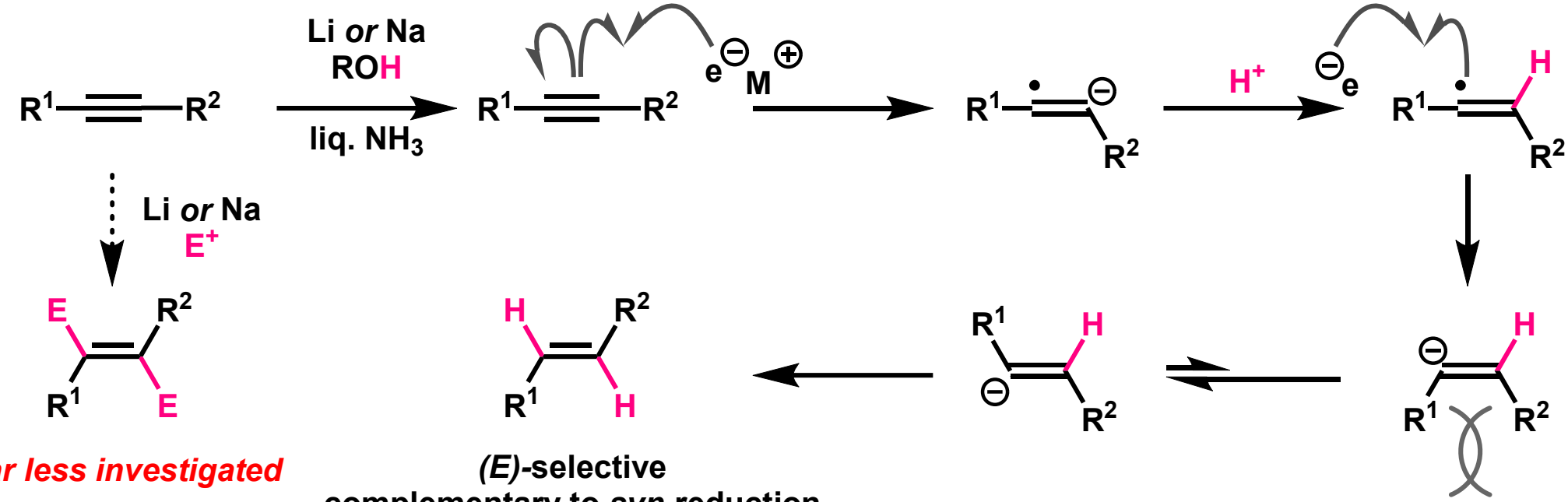
Reductive Difunctionalization of Alkyne

Literature Seminar
2025. 6. 14

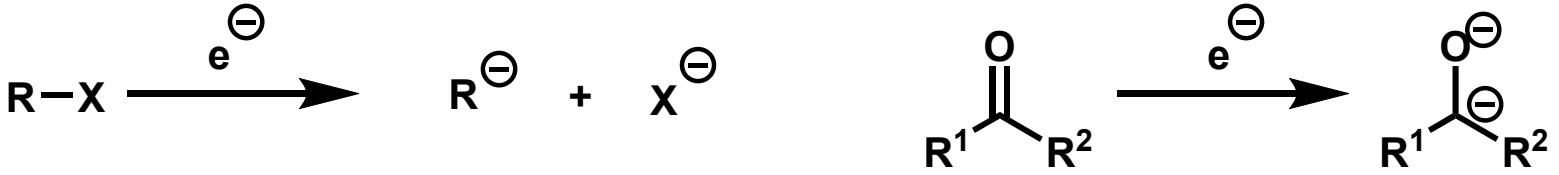
Kyohei Takaoka

1. **Introduction**
2. ***E/Z*-selective Difunctionalization**
3. **Regioselective Difunctionalization (main paper)**

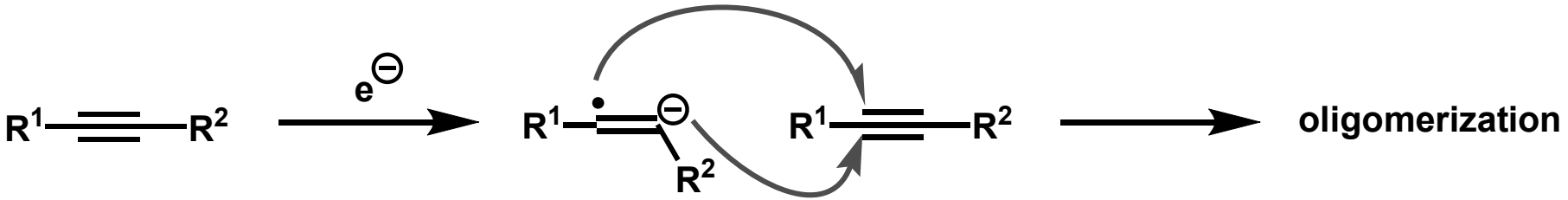
Single Electron Reduction of Alkyne, Limitation



Most of common electrophiles are labile to single reduction



Difficult to regulate the reactive intermediate



1. Introduction

2. *E/Z*-Selective Difunctionalization

3. Regioselective Difunctionalization (main paper)

Prof. Hideki Yorimitsu

Prof. Hideki Yorimitsu

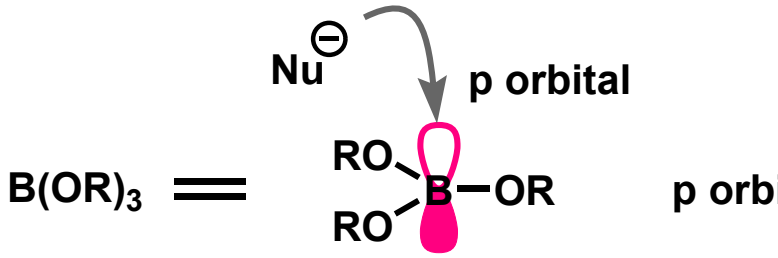
Career:

2002:	**Ph. D. @Kyoto University (Prof. K. Oshima)**
2002-2003:	**Postdoctoral Fellow @University of Tokyo (Prof. E. Nakamura)**
2003-2008:	**Assistant professor @Kyoto University (Prof. K. Oshima)**
2008-2009:	**Associate professor @Kyoto University (Prof. K. Oshima)**
2009-2015:	**Associate professor @Kyoto University (Prof. Osuka)**
2015-:	**Professor @Kyoto University**

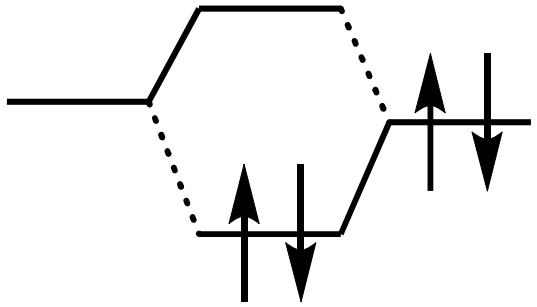
Research Interest:

Aromatic Metamorphosis, Chemistry of Sulfur atom, Reductive Functionalization, Silicon Chemistry

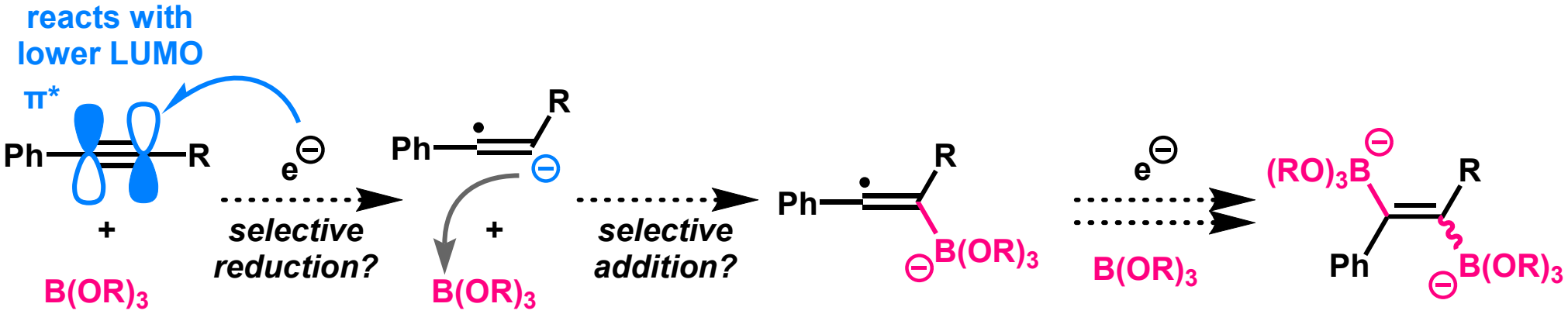
Working Hypothesis: Use of Boric Ester



vacant p orbital = electrophile

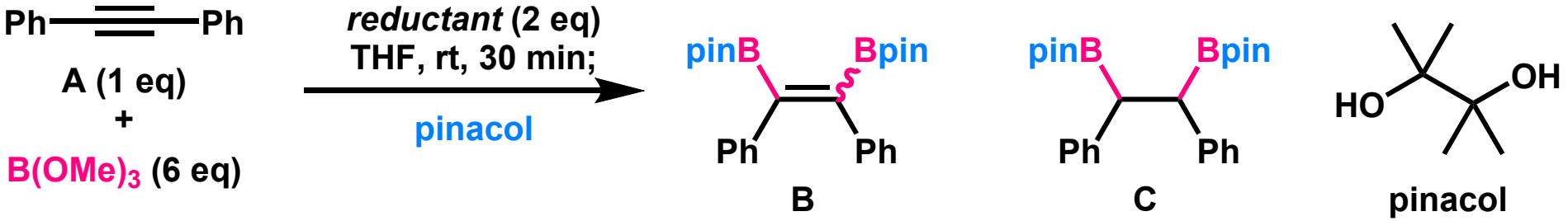


LUMO of $B(OMe)_3$ would be higher by resonance effect
→ Higher torelance to single electron reduction



Is it possible to regulate the reaction by combining condugated alkyne and $B(OMe)_3$?

Diboration of Alkyne



reductant	deviations	B yield	B B (*Z* : *E*)	C
Na dispersion	**-**	**89%**	**100 : 0**	**2%**
Na dispersion	Na dispersion (1 min) then $B(OMe)_3$	<5%	-	0%
Li powder	2 h before pinacol addition	50%	96 : 4	6%
$LiC_{10}H_8$	-	28%	99 : 1	1%
$NaC_{10}H_8$	-	30%	97 : 3	1%
Na dispersion	Et_2O instead of THF	45%	100 : 0	5%
Na dispersion	$B(O\textit{i}\text{-}Pr)_3$ instead of $B(OMe)_3$	25%	68 : 32	2%
Na dispersion	MeOBpin instead of $B(OMe)_3$	48%	79 : 21	21%
Na dispersion (2.2 eq)	**$B(OMe)_3$ (3 eq)**	**93%**	**100 : 0**	**0%**

Na dispersion
particle size:
~10 μm

cf. Li powder
120-250 μm

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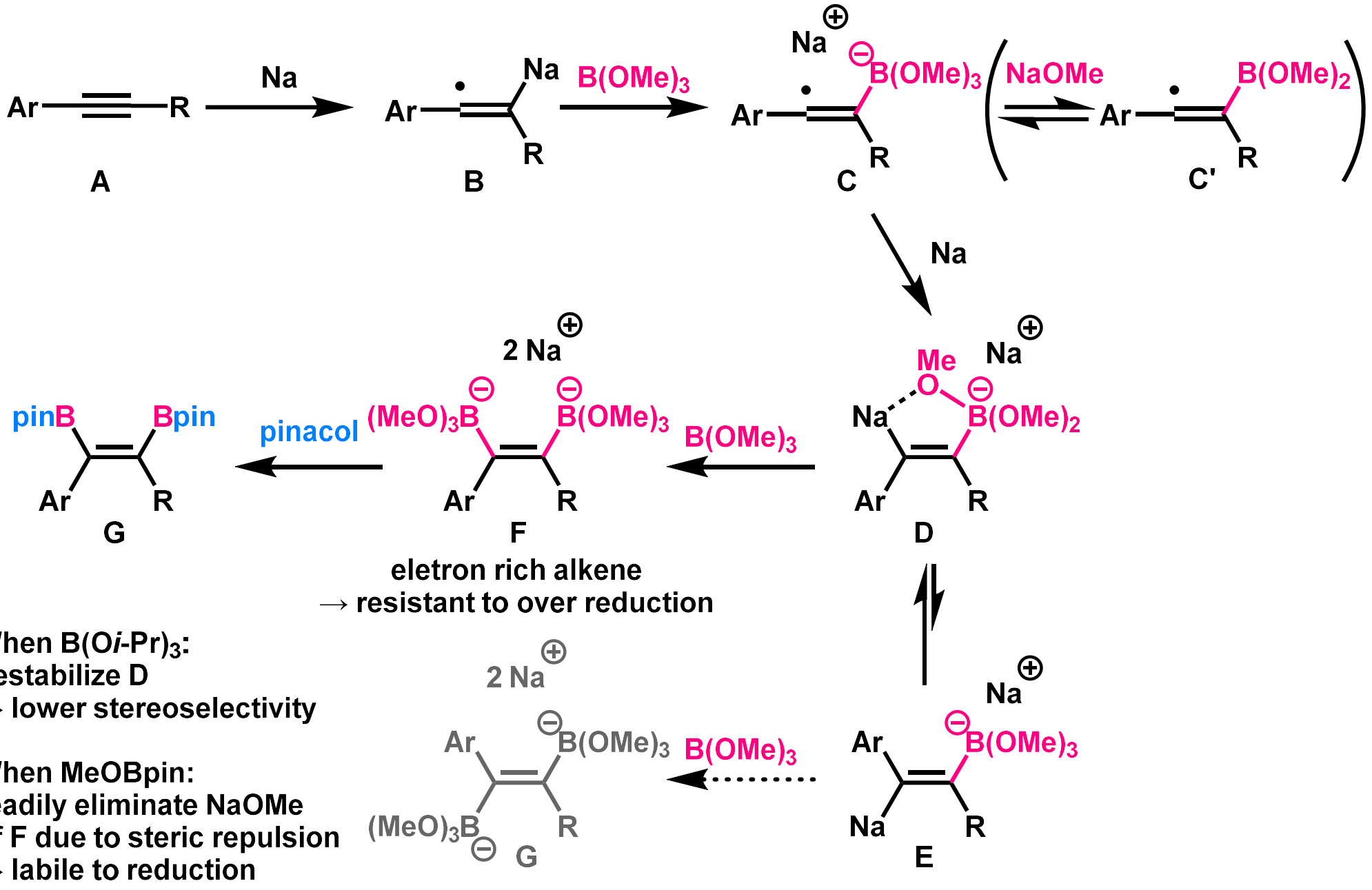
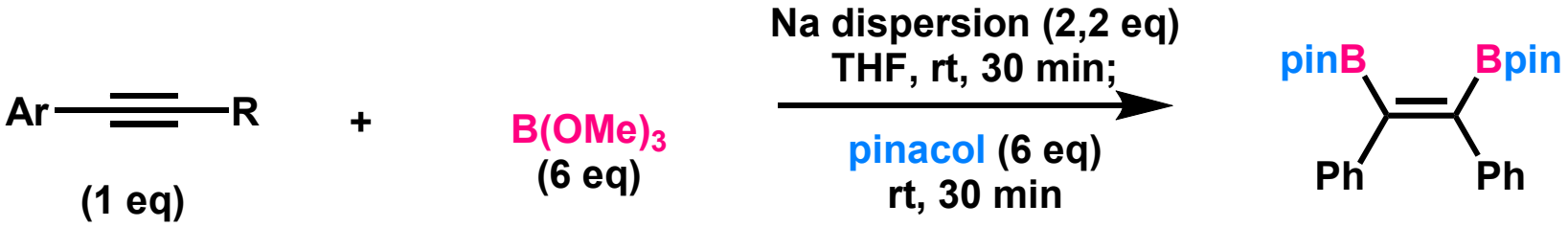
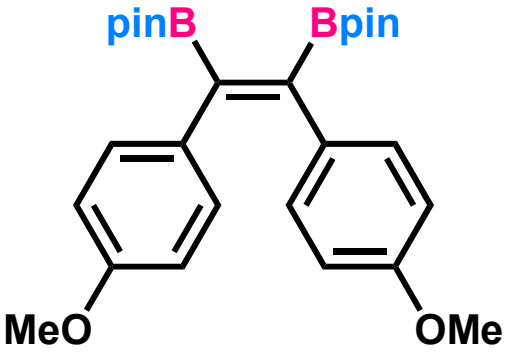
Rationale for Stereoselectivity

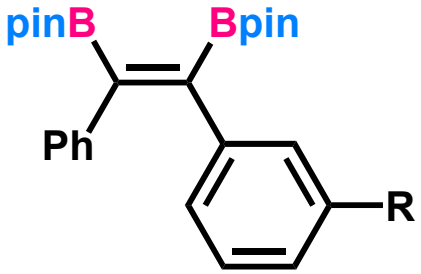


Substrate Scope and Limitation

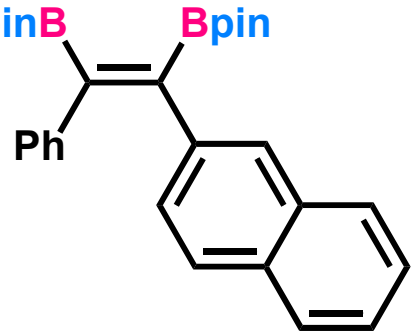




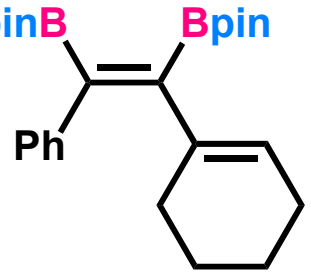
58% (83%[a])



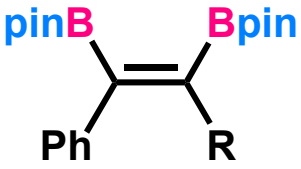
R = SMe: 52% (76%[a])
R = F: 44% (78%[a])



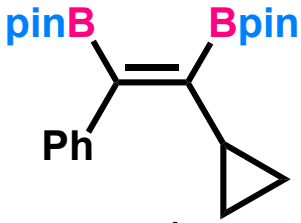
45% (55%[a])



53%, *E*:*Z* = 4:96
(63%[a])



R = Me: 80%[b]
R = Bu: 72%[b]
R = TMS: 65%[b]
R = H: 27%[b,c]

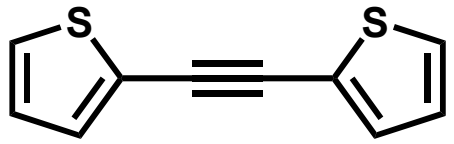


72%[b,c]

unsuccessful alkynes:

(R = CH_2Cl, OTs, OH, CN)

complex mixture
(29%[b,c])

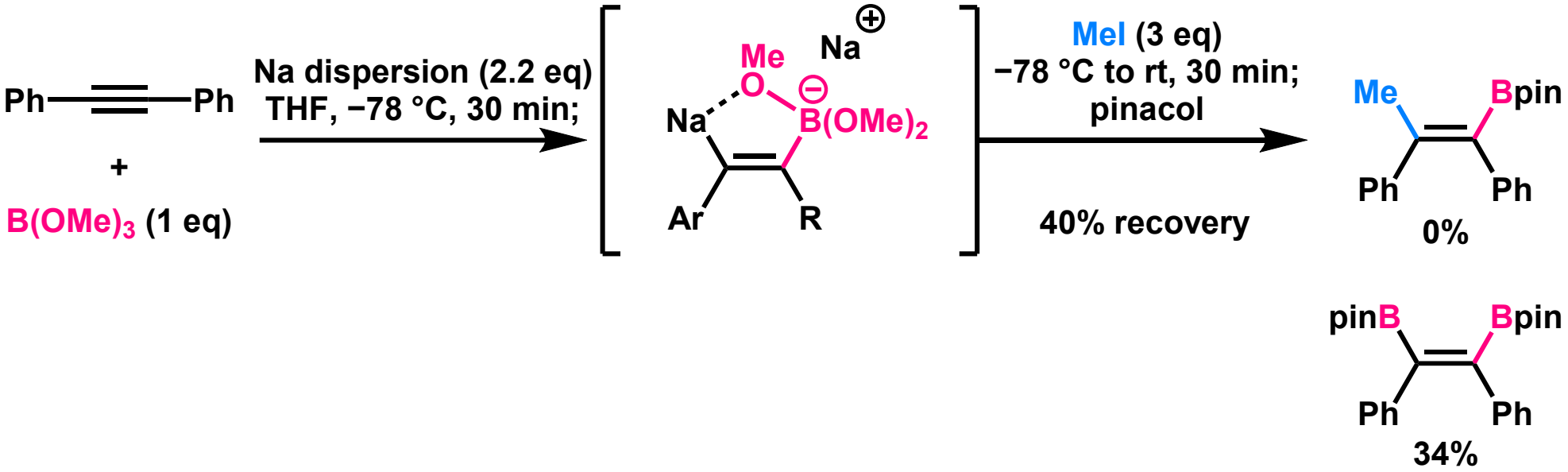


[a] NMR yield [b] $B(OMe)_3$ (6 eq), Na dispersion (3 eq) [c] at −78 °C

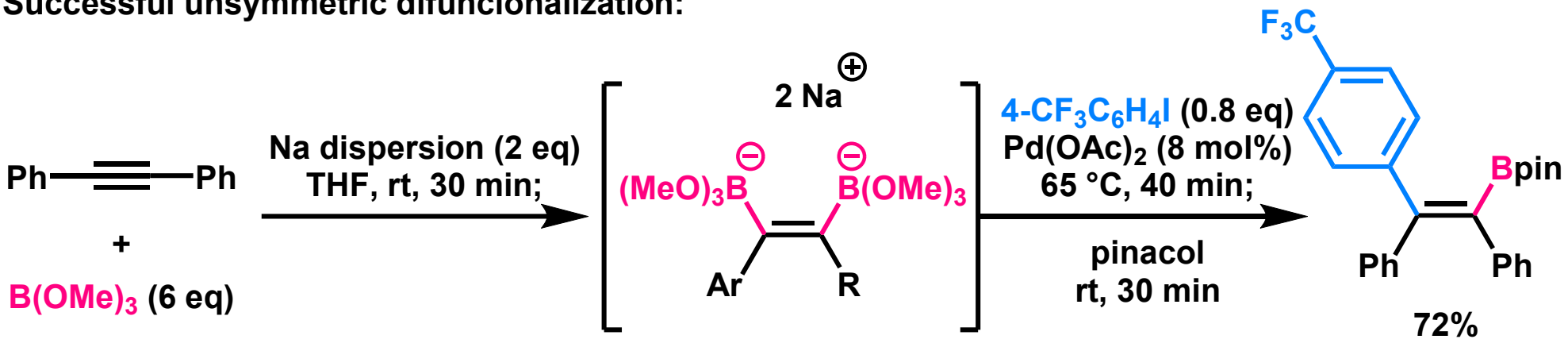
Ito, S.; Fukazawa, M.; Takahashi, F.; Nogi, K.; Yorimitsu, H. *Bull. Chem. Soc. Jpn.* **2020**, *93*, 1171.

Trial of Unsymmetric Difunctionalization

Unsuccessful unsymmetric difuncionalization:



Successful unsymmetric difuncionalization:



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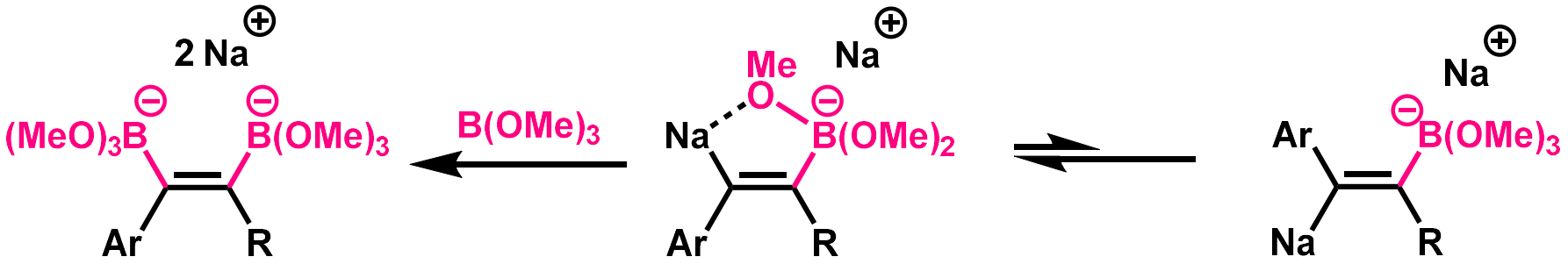
(E)-Selective Difunctionalization

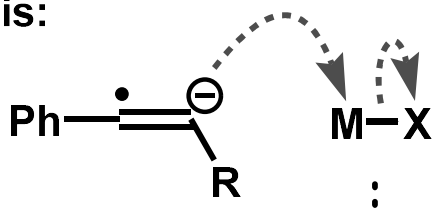


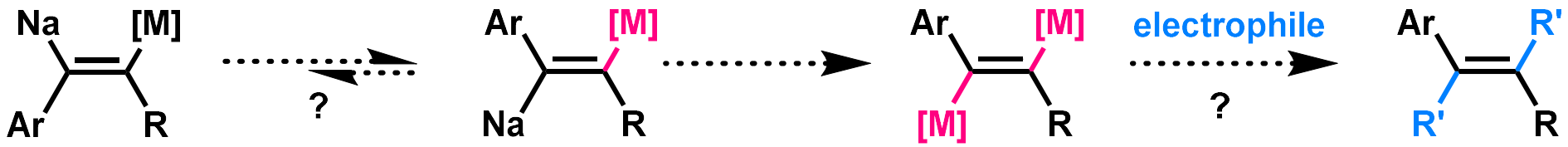
(*Z*)-selective

to (*E*)-isomer

Methoxy group acted as a ligand to stabilize the (*Z*)-isomer.
However, the generated borate is less nuculeophilic.

Working hypothesis:

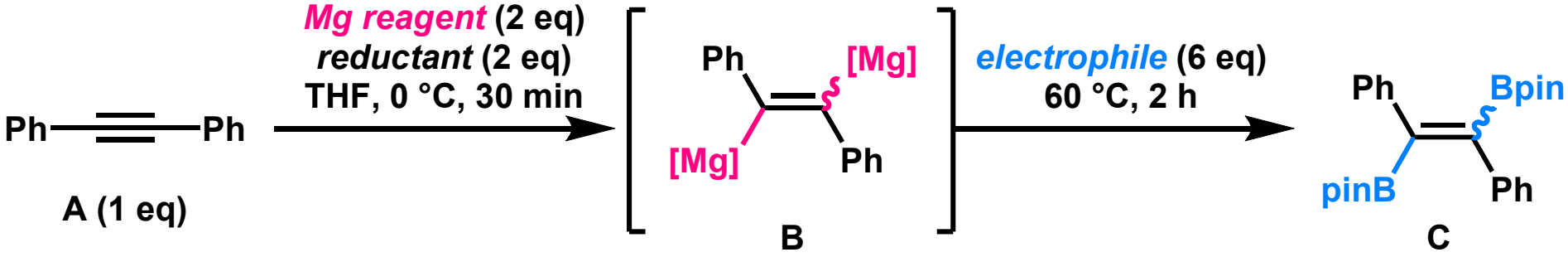




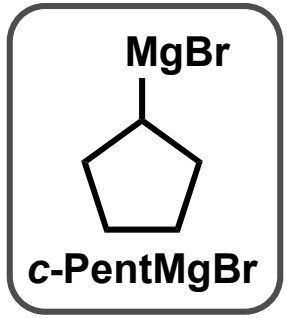
to (*Z*)-isomer [M]: no donative substituent (*E*)-selective

Is it possible to reverse *E*/*Z* selectivity?
Is it possible to conduct nucleophilic attack from generated dimetal?
→ For electrophile: RMgX *or* R_2AlX (MgX_2 would be reduced to Mg^0 under the conditions)

(E)-Selective Dimetalation



Mg reagent	*reductant*	*electrophile*	C yield	C (*Z* : *E*)
i-PrMgBr	Na dispersion	MeOBpin	90%	57 : 43
i-PrMgBr	Na dispersion	EtOBpin	86%	78 : 22
i-PrMgBr	Na dispersion	*i*-PrOBpin	75%	80 : 20
MeMgBr	Na dispersion	*i*-PrOBpin	49%	47 : 53
t-BuMgBr	Na dispersion	*i*-PrOBpin	75%	72 : 28
c-PentMgBr	Na dispersion	*i*-PrOBpin	85%	88 : 12
c-PentMgBr	Na lump	*i*-PrOBpin	25%	76 : 24
c-PentMgBr	Li powder	*i*-PrOBpin	59%	51 : 49
c-PentMgBr	$NaC_{10}H_8$	*i*-PrOBpin	74%	91 : 9



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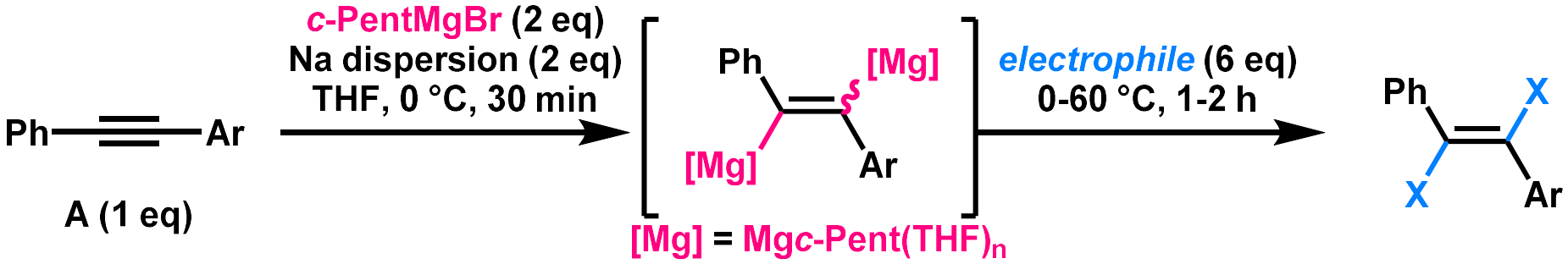
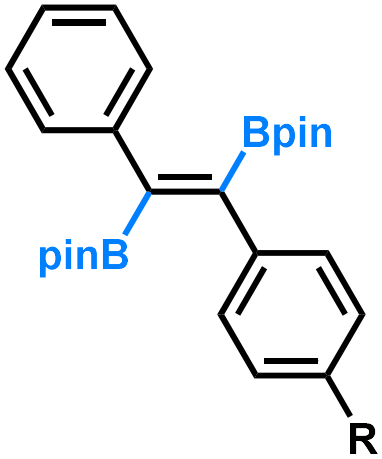
Substrate Scope

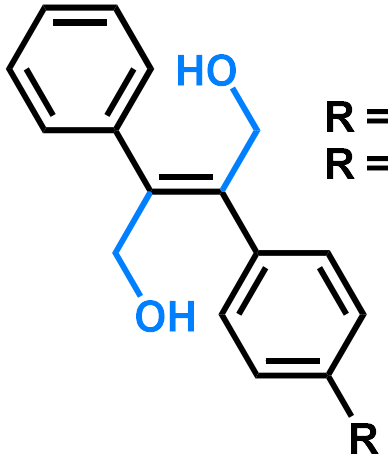


electrophile: *i*-PrOBpin



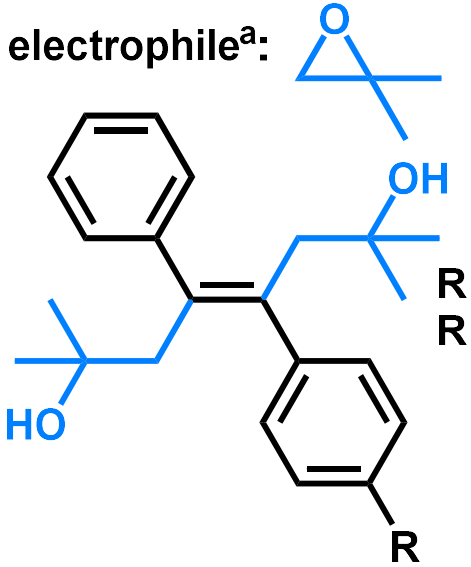
R = H: 74%
R = *o*-OMe: 63%
R = *m*-OMe: 70%
R = *p*-OMe: 65%
R = *m*-SMe: 61%
R = *m*-F: 55%
R = *p*-TMS: 75%

electrophile: $(CH_2O)_n$



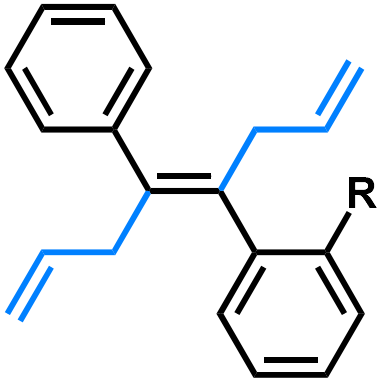
R = H: 66%
R = OMe: 67%

electrophile[a]:



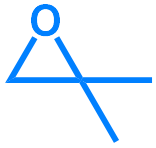
R = H: 67%
R = *m*-F: 71%

electrophile[a]:



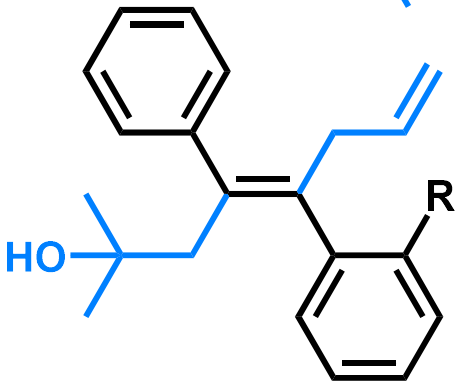
R = H: 71% (*E*:*Z* = >40:1)
R = OMe: 71% (*E*:*Z* = >40:1)

electrophile[a]:



(1 eq);

(1 eq)



R = H: 53% (*E*:*Z* = >30:1)
R = OMe: 54% (*E*:*Z* = >30:1)

[a] with 10 mol% of CuCN•2LiCl

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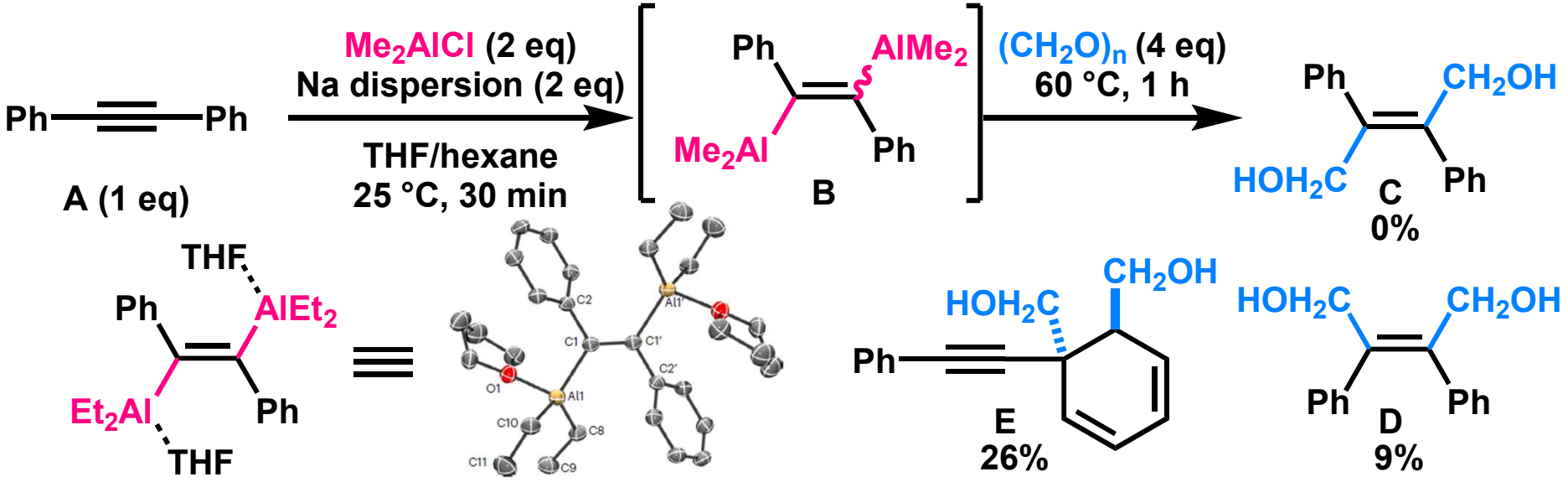
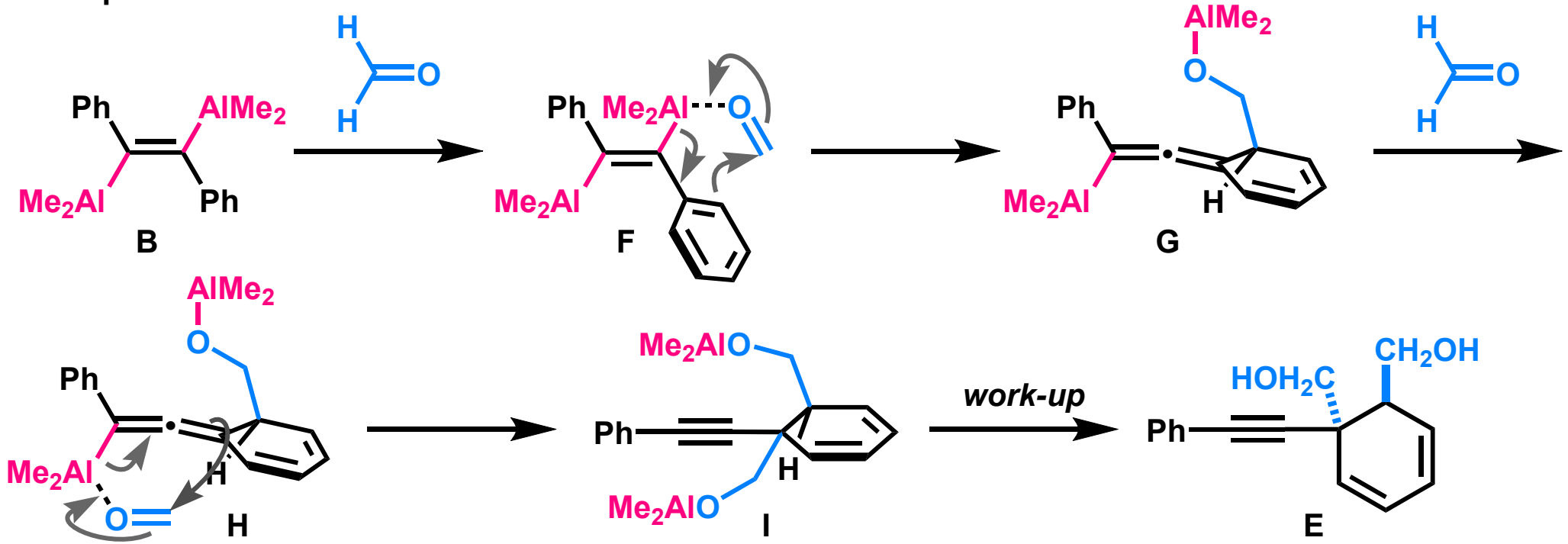
Unique Reactivity of Dialminoalkene (1)



Proposed mechanism:



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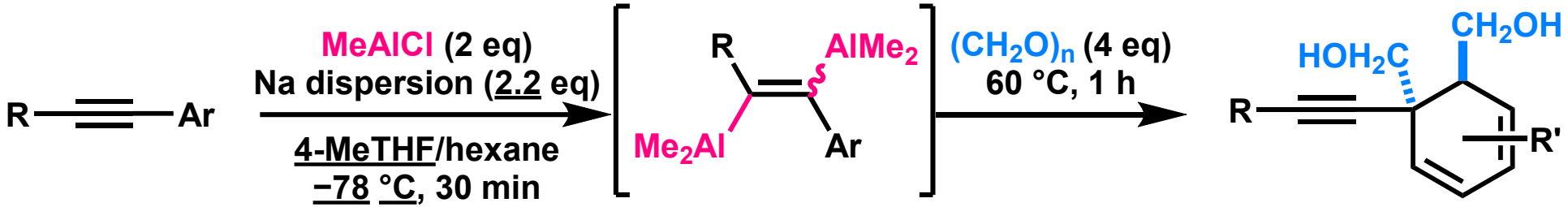
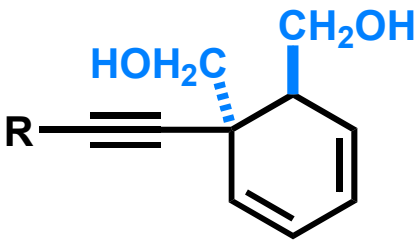
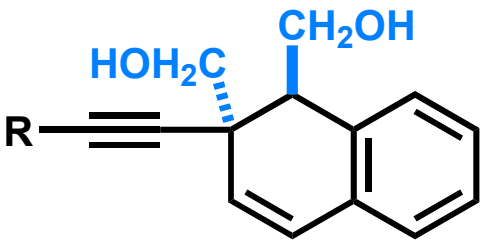
Unique Reactivity of Dialminoalkene (1)

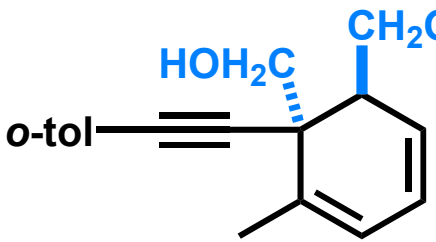


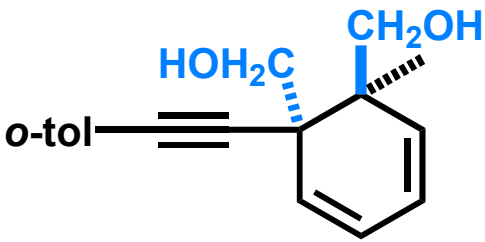


R = Ph: 86%
R = *t*-Bu: 75%
R = *n*-Bu: 57%



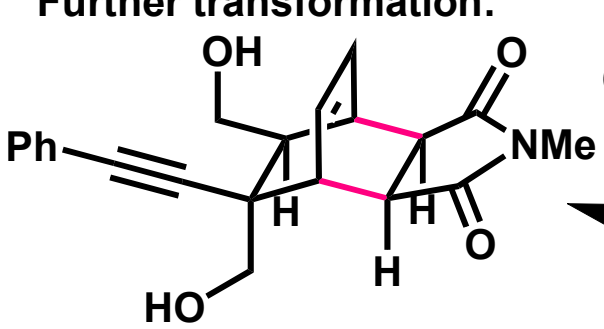
R = Ph: 57%
R = TMS: 48%

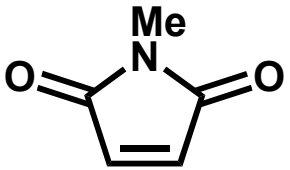




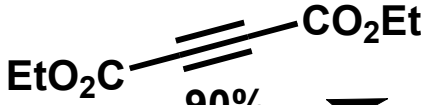
total: 60%
(r.r. = 70: 30)

Further transformation:

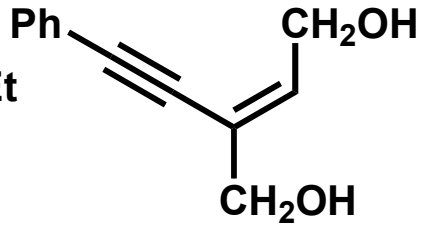


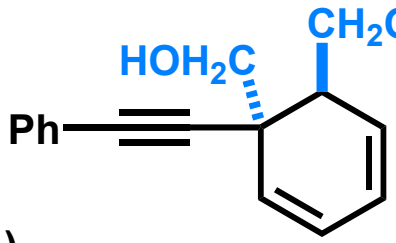


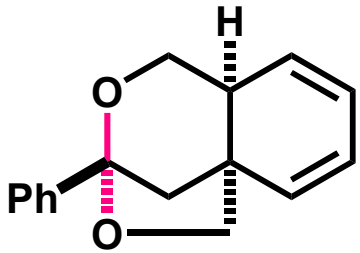
84%



90%

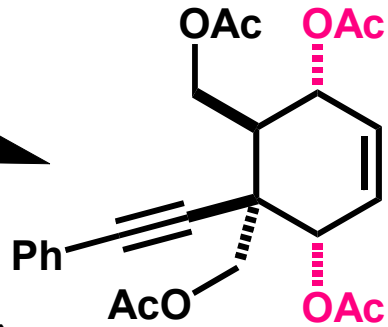






$AuCl(PPh_3)_4$
AgOTf
p-TsOH
92%

1. $^1O_2$;
thiourea
2. Ac_2O
pyridine
34% (2 steps)



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1. Introduction
2. *E*/*Z*-Selective Difunctionalization
3. **Regioselective Difunctionalization (main paper)**

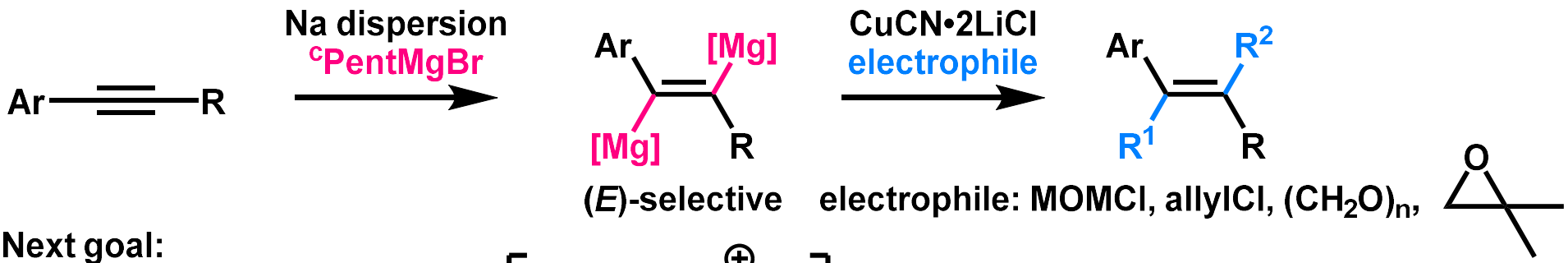
nature synthesis

Article

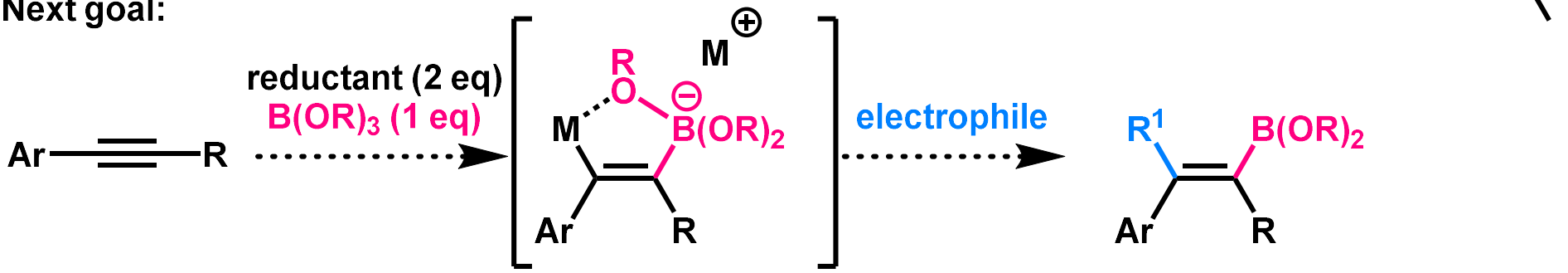
https://doi.org/10.1038/s44160-023-00439-8

Reductive stereo- and regiocontrolled boryllithiation and borylsodiation of arylacetylenes using flow microreactors

Unsymmetric Difunctionalization

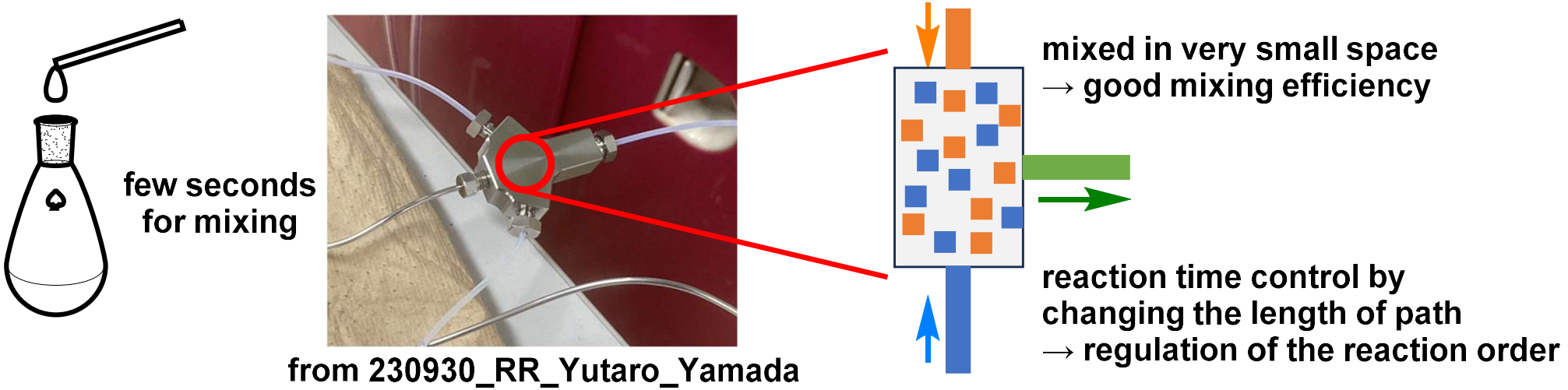


Next goal:



Challenge: Controlling of the reactive intermediate →application of flow system (micro reactor)

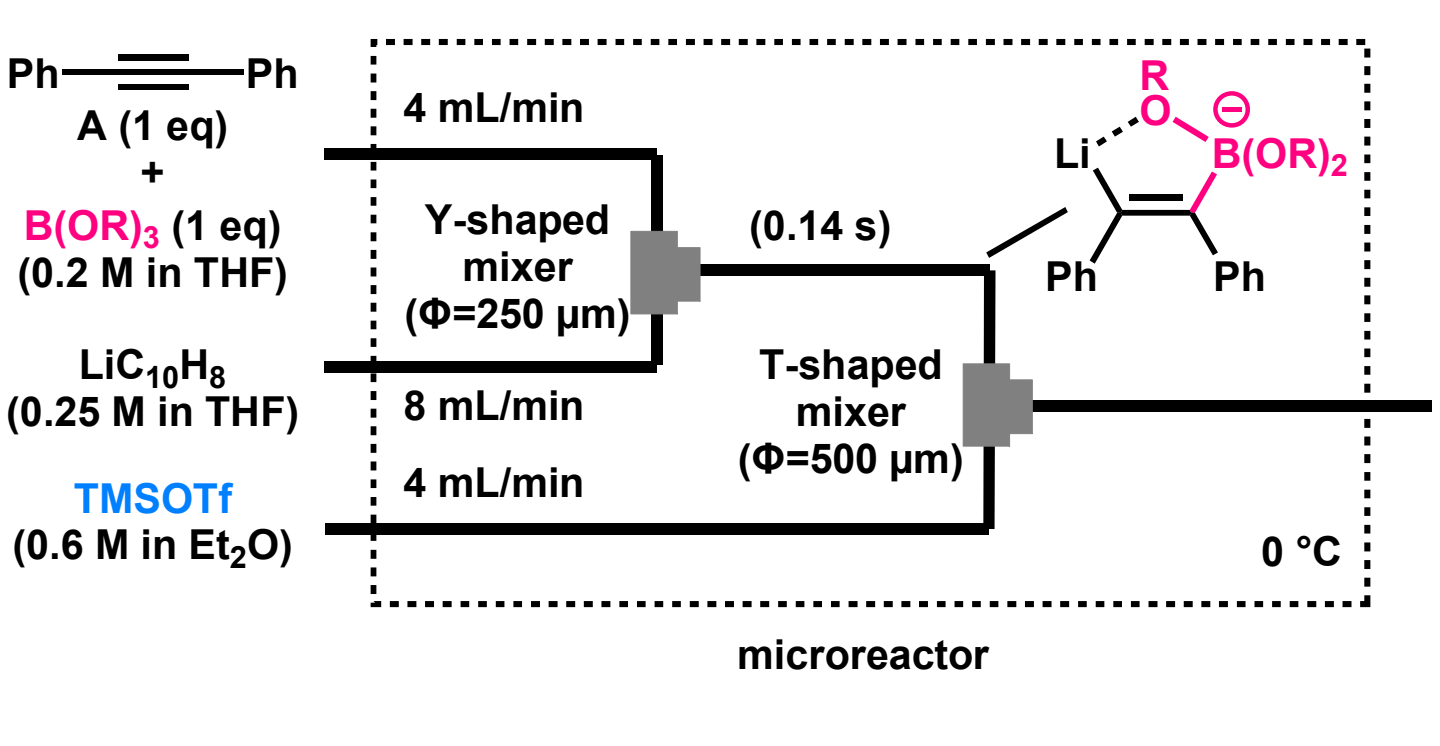
Advantage of microreactor: mixing efficiency, applicable to short-lived intermediate

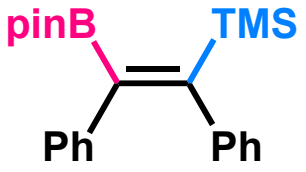


from 230930_RR_Yutaro_Yamada

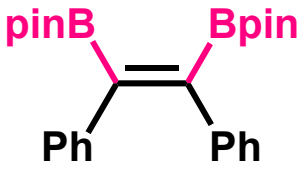
1. Hartman, R. L.; McMullen, J. P.; Jensen, K. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 7502.
2. See also. 230203_LS_Masanori_NAGATOMO, 140301_Takefumi_Kuranaga

Optimization in Microreactor (1)

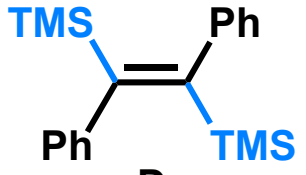




B (desired)



C



D

$B(OR)_3$	B	C	D
$B(OMe)_3$[a]	15%	0%	9%
$B(O\textit{i}\text{-}Pr)_3$[a]	12%	0%	22%
MeOBpin	60%	trace	5%
EtOBpin	72%	trace	4%
i-PrOBpin	68%	0%	3%

[a] the resulting solution was treated with pinacol (1.5 eq)

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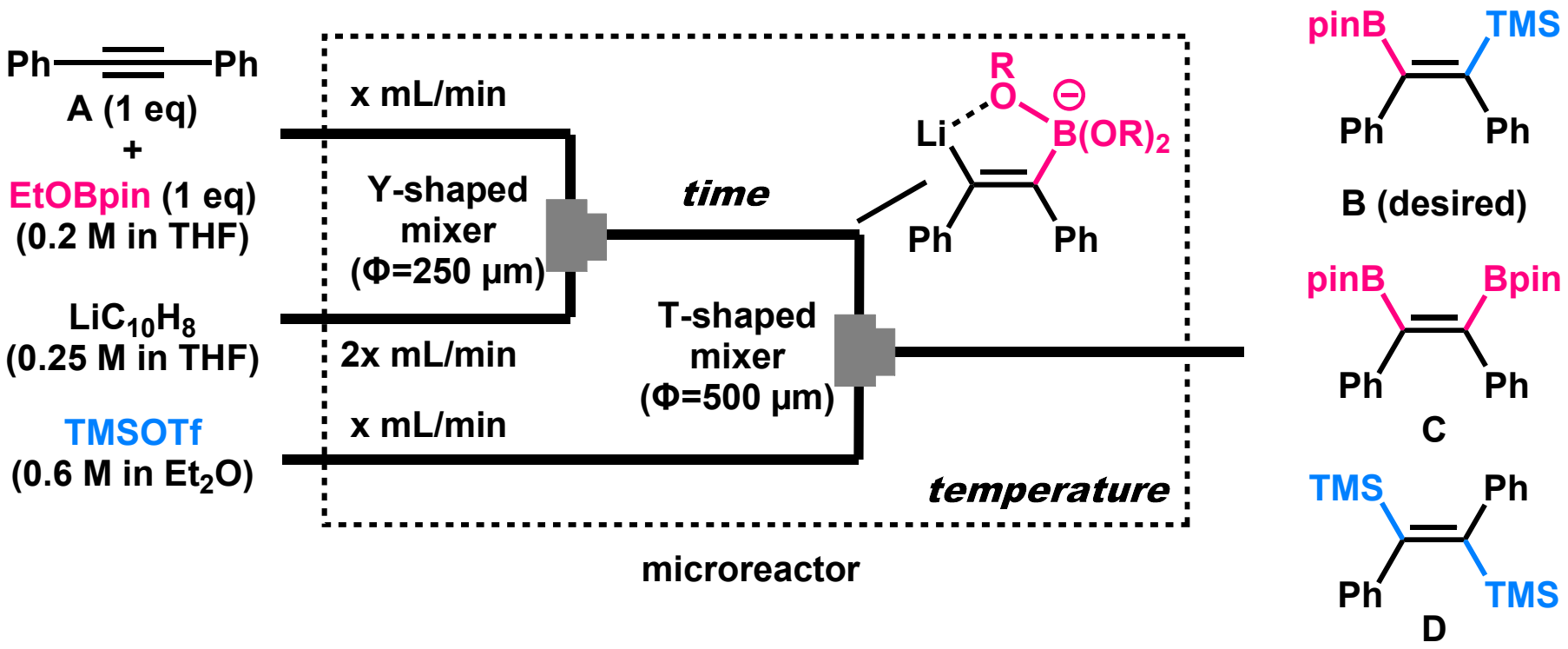
Optimization in Microreactor (2)



temperature	*x*	*time*	A (rec.)	B	C	D
0 °C	x = 4	0.14 s	0%	72%	trace	4%
−20 °C	x = 4	0.14 s	0%	84%	trace	3%
−40 °C	x = 4	0.14 s	0%	64%	0%	2%
−20 °C	x = 4	1.96 s	0%	75%	1%	2%
−20 °C	x = 1	0.14 s	35%	34%	1%	4%

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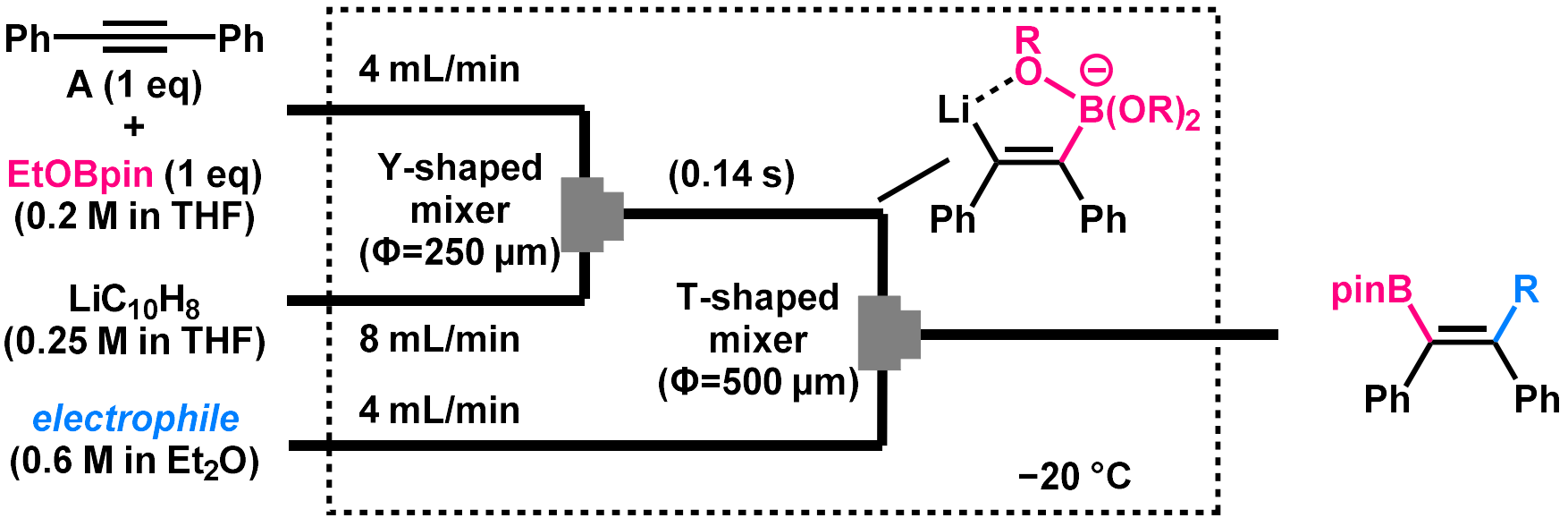
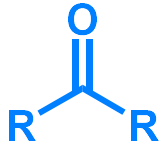
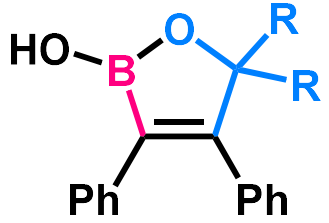
Substrate Scope



electrophile	pinB, R, Ph, Ph	*electrophile*	pinB, R, Ph, Ph	*electrophile*	pinB, R, Ph, Ph
TMSOTf	R = TMS (81%)	C_2Cl_6	R = Cl (84%)	C_6F_6[a]	R = C_6F_5 (78%)
CD_3OD	R = D (77%, 97%D)	PhCN	R = COPh (47%)		
n-Bu_3SnCl	R = Sn(*n*-Bu)$_3$ (79%, *E*:*Z* = 96:4)	PhCNO	R = CONHPh (70%)		
MeOTf	R = Me (88%)	$Ph_2P(=O)Cl$	R = $POPh_2$ (66%)		
$FN(SO_2Ph)_2$	R = F (57%)	MeSSMe	R = SMe (79%)		
		PhSeSePh	R = SePh (71%)		

R = Ph, H: 86%
R = Me, Me: 42%
R = −$(CH_2)_3$−: 75%

[a] $NaC_{10}H_8$ was used instead of $LiC_{10}H_8$

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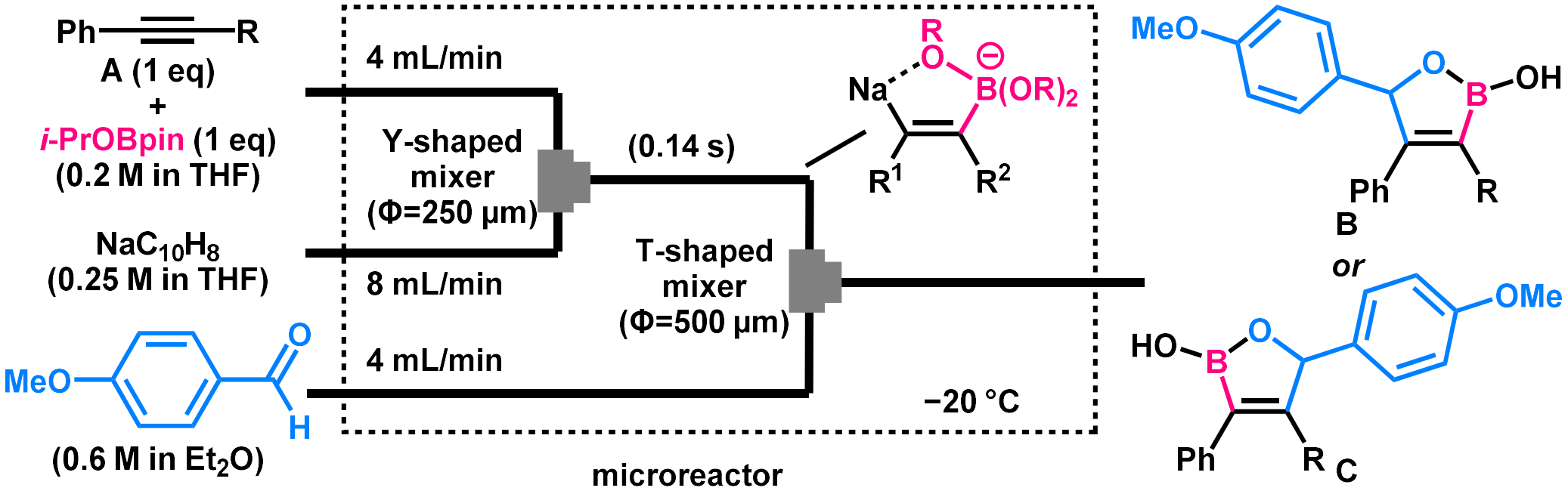
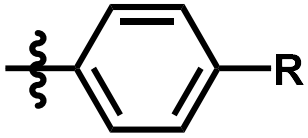
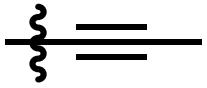
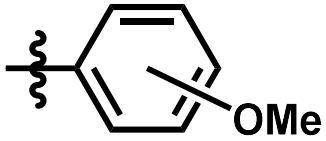
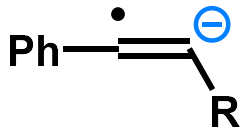
Regioselective Reductive Difuncionalization



R	yield (B:C)	R	yield (B:C)
	R = Me: 67% (91:9) R = TMS: 79% (<1:99) R = Ph: 73% (<1:99) R =  Ph : 58% (<1:99)		*p*-OMe: 76% (>99:1) *m*-OMe: 90% (28:72) *o*-OMe: 51% (<1:99)
Me[a]	52% (>99:1)		
n-Bu[a]	59% (95:5)		

[a] LiDBB was used instead of $NaC_{10}H_8$

Rationale for regioselectivity (my proposal)



When R is electron rich, anion is more reactive due to electron repulsion.

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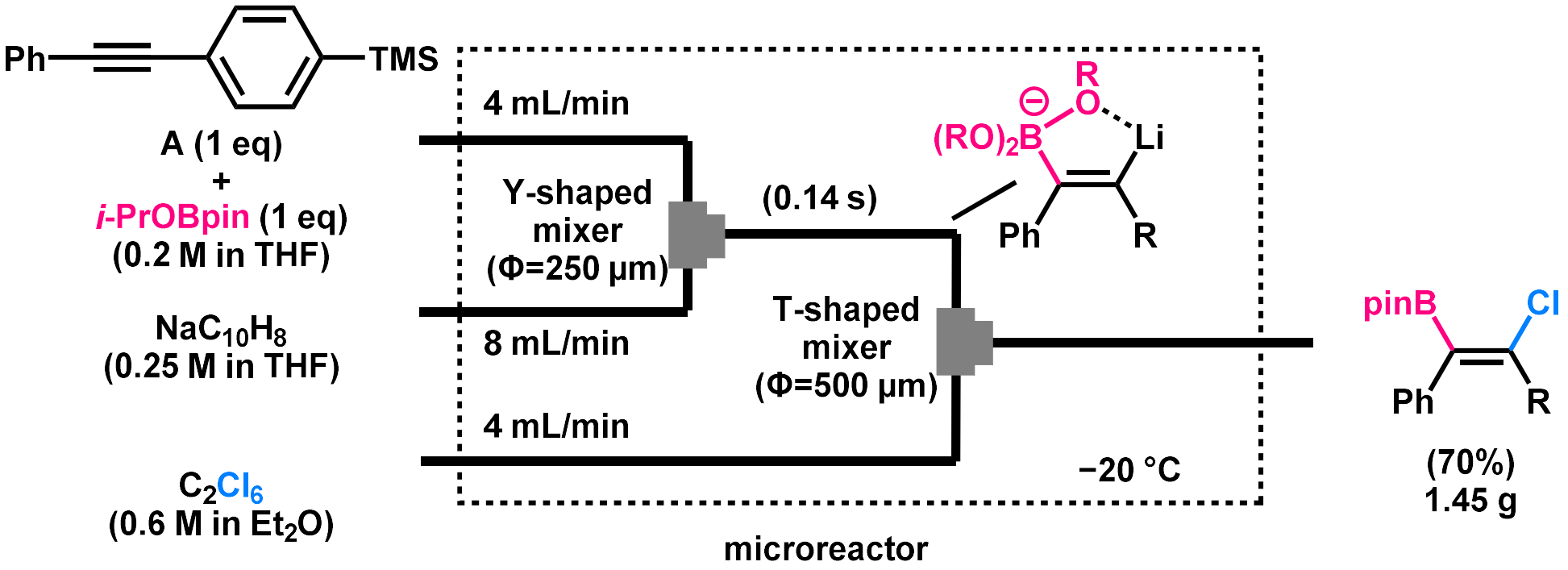
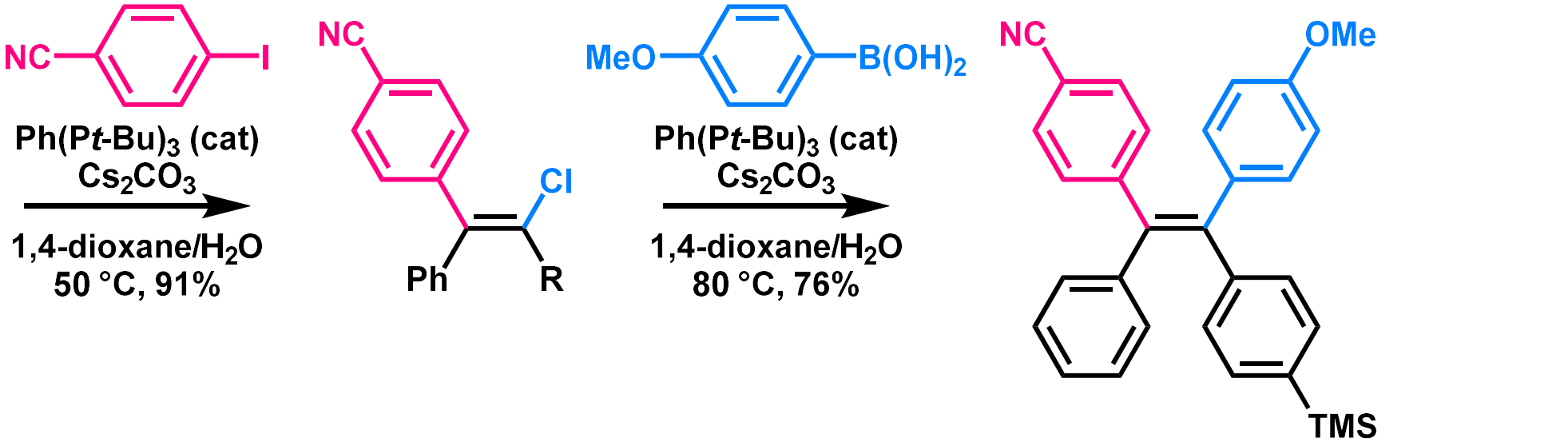
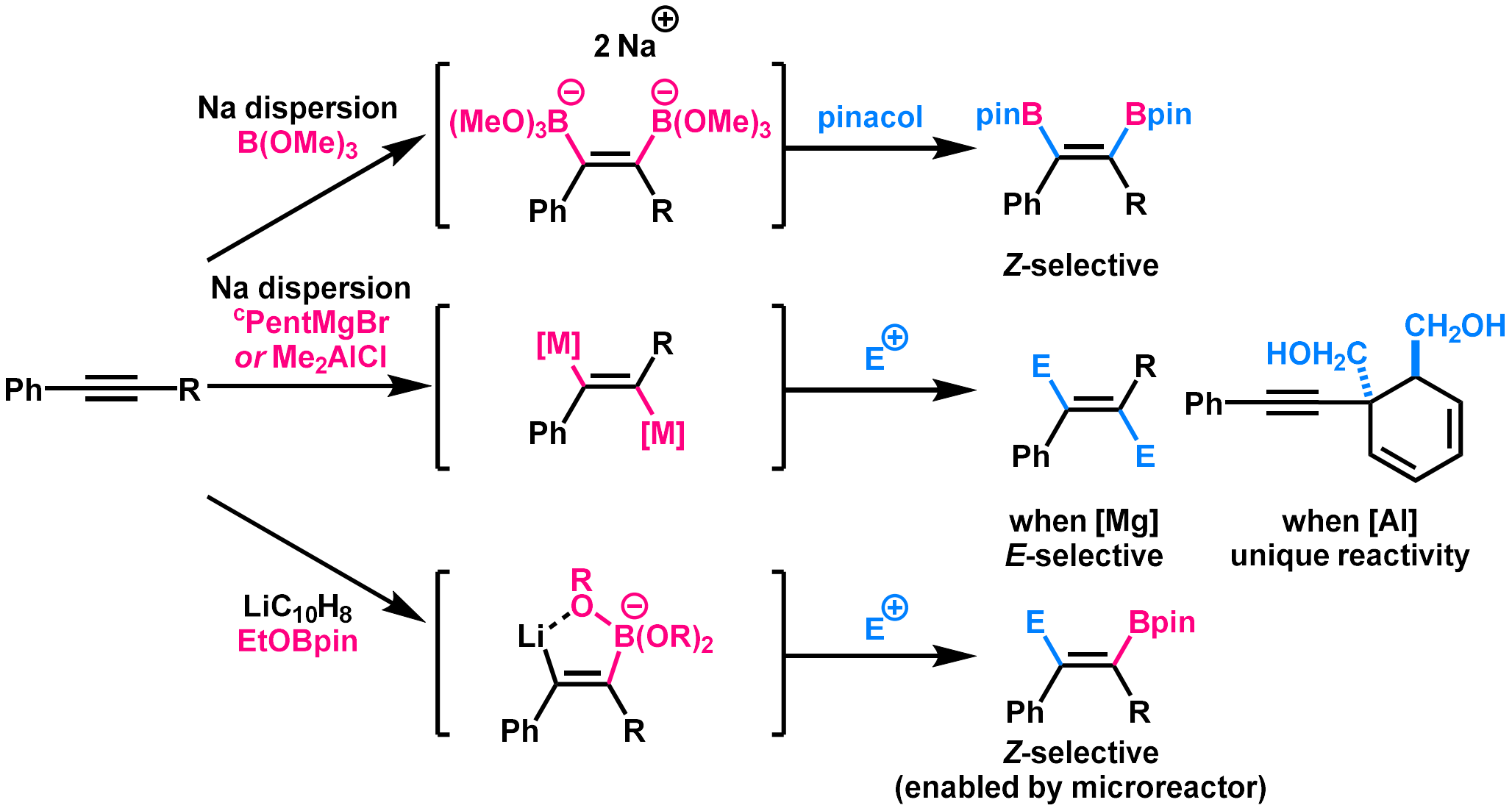
Further Transformation





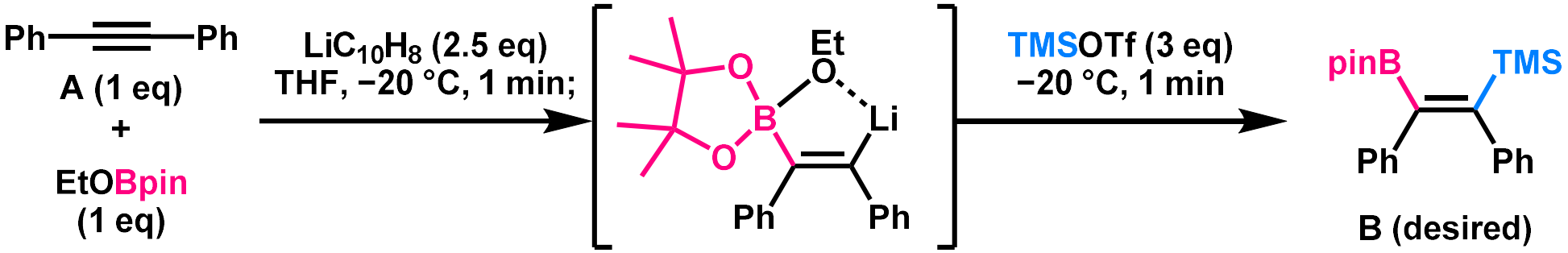
substituted with four different aromatic rings

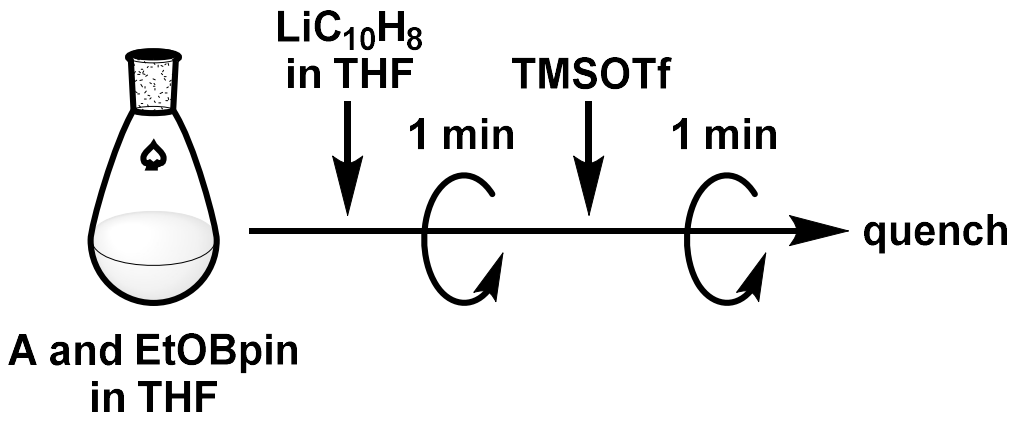
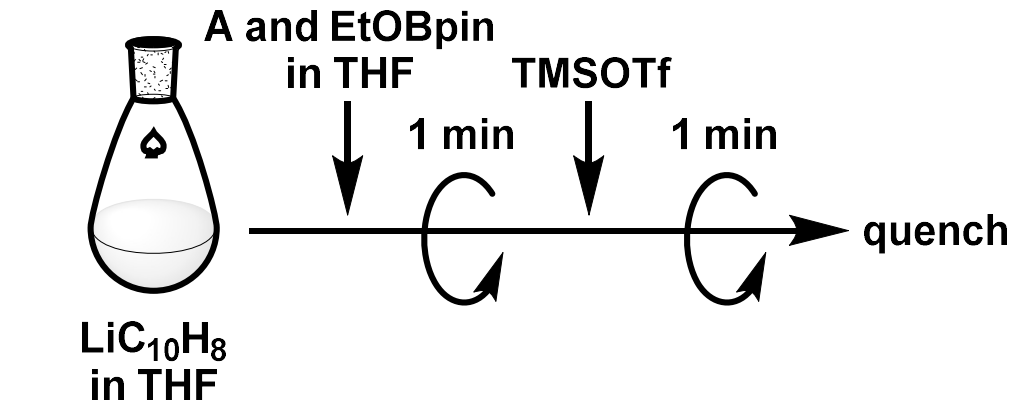
Summary

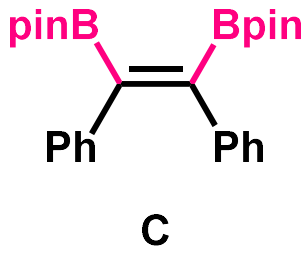

2 Na⊕
Na dispersion
B(OMe)3
(MeO)3B⊖
B(OMe)3⊖
Ph
R
pinacol
pinB
Bpin
Ph
R
Z-selective
Na dispersion
cPentMgBr
or Me2AlCl
Ph
R
[M]
R
Ph
[M]
E⊕
E
R
Ph
E
when [Mg]
E-selective
HOH2C
CH2OH
Ph
when [Al]
unique reactivity
LiC10H8
EtOBpin
R
O⊖
Li
B(OR)2
Ph
R
E⊕
E
Bpin
Ph
R
Z-selective
(enabled by microreactor)

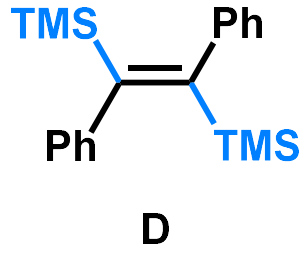
Appendix

Control Experiment in Batch Reaction



procedure	yield (%) A	B	C	D
	10	14	6	12
	9	27	11	4





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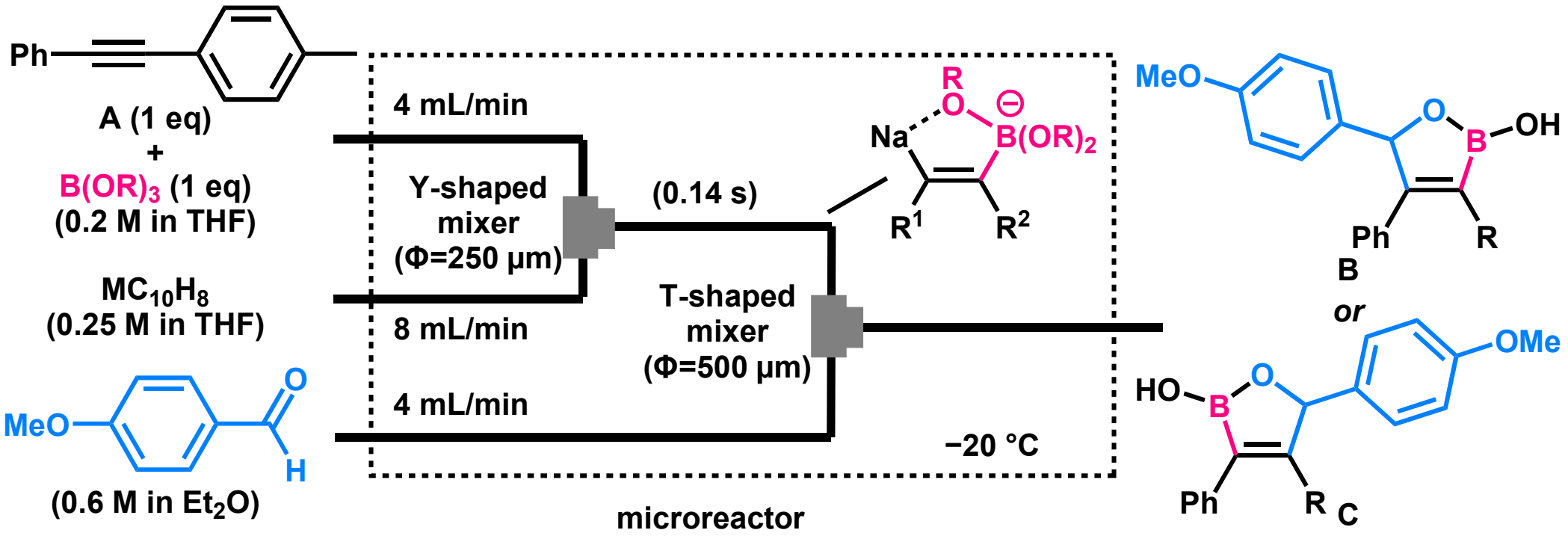
Optimization of Regioselective Difuncionalization



$B(OR)_3$	$MC_{10}H_8$	B	C	B : C
EtOBpin	$LiC_{10}H_8$	44%	26%	63 : 37
EtOBpin	$NaC_{10}H_8$	52%	9%	85 : 15
MeOBpin	$NaC_{10}H_8$	45%	9%	83 : 17
i-PrOBpin	$NaC_{10}H_8$	60%	6%	92 : 8

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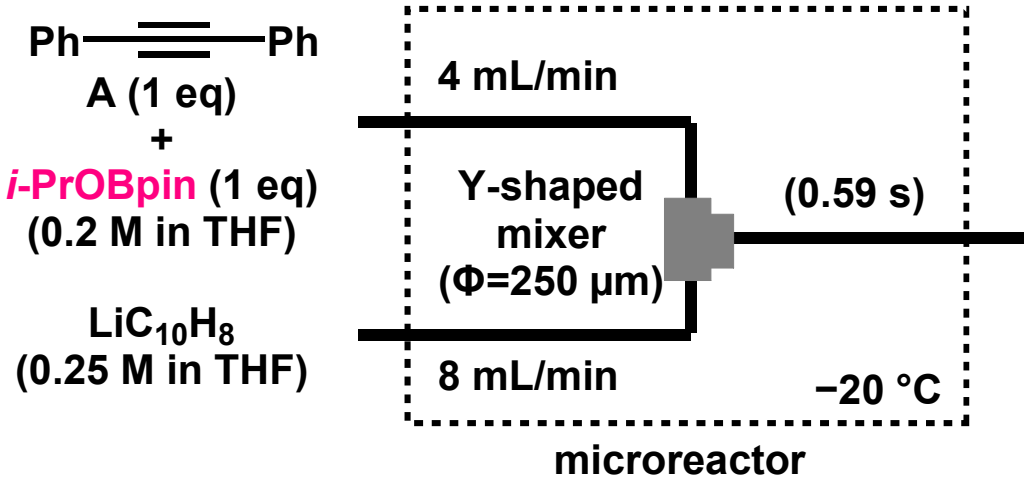
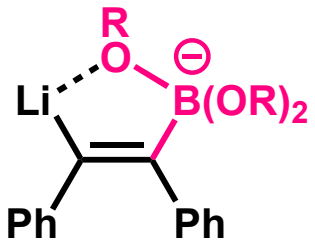
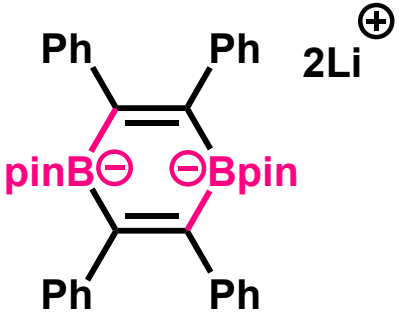
Trial of Isolation of Intermediate

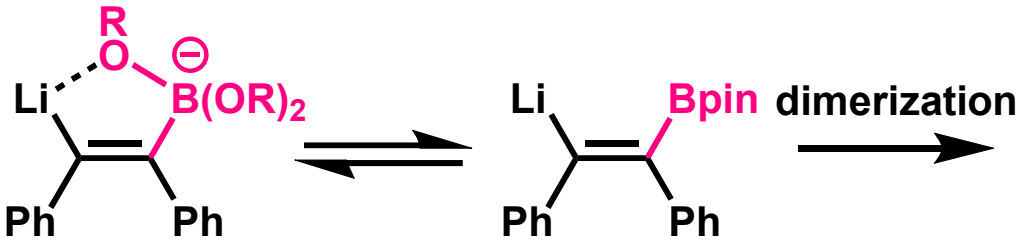


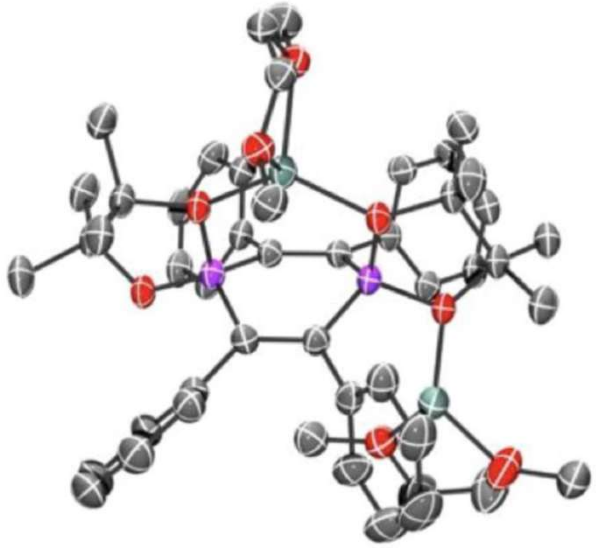


not isolated



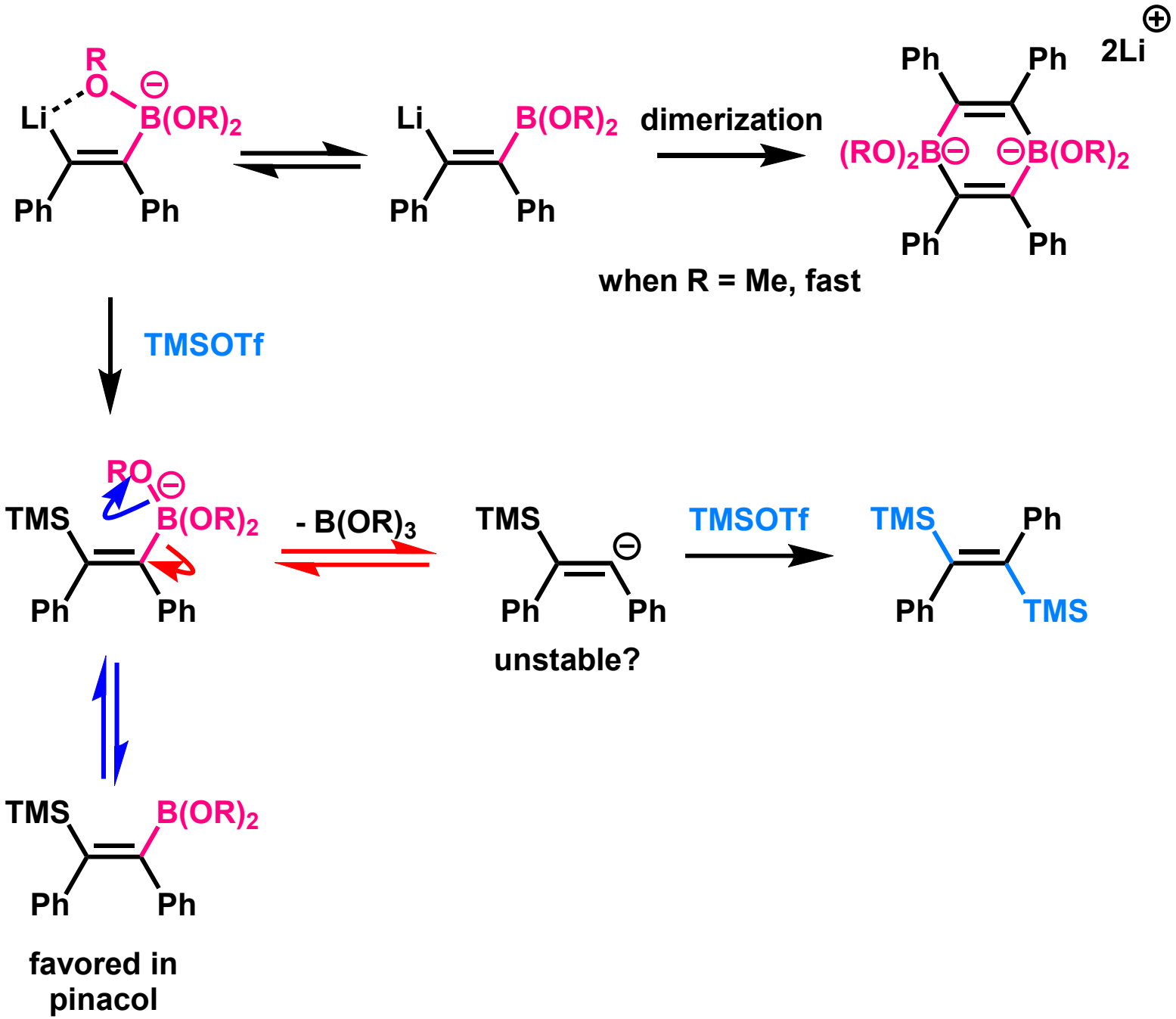
isolated



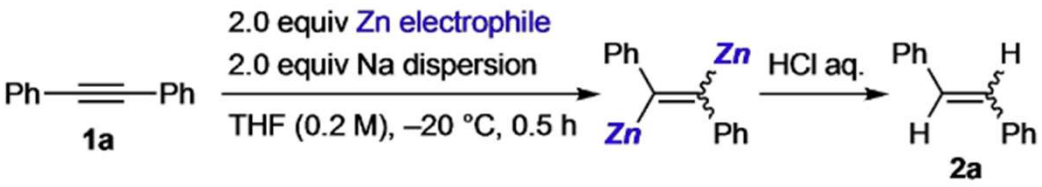


with $MeOCH_2CH_2OMe$

Rationale of the Stability of Intermediate

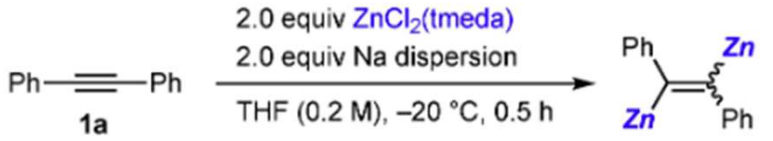


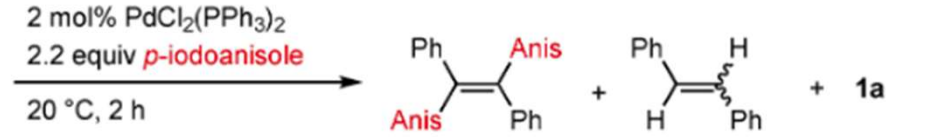
Anti-Dizincation



Entry	Zn electrophile	yield (%)[a]	*E*:*Z*[a]
1	$ZnCl_2$, at 0 °C	38	90:10
2	$ZnCl_2$	62	99:1
3	3.0 equiv $ZnCl_2$[b]	77	90:10
4	$ZnBr_2$	64	94:6
5	ZnI_2	33	78:22
6	$ZnCl_2$(tmeda)[c]	94	93:7
7	$ZnBr_2$(tmeda)[c]	80	94:6
8	ZnI_2(tmeda)[c]	79	90:10
9	$ZnCl_2$(tmpda)[d]	47	85:15
10	$ZnCl_2$(teeda)[e]	99	83:17
11	$ZnCl_2$(btmeda)[f]	99	86:14
12	$ZnCl(OCH_2CH_2NMe_2)$	87	70:30

[a] Yields and *E*/*Z* ratios were determined by ^{1}H NMR using dibromomethane as an internal standard. The remainder is the recovery of 1 a. [b] 3.0 equiv. of both $ZnCl_2$ and Na dispersion. [c] tmeda = $Me_2NCH_2CH_2NMe_2$. [d] tmpda = $Me_2NCH_2CH_2CH_2NMe_2$. [e] teeda = $Et_2NCH_2CH_2NEt_2$. [f] btmeda = $(CH_2)_4NCH_2CH_2N(CH_2)_4$.



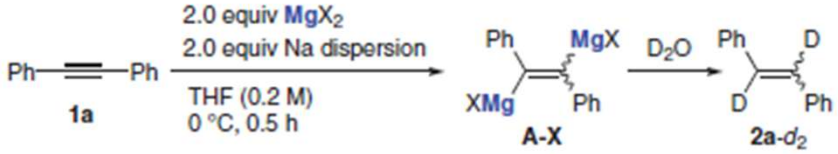


additional conditions for cross-coupling	**3a**	**2a**	recovery
no additive	0%	82% *E*:*Z* = 98:2	15%
4.0 equiv $ZnCl_2$	72%	0%	7%
4.0 equiv $ZnCl_2$ 60 °C, 3 h	93%	0%	5%

Anis = *p*-$MeOC_6H_4$.

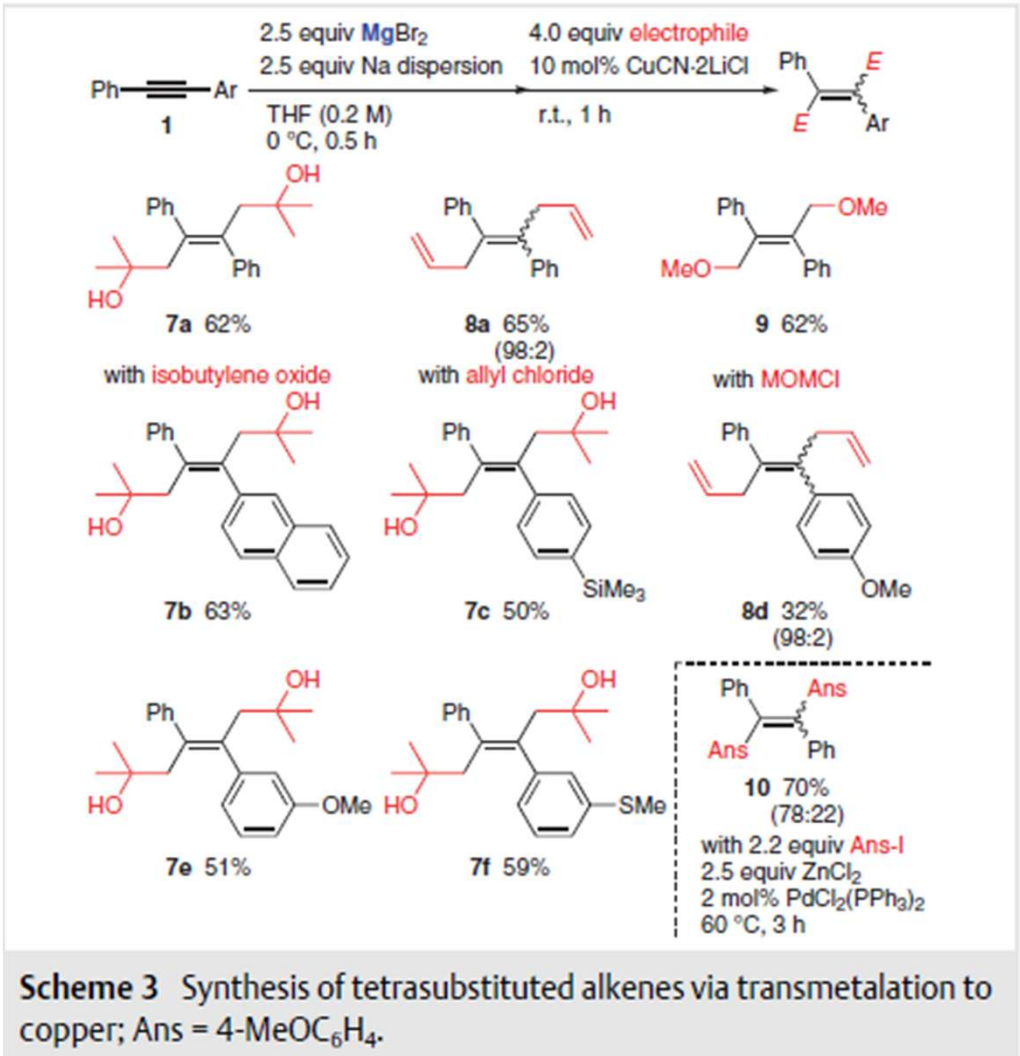
Yamaguchi, H.; Takahashi, F.; Kurogi, T.; Yorimitsu, H. *Chem Asian J.* **2024**, *19*, e202400384.

Dimagnesiation with MgX_2



Entry	MgX_2	Yield (%) of 2a[a]	%D[b]	E/Z[a]
1	$Mg(OTf)_2$	<1	–	–
2	MgF_2	<1	–	–
3	$MgCl_2$	<1	–	–
4	$MgBr_2$	71	98	89:11
5	$MgBr_2$ (2.5 equiv)[c]	98	97	87:13
6	MgI_2	37	–[d]	62:38

[a] Yields and *E*/*Z* ratios were determined by FID-GC analysis using tetradecane as an internal standard.
[b] Deuterium incorporations in (*E*)-**2a** were determined by ^{1}H NMR spectroscopy.
[c] With Na dispersion (2.5 equiv).
[d] Deuterium incorporation in (*E*)-**2a** could not be determined due to overlapping with ^{1}H NMR signals of other products.



Scheme 3 Synthesis of tetrasubstituted alkenes via transmetalation to copper; Ans = 4-$MeOC_6H_4$.