

Reviews:

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

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.

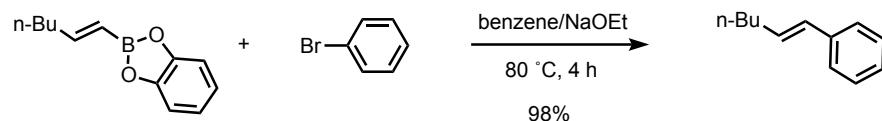
B-Alkyl Suzuki reaction:

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

Solid phase:

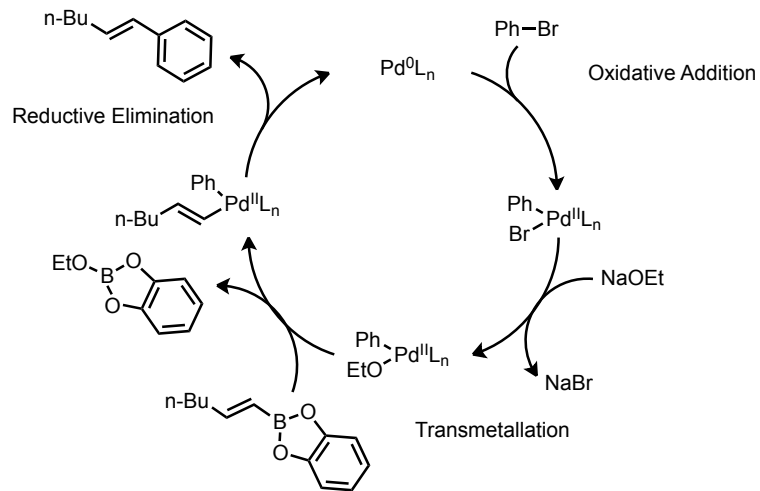
Franzén, R. *Can. J. Chem.* **2000**, 78, 957–962.

- 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.

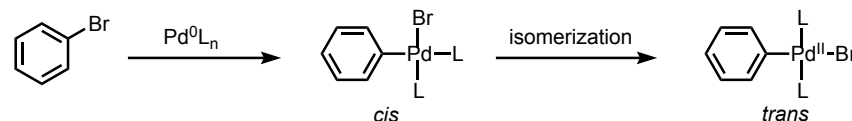
Mechanism:



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

Analysis of Elementary Steps in the Reaction Mechanism

Oxidative Addition



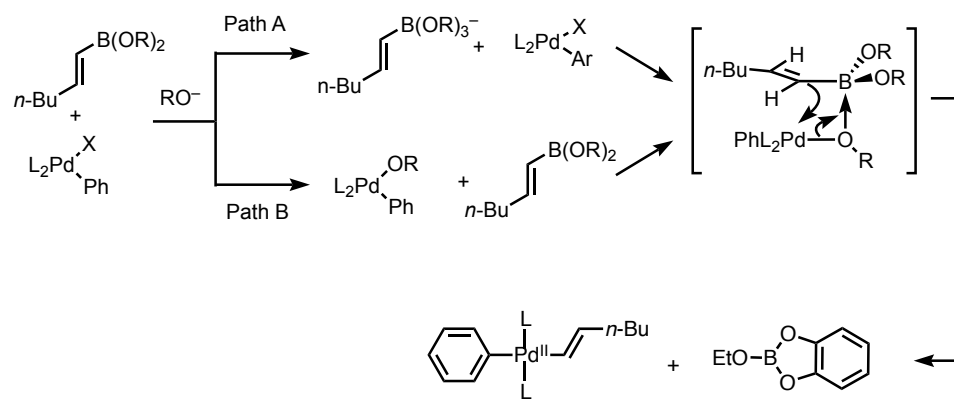
- Relative reactivity of leaving groups: $\text{I}^- > \text{OTf}^- > \text{Br}^- \gg \text{Cl}^-$.
- Oxidative addition is known to proceed with retention of stereochemistry with vinyl halides and with inversion with allylic or benzylic halides.

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

- Oxidative addition initially gives a *cis* complex that rapidly isomerizes to its *trans* isomer.

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

Transmetalation



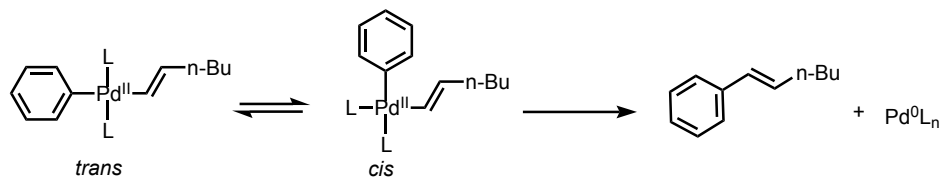
- Organoboron compounds are highly covalent in character, and do not undergo transmetalation readily in the absence of base.
- The base is postulated to serve one of two possible roles: reaction with the organoboron reagent to form a trialkoxyboronate which then attacks the palladium halide complex (Path A), or by conversion of the palladium halide to a palladium oxo complex that reacts with the neutral organoboron reagent (Path B).

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

Carrow, B.P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, 133, 2116–2119.

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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.

Conditions

R-BY ₂ + X-R'		P(PPh ₃) ₄ benzene, 80 °C		R-R'
		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
			4	98 ^b
Cl-Ph	NaOEt	2	3 ^b	
<hr/>				
		NaOEt	4	93 ^b
	I-Ph	2M NaOH	6	62 ^c
	Br-Ph	2M Na ₂ CO ₃	6	88 ^c
	Cl-Ph	NaOEt	6	0 ^c
<hr/>				
		2M NaOH	2	87 ^d
		2M NaOH	2	99 ^d

- The conditions shown on the left 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.

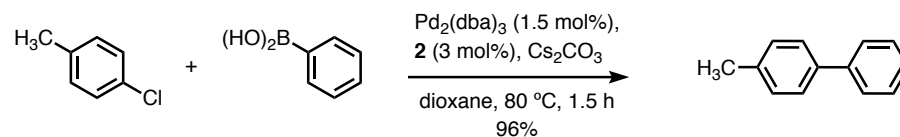
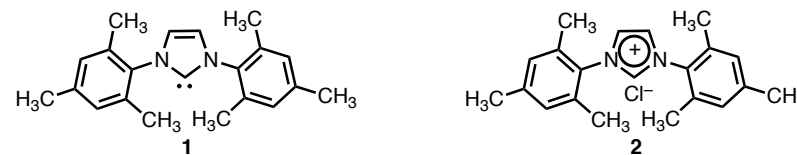
^c Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513-519.

^d Miyaura, N.; Yano, T.; Suzuki, A. *Tetrahedron Lett.* **1980**, *21*, 2865-2868.

Catalyst and ligands

- The most commonly used system is Pd(PPh₃)₄, but other palladium sources have been used including Pd^{II} pre-catalysts that are reduced to the active Pd⁰ *in situ*:
 - Pd₂(dba)₃ + PPh₃
 - Pd(OAc)₂ + PPh₃
 - PdCl₂(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.



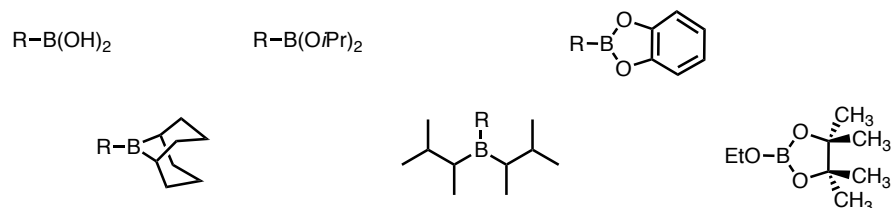
- The nucleophilic N-heterocyclic carbene **1** is the active ligand, and is formed *in situ* from **2**.
- The use of ligand **1** allows for utilization of aryl chlorides in the Suzuki reaction (see the section on bulky, electron-rich phosphines as ligands for use of aryl chlorides as coupling partners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

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

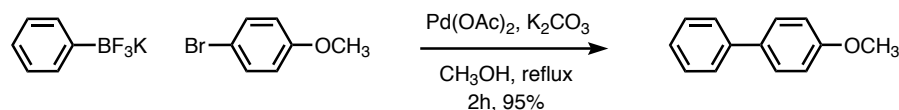
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Organoboranes: A variety of organoboranes may be used to effect the transfer of the organic coupling partner to the reactive palladium center via transmetalation. Choice of the appropriate organoborane will depend upon the compatibility with the coupling 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.

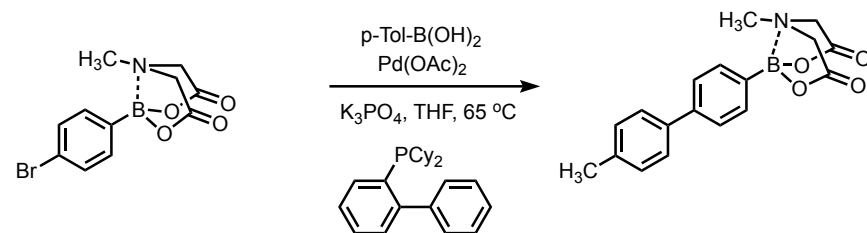
Molander, G. A.; Biolatto, B. J. *Org. Chem.* **2003**, *68*, 4302–4314.

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.

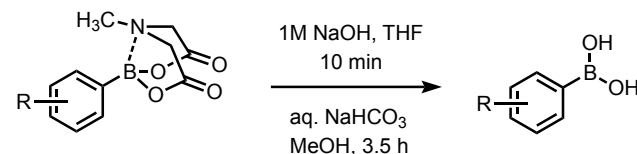
Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324–4330.

N-methyliminodiacetic acid (MIDA) Boronates

- This trivalent boron protecting group attenuates transmetalation, and is unreactive under anhydrous coupling conditions (see example below).



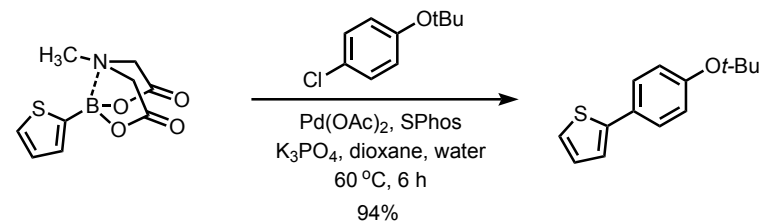
- MIDA boronates are stable to chromatography but are readily cleaved under basic aqueous conditions:



Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6716–6717.

Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 14084–14085.

- Many unstable boronic acids, such as 2-heteroaryl, vinyl and cyclopropyl, form bench-stable MIDA complexes.
- "Slow release" of boronic acid allows effective coupling of these substrates.

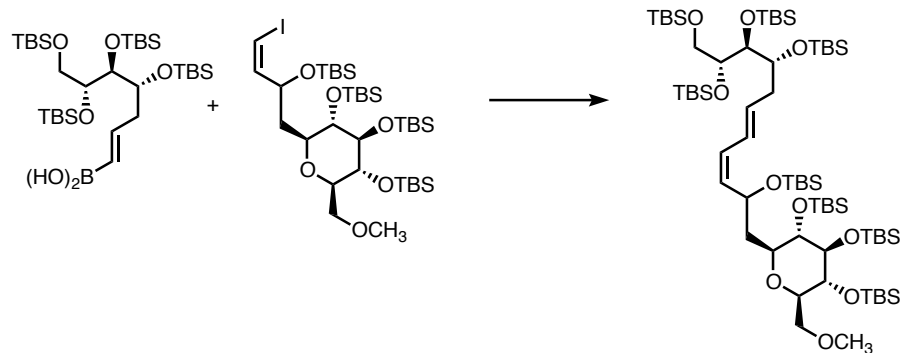


(Yield from the corresponding boronic acid: 37%)

Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961–6963.

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TIOH and TIOEt as Rate-Enhancing Additives for the Suzuki Reaction

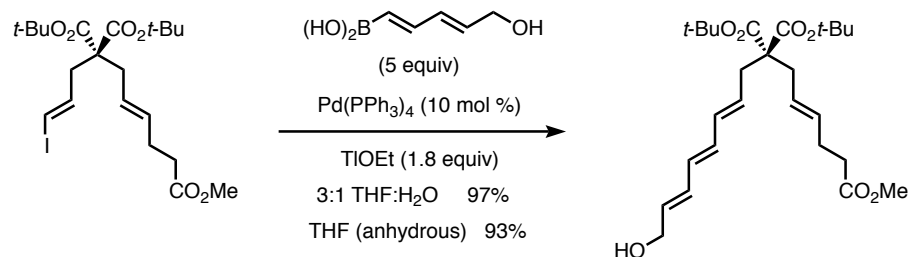


base	temp (°C)	time	yield	relative rate
KOH	23	2 h	86	1
TIOH	23	<<30 s	92	1000

- TIOH greatly accelerates 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.

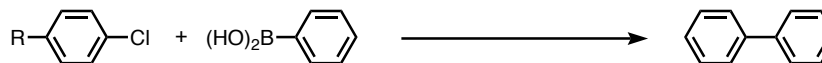
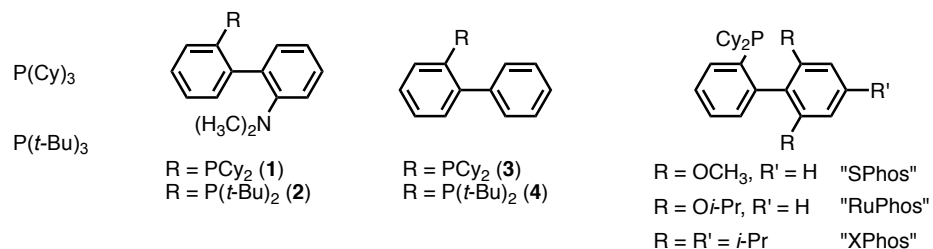
- TIOH vs. TIOEt



- Roush has found that TIOEt is a generally superior source of TI for Suzuki couplings. Pure TIOH is available from only a single source, aqueous solutions of TIOH have a poor shelf life, and the aqueous solutions are both air and light sensitive.
- The largest problem with using TIOEt is that some boronic acid–TIOEt 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	ligand	Pd source	base	solvent	temp (°C)	time (h)	yield (%)
CH ₃	PPh ₃	Pd ₂ (dba) ₃	Cs ₂ CO ₃	dioxane	80	5	0 ^a
CH ₃	$\left\{ \begin{array}{l} P^t-Bu_3 \\ \mathbf{4} \end{array} \right.$	Pd ₂ (dba) ₃	Cs ₂ CO ₃	dioxane	80	5	86 ^a
		Pd(OAc) ₂	KF	THF	23	6	95 ^b
CH ₃ O	$\left\{ \begin{array}{l} P^t-Bu_3 \\ \mathbf{4} \end{array} \right.$	Pd ₂ (dba) ₃	Cs ₂ CO ₃	dioxane	80	5	89 ^a
		Pd(OAc) ₂	KF	THF	45	6	93 ^b
NH ₂	P ^t -Bu ₃	Pd ₂ (dba) ₃	Cs ₂ CO ₃	dioxane	80	5	92 ^a
H ₃ C	P ^t -Bu ₃	Pd ₂ (dba) ₃	Cs ₂ CO ₃	dioxane	80	5	91 ^a

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

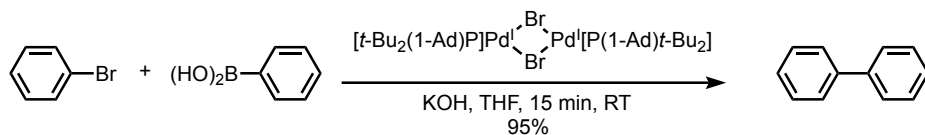
^b Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561.

- Bulky phosphine ligands lead to a monoligated palladium species which is highly reactive to oxidative addition.
- These ligands are commercially available.
- The increased activity of the ligands shown above allows unactivated aryl chlorides and bromides to be employed in Suzuki couplings under mild conditions.

Christmann, U.; Vilar, R. *Angew. Chem. Int. Ed.* **2005**, *44*, 366–374.

Fu, G. *Acc. Chem. Res.* **2008**, *41*, 1555–1564.

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

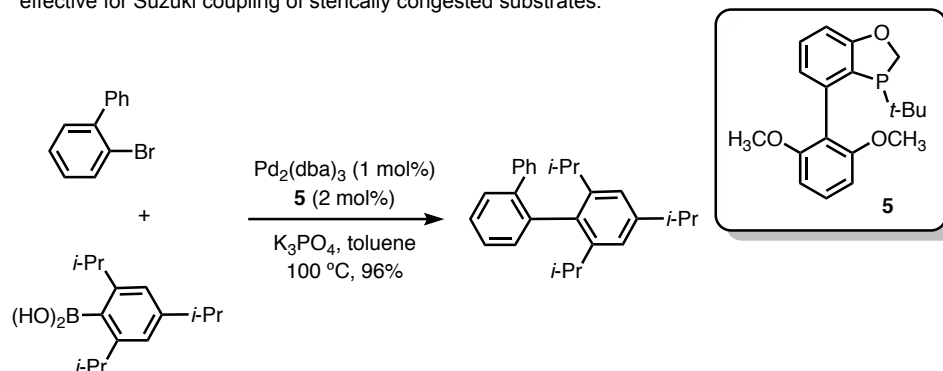


- As a solid, the catalytic complex is stable indefinitely in the air. It is believed that the catalyst fragments to form the monomeric subunits under the reaction conditions.

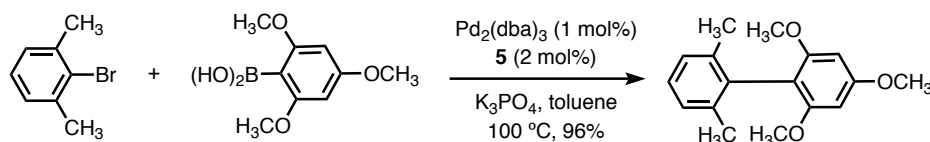
- Reactions of phenylboronic acids with (deactivated) aryl chlorides occurred rapidly at room temperature, but conversion did not exceed 70%.

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

- Ligand **5**, accessible in kilogram quantities and stable indefinitely in the air, was found to be highly effective for Suzuki coupling of sterically congested substrates.



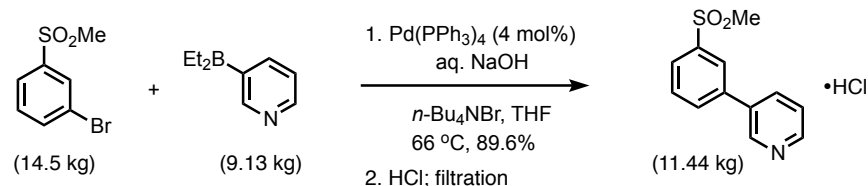
- Other ligands such as SPhos, RuPhos, XPhos, PPh₃, PCy₃, and *Pt*-Bu₃ generally proceeded with <20% conversion.



Tang, W.; Capacci, A. G.; Wei, X.; Li, W.; White, A.; Patel, N.; Savoie, J.; Gao, J. J.; Rodriguez, S.; Qu, B.; Haddad, N.; Lu, B. Z.; Krishnamurthy, D.; Yee, N. K.; Senanayake, C. *Angew. Chem. Int. Ed.* **2010**, *49*, 5879-5883.

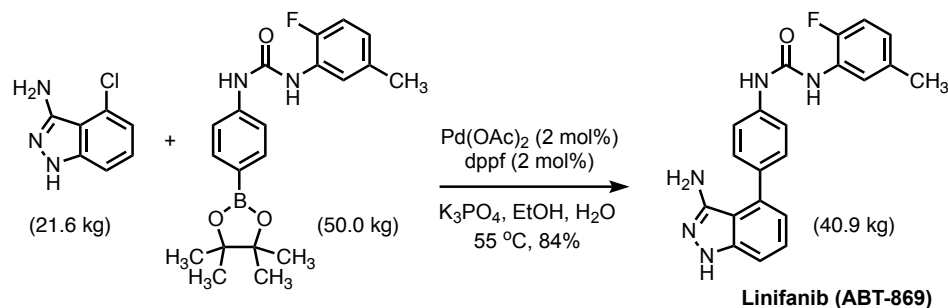
Selected Applications in Industry

- The Suzuki reaction is routinely used in the fine chemical, agrochemical and pharmaceutical industries.



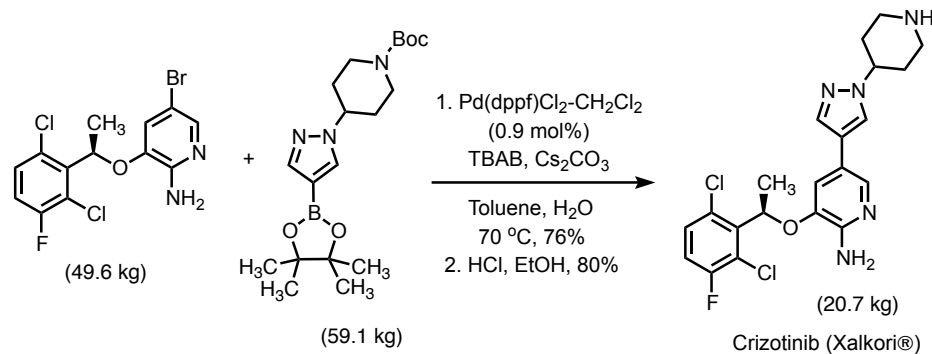
Lipton, M. F.; Mauragis, M. A.; Maloney, M. T.; Velej, M. F.; VanderBor, D. W.; Newby, J. J.; Appell, R. B.; Daugs, E. D. *Org. Proc. Res. Dev.* **2003**, *7*, 385-392.

- Application to the synthesis of a tyrosine kinase inhibitor:



Kruger, A. W.; Rozema, M. J.; Chu-Kung, A.; Gandarilla, J.; Haight, A. R.; Kotecki, B. J.; Richter, S. M.; Schwartz, A. M.; Wang, Z. *Org. Proc. Res. Dev.* **2009**, *13*, 1419-1425.

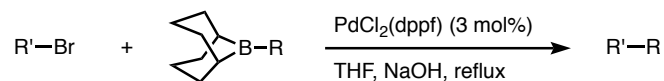
- Application to the synthesis of Xalkori®, an anti-cancer drug for treatment of non-small cell lung carcinoma:



de Koning, P. D. *et. al. Org. Proc. Res. Dev.* **2011**, *15*, 1018-1026.

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B-Alkyl Suzuki Reaction



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

• With the advent of the PdCl₂(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.

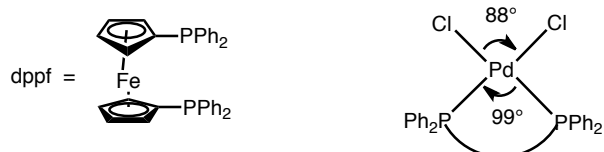
• Secondary alkyl boron compounds are not suitable coupling partners for this reaction.

• Alkyl boronic esters are also viable substrates in the B-alkyl Suzuki reaction when thallium salts such as TlOH or Tl₂CO₃ 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.

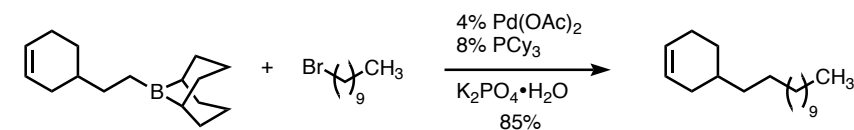


Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158–163.

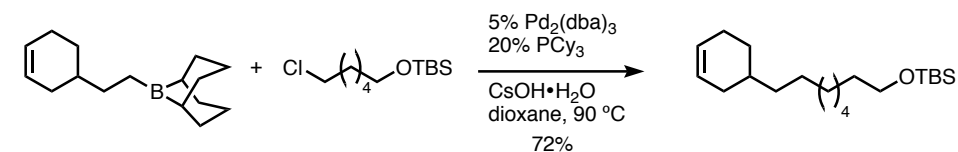
Brown, J. M.; Guiry, P. J. *Inorg. Chim. Acta.* **1994**, *220*, 249–259.

sp³-sp³ 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:



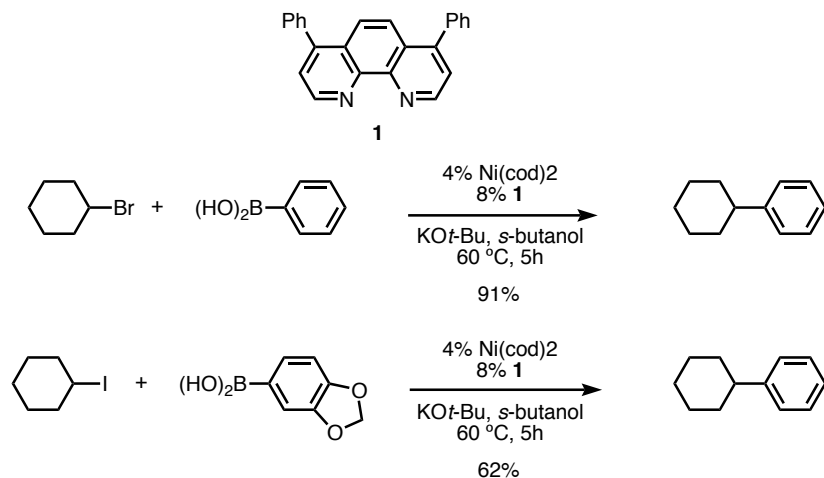
Netherton, M. R.; Dai, C.; Klaus, N.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099–10100.



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

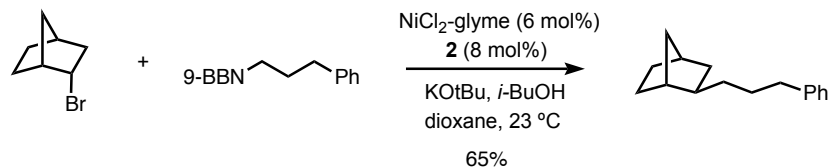
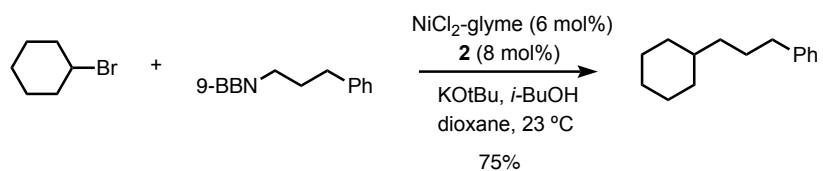
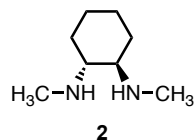
• Fu and coworkers have developed a Ni⁰-catalyzed Suzuki coupling of unactivated secondary alkyl bromides and iodides:



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

sp³-sp³ Suzuki Cross-Coupling of Unactivated Secondary Alkyl Halides

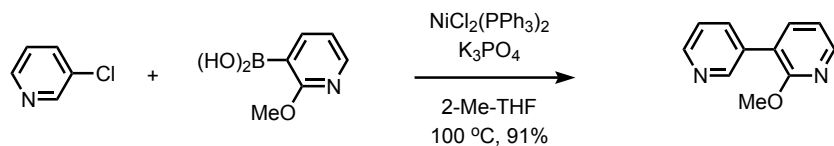
- Diamine **2** was found to be an effective ligand for metal-catalyzed cross-coupling of unactivated alkyl electrophiles.



- "endo-2-bromonorbornane is converted into the exo product, most likely due to a radical pathway for oxidative addition." — Gonzalez-Bobes, F.; Fu, G. *J. Am. Chem. Soc.* **2006**, *128*, 5360–5361.

Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602–9603.

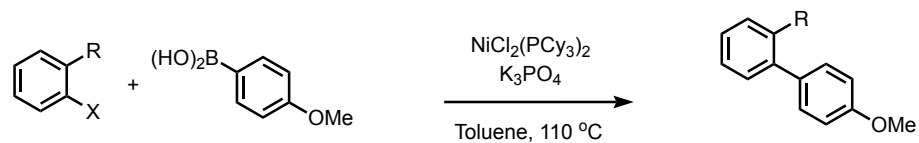
Nickel Catalyzed Suzuki Couplings



Ramgren, S.D.; Hien, L.; Ye, Y.; Garg, N. K. *Org. Lett.* **2013**, *15*, 3950–3953

- Nickel catalysts have been effective with electrophiles that are inert to palladium catalysts, including carbonates, carbamates, sulfamates, esters, phosphate esters and ethers.

Han, F.-S. *Chem. Soc. Rev.* **2013**, *42*, 5270–5298.

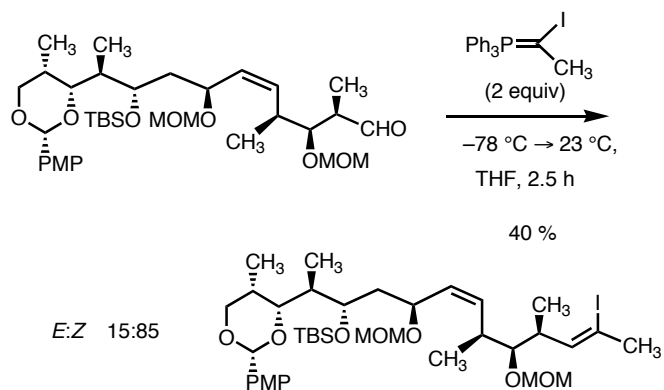


X = OC(O)NEt ₂	R = H	52%
X = OSO ₂ NMe ₂	R = H	83%
X = OPiv	R = Me	79%

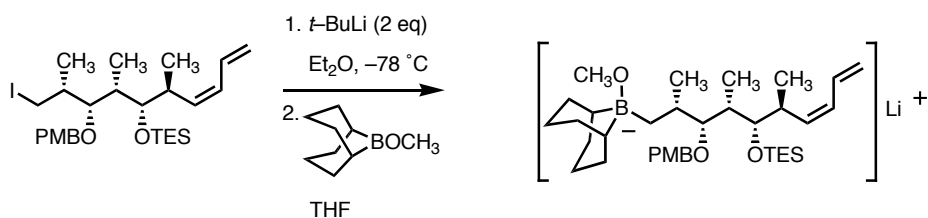
Quasdorf, K. W.; Reiner, M.; Petrova, K. V.; Garg, N. K. *J. Am. Chem. Soc.* **2009**, *131*, 17748–17749.

Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422–14423.

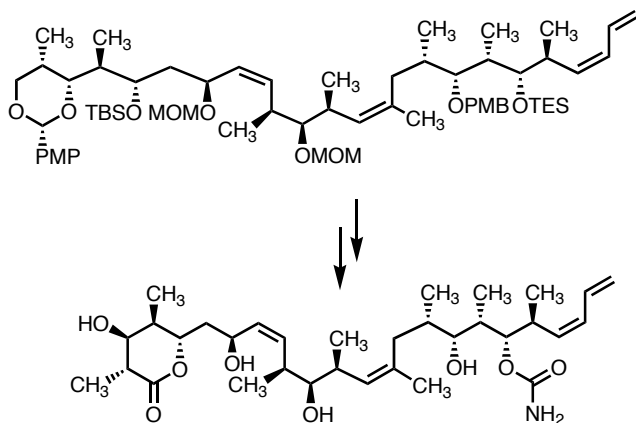
(+)-Discodermolide (*B*-Alkyl Suzuki Reaction)



A



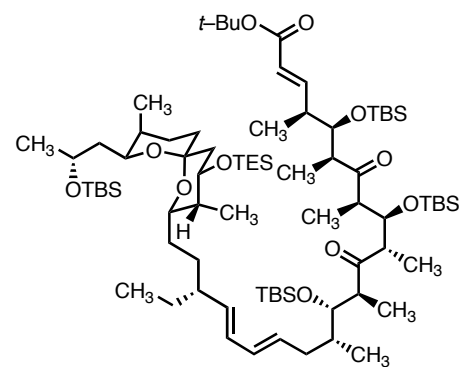
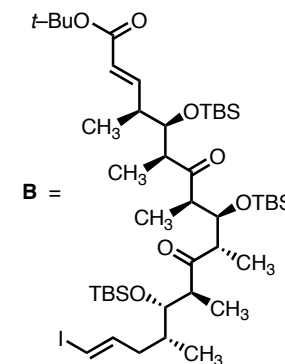
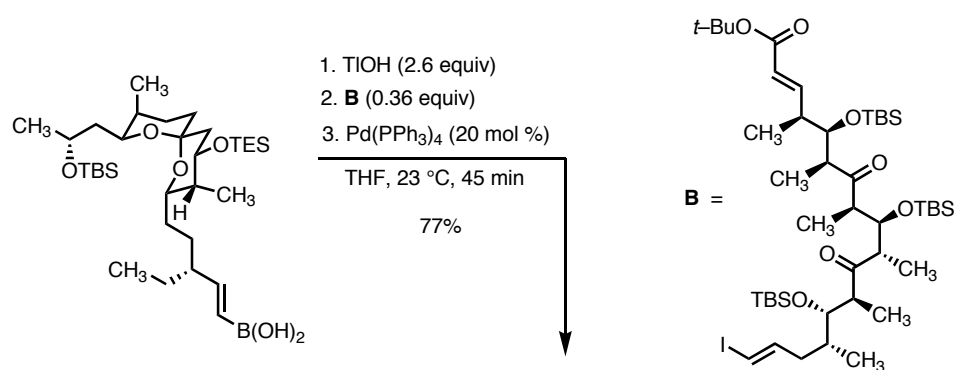
1. K_3PO_4 (2.3 equiv), $23\text{ }^\circ\text{C}$
 2. **A**, DMF
 3. $\text{PdCl}_2(\text{dppf})$ (10 mol %), 16 h
 74%



(+)-Discodermolide

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

Rutamycin B

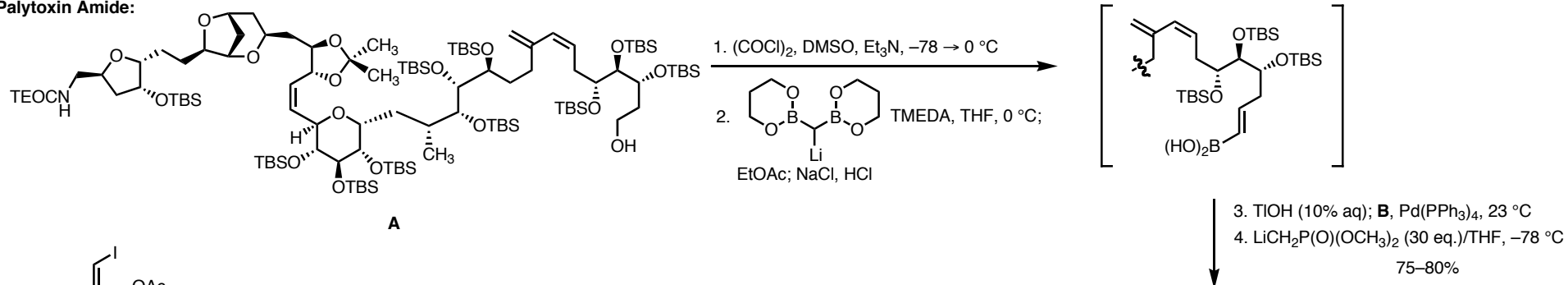


Rutamycin B

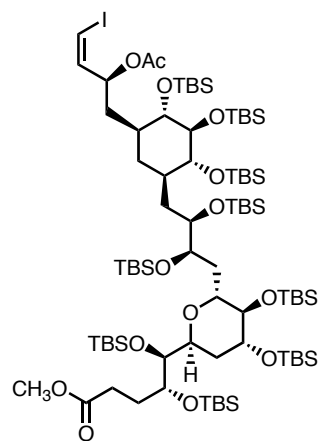
Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446–11459.

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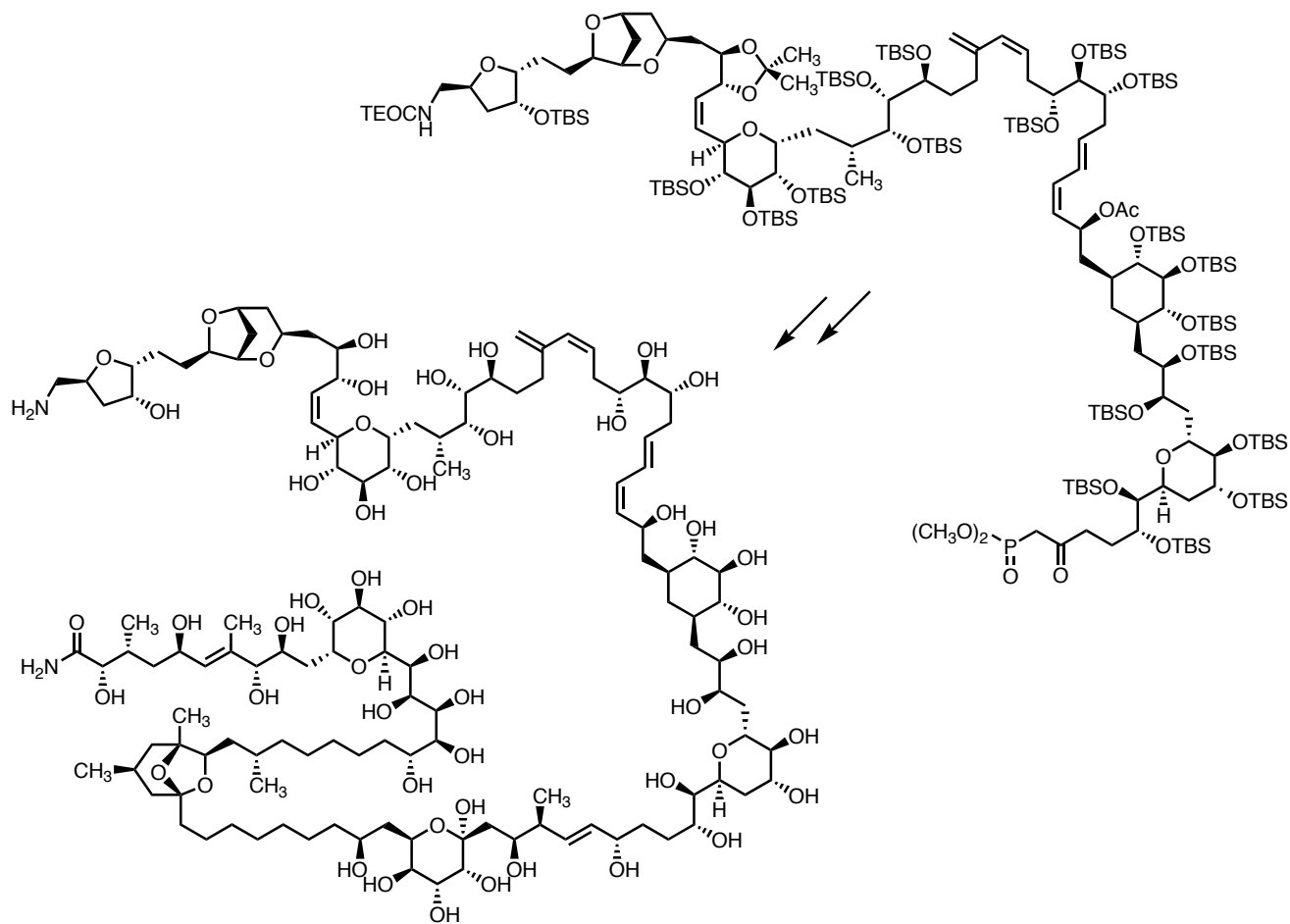
Palytoxin Amide:



A



B



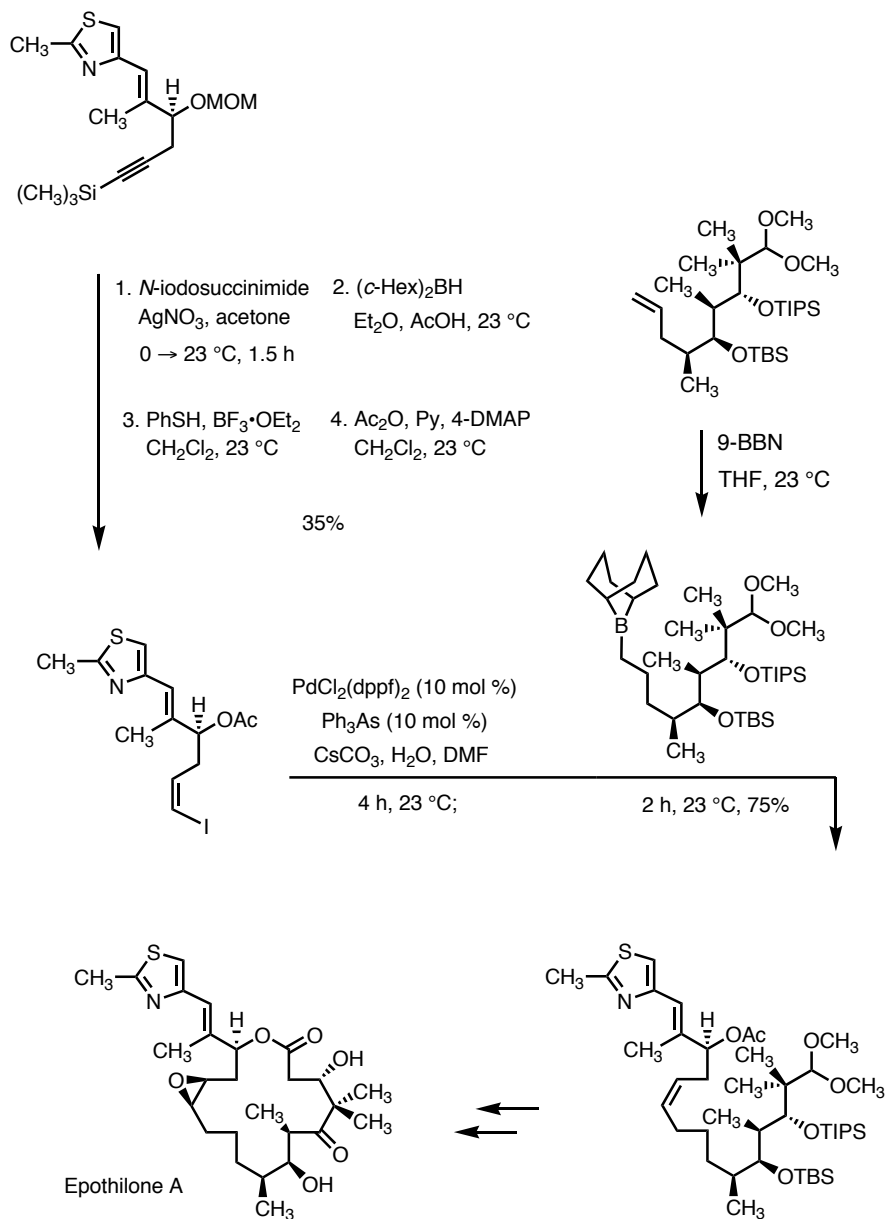
Palytoxin amide

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

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

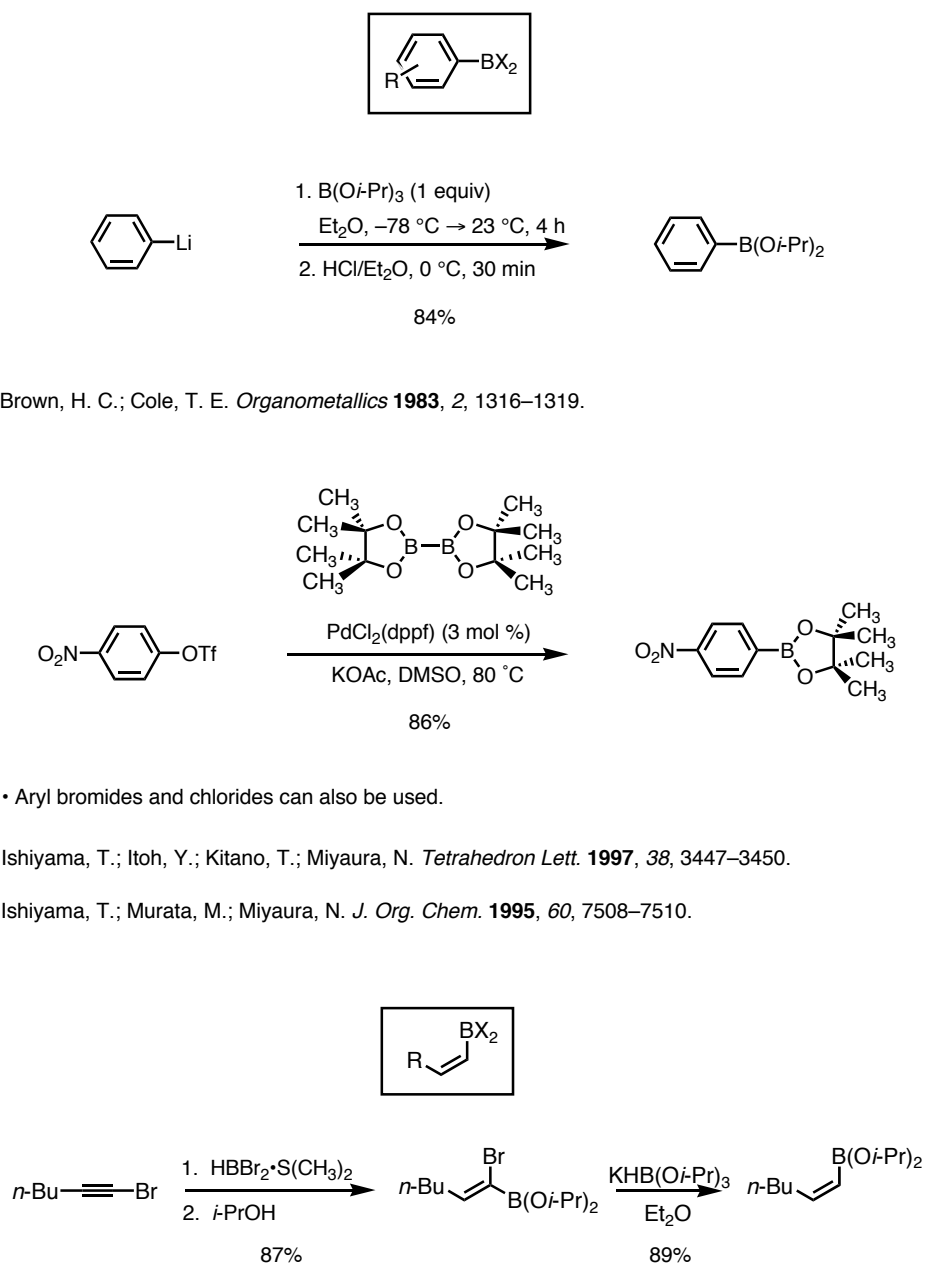
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Epothilone A:



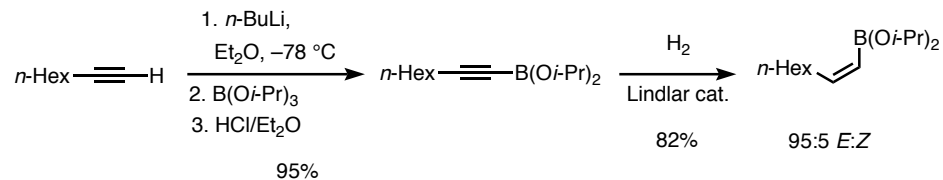
Meng, D.; Bertinato, P.; Balog, A.; Su, D.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S., J. *J. Am. Chem. Soc.* **1997**, *119*, 10073–10092.

Synthesis of organoboron compounds:



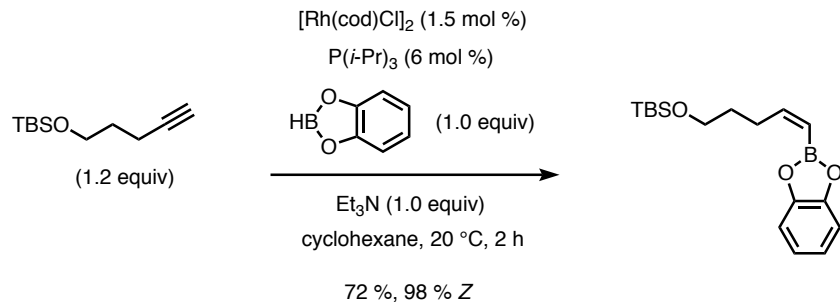
Brown, H. C.; Imai, T. *Organometallics* **1984**, *3*, 1392–1395.

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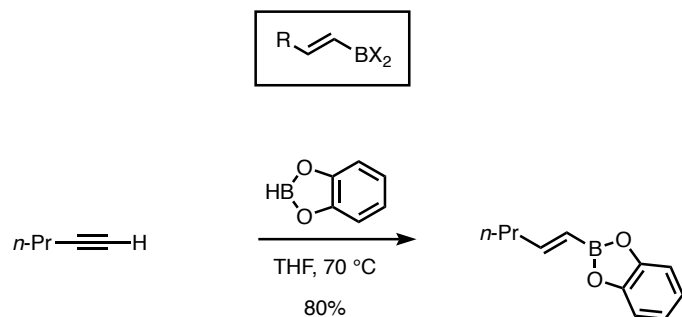


Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tetrahedron Lett.* **1988**, *29*, 2631–2634.

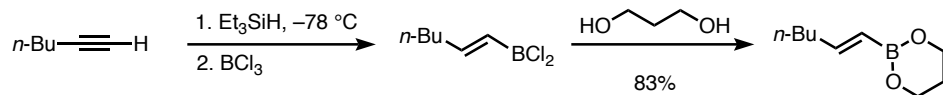
Srebnik, M.; Bhat, N. G.; Brown, H. C. *Tetrahedron Lett.* **1988**, *29*, 2635–2638.



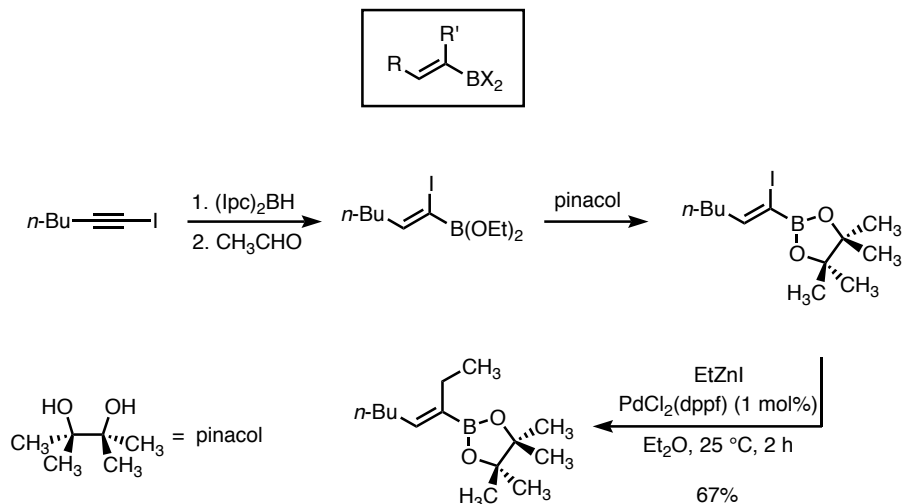
Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, *122*, 4990–4991.



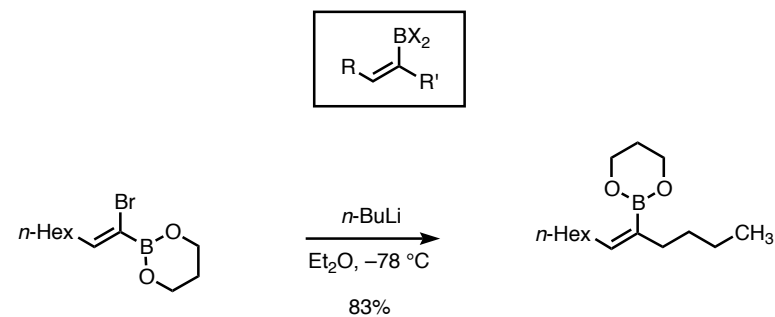
Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370–4371.



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

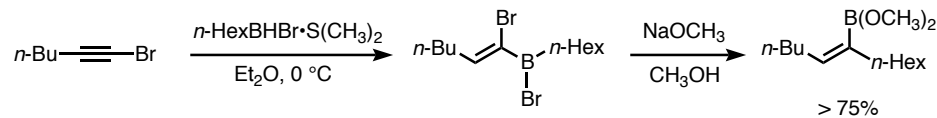


Moriya, T.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1993**, 1429–1432.



• Grignard reagents can also be used.

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



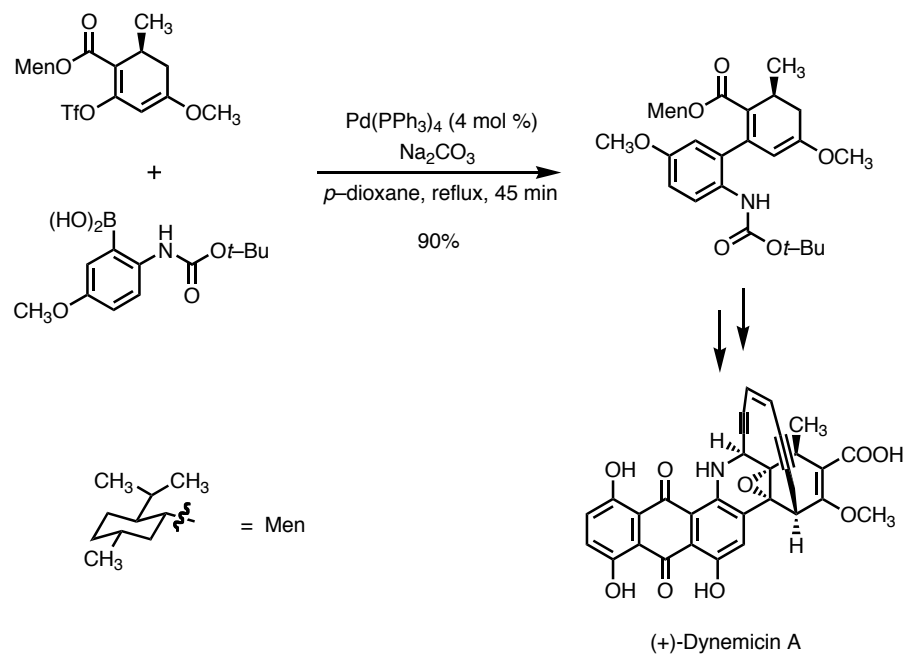
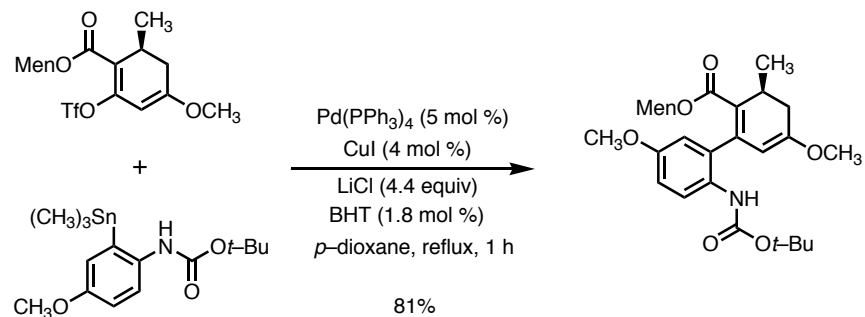
• Exact yield not specified because the vinyl borane shown was oxidized to a ketone.

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

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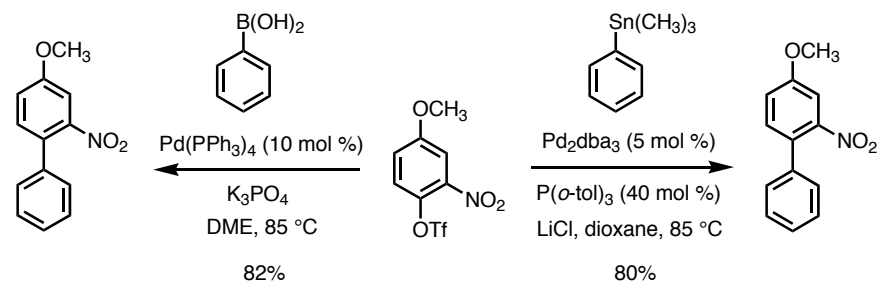
Comparison of the Stille and Suzuki cross-coupling methods:

- The yields are often comparable:



- 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.

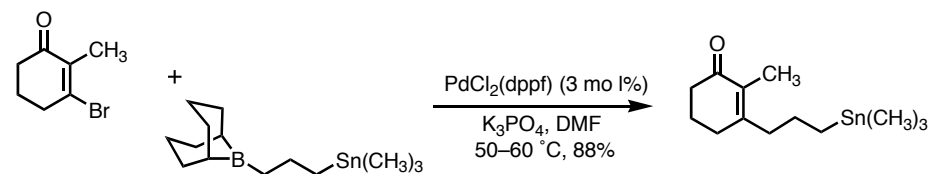


Holzappel, C. W.; Dwyer, C. *Heterocycles* **1998**, *48*, 1513–1518.

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

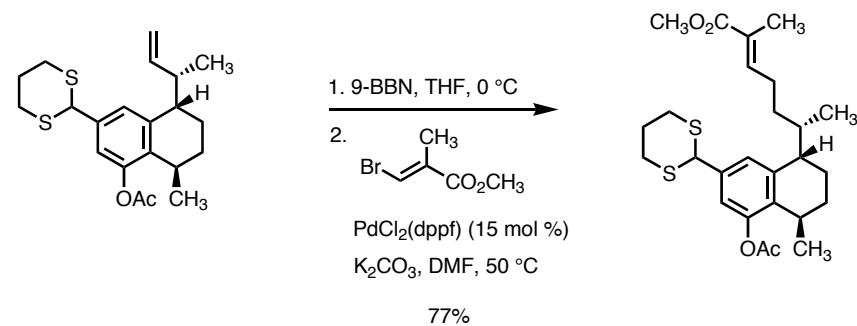
Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1998**, *50*, 1–652.

- 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.

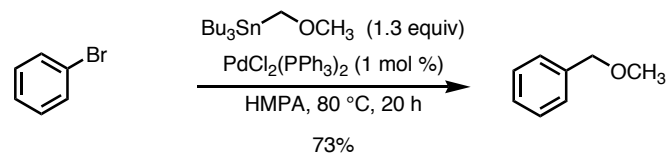
- The cross-coupling reaction of primary organoboranes is possible, while primary organostannanes are not typically used.



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

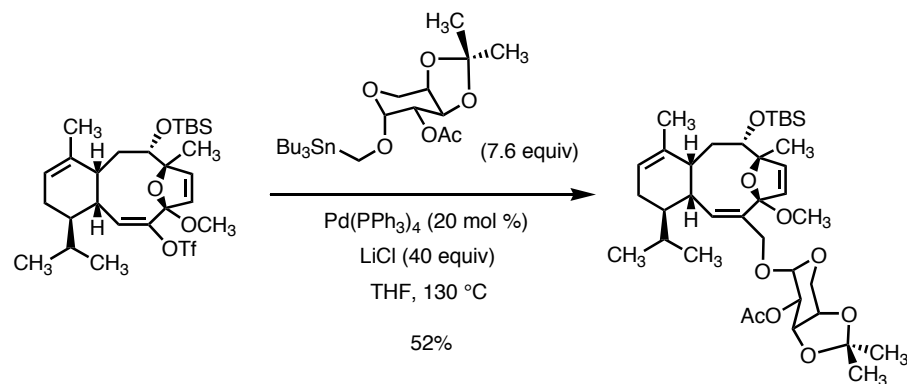
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- Stille couplings with primary organostannanes typically involve special structural features, such as an α -heteroatom, and typically cannot undergo β -hydride elimination.



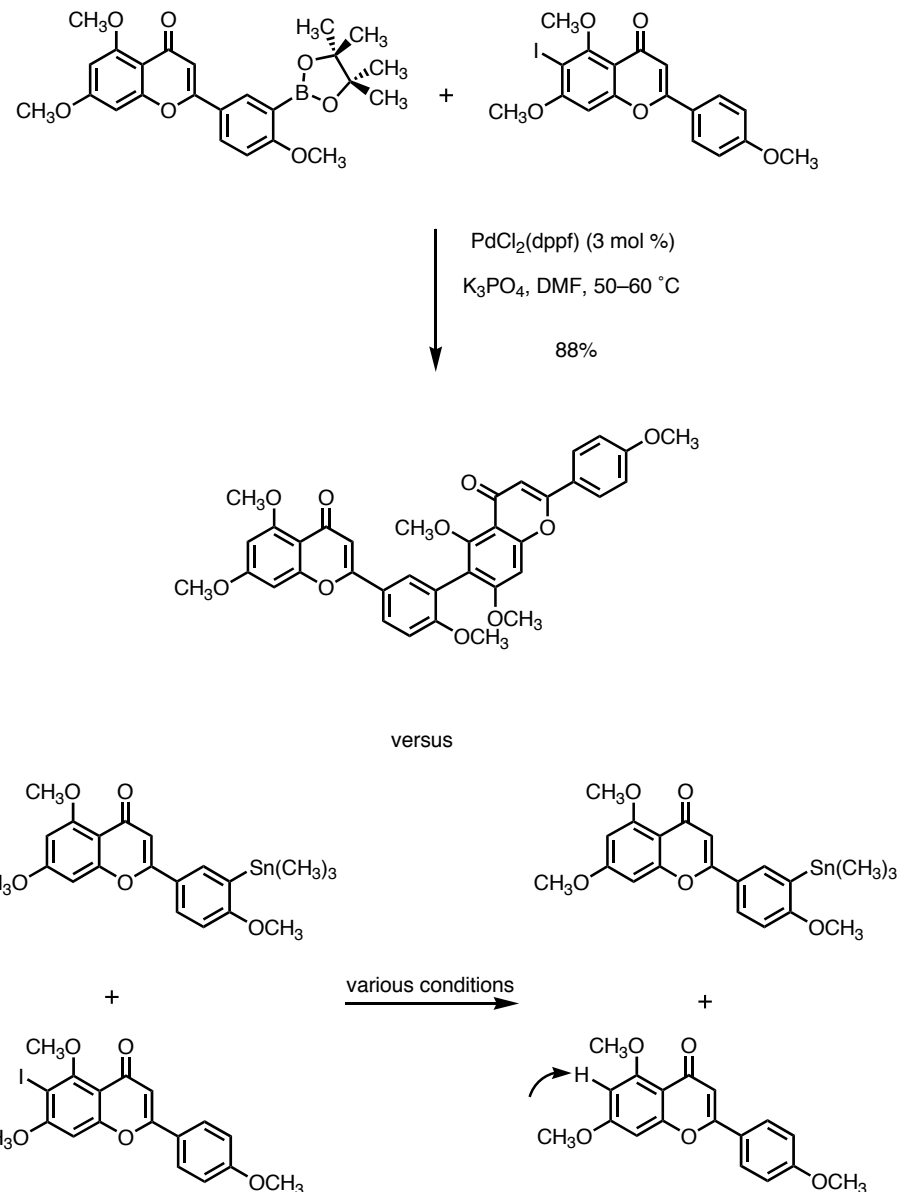
Kosugi, M.; Sumiya, T.; Ogata, T.; Sano, H.; Migita, T. *Chemistry Lett.* **1984**, 1225–1226.

- 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 transmetalation in the Stille reaction.



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

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