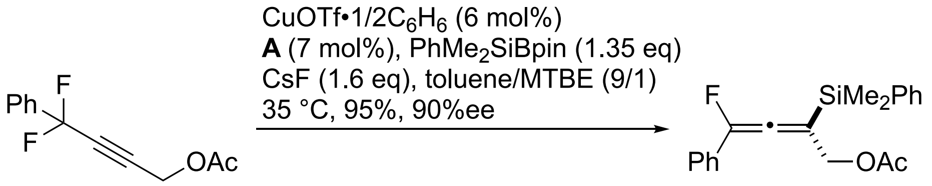
Problem Session (4)

2025/06/21 Takahiro Migita

Topic: Enantioselective Reactions on Allenyl Silanes

Problem 1

Please provide the mechanisms for the following reaction.

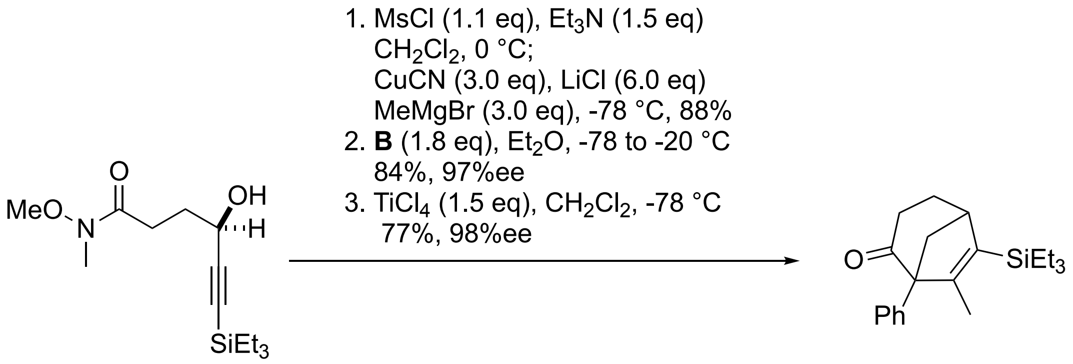


$CuOTf•1/2C_6H_6$ (6 mol%)
A (7 mol%), $PhMe_2SiBpin$ (1.35 eq)
CsF (1.6 eq), toluene/MTBE (9/1)
35 °C, 95%, 90%ee

1-1 **1-2**

Problem 2

Please provide the mechanisms for the following reactions and guess the stereochemistry of **2-2**.

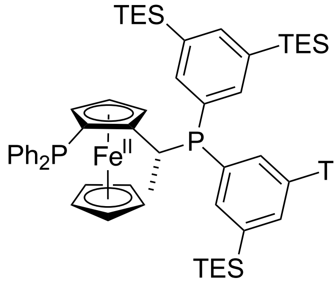


1. MsCl (1.1 eq), Et_3N (1.5 eq)
   CH_2Cl_2, 0 °C;
   CuCN (3.0 eq), LiCl (6.0 eq)
   MeMgBr (3.0 eq), -78 °C, 88%
2. **B** (1.8 eq), Et_2O, -78 to -20 °C
   84%, 97%ee
3. $TiCl_4$ (1.5 eq), CH_2Cl_2, -78 °C
   77%, 98%ee

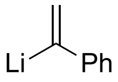
2-1
94%ee

2-2

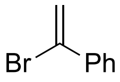
*CuCN (3.0 eq), LiCl (6.0 eq), and MeMgBr (3.0 eq) were stirred in THF at 0 °C for 1 h before addition.
*The preparation of **B** was not mentioned in detail. According to the scheme in SI section, it seemed to be prepared from **C** and *t*-BuLi before addition.



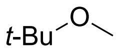
A



B



C

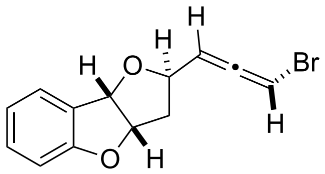


MTBE

Problem Session (4) -Answer-

2025/06/21 Takahiro Migita

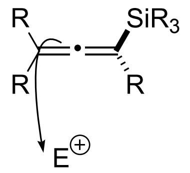
Topic: Enantioselective Reactions on Allenylsilanes



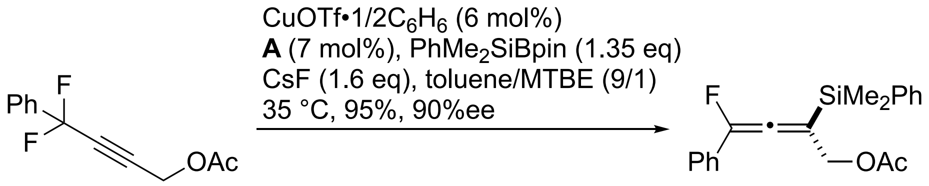
panacene (**0-1**)

Introduction: Why is it important to synthesize allenes enantioselectively?

→Most of the natural allenic compounds are nonracemic (like **0-1**, see *Angew. Chem., Int. Ed.* **2004**, 43, 1196. for review). Therefore, axial chiral allenes are utilized as useful building blocks for synthesis. Also, allenes show various reactivity, which make them the foothold for further transformation. Especially, allenylsilanes are often utilized as chiral pool (see also 131130_PS_Shun_YOSHIOKA_ene_reaction).

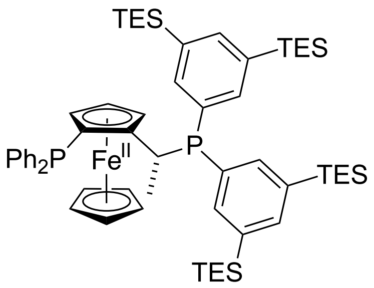


1



CuOTf•1/2C_6H_6 (6 mol%)
A (7 mol%), $PhMe_2SiBpin$ (1.35 eq)
CsF (1.6 eq), toluene/MTBE (9/1)
35 °C, 95%, 90%ee

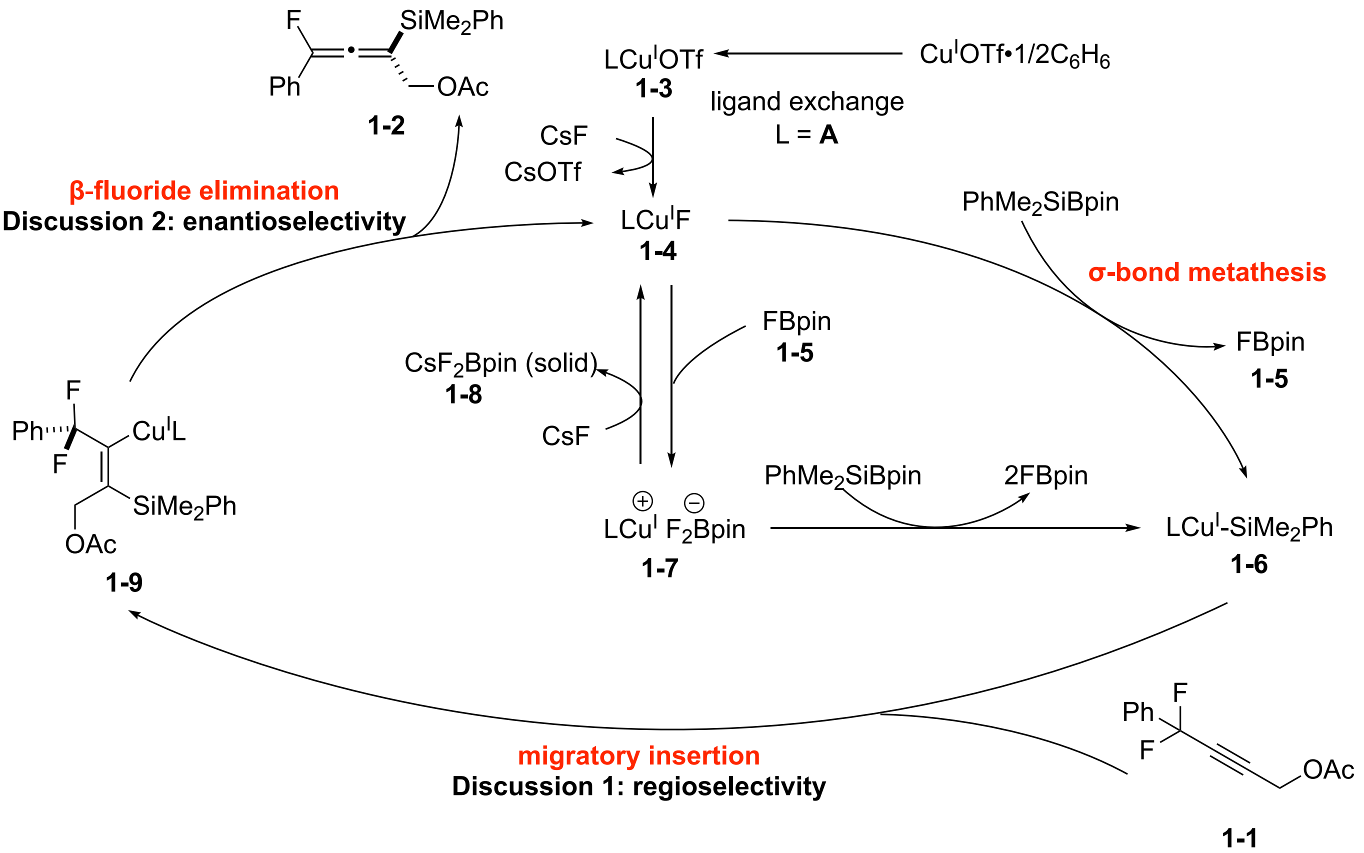
1-1 **1-2**



A

O'Connor, T. J.; Mai, B. K.; Nafie, J.; Liu, P.; Toste, F. D. *J. Am. Chem. Soc.* **2021**, *143*, 13759.

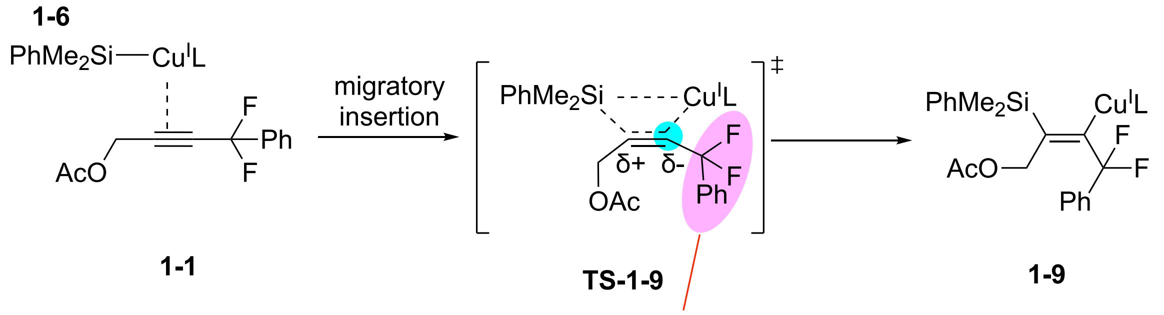
proposed catalytic cycle



Generation of **1-4**, **1-6**, and **1-7** was confirmed by utilizing ^1H, ^{19}F, and ^{11}B NMR studies. Fluoride source CsF also contributed to capturing FBpin **1-5**.

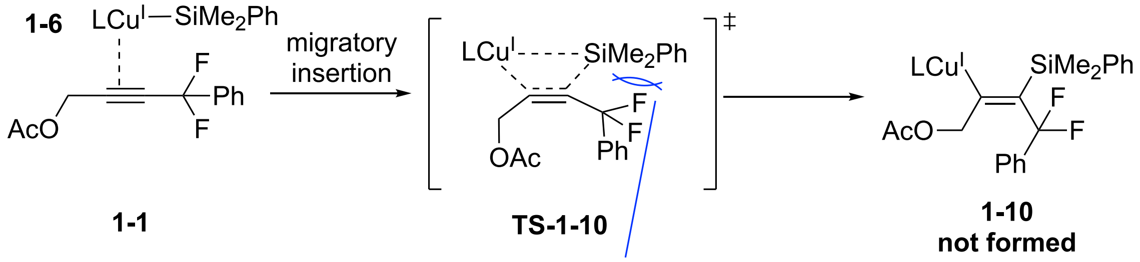
Discussion 1: Regioselectivity of migratory insertion

favoured path



Electron-withdrawing CF_2Ph group stabilized δ- by inductive effects.

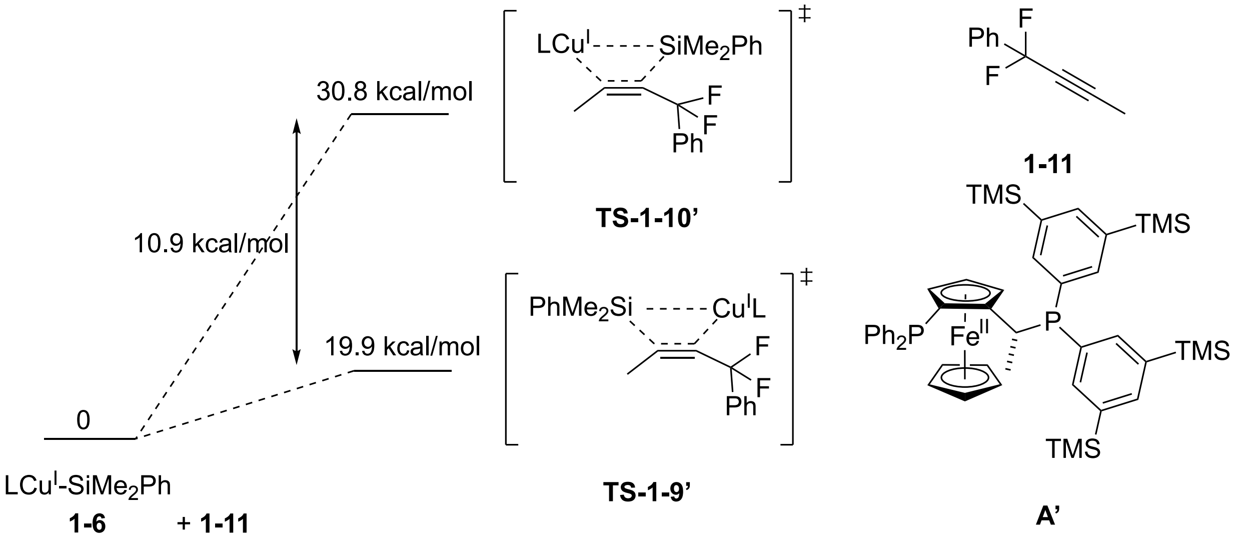
unfavoured path



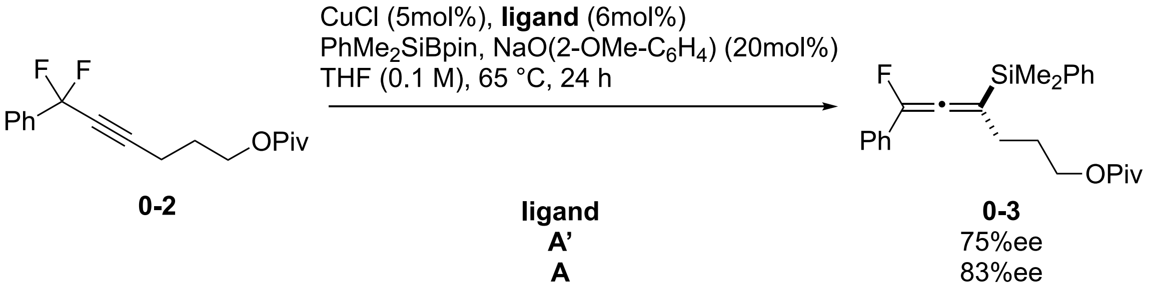
Large steric repulsion between $SiMe_2Ph$ and CF_2Ph distabilized **TS-1-10**.

Supporting calculation using model compounds

* After this, all calculations were conducted with M06/SDD(Cu,Fe,Cs)-6-311+G(d,p)/SMD-(toluene)//B3LYP-D3(zero)/SDD(Cu,Fe,Cs)-6-31G(d) level of theory using **1-11** and less bulky ligand **A’** as model substrates.



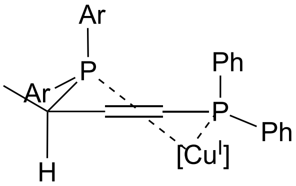
* In ligand screening, ligand **A’** also showed slightly lower *ee* than ligand **A**. (This is also suggesting that bulkiness of the substituents is key to the enantioselectivity.)



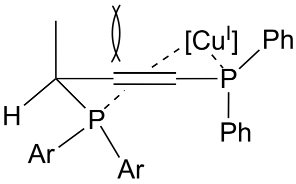
Discussion 2: Enantioselectivity of β-fluoride elimination

<conformation of ligand **A**>

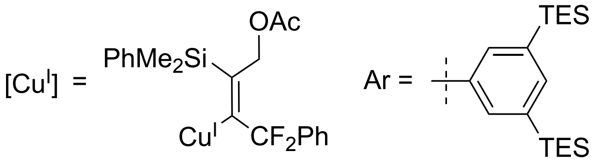
- Ligand **A** functioned as a bidentate ligand to Cu. The conformation of ligand **A** in **1-9** would be half-chair **X** depicted in half-chair conformation as below. The methyl group will be oriented to avoid repulsion with vinyl cupper species.



half-chair **X**

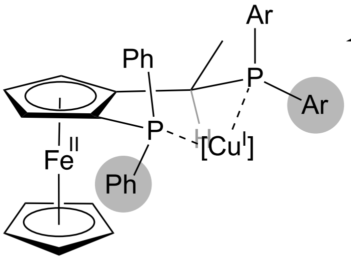


half-chair **Y**

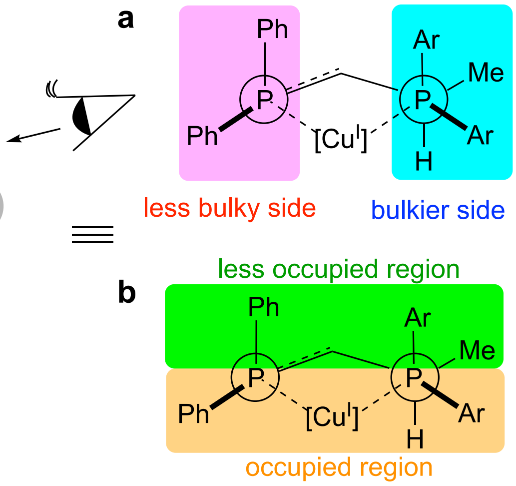


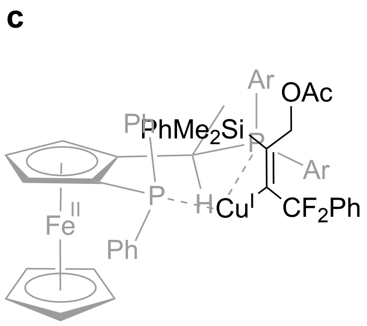
Cp rings and Fe are omitted to simplify.

- Grey-highlighted aromatic rings orienting to the side of cupper species and the differences in the bulkiness between Ph and Ar on P atoms are key to substrate recognition.



1-9
half-chair X



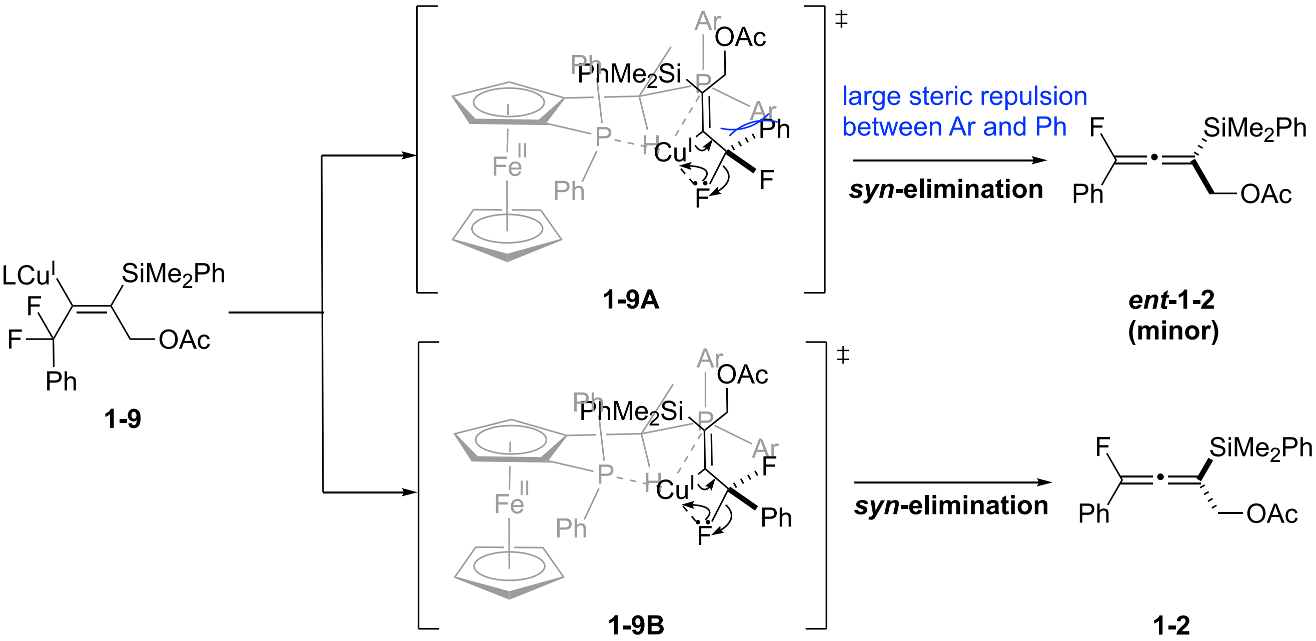


Bulky silyl group is located in less occupied region.

*The two C-P bonds are not parallel actually. To simplify, the differences in the angles were intentionally ignored in Newman projection **a** and **b**.

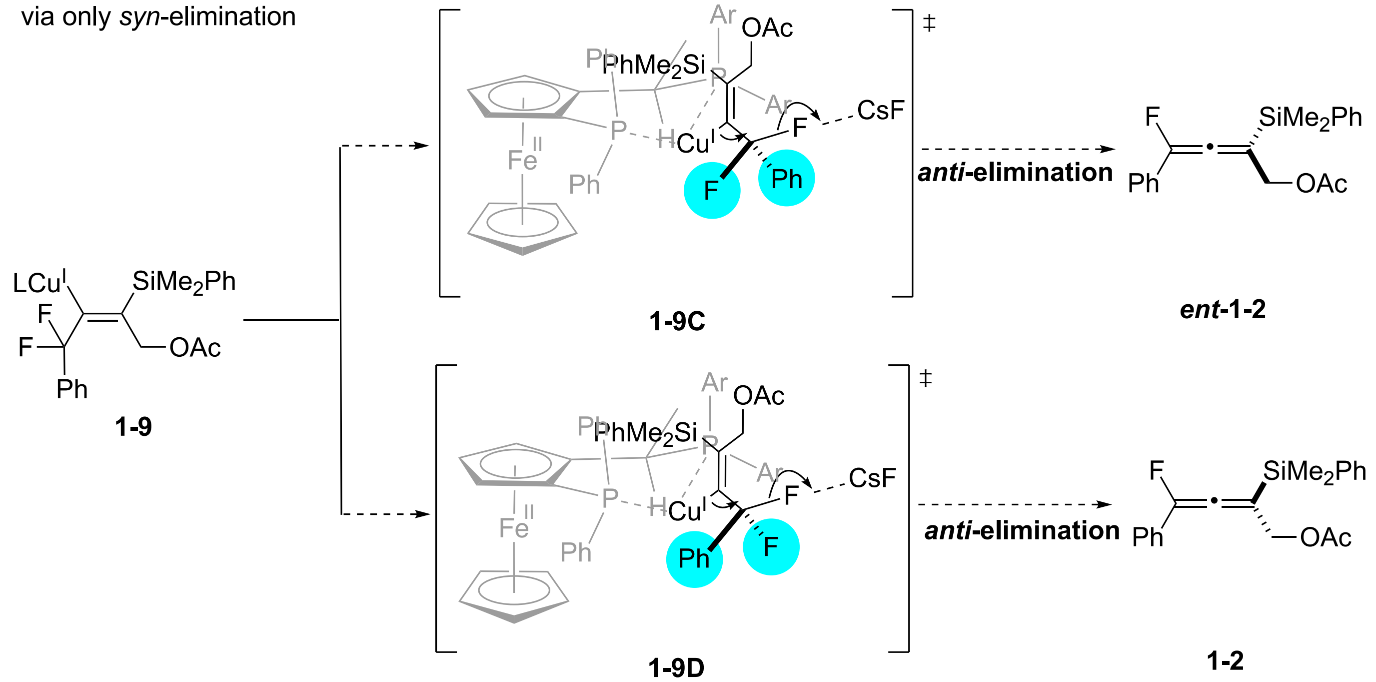
<*syn*-elimination>

- Large steric repulsion between Ar and Ph destabilized **1-9A**. In **1-9B**, no significant steric repulsion was observed.



<*anti*-elimination>

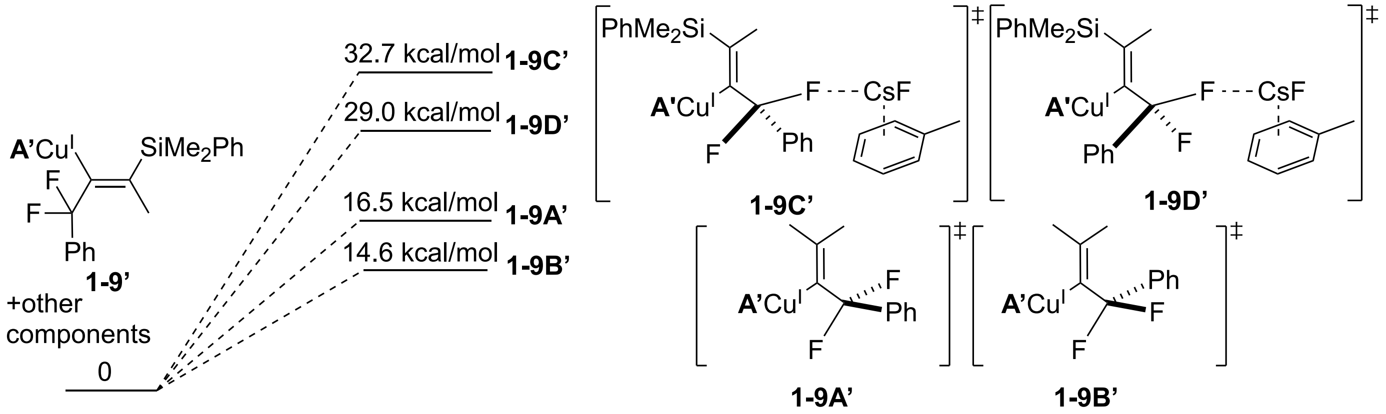
- In the case of *anti*-elimination, strong C-F bond should be activated by Lweis acid CsF. However, large Cs cannot approach the F atom due to the bulkiness of the ligand. In addition, blue-highlighted Ph and F groups became closer to the ligand than in the case of *syn*-elimination. Therefore, enantioselective β-fluoride elimination should proceed via only *syn*-elimination



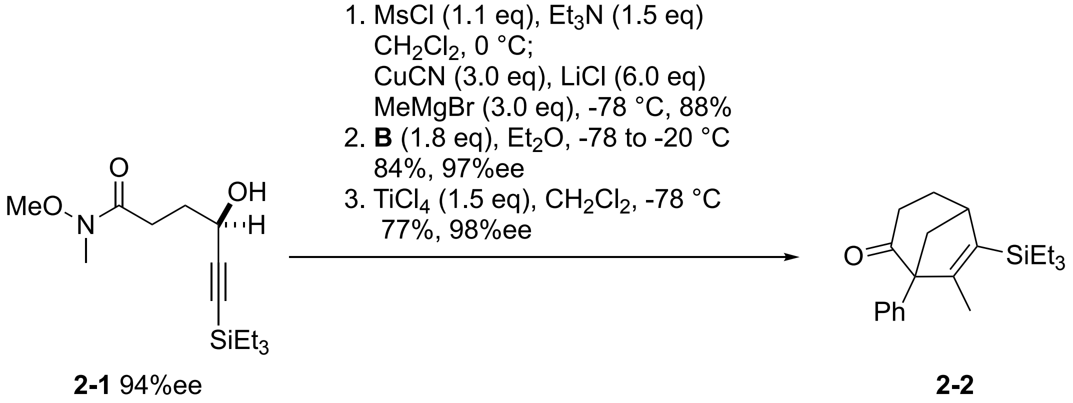
*Anti-elimination was proposed in the case of *J. Am. Chem. Soc.* **2019**, *141*, 19917 under existence of Lewis acid and intramolecular chelation.

Supporting calculation using model compounds

Calculation also suggested *anti*-elimination was much more disadvantageous than *syn*-elimination.



2



1. MsCl (1.1 eq), Et_3N (1.5 eq)
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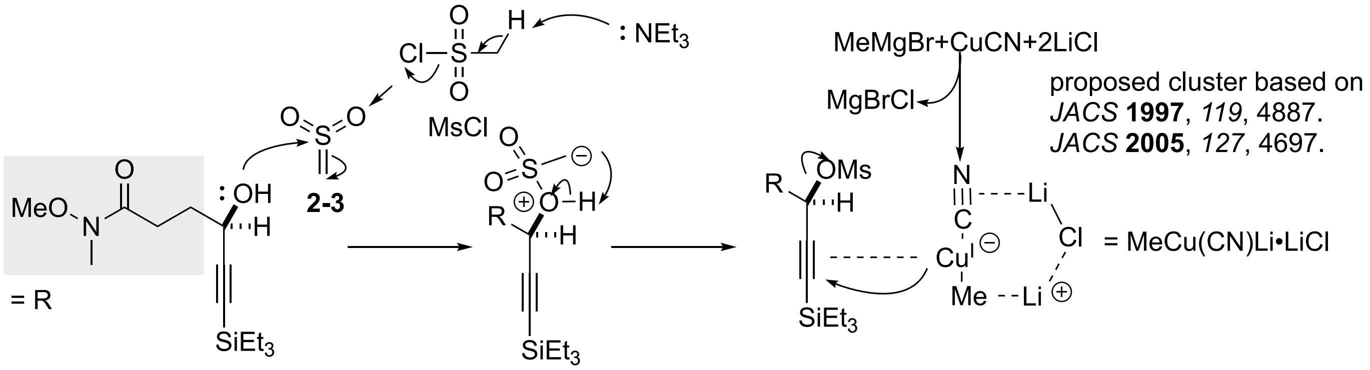
   84%, 97%ee
3. $TiCl_4$ (1.5 eq), CH_2Cl_2, -78 °C
   77%, 98%ee

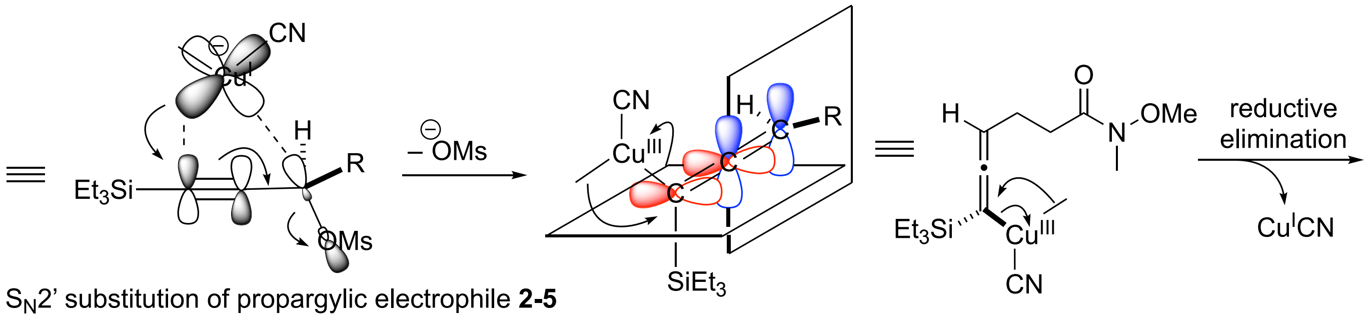
Li, L. Z.; Huang, Y. R.; Xu, Z. X.; He, H. S.; Ran, H. W.; Zhu, K. Y.; Han, J. C.; Li, C. C. *J. Am. Chem. Soc.* **2024**, *146*, 24782.



2-3

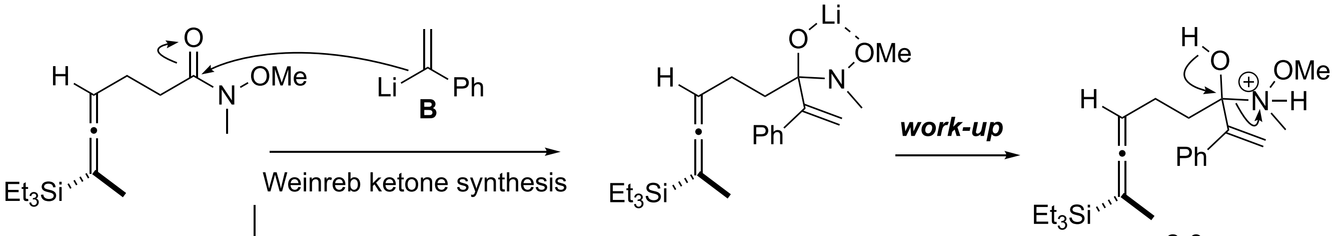
2-1 **2-4** **2-5**

proposed cluster based on
JACS **1997**, *119*, 4887.
JACS **2005**, *127*, 4697.

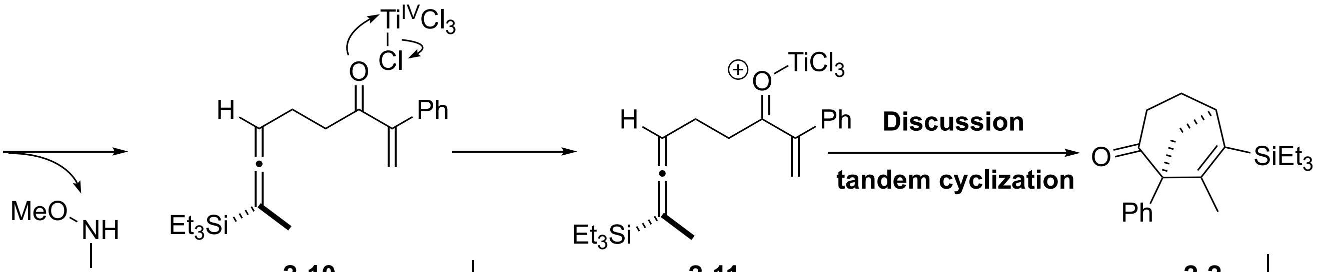


S$_N$2' substitution of propargylic electrophile **2-5** proceeded with anti-stereoselectivity.
Chem. Rev. **2012**, *112*, 2339.

2-6



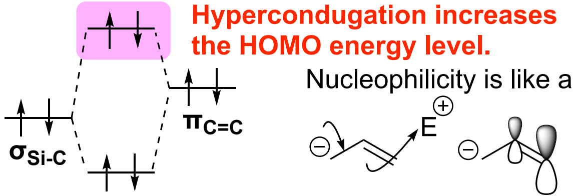
2-7 step 1 **2-8** **2-9**



2-10 step 2 **2-11** **2-2** step 3

Discussion: tandem cyclization

Allenylsilane electrophililc addition



Hypercondugation increases the HOMO energy level.

Nucleophilicity is like allyl aninon…

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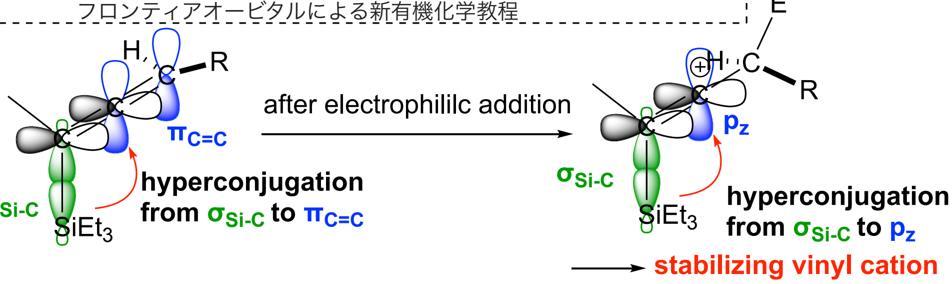
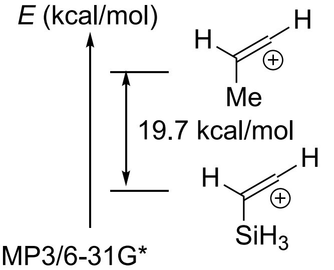


hyperconjugation from σ$_{Si-C}$ to π$_{C=C}$

hyperconjugation from σ$_{Si-C}$ to p$_z$

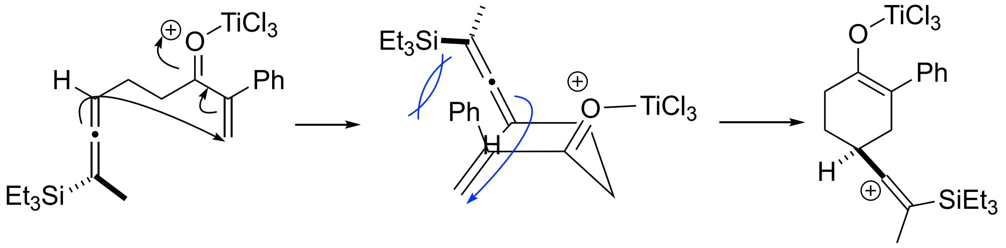
→ **stabilizing vinyl cation**

Stabilization of vinyl cation by β-silicon effect



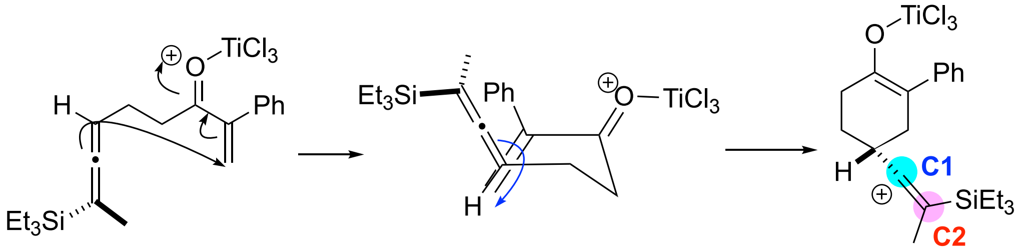
MP3/6-31G*
JACS. **1985**, *107*, 1496.
Synthesis, **2020**, *52*, 2147.

Allenylsilane moiety acted as nucleophile and attacked the enone in 1,4-addition manner. To maintain enone conjugation and s-trans form, the addition would proceed in boat-like conformation. If the allenylsilane moiety approaches like **2-12'**, bulky TES group orients to the Ph group of enone moiety. Occurring steric repulsion prevented the allenylsilane moiety from approaching like **2-12'**.



2-11 **2-12'** **2-12**
not formed

On the other hand, when the allenylsilane moiety approached like **2-13'**, the cyclization smoothly proceeded to afford **2-13** with 6-membered ring without generating large repulsion. Cation **2-13** was stabilized by β-silicon stabilization.

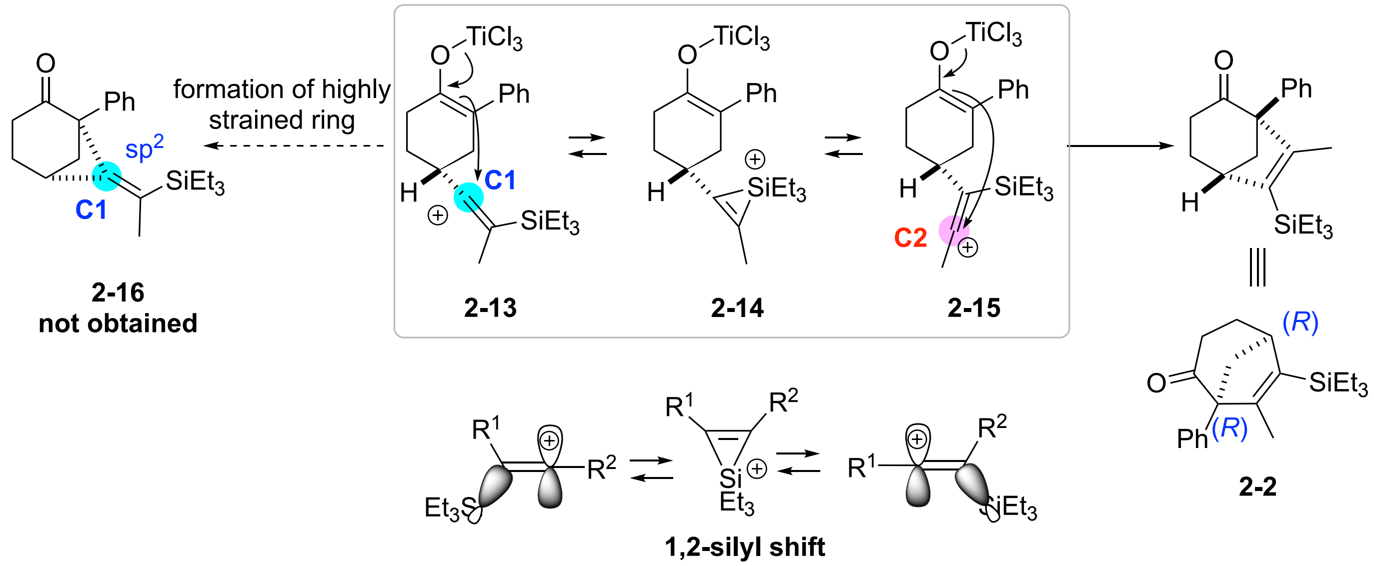


2-11 **2-13'** **2-13**

1,2-silyl shift provided two possible reacting points C1 and C2. Population of silyl cation intermediate **2-14** would be small due to its strained 3-membered ring with two sp^2 carbon. Therefore, vinyl cation **2-13** or **2-15** should be the precursor for the cyclization. The reaction proceeded at −78 °C, which suggested desired **2-2** was kinetic product.

(1) **C1**→Formation of four-membered ring with sp^2 carbon was very slow at −78 °C.

(2) **C2**→The cyclization would proceed to afford five-membered ring, which is more readily occurred.



2-16
not obtained

2-13 **2-14** **2-15** **2-2**

Therefore, the stereochemistry to be guessed is R in both C-C bonds.