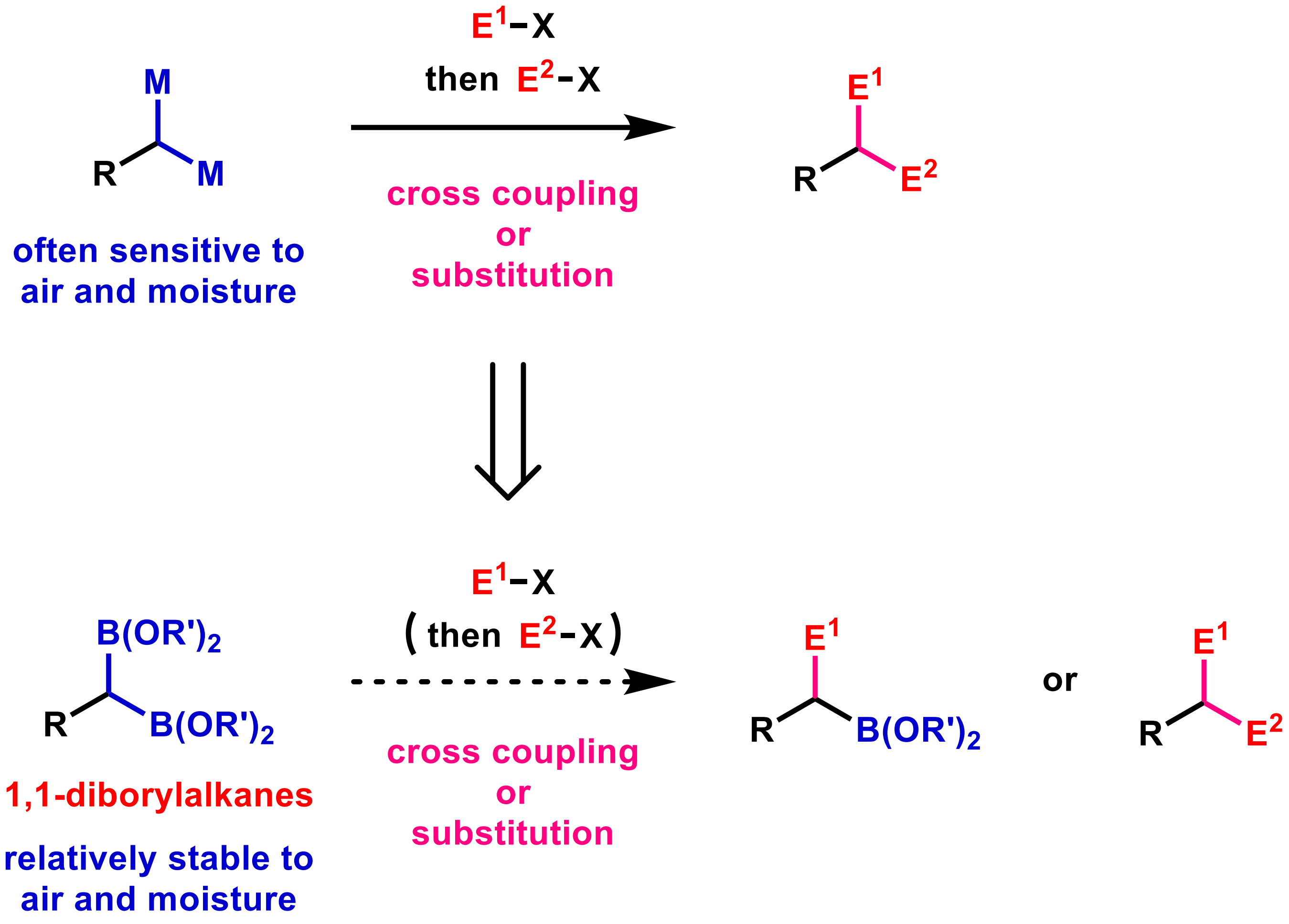
Chemistry around 1,1-Diborylalkanes

Literature Seminar

2016/11/19 Koichi Hagiwara

Why 1,1-Diborylalkanes?



E^1–X

then E^2–X

cross coupling

or

substitution

often sensitive to air and moisture

E^1–X

(then E^2–X)

cross coupling

or

substitution

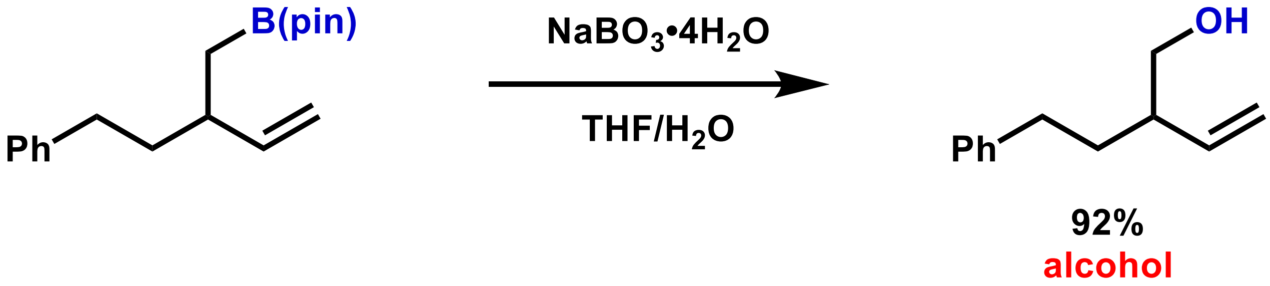
or

1,1-diborylalkanes

relatively stable to air and moisture

Transformation of Boronic Ester

- **oxidation**



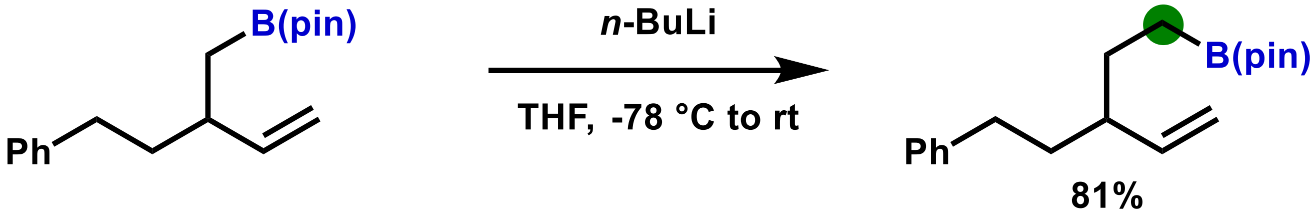
$NaBO_3•4H_2O$

THF/H_2O

92%

alcohol

- **one carbon homologaton**



ICH_2Cl

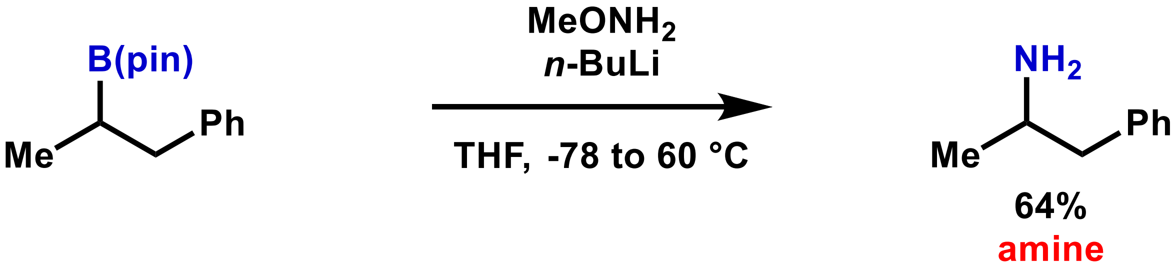
n-BuLi

THF, -78 °C to rt

81%

Kim, J.; Park. S.; Park, J.; Cho, S. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 1498.

- **transformation to amine**



$MeONH_2$

n-BuLi

THF, -78 to 60 °C

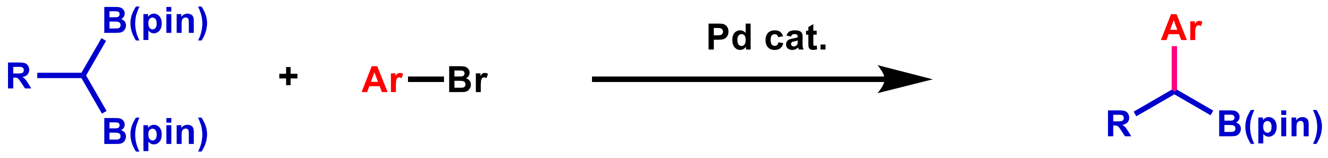
64%

amine

Hong, K.; Liu, X.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 10581.

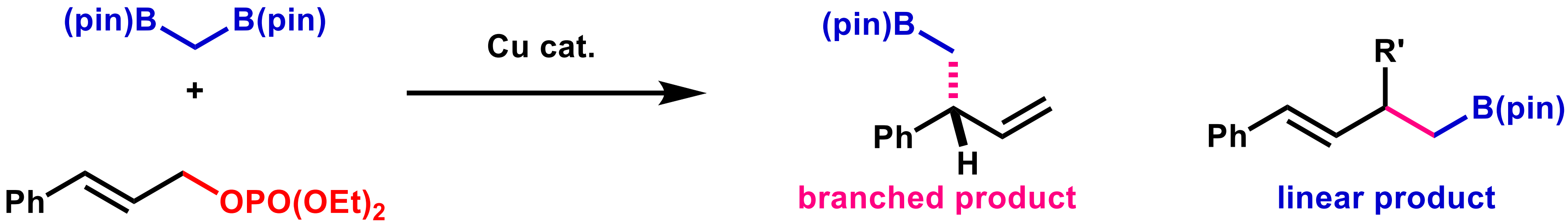
Today's contents

1. Suzuki-Miyaura coupling



2. Alkoxide-Promoted Deborylative Alkylation

3. Allylic substitution reaction



branched product
(S_N2')

linear product
(S_N2)

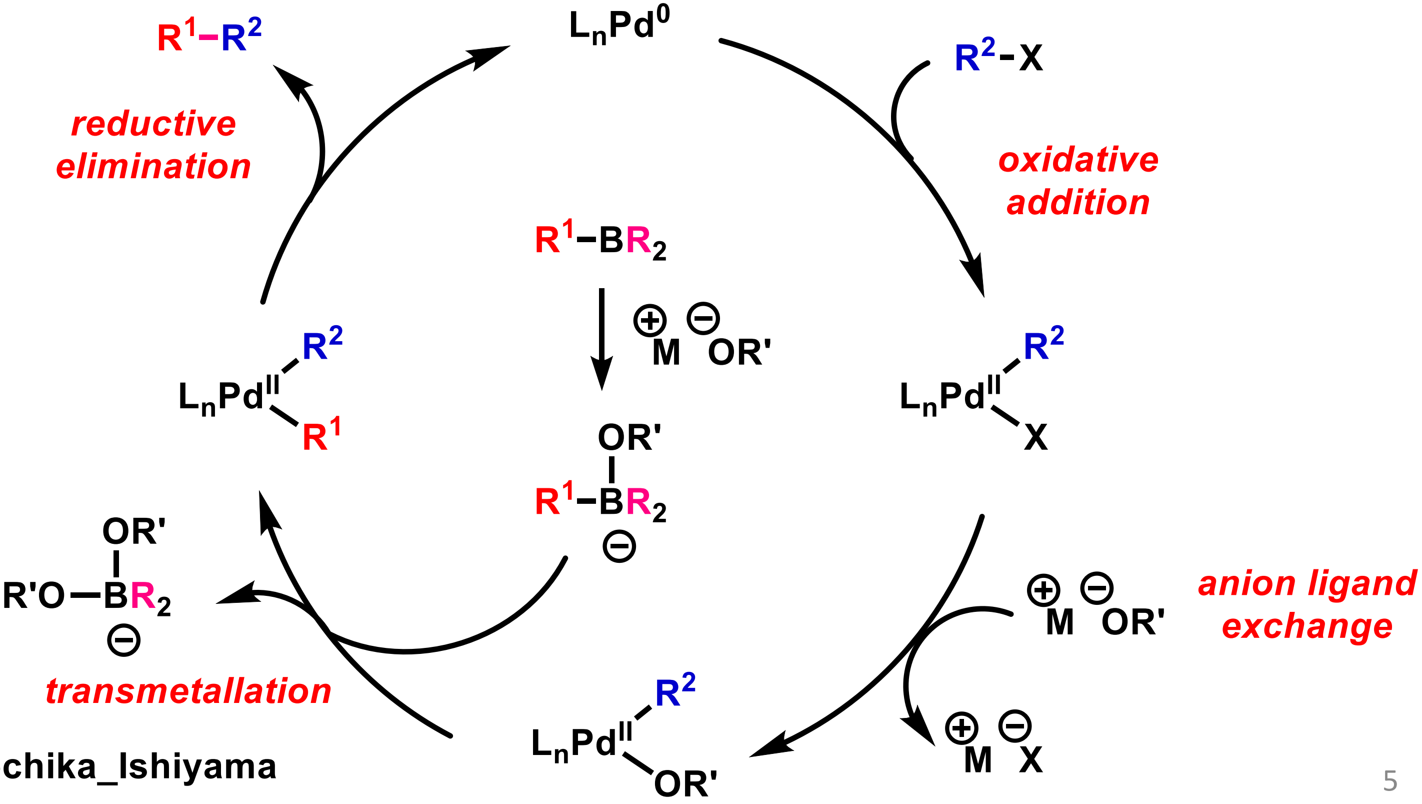
Suzuki-MIyaura Coupling

$$R^1{-}BR_2 \quad + \quad R^2{-}X \xrightarrow[\text{base, ligand}]{\text{Pd}^0\text{ (cat.)}} R^1{-}R^2$$

R^1 = alkyl, allyl, alkenyl
alkynyl, aryl
R = alkyl, OH, O-alkyl, …

R^2 = alkyl, allyl
alkenyl, aryl
X = I, Br, Cl, OTf…

- reaction mechanism



L_nPd^0

R^2-X

oxidative addition

$L_nPd^{II}(R^2)(X)$

$\oplus$ M $\ominus$ OR'

anion ligand exchange

$\oplus$ M $\ominus$ X

$L_nPd^{II}(R^2)(OR')$

R^1–BR_2

$\oplus$ M $\ominus$ OR'

R^1–$B(OR')R_2$ $\ominus$

$R'O$–$B(OR')R_2$ $\ominus$

transmetallation

$L_nPd^{II}(R^2)(R^1)$

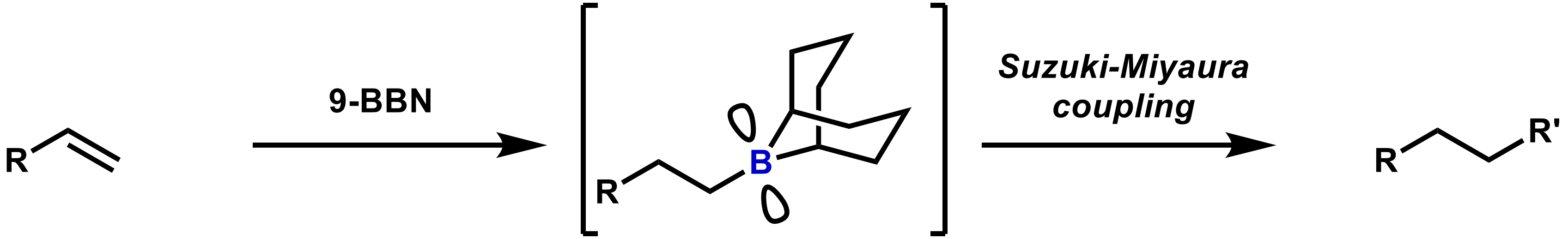
reductive elimination

R^1–R^2

see LS_Tomochika_Ishiyama
(2010/06/26)

Borane Species Reactive for Suzuki-Miyaura Coupling

- **organoborane**



organoborane

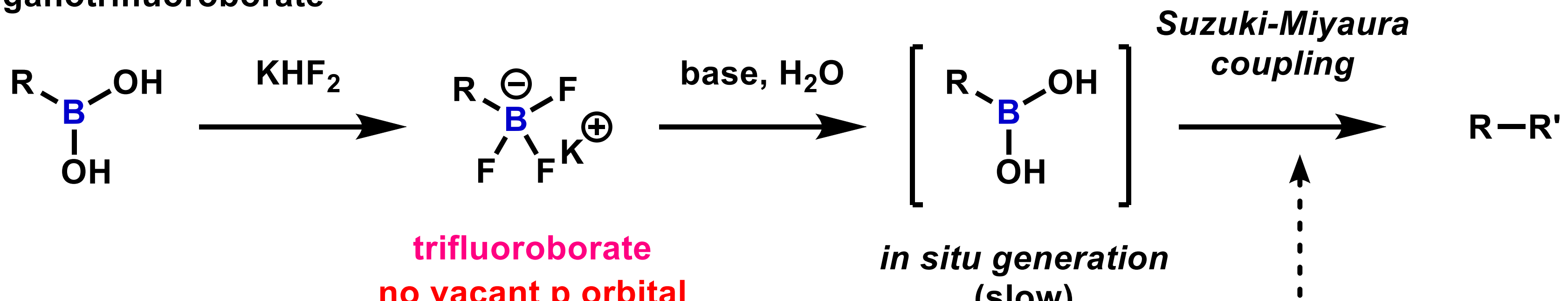
in situ preparation

vacant p orbital

↓

more reactive to oxidants, nucleophile, base

- **organotrifluoroborate**



trifluoroborate

no vacant p orbital

↓

less reactive to oxidants, nucleophile

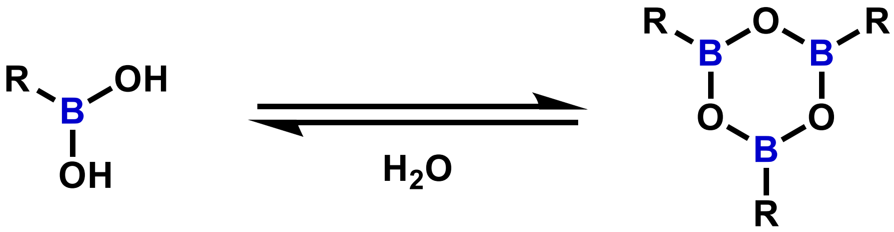
in situ generation

(slow)

alkyl (secondary) trifluoroborate is less ractive

Boronic Acids

- **Easy dehydration**

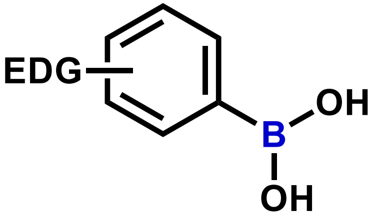


boronic acid **boroxin**

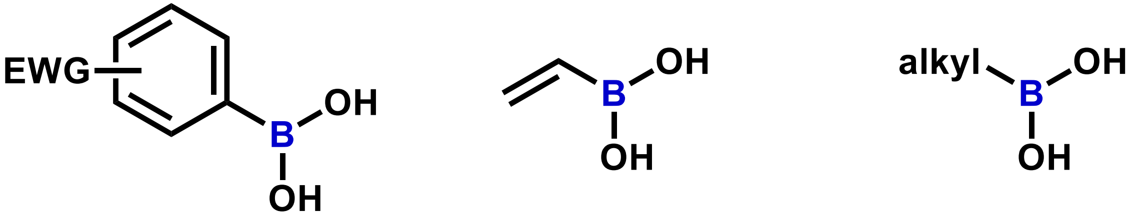
- **difficult to control the equivalent**
- **difficult purification**
- **more reactive for Suzuki-Miyaura coupling**

- **Stability**

more stable

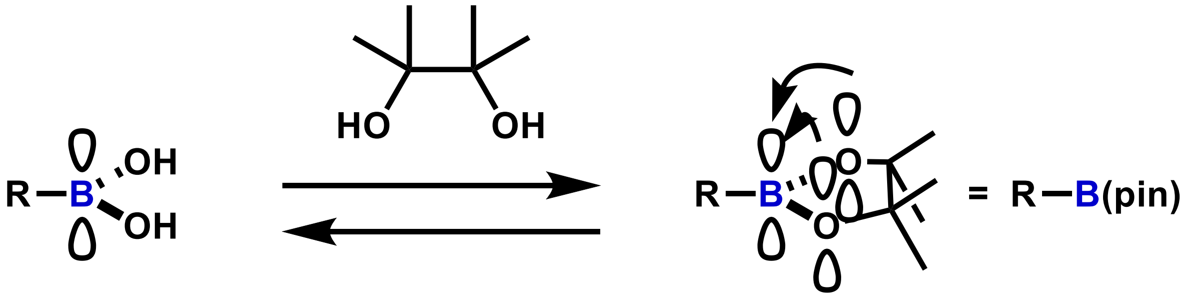


less stable



Protected Boronic Ester

- **boronic ester**



boronic acid

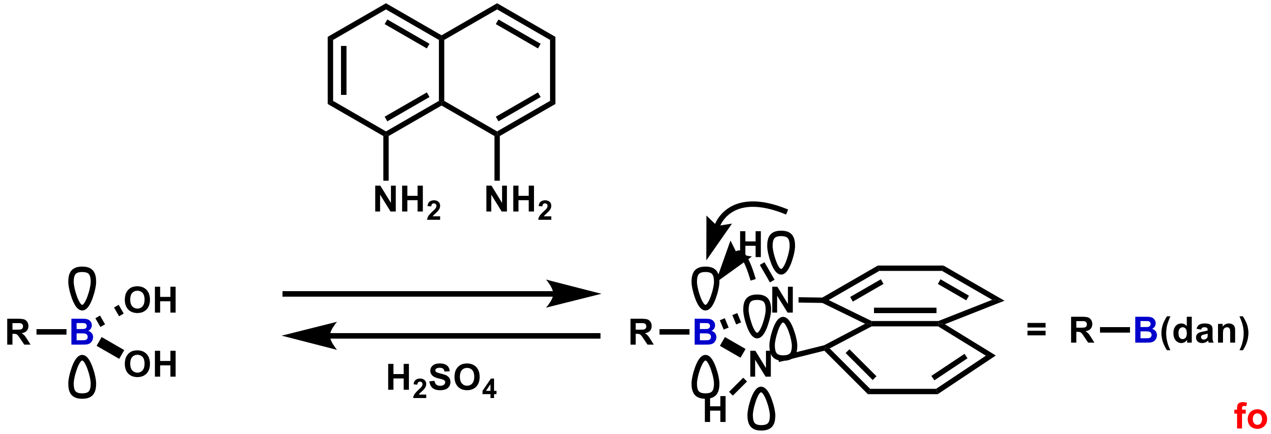
bronic ester

reduced Lewis acidity

↓

less reactive
for Suzuki-MIyaura coupling

- **1,8-naphthalenediaminatoborane**



boronic acid

1,8-naphthalenediaminatoborane

reduced Lewis acidity

↓

less reactive
for Suzuki-MIyaura coupling

(reactivity:RB(pin)>RB(dan))

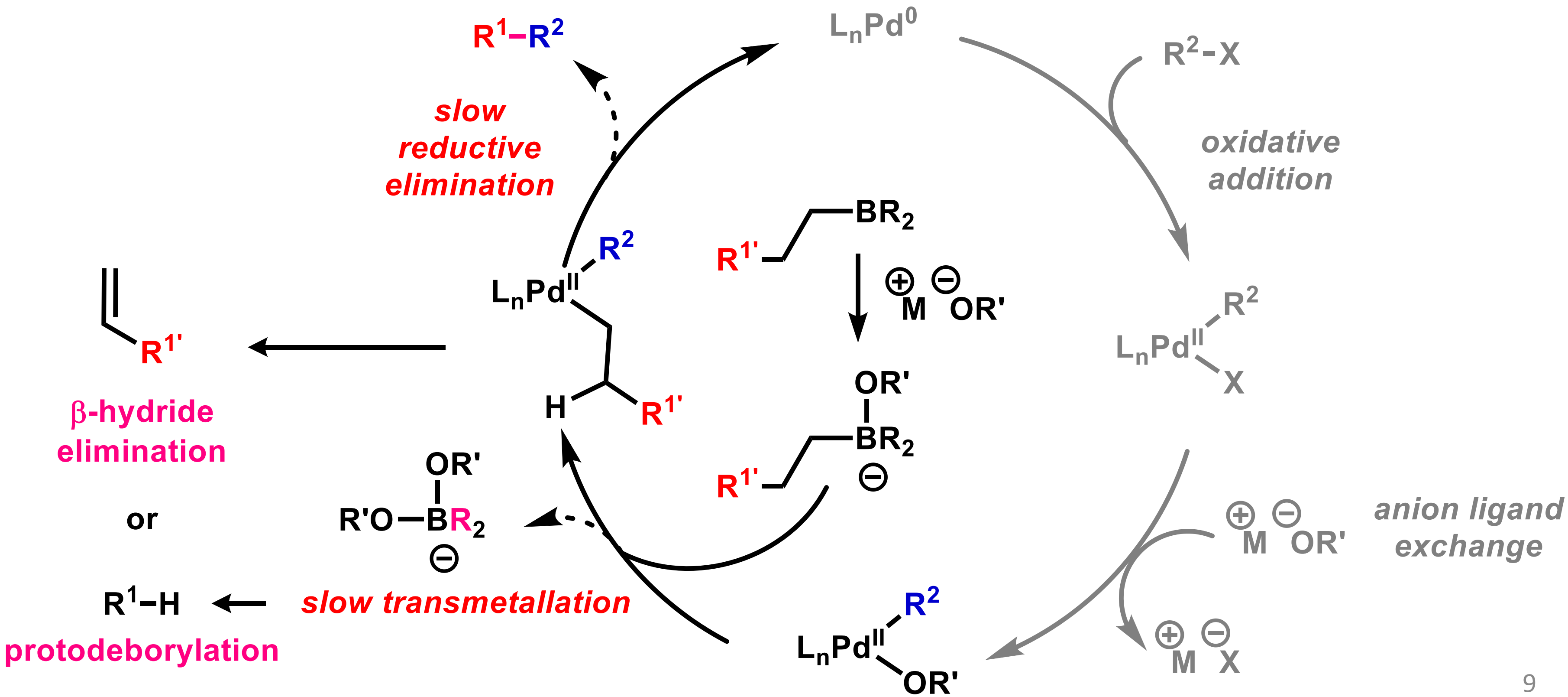
Problem of Suzuki-MIyaura Coupling on Sp^3-Carbon

$$R^1\text{–}BR_2 \quad + \quad R^2\text{–}X \xrightarrow[\text{base, ligand}]{Pd^0 \text{ (cat.)}} R^1\text{–}R^2$$

R^1 = alkyl, allyl, alkenyl
alkynyl, aryl
R = alkyl, OH, O-alkyl, …

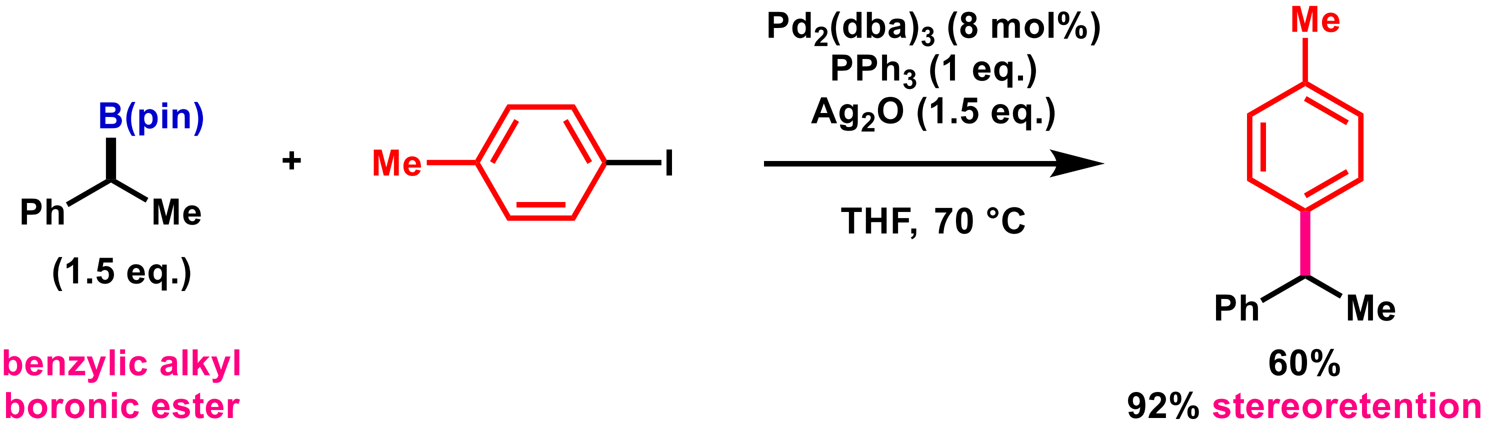
R^2 = alkyl, allyl
alkenyl, aryl
X = I, Br, Cl, OTf…

- reaction mechanism



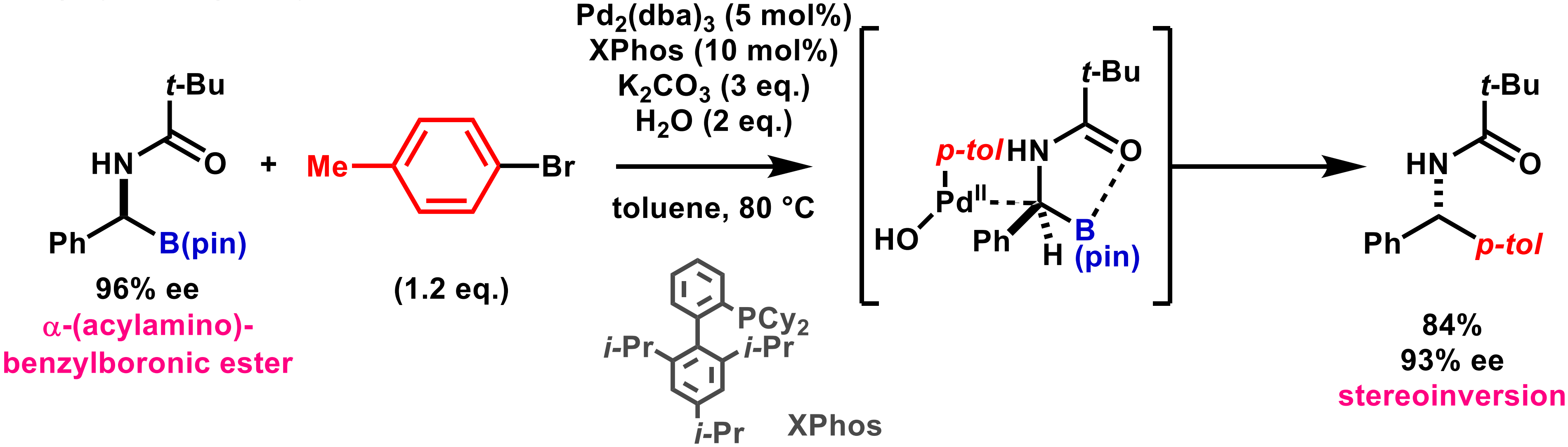
Successful Suzuki-MIyaura Coupling on Sp^3-Carbon with B(pin) Moiety

- **benzylic alkyl boronic ester**



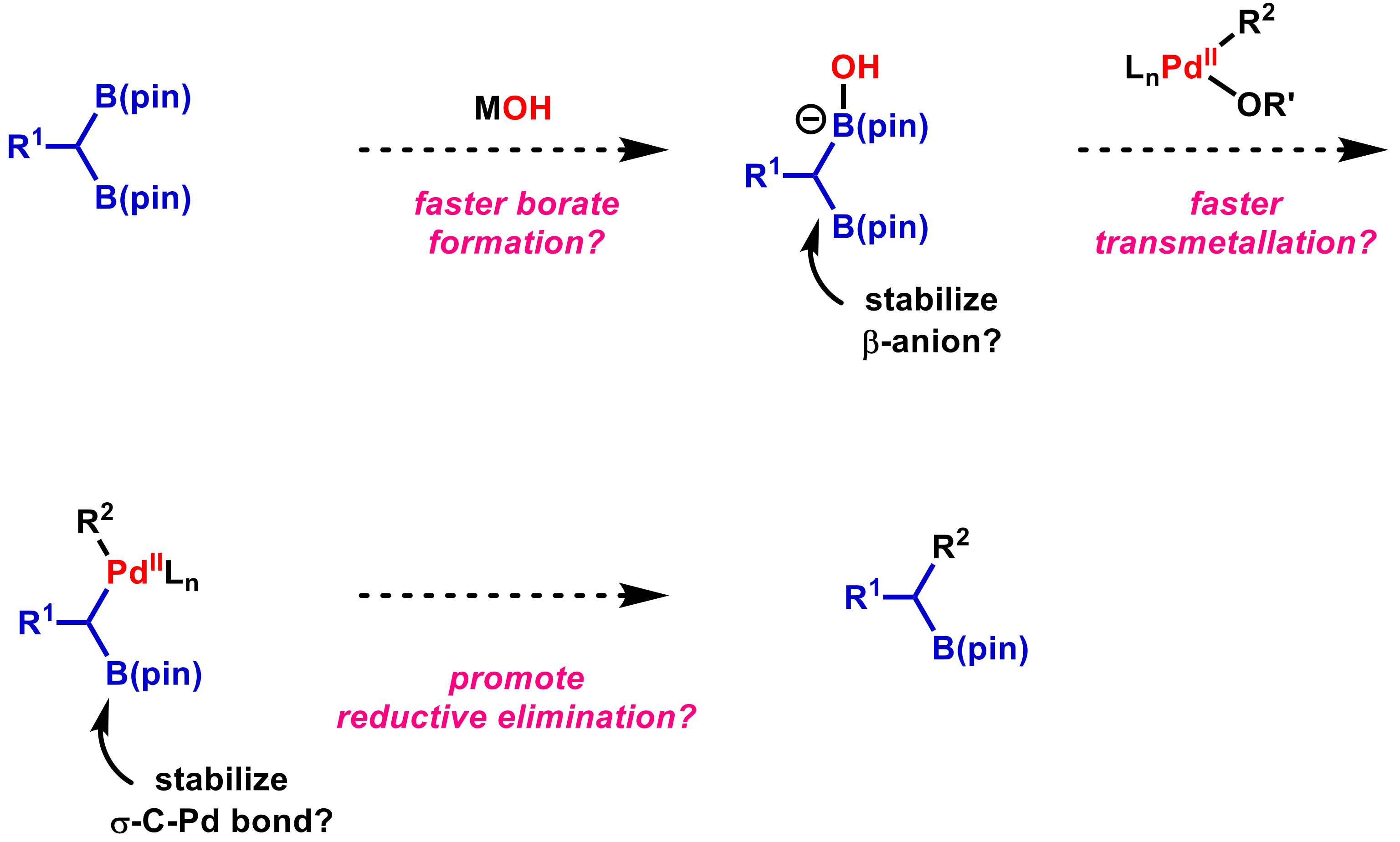
Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024.

- **α-(acylamino)benzylboronic ester**



Ohmura, T.; Awano, T.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 13191.

Working Hypothesis for Suzuki-MIyaura Coupling of 1,1-Diborylalkanes



faster borate formation?

stabilize β-anion?

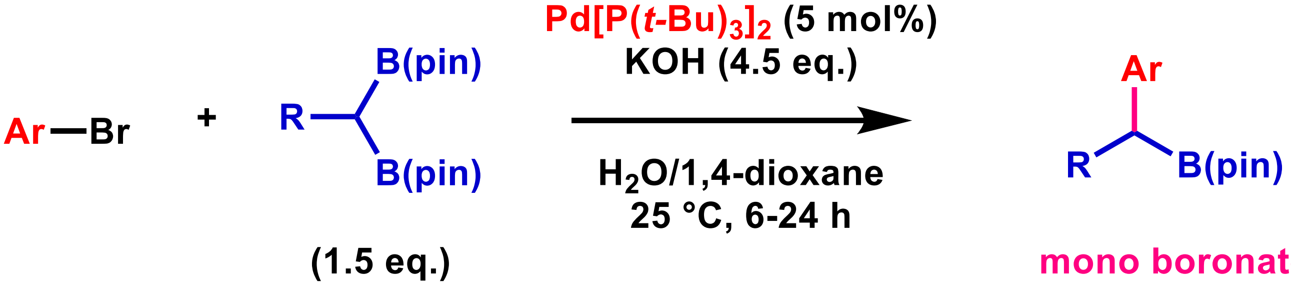
faster transmetallation?

stabilize σ-C-Pd bond?

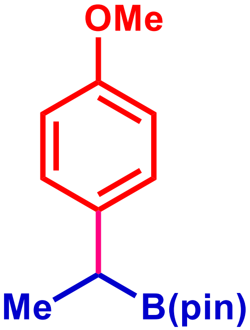
promote reductive elimination?

Endo, K.; Ohkubo, T.; Hirokami, M.; Shibata, T. *J. Am. Chem. Soc.* **2010**, *132*, 11033.

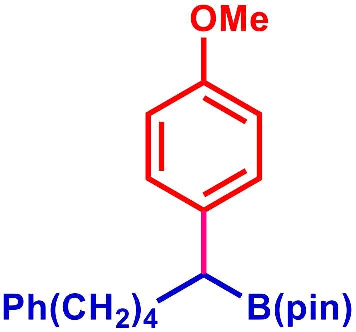
Suzuki-MIyaura Coupling of 1,1-Diborylalkanes



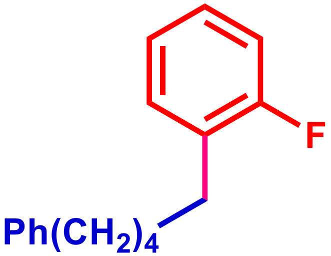
mono boronate
21 examples
55-98% (NMR yield)
42-95% (isolated yield)



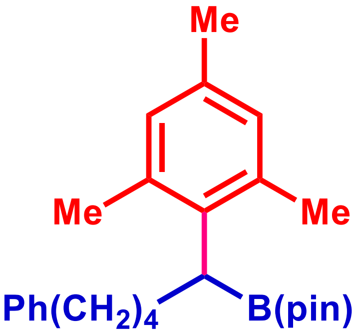
88% (NMR yield)
68% (isolated yield)



98% (NMR yield)
75% (isolated yield)



73% (isolated yield)

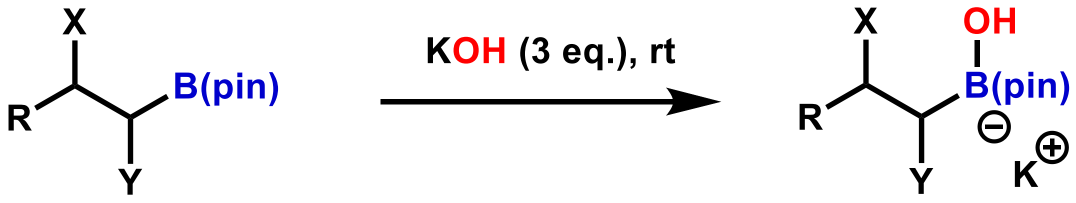


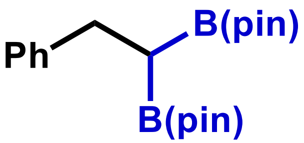
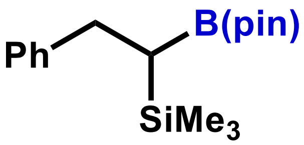
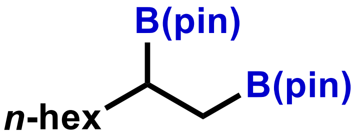
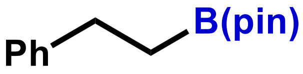
69% (isolated yield)

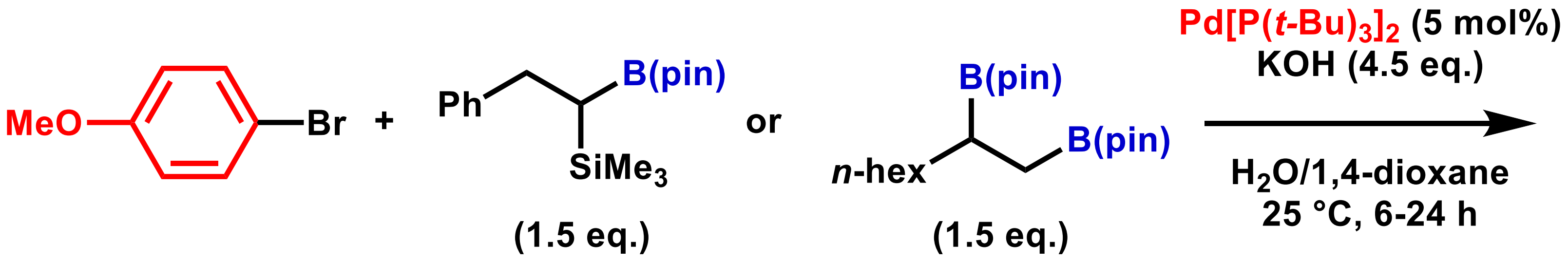
Endo, K.; Ohkubo, T.; Hirokami, M.; Shibata, T. *J. Am. Chem. Soc.* **2010**, *132*, 11033.

Generation of Borate Intermediate

- **confirmation of borate formation by ^{11}B NMR**



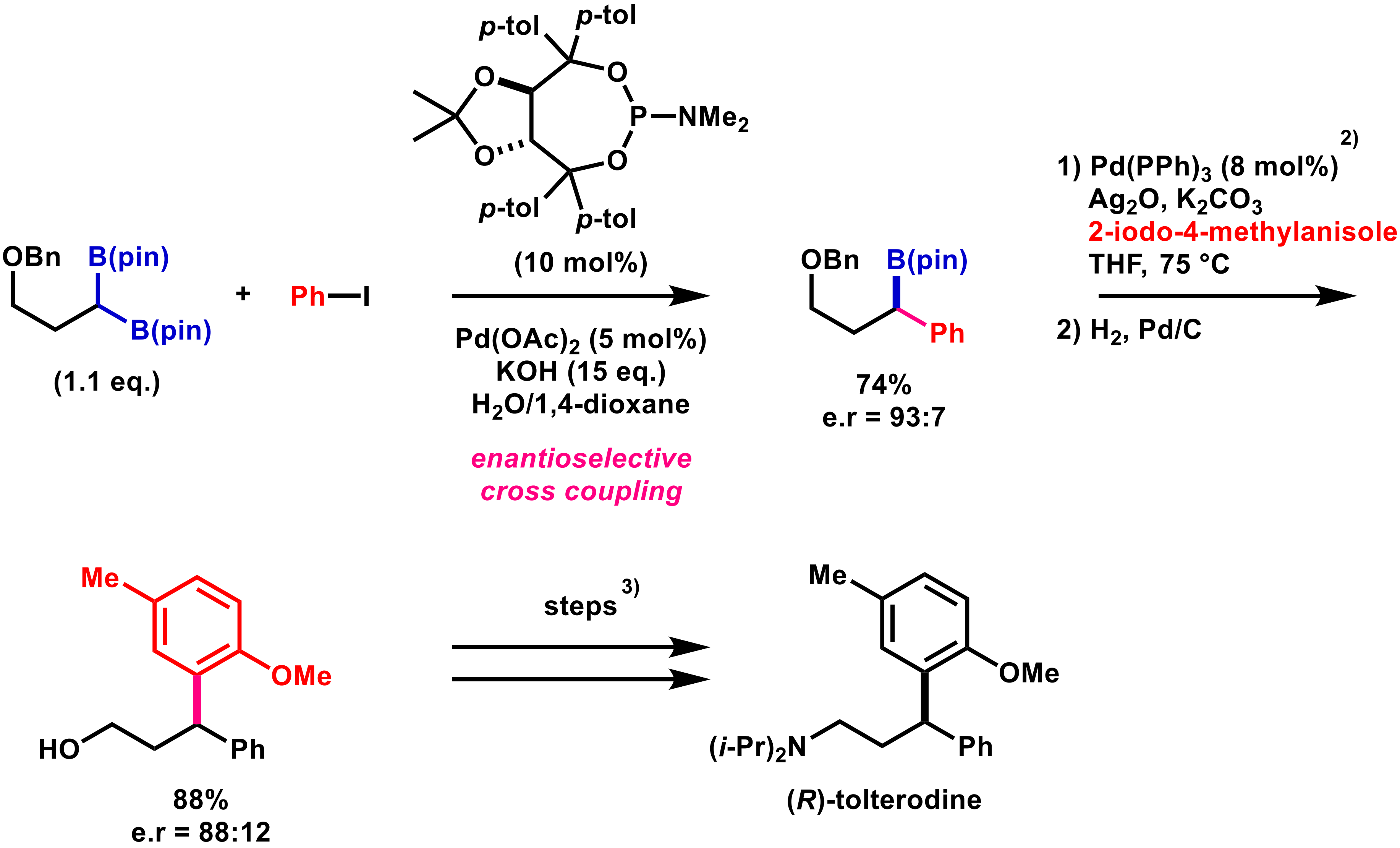
				
^{11}B NMR (δ, ppm)				
without KOH	**34.8**	**34.8**	**33.4**	**34.4**
with KOH	**35.5, -0.6 (1:1)**	**34.6**	**34.0, 10.5 (15:1)**	**34.4**
borate formation	**Yes**	**No**	**little**	**No**



no raection

Endo, K.; Ohkubo, T.; Hirokami, M.; Shibata, T. *J. Am. Chem. Soc.* **2010**, *132*, 11033.

Enantioselective Suzuki-MIyaura Coupling of 1,1-Diborylalkanes 1)



(1.1 eq.)

(10 mol%)

$Pd(OAc)_2$ (5 mol%)
KOH (15 eq.)
H_2O/1,4-dioxane

enantioselective cross coupling

74%
e.r = 93:7

1) $Pd(PPh)_3$ (8 mol%) 2)
Ag_2O, K_2CO_3
2-iodo-4-methylanisole
THF, 75 °C

2) H_2, Pd/C

steps 3)

88%
e.r = 88:12

(*R*)-tolterodine

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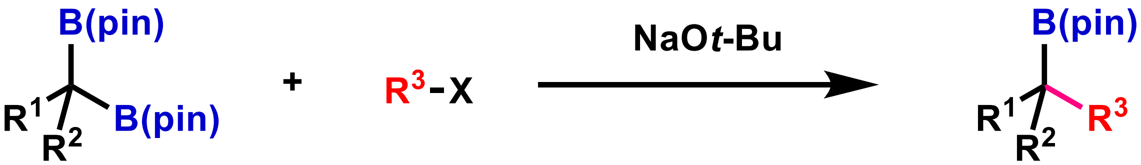
1) Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534. 2) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024. 3) Jonsson, N. A. et. al. U.S. Patent 5,382,600 A1, 1995.

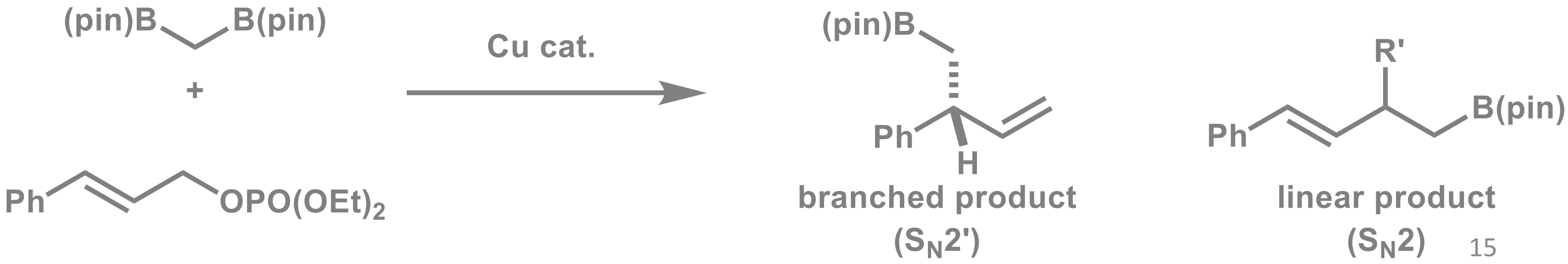
Today's contents

1. Suzuki-Miyaura coupling

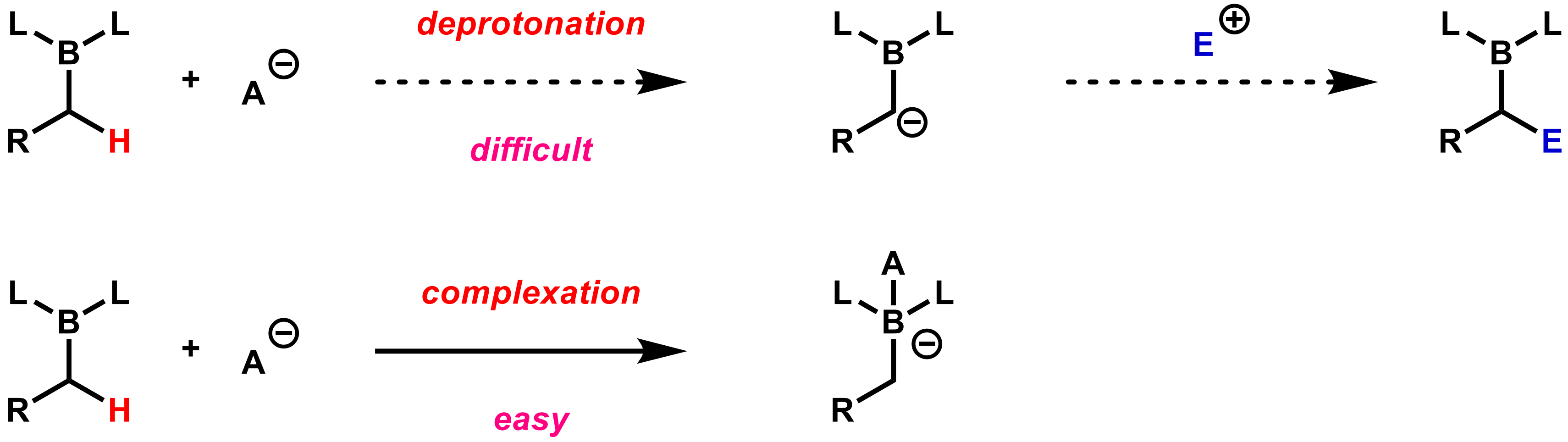
2. Alkoxide-Promoted Deborylative Alkylation

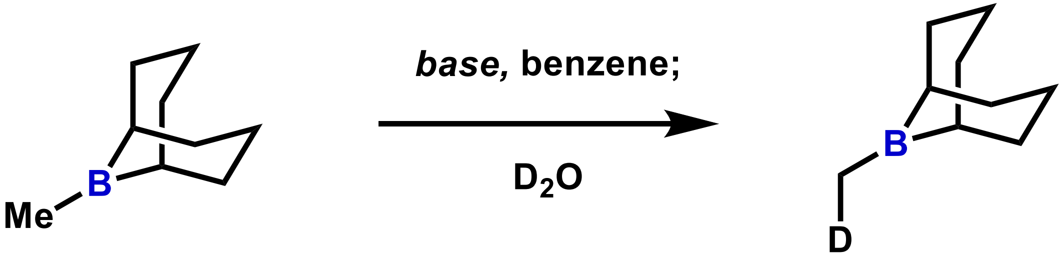


3. Allylic substitution reaction



Deprotonation vs Complexation

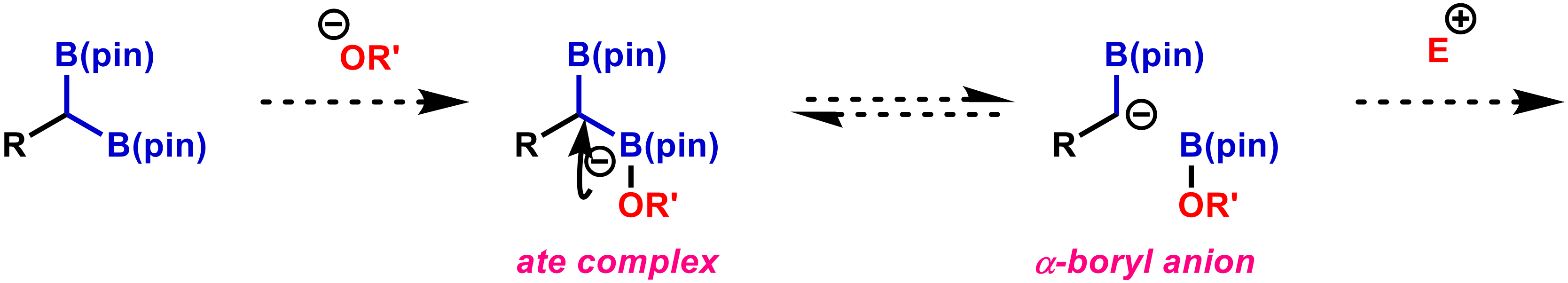


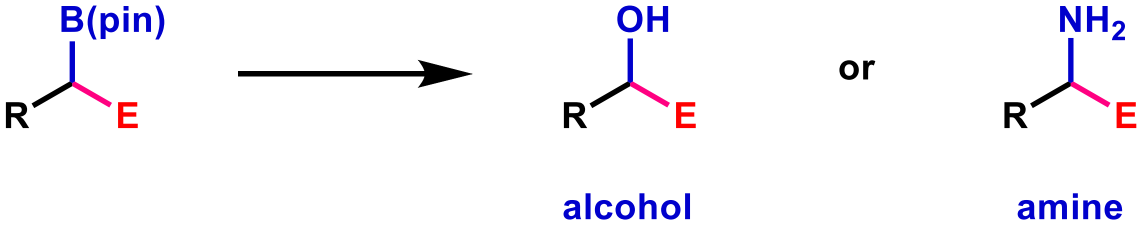


LDA	0%
LiTMP	50% (12 h)

Rathke, M. W.; Kow, R. *J. Am. Chem. Soc.* **1972**, *94*, 6854.

Working Hypothesis of the Generation of α-Boryl Carbanion

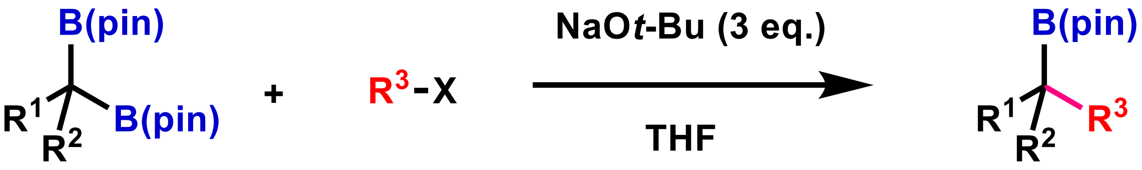


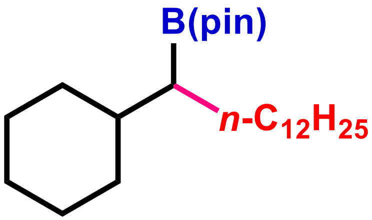


umploung construction

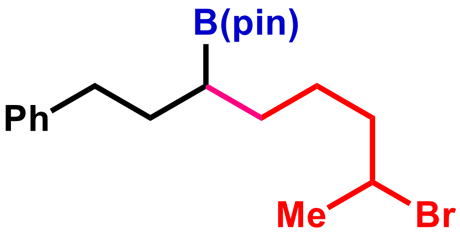
Hong, K.; Liu, X.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 10581.

Alkoxide-Promoted Deborylative Alkylation



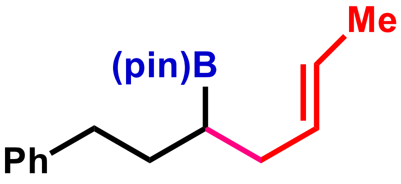


87%
X = Br
(40 °C, 14 h)



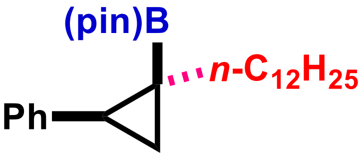
84%
X = Br
(rt, 3 h)

only primary Br reacted



91%
X = Cl
(rt, 3 h)

S_N2 adduct

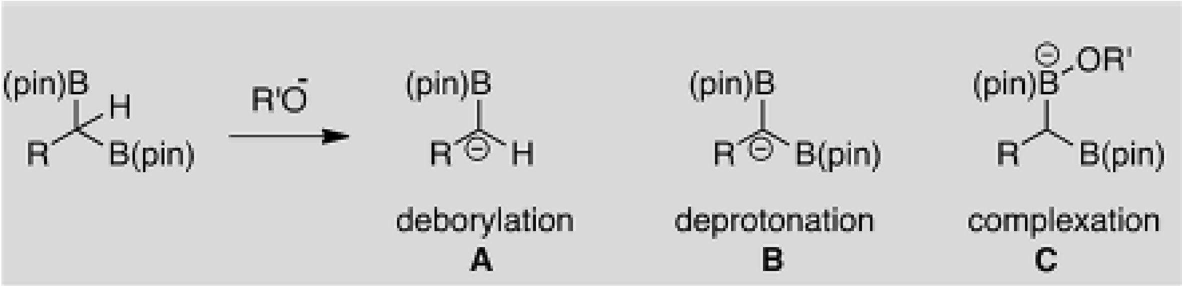


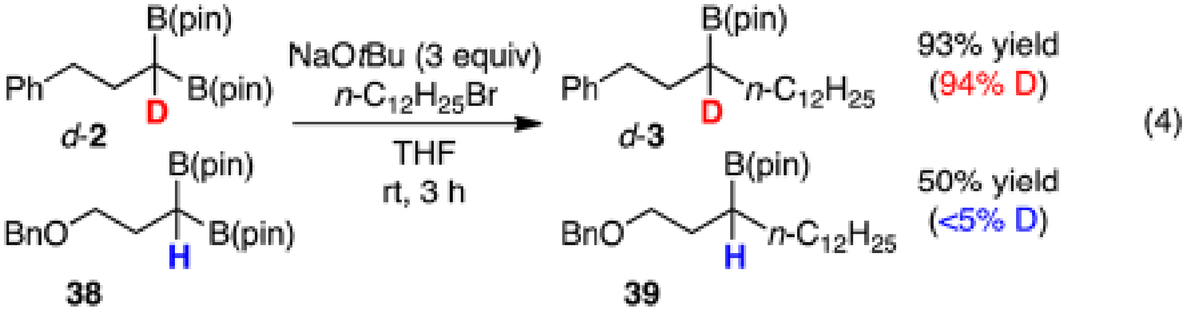
66%, d.r = >20:1
X = Br
(60 °C, 14 h)

quaternary carbon formation

Hong, K.; Liu, X.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 10581.

Mechanistic Study 1



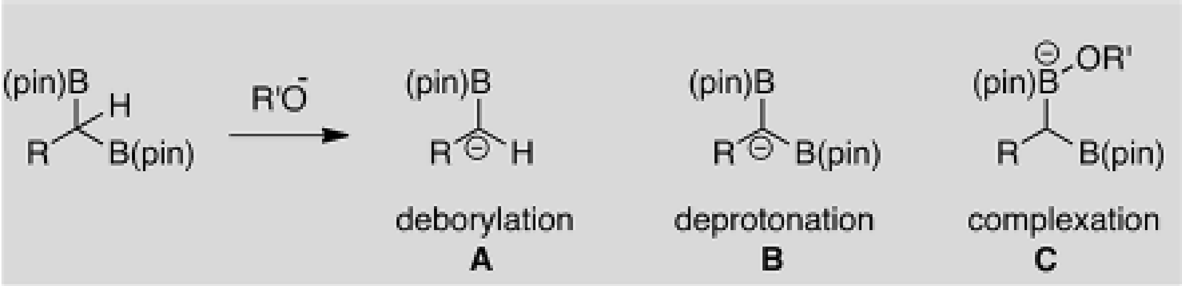


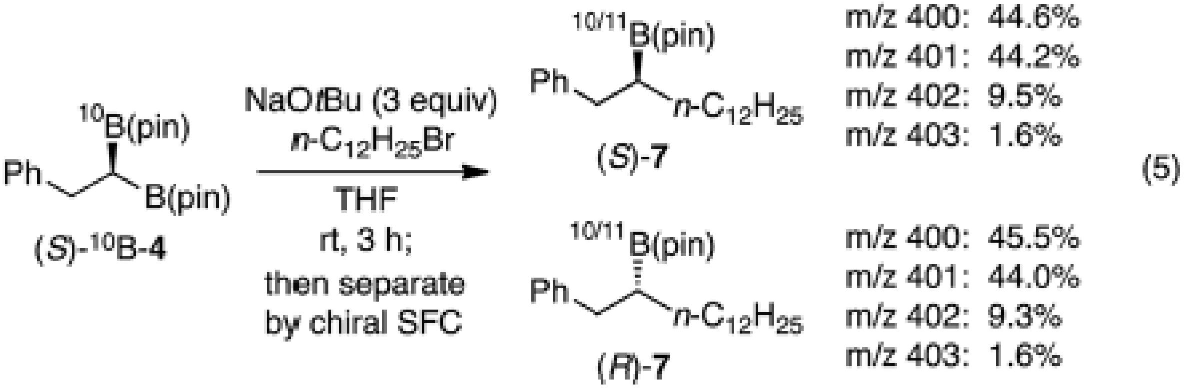
↓

not B

Hong, K.; Liu, X.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 10581.

Mechanistic Study 2





(S)-7:
m/z 400: 44.6%
m/z 401: 44.2%
m/z 402: 9.5%
m/z 403: 1.6%

(R)-7:
m/z 400: 45.5%
m/z 401: 44.0%
m/z 402: 9.3%
m/z 403: 1.6%

in Nature;
B^{10}:B^{11} = 20:81

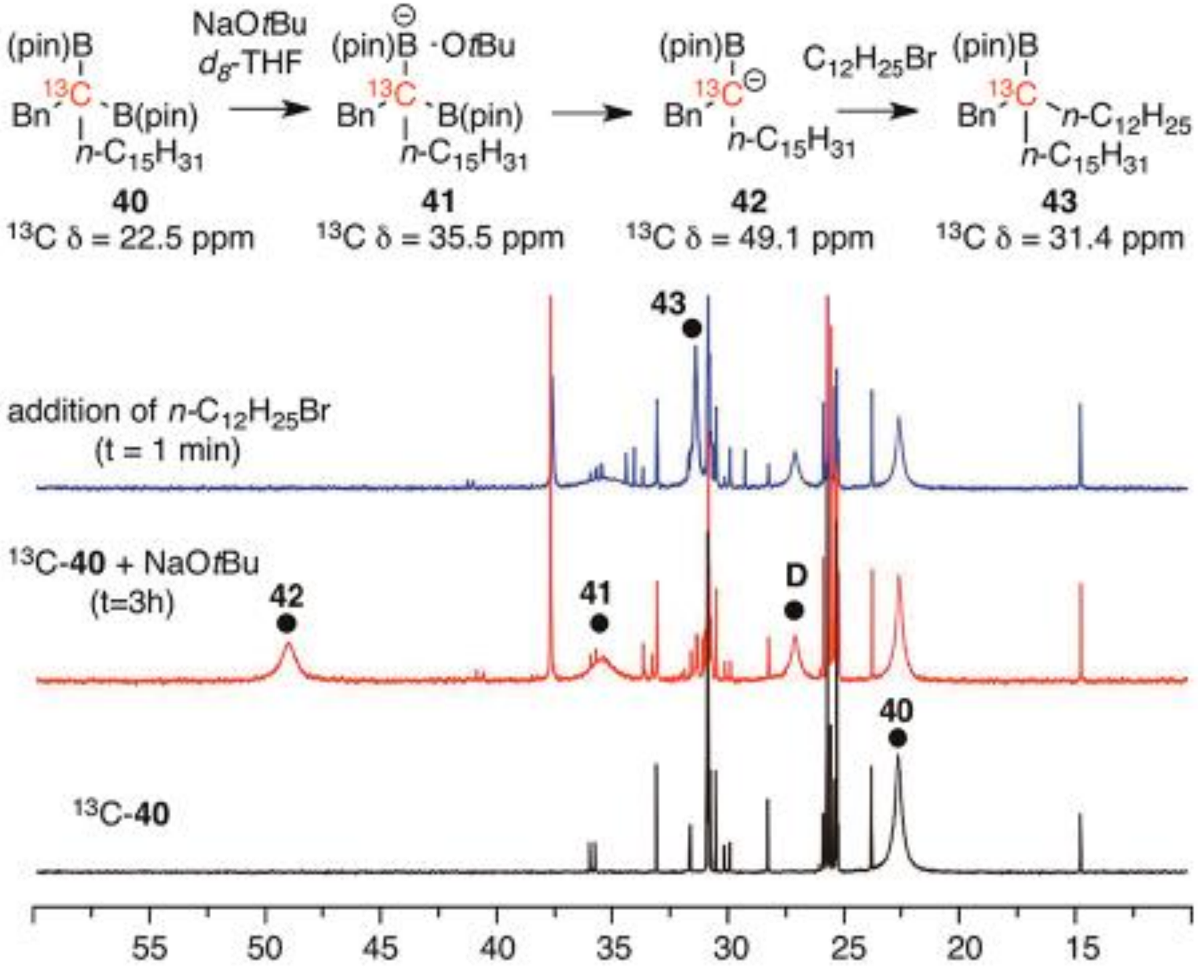
→ **If the reaction had proceeded via C in S_N2 fasgion,**
(*S*)-^{10}B-4 would give ^{10}B rich (*R*)-7 (m/z 400: major) and ^{11}B rich (*S*)-7 (m/z 401: major).

→ **not C** **A: the most plausible**

Hong, K.; Liu, X.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 10581.

^{13}C NMR Analysis

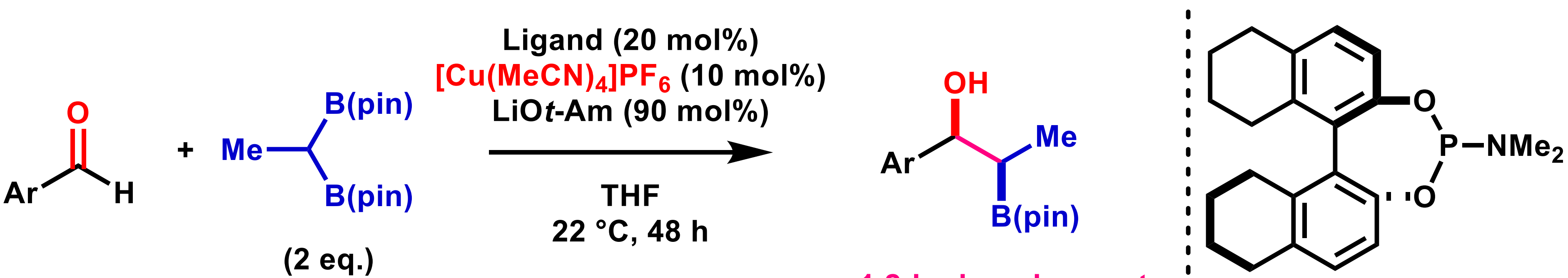
Scheme 5. ^{13}C-NMR Analysis of Deborylative Alkylation



Hong, K.; Liu, X.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 10581.

Enantioselective Addition to Aldehyde

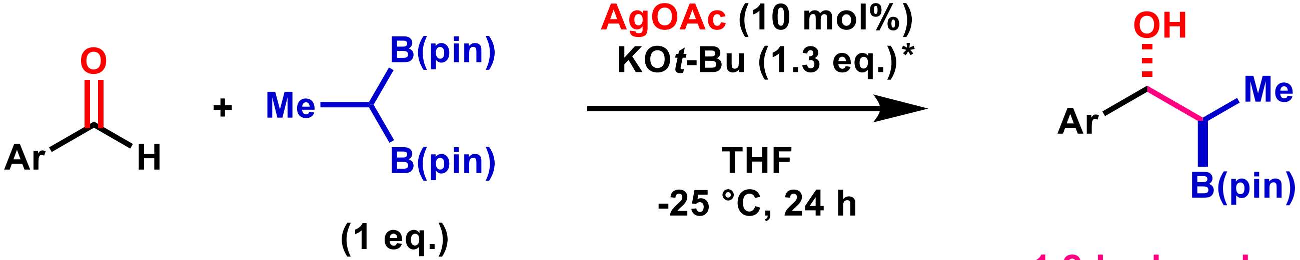
- **Cu catalyst (enantioselective)**



syn-1,2-hydroxyboronate
12 examples
34-91%
d.r = 83:17->99:1, e.r = 90:10-98:2

Joannou, M. V.; Moyer, B. S.; Meek, S. J. *J. Am. Chem. Soc.* **2015**, *137*, 6176.

- **Ag catalyst (racemic)**



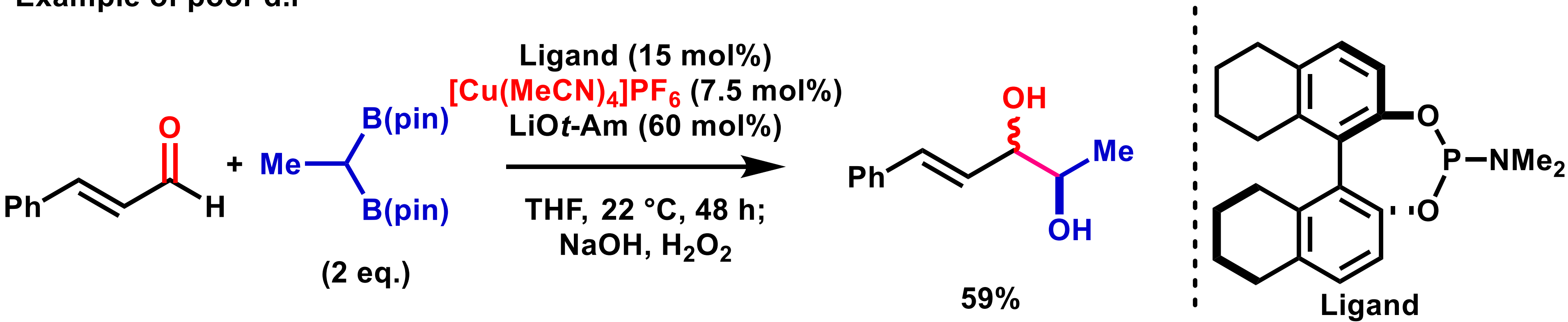
syn-1,2-hydroxyboronate
14 examples
40-77%
d.r = 86:14-99:1

*** *n*-BuLi (1.0 eq.) was effective in some cases instead of KO*t*-Bu.**

Joannou, M. V.; Moyer, B. S.; Goldfogel, M. J.; Meek, S. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 14141.

Consideration of Reaction Mechanism - Cu catalyst -

- **Example of poor d.r**



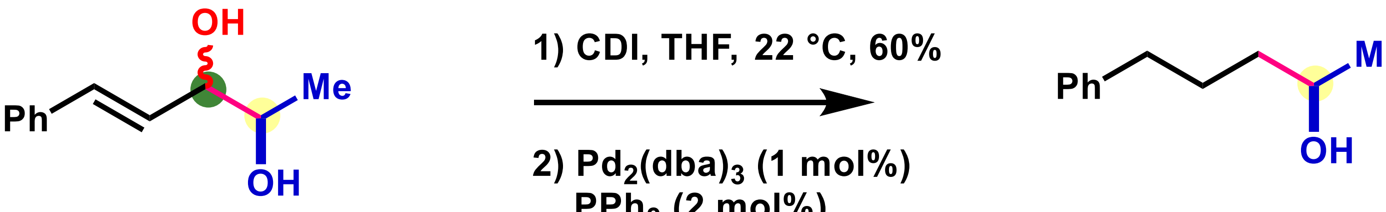
(2 eq.)

Ligand (15 mol%)
$[Cu(MeCN)_4]PF_6$ (7.5 mol%)
LiO*t*-Am (60 mol%)

THF, 22 °C, 48 h;
NaOH, H_2O_2

59%
***anti*:*syn* = 54:46**
e.r = 97:3 (*anti*), 92:8 (*syn*)

- **which stereocenter was controlled?**



***anti*:*syn* = 56:44**
e.r = 97:3 (*anti*), 90:10 (*syn*)

1) CDI, THF, 22 °C, 60%

2) $Pd_2(dba)_3$ (1 mol%)
PPh_3 (2 mol%)
Et_3N, HCO_2H
THF, 0 to 22 °C
3) H_2, Pd/C, MeOH, 22 °C
50% (2 steps)

e.r = 92:8 !

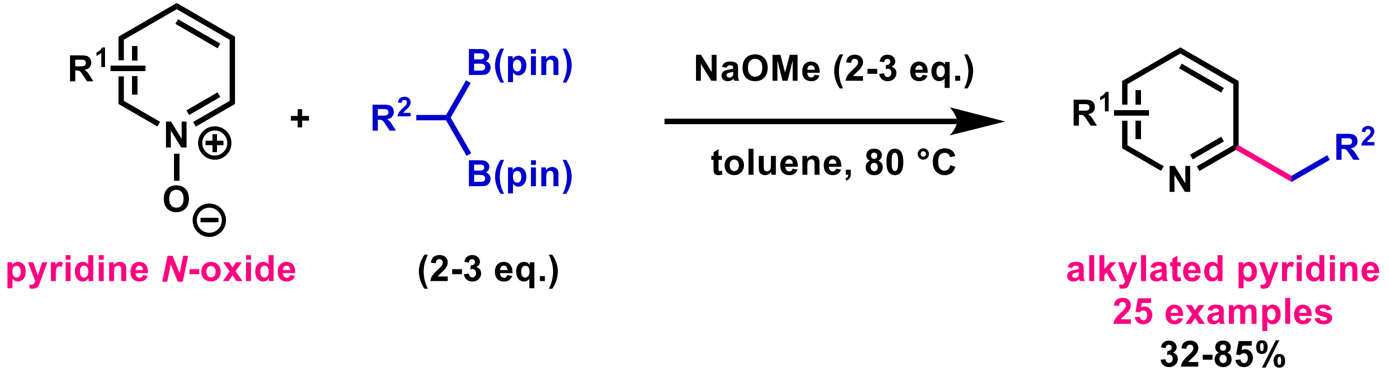
α-boryl nucleophile was formed with high enentioselectivity by chiral Cu complex

low diastereoselectivity was a result of poor facial discrimination of the C=O by Cu

Joannou, M. V.; Moyer, B. S.; Meek, S. J. *J. Am. Chem. Soc.* **2015**, *137*, 6176.

Alkylation of Pyridine N-Oxides

- **alkylation of pyrdine *N*-oxide**

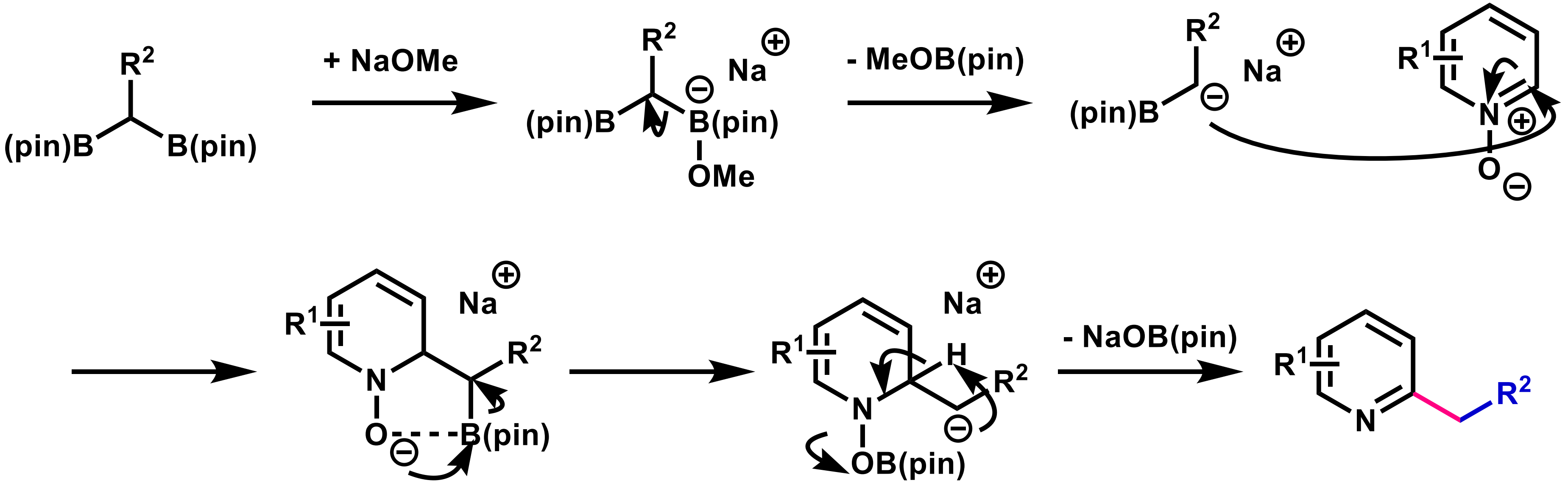


pyridine *N*-oxide

(2-3 eq.)

alkylated pyridine
25 examples
32-85%

- **proposed mechanism**



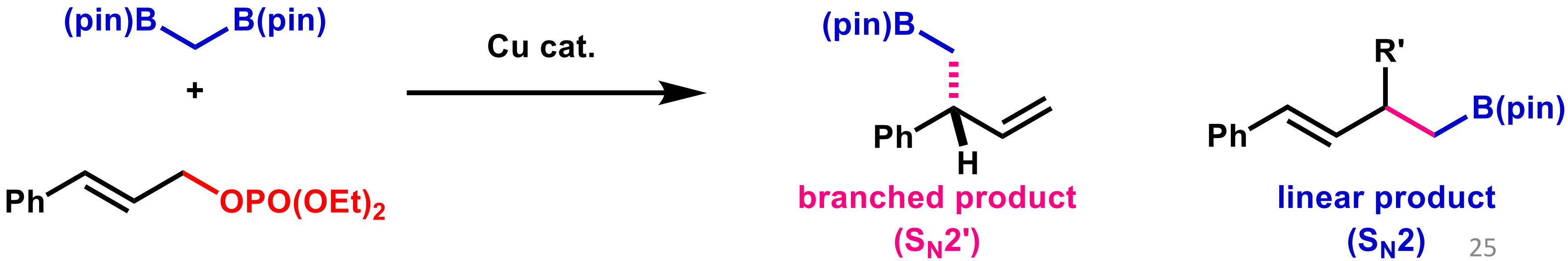
Jo, W.; Kim, J.; Choi, S.; Cho, S. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 6960.

Today's contents

1. Suzuki-Miyaura coupling

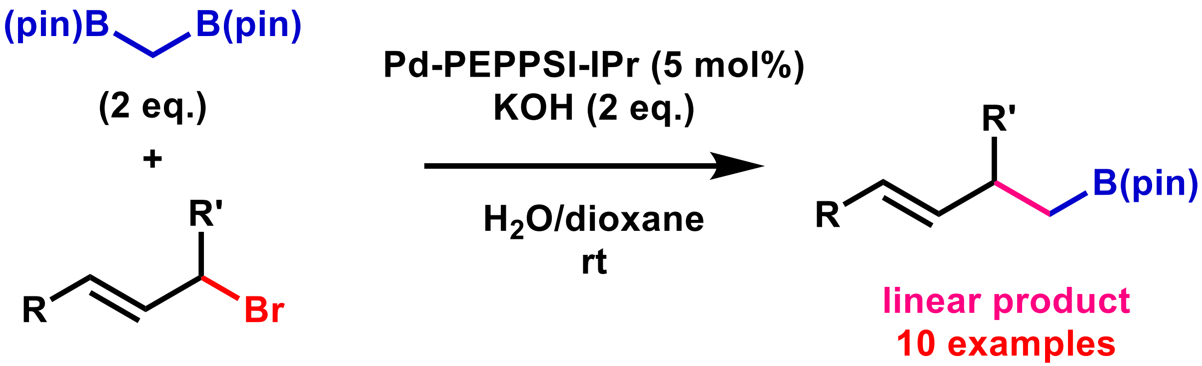
2. Alkoxide-Promoted Deborylative Alkylation

3. Allylic substitution reaction



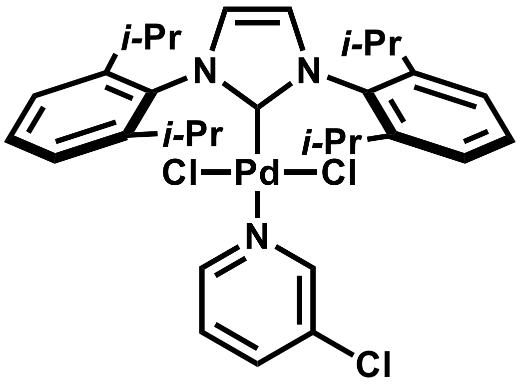
Cross Coupling - Allylic Nucleophile, S_N2 type -

- **Pd catalyst**



Pd-PEPPSI-IPr (5 mol%)
KOH (2 eq.)
H_2O/dioxane
rt

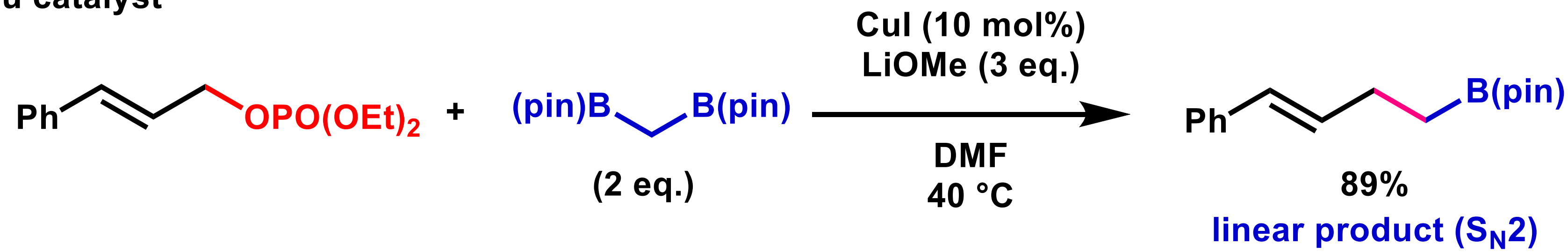
linear product
10 examples



Pd-PEPPSI-IPr

Endo, K.; Ohkubo, T.; Ishioka, T.; Shibata, T. *J. Org. Chem.* **2012**, *77*, 4826.

- **Cu catalyst**



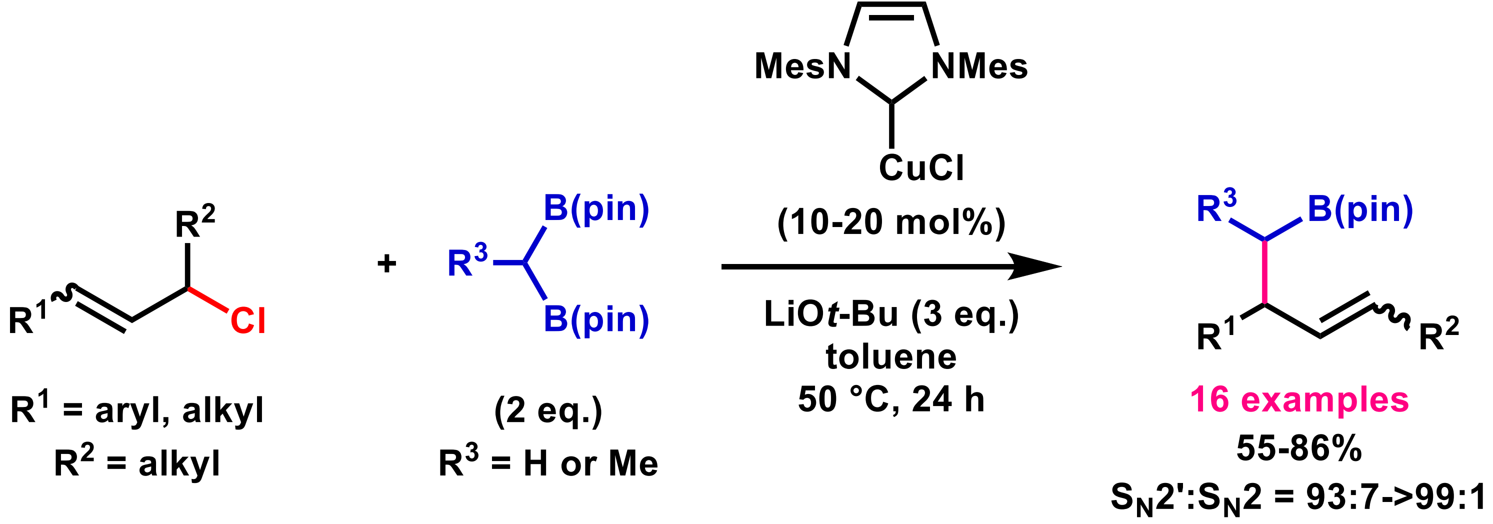
CuI (10 mol%)
LiOMe (3 eq.)
DMF
40 °C

89%
linear product (S_N2)

Zhang, Z.-Q.; Yang, C.-T.; Liang, L.-J.; Xiao, B.; Lu, X.; Liu, J.-H.; Sun, H.-H.; Marder, T. B.; Fu, Y.
Org. Lett. **2014**, *16*, 6342.

Cu-Catalyzed S_N2'-Selective Substitution

- **non-chiral ligand**



(10-20 mol%)

LiO*t*-Bu (3 eq.)
toluene
50 °C, 24 h

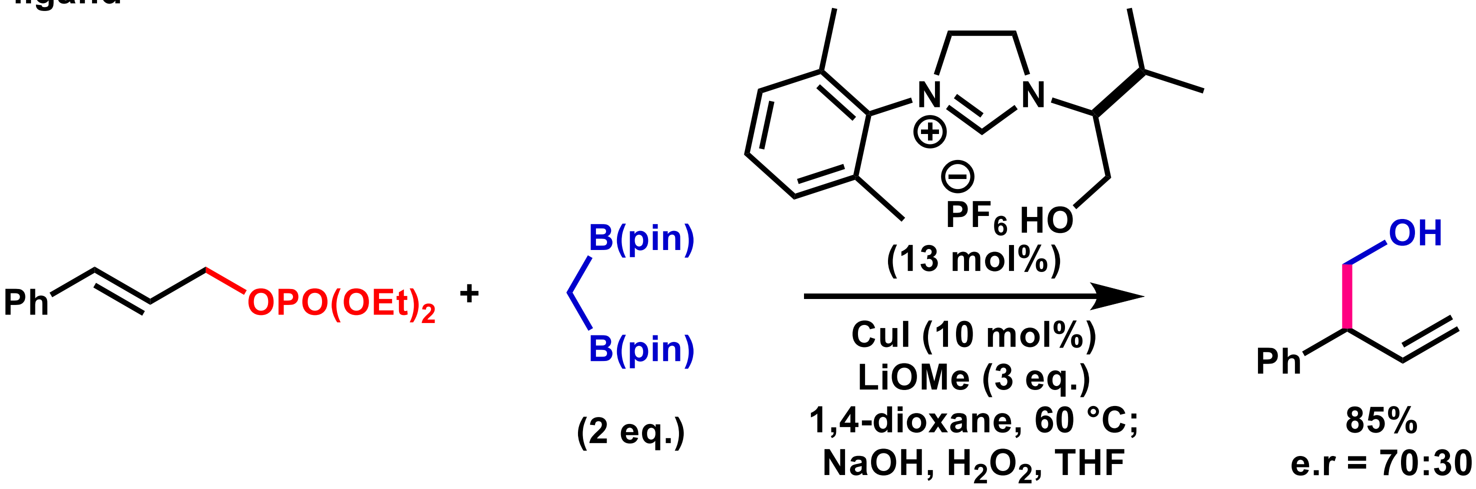
R^1 = aryl, alkyl
R^2 = alkyl

(2 eq.)
R^3 = H or Me

16 examples
55-86%
S_N2':S_N2 = 93:7->99:1

Kim, J.; Park. S.; Park, J.; Cho, S. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 1498.

- **chiral ligand**



(13 mol%)

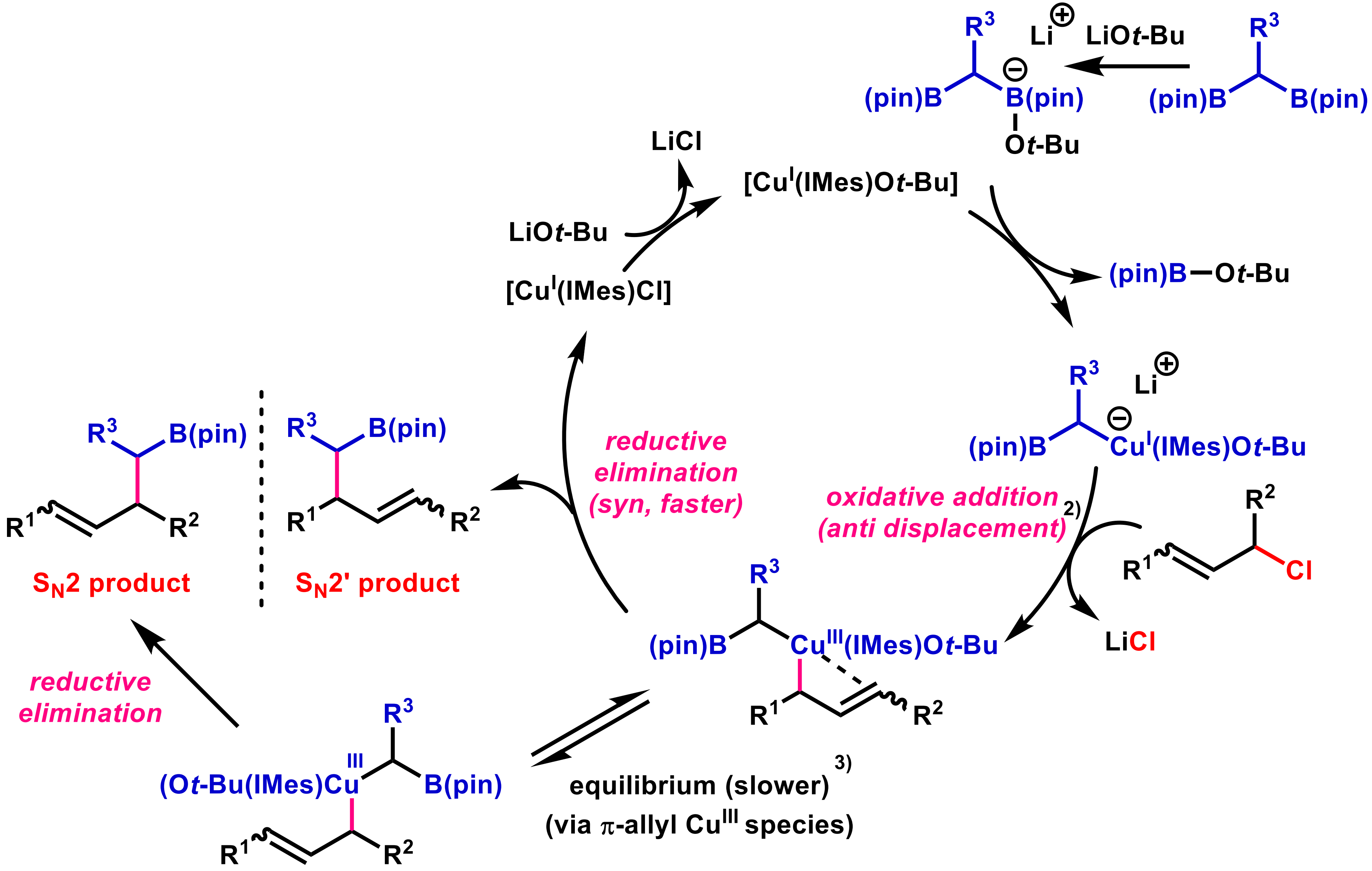
CuI (10 mol%)
LiOMe (3 eq.)
1,4-dioxane, 60 °C;
NaOH, H_2O_2, THF

(2 eq.)

85%
e.r = 70:30

Zhang, Z-Q.; Zhang, B.; Lu, X.; Liu, J.-H.; Lu, X.-Y.; Xiao, B.; Fu, Y. *Org. Lett.* **2016**, *18*, 952.

Plausible Reaction Mechanism



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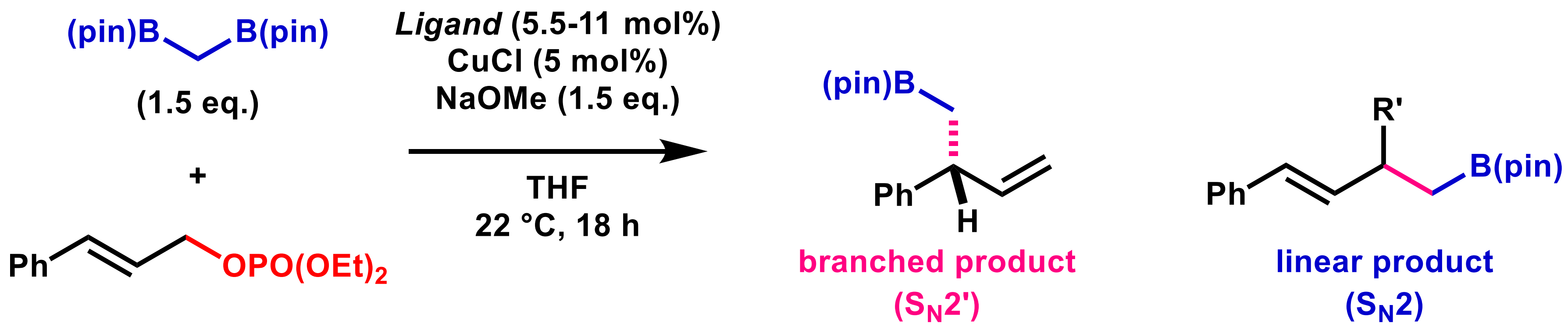
1) Kim, J.; Park. S.; Park, J.; Cho, S. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 1498. 2) Takeda, M.; Takatsu, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2014**, *79*, 2354. 3) Yasuda, Y.; Ohmiya, H.; Sawamura, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 10816.

Optimization of Ligand



Ligand (5.5-11 mol%)
CuCl (5 mol%)
NaOMe (1.5 eq.)

THF
22 °C, 18 h

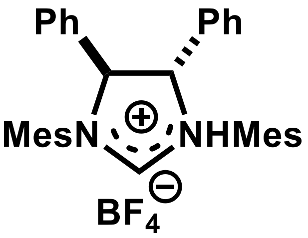
branched product
(S_N2')

linear product
(S_N2)

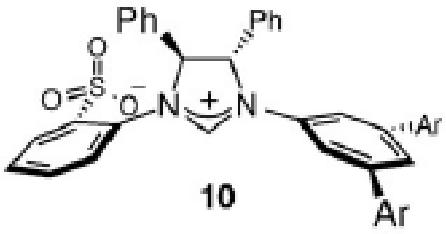
---

none

21%
$S_N2':S_N2$ = <2:>98



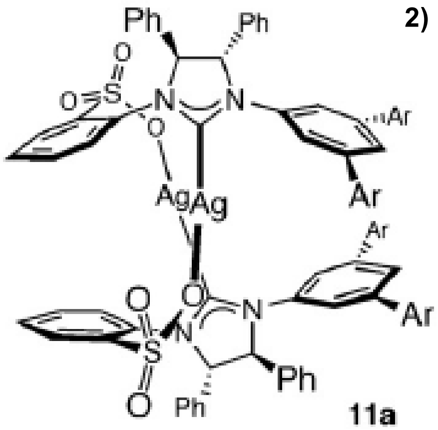
54%
$S_N2':S_N2$ = 20:80



10

77%
$S_N2':S_N2$ = 76:24
e.r = 97:3
(Ar = 2,4,6-(i-Pr)$_3C_6H_2$)
(slower regand exchange)

2)



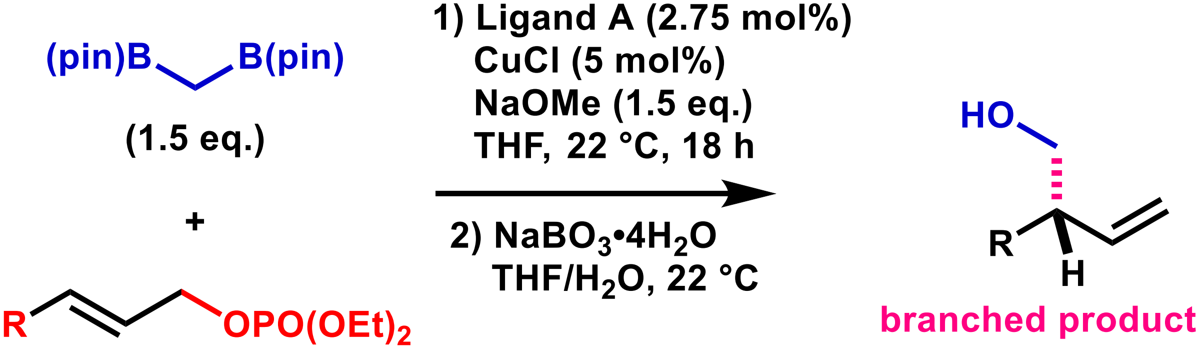
11a

83%
$S_N2':S_N2$ = 95:5
e.r = 97:3
(Ar = 2,4,6-(i-Pr)$_3C_6H_2$)
(faster regand exchange)

---

1) Shi, Y.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 3455.
2) May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2008**, *47*, 7358.

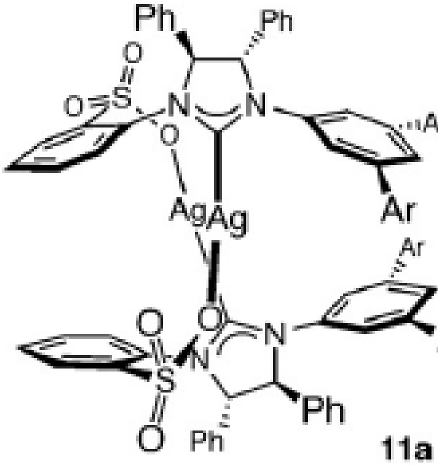
Substrate Scope



1) Ligand A (2.75 mol%)
CuCl (5 mol%)
NaOMe (1.5 eq.)
THF, 22 °C, 18 h

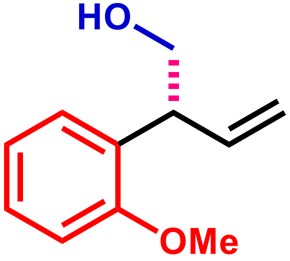
2) $NaBO_3 \cdot 4H_2O$
THF/H_2O, 22 °C

branched product
(S_N2')
15 examples

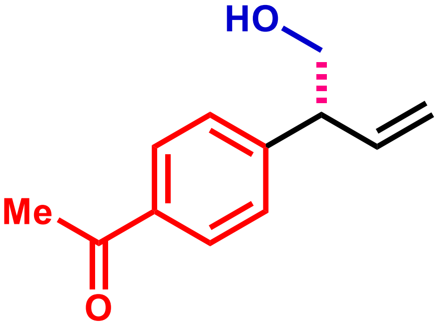


11a

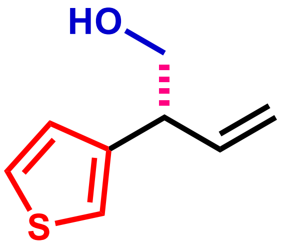
Ligand A (Ar = 2,4,6-(i-Pr)$_3C_6H_2$)



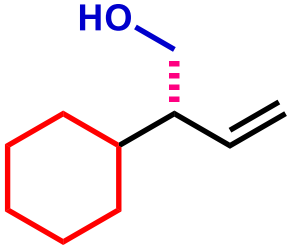
71%
S_N2':S_N2 = 94:6
99:1 e.r.



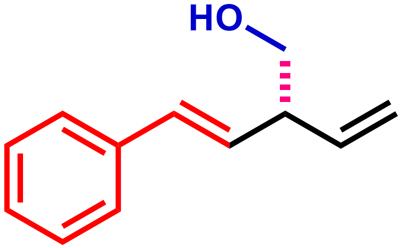
78%
S_N2':S_N2 = 92:8
97:3 e.r.



75%
S_N2':S_N2 = 93:7
94:6 e.r.



63%
S_N2':S_N2 = >98:2
96:4 e.r.

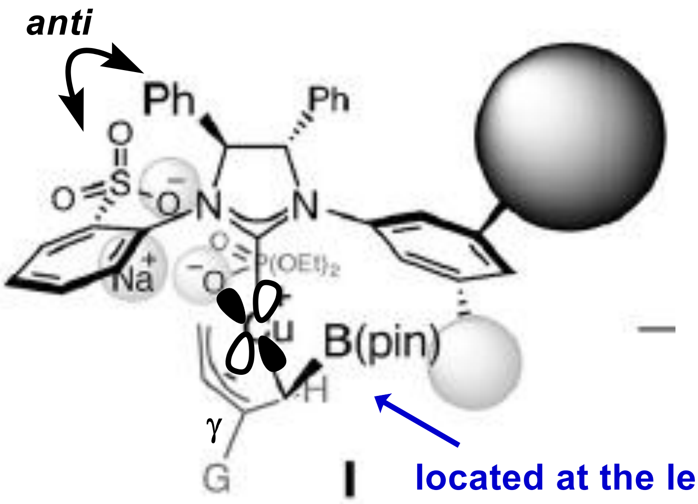


71%
S_N2':S_N2 = 88:12
85:15 e.r.

Shi, Y.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 3455.

Explanation of S_N2' Selectivity of Allylic Substitution of Diborylmethane Reagent

- **Mechanistic model**

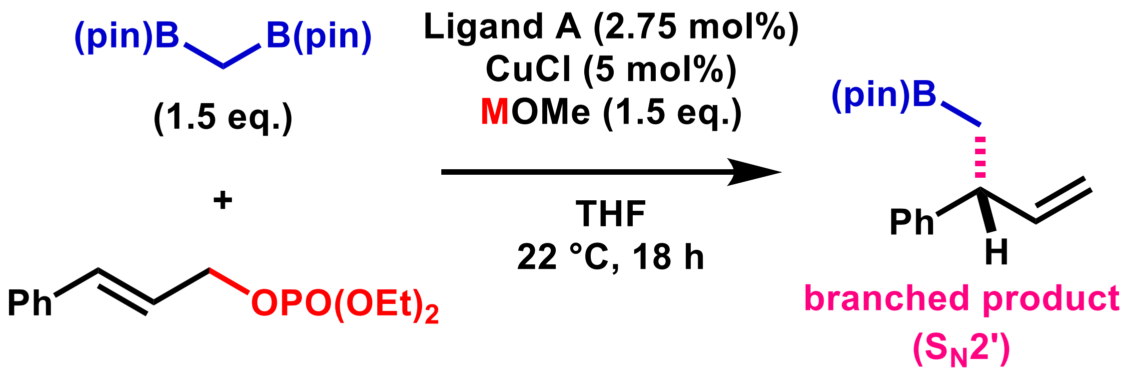


I

located at the least hindered coordination site

propargyl group and γ position are syn
&
good orbital match
↓
$S_N2' >> S_N2$

- **Effect of cationic metal**



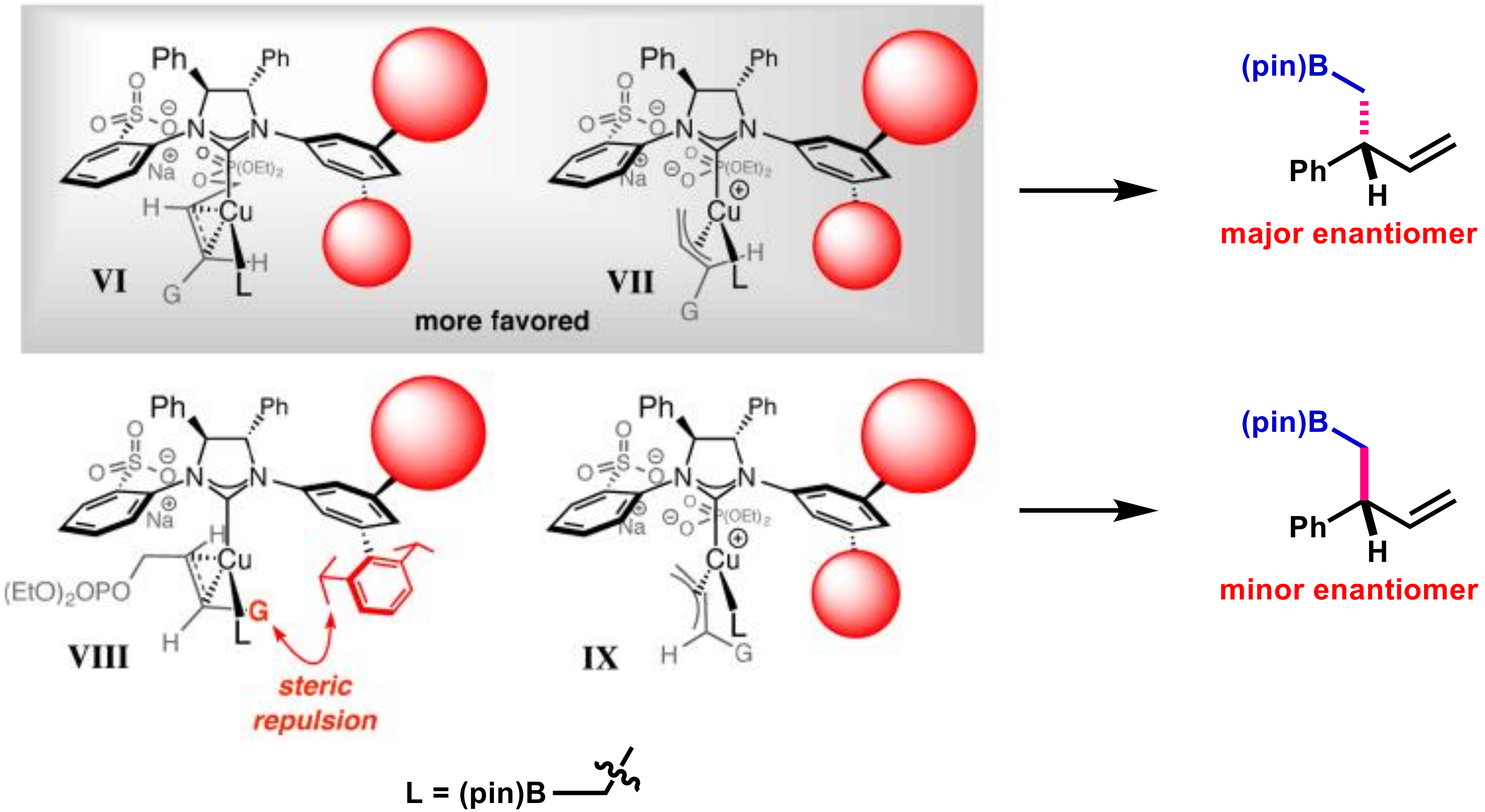
branched product (S_N2')

more Lewis acidic
↕
less Lewis acidic

M	yield	$S_N2':S_N2$	e.r.
Li	29%	>98:2	94:6
Na	83%	>98:2	94:6
K	45%	>98:2	94:6

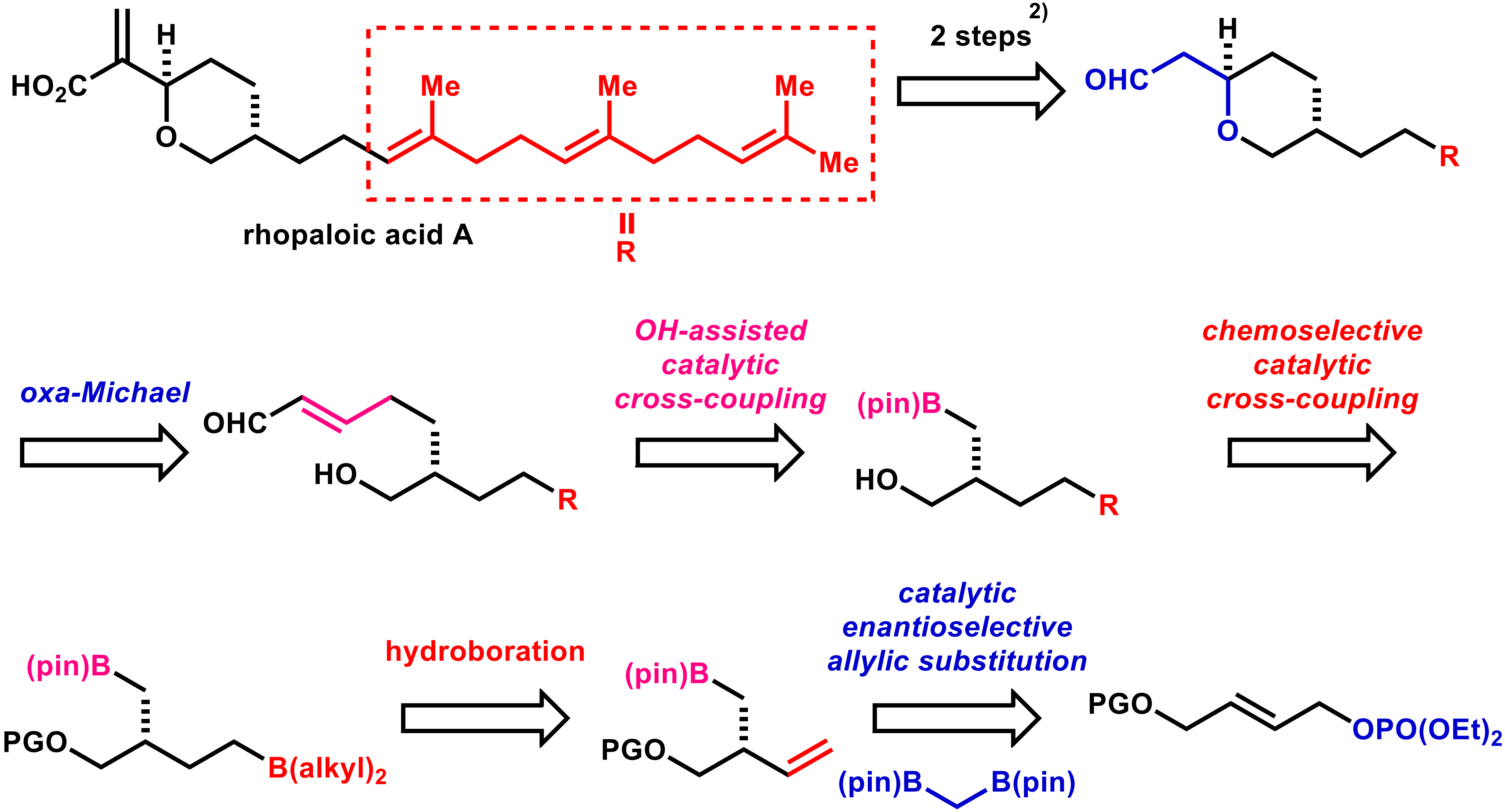
Shi, Y.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 3455.

Mechanistic Model to Account for Enantioselectivity



Shi, Y.; Jung, B.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2015**, *137*, 8948.

Retrosynthetic Analysis of Rhopaloic Acid A



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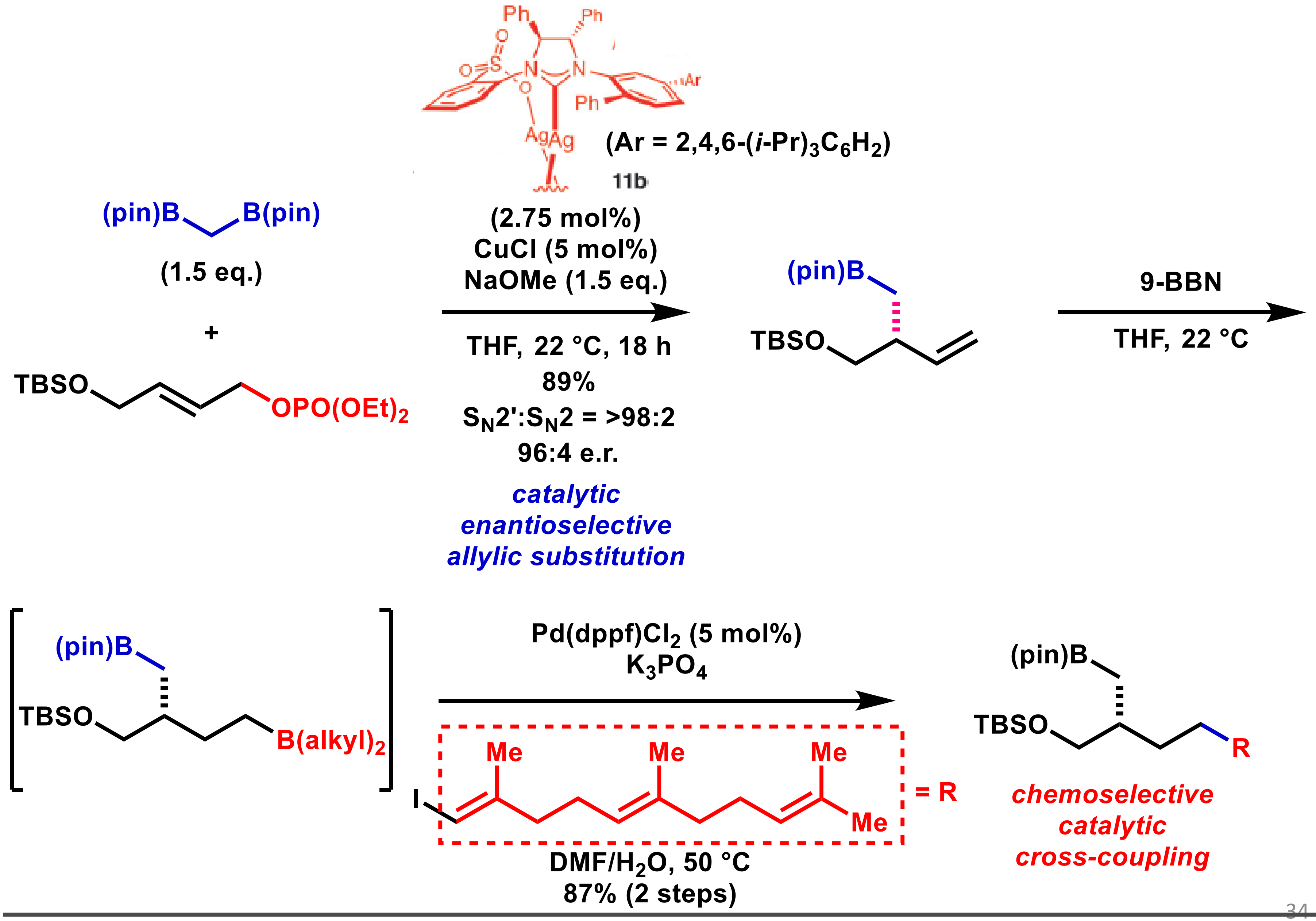
1) Shi, Y.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 3455.

2) Brioche, J. C. R.; Goodenough, K. M.; Whatrup, D. J.; Harrity, J. P. A. *Org. Lett.* **2007**, *9*, 3941.

Synthesis of Pinacolatoboron



(Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$)

(1.5 eq.)

\+

(2.75 mol%)
CuCl (5 mol%)
NaOMe (1.5 eq.)

THF, 22 °C, 18 h
89%
S_N2':S_N2 = >98:2
96:4 e.r.

catalytic enantioselective allylic substitution

9-BBN

THF, 22 °C

Pd(dppf)Cl$_2$ (5 mol%)
K$_3$PO$_4$

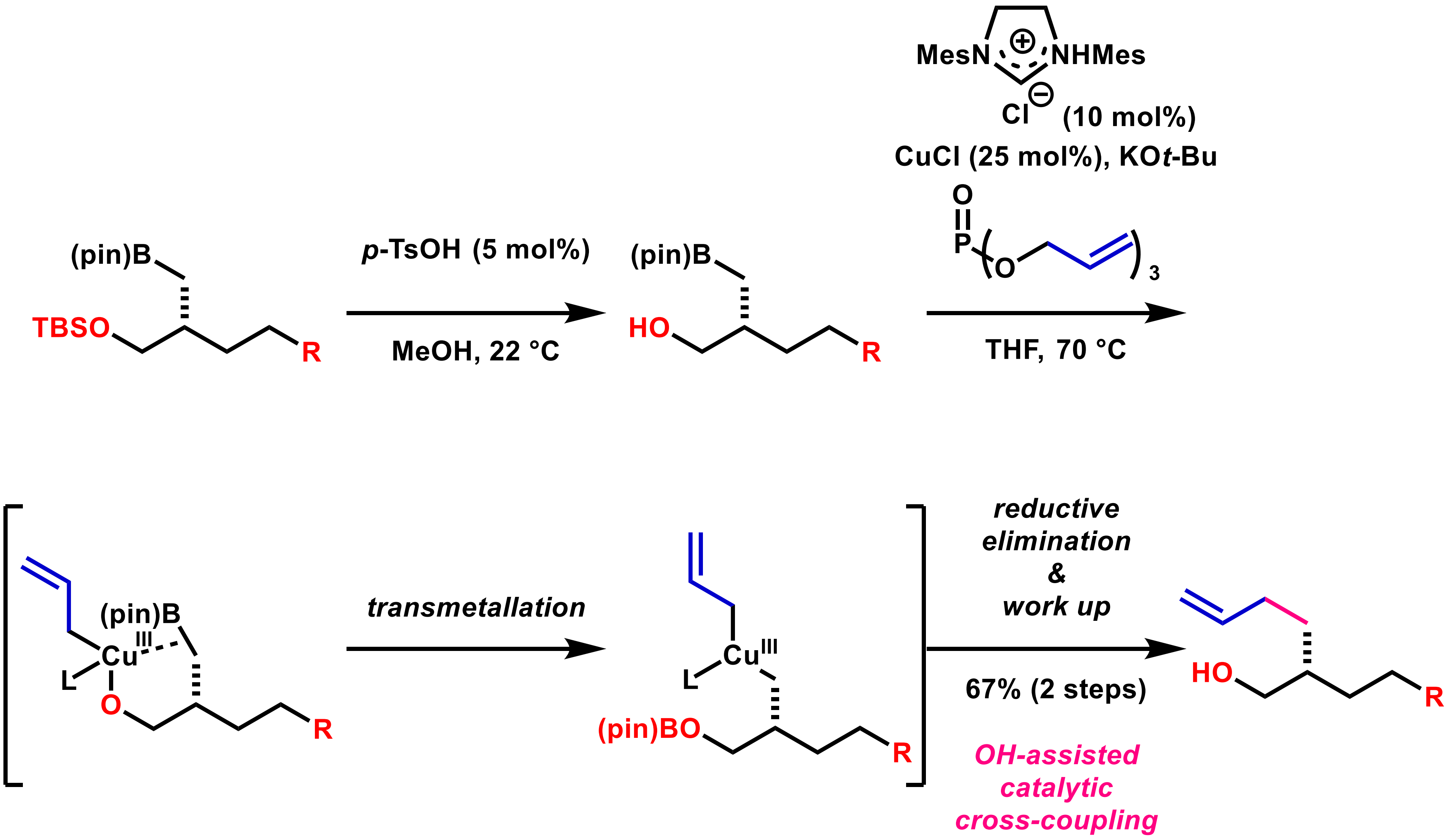
= R

DMF/H$_2$O, 50 °C
87% (2 steps)

chemoselective catalytic cross-coupling

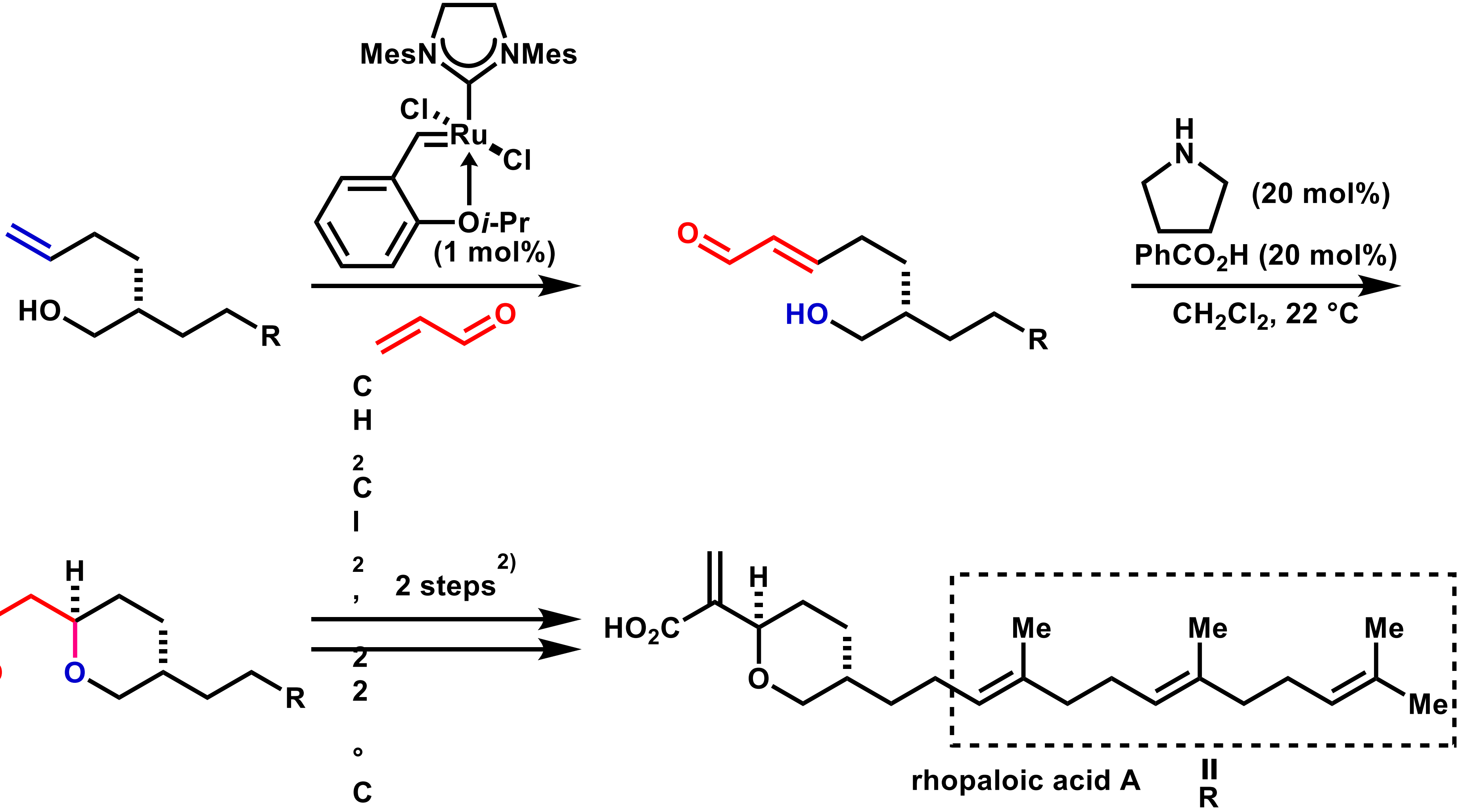
Shi, Y.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 3455.

OH-Directed Cross-Coupling



Shi, Y.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 3455.

Completion of the Formal Synthesis of Rhopaloic Acid A



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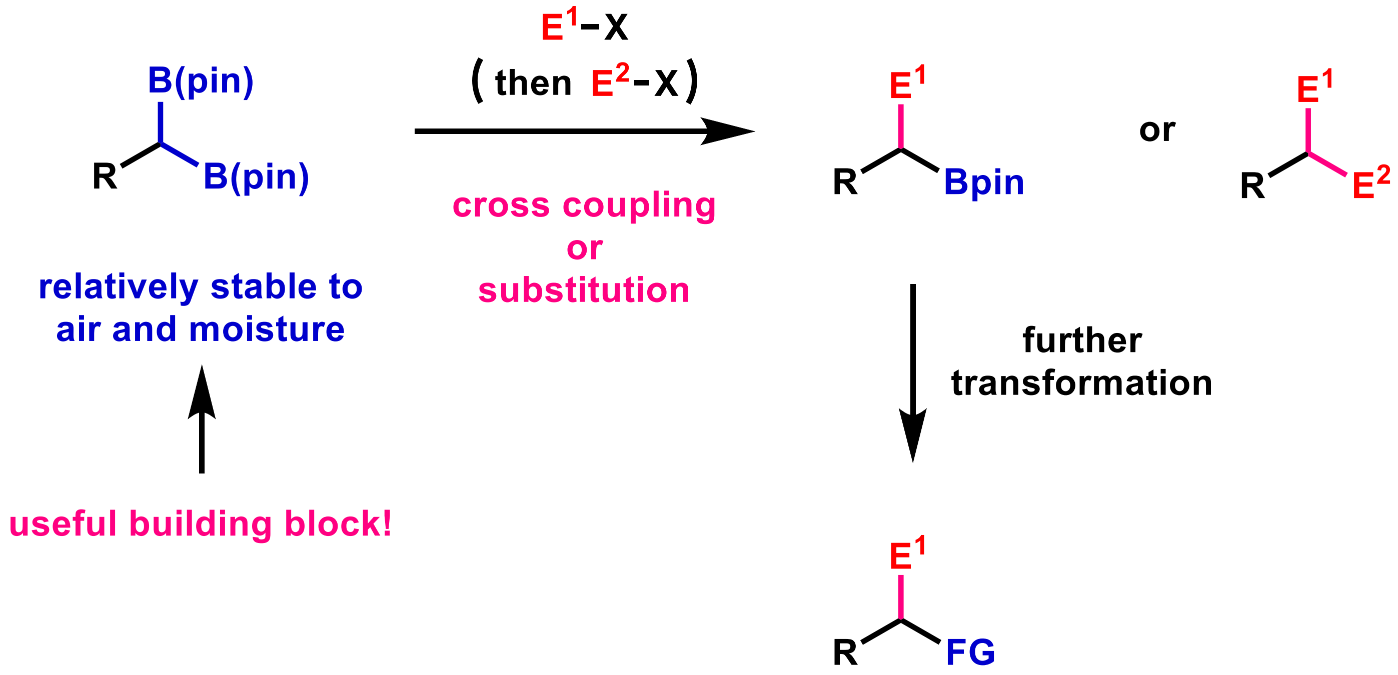
1) Shi, Y.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 3455.

2) Brioche, J. C. R.; Goodenough, K. M.; Whatrup, D. J.; Harrity, J. P. A. *Org. Lett.* **2007**, *9*, 3941.

Summary



relatively stable to air and moisture

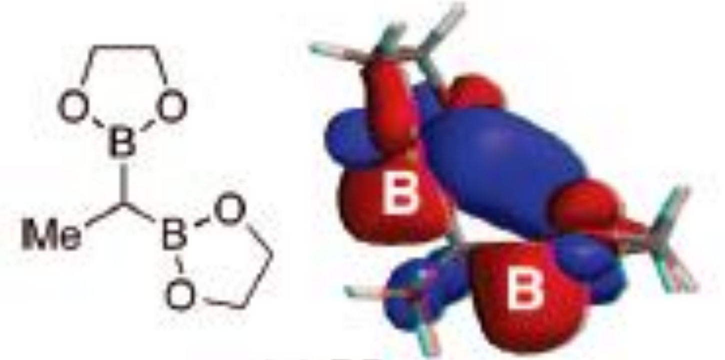
useful building block!

cross coupling or substitution

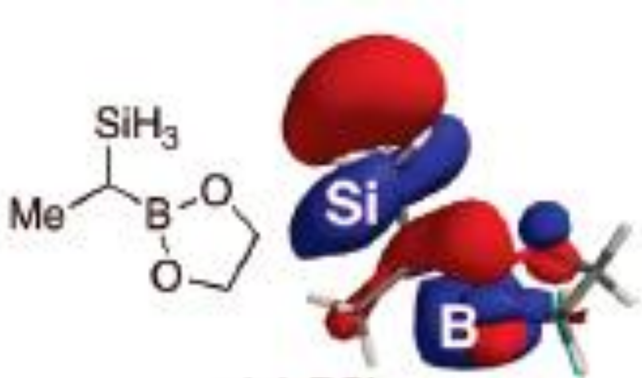
further transformation

Appendix

App. Calculation of LUMO Orbital



1,1-BB



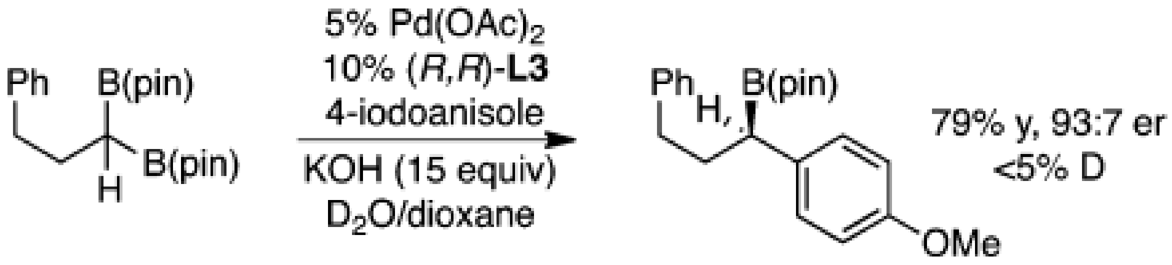
1,1-BSi

borate formation at rt	**Yes**	**No** **(not SiH_3, but $SiMe_3$)**

B3LYP/6-31G level of theory**

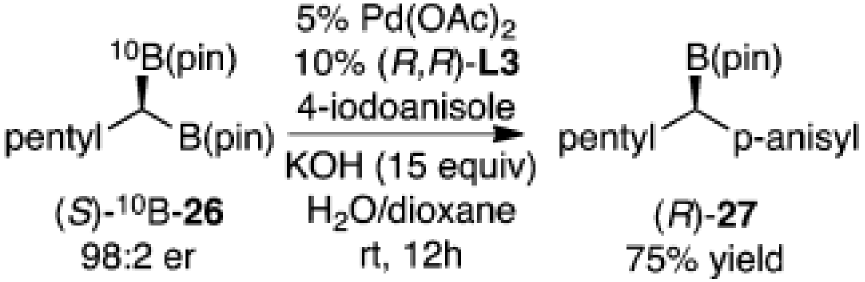
Endo, K.; Ohkubo, T.; Hirokami, M.; Shibata, T. *J. Am. Chem. Soc.* **2010**, *132*, 11033.

Mechanistic Study 1



79% y, 93:7 er
<5% D

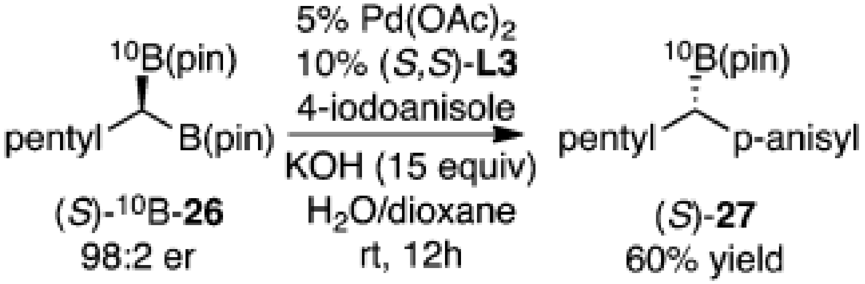
not deprotonated ⟶ **reductive elimination is NOT enantio-determining step**



(*S*)-^{10}B-**26**
98:2 er

(*R*)-**27**
75% yield
92:8 er

calc'd: reaction of ^{10}B(pin)	found
m/z 318: 22.5%	24.5%
m/z 319: 63.6%	63.8%
m/z 320: 12.5%	10.6%
m/z 321: 1.2%	1.1%



(*S*)-^{10}B-**26**
98:2 er

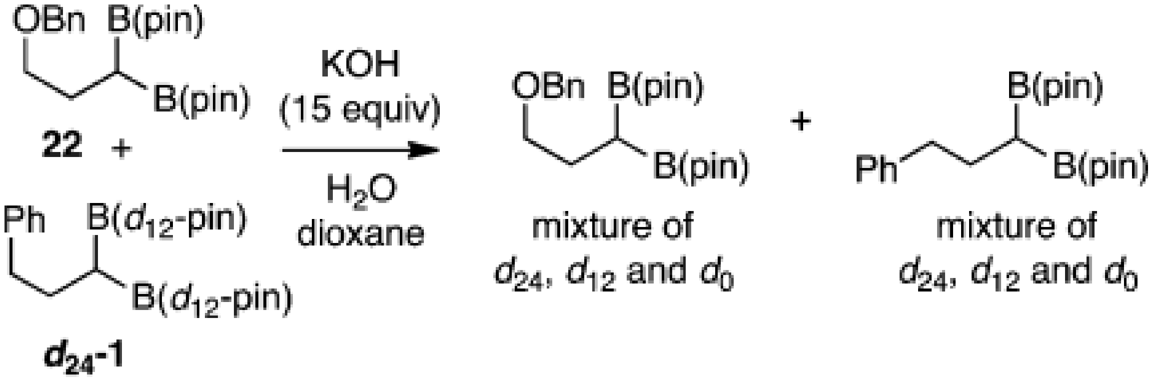
(*S*)-**27**
60% yield
92:8 er

calc'd: reaction of B(pin)	found
m/z 318: 75.2%	77.6%
m/z 319: 21.7%	19.4%
m/z 320: 2.8%	2.7%
m/z 321: 0.1%	0.3%

stereoinversion

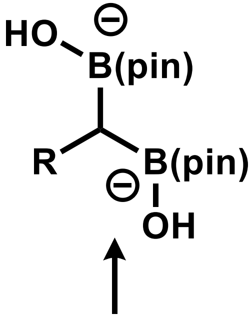
Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534

Mechanistic Study 2

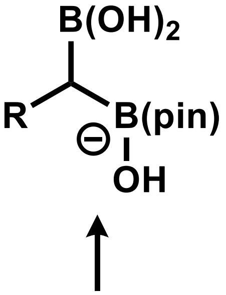


hydrolysis occurred in this condition

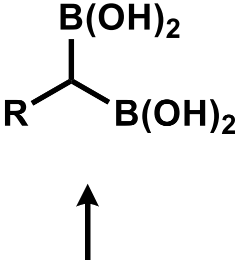
candidate for active species of enantio-determining transmetallation



desymmetrization by ligand?



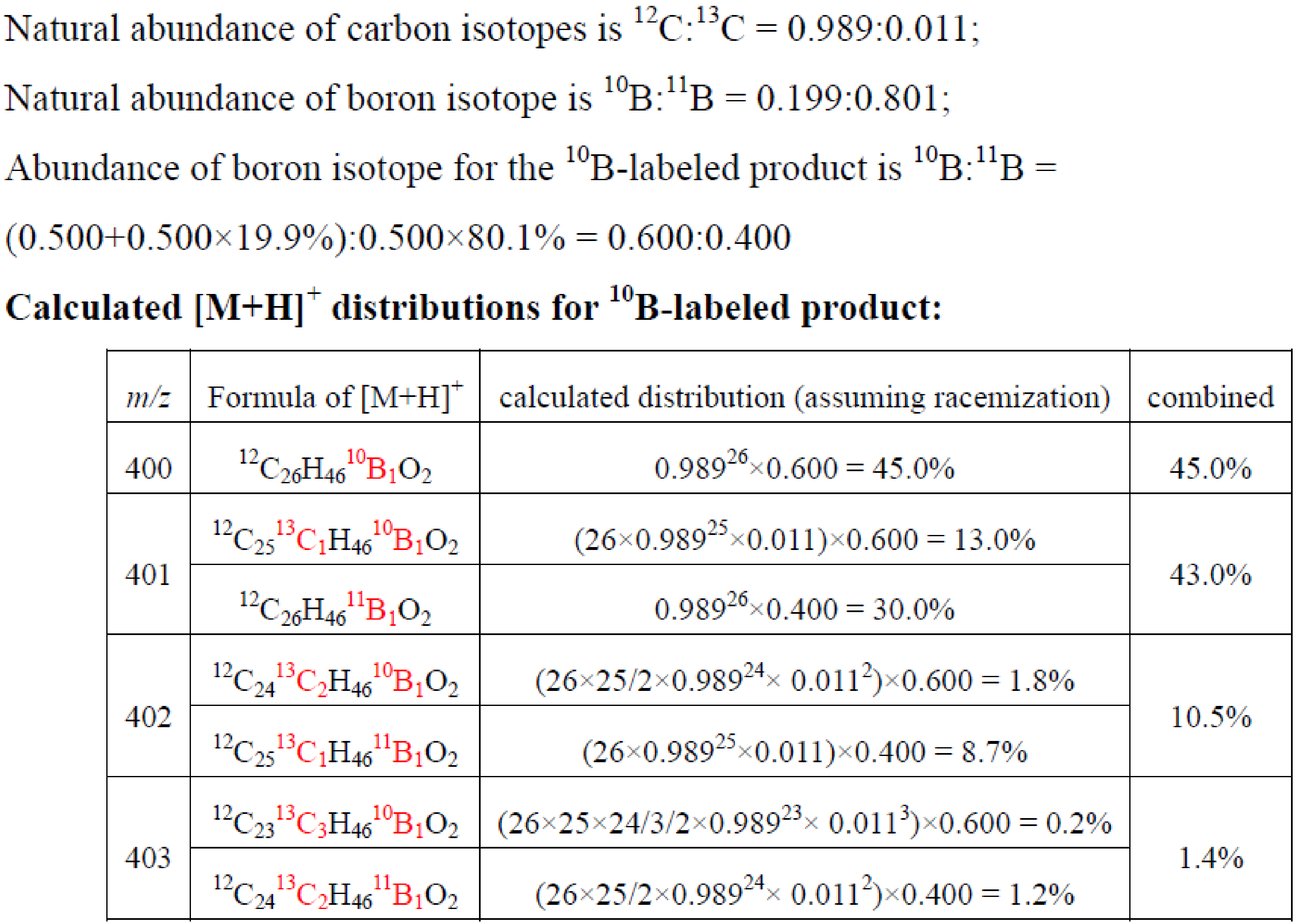
dynamic kinetic resolution by ligand?



desymmetrization by ligand?

Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534

Calculated [M+H]$^+$ Distributions



Natural abundance of carbon isotopes is ^{12}C:^{13}C = 0.989:0.011;

Natural abundance of boron isotope is ^{10}B:^{11}B = 0.199:0.801;

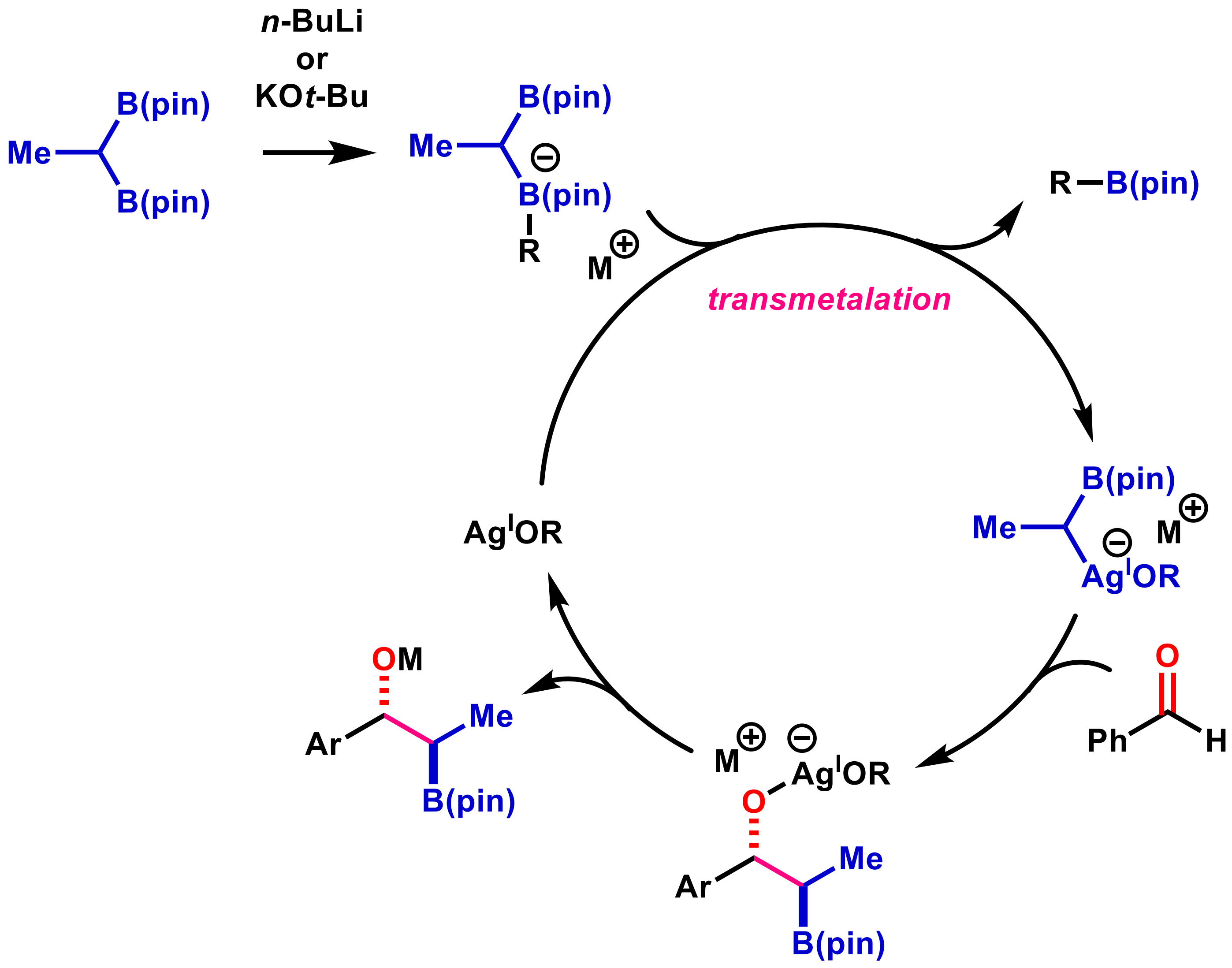
Abundance of boron isotope for the ^{10}B-labeled product is ^{10}B:^{11}B = (0.500+0.500×19.9%):0.500×80.1% = 0.600:0.400

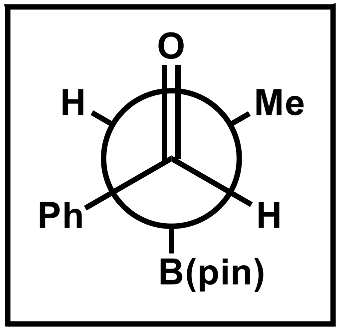
Calculated [M+H]$^+$ distributions for ^{10}B-labeled product:

m/z	Formula of [M+H]$^+$	calculated distribution (assuming racemization)	combined
400	$^{12}C_{26}H_{46}{}^{10}B_1O_2$	$0.989^{26}\times0.600 = 45.0\%$	45.0%
401	$^{12}C_{25}{}^{13}C_1H_{46}{}^{10}B_1O_2$	$(26\times0.989^{25}\times0.011)\times0.600 = 13.0\%$	43.0%
	$^{12}C_{26}H_{46}{}^{11}B_1O_2$	$0.989^{26}\times0.400 = 30.0\%$	
402	$^{12}C_{24}{}^{13}C_2H_{46}{}^{10}B_1O_2$	$(26\times25/2\times0.989^{24}\times 0.011^2)\times0.600 = 1.8\%$	10.5%
	$^{12}C_{25}{}^{13}C_1H_{46}{}^{11}B_1O_2$	$(26\times0.989^{25}\times0.011)\times0.400 = 8.7\%$	
403	$^{12}C_{23}{}^{13}C_3H_{46}{}^{10}B_1O_2$	$(26\times25\times24/3/2\times0.989^{23}\times 0.011^3)\times0.600 = 0.2\%$	1.4%
	$^{12}C_{24}{}^{13}C_2H_{46}{}^{11}B_1O_2$	$(26\times25/2\times0.989^{24}\times 0.011^2)\times0.400 = 1.2\%$	

Hong, K.; Liu, X.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 10581.

Plausible Mechanism - Silver Catalyst -

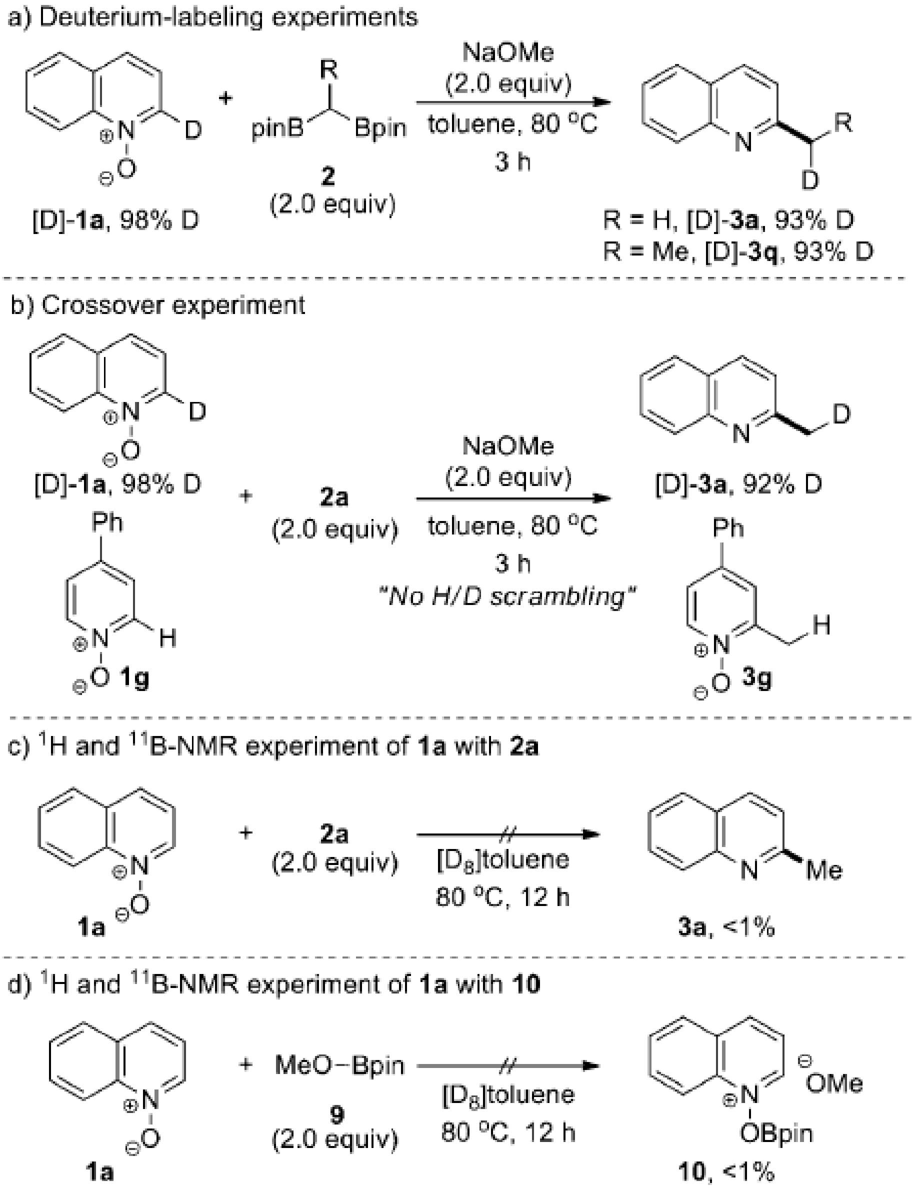




***Anti* selectivity could be explained by this model.**

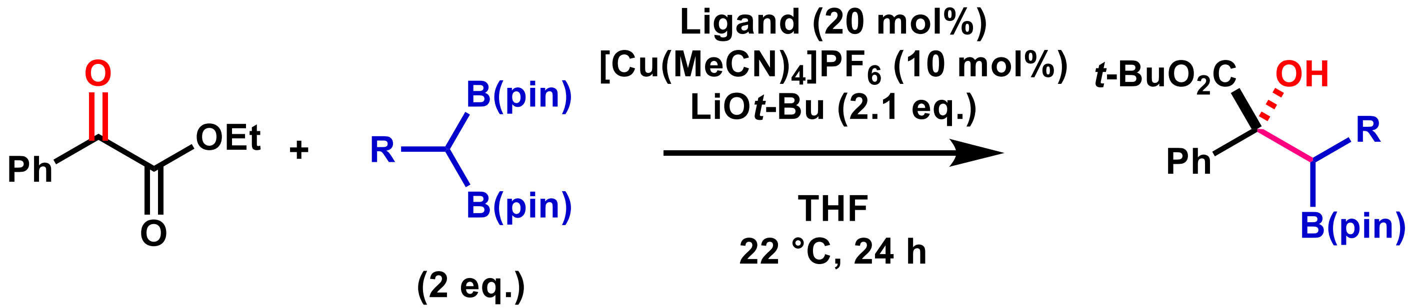
Joannou, M. V.; Moyer, B. S.; Goldfogel, M. J.; Meek, S. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 14141.

App. Mechanistic Study



Jo, W.; Kim, J.; Choi, S.; Cho, S. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 6960.

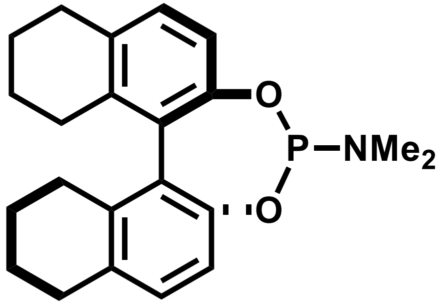
Enantio- and Diastereoselective 1,2-Addition to α-Ketoester



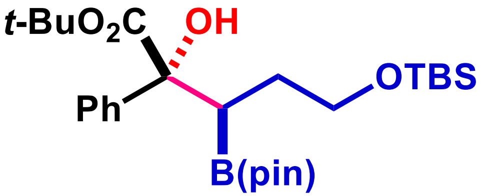
(2 eq.)

Ligand (20 mol%)
$[Cu(MeCN)_4]PF_6$ (10 mol%)
LiO*t*-Bu (2.1 eq.)

THF
22 °C, 24 h

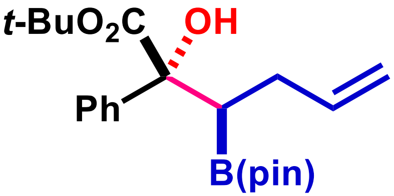


Ligand

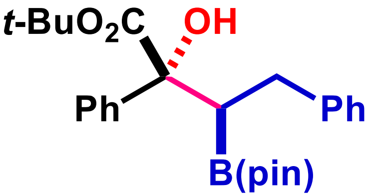


51%
d.r = 3.3:1
e.r = 98:1

which step is less selective?
(transmetalation or
nucleophilic addition)

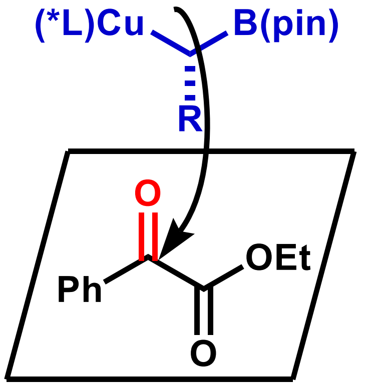


50%
d.r = >20:1
e.r = 94:6



<5% conversion

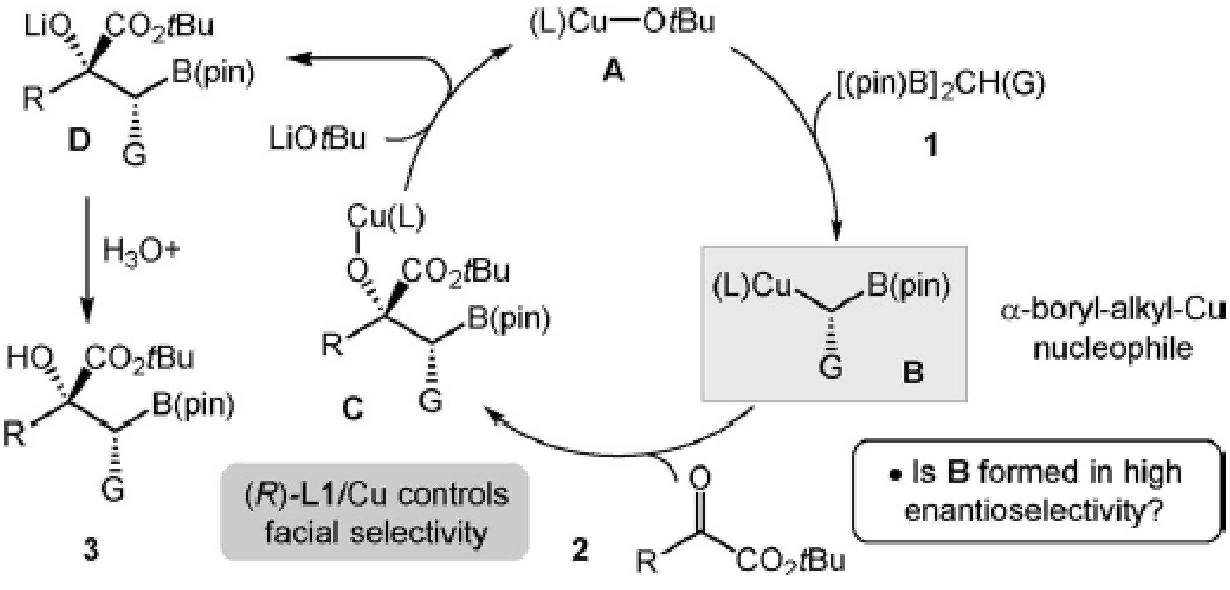
sensitive to steric demand
of 1,1-diboron reagent



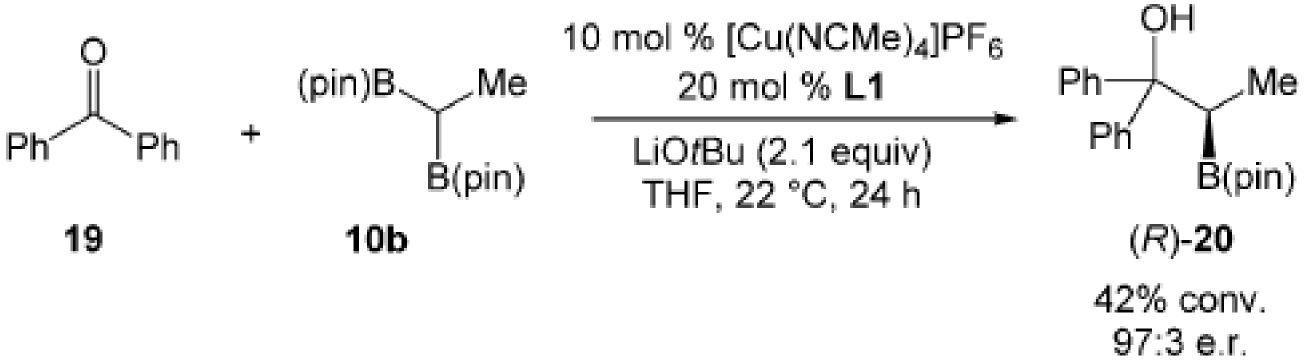
addition from *Si* face
(controlled by chiral
phosphine/Cu cat.)

Murray, S. A.; Green, J. C.; Tailor, S. B.; Meek, S. J. *Angew. Chem. Int. Ed.* **2016**, *55*, 9065.

App. Plausible Mechanism for Enantio- and Diastereoselective 1,2-Addition to α-Ketoester



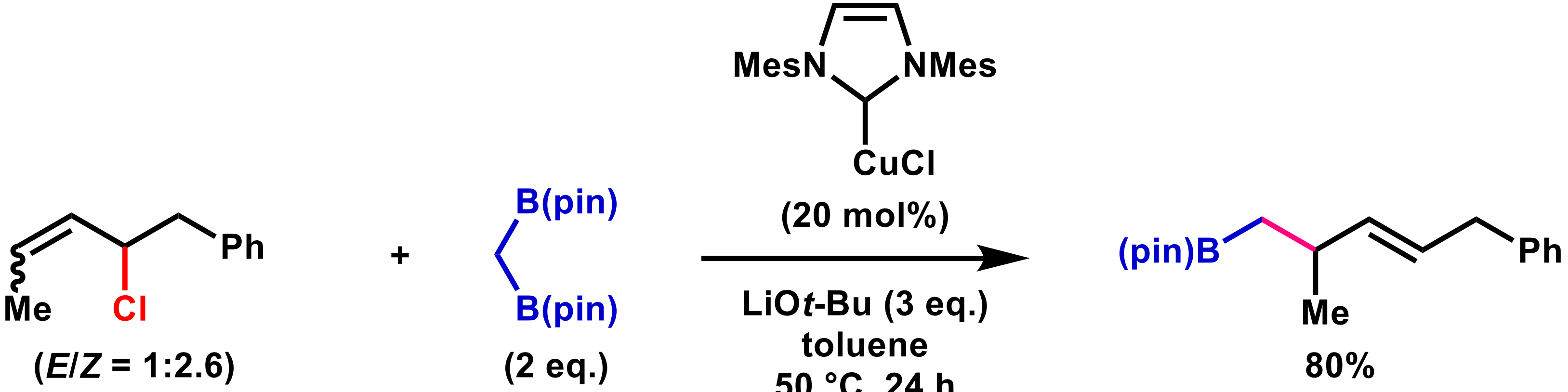
•evidence for enantioenriched α-boryl-Cu formation



Murray, S. A.; Green, J. C.; Tailor, S. B.; Meek, S. J. *Angew. Chem. Int. Ed.* **2016**, *55*, 9065.

Uncertain Experimental Results

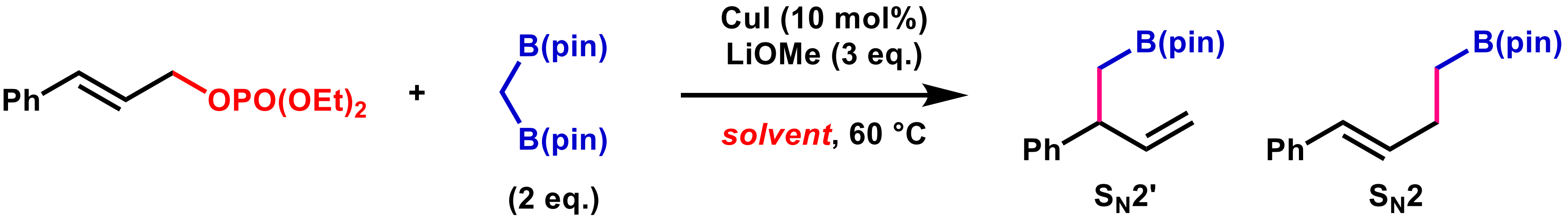
- **Is *anti* displacement true? (or is reductive elimination fast?)**



80%
***E*/*Z* = >99:1**
S_N2':S_N2 = >99:1

Kim, J.; Park. S.; Park, J.; Cho, S. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 1498.

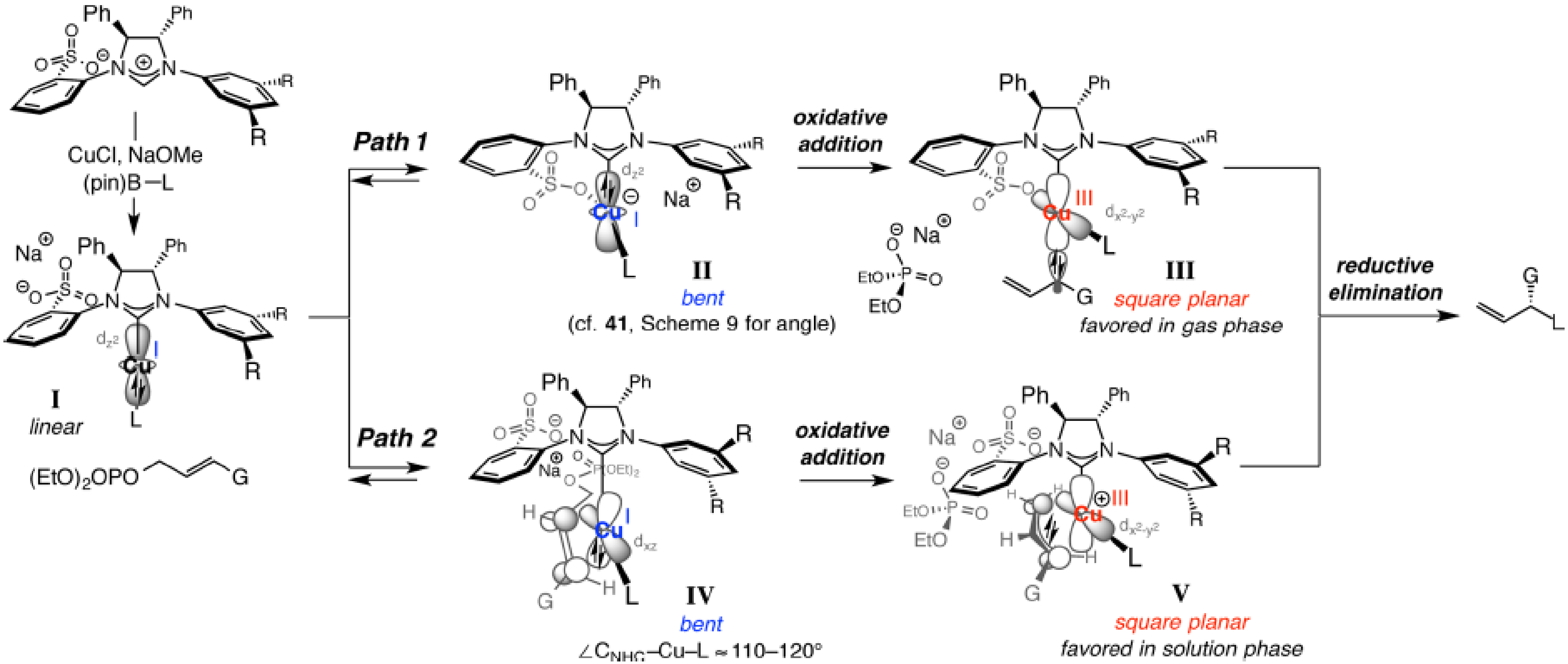
- **unclear solvent effect**



DMF 87%, S_N2':S_N2 = 4:96
1,4-dioxane 68%, S_N2':S_N2 = 87:13

Zhang, Z-Q.; Zhang, B.; Lu, X.; Liu, J.-H.; Lu, X.-Y.; Xiao, B.; Fu, Y. *Org. Lett.* **2016**, *18*, 952.

App. Possible Intermediates



Energy: d^8 Cu(III) > d^{10} Cu(I) ⟶ Transition states of the oxidative addition and the reductive elimination would resemble a square planar Cu(III). (Hammond postulate)

Shi, Y.; Jung, B.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2015**, *137*, 8948.

DFT Calculation of Possible Cu(III) Intermediates

Sulfonate binding 3 – η^1 vs η^3-allyl species (cf. Scheme 10 in manuscript)

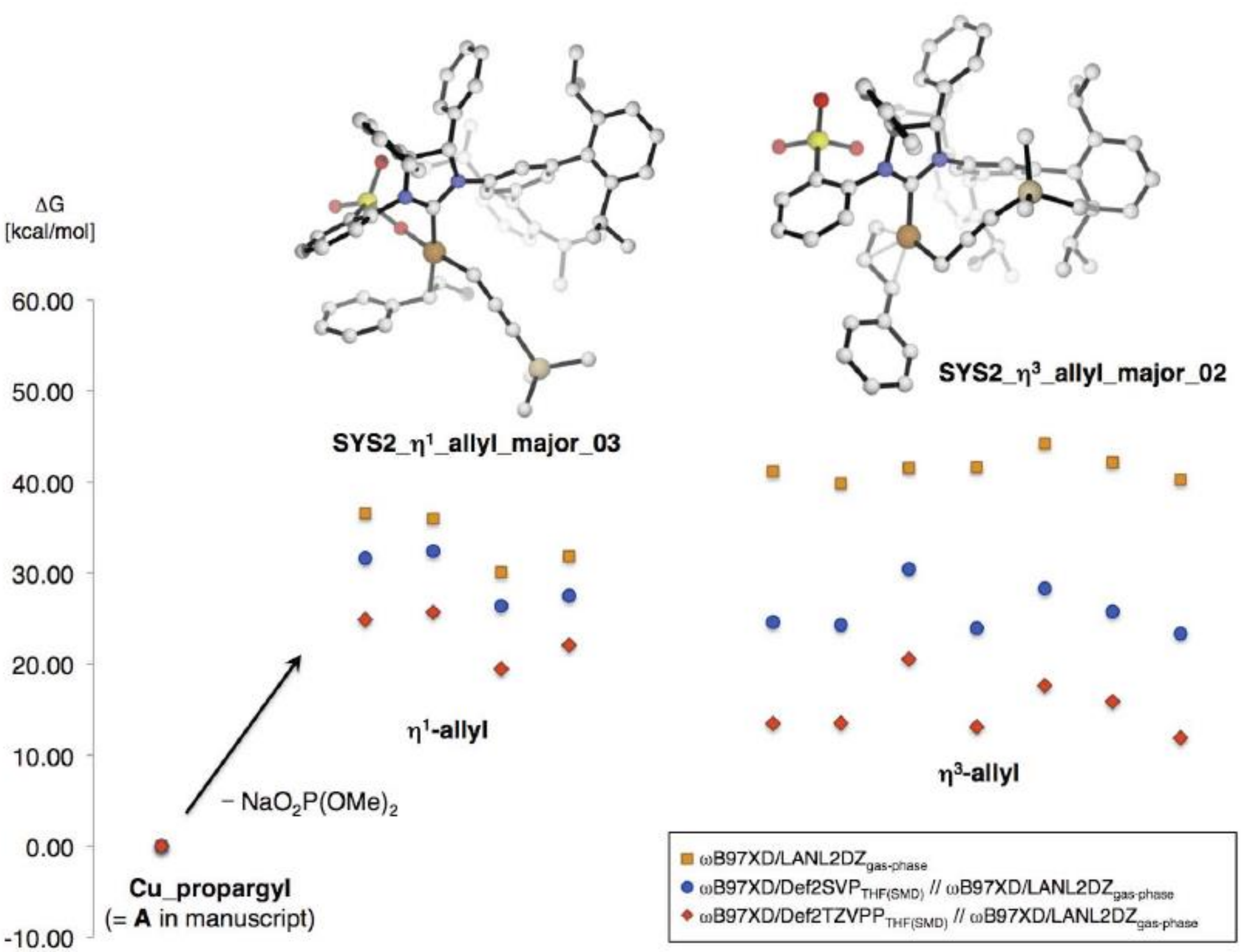
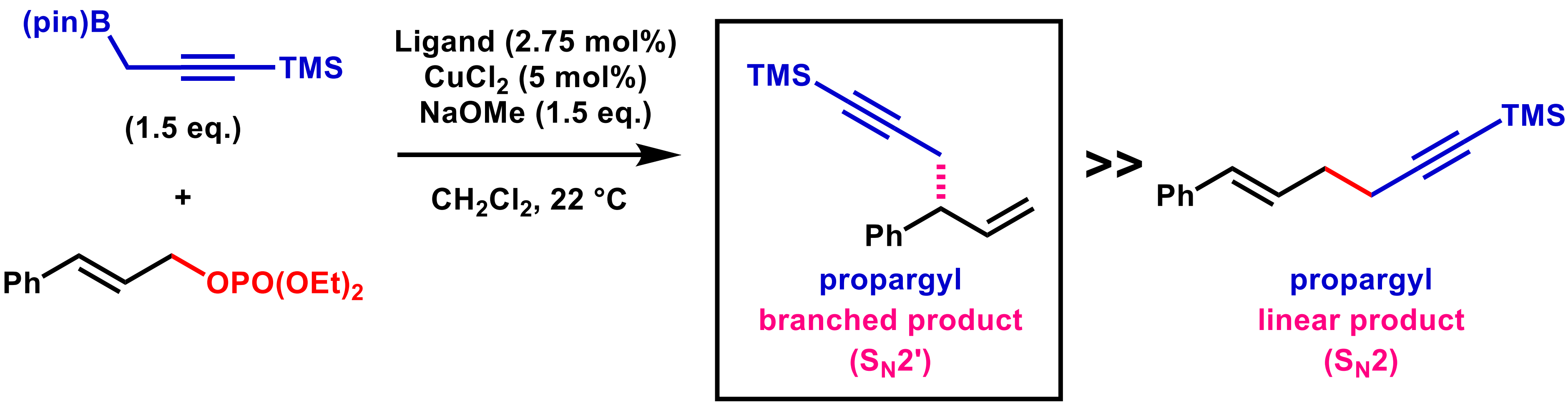


Figure S3. Comparison of SO_3–binding in square planar Cu(III) intermediates as a function of basis set and solvation (THF); two representative structures are shown (for geometries see section 13).

Shi, Y.; Jung, B.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2015**, *137*, 8948.

NHC-Copper-Catalyzed Allylic Substitution with Propargyl(pinacolato)broron



(1.5 eq.)

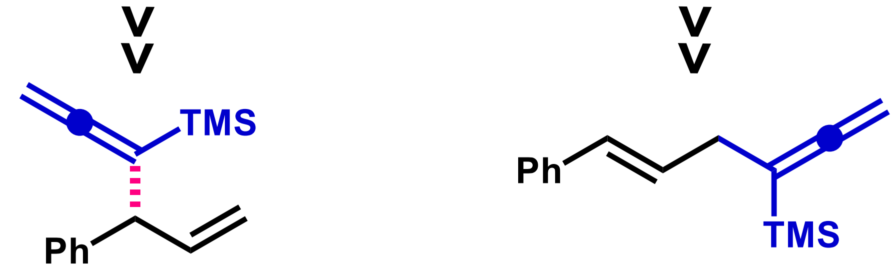
+

Ligand (2.75 mol%)
$CuCl_2$ (5 mol%)
NaOMe (1.5 eq.)

CH_2Cl_2, 22 °C

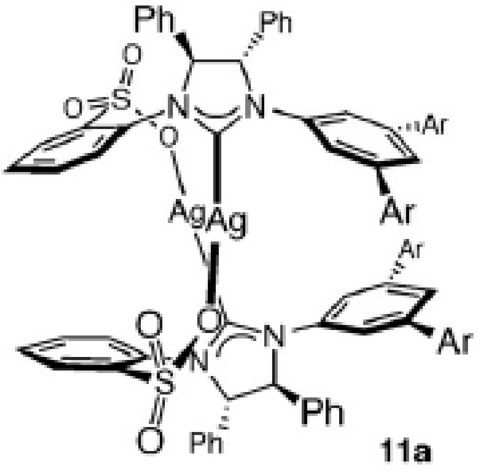
propargyl
branched product
(S_N2')

propargyl
linear product
(S_N2)



allenyl
branched product
(S_N2')

allenyl
linear product
(S_N2)



11a

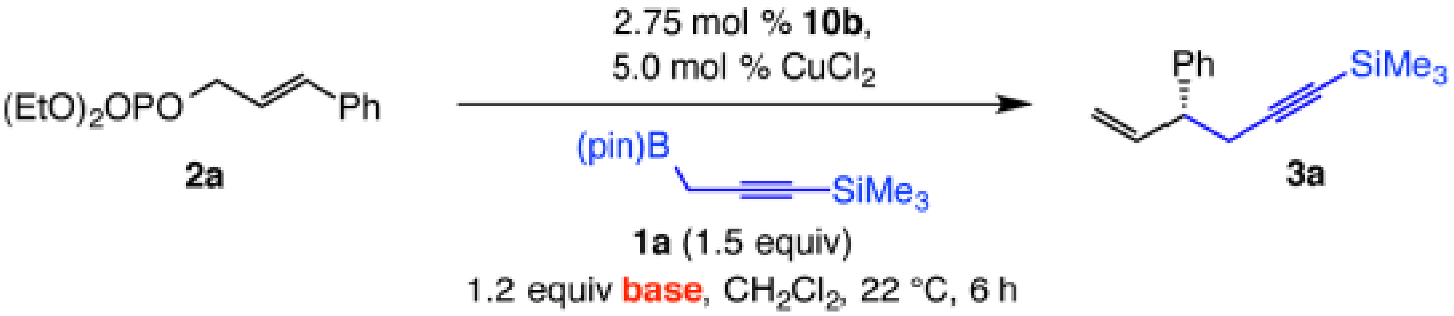
Ligand (Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$)

88%
propargyl:allenyl = 94:6
S_N2':S_N2 = 97:3
96:4 e.r.

Shi, Y.; Jung, B.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2015**, *137*, 8948.

App. Effect of Cationic Metal and Leaving Group

b. Experimental support for the coordinating/directing function of the cationic metal:



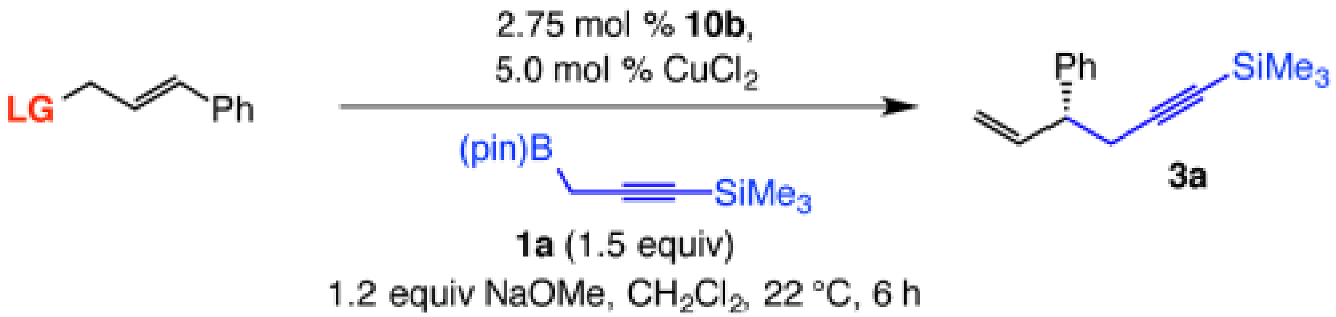
2a

1a (1.5 equiv)

3a

with **NaOMe**
>98% conv, 88% yield,
94:6 propargyl:allenyl
97:3 S_N2':S_N2, 96:4 er

with **KOMe**
>98% conv, 93% yield,
93:7 propargyl:allenyl
85:15 S_N2':S_N2, 96:4 er



1a (1.5 equiv)

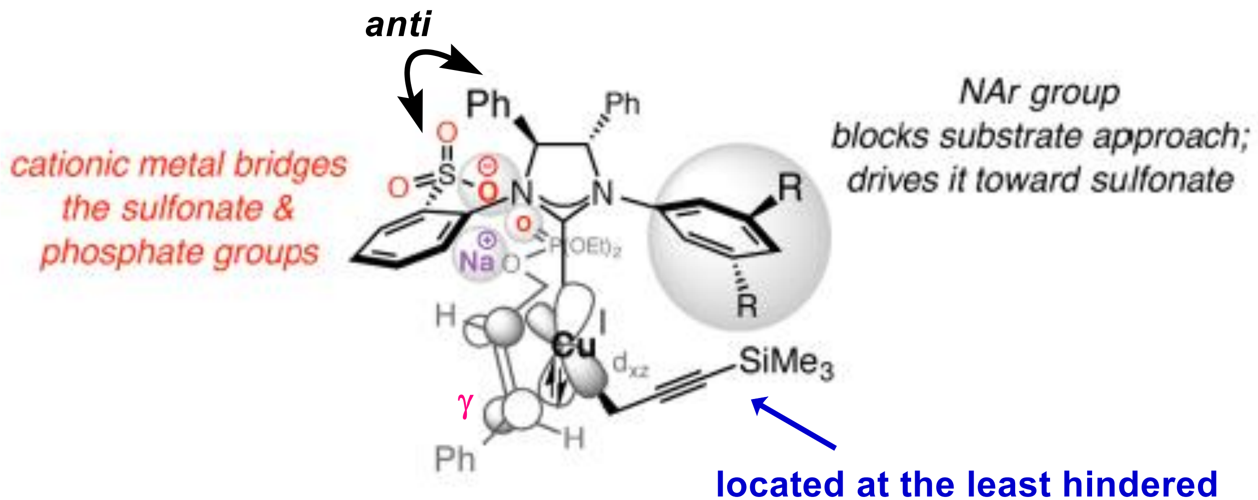
3a

LG = OCO_2Ph
14% conv, 9% yield,
94:6 propargyl:allenyl
53:47 S_N2':S_N2, 95:5 er

LG = OAc
51% conv, 35% yield,
84:16 propargyl:allenyl
74:26 S_N2':S_N2, 91:9 er

Shi, Y.; Jung, B.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2015**, *137*, 8948.

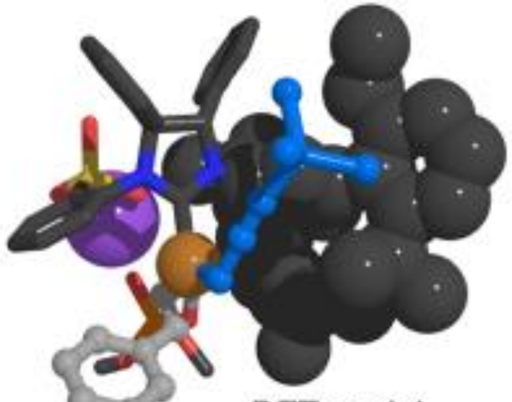
DFT Calculated Model for the Explanation of S_N2' Selectivity



cationic metal bridges the sulfonate & phosphate groups

NAr group blocks substrate approach; drives it toward sulfonate

located at the least hindered coordination site



DFT model
[R = (2,6-(i-Pr)$_2$C$_6$H$_3$]:
TMS-propargyl (blue),
substrate **2a** (gray)

propargyl group and γ position are syn
&
good orbital match

↓

$S_N2' >> S_N2$

ω-B97XD/Def2TZVPP$_{DCM(SMD)}$//
ω-B97XD/Def2SVP level

Shi, Y.; Jung, B.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2015**, *137*, 8948.

App. DFT Calculation - Propargyl vs Allenyl -

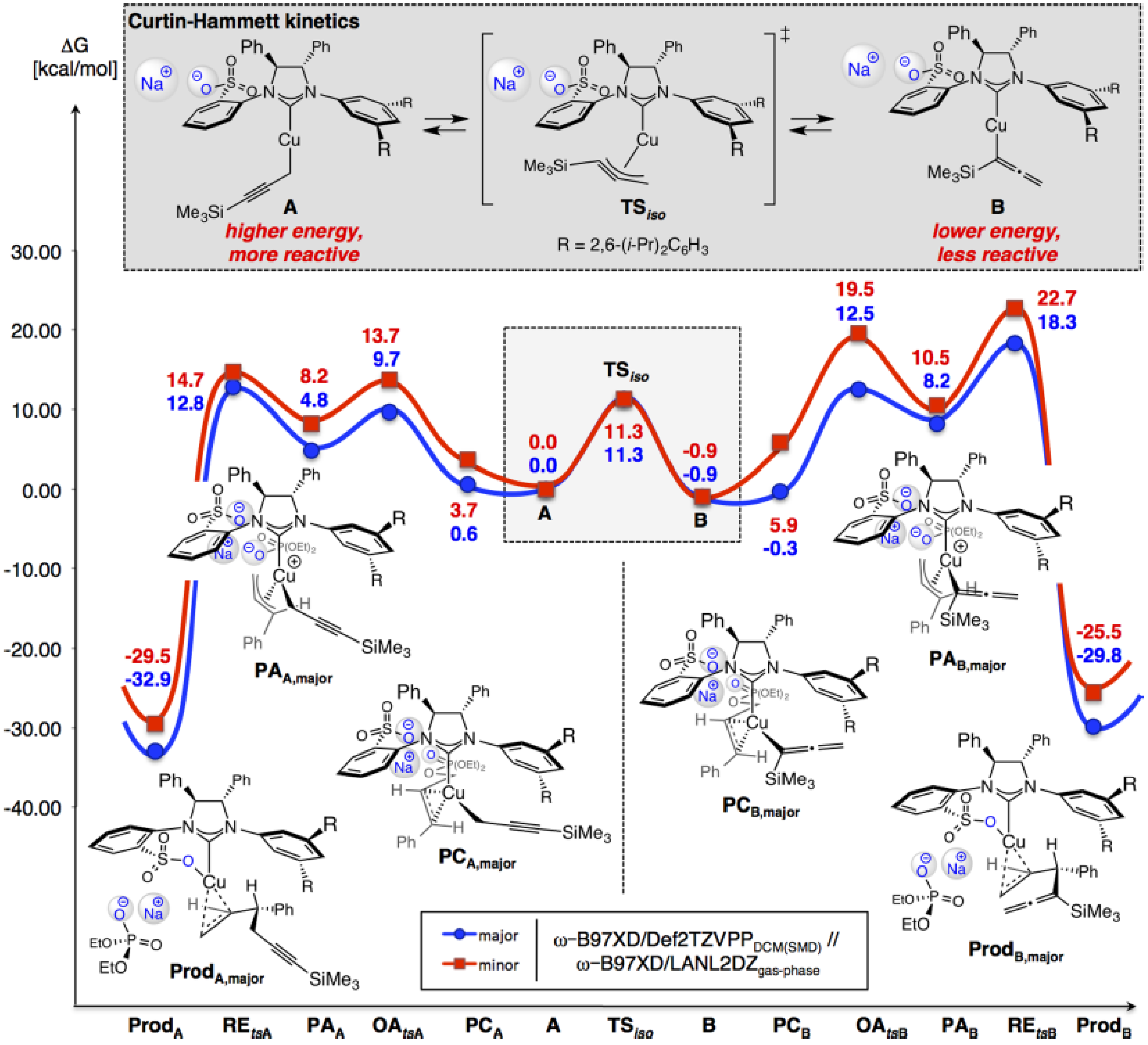
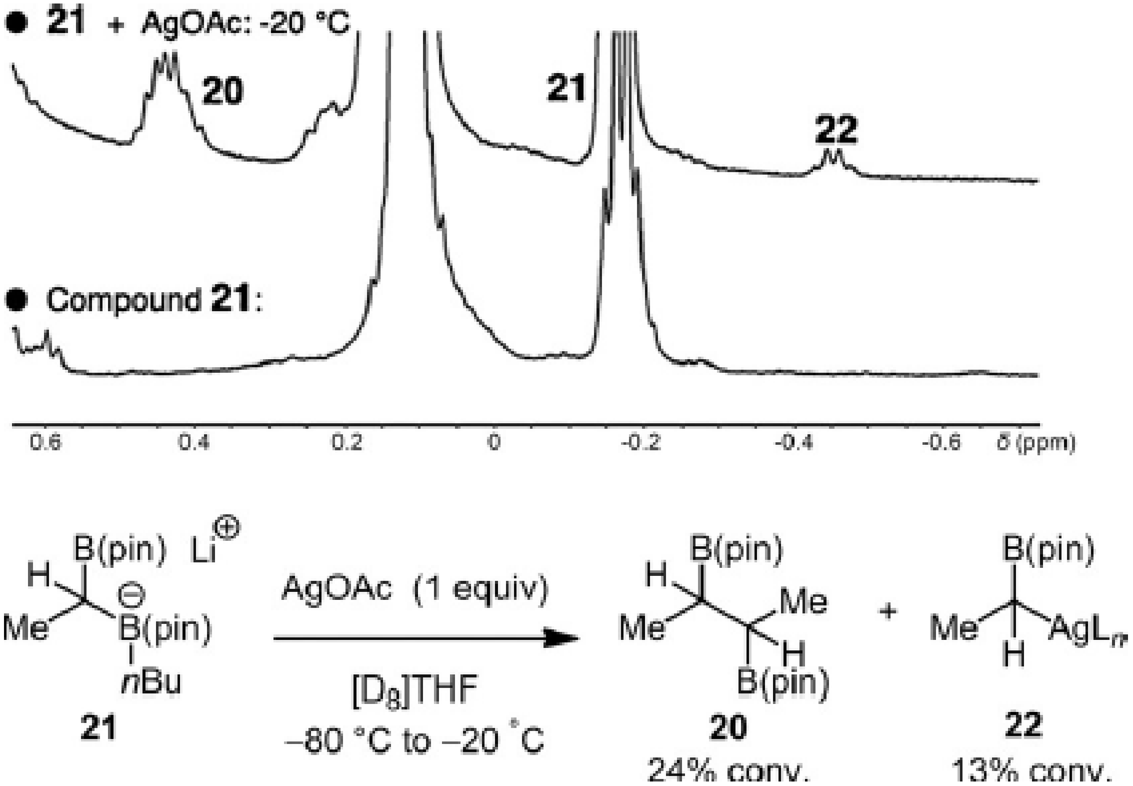


Figure 2. Energy profile regarding the origin of high site and group transfer selectivity (high S_N2':S_N2 and propargyl/allenyl addition) derived from DFT calculations. Abbreviations: RE, reductive elimination; TS, transition state; OA, oxidative addition; PA, π-allyl; PC, π complex.

Shi, Y.; Jung, B.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2015**, *137*, 8948.

App. Detection of α-Boryl Alkyl Silver Species



Scheme 6. Low-temperature ^{1}H NMR detection (−80 to −20 °C) of a putative α-boryl alkyl silver species.

20 seemed to be generated by reductive dimerization.

Joannou, M. V.; Moyer, B. S.; Goldfogel, M. J.; Meek, S. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 14141.