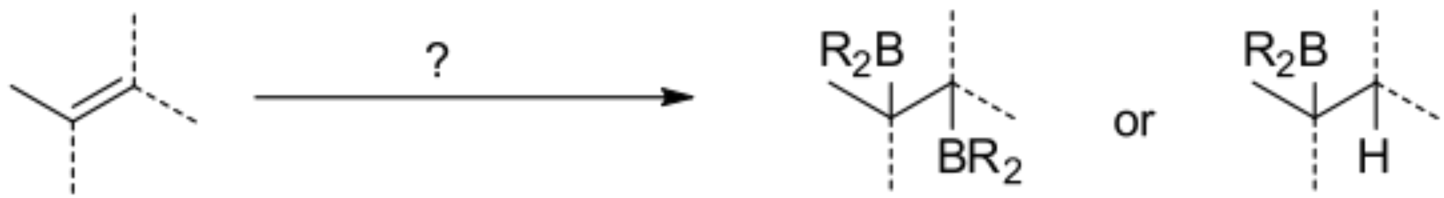
Enantioselective Borylations

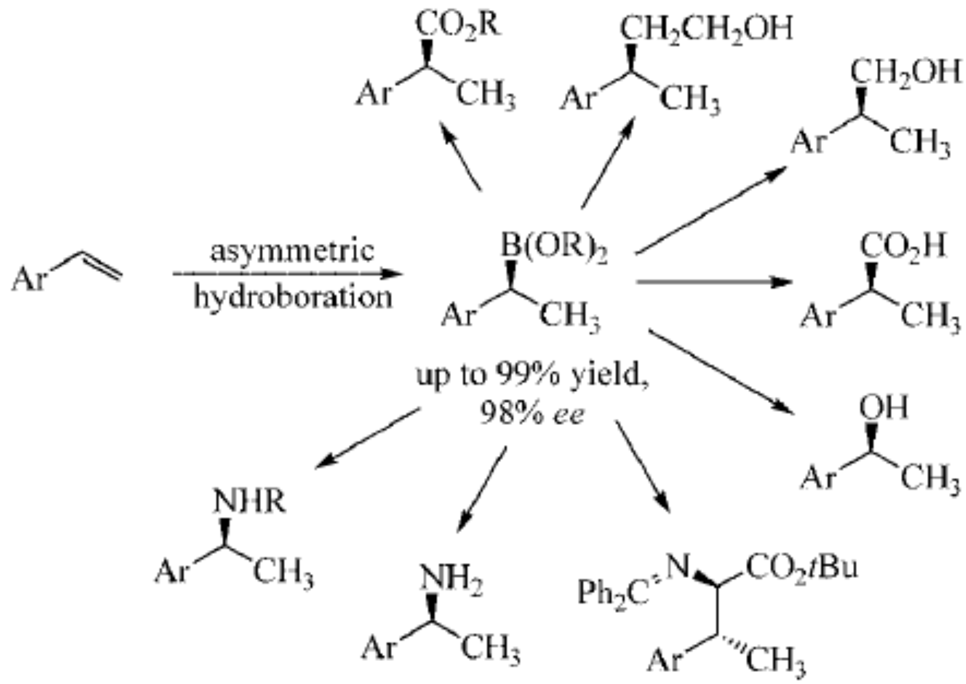
David Kornfilt
Denmark Group Meeting
Sept. 14th 2010

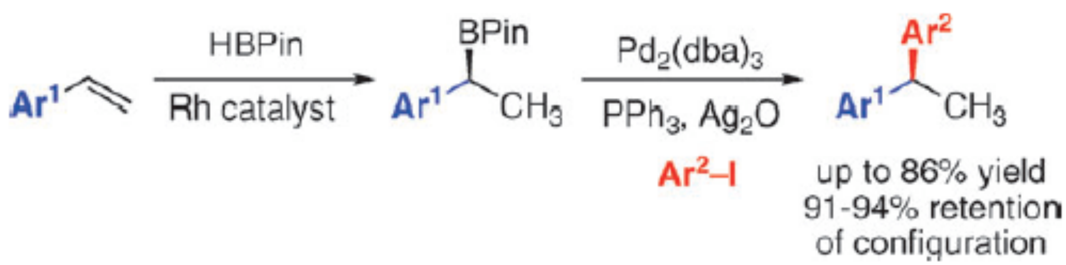
30.000–foot View



Good yield
Good dr
Good er
Good chemoselectivity

Enantioenriched Organoboranes
What to do with them…



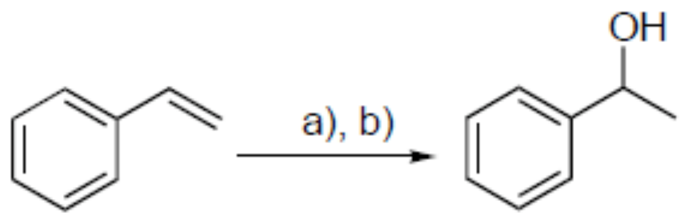


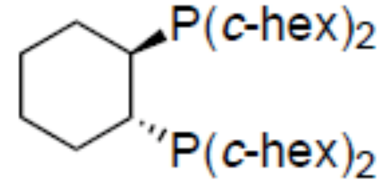
Crudden C. M. et. al., Eur. J. Org. Chem. 2003, 46
4712

Enantioselective Borylations

- Addition of $HB(OR_2)$ to styrenes
- Addition of $HB(OR_2)$ to olefins with electron withdrawing groups
- Addition of $HB(OR_2)$ to other olefins
- Desymmetrizations and Cyclopropanations
- Addition of $B_2(OR_2)_2$ to simple alkenes
- Addition of $B_2(OR_2)_2$ to higher olefins

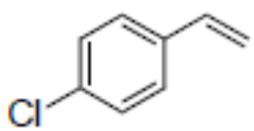
Alkene Monoborylation





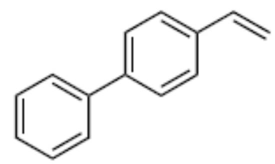
7d

Scheme 4. Rhodium-catalyzed asymmetric hydroboration of styrene with ligands **7a–f**. a) $[Rh(cod)_2]BF_4$ (1.0 mol%), **7a–f** (1.2 mol%), catecholborane (1.2 equiv), solvent; b) 3M KOH, H_2O_2.



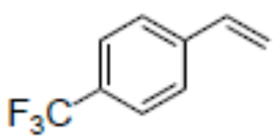
8d

84%, 85% ee



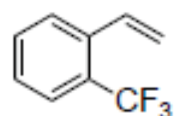
8j

50%, 84% ee



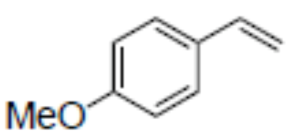
8e

80%, 58% ee



8n

81%, 82%ee

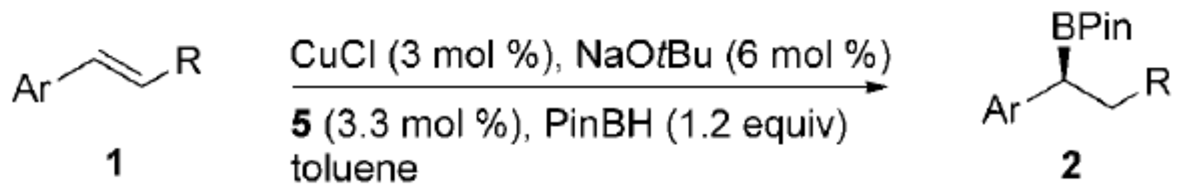


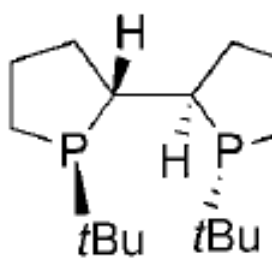
8f

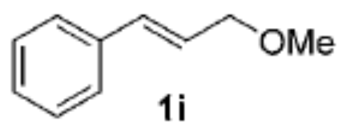
69%, 93% ee

Knochel P. et. al. Angew. Chem. Int. Ed. 2001, 40,

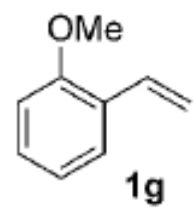
Alkene Monoborylation







61%, 88% ee



90%, 91% ee

- •Very good ee (82–93%) even with o-substituents
- •Naphthyl groups gave poor ee
- •61–95% yield

Yun J. et. al. Angew. Chem. Int. Ed. 2009, 48, 606

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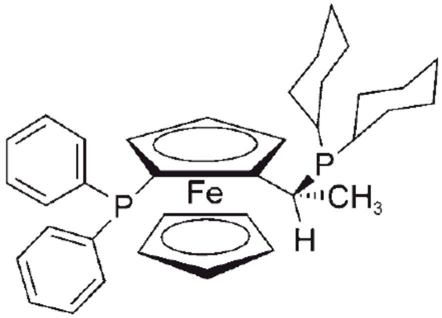
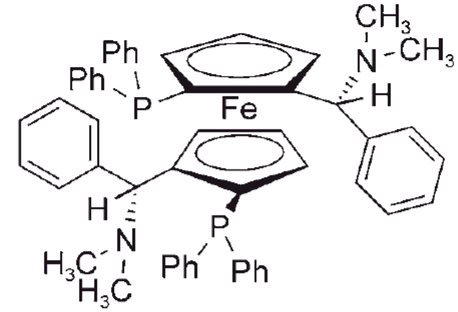
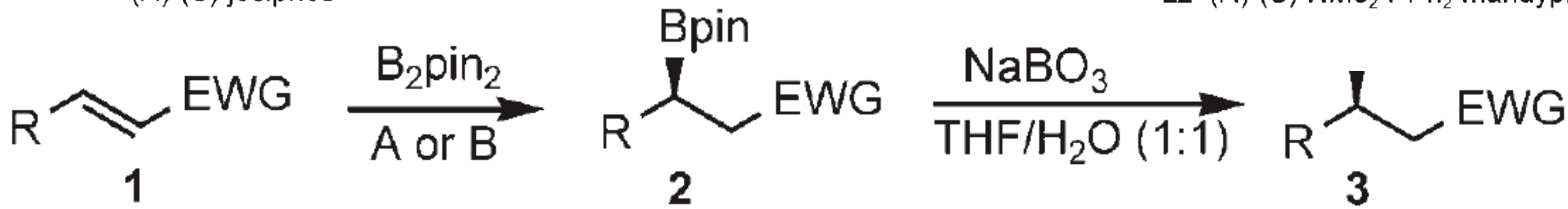


L1 (*R*)-(*S*)-josiphos

β-borylation



L2 (*R*)-(*S*)-NMe_2-PPh_2-mandyphos



Condition A: 2% CuCl, 3% NaOtBu, 4% L1, 2 equiv. MeOH, 1.1 equiv B2pin2 in THF

condition B: 3% CuCl, 3% NaOtBu, 3% L2, 2 equiv. MeOH 1.1 equiv B2pin2 in THF

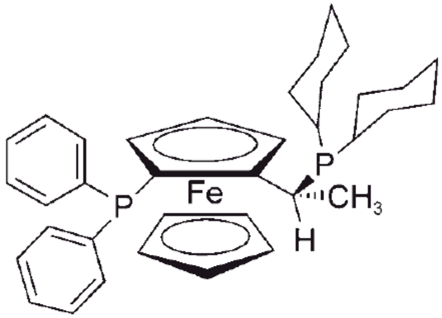
Amides : 3% CuCl, 9% NaOtBu, 3% L2, 2 equiv. MeOH 1.1 equiv B2pin2 in THF

Enones: 3% CuCl, 3% NaOtBu, 3% L2, 1 equiv. MeOH 1 equiv B2pin2 in THF

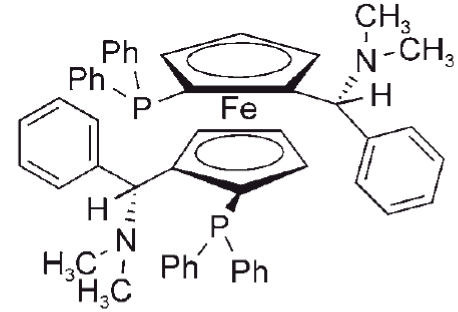
- EWG = Ester, nitrile, amide, ketone
- R = alkyl, aryl, branched alkyl
- High yield (89-97%), 82-92 % ee. Insensitive to character of R-group or ketone/ester fragment
- MeOH additive found to be critical for this reaction

Yun J. et. al., Adv. Synth. Catal. 2009, 351, 85
Yun J. et. al., Angew. Chem. Int. Ed. 2008, 47,
Yun J. et. al., Chem. Eur. J. 2009, 15, 1939 – 1

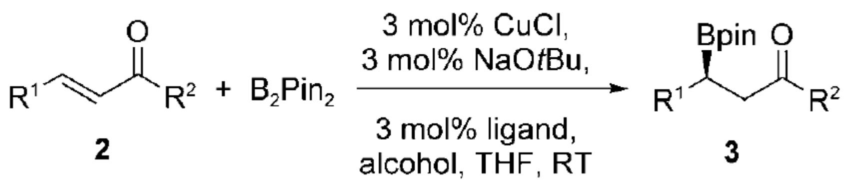
β-borylation

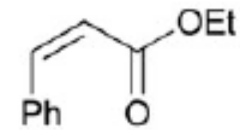


L1 (*R*)-(*S*)-josiphos



L2 (*R*)-(*S*)-NMe_2-PPh_2-mandyphos





(*Z*)-2

With Rh(phebox)
77%, 93% ee

Investigated solvent effects :

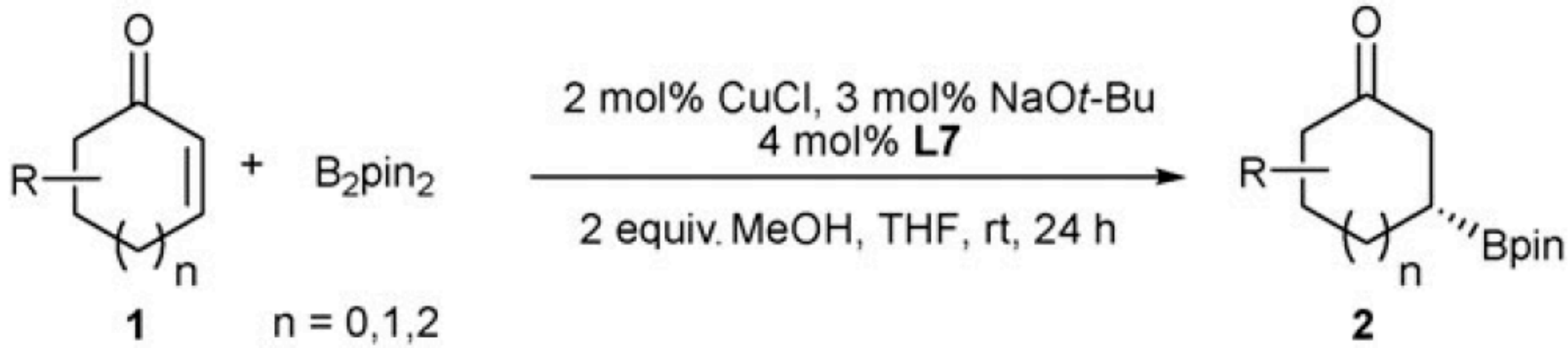
- MeOH, iPrOH and tBuOH all effective
- Solvent affects product enantiomer ratio

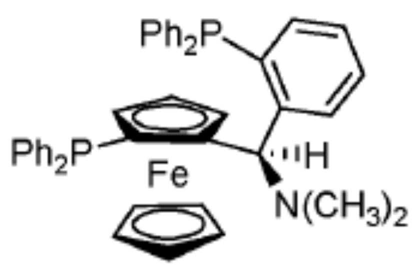
Results :

- Steric factors at R^1 are minimal for all classes.
- Mainly controlled by R^2 for ketones.
- Can add into extended dienones.

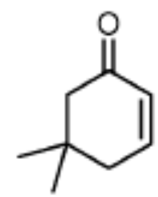
Yun J. et. al., Chem. Eur. J. 2009, 15, 1939 – 19
Nishiyama H., et al. Chem. Commun., 2009, 59

Yun's Addition into Cyclic Enones



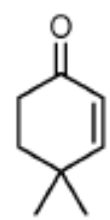


L7 = (*R*,*S*)-Taniaphos



1c

92% yield,
>99% ee

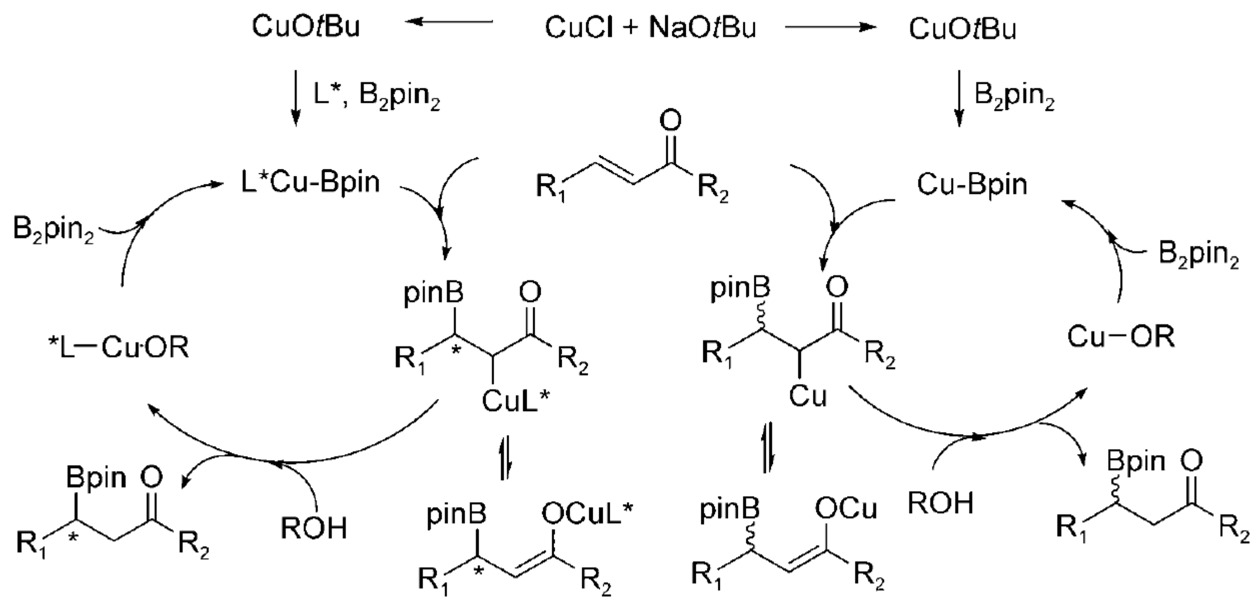


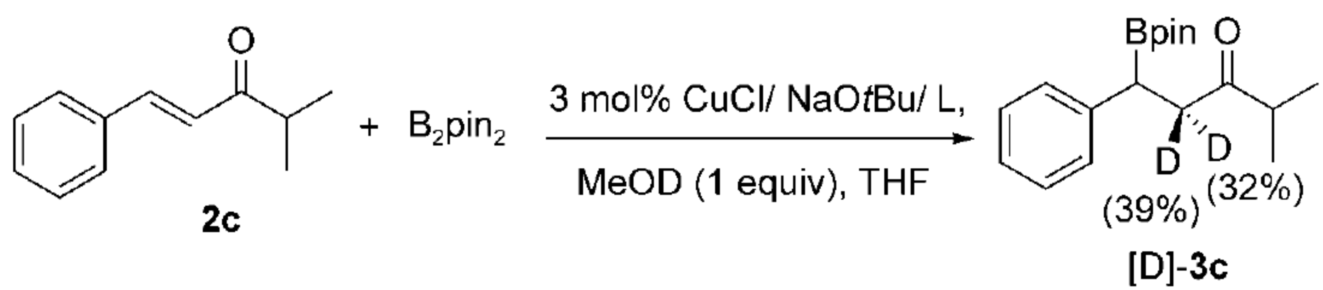
1d

0% yield

Yun J. et. al. Chem. Commun., 2009, 6577

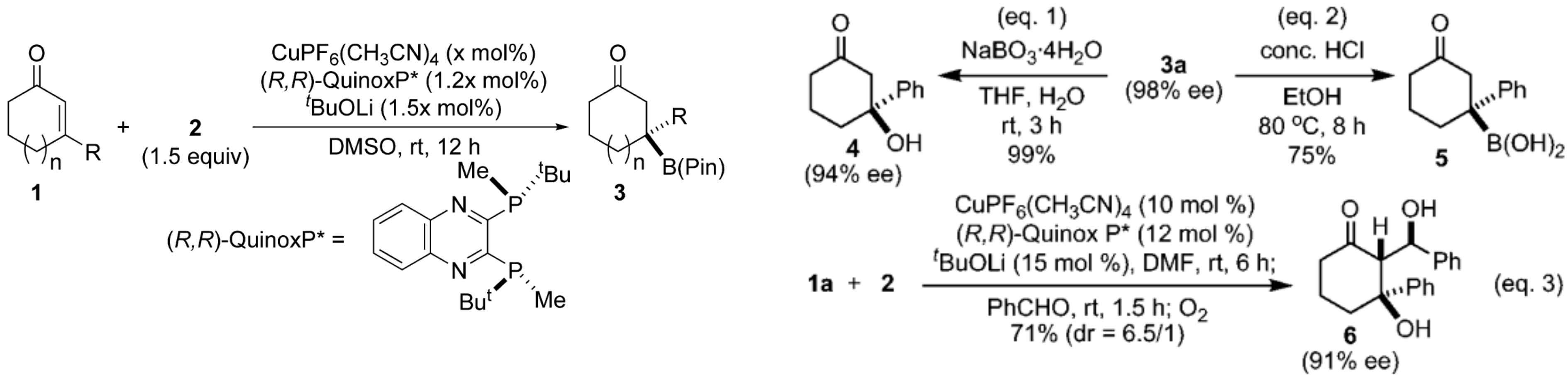
β-borylation : Yun's Mechanism





Yun J. et. al., Chem. Eur. J. 2009, 15, 193

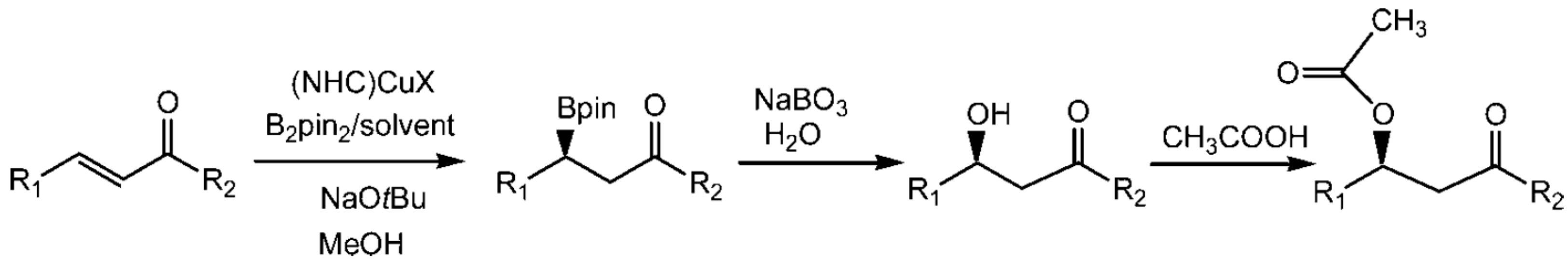
β-borylation

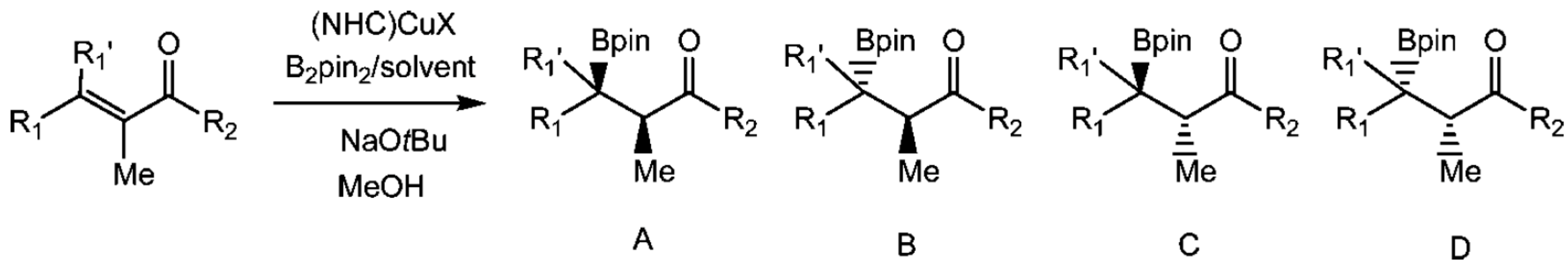


- PF_6 salt hypothesized to accelarate catalyst regeneration
  by formation of $LiPF_6$
- No protic additive necessary
- Wide scope in R for n=0,1,2: various aryl, unbranched and branched alkyl (80–99% yield, 70–98% ee)

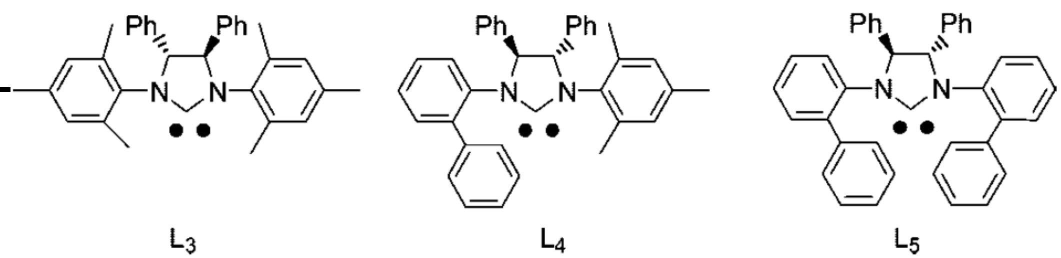
Shibasaki M.,et. al. J. AM. CHEM. SOC. 2009, 131,

Fernandez' NHC borylation



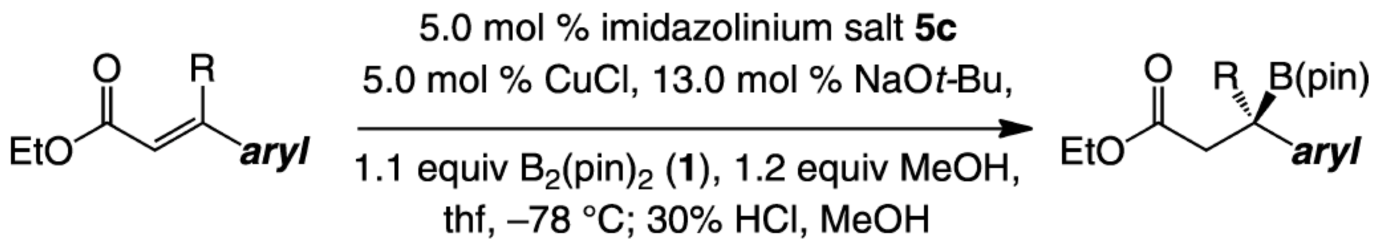


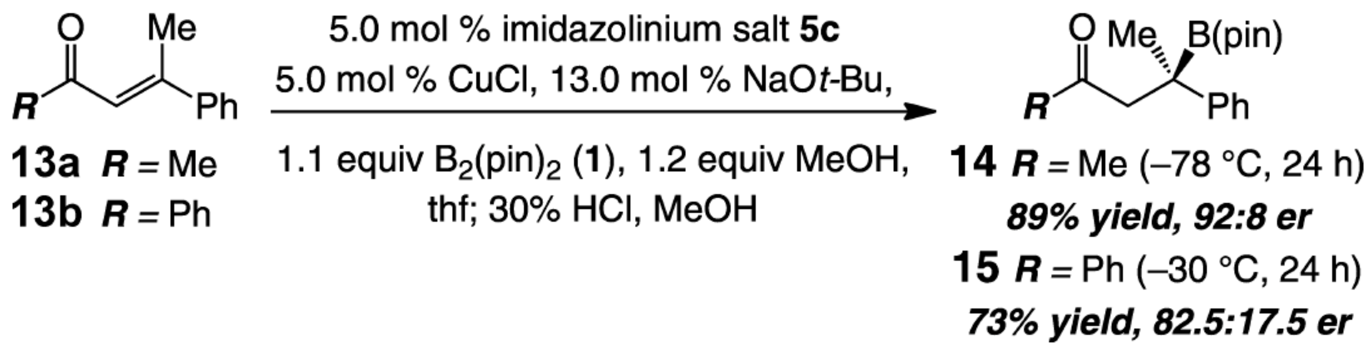
- ee better for syn than anti
- Syn ee 35-74%, anti ee 5-42%
- Poor dr (70:30 syn best case)
- R_2 is an alkoxy group for all substrates

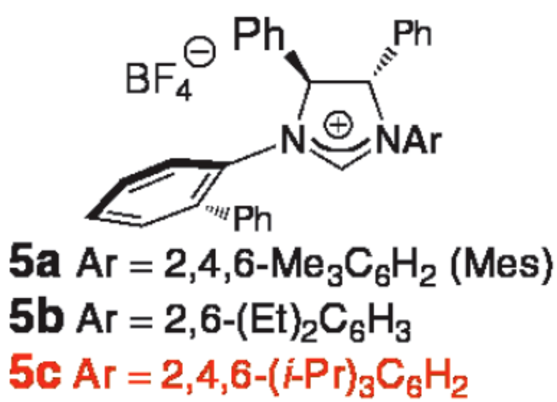


Fernandez et. al. Organometallics, 2009, 28, 659

β-borylation – Hoveyda



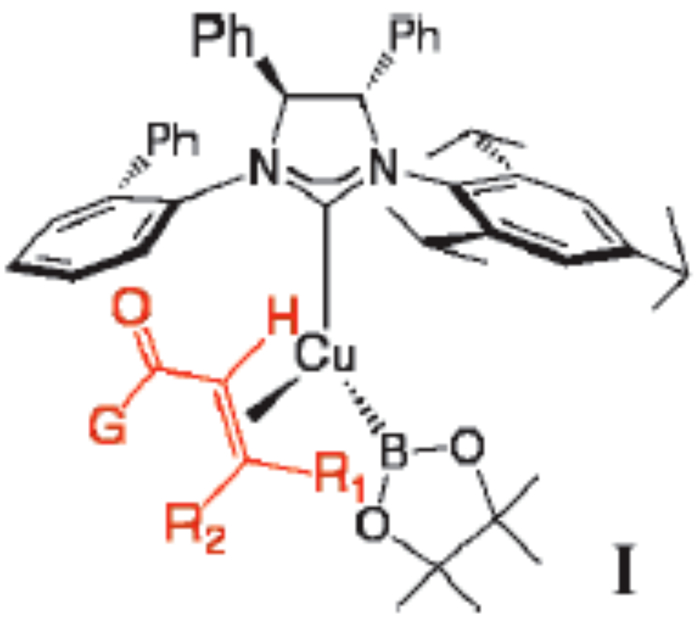




- Viable with esters, thioesters, ketones
- MeOH is not required (can access boron enolate for further transformations)
- Can add to alkyl-substituted esters as well

Hoveyda A. H. et. al., J. AM. CHEM. SOC. 2010, 132,

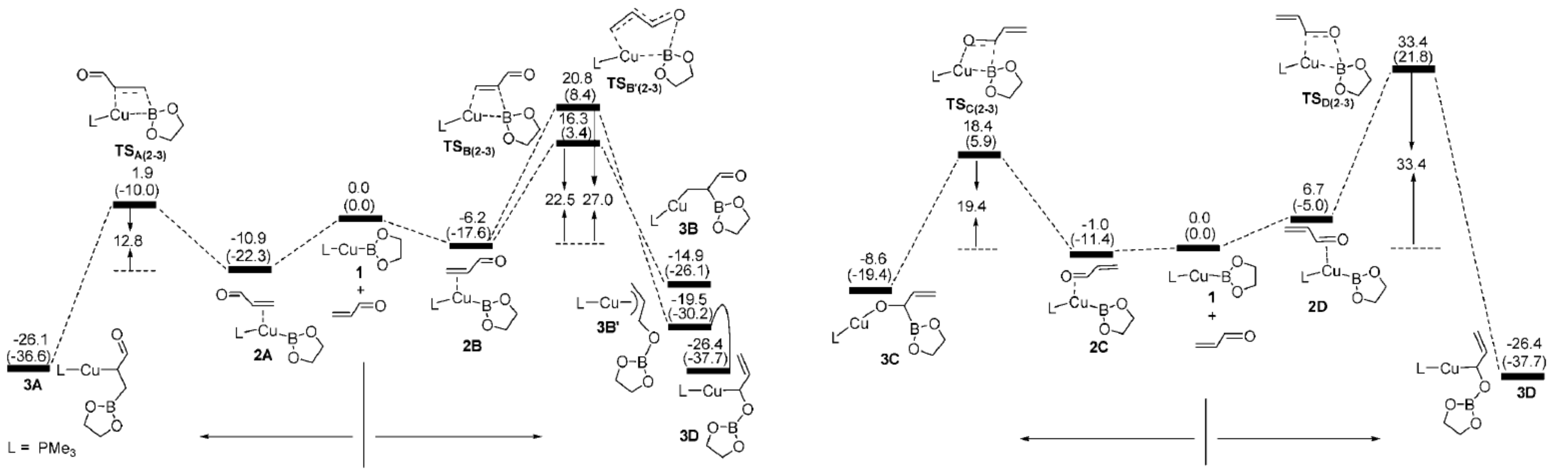
Stereochemical Model



No α–substituted α,β–unsaturated esters tried to check proposal

Hoveyda A. H. et. al., J. AM. CHEM. SOC. 2010, 132, 106

DFT Calculations

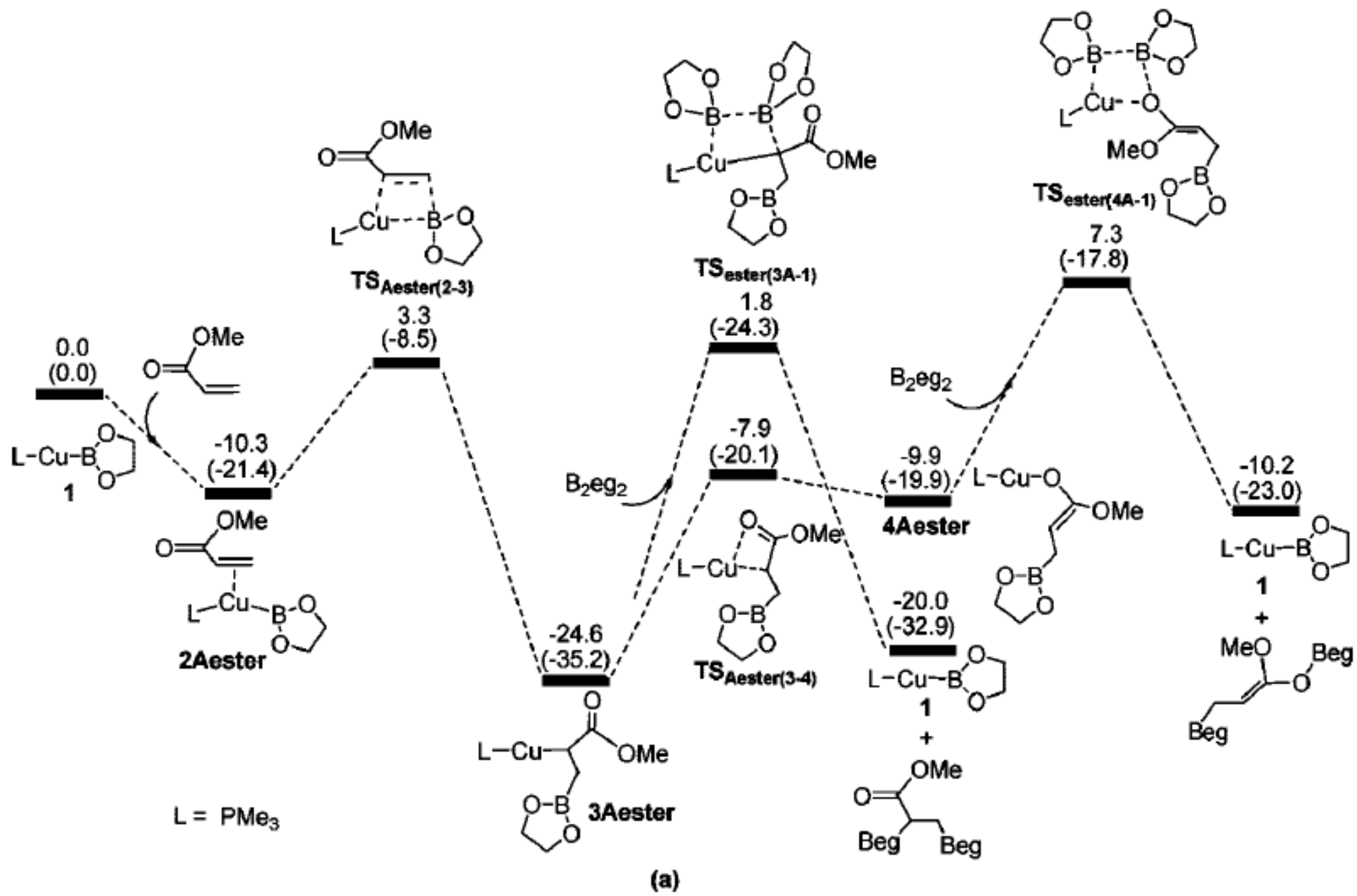


1,4 addition

1,2-addition

Marder T. B. et. al. Organometallics 2008, 27, 444

DFT Calculations with Esters



1,4-addition

Marder T. B. et. al. Organometallics 2008, 27, 444

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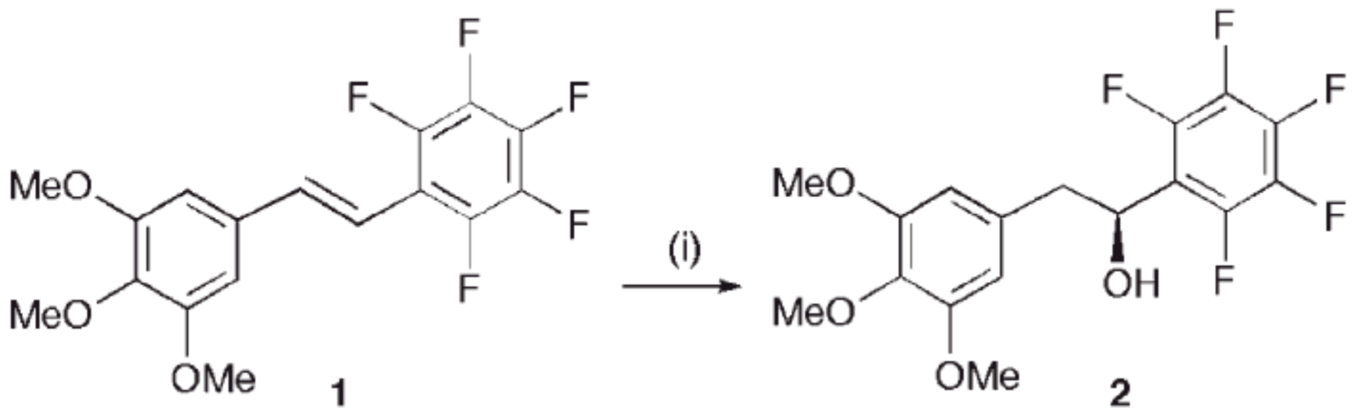
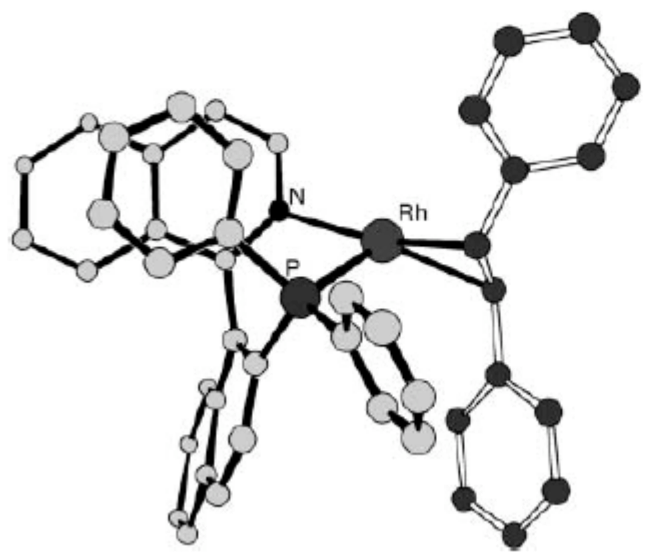
trans-Alkene Monoborylation

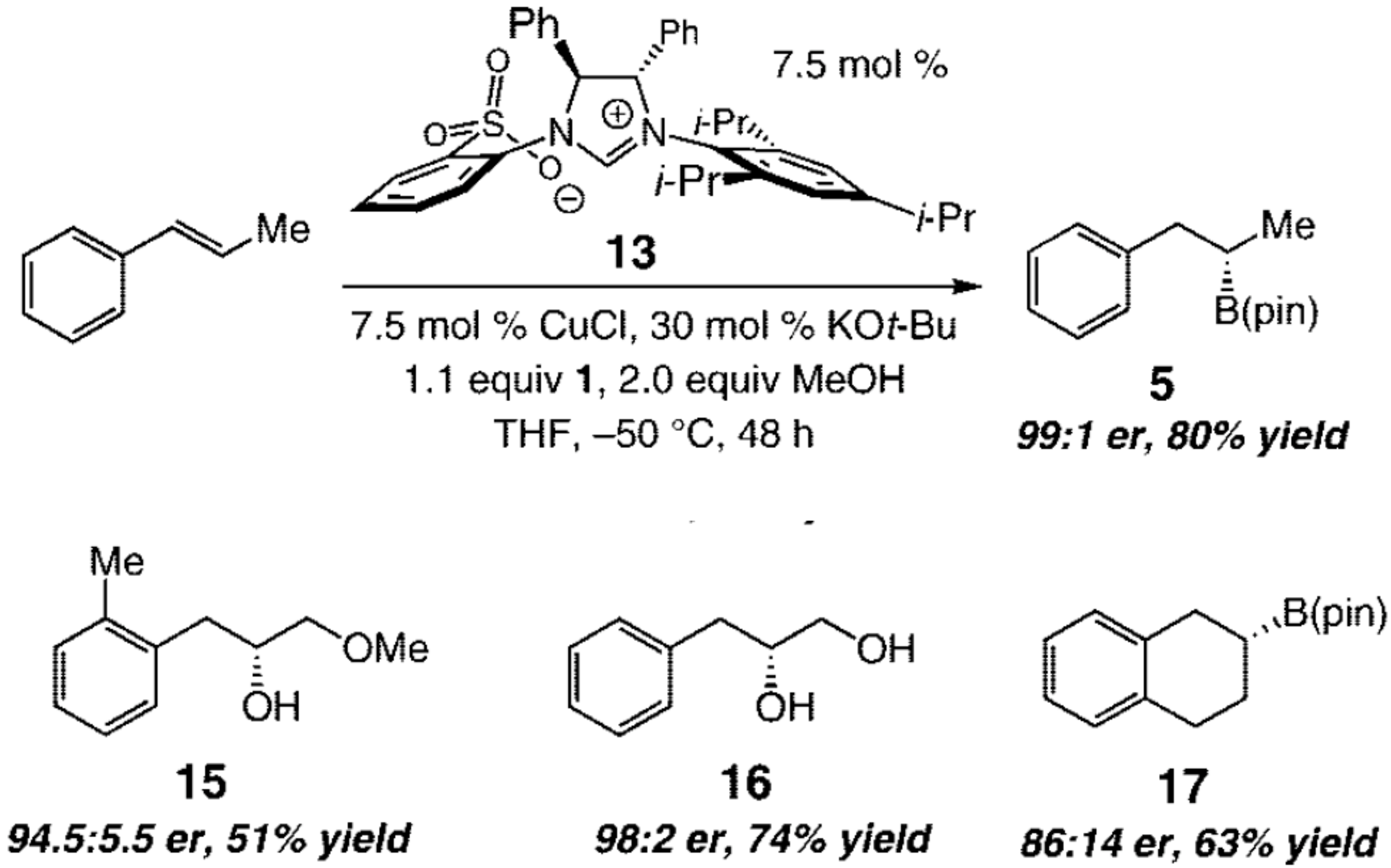


QuinapRh+ **>98%**; 88% e.e.; 77% yield



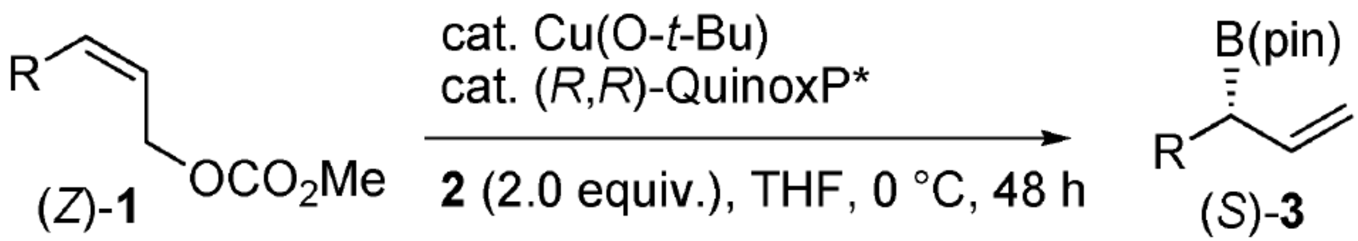
Pichon C. et. al. Chem. Commun., 2005, 528

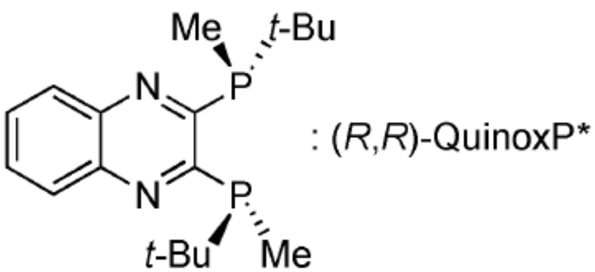
trans-Alkene Monoborylation



Hoveyda A. H. et. al. J. AM. CHEM. SOC. 2009, 131,

Borylation of (Z)-allylcarbonates

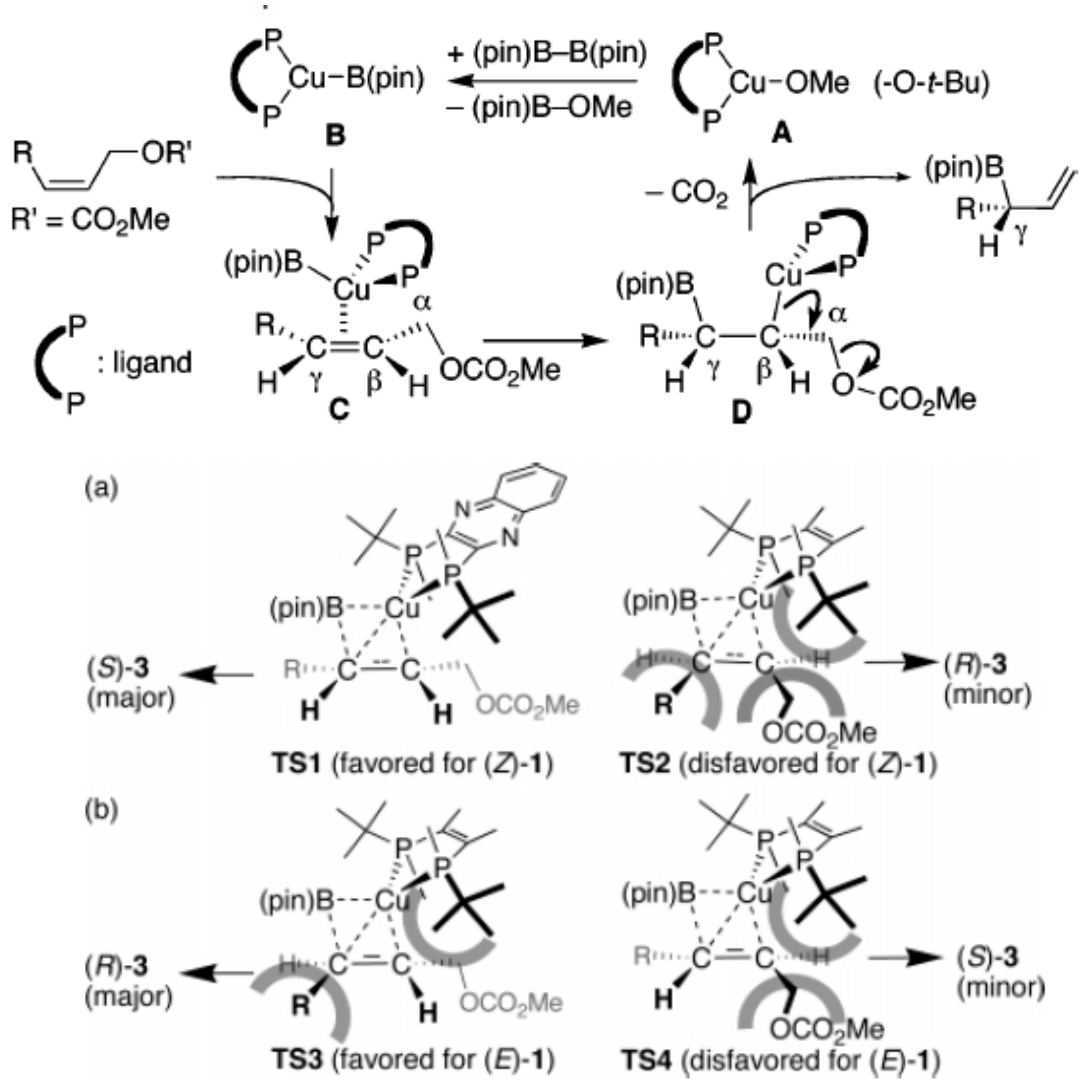




- 64–70%, >90% ee for R=alkyl
- No aryl demonstrated
- No branching at the α-position of R tolerated

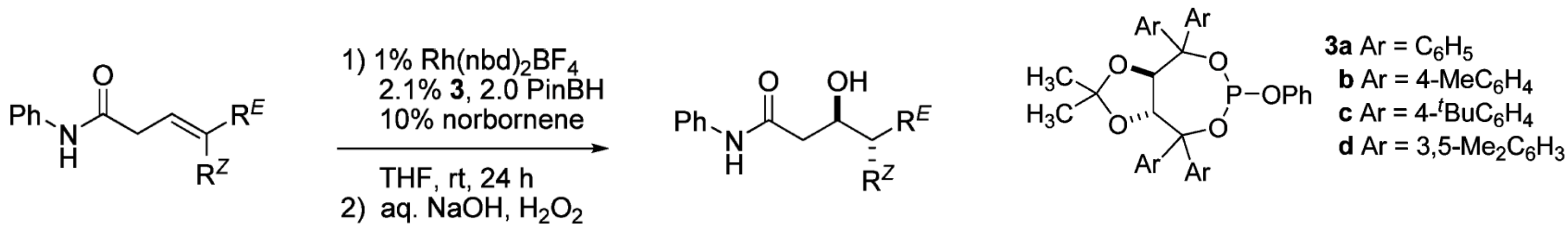
Ito et. al., Pure Appl. Chem., 80,

Stereochemical Model



Ito et. al., J. AM. CHEM. SOC. 2007, 129, 1485

Hindered Alkene borylation



- Scope only demonstrated for alkyl substrates.
- Norbornene additive increasec ee
- Amide required for 2-point binding.
- Stereospecific

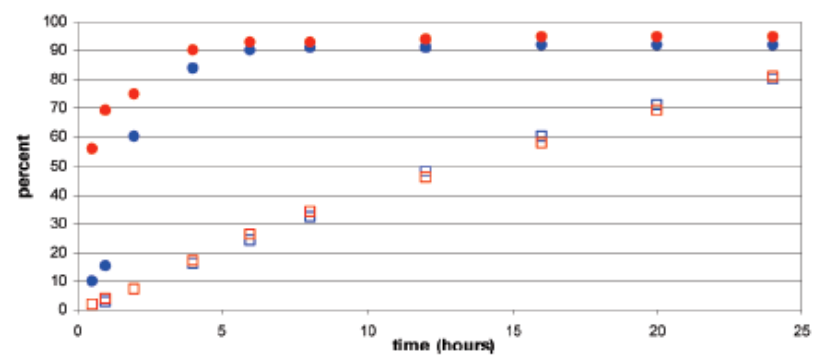
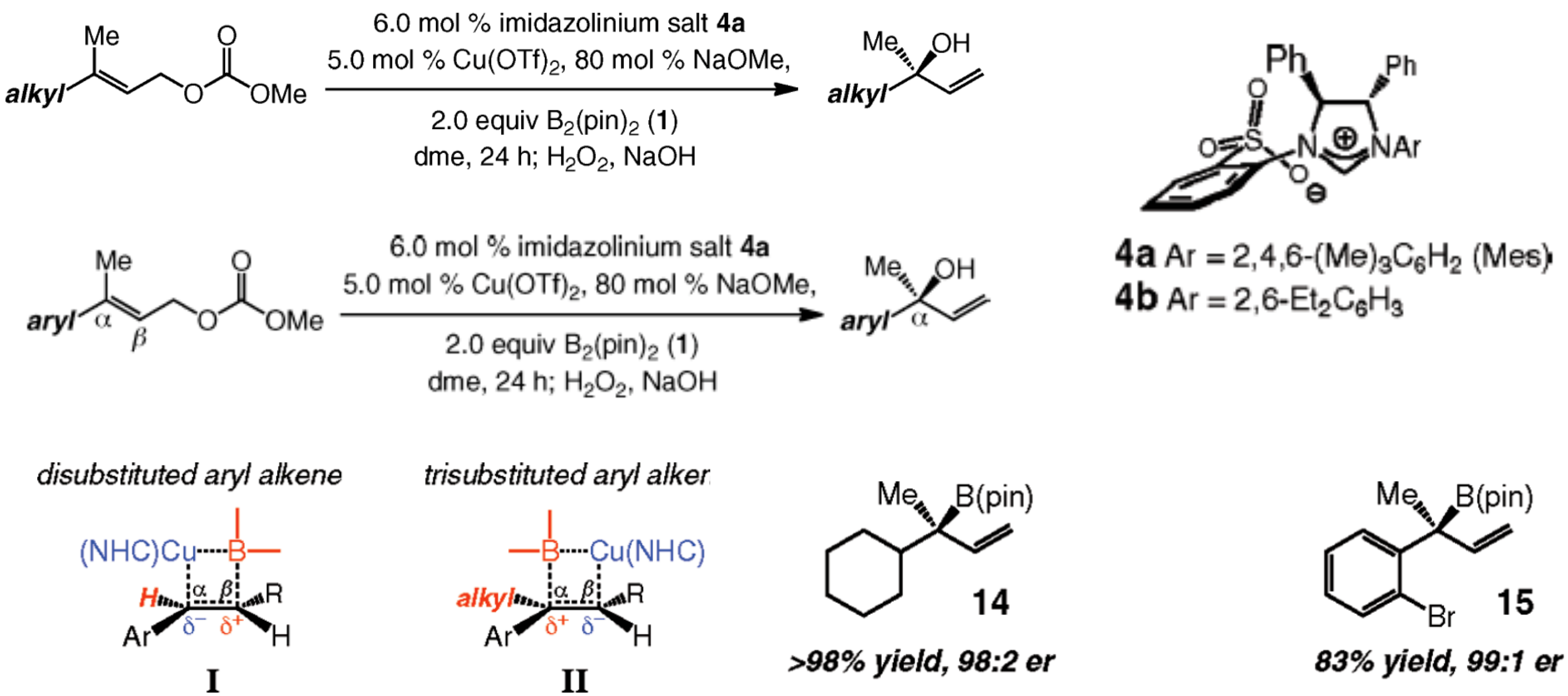


Figure 2. Comparing the yield of *anti*-**6** (□) and its enantiomeric excess (●) over time with (red) and without (blue) added norbornene.

Takacs J. M. et. al. J. AM. CHEM. SOC. 2010, 132,

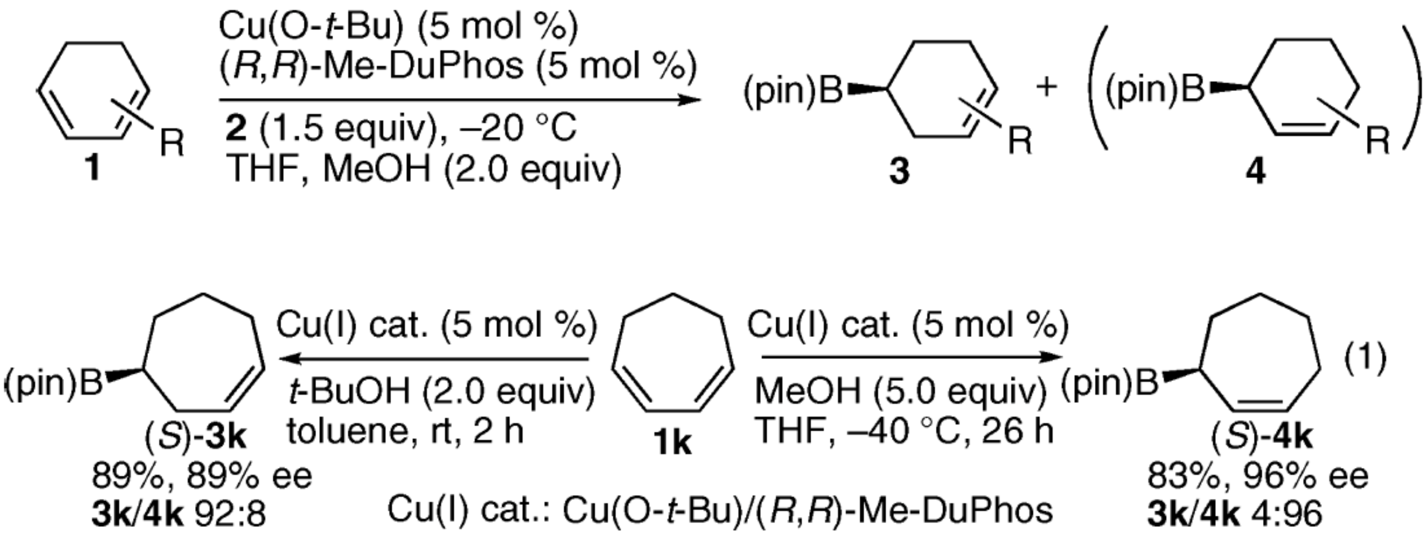
Addition into Trisubstituted olefins

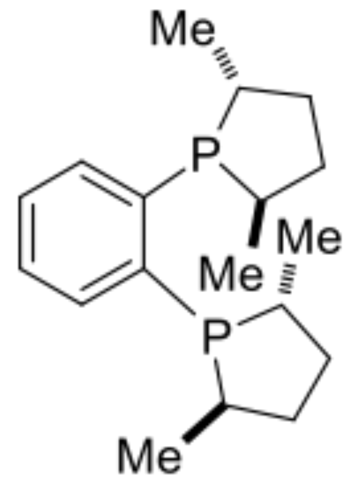


- Stereospecific S_N2’ addition, no S_N2 products detected.
- Also works with disubstituted alkenes (er >90:10)

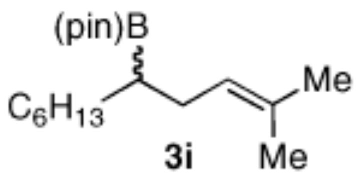
Hoveyda A. H. et. al., J. AM. CHEM. SOC. 2010, 132, 106

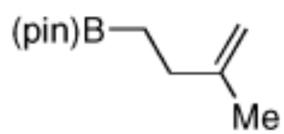
Monoborylation of Dienes

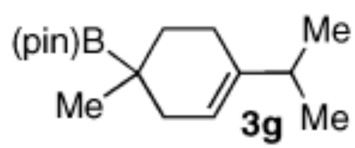




(R,R)-Me-DuPhos







78% ,42% ee

97%

NR

Ito H. et. al., J. AM. CHEM. SOC. 2010, 132,

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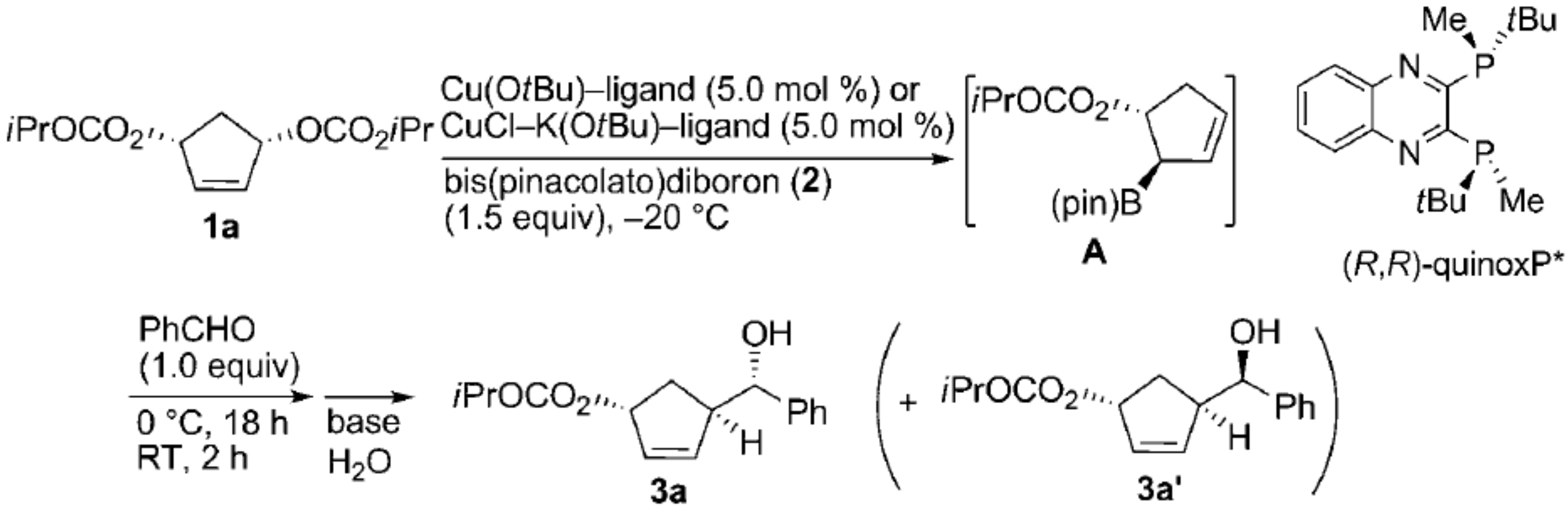
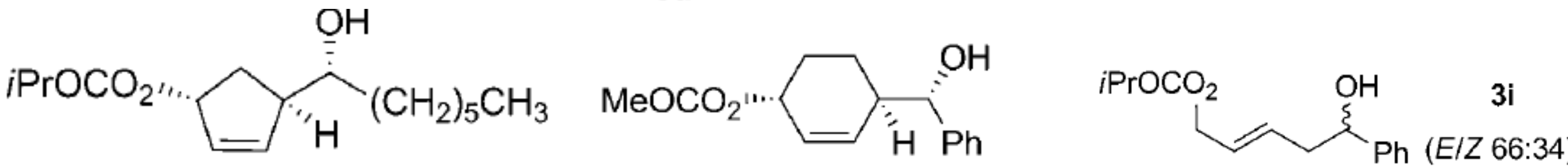
Borodesymmetrization





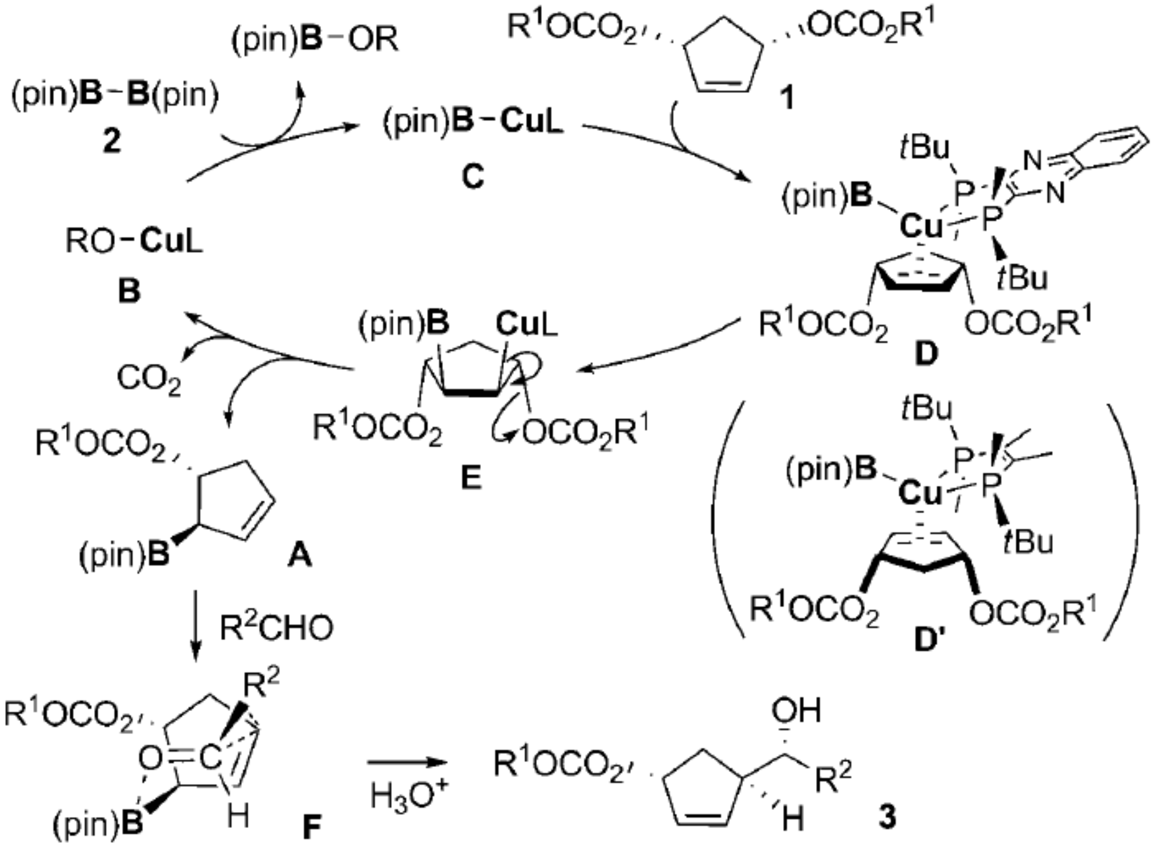
81%, 97%ee, 98:2 dr

43%, 95% ee, 99:1 dr

36% yield, 84% ee

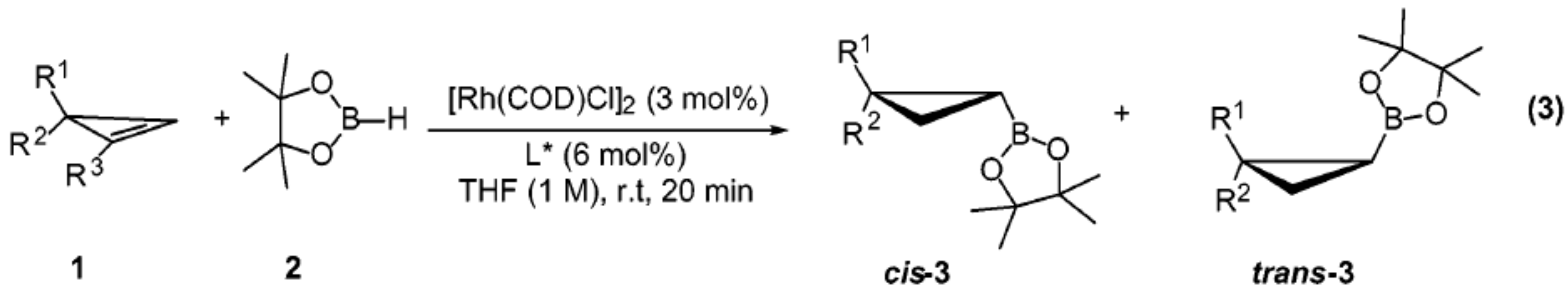
Ito et. al., Angew. Chem. Int. Ed. 2010, 49, 5

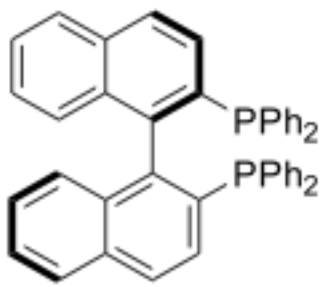
Stereochemical Course



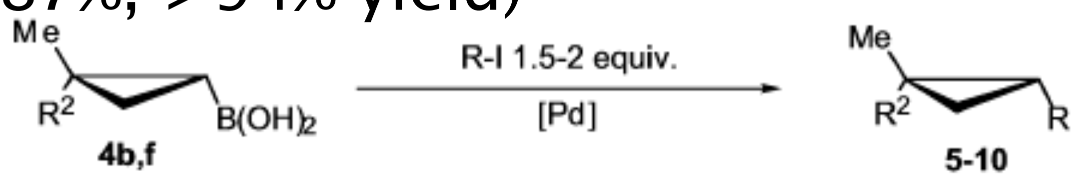
Ito et. al., Angew. Chem. Int. Ed. 2010, 49, 5

Gevorgyan's Cyclopropanes





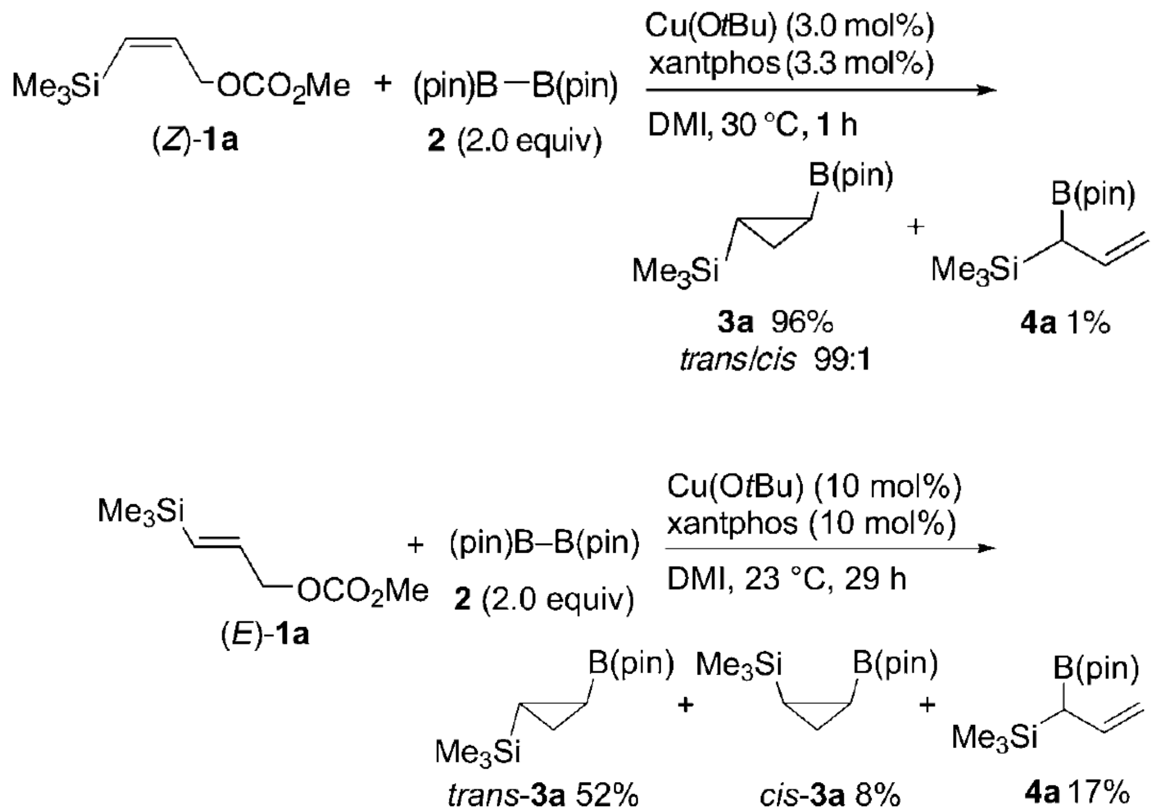
- R^3 is H, otherwise rearrangement to furans observed
- Esters, Alkyl, Aryl groups tolerated. Excellent ee (>87%, >94% yield)



- Further Suzuki coupling possible.

Gevorgyan V. et. al., J. AM. CHEM. SOC. 2003, 125, 71

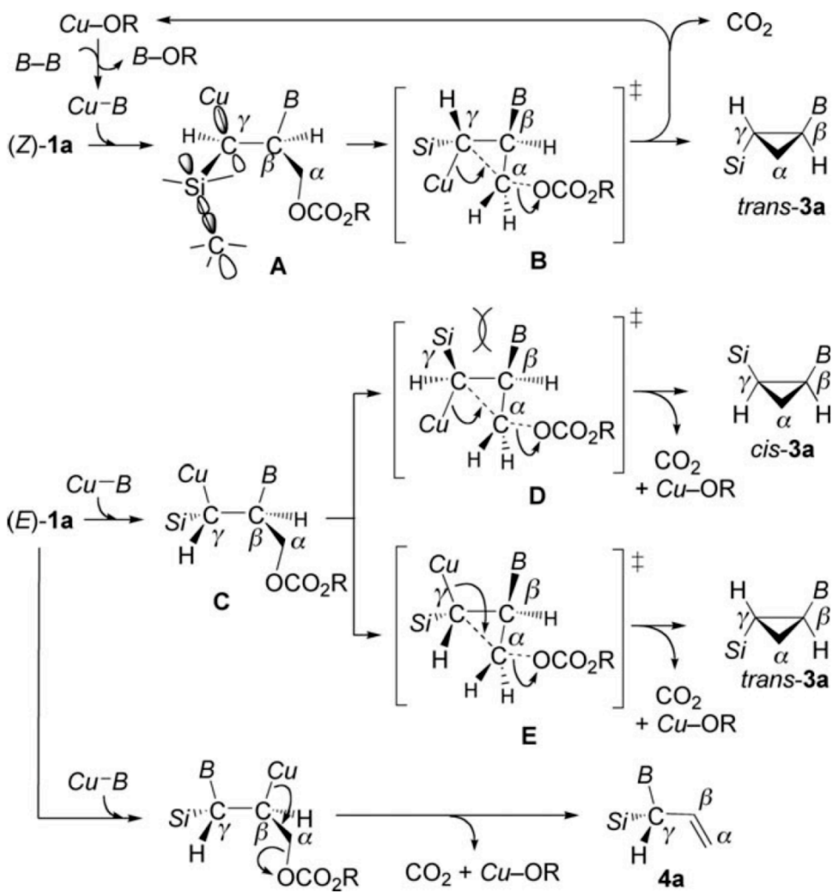
Group Problem



Propose a mechanism, and explain the selectivites

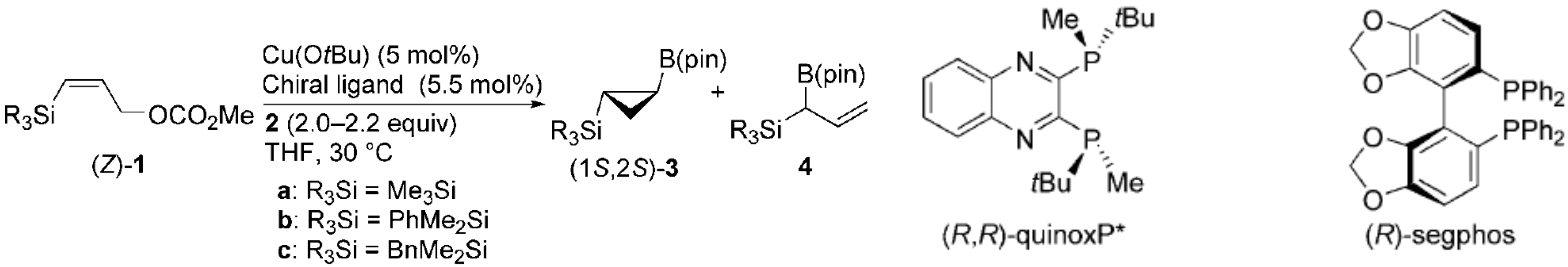
Ito H., Sawamura M. et. al., Angew. Chem. Int. Ed. 2008, 47, 7

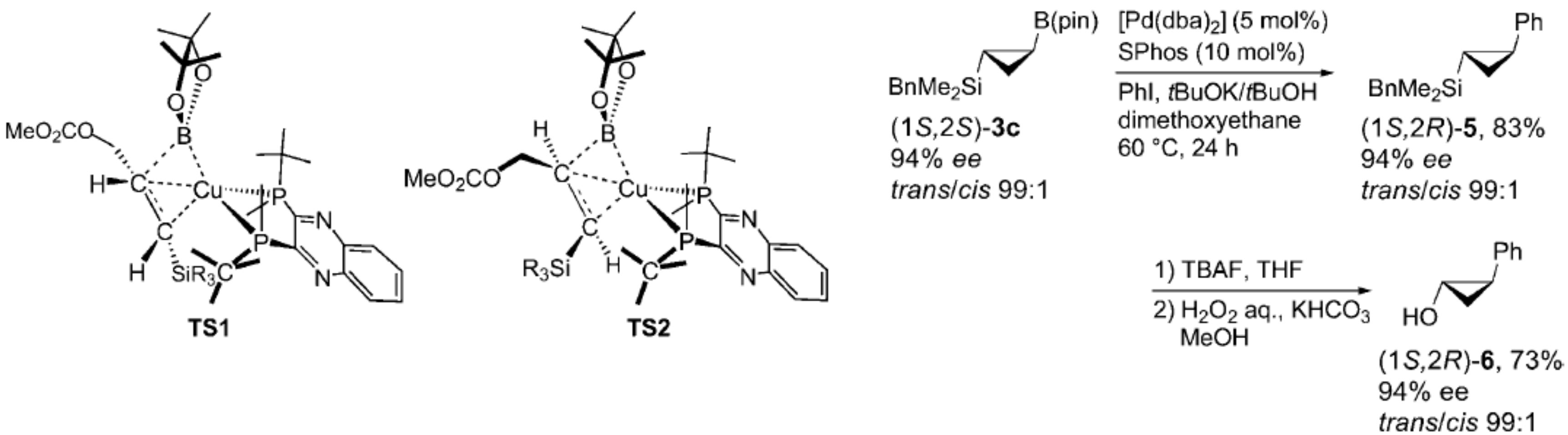
Group Answer



Ito H., Sawamura M. et. al., Angew. Chem. Int. Ed. 2008, 47, 7

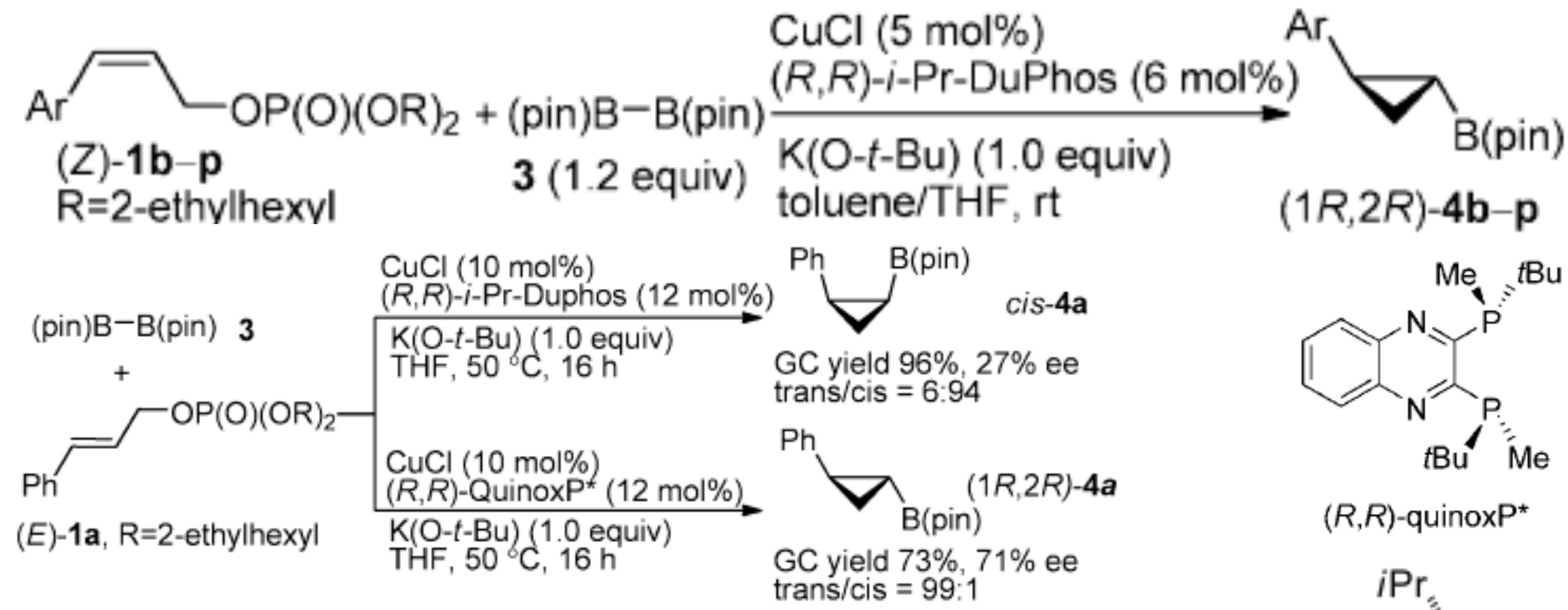
Synthesis of bifunctionalized cyclopropanes from allylcarbonate borylation

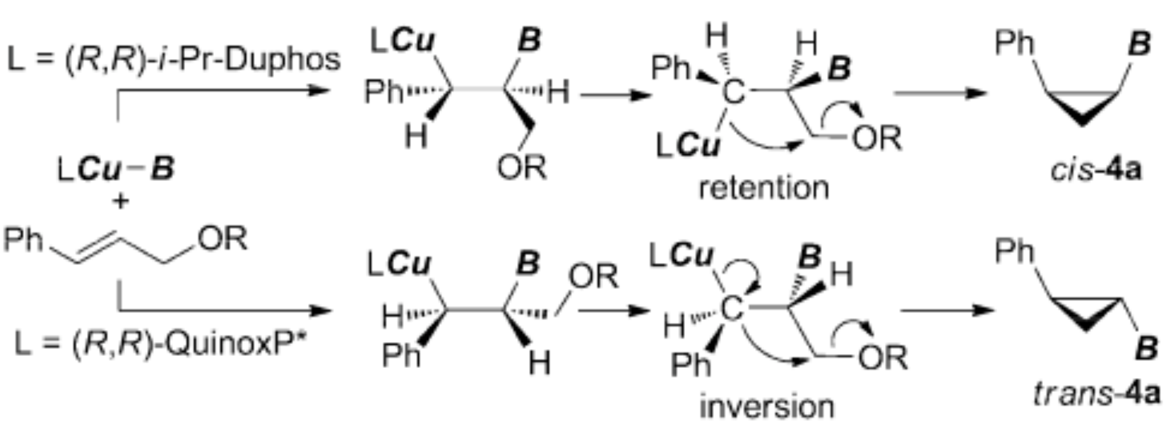


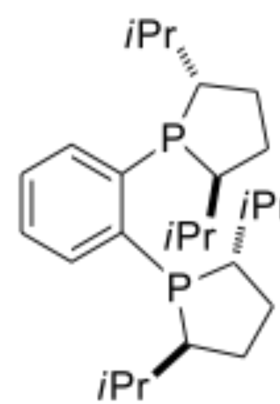


Ito H., Sawamura M. et. al., Angew. Chem. Int. Ed. 2008, 47, 7

Synthesis of Cyclopropanes







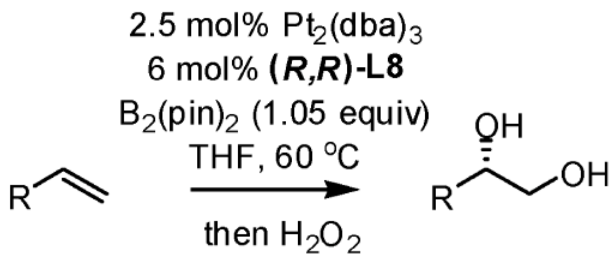
iPr–DuPhos

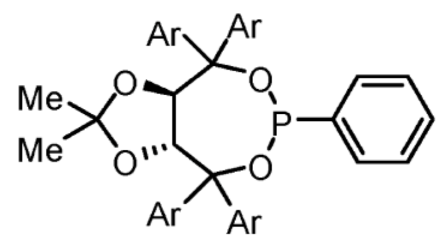
Ito et. al., J. AM. CHEM. SOC. 2010, 132,

Enantioselective Borylations

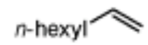
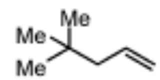
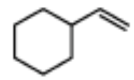
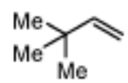
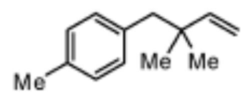
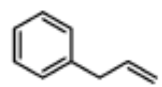
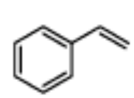
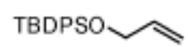
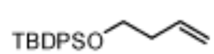
- Addition of $HB(OR_2)$ to styrenes
- Addition of $HB(OR_2)$ to olefins with electron withdrawing groups
- Addition of $HB(OR_2)$ to other olefins
- Desymmetrizations and Cyclopropanations
- Addition of $B_2(OR_2)_2$ to simple alkenes
- Addition of $B_2(OR_2)_2$ to higher olefins

Styrene diborylation



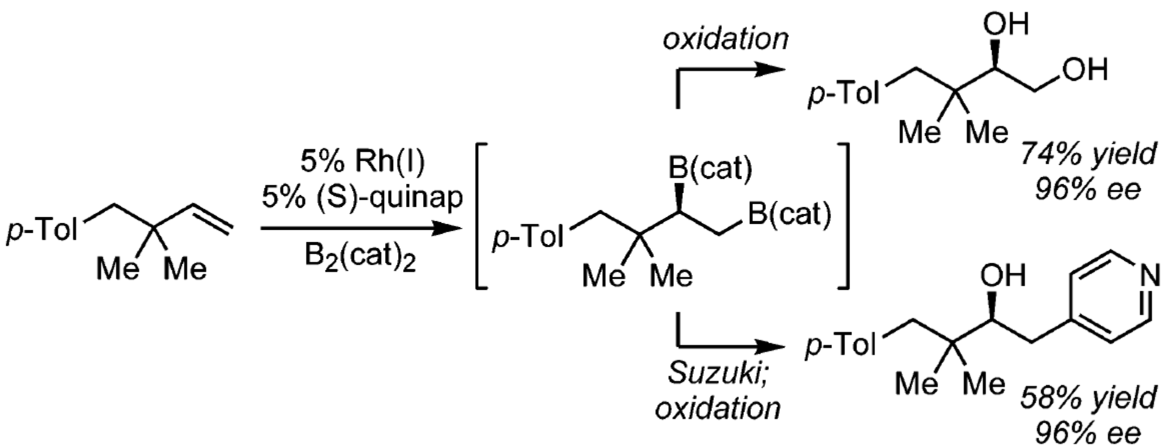


(***R,R***)**-L8**: Ar = 3,5-diethylphenyl

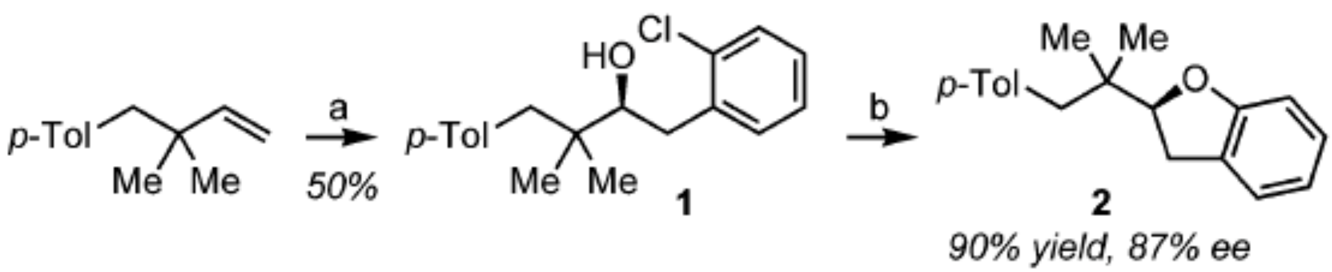
substrate	yield (%)[b]	ee (%)[c]
	83	92
	77	94
	80	94
	87	94
	46	90
	52	87
	86	93
	84	86
	93	90[d]
	92	90

Morken J. P. et. al. J. AM. CHEM. SOC. 2009, 131,

Diborylation of Terminal Olefins

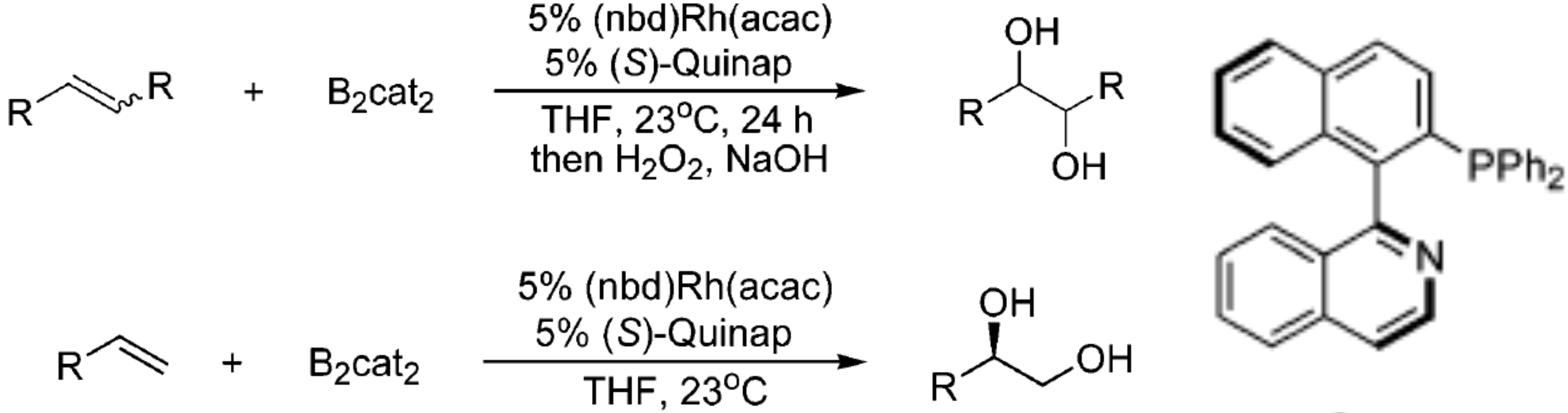


- Best ee's (>93%) when allylic position is a quaternary cent
  Highly sensitive to substitution
- 41-82% yields, 48-77 % over two steps for terminal olefin
  no allylic hydrogens
- Can couple with numerous bromides and triflates



Morken J. P. et.al., ORGANIC LETTERS 2004,

Extensions by Morken

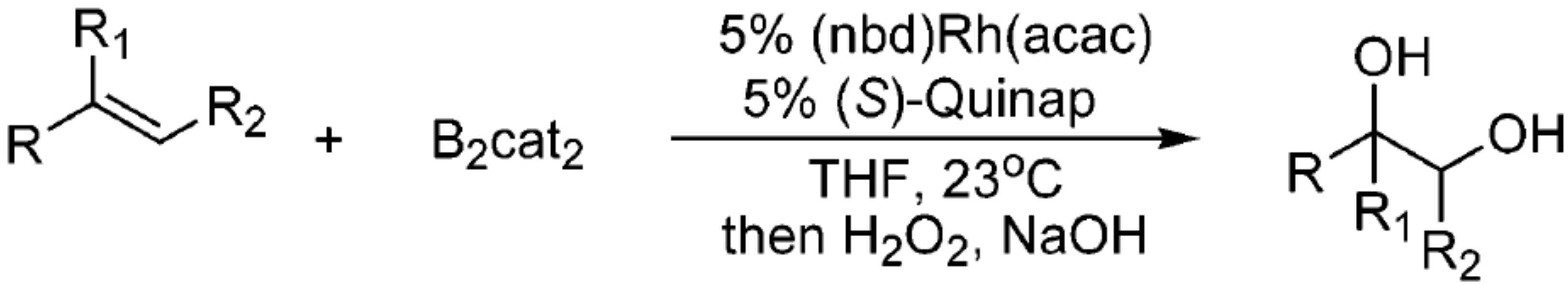


6

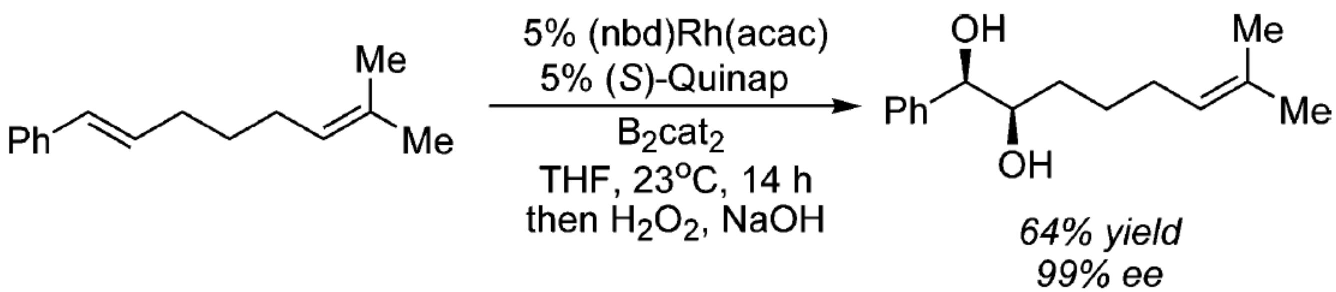
- Best results with trans alkenes (>97% ee)
- Poor selectivity observed without steric hindrance at allylic position for terminal alkenes.

Morken J. P. et. al., J. Org. Chem. 2005, 70,

Alkene Diborylation

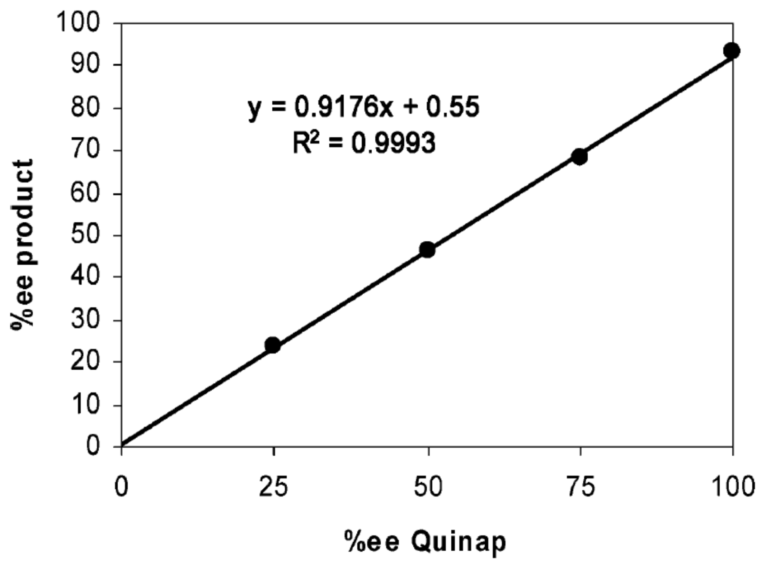


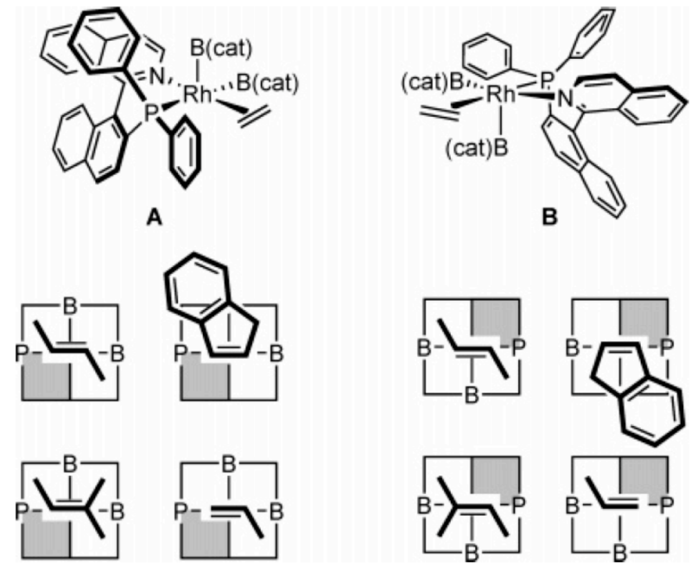
1,1-disubstituted gives poor ee (25-41%), moderate yield (67-79%)
Good ee (>90%) for trisubstituted, poor yield (8-17%)

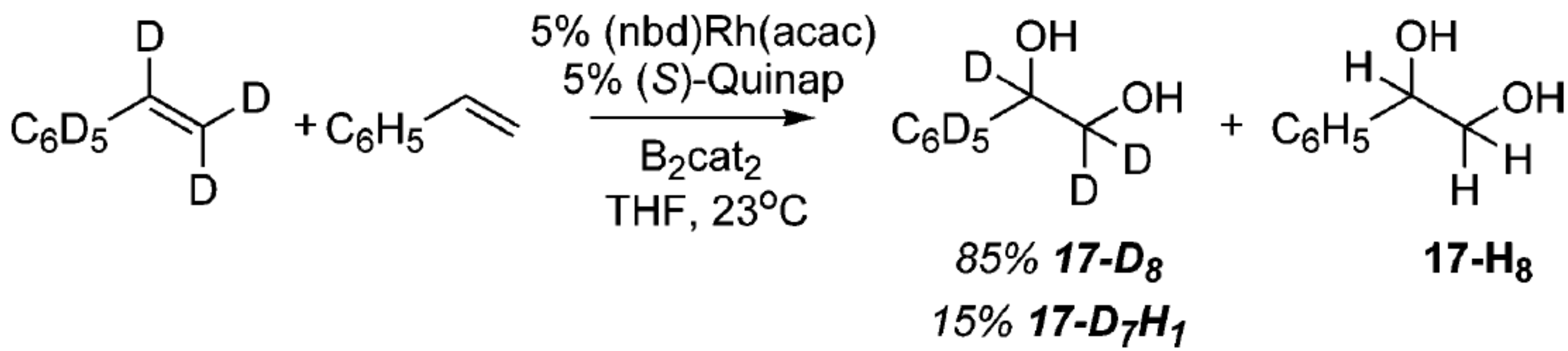


Morken J. P. et. al., J. Org. Chem. 2005, 70, 95

Alkene Diborylation







Morken J. P. et. al., J. Org. Chem. 2005, 70, 95

Enantioselective Borylations

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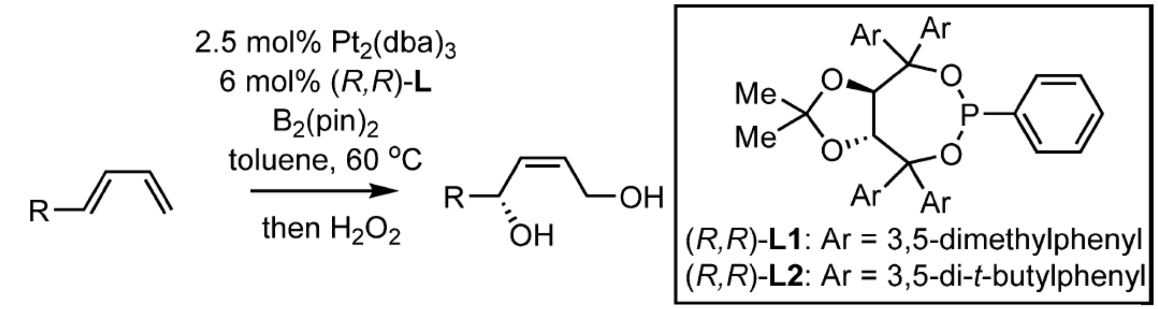
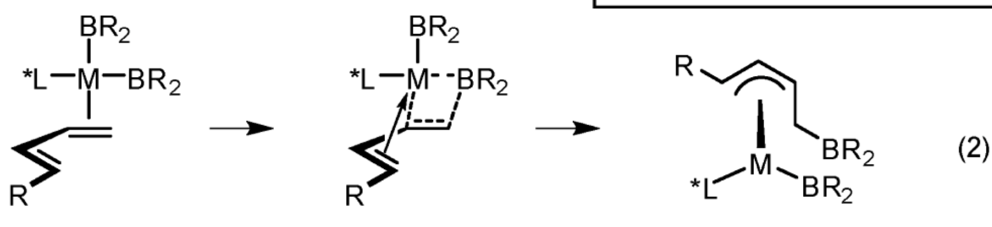
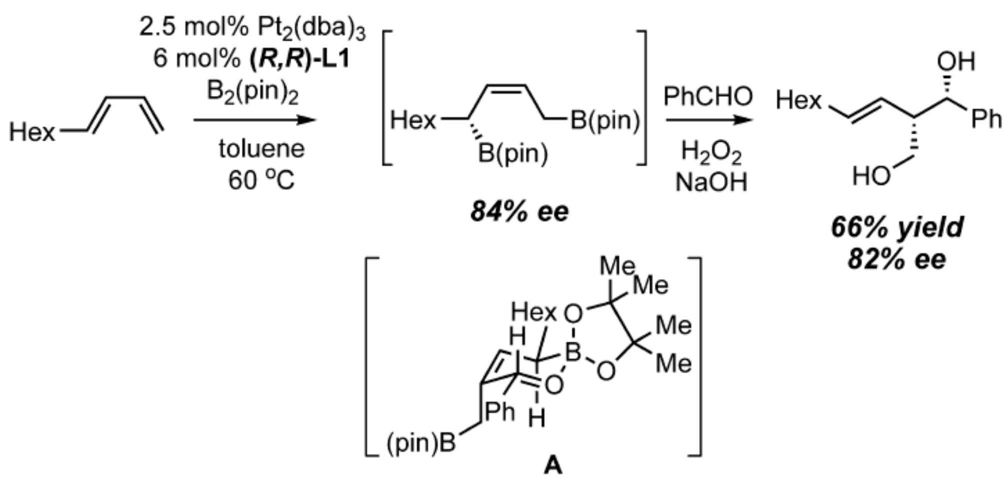
- Addition of $B_2(OR_2)_2$ to higher olefins

Diborylation of Dienes



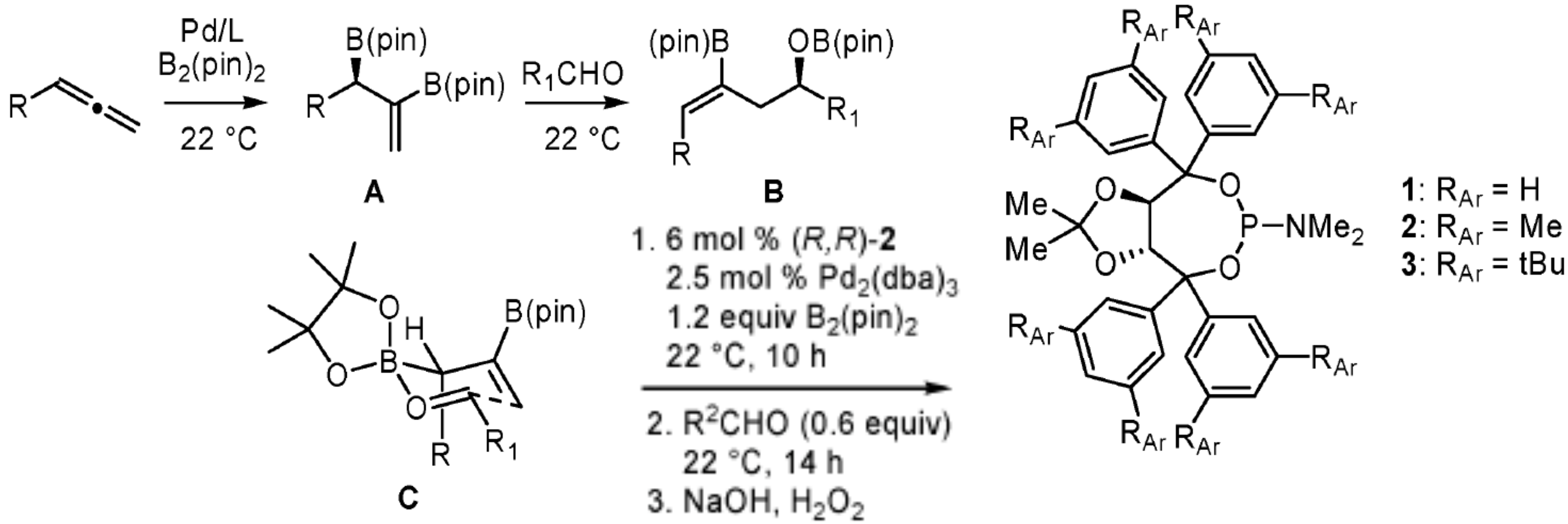


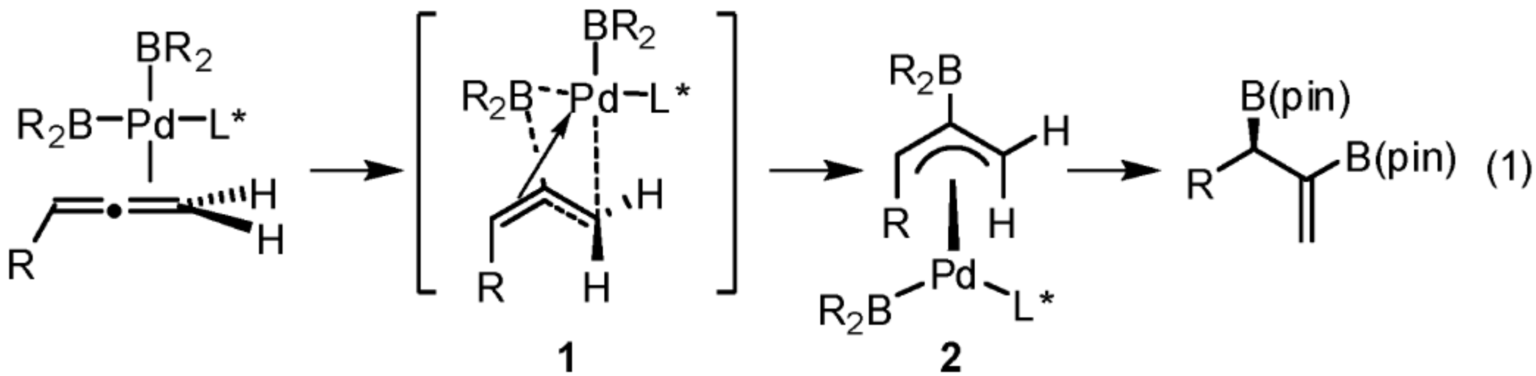


- •70-92% yield, >84% er
- •Cyclic, acyclic dienes
- •Low yield when α-carbon is a quaternary center
- •NR with Z-diene

Morken J. P. et. al. J. AM. CHEM. SOC. 2009, 131,

Allene borylation

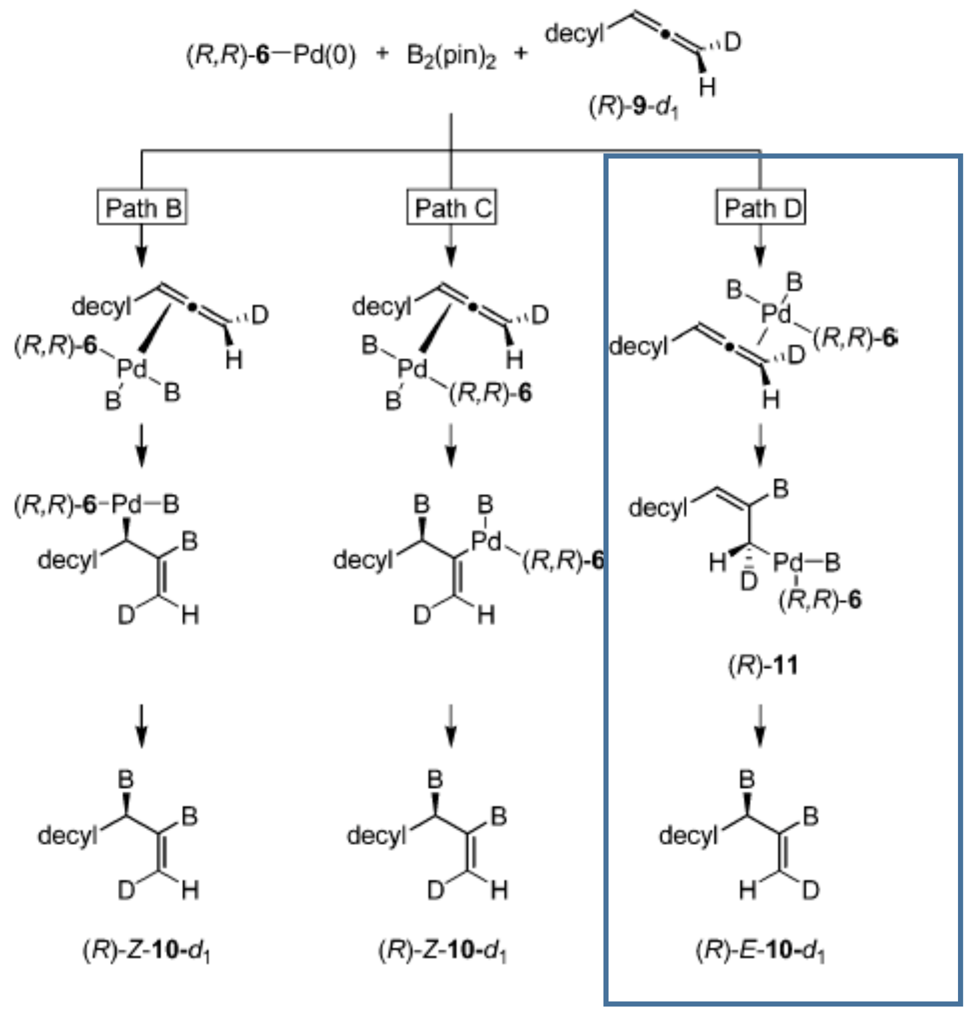




Morken J. et. al., J. AM. CHEM. SOC. 2007, 129, 87
Morken J. P. et. al., ORG. LETT. 2005, 7, 5505-550

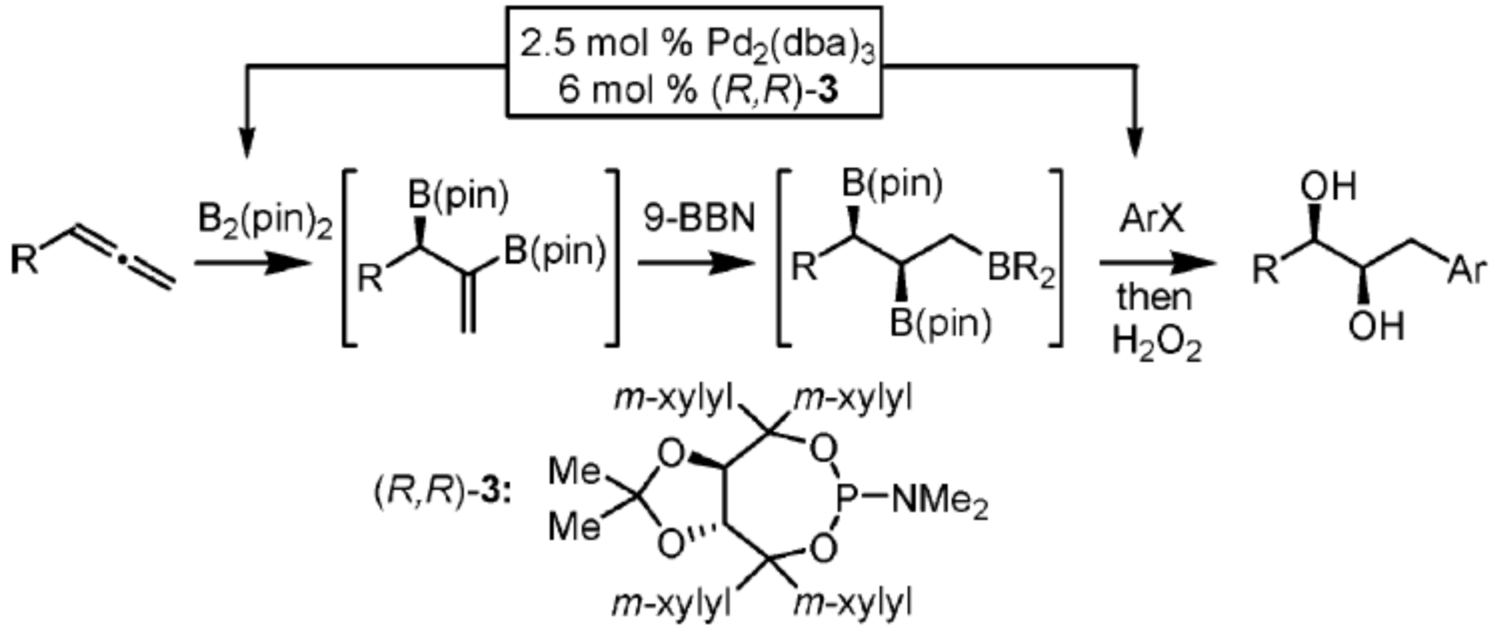
Allene Borylation

Scheme 6



Morken J. et. al., J. AM. CHEM. SOC. 2007, 129, 87

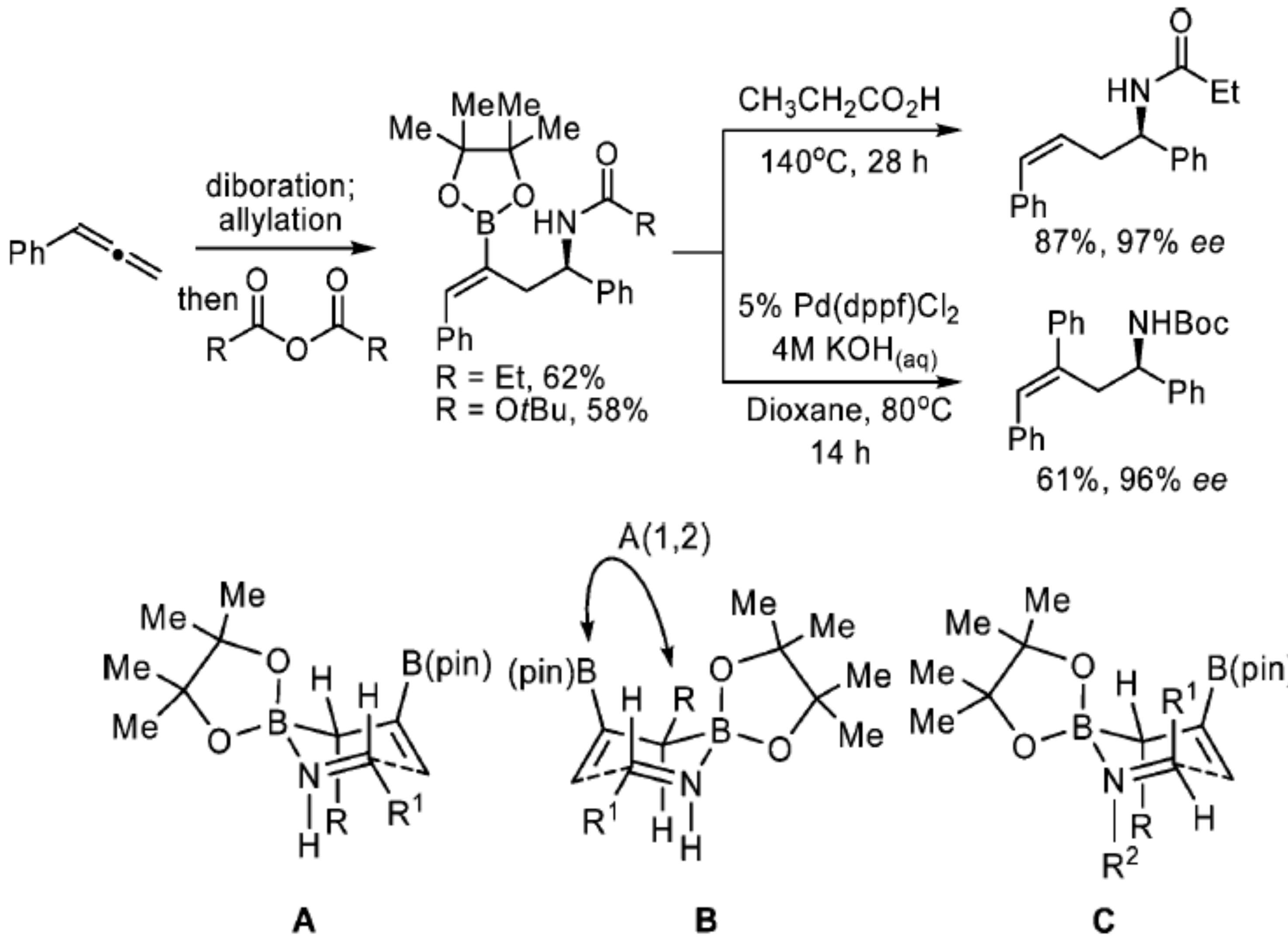
Allene Borylation One-Pot



•R alkyl, branched, benzyl, aryl 37-62% yield, 91-94% ee
•Can couple with aryl, vinyl halides, pseudohalides

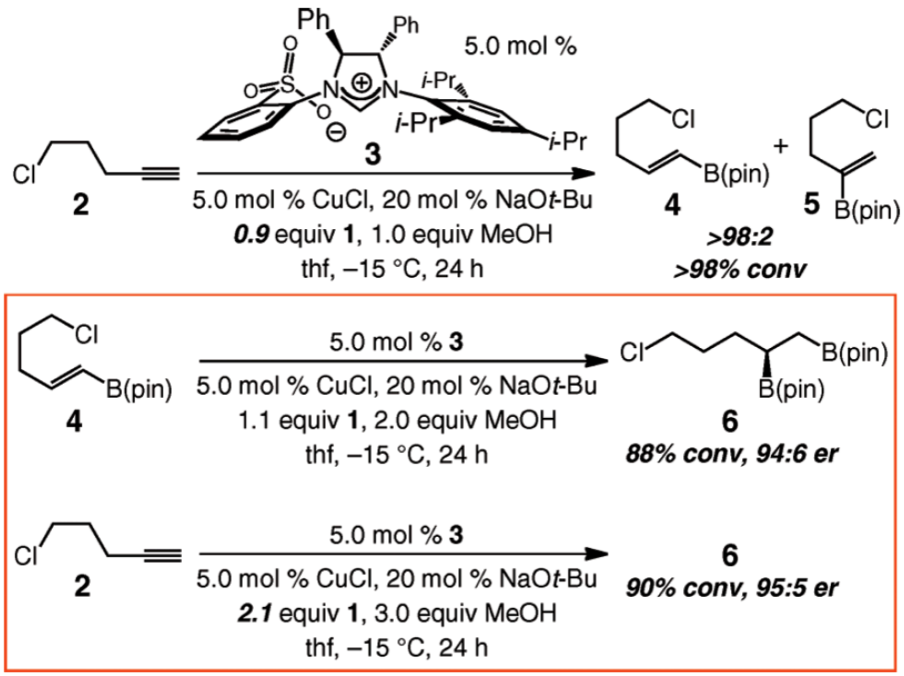
Morken J. P. et. al., ORGANIC LETTERS 2006, 8, 1557–1559

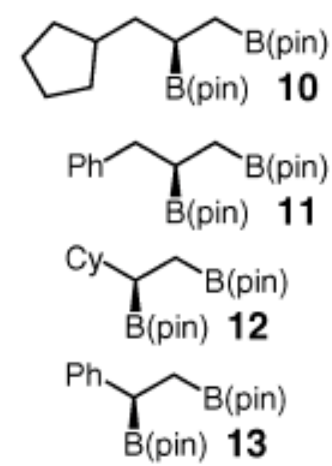
Allene borylation – Tandem Reactions



Morken J. P. et. al. J. AM. CHEM. SOC. 2006, 128

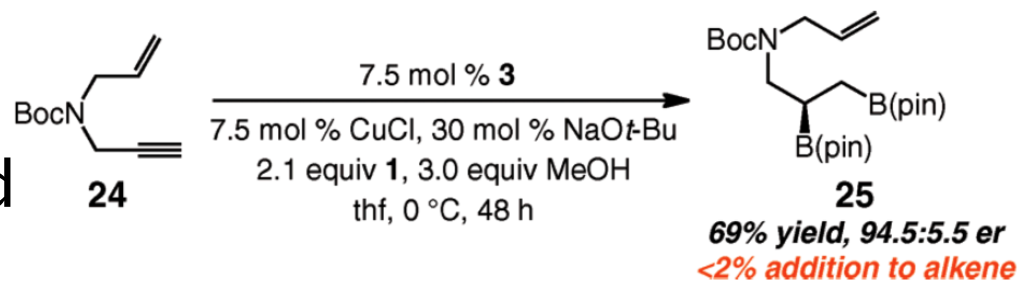
Sequential Alkyne Diborylation





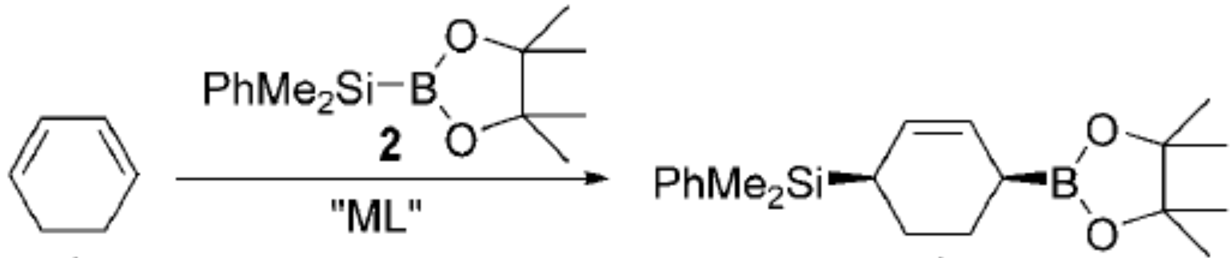
	Product	Yield	er
5	10	78	96.5:3.5
6	11	60	96.5:3.5
7	12	76	97:3
8	13	61[e]	97.5:2.5

Can also control regioselectivity based on NHC catalyst



Hoveyda A. H. et al. J. AM. CHEM. SOC. 2009, 131,

Silaborations



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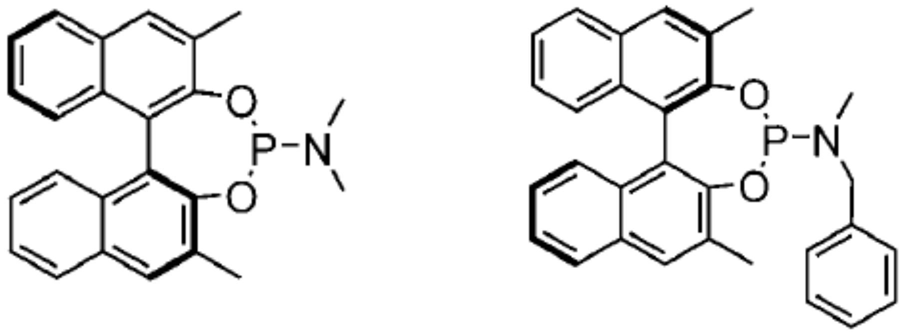

10 15

Entry	Metal complex[a]	Ligand[b]	Time [h]	Conversion [%][c]	ee [%] (product)
1	Pt(acac)$_2$	(*S*)-**10**	48	84	57 (**3**)
2	Pt(acac)$_2$	(*S*)-**11**	48	50	27 (**3**)
3	Pt(acac)$_2$	**12**	48	52	32 (**3**)
4	Pt(acac)$_2$	**13**	48	26	21 (**3**)
5	Pt(acac)$_2$	**14**	48	11	13 (**3**)
6	Pt(acac)$_2$	**15**	48	92	58 (*ent*-**3**)

Gerdin M. et al. Adv. Synth. Catal. 2005, 347, 7

Conclusions

- Asymmetric Borylation is a highly selective and synthetically useful of installing C–B bonds.
- Products are versatile and can be used in allylations, oxidations, cross-coupling reactions etc.
- Can synthesize tertiary allylic alcohols, and tertiary chiral allylborons.
- Boron is a cheap and non-toxic element.
- Product stability limits the utility of boron chemistry – more stable boron esters will increase use.
- Asymmetric borylation of cis-alkenes continues to be an unsolved problem.