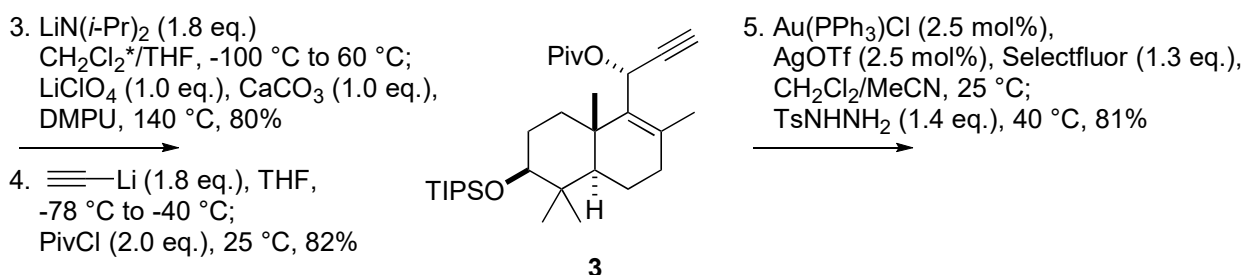
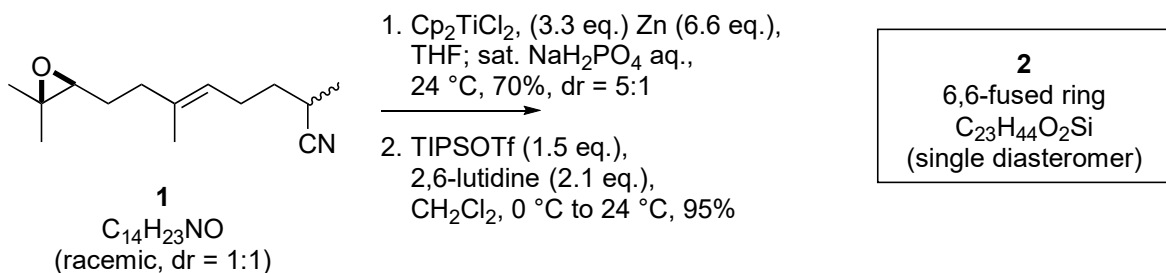


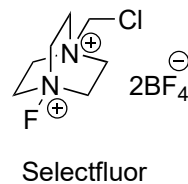
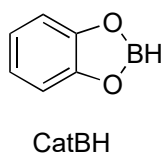
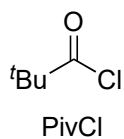
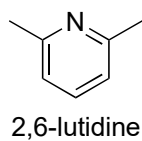
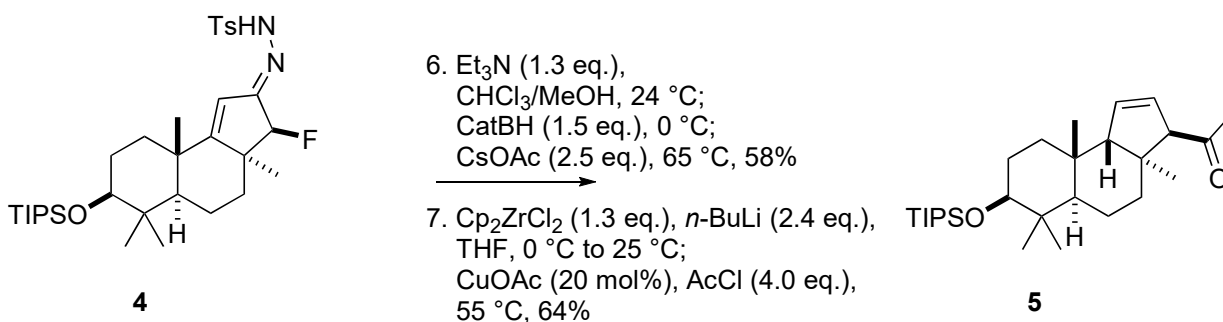
Problem Session (3)

2019. 10. 26. Takahiro Watanabe

Please provide each reaction mechanisms, fill in the blank, and explain the stereoselectivities.



* CH_2Cl_2 reacts with $LiN(i-Pr)_2$ and serves as a one-carbon unit.

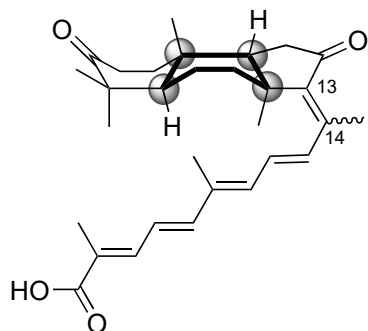


Problem Session (3)

2019. 10. 26. Takahiro Watanabe

Topic: Total synthesis of Isomalabaricane Triterpenoids

Boyko, Y. D.; Huck, C. J.; Sarlah, D. *J. Am. Chem. Soc.* **2019**, *141*, 14131.



$\Delta^{13(14)} = E$, rhabdastrellic acid A
 $IC_{50} = 1.46 \mu M$ (HL-60)

$\Delta^{13(14)} = Z$, stelletin E
 $IC_{50} = 3.9 nM$ (HCT-116)

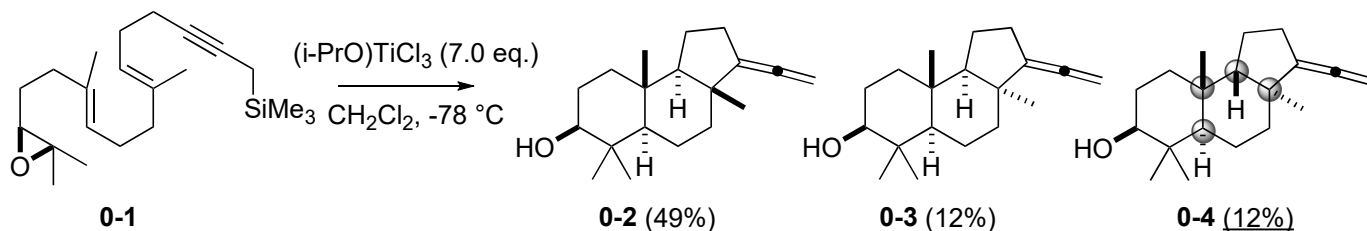
- Common structural feature:

trans-syn-trans perhydrobenz[e]indene core (boat-boat conformation)

-> Construction of the core is one of the challenging tasks.

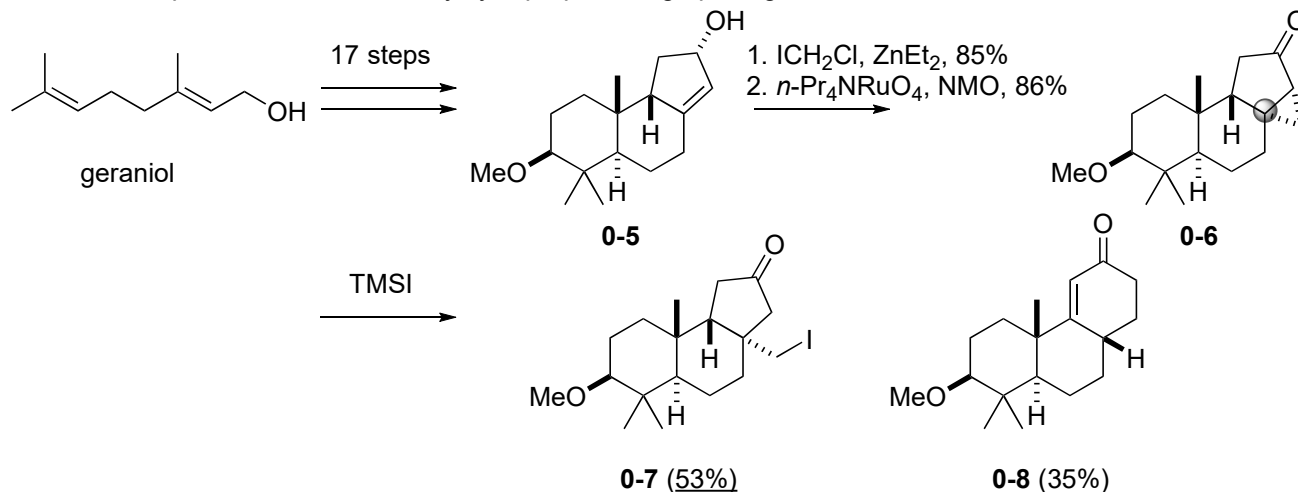
Reported construction of *trans-syn-trans* perhydrobenz[e]indene core:

1. As a minor component of a mixture of products via polyene cyclization:



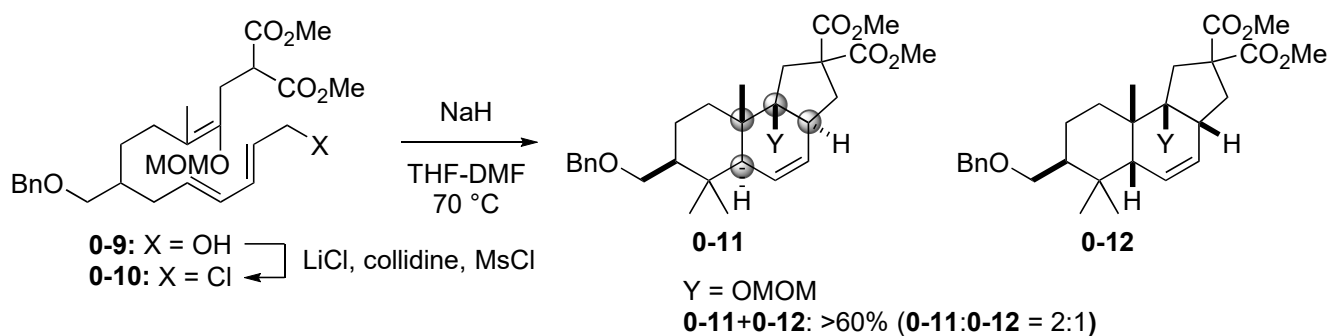
Fish, V. P.; Sudhakar, A. R.; Johnson, W. S. *Tetrahedron Lett.* **1993**, *34*, 7849.

2. As one component of 3:2 mixture by cyclopropane ring opening:

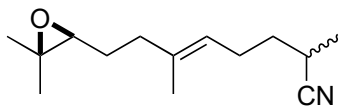


Raepfel, F.; Weibel, J.-M.; Heisser, D. *Tetrahedron Lett.* **1999**, *240*, 6377.

3. As one component by transannular Diels-Alder reaction:



Berube, G.; Deslongchamps, P. *Tetrahedron Lett.* **1987**, *28*, 5255.

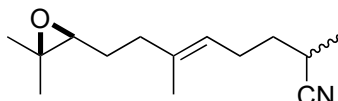
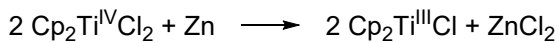


1 (racemic, dr = 1:1)

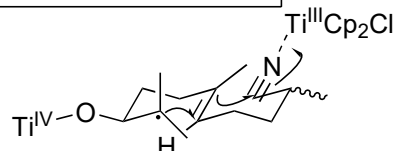
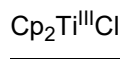
1. Cp_2TiCl_2 , (3.3 eq.) Zn (6.6 eq.),
THF; sat. NaH_2PO_4 aq., 70%

2. TIPSOTf (1.5 eq.),
2,6-lutidine (2.1 eq.), CH_2Cl_2 , 95%

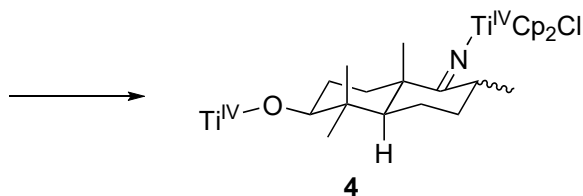
2
6,6-fused ring
 $\text{C}_{23}\text{H}_{44}\text{O}_2\text{Si}$
(single diastomer)



1 (racemic, dr = 1:1)

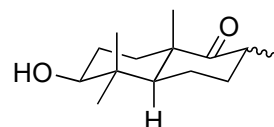


3



4

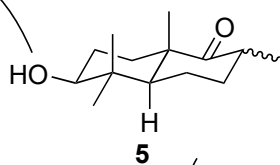
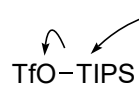
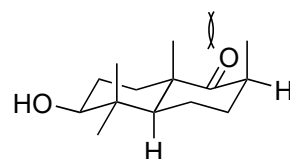
sat. NaH_2PO_4 aq.
hydrolysis



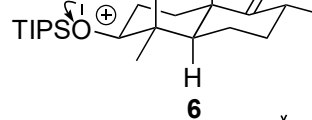
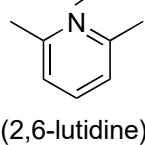
5 (dr = 5:1*)

step 1

* Epimerization will also proceed
to avoid 1,3-diaxial interaction.

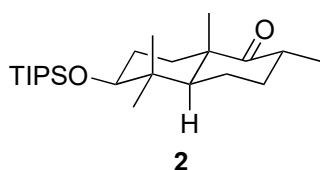
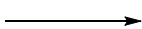
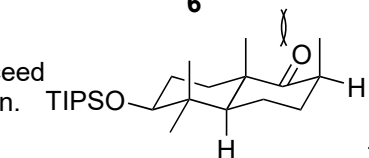


5

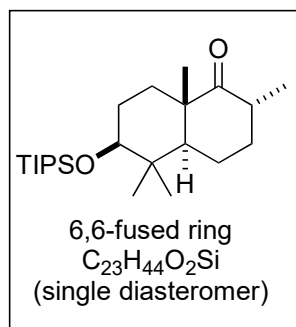


6

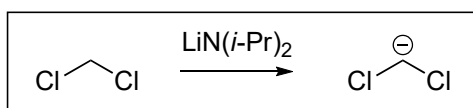
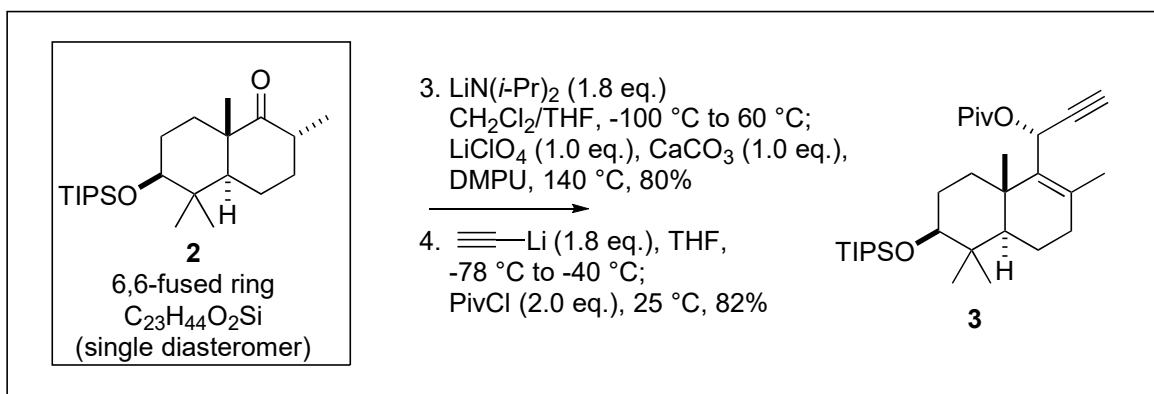
* Epimerization will also proceed
to avoid 1,3-diaxial interaction.



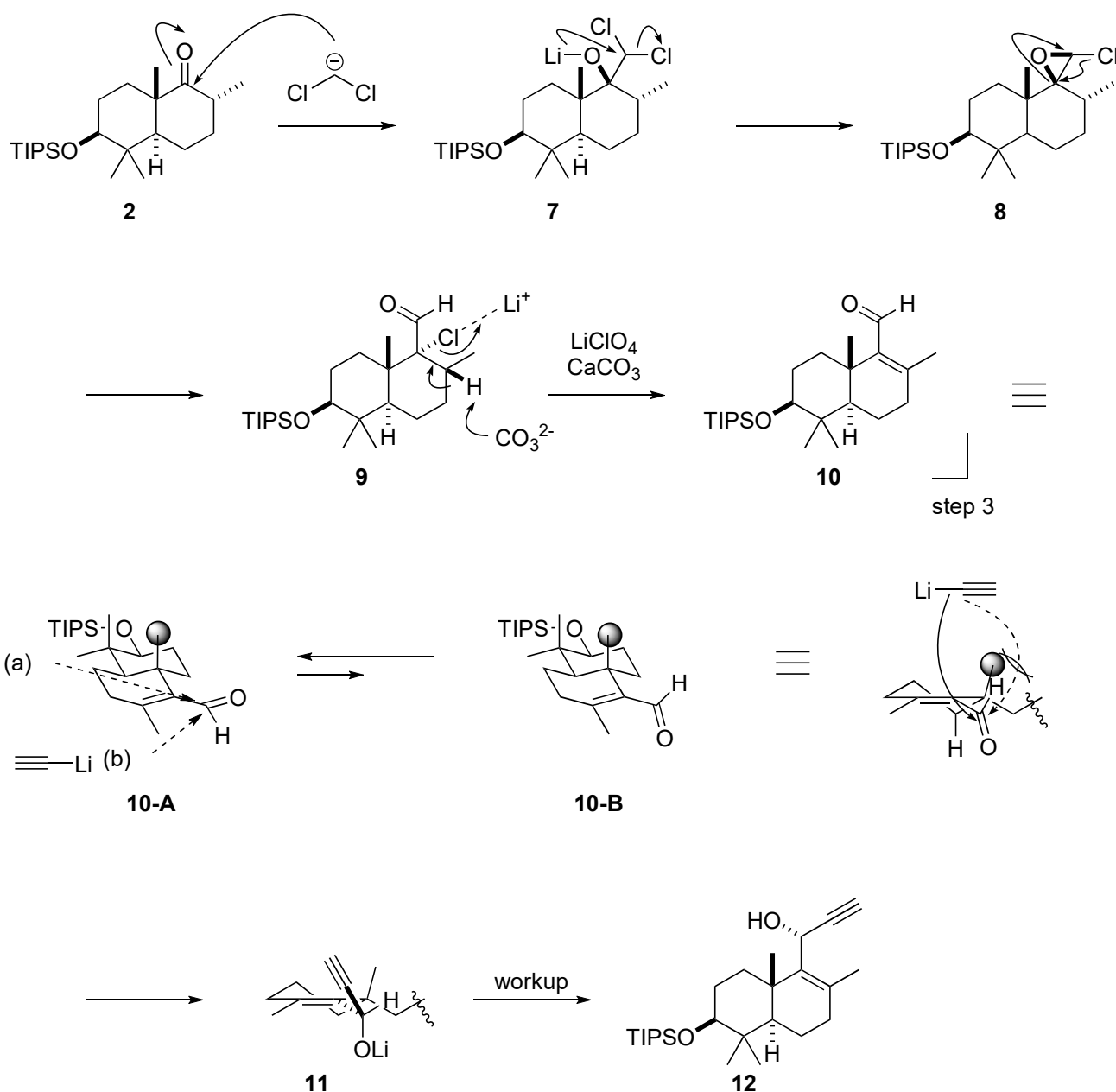
2



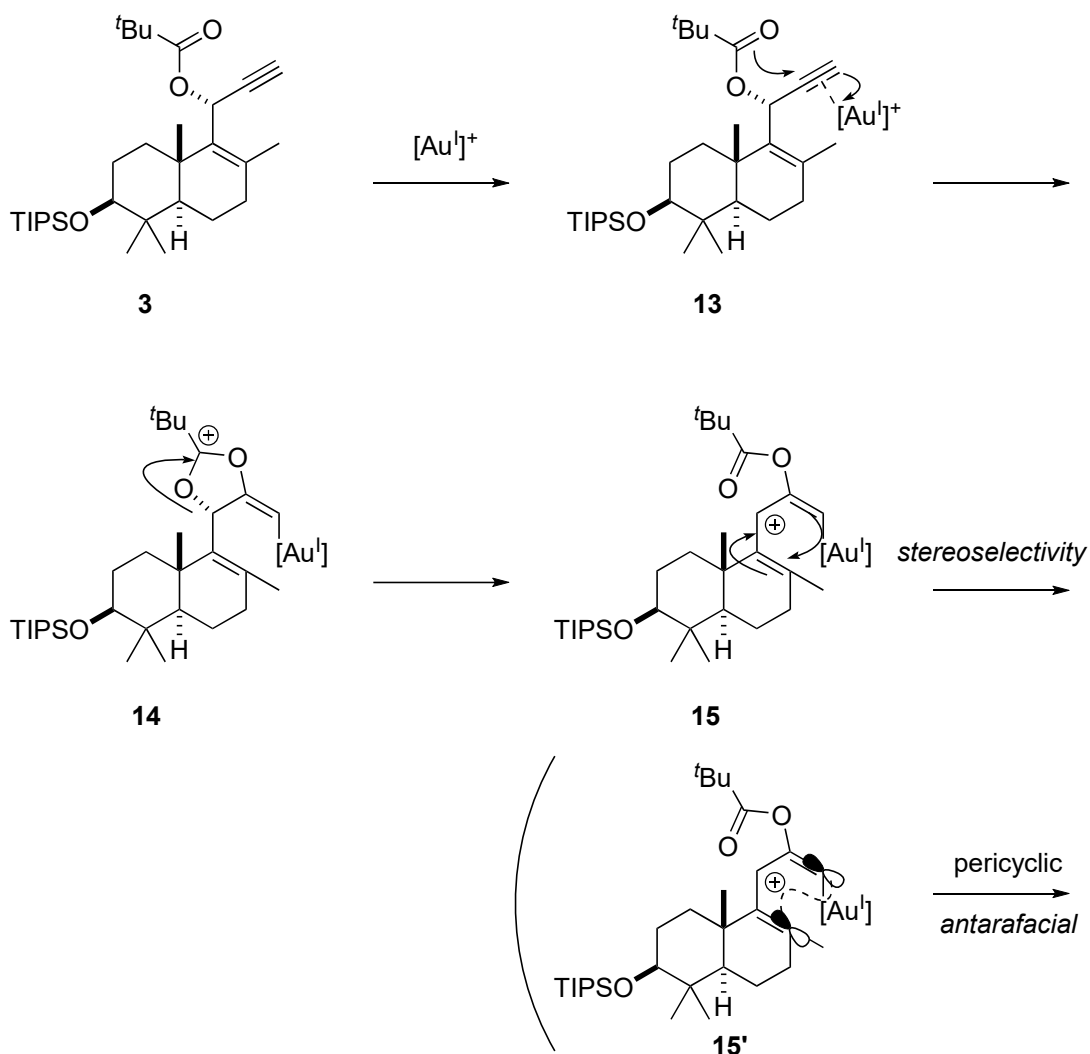
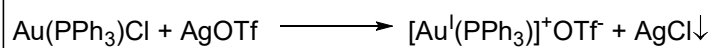
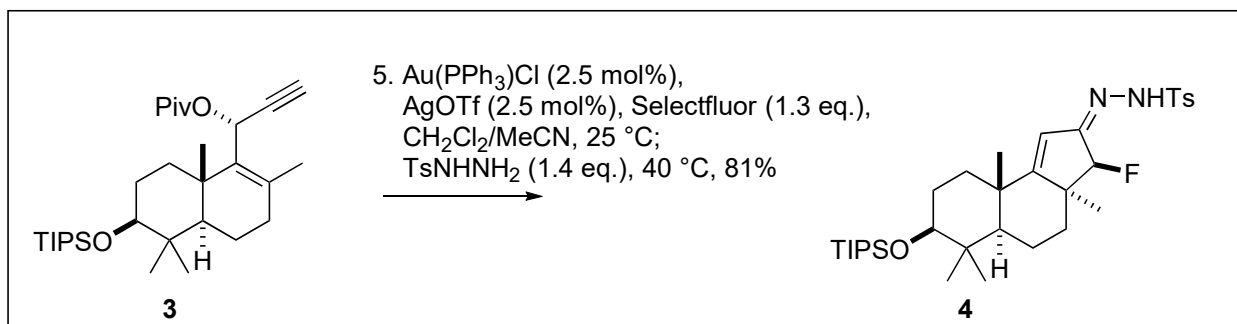
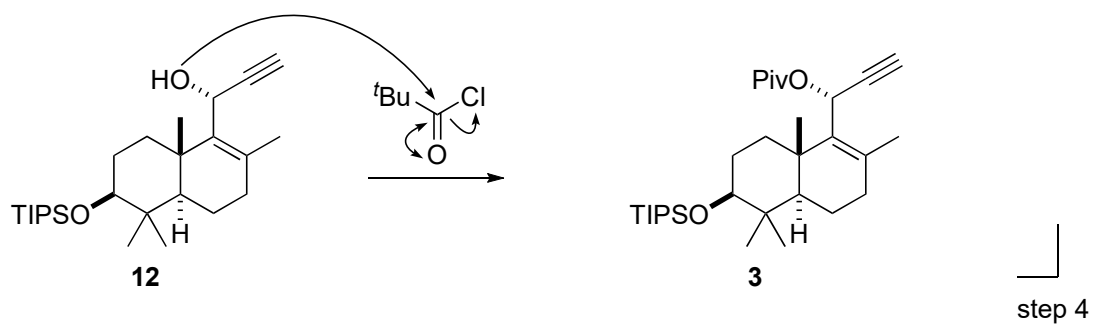
step 2

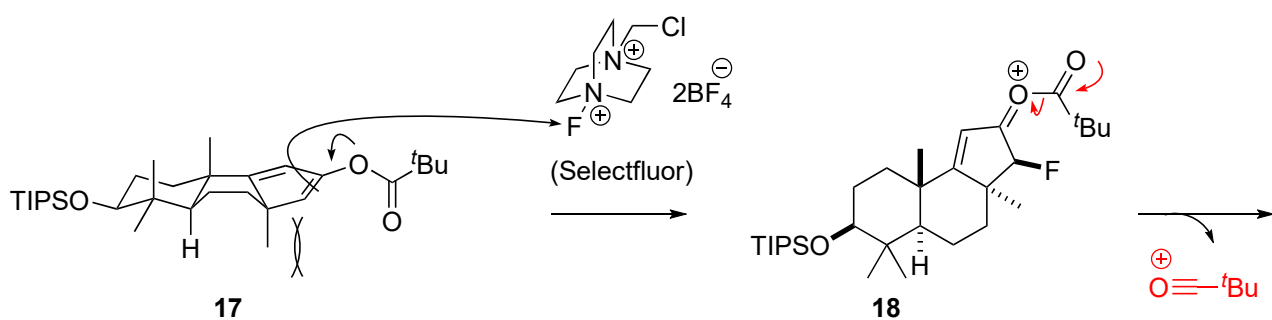
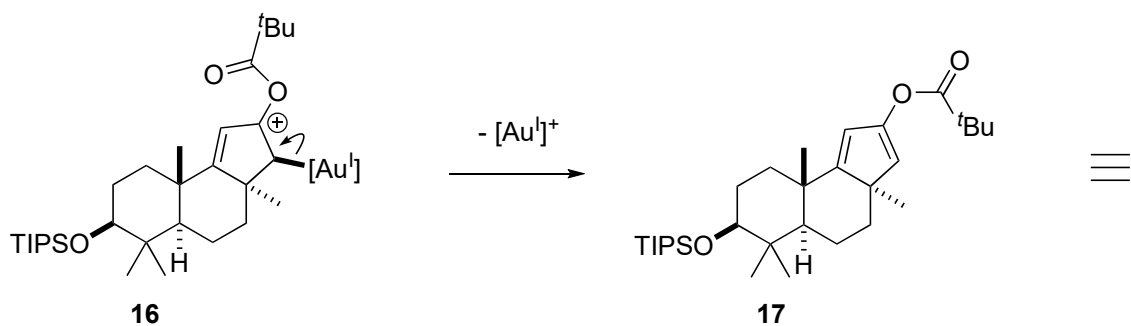


* When CH₂Cl₂ is treated with *n*-BuLi at -35 °C to -40 °C, chlorocarbene is generated.
Closs, G. L. and Closs, L. E. *JACS*. **1960**, *82*, 5723.

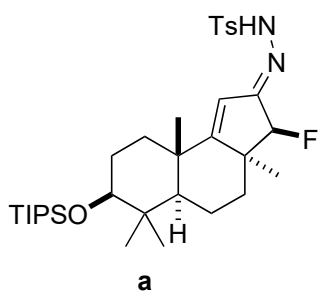
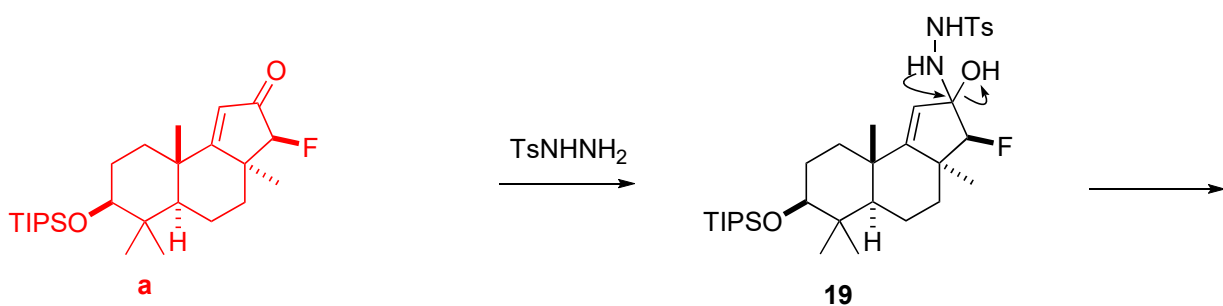


In the conformer **10-A**, the Lithium reagent will attack from below side (b) rather than upper side (a), and the product is **12**. In the conformer **10-B**, which will be minor one, the lithium reagent will attack to avoid the axial methyl group. Therefore, **12** is obtained as a major diastereomer.

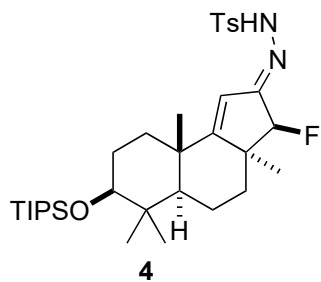




The acylium cation will be trapped by some species.

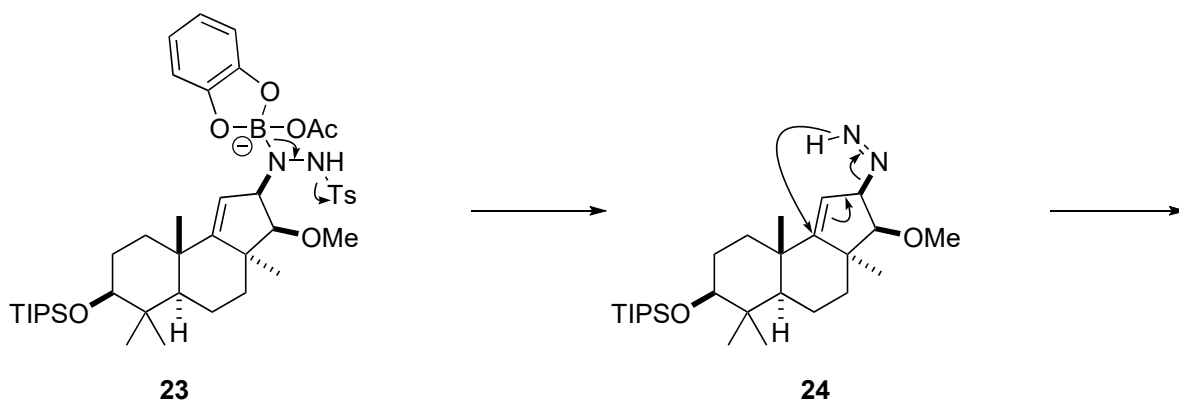
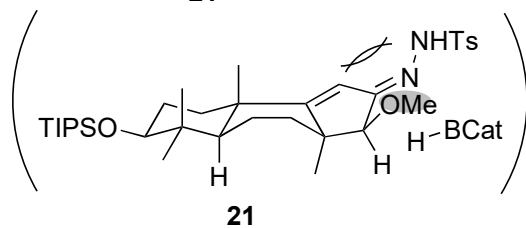
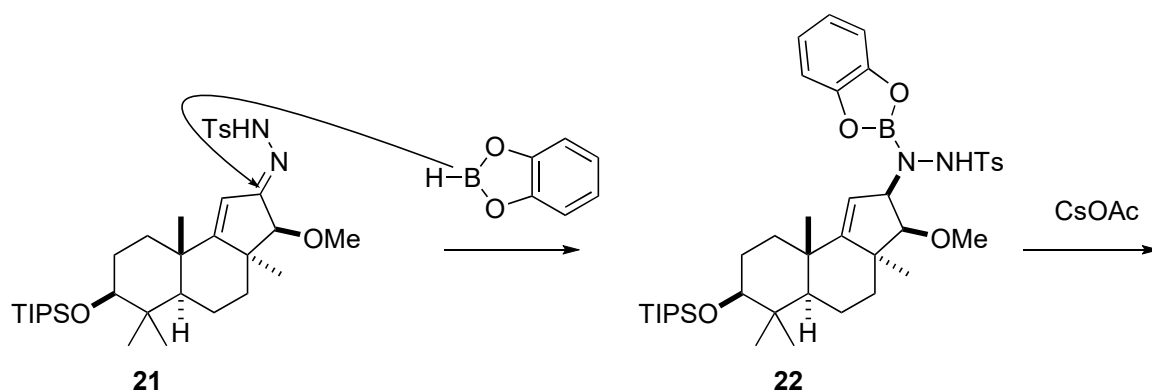
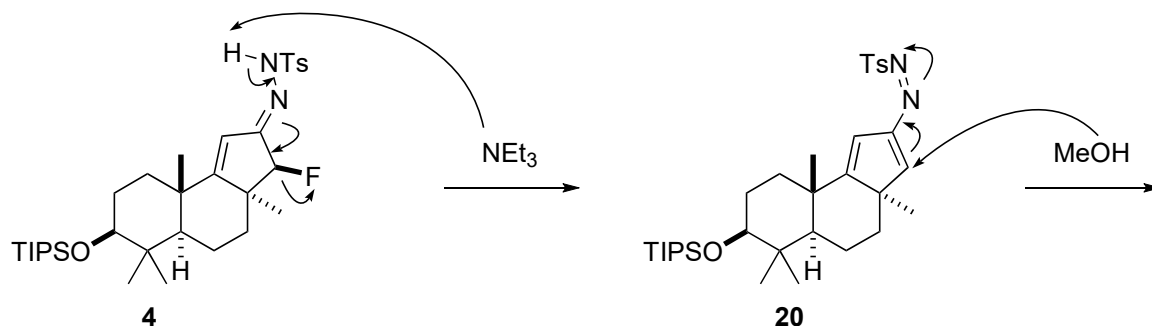
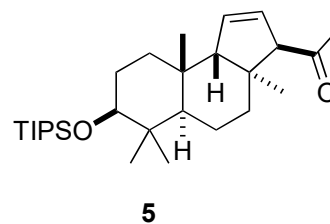


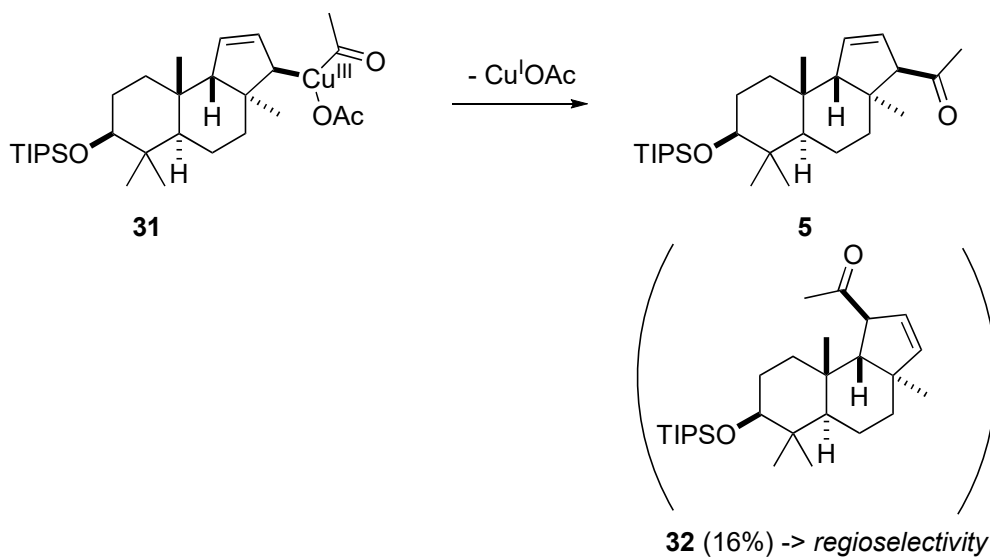
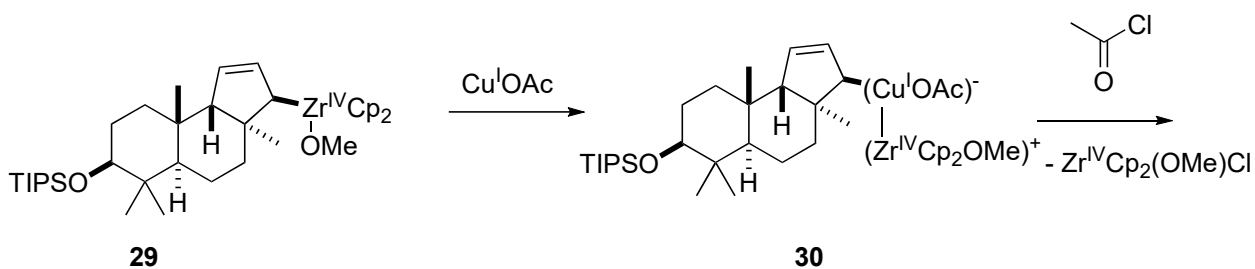
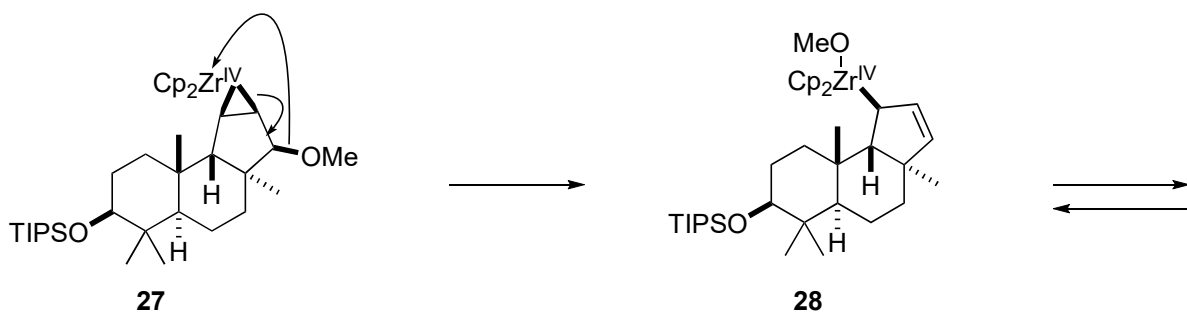
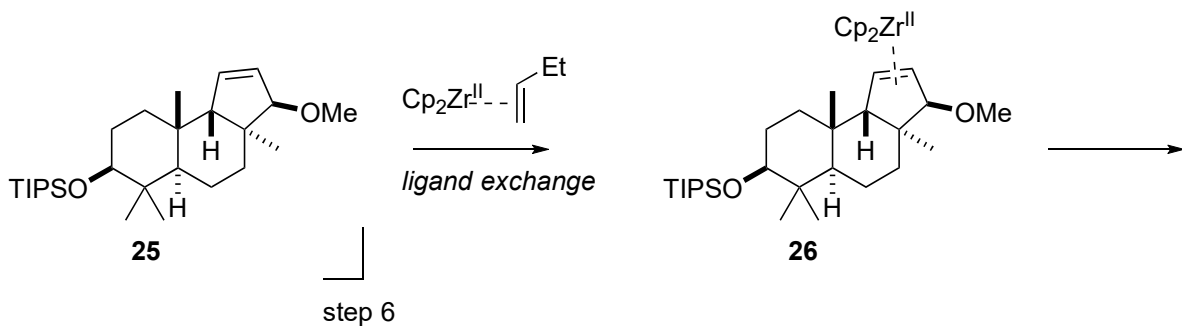
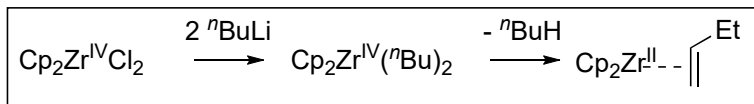
step 5



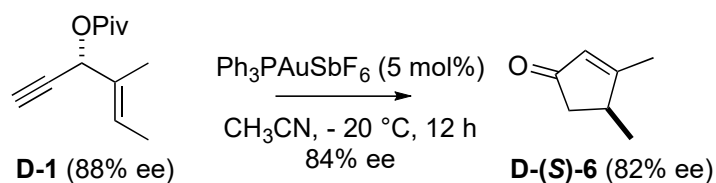
6. Et₃N (1.3 eq.),
CHCl₃/MeOH, 24 °C;
CatBH (1.5 eq.), 0 °C;
CsOAc (2.5 eq.), 65 °C, 58%

7. Cp₂ZrCl₂ (1.3 eq.), *n*-BuLi (2.4 eq.),
THF, 0 °C to 25 °C;
CuOAc (20 mol%), AcCl (4.0 eq.),
55 °C, 64%





discussion 1: Gold-Catalyzed Rautenstrauch reaction



-> Chirality of **D-1** is transferred to **D-(S)-6**.

Mechanistic study: de Lera et al. *J. Am. Chem. Soc.* **2006**, *128*, 2434.
(For simplicity, Piv and Ph₃P are changed to Ac and PH₃, respectively.)

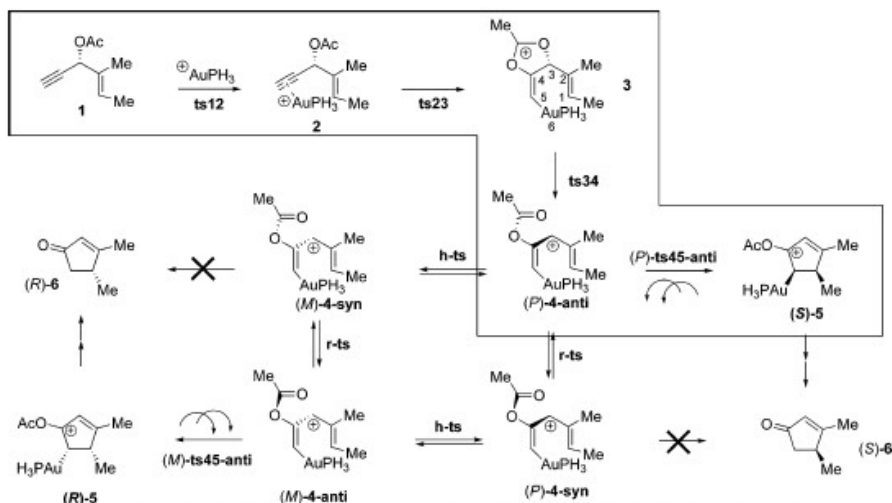


Figure 3. Mechanistic manifold for the gold-catalyzed Rautenstrauch rearrangement of (*E*)-1-ethynyl-2-methylbut-2-enyl acetate **1**.

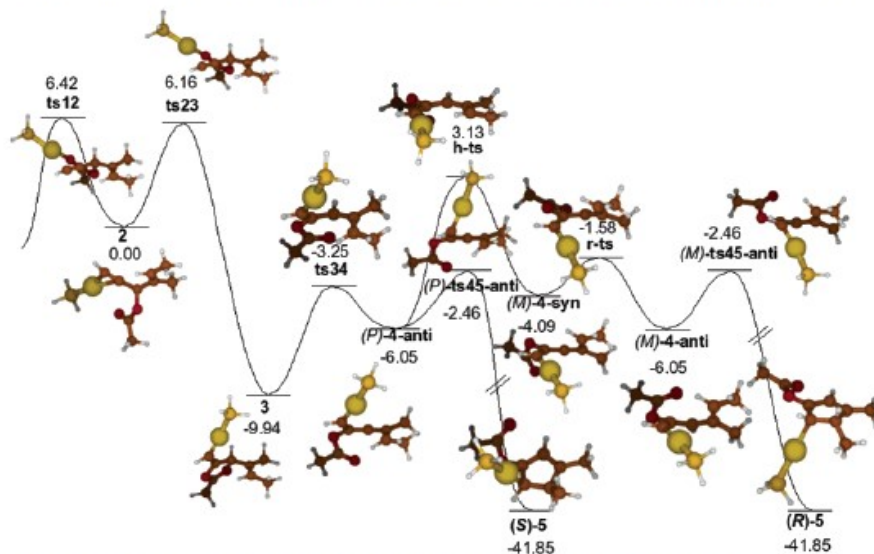


Figure 4. Reaction energy profile for the gold(I)-catalyzed rearrangement of (*E*)-1-ethynyl-2-methylbut-2-enyl acetate **1** (Figure 3).

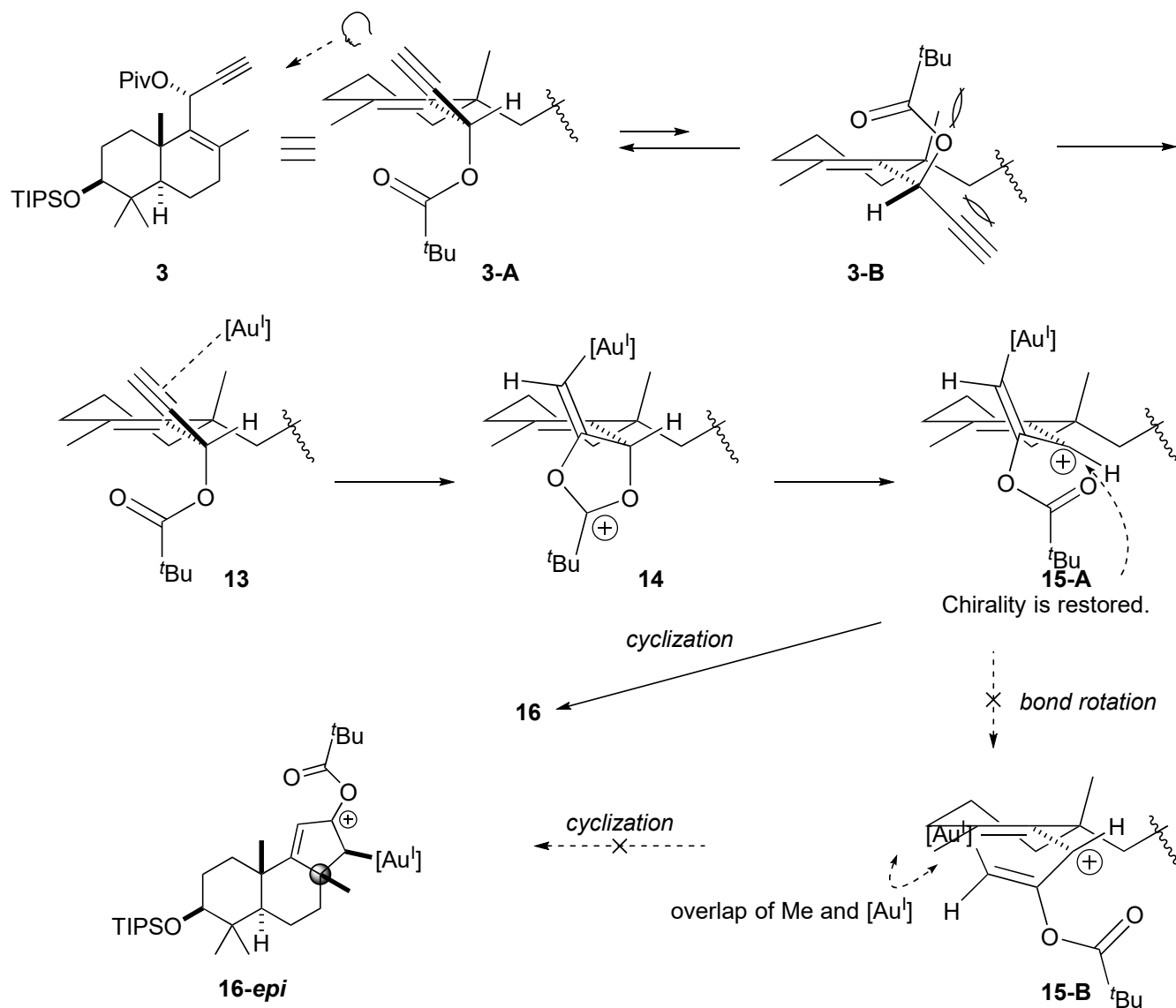
(B3LYP/6-31G*)

summary:

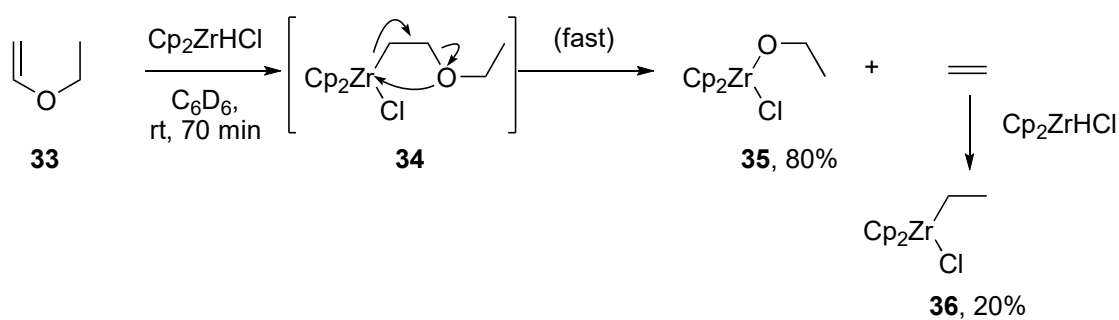
1. Not concerted mechanism (carbocation (*P*)-4 anti is generated.)
2. Rotation of bond needs more energy than cyclization (**h-ts** vs. (*P*)-ts45-anti).

-> reflection of the stereochemistry of OAc group

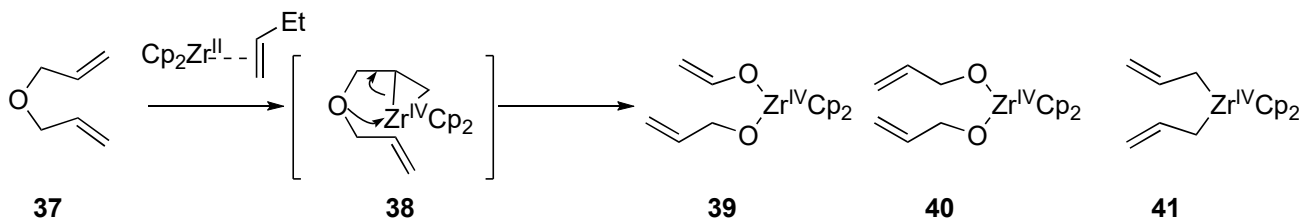
* Authors (*JACS* **2006**, *128*, 2434) mention the process cannot be clearly described as ionic or pericyclic.



discussion 2: reductive zirconation and Cu-catalyzed cross-coupling
 1. β -elimination of alkoxy group



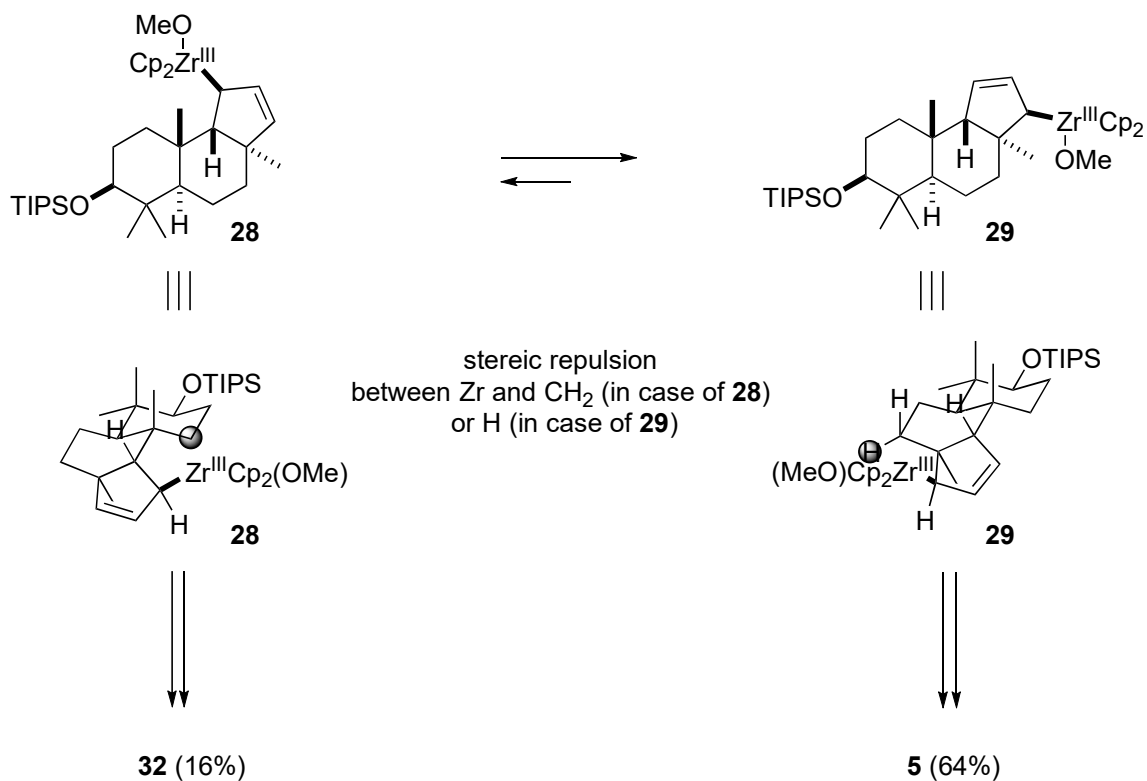
Buchwald S. L.; Nielsen, R. B.; Dewan J. C. *Organometallics* **1988**, *7*, 2324.



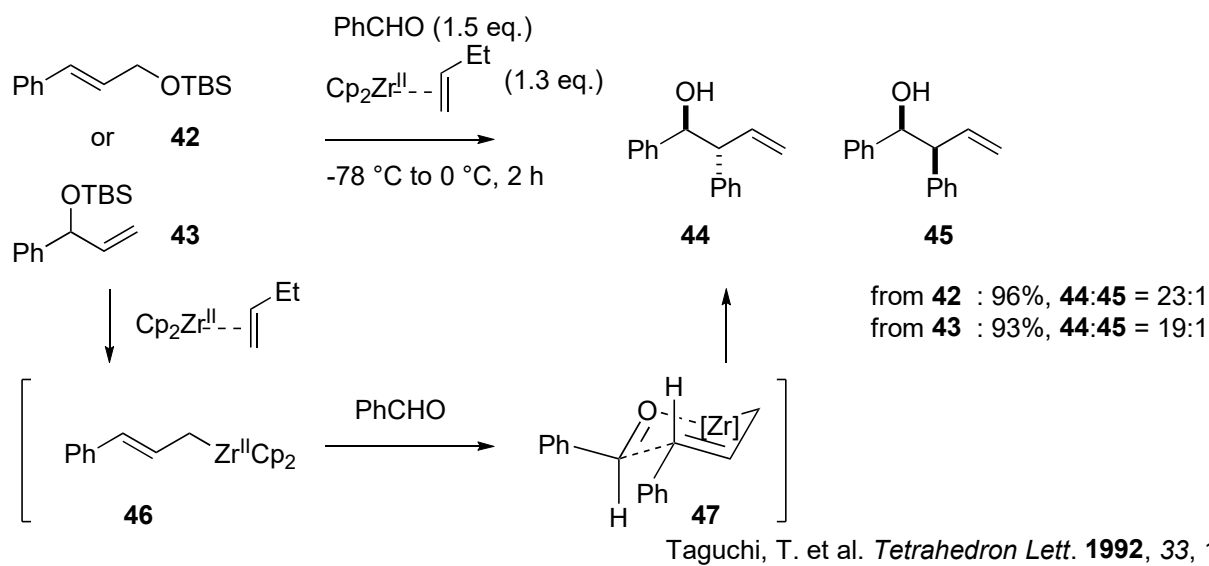
(Yields are not reported.)

Negishi, E. et al. *Tetrahedron Lett.* **1989**, *30*, 5105.

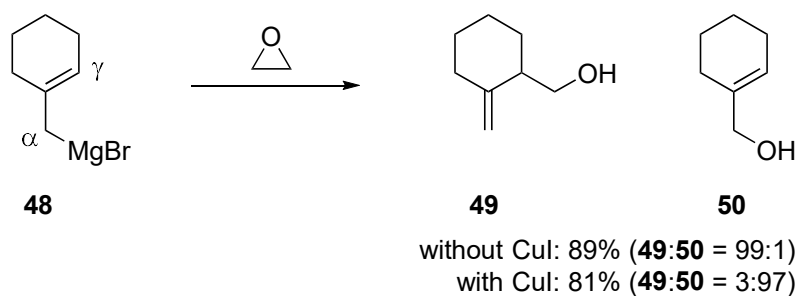
2. My proposal for regioselectivity



1) Supporting evidence of 1,3-rearrangement of Zr



2) Regioselectivity between α vs. γ position of Cu-reagent



Linstrumelle, G. et al. *Tetrahedron Lett.* **1978**, 42, 4069.

Though metal combination is Cu and Mg, α -selectivity will increase in organocopper reagents.