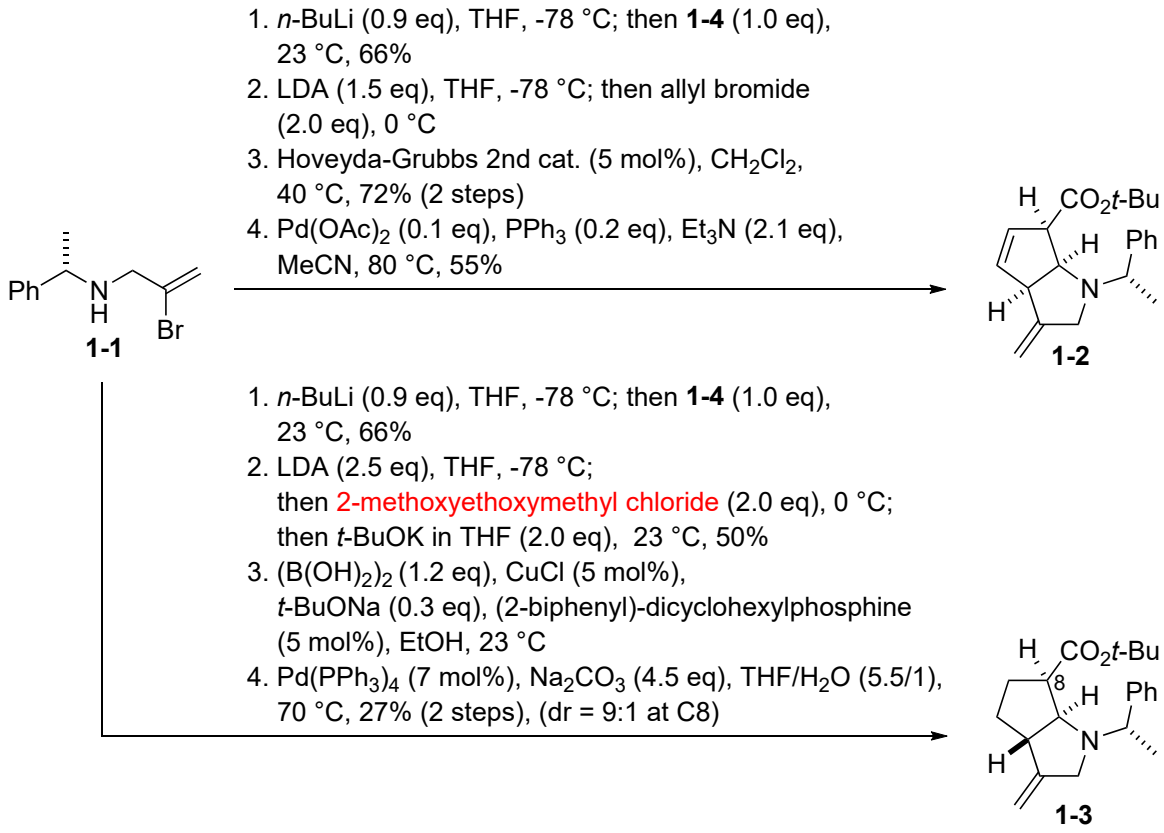
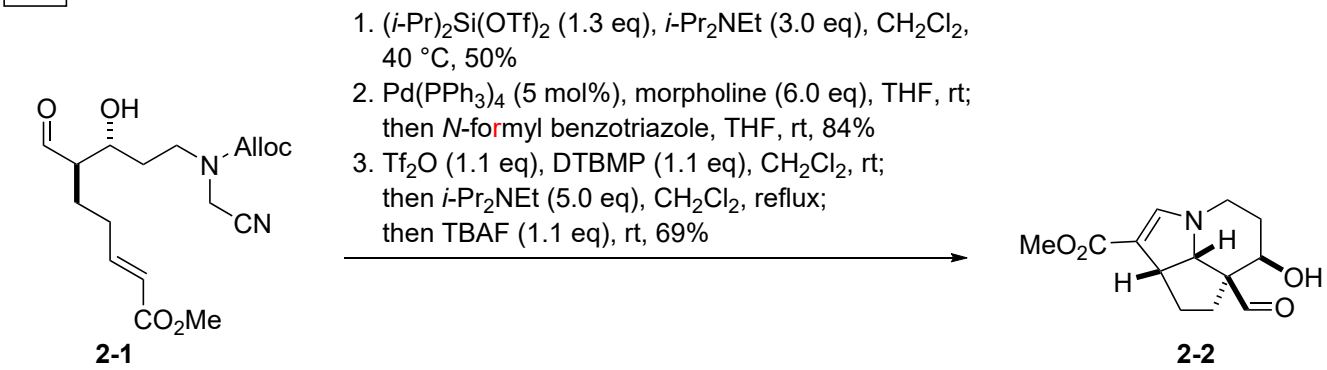
Problem Session (4)

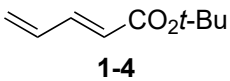
19/11/16 Koichi Kamiya

1 Please provide plausible mechanisms and stereoselectivity for each reaction.

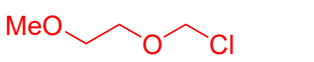


2 Please provide plausible mechanisms for each reaction.

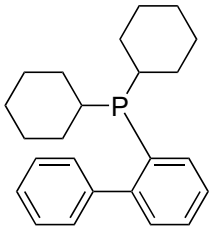




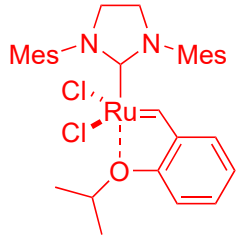
1-4



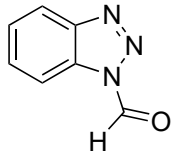
2-methoxyethoxymethyl chloride



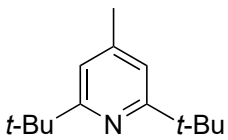
(2-biphenyl)-dicyclohexylphosphine



Hoveyda-Grubbs 2nd cat.

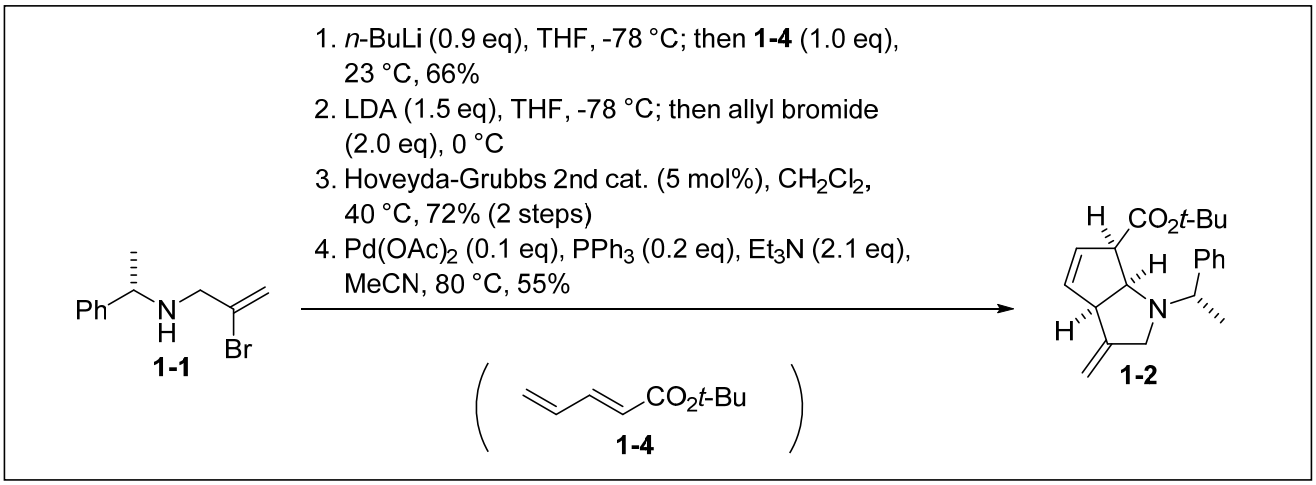


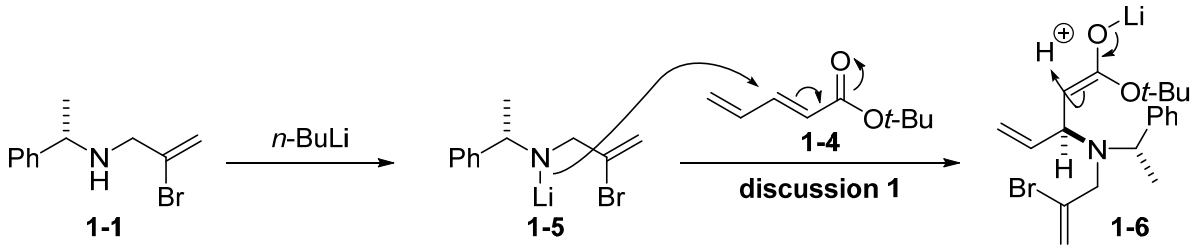
N-formyl benzotriazole

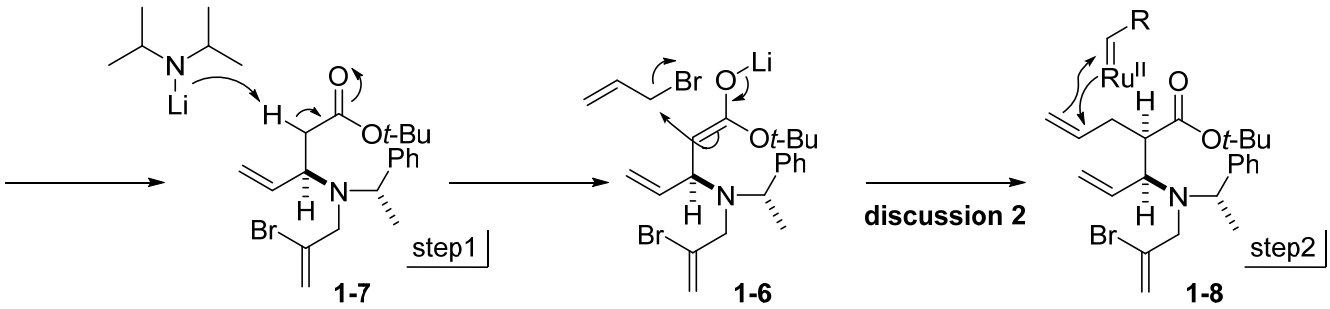


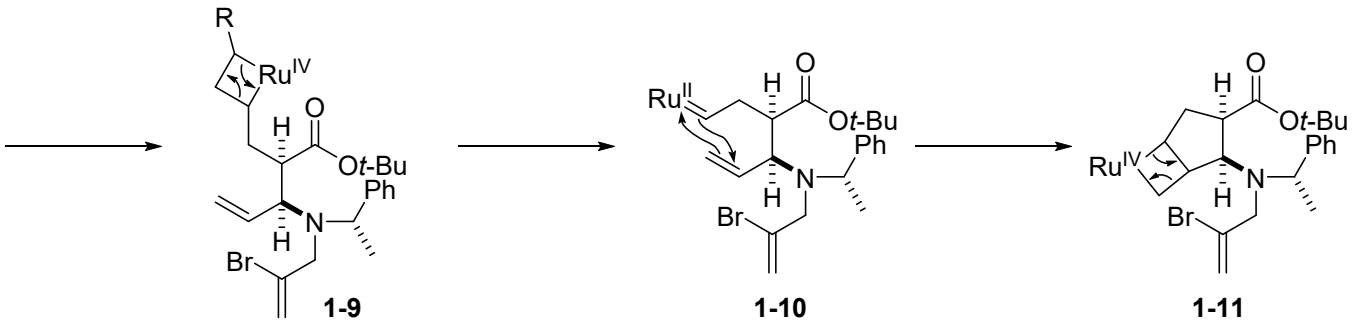
DTBMP

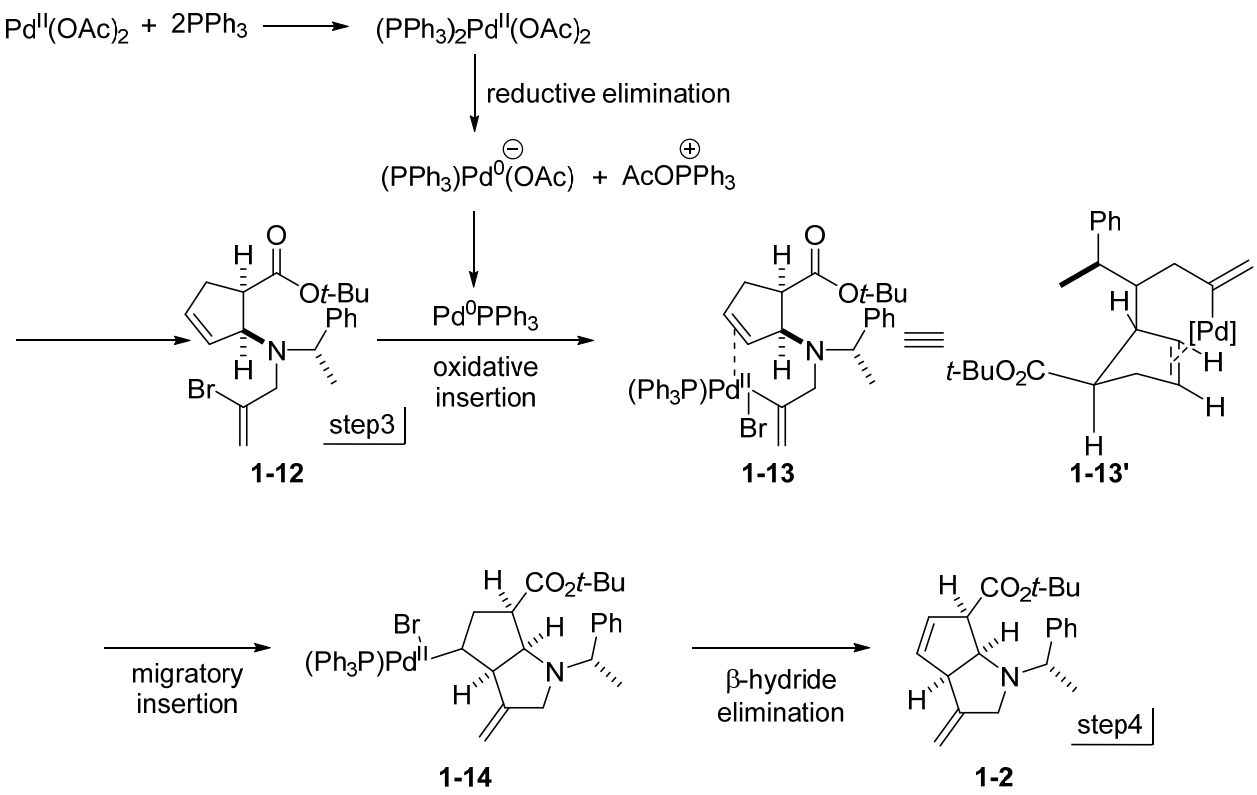
1 Hugelshofer, C. L.; Palani, V.; Sarpong, R. *J. Org. Chem.* **2019**, *84*, 14069.







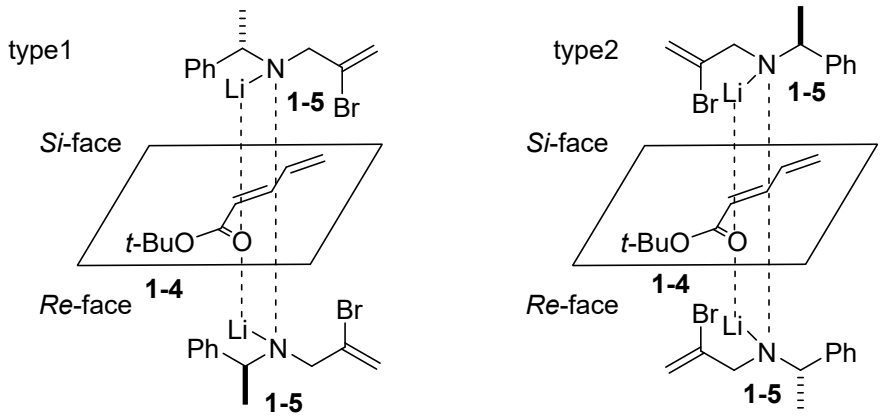


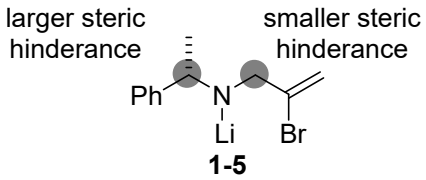


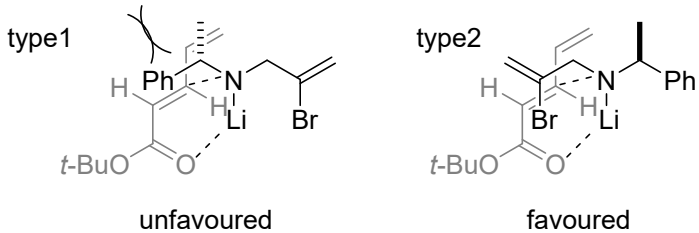
Discussion 1-1

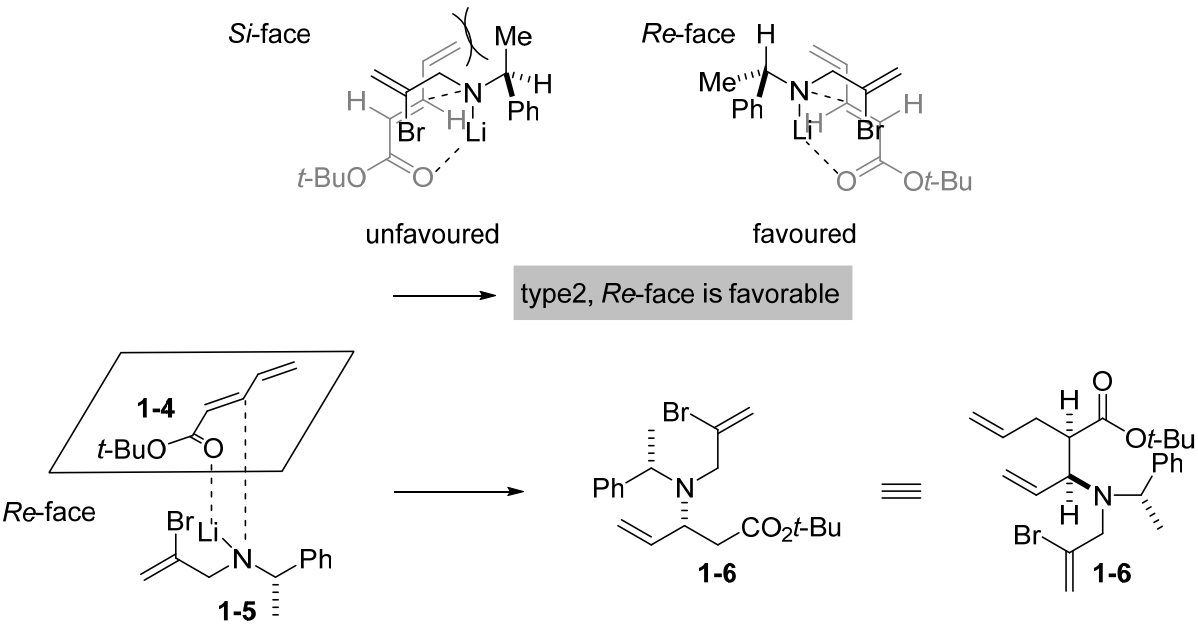
- Stereoselectivity of 1,4-addition

Nieto, C. T.; Diez, D.; Garrido, N. M. *Journal of Computational Chemistry* **2014**, *35*, 1846.



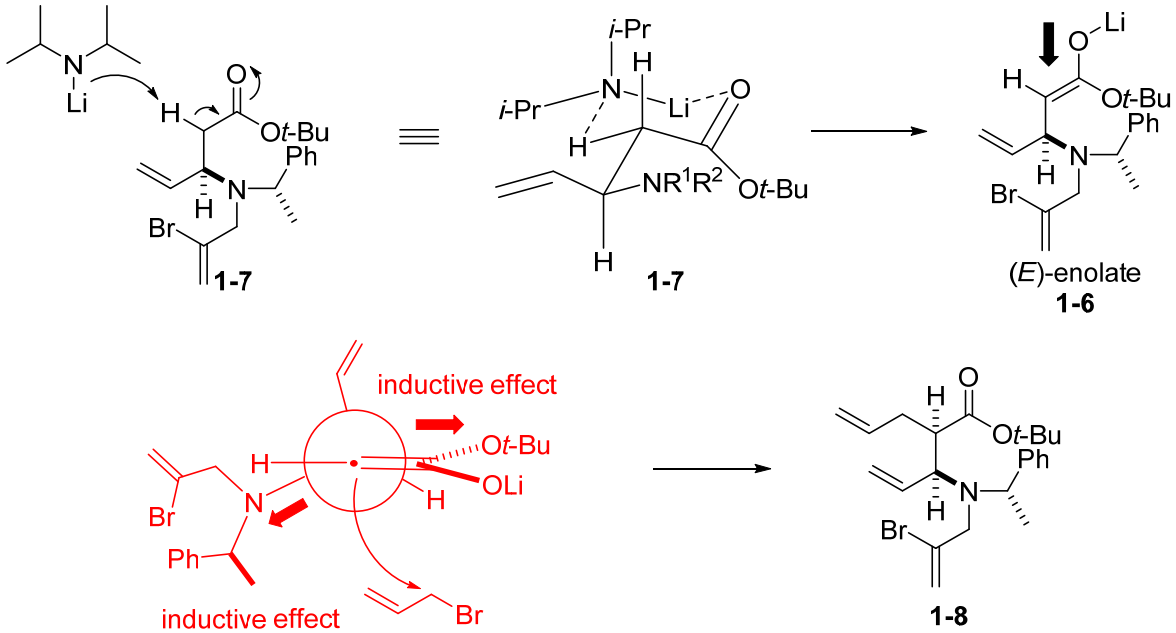




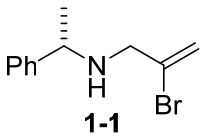


Discussion 2

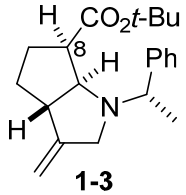
- Proposed stereoselectivity



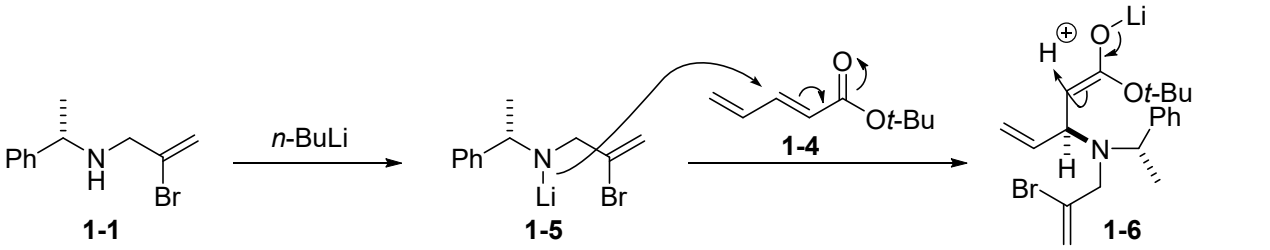
1. *n*-BuLi (0.9 eq), THF, -78 °C; then **1-4** (1.0 eq), 23 °C, 66%
2. LDA (2.5 eq), THF, -78 °C; then 2-methoxyethoxymethyl chloride (2.0 eq), 0 °C; then *t*-BuOK in THF (2.0 eq), 23 °C, 50%
3. $(B(OH)_2)_2$ (1.2 eq), CuCl (5 mol%), *t*-BuONa (0.3 eq), (2-biphenyl)-dicyclohexylphosphine (5 mol%), EtOH, 23 °C
4. $Pd(PPh_3)_4$ (7 mol%), Na_2CO_3 (4.5 eq), THF/H_2O (5.5/1), 70 °C, 27% (2 steps), (dr = 9:1 at C8)



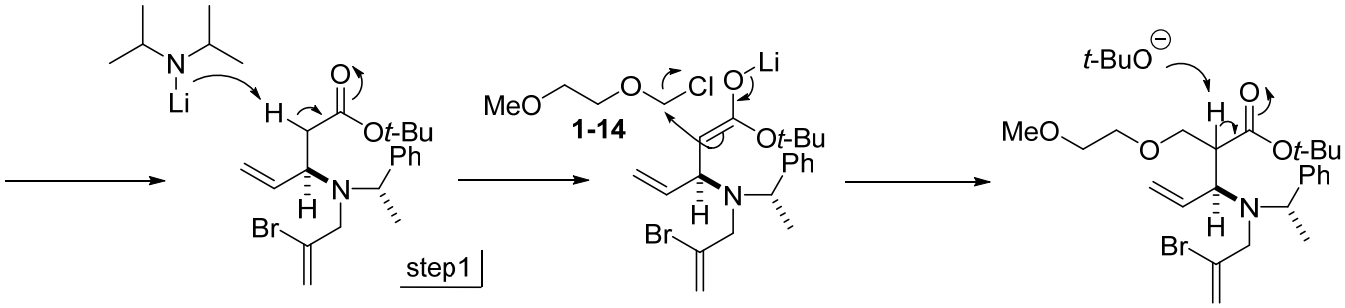
1-1



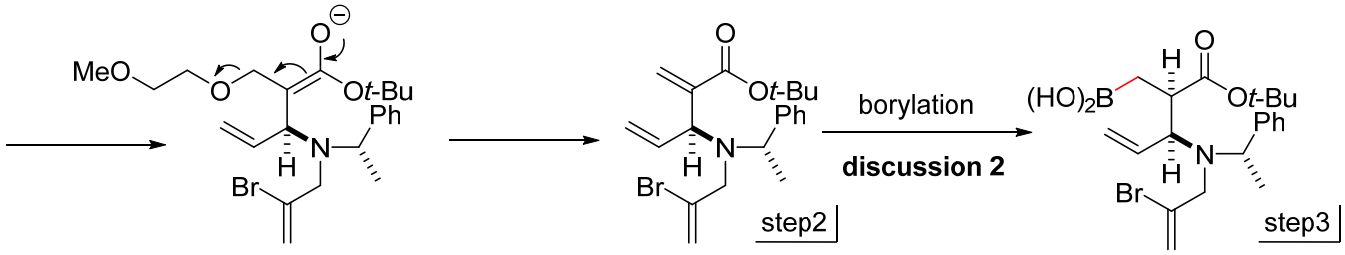
1-3



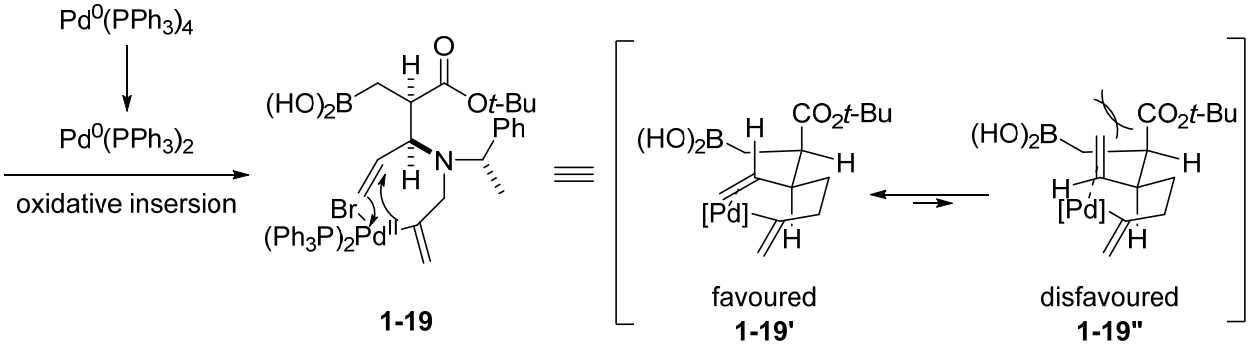
1-1 **1-5** **1-6**



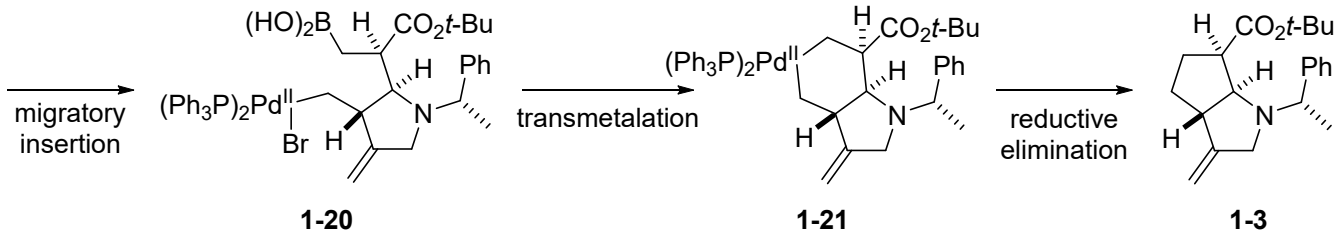
1-7 **1-6** **1-15**



1-16 **1-17** **1-18**



1-19 favoured **1-19'** disfavoured **1-19"**



Discussion 2 : reaction mechanism of borylation

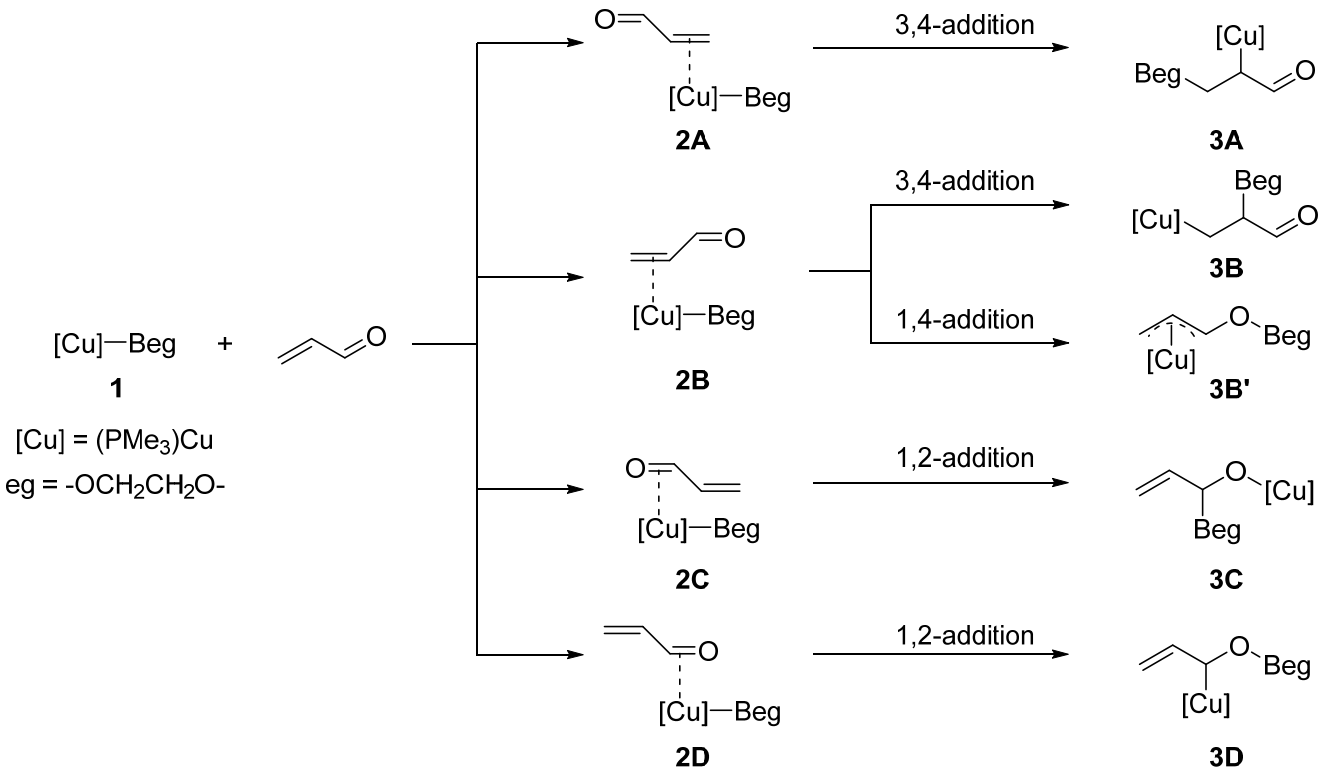
- DFT studies on the borylation of α,β-unsaturated carbonyl compounds was conducted by Marder et. al.

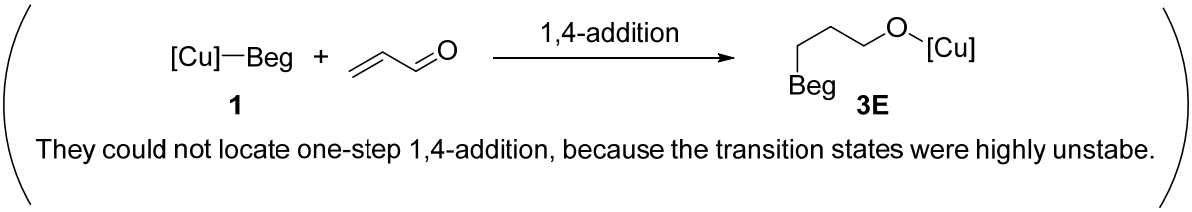
(Dang, L.; Lin, Z.; Marder, T. B. *Organometallics* **2008,** *27*, 4443.)

computational details

Molecular geometries of the model complexes were optimized without constraints via DFT calculations using the Becke3LYP (B3LYP) functional. Transition states were located using the Berny algorithm. Intrinsic reaction coordinates (IRC) were calculated for the transition states to confirm that such structures indeed connect two relevant minima. The 6-311G* Pople basis set was used for B in the boryl ligand and the C and O atoms in the α,β-unsaturated aldehyde substrate while the 6-311G* Wachters–Hay basis set was used for Cu.
For all other atoms, the 6-31G basis set was used.
All of the DFT calculations were performed with the Gaussian 03 package.

- Transition states for five possible Cu-B additions (shown below) were located from the calculations.





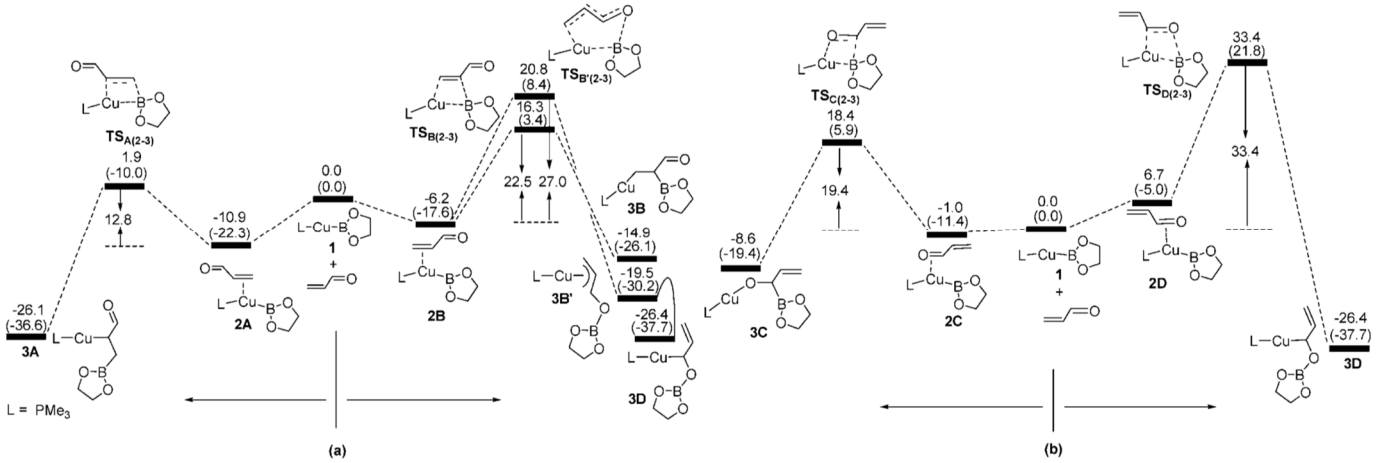
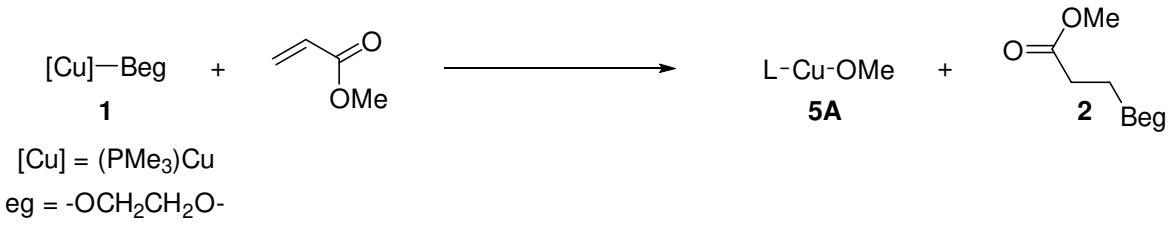


Figure 1. Energy profiles calculated for various pathways for the insertion of acrolein into the Cu–B bond of the (PMe3)Cu(boryl) complex. The relative free energies and electronic energies (in parentheses) are given in kcal/mol

➡ Diffect 3,4-addition (**2A** to **3A**) is the most likely pathway to form C-Cu and C-B bonds.

- Next, calculation of borylation of methylacrylate was coducted



[Cu] = (PMe$_3$)Cu

eg = -OCH$_2$CH$_2$O-

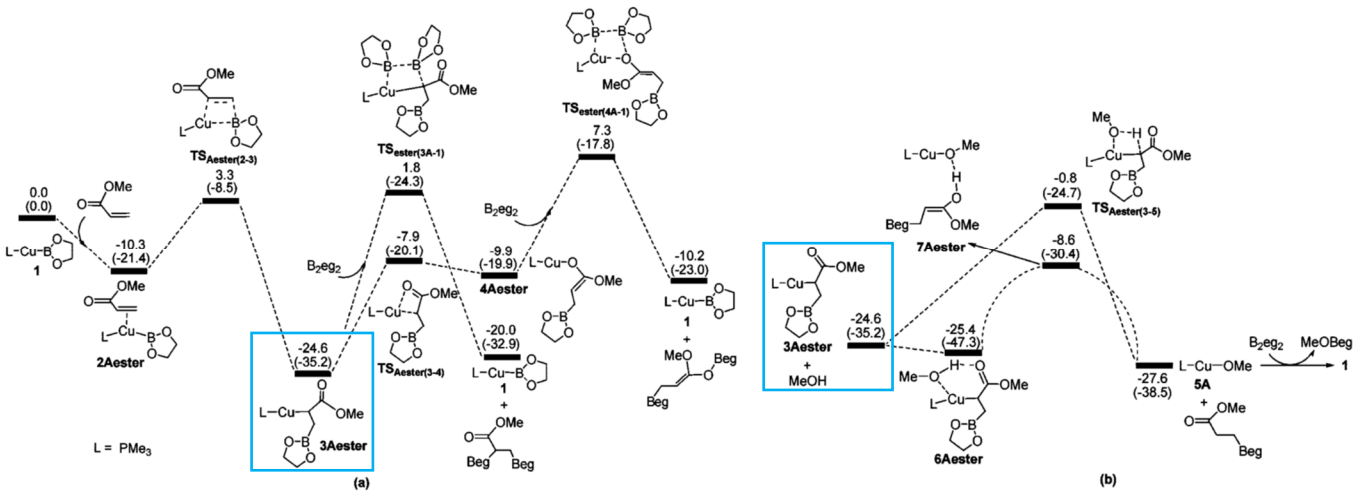
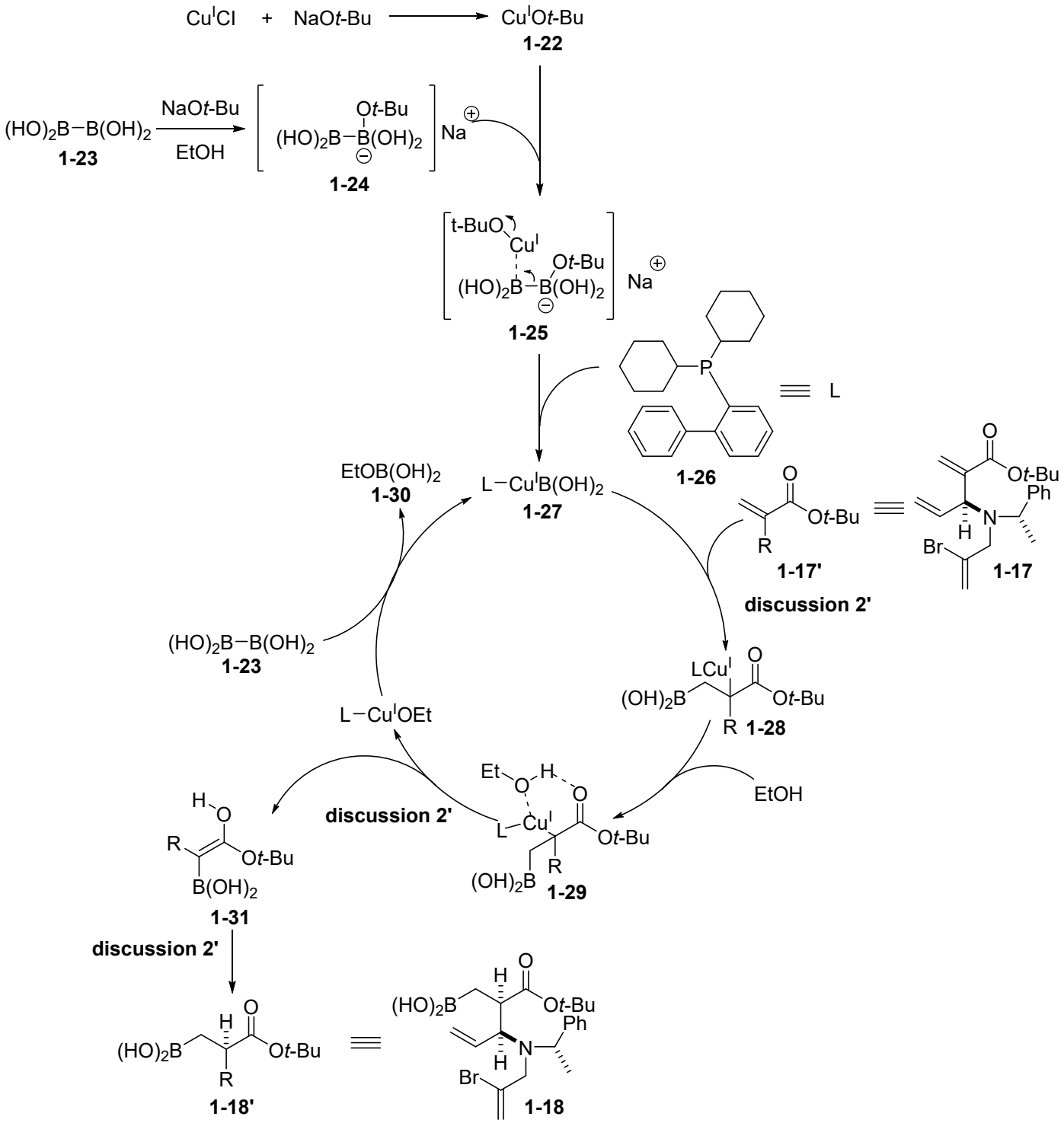


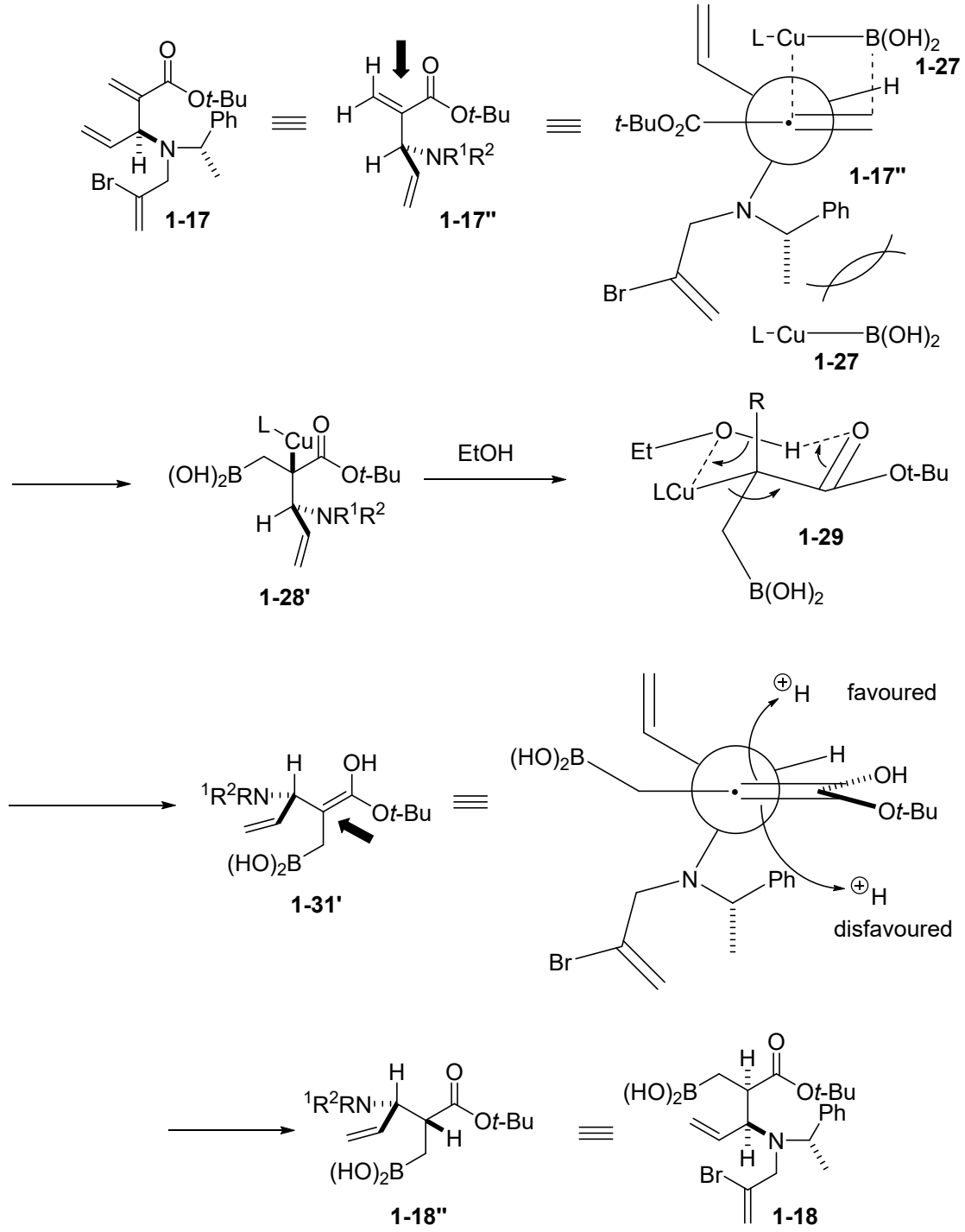
Figure 2. (a) Energy profiles related to the reaction of B_2eg_2 with methylacrylate, a model of α,β-unsaturated ester substrate, catalyzed by **1**. (b) Energy profiles calculated for alcoholysis of **3Aester** with methanol. The relative free energies and electronic energies (in parentheses) are given in kcal/mol.

➡ Under existence of MeOH, pathway (**3Aester**→**6Aester**→**7Aester**) is the most likely.

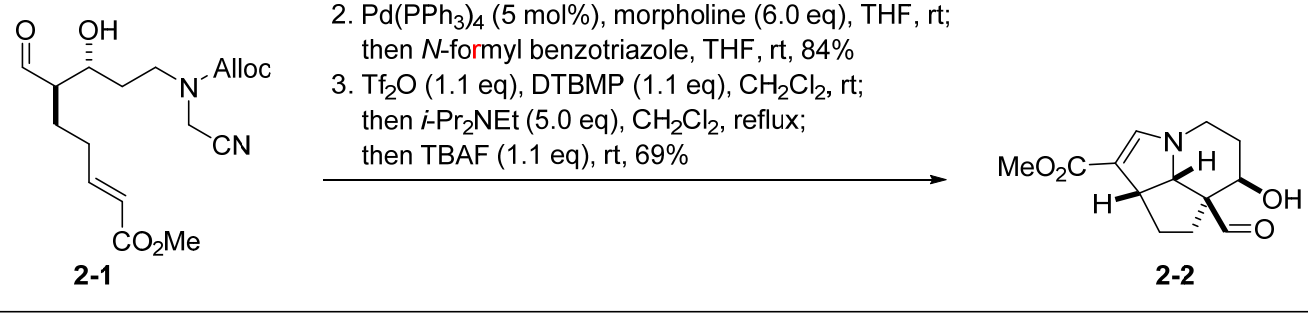
• Proposed reaction mechanism of borylation

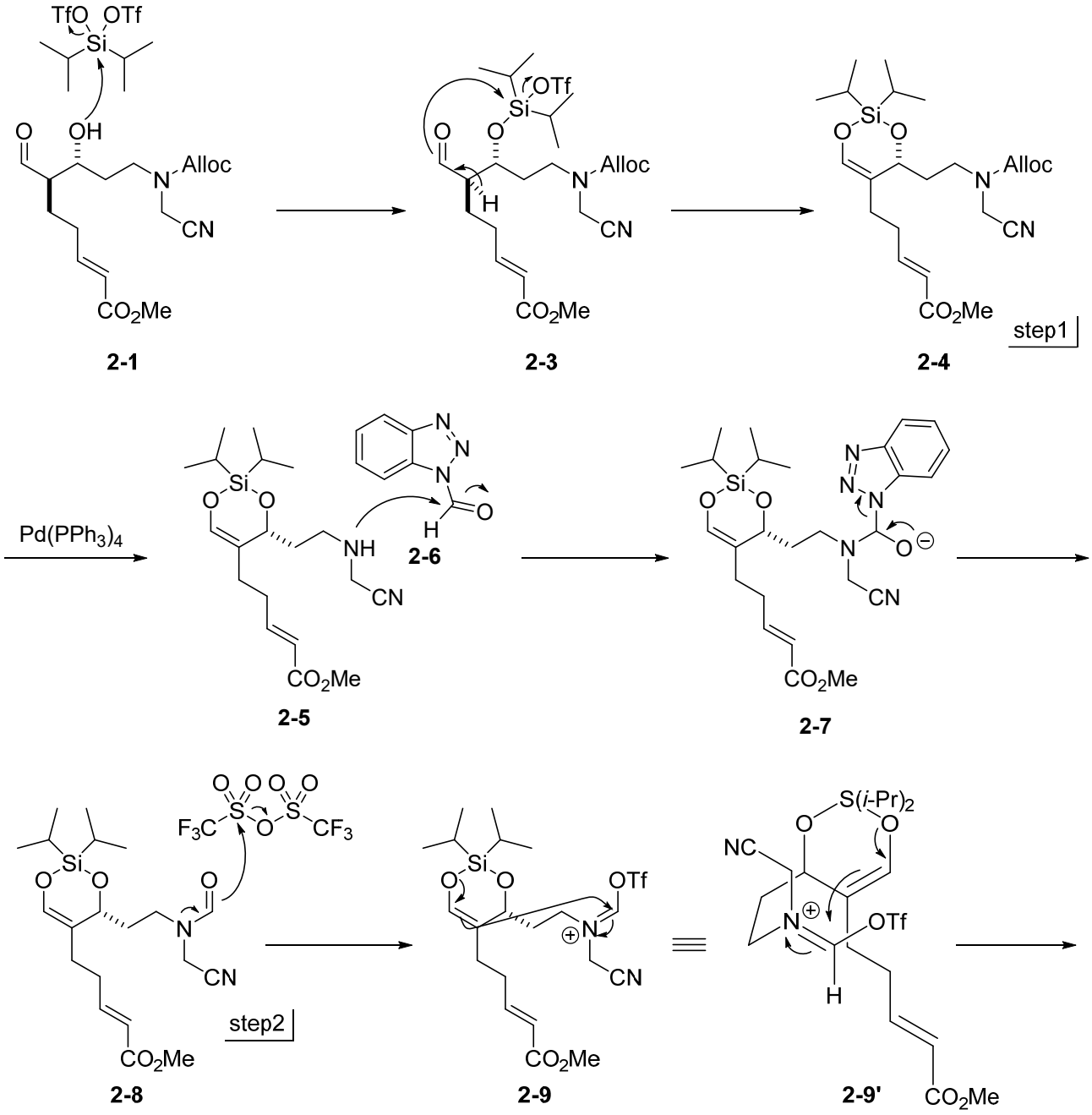


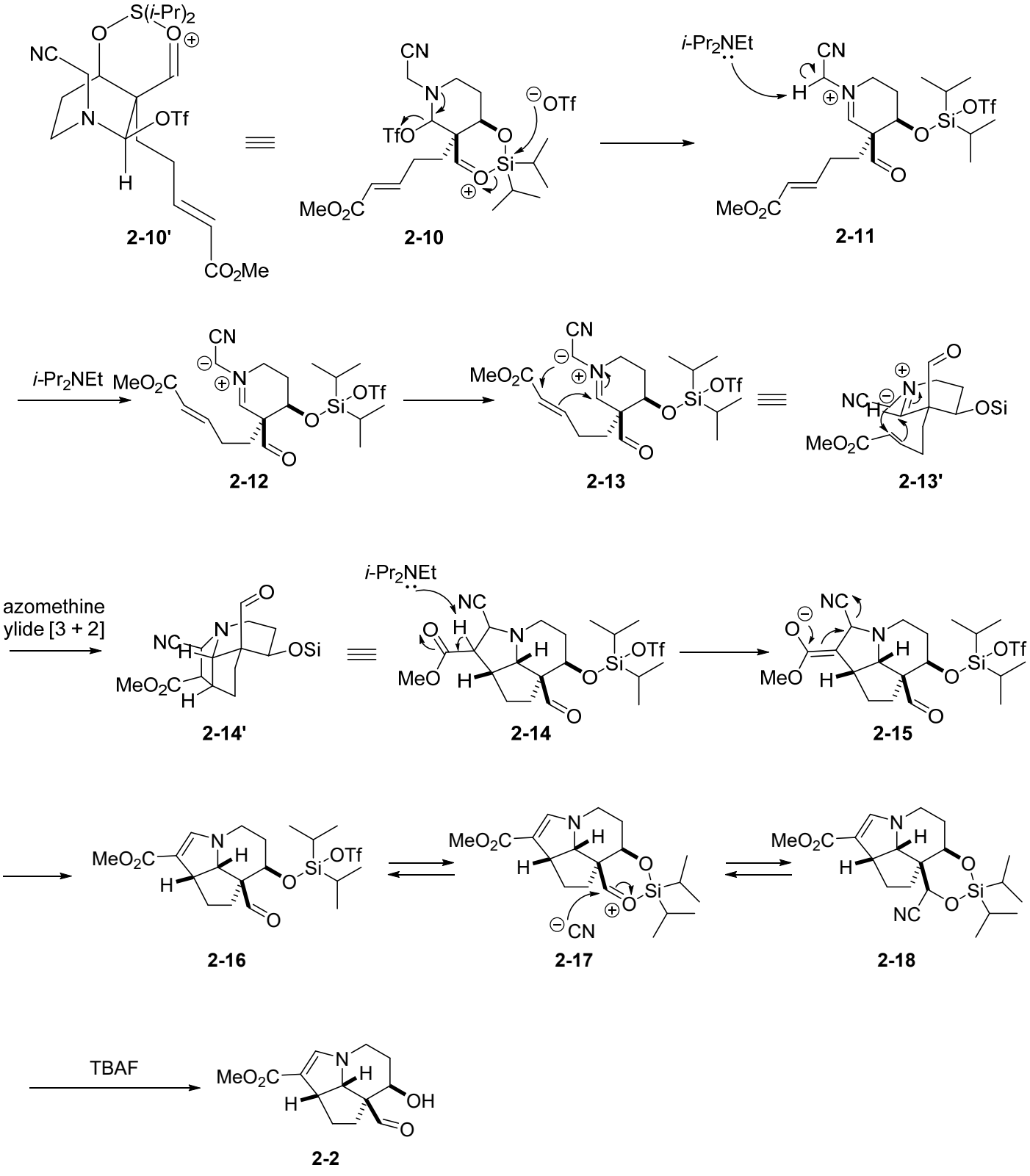
discussion 2' : Stereoselectivity of borylation



2 Boissarie, P.; Bélanger, G. *Org. Lett.* **2017**, *19*, 3739.






S(i-Pr)2
NC
OTf
H
CO2Me
2-10'
CN
TfO
OTf
MeO2C
2-10
i-Pr2NEt
2-11
2-12
2-13
2-13'
azomethine
ylide [3 + 2]
OSi
2-14'
2-14
2-15
MeO
2-16
2-17
2-18
TBAF
OH
2-2