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"PROPYLENE SPACED" ALLYL TIN REAGENTS: A NEW CLASS OF FLUOROUS TIN REAGENTS FOR ALLYLATIONS UNDER RADICAL AND METAL-CATALYZED CONDITIONS

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Abstract: A new generation of propylene-spaced fluorous allyltin reagents $[(Rf(CH_2)_3)_3SnCH_2CH{=}CH_2]$ is described. These succeed in radical allylations where their lower homologs (ethylene-spaced) fail, and they provide improved performance in transition metal catalyzed allylations. The reagents and byproducts are readily separated by simple fluorous–organic liquid–liquid or solid–liquid extractions.

Introduction

An emerging suite of fluorous techniques is starting to provide new options for the coupling of reaction and separation chemistry.[1] The powerful technique of "fluorous biphasic catalysis", introduced by Horvath and Rabai,[2] has gained a strong foothold in organometallic chemistry.[3] This technique uses fluorous solvents at both the reaction[4] and separation stages of a synthetic process. However, for certain kinds of reactions, this can be disadvantageous at the reaction stage because fluorous solvents are extraordinarily nonpolar. We have introduced a number of techniques that strive to operate under standard reaction conditions—that is, homogenous with no perfluorocarbon solvents—but still use fluorous/organic separations to facilitate product isolation.[5–10]

Much of our early work with fluorous reagents focused on *tris*-perfluorohexylethyltin compounds[7–9] because these are both readily available and highly fluorous (Figure 1). In addition to detailed studies on the tin hydride, we have made and studied the tin azide and assorted aryl and vinyl stannanes. In a number of reactions, these reagents paralleled their tributyltin analogs quite well in terms of both reactivity and selectivity. However, we likewise uncovered a number of reactions where *tris*-perfluorohexylethyltin reagents were not comparable substitutes for their tributyltin parents. This lead us to synthesize and study new reagents with different carbon numbers in both the fluorocarbon (phase tag) and hydrocarbon (spacer) parts of the chain. We report herein results in both radical and transition metal catalyzed allylations that begin to illuminate how variations of these features can clearly effect the outcome of standard reactions.

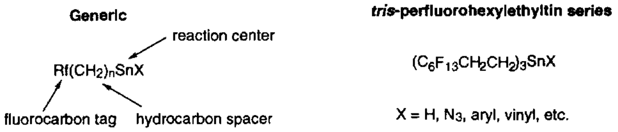

Figure 1. Fluorous Tin Reagents

Changing the length of the fluorocarbon tag and the hydrocarbon spacer can tune the reagents in a number of ways. Solubility and partition coefficients can obviously be effected. Very long fluorocarbon tails provide high partition coefficients into the fluorous phase at the price of relatively low overall solubility. Presumably, lengthening the hydrocarbon spacer should decrease partitioning into a fluorous phase. Especially when used at high concentrations, reagents with long tails could also have a "solvent effect" on reactions due to their large mass and low polarity. The length of the spacer also has clear implications on the electronic environment at tin. Taking pK_a measurements of fluorinated acids $(Rf(CH_2)nCO_2H)$ as a guide,[11] a two-carbon spacer will not be enough to

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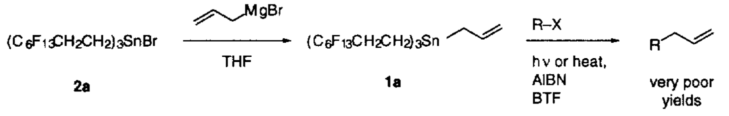
completely insulate the reacting tin center from the fluoroalkyl groups. Recent studies by Horvath and coworkers[12] provide useful data on the similarities and differences of metal-complexed fluorous and alkyl phosphines that complement our data in very different settings with tin and silicon reagents.

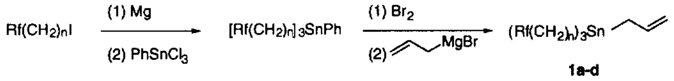
Radical Allylations of Halides: This study was initiated by some surprising observations during the study of radical allylations with ethylene-spaced fluorous tin reagent **1a** (Eq 1). This reagent is readily available by the reaction of the tin bromide **2a** with allyl magnesium bromide.[13] Radical allylations[14] with a number of allyl halides under Keck's standard thermal and photochemical conditions[15] gave disappointing results. The reactions were all inefficient, and gave mixtures of products. Over a dozen experiments were conducted (Eq 1) and expected products formed in some reactions, but none of the reactions was clean and high yielding. These poor results in radical allylations contrast the general success in radical reactions of the related fluorous tin hydride.



Eq 1

BTF = benzotrifluoride, $C_6H_5CF_3$

These failures prompted us to study the series of four allyltin reagents **1a–d** shown in Figure 2. The perfluorobutylethyl reagent **1b** is a less fluorous analog of **1a** and was made by the same method. The perfluorohexylpropyl **1c** and perfluorobutylpropyl **1d** reagents were likewise made by the same pathway starting from the known perfluoroalkylpropyl iodides.[16] All these reagents are stable, distillable liquids that were fully characterized by standard spectroscopic means.[13]



Partition coefficients[a]

	1a (Rf_6h_2)	1b (Rf_4h_2)	1c (Rf_6h_3)	1d (Rf_4h_3)
FC-72/benzene	48	9	25	4
FC-72/acetonitrle	96	6[b]	47	14

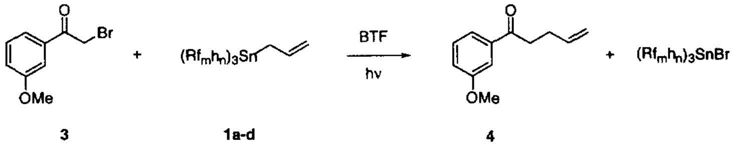
(a) about 1 g of allyltin was partitioned in a separating funnel between t two solvents. The layers were separated and evaporated.
(b) Average of two trials.

	R_f	n	Name	Abbrev.
1a	C_6F_3	2	perfluorohexylethyl	Rf_6h_2
1b	C_4F_9	2	perfluorobutylethyl	Rf_4h_2
1c	C_6F_{13}	3	perfluorohexylpropyl	Rf_6h_3
1d	C_4F_9	3	perfluorobutylpropyl	Rf_4h_3

Figure 2. Synthesis and Structure of Fluorous Allyltin Reagents

Approximate partition coefficients were measured by a simple partitioning in a separatory funnel between FC-72 (perfluorohexanes) and benzene or acetonitrile, and are shown in Figure 2. All these reagents partitioned preferentially into the FC-72 phase, but with widely different selectivities. Allyltin **1a**, which has 39 fluorines and the ethylene spacer, showed the highest partition coefficients into FC-72, followed by **1c** which also has 39 fluorines but the propylene spacer. The reagents **1b** and **1d** bearing 27 fluorines had lower but still significant partition coefficients. Unlike the other three, reagent **1b** partitioned more effectively into acetonitrile than benzene.

Radical allylations of these four reagents were conducted under identical conditions with bromoketone **3** to assess synthetic prospects (Eq 2). All the reagents are soluble in benzotrifluoride (BTF),[17] so this was selected as the common solvent. Reactions were irradiated with a sunlamp and followed by TLC until the starting ketone was consumed. After evaporation of most of the BTF, the mixtures were diluted with acetonitrile and washed a number of times with FC-72 to remove fluorous tin products to a level where they could not be detected by ^1H NMR. The data for this series of experiments are shown in Eq 2. As presaged by the earlier experiments, reactions with ethylene spaced reagents **1a** and **1b** were slow and not clean; analysis or purification of the products was pointless. In contrast, reactions with **1c** and **1d** occurred smoothly over 3 h and provided clean crude product **4** in 76 and 67% yields. Tin reagents with 39 fluorines were effectively removed by four washings of the acetonitrile by equal volumes of FC-72, while those with 27 fluorines required eight or ten washings.

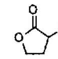
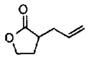
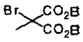
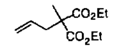
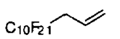
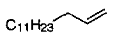
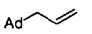
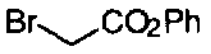
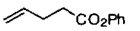
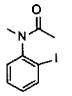
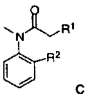
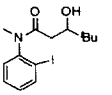
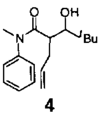


Eq 2

Tin reagent		Time (h)	Yield	FC-72 Washes	Comments
1a	Rf_6h_2	72	—	4	complex organic mixture
1b	Rf_4h_2	72	—	8	complex organic mixture
1c	Rf_6h_3	3	76%	4	clean product
1d	Rf_4h_3	8	67%	10	clean product
Control	$Bu_3SnCH_2CH{=}CH_2$	1.5	—	0	clean product, but not separated from tin

Having identified **1c** and **1d** as potentially useful radical allylating reagents, we then conducted allylations of a number of readily available halides. Table 1 lists the yields of the crude products of these reactions after fluorous/organic liquid–liquid extraction with acetonitrile/FC-72 (or sometimes dichloromethane/FC-72). The products were quite pure as assessed by ^1H NMR. Reactions were conducted under both thermal (at 80 °C) and photochemical (at 25 °C) conditions, and the selection between the two is important for some examples. For example, malonyl bromide (entries 3,4) gives a better yield under the thermal conditions than photochemical, while photochemical conditions failed entirely for entry 1.

Table 1. Radical Allylations with "Propylene Spacer" Tin Reagents

Entry	Halide	Tin	Produc	Conditions/Solvent[a]	Separation[b]	Yield
1		**1c**		A/BTF	liq–liq	94%
2	"	**1c**	"	A/C_6H_6	liq–liq	89%
3		**1c**		B/BTF	liq–liq	38%
4	"	**1c**	"	A/BTF	liq–liq	76%
5	$C_{10}F_{21}I$	**1c**		A/BTF	liq–liq	75%
6	$C_{11}H_{23}I$	**1c**		A/BTF	liq–liq	75%
7	Ad-I	**1c**		B/None	liq–liq	89%
8		**1c**		B/BTF	liq–liq	72%
9		**1c**	 c	B/C_6H_6	liq–liq	63%[c]
10		**1c**		B/BTF	liq–liq	63% 13/87 syn/ anti
11	**3**	**1d**	**4**	A/BTF	sol–liq	92%

[a] A = AIBN or benzoyl peroxide 80 °C 2–5 h; B = hv(sunlamp), 25 °C, 3–30 h. [b] liq–liq = liquid–liquid extraction; sol–liq = solid–iquid extraction. [c] 1.6/1 mixture of regioisomers, R^1 = allyl, R^2 = H and R^1 = H, R^2 = allyl

The radical translocation experiments in entries 9 and 10 are modeled after our prior work,[18] and the fluorous allyl tin reagent **1c** provides similar results to allyltributyltin in terms of chemo- (entry 9) and stereoselection (entry 10). Two of the reactions were conducted not in BTF but in benzene (entries 2 and 9). While these reactions remained cloudy over their entire course, the products were nonetheless formed in high yield. Since we generally had very poor results with two-phase tin hydride reactions,[7] we conclude that the fluorous allyl tin reagent **1c** must have a fairly substantial solubility in benzene. Two halides did not perform acceptably: $PhOCH_2CH_2I$ did give the desired product, but it was contaminated by an unknown fluorous impurity while 2-naphtylCH_2CH_2I gave a complex mixture.

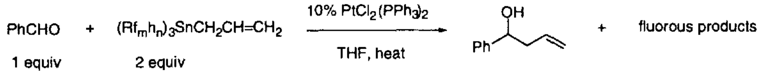
The FC-72 phases of all of the reactions with **1c** were concentrated and combined regardless of halide precursors. We did not attempt to characterize this mixture, which presumably contains tin bromides and iodides along with the allyltin reagent **1c** (which was used in excess). However, we did show that the mixture was readily recyclable. Treatment of 1.4 g of combined recovered tin product with allyl magnesium bromide followed by flash chromatography returned 1.2 g of pure allyltin **1c**. This was then reused in later experiments.

Most of the reactions were done with the F39 reagent **1c** because the prolonged extraction procedure (about 10 washings) needed for **1d** was too tedious. However, we did show with a single experiment (entry 11) that this reagent could be used in conjunction with our new solid phase extraction procedure.[9a] The reaction in Eq 2 was repeated and the crude product was passed through a short pad of fluorous reverse phase silica gel eluting with acetonitrile. Concentration of the acetonitrile produced **4** in good purity in 92% yield.

In short, the radical allylation with the propylene spacer allyltin reagents **1c** and **1d** are clearly superior to their lower homologs **1a** and **1b** and appear to be qualitatively comparable to allyltributylstannane. The results suggest that solubility is not the major factor accounting for the improved performance of the propylene spaced reagents, and the well known insensitivity of most radical reactions to solvent effects suggests that differing medium effects imparted by the fluoroalkyl chains are not responsible either. Left by default are electronic effects (usually called "polar effects" in radical chemistry), which indeed seem reasonable based on the known polarization in additions to allyltins.[14,15] We therefore tentatively conclude that despite the ethylene spacer, the unfavorable polar effects imparted by the three fluoroalkyl chains are sufficiently large to upset the favored electronic pairing in radical additions to **1a** and **1b**.

Transition Metal-Catalyzed Allylations of Aldehydes: Allyltin reagents are quite versatile and are often used as nucleophiles in various settings with electrophiles such as aldehydes.[19] We have already reported that Lewis acid promoted allylations of aldehydes with **1a** do not work well, but that thermal allylations are moderately successful.[9a] However, high reaction temperatures limit the thermal procedure, so we sought both Lewis acid promoted and transition metal catalyzed alternatives. In a separate paper, we report that propylene spaced reagents **1c** and **1d** can be used in allylations promoted by $SnCl_4$ and describe examples in a parallel setting.[20] We report herein on studies in transition metal catalyzed allylations, describing reaction conditions and studying the scope with a small parallel experiment conveniently purified by solid phase extraction.

Allylation of aldehydes with allyltributyltin are catalyzed by triphenylphosphine platinum dichloride in THF.[21] Accordingly, we studied reactions of benzaldehyde with the four fluorous allyltin reagents **1a–d**. A few reactions were worked up by using the liquid–liquid extraction procedure, but the solid-phase extraction procedure is more convenient and was used for most of the experiments. Relevant data from some of these experiments are summarized in Eq 3. In most of these experiments, isolated yields were not determined because the crude organic product, while fluorous-free, is contaminated by the catalyst and any catalyst derived byproducts.



Eq 3

Entry	Tin reagent		Temp	Time (h)	Observations from ^1H NMR of organic fraction[a]
1	**1a**	Rf_6h_2	100 °C	48	product & small organic impurities
2	**1b**	Rf_4h_2	100 °C	48	product & small organic impurities
3	**1c**	Rf_6h_3	100 °C	19	clean product
4	**1d**	Rf_6h_3	100 °C	19	clean product
5	**1c**	Rf_6h_3	100 °C	19	trace product[b]
6	**1c**	Rf_6h_3	70 °C	24	no product[b]

[a]All organic products were contaminated with the catalyst. [b]Control, no catalyst was added.

In contrast to the radical and ionic reactions, where the ethylene-spacer reagents were vastly inferior to the propylene analogs, the platinum catalyzed reactions were successful with both classes. Nonetheless, the propylene reagents were clearly more reactive (as judged by total reaction time) and gave cleaner crude products. Small, unidentified peaks were discernible in the spectra of entries 1 and 2 that could not been seen in those of 3 and 4. Control experiments in the absence of catalyst showed that a small amount (<5%) of product was formed at 100 °C but essentially no product was formed at 70 °C (entries 5, 6). To ensure that the reactions were not occurring thermally, we conducted the subsequent parallel experiment at 70 °C.

Based on their improved performance, propylene-spaced reagents **1c** and **1d** were selected for a series of eight parallel experiments. These reactions were conducted by heating 0.5 mL THF containing 0.25 mmol of aldehyde, 0.5 mmol of fluorous allyltin, and 0.025 mmol catalyst (10%) in sealed tubes at 70 °C for 24 h. Most of the THF was then evaporated and the mixtures where charged to eight parallel tubes containing 3.5 g of fluorous reverse phase silica gel.[9] The columns were eluted with 8 mL of acetonitrile, which was then concentrated. Since this concentrated organic fraction still contained catalyst residue, triphenylmethylsilane was added as a ^{1}H NMR standard and yields and conversions were determined by integration. The results of these experiments are shown in Table 2.

Table 2. Parallel Experiments with 1c and 1d.

		PhCHO	*o*-MeC$_6$H$_4$CHO	*o*-NOC$_6$H$_4$CHO	1-Naphthaldehyde
1c	conversion, yield	100%, 66%	49%, 74%	100%, 90%	85%, 84%
1d	conversion, yield	100%, 62%	49%, 67%	100%, 81%	91%, 85%

In all cases, the product spectra were free of resonances from the propylene spacer. Unfortunately, the reaction conditions determined with benzaldehyde proved too mild for the less reactive *o*-methoxybenzaldehyde and naphthaldehyde, although the more reactive *O*-nitrobenzaldehyde was completely consumed. Yields based on conversions were good, and subsequent individual experiments showed that the conversion can be increased by heating longer or at higher temperatures.

We also conducted two control experiments to probe the separation features of the chemistry. In particular, we wondered whether the fluorous features were needed at all: can polar products like alcohols be separated from normal alkyl tin reagents by a standard solid phase extraction procedure?[22] To probe this question, we reacted both allyl tributyltin and allyl trioctyltin with benzaldehyde under the standard conditions. According to TLC analysis, both reactions went smoothly to completion. Each mixture was then split in half and one portion was eluted through the fluorous reverse phase silica gel while the other was eluted through standard C18 reverse-phase silica gel under the identical conditions as in the parallel experiment. The product fractions from from both reactions contained the expected alcohol contaminated by substantial amounts of tin products. These results by no means show that chromatographic separation procedures based on standard alkyl tin reagents cannot be developed,[23] but they do suggest that the "like-attracts-like" features of the fluorous tin reagents and the fluorous silica gel are well suited to developing filtration based methods that are solid phase extractions rather than chromatographies.[24]

In the radical allylations, the change from ethylene to propylene spacer tin reagents crossed the line between failure and success. In contrast, this change in the platinum mediated allylation resulted in an incremental yet significant improvement. Clearly, it will be generally important in fluorous chemistry to investigate spacer effects when developing reagents and catalysts, and we will report separately on related studies in the tin hydride series which provide additional insights. A general problem in transition metal chemistry that uses fluorous reagents is that the simple purification procedure does not suffice to separate the catalyst residue from the desired products. In some cases where very small amounts of catalysts are used, this inadequacy may be tolerable. However, in the case at hand (10% catalyst used) it is not; the catalyst residue is easily detected in the ^{1}H NMR spectrum of the organic residue and by the crude weight yield of the products (which routinely exceeds 100%). We have recently solved this problem by making a fluorous version of the platinum catalyst, and we will report these results in due course.

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13. Allyl-tris-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecaffluorooctyll)stannane **1a**: ^{1}H NMR (CDCl$_3$) δ 5.95–5.83 (m, 1 H), 4.96–4.81 (dd, J = 16.8, 10.2, 2 H), 2.38–2.21 (m, 6 H), 1.98 (d, J = 8.5, $J_{\text{Sn-H}}$ = 33.2, 2 H), 1.13 (t, J = 8.2, $J_{\text{Sn-H}}$ = 34.4, 6 H); ^{13}C NMR (CDCl$_3$) δ 135.7, 119.6–105.2, 28.0, 16.0, –1.8; ^{119}Sn NMR (CDCl$_3$) δ –11.2; LRMS *m/z* (relative intensity): 1161 (M$^+$ – CH$_2$CH=CH$_2$, 66%), 855 (55%), 467 (21%), 327 (45%), 289 (100%), 239 (71%); IR (thin film) 2942, 1630, 1440, 1350 cm^{-1}. Allyl-tris-(3,3,4,4,5,5,6,6,6-nonafluorohexyl)-stannane **1b**: ^{1}H NMR (CDCl$_3$) δ 5.98–5.83 (m, 1 H), 4.96–4.81 (dd, J = 16.8, 10.2, 2 H), 2.43–2.21 (m, 6 H), 1.99(d, J = 8.5, $J_{\text{Sn-H}}$ = 33.1, 2 H), 1.13 (t, J = 13.0, $J_{\text{Sn-H}}$ = 71.6, 6 H); ^{13}C NMR (CDCl$_3$) δ 135.7, 122.1–106.0, 27.9, 16.1, –1.7; ^{119}Sn (CDCl$_3$) δ –10.1; LRMS *m/z* (relative intensity) 903 (M$^+$, 7%), 861 (15%), 656 (9%), 227 (17%), 189 (100%), 145 (64%); IR (thin film) 2949, 1630, 1440, 1354 cm^{-1}. Allyl-tris-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)stannane **1c**: ^{1}H NMR (CDCl$_3$) δ 5.95–5.87 (m, 1 H), 4.90–4.75 (dd, J = 16.9, 10.4, 2 H), 2.18–2.01 (m, 6 H), 1.92–1.78 (m, 8 H), 0.99 (t, J = 8.5, $J_{\text{Sn-H}}$ = 49.2, 6 H); ^{13}C NMR (CDCl$_3$) δ 136.6, 119.5–105.1, 35.5, 18.0, 15.7, 8.6; ^{119}Sn NMR (CDCl$_3$) δ –24.1. LRMS *m/z* (relative intensity) 1203 (M$^+$ – CH$_2$CH=CH$_2$, 81%), 883 (35%), 479 (12%), 341 (20%), 303 (100%); IR (thin film) 2942, 1628, 1367 cm^{-1}. Allyl-tris-(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)stannane (**1d**): ^{1}H NMR (CDCl$_3$) δ 5.98–5.84, (m, 1 H), 4.90–4.74 (dd, J = 16.9, 11.7, 2 H), 2.18–2.01 (m, 6 H), 1.92–1.77 (m, 8 H), 0.99 (t, J = 8.5, 6 H); ^{13}C NMR (CDCl$_3$) δ 136.7, 121.7–107.5, 35.5, 18.1, 15.7, 8.6; ^{119}Sn NMR (CDCl$_3$) δ –24.1; LRMS *m/z* (relative intensity) 943 (M$^+$, 8%), 903 (M$^+$ – CH$_2$CH=CH$_2$, 100%), 683 (81%), 604 (10%), 381 (18%), 241 (28%), 203 (84%); IR (thin film) 2944, 1623, 1360 cm^{-1}.
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