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Palladium-Catalyzed Stille Couplings with Fluorous Tin Reactants

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A new class of "fluorous" aryl tin reactants was investigated for use in the Stille coupling. Fluorous compounds partition into a fluorocarbon (fluorous) phase in a fluorous/organic extraction. The coupling of tris[(perfluorohexyl)ethyl]phenyl tin [$(C_6F_{13}CH_2CH_2)_3SnPh$] with bromobenzene occurs smoothly in DMF/THF (1/1) at 80 °C in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ and 3 equiv of LiCl. Partitioning between CH_2Cl_2 and FC-72 (a mixture of perfluorohexanes) provided biphenyl in 90% yield from the organic phase and tris[(perfluorohexyl)ethyl]tin chloride in >90% yield from the fluorous phase. The tin chloride was reacted with phenylmagnesium bromide to regenerate the starting tin reactant. A study to optimize reaction conditions is described, and the scope of the method is illustrated with 20 coupling reactions. The beneficial effect of lithium choride is an unusual feature of the reaction, but it also promotes the formation of some fluoroalkyl-coupled products. These can be suppressed by adding CuI. The paper describes a prototypical example of how to render a tin reactant fluorous. This process should be advantageous in small- and large-scale synthesis, as well as in automated synthesis.

Introduction

One of the current driving forces in organic synthesis is efficiency. In the small scale area, parallel synthesis is helping to make new compounds available more quickly, so the discovery of interesting new molecules becomes more efficient with respect to time.[1−3] On the large-scale front, atom economy[4] and associated needs to recycle reagents and to minimize waste provide different kinds of driving forces for chemical efficiency. Much of the effort to increase efficiency has focused on the purification stage of organic reactions, where there has been renewed interest in using simple phase separation techniques to accomplish substantive separations. For example, diverse solid-phase methods exploit the power of the simple technique of filtration.[1,2,5]

Purifications based on extractions are usually limited to the separation of neutral organic compounds from inorganic compounds or organic salts. Organic−aqueous extractions are used routinely, yet they lack the power to effect substantive separations of most types of organic compounds. Inspired by the work of Zhu[6] and Horváth and Rábai,[7] we have suggested that the "fluorous liquid phase" provides a third liquid phase of untapped potential for facilitating purifications in organic synthesis.[8,9] For extraction purposes, the fluorous liquid phase consists of low-boiling, perfluorinated or highly fluorinated hydrocarbons, ethers, and amines.[10] Many of these liquids are commercially available and are routinely used in areas outside synthetic chemistry. In the simple view,[8] the fluorous liquid phase constitutes a third extraction phase because its members are all immiscible in water, and they are immiscible in many common organic solvents as well. An assortment of two- and three-phase extractions can be conducted with fluorous, organic, and water (acid, base, or neutral) phases.

Organic compounds will not generally partition into a fluorous phase, so the use of a fluorous phase in an extraction requires that at least one of the reaction components be neither organic nor inorganic but fluorous. Our research is focusing methods to convert organic compounds to fluorous ones for use in synthesis. This was accomplished in a "permanent" fashion by Horváth and Rábai,[7] who prepared and used a fluorous phosphine: $(C_6F_{13}CH_2CH_2)_3P$. We have recently introduced a new tin hydride[11] [$(C_6F_{13}CH_2CH_2)_3SnH$] as example of a fluorous reagent (and catalyst), and we have communicated the use of fluorous aryltin reactants[11] for Stille couplings.[12a] In these embodiments of the fluorous strategy, the substrate and the product are organic and one of the other reaction components and its byproduct are fluorous. More recently, we have used organic and inorganic reagents in combination with "temporarily" fluorous substrates and products.[13] In this paper, we report the full details of our study of the Stille coupling

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with fluorous aryltin reactants.[12a] In a parallel paper, we describe a microwave version of this reaction that is both convenient and of broad scope.[12b]

The Stille,[14] Suzuki,[15] and related cross couplings have made accessible, even routine, the formation of many kinds of carbon−carbon bonds that were previously difficult to make under mild conditions. Solid-phase variants have recently been introduced.[16] The defining feature of the Stille coupling is the use of a trialkyltin reagent in a palladium-catalyzed coupling with a halide or triflate. The alkyl groups, usually methyl or butyl,[17] are designed as "non-transferable" ligands, and the fourth ligand on tin is coupled to a halide or triflate.

$$(\mathrm{Alkyl})_3\mathrm{Sn{-}R}^1 + \mathrm{R}^2\text{-X} \xrightarrow{\mathrm{Pd}^0} \mathrm{R}^1{-}\mathrm{R}^2 + (\mathrm{Alkyl})_3\mathrm{Sn{-}X} \qquad (1)$$

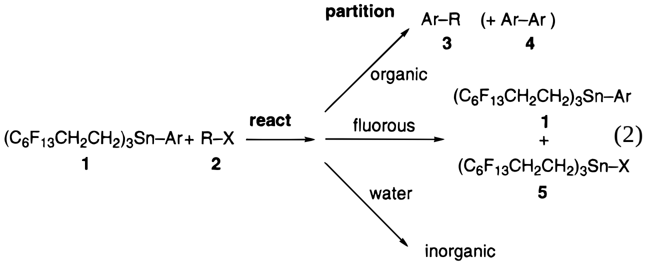
Alkyl = Me, Bu X = I, Br, Cl, OTf
R^1= sp, sp^2, allyl, etc.

The Stille reaction is popular because of its scope and functional group tolerance and because tin reagents are easy to make and are very stable compared to most organometallic derivatives. Like most areas of tin chemistry, the detractions come not in the reaction stage but in the purification stage. Low molecular weight trialkyltin compounds are toxic, can be difficult to separate, and are rarely recovered and recycled. Comparing the tin derivatives used in the Stille couplings, trimethyltin halides are easy to remove because of their water solubility and volatility, but they are toxic. Also, methyl transfer sometimes occurs as a significant side reaction with trimethyltin reagents. Tributyltin halides are less toxic but much more difficult to remove because they are nonvolatile and insoluble in water but soluble in most common organic solvents.[18]

These features make the Stille coupling a prime target as a test for the strategy of using fluorous reactants. We therefore set out to see if aryltin reagents could be rendered "fluorous" by suitable substitutions and to learn (1) whether the resulting reactants were suitable for Stille couplings and (2) whether the expected purification features of the fluorous method were manifested.

Results and Discussion

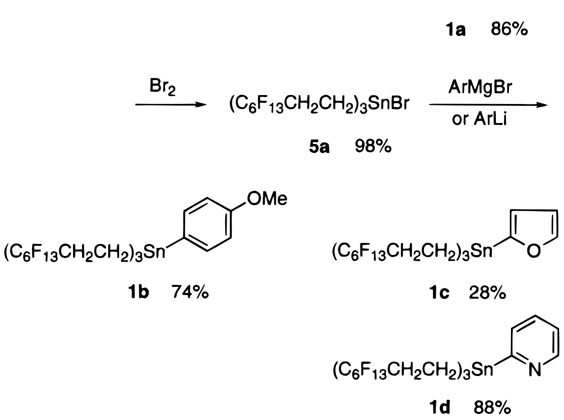
Equation 2 shows the reaction and purification strategy for Stille couplings with fluorous tin reactants. We decided to synthesize and study the reactions of tris(2-(perfluorohexyl)ethyl]aryltin [**1**, $(\mathrm{C_6F_{13}CH_2CH_2})_3\mathrm{SnAr}$] as a prototypical example of a fluorous tin reagent. Compound **1** has perfluorohexylethyl groups in place of the usual butyl groups as nontransferable ligands on tin. The perfluorohexyl group supplies fluorous solubility while the ethylene spacer[7] serves to insulate the tin from the powerful inductive effect of the perfluorohexyl group.



(2)

The procedure is designed to facilitate the purification of the target organic product and to allow ready recovery of fluorous tin compounds for reuse. In the reaction stage of the Stille coupling, a substrate **2** is treated under typical Stille conditions with **1**, which can be used either in stoichiometric quantities or in excess. The purification stage begins with three-phase extraction between an organic solvent, a fluorous solvent, and water. The organic phase of the extraction contains the target cross-coupled product **3** along with a small amount of homocoupled product **4** derived from **1**. (Homocoupling is a common side reaction in Stille couplings.)[14] The fluorous phase contains excess **1**, if any, and the fluorous tin halide **5**, which can readily be recycled to the same or a different fluorous tin reactant. The water phase contains inorganic salts, and this is discarded. If necessary, the organic components of the reaction can be further separated by conventional means.

Equation 3 shows the syntheses of the main fluorous tin reactants used in this study. Preparation of the Grignard reagent from commercially available 2-(perfluorohexyl)-1-iodoethane and quenching with phenyltrichlorotin provided fluorous phenyltin reactant **1a** [tris[2-(perfluorohexyl)ethyl]phenyl tin].[11] Brominolysis



(3)

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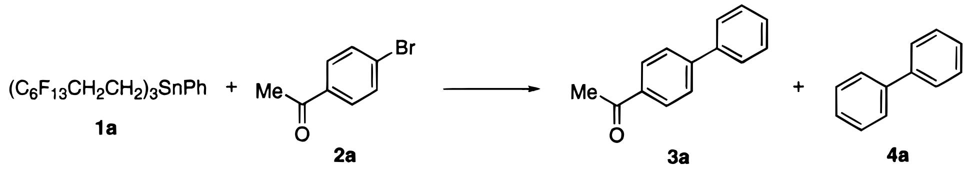
Table 1. Effect of Varying Reaction Conditions on the Coupling between 1a and Aryl Halide 2a[a]



entry	catalyst	LiCl	solvent	T (°C)	% yield of **3a**[b]	% yield of **4a**[c]
1	$PdCl_2(PPh_3)_2$	−	THF	67	incomplete (both **2a**/**3a**[d])	
2	$PdCl_2(PPh_3)_2$	+	THF	67	90	6
3	$Pd(PPh_3)_4$	+	THF	67	incomplete (mostly **2a**[d])	
4	Pd_2dba_3+$AsPh_3$[e]	+	THF	67	incomplete (both **2a**/**3a**[d])	
5	$PdCl_2(PPh_3)_2$	−	DMF	80	incomplete (both **2a**/**3a**[d])	
6	$PdCl_2(PPh_3)_2$	+	DMF	80	82	5
7	$Pd(PPh_3)_4$	+	DMF	80	88	5
8	Pd_2dba_3+$AsPh_3$[e]	+	DMF	80	incomplete (mostly **2a**[d])	
9	Pd_2dba_3+$AsPh_3$[e]	+	NMP	80	incomplete (both **2a**/**3a**[d])	
10	Pd/C+$AsPh_3$+CuI[f]	−	NMP	80	incomplete (mostly **2a**[d])	
11	$PdCl_2(PPh_3)_2$	+	BTF	80	incomplete (both **2a**/**3a**[d])	

[a] Reactions were performed for 46 h under N_2, 48 mM **1a**, 40 mM **2a**, 0.8 mM catalyst unless otherwise stated, 0.12 M LiCl if it was added. [b] Isolated yield based on **2a**. [c] Isolated yield based on **1a**. [d] Estimated by TLC with UV visualization; mostly **2a** = TLC spot for **2a** clearly larger; mostly **3a** = TLC spot for **3a** clearly larger; both **2a**/**3a** = TLC spots roughly comparable. [e] 0.4 mM Pd_2dba_3, 3.2 mM $AsPh_3$. [f] 0.24 mM Pd/C, 8 mM $AsPh_3$, 4 mM CuI.

of **1a** provided the tin bromide **5a**, which served as the precursor for preparing the 4-methoxyphenyl (**1b**), 2-furyl (**1c**), and 2-pyridyl (**1d**) fluorous tin reactants by standard reactions with either Grignard or aryllithium reagents. As an aside, the tin bromide **5a** also serves as the precursor for a fluorous tin hydride[11] and several other fluorous tin reagents.[14]

A number of efficient reaction conditions for Stille couplings now exist,[15a−e] and we initially surveyed some of these to identify any characteristic behavior of fluorous tin compounds. At the outset, we were seriously concerned that fluorous tin reactants might be less reactive than standard alkyltin reagents. While little is known about the effects of electron-withdrawing groups on the "dummy ligands" of tin, it is well-known that the R_3SnX (X = halide) products of Stille couplings are very resistant to a second Stille coupling. This raises the concern that the perfluoroalkyl groups might retard Stille couplings if the ethylene spacer were an insufficient insulator. In addition to the effects on transmetalation, we viewed with special importance the task of identifying suitable reaction solvents because the fluorous tin reagents are not "organic" (as measured by fluorous/organic extraction) and because Stille couplings are often affected by the combination of reaction solvent, Pd catalyst, and additive.

An initial series of experiments was conducted with fluorous phenyltin reactant **1a** and 4′-bromoacetophenone (**2a**), and the results of some of these experiments are shown in Table 1. Reactions were conducted in THF, DMF, and NMP (*N*-methylpyrrolidinone), with an assortment of catalysts in the presence and absence of lithium chloride. A 20% excess of fluorous phenyl tin reagent **1a** was used relative to **2a**. Reactions judged complete by TLC were worked up by three-phase extraction, and the isolated yields of the cross-coupled and homocoupled products were determined by preparative TLC. Many of the reactions were still incomplete after 46 h, and these were not worked up or purified. For these we provide a very rough estimate of the progress of the reaction. This estimate is based on TLC spot intensity, so it has no quantitative meaning. Furthermore, reaction rates were not measured, so we cannot differentiate reactions that are inherently slow from those that proceeded for some time prior to catalyst deactivation. This differentiation was not deemed crucial at this stage since neither type of reaction is suitable for preparative purposes.

THF was the first solvent that we tried because it has good dissolving power for both organic and fluorous compounds. Indeed, the reactions in THF were homogeneous from start to finish as judged by the naked eye (Table 1, entries 1−4). While the reaction with $PdCl_2(PPh_3)_2$ at reflux in the absence of LiCl was slow and incomplete even after 46 h (Table 1, entry 1), the same reaction in the presence of 3 equiv of LiCl was complete and gave 90% yield of desired cross-coupled product **3a** and 5% yield of homocoupled product **4a** derived from **1a** (Table 1, entry 2). These results are interesting because LiCl is not usually beneficial in reactions of normal aryltin reactants with aryl halides. The effect of LiCl and other additives was later studied in more detail as described below. The reaction with $Pd(PPh_3)_4$ and LiCl in THF proceeded very slowly and was incomplete after 16 h (Table 1, entry 3), while Pd_2dba_3 + $AsPh_3$ + LiCl[19] was an even less effective combination (Table 1, entry 4).

Next, the use of DMF as reaction solvent was studied (Table 1, entries 5−8). At the standard reaction concentration (0.05 M in **1a**), DMF partially dissolves fluorous phenyltin **1a** at 80 °C, and it dissolves the fluorous tin chloride **5b** even better. The reaction mixture in DMF was two phases at the beginning, and then it became homogeneous as the reaction proceeded. In DMF at 80 °C with LiCl present, $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ both catalyzed the reaction well (Table 1, entries 6 and 7). However, in the absence of LiCl the reaction was again slow and incomplete (Table 1, entry 5). Pd_2dba_3 + $AsPh_3$ did not give complete conversion in either DMF or NMP (Table 1, entries 8 and 9), though the NMP reaction mixture was homogeneous from the beginning. The reaction with Pd/C + $AsPh_3$ + CuI[20] in NMP also did not proceed well (Table 1, entry 10). The partially fluorinated solvent BTF (benzotrifluoride, $C_6H_5CF_3$) dissolves both **1a** and **2a** even at room temperature, but the

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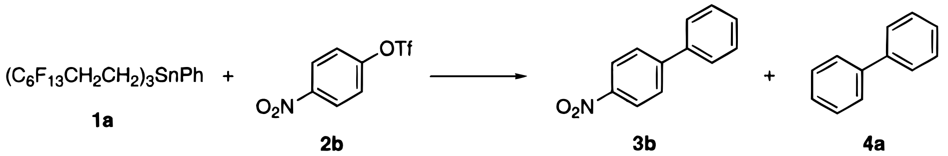
Table 2. Effect of Varying Reaction Conditions on the Coupling between 1a and Aryl Halide 2b[a]



entry	catalyst	LiCl	solvent	T (°C)	% yield of **3b**[b]	% yield of **4a**[c]
1	$PdCl_2(PPh_3)_2$	+	THF	67	incomplete (trace **3b**[d])	
2	$Pd(PPh_3)_4$	+	THF	67	no reaction	
3	Pd_2dba_3+$AsPh_3$[e]	+	THF	67	incomplete (trace **3b**[d])	
4	$PdCl_2(PPh_3)_2$	+	dioxane	100	no reaction	
5	$Pd(PPh_3)_4$	+	dioxane	100	no reaction	
6	$PdCl_2(PPh_3)_2$	+	DMF	80	82	9
7[f]	$Pd(PPh_3)_4$	+	DMF	80	70[g]	6

[a] Reactions were performed under N_2 for 25 h except entry 7, 48 mM **1a**, 40 mM **2b**, 0.8 mM catalyst unless otherwise stated, 0.12 M LiCl if it was added. [b] Isolated yield based on **2b**. [c] Isolated yield based on **1a**. [d] Observed by TLC with UV visualization. [e] 0.4 mM Pd_2dba_3, 3.2 mM $AsPh_3$. [f] Reaction was performed for 46 h. [g] 17% of *p*-nitrophenol was also isolated.

Table 3. Use of Mixtures of Reaction Solvents for the Coupling between 1a and Aryl Halide 2a Catalyzed by $PdCl_2(PPh_3)_2$ in the Presence of LiCl[a]

entry	solvent	T (°C)	reaction time (h)	yield (%) **3a**[b]	yield (%) **4a**[c]
1	DMF	80	46	82	5
2	DMF/THF (1:1)	67	22	90	7
3	DMF/BTF (1:1)	67	22	92	9

[a] Reactions were performed under N_2, 0.24 M **1a**, 0.20 M **2a**, 4 mM $PdCl_2(PPh_3)_2$, 0.6 M LiCl. [b] Isolated yield based on **2a**. [c] Isolated yield based on **1a**.

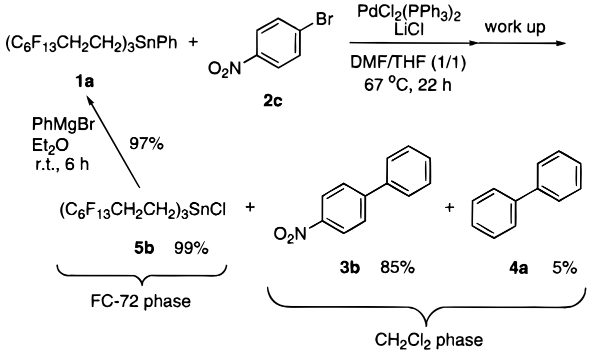
reaction in BTF with $PdCl_2(PPh_3)_2$ was only about half complete after 46 h (Table 1, entry 11).

Next, we studied the coupling of 4-nitrophenyl triflate **2b** because triflates often require different reaction conditions from halides (Table 2). It is expected from past studies[15l,n] that LiCl will be required for the triflate coupling, so this was included in all reactions. In THF, none of the catalysts tried gave significant amounts of the Stille product **3b** after reflux for 25 h (Table 2, entries 1−3). Reactions in dioxane at 100 °C were homogeneous but gave no product **3b** at all (Table 2, entries 4 and 5). On the other hand, in DMF at 80 °C, both of $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ catalyzed the reaction well, but $PdCl_2(PPh_3)_2$ gave a better isolated yield (82%) of **3b** in a shorter reaction time (Table 2, entries 6 and 7).

These results suggested that the use of $PdCl_2(PPh_3)_2$ in the presence of LiCl in DMF provided a single set of reaction conditions suitable for couplings with both halides and triflates. That common reaction conditions can be used for different types of substrates is advantageous for parallel synthesis. However, these reactions were still rather slow in some cases. To provide better solubility for the fluorous tin reagent, we used mixtures of DMF and another solvent. Equal parts of DMF/THF and DMF/$C_6H_5CF_3$ both gave homogeneous reaction mixtures from the start, and the reactions occurred at reasonable rates (<22 h) at 67 °C to provide a high yield of desired product **3a** (Table 3). The use of $PdCl_2(PPh_3)_2$ in the presence of LiCl in DMF/THF mixture (1/1) was selected for the standard experiments. As we describe below, the reaction time in DMF/THF can be reduced to 10 h by heating at 80 °C in a sealed tube.

We selected FC-72 as the fluorous solvent for the three-phase extraction that is the crucial feature of the purification stage. This is a commercially available fluorocarbon fluid that is part of the 3M Fluorinert Liquids family. It consists mostly of isomers of perfluorohexane C_6F_{14} with the linear isomer being the major one. FC-72 has a convenient boiling point (56 °C), and it provides favorable partition coefficients for the fluorous tin reagents when paired with many organic solvents; however, it is rather inexpensive (1 L ≈ \$200). FC-77 (perfluorooctanes) can be used interchangeably with FC-72, and although the price of FC-77 is about the same as FC-72, its higher boiling point (90 °C) makes it easier to recover for reuse. Simple extractions demonstrated that fluorous tin reactants **1a** and fluorous tin byproduct $(C_6F_{13}CH_2CH_2)_3SnCl$ (**5b**) readily partition into the FC-72 phase. We estimate that the partition coefficients of **1a** and **5b** between FC-72 and either dichloromethane or toluene are ≥97/3. However, DMF does have a detrimental effect on the fluorous tin halide partitioning (see below).

A preparative reaction was conducted with phenyltin reactant **1a** (2.4 mmol) and 1-bromo-4-nitrobenzene **2c** (2 mmol) in the presence of $PdCl_2(PPh_3)_2$ (4×10^{-3} mmol) and LiCl (6 mmol) in 10 mL of 1/1 DMF/THF at 67 °C for 22 h (eq 4). Both the substrate **2c** and tin reactant **1a** were consumed according to TLC analysis. The reaction mixture was evaporated with toluene at 75 °C (to remove the THF and some of the DMF) and then partitioned in a three-phase extraction between water (top), dichloromethane (middle), and FC-72 (bottom). After this first extraction, only 81% of fluorous tin chloride **5b** was recovered from the FC-72 phase. The dichloromethane phase was then washed three more times with water and FC-72 (together) to remove the remaining fluorous products and DMF. Evaporation of



(4)

Table 4. Yields[a] of Cross-Coupled Products 3 Formed from Fluorous Tin Reactants 1 and Substrates 2[b,c]

substrate **2**	tin reactant **1** **1a** (% yield)	 **1b** (% yield)	 **1c** (% yield)
C_6H_5I	90[d,e]	97 (10)	45[f]
4-$CH_3COC_6H_4Br$, **2a**	90 (7)	87 (6)	72
4-$NO_2C_6H_4Br$, **2c**	94 (9)[e]	98 (8)	93
4-$NO_2C_6H_4OTf$, **2b**	82 (9)[g]	86 (8)[h]	83
$C_6H_5CH_2Br$	77 (5)	98 (7)	32[f]

[a] Isolated yield based on **2**. [b] Unless otherwise stated, reactions were performed in sealed tubes at 80 °C for 22 h under N_2, **1** (0.24 mmol), **2** (0.2 mmol), $PdCl_2(PPh_3)_2$ (4×10^{-3} mmol), LiCl (0.6 mmol), mixture (1:1) of DMF/THF (1 mL). [c] Isolated yields (%) of symmetrical biaryl **4** based on **1** in parentheses. [d] **3** and **4** are the same (biphenyl). [e] Solvent was THF (5 mL), in unsealed tube at 67 °C for 9 h. [f] Volatile product. [g] Solvent was DMF (5 mL), in unsealed tube at 80 °C for 25 h. [h] About 10% of 4-nitrophenol was also isolated.

these combined fluorous phases provided 18% more of the tin chloride **5b**, raising its total recovered yield to 99%.

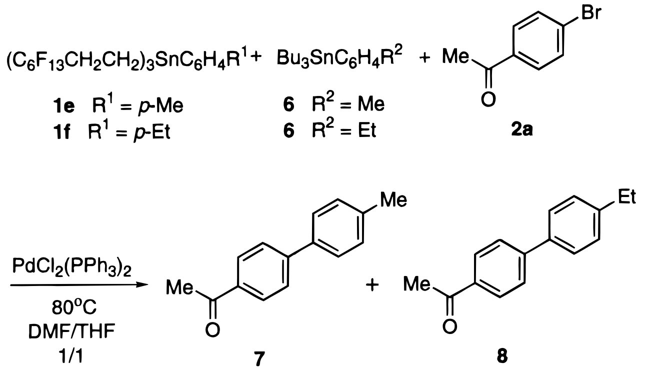
The crude organic product from the dichloromethane phase was purified by flash chromatography to provide 4-nitrobiphenyl (**3b**) (85% yield based on **2c**) and biphenyl (**4a**) (5% yield based on **1a**). The crude fluorous tin chloride **5b** from the FC-72 phase was treated with phenylmagnesium bromide to provide the original tin reactant **1a** (96% overall yield from original **1a**) after purification by passing through a short column of neutral alumina.

To survey the scope of the reaction, we conducted 20 small-scale (0.2 mmol) Stille reactions. Couplings between various fluorous tin reactants (**1a**–**d**) and halides or triflates (**2a**–**e**) were performed under the standard reaction conditions in sealed tubes at 80 °C for 22 h. Reactions were conducted in individual vessels in groups of five (one tin reagent was reacted simultaneously in different flasks with all five partners). After the reaction, each mixture was evaporated to remove some of the solvent, and a three-phase extraction was conducted as above. Evaporation of the FC-72 phase provided the byproduct fluorous tin chloride **5b** (80–90% yield),[21] which was routinely recycled (see above). Evaporation of the organic phase provided a crude organic product that was further purified by preparative TLC to provide the major cross-coupled biaryl or diarylmethane **3** along with small amounts of the symmetrical biaryl **4** derived from the tin reactant **1**. The results of the 15 most successful couplings are shown in Table 4.

Tin reactants **1a**–**c** gave very clean crude products with all partners. Isolated yields of **3** were generally high (>80%), except for a few cases with the furyl tin reactant **1c** where the products are somewhat volatile and unstable.[22] For **1a,b** the isolated yields of the symmetrical biaryl **4** (biphenyl from **1a** and 4-methoxybiphenyl from **1b**) ranged from 5 to 10%. We believe that comparable amounts of bifuryl were formed from **1c**, but isolated yields (not shown) were much lower because this compound is volatile and unstable.

The five crude organic products from the pyridyl tin reactant **1d** were not very clean, so these reaction mixtures were not fully purified. Significant amounts of cross-coupled products (estimated 25–50%) were produced with 4-nitrophenyl triflate and bromide and with iodobenzene; however, yields of pure products were not determined. These poor results parallel observations under similar conditions with the related pyridyltributyltin reagent.[23]

Table 5. Comparison Between Fluorous Tin Reactants 1e,f and Butyltin Reactants 6a,b



entry	LiCl	R^1	R^2	ratio **7**/**8**	yield (%)	reactn time (n)
1	+	Et	Me	1/2.3	91	1
2	−	Et	Me	1.8/1	84	8
3	+	Et	Me	1.8/1	80	1
4	−	Me	Et	1/2.1	85	20[b]

[a] Reactions were performed in sealed tubes under Ar with 0.4 M **1e**,**f** 0.2 M **2a**, 0.004 M Pd, and 0.6 M LiCl (if used). [b] At 75% conversion.

To compare the reactivities between fluorous tin reactants and normal tin reactants, we conducted a series of simple competition experiments, as summarized in Table 5. The new fluorous tin reactants **1e** (*p*-methylphenyl) and **1f** (*p*-ethylphenyl) were prepared by the standard route (see eq 1). Each of these was then coupled in competition with the corresponding tributyltin derivative **6a** or **6b** under a fixed protocol where 1 equiv of *p*-bromoacetophenone **2a** was reacted with 2 equiv each of a pair of tin reagents in the presence and absence of lithium chloride.

In the presence of lithium chloride, the fluorous reactants **1e** and **1f** were more reactive than **6a** or **6b** by a factor of about 2 (Table 5, entries 1 and 3). As expected, the reactions were fast (only 1 h) and high yielding. In contrast, the normal trialkyltin reagents won out by a factor of about 2 when reactions were conducted in the absence of lithium chloride (Table 5, entries 2 and 4). These reactions were much slower; indeed, the coupling of **1e** with **6b** appears to stop due to catalyst deactivation. This reaction was terminated after 20 h, at which time about 25% of *p*-bromoacetophenone still remained. These results show that the coupling of the fluorous tin reactants is promoted by LiCl, as anticipated from the results in Table 1.

In the two experiments containing lithium chloride in Table 5, we noticed resonances for a small impurity that was not present in the experiments without lithium chloride. Especially characteristic was a multiplet of about δ 3.0 that we attributed to the benzylic methylene protons of **9a**, the product of cross-coupling between **2a** and a fluoroalkyl group of **1e** or **1f** (eq 5). The analogous

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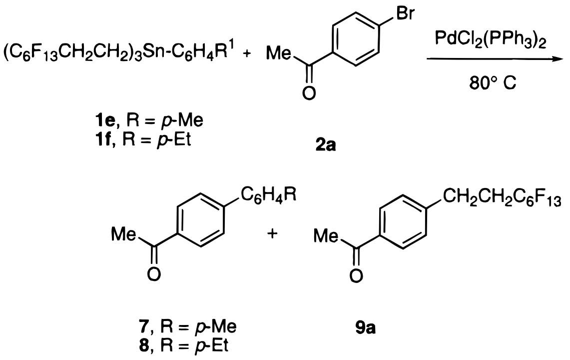
(21) Most of the residual 10–20% remained in the organic phase. If desired, this can be removed by washing with FC-72, as shown in the preparative procedure.

(22) Pelter, A.; Rowlands, M.; Clements, G. *Synthesis* **1987**, 51.

(23) See, Gronowitz, S.; Bjórk, P.; Malm, J.; Hórnfeldt, A.-B. *J. Organomet. Chem.* **1993**, *460*, 127. The yield problem can be solved by adding copper salts. This technique is likewise successful in the microwave variant of the fluorous Stille coupling (ref 12b).

product of butyl transfer is a well-known side product in the Stille coupling.[14,24]



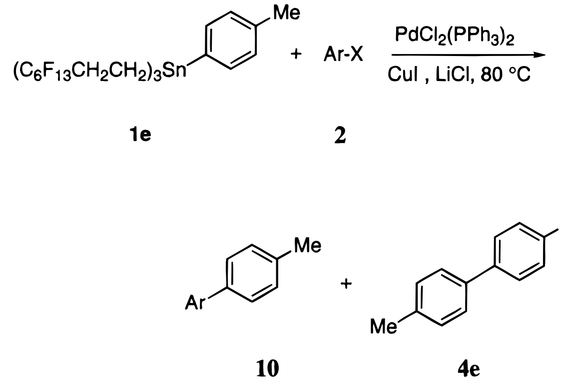
(5)

1e, with LiCl, **7**/**9a**, 90%, 9/1, 1 h
1e, without LiCl, **7** only, 79%, 24 h
1f, with LiCl, **8**/**9a**, 77%, 15/1, 1 h
1f, without LiCl, **8** only, 80%, 24 h

An attempt to prepare an authentic sample of **9a** by reaction of $(C_6F_{13}CH_2CH_2)_4Sn$ with **2a** was not successful, nor was it possible to separate this product from the major cross-coupled product. However, GCMS analysis of preparative reactions provided clear evidence for the structure of **9a**. Coupling of **1e** and **1f** with **2a** provided different major products but the same side product in ratios of 9/1 and 15/1, respectively, according to ^{1}H NMR analysis. A GCMS analysis of the minor peak showed a molecular ion peak for **9a** at *m*/*e* 466 with a large fragmentation peak of *m*/*e* 451 ($M^+ - Me$). In contrast to the failure to prepare pure **9a**, we were able to prepare and characterize the related product *p*-$NO_2C_6H_4CH_2CH_2C_6F_{13}$ **9b** by cross coupling of $(C_6F_{13}CH_2CH_2)_4Sn$ with *p*-$NO_2C_6H_4Br$, although the yield was poor (15%, see the Experimental Section). Reviews of the crude ^{1}H NMR spectra for some of the other products in Table 4 also showed resonances consistent with the formation of this side product in low yield (0−10%).

Farina and Liebeskind[21] have shown that CuI can be used to suppress butyl transfer in normal Stille couplings with aryltributylstannanes. We therefore conducted a series of couplings of **1e** with several halides as shown in Table 6. Indeed, the production of fluoroalkyl-coupled products was suppressed, and yields were generally good. The only exception was with *p*-methoxybromobenzene (not shown). This reaction appeared to stop after a 1 h (Pd black observed), and a 1/1 mixture of product and starting material was obtained. As before, LiCl was essential; a control reaction in its absence rapidly deposited palladium black and the starting materials were not consumed.

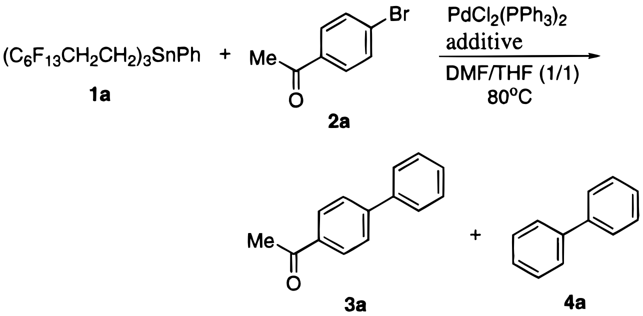
Table 6. Yields of Cross-Coupled Products 10 Formed from Fluorous Tin Reactants 1e and Substrates 2 with CuI[a]



substrate **2**	time (h)	**10** (% yield)[b,c]	**4e** (% yield)[d]
4-$MeCOC_6H_5Br$	3	98	
4-$NO_2C_6H_4Br$	6	98	6
4-$NO_2C_6H_4OTf$	6	91	11
C_6H_5I	1	95	
$C_6H_5CH_2Br$	2	72	16

[a] Reactions were performed in sealed tubes under argon, 0.24 M **1e**, 0.2 M **2**, 4 mM $PdCl_2(PPh_3)_2$, 0.6 M LiCl, 16 mM CuI, DMF/THF (1:1). [b] Isolated yields based on **2**. [c] No fluoroalkyl transfer was observed. [d] Isolated yields based on **1e**.

Table 7. Effect of Additives on the Coupling of Fluorous Tin Reactant 1a and Aryl Halides 2a[a]



entry	additive[b]	reaction time (h)	% yield of **3a**[c]	% yield of **4a**[d]
1	LiCl (3 equiv)	10	89	6
2	no additive	46[e]	77	7
3	LiCl (0.4 equiv)	46[e]	77	6
4	LiCl (1.2 equiv)	24	84	10
5	LiBr (3 equiv)	10	72	12
6	LiI (3 equiv)	46[e]	86	13
7	Bu_4NCl (3 equiv)	10	80	5
8	Bu_4NI (3 equiv)	46[e]	86	4
9	$LiCl_4O$	46	90	8

[a] Reactions were performed in sealed tubes at 80 °C under N_2, 0.24 M **1a**, 0.20 M **2a**, 4 mM $PdCl_2(PPh_3)_2$. [b] Equiv was based on **2a**. [c] Isolated yield basded on **2a**. [d] Isolated yield based on **1a**. [e] Even after 46 h, some amount of **2a** remained.

With normal trialkyltin reactants, LiCl generally does not affect the couplings when the partners are aryl halides, but it is necessary to induce couplings when partners are triflates. In the later case, the chloride ion is thought to convert the organopalladium triflate complex to the more reactive organopalladium chloride complex before transmetalation.[14l,n,25] To provide more insight into the unusual observations with the fluorous tin reagents, we studied effects of LiCl and other additives on the coupling between fluorous tin reactant **1a** and aryl halide **2a** in detail as shown in Table 7. All reactions were run under the standard conditions; only the nature and amount of additive were varied.

At 80 °C in a sealed tube, the coupling in the presence of 3 equiv of LiCl was complete (both **1a** and **2a** were consumed according to TLC analysis) within 10 h (Table 7, entry 1). On the other hand, the coupling in absence of LiCl proceeded very slowly and was unfinished even after 46 h (Table 7, entry 2). The addition of 0.5 equiv of LiCl promoted the coupling at first (as judged by TLC), but the effect tapered off and in the end the reaction required almost as much time as that without LiCl (Table 7, entry 3). These observations are consistent with the

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(24) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434.

isolation of the tin chloride **5b** from all the reactions with bromides and triflates. As the reaction progresses, the lithium chloride is consumed on a stoichiometric basis. With the use of 1.2 equiv of LiCl, the reaction rate was not as high as with the use of 3 equiv of LiCl, but the coupling proceeded to completion in 24 h and provided a good yield of **3a** (Table 7, entry 4).

The replacement of LiCl with other salts was studied. LiBr (Table 7, entry 5) and Bu_4NCl (Table 7, entry 7) enhanced the reaction rate at a level roughly comparable to LiCl, but LiI (Table 7, entry 6), Bu_4NI (Table 7, entry 8), and $LiClO_4$ (Table 7, entry 9) had modest rate enhancement at best. All additives in Table 7 except LiBr eventually gave the desired product **3a** in more than 80% yield. The reaction with LiBr was not as clean as the others, and unidentified byproducts were formed. The use of Bu_4NCl and Bu_4NI caused a problem in the three-phase extraction because the first dichloromethane phase contained all the tetrabutylammonium salts and a considerable amount (about 70%) of fluorous tin halides. Considering the results in every respect (reaction time, yield of desired product **3a**, and workup), LiCl was the best of the additives that were studied here.

It is not currently clear why the chloride ion improves the Stille couplings with fluorous tin reactants. One possibility is that an interaction between the chloride ion and the fluoroalkyltin reagent helps to promote transmetalation. However, it is also clear from our results that the lithium chloride helps preserve the active catalyst, so it is possible that there is no specific interaction of the chloride ion with the fluorous tin reagent. However, if the chloride ion is operating only with the catalyst, it is not clear why the relative reactivity of tributyltin and fluoroalkyltin reagents is changed by the presence or absence of LiCl.

Conclusions

Although the scope and generality of fluorous Stille couplings will only be revealed by more extensive studies, the results reported herein provide an encouraging outlook. Despite the alteration of solubility that attends the use of the fluorous tin reagents, Stille couplings still occur smoothly in a number of organic solvents that can solubilize both organic and fluorous compounds. While the beneficial effect of lithium chloride was unanticipated, the reaction conditions and results with the fluorous aryltin reactions otherwise seem to parallel those of standard alkyltin reactants.

In the purification stage, the fluorous reagents exhibited the anticipated advantages. From the standpoint of traditional organic synthesis, the simple extractive separation not only allows the convenient separation of the fluorous tin products from the organic products but also facilitates the recycling of the resulting fluorous tin chloride to the same or another fluorous tin reagent. Indeed, we routinely recycle our fluorous reagents, and some of the couplings reported in this paper were doubtless conducted with the same individual tin group or with a tin group that had been used previously in a different kind of reaction. The material balance with respect to the fluorous component is consistently excellent, often nearly quantitative, adding an additional attraction to the recycling strategy. We are reporting separately on additional extensions of the fluorous tin and silicon chemistry.[14]

The chemistry also exhibits favorable features for small-scale parallel synthesis. In this kind of chemistry, disposal and recycling are lesser concerns, but there is a premium placed on simple and effective separations. Assuming that simple two- and three-phase extractions could be automated, it would be possible to use excess fluorous reactants or reagents and to separate all the organic products both from the excess reagents themselves and from any byproducts derived from their reactions (provided that the byproducts retain the fluorous group).

Experimental Section

General Methods. Reactions were carried out under nitrogen using dried glassware. Anhydrous DMF, NMP, BTF, and dioxane were obtained from Aldrich. THF and diethyl ether were obtained by distillation from sodium/benzophenone prior to use. FC-72 was obtained from 3M. In the ^{119}Sn NMR spectra, chemical shifts are relative to tetramethyltin.

Tris(3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl)phenyltin (Tris[2-(Perfluorohexyl)ethyl]phenyltin) (1a).[11] To the Grignard reagent, prepared from 2-(perfluorohexyl)-1-iodoethane (100.0 g, 211 mmol) and magnesium (6.53 g, 269 mmol) in dry ether (150 mL), was added phenyltin trichloride (15.9 g, 52.7 mmol) dissolved in dry benzene (100 mL). After being refluxed for 4 h, the reaction was stirred for 16 h at 25 °C. The reaction mixture was quenched with NH_4Cl solution, and the organic phase was washed with 5% $Na_2S_2O_3$ solution and deionized water and then dried over anhydrous $MgSO_4$. The mixture was concentrated under reduced pressure. After removal of the major byproduct, 1,4-bis(perfluorohexyl)butane, by vacuum distillation (87−92 °C, 0.2 mmHg), the resulting residue was purified by column chromatography on neutral alumina with hexane to give pure compound **1a** (56.1 g, 86%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.41 (s, 5 H), 2.31 (m, 6 H), 1.31 (t, $J = 8.3$ Hz, ^2J ($^{119}Sn-H$) = 53.4 Hz, 6 H); ^{119}Sn NMR ($CDCl_3$) −11.7 ppm; IR (thin film) 3100, 2950, 1238, 1190, 1144, 655 cm^{-1}; MS *m/z* 1161 ($M^+ - Ph$), 891 ($M^+ - CH_2CH_2C_6F_{13}$).

BromoTris(3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl)tin (Bromotris[2-(perfluorohexyl)ethyl]tin) (5a). Bromine (5.83 g, 36.5 mmol) in ether (10 mL) was added dropwise to an ice-cold solution of **1a** (43.0 g, 34.8 mmol) in dry ether (80 mL). The mixture was warmed to 25 °C over 2 h with stirring. Removal of the ether, bromobenzene, and excess bromine by evaporation under reduced pressure resulted in an orange oil. Purification by vacuum distillation (150−152 °C, 0.5 mmHg) yielded compound **5a** (42.4 g, 98%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 2.42 (m, 6 H), 1.56 (t, $J = 8.3$ Hz, ^2J ($^{119}Sn-H$) = 53.4 Hz, 6 H); ^{119}Sn NMR (hexane) 259.2 ppm (m); IR (thin film) 3600, 1250, 1227, 1145, 534 cm^{-1}; MS *m/z* 1161 ($M^+ - Br$), 893 ($M^+ - CH_2CH_2C_6F_{13}$).

Tris(3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl)(4′-methoxyphenyl)tin (Tris[2-(Perfluorohexyl)ethyl](4′-methoxyphenyl)tin) (1b). To the Grignard reagent prepared from 4-bromoanisole (681 mg, 3.64 mmol) and magnesium (102 mg, 4.20 mmol) in dry ether (20 mL) was added a solution of **5a** (3.47 g, 2.80 mmol) in dry ether (10 mL). After being refluxed for 1 h, the reaction was allowed to stand 16 h at 25 °C. The reaction mixture was quenched with NH_4Cl solution and diluted with ether, and the organic phase was washed with deionized water and then dried over anhydrous $MgSO_4$. The mixture was concentrated under reduced pressure. Purification by vacuum distillation (166 °C, 0.25 mmHg) and then column chromatography on neutral alumina with hexane yielded pure compound **1b** (5.20 g, 74%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.30 (d, $J = 8.3$ Hz, 2 H), 6.98 (d, $J = 8.3$ Hz, 2 H), 3.82 (s, 3 H), 2.29 (m, 6 H), 1.27 (t, $J = 8.3$ Hz, ^2J($^{119}Sn-H$) = 54.0 Hz, 6 H); ^{119}Sn NMR ($CDCl_3$) −26.3 ppm; IR (thin film) 1500, 1375, 1240, 1205, 1145, 1065, 745, 700 cm^{-1}; MS *m/z* 1267 (M^+), 1161 ($M^+ - PhOMe$), 921 (M^+ - $CH_2CH_2C_6F_{13}$).

Tris(3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl)(2′-furyl)tin (Tris[2-(Perfluorohexyl)ethyl](2′-furyl)tin) (1c). To the solution of furan (667 mg, 9.80 mmol) in dry THF (25 mL) at 0 °C was added 1.5 M LDA/cyclohexane (6.53 mL, 9.80 mmol). After 1 h at 0 °C, the resulting mixture was treated with a solution of **5a** (8.67 g, 7.00 mmol) in dry THF (15 mL). The reaction mixture was warmed to 25 °C over 1 h and then stirred 16 h at 25 °C. The reaction mixture was quenched with NH_4Cl solution and diluted with ether, and the organic phase was washed with deionized water and then dried over anhydrous $MgSO_4$. The mixture was concentrated under reduced pressure. Column chromatography on neutral alumina with hexane yielded pure compound **1c** (2.44 g, 28%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.76 (s, 1 H), 6.63 (s, 1 H), 6.47 (s, 1 H), 2.35 (m, 6 H), 1.29 (t, $J = 9.7$ Hz, $^2J(^{119}Sn-H) = 56.8$ Hz, 6 H); ^{119}Sn NMR ($CDCl_3$) −49.3 ppm; IR (thin film) 1445, 1355, 1240, 1205, 1145, 1065, 745, 700 cm^{-1}; MS *m/z* 1228 (M^+), 1161 ($M^+ -$ furyl), 881 (M^+ - $CH_2CH_2C_6F_{13}$).

Tris(3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl)(2′-pyridyl)tin (*Tris*[2-(Perfluorohexyl)ethyl](2′-pyridyl)tin) (1d). To the Grignard reagent prepared from 2-bromopyridine (822 mg, 5.20 mmol) and magnesium (146 mg, 6.20 mmol) in dry ether (30 mL) was added a solution of **5a** (2.48 g, 2.00 mmol) in dry ether (5 mL). After refluxing for 1 min, the reaction was allowed to stand for 16 h at 25 °C. The reaction mixture was quenched with NH_4Cl solution and diluted with ether, and the organic phase was washed with deionized water and then dried over anhydrous $MgSO_4$. The solvent was evaporated to dryness, and the resulting residue was dissolved in toluene and FC-72. The two phases were separated. The FC-72 phase was washed with toluene and concentrated to afford pure compound **1d** (2.18 g, 88%) as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 8.71 (d, $J = 4.3$ Hz, 1 H), 7.58 (t, $J = 7.7$ Hz, 1 H), 7.36 (d, $J = 7.3$ Hz, 1 H), 8.20 (m, 1 H), 2.29 (m, 6 H), 1.34 (t, $J = 8.2$ Hz, ^2J ($^{119}Sn-H$) = 54.3 Hz, 6 H); ^{119}Sn NMR ($CDCl_3$) −61.4 ppm; IR (thin film) 1570, 1450, 1360, 1240, 1205, 1145, 1060, 735, 700 cm^{-1}; MS *m/z* 1238 (M^+), 1161 ($M^+ -$ pyridyl), 892 ($M^+ - CH_2CH_2C_6F_{13}$).

Tris(3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl)(4′-methylphenyl)tin (1e). To the Grignard reagent prepared from 1-bromo-4-methylbenzene (533 mg, 3.12 mmol) and magnesium (89 mg, 3.56 mmol) in dry ether (16 mL) was added a solution of **5a** (2.97 g, 2.39 mmol) in dry ether (8 mL). After being refluxed for 1 h, the reaction was allowed to stir overnight at 25 °C. The reaction mixture was quenched with NH_4Cl solution and diluted with ether, and the organic phase was washed with deionized water and then dried over anhydrous $MgSO_4$. The mixture was concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel with hexane to give pure **1e** (2.71 g, 91%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.3−7.19 (m, 4 H), 2.4−2.2 (m, 6 H), 2.39 (s, Me), 1.28 (t, $J = 8.3$ Hz, $^2J(^{119}Sn-H) = 53.4$ Hz, 6 H); ^{119}Sn NMR (BTF/C_6D_6) −36.3 ppm; IR (thin film) 2930, 2430, 1230, 1060 cm^{-1}; MS *m/z* 1161 $M^+ - C_6H_4Me$), 905 ($M^+ - CH_2CH_2C_6F_{13}$).

Tris(3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl)(4′-ethylphenyl)tin (1f). To the Grignard reagent prepared from 1-bromo-4-ethylbenzene (682 mg, 3.69 mmol) and magnesium (103 mg, 4.41 mmol) in dry ether (20 mL) was added a solution of **5a** (1.80 g, 1.45 mmol) in dry ether (8 mL). After being refluxed for 1 h, the reaction was allowed to stir overnight at 25 °C. The reaction mixture was quenched with NH_4Cl solution and diluted with ether, and the organic phase was washed with deionized water and then dried over anhydrous $MgSO_4$. The mixture was concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel with hexane to give the pure compound **1f** (1.66 g, 91%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.35−7.25 (m, 4 H), 2.71 (q, $J = 7.4$ Hz, 2 H), 2.32 (m, 6 H), 1.35−1.2 (m, 9 H); ^{119}Sn NMR (BTF/C_6D_6) −34.7 ppm; IR (thin film) 2970, 1440, 1235, 1200, 1150, 1060 cm^{-1}; MS *m/z* 1265 (M^+), 1161 ($M^+ - C_6H_4Et$), 919 ($M^+ - CH_2CH_2C_6F_{13}$)

General Procedure for the Stille Couplings (Table 4). A tube under nitrogen was charged with tin reactant **1** (0.24 mmol), substrate **2** (0.20 mmol), lithium chloride (25.4 mg, 0.60 mmol), dichlorobis(triphenylphosphine)palladium(II) (2.8 mg, 0.004 mmol), dry DMF (0.5 mL), and dry THF (0.5 mL). The tube was sealed, the mixture was heated to 80 °C, and a homogeneous solution resulted. After 22 h, the solvent was evaporated under reduced pressure and the residue was partitioned between water (10 mL), dichloromethane (15 mL), and FC-72 (15 mL). The three phases were separated, and the dichloromethane phase was dried over anhydrous $MgSO_4$. Evaporation of the FC-72 phase provided chlorotris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)tin (**5b**) (chlorotris[2-(perfluorohexyl)ethyl]tin), which was routinely reused. Evaporation of the dichloromethane phase provided the crude organic product, which was further purified by preparative TLC (silica gel) to provide the major cross-coupled product **3** and a small amount of the symmetrical biaryl **4** derived from the tin reactant.

Chlorotris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)tin (5b) (Chlorotris[2-(perfluorohexyl)ethyl)tin]: ^1H NMR ($CDCl_3$) δ 2.46 (m, 6 H), 1.53 (t, $J = 7.9$ Hz, ^2J ($^{119}Sn-H$) = 47.6 Hz, 6 H); ^{119}Sn NMR ($CDCl_3$) 273 ppm; IR (thin film) 1450, 1360, 1240, 1205, 1145, 1065, 735, 700 cm^{-1}; MS *m/z* 1161 ($M^+ -$ Cl), 849 ($M^+ - CH_2CH_2C_6F_{13}$).

Example of a Preparative Stille Coupling (Eq 4). A tube under nitrogen was charged with tin reactant **1a** (2.97 g, 2.40 mmol), 1-bromo-4-nitrobenzene (**2c**) (404.0 mg, 2.00 mmol), lithium chloride (254.3 mg, 6.00 mmol), dichlorobis(triphenylphosphine)palladium(II) (28.1 mg, 0.04 mmol), dry DMF (5 mL), and dry THF (5 mL). The tube was sealed, the mixture was heated to 80 °C, and a homogeneous solution resulted. The mixture was stirred at 80 °C for 22 h. After azeotropic evaporation under reduced pressure with toluene at 75 °C (to remove some of the DMF), the resulting residue was partitioned between water (40 mL), dichloromethane (60 mL), and FC-72 (40 mL). The three phases were separated. Evaporation of the FC-72 phase provided 2.31 g (80.6% from **1a**) of tin chloride **5b** as a colorless oil. The dichloromethane phase was washed three more times with water (40 mL) and FC-72 (40 mL) to remove DMF and fluorous products (mostly chlorotris[2-(perfluorohexyl)ethyl]tin). Evaporation of all the FC-72 phase (including the first phase) provided 2.85 g (99.4% from **1a**) of tin chloride **5b**. The final dichloromethane phase was dried over anhydrous $MgSO_4$ and evaporated to give yellow crystals free of fluorous reactant **1a** and fluorous tin halides. The crude organic product was further purified by column chromathography on silica gel to provide the cross-coupled product 4-nitrobiphenyl (**3b**) (337 mg, 85%) as yellow crystals and the homocoupled product biphenyl (**4a**) (17 mg, 5%) as white crystals.

Example of a Recycle of the Tin Reactants (Eq 4). The tin chloride **5b** (2.85 g) isolated by evaporation of FC-72 phase after the above Stille coupling was treated with a 3 M solution of phenylmagnesium bromide (1.04 mL, 3.12 mmol in ether) in dry ether (25 mL) under stirring at 25 °C for 6 h. The reaction mixture was quenched with NH_4Cl solution and diluted with ether, and the organic phase was washed with deionized water and dried over anhydrous $MgSO_4$. The mixture was concentrated under reduced pressure. Column chromathography on neutral alumina with hexane yielded pure compound **1a** (2.85 g, 96% overall from **1a** in the preceding section) as a colorless oil.

Example of a Stille Coupling with CuI.[21] A tube under argon was charged with 4-bromoacetophenone (**2a**) (39.8 mg, 0.2 mmol), lithium chloride (25.4 mg, 0.6 mmol), dichlorobis(triphenylphosphine)palladium(II) (2.9 mg, 0.004 mmol), tin reactant **1d** (300.3 mg, 0.24 mmol), copper(I)iodide (3.0 mg, 0.016 mmol), dry DMF (0.5 mL), and dry THF (0.5 mL). The tube was sealed, and the mixture was heated at 80 °C for 3 h. The red-brown solution was cooled to room temperature, and the solvent was evaporated. The resulting residue was partitioned between water, dichloromethane, and FC-72. The three phases were separated, and the dichloromethane phase was washed three more times with water and FC-72. The final dichloromethane phase was dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated, and a solid was obtained. Further purification by flash chromatography (hexane/ether 6:1) over silica gel provided 4-acetyl-4′-methylbiphenyl (**7**) (41.0 mg, 98%) as white crystals.

1-Nitro-4-[2-(perfluorohexyl)ethyl]benzene (9b) was prepared according to the general procedure for the Stille couplings. After purification by preparative TLC, pure compound **9b** (14.1 mg, 15%) was given as pale yellow crystals: mp 39 °C; ^{1}H NMR ($CDCl_3$) δ 8.20 (d, $J = 8.6$ Hz, 2 H), 7.40 (t, $J = 8.6$ Hz, 2 H), 3.05(m, 2 H), 2.42 (m, 2 H); IR (thin film) 3020, 2855, 1525, 1350, 1240, 1215, 1145, 765 cm^{-1}; MS *m*/*z* 469 (M^+), 423 ($M^+ - NO_2$).

All of the isolated products **3**, **4**, and **7** are known.

4-Acetylbiphenyl (3a): CAS registry no. 92-91-1 provided by the author.

4-Nitrobiphenyl (3b): CAS registry no. 92-93-3 provided by the author.

Diphenylmethane (product between 1a and benzyl bromide): CAS registry no. 101-81-5 provided by the author.

4-Methoxybiphenyl (product between 1b and iodobenzene): CAS registry no. 613-37-6 provided by the author.

4-Acetyl-4'-methoxybiphenyl (product between 1b and 4'-bromoacetophenone): CAS registry no. 13021-18-6 provided by the author.

4-Methoxy-4'-nitrobiphenyl (product between 1b and either 1-bromo-4-nitrobenzene or 4-nitrophenyl trifluoromethanesulfonate): CAS registry no. 2143-90-0 provided by the author.

1-Methoxy-4-(phenymethyl)benzene (product between 1b and benzyl bromide): CAS registry no. 13021-18-6 provided by the author.

2-Phenylfuran (product between 1c and iodobenzene): CAS registry no. 17113-33-6 provided by the author.

2-(4-Acetylphenyl)furan (product between 1c and 4'-bromoacetophenone): CAS registry no. 35216-08-01 provided by the author.

2-(4-Nitrophenyl)furan (product between 1c and either 1-bromo-4-nitrobenzene or 4-Nitrophenyl trifluoromethanesulfonate): CAS registry no. 28123-72-0 provided by the author.

2-(Phenylmethyl)furan (product between 1c and benzyl bromide): CAS registry no. 37542-92-0 provided by the author.

Biphenyl (4a): CAS registry no. 92-52-4 provided by the author.

4,4'-Dimethoxybiphenyl (homocoupled product from 1b): CAS registry no. 2132-80-1 provided by the author.

4-Acetyl-4′-methylbiphenyl (3c): CAS registry no. 7722-84-1 provided by the author.

4′-Ethyl-4-acetylbiphenyl (3d): CAS registry no. 5730-92-7 provided by the author.

4′-Methylbiphenyl (product between 1e and iodobenzene): CAS registry no. 188701-34-0 provided by the author.

4-Methyl-4′-nitrobiphenyl (product between 1e and either 1-bromo-4-nitrobenzene or 4-nitrophenyl trifluoromethanesulfonate): CAS registry no. 2143-88-6 provided by the author.

4-Methoxy-4′-methylbiphenyl (product between 1e and 1-bromo-4-methoxybenzene): CAS registry no. 53040-92-9 provided by the author.

4-(Methylphenyl)phenylmethyl (4b): CAS registry no. 613-33-2 provided by the author.

4-Acetyl-2'-methylbiphenyl (9): CAS registry no. 76650-29-8 provided by the author.

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