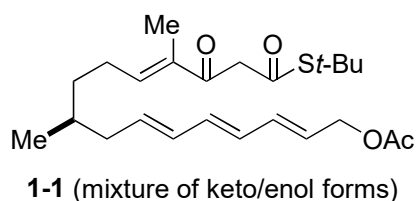


Problem Session (6)

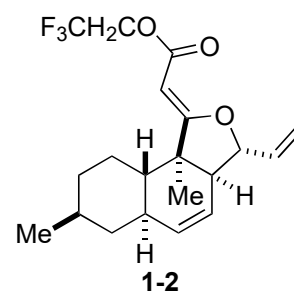
2018.7.14 Haruka Fujino

Please provide the reactin mechanism.

(1-1)



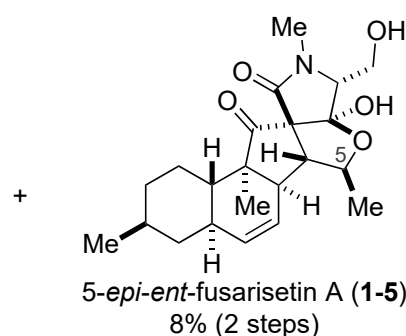
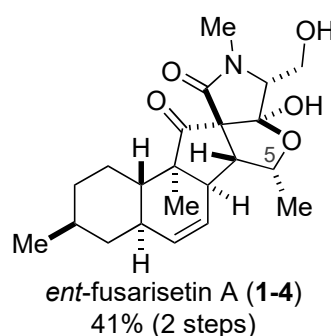
1. $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$ to $-40\text{ }^\circ\text{C}$, 63%
2. $\text{Ag}(\text{OCOCF}_3)$, EtOH , $\text{CF}_3\text{CH}_2\text{OH}$, $0\text{ }^\circ\text{C}$ to $22\text{ }^\circ\text{C}$, 91%



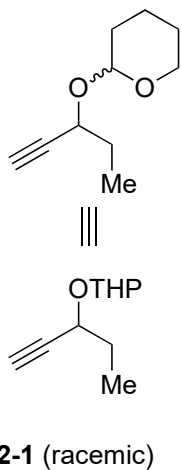
(1-2)

3. $n\text{-Bu}_3\text{P}$, $\text{Pd}(\text{OAc})_2$, CH_3CN , $22\text{ }^\circ\text{C}$, 75%
4. **1-3**, DMAP, toluene, $90\text{ }^\circ\text{C}$, 72%
5. PdCl_2 , CuCl , O_2 , $\text{DMF}/\text{H}_2\text{O}$, $22\text{ }^\circ\text{C}$, 79%
6. NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, MeOH , $-20\text{ }^\circ\text{C}$
7. NaOMe , MeOH , $0\text{ }^\circ\text{C}$ to $22\text{ }^\circ\text{C}$

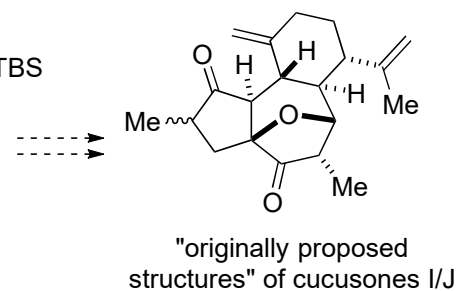
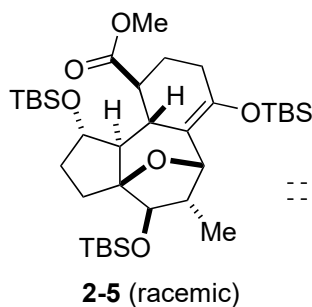
1-2



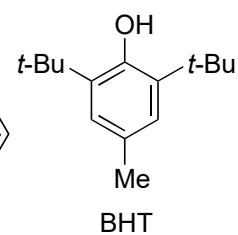
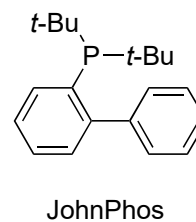
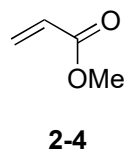
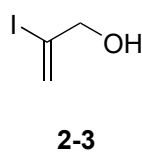
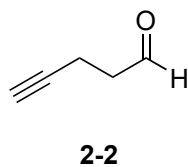
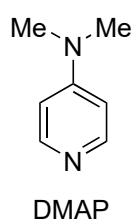
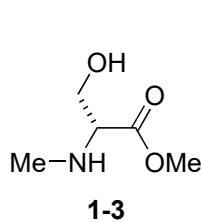
(2)



1. $n\text{-BuLi}$, THF, $-78\text{ }^\circ\text{C}$; **2-2**
2. LiAlH_4 , Et_2O , $0\text{ }^\circ\text{C}$
3. TBSCl, imidazole, CH_2Cl_2 , 45% (3 steps)
4. **2-3**, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, CuI , $i\text{-Pr}_2\text{NH}$, THF, 89%
5. JohnPhosAuNTf₂, MS 4A (CH_2Cl_2)₂, $0\text{ }^\circ\text{C}$ to rt, 58%
6. $\text{BH}_3 \cdot \text{THF}$; NaBO_3 , H_2O , $0\text{ }^\circ\text{C}$ to rt, 80%
7. SeO_2 , toluene, $100\text{ }^\circ\text{C}$
8. MnO_2 , CH_2Cl_2 , 71% (2 steps)
9. TBSOTf, Et_3N , CH_2Cl_2 , 96%
10. **2-4**, BHT, toluene, $100\text{ }^\circ\text{C}$, 84%



* From steps 1 to 4, you can ignore any stereochemistries.



Problem Session (6) [Answer]

2018.7.14 Haruka Fujino

Problem 1: Total synthesis of fusarisetin A

(Li, A. *et al. J. Am. Chem. Soc.* **2012**, *134*, 920.)

(0) introduction

0.1 (+)-fusarisetin A (1-4')

♣ isolation:

from a soil fungus, *Fusarium sp.* FN080326

(Ahn, J. S. *et al. J. Am. Chem. Soc.* **2011**, *133*, 6865.)

♣ bioactivity:

inhibition of cancer cell migration, acinar morphogenesis and cell invasion

(*ibid.*)

♣ structural determination:

♦ relative stereochemistry: determined to *ent*-1-4' (= 1-4) by Prof. Ahn group (*ibid.*)

♦ absolute stereochemistry: revised to 1-4' by Prof Li's total synthesis study

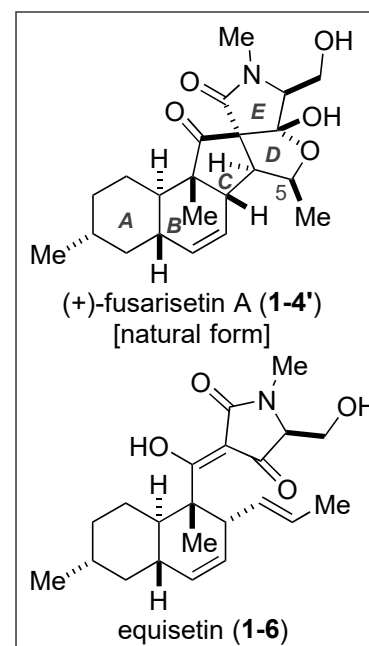
(Li, A. *et al. J. Am. Chem. Soc.* **2012**, *134*, 920.)

♣ structural features:

♦ 6,6,5,5-fused pentacyclic ring system bearing 10 stereogenic centers

♣ related natural product:

equisetin (1-6)

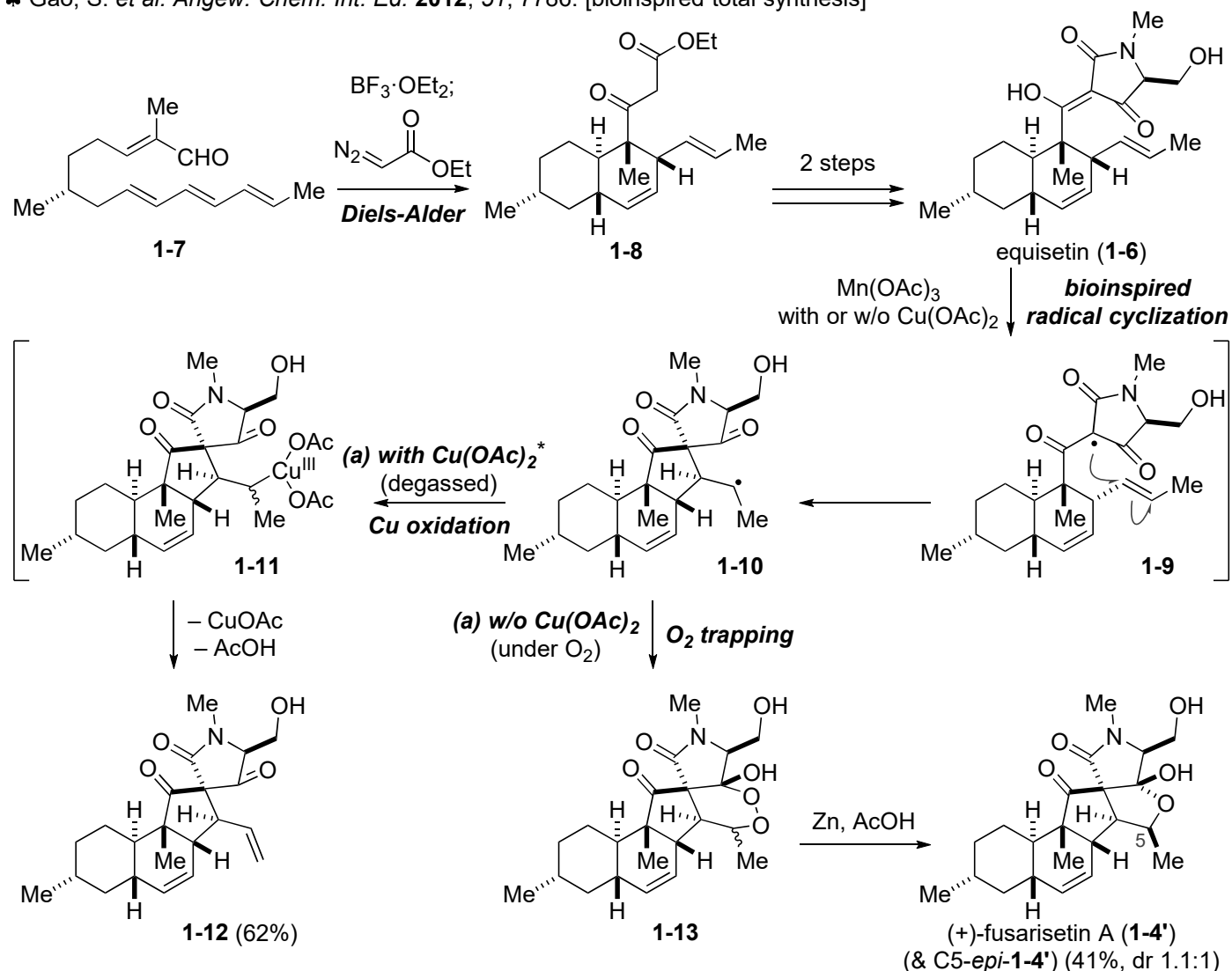


0.2 five total synthesis of (+)-fusarisetin A (1-4') [and *ent*-1-4' (= 1-4)]

♣ Li, A. *et al. J. Am. Chem. Soc.* **2012**, *134*, 920. [total synthesis of *ent*-1-4' (= 1-4)] -> **Problem 1**

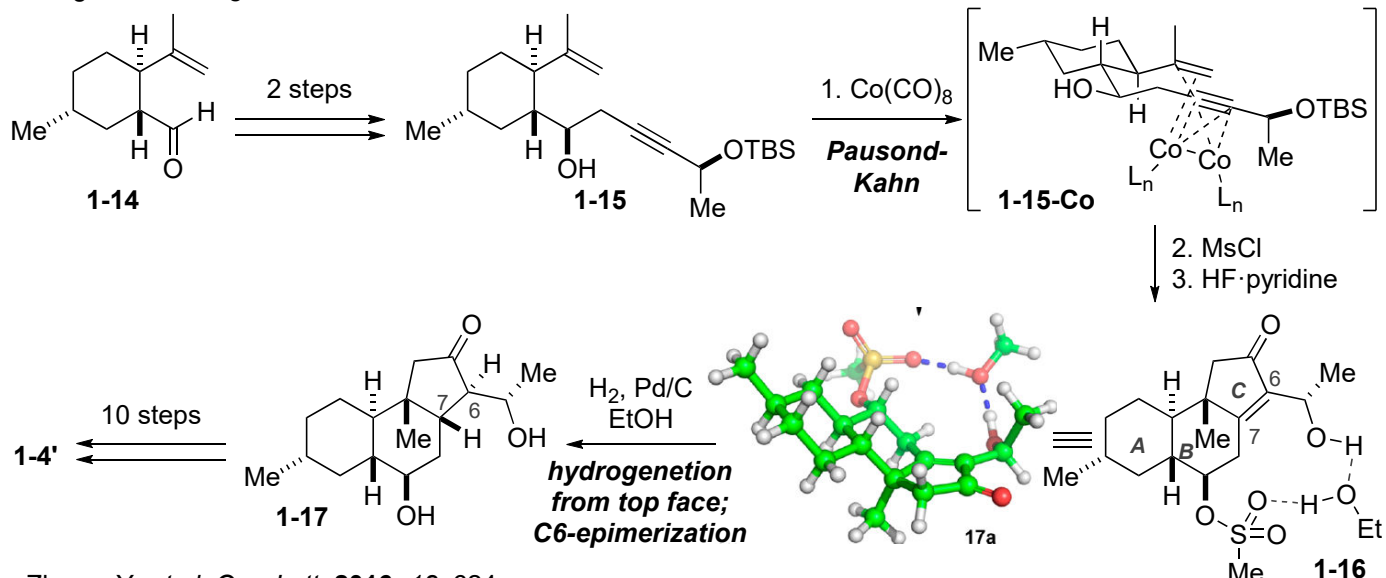
♣ Theodorakis, E. A. *et al. J. Am. Chem. Soc.* **2012**, *134*, 5072. -> 120421_LS_Shun_Yoshioka.

♣ Gao, S. *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 7786. [bioinspired total synthesis]



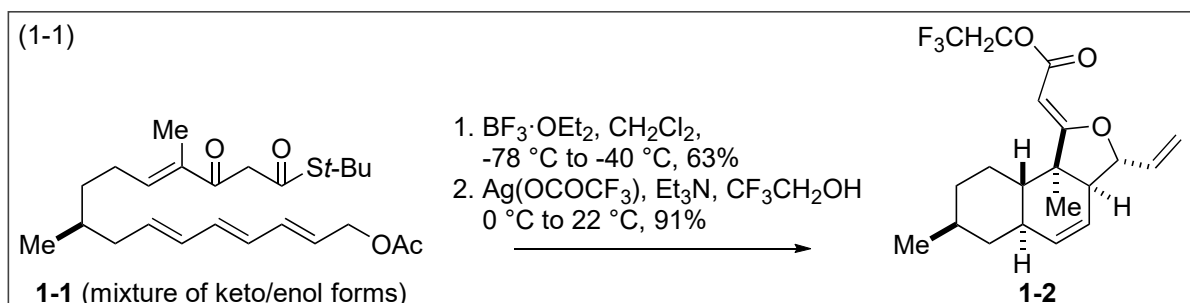
* For effect of Cu(OAc)₂, see also 180602_PS_Kotaro_Tokumoto and references herein.

♣ Yang, Z. *et al. Org. Lett.* **2013**, *15*, 4018.

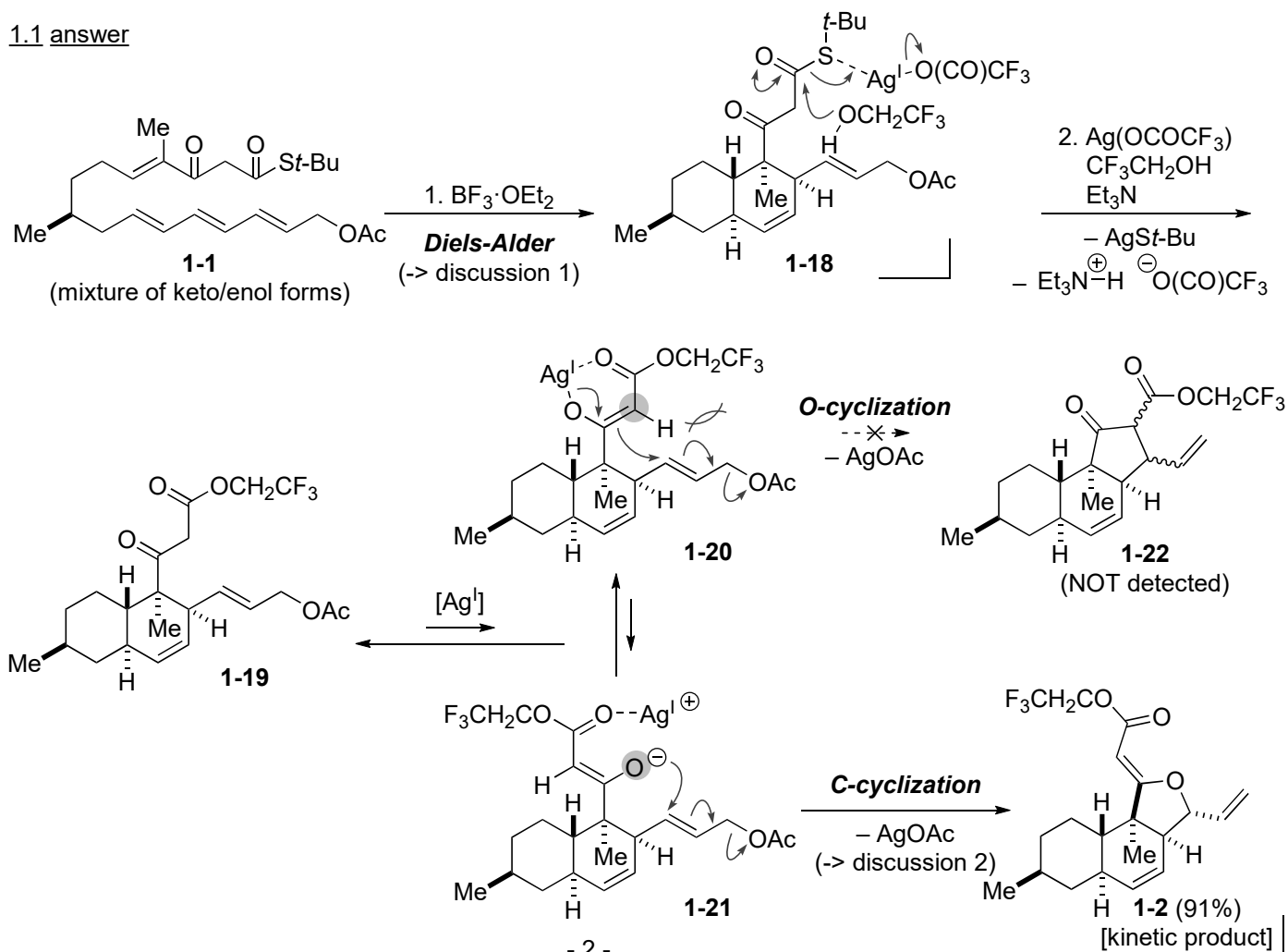


♣ Zheng, Y. *et al. Org. Lett.* **2016**, *18*, 624.

(1) problem (1-1)



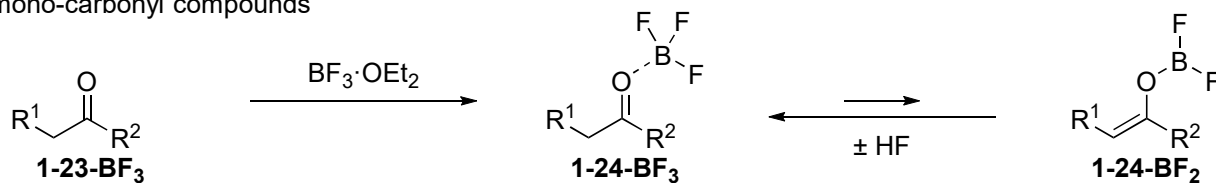
1.1 answer



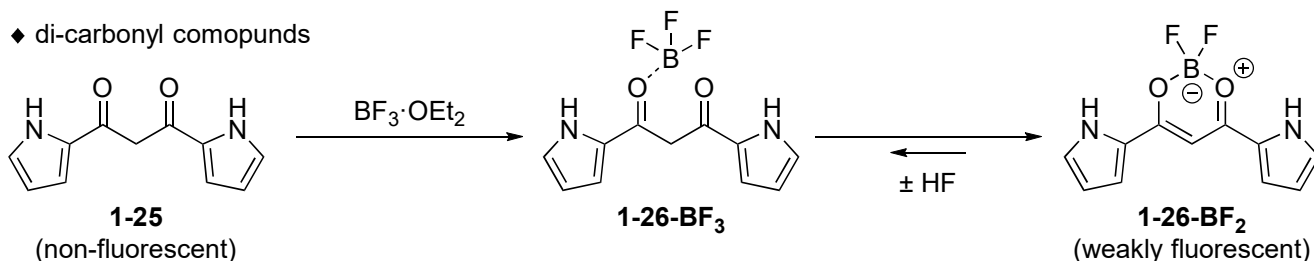
1.2 discussion

1.2.1 discussion 1: Diels-Alder reaction

- ♣ formation of BF_2 -complex
- ◆ mono-carbonyl compounds



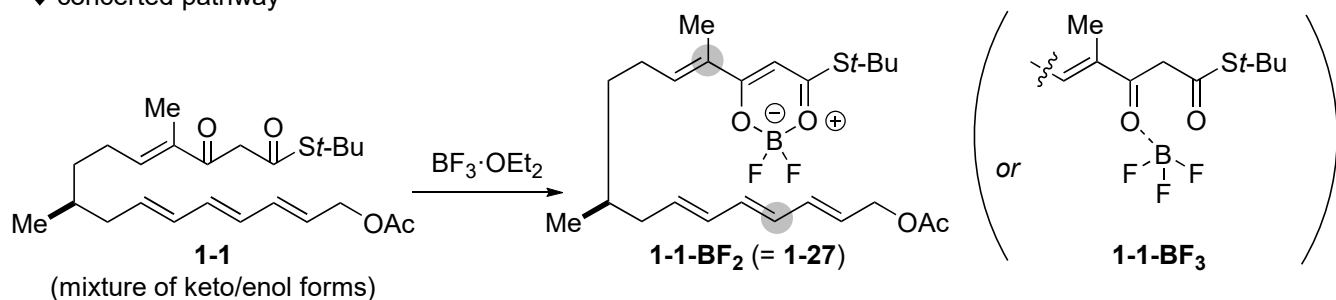
- ◆ di-carbonyl compounds



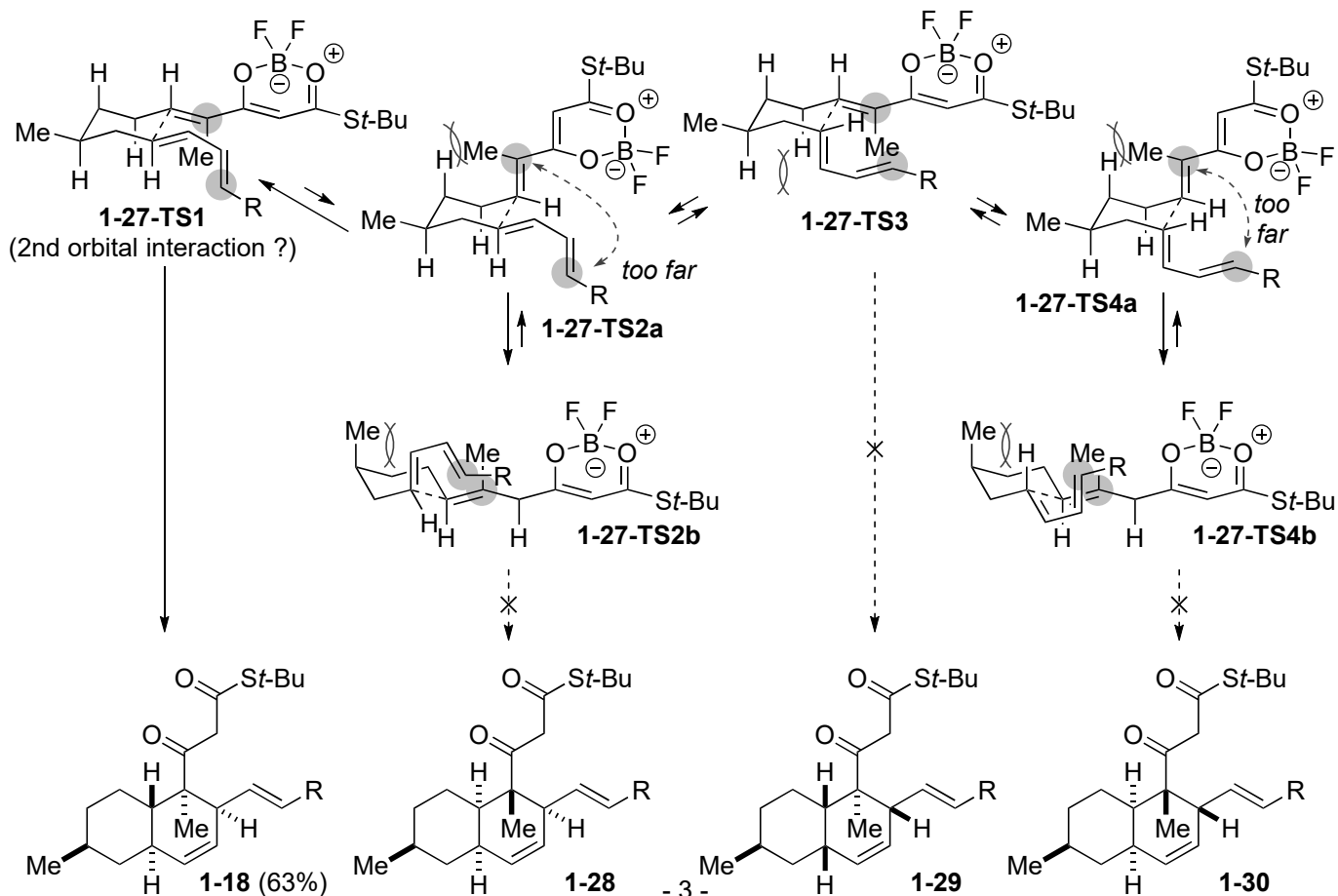
-> Combination of a di-carbonyl compound and BF_3 is easy to form an enol-type BF_2 complex.

Maeda, H. *et al.* *J. Am. Chem. Soc.* **2007**, *129*, 13661.

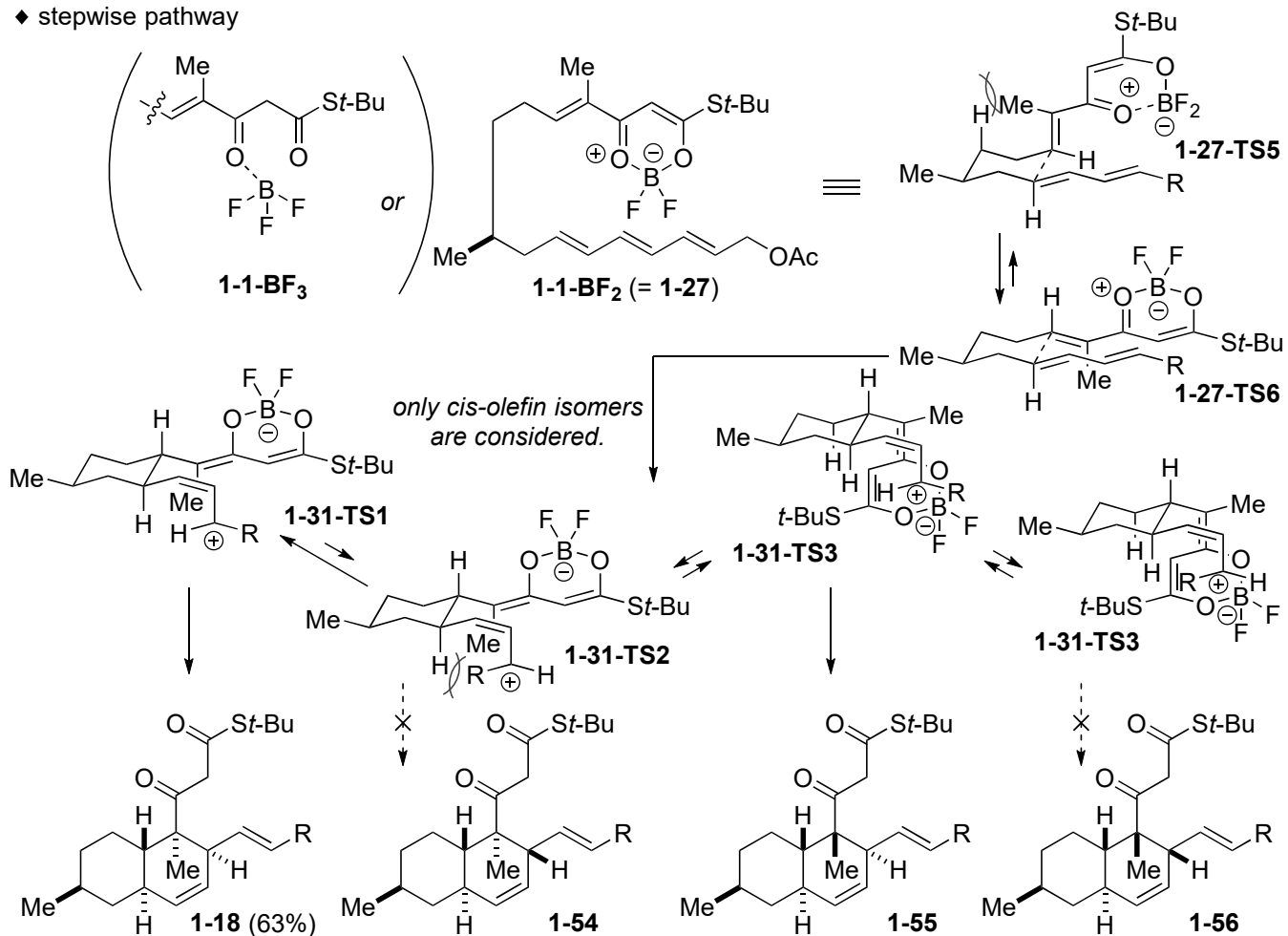
- ♣ stereoselectivity
- ◆ concerted pathway



|||

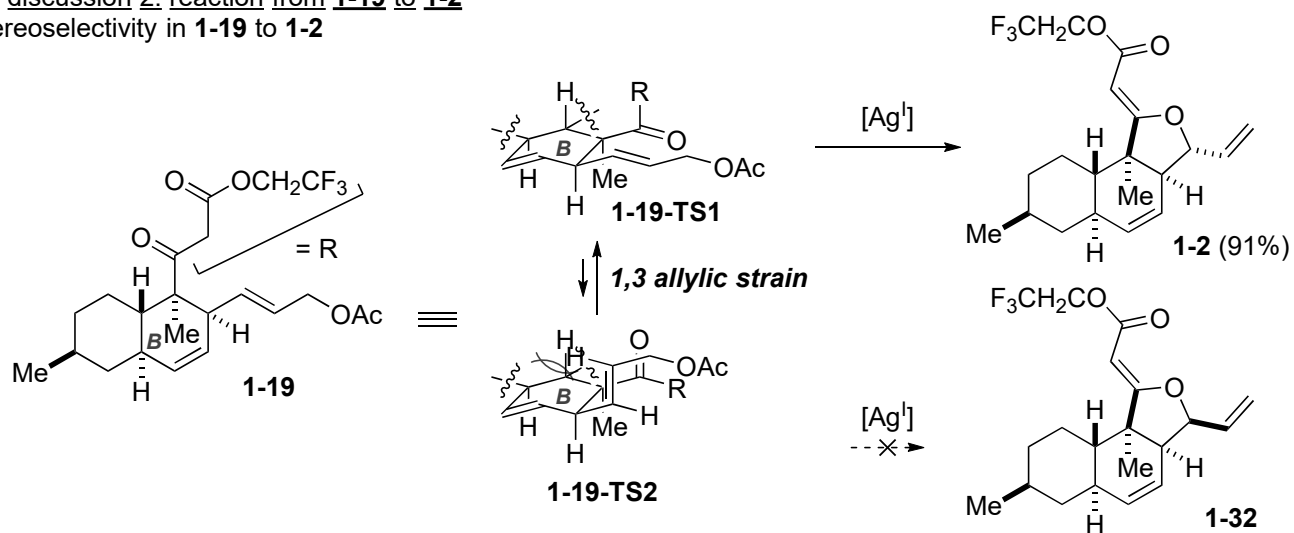


◆ stepwise pathway

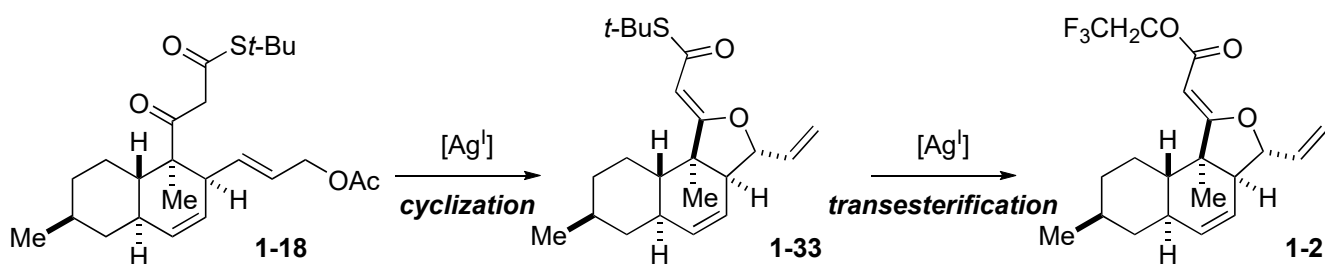


1.2.2 discussion 2: reaction from **1-19** to **1-2**

♣ stereoselectivity in **1-19** to **1-2**

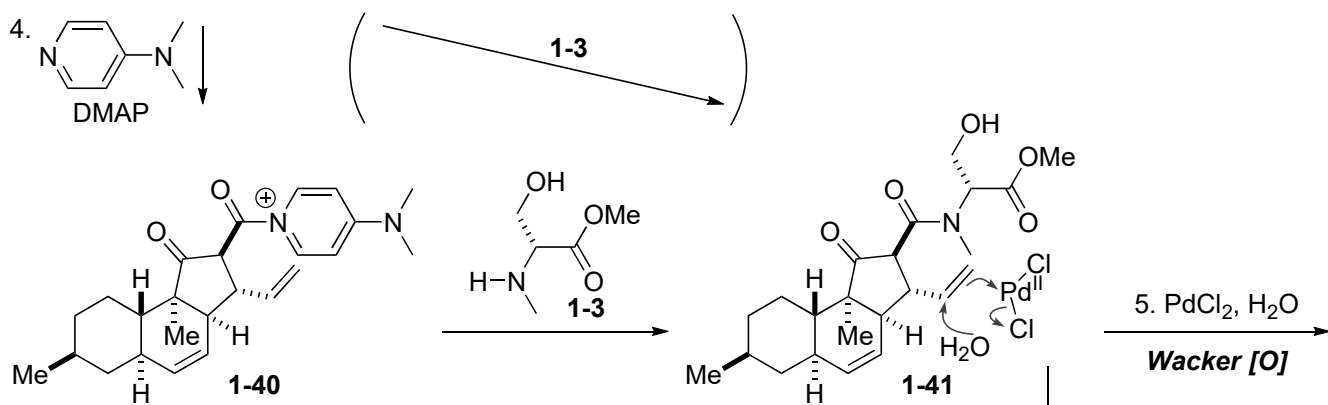
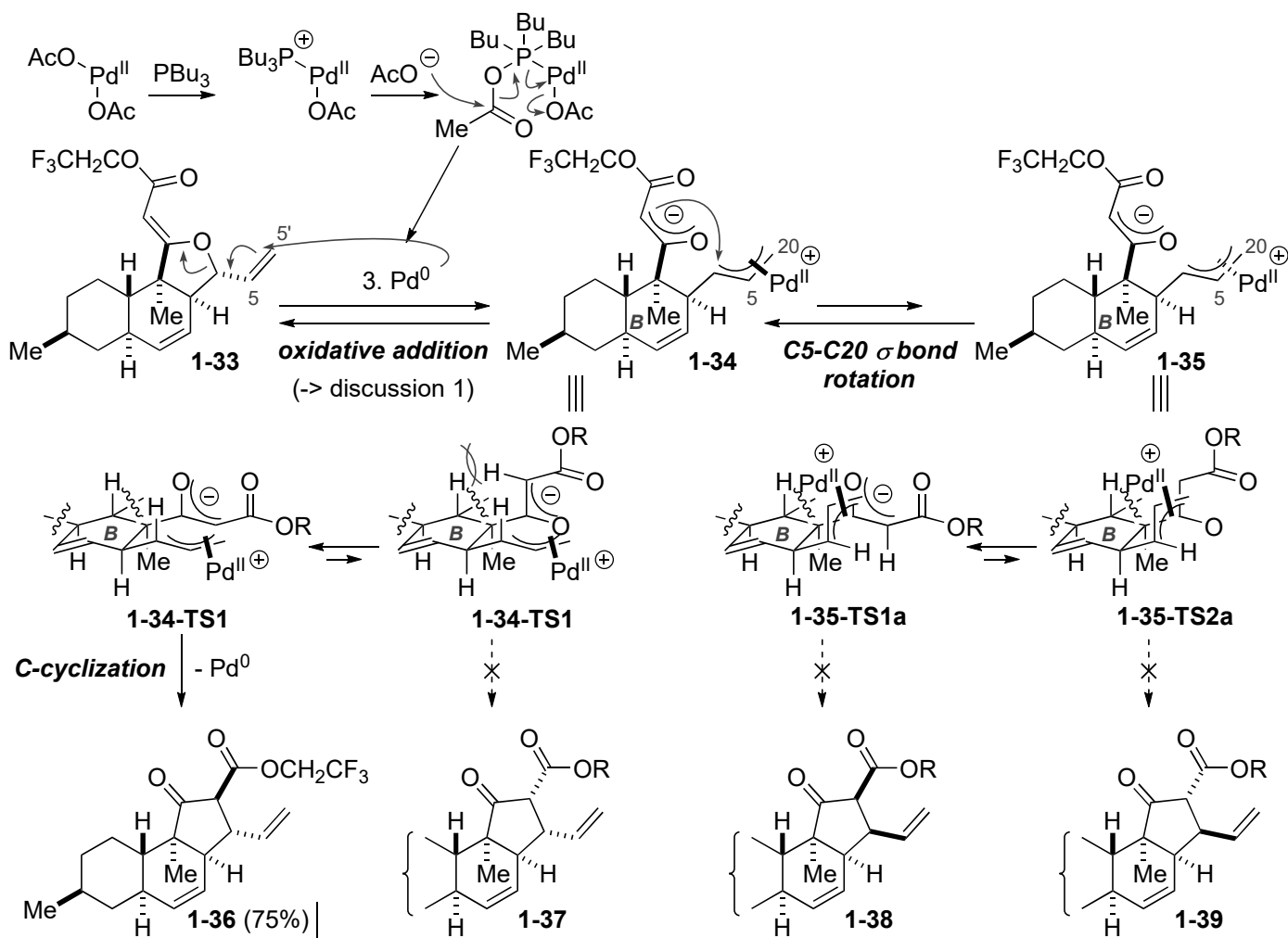
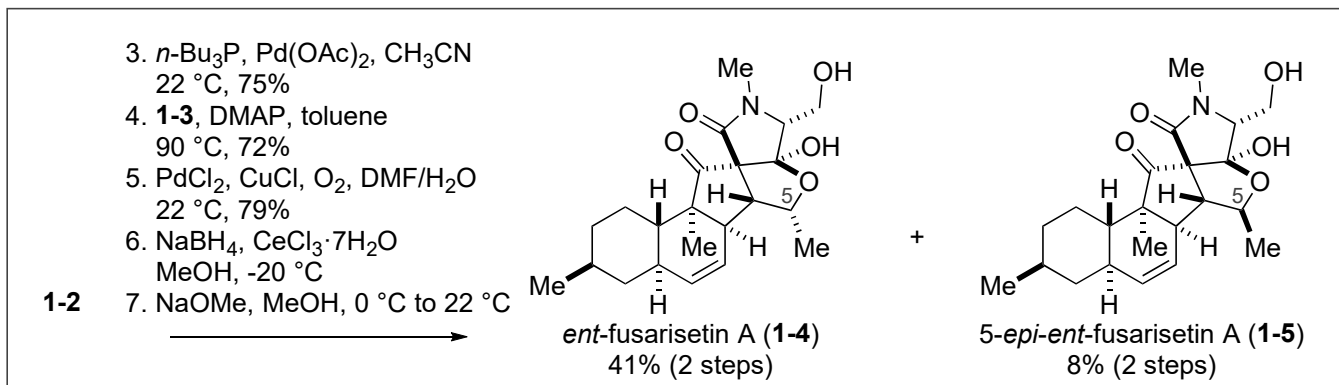


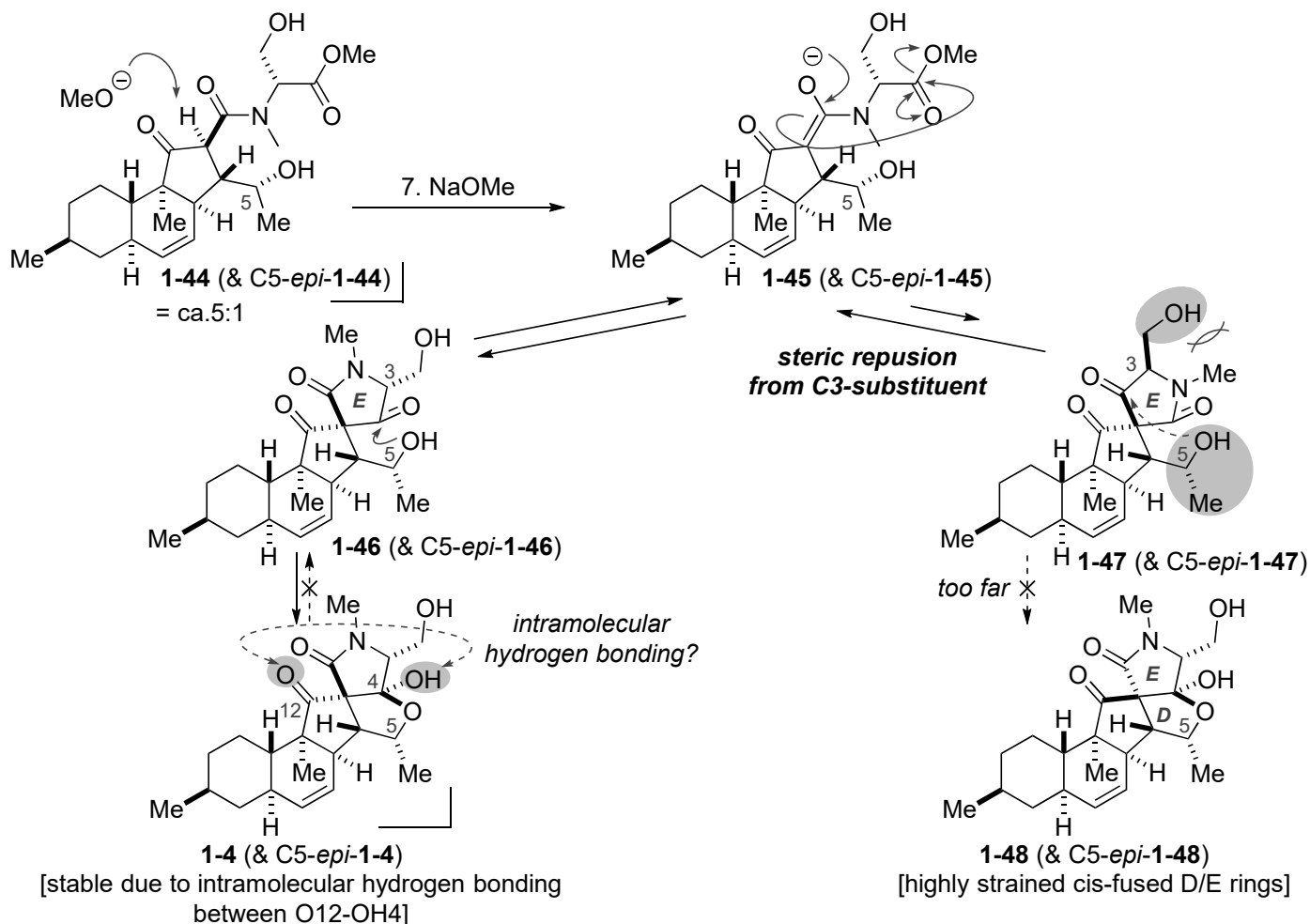
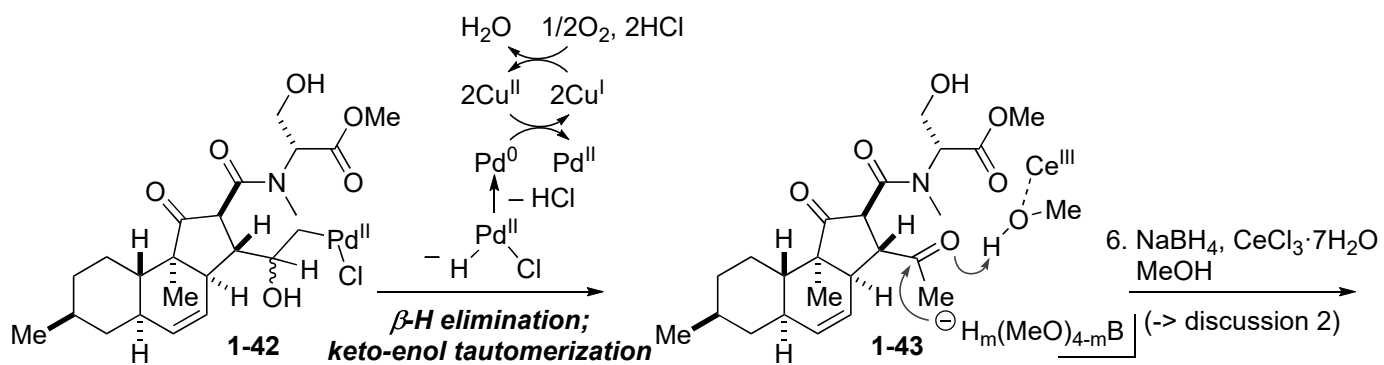
♣ the other pathway



-> Pathway via **1-33** is also possible.

(2) problem (1-2)

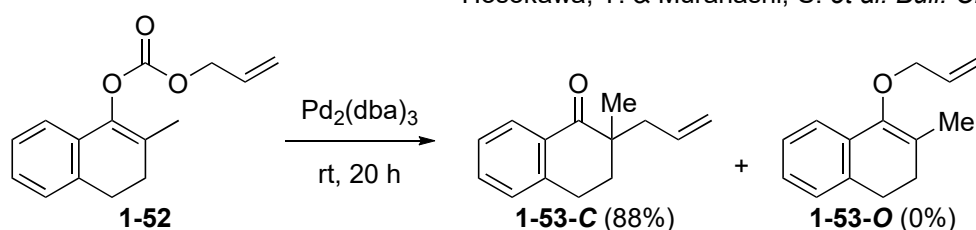
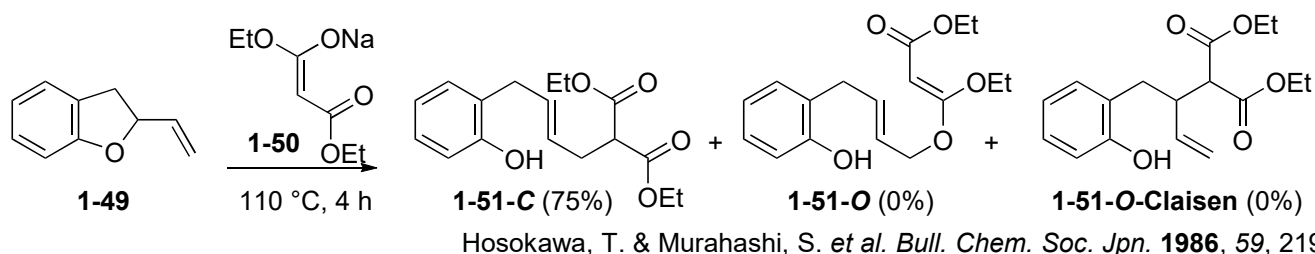




2.2 discussion

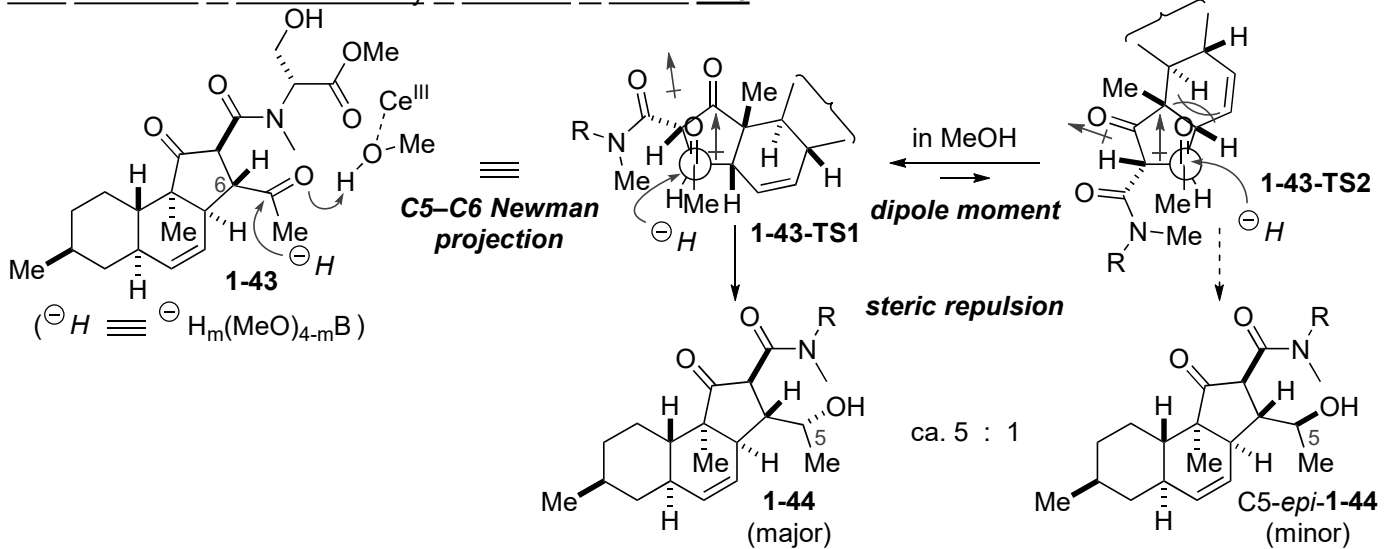
2.2.1 discussion 1: O→C migration

♣ C-attacked compounds are more thermodynamically stable than O-attacked compounds.

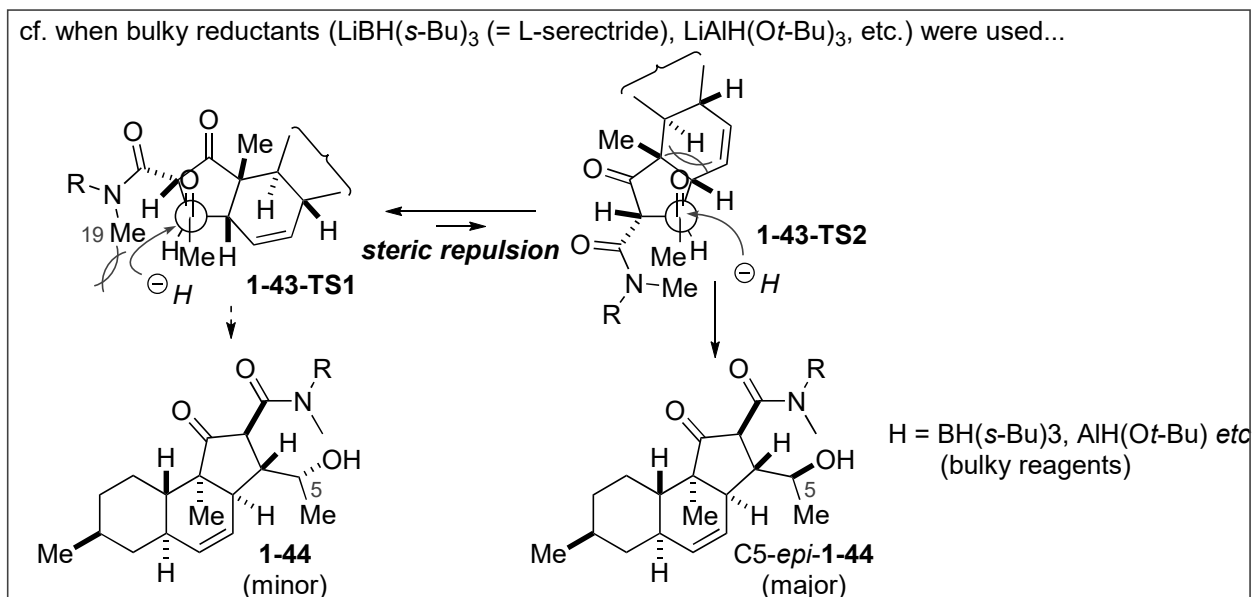


Trost, B. M. *et al. J. Am. Chem. Soc.* **2005**, *127*, 2846.

2.2.2 discussion 2: stereoselectivity in reduction of ketone **1-43**



cf. when bulky reductants ($\text{LiBH}(s\text{-Bu})_3$ (= L-serectride), $\text{LiAlH}(\text{O}t\text{-Bu})_3$, etc.) were used...



Problem 2: Total synthesis of "the proposed structures" of curcusons J (& I)

(Li, Y.; Dai, M. *Angew. Chem. Int. Ed.* **2017**, 56, 11624.)

(0) introduction

0.1 curcusons J (& I)

♣ isolation:

from roots of *Jatropha curcas*.

(Qiu, M.-H. *et al. Phytochemistry* **2013**, 96, 265.)

♣ bioactivity:

unknown for curcusons

Generally, rhamnofolane/daphnane/tigliane diterpenes show anti-cancer, anti-HIV, antimicrobial, antimalarial and neurotrophic bioactivities.

♣ structural determination:

♦ originally assigned to **2-6** by 1D/2D NMR experiments (*ibid.*)

♣ structural features:

♦ rhamnofolane diterpenes

♦ [5-7-6] tricyclic skeleton with an oxa-bridge

♣ total synthesis of **2-6**

Li, Y.; Dai, M. *Angew. Chem. Int. Ed.* **2017**, 56, 11624.

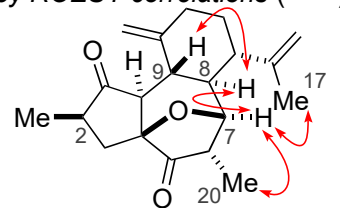
-> Spectral properties were not matched with those of natural products.

♣ Structural revision from **2-6** to **2-7**

computational chemistry (DP4+ method)

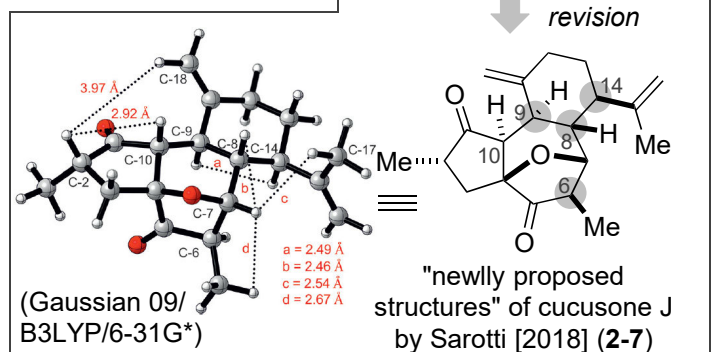
Sarotti, A. M. *Org. Biomol. Chem.* **2018**, 16, 944.

key ROESY correlations (↔)



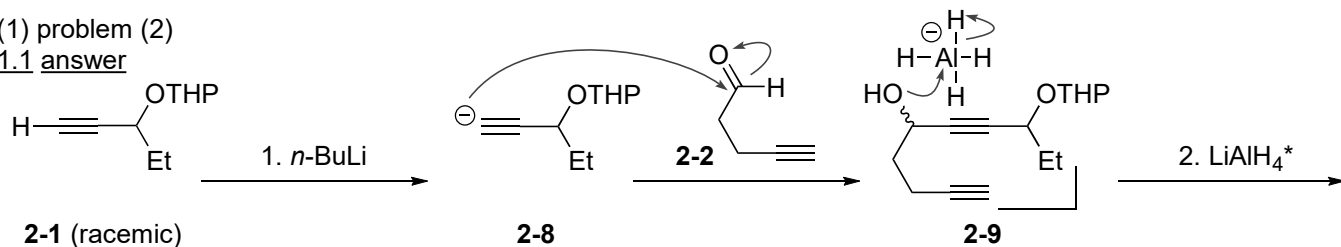
"originally proposed structures" of curcusone J by Qiu [2013] (**2-6**)

structural revision

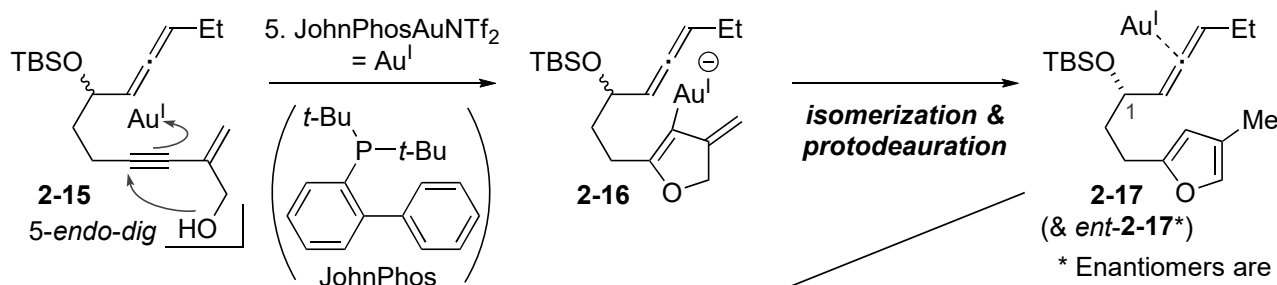
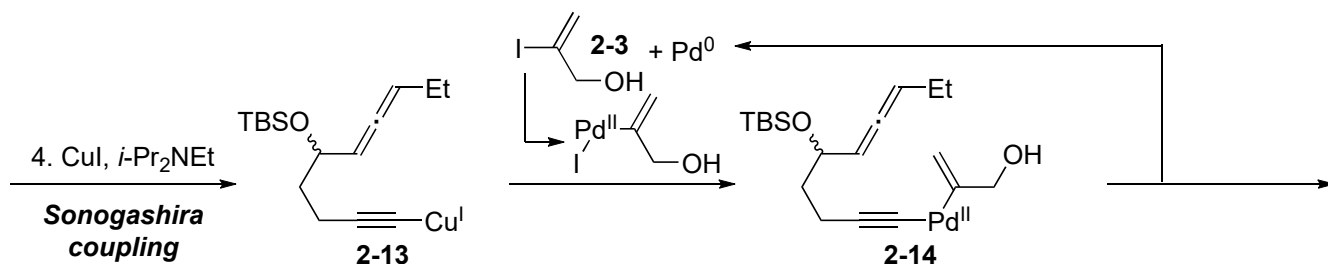
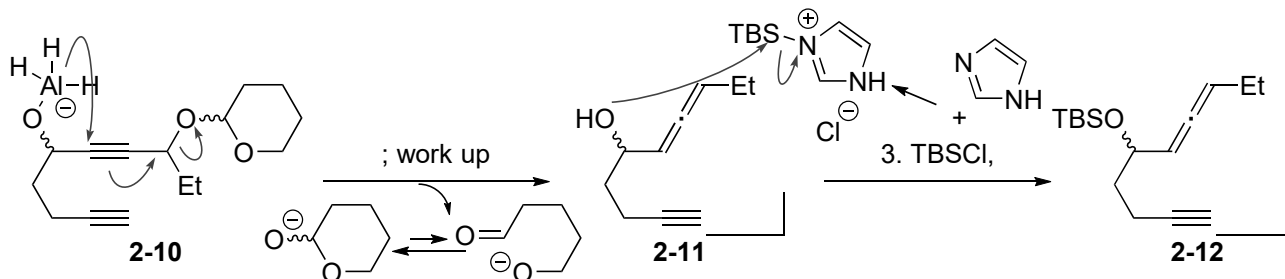


(1) problem (2)

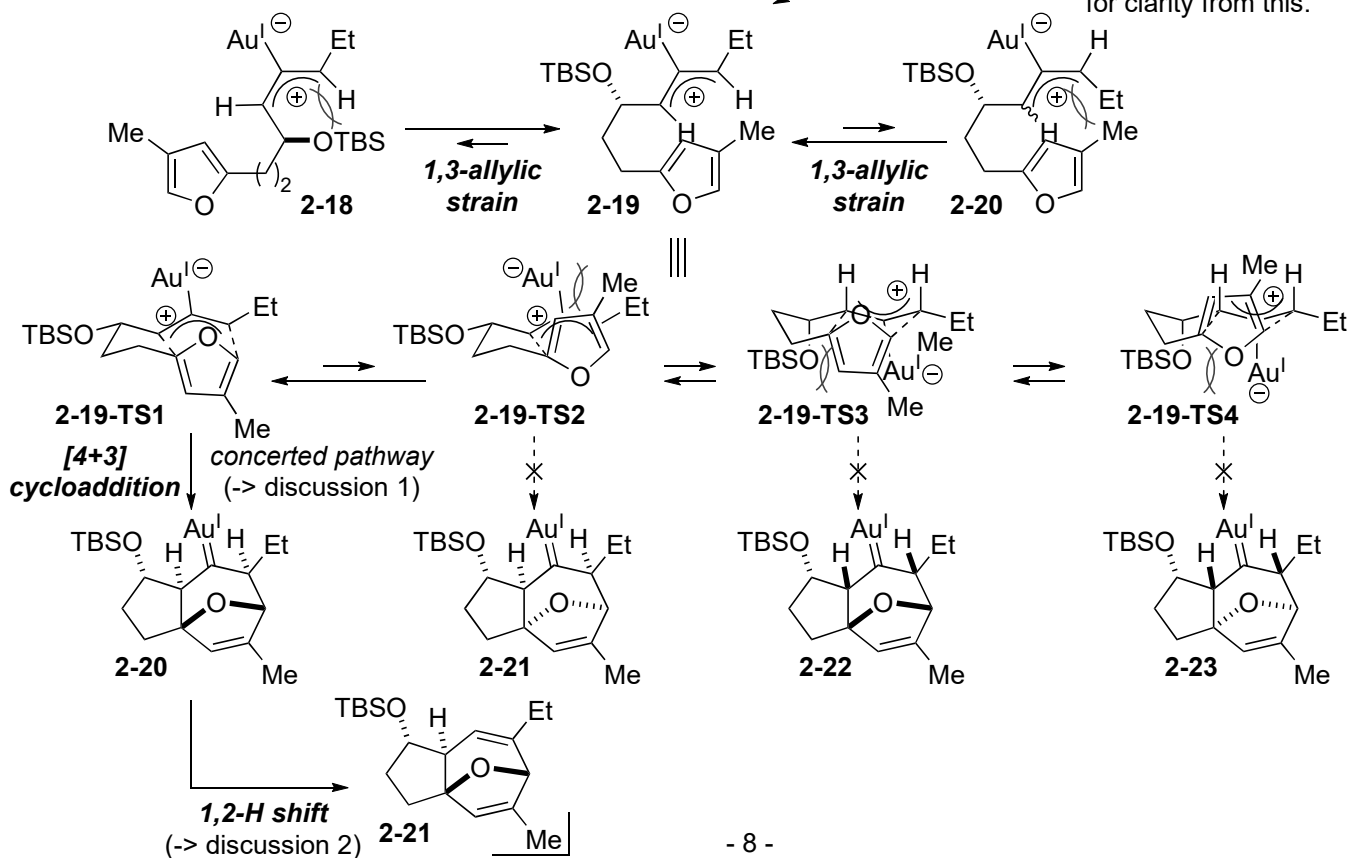
1.1 answer

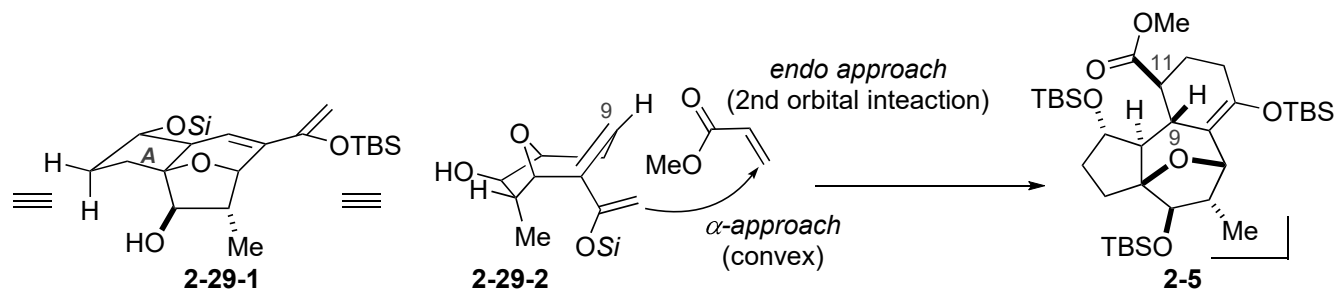
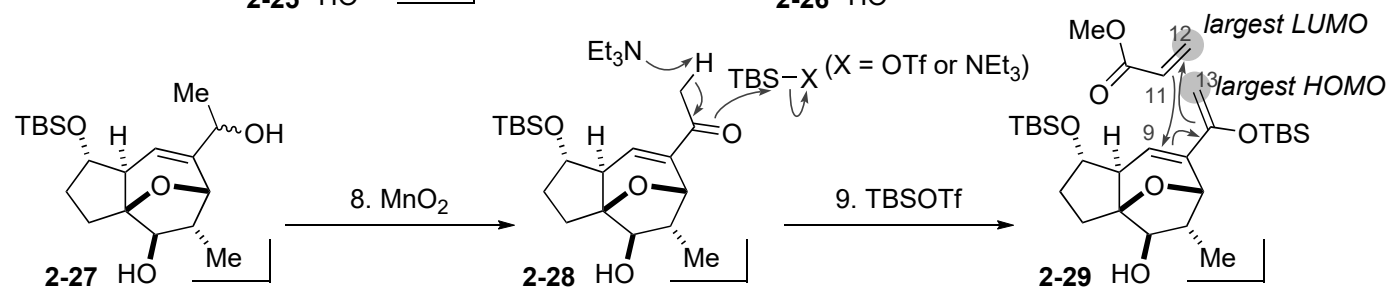
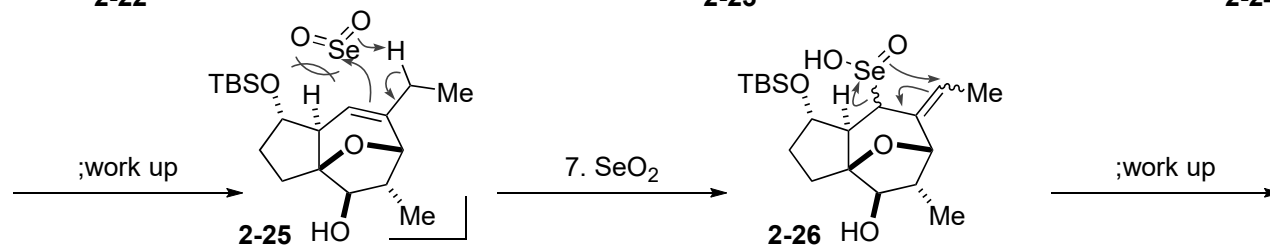
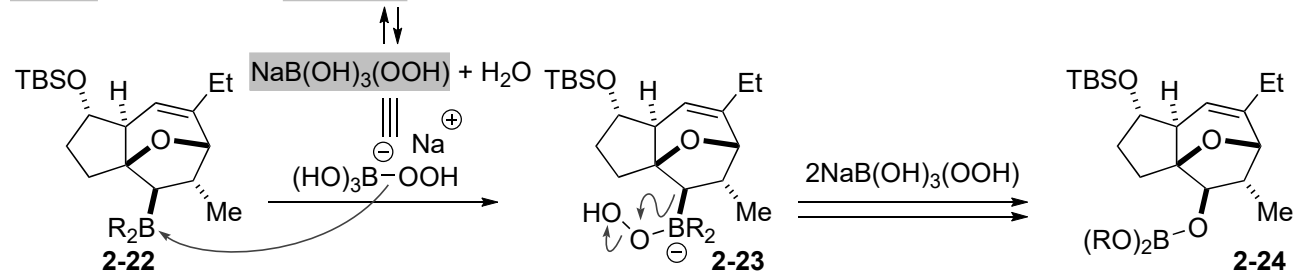
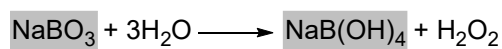
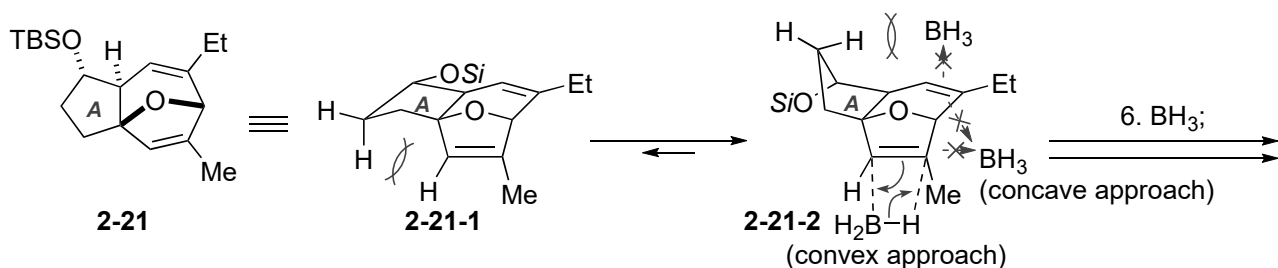


* Landor, S. R. et al. *J. Chem. Soc., Perkin 1* 1973, 720.



* Enantiomers are omitted for clarity from this.

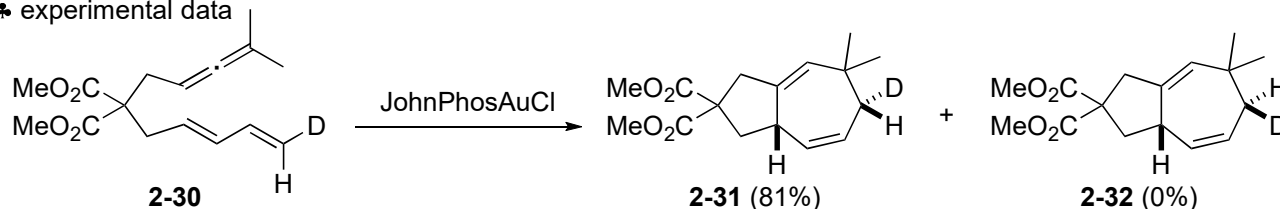




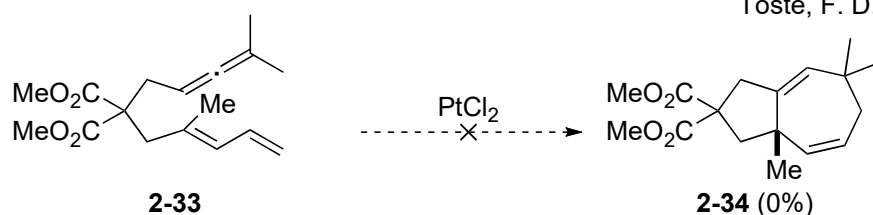
1.2 discussion

1.2.1 discussion 1: concerted pathway vs. stepwise pathway (from **2-19** to **2-20**)

♣ experimental data



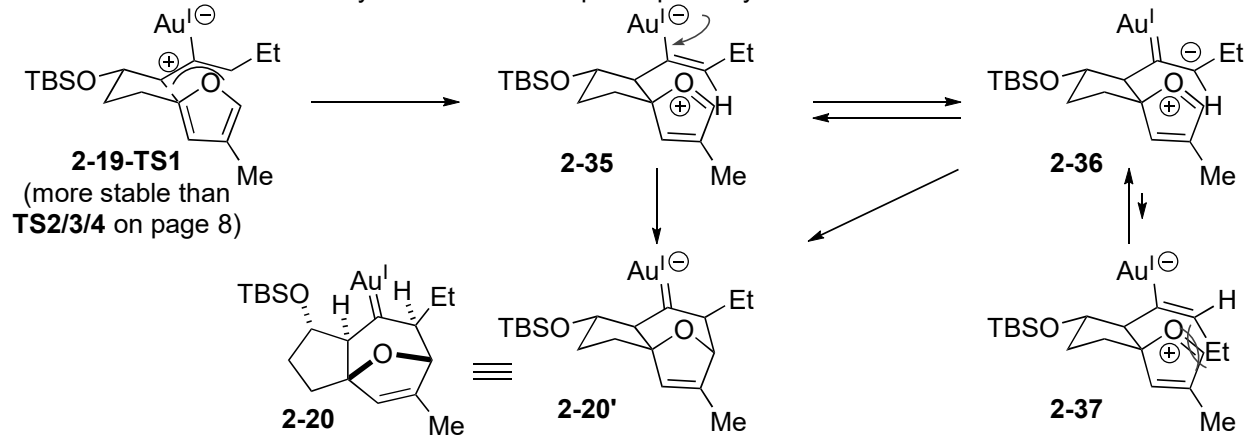
Toste, F. D. *et al. J. Am Chem. Soc.* **2009**, *131*, 6348.



-> Concerted pathway is more possible, however stepwise pathway can not be fully denied.

Mascareñas, J. L. *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 951.

♣ rationale for stereoselectivity in case of the stepwise pathway



1.2.2 regioselectivity in 1,2-H shift

♣ experimental data

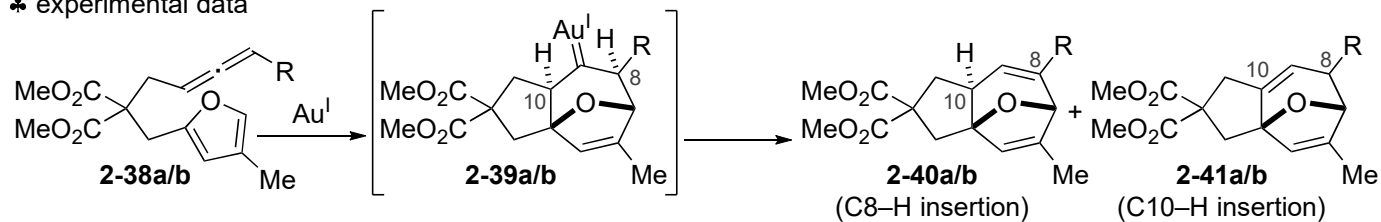
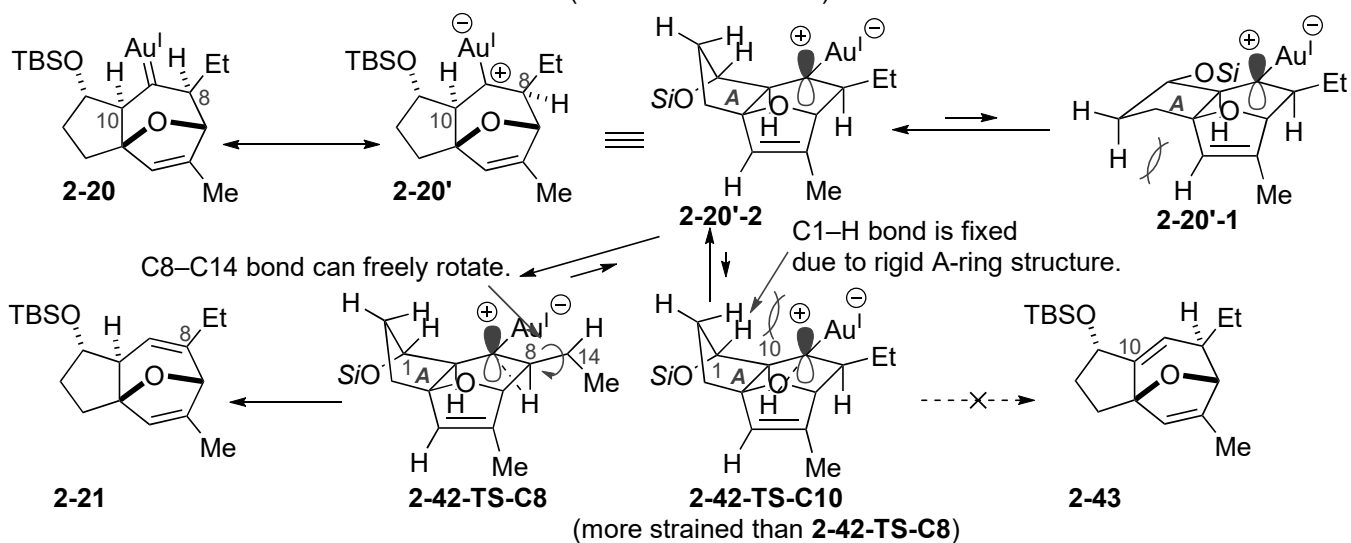


Table 1.

entry	2-38	results	
1	2-38a : R = CH_2Bn	2-40a : 64%	♣ Electron-deficient gold carbenoid inserts in electron-rich 3°C-H bonds.
2	2-38b : R = H	2-41b : 50%	♣ When both C8-H/C10-H bonds are 3°C-H, C8-H insertion preferentially occurs.

♣ transition state of C α -H insertion of carbenoid (3°C8-H vs 3°C10-H)



♣ ligand effect on cyclization mode ([4+3] vs [4+2])

