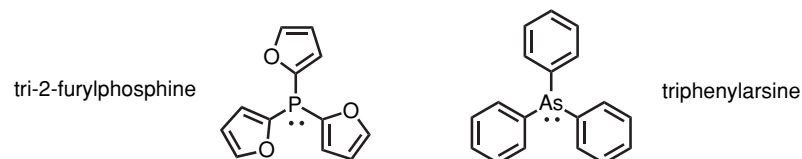


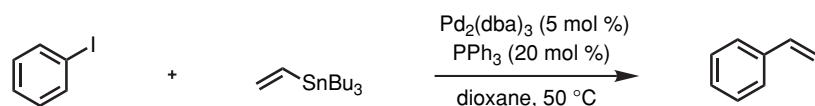
- Ligands: Phosphine (PR_3) ligands are often added when the Pd source doesn't contain strong ligands.

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 $>10^2$.

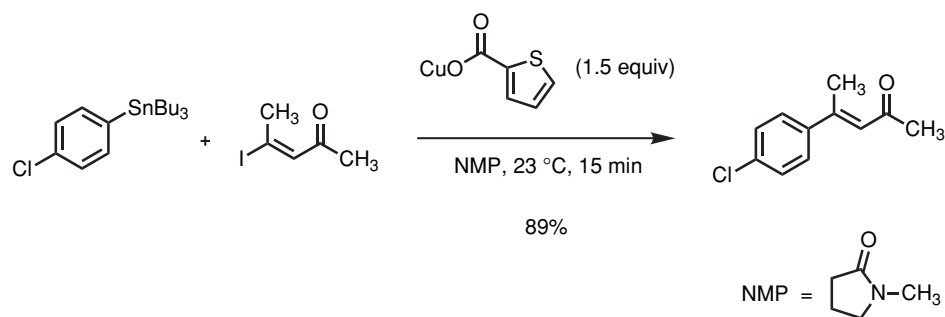


mol % CuI	relative rate
0	1
10	114

- 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.

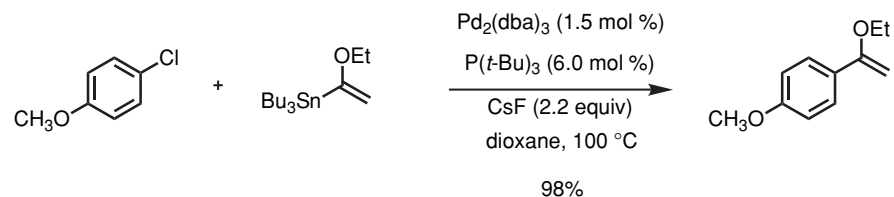
Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905–5911.

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



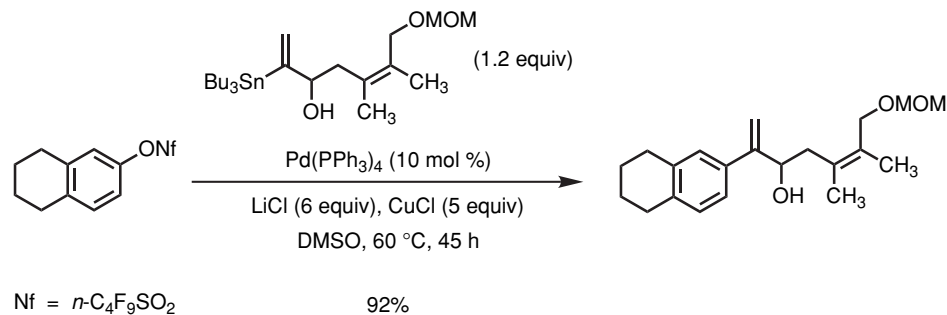
Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748-2749.

- 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.

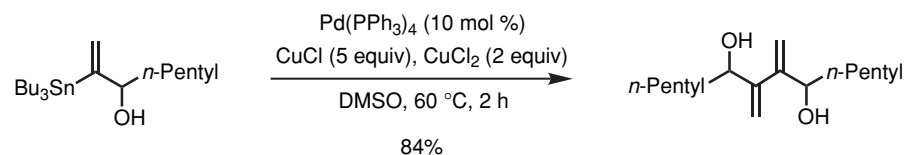


Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2411-2413.

- 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.



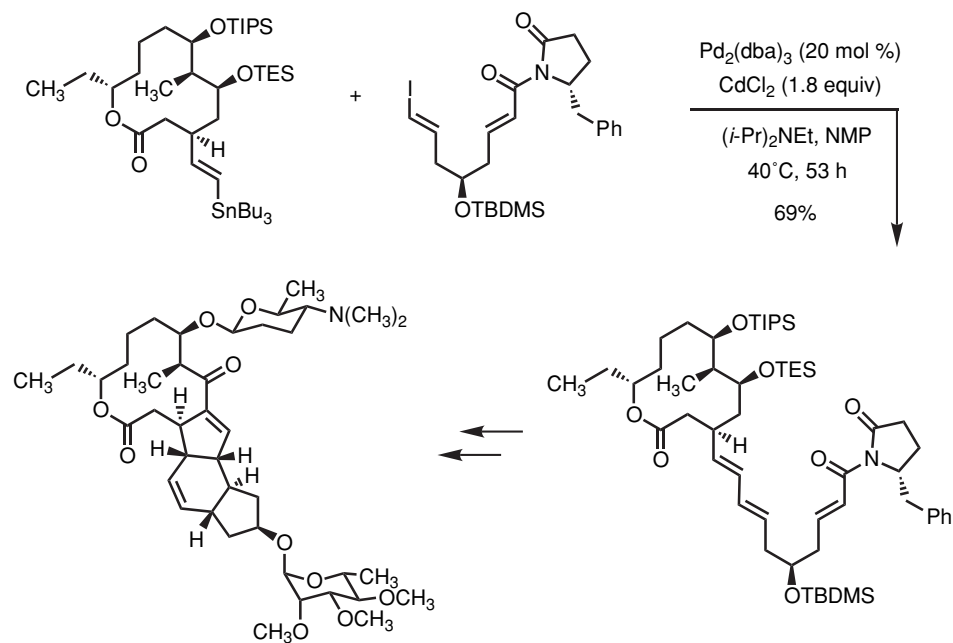
- Transmetalation of Bu_3Sn with CuCl is proposed to increase the rate of this reaction. Isolation of the homocoupling product in the following experiment was taken as evidence for a transmetalation event.



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

Examples:

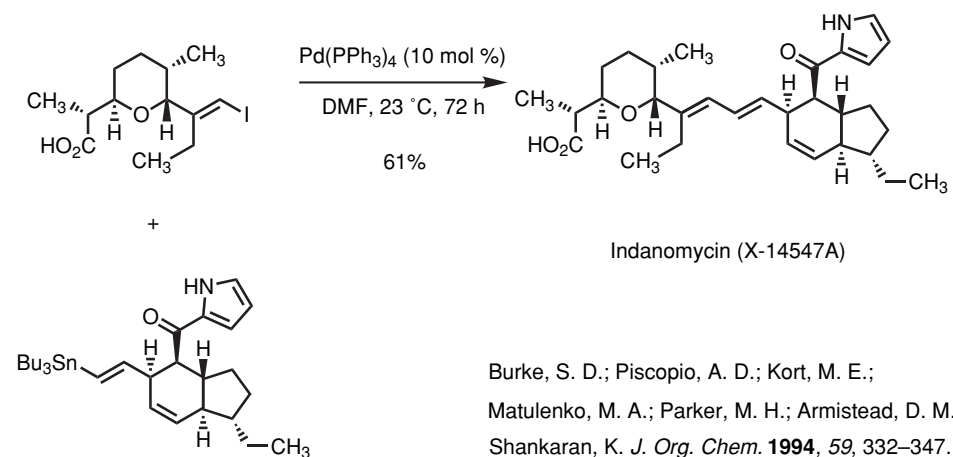
- Alkenes as coupling partners:



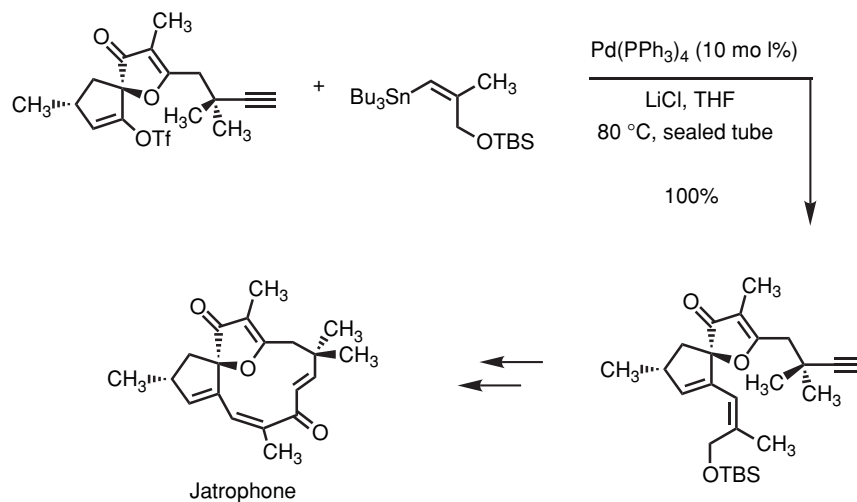
(+)-A83543A, (+)-Lepicidin

- CdCl_2 serves as a transmetalation cocatalyst. Without it, homodimerization of both coupling partners was observed.

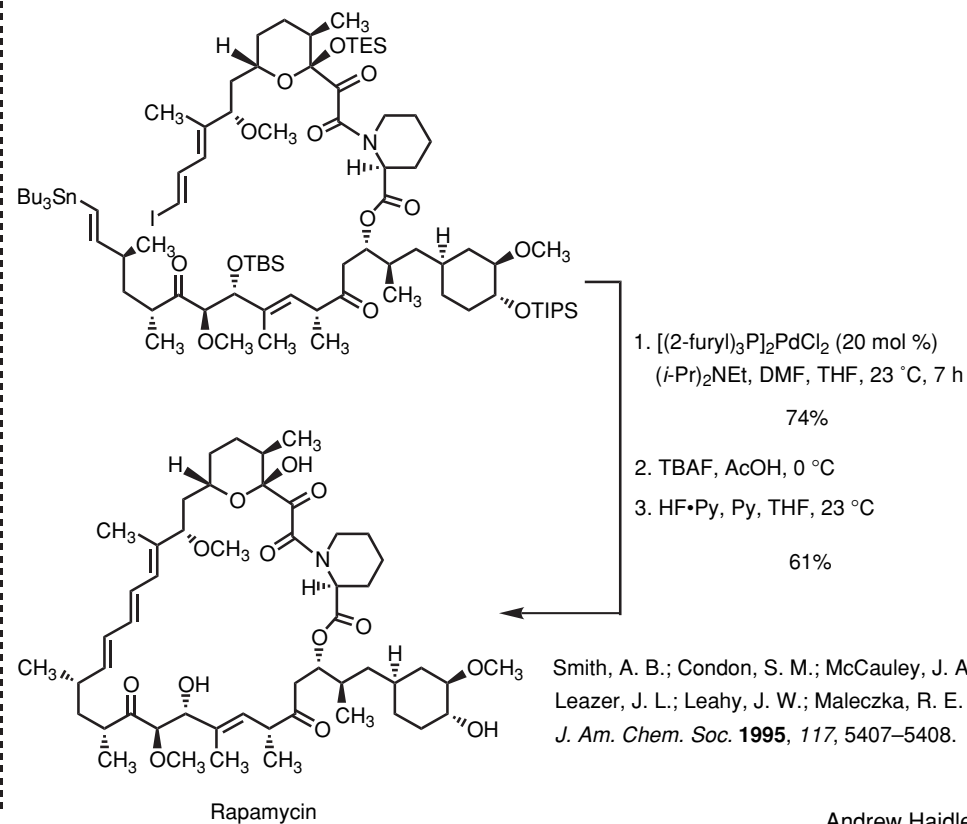
Evans, D. A.; Black, W. D. *J. Am. Chem. Soc.* **1993**, *115*, 4497–4513.



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.

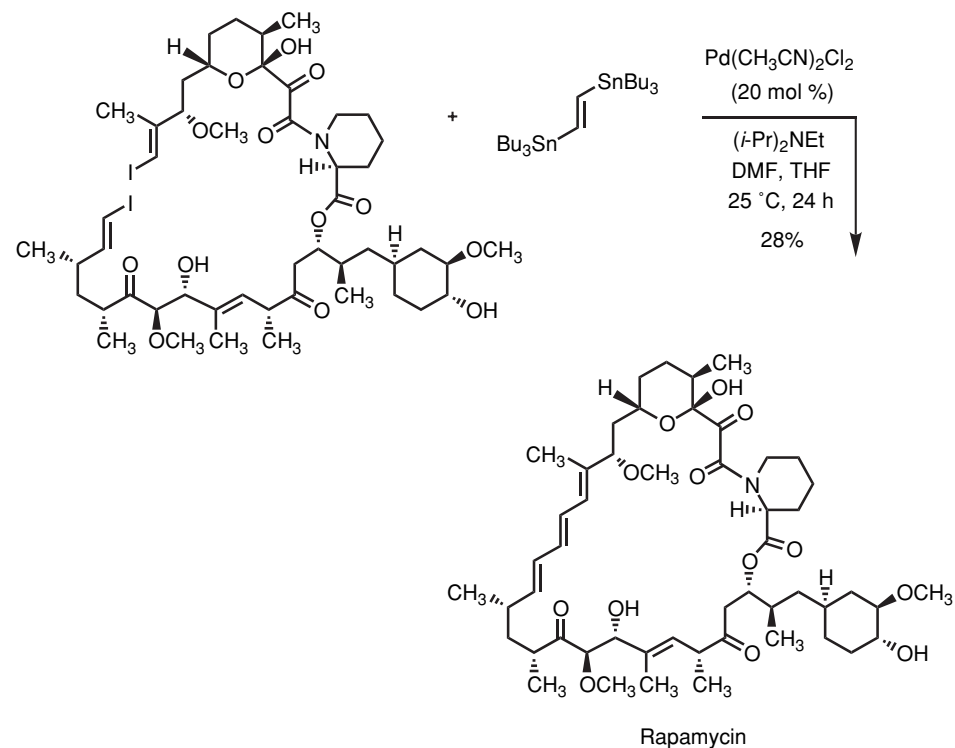


Han, Q; Wiemer, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 7692–7697.



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.

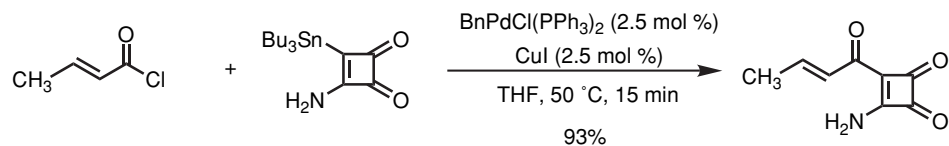
Further Examples:



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

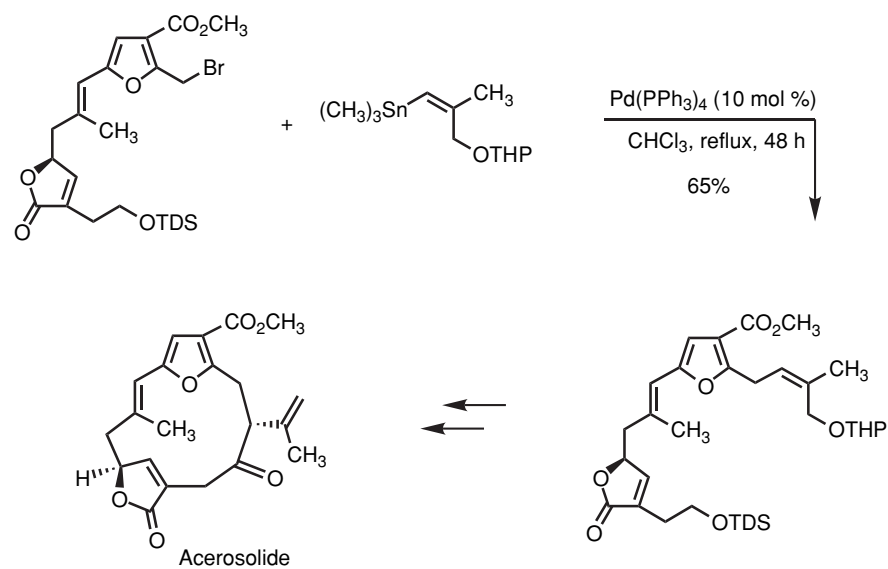
• Acid chlorides can be used as coupling reagents (the Stille reaction, as first reported, used acid chlorides).

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

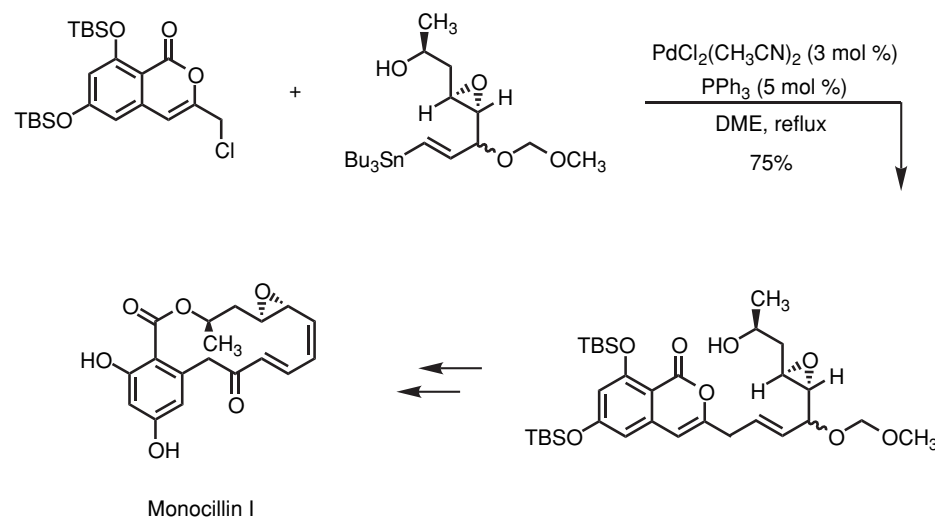


Liesbeskind, L. S.; Yu, M. S.; Fengl, R. W. *J. Org. Chem.* **1993**, *58*, 3543–3549.

• Allylic, benzylic halides:

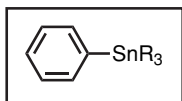


Paquette, L. A.; Astles, P. C. *J. Org. Chem.* **1993**, *58*, 165–169.



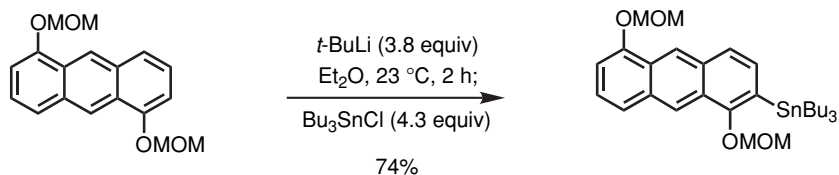
Lampilas, M.; Lett, R. *Tetrahedron Lett.* **1992**, *33*, 777–780.

Synthesis of Aryl and Vinyl Stannanes:

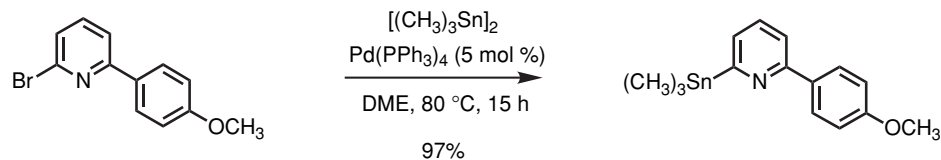


• Directed *ortho* metalation followed by addition of a stannyl chloride is a standard method.

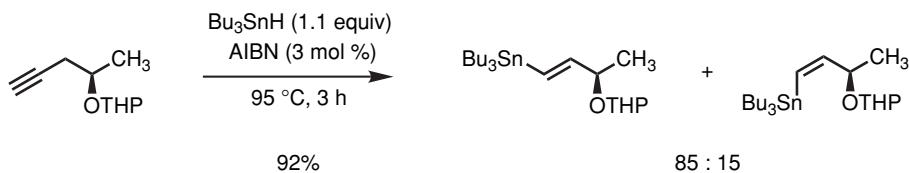
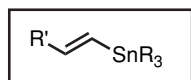
Snieckus, V. *Chem. Rev.* **1990**, *90*, 923–924.



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

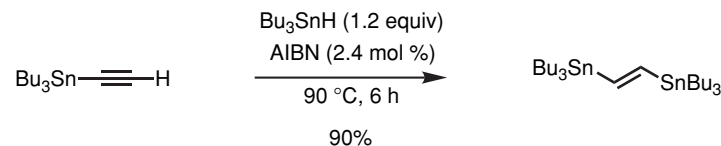
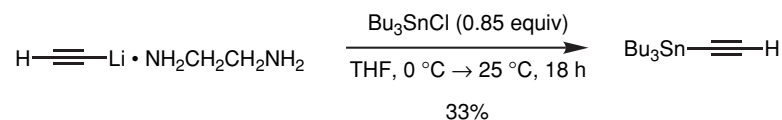


Benaglia, M.; Toyota, S.; Woods, C. R.; Siegel, J. S. *Tetrahedron Lett.* **1997**, *38*, 4737-4740.

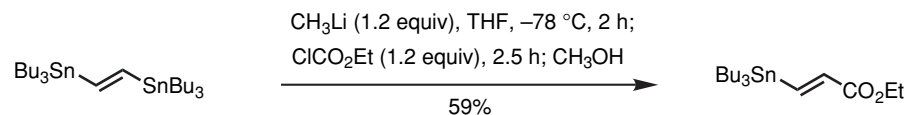


• The addition of stannyl radicals to alkynes is reversible under these conditions. The product ratio reflects the thermodynamic equilibrium.

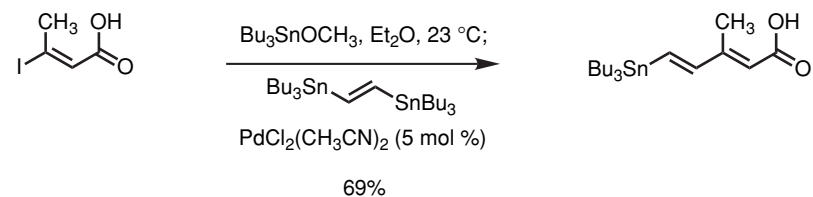
Corey, E. J.; Ulrich, P.; Fitzpatrick, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 222–224.



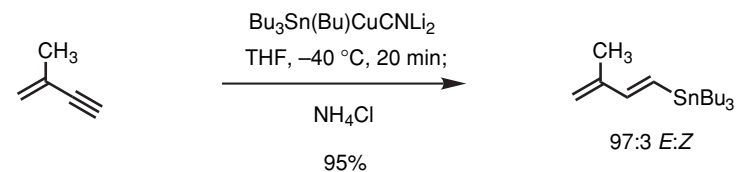
Renaldo, A. F.; Labadie, J. W.; Stille, J. K. *Org. Synth.* **1988**, *67*, 86–97.



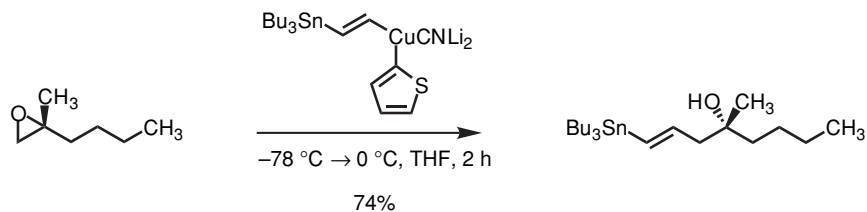
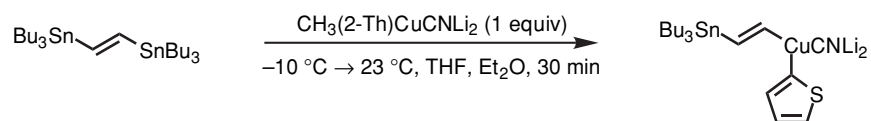
Renaldo, A. F.; Labadie, J. W.; Stille, J. K. *Org. Synth.* **1988**, *67*, 86–97.



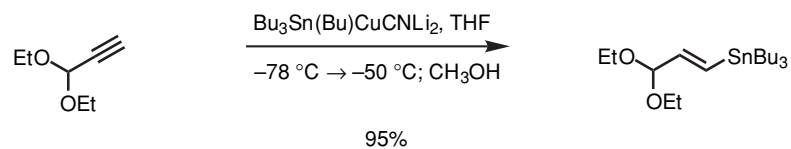
Thibonnet, J.; Abarbi, M.; Parrain, J.-L.; Duchêne, A. *Synlett* **1997**, 771–772.



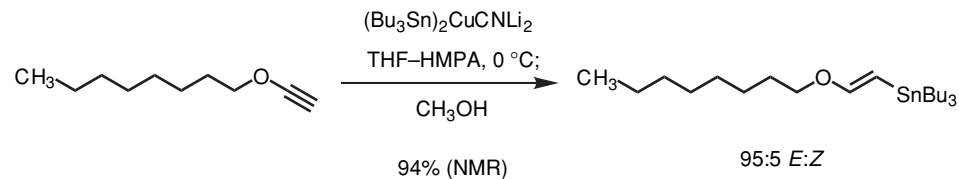
Aksela, R.; Oehlschlager, A. C. *Tetrahedron* **1991**, *47*, 1163–1176.



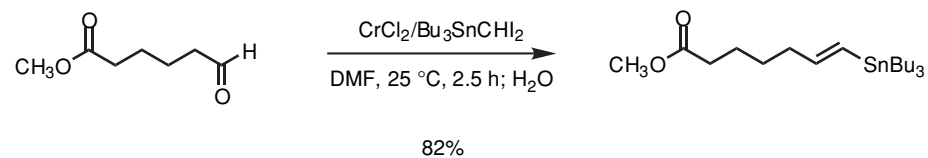
Behling, J. R.; Ng, J. S.; Babiak, K. A.; Campbell, A. L.; Elsworth, E.; Lipshutz, B. H. *Tetrahedron Lett.* **1989**, *30*, 27–30.



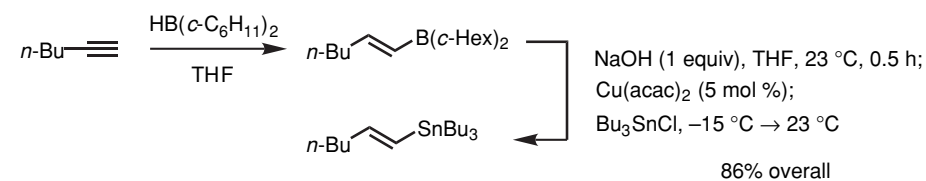
Marek, I.; Alexakis, A.; Normant, J.-F. *Tetrahedron Lett.* **1991**, *32*, 6337–6340.



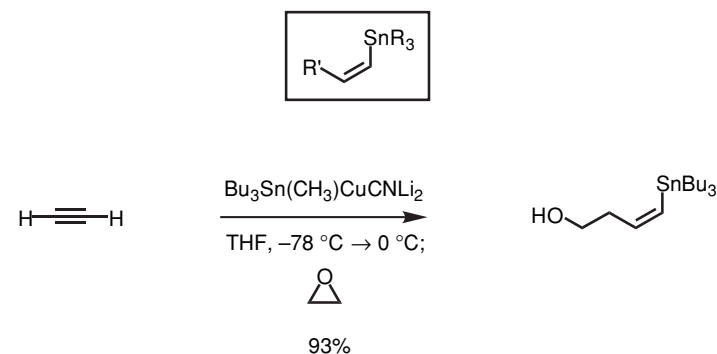
Cabezas, J. A.; Oehlschlager, A. C. *Synthesis* **1994**, 432–442.



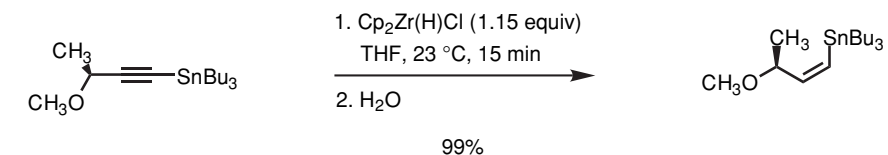
Hodgson, D. M.; Foley, A. M.; Lovell, P. J. *Tetrahedron Lett.* **1998**, *39*, 6419–6420.



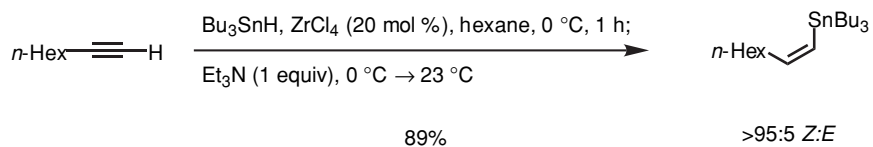
Hoshi, M.; Takahashi, K.; Arase, A. *Tetrahedron Lett.* **1997**, *38*, 8049–8052.



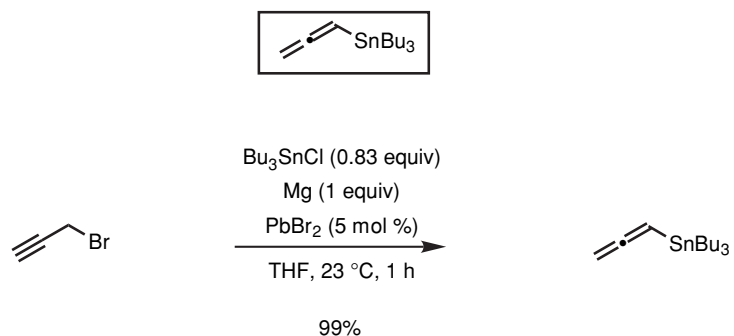
Barbero, A.; Cuadrado, P.; Fleming, I.; Gonzalez, A. M.; Pulido, F. J. *J. Chem. Soc., Chem. Commun.* **1992**, 351–353.



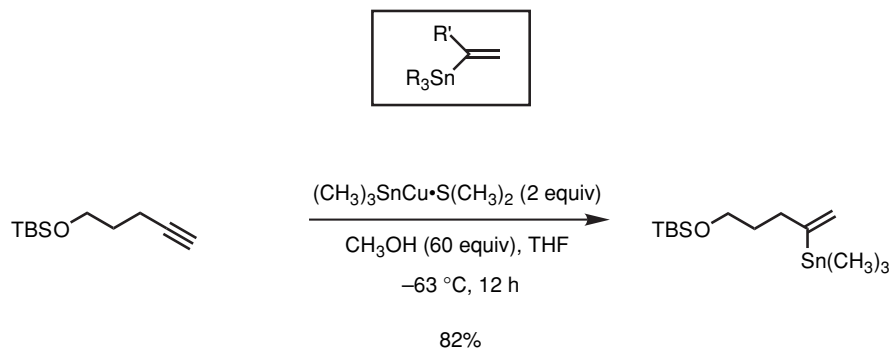
Lipshutz, B. H.; Kell, R.; Barton, J. C. *Tetrahedron Lett.* **1992**, *33*, 5861–5864.



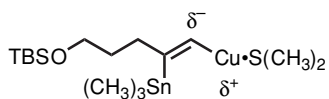
Asao, N.; Liu, J.-X.; Sudoh, T.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 2405–2406.



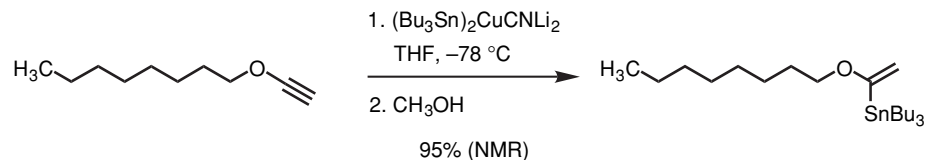
Tanaka, H.; Abdul Hai, A. K. M.; Ogawa, H.; Torii, S. *Synlett* **1993**, 835–836.



- 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.



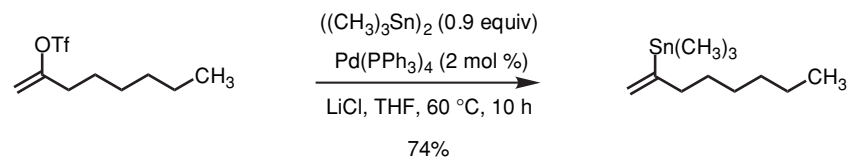
Piers, E.; Chong, J. M. *Can. J. Chem.* **1988**, *66*, 1425–1429.



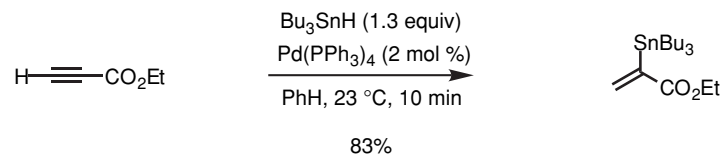
Cabezas, J. A.; Oehlschlager, A. C. *Synthesis* **1994**, 432–442.



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

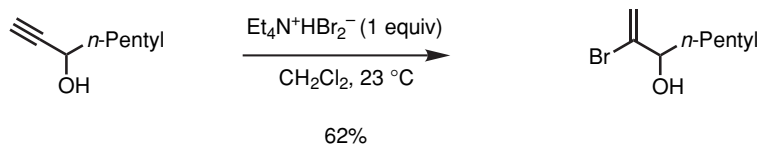


Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277–279.

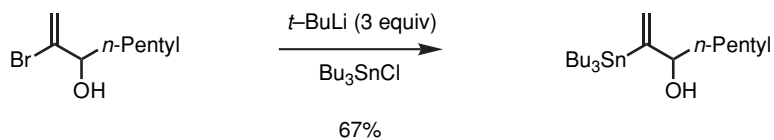


Miyake, H.; Yamamura, K. *Chemistry Lett.* **1989**, 981–984.

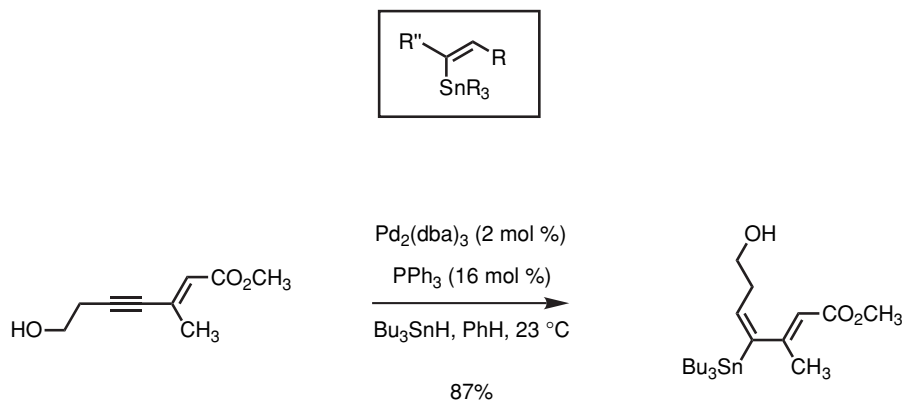
- An alternate route:



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

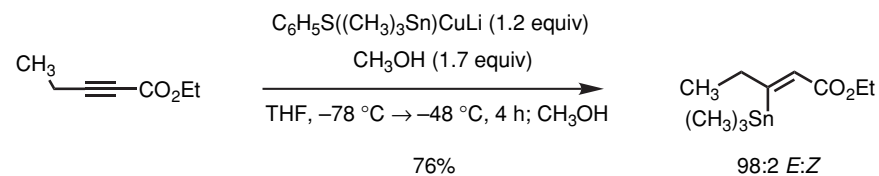


Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605.

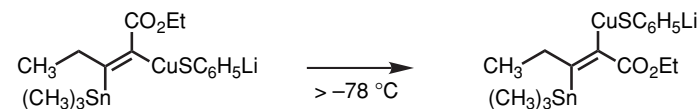


- The regiochemistry of the addition is explained as the result of hydride addition to the more electron-deficient terminus of the acetylene.

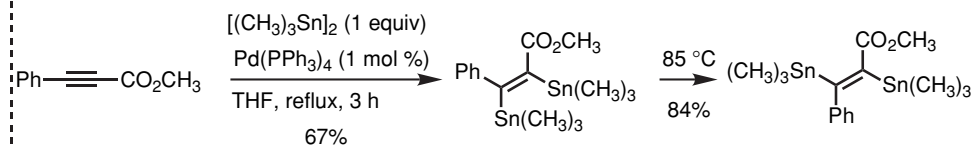
Trost, B. M.; Li, C-J. *Synthesis* **1994**, 1267–1271.



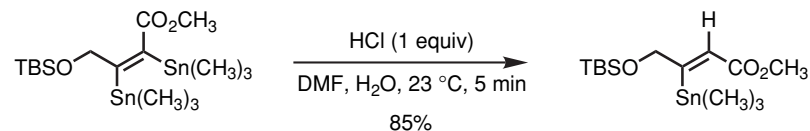
- The initially formed *cis* adduct is stable at $-100\text{ }^{\circ}\text{C}$, but at higher temperatures ($-48\text{ }^{\circ}\text{C}$), the equilibrium favors the Cu/Sn *trans* isomer.



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.

