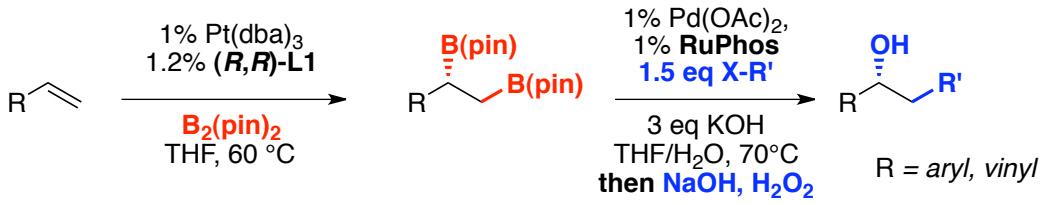
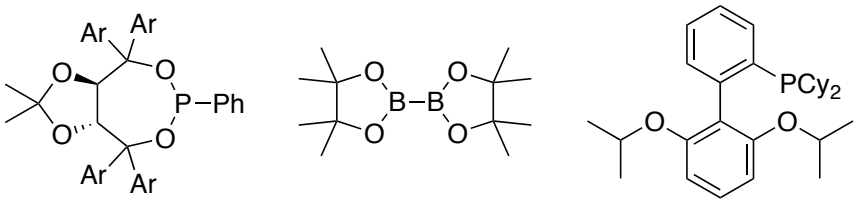
Asymmetric synthesis from terminal alkenes by cascades of diboration and cross-coupling

Scott N. Mlynarski, Christopher H. Schuster & James P. Morken

Nature, **2014**, *505*, 386-390

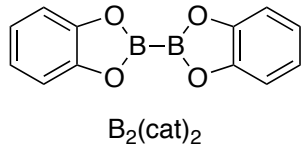




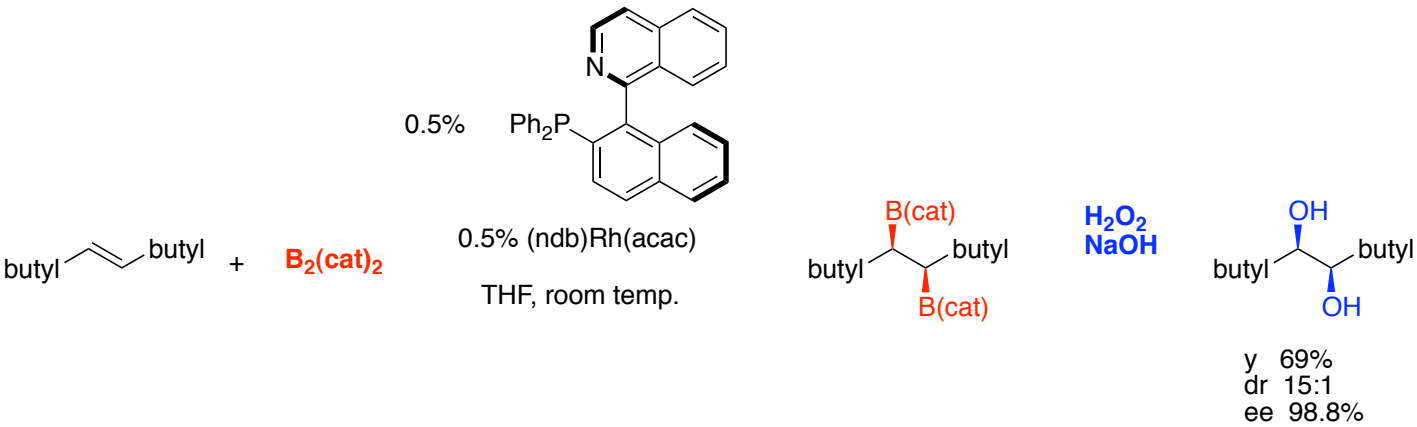
Raffaele Colombo – 1/18/2014

Previous studies – cat. diboration

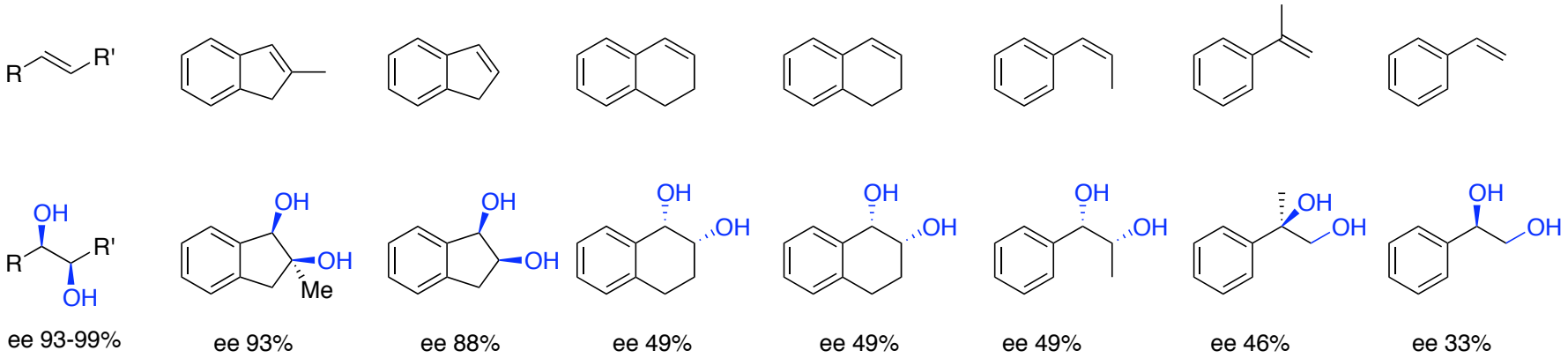
Morken @ University of North Caroline at Chapel Hill



$B_2(cat)_2$



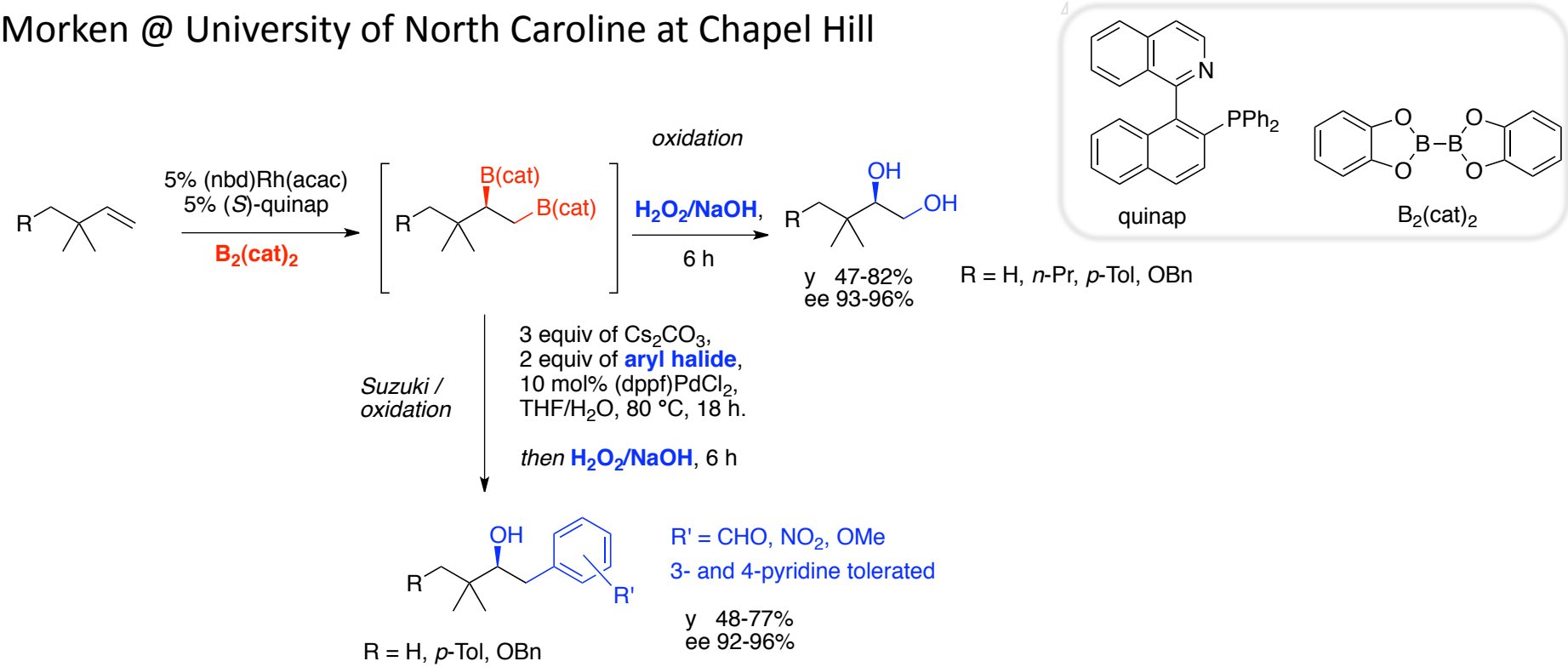
Poor enantioselectivity with trisubstituted-cyclic, *cis*-acyclic and terminal alkenes !



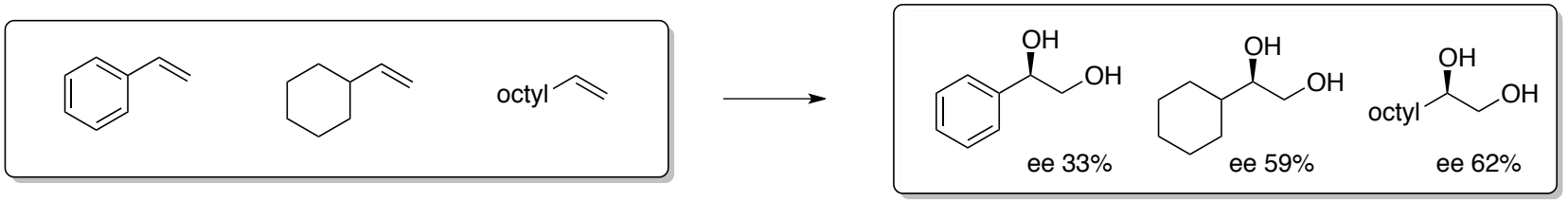
Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702-8703

Previous studies – quinap/$B_2(cat)_2$

Morken @ University of North Caroline at Chapel Hill



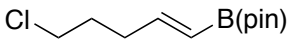
Poor enantioselectivity with more useful substrates



Miller, S. P., Morgan, J. B., Nepveux, F. J., Morken, J. P. *Org. Lett.* **2004**, *6*, 131–133

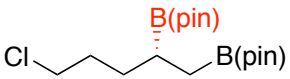
Previous studies – NHC/$B_2(pin)_2$

Hoveyda @ Boston College

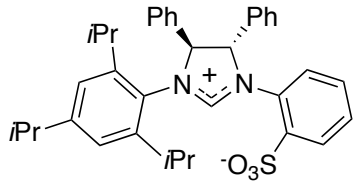


5% **NHC**

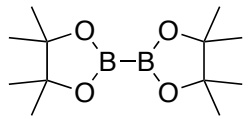
5% CuCl, 20% NaO*t*Bu
1.1 eq $B_2(pin)_2$, 3.0 eq MeOH
THF, -15°C, 24 h



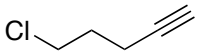
y 88%
ee 88%



NHC

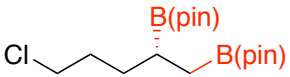


$B_2(pin)_2$



5% **NHC**

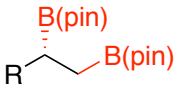
5% CuCl, 20% NaO*t*Bu
2.1 eq $B_2(pin)_2$, 3.0 eq MeOH
THF, -15°C, 24 h



y 90%
ee 90%

5% **NHC**

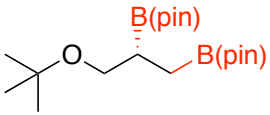
5% CuCl, 20% NaO*t*Bu
2.1 eq $B_2(pin)_2$, 3.0 eq MeOH
THF, -15°C, 24 h



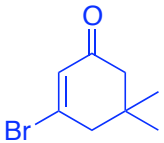
y 60-93%
ee 87-95%

R = *Ph, alkyl*

-O*t*Bu, -NHBoc tolerated

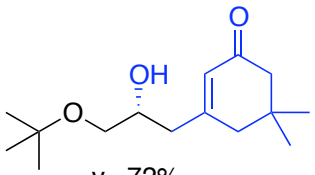


ee 93%



10% $Pd(dppf)Cl_2 \cdot CH_2Cl_2$
3 eq Cs_2CO_3,
10:1 THF/H_2O, 80°C, 14h

then **$NaBO_3 \cdot 4H_2O$**
1:1 THF/H_2O, rt, 1 h

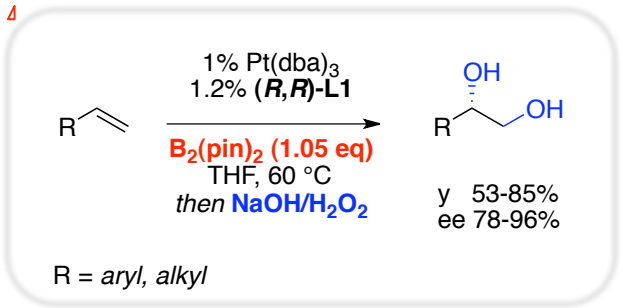


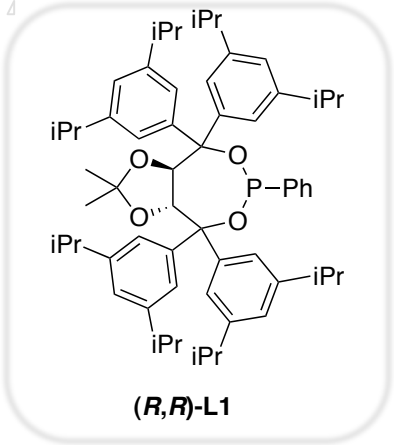
y 72%
ee 93%

Lee, Y.; Jang, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 18234–18235

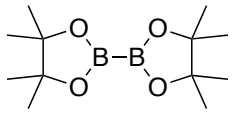
Previous studies – TADDOLPPh/$B_2(pin)_2$

Morken @ Boston College

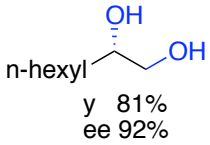


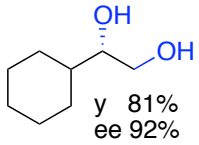


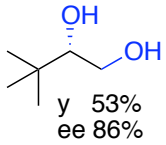
(*R*,*R*)-L1

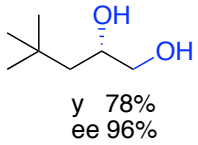


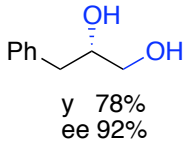
$B_2(pin)_2$

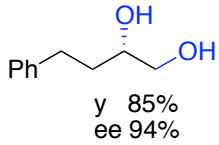


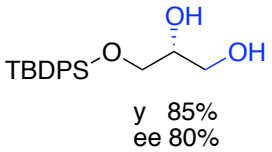


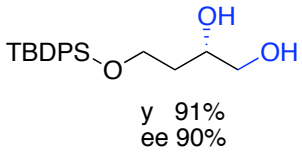


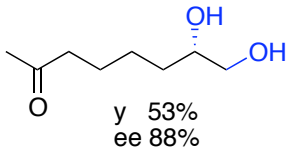


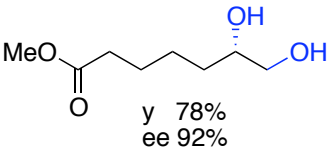


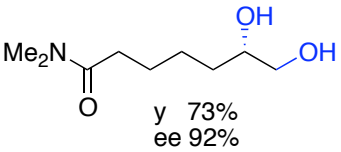


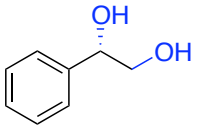


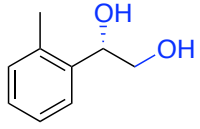


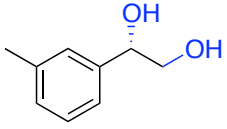


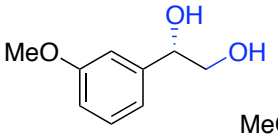


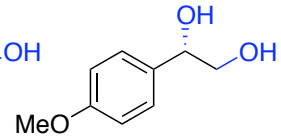


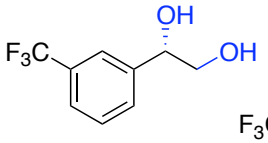


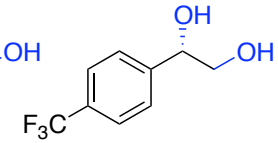








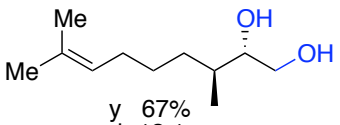
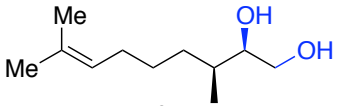
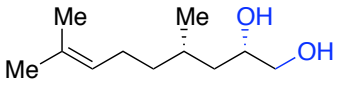
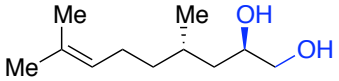
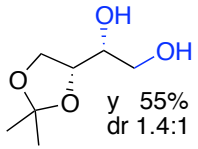
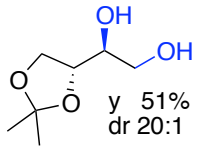
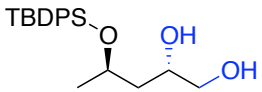
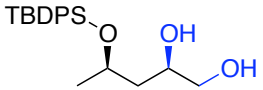


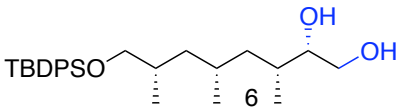


Miller, S. P., Coombs, J. R., Haefner, F., Kliman, L. T., Morken, J. P. *J. Am. Chem. Soc.* **2013**, *135*, 11222–11231

Scope of the reaction

Diastereoselectivity:

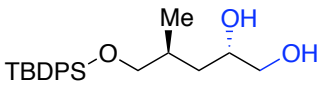
(*R*,*R*)-L1	(*S*,*S*)-L1
 y 67% dr 12:1	 y 70% dr 20:1
 y 82% dr >20:1	 y 76% dr >20:1
 y 55% dr 1.4:1	 y 51% dr 20:1
 y 89% dr 18:1	 y 86% dr 20:1



y 98%
de >95%

Minnard *et al.*
Total synthesis of diacylated sulfoglycolipid Ac_2SGL

Chem. Sci., 2013, **4**, 709



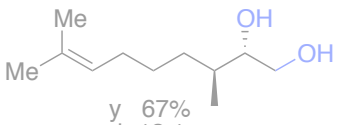
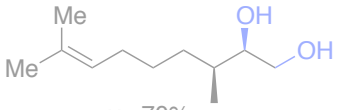
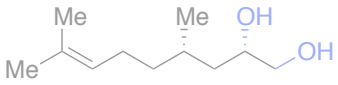
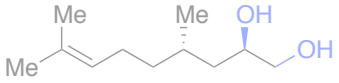
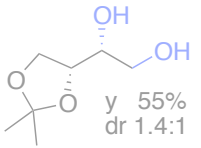
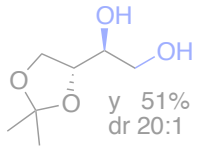
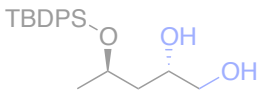
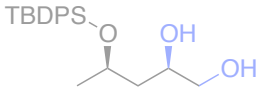
y 70-90%
dr 12:1

Shindo *et al.*
Total synthesis of Xantathin

Tetrahedron, 2013, **69**, 1043

Scope of the reaction

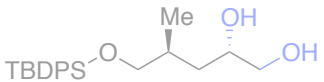
Diastereoselectivity:

(*R*,*R*)-L1	(*S*,*S*)-L1
 y 67% dr 12:1	 y 70% dr 20:1
 y 82% dr >20:1	 y 76% dr >20:1
 y 55% dr 1.4:1	 y 51% dr 20:1
 y 89% dr 18:1	 y 86% dr 20:1


y 98%
de >95%

Minnard *et al.*
Total synthesis of diacylated sulfoglycolipid Ac_2SGL

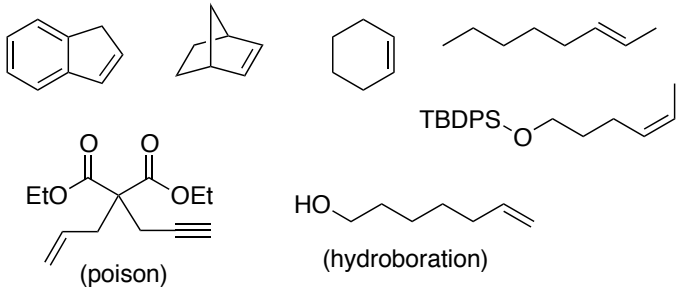
Chem. Sci., 2013, **4**, 709


y 70-90%
dr 12:1

Shindo *et al.*
Total synthesis of Xantathin

Tetrahedron, 2013, **69**, 1043

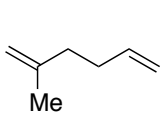
Unreactive substrate:



(poison)

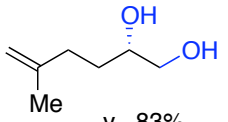
(hydroboration)

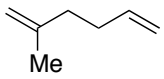
Sharpless vs. Morken:



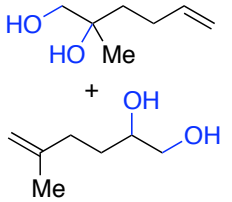
1% $Pt(dba)_3$
1.2% (***R*,*R*)-L1**

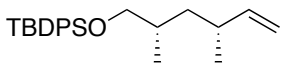
$B_2(pin)_2$ (1.05 eq)
THF, 60 °C
then $NaOH/H_2O_2$

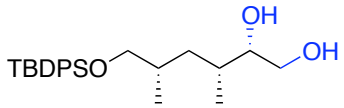

y 83%
ee 94%



(DHQD)-PHAL
$K_3Fe(CN)_6$

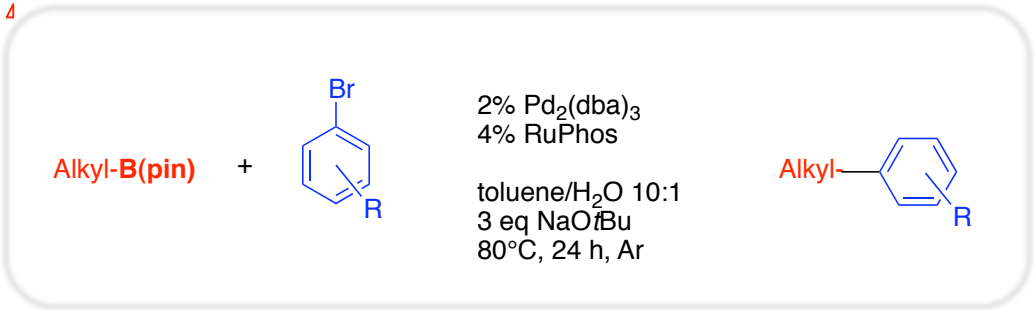

y 42%
5:1 mixture

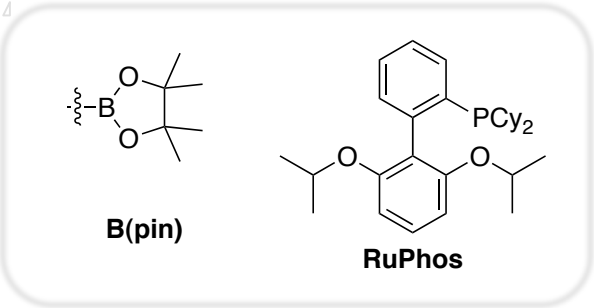


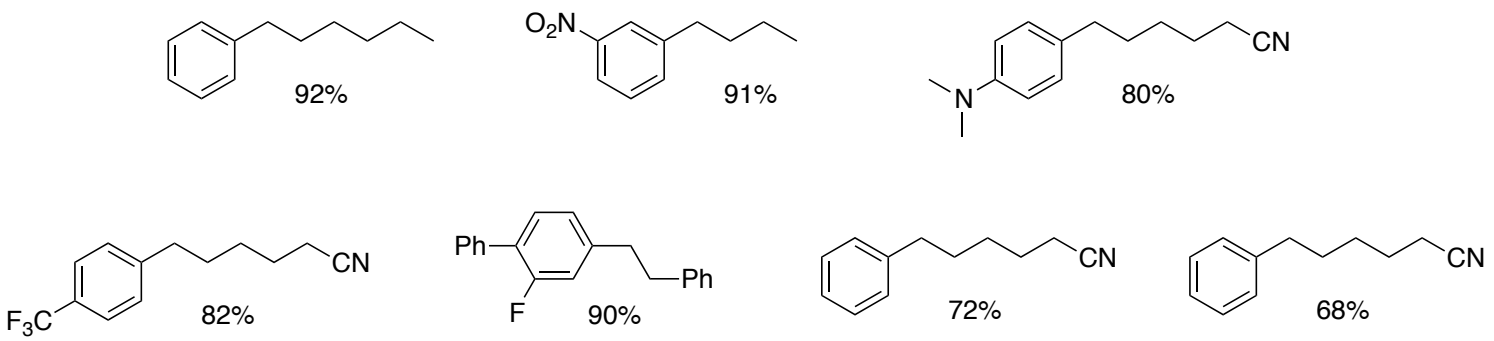


Sharpless: y 79%, de 70%
Morken: y 75%, de >95%

Alkyl pinacol boronates – Suzuki coupling

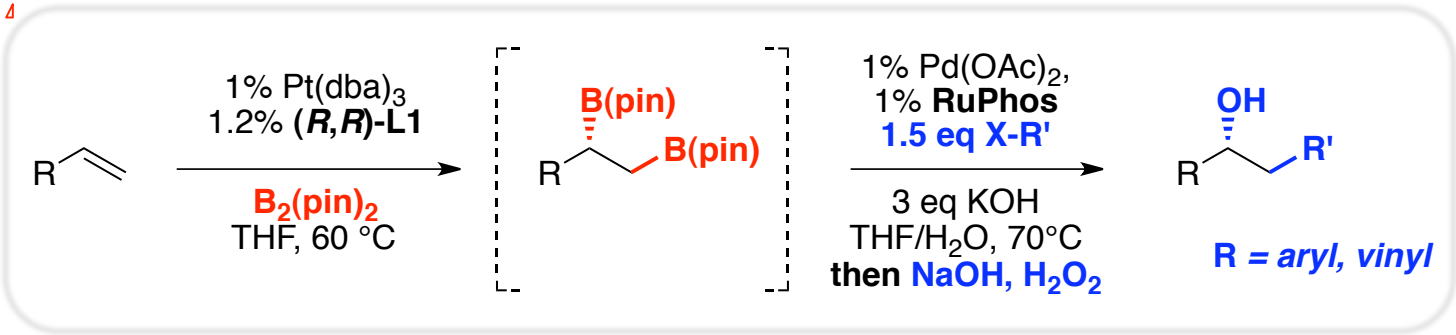


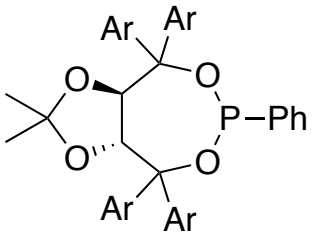




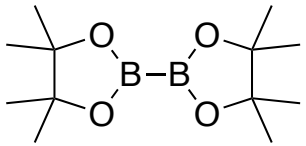
Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-L.; Fu, Y.; Czyzewska, M.; Steel, P. G.; **Marder**, T. B.; **Liu**, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 528–532

This work: DCC (diboration cross-coupling cascade)

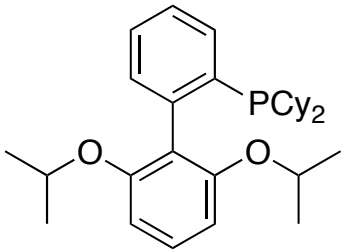




(*R*,*R*)-L1

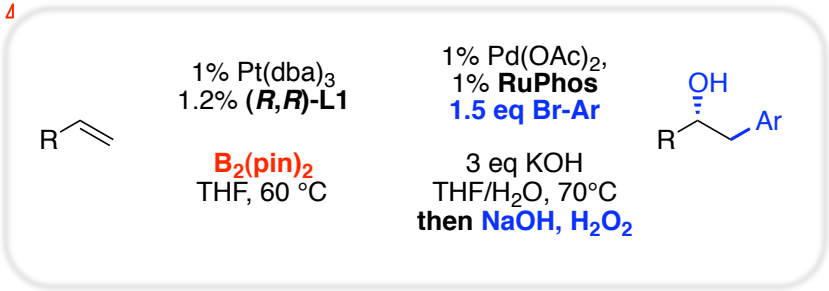


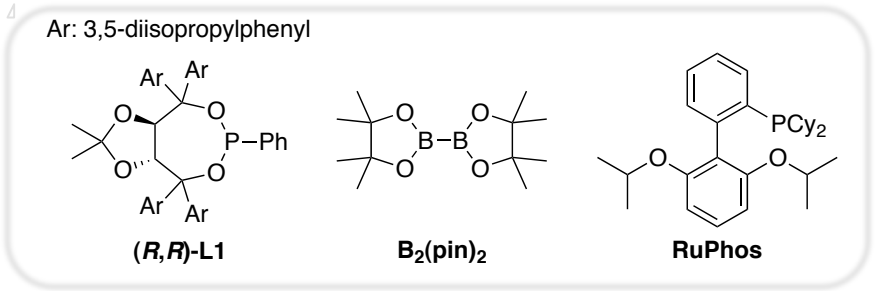
$B_2(pin)_2$

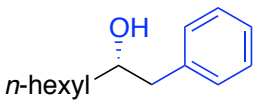


RuPhos

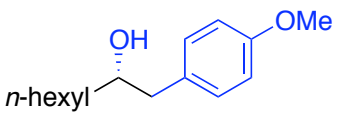
Diboration / aryl bromide coupling



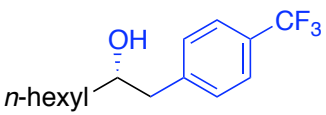




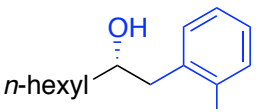
y 96%
ee 94%



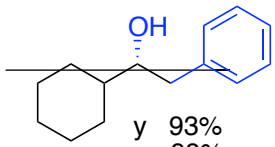
y 91%
ee 94%



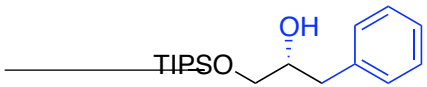
y 85%
ee 94%



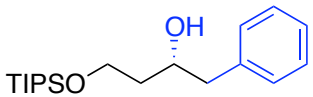
y 80%
ee 88%



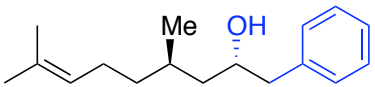
y 93%
ee 98%



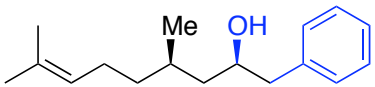
y 82%
ee 88%



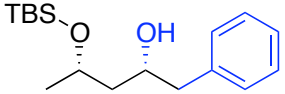
y 97%
ee 90%



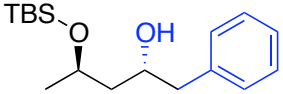
y 97%
dr 20:1



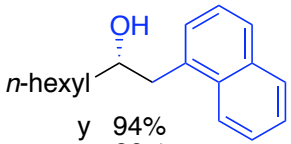
y 96%
dr 20:1



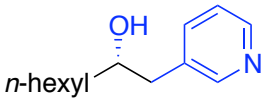
y 88%
dr 20:1



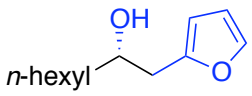
y 94%
dr 17:1



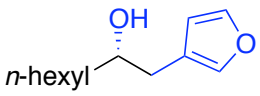
y 94%
ee 90%



y 86%
ee 94%

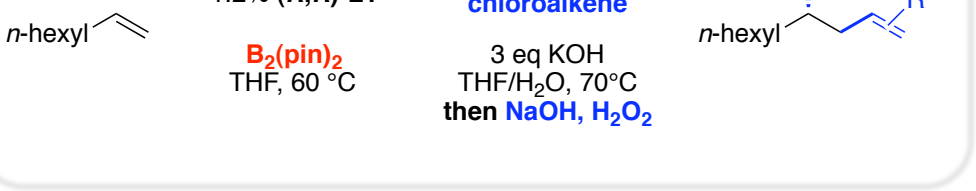


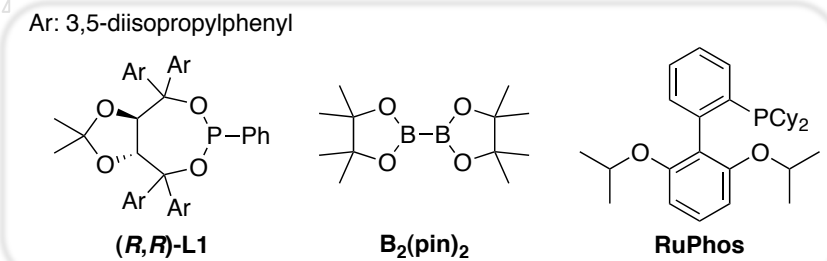
y 79%
ee 92%

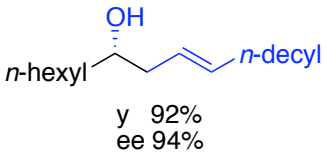


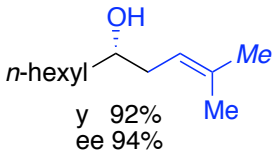
y 63%
ee 92%

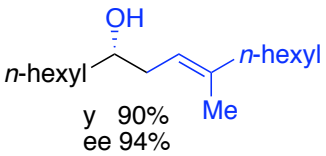
Diboration / chloroalkene coupling

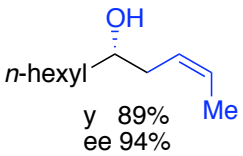


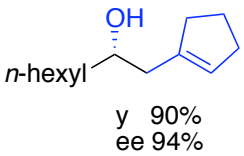


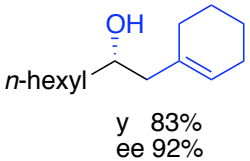


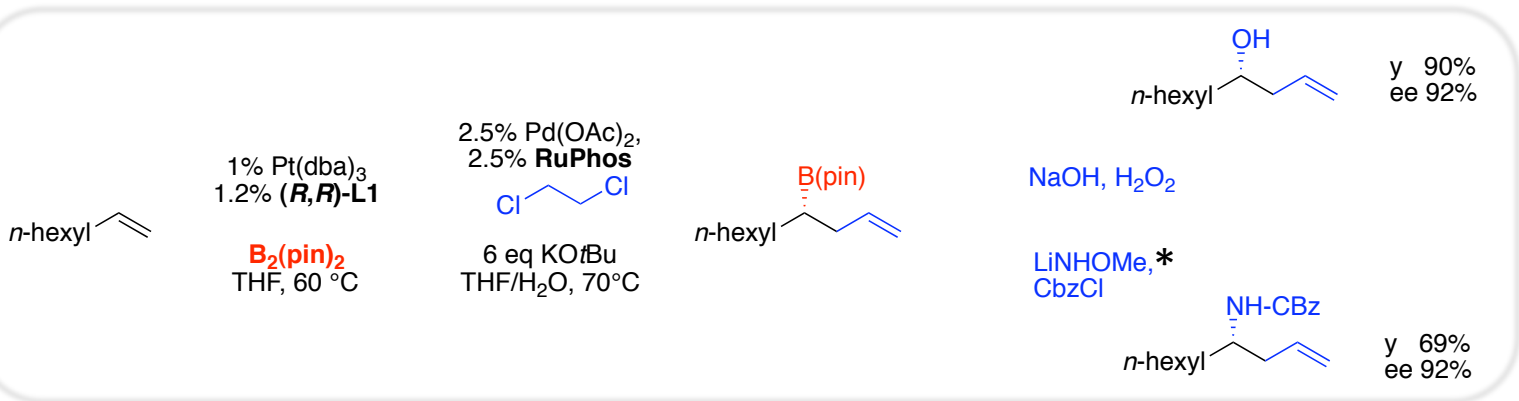






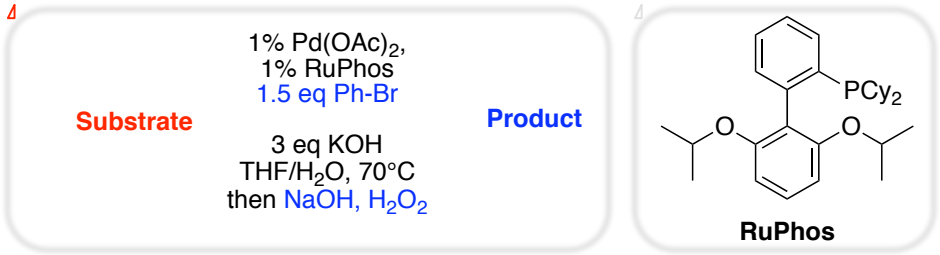




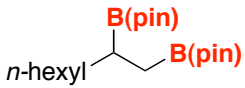


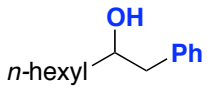
* For stereospecific amination of alkyl and aryl pinacol boronates see: Morken *et al. J. Am. Chem. Soc.* **2012**, *134*, 16449–16451

Mechanism considerations



RuPhos





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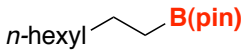

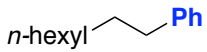

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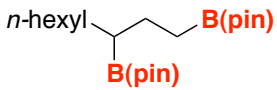

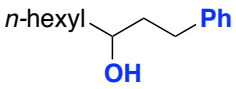

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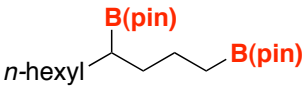

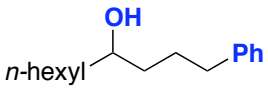

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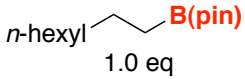
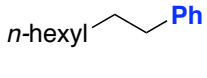




2%

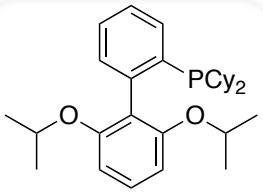
96%

Effect of vicinal bis-boronate

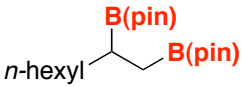
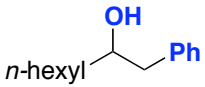
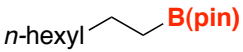
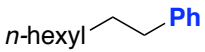
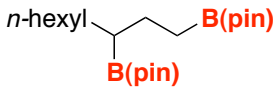
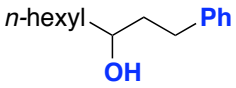
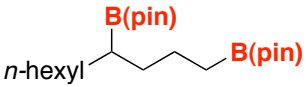
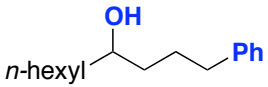
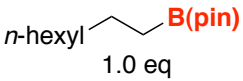
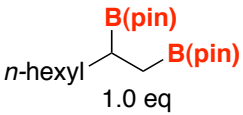
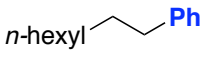
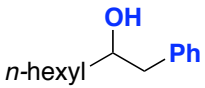
Substrate → **Product**

1% $Pd(OAc)_2$,
1% RuPhos
1.5 eq Ph-Br

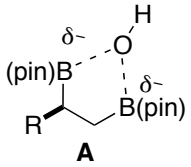
3 eq KOH
THF/H_2O, 70°C
then NaOH, H_2O_2



RuPhos

Substrate	Product	
		**91%**
		<5%
		<5%
		9%
 1.0 eq +  1.0 eq	 + 	2% + **96%**

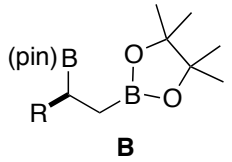
Internal Lewis base donation



A

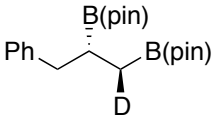
(outer-sphere path)
inversion

internal Lewis acid activation



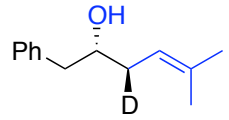
B

(inner-sphere path)
retention



1% $Pd(OAc)_2$,
1% RuPhos
chloroisobutylene

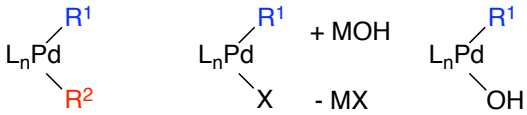
3 eq KOH
THF/H_2O, 70°C
then NaOH, H_2O_2



R^1-R^2

L_nPd

R^1-X

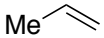


R^2-BY_2 or R^2-$\overset{-}{B}Y_2$ Z

neutral *anionic*

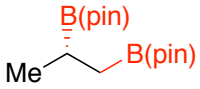
Applications: *N*-Boc-(*S*)-amphetamine & (*S*)-fenpropimorph

N-Boc-(*S*)-amphetamine



1% $Pt(dba)_3$
1.2% **(*R*,*R*)-L1**

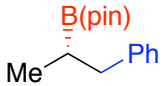
$B_2(pin)_2$
THF, 60 °C



y 98%
ee 92%

1% $Pd(OAc)_2$,
1% **RuPhos**
1.1 eq Ph-Br

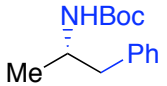
3 eq KOH
THF/H_2O, 70°C



83%

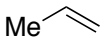
$MeONH_2$
***t*-BuLi**, THF,
-78°C to 60°C

then Boc_2O



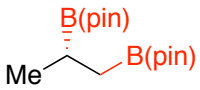
y 74%
(60% over 3 steps)
ee 92%

(*S*)-Fenpropimorph



1% $Pt(dba)_3$
1.2% **(*R*,*R*)-L1**

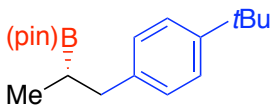
$B_2(pin)_2$
THF, 60 °C



y 98%
ee 92%

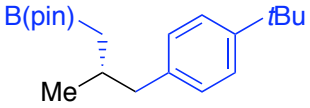
1% $Pd(OAc)_2$,
1% **RuPhos**
1.1 eq 4-*t*BuPh-Br

3 eq KOH
THF/H_2O, 70°C



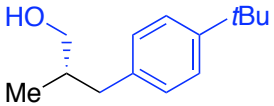
95%

$Cl\text{-}CH_2\text{-}Li$
-78°C to rt



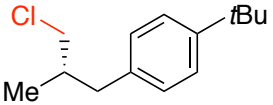
Organometallics, **1985,** *4,* 1687-1689

then
$NaOH, H_2O_2$

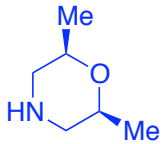


85%

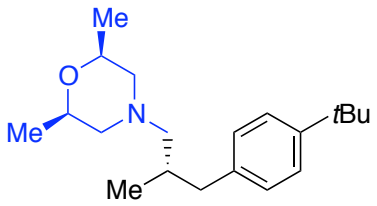
NCS, Ph_3P



75%



DMF, 120°C

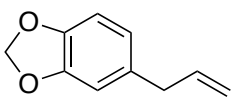


82%
(52% over 5 steps)

Fungicide (40000 tons/year)

Applications: lignan precursor & (*S*)-pregabalin

Lignan Lactone Precursor

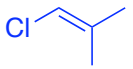


Safrole

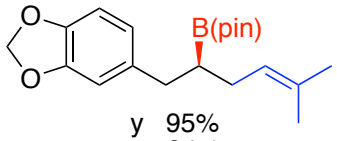
1% $Pt(dba)_3$
1.2% **(*S*,*S*)-L1**

$B_2(pin)_2$
THF, 60 °C

2.5% Pd(OAc)
2.5% **RuPhos**

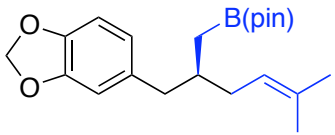


3 eq KOH
THF/H_2O, 70°C

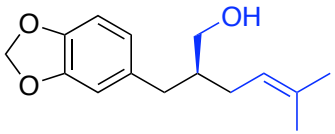


y 95%
ee 94%

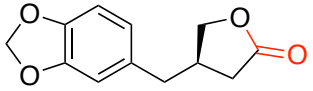
$Cl\text{-}CH_2\text{-}Li$
-78°C to rt



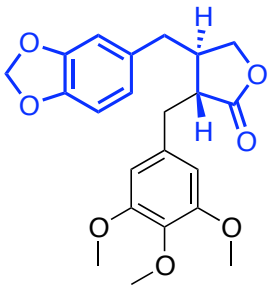
then
$NaOH, H_2O_2$



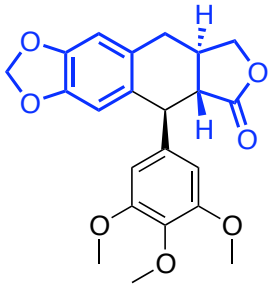
O_3, NaOH,
CH_2Cl_2, MeOH



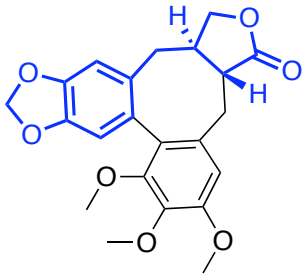
53% (over two steps)
50% (from safrole)



(-)-yatein

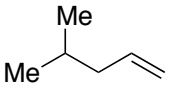


(-)-isodeoxypodophyllotoxin



(+)-isostegane

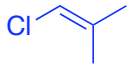
(S)-(+)-Pregabalin Hydrochloride



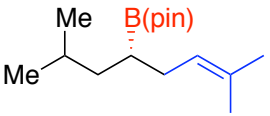
1% $Pt(dba)_3$
1.2% **(*R*,*R*)-L1**

$B_2(pin)_2$
THF, 60 °C

2.5% Pd(OAc)
2.5% **RuPhos**



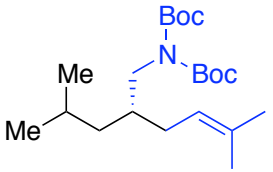
3 eq KOH
THF/H_2O, 70°C



y 97%
ee 95%

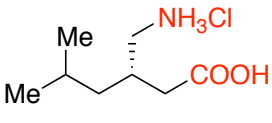
1) **$Cl\text{-}CH_2\text{-}Li$**
-78°C to rt

2) **$MeONH_2$**
***t*-BuLi**, THF,
-78°C to 60°C,
then **Boc_2O**, 60°C



1) **5% RuCl**
$NaIO_4$, rt,
$CH_3CN/CCl_4/H_2O$

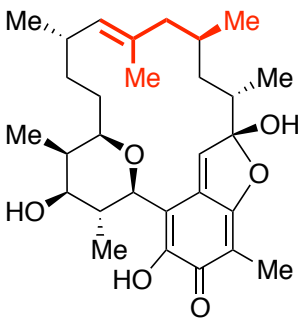
2) **HCl**, MeOH



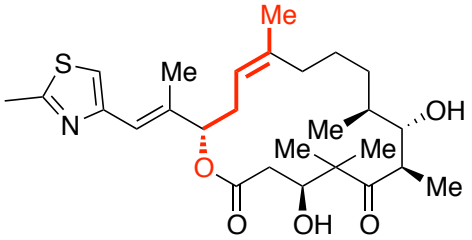
35% (over 5 steps)

Lyrica, Nervalin: anticonvulsant drug used for neuropathic pain

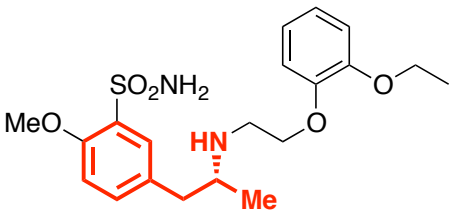
Potential applications



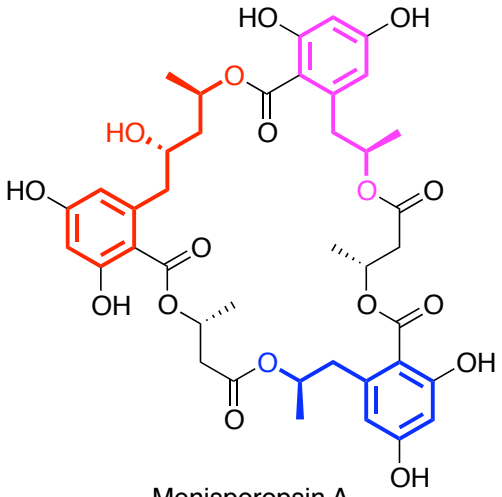
Kendomycin
antitumor macrolide antibiotic



Epothilone C
anticancer drug



Tamsulosin
(Flowmax)
apha1a-selective alpha blocker used in the symptomatic treatment of benign prostatic hyperplasia



Menisporopsin A
antimalarial, antimycobacterial, and cytotoxic activities


Here We Go
Steelers
Here We Go
Wipf Group

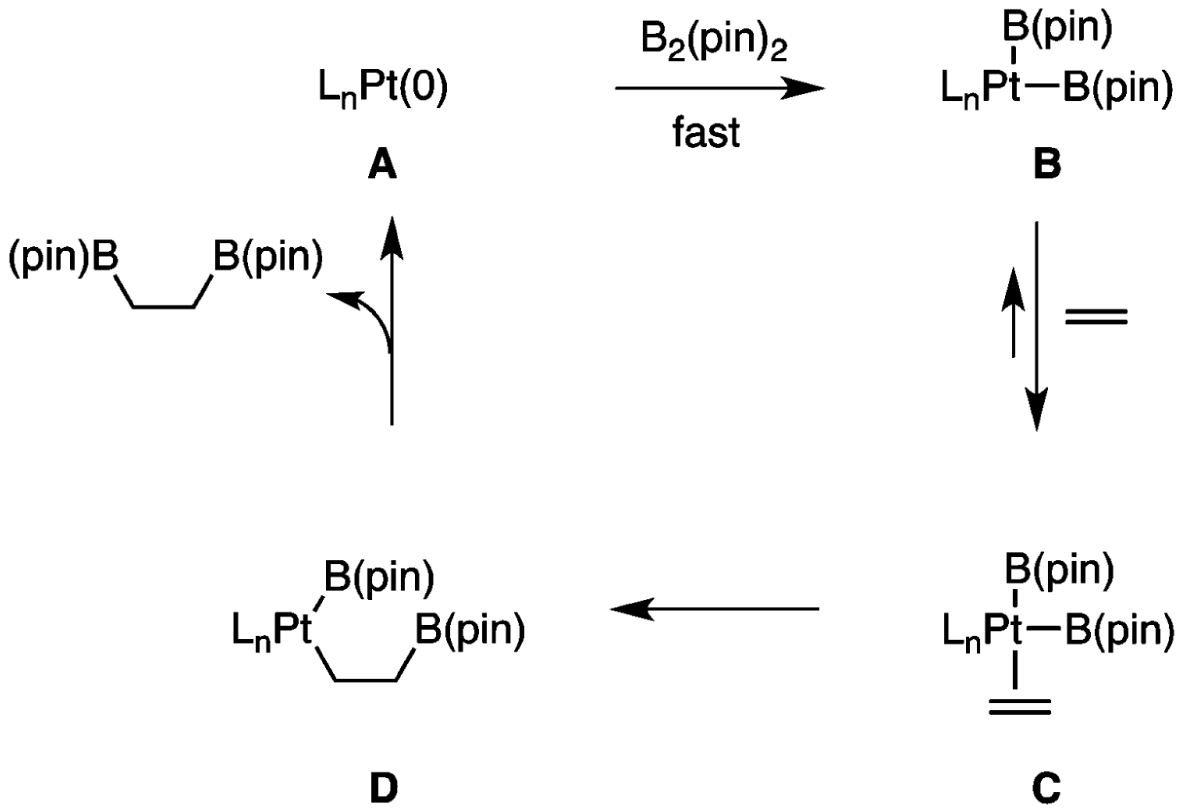
Key step procedures

$Pt(dba)_3$ (1.0 mol%), (*R,R*)-**L1** (1.2 mol%), $B_2(pin)_2$ (1.05 equiv.) and anhydrous THF ([substrate] = 1.0 M) are stirred together at 80 °C for 15 min. After cooling to ambient temperature, the alkene (1.0 equiv.) is added and the reaction mixture is stirred at 60 °C for 3 h.

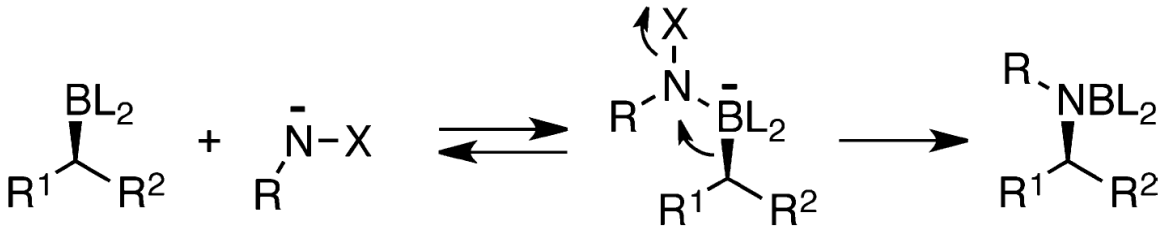
On cooling to ambient temperature, $Pd(OAc)_2$ (1.0 mol%), followed by RuPhos (1.0 mol%), the electrophile (1.5 equiv.), KOH (3.0 equiv.), additional THF and deoxygenated water ([substrate] = 0.1 M; 10:1 v:v THF:H2O) are added and the reaction mixture is heated to 70 °C for 12 h.

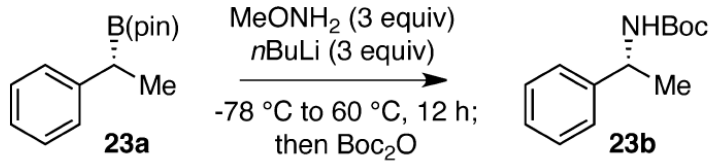
The reaction is then cooled to 0 °C and treated with 3 M aqueous NaOH and 30% H_2O_2. After 4 h at ambient temperature, excess H_2O_2 is carefully quenched with saturated aqueous $Na_2S_2O_3$, followed by extraction with ethyl acetate. The combined organics are dried over Na_2SO_4, filtered and concentrated. The resulting material is purified by flash chromatography on silica gel…

formation of diboronate



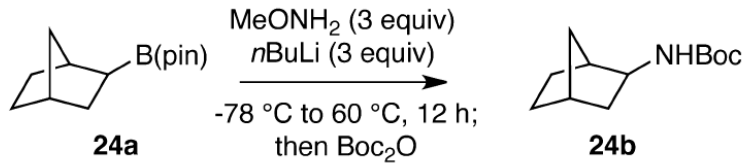
Stereoselective amination



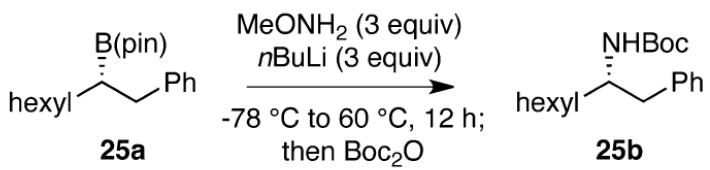


83% ee

84% yield
83% ee



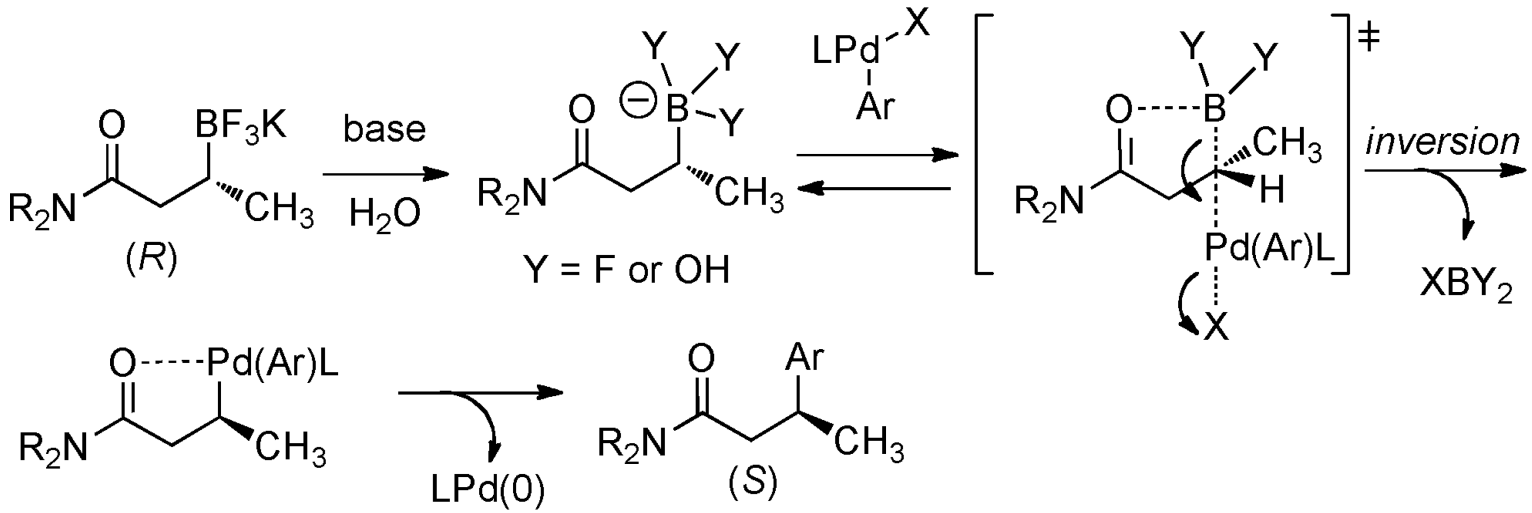
50% yield



93% ee

78% yield
93% ee

Outer sphere - inversion



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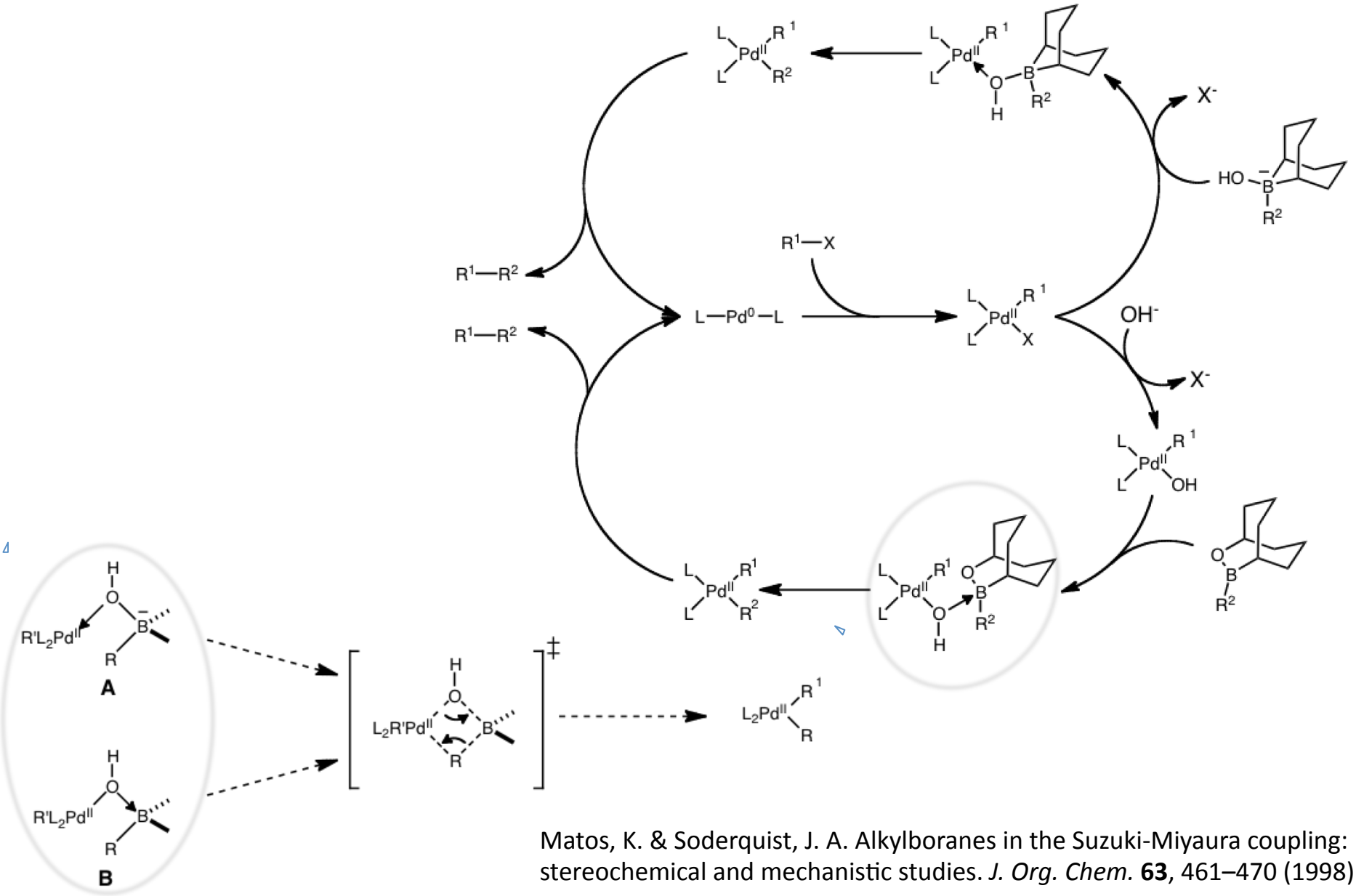
Inner sphere - retention



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