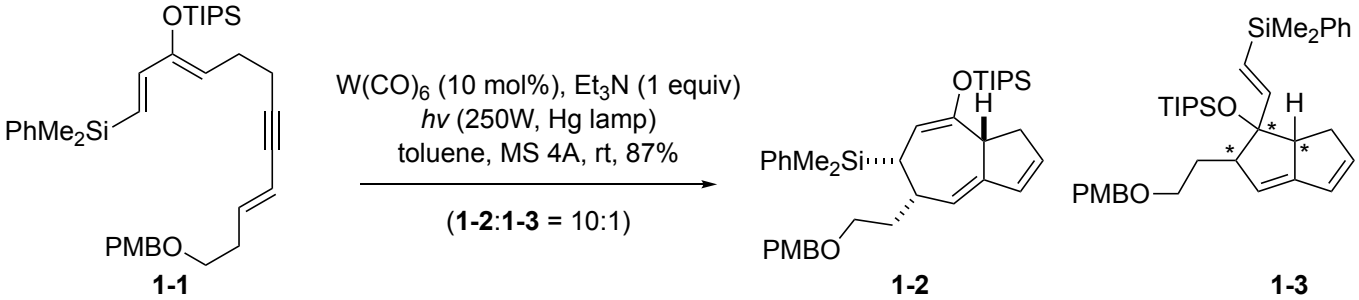
Problem Session (5) -Answer-

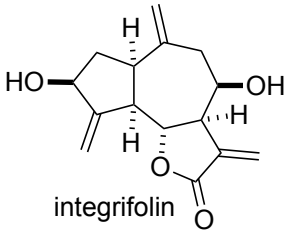
2023.7.22. Yuto Hikone

Topic: Guaianolide sesquiterpenes

1 A. Please provide reaction mechanism.

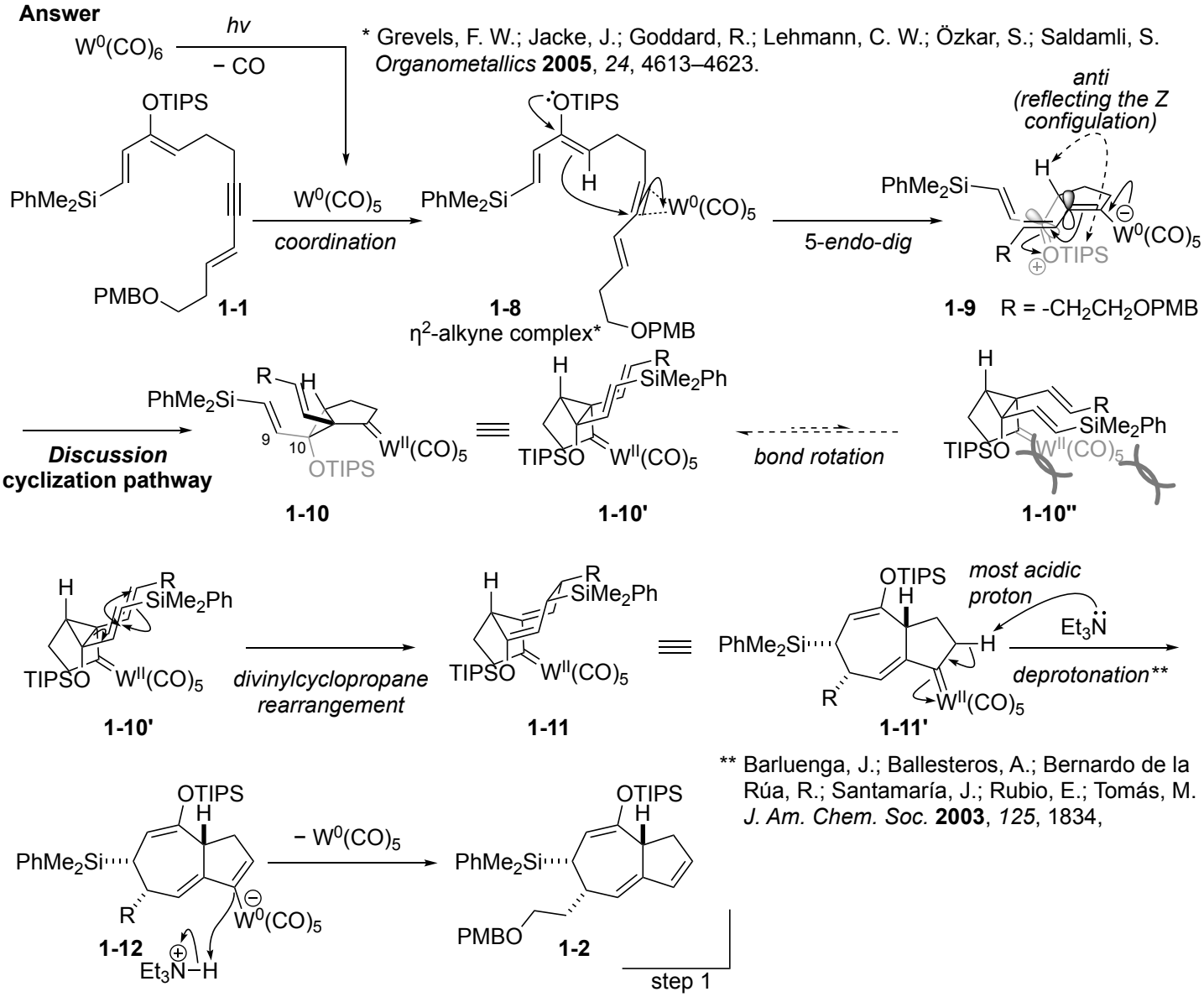


* Authors did not determine the relative stereochemistries.



Shimomaki, K.; Kusama, H.; Iwasawa, N.
Chem.−Eur. J. **2016**, *22*, 9953−9957.

Answer

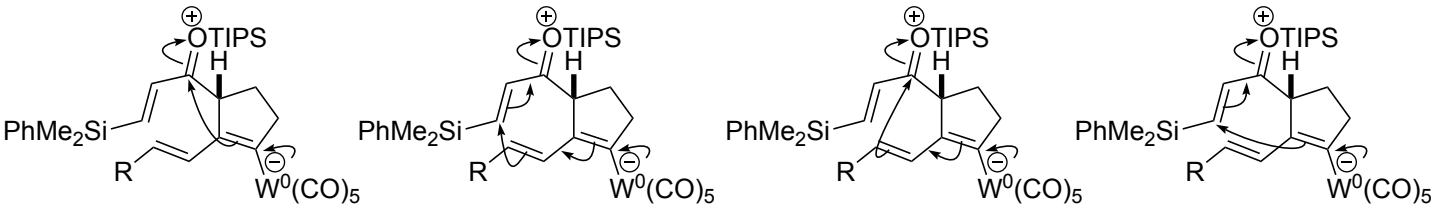


* Grevels, F. W.; Jacke, J.; Goddard, R.; Lehmann, C. W.; Özkar, S.; Saldamli, S. *Organometallics* **2005**, *24*, 4613–4623.

** Barluenga, J.; Ballesteros, A.; Bernardo de la Rúa, R.; Santamaría, J.; Rubio, E.; Tomás, M. *J. Am. Chem. Soc.* **2003**, *125*, 1834,

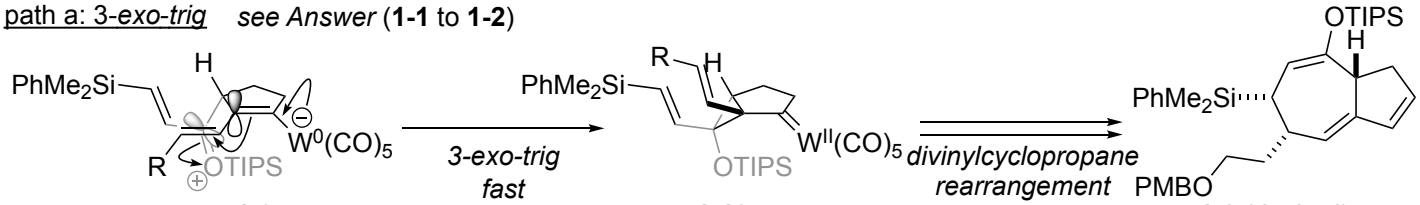
Discussion **: cyclization pathway**

Four possible cyclization modes from **1-9** can be considered.



path a: 3-*exo-trig* path b: 7-*endo-trig* path c: 5-*exo-trig* path d: 5-*endo-trig*

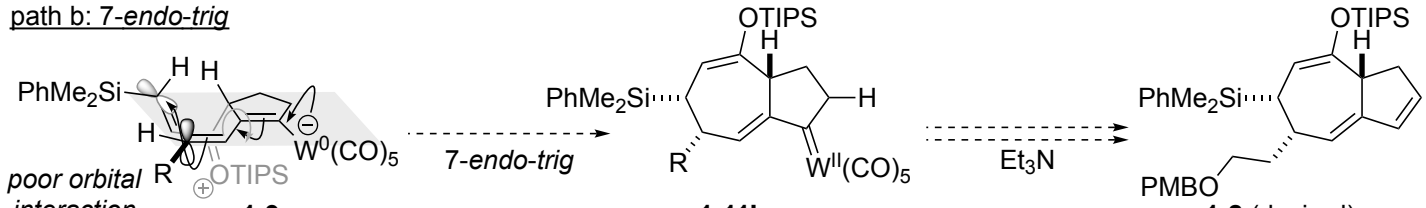
<u>path a: 3-*exo-trig*</u> *see Answer* (**1-1** to **1-2**)



1-9 **1-10** **1-2** (desired)

Reaction sites were close to each other, making three-membered ring formation favourable.

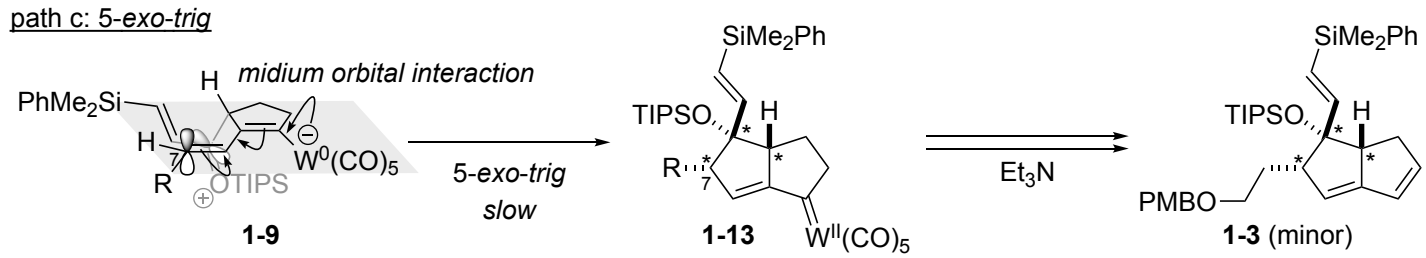
<u>path b: 7-*endo-trig*</u>



1-9 **1-11'** **1-2** (desired)

7-membered ring formation is unfavourable. Poor orbital interaction would make this pathway sluggish.

<u>path c: 5-*exo-trig*</u>

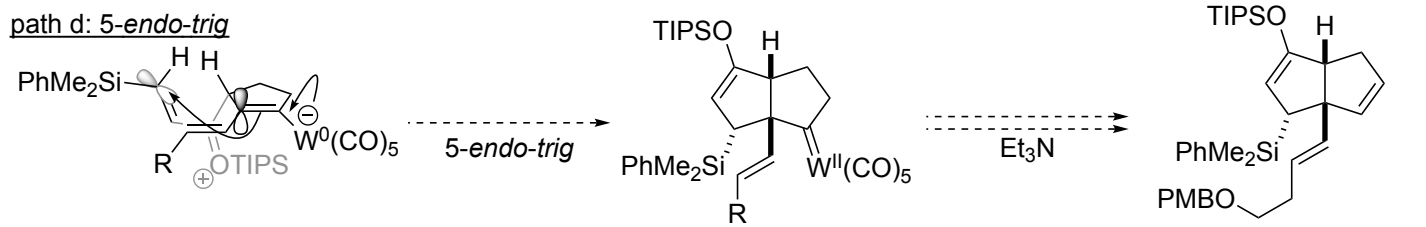


1-9 **1-13** **1-3** (minor)

* Proposed stereochemistries

Diene moiety should be planar to make nucleophilic attack at C7 position possible. As a result, orbital interaction would become relatively poor. Thus 5-*exo-trig* product **1-3** was formed as a minor one.

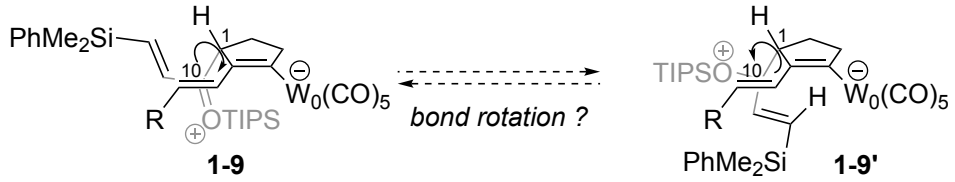
<u>path d: 5-*endo-trig*</u>



1-9 **1-14** **1-15**
not observed

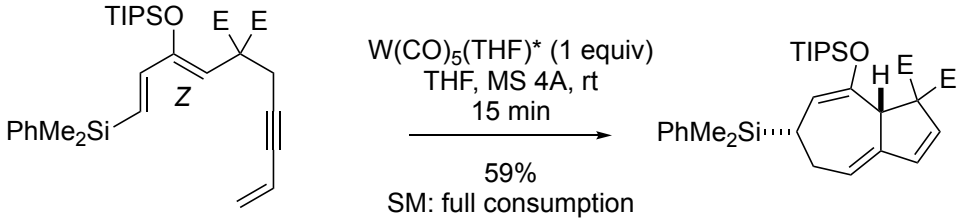
Reaction sites were too far to form C−C bond.

Is there any possibility that enone moiety rotates around C1−C10 bond? (*see Next page*)

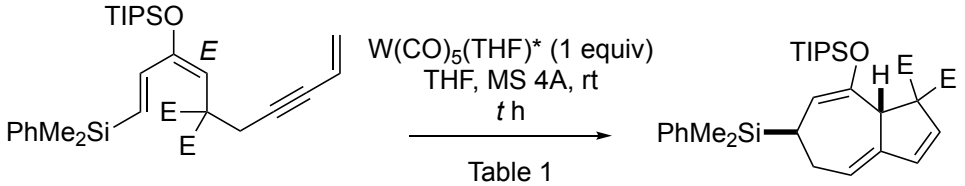


1-9 **1-9'**

1 B. Please provide rational reason why bicyclic formation from **1-4** is much faster than that from **1-6**.



1-4 (E = CO_2Me) **1-5**



1-6 (E = CO_2Me) **1-7**

Table 1

t	**1-7**	**rcv. 1-6**
1	39%	31%
5	48%	19%
20	52%	10%

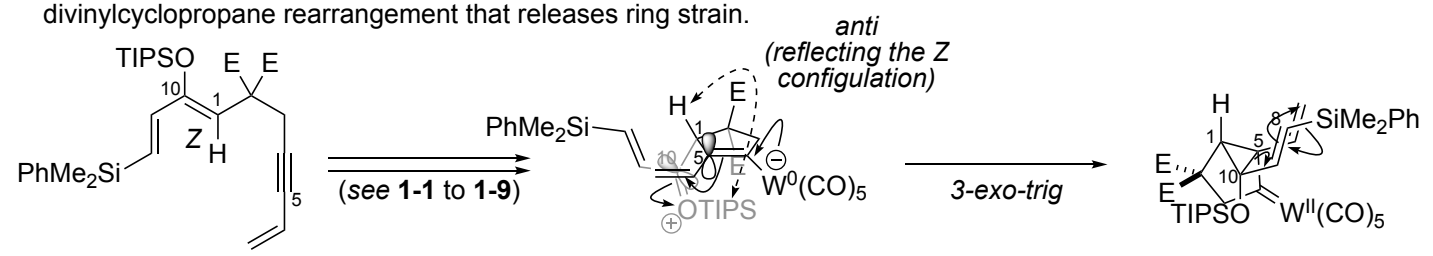
* To eliminate possibility of olefin isomerization by light, $W(CO)_5$(THF) was used. Dissociation of THF generates $W(CO)_5$ without irradiation.

Onizawa, Y.; Hara, M.; Hashimoto, T.; Kusama, H.; Iwasawa, N. *Chem.−Eur. J.* **2010**, *16*, 10785−10796.

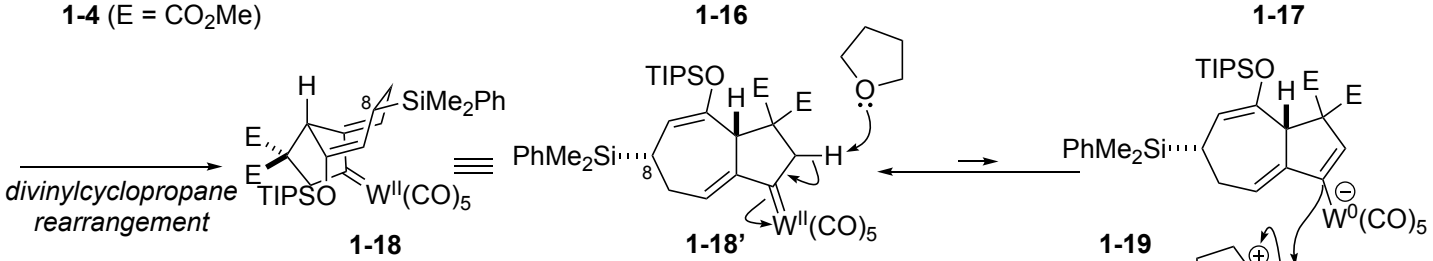
Answer

For *Z*-olefin **1-4** :

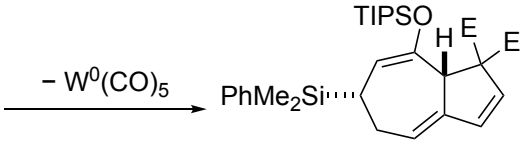
Transformation from **1-4** to **1-6** was fast. The reasons are 1. entropically favoured 3-*exo-trig* cyclization, 2. rapid divinylcyclopropane rearrangement that releases ring strain.



1-4 (E = CO_2Me) **1-16** **1-17**

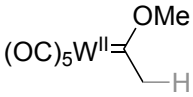


1-18 **1-18'** **1-19**



1-5

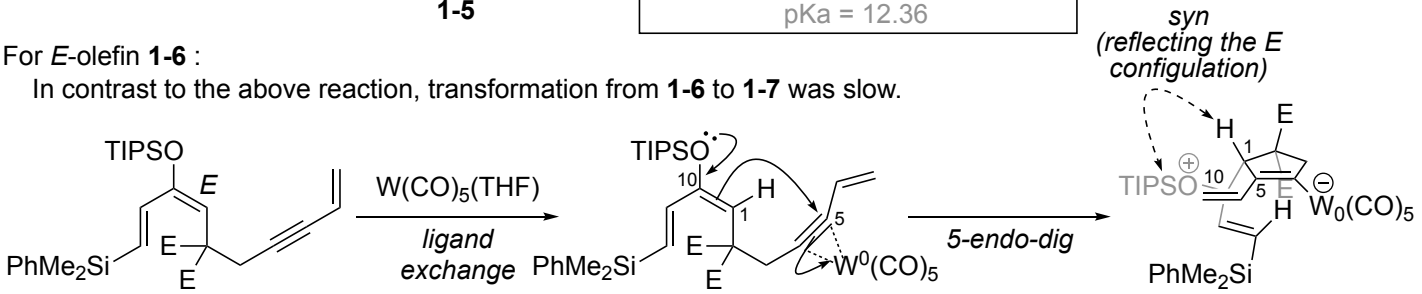
cf. Bernasconi, C. F.; Sun, W. *Organometallics* **1997**, *16*, 1926.



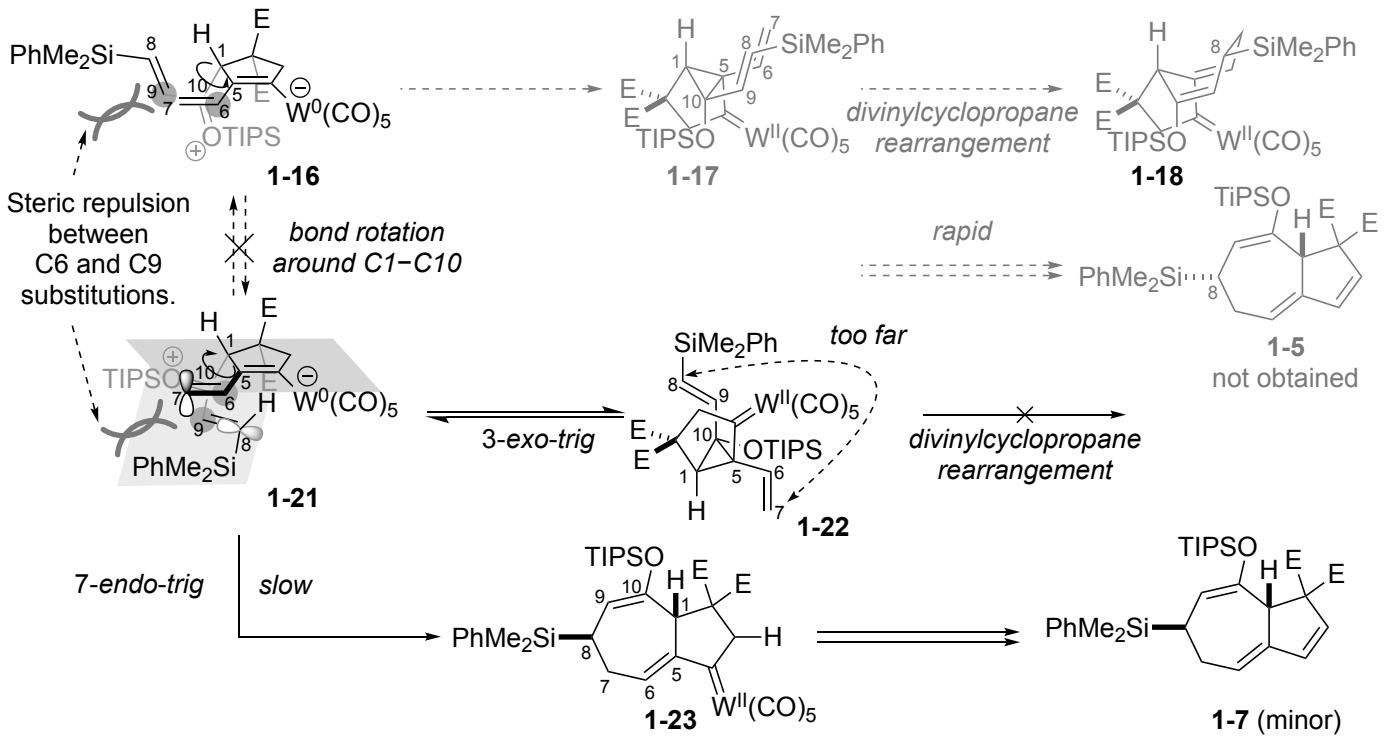
pKa = 12.36

For *E*-olefin **1-6** :

In contrast to the above reaction, transformation from **1-6** to **1-7** was slow.

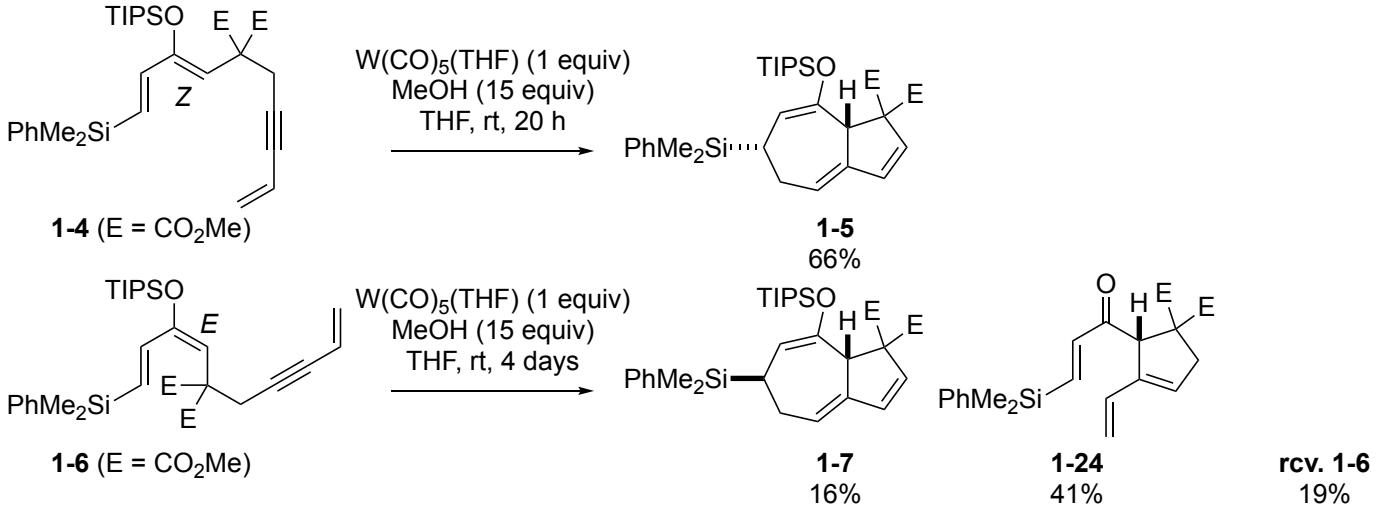


1-6 (E = CO_2Me) **1-20** **1-21**



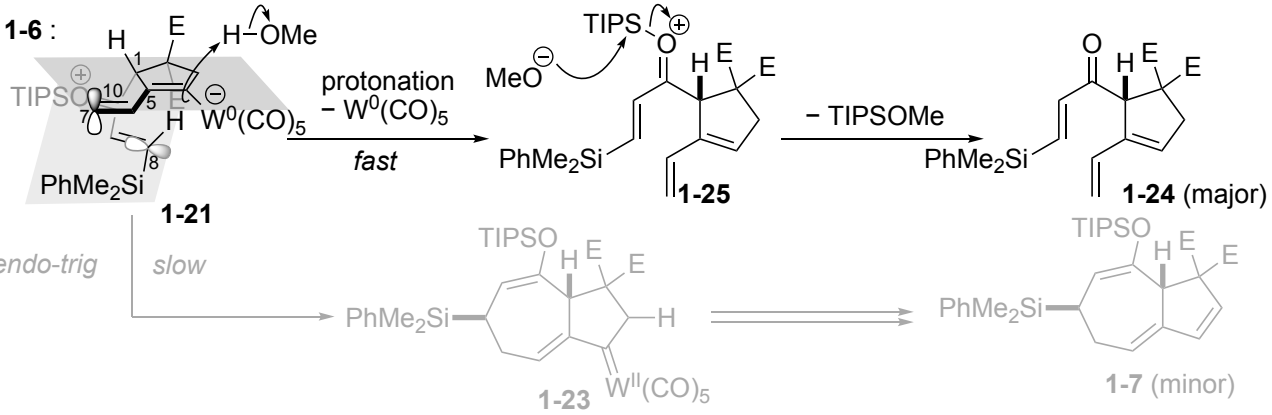
In the case of *E*-isomer, seven-membered ring would be formed via 7-*endo-trig* cyclization pathway. Due to the sluggishness associated with this cyclization manner, efficiency of transformation from *E*-isomer was much worse than that from *Z*-isomer.

Futher insight into the difference of the reaction rate: Addition of MeOH



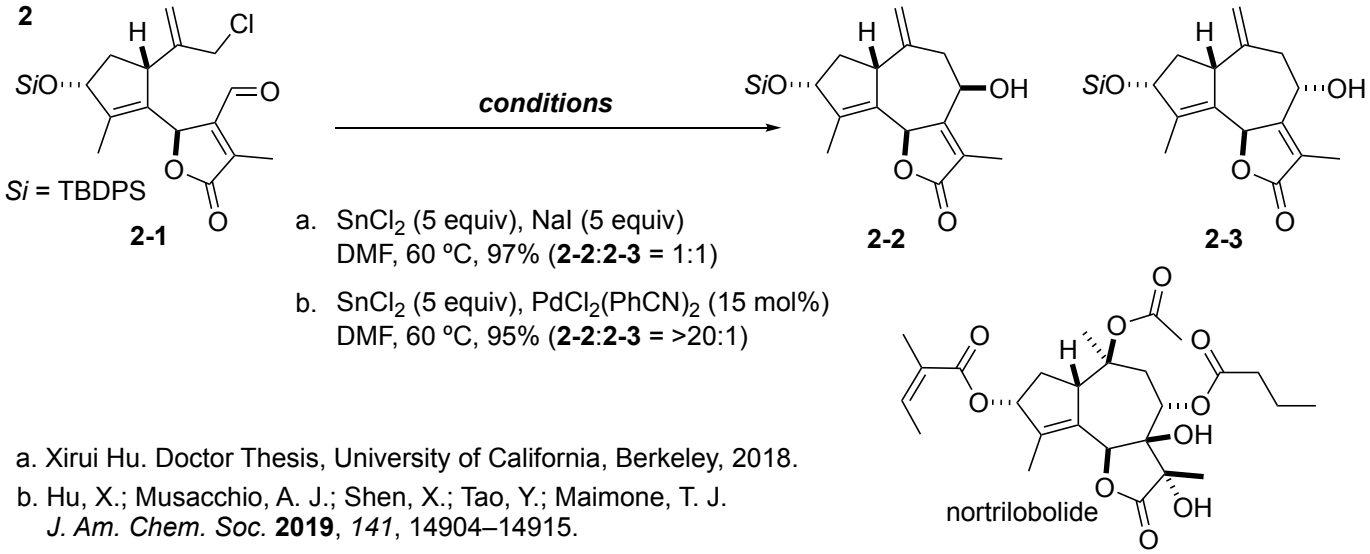
For *Z*-olefin **1-4** : 3-*exo-trig* cyclization (**1-16** to **1-17**) and divinylcyclopropane rearrangement (**1-17** to **1-18**) were so fast that intermediates could not be trapped by MeOH.

For *E*-olefin **1-6** :



Because 7-*endo-trig* cyclization was slow, intermediate **1-21** was intercepted by MeOH to afford **1-24**.

2



a. $SnCl_2$ (5 equiv), NaI (5 equiv)
DMF, 60 ºC, 97% (**2-2**:**2-3** = 1:1)

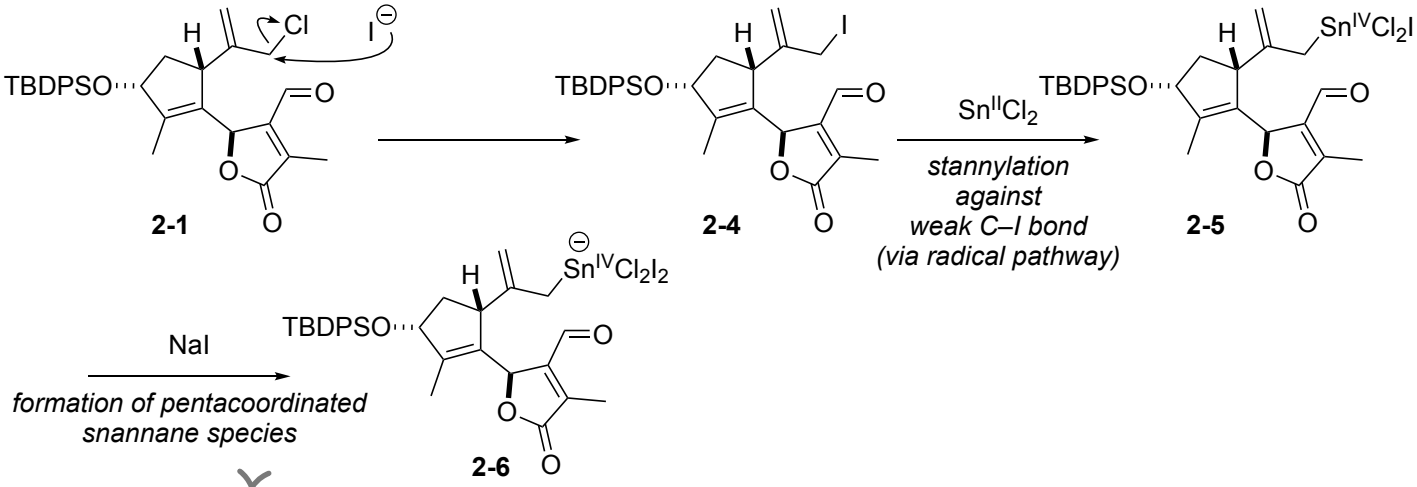
b. $SnCl_2$ (5 equiv), $PdCl_2(PhCN)_2$ (15 mol%)
DMF, 60 ºC, 95% (**2-2**:**2-3** = >20:1)

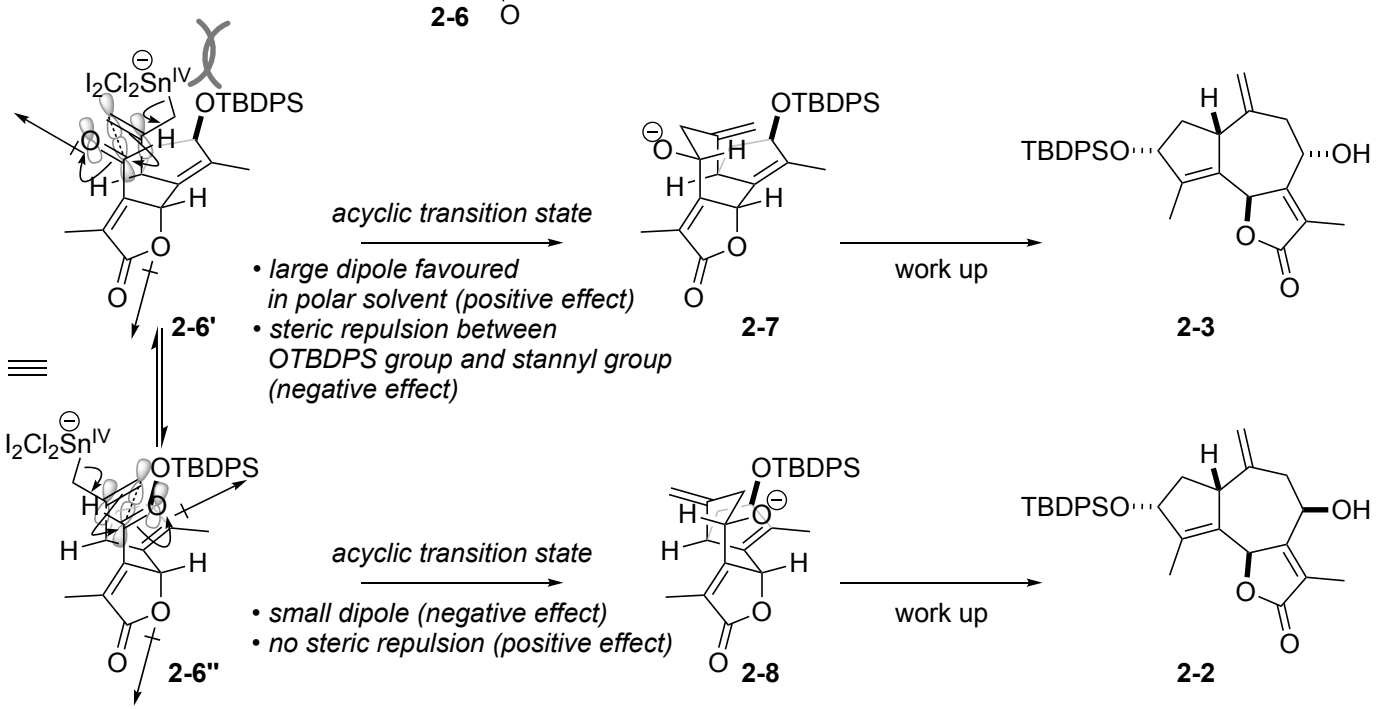
a. Xirui Hu. Doctor Thesis, University of California, Berkeley, 2018.

b. Hu, X.; Musacchio, A. J.; Shen, X.; Tao, Y.; Maimone, T. J. *J. Am. Chem. Soc.* **2019**, *141*, 14904–14915.

Answer

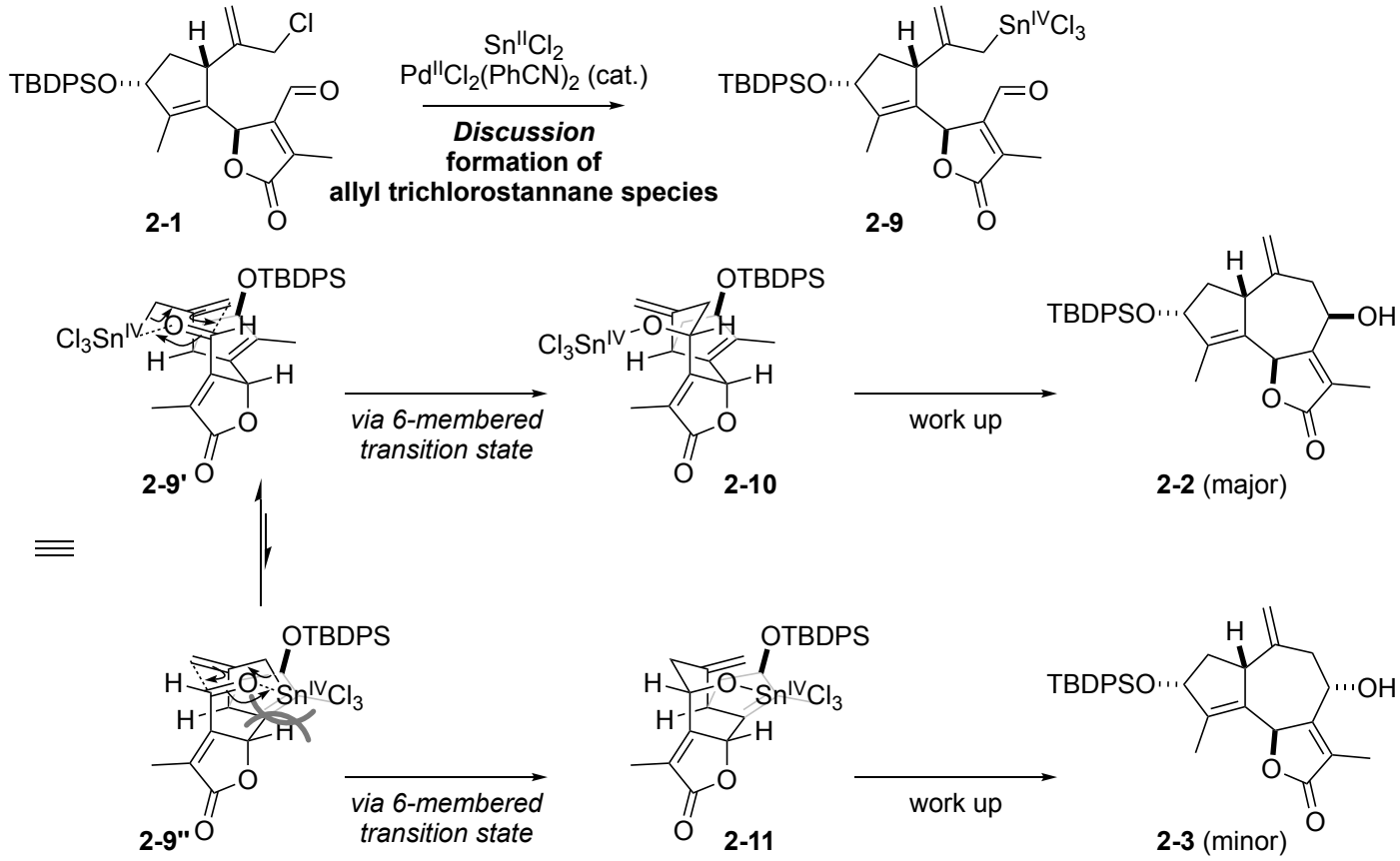
• conditions a: $SnCl_2$ (5 equiv), NaI (5 equiv), DMF, 60 ºC, 97% (**2-2**:**2-3** = 1:1)





No stereoselectivity was observed because diplole moment and steric repulsion seen in **2-6'** and **2-6''** canceled each other.

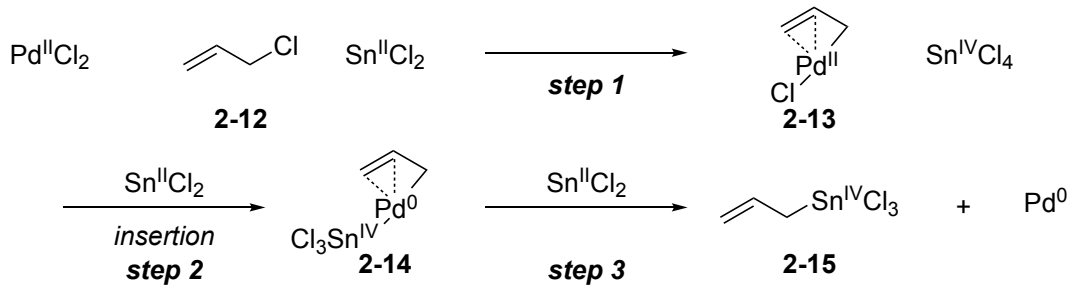
• conditions b: $SnCl_2$ (5 equiv), $PdCl_2(PhCN)_2$ (15 mol%), DMF, 60 ºC, 95% (**2-2**:**2-3** = >20:1)



Discussion **: formation of allyl trichlorostannane species**

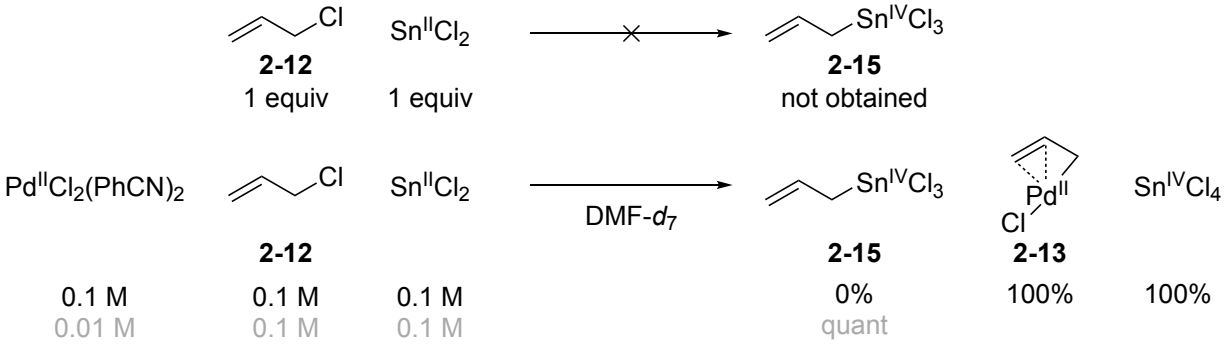
Mechanism of formation of allyl trichlorostannane using allylchloride, $Sn^{II}Cl_2$ and catalytic $Pd^{II}Cl_2(PhCN)_2$

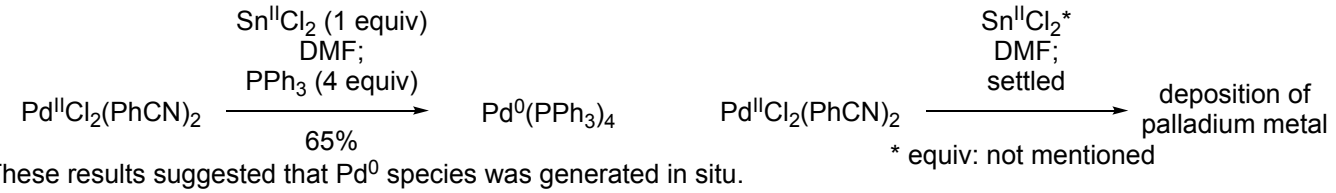
• Overall reaction at the initiation of catalytic cycle



step 1 **: Formation of *π*-allyl palladium complex**

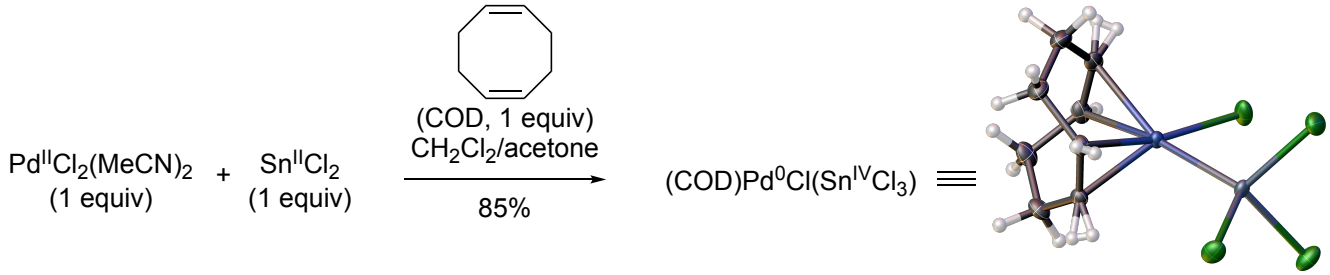
1-1. Generation of Pd^0 species[ref 1]



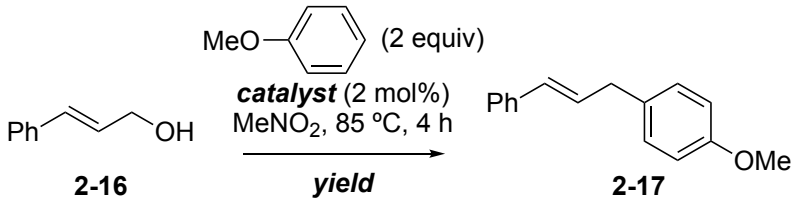


These results suggested that Pd^0 species was generated in situ.

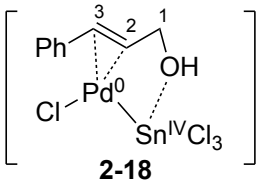
1-2. Pd-Sn bimetallic complex as an active species at the initiation step[ref 2]



electronegativity (Pauling scale): Pd 2.20, Sn 1.96, C 2.55, Cl 3.16



catalyst	yield
$(COD)Pd^0Cl(Sn^{IV}Cl_3)$	74%
$Pd^{II}Cl_2$	12%
$Sn^{II}Cl_2$	34%
$Sn^{IV}Cl_4$	32%

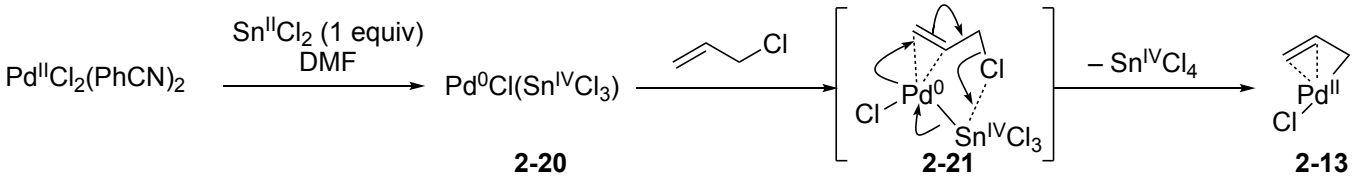


downfield shift on ^{13}C NMR at rt
δ 0.47 (C1)
0.14 (C2)
0.44 (C3)

proposed dual activation

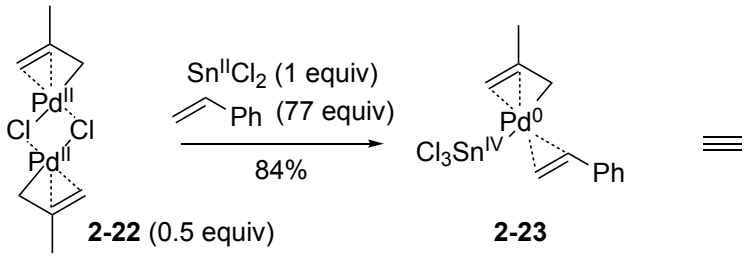
Pd-Sn bimetallic catalyst promoted the replacement of allylic hydroxy group with anisole, a soft nucleophile. Authers proposed dual-activation model **2-18** based on the NMR measurement. When **2-16** was mixed with Pd-Sn bimetallic catalyst, ^{13}C chemical shift of C1, C2 and C3 positions were shifted downfield. In **2-18**, soft Pd center is coordinated with alkene whereas hard Sn center is with hydroxy group.

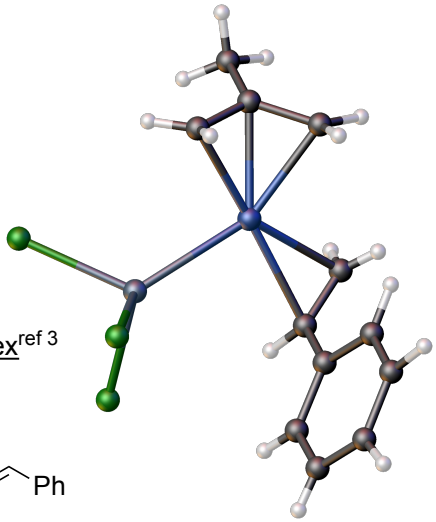
my proposal (at the initiation step)



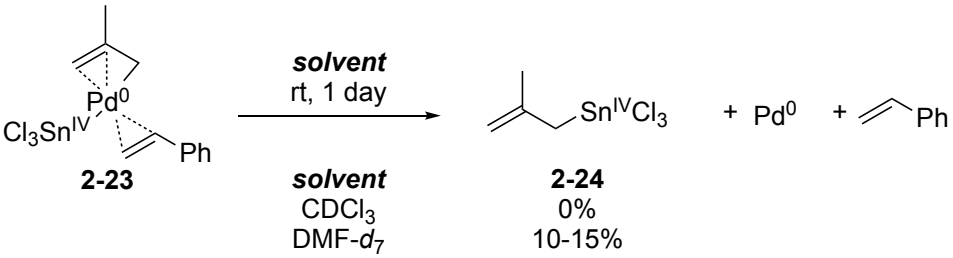
***step 2* : Insertion of $SnCl_2$**

2-1. Insertion of $Sn^{II}Cl_2$ to η^3-allyl-chloro-palladium complex[ref 3]





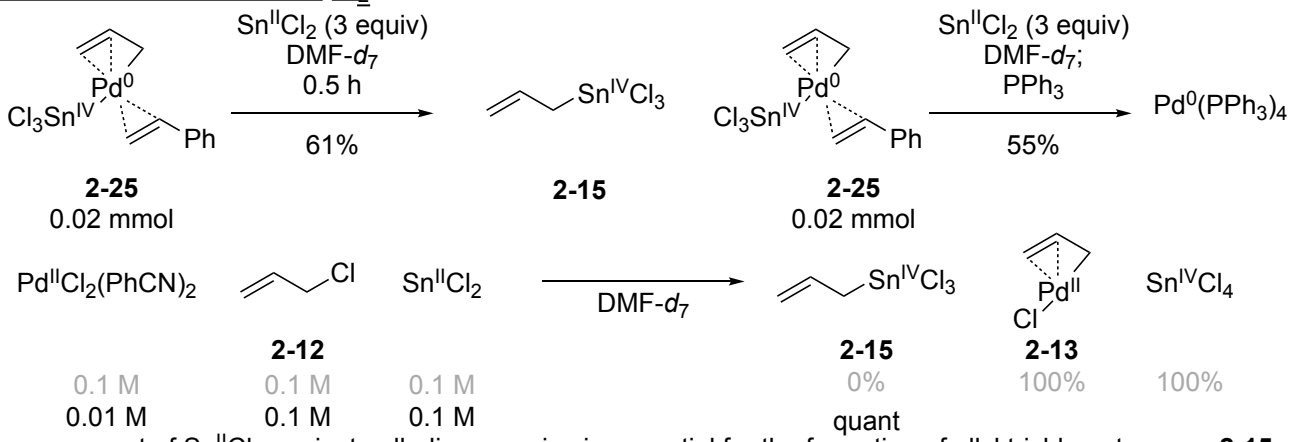
2-2. Sluggish reductive elimination from η^3-allyl-trichlorostannly-palladium complex[ref 3]



solvent	2-24
$CDCl_3$	0%
DMF-d_7	10-15%

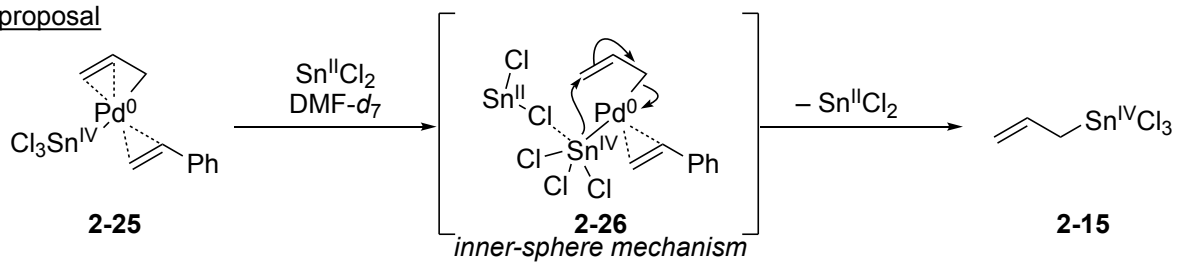
step 3 **:** Formation of allyl trichlorostannane

• Effect of excess amount of $Sn^{II}Cl_2$ [ref 1]



Excess amount of $Sn^{II}Cl_2$ against palladium species is essential for the formation of allyl trichlorostannane **2-15**. Reaction mechanism for generation of **2-15** from **2-25** has not elucidated yet.

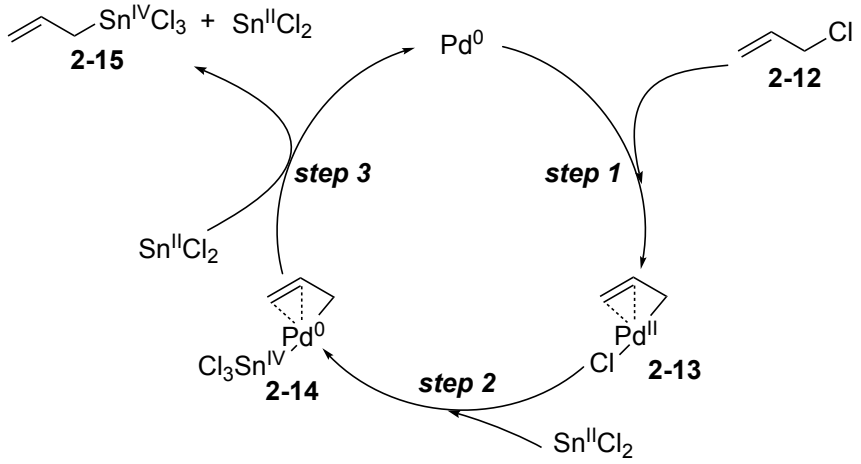
my proposal



It is well known that $Sn^{II}Cl_2$ binds to another $Sn^{II}Cl_2$ through chloride bridges ($ClSn^{II}$–Cl ····· $Sn^{II}Cl_2$). This type of coordination is common to tin compounds, and can also be observed in a single molecule.[ref 4]
Considering this property, it can be suggested that allyl trichlorostannane **2-15** could be formed from complex **2-25** via inner-sphere attack of tin (IV) center whose nucleophilicity would be enhanced by coordination of $Sn^{II}Cl_2$.

It is unlikely that $Sn^{II}Cl_3^-$ would be formed *in situ*, considering that free Cl ion would not exist in this synstem. Thus, possibility of outer-sphere attack of $Sn^{II}Cl_3^-$ would be low.

* After the initiation is over, Pd^0 species, not Pd-Sn bimetallic catalyst, catalyzes the formation of allyl trichlorostannane species (shown below).



Reference

ref 1. Hirako, K.; Miyamoto, Y.; Kakiuchi, K.; Kurosawa, H. *Inorganica Chimica Acta*, **1994**, *222*, 21.
ref 2. Das, D.; Pratihar, S.; Roy, U. K.; Mal, D.; Roy, S. *Org. Biomol. Chem.* **2012**, *10*, 4537.
ref 3. Musco, A.; Pontellini, R.; Grassi, M.; Sironi, A.; Meille, S. V.; Ruegger, H.; Ammann, C.; Pregosin, P. S. *Organometallics* **1988**, *7*, 2130.
ref 4. Schulte, M.; Gabriele, G.; Schürmann, M.; Jurkschat, M. K.; Duthie, A.; Dakternieks, D. *Organometallics* **2003**, *22*, 328.