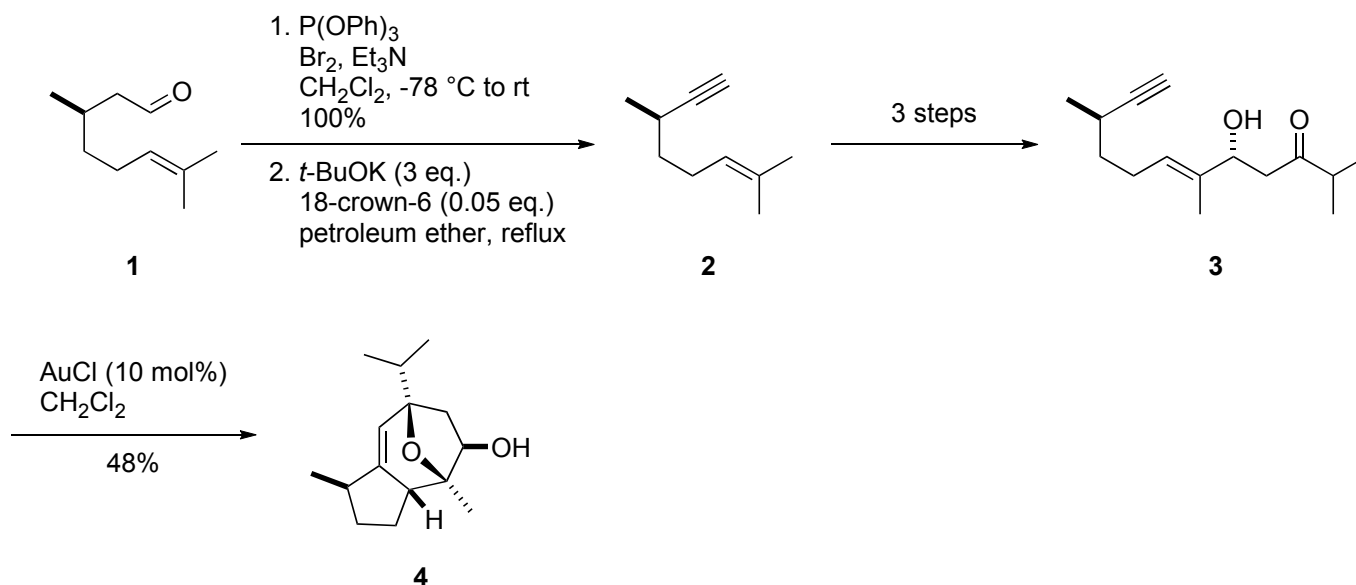
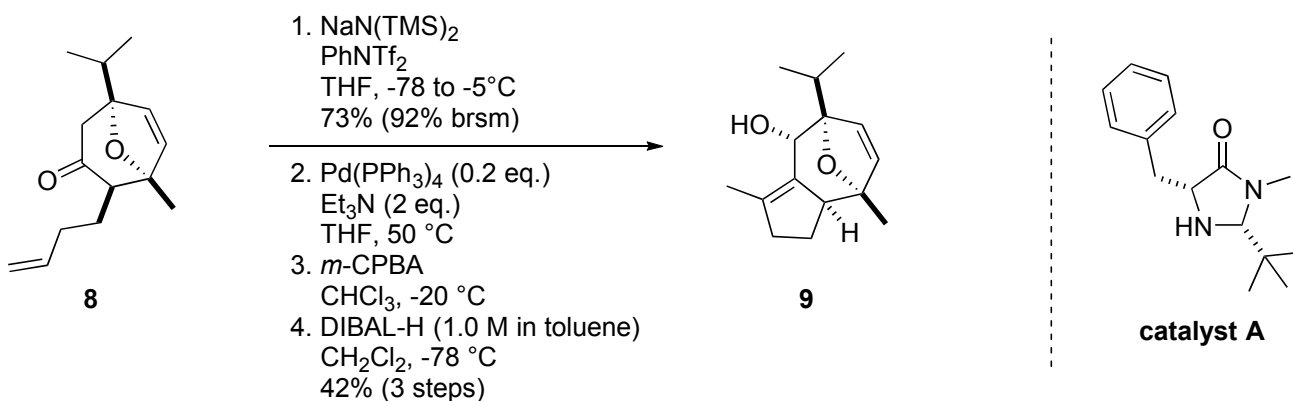
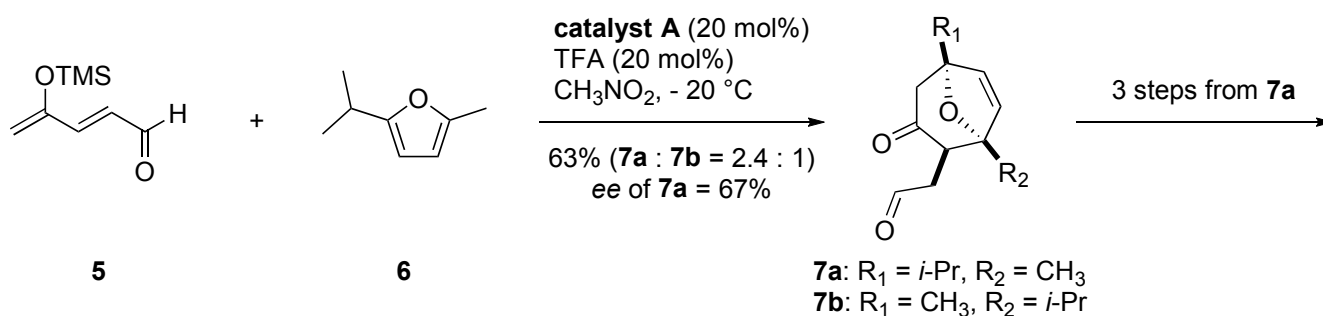


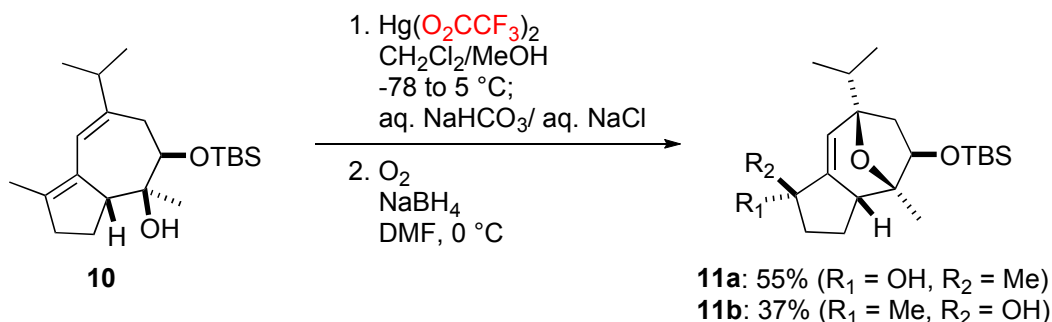
1. Please provide the reasonable reaction mechanisms (1 => 2, 3 => 4) and explain the stereoselectivity (3 => 4).



2. Please explain the reaction mechanisms in each reactions, and explain the stereoselectivity.



3. Please provide the reasonable reaction mechanisms in each reactions.
 (You don't need to explain the stereoselectivity.)



Problem Session ~ Answer ~

2016. 5. 30. Hiroki Fujisawa

Topic: Synthetic Studies of Englerin A

0. Introduction

0-1. Introduction of Englerin A.

Isolation: stem bark of *Phyllanthus englerin*

(Ratnayake, R.; Covell, D.; Ransom, T. T.; Gustafson, K. R. *Org. Lett.* **2009**, *11*, 57.)

biological activity: inhibitor of renal cell carcinoma (RCC)

(Ratnayake, R.; Covell, D.; Ransom, T. T.; Gustafson, K. R. *Org. Lett.* **2009**, *11*, 57.)

structural features:

-tricyclic skeleton including trans-fused 5-7 membered ring (guaiane sesquiterpene)

-oxabicyclo[3,2,1]octane skeleton

-consecutive 7 stereocenters including 2 tetrasubstituted carbons.

synthetic study

- total synthesis

Christmann's group (1. *Angew. Chem. Int. Ed.* **2009**, *48*, 9105.

2. *Angew. Chem. Int. Ed.* **2011**, *50*, 3998.)

Ma's group (*Angew. Chem. Int. Ed.* **2010**, *49*, 3513.)

Echavarren's group (*Angew. Chem. Int. Ed.* **2010**, *49*, 3517.)

Nicolaou's group (*J. Am. Chem. Soc.* **2010**, *132*, 8219.)

Chain's group (*J. Am. Chem. Soc.* **2011**, *133*, 6553.)

Hatakeyama's group (*J. Org. Chem.* **2012**, *77*, 7364.)

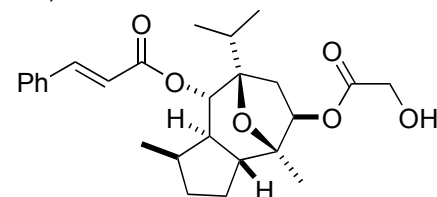
Sun and Lin's group (*Chem. Eur. J.* **2013**, *19*, 2539.)

Metz's group (*Angew. Chem. Int. Ed.* **2013**, *52*, 5390.)

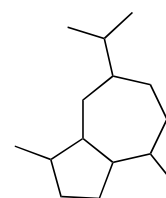
Shen's group (*Tetrahedron, Lett.* **2014**, *55*, 1339.)

Hashimoto's group (*Chem. Eur. J.* **2015**, *21*, 11671.)

Iwasawa's group (*Chem. Asian J.* **2016**, *11*, 64.)



englerin A



guaiane skeleton

-formal synthesis

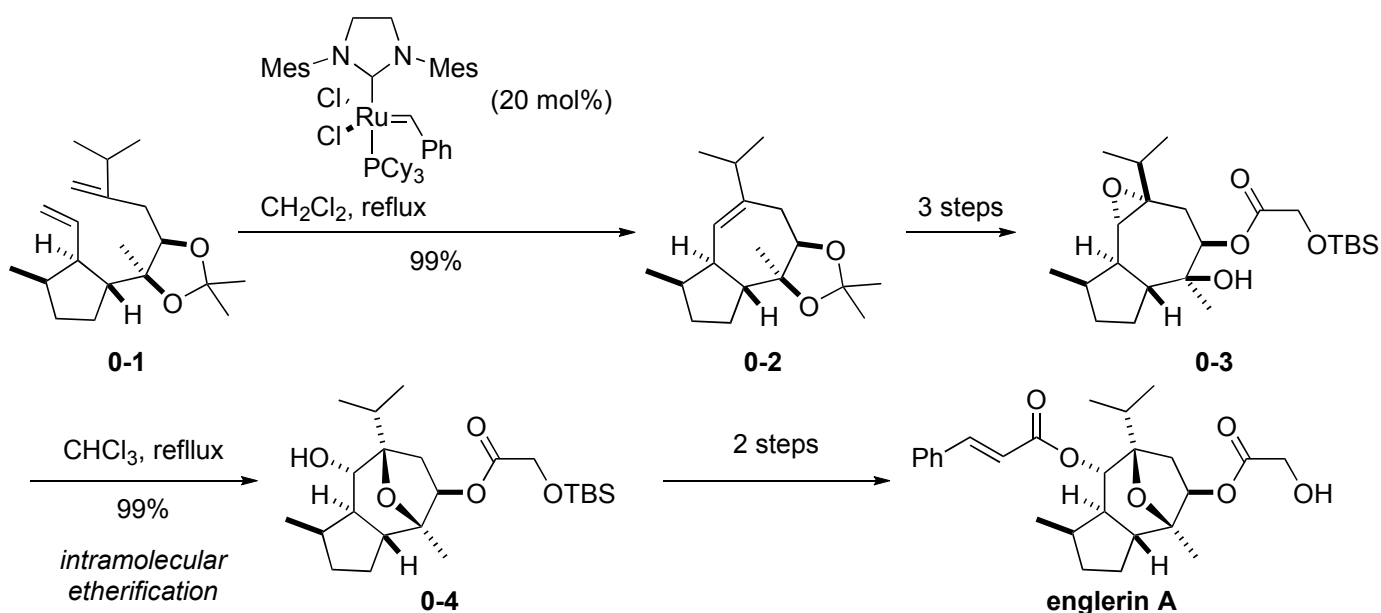
Theodorakis's group (1. *Org. Lett.* **2010**, *12*, 3708. 2. *Chem. Asian J.* **2012**, *7*, 1052)

Parker's group (*Org. Lett.* **2012**, *14*, 2682.)

Cook's group (*Org. Lett.* **2012**, *14*, 3340.)

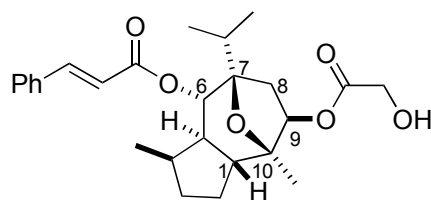
0-2. Synthetic strategy of Englerin A (focus on construction of oxabicyclo[3,2,1]octane skeleton)

0-2-1. Transannulation strategy (Christmann, Hatakeyama, Metz) problem 3



Radtke, L.; Willot, M.; Ziegler, S.; Sauerland, S.; Strohmam, C.; Fröhlich, R.; Habenberger, P.; Waldmann, H.; Christmann, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 3998.

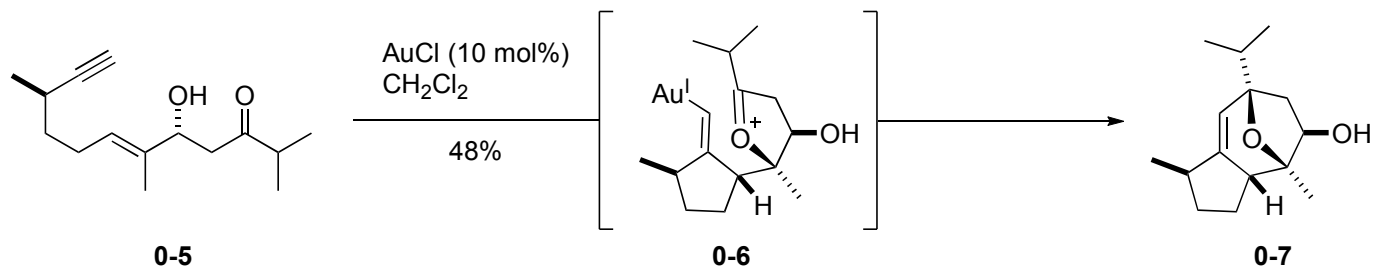
0-2-2. Cycloaddition strategy



englerin A

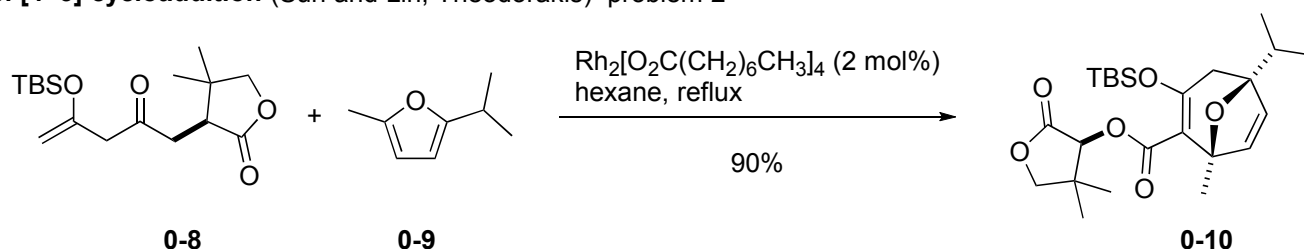
0-2-2-1. C6-C7 and C1-C10 bond formation.

a. [2+2+2] alkyne/alkene/carbonyl cycloaddition (Ma, Echevarrene) problem 1



Zhou, Q.; Chen, X.; Ma, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 3513.

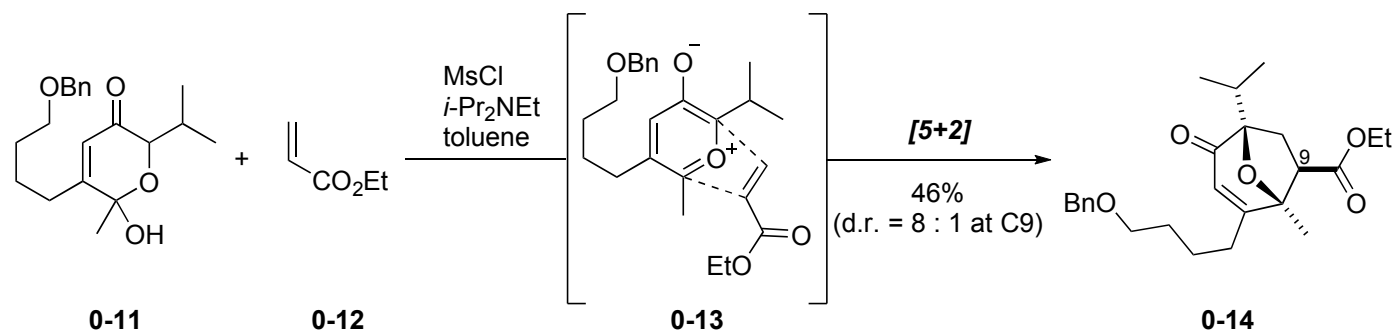
b. [4+3] cycloaddition (Sun and Lin, Theodorakis) problem 2



Xu, J.; Caro-Diaz, E. J. E.; Theodorakis, E. A. *Org. Lett.* **2010**, *12*, 3708.

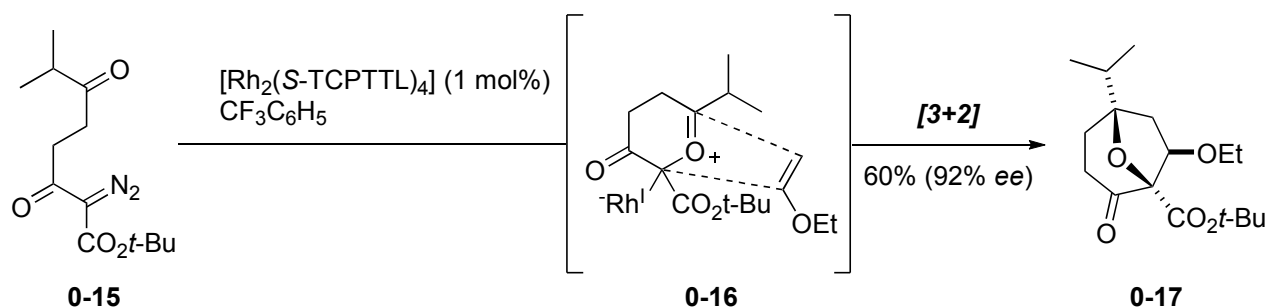
0-2-2-2. C7-C8 and C9-C10 bond formation.

a. [5+2] cycloaddition (Nicolaou)

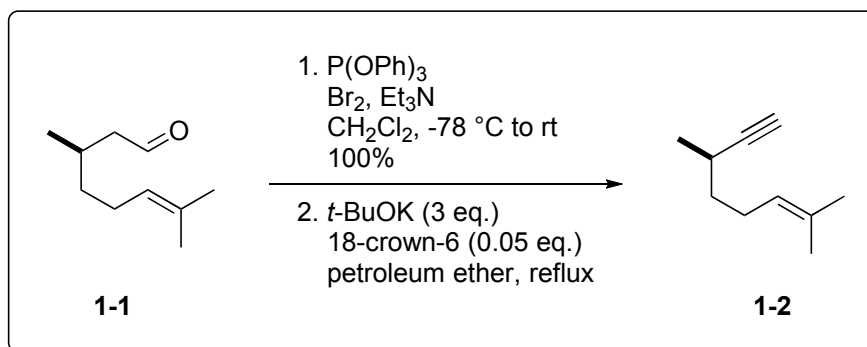


Nicolaou, K.C.; Kang, Q.; Ng, S. Y.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2010**, *132*, 8219.

b. [3+2] cycloaddition (Hashimoto, Iwasawa)

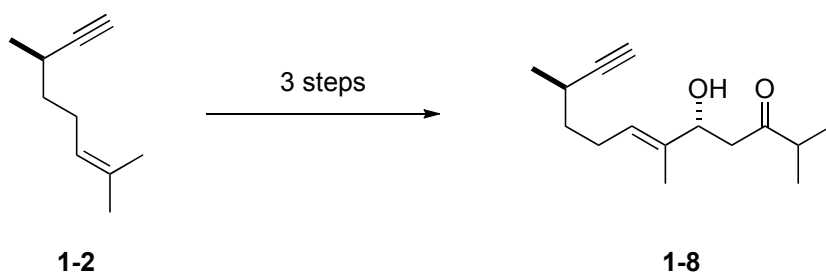
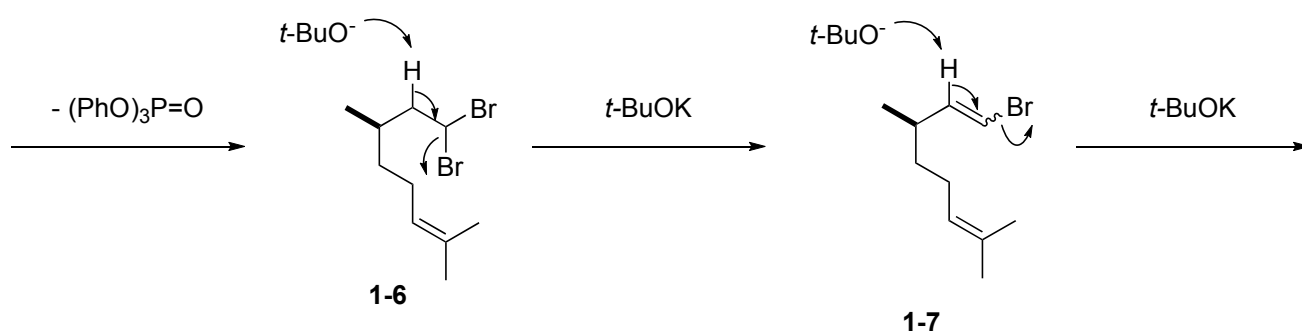
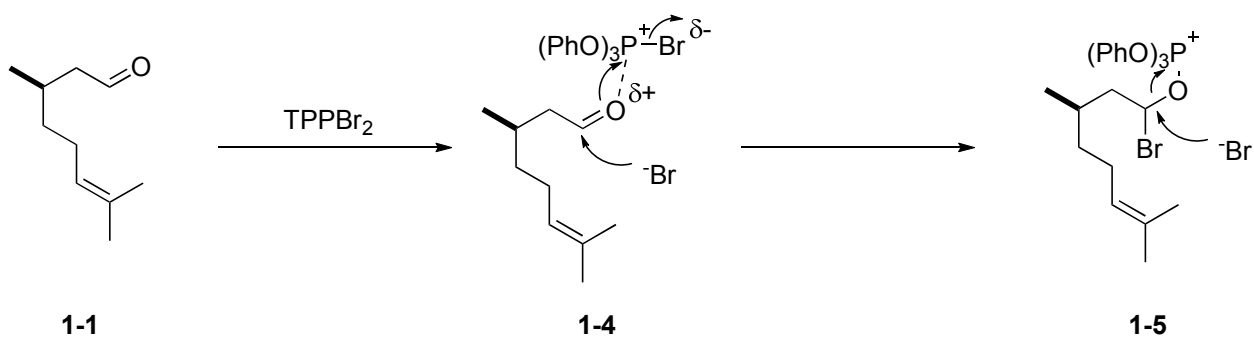
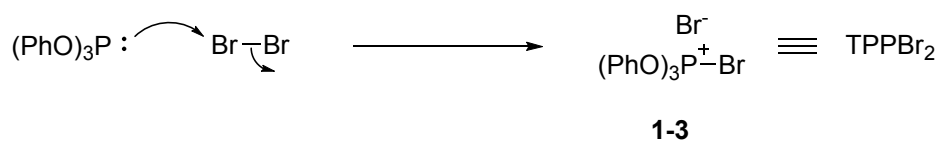


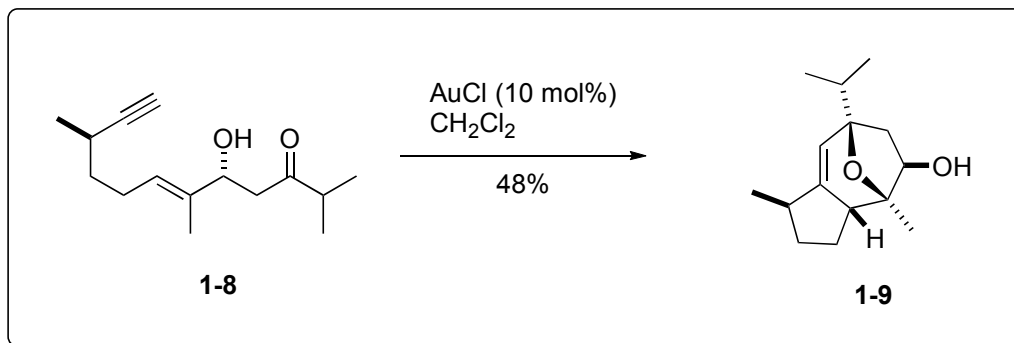
Hanari, T.; Shimada, N.; Kurosaki, Y.; Thrimurtulu, N.; Nambu, H.; Anada, M.; Hashimoto, S. *Chem. Eur. J.* **2015**, *21*, 11671.



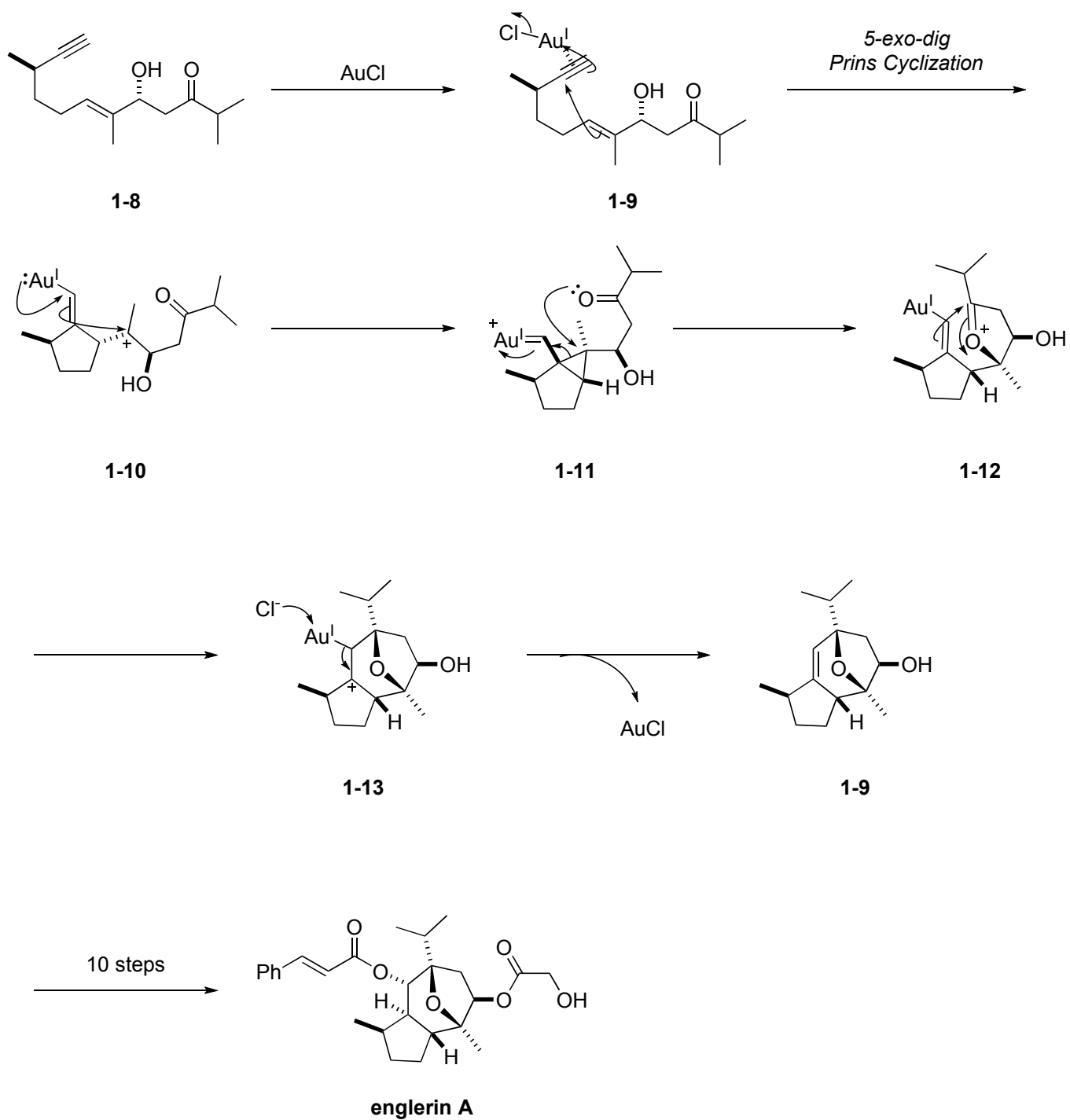
Zhou, Q.; Chen, X.; Ma, D. *Angew. Chem. Int. Ed.* **2010**, 49, 3513.

Answer:





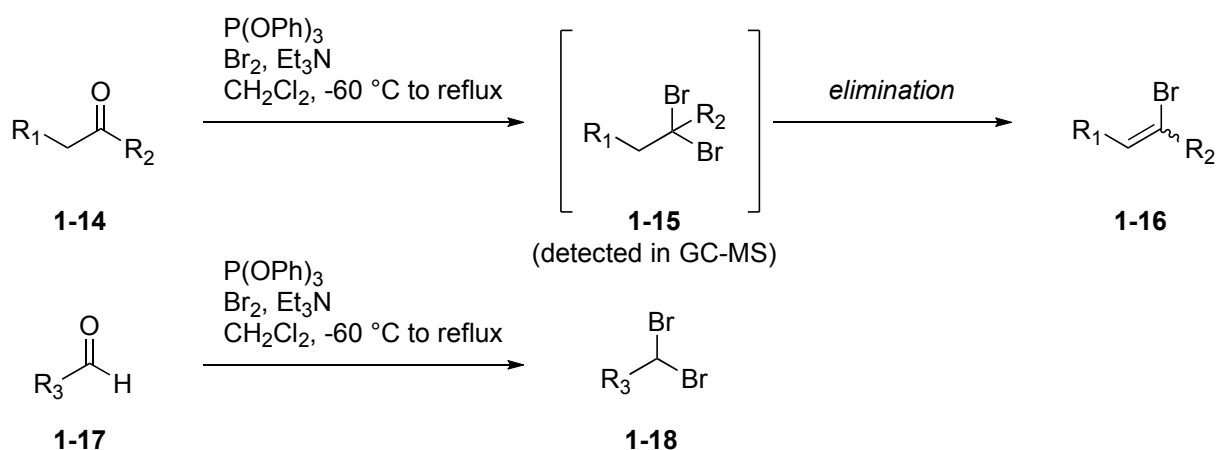
Answer:



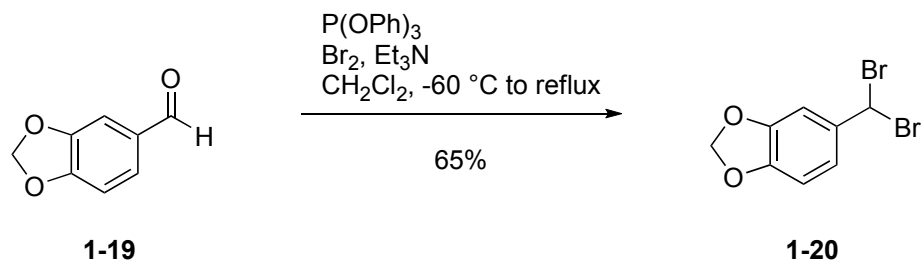
Discussions:

1. Synthesis of vinylhalide and *gem*-dihalide.

1-1. Introduction (Spaggiari, A.; Vaccari, D.; Davoli, P.; Torre, G.; Prati, F. *J. Org. Chem.* **2007**, 72, 2216.)

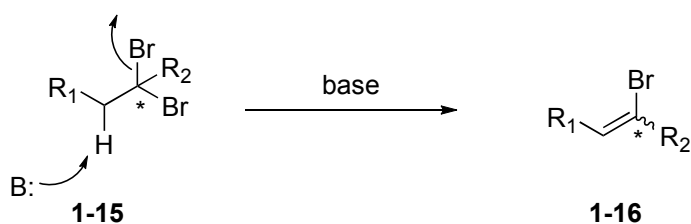
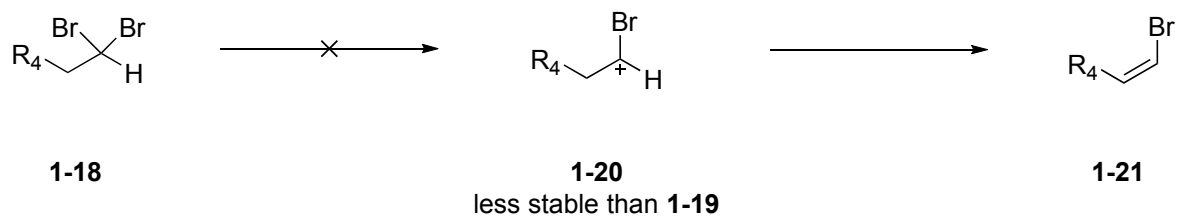
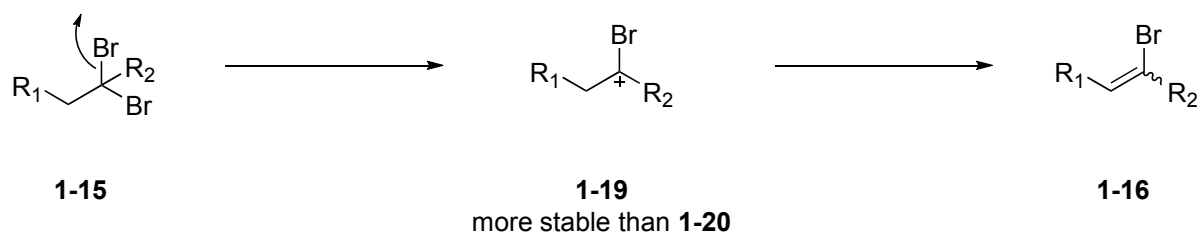


1-2. *Gem*-dihalide formation using non-enolizable aldehyde.



Aldehyde is not necessarily enolizable.

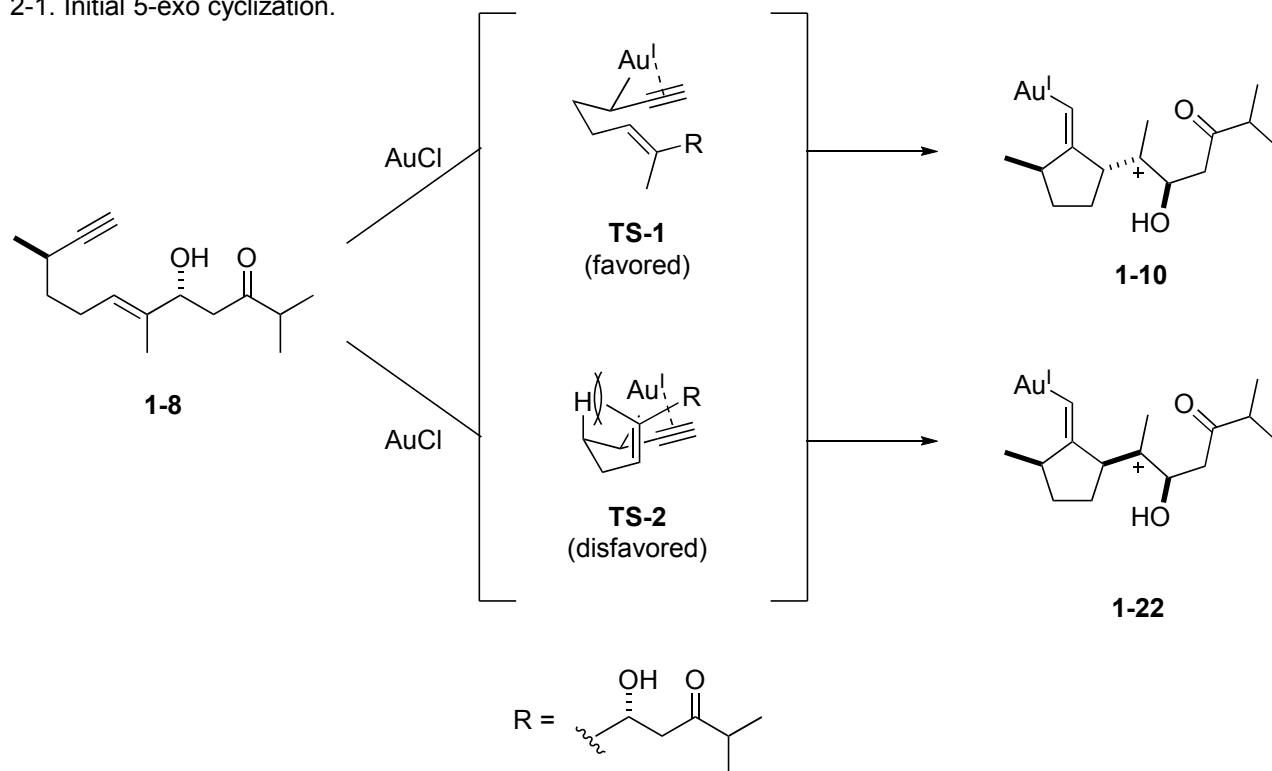
1-3. Possible explanation of difference between ketone and aldehyde. (My proposal)



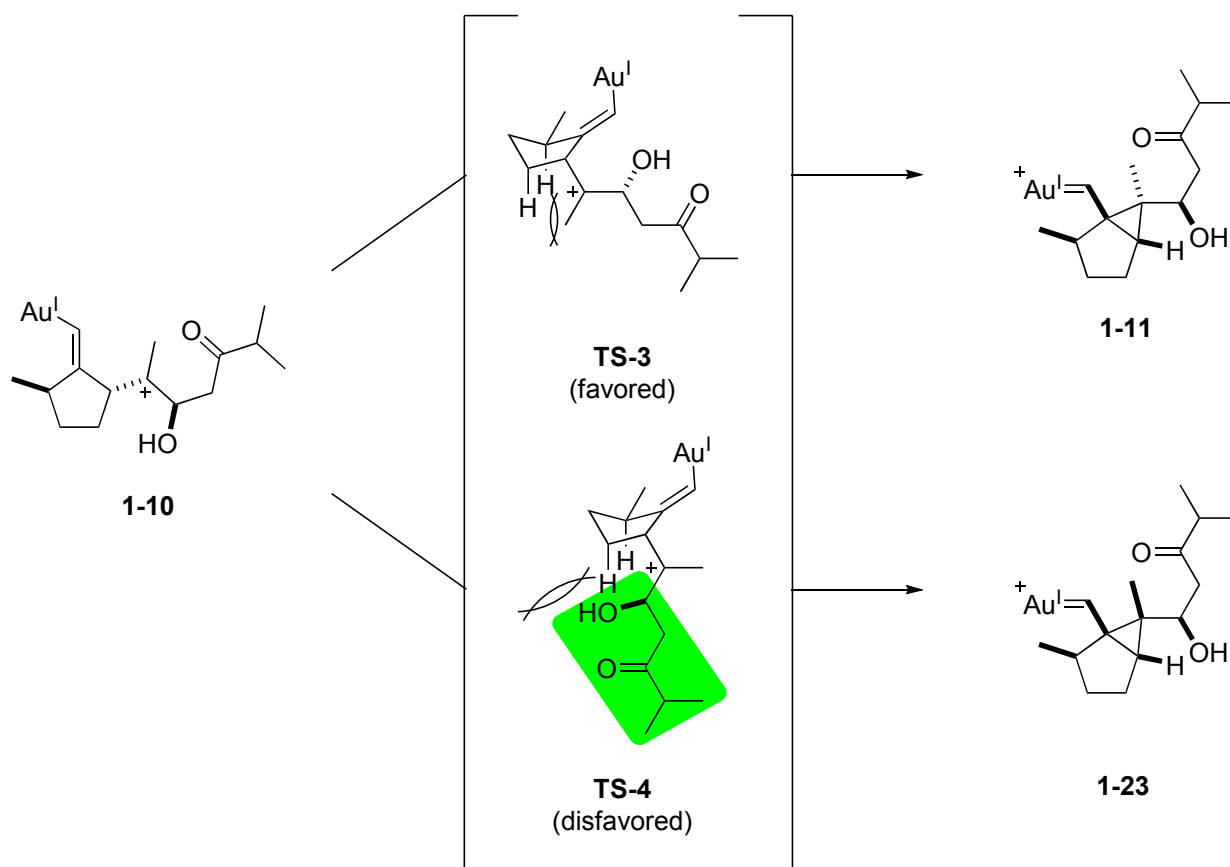
Or decrease the steric hindrance around C* carbon promotes elimination reaction?

2. Stereoselectivity in Au^I-catalyzed cycloisomerization.

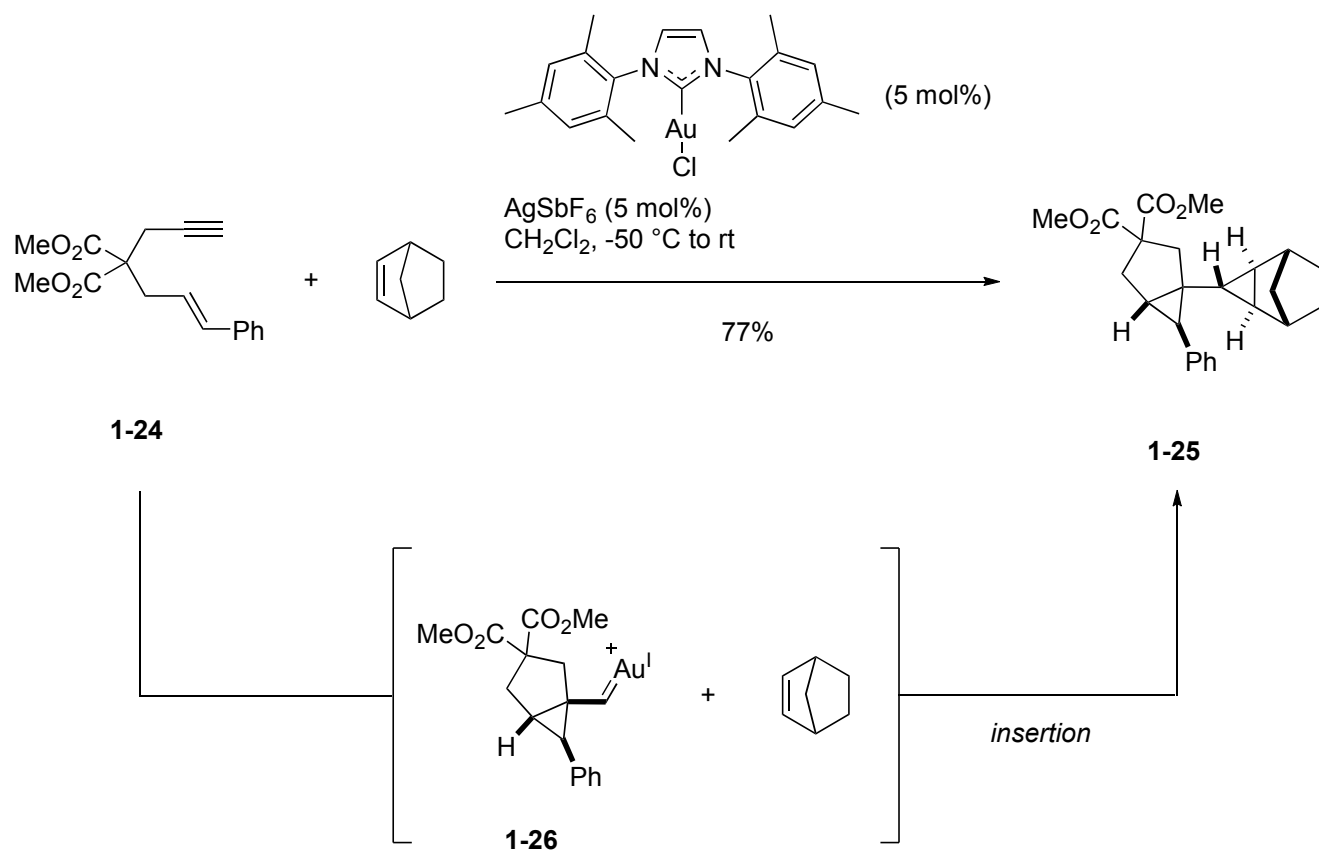
2-1. Initial 5-exo cyclization.



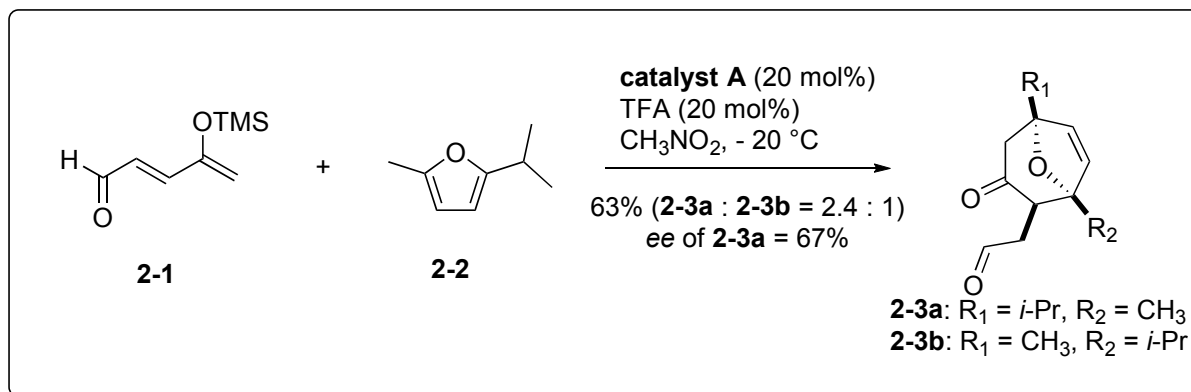
2-2. Following cyclopropanation.



3. One evidence for the formation of cyclopropane ring and the involvement of metal carbene.

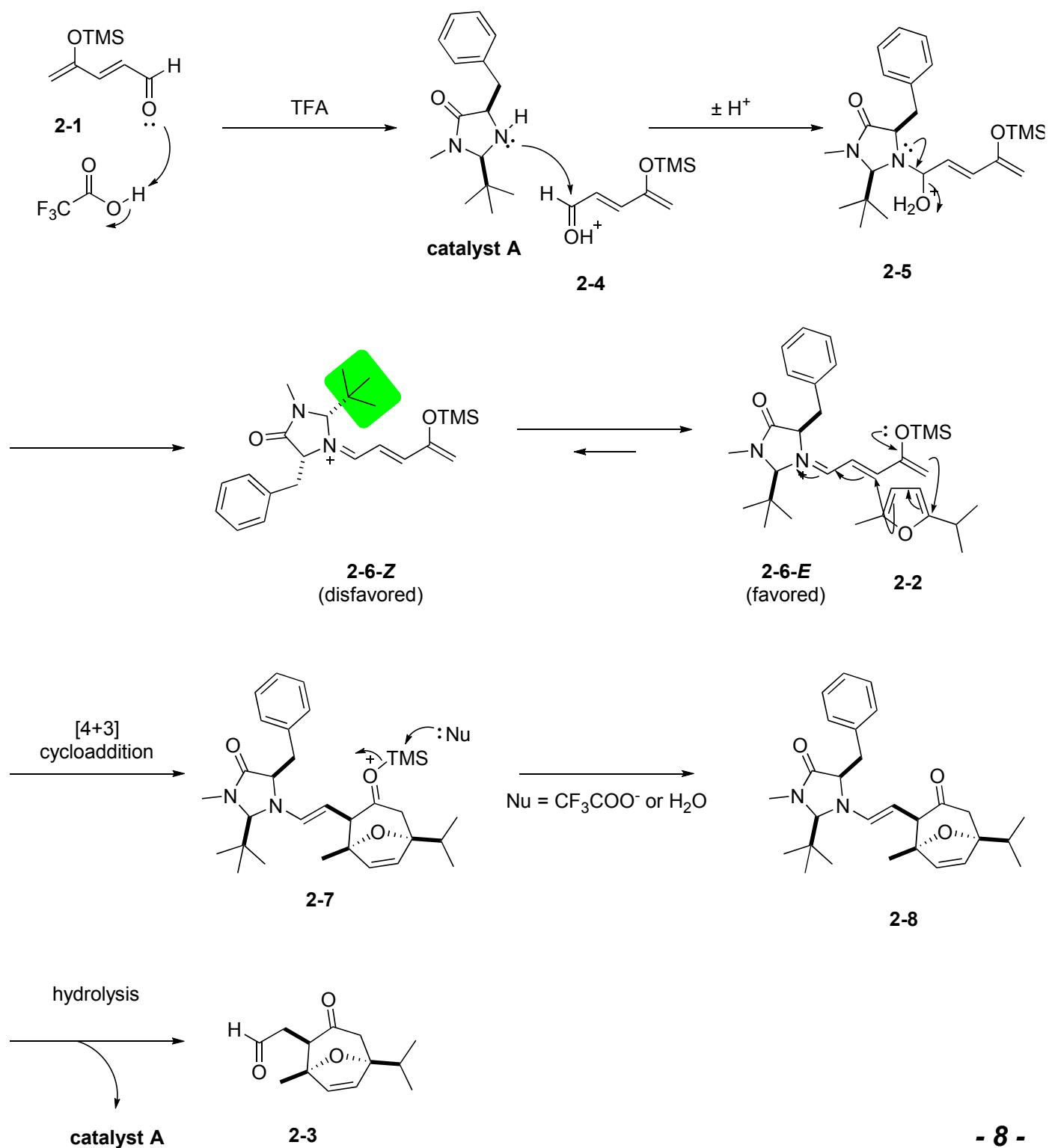


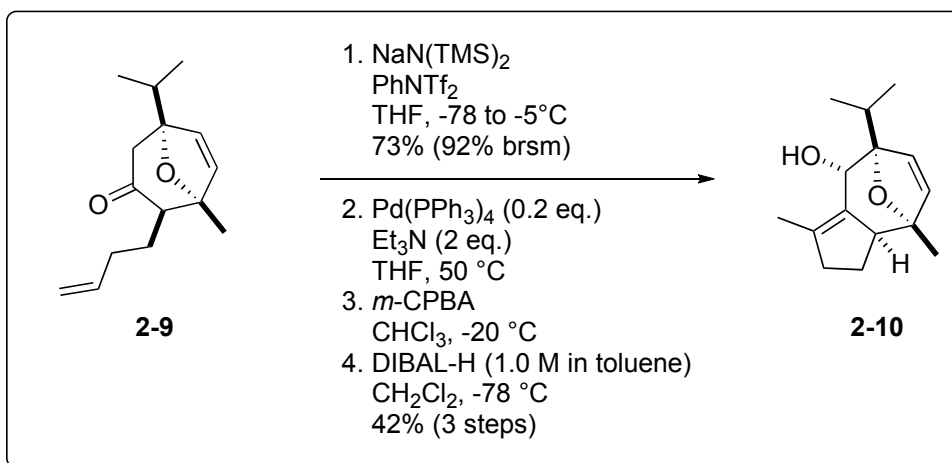
López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, 45, 6029.



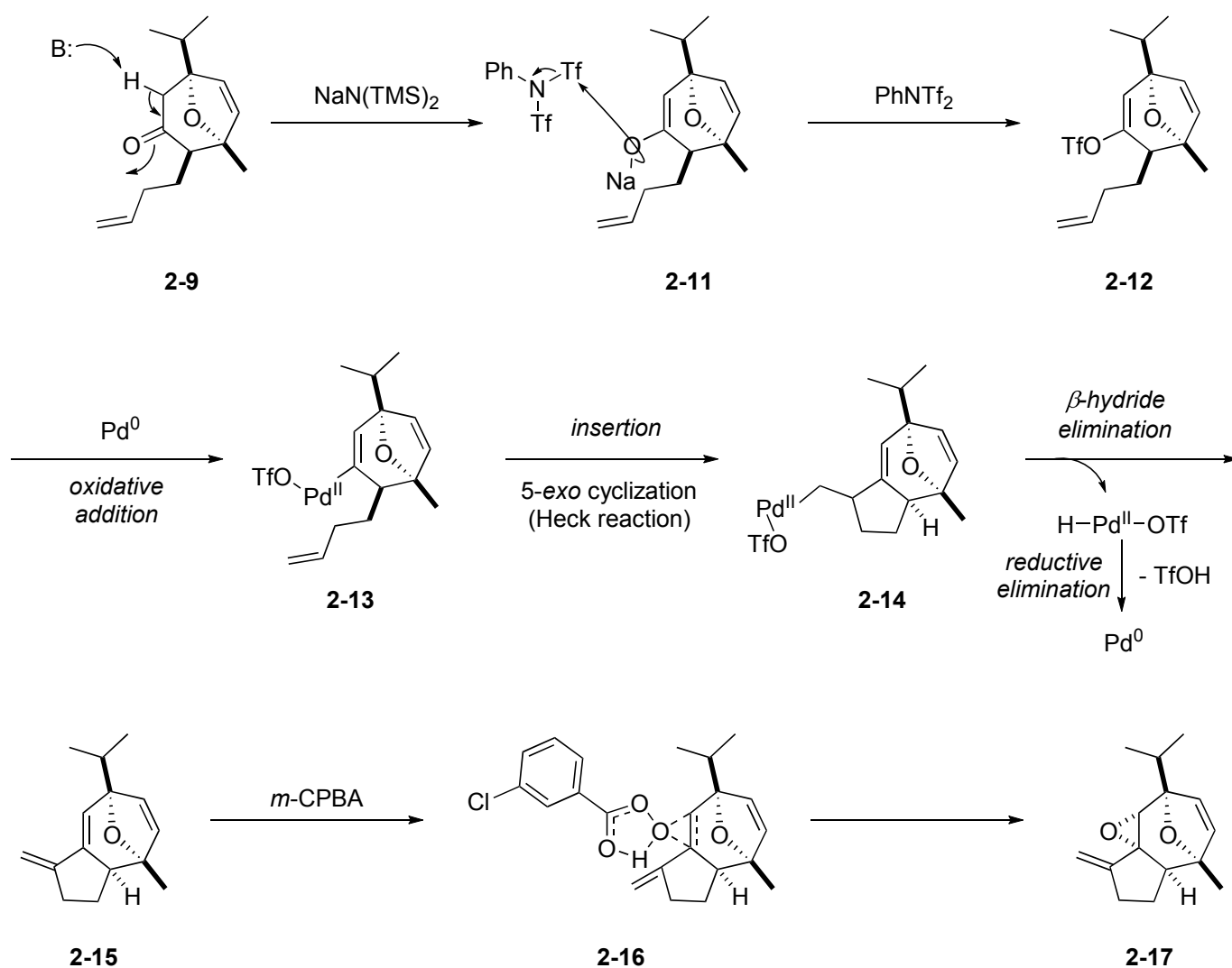
Wang, J.; Chen, S.-G.; Sun, B.-F.; Lin, G.-Q.; Shang, Y.-J. *Chem. Eur. J.* **2013**, *19*, 2539.

Answer:

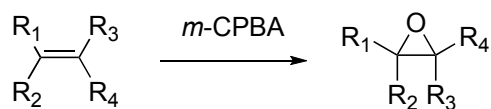




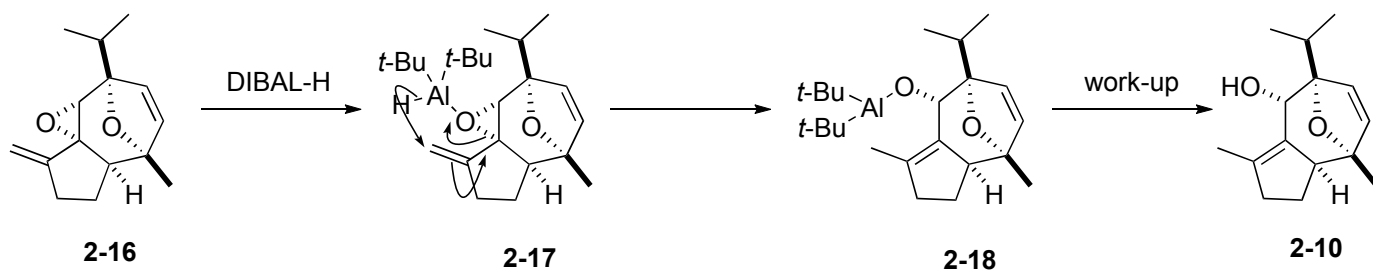
Answer:



cf. Reaction rate of epoxidation.



1	24	500	500	6500	>6500



Discussions:

1. Explanation for selectivity.

* I defined "syn" and "anti" as shown in figure 1.

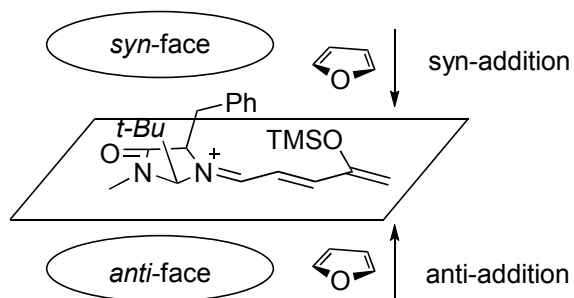
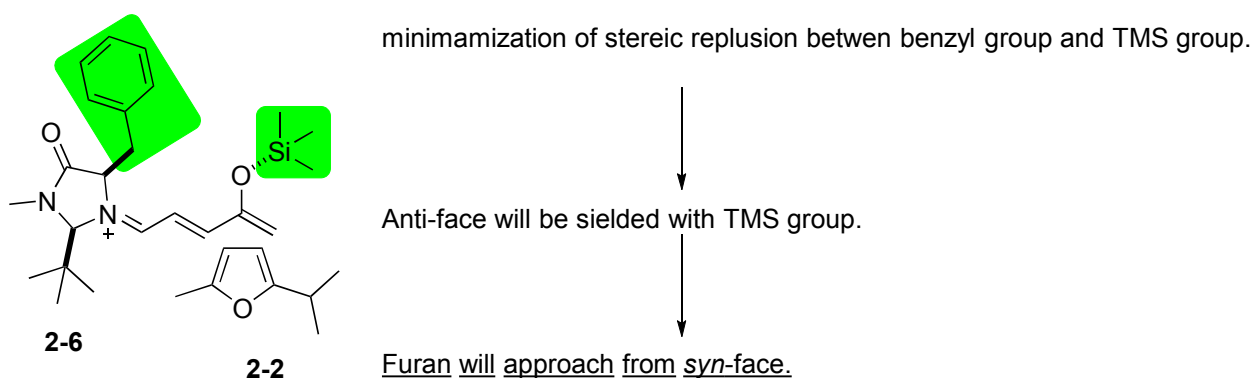
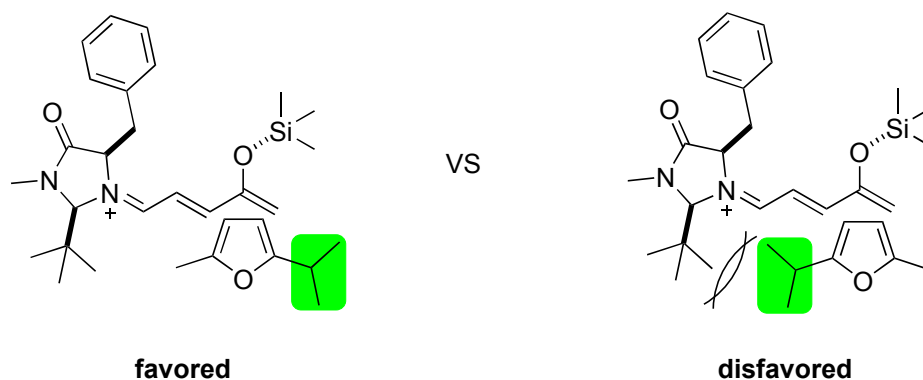


figure 1

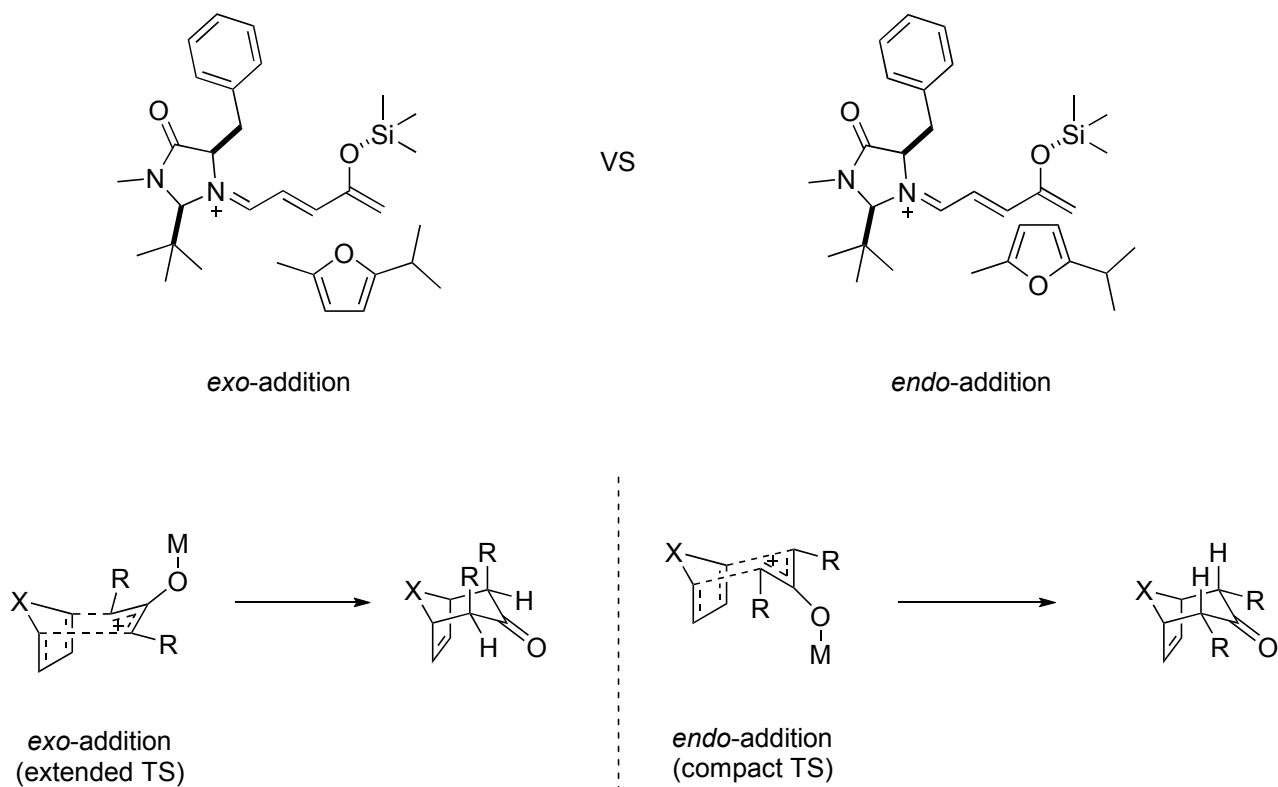
1-1. Face-selectivity.



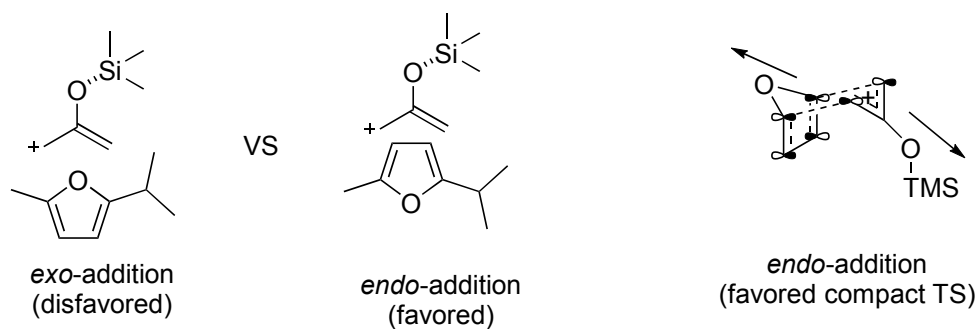
1-2. Regio-selectivity.



1-3. Exo-endo-selectivity.



In case of furan, *endo*-addition via compact TS is favored in order to minimize the dipole moment.



About oxallyl cation involving [4+3] cycloaddition, please also see following reviews:

Hoffmann, H. M. R. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 819.

Hoffmann, H. M. R. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 1.

Mann, J. *Tetrahedron*, **1986**, *42*, 4611.

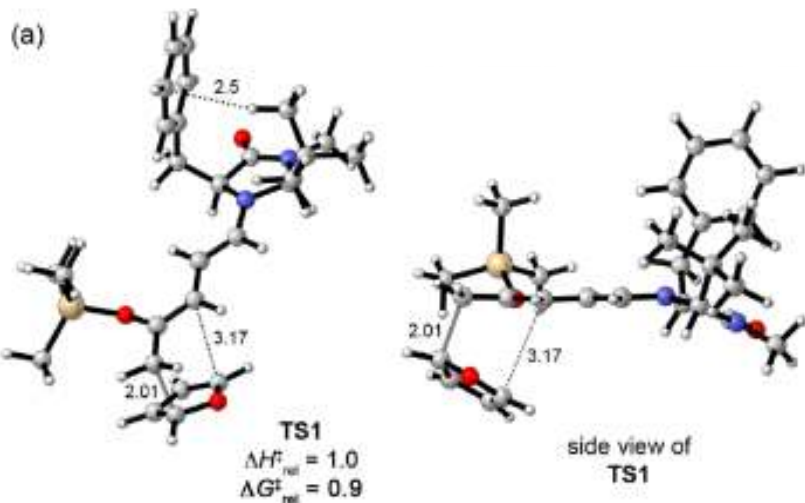
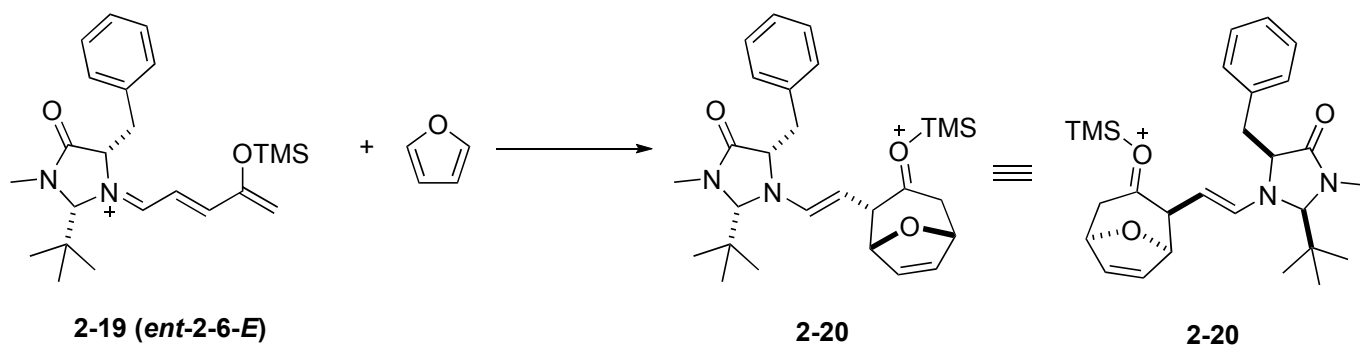
Rigby, J. H.; Pigge, F. C. *Org. React.* **1997**, *51*, 351.

Harmata, M. *Chem. Commun.* **2010**, *46*, 8904.

See also Hagiwara-kun's PS on 140301.

1-4. Computational analysis (B3LYP/6-31G(d) level, values kcal/mol (298 K, gas phase))

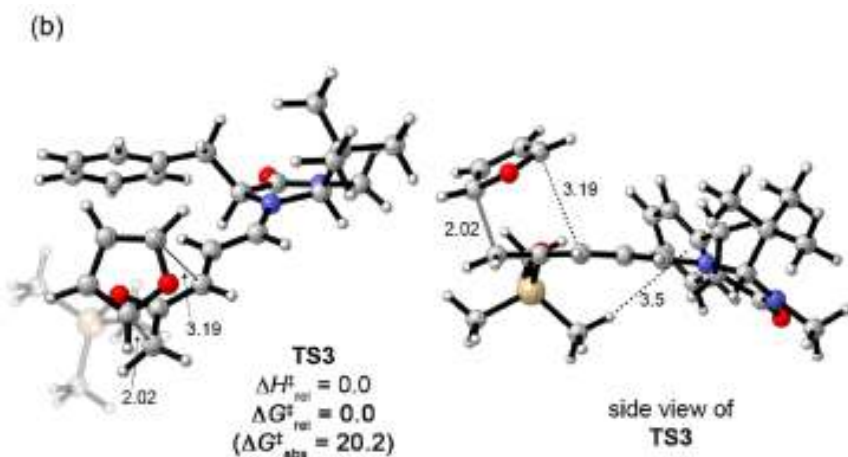
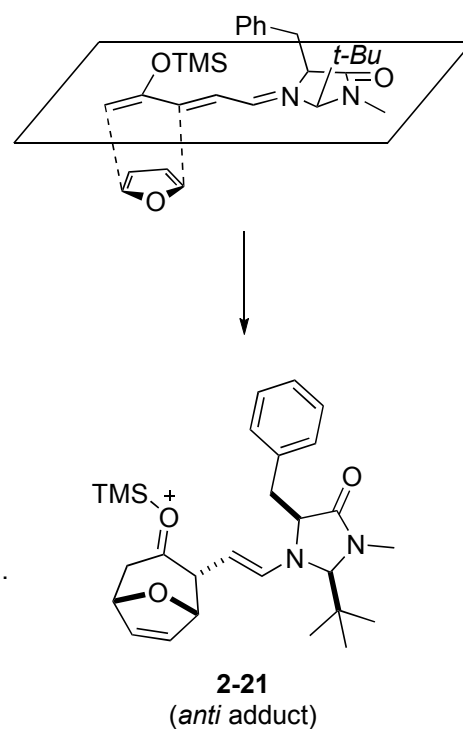
1-4-1. Face-selectivity



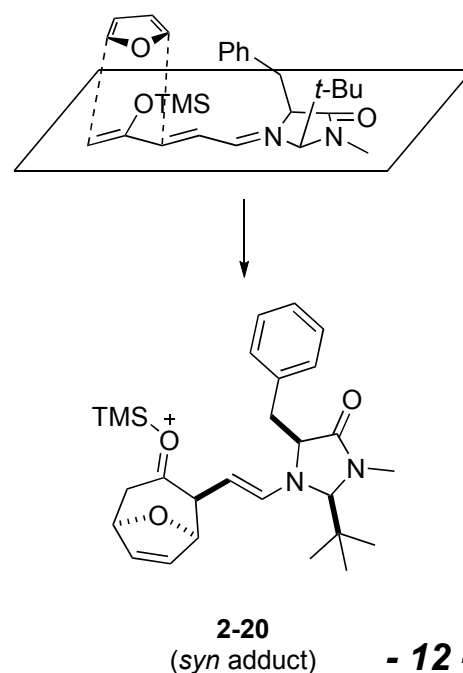
(a) disfavored *anti*-addition

If furan approaches from *anti*-face,
 \Rightarrow TMS group will position at *syn*-face to avoid the approaching furan ring.
 \Rightarrow Benzyl group avoids the TMS group.
 \Rightarrow Benzyl group becomes close to *t*-Bu group. \Rightarrow unstable!

as a result, *anti*-addition will be unfavorable.

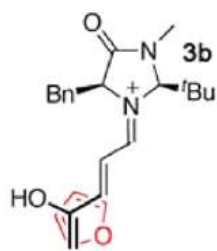


(b) favored *syn*-addition



1-4-2. Importance of silyl group

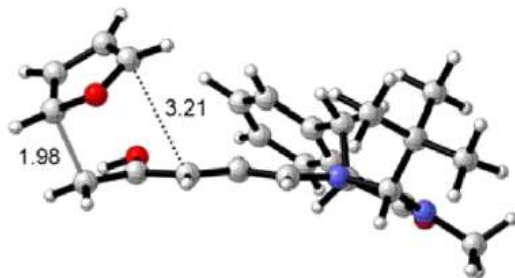
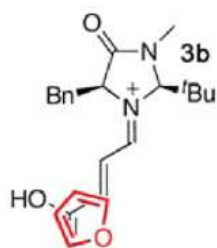
Addition to *anti* face



$$\begin{aligned} \text{TS-OH-}\alpha \\ \Delta H_{\text{rel}}^{\ddagger} &= 0.0 \\ \Delta G_{\text{rel}}^{\ddagger} &= 0.0 \end{aligned}$$

favored

Addition to *syn* face

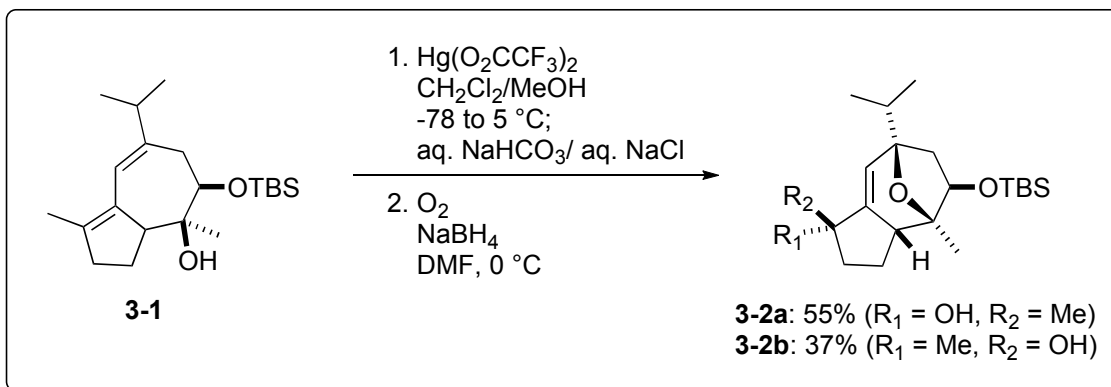


$$\begin{aligned} \text{TS-OH-}\beta \\ 0.8 \\ 0.8 \end{aligned}$$

disfavored

Without silyl group, *anti*-addition will be favored.

Krenske, E. H.; Houk, K. N.; Harmata, M. *J. Org. Chem.* **2015**, *80*, 744.



Answer:

Lee, J.; Parker, K. A. *Org. Lett.* **2012**, *14*, 2682.

