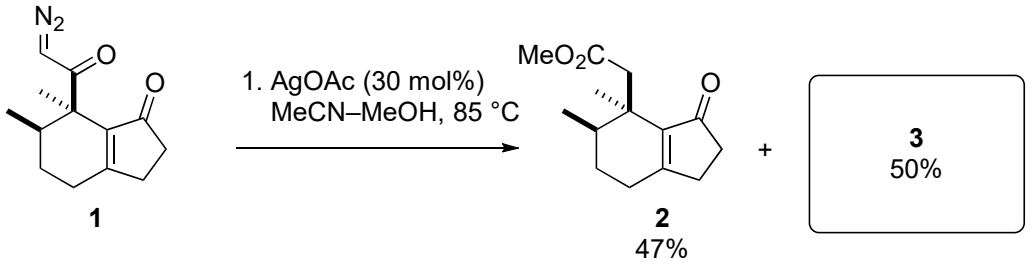
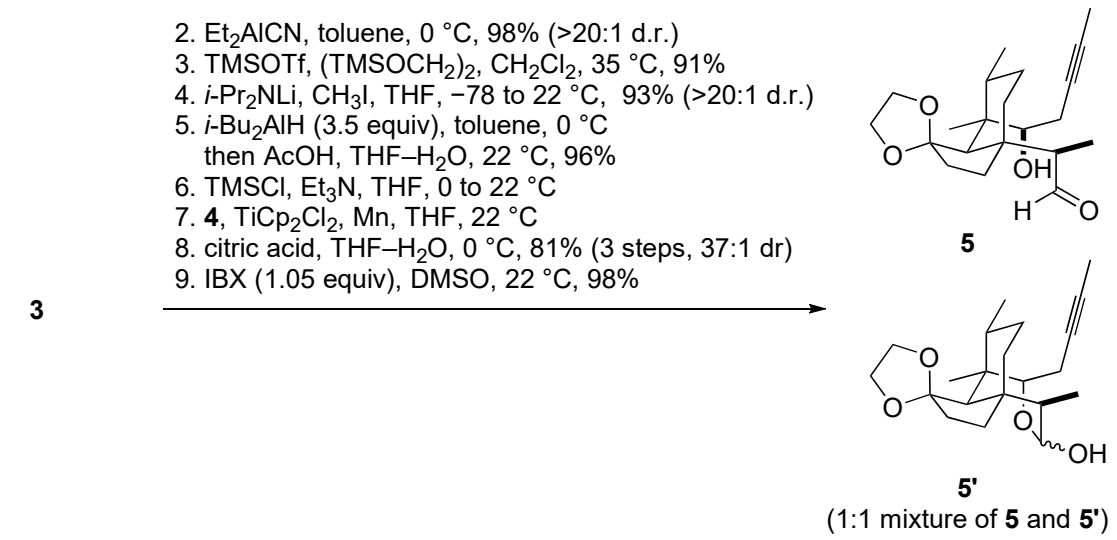
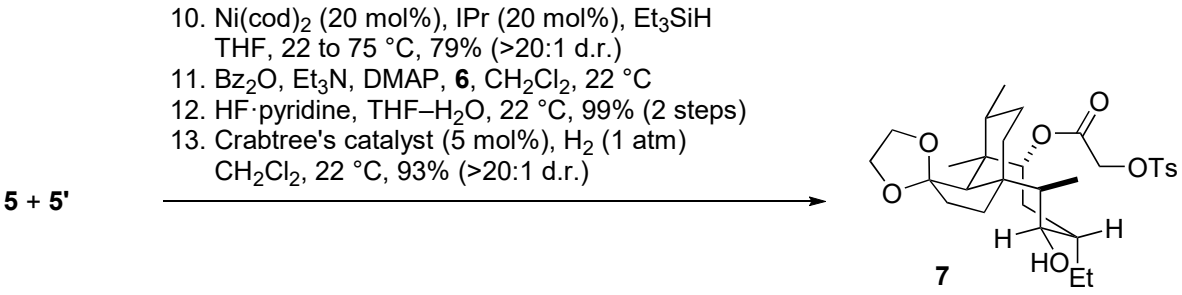
Problem Session (7) - Problem

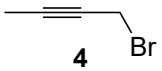
2022.10.29. Yusuke Imamura

Please provide the reaction mechanisms.

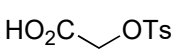




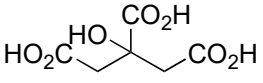




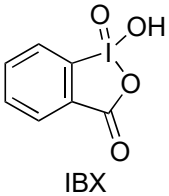
4



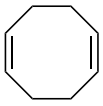
6



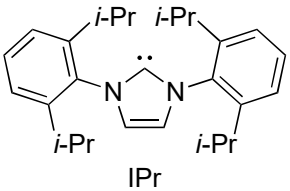
citric acid



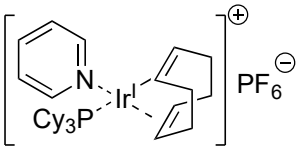
IBX



cod



IPr



Crabtree's catalyst

Problem Session (7) - Answer

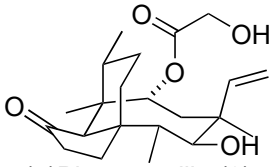
Topic: Synthesis of pleuromutilin analogue by S. B. Herzon

0. Introduction

Isolation: edible mushroom *Pleurotus mutilus* (Kavanagh, F. et al. *PNAS*, **1951***, 37*, 570.)

Biological activity: bacterial protein synthesis inhibition

Structureal feature: eight-membered ring, three quternary carbons

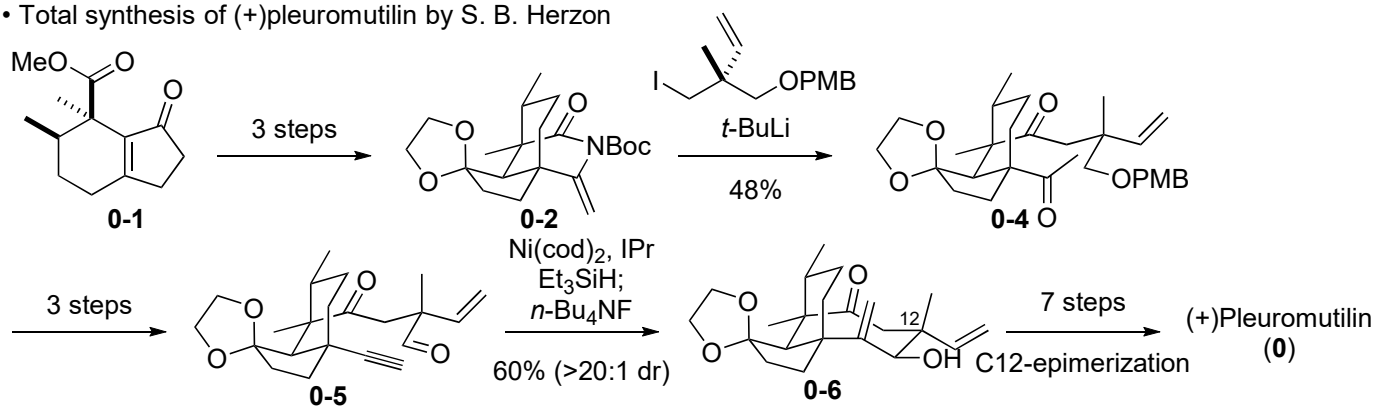

(+)Pleuromutilin (**0**)

Total synthesis:

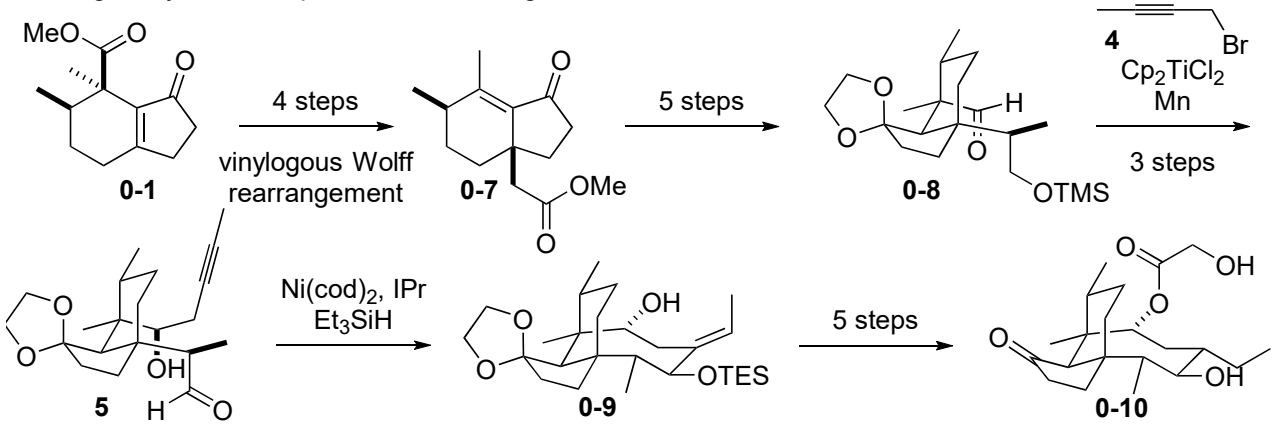
1. Gibbons, E. G. et al. *J. Am. Chem. Soc.* **1982**, *104*, 1767. (racemic)
2. Boeckman, R. K. Jr. et al. *J. Am. Chem. Soc.* **1989**, *111*, 8284. (racemic)
3. Procter, D. J. et al. *Chem. Eur. J.* **2013**, *19*, 6718. (asymmetric)
4. Herzon, S. B. et al. *Science* **2017**, *356*, 956. (asymmetric)
5. Herzon, S. B. et al. *J. Am. Chem. Soc.* **2017**, *139*, 16377. (asymmetric)
6. Reisman, S. E. et al. *J. Am. Chem. Soc.* **2018**, *140*, 1267. (asymmetric)
7. Pronin, S. V. et al. *J. Am. Chem. Soc.* **2022**, *144*, 10174. (racemic)

Seminar: 130622_PS_Taro_Asaba, 170617_LS_Hiroaki_Matoba, 180707_PS_Yuri_Takada, 220624_PS_Wentao_Wang

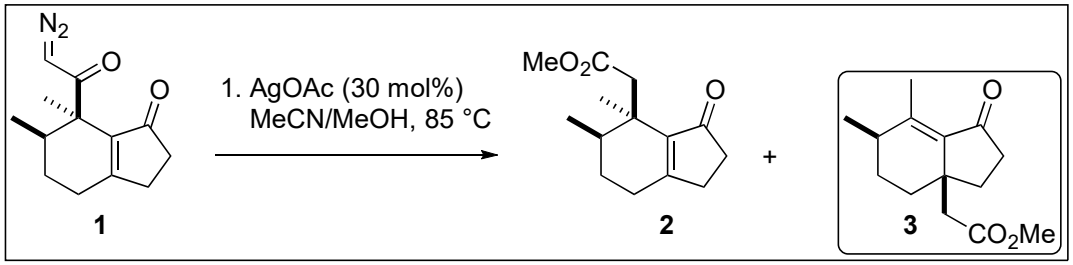
• Total synthesis of (+)pleuromutilin by S. B. Herzon



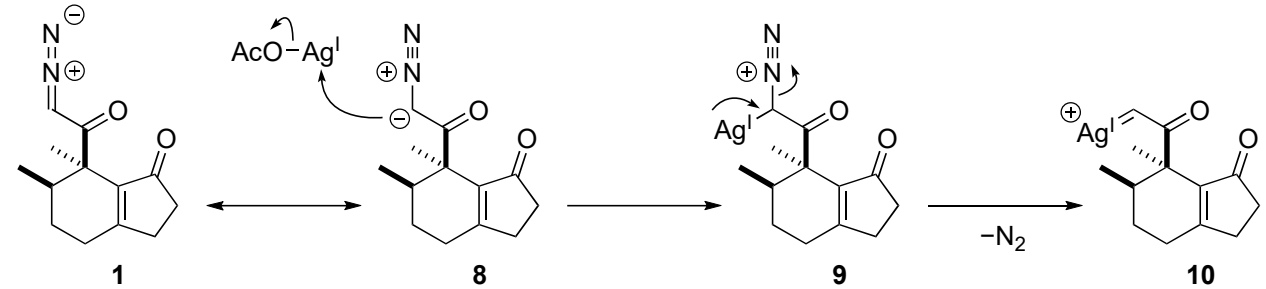
• Divergent synthesis of pleuromutilin analogue

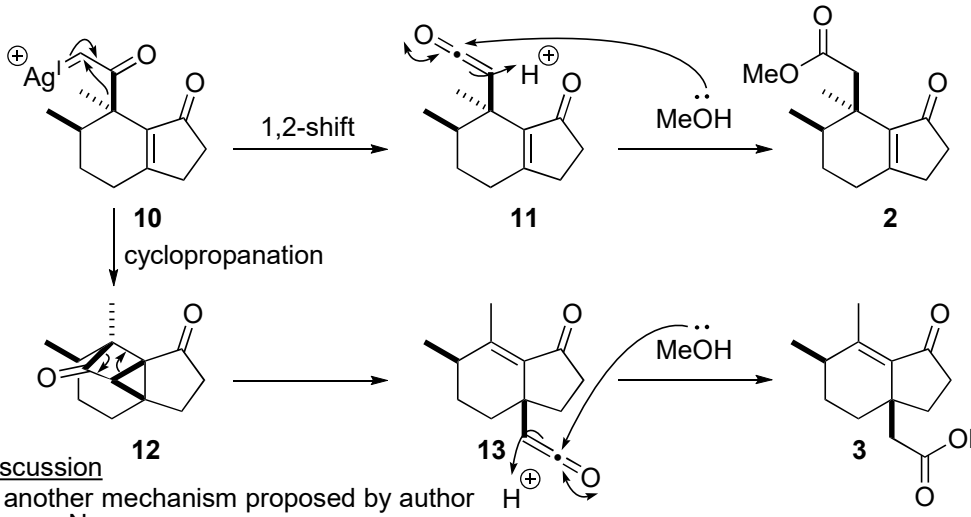


1. Answer



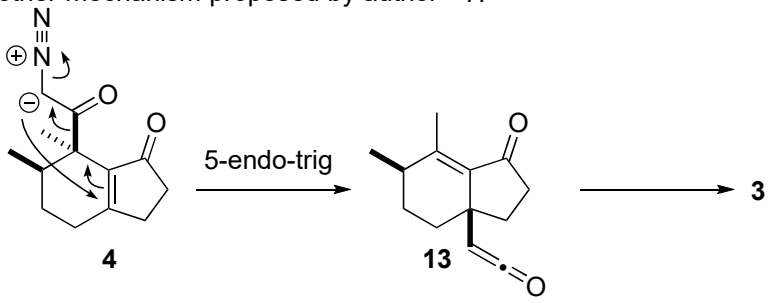
mechanism



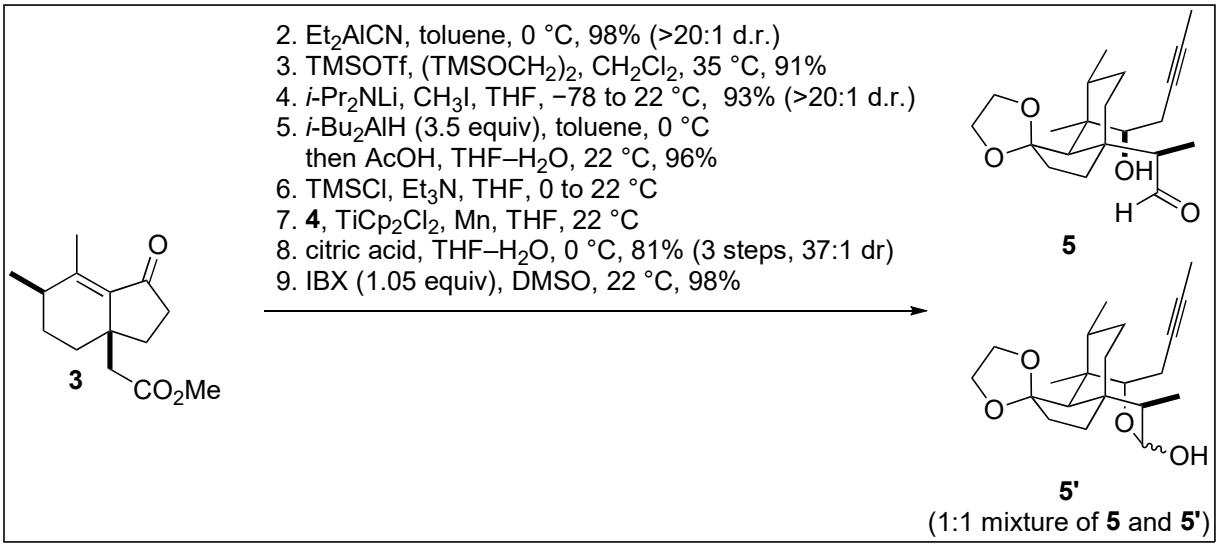


Discussion

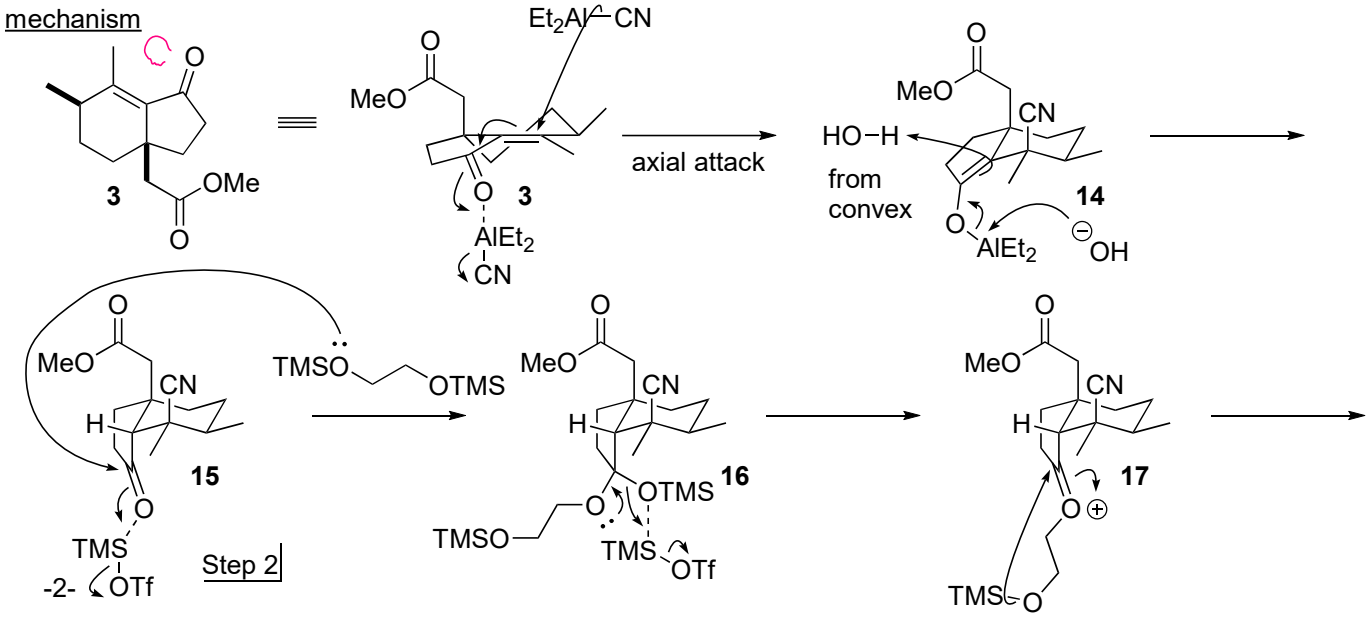
1. another mechanism proposed by author

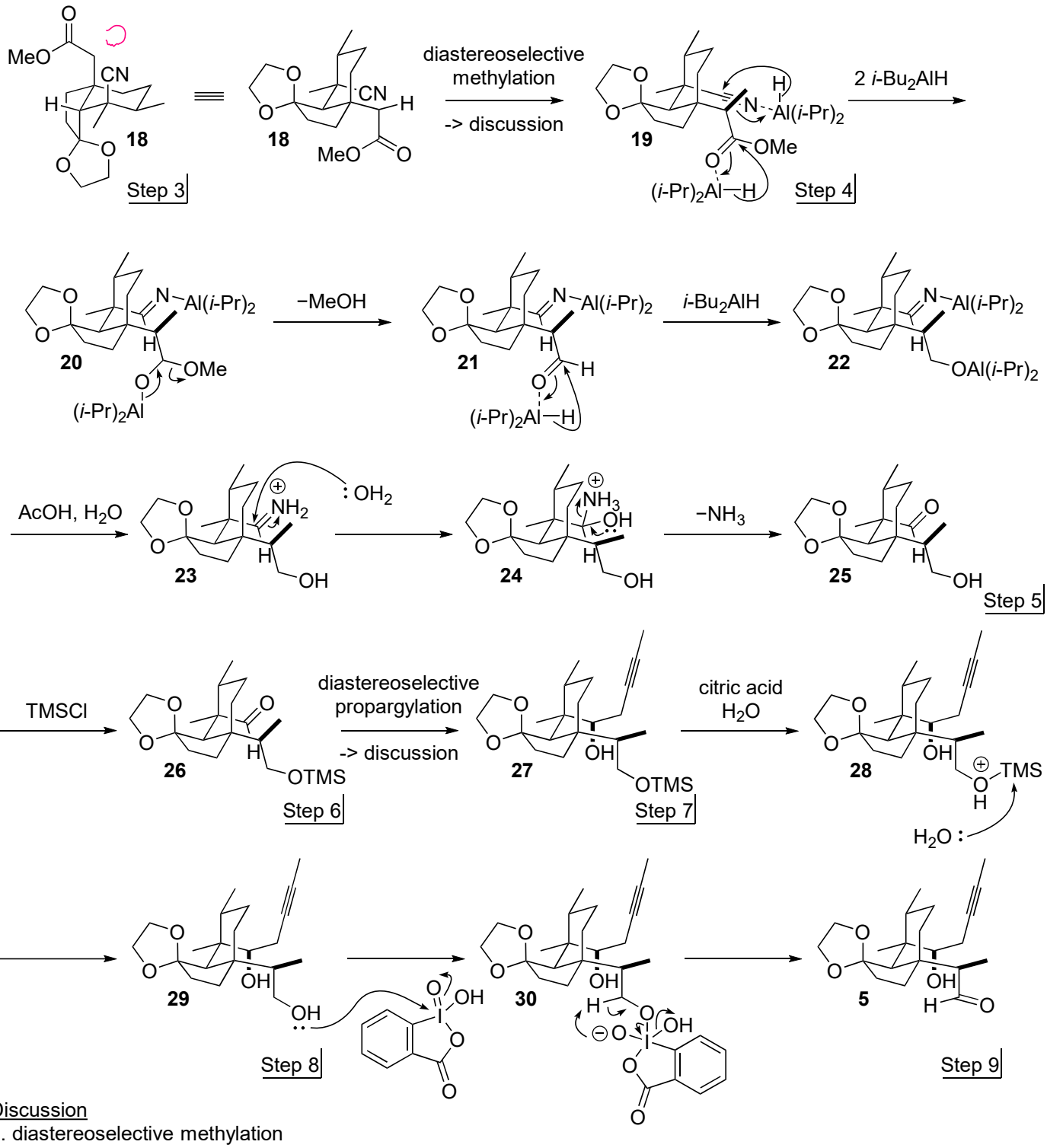


Altough the electron deficient olefin reacted with anion, the ciclization mode is unfavorable.
Reaction via carbenoid should be more favorable?



mechanism

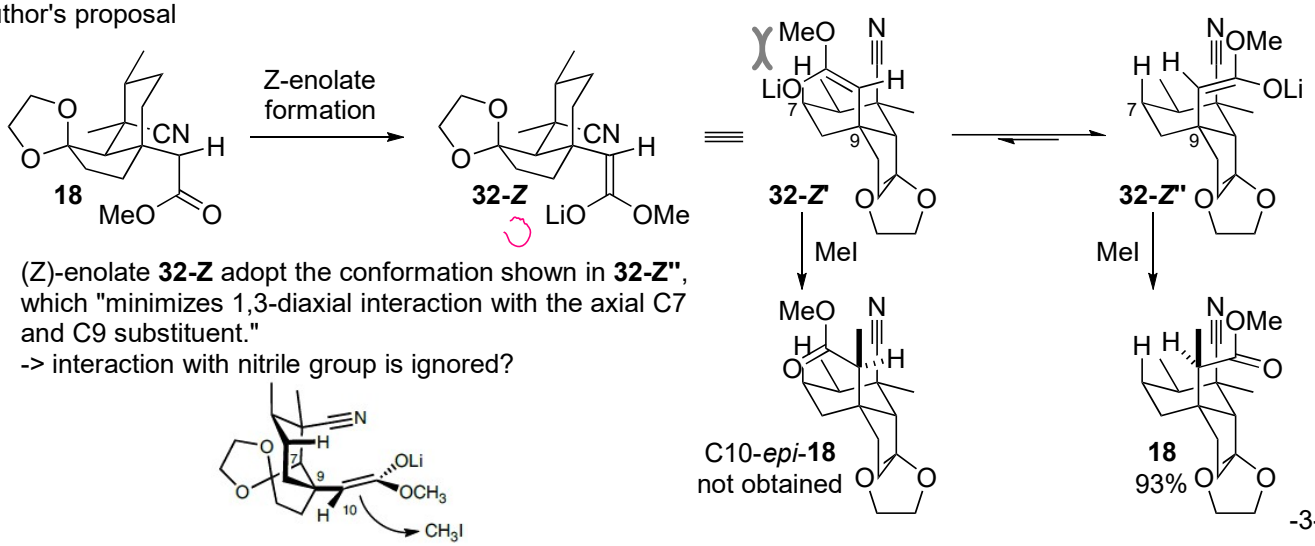




Discussion

1. diastereoselective methylation

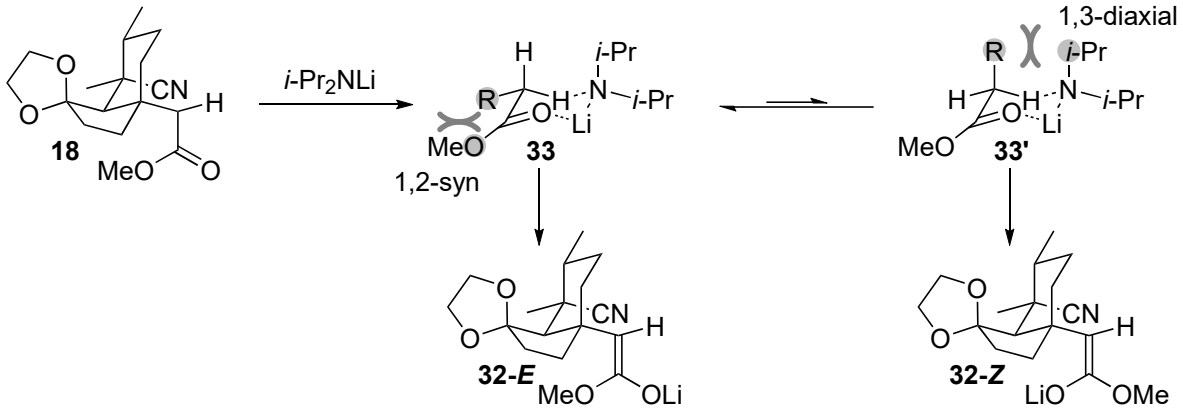
author's proposal



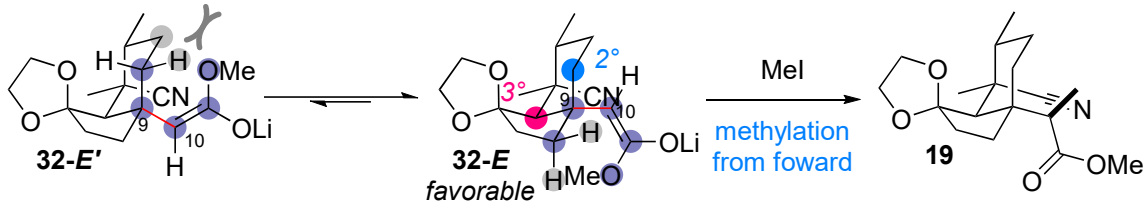
(Z)-enolate **32-Z** adopt the conformation shown in **32-Z''**, which "minimizes 1,3-diaxial interaction with the axial C7 and C9 substituent."

-> interaction with nitrile group is ignored?

my proposal

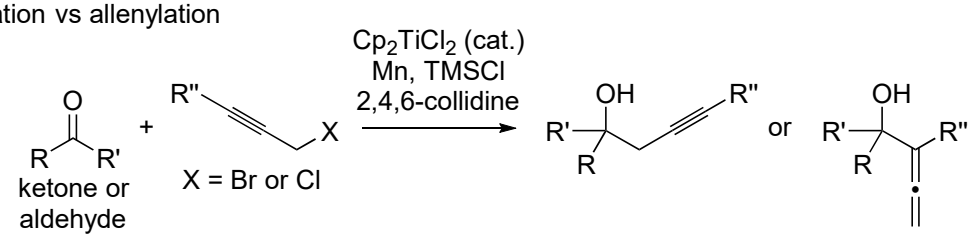


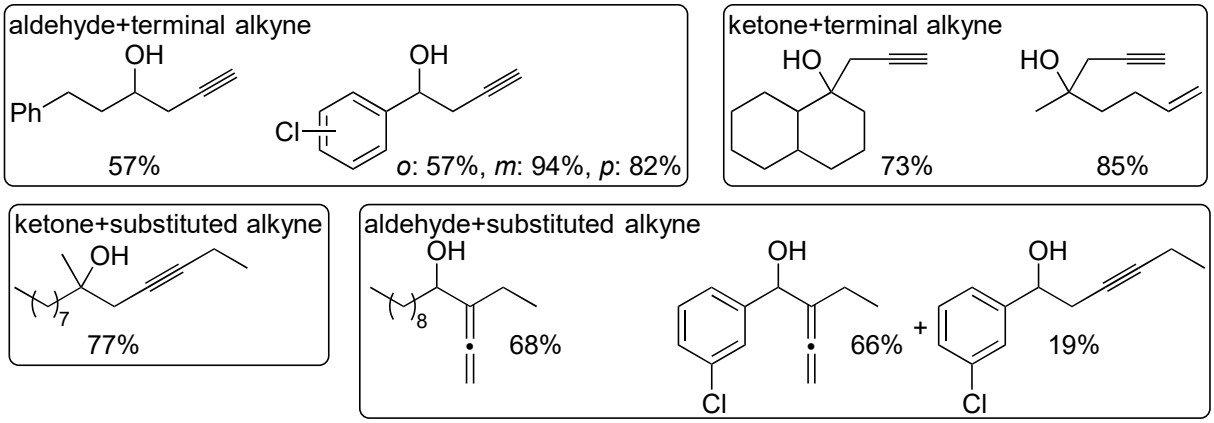
Although the enolate geometry of olefin is not related to the following result, favorable enolate should be *E*-enolate?
For more information about enolatization in various solvents, see *Angew. Chem. Int. Ed.* **2007**, *46*, 3002.



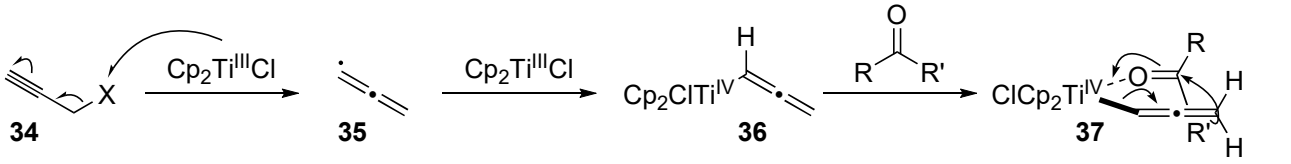
When the 1,3-allylic strain was considered as major factor, there are three possible conformations.
(Another one is ignored. Purple atoms are in the same plane.)
The substituents facing toward OMe group are highlighted in gray.
Compareing these two conformations, **32-*E*** seems to be more favorable.

2. Ti(III) mediated propalgylation (Rosales, A.; Oltra, J. E. et al. *Chem. Eur. J.* **2012**, *18*, 14479.)
2.1. propargylation vs allenylation





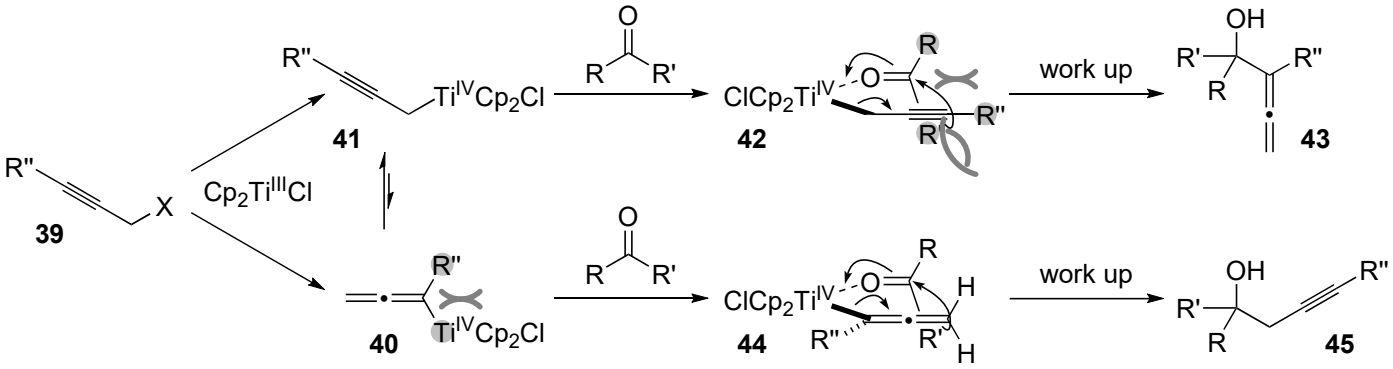
In case of R" = H (terminal alkyne)



36 detected on NMR experiment
(δ = 78.2 (CH_2), 122.2 (CH), 218.1 (C))
(propalgyl chloride + $Cp_2Ti^{III}Cl$ in THF-d8, 1 h)

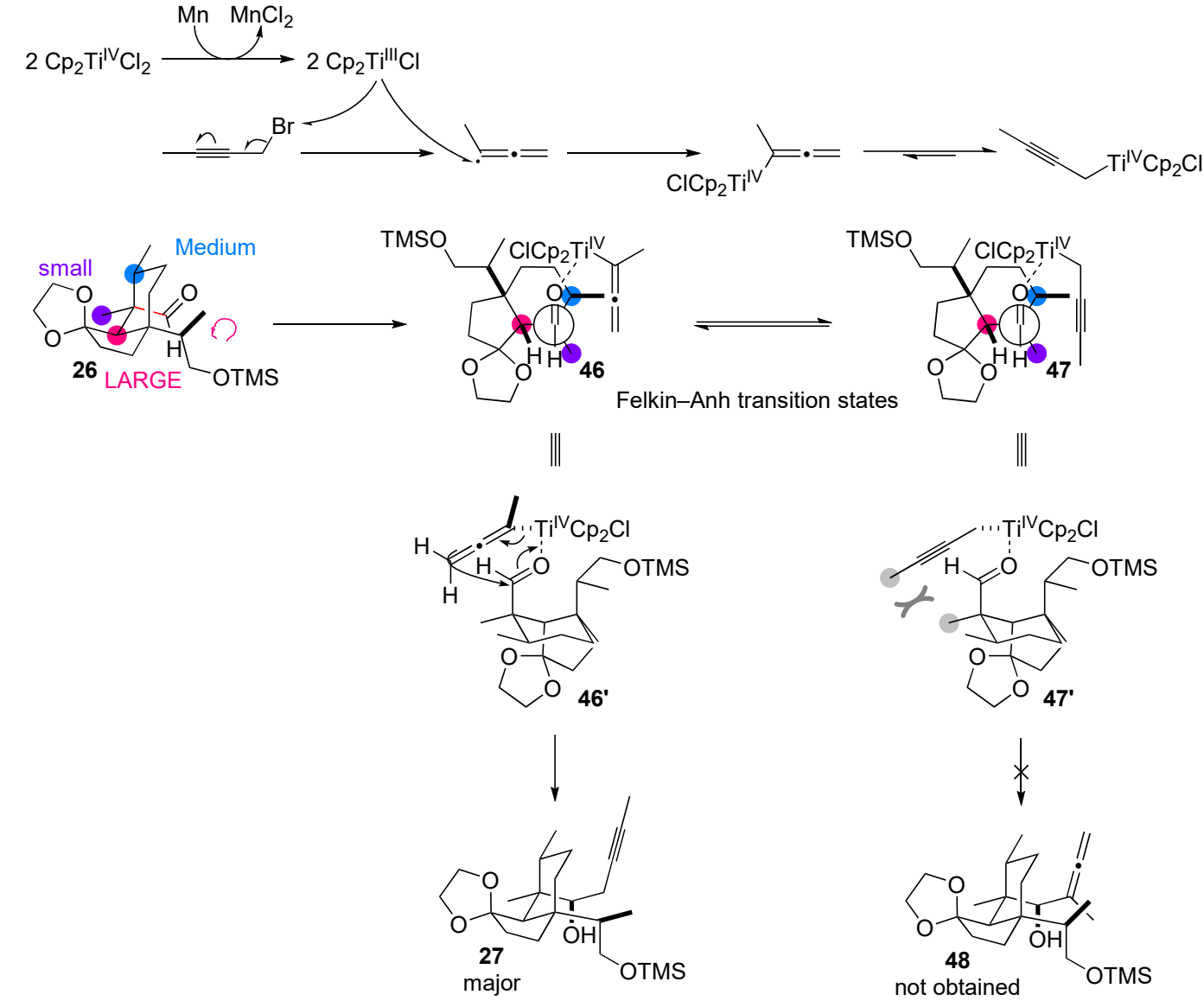
larger steric repulsion (sp3)

In case of R" ≠ H (substituted alkyne)

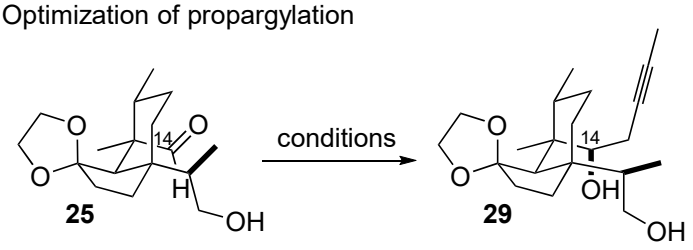


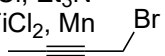
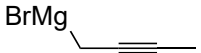
If R" ≠ H, allenyl titanium spieces **40** isomerized to propargyl titanim **41** to avoid geminal substituent interaction. Furthermore, if R' = H (alehydes), interaction between propargyl titanium and aldehyde is small (as in **42**) and aldehyde reacts with more populated titanium speices **41** to yield α-hydroxy-allenes **43**.
Else if R, R' ≠ H (ketones), the steric repusion between substituent on alkyne and ketone becomes larger (in **42**) and the transition state **44** becomes unfavorable. Therefore, the reaction proceed from allenyl titanim **40** to yield homopropargylic alcohols **45**.

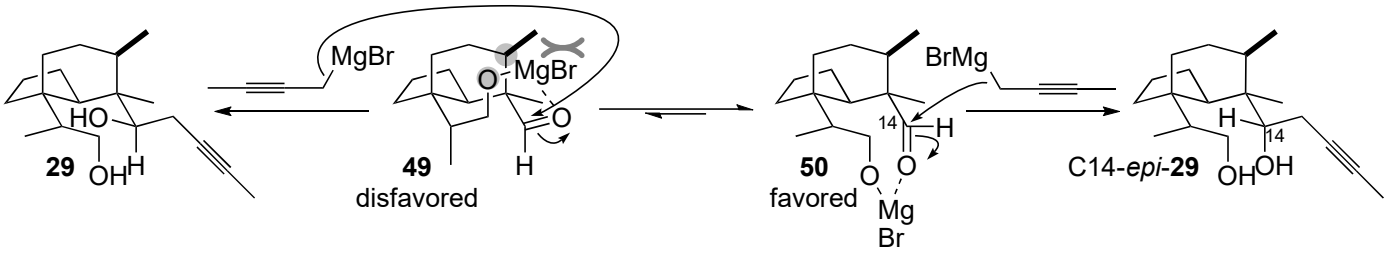
Reaction mechanism from aldehyde **26** to homoproprgylic alcohol **27**



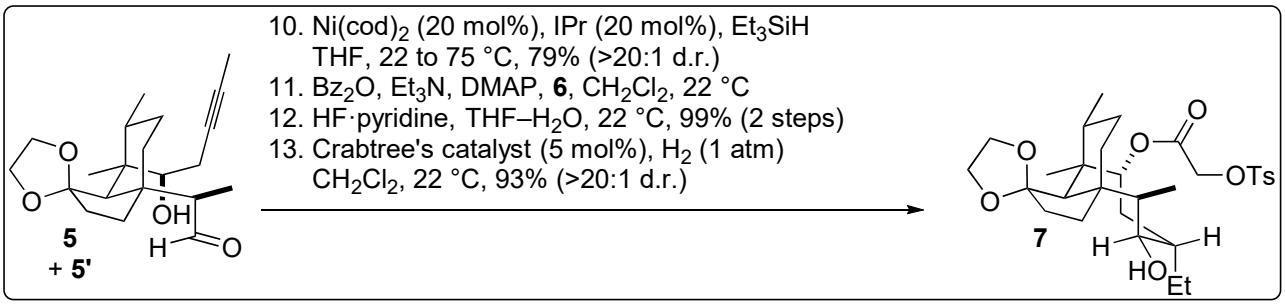
Optimization of propargylation



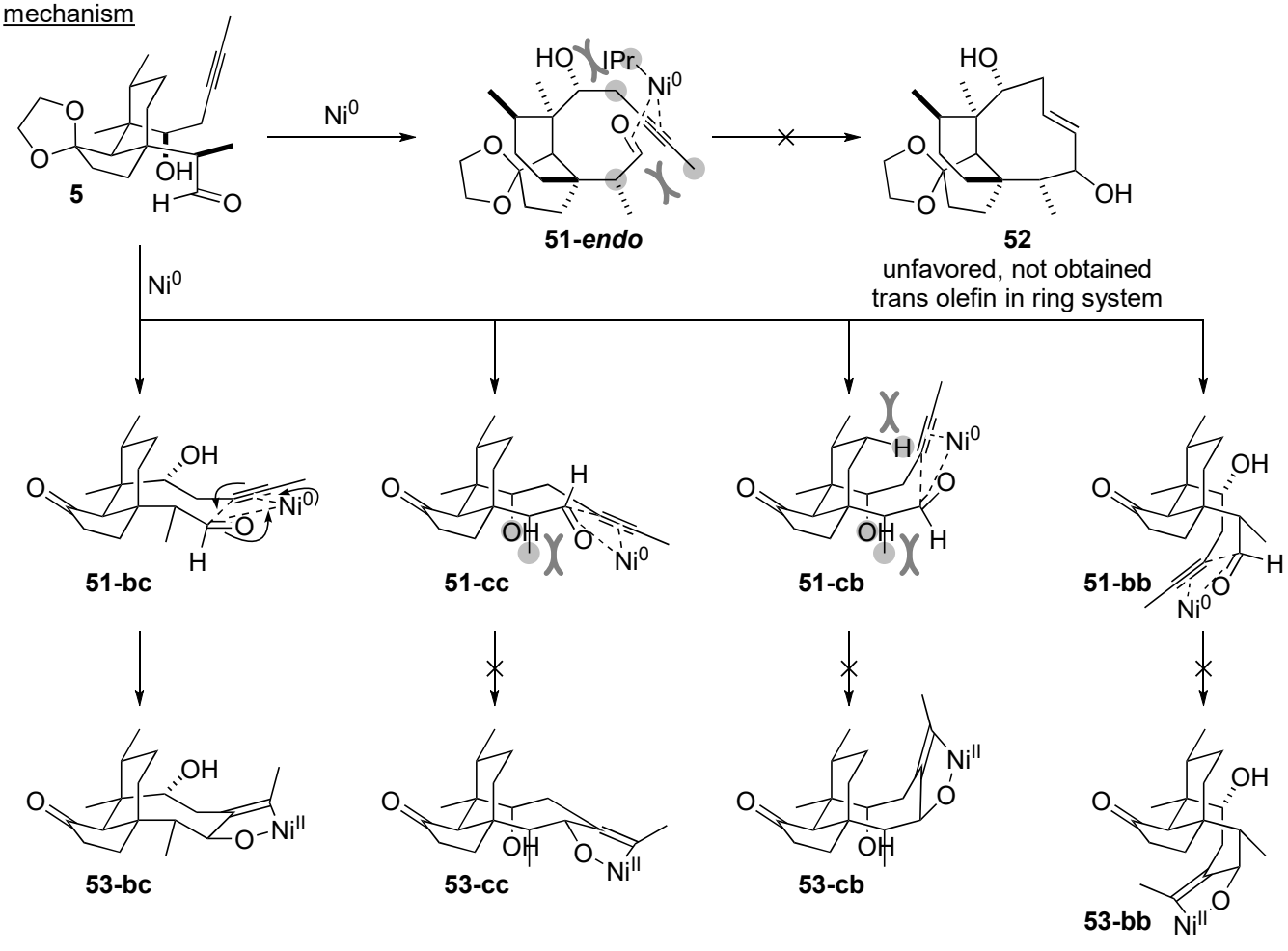
conditions	result
1. TMSCl, Et_3N 2. Cp_2TiCl_2, Mn, THF,  3. citric acid, THF–H_2O	**29**: 81% (37:1 d.r.)
 DME	C14-*epi*-**29**: 66% (>20:1 d.r.)

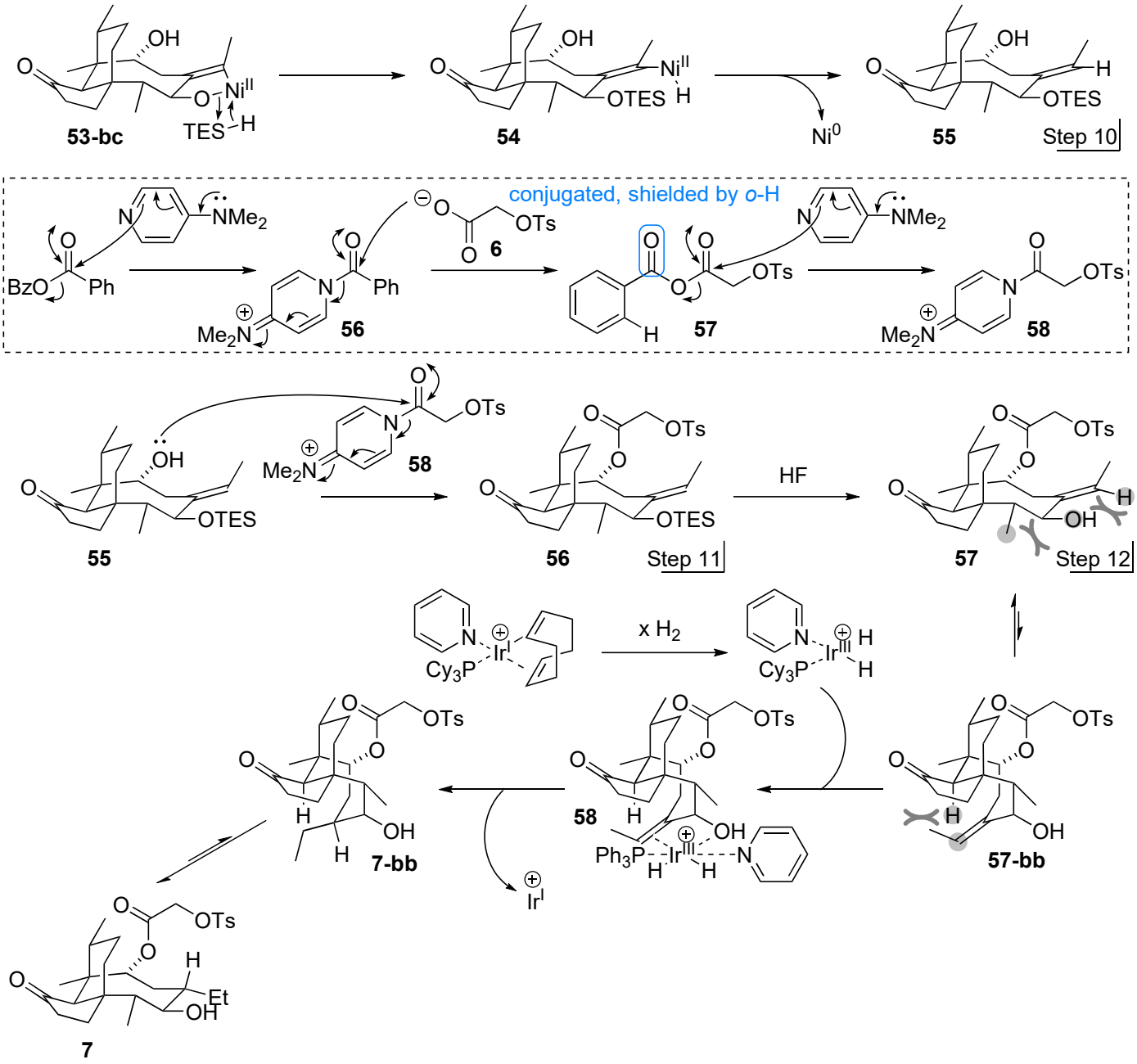


When unprotected **25** was treated with propargyl grignard reagent, the diastereoselectivity changed. This diastereoselectivity can be explained by chelation model.



mechanism




53-bc
54
55
Step 10
conjugated, shielded by o-H
6
56
57
58
Step 11
HF
Step 12
x H2
57-bb
7-bb
7