Organic-Fluorous Phase Switches: A Fluorous Amine Scavenger for Purification in Solution Phase Parallel Synthesis

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Received November 30, 1998

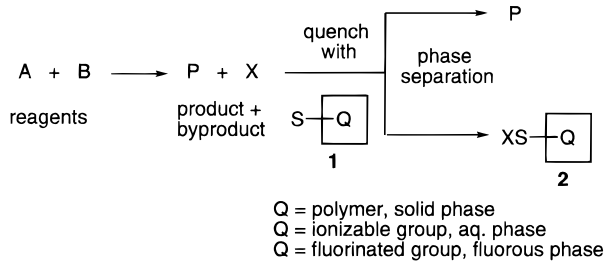
The synthesis of the fluorous amine scavenger $[(C_6F_{13}CH_2CH_2)_3SiCH_2CH_2CH_2]_2NH$ and its successful application in the automated solution phase parallel synthesis of a urea library are described. Ureas were made by robotic synthesis from organic amines and excess isocyanates. The amine scavenger reacts with excess isocyanate, and the fluorous tag serves to solubilize the resulting adduct in the fluorous phase so it can be removed by fluorous-organic extraction. Organic urea products are isolated in high yields and purities after liquid−liquid extraction. Preliminary biological evaluation shows that several of the ureas have ion channel modulation abilities. In contrast to polymer and ionic quenching methods, the fluorous quench works whether the product is soluble or insoluble in the reaction medium, and ionizable functional groups are tolerated in the products.

Introduction

The successful implementation of solution phase chemistry in parallel synthesis is hampered by time-consuming workup and purification procedures. This is in contrast with reactions on solid support, where simple filtration effects purification in ideal cases.[1] However, by incorporating workup into the overall reaction planning, one can design reaction components and isolation procedures that meet parallel synthesis standards in terms of speed and efficiency. The best strategies allow the products to be separated by simple phase-separation methods such as filtration, extraction, and evaporation.[2]

Techniques that use scavenging (quenching) agents are highly effective for rapid purification and isolation of the desired products obtained in a solution phase reaction.[3−9] The concept is based on complementary reactivity of the components of the mixture after the reaction, and is illustrated in Scheme 1. Combination of reactants **A** and **B** leads to a product **P** and a byproduct **X**, which can either be an excess of one of the reactants or a side product. Separation of **P** from **X** is achieved by a rapid second reaction of **X** with a scavenging agent **1** containing a phase tag. The resulting tagged adduct **2** is removed by a simple phase separation, leaving behind the pure product **P** in organic solution. More broadly speaking, scavenging is one of several useful "phase switching" techniques where chemoselective reactions are used to switch the phase of one (or more) products relative to another.[2]

Scheme 1



To date, most scavengers have been bound to polymers.[3−8] Scavengers attached to a solid support (Q = insoluble polymer, Scheme 1) cause the transfer of the captured species from the organic liquid phase to the solid phase, where it is easily removed by filtration. This technique combines the attractive features of solution phase reactions with the convenience and effectiveness of workup in solid-phase chemistry. Alternatively, a scavenger can be linked to an ionizable functional group[7−9] (for example Q = COOH or NR_2), and the trapped species can be removed by pH-adjusted liquid/liquid extraction or by solid/liquid extraction.

In early 1997, we introduced a number of "fluorous synthesis" techniques,[10] among which was included a cursory description of fluorous quenching of alkenes with a tin hydride reagent.[11] In a simple view, the "fluorous phase" constitutes a third liquid phase which is mutually immiscible with water and most common organic sol-

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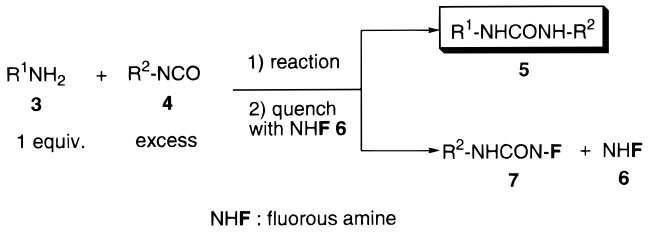
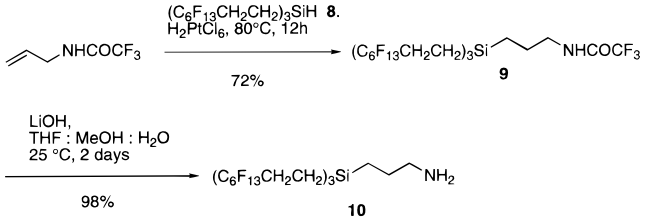
10.1021/jo9823442 CCC: $18.00
Published on Web 03/26/1999

Scheme 2



Scheme 3



vents.[12] Typical organic compounds have little or no solubility in fluorous solvents such as FC-72 (perfluorohexanes, commercially available from 3M) or other perfluorinated liquids. However, organic compounds can be rendered fluorous—that is, induced to partition out of an organic liquid phase and into a fluorous phase—by attaching a suitable fluorous phase tag. In this regard, the readily available tris(perfluorohexylethyl)silyl group [$(C_6F_{13}CH_2CH_2)_3Si$] and related groups prove valuable as phase tags in a number of fluorous synthesis techniques.[13] Such tags bearing 39 fluorines effectively convert relatively small (MW < 200) nonpolar organic molecules into fluorous ones. However, the fluorous phase is very nonpolar, and it is currently not clear what is required to switch relatively polar organic molecules to the fluorous phase. We decided to address this question in the context of a fluorous amine quenching scheme.

In this paper, we report a new variant on the scavenging technique, wherein an amine scavenger is linked to a fluorous label (Q = fluorous tag). The separation procedure is a fluorous organic liquid/liquid extraction. This method complements and supplements methods using ionizable or polymeric tags. Unlike filtration-based methods, fluorous quenching succeeds independent of whether the final organic products remain in solution or precipitate out. And since fluorous quenching is not an ionization method, there is no limit to the presence of ionizable groups in a library. Fluorous amine quenching is easily adaptable for automated synthesis as demonstrated by the robotic parallel synthesis of several small libraries of aryl ureas. The library members have been evaluated for their effects on cAMP-stimulated transepithelial Cl-secretion across a human colonic cancer cell line T84, and a number of active compounds have been identified.

Results and Discussion

Development of a Fluorous Amine Quenching Reagent. Scheme 2 illustrates the general reaction and purification plan pursued in this work. Ureas **5** were prepared in a straightforward fashion by mixing a limiting amount of an amine **3** with an excess of isocyanate **4**. After the prescribed reaction time, an excess of fluorous amine quenching reagent **6** was introduced to convert the unreacted isocyanate **4** to a fluorous urea **7**. Fluorous-organic liquid/liquid extraction was then conducted to separate the organic urea product **5** from the fluorous urea **7** and the excess fluorous amine **6**.

At the outset of this work, it was not at all clear what kinds of fluorinated amines would be needed to provide ureas **7** that partitioned efficiently out of the organic phase and into the fluorous phase. To address this question, we initially decided to prepare primary amine **10** containing 39 fluorines. The synthesis of **10** is straightforward as shown in Scheme 3. Hydrosilylation of *N*-allyl trifluoroacetamide[14] with the tris(perfluorohexylethyl) silicon hydride [$(C_6F_{13}CH_2CH_2)_3SiH$] **8**[15] leads to the adduct **9** in 72% yield. No solvent was used in the hydrosilylation reaction, and the trifluoroacetyl group was necessary to solubilize the allylamine in the fluorous silyl hydride. (Attempts to hydrosilylate allylamine were not very successful.) The trifluoroacetyl group also facilitates purification of **9** by column chromatography. Deprotection of the fluorous trifluoroacetamide derivative **9** leads to the desired fluorous amine **10** in 98% yield. Amine **10** was isolated as a clear oil and was fully characterized by normal spectroscopic techniques.

Model experiments (not shown) for urea formation were conducted in chloroform with benzylamine and excess benzyl isocyanate. However, addition of the fluorous amine **10** followed by fluorous-organic liquid/liquid extraction with $CHCl_3$ and FC-72 did not provide pure organic product (dibenzyl urea) from the organic phase. The organic urea was instead contaminated with the urea resulting from trapping of benzyl isocyanate with **10** as evidenced from the ^1H NMR spectrum of the organic product. Recombining the organic and fluorous products, and repeating the extraction procedure with other solvents such as acetonitrile or methanol, did not result in effective separation. Similar experiments for the formation of amides and sulfonamides by quenching the excess of acid chloride or sulfonyl chloride with fluorous amine quenching agent **10** gave analogous organic products with fluorous impurities. In contrast to the trapped derivatives of **10**, the residual unreacted fluorous amine **10** itself was not detected in the organic phase of these extractions; it efficiently partitioned into the fluorous phase.

These results suggested that the products derived from quenching with **10** have partition coefficients that are too low for effective separation. This was readily shown by independently synthesizing some representative trapping products (**11**−**15**) and by determining their partition coefficients ($P = c_{\text{Fluorous phase}}/c_{\text{Organic phase}}$) between FC-72 and several organic solvents. This was generally done gravimetrically on larger amounts or by HPLC analysis on smaller amounts (see Experimental Section). The results of this series of experiments are shown in Figure 1.

(11) See ref 18 in cited in the above paper. A full paper describing the details of quenching with the fluorous tin hydride will be forthcoming. Curran, D. P.; Kim, S.-Y.; Hadida, S., Luo, Z. *J. Am. Chem. Soc.*, in press.

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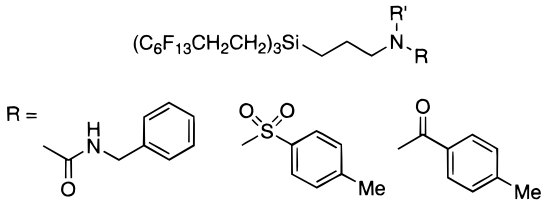


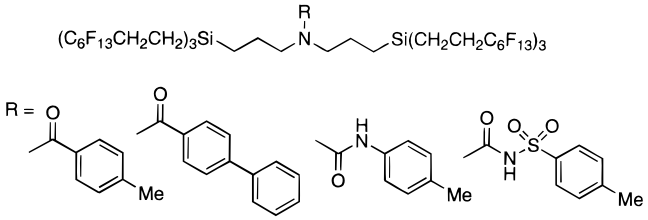
R' =	H	H	Me	H	Me
	11	**12**	**13**	**14**	**15**
P_{CHCl_3}	0.27	0.71	0.20	-	-
P_{CH_3CN}	1.0	0.37	0.77	1.2	1.8
P_{CH_3OH}	0.27	2.0	6.5	1.3	2.7
P_{THF}	-	0.05	0.10	-	-

Figure 1. Partition coefficients of some F_{39} fluorous derivatives.

In contrast to nonfluorinated ureas and sulfonyl ureas, which are essentially insoluble in FC-72, all of the compounds have substantial solubility in FC-72. Thus, it is possible to draw polar functionalities into a fluorous phase by fluorination. However, none of these compounds **11**−**15** is highly fluorous as measured by partition coefficient.[16] For example, the fluorous benzylurea **11** partitions preferentially to organic phases such as chloroform ($P = 0.27$) and methanol ($P = 0.27$) while with acetonitrile, there is equal product distribution over the two phases ($P = 1.00$). Similar results were found for the fluorous *p*-toluenesulfonamide derivative **12**: preferential partitioning into the organic phase was observed with chloroform (0.73), acetonitrile (0.37), and tetrahydrofuran (0.05). The partition coefficient in THF is especially low. This is expected because THF has good solubilizing power for fluorous compounds. To probe if hydrogen bonding is a contributing factor in the partitioning, a fluorous derivative **13** that cannot donate a hydrogen bond was synthesized. Despite the higher molecular weight of **13** relative to **12**, enhanced partitioning to the fluorous phase is indeed observed, except with chloroform as solvent. However, the effect is small. Similar results are found for the fluorous *p*-toluoylamide derivatives **14** and **15**. Thus, it appears that hydrogen bonding is not a major factor contributing to the low partition coefficients of these compounds.

Increasing number of fluorine atoms in the fluorous scavenger should increase the partition coefficient of the scavenged product toward the fluorous phase. This can be done either by increasing the length of the existing fluorous chains or by adding more chains. Past experience has shown that increasing the length of the chains tends to lead to waxy compounds with high partition coefficients but low absolute solubilities.[13a] We opted therefore to increase the number of chains, and secondary amine **16** was designed as a fluorous scavenger. Amine **16** contains 78 fluorine atoms present in six chains.

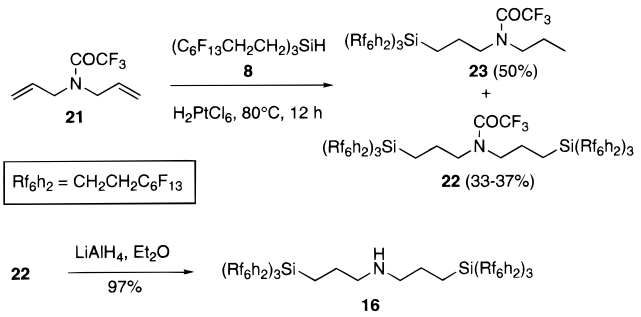
Amine **16** was again synthesized by hydrosilylation, as shown in Scheme 4. Although *N*,*N*-diallyl trifluoroacetamide **21**[17] was fully soluble in the fluorous silyl hydride **8**, the yield of the hydrosilylation reaction leading to **22** was much lower (33−37%) compared to the hydrosilylation of *N*-allyltrifluoro acetamide (Scheme 3). This was due to competing reduction of the double bond,[18] leading to **23** as the main product in 50% isolated yield. The two compounds could easily be separated by column chromatography. As expected, the desired doubly hydrosilylated compound **22** has a higher R_f value than the singly hydrosilylated side product **23** (solvent = hexanes: benzotrifluoride (BTF)[19] 55:45). Removal of the trifluoroacetamide group in **22** with LAH occurred in 98% yield to give **16** as a clear, colorless oil of moderate viscosity.



	17	**18**	**19**	**20**
P_{CHCl_3}	26	6	27	37
P_{CH_3CN}	>100	-	>50	-
P_{CH_3OH}	>100	>100	>100	-
P_{THF}	9.0	-	11	16

Figure 2. Partition coefficients of some F78 fluorous derivatives.

Scheme 4



Derivatization of **16** with different electrophiles led to products **17**−**20** (Figure 2), for which the partition coefficients were determined in different fluorous/organic solvent mixtures. The partition coefficients of these compounds containing 78 fluorines are dramatically increased relative to the compounds containing 39 fluorines and are sufficiently high for effective extraction. Even in THF, the partition coefficient lies within a useful range for liquid−liquid extraction. As a result, we considered **16** to be a suitable fluorous scavenger.

Not surprisingly, scavenger **16** is not very soluble in common organic solvents. Apart from fluorous solvents, it dissolves in benzotrifluoride (BTF). However, since many ureas are not soluble in BTF, this solvent seemed unsuitable for the quenching procedure. Furthermore, BTF tends to homogenize fluorous and organic solvents so it would have to be removed prior to the extraction. By conducting a few trial experiments, we found that biphasic reaction conditions can be used for the scavenging reaction with THF as the organic solvent and FC-72 as the fluorous solvent. Thus, the method outlined in

(16) Nonpolar compounds of roughly comparable fluorous/organic ratios exhibit higher partition coefficents. See, for example: (a) Guillevic, M. A.; Rocaboy, C.; Arif, A. M.; Horvath, I. T.; Gladysz, J. A. *Organometallics* **1998**, *17*, 707−717. (b) Curran, D. P.; Hadida, S. *J. Am. Chem. Soc.* **1996**, *118*, 2531−2532. (c) Curran, D. P.; Luo, Z. *Med. Chem. Res.* **1998**, *8*, 261−265.

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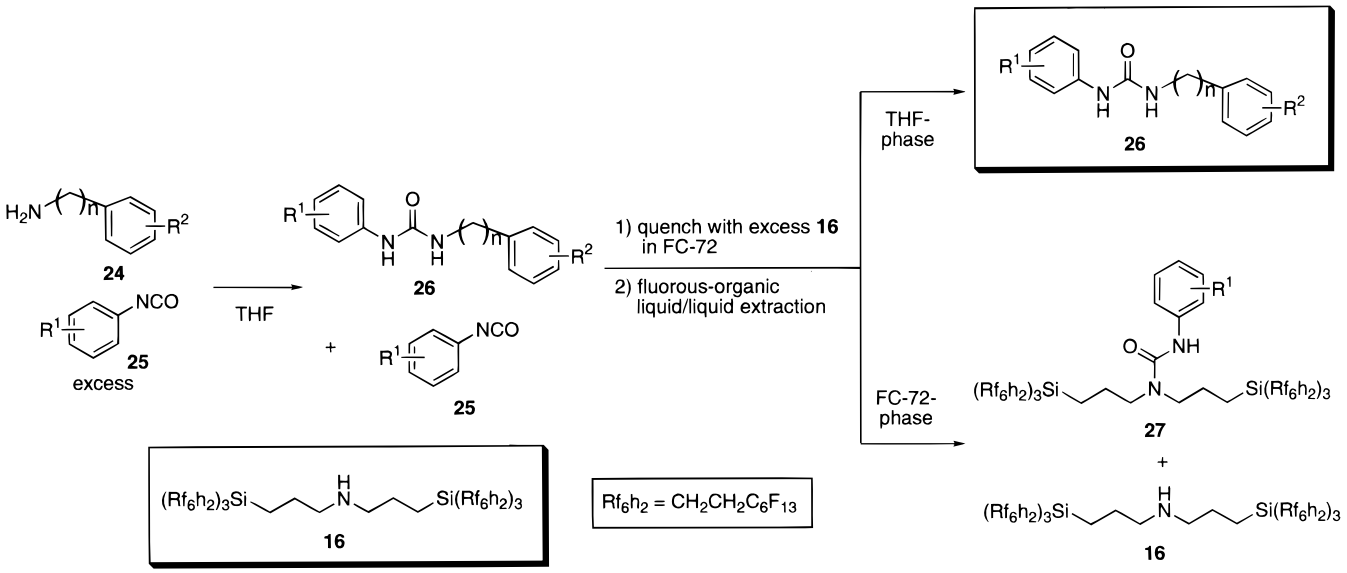
Scheme 5

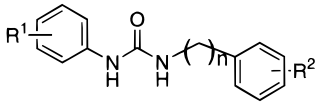


Scheme 5 was developed with automated parallel synthesis experiments in mind. Amine **24** and excess isocyanate **25** were allowed to react for 2 h in THF. Fluorous quenching agent **16** dissolved in FC-72 was then added to scavenge the excess isocyanate **25**. The scavenging reaction was complete after 5 h at ambient temperature. Separation of the THF and FC-72 phases followed by two more fluorous washes of the THF phase led to pure organic urea **26** after evaporation of the THF (^{1}H NMR).

Robotic Synthesis with Fluorous Scavenging. The usefulness of the scavenging method for automated parallel synthesis of libraries was demonstrated through the synthesis of 25 disubstituted ureas. A Hewlett-Packard automatic synthesizer (HP 7686) was used to conduct all of the operations involved in the reaction and isolation; product analyses were conducted manually. The robot was programmed to perform the following sequence of handlings:[20] (1) preparation of a 0.5 M solution in THF of the starting materials by transferring the required amount of reactant into a separate vial and dilution with THF, (2) combination of the amine and isocyanate in a 1:1.5 molar ratio followed by vortex mixing, (3) dissolution of the fluorous scavenger in FC 72 and addition of this solution to the reaction vials followed again by vortexing (two times, 15 min each), (4) separation of the organic and fluorous phases, (5) extraction of the organic phase four more times with FC-72, and finally (6) evaporation of the organic solvent in the reaction vial. The resulting solids were then removed from the robot and dried in their uncapped vials in a vacuum oven at 50 °C for 12 h. All amines and isocyanates were used as obtained from commercial sources. Some isocyanates were filtered before use to remove solid impurities (presumably *sym*-ureas derived from hydrolysis during storage). The results of the initial 3 × 4 library experiment are listed in Table 1.

In this first experiment, the yields of the expected unsymmetrical ureas varied from 34 to 96% (average 61%), but the HPLC purities were excellent (94.4−99.0%, average 97.5%). All products gave clean ^{1}H NMR spectra (see Supporting Information). We also measured by HPLC the content of symmetrical urea, which is formed through hydrolysis of the starting isocyanate. These amounts proved to be very low (0.2−2.5%, average 0.9%), showing that the robot was able to make all the transfers without introducing significant amounts of water. (Indeed, we believe that most of the *sym*-urea derives from the starting isocyanates, see below). The absence of the starting isocyanate and the small amounts of symmetrical urea demonstrate that the fluorous scavenging was successful. In a separate control experiment, *tert*-butylamine (1.5 equiv) was added after the fluorous quenching reaction, followed by another 1 h of reaction time. The organic product, obtained after fluorous organic extraction and evaporation of the solvent, contained less than 1% of *tert*-butyl containing urea product, proving that all the excess isocyanate was quenched by the fluorous scavenger.[21]

Table 1. Initial 3 × 4 Library



entry	no.	R^1	R^2	*n*	urea yield (%)	HPLC purity[a] (%)	%F[b]
1	**26a**	4-MeO	4-MeO	2	48	94.4 (0.6)	−
2	**26b**	4-MeO	4-MeO	1	96	97.3 (d)	−
3	**26c**	4-MeO	4-CF_3	1	95	97.7 (0.2)	*c*
4	**26d**	4-MeO	4-F-3-CF_3	0	34	99.0 (1.0)	0.6
5	**26e**	4-CF_3O	4-MeO	2	52	97.6 (0.4)	*c*
6	**26f**	4-CF_3O	4-MeO	1	46	98.3 (1.0)	0.2
7	**26g**	4-CF_3O	4-CF_3	1	69	98.5 (0.3)	0.1
8	**26h**	4-CF_3O	4-F-3-CF_3	0	47	98.9 (d)	0.2
9	**26i**	3-Me	4-MeO	2	70	96.9 (1.8)	−
10	**26j**	3-Me	4-MeO	1	64	96.2 (0.8)	−
11	**26k**	3-Me	4-CF_3	1	67	98.5 (0.6)	0.2
12	**26l**	3-Me	4-F-3-CF_3	0	38	97.5 (2.5)	0.3

[a] Waters Nova-Pack C18 3.9 × 150 mm. Flow rate 1.5 mL/min. Detection at 210 nm, solvent: acetonitrile 40 to 60% in water. The numbers in parentheses refer to the amount of symmetrical urea. [b] Mol %, determined in the ^{19}F NMR spectrum, relative to the product-CF_3-group. [c] Not detectable in the ^{19}F-spectrum. [d] Sum of product and symmetrical urea.

(20) See Supporting Information for a detailed description of the programs used.

(21) A control experiment showed that *tert*-butylamine does not react with diarylurea product.

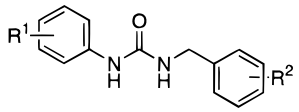
The products were also analyzed for fluorous impurities by measuring their ^{19}F NMR spectra. The reagents in this initial series of experiments were chosen such that half of the ureas contained fluorine atoms, and these served as internal standards. The signal for the terminal CF_3 of the perfluorohexyl group ($\delta = -80$ ppm) was integrated to determine the mol % of fluorous impurity. This is a sensitive analysis because there are 18 fluorines per molecule of fluorous contaminant and because all the CF_3 groups of all possible contaminants are expected to have the same chemical shift (In other words, the assay provides the sum of all fluorous impurities without providing their structures.) The amount of fluorous derivatives was lower than 0.6 mol %,[22] proving that the fluorous-organic extraction is effective in removing fluorous product from the organic phase. Indeed, the fluorous content is so low that it escapes detection if the spectrometer is not tuned to perfection. We presume that the nonfluorinated ureas have similar trace levels of fluorous contaminants (<1%), but these are difficult to quantify without the internal standard.

Although the product purities are excellent, the isolated yields in these experiments are lower and more variable than expected for simple urea formation. We traced this problem to the robotic extractions; the "fluorous waste" from the extractions contained variable but significant amounts of THF (easily seen by the naked eye) and the THF in turn contained organic urea. The robot performs the extraction by drawing the lower (fluorous) phase up through a needle. The extraction is not controlled by monitoring the meniscus but by the input of a fixed volume to be withdrawn. In these initial experiments, we had set the volume of the fluorous phase to be removed to be slightly higher (105%) than the volume initially added. However, the results suggest that this is too high. Control experiments showed that when mixing pure FC-72 and THF, the volume of the THF phase increases, indicating that more FC-72 dissolves in the THF phase than vice versa. However, when a concentrated solution of fluorous urea (100 mg/0.7 mL) and pure THF are mixed, the volume of the FC-72 phase increases, indicating that there is a net flow of THF into the fluorous phase. These effects are solute dependent since after fluorous organic extraction, the amount of THF phase in the fluorous waste vials differed significantly in individual cases.

In two cases (entries 2, 3), a precipitated product was clearly visible to the naked eye prior to extraction, and the yield was very high in these cases. Apparently, the unintentional removal of the organic phase during extraction did not remove the product because it was not dissolved. The solid was suspended in the (upper) organic phase and did not clog the needle when the (lower) fluorous phase was removed by the robot. That product precipitation does not have a negative effect on the scavenging reaction/extraction procedure is advantageous since it is possible—even probable—that some members of a structurally diverse library will not be soluble in the reaction medium. Product precipitation cannot easily be accommodated in polymer quenching or ion exchange procedures since the desired insoluble product would be removed during the filtration of the insoluble scavenging reagents and products.

(22) We assume that the major impurity is the fluorous urea, and the mol % was calculated based on this assumption.

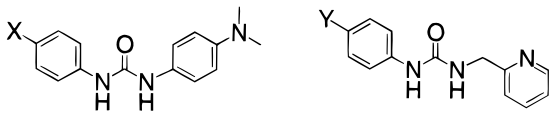
Table 2. 3 × 3 Library with Optimized Extraction Procedure



entry	no.	R^1	R^2	urea yield (%)	HPLC purity[a] (%)	%F[b]
1	**26m**	4-Br	4-CF_3	87	98.0 (0.5)	0.5
2	**26n**	4-Br	3-CF_3	80	98.5 (0.4)	0.3
3	**26o**	4-Br	2-CF_3	90	98.4 (0.2)	0.4
4	**26p**	3-Br	4-CF_3	79	95.7 (2.4)	0.3
5	**26q**	3-Br	3-CF_3	93	96.5 (1.7)	0.3
6	**26r**	3-Br	2-CF_3	85	96.8 (0.9)	0.3
7	**26s**	2-Br	4-CF_3	73	92.3 (4.4)	0.2
8	**26t**	2-Br	3-CF_3	96	94.0 (3.6)	0.2
9	**26u**	2-Br	2-CF_3	90	93.6 (3.6)	0.3

[a] Waters Nova-Pack C18 3.9 × 150 mm. Flow rate 1.5 mL/min. Detection at 210 nm, solvent: acetonitrile 40 to 60% in water. The numbers in parentheses refer to the amount of symmetrical urea. [b] Mol %, determined in the ^{19}F NMR spectrum, relative to the product-CF_3-group.

Table 3. 2 × 2 Library of Ureas Containing Basic Functionalities



entry	no.		urea yield (%)	HPLC purity[a] (%)	%F[b]
1	**26v**	X = Br	78	96.5 (2.4)	–
2	**26w**	X = OCF_3	68	94.6 (2.4)	0.4
3	**26x**	Y = Br	82	96.4 (3.6)	–
4	**26y**	Y = OCF_3	55	95.0 (2.0)	0.5

[a] Waters Nova-Pack C18 3.9 × 150 mm. Flow rate 1.5 mL/min. Detection at 210 nm, solvent: acetonitrile 40 to 60% in water. The numbers in parentheses refer to the amount of symmetrical urea. [b] Mol %, determined in the ^{19}F NMR spectrum, relative to the product-CF_3-group.

Table 2 shows the results of a second 3 × 3 library. In this experiment, the settings for the fluorous extraction procedure were adjusted to call for a lower extraction volume, so little or no organic phase was concomitantly removed. The yields were considerably higher with the revised extraction volume (73–96%, average 86%) while the excellent level of purity of the products was maintained. In this experiment, we can trace the *sym*-urea impurity back to the starting isocyanate since the level of this impurity is a direct function of the starting isocyanate (compare the yields of *sym*-urea in entries 1–3, 4–6, and 7–9).

To demonstrate the broader applicability of the fluorous quenching method compared to ionic quenching methods, a very small library of four ureas containing basic side chain functionalities was prepared by robot (Table 3). Ureas **26v–y** are not accessible via an acid/base extraction workup procedure since acidic washing to remove excess amine reagent would be unselective and would remove the urea product as well from the organic phase.

Biological Evaluation of Library Components. An important subgoal of this work was the synthesis of ureas that would exhibit ion channel modulating effects. Transepithelial Cl^- secretion is an integrated process that involves the polarized distribution of several membrane

transporters.[23] Several biophysically, pharmacologically, and molecularly distinct types of K^+ and Cl^- channels, as well as ion pumps and ion co-transporters, are thought to be involved in Cl^- secretion. Potential therapeutic uses of Cl^- secretion/absorption modulators include treatment of respiratory disorders such as the genetic disease cystic fibrosis (which affects one in 4000 live births worldwide), asthma, sinusitis, rhinorrhea, and COPD (congestive obstructive pulmonary disease).[24] Defective Cl^- secretion/absorption is also shown to play a major role in gastrointestinal disorders such as diarrhea, several cardiovascular, neuronal, skeletal, and smooth muscle disorders, and other diseases such as sickle cell anemia, ischemia, hypertension, myotonia, and Dent's disease.

We have evaluated the activity of aryl ureas generated in this combinatorial library for their effects on cAMP-stimulated transepithelial Cl^- secretion across a human colonic cancer cell line T84 in Ussing chambers using published protocols.[25] The initial screening was done with a concentration of 100 μM of aryl ureas, and the ones that were promising were further evaluated in a dose-dependent manner to calculate their inhibition constant (K_i). Several of the compounds were entirely inactive at 100 μM while others, e.g., **26q**, **26e** and **26g**, demonstrated K_i's of 1.5, 2.4, and 2.5 μM, respectively, and are therefore better than the existing Cl^- secretion inhibitors. Studies are in progress to obtain a more complete evaluation of the biological activity of the diarylureas and to ascertain their site and mechanism of action and will be presented in a separate manuscript.

Conclusions

We have developed a fluorous scavenging method for trapping of electrophiles in a solution phase reaction with a fluorous secondary amine. The method is based on liquid−liquid extraction and is complementary to resin capture and ionization methods, which are based on filtration. The method succeeds whether the final products remain in solution or precipitate out, and ionizable functional groups in the product do not interfere with the separation. The chemical yields and the purities are good to excellent, and the method is nicely suited for robotic execution.

Along with these advantages come some potential limitations. The molecular weight of the quenching agent is quite high, and it thus has limited utility if a very large excess of the component to be quenched is used. (However, the reactions are conducted in solution, so very large excesses of this reagent should not generally be needed.) The high molecular weight is caused by the large number of fluorine atoms, which also leads to limited solubility in organic solvents. This could cause problems with effective quenching due to biphasic reactions. In this work, the robotic vortexing provided a convenient solution to this problem. At this stage, we do not have a good gauge on the absolute reactivity of amine quenching reagent. The isocyanates used in this study are reasonably reactive electrophiles and it is premature to conclude that amine **10** will be useful for less reactive electrophiles.

Limitations notwithstanding, the work clearly suggests that fluorous quenching procedures have features and capabilities that make them convenient and attractive for use in small scale parallel synthesis.

Experimental Section

General Methods. All glassware was dried in an oven at 120 °C prior to use. All experiments were conducted under an atmosphere of dry nitrogen unless indicated otherwise. Solvents were dried as follows: THF was distilled from sodium/benzophenone. Dichloromethane was distilled from calcium hydride; chloroform and benzotrifluoride were distilled from potassium carbonate. ^{19}F NMR spectra were recorded with fluorotrichloromethane as an internal standard.

***N*-[3-[Tris(2-perfluorohexylethyl)silyl]propyl]trifluoroacetamide 9.** tris(2-Perfluorohexylethyl)silane (1.0 g, 0.93 mmol) was mixed with *N*-allyltrifluoroacetamide **8** (286 mg, 1.87 mmol) in a sealed tube under nitrogen gas, and H_2PtCl_6 (10.6 μL of a 10% solution in *i*-PrOH) was added. The vigorously stirred mixture was heated overnight at 80 °C in the dark, and then it was diluted with FC-72 and extracted with dichloromethane. The fluorous phase was evaporated, and the residue was purified by column chromatography (hexanes/acetone 95:5 to 9:1), yielding **9** as a colorless oil (762 mg, 72%): IR (cm^{-1}): 3310 (w), 2942 (w), 1713 (m), 1569 (w), 1452 (w), 1226 (s, br), 1082 (m), 739 (m); MS (EI) (*m*/*e*): 1223 ($M^{+\bullet}$, 7), 1204 (10), 1154 (19), 954 (5), 876 (100), 826 (5), 548 (30). ^{1}H NMR (300 MHz, acetone-d_6): 8.47 (1H, bs), 3.37 (2H, q, J = 6.6 Hz), 2.34 (6H, m), 1.72 (2H, m), 1.09 (6H, m), 0.93 (2H, m) ppm; ^{13}C NMR (75 MHz, acetone-d_6): 157.9 (q, J = 36.0 Hz), 124.5−107.8 (m), 43.5, 26.3 (t, J = 23.3 Hz), 23.8, 8.9, 1.7 ppm; ^{19}F NMR (471 MHz, acetone-d_6): −76.5 (3F), −81.3 (9F), −116.6 (6F), −122.5 (6F), −123.4 (6F), −123.8 (6F), −126.7 (6F) ppm.

3-[Tris(2-perfluorohexylethyl)silyl]propylamine 10. To a solution of **10** (1.1 g, 0.9 mmol) in a THF (15 mL)−MeOH (7.5 mL)−H_2O (3.75 mL) mixture was added LiOH−H_2O (566 mg, 13.5 mmol). The mixture was stirred at room temperature for 45 h. After evaporation of the organic solvents, dichloromethane was added, and this was extracted with FC72 (3×). The combined fluorous phases were dried over $MgSO_4$ and evaporated, yielding **10** (992 mg, 98%) as a colorless liquid: IR (cm^{-1}): 2935 (m), 2347 (w), 1385−1001 (s, br); MS (EI) (*m*/*e*): 1127 ($M^{+\bullet}$, 5), 1108 (5), 858 (5), 780 (100), 433 (3). ^{1}H NMR (300 MHz, $CDCl_3$): 2.73 (2H, t, J = 6.9 Hz), 2.04 (6H, m), 1.43 (2H, m), 0.89 (6H, m), 0.70 (2H, m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): 121.3−107.5 (m), 45.1, 27.3, 25.5 (t, J = 25.6 Hz), 8.3, 1.2 ppm; ^{19}F NMR (282 MHz, $CDCl_3$): −81.3 (9F), −116.6 (6F), −122.5 (6F), −123.4 (6F), −123.8 (6F), −126.7 (6F) ppm.

***N*,*N*-Bis[3-[tris(2-perfluorohexylethyl)silyl]propyl]trifluoroacetamide 22.** To a well-stirred mixture of tris(2-perfluorohexylethyl)silane **7** (4.85 g, 4.5 mmol) and *N*,*N*-diallyltrifluoroacetamide **21** (417 mg, 2.2 mmol) under Ar was added H_2PtCl_6 (10% in *i*PrOH, 124 mL). The mixture was stirred in a sealed tube for 17 h at 80 °C, shielded from light. The crude product was purified by gradient chromatography (BTF/hexanes 45:55 to 50:50) to yield the bissilylated product **22** (1.93 g) and the monosilylated product **23** (1.30 g, 47%), both as colorless oils. Product **22** was further purified by HPLC (BTF:hexanes 40:60) to yield 1.67 g (33%).

22: IR (cm^{-1}): 2956 (m), 1700 (s), 1448 (m), 1367 (m), 1251−1136 (s, br), 1075 (m); MS (EI) (*m*/*e*): 2333 ($M^{+\bullet}$, 10), 2314 (7), 2264 (6), 2236 (1), 1986 (100), 1658 (30), 1330 (17); ^{1}H NMR (300 MHz, acetone-d_6): 3.48 (4H, m), 2.33 (12H, m), 1.78 (4H, m), 1.09 (12H. m), 0.78 (4H, m) ppm; ^{13}C NMR (125 MHz, acetone-d_6): 156.9 (q, J = 35.6 Hz), 121.7−109.0 (m), 51.2 and 50.5, 26.0 (t, J = 23.0 Hz), 23.6 and 21.5, 8.7 and 8.4, 1.6 ppm; ^{19}F NMR (282 MHz, acetone-d_6): −68.6 (3F), −80.6 (18F), −115.4 (12F), −121.5 (12F), −122.4 (12F), −122.8 (12F), −125.8 (12F) ppm.

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23: IR (cm^{-1}): 2985 (m), 2944 (m), 1690 (s), 1441 (m), 1361 (m), 1240−1143 (s, br), 1070 (m), 900 (m); MS (EI) (*m*/*e*): 1265 ($M^{+\bullet}$, 14), 1246 (12), 1236 (5), 1196 (25), 918 (90), 590 (15), 168 (100); ^1H NMR (300 MHz, acetone-d_6): 3.50−3.36 (4H, m), 2.34 (6H, m), 1.82−1.58 (4H, m), 1.10 (6H, m), 0.94−0.85 (5H, m) ppm; ^{13}C NMR (75 MHz, acetone-d_6): 156.9 (q, J = 27.8 Hz), 124.4−105.7 (m), 51.2 and 50.1, 50.6 and 49.3, 26.1 (t, J = 23.3 Hz), 23.7 and 22.7, 21.6 and 20.9, 11.3 and 11.0, 8.8 and 8.5, 1.7 ppm; ^{19}F NMR (282 MHz, acetone-d_6): −68.59 and −68.64 (3F), −80.71 (9F), −115.5 (6F), −121.4 (6F), −122.4 (6F), −122.8 (6F), −125.8 (6F) ppm.

***N*,*N*-Bis[3-[tris(2-perfluorohexylethyl)silyl]propyl]-amine 16.** To a solution of *N*,*N*-bis[3-[tris(2-perfluorohexylethyl)silyl]propyl]trifluoroacetamide **22** (1.34 g, 0.57 mmol) in a mixture of BTF (20 mL) and THF (10 mL) was added $LiAlH_4$ (1.0 M solution in Et_2O, 2.0 mL). After stirring at room temperature for 5 h, the mixture was quenched with saturated Na_2SO_4, and the resulting mixture was stirred for 2 h. The solids were removed by filtration, and the solvent was evaporated. The resulting light yellow oil was dissolved in FC-72 and decolorized with active charcoal. Filtration and evaporation yielded the fluorous amine **16** (1.26 g, 98%) as a colorless oil: IR (cm^{-1}): 2938 (m), 1442 (m), 1365 (m), 1269−1140 (s, br), 1077 (m), 1018 (m); MS (EI) (*m*/*e*): 2236 ($M^{+\bullet}$ − 1, 5), 2218 (5), 1890 (21), 1140 (100), 792 (15); ^1H NMR (300 MHz, acetone-d_6): 2.61 (4H, t, J = 6.7 Hz), 2.33 (12H, m), 1.58 (4H, m), 1.05 (12H, m), 0.90 (4H, m) ppm; ^{13}C NMR (125 MHz, acetone-d_6): 120.6−108.3 (m), 53.4, 26.1 (t, J = 23.4 Hz), 24.6, 9.1, 1.7 ppm; ^{19}F NMR (282 MHz, acetone-d_6): −80.7 (18F), −115.4 (12F), −121.5 (12F), −122.4 (12F), −122.7 (12F), −125.8 (12F) ppm.

Representative Quenching Experiment with Fluorous Scavenger 6. To a solution of benzylamine (14.7 mL, 0.14 mmol) in acetonitrile (0.50 mL) was added a solution of benzyl isocyanate (33.3 mL 0.27 mmol) in acetonitrile (0.50 mL) at room temperature. The mixture was stirred for 1 h, followed by quenching with **16** (380 mg, 0.38 mmol) in an 1.4:1 acetonitrile/benzotrifluoride mixture (1.7 mL). After stirring for 1 h at room temperature, acetonitrile (2 mL) was added, and the organic phase was extracted twice with FC-84 (2 × 3 mL). Evaporation of the organic phase gave dibenzylurea, contaminated with 15% (^1H NMR) of the fluorous benzylurea (59.7 mg, theor 32.3 mg).

Representative Quenching Experiment with Fluorous Scavenger 16. To a solution of *p*-methoxybenzylamine (17.6 mL, 0.14 mmol) in THF (1 mL) was added a solution of *p*-tolyl isocyanate (25.5 mL, 0.20 mmol) in THF (1 mL) at room temperature. The mixture was stirred for 2 h, followed by quenching with **16** (300 mg, 0.14 mmol) in FC-72 (2 mL). After stirring for 5 h at room temperature, the phases were separated, and the organic phase was extracted three more times with FC 72 (3 × 2 mL). Evaporation of the organic phase gave *p*-methoxybenzyl *p*-tolyl urea (35.7 mg, 98%).

General Procedure for Derivatization of Fluorous Scavenger 10 Leading to 11, 12, and 14. To a solution of **6** in chloroform/BTF (0.05−0.08 M) was added triethylamine (4 equiv) and a solution of electrophile (1.2−1.5 equiv) in chloroform. After 3 h, the mixture was extracted with water or 1 M HCl. After drying ($MgSO_4$) and evaporation of the solvent, the crude mixture was purified by column chromatography (hexanes/acetone 9:1) to obtain **11**, **12**, and **14** in 55−75% yield.

11: IR (cm^{-1}): 3324 (m, br), 2929 (m), 1633 (s), 1579 (s), 1454 (m), 1360 (m), 1317−1120 (s, br), 1068 (s), 902 (m); MS (EI) (*m*/*e*): 1260 ($M^{+\bullet}$, 31), 1241 (7), 913 (23), 823 (25), 780 (15), 150 (100); ^1H NMR (300 MHz, acetone-d_6): 7.24 (5H, m), 5.82 (1H, m), 5.62 (1H, m), 4.34 (2H, d, J = 6.0 Hz), 3.16 (2H, m), 2.32 (6H, m), 1.58 (2H, m), 1.07 (6H, m), 0.85 (2H, m) ppm; ^{13}C NMR (75 MHz, acetone-d_6): 159.2, 142.2, 129.2, 128.2, 127.6, 123.9−106.2 (m), 44.5, 44.0, 26.1 (t, J = 23.0 Hz), 25.4, 8.9, 1.7 ppm; ^{19}F NMR (282 MHz, acetone-d_6): −80.6 (9F), −115.4 (6F), −121.4 (6F), −122.4 (6F), −122.7 (6F), −125.7 (6F) ppm.

12: mp 47 °C; IR (cm^{-1}): 3282 (m, br), 2941 (m), 2874 (m), 1600 (w), 1441 (m), 1320 (m), 1238−1145 (s, br), 1072 (m); MS (EI) (*m*/*e*): 1262 ($M^{+\bullet}$ − 19, 4), 1126 (1), 1012 (1), 934 (35), 184 (100). ^1H NMR (300 MHz, acetone-d_6): 7.72 (2H, d, J = 8.3 Hz), 7.39 (2H, d, J = 8.1 Hz), 6.41 (1H, t, J = 6.1 Hz), 2.91 (2H, m), 2.41 (3H, s), 2.31 (6H, m), 1.59 (2H, m), 1.03 (6H, m), 0.85 (2H, m) ppm; ^{13}C NMR (75 MHz, acetone-d_6): 143.8, 139.4, 130.5, 127.9, 123.9−105.7 (m), 47.1, 26.1 (t, J = 23.3 Hz), 24.5, 21.4, 8.8, 1.6 ppm; ^{19}F NMR (282 MHz, acetone-d_6): −80.7 (9F), −115.4 (6F), −121.4 (6F), −122.4 (6F), −122.7 (6F), −125.8 (6F) ppm.

14: IR (cm^{-1}): 3275 (w), 2940 (w), 2876 (w), 1634 (s), 1549 (m), 1507 (m), 1360 (m), 1237−1144 (s, br), 1072 (m), 904 (m); MS (EI) (*m*/*e*): 1245 ($M^{+\bullet}$, 3), 1226 (5), 1216 (1), 1204 (1), 898 (25); ^1H NMR (300 MHz, acetone-d_6): 7.77 (2H, d, J = 8.2 Hz), 7.73 (1H, m), 7.23 (2H, d, J = 8.1 Hz), 3.42 (2H, q, J = 6.6 Hz), 2.35 (3H, s), 2.34 (6H, m), 1.72 (2H, m), 1.08 (6H, m), 0.94 (2H, m) ppm; ^{13}C NMR (75 MHz, acetone-d_6): 167.3, 142.1, 133.5, 129.7, 128.1, 124.4−105.7 (m), 43.5, 26.1 (t, J = 23.2 Hz), 24.5, 21.4, 9.0, 1.7 ppm; ^{19}F NMR (282 MHz, acetone-d_6): −80.6 (9F), −115.3 (6F), −121.4 (6F), −122.4 (6F), −122.7 (6F), −125.7 (6F) ppm.

General Procedure for Preparation of 13 and 15. The *N*-methyl analogue of **10** was prepared as above, except *N*-methyl-*N*-allyltrifluoroacetamide was used as substrate for the hydrosilylation (71%), and $LiAlH_4$ in THF was used for the removal of the trifluoroacetamide group (100%). *N*-Me **10** was dissolved in BTF (0.06−0.1 M), followed by addition of triethylamine (4 equiv), a solution of electrophile (1.5 equiv) in BTF, and a catalytic amount of DMAP. The reaction was stirred for 6−10 h. The organic phase was washed with 10% HCl and brine and dried ($MgSO_4$). After evaporation of the solvent, the obtained crude mixture was purified by column chromatography (hexanes:acetone 9:1) to yield **13** (84%) and **15** (94%).

13: IR (cm^{-1}): 2937 (w), 1600 (w), 1441 (w), 1346 (m), 1232−1143 (s, br), 1069 (m). MS (EI) (*m*/*e*): 1295 ($M^{+\bullet}$, 1), 1276 (6), 1230 (1), 1140 (1), 1026 (2), 948 (20), 198 (100). ^1H NMR (300 MHz, acetone-d_6): 7.70 (2H, d, J = 8.2 Hz), 7.42 (2H, d, J = 8.1 Hz), 3.01 (2H, t, J = 7.0 Hz), 2.70 (3H, s), 2.43 (3H, s), 2.35 (6H, m), 1.67 (2H, m), 1.09 (6H, m), 0.88 (2H, m) ppm; ^{13}C NMR (75 MHz, acetone-d_6): 144.2, 136.0, 130.6, 128.4, 124.4−105.7 (m), 53.8, 35.1, 26.1 (t, J = 23.2 Hz), 22.4, 21.4, 8.5, 1.7 ppm; ^{19}F NMR (282 MHz, acetone-d_6): −80.5 (9F), −115.3 (6F), −121.4 (6F), −122.3 (6F), −122.7 (6F), −125.7 (6F) ppm.

15: IR (cm^{-1}): 2931 (s), 2883 (m), 1640 (s), 1515 (m), 1441 (m), 1365 (m), 1315−1120 (m, br), 1070 (m), 899 (m); MS (EI) (*m*/*e*): 1259 ($M^{+\bullet}$, 8), 1240 (6), 912 (12), 50 (100); ^1H NMR (300 MHz, acetone-d_6): 7.28 (2H, d, J = 7.8 Hz), 7.21 (2H, d, J = 7.9 Hz), 3.50 and 3.33 (2H, bs), 2.97 (3H, s), 2.35 (9H, m), 1.74 (2H, bs), 1.08 (6H, bs), 0.92 and 0.69 (2H, bs) ppm; ^{13}C NMR (125 MHz, acetone-d_6): 171.9 and 171.4, 139.9 and 139.8, 135.8 and 135.6, 129.6, 128 and 127.7, 121.1−109.3 (m), 54.6 and 50.8, 37.7 and 32.7, 26.0 (t, J = 22.8 Hz), 22.9 and 21.6, 21.3, 8.6 and 8.4, 1.6 ppm; ^{19}F NMR (282 MHz, acetone-d_6): −80.6 (9F), −115.3 (6F), −121.4 (6F), −122.4 (6F), −122.7 (6F), −125.7 (6F) ppm.

General Procedure for Derivatization of Fluorous Scavenger 16 Leading to 17−20. To a solution of **16** in BTF, or a BTF−THF mixture (0.02 M), was added electrophile (neat or dissolved in THF or BTF, 2−5 equiv). Triethylamine (4−6 equiv) and DMAP (cat) were added, for **17** and **18**. After 4−6 h, water or 5% $NaHCO_3$ was added, and the mixture was extracted with FC-72. The phase separation was generally difficult. The fluorous phase was washed with brine and after evaporation was purified by column chromatography (BTF/hexanes 1:1; for **20**: hexanes/acetone 9:1) to obtain **17**−**20** in 58−89% yield.

17: IR (cm^{-1}): 2933 (m, br), 1637 (s), 1425 (m), 1362 (s), 1321−1120 (s, br), 1070 (s), 903 (m); MS (EI) (*m*/*e*): 2355 ($M^{+\bullet}$, 12), 2336 (7), 2008 (15), 1680 (7), 1352 (6), 1286 (32), 898 (36), 792 (48), 145 (100); ^1H NMR (500 MHz, acetone-d_6): 7.25 (2H, d, J = 7.9 Hz), 7.19 (2H, d, J = 7.9 Hz), 3.50 and 3.32 (4H, bs), 2.33 (15H, m), 1.78 and 1.68 (4H, bs), 1.06 (12H, m), 0.90 and 0.65 (4H, bs) ppm; ^{13}C NMR (125 MHz, acetone-d_6): 171.0, 138.7, 135.1, 128.6, 126.5, 120.7−108.0 (m), 51.6 and 47.1, 25.0 (t, J = 23.1 Hz), 22.4 and 21.1, 20.2, 7.6, 0.6 ppm; ^{19}F NMR

(282 MHz, acetone-d_6): −80.6 (18F), −115.4 (6F), −121.4 (6F), −122.4 (6F), −122.7 (6F), −125.8 (6F) ppm.

18: IR (cm^{-1}): 2943 (w), 1634 (m), 1442 (m), 1360 (m), 1235−1130 (s, br), 1070 (m), 904 (m); MS (FAB) (*m*/*e*): 2418 ($[M + H]^+$, 24), 2195 (5), 862 (20), 577 (80), 488 (100); ^{1}H NMR (500 MHz, acetone-d_6): 7.67 (4H, m), 7.46 (4H, m), 7.39 (1H, m), 3.53 and 3.40 (4H, bs), 2.32 (12H, m), 1.81 and 1.73 (4H, bs), 1.07 (12H, m), 0.92 and 0.69 (4H, bs) ppm; ^{13}C NMR (75 MHz, acetone-d_6): 170.8, 141.6, 140.2, 136.9, 129.0, 127.8, 127.3, 126.8, 123.0−105.3 (m), 51.8 and 47.2, 25.2 (t, $J = 23.1$ Hz), 22.6 and 21.3, 8.0, 0.7 ppm; ^{19}F NMR (282 MHz, acetone-d_6): −80.6 (18F), −115.3 (12F), −121.4 (12F), −122.4 (12F), −122.7 (12F), −125.8 (12F) ppm.

19: mp 42 °C; IR (cm^{-1}): 2947 (w), 2872 (w), 1644 (m), 1593 (w), 1520 (m), 1361 (m), 1251−1145 (s, br), 1067 (m), 897 (m); MS (EI) (*m*/*e*): 2370 ($M^{+\bullet}$, 12), 2351 (3), 2236 (15), 2218 (15), 2023 (6), 1968 (11), 1890 (62), 1562 (10), 1140 (100), 792 (65); ^{1}H NMR (300 MHz, acetone-d_6): 7.46 (1H, s), 7.34 (2H, d, $J =$ 8.4 Hz), 6.99 (2H, d, $J = 8.3$ Hz), 3.41 (4H, t, $J = 7.3$ Hz), 2.37 (12H, m), 2.23 (3H, s), 1.76 (4H, m), 1.09 (12H, m), 0.87 (4H, m) ppm; ^{13}C NMR (125 MHz, acetone-d_6): 155.8, 139.0, 131.9, 129.5, 120.9, 121.7−109.1 (m), 50.9, 26.1 ($J = 23.1$ Hz), 23.3, 20.7, 8.8, 1.7 ppm; ^{19}F NMR (282 MHz, acetone-d_6): −80.7 (18F), −115.5 (12F), −121.5 (12F), −122.5 (12F), −122.7 (12F), −125.8 (12F) ppm.

20: IR (cm^{-1}): 3291 (w, br), 2933 (w, br), 1686 (s), 1588 (s), 1545 (s), 1476 (s), 1463 (s), 1443 (s), 1426 (s), 1364−1078 (s, br), 904 (s); MS (FAB) (*m*/*e*): 2435 ($[M + H]^+$, 90), 2363 (5), 2238 (10), 2166 (3), 2087 (11); 1140 (23), 368 (100) ^{1}H NMR (500 MHz, acetone-d_6): 9.07 (1H, s), 7.85 (2H, d, $J = 8.3$ Hz), 7.33 (2H, d, $J = 8.2$ Hz), 3.30 (4H, bs), 2.40 (3H, s), 2.29 (12H, m), 1.65 (4H, bs), 1.05 (12H, m), 0.77 (4H, bs) ppm; ^{13}C NMR (125 MHz, acetone-d_6): 152.3, 144.5, 139.1, 129.8, 129.2, 123.1−109.1 (m), 50.31, 25.97 (t, $J = 22.5$ Hz), 22.8, 21.4, 8.7, 1.6 ppm; ^{19}F NMR (282 MHz, acetone-d_6): −80.6 (18F), −115.4 (12F), −121.4 (12F), −122.4 (12F), −122.7 (12F), −125.8 (12F) ppm.

Determination of the Partition Coefficients. (A) Gravimetric: a mixture of the fluorous compound (80−150 mg) in FC-72 (50 mL) and organic solvent (50 mL) was vigorously shaken in a separating funnel. The phases were allowed to settle and were separated. The solvent was removed and the partition coefficient was determined as the ratio of the amount of product that was dissolved in each phase.

(B) By HPLC: a mixture of the fluorous compound (1−10 mg) in FC-72 (1 mL) and organic solvent (1 mL) was vigorously stirred in a vial. The phases were allowed to settle, and the amount of product present in each phase was determined by analytical HPLC (column: NEOS Fluofix, flow rate: 1 mL/min, solvent: THF, injection volume: 10−50 μL). The partition coefficient was determined by the ratio of the peak areas. The injection volume was chosen so that the ratios of the obtained peak areas did not exceed 15:1. In some cases, the fluorous phase had to be diluted.

Acknowledgment. Bruno Linclau is indebted to the Belgian American Educational Foundation (BAEF) for a fellowship. We thank Hewlett-Packard for the loan of the HP 7686 synthesizer, and Drs. Paul Hoeprich, William Leber, and Charles Knipe for their helpful advice. We are thankful to Dr. Kasi V. Somayajula and Vyacheslow N. Fishman for the mass spectral data. We acknowledge Prof. Robert J. Bridges for all the helpful discussions regarding biological evaluation of the combinatorial libraries, the technical assistance of Maitrayee Sahu in tissue culture, and Matthew Green in Ussing chamber experiments. This work was supported by the Drug Chemistry Core (A.K.S.) funded by the Cystic Fibrosis Foundation Research Development Program (RDP) FRIZZE 97R0 and by the National Institutes of Health (D.P.C.). We thank OxyChem for providing BTF and Elf Atochem for perfluoroaklyl iodides.

Supporting Information Available: Contains a description of the programming sequence used for the robotic experiments, HRMS data for the urea products, and copies of the ^{1}H NMR spectra of the fluorous amine **16** and its precursor **22** and the crude urea products from the library experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9823442