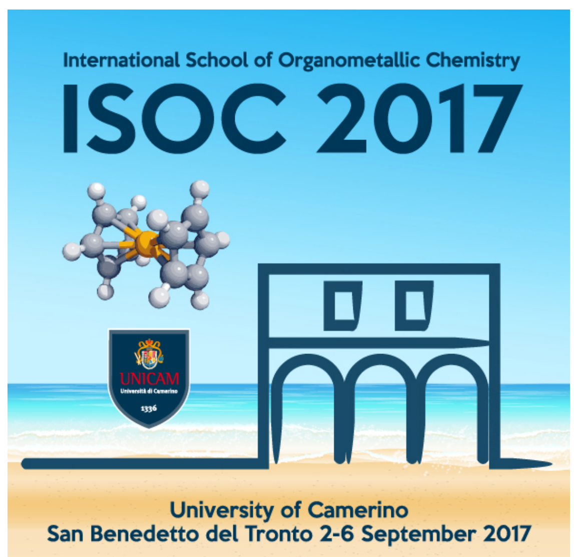
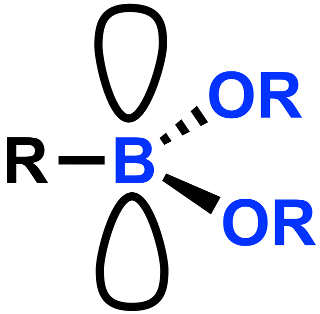
IAdChem
Institute for Advanced Research in Chemistry
Universidad Autónoma de Madrid | Faculty of Science
Department of Organic Chemistry

Nucleophilic Boron: New Opportunities for Carbon-Boron Bond Formation

Mariola Tortosa



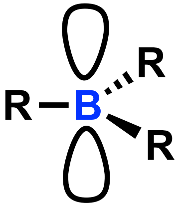
Boronic Esters in Synthetic Chemistry



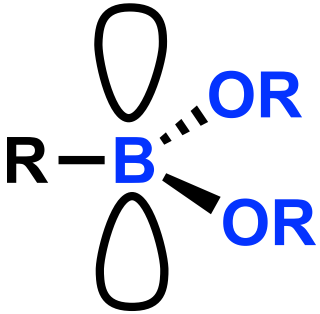
Boronic Ester

Hall, D. In Boronic Acids: *Preparation and Applications in Organic Synthesis and Medicine*; Wiley-VCH: Weinheim, 2011.

Boronic Esters in Synthetic Chemistry



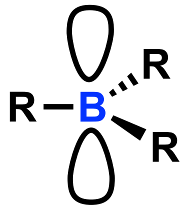
Boranes



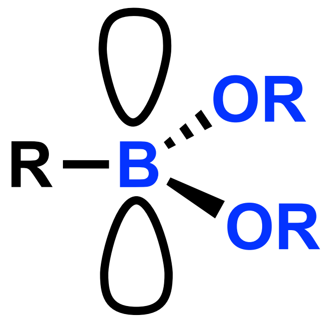
Boronic Ester

Hall, D. In Boronic Acids: *Preparation and Applications in Organic Synthesis and Medicine*; Wiley-VCH: Weinheim, 2011.

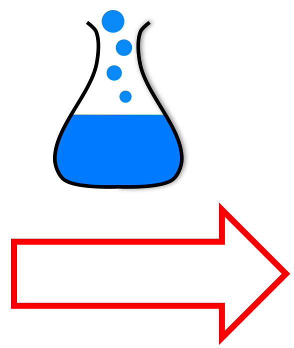
Boronic Esters in Synthetic Chemistry



Boranes



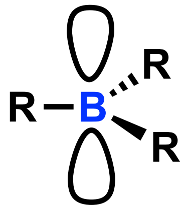
Boronic Ester



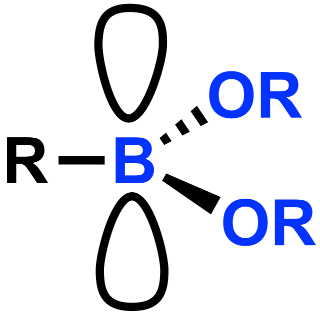
- ✓ ***Mild organic Lewis acids***
- ✓ ***Mitigated reactivity profile***
- ✓ ***Stability, easy of handling***

Hall, D. In Boronic Acids: *Preparation and Applications in Organic Synthesis and Medicine*; Wiley-VCH: Weinheim, 2011.

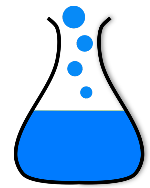
Boronic Esters in Synthetic Chemistry



Boranes



Boronic Ester

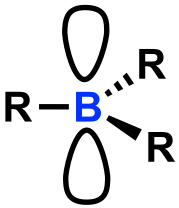


- ✓ ***Mild organic Lewis acids***
- ✓ ***Mitigated reactivity profile***
- ✓ ***Stability, easy of handling***

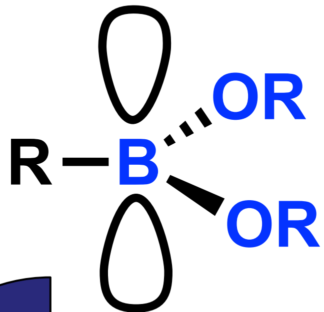
- ✓ ***Low toxicity***
- ✓ ***Degradation into boric acid***
- ✓ ***"Green" compounds***

Hall, D. In Boronic Acids: *Preparation and Applications in Organic Synthesis and Medicine*; Wiley-VCH: Weinheim, 2011.

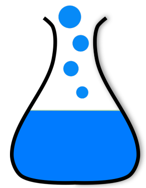
Boronic Esters in Synthetic Chemistry



Boranes



Boronic Ester



- ✓ *Mild organic Lewis acids*
- ✓ *Mitigated reactivity profile*
- ✓ *Stability, easy of handling*

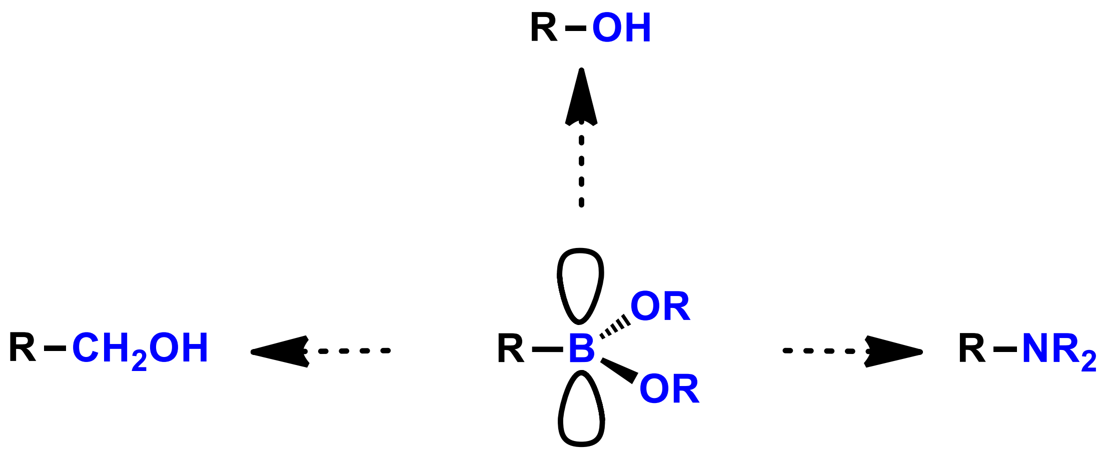
- ✓ *Low toxicity*
- ✓ *Degradation into boric acid*
- ✓ *“Green” compounds*

Attractive class of synthetic intermediates

Hall, D. In Boronic Acids: *Preparation and Applications in Organic Synthesis and Medicine*; Wiley-VCH: Weinheim, 2011.

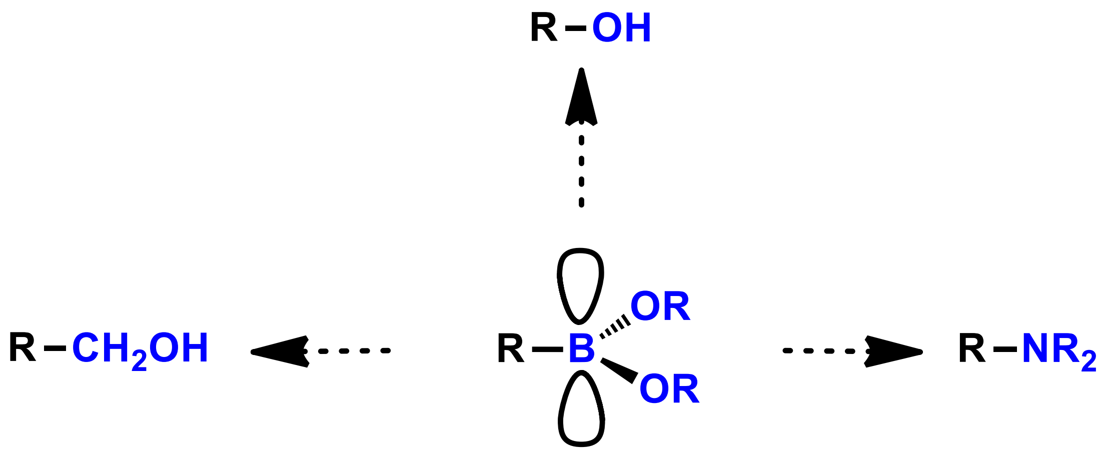
Boronic Esters in Synthetic Chemistry

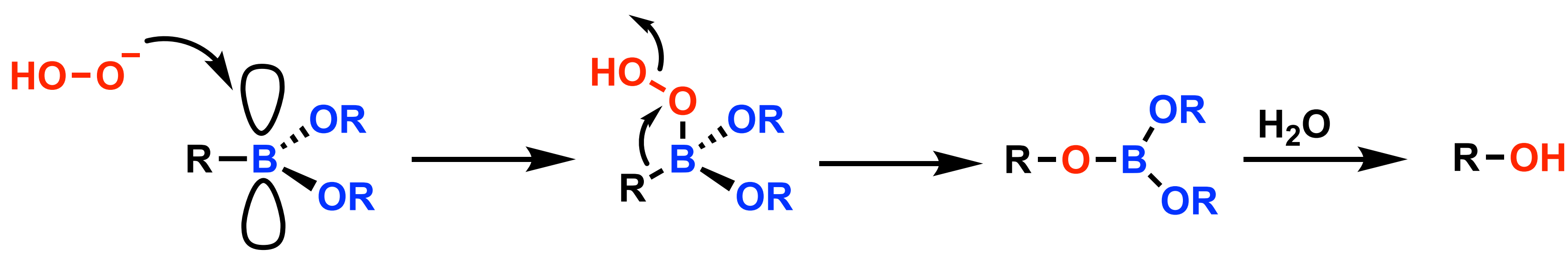
Versatile Intermediates



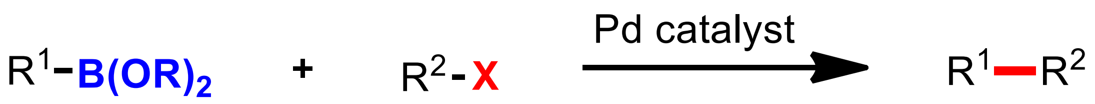
Boronic Esters in Synthetic Chemistry

Versatile Intermediates



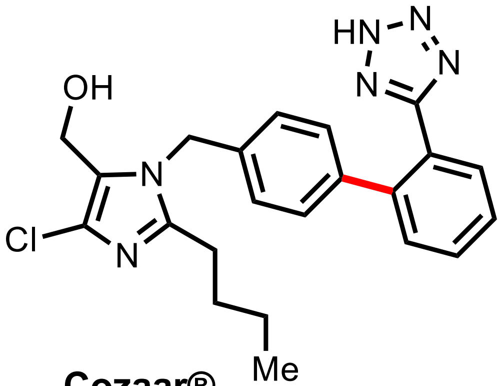


Suzuki- Miyaura Coupling

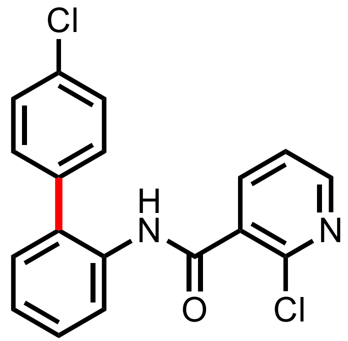


X = halogen, triflate

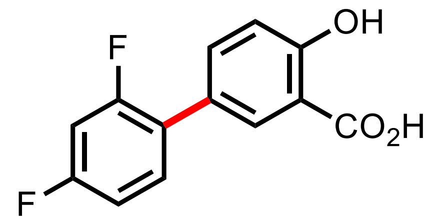
Nobel Prize 2010



Cozaar®
(Merck)

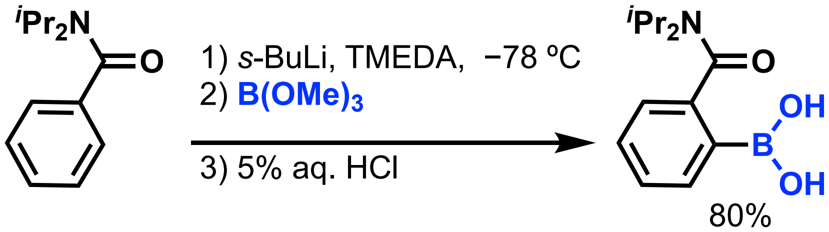


Pageant®
(BASF)



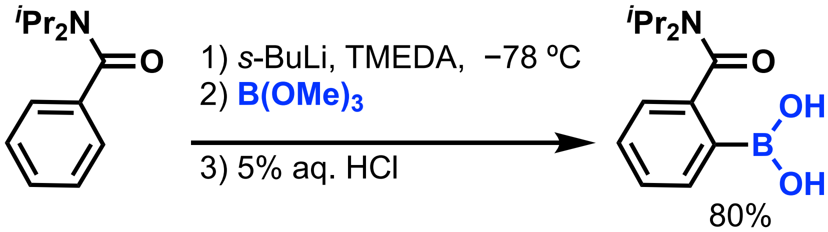
Dolobid®
(Merck)

Catalysis for the Preparation of Boronic Esters

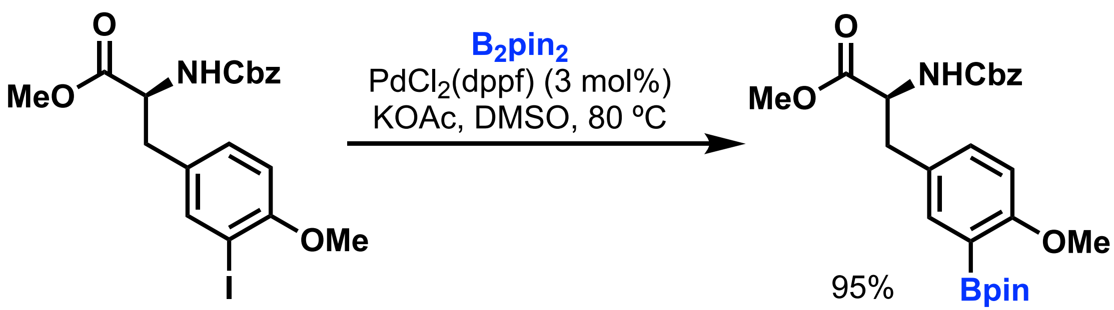


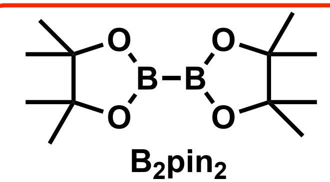
Snieckus et al. *Tetrahedron Lett.* **1985**, *49*, 5997

Catalysis for the Preparation of Boronic Esters



Snieckus et al. *Tetrahedron Lett.* **1985**, *49*, 5997

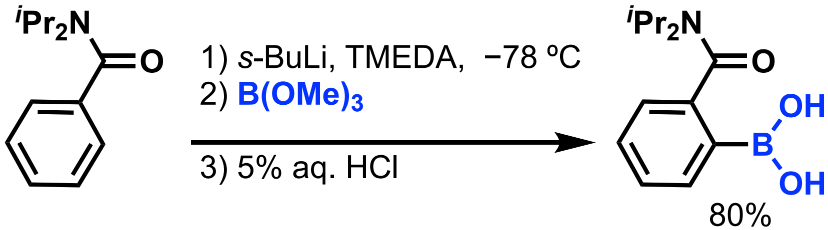




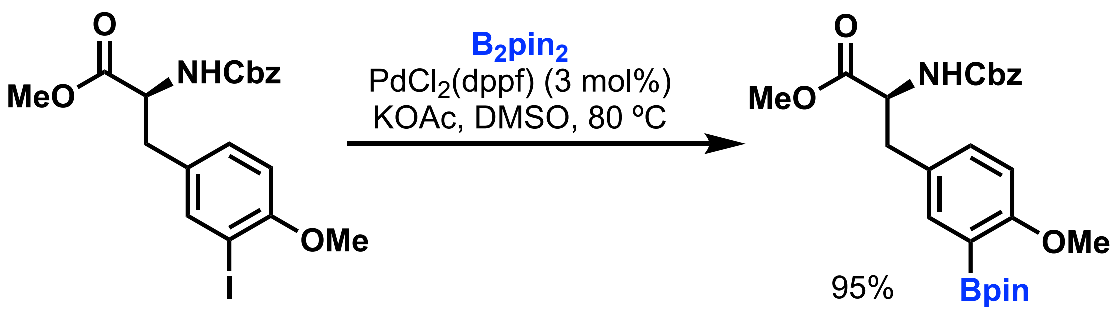
a) Miyaura et al. *J. Org. Chem*. **1995**, *60*, 7508

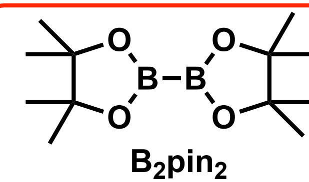
b) Danishefsky et al. *Angew. Chem. Int. Ed*. **2001**, *40*, 1967

Catalysis for the Preparation of Boronic Esters

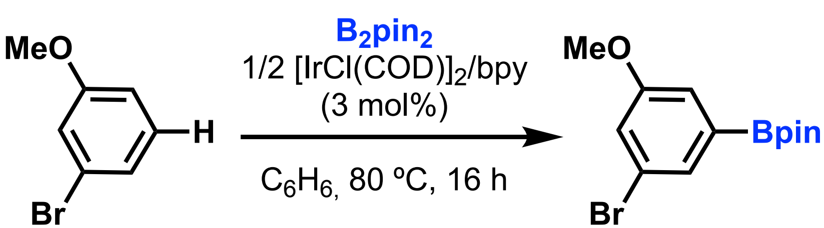


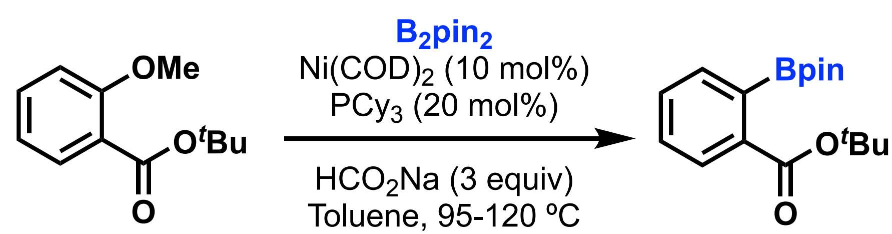
Snieckus et al. *Tetrahedron Lett.* **1985**, *49*, 5997





a) Miyaura et al. *J. Org. Chem.* **1995**, *60*, 7508
b) Danishefsky et al. *Angew. Chem. Int. Ed.* **2001**, *40*, 1967



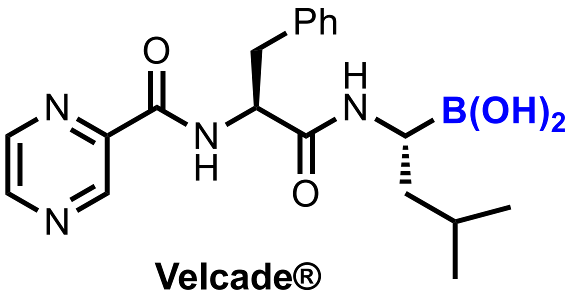


Hartwig et. al. *J. Am. Chem. Soc.* **2002**, *124*, 390

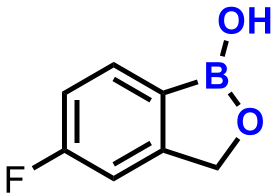
Martin et al. *J. Am. Chem. Soc.* **2015**, *137*, 6754

Boronic Esters in Biomedicine and Materials

New Drugs



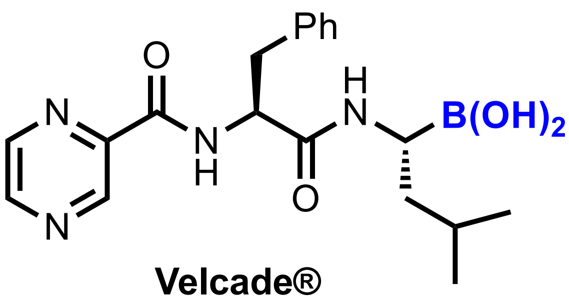
Velcade®



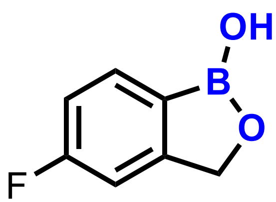
Kerydin

Boronic Esters in Biomedicine and Materials

New Drugs

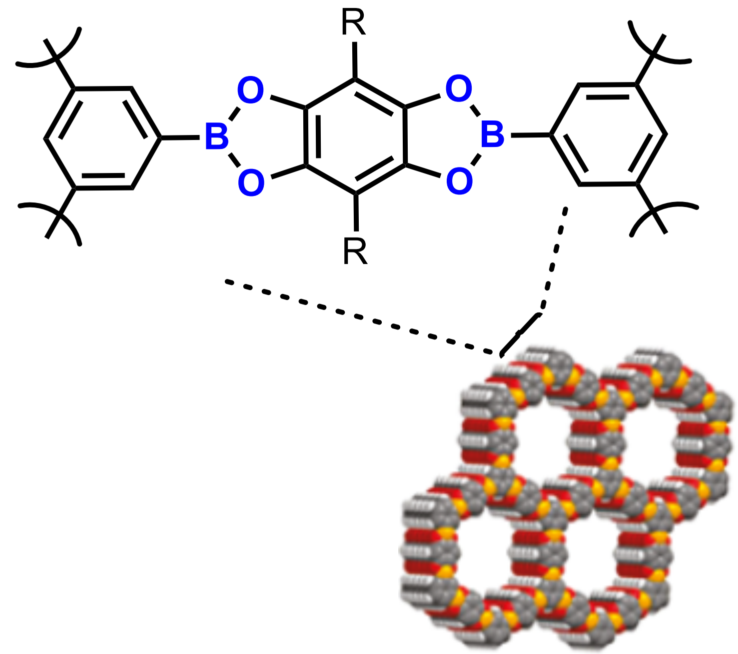


Velcade®

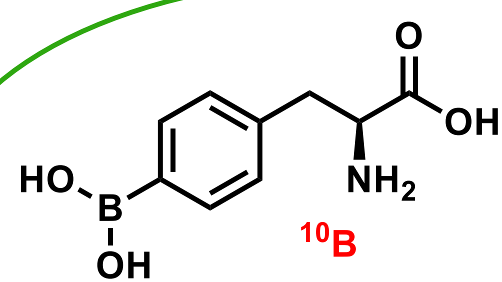


Kerydin

Covalent Organic Frameworks



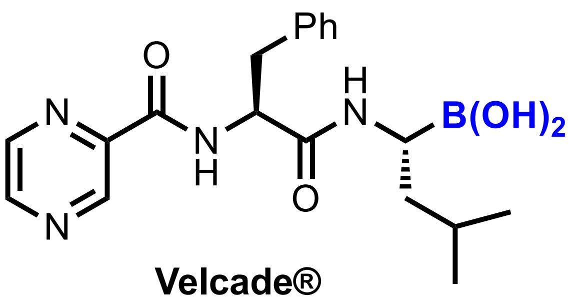
Radiotherapy



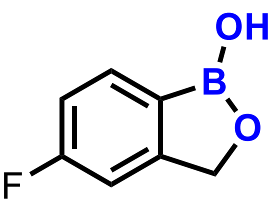
Boron neutron capture

Boronic Esters in Biomedicine and Materials

New Drugs

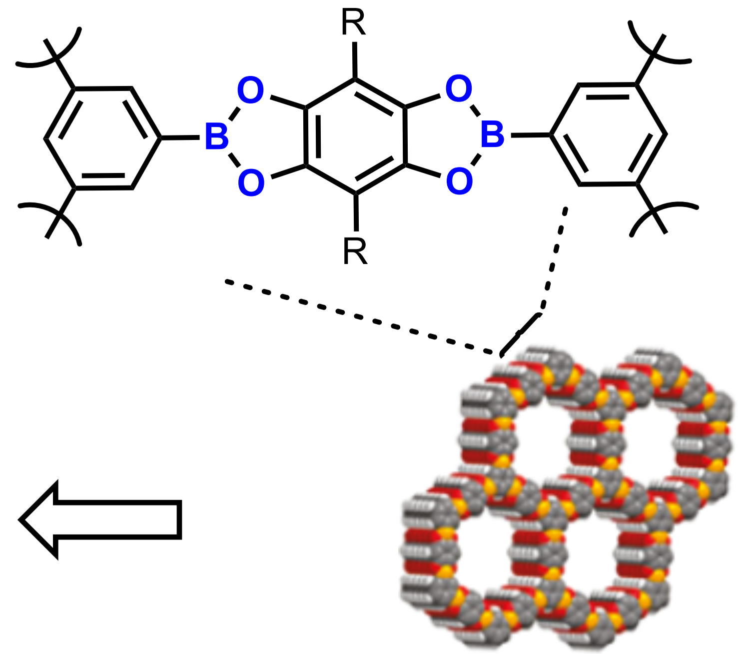


Velcade®



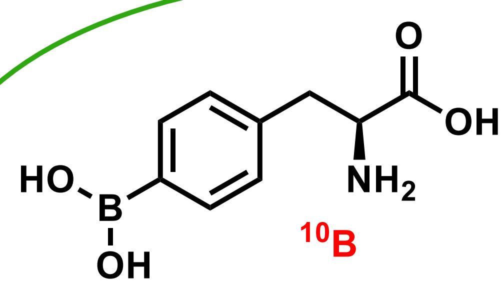
Kerydin

Covalent Organic Frameworks



C — B
Bond Formation

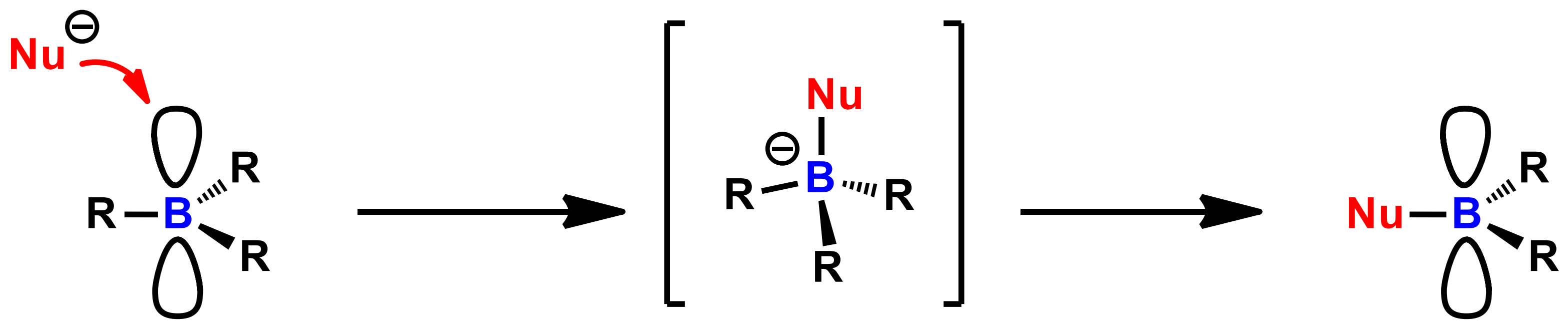
Radiotherapy



Boron neutron capture

Carbon-Boron Bond Formation

Classical C-B bond formation

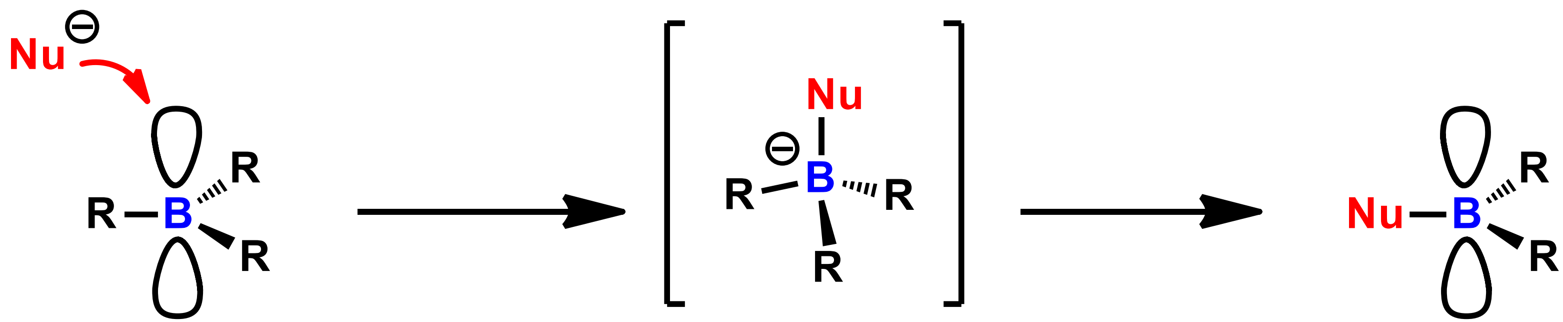


Electrophilic Boron

Limited C-B Bond Formation

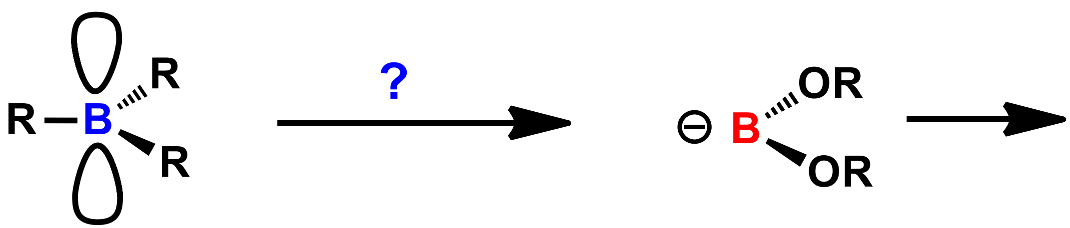
Nucleophilic Boron

Classical C-B bond formation



Electrophilic Boron

Limited C-B Bond Formation

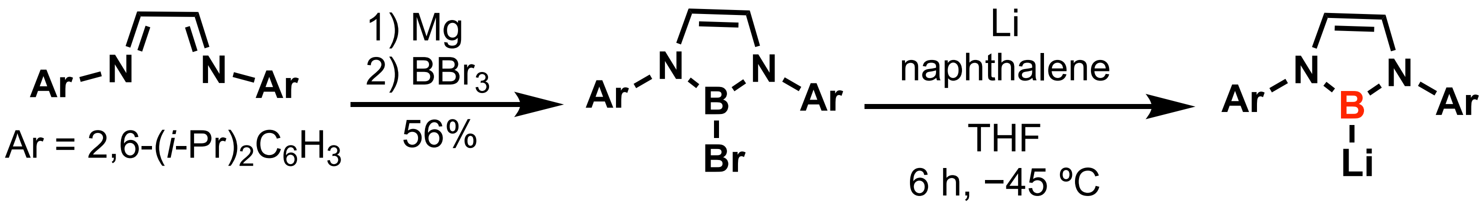


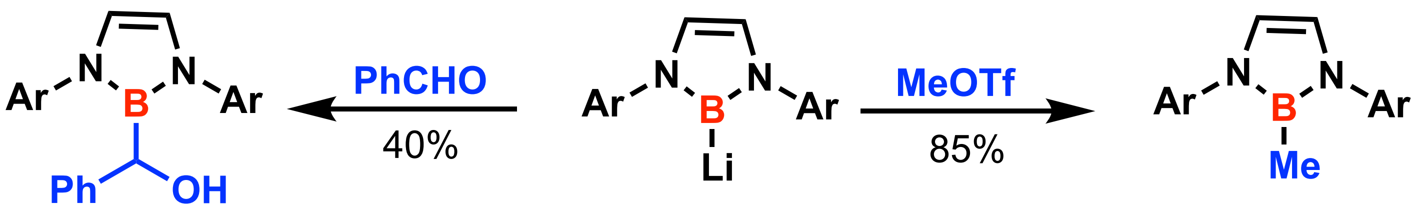
Unprecedented C-B bond formation

Electrophilic Boron

Nucleophilic Boron

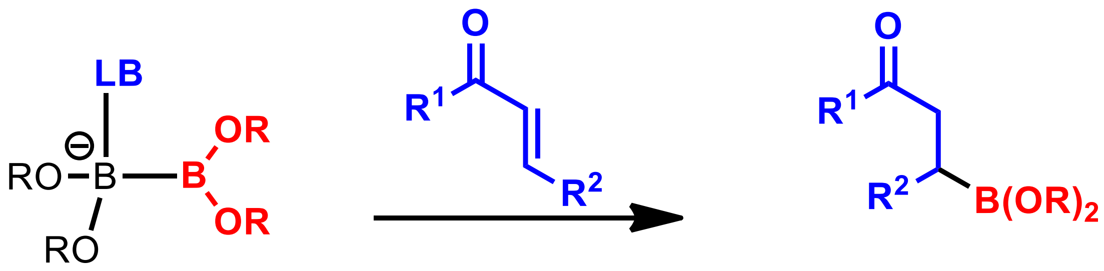
Nucleophilic Boron: Boryllithium





Nozaki, K. et al. *Science* **2006**, *314*, 113
Nozaki, K. et al. *J. Am. Chem. Soc.* **2008**, *130*, 16069

Nucleophilic Boron: Lewis Base Activation



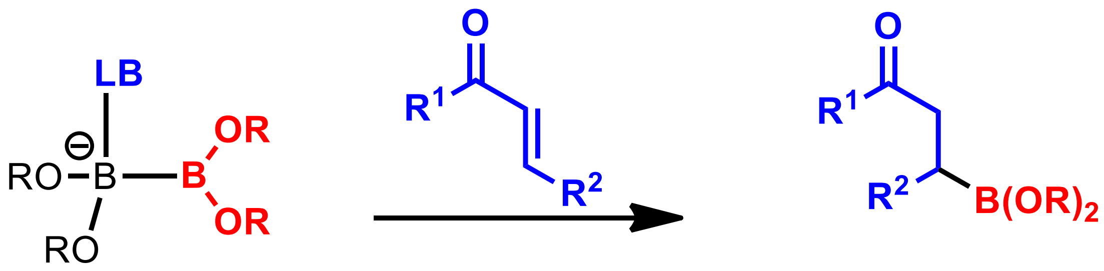
LB = Lewis Base (NHC, RO$^-$)

Formal sp^2 boron nucleophiles

Metal-free conditions

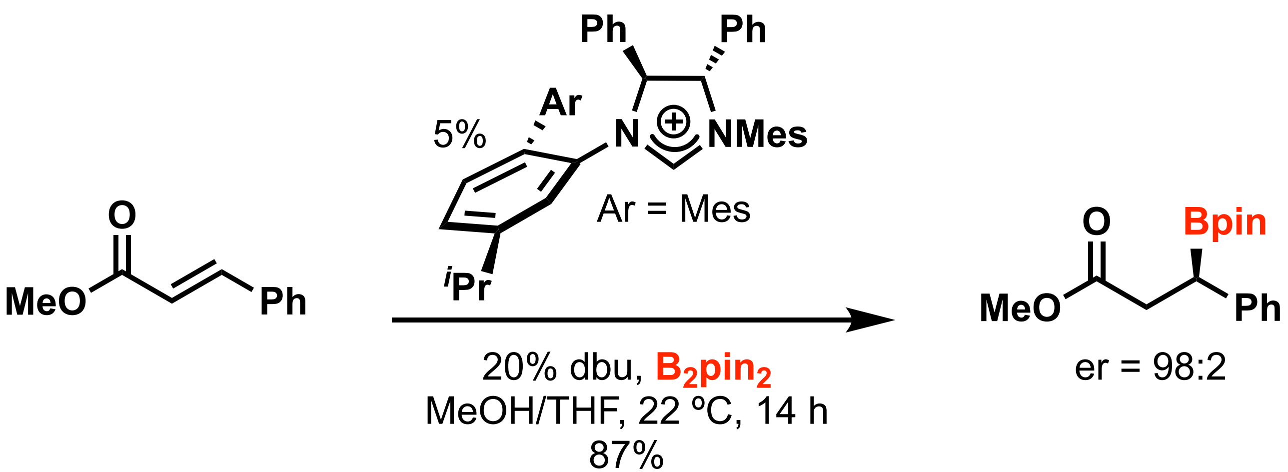
Hoveyda, A. H. et al. *J. Am. Chem. Soc*. **2009**, *131*, 7253
Fernández, E. et al. *Angew. Chem. Int. Ed.* **2010**, *49*, 5130
Bo, C.; Fernández E. et al. *Angew. Chem. Int. Ed*. **2011**, *50*, 7158

Nucleophilic Boron: Lewis Base Activation



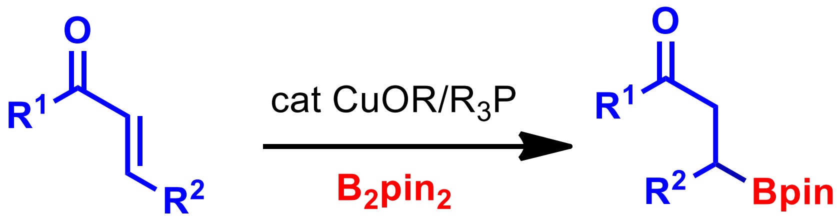
LB = Lewis Base (NHC, RO⁻)
Formal sp^2 boron nucleophiles
Metal-free conditions

Hoveyda, A. H. et al. *J. Am. Chem. Soc*. **2009**, *131*, 7253
Fernández, E. et al. *Angew. Chem. Int. Ed.* **2010**, *49*, 5130
Bo, C.; Fernández E. et al. *Angew. Chem. Int. Ed*. **2011**, *50*, 7158

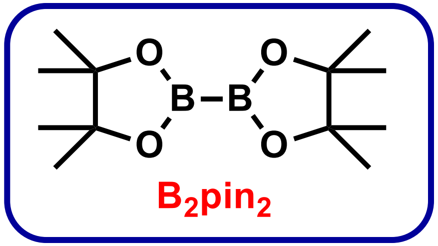


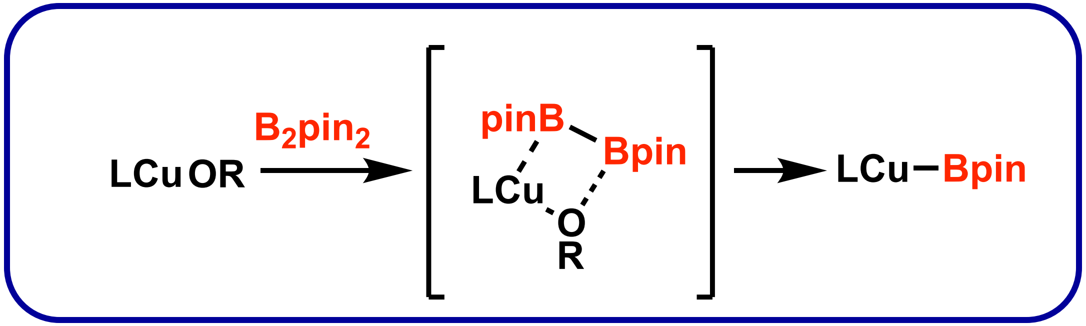
Hoveyda, A. H. et al. *J. Am. Chem. Soc.* **2012**, *134*, 8277

Nucleophilic Boron: Copper-Catalysis



Hosomi, A. et al*. Tetrahedron Lett*. **2000**, *41*, 6821
Miyaura, N. et al*. J. Organomet. Chem*. **2001**, *625*, 47

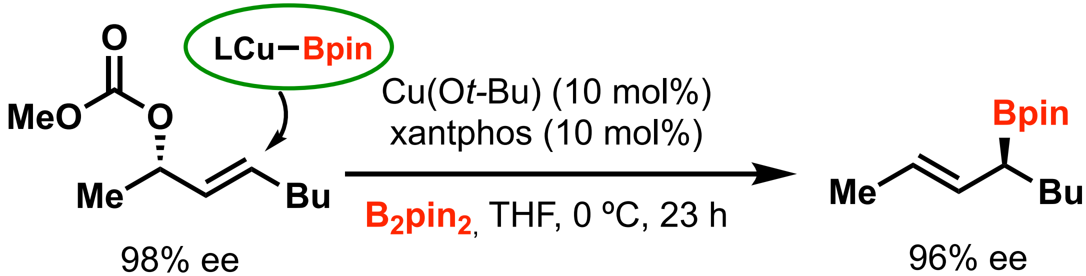




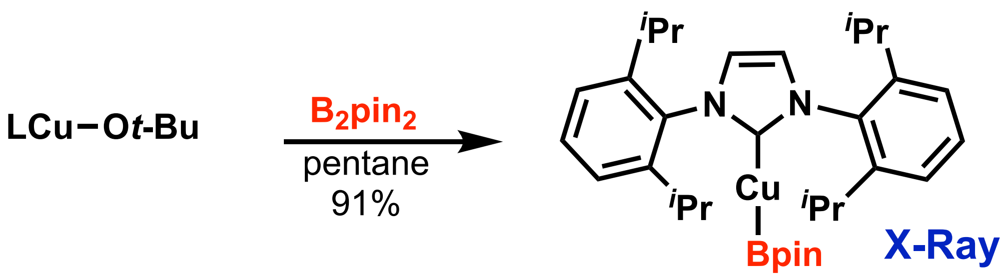
Formal boron nucleophile

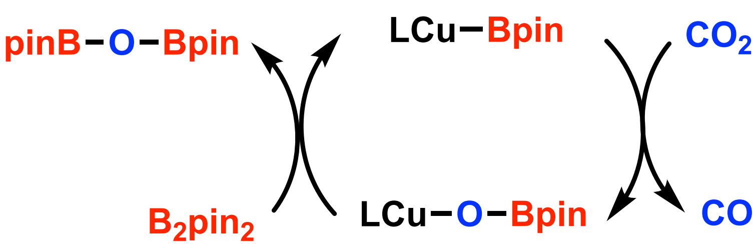
Reviews: a) Westcott, S. A.; Marder, T. B. et al. *Chem Rev.* **2016**, *116*, 9091. b) Yoshida, H. *ACS Catal*. **2016**, *6*, 1799

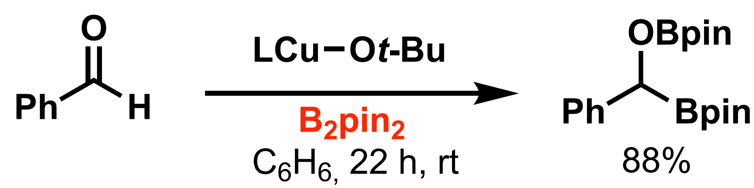
Nucleophilic Boron: Copper-Catalysis



Ito, H.; Sawamura, M. et al. *J. Am. Chem. Soc.* **2005**, *127*, 16034

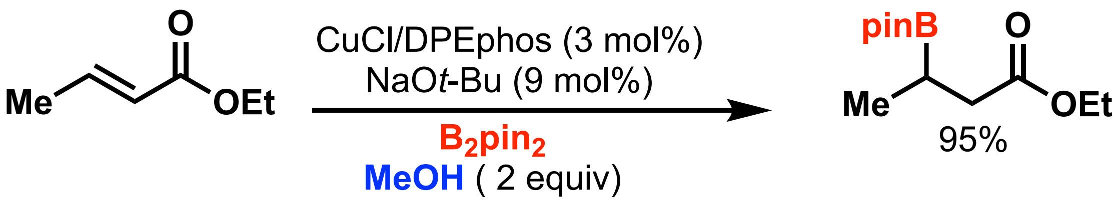


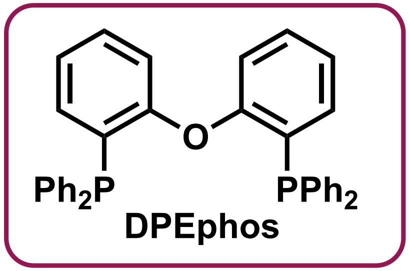




Sadighi, J. P. et al. *J. Am. Chem. Soc.* **2005**, *127*, 17196
J. Am. Chem. Soc. **2006**, *128*, 11036

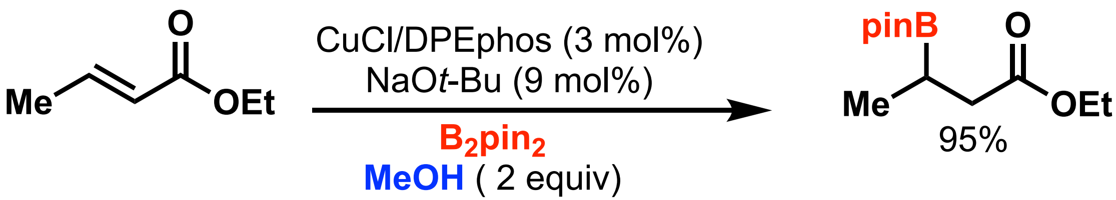
Nucleophilic Boron: Copper-Catalysis

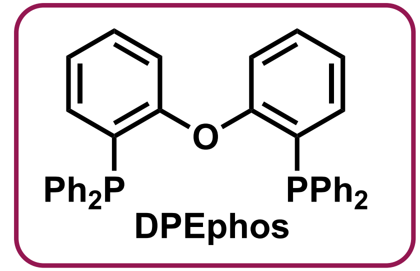




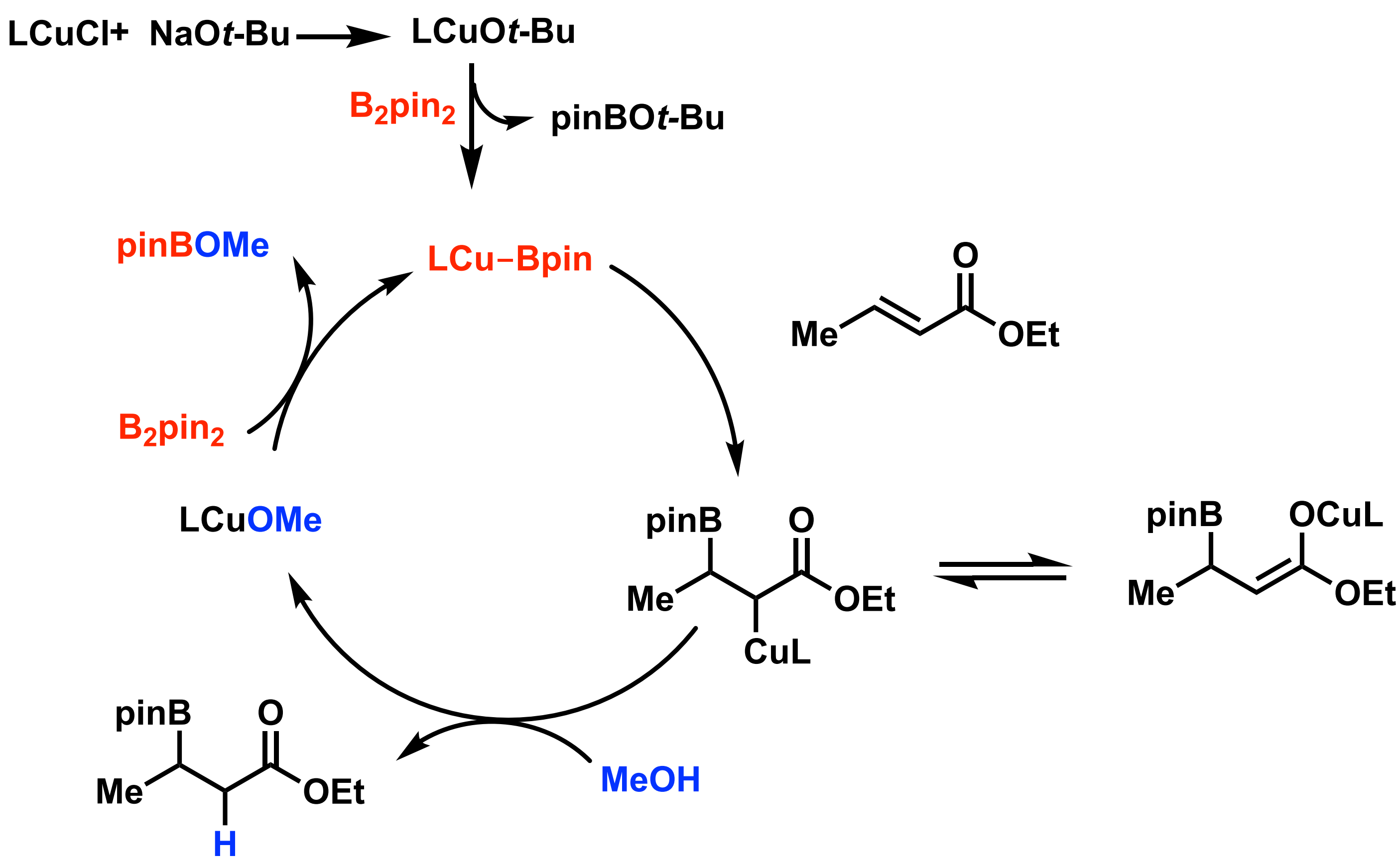
Yun, J. et al. *Org. Lett*. **2006**, *8*, 4887

Nucleophilic Boron: Copper-Catalysis

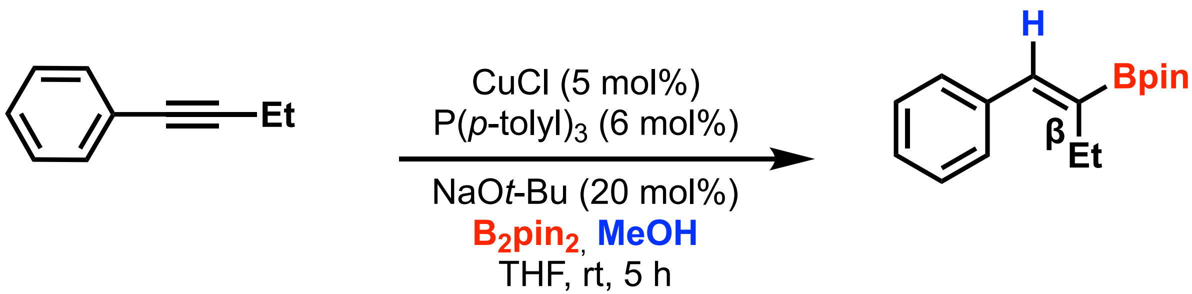




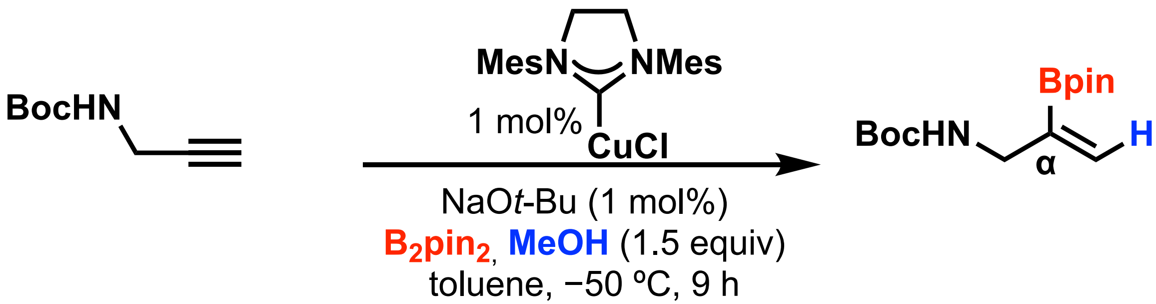
Yun, J. et al. *Org. Lett.* **2006**, *8*, 4887



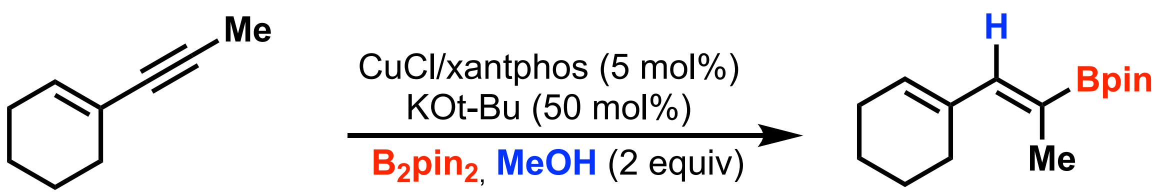
Nucleophilic Boron: Copper-Catalysis



Yun, J. et al. *Chem. Commun.* **2011**, *47*, 2943

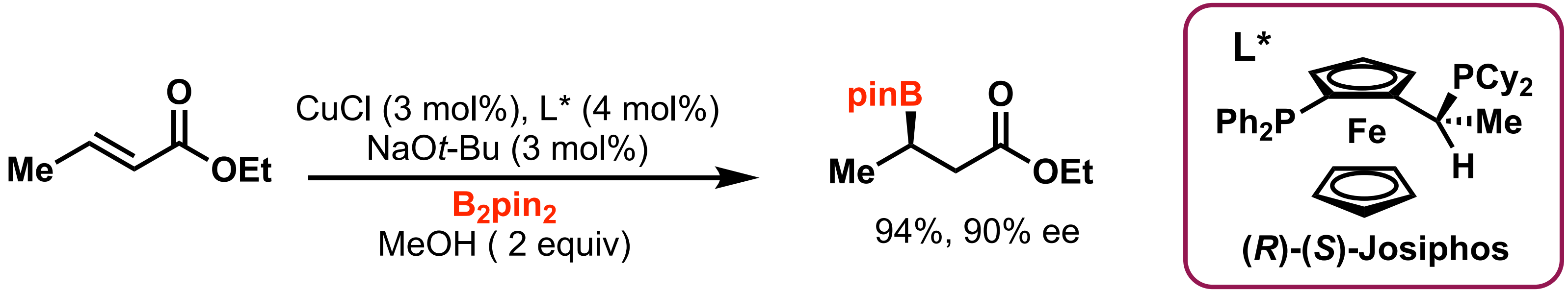


Hoveyda, A. H. et al. *J. Am. Chem. Soc.* **2011**, *133*, 7859



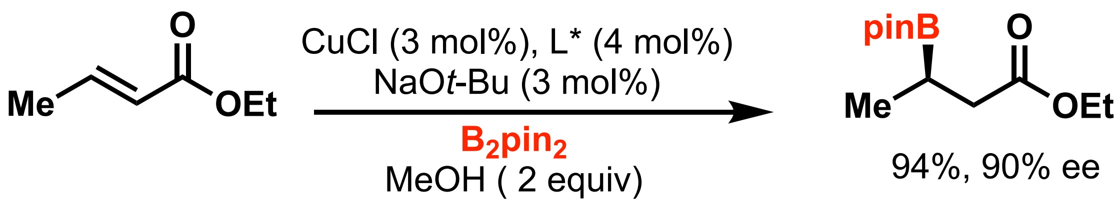
Sawamura, M. et al. *Angew. Chem. Int. Ed.* **2011**, *50*, 2778

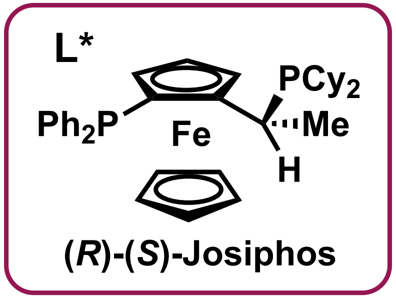
Nucleophilic Boron: Copper-Catalysis



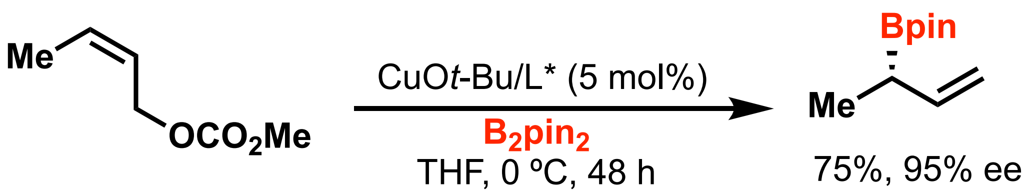
Yun, J. et al. *Angew. Chem. Int. Ed*. **2008**, *47*, 145

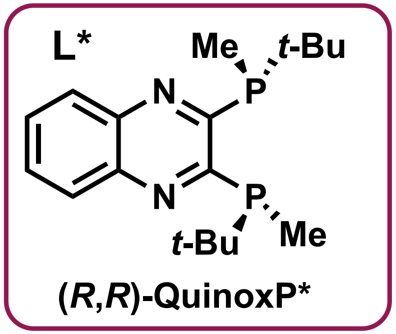
Nucleophilic Boron: Copper-Catalysis





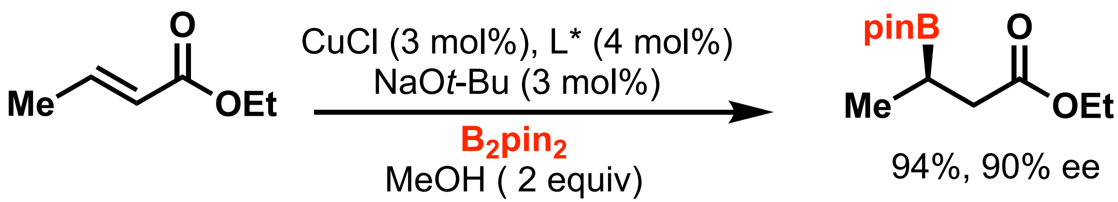
Yun, J. et al. *Angew. Chem. Int. Ed.* **2008**, *47*, 145

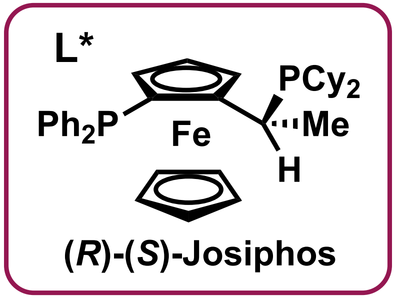




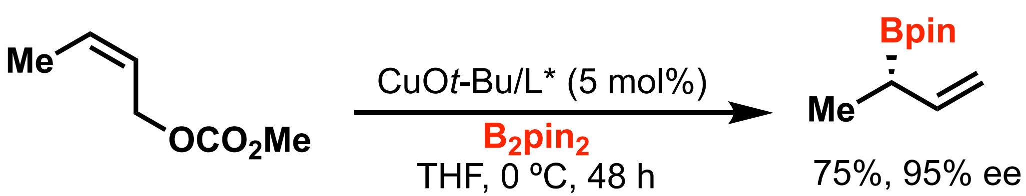
Ito, H.; Sawamura, M. et al. *J. Am. Chem. Soc.* **2007**, *129*, 14856

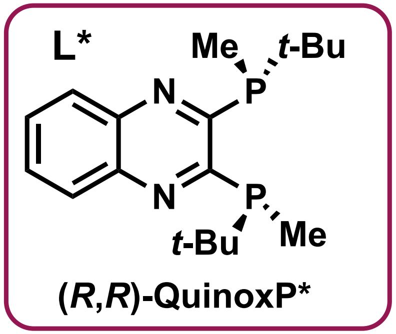
Nucleophilic Boron: Copper-Catalysis



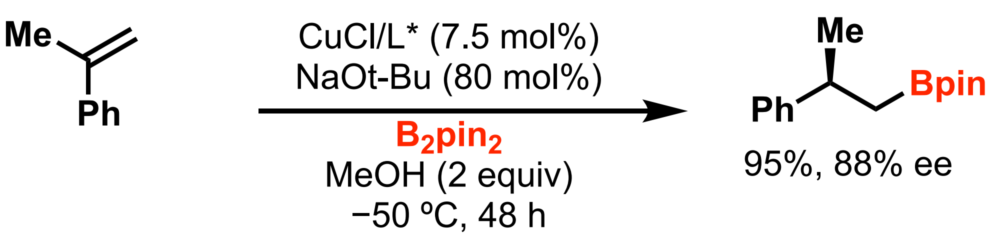


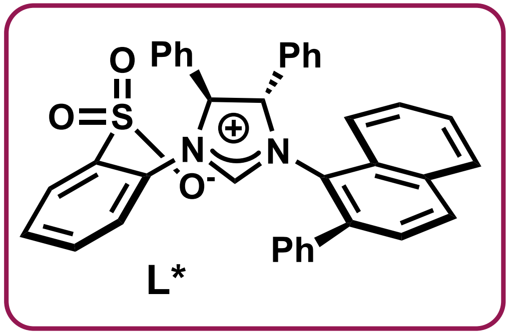
Yun, J. et al. *Angew. Chem. Int. Ed.* **2008**, *47*, 145





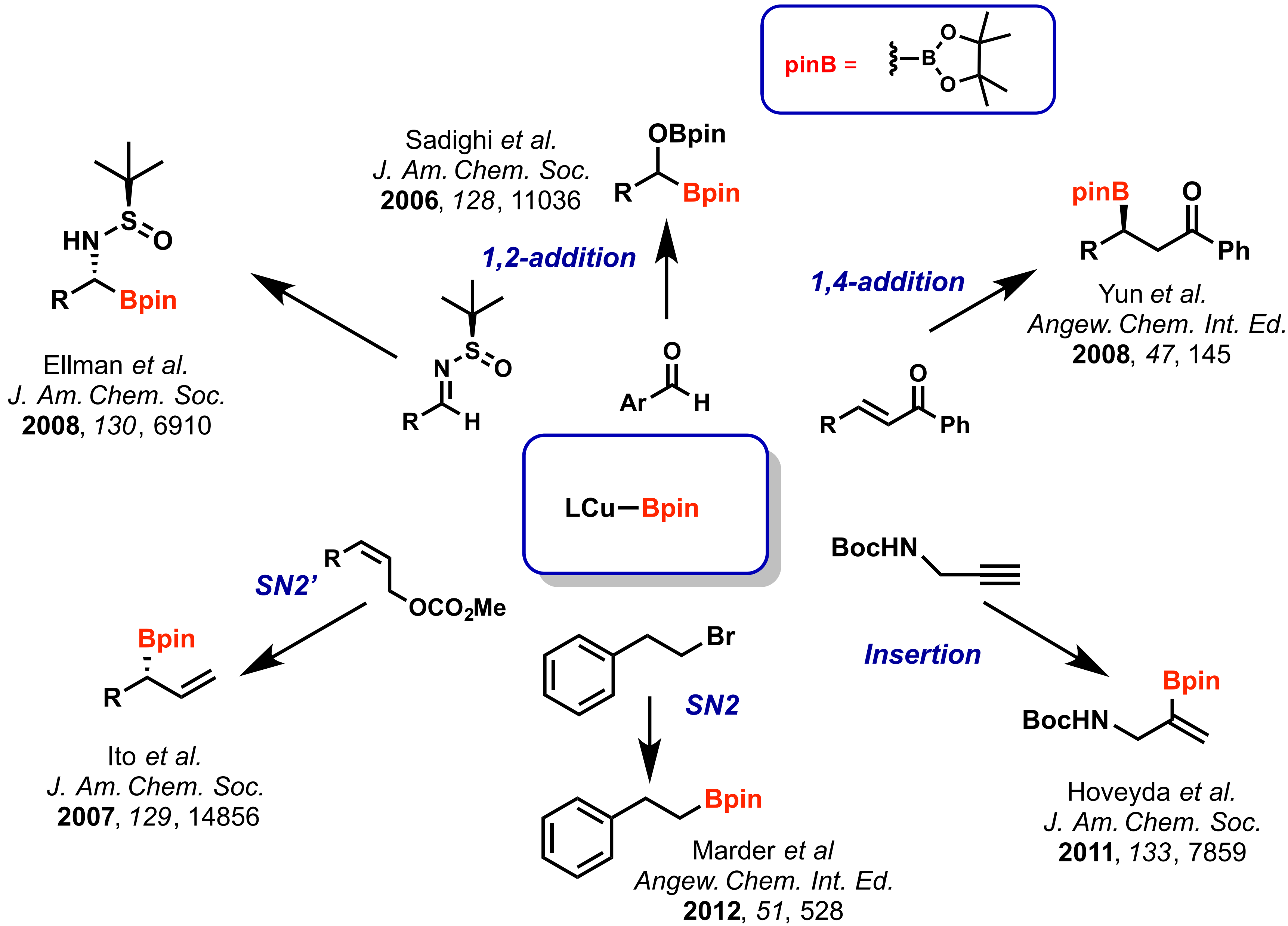
Ito, H.; Sawamura, M. et al. *J. Am. Chem. Soc.* **2007**, *129*, 14856



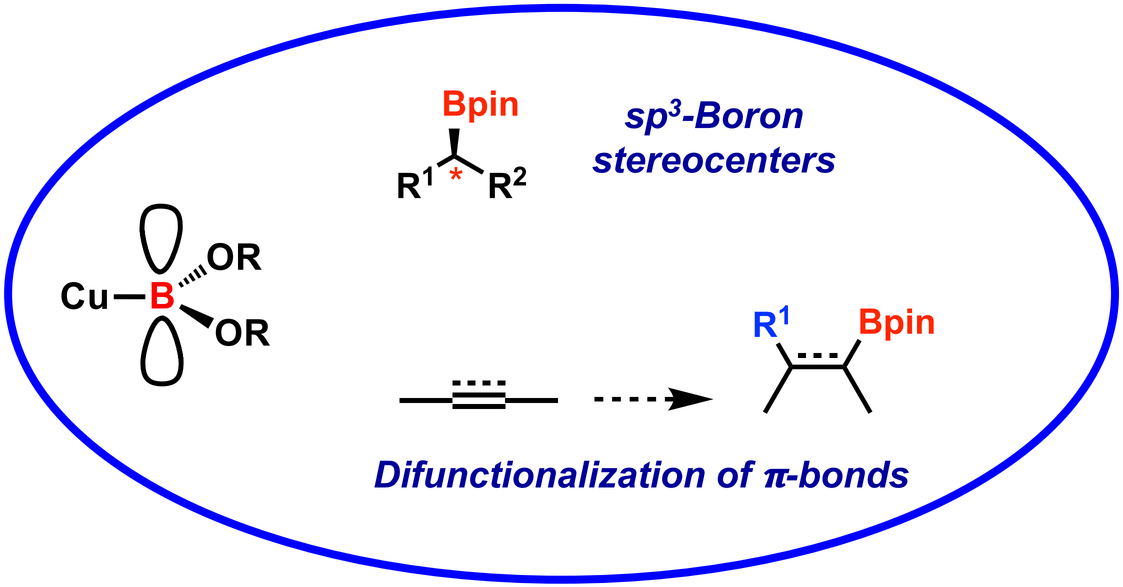


Hoveyda, A. H. et al. *Angew. Chem. Int. Ed.* **2011**, *50*, 7079

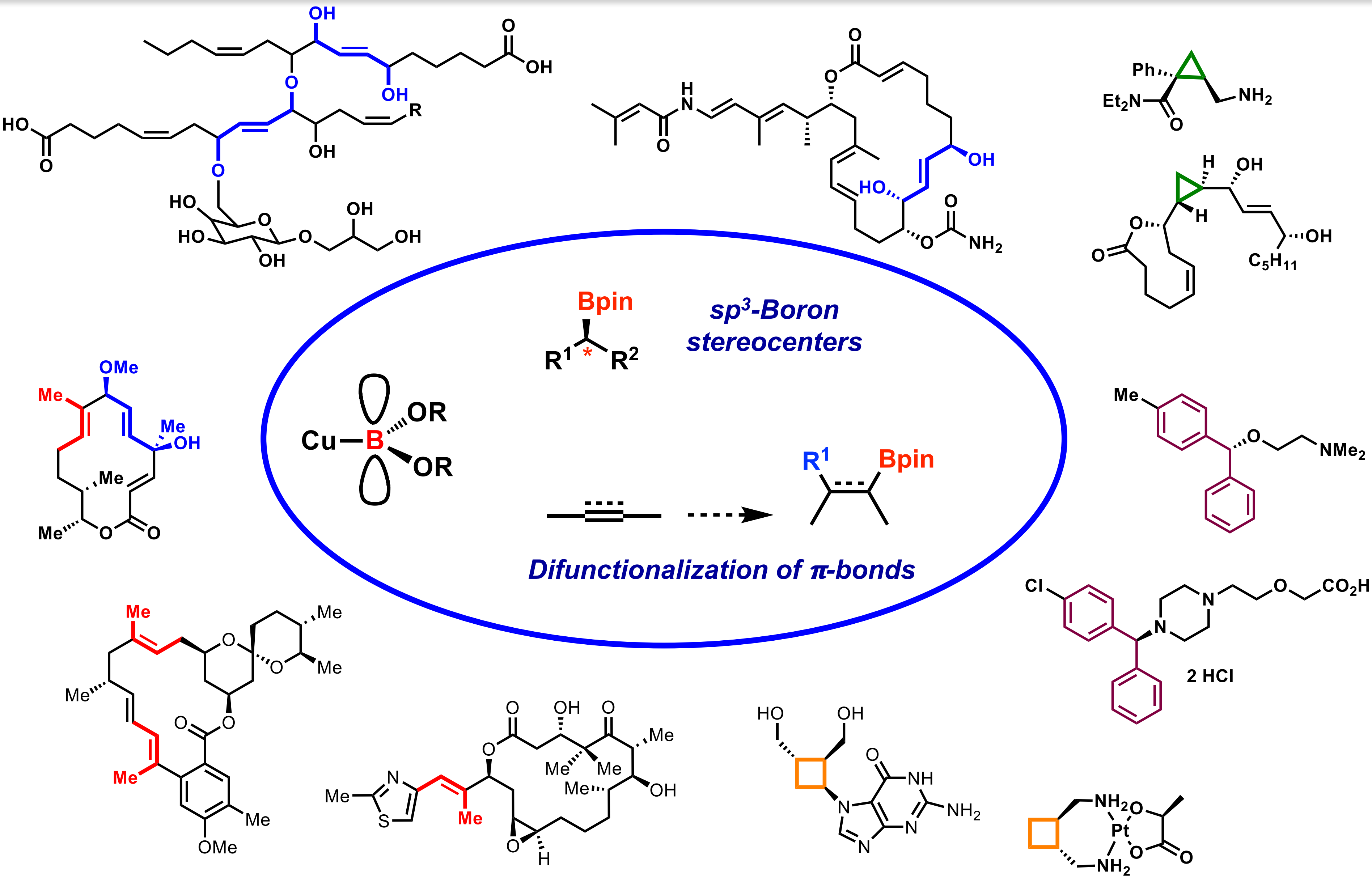
Copper-Catalyzed Borylations



Our Inspiration

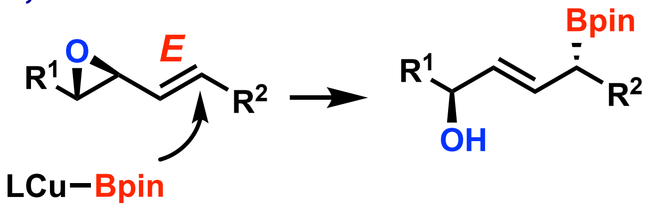


Our Inspiration



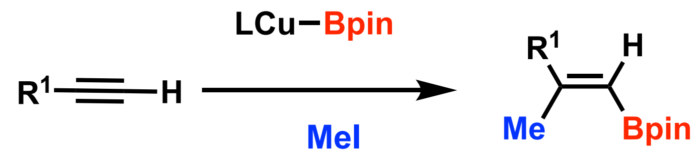
Our Contribution

1,4-Diols



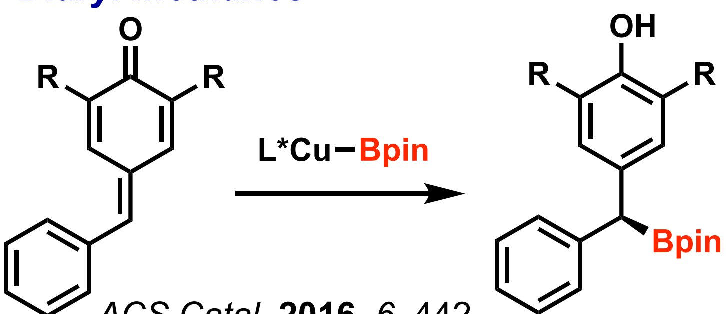
Angew. Chem. Int. Ed. **2011**, *50*, 3950

Vinyl Boronates



J. Am. Chem. Soc. **2012**, *134*, 15165

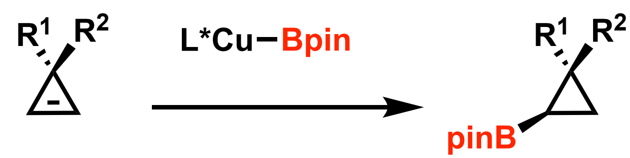
Diaryl methanes



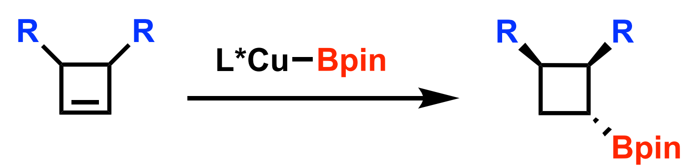
ACS Catal. **2016**, *6*, 442
Chem. Comm. **2015**, *51*, 17684

LCu–Bpin

Cyclopropyl and Cyclobutyl Boronates

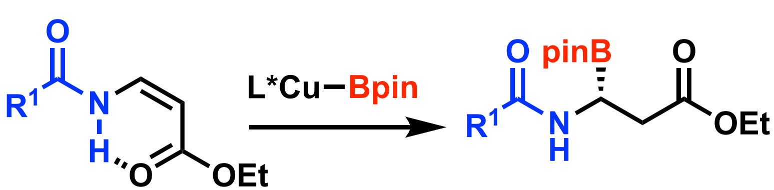


J. Am. Chem. Soc. **2014**, *136*, 15833



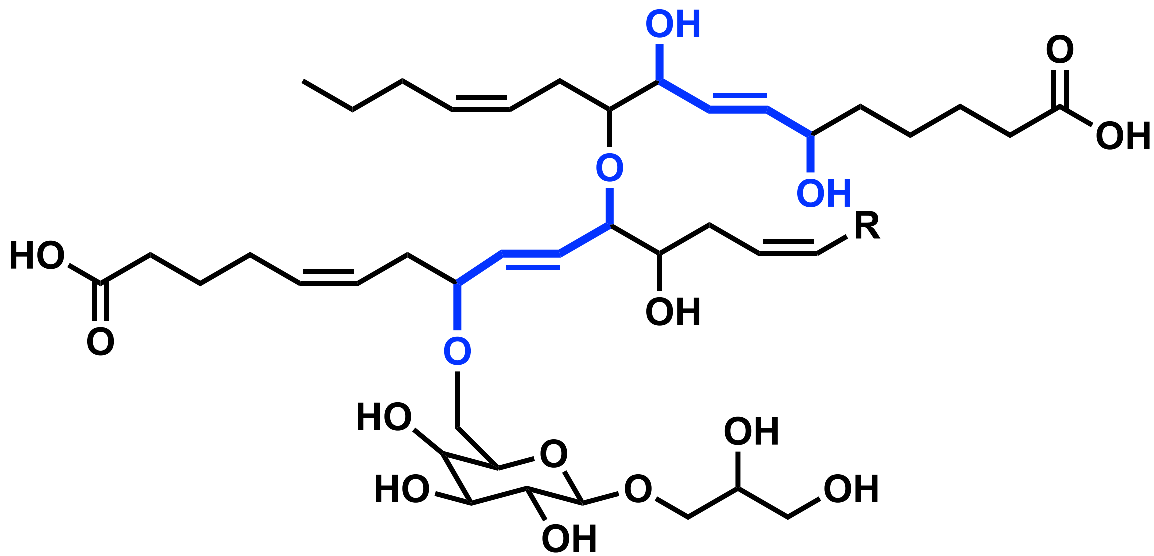
Angew. Chem. Int. Ed. **2016**, *55*, 6969

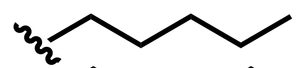
α-Amino boronates

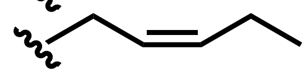


Unpublished results

Where it all began



Nigricanoside A, R = 

Nigricanoside B, R = 

Andersen R. J. et al. *J. Am. Chem. Soc.* **2007**, *129*, 5822

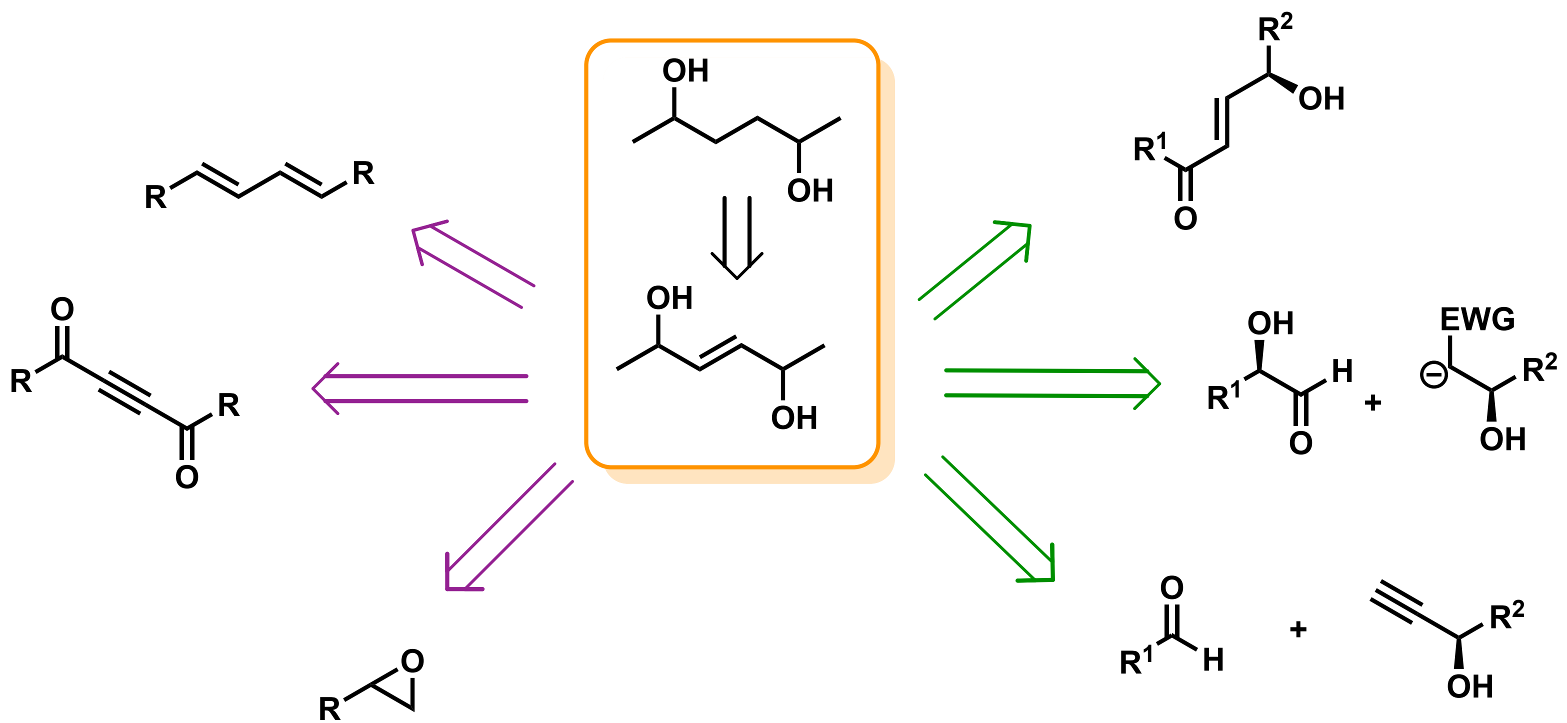
Diastereoselective Synthesis of 1,4-Diols

Symmetric Diols

Non-Symmetric Diols

symmetric diols

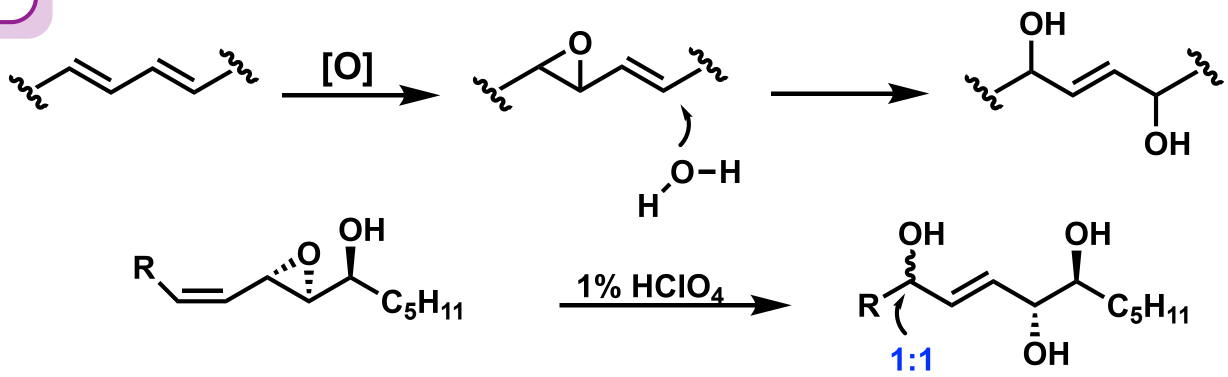
non-symmetric diols



Two Chiral Sources

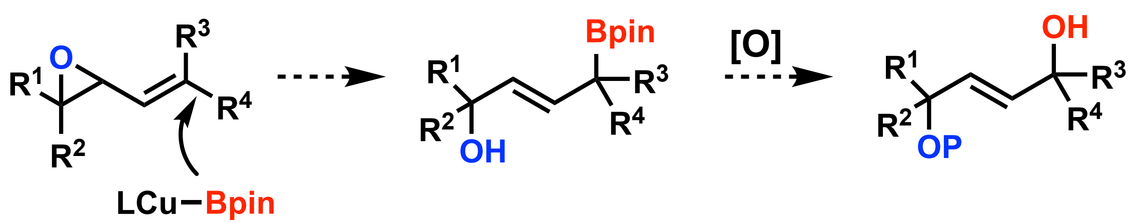
Formal Stereocontrolled Hydrolysis of Vinyl Oxiranes

1,4-diols in Nature



Conrow, R. E. *Org. Lett.* **2006**, *8*, 2441

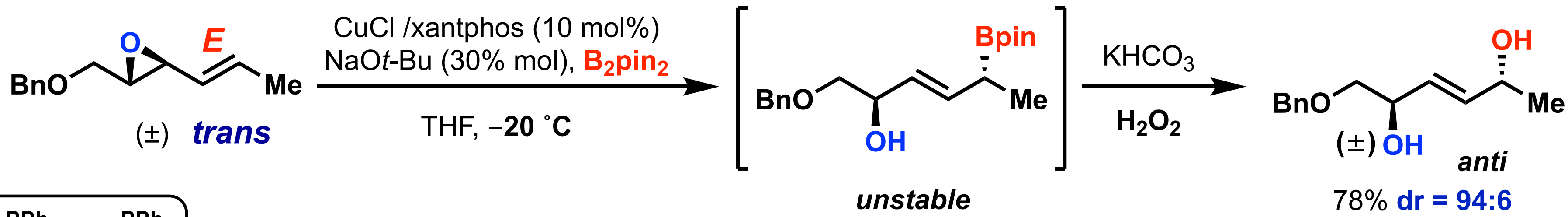
Our Approach

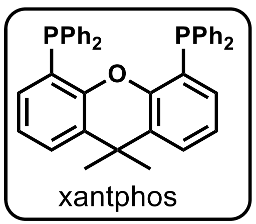


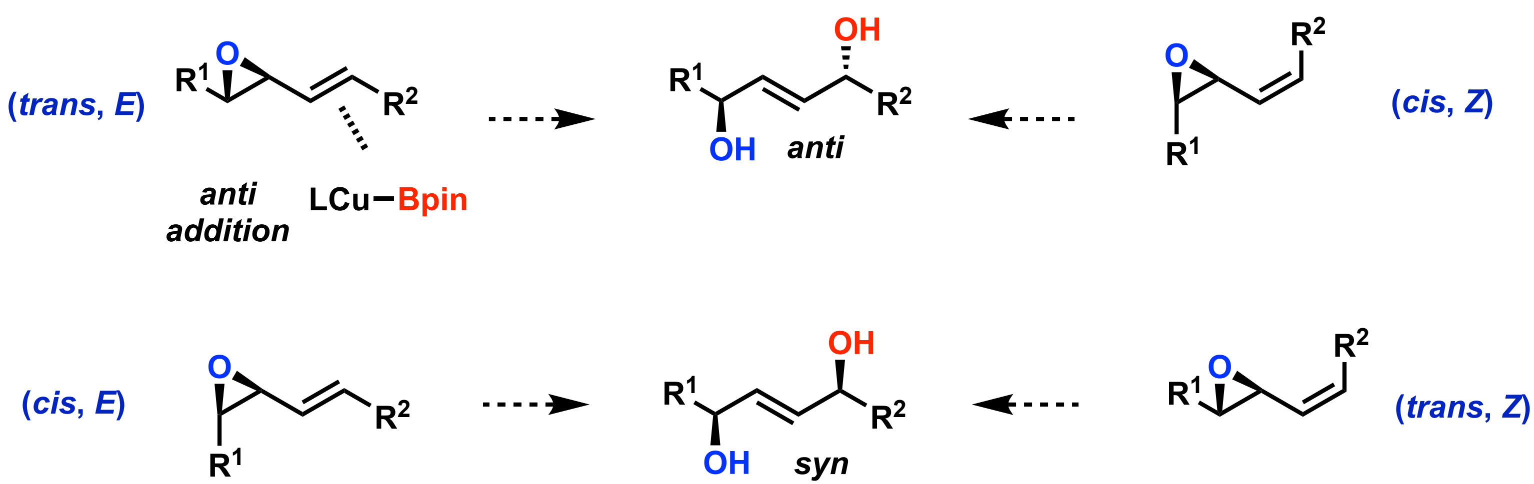
Formal Stereocontrolled Hydrolysis

- ***Access to primary, secondary and tertiary diols***
- ***Access to syn and anti diols***
- ***Access to orthogonally protected 1,4-diols***

First Experiments

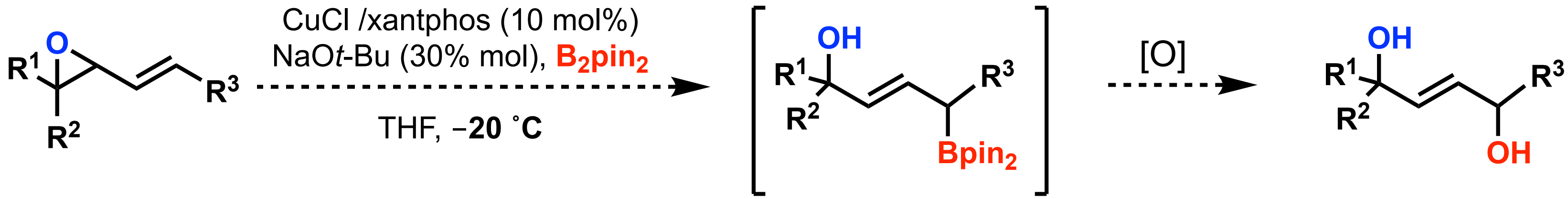


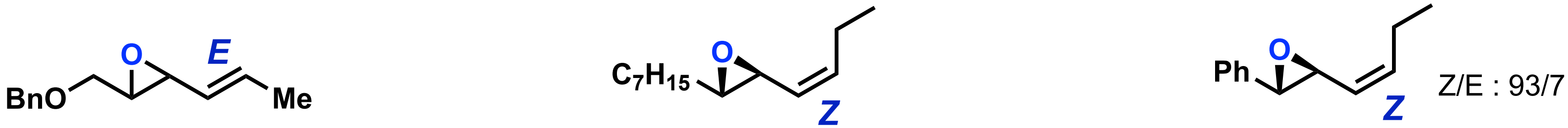




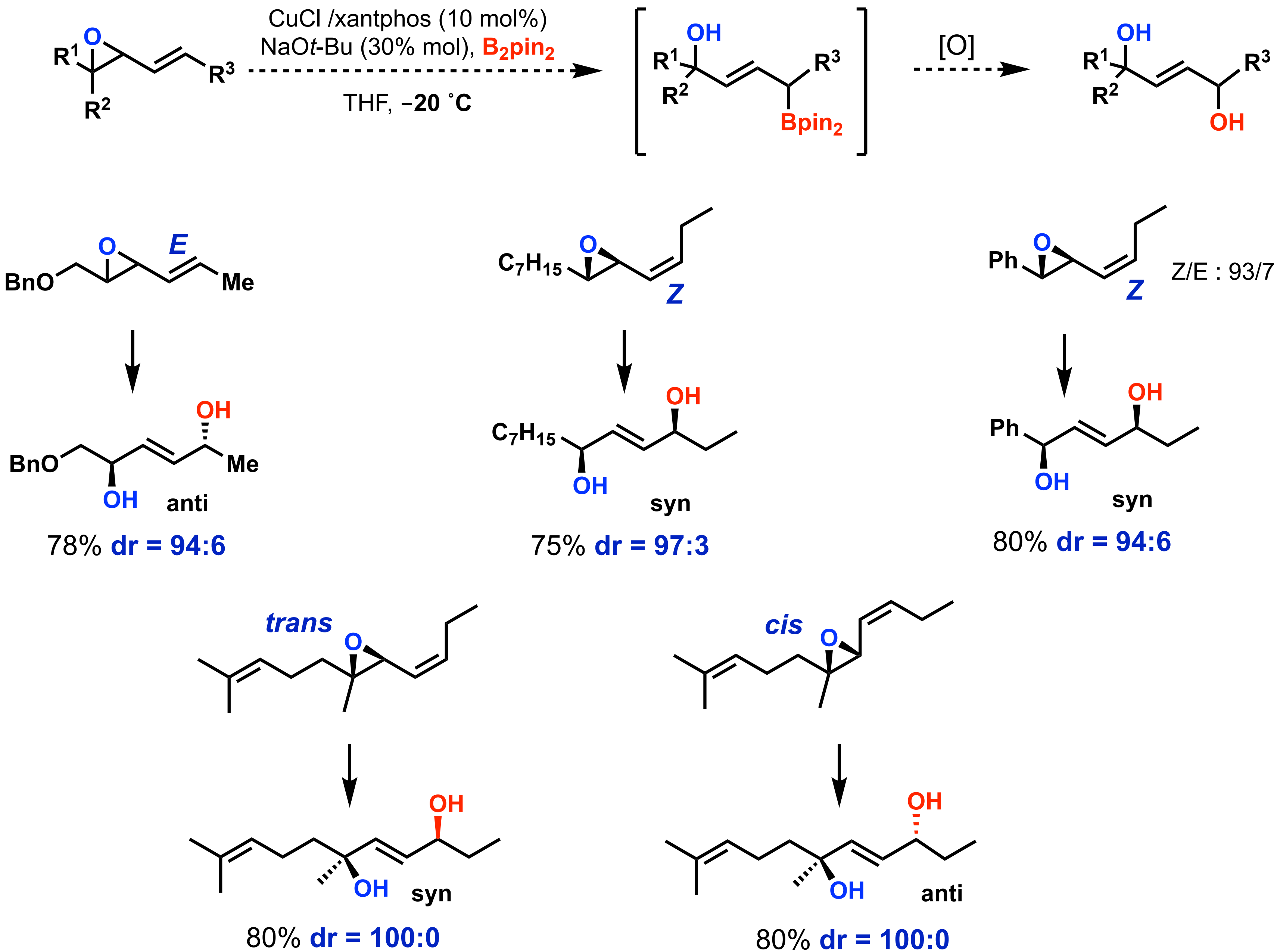
Angew. Chem. Int. Ed. **2011**, *50*, 3950

Scope of the Addition

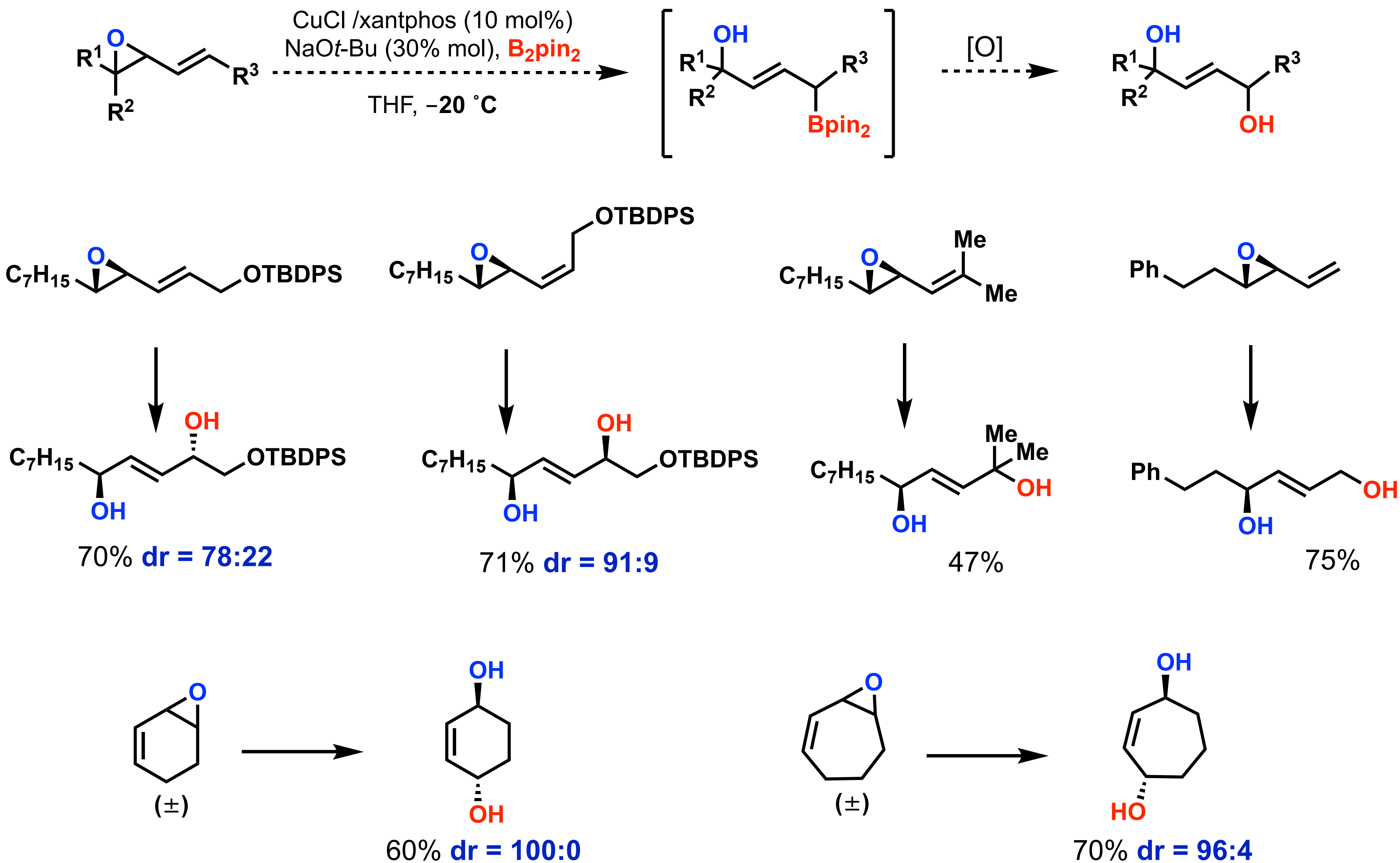




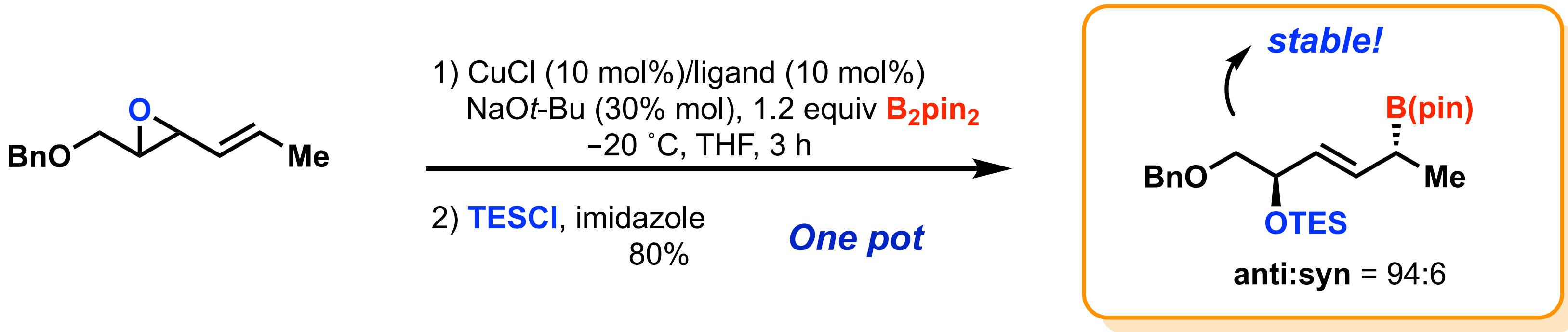
Scope of the Addition

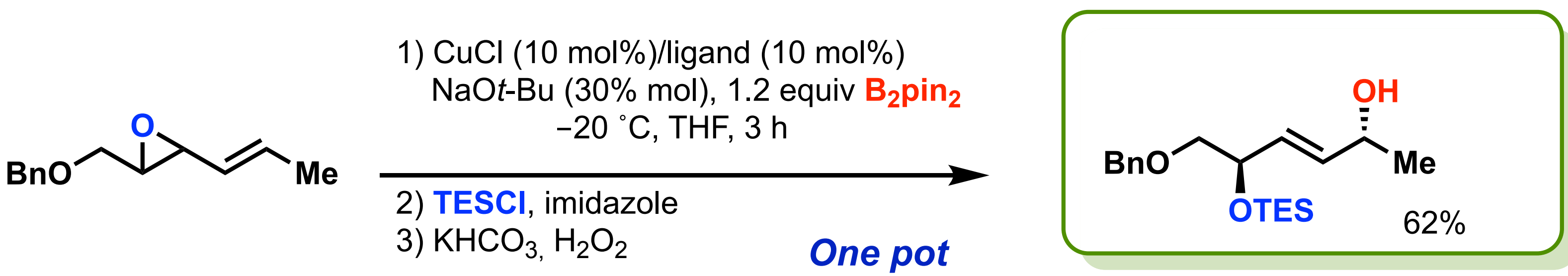


Scope of the Addition



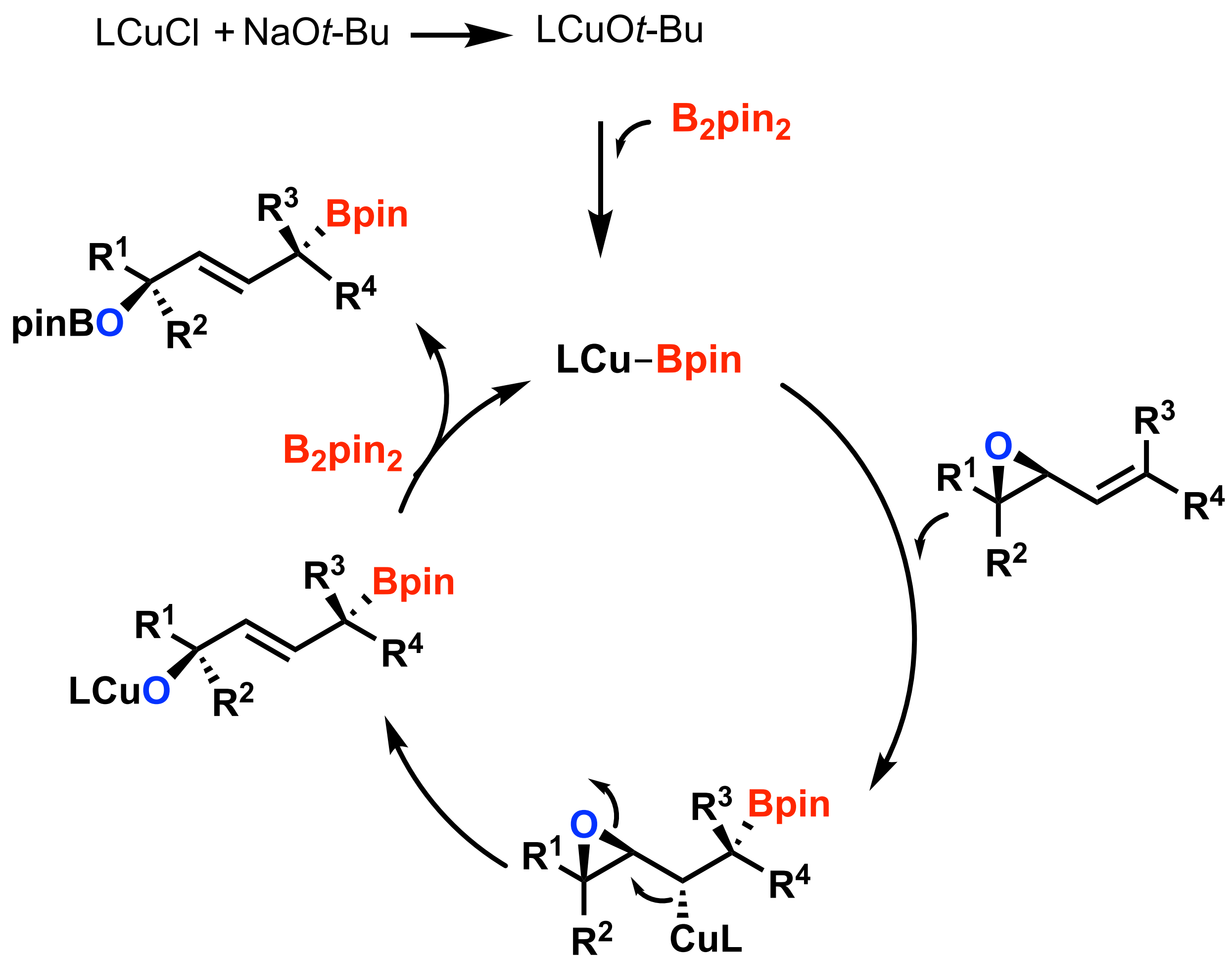
Silyloxy Boronates and Orthogonally Protected Diols





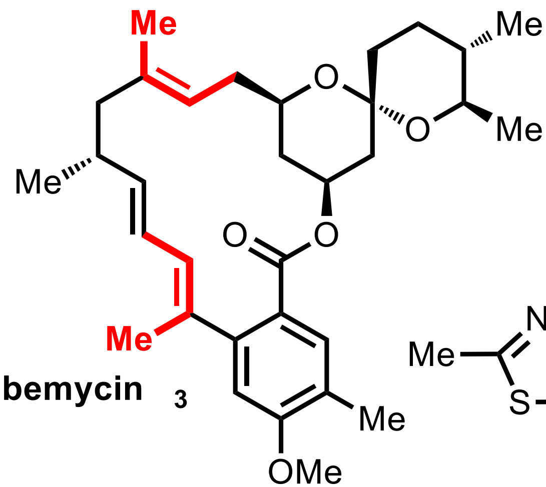
Orthogonally protected triols

Proposed Mechanism

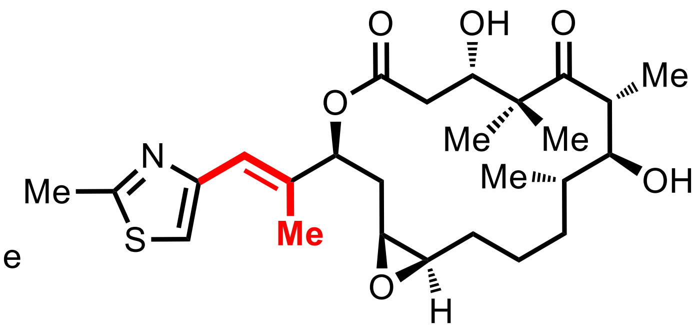


Angew. Chem. Int. Ed. **2011**, *50*, 3950

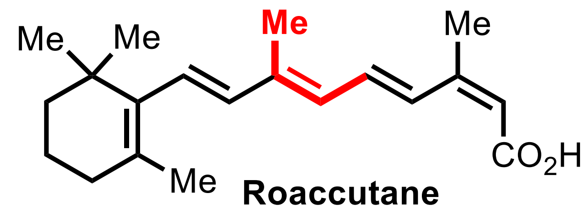
Trisubstituted Methyl-Branched Alkenes



Milbemycin 3

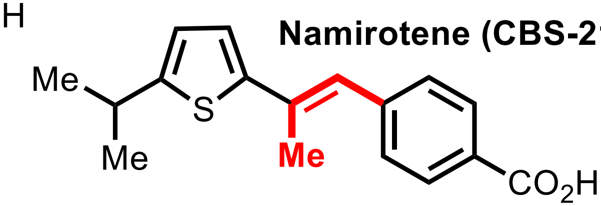


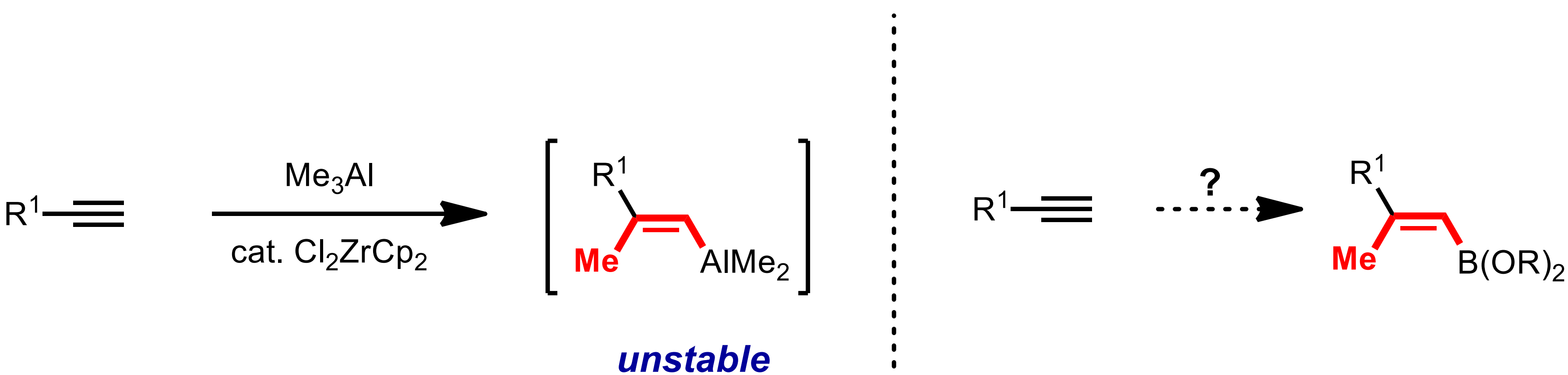
Epothilone A



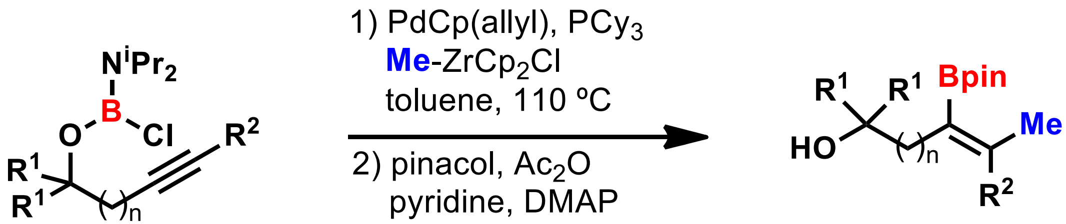
Roaccutane

Namirotene (CBS-211A)

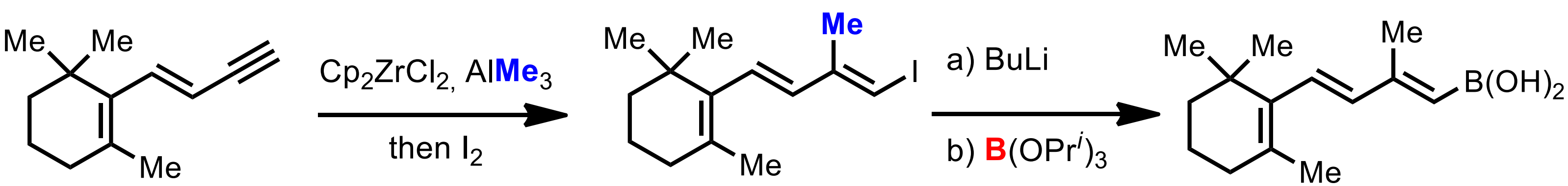




Synthesis of *Cis* Methyl-Branched Vinyl Boronates

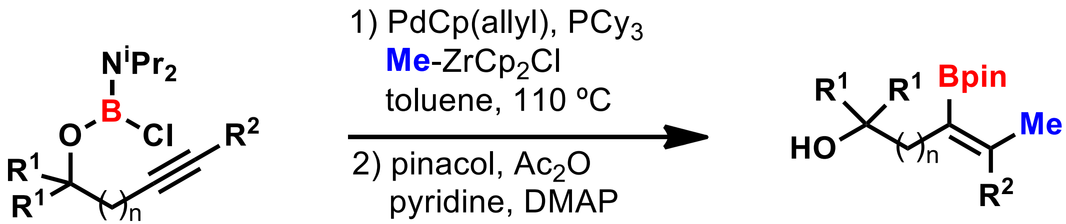


Daini, M.; Yamamoto, A.; Suginome, M. *J. Am. Chem. Soc.* **2008**, *130*, 2918

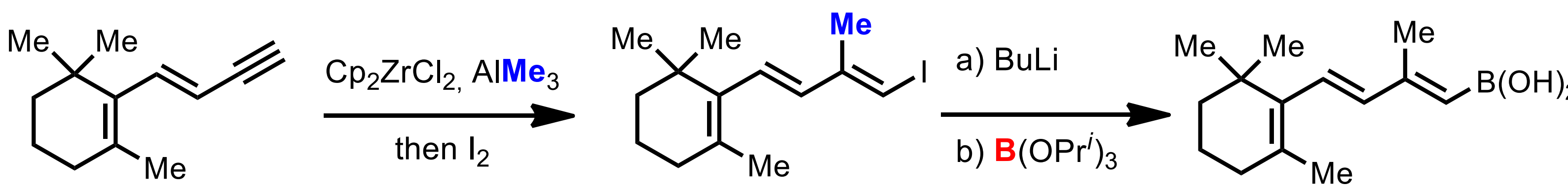


Uenishi, J.; Matsui, K.; Wada, A. *Tetrahedron Lett*. **2003**, *44*, 3093

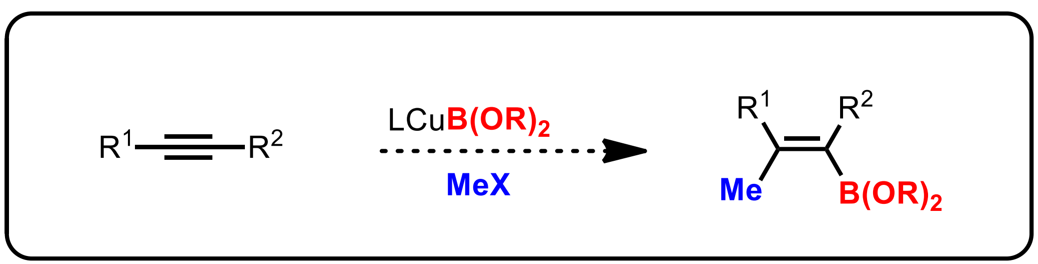
Synthesis of *Cis* Methyl-Branched Vinyl Boronates



Daini, M.; Yamamoto, A.; Suginome, M. *J. Am. Chem. Soc.* **2008**, *130*, 2918

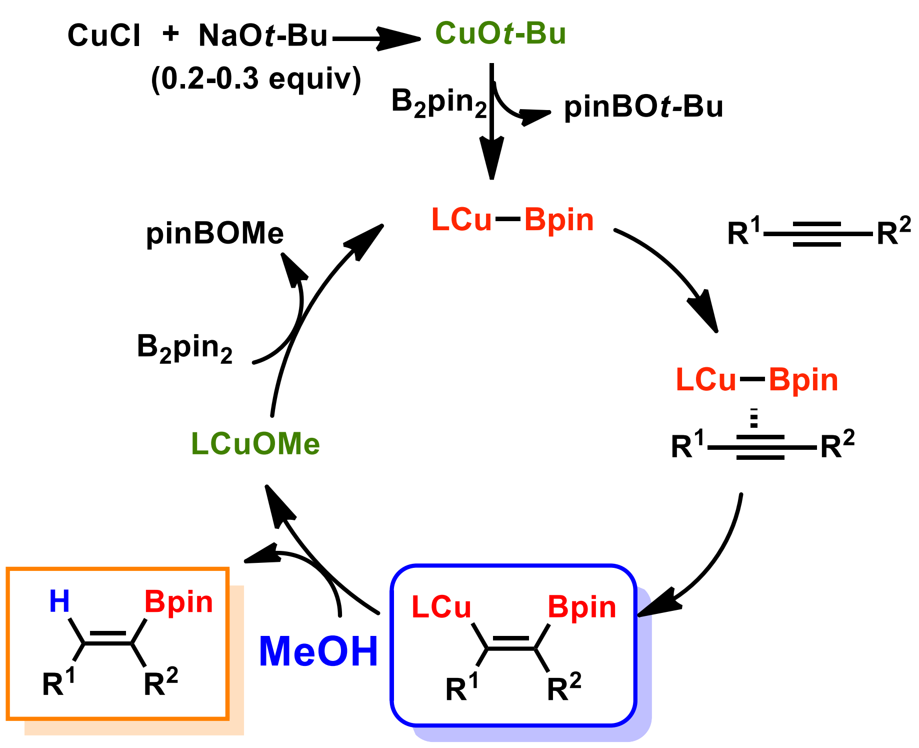


Uenishi, J.; Matsui, K.; Wada, A. *Tetrahedron Lett*. **2003**, *44*, 3093



Copper-Catalyzed Hydro- and Carboboration of Alkynes

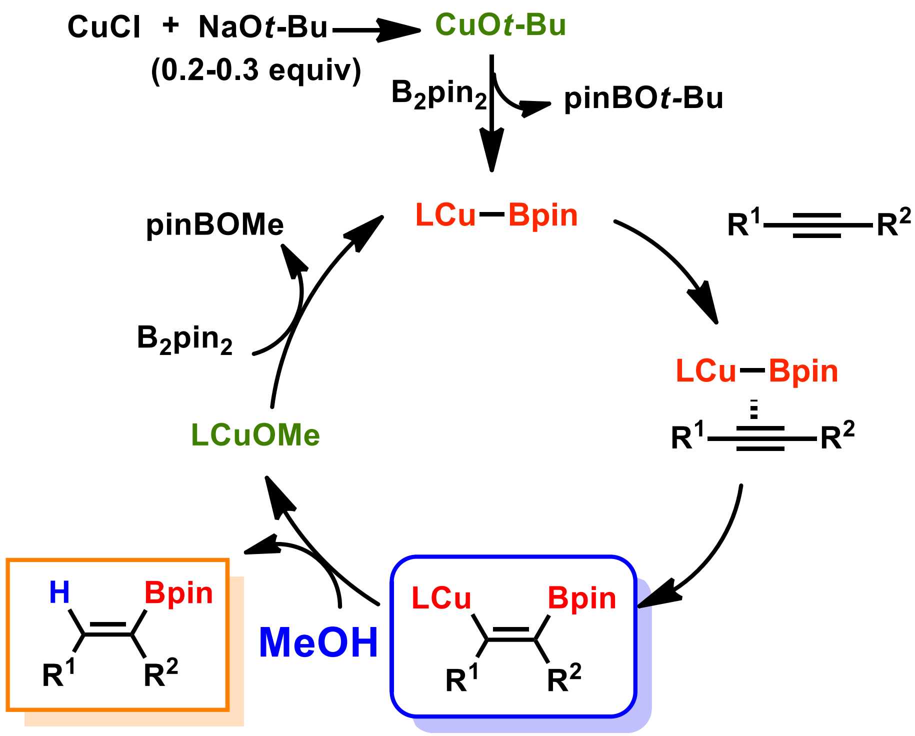
Alkyne Hydroboration



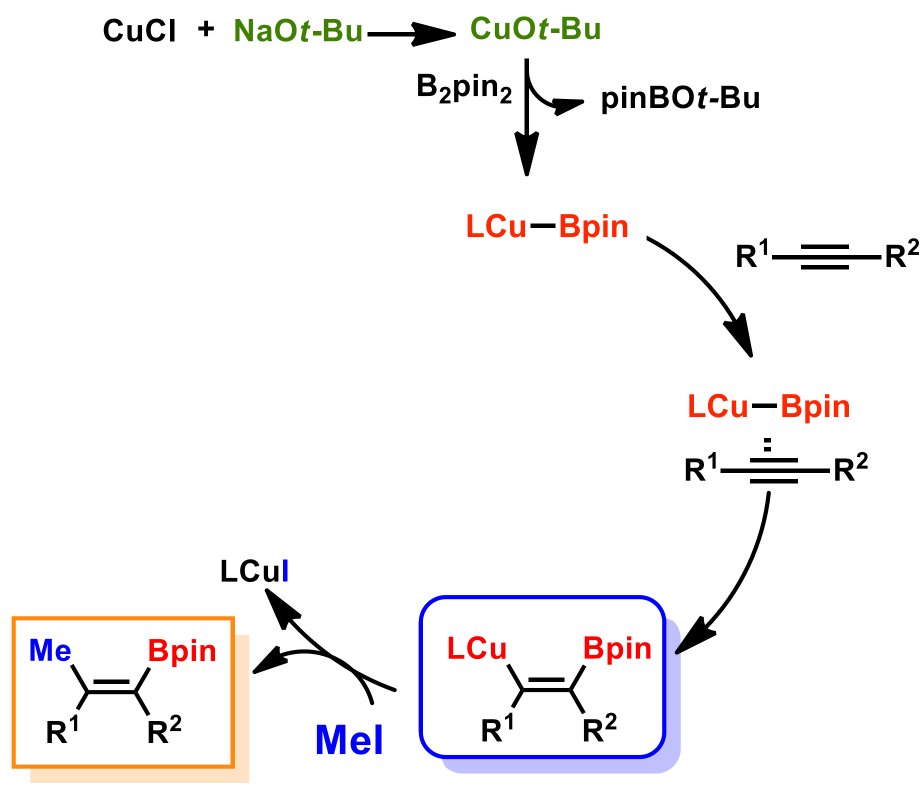
Hoveyda *et al* *J. Am. Chem. Soc.* **2011**, *133*, 7859
Yun *et al* *Chem. Comm*. **2011**, *47*, 2943
Sawamura *et al* *Angew. Chem. Int. Ed.* **2011**, *50*, 2778

Copper-Catalyzed Hydro- and Carboboration of Alkynes

Alkyne Hydroboration



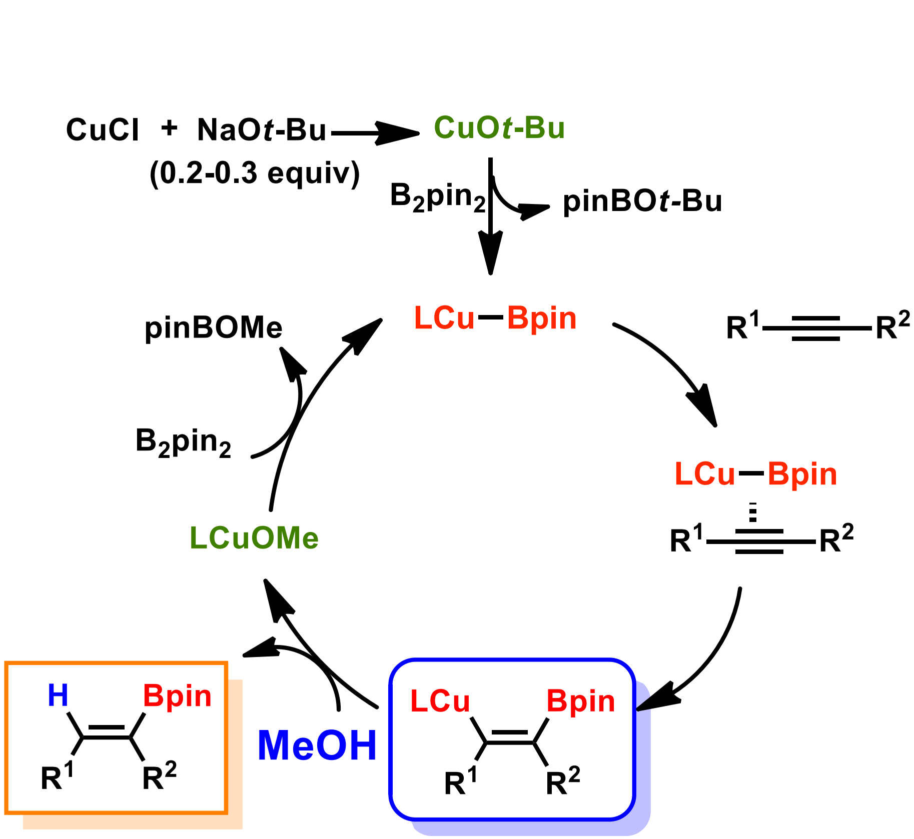
Alkyne Carboboration



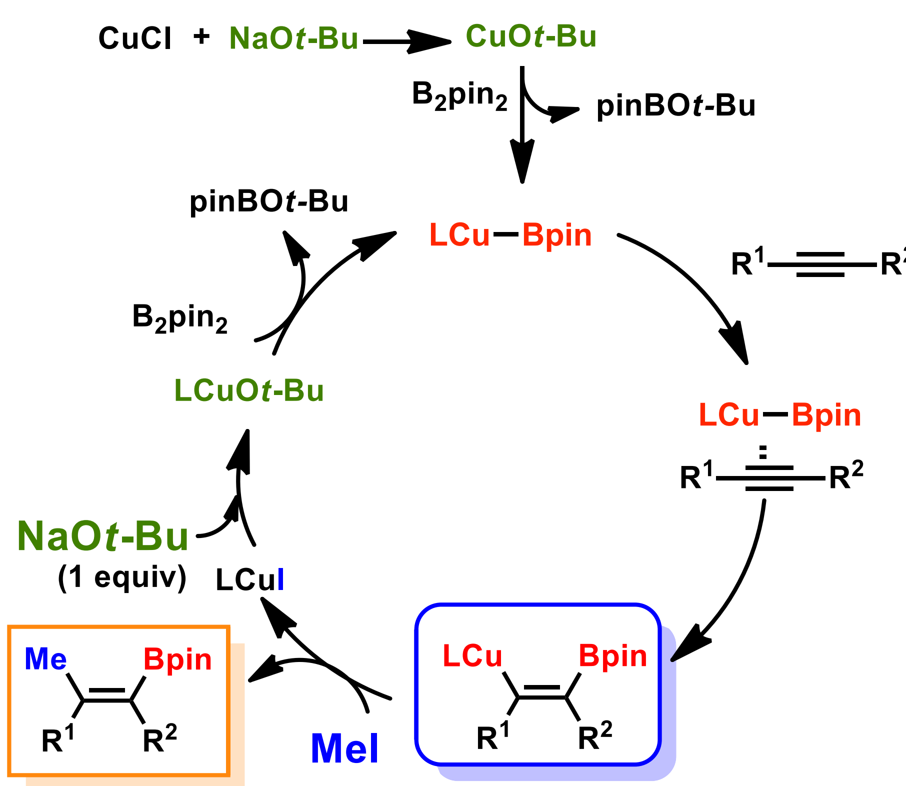
Hoveyda *et al J. Am. Chem. Soc.* **2011**, *133*, 7859
Yun *et al Chem. Comm.* **2011**, *47*, 2943
Sawamura *et al Angew. Chem. Int. Ed.* **2011**, *50*, 2778

Copper-Catalyzed Hydro- and Carboboration of Alkynes

Alkyne Hydroboration

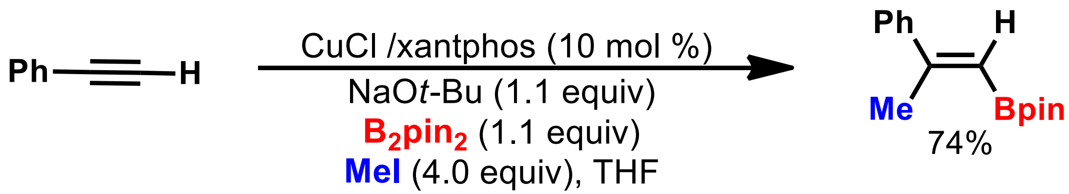


Alkyne Carboboration



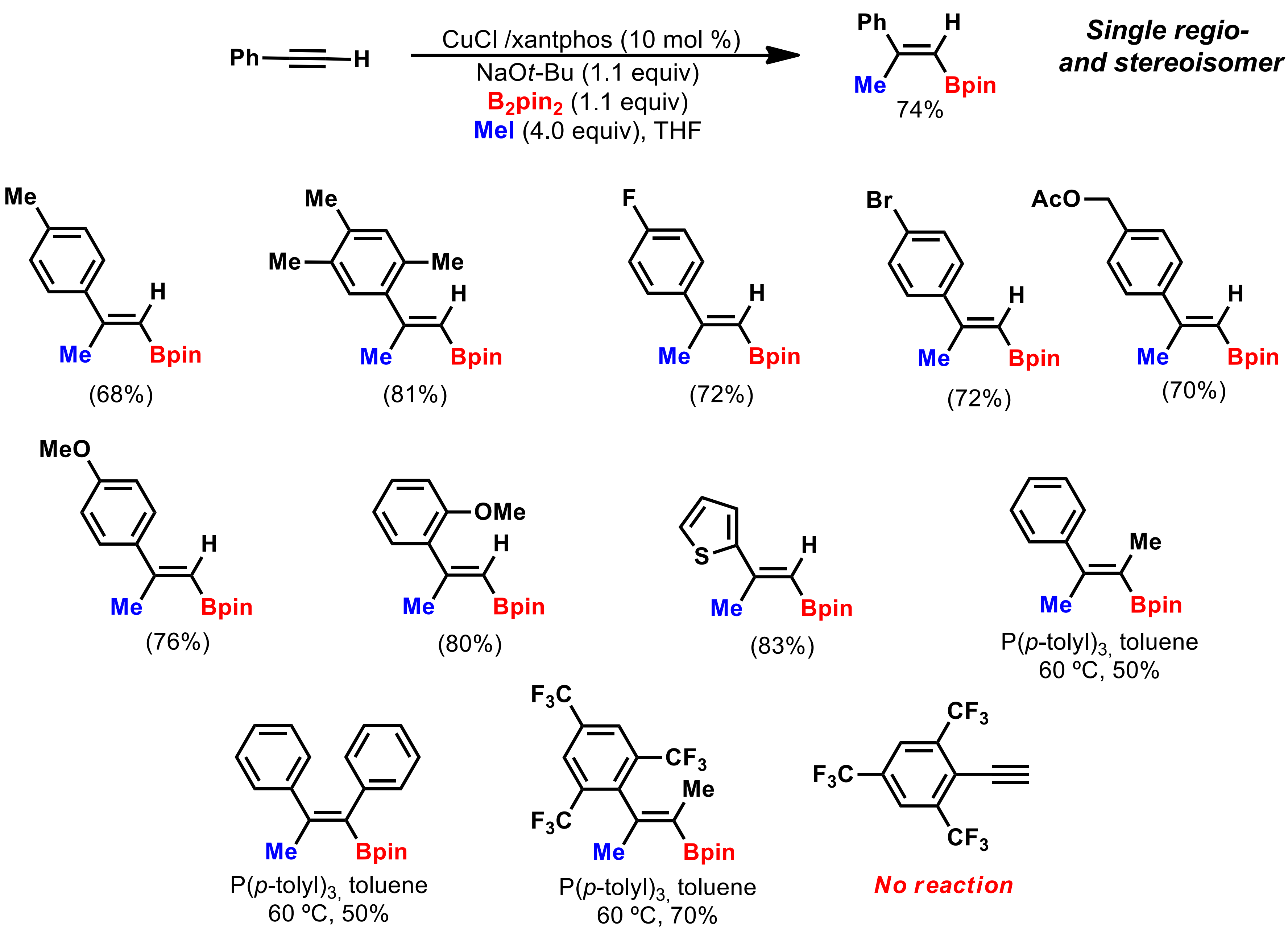
Hoveyda *et al J. Am. Chem. Soc.* **2011**, *133*, 7859
Yun *et al Chem. Comm.* **2011**, *47*, 2943
Sawamura *et al Angew. Chem. Int. Ed.* **2011**, *50*, 2778

Copper-Catalyzed Carboboration of Alkynes

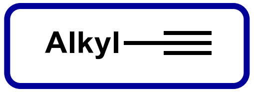


Single regio- and stereoisomer

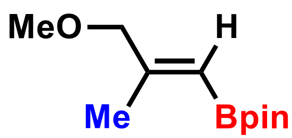
Copper-Catalyzed Carboboration of Alkynes



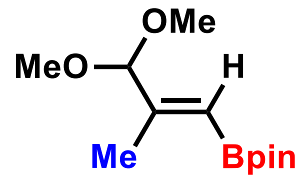
Copper-Catalyzed Carboboration of Alkynes



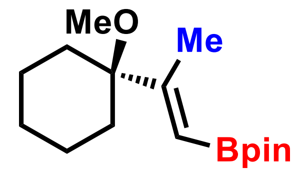
No reaction



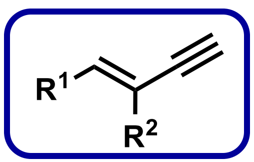
(59%)

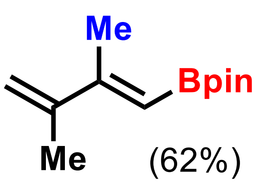


(56%)

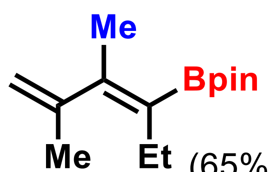


(57%)

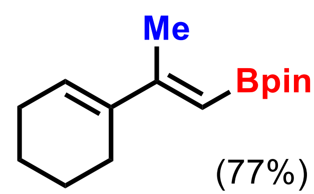




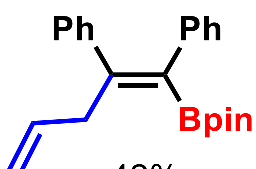
(62%)



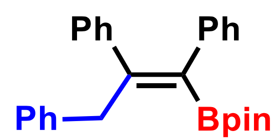
(65%)



(77%)



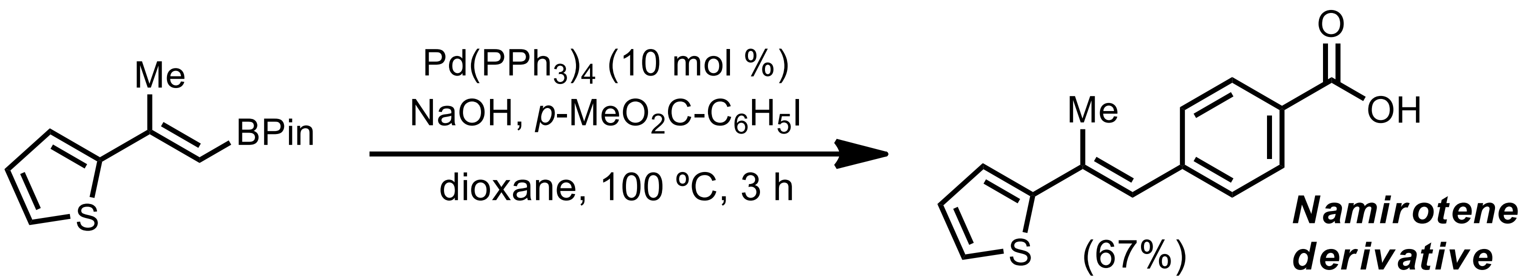
42%

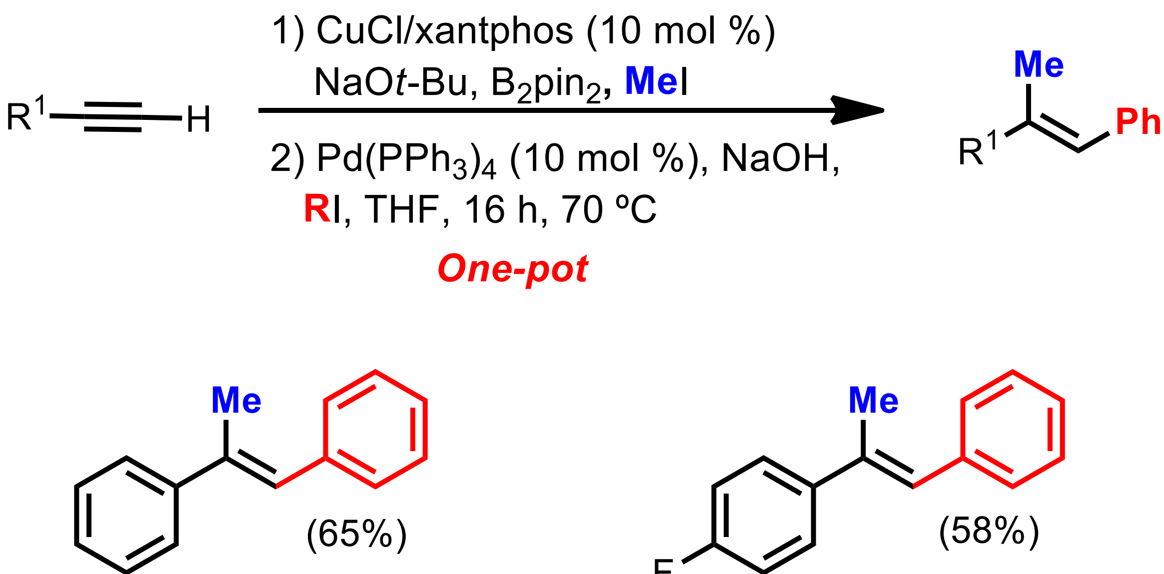


60%

J. Am. Chem. Soc. **2012**, *134*, 15165

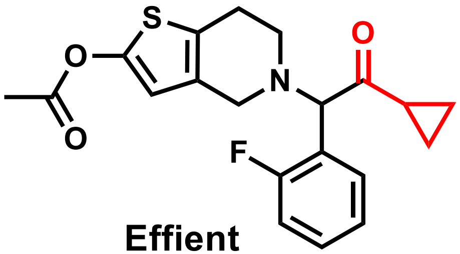
Synthesis of Trisubstituted Alkenes



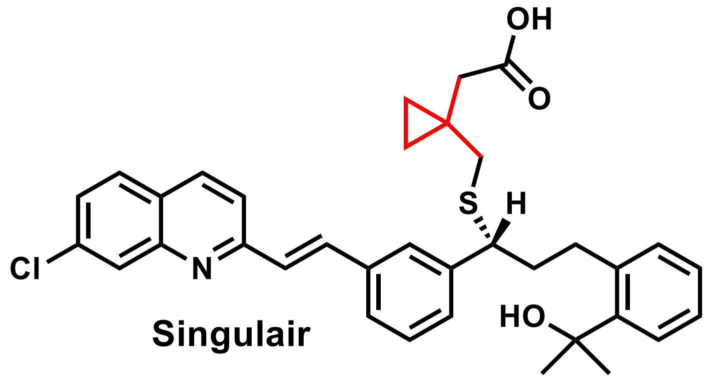


J. Am. Chem. Soc. **2012**, *134*, 15165
Yoshida et al. *Org. Lett*. **2013**, *15*, 952
Cazin et al. *ACS Catal*. **2014**, *4*, 1564
Kanai et al. *J. Am. Chem. Soc.* **2016**, *138*, 7528

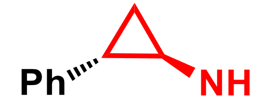
Cyclopropanes in Drugs



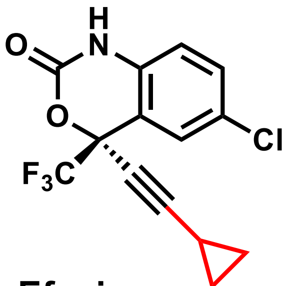
Effient



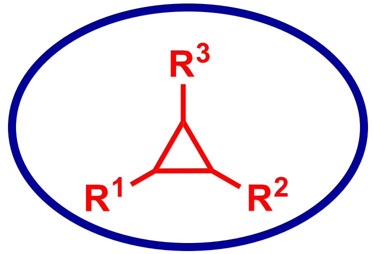
Singulair

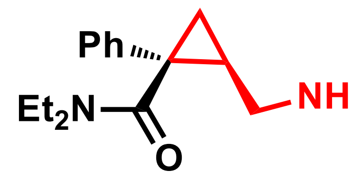


Tranylcypromine



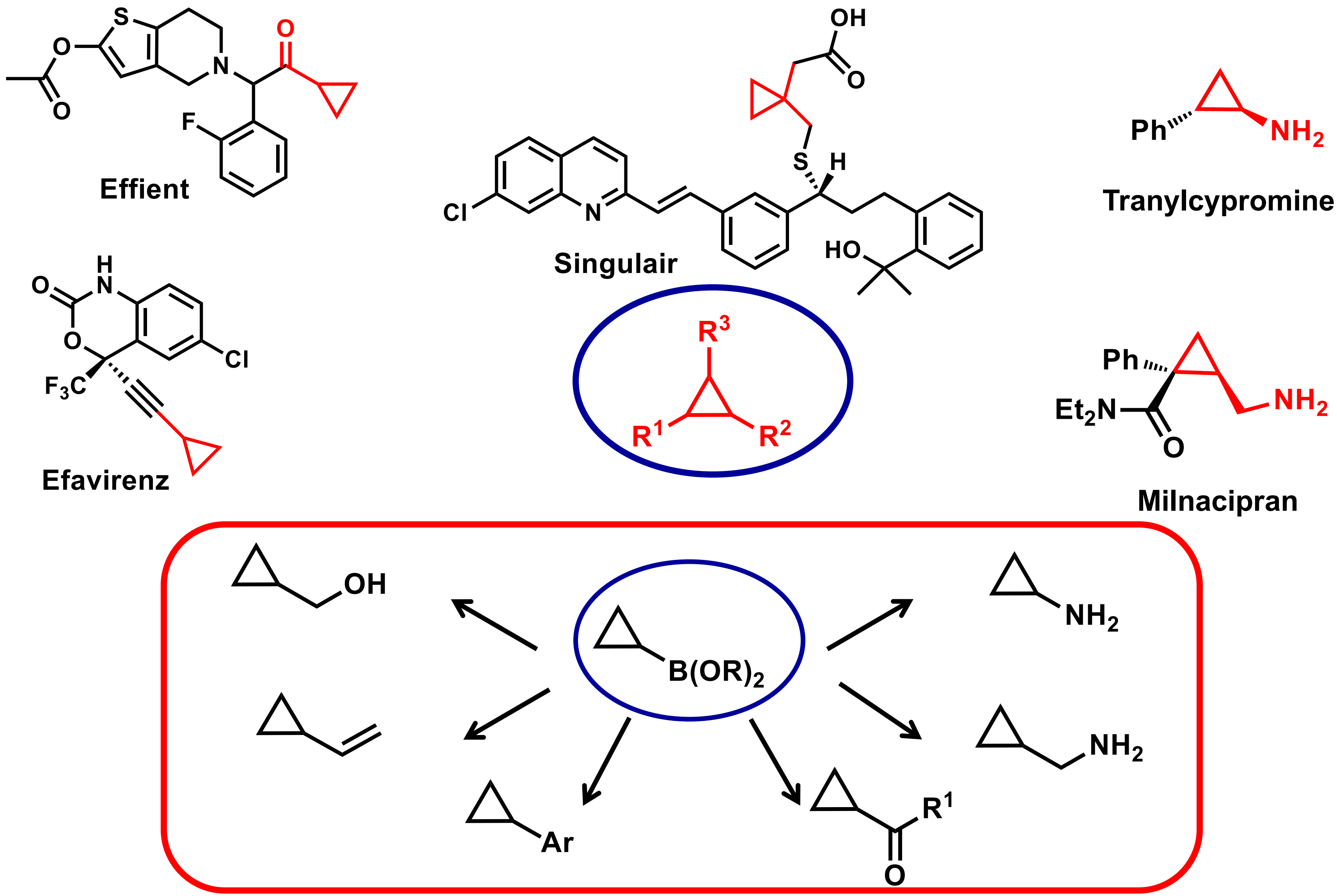
Efavirenz





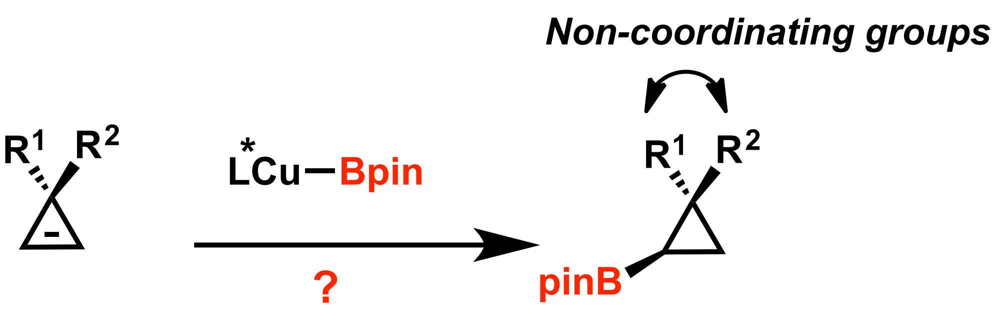
Milnacipran

Cyclopropanes in Drugs



Chiral Cyclopropylboronates: Deng et al *Angew. Chem. Int. Ed.* **1998**, *37*, 2845
Gevorgyan et al, *J. Am. Chem. Soc.* **2003**, *125*, 7198;
Ito et al, *J. Am. Chem. Soc.* **2010**, *132*, 11440

Copper-Catalyzed Desymmetrization

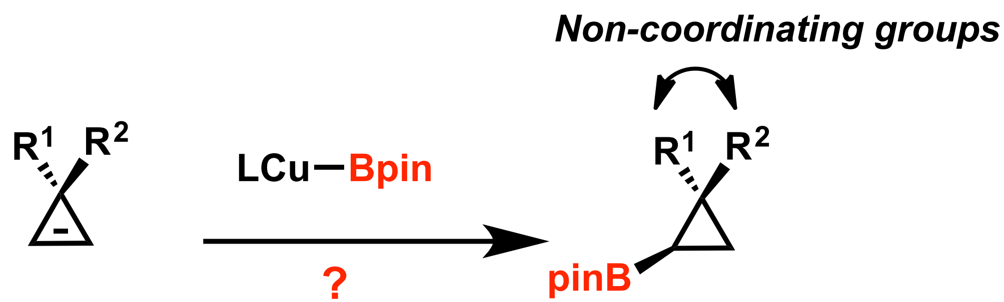


Diastereoselectivity?

Enantioselectivity?

(a) Liu, X.; Fox, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 5600. (b) Simaan, S.; Masarwa, A.; Bertus, P.; Marek, I. *Angew. Chem. Int. Ed.* **2006**, *45*, 3963. (c) Yang, Z.; Xie, X.; Fox, J. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 3960. (d) Masarwa, A.; Stanger, A.; Marek, I. *Angew. Chem, Int. Ed*. **2007**, *46*, 8039. (e) Tarwade, V.; Liu, X.; Yan, N.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 5382. (f) Simaan, S.; Masarwa, A.; Zahor, E.; Stanger, A.; Bertus, P.; Marek, I. *Chem. Eur. J.* **2009**, *15*, 8449.

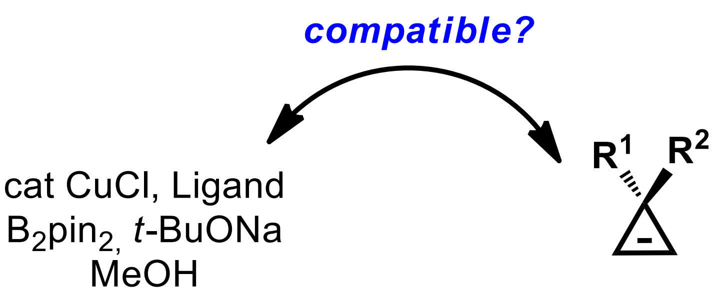
Copper-Catalyzed Desymmetrization

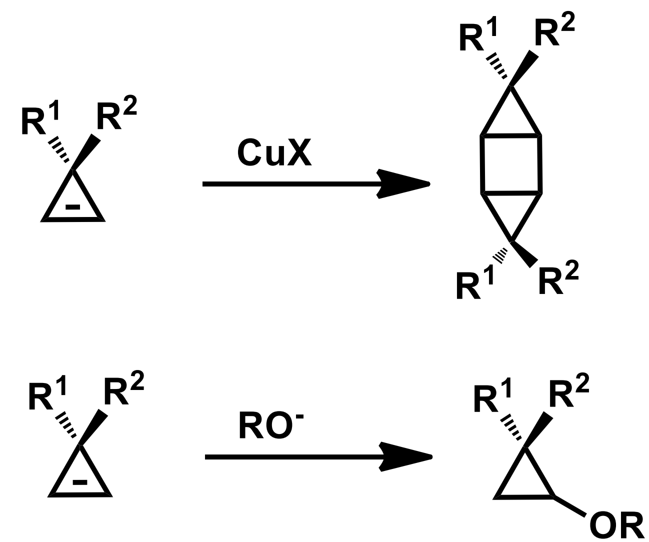


Diastereoselectivity?

Enantioselectivity?

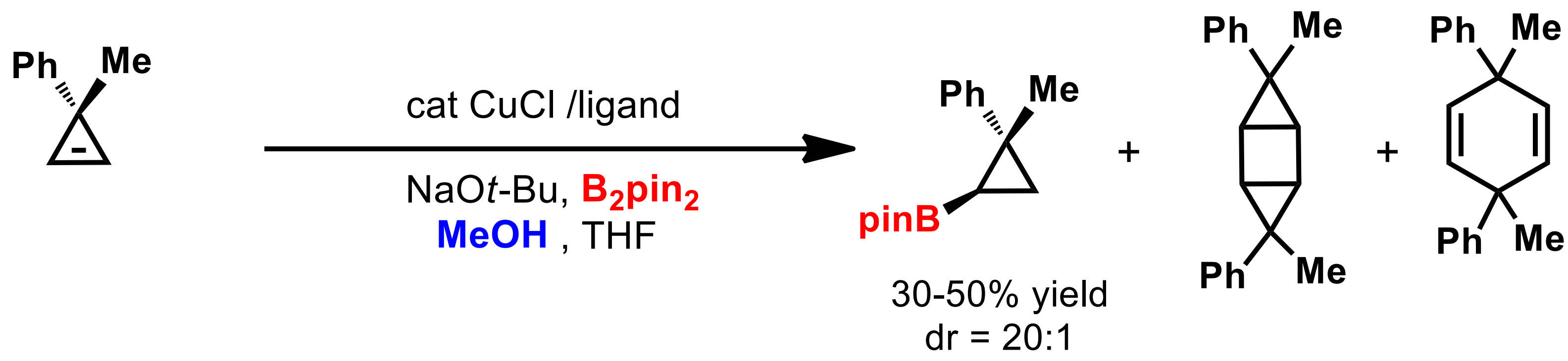
Challenges:



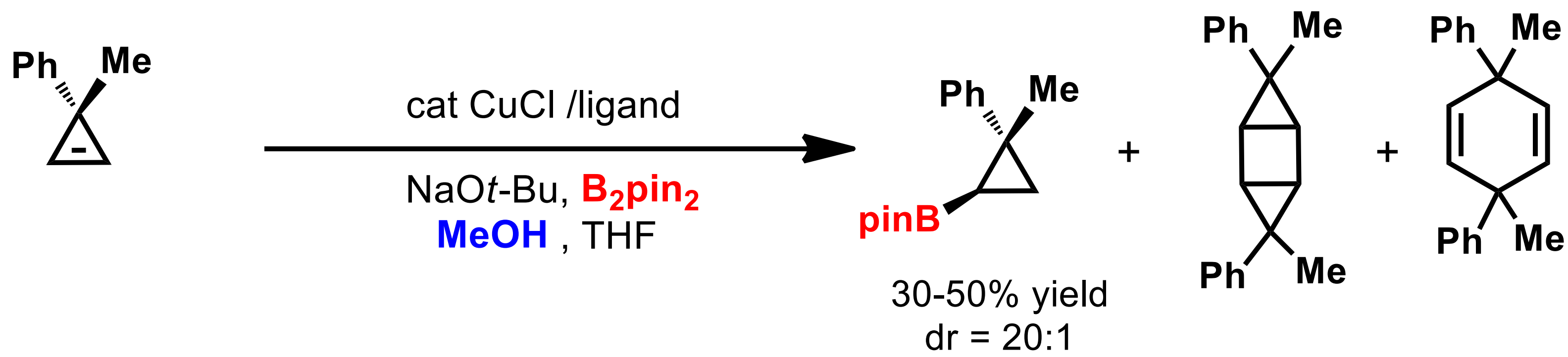


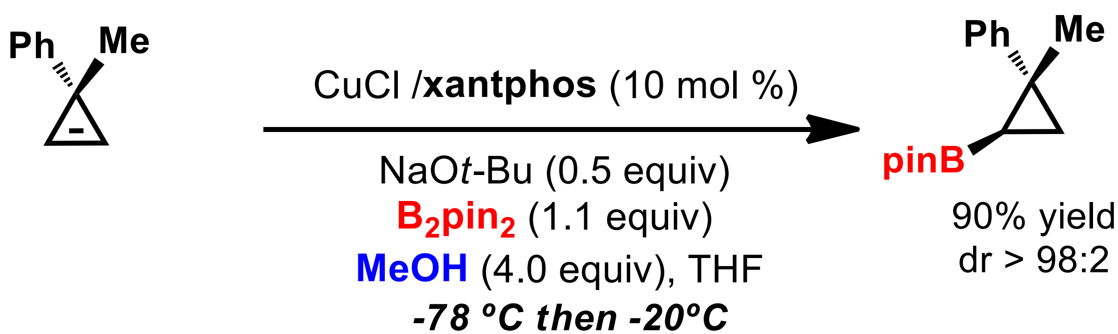
(a) Liu, X.; Fox, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 5600. (b) Simaan, S.; Masarwa, A.; Bertus, P.; Marek, I. *Angew. Chem. Int. Ed.* **2006**, *45*, 3963. (c) Yang, Z.; Xie, X.; Fox, J. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 3960. (d) Masarwa, A.; Stanger, A.; Marek, I. *Angew. Chem, Int. Ed*. **2007**, *46*, 8039. (e) Tarwade, V.; Liu, X.; Yan, N.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 5382. (f) Simaan, S.; Masarwa, A.; Zahor, E.; Stanger, A.; Bertus, P.; Marek, I. *Chem. Eur. J.* **2009**, *15*, 8449.

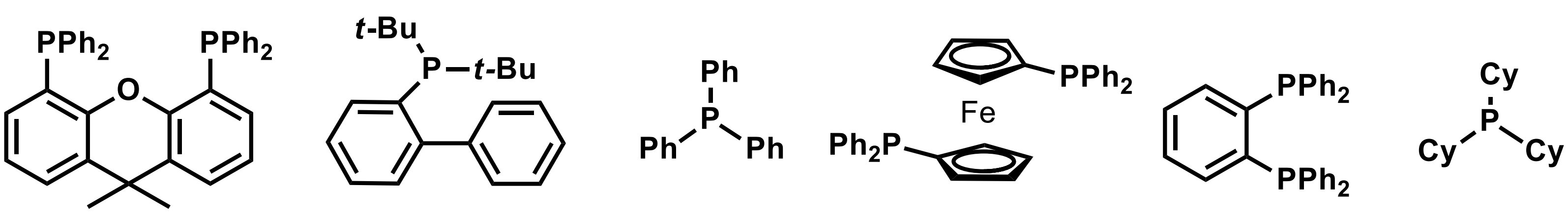
First Problem: Dimer Formation



First Problem: Dimer Formation

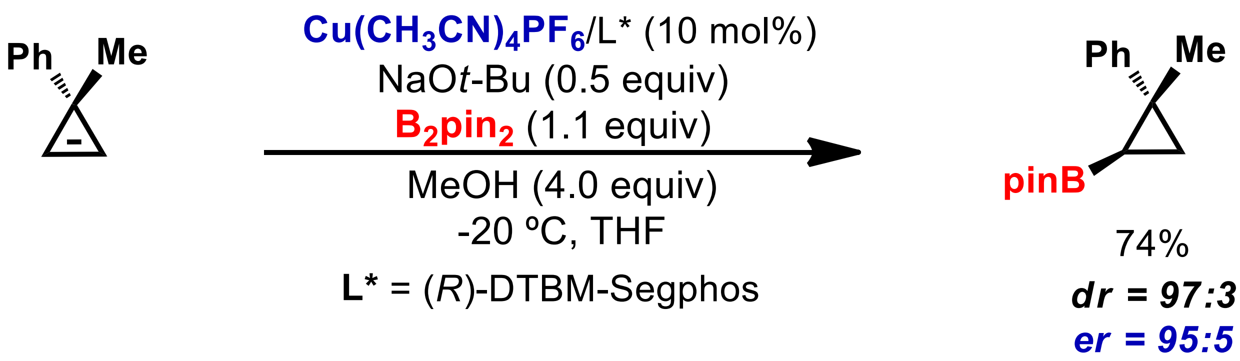


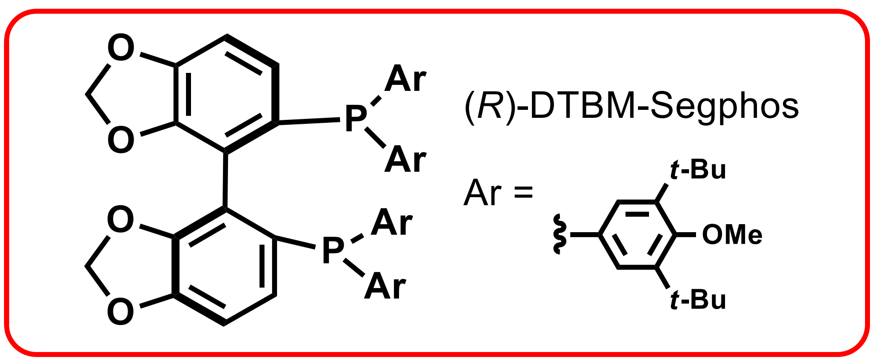




dr 98:2	**dr = 86:14**	**dr = 85:15**	**dr 98:2**	**dr = 75:25**	**dr = 82:18**
90%	41%	43%	14%	29%	18%

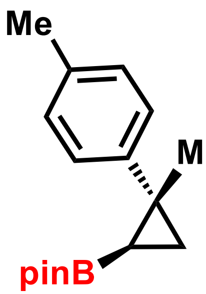
Screening Chiral Ligands



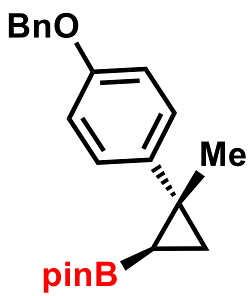


J. Am. Chem. Soc. **2014**, *136*, 15833

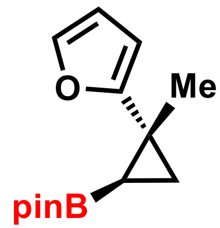
Scope of the Reaction



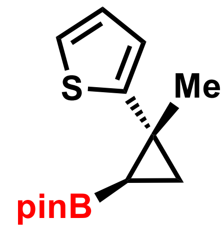
68%
dr ≥ 98:2, er = 95:5



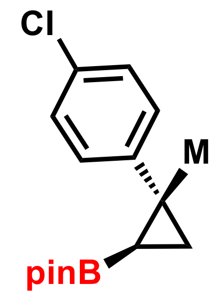
61%
dr = 97:3, er = 96:4



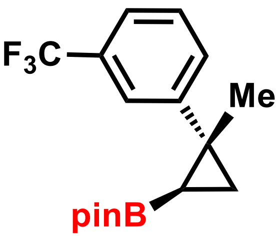
62%
dr = 97:3, er = 95:5



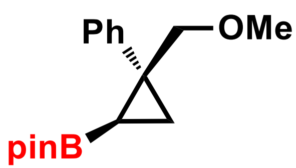
53%
dr = 98:2, er = 96:4



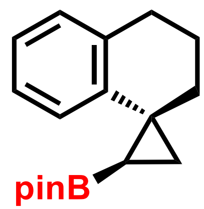
70%
dr = 95:5, er = 93:7



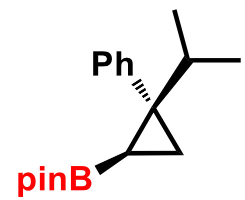
43%
dr ≥ 98:2, er = 92:8



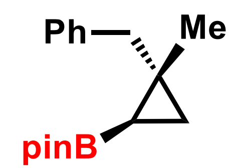
52%
dr ≥ 98:2, er = 97:3



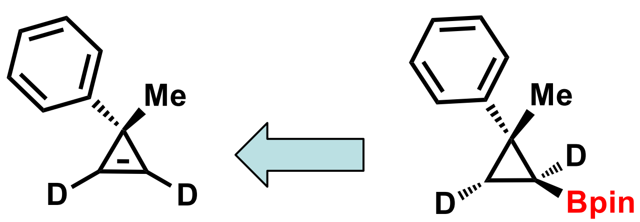
60%
dr ≥ 98:2, er = 92:8



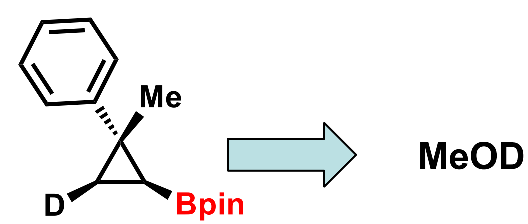
54%
dr = 81:19, er = 96:4



50%
dr = 80:20, er = 98:2

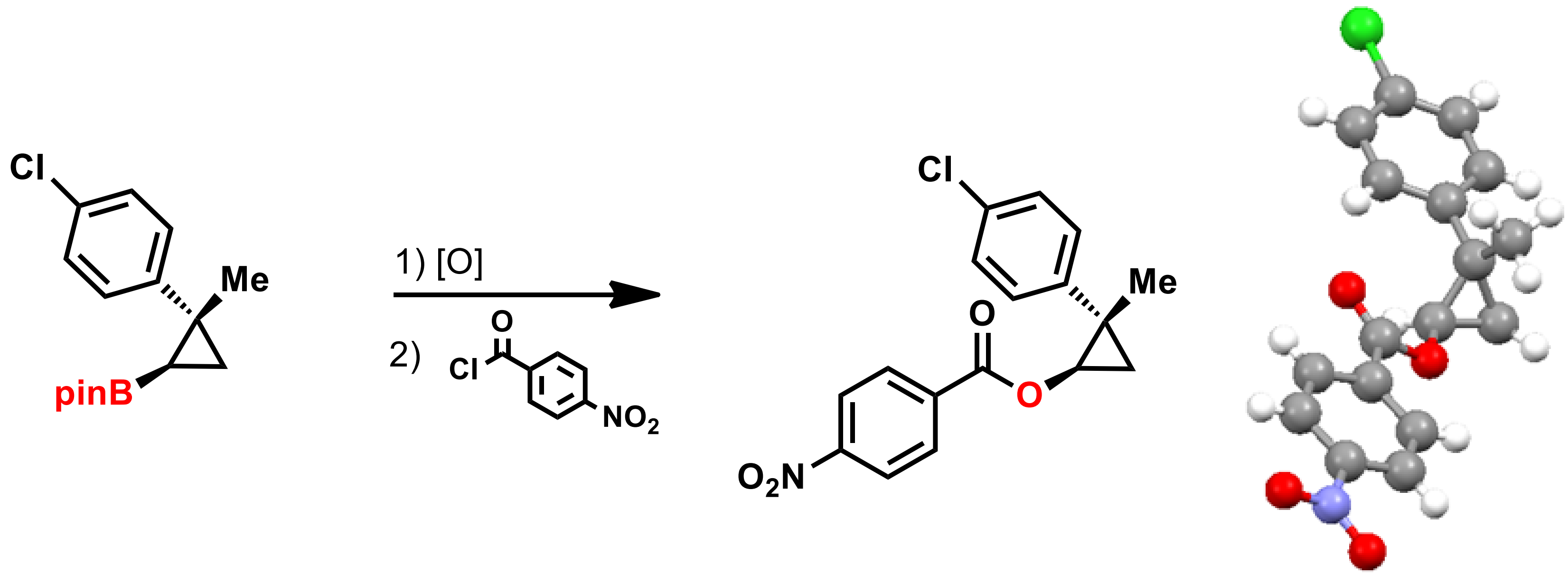


73%
dr = 98:2, er = 91:9



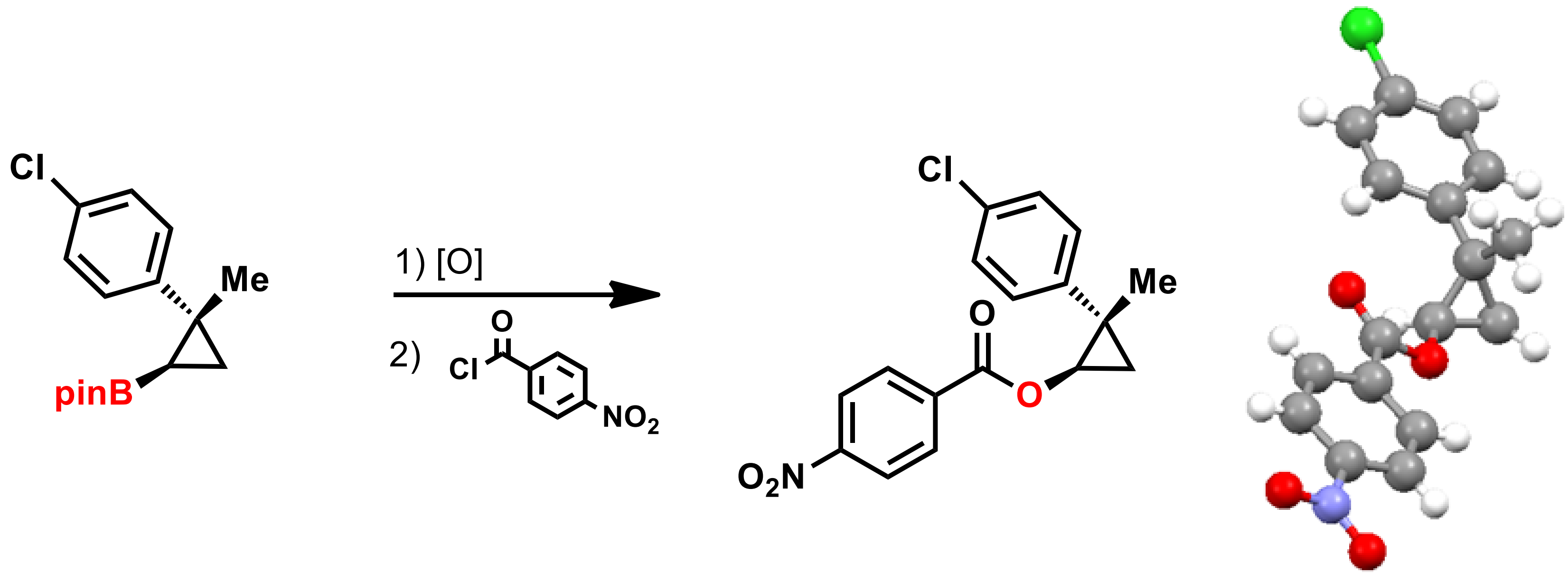
56%
dr = 98:2, er = 93:7

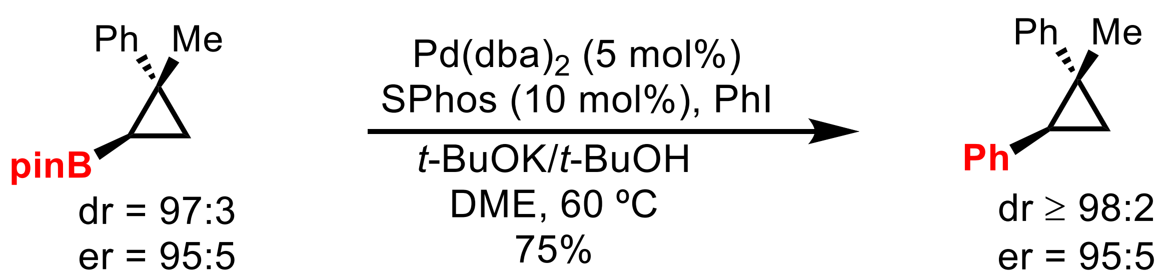
Functionalization of the C-B bond



J. Am. Chem. Soc. **2014**, *136*, 15833

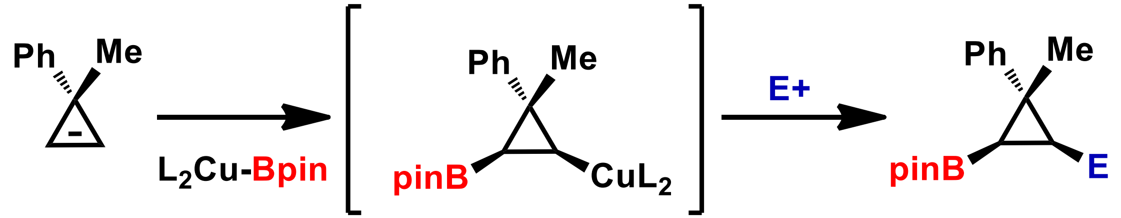
Functionalization of the C-B bond

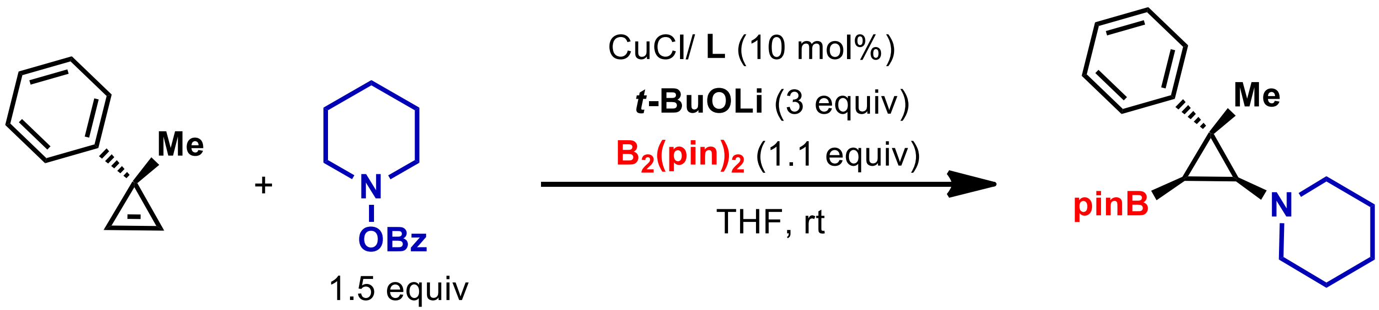


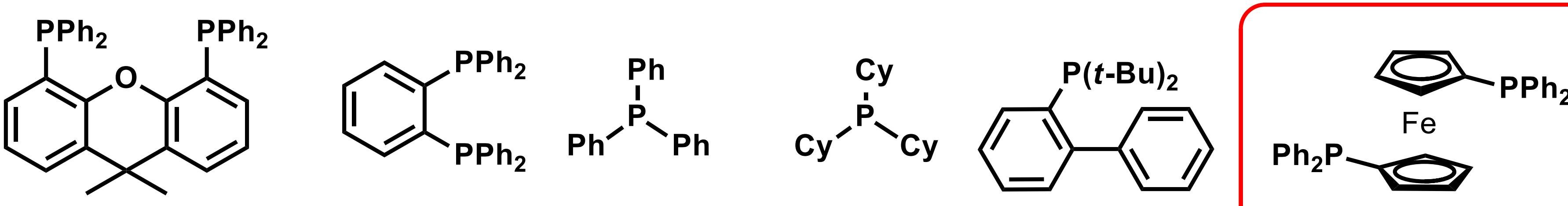


J. Am. Chem. Soc. **2014**, *136*, 15833

Cyclopropyl Amino-Boronic Esters



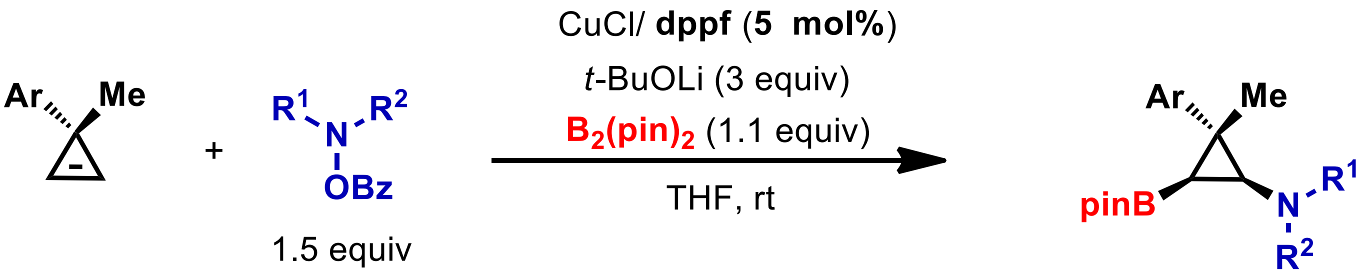


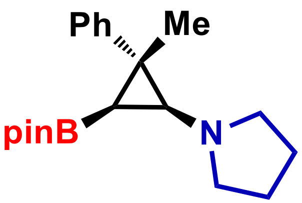


xantphos **dr = 88:12** | **dppbz** **dr = 52:48** | **dr = 76:24** | **dr = 76:24** | **Johnphos** **dr = 64:36** | **dppf** **dr = 97:3**

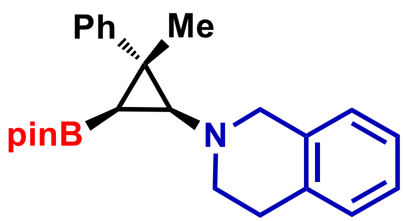
J. Am. Chem. Soc. **2014**, *136*, 15833

Cyclopropyl Amino-Boronic Esters

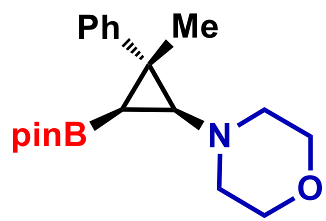




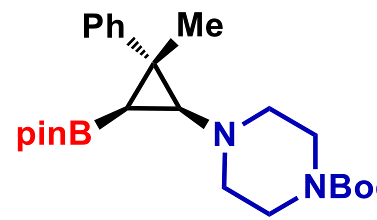
65%, dr 98:2



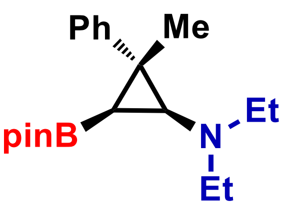
46%, dr = 97:3



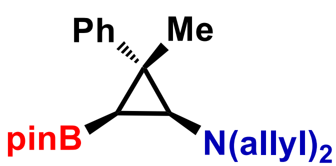
58%, dr = 95:5



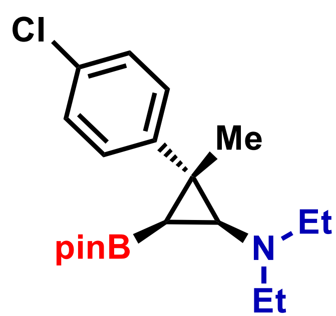
53%, dr 98:2



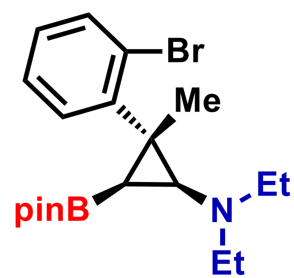
70%, dr = 97:3



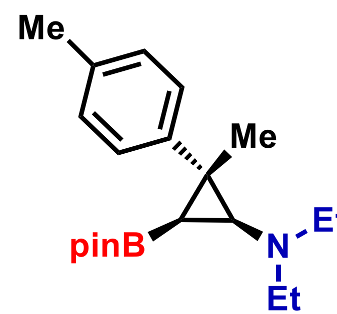
77%, dr = 95:5



65%, dr 98:2



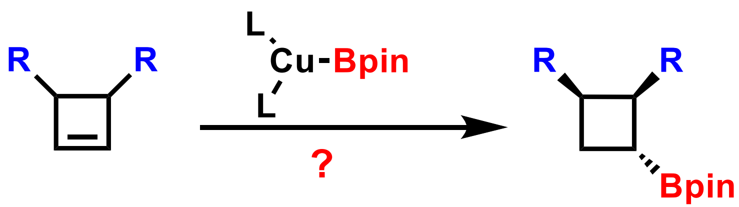
61%, dr 98:2



69%, dr = 97:3

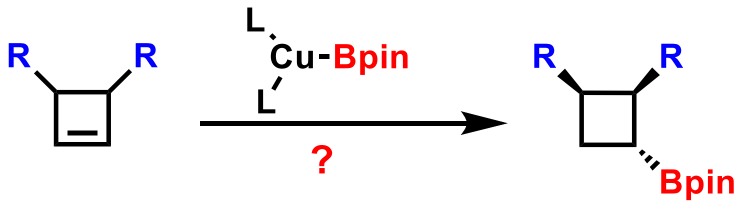
J. Am. Chem. Soc. **2014**, *136*, 15833

Cyclobutyl Boronates



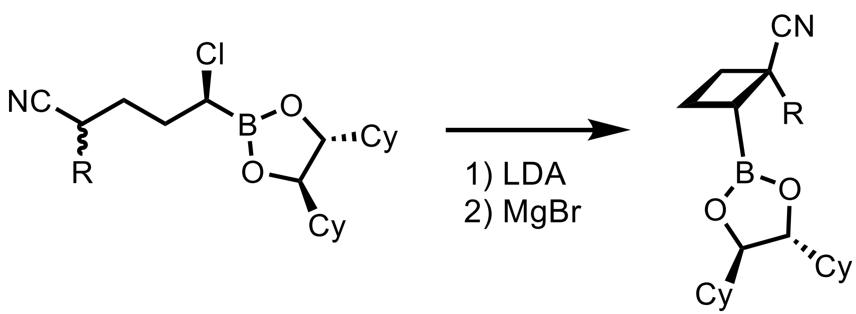
- Novel desymmetrization
- First catalytic approach
- Synthetic handle for derivatization

Cyclobutyl Boronates

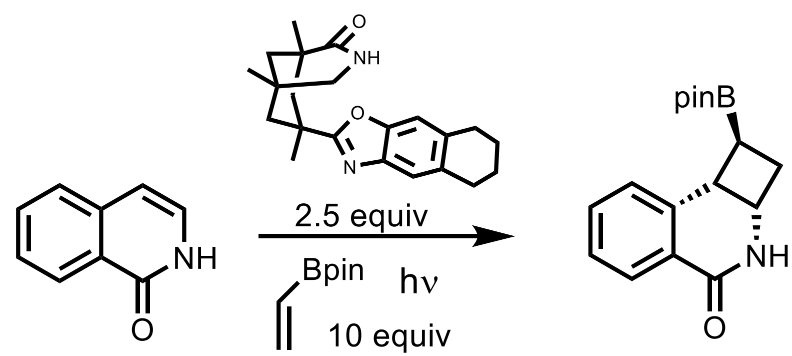


- **Novel desymmetrization**
- **First catalytic approach**
- **Synthetic handle for derivatization**

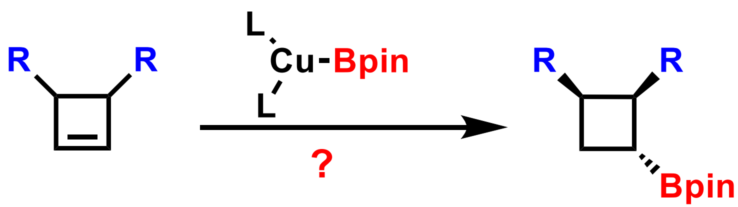
Matteson *et a*l, *Org. Lett*. **1999**, *1*, 379



Bach, T. *et al J. Am. Chem. Soc*. **2013**,*135*, 14948

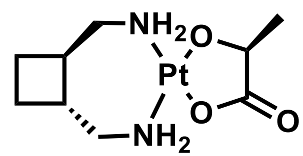


Cyclobutyl Boronates

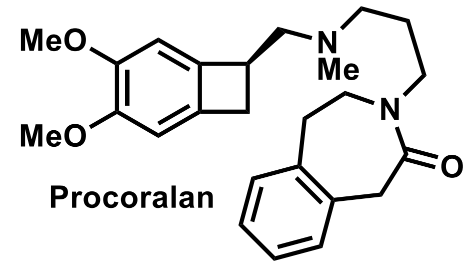


- Novel desymmetrization
- First catalytic approach
- Synthetic handle for derivatization

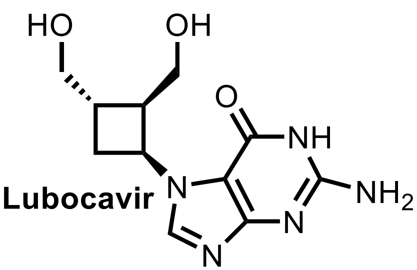
Template for Drug Discovery



Lobaplatin



Procoralan

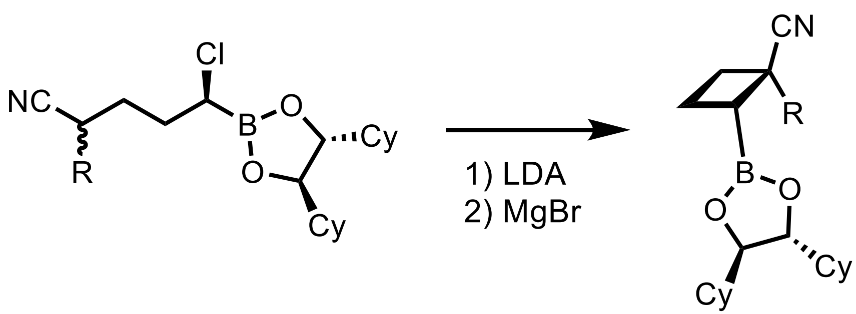


Lubocavir

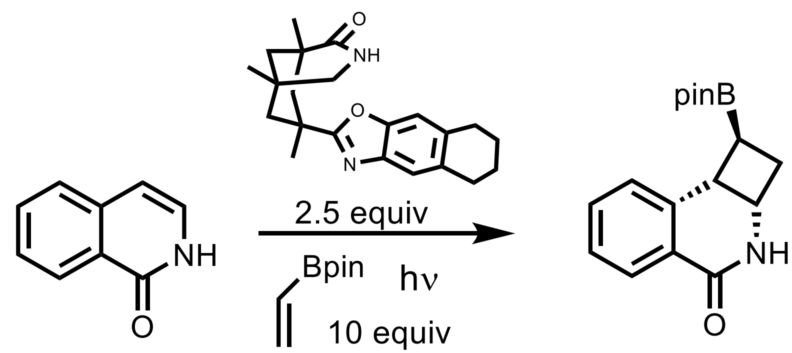
rigid sp3 scaffold

> three dimensionality

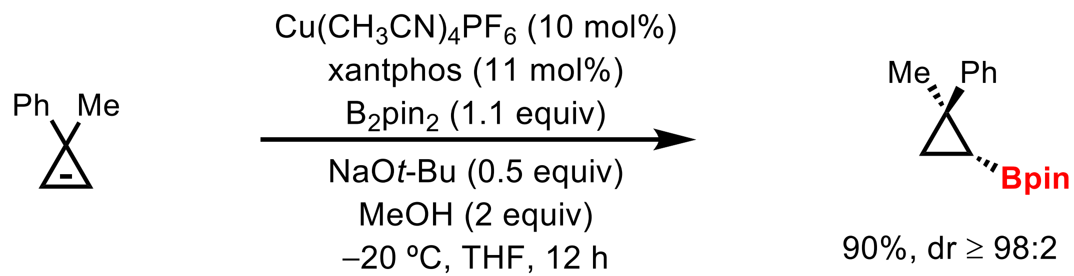
Matteson *et a*l, *Org. Lett*. **1999**, *1*, 379

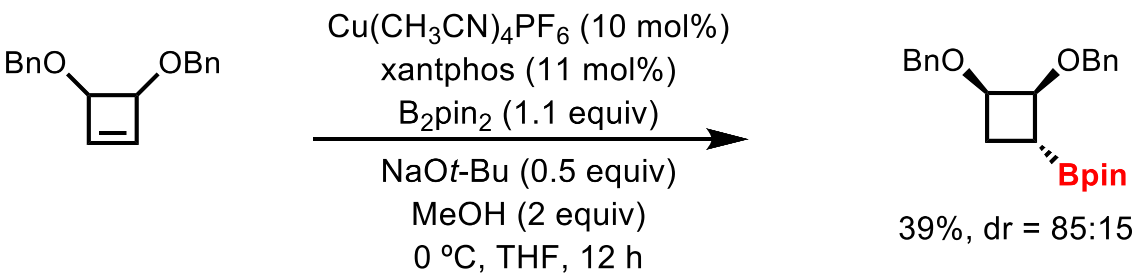


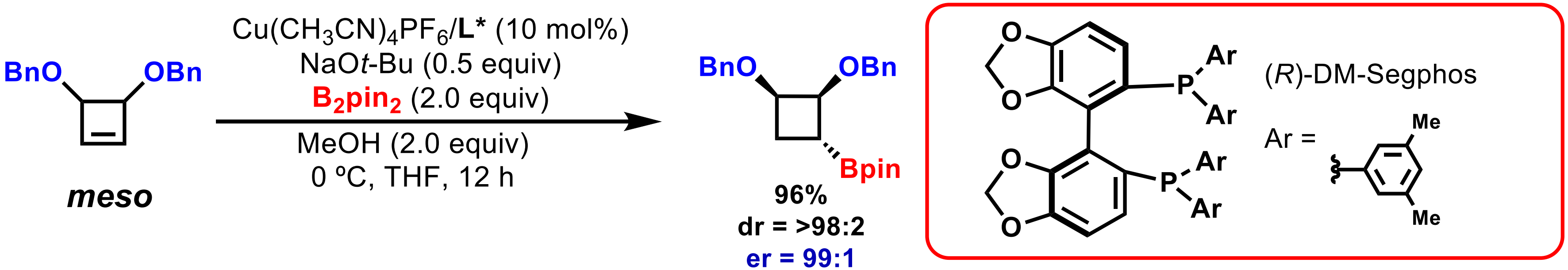
Bach, T. *et al J. Am. Chem. Soc.* **2013**,*135*, 14948



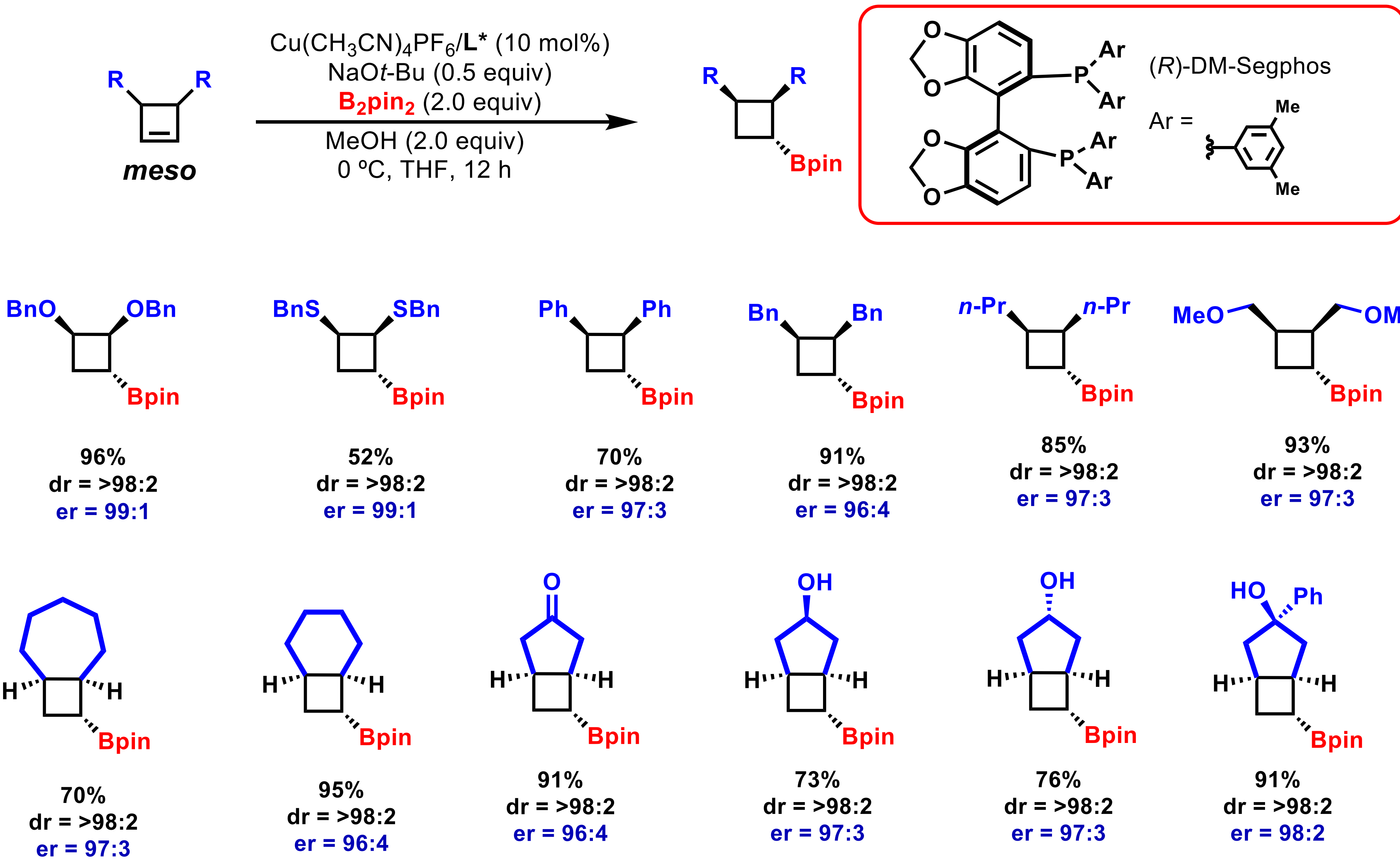
Cyclobutyl Boronates





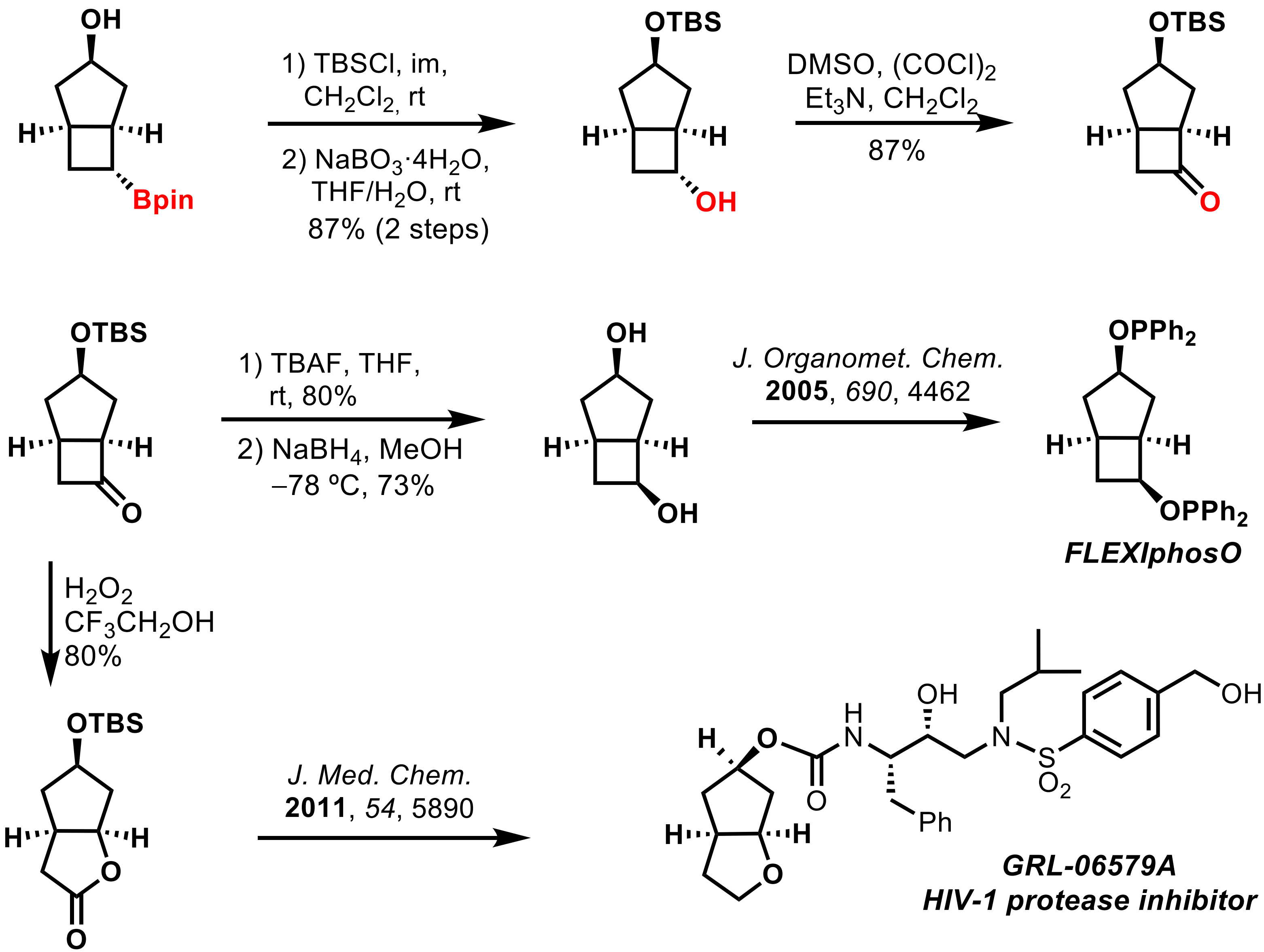


Cyclobutyl Boronates



Angew. Chem. Int. Ed. **2016,** *55*, 6969

Cyclobutyl Boronates: Versatile Intermediates



Angew. Chem. Int. Ed. **2016,** *55*, 6969

BORON INNOVATION