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Stille Couplings Catalytic in Tin: A "Sn–F" Approach

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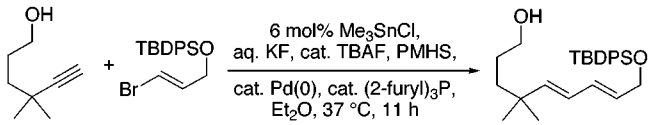
ABSTRACT



A new tin recycling method for Stille couplings catalytic in tin is reported. PMHS made hypercoordinate by $KF_{(aq)}$ allows Me_3SnH to be efficiently recycled during a Pd(0)-catalyzed hydrostannation/Stille cascade. Relative to previously disclosed protocols, reaction times are shorter and because this process is believed to proceed through a Me_3SnF intermediate the hazards and problems associated with trimethyltins are also diminished.

The Stille reaction is a commonly employed tactic in organic synthesis.[1] Despite its wide use, the reaction's reliance on organostannanes has traditionally been viewed negatively given the toxicity,[1b,2] associated purification problems,[1b,3] and expense of these chemicals. To address the concerns over organotin use, new organotin derivatives[1a,b,4] and techniques[1b,3a,b] have been designed to facilitate removal of the tin waste.[5]

We have pursued a complementary approach to solving the Stille "tin problem"; the development of a Pd(0)-catalyzed hydrostannation/Stille coupling that is *catalytic* in tin. First examples of such a process proved reasonably successful as reactions employing only 0.06 equiv. of Me_3SnCl often afforded cross-coupled products in 51−91% yield.[6] Unfortunately, reaction yields suffered greatly when Bu_3SnCl was substituted for Me_3SnCl or when tin loads were lowered.[6] This was significant since organotin toxicity and volatility increase as the alkyl group size decreases.[2] Trimethyltin halides (Cl, Br, I) and the presumed trimethyltin carbonate intermediate (Scheme 1, "Sn−O" approach) are also water soluble,[1b] thereby complicating disposal of aqueous phases produced during workup. Furthermore, the reactivity and structure of $(Me_3SnO)CO$ is not well defined,[7] bringing into question its competence within the catalytic cycle.

Thus, we set out to develop a new but equally efficient way to recycle Me_3SnH that did not involve tin carbonates and/or minimized the hazards and problems associated with trimethyltins. In pursuing this goal, we became attracted to the possibility of a catalytic cycle mediated by Me_3SnF.

Organotin fluorides are nonvolatile aggregated solids not easily absorbed through the skin and sparingly soluble in

(1) (a) Mitchell, T. N. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 4. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652. (c) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−523.

(2) (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. (c) Krigman, M. R.; Silverman, A. P. *Neurotoxicology* **1984**, *5*, 129−140.

(3) (a) Saloman, C. J.; Danelon, G. O.; Mascaretti, O. A. *J. Org. Chem.* **2000**, *65*, 9220−9222 and references cited. (b) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 7200−7201. (c) Farina, V. *J. Org. Chem.* **1991**, *56*, 4985−4987.

(4) Examples include: (a) monoorganotins (Fouquet, E.; Rodriguez, A. L. *Synlett* **1998**, 1323−1324), (b) stannatranes (Yang, C.; Jensen, M. S.; Conlon, D. A.; Yasuda, N.; Hughes, D. L. *Tetrahedron Lett.* **2001**, *41*, 8677−8681 and references cited), (c) polymer bound organotins (Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Murphy, F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2534−2537 and references cited), and (d) alkyltrichlorostannanes (Bumagin, N. A.; Roshchin, A. I. *Russ. J. Gen. Chem.* **2000**, *70*, 57−63 and references cited).

(5) Tin toxicity has also spurred development of reactions with Zn (Negishi) and B (Suzuki) compounds (ref 1a, Chapters 1−2) as well as advances in Si (Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2001**, *123*, 6439−6440 and references cited. Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053−2055. Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684−1688) and In-based cross-couplings (Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155−4160).

(6) (a) Maleczka, R. E., Jr.; Terstiege, I. *J. Org. Chem.* **1998**, *63*, 9622−9623. (b) Maleczka, R. E., Jr.; Gallagher, W. P.; Terstiege, I. *J. Am. Chem. Soc.* **2000**, *122*, 384−385. (c) Gallagher, W. P.; Terstiege, I.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 3194−3204.

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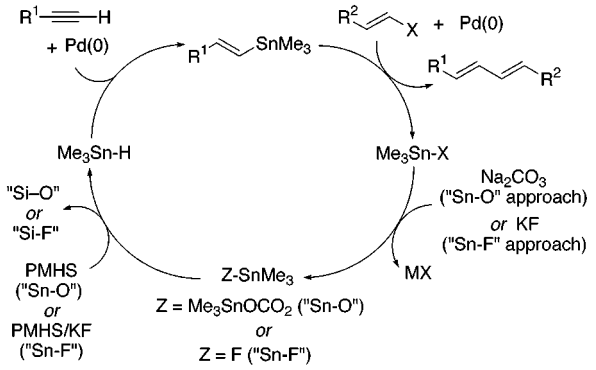
Scheme 1



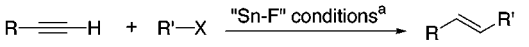
most solvents.[2a,b] As such, the risks posed by organotin fluorides are less than those of other organotins. Indeed, tin-mediated reactions are often subjected to a fluoride workup so as to convert the organotin waste into the relatively benign and easily filterable organotin fluorides.[8]

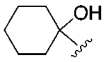
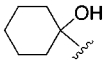
In 1986, Scott and Stille[9] showed that the presence of CsF during the efficient cross-coupling of organostannanes with vinyltriflates allowed for 80% of the tin waste to be removed by filtration. More recently, we reported on Pd(0)-mediated hydrostannations via R_3SnH generated in situ by reduction of R_3SnF or R_3SnCl with hypercoordinate polymethylhydrosiloxane (PMHS + fluoride).[10]

On the basis of these precedents, we considered a "Sn−F" approach to Stille reactions catalytic in tin such as that illustrated by Scheme 1 ("Sn−F" approach). A Me_3SnF-mediated sequence would lessen the aforementioned problems associated with our prior use[6] of trimethyltins.[11] Furthermore, fluoride-activation of vinylstannanes can facilitate their coupling;[12] therefore we wanted to explore if fluoride would positively impact reaction effectiveness.

In practice, a variety of alkynes and electrophiles underwent a successful hydrostannation/Stille reaction in the presence of KF, catalytic TBAF,[13,14] catalytic Pd(0), and 0.06 equiv of Me_3SnCl (Table 1). We were pleased to find that compared to our original "Sn−O" method,[6] the "Sn−F" approach afforded the Stille products in similar yields but

Table 1



entry	alkyne	R'—X	product yield[b]
1	R = $HO(Me)_2C$-	Ph—Br	88%
2	R = 	I—(CH2)8—CO2Me	73%
3	R = HO(Me)(*i*-Bu)C-	Ph—Br	89%
4	R = $HO(Me)_2C$-	MeO—I	78%
5	R = $H_2N(Et)_2C$-	Ph—Br	82%
6	R = 	Ph—Br	90%
7	R = HO(Pr)CH-	Ph—Br	60%
8	R = HO(Ph)CH-	Ph—Br	68%
9	R = $HO(Me)_2C$-	Br—Ph	85%
10		Ph—Br	61%

[a] "Sn−F" conditions: 6 mol % of Me_3SnCl, aqueous KF, catalytic TBAF, PMHS, 1 mol % of $PdCl_2(PPh_3)_2$, 1 mol % of Pd_2dba_3, 4 mol % of (2-furyl)$_3$P, Et_2O, 37 °C, 11 h. [b] Average isolated yield of three runs.

in approximately 25% less time (11 vs 15 h). Beyond the key substitution of fluoride for Na_2CO_3, this new approach required only minor alterations to our original procedure. Instead of adding the electrophile last (per our "Sn−O" protocol), a solution of alkyne and PMHS in Et_2O was slowly added to the reaction mixture via syringe pump. This reverse addition minimized electrophile reduction and generally gave cleaner and higher yielding reactions.

In terms of substrate tolerance, the "Sn−F" and "Sn−O" [6] approaches proved similar. Reaction efficiency was highly influenced by the regioselectivity of the Pd(0)-catalyzed hydrostannation step.[15] Alkynes that were trisubstituted at the propargylic position (entries 1−6 and 9) worked better than those that are disubstituted (entries 7−8), while unhindered alkynes required the regiochemical assistance of a 1-bromo group[6c,15a,16] (entry 10). As for electrophiles, vinyl, aryl, and benzyl halides were amenable to the new conditions, while allyl bromide, methyl iodide, and an aryl nonaflate were not.

To further test the synthetic utility of the "Sn−F" approach, we sought to synthesize diene **1**, a key intermediate from Jauch's[17] recently reported synthesis of the reverse transcriptase inhibitor kuehneromycin A.[18] While Jauch formed **1** via Horner−Wadsworth−Emmons olefination of

(7) Kümmerlen, J.; Sebald, A. *J. Organomet. Chem.* **1992**, *427*, 309−323.

(8) (a) Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449−450. (b) Edelson, B. S.; Stoltz, B. M.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 6729−6730.

(9) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033−3040.

(10) (a) Maleczka, R. E., Jr.; Terrell, L. R.; Clark, D. H.; Whitehead, S. L.; Gallagher, W. P.; Terstiege, I. *J. Org. Chem.* **1999**, *64*, 5958−5965. (b) Maleczka, R. E., Jr.; Terstiege, I. *J. Org. Chem.* **1999**, *64*, 342−343. (c) Maleczka, R. E., Jr.; Terstiege, I. *J. Org. Chem.* **2000**, *65*, 930.

(11) Applying tributyltins to this approach proved disappointing (see ref 10b).

(12) (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411−2413. (b) Fugami, K.; Ohnuma, S.; Kameyama, M.; Saotome, T.; Kosugi, M. *Synlett* **1999**, 63−64.

(13) Hydrostannations with R_3SnX/PMHS/KF generated R_3SnH are accelerated by adding a catalytic amount of TBAF which presumably facilitates phase transfer (ref 10).

(14) Reaction of stoichiometric TBAF with R_3SnH can give R_3SnSnR_3 (Kawakami, T.; Shibata, I.; Baba, A. *J. Org. Chem.* **1996**, *61*, 82−87), a terminating event for the catalytic cycle.

(15) (a) Zhang, H. X.; Guibé F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857−1867. (b) Smith, N. D.; Mancuso, J.; Lautens, M. *Chem. Rev.* **2000**, *100*, 3257−3282. (c) Rice, M. B.; Whitehead, S. L.; Horvath, C. M.; Muchnij, J. A.; Maleczka, R. E., Jr. *Synthesis* **2001**, 1495−1504 and references cited.

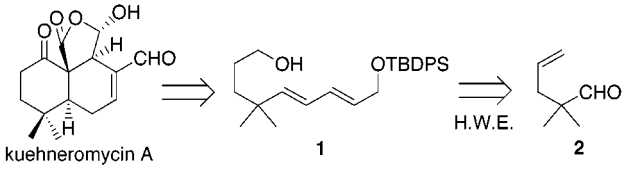
(16) Boden, C. D. J.; Pattenden, G.; Ye, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2417−2419.

(17) Jauch, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2764−2765.

(18) Erkel, G.; Lorenzen, K.; Anke, T.; Velten, R.; Gimenez, A.; Steglich, E. *Z. Naturforsch. C* **1995**, *50*, 1−10.

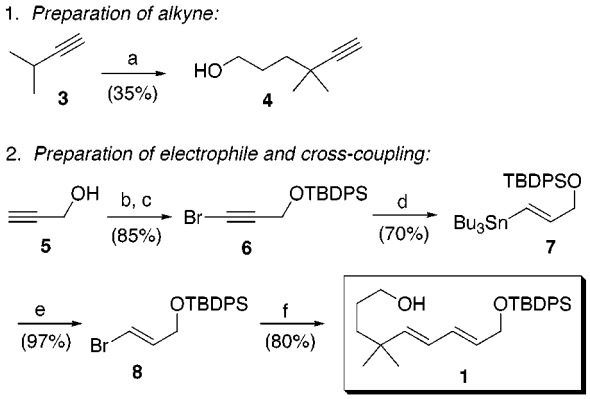
aldehyde **2** (Scheme 2), our route started with 4,4-dimethylhex-5-yn-1-ol (**4**).

Scheme 2. Jauch's Retrosynthesis of Kuehneromycin A



In our hands, the reported synthesis[19] of **4** proved tedious. Therefore a dianion alkylation[20] based construction was investigated. Exposing isopropylacetylene (**3**) to 2 equiv of *n*-BuLi and 1 equiv of TMEDA in Et_2O at 50 °C resulted in formation of a red dianion solution (Scheme 3). This solution

Scheme 3. Synthesis of Jauch Intermediate **1**[a]



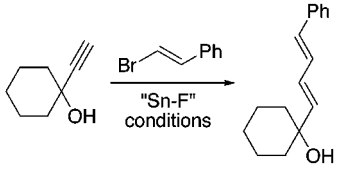
[a] Reagents and conditions: (a) *n*-BuLi (2 equiv), Et_2O, 0 °C then TMEDA (1 equiv), 50 °C, 15 h then oxetane, $BF_3{\cdot}EtO_2$, −78 °C, 6 h; (b) BPSCl, imidazole, DMF, 25 °C, 5 h; (c) NBS, $AgNO_3$, 8 h; (d) Bu_3SnCl, aqueous KF, PMHS, TBAF, $PdCl_2(PPh_3)_2$, rt, THF, 2 h; (e) NBS, CH_2Cl_2, 1 h, 0 °C; (f) **4**, 6 mol % of Me_3SnCl, catalytic TBAF, 1 mol % of $PdCl_2(PPh_3)_2$, 1 mol % of Pd_2dba_3, 4 mol % of $(2\text{-furyl})_3P$, aqueous KF, PMHS, Et_2O, 37 °C, 11 h.

was treated with oxetane[21] followed by slow addition[22] of $BF_3{\cdot}Et_2O$ at −78 °C. The oxetane was thus ring opened and alkyne (**4**) was formed in 35% yield.

Synthesis of the electrophilic partner (**8**) began with the protection of propargyl alcohol as its *tert*-butyldiphenylsilyl (TBDPS) ether (Scheme 3). Conversion to 1-bromoalkyne **6** was carried out to enhance selectivity during the subsequent Pd(0)-catalyzed vinyltin formation.[15a,16] In practice, hydrostannation of **6** using Bu_3SnCl/KF/PMHS as an in situ source of Bu_3SnH[10] provided a separable 11:1 mixture of (*E*)-vinylstannane **7** and its proximal isomer. Tin−halogen exchange with NBS ultimately afforded (3-bromoallyloxy)-*tert*-butyldiphenylsilane (**8**)[23] in 58% combined yield from propargyl alcohol. Vinyl bromide **8**[24] and alkyne **4** were then reacted via the Me_3SnF-mediated hydrostannylation[25]/Stille protocol to afford diene **1**[26] in 72% yield. This example highlights the method's tolerance toward silyl protective groups.

Tin loading requirements were similar for both the "Sn−F" and "Sn−O" approaches. Dropping below 6 mol % of tin resulted in substantial yield reduction (Table 2), while higher loads (up to 20 mol %) offered little advantage.

Table 2. Tin Loading Experiments



Me_3SnCl (mol%)	Sn turnovers	yield
6	15	88%
4	16	63%
2	19	39%
1	19	19%

For entry 1 in Table 1, 6 mol % of Me_3SnF or the corresponding vinylstannane could be substituted for Me_3SnCl as the initial tin source with very little effect on the yield of the cross-coupled product. Furthermore, stoichiometric experiments followed by ^1H NMR indicated that the reduction of Me_3SnCl (δ 0.60 ppm in CD_3OD) to Me_3SnH (δ 0.14) proceeds through Me_3SnF (δ 0.45). Thus while the presence of multiple aggregates of Me_3SnF, $[Me_3SnF(Cl)]K$, or related "ate" intermediates has not been completely ruled out, we believe the spectroscopic and chemical data suggest the sequence to be proceeding via a cycle like that illustrated in Scheme 1. Work to further identify reaction intermediates continues.

In summary, we have developed a modified protocol for carrying out Stille reactions with catalytic amounts of tin. In comparison to our original "Sn−O" route, the "Sn−F" approach offers several advantages. Reactions can be completed in 25% less time with little loss in yield. Although trimethylstannanes are still required, the reaction proceeds via the less hazardous organotin fluoride,[2] which can be filtered off at the end of the reaction sequence.[9] In contrast, trimethyltin residue from the "Sn−O" approach resides in both the organic and aqueous phases, requiring additional manipulation and/or creating undesirable exposure and disposal problems.

(19) Harada, T.; Iwazaki, K.; Otani, T.; Oku, A. *J. Org. Chem.* **1998**, *63*, 9007−9112.

(20) (a) Bhanu, S.; Scheinman, F. *J. Chem. Soc., Chem. Commun.* **1975**, 817. (b) McMurry, J. E.; Matz, J. R.; Kees, K. L. *Tetrahedron* **1987**, *43*, 5489−5498.

(21) Yamaguchi, M.; Nobayashi, Y.; Hirao, I. *Tetrahedron* **1984**, *40*, 4261−4266 and references cited.

(22) Adding $BF_3{\cdot}EtO_2$ in one portion resulted in a 20% yield of **4**.

(23) Although tin-free preparations of **8** can be envisaged, prior work by us and the immediate availablity of intermediates favored the chosen route.

(24) Under traditional Stille conditions the analogous vinyl iodide gave an intrusive amount of homocoupling.

(25) Pd(0)-catalyzed hydrostannation of **4** exclusively gave the (*E*) isomer (88% yield).

(26) Spectral data for **1** was not reported (ref 17); however its structure as well as those assigned all new compounds are in accord with their infrared, 300- or 500 MHz ^1H NMR, and 62.5- or 125-MHz ^{13}C NMR spectral data, as well as appropriate ion identification by high-resolution mass spectrometry. See Supporting Information for details.

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

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