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A Strategic Alternative to Solid Phase Synthesis: Preparation of a Small Isoxazoline Library by "Fluorous Synthesis"

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Abstract: The preparation of a highly fluorinated silyl group and its use as a "fluorous label" are described. Allyl and propargyl alcohols are rendered fluorous upon attachment to the fluorous label. Cycloaddition of the fluorous dipolarophiles to nitrile oxides provides the corresponding isoxazol(in)es which are purified by simple liquid–liquid extractions. After detachment of the label and renewed extraction, the organic isoxazol(in)es are obtained. This new fluorous methodology allows the preparation of isoxazol(in)es in high purities without using chromatography. © 1997 Elsevier Science Ltd.

Introduction

During the past five years, combinatorial chemistry has rapidly become an important tool in drug discovery.[1] The ability to prepare a large number of different compounds in a short time provides the diversity needed for the discovery of lead compounds. Rapid access to derivatives by combinatorial synthesis allows the prompt optimization of a lead compound. Combinatorial synthesis has also been successfully applied in supramolecular chemistry,[2] in the development of chiral catalysts,[3] and even in material science.[4]

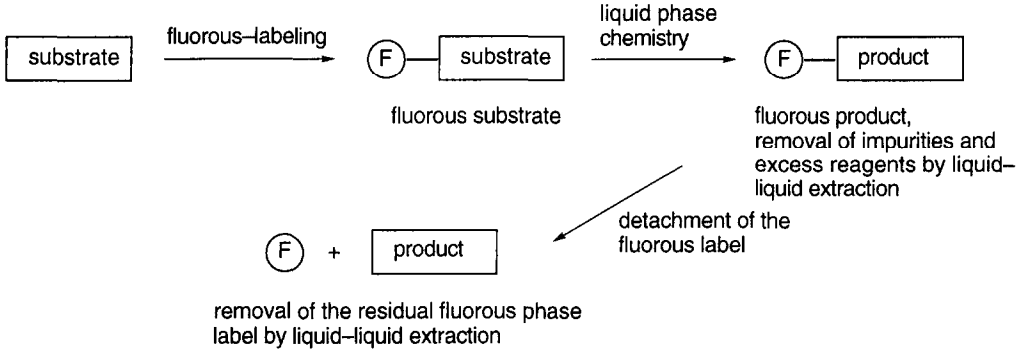
The demands of combinatorial synthesis have sparked a move away from traditional synthesis of small organic molecules in the liquid phase towards solid phase synthesis.[1,5] Solid phase synthesis uses polymer-bound substrates and this provides a significant advantage over liquid phase synthesis at the stage of purification: polymer-bound products can easily be separated by filtration from non-polymeric reaction components of any type. However, this advantage does not come without a price. The phase separation that is such an advantage at the purification stage can be a detraction at the reaction stage, where the long course of research in organic synthesis has shown the benefits of reactions in solution. In addition, both identification and analysis are more difficult with polymer-bound organic molecules than with small, soluble organic molecules. The dramatic advances in small molecule synthesis on the solid phase, as typified by the articles in the Symposium in Print, clearly show that these problems can be solved.

Recently, solid phase combinatorial synthesis has be supplemented by new methods based on liquid phase synthesis either with soluble polymers[6] or with small organic molecules.[7,8] These methods often combine liquid phase reactions with simple purifications based filtration[6] or extraction.[8] We describe herein a fundamental strategic alternative to solid phase synthesis termed "fluorous synthesis". The strategy is designed to unite the advantages of solid phase synthesis with the advantages of traditional organic synthesis of small molecules in the liquid phase.

By the late 40s, the special properties of perfluorinated solvents toward fluorinated and non-fluorinated compounds were known.[9] However, it took almost 50 years for synthetic chemists to recognize the potential of these special properties for purification purposes in preparative organic chemistry. Following the introduction of fluorous biphasic systems in seminal papers by Zhu[10] and Horváth and Rábai,[11] we[12,13] and others[14] have further explored fluorous[11] chemistry. "Fluorous" molecules are rich in carbon-fluorine bonds and they partition out of an organic (or water) phase and into a perfluorinated (or highly fluorinated) phase in any phase separation technique. For example, perfluorocarbon solvents are not miscible in many organic solvents, so it is easy to conduct "fluorous/organic" extractions.

Very recently, we have communicated a number of fluorous strategies designed for traditional and automated (combinatorial) synthesis.[13] In several of these strategies, an organic substrate is rendered fluorous by attachment to a "fluorous phase label."[15] Reactions are then conducted and the fluorous-labeled products are purified by liquid-liquid extraction. The excess reagents used in the reaction and the organic impurities partition into the organic or water phases. At the end of the synthesis, the target organic product is released by detachment from the fluorous label (Figure 1). In the present paper, we describe in full detail[13] the preparation of a small isoxazole and isoxazoline library by using fluorous synthesis.

Figure 1. Fluorous Synthesis



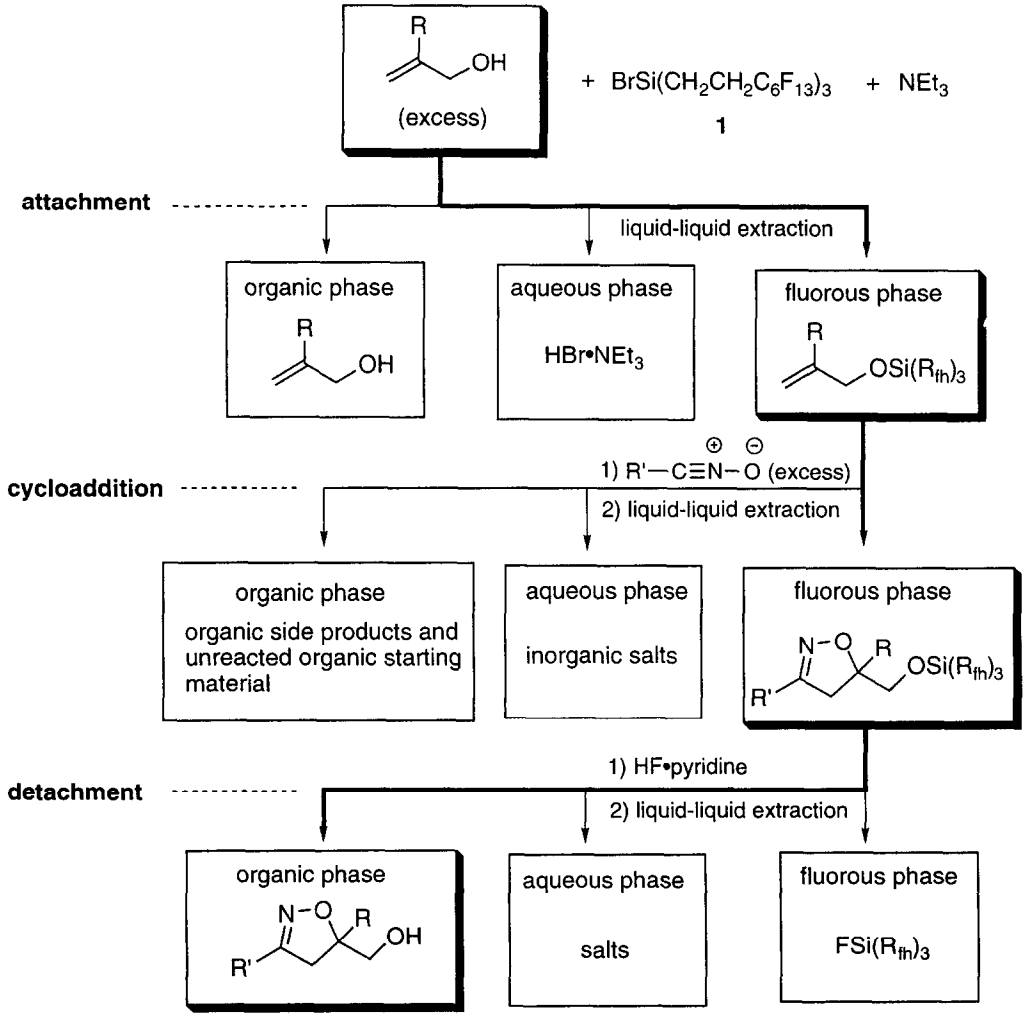
Results and Discussion

As a test reaction to demonstrate the possibilities of fluorous synthesis, we chose the 1,3-dipolar cycloaddition of nitrile oxides to alkenes and alkynes.[16] The general strategy for the preparation of an isoxazoline library by using this fluorous protocol is shown in Scheme 1. The process occurs in three stages: attachment of the fluorous label, cycloaddition, and detachment. At each stage, a reaction is conducted and the products are purified by a three-phase extraction with an organic solvent, water, and a fluorous solvent. The diagram shows the components of each phase in order from left to right. Thick arrows and shadow boxes track the phase of the target compound as it moves through the synthesis.

The labeling step comprises the attachment of the labeling-reagent, a highly fluorinated bromo silane **1**, to an allyl alcohol. After three-phase extraction, the fluorous allyl silyl ether is isolated by evaporation of the fluorous phase. The excess allyl alcohol partitions into the organic phase, and the

inorganic salts formed during the reaction partition into the aqueous phase. In the cycloaddition step, the fluorous silyl ether is reacted with a nitrile oxide to form the corresponding cycloadduct (an isoxazoline is shown). As in solid phase synthesis, excess reagents are used to drive the reaction to completion. However, most of these cycloadditions are expected to occur in high yield, so the real purpose for using excess reagents in these demonstration experiments is to probe the efficiency of the separation design by producing "organic impurities." Three-phase extraction provides the target fluorous isoxazoline. The aqueous phase contains the inorganic salts and the organic phase contains all the unreacted organic reaction components and impurities derived therefrom. In the final stage, cleavage of the fluorous silyl group under standard conditions affords the organic isoxazoline, which is purified by renewed three-phase extraction. The final product is isolated from the organic phase, and any remnants of the label are left in the fluorous phase.

Scheme 1

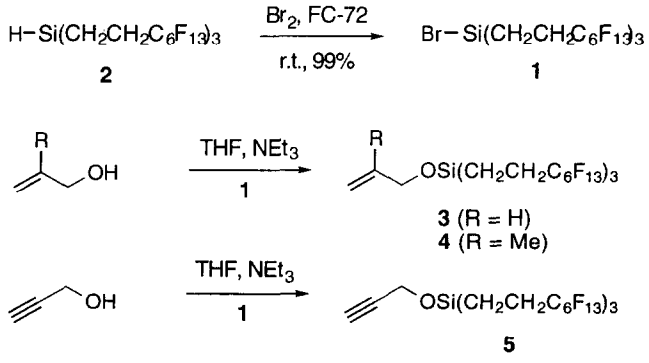


The initial sequence of experiments was conducted along the lines of traditional "synthetic methods" development. The products from both the organic and fluorous phases were analyzed by ^{1}H NMR spectroscopy, and the "target products" (in shadow boxes in Scheme 1) were fully characterized by the usual spectroscopic methods (^{1}H-NMR, ^{13}C-NMR, IR, and EI-MS). In a second stage, a small "library" (six compounds) was generated by direct conversion of the alcohols to the final organic heterocycles without characterization of any of the fluorous intermediates.

The synthesis of the label and the labeling process are shown in Scheme 2. Silanes are very useful protecting groups in organic synthesis,[17] and we therefore selected a fluorous phase label based on silane chemistry. Treatment of the known[18] silane **2** with bromine in FC-72[19] afforded the corresponding fluorous bromosilane **1** in quantitative yield (Scheme 2).

Silylations of the alcohols were performed in THF with Et_3N. The alcohol was used in excess (2-4 equiv) to simulate incomplete conversion. After completion of the reaction and evaporation of the solvent, the crude reaction mixture was purified by a three-phase extraction using FC-72[19] (bottom), CH_2Cl_2 (middle), and water (top). The organic-aqueous bilayer was additionally extracted twice with FC-72. In the ^{1}H-NMR spectra of the CH_2Cl_2 extracts, we could not observe any resonances of fluorinated products, showing the efficient partitioning of the fluorous compounds into FC-72 during extraction. Evaporation of the combined fluorous layers yielded the desired silyl ethers **3**-**5** in 85-90% yield. A side product, tentatively identified as the silanol derived from **1**, was formed (10-15%) as determined by ^{1}H-NMR analysis.[20] A limitation of the extractive purification procedure is that fluorous side products, if formed, are not separated from the tagged products. However, since the fluorous silanol does not interfere with the cycloaddition and will be removed in the final extraction, crude silyl ethers can be used for the subsequent reactions. Silyl ether **5** was used for the cycloaddition without further purification as a 87:13 mixture of **5** and silanol.[20] However, silyl ethers **3** and **4** were further purified by flash chromatography (SiO_2, 40-50% yield due to partial cleavage of the silyl group). The overall yields and purities of reaction products from pure **3** and **4** were comparable with those from crude **5**, thereby showing that the removal of residual fluorous impurity is not needed.

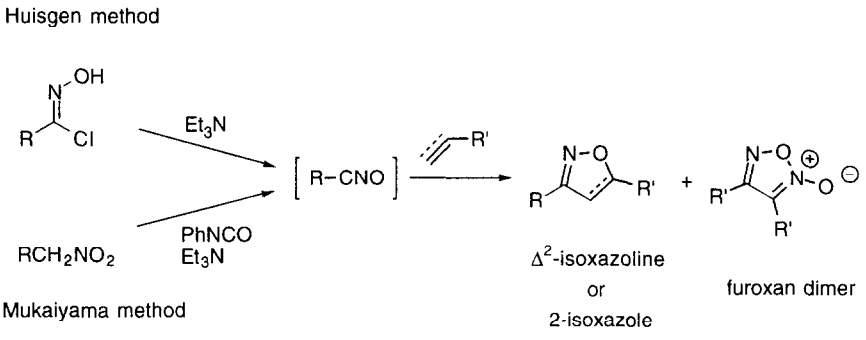
Scheme 2



To generate different impurity profiles in the cycloadditions, we used both of the popular procedures to generate nitrile oxides (Figure 2). In the Huisgen method, an oximic acid chloride is treated with NEt_3 to provide the corresponding nitrile oxide.[21] The more popular method is the dehydration of a nitroalkane with phenylisocyanate, as first described by Mukaiyama.[22] In the

Mukaiyama procedure, *sym*-diphenyl urea (PhNHCONHPh) is generated as a byproduct during the nitrile oxide formation. Nitrile oxides, if used in excess or in the reaction with unreactive dipolarophiles, dimerize to form the corresponding furoxan as a side product. According to the conventional Huisgen and Mukaiyama cycloaddition protocols, the byproducts, excess reagents, and furoxan are separated from the desired cycloadducts by chromatography.

Figure 2. Methods of Nitrile Oxide Generation



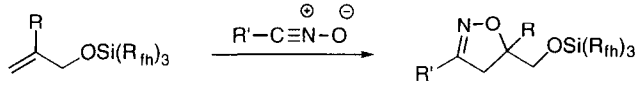
tert-Butyl nitrile oxide and benzonitrile oxide were prepared by Huisgen's method from the corresponding oximic acid chlorides and Et_3N. The cycloadditions were performed in CH_2Cl_2 at room temperature for 24 h. The silyl ethers **3-5** were not completely soluble in CH_2Cl_2, as determined by the naked eye.[23] Cycloadditions of nitrile oxides with terminal alkenes occur in high yield. However, the nitrile oxides were used in large excess (4-8 equiv) to simulate the need to drive reactions of less reactive substrates to completion and to generate large amounts of furoxan to separate from the fluorous products. After removal of the solvent, the residue was purified by three-phase extraction using FC-72 (bottom), water (middle), and benzene (top). The isoxazolines **6-9** were isolated in nearly quantitative yield as determined by simple weighing (Schemes 3a,b).

In the ^{1}H-NMR spectra of the fluorous heterocycles **6-8**, no impurities could be observed. In the reaction of the disubstituted alkene **4** with benzonitrile oxide to form isoxazoline **9**, 3% of starting alkene **4** remained, as determined by ^{1}H-NMR analysis of the fluorous extracts. For isoxazolines **7** and **12**, weighed yields were slightly over 100%. It is not clear whether this is due to experimental error or to the presence of small amounts of impurities. That all the yields were not well over 100% is significant evidence that the extractive purification was successful, especially considering the large excess of reagents that was added. The yield of isoxazole **14** was corrected for the presence of the silanol. The amount of silanol[20] observed (13% as estimated by ^{1}H-NMR integration) corresponded to the amount of silanol present in the starting propargyl ether **5**. Partial cleavage of the fluorous silyl group under the reaction conditions was observed in the reaction of silyl ether **5** with benzonitrile oxide. After extraction, isoxazole **15** containing 40% of the silanol[20] was isolated. Considering that the starting silyl ether **5** contained only 13% of silanol, we assume that about 27% of the silyl group was cleaved during the reaction. Indeed, resonances of the desilylated isoxazole **27** could be identified in the ^{1}H-NMR spectrum of the benzene layer. Although the desilylation is not a desired process at this stage, the ability to extractively separate the organic alcohol from the fluorous silyl ether showed that the final detachment and purification stage would work. In the other cases, the corresponding desilylated isoxazoles and isoxazolines could not be observed in the ^{1}H NMR spectrum of the benzene layer.

Cycloadditions by the Mukaiyama method illustrate how the labels can double as protecting groups. Unprotected primary and secondary alcohols cannot generally be used in this method because they react with the isocyanate faster than the nitro compound does. In the case of methyl and propyl nitrile oxide, the dipoles were prepared according to Mukaiyama's method by dehydration of nitroethane and nitrobutane. The reactions were run at room temperature for 3 days in benzotrifluoride (BTF, trifluoromethylbenzene, $C_6H_5CF_3$).[12a] As before, an unduly large excess of (10 equiv) of the nitrile oxide was generated. Extractive purification as described above afforded isoxazolines **10-13** and isoxazoles **16** and **17** in excellent yields. In the reaction of propyl nitrile oxide with silyl ether **4**, isoxazoline **13** was isolated from the fluorous extracts as a 94:6 mixture of **13** and unreacted starting alkene **4**. The yields of isoxazoles **16** and **17** were corrected based on pure silyl propargyl ether **5**, as discussed above.

The high purities obtained after the fluorous extraction are impressive considering that the desired fluorous product results from the reaction of the lone equivalent of fluorous alkene with only one of the 30 equiv of organic reactants added (10 equiv of nitro compound and 20 equiv of phenyl isocyanate). Unreacted nitro and isocyanate precursors, furoxan, the urea, and any other organic side products were successfully removed from the cycloadducts by extraction. For every extraction, the benzene layer was also analyzed by ^{1}H-NMR spectroscopy. Characteristic resonances of fluorous compounds were not observed, proving the high partition of the fluorous compounds into the fluorous phase during extraction. The appropriate choice of the organic solvent in the extraction of a fluorous compound from an organic solvent with FC-72 is crucial. A solvent in which the fluorous compound shows low solubility is preferable. If CH_2Cl_2 was used as organic phase in the extraction of isoxazoline **6**, around 5% of **6** remained in the organic phase even after threefold extraction with FC-72.

Scheme 3a. Weighed Yields of Crude Isoxazolines



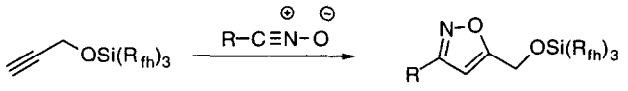
3,4 **6-13**

(R_{fh} = $CH_2CH_2C_6F_{13}$)

R \ R'	*t*-Bu	Ph	Me	Pr
H (% yield)	99% (**6**)	96% (**8**)	100% (**10**)	105% (**12**)
Me (% yield)	101% (**7**)	97% (**9**)[1]	99% (**11**)	94% (**13**)[1]

[1]Remaining material was unreacted alkene.

Scheme 3b. Weighed Yields of Crude Isoxazoles



5 14-17

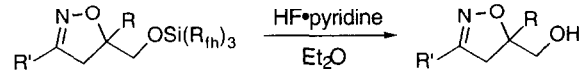
R	*t*-Bu	Ph	Me	Pr
% yield[1]	99% (**14**)	73% (**15**)[2]	99% (**16**)	99% (**17**)

[1]Yields are corrected for pure starting material, see text.

[2]Remaining material is silanol formed by desilyation during the rea

Desilylations of the isoxazolines **6-13** were performed with HF•pyridine in Et_2O at room temperature (Schemes 4a,b). After evaporation of the solvent and liquid-liquid extraction (FC-72, CH_2Cl_2, aq. NH_4Cl), the isoxazolines **18-25** were obtained from the organic extracts with high purities (GC-analysis, >91%) in moderate to excellent yields (29-99%). Although GC analysis may not detect all possible impurities, ^{1}H-NMR analysis of the desilylated products supported the purities determined by GC-analysis. The low yields observed for isoxazolines **22-24** are probably due to the volatility of these heterocycles. Deprotection of isoxazoles **14-17** was conducted under similar conditions. The corresponding 5-hydroxymethyl substituted isoxazoles **26-29** were isolated in quantitative yield with high purity (>97% by GC).

Scheme 4a. Isoxazolines from Desilylation

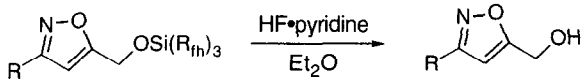


6-13 18-25

R'	R	yield (%)	purity (%)[1]	compound
t-Bu	H	99	91	**18**
t-Bu	Me	99	99	**19**
Ph	H	99	95	**20**
Ph	Me	95	98	**21**
Me	H	29	93	**22**
Me	Me	31	99	**23**
Pr	H	48	94	**24**
Pr	Me	99	99	**25**

[1]Determined by GC-analysis

Scheme 4b. Isoxazoles from Desilylation



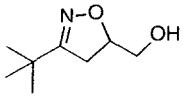
14-17 **26-29**

R	yield (%)	purity (%)[1]	compound
t-Bu	99	99	**26**
Ph	99	98	**27**
Me	99	99	**28**
Pr	99	97	**29**

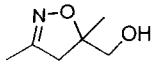
[1]Determined by GC-analysis.

After studying the individual steps in the fluorous isoxazole and isoxazoline synthesis, we next executed the overall reaction sequence as outlined in Scheme 1 without analyzing any intermediates. Reactions were run on 0.3-0.7 mmol scale. Brominolysis of silane **2** followed by silylation of the alcohol provided after fluorous extraction the corresponding alkene or alkyne. Cycloaddition by using either the Huisgen or Mukaiyama method as described before afforded after extractive purification the perfluorinated isoxazoles and isoxazolines. Desilylation with HF•pyridine and renewed extraction completed the reaction sequence. In this manner, isoxazolines **18**, **23**, **24**, and **30a,b** were obtained in 32-83% overall yield based on starting silane **2**, with 94-99% GC purity (Figure 3). Isoxazole **29** was isolated in 83% overall yield (97% purity). Interestingly, the perfluorinated silyl group has no special effect as stereo-directing group in the cycloaddition with the fluorous silyl ether of 3-buten-2-ol. The *anti:syn* ratio (70:30) of **30a,b** is similar to that obtained for the reaction of benzonitrile oxide with the corresponding trimethylsilyl protected alcohol (71:29).[24]

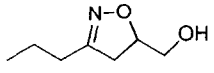
Figure 3



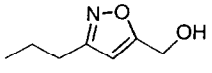
18 (66% yield/99% purity)



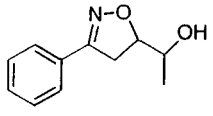
23 (32% yield/99% purity)



24 (73% yield/94% purity)



29 (83% yield/97% purity)



(*anti:syn* = 70:30)

30a,b (62% yield/97% purity)

Conclusions

The results of this study validate the idea that "fluorous synthesis" is a useful strategy. As suggested in the introduction, the fluorous strategy has many of the favorable features of both solid phase and organic liquid phase synthesis. Like solid phase synthesis, the substrates are labeled with a group that influences their phase behavior. This facilitates the separation stage of each synthetic step, and permits the use of excess reagents and reactants. Since nearly all known reagents and reactants are organic or inorganic, the labeling of a substrate as fluorous immediately differentiates that substrate and all its subsequent products from everything else that is added to a reaction.

However, like organic liquid phase synthesis, the substrates are single entities that can be co-dissolved with organic and inorganic reagents and reactants in suitable solvents. Also like organic synthesis, it is possible to follow reactions by standard techniques (TLC was used in this work) and to partially or fully characterize any or all fluorous intermediates by standard spectroscopic methods. These intermediates can also be purified, if desired. In solid phase synthesis, bound intermediates cannot be purified, and although new characterization methods for polymers are very helpful, the characterization of fluorous intermediates will probably always be easier if for no other reason than because they are single entities. In this work, we have fully characterized all of the fluorous intermediates in the isoxazoline synthesis. These fluorous intermediates have molecular weights between 1,124 and 1,259, and can be characterized by normal spectroscopic methods (^{1}H-NMR, ^{13}C-NMR, IR, and EI-MS). Despite the high molecular weights, mass spectroscopy is not difficult because of the well known characteristic of organofluorine molecules to have low volatilities.[9c] ^{19}F-NMR spectroscopy can also be used as a tool, but for these molecules it is not very helpful because the differences in chemical shifts are very small.

Major limitations of fluorous phase synthesis are not yet apparent at this early stage, but several are possible. Solubility is an obvious concern, since the fluorous label makes molecules "less organic". However, so far we have had good success in using for reactions organic solvents known to solubilize fluorous compounds or "hybrid solvents" like benzotrifluoride, which dissolve both organic and fluorous compounds. Steric or electronic effects of the fluorous label could also modify the inherent reactivity profile of an attached organic substrate. Another major concern is the size of the label needed to render an organic molecule fluorous. The final products in this early work all have molecular weights under 200. Indeed, we already know that labeling reagent **1** probably does not have sufficient fluorine content to render organic molecules in the molecular weight range of 300-500 fluorous as measured by an organic-fluorous liquid-liquid extraction.[25] The problem of generating labels for larger molecules has already been solved in another setting,[13] and the details of the synthesis of small libraries of Ugi and Biginelli reaction products with molecular weights of up to 500 will be reported in due course.

We have recently suggested that a valuable goal in both traditional and library synthesis is the strategic planning of steps such that the phase of the final product is different from the phases of everything else in the reaction mixture.[12c,13] When this goal is met, products can be purified simply by extraction, evaporation or filtration. In this paper, we have introduced the application of a perfluorinated silyl protecting group as a fluorous phase label for use in "fluorous synthesis". The fluorous strategy is analogous to the now common use of polymers in small molecule synthesis yet it retains many of the advantages of traditional small molecule synthesis in solution. Fluorous synthesis is one member of a larger collection of fluorous techniques that provide synthetic chemists with simple new methods to differentiate the phase of one reaction component from that of others, and thereby advance the goal of purification by phase separation.[12,13]

Experimental

General. Anhydrous solvents were freshly distilled from either sodium benzophenone ketyl, P_2O_5, or CaH_2. FC-72™ and FC-84™ were obtained from 3M. FC-84 consists of mostly of isomers of C_7F_{16} (bp 80 °C) and can be used instead of FC-72.

Bromo *tris*(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silane, (Bromo *tris*(2-perfluorohexylethyl)silane (1): *Tris*(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silane (**2**)[18] (1.00 g, 0.94 mmol) was dissolved in FC-72 (4 mL) at 25 °C under argon. Bromine (0.08 mL, 1.41 mmol) was slowly added and the resulting solution was stirred for 8 h at 25 °C. The reaction mixture was washed twice with CH_2Cl_2. Evaporation of the fluorous layer yielded the bromosilane **1** as a colorless oil (1.08 g, 99%): IR (neat) 2952, 1443, 1362, 1317, 1240, 1209, 1145, 1122, 1073, 905, 812, 737, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24-1.30 (m, 6 H), 2.11-2.28 (m, 6 H); ^{19}F NMR (470MHz, $CDCl_3$) δ (rel. to $FCCl_3$) −126.82, −123.88, −123.53, −122.55, −116.32, −81.43.

Allyloxy-*tris*(2-perfluorohexylethyl)silane (3): Allyl alcohol (0.06 mL, 0.91 mmol) and triethylamine (0.13 mL, 0.91 mmol) were dissolved in dry THF (2 mL) under argon. A mixture of bromo *tris*(2-perfluorohexylethyl)silane **1** (260 mg, 0.23 mmol) in THF (2 mL) was slowly added to the above mixture at 25 °C. The resulting mixture was stirred at 25 °C for 3 h. After removal of the solvent, the residue was purified by three-phase extraction with FC-72 (10 mL), CH_2Cl_2 (10 mL), and H_2O (10 mL). The organic-aqueous biphase was additionally extracted twice with FC-72 (10 mL). After evaporation of the combined fluorous extracts, the residue was further purified by flash-chromatography (hexanes-Et_2O, 50:1), yielding **3** as a colorless oil (115 mg, 45%): IR (neat) 2949, 2910, 1362, 1317, 1234, 1211, 1196, 1144, 1121, 1075, 1040, 904, 845, 812, 736, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93-0.99 (m, 6 H), 2.03-2.20 (m, 6 H), 4.21 (d, J = 5.0 Hz, 2 H), 5.18 (dd, J_1 = 10.4 Hz, J_2 = 1.5 Hz, 1 H), 5.26 (dd, J_1 = 17.1 Hz, J_2 = 1.5 Hz, 1 H), 5.84-5.97 (m, 1 H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 3.44, 25.56 (t, J = 23.3 Hz), 64.93, 108.21-123.06 (m, CF_2, CF_3), 115.93, 137.85; ^{19}F NMR (470 MHz, $CDCl_3$) δ (rel. to $CFCl_3$) −126.89 (t, J = 4.7 Hz), −124.06, −123.60, −122.64, −116.96 (t, J = 18.8 Hz), −81.57 (t, J = 9.4 Hz); MS *m/z* 1126 (M^+), 451, 349, 309, 239, 195.

***tris*(2-Perfluorohexylethyl)-(2-methylallyloxy)silane (4):** 2-Methyl-2-propen-1-ol (0.47 mL, 5.59 mmol) and triethylamine (0.79 mL, 5.59 mmol) were dissolved in dry THF (10 mL) under argon. A mixture of bromo *tris*(2-perfluorohexylethyl)silane (**1**) (1.60 g, 1.39 mmol) in THF (5 mL) was slowly added to the above solution at 25 °C. The resulting mixture was stirred at 25 °C for 2 h. After removal of the solvent, the residue was purified by three-phase extraction with FC-72 (20 mL), CH_2Cl_2 (20 mL), and H_2O (20 mL). The organic-aqueous biphase was additionally extracted twice with FC-72 (20 mL). After evaporation of the combined fluorous extracts, the residue was further purified by flash-chromatography (hexanes-Et_2O, 50:1), yielding **4** as a colorless oil (602 mg, 46%): IR (neat) 2949, 2916, 1362, 1317, 1237, 1206, 1145, 1121, 1074, 905, 736, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94-0.99 (m, 6 H), 1.72 (s, 3 H), 2.03-2.21 (m, 6 H), 4.08 (s, 3 H), 4.89 (s, 1 H), 4.94 (s, 1 H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 3.48, 18.96, 25.68 (t, J = 22.5 Hz), 67.65, 105.87-124.09 (m, CF_2, CF_3), 111.91, 145.11; ^{19}F NMR (470 MHz, $CDCl_3$) δ (rel. to $CFCl_3$) −126.95 (q, J = 4.7 Hz), −124.13, −123.64, −122.68, −117.01 (t, J = 14.1 Hz), −81.64 (t, J = 9.4 Hz); MS *m/z* 1140 (M^+), 239, 137.

***tris*(2-Perfluorohexylethyl)(prop-2-ynyloxy)silane (5):** Propargyl alcohol (0.10 mL, 1.74 mmol) and triethylamine (0.26 mL, 1.74 mmol) were dissolved in dry THF (10 mL) under argon. A mixture of bromo *tris*(2-perfluorohexylethyl)silane (**1**) (1.00 g, 0.87 mmol) in THF (2 mL) was slowly added to the above solution at 25 °C. The resulting suspension was stirred at 25 °C for 3 h. After removal of the solvent, the residue was purified by three-phase extraction with FC-72 (15 mL), CH_2Cl_2 (15 mL), and H_2O (15 mL). The organic-aqueous biphase was additionally extracted twice with FC-72 (15 mL). Evaporation of the combined fluorous extracts yielded a mixture of **5** and silanol in a ratio of 87 to 13 as a colorless oil (960 mg, 98 %): IR (neat) 3317, 2950, 2911, 1443, 1362, 1317, 1244, 1234, 1221, 1198, 1144, 1120, 1076, 905, 812, 736, 708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98-1.04 (m, 6 H), 2.07-2.24 (m, 6 H), 2.50 (t, J = 2.5 Hz, 1 H), 4.38 (d, J = 2.6, 2 H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 3.72, 25.71 (t, J = 23.3 Hz), 52.50, 75.85, 82.46, 105.94-124.18 (m, CF_2, CF_3); MS *m/z* 778 ($(M^+ + 1) - CH_2CH_2(CF_2)_5CF_3$), 374, 293, 226, 184.

General Procedure for the Preparation of Isoxazol(in)es by Mukaiyama's Method (General Procedure 1): To a solution of the silyl ether (0.10 mmol) in BTF (4 mL) were added the nitro alkane (0.99 mmol), phenyl isocyanate (0.22 mL, 1.98 mmol), and two drops of triethylamine. The reaction mixture was

stirred at 25 °C for 3 days. After removal of the solvent, the residue was purified by three-phase extraction with FC-72 (20 mL), H_2O (20 mL), and benzene (20 mL). The organic-aqueous biphase was additionally extracted twice with FC-72 (20 mL). The combined fluorous extracts were evaporated to yield the desired isoxazol(in)e. (For small scale reactions the crude reaction mixture was diluted with benzene and extracted three times with FC-72. The combined fluorous extracts were filtered and evaporated.)

General Procedure for the Preparation of Isoxazol(in)es by Huisgen's Method (General Procedure 2): The silyl ether (0.09 mmol) and the oxime (0.36 mmol) were placed at 25 °C in CH_2Cl_2 (6 mL), triethylamine (0.36 mmol) was added and the reaction mixture was stirred at 25 °C for 24 h. After removal of the solvent, the residue was purified by three-phase extraction with FC-72 (15 mL), H_2O (15 mL), and benzene (15 mL). The organic-aqueous biphase was additionally extracted twice with FC-72 (15 mL). The combined fluorous extracts were evaporated to yield the desired isoxazol(in)e. (For small scale reactions the crude reaction mixture was diluted in benzene and extracted three times with FC-72.)

3-*tert*-Butyl-5-*tris*(2-perfluorohexylethyl)silanyloxymethyl-4,5-dihydroisoxazole (6): Prepared according to general procedure 2 with the allyl silyl ether **3** (0.054 g, 0.048 mmol), *tert*-butyl hydroximic acid chloride (46.0 mg, 0.34 mmol), and triethylamine (0.05 mL, 0.34 mmol) in CH_2Cl_2 (4 mL) to afford isoxazoline **6** (59 mg, 99%): IR (neat) 2363, 1442, 1363, 1317, 1240, 1199, 1144, 1121, 1072, 905, 811, 744, 737, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91-1.00 (m, 6 H), 1.10 (s, 9 H), 2.04-2.22 (m, 6 H), 2.78 (dd, J_1 = 16.9 Hz, J_2 = 7.2 Hz, 1 H), 3.00 (dd, J_1 = 16.9 Hz, J_2 = 10.6 Hz, 1 H), 3.66 (dd, J_1 = 11.4 Hz, J_2 = 4.9 Hz, 1 H), 3.76 (dd, J_1 = 11.2 Hz, J_2 = 3.3 Hz, 1 H), 4.57-4.65 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.78, 24.61 (t, J = 23.3 Hz), 27.71, 32.86, 35.42, 64.59, 79.47, 104.54-122.85 (m, CF_2, CF_3), 165.81; ^{19}F NMR (470 MHz, $CDCl_3$) δ (rel. to $CFCl_3$) −126.78 (t, J = 4.7 Hz), −123.87, −123.50, −122.54, −116.72 (t, J = 14.1 Hz), −81.41 (t, J = 14.1 Hz); MS *m/z* 1206 (M^+ − F), 309, 239, 195, 126.

3-*tert*-Butyl-5-methyl-5-*tris*(2-perfluorohexylethyl)silanyloxymethyl-4,5-dihydroisoxazole (7): Prepared according to general procedure 2 with the allyl silyl ether **4** (0.104 g, 0.091 mmol), *tert*-butyl hydroximic acid chloride (50.0 mg, 0.36 mmol), and triethylamine (0.054 mL, 0.364 mmol) in CH_2Cl_2 (4 mL) to afford isoxazoline **7** (115 mg, 101%): IR (neat) 2976, 2939, 2913, 2875, 2361, 2343, 2331, 1365, 1316, 1239, 1208, 1144, 1120, 1073, 899, 745, 736, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94-0.99 (m, 6 H), 1.16 (s, 9 H), 1.31 (s, 3 H), 2.10-2.21 (m, 6 H), 2.61 (d, J = 16.7 Hz, 1 H), 2.94 (d, J = 16.7 Hz, 1 H), 3.57 (d, J = 10.9 Hz, 1 H), 3.62 (d, J = 11.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.89, 22.15, 24.73 (t, J = 24.0 Hz), 27.73, 33.03, 41.32, 67.80, 85.22, 105.16-122.96 (m, CF_2, CF_3), 165.95; ^{19}F NMR (470 MHz, $CDCl_3$) δ (rel. to $CFCl_3$) −127.06 (t, J = 4.7 Hz), −124.10, −123.72, −122.74, −116.96 (t, J = 14.1 Hz), −81.79 (t, J = 14.1 Hz); MS *m/z* 1220 (M^+ − F), 1126, 795, 475, 309, 239, 195, 140.

3-Phenyl-5-*tris*(2-perfluorohexylethyl)silanyloxymethyl-4,5-dihydroisoxazole (8): Prepared according to general procedure 2 with the allyl silyl ether **3** (0.069 g, 0.061 mmol), phenyl hydroximic acid chloride (38.0 mg, 0.25 mmol), and triethylamine (0.037 mL, 0.25 mmol) in CH_2Cl_2 (4 mL) to afford isoxazoline **8** (73 mg, 96%): IR (neat) 2945, 2912, 1442, 1359, 1316, 1240, 1205, 1144, 1122, 1072, 1018, 904, 745, 737, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91-1.00 (m, 6 H), 2.01-2.19 (m, 6 H), 3.20 (dd, J_1 = 16.6 Hz, J_2 = 8.1 Hz, 1 H), 3.40 (dd, J_1 = 16.6 Hz, J_2 = 10.9 Hz, 1 H), 3.78 (dd, J_1 = 11.5 Hz, J_2 = 4.4 Hz, 1 H), 3.91 (dd, J_1 = 11.5 Hz, J_2 = 2.9 Hz, 1 H), 4.79-4.87 (m, 1 H), 7.35-7.40 (m, 3 H), 7.63-7.66 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.95, 24.66 (t, J = 23.3 Hz), 36.13, 64.85, 80.47, 104.61-119.13 (m, CF_2, CF_3), 126.55, 128.74, 129.06, 130.28, 156.51; ^{19}F NMR (470 MHz, $CDCl_3$) δ (rel. to $CFCl_3$) −126.72 (t, J = 4.7 Hz), −123.86, −123.45, −122.52, −116.72 (t, J = 14.1 Hz), −81.34 (t, J = 9.4 Hz); MS *m/z* 1245 (M^+), 1226 (M^+ − F), 898 (M^+ − $(CH_2)_2(CF_2)_5CF_3$), 378, 309, 239, 195.

5-Methyl-3-phenyl-5-*tris*(2-perfluorohexylethyl)silanyloxymethyl-4,5-dihydroisoxazole (9): Prepared according to general procedure 2 with the allyl silyl ether **4** (0.098 g, 0.086 mmol), phenyl hydroximic acid chloride (53.0 mg, 0.34 mmol), and triethylamine (0.051 mL, 0.34 mmol) in CH_2Cl_2 (4 mL) to afford isoxazoline **9** and starting silyl ether **4** (ratio 97:3): IR (neat) 2934, 2915, 2363, 1443, 1361, 1316, 1238, 1206, 1144, 1121, 1074, 907, 736, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93-0.99 (m, 6 H), 1.43 (s, 3 H), 2.02-2.16 (m, 6 H), 3.03 (d, J = 16.6 Hz, 1 H), 3.37 (d, J = 16.6 Hz, 1 H), 3.69 (d, J = 11.1 Hz, 1 H), 3.74 (d, J = 11.0 Hz, 1 H), 7.37-7.42 (m, 3 H), 7.60-7.63 (m, 2 H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 3.47, 22.66, 25.45 (t, J = 22.5 Hz), 42.57, 68.98, 87.86, 105.75-123.50 (m, CF_2, CF_3), 127.26, 129.50, 130.58, 131.39, 157.25; ^{19}F NMR (470 MHz, $CDCl_3$) δ (rel. to $CFCl_3$) −126.78 (t, J = 4.7 Hz), −123.73, −123.51, −122.57, −116.78 (t, J = 14.1 Hz), −81.43 (t, J = 9.4 Hz); MS *m/z* 1240 (M^+ − F), 990, 912 (M^+ − $(CH_2)_2(CF_2)_5CF_3$), 795, 309, 239, 160.

3-Methyl-5-*tris*(2-perfluorohexylethyl)silanyloxymethyl-4,5-dihydroisoxazole (10): Prepared according to general procedure 1 with allyl silyl ether **3** (0.050 g, 0.044 mmol), BTF (2 mL), nitroethane (0.03 mL, 0.44 mmol), and phenyl isocyanate (0.10 mL, 0.88 mmol) to afford isoxazoline **10** (53 mg, 100%): IR (neat) 2947, 2932, 1441, 1361, 1352, 1317, 1236, 1206, 1144, 1122, 1071, 1022, 905, 845, 811, 737, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91-1.00 (m, 6 H), 1.96 (s, 3 H), 2.00-2.22 (m, 6 H), 2.75 (dd, J_1 = 17.1 Hz, J_2 = 7.3 Hz, 1 H), 2.98 (dd, J_1 = 17.0 Hz, J_2 = 10.8 Hz, 1 H), 3.68 (dd, J_1 = 11.4 Hz, J_2 = 4.5 Hz, 1 H), 3.80 (dd, J_1 = 11.4 Hz, J_2 = 3.1 Hz, 1 H), 4.57-4.66 (m, 1 H); ^{13}C NMR (750 MHz, $CDCl_3$) δ 2.94, 12.74, 24.68 (t, J = 23.3 Hz), 39.85, 64.73, 79.51, 104.61-121.39 (m, CF_2, CF_3), 155.11; ^{19}F NMR (470 MHz, $CDCl_3$) δ (rel. to $CFCl_3$) −126.74 (t, J = 4.7 Hz), −123.86, −123.46, −122.51, −116.72 (t, J = 14.1 Hz), −81.37 (t, J = 9.4 Hz); MS *m/z* 1164 (M^+ − F), 936, 836, 508, 309, 239, 195; HRMS calcd. for $C_{21}H_{16}NO_2F_{26}Si$ ($M^+ - (CH_2)_2(CF_2)_5CF_3$) *m/z* 836.0535, found 836.0514.

3,5-Dimethyl-5-*tris*(2-perfluorohexylethylsilanyloxymethyl-4,5-dihydroisoxazole (11): Prepared according to general procedure 1 with the allyl silyl ether **4** (0.107 g, 0.094 mmol), BTF (4 mL), nitroethane (0.07 mL, 0.94 mmol), and phenyl isocyanate (0.20 mL, 1.88 mmol) to afford isoxazoline **11** (112 mg, 99%): IR (neat) 2935, 1442, 1362, 1352, 1336, 1316, 1238, 1206, 1144, 1120, 1072, 906, 811, 745, 736, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93-0.99 (m, 6 H), 1.30 (s, 3 H), 1.91 (s, 3 H), 2.02-2.19 (m, 6 H), 2.58 (d, J = 17.1 Hz, 1 H), 2.91 (d, J = 17.1 Hz, 1 H), 3.57 (d, J = 11.0 Hz, 1 H), 3.63 (d, J = 10.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.87, 12.92, 22.26, 24.68 (t, J = 24.0 Hz), 45.68, 68.06, 85.35, 105.16-122.96 (m, CF_2, CF_3), 155.05; MS *m/z* 1178 (M^+ − F), 928, 850 ($M^+ - (CH_2)_2(CF_2)_5CF_3$), 795, 309, 239.

3-Propyl-5-*tris*(2-perfluorohexylethyl)silanyloxymethyl-4,5-dihydroisoxazole (12): Prepared according to general procedure 1 with the allyl silyl ether **3** (0.111 g, 0.099 mmol), BTF (4 mL), nitrobutane (0.10 mL, 0.99 mmol), and phenyl isocyanate (0.22 mL, 1.98 mmol) to afford isoxazoline **12** (125 mg, 105%): IR (neat) 2971, 2944, 2914, 2881, 1362, 1317, 1239, 1207, 1144, 1121, 1071, 906, 745, 736, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89-1.00 (m, 9 H), 1.51-1.63 (m, 2 H), 2.03-2.21 (m, 6 H), 2.29 (t, J = 7.4 Hz, 2 H), 2.73 (dd, J_1 = 17.0 Hz, J_2 = 7.3 Hz, 1 H), 2.96 (dd, J_1 = 17.0 Hz, J_2 = 10.8 Hz, 1 H), 3.67 (dd, J_1 = 11.4 Hz, J_2 = 4.7 Hz, 1 H), 3.78 (dd, J_1 = 11.3 Hz, J_2 = 3.1 Hz, 1 H), 4.57-4.65 (m, 1 H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 3.48, 13.98, 20.44, 25.47 (t, J = 23.3 Hz), 38.85, 65.81, 80.38, 109.32-123.54 (m, CF_2, CF_3), 159.19; MS *m/z* 1211 (M^+), 1192 (M^+ − F), 848, 803, 293, 226, 157.

5-Methyl-3-propyl-5-*tris*(2-perfluorohexylethyl)silanyloxymethyl-4,5-dihydroisoxazole (13): Prepared according to general procedure 1 with the allyl silyl ether **4** (0.100 g, 0.088 mmol), BTF (4 mL), nitrobutane (0.09 mL, 0.88 mmol), and phenyl isocyanate (0.19 mL, 1.76 mmol) to afford isoxazoline **13** and starting silane (ratio 94:6, 106 mg): IR (neat) 2974, 2943, 2914, 2881, 1442, 1362, 1317, 1236, 1207, 1144, 1121, 1072, 907, 811, 736, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89-0.99 (m, 9 H), 1.31 (s, 3 H), 1.49-1.62 (m, 2 H), 2.03-2.19 (m, 6 H), 2.26 (t, J = 7.4 Hz, 2 H), 2.56 (d, J = 16.7 Hz, 1 H), 2.90 (d, J = 16.7 Hz, 1 H), 3.58 (d, J = 10.9 Hz, 1 H), 3.63 (d, J = 10.9 Hz, 1 H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 3.49, 13.96, 20.44, 22.65, 25.50 (t, J = 23.2 Hz), 44.73, 68.86, 85.92, 105.76-124.42 (m, CF_2, CF_3), 159.13; MS *m/z* 1226 (M^+ + 1), 1206 (M^+ − F), 878 ($M^+ - (CH_2)_2(CF_2)_5CF_3$), 795, 309, 239, 195.

3-*tert*-Butyl-5-*tris*(2-perfluorohexylethyl)silanyloxymethylisoxazole (14): Prepared according to general procedure 2 with propargyl silyl ether **5** (0.100 g, 0.089 mmol) (containing around 13% of silanol), *tert*-butyl hydroximic acid chloride (97.0 mg, 0.72 mmol), and triethylamine (0.11 mL, 0.72 mmol) in CH_2Cl_2 (6 mL) to afford isoxazoline **14** (108 mg, 99%) (containing around 13% silanol): IR (neat) 2973, 2950, 2912, 2360, 2342, 1367, 1317, 1237, 1206, 1144, 1121, 1076, 904, 812, 745, 736, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95-1.01 (m, 6 H), 1.31 (s, 9 H), 2.00-2.17 (m, 6 H), 4.77 (s, 2 H), 6.11 (s, 1 H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 3.42, 25.46 (t, J = 23.3 Hz), 32.76, 57.81, 101.19, 105.78-124.00 (m, CF_2, CF_3), 170.96, 172.74; MS *m/z* 1209 (M^+ − 14), 1204 (M^+ − F), 918, 871, 813, 462, 310.

3-Phenyl-5-*tris*(2-perfluorohexylethyl)silanyloxymethylisoxazole (15): Prepared according to general procedure 2 with propargyl silyl ether **5** (0.100 g, 0.089 mmol) (containing around 13% of silanol), phenyl hydroximic acid chloride (110 mg, 0.71 mmol), and triethylamine (0.11 mL, 0.71 mmol) in CH_2Cl_2 (6 mL) to afford isoxazoline **15** and silanol (40 % silanol as determined by ^1H-NMR). ^1H NMR (300 MHz, $CDCl_3$) δ 1.00-1.06 (m, 6 H), 2.04-2.21 (m, 6 H), 4.87 (s, 2 H), 6.53 (s, 1 H), 7.45-7.47 (m, 3 H), 7.76-7.80 (m, 2 H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 3.35, 25.37 (t, J = 23.3 Hz), 57.71, 101.37, 107.77-123.44 (m, CF_2, CF_3), 127.55, 129.87, 130.10, 131.01, 163.23, 172.26; MS *m/z* 1243 (M^+), 1224 (M^+ − F), 893, 568, 309, 240, 158.

3-Methyl-5-*tris*(2-perfluorohexylethyl)silanyloxymethylisoxazole (16): Prepared according to general procedure 1 with propargyl silyl ether **5** (0.104 g, 0.089 mmol) (containing around 13% silanol), BTF (6 mL), nitroethane (0.064 mL, 0.89 mmol), and phenyl isocyanate (0.18 mL, 1.78 mmol) to afford isoxazoline **16** (105 mg, 104%) (containing around 13% of silanol): IR (neat) 2947, 2910, 1443, 1364, 1317, 1295, 1244, 1197, 1144, 1121, 1075, 904, 845, 812, 745, 736, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95-1.01 (m, 6 H), 1.99-2.17 (m, 6 H), 2.28 (s, 3 H), 4.77 (s, 2 H), 6.05 (s, 1 H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 3.37, 11.17, 25.41 (t, J = 23.3 Hz), 57.61, 103.98, 105.27-124.41 (m, CF_2, CF_3), 160.53, 171.10; MS *m/z* 1162 (M^+ – F), 910, 828, 506, 309, 239.

3-Propyl-5-*tris*(2-perfluorohexylethyl)silanyloxymethylisoxazole (17): Prepared according to general procedure 1 with propargyl silyl ether **5** (0.100 g, 0.089 mmol) (containing around 13% of silanol), BTF (6 mL), nitrobutane (0.09 mL, 0.89 mmol), and phenyl isocyanate (0.18 mL, 1.78 mmol) to afford the isoxazoline **17** (107 mg, 99%) (containing around 13% of silanol): IR (neat) 2972, 2945, 2912, 2883, 1443, 1362, 1317, 1294, 1237, 1209, 1144, 1121, 1075, 905, 812, 745, 736, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94-1.02 (m, 9 H), 1.64-1.71 (m, 2 H), 2.00-2.17 (m, 6 H), 2.62 (t, J = 7.4 Hz, 2 H), 4.77 (s, 2 H), 6.06 (s, 1 H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 3.39, 13.91, 22.29, 25.43 (t, J = 23.3 Hz), 28.54, 57.74, 102.90, 105.75-123.47 (m, CF_2, CF_3), 164.63, 171.06; MS *m/z* 1209 (M^+), 1190 (M^+ – F), 857, 309, 239, 195.

General Procedure for Cleavage of the Silyl Group (General Procedure 3): The silylated isoxazol(in)e (0.079 mmol) was dissolved in Et_2O (THF) (3 mL) at 25 °C. HF•pyridine (0.1 mL) was added and the solution was stirred for 1 h at 25 °C. After removal of the solvent the residue was dissolved in CH_2Cl_2 (20 mL). Sat. aq. NH_4Cl (10 mL) was added and the organic-aqueous biphase was washed twice with FC-72 (10 mL). After separation of the layers, the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and evaporated to yield the deprotected isoxazol(in)e. The purity was determined by GC-analysis.

(3-*tert*-Butyl-4,5-dihydroisoxazol-5-yl)methanol (18): Prepared according to general procedure 3 with isoxazoline **6** (0.085 g, 0.069 mmol) and HF•pyridine (0.1 mL) in THF (3 mL) to afford after extraction isoxazoline **18** (10.6 mg, 99%) with 91% purity. The physical data are in agreement with those reported in literature.[26a]

(3-*tert*-Butyl-5-methyl-4,5-dihydroisoxazol-5-yl)methanol (19): Prepared according to general procedure 3 with isoxazoline **7** (0.113 g, 0.091 mmol) and HF•pyridine (0.1 mL) in Et_2O (3 mL) to afford after extraction isoxazoline **19** (15.6 mg, 99%) with 99% purity: IR (neat) 3700-3100 br., 2968, 2931, 2871, 2361, 2342, 1479, 1462, 1434, 1395, 1367, 1340, 1260, 1244, 1205, 1126, 1056, 895, 797 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 9 H), 1.31 (s, 3 H), 1.98 (s, br 1 H), 2.62 (d, J = 16.7 Hz, 1 H), 3.08 (d, J = 16.7 Hz, 1 H), 3.46 (d, J = 12.0 Hz, 1 H), 3.62 (d, J = 11.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.56, 28.21, 33.36, 41.59, 67.49, 86.20, 167.03; MS *m/z* 171 (M^+), 140, 98, 82; HRMS calcd. for $C_9H_{17}NO_2$ *m/z* 171.1259, found 171.1253.

(3-Phenyl-4,5-dihydroisoxazol-5-yl)methanol (20): Prepared according to general procedure 3 with isoxazoline **8** (0.097 g, 0.078 mmol) and HF•pyridine (0.1 mL) in THF (3 mL) to afford after extraction isoxazoline **20** (13.6 mg, 99%) with 95% purity. The physical data are in agreement with those reported in literature.[26b]

(5-Methyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methanol (21): Prepared according to general procedure 3 with isoxazoline **9** (0.080 g, 0.064 mmol) and HF•pyridine (0.1 mL) in THF (3 mL) to afford after extraction isoxazoline **21** (11.5 mg, 95%) with 98% purity. **21** is a known coumpound.[26c]

(3-Methyl-4,5-dihydroisoxazol-5-yl)methanol (22): Prepared according to general procedure 3 with isoxazoline **10** (0.300 g, 0.254 mmol) and HF•pyridine (0.2 mL) in Et_2O (6 mL) to afford after extraction isoxazoline **22** (8.5 mg, 29%) with 93% purity. **22** is a known compound.[26d]

(3,5-Dimethyl-4,5-dihydroisoxazol-5-yl)methanol (23): Prepared according to general procedure 3 with isoxazoline **11** (0.120 g, 0.100 mmol) and HF•pyridine (0.1 mL) in THF (3 mL) to afford after extraction isoxazoline **23** (4 mg, 31%) with 99% purity: IR ($CHCl_3$) 3588, 2976, 2954, 2925, 2874, 1431, 1388, 1353, 1334, 1241, 1222, 1178, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 3 H), 1.95 (s, 3 H), 2.55 (s, br 1 H), 2.58 (d, J = 17.0 Hz, 1 H), 3.04 (dd, J_1 = 17.0 Hz, J_2 = 0.9 Hz, 1 H), 3.44 (d, J = 12.0 Hz, 1 H), 3.61 (d, J = 11.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.59, 22.73, 45.92, 67.46, 86.36, 156.29; MS *m/z* 129 (M^+), 98, 74, 59; HRMS calcd. for $C_6H_{11}NO_2$ *m/z* 129.0790, found 129.0790.

(3-Propyl-4,5-dihydroisoxazol-5-yl)methanol (24): Prepared according to general procedure 3 with isoxazoline **12** (0.096 g, 0.079 mmol) and HF•pyridine (0.1 mL) in THF (3 mL) to afford after extraction isoxazoline **24** (5.4 mg, 48%) with 94% purity: IR (neat) 3700-3100 br., 2962, 2935, 2875, 1462, 1435, 1383, 1361, 1334, 1313, 1096, 1074, 1049, 908, 874, 849 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, J = 7.9 Hz, 3 H), 1.54-1.66 (m, 2 H), 1.92 (s, br 1 H), 2.32 (t, J = 7.4 Hz, 2 H), 2.82 (dd, J_1 = 17.0 Hz, J_2 = 7.6 Hz, 1 H), 2.96 (dd, J_1 = 17.0 Hz, J_2 = 10.7 Hz, 1 H), 3.56 (dd, J_1 = 12.1 Hz, J_2 = 4.6 Hz, 1 H), 3.77 (dd, J_1 = 12.1 Hz, J_2 = 3.1 Hz, 1 H), 4.62-4.70 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.79, 19.78, 29.61, 38.50, 63.68, 80.00, 159.66; MS *m/z* 143 (M^+), 115, 112, 84; HRMS calcd. for $C_7H_{13}NO_2$ *m/z* 143.0946, found 143.0943.

(5-Methyl-3-propyl-4,5-dihydroisoxazol-5-yl)methanol (25): Prepared according to general procedure 3 with isoxazoline **13** (0.062 g, 0.051 mmol) and HF•pyridine (0.1 mL) in Et_2O (3 mL) to afford after extraction isoxazoline **25** (8 mg, 99%) with 99% purity: IR (neat) 3700-3100 br., 2963, 2929, 2874, 2855, 1457, 1434, 1378, 1363, 1336, 1317, 1236, 1054, 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J = 7.4 Hz, 3 H), 1.32 (s, 3 H), 1.58 (q, J = 7.5 Hz, 2 H), 1.97 (s, br 1 H), 2.29 (t, J = 7.6 Hz, 2 H), 2.58 (d, J = 17.0 Hz, 1 H), 3.04 (d, J = 17.0 Hz, 1 H), 3.46 (d, J = 11.9 Hz, 1 H), 3.63 (d, J = 11.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.92, 19.94, 22.79, 30.03, 44.27, 67.59, 85.93, 159.97; MS *m/z* 157 (M^+), 126, 97; HRMS calcd. for $C_8H_{15}NO_2$ *m/z* 157.1103, found 157.1099.

(3-*tert*-Butylisoxazol-5-yl)methanol (26): Prepared according to general procedure 3 with isoxazole **14** (0.099 g, 0.073 mmol, around 10% of silanol) and HF•pyridine (0.1 mL) in Et_2O (3 mL) to afford after extraction isoxazole **26** (11.4 mg, 99%) with 99% purity: IR (neat) 3700-3100 br., 2966, 2935, 2910, 2872, 1607, 1488, 1465, 1409, 1367, 1211, 1193, 1068, 1042, 998 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 9 H), 2.57 (s, br 1 H), 4.71 (s, 2 H), 6.15 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.63, 32.22, 56.67, 100.03, 171.09, 172.36; MS *m/z* 155 (M^+), 140, 124, 94, 68, 57; HRMS calcd. for $C_8H_{13}NO_2$ *m/z* 155.0946, found 155.0939.

(3-Phenylisoxazol-5-yl)methanol (27): Prepared according to general procedure 3 with isoxazole **15** (0.05 g, 0.04 mmol) and HF•pyridine (0.1 mL) in Et_2O (3 mL) to afford after extraction isoxazole **27** (6.8 mg, 99%) with 98% purity. The physical data are in agreement with those reported in literature.[26e]

(3-Methylisoxazol-5-yl)methanol (28): Prepared according to general procedure 3 with isoxazole **16** (0.098 g, 0.075 mmol, around 10% of silanol) and HF•pyridine (0.1 mL) in Et_2O (3 mL) to afford after extraction isoxazole **28** (8.5 mg, 99%) with 99% purity. The physical data are in agreement with those reported in literature.[26f]

(3-Propylisoxazol-5-yl)methanol (29): Prepared according to general procedure 3 with isoxazole **17** (0.102 g, 0.076 mmol, around 10% of silanol) and HF•pyridine (0.1 mL) in Et_2O (3 mL) to afford after extraction isoxazole **29** (10,7 mg, 99%) with 97% purity. **29** is a known compound.[26g]

Simulated Combinatorial Synthesis without Characterization of Intermediates:

(3-*tert*-Butyl-4,5-dihydroisoxazol-5-yl)methanol (18): The allyl silyl ether **3** was prepared as described before with 0.65 mmol of bromo *tris*(2-perfluorohexylethyl)silane (**1**) without purification by flash-chromatography. Cycloaddition according to general procedure 2 with crude allyl silyl ether **3**, *tert*-butyl hydroxamic acid chloride (440 mg, 3.20 mmol), and triethylamine (0.48 mL, 3.20 mmol) in CH_2Cl_2 (20 mL) afforded the isoxazoline **6**. Silyl cleavage according to general procedure 3 with HF•pyridine (0.5 mL) in Et_2O (20 mL) afforded after extraction isoxazoline **18** (68 mg, 66%) with 99% purity.

(3,5-Dimethyl-4,5-dihydroisoxazol-5-yl)methanol (23): The allyl silyl ether **4** was prepared as described before with 0.38 mmol of bromo *tris*(2-perfluorohexylethyl)silane (**1**) without purification by flash-chromatography. Cycloaddition according to general procedure 1 with crude allyl silyl ether **4**, nitro ethane (0.27 mL, 3.80 mmol) and phenyl isocyanate (0.73 mL, 7.20 mmol) in BTF (15 mL) afforded isoxazoline **11**. Silyl cleavage according to general procedure 3 with HF•pyridine (0.4 mL) in Et_2O (12 mL) afforded after extraction isoxazoline **23** (15.5 mg, 32%) with 99% purity.

(3-Propyl-4,5-dihydroisoxazol-5-yl)methanol (24): The allyl silyl ether **3** was prepared as described before with 0.38 mmol of bromo *tris*(2-perfluorohexylethyl)silane (**1**) without purification by flash-chromatography. Cycloaddition according to general procedure 2 with crude allyl silyl ether **3**, nitrobutane (0.38 mL, 3.80 mmol) and phenyl isocyanate (0.73 mL, 7.20 mmol) in BTF (15 mL) afforded isoxazoline **12**.

Silyl cleavage according to general procedure 3 with HF•pyridine (0.4 mL) in Et_2O (12 mL) afforded after extraction isoxazoline **24** (39.5 mg, 73%) with 94% purity.

(3-Propylisoxazol-5-yl)methanol (29): Silyl propargyl ether **5** was prepared as described before with 0.31 mmol of bromo *tris*(2-perfluorohexylethyl)silane (**1**). Cycloaddition according to general procedure 1 with nitrobutane (0.31 mL, 3.10 mmol) and phenyl isocyanate (0.63 mL, 6.20 mmol) in BTF (15 mL) afforded the isoxazole **17**. Silyl cleavage according to general procedure 3 with HF•pyridine (0.5 mL) in Et_2O (10 mL) afforded after extraction isoxazoline **29** (37.3 mg, 83%) with 97% purity.

***erythro/threo*-α-Methyl-3-phenyl-2-isoxazoline-5-methanol (30a,b):** *rac*-3-Buten-2-ol (0.083 mL, 0.960 mmol) and triethylamine (0.14 mL, 0.96 mmol) were dissolved in dry THF (4 mL) under argon. A mixture of bromo *tris*(2-perfluorohexylethyl)silane (**1**) (275 mg, 0.24 mmol) in THF (2 mL) was slowly added to the above solution at 25 °C. The resulting suspension was stirred at 25 °C for 3 h. Workup as described for the preparation of the allyl silyl ether afforded crude *rac-tris*(2-perfluorohexylethyl)-(1-methylallyloxy)silane. Cycloaddition according to general procedure 2 with *rac-tris*(2-perfluorohexylethyl)-(1-methylallyloxy)silane (100 mg) and phenyl hydroximic acid chloride (53 mg, 0.35 mmol), and triethylamine (0.055 mL, 0.37 mmol) in CH_2Cl_2 (6 mL) afforded the isoxazoline. Silyl cleavage according to general procedure 3 with HF•pyridine (0.5 mL) in Et_2O (20 mL) afforded after extraction *erythro/threo*-α-methyl-3-phenyl-2-isoxazoline-5-methanol **30a,b** (10.4 mg, 62%) as a 70:30 diastereoisomer mixture with 97% purity. The diastereoisomer ratio was determined by ^1H NMR analysis. The physical data are in agreement with those reported in literature.[24]

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References and Notes

1. (a) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233, 1386. (b) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135. (c) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (d) Rinnova, M.; Lebl, M. *Collect. Czech. Chem. Commun.* **1996**, *61*, 171. (e) Balkenhohl, F.; Von dem Busschehunnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2289.
2. (a) Cheng, Y.; Suenaga, T.; Still, W. C. *J. Am. Chem. Soc.* **1996**, *118*, 1813. Burger, M. T.; Still, W. C. *J. Org. Chem.* **1995**, *60*, 7382. (b) Goodman, M. S.; Jubian, V.; Linton, B.; Hamilton, A. D. *J. Am. Chem. Soc.* **1995**, *117*, 11610.
3. Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1668.
4. Hsieh-Wilson, L. C.; Xiang, X.-D.; Schultz, P. G. *Acc. Chem. Res.* **1996**, *29*, 164.
5. (a) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527. (b) Früchtel, J.; Jung, G. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 17.
6. Han, H.; Wolfe, M. M.; Brenner, S.; Janda, K. D. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 6419.
7. Carell, T.; Wintner, E. A.; Bashir-Hashemi, A.; Rebek, J., Jr. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2059. Carell, T.; Wintner, E. A.; Rebek, J., Jr. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2061. See also: Carell, T.; Wintner, E. A.; Sutherland, A. J.; Rebek, J., Jr.; Dunayevskiy, Y. M.; Vourous, P. *Chemistry and Biology* **1995**, *2*, 171. Shipps, G. W. Jr.; Spitz, U. P.; Rebek, J. Jr. *Bioorg. Med. Chem.* **1996**, *4*, 655.
8. Cheng, S.; Comer, D. D.: Williams, J. P.; Myers, P. L.; Boger, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 2567. Boger, D. L.; Tarby, C. M.; Myers, P. L.; Caporale, L. H. *J. Am. Chem. Soc.* **1996**, *118*,

2109. Cheng, S.; Tarby, C. M.; Comer, D. D.; Williams, J. P.; Caporale, L. H.; Myers, P. L.; Boger, D. L. *Bioorg. Med. Chem.* **1996**, *4*, 727.

9. (a) Scott, R. L. *J. Am. Chem. Soc.* **1948**, *70*, 4090. Scott, R. L. *J. Phys. Chem.* **1958**, *62*, 136. (b) Hildebrand, J. H.; Cochran, D. R. F. *J. Am. Chem. Soc.* **1949**, *71*, 22. See also: (c) Hudlicky, M. *Chemistry of Organic Fluorine Compounds*; Ellis Horwood: Chichester, UK, 1992.
10. Zhu, D.-W. *Synthesis* **1993**, 953.
11. Horváth, I. T.; Rábai, J. *Science* **1994**, *266*, 72. See also: (a) Gladysz, J. A. *Science* **1994**, *266*, 55. (b) Bergbreiter, D. E. *Chemtracts–Organic Chemistry* **1995**, *8*, 108.
12. (a) Curran, D. P.; Hadida, S. *J. Am. Chem. Soc.* **1996**, *118*, 2531. (b) Curran, D. P.; Hoshino, M. *J. Org. Chem.* **1996**, *61*, 6480. (c) Curran, D. P. *Chemtracts-Org. Chem.* **1996**, *9*, 75.
13. Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P.; *Science* **1997**, in press.
14. (a) Hughes, R. P.; Trujillo, H. A. *Organometal.* **1996**, *15*, 286. (b) DiMagno, S. G.; Dussault, P. H.; Schultz, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 5312.
15. The fluorous phase label does not have to be a silyl group, see ref. 13.
16. P. Caramella; Grünager, P. *1,3-Dipolar Cycloaddition Chemistry*; Wiley-Interscience: New York, 1984; Vol. 1, p 291.
17 (a) Greene, W. T.; Wuts, P. G. *Protective Groups in Organic Synthesis*; John Wiley & Sons, Inc: New York, 1991. (b) Armitage, D. A. *Comprehensive Organometallic Chemistry II*; Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. 2, p. 1.
18. Boutevin, B; Guida-Pietrasanta, F.; Ratsimihety, A.; Caporiccio, G.; Gornowicz, G. *J. Fluorine Chem.* **1993**, *60*, 211.
19. FC-72™ is a commercially available (3M) fluorocarbon liquid consisting of mostly of isomers of C_6F_{14} (bp 56° C).
20. An authentic sample of the silanol was prepared by treatment of a THF solution of **1** with a large excess of H_2O: ^1H NMR (300 MHz, $CDCl_3$) δ 0.93-0.98 (m, 6 H), 1.94 (s, 1 H), 2.05-2.20 (m, 6 H), MS *m/z* 1087 ($M^+ + H$), 391, 309, 239, 195. The ^1H NMR resonances of the side product are in agreement to those observed for the authentic sample. However, also for disiloxane (no authentical sample prepared) the ^1H NMR spectrum may look very similar. Therefore, we assume that the side product may also be disiloxane or a mixture of both.
21. Huisgen, R. *Angew. Chem.* **1963**, *75*, 604.
22. Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.
23. In a competition experiment we showed that under these reaction conditions (CH_2Cl_2) tributylsilyl allyl ether reacts only slightly faster with *tert*-butyl nitrile oxide than the perfluorinated silyl ether **3** (^1H-NMR analysis of the reaction mixture).
24. Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880.
25. Studer, A., unpublished observations.
26. (a) Curran, D. P.; Kim, B. H.; Piyasena, H. P.; Loncharich, R. J.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 2137. (b) Curran, D. P.; Jeong, K.-S.; Heffner, T. A.; Rebek, Jr., J. *J. Am. Chem. Soc.* **1989**, *111*, 9238. (c) Rheinheimer, J.; Eiken, K.; Theobald, H.; Kuckenhoeher, T.; Westphalen, K. O. Eur. Pat. Appl. EP 334,120. (d) Curran, D. P.; Kim, B. H.; Daugherty, J; Heffner, T. A. *Tetrahedron Lett.* **1988**, *29*, 3555. (e) Padwa, A.; Bullock, W. H.; Norman, B. H.; Perumattam, J. *J. Org. Chem.* **1991**, *56*, 4252. (f) Taddei, M.; Ricci, I. *Synthesis* **1986**, 633. (g) Kuekenhoener, T; Theobald, H.; Goetz, N; Becker, R. Eur. Pat. Appl. EP 302,491.

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