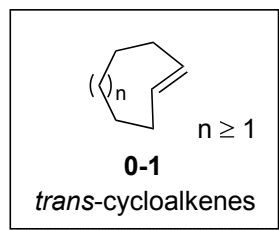


## Topic : Transannular reaction and rearrangement related to *trans*-cycloalkenes



cycloalkene	<i>cis</i>	<i>trans</i>
ring-size	≥3	≥7

$n = 1$  : *trans*-cycloheptene is very unstable, and easily isomerized to *cis*-form.  
 $n \geq 2$  : stable at room temperature

- medium-sized *trans*-cycloalkenes have planer chirality.

Relative energies of the *cis/trans* isomers

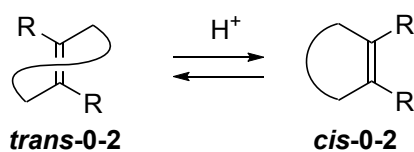
**Table 1.**

ring-size	$\Delta\Delta_f H$ (kcal/mol)
7	29.9
8	11.4
9	4.2
10	3.8
11	-0.6

$$\Delta\Delta_f H = E_{trans} - E_{cis}$$

Barrows, S.; Eberlein, T. H. *J. Chem. Edu.* **2005**, *82*, 1334.

(0-1) Acid catalyzed isomerization of cycloalkenes

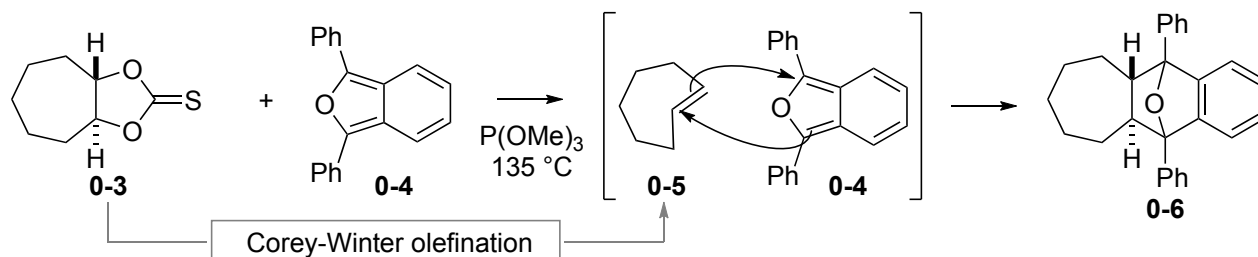


**Table 2.**

ring-size	R, R	[ <i>cis</i> ] / [ <i>trans</i> ]	ring-size	R, R	[ <i>cis</i> ] / [ <i>trans</i> ]
8	H, H	very large	11	H, H	0.4
9	H, H	232	12	H, H	0.5
9	CH <sub>3</sub> , H	> 5000	12	CH <sub>3</sub> , H	1.5
10	H, H	12.2	12	CH <sub>3</sub> , CH <sub>3</sub>	4
10	CH <sub>3</sub> , H	> 2000			

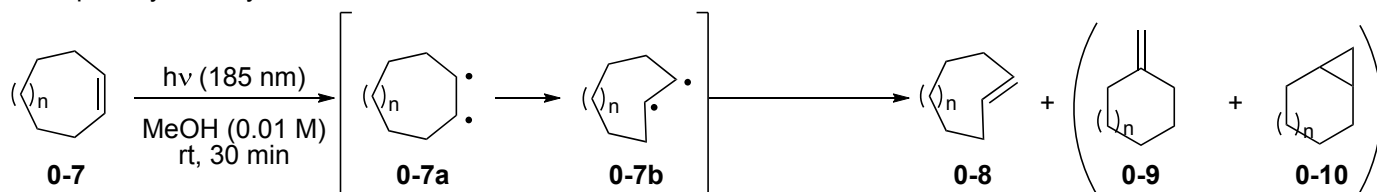
Marshall, J. A. *Acc. Chem. Res.* **1980**, *13*, 213.

(0-2) Existence of *trans*-cycloheptene firstly reported by E. J. Corey in 1965



Corey, E. J.; Carey, F. A.; Winter, R. A. E. *J. Am. Chem. Soc.* **1965**, *87*, 934.

(0-3) Direct photolysis of cycloalkenes

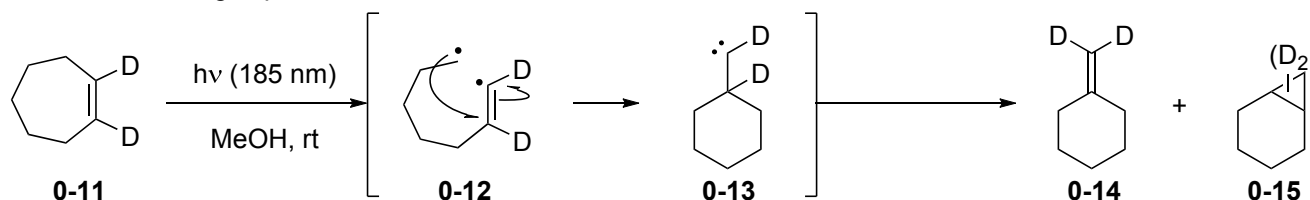


**Table 3.**

entry	n	0-8	0-9	0-10	recovery (0-7)
1	0	not mentioned	7%	13%	69%
2	1	not mentioned	10%	8%	70%
3	2	40%	<1%	<1%	57%

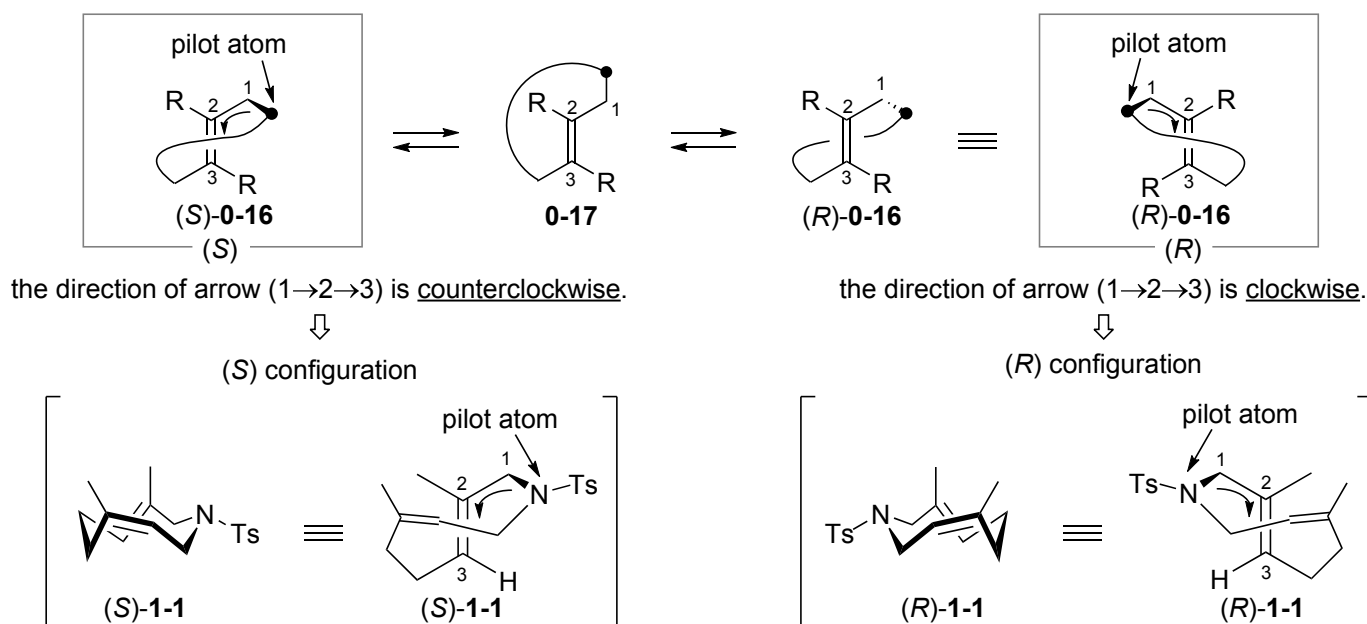
⇒ lifetime of *trans*-cycloheptene : 47 s (rt)

### Deuterium labeling experiment



Inoue, Y.; Takamuku, S.; Sakkurai, H. *J. Chem. Soc., Perkin Trans. 2*, **1977**, 1635.

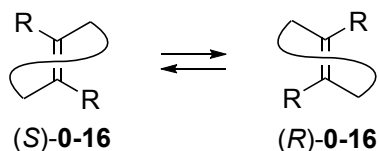
(0-4) Definition of *R* or *S* configuration of *trans*-cycloalkenes



Marshall, J. A. *Acc. Chem. Res.* **1980**, *13*, 213.

(0-5) Optical stability of *trans*-cycloalkenes

isomerization between (*S*) and (*R*)



**Table 4.**

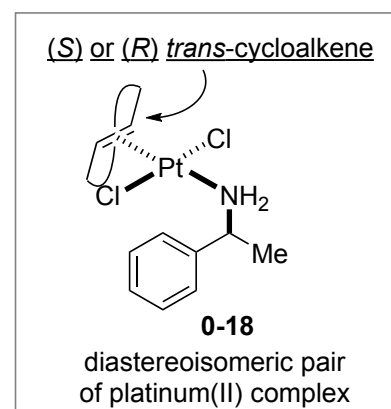
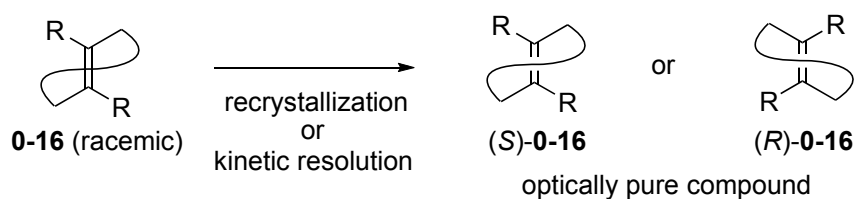
ring-size	R, R	optical activity	half-life period <sup>a</sup>
8	H, H	○	~10 <sup>5</sup> years
9	H, H	×	~10 s
10	Me, Me	○	—
11	Me, Me	○	—
12	Me, Me	×	—

<sup>a</sup> room temperature

Marshall, J. A.; Konicek, T. R.; Flynn, K. E. *J. Am. Chem. Soc.* **1980**, *102*, 3287.

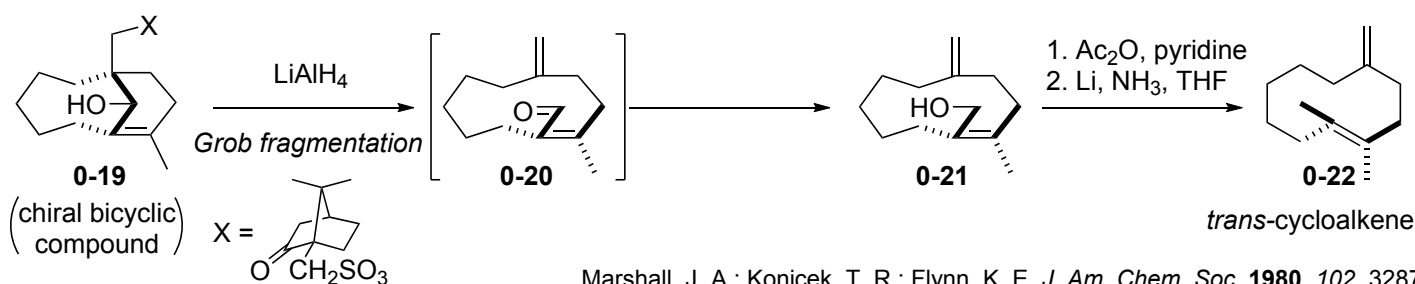
(0-6) Preparation method of optical pure *trans*-cycloalkenes

(0-6-1) Recrystallization or kinetic resolution method

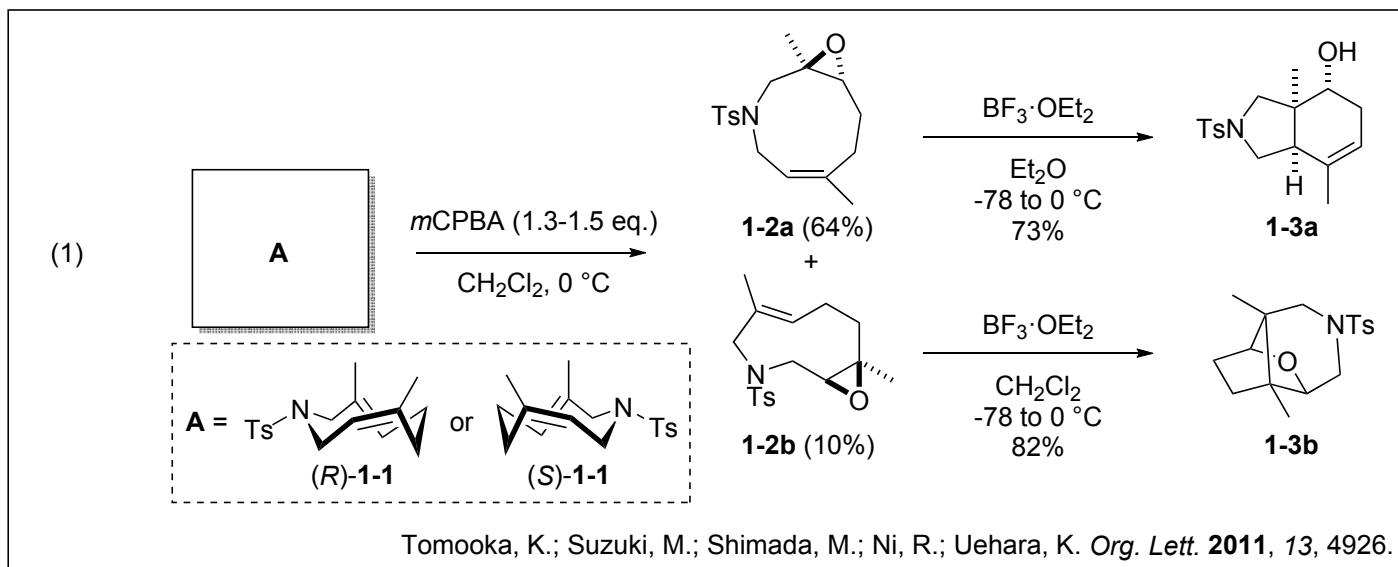


Cope, A. C.; Gamellin, C. R.; Johnson, H. W., Jr.; van Auken, T. V. *J. Am. Chem. Soc.* **1963**, *85*, 3276.

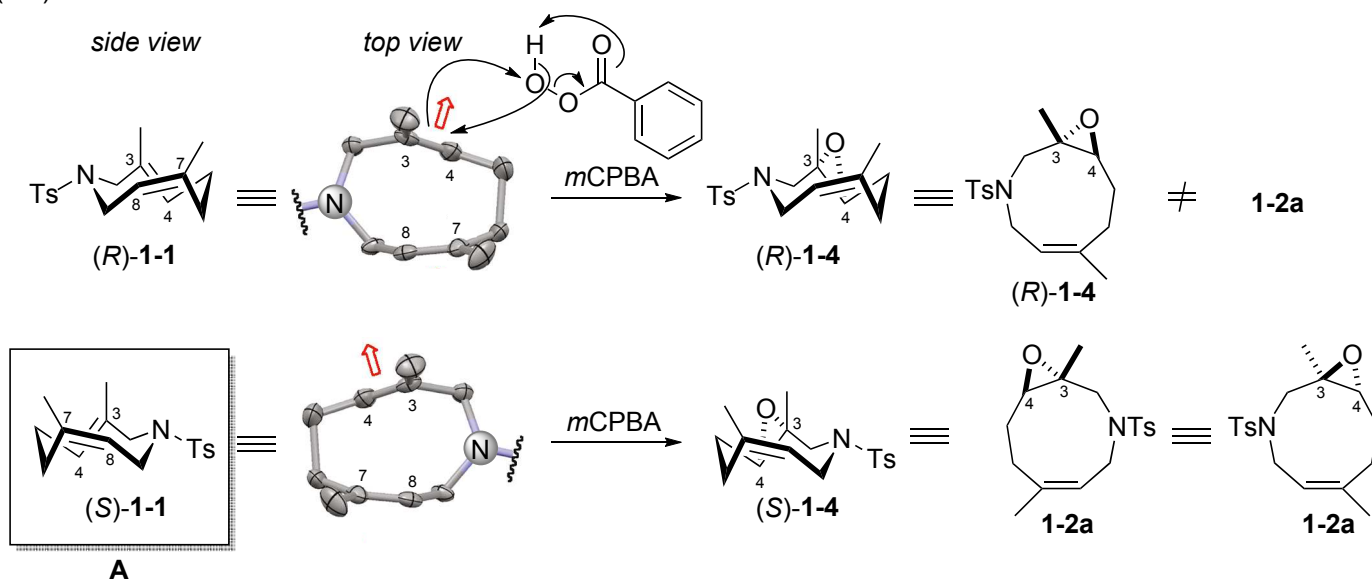
(0-6-2) Another method



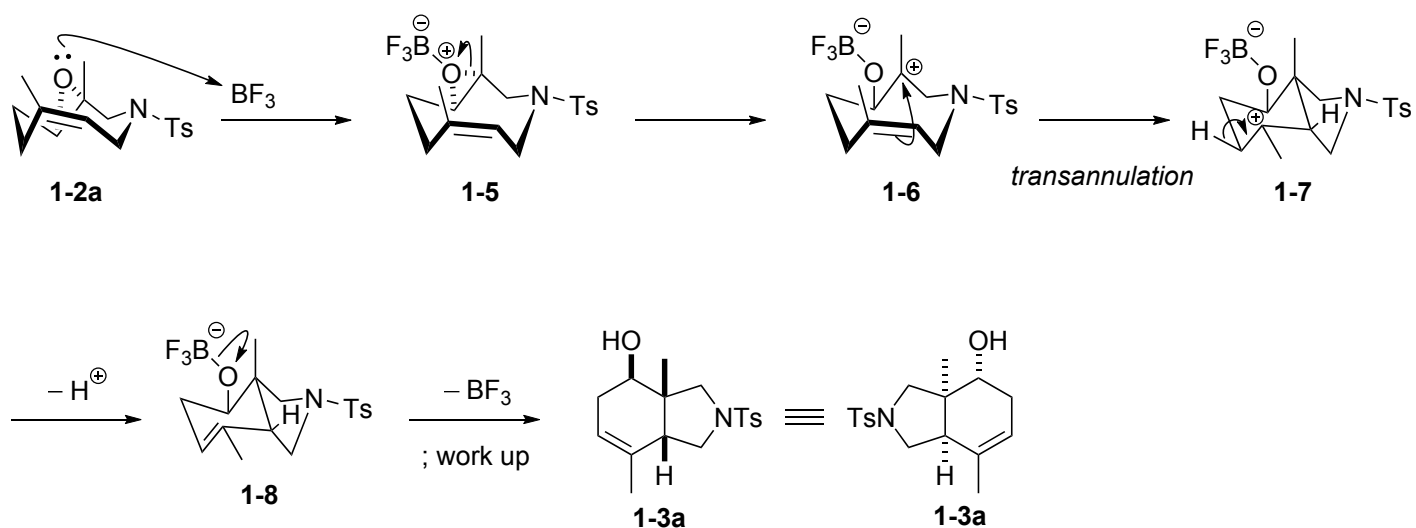
Marshall, J. A.; Konicek, T. R.; Flynn, K. E. *J. Am. Chem. Soc.* **1980**, *102*, 3287.



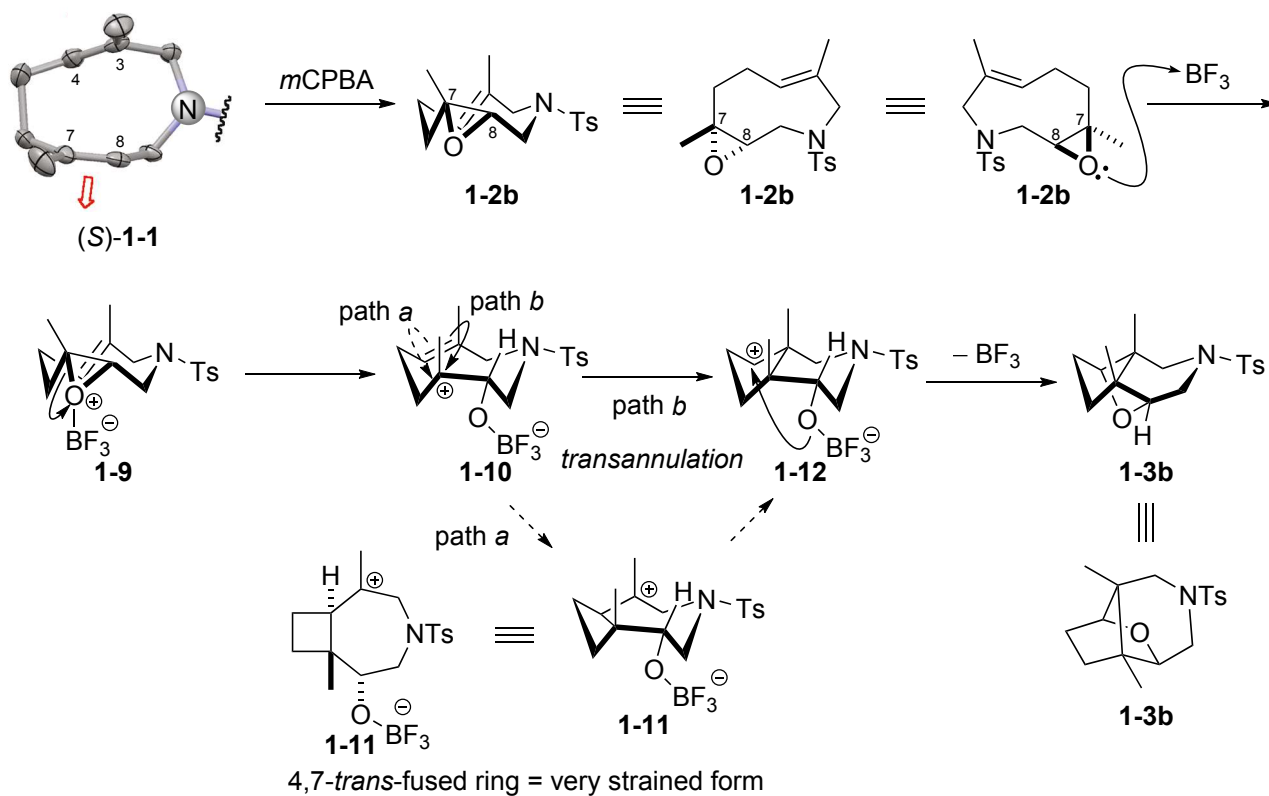
(1-1) Answer of **A**



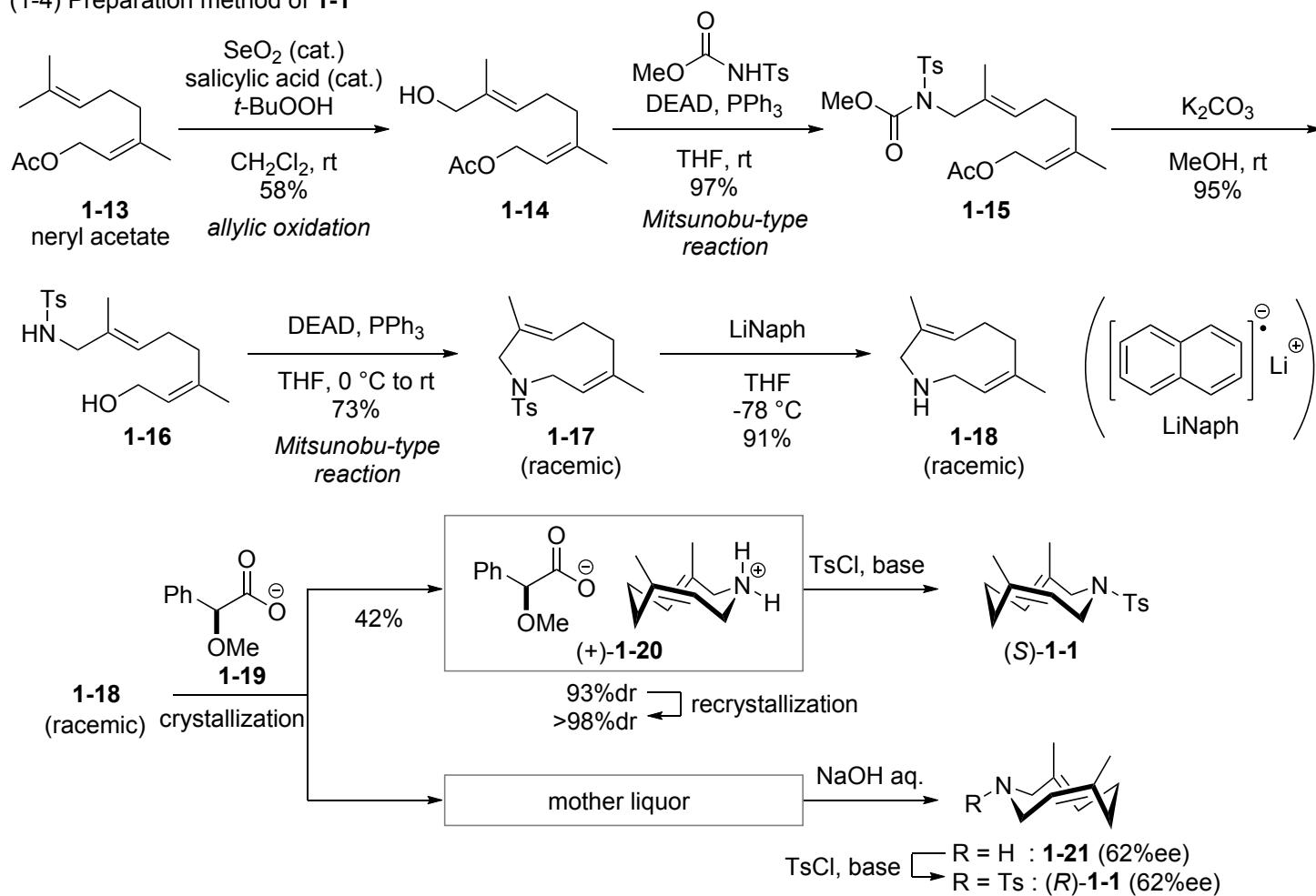
(1-2) Proposed mechanisms from **1-2a** to **1-3a**



(1-3) Proposed mechanisms from (S)-1-1 to 1-3b

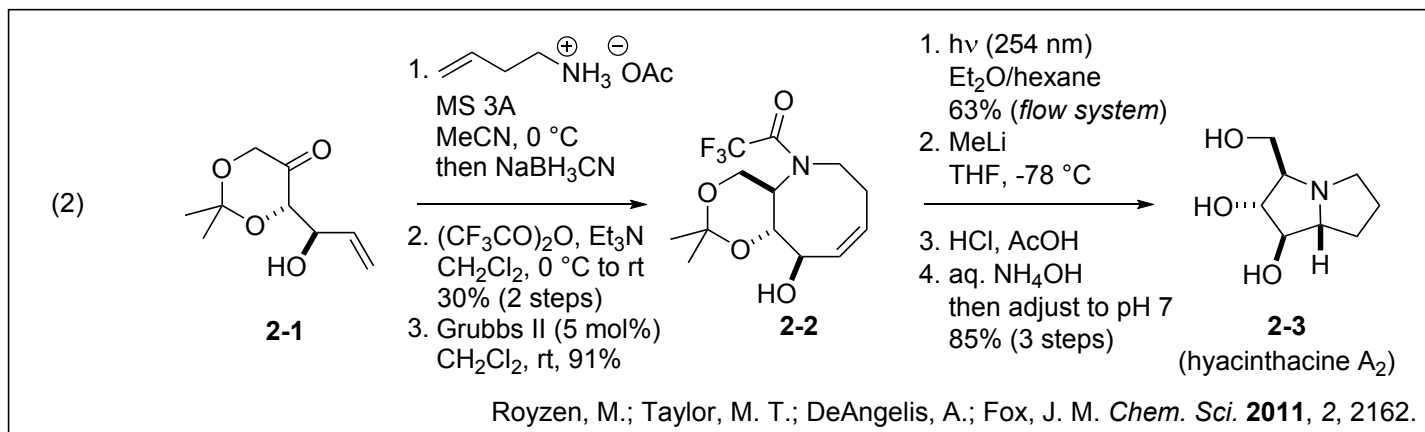


(1-4) Preparation method of 1-1

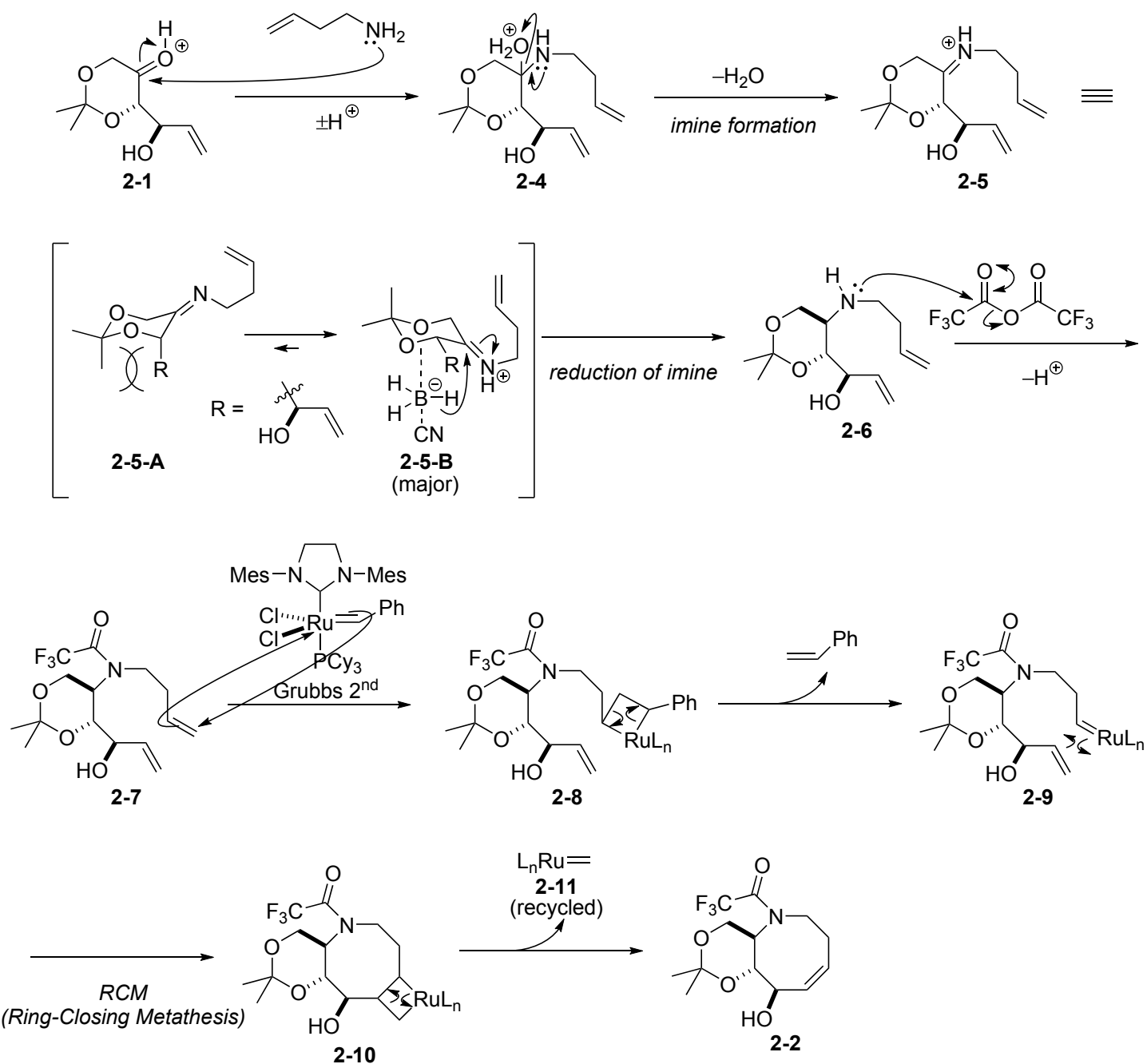


half-life of optical activity of 1-1 : 203 days (in solution)

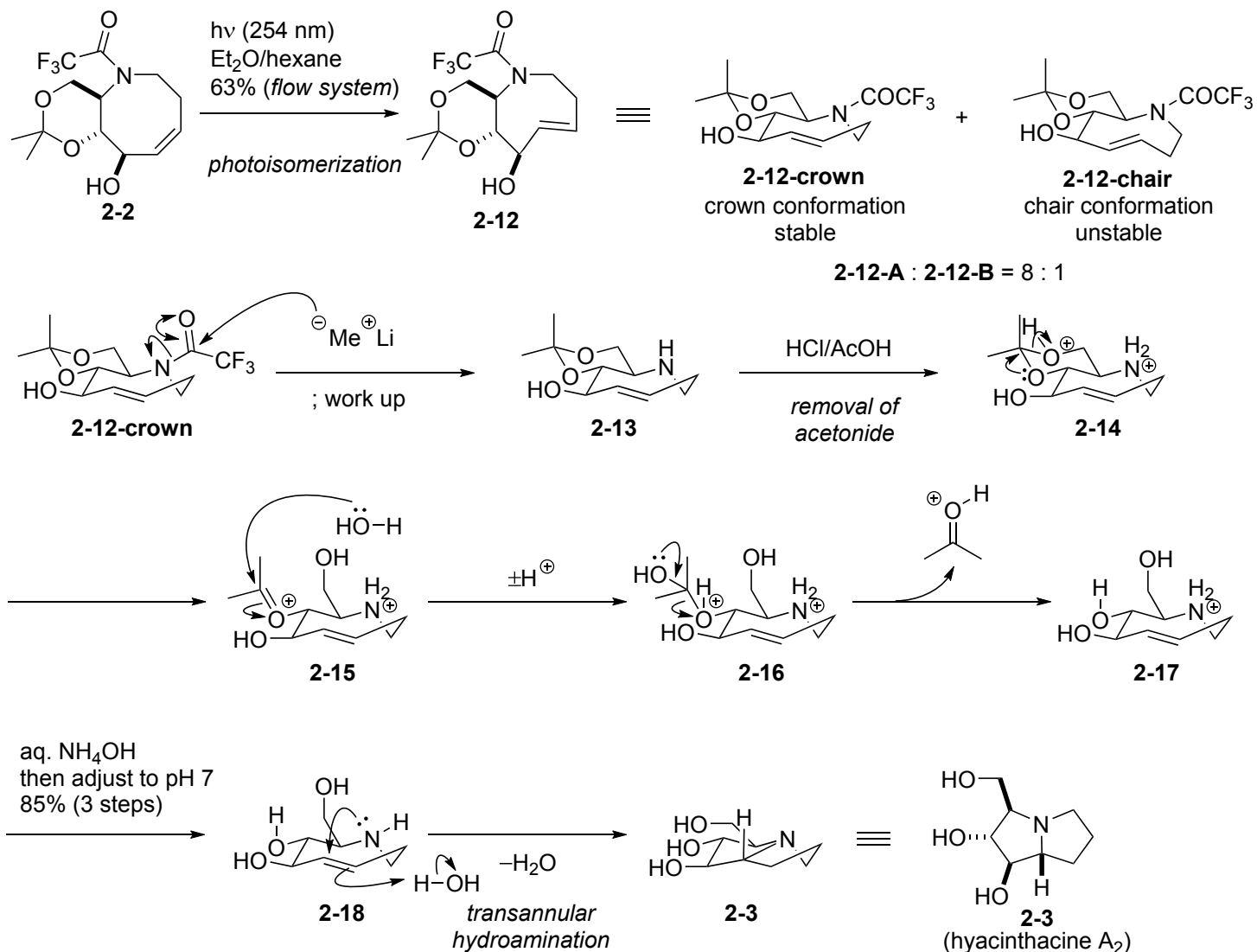
Tomooka, K.; Suzuki, M.; Shimada, M.; Yanagitsuru, S.; Uehara, K. *Org. Lett.* **2006**, *8*, 963.



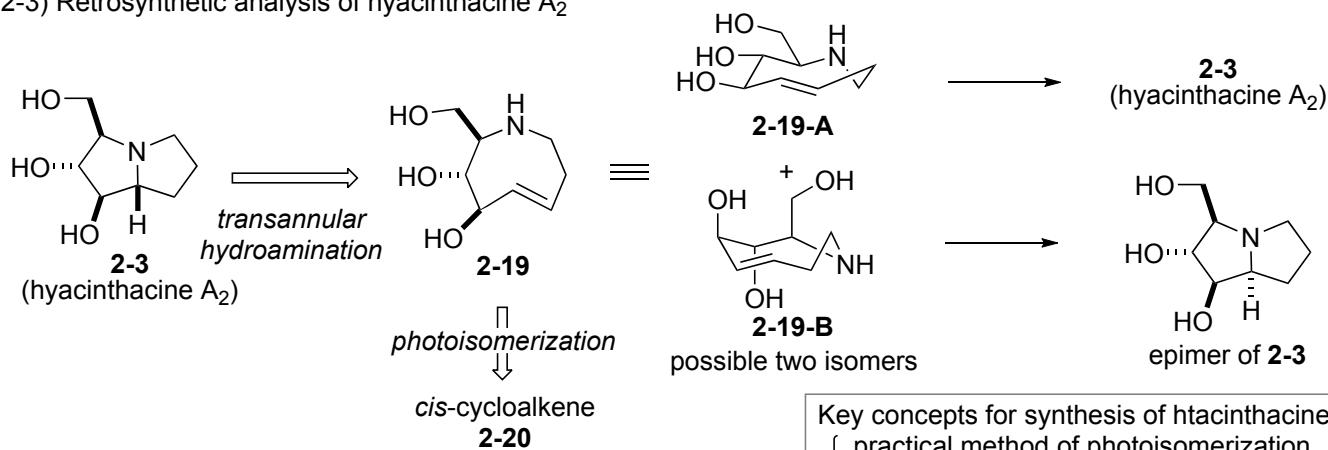
(2-1) Proposed mechanisms from 2-1 to 2-2



(2-2) Proposed mechanisms from **2-2** to **2-3**

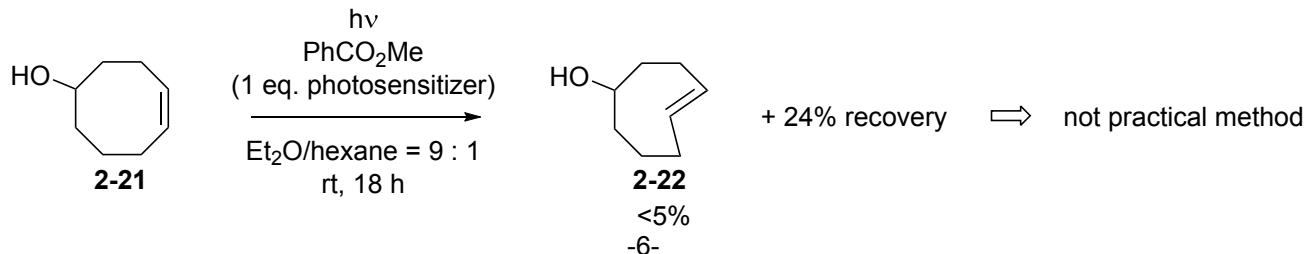


(2-3) Retrosynthetic analysis of hyacinthacine A<sub>2</sub>



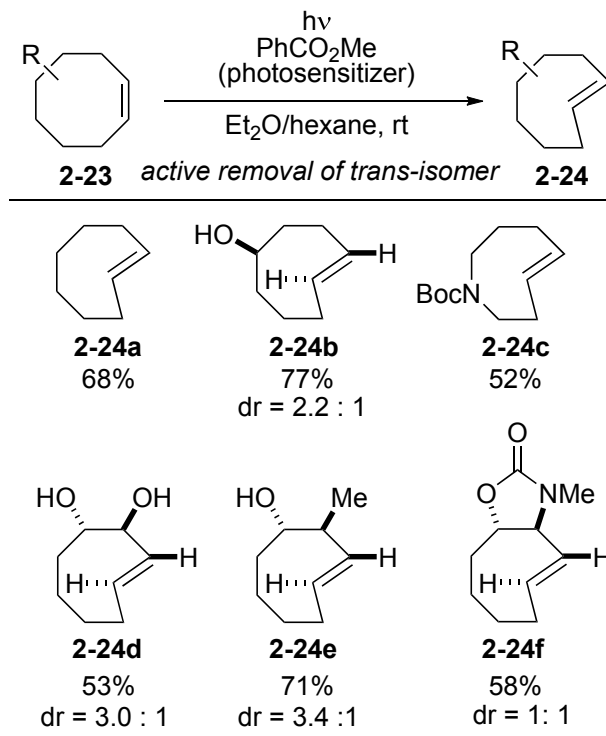
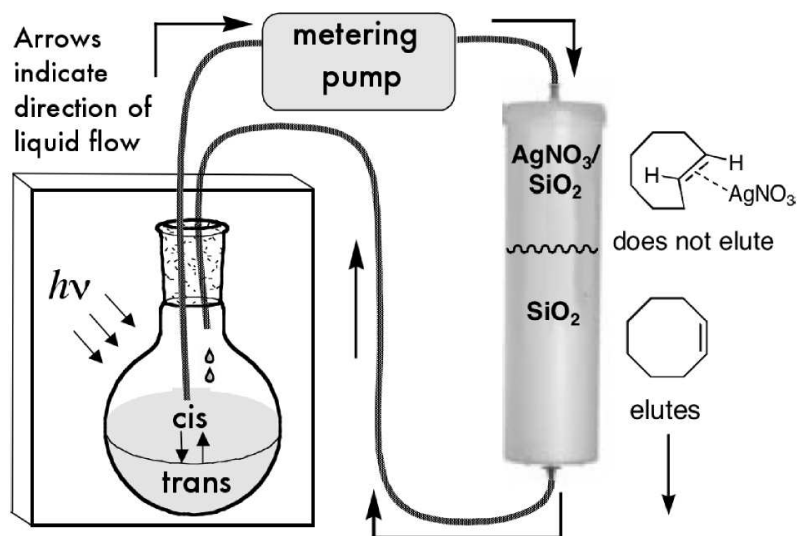
(2-4) Development of practical photoisomerization method of *trans*-cyclooctene

(2-4-1) Conventional batch reaction



(2-4-2) Practical method developed by Joseph M. Fox

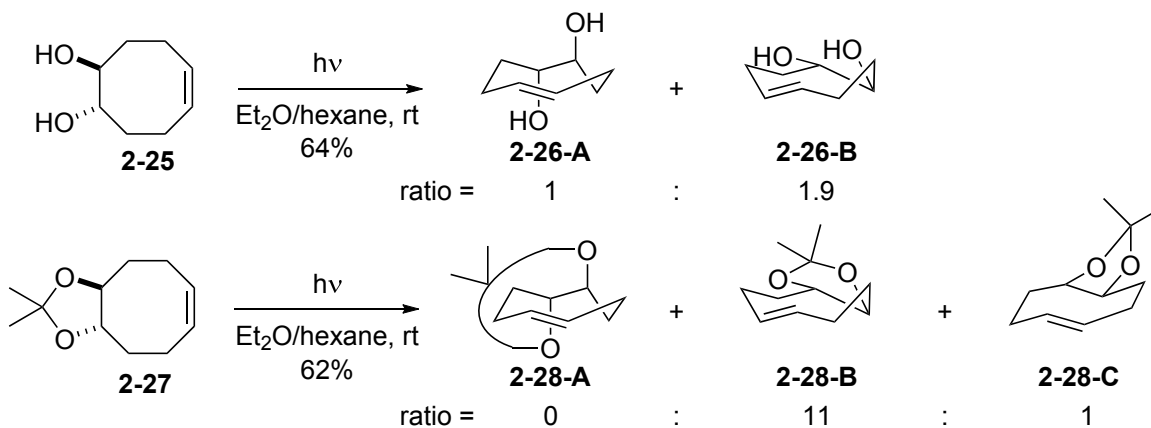
flow system + selective metal complexation of the *trans*-isomer



Royzen, M.; Yap, G. P. A.; Fox, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 3760.

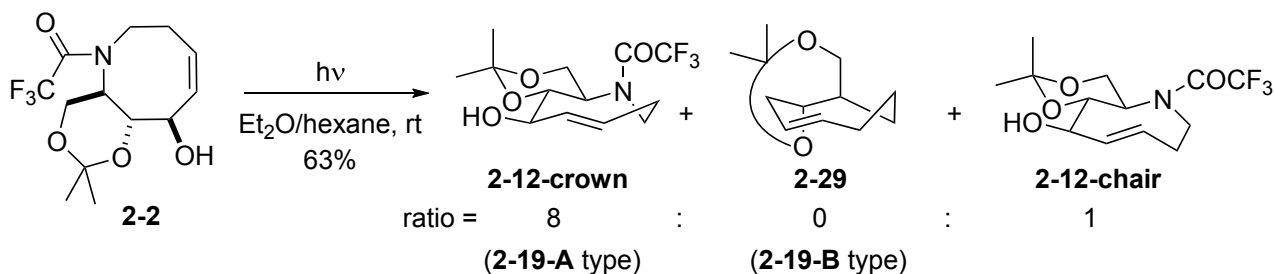
(2-5) Stereocontrol in photoisomerization step

Previous study of acetonide ring fusion effect

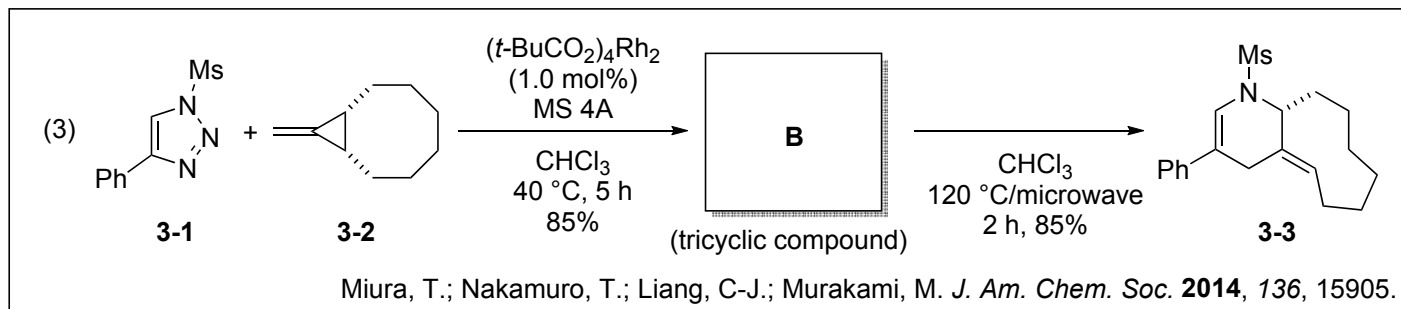


Royzen, M.; Yap, G. P. A.; Fox, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 3760.

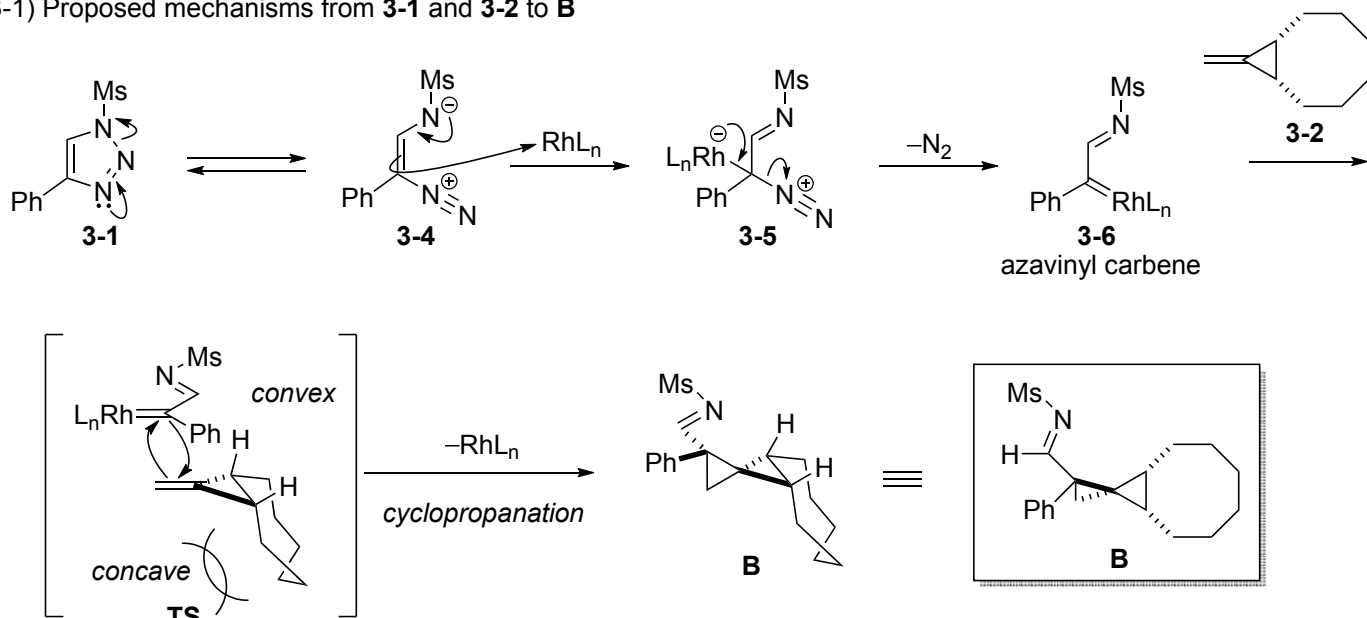
This study



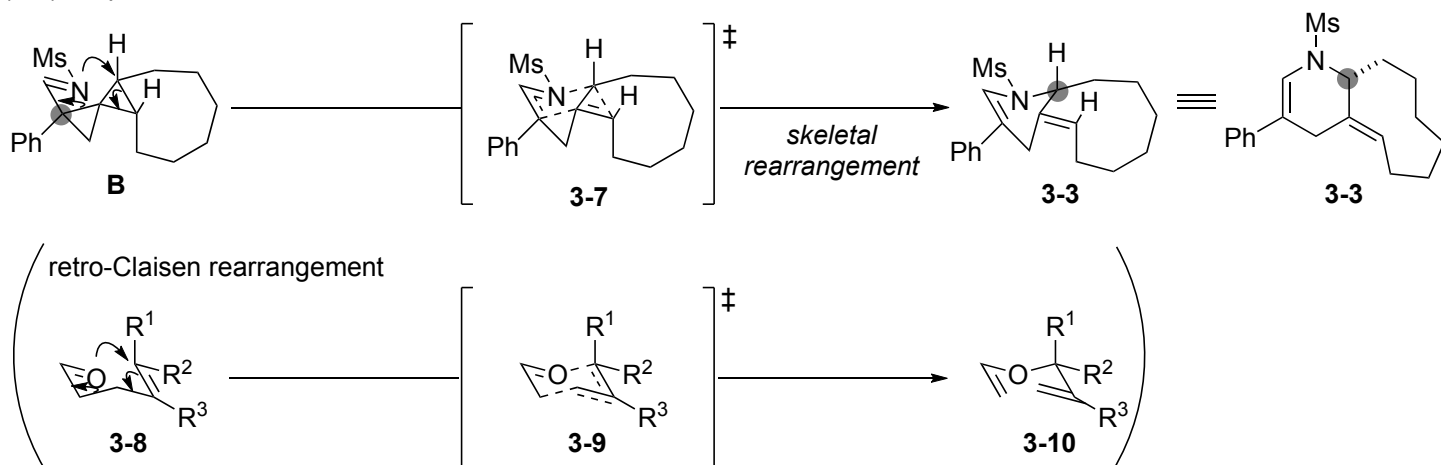
Royzen, M.; Taylor, M. T.; DeAngelis, A.; Fox, J. M. *Chem. Sci.* **2011**, *2*, 2162.



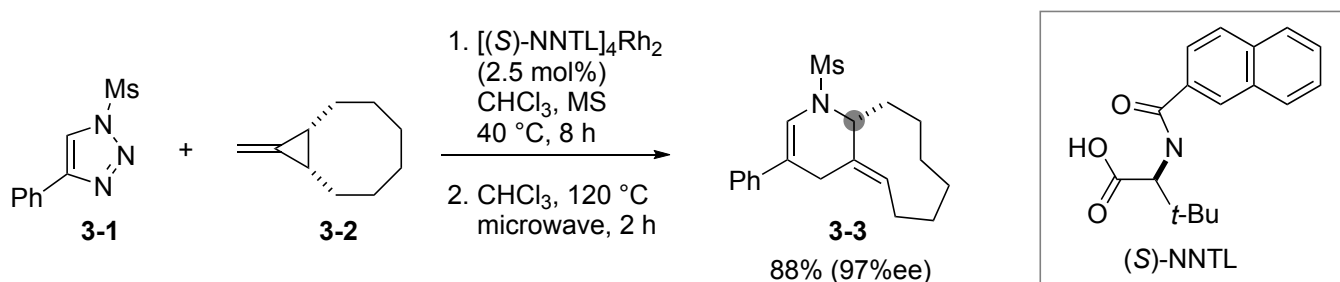
(3-1) Proposed mechanisms from **3-1** and **3-2** to **B**



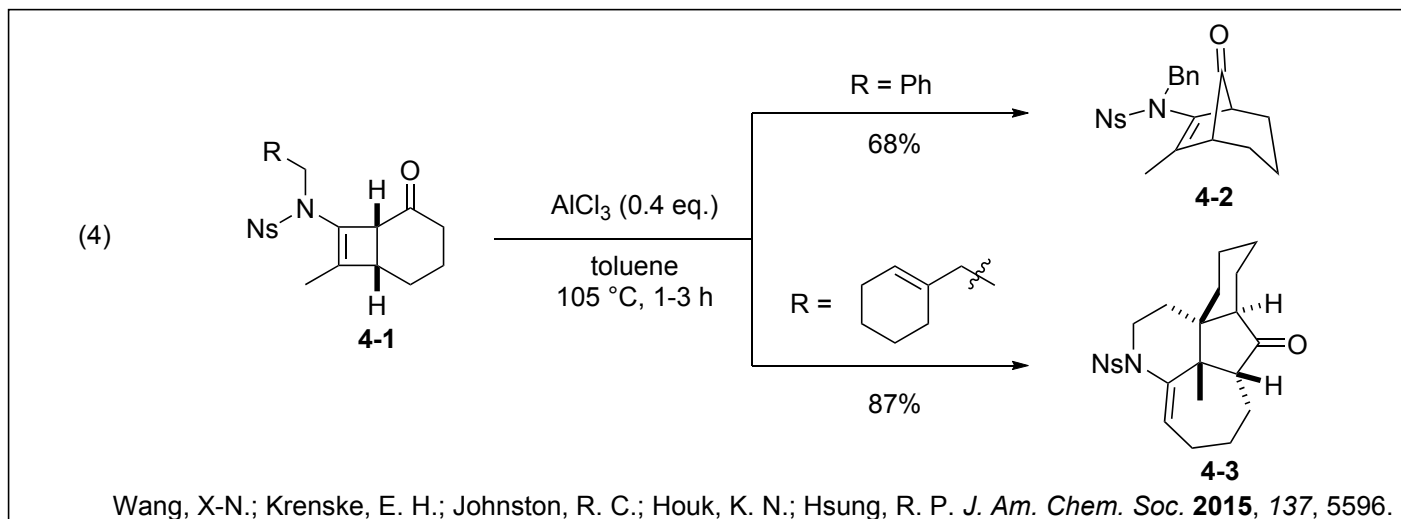
(3-2) Proposed mechanisms from **B** to **3-3**



(3-3) Example of asymmetric synthesis of *trans*-alkene

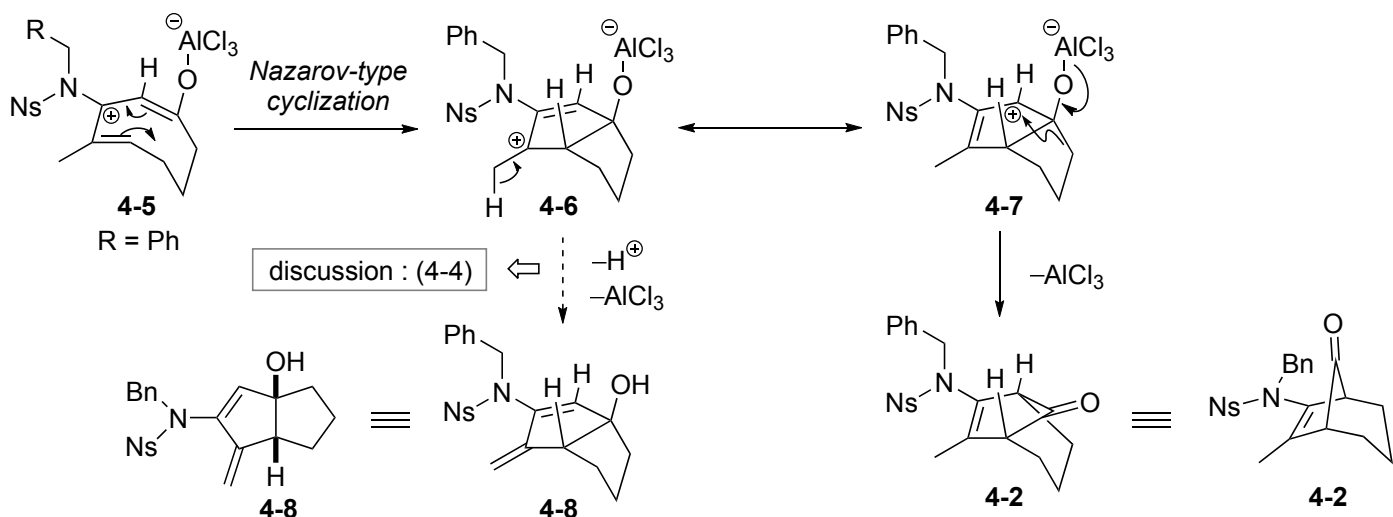
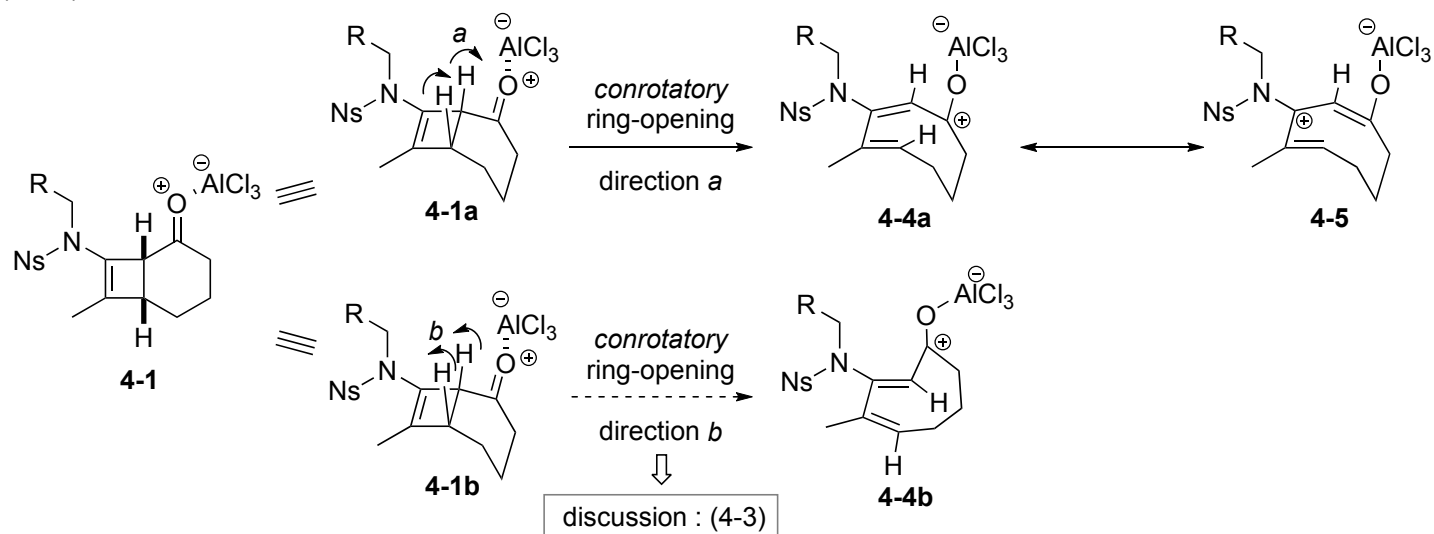




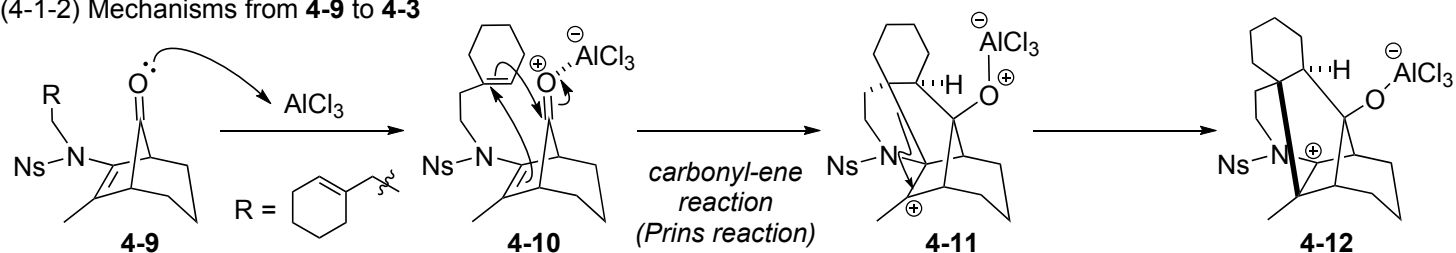


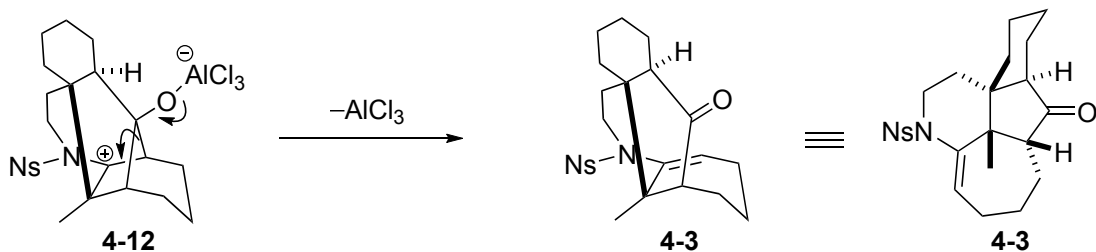
(4-1) Proposed mechanisms

(4-1-1) Mechanisms from **4-1** to **4-2**

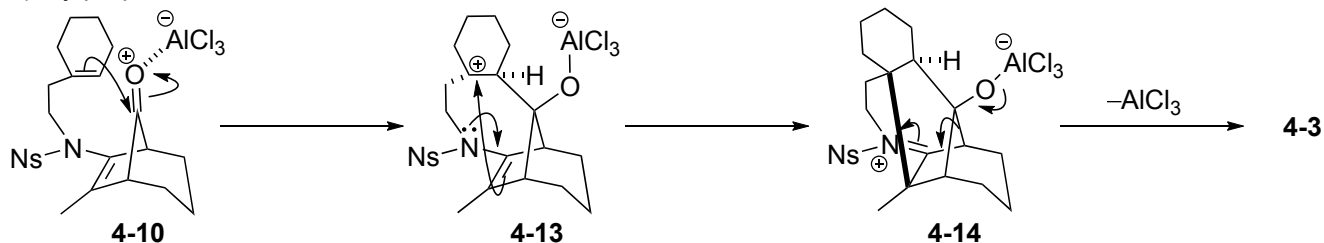


(4-1-2) Mechanisms from **4-9** to **4-3**

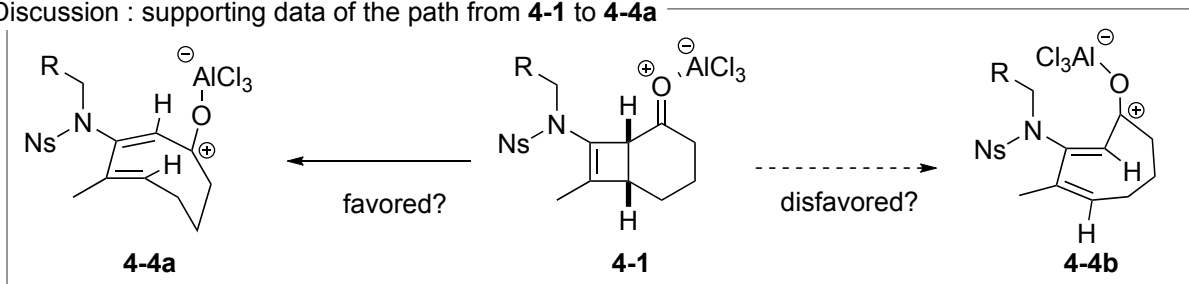




(4-2) My proposed mechanisms from 4-10 to 4-3



(4-3) Discussion : supporting data of the path from 4-1 to 4-4a



Thermal rearrangements of 4,6-fused cyclobutenamide 4-15

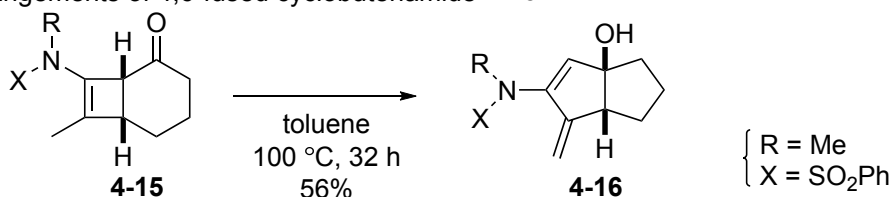
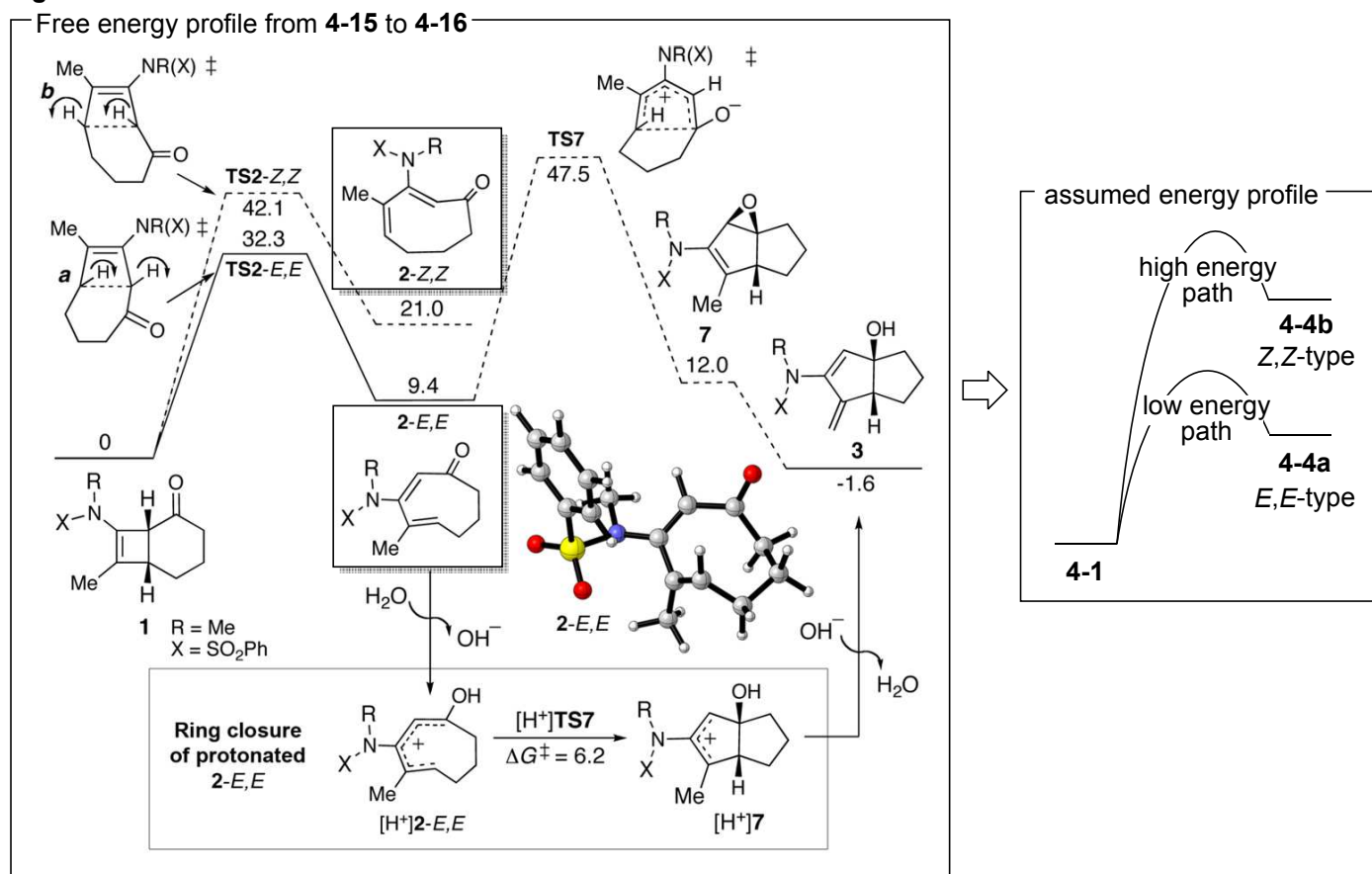


Figure 1.



(4-4) Discussion : supporting data of the path from 4-6 to 4-2

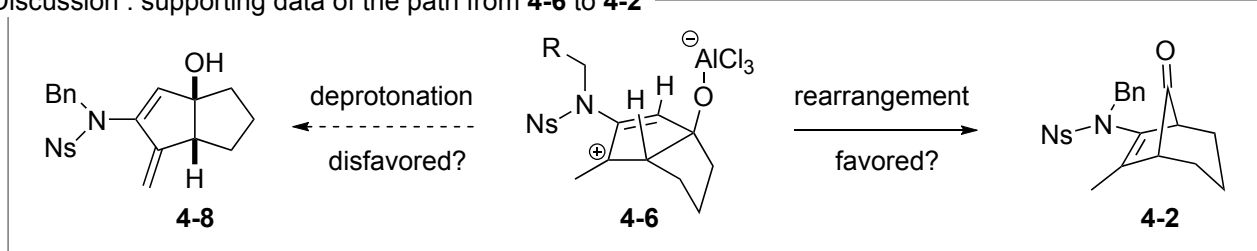
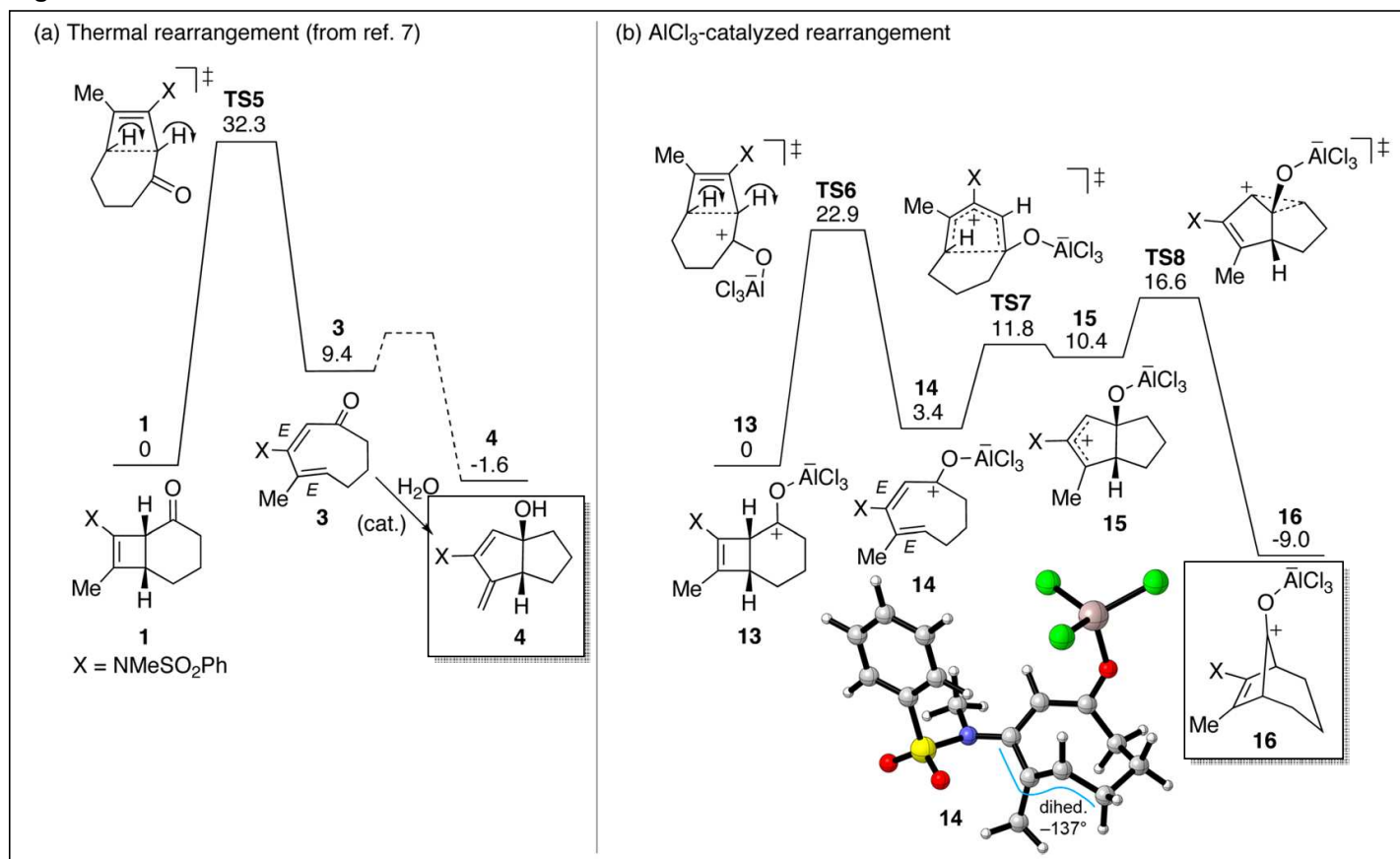


Figure 2.



Wang, X-N.; Krenske, E. H.; Johnston, R. C.; Houk, K. N.; Hsung, R. P. *J. Am. Chem. Soc.* **2015**, *137*, 5596.