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Microwave-Assisted One-Pot Hydrostannylation/Stille Couplings

Robert E. Maleczka, Jr.,* Jérôme M. Lavis, Damon H. Clark, and William P. Gallagher

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

maleczka@cem.msu.edu

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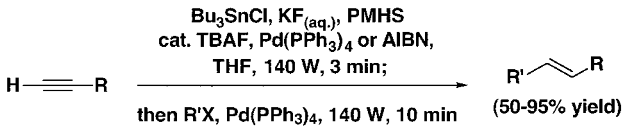
ABSTRACT



In a fraction of the time required by conventional methods, microwave-accelerated one-pot hydrostannylation/Stille coupling allows 1-alkynes to be efficiently transformed into 1,3-dienes or styrenes.

The Stille cross-coupling[1] of organic halides with vinylstannanes has become an attractive method in modern organic synthesis. Under classical Stille conditions, most substrates cross-couple at reaction temperatures of 45−100 °C with reaction times ranging from hours to days. Recently Larhed, Hallberg, and others[2] have shown that the cross-coupling time for fluorous and organic-phase Stille couplings can be reduced to only minutes by using microwave flash heating.[3]

Of course, the overall speed in which a Stille product can be accessed is also dependent on the time required to (a) prepare the starting materials and (b) isolate the product. Thus, we viewed applying microwave assistance to a one-pot hydrostannylation/Stille sequence[4] as an advance of both methodologies. We also sought to carry out these transformations in an easily removable solvent (THF as opposed to DMF or NMP) so as to facilitate product isolation and thereby further condense the time line to prepare 1,3-dienes from 1-alkynes.

To achieve efficient one-pot palladium-mediated hydrostannylation/Stille couplings, it is crucial that Pd(0)-catalyzed conversion[5] of Bu_3SnH into $Bu_3SnSnBu_3$ be minimized. Therefore, we decided to employ Bu_3SnCl, aqueous KF, polymethylhydrosiloxane (PMHS), and catalytic TBAF as an in situ source of Bu_3SnH.[6] In addition to being relatively cheap and mild, these reagents allow a controlled production of tin hydride, thereby decreasing the opportunity for Pd(0)-mediated tin dimerization.[7]

Initial experiments involved irradiating a pressure tube containing a THF solution of Bu_3SnCl, aqueous KF, PMHS, an alkyne, electrophile, and Pd(0) in a commercial microwave oven.[8,9] Although this led to the formation of Stille products within minutes, yields varied widely and could not be consistently reproduced. Furthermore, electrophile reduc-

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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] (a) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582−9584. (b) Olofsson, K.; Kim, S.-Y.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1999**, *64*, 4539−4541. (c) Larhed, M.; Hoshino, M.; Hadida, S.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 5583−5587.

[3] For other methods of accelerating Stille reactions, see: (a) Han, X. J.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600−7605. (b) Fugami, K.; Ohnuma, S.-y.; Kameyama, M.; Saotome, T.; Kosugi, M. *Synlett* **1999**, 63−64. (c) Fouquet, E.; Rodriguez, A. L. *Synlett* **1998**, 1323−1324. (d) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73−78. (e) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748−2749.

[4] (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.

[5] Mitchell, T. N.; Amamria, A.; Killing, H.; Rutschow, D. *J. Organomet. Chem.* **1986**, *304*, 257−265.

[6] Terstiege, I.; Maleczka, R. E., Jr. *J. Org. Chem.* **1999**, *64*, 342−343.

[7] 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.

[8] See cautionary notes (vide infra).

[9] Kenmore (model 721.69182) variable power 700 W microwave oven.

[10] (a) Taniguchi, M.; Takeyama, Y.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2593−2595. (b) Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 452−461. (c) Pri-Bar, I.; Buchman, O. *J. Org. Chem.* **1986**, *51*, 734−738. (d) Pri-Bar, I.; Buchman, O. *J. Org. Chem.* **1984**, *49*, 4009−4011.

[11] (a) Zapf, A.; Beller, M. *Chem. Eur. J.* **2000**, *6*, 1830−1833. (b) Albisson, D. A.; Bedford, R. B.; Lawrence, S. E.; Scully, P. N. *J. Chem. Soc., Chem. Commun.* **1998**, 2095−2096.

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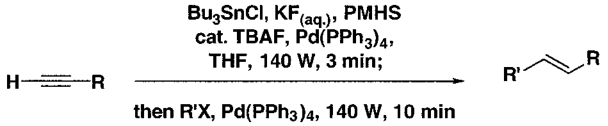
Table 1



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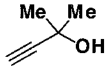
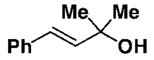
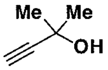
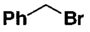
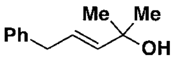
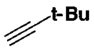
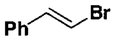
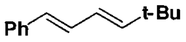
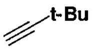
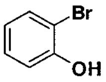
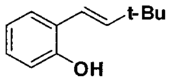
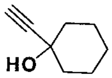
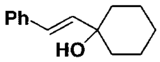
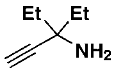
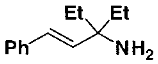
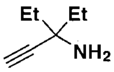
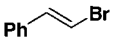
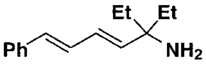
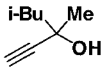
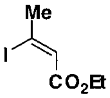
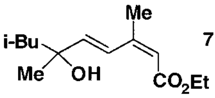
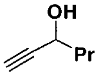
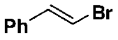
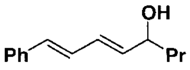
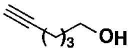
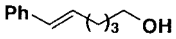
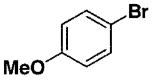
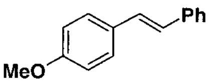
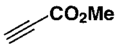
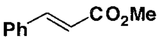
1		PhBr		94%
2				90%
3				91%
4				86%
5		PhBr		57%
6		PhBr		90%
7				81%[b]
8				71%[b]
9				55%
10		PhBr	 E/Z/internal = 14:1.6:1	57%
11				86%
12		PhBr		80%

[a] yields refer to average isolated yield of three trials.
[b] cross-coupling complete after 5 min.

tion[10] often accompanied cross-coupling. The reactions also produced a black participate, suggesting thermal decomposition of the palladium catalyst.[11]

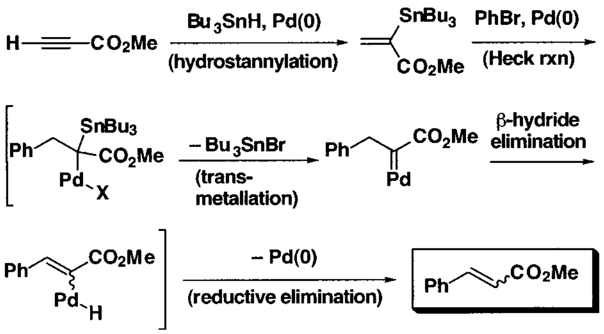
To circumvent these problems, we ran the hydrostannylation with 1 mol % $Pd(PPh_3)_4$ in the absence of the electrophile. After 3 min of microwave irradiation at 140 W, the reaction vessel was either air cooled[8] or cooled by placement in tepid water, after which another 1 mol % of $Pd(PPh_3)_4$ was added along with the electrophile. After reheating in the microwave for an additional 5 min the reaction progress was checked. If not complete, a third portion of catalyst was added and the reaction irradiated for an additional 5 min.[12]

Via this modified procedure, a variety of alkynes[13] underwent microwave-accelerated hydrostannylation/Stille couplings with aryl, benzyl, and vinyl electrophiles.[14] The expected dienes or styrenes were provided in good yields after totals of 8−13 min of microwave irradiation (Table 1). In comparison, Stille coupling of 2-methyl-3-butyn-2-ol with bromobenzene took 16 h in THF at reflux and afforded the diene in 60% yield.

Most of the alkynes employed in Table 1 (entries 1−8) were trisubstituted at the propargylic position. Such highly substituted alkynes are strongly biased toward formation of the *E*-distal stannane upon palladium-mediated addition of tributyltin hydride,[4,7,15] and thus subsequent cross-couplings were not complicated by a nonregioselective hydrostannylation. In contrast, palladium-catalyzed hydrostannylations of unhindered alkynes typically afford mixtures of both distal and proximal vinylstannanes. As such, it is not surprising that less substituted alkynes (entries 9 and 10) gave cross-coupled products in somewhat lower yields or as isomeric mixtures. What did surprise us was the observation of the *Z*-isomer in entry 10. $Pd(PPh_3)_4$-catalyzed hydrostannylation of 5-hexyn-1-ol unassisted by microwave irradiation affords a 2.7:1 ratio of *E*- to internal stannane without any observable formation of the *Z*-isomer. As postproduction isomerization seemed unlikely (vide infra), this result suggests that under the high microwave temperatures free radical hydrostannylation may be competing with the Pd-catalyzed reaction.

Phenyl acetylene and methyl propiolate (entries 11 and 12) gave cross-coupled products corresponding to those expected from the *distal* vinyltins. Yet, product analysis after the hydrostannylation portion of the sequence indicated a 2.5/1 to 10/1 (entries 11 and 12, respectively) preference for the *proximal* vs distal vinyltins. These substrates may, in part, be reacting via a mechanism similar to that proposed by Busacca[16] for the cross-coupling of methyl α-tributylstannylacrylate (Scheme 1).

Scheme 1



As entry 10 of Table 1 suggests the possible occurrence of free radical processes, we next sought to purposely carry out the hydrostannylation portion of the sequence under free radical conditions. As indicated by Table 2, substituting

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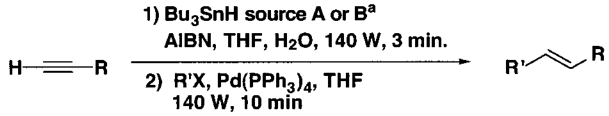
(12) In an attempt to eliminate the need to add the Pd(0) in portions, we investigated the use of the thermally more robust $Pd[P(OAr)_3]_2$ (ref 11). However, no clear preparative advantage over $Pd(PPh_3)_4$ was realized with this catalyst.

Table 2



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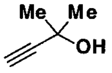
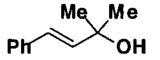
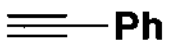
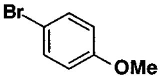
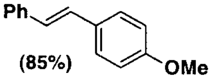
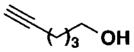
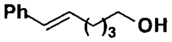
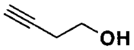
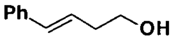
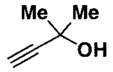
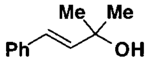
1		PhBr	A	 (86%) E/Z/internal = 20/1/1
2			A	 (85%)
3		PhBr	B	 (48%) E/Z/internal = 31/7/1
4		PhBr	B	 (46%) E/Z/internal = 27/4/1
5		PhBr	B	 (79%, E/Z = 23/1)

[a] Bu_3SnH source: method A: Bu_3SnCl, KF, PMHS, TBAF (cat.). method B: Bu_3SnH.

AIBN for $Pd(PPh_3)_4$ during the first stage of the reaction gave similar results with 2-methyl-3-butyn-2-ol and phenyl acetylene (entries 1 and 2).[17]

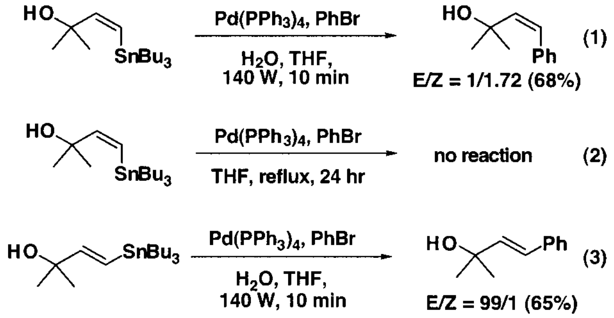
We also wished to establish that the protocol did not require the Bu_3SnH to be derived from our Bu_3SnCl/aqueous KF/PMHS combination. Thus, several reactions were run using commercial Bu_3SnH (Table 2, entries 3−5). In these cases, it proved critical that water be included in the reaction mixture, as in an anhydrous environment the reaction did not proceed. Apparently, the water serves as a microwave heat sink.

In principle, formation of the vinylstannanes under free radical conditions also allows for an added element of regiocontrol. In contrast to palladium-mediated hydrostannylations, free radical hydrostannylations strongly favor distal vinyltin formation even when the alkynes are unhindered.[18] As indicated by Table 2, unsubstituted alkynes (entries 3 and 4) gave the cross-coupled products in relatively good yields with only minor contamination by other geometric or regioisomers.

In fact, *E*/*Z* product ratios were greater than those obtained during the hydrostannylation step alone. AIBN-initiated[19] hydrostannylation of 2-methyl-3-butyn-2-ol reaches a 20:8:1 (*E*/*Z*/internal) ratio of vinylstannanes after 3 min of microwave irradiation, whereas the cross-coupled product displayed an *E*/*Z*/internal ratio of 20:1:1 (Table 2, entry 1).[20]

To investigate this in more detail, isomerically pure vinylstannanes were irradiated for 10 min in the presence of bromobenzene and Pd(0). As illustrated in Scheme 2, microwave-assisted cross-coupling of pure *Z*-vinyltin and bromobenzene afforded a 1:1.7 mixture of *E*- and *Z*-cross-coupled product in 68% yield (eq 1), whereas attempted Stille coupling of these partners gave no reaction after 24 h in refluxing THF (eq 2).

Scheme 2



A possible explanation of these results would be that in the high temperatures of the microwave, reaction byproducts (Bu_3SnBr, $Bu_3SnSnBu_3$, etc.) or other components were facilitating geometric isomerization of the vinylstannane by a free radical (or other) processes. Thus, preferential cross-coupling of the *E*-vinyltin would lead to a kinetic resolution and stereoselective formation of the *E*-product. Alternatively, the product itself could be undergoing an isomerization leading to the observed *E*/*Z* ratio.

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(13) Subjecting internal alkynes to the reaction conditions resulted in the formation of complex mixtures.

(14) Cinnamyl chloride and *p*-chloroaniline were also examined as potential coupling partners. However, under our standard conditions no Stille reactions were observed with these electrophiles. The performance of catalysts specifically designed to couple chlorides (see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411−2413) will be discussed in a full account of this work.

(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.

(16) Busacca, C. A.; Swestock, J.; Johnson, R. E.; Bailey, T. R.; Musza, L.; Rodger, C. A. *J. Org. Chem.* **1994**, *59*, 7553−7556.

(17) For entry 2, the reaction was contaminated by a minor amount of *trans*-stilbene.

(18) (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.

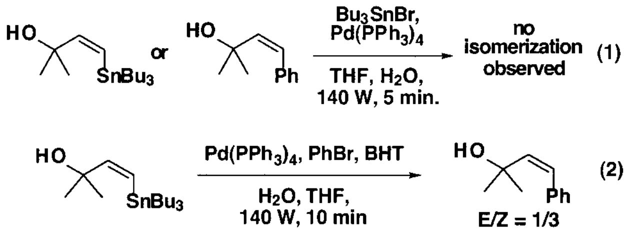
(19) Reactions without AIBN proceeded but were less stereoselective.

(20) For reports of geometric isomerization during the course of Stille cross-couplings, see ref 1c and articles cited therein.

(21) **Representative procedure:** To a thick walled Pyrex tube containing 5 mL of THF were added $Pd(PPh_3)_4$ (12 mg, 0.01 mmol), 2-methyl-3-butyn-2-ol (0.10 mL, 1 mmol), Bu_3SnCl (0.33 mL, 1.2 mmol), PMHS (90 mg, 1.5 mmol), KF (174 mg, 3.0 mmol), 1 mL of H_2O, and catalytic TBAF (1 drop of a 1 M THF solution). The reaction was closed,[8] placed in a 250-mL beaker set in the center of a domestic microwave oven[9] (glass turntable removed), and heated for 3 min at 140 W (20% power setting on a 700 W microwave oven). After the mixture was allowed to air cool for 10 min, $Pd(PPh_3)_4$ (12 mg, 0.01 mmol)[22] and bromobenzene (0.16 mL, 1.5 mmol) were added, and the sealed tube was irradiated at 140 W for 5 min. Upon cooling, the reaction was checked by TLC before a third portion of $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) was added, and the sealed tube was again irradiated at 140 W for another 5 min. After cooling, TLC showed the reaction to be complete. A saturated aqueous solution of KF (2 mL) was added, and the mixture was stirred for 30 min. The phases were separated, and the organics were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by flash chromatography (silica gel; 90/10 pentane/EtOAc with 1% TEA) to afford 153 mg (94%) of *E*-2-methyl-4-phenyl-but-3-en-2-ol.[23]

To explore these possibilities, *Z*-enriched vinyltins and cross-coupled products were both subjected to microwave irradiation in the presence of the experimental reagents and/or Bu_3SnBr (Scheme 3, eq 1). Under such conditions no isomerization was observed. However, addition of radical scavenger butylhydroxytoluene (BHT) to the Stille reaction of bromobenzene and *Z*-(1-tributylstannyl)-3-methyl-but-1-en-3-ol did lessen the extent to which isomerization was observed in the product (*E/Z* = 1:3) (Scheme 3, eq 2). This indicates that some adventitious free radical source may be contributing to the observed isomerizations. However, these results also suggest that the reaction conditions brought about by microwave irradiation may be leading to a nonradical isomerization process occurring during the course of the Stille coupling. Additional mechanistic investigations are currently underway.

Scheme 3



In conclusion, we have developed an efficient microwave-assisted one-pot hydrostannylation/Stille coupling protocol. The hydrostannylation portion of the sequence can be carried out under Pd-catalyzed or free radical conditions. Under the latter conditions, the bias for trans products is greater than the inherent selectivity of the hydrostannylation. Irrespective of the hydrostannylation method employed, this protocol allows commercially available 1-alkynes to be transformed into purified 1,3-dienes or styrenes with a *bottle-to-bottle* time of approximately 2.5 h.[21]

Cautionary Notes: Extreme caution should be taken when heating a sealed tube in a microwave. Do not fill the reaction vessel beyond half volume and avoid highly concentrated reactions.[24] High pressures and temperatures are generated which have led to **explosions**. In the event of such explosions, glass shards from the reaction vessel can penetrate the walls of the oven. Thus, all reactions must be run in a fume hood with appropriate blast shielding in place. Pressure tubes were purchased from Ace glass and fitted with Teflon plugs and Teflon encapsulated O-rings. These O-rings were discarded after approximately 250 min of microwave irradiation. (Using non-Teflon coated O-rings often resulted in catastrophic failure of the seal.) When cleaning the pressure tube, we recommend soaking and *not* scrubbing the tube, as scratches from metal brushes can weaken the vessel and facilitate its rupture.

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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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(22) Different commercial batches of $Pd(PPh_3)_4$ varied in activity; occasionally necessitating a doubling of the catalyst load.

(23) For spectroscopic data, see: Marko, I. E.; Leung, C. W. *J. Am. Chem. Soc.* **1994**, *116*, 371−372.

(24) Reactions run with 5 mmol alkyne in 5 mL of THF were prone to explode.