A water soluble, recyclable organostannatrane

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Abstract—Synthesis of a water-soluble recyclable organostannatrane has been accomplished via a straightforward three-step synthesis. The organostannatrane exhibits excellent water-solubility (0.33 M) and can be recovered from aqueous solutions via removal of water in vacuo. The compound can be readily converted by standard transformations into reagents suitable for Stille cross-coupling reactions. The reagent can also be transformed into a reactive, water-soluble organotin hydride. © 2001 Elsevier Science Ltd. All rights reserved.

Metal-mediated cross-coupling reactions leading to the formation of C–C bonds have become very important methods in organic synthesis. Metal-mediated cross-coupling reactions which are utilized most often include the Negishi–Knochel coupling (utilizing organozinc reagents), the Suzuki coupling (utilizing organoboron reagents), and the Stille coupling (utilizing organotin reagents).[1] While all three are synthetically useful, undoubtedly the most versatile of these reactions is the Stille coupling. The organostannanes typically employed are easy to handle; most are air- and moisture-insensitive; can be distilled, recrystallized, or chromatographed; and can be used in the presence of other reactive functionalities (amines, aldehydes, carboxylic acids, etc.). A wide range of organostannanes have been successfully used in cross-coupling reactions.

Despite the myriad of positive attributes, the use of problematic tributyl- and trimethylstannanes has caused the Stille reaction to remain underutilized in the pharmaceutical industry. Tributylstannanes are cheap and versatile reagents in the cross-coupling reaction. Tributyltin halide, the byproduct of the Stille reaction, has moderate toxicity (LD_{50} 122–349 mg/kg for Bu_3SnCl),[2] but its main drawback is that it is extremely difficult to completely remove from a reaction mixture. In contrast, trimethylstannanes are readily removed from reaction mixtures via an aqueous wash and are usually more reactive than the complimentary tributyl-stannanes. Unfortunately, the residue has a higher toxicity (LD_{50} 9–20 mg/kg for Me_3SnCl)[2] and the starting materials for making trimethylstannane reactants are quite expensive. Further complicating this picture is that neither the tributyl- nor trimethyltin residues gen-
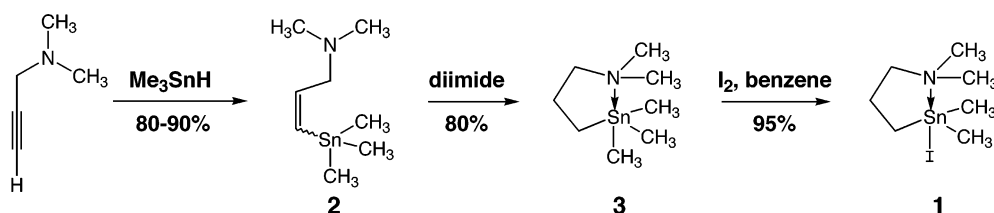
Scheme 1.

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erated during the cross-coupling reaction are typically recycled. This results in hazardous waste disposal issues and its associated costs.

We were interested in research performed by Tzachach on the formation of stannatranes.[3] In these systems, a pendant nitrogen atom forms a dative bond to tin generating trigonal bipyramidal geometry on the metal, which results in an increased bond length of the opposing axial ligand. This lengthened bond leads to enhanced reactivity of the axial group, especially during the Stille cross-coupling reaction's transmetalation step.[4] We wanted to take advantage of this phenomenon and generate a stannatrane that was water soluble, easily recyclable, and synthetically easy to produce. A stannatrane of this kind would permit complete removal of tin residues from Stille reactions via an aqueous wash during work-up as is common when using trimethylstannanes. Maintaining water-solubility while decreasing volatility would permit recovery of the spent haloorganostannatrane by simple removal of water in vacuo. This would drastically reduce hazardous waste disposal costs and allow continual recycling of the stannatrane. Finally, an easily recyclable stannatrane synthesized in a short straightforward manner would be preferred over current recycling methods, which use perfluorinated solvents to remove perfluorinated tin residues[5] or another organostannatrane which is more difficult to make and is recovered after a complex work-up.[6] Thus, we chose to synthesize the small molecule organostannatrane **1** which we anticipated as having all of the desired properties.

Synthesis of **1** (Scheme 1) starts via reaction of *N,N*-dimethylpropargylamine[7] (2.6 M solution in cyclohexane) with trimethyltin hydride[8] (0.95 equiv., 60°C, 6 h). This afforded an 80–90% yield of the vinylstannane **2** as a 2:1 to 1:2 mixture of *Z/E* isomers upon concentration of the reaction mixture in vacuo.[9] Diimide reduction of the olefin mixture is accomplished by careful addition of NaIO$_4$ (5 equiv., 0.6 M aqueous solution) via syringe pump over a 2 h period to a 0°C solution of the *Z/E* vinylstannanes (0.17 M solution in THF) containing hydrazine hydrate (40 equiv.), copper (II) sulfate (saturated aqueous, 0.2 equiv.) and glacial acetic acid (3.5 equiv.).[10] Immediate extraction into CH$_2$Cl$_2$ and removal of solvent in vacuo affords a yellow oil. Distillation under reduced pressure (bp 45–55°C/1.5–2.0 torr) gives **3** as a clear colorless oil in 80% yield.[11] Selective cleavage of the axial methyl group is accomplished by treating **3** (1.2 M in benzene) with I$_2$ (0.95 equiv., 0.57 M in benzene) at 0°C overnight in the
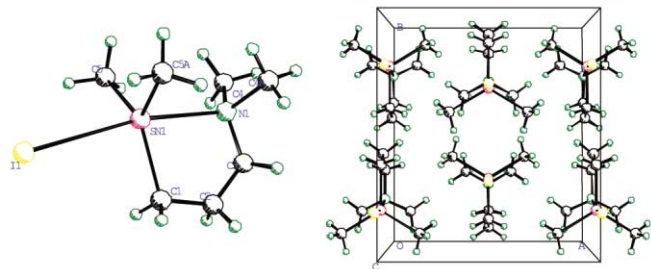
dark.[12] Removal of solvent in vacuo affords **1** as a pale yellow solid in 95% yield (mp 162–165°C).

Compound **1**'s crystal structure and unit cell are shown in Fig. 1.[13] The molecule has a plane of symmetry and an N–Sn–I bond angle of 169.4(3)°. More interesting is that a strong dative bond exists between the N and Sn atoms (Sn–N 2.38(1) Å) resulting in a very long Sn–I bond of 3.0567(6) Å. This bond length is longer than the atomic radii of both Sn and I, thus imparting salt-like characteristics on the molecule.[14] The stannatrane has excellent water-solubility (0.33 M at ambient temp.) and can be readily recovered from water via removal of solvent in vacuo. The material can be heated in boiling water for over 6 h and still be recovered quantitatively and completely unchanged.

While iodide **1** can be converted to reagents for Stille cross-coupling reactions,[15] more importantly it can be transformed into a new reactive, water-soluble tin hydride (Scheme 2). Thus, treatment of **1** with borane in THF followed by a pH 7 phosphate buffer work-up as per the conditions of Breslow[16] readily affords the water-soluble tin hydride **4** as a clear colorless oil.[17]

Hydride **4** has excellent water-solubility (0.22 M at ambient temperature) thus representing a 7-fold increase in water-solubility compared to Breslow's tris[3-(2-methoxyethoxy)propyl]tin hydride (0.03 M). The internal activation of the tin hydride causes it to be highly reactive in dehalogenation processes. Treatment of simple iodobenzoic acids with **4** in water at ambient temperature effects dehalogenation (<1 h) in high yields (84–87%) without addition of an initiator.[15] While the hydride does not require special handling, it should be used as soon as possible after its formation. Dilute solutions of **4** in pentane (0.1 M) can be made and stored at −20°C with minimal decomposition.[18] It may be more feasible to generate **4** in situ although this was never attempted.

Recycling of compound **1** is readily accomplished by extracting into water followed by removal of water in vacuo. This affords a material suitable for use in most reactions. If necessary, the iodide can be recrystallized (benzene) prior to reuse. For reactions performed in water, the iodide can conveniently be extracted into normal organic solvents such as diethyl ether or chloroform.

In conclusion, we have synthesized a water-soluble, recyclable organostannatrane. This compound is readily synthesized in high yield via a straightforward synthetic pathway. Although this pathway involves the use of the relatively expensive trimethyltin hydride, the fact that the reagent is continuously recycled from the reaction mix-

Figure 1.
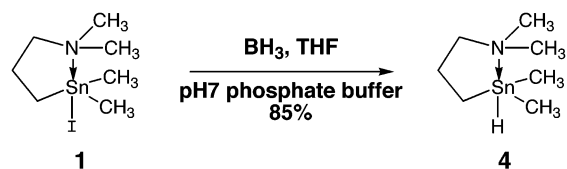
Scheme 2.

tures dramatically reduces both the overall cost of the reagent as well as the hazardous waste disposal of organotin residues. Finally, the iodostannatrane can be readily converted to reagents useful in Stille cross-coupling reactions in addition to an extremely water-soluble tin hydride which, with the addition of a stereocenter, could conceivably be utilized as a chiral hydride source.

References

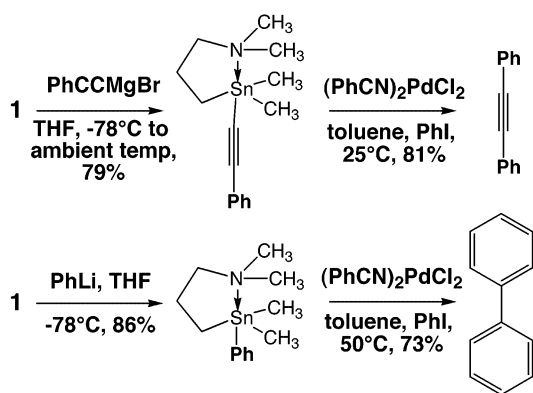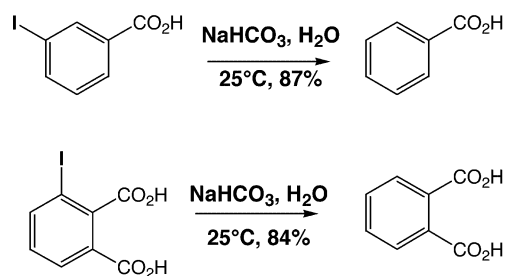1. For recent reviews of all 3 reactions see: (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147; (b) Losterzo, C. *Syn. Lett.* **1999**, *41*, 1704; (c) Stanforth, S. *Tetrahedron* **1998**, *54*, 263; (d) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1; (e) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
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15. Iodide **1** can also be converted to reagents for Stille cross-coupling reactions which then readily undergo the cross-coupling processes. Yields shown are not optimized. The Stille reactions shown were both complete in less than 3 h.

STILLE REACTIONS

REDUCTIONS

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