Development of a One-Pot Palladium-Catalyzed Hydrostannylation/ Stille Coupling Protocol with Catalytic Amounts of Tin

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The Stille cross-coupling of vinyl halides with vinylstannanes is a mild method for the stereoselective synthesis of 1,3-dienes, a structural unit that is often found in natural products. Despite its wide use, this reaction bears some problems. The vinyl halide and the vinyltin compound have to be prepared stereoselectively in separate steps, prior to their employment in the coupling reaction. Furthermore, some vinyltins undergo protiodestannylation during chromatographic purification, and stoichiometric amounts of toxic organotin halides are produced as a byproduct. Therefore, we view the development of a one-pot protocol for the stereoselective generation of vinyltins and their subsequent cross-coupling, employing only catalytic amounts of tin, as highly desirable.

Toward this end, Boden et al. have shown that upon the complete palladium-mediated hydrostannylation of 1-bromoalkynes the addition of a further quantity of Pd catalyst and a vinyl bromide could furnish the desired Stille product. This procedure represents a means of obviating the isolation of the vinylstannane intermediate. However, the stepwise nature of the sequence was prohibitive toward our own goal of developing a protocol catalytic in tin in which all reaction components are present at the beginning of the reaction sequence.

While the Pd-catalyzed hydrostannylation is a well-established synthetic tool, the feasibility of carrying out Pd-catalyzed hydrostannylation in the presence of a Stille electrophile was by no means assured. We would need to strike a balance between the catalyst requirements for high-yielding hydrostannylation (strong donor ligands such as PPh3) and efficient cross-couplings (weaker donor ligands). Equally important was the need to minimize side reactions, especially the Pd-mediated Bu3SnH reduction of vinyl halides. Furthermore, understanding the regiochemical consequence of Pd-catalyzed hydrostannylation remains an active area of investigation. As the focus of our study was the combination of the hydrostannylation and cross-coupling reactions, we wished to minimize any complications that could arise from the hydrostannylation step being nonregioselective. Therefore, we chose a-trisubstituted alkenes, which are highly biased toward (E)-vinylstannanes upon Pd-catalyzed hydrostannylation as our substrates.

Our initial experiments focused on the one-pot hydrostannylation/Stille coupling utilizing Bu3SnH and (Ph3P)2PdCl2 as the catalyst. We were pleased to find that the reaction of Bu3SnH with a variety of alkynes in the presence of 1.1 equiv of bromostyrene and 0.3 mol % (Ph3P)2PdCl2 resulted in formation of the anticipated 1,3-dienes (Scheme 1) in yields that were comparable or superior to that of the stepwise variant. With the feasibility of the one-pot Pd-catalyzed hydrostannylation/Stille cross-coupling secured, we then focused on the employment of alternative sources for the relatively expensive and unstable tin hydride. Hayashi et al. have shown that tin hydride can be generated from (Bu3Sn)2O and polymethylhydroxiloxane (PMHS). These two starting materials represent a stable and cheap storage form of tributyltin hydride and have been shown to work well in free-radical hydrostannylation of 1-alkynes. Furthermore, PMHS has been used extensively by Fu and co-workers as the stoichiometric reducing agent in reactions catalytic in tin. However, to the best of our knowledge, the (Bu3Sn)2O/PMHS combination had never been reported for the in situ

Scheme 1

<table>
<thead>
<tr>
<th>alkene</th>
<th>product</th>
<th>Bu3SnH yields‡ PMHS/ (Bu3Sn)2O step-wise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bu3SnH</td>
<td>Bu3SnH</td>
<td>89% 52% 43%</td>
</tr>
<tr>
<td>HBu</td>
<td>HBu</td>
<td>75% 69% 56%</td>
</tr>
<tr>
<td>MeOH</td>
<td>MeOH</td>
<td>87% 66% 65%</td>
</tr>
<tr>
<td>MeOH</td>
<td>MeOH</td>
<td>86% 60% 70%</td>
</tr>
<tr>
<td>EtOH</td>
<td>EtOH</td>
<td>78% 58% 50%</td>
</tr>
<tr>
<td>EtOH</td>
<td>EtOH</td>
<td>40% 40% 47%</td>
</tr>
</tbody>
</table>

‡ Unless otherwise stated all yields refer to isolated products.

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formation and reaction of Bu3SnH in Pd-mediated processes. Our experiments (Scheme 1) showed that treatment of 1-alkynes with a mixture of (Bu3Sn)2O11 and PMHS in the presence of bromostyrene and Pd resulted in hydrostannylation of the alkyne and subsequent Stille coupling, providing the dienes in yields that were comparable to the direct employment of Bu3SnH.12

Able to perform a one-pot hydrostannylation/Stille reaction, either with Bu3SnH or in situ generated tin hydride, and having established the compatibility of PMHS with the other components in the reaction mixture, we next focused on the in situ conversion of the tributyltin halide Stille byproduct into a tin oxide. We believed that by efficiently effecting such a transformation our protocol could be made catalytic in tin as PMHS reduction of the newly formed Sn–O bond would regenerate Bu3SnH and thus establish the catalytic cycle (Scheme 2).13

To accomplish this task, we clearly need an oxygen nucleophile that would be unreactive toward PMHS. During this study, we found that tin chloride in the presence of aqueous Na2CO3 and PMHS forms tin hydride, with little decomposition of the silane.14 With this information in hand, we returned to our hydrostannylation/Stille sequence where we clearly demonstrated the ability to recycle the tin with an average turnover of 2.5 (Scheme 3).15 When we employed aqueous Na2CO3, PMHS, and only 4 mol % of tin chloride, five turnovers of tin were achieved, providing the 1,3-diene in 22% yield.16 Furthermore, when the tin load was increased to 20%, product yields approached that of the overall stepwise protocol despite an 80% reduction in tin. We view these results as somewhat remarkable in that the tin species has to undergo four separate reaction steps in one turnover.

Our study demonstrates the feasibility of a one-pot tandem Pd-catalyzed hydrostannylation/Stille coupling with either Bu3SnH or (Bu3Sn)2O and PMHS serving as the tin hydride source. Furthermore, we have shown that with the addition of Na2CO3 it is possible to carry out this fairly complex sequence of reactions with catalytic amounts of tin. Further studies to improve the turnover numbers and overall yields are ongoing in order to apply this methodology to more complex and less accessible substrates.

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Supporting Information Available: Spectroscopic data for all new compounds pictured as well as selected experimental procedures (19 pages).

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11) The generation of a full 2 equiv of Bu3SnH from one molecule of (Bu3Sn)2O occurs only at elevated temperatures (ref 8). Therefore, under our reaction conditions a 2-fold excess of bistributyltin oxide is required for complete consumption of the alkyne.

12) We observed no evidence of palladium-mediated hydrosilylation with PMHS, although other silanes, such as phenylsilane, did show a propensity for hydrosilylation.

13) The use of catalytic quantities of tin salts and equimolar amounts of NaBH4 has proven an effective means for the in situ conversion of tin halides to tin hydrides in free radical reactions (a) Corey, E. J.; Suggs, J. W. J. Org. Chem. 1975, 40, 2554–2555. (b) Suggs, J. W.; Corey, E. J. J. Org. Chem. 1989, 54, 6105–6114 and references therein). For our purposes though, this method appeared less than ideal as hydride reducing agents are known to reduce Pd(II) intermediates (Tsuij, J.; Palladium Reagents and Catalysts; Wiley: Toronto, 1995; p 148). Furthermore, strong hydride donors would severely curtail the broad functional group tolerance normally associated with the Stille reaction.

14) More basic metal alkoxides (NaOMe, NaOPh, etc.) reacted with PMHS. Not surprisingly, application of such alkoxides to the hydrostannylation/Stille coupling with catalytic amounts of tin was largely unsuccessful.


16) During our study of the catalytic reactions (2-furyl)p)Pd and diethyl ether proved to be the Pd catalyst and solvent of choice.