between **(2S)-1-9a** and **(2S)-1-9b** would be difficult.

- Epimerization at C8 via deprotonation followed by protonation from the opposite side is unlikely to occur considering the instability of the resulting **(2RS,8R)-1-8b**.

- It could be said that the chirality of **1-8** at C8 was converted into the axial chirality of the enolate **1-9**.

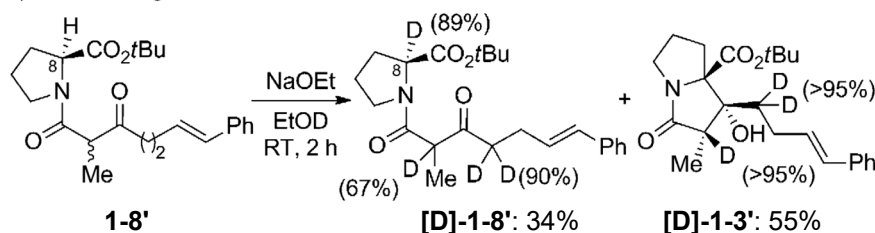




- 1-3 "was the only aldol product that appeared from the beginning of the reaction" and "other diastereomers were not detected during the reaction."  
 $\therefore$  1-3 would be the kinetic product.

### 1.3. Support for "memory of chirality"

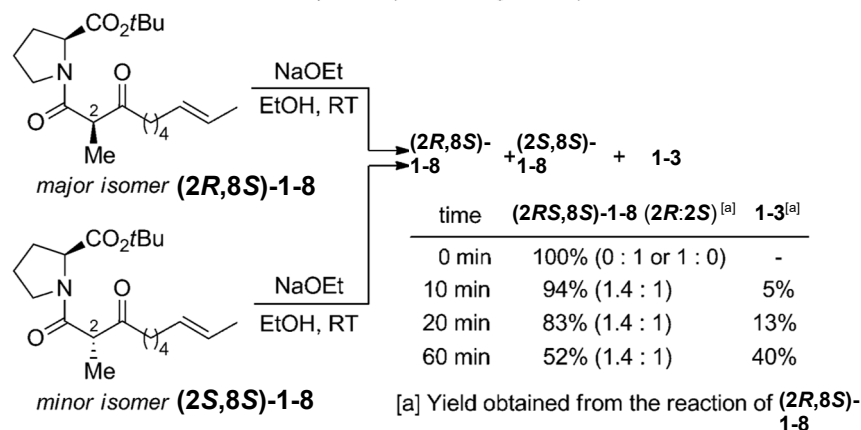
a) H/D exchange of **3'** in EtOD.



- Although D atom was incorporated at C8, the proline stereocenter was not racemized. This observation indicates that the unreacted ester enolate intermediate was protonated with complete retention of configuration.

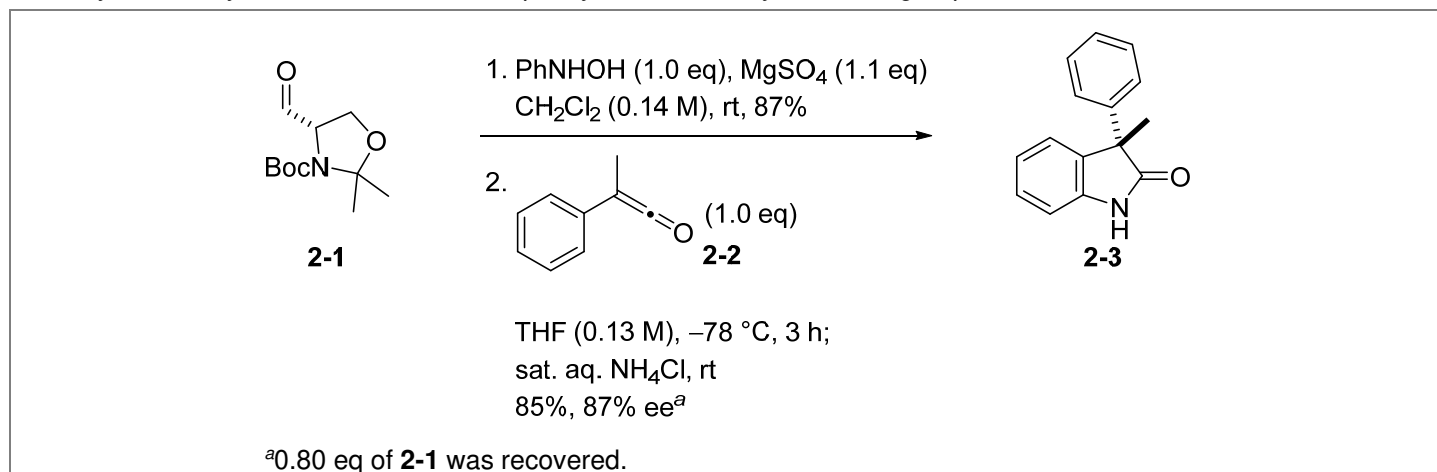
### 1.4. Support for dynamic kinetic resolution

b) DKR of the C2 diastereomers (arbitrary C2 configuration).



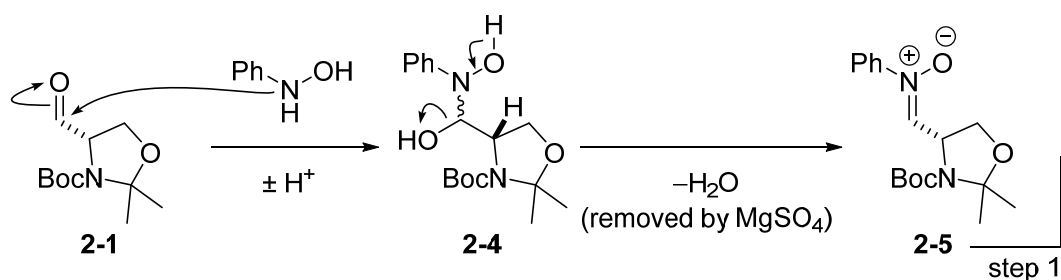
- Treatment of the two separated C2 diastereomers were independently subjected to the optimized reaction condition. Epimerization at C2 was fast, and the diastereomeric ratio became constant after 10 min. Aldol product **1-3** was gradually formed as the only diastereomer.

2. Asymmetric synthesis of oxindoles via pericyclic cascade by Dr. Smith group<sup>3)</sup>

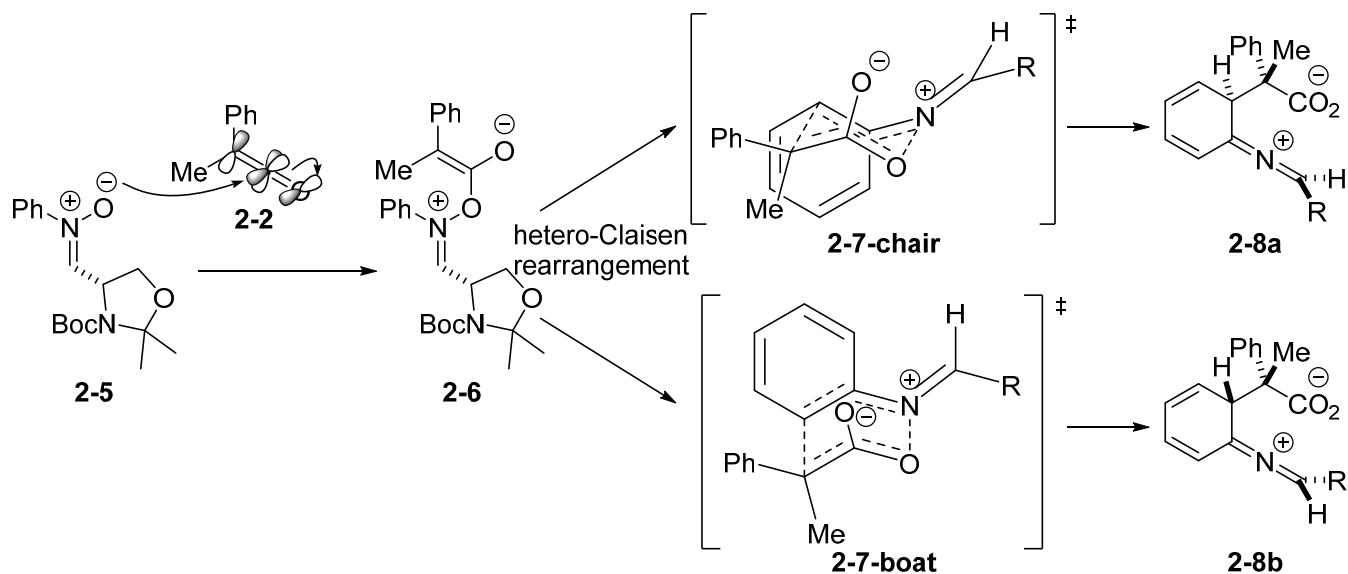


2.1. Reaction mechanism

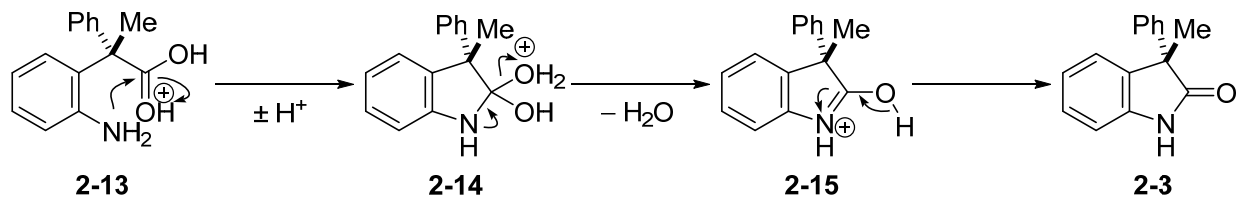
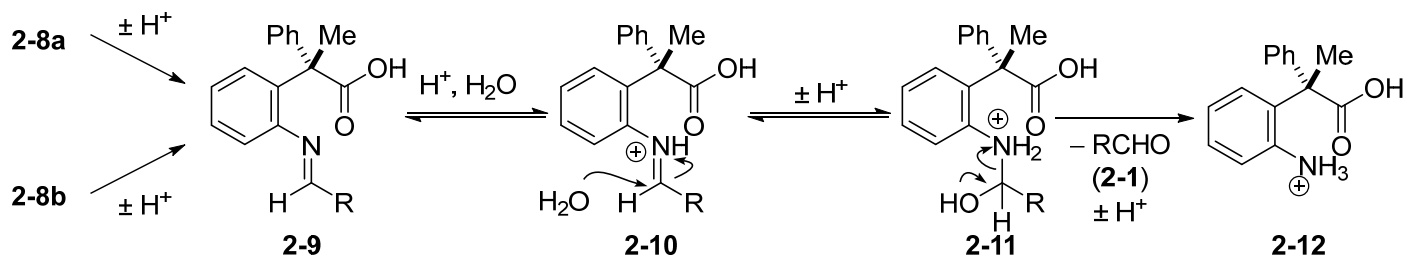
2.1.1. Nitron formation



2.1.2. Oxindole formation (originally proposed)<sup>3a)</sup>

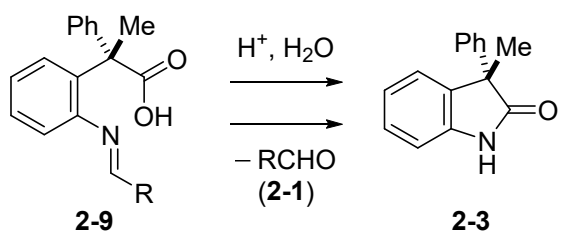
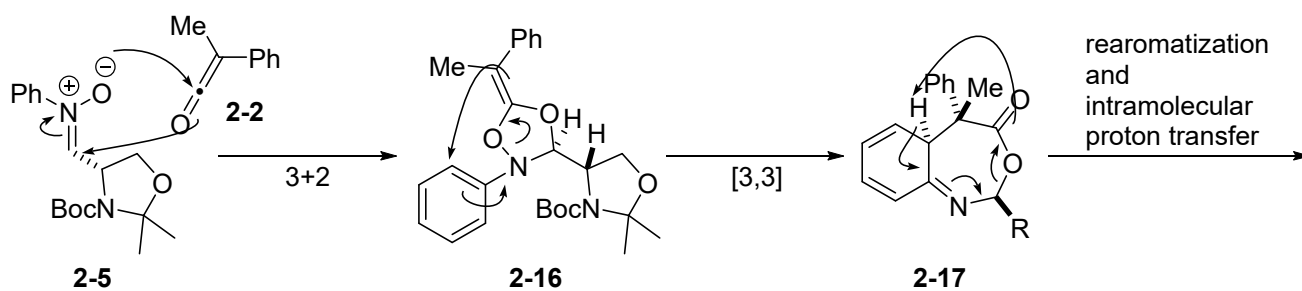


<sup>3</sup> (a) Duguet, N.; Slawin, A. M. Z.; Smith, A. D. *Org. Lett.* **2009**, *11*, 3858. (b) Çelebi-Ölçüm, N.; Lam, Y.-H.; Richmond, E.; Ling, K. B.; Smith, A. D.; Houk, K. N. *Angew. Chem., Int. Ed.* **2011**, *50*, 11478.

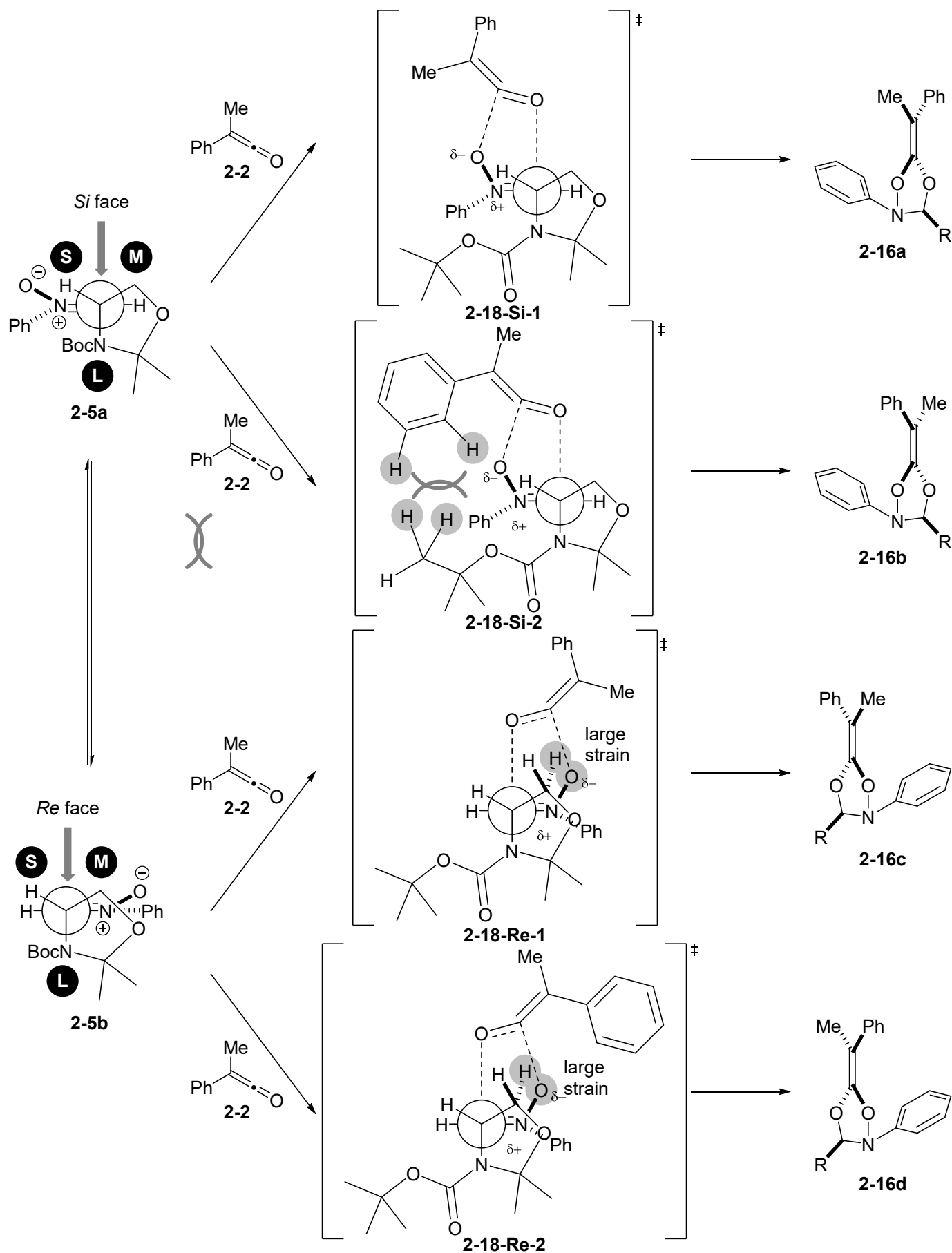


- "Attempts to locate the TS for this step (hetero-Claisen rearrangement) by constraining the forming C–C and the breaking N–O bonds at various partial bond distances in the gas phase and in solution yielded highly unstable TSs with a free energy of at least  $44.1 \text{ kcal mol}^{-1}$  relative to the separated reactants<sup>3b</sup>."

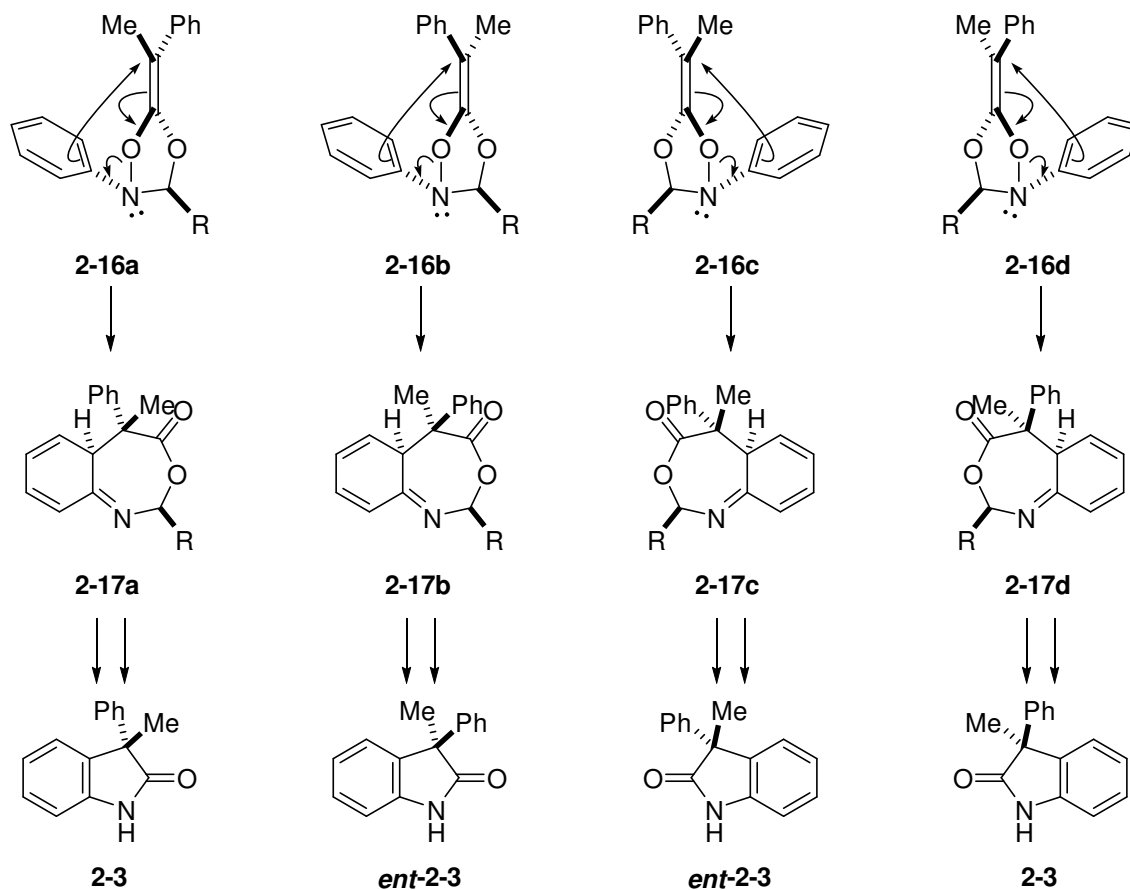
### 2.1.3. Oxindole formation (revised)<sup>3b</sup>



## 2.2. Explanation for the stereoselectivity



- 2-18-Si-1 is likely to be the most stable TS.



- 2-16a, derived from the presumably stable TS (2-18-Si-1), is expected to afford the major product 2-3.

### 2.3. Computational study

#### 2.3.1. A simplified model

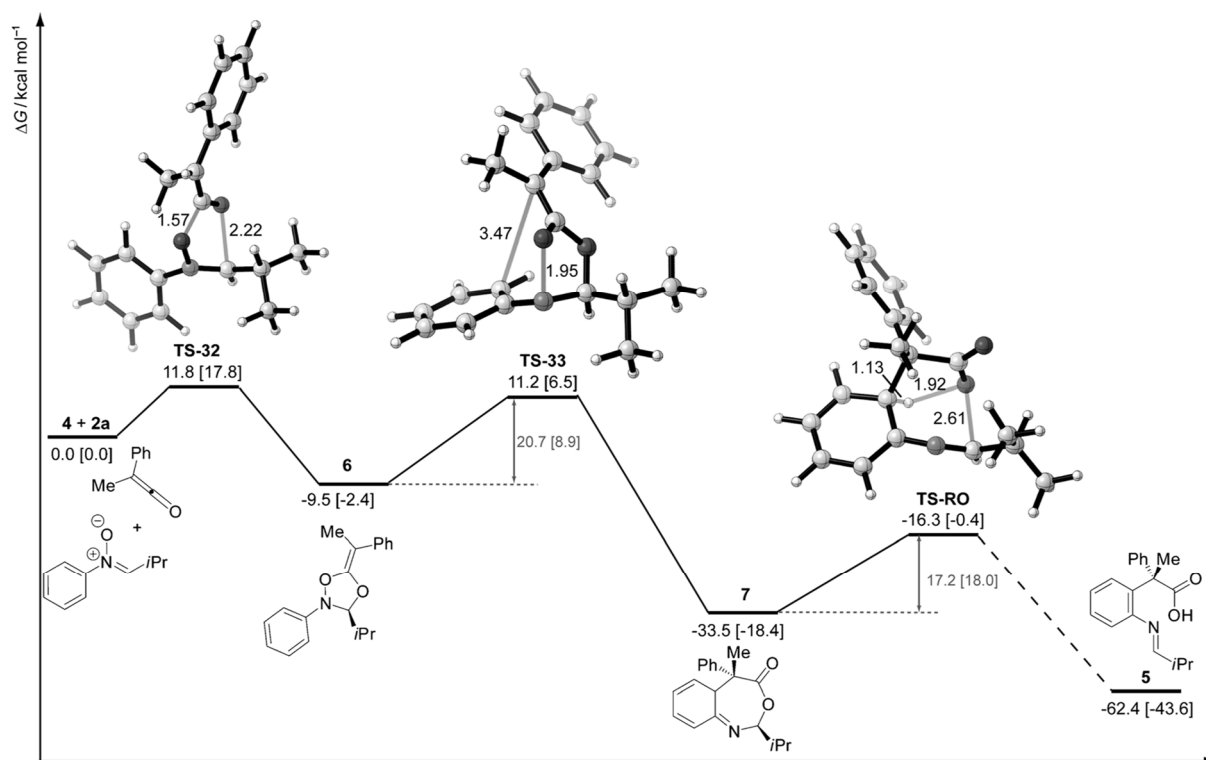


Figure 1. Energy profile for the pericyclic cascade mechanism of 4 and 2a. TS-32, TS-33, and TS-RO refer to the transition structures for the 3+2 cycloaddition, the hetero-Claisen rearrangement, and the rearomatization with concomitant ring opening, respectively. (M06-2X/6-311+G-(d,p)(THF)//B3LYP/6-31G(d), gas-phase B3LYP/6-31G(d) energies are given in brackets).

- The revised mechanism is energetically viable under the experimental conditions.

- The aromatic hetero-[3,3]-rearrangement is likely to proceed because the exocyclic alkylidene group is suitably positioned with respect to the nitrogen-bound phenyl ring. The TS of hetero-[3,3]-rearrangement is highly asynchronous. However, no intermediates were found (concerted reaction).

### 2.3.2. Optimized TSs for the real substrate

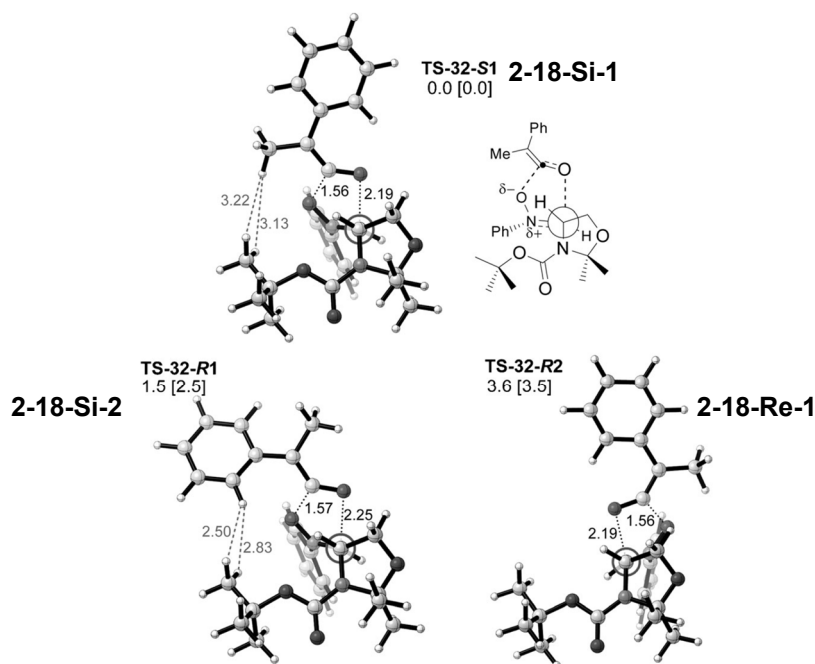


Figure 2. Stereoisomeric transition structures and their relative free energies. (M06-2X/6-311+ G(d,p)(THF) // B3LYP/6-31G(d), gas-phase B3LYP/6-31G(d) energies are given in brackets).

- **2-18-Re-2** is over 5 kcal/mol higher in energy than **2-18-Si-1**.
- The free energy difference between **2-18-Si-1** and **2-18-Si-2** (1.5 kcal/mol) corresponds to 84%ee, in good agreement with experiment (87%ee).