Published in final edited form as:

Chem Commun (Camb). 2010 June 28; 46(24): 4297–4299. doi:10.1039/c0cc00679c.

Regioselective Formation of 1,1-Disubstituted Allenylsilanes via Cross-Coupling Reactions of 3-Tri-*n*-butylstannyl-1-trimethylsilyl-1-propyne

David R. Williams* and Akshay A. Shah

Abstract

The regioselective Stille cross-coupling reactions of 3-tri-*n*-butylstannyl-1-trimethylsilyl-1-propyne demonstrate isomerization following the initial transmetalation step resulting in allenyl palladium intermediates for reductive coupling to yield conjugated 1,1-disubstituted allenylsilanes.

Recent studies in our laboratories have examined the development of bifunctionalized reagents which provide for sequential execution of S_E' reactions and cross-coupling processes. Conceptually, the linkage of stereocontrolled allylations for asymmetric induction in tandem with the versatility of cross-coupling reactions provides a powerful strategy for the rapid assembly of molecular complexity. In this fashion, we have described the use of *bis*-tri-*n*-butylstannyl reagents for an initial asymmetric S_E' reaction resulting in the production of an alkenylstannane for subsequent Stille reactions.¹ We have also recently explored the S_E' chemistry of 3,3-bis(trimethyl)-2-methyl-1-propene and related alkenes for the stereocontrolled formation of the 3,4-*anti*-(*E*)-1-trimethylsilyl-3-methyl-4-penten-4-ol motif as a convenient precursor to the corresponding (*E*)-alkenyl iodides to advance cross-coupling processes.²

In this communication, recent studies of Stille cross-coupling reactions of alkenyl iodides **1** with bifunctional-3-tri-*n*-butylstannyl-1-trimethylsilyl-1-propyne (**2**) are described. In this process, two outcomes may be realized since allylic bond formation with respect to the propargylic stannane **2** could deliver the TMS-allene **3** via sp^2 – sp^2 coupling whereas a direct replacement of tin in the usual fashion features the sp^2 – sp^3 cross-coupling leading to the nonconjugated enyne **4**. Our plans sought the production of the trimethylsilyl allene **3** to be employed in subsequent Sakurai S_E' reactions as a strategy toward the selective preparation of (*E*)- and (*Z*)-conjugated enynes. Rationale for the formation of **3** is based on literature precedents which have recognized the interconversions of η^1 -propargyl and η^1 -allenylpalladium complexes as well as η^3 -propargylpalladium(II) species.^{3,4} However, these studies have generally utilized propargyl chlorides and bromides for initial insertion reactions with palladium catalysts followed by transmetalations of organostannanes leading primarily to nonconjugated enyne products **4**. The specific example of the Stille cross-coupling of 3-trimethylsilylpropargyl bromide with an alkenylstannane demonstrates regioselective production of the skipped enyne.⁵

In fact, Ma and Zhang⁶ have reported analogous Negishi couplings of allenic/propargylic zinc species with aryl and alkenyl iodides resulting in major adducts corresponding to enynes **4**, and related studies by Jamison⁷ have described similar results for cross-coupling reactions of alkenyl iodides with propargyl copper intermediates. In these studies,

transmetalations of propargyllithium reagents are assumed to provide access to an equilibration of allenic and propargylic copper and zinc species, respectively. On the other hand, site-selective Stille reactions of tri-*n*-butylallenylstannanes have afforded an effective route to substituted allenes.⁸ Alternatively, Nakamura and coworkers have recently reported palladium-catalyzed hydrogen-transfer reactions of *N,N*-dialkyl propargyl amines for the synthesis of allenes.⁹

Our initial cross-coupling experiments of iodobenzene (**1a**) with 3-tri-*n*-butylstannyl-1-trimethylsilyl-1-propyne (**2**) cleanly produced the allenylsilane **3a** in 76% isolated yield.¹⁰ The observation of an allylic transposition which affords selective coupling to give **3a** is unprecedented based on the results of the prior art. Further efforts have examined the generality of this reaction, and our results are compiled in Table 1.

A convenient preparation of the starting stannane **2** utilized 1-trimethylsilyl-1-propyne for deprotonation at -78°C in THF solution with *tert*-butyllithium (1.7 M in Hexanes) followed by addition of tri-*n*-butylstannyl chloride. Nearly quantitative yields of **2** were isolated after flash silica gel chromatography using pentane. Alkyne **2** was stored in the freezer under N₂ without evidence of decomposition or isomerization. Subsequent cross-coupling reactions of **2** have been optimized using Pd₂(dba)₃ in dry DMF containing triphenylarsine and purified cuprous iodide. Examples of alkenyl iodides, aryl iodides and heteroaromatic iodides (entries 1–12) are generally consumed within eight to fifteen hours under the reaction conditions. Attempts using the corresponding alkenyl and aryl bromides proceed to allene products with much slower reaction rates. The reactions of Table 1 (entries 1–12) are standardized using 20 mol % Pd₂(dba)₃ based on starting iodide. Efforts utilizing 10 mol % catalyst and 5 mol % catalyst led to incomplete (50–70%) consumption of **1** after 24 h, and subsequent sequential additions of catalyst in small quantities provided only modest improvement. We examined several ligands and found that AsPh₃ provided the most effective reaction rates. Some success was achieved with the addition of tri-2-furylphosphine, whereas triphenylphosphine led to very slow rates of consumption of **1**, and *Fu* conditions¹¹ using P(^{*t*}Bu)₃ and cesium fluoride afforded similar results. Finally, we have found that the addition of small amounts of CuI produced further enhancement of the rates of our reactions without altering the observed regioselectivity.¹² Aryl iodides (entries 1, 7 and 12) have efficiently produced good yields of allenes **3**. The thiophene and furan examples (entries 8 and 10) also proceeded readily to give **3i** and **3k**, respectively, although the isolated yields are somewhat diminished by the volatility of these products. Slower reactions are observed in the case of entries 5, 6 and 11, and small amounts of unreacted alkenyl iodides (approximately 10%) are recovered after 15 hours. Isomerization to the more stable *E*-unsaturated ester **3g** occurs after the cross-coupling event since the corresponding *E*-iodide of **1g** demonstrates a very slow rate of coupling with **2**. On the other hand, the progress of reactions with **1g** was monitored by ¹H NMR studies using DMF(*d*₆) and clearly indicated the production of the *trans*-ester **3g** prior to isolation by flash chromatography.

Preliminary investigations have been undertaken to gain mechanistic insight into these processes. For example, the Stille coupling of 1-tri-*n*-butylstannyl-2-octyne (**5**) with aryl iodide **1b** gave allene **7** in high yield (95%) (Scheme 2). Under identical reaction conditions, an enriched mixture of stannane isomers **6** and **5** (70:30 ratio) exclusively led to the production of **7** (72%). Thus, the allylic transposition observed for reactions of **5** is not

apparent in the reactions of allenylstannane **6**. In addition, the formation of **7** precludes specific electronic or steric considerations due to the presence of TMS substitution in **2**, and suggests substrate generality for our reaction conditions.

Finally, reaction mixtures lacking alkenyl iodide were constituted in anhydrous DMF(d_6). Under these conditions, ^1H NMR spectroscopy documented the stability of **2** with no evidence of isomerization to the corresponding allenylstannane over 24 hours at 22 °C. These observations suggest intriguing possibilities that initial transmetalation following the oxidative insertion of alkenyl iodide **1** may lead to the propargylic η^1 -palladium species **8** which undergoes isomerization to the η^1 -allenyl complex **9** via an η^3 -Pd intermediate (Scheme 3). Formation of the allene product **3** indicates a dynamic equilibration favoring the more stable palladium(II) complex **9** prior to reductive elimination. Alternatively, the mechanism for transmetalation of **2** may directly produce the η^1 -allenyl complex **9**. In view of prior art leading to skipped enynes, we postulate that the transmetalation of propargylstannanes may be an important factor leading to the production of allenes **3**.

In summary, our studies of Stille reactions, involving 3-tri-*n*-butylstannyl-1-trimethylsilyl-1-propyne with aryl and alkenyl iodides, lead to the regioselective formation of allenylsilanes. This novel cross-coupling event generates useful reactive functionality which may be generally applicable. The examples of Table 1 have shown that preexisting functionality in starting alkenyl iodides is well tolerated, and this variant of the Stille reaction may have potential for applications in complex molecule synthesis.

Acknowledgments

We acknowledge the financial support of Indiana University and partial support by the National Institutes of Health (GM042897).

Notes and references

1. (a) Williams DR, Meyer KG. J Am Chem Soc 2001;123:765. [PubMed: 11456603] (b) Williams DR, Fultz MW. J Am Chem Soc 2005;127:14550. [PubMed: 16231889]
2. Williams DR, Morales-Ramos AI, Williams CM. Org Lett 2006;8:4393. [PubMed: 16986908]
3. (a) Elsevier CJ, Kleijn H, Boersma J, Vermeer P. Organometallics 1986;5:716. (b) Tsutsumi K, Kawase T, Kakiuchi K, Ogoshi S, Okada Y, Kurosawa H. Bull Chem Soc Jpn 1999;72:2687.
4. Tsutsumi K, Ogoshi S, Kakiuchi K, Nishiguchi S, Kurosawa H. Inorg Chim Acta 1999;296:37.
5. Tsubuki M, Takahashi K, Sakata K, Honda T. Heterocycles 2005;65:531.
6. Ma S, Zhang A. J Org Chem 2002;67:2287. [PubMed: 11925243]
7. Heffron TP, Trenkle JD, Jamison TF. Tetrahedron 2003;59:8913.
8. (a) Huang CW, Shanmugasundaram M, Chang HM, Cheng CH. Tetrahedron 2003;59:3635. (b) Mukai C, Takahashi Y. Org Lett 2005;7:5793. [PubMed: 16354068]
9. Nakamura H, Kamakura T, Ishikura M, Biellmann JF. J Am Chem Soc 2004;126:5958. [PubMed: 15137748]
10. For leading references that describe the formation of allene **3a**: (a) Kjellgren J, Sundén H, Szabó KJ. J Am Chem Soc 2005;127:1787. [PubMed: 15701014] (b) Westmuze H, Vermeer P. Synthesis 1979:390.
11. Littke AF, Schwarz L, Fu GC. J Am Chem Soc 2002;124:6343. [PubMed: 12033863]
12. For background on Stille coupling, including Cu(I)-mediated reactions, see: (a) Farina V, Krishnamurthy V, Scott WJ. Org React 1997;50:1. (b) Liebeskind LS, Fengl R. J Org Chem 1990;55:5359. (c) Han X, Stoltz BM, Corey EJ. J Am Chem Soc 1999;121:7600. (d) Bellina F, Carpita A, De Santis M, Rossi R. Tetrahedron 1994;50:12029.

Scheme 1.
Stille reactions of propyne (2).

Scheme 2.
Stille reactions of propargyl and allenylstannanes **5** and **6**.

Scheme 3.
Mechanistic considerations.

Yield^b
61%

Product^a

3c

Yield^b
46%

Product^a

3d

Yield^b
64%

Product^a

3e

Yield^b
50%

Product^a

3g

Yield^b
77%

Product^a

3h

Yield^b
65%

Product^a

3i

Yield^b
62%

Product^a

3j

Yield^b
72%

Product^a

3k

Yield^b
54%

Product^a

31

Yield^b
71%

Product^a

^aReaction Conditions: Starting iodides **1** (1.0 eq) were combined with propargyl stannane **2** (1.3 eq) and AsPh₃ (0.8 eq) followed by addition of Pd₂(dba)₃ (20 mol %) and CuI (0.8 eq). Stirring under N₂ at 22 °C for 8–15 h led to the complete consumption of **1**. For entry **1**, iodide **1b** was reacted at 45 °C, and for entry **11**, iodide **11** was reacted at 70 °C. For entry **2**, we have found that tri-(2-furyl)phosphine (0.8 eq) is effectively used in place of AsPh₃.

^bYields are given for purified products isolated via flash silica gel chromatography.

^cIodide **1d** is somewhat unstable and slowly leads to decomposition at room temperature.