Catalytic Enantioselective Copper-Boryl Additions to Alkenes

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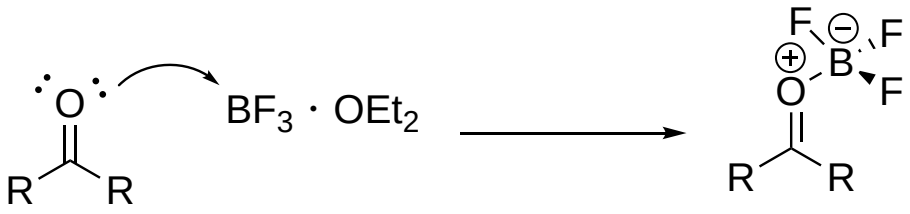
Denmark Group Meeting May 19th, 2020

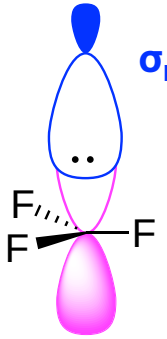
Outline

I. Introduction
II. Mechanism and Stereochemistry
III. Scope and Applications

Trivalent boron as a nucleophile

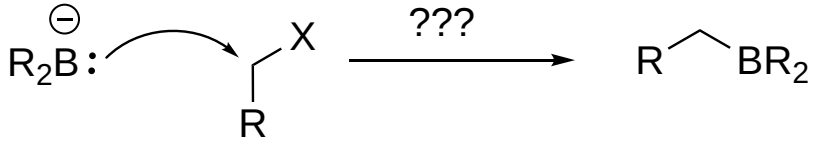
Well known examples as a Lewis acid, i.e. Mukaiyama aldol:

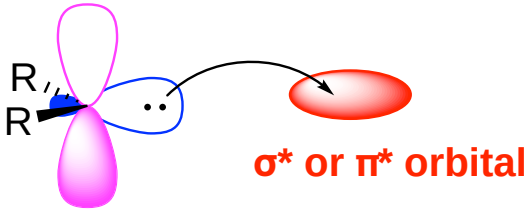




Strong σ-withdrawing ligands, minimal stabilization of empty boron π orbital

Boron as a nucleophile:

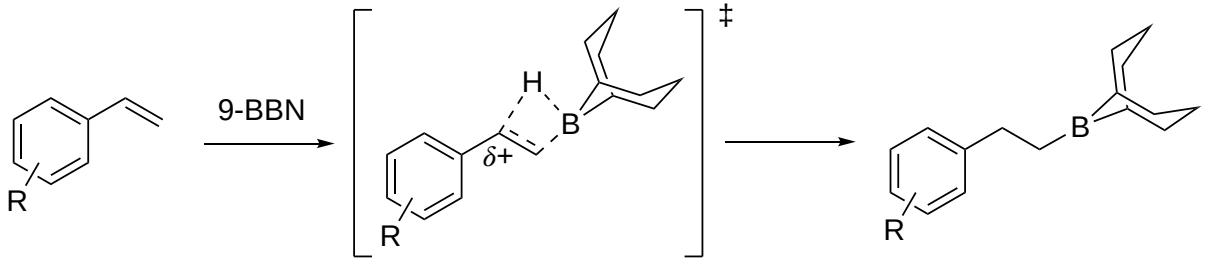




Requirements for ligands:

- π-donation to stabilize empty boron p orbital
- σ-donation, i.e. more electropositive than boron
- Non-hydritic

Boron behaves as an electrophile in hydroboration reactions:



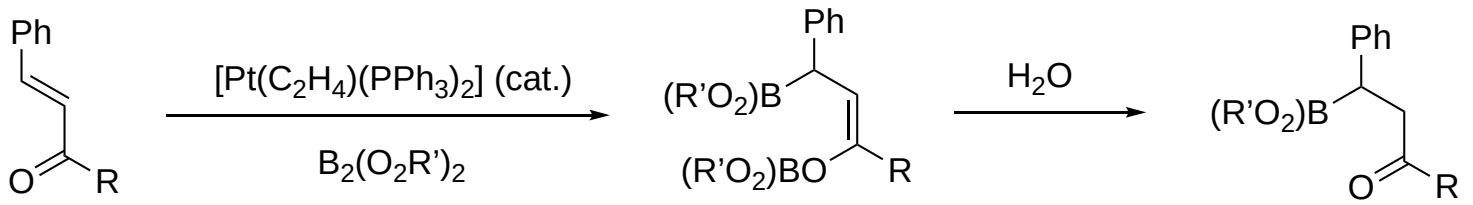
ρ = -0.35, consistent with buildup of positive charge on benzylic carbon

substituent	k_X/k_H ± std dev	substituent	k_X/k_H ± std dev
p-CH_3O	2.95 ± 0.22	*p*-Cl	0.69 ± 0.01
p-CH_3	1.51 ± 0.04	*m*-Cl	0.63 ± 0.02
none	1.00	*m*-NO_2	0.60 ± 0.04
p-F	0.89 ± 0.03		

J. Org. Chem. **1980**, *45*, 5306-5308. *Chem. Soc. Rev.* **2018**, *47*, 4388-4480.

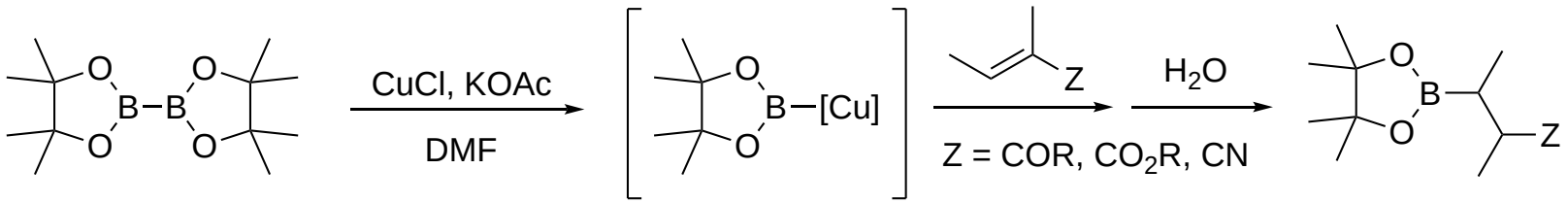
Boron(III) species as nucleophiles in protioborylation of α,β-unsaturated carbonyls

Catalytic 1,4-addition of a diborane into an α,β-unsaturated ketone (Marder, 1997):

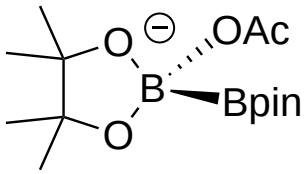


R = Me, Ph $\qquad$ O_2R' = pin, cat

First example of *in situ* boryl-copper bond formation (Miyaura, 2000):

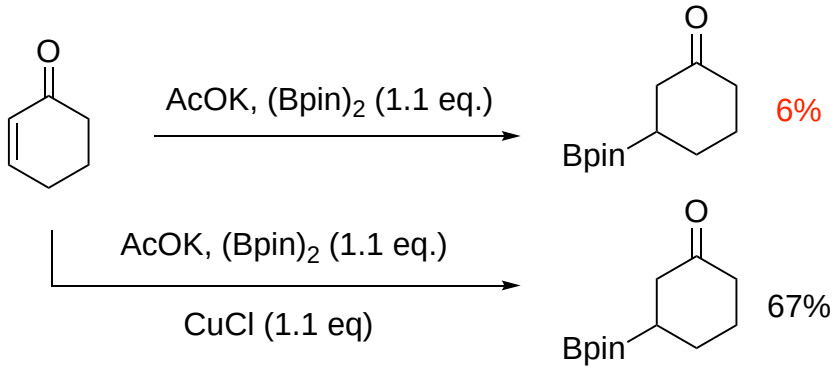


Acetate salt needed to form more nucleophilic $(Bpin)_2$ ate complex:

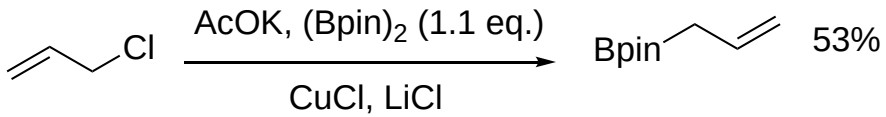


"Such complexation prior to transmetalation might be a crucial steps in essentially all ionic reactions of organoboron compounds because of their highly electrophilic but weakly nucleophilic natures."

Copper is required to facilitate conjugate addition:



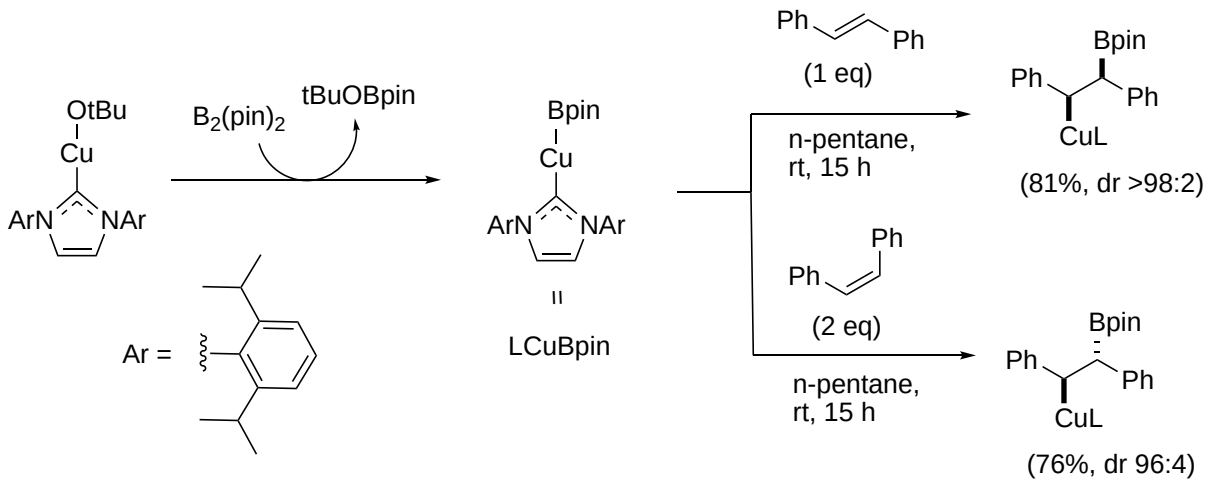
Coupling with allyl chloride is further evidence of a [Cu]-B intermediate:

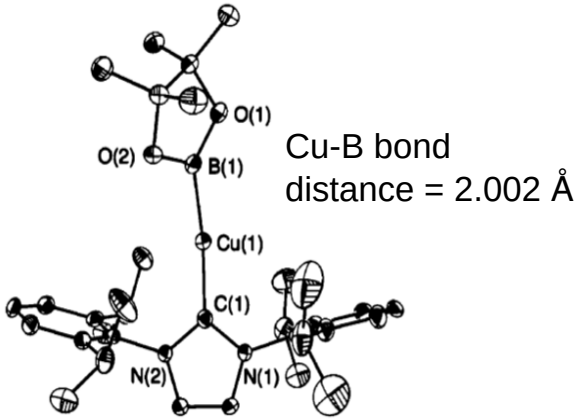


Chem. Commun. **1997,** 2051. *Chem. Lett.* **2000,** 982. *J. Organomet. Chem.* **2001,** 625, 47–53.

Addition of copper-boryl complexes across alkenes proceeds with *syn* stereospecificity

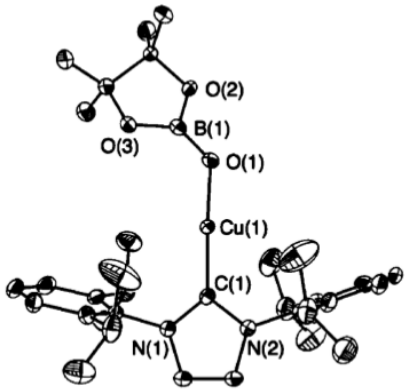
Stoichiometric formation and reactivity of a copper-boryl-NHC complex:





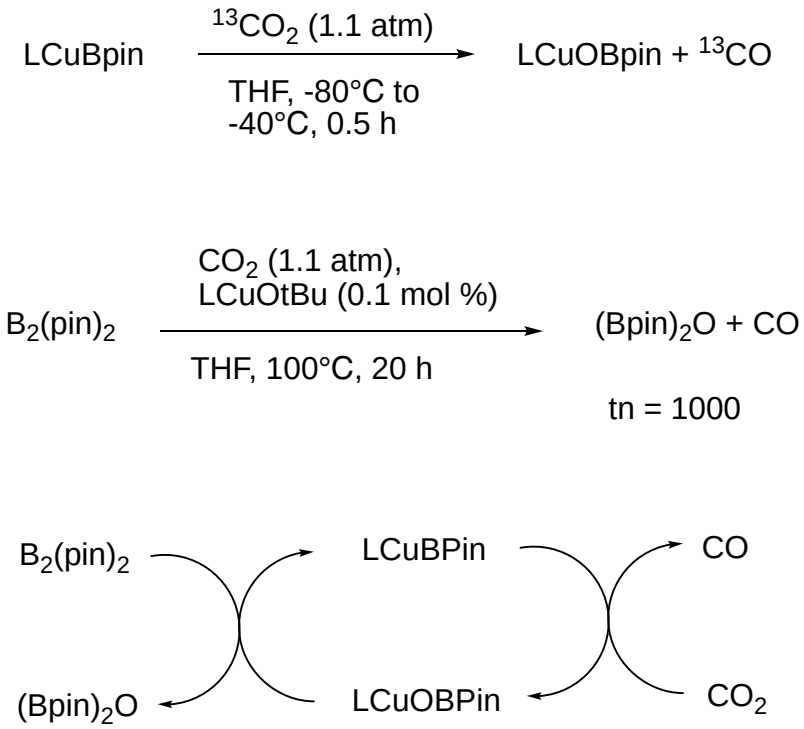
Cu-B bond distance = 2.002 Å

LCuBPin crystal structure
^{11}B NMR (C_6D_6) δ 41.7



LCuOBPin crystal structure
^{11}B NMR (C_6D_6) δ 21.8

Copper-boryl-NHC complex catalytically reduces carbon dioxide:

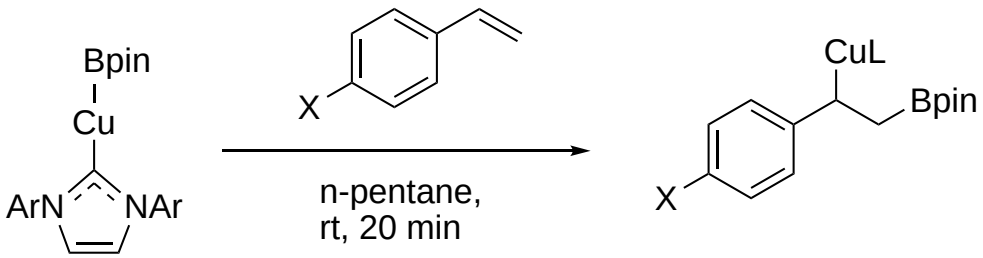


bond enthalpy of C═OC is 532 kJ/mol !

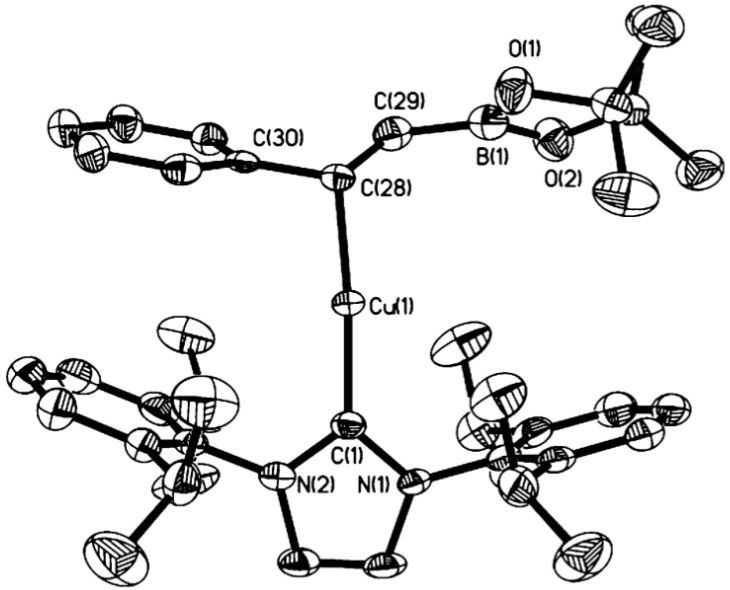
Organometallics. **2006**. 25, *10*, 2405. *J. Am. Chem. Soc.* **2005**, 127, 17196-17197.

Copper-boryl complexes provide a source of nucleophilic, trivalent boron

Hammett analysis of copper-boryl-NHC addition across styrenyl olefins:

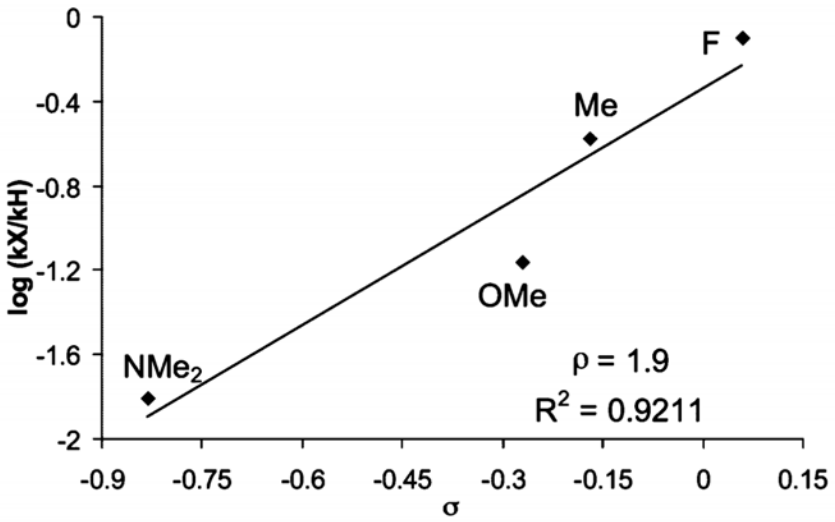


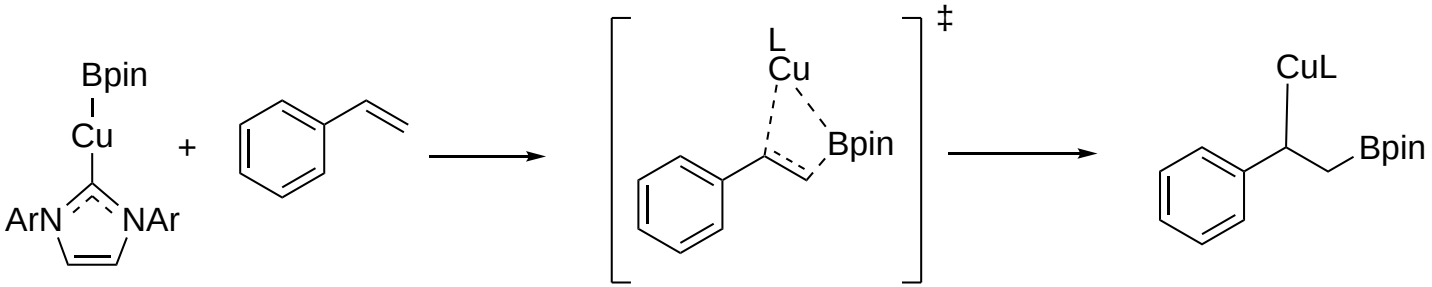
X	yield (%)
H	91
F	70
Me	88
OMe	92
NMe_2	89



Product crystal structure when X = H. Note how much longer the Cu-C bond (1.948 Å) is relative to the B-C bond (1.579 Å).

Positive ρ value indicates accumulation of negative charge on the benzylic carbon. Contrast with hydroboration, which typically have small **negative ρ** values.





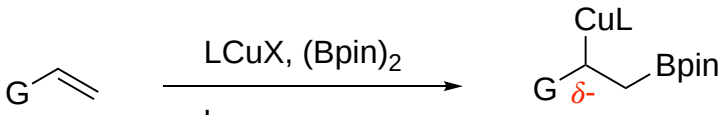
forming Cu-C bond is longer than B-C bond in TS

How does this affect regioselectivity?

Organometallics. **2006**. 25, *10*, 2405.

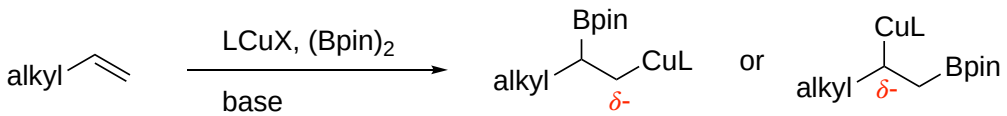
Copper-boryl addition regioselectivity depends on both steric and electronic factors

Electronic preference places copper on the carbon position that best stabilizes negative charge of cuprate:



G = aryl, boryl, silyl

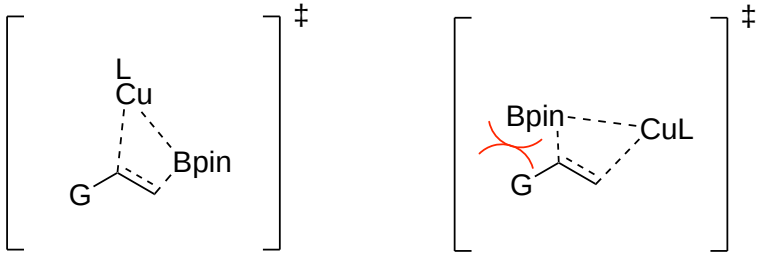
Favored sterically and electronically

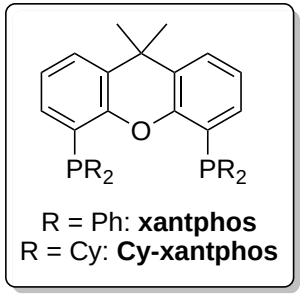


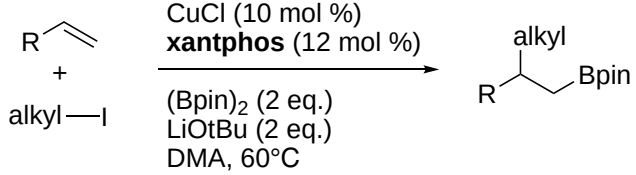
Favored electronically

Favored sterically

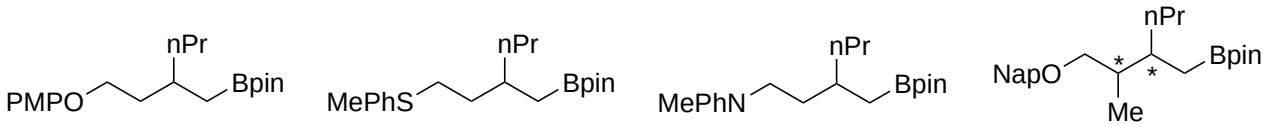
Long Cu-C bond in TS results in less significant Cu steric affect:





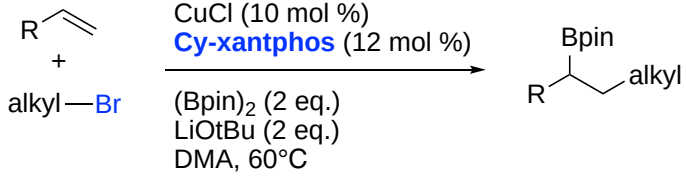


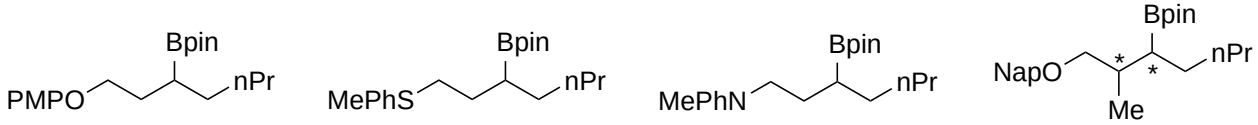
Anti-Markovnikov borylation products obtained in moderate to excellent cr:



71%, 21:1 cr | 64%, 11:1 cr | 52%, 3.2:1 cr | 61%, 16:1 cr, 1:1 dr

Markovnikov borylation products obtained from sterically demanding ligand:

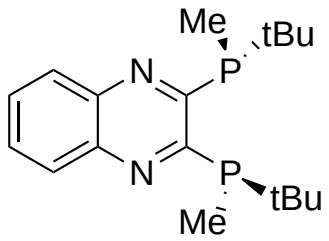




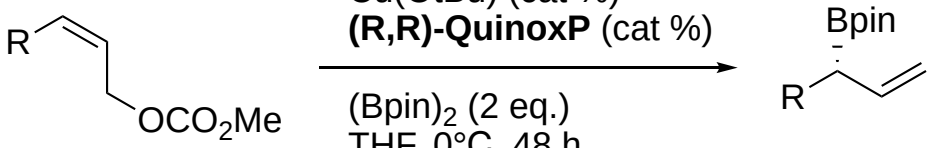
67%, 5.8:1 cr | 48%, 3.2:1 cr | 62%, 6:1 cr | 46%, 3.7:1 cr, 1:1 dr

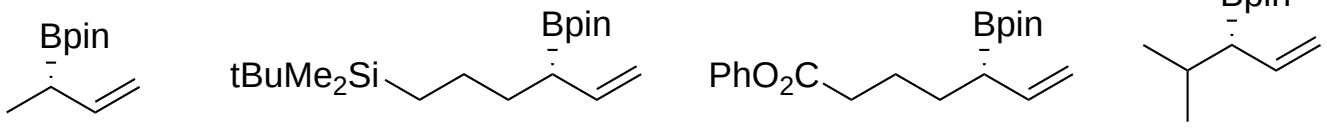
Angew. Chem. Int. Ed. **2015**, 54, 12957–12961.

Copper-boryl addition regioselectivity: hyperconjugative stabilization from silicon



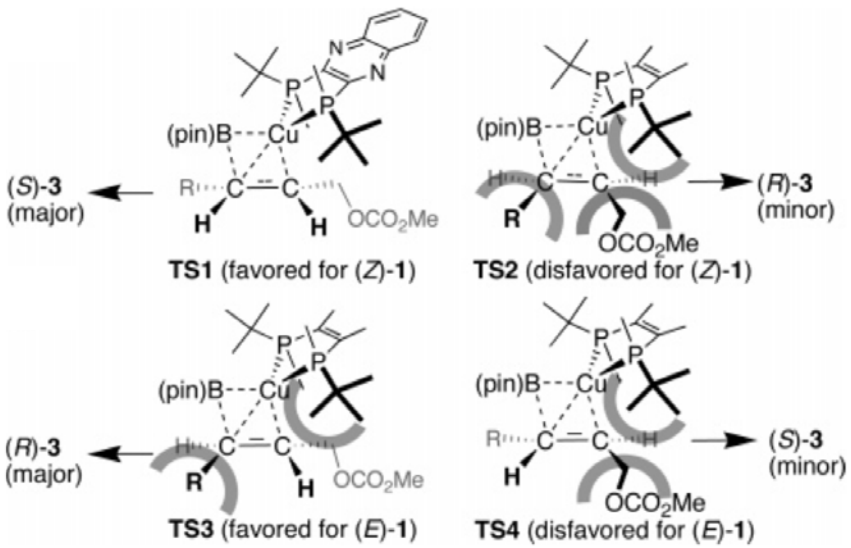
(R,R)-QuinoxP

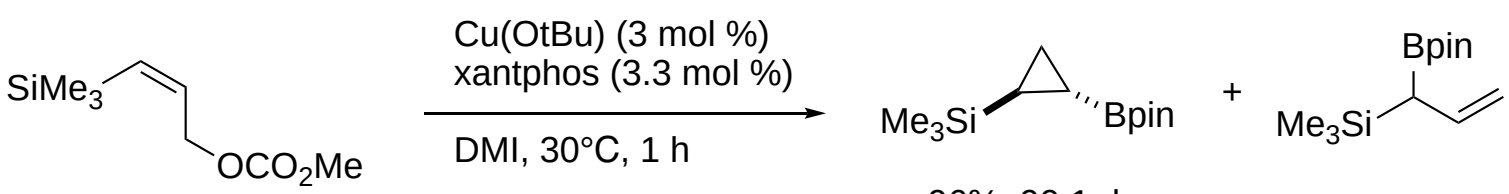




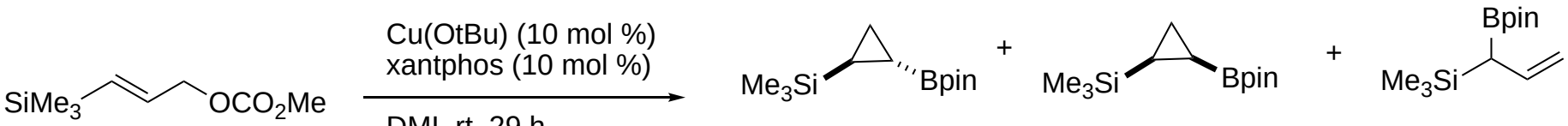
68%, 95% ee | 70%, 94% ee | 67%, 94% ee | 0%

(*E*)-alkene starting material gave poorer enantioselectivity:



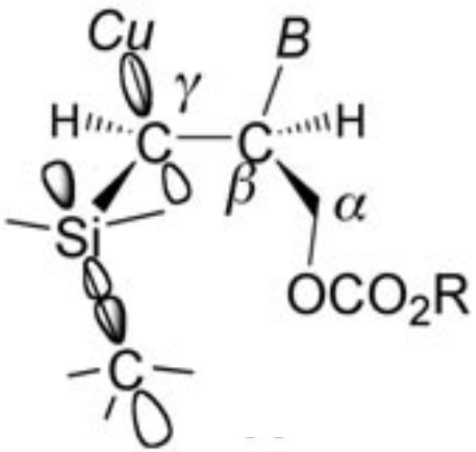


96%, 99:1 dr | 1%



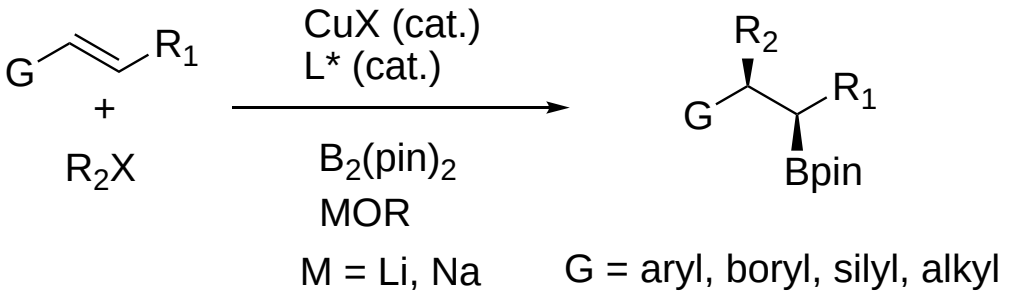
52% | 8% | 17%

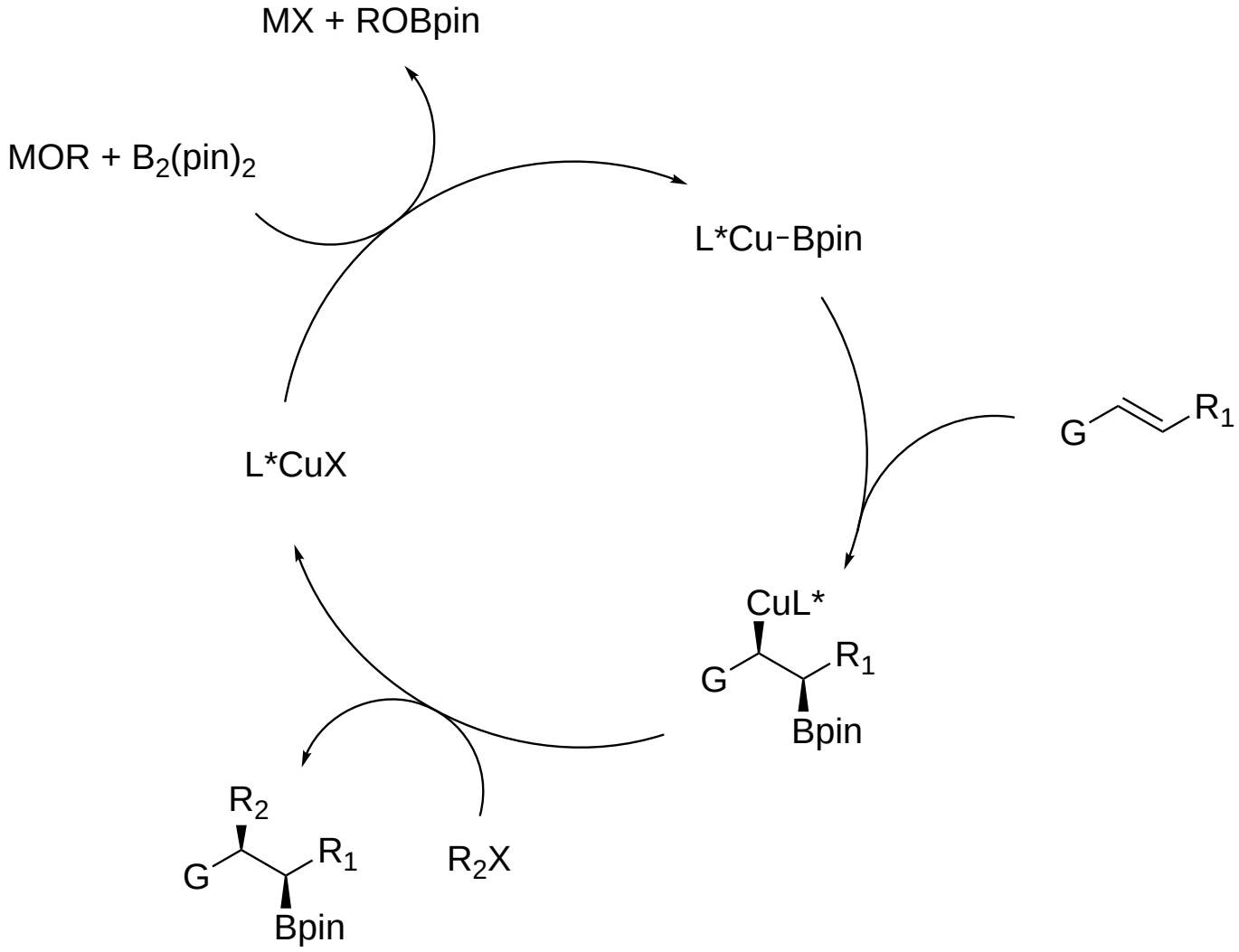
γ-silicon atom stabilizes cuprate:



Angew. Chem. Int. Ed. **2008**, 47, 7424–7427. *J. Am. Chem. Soc.* **2007,** 129, 14856-14857.

General catalytic cycle for copper-boryl additions to alkenes



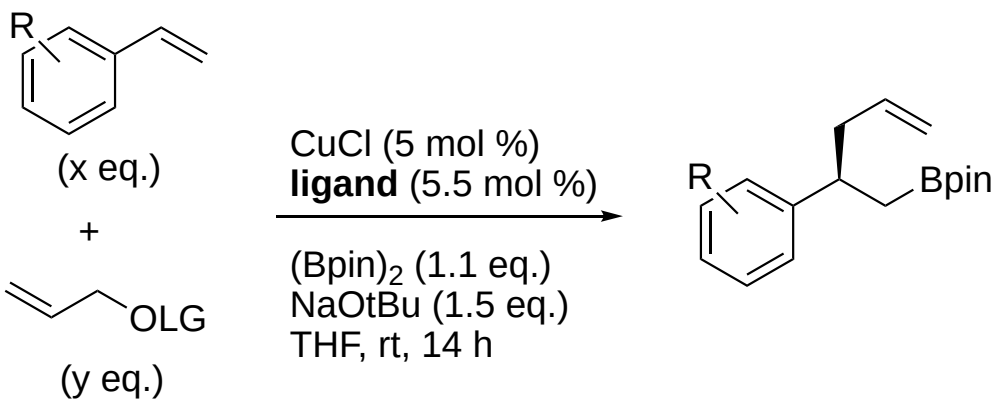


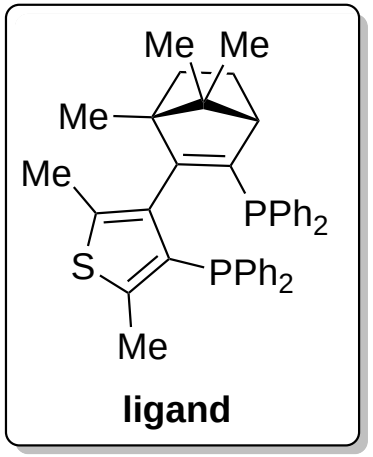
Key features are established:

- Presence of [Cu]-Bpin species as a catalytic intermediate
- *Syn*-stereospecific addition of [Cu]-Bpin to alkene
- Regioselectivity favors copper at the position that can best stabilize negative charge
- Stereoretentive nucleophilicity of resulting cuprate
- Oxidation of $B_2(pin)_2$ turns over the cycle

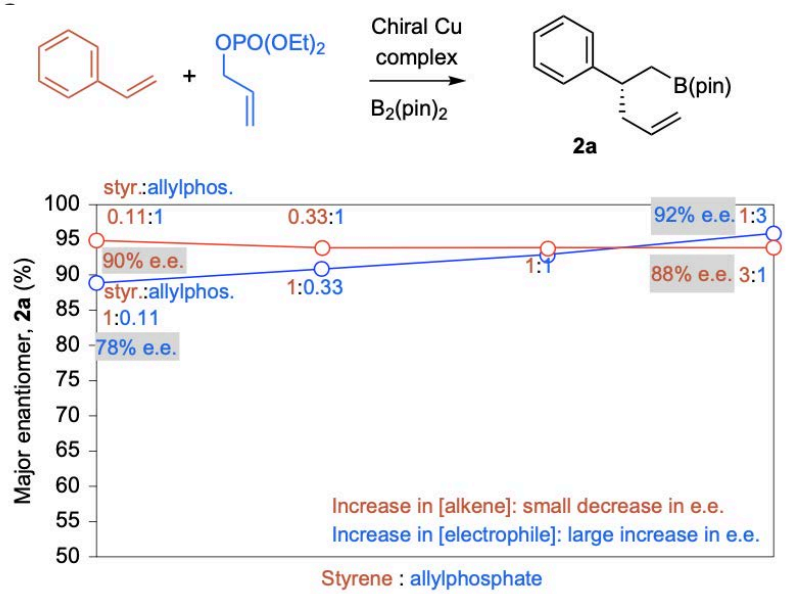
Recent mechanistic insights on a typical carboborylation reaction

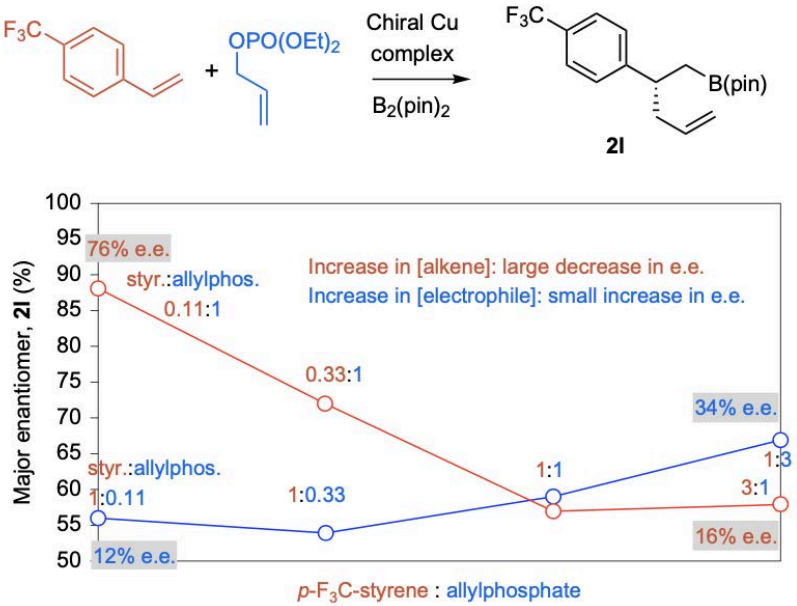
Electron-deficient olefins are more sensitive to the electrophile used to capture the alkyl cuprate:





R	LG	x:y	yield	er
none	PO(OEt)$_2$	3:1	67%	95:5
2-OMe	PO(OEt)$_2$	3:1	59%	95:5
2-CF$_3$	PO(OEt)$_2$	3:1	46%	83:17
2-CF$_3$	CO$_2$Ph	1:3	50%	96:4
2-F	PO(OEt)$_2$	3:1	54%	89:11
2-F	CO$_2$Ph	3:1	64%	96:4
4-CF$_3$	PO(OEt)$_2$	3:1	70%	58:42
4-CF$_3$	CO$_2$Ph	1:3	68%	96:4

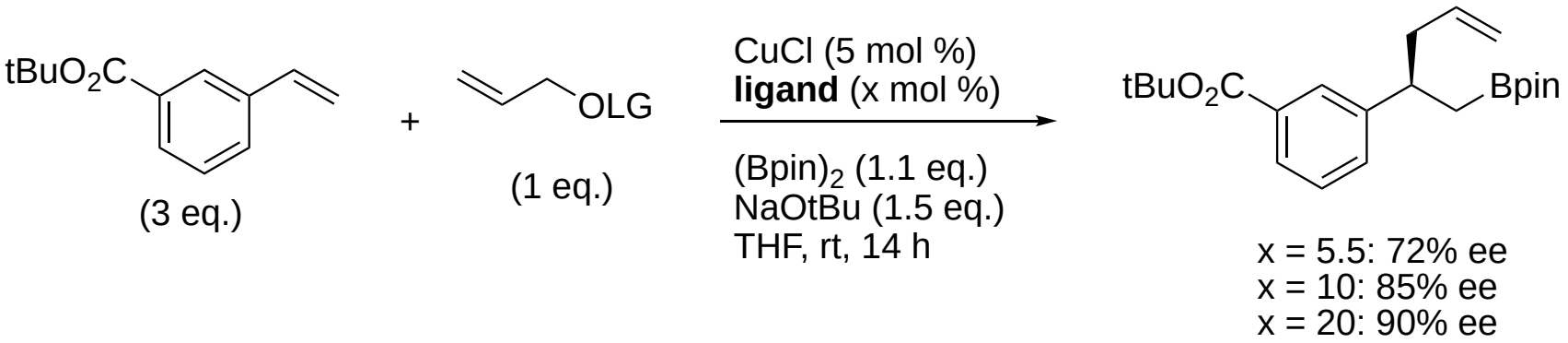




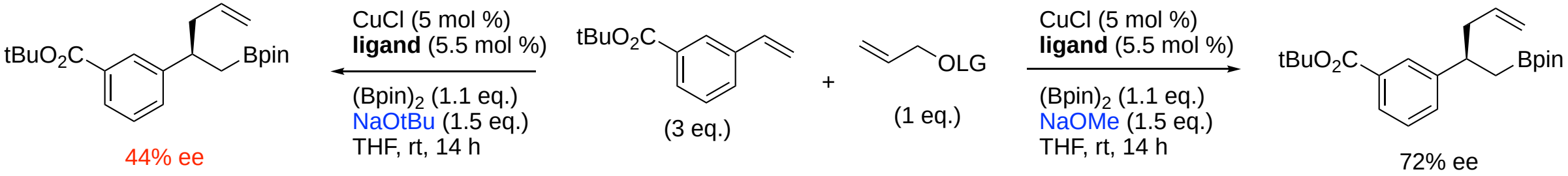
Nat. Chem. **2018,** 10, 99.

Recent mechanistic insights on a typical carboborylation reaction

Electron-deficient olefins also show higher enantioselectivity in the presence of higher concentrations of ligand:



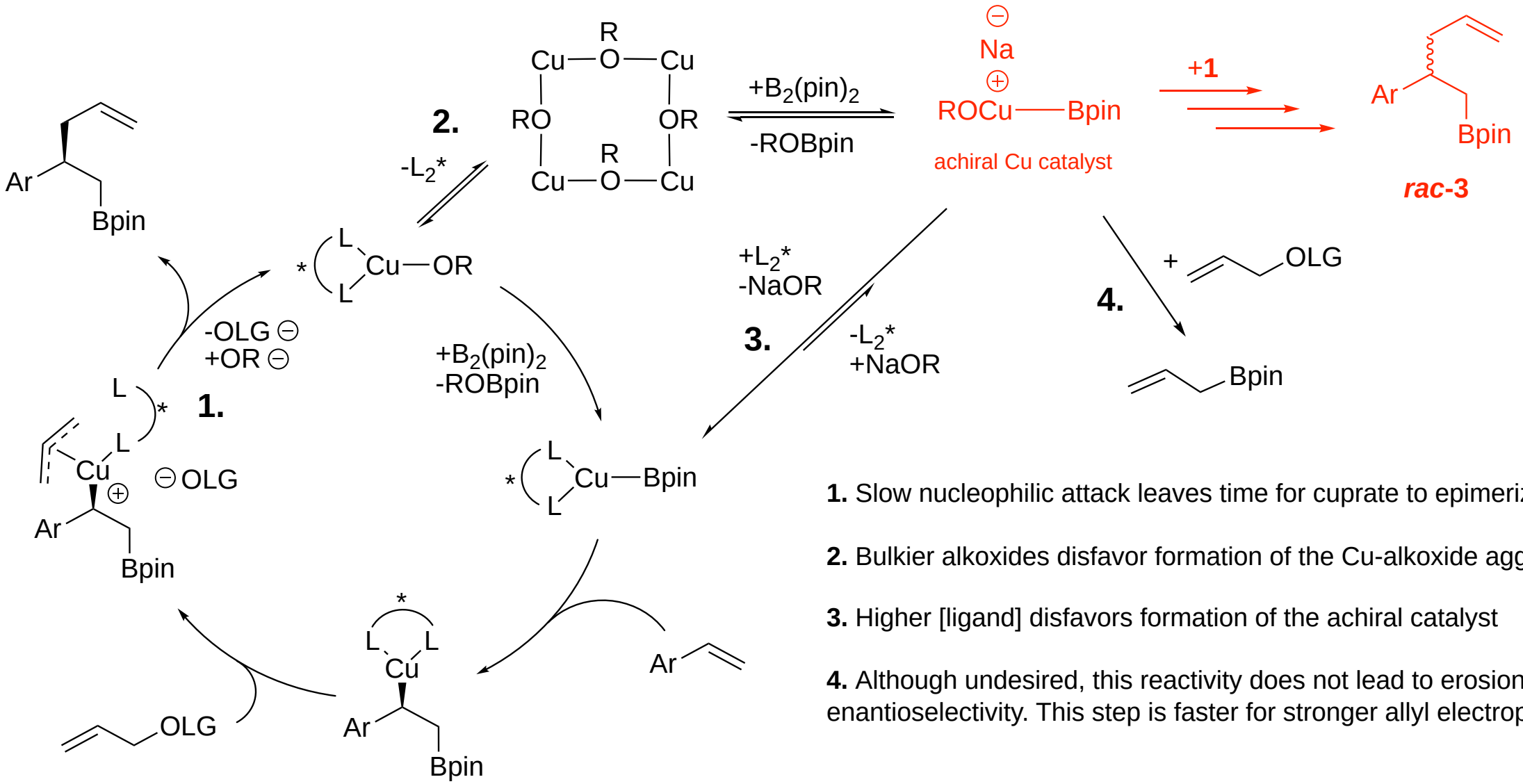
Bulkier alkoxide sources are a major contributor to improved enantioselectivity:



Copper-mediated oxidation of $(Bpin)_2$ by the alkoxide occurs *after* all stereo-determining steps in the basic mechanism...

Nat. Chem. **2018,** 10, 99.

The full picture: equilibrium with achiral alkoxide ligand can erode enantioselectivity



1. Slow nucleophilic attack leaves time for cuprate to epimerize.

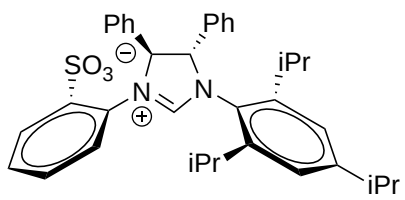
2. Bulkier alkoxides disfavor formation of the Cu-alkoxide aggregate

3. Higher [ligand] disfavors formation of the achiral catalyst

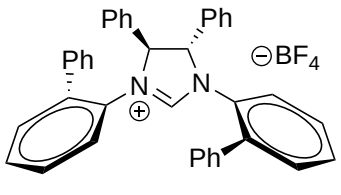
4. Although undesired, this reactivity does not lead to erosion of enantioselectivity. This step is faster for stronger allyl electrophiles.

Nat. Chem. **2018,** 10, 99.

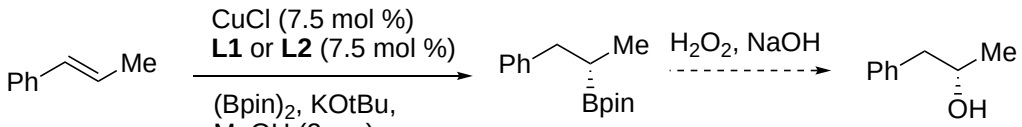
Protioborylation: Early examples of asymmetric protioborylation of aryl alkenes



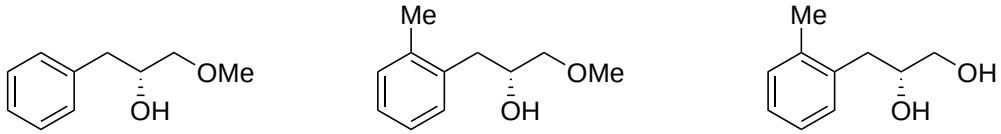
L1



L2



L1 is employed for acyclic substrates:

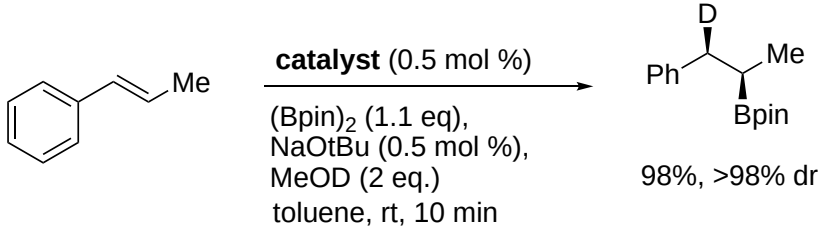


75%, 98:2 er | 51%, 94.5:5.5 er | 74%, 98:2

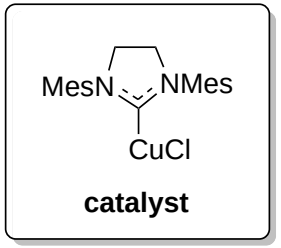
L2 was optimal for cyclic substrates:

63%, 86:14 er | 98%, 94.5:5.5 er

MeOH is a necessary additive to affect proto-decupration of the copper-boryl species:

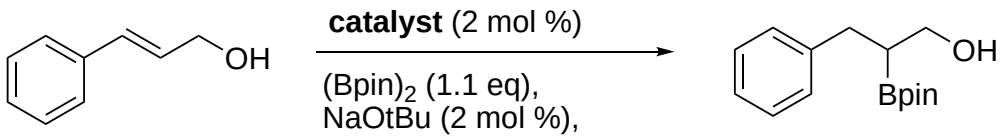


98%, >98% dr



catalyst

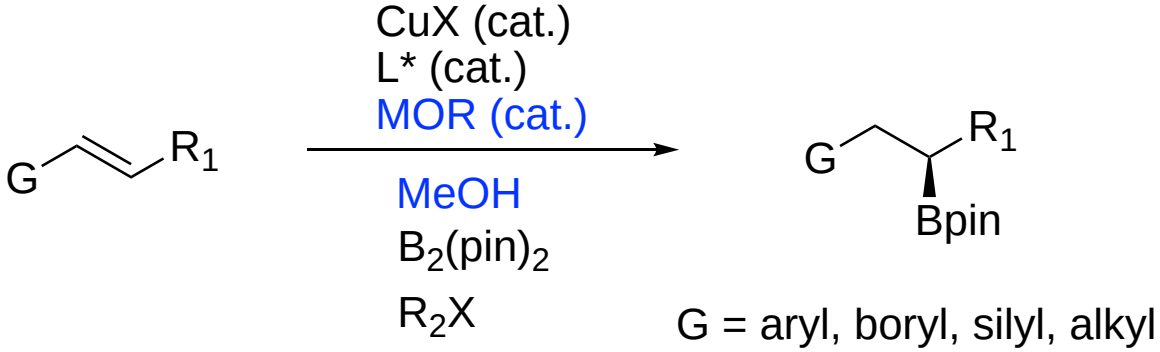
Protic substrates can proto-decuprate without MeOH present:

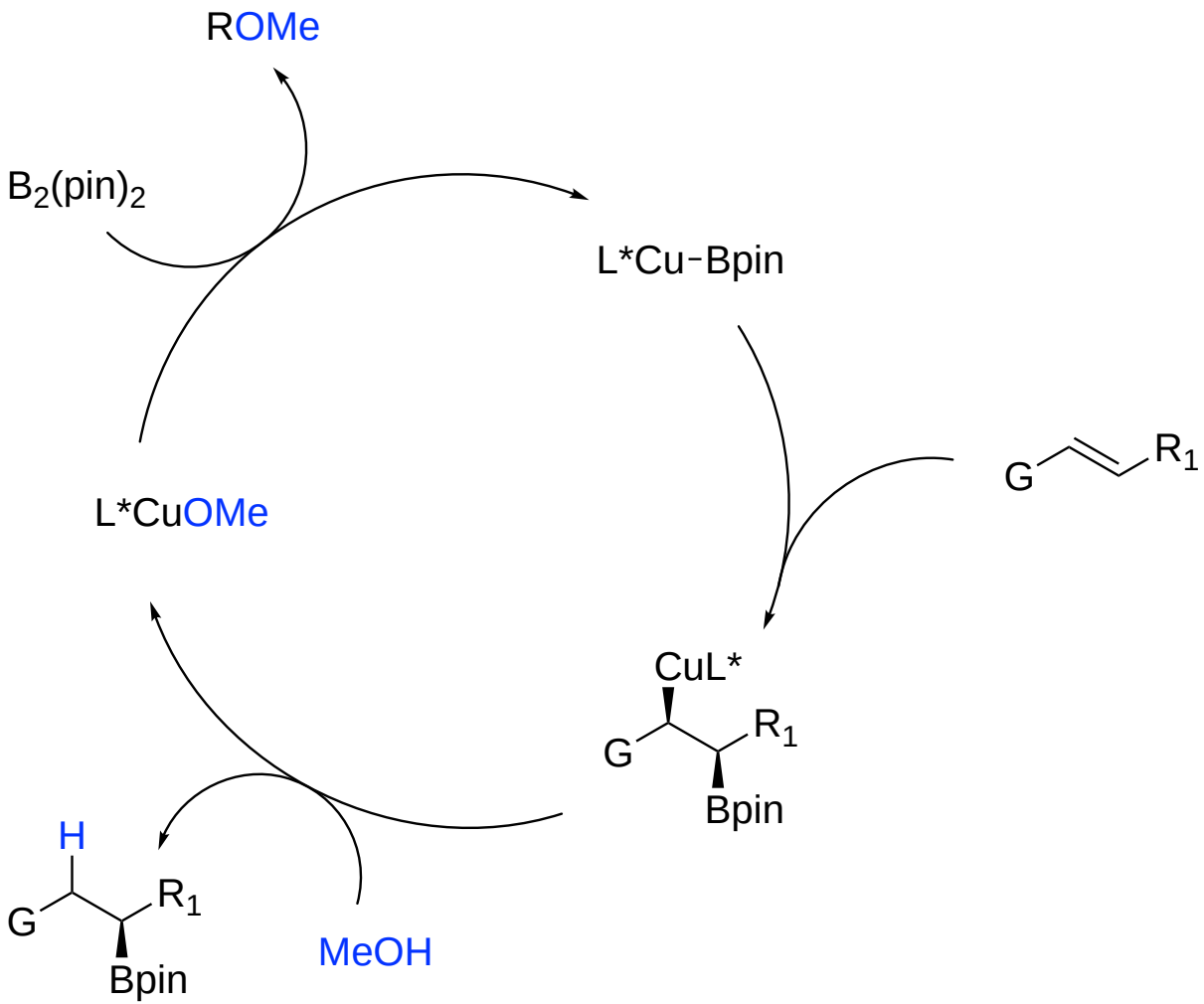


80%

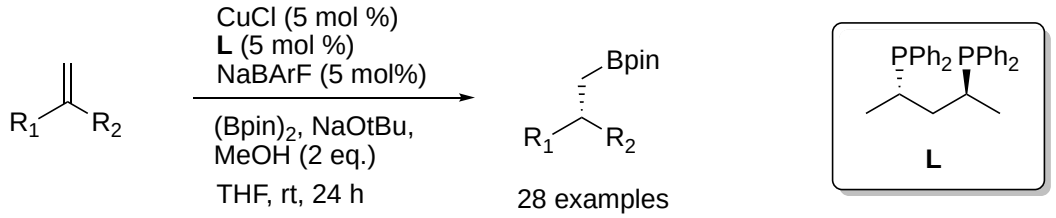
J. Am. Chem. Soc. **2009**, *131*, 3160–3161.

Protioborylation: Catalytic base and stoichiometric methanol in general mechanism

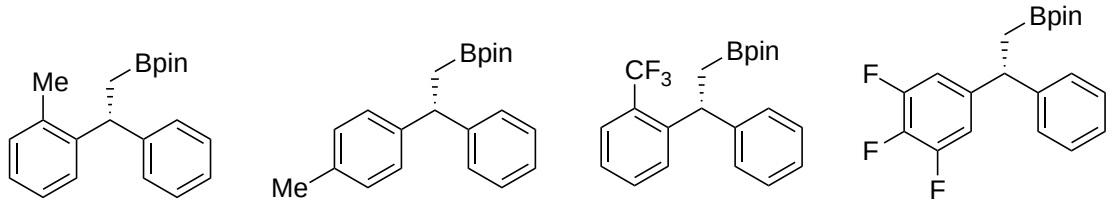




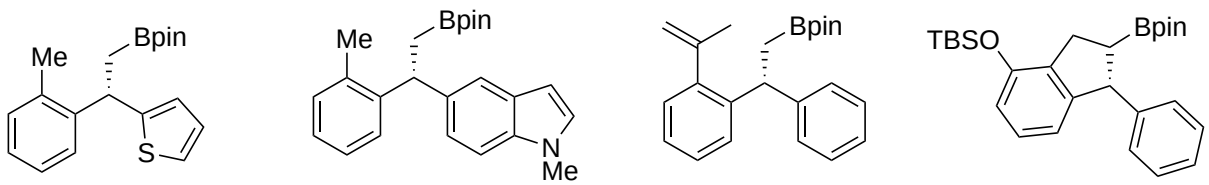
Protioborylation: Asymmetric protioborylation of 1,1-disubstituted alkenes



28 examples



86%, 98:2 er | 84%, 60:40 er | 76%, 90.5:9.5 er | 60%, 67:33 er

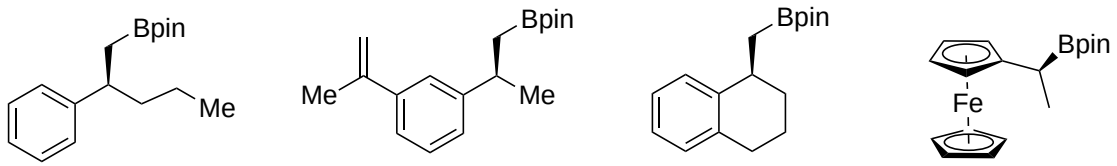


78%, 93.5:6.5 er | 31%, 95.5:4.5 er | 81%, 96.5:3.5 er | 70%, 90:10 er

NaBArF was included as an additive to provide a non-coordinating anion.

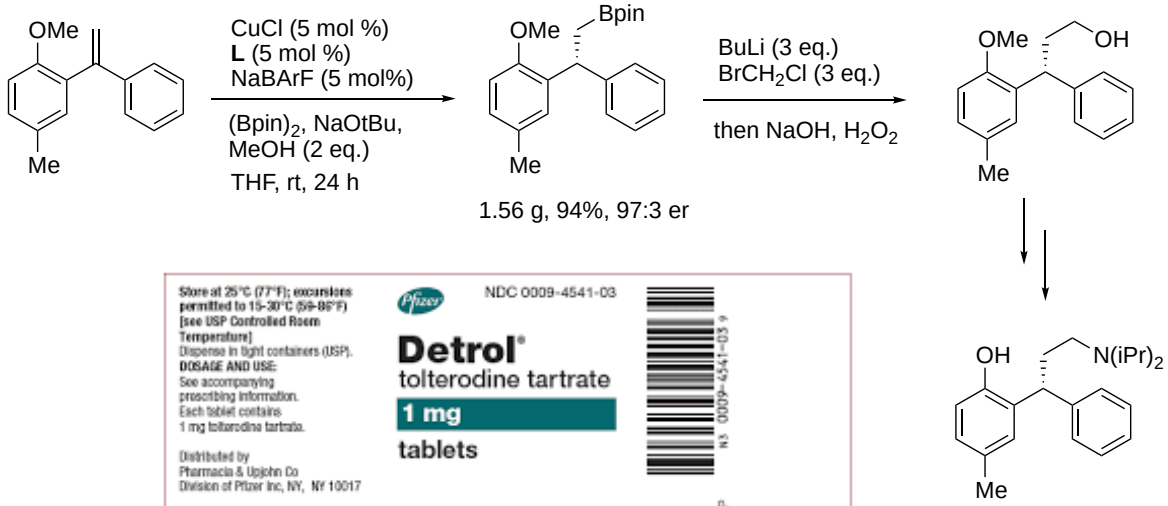
Difficulty in discriminating the enantiotopic faces of 1,1-diaryl alkenes makes them especially challenging substrates.

1,1-arylalkyl substituted substrates are also competent, with generally excellent enantioselectivity:



65%, 91:9 er | 74%, 94.5:5.5 er | 72%, 96.5:3.5 er | 78%, 91:9 er

Applied in the enantioselective total synthesis of tolterodine:

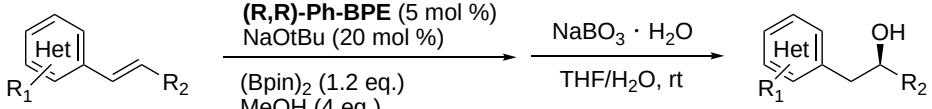


1.56 g, 94%, 97:3 er

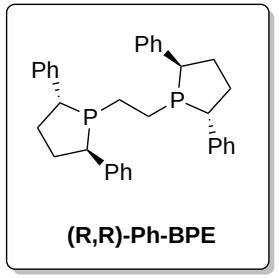
(R)-tolterodine

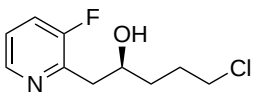
Org. Lett. **2017**, 19, 3067–3070.

Protioborylation: Asymmetric protioborylation of heteroaryl-substituted alkenes

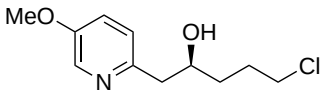


30 examples, excellent er's with 2-heteroarenes only

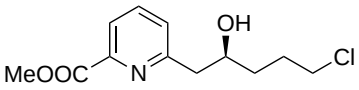




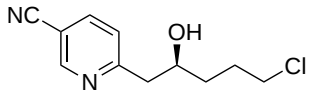
84%, 97:3 er



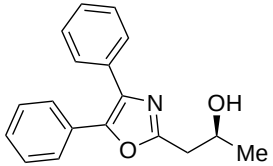
60%, 99:1 er



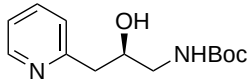
88%, 92:8 er



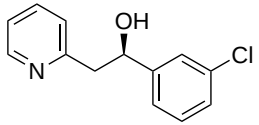
89%, 88:12 er



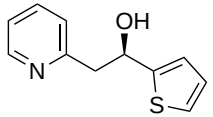
91%, 98:2 er



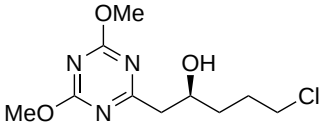
62%, 96:4 er



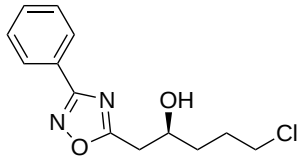
39%, 86:14 er



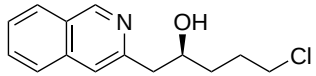
46%, 90:10 er



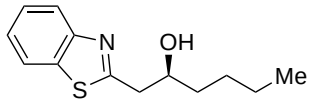
87%, 90:10 er



97%, 95:5 er

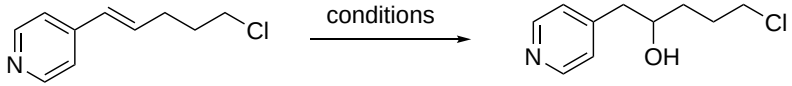


92%, 96:4 er

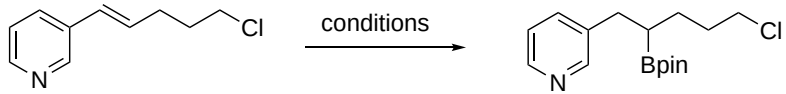


97%, 95.5:4.5 er

2-heteroarenes are optimal. Huge drops in enantioselectivity and yield are seen in 3- and 4-substituted heteroarenes:



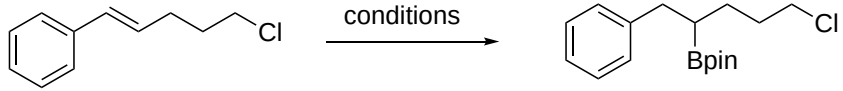
41%, 60:40 er



< 2% conversion

2-heteroatom binds copper, approximating it to the olefin and organizing the enantio-determining transition state.

Lower yield and enantioselectivity is obtained with non-heteroarenes:



55%, 87:13 er

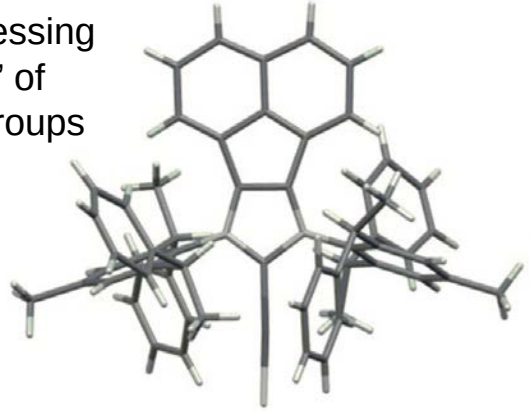
Org. Lett. **2017**, 19, 6610–6613.

Protioborylation: New ligands enable protioborylation of alkyl-substituted alkenes

V_{bur} = buried volume

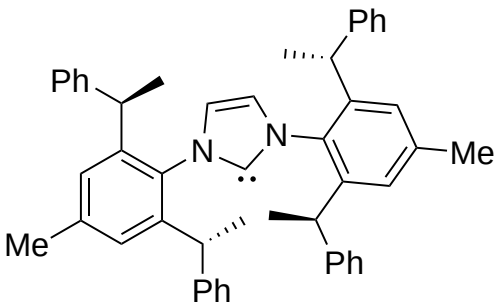
ent-**L1**/CuCl (52.1% V_{bur})

"buttressing effect" of aryl groups

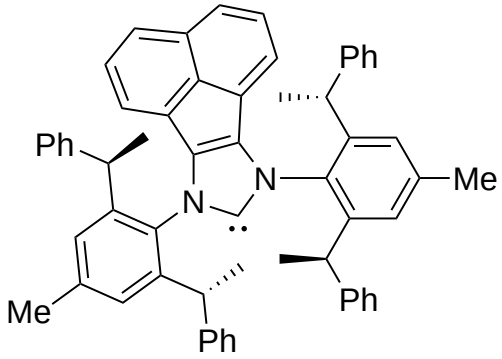


L2/CuCl (55.3% V_{bur})

New ligands:



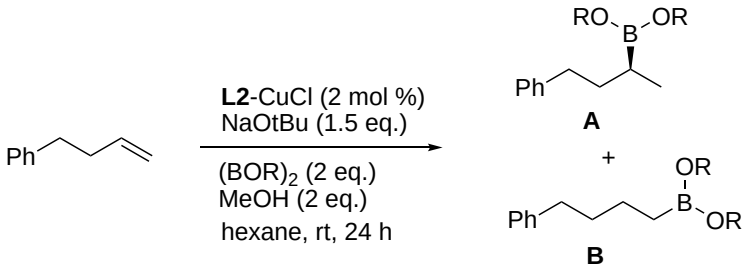
L1



L2

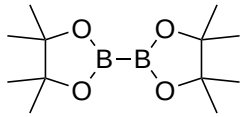
Unactivated olefins are a challenging substrate class, both in terms of enantioselectivity and regioselectivity.

Recent advances have applied sterically demanding NHC ligands combined with bulky diboranes to affect enantio- and site-selectivity.

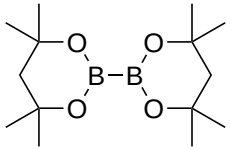


conditions	conversion	A:B	ee
$(Bpin)_2$	67%	76:24	76%
$(Bdmpd)_2$	99%	80:20	96%
BpinBdan	21%	19:81	-
L1 instead of **L2**	99%	75:25	80%
KOtBu instead of NaOtBu	79%	78:22	70%
LiOtBu instead of NaOtBu	57%	79:21	96%

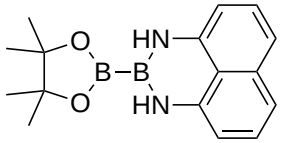
New diboranes:



$(Bpin)_2$



$(Bdmpd)_2$

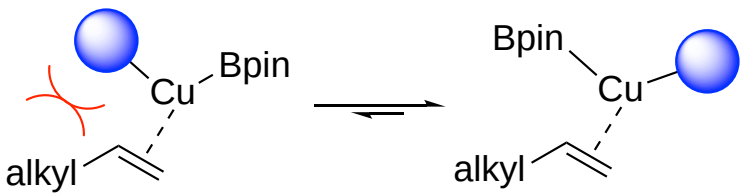


BpinBdan

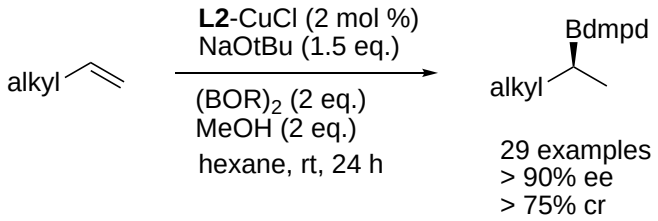
Angew. Chem. Int. Ed. **2018,** 57, 1376 –1380.

Protioborylation: New ligands enable protioborylation of alkyl-substituted alkenes

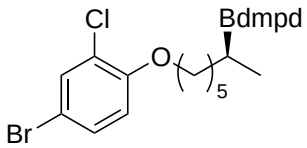
Bulky NHC ligands prefer Markovnikov addition to avoid steric clashing with the substrate:



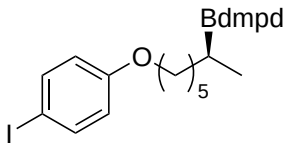
ligand =



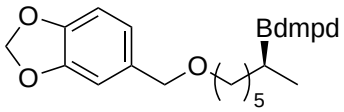
29 examples
> 90% ee
> 75% cr



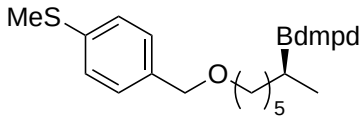
62%, 85:15 cr
92% ee



55%, 82:18 cr
94% ee



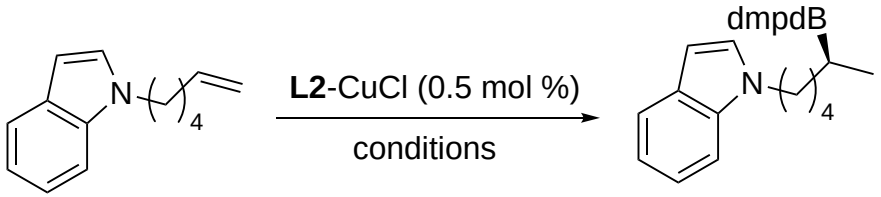
67%, 66:14 cr
91% ee



63%, 85:15 cr
90% ee

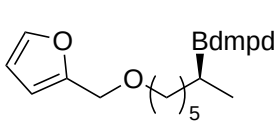
Poor reactivity with α-substituted olefin substrate.

The method is scalable, and can be used on gram scale with even lower catalyst loadings:

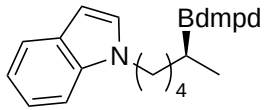


6.8 mmol, 1.35 g

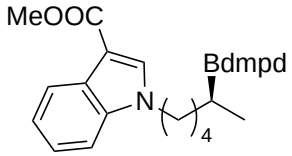
1.41 g, 61%
84:16 cr, 98% ee



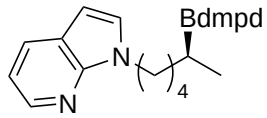
53%, 83:17 cr
92% ee



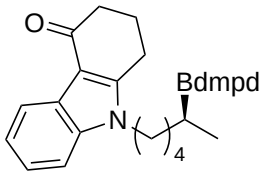
60%, 84:16 cr
98% ee



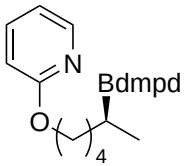
67%, 85:15 cr
97% ee



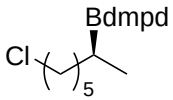
56%, 85:15 cr
91% ee



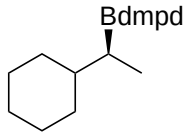
43%, 85:15 cr
97% ee



53%, 83:17 cr
90% ee



65%, 85:15 cr
91% ee



30%, 75:25 cr
92% ee

Angew. Chem. Int. Ed. **2018,** 57, 1376 –1380.

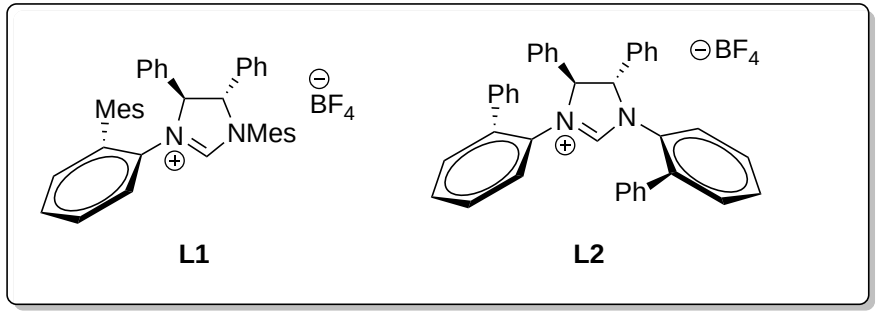
Protioborylation: Substrate vs. catalyst control in silicon-substituted alkenes

Striking differences are observed in the site-selectivity of protioborylation on alkylsilyl-1,2-disubstituted olefins vs. arylsilyl-1,2-disubstituted olefins.

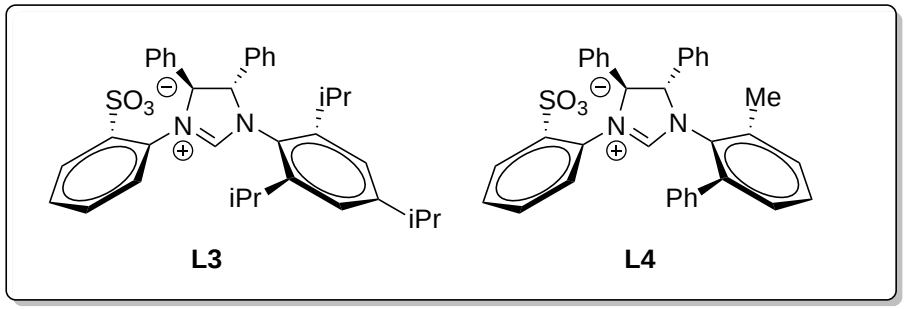
Alkylsilyl-1,2-disubstituted olefins gave vicinal borylsilyl alkanes exclusively, regardless of the ligand employed.

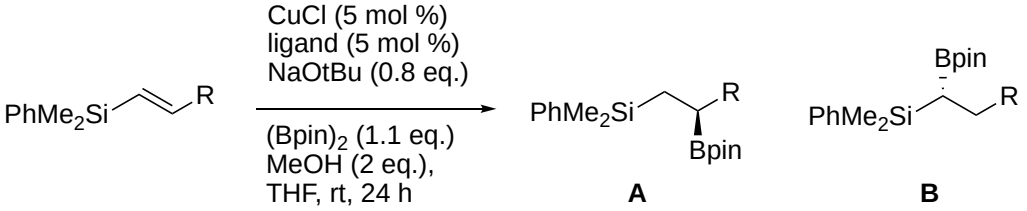
Arylsilyl-1,2-disubstituted olefins gave mixtures of constitutional isomers for most ligands, however bidentate NHC-sulfonate ligands could affect regioselective protioborylation to afford β-geminal borylsilyl arenes.

Monodentate NHC ligands:



Bidentate NHC ligands have a carbene/sulfonate chelate:

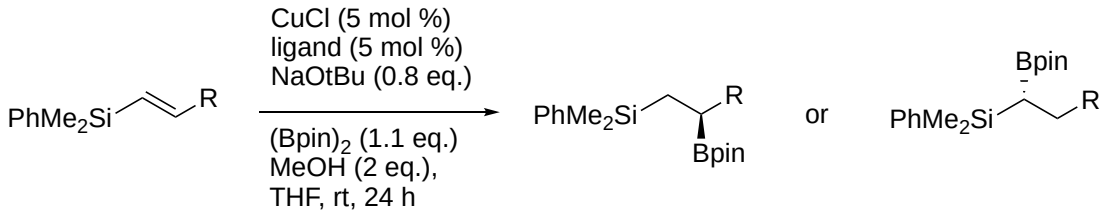


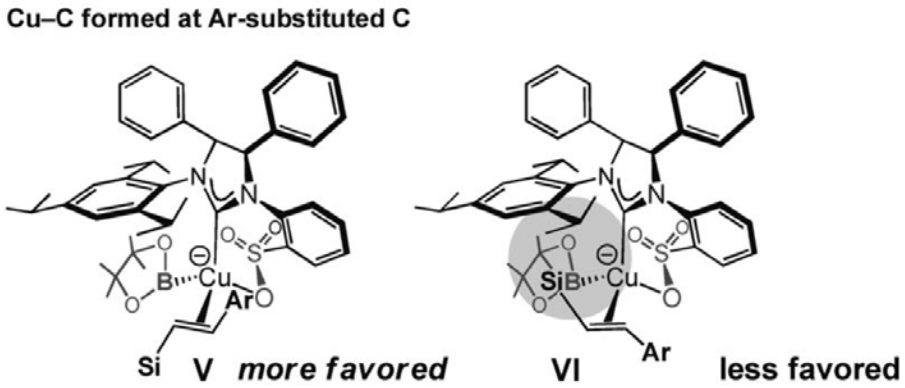


ligand	R	yield	A:B	er
L1	nBu	93	>98:2	85:15
L2	nBu	30	>98:2	57:43
L3	nBu	44	>98:2	34.5:65.5
L4	nBu	84	>98:2	45:55
L1	Ph	75	30:70	56:44
L2	Ph	74	37:63	62:38
L3	Ph	90	8:92	98:2
L4	Ph	81	10:90	95:5

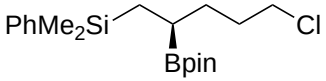
Chem. Eur. J. **2013**, 19, 3204–3214.

Protioborylation: Substrate vs. catalyst control in silicon-substituted alkenes

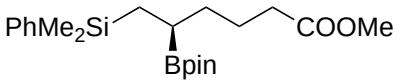




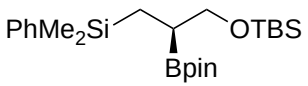
Prepared with monodentate NHC ligand:



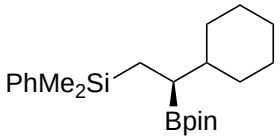
89%, >98:2 cr, 91.5:8.5 er



94%, >98:2 cr, 92:8 er

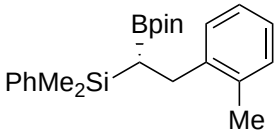


59%, >98:2 cr, 84:16 er

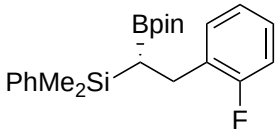


33%, >98:2 cr, 96.5:3.5 er

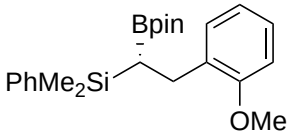
Prepared with bidentate NHC-sulfonate ligand **L4**:



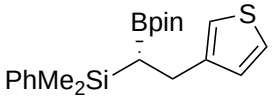
62%, 11:89 cr, 96.5:3.5 er



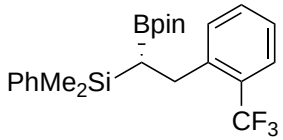
75%, 8:92 cr, 93.5:6.5 er



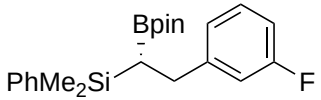
69%, 15.5:84.5 cr, 93:7 er



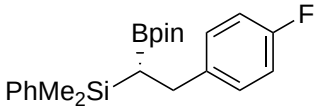
84%, 11:89 cr, 98.5:1.5 er



94%, 2:98 cr, 93:7 er



90%, 2:98 cr, 95:5 er



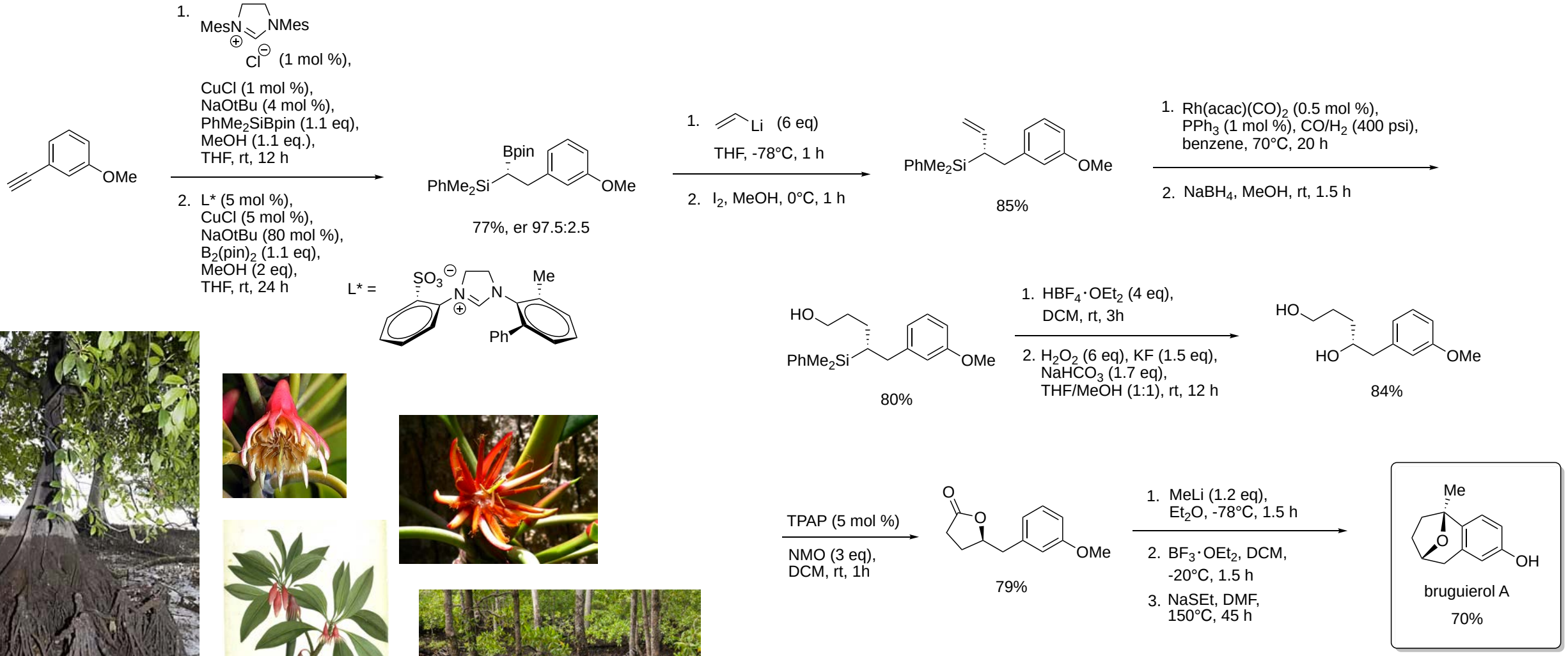
84%, 16:84 cr, 98:2 er

Copper-boryl addition to alkylsilyl olefins is under substrate control. Vicinal borylsilanes are afforded exclusively, forming the alkylcuprate at the electronically-preferred position.

Addition to arylsilyl olefins proceeds through catalyst control. A bidentate ligand is necessary to sterically enforce a regioselectivity that is not otherwise biased by substrate electronics.

Chem. Eur. J. **2013**, 19, 3204–3214.

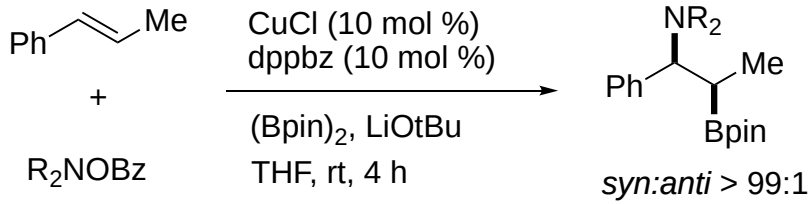
Application in the enantioselective total synthesis of bruguierol A



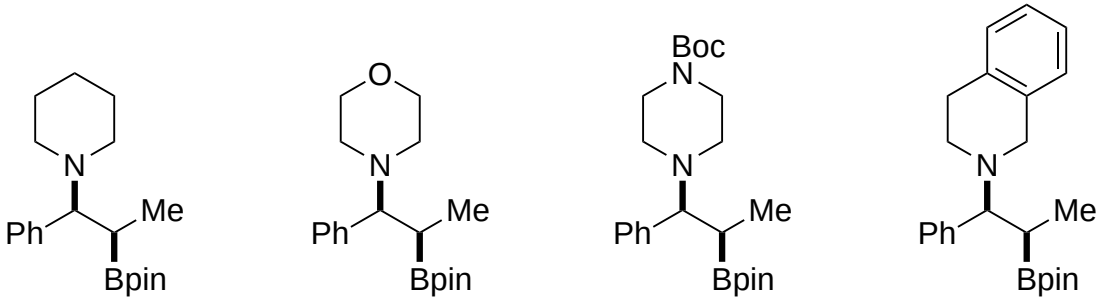
Chem. Eur. J. **2013,** 19, 3204–3214.

Aminoborylation: Early examples demonstrate product scope and stereospecificity

Various 2° amines are tolerated:



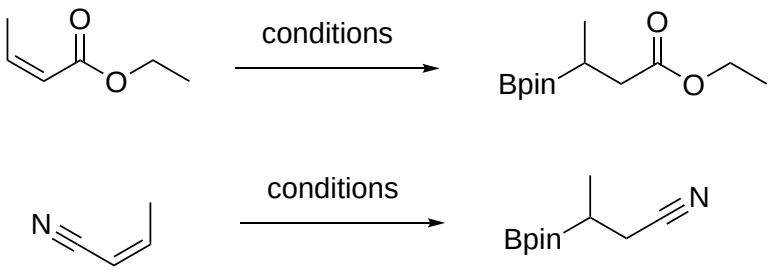
syn:anti > 99:1



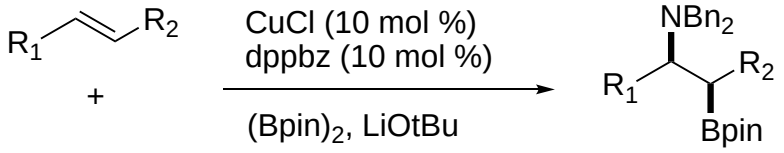
74% 44% 58% 64%

Primary amines do not react.

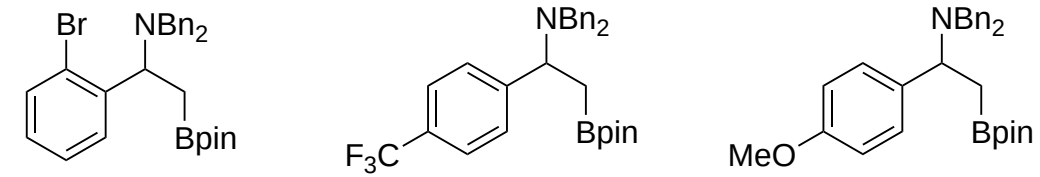
The protio-borylation product was obtained with α,β-unsaturated esters or nitriles:



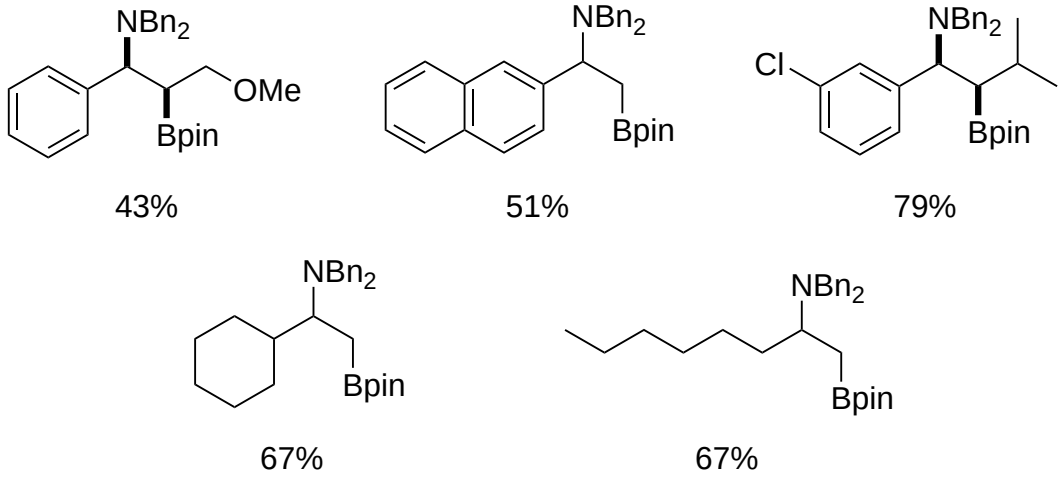
Diverse alkene substituents are tolerated:



syn:anti > 99:1



66% 77% 78%



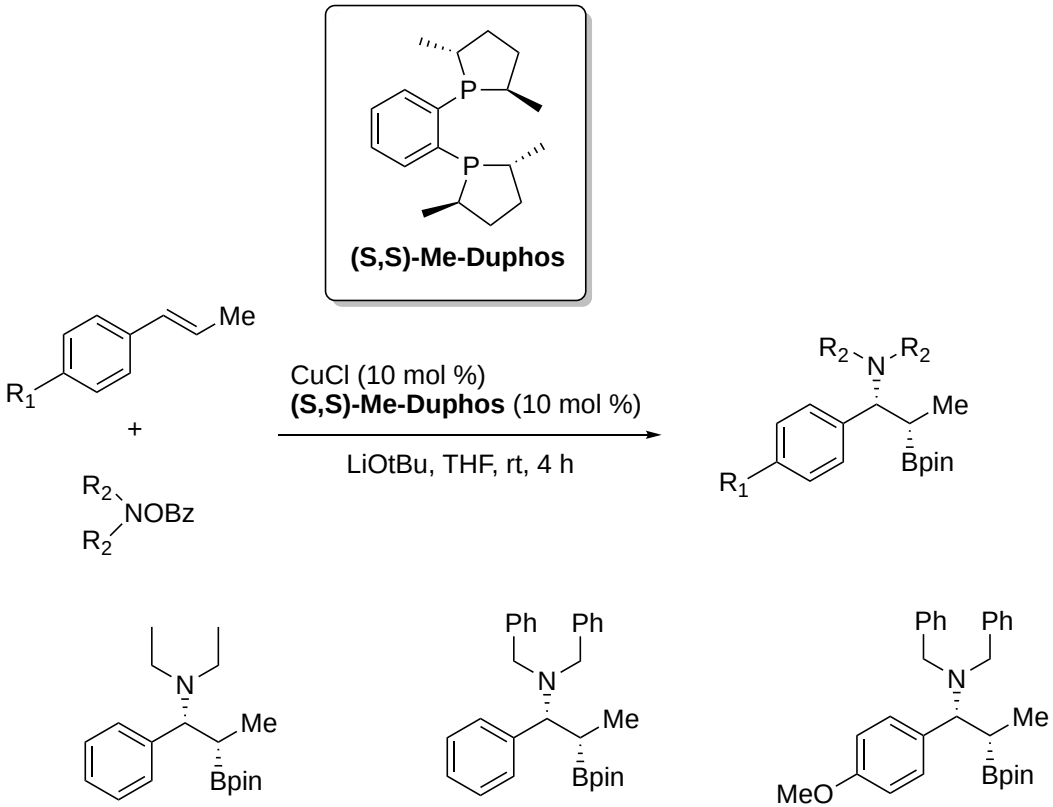
43% 51% 79%

67% 67%

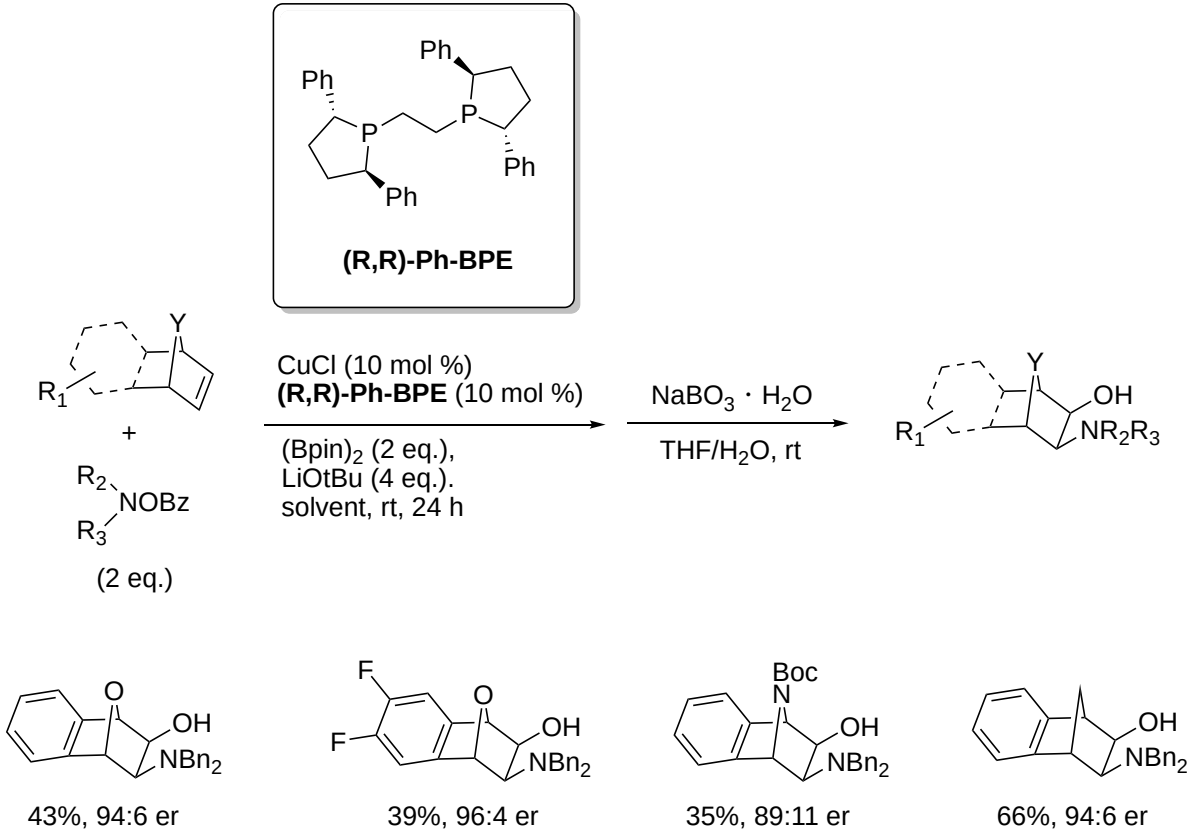
J. Am. Chem. Soc. **2013**, 135, 4934–4937.

Aminoborylation: Asymmetric aminoborylation of bicyclic alkenes

First examples of asymmetric aminoborylation (Miura 2013):



Asymmetric aminoborylation of bicyclic alkenes (Miura 2015):

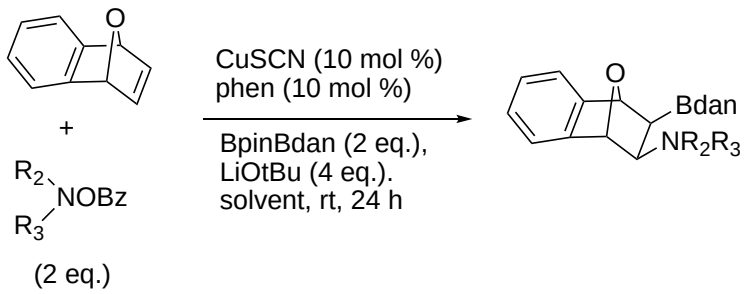


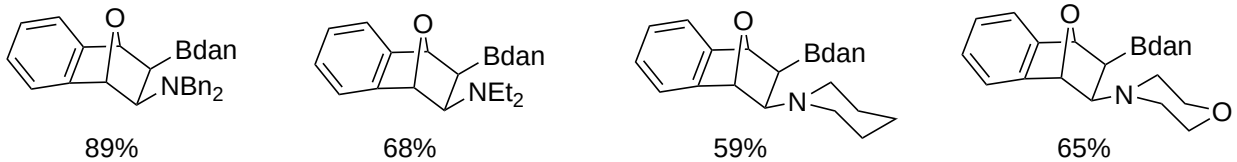
Additionally, methyl substituents on one or both bridgehead carbon atoms are shown to be well tolerated (yields >91%).

J. Am. Chem. Soc. **2013**, 135, 4934–4937.
Angew. Chem. Int. Ed. **2015**, 54, 613 –617.

Aminoborylation: Modifying the boryl group to improve product stability

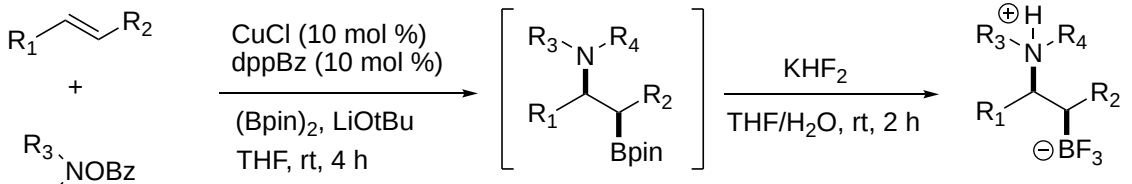
Bpin moiety can be unstable to column chromatography. The Bdan group is more stable to silica, and is also competent in the reaction:



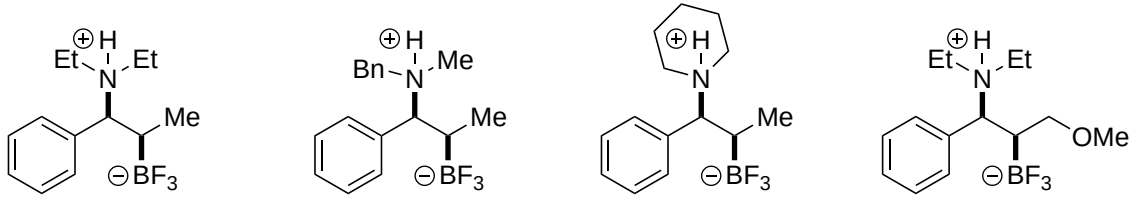


Note that the Bdan moiety transmetalates to copper preferentially over the Bpin moiety. Only Bdan-derived products are obtained, despite the use of mixed BpinBdan as the boron source.

Alternatively, *in situ* formation of the BF_3 salt causes the product to precipitate, which can be collected by simple filtration:

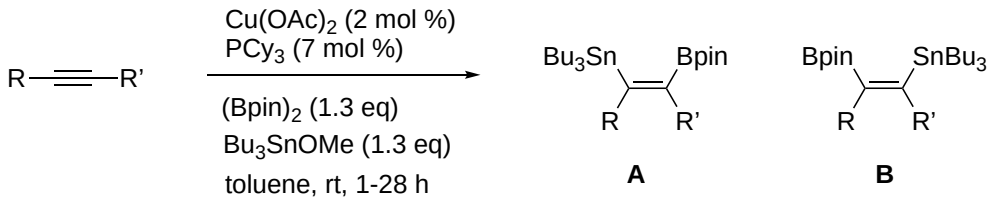


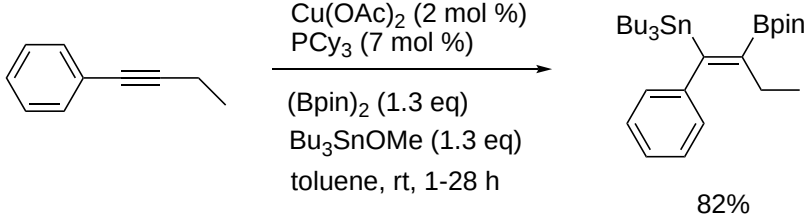
syn:anti > 99:1

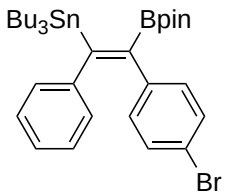


J. Am. Chem. Soc. **2013**, 135, 4934–4937.
Angew. Chem. Int. Ed. **2015**, 54, 613 –617.

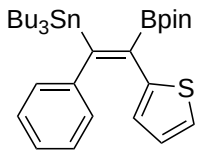
Borylstannylation: Stereoselective *syn* borylstannylation of alkynes



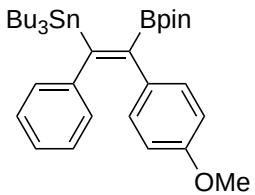




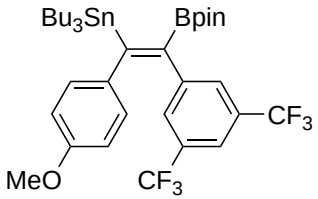
86%
A:**B** = 57:43



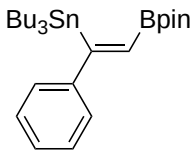
75%
A:**B** = 52:48



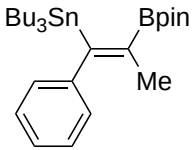
85%
A:**B** = 56:44



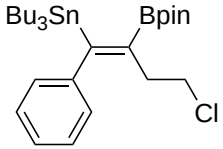
66%
A:**B** = 99:1



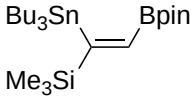
63%
A:**B** = 93:7



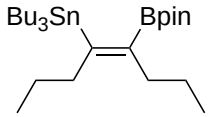
71%
A:**B** = 99:1



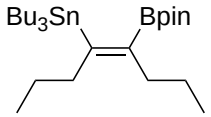
81%
A:**B** = 99:1



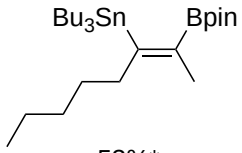
41%
A:**B** = 99:1



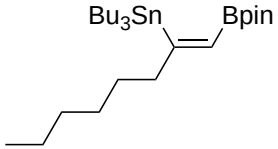
48%



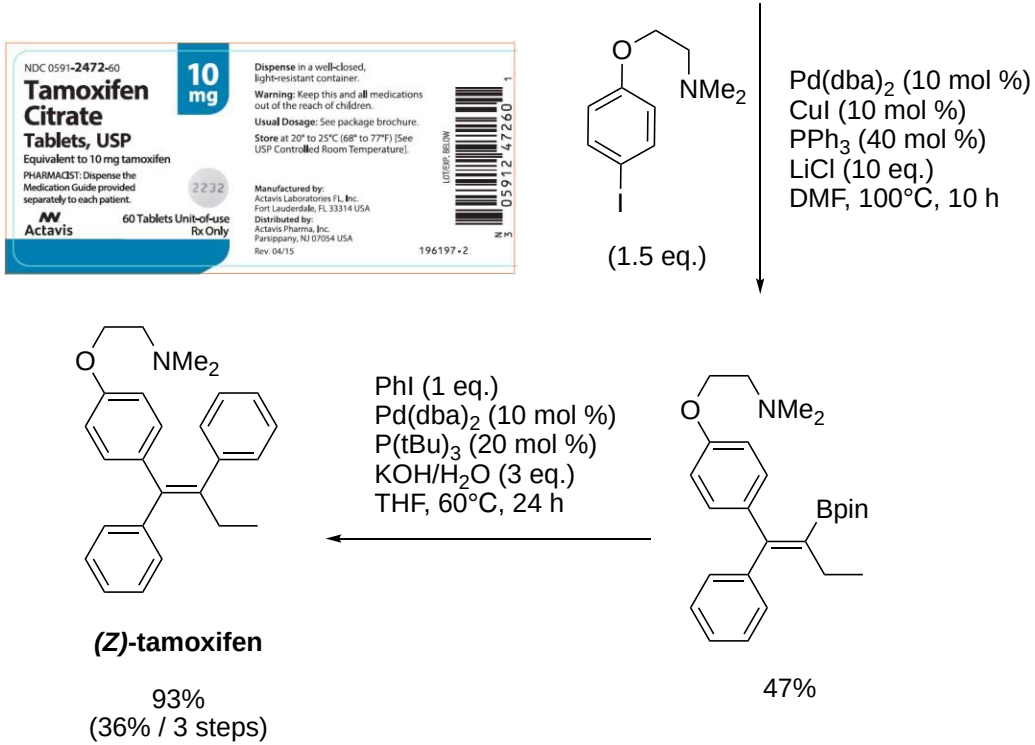
72%*



53%*
A:**B** = 88:12

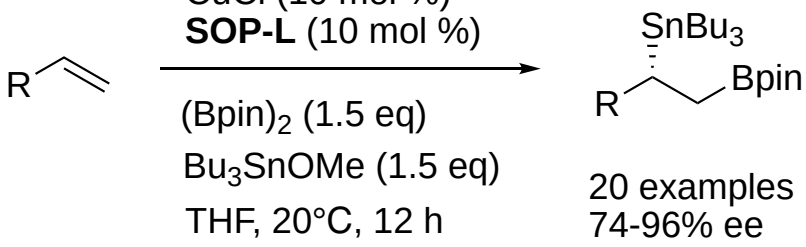


36%*
A:**B** = 83:17

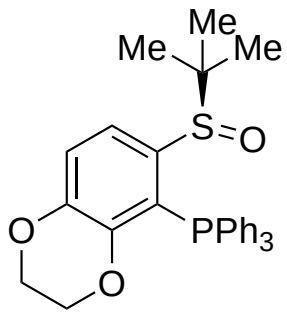


Chem. Eur. J. **2012**, 18, 14841–14844.

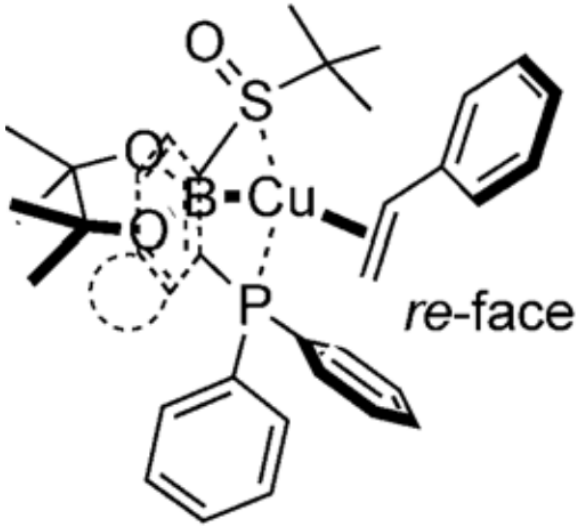
Borylstannylation: Asymmetric borylstannylation of alkenes

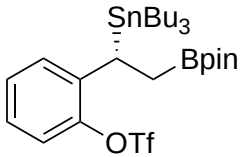


20 examples
74-96% ee

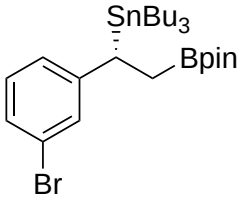


SOP-L

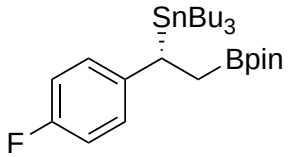




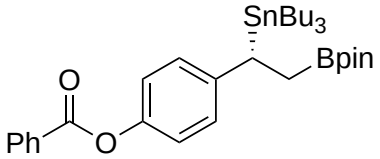
90%, 87% ee



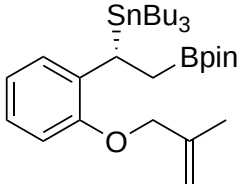
99%, 94% ee



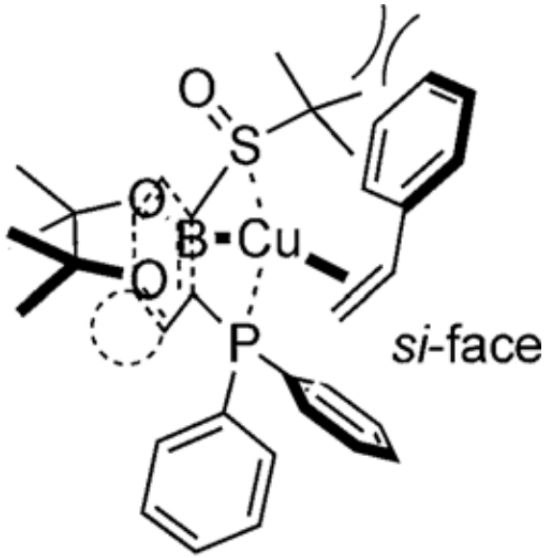
90%, 93% ee

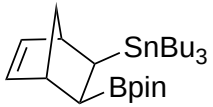


90%, 93% ee

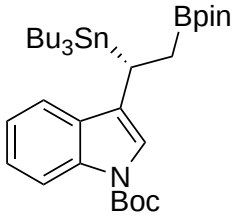


76%, 89% ee

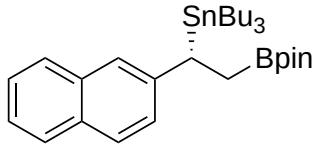




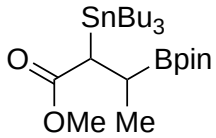
92%, 74% ee



69%, 92% ee



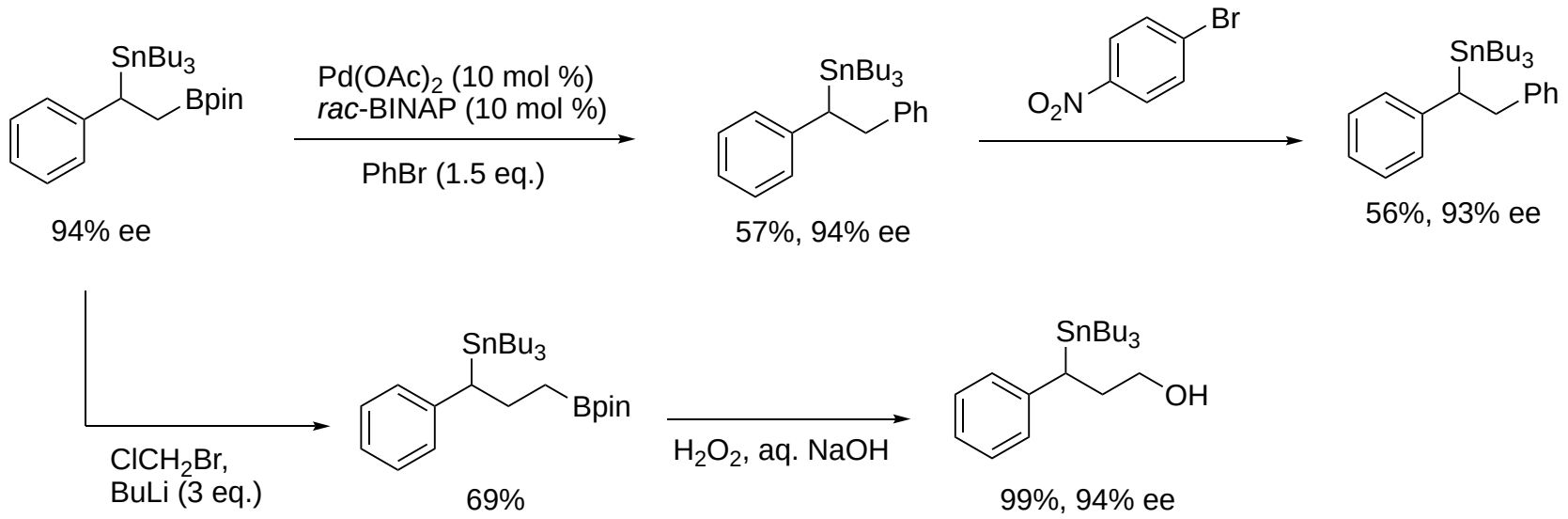
48%, 93% ee

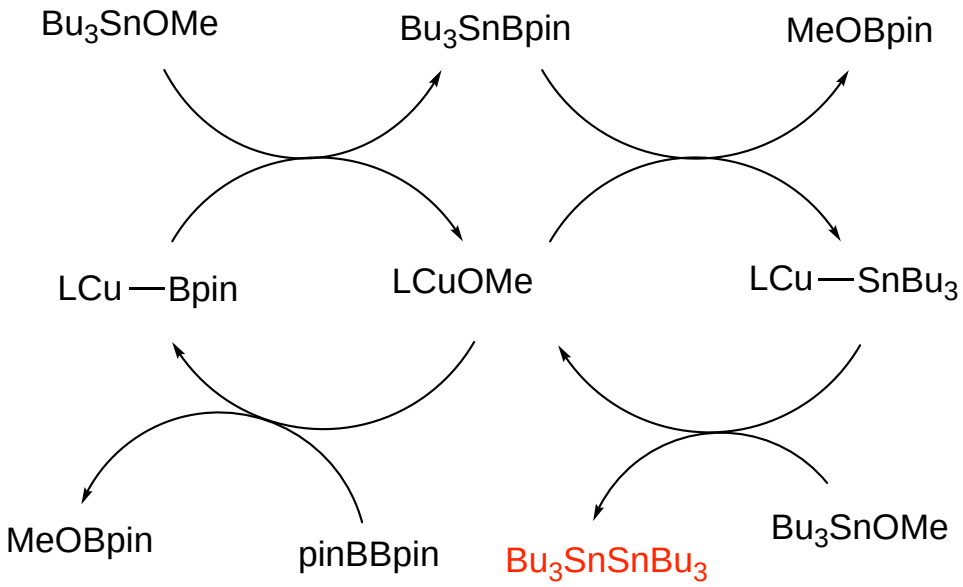


66%, 89% ee, 40% de

Chem. Eur. J. **2015**, 21, 4918–4922.
Synthesis. **2014**, 46, 3024–3032.

Borylstannylation: Useful product derivatization and undesired side reactivity

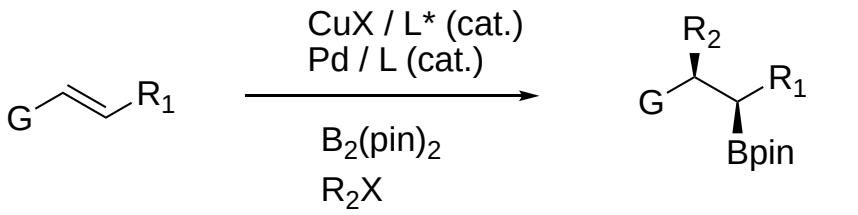




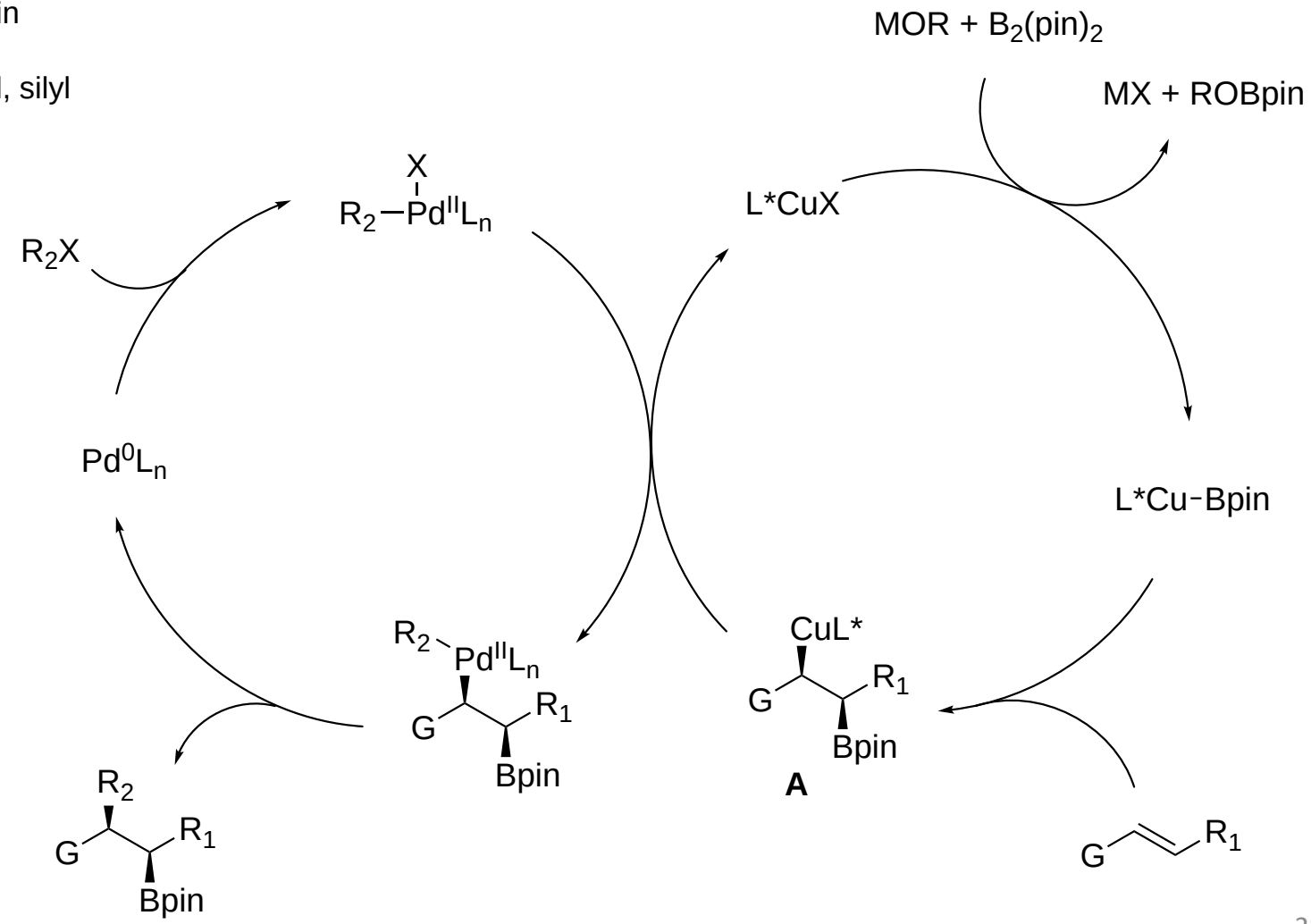
Tin-tin homocoupling is a problematic side reaction for borylstannylation.

Chem. Eur. J. **2015,** 21, 4918–4922.

Carboborylation: General catalytic cycle for dual Cu/Pd catalytic systems



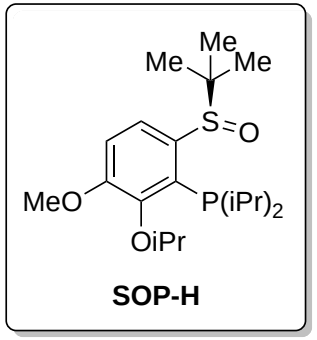
G = aryl, boryl, silyl

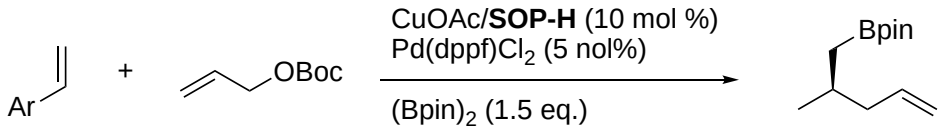


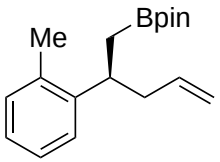
J. Am. Chem. Soc. **2015**, 137, 13760–13763.

Carboborylation: Duel catalytic Cu/Pd systems for allyl-carboborylation

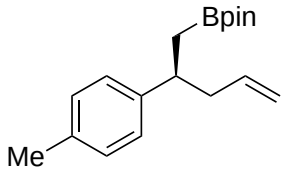
SOP ligands were found to be optimal, both for enantioselectivity, as well as limiting side products from β-hydride elimination and proto-decupration.



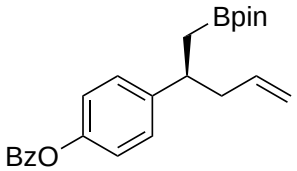




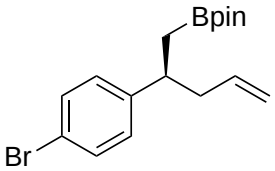
91%, 97% ee



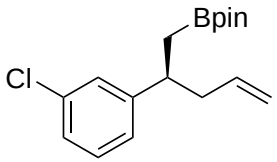
53%, 91% ee



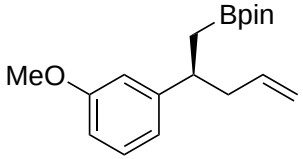
62%, 96% ee



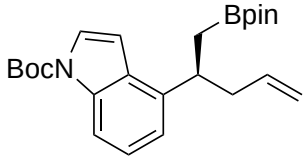
43%, 96% ee



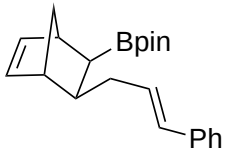
73%, 94% ee



78%, 96% ee

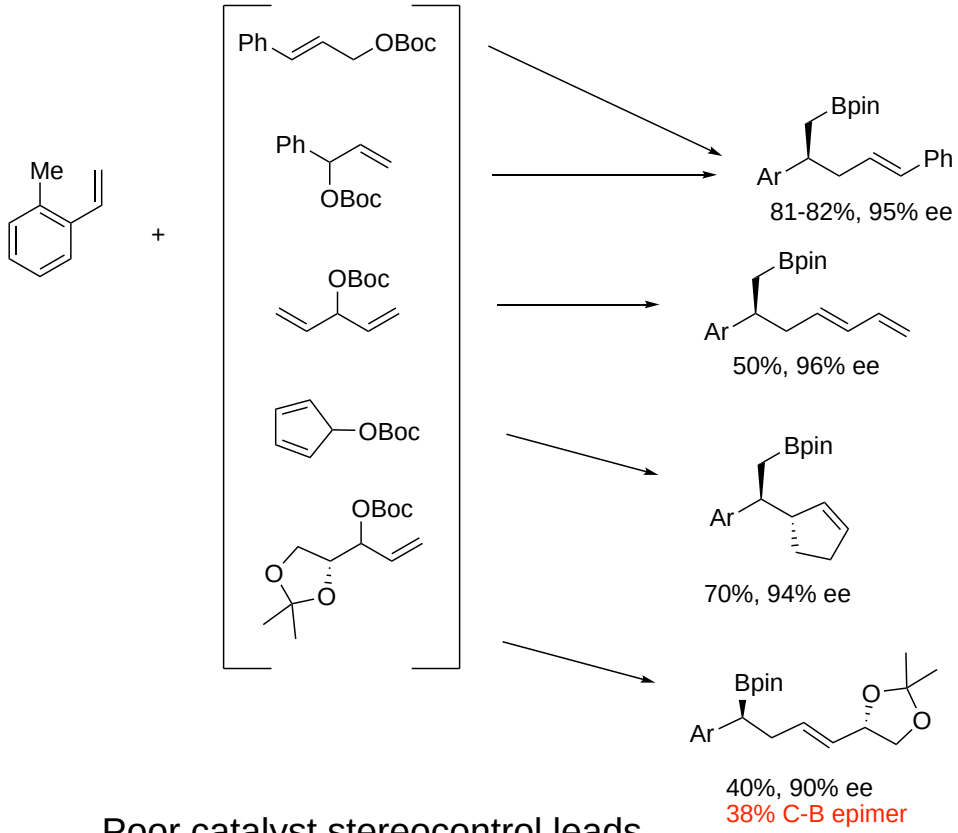


77%, 94% ee



71%, 67% ee

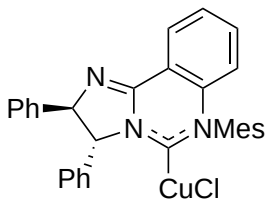
Only linear allylation products are obtained, regardless of the carbonate starting material employed:



Poor catalyst stereocontrol leads to low diastereoselectivity

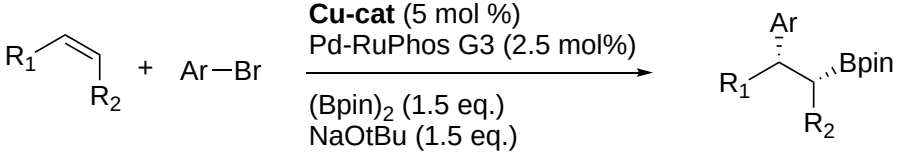
J. Am. Chem. Soc. **2015**, 137, 13760–13763.

Carboborylation: Duel catalytic Cu/Pd systems for Csp^2-carboborylation

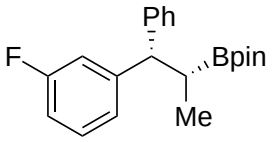


Cu-cat

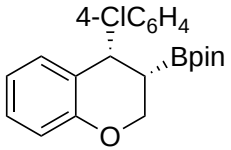
Stereoretentive transmetalation from Cu to Pd permits enantioselective installation of two chiral carbon centers in one synthetic procedure.



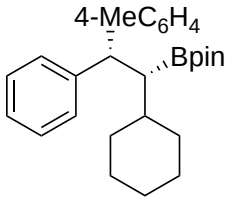
21 examples



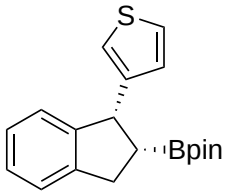
72%, 96:4 er



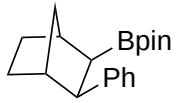
53%, 98:2 er



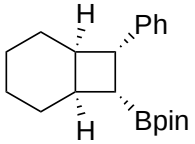
> 2%



56%, 97:3 er

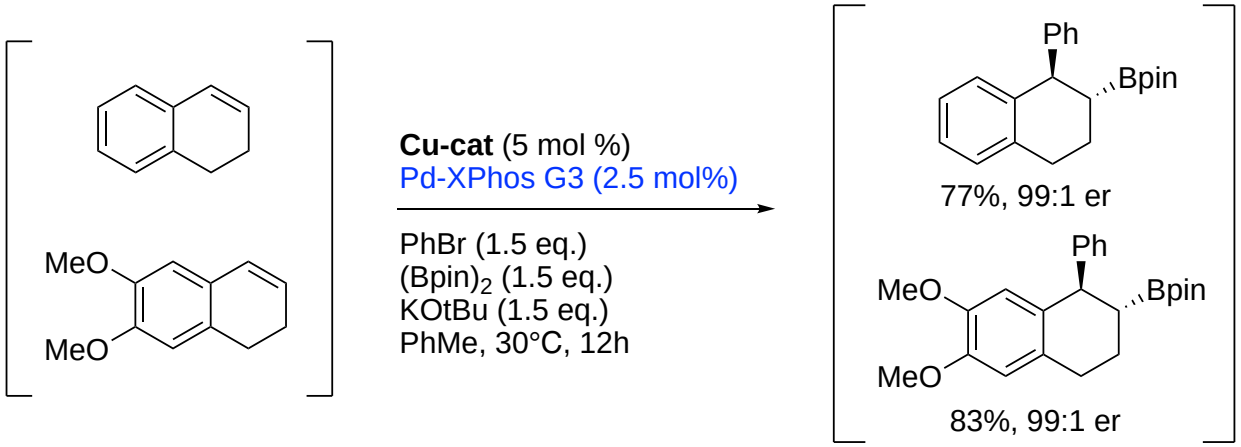


79%, 92.5:7.5 er

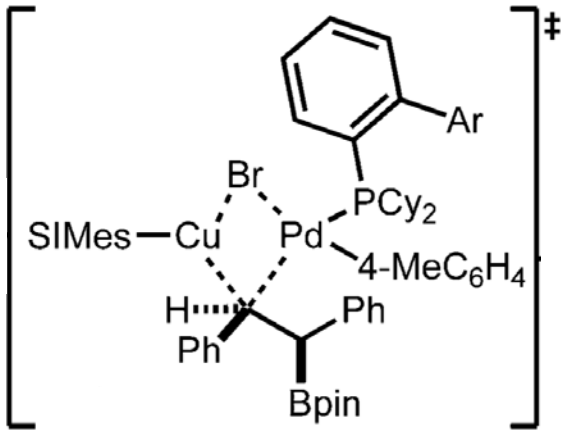


69%, 86:14 er

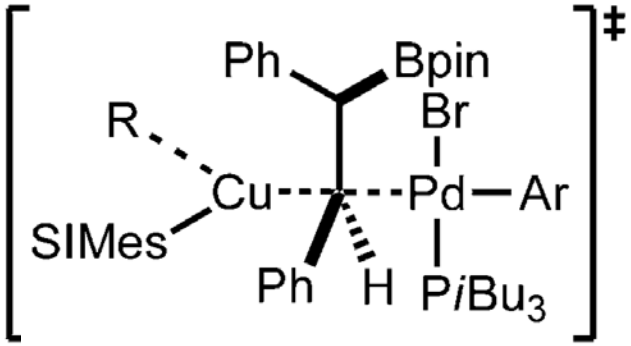
Switching to Pd-Xphos G3 as the cocatalyst flips diastereoselectivity:



Closed TS with Pd-Ruphos G3:



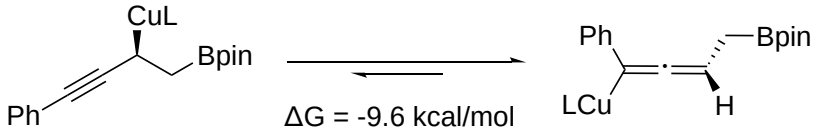
Open TS with Pd-Xphos G3:

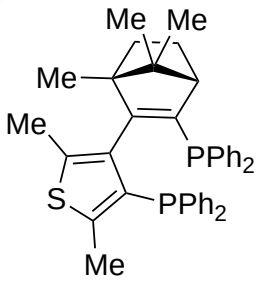


Angew. Chem. Int. Ed. **2015,** 54, 5228–5231. *ACS Catal.* **2017,** 7, 2425–2429. *Angew. Chem. Int. Ed.* **2015,** 54, 5228-5231.

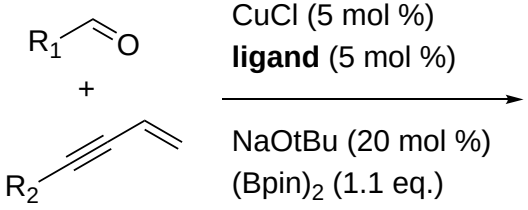
Carboborylation: Eneynes in asymmetric carboborylation, aldehyde addition reactions

DFT calculations show that α-Cu-yne can readily collapse into an allenyl cuprate:





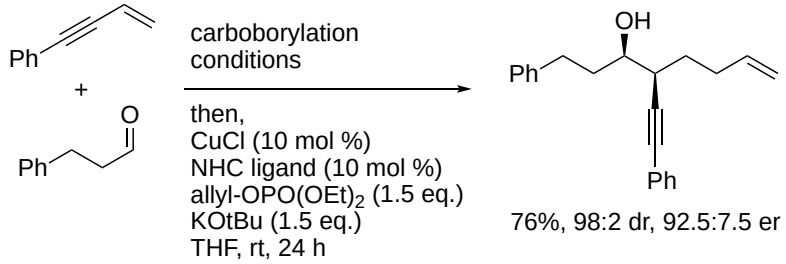
ligand



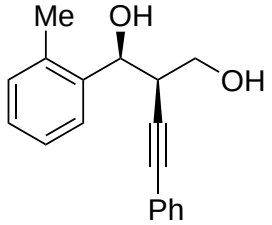
17 examples

Excellent catalyst control!

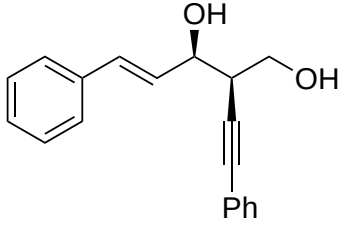
Conditions are amenable to one-pot, two-step carboborylation/allylation procedure:



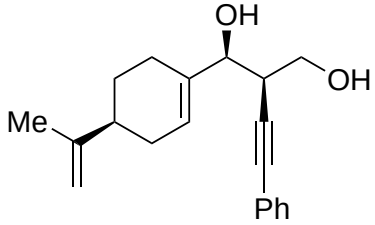
76%, 98:2 dr, 92.5:7.5 er



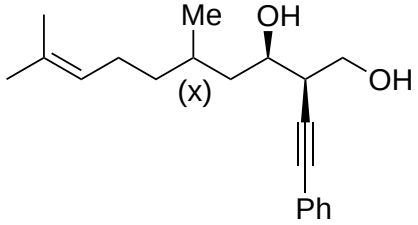
83%, 92:8 dr, 97:3 er



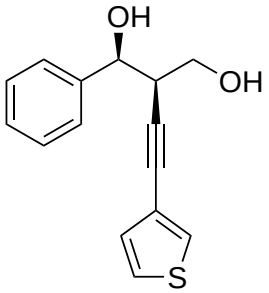
66%, 96:4 dr, 96:4 er



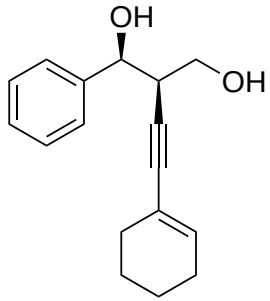
79%, 98:2 dr, 99:1 er



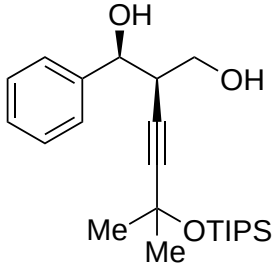
x = R: 74%, 98:2 dr, 98:2 er
x = S: 76%, 98:2 dr, 98:2 er



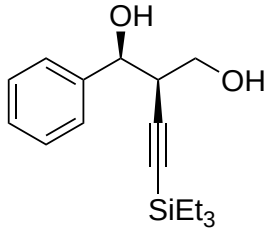
73%, 97:3 dr, 96:4 er



70%, 96:4 dr, 97:3 er



74%, 94:6 dr, 94:6 er



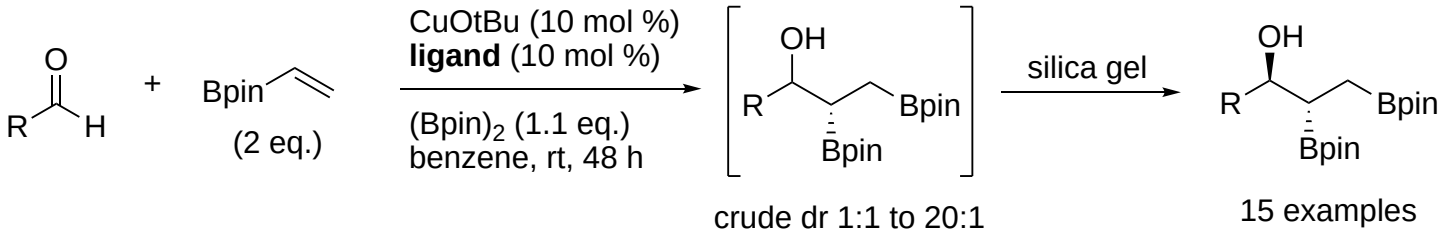
83%, 94:6 dr, 85:15 er

J. Am. Chem. Soc. **2014**, 136, 11304–11307.

Carboborylation: Tandem borylation, aldehyde addition of vinylboronates

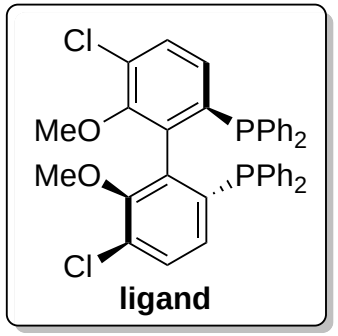
Phosphoramidates and alkyl-substituted phosphine ligands were ineffective at catalyzing the process (yields < 12%).

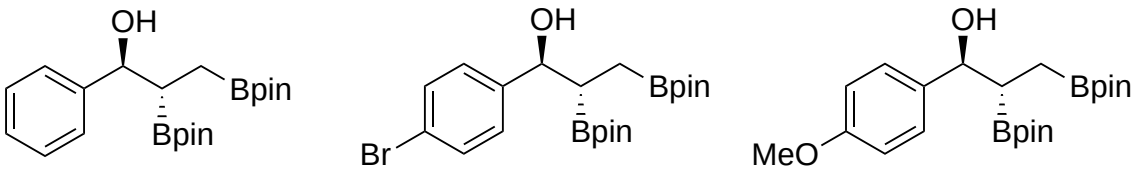
Substitution on aldehyde has only a minor effect on reactivity.



crude dr 1:1 to 20:1

15 examples

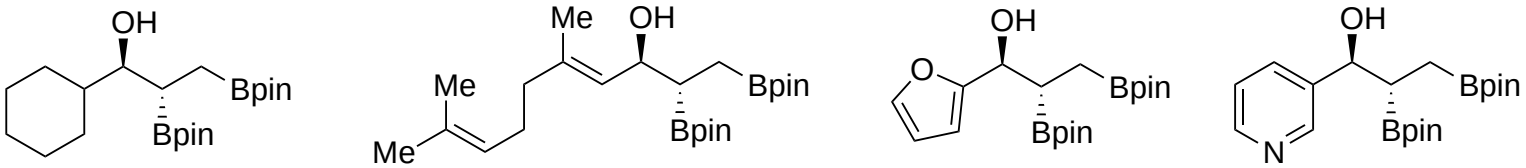




74%, 20:1 dr, 96:4 er

68%, 5.7:1 dr, 95:5 er

70%, 20:1 dr, 94:6 er



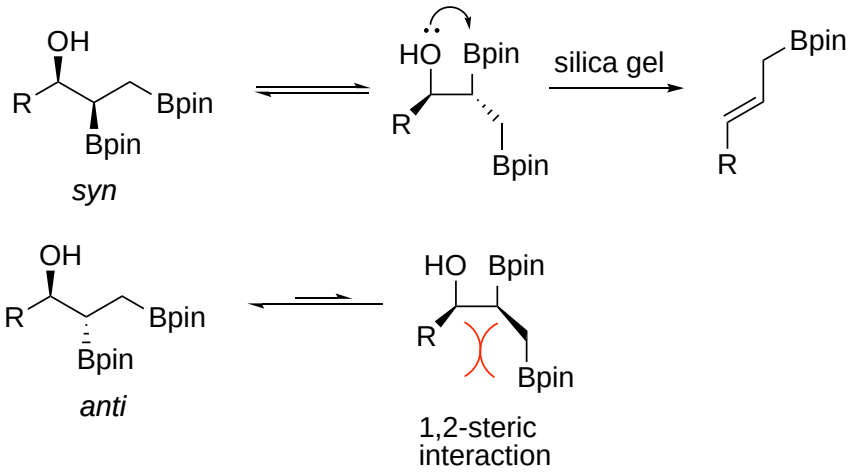
63%, 20:1 dr, 92:8 er

78%, 20:1 dr, 93:7 er

52%, 20:1, 97:3

18% (NMR yield)

Only the *anti* addition product is isolated. The *syn* addition product decomposes on silica gel via a boron Wittig process:

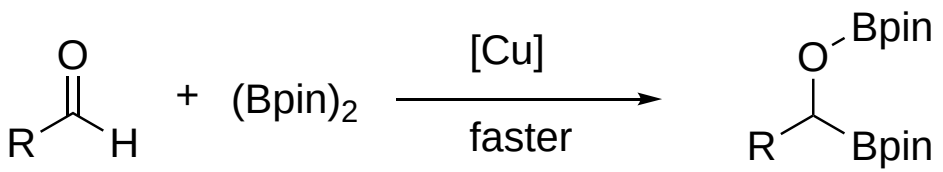


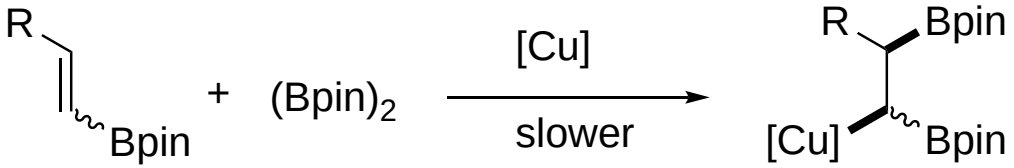
3-heteroarenes remain a challenging substrate under these conditions.

ACS Catal. **2017**, *7*, 4441−4445. *Org. Lett.* **2015**, *17*, 1708−1711.

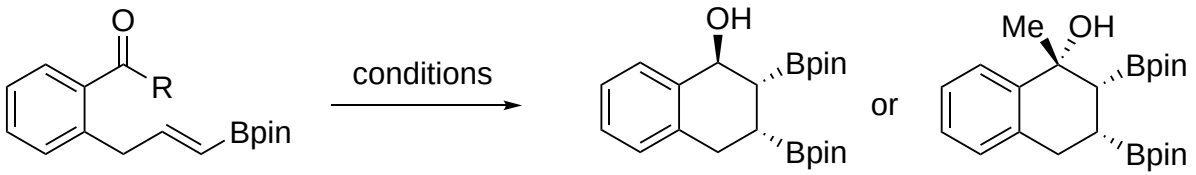
Carboborylation: Tandem borylation, aldehyde addition of vinylboronates

3-component reactions were attempted with β-substitution on the vinylboronate. Diborylation of the aldehyde outcompeted the desired reactivity in these cases:



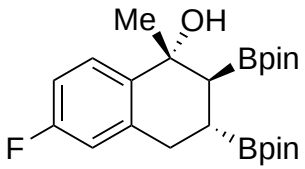


Diastereoselectivity changes when switching to a ketone electrophile:

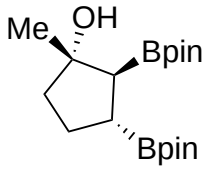


R = H
49%, 20:1 dr,
98.5:1.5 er

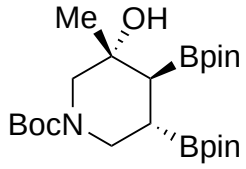
R = Me
95%, 20:1 dr,
94:6 er



73%, 20:1 dr, 95.5:4.5 er

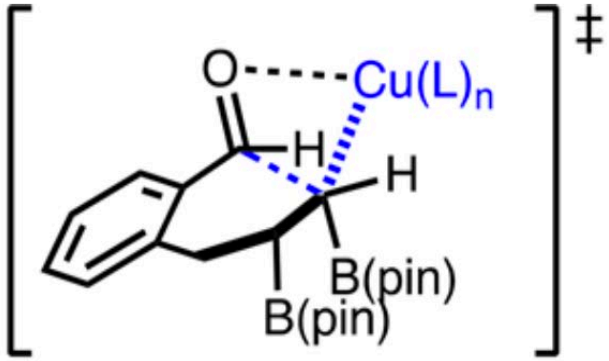


59%, 20:1 dr, 88:12 er

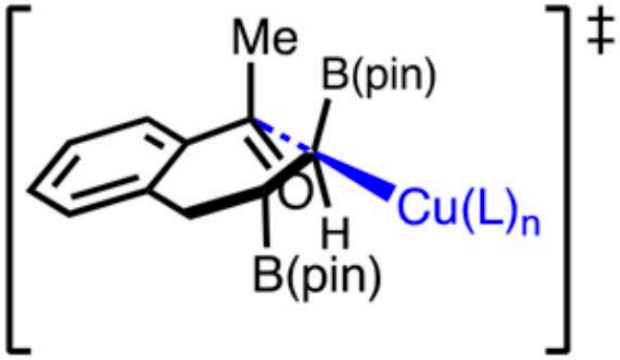


58%, 20:1 dr, 97:3 er

Stereoretentive attack on aldehyde:

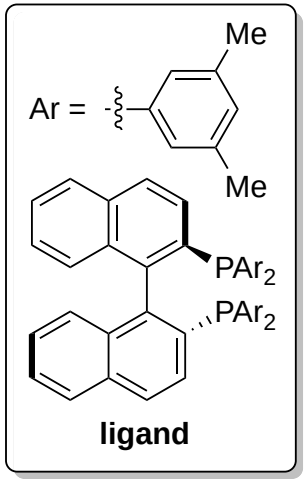


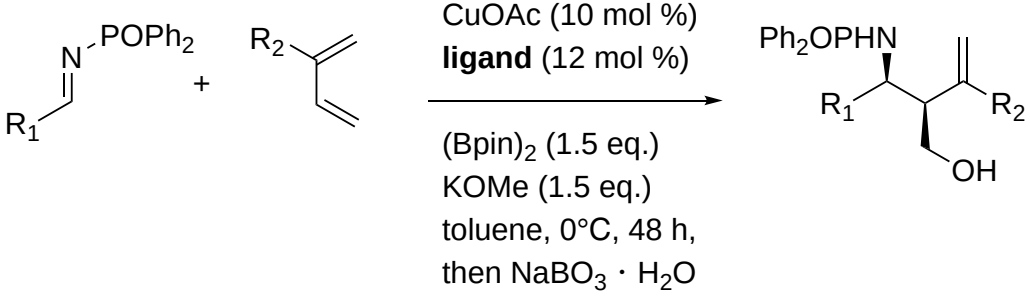
Stereoinvertive attack on ketone:



ACS Catal. **2017**, *7*, 4441–4445. *J. Am. Chem. Soc.* **2006**, *128*, 11036-11037.

Carboborylation: Tandem borylation, aldimine addition of conjugated dienes



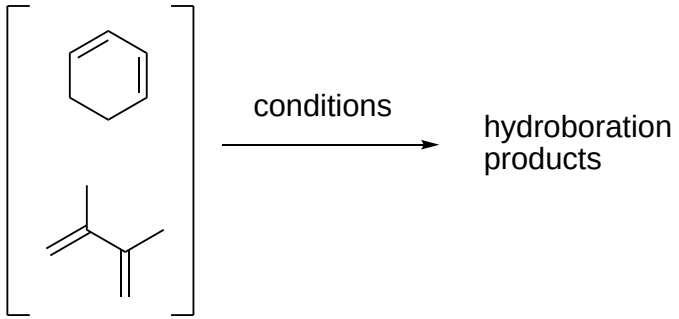


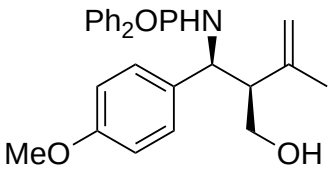
SOP ligands were tried, but gave poor *syn*/*anti* diastereoselectivity.

BINAP ligands were suggested to be important in enforcing a boat-like TS to achieve high diastereoselectivity.

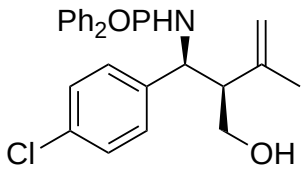
Alkyl-substituted aldimines were not stable to the reaction conditions.

Tetrasubstituted and non-terminal conjugated dienes afforded hydroboration side products:

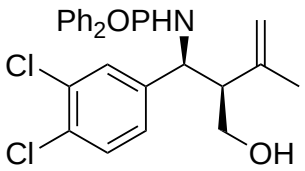




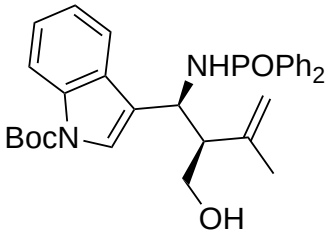
88%, 98% ee



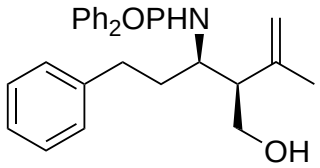
71%, 95% ee



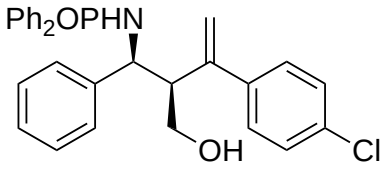
52%, 96% ee



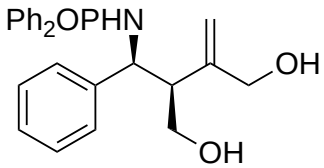
98%, 96% ee



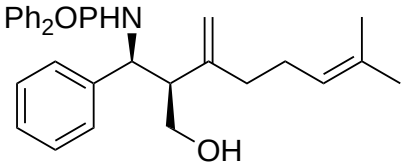
31%, 95% ee, 94:6 dr



69%, 97% ee



45%, 99% ee



99%, 98% ee

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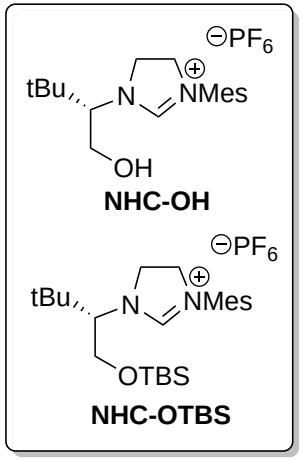
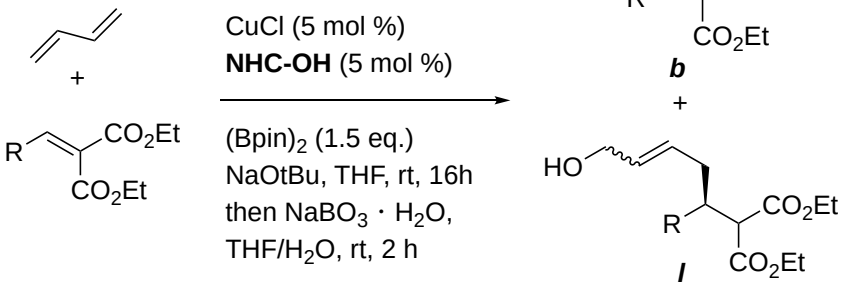
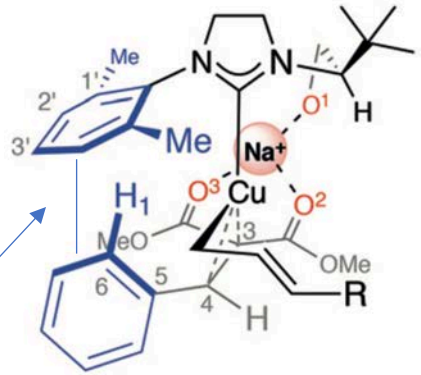
Carboborylation: Tandem borylation, conjugate addition of dienes to diesters

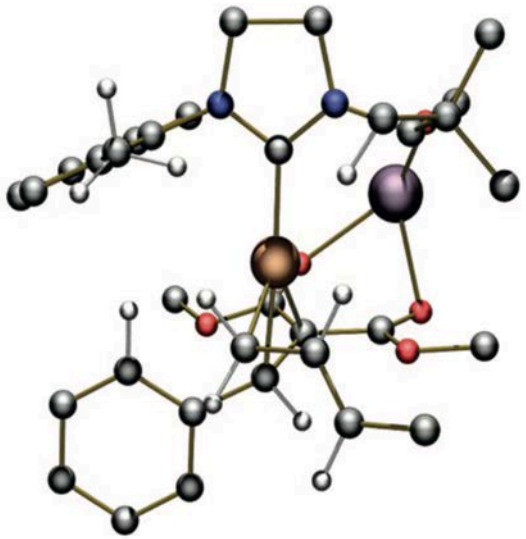


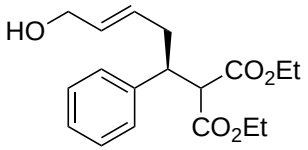


mixture of (E) and (Z)

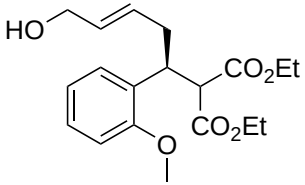
Various bisphosphines and BINAP ligands were tried, but high enantioselectivity required a new ligand, **NHC-OH**. DFT calculations show the OH group is critical in organizing the TS through interaction with an Na ion bound to the diester:



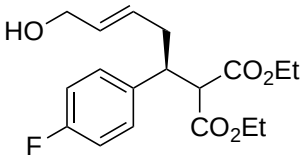




77%, ***l***:***b*** = 98:2,
E:Z = 76:24, 96:4 er
9% Bpin conj. addn.

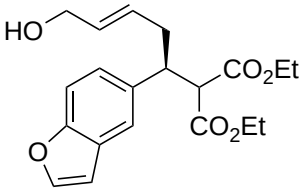


51%, ***l***:***b*** = 98:2,
E:Z = 73:27, 93:7 er
32% Bpin conj. addn.

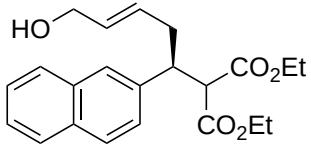


52%, ***l***:***b*** = 98:2,
E:Z = nd, 97:3 er
2% Bpin conj. addn.

Alkyl diesters give more boron conjugate addition product and lower enantioselectivity…
π edge-to-face interaction with aryl substrates stabilizes TS for arene substituted diesters.

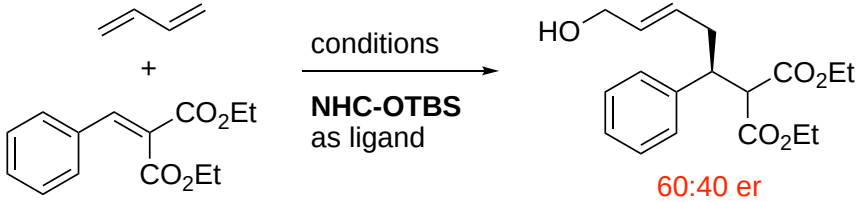


45%, ***l***:***b*** = 98:2,
E:Z = 75:25, 96:4 er
11% Bpin conj. addn.



55%, ***l***:***b*** = 98:2,
E:Z = 74:26, 94:6 er
8% Bpin conj. addn.

Poor enantioselectivity when ligand OH is protected:



60:40 er

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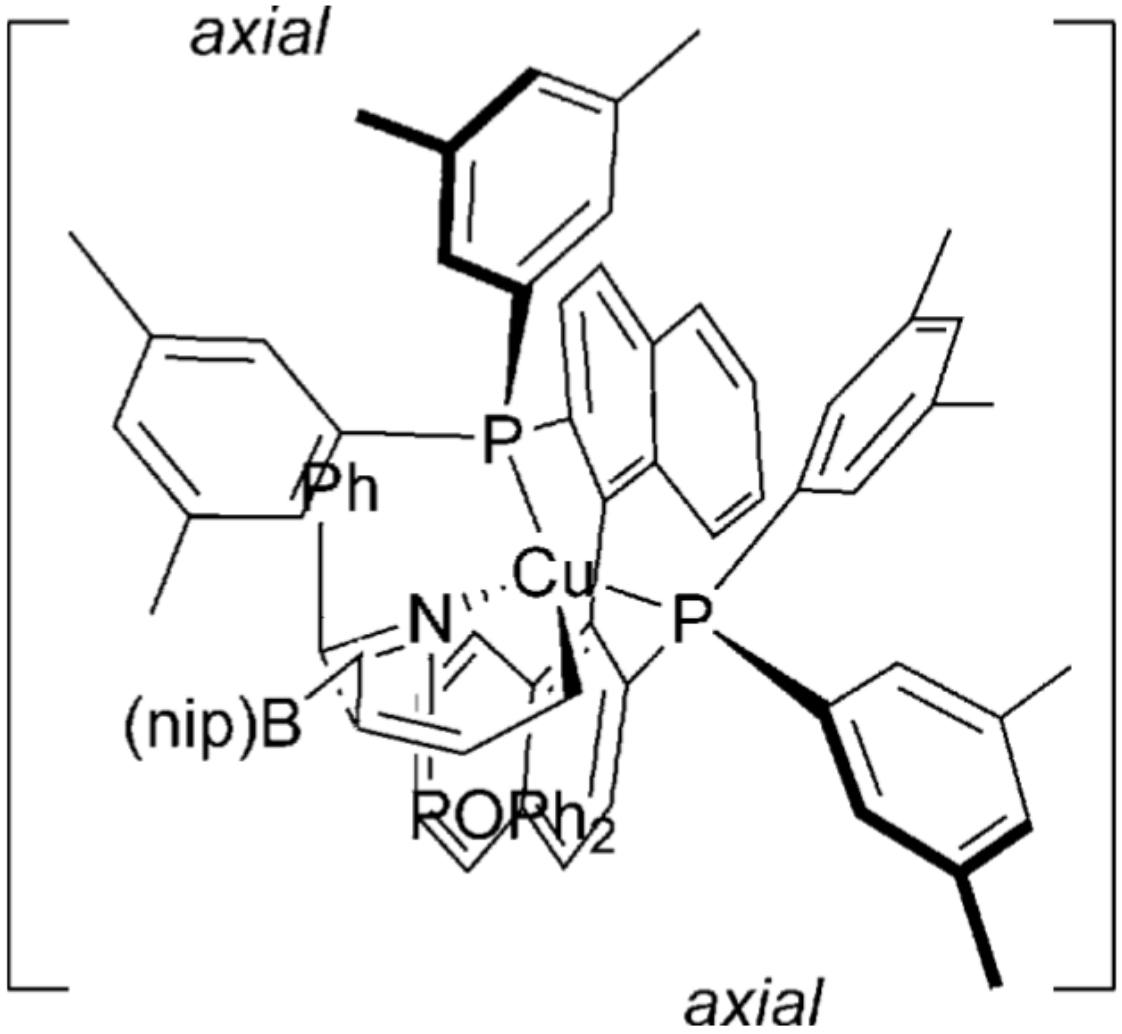
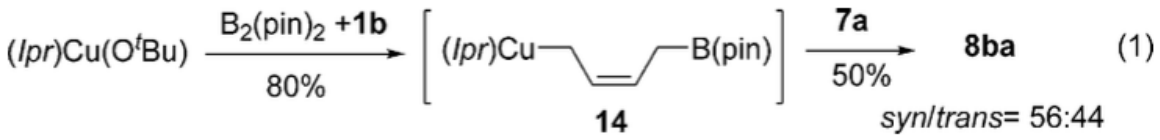
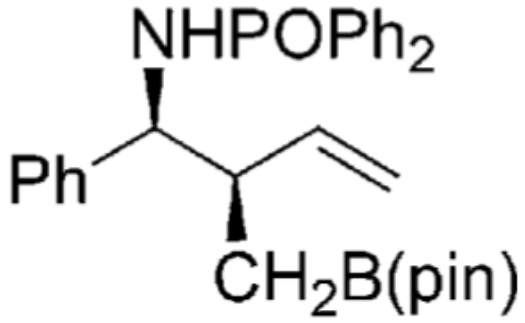
Backup: boat like TS







(*1R*,*2S*)-**8ba**

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