

Fluorous Tin Hydrides: A New Family of Reagents for Use and Reuse in Radical Reactions

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Abstract: Eight members of a new family of highly fluorinated (fluorous) tin hydrides have been synthesized and studied as reagents for radical reactions. Tin hydrides of the general formulas $[\text{Rf}(\text{CH}_2)_n]_3\text{SnH}$ and $[\text{Rf}(\text{CH}_2)_n]_2\text{Me}_2\text{SnH}$ have been prepared where Rf is C_4F_9 , C_6F_{13} , C_8F_{17} , or $\text{C}_{10}\text{F}_{21}$ and n is 2 or 3. These reagents are highly soluble in fluorinated solvents, and partition coefficients between perfluorohexanes and several organic solvents have been measured. The reagents are generally useful for reductive radical reactions and hydrostannation reactions that would typically be conducted with tributyltin hydride. Stoichiometric and catalytic procedures have been developed, and both feature very easy separation of the tin products from the organic products by convenient liquid–liquid or solid–liquid extractions. The tin reagents are recovered from reactions in high yields and are routinely reused. Rate constant measurements suggest that the fluorous tin hydrides are about as reactive as (or in some cases, slightly more reactive than) tributyltin hydride. The reagents show excellent potential for large-scale application in “green” (environmentally friendly) processes. In addition, they are useful for combinatorial and parallel synthesis applications both as reagents and as scavengers in phase-switching procedures.

Introduction

The organic chemistry of tin is featured in a diverse assortment of important reactions and is therefore central to the discipline of organic synthesis.¹ Nowhere is this truer than in radical chemistry, where trialkyltin hydrides, especially tributyltin hydride, hold a privileged role as reagents for reductive radical reactions.² The privileged role of trialkyltin reagents persists in radical chemistry and elsewhere despite the broadly acknowledged problems of separation, toxicity, and disposal that many tin reagents present.¹ In tin hydride radical chemistry, these problems can be reduced though not eliminated by using increasingly popular catalytic procedures.^{2,3} However, in other areas of radical chemistry and in organometallic chemistry stoichiometric quantities of tin components are often *de rigour*.

The vexing purification problems have been addressed in two ways. First, an assortment of workup procedures has been devised with the goal of removing trialkyltin products from reaction mixtures.⁴ Unfortunately, most workup methods provide only for the separation of tin and not for its recovery in a useful form. Second, a number of alternative classes of reagents have

been introduced with the goal of facilitating separation or reducing toxicity.⁵ In the field of radical hydrogen transfer reactions, these include water-⁶ and acid-soluble tin hydrides,⁷ and polymer-bound tin hydrides.⁸ However, most of these reagents are rarely used, and only tris-trimethylsilylsilicon hydride (Chatgililoglu's reagent) has emerged as a popular alternative to tributyltin hydride.⁹

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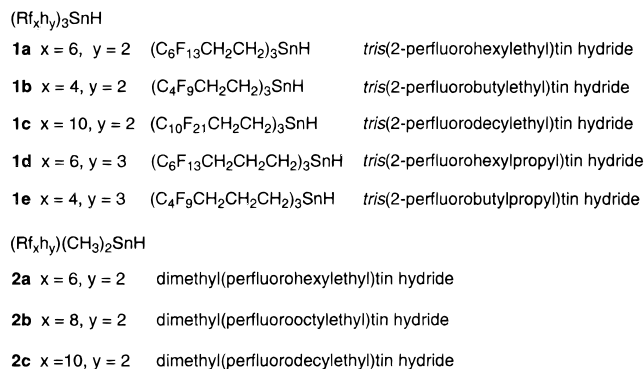


Figure 1. Fluorous tin hydrides.

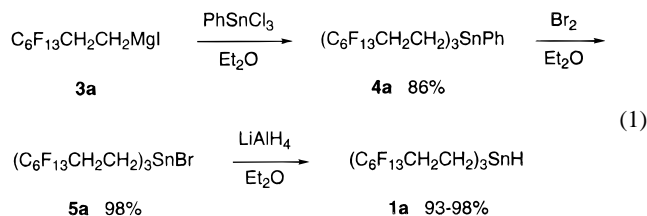
Fluorocarbon liquids are extremely poor solvents for organic compounds,^{10,11} and the technique of “fluorous biphasic catalysis”^{12–14} takes advantage of this property to immobilize a catalyst in a fluoruous phase and allow simple reaction and separation. Starting in 1996, we have published a series of papers^{15–17} that has extended and generalized the concept of the fluoruous phase as a strategic alternative to the other commonly used phases in organic synthesis: the gas phase, the water phase, the organic liquid phase, and the solid phase. These simple concepts of fluoruous synthesis, phase planning, phase switching, etc., which apply to both traditional and parallel (combinatorial) synthesis, have been outlined elsewhere,^{11,18} and they will be used here as relevant without extensive reiteration.

This full paper provides complete details of our study of a new class of fluoruous tin hydrides. The work described was our initial foray into the fluoruous field, and it set both the conceptual and experimental tone for subsequent new directions both in and beyond tin chemistry. The family of fluoruous tin hydrides described in this work is summarized by structures **1** and **2** (Figure 1). Reagents consist of a tin hydride separated from a longer perfluorinated chain by a shorter “perhydrogenated” spacer. We use the abbreviation “Rfh” to represent such partially fluorinated/partially hydrogenated chains,¹¹ and the numbers *x* and *y* in “Rf_xh_y” represent the number of perfluorinated and perhydrogenated carbon atoms, respectively. In naming the compounds, we typically use the convenient, if unofficial, nomenclature where the perfluoroalkyl chain is

named as a substituent on the perhydrogenated chain. This aggregated study provides some of the first detailed information on how the nature and composition of fluoruous chains affects the reactivity and solubility of fluoruous reagents.^{13b,c,f}

Results and Discussion

tris(2-Perfluorohexylethyl)tin Hydride. We developed several different routes to the initial tin hydride reagent **1a**, and details of these are provided in the Supporting Information. Equation 1 shows the preferred route to the tin hydride **1a**



through tin bromide **5a** that has been optimized over time and now can be routinely executed in excellent yield. Grignard reagent **3a** was reacted with phenyl trichlorotin to provide fluoruous phenyl tin compound **4a** in 86% isolated yield after rapid chromatography (or distillation) to free it from small amounts of the Wurtz coupled dimer (not shown) resulting from the Grignard reagent. This was then treated with bromine to provide the crude (but very pure) bromide **5a**, which was in turn directly treated with LiAlH₄ in ether. Standard workup and purification by vacuum distillation provided the tin hydride **1a** in 93–98% yield. Overall yields on a 20–40 g scale range from 80% to 83% for the three steps. The intermediates **4a** and **5a** are important compounds in their own right; phenyl tin compound **4a** has been used in fluoruous Stille couplings,^{16a,b,d} while tin bromide **5a** is a precursor of an assortment of other fluoruous tin compounds.¹⁷

The fluoruous tin hydride **1a** has unusual properties when compared to standard organotin compounds, but these properties are representative of related fluoruous tin compounds. Despite its high molecular weight (1162), it is a crystal clear, free flowing liquid with a boiling point of 115 °C at about 0.1 mmHg. Despite its vapor pressure, it lacks the unpleasant odor of alkyltin compounds and indeed has no detectable smell at all. It is freely soluble in fluoruous solvents such as perfluorohexane (FC-72) but sparingly soluble or insoluble in most organic solvents.

Tin hydride **1a** is sufficiently soluble in CDCl₃ to record a ¹H NMR spectrum. The tin hydride proton resonates at 5.27 ppm (compared to 4.80 ppm for tributyltin hydride), and two 2-proton multiplets with the expected multiplicities (coupling to H and F) are seen at 2.35 and 1.16 ppm. A pleasant harbinger of things to come was observed when the NMR sample was allowed to stand in the light overnight; the tin hydride was converted into the corresponding tin chloride [(C₆F₁₃CH₂CH₂)₃-SnCl], presumably by radical chain reduction of the CDCl₃. The ¹⁹F NMR spectrum of **1a** is first-order and shows individual resonances for the five difluoromethylene groups and the trifluoromethyl group with the expected couplings. The uncoupled (or H-decoupled) ¹³C spectrum is less informative; the two carbons of the ethylene spacer are clearly visible (coupled to H and F), but the carbons bearing fluorine appear as a forest of peaks between about 100 and 110 ppm due to coupling to fluorine. Such spectra would best be recorded with ¹⁹F decoupling, but we do not currently have this capability. The ¹¹⁹Sn NMR spectrum shows a single resonance at –84.5 ppm (¹J

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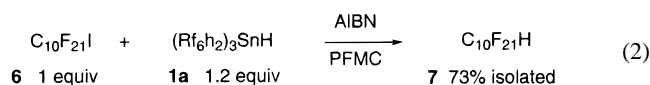
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($^{119}\text{Sn-H}$) = 1835 Hz). The stretching frequency of the tin hydrogen bond in the IR is 1842 cm^{-1} (compared to 1812 for Bu_3SnH). The molecule is amenable to standard EIMS analysis; it does not show a parent ion but shows important fragment peaks at m/e 1161 ($\text{M}^+ - \text{H}$) and 813 ($\text{M}^+ - \text{CH}_2\text{CH}_2\text{C}_6\text{F}_{13}$).

Despite the success in reducing chloroform with **1a**, we initially had considerable difficulties conducting the simple reduction of adamantyl bromide to adamantane. We attempted reductions in organic solvents (like benzene, toluene, and *tert*-butyl alcohol), in a fluorous solvent (perfluoromethylcyclohexane, PFMC) à la Zhu,¹⁰ and in biphasic solvent mixtures à la Horváth and Rábai.^{13a} In all cases, we observed very slow conversion of adamantyl bromide to adamantane. It was necessary to periodically add AIBN to prevent the painfully slow reactions from stopping entirely. Some reactions were run at $80\text{ }^\circ\text{C}$ for as long as 3 days, but maximum conversions of adamantyl bromide never exceeded 50%.

A number of observations suggested that the problem with these reactions was phase separation. None of the reactions are homogeneous to the naked eye; adamantyl bromide is not soluble in perfluoromethylcyclohexane and tin hydride **1a** is not soluble in benzene, toluene, or *tert*-butyl alcohol. Consistent with the analysis, better reduction results were obtained in solvents such as hexane or THF that have some ability to dissolve the fluorous tin hydride **1a**. To confirm that the problem was solubility, we conducted a “fully fluorous” reduction (eq 2). A solution of perfluorodecyl iodide **6** (1 equiv), tin hydride



1a (1.2 equiv), and AIBN (5%) in PFMC was heated at $80\text{ }^\circ\text{C}$. After 2 h, the peak for iodide **6** in the GC had disappeared and was replaced by that of 1(*H*)-perfluorodecane **7**, which was isolated in 73% yield after evaporation of the solvent and flash chromatography.

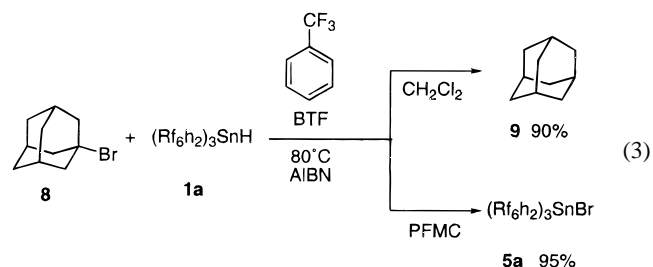
Two important implications derive from this simple experiment. First, the success of this homogeneous reduction supports the suggestion that the poor results in the reduction of adamantyl bromide can be attributed to phase separation. Due to the insolubility of the fluorous and organic solvents and reaction components, there simply is not a high enough concentration of all needed components in any one phase for the radical chain to propagate; in essence, termination competes effectively with propagation and chains are not maintained. The second implication is that tin hydride **1a** and related compounds should be useful reagents in the branch of organofluorine chemistry that deals with highly fluorinated compounds. These are often insoluble or sparingly soluble in organic solvents, but they can now be reduced in fluorinated solvents with tin hydride **1a**.

This series of preliminary experiments pointed to the need for a reaction solvent that would substantially or completely dissolve both the fluorous tin hydride **1a** and typical organic compounds. One approach to address the reaction solvent problem is to use miscible combinations of fluorous and organic solvents.^{10,14} However, fluorous solvents are extraordinarily nonpolar and are poor solvents for organic compounds.¹⁹ It follows that blends of fluorous and organic solvents might not have the general dissolving capability to be broadly useful in synthesis. We instead adopted a complementary solution. This involves the use of a lightly fluorinated organic solvent like

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trifluoromethylbenzene ($\text{C}_6\text{H}_5\text{CF}_3$, benzotrifluoride, hereafter abbreviated BTF). BTF is a very inexpensive compound produced on ton scale per year by OxyChem under the trade name Oxsol2000.²⁰ We find BTF to be a good solvent for organic reactions both in fluorous settings^{16–18} and in traditional settings.²¹

Mixing of adamantyl bromide **8**, tin hydride **1a**, and AIBN in benzotrifluoride resulted in a homogeneous (to the naked eye) reaction mixture even at room temperature (eq 3). This mixture



was heated for 3 h at $80\text{ }^\circ\text{C}$, at which time the peak for adamantyl bromide **8** in the GC was consumed and a single new peak was identified as adamantane **9** appeared. The reaction was cooled, and the BTF was partially evaporated prior to partitioning between dichloromethane (top) and PFMC. The layers were separated, and the dichloromethane phase was washed twice with PFMC. Evaporation of the dichloromethane phase provided adamantane **9** in 90% yield (as determined by GC). The ^1H NMR spectrum of the product was essentially indistinguishable from a commercial sample; no resonances for methylene protons on a fluorous tin compound could be detected. Combination of the PFMC phases and evaporation provided the tin bromide **5a** in 95% yield; the ^1H NMR spectrum of this sample was essentially indistinguishable from that made by bromination of **4a** (eq 1). This simple yet crucial experiment established conditions for reaction and separation that over time have proven generally useful. This procedure is hereafter called the “stoichiometric procedure”. In later experiments, we routinely used perfluorohexane (FC-72) in place of the more expensive perfluoromethylcyclohexane for the fluorous extraction solvent.

We then surveyed the reduction of a number of different types of compounds with tin hydride **1a**. Additional halides will be shown below. Reductions of several phenyl selenides, 3°-nitro compounds, and 2°-xanthates are shown in Figure 2. These were reduced by the standard procedure to the corresponding products in the indicated isolated yields after flash chromatography. Importantly, the crude ^1H NMR spectra of the crude organic fractions never showed resonances that could be attributed to fluorous products. Thus, in all cases, the liquid–liquid extractive workup served its purpose admirably.

While the “stoichiometric procedure” is practical and effective for small-scale work, it will not win any awards for atom economy;²² tin hydride **1a** (MW >1100) is used to deliver a hydrogen atom (MW = 1). We therefore developed a catalytic procedure fashioned after the popular procedure of Stork and Sher.²³ This procedure features a three-phase extraction in the

(20) “Introducing OXSOL2000” Oxychem Specialty Business Group No. BCG-OX-37, 5/96. Available from Occidental Chemical Corporation. See also Material Safety Data Sheet (MSDS) M35459.

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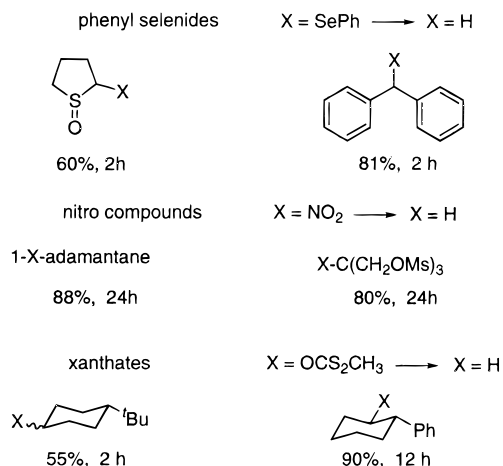
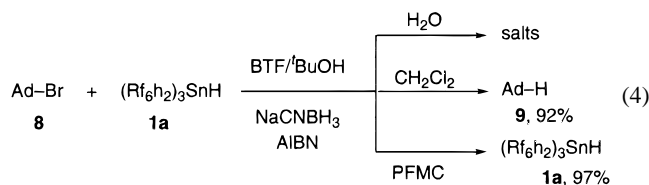


Figure 2. Isolated yields and reaction times of reductions by the “stoichiometric procedure”.

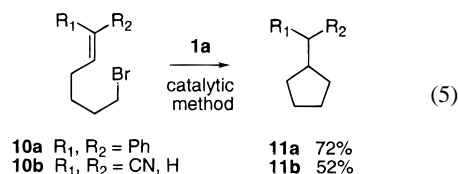
workup (eq 4). Under the standard “catalytic procedure”,



adamantyl bromide was heated at 80 °C in a 1/1 mixture of benzotrifluoride and *tert*-butyl alcohol with 10% tin hydride **1a**, 1.3 equiv sodium cyanoborohydride (NaCNBH_3), and AIBN. *tert*-Butyl alcohol is required to aid in the gradual dissolution of the NaCNBH_3 . After being heated for 3 h, the mixture was cooled, concentrated, and partitioned in a three-phase liquid extraction between water (top), dichloromethane (middle), and PFMC (bottom). The aqueous phase containing the borohydride salts was discarded, while the organic and fluoros phases were evaporated and analyzed. The only detectable product in the organic phase was adamantane (92% isolated yield). We estimate detection limits in these experiments on the order of 1%. The tin hydride was recovered from the fluoros phase in 97% yield, and its ^1H NMR spectrum was clean and free of adamantane resonances.

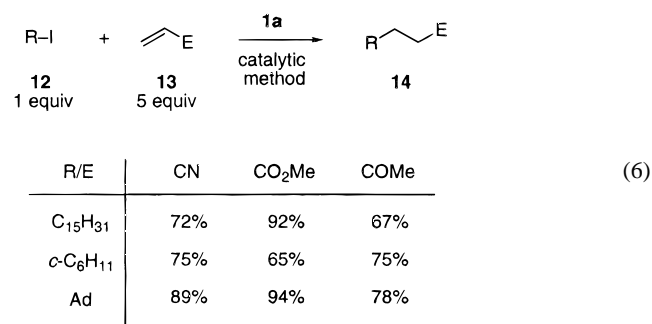
We conducted a number of experiments to assess the robustness of this procedure with regard to efficient use of the tin. We first repeated the reduction of adamantyl bromide under the standard catalytic procedure and then recovered the tin hydride and (without analysis or purification) repeated the reduction of a fresh sample of adamantyl bromide. The tin hydride was reused five times in this way for a total of six reductions with the same sample of tin (1.6 mol % tin per reduction). In each reduction, the yield of adamantane was essentially quantitative (peak-to-peak conversion in the GC). Although the purity of the recovered tin fraction was not analyzed, its weight indicated >95% recovery at each stage. The first four reactions were completed in 3 h while the last two took 5 h, suggesting that some degradation of the tin hydride might be occurring. We also conducted a reduction using 1% tin hydride, and this provided pure adamantane in 95% yield. The ability to use 1–10% tin catalyst and to recover the catalyst is attractive for preparative applications.

We also conducted a number of preparative reactions where cyclization products were expected. Reductive cyclization of 6-bromo-1,1-diphenyl-1-hexene **10a** (eq 5, catalytic procedure)



gave diphenylmethylcyclopentane **11a** in 72% yield after three-phase extractive workup and purification by flash chromatography, while reductive cyclization of 6-bromo-1-cyano-1-hexene **10b** provided cyanomethylcyclopentane **11b** in 52% isolated yield. The isolated yields are comparable to those reported by Newcomb for tributyltin hydride.²⁴ These results strongly suggest that a standard radical chain mechanism is operating. Information on the rate constant for reduction of radicals by **1a** will be presented below along with the rate data of the other tin hydrides.

The catalytic procedure can also be used to conduct intermolecular reactions, as shown by the series of Giese reactions in eq 6. These nine experiments (3 halides **12** with 3 alkenes



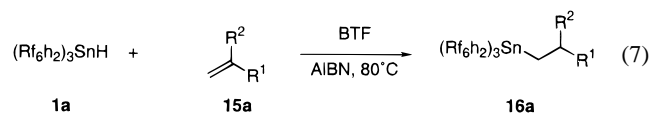
13) were designed to show the useful features of fluoros reagents for solution phase combinatorial chemistry^{17,18} and were conducted in parallel in nine test tubes. After the reaction and three-phase extractive workup, the organic phase remaining in the test tube was evaporated to dryness and analyzed. Yields of the nine products **14** in eq 6 were determined by ^1H NMR spectroscopy against a standard, and purities were all >95% according to GC analysis. All products **14** were substantially free of fluoros compounds as determined by ^1H NMR and weighing (due to its high weight, a fluoros tin impurity is readily detected when the weight yield exceeds the NMR yield). The whole experiment was reproduced a second time with similar results. This time ^{19}F NMR spectra of all nine organic products were also recorded; no spectrum showed any resonance.

In addition to providing added information on the scope of the tin hydride reagent **1a**, this parallel experiment is a simple example of the power of phase planning.¹⁸ The reagents are chosen and the conditions are designed such that the starting iodide **12** is completely converted to the reductive addition product **14** and such that the reductive addition product is the only product left in the organic liquid phase after workup. The tin hydride **1a** is removed in the fluoros phase (all nine fluoros products were combined without analysis and saved for later reuse), the inorganic salts are in the water phase, and the excess alkene **13** (which is required for a high yield of **14**) is removed by evaporation. From the perspective of library synthesis, the

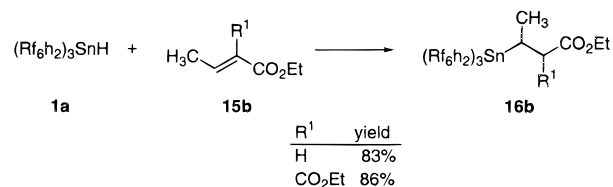
(24) (a) Park, S.-U.; Chung, S.-K.; Newcomb, M. *J. Am. Chem. Soc.* **1986**, *108*, 240. (b) Newcomb, M.; Varick, T. R.; Ha, C.; Manek, M. B.; Yue, X. *J. Am. Chem. Soc.* **1992**, *114*, 8158. (c) Ha, C.; Horner, J. H.; Newcomb, M.; Varick, T. R.; Arnold, B. R.; Luszyk, J. *J. Org. Chem.* **1993**, *58*, 1194.

removal of an excess reactant by evaporation is a liability since it limits the number of reactants that can be input to make a library. However, excess nonvolatile alkene can be removed by fluororous switching, as shown below.

In addition to the reductive removal of functional groups, the other characteristic radical reaction of tin hydrides is hydrostannation of multiple bonds.² To assess this reaction, we studied the radical addition of fluororous tin hydride **1a** to a number of alkenes and alkynes. Although test reactions with **1a** proceeded smoothly in neat conditions, we elected to use a minimum amount of BTF to ensure homogeneous reaction mixtures. The reactions shown in eq 7 were carried out by

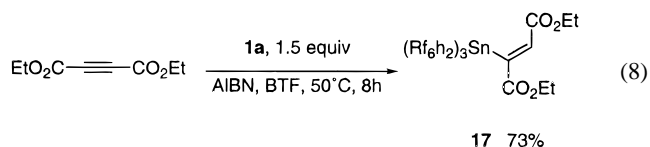


R ¹	R ²	isolated yield 16a
Ph	H	86%
CO ₂ Bn	H	77%
Ph	CH ₃	92%
CON ₂ C ₆ H ₄	H	63%

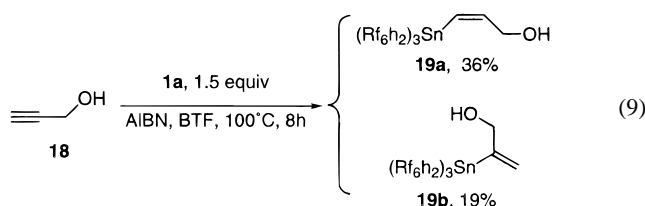


heating a mixture of the alkene **15a,b**, 1.5 equiv of fluororous tin hydride **1a**, and a catalytic amount of AIBN in 0.1 mL of BTF at 80 °C for 8 h. The solvent was evaporated, and the residue was partitioned between FC-72 and CH₂Cl₂. The hydrostannation products partitioned into the fluororous phase, and after evaporation of the FC-72, the residue was purified from excess tin hydride by column chromatography. This provided the tetraalkytin compounds **16a,b** in good to excellent yields (eq 7).

We also studied the hydrostannation of several alkynes. In the case of activated alkynes such as diethyl acetylenedicarboxylate, the reaction was carried out with 1.5 equiv of **1a** in BTF solution at 50 °C for 8 h. The fluororous product **17** was isolated as a single (*Z*) isomer in 73% yield from the fluororous phase after fluororous/organic extraction and column chromatography (eq 8).

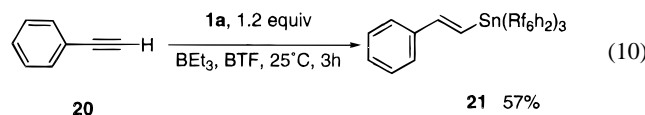


In the case of propargyl alcohol **18**, the best results were obtained when the reaction mixture was heated at 100 °C for 8 h (eq 9). Two products were isolated from the reaction; a minor product **19b**, derived from α -addition of the triple bond, was isolated in 19% yield and a major one, **19a**, from *cis*- β addition, was isolated in 36% yield. The addition of triethyl- and triphenyltin hydride to propargyl alcohol has been reported²⁵



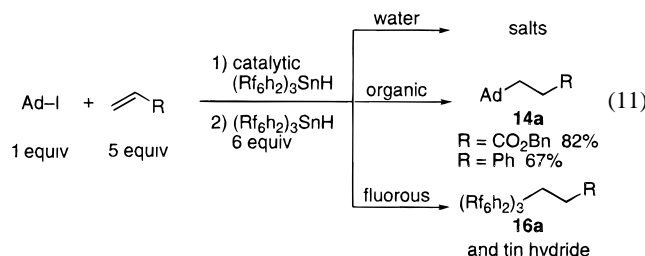
to yield mixtures of three products (α , *cis*- β , and *trans*- β , 25:45:30 and 5:45:50). In our case, no product coming from the addition of tin hydride **1a** in a *trans*- β fashion was observed in the crude ¹H NMR spectrum of the reaction mixture.

The addition of fluororous tin hydride **1a** to phenyl acetylene **20** was conducted at 25 °C with triethylborane initiation (eq 10).²⁶ The (*E*) alkene **21** was isolated in 57% yield as the only



product of the reaction. The differences in *E/Z* selectivity in eqs 9 and 10 and literature results may be due to reversible additions²⁷ of tin radicals to the products; unactivated alkyne **18** provides the kinetic *Z* product while activated alkyne **20** provides the equilibrated *E* product. However, the relative extent of kinetic and thermodynamic control in these reactions remains to be elucidated.

That all of the products of these reactions partition into the fluororous phase preferentially suggests that the hydrostannation reaction can be used as a means to remove excess alkenes from reaction mixtures. We used this reaction to introduce the technique of “fluorous quenching”^{17a,18} whereby a residual undesired organic reaction component at the end of a reaction is switched to the fluororous phase to allow its removal during workup. We first demonstrated this potential in Giese reactions such as those shown in eq 6, but now we use nonvolatile radical acceptors. In two experiments, adamantyl iodide was reductively added to an excess of benzyl acrylate and styrene with tin hydride **1a** under the standard catalytic conditions (eq 11). After



three-phase extractive workup, ¹H NMR spectra of the residue from the organic phase showed that the major component of the mixture was unreacted styrene or benzyl acrylate and the minor component was the Giese adduct (as expected from the stoichiometry of the reaction). A similarly generated mixture was subjected to the hydrostannation with excess tin hydride **1a** followed by FC-72/dichloromethane extraction. From the organic phase we isolated the adducts **14a** in 82% (R = CO₂-Bn) and 67% (R = Ph) yield, free from the starting alkene (as assessed by ¹H NMR). Of course, the fluororous product from

(26) Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron* **1989**, *45*, 923.

(27) (a) Ferreri, C.; Ballestri, M.; Chatgililoglu, C. *Tetrahedron Lett.* **1993**, *34*, 5147. (b) Chatgililoglu, C.; Ballestri, M.; Ferreri, C.; Vecchi, D. *J. Org. Chem.* **1995**, *60*, 3826.

(25) Leusink, A. J.; Budding, H. A.; Marsman, J. W. *J. Organomet. Chem.* **1967**, *9*, 285.

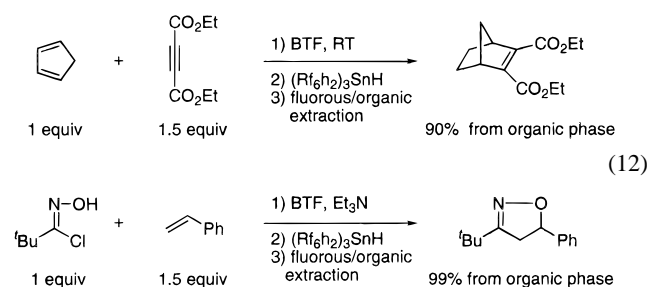
Table 1. Partition Coefficients of Tin Hydrides

tin hydride	F/H ^a	% F ^b	FC-72/CH ₃ CN	FC-72/C ₆ H ₆
Bu ₃ SnH	na	0	<1/150	<1/350
1a (Rf ₆ h ₂) ₃ SnH	3.25	64	160/1	45/1
1b (Rf ₄ h ₂) ₃ SnH	2.25	60	5.8/1	10.5/1
1c (Rf ₁₀ h ₂) ₃ SnH	5.25	68	high ^c	high ^c
1d (Rf ₆ h ₃) ₃ SnH	2.17	62	6.4/1	10.0/1
1e (Rf ₄ h ₃) ₃ SnH	1.50	57	2.3/1	1.2/1
2a (Rf ₆ h ₂)SnMe ₂ H	0.87	50	2.4/1	0.7/1
2b (Rf ₆ h ₂)SnMe ₂ H	1.13	54	14/1	2.5/1
2d (Rf ₁₀ h ₂)SnMe ₂ H	1.40	57	48/1	4.7/1

^a Ratio of fluorines to hydrogens. ^b Percent fluorine by molecular weight. ^c Due to low solubility, the partition coefficient measurements are not reliable.

this reaction cannot be reused directly because it contains a mixture of tin hydride **1a** and hydrostannated products **16**.

We also conducted the standard Diels–Alder and nitrile oxide cycloaddition reactions shown in eq 12 by using excess alkene.



These reactions were conducted in BTF and were then subjected to hydrostannation with **1a** and fluorous/organic extraction. The expected cycloadducts were obtained by evaporation of the organic phase and were free from starting alkene. The fluorous phases of these reactions contained the respective hydrostannated products along with residual tin hydride. The simple technique of fluorous quenching is readily automated and has excellent potential to expedite solution phase combinatorial and parallel syntheses.^{17f}

The results so far suggest that, despite its unusual physical and solubility properties, tin hydride **1a** reacts more or less like a standard trialkyltin hydride in radical reactions, provided that the reactions are not biphasic. However, this is not the case in ionic reactions. Attempts to reduce simple aldehydes and ketones in diethyl ether in the presence of Lewis acids under standard conditions²⁸ were not very successful. Reactions were very sluggish, and the starting materials were generally recovered. Since the tin hydride is reasonably soluble in ether, we do not think that solubility is the problem here. Simple aldehydes such as benzaldehyde can be reduced by using 20 equiv of ZnCl₂ (see Supporting Information), but this procedure is not very practical or general. Ionic (and even radical) reactions of related “ethylene-spaced” fluorous allyl stannanes do not give preparatively acceptable results either.^{16f,g} These are clear indications that the nature of the spacer will be crucial for some applications in fluorous chemistry.

Other Fluorous Tin Hydrides. To study the effects of the spacer and the fluorous chain on the reactivity and solubility, we prepared four related tin hydrides **1b–e** bearing three fluorous chains and three tin hydrides **2a–c** bearing one fluorous chain and two methyl groups. The structures of these reagents are shown in Figure 1 and Table 1, and the syntheses are detailed in the Supporting Information.

(28) Leusink, A. J.; Budding, H. A.; Drenth, W. *J. Organomet. Chem.* **1968**, *13*, 163.

We conducted a series of experiments to compare the spectroscopic, solubility, and reactivity properties of these new reagents. Information about partition coefficients is contained in Table 1. Partition coefficients were estimated in two pairs of solvents: FC-72/CH₃CN and FC-72/C₆H₆. In these experiments, 0.5–1.0 g of fluorous tin hydride was partitioned between 10 mL of FC-72 and 10 mL of acetonitrile or benzene. The biphasic mixture was stirred vigorously for 10 min. The two layers were separated and evaporated to dryness, and the residue was weighed. Also listed in Table 1 are two crude measures of the “fluorosity” of a molecule: the ratio of fluorines to hydrogens (F/H) and the percent fluorine by molecular weight.

Compound **1c** bearing 63 fluorines proved, not surprisingly, to be highly insoluble in organic solvents. But it was also only sparingly soluble in BTF and FC-72, and we therefore did not attempt to measure a partition coefficient. We presume that this is very high because the denominator (organic solubility) is close to zero. However, the partition coefficient does not tell the whole story, as attempted reductions with **1c** were largely unsuccessful, presumably due to its insolubility. In effect, **1c** is on the borderline between a fluorous tin hydride and a “Teflon-bound” tin hydride. At the other extreme is tributyltin hydride, which is essentially insoluble in FC-72.

The original tin hydride **1a** is also quite fluorous as measured by partition coefficients, and two or three washes of an organic solvent with FC-72 are sufficient to remove >99% of this compound, as shown by the experimental results above. Shortening of the fluorocarbon tag by two CF₂ groups leads to considerably decreased, but still substantial, coefficients favoring partitioning of **1b** into the fluorous phase. The propylene spacer reagent **1d** bearing C₆F₁₃ is also considerably “less fluorous” than its ethylene spacer analogue. Propylene-spaced reagent **1e** with C₄F₉ group splits between the organic and fluorous solvents but still with a preference for the fluorous phase.

With this limited data, it is too early to analyze in detail the partition coefficient trends as a function of the fluorous chains; however, one obvious trend that emerges from Table 1 does appear to be significant: subtraction of two CF₂ groups or insertion of one CH₂ group from the basic reagent **1a** leads to an analogue with significantly reduced partition coefficients. While we have not measured absolute solubilities, it is clear from the preparative results (see below) that this change in partition coefficient must be due in large measure to increased solubility in the organic solvents. This can be a significant benefit in the reaction chemistry. We have not extensively measured the partition coefficients of the fluorous products of the radical reactions, but we do know at least qualitatively that tin halides are more susceptible to partition into organic solvents than tin hydrides and that this partitioning can be effected by other cosolvents.¹⁶

The new tin hydrides were fully characterized, and relevant spectral data are summarized in Table 2 for comparison. These data include the following: the stretching frequency of the Sn–H bond in the IR spectrum, the chemical shift of the proton bonded to tin (¹H NMR), and the chemical shift and coupling constant (to H) of the tin (¹¹⁹Sn NMR). The propylene-spaced reagents **1d,e** and the monofluorous ethylene-spaced reagents **2a–c** show values closer to the standard trialkyltin hydrides than the trifluorous ethylene-spaced reagents **1a–c**. The deshielding effect of the (presumably more electronegative) ethylene spacer on the chemical shift of the hydrogen bonded to tin is counterintuitive based on inductive effects but is nonetheless expected based on prior measurements.²⁹

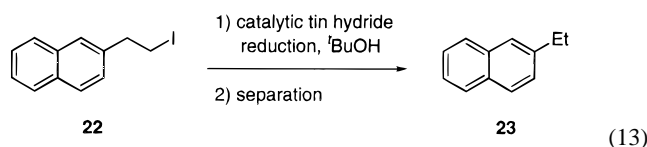
(29) Duffermont, J.; Maire, J. C. *J. Organomet. Chem.* **1967**, *7*, 415.

Table 2. Selected Spectroscopic Data for Tin Hydrides **1** and **2**

tin hydride	δ SnH ^a	δ SnH ^b	$J_{119\text{Sn-H}}$	Sn-H (cm ⁻¹) ^c
Me ₃ SnH	4.73		1744	1833
Bu ₃ SnH	4.80	-86.6 (CDCl ₃)	1609	1812
1a (Rf ₆ h ₂) ₃ SnH	5.27	-84.5 (CDCl ₃)	1835	1842
1b (Rf ₄ h ₂) ₃ SnH	5.22	-64.9 (BTF-C ₆ D ₆)	1858	1862
1c (Rf ₁₀ h ₂) ₃ SnH	5.48	nd ^d	nd ^d	nd ^d
1d (Rf ₆ h ₃) ₃ SnH	4.87	-95.1 (BTF-C ₆ D ₆)	1583	1838
1e (Rf ₄ h ₃) ₃ SnH	4.88	-94.2 (BTF-C ₆ D ₆)	1791	1843
2a (Rf ₆ h ₂)SnMe ₂ H	4.75	-86.8 (C ₆ D ₆)	nd ^d	1839
2b (Rf ₈ h ₂)SnMe ₂ H	4.74	-86.8 (C ₆ D ₆)	1782	1841
2c (Rf ₁₀ h ₂)SnMe ₂ H	4.75	-86.9 (C ₆ D ₆)	nd ^d	1840

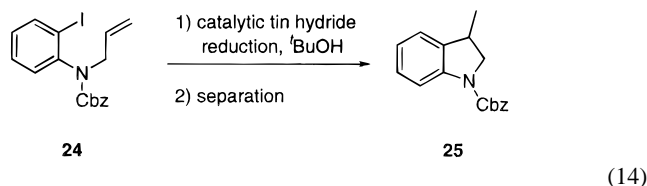
^a From the ¹H NMR in CDCl₃. ^b From the ¹¹⁹Sn NMR in CDCl₃. ^c Of a thin film by FTIR. ^d Not determined.

To probe the reactivity of these tin hydrides, we conducted the radical reduction of 2-iodoethylnaphthalene **22** (eq 13) and



tin hydride	separation methods	yield
1b	liq. - liq.	95%
1c	liq. - liq.	poor reaction
1d	liq. - liq.	91%
1e	liq. - liq.	85%
2a	sol. - liq.	fluorous impurities
2b	sol. - liq.	fluorous impurities
2c	sol. - liq.	83%

the cyclization of the aniline derivative **24** (eq 14). Attempts to



tin hydride	separation methods	yield
1b	liq. - liq.	91%
1c	-	not tried
1d	liq. - liq.	89%
1e	liq. - liq.	82%
2a	evaporation	78%
2b	sol. - liq.	fluorous impurities
2c	sol. - liq.	75%

use the tin hydride **1c** bearing 63 fluorines were irreproducible and generally unsuccessful, presumably due to its insolubility. However, in a separate paper we report that highly fluoruous reagents such as **1c** can be coaxed to react under microwave conditions.³⁰ All of the other tin hydrides were well-behaved. Indeed, in contrast to tin hydride **1a**, we discovered that the other tin hydrides could be used in the catalytic procedure without the need for BTF as a cosolvent. While these reactions were cloudy, suggesting incomplete dissolution of the fluoruous tin components, they all nonetheless worked smoothly and in good yield. Thus, the increased solubility of these reagents relative to the prototype **1a** is an attractive feature because it extends the range of solvents that can be used. Reactions were worked up by the standard three-phase extraction with water, FC-72, and benzene. The benzene phase was washed with FC-

(30) Olofsson, K.; Kim, S.-Y.; Larhed, M.; Curran, D. P.; Hallberg, A. submitted for publication.

72 (3–8 times) and evaporated to provide the crude products, which were substantially pure as assessed by ¹H NMR. Thus, while these reagents are “less fluoruous” than **1a**, it is still possible to separate them from the reaction products by liquid–liquid extraction. Although not studied with reagents **1a–d**, the convenient solid–liquid extractive workup described below could also surely be used.

During the course of these reactions, we noticed that the propylene-spaced tin hydrides were considerably less stable than the ethylene-spaced analogues. The reasons for this difference are not currently clear, but it was confirmed by several simple experiments. Heating of tin hydride **1a** in CDCl₃ in the dark for 18 h resulted in only a small decrease in the intensity of the SnH signal relative to an integration standard, but the signal from the tin hydride in **1d** had almost completely disappeared after 18 h in an analogous experiment. The progress of this transformation was followed over time, but the resulting ¹H NMR spectra were very complex and no decomposition products could be identified. This thermal instability does not seem to compromise the utility of the reagents in standard radical reactions, but it could detract from practicality if the tin product is not recovered in a pure form after the reaction.

A similar series of experiments was conducted with the tin hydrides **2a–c** bearing one fluoruous chain and two methyl groups (eqs 13, 14). These compounds all bear ethylene spacers, and we again used the catalytic procedures which regenerate the tin hydride. The partition coefficients of these three tin hydrides are shown in the lower part of Table 1. Compound **2a** does not have partition coefficients that are high enough to permit simple extractive removal. However, both **2b** and **2c** exhibit good partitioning out of acetonitrile and into FC-72. In all three cases, extraction against acetonitrile is considerably better than that against benzene.

Iodides **22** and **24** were then reduced with all three tin hydrides by the standard catalytic procedure with sodium cyanoborohydride. Reactions occurred smoothly in *tert*-butyl alcohol, and benzotrifluoride was not required as a cosolvent due to the acceptable organic solubility of these molecules. Reactions were purified by a simple solid-phase extraction through fluoruous reverse-phase silica gel eluting with acetonitrile.^{16c,f,g} In the case of **2c**, evaporation of the acetonitrile provided pure 2-ethylnaphthalene in 83% yield; no resonances from the fluoruous tin compound were detected in the ¹H NMR spectrum. However, in the products from **2a** and **2b**, small but clear resonances for the tin methyl groups and spacer protons could be identified, thus showing that the separation was not completely effective. The product from **2a** was dried overnight on a vacuum pump, which resulted in evaporation of both the product and the tin hydride to leave nothing. This suggested that less volatile products could be separated from the tin hydride by vacuum-drying, and indeed reduction of **24** with **2a** followed by vacuum-drying overnight gave **25** in 78% yield free from fluoruous tin residues in the ¹H NMR. Reduction with **2c** followed by solid-phase extraction provided pure **25** in 75% yield. However, neither the simple solid-phase extraction nor overnight pumping removed all of the fluoruous resonances from the ¹H NMR spectrum of the product of **2b**.

All of the preparative results suggest that the new tin hydrides show reactivities that are qualitatively similar to those of standard trialkyltin hydrides. Problematic behavior was only observed when the tin hydride was substantially insoluble in the reaction medium. To provide a more quantitative measure of the effects of the fluoruous substituents, we measured rate constants for several of the new tin hydrides using Newcomb’s

Table 3. Rate Constants for Tin Hydrides

26 red. cyc.

R_3SnH	overall yield (%)	red/cyc	$[(R)_3SnH]$ (M)	k_H (80) ($M^{-1} s^{-1}$)	average ($M^{-1} s^{-1}$)
$(C_6F_{13}CH_2CH_2CH_2)_3SnH$ 1a	84	0.14	0.03	1.0×10^7	1.1×10^7
	83	0.43	0.10	1.0×10^7	
	64	0.40	0.07	1.4×10^7	
$(C_4F_9CH_2CH_2)_3SnH$ 1b	92	0.34	0.08	1.0×10^7	1.2×10^7
	81	0.48	0.23	1.5×10^7	
		0.16	0.03	1.2×10^7	
$(C_4F_9CH_2CH_2CH_2)_3SnH$ 1d	79	0.25	0.08	7.3×10^6	1.0×10^7
	75	0.19	0.03	1.4×10^7	
$C_{10}F_{21}Me_2SnH$ 2c	64	0.07	0.03	5.1×10^6	5.2×10^6
		0.36	0.15	5.3×10^6	

Table 4. Biphasic “Pseudo-Dilution” Experiments

26 cyc. red.

$(Rf)_3SnH$	benzene/FC-72	red/cyc	temp	overall yield	effective ^a $[(R)_3SnH]$	calculated ^b $[(R)_3SnH]$	results
$(C_4F_9CH_2CH_2)_3SnH$	1:1	0.28	80	92	0.051	0.020	2.3 times higher
$(C_6F_{13}CH_2CH_2CH_2)_3SnH$	1:1	0.40	80	81	0.082	0.020	4.1 times higher
	1:1	1.1	rt		0.11	0.020	5.5 times higher
	1:4	0.28	80	95	0.058	0.0054	10.7 times higher

^a Calculated by using rate constants in Table 3. ^b Calculated by using partition coefficients in Table 1.

probe **26**.³¹ The measurements were anchored for **1a** by an absolute determination of the rate constant in the laboratories of Prof. M. Newcomb.^{15b} This showed $k_H = 1 \times 10^7 M^{-1} s^{-1}$ at 80 °C in BTF, while the rate constant for Bu_3SnH at 80 °C is $6 \times 10^6 M^{-1} s^{-1}$. The other substrates were then subjected to standard competitive experiments with **26** as the cyclizable probe. BTF was used as the solvent for all of these experiments since the rate constant for tin hydride **1a** was determined in BTF and since it is the only solvent in which all the tin hydrides are soluble enough so that we can be confident of the concentrations. The results of these experiments are shown in Table 3. All the trifluorous tin hydrides appear to be marginally more reactive than tributyltin hydride. The difference (less than a factor of 2) is probably large enough to be real but small enough so as not to merit extensive discussion or interpretation. Monofluorous tin hydride **2c** was, within experimental error, of equal reactivity to Bu_3SnH .

The combined knowledge of partition coefficients and rate constants for cyclization provided us with an opportunity to test ideas about using biphasic mixtures as a way to control concentrations of fluororous tin reagents in an organic phase. The first example of this has been recently described in asymmetric protonation chemistry; a prochiral samarium enolate and a catalytic quantity of a chiral proton source were protected from a stoichiometric achiral proton source by partitioning of the achiral proton source into a fluororous phase.^{17e} In radical chemistry, the use of low concentrations of tin hydride to conduct slow radical reactions is common, and this can be done

by using either low stationary concentrations or syringe pump addition. We hypothesized that a biphasic reaction with a fluororous tin hydride could establish a low, stationary tin hydride concentration in an organic phase while holding most of the tin hydride in reserve in the fluororous phase.

To test this possibility, we conducted cyclizations with tin hydrides **1b** and **1d** and probe **26** in mixtures of FC-72 and benzene (Table 4). The use of the cyclizable probe allows us to measure an “effective tin hydride concentration” if we assume that the radical cyclizations and reductions take place in the organic phase. This number can also be calculated by assuming that the partition coefficients measured in Table 1 are not temperature-dependent and are not affected by the other reaction components. In principle, the measured and calculated concentrations should be identical. In practice, the comparison of the measured effective tin hydride concentrations to the calculated ones suggests that there is clearly a flaw in this simple analysis. In all cases, we observe significantly more (2–10 times) of the direct reduction product than the analysis predicts. This trend holds even in the experiment conducted at room temperature, suggesting that the effect cannot be attributed to temperature dependence on partition coefficients. Thus, there is a “pseudo-dilution” effect in these biphasic experiments, but it is much smaller than the partition coefficients would suggest.

Conclusions

The extensive reactivity and solubility studies of the eight tin hydrides reported herein begin to provide some much needed insight into how to design fluororous reagents with desired reactivity and separation features. Nicely complementing this

(31) (a) Johnson, C. C.; Horner, J. H.; Tronche, C.; Newcomb, M. J. *Am. Chem. Soc.* **1995**, *117*, 1684. (b) Tronche, C.; Martinez, F. N.; Horner, J. H.; Newcomb, M.; Senn, M.; Giese, B. *Tetrahedron Lett.* **1996**, *37*, 5845.

work in the organotin area are detailed studies of assorted fluororous phosphines and derived organometallic complexes by Horváth, Gladysz, and others.^{13,14}

On the basis of early work, both we^{14b} and Horváth suggested that molecules bearing about 60% fluorine by molecular weight would partition well into fluororous solvents. While this remains a useful guideline, the data in Table 1 clearly show that the %F is only one factor determining partition coefficients. For example, the addition of one methylene group to **1a** to give **1d** reduces the fluorine content from 64% to 62%, yet the partition coefficient of **1d** into CH₃CN is more than 10 times smaller than **1a**. In contrast, **1b** and **1e** (which also differ by a CH₂ group) have rather similar partition coefficients. The monofluorous tin hydride with the longest (C₁₀F₂₁) chain is only 57% F, yet it exhibits much higher partition coefficients than **1d** (62% F). So it is clear that, even with relatively nonpolar molecules, partition coefficients depend on structures and not just fluorine content. The partition coefficients also vary from solvent to solvent, with higher partitioning usually (but not always) observed out of acetonitrile compared to benzene. We classify both acetonitrile and benzene (as well as other aromatic solvents) as relatively “anti-fluorous”; that is, they have relatively poor capability to dissolve polyfluorinated molecules.

Taken together, the work with tin reagents and phosphines suggests that three perfluorohexylethyl chains bring together the features needed to make fluororous reagents with very high partition coefficients. These high partition coefficients result, at least in part, from low solubilities in organic solvents. Subtraction of two CF₂ groups or addition of one CH₂ group results in molecules that retain substantial solubility in fluororous solvents but have increased solubility in organic solvents. This results in lower partition coefficients, so more extractions are needed if reactions are worked up by liquid–liquid methods. However, the solid–liquid extractions provide a convenient alternative when liquid–liquid extractions become impractical. Going in the other direction, the simultaneous lengthening of the three chains to C₁₀F₂₁ results in reagents that are essentially insoluble in organic solvents and are not very soluble in fluororous solvents, either.

Although they have not yet been studied extensively, the tin hydrides bearing one fluororous chain provide a new direction in the fluororous field. Reducing the number of chains from three to one should provide reagents that more closely resemble the parents, and these reagents also show better solubility in organic solvents. Even reagents bearing a single long fluorinated chain show good solubility properties in both fluororous and organic solvents. Indeed, reagent **2c** has proved popular in our group for conducting preparative radical cyclizations.

Although calculations in the phosphine series suggested that an ethylene spacer should provide a reasonable insulation of the phosphorus atom of (RfCH₂CH₂)₃P from the perfluoroalkyl group, the effects of this group are nonetheless readily detected.^{13,14} In the tin series, spacer effects seem especially significant. Reagents such as **1a** bearing three fluororous chains and ethylene spacers can be used in tin hydride radical chemistry, but they do not work well in radical allylations or ionic reactions. Early work suggests that the propylene-spaced reagents are much better for these types of reactions.^{16f,g}

While early work in the fluororous field focused on biphasic reaction conditions with fluororous solvents, there are now a

number of other solutions to the reaction solvent problem that do not require the use of fluorinated solvents. Oxygenated solvents such as THF and ether have reasonably good dissolving power for fluororous compounds. Additionally, the strategy of using partially fluorinated solvents (exemplified by BTF) looks especially general. Other partially fluorinated solvents that are commercially available include *para*-chlorobenzotrifluoride, trifluoroethanol, and 1,2,2-trifluoro-1,1,2-trichloroethane. Finally, perhaps the most expedient strategy for standard synthesis applications is simply to use the more lightly fluorinated reagents, which have expanded solubility in the full range of organic solvents.

This work with tin hydrides provides a prototype for rendering a standard “organic” reagent fluororous. The result of the process is not a single reagent but instead a family of reagents with tunable reactivity and solubility properties. The chemistry described here for tin hydrides serves as a model for other types of organotin reagents, some of which have already been made and studied.¹⁶ Suitable fluororous tin reagents mimic the reactivity of their organic parents, but they are readily separated from organic products and can routinely be reused. The issue of toxicity is still an open question, and while there is some reason to believe that these reagents could be less toxic than alkyl tin compounds, this notion has not yet been tested experimentally. In the meantime, we recommend that fluororous tin reagents be handled with the standard precautions used for regular alkyltin reagents. Special care should be taken with the monofluorous series **2**; even if these fluororous compounds do prove to have reduced toxicity, there is still the potential that the fluororous chain would be lost in the environment or by metabolism. This would generate fragments Me₂SnXY, which are well-known to be toxic.¹

Although still in its infancy, fluororous chemistry stands poised to impact across the discipline of organic synthesis from small-scale parallel synthesis to process chemistry. The attraction of fluororous methods is that they couple synthesis and separation.¹⁷ While a number of other general methods to do this are now emerging, the features of fluororous chemistry (stability of perfluorocarbon fragments, ease of synthesis, tunability by substituent effects, etc.) suggest that there is still vast untapped potential.

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Supporting Information Available: Complete details on the preparation and characterization of all fluororous tin compounds and experimental procedures for their use. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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