Pergamon

Tetrahedron 55 (1999) 8997–9006

TETRAHEDRON

tris(2-Perfluorohexylethyl)tin azide: A New Reagent for Preparation of 5-Substituted Tetrazoles from Nitriles with Purification by Fluorous/Organic Liquid-Liquid Extraction

Dennis P. Curran,* Sabine Hadida and Sun-Young Kim
Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA

Received 10 February 1999; accepted 26 April 1999

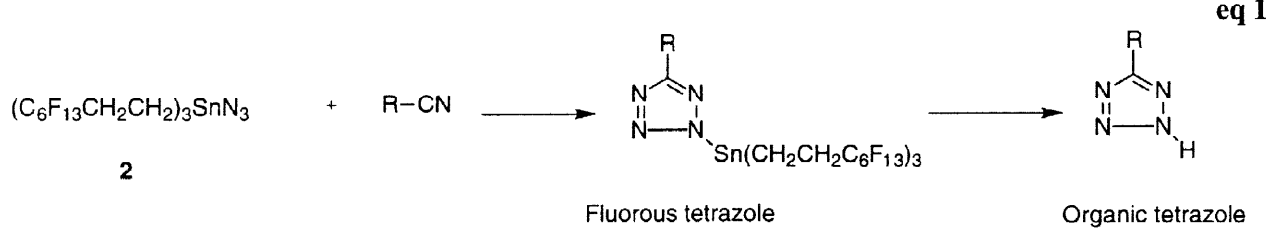
Summary: *The synthesis of a new fluorous tin azide, $(C_6F_{13}CH_2CH_2)_3SnN_3$, is reported and this reagent is used to make tetrazoles in both traditional and phase-switching modes. In the traditional mode, the tin azide is reacted with nitriles followed by HCl cleavage to provide the tetrazoles and the fluorous tin chloride (which can be reconverted into the tin azide). In the switching mode, the initial tin tetrazole is purified by fluorous/organic liquid-liquid extraction prior to destannylation. This provides pure products even in incomplete reactions or with impure starting materials, but it only works for smaller nitriles.*

Keywords: fluorous, tin azide, tetrazole, dipolar cycloaddition, phase switch

Introduction

Fluorous techniques for synthesis and separation are beginning to provide new options for both traditional and parallel solution phase reactions.[1] Generally speaking, a reaction component (or subset of components) is rendered fluorous by using one or more perfluoroalkyl substituents.[2] This makes separation facile at the workup stage because fluorous compounds can often be separated from organic ones by simple liquid-liquid or solid-liquid[3] extraction techniques. In the organometallic area, the technique of fluorous biphasic catalysis—introduced by Horváth and Rábai—is becoming increasingly important as a catalyst immobilization method. We have introduced a number of fluorous reagents, reactants[4] and protecting groups,[5] and used these to illustrate simple concepts of strategy level purification including fluorous synthesis, fluorous phase switching, and others.[2b] We report here on our study of the new fluorous tin reagent *tris*(2-perfluorohexylethyl)tin azide **2**. Cycloadditions of this azide with nitriles were used briefly in a preliminary communication[1b] to introduce the technique of fluorous phase switching in a setting where the phase switch is directly coupled to a target synthetic transformation. We report herein the full details of our study with this reagent and its uses both in a phase-switching mode and as a standard reagent to make tetrazoles from nitriles. The basic reaction is shown in eq 1.

eq 1



email: curran+@pitt.edu

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00458-5

Tetrazoles are an important class of heterocycles in their own right, and they are often featured in medical chemistry studies as substitutes for carboxylic acids.[6] Tetrazoles are most commonly prepared from nitriles by cycloadditions with an azide.[7] The classical method, reaction with in situ generated HN_3, is an explosion hazard especially on large scale. The most commonly used laboratory method for tetrazole synthesis is cycloaddition with tributyltin azide,[8] but this suffers from the usual separation and toxicity problems associated with small alkyltin reagents.

Results and Discussion

Preparation of Tin Azide **2***:* Tin azide **2** was prepared in 97% crude yield by treatment of the readily available fluorous tin bromide **1**[4a,g] with 1.2 equiv of sodium azide in a biphasic mixture of water and ether (eq 2). Separation of the phases and evaporation of the ether layer gave the tin azide **2**, which was used directly without further purification. The existence of the Sn–N_3 bond was supported by the presence of an intense band in the infrared spectrum at 2,080 cm^{-1} (compared to 2,067 cm^{-1} for tributyltin azide), which we attribute to the asymmetric stretching vibration of the azide. The purity of tin azide **2** was satisfactory; the crude product exhibited only one signal in the ^{119}Sn NMR at 11.5 ppm (compared to the signal of **1** at 259.2 ppm).

eq 2

$$\underset{\mathbf{1}}{(C_6F_{13}CH_2CH_2)_3SnBr} + NaN_3 \xrightarrow[25°C,\ 97\%]{\text{ether/}H_2O} \underset{\mathbf{2}}{(C_6F_{13}CH_2CH_2)_3SnN_3}$$

Compound **2** begins as a very viscous oil that solidifies on standing. It lacks the strong and repulsive odor of trialkyltin compounds. As expected, the presence of the fluorous chains drastically alters the solubility properties of this reagent. Tin azide **2** shows very little solubility in organic solvents such as benzene, toluene and acetonitrile, but good solubility in fluorinated solvents (FC-72®), ethers (ethyl ether, THF) and hybrid (partially fluorinated) solvents such as BTF.[9]

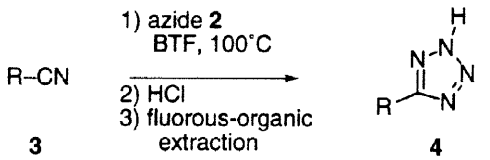
We assessed the stability of fluorous tin azide **2** by exposing it to heat. After heating at 100°C for 12 h, a 1 g sample of **2** (neat) showed no apparent decomposition. During this 12 h, samples were taken every hour and an FT-IR spectrum of each was recorded. All twelve IR spectra were essentially superimposable with the starting spectrum. Adequate caution should be used in all reactions involving azides; however, fluorous tin azide **2** seems to be stable to heat at levels typically used for its reactions. We also used a reaction to index the stability of the tin azide. These results, which are presented below, confirm that the fluorous tin azide resists thermal degradation.

Reactions of Tin Azide **2***—Traditional Mode:* We first studied the reactions of tin azide **2** in a traditional mode—that is, by direct analogy to the reactions with tributyltin azide. The goal was to convert nitriles to free tetrazoles without isolation of the intermediate tin tetrazoles. The results of a series of experiments with simple nitriles are shown in Table 1. In general, a BTF solution of the nitrile (1 equiv) and tin azide **2** (1-3 equiv, see Table) was heated at reflux (103°C) for 12 h. The solvent was then evaporated and the residue was briefly exposed to ethereal HCl (to cleave the tin tetrazole) prior to partitioning between acetonitrile and FC-72. The tetrazole was isolated from the organic phase in the yields indicated in Table 1. The corresponding tin chloride [$(C_6F_{13}CH_2CH)_3SnCl$] was recovered from the fluorous phase and reconverted to tin azide **2** by treatment with NaN_3.

Simple 1°-aliphatic and aromatic nitriles (provided they are not too electron poor) give essentially quantitative yields of tetrazoles when 2-2.5 equiv of the tin azide are used. With only 1

equiv (see below), some starting material tends to remain at the end of the reaction. More substituted nitriles benefit from additional excess of tin azide, as shown for the tertiary nitriles in entries 5-11. The sequence of experiments with *tert*-butyl nitrile (entries 8-11) suggests that there is not much point in adding more than about 4-5 equiv of azide reagent for recalcitrant substrates.

Table 1. Conversion of Nitriles to Tetrazoles: Traditional Mode



3 4

Entry	R in **3**	Equiv **2**	Yield of **4** (%)
1	*p*-MeC_6H_4	2.0	99 **4a**
2	*p*-$MeOC_6H_4$	2.5	95 **4b**
3	$C_6H_5CH_2$	2.5	98 **4c**
4	C_6H_5	2.5	99 **4d**
5	$C_6H_5(Me)_2C$	3	71 **4e**
6	$C_6H_5(Me)_2C$	5	96 **4e**
7	$C_6H_5C(CH_2)_4$	5	21 **4f**
8	$(Me)_3C$	1	23 **4g**
9	$(Me)_3C$	2.8	39 **4g**
10	$(Me)_3C$	4.5	59 **4g**
11	$(Me)_3C$	8	55 **4g**

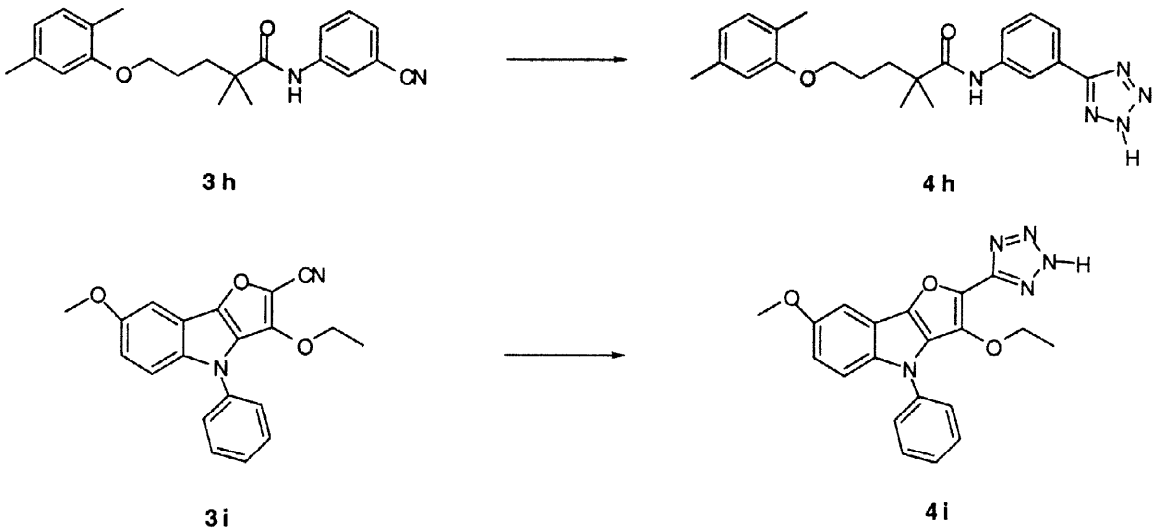
A second type of experiment was conducted to study the stability of fluorous tin azide **2** to heating in BTF. We prepared 4 x 0.5 M solutions of tin azide **2** in BTF and added successively 1 equiv of *p*-methoxybenzonitrile (**3b**) after refluxing the azide solution for 0, 1, 2 and 5 h. After heating 12 more h, the reactions were processed as described above. The yields for the obtained tetrazole **4b** are represented in Table 2. There is not a substantial variation of the amount of tetrazole **4b** obtained in these experiments. This proves that tin azide **2** is stable to heat at reflux in BTF, at least over the course of several hours.

Table 2. Yield of 4b After Preheating Tin Azide in BTF at Reflux

time at reflux	0 h	1 h	2 h	5 h
yield **4b**	86%	87%	88%	90%

We also used this procedure to make tetrazoles from two more complex nitriles (eq 3). Samples of these nitriles, as well as authentic samples of the tetrazole products, were kindly provided by Dr. J. Hodges of the Parke-Davis Co. Due to the high insolubility of nitriles **3h** and **3i** in BTF, the reactions were run in the mixture of BTF and DMF. Three equiv of tin azide **2** was used to assure completion of the reaction. After fluorous/organic extraction, the acetonitrile layer yielded the 5-substituted tetrazoles (93 % and 98 %, respectively). These were identified by comparing the ^1H NMR spectra obtained with the NMR data of the authentic samples.

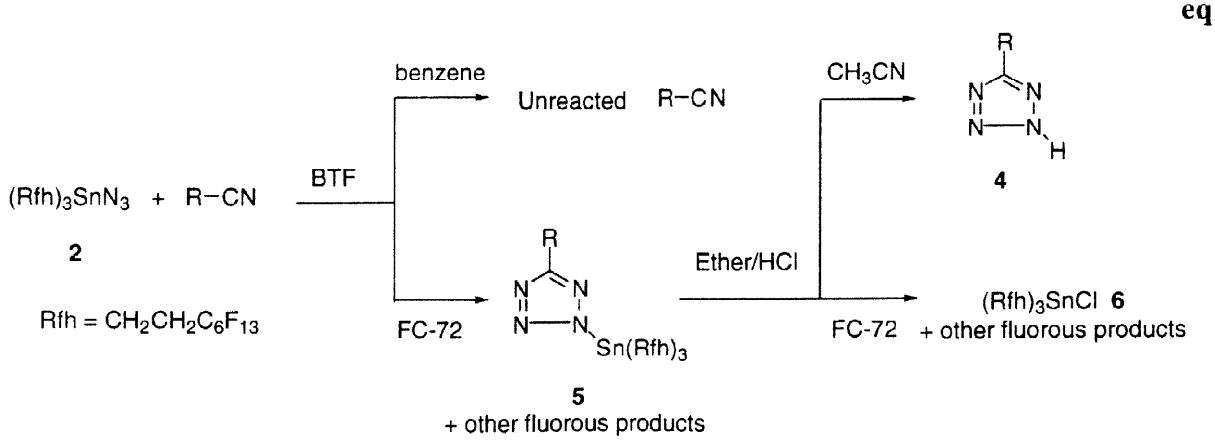
eq 3



These results suggest that the new fluorous tin azide has good potential as an alternative to tributyltin azide. The azide is stable and provides representative tetrazoles in yields that are comparable to tributyltin azide. But the tin products can be separated very easily from the reaction mixture by liquid-liquid extraction, even when more than 5 equiv of the tin reagent is used to improve the yield.

Reactions of Tin Azide 2—Phase-Switching Mode: We have also used the reactions of tin azide **2** to illustrate simple concepts of fluorous phase switching.[2b] In favorable cases, the reaction of an organic nitrile with the fluorous tin azide reagent provides a fluorous tin tetrazole—in other words, the tin tetrazole intermediate will partition out of an organic phase and into a fluorous phase during workup. This "organic-to-fluorous" switch then provides a convenient means of purification of reaction product from either unreacted starting material or any other contaminants that are not labeled with the fluorous tin tag. The sequence of steps is illustrated in eq 4. After reaction and a first fluorous/organic separation, the fluorous tin tetrazole **5** (perhaps containing other fluorous compounds such as unreacted tin azide) is then treated with HCl and the crude mixture is resubjected to a second fluorous/organic extraction. This "double phase switch" is designed to provide the organic tetrazole product **4** free from both probable organic and fluorous impurities.

eq 4



To demonstrate the purification features of the experiment, we conducted reactions at 100°C for 12 h using 1 equiv of tin azide **2** and 2 equiv of the starting nitriles **3**. This stoichiometry guarantees incomplete conversion of the nitrile. (We emphasize that these reaction conditions were chosen to demonstrate the purification features; for real applications where a maximum yield of tetrazole is desired, it would surely be preferable to use an excess of tin azide as shown above.) A series of seven different nitriles was processed through the two step sequence with the double phase switch, and the yields of tetrazoles **4** from the final organic phase are shown in Table 3. Tetrazoles **4** were obtained in moderate to high yields, except in entry 4 where only traces of tetrazole **4b** were isolated. These yields are comparable to those obtained with tributyltin azide.

Table 3. Conversion of Nitriles to Tetrazoles: Phase-Switching Mode.

Entry	R in **3**	Yield tetrazole **4**
1	*p*-MeC_6H_4	61% **4a**
2	*p*-$MeOC_6H_4$	72% **4b**
3	C_6H_5	59% **4d**
4	*p*-$NO_2C_6H_5$	traces **4j**
5	CH_3	83% **4k**
6	$(Me)_2CH$	87% **4l**
7	$C_6H_5CH_2$	77% **4c**

In each case, the crude tetrazole product was of excellent purity as assessed by ^1H NMR. In no case were resonances for any of the starting nitriles detectable in the NMR spectrum of the tetrazole product. This confirms the success of the phase switch, since each reaction mixture must have had at least one equiv of unreacted nitrile prior to the first workup. Representative ^1H NMR spectra for the reaction of **2** with *p*-methoxylbenzonitrile (Table 2, entry 2) are shown in Figures 1 and 2. Figure 1 shows the spectrum of the crude reaction product after treatment of the initial fluorous product with HCl/ether, but prior to fluorous/organic extraction. No resonances for the starting nitrile are visible, and the resonances for the tetrazole **4b** are evident (8.1, 7.1, 3.8 ppm). The resonances for the "spacer" protons of the fluorous tin chloride **6** dominate the upfield region of the spectrum. Figure 2 then shows the ^1H NMR spectrum of the crude product from the acetonitrile phase after the fluorous/organic extraction. All the "spacer" resonances are gone, and only the resonances for tetrazole **4b** are evident.

Figure 1. ^1H NMR Spectrum of the Crude Reaction Mixture Containing 4b After Treatment with Ether/HCl

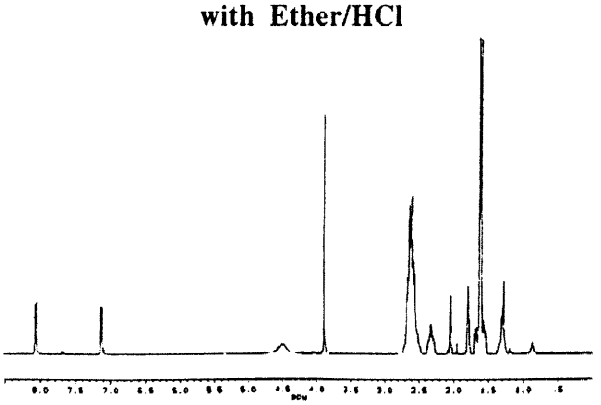
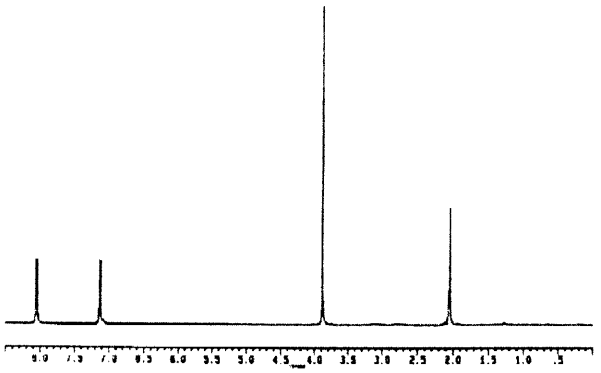


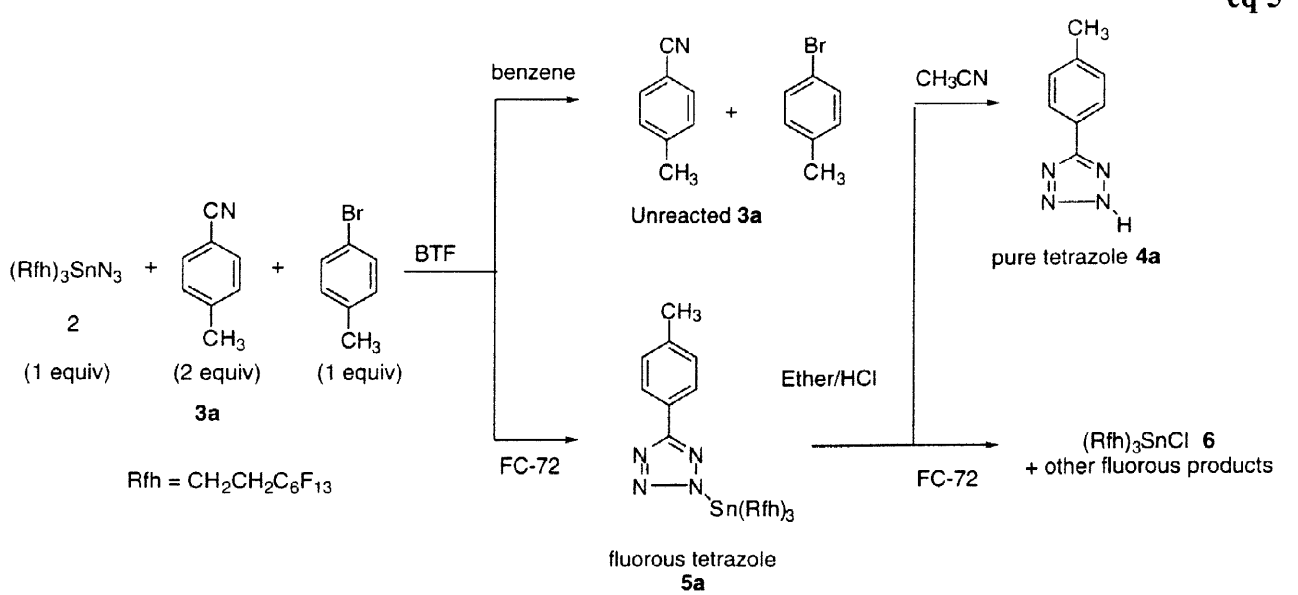
Figure 2. The ^{1}H NMR of the Acetonitrile Layer After Extraction with FC-72/CH_3CN



To demonstrate the possibility of regenerating the tin azide **2** from the tin chloride **6**, a larger scale experiment involving 2 g (1.66 mmol) of tin azide **2** and 443 mg (3.32 mmol) of *p*-methoxybenzonitrile was carried out. The tin chloride **6** obtained from the fluorous phase was reconverted into the tin azide **2** by treatment with sodium azide (eq 2). This tin azide was reused to make more tetrazole **4b**. In both experiments, the final tetrazole was pure by ^{1}H NMR (spectra indistinguishable from that of Figure 2), and the tetrazole yields were both identical to the small scale reaction in Table 3, entry 2 (~72%).

The experiment represented in eq 5 was designed to demonstrate the use of fluorous tin azide **2** as a labeling reagent for organic molecules and illustrate its suitability in parallel synthesis. The idea was to simulate a reaction in which the starting material was already impure from a prior step in the synthesis, and to show how this defect could be corrected without chromatography by the organic-fluorous-organic switch. The procedure involved the use of *p*-toluonitrile **3a** (2 equiv) doped with 4-bromotoluene (1 equiv) and then reacted with the tin azide (1 equiv) under the usual conditions. The experiment simulates an incomplete reaction in the hypothetical synthesis of *p*-toluonitrile from 4-bromotoluene, and it is designed to leave both nitrile and bromide at the end of the first step (that is, it simulates incomplete conversion of an impure starting material). The pure organic tetrazole **4a** was separated from the organic "impurities" by the two liquid-liquid extractions shown in eq 5 without any alteration to its yield (61%) and purity compared to the result in Table 3, entry 1.

eq 5



Conclusions

The results suggest that tin azide **2** is a potentially useful reagent in organic synthesis in a number of different contexts. In a traditional setting—as a replacement for tributyltin azide—yields of tetrazoles seem comparable to the tributyltin reagent, and the separation procedure is simple and very general.[10] Hexane/acetonitrile extractions can be used to purify some reactions of trialkyltin reagents, but the replacement of hexane by perfluorohexane coupled with the use of a fluorous reagent is much more general since organic compounds do not partition into perfluorohexane. A disadvantage of the reagent, especially on large scale, is its high molecular weight (about 1,200). Catalytic procedures would be desirable, but are not yet available. The next best thing is the ability to recycle and reuse the reagent, which we have done routinely throughout this work.

While our product samples are free from fluorous tin resonances in the ^{1}H NMR spectrum, we certainly do not imply that the samples are "tin free" at any level of trace analysis. It would be desirable in medicinal chemistry settings to conduct trace analysis of the tin and also to test whether any tin contaminants effect biological assays. Given that highly fluorinated molecules are not readily absorbed by biological media,[11] there is reason to speculate that toxicity and assay interference will be a lesser problem compared to standard alkyltin reagents, but this speculation currently lacks experiential support.

The use of tin azide **2** as a phase switching reagent has also been demonstrated by this work. This provides an example of "strategy level separation"[2b]—that is, where the synthesis plan controls the separation. In this instance, the reaction of the tin azide with a nitrile occurs with retention of the fluorous tag. Thus, the occurrence of the desired reaction dictates the phase switch of an organic starting material to a fluorous product. This is fundamentally different from a reaction like the Stille coupling with a fluorous tin reagent,[4f,g] where the reaction cuts out the fluorous tag and both the starting material and the product are organic. The potential ability of this type of phase switch to provide pure products in reactions with impure starting materials and which do not go to 100% conversion based on starting material is clear from this work. The phase switch could also be used in a "fluorous quenching" mode to remove residual nitriles after some other type of reaction has been conducted.

Conceptual issues aside, there are still some problems with practical application of the tin azide **2** in phase switching applications. While small tin tetrazoles like those in Table 1 can be extracted preferentially into a fluorous solvent, larger ones cannot. For example, we also tried the phase switching mode of reactions with larger nitriles like **3h** and **3i**, but the tin tetrazole products of these reactions did not partition preferentially into the fluorous phase. This may be because there are not enough fluorines in tin azide **2** to render the derived products fluorous, but it may also be due to the tetrazole itself. Tetrazoles are inherently polar functional groups, and perfluorocarbon solvents like FC-72 are very non-polar. To solve the size problem, we prepared and briefly surveyed the fluorous tin azide $(C_{10}F_{21}CH_2CH_2)_3SnN_3$ containing 63 fluorines. However, preliminary results were not encouraging; this tin azide is highly insoluble in organic solvents and also relatively insoluble in solvents like BTF and FC-72. Attempts to make some tin tetrazoles by the methods outlined in this paper met with very limited success, and the resulting fluorous tetrazoles were also generally insoluble molecules that were difficult to handle. In effect, the reagent bearing 63 fluorines in straight chains starts to behave more like a "Teflon-bound" tin azide than a fluorous tin azide.

While we do not have any immediate plans to extend this chemistry, there are a number of worthwhile avenues that are already open. For example, we have recently introduced the technique

of fluorous solid phase extraction over fluorous reverse phase silica gel,[3] and this simple technique might be applied to the tin azide chemistry as well. In addition, we now have access to an assortment of tin halides with different numbers of fluorous chains, and different lengths of both fluorocarbon and hydrocarbon units.[4e] We have shown that adjusting these features can be used to tune to advantage both the reactivity and the solubility features of tin hydrides and allyltin reagents. Analogous options are now available for study in the tin azide chemistry.[4k-m]

Experimental:

***tris*(2-Perfluorohexylethyl)tin azide; *tris*(3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl)tin azide:** To a solution of bromo *tris*(2-perfluorohexylethyl)tin (10 g, 8.06 mmol) in ether (14 ml) was added a solution of sodium azide (629 mg, 9.67 mmol) in water (2 ml) with vigorous stirring. The resulting biphasic mixture was stirred at 25 °C for 12 h. Then ether (20 ml) and water (20 ml) were added to the reaction mixture and the two layers were separated. The ethereal phase was washed with water (3 x 20 ml), and dried with anhydrous $MgSO_4$. The solvent was evaporated to dryness to yield fluorous tin azide **2** (9.4 g, 97% yield) as a colorless oil.: ^1H NMR ($CDCl_3$) δ 2.48 (m, 6H), 1.51 (m, 6H); ^{119}Sn NMR (BTF-C_6D_6) δ 11.53; IR (thin film) 2080, 1360, 734 cm^{-1}; M/S (*m/z*) 1161 ($M^+ - N_3$), 856 ($M^+ - CH_2CH_2C_6F_{13}$), 467 ($SnCH_2CH_2C_6F_{13}$).

Experimental procedure for the preparation of 5-substituted tetrazoles, Traditional Mode: A solution of *tris*(2-perfluorohexylethyl)tin azide (409 mg, 0.340 mmol) and *p*-tolunitrile (20 mg, 0.17 mmol) in 0.34 ml of benzotrifluoride (BTF) was heated in a sealed tube at 80 °C for 12 h. The BTF was evaporated and the crude residue was dissolved in a 1.0 M HCl in ether (10 ml). The resulting mixture was stirred for 12 h at 25 °C. After the evaporation of the ether, the residue was partitioned between FC-72 (10 ml) and acetonitrile (10 ml). After separation of the two layers, the organic phase was washed with FC-72 (3 x 10 ml). Evaporation of the acetonitrile phase yielded the 5-*p*-tolyltetrazole (27 mg, 99 %). The FC-72 phase was evaporated as well yielding *tris*(2-perfluorohexylethyl)tin chloride (367 mg, 90%) as a colorless oil, m.p. 242-244 °C (lit. 242-243 °C) which was identified by comparing the ^1H NMR and MS (*m/z*) spectra with those of the authentic sample.

Experimental procedure for the preparation of 5-substituted tetrazoles, Phase-Switching Mode: A solution of *tris*(2-perfluorohexylethyl)tin azide (0.5 g, 0.416 mmol) and 4-methoxybenzonitrile (111 mg, 0.832 mmol) in 0.84 ml of benzotrifluoride (BTF) was heated in a sealed tube at 80 °C for 12 h. The BTF was evaporated and the reaction mixture was partitioned between benzene and FC-72 (10 ml each). After separation of the two layers, the benzene layer was extracted twice with FC-72 (10 ml). Evaporation of the benzene phase yielded the unreacted 4-methoxybenzonitrile. The fluorinated phase was evaporated and redissolved in 10 ml HCl in ether (1 M). The mixture was stirred for 12 h at 25 °C. After evaporation of the ether, the residue was partitioned between 10 ml of each FC-72 and acetonitrile. After separation of the two layers, the organic phase was washed with FC-72 (3 x 10 ml). Evaporation of the acetonitrile phase yielded the 5-(4-methoxyphenyl)ltetrazole (55 mg, 76% yield) which was identified by comparing the ^1H NMR and MS (*m/z*) spectra with those of the authentic sample. The FC-72 phase was evaporated as well yielding *tris*(2-perfluorohexylethyl)tin chloride (449 mg, 90%) as a colorless oil.

Representative procedure for the formation of 5-substituted tetrazoles from nitriles 3h and 3i;

5-(2,5-Dimethylphenoxy)-2,2-dimethyl-pentanoic acid [3-(2H-tetrazole-5-yl-phenyl]-amide: A mixture of **3h** (37.3 mg, 0.11 mmol) and **2** (383 mg, 0.32 mmol) in BTF (0.1 ml) and DMF (0.1 ml) was heated in a sealed tube at 80 ^{o}C for 1 day under nitrogen. The reaction mixture was transferred to a round-bottom flask while it was still warm. After the evaporation of the solvent under reduced pressure, the crude mixture was directly treated with 1.0 M HCl in ether for 12 h at room temperature. After the evaporation of ether, the residue was partitioned between FC-72 (10 ml) and acetonitrile (10 ml). The separated acetonitrile layer was washed with FC-72 (3 x 10 ml). The evaporation of acetonitrile layer yielded 39.2 mg of product (93 %): ^{1}H NMR (CD_3COCD_3) δ 1.35 (s, 6H), 1.81-1.90 (m, 4H), 2.08 (s, 3H), 2.20 (s, 3H), 3.93-3.97 (t, 2H, J = 6.0 Hz), 6.56-6.59 (d, 1H, J = 7.4 Hz), 6.66 (s, 1H), 6.91-6.94 (d, 1H, J = 7.4 Hz), 7.46-7.48 (t, 1H, J = 15.9 Hz), 7.78-7.85 (m, 2H), 8.52 (s, 1H), 8.93 (s, 1H).

1-Ethoxy-5-methoxy-8-phenyl-2-(2H-tetrazol-5-yl)-8H-3-oxa-8-aza-cyclopenta[a]indene: The nitrile **3i** (28.7 mg, 0.086 mmol) was used to yield 31.5 mg of the product (98 %): ^{1}H NMR (CD_3COCD_3) δ 1.10-1.15 (t, 3H, J = 6.8 Hz), 2.85 (bs, 1H), 3.91 (s, 3H), 3.90-3.97 (q, 2H, J = 6.8 Hz), 6.96-7.00 (dd, 1H, J = 2.6 and 9.3 Hz), 7.34 (d, 1H, J = 2.6 Hz), 7.49-7.52 (d, 1H, J = 9.3 Hz), 7.48-7.50 (m, 1H), 7.66-7.68 (m, 4H).

Acknowledgments: We thank the National Institutes of Health and the Parke-Davis Co. for funding of this work. We are also grateful to Elf AtoChem for generous samples of perfluoroalkylethyl iodides and OxyChem for BTF. SH thanks the Spanish Ministry of Education for a postdoctoral fellowship.

References and Notes

1. a) Horváth, I. T.; Rábai, J. *Science* **1994**, *266*, 72. b) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823. c) Cornils, B. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2057. d) Horváth, I. T. *Acc. Chem. Res.* **1998**, *31*, 641.
2. a) Curran, D. P. *Chemtracts—Org. Chem.* **1996**, *9*, 75. This paper also contains a brief overview of the physical and chemical properties of fluorinated liquids (fluorous solvents) as related to organic synthesis. b) Curran, D. P. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1175.
3. a) Curran, D. P.; Hadida, S.; He, M. *J. Org. Chem.* **1997**, *62*, 6714. b) Kainz, S.; Luo, Z. Y.; Curran, D. P.; Leitner, W. *Synthesis* **1998**, 1425.
4. Tin hydrides: a) Curran, D. P.; Hadida, S. *J. Am. Chem. Soc.* **1996**, *118*, 2531. b) Horner, J. H.; Martinez, F. N.; Newcomb, M.; Hadida, S.; Curran, D. P. *Tetrahedron Lett.* **1997**, *38*, 2783. c) Hadida, S.; Super, M. S.; Beckman, E. J.; Curran, D. P. *J. Am. Chem. Soc.* **1997**, *119*, 7406. d) Ryu, I.; Niguma, T.; Minakata, S.; Komatsu, M.; Hadida, S.; Curran, D. P. *Tetrahedron Lett.* **1997**, *38*, 7883. e) Curran, D. P.; Hadida, S.; Kim, S.-Y.; Luo, Z., full paper submitted for publication. Other tin chemistry: f) Curran, D. P.; Hoshino, M. *J. Org. Chem.* **1996**, *61*, 6480. g) Larhed, M.; Hoshino, M.; Hadida, S.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 5583. h) Hoshino, M.; Degenkolb, P.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 8341. i) Spetseris, N.; Hadida, S.; Curran, D. P.; Meyer, T. Y. *Organometallics* **1998**, *17*, 1458. j) Larhed, M.; Hallberg, A.; Kim, S.-Y.; Curran, D. P., submitted for publication. k) Komatsu, M.; Ryu, I.; Luo, Z.; Curran, D. P., *Tetrahedron Lett.*, in press. l) Curran, D. P.; Luo, Z.; Degenkolb, P. *Bioorg.*

Med. Chem. Lett. **1998**, *8*, 2403. m) Curran, D. P.; Luo, Z. *Med. Chem. Res.* **1998**, *8*, 261.

5. a) Studer, A.; Curran, D. P. *Tetrahedron* **1997**, *53*, 6681. b) Studer, A.; Jeger, P.; Wipf, P.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 2917. c) Curran, D. P.; Ferritto, R.; Hua, Y. *Tetrahedron Lett.* **1998**, *39*, 4937.
6. a) Wittenberger, S. J. *Org. Prep. Proced. Int.* **1994**, *26*, 499. b) Meier, H. R.; Heimgartner, H. In *Heteroarenes III, Part 4*; 4th ed.; E. Schaumann, Ed.; Thieme-Verlag: Stuttgart, 1994; Vol. Ed; pp 664. c) Koldobskii, G. I.; Ostrovskii, V. A. *Russ. Chem. Rev. (Engl. Transl.)* **1994**, *63*, 797. d) Palkowitz, A. D.; Thrasher, K. J.; Hauser, K. L. *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A., ed; Wiley: NY; 1995, Vol 7, pp. 5035-5037.
7. a) Butler, R. N. *Advances in Heterocyclic Chemistry*; Katritzky,A. R.;Boulton, A. J.; Eds.: Academic Press, New York, NY, 1977; vol 21, pp. 323-435. b) Benson, F. R. *Heterocyclic Compounds*; Elderfield, R., Ed.; Wiley; NY, 1967; vol. 8, pp 1-104.
8. a) Duncia, J. V.; Pierce, M. E.; Santella, J. B. III; *J. Org. Chem.* **1991**, *56*, 2395. b) Sisido, K.; Nabika, K.; Isida, T.; Kozima, S.; *J. Organometal. Chem.* **1971**, *33*, 337.
9. BTF is benzotrifluoride ($C_6H_5CF_3$, bp = 103°C, mp = –29°C), sold inexpensively under the trade name Oxsol2000® by **OxyChem**. See: a) Ogawa, A.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 450. b) Maul, J. J.; **Ostrowski**, P. J.; Umblacker, G. A; Linclau, B.; Curran, D. P. In "Modern Ogranic Solvents", Knochel, P, ed.; Springer-Verlag, in press.
10. Merge, J. M.; Roberts, S. M. *Synthesis* **1979**, 471.
11. Hudlicky, M. *Chemistry of Organic Fluorine Compounds;* 2nd (revised) edition ed.; Ellis-Horwood: NY, 1992, pp 903.