Communications to the Editor

Stille Couplings Catalytic in Tin: Beyond Proof-of-Principle

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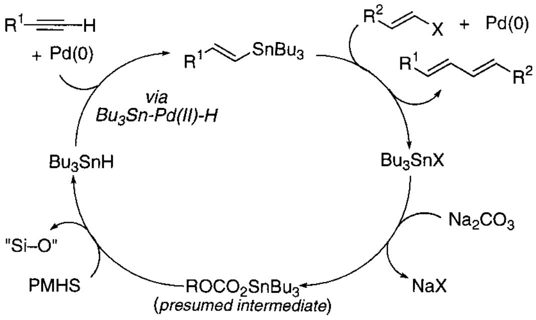
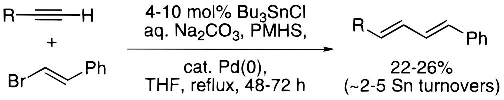
Stille cross-couplings[1] often involve the palladium-catalyzed union of vinyl or aryl halides with vinylstannanes to form 1,3-dienes. Stille reactions are quite tolerant to a large array of functionality, typically proceed with a conservation of olefin geometry, and are most often regiospecific with regards to the newly formed C−C σ-bond. As such, Stille reactions have proven useful in natural product synthesis,[2] the construction of new materials,[3] heterocycle preparation,[4] carbohydrate chemistry,[5] and support of bioorganic research.[6] Furthermore, Stille couplings are quite compatible with various new technologies. They behave well in a combinatorial setting,[2a,7] are rapidly accelerated under microwave irradiation,[8] have proven amenable to reaction in the fluorous phase,[8b,9] and offer great potential in the very nonpolar environment of supercritical carbon dioxide.[10] Despite such synthetic utility, a historic drawback of the Stille reaction has been its reliance on stoichiometric quantities of toxic, costly, and occasionally unstable organostannanes.[11,12] Therefore, we believe a Stille reaction, which is catalytic in tin, would be of considerable benefit.[13]

Scheme 1



Scheme 2



The invention of such a catalytic method poses several challenges. Perhaps most fundamental among these is that while many important advances in the development of catalytic versions of tin-mediated reactions have been realized,[11,14] most prior efforts have focused on tin reagents such as Bu_3SnH, Bu_2SnO, $(BuCH(Et)CO_2)_3SnBu$, etc. Little attention has been given to the invention of catalytic variants for chemical transformations, where the organotin species is a reactant covalently bonded to the organic molecular material of interest. In short, rendering the Stille reaction catalytic in tin would require an initial molecule of organotin hydride to participate in a chemoselective sequence of in situ vinyltin generation, cross-coupling, and then a final transformation of the organotin halide byproduct back to tin hydride.

Our initial efforts on the development of such a reaction sequence were reported last year.[14a,15] In the first of these early studies,[15] we established a one-pot palladium-mediated hydrostannylation/ Stille cross-coupling protocol. Furthermore, by running the reaction sequence in the presence of aqueous Na_2CO_3 and polymethylhydrosiloxane (PMHS), in situ conversion of the tributyltin halide Stille byproduct into a tin oxide species, followed by PMHS reduction[16] of the newly formed Sn−O bond,[17] regenerated Bu_3SnH and established our catalytic cycle (Scheme 1). In these first examples of tin-catalyzed Stille cross-couplings, the employment of 4−10 mol % Bu_3SnCl afforded 1,3-dienes in approximately 22−26% yield, representing a very modest 2−5 tin turnovers (Scheme 2).

In part, these less than ideal results can be traced to the sluggishness (48−72 h) of the cross-coupling portion of our sequence. This allows the tin ample time to react in nonproductive

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[1] (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−523. (b) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813−817. (c) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652.

[2] For examples see: (a) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Murphy, F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2534−2537. (b) Alcaraz, L.; Macdonald, G.; Ragot, J.; Lewis, N. J.; Taylor, R. J. K. *Tetrahedron* **1999**, *55*, 3707−3716. (c) Duncton, M. A. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1235−1246.

[3] For examples see: (a) Yao, Y. X.; Tour, J. M. *Macromolecules* **1999**, *32*, 2455−2461. (b) Hucke, A.; Cava, M. P. *J. Org. Chem.* **1998**, *63*, 7413−7417.

[4] For an example see: Beccalli, E. M.; Clerici, F.; Gelmi, M. L. *Tetrahedron* **1999**, *55*, 781−786.

[5] For an example see: Kuribayashi, T.; Gohya, S.; Mizuno, Y.; Satoh, S. *J. Carbohyd. Chem.* **1999**, *18*, 383−392.

[6] For examples see: (a) Nicolaou, K. C.; King, N. P.; Finlay, M. R. V.; He, Y.; Roschangar, F.; Vourloumis, D.; Vallberg, H.; Sarabia, F.; Ninkovic, S.; Hepworth, D. *Bioorg. Med. Chem.* **1999**, *7*, 665−697. (b) Thibonnet, T. J.; Abarbri, M.; Duchene, A.; Parrain, J. L. *Synlett* **1999**, 141−143.

[7] (a) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549−1581. (b) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385−15443 and references therein.

[8] (a) Larhed, M.; Hoshino, M.; Hadida, S.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 5583−5587. (b) Olofsson, K.; Kim, S.-Y.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1999**, *64*, 4539−4541.

[9] (a) Hoshino, M.; Degenkolb, P.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 8341−8349. (b) Curran, D. P.; Hadida, S. *J. Am. Chem. Soc.* **1996**, *118*, 2531−2532.

[10] Jessop, P. G.; Ikariya, T.; Noyori, R. *Chem. Rev.* **1999**, *99*, 475−493.

[11] (a) *Chemistry of Tin*; Smith, P. J., Ed.; Blackie Academic & Professional: New York, 1998. (b) Davies, A. G. In *Organotin Chemistry*; VCH: New York, 1997.

[12] (a) Hitchcock, S. A.; Mayhugh, D. R.; Gregory, G. S. *Tetrahedron Lett.* **1995**, *36*, 9085−9088. (b) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857−1867.

[13] Problems associated with the employment of tin in the Stille reaction have, in part, fueled the development of "tin free" cross-coupling protocols, most prominently the Suzuki coupling. Though a powerful method, the Suzuki coupling has not supplanted the Stille reaction as a synthetic tool. Evidence of this can be seen in a 1997−1999 ISI citation search, of the primary Stille[1a] and Suzuki (Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483) reviews. Such a search reveals a comparable 420 and 350 citations of the Stille and Suzuki reviews, respectively.

[14] (a) Terstiege, I.; Maleczka, R. E., Jr. *J. Org. Chem.* **1999**, *64*, 342−343. (b) Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett.* **1999**, *1*, 447−450. (c) Spino, C.; Barriault, N. *J. Org. Chem.* **1999**, *64*, 5292−5298. (d) Lopez, R. M.; Fu, G. C. *Tetrahedron* **1997**, *53*, 16349−16354. (e) Hays, D. S.; Fu, G. C. *Tetrahedron* **1999**, *55*, 8815−8832 and references therein.

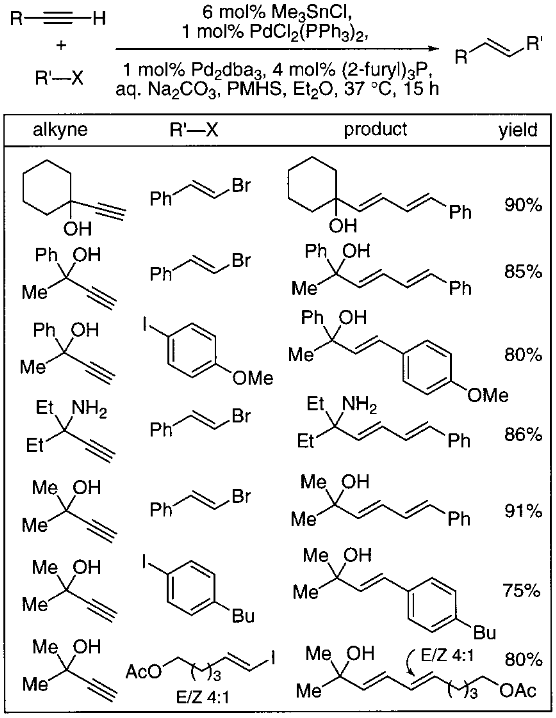
[15] Maleczka, R. E., Jr.; Terstiege, I. *J. Org. Chem.* **1998**, *63*, 9622−9623.

[16] Hayashi, K.; Iyoda, J.; Shiihara, I. *J. Organomet. Chem.* **1967**, *10*, 81−94.

[17] We assume the "Sn−O" species to be an organotin carbonate. However, this has yet to be firmly established.

10.1021/ja993446s CCC: $19.00

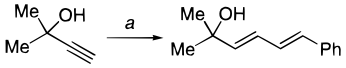
Scheme 3



ways, i.e., formation of hexabutylditin.[18] Since it is generally believed that transmetalation is the rate-determining step of the Stille reaction,[1] we rationalized that switching from tributyltins to the less sterically demanding trimethyltins should facilitate the overall reaction sequence.

As illustrated in Scheme 3, syringe pump addition[19] of 1.5 equiv of various Stille electrophiles to a 37 °C ethereal mixture of alkyne, aqueous Na_2CO_3, PMHS, Pd_2dba_3, trifurylphosphine, $PdCl_2(PPh_3)_2$,[20] and 0.06 equiv of Me_3SnCl over a period of 15 h afforded the corresponding cross-coupled products in 75−91% yield, representing an average of ~15 tin turnovers. Furthermore, since one cycle requires the tin to undergo four transformations, each molecule of organostannane is experiencing a minimum of 60 reactions over the course of the hydrostannylation/Stille sequence. Significantly, all Stille products were formed in similar or superior yields to those realized under "classic" two-pot, stoichiometric conditions.

Scheme 4



[a] (cat.) Me_3SnCl, aq. Na_2CO_3, PMHS, Pd_2dba_3, $(2\text{-furyl})_3P$, $PdCl_2(PPh_3)_2$, bromostyrene, Et_2O, 37 °C, 15 h

Me_3SnCl [mol%]	Sn turn-overs	yield
6	15	91%
4	17	67%
1	18	18%

Little improvement was observed in the efficiency of these reactions when higher loads of Me_3SnCl were employed. However, dropping below 6 mol % tin resulted in fairly substantial reductions in yield (Scheme 4). For example, at 1 mol % Me_3SnCl, the 1,3-diene was formed in only 18% yield.

Work to improve the turnover numbers of our protocol will continue, as will our efforts to more fully address the regiochemical impact of carrying out the reaction sequence with sterically less demanding alkynes.[21] We also seek to balance the increased safety concerns associated with trimethylstannanes.[11,22] Nonetheless, our method for performing one-pot hydrostannylation/Stille couplings with catalytic amounts of tin has advanced beyond the proof-of-principle stage, with us now able to form diverse arrays of Stille products in excellent yields, while at the same time reducing the traditional tin requirement by 94%.

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Supporting Information Available: Spectroscopic data for all new compounds pictured, as well as detailed experimental procedures (PDF). This material is available free of charge via the Internet at http:/pubs.acs.org.

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(18) Attempts to accelerate the reaction through the use of polar solvents (DMF or NMP) or highly active catalysts such as $(MeCN)_2PdCl_2$ resulted in overall diminished yields, as Pd-catalyzed conversion of Bu_3SnH into hexabutylditin (Mitchell, T. N.; Amamria, A.; Killing, H.; Rutschow, D. *J. Organomet. Chem.* **1986**, *304*, 257−265) predominated the reaction. Furthermore, the addition of copper salts provided little or no improvement (see: (a) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748−2749. (b) Han, X. J.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600−7605).

(19) Addition of the electrophiles, particularly the iodides, in a single portion resulted in intrusive levels of hydrodehalogenation, presumably via Pd(0)-catalyzed reduction by $PMHS/Na_2CO_3$.

(20) Though the reason remains unclear, the mixed Pd system of 1 mol % Pd_2dba_3, 4 mol % $(2\text{-furyl})_3P$, and 1 mol % $PdCl_2(PPh_3)_2$ in Et_2O gave the best yields.

(21) We limited this study to α-trisubstituted alkynes containing a lone pair on one of the propargylic substituents as bulky alkynes give (*E*)-vinylstannanes upon Pd-catalyzed hydrostannylation. (See: (a) Blaskovich, M. A.; Kahn, M. *J. Org. Chem.* **1998**, *63*, 1119−1125. (b) Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768−7780.) Detailed studies of our protocol under less regiocontrolled circumstances are underway. We will report the results of these investigations as they develop.

(22) (a) Scott, W. J.; Moretto, A. F. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: New York, 1995; Vol 7, pp 5327−5328. (b) Dyer, R. S.; Walsh, T. J.; Wonderlin, W. F.; Bercegeay, M. *Neurobehav. Toxicol. Teratol.* **1982**, *4*, 127−133.