

**Reviews:**

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

Mitchell, T. N. In *Metal-catalyzed Cross-coupling Reactions*, Diederich, F., and Stang, P. J., Eds.; Wiley-VCH: New York, **1998**, pp. 167–202.

Farina, V.; Krishnamurthy, V.; Scott, W. J. *The Stille Reaction*; John Wiley & Sons: New York, **1998**.

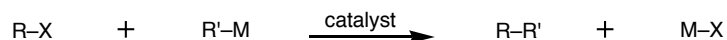
Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524.

- Intramolecular:

Dunston, M. A. J.; Pattenden, G. J. *Chem. Soc., Perkin Trans. 1* **1999**, 1235–1246.

- Solid phase:

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

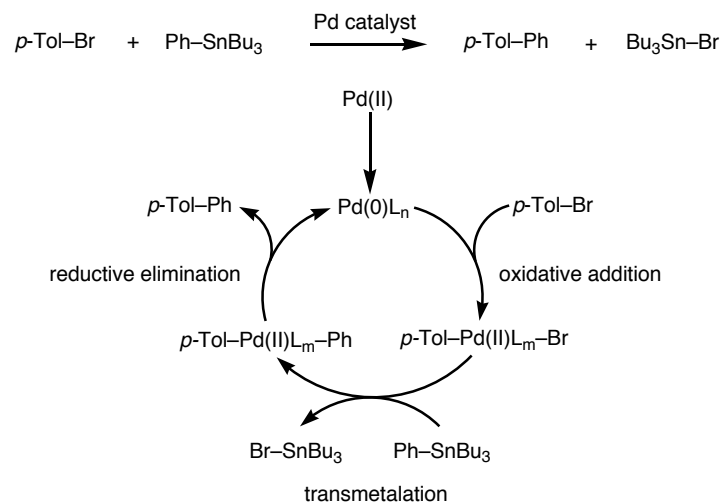
**Generalized Cross-Coupling:**

Typically:

- R and R' are sp<sup>2</sup>-hybridized
- M = Sn, B, Zr, Zn
- X = I, OSO<sub>2</sub>CF<sub>3</sub>, Br, Cl
- catalyst = Pd (sometimes Ni)

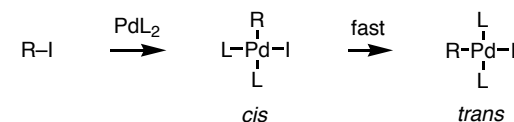
**Mechanism:**

- A specific example:



- Many functional groups are tolerated (e.g., CO<sub>2</sub>R, CN, OH, CHO).

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



- Oxidative addition and reductive elimination steps occur with retention of configuration for sp<sup>2</sup>-hybridized substrates.

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

- Relative order of ligand transfer from Sn:

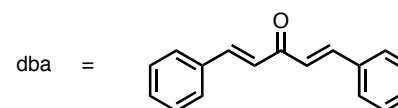
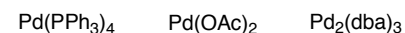


- The details of the mechanism are still being elucidated, and the mechanism may change with different reaction conditions:

Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978–8985.

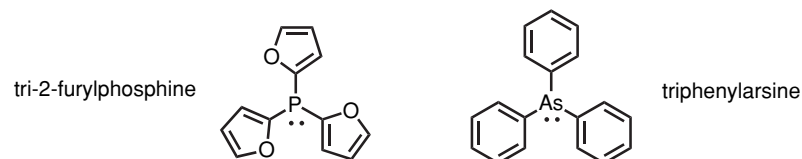
**Stille Reaction conditions:**

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



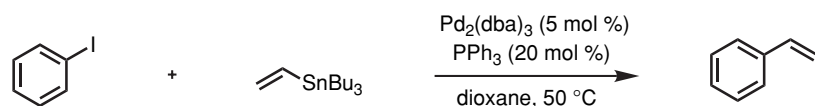
- Ligands: Phosphine ( $\text{PR}_3$ ) ligands are often added when the Pd source doesn't contain strong ligands.

Large rate enhancements ( $10^2$ – $10^3$ ) occur with poorly electron-donating ligands:



Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585-9595.

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

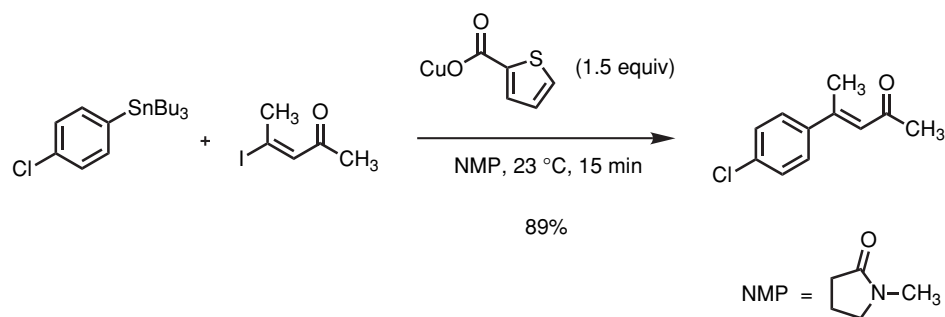


mol % CuI	relative rate
0	1
10	114

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

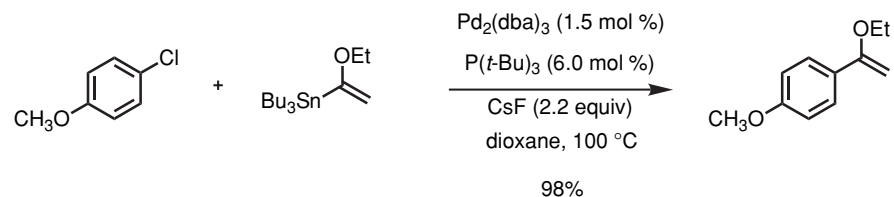
Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905–5911.

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



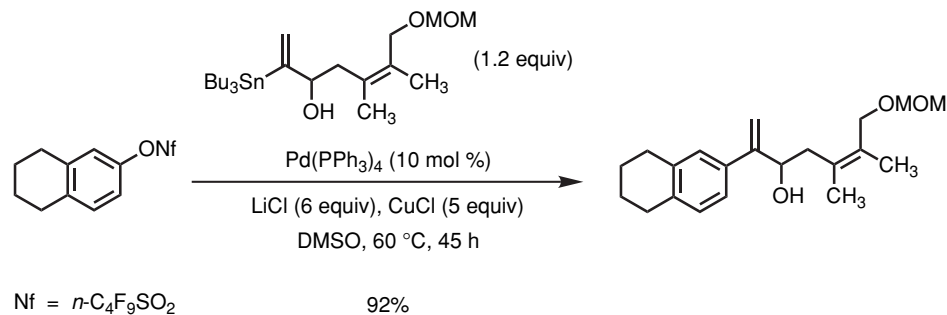
Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748-2749.

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

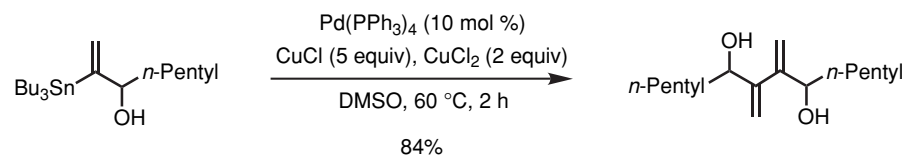


Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2411-2413.

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



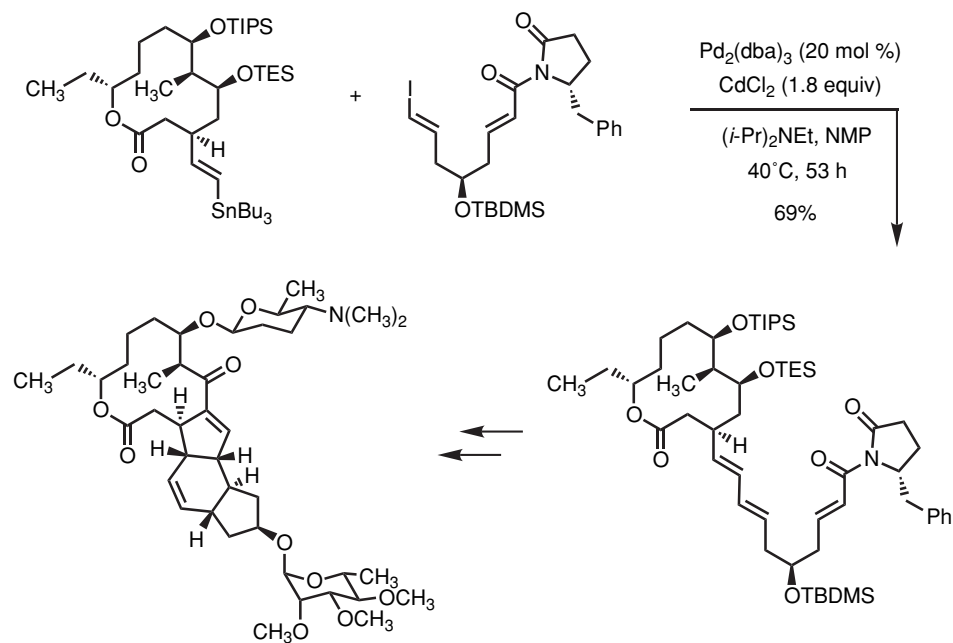
- Transmetalation of  $\text{Bu}_3\text{Sn}$  with CuCl is proposed to increase the rate of this reaction. Isolation of the homocoupling product in the following experiment was taken as evidence for a transmetalation event.



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

**Examples:**

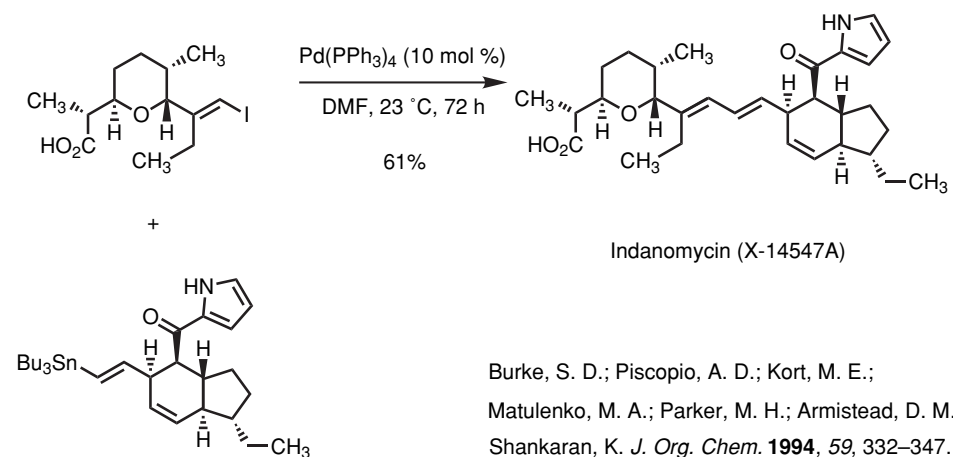
- Alkenes as coupling partners:



(+)-A83543A, (+)-Lepicidin

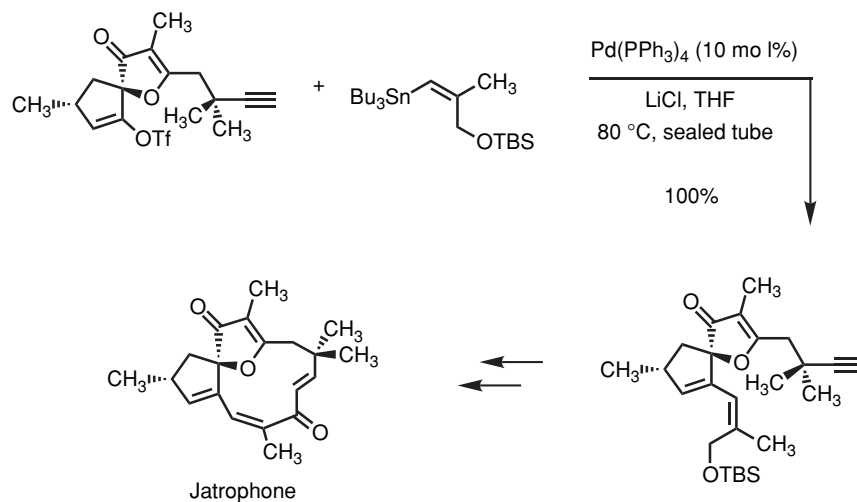
- $\text{CdCl}_2$  serves as a transmetalation cocatalyst. Without it, homodimerization of both coupling partners was observed.

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



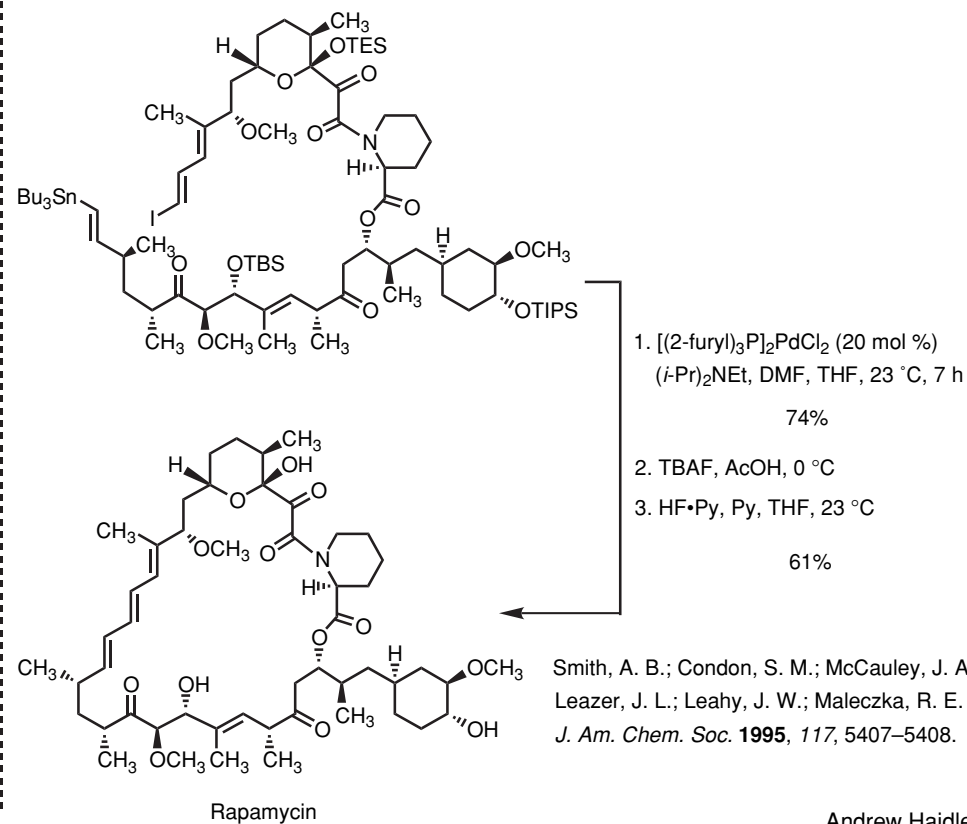
Indanomycin (X-14547A)

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.

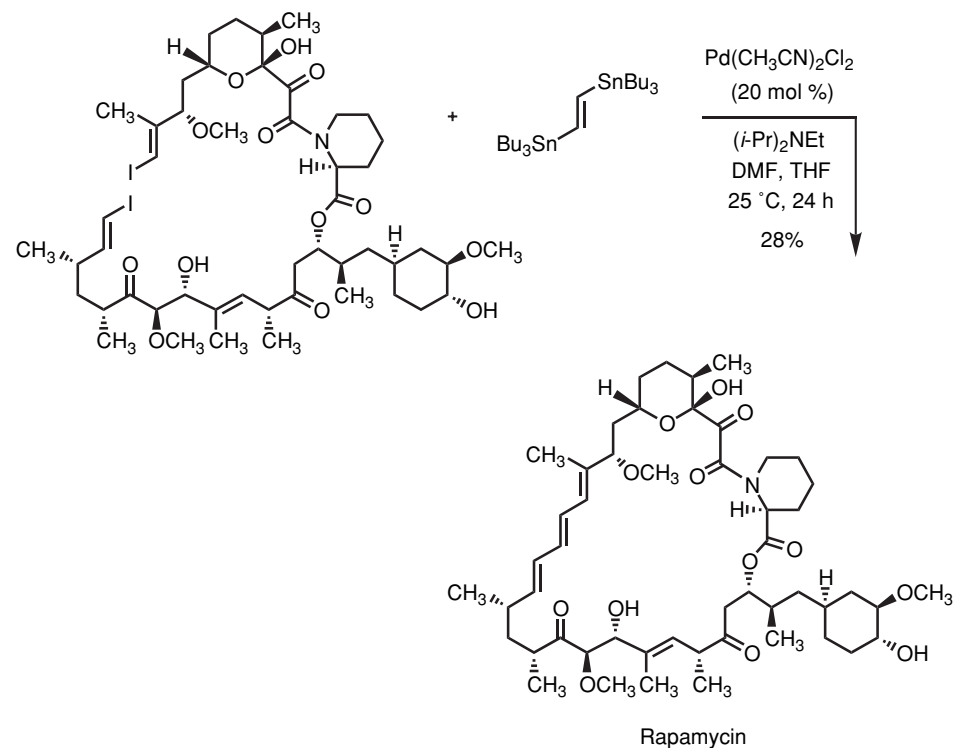


Rapamycin

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

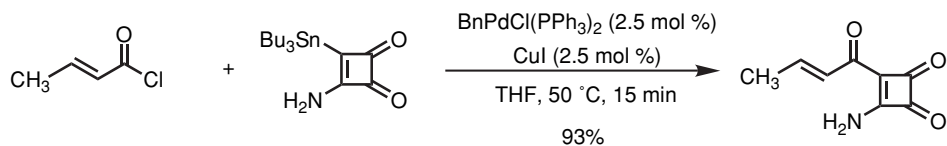
Further Examples:



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

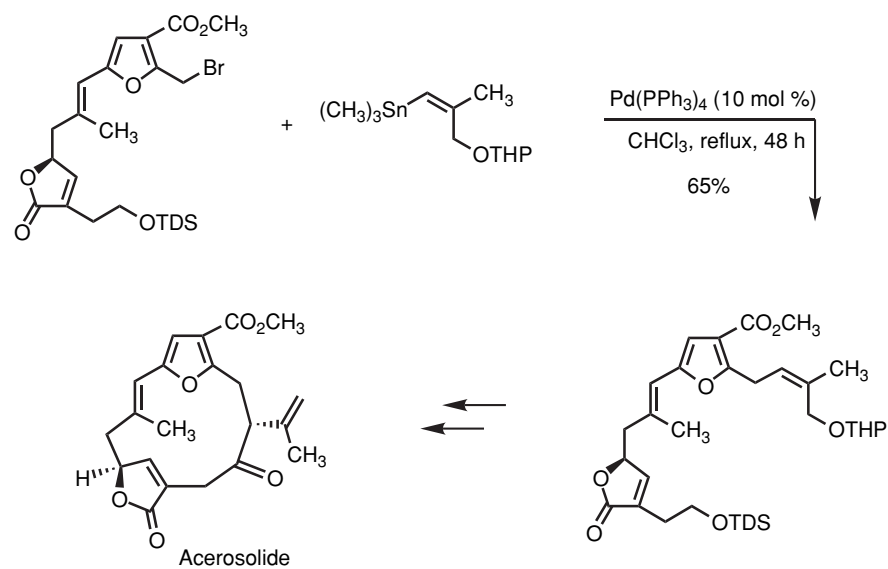
• Acid chlorides can be used as coupling reagents (the Stille reaction, as first reported, used acid chlorides).

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

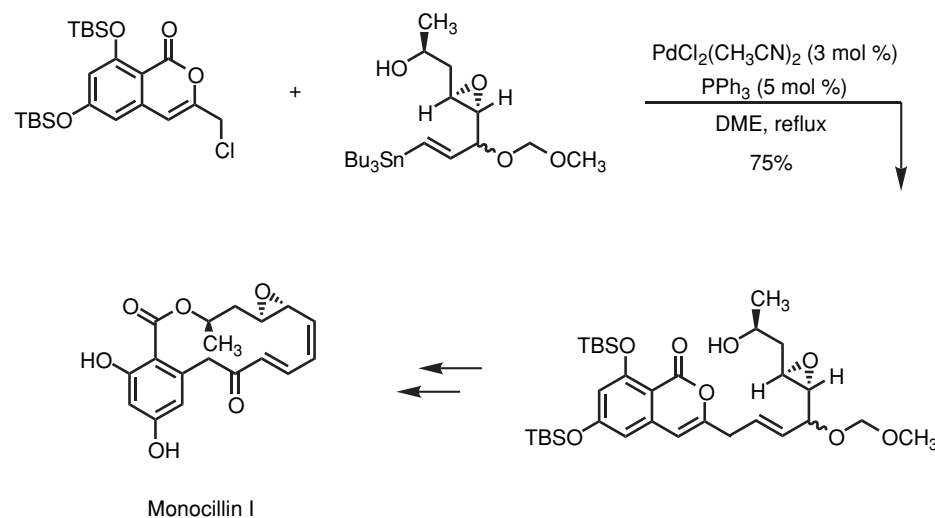


Liesbeskind, L. S.; Yu, M. S.; Fengl, R. W. *J. Org. Chem.* **1993**, *58*, 3543–3549.

• Allylic, benzylic halides:

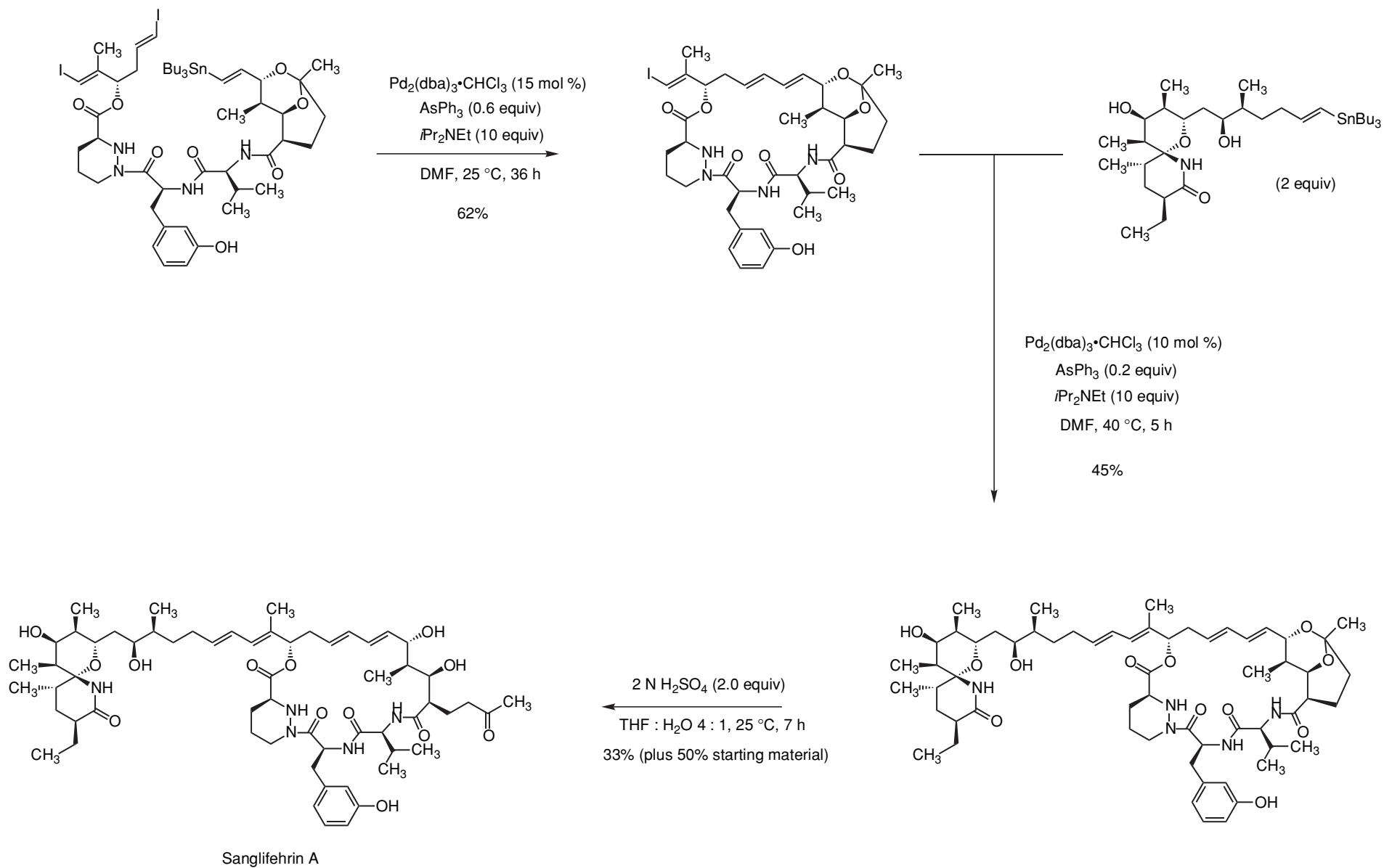


Paquette, L. A.; Astles, P. C. *J. Org. Chem.* **1993**, *58*, 165–169.



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

Further Examples:

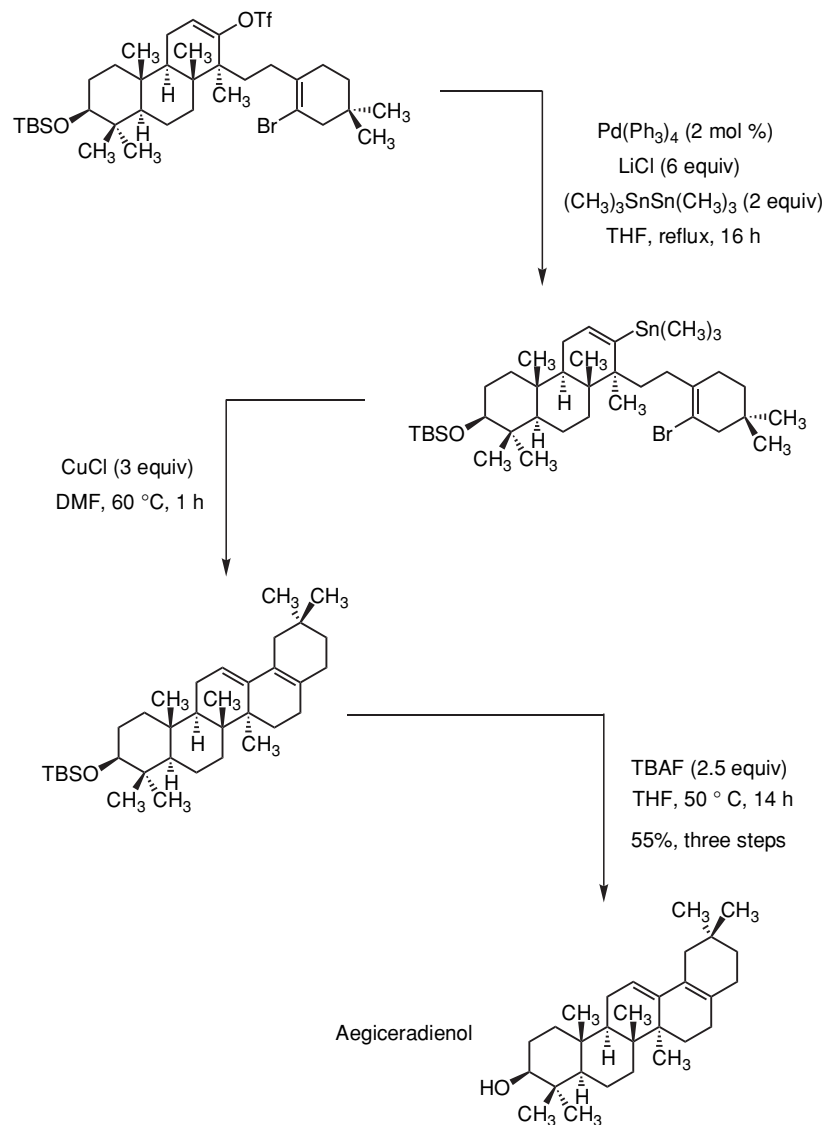


• In the first Stille coupling, none of the regioisomeric coupling product was isolated.

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.

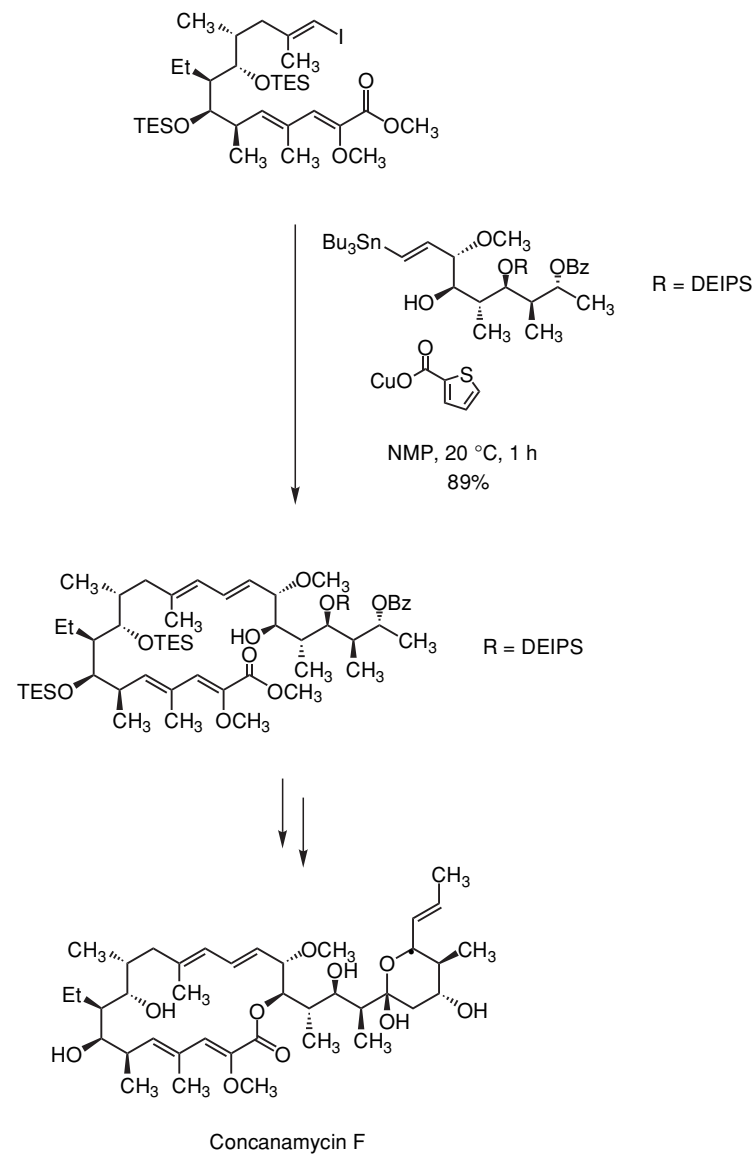
### Examples involving copper(I):

- 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.



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

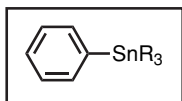
- Liebeskind's copper(I) thiophene-2-carboxylate promoted coupling reaction was used for the total synthesis of concanamycin F. This reaction failed intramolecularly when the two coupling partners had already been joined via the ester linkage.



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

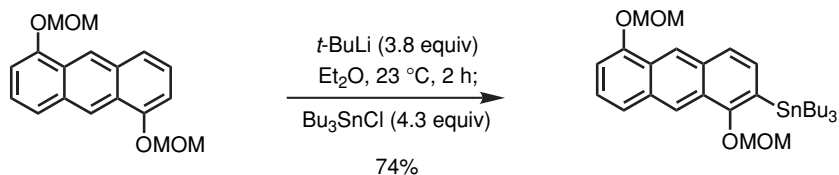
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## Synthesis of Aryl and Vinyl Stannanes:

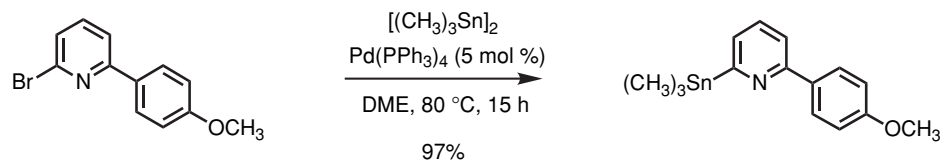


• Directed *ortho* metalation followed by addition of a stannyl chloride is a standard method.

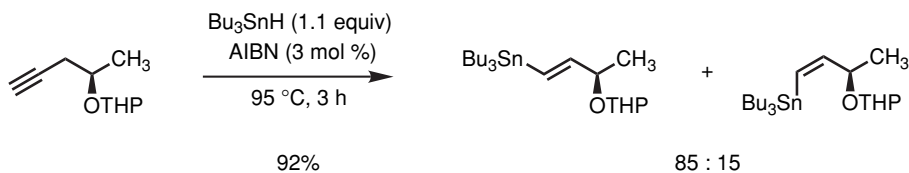
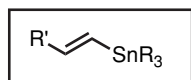
Snieckus, V. *Chem. Rev.* **1990**, *90*, 923–924.



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

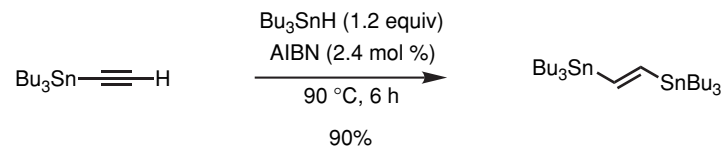
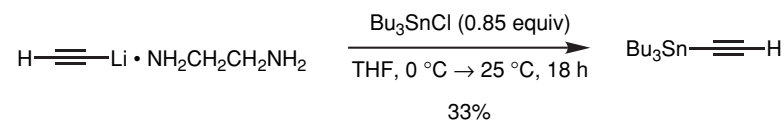


Benaglia, M.; Toyota, S.; Woods, C. R.; Siegel, J. S. *Tetrahedron Lett.* **1997**, *38*, 4737-4740.

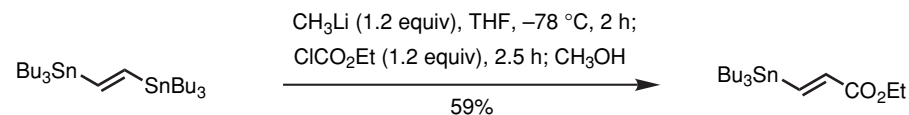


• The addition of stannyl radicals to alkynes is reversible under these conditions. The product ratio reflects the thermodynamic equilibrium.

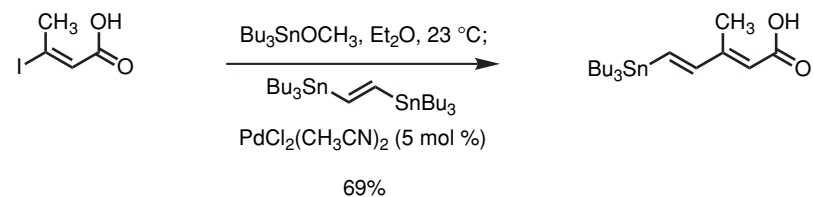
Corey, E. J.; Ulrich, P.; Fitzpatrick, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 222–224.



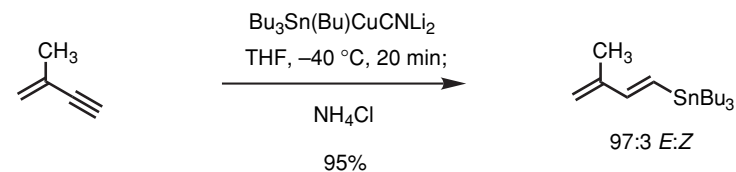
Renaldo, A. F.; Labadie, J. W.; Stille, J. K. *Org. Synth.* **1988**, *67*, 86–97.



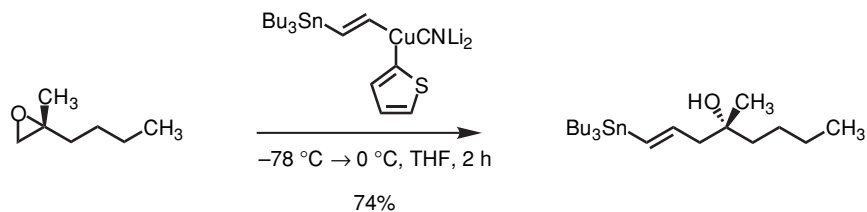
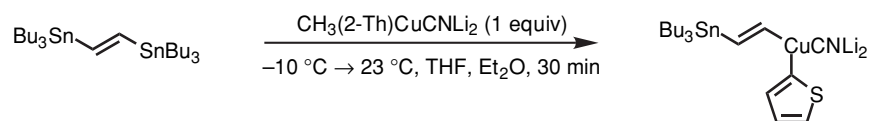
Renaldo, A. F.; Labadie, J. W.; Stille, J. K. *Org. Synth.* **1988**, *67*, 86–97.



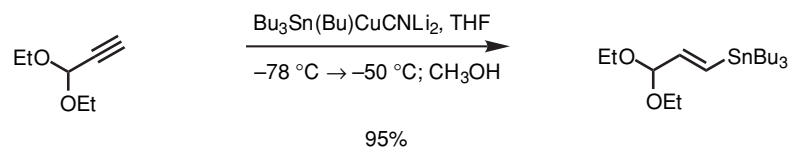
Thibonnet, J.; Abarbi, M.; Parrain, J.-L.; Duchêne, A. *Synlett* **1997**, 771–772.



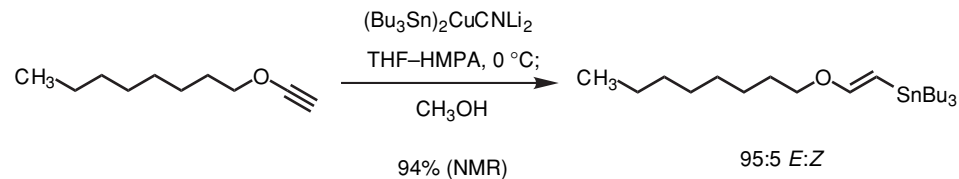
Aksela, R.; Oehlschlager, A. C. *Tetrahedron* **1991**, *47*, 1163–1176.



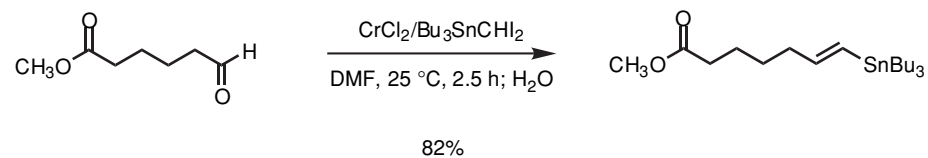
Behling, J. R.; Ng, J. S.; Babiak, K. A.; Campbell, A. L.; Elsworth, E.; Lipshutz, B. H. *Tetrahedron Lett.* **1989**, *30*, 27–30.



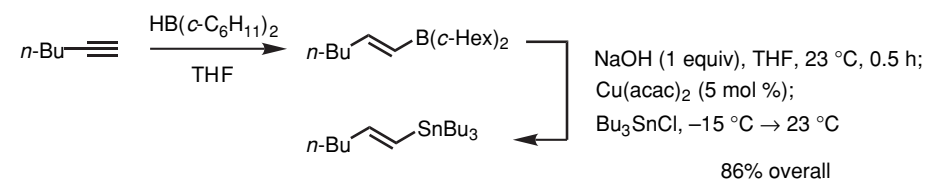
Marek, I.; Alexakis, A.; Normant, J.-F. *Tetrahedron Lett.* **1991**, *32*, 6337–6340.



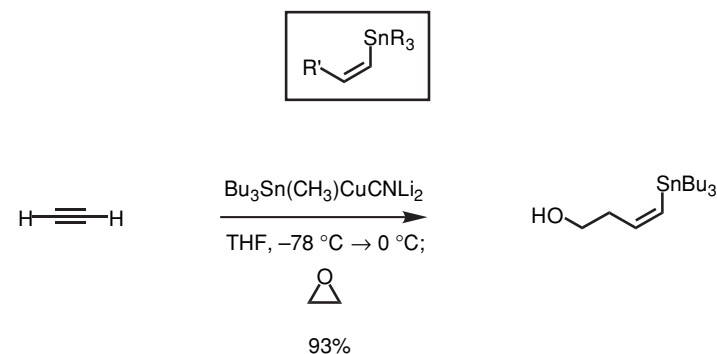
Cabezas, J. A.; Oehlschlager, A. C. *Synthesis* **1994**, 432–442.



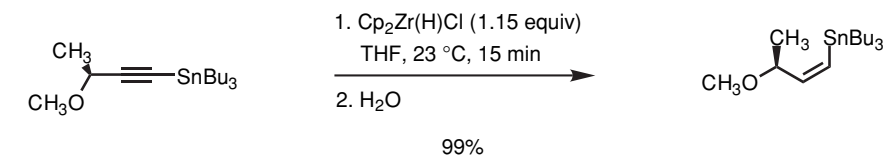
Hodgson, D. M.; Foley, A. M.; Lovell, P. J. *Tetrahedron Lett.* **1998**, *39*, 6419–6420.



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

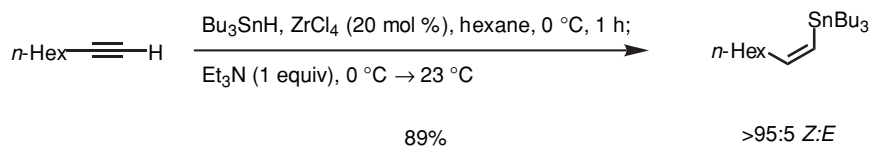


Barbero, A.; Cuadrado, P.; Fleming, I.; Gonzalez, A. M.; Pulido, F. J. *J. Chem. Soc., Chem. Commun.* **1992**, 351–353.

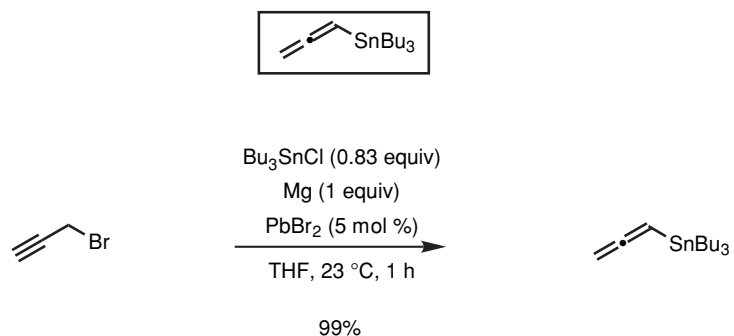


Lipshutz, B. H.; Kell, R.; Barton, J. C. *Tetrahedron Lett.* **1992**, *33*, 5861–5864.

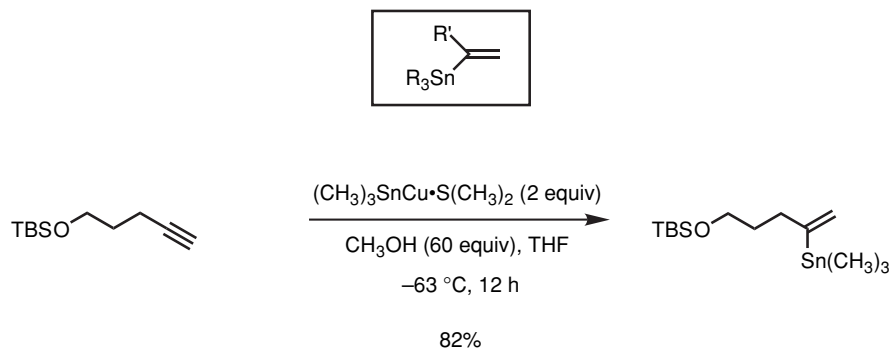




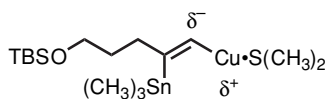
Asao, N.; Liu, J.-X.; Sudoh, T.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 2405–2406.



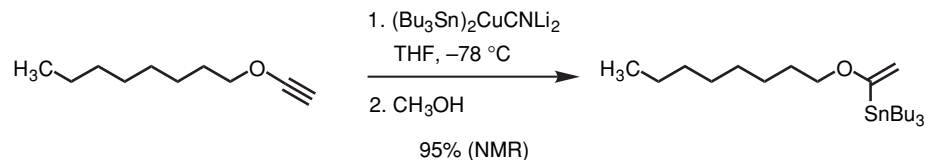
Tanaka, H.; Abdul Hai, A. K. M.; Ogawa, H.; Torii, S. *Synlett* **1993**, 835–836.



- 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.



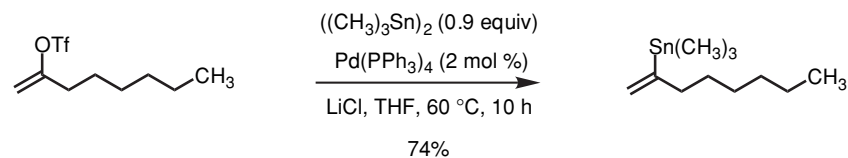
Piers, E.; Chong, J. M. *Can. J. Chem.* **1988**, *66*, 1425–1429.



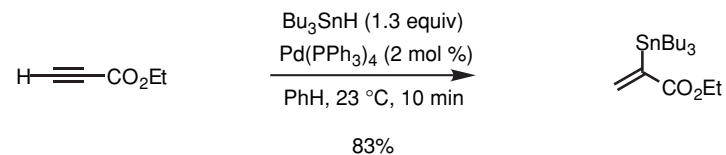
Cabezas, J. A.; Oehlschlager, A. C. *Synthesis* **1994**, 432–442.



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

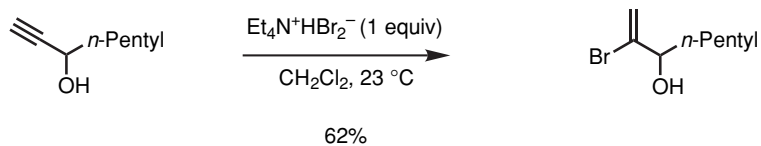


Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277–279.

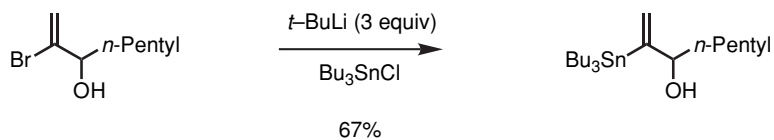


Miyake, H.; Yamamura, K. *Chemistry Lett.* **1989**, 981–984.

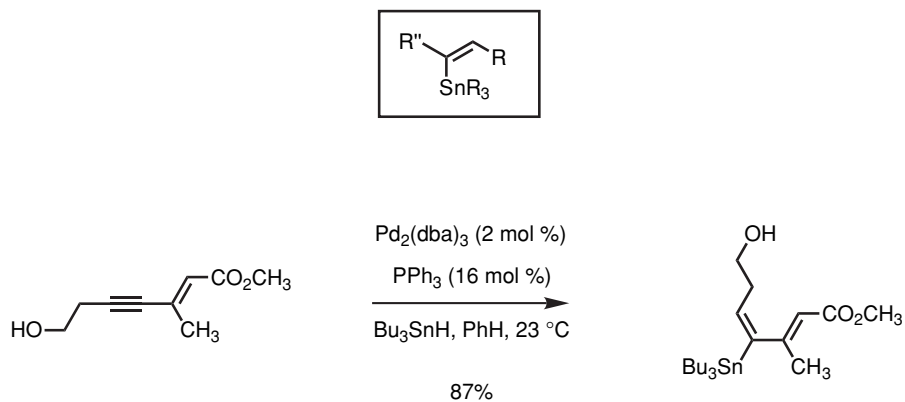
- An alternate route:



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

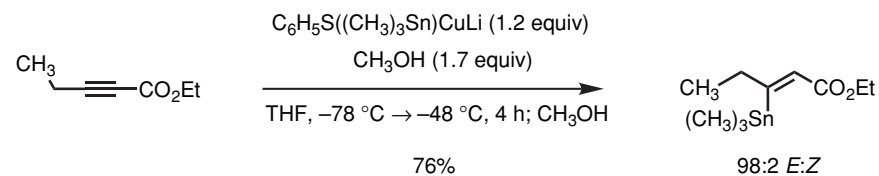


Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605.

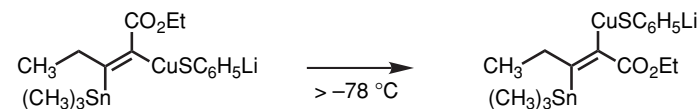


- The regiochemistry of the addition is explained as the result of hydride addition to the more electron-deficient terminus of the acetylene.

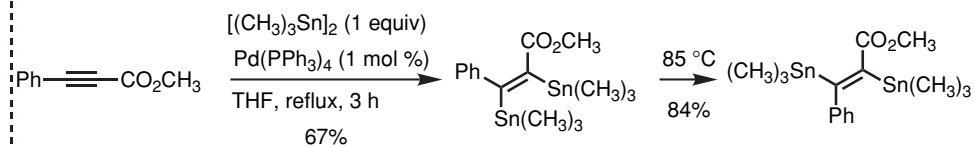
Trost, B. M.; Li, C-J. *Synthesis* **1994**, 1267–1271.



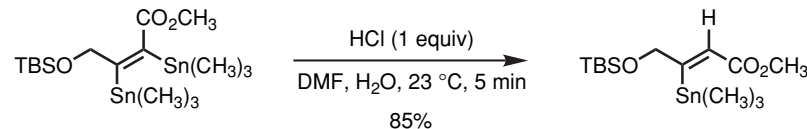
- The initially formed *cis* adduct is stable at  $-100\text{ }^\circ\text{C}$ , but at higher temperatures ( $-48\text{ }^\circ\text{C}$ ), the equilibrium favors the Cu/Sn *trans* isomer.



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.

