Stille Reactions Catalytic in Tin: A “Sn–F” Route for Intermolecular and Intramolecular Couplings†

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Polymethylhydrosiloxane (PMHS) made hypercoordinate by KF(aq) allows Me3SnH to be recycled during a Pd(0)-catalyzed hydrostannation/Stille cascade. Starting with a variety of alkynes, in situ vinyltin formation is followed by Stille reaction with aryl, styryl, benzyl, or vinyl electrophiles present in the reaction mixture. Both inter- and intramolecular versions of the process are possible with tin loads of approximately 6 mol %. Regeneration of the organotin hydride is believed to proceed through a Me3SnF intermediate. Given the aggregated nature of organotin fluorides and the ability to use these organotins in substoichiometric quantities, the hazards and purification problems associated with the removal of organotin wastes from reaction mixtures are minimized.

Introduction

The palladium-catalyzed cross-coupling of organostannanes with a variety of organic electrophiles is commonly referred to as the Stille reaction.1 Due to its versatility and functional group compatibility, the Stille reaction has long been a popular method for the construction of sp2–sp2 carbon–carbon bonds via σ bond formation.2 That said, Stille reactions typically demand the management of stoichiometric amounts of tin before, during, and after the cross-couplings. This is unattractive because of troubles associated with the cost and toxicity of organotins as well as the general difficulty of their removal from reaction mixtures.3 Such problems have, in part, driven the development of cross-coupling reactions that replace the tin with other metals, boron, silicon, zinc, and indium among them.4 Despite the clear value of these other cross-coupling methods, recognition of the aforementioned positive features of the tin-mediated process has prompted the invention of more appealing organostannane derivatives for use in Stille reactions5 and better methods for the removal of tin-containing byproducts.6 We too have

† Dedicated to Professor Amos B. Smith, III, in honor of his 60th birthday and 40 years in organic chemistry.

focused on this more direct approach to the “tin problem” by developing a Stille reaction that is catalytic in tin.7,8

Results and Discussion

Our early efforts toward such a process focused on connecting a one-pot Pd-mediated alkyne hydrostannylation and cross-coupling sequence by recycling the organotin halide Stille byproduct back to tin hydride via polyethylene glycol (PMHS) reduction of a putative tin carbonate intermediate (Scheme 1).8 While this first-generation protocol proved to be reasonably successful, improvements were sought by others and us. Kilburn and co-workers nicely addressed the continuing issue of tin residue removal, thus rendering those reactions catalytic in tin.13

In initiating this study, we immediately focused on prior work from our labs that showed how a combination of Bu3SnCl, aqueous KF, and PMHS produced Bu3SnH in high yield13 and how organotin hydrides prepared in this way could efficiently hydrostannylate alkynes in situ when formed in the presence of a palladium catalyst.14 We also knew that aqueous KF and PMHS could regenerate Bu3SnH from Bu3SnX produced during dehalogenations, thus rendering those reactions catalytic in tin.13 Finally, as all evidence pointed to Bu3SnH as the primary intermediary for these reactions, we hypothesized that the appropriate combination of R3SnX, PMHS, and fluoride would enable a one-pot hydrostannation/Stille cascade requiring only catalytic amounts of tin (Scheme 2).

In practice, mixing a THF solution of 2-methyl-3-butyn-2-ol (1) and iodobenzene with PMHS, aqueous KF, and catalytic amounts of Pd2dba3, tri-2-furylphosphine, and 6 mol % Me3SnCl afforded diene 2 in 21% yield (Scheme 2).13 The results of this experiment indicated that the tin was being recycled, albeit in unacceptably low turnover numbers. While disappointing, the relatively poor performance of this reaction was not surprising in light of earlier observations. During our “Sn−O” studies,8 the use of Me3SnCl instead of Bu4SnCl proved to be essential for the success of the reaction sequence. Thus, rather than exploring higher tin loads or modifying other reaction conditions, we moved immediately to experiments with Me3SnCl.

This proved to be rather successful,15 as reacting alkylene 3 in the presence of KF, catalytic TBAF, catalytic Pd(0), bromostyrene, and 6 mol % Me3SnCl afforded diene 4 in 90% yield, representing a minimum of 15 tin turnovers (Scheme 3). Examination of other reaction parameters also revealed aqueous KF as the best fluoride
source. Replacing KF with CsF or a CsF:CsOH fused salt afforded high yields of Sonogashira-like enynes instead of the desired Stille products. TBAF also could not be used as the sole fluoride source since reaction of stoichiometric TBAF with R₃SnH affords intrusive amounts of R₃SnSnR₃ in what is a terminating event for the catalytic cycle. Despite previous successes with microwave-accelerated one-pot hydrostannation/Stille reactions using stoichiometric amounts of R₃SnH, reactions with catalytic quantities of tin carried out in a conventional microwave oven afforded low yields of the expected dienes. Finally, while higher loads of Me₃SnCl led to little improvement, loadings below 6 mol % resulted in fairly significant reductions in yield (Scheme 3). Thus, 6 mol % would become the standard amount of organotin employed in subsequent explorations of the reaction sequence.

In an effort to gain an appreciation of the reaction’s scope, a variety of alkynes and electrophiles were subjected to the hydrostannation/Stille sequence (Table 1). Vinyl and aryl iodides and bromides acted as good electrophiles, as did benzyl bromide (entry 6). In contrast, methyl iodide, allyl bromide, and an aryl nonaflate did not couple under these conditions (entries 5, 7, and 8). Importantly, despite the presence of fluoride, the electrophilic partners could possess TBS ethers (entries 2 and 3). As with our “Sn-O” protocol, α-trisubstituted alkynes (entries 1–11) and α-disubstituted alkynes (entries 12 and 13) coupled well, but reactions with monosubstituted alkynes proceeded poorly (entry 14). To efficiently couple these substrates they were transformed into their bro-moalkyne derivatives. These 1-bromoalkynes proved to be successful, giving us the coupled products in modest 61 and 52% yields, respectively (entries 15 and 16).

Of course the Stille reactions detailed in Table 1 are all intermolecular in nature. Over the past decade the intramolecular Stille reaction has emerged as a mild and useful way to form variously sized rings. Thus, we wondered if our protocol could be made amenable to a one-pot Pd-mediated hydrostannation/intramolecular Stille coupling. To answer this question we first needed to obtain a suitable starting compound. Alkyne-aryl iodide 26 was targeted for this purpose; its synthesis being shown in Scheme 4.

(16) Use of CsF in combination with PMHS has been explored to produce enynes; see: (a) Gallagher, W. P.; Maleczka, R. E. Synlett 2003, 537–541. (b) Gallagher, W. P.; Maleczka, R. E. J. Org. Chem. 2003, 68, 6775–6779 and references cited therein.
Interestingly, and in contrast to the intermolecular counterparts, we also thought it sensible to sort out efficient cross-coupling conditions with any vinyltin-aryl iodides prepared from 26.

In practice, Pd-mediated hydrostannation with PMHS/KF/R3SnCl generated tin hydride afforded vinylstannanes 27 and 28 in excellent yield (Scheme 5) and without hydrodehalogenation of the aryl iodide. Next, a survey of catalyst/ligand combinations and conditions was conducted. On the basis of this assessment, Pd2dba3/TFP in THF was chosen as the catalyst/ligand/solvent mix for attempts at the tin-catalyzed one-pot hydrostannation/intramolecular Stille sequence (Scheme 5).

Thus, first experiments were carried out under these Pd-catalyst conditions in union with the general “Sn–F” conditions noted in Table 1. When all reagents were added at once to a 70 °C 0.005 M THF solution (Scheme 5) and the ensuing reaction was allowed to proceed for 14 h, a 23% yield of macrocycle 29 was obtained along with traces of the dehalogenated starting material (GC-MS). Adding 26 via a syringe pump over 8 h slightly improved the process, as 29 was produced in 29% yield and no dehalogenated starting material was detected. Interestingly, and in contrast to the intermolecular results, a modified version of our original “Sn–O” approach (see Scheme 1) to Stille reactions catalyzed in tin were superior in the intramolecular version as applied to 26. A 0.005 M THF solution of 5 mol % Me3SnF, Pd-catalyst, ligand, PMHS, and Na2CO3 with all of 26 added at the beginning of the reaction afforded a 41% yield of 29 after 12 h at 70 °C. Again, the slow addition of 26 netted a small gain in yield (47%). It should also be noted that the Na2CO3-based conditions did not produce any detectable amounts of dehalogenated material. Furthermore, in the absence of tin, only starting material was recovered, thus ruling out the occurrence of Heck-type reaction pathways to 29.

To conclude our evaluation of scope and synthetic utility, we sought to apply our “Sn–F” method to the synthesis of a literature target molecule, namely, diene 30. Several years ago, Jauch reported the synthesis of the reverse transcriptase inhibitor kuehneromycin A. Although Grigg had previously demonstrated the hydrostannation of an alkyne in the presence of an aryl iodide, it was deemed prudent to learn if 26 could be converted into its vinyltin without reduction of the iodide moiety. Furthermore, as intramolecular Stille reactions tend to be more substrate dependent than their intermolecular counterparts, we also thought it sensible to sort out efficient cross-coupling conditions with any vinyltin-aryl iodides prepared from 26.

Alkyne 7 was also synthesized before, but in our hands the prior preparation proved too time consuming. Thus, we chose to investigate a diaminalkylation route to this molecule. After some experimentation (Table 2), we found that treating isopropylacetylene with 2 equiv of BuLi and 1 equiv of TMEDA in Et2O at 50 °C resulted in the formation of a red diamin solution. This solution was then treated with oxetane, followed by slow addition of BF3·Et2O at −78 °C. The oxetane was thus ring opened, and alkyne 7 was formed in a synthetically usable 35% yield.

**Scheme 5**

![Scheme 5](image)

**Scheme 6. Intersecting Jauch’s Retrosynthesis of Kuehneromycin A**

![Scheme 6](image)

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(24) Both 27 and 28 were also prepared via a separate route to confirm their structure: (1) hydrostannation of 25 followed by (2) DCC coupling with 2-iodobenzoic acid. See Supporting Information for full details.

(25) Similar results were observed when, per our original protocol, Me3SnCl was used as the starting material.


The remaining SnF-catalyzed protocol afforded diene 30 proposed tin intermediates. Indeed, using Me3SnCl, Me3-1, we could start the reaction with 6 mol % of any of the (Scheme 2). For the reaction described in entry 1 of Table of providing support for our putative catalytic cycle toward silyl ethers.

In addition to providing a very modest example of the method’s performance in target synthesis, the preparation of multiple aggregates of Me₃SnF, [Me₃SnF(Cl)]K or related “ate” intermediates cannot be completely ruled out.

ICP Analysis. Finally, we scrutinized the end of the reaction to determine the final fate of the tin. During the course of the reaction, a solid material was always present. Filtration and analysis suggested this material to be Me₃SnF, but somewhat surprisingly this recovered solid accounted for only ~20% of the possible tin. ICP analysis of the organic and aqueous phases separated from the reaction mixture indicated that ~75% of the tin used in the reaction could be accounted for in the aqueous phase. The crude organics contained ~0.5% of the reaction’s tin or 4.8 ppb. Significantly, after column chromatography, ICP analysis of the purified product measured no detectable amounts of tin.

Summary
In conclusion, we have developed a complementary method for performing one-pot hydrostannation/Stille reactions with catalytic amounts of tin. In addition to lowering the typical tin requirements of these reactions by ~94%, the use of the organotin fluorides allows for removal of most tin byproducts through a straightforward combination of filtration and extraction. Moreover, after column chromatography, the cross-coupled products can be completely isolated from any measurable amounts of tin.

Experimental Section
General Procedure for the Me₃SnCl-Catalyzed One-Pot Hydrostannation/Stille Coupling. Tri-2-furylphosphine (9.3 mg, 0.04 mmol) was added to a solution of Pd₂dba₃ (9.2 mg, 0.01 mmol) in Et₂O (5 mL). After the solution was stirred at room temperature for 15 min, electrophile (1.5 mmol), Me₃SnCl (0.06 mL, 0.06 mmol; 1 M solution in THF), aq KF (0.1743 g, 3 mmol, 1 mL H₂O), TBAF (1 drop of a 1 M solution in THF (ca. 8 mL or 0.8 mol %)), and PdCl₂(PPh₃)₂ (7.0 mg, 0.01 mmol) were all added to the solution. The solution was heated to reflux, and then a solution of alkene (1 mmol) and PMHS (0.09 mL, 1.5 mmol) in Et₂O (4 mL) was added via a syringe pump over 11 h. The phases were separated and the organics washed with brine, dried over MgSO₄, filtered, and concentrated. The resulting residue was purified by column chromatography. Full experimental details are given in Supporting Information.

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TABLE 2. Modified Synthesis of Alkyne 7

<table>
<thead>
<tr>
<th>entry</th>
<th>method of addition</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>addition of oxetane to dianion followed by BF₃·OEt₂ dropwise at -78 °C</td>
<td>35%</td>
</tr>
<tr>
<td>4</td>
<td>addition of dianion to a solution of oxetane/BF₃·OEt₂ at -45 °C</td>
<td>22%</td>
</tr>
<tr>
<td>3</td>
<td>addition of dianion to a solution of oxetane/BF₃·OEt₂ at -78 °C</td>
<td>27%</td>
</tr>
<tr>
<td>2</td>
<td>addition of oxetane to dianion followed by BF₃·OEt₂ in one portion at -78 °C</td>
<td>20%</td>
</tr>
</tbody>
</table>

TABLE 3. Evaluating Different Initial Sources of Tin

<table>
<thead>
<tr>
<th>entry</th>
<th>tin source</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me₃SnCl</td>
<td>88%</td>
</tr>
<tr>
<td>2</td>
<td>Me₃SnF</td>
<td>85%</td>
</tr>
<tr>
<td>3</td>
<td>Me₃SnH</td>
<td>86%</td>
</tr>
</tbody>
</table>

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(30) The corresponding vinyl iodide gave intrusive amounts of homocoupling under traditional Stille conditions.
(31) See Supporting Information for preparation of vinylstannane 34.
(32) The remaining ~4.5% of the tin was unaccounted for.
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Supporting Information Available: Experimental procedures for Schemes 2–5 and 7 and Tables 1 and 2, additional experimental details for the preparations of compounds 5, 8, 10, 27, 28, and 34, descriptions of control experiments and ligand surveys, and $^1$H and $^{13}$C NMR spectra for all reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.