Recent Reviews:

Williams, R. *Org. Synth.* **2011**, *88*, 197–201.
Selig, R.; Schollmeyer, D.; Albrecht, W.; Laufer, S. *Tetrahedron* **2011**, 67, 9204–9213.
Tietze, L. F.; Dufert, A. *Pure Appl. Chem.*, **2010**, *82*, 1375–1392.

Generalized Cross-Coupling:

$$\mathrm{R{-}X} \;+\; \mathrm{R'{-}M} \xrightarrow{\text{catalyst}} \mathrm{R{-}R'} \;+\; \mathrm{M{-}X}$$

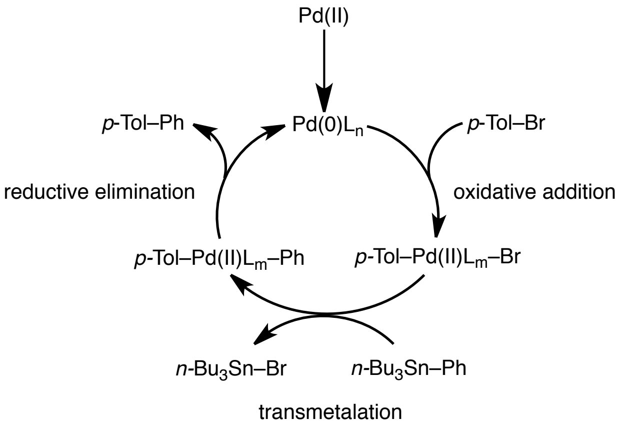
Typically:

- R and R' are sp^2–hybridized
- X = I, OSO_2CF_3, Br, Cl
- M = Sn, B, Zr, Zn
- catalyst = Pd (sometimes Ni)

Mechanism:

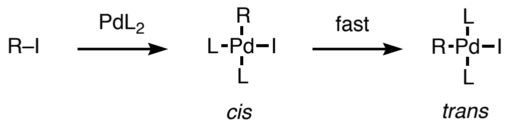
- A specific example:

$$p\text{-Tol–Br} \;+\; n\text{-Bu}_3\text{Sn–Ph} \xrightarrow{\text{Pd catalyst}} p\text{-Tol–Ph} \;+\; n\text{-Bu}_3\text{Sn–Br}$$



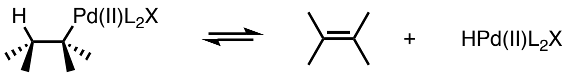
- Many functional groups are tolerated (e.g., CO_2R, CN, OH, CHO).

- Oxidative addition initally gives a *cis* complex that can rapidly isomerize to the *trans* isomer:



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

- β-hydride elimination can be a serious side reaction within alkyl palladium intermediates. This typically requires a *syn* coplanar alignment of hydride and palladium:



- Oxidative-addition and reductive-elimination steps occur with retention of configuration for sp^2-hybridized substrates.

- Transmetalation is proposed to be the rate-determining step with most substrates.

- Relative order of ligand transfer from Sn:

  alkynyl > alkenyl > aryl > allyl = benzyl > α-alkoxyalkyl > alkyl

- **Electron-rich** and sterically hindered aryl halides undergo **slower** oxidative addition and are often **poor** substrates as a result.

- **Electron-poor** stannanes undergo **slower** transmetallation and are often **poor** substrates as a result.

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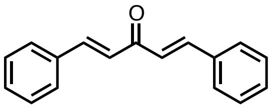
Stille Reaction conditions:

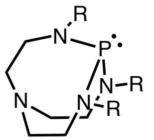
- **Catalyst**: Commercially available Pd(II) or Pd(0) sources. Examples:

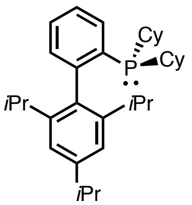
$Pd(PPh_3)_4$ $Pd(OAc)_2$ $Pd_2(dba)_3$

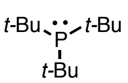
dba =



- **Ligand Additives: Sterically hindered**, **electron-rich** ligands typically **accelerate** coupling.







1 tris-*N*-*iso*-butyl Ar-Cl

2 *N*-*iso*-butyl-bis-*N*-benzyl Ar-Cl, Ar-Br

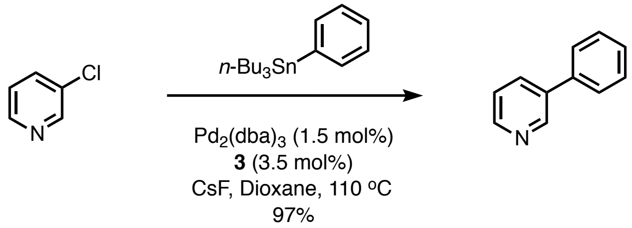
3 tris-*N*-benzyl Ar-Cl, Ar-Br, Ar-OTf, vinyl-Cl

(leading references in examples below)

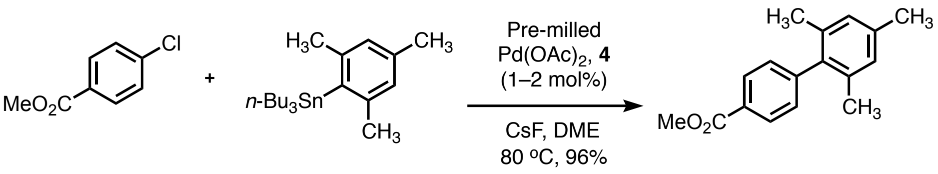
4 "X-Phos"

5

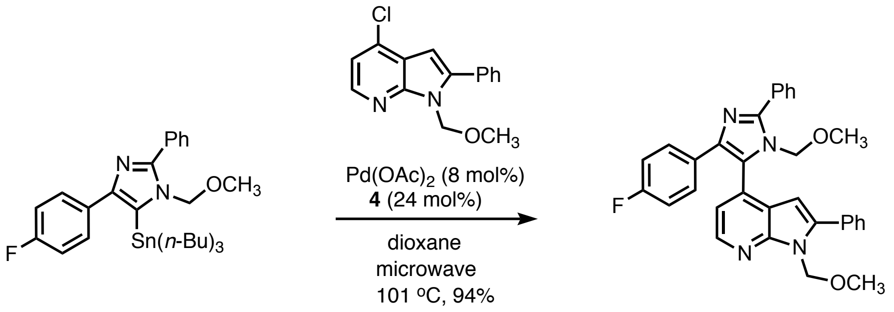
- Examples:



Verkade, J.G.; Su, W.; Urgaonkar, S.; McLaughlin, P.A. *J. Am. Chem. Soc.* **2004**, *126*, 16433-16439



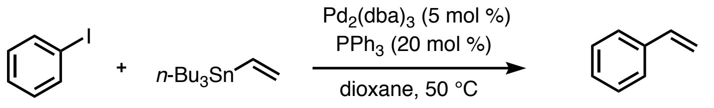
Buchwald, S.L.; Naber, J.R. *Adv. Synth. Catal.* **2008**, *350*, 957-961



This catalyst system and microwave heating limited the formation of a destannylated byproduct.

Selig, R.; Schollmeyer, D.; Wolfgang, A.; Saufer, S. *Tetrahedron* **2011**, *67*, 9204 - 9213

- **Additives**: CuI can increase the reaction rate by >10^2:

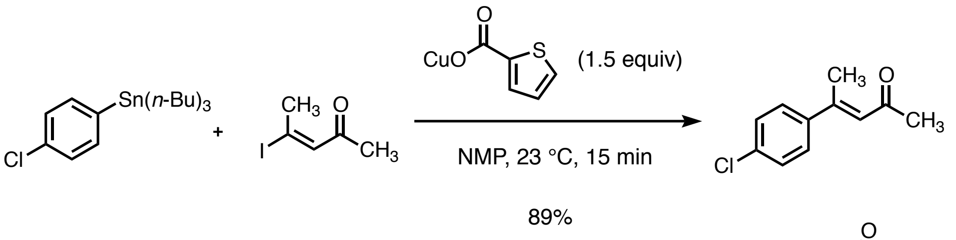


mol % CuI	relative rate
0	1
10	114

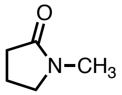
- The rate increase is attributed to the ability of CuI to scavenge free ligands; strong ligands in solution are known to inhibit the rate-limiting transmetalation step.

Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. J. Org. Chem. 1994, 59, 5905–5911.

- Stoichiometric Cu itself can sometimes mediate cross-coupling reactions under mild conditions, without Pd:



NMP =



Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748-2749.

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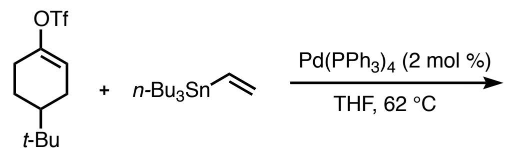
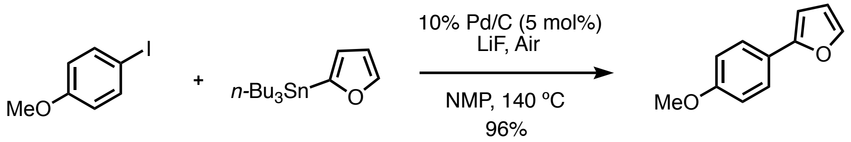
- **Additives**: fluoride can coordinate to the organotin reagent to form a hypervalent tin species that is believed to undergo transmetallation at a faster rate:



Salt (equiv)	relative rate	yield
LiCl (3)	1	>95
$Bu_4NF{\bullet}H_2O$ (1.3)	3	87

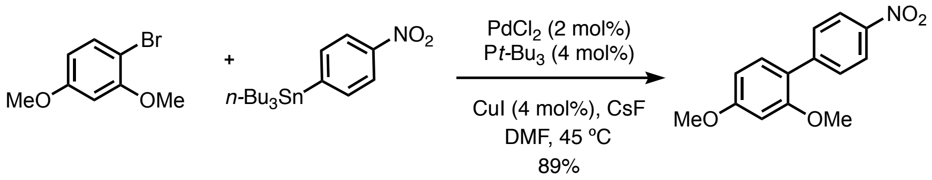
Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033–3040.

- Examples:



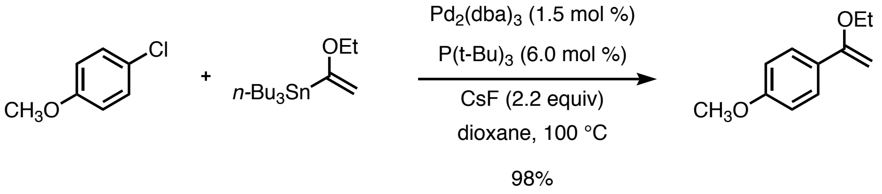
Sajiki, H.; Yabe, Y.; Maegawa, T.; Monguchi, Y. *Tetrahedron* **2010**, *66*, 8654–8660

- The following difficult coupling between an electron-rich aryl halide and electron-poor aryl stannane was accomplished using both copper and fluoride additives:



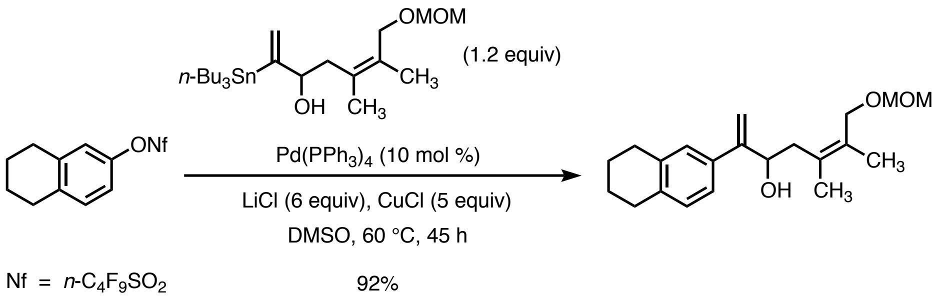
Baldwin, J. E.; Mee, S. P.H.; Lee, V. *Chem. Eur. J.* **2005**, *11*, 3294–3308

- A general Stille cross-coupling reaction employing aryl chlorides (which are more abundant and less expensive than aryl iodides, aryl bromides, and aryl triflates) has been developed:



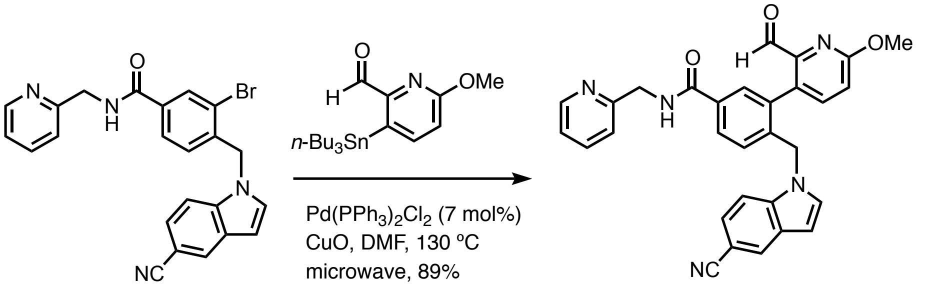
Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2411–2413.

- 1-substituted vinylstannanes can be poor substrates for the Stille reaction, probably due to steric effects. However, conditions have been discovered that provide the desired Stille coupling product in excellent yields:



Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600–1605.

- Examples of Stille coupling in drug discovery:



Smallheer, J. M.; Quan, M. L.; Wang, S.; Bisacchi, G. S. Patent: US2004/220206 A1, 2004

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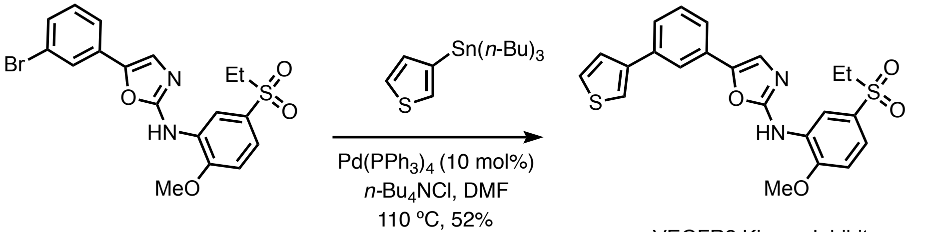
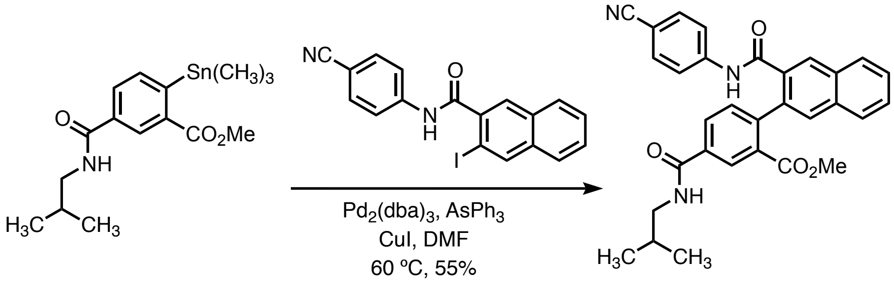


VEGFR2 Kinase Inhibitor

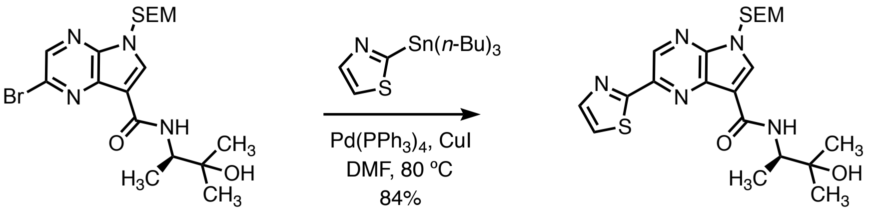
Harris, P. A.; Cheung, M.; Hunter III, R. N.; Brown, M. L.; Veal, J. M.; Nolte, R. T.; Wang, L.; Liu, W.; Crosby, R. M.; Johnson, J. H.; Epperly, A. H.; Kumar, R.; Luttrell, D. K.; Stafford, J. A. *J. Med. Chem.* **2005** , *48*, 1610–1619

- Both $AsPh_3$ and CuI are required to provide the coupled product in the following example:



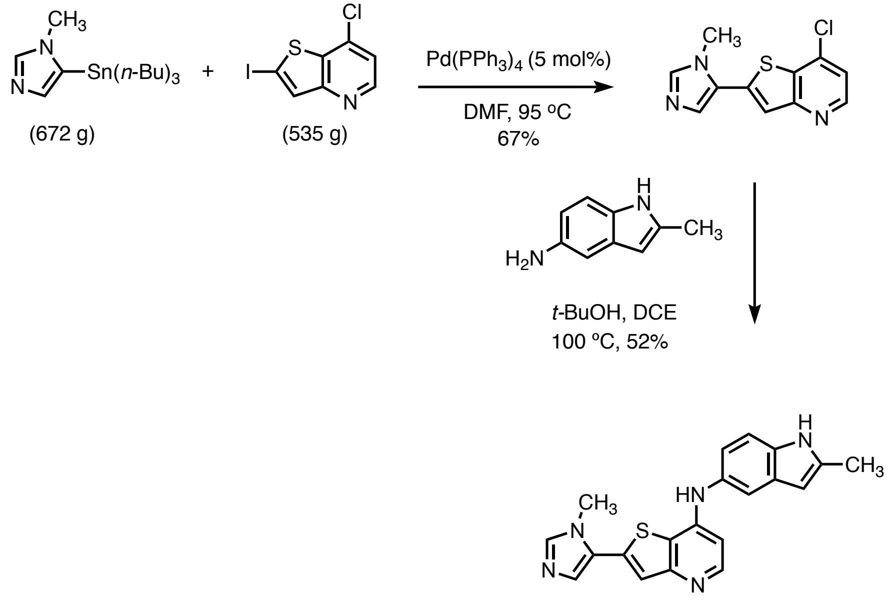
Kohrt, J. T.; Filipski, K. J.; Rapundalo, S. T.; Cody, W. L.; Edmunds, J. J. *Tetrahedron Lett.* **2000**, *41*, 6041–6044

- Note the presence of both OH and NH groups is tolerated under Stille coupling conditions:



Hendricks, R. T.; Hermann, J. C.; Jaime-Figueroa, S.; Kondru, R. K.; Lou, Y.; Lynch, S. M.; Owens, T. D.; Soth, M.; Yee, C. W. Patent: WO2011/144585

- **Industrial examples of the Stille Reaction in Large-Scale Process Chemistry**
- Many organostannanes are toxic and therefore tolerance for residual tin in pharmaceutical products is extremely low. The following examples show methods by which residual tin can be minimized:



VEGFR Kinase Inhibitor

- The Stille reaction was the only reliable coupling method at > 50-g scale.
- Residual tin was minimized by slurring the coupling product in MTBE followed by recrystallization from ethyl acetate.

Ragan, J. A.; Raggon, J. W.; Hill, P. D.; Jones, B. P.; McDermott, R. E.; Munchhof, M. J.; Marx, M. A.; Casavant, J. M.; Cooper, B. A.; Doty, J. L.; Lu, Y. *Org. Proc. Res. Dev*. **2003**, *7*, 676 - 683

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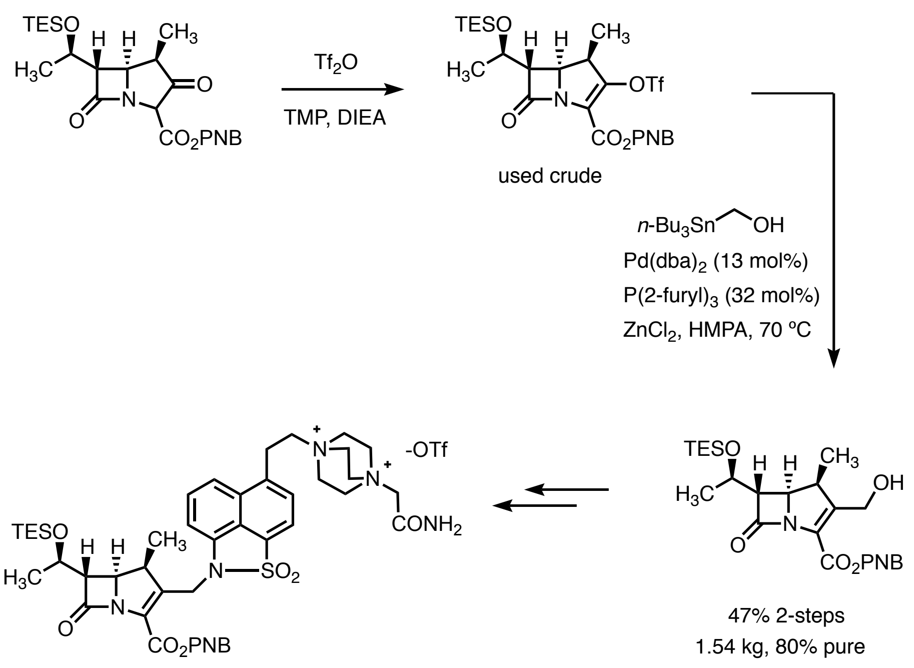


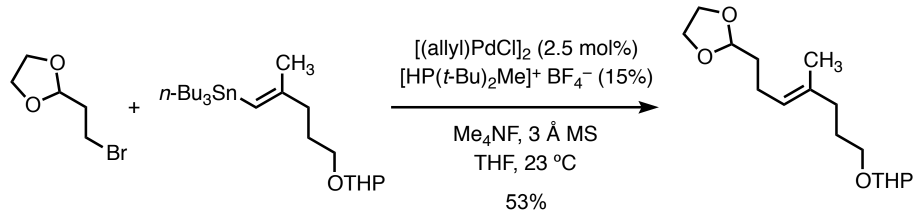
L-786,392, a "carbapenem" antibiotic candidate with activity against methicillin-resistant Staphylococcus aureus (MRSA).

- HMPA, a somewhat toxic ligand, was essential for successful coupling.
- Tin residues were minimized by silica-gel chromatography followed by recrystallization from hexane.

Yasuda, N.; Yang, C.; Wells, K. M.; Jensen, M. S.; Hughes, D. L. *Tetrahedron Lett.* **1999**, *40*, 427–430.

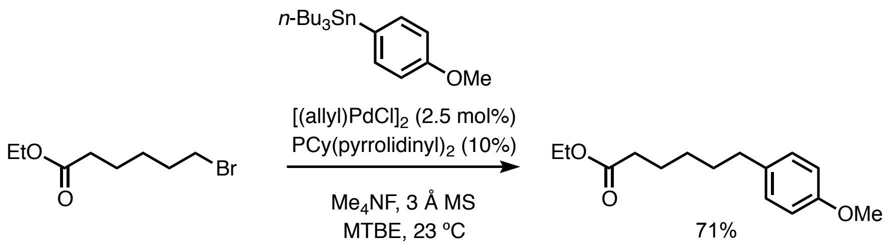
Alkyl Stille Coupling Reactions - sp^2-sp^3:

- Initially, "alkyl" Stille couplings were mostly limited to the transfer of Me, Allyl and Benzyl groups.
- Coupling of higher *n*-alkyl groups was limited by β-hydride eliminations. This limitation has been overcome by innovations in the ligand and Pd sources.
- **sp^2-sp^3 coupling:** alkyl-Br + vinyl-SnR$_3$



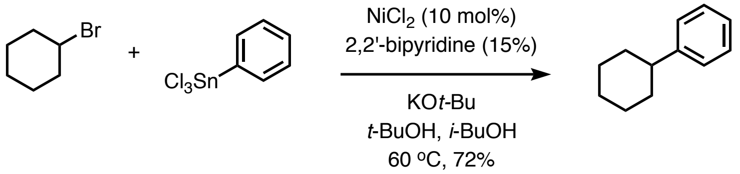
Fu, G.C.; Menzel, K. *J. Amer. Chem. Soc.* **2003**, *125*, 3718.

- using the electron-rich PCy(pyrrolidinyl)$_2$ ligand allows couplings of both vinyl and aryl stannanes with higher alkyl bromides:



Fu, G.C.; Menzel, K.; Tang, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 5079.

- **Secondary Alkyl Couplings:** secondary alkyl halides are also prone to undergo β-hydride elimination in Stille coupling. This limitation has been overcome by using a Ni catalyst:



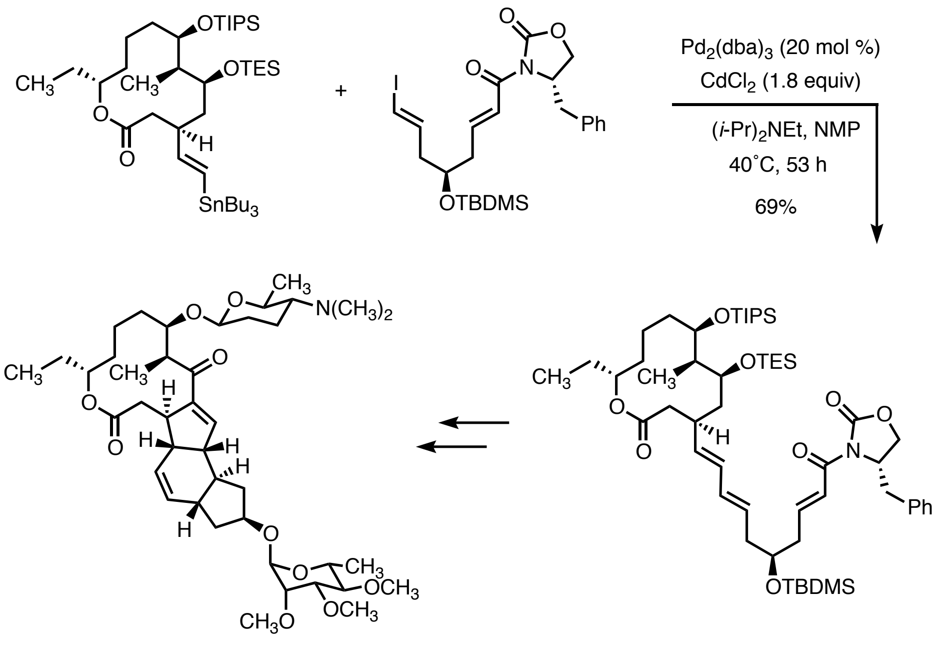
The use of PhSnCl$_3$ facilitated the removal of toxic by-products during reaction work-up.

Fu, G.C.; Maki, T.; Powell, D.A. *J. Amer. Chem. Soc.* **2005**, *127*, 510

Jeff Kohrt

Examples:

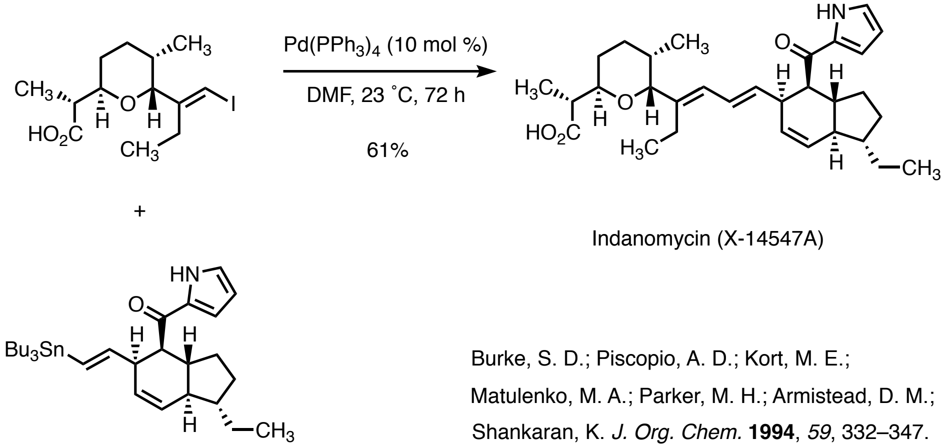
- Alkenes as coupling partners:



(+)-A83543A, (+)-Lepicidin

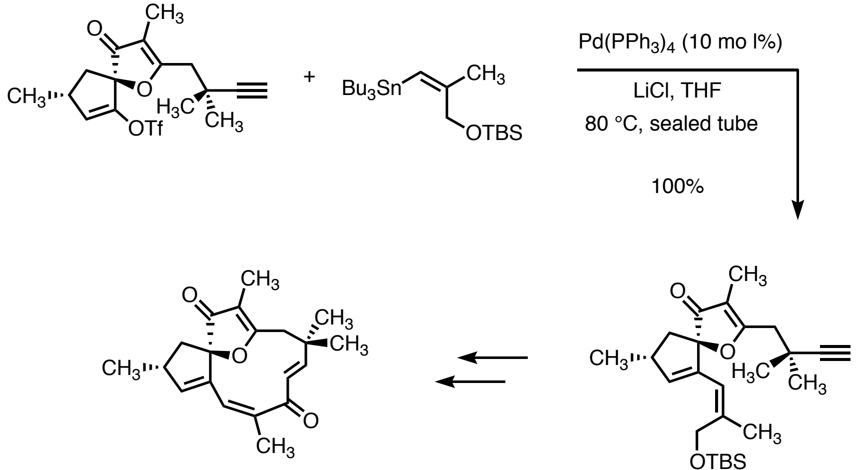
- CdCl$_2$ serves as a transmetalation cocatalyst. Without it, homodimerization of both coupling partners was observed.

Evans, D. A.; Black, W. D. *J. Am. Chem. Soc.* **1993**, *115*, 4497–4513.



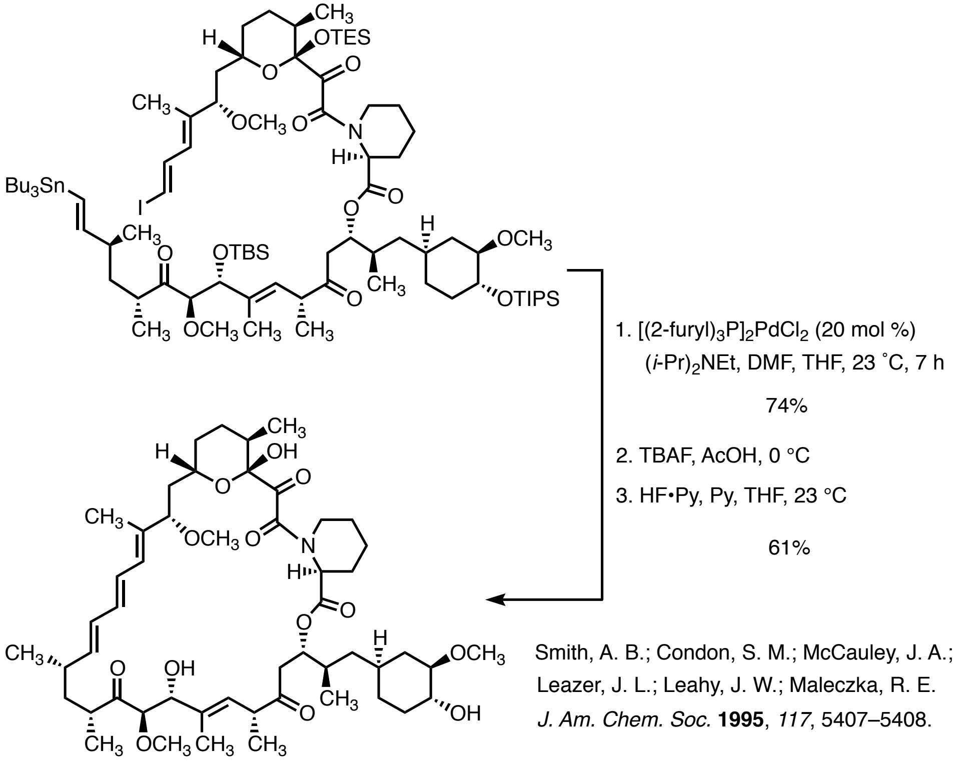
Indanomycin (X-14547A)

Burke, S. D.; Piscopio, A. D.; Kort, M. E.; Matulenko, M. A.; Parker, M. H.; Armistead, D. M.; Shankaran, K. *J. Org. Chem.* **1994**, *59*, 332–347.



Jatrophone

Han, Q; Wiemer, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 7692–7697.

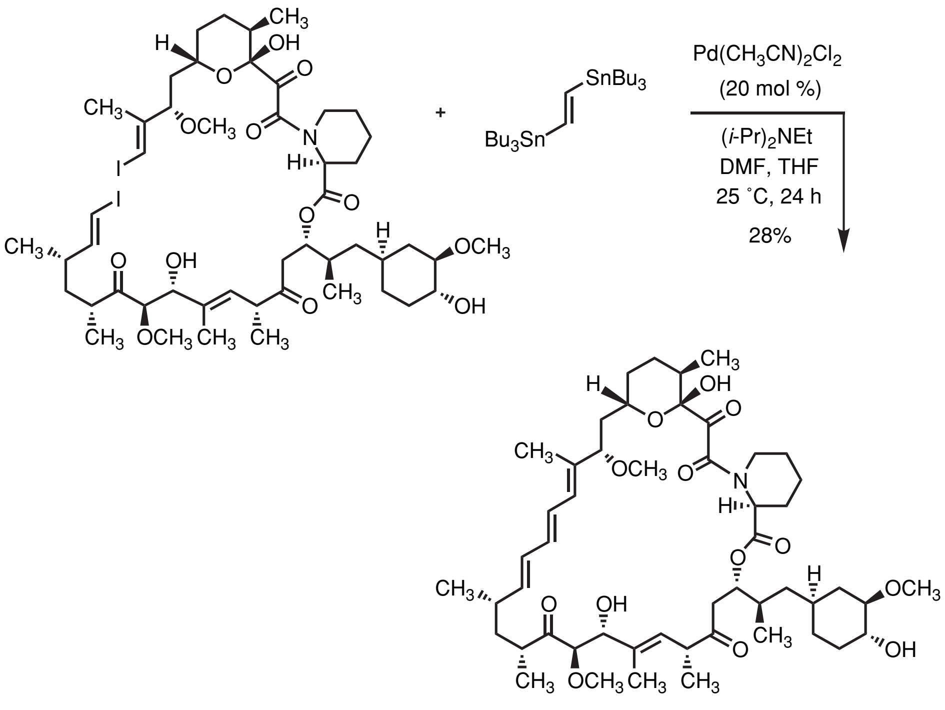


Rapamycin

Smith, A. B.; Condon, S. M.; McCauley, J. A.; Leazer, J. L.; Leahy, J. W.; Maleczka, R. E. *J. Am. Chem. Soc.* **1995**, *117*, 5407–5408.

Andrew Haidle

Further Examples:

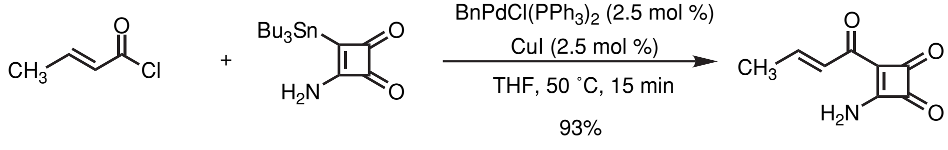


Rapamycin

Nicolaou, K. C.; Chakraborty, T. K; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419–4420.

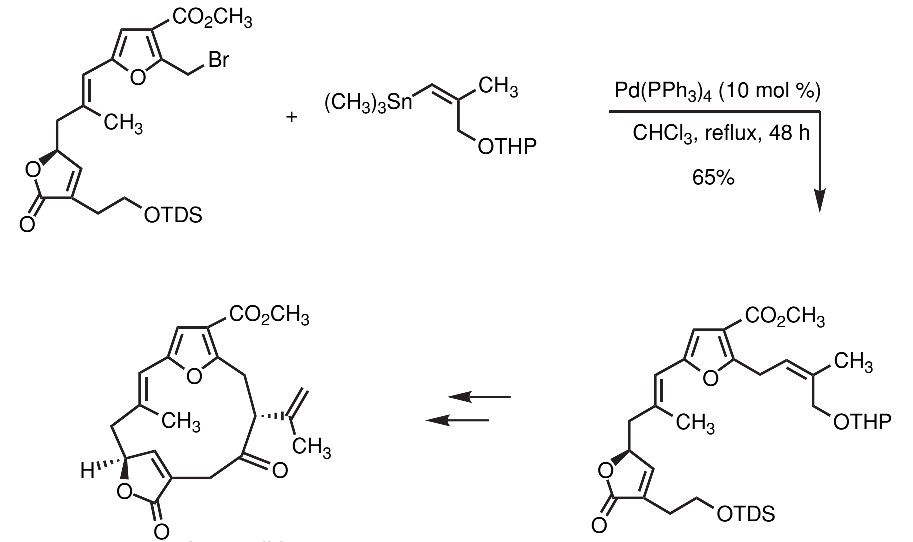
- Acid chlorides can be used as coupling reagents (the Stille reaction, as first reported, used acid chlorides).

Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636–3638.



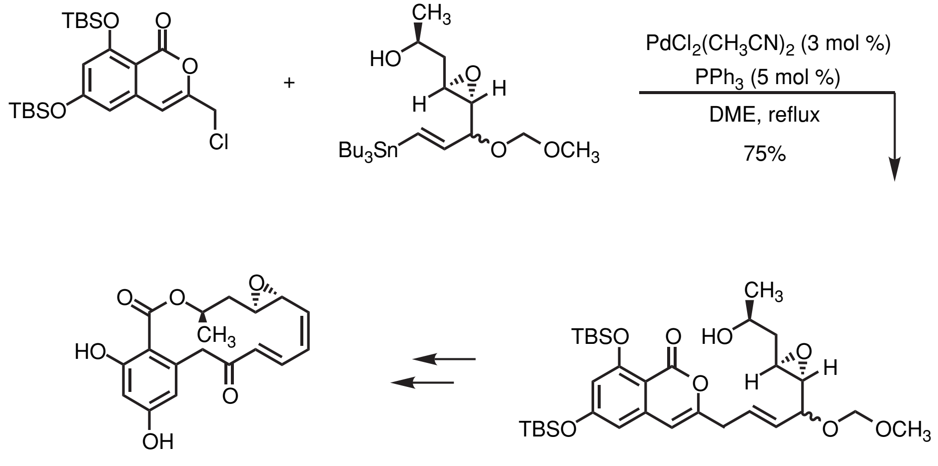
Liebeskind, L. S.; Yu, M. S.; Fengl, R. W. *J. Org. Chem.* **1993**, *58*, 3543–3549.

- Allylic, benzylic halides:



Acerosolide

Paquette, L. A.; Astles, P. C. *J. Org. Chem.* **1993**, *58*, 165–169.

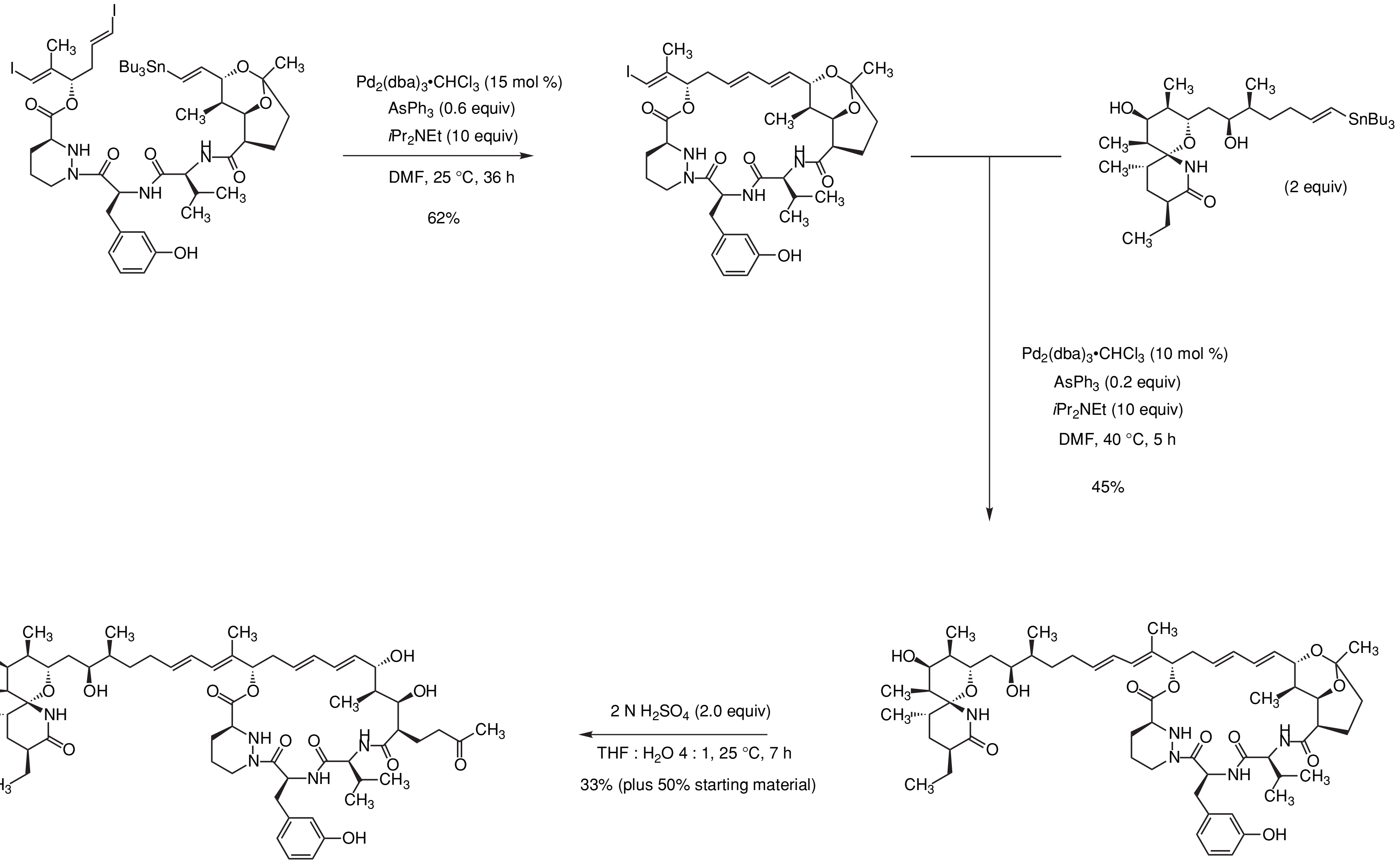


Monocillin I

Lampilas, M.; Lett, R. *Tetrahedron Lett.* **1992**, *33*, 777–780.

Andrew Haidle

Further Examples:



$Pd_2(dba)_3$•$CHCl_3$ (15 mol %)
$AsPh_3$ (0.6 equiv)
iPr_2NEt (10 equiv)
DMF, 25 °C, 36 h
62%

(2 equiv)

$Pd_2(dba)_3$•$CHCl_3$ (10 mol %)
$AsPh_3$ (0.2 equiv)
iPr_2NEt (10 equiv)
DMF, 40 °C, 5 h
45%

2 N H_2SO_4 (2.0 equiv)
THF : H_2O 4 : 1, 25 °C, 7 h
33% (plus 50% starting material)

Sanglifehrin A

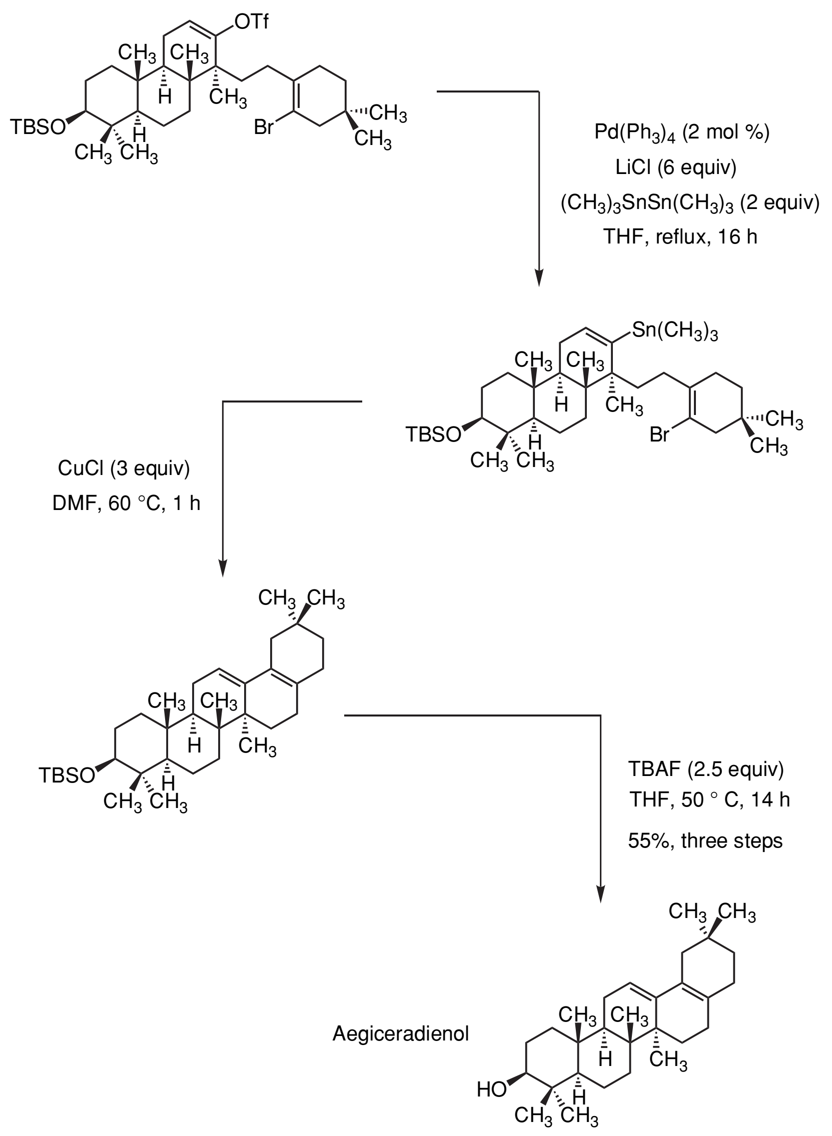
- In the first Stille coupling, none of the regioisomeric coupling product was isolated.

Nicolaou, K. C.; Murphy, F.; Barluenga, S.; Ohshima, T.; Wei, H.; Xu, J.; Gray, D. L. F.; Baudoin, O. *J. Am. Chem. Soc.* **2000**, *122*, 3830–3838.

Andrew Haidle

Examples involving copper(I):

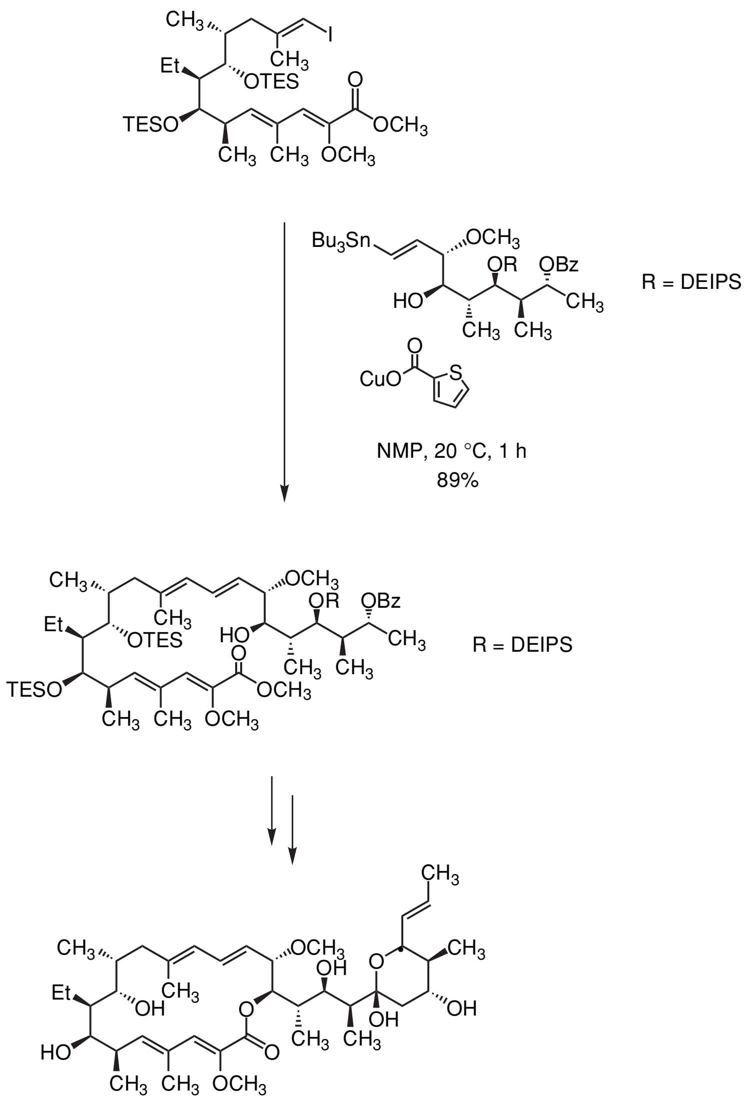
- The copper(I)-mediated coupling of a vinyl stannane and a vinyl bromide succeeded when palladium catalysis failed. Note the selective transformation of the vinyl triflate to the vinyl stannane in the presence of the vinyl bromide.



Aegiceradienol

Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999–10003.

- Liebeskind's copper(I) thiophene-2-carboxylate promoted coupling reaction was used for the total synthesis of concanamycin F. This reaction failed intramolecularly when the two coupling partners had already been joined via the ester linkage.



Concanamycin F

Paterson, I.; Doughty, V. A.; McLeod, M. D.; Trieselmann, T. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1308–1312.

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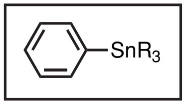
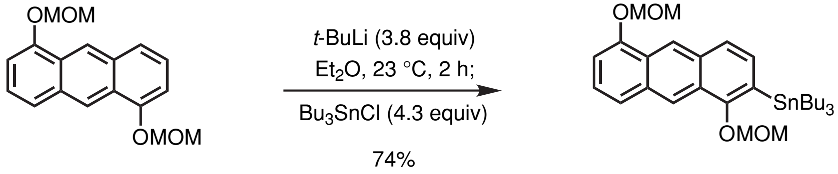
Synthesis of Aryl and Vinyl Stannanes:

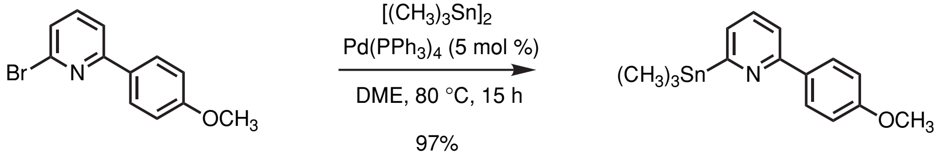


- Directed *ortho* metalation followed by addition of a stannyl chloride is a standard method.

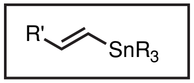
Snieckus, V. *Chem. Rev.* **1990**, *90*, 923–924.

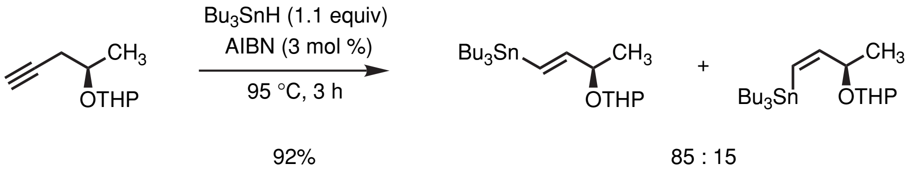


Tius, M. A.; Gomez-Galeno, J.; Gu, X.; Zaidi, J. H. *J. Am. Chem. Soc.* **1991**, *113*, 5775-5783.



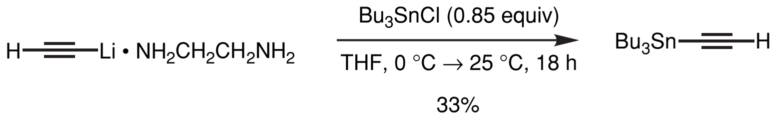
Benaglia, M.; Toyota, S.; Woods, C. R.; Siegel, J. S. *Tetrahedron Lett.* **1997**, *38,* 4737-4740.

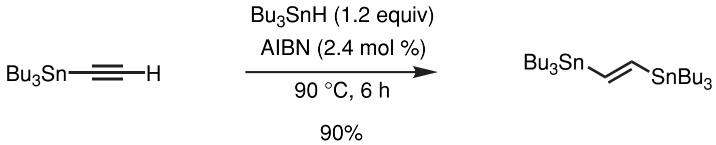




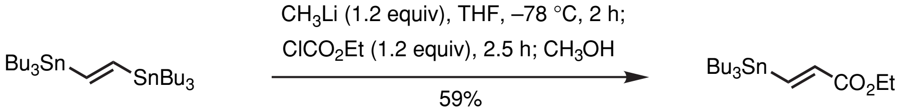
- The addition of stannyl radicals to alkynes is reversible under these conditions. The product ratio reflects the thermodynamic equilibrium.

Corey, E. J.; Ulrich, P.; Fitzpatrick, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 222–224.

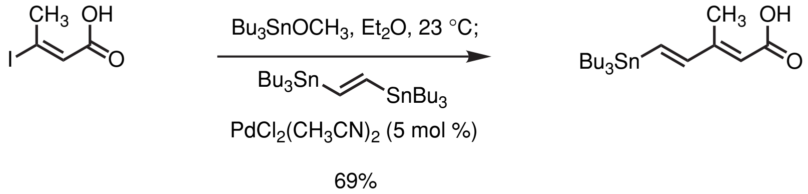




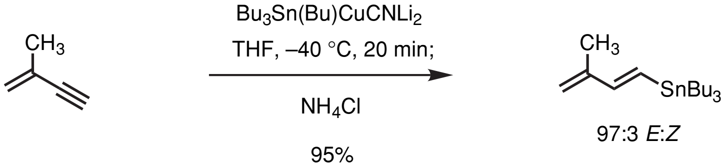
Renaldo, A. F.; Labadie, J. W.; Stille, J. K. *Org. Synth.* **1988**, *67*, 86–97.



Renaldo, A. F.; Labadie, J. W.; Stille, J. K. *Org. Synth.* **1988**, *67*, 86–97.



Thibonnet, J.; Abarbi, M.; Parrain, J.-L.; Duchêne, A. *Synlett* **1997**, 771–772.



Aksela, R.; Oehlschlager, A. C. *Tetrahedron* **1991**, *47*, 1163–1176.

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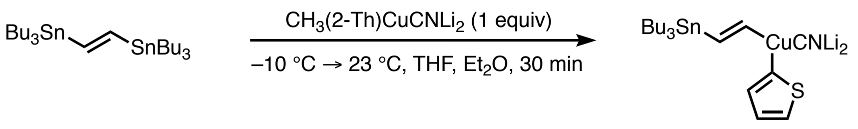
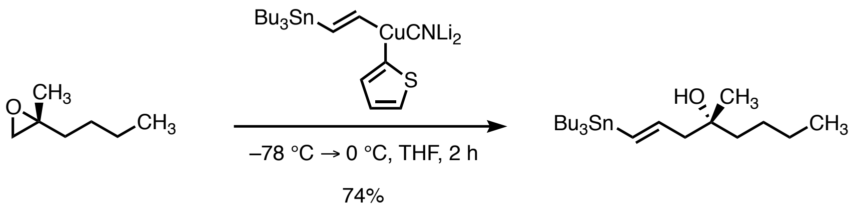
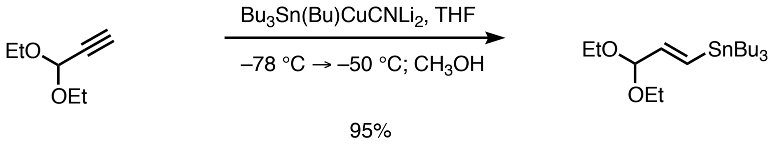
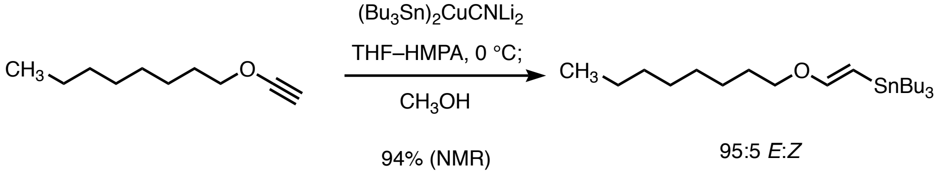




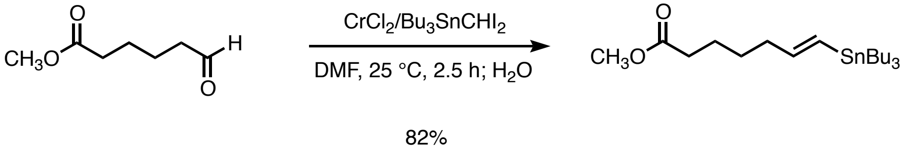
Behling, J. R.; Ng, J. S.; Babiak, K. A.; Campbell, A. L.; Elsworth, E.; Lipshutz, B. H. *Tetrahedron Lett.* **1989**, *30*, 27–30.



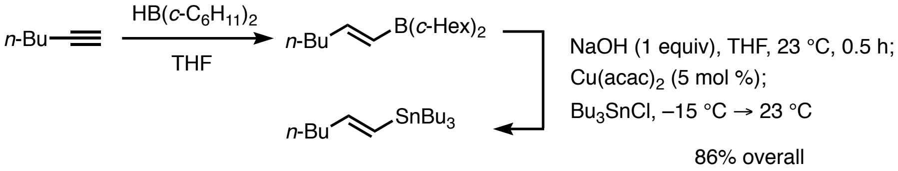
Marek, I.; Alexakis, A.; Normant, J.–F. *Tetrahedron Lett.* **1991**, *32*, 6337–6340.



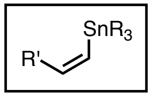
Cabezas, J. A.; Oehlschlager, A. C. *Synthesis* **1994**, 432–442.

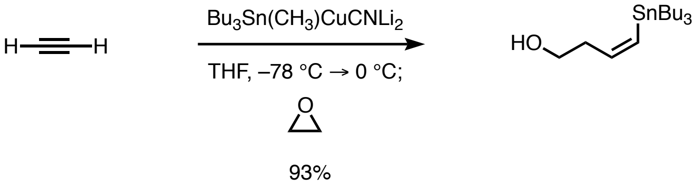


Hodgson, D. M.; Foley, A. M.; Lovell, P. J. *Tetrahedron Lett.* **1998**, *39*, 6419–6420.

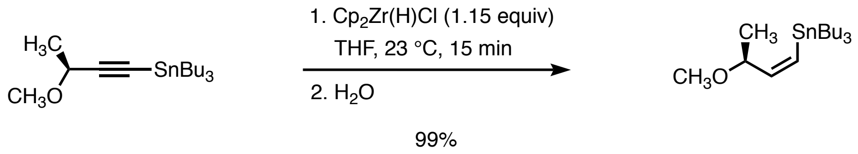


Hoshi, M.; Takahashi, K.; Arase, A. *Tetrahedron Lett.* **1997**, *38*, 8049–8052.

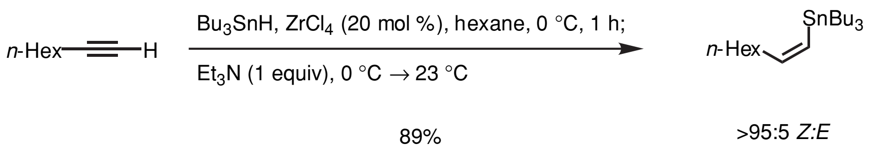




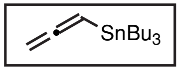
Barbero, A.; Cuadrado, P.; Fleming, I.; Gonzalez, A. M.; Pulido, F. J. *J. Chem. Soc., Chem. Commun.* **1992**, 351–353.

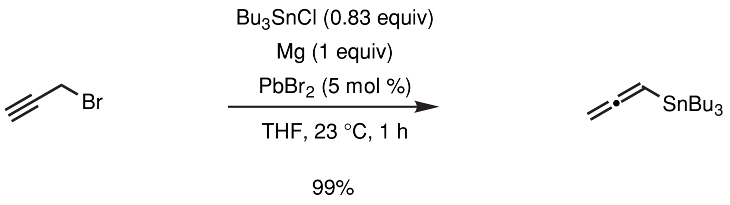


Lipshutz, B. H.; Kell, R.; Barton, J. C. *Tetrahedron Lett.* **1992**, *33*, 5861–5864.

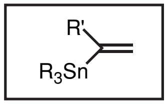


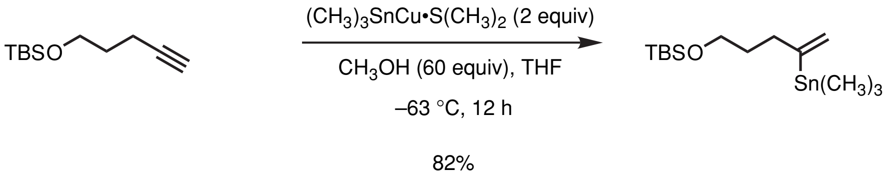
Asao, N.; Liu, J.–X.; Sudoh, T.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 2405–2406.



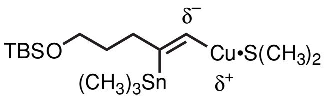


Tanaka, H.; Abdul Hai, A. K. M.; Ogawa, H.; Torii, S. *Synlett* **1993**, 835–836.

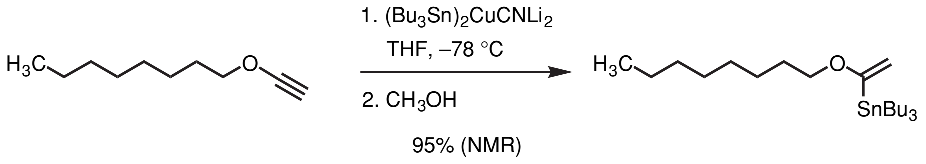




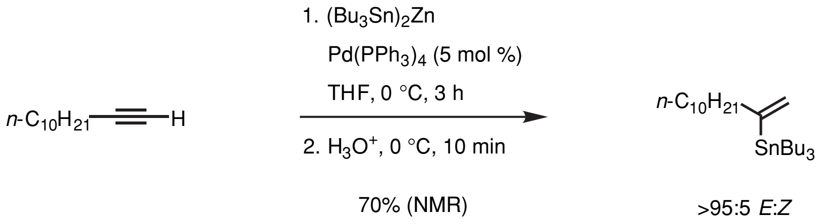
- The addition of the cuprate reagent is reversible. The authors attribute the observed regioselectivity to the higher stability of the polarized carbon-copper bond when copper is attached to the less electronegative terminal carbon.



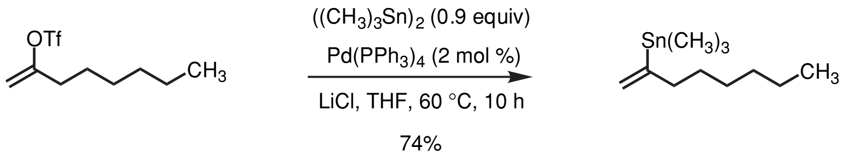
Piers, E.; Chong, J. M. *Can. J. Chem.* **1988**, *66*, 1425–1429.



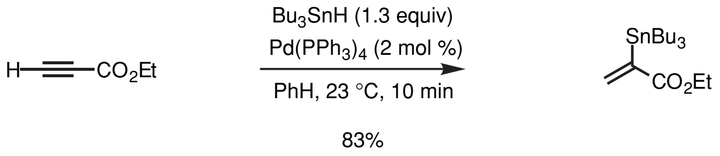
Cabezas, J. A.; Oehlschlager, A. C. *Synthesis* **1994**, 432–442.



Matsubara, S.; Hibino, J.–I.; Morizawa, Y.; Oshima, K.; Nozaki, H. *J. Organomet. Chem.* **1985**, *285*, 163–172.

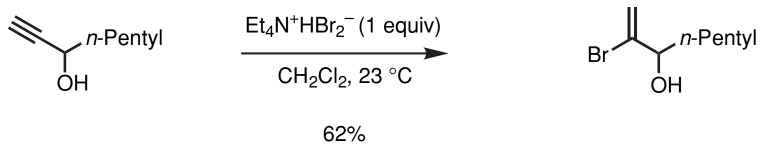


Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277–279.

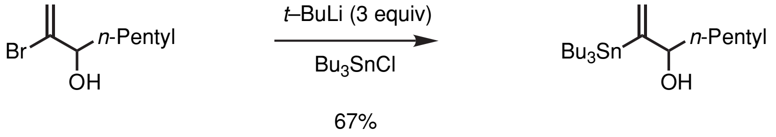


Miyake, H.; Yamamura, K. *Chemistry Lett.* **1989**, 981–984.

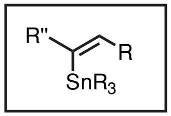
- An alternate route:

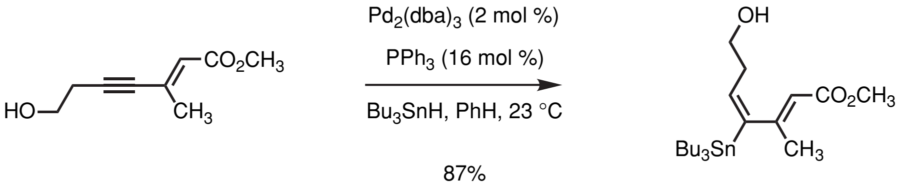


Marshall, J. A.; Sehon, C. A. *Org. Synth.* **1999**, *76*, 263–270.



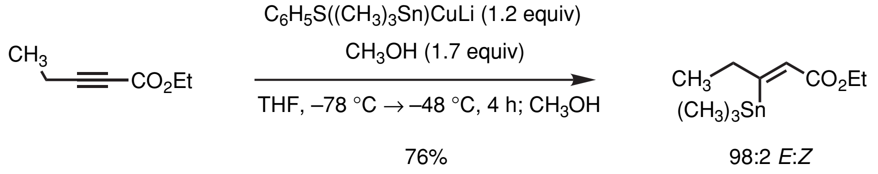
Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605.



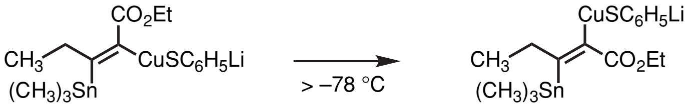


- The regiochemistry of the addition is explained as the result of hydride addition to the more electron-deficient terminus of the acetylene.

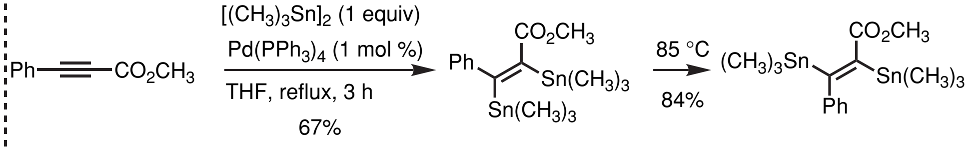
Trost, B. M.; Li, C–J. *Synthesis* **1994**, 1267–1271.



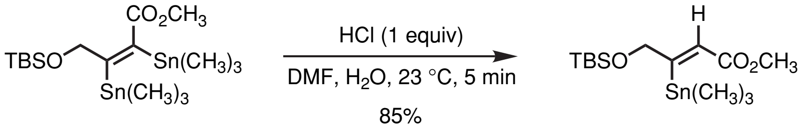
- The initially formed *cis* adduct is stable at –100 °C, but at higher temperatures (–48 °C), the equilibrium favors the Cu/Sn *trans* isomer.



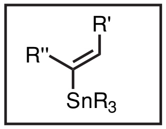
Piers, E.; Morton, H. E. *J. Org. Chem.* **1980**, *45*, 4263–4264.

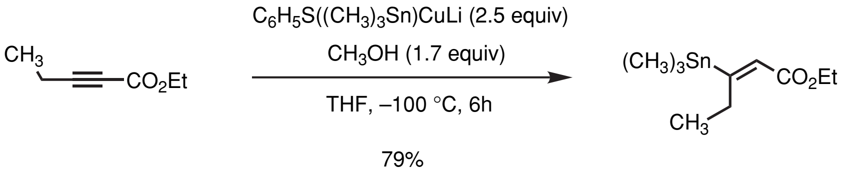


Piers, E.; McEachern, E. J.; Romero, M. A. *J. Org. Chem.* **1997**, *62*, 6034–6040.

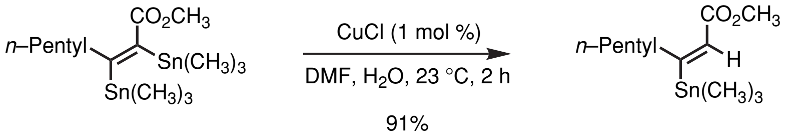


Piers, E.; McEachern, E. J.; Romero, M. A. *J. Org. Chem.* **1997**, *62*, 6034–6040.

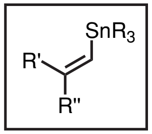


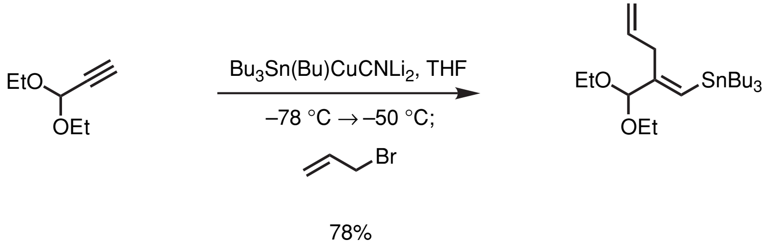


Piers, E.; Morton, H. E. *J. Org. Chem.* **1980**, *45*, 4263–4264.

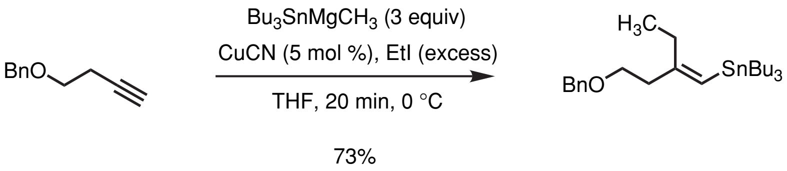


Piers, E.; McEachern, E. J.; Romero, M. A. *J. Org. Chem.* **1997**, *62*, 6034–6040.





Marek, I.; Alexakis, A.; Normant, J.–F. *Tetrahedron Lett.* **1991**, *32*, 6337–6340.

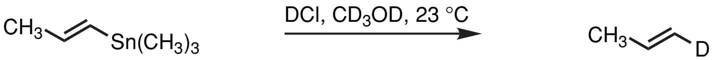


Matsubara, S.; Hibino, J.-I.; Morizawa, Y.; Oshima, K.; Nozaki, H. *J. Organomet. Chem.* **1985**, *285*, 163–172.

Vinylstannanes:

- are sensitive to acids, undergoing protodestannylation with retention of stereochemistry.

Seyferth, D. *J. Am. Chem. Soc.* **1957**, *79*, 2133–2136.



Cochran, J. C. et al. *Organometallics* **1982**, *1*, 586–590.

- frequently are unstable to chromatography on silica gel (addition of triethylamine to the eluent can prevent decomposition during chromatography).

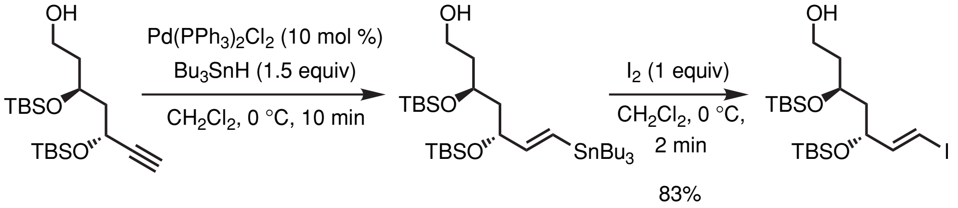
- can be purified by a chromatographic technique that uses C-18 silica, which has been made hydrophobic by capping the silanol residues with octadecyldimethylsilyl groups.

Farina, V. *J. Org. Chem.* **1991**, *56*, 4985–4987.

- can be difficult to separate from unwanted tin by-products after the reaction. For leading references on the work-up of tin reactions, see:

Renaud, P.; Lacôte, E.; Quaranta, L. *Tetrahedron Lett.* **1998**, *39*, 2123–2126.

- react cleanly and efficiently with I_2 to form vinyl iodides with retention of stereochemistry. For example:



Smith, A. B.; Ott, G.R. *J. Am. Chem. Soc.* **1998**, *120*, 3935–3948.

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