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# Tris(2-(perfluorohexyl)ethyl)tin Hydride: A New Fluorous Reagent for Use in Traditional Organic Synthesis and Liquid Phase Combinatorial Synthesis

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The simplest methods to purify the products of organic reactions involve phase separations. Four phases are commonly used in standard laboratory separation methods: gas, solid, organic liquid, and aqueous. It has long been known that low-boiling perfluorinated fluids are immiscible in both water and many organic solvents at ambient laboratory temperatures,[1] yet this property has rarely been exploited in organic synthesis. Zhu[2] has recently described transesterification reactions of esters in a fluorinated solvent. In these reactions, both the ester and alcohol products are separated from each other and from the solvent by phase separation techniques. In a further reaching report,[3,4] Horváth and Rábai introduced a catalyst generated from a partially fluorinated phosphine $[(C_6F_{13}CH_2CH_2)_3P]$[5] and $Rh(CO)_2acac$, showed that the catalyst functioned in a typical hydroformylation reaction in a biphasic mixture of toluene and perfluoromethylcyclohexane (PFMC), separated the catalyst from the products by simple phase separation, and reused the recovered catalyst solution for another hydroformylation. These early successes suggest that the "fluorous" phase provided by low-boiling fluorocarbon solvents could become an important new synthetic tool as fluorous reagents become available.

In this communication, we introduce a prototypical example of a fluorous reagent, tris(2-(perfluorohexyl)ethyl)tin hydride [**3**, $(C_6F_{13}CH_2CH_2)_3SnH$].[6] This behaves like normal tin hydride reagent in radical reductions, yet it has significant practical (and possibly also ecological) advantages over tributyltin hydride,[7] tris(trimethylsilyl)silicon hydride,[8] and related reagents. We also introduce the use of a partially fluorinated solvent, benzotrifluoride (BTF, $C_6H_5CF_3$, (trifluoromethyl)toluene), to provide a homogeneous reaction medium. Finally, we suggest that fluorous reagents will provide simple new reactions and separation options for the burgeoning field of combinatorial synthesis.

Equation 1 summarizes the best of several methods that we have investigated to prepare **3**.[9] Preparation of the Grignard reagent from 2-perfluorohexyl-1-iodoethane and quenching with phenyltrichlorotin provided **1**. Brominolysis of the phenyl−tin bond and reduction of the resulting tin bromide **2** with lithium aluminum hydride in ether provided the new tin hydride **3**. This was isolated in 65% overall yield as a clear liquid after purification by vacuum distillation.

$$\underset{\mathrm{Rf} = \mathrm{C_6F_{13}}}{\mathrm{Rf(CH_2)_2MgI}} \xrightarrow{\mathrm{Cl_3SnPh}} \underset{\mathbf{1}}{\mathrm{(Rf(CH_2)_2)_3SnPh}} \xrightarrow{\mathrm{Br_2}} \underset{\mathbf{2}}{\mathrm{(Rf(CH_2)_2)_3SnBr}} \qquad (1)$$

$$\xrightarrow{\mathrm{LiAlH_4}} \underset{\mathbf{3}}{\mathrm{(C_6F_{13}CH_2CH_2)_3SnH}} \qquad \begin{matrix}\text{overall yield: 65\%}\\ \text{(3 steps)}\end{matrix}$$

Attempts to reduce a typical organic substrate, 1-bromoadamantane, under fluorous conditions like those used by Zhu,[2] under biphasic conditions like those used by Horváth and Rábai,[3] or in normal organic solvents like benzene were not very successful. Apparently, the partition coefficients for the reactants[10] are such that the phase separation prevents a radical chain from propagating with bromoadamantane. In contrast, treatment of perfluorodecyl iodide with 1.2 equiv of tin hydride **3** and 10% AIBN in refluxing PFMC provided the corresponding reduced compound **4** in 72% yield (eq 2). This success suggested that a homogeneous medium was important. Although homogeneous organic/fluorous solvent mixtures are known,[1] we decided instead to try a "mixed" (part hydrocarbon and part fluorocarbon) solvent. BTF was selected because of its favorable properties and low cost.[11] Indeed, adamantyl bromide was cleanly reduced over 3 h with 1.2 equiv of **3** in refluxing BTF (stoichiometric procedure). After evaporation of the BTF and liquid−liquid extraction (PFMC−$CH_2Cl_2$) to separate the tin products, adamantane was isolated in 90% yield (as determined by GC integration). Under the stoichiometric procedure, reagent **3** reduces a number of other functional groups besides halides, as shown in Figure 1.

$$\mathrm{C_{10}F_{21}I} + \underset{\mathbf{3}}{\mathrm{(C_6F_{13}CH_2CH_2)_3SnH}} \xrightarrow[\substack{\text{PFMC}\\ \text{reflux}}]{\text{AIBN}} \underset{\mathbf{4}\ (72\%)}{\mathrm{C_{10}F_{21}H}} \qquad (2)$$

$$\text{Ad-Br} + \underset{\mathbf{3}}{\mathrm{(C_6F_{13}CH_2CH_2)_3SnH}} \xrightarrow[\text{reflux}]{\text{AIBN}} \text{Ad-H}$$

| equivalents | Solvent | yields |
|---|---|---|
| 1.2 | BTF | 90% |
| 0.1 | BTF/*t*-BuOH (1/1) | 92% |
| 0.01 | BTF/*t*-BuOH (1/1) | 95% |

A catalytic procedure[12] was also developed by using 10% tin hydride **3** and 1.3 equiv of $NaCNBH_3$ in a 1/1 mixture of BTF and *tert*-butyl alcohol at reflux. After 3 h, the reduction of 1-bromoadamantane was complete. After evaporation, the products were isolated by partitioning between three liquid phases: water removes the inorganic salts, methylene chloride extracts the adamantane (isolated in 92% yield), and perfluoromethylcyclohexane takes the tin products. Analyses by $^1H$ NMR and $^{19}F$ NMR (estimated detection limit 1−2%) failed to detect any fluorinated products in the residue from the methylene chloride phase, and likewise no adamantane was detected in the fluorous extract. The residue from the fluorous extract was reused 5 times to reduce bromoadamantane by this catalytic procedure with no decrease in yield. In separate experiments, successful reductions of 1-bromoadamantane were observed with as little as 1% of the tin reagent **2**. A control experiment showed

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[1] Hudlicky, M. *Chemistry of Organic Fluorine Compounds*; Ellis Horwood: Chichester, UK, 1992.

[2] Zhu, D.-W. *Synthesis* **1993**, 953.

[3] Horváth, I. T.; Rábai, J. *Science* **1994**, *266*, 72.

[4] Highlights of the chemistry in refs 3 and 4: (a) Gladysz, J. A. *Science* **1994**, *266*, 55. (b) Bergbreiter, D. E. *Chemtracts: Org. Chem.* **1995**, *8*, 108.

[5] The "ethylene spacer" serves to insulate the phosphorous from the powerful inductive effect of the perfluoroalkyl group.

[6] The indicated name is only for convenience. The approved name of **3** is tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)tin hydride.

[7] Neumann, W. P. *Synthesis* **1987**, 665.

[8] Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.

[9] Compounds **1**−**3** are new, but a number of compounds related to **1** and **2** are known, see: De Clercq, L.; Willem, R.; Gielen, M.; Atassi, G. *Bull. Chem. Soc. Belg.* **1984**, *93*, 1089.

[10] Simple extractions provide crude estimates of partition coefficients. Tin hydride **3** (1.0 g) was partitioned between PFMC (10 mL) and an organic solvent (10 mL) by shaking for 5 min in a separatory funnel. Evaporation of the organic layer provided the following weights: benzene, 22 mg; MeOH, 30 mg; $CH_2Cl_2$, 47 mg; EtOAc, 104 mg; $CHCl_3$, 141 mg.

[11] BTF: bp 102 °C, $d \approx 1.2$, 1 kg = $40 (information taken from the 1995 Aldrich catalog). This has occasionally been used as a solvent, though we are not aware of applications in organic synthesis. Raner, K. D.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1989**, *111*, 3652. Surya Prakash, G. K. In *Synthetic Fluorine Chemistry*; Olah, G. A., Chambers, R. D., Surya Prakash, G. K., Eds.; Wiley: New York, 1992; pp 227−57 (see uncited reaction on p 256).

[12] Designed after the procedure in the following: Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303.

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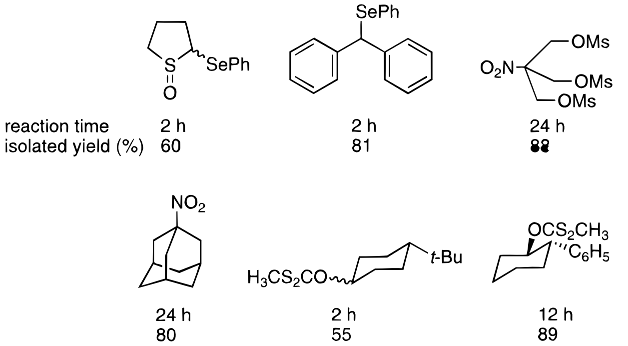
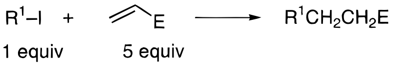


**Figure 1.**

that 1-bromoadamantane was not reduced by $NaCNBH_3$ alone under these conditions over 24 h.

Synthetic chemists have long lauded the ionic and radical reactivity profile of tributyltin hydride, but bemoaned its separation and toxicity problems.[13] Although more detailed studies are needed, the early results suggest that **3** retains the laudable reactivity profile of tributyltin hydride. Yet it can be separated from organic products by liquid−liquid extraction. The ability to use reagent **3** in catalytic amounts and to repeatedly reuse the fluorous residue suggests that large scale applications of **3** or a suitable relative might be practical because it is not necessary to synthesize or to dispose of large quantities of tin. We envision that a family of related tin reagents will in the future provide similar practical benefits for other important organotin reactions.[14] In preliminary experiments, we have successfully conducted ionic reductions with tin hydride **3** and Stille couplings with phenyltin **1**.[15]

We also envision that reagents like this fluorous tin hydride will have important applications in combinatorial synthesis.[16] Most current combinatorial synthetic strategies place the substrate on the solid phase so that it can be separated from other compounds in the reaction mixture by the phase separation technique of filtration. However, there are a number of synthetic advantages to combinatorial strategies that place the substrate in the organic liquid phase, especially for syntheses of relatively small libraries (say tens to hundreds of compounds).[17] Fluorous reagents will provide new options for these types of syntheses because the reagents (fluorous) and the substrates (organic soluble) can be separated by the phase separation technique of extraction.



| $R^1$ : E | CN | $CO_2Me$ | COMe |
|---|---|---|---|
| $C_{15}H_{31}$ | 72% | 92% | 67% |
| $c$-$C_6H_{11}$ | 75% | 65% | 75% |
| Ad | 89% | 94% | 78% |

**Figure 2.**

To illustrate the possibilities, we simulated a “fluorous/organic” step in a liquid phase combinatorial synthesis by conducting a series of radical additions in parallel.[18] The results, which double as a traditional study of scope and limitations, are shown in Figure 2. Three halides were crossed with three alkenes (used in excess), and reactions were conducted simultaneously under the catalytic procedure. Products were “purified” only by three-phase liquid−liquid extraction (conducted in the original reaction vial) and evaporation. Yields were then determined by recording NMR spectra in the presence of an internal standard. The crude products were quite pure (no identifiable starting materials or side products as assayed by capillary GC) and could hypothetically be used directly in the next step of a sequence. Automation of the extractions would make more parallel reactions possible.

Combinatorial synthesis with substrates in the organic liquid phase can already be conducted without chromatography if all the other reagents are volatile, water soluble, or on a solid phase. As more and more fluorous reagents become available, the possibilities for liquid phase combinatorial synthesis[19] in a spatially separated mode will expand.[20] Like filtration, the phase separation techniques of extraction and evaporation also allow ready separation of components, so excesses of reagents can be used. The pairing of organic substrates with fluorous reagents is expected to be especially important since a full range of traditional (including anhydrous) reactions can in principle be conducted under homogeneous liquid phase conditions, yet the products and reagents can still be separated by extraction. In short, the detractions to synthesis posed by phase separation can be divorced from its advantages in purification.[20]

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**Supporting Information Available:** Contains complete details on the preparation and characterization of **1**−**3**, representative stoichiometric and catalytic experimental procedures, and copies of GC chromatograms and NMR spectra assessing the purity of adamantane and the nine products of eq 2 (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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[13] Other alternatives to tributyltin hydride are as follows: Polymeric hydrides: (a) Neumann, W. P.; Peterseim, M. *React. Polym.* **1993**, *20*, 189. Acid soluble tin hydrides: (b) Clive, D. L. J.; Yang, W. *J. Org. Chem.* **1995**, *60*, 2607. (c) Vedejs, E.; Duncan, S. M.; Haight, A. R. *J. Org. Chem.* **1993**, *58*, 3046. Water soluble tin hydrides: (d) Light, J.; Brelsow, R. *Tetrahedron Lett.* **1990**, *31*, 2957. (e) Rai, R.; Collum, D. B. *Tetrahedron Lett.* **1994**, *35*, 6221.

[14] Pereyre, M.; Quintard, J. P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1986.

[15] Hadida, S.; Hoshino, M. Unpublished results.

[16] Reviews: (a) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135. (b) Liskamp, R. M. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 633. (c) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233, 1385.

[17] Such syntheses have been christened “mutiplex syntheses”. Mitscher, L. A. *Chemtracts: Org. Chem.* **1995**, *8*, 19.

[18] All the products are known compounds. Giese, B. *Angew. Chem.* **1983**, *95*, 771.

[19] The reagents may also find use in the liquid phase synthesis of mixtures. See: Carell, T.; Wintner, E. A.; Sutherland, A. J.; Rebek, J., Jr.; Dunayevskiy, Y. M.; Vouros, P. *Chem. Biol.* **1995**, *2*, 171.

[20] For a discussion of the possibilities for liquid phase combinatorial synthesis, see: Curran, D. P. *Chemtracts: Org. Chem.*, in press.