Reviews:

Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*, Diederich, F., and Stang, P. J., Eds.; Wiley-VCH: New York, **1998**, pp. 49-97.

Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.

Suzuki, A. *J. Organometallic Chem.* **1999**, *576*, 147–168.

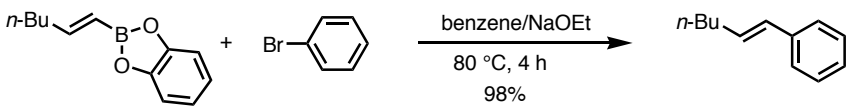
• *B*-Alkyl Suzuki reaction:

Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 4544–4568.

• Solid phase:

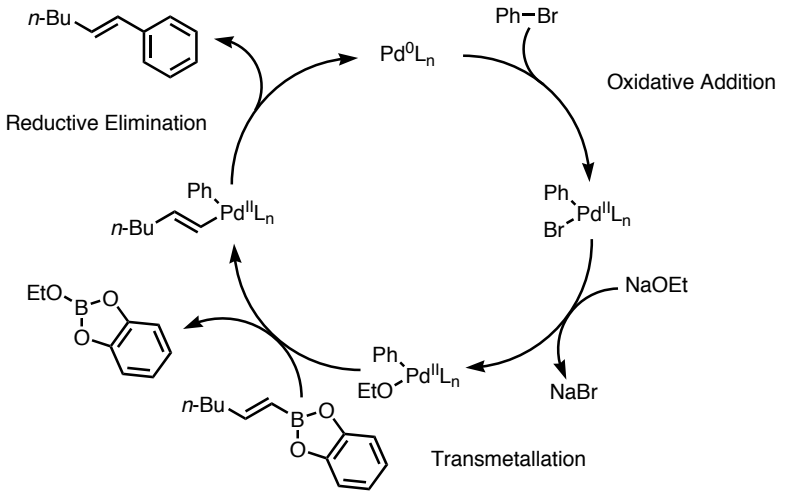
Franzén, R. *Can. J. Chem.* **2000**, *78*, 957–962.

• The Suzuki reaction is the coupling of an aryl or vinyl boronic acid with an aryl or vinyl halide or triflate using a palladium catalyst. It is a powerful cross coupling method that allows for the synthesis of conjugated olefins, styrenes, and biphenyls:



Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866–867.

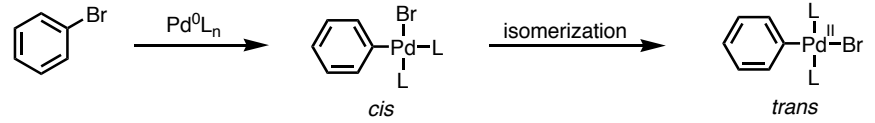
Mechanism:



Suzuki, A. *Pure & Appl. Chem.* **1985**, *57*, 1749–1758.

Analysis of Elementary Steps in the Reaction Mechanism

Oxidative Addition



• Relative reactivity of leaving groups: $I^- > OTf^- > Br^- >> Cl^-$.

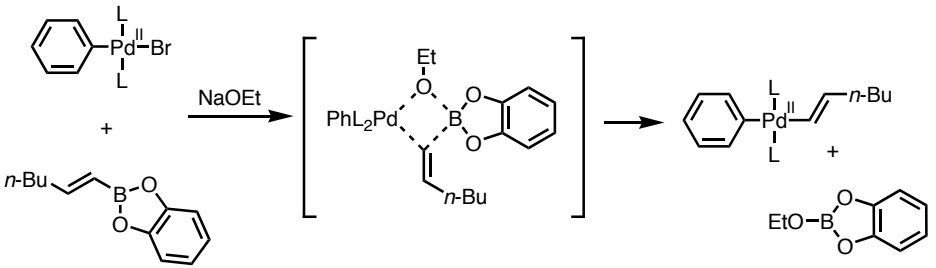
• Oxidative addition is known to proceed with retention of stereochemistry with vinyl halides and with inversion with allylic and benzylic halides.

Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434–442.

• Oxidative addition intially gives a *cis* complex that rapidly isomerizes to its *trans* isomer.

Casado, A. L.; Espinet, P. *Organometallics* **1998**, *17*, 954–959.

Transmetallation

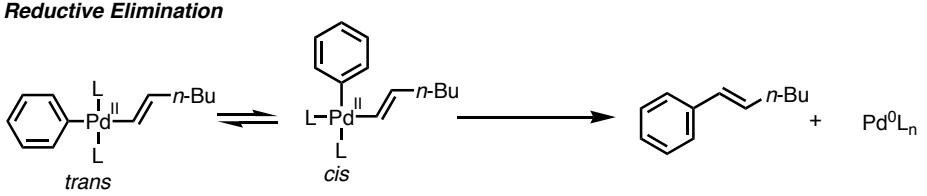


• Organoboron compounds are highly covalent in character, and do not undergo transmetallation readily in the absence of base.

• The role of the base during transmetalation is unresolved. Boron "ate" complexes, formed via quaternization of the boron with a negatively charged base, are frequently invoked.

Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461–470.

Reductive Elimination



• Isomerization to the *cis* complex is required before reductive elimination can occur.

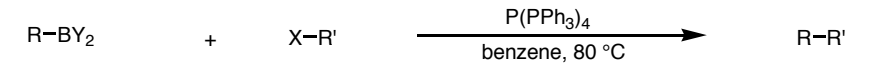
• Relative rates of reductive elimination from palladium(II) complexes:

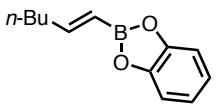
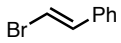
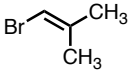
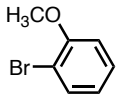
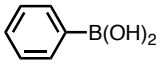
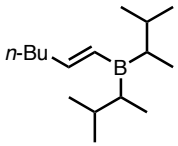
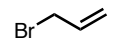
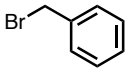
aryl–aryl > alkyl–aryl > *n*-propyl–*n*-propyl > ethyl–ethyl > methyl–methyl

Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.

Andrew Haidle/Chris Coletta

Conditions



		base	time (h)	yield (%)
		NaOEt	2	80[a]
		NaOEt	2	80[a]
		NaOEt	2	81[a]
	I–Ph	NaOEt	2	100[b]
	Br–Ph	NaOEt	2	63[b]
		NaOEt	4	98[b]
	Cl–Ph	NaOEt	2	3[b]
		NaOEt	4	93[b]
	I–Ph	2M NaOH	6	62[c]
	Br–Ph	2M Na_2CO_3	6	88[c]
	Cl–Ph	NaOEt	6	0[c]
		2M NaOH	2	87[d]
		2M NaOH	2	99[d]

- The conditions shown above are the original conditions developed for the cross coupling by Suzuki and Miyaura.
- The reaction is stereo- and regiospecific, providing a convenient method for the synthesis of conjugated alkadienes, arylated alkenes, and biaryls.
- Note that under the conditions shown above, aryl chlorides are not acceptable substrates for the reaction, likely due to their reluctance to participate in oxidative addition.

[a] Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437–3440.

[b] Miyaura, N.; Suzuki, A. J. Chem. Soc.*, Chem. Commun.* **1979**, 866–867.

[c] Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513–519.

[d] Miyaura, N.; Yano, T.; Suzuki, A. *Tetrahedron Lett.* **1980**, *21*, 2865–2868.

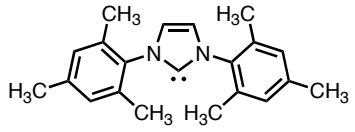
Catalyst and Ligands: The most commonly used system is $Pd(PPh_3)_4$, but other palladium sources have been used including Pd^{II} pre-catalysts that are reduced to the active Pd^0 *in situ:*

- $Pd_2(dba)_3 + PPh_3$
- $Pd(OAc)_2 + PPh_3$
- $PdCl_2(dppf)$ (for sp3-sp2 couplings-see section on *B*-alkyl Suzuki reaction)

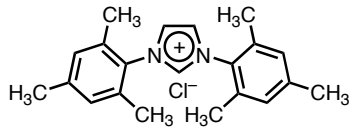
- "Ligand-free" conditions, using $Pd(OAc)_2$, have also been developed. Side reactions often associated with the use of phosphine ligands (phosphonium salt formation and aryl-aryl exchange between substrate and phosphine) are thus avoided.

Goodson, F. E.; Wallow, T. I.; Novak, B. M. *Org. Synth.* **1997**, *75*, 61–68.

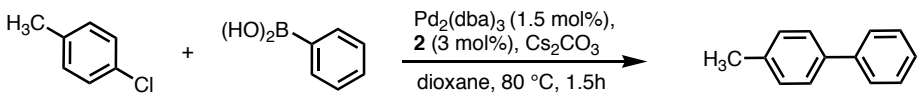
- Use of N-heterocyclic carbenes as an alternative to phosphine ligands:



1



2

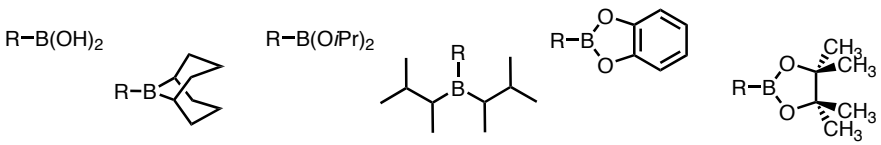


- The nucleophilic *N*-heterocyclic carbene **1** is the active ligand, and is formed *in situ* from **2**.
- The use of ligand **1** allows for utilization of aryl chlorides in the Suzuki reaction (see the section on bulky, electron rich phosphines as ligands for use of aryl chlorides as coupling partners as well).

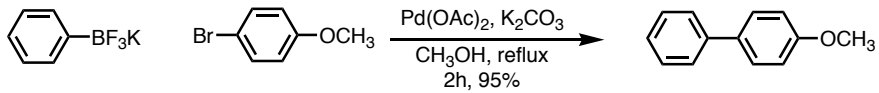
Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804-3805.

Organoboranes: A variety of organoboranes may be used to effect the transfer of the organic coupling partner to the reactive palladium center via transmetallation. Choice of the appropriate organoborane will depend upon the compatability with the coupling partners and availability (see section on synthesis of organoboranes).

Some of the more common organoboranes used in the Suzuki reaction are shown below:



- Use of Aryltrifluoroborates as Organoboranes for the Suzuki Reaction:



- The aryltrifluoroborates are prepared by treatment of the corresponding arylboronic acid with excess KHF_2.
- According to the authors, aryltrifluoroborates are more robust, more easily purified, and less prone to protodeboronation compared to aryl boronic acids.

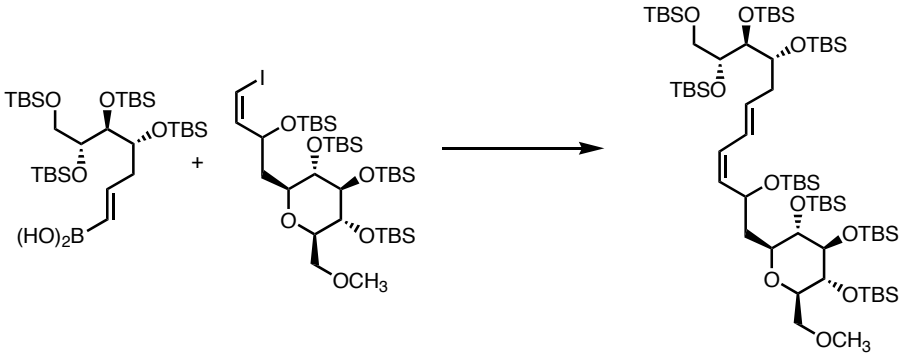
Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302–4314.

Solvent: The Suzuki reaction is unique among metal-catalyzed cross-coupling reactions in that it can be run in biphasic (organic/aqueous) or aqueous environments in addition to organic solvents.

Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324–4330.

Andrew Haidle/Chris Coletta

TlOH and TlOEt as Rate-Enhancing Additives for the Suzuki Reaction

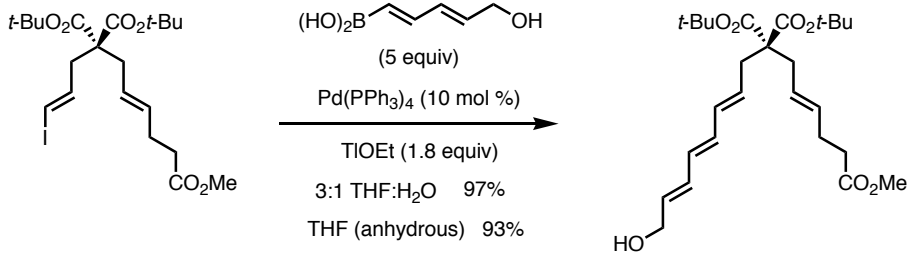


base	temp (°C)	time	yield	relative rate
KOH	23	2 h	86	1
TlOH	23	<<30 sec	92	1000

- TlOH greatly increases the rate of coupling, which the authors attribute to acceleration of the hydroxyl–halogen exchange at palladium.

Uenishi, J.; Beau, J.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756–4658.

- TlOH vs. TlOEt



- Roush has found that TlOEt is a generally superior source of Tl for Suzuki couplings. Pure TlOH is available from only a single source, aqueous solutions of TlOH have a poor shelf life, and the aqueous solutions are both air- and light-sensitive.

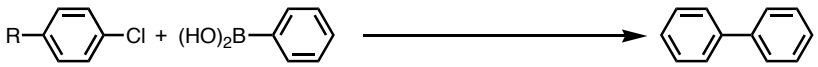
- The largest problem with using TlOEt is that some boronic acid–TlOEt adducts are not very soluble. Using water as a cosolvent helps to alleviate this problem in many cases.

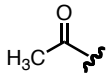
Frank, S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. *Org. Lett.* **2000**, *2*, 2691–2694.

Bulky, Electron-Rich Phosphines as Ligands for the Suzuki Reaction

R = PCy_2 (**1**)
R = P(*t*-Bu)$_2$ (**2**)

R = PCy_2 (**3**)
R = P(*t*-Bu)$_2$ (**4**)



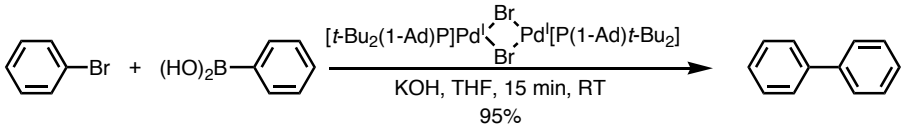
R	ligand	Pd source	base	solvent	temp (°C)	time (h)	yield (%)
CH_3	PPh_3	$Pd_2(dba)_3$	Cs_2CO_3	dioxane	80	5	0[a]
CH_3	P*t*-Bu_3	$Pd_2(dba)_3$	Cs_2CO_3	dioxane	80	5	86[a]
	4	$Pd(OAc)_2$	KF	THF	23	6	95[b]
CH_3O	P*t*-Bu_3	$Pd_2(dba)_3$	Cs_2CO_3	dioxane	80	5	89[a]
	4	$Pd(OAc)_2$	KF	THF	45	6	93[b]
NH_2	P*t*-Bu_3	$Pd_2(dba)_3$	Cs_2CO_3	dioxane	80	5	92[a]
	P*t*-Bu_3	$Pd_2(dba)_3$	Cs_2CO_3	dioxane	80	5	91[a]

- Previous to the introduction of the bulky, electron-rich phosphine ligands shown above, most aryl chlorides were not suitable substrates for the Suzuki reaction.
- These ligands are either commercially available (P*t*-Bu_3) or readily synthesized from commercial starting materials (**1**-**4**).
- The increased activity of the ligands shown above allows for the Suzuki reaction of aryl bromides at room temperature.

[a] Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.

[b] Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561.

- **Alkyl Di-*tert*-butylphosphane-Ligated Palladium(I) dimers as catalyst for the Suzuki Reaction**

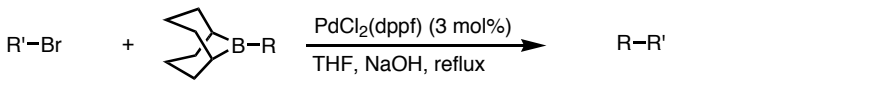


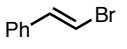
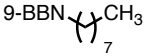
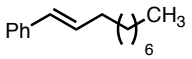
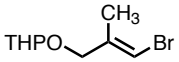
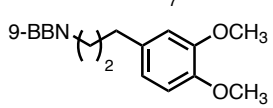
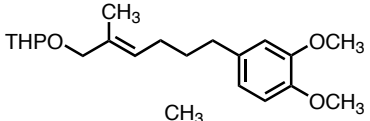
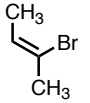
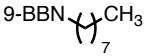
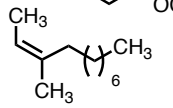
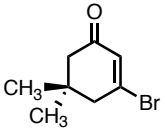
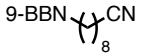
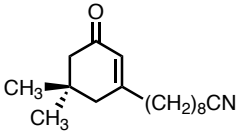
- As a solid, the catalytic complex is stable indefinitely in the air. it is believed that the catalyst fragments to form the monomeric subunits under the reaction conditions.
- Reactions of phenyl boronic acids with (deactivated) aryl chlorides occurred rapidly at room temperature, but conversion did not exceed 70%.

Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2002**, *41*, 4746-4748.

Chris Coletta

B-Alkyl Suzuki Reaction



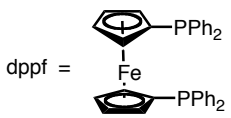
vinyl bromide	9-alkyl-9-BBN	product	yield (%)
			85
			80
			98
			81

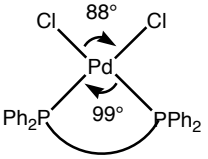
- With the advent of the $PdCl_2$(dppf) catalyst, primary alkyl groups can be transferred by Suzuki coupling, typically using 9-BBN reagents.
- Other suitable coupling partners include aryl or vinyl triflates and aryl iodides.
- Secondary alkyl boron compounds are not suitable coupling partners for this reaction.
- Alkyl boronic esters are also be viable substrates in the B-alkyl Suzuki reaction when thallium salts such as TlOH or Tl_2CO_3 are used as the base.

Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321.

Sato, M.; Miyaura, Suzuki, A. *Chem. Lett.* **1989**, 1405-1408.

- The large bite angle of the dppf ligand has been noted and is believed to provide a catalyst with a more favorable ratio of rate constants for reductive elimination versus β-hydride elimination.



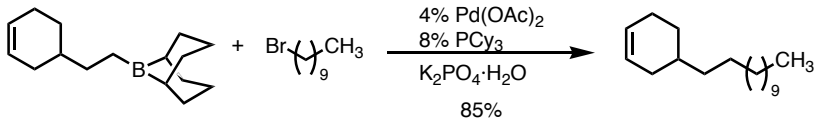


Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158–163.

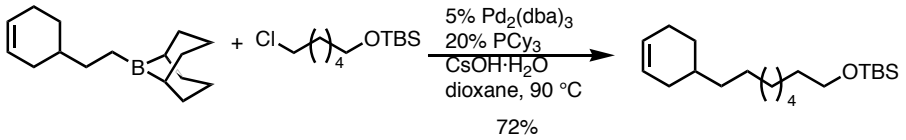
Brown, J. M.; Guiry, P. J. *Inorg. Chim. Acta.* **1994**, *220*, 249–259.

sp^3-sp^3 Suzuki Coupling

- By employing a bulky, electron-rich ligand (similar to the ligands used in aryl chloride Suzuki couplings) Fu and coworkers are able to effect the Suzuki coupling of primary alkyl bromides or chlorides and 9-alkyl-9BBN:



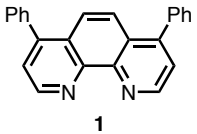
Netherton, M. R.; Dai, C.; Klaus, N.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099-10100.



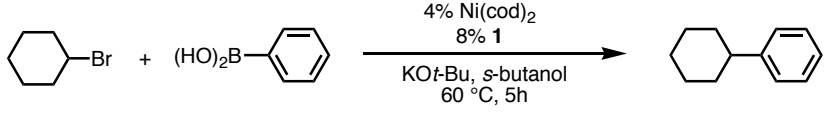
Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1945-1947.

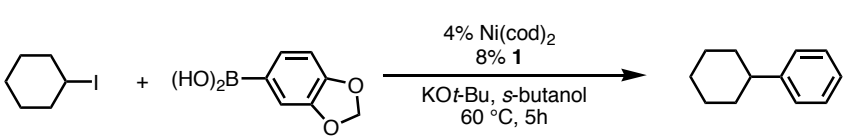
Suzuki Cross-Coupling of Unactivated Secondary Alkyl Halides

- Recently, Fu and coworkers have developed a Ni^0-catalyzed Suzuki coupling of unactivated alkyl bromides and iodides:



1

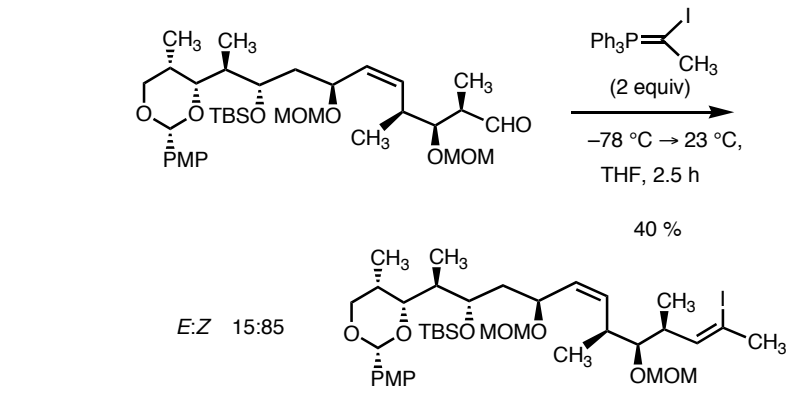


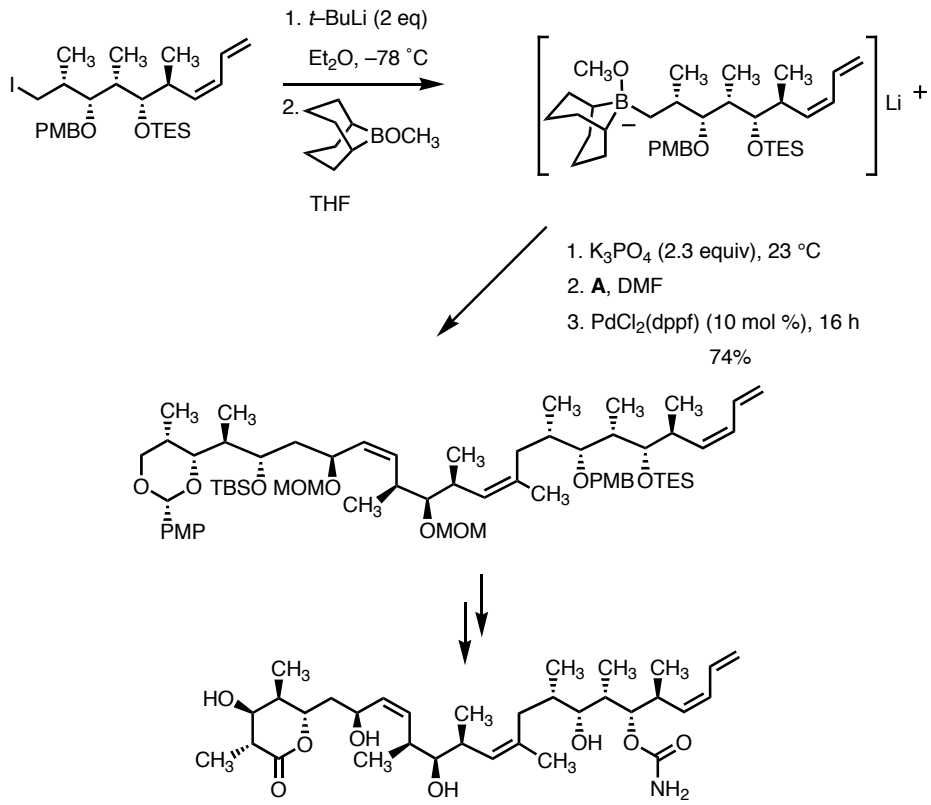


Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340-1341.

Chris Coletta

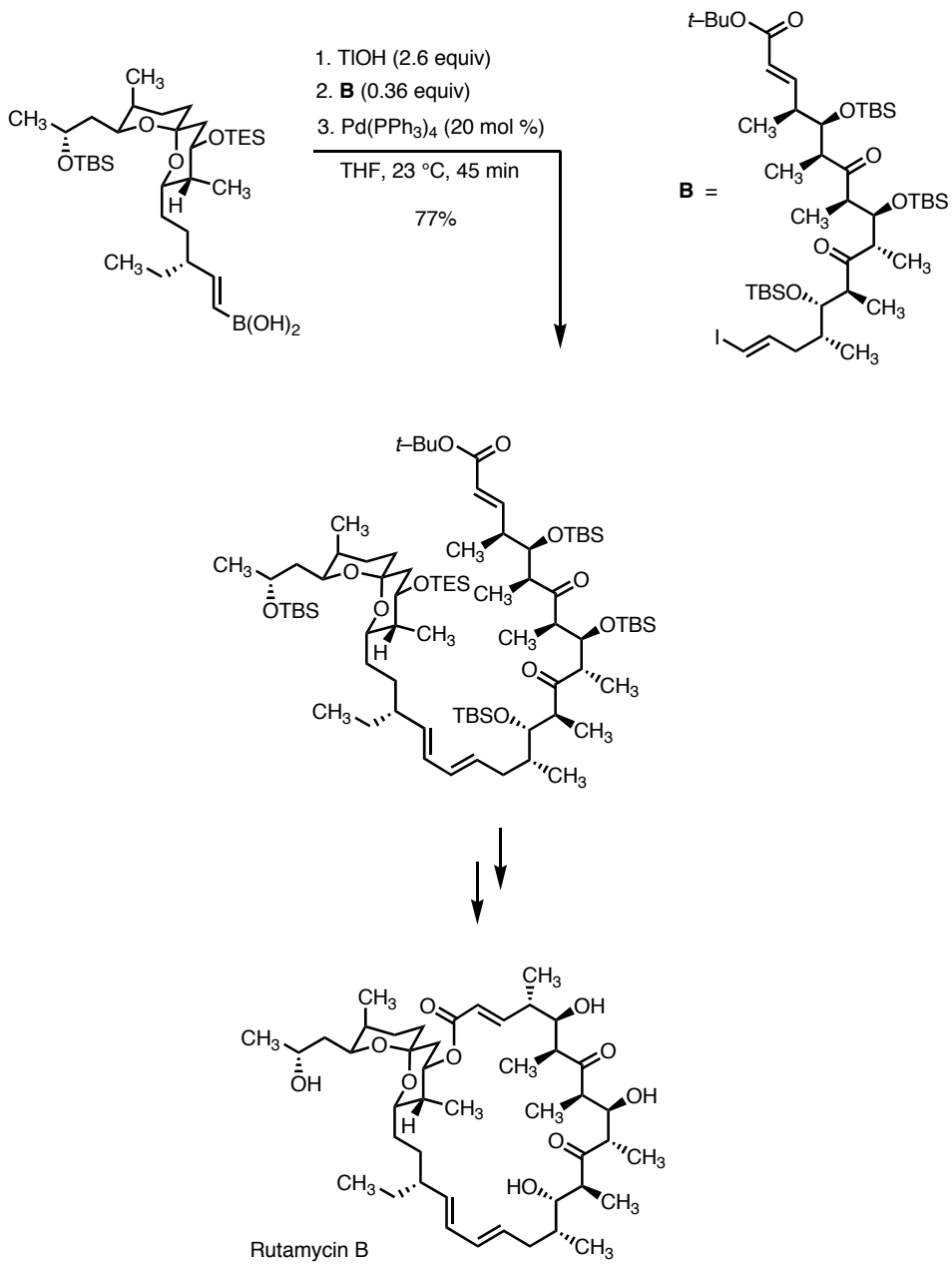
(+)-Discodermolide (*B*-Alkyl Suzuki Reaction)





Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885–7892.

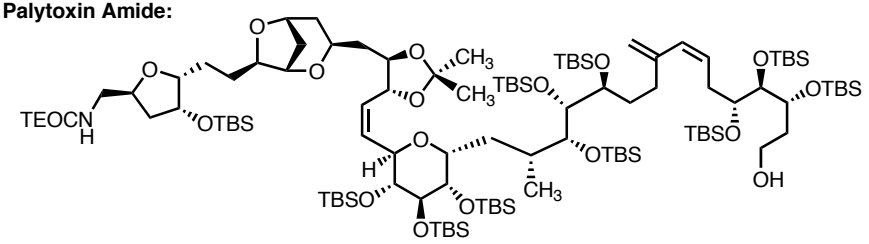
Rutamycin B



Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446–11459.

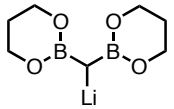
Andrew Haidle

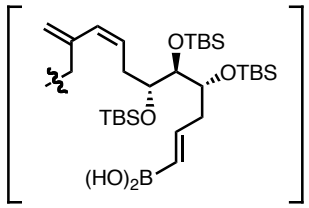
Palytoxin Amide:



A

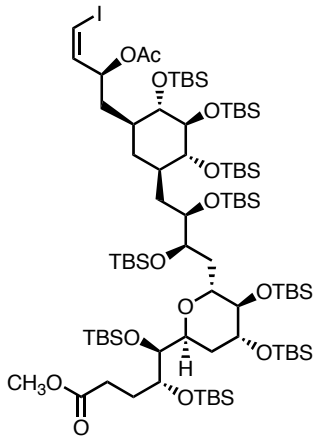
1. $(COCl)_2$, DMSO, Et_3N, –78 → 0 °C

2. 
TMEDA, THF, 0 °C;
EtOAc; NaCl, HCl

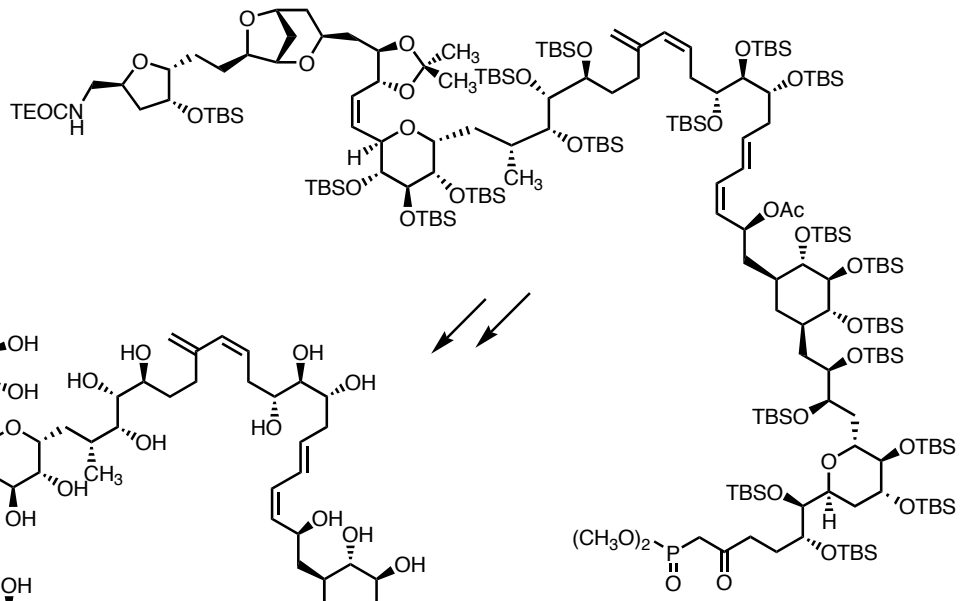


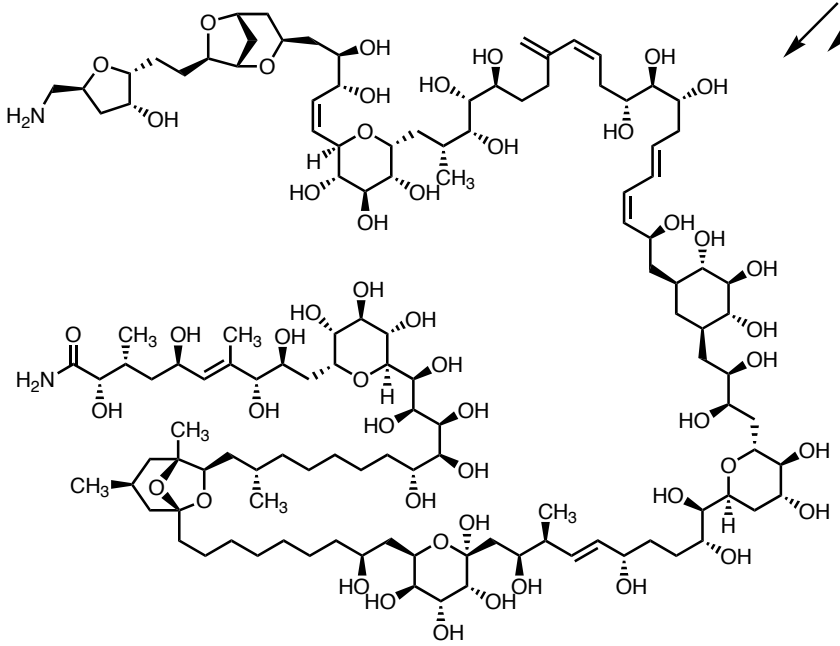
3. TlOH (10% aq); **B**, $Pd(PPh_3)_4$, 23 °C
4. $LiCH_2P(O)(OCH_3)_2$ (30 eq.)/THF, –78 °C

75–80%



B





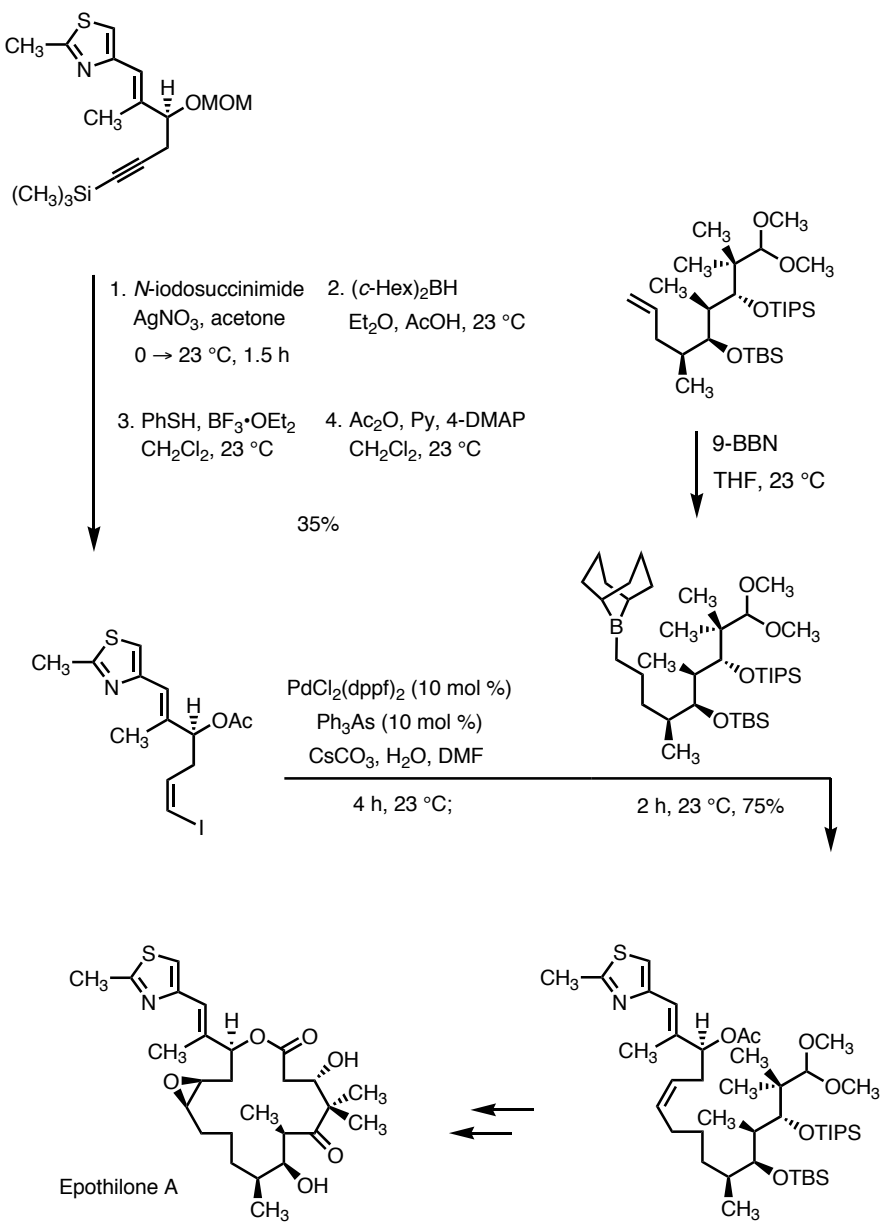
Palytoxin amide

Kishi, Y., et al. *J. Am. Chem. Soc.* **1989**, *111*, 7525–7530.

Kishi, Y., et al. *J. Am. Chem. Soc.* **1989**, *111*, 7530–7533.

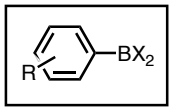
Andrew Haidle

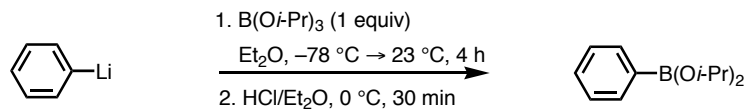
Epothilone A:



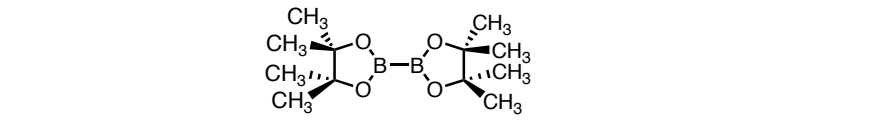
Meng, D.; Bertinato, P.; Balog, A.; Su, D.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S., J. *J. Am. Chem. Soc.* **1997**, *119*, 10073–10092.

Synthesis of organoboron compounds:





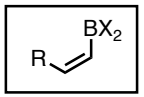
Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316–1319.

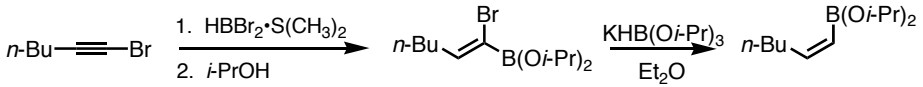


• Aryl bromides and chlorides can also be used.

Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447–3450.

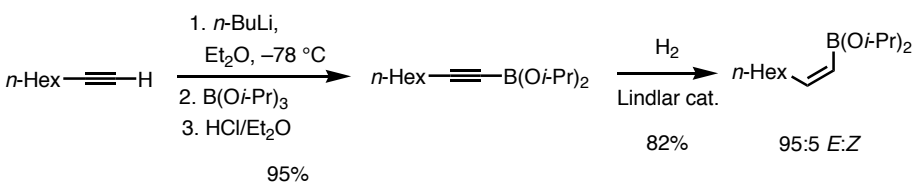
Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510.





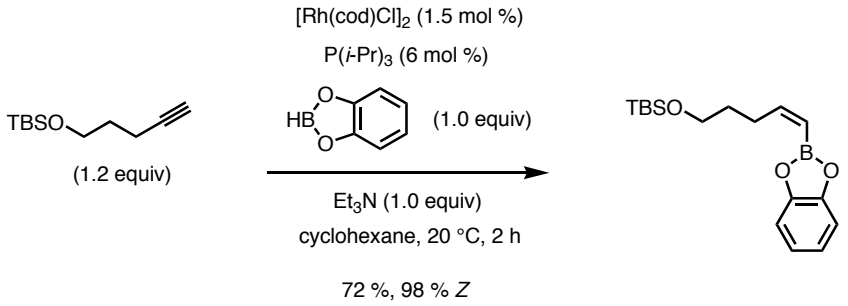
Brown, H. C.; Imai, T. *Organometallics* **1984**, *3*, 1392–1395.

Andrew Haidle

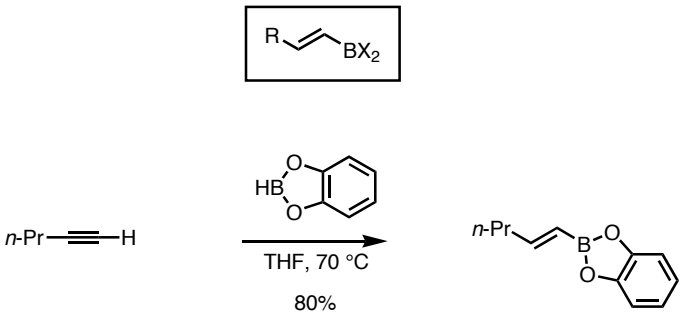


Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tetrahedron Lett.* **1988**, *29*, 2631–2634.

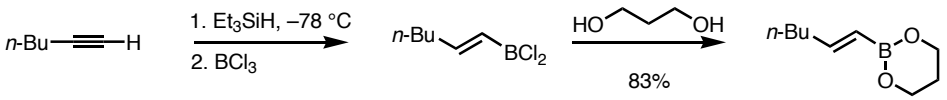
Srebnik, M.; Bhat, N. G.; Brown, H. C. *Tetrahedron Lett.* **1988**, *29*, 2635–2638.



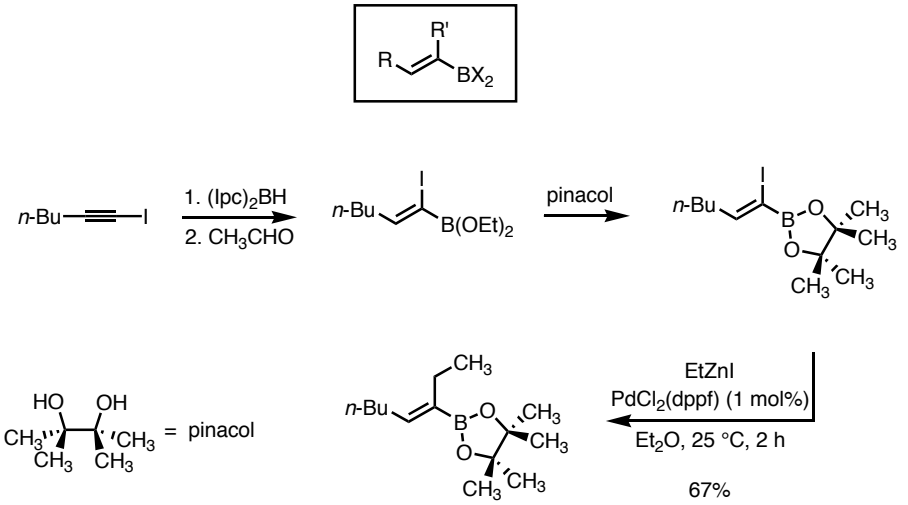
Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, *122*, 4990–4991.



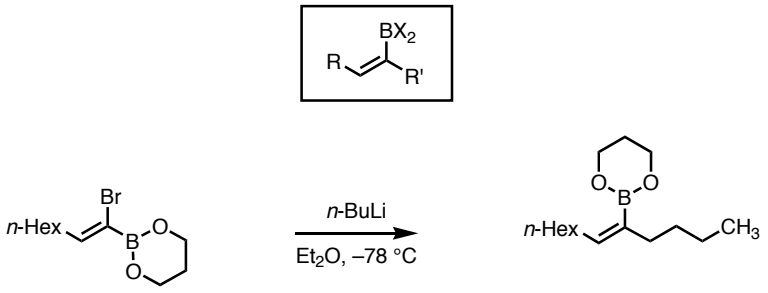
Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370–4371.



Soundararajan, R.; Matteson, D. S. *J. Org. Chem.* **1990**, *55*, 2274–2275.

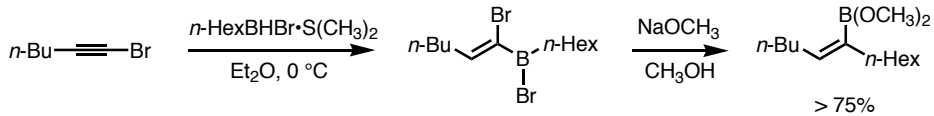


Moriya, T.; Miyaura, N.; Suzuki, A. *Chemistry Lett.* **1993**, 1429–1432.



• Grignard reagents can also be used.

Brown, H. C.; Imai, T.; Bhat, N. G. *J. Org. Chem.* **1986**, *51*, 5277–5282.



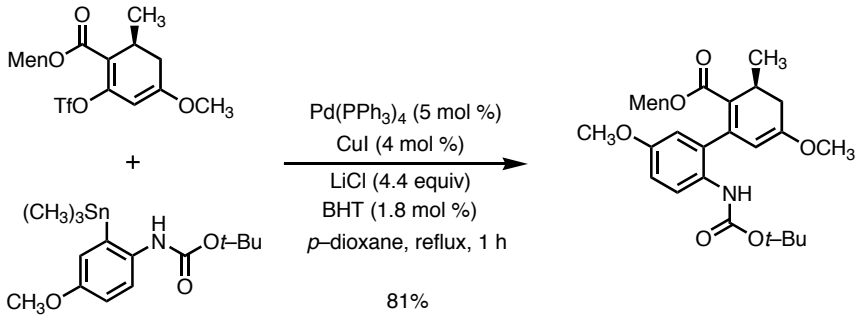
• Exact yield not specified because the vinyl borane shown was oxidized to a ketone.

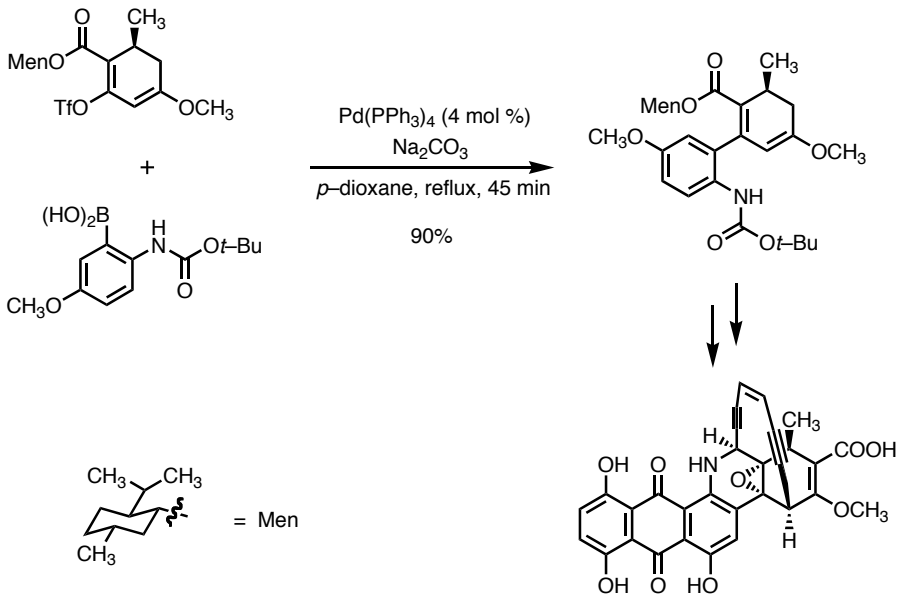
Brown, H. C.; Basavaiah, D.; Kulkarni, S. U. *J. Org. Chem.* **1982**, *47*, 3808–3810.

Andrew Haidle

Comparison of the Stille and Suzuki cross-coupling methods:

• The yields are often comparable:

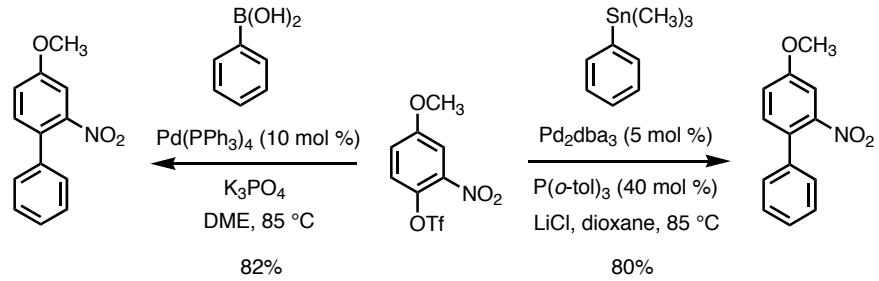




(+)-Dynemicin A

• The higher cost and toxicity of organostannanes makes the Suzuki coupling the preferred method.

Myers, A. G.; Tom., N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072–6094.

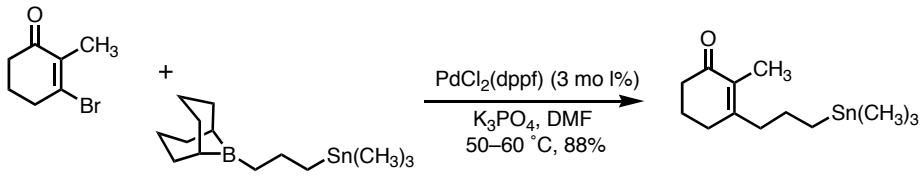


Holzapfel, C. W.; Dwyer, C. *Heterocycles* **1998**, *48*, 1513–1518.

• Some highly sensitive compounds do not tolerate the basic conditions of the Suzuki reaction.

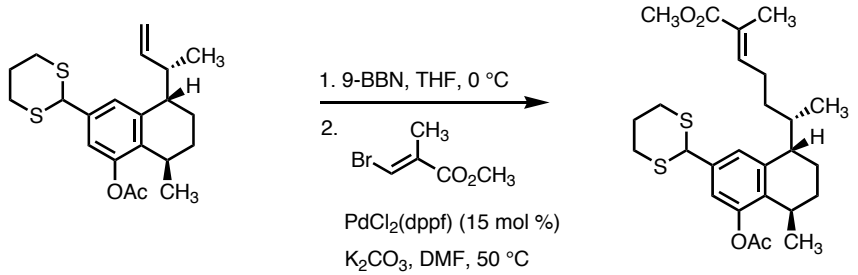
Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1998**, *50*, 1–652.

• When alkylboron and alkylstannane groups are present in the same molecule, the organoboron groups react preferentially under basic conditions.



Ishiyama, T.; Miyaura, N.; Suzuki, A. *Synlett* **1991**, 687–688.

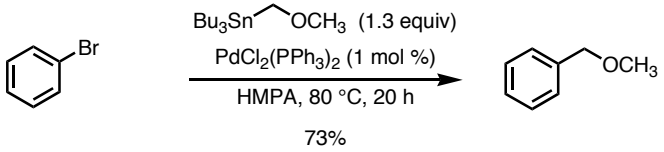
• The cross-coupling reaction of primary organoboranes is possible, while primary organo–stannanes are not typically used.



Uemura, M.; Nishimura, H.; Minami, T.; Hayashi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 5402–5410.

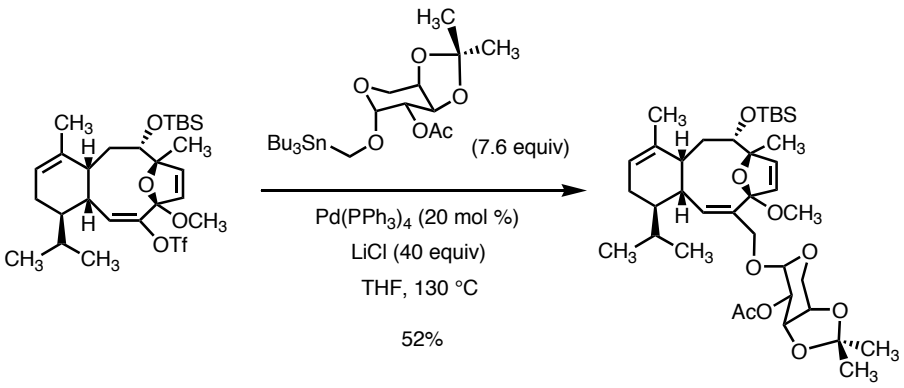
Andrew Haidle

• Stille couplings with primary organostannanes typically involve special structural features, such as an α-heteroatom, and typically cannot undergo β-hydride elimination.



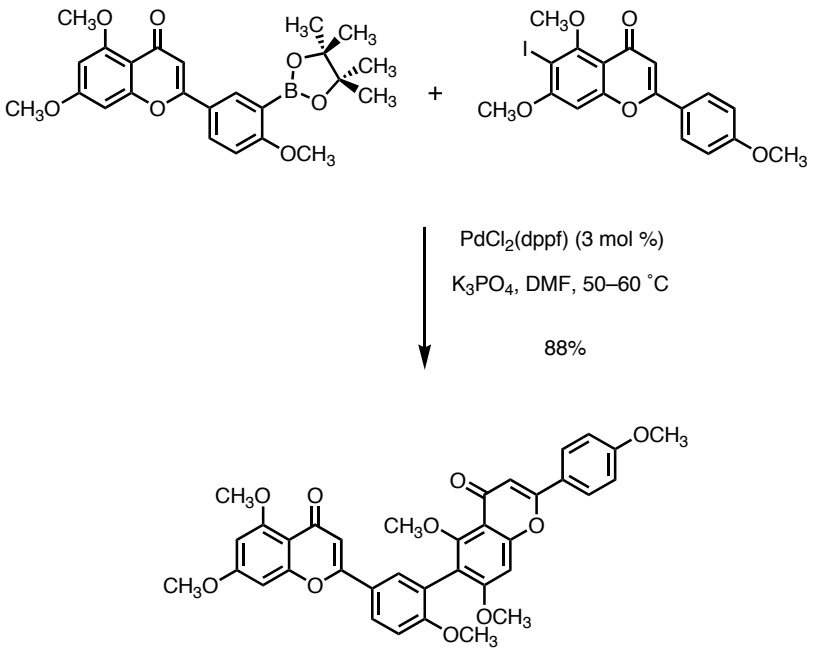
Kosugi, M.; Sumiya, T.; Ogata, T.; Sano, H.; Migita, T. *Chemistry Lett.* **1984**, 1225–1226.

• The Stille coupling has been used for the introduction of glycosylmethyl groups.



Chen, X.-T.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 6563–6579.

• In the following examples, the Suzuki coupling was successful but the corresponding Stille reaction failed. This was attributed to a proposed slower rate of transmetalltion in the Stille reaction.



Zembower, D.E.; Zhang, H. *J. Org. Chem.* **1998**, 9300–9305.

Andrew Haidle