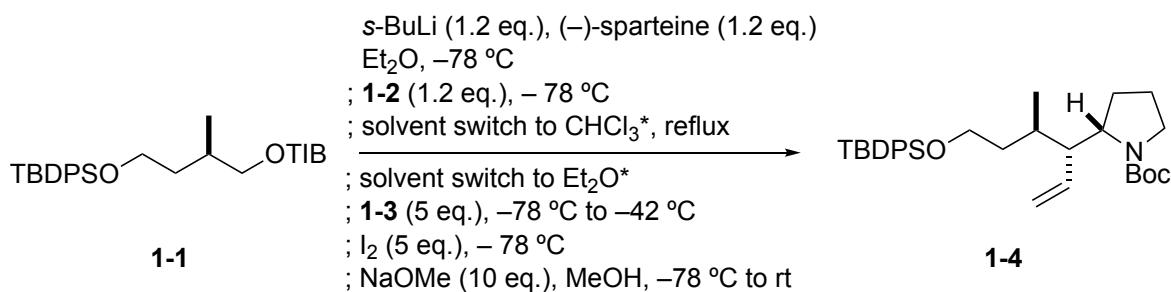


## Problem Session (4)

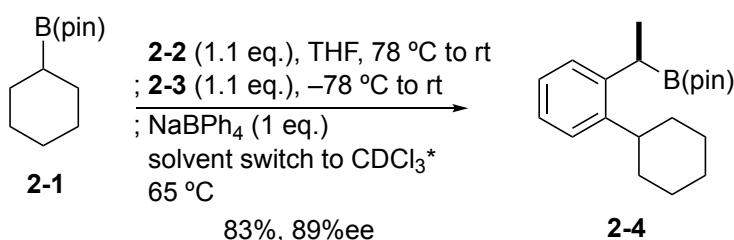
2018. 2. 22. Daiki Kamakura

- 1) Please provide the reaction mechanisms.
  - 2) Please fill in the blank **3-6**.

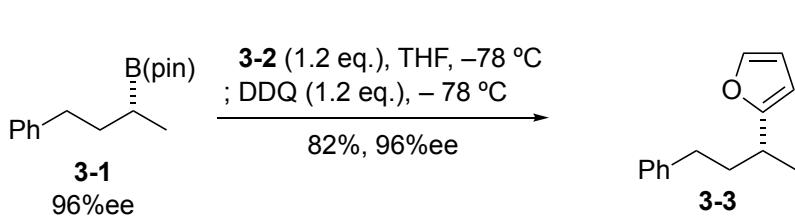
1



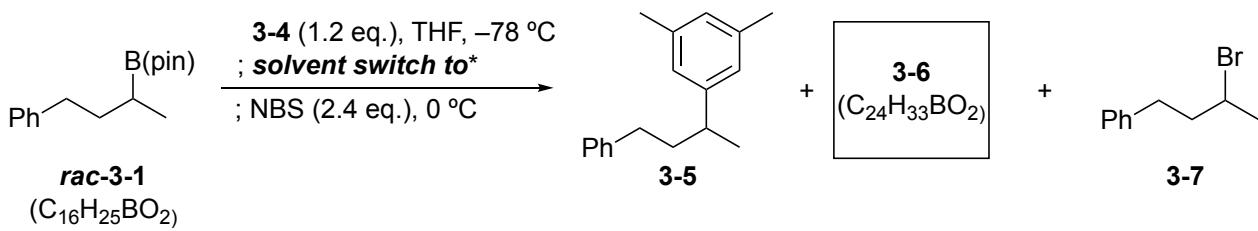
2



3



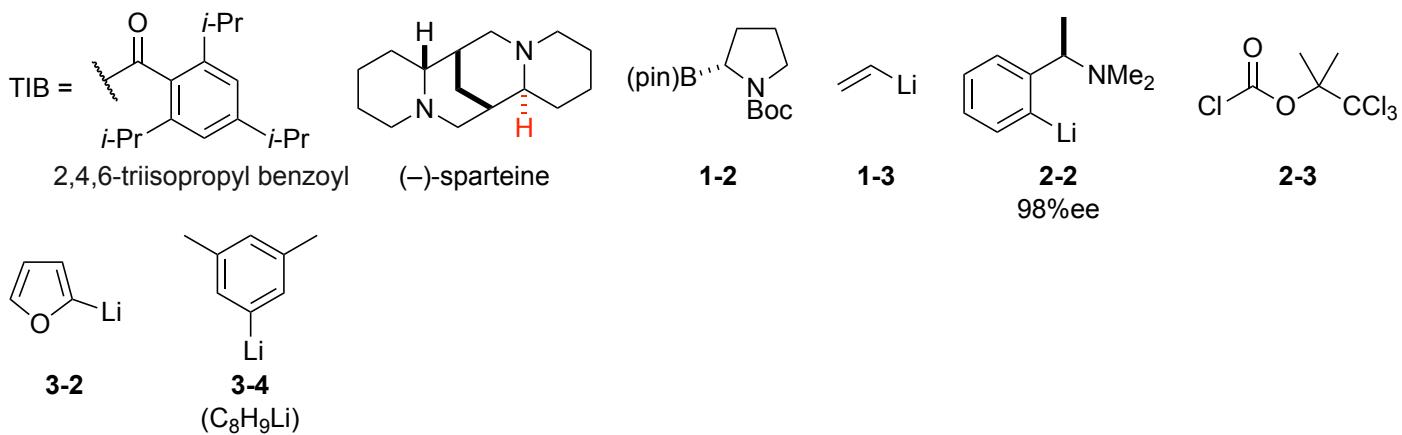
3-2



entry	<i>solvent switch to*</i>	3-5	3-6	3-7
1	– (THF)	<1%	<1%	99%
2	MeOH	60%	37%	3%
3	CH <sub>3</sub> CN/i-PrOH (1/1)	2%	90%	4%

\*Reaction mixture was warmed to rt and the solvent was removed under high vacuum.

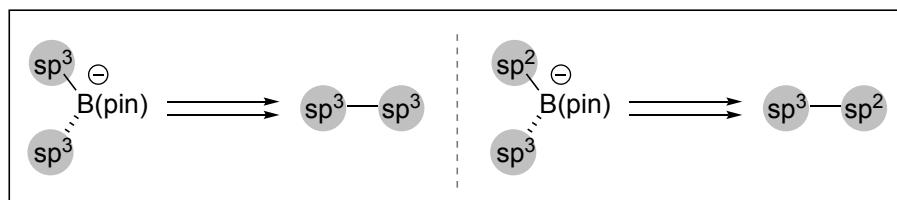
Then obtained mixture was dissolved in new solvent.



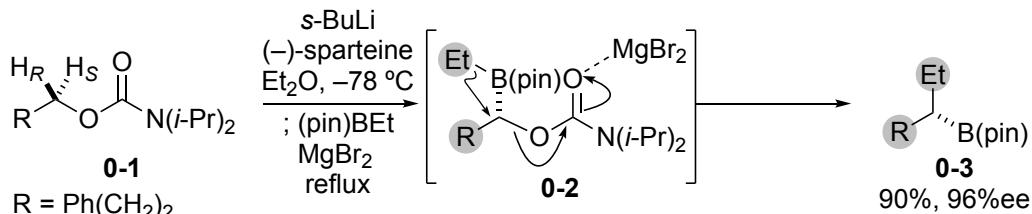
# Problem Session (4)-Answer

2018. 2. 22. Daiki Kamakura

Topic: C–C bond formation using organoborane reported by Prof. V. K. Aggarwal

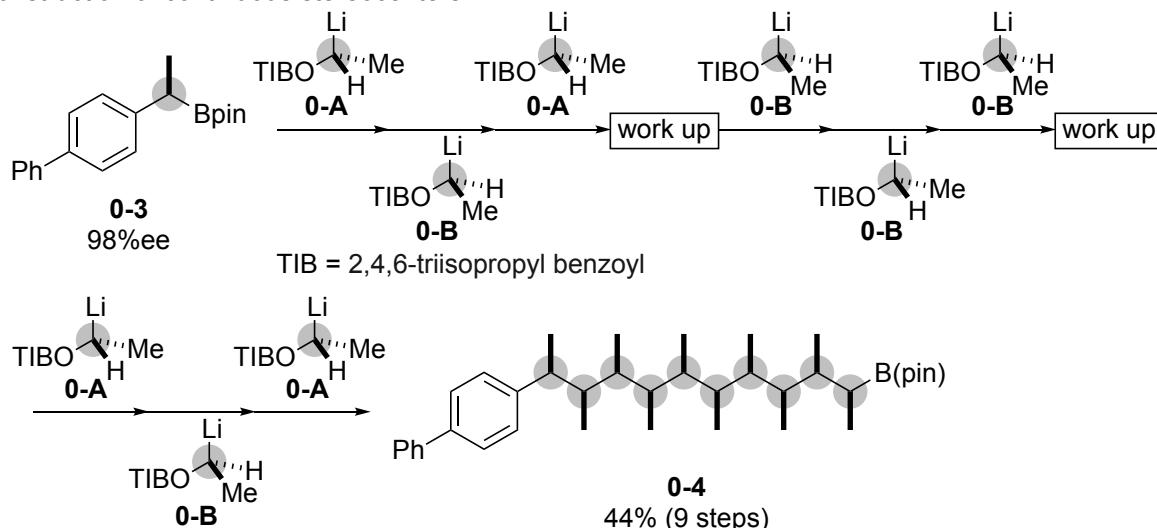


0-1. Homologation of lithiated carbamate with borane (sp<sup>3</sup>-sp<sup>3</sup> bond formation)



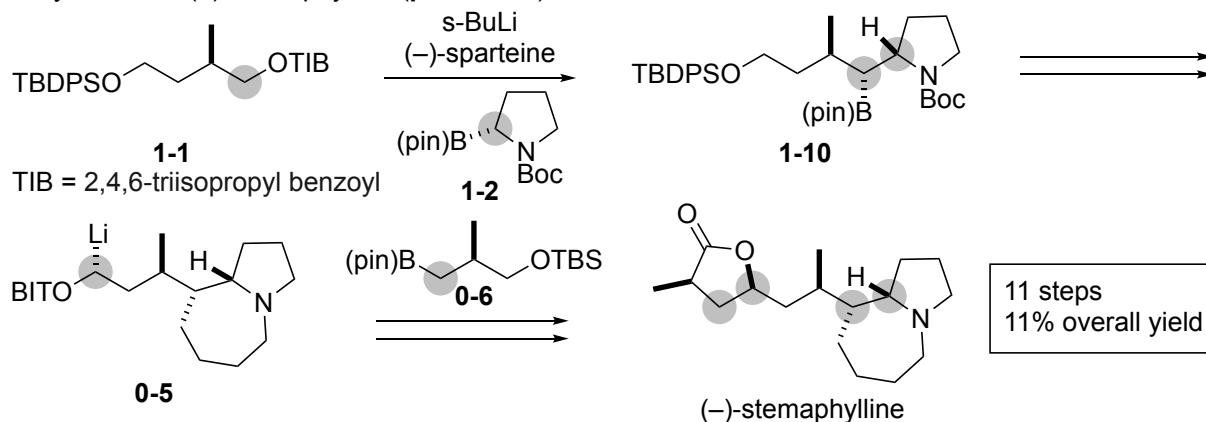
Stymiest, J. L.; Dutheuil, G. D.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2007**, *46*, 7491.  
Homologation reaction using lithiated carbamate: 140614\_LS\_Keiichiro\_Fukushima

0-2: Construction of continuous stereocenters



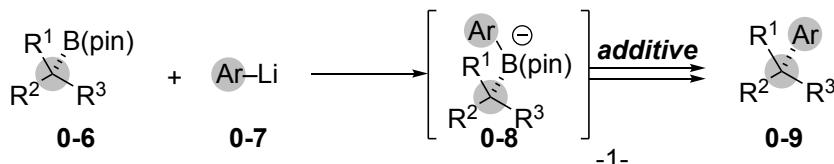
Burns, M.; Seeafi, S.; Bame, J. R.; Bull, S. P.; Webster, M. P.; Balieu, S.; Dale, J. W.; Butts, C. P.; Harvey, J. N.; Aggarwal, V. K. *Nature*, **2014**, *513*, 183.

0-3: Total synthesis of (−)-stemaphylline (**problem 1**)

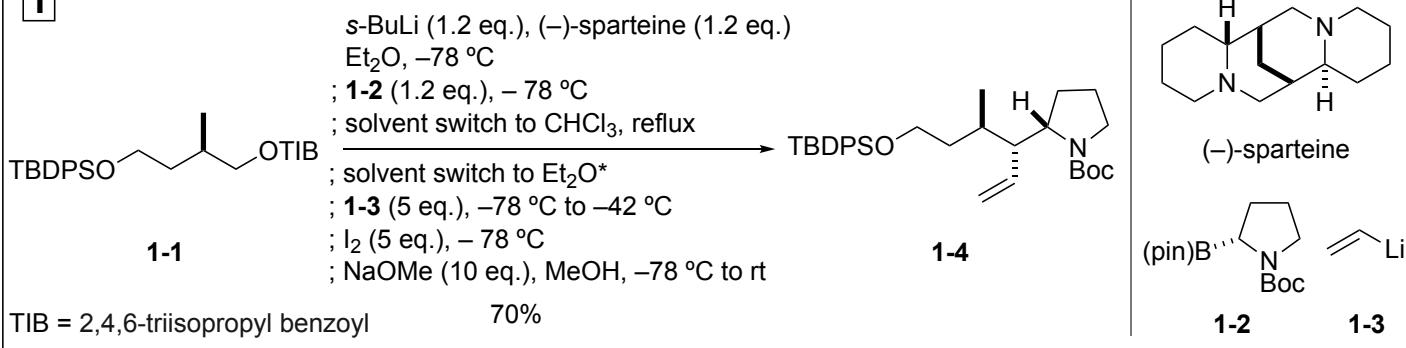


Varea, A.; Garve, L. K. B.; Leonori, D.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 2127.

0-4: Coupling reaction of arane with hydrocarbon unit (sp<sup>2</sup>-sp<sup>3</sup> bond formation, **problem 2, 3**)

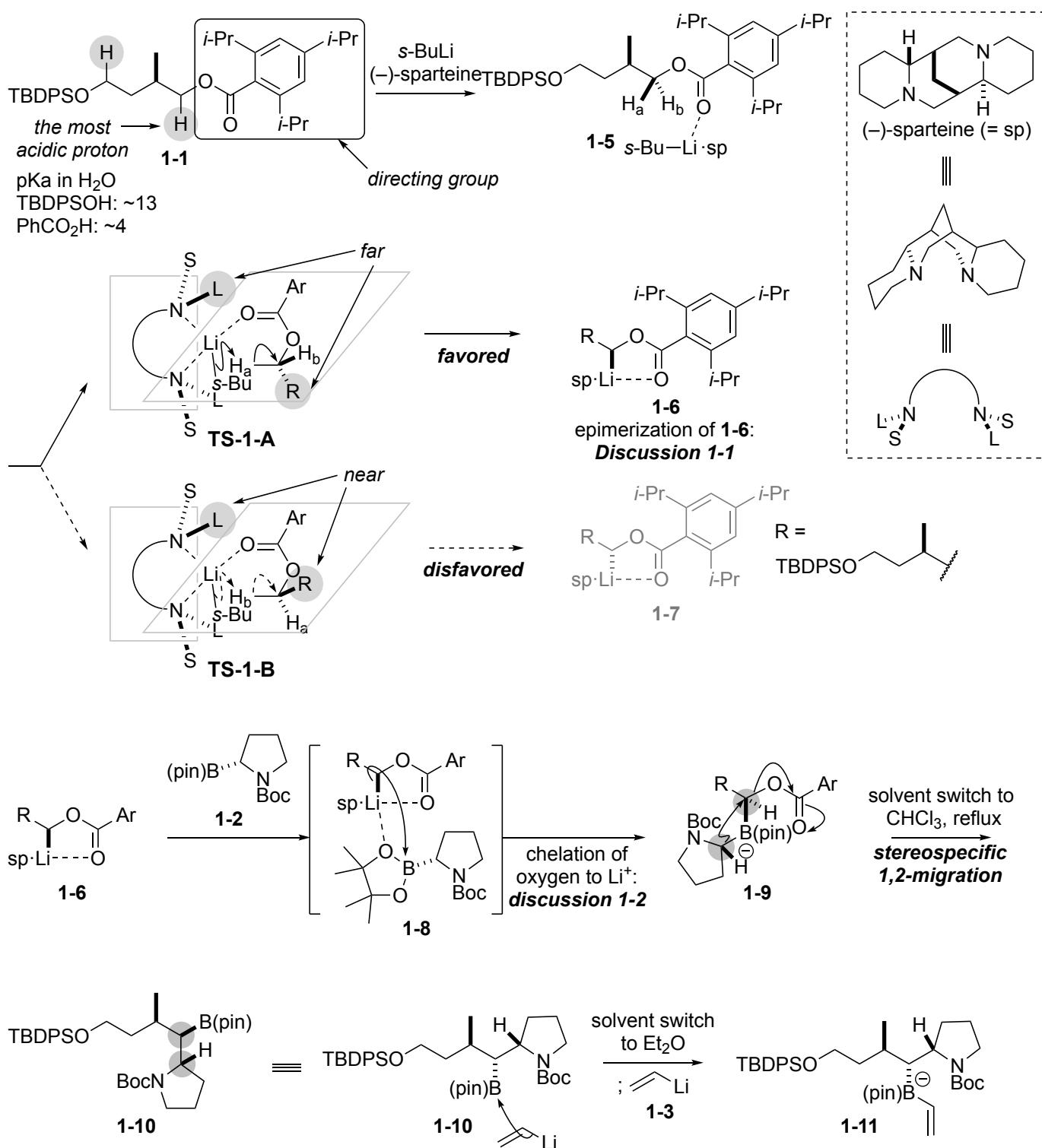


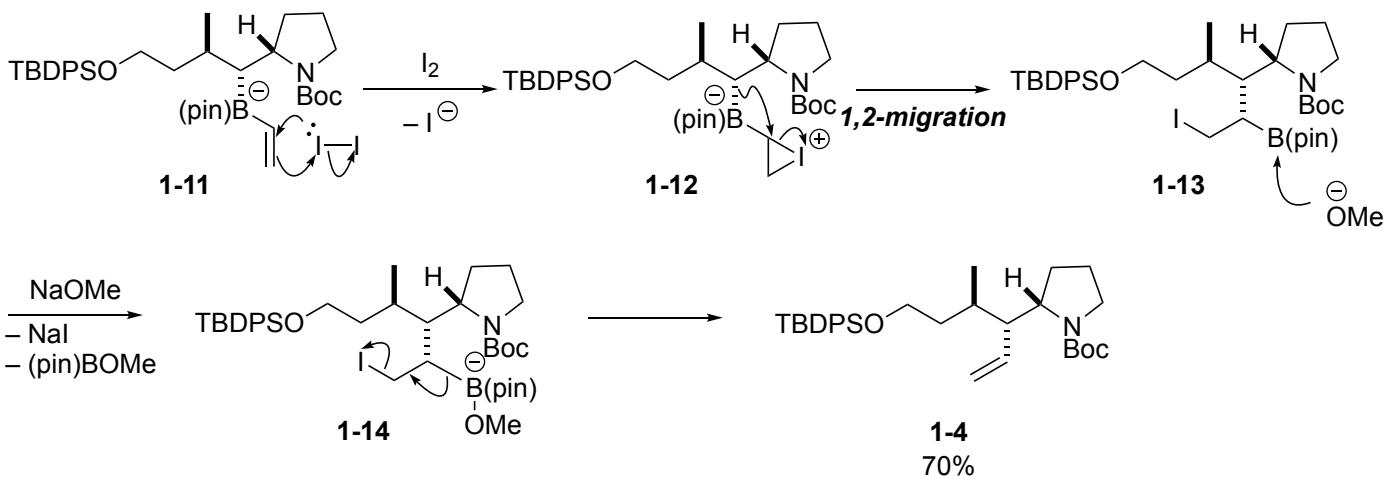
1



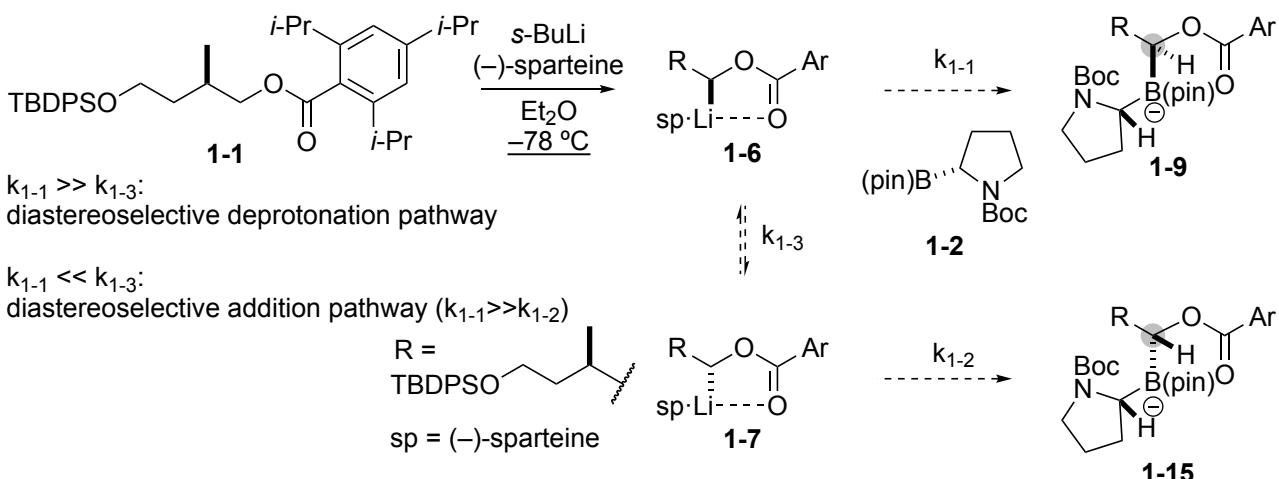
Varea, A.; Garve, L. K. B.; Leonori, D.; Aggaewal, V. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 2127.

**Answer:**

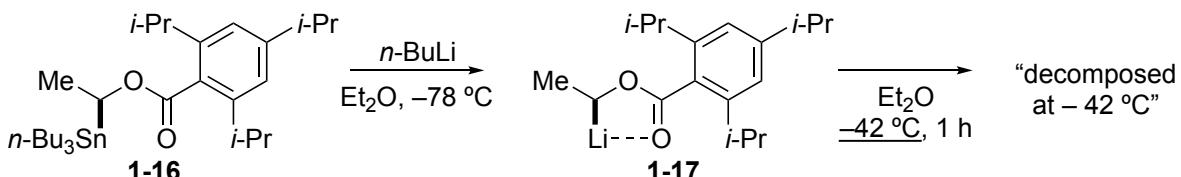




### Discussion 1-1: thermal stability of 1-6

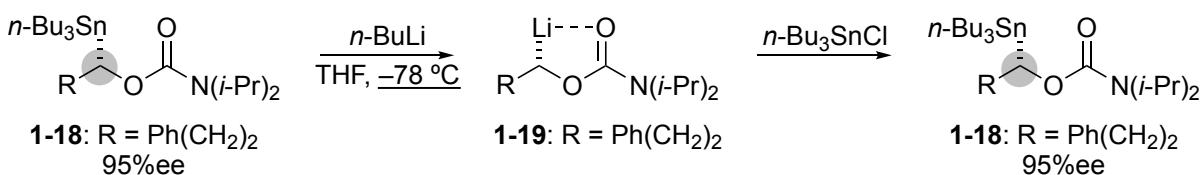


### 1. Thermal stability of chiral anion 1-17 at relatively high temperature ( $-42^{\circ}\text{C}$ )



Burns, M.; Seeafi, S.; Bame, J. R.; Bull, S. P.; Webster, M. P.; Balieu, S.; Dale, J. W.; Butts, C. P.; Harvey, J. N.; Aggarwal, V. K, *Nature*, **2014**, 513, 183.

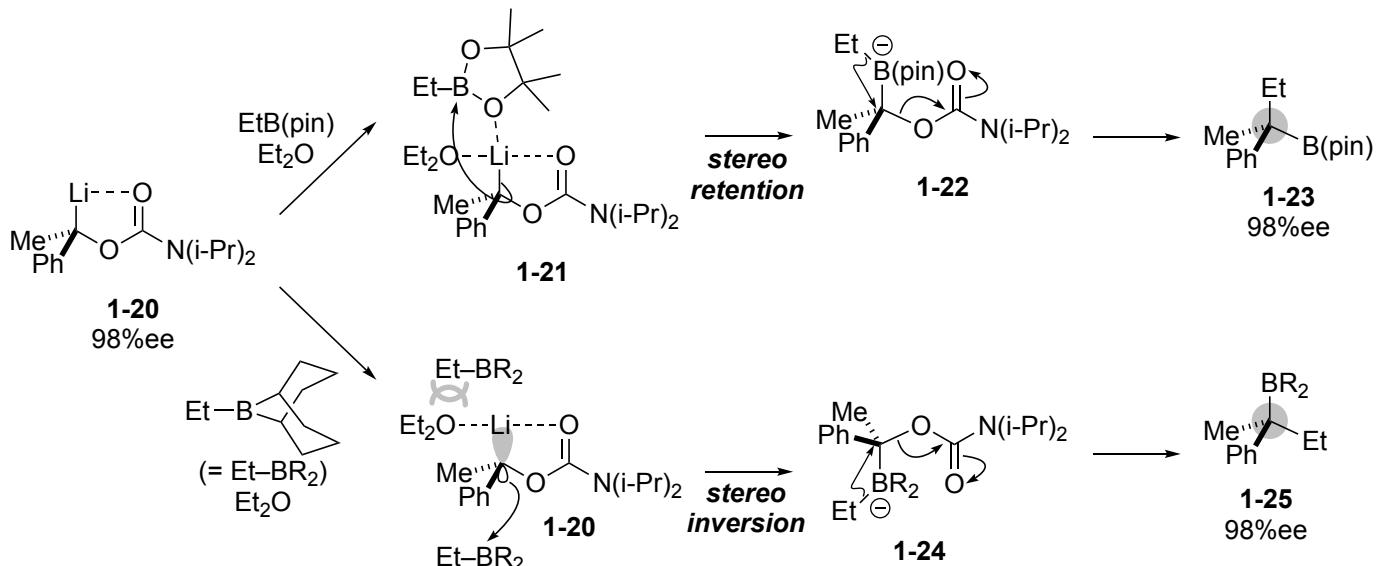
### 2. Reaction of chiral anion 1-19 with *n*-Bu<sub>3</sub>SnCl



Tomooka, K.; Shimizu, H.; Nakai, T. J. *Organomet. Chem.* **2001**, 624, 364.

→ This result indicates that chiral anion 1-6 would be stable (not epimerized) at  $-78^{\circ}\text{C}$ .  
So diastereoselective deprotonation of 1-1 by s-BuLi/(-)-sparteine occurred in this reaction.

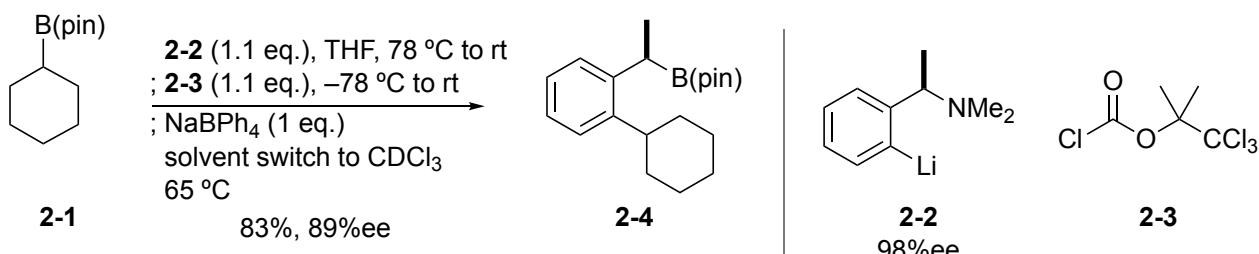
**Discussion 1-2:** chelation of oxygen to  $\text{Li}^+$



Stymiest, J. L.; Bagurski, V.; French, R. M.; Aggarwal, V. K. *Nature*, **2008**, 456, 778

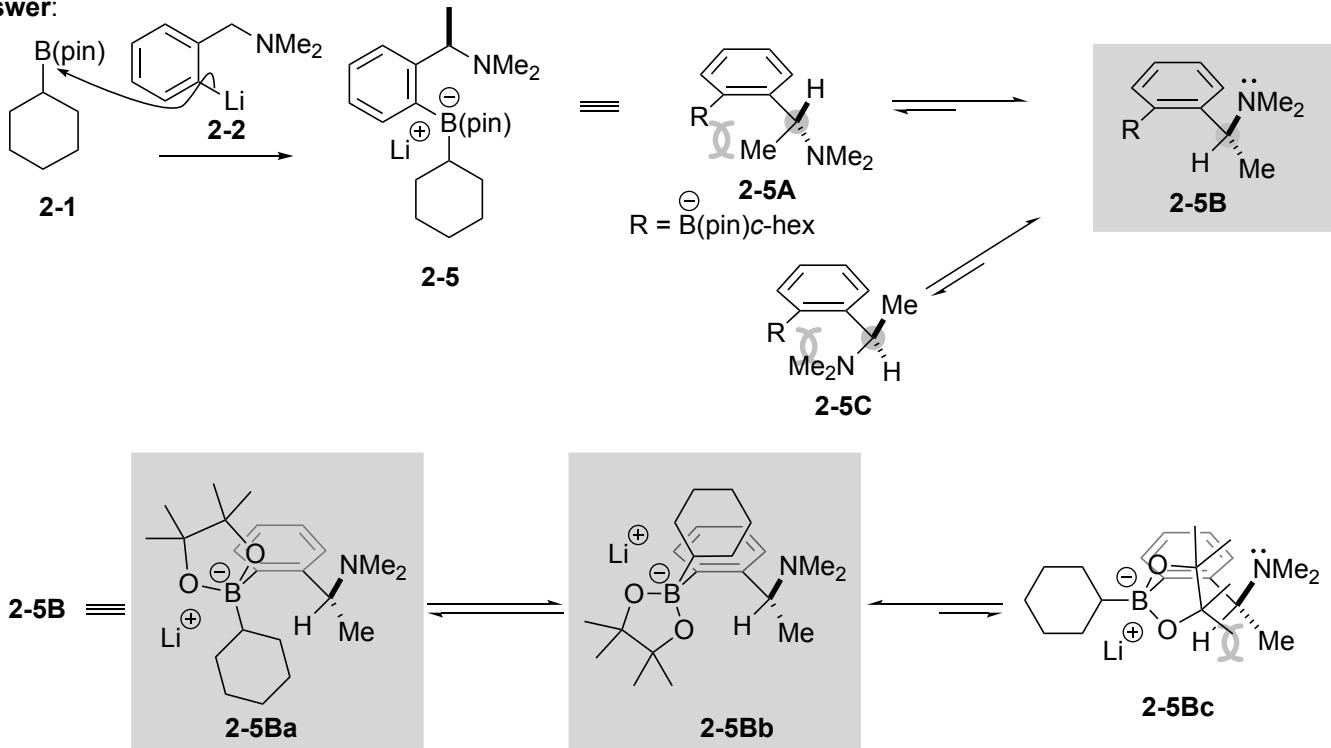
→ In the case of boronic ester, the oxygen of the ester complexes with the lithium of the metallated carbamate and so is delivered on the same face as the metal. In the case of the trialkyl borane, reaction occurs on the face opposite to the lithium because borane.

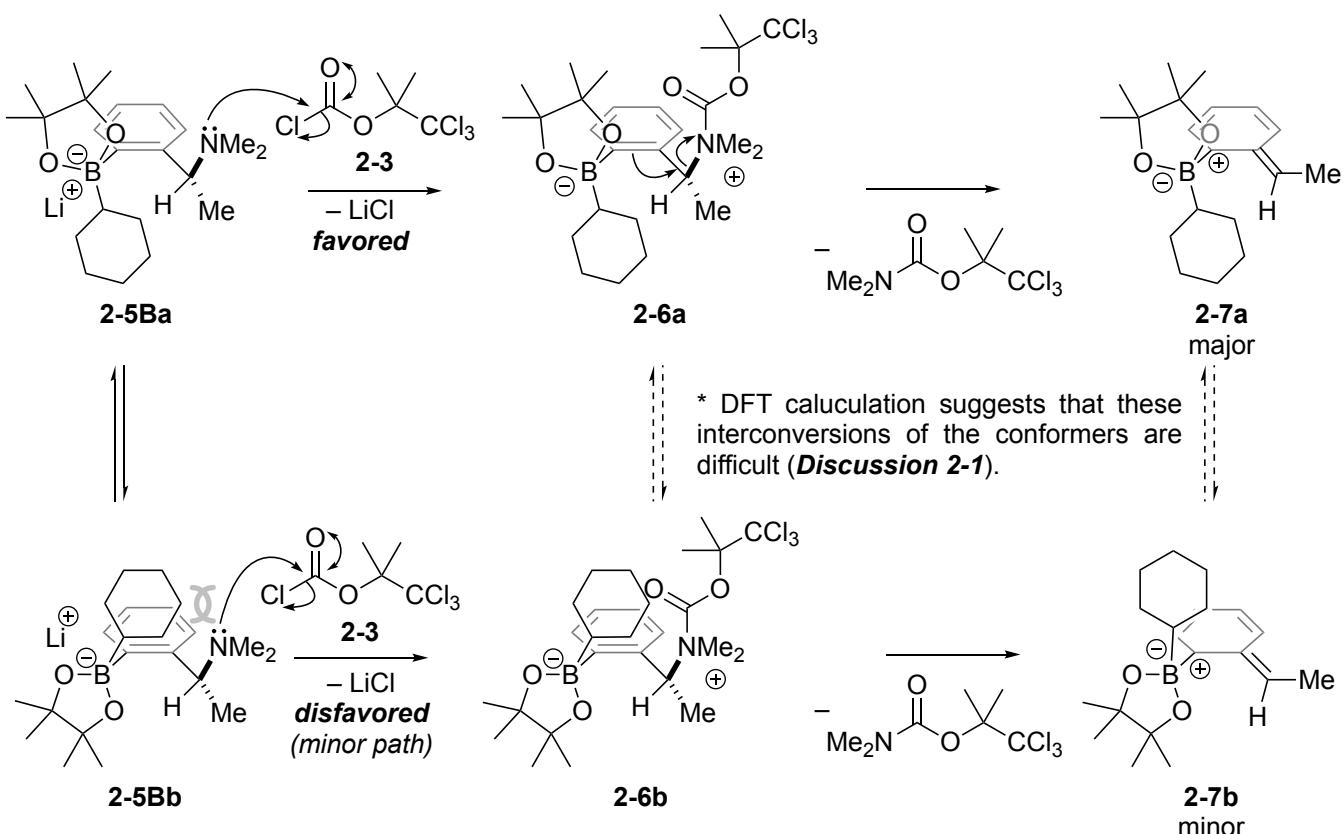
**2**



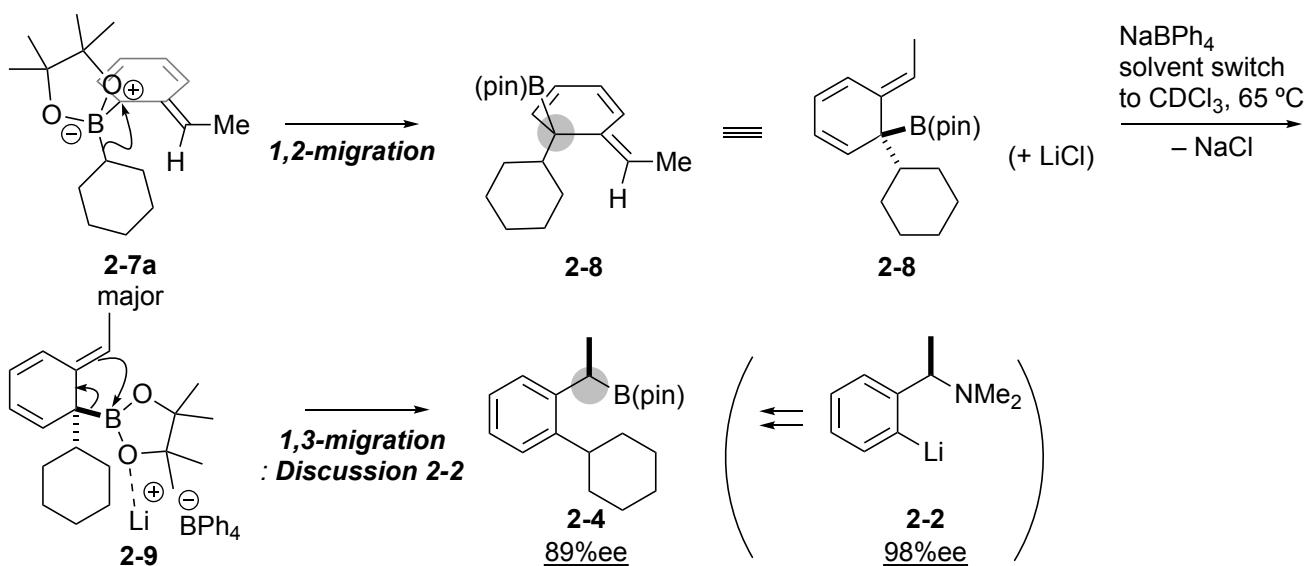
Aichhorn, S.; Bigler, R.; Myers, E. L.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2017**, 139, 9519.

**Answer:**

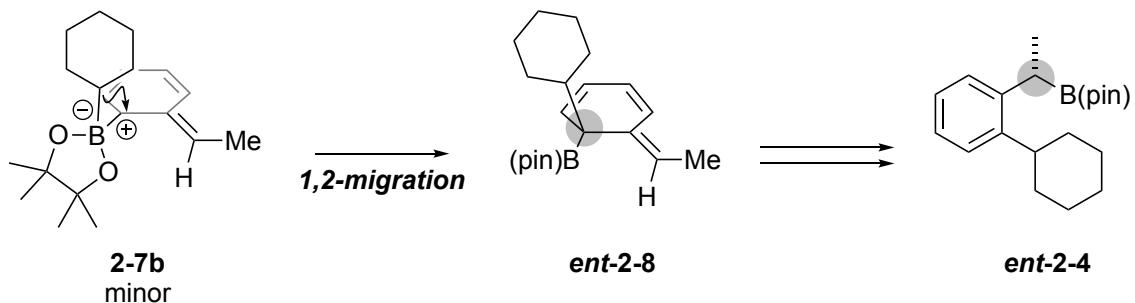




<major path>

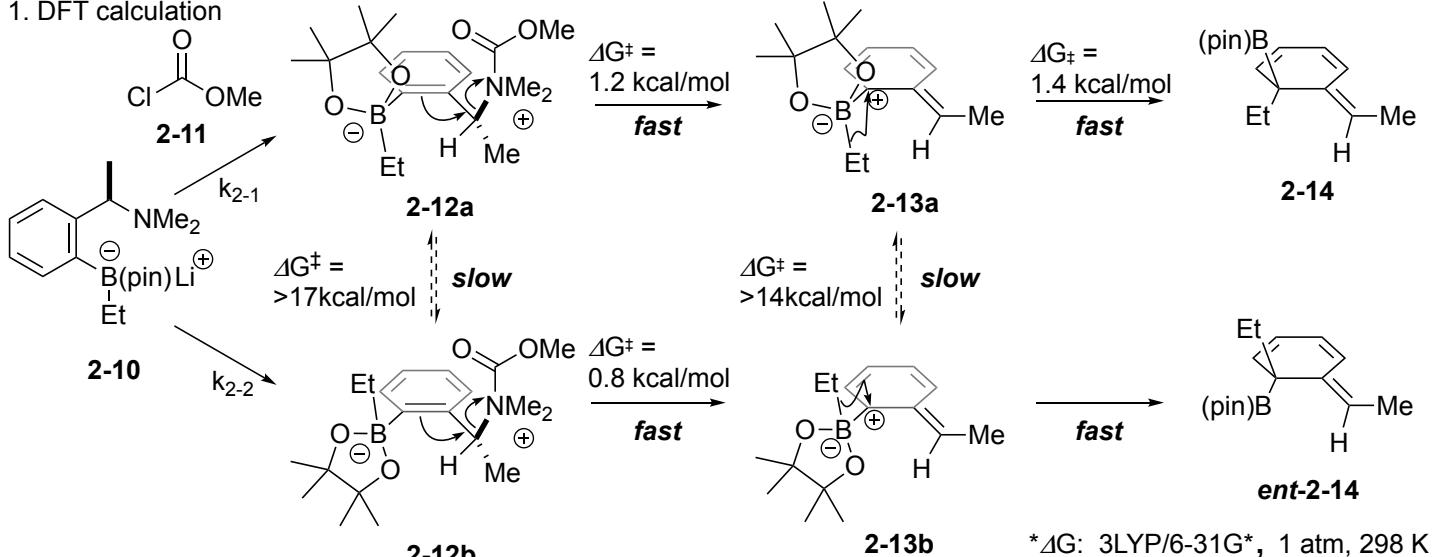


<minor path>



## Discussion 2-1: Consideration on reaction rate

### 1. DFT calculation



→ DFT calculation reveals that 1,2-migration of Et group is fast from both 2-12a and 2-12b.

It also shows that interconversions from 2-12a to 2-12b and 2-13a to 2-13b are slow (high-barrier).

Judging from these results, selective formation of 2-12a ( $k_{2-1} > k_{2-2}$ ) would occur to give 2-14 dominantly.

### 2. effects of alkyl group on borane

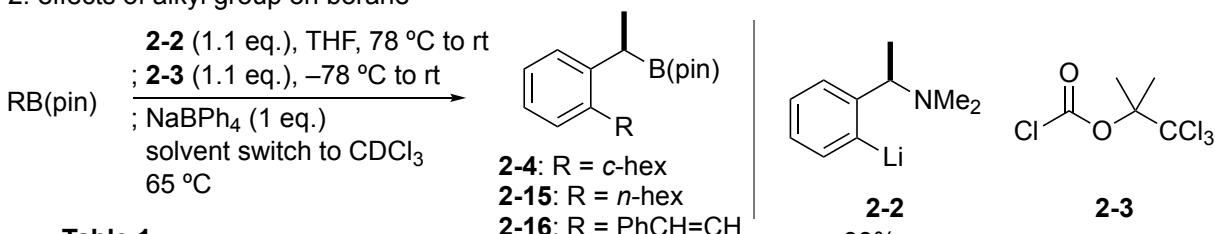
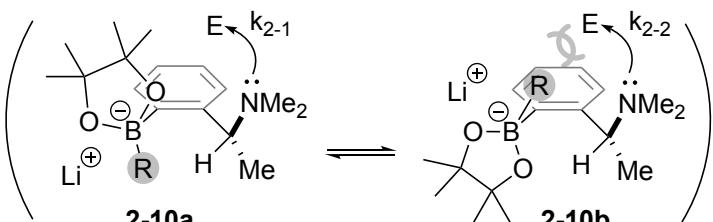


Table 1

entry	R	results
1		2-4: 83%, <u>89% ee</u>
2		2-15: 79%, <u>79% ee</u>
3		2-16: 48%, <u>70% ee</u>

→ Bulky alkyl chain gives the coupling product in high enantioselectivity.  
These results support that enantio-determining step is acylation step ( $= k_{2-1} > k_{2-2}$ ).



### Discussion 2-2: Effect of NaBPh<sub>4</sub>

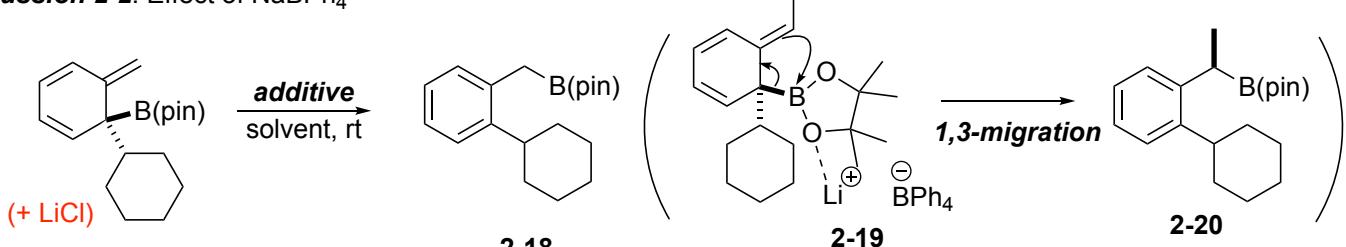


Table 2

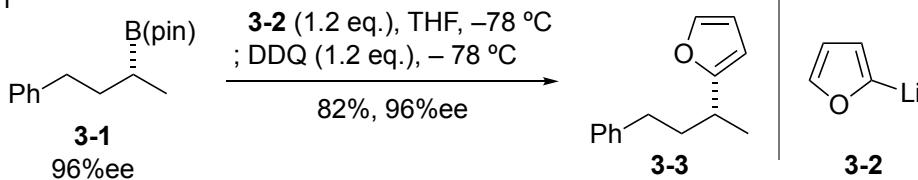
entry	additive (eq.)	solvent	time	2-18 <sup>a</sup>	2-17 <sup>a</sup>
1	none	THF	24 h	63%	–
2	NaBPh <sub>4</sub> (1 eq.)	THF	1 h	84%	–
3	NaBPh <sub>4</sub> (1 eq.)	CDCl <sub>3</sub>	1 h	85%	–
4	12-crown-4 (1.5 eq.)	CDCl <sub>3</sub>	48 h	–	62%

\* Metal  $\text{BAr}_4$  salts are known as naked metal cation source because  $\text{BAr}_4^-$  has low nucleophilicity.

Fujii, K.; Ikeda, S.; Kobayashi, H.; More, A.; Nagira, A.; Nie, J.; Sonoda, T.; Yagolinski, Y. *Chem. Lett.* **2000**, 61.

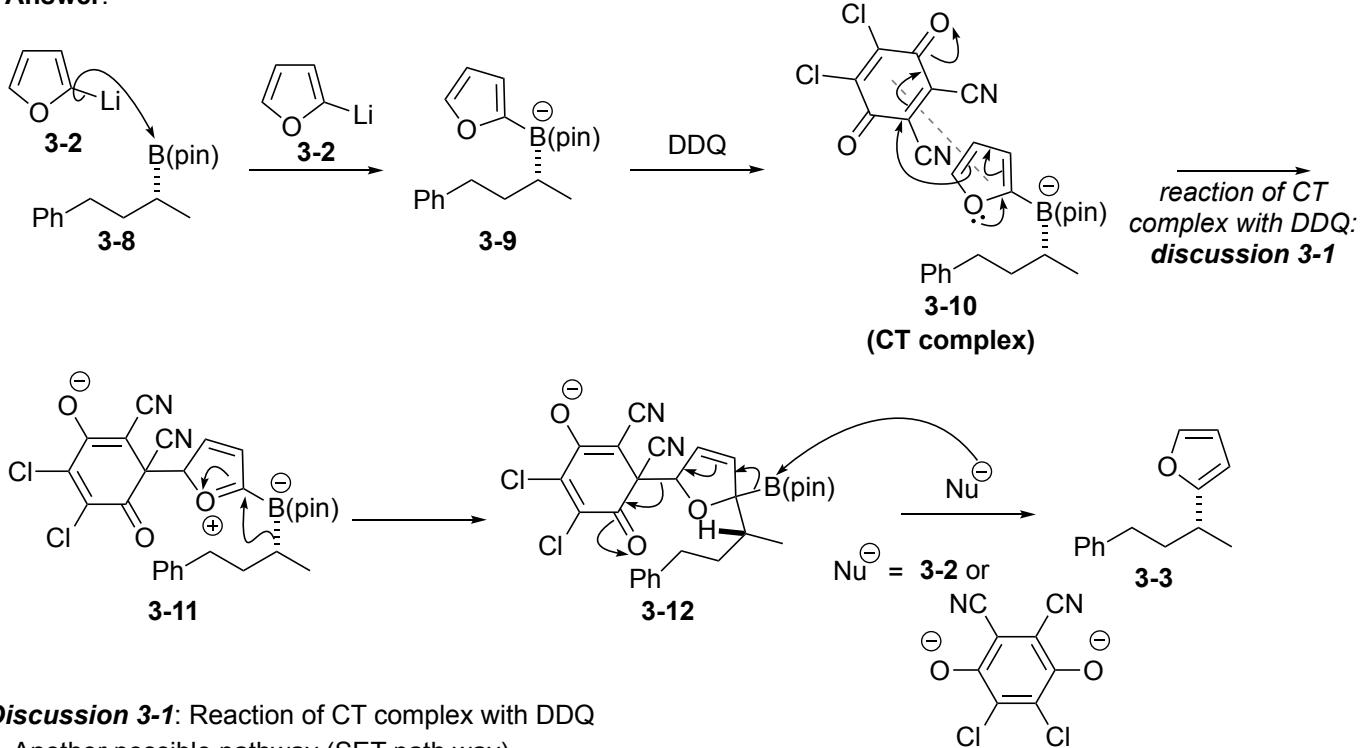
→ Naked  $\text{Li}^+$  would accelerate 1,3-migration to activate boronic ester (decrease LUMO energy of borane).

<sup>a</sup> NMR yield.

**3**

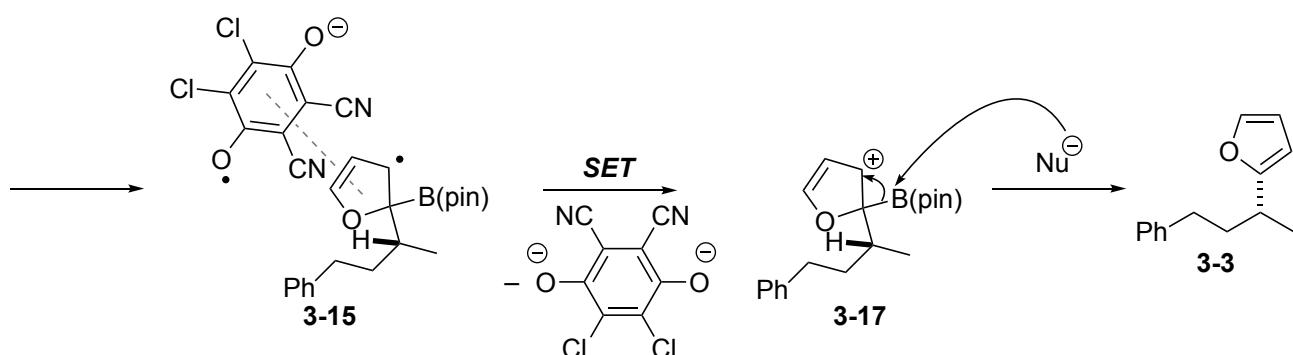
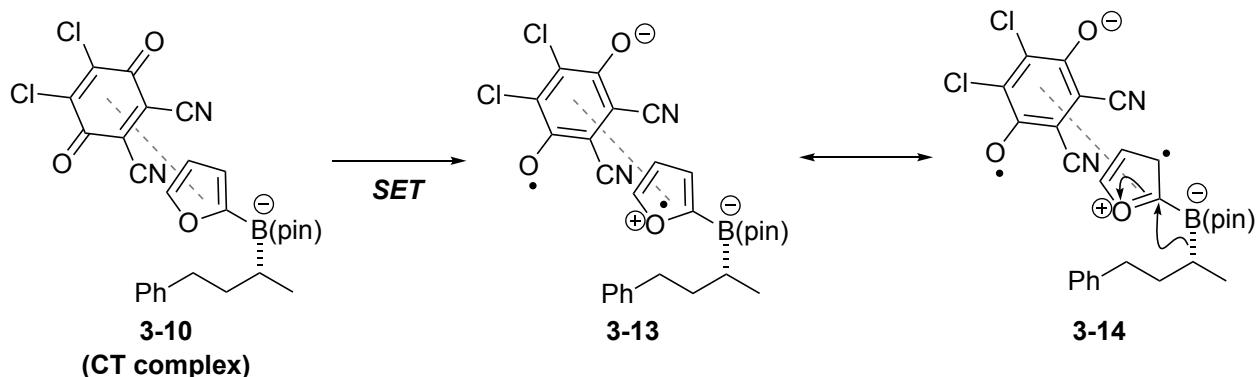
Odachowski, M.; Bonet, A.; Essafi, S.; Conti-Ramsden, P.; Harvey, J. N.; Leonori, D.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2016**, *138*, 9521.

**Answer:**

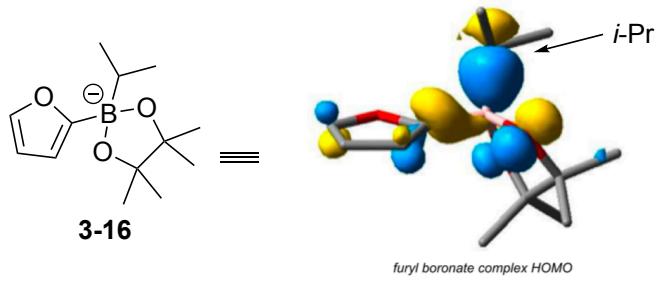


#### Discussion 3-1: Reaction of CT complex with DDQ

1. Another possible pathway (SET path way)

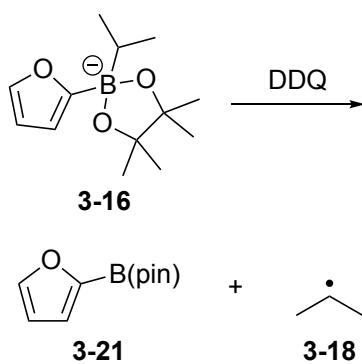


## 2. HOMO of furyl boronate complex



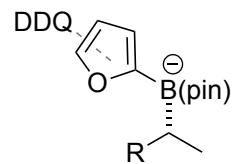
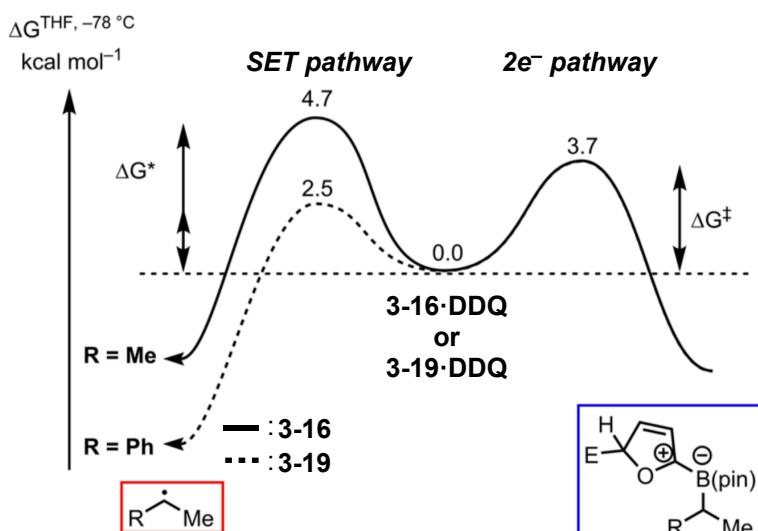
→ HOMO of **3-16** mainly localized on C(*i*-Pr)-B bond.  
So SET would be prefer to occur at C-B bond.

## 3. possible side reaction via SET pathway



## 4. DFT calculation

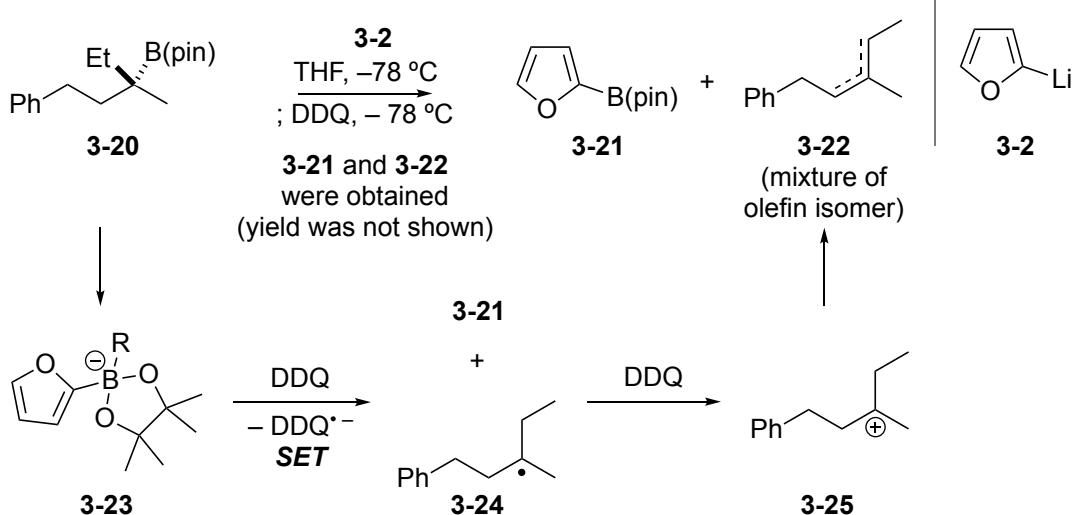
### E) SET vs S<sub>E</sub>Ar pathway – energy diagram



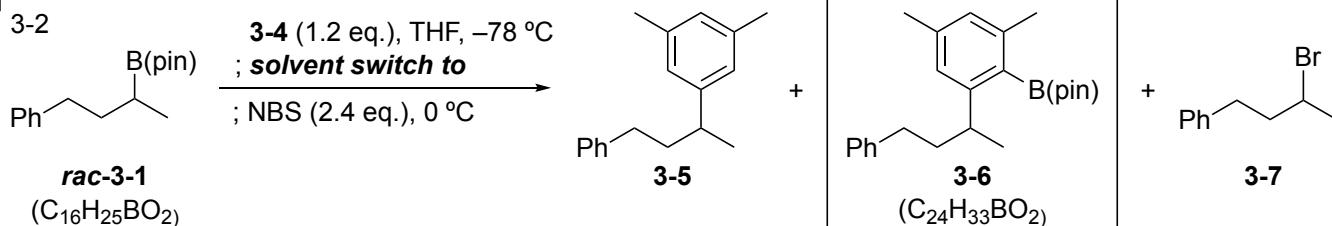
2e<sup>-</sup> pathway would be favore

$\Delta G$ : B3LYP/6-31+G(d), 1 atm, 195 K

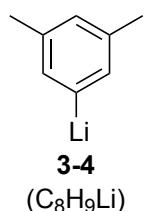
## 5. Oxidation of C–B bond by the usage of boronic ester having a *tert*-alkyl group



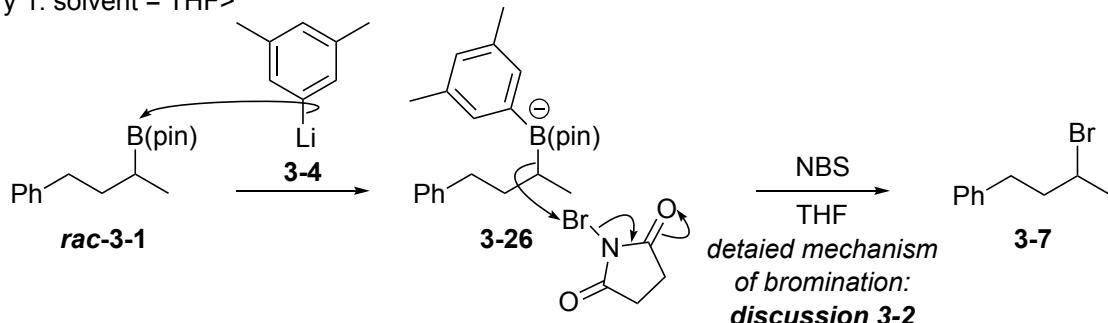
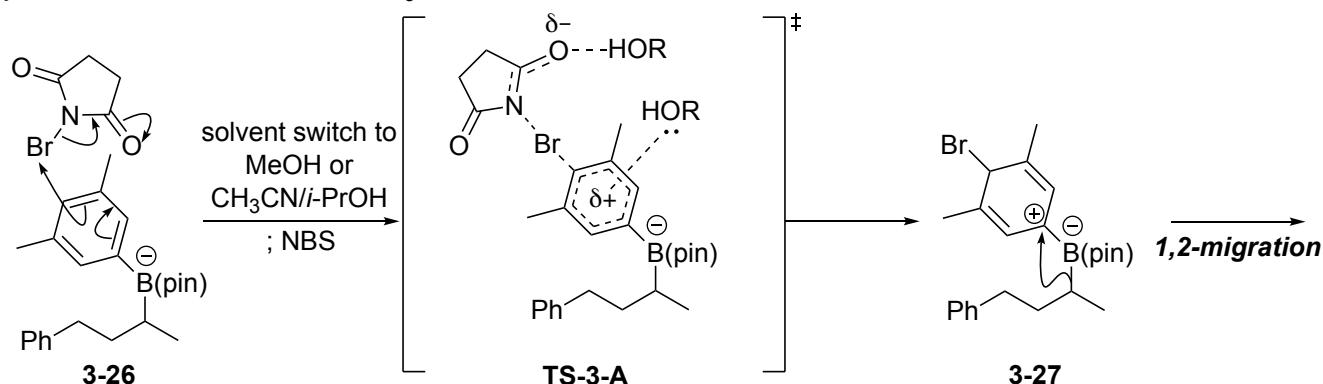
3



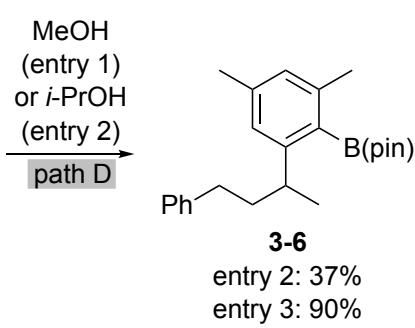
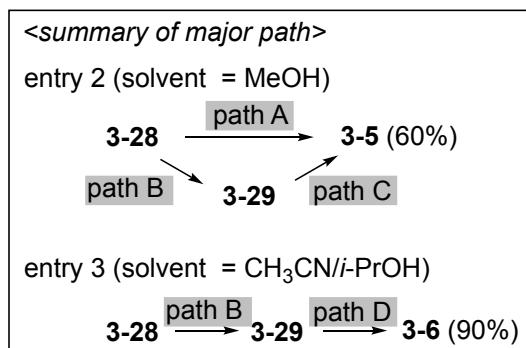
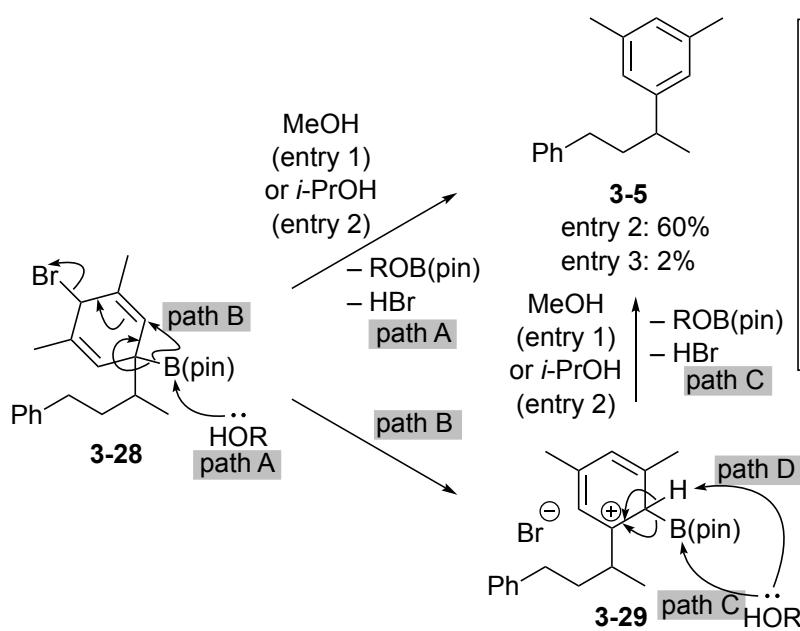
entry	solvent switch to	3-5	3-6	3-7
1	- (THF)	<1%	<1%	99%
2	MeOH	60%	37%	3%
3	CH <sub>3</sub> CN/ <i>i</i> -PrOH (1/1)	2%	90%	4%

**Answer:**

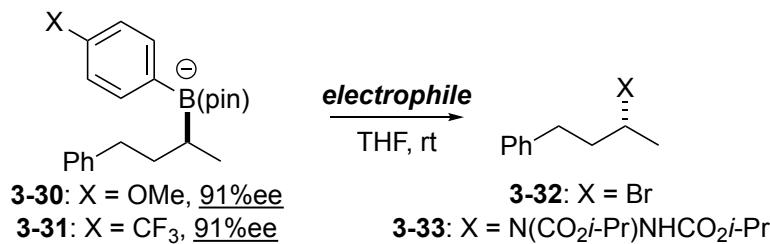
&lt;entry 1: solvent = THF&gt;

<entry 2 and 3: solvent = MeOH or CH<sub>3</sub>CN/*i*-PrOH>

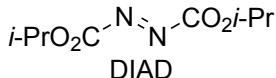
TS-3-A would be stabilized by polar solvent (MeOH, *i*-PrOH and CH<sub>3</sub>CN): **Discussion 3-3**



### Discussion 3-2: Detailed mechanism of bromination



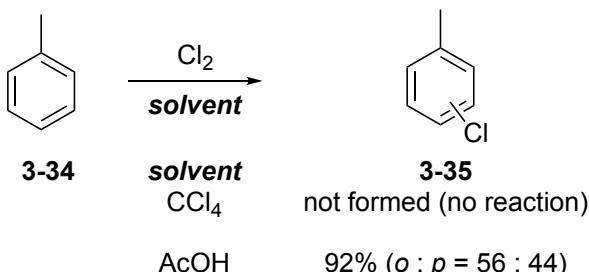
entry	borate	electrophile	results
1	3-30 (X = OMe)	NBS	3-32: X = Br 50%, 82% ee
2	3-30 (X = OMe)	DIAD	3-33: X = N(CO <sub>2</sub> i-Pr)NHCO <sub>2</sub> i-Pr 82%, 12% ee
3	3-31 (X = CF <sub>3</sub> )	DIAD	3-33: X = N(CO <sub>2</sub> i-Pr)NHCO <sub>2</sub> i-Pr 74%, 66% ee



Gauthier, R. L.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2011**, 133, 16794.

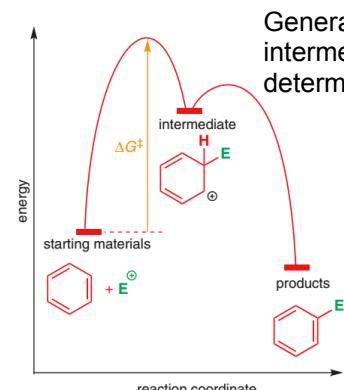
### Discussion 3-3: Cationic intermediate in polar solvent

#### 1. S<sub>E</sub>Ar reaction in polar solvent



O'Connell, J. L.; Simpson, J. S.; Dumanski, P. G.; Simpson, G. W.; Easton, C. J. *Org. Biomol. Chem.* **2006**, 4, 2716

#### <General energy diagram of S<sub>E</sub>Ar reaction>

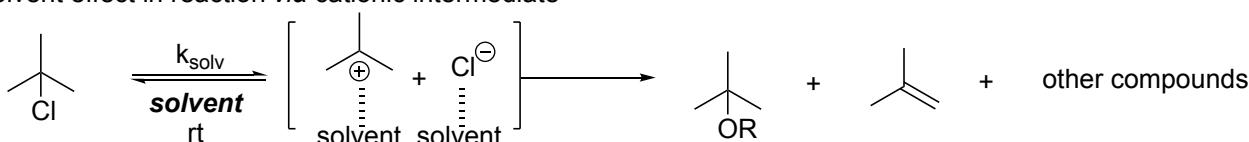


Generally, formation of cationic intermediate ( $\sigma$ -complex) is rate determining step.

Clayden, J.; Greeves, N.; Warren, S. *Organic Chemistry*, 2nd Ed.

→ S<sub>E</sub>Ar reaction is promoted in polar solvent because cationic TS is stabilized by solvation.

#### 2. Solvent effect in reaction via cationic intermediate



entry	solvent	relative rate $k_{\text{solv}}/k_{\text{benzene}}$	relative permittivity $\epsilon_r$
1	benzene	1	2.3
2	acetone	10 <sup>2</sup>	20.7
3	MeOH	10 <sup>6</sup>	32.7
4	H <sub>2</sub> O	10 <sup>11</sup>	78.3

→ There is a correlation between reaction rate and relative permittivity  $\epsilon_r$

relative permittivity  $\epsilon_r$

THF: 7.5

*i*-PrOH: 18

CH<sub>3</sub>CN: 37.5

→ In MeOH or *i*PrOH/CH<sub>3</sub>CN, TS to give cationic intermediate would be significantly stabilized compared to THF.

Fainberg, A. H.; Winstein, S. *J. Am. Chem. Soc.* **1956**, 78, 2770.