B-Alkyl Suzuki Couplings

MacMillan Group Meeting
Nicole Goodwin
February 16, 2005

B-*Alkyl Suzuki Couplings*

Outline

- Introduction
- Mechanism of the general Suzuki Coupling with Pd(0)
  - oxidative addition
  - transmetalation - emphasis on *B*-alkyl systems
  - reductive elimination
  - phosphine ligand effects
  - nickel
- Synthesis of alkyl boranes and borates - hydroboration
- Reaction Scope with *B*-alkyl substrates
  - Aryl and Vinyl Halides and Triflates
  - Aryl chlorides
  - Potassium alkyltrifluoroborates
  - Alkyl halides and triflates
  - Asymmetric system
  - Macrocyclization
- *B*-alkyl Suzuki couplings in natural products

Relevant and Comprehensive Reviews:

Chemler, S. R.; Trauner, D.; Danishefsky, S. J. "The *B*-alkyl Suzuki-Miyaura cross-coupling reaction: a versatile C–C bond-forming tool." *Angew. Chem. Int. Ed.* **2001**, *40*, 4544-4568.

Miyaura, N. "Metal-Catalyzed Cross-Coupling Reactions of Organoboron Compounds with Organic Halides." Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions, 2nd Edition.* Wiley-VCH, Weinheim, **1998**, Ch. 2.

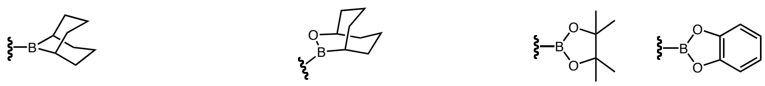
Echavarren, A.M.; Cardenas, D. J. "Mechanistic Aspects of Metal-Catalyzed C,C- and C,X-Bond-Forming Reactions." Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions, 2nd Edition.* Wiley-VCH, Weinheim, **1998**, Ch. 1.

Miyaura, N; Suzuki, A. "Transition-Metal Systems Bearing a Nucleophilic Carbene Ancillary Ligand: from Thermochemistry to Catalysis." *Chem. Rev.* **1995**, *95*, 2457-2483.

B-*Alkyl Suzuki Couplings*

Abbreviations

- Boron substituents



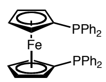
9-BBN-H
9-borabicyclo[3.3.1]nonane

OBBD
9-oxa-10-borabicyclo[3.3.2]decane

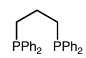
Bpin
B-pinacol

Bcat
B-catechol

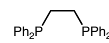
- Some ligands



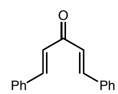
dppf
bis(diphenylphosphanyl)ferrocene



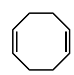
dppp
bis(diphenylphosphanyl)propane



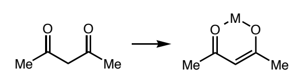
dppe
bis(diphenylphosphanyl)ethane



dba
dibenzylideneacetone



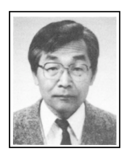
cod
cyclooctadiene



acac
acetylacetonate

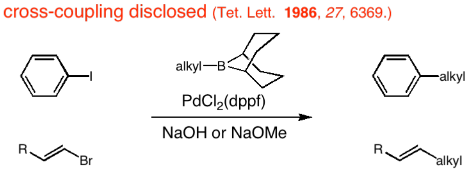
Suzuki and Miyaura in the 80s

Akira Suzuki



Norio Miyaura

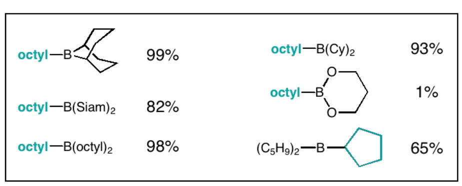
- 1981 - Arylboron cross-coupling disclosed (Synth. Commun. **1981**, 11, 513.)
- 1983 - Alkenylboron cross-coupling disclosed (Tetrahedron. **1983**, 39, 3271.)
- 1986 - Alkylboron cross-coupling disclosed (Tet. Lett. **1986**, *27*, 6369.)

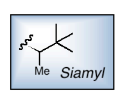


- 1989 - Full report reveals reactivity of alkyl boranes (*JACS*. **1989**, *111*, 314.)

R-BR_2 I-Ph $\xrightarrow[\text{NaOH, THF/}H_2O\text{, 65 °C or } K_2CO_3\text{, DMF/THF, 50 °C}]{PdCl_2(dppf)}$ R-Ph

K_2CO_3, DMF/THF, 50 °C ← *for base-sensitive compounds*





Why Boron?

■ The appeal of the Suzuki coupling can be attributed to

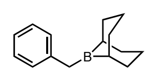
- mild and versatile methods for synthesizing boranes
- easy incorporation of non-transferable boron ligands
- commercial availability of boronates and boronic acids

  Aldrich and Frontier Scientific sell over 100 boronic acids each
- tolerance of a broad range of function groups
- air-stable
- water tolerant
- non-toxic nature of starting materials and borate by-products

■ Drawbacks to the *B*-alkyl Suzuki couplings

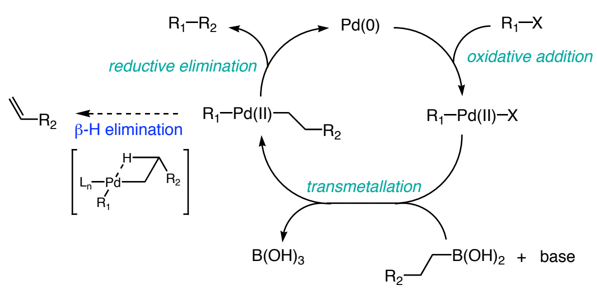
- not air-stable
- trialkylboranes must be synthesized *in situ* without isolation
- not commercially available

  10 alkyl boronic acids/esters available, only 1 alkyl BBN available



The Catalytic Cycle

■ The catalytic cycle of the Suzuki-Miyaura alkyl coupling is similar to other metal-catalyzed couplings



■ The *B*-alkyl Suzuki coupling is effected by all reaction partners

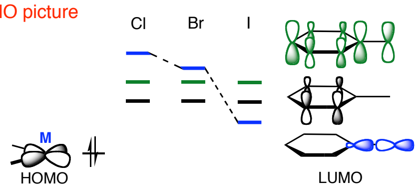
- type of organoborane
- type of aryl/alkenyl/alkyl halide
- base
- solvent
- metal catalyst

The Catalytic Cycle
Oxidative Addition

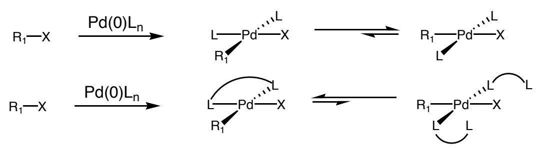
- Competition experiments determined the order of reactivity for oxidative addition

I >> Br > OTf >> Cl

- Qualitative FMO picture

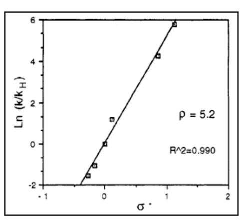


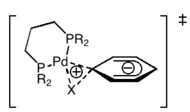
- Bidentate ligands keep a *cis* complex (also a huge factor in facilitating reductive elimination and thus preventing of β-H elimination of alkyl–M complexes)



The Catalytic Cycle
Oxidative Addition

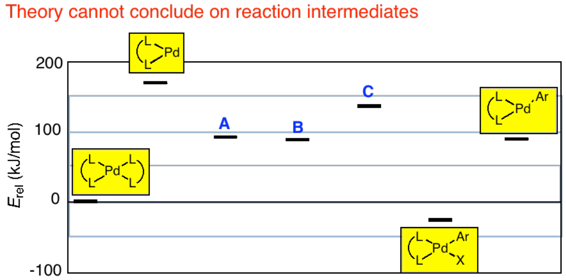
- Electron-rich metal centers are believed to stabilize the oxidative addition process for sp^2

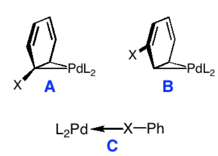




σ^- values give a better correlation than σ values whenever direct conjugation of a pair of electrons at the reaction site with the substituent is possible. Such a substituent effect indicates a likely charged transition state

- Theory cannot conclude on reaction intermediates



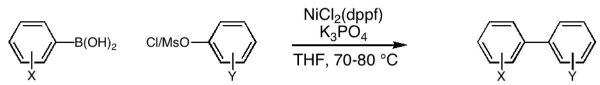


Milstein, D.; Portnoy, M. *Organometallics.* **1993**, *12*, 1665.
Amatore, D.; Pfluger, F. *Organometallics.* **1990**, *9*, 2276.

Senn, H. M.; Ziegler, T. *Organometallics.* **2004**, *23*, 2980.
Gooβen, L. J.; Thiel, W. et al. *Chem. Comm.* **2004**, 2141.

What About Nickel?

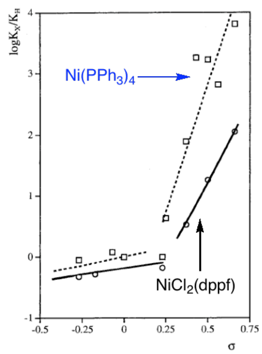
- Initial Suzuki couplings with aryl mesylates/chlorides utilized Ni(0) due to its higher reactivity



Mesylates (add Zn): Percec, V. et al. *J. Org. Chem.* **1995**, *60*, 1060.
Chlorides: Miyaura, N. et al. *J. Org. Chem.* **1997**, *62*, 8024.

- Nickel is having renewed interest based on economic practicality in reactions - not have to recycle the catalyst

- Reduction of Ni(II) with base gives inactive nickel hydroxides/oxides ⟹ Zn, BuLi, DIBAL



- 2 mechanisms for rate-determining oxidative addition

$$[Ni(PPh_3)_3] + ArX \longrightarrow [Ni(PPh_3)_2(Ar)(X)] + PPh_3$$
$$[Ni(PPh_3)_2] + ArX \longrightarrow [Ni(PPh_3)_2(Ar)(X)]$$

- Pd(0) oxidative addition shuts down with $\sigma < 0.33$

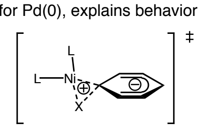
- Exact mechanism is under debate
  - radical pathway or charged transition state??

- No alkyl boranes/borates reported in a methodology yet

Ni(PPh$_3$)$_4$: Foa, M.; Cassar, L. *J.C.S. Dalton Trans.* **1975**, 2572.
NiCl$_2$(dppf): Saito, S.; Oh-tani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62*, 8024.

What About Nickel?

- 2 mechanisms for rate-determining oxidative addition
  - charged intermediate as seen for Pd(0), explains behavior of Hammett studies

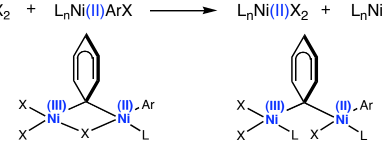


  - 1 electron oxidation of a Ni(II) to a Ni(III) was shown to occur at Pt electrodes

$$L_nNi(0) + ArX \xrightarrow{e^-} [L_nNi^{+\bullet}][ArX^{-\bullet}] \longrightarrow L_nNi(I)X + Ar^{\bullet} \;......$$

initiation $L_nNi(I)X + ArX \longrightarrow L_nNi(III)ArX_2$

$$L_nNi(III)ArX_2 + L_nNi(II)ArX \longrightarrow L_nNi(II)X_2 + L_nNi(III)Ar_2X$$



$$L_nNi(III)Ar_2X \longrightarrow Ar\text{–}Ar + L_nNi(I)X$$

  - inhibition occurs in the process upon the addition of one-electron acceptors that form stable radicals (quinones, nitroaromatics)

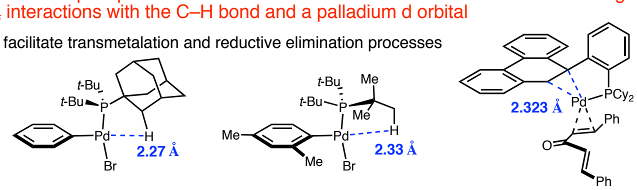
Radical Pathway Studies: Kochi, J. K. *Pure Appl. Chem.* **1980**, *52*, 571.

Oxidative Addition

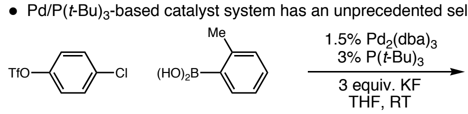
The Role of Electron-Rich, Bulky Phosphines

■ Electron-rich phosphines can stabilize the oxidative addition intermediate through agostic and C_σ interactions with the C–H bond and a palladium d orbital

- facilitate transmetalation and reductive elimination processes



- Pd/P(t-Bu)$_3$-based catalyst system has an unprecedented selectivity for aryl chlorides

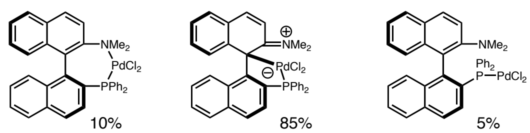


95%

changing the ligand to PCy_3 results in exclusive oxidative addition on the C–OTf bond

Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

■ C_σ interactions between *ortho*-aryl groups and palladium is also noted in a seemingly bidentate system by Kocovsky, et al. (*J. Am. Chem. Soc.* **1999**, *121*, 7714.)

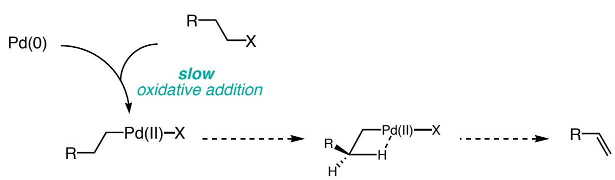


10% 85% 5%

observations made by *[31]P NMR and X-ray crystallography*

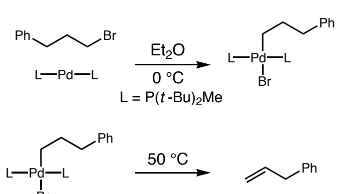
Oxidative Addition of Alkyl Halides

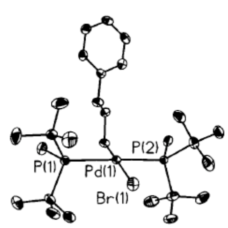
■ β-H elimination strikes again



■ Oxidative addition intermediate is unstable ⟹ electron-rich ligands help stabilize

■ With electron-rich phosphines, Fu is able to effect oxidative addition under mild conditions and obtain an x-ray crystal of the intermediate

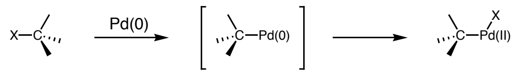




Fu, G. C. et al. *J. Am. Chem. Soc.* **2002**, *124*, 13662.

Oxidative Addition of Alkyl Halides

■ Oxidative addition of C(sp^3)–X to Pd(0) is usually via an associative bimolecular process (S_n2)



■ Exact mechanism of oxidative addition is not known

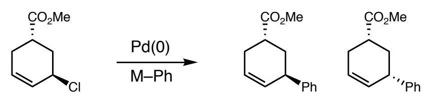
- radical and concerted nucleophilic addition mechanisms have been proposed

"The mechanism of the oxidative addition reaction to a coordinatively unsaturated species is controversial, and indeed different mechanisms may be operating depending on the alkyl group, the halogen, the phosphine ligands, and the metal."

- J. Stille, "Mechanisms of Oxidative Addition of Organic Halides to Group 8 Transition Metal Complexes". *Acct. Chem. Res.* **1977**, *10*, 439.

■ Allylic electrophiles are a whole different scenario

- convoluted by competing S_n2' pathways
- usually goes with inversion in polar, coordinating solvents
- stereochemistry tends to be retained in non-coordinating solvents (benzene, CH_2Cl_2)



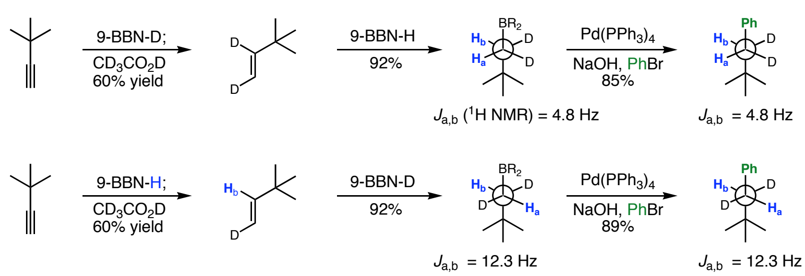
benzene	96	4
MeCN	0	100

The Catalytic Cycle

Stereochemistry of Transmetallation

■ Alkyl boranes will not couple without added base - *what is really happening in the transmetallation step?*

■ Soderquist and Woerpel independently show transmetallation goes with retention of stereochemistry.

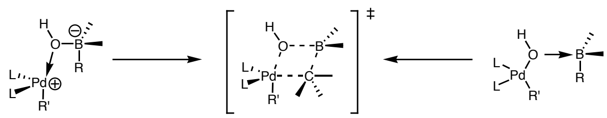


Ridgway, B. H.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 458.
Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461.

The Catalytic Cycle
Mechanism of Transmetallation


John Soderquist

- Soderquist proposes a μ_2-hydroxo-bridged transition state to account for stereochemistry retention



Which pathway is it to the intermediate?

$$\text{Ph-Br} + \text{hexyl-BBN} \xrightarrow[\text{NaOH, THF}]{\text{Pd(PPh}_3)_4} \text{Ph-hexyl}$$

1 equiv. NaOH (75%)
2 equiv. NaOH (100%)

What is the role of the base in the Suzuki-Miyaura coupling??

the base makes the alkylborane coupling distinct from boronic acids and esters

- Effects of base on the alkyl borane substituent

$\delta(^{11}B) = 87.7$ | $\delta(^{11}B) = 3.3$ | $\delta(^{11}B) = 54.1$ | not observed

Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461.

The Catalytic Cycle
Mechanism of Transmetallation

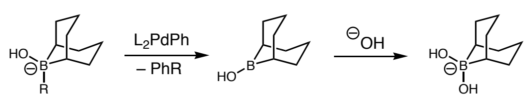
- Effects of base on palladium catalyst

$$\text{PdL}_4 \underset{\text{L = PPh}_3}{\overset{-\text{L}}{\rightleftharpoons}} \text{PdL}_3 \overset{-\text{L}}{\rightleftharpoons} \text{PdL}_2 \xrightarrow[27\ ^\circ\text{C}]{\text{PhBr}} \text{L}_2\text{Pd(Ph)(Br)} \xrightarrow{^{\ominus}\text{OH}} \text{L}_2\text{Pd(Ph)(OH)}$$

$\delta(^{31}P) = 18$ | $\delta = 26.1$ | $\delta = 23.6$

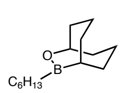
33% - 2h, 27 °C
90% - 2h, 65 °C

- Base is consumed in the formation of the hydroxy "ate" complex



$\delta(^{11}B) = 56.3$ | $\delta(^{11}B) = 9.6$

- Effects of base are not as pronounced with 9-OBBD systen



$$\xrightarrow[\text{NaOH, THF}]{\text{Ph-Br, Pd(PPh}_3)_4} \text{Ph-hexyl}$$

1 equiv. NaOH (92%)
2 equiv. NaOH (100%)

Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461.

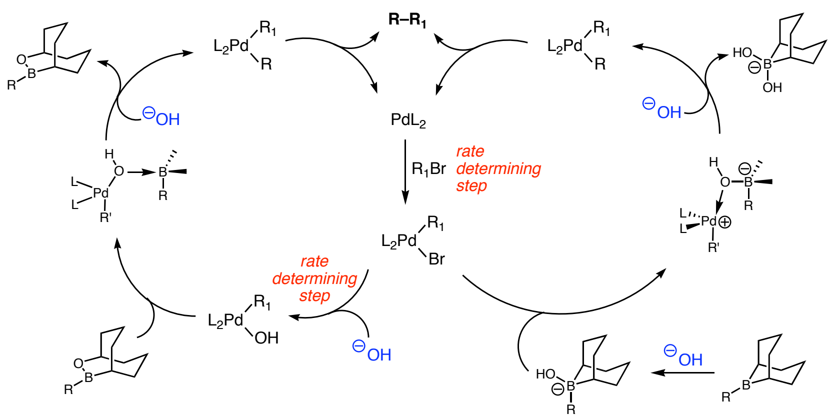
The Catalytic Cycle

Mechanism of Transmetallation

- Five possible roles for the base in the cross-coupling

1. formation of hydroxyborate complexes
2. hydrolysis of Pd(II)X to monomeric Pd(II)OH
3. complexation of BBN-OH byproducts
4. catalyst regeneration
5. accelerated coupling rates for OBBD reactions

- New catalytic cycles proposed, emphasizing the importance of the base in the reaction

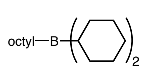
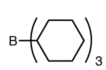
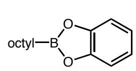
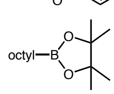


The Catalytic Cycle

Rates of Transmetalation

- Unhindered, electron-rich alkyl boranes react most efficiently

$$PhI + R\text{–}BX_2 \xrightarrow[50\ °C]{PdCl_2(dppf)} Ph\text{–}R$$

Entry	Organoborane	Base (equiv.)	Solvent	Yield	
1	octyl—BBN	NaOH (3)	THF/H_2O	99%	
2		NaOH (3)	THF/H_2O	93%	1° > 2°
3		KOH (3)	THF/H_2O	93%	
4		KOH (3) TlOEt (3) Tl_2CO_3 (1.5) TlOH (3)	THF/H_2O THF/H_2O THF benzene	trace 41% 93% 84%	
5		TlOH (3) Tl_2CO_3 (1.5)	THF/H_2O THF	34% trace	
6	octyl—$B(OH)_2$	TlOH (3)	THF/H_2O	trace	ThX↓

- No examples of 2° alkyl borane coupling in preparative synthesis

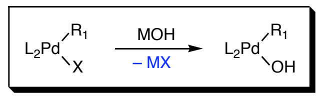
Effect of Bases

■ Effects of bases (MB) can be roughly estimated by the basic strength and affinity of M^+ for halide ions (stability constant).

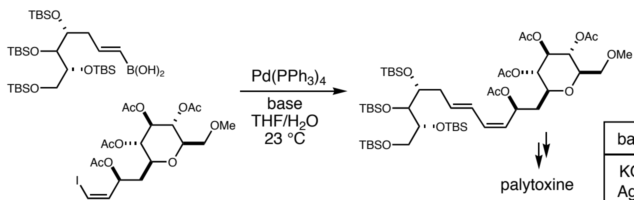
stability constants for X^- (log K at 25 °C)

	K^+	Cs^+	Ba^{2+}	Bu_4N^+	Tl^+	Cu^+	Ag^+
Cl^-	-0.7	-0.39	-0.13	0.40	0.49	2.7	3.3
Br^-	–	0.03	–	0.49	0.91	5.9	4.7
I^-	-0.19	-0.03	–	0.78	–	8.9	6.6

reactions can be fast for M^+ with high stability constant



■ Kishi is the first to observe the thallium effect (*J. Am. Chem. Soc.* **1989**, *111*, 7525)



base	cat(mol%)	min.	yield
KOH	25	120	86%
Ag_2O	25	5	92%
TlOH	3	30	94%

■ Bases with alkyl boranes/borates are solvent dependent

- strong bases (NaOH, TlOH, NaOMe) perform well in THF/H_2O
- weaker bases (K_2CO_3, K_3PO_4) perform well in DMF

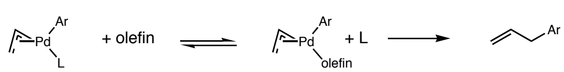
The Catalytic Cycle

Reductive Elimination

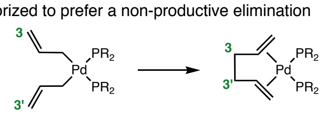
■ Reductive elimination is not typically the rate determining step in cross-coupling

- one exception is allylic electrophiles

– needs *p*-benzoquinone or other electron-withdrawing olefins to promote reductive elimination

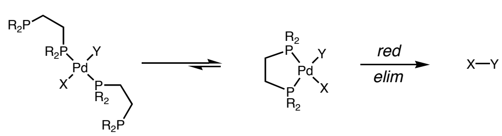


– bisallyl coupling is theorized to prefer a non-productive elimination



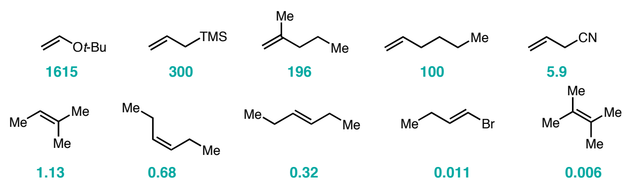
Cardenas, D. J.; Echavarren, A. M. et al. *Chem. Eur. J.* **2002**, *8*, 3620.

■ Bidentate ligands can facilitate reductive elimination by forcing substituents *cis*

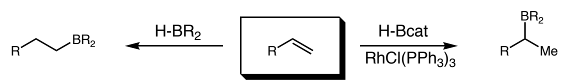


Hydroboration Allows Easy Access to Alkyl Boranes

- Hydroboration is highly chemo-, regio-, and stereoselective
  - electron-rich, unhindered olefins react most rapidly



  - regiochemistry can be reversed with catalyzed and uncatalyzed systems

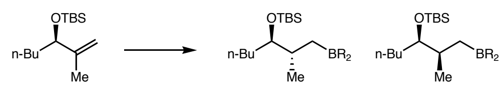


- changing to pinacolborane will give anti-Markovnikov product with Rh-system
- different substituents on olefin will effect product distribution
- Sm-catalysis gives anti-Markovnikov

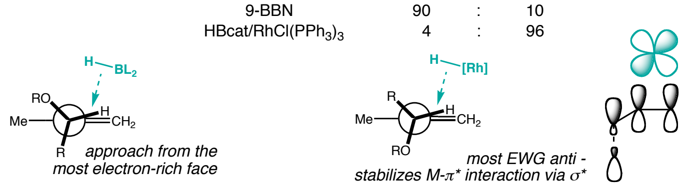
Review on Catalytic, Asymmetric Hydroboration: Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem.* **2003**, 4695.

Hydroboration Allows Easy Access to Alkyl Boranes

- Hydroboration is highly chemo-, regio-, and stereoselective
  - diastereoselective hydroborations - sensitive to steric and electronic factors



9-BBN	90	:	10
HBcat/$RhCl(PPh_3)_3$	4	:	96

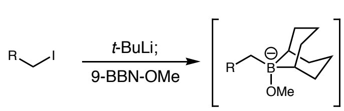


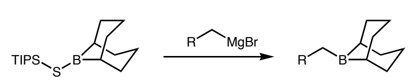
approach from the most electron-rich face

most EWG anti - stabilizes M-π^* interaction via σ^*

Burgess, K. et al. *J. Am. Chem. Soc.* **1991**, *113*, 6139.

- Alkyl lithium additions are used left frequently





Marshall, J. A. et al. *J. Org. Chem.* **1998**, *63*, 7885.

Soderquist, J. A. et al. *Tet. Lett.* **2000**, *41*, 3537.

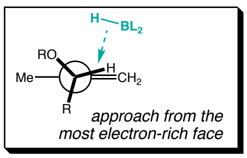
Hydroboration Allows Easy Access to Alkyl Boranes

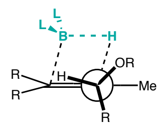
■ Hydroboration is highly chemo-, regio-, and stereoselective

- diastereoselective hydroborations - sensitive to steric and electronic factors

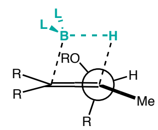
■ Quick comment on stereoselective hydroboration with substrate chirality

- electronic influence is shown by Houk to prefer approach of the borane from the most electron-rich face (after $A^{1,3}$ and $A^{1,2}$ strain minimization)



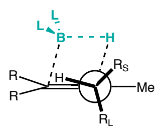


R = ether



R = H

- without ether or hydroxyl substituents α to the olefin, steric influence goes as expected with minimization of $A^{1,3}$ strain and approach from less-hindered face



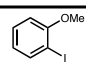
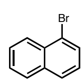
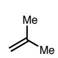
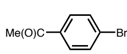
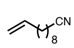
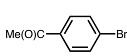
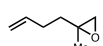
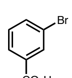
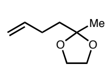
Houk, K. N. et al. *Tetrahedron.* **1984**, *40*, 2257.

Substrate Generality

Vinyl or Aryl Halides

■ Substrates that are base-sensitive can be coupled with different base/solvent combinations

Ar–X + R–BBN* ⟶ Ar–R

Ar–X	Alkene	Yield	Conditions
	1-octene	90, 71	a, b
		88, 71	a,b
		98	c
		52	c
		77	c

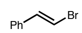
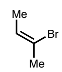
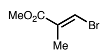
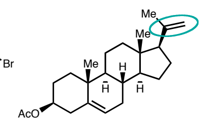
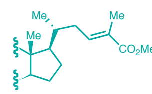
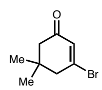
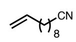
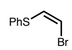
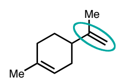
* from alkene (1 equiv.) and 9-BBN-H (1.1 equiv.)

a) $PdCl_2$(dppf) (3 mol %), NaOH (3 equiv.), THF, reflux
b) $PdCl_2$(dppf) (3 mol %), NaOMe (3 equiv.), THF, reflux
c) $PdCl_2$(dppf) (3 mol %), K_2CO_3 (2 equiv.), DMF/THF, 50 °C

Substrate Generality
Vinyl or Aryl Halides

- Vinyl bromides couple with retention of olefin geometry

vinyl–X + R–BBN* ⟶ Ar–R

	vinyl–X	Alkene	Yield	Conditions	
		1-octene	85	a	
		1-octene	98	a	
chemoselective and diastereoselective hydroboration			73, 79	c	
			81, 72	b, c	
chemoselective hydroboration			90	c	

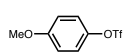
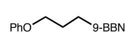
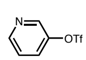
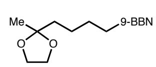
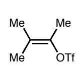
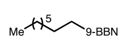
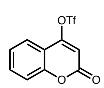
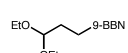
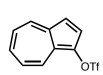
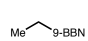
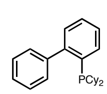
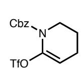
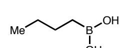
* from alkene (1 equiv.) and 9-BBN-H (1.1 equiv.)

a) $PdCl_2$(dppf) (3 mol %), NaOH (3 equiv.), THF, reflux
b) $PdCl_2$(dppf) (3 mol %), K_2CO_3 (2 equiv.), DMF/THF, 50 °C
c) $PdCl_2$(dppf) (3 mol %), K_3PO_4 (1 equiv.), DMF/THF, 50 °C

Substrate Generality
Vinyl or Aryl Halides

- Aryl and vinyl triflates are readily accessible from phenols or enolates

$C(sp^2)$–X + R–BR_2 ⟶ Ar–R

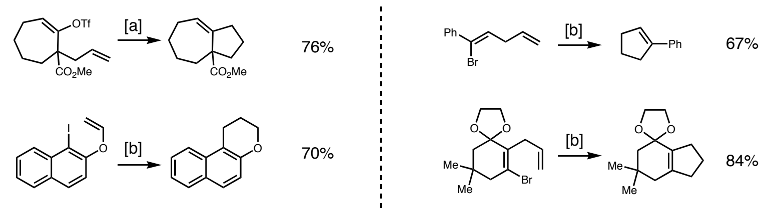
$C(sp^2)$–X	R–BR_2	Yield	Conditions
		92	a
		65	a
		67	b
		64	a
		56	 $Pd(OAc)_2$ (5 %), L* (7.5 %), Cs_2CO_3 (3 equiv.), THF, r.t.
		93	$PdCl_2$(dppf) (5%), K_2CO_3 (2 equiv.), Ag_2O (2 equiv.), toluene, 85 °C

a) $PdCl_2$(dppf) (2.5 mol %), K_3PO_4 (1.5 equiv.), dioxane, 85 °C
b) $PdCl_2$(dppf) (2.5 mol %), K_3PO_4 (1.5 equiv.), THF, reflux

Substrate Generality

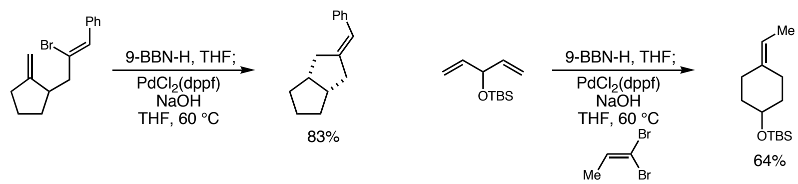
Intramolecular Coupling

■ 5- and 6-membered rings can be formed in an intramolecular fashion, larger rings were not possible



a) 9-BBN-H, THF; $PdCl_2$(dppf), K_3PO_4, dioxane/THF, 85 °C
b) 9-BBN-H, THF; $PdCl_2$(dppf), NaOH, THF/H_2O, 60 °C

■ Exocyclic olefins can be formed



Suzuki; Miyaura et al. *Tet. Lett.* **1992**, *33*, 2571.

Soderquist et al. *Tet. Lett.* **1995**, *36*, 3119

Substrate Generality

Aryl Chlorides

■ Unactivated aryl chlorides are famously less reactive towards oxidative addition

- heteroaryl and aryl chlorides with electron-withdrawing groups are considered activated
- complexation of aryl chlorides with $Cr(CO)_3$ make them reactive partners in Suzuki couplings

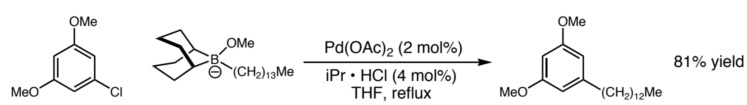
Review of Aryl Chloride Pd-couplings: Fu, G. C.; Littke, A. F. *Angew. Chem. Int. Ed.* **2002**, *41*, 4176.

■ Low reactivity usually attributed to the strength of the C–Cl bond

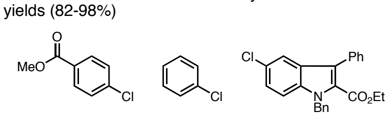
bond dissociation energies for Ph–X:

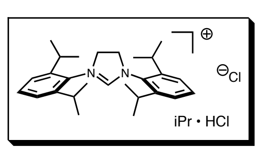
Cl = 96 kcal/mol   Br = 81 kcal/mol   I = 65 kcal/mol

■ Despite remarkable progress of Ar–Cl couplings since 1998, only one example of *B*-alkyl-BBN couplings to aryl chlorides by Furstner and Leitner (*Synlett.* **2001**, *2*, 290)



- electron-deficient and electron-rich aryl chlorides tolerated in good yields (82-98%)



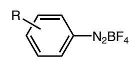


- alkyl, alkynyl, allyl, and cyclopropyl borates couple as well

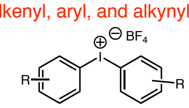
Potassium Alkyltrifluoroborates

- Initially prepared by Vedejs for complexing amino acids. R–BF_3K are noted as a surrogate for R–BF_2 (*J. Org. Chem.* **1995**, 3020 and *J. Am. Chem. Soc.* **1999**, 2460.)

- Early palladium-catalyzed Suzuki couplings with alkenyl, aryl, and alkynyl BF_3K salts



Genet, J.-P. et al.
Eur. J. Org. Chem. **1999**, 1875.



Xia, M.; Chen, Z.-C.
Synth. Commun. **1999**, *29*, 2457.

- Molander reopens the field with Alkyl–BF_3K couplings to C(sp^2)–OTf in 2001
  - Why are alkyl (and other) BF_3K of interest??
    - greater nucleophilicity than boronic acids or esters
    - preparative on large scales (>200g)
    - monomeric solids are readily isolated
      boronic acids can be hard to isolate from the diol of the parent boronic ester
    - long shelf lives
      boronic acids have variable shelf lives, trialkylboranes are not stable

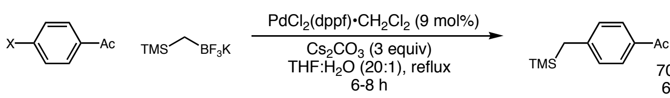
- Preparation of salts follows standard hydroboration procedures

$$\text{R–BX}_2 + 2\,\text{KHF}_2 \xrightarrow[\text{H}_2\text{O}]{\text{Et}_2\text{O}} \text{R–BF}_3\text{K} + 2\,\text{HX} + \text{KF} \qquad (\text{X = halogen, OH, OR, NR}_2)$$

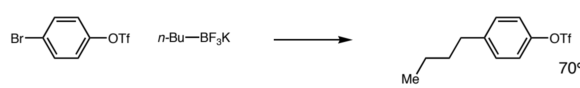
Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393.
Molander, G. A.; Yun, C.-S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 5534.

Potassium Alkyltrifluoroborates

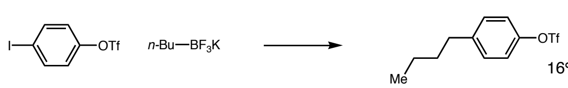
- Aryl/alkenyl triflates are slightly more reactive than C(sp^2) bromides; C(sp^2) iodides and chlorides are not compatible with this system.



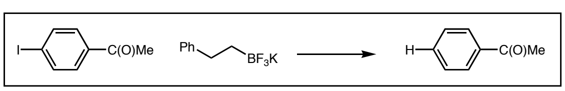
70% (X = OTf)
65% (X = Br)



70%



16%



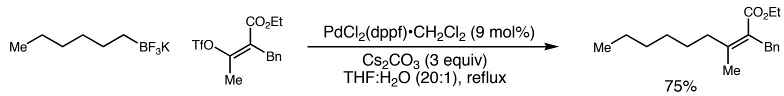
lack of reactivity in the transmetalation step

- Secondary BF_3K salts and electron-rich aryl bromides/triflates suffer from low reactivity

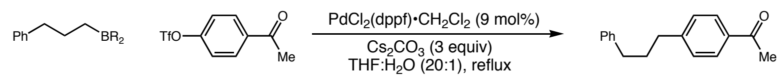
- Very good functional group tolerance is maintained: nitrile, ketone, ester, amide, and nitro

Potassium Alkyltrifluoroborates

■ Synthesis of tetra-substituted olefins



■ Alkyl boronic acids function similarly under reaction conditions ⇨ mechanistic implications?



84% (BR_2 = BF_3K)
77% (BR_2 = $B(OH)_2$)
60% (BR_2 = Bpin)

is a similar catalytic cycle operable with alkyl BF_3K cross-coupling as with alkyl borates?

■ The reactive transmetalling species is not known yet

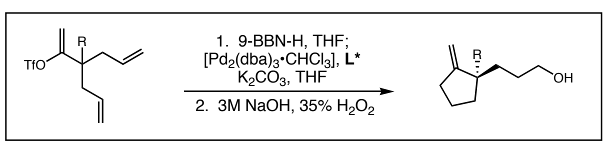
- slow internal hydrolysis of $R–BF_3K$ [$\delta(^{11}B)$=5.6] to $R–B(OH)_2$ [$\delta(^{11}B)$=33.5]
- fluorinated species such as $R–BF_3^-$, $R–BF_2(OH)^-$, and/or $R–BF(OH)_2^-$ might be involved
- the reaction may be accelerating the reaction

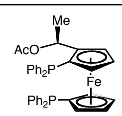
conclusions to these questions await detailed kinetic and mechanistic investigations

Substrate Generality

Asymmetric advances, Macrocyclizations

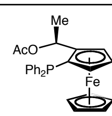
■ Cho and Shibasaki report cyclopentane asymmetric desymmetrizations using chiral ligands to give modest enantioselectivity (*Tet. Asymmetry.* **1998**, *9*, 3751)





R = H

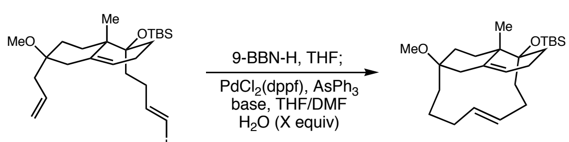
58% yield
28% *e.e.*

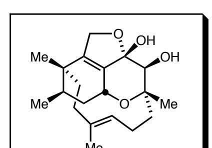


R = CH_2OTBS

42% yield
31% *e.e.*

■ Macrocyclizations can be done satisfactorily, dependent on the reaction conditions and substrates; even highly strained systems with transannular interactions





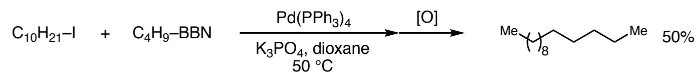
phomactin A

40% yield (3 equiv. Cs_2CO_3, 40 equiv. H_2O)
60% yield (3 equiv. TlOEt, 5 equiv. H_2O)

Chemler, S. R.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 2695.

sp^3 - sp^3 Cross-Coupling

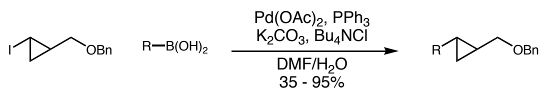
- Suzuki discovers in 1992 that alkyl iodides and alkyl boranes can couple



Miyaura, N.; Suzuki, A. et al. *Chem. Lett.* **1992**, 691.

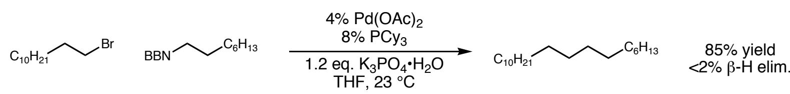
"alkyl bromides ... never provide the corresponding coupling products"
"The cross-coupling with inactivated alkyl halides is still difficult to achieve in high yields with palladium-catalyst, but the potentiality and synthetic utility thus suggested should be explored in the future"

- Charette shows iodocyclopropanes can undergo oxidative addition.



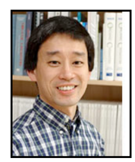
Charette, A. B.; Giroux, A. *J. Org. Chem.* **1996**, *61*, 8718.

- Fu breaks open this field with his inital report of alkyl bromide and alkyl borane coupling under very mild conditions



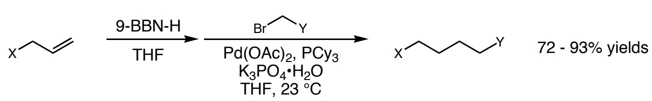
Netherton, M. R.; Dai, C.; Neuschutz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099.

Fu expands the scope of the alkyl-alkyl coupling

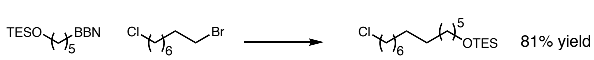


Greg Fu

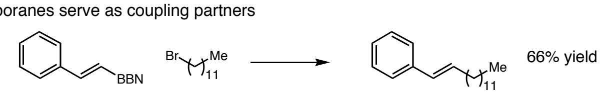
- Fu discovers the first Suzuki cross coupling of alkyl bromides in 2001



- PCy_3 is uniquely effective; triarylphosphines, arsines, trialkylphosphines, and bidentate ligands do not work (Pi-Pr_3 gives 68%)
- functional group tolerant: amines, alkenes, esters, alkynes, ethers and nitriles
- alkyl bromides react faster than alkyl chlorides



- vinyl boranes serve as coupling partners



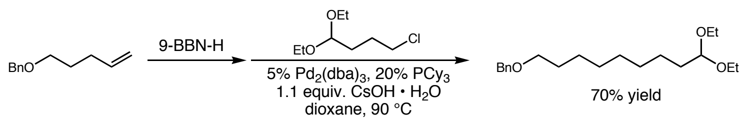
- water is essential - anhydrous K_3PO_4 gives almost no reaction
- NMR studies are consistent with hydroxy-bound borate adduct as reactive species

- Cloake (U. Sussex) - same transformation with $Pd(dba)_2$ (3%), iPr•HCl (3%), KOMe, TBAB (10%), in toluene at 40 °C (*Tet. Lett.* **2004**, *45*, 3511.)

Netherton, M. R.; Dai, C.; Neuschutz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099.

Fu expands the scope of the alkyl-alkyl coupling

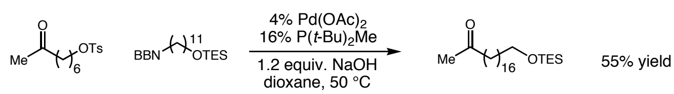
■ Alkyl chlorides are the next substrate for Fu to solve



- again, PCy_3 is unique for this transformation although $P(c\text{-}C_5H_9)_3$ and $P(i\text{-}Pr)_3$ can work
- N-heterocyclic carbenes (IMes) only gives minor reaction
- functional group tolerant: aryls, ethers, acetals, olefins, amines, nitriles, and esters

Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 1945.

■ Alkyl chlorides down, alkyl tosylates up.



R =	*i*-Pr	Et	Me	Cy
PCy_2R	44%	70%	48%	46%
$Pt\text{-}Bu_2R$	<2%	<2%	**78%**	--

- *oxidation addition* proceeds with *inversion* and *reductive elimination* proceeds with *retention*
- $[HP(t\text{-}Bu)_2Me]BF_4$ is a surrogate for air-sensitive $P(t\text{-}Bu)_2Me$

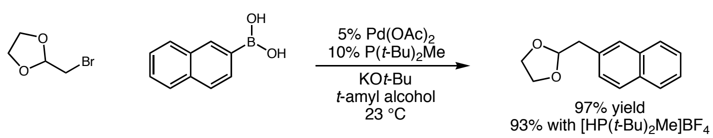
"...we have not yet determined the origin of this striking dependence of reactivity on phosphane strucure"

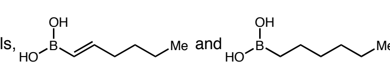
Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3910.

Fu ...he keeps going and going.....

■ Alkyl bromides with alkyl boronic acids instead of alkyl boranes

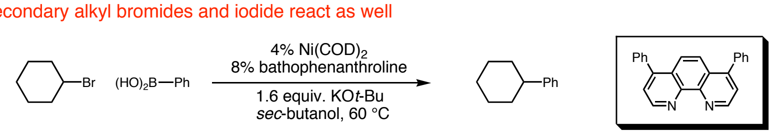
- need to use a more reactive ligand and different solvent for solubility of reactants



- function group tolerant for alkyl bromide
- scope of boronic acid compenent limited to aryls, 

Kirchoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662.

■ Secondary alkyl bromides and iodide react as well

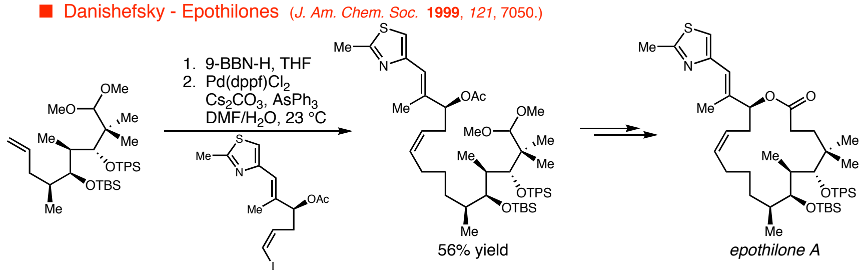


- unactivated primary and secondary iodides react in 62 - 75% yield
- boronic acid scope limited to aryl systems for bromides, aryl and alkenyl systems for iodides

Zhou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340.

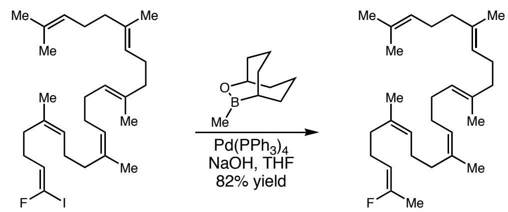
Alkyl Boranes in Natural Products

■ Danishefsky - Epothilones (*J. Am. Chem. Soc.* **1999**, *121*, 7050.)



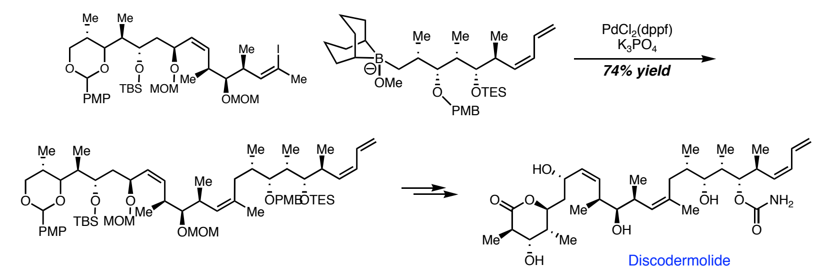
- macrocyclization approaches did not work

■ Moore - Squalene Epoxidase Inhibitors (*J. Am. Chem. Soc.* **1992**, *114*, 360.)

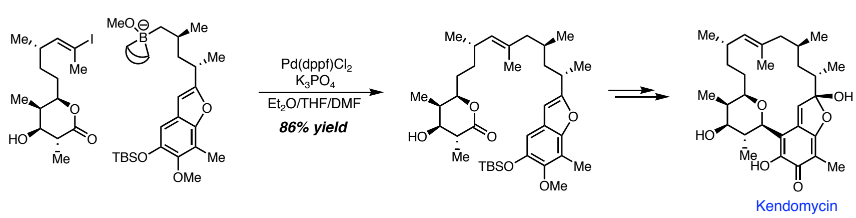


Alkyl Boranes in Natural Products

■ J. Marshall - Discodermolide (*J. Org. Chem.* **1998**, *63*, 7885.)

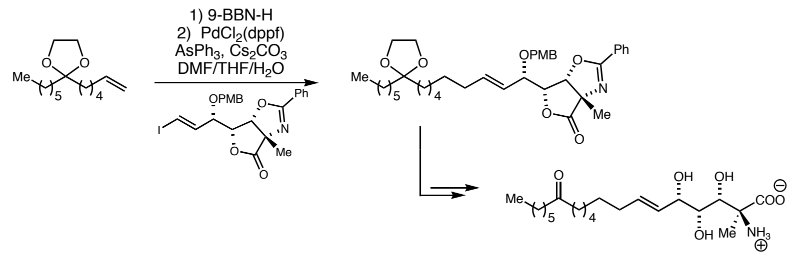


■ C. Lee - Kendomycin (*J. Am. Chem. Soc.* **2004**, *126*, 14720.)

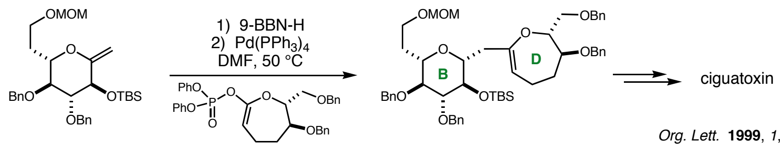


Alkyl Boranes in Natural Products

- Trost - Sphingofungin F (*J. Am. Chem. Soc.* **1998**, *120*, 6818.)



- Sasaki - relied heavily on *B*-alkyl Suzuki coupling for polyether natural products like brevetoxins, ciguatoxins, and gambierol.



Org. Lett. **1999**, *1*, 1075.

first example of vinyl phosphonate used for B-alkyl Suzuki-Miyaura coupling

B-*Alkyl Suzuki Couplings*

Conclusion

- *B*-alkyl Suzuki-Miyaura couplings are a very powerful tool for C–C bond formation
- Catalytic cycle is generally well understood, however each reaction should be considered on a case-by-case basis.
- Advancements have been rapidly reported in the past 20 years
- Catalyst-controlled chirality - one example
- *B*-alkyl Suzuki couplings can be used in complex natural products due to functional group compatability and the ability to alter conditions accordingly

Relevant and Comprehensive Reviews:

Chemler, S. R.; Trauner, D.; Danishefsky, S. J. "The *B*-alkyl Suzuki-Miyaura cross-coupling reaction: a versatile C–C bond-forming tool." *Angew. Chem. Int. Ed.* **2001**, *40*, 4544-4568.

Miyaura, N. "Metal-Catalyzed Cross-Coupling Reactions of Organoboron Compounds with Organic Halides." Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions, 2nd Edition.* Wiley-VCH, Weinheim, **1998**, Ch. 2.

Echavarren, A.M.; Cardenas, D. J. "Mechanistic Aspects of Metal-Catalyzed C,C- and C,X-Bond-Forming Reactions." Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions, 2nd Edition.* Wiley-VCH, Weinheim, **1998**, Ch. 1.

Miyaura, N; Suzuki, A. "Transition-Metal Systems Bearing a Nucleophilic Carbene Ancillary Ligand: from Thermochemistry to Catalysis." *Chem. Rev.* **1995**, *95*, 2457-2483.