JOURNAL OF combinatorial CHEMISTRY

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J. Comb. Chem., **2000**, 2 (3), 266-275• DOI: 10.1021/cc990077n • Publication Date (Web): 12 April 2000

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Application of Base Cleavable Safety Catch Linkers to Solid Phase Library Production

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Received December 1, 1999

We have used sulfide "Safety Catch" linkers to anchor typical medicinal chemistry functional groups to amine resins. Compounds are loaded as the ester, carbamate, or amine. At the end of the synthesis, the linker is activated by peracid. The sulfone resins are then cleaved by β-elimination in the gas phase or in solution by secondary amines to produce acids and primary, secondary, or tertiary amines. Comparison of cleavage rates to other sulfone resins including SEM showed significantly faster cleavage for this system with conditions similar to Fmoc deprotection. Application of this strategy to a medicinal chemistry library gives good yields and purities of the resulting compounds.

Introduction

Solid phase synthesis has seen explosive growth in the past five years and, with the rapid advances of the field, has become a useful tool for medicinal chemistry. Solid phase chemistry is attractive both for its automation potential and opportunities for increased synthetic efficiency. Recent reviews[1] have highlighted the increased synthetic range and ability to use excess reagents without penalty in the synthesis of interesting drug-like molecules. However, the solid phase synthesis process necessarily adds an attachment step and a cleavage step to the synthetic plan. Often, the decision to choose a solid or solution phase route to a chemical library rests on the adaptability and convenience of these steps. While the only constraint for attachment is a high yield of resin bound product, the cleavage step must be orthogonal to the proposed synthesis scheme. Initially, most investigators concentrated on adapting the acid sensitive linkers used in peptide chemistry to more varied conditions, accepting the loss of acidic chemistry in return for well-precedented cleavage conditions and a significant inventory of suitably protected starting materials.[2] However, there are many interesting pharmacophores that cannot be readily made using these resins. To overcome cleavage limitations and expand the synthetic range, many groups have developed "Safety Catch" linking strategies,[3] where the connection to the resin is stable until activated by a specifically targeted reagent. This allows a wider range of synthetic conditions at the cost of one activation step.

Using peptide linkers in medicinal chemistry has also led to the production of compounds with vestigial functional groups, typically carboxylate or secondary amide. An attractive alternative is the "traceless" linker where the connection to the resin is replaced by an electron lone pair or a hydrogen atom. While many groups have developed traceless linkers for CH bonds, it would be sufficient for many drug discovery projects to provide a general method for connection to heteroatoms. This capitalizes on the relative ease of carbon-heteroatom bond formation and allows more efficient use of the available synthesis pool. In this regard, the popular methoxy benzaldehyde linkers are "traceless" examples of this strategy, allowing solid phase attachment to a wide range of available primary amines and cleavage of the corresponding secondary amides.[4]

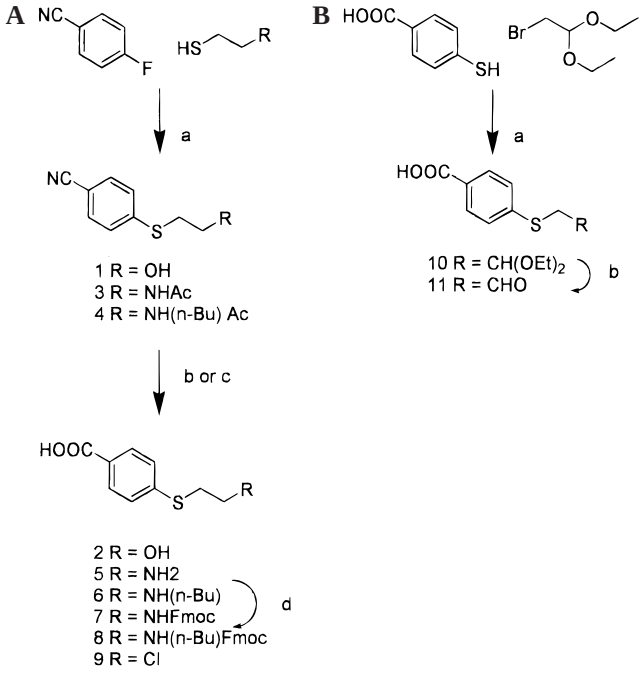
Thus, an ideal solid phase linker would combine high stability to synthetic conditions, rapid and efficient cleavage, and a traceless linkage. For this reason, considerable activity has been focused on the sulfone group as a stable linkage that can be cleaved under mild conditions.[5] Additionally, the sulfide form can be used as a "Safety Catch" precursor, then activated by oxidation.[5b,6] We report here our utilization of a family of linkers that use this combination of a "Safety Catch" cleavage strategy with "traceless" cleavage by β-elimination. Connections to the solid phase are made analogous to traditional protecting groups, and the released functional groups are common in drugs and drug candidates. The linker family is activated under similar conditions and is cleaved with amine bases, either in solution or in the gas phase. Practically, this results in a potential diversity site at the resin attachment point, with functional groups including amines and acids being cleaved under chemically similar conditions. As a bonus, the β-elimination strategy leads to relatively unhindered connections to the resin and resin bound functional groups with normal stability characteristics.

Results and Discussion

Linker Design Strategy. Initial design efforts were directed toward linkers that could be used for large mix and split libraries. To incorporate our tagging strategy,[7] we required a linker that could be coupled through an amide bond to the tagged resin, a simple activation strategy, and a gas phase cleavage protocol to facilitate bead processing. All these could be readily achieved with the classical TFA cleavable linkers,[8] but there are several shortcomings to acid cleavage. First, this limits synthetic sequences to steps with acid strengths no greater than glacial acetic acid and thus removes one commonly used orthogonal protecting group

10.1021/cc990077n CCC: $19.00 © 2000 American Chemical Society
Published on Web 04/12/2000

Scheme 1. Linker Synthesis[a] and Aldehyde Linker Synthesis[b]



[a] Part A Reagents: (a) K_2CO_3, CH_3CN; (b) H_3O^+, Δ; (c) KOH, Δ; (d) FmocNHS. [b] Part B reagents: (a) DBU; (b) H_3O^+.

strategy. Second, TFA is highly corrosive and cannot be completely removed from cleavage products without purification. This can result in significant instability upon compound storage. Indeed, a common HPLC "impurity" seen in TFA cleaved acids is the methyl ester formed from solvent methanol. Third, stable cations produced in acid cleavages need to be scavenged to prevent modification of sensitive functionality,[9] and the resultant cleavage cocktail is even more difficult to remove and could interfere with biological activity assays. For these reasons we turned to a base cleavable system.

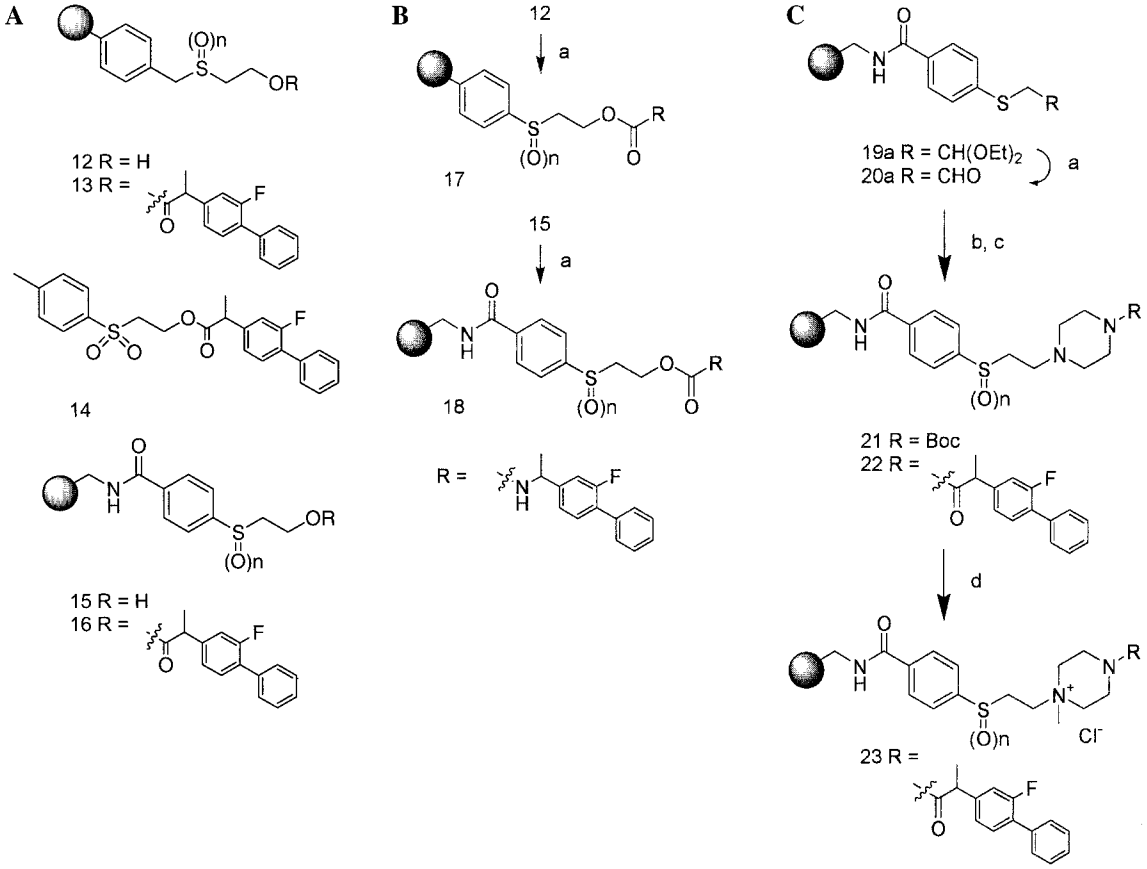
Linker Synthesis. β-Elimination has been used for peptide synthesis since 1967,[10] but has not seen much usage, presumably because the cleavage conditions as described needed to be tightly controlled.[10a] Linker **2** was first described in 1984 and used for the synthesis of peptides and oligonucleotides.[5f] With our specific requirements in mind, we revisited this linker and found that it was readily extendable to other terminal functional groups. The initial synthetic route started with 4-mercaptobenzoic acid, illustrating that either S bond connection is possible depending on the availability of starting materials. As shown in Scheme 1a, we chose to synthesize most of the linkers by nucleophilic aromatic substitution using 4-fluorobenzonitrile as the common precursor. A strong acid step then converted the nitrile to the carboxylic acid, with concomitant cleavage of any other acid sensitive group. Synthesis of linker **2** proved to be the most problematic by this route. High concentrations of mineral acid provided the chloro compound **9**, while low acid concentrations favored partial hydrolysis to the aggressively crystalline primary amide. Eventually two ways were found to circumvent this difficulty. Refluxing 2 N sulfuric acid at low compound concentrations worked well, but was difficult to perform on larger scale. Alternatively, refluxing in aqueous potassium hydroxide afforded the acid linker in good yield and purity after acidification. The aldehyde linker **11** proved easiest to make using the 4-mercaptobenzoic acid route as shown in Scheme 1b. The linkers were coupled to aminomethyl resin in high yield using the preformed HOBt ester.

Compound Loading. Linker **2** has reactivity similar to ethyl alcohol and was more easily loaded to high capacity than Wang and related benzyl resins by standard DIC coupling methods. Presumably the carbamate loaded linker could be generated from the nitrophenyl carbonate[5a,11] or the acylimidazolide[12] of **2**, though we chose to use the Curtius rearrangement described in Scheme 2b to demonstrate the carbamate loading as a catch and release option. On cleavage of resin **18c** this method gives 2% acid, presumably from direct acylation by the acyl azide intermediate. Preparation of tertiary amine resins could be accomplished by reductive amination of the primary or secondary amine linkers **5** and **6**. Alternatively, amines could be loaded by mesylate displacement, both on and off the resin, or by reductive amination of aldehyde resin **20**. Resin **21a** was prepared by this latter route, then converted to cleavage substrate **23c** in the unoptimized synthesis described in Scheme 2c. In our hands, the amine and ammonium salt resins acted as anion exchange resins when exposed to acids, and repeated washes with 2 N hydrochloric acid were necessary to replace organic acid counterions.

Linker Activation. Activation was easily achieved by incubation of the loaded resin with low concentrations of MCPBA. The cleavable functional group was identified as the sulfone **16c** by NMR. The sulfoxide resin **16b** could be prepared by the method of Bonadies et al.,[13] but did not give cleaved product. While we did not detect any side products of amine or double bond oxidation (see below), a second method was also developed using tetrabutylammonium oxone[14] at 40 °C. Heating was necessary in order to get complete reaction and to avoid an uncharacterized minor side product. The slightly stronger conditions needed reflect the difference between solution phase and gel phase polystyrene. As treatment of the sulfide resin **16a** at −15 °C with MCPBA for 3 h gives 70% sulfone and cleavage, it should also be possible to decrease side reactions this way. Obviously this linker is incompatible with sulfoxide or sulfide containing compounds.

Compound Cleavage. Despite being available for 30 years, sulfone resins have been underutilized in combinatorial chemistry. This is most probably because the cleavage conditions reported, sodium or ammonium hydroxide, are not readily adapted to parallel synthesis. Parallel removal of inorganic salts remains a difficult problem. Additionally, there are three possibilities for connection of the sulfone to polystyrene resin as shown in Scheme 2a. Because we expected to see differences in cleavage rates and protocols based on the electron density of the sulfone, we investigated all three possibilities. The benzyl sulfide **12a** and sulfone resin **12c** are synthetic intermediates for the commercially available SEM resin,[5d] the preparation of the amide connected resins **16a**−**c** is detailed here and in the literature,[5f] and 2-hydroxyethylthiopolystyrene could be synthesized from

Scheme 2. Ester Resins,[a] Carbamate Resin Synthesis,[a,b] and Ammonium Salt Resin Synthesis[a,c]



[a] Oxidation states for parts A, B, and C: (a) sulfide, $n = 0$, (b) sulfoxide, $n = 1$; (c) sulfone, $n = 2$. [b] Part B reagents: (a) flurbiprofen, DPPA, Δ. [c] Part C reagents: (a) H_3O^+; (b) BOC piperazine, $NaBH(OAc)_3$; (c) TFA; (d) MeI.

thiopolystyrene.[15] We used tolylethyl sulfone **14c** as a substitute for resin prepared by the third method. Any of these resins could be used as a safety catch system or preactivated to the sulfone.

Because the mildest possible cleavage conditions were desired, a general method of cleavage quantitation that permits kinetics to be measured was developed. In principle it is applicable to any resin cleavage conditions. Flurbiprofen and derived compounds were used to functionalize the resin. Flurbiprofen provided a typical medicinal carboxylic acid with a normal carboxylic acid pK_a and a detection limit of 1−2% cleavage. Importantly, the final resin loading could be measured by NMR[16] and fluorine elemental analysis, then the amount cleaved could be determined by HPLC using an internal standard. This gave true measurements of cleavage yields, with multiple cleavages of the same oxidized resin typically within 5% of each other.

In general, cleavage rates were pseudo first order in substrate and consistent with the accepted E1cB mechanism,[17] a potentially reversible deprotonation followed by an E1 elimination, and were correlated with the leaving group ability. With the exception of the ammonium salt **23c**, cleavage with tertiary amines was too slow to be practical. Resin **23c** was cleaved extremely rapidly with secondary amines, being complete in <15 min with a 0.5% amine solution. By using low concentrations of secondary amine, this cleavage method avoids the salt formation observed with tertiary amine cleavage or the need for a second resin.[18] It also indicates that the quaternization solvent must be free of secondary amines to achieve good yields of sulfone ammonium salts such as **23c**. Linker **2** was also a true safety catch system with 90−95% of the fluorine containing compound released from MCPBA activated **16c**, 70−80% from oxone activated **16c**, and <2% from resins **16a** or **16b**.

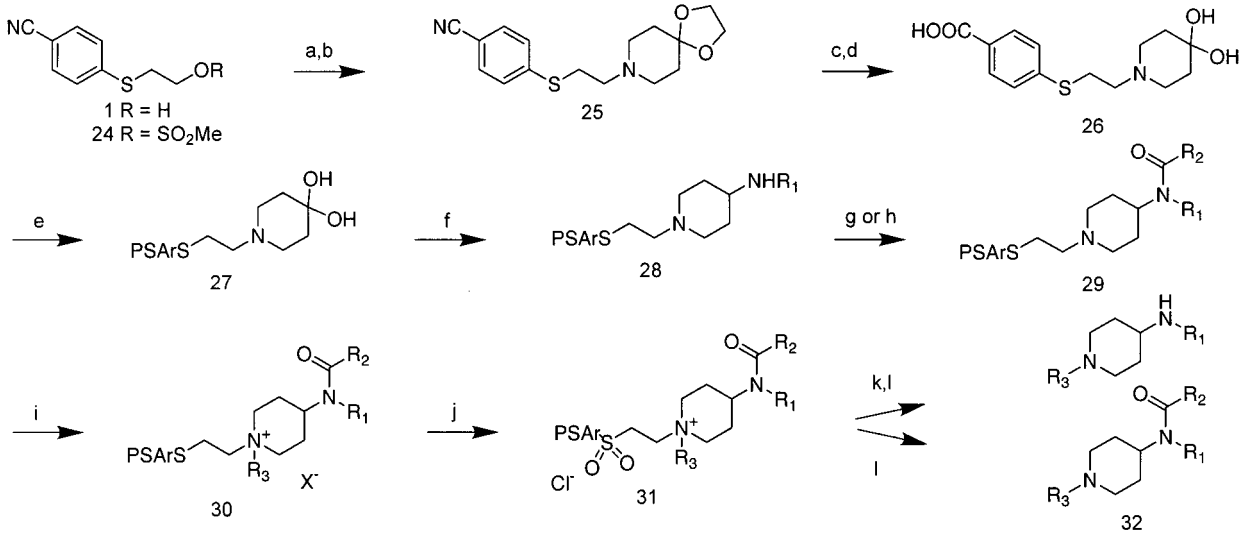
Table 1. Comparative Cleavage Rates of Differently Linked Resin Sulfones

	13c		**14c**		**16c**	
cleavage reagent	$t_{1/2}$[a]	complete[b]	$t_{1/2}$[a]	complete[b]	$t_{1/2}$[a]	complete[b]
5% DMA/THF:H_2O	297	40	121	17	35	5
20% DMA/THF	149	20	224	30	28	4
5% DEA/DMSO	140	19	40	6	15	2

[a] Cleavage half-life (min). [b] Complete cleavage time (h) measured for **16c**, calculated as 8 × $t_{1/2}$ for **13c** and **14c**.

Sulfone elimination rates are highly dependent on solvent polarity,[17] so three cleavage methods were developed for the ester resins. The simplest protocol was to use the 40% dimethylamine in water solution diluted in THF. Evaporation of the solvents gave the free acid directly. No flurbiprofen dimethylamide was detected by HPLC. As shown in Table 1, cleavage rates were significantly different between the three linkers. All three resins cleave completely within 3 h at >15% water and >2 M amine in THF. However, at lower amine and water conditions, the cleavage rate matches the relative acidity of the sulfone α-protons with **16c** faster than **14c** faster than **13c** (see Table 1). For resin **16c**, a 12.5% solution of 40% aqueous dimethylamine in THF (final

Scheme 3. Library Synthesis[a]



[a] Reagents: (a) MsCl; (b) piperidine-4-dioxolane, Δ; (c) 1 N HCl, Δ; (d) 6 N HCl, Δ; (e) DIC, HOBt; (f) R_1NH_2, $NaBH(OAc)_3$; (g) R_2COCl; (h) Boc_2O, DMAP; (i) R_3X, (j) MCPBa; (k) TFA; (l) Me_2NH.

concentration 5% amine) will cleave the acid completely in 4.5 h. The same conditions would require 42 h for **13c**. Alternatively, water free conditions were developed for sensitive systems. For resin **16c**, 20% anhydrous dimethylamine in THF gave reasonable cleavage rates. Dimethylamine could be replaced by diethylamine, but with a 4-fold drop in cleavage rate. 5% Diethylamine in DMSO also gave reasonable rates, and the DMSO could be replaced by any similar aprotic solvent. This is consistent with the polarity of cleavage media affecting the deprotonation equilibrium. Resins **12c** and **14c** were roughly 8- and 38-fold slower under most conditions. Compound **14c** is apparently sparingly soluble in anhydrous dimethylamine in THF, giving an initial burst of cleavage, followed by a slower than expected rate. Addition of 5% DMSO sped up cleavage rates for all three compounds and restored the typical rate order. The DMSO conditions, while clearly not designed for isolating final compounds, could be used for direct to preparative HPLC protocols or crude stock solutions.

The carbamate resin represents the worst leaving group that can cleaved productively, and here linker **2** proved clearly superior. Resin **18c** had reasonable cleavage rates with 15% aqueous dimethylamine affording complete cleavage within 6 h. The slower rates of the benzyl sulfone carbamate **17c** (>48 h) eliminate simple secondary amine cleavage as a viable option, and so for this resin the hydroxide conditions in the literature[5b] are probably necessary. Clearly, linker **2** extends the range of functional groups that can be cleaved with the secondary amine protocol.

The ester resin **16c** was also completely cleaved in the gas phase by dimethylamine vapor in 3 h at room temperature. This is within the range of conditions suitable for individual bead analysis.[19] In contrast, resin **13c** was cleaved 40% under identical conditions and 85% at 12 h. The carbamate resin **18c** was cleaved more slowly, giving a 45% yield at 12 h and 55% at 24 h. The benzyl sulfone carbamate resin **17c** was cleaved to only 10% in 24 h. The quaternary ammonium resins have been shown to cleave with ammonia vapor,[20] and indeed resin **23c** was cleaved completely in 0.5 h with dimethylamine vapor.

Table 2. Overall Yields of Library Compounds Synthesized

entry	R_1	R_2	R_3	% yield
a	n-Pr	CH_2Ph	CH_2Ph(2-Ph)	20
b	i-Bu	CH_2Ph	Me	41
c	*n*-Hex		CH_2Ph(4-Cl)	41
d	*n*-Hex	Me	CH_2Ph(4-Cl)	33
e	*n*-Hex	CH_2Ph	CH_2Ph(4-Cl)	25
f	*n*-Hex	$CHPh_2$	CH_2Ph(4-Cl)	32
g	CH_2Ph	CH_2Ph	allyl	28
h	$CHPh_2$	CH_2Ph	CH_2Ph(4-Cl)	18
I	CH_2CH_2Ph	CH_2Ph	CH_2-cPr	8
j	$CH(Ph)CH_2Ph$	CH_2Ph	CH_2Ph	21
k	CH_2CHPh_2	CH_2Ph	t-$CH_2CHCHPh$	17
l	$CH_2CH_2CH_2Ph$	CH_2Ph	$CH_2CON(Me)$n-Bu	13
m	$CH_2CH_2CHPh_2$	CH_2Ph	CH_2Ph(4-Cl)	18

Library Production. To demonstrate the potential for medicinal chemistry synthesis, the reaction sequence in Scheme 3 was carried out to produce the compounds in Table 2. Compounds **32a**−**m** are simple analogues of G-coupled protein receptor agonists or antagonists. To minimize the number of solid phase reaction steps and improve the handling the intermediates, the 4-piperidone core and linker were coupled separately and then attached to aminomethyl resin. Nucleophilic displacement of mesylate **24** was nearly quantitative. We were unable to find conditions for direct production of the keto acid **26**. Acid deprotection with 6 N HCl converted the nitrile to the acid without affecting the ketal, while more dilute acid cleaved the ketal without affecting the nitrile. On larger scale, it proved easiest to deprotect the ketal first, remove the ethylene glycol with a water workup, and then hydrolyze the nitrile with strong acid to produce compound **26**. Coupling to aminomethyl resin proceeded in high yield.

The resin was split into 100 mg portions for solid phase synthesis. By IR, ketone **27** was still present after the first reductive amination coupling, so it was repeated to give the secondary amine resins **28**. Coupling of the three acyl chlorides was straightforward, but production of carbamate

29c (Scheme 3, R_2 = OtBu) with di-*tert*-butyl dicarbonate required DMAP in alternating DCM and DMA to be complete as evidenced by a negative chloranil test. Alkylation with active halides to give **30a**−**m** followed the literature method.[5d] Activation and cleavage as above gave the final compounds **32a**,**b**,d−**m**. Resin **31c** was deprotected with TFA after activation and then cleaved by the standard procedure to give **32c**, highlighting the ability to use acid sensitive protecting groups in synthetic schemes with these linkers.

Characterization of the products showed that the major product in all cases was the correct one. HPLC and nanoprobe NMR[21] showed a small amount of UV active impurity consistent with 3-chlorobenzoic acid, so the compounds were purified by reverse phase HPLC. This impurity could be avoided by extended washing of the activated resin with HCl, presumably exchanging the anions of the ammonium salt for chloride. The NMR spectrum of the products revealed two sets of signals for each proton that merged at high temperature, indicating the presence of rotational isomers. The cyclopropylmethyl compound gave significantly lower yields than the other alkylation reagents, suggesting that the room temperature reactivity limit has been reached. However, unlike the sulfone based linkers, it should be possible to increase reaction time, temperature, and base strength for this reaction to complete the alkylation. The extreme lability of the quaternary ammonium salts suggests that yields might be limited for sulfone linkers such as **22c** by the presence of secondary amine in the solvents used for the quaternization.

Conclusion

Sulfone elimination has the potential to be a main line strategy for solid phase compound cleavage. While no linker and cleavage strategy can be stable to the full range of conditions available to the synthetic chemist, the oxidative activation/elimination strategy promises to substantially increase the available options. The sulfide linkers should further increase the range of anion chemistry by decreasing the acidity of the neighboring protons. For the tertiary amine production, it is also possible to oxidize the resin before synthesis to handle more oxidation sensitive systems, as described in the literature.[5d] Here the advantage of the sulfide safety catch is decreased sensitivity of the alkylated product to β-elimination, which could be utilized to increase yield or extend the available alkylating agents to less activated systems. The carbamate linkage could also be preoxidized if the rest of the synthesis avoided strong base.

We have demonstrated here that it is possible with the appropriate choice of linker to use both acid and base chemistry during compound synthesis, activate by oxidation, and then cleave under conditions very similar to those used for Fmoc deprotection. The functional groups readily available, acids and primary, secondary, and tertiary amines, are typical groups found in medicinal chemistry because they tend to make strong interactions with biological targets. The simplicity of the cleavage conditions is an important factor for combinatorial drug discovery, since sample processing after a completed synthesis is a major part of the total production time. Importantly, the cleavage agents and solvents are volatile, cheap, and available, and processing can be accomplished in the gas phase. The activation and cleavage strategy described here is also well suited for IRORI technology because the activation procedure can be done to all compounds in batch and then cleaved individually. We have used this combination at Abbott to build larger libraries of interesting medicinal compounds.

Finally, this approach allows the connection point to the resin to become a potential site of functional group diversity. We expect that any functional group with a leaving group ability equivalent to the carbamate could be cleaved under similar conditions. Solid phase chemistry becomes more attractive as an option as the synthesis becomes more combinatorial in nature. Linkage diversity adds an additional variable position to any existing synthesis at low cost in compound size and polarity. With relatively simple loading and cleavage conditions, this might be enough to tip the balance toward solid phase synthesis during the library design phase.

Experimental Section

General Methods. Solid phase reactions were performed in glass fritted tubes or in a Quest 210 synthesizer with manual washing. All reactions were performed under nitrogen atmosphere. Analytical HPLC was performed on a HP1100 system running at 1.5 mL/min with ELSD (Sedex) and DAD detection. Aliquots (5 μL) were injected onto a 5 μm 4 mm × 5 cm YMC ODS-AQ column, washed with 0.5 min 100% ammonium acetate, and eluted with an 8 min linear gradient from 100% buffer to 5% buffer, 95% acetonitrile followed by 2 min at 95% acetonitrile and reequilibration. Total cycle time was 14 min. Standards were synthesized by a method similar to the resin procedure and were analytically pure. LC/MS was performed on a HP1100 HPLC system interfaced to a Finnigan Navigator detector taking alternate positive and negative ion scans, using a 5 min gradient with the same buffer system as above. Resin IR was performed with a Perkin-Elmer Paragon 1000 FT-IR spectrometer. Resin NMR was performed on a 1 mg sample using gel phase MAS and the nano-NMR probe.[21] Elemental analyses were performed by Robertson Microlit, Madison, NJ. Resins were dried to constant weight before analysis. Loadings were calculated from the mole fraction of indicator elements Cl, F, S, or N. For better accuracy with Cl, THF was used to wash out residual DCM before drying. When necessary, N amounts were corrected for the resin amide by subtracting a mole equivalent of linker as measured by the fraction of S.

Materials. Aminomethyl resin, lot AMS 028, 1.76 mmol/g, sieved to 146−200 μm, was purchased from Polymer Labs. *N*-Butyl-*N*-methyl-bromoacetamide was synthesized from the amine and bromoacetyl bromide. *N*-Acetyl-*N*-butylcystamine was prepared by bis-acetylation and hydrolysis of the thioester, and 25% dimethylamine in THF was prepared at 0 °C from anhydrous dimethylamine. All other reagents and precursors were commercially available and used as received.

4-(2-Hydroxyethylthio)benzonitrile 1. To a solution of 16.9 g (0.14 mol) of 4-fluorobenzonitrile and 16.35 g (0.21

mol) of 2-mercaptoethanol in 200 mL of acetonitrile was added 28.9 g (0.21 mol) of potassium carbonate, and the suspension was stirred for 18 h. The solid was filtered off through Celite, and the filter cake was washed with acetonitrile (2 × 50 mL). The filtrate was evaporated, then resuspended in 250 mL of ethyl acetate, and washed with 5% sodium carbonate (3 × 100 mL) and brine (3 × 100 mL), dried over sodium sulfate, and evaporated to a cream colored solid containing up to 5% of the primary amide hydrolysis product from the nitrile. Yield: 25 g (quantitative), of sufficient purity for the next step. ^{1}H NMR 300 MHz ($CDCl_3$) δ 7.54 (dt, 2H, ArH, J = 8.5, 2 Hz), 7.38 (dt, 2H, ArH, J = 8.5, 2 Hz), 3.86 (t, 2H, OCH_2, J = 6 Hz), 3.21 (t, 2H, SCH_2, J = 6 Hz). DCIMS *m*/*z* (rel intensity) 197 (100, M + NH_4), 179 (10, M^+). Anal. Calcd for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.81; O, 8.93; S, 17.89. Found: C, 59.3; H, 5.02; N, 7.26; S, 18.21.

4-(2-Hydroxyethylthio)benzoic Acid 2 by Acidic Hydrolysis. A suspension of 9.15 g (51 mmol) of **1** in 180 mL of 20% sulfuric acid in 1:1 dioxane:water was heated at reflux for 36 h. Dioxane was added as necessary to make a light suspension. The suspension was cooled to room temperature and extracted with ethyl acetate (2 × 200 mL). The organic layer was evaporated, and the residue was resuspended in 100 mL of 20% sodium hydroxide and stirred for 1 h. The primary amide was removed by filtration (2×), and the clear solution was acidified to pH 2 with dilute sulfuric acid. The precipitate was collected and washed with water to give **2** as a white solid. Yield: 6.55 g (33 mmol, 65%). ^{1}H NMR 300 MHz (DMSO-d_6) δ 12.85 (bs, 1H, COOH), 7.84 (dt, 2H, ArH, J = 8.5, 2 Hz), 7.39 (dt, 2H, ArH, J = 8.5, 2 Hz), 3.61 (t, 2H, OCH_2, J = 6 Hz), 3.13 (t, 2H, SCH_2, J = 6 Hz). DCIMS *m*/*z* (rel intensity) 216 (100, M + NH_4), 198 (52). Anal. Calcd for $C_9H_{10}O_3S$: C, 54.53; H, 5.08; S, 16.18; Found: C, 54.60; H, 4.84; S, 16.22.

Basic Hydrolysis of 1. Potassium hydroxide (343 mg, 6 mmol) was dissolved in 1.7 mL of 5% 2-methoxyethanol in water, and 183 mg (1 mmol) of **1** was added. The reaction was heated at 100 °C for 48 h, cooled to room temperature, acidified to pH 4 with sulfuric acid, and partitioned between the aqueous layer and ethyl acetate. The organic layer was washed with 1 N hydrochloric acid and saturated brine (1 × 50 mL), dried, and evaporated to a white solid. Yield: 131 mg of **2** (0.66 mmol, 68%). NMR, MS equivalent to above. Anal. Calcd for $C_9H_{10}O_3S$: C, 54.53; H, 5.08; S, 16.18; Found: C, 54.25; H, 5.05; N, <0.02; S, 16.10.

4-(2-Acetamidoethylthio)benzonitrile 3. To a solution of 11.37 g (94 mmol) of 4-fluorobenzonitrile and 10 mL (94 mmol) of *N*-acetylcystamine in 100 mL of acetonitrile was added 15 g (109 mmol) potassium carbonate, and the suspension was stirred for 18 h. The reaction mixture was diluted with 250 mL of water and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (1 × 100 mL), dried over sodium sulfate, and evaporated to a cream colored solid of sufficient purity to use directly in the next step. Yield: 16.3 g (79%). ^{1}H NMR 300 MHz (DMSO-d_6) δ 8.12 (bs, 1H, NH), 7.74 (dt, 2H, ArH, J = 8.5, 2 Hz), 7.51 (dt, 2H, ArH, J = 8.5, 2 Hz), 3.27 (dt, 2H, NCH_2, J = 7, 6 Hz), 3.12 (dd, 2H, SCH_2, J = 8, 6 Hz), 1.8 (s, 3H, $COCH_3$). Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72; S, 14.56. DCIMS *m*/*z* (rel intensity) 238 (100, M + NH_4), 221 (10, M + H). Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72; S, 14.56. Found: C, 59.40; H, 5.60; N, 12.59; S, 14.63.

4-(2-(*N*-Butylacetamido)ethylthio)benzonitrile 4. As above, 11.12 g (63.4 mmol) of *N*-acetyl-*N*-butylcystamine gave 15.1 g of **4** (54.5 mmol, 86%) as an off-white solid. ^{1}H NMR 300 MHz ($CDCl_3$, mixture of rotamers) δ 7.55 (dt, 2H, ArH, J = 8.5, 2 Hz), 7.48 (dt, 2H, ArH, J = 8.5, 2 Hz), 3.52 (m, 2H, NCH_2CH_2S), 3.28 (m, 2H, SCH_2), 3.18 (m, 2H, $NHCH_2CH_2CH_2$), 2.08 (s, 3H, $COCH_3$), 1.55 (m, 2H, $CH_2CH_2CH_2$), 1.34 (m, 2H, CH_2CH_3), 0.97 (t, 3H, CH_2CH_3, rotamer a, J = 7 Hz), 0.94 (t, 3H, CH_2CH_3, rotamer b, J = 7 Hz). DCIMS *m*/*z* (rel intensity) 294 (100, M + NH_4), 277 (56, M + H).

4-(2-Aminoethylthio)benzoic Acid 5. A solution of 16.3 g (74 mmol) of **3** in 250 mL of 6 N hydrochloric acid was heated at reflux for 18 h. The suspension was cooled slowly to 4 °C, and the precipitate was collected and washed with water to give the white hydrochloride salt of **5**. Yield: 15.56 g (66.5 mmol, 90%). ^{1}H NMR 300 MHz (DMSO-d_6) δ 12.9 (v bs, 1H, COOH), 8.1 (bs, 2H, NH_2), 7.89 (dt, 2H, ArH, J = 8.5, 2 Hz), 7.48 (dt, 2H, ArH, J = 8.5, 2 Hz), 3.31 (t, 2H, NCH_2, J = 7 Hz), 3.01 (t, 2H, SCH_2, J = 7 Hz). ESIMS *m*/*z* (rel intensity) + ion 198 (100, M + H); − ion 196 (100, M − H). Anal. Calcd for $C_9H_{11}NO_2S$·HCl: C, 46.25; H, 5.18; Cl, 15.17; N, 5.99; S, 13.72. Found: C, 46.22; H, 5.21; N, 5.94; S, 13.61.

4-(2-(*N*-Butylamino)ethylthio)benzoic Acid 6. Prepared as above from 15.08 g (52 mmol) of **4**. Yield: 8.5 g (23 mmol, 44%) of **6** as a white solid hydrochloride salt. ^{1}H NMR 300 MHz (DMSO-d_6) δ 12.99 (bs, 1H, COOH), 9.1 (bs, 2H, NH_2+), 7.88 (dt, 2H, ArH, J = 8.5, 2 Hz), 7.50 (dt, 2H, ArH, J = 8.5, 2 Hz), 3.41 (t, 2H, NCH_2CH_2S, J = 7 Hz), 3.10 (t, 2H, SCH_2, J = 7 Hz), 2.91 (t, 2H, $NCH_2CH_2CH_2$, J = 7 Hz), 1.59 (q, 2H, $NCH_2CH_2CH_2$, J = 7 Hz), 1.32 (sextet, 2H, CH_2CH_3, J = 7 Hz), 0.89 (t, 3H, CH_3, J = 7 Hz). DCIMS *m*/*z* (rel intensity) 254 (24, M + H). Anal. Calcd for $C_{13}H_{19}NO_2S$·HCl: C, 53.87; H, 6.96; Cl, 12.23; N, 4.83; S, 11.06. Found: C, 53.54; H, 6.97; N, 4.75; Cl, 12.23; S, 11.17.

Fmoc-4-(2-Aminoethylthio)benzoic Acid 7. A 14.0 g (60 mmol) sample of **5** was suspended in 200 mL of water containing 8.36 mL of triethylamine (60 mmol) and 3.6 g of sodium hydroxide (90 mmol). A solution of Fmoc NHS carbonate (20.2 g, 60 mmol) in 200 mL of acetonitrile was added in one portion with stirring, and the pH was adjusted to 9 with triethylamine as needed until the pH was constant for 15 min. The reaction was stirred for 2 h and filtered, the acetonitrile was removed in vacuo, and the aqueous layer poured into 200 mL of 1.5 N hydrochloric acid with stirring. The precipitate was collected and washed with water and then dried to give a white solid. Yield: 24.99 g (50.9 mmol, 98%). ^{1}H NMR 300 MHz (DMSO-d_6) δ 12.89 (bs, 1H, COOH), 7.89 (d, 2H, ArH, J = 7.5 Hz), 7.85 (t, 2H, ArH, J = 8.5 Hz), 7.69 (d, 2H, ArH, J = 7.5 Hz), 7.57 (t, 1H, NH, J = 5.5 Hz), 7.42 (d, 2H, ArH, J = 8.5 Hz), 7.41 (t, 2H, ArH, J = 7 Hz), 7.33 (t, 2H, ArH, J = 7.5 Hz), 4.34 (d,

2H, OCH_2, $J = 6.5$ Hz), 4.22 (t, 1H, CH_2CH, $J = 6.5$ Hz), 3.24 (t, 2H, NCH_2, $J = 6$ Hz), 3.11 (t, 2H, SCH_2, $J = 6$ Hz). DCIMS *m/z* (rel intensity) 437 (100, M + NH_4), 420 (35, M + H) Anal. Calcd for $C_{24}H_{21}NO_4S$: C, 68.72; H, 5.05; N, 3.34; S, 7.64. Found: C, 68.52; H, 4.98; N, 3.23; S, 7.47.

Fmoc-4-(2-(*N*-Butylamino)ethylthio)benzoic Acid 8. Prepared as above from 7.92 g of **6** (22.4 mmol). Yield: 10.68 g (22.4 mmol, quant). ^{1}H NMR 300 MHz (DMSO-d_6, rotameric mixture) δ 12.87 (bs, 1H, COOH), 7.87 (d, 2H, ArH, $J = 7.5$ Hz), 7.82 (t, 2H, ArH, $J = 8.5$ Hz), 7.69 (d, 2H, ArH, $J = 7.5$ Hz), 7.57 (t, 1H, NH, $J = 5.5$ Hz), 7.41 (d, 2H, ArH, $J = 8.5$ Hz), 7.41 (t, 2H, ArH, $J = 7$ Hz), 7.33 (t, 2H, ArH, $J = 7.5$ Hz), 4.54 (d, 2H, OCH_2, rotamer a, $J = 4.5$ Hz),), 4.47 (d, 2H, OCH_2, rotamer b, $J = 4.5$ Hz), 4.25 (m, 1H, CH_2CH), 3.28 (m, 2H, NCH_2CH_2S, rotamer a), 3.09 (m, 2H, SCH_2 + NCH_2CH_2S, rotamer b), 2.81 (m, 2H, $NHCH_2CH_2CH_2$), 1.33 (m, 2H, $NCH_2CH_2CH_2$, rotamer a), 1.13 (q, 2H, CH_2CH_3, rotamer a, $J = 7$ Hz), 1.02 (m, 2H, $NCH_2CH_2CH_2$, rotamer b), 0.90 (q, 2H, CH_2CH_3, rotamer b, $J = 7$ Hz), 0.81 (t, 3H, CH_3, rotamer a, $J = 7$ Hz), 0.70 (t, 3H, CH_3, rotamer b, $J = 7$ Hz). DCIMS *m/z* (rel intensity) 493 (15, M + NH_4), 476 (1, M + H), 179 (100). Anal. Calcd for $C_{28}H_{29}NO_4S$: C, 70.71; H, 6.15; N, 2.87; S, 6.74. Found: C, 70.64; H, 6.05; N, 2.87; S, 6.78.

4-(2-Chloroethylthio)benzoic Acid 9. Hydrochloric acid (6 N) hydrolysis of 0.5 g (2.8 mmol) **1** as above gave 0.38 g (1.75 mmol, 64%) of **9**.^{1}H NMR 300 MHz (DMSO-d_6) δ 12.89 (s, 1H, COOH), 7.87 (dt, 2H, ArH, $J = 8.5$, 2 Hz), 7.45 (dt, 2H, ArH, $J = 8.5$, 2 Hz), 3.80 (t, 2H, $ClCH_2$, $J = 6$ Hz), 3.46 (t, 2H, SCH_2, $J = 6$ Hz). APCIMS *m/z* (rel intensity) + ion 395 (100, 2M − 2HCl + $2NH_4$), 218 (24, M + 2 + H), 216 (70, M + H), 198 (48, M − HCl + NH_4); − ion 217 (34, M + 2 − H), 215 (100, M − H). Anal. Calcd for $C_9H_9ClO_2S$: C, 49.89; H, 4.19; Cl, 16.36; S, 14.80. Found: C, 50.14; H, 4.09; Cl, 16.07; S, 14.91.

4-(2,2-Diethoxyethylthio)benzoic Acid 10. A 4.87 g (32 mmol) sample of 4-mercaptobenzoic acid was dissolved in 100 mL of methanol, 5.7 mL (38 mmol) of bromoacetaldehyde diethyl acetal was added, followed by 19.8 mL (133 mmol) of DBU. The reaction was heated at reflux for 18 h and then evaporated. The residue was taken up in 200 mL of ethyl acetate, washed with 1 N HCl (2 × 100 mL) and saturated brine (3 × 100 mL), dried over sodium sulfate, and evaporated. The crude product was dissolved in 1:1 hexane:ethyl acetate, run through a silica plug, evaporated, and triturated with hexane (3 × 100 mL). Yield: 6.5 g (29 mmol, 90%). ^{1}H NMR 300 MHz (DMSO-d_6) δ 12.83 (bs, 1H, COOH), 7.84 (dt, 2H, ArH, $J = 8.5$, 2 Hz), 7.42 (dt, 2H, ArH, $J = 8.5$, 2 Hz), 4.66 (t, 1H, $CH(O)_2$, $J = 5.5$ Hz), 3.63 (q, 1H, OCH_2, $J = 7$ Hz), 3.60 (q, 1H, OCH_2, $J = 7$ Hz), 3.51 (q, 1H, OCH_2, $J = 7$ Hz), 3.48 (q, 1H, OCH_2, $J = 7$ Hz), 3.23 (d, 2H, SCH_2, $J = 5.5$ Hz), 1.10 (t, 6H, CH_3, $J = 7$ Hz). DCIMS *m/z* (rel intensity) 288 (70, M + NH_4), 213 (94), 196 (100). Anal. Calcd for $C_{13}H_{18}O_4S$: C, 57.76; H, 6.71; S, 11.86. Found: C, 57.79; H, 6.75; S, 11.80.

4-(2-Oxoethylthio)benzoic Acid 11. To 250 mg (0.92 mmol) of compound **10** was added 50 mL of 1 N HCl and 2 mL of 2-methoxyethanol. The reaction was heated to 120 °C for 2 h, then a small quantity of activated charcoal was added, and the reaction was heated at 120 °C for 15 min. The carbon was filtered while hot, the filtrate was cooled to room temperature, and the white precipitate was collected and dried. Yield: 140 mg (70%) as the hydrate. ^{1}H NMR 300 MHz (DMSO-d_6) δ 12.85 (bs, 1H, COOH), 7.82 (dt, 2H, ArH, $J = 8.5$, 2 Hz), 7.38 (dt, 2H, ArH, $J = 8.5$, 2 Hz), 6.15 (d, 2H, OH, $J = 6$ Hz), 4.96 (t, 1H, $CH(OH)_2$, $J = 6$ Hz), 3.08 (d, 2H, SCH_2, $J = 6$ Hz). DCIMS *m/z* (rel intensity) 214 (100, M + NH_4). Anal. Calcd for $C_9H_{10}O_4S$: C, 50.46; H, 4.70; S, 14.97. Found: C, 50.67; H, 4.72; S, 15.54.

Linker Functionalized Resin 15a. A suspension of linker **2** (2.31 g, 11.6 mmol) and HOBt (1.36 g, 10 mmol) in 20 mL of 20% NMP was cooled to 4 °C, and 1.6 mL (10.2 mmol) of diisopropylcarbodiimide was added. The mixture was allowed to warm to room temperature over 15 min and then added to a 2.54 g (5.1 mmol) aminomethyl resin preswollen in dichloromethane (DCM). DCM was added to liquefy the suspension (~40 mL), and the reaction was rocked at room temperature for 18 h, drained, then washed with dichloromethane (2 × 50 mL), dimethylformamide (3 × 50 mL), dichloromethane (3 × 50 mL), and THF (3 × 50 mL), and dried under vacuum to give resin **15a**. Yield: 3.43 g. Loading: 1.25 mmol/g by S microanalysis. Analysis Found C, 81.31; H, 7.06; N, 1.93; S, 4.04.

Flurbiprofen Loading of 15a. A solution of flurbiprofen (1.05 g, 4.3 mmol) and 4-(dimethylamino)pyridine (55 mg, 0.97 mmol) in dichloromethane was added to a 1.04 g (1.3 mmol OH) sample of resin **15a**. The resin was cooled to 4 °C, and 675 μL (4.3 mmol) of diisopropylcarbodiimide was added. The reaction was mixed by rocking for 18 h, and then the resin was drained, washed with dichloromethane (2 × 40 mL), dimethylformamide (3 × 40 mL), dichloromethane (3 × 40 mL), THF (3 × 4 mL), and ether (2 × 40 mL), and dried to give resin **16a**. Loading: 0.93 mmol/g (88% of available OH) by fluorine analysis. ^{1}H NMR 300 MHz ($CDCl_3$, gel phase, MAS) δ 3.7 (2H, OCH_2), 3.1 (2H, SCH_2). Analysis Found: C, 80.70; H, 6.34; N, 1.48; F, 1.77; S, 3.41.

Curtius Rearrangement and Resin Capture. Resin **15a** (100 mg, 0.13 mmol) was swelled in 5 mL of toluene, and 153 mg (0.63 mmol) of flurbiprofen was added, followed by 0.35 mL (2.5 mmol) of triethylamine and 0.16 mL (0.74 mmol) of diphenylphosphoryl azide. The reaction was heated to 100 °C for 18 h and cooled to room temperature. The urea was separated by flotation with methanol, and the resin was washed with toluene (1 × 4 mL), dimethylformamide (3 × 4 mL), methanol (3 × 4 mL), dichloromethane (3 × 4 mL), methanol (3 × 4 mL), and ethyl ether (2 × 4 mL) and then dried to give resin **18a**. Loading: 0.87 mmol/g (94% of available OH) by fluorine analysis. ^{1}H NMR 300 MHz ($CDCl_3$, gel phase, MAS) δ 4.8 (1H, NCH), 4.2 (2H, OCH_2), 3.1 (2H, SCH_2), 1.4 (2H, CH_3). ^{19}F NMR 470 MHz ($CDCl_3$, gel phase, MAS) δ −117.95. Analysis Found: C, 79.50; H, 6.90; N, 2.51; F, 1.66.

Resin 20a by Acetal Deprotection. A 200 mg (0.22 mmol) sample of resin **19a** was suspended in 2 mL of dioxane, 2 mL of 2 N hydrochloric acid was added, and the reaction was heated at 80 °C for 3 h with mixing on the

Quest. The resin was cooled to room temperature, and washed with NMP (3 × 4 mL), DCM (3 × 4 mL), and THF (3 × 4 mL). Yield: 189 mg.

Resin 21a by Reductive Amination. A 200 mg (0.22 mmol) sample of resin **20a** was suspended in 4 mL of 5% acetic acid in DCM. Boc piperazine (245 mg, 1.32 mmol) was added, followed by sodium triacetoxyborohydride (252 mg, 1.2 mmol), and the reaction was mixed at room temperature on the Quest. After 18 h, the reaction was drained, and the resin was washed with DCM (2 × 4 mL), NMP (3 × 4 mL), 5% triethylamine in NMP (2 × 4 mL), NMP (2 × 4 mL), DCM (3 × 4 mL), and THF (3 × 4 mL) and dried. Yield: 219 mg. Loading: 0.75 mmol/g by N analysis. NMR 300 MHz ($CDCl_3$, gel phase, MAS) δ 3.45 (4H, CH_2NCO_2), 3.09 (2H, SCH_2), 2.66 (2H, SCH_2CH_2N), 2.43 (4H, $SCH_2CH_2NCH_2$), 1.47 (9H, t-Bu). Analysis Found: C, 77.95; H, 7.55; N, 3.48; S, 3.16.

Resin 22a by Flurbiprofen Coupling. Compound **21a** (200 mg, 0.15 mmol) was treated with 1:1 TFA:DCM (2 × 4 mL, 15 min incubations) and washed with DCM (2 × 4 mL), 5% DIEA in DCM (2 × 4 mL), and DCM (3 × 4 mL). Simultaneously, to a solution of 123 mg (0.5 mmol) of flurbiprofen and 67 mg of HOBt (0.5 mmol) in 4 mL of DCM at 0 °C was added 80 μL (0.5 mmol) diisopropylcarbodiimide, and the reaction was allowed to warm to room temperature over 15 min. The solution was added to the resin, mixed on the Quest for 18 h, then washed with NMP (3 × 4 mL), DCM (3 × 4 mL), and THF (3 × 4 mL), and dried. Yield: 286 mg. A portion was washed with 2 N hydrochloric acid in 1:1 THF:water (2 × 2 mL), NMP (3 × 2 mL), DCM (3 × 2 mL), and THF (3 × 2 mL) for analysis. Loading: 0.4 mmol/g (45% of the available amine) by fluorine analysis when corrected for 30 mol % TFA (NMR). Analysis Found: C, 75.93; H, 7.20; N, 2.87; Cl, 2.26; F; 1.54, S, 2.75.

Quaternary Ammonium Salt 23a. A 75 mg sample of **22a** was suspended in 4 mL of dimethylacetamide, and 125 μL (2 mmol) of methyl iodide was added. The reaction was mixed on the Quest for 18 h, then washed with NMP (3 × 4 mL), 2 N hydrochloric acid in 1:1 THF:water (2 × 4 mL), NMP (3 × 4 mL), DCM (3 × 4 mL), and THF (3 × 4 mL), and dried. The resulting resin contained 30 mol % TFA by NMR and <15 μmol/g flurbiprofen. Yield: 85 mg. Analysis Found: C, 75.33; H, 7.07; N, 2.96; Cl, 2.38; F, 1.51; S, 2.69.

Sulfone Formation by Peracid. A 0.1 g sample of resin **16a** was suspended in a minimum of 2 mL of a 17 mg/mL MCPBA solution in dichloromethane and was mixed for 1 h at room temperature. The resin was washed with dichloromethane (2 × 4 mL), dimethylacetamide (3 × 4 mL), dichloromethane (3 × 4 mL), and THF (3 × 4 mL) and then dried under vacuum to give resin **16c**: ^{1}H NMR 300 MHz ($CDCl_3$, gel phase, MAS) δ 3.6 (2H, OCH_2), 3.4 (2H, SO_2CH_2). All other peracid oxidations followed this general procedure, with the exception that ammonium salt resins were washed further with 2 N hydrochloric acid in THF (3 × 4 mL), then THF (3 × 4 mL) to remove 3-chlorobenzoic acid thoroughly.

Sulfone Formation by Oxone. A 32 mg sample resin **16a** was suspended in 2 mL of dichloroethane or benzotrifluoromethane, 0.5 mL DMF, and 170 mg (0.2 mmol) tetrabutylammonium oxone and mixed for 8 h at 40 °C. The resin was cooled to room temperature and washed with dimethylformamide (3 × 5 mL), dichloromethane (3 × 5 mL), and THF (3 × 4 mL) and then dried under vacuum to give resin **16c**.

Sulfoxide Formation. A 0.1 g sample of resin **16a** was suspended in 4 mL of dichloromethane, and 10 mg (43 μmol) of camphorsulfonic acid was added followed by 160 μL of *tert*-butylhydroperoxide in nonane (0.8 mmol). The reaction was mixed for 3 h at room temperature, and the resin was collected and washed with dichloromethane (3 × 4 mL) and THF (3 × 4 mL), and dried, yielding resin **16b**, 3:1 sulfoxide: sulfide. ^{1}H NMR 300 MHz ($CD2Cl_2$, gel phase, MAS) δ 3.7 (2H, OCH_2), 3.2 (2H, $S(O)CH_2$), 3.0 (2H, SCH_2).

Solution Phase Cleavage Quantitation. Stock solutions (25 mM) of flurbiprofen or a derivative and 4-biphenylcarboxamide, the internal standard, were prepared in THF or DMSO. The internal standard was diluted to 6.25 mM with THF or DMSO. To a 3−5 mg sample of an activated resin was added 10 μL/mg of the internal standard stock solution, then 1 mL of the cleavage solution. After 1−3 h, the resin was filtered off and the solution analyzed by HPLC. Response factors were determined for each experiment using a three-point calibration curve with flurbiprofen solution concentrations of 1000 nmol/mg, 250 nmol/mg, and 25 nmol/mg. The product peak area ratio to the internal standard was converted to nmol/mg from the fitted calibration curve, then divided by the compound loading to determine the cleavage yield. Calibration curves were strictly linear over the analysis range.

Gas Phase Cleavage. A 1−3 mg sample of an activated resin was placed in an HPLC vial and exposed to dimethylamine vapor (10 μL of 25% anhydrous dimethylamine in THF per milliliter of enclosing volume) for the desired time. The resin was dried in vacuo, 20 μL/mg of the internal standard stock solution was added, and the cleavage products were diluted with 1 mL of THF. The solution analyzed by HPLC as above.

HPLC Solution Cleavage Kinetics. To a 1−2 mg sample of sulfone **14c** was added 100 μL of the base solvent (THF or DMSO). A 900 μL aliquot of the appropriate concentration cleavage solution was then added and immediately injected into the HPLC, and reinjected from the reaction vial approximately every 14 min. The peak areas were fitted to standard first order decay or production curves, and the half-life determined from the best fit to the product concentration.

HPLC Solid Phase Cleavage Kinetics. To a 1−3 mg sample of an activated resin was added 20 μL/mg of the internal standard solution in the appropriate solvent, then enough solvent to make 100 μL. A 900 μL aliquot of the appropriate concentration cleavage solution was then added and immediately injected into the HPLC, and reinjected from the reaction vial approximately every 14 min. The peak areas were fitted to standard first order production curves, and the half-life was determined from the best fit to the product concentration. For faster cleavage rates, the 14 min point was abnormally high, presumably because the cleavage rate was faster than the diffusion rate in solution, and was not

included in the analysis. The internal standard was used to quantitate the total cleavage amount as above.

Library Synthesis. 4-(2-Mesyloxyethylthio)benzonitrile 24. A 25.1 g (140 mmol) sample of **1** was dissolved in 100 mL of THF and 100 mL of pyridine, and 16.25 mL (210 mmol) of methanesulfonyl chloride was added. The reaction was stirred at room temperature for 18 h, then diluted with 250 mL of ethyl acetate and 250 mL water, and acidified to pH 3 with concentrated hydrochloric acid. The organic layer was separated and washed with saturated brine (3 × 100 mL), dried, and evaporated to give a white powder of sufficient purity to use in the next step. Yield: 36.0 g (140 mmol, quant). ^{1}H NMR 300 MHz ($CDCl_3$) δ 7.59 (dt, 2H, ArH, J = 8.5, 2 Hz), 7.40 (dt, 2H, ArH, J = 8.5, 2 Hz), 4.37 (t, 2H, OCH_2, J = 7 Hz), 3.35 (t, 2H, SCH_2, J = 7 Hz), 3.03 (s, 3H, CH_3). DCIMS *m*/*z* (relative intensity) 275 (90, M−H), 215 (100). Anal. Calcd for $C_{10}H_{11}NO_3S_2$: C, 46.67; H, 4.31; N, 5.44; S, 24.92. Found C, 47.06; H, 4.56; N, 5.53; S, 23.71.

4-(2-(4-Dioxylylpiperidinyl)ethylthio)benzonitrile 25. A solution of 15.89 g (61.7 mmol) of **24** and 19.45 g (135.8 mmol, 2.2 equiv) of piperidine-4-dioxolane in 220 mL of acetonitrile was heated to 90 °C for 18 h, then cooled, and evaporated. The residue was taken up in water (200 mL) and ethyl acetate (200 mL). The layers were separated, and the organic layer was washed with brine (3 × 75 mL), dried over sodium sulfate, and evaporated to a yellow oil of sufficient purity to be used in the next step. Yield: 18.7 g (61.7 mmol, quant). ^{1}H NMR 300 MHz ($CDCl_3$) δ 7.53 (dt, 2H, ArH, J = 8.5, 2 Hz), 7.33 (dt, 2H, ArH, J = 8.5, 2 Hz), 3.96 (s, 4H, OCH_2), 3.13 (dd, 2H, NCH_2CH_2S, J = 8, 6 Hz), 2.71 (dd, 2H, SCH_2, J = 8, 6 Hz), 2.61 (t, 4H, NCH_2-CH_2CO_2, J = 5.5 Hz), 1.77 (t, 4H, CH_2CO_2, J = 5.5 Hz). DCIMS *m*/*z* (rel intensity) 305 (100, M + H). Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20; S, 10.53. Found: C, 62.58; H, 6.59; N, 8.95; S, 11.23.

4-(2-(4-Ketopiperidinyl)ethylthio)benzoic Acid 26. Compound **25** (18.7 g, 61.7 mmol) was suspended in 360 mL of 1 N hydrochloric acid and heated at reflux for 1 h. The reaction was cooled to 4 °C and made basic with saturated sodium carbonate. The ppt was collected, and the water layer was extracted with ethyl acetate (2 × 250 mL). The organic layers were combined, washed with water (2 × 250 mL), and evaporated. Both fractions were the keto nitrile. ^{1}H NMR 300 MHz (DMSO-d_6) δ 7.72 (dt, 2H, ArH, J = 8.5, 2 Hz), 7.45 (dt, 2H, ArH, J = 8.5, 2 Hz), 3.19 (t, 2H, NCH_2CH_2S, J = 7 Hz), 2.57 (t, 2H, SCH_2, J = 8, 6 Hz), 2.41 (m, 4H, $NCH_2CH_2CO_2$), 1.54 (t, 4H, CH_2CO_2, J = 6 Hz). The combined solids were heated at reflux in 200 mL of 6 N hydrochloric acid. The reaction was cooled to room temperature, the aqueous volume was reduced to 100 mL, and a cream colored solid was collected. The compound was purified by recrystallization from ethanol, followed by removal of the ethyl acetal with 1 N hydrochloric acid as above to give the white monohydrate monohydrochloride salt. Yield: 13.15 g (39 mmol, 64%). ^{1}H NMR 300 MHz (DMSO-d_6) δ 12.95 (bs, 1H, COOH), 11.97 (s, 2H, OH), 7.88 (dt, 2H, ArH, J = 8.5, 2 Hz), 7.53 (dt, 2H, ArH, J = 8.5, 2 Hz), 3.78 (m, 2H, $NCHaHbCH_2CO$), 3.59 (dd, 2H, NCH_2CH_2S, J = 9, 7 Hz), 3.40 (m, 6H, SCH_2, $NCHaHbCH_2$-CO, $NCH_2CHaHbCO$), 2.90 (m, 2H, $NCH_2CHaHbCO$). DCIMS *m*/*z* (rel intensity) 288 (70, M + NH_4).ESIMS *m*/*z* (rel intensity) + ion 280 (100, M + H); − ion 278 (100, M − H). Anal. Calcd for $C_{14}H_{19}NO_4S.HCl$: C, 50.37; H, 6.04; N, 4.20; S, 9.61. Found: C, 50.66; H, 6.08; N, 4.16; S, 9.54.

Library Core Resin 27. A suspension of 8 g (14.1 mmol NH_2) of aminomethyl polystyrene was incubated with the HOBt ester prepared from 9.40 g (28.2 mmol) of **26** as described for resin **15a**. Loading: 1.1 mmol/g by S analysis (95%). Anal. Found: C, 80.87; H, 7.26; N, 3.18; S, 3.54.

Resins 28a−m. Compound **27** (100 mg, 0.11 mmol) and sodium triacetoxyborohydride (187 mg, 0.88 mmol) were weighed into Quest 5 mL reaction vessels. If the amine was a solid, 0.88 mmol was weighed into the vessel. The vessels were placed on the machine, and 4 mL of 5% acetic acid in DCM was added, followed immediately by 0.88 mmol of liquid amine if not weighed earlier. The reactions were mixed with vent port open for 1 h to allow hydrogen escape, and then the vent port was closed and the reactions were mixed for 18 h. The resins were washed with methanol (3 × 4 mL), dimethylformamide (3 × 4 mL), methanol (3 × 4 mL), dichloromethane (3 × 4 mL), and THF (3 × 4 mL) and dried. IR showed ketone at 1710 cm^{-1} remaining, so the procedure was repeated. This time the ketone stretch was nearly undetectable.

Resins 29a,b,d−m. Resins **28** were suspended in 4 mL of dimethylacetamide, and 1.76 mmol of the appropriate acid chloride and 0.92 mL (5.28 mmol) of diisopropylethylamine were added. The resins were mixed for 18 h on the Quest, then drained and washed with dimethylformamide (3 × 4 mL), methanol (3 × 4 mL), dichloromethane (3 × 4 mL), and THF (3 × 4 mL) and dried. The chloranil test was positive, so the acylation was repeated. This time reaction was complete as indicated by a negative chloranil test.

Resin 28c. The resin was suspended in 4 mL of dimethylacetamide, and 384 mg (1.76 mmol) of diboc carbonate was added, followed by 43 mg (0.35 mmol) of DMAP. After 18 h, the resin was washed with the others. As above, the procedure was repeated. The chloranil test was still positive, so the procedure was repeated using DCM as a solvent. This time, the reaction was complete.

Resins 30a−m. Resins **29** were suspended in 4 mL of THF and treated with 1.76 mmol of the alkyl bromide. After an 18 h incubation on the Quest, the resins were washed with THF (2 × 4 mL), dimethylformamide (3 × 4 mL), methanol (3 × 4 mL), dichloromethane (3 × 4 mL), methanol (3 × 4 mL), and diethyl ether (2 × 4 mL) and dried. The alkylation was repeated using DMF as the solvent, washed as before, and the resins were dried thoroughly.

Compounds 32a−m. Resins **30** were activated by the standard procedure described for **16c**. The Boc group of resin **31c** was removed with 50% TFA in DCM (2 × 1 h) followed by washing with DCM (3 × 4 mL), dimethylformamide (3 × 4 mL), DCM (3 × 4 mL), methanol (3 × 4 mL), and diethyl ether (2 × 4 mL). The reactions were then cleaved with 2 mL of 20% dimethylamine as above, the resins were washed once with 1 mL of THF, and the solutions and washings were collected in 4 mL vials in the Quest rack

and evaporated by speedvac to dryness. The compounds were purified by preparative RP HPLC (Waters Nova-Pak HR C18, 6 μm, 60 Å, 25 × 100 mm, 0−95% MeCN/10 mM NH_4OAc over 10 min at 40 mL/min). Compounds were a 1:1 mixture of rotamers, with NMR spectrums that coalesced above 90 °C. Average Yield: 27 μmol (8.5−45 μmol), 24% for six steps (8−41%).

Acknowledgment. The authors thank Dr. Philip Searle for the HPLC purifications, David Whittern and Susan Malvar for MAS NMR, and Dr. Gary Wang for input and suggestions.

Supporting Information Available. Typical cleavage HPLC chromatograms for **13c**, **16c**, **17c**, **18c**, and **23c**. Cleavage kinetics curves for **16c** under the three cleavage conditions. ^{1}H NMR of **32a,b,d−g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC990077N