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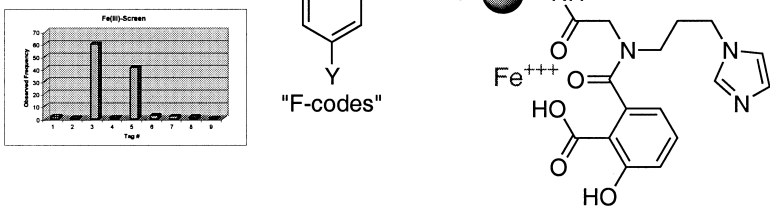

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^{19}F-Encoded Combinatorial Libraries: Discovery of Selective Metal Binding and Catalytic Peptoids

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A ^{19}F NMR method for encoding of combinatorial libraries has been developed. Aryl fluorides whose chemical shifts are modified by aromatic substituents were prepared and attached to resin support beads that were used in the split-pool synthesis of peptoids. The detection of the ^{19}F NMR signal of tags derived from a single "big bead" was demonstrated. The library diversity arises from peptoid amines and the cyclic anhydrides used in their acylation. The resulting 90-compound library was examined for metal ion binding, and novel ligands for iron and copper were discovered. Their binding constants were determined to be in the low micromolar range using conventional methods. The library was also examined for autocatalysis of acylation, and a molecule possessing the catalytic triad of serine proteases was deduced.

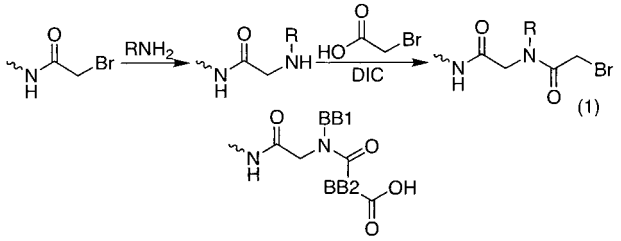
The preparation of "one-bead, one-compound" combinatorial libraries on solid phase by split-pool synthesis has been a powerful method that has seen wide application.[1] In a few instances, such as peptides, it is possible to directly determine the structure of a molecule on a single polymer bead using microanalytical methods such as the Edman degradation.[2] Peptide sequences can also be determined by mass spectrometry using a "sequencing by terminated synthesis" method[3] that is conceptually similar to dideoxynucleotide DNA sequencing. The structures of small molecules have also been determined by mass spectrometry from single, large synthesis beads.[4] For many applications in combinatorial chemistry, however, the most powerful method of structural elucidation from single "hit" beads is based on the reading of a molecular code. Many different types of codes (and corresponding decoding methods) have been developed,[5] among them halogenated alkyl ethers (electron-capture GC),[6] secondary amines (fluorescence HPLC),[7] inert functional groups (near-IR and Raman hyperspectral imaging),[8] isotopes (mass spectrometry),[9] and even molecular shape (eye).[10] Many of these methods require very specialized instrumentation that may not be readily available in all chemistry departments. Methods that utilize conventional instruments that are broadly accessible to all chemists therefore offer an important figure of merit. This work has focused on using ^{19}F NMR for decoding of aryl fluoride molecular tags. NMR encoding has been discussed earlier,[11] and related publications on applications of high-resolution MAS ^{19}F NMR to encoding have appeared.[12,13]

This novel tagging system exploits a tool present in almost every chemistry lab today: NMR. Fluorine has a large chemical shift dispersion (∼1000 ppm overall, ∼200 ppm in organofluorine compounds), so it should be possible to analyze a large number of tags that are unambiguously separated by a significant chemical shift difference. There is also essentially no background of fluorine in the chemical laboratory environment, making ^{19}F NMR a high-sensitivity analytical technique. The molecules we use as tags are aryl fluorides, whose chemical shifts are exquisitely sensitive to aromatic ring substitution. The substituent-induced chemical shifts for fluorobenzene bearing various groups are summarized in Table 1.[14] These shifts are readily organized into a group of 16 tags that have chemical shift ranges from +55 to −25 ppm relative to fluorobenzene, in ∼5 ppm increments. The aryl fluorides are also chemically very robust and should be tolerant of a wide variety of chemical transformations in solid-phase synthesis.

Table 1

substituent	approx Δδ (ppm)	substituent	approx Δδ (ppm)
o-I	−20	*p*-Me	+5
p-CN	−10	*p*-OR	+10
o-Br	−5	*p*-NR_2	+15
o-Me	+5	*o*-OR	+20

As a model system for the preparation of combinatorial libraries using these fluorinated tags, we chose peptoids.[15] Peptoids, or poly-*N*-alkylglycines, have been widely exploited in combinatorial chemistry and are readily prepared by a submonomer synthesis protocol involving displacement of a bromoacetamide by an amine and acylation with bromoacetic acid (eq 1). We have here applied peptoids to



(1)

the discovery of selective metal binding reagents as well as to the formation of serine protease mimics. The strategy uses a primary amine as a point of diversity in the first stage and an anhydride as a point of diversity in the second stage. With appropriate substitution in the building

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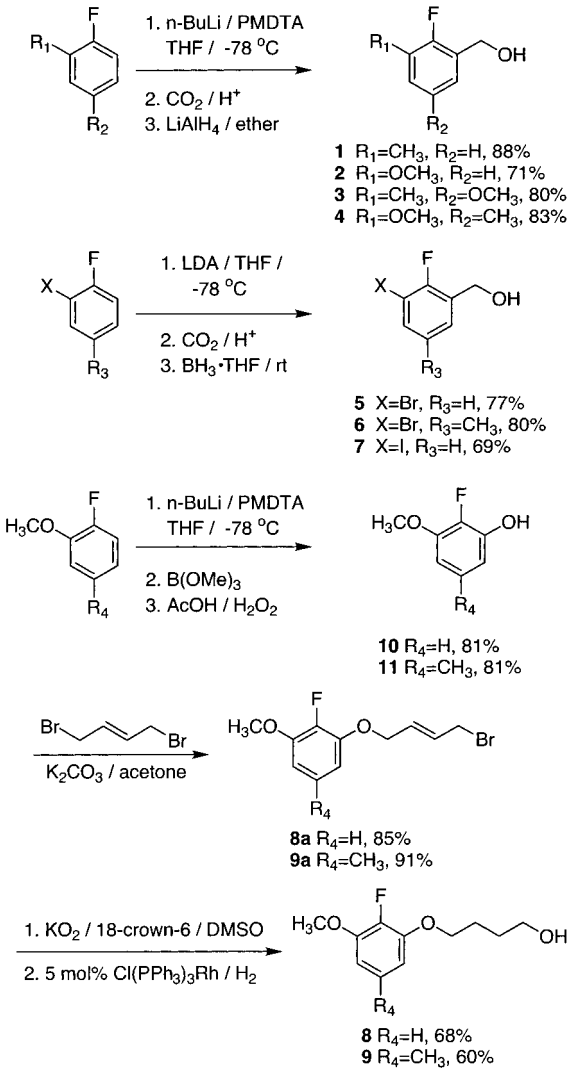
Scheme 1



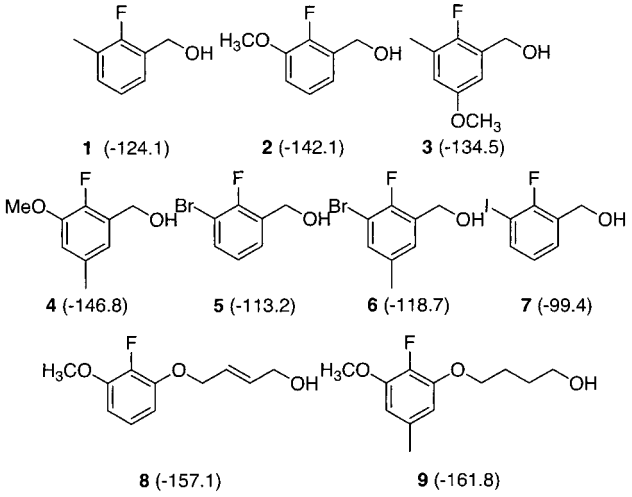
blocks (BB1, BB2), the products of this sequence possess acidic, basic, and ligating groups that would be expected to bind metal ions and in some cases also to possess a nucleophilic hydroxyl group.

Results

The detection sensitivity in ^{19}F NMR that could be expected for fluoroarene tag molecules was first established. When a 140 μL capillary microcell in a standard 5 mm NMR tube is used, 2-fluoro-*m*-xylene can be detected in a 40 min acquisition at 332 MHz with 10:1 *S*/*N* ratio at a concentration of 5 mM in 13 μL $CDCl_3$ (65 nmol). We also have used a 25 μL microcell to drop the detection threshold by 5×, to 12 nmol. This sensitivity easily permits the encoding of first position diversity on 500 mm polystyrene beads ("big beads") bearing ~500 nmol/bead of functional groups.

The structures of the fluorinated tags we have prepared are collected in Chart 1. They are designed with an ortho link to the support that eliminates one large H−F *J* coupling. The other ortho position is also substituted. The para position is available for substitutions that also affect the fluorine chemical shift. The tags are in two molecular classes, hydroxybutyl ethers of phenols and benzyl alcohols.

Chart 1



Tags **1**−**9** were prepared by two main routes, exploiting classical aromatic substitution chemistry by directed metalation ortho to the fluorine group. Metalation/carboxylation[16] of commercially available fluoroarenes followed by $LiAlH_4$ reduction was very successful to gain the benzylic alcohols **1**−**4**. However, when the arene bears a second halogen, the tendency for nucleophilic aromatic substitution as a side reaction in both the metalation and reduction steps required a modified route. Using LDA in the metalation[17] and borane[18] in the reduction enabled **5**−**7** to be obtained as effectively as **1**−**4**. Alcohols **1**−**7** are the molecular codes that are detected in the NMR decoding experiment. To facilitate attachment to the support, they were converted in >90% yields to the corresponding bromides **1a**−**7a** by treatment with CBr_4/Ph_3P at room temperature for 5 h. Two fluoroaryl ether tags were prepared by boronation of the lithiated fluoroarene and oxidation to the phenol,[19] which was alkylated with 1,4-dibromo-2-butene, giving bromides **8a** and **9a** directly. While the ^{19}F chemical shift is unlikely to be very sensitive to such a remote substitution, to ensure no untoward effects, the bromides were hydrolyzed[20] to the alcohols **8** and **9**[21] that are actually read. The chemical shifts of each of the tag alcohols relative to internal fluorobenzene are given below each structure in Chart 1. The ^{19}F NMR chemical shift dispersion of this set of nine tags (determined at the stage of the alcohols, the state in which they are read) is >62 ppm, and the minimum chemical shift separation between tags is 4.7 ppm (Figure 1).

The fluoroarene tags were attached to a linker that permits the alcohol to be released photochemically and bears a primary amine for peptoid synthesis (Scheme 2). Photolinker **12** initially reported by Holmes[22] was subjected to the Yamada[23] modification of the Curtius reaction (without protection of the secondary alcohol). The resulting **13** was O-alkylated by **1a**−**9a** to give tagged protected amines **14**−**22**. The amines were deprotected (25% TFA/CH_2Cl_2/room temp/5 h) in quantitative yield in preparation for solid-phase peptoid synthesis.

To validate the synthetic methods for the intended peptoid synthetic targets, one building block combination was prepared such that it could be cleaved from the support. PS-benzylamine beads (500−550 mm) were derivatized with

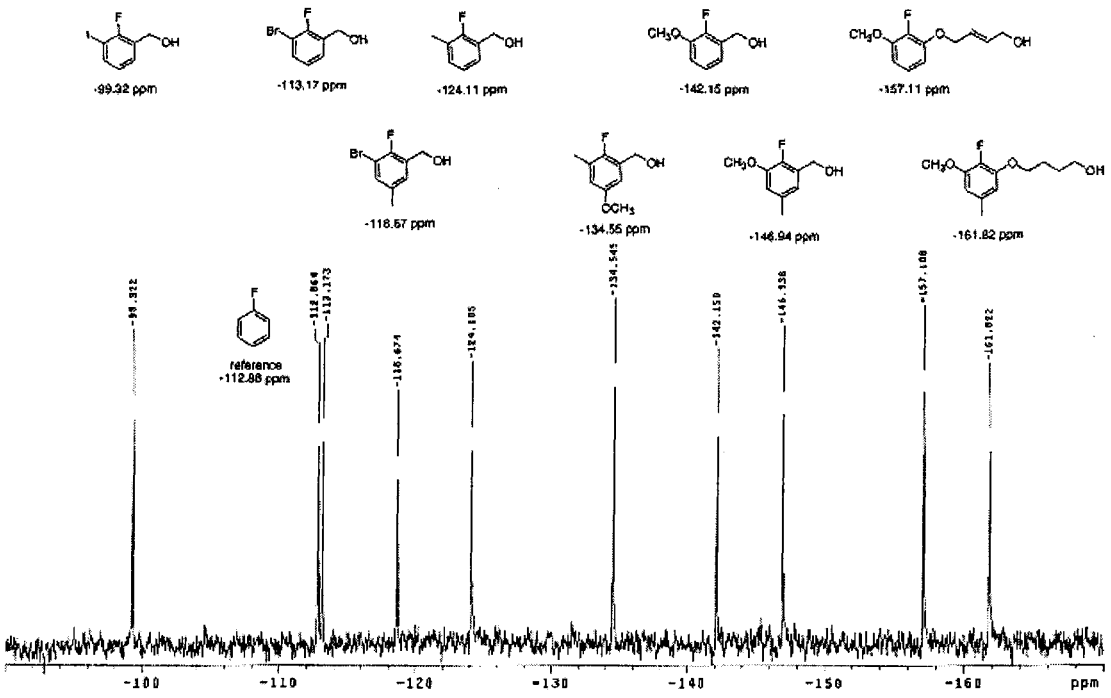
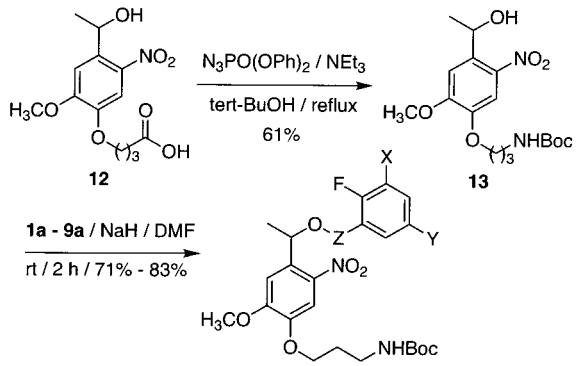


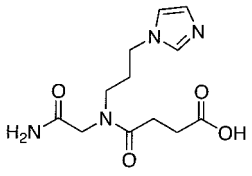
Figure 1. [19]F NMR spectrum of a mixture of the tags **1**−**9**, with an internal standard of fluorobenzene.

Scheme 2



14 X = Me, Y = H, Z = CH_2
15 X = OMe, Y = H, Z = CH_2
16 X = Me, Y = OMe, Z = CH_2
17 X = OMe, Y = Me, Z = CH_2
18 X = Br, Y = H, Z = CH_2
19 X = Br, Y = Me, Z = CH_2
20 X = I, Y = H, Z = CH_2
21 X = OMe, Y = H, Z = $CH_2CH{=}CHCH_2O$
22 X = OMe, Y = Me, Z = $(CH_2)_4O$

the Fmoc-Rink linker, which was deprotected and bromoacetylated. Substitution with 3-imidazol-1-ylpropylamine was followed by acylation with succinic anhydride and cleavage (30% TFA/CH_2Cl_2), giving **23** in quantitative yield and >95% purity by HPLC. Related experiments were



23 (=3{1})

performed with each of the building blocks shown below to qualify them for inclusion in the library.

Chart 2

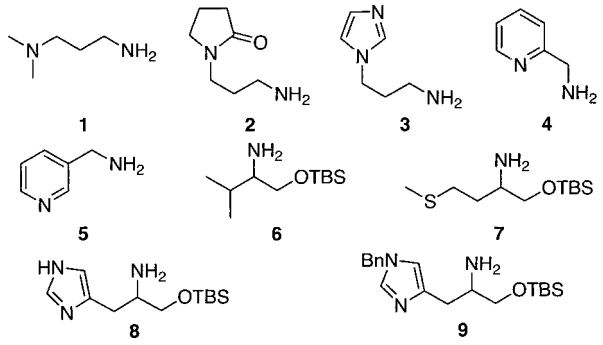
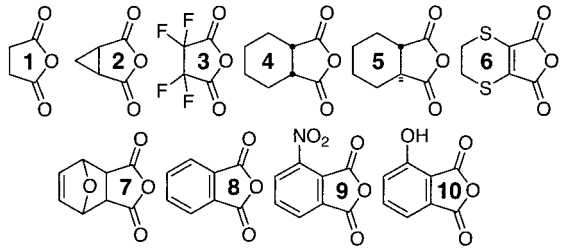


Chart 3



The synthesis of the peptoid library utilized 9 amine (Chart 2) and 10 anhydride (Chart 3) building blocks, giving a 90-compound library overall. The chemset convention for describing these compounds is that the amine appears first (i.e., **4**{*10*} is amine **4** and anhydride **10**). The fluorinated tags were used to encode the amine building blocks, so 9 supports were separately generated using tagged compounds **14a**−**22a** as the first peptoid amine (Scheme 3). After bromoacetylation, each support was coupled with its cognate amine and all supports were pooled. After the split into 10 pools, 10 anhydrides were used for acylation of the amine. Finally, desilylation of each pool was performed with TBAF (for the alcohol-protected amine building blocks).

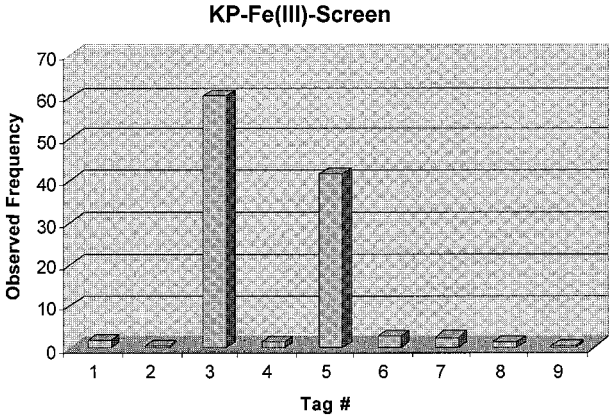
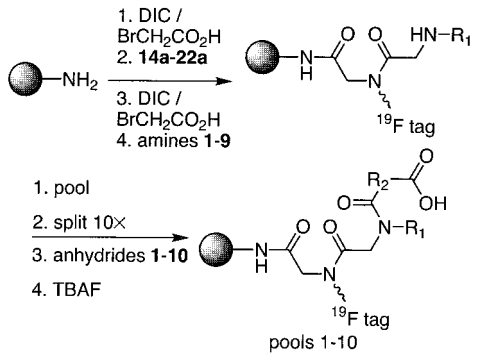


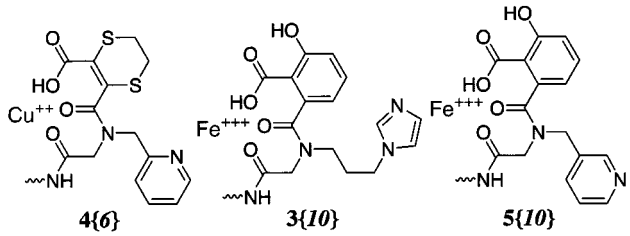
Figure 2. Observed frequency of each tag (total of 9) in pool 10 in the solid-phase binding assay for Fe^{3+}. A high observed frequency indicates peptoids that effectively bound Fe^{3+}. Each tag indicates the individual amine (total of 9) used to make the peptoid. Colored beads in pool 10 were divided into four groups, (A) dark-red beads (only two tags, nos. 3 and 5, were found), (B) red beads, (C) red-orange beads, and (D) orange-yellow beads, depending on color intensity, and tags were released from the beads in each group through photochemical reaction. Observed frequency = (^{19}F peak height of each tag/sum of ^{19}F peak height of all tags in group A) × 100 + (^{19}F peak height of each tag/sum of ^{19}F peak height of all tags in group B) × 10 + (^{19}F peak height of each tag/sum of ^{19}F peak height of all tags in group C) × 1 + (^{19}F peak height of each tag/sum of ^{19}F peak height of all tags in group D) × 0.1.

Scheme 3



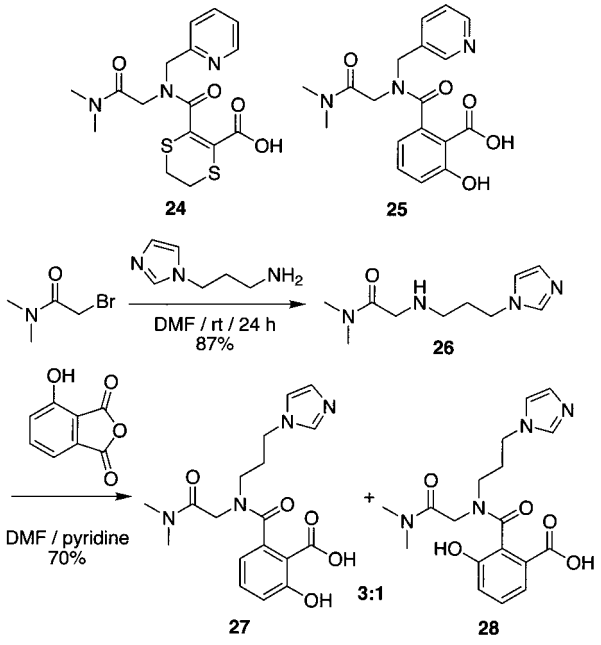
This library was screened for several different types of binding activity. As a control, beads bearing only tags and linker were also stained with each treatment. None was stained, showing that the beads, tags, and linker have no intrinsic binding ability and that the observed binding is derived from the peptoid library. The first screen was for binding to copper. Bead pools were treated with Cu^{2+} in acetonitrile (room temp, 48 h) at concentrations increasing from 0.1 mM. One (pool 6) showed many sky-blue beads at 4 mM, and no other pools were colored at concentrations up to 100 mM. Ten blue beads were selected from this pool and subjected to irradiation in THF at 350 nm for 12 h. The released tags were isolated by filtration/evaporation and submitted to ^{19}F NMR analysis in the presence of an internal standard. A single peak was observed corresponding to a single tag, **4**, encoding peptoid **4**{*6*}, which is the binding unit in structure **24**. This compound was prepared and analyzed in solution as described later.

The 10 pools of the library were also screened for binding to Fe^{3+} and Co^{2+}. For the former, only one (pool 10) was stained, in color gradations from dark-red to orange-yellow.



The colored beads were washed with THF and stratified into four groups based on the intensity of their colors. Each of these groups was individually decoded, and the data are presented in Figure 2. Codes were weighted by powers of 10 determined by the staining intensity in the four strata to compute an observed frequency factor. Two amine codes **3** and **5** are prevalent for iron binders, identifying peptoids **3**{*10*} and **5**{*10*}. These correspond to the binding unit in structures **25**, **27**, and **28**, which were prepared and analyzed in solution as described later. For cobalt binding, many beads in many pools were stained, and a similar stratification of each pool based on color intensity was performed. The data (Figure S1 of Supporting Information) demonstrate low specificity, and this was not further investigated.

Verification of the metal-binding ability of these library compounds was performed by synthesis and analysis of cognate *N*,*N*-dimethylpeptoids. Dimethylbromoacetamide[24] was subjected to substitution with (2-pyridyl)methylamine and acylation with anhydride **6** to prepare **24**. Likewise,



dimethylbromoacetamide was treated with (3-pyridyl)methylamine and hydroxyphthalic anhydride to prepare **25**. While the two carbonyl groups of hydroxyphthalic anhydride are different and its reaction with amines could lead to a mixture of regioisomeric amides, evidently the reactivity of the carbonyl ortho to the hydroxyl group is sufficiently reduced that only one regioisomer is observed in this reaction. This was presumably also the case for the library synthesis on solid phase. Use of 3-imidazol-1-ylpropylamine in this sequence was more problematic, since acylation gave a 3:1

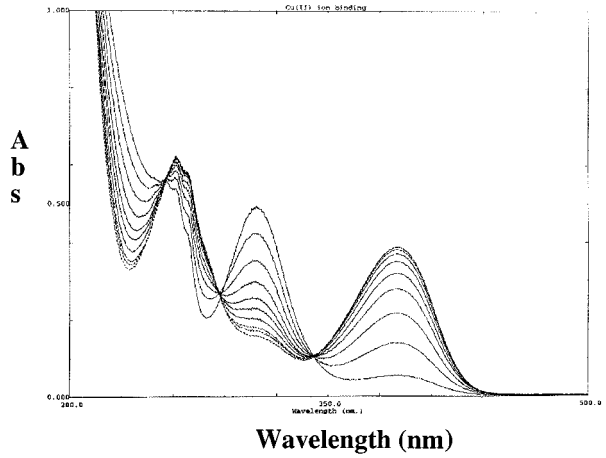


Figure 3. UV spectra in acetonitrile of the titration of peptoid **24** with Cu^{2+}.

mixture of regioisomers **27** and **28**. We presume that a similar regioisomeric mixture was created in pool 10 of the library during solid-phase synthesis. The structures of **25** and **27** were confirmed by comparison with the structures of the single amides obtained by reaction of 4-(triisopropylsilanyloxy)phthalic anhydride with the amines, which gives exclusively one amide because of the combined steric and electronic shielding of the carbonyl group ortho to the TIPS-O group. Independent synthesis of authentic samples of **25** and **27** was necessary because **24**, **25**, **27**, and **28** all exhibit slow conformational exchange that complicates interpretation of spectral data.

Metal binding by these compounds was evaluated by spectrophotometric titration against a reference containing no peptoid dimethylamide.[25] The UV spectrum from 340 to 450 nm was recorded as Cu^{2+} was added to a 50 mM solution of **24** in acetonitrile. As shown in Figure 3, the titration shows three isosbestic points. A plot of the absorbance at 390 nm vs titrant (Figure S2 of Supporting Information) gave an endpoint that permitted the determination of a K_D of 44 mM. The UV−visible spectrum from 390 to 600 nm was recorded as Fe^{3+} in THF/acetonitrile added to a 60 mM solution of **25** in acetonitrile. A plot of the absorbance at 485 nm vs titrant gave an endpoint that permitted the determination of a K_D of 31 mM. A similar titration with the **27**/**28** mixture gave a K_D of 36 mM. This result is not consistent with Figure 2, which shows that this compound should have a higher affinity for Fe^{3+}, since its tag is overrepresented in the pool.However, after correction for the fact that **27** is only 75% of the material, the actual K_D for **27** would be 27 mM.

The ability of members of this library to catalyze a chemical process was next investigated. Given the presence within the library building blocks of hydroxyl, imidazole, and carboxyl groups, the catalytic triad of the serine proteases, it was conceivable that library members could exhibit nucleophilic catalysis. It would be most convenient to follow the acylation step in the screening of the library, so an ester acylating agent that also carried a dye was required. Many of the available dyes are polar and charged and exhibit nonspecific binding to the library, so a nonpolar dye was sought. Azulenes are intensely colored and nonpolar and can be readily functionalized by electrophilic aromatic

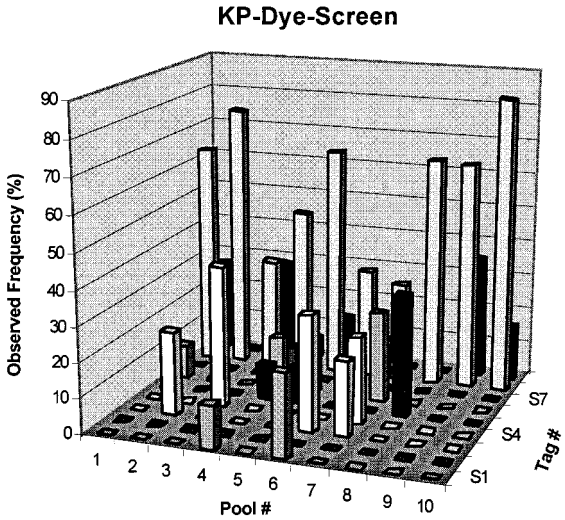
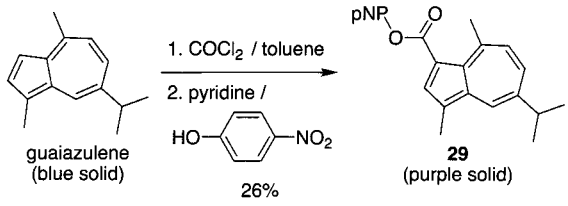
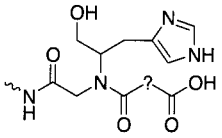


Figure 4. Observed frequency of each tag (total of 9) in each pool (total of 10) in the solid-phase acylation assay with dye-ester **29**. Observed frequency (%) = (^{19}F peak height of each tag/sum of ^{19}F peak height of all tags in individual pool) × 100. A high observed frequency indicates peptoids that were effectively acylated. Tags were released from purple beads found in each pool through photochemical reaction. Each tag indicates the individual amine (total of 9), and each pool number indicates the individual anhydride (total of 10) used to make the peptoid libraries.

substitution.[26] Commercially available guaiazulene was therefore treated with phosgene, and the acid chloride was used to acylate *p*-nitrophenol, giving nonpolar dye-ester **29**.





Treatment of the library with this dye gave purple beads whose decoding led to the results summarized in Figure 4. Little selectivity among the anhydride diversity is noted, but histidinol does appear as the predominant building block among amines in promoting self-acylation.

Discussion

The method described above has permitted the discovery from the same naive combinatorial library of peptoids selective for binding two of three metals examined. One of the principle advantages of combinatorial chemistry, that it leads naturally to molecules that could never have been envisioned by logic, is evident in a comparison of structures **4**{*6*} and **5**{*10*}. That the *o*-pyridylmethylamide would be selective for copper while the *m*-pyridylmethylamide would be selective for iron is completely nonintuitive. Of course, the anhydride diversity differs between these compounds, so the amine is not the *only* determinant of selectivity.

Regarding catalysts for self-acylation, it is reasonable that histidinol is the dominant amine building block but no particular cyclic anhydride was selected. Histidinol bears imidazole and alcohol functionalities, and with a carboxy group that can be contributed from the opening of any of the cyclic anhydrides, these results suggest that the catalytic triad of the serine proteases has been repeated in **30**.

Conclusion

With minimal further investigation of other substituents, it is readily projected that several more ^{19}F arene tags with even greater chemical shift dispersion can be introduced. The addition of a few other commercially available or readily prepared fluorinated organic compounds enables other tags to be generated, as was reported by Hochlowski.[13]

In designing these tags, we considered placing the linker at the meta position, which has a much smaller influence on the fluorine chemical shift, and thereby including an ortho hydrogen that could be subject to heteronuclear decoupling to gain the sensitivity advantage of a nuclear Overhauser effect. However, spectrometers that can acquire proton-decoupled fluorine spectra are relatively specialized and not available in many chemistry laboratories. Since we aimed to develop the most widely applicable tagging methodology, we chose molecules without large ortho *J* couplings. In the future, it might also be desirable to investigate tags that can be directly analyzed by NMR while still attached to the bead so that no cleavage step is needed. In general, this requires tags with significant mobility. A number of studies of TentaGel with high-resolution MAS NMR have shown that solution-like spectra can be obtained. Fluorine spectra have specifically been reported but only using gel-phase methods.[27] It should therefore be possible to obtain fluorine spectra of tags that are still bound to the bead by putting in a long PEG linker instead of the sasrin linker. We cannot provide an informed opinion on the viability of decoding single beads with on-resin NMR because the experiments we performed address only solution-phase decoding. We did establish a detection limit of 12 nmol for aryl fluorides in solution, using conventional NMR instrumentation. This sensitivity should permit the use of smaller beads in ^{19}F-encoded combinatorial chemistry or might permit the incorporation of multiple fluorinated tags on big beads to implement a binary encoding scheme. Finally, the recent emergence of "fluorous" synthesis technologies[28] suggests the use of fluorous tags not only for separation but also for ^{19}F encoding of library members.

Experimental Section

General. All reagents were purchased from Aldrich Chemical Co. unless otherwise indicated and were verified and/or titrated before use. Diethyl ether and THF were distilled from sodium/benzophenone immediately prior to use. Triethylamine and diisopropylamine were distilled from calcium hydride and stored under argon. Acetonitrile, pyridine, benzene, and dichloromethane were freshly distilled from calcium hydride. Methanol was distilled from magnesium turnings immediately prior to use. All reactions were performed in oven-dried glassware under argon atmosphere unless otherwise noted. Flash column chromatography was carried out on EM Reagents silica gel 60 (230−400 mesh). Silica gel was deactivated by forming a slurry in 10% triethylamine in hexanes, filtering, and washing with copious amounts of hexanes. Thin-layer chromatography (TLC) was performed using glass-backed silica gel 60 F_{254} (EM Science, 250 mm thickness). HPLC was performed with a Hewlett-Packard 1100 equipped with a 4.6 mm i.d. × 250 mm ECONOSIL C18 5 μm column (Alltech) and a computing integrator. Melting points were determined using a Haake Buchler apparatus and are uncorrected. ^1H NMR spectra were obtained on a Varian MVX-300 (300 MHz) or a Varian INOVA 400 (400 MHz) spectrometer. Chemical shifts were reported in ppm using tetramethylsilane (δ 0.0) as an internal standard. ^{13}C NMR spectra were obtained on a Varian MVX-300 (75 MHz) or a Varian INOVA 400 (100 MHz) spectrometer, and chemical shifts were reported in ppm using $CDCl_3$ (δ 77.0) as an internal standard. ^{19}F NMR spectra were obtained on a Varian MVX-300 (282 MHz) or a Varian INOVA 400 (376 MHz) spectrometer, and chemical shifts were reported in ppm using fluorobenzene (δ −112.86) as an internal standard, which was calibrated from $CFCl_3$ (δ 0.0) in $CDCl_3$. FT-IR spectra were obtained using a Bomem infrared spetrophotometer. UV spectra were obtained using a Shimadzu UV 160U spetrophotometer. Irradiations were performed using a Rayonet photochemical reactor containing 16 phosphor-coated 350 nm lamps. Elemental analyses were performed by Atlantic Microlabs. High-resolution mass spectra (HRMS, FAB) were performed using a JEOL JMS-SX 102A mass spectrometer.

General Procedure A for the Carboxylation of Fluoroaromatic Compounds As Described for 2-Fluoro-3-methylbenzoic Acid. *N*,*N*,*N*′,*N*′,*N*″-Pentamethyldiethylenetriamine (PMDTA) (10.4 mL, 49.9 mmol) was added to a solution of 2-fluorotoluene (5.0 g, 45.4 mmol) in THF (150 mL), and the solution was cooled to −78 °C. *n*-Butyllithium (2.5 M in hexanes, 18.2 mL, 49.9 mmol) was slowly added to the solution. After being stirred for 2 h, the reaction mixture was transferred into a flask containing a large excess of freshly crushed dry ice that had been flushed with argon at −78 °C. The dry ice mixture was allowed to warm to room temperature. The solution was concentrated under reduced pressure, and the residue was dissolved in 10% NaOH aqueous solution (100 mL). The aqueous solution was washed with ether (100 mL) and acidified with concentrated HCl. The cloudy precipitate was extracted with CH_2Cl_2 (3 × 150 mL) and dried over Na_2SO_4. Evaporation of the solvent gave 2-fluoro-3-methylbenzoic acid (6.41 g, 92%) as a white solid that was used in the next step without further purification.

2-Fluoro-3-methoxybenzoic Acid. This compound was synthesized from 2-fluoroanisole as a pale-yellow solid (76%) according to general procedure A.

2-Fluoro-5-methoxy-3-methylbenzoic Acid. This compound was synthesized from 2-fluoro-5-methoxytoluene as a white solid (85%) according to general procedure A.

2-Fluoro-3-methoxy-5-methylbenzoic Acid. This compound was synthesized as a white solid (85%) according to the general procedure A from 1-fluoro-2-methoxy-4-methylbenzene, which was prepared by the methylation of

2-fluoro-5-methylphenol (CH_3I, K_2CO_3, acetone/reflux, 20 h, quantitative yield).

General Procedure B for the Carboxylation of Fluoroaromatic Compounds As Described for 3-Bromo-2-fluorobenzoic Acid. LDA (2.0 M in THF, 23.6 mL, 47.1 mmol) was added to a solution of 1-bromo-2-fluorobenzene (7.5 g, 42.9 mmol) in THF (200 mL) at −78 °C. After being stirred for 2 h, the reaction mixture was transferred into a flask containing a large excess of freshly crushed dry ice that had been flushed with argon at −78 °C. The dry ice mixture was allowed to warm to room temperature. The solution was concentrated under reduced pressure, and the residue was dissolved in 10% NaOH aqueous solution (150 mL). The aqueous solution was washed with ether (150 mL) and acidified with concentrated HCl. The cloudy precipitate was extracted with CH_2Cl_2 (3 × 200 mL) and dried over Na_2SO_4. Evaporation of the solvent gave 3-bromo-2-fluorobenzoic acid (7.60 g, 81%) as a white solid that was used in the next step without further purification.

3-Bromo-2-fluoro-5-methylbenzoic Acid. This compound was synthesized from 3-bromo-4-fluorotoluene as a white solid (83%) according to the general procedure B.

2-Fluoro-3-iodobenzoic Acid. This compound was synthesized from 1-fluoro-2-iodobenzene as a paleyellow solid (73%) according to the general procedure B.

General Procedure C for the Reduction of Fluoroaromatic Carboxylic Acids with $LiAlH_4$ As Described for (2-Fluoro-3-methylphenyl)methanol (1). 2-Fluoro-3-methylbenzoic acid (5.0 g, 32.4 mmol) was slowly added to a slurry of $LiAlH_4$ (2.46 g, 64.8 mmol) in ether (200 mL) as the solution was gently refluxed without heating (exothermic reaction). After the resulting solution was stirred for 1 h, 15% NaOH aqueous solution was added carefully to the mixture until no more H_2 gas evolved. The white precipitate was filtered, and the filtrate was washed with 10% NaOH aqueous solution (150 mL), water (150 mL), and brine (150 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography using 15% ethyl acetate in hexanes as eluent to afford pure 2-fluoro-3-methylbenzyl alcohol (4.36 g, 96%) as a pale-yellow oil. R_f = 0.28 (1:4, EtOAc/hexane); IR (thin film) 3347, 2927, 2882, 1470, 1189 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.17 (ddt, J = 0.6, 1.2, 7.5 Hz, 1H), 7.08 (dt, J = 1.2, 7.5 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 4.66 (s, 2H), 2.67 (bs, 1H), 2.24 (d, J = 2.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 158.8 (d, J = 244.5 Hz), 130.6 (d, J = 4.8 Hz), 127.3 (d, J = 16.4 Hz), 126.4 (d, J = 4.6 Hz), 124.5 (d, J = 16.9 Hz), 123.5 (d, J = 4.0 Hz), 59.2 (d, J = 4.9 Hz), 14.4 (d, J = 4.6 Hz); ^{19}F NMR ($CDCl_3$) δ −124.1. HRMS (FAB) calcd for C_8H_9FO $[M]^+$: 140.0637. Found: 140.0635. Anal. Calcd for C_8H_9FO: C, 68.57; H, 6.43. Found: C, 68.34; H, 6.47.

(2-Fluoro-3-methoxyphenyl)methanol (2). This compound was synthesized from 2-fluoro-3-methoxybenzoic acid as white crystals (94%) according to the general procedure C. R_f = 0.14 (1:4, EtOAc/hexane); IR (thin film) 3322, 2965, 2841, 1479, 1373, 1195, 1044 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.06−6.85 (m, 3H), 4.69 (s, 2H), 3.85 (s, 3H), 2.68 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 149.9 (d, J = 245.1 Hz), 147.2 (d, J = 10.6 Hz), 128.6 (d, J = 12.0 Hz), 123.8 (d, J = 4.3 Hz), 120.2 (d, J = 2.9 Hz), 112.5, 58.8, 56.2; ^{19}F NMR ($CDCl_3$) δ −142.1. HRMS (FAB) calcd for $C_8H_9FO_2$ $[M]^+$: 156.0587. Found: 156.0587. Anal. Calcd for $C_8H_9FO_2$: C, 61.54; H, 5.77. Found: C, 61.66; H, 5.82.

(2-Fluoro-5-methoxy-3-methylphenyl)methanol (3). This compound was synthesized from 2-fluoro-5-methoxy-3-methylbenzoic acid as a colorless oil (94%) according to the general procedure C. R_f = 0.29 (3:7, EtOAc/hexane); IR (thin film) 3362, 2940, 2840, 1603, 1485, 1199, 1058 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.55 (ddd, J = 0.3, 3.0, 5.7 Hz, 1H), 6.42 (dd, J = 3.0, 5.7 Hz, 1H), 4.47 (s, 2H), 3.55 (s, 3H), 2.45 (bs, 1H), 2.04 (d, J = 2.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 154.7, 152.9 (d, J = 236.7 Hz), 127.8 (d, J = 17.1 Hz), 125.0 (d, J = 18.6 Hz), 115.3 (d, J = 4.6 Hz), 110.5 (d, J = 3.8 Hz), 58.8 (d, J = 4.5 Hz), 55.3, 14.5 (d, J = 3.7 Hz); ^{19}F NMR ($CDCl_3$) δ −134.5. HRMS (FAB) calcd for $C_9H_{11}FO_2$ $[M]^+$: 170.0743. Found: 170.0750. Anal. Calcd for $C_9H_{11}FO_2$: C, 65.53; H, 6.47. Found: C, 63.41; H, 6.40.

General Procedure D for the Reduction of Fluoroaromatic Carboxylic Acids with BH_3·THF As Described for 3-Bromo-2-fluorophenyl)methanol (5). 3-Bromo-2-fluorobenzoic acid (2.5 g, 11.4 mmol) was dissolved in THF (20 mL), and the solution was cooled to 0 °C. BH_3·THF (1.0 M in THF, 17.1 mL, 17.1 mmol) was slowly added to the solution, and the solution was vigorously stirred for 3 h at room temperature. Excess hydride was carefully destroyed with water, and the mixture was concentrated to remove most of the THF. The residue was dissolved in ether (30 mL), and the aqueous phase was saturated with potassium carbonate. The organic layer was separated, and the aqueous phase was extracted with ether (3 × 30 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography using 15% ethyl acetate in hexanes as eluent to afford pure 3-bromo-2-fluorobenzyl alcohol (2.23 g, 95%) as a colorless oil. R_f = 0.31 (3:7, EtOAc/hexane); IR (thin film) 3330, 2931, 2882, 1453, 1226, 1016 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.46 (m, 1H), 7.33 (m, 1H), 7.00 (dt, J = 0.9, 7.8 Hz, 1H), 4.72 (s, 2H), 2.47 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 156.2 (d, J = 247.1 Hz), 132.4, 129.0 (d, J = 15.8 Hz), 127.8 (d, J = 4.0 Hz), 124.9 (d, J = 4.1 Hz), 108.6 (d, J = 20.9 Hz), 58.6 (d, J = 3.7 Hz); ^{19}F NMR ($CDCl_3$) δ −113.2. HRMS (FAB) calcd for C_7H_6BrFO [M, ^{79}Br]$^+$: 203.9586. Found: 203.9590. Anal. Calcd for C_7H_6BrFO: C, 41.00; H, 2.93. Found: C, 41.16; H, 2.97.

(2-Fluoro-3-methoxy-5-methylphenyl)methanol (4). This compound was prepared from 2-fluoro-3-methoxy-5-methylbenzoic acid as a colorless oil (96%) according to the general procedure D. When general procedure C was used, the yield was 83%. R_f = 0.30 (3:7, EtOAc/hexane); IR (thin film) 3358, 2940, 1604, 1501, 1332, 1148 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.76 (ddd, J = 0.6, 1.8, 6.0 Hz, 1H), 6.69 (dd, J = 1.8, 8.1 Hz, 1H), 4.67 (d, J = 1.2 Hz, 2H), 3.84 (s, 3H), 2.30 (d, J = 0.6 Hz, 3H), 2.27 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 147.8 (d, J = 242.2 Hz), 146.5 (d, J = 10.6 Hz), 133.3 (d, J = 4.0 Hz), 127.9 (d, J = 12.0 Hz), 120.2 (d, J = 2.6 Hz), 113.0, 58.4 (d, J = 5.1 Hz), 55.9, 20.9; ^{19}F NMR ($CDCl_3$)

δ −146.8. Anal. Calcd for $C_9H_{11}FO_2$: C, 65.53; H, 6.47. Found: C, 63.41; H, 6.40.

(3-Bromo-2-fluoro-5-methylphenyl)methanol (6). This compound was synthesized from 3-bromo-2-fluoro-5-methylbenzoic acid according to the general procedure D. The residue was purified by flash column chromatography or recrystallized with $CHCl_3$ to afford pure (3-bromo-2-fluoro-5-methylphenyl)methanol (96%) as white crystals. $R_f = 0.36$ (3:7, EtOAc/hexane); mp 73.5−74.5 °C; IR (thin film) 3222, 2927, 2870, 1472 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.28 (dd, J = 1.8, 6.3 Hz, 1H), 7.16 (ddd, J = 0.3, 1.2, 6.6 Hz, 1H), 4.73 (s, 2H), 2.31 (s, 3H), 1.93 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 154.6 (d, J = 244.0 Hz), 134.9 (d, J = 4.3 Hz), 132.7, 128.57 (d, J = 15.5 Hz), 128.56 (d, J = 3.8 Hz), 108.3 (d, J = 20.9 Hz), 59.3 (d, J = 4.0 Hz), 20.5; ^{19}F NMR ($CDCl_3$) δ −118.7. Anal. Calcd for C_8H_8BrFO: C, 43.86; H, 3.65. Found: C, 44.01; H, 3.64.

(2-Fluoro-3-iodophenyl)methanol (7). This compound was synthesized from 2-fluoro-3-iodobenzoic acid as a colorless oil (94%) according to the general procedure D. $R_f = 0.33$ (3:7, EtOAc/hexane); IR (thin film) 3328, 2944, 2881, 1445, 1221, 1124, 1015 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.65 (ddd, J = 1.8, 6.0, 7.8 Hz, 1H), 7.36 (m, 1H), 6.89 (t, J = 7.8 Hz, 1H), 4.71 (s, 2H), 2.53 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 158.7 (d, J = 245.0 Hz), 138.2, 128.9 (d, J = 4.0 Hz), 128.3 (d, J = 16.9 Hz), 125.6 (d, J = 3.7 Hz), 81.2 (d, J = 25.4 Hz), 58.8 (d, J = 3.4 Hz); ^{19}F NMR ($CDCl_3$) δ −99.4. HRMS (FAB) calcd for C_7H_6FIO [M]$^+$: 251.9447. Found: 251.9443.

General Procedure E for the Bromination of Benzyl Alcohols As Described for 1-Bromomethyl-2-fluoro-3-methylbenzene (1a). (2-Fluoro-3-methylphenyl)methanol (**1**) (2.00 g, 14.3 mmol) was dissolved in CH_2Cl_2 (80 mL), and triphenylphosphine (4.49 g, 17.1 mmol) was added to the solution at room temperature. Carbon tetrabromide (5.68 g, 17.1 mmol) was slowly added to the solution, and the mixture was stirred for 5 h at room temperature. The solution was concentrated to 15 mL (20% of total volume) and diluted with ether. The white precipitates were filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography using 5% ethyl acetate in hexanes as eluent to afford pure 1-bromomethyl-2-fluoro-3-methylbenzene (**1a**) (2.78 g, 96%) as a colorless oil. $R_f = 0.59$ (1:9, EtOAc/hexane); IR (thin film) 2989, 2895, 1511, 1421 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.17 (m, 2H), 6.99 (t, J = 7.5 Hz, 1H), 4.50 (d, J = 0.9 Hz, 2H), 2.27 (d, J = 2.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 158.9 (d, J = 248.5 Hz), 131.8 (d, J = 5.1 Hz), 128.3 (d, J = 2.3 Hz), 125.1 (d, J = 16.9 Hz), 124.6 (d, J = 15.2 Hz), 123.7 (d, J = 4.3 Hz), 26.2 (d, J = 5.1 Hz), 14.4 (d, J = 4.0 Hz). HRMS (FAB) calcd for C_8H_8BrF [M, ^{79}Br]$^+$: 201.9793. Found: 201.9794.

1-Bromomethyl-2-fluoro-3-methoxybenzene (2a). This compound was prepared from (2-fluoro-3-methoxyphenyl)-methanol (**2**) as a colorless oil (93%) according to the general procedure E. $R_f = 0.34$ (1:9, EtOAc/hexane); IR (thin film) 2997, 2988, 1506, 1465 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.04 (ddd, J = 1.2, 7.8, 7.8 Hz, 1H), 6.92 (m, 2H), 4.50 (d, J = 1.5 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 150.1 (d, J = 249.4 Hz), 147.5 (d, J = 10.3 Hz), 125.6 (d, J = 11.7 Hz), 123.9 (d, J = 4.9 Hz), 121.9 (d, J = 2.0 Hz), 113.4 (d, J = 2.0 Hz), 56.1, 25.5 (d, J = 5.7 Hz). HRMS (FAB) calcd for C_8H_8BrFO [M, ^{79}Br]$^+$: 217.9742. Found: 217.9744.

1-Bromomethyl-2-fluoro-5-methoxy-3-methylbenzene (3a). This compound was prepared from (2-fluoro-5-methoxy-3-methylphenyl)methanol (**3**) as white crystals (94%) according to the general procedure E. $R_f = 0.43$ (1:9, EtOAc/hexane); IR (thin film) 2999, 2989, 1509, 1411 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.68 (m, 2H), 4.47 (d, J = 0.6 Hz, 2H), 3.76 (s, 3H), 2.25 (d, J = 1.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 154.8 (d, J = 2.6 Hz), 153.4 (d, J = 241.1 Hz), 126.0 (d, J = 18.9 Hz), 124.9 (d, J = 16.9 Hz), 117.2 (d, J = 4.6 Hz), 112.6 (d, J = 2.9 Hz), 55.6, 26.4 (d, J = 4.8 Hz), 14.8 (d, J = 4.0 Hz). HRMS (FAB) calcd for $C_9H_{10}BrFO$ [M, ^{79}Br]$^+$: 231.9899. Found: 231.9903.

1-Bromomethyl-2-fluoro-3-methoxy-5-methylbenzene (4a). This compound was prepared from (2-fluoro-3-methoxy-5-methylphenyl)methanol (**4**) as white crystals (95%) according to the general procedure E. $R_f = 0.36$ (1:9, EtOAc/hexane); IR (thin film) 3007, 2981, 1518, 1461 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.73 (dd, J = 2.1, 5.4 Hz, 2H), 4.46 (d, J = 1.2 Hz, 2H), 3.86 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.3 (d, J = 246.5 Hz), 147.1 (d, J = 10.6 Hz), 133.7 (d, J = 4.6 Hz), 125.1 (d, J = 12.0 Hz), 122.1 (d, J = 1.7 Hz), 114.4 (d, J = 2.0 Hz), 56.2, 25.8 (d, J = 5.7 Hz), 21.1. HRMS (FAB) calcd for $C_9H_{10}BrFO$ [M, ^{79}Br]$^+$: 231.9899. Found: 231.9901.

1-Bromo-3-bromomethyl-2-fluorobenzene (5a). This compound was prepared from (3-bromo-2-fluorophenyl)-methanol (**5**) as white crystals (93%) according to the general procedure E. $R_f = 0.47$ (1:9, EtOAc/hexane); IR (thin film) 3005, 2991, 1511, 1455 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.50 (ddd, J = 1.5, 6.3, 8.1 Hz, 1H), 7.33 (ddd, J = 1.8, 6.3, 8.1 Hz, 1H), 7.01 (dt, J = 0.9, 7.5 Hz, 1H), 4.50 (d, J = 1.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 156.8 (d, J = 250.2 Hz), 133.8, 130.1 (d, J = 11.4 Hz), 126.6 (d, J = 15.5 Hz), 125.2 (d, J = 4.9 Hz), 109.4 (d, J = 20.9 Hz), 25.2 (d, J = 4.1 Hz). HRMS (FAB) calcd for $C_7H_5Br_2F$ [M, ^{79}Br]$^+$: 265.8742. Found: 265.8747.

1-Bromo-3-bromomethyl-2-fluoro-5-methylbenzene (6a). This compound was prepared from (3-bromo-2-fluoro-5-methylphenyl)methanol (**6**) as a white solid (92%) according to the general procedure E. $R_f = 0.51$ (1:9, EtOAc/hexane); IR (thin film) 3003, 2990, 2983, 1512, 1407 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 1H), 7.11 (ddd, J = 0.9, 2.4, 6.3 Hz, 1H), 4.45 (d, J = 1.2 Hz, 2H), 2.29 (t, J = 1.2 3H); ^{13}C NMR ($CDCl_3$) δ 154.9 (d, J = 247.7 Hz), 135.1 (d, J = 4.6 Hz), 133.9, 130.5 (d, J = 2.3 Hz), 125.8 (d, J = 15.5 Hz), 108.7 (d, J = 20.9 Hz), 25.4 (d, J = 4.0 Hz), 20.4. HRMS (FAB) calcd for $C_8H_7Br_2F$ [M, ^{79}Br]$^+$: 279.8898. Found: 279.8899.

1-Bromomethyl-2-fluoro-3-iodobenzene (7a). This compound was prepared from (2-fluoro-3-iodophenyl)methanol (**7**) as white crystals (94%) according to the general procedure E. $R_f = 0.23$ (1:9, EtOAc/hexane); IR (thin film) 2997, 2988, 1508, 1409 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.70 (ddd, J = 1.5, 5.7, 7.8 Hz, 1H), 7.35 (ddd, J = 1.5, 7.8, 7.8 Hz, 1H), 6.89 (t, J = 7.8 Hz, 1H), 4.49 (d, J = 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 159.2 (d, J = 248.3 Hz), 139.6 (d, J = 1.7

Hz), 131.2 (d, $J = 2.6$ Hz), 125.9 (d, $J = 4.3$ Hz), 125.7 (d, $J = 17.1$ Hz), 81.7 (d, $J = 25.7$ Hz), 25.5 (d, $J = 3.4$ Hz). HRMS (FAB) calcd for C_7H_5BrIF [M, ^{79}Br]$^+$: 313.8603. Found: 313.8607.

2-Fluoro-3-methoxyphenol (10). *N*,*N*,*N*′,*N*′,*N*″-Pentamethyldiethylenetriamine (PMDTA) (13.7 mL, 65.4 mmol) was added to a solution of 2-fluoroanisole (7.5 g, 59.5 mmol) in THF (250 mL), and the solution was cooled to −78 °C. *n*-Butyllithium (2.5 M in hexanes, 26.2 mL, 65.4 mmol) was slowly added to the solution, and the mixture was stirred for 2 h. Trimethyl borate (7.33 mL, 65.4 mmol) was added to the reaction mixture, which was stirred for an additional 30 min and allowed to warm to room temperature. After glacial acetic acid (5.11 mL, 89.3 mmol) was added to the mixture, 30% H_2O_2 (7,42 mL, 65.4 mmol) was slowly added to the solution, which was then stirred at room temperature overnight. Water (100 mL) was added, and the solution was concentrated under reduced pressure to remove most of THF. The residue was extracted with ether (3 × 100 mL), and the combined extracts were washed with water (200 mL), saturated aqueous $FeSO_4$ solution (2 × 200 mL), water, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography using 20% ethyl acetate in hexanes as eluent to afford pure 2-fluoro-3-methoxyphenol (6.85 g, 81%) as a pale-yellow oil. $R_f = 0.38$ (3:7, EtOAc/hexane); IR (thin film) 3416, 2943, 2843, 1631, 1485, 1083 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.90 (ddd, $J = 2.4$, 8.0, 8.0 Hz, 1H), 6.61 (dt, $J = 0.9$, 8.0 Hz, 1H), 6.51 (dt, $J = 1.2$, 8.0 Hz, 1H), 5.67 (d, $J = 4.2$ Hz, 1H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.9 (d, $J = 8.6$ Hz), 144.2 (d, $J = 11.8$ Hz), 141.3 (d, $J = 235.6$ Hz), 123.5 (d, $J = 4.9$ Hz), 109.5, 105.0, 56.4. HRMS (FAB) calcd for $C_7H_7FO_2$ [M]$^+$: 142.0432. Found: 142.0432.

1-(4-Bromo-but-2-enyloxy)-2-fluoro-3-methoxybenzene (8a). A slurry of 2-fluoro-3-methoxyphenol (**10**) (2.0 g, 14.1 mmol), 1,4-dibromo-2-butene (6.01 g, 28.1 mmol), and K_2CO_3 (2.92 g, 21.1 mmol) in acetone (50 mL) was stirred for 3 h at room temperature. K_2CO_3 was removed by filtration through Celite, and the filtrate was concentrated. The residue was purified by flash column chromatography using 10% ethyl acetate in hexanes as eluent to afford pure 1-(4-bromo-but-2-enyloxy)-2-fluoro-3-methoxybenzene (**8a**) (3.29 g, 85%) as white crystals. $R_f = 0.40$ (1:4, EtOAc/hexane); IR (thin film) 2963, 2919, 2869, 1627, 1602, 1511, 1482, 1105 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.94 (ddd, $J = 2.4$, 8.4, 8.4 Hz, 1H), 6.59 (m, 2H), 6.02 (m, 2H), 4.59 (dd, $J = 0.9$, 5.7 Hz, 2H), 3.97 (dd, $J = 0.9$, 5.7 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.2 (d, $J = 8.3$ Hz), 146.8 (d, $J = 8.4$ Hz), 142.3 (d, $J = 243.4$ Hz), 129.2, 129.0, 122.8 (d, $J = 5.4$ Hz), 107.0, 105.8, 68.3, 56.0, 31.5. HRMS (FAB) calcd for $C_{11}H_{12}BrFO_2$ [M, ^{79}Br]$^+$: 274.0005. Found: 274.0008.

4-(2-Fluoro-3-methoxyphenoxy)but-2-en-1-ol (8). A solution of 1-(4-bromo-but-2-enyloxy)-2-fluoro-3-methoxybenzene (**8a**) (100 mg, 0.363 mmol), 18-crown-6 (90 mg, 0.363 mmol), and KO_2 (26 mg, 0.363 mmol) in DMSO (2 mL) was stirred for 2 h at room temperature. The reaction mixture was quenched by the addition of H_2O and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (3 × 15 mL) and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography using 40% EtOAc in hexanes as eluent to afford pure 4-(2-fluoro-3-methoxyphenoxy)-but-2-en-1-ol (**8**) (52 mg, 68%) as a yellow oil. $R_f = 0.18$ (2:3, EtOAc/hexane); IR (thin film) 3365, 2938, 2867, 1622, 1507, 1480 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.94 (ddd, $J = 2.4$, 8.4, 8.4 Hz, 1H), 6.60 (m, 2H), 5.97 (m, 2H), 4.59 (dd, $J = 1.2$, 4.5 Hz, 2H), 4.18 (dd, $J = 1.2$, 4.5 Hz, 2H), 3.87 (s, 3H), 1.84 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 148.3 (d, $J = 8.6$ Hz), 147.1 (d, $J = 8.3$ Hz), 142.6 (d, $J = 243.4$ Hz), 133.2, 125.2, 122.9 (d, $J = 5.1$ Hz), 107.4, 105.9, 69.3, 62.4, 56.3; ^{19}F NMR ($CDCl_3$) δ −157.1. HRMS (FAB) calcd for $C_{11}H_{13}FO_3$ [M]$^+$: 212.0849. Found: 212.0851.

2-Fluoro-3-methoxy-5-methylphenol (11). This compound was obtained as a pale-brown oil (81%) from 1-fluoro-2-methoxy-4-methylbenzene (which was prepared by the methylation of 2-fluoro-5-methylphenol (CH_3I, K_2CO_3, acetone/reflux, 20 h, quantitative yield)) according to the same procedure described for the synthesis of **10**. $R_f = 0.46$ (3:7, EtOAc/hexane); IR (thin film) 3415, 2954, 2850, 1613, 1519, 1467, 1105 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.42 (m, 1H), 6.32 (dd, $J = 2.1$, 7.2 Hz, 1H), 5.30 (s, 1H), 3.85 (s, 3H), 2.25 (d, $J = 0.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 147.3 (d, $J = 8.3$ Hz), 143.5 (d, $J = 11.7$ Hz), 139.3 (d, $J = 233.0$ Hz), 133.4 (d, $J = 4.3$ Hz), 109.9, 105.7, 56.2, 21.3. HRMS (FAB) calcd for $C_8H_9FO_2$ [M]$^+$: 156.0587. Found: 156.0589.

1-(4-Bromobut-2-enyloxy)-2-fluoro-3-methoxy-5-methylbenzene (9a). This compound was prepared from 2-fluoro-3-methoxy-5-methylphenol (**11**) as white crystals (91%) according to the same procedure as described for the synthesis of **8a**. $R_f = 0.44$ (1:4, EtOAc/hexane); IR (thin film) 3039, 3002, 2857, 1613, 1522, 1452, 1248, 1131 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.40 (m, 2H), 6.02 (m, 2H), 4.59 (dd, $J = 0.9$, 6.6 Hz, 2H), 3.97 (dd, $J = 0.9$, 6.6 Hz, 2H), 3.85 (s, 3H), 2.28 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 147.7 (d, $J = 8.3$ Hz), 146.3 (d, $J = 8.5$ Hz), 140.7 (d, $J = 240.8$ Hz), 132.8 (d, $J = 4.8$ Hz), 129.5, 129.2, 108.0, 106.7, 68.6, 56.2, 31.6, 21.5. Anal. Calcd for $C_{12}H_{14}BrFO_2$: C, 49.84; H, 4.85. Found: C, 50.02; H, 4.88.

4-(2-Fluoro-3-methoxy-5-methylphenoxy)butan-1-ol (9). This compound was prepared from 1-(4-bromo-but-2-enyloxy)-2-fluoro-3-methoxy-5-methylbenzene (**9a**) as a colorless oil (60% in two steps) according to the same procedure as described for the synthesis of **8** followed by hydrogenation (5 mol % of $Cl(PPh_3)_3Rh$ (Wilkinson's catalyst), H_2, CH_3OH, room temp, 20 h). $R_f = 0.11$ (3:7, EtOAc/hexane); IR (thin film) 3361, 2943, 2875, 1611, 1516, 1124 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.41 (s, 1H), 6.39 (s, 1H), 4.04 (t, $J = 6.3$ Hz, 2H), 3.85 (s, 3H), 3.71 (t, $J = 6.0$ Hz, 2H), 2.28 (s, 3H), 1.89 (m, 2H), 1.76 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 147.7 (d, $J = 8.5$ Hz), 146.9 (d, $J = 8.6$ Hz), 140.7 (d, $J = 240.6$ Hz), 132.7 (d, $J = 4.9$ Hz), 107.8, 106.4, 69.3, 62.1, 56.2, 29.1, 25.7, 21.5; ^{19}F NMR ($CDCl_3$) δ −161.8. Anal. Calcd for $C_{12}H_{17}FO_3$: C, 63.16; H, 7.46. Found: C, 63.01; H, 7.48.

{3-[4-(1-Hydroxyethyl)-2-methoxy-5-nitrophenoxy]-propyl}carbamic Acid *tert*-Butyl Ester (13). A solution of 4-[4-(1-hydroxyethyl)-2-methoxy-5-nitrophenoxy]butyric acid (**12**) (10 g, 33.4 mmol), diphenylphosphoryl azide (10.8 mL, 50.1 mmol), and triethylamine (6.98 mL, 50.1 mmol) in

2-methyl-2-propanol (*t*-BuOH, 250 mL) was refluxed for 24 h. The reaction solution was concentrated, and the residue was dissolved in EtOAc (200 mL). The organic solution was successively washed with 5% citric acid (3 × 200 mL), H_2O, saturated $NaHCO_3$, and brine. The solution was dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography using 30% ethyl acetate in hexanes as eluent to afford pure BOC-protected photolabile linker **11** (7.55 g, 61%) as a yellow crystal. $R_f = 0.24$ (1:1, EtOAc/hexane); IR (thin film) 3408, 2975, 2934, 2250, 1696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52 (s, 1H), 7.32 (s, 1H), 5.54 (q, J = 6.6 Hz, 1H), 5.38 (bs, 1H), 4.13 (dt, J = 2.1, 6.0 Hz, 2H), 3.98 (s, 3H), 3.34 (m, 2H), 2.99 (s, 1H), 2.04 (qn, J = 6.0 Hz, 2H), 1.53 (d, J = 6.6 Hz, 3H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.9, 153.7, 146.4, 139.0, 137.5, 108.5, 108.4, 79.1, 68.2, 65.4, 56.2, 38.7, 29.0, 28.4 (3C), 24.5. HRMS (FAB) calcd for $C_{17}H_{26}N_2O_7$ $[M]^+$: 370.1740. Found: 370.1738. Anal. Calcd for $C_{17}H_{26}N_2O_7$: C, 55.13; H, 7.03; N, 7.57. Found: C, 54.98; H, 6.92; N, 7.56.

General Procedure F for the Coupling Reaction between Fluoroaromatic Tags 1a−9a and BOC-Protected Photolabile Linker 13 As Described for (3-{4-[1-(2-Fluoro-3-methylbenzyloxy)ethyl]-2-methoxy-5-nitrophenoxy}propyl)carbamic Acid *tert*-Butyl Ester (14). NaH (97 mg, 4.05 mmol) was added to the solution of BOC-protected photolabile linker **13** (1.00 g, 2.70 mmol) in anhydrous DMF (13 mL), and the mixture was stirred for 10 min at room temperature. A solution of 1-bromomethyl-2-fluoro-3-methylbenzene (**1a**) (521 mg, 2.56 mmol) in anhydrous DMF (2 mL) was added to the solution, and the reaction mixture was stirred for 2 h at room temperature. The mixture was quenched by the addition of H_2O, and the resulting solution was extracted with ether (3 × 50 mL). The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography using 20% ethyl acetate in hexanes as eluent to afford *tert*-butyl carbamate **14** (1.10 g, 83%) as a pale-yellow oil. $R_f = 0.29$ (3:7, EtOAc/hexane); IR (thin film) 3415, 2976, 2932, 1712, 1516, 1503, 1470, 1271 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.58 (s, 1H), 7.32 (s, 1H), 7.15 (m, 2H), 7.00 (t, J = 7.2 Hz, 1H), 5.37 (bs, 1H), 5.29 (q, J = 6.3 Hz, 1H), 4.42 (dd, J = 0.6, 10.8 Hz, 1H), 4.33 (dd, J = 0.9, 10.8 Hz, 1H), 4.16 (t, J = 6.0 Hz, 2H), 3.97 (s, 3H), 3.38 (dt, J = 5.7, 6.0 Hz, 2H), 2.24 (d, J = 2.1 Hz, 3H), 2.06 (qn, J = 6.0 Hz, 2H), 1.55 (d, J = 6.3 Hz, 3H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 159.2 (d, J = 245.7 Hz), 155.8, 154.0, 146.6, 140.1, 135.5, 131.1 (d, J = 4.8 Hz), 127.7 (d, J = 4.0 Hz), 124.6 (d, J = 17.5 Hz), 124.2 (d, J = 15.8 Hz), 123.5 (d, J = 4.0 Hz), 108.5, 108.4, 78.9, 73.5, 68.3, 65.5 (d, J = 3.5 Hz), 56.1, 38.7, 29.1, 28.4 (3C), 23.7, 14.4 (d, J = 4.3 Hz). Anal. Calcd for $C_{25}H_{33}FN_2O_7$: C, 60.98; H, 6.71; N, 5.69. Found: C, 60.81; H, 6.70; N, 5.63.

(3-{4-[1-(2-Fluoro-3-methoxybenzyloxy)ethyl]-2-methoxy-5-nitrophenoxy}propyl)carbamic Acid *tert*-Butyl Ester (15). This compound was synthesized from 1-bromomethyl-2-fluoro-3-methoxybenzene (**2a**) and BOC-protected photolabile linker **13** as a pale-yellow oil (76%) according to the general procedure F. $R_f = 0.44$ (1:1, EtOAc/hexane); IR (thin film) 3414, 2975, 2936, 2873, 1704, 1615, 1583, 1508, 1463 1334, 1272, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.58 (s, 1H), 7.32 (s, 1H), 7.05 (ddd, J = 1.2, 8.1, 8.1 Hz, 1H), 6.92 (m, 2H), 5.42 (bs, 1H), 5.30 (q, J = 6.6 Hz, 1H), 4.46 (dd, J = 1.2, 11.4 Hz, 1H), 4.35 (dd, J = 1.5, 11.4 Hz, 1H), 4.16 (t, J = 5.7 Hz, 2H), 3.98 (s, 3H), 3.86 (s, 3H), 3.38 (dt, J = 5.7, 5.7 Hz, 2H), 2.06 (qn, J = 5.7 Hz, 2H), 1.54 (d, J = 6.6 Hz, 3H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.7, 153.9, 150.2 (d, J = 246.5 Hz), 147.2 (d, J = 10.6 Hz), 146.5, 139.9, 135.2, 125.4 (d, J = 12.3 Hz), 123.6 (d, J = 4.6 Hz), 121.2 (d, J = 3.4 Hz), 112.8 (d, J = 1.7 Hz), 108.4, 108.1, 78.6, 73.5, 68.1, 65.0 (d, J = 4.3 Hz), 56.0 (2C), 38.5, 29.0, 28.3 (3C), 23.5. Anal. Calcd for $C_{25}H_{33}FN_2O_8$: C, 59.06; H, 6.50; N, 5.51. Found: C, 59.08; H, 6.42; N, 5.42.

(3-{4-[1-(2-Fluoro-5-methoxy-3-methylbenzyloxy)ethyl]-2-methoxy-5-nitrophenoxy}propyl)carbamic Acid *tert*-Butyl Ester (16). This compound was synthesized from 1-bromomethyl-2-fluoro-5-methoxy-3-methylbenzene (**3a**) and BOC-protected photolabile linker **11** as a pale-yellow oil (74%) according to the general procedure F. $R_f = 0.42$ (2:3, EtOAc/hexane); IR (thin film) 3407, 2975, 2936, 2861, 1725, 1590, 1515, 1274 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.57 (s, 1H), 7.31 (s, 1H), 6.71 (dd, J = 3.3, 5.4 Hz, 1H), 6.63 (dd, J = 3.3, 6.0 Hz, 1H), 5.44 (bs, 1H), 5.28 (q, J = 6.0 Hz, 1H), 4.39 (dd, J = 0.9, 11.4 Hz, 1H), 4.30 (dd, J = 1.5, 11.4 Hz, 1H), 4.16 (t, J = 5.7 Hz, 2H), 3.98 (s, 3H), 3.76 (s, 3H), 3.39 (dt, J = 5.7, 6.0 Hz, 2H), 2.21 (d, J = 2.4 Hz, 3H), 2.06 (p, J = 5.7 Hz, 2H), 1.55 (d, J = 6.0 Hz, 3H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.6, 154.7 (d, J = 2.3 Hz), 153.8, 153.3 (d, J = 237.9 Hz), 146.5, 139.9, 135.2, 125.2 (d, J = 19.2 Hz), 124.6 (d, J = 17.4 Hz), 115.8 (d, J = 4.5 Hz), 112.1 (d, J = 3.7 Hz), 108.3, 108.2, 78.6, 73.4, 68.1, 65.3 (d, J = 3.4 Hz), 55.9, 55.3, 38.4, 29.0, 28.3 (3C), 23.5, 14.5 (d, J = 4.0 Hz). Anal. Calcd for $C_{26}H_{35}FN_2O_8$: C, 59.77; H, 6.70; N, 5.36. Found: C, 59.82; H, 6.86; N, 5.32.

(3-{4-[1-(2-Fluoro-3-methoxy-5-methylbenzyloxy)ethyl]-2-methoxy-5-nitrophenoxy}propyl)carbamic Acid *tert*-Butyl Ester (17). This compound was synthesized from 1-bromomethyl-2-fluoro-3-methoxy-5-methylbenzene (**4a**) and BOC-protected photolabile linker **13** as a pale-yellow oil (75%) according to the general procedure F. $R_f = 0.39$ (2:3, EtOAc/hexane); IR (thin film) 3415, 2975, 2935, 1712, 1605, 1517, 1503 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.57 (s, 1H), 7.32 (s, 1H), 6.72 (s, 1H), 6.70 (s, 1H), 5.46 (bs, 1H), 5.28 (q, J = 6.3 Hz, 1H), 4.41 (dd, J = 0.9, 11.1 Hz, 1H), 4.29 (dd, J = 1.8, 11.1 Hz, 1H), 4.16 (t, J = 5.7 Hz, 2H), 3.98 (s, 3H), 3.84 (s, 3H), 3.39 (dt, J = 5.7, 5.7 Hz, 2H), 2.30 (s, 3H), 2.06 (qn, J = 5.7 Hz, 2H), 1.54 (d, J = 6.3 Hz, 3H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.6, 153.8, 148.3 (d, J = 243.7 Hz), 146.7 (d, J = 10.9 Hz), 146.4, 139.8, 135.1, 133.1 (d, J = 4.6 Hz), 124.6 (d, J = 12.6 Hz), 121.5 (d, J = 2.6 Hz), 113.6, 108.2, 108.1, 78.5, 73.3, 68.0, 65.0 (d, J = 4.1 Hz), 55.9, 55.8, 38.4, 28.9, 28.2 (3C), 23.4, 20.8. Anal. Calcd for $C_{26}H_{35}FN_2O_8$: C, 59.77; H, 6.70; N, 5.36. Found: C, 59.80; H, 6.66; N, 5.28.

(3-{4-[1-(3-Bromo-2-fluorobenzyloxy)ethyl]-2-methoxy-5-nitrophenoxy}propyl)carbamic Acid *tert*-Butyl Ester

(18). This compound was synthesized from 1-bromo-3-bromomethyl-2-fluorobenzene (**5a**) and BOC-protected photolabile linker **13** as a pale-yellow oil (71%) according to the general procedure F. $R_f = 0.23$ (3:7, EtOAc/hexane); IR (thin film) 3415, 3007, 2976, 2933, 1711, 1517, 1270 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.57 (s, 1H), 7.48 (ddd, $J = 1.8$, 6.9, 8.1 Hz, 1H), 7.33 (m, 1H), 7.27 (s, 1H), 7.01 (dt, $J = 0.9$, 8.1 Hz, 1H), 5.36 (bs, 1H), 5.30 (q, $J = 6.0$ Hz, 1H), 4.45 (dd, $J = 1.2$, 11.7 Hz, 1H), 4.38 (dd, $J = 1.5$, 11.7 Hz, 1H), 4.16 (t, $J = 6.0$ Hz, 2H), 3.97 (s, 3H), 3.38 (dt, $J = 6.0$, 6.0 Hz, 2H), 2.06 (p, $J = 6.0$ Hz, 2H), 1.56 (d, $J = 6.0$ Hz, 3H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 156.6 (d, $J = 247.7$ Hz), 155.6, 153.8, 146.6, 139.9, 134.8, 132.8, 129.0 (d, $J = 3.7$ Hz), 126.3 (d, $J = 15.7$ Hz), 124.8 (d, $J = 4.3$ Hz), 108.7 (d, $J = 20.9$ Hz), 108.3, 108.0, 78.6, 73.6, 68.1, 65.1 (d, $J = 2.9$ Hz), 56.0, 38.4, 28.9, 28.2 (3C), 23.4. Anal. Calcd for $C_{24}H_{30}BrFN_2O_7$: C, 51.71; H, 5.39; N, 5.03. Found: C, 51.43; H, 5.38; N, 4.97.

(3-{4-[1-(3-Bromo-2-fluoro-5-methylbenzyloxy)ethyl]-2-methoxy-5-nitrophenoxy}propyl)carbamic Acid *tert*-Butyl Ester (19). This compound was synthesized from 1-bromo-3-bromomethyl-2-fluoro-5-methylbenzene (**6a**) and BOC-protected photolabile linker **11** as a pale-yellow oil (81% based on recovered photolabile linker **13**) according to the general procedure F (1.0 equiv of NaH was used instead of 1.5 equiv of NaH to avoid an undesired debromination reaction). $R_f = 0.50$ (2:3, EtOAc/hexane); IR (thin film) 3415, 2976, 2934, 2873, 1712, 1694, 1582, 1535, 1276 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 1H), 7.27 (m, 2H), 7.09 (dd, $J = 1.5$, 6.0 Hz, 1H), 5.41 (bs, 1H), 5.28 (q, $J = 6.3$ Hz, 1H), 4.40 (dd, $J = 0.9$, 11.4 Hz, 1H), 4.33 (dd, $J = 1.2$, 11.4 Hz, 1H), 4.17 (t, $J = 5.7$ Hz, 2H), 3.98 (s, 3H), 3.39 (dt, $J = 5.7$, 6.0 Hz, 2H), 2.30 (s, 3H), 2.07 (p, $J = 5.7$ Hz, 2H), 1.55 (d, $J = 6.3$ Hz, 3H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 154.8 (d, $J = 245.1$ Hz), 155.6, 153.8, 146.6, 139.9, 134.9, 134.6 (d, $J = 4.3$ Hz), 133.0, 129.7 (d, $J = 3.5$ Hz), 125.5 (d, $J = 16.0$ Hz), 108.3, 108.2 (d, $J = 20.9$ Hz), 108.1, 78.6, 73.6, 68.2, 65.3 (d, $J = 2.6$ Hz), 56.0, 38.5, 29.0, 28.3 (3C), 23.5, 20.2. Anal. Calcd for $C_{25}H_{32}BrFN_2O_7$: C, 52.55; H, 5.61; N, 4.90. Found: C, 52.45; H, 5.61; N, 4.91.

(3-{4-[1-(2-Fluoro-3-iodobenzyloxy)ethyl]-2-methoxy-5-nitrophenoxy}propyl)carbamic Acid *tert*-Butyl Ester (20). This compound was synthesized from 1-bromomethyl-2-fluoro-3-iodobenzene (**7a**) and BOC-protected photolabile linker **13** as a pale-yellow oil (71%) according to the general procedure F. $R_f = 0.28$ (3:7, EtOAc/hexane); IR (thin film) 3415, 2975, 2932, 1712, 1694, 1515, 1503, 1273 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.66 (ddd, $J = 1.5$, 6.0, 7.8 Hz, 1H), 7.57 (s, 1H), 7.35 (ddd, $J = 1.5$, 6.6, 7.8 Hz, 1H), 7.27 (s, 1H), 6.89 (dt, $J = 0.6$, 7.8 Hz, 1H), 5.41 (bs, 1H), 5.30 (q, $J = 6.3$ Hz, 1H), 4.43 (d, $J = 11.7$ Hz, 1H), 4.37 (dd, $J = 0.9$, 11.7 Hz, 1H), 4.17 (t, $J = 5.7$ Hz, 2H), 3.98 (s, 3H), 3.39 (dt, $J = 5.4$, 5.7 Hz, 2H), 2.07 (p, $J = 5.7$ Hz, 2H), 1.55 (d, $J = 6.3$ Hz, 3H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 159.7 (d, $J = 245.9$ Hz), 156.1, 154.3, 147.1, 140.4, 139.2, 135.4, 130.7 (d, $J = 4.1$ Hz), 126.1 (d, $J = 17.5$ Hz), 126.0 (d, $J = 4.0$ Hz), 108.9, 108.6, 81.7 (d, $J = 25.5$ Hz), 79.1, 74.2, 68.7, 65.9 (d, $J = 2.6$ Hz), 56.6, 39.0, 29.5, 28.8 (3C), 24.0. Anal. Calcd for $C_{24}H_{30}BrFN_2O_7$: C, 47.69; H, 4.97; N, 4.64. Found: C, 47.61; H, 5.06; N, 4.57.

[3-(4-{1-[4-(2-Fluoro-3-methoxyphenoxy)but-2-enyloxy]-ethyl}-2-methoxy-5-nitrophenoxy)propyl]carbamic Acid *tert*-Butyl Ester (21). This compound was synthesized from 1-(4-bromobut-2-enyloxy)-2-fluoro-3-methoxybenzene (**8a**) and BOC-protected photolabile linker **13** as a pale-yellow oil (78%) according to the general procedure F. $R_f = 0.34$ (2:3, EtOAc/hexane); IR (thin film) 3414, 2975, 2934, 1708, 1513, 1480, 1271 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 1H), 7.23 (s, 1H), 6.95 (ddd, $J = 2.4$, 8.4, 8.4 Hz, 1H), 6.60 (m, 2H), 5.95 (m, 2H), 5.40 (bs, 1H), 5.21 (q, $J = 6.0$ Hz, 1H), 4.58 (d, $J = 3.0$ Hz, 2H), 4.15 (t, $J = 6.0$ Hz, 2H), 3.96 (s, 3H), 3.87 (s, 3H), 3.86 (m, 2H), 3.38 (td, $J = 5.7$, 6.0 Hz, 2H), 2.05 (p, $J = 6.0$ Hz, 2H), 1.51 (d, $J = 6.0$ Hz, 3H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.6, 153.8, 148.2 (d, $J = 8.6$ Hz), 146.9 (d, $J = 8.3$ Hz), 146.5, 142.4 (d, $J = 243.4$ Hz), 139.8, 135.2, 129.8, 126.6, 122.7 (d, $J = 5.4$ Hz), 108.3, 107.9, 107.0, 105.7, 78.5, 72.8, 68.9, 68.3, 68.0, 56.1, 56.0, 38.4, 28.9, 28.2 (3C), 23.2. Anal. Calcd for $C_{28}H_{37}FN_2O_9$: C, 59.57; H, 6.56; N, 4.96. Found: C, 59.42; H, 6.63; N, 4.88.

[3-(4-{1-[4-(2-Fluoro-3-methoxy-5-methylphenoxy)butoxy]ethyl}-2-methoxy-5-nitrophenoxy)propyl]carbamic Acid *tert*-Butyl Ester (22). This compound was obtained by the coupling reaction 1-(4-bromobut-2-enyloxy)-2-fluoro-3-methoxy-5-methylbenzene (**9a**) and BOC-protected photolabile linker **13** by using general procedure F followed by hydrogenation (5 mol % of $Cl(PPh_3)_3Rh$ (Wilkinson's catalyst), H_2, MeOH, room temp, 20 h). The reaction mixture was concentrated, and the residue was purified by flash column chromatography using 20% ethyl acetate in hexanes as eluent to afford pure *tert*-butyl carbamate **22** (71% in two steps) as a pale-yellow oil. $R_f = 0.40$ (2:3, EtOAc/hexane); IR (thin film) 3414, 2939, 2873, 1712, 1612, 1027 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 1H), 7.22 (s, 1H), 6.38 (m, 2H), 5.35 (bs, 1H), 5.14 (q, $J = 6.3$ Hz, 1H), 4.14 (t, $J = 6.0$ Hz, 2H), 4.02 (t, $J = 6.3$ Hz, 2H), 3.97 (s, 3H), 3.85 (s, 3H), 3.44−3.27 (m, 4H), 2.28 (s, 3H), 2.05 (p, $J = 6.0$ Hz, 2H), 1.93−1.72 (m, 4H), 1.49 (d, $J = 6.3$ Hz, 3H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.8, 154.0, 147.8 (d, $J = 8.3$ Hz), 147.0 (d, $J = 8.3$ Hz), 146.6, 140.8 (d, $J = 240.8$ Hz), 140.0, 136.0, 132.7 (d, $J = 4.9$ Hz), 108.5, 108.1, 107.9, 106.4, 78.9, 73.5, 69.2, 68.8, 68.3, 56.3, 56.2, 38.6, 29.1, 28.4 (3C), 28.3, 26.3, 23.5, 21.6. Anal. Calcd for $C_{29}H_{41}FN_2O_9$: C, 60.00; H, 7.07; N, 4.83. Found: C, 60.05; H, 7.19; N, 4.71.

1-(*tert*-Butyldimethylsilanyloxymethyl)-2-methylpropylamine (6). To a solution of DL-valinol (2.0 g, 19.4 mmol), triethylamine (3.24 mL, 23.3 mmol), and 4-(dimethylamino)-pyridine (DMAP, 95 mg, 0.78 mmol) in CH_2Cl_2 was added *tert*-butyldimethylsilyl chloride (3.21 g, 21.3 mmol). After being stirred overnight, the solution was washed with water and saturated NH_4Cl solution. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography using 5% MeOH in CH_2Cl_2 as eluent to afford pure 1-(*tert*-butyldimethylsilanyloxymethyl)-2-methylpropylamine (**6**) (3.83 g, 91%) as a pale-yellow oil. $R_f = 0.45$ (1:9, MeOH/CH_2Cl_2); IR (thin film) 3381, 2957, 2931, 2859, 1257, 1096 cm^{-1}; ^{1}H NMR ($CDCl_3$)

δ 3.64 (dd, $J = 3.6, 9.6$ Hz, 1H), 3.39 (dd, $J = 8.1, 9.6$ Hz, 1H), 2.57 (ddd, $J = 3.6, 6.6, 8.1$ Hz, 1H), 1.62 (oct, $J = 6.6$ Hz, 1H), 1.40 (bs, 2H), 0.91 (dd, $J = 2.4, 6.6$ Hz, 6H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 66.4, 58.3, 30.5, 25.9 (3C), 19.5, 18.3 (2C), −5.31, −5.34. HRMS (FAB) calcd for $C_{10}H_{24}NOSi$ $[M - CH_3]^+$: 202.1627. Found: 202.1628.

1-(*tert*-Butyldimethylsilanyloxymethyl)-3-methylsulfanylpropylamine (7). This compound was prepared from (*S*)-methioninol as a pale-yellow oil (94%) according to the same procedure as described for the synthesis of **6**. $R_f = 0.44$ (1:9, MeOH/CH_2Cl_2); IR (thin film) 3371, 2955, 1919, 2857, 1256, 1103 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.56 (dd, $J = 4.5, 9.6$ Hz, 1H), 3.39 (dd, $J = 6.6, 9.6$ Hz, 1H), 2.93 (m, 1H), 2.60 (m, 2H), 2.11 (s, 3H), 1.73 (m, 1H), 1.55 (m, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 68.0, 52.0, 33.0, 31.1, 25.8 (3C), 18.2, 15.4, −5.4 (2C). HRMS (FAB) calcd for $C_{11}H_{27}NOSSi$ $[M]^+$: 249.1583. Found: 249.1580.

2-(1-Benzyl-1*H*-imidazol-4-yl)-1-(*tert*-butyldimethylsilanyloxymethyl)ethylamine (9). To a stirring suspension of $LiAlH_4$ (371 mg, 9.78 mmol) in dry THF was added *im*-benzyl-L-histidine (2.0 g, 8.15 mmol) portionwise. The resulting suspension was stirred at reflux for 5 h and cooled to room temperature. The reaction mixture was quenched by the addition of 30% aqueous KOH solution. The resulting white precipitate was filtered and washed with THF. The combined organic solution was dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography using 10% MeOH in CH_2Cl_2 as eluent to afford pure *im*-benzyl-L-histidinol as a colorless oil. This compound was protected by using the same procedure as described for the synthesis of **6** to afford 2-(1-benzyl-1*H*-imidazol-4-yl)-1-(*tert*-butyldimethylsilanyloxymethyl)-ethylamine (**9**) as a colorless oil (2.06 g, 73% in two steps). IR (thin film) 3373, 2955, 2930, 2857, 1500, 1252, 1095 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45 (d, $J = 1.2$ Hz, 1H), 7.32 (m, 3H), 7.13 (m, 2H), 6.68 (d, $J = 1.5$ Hz, 1H), 5.03 (s, 2H), 3.61 (dd, $J = 4.5, 9.9$ Hz, 1H), 3.44 (dd, $J = 6.6, 9.9$ Hz, 1H), 3.18 (m, 1H), 2.69 (ddd, $J = 0.6, 4.8, 14.4$ Hz, 1H), 2.48 (dd, $J = 8.1, 14.4$ Hz, 1H), 1.73 (bs, 1H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 140.3, 136.6, 136.0, 128.7 (2C), 127.9, 127.0 (2C), 116.3, 67.6, 52.7, 50.6, 32.7, 25.8 (3C), 18.2, −5.4 (2C). HRMS (FAB) calcd for $C_{19}H_{32}N_3OSi$ $[M + H]^+$: 346.2314. Found: 346.2318.

1-(*tert*-Butyldimethylsilanyloxymethyl)-2-(1*H*-imidazol-4-yl)ethylamine (8). A suspension of 2-(1-benzyl-1*H*-imidazol-4-yl)-1-(*tert*-butyldimethylsilanyloxymethyl)-ethylamine (**9**) (0.95 g, 2.75 mmol) and Pd/C (10 wt % on C, 0.585 g, 0.550 mmol) in MeOH was stirred for 2 days at room temperature under a H_2 atmosphere. The reaction mixture was filtered through Celite, and the filtrate was concentrated. The residue was purified by flash column chromatography using deactivated silica gel and 20% MeOH in CH_2Cl_2 (containing 3% NEt_3) as eluent to afford pure 1-(*tert*-butyldimethylsilanyloxymethyl)-2-(1*H*-imidazol-4-yl)-ethylamine (**8**) (0.575 g, 90% based on recovered **9** (10%)) as a pale-yellow oil. IR (thin film) 3090, 2931, 2858, 1472, 1256, 1102 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.51 (d, $J = 0.9$ Hz, 1H), 6.80 (s, 1H), 5.75 (bs, 3H), 3.61 (dd, $J = 4.5, 10.2$ Hz, 1H), 3.47 (dd, $J = 6.6, 10.2$ Hz, 1H), 3.17 (m, 1H), 2.77 (dd, $J = 4.2, 14.4$ Hz, 1H), 2.58 (ddd, $J = 8.4, 14.4$ Hz, 1H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 134.5, 133.3, 118.7, 67.2, 53.0, 30.2, 25.9 (3C), 18.3, −5.3 (2C). HRMS (FAB) calcd for $C_{12}H_{26}N_3OSi$ $[M + H]^+$: 256.1845. Found: 256.1843.

***N*-Carbamoylmethyl-*N*-(3-imidazol-1-ylpropyl)succinamic Acid (23).** A peptide synthesis vessel was charged with 200 mg (0.19 mmol) of aminomethyl-PS resin (0.95 mmol/g, 500−550 mm, Rapp polymere). A solution of 30% triethylamine in CH_2Cl_2 (5 mL) was added to the resin, and this solution was agitated for 10−15 min to remove acidic impurities. The solution was drained, and this step was repeated a second time. The resin was washed with CH_2Cl_2 (5 × 5 mL) and DMF (5 × 5 mL). To this resin were added Fmoc-Rink linker (205 mg, 0.38 mmol), 1,3-diisopropylcarbodiimide (0.06 mL, 0.38 mmol), 1-hydroxybenzotriazole (51 mg, 0.38 mmol), and DMF (0.40 mL). The reaction solution was agitated for 20 h at room temperature. The solution was drained, and the resin was washed with DMF (5 × 5 mL). A solution (5 mL) of 20% piperidine in DMF was added to this resin, and the reaction solution was agitated for 30 min at room temperature. Another 5 mL of 20% piperidine in DMF was added, and the resin was agitated for 30 min. The resin was then washed with DMF (5 × 5 mL). The deprotected amine was acylated by adding 3.2 mL of 0.6 M bromoacetic acid in DMF (3.8 mmol) and 0.8 mL of 3.2 M 1,3-diisopropylcarbodiimde in DMF (3.8 mmol). The solution was agitated for 1 h at room temperature and then drained. This step was repeated. The resin was washed with DMF (5 × 5 mL) and DMSO (2 × 5 mL). To this resin was added 1-(3-aminopropyl)imidazole (0.23 mL, 1.9 mmol) in DMSO (1.7 mL), and the solution was agitated for 12 h at room temperature and then drained. The resin was washed with DMSO (5 × 5 mL) and DMF (5 × 5 mL). To the resulting resin was added a solution of succinic anhydride (190 mg, 1.9 mmol) in DMF (1.7 mL) and pyridine (0.15 mL, 1.9 mmol), and the solution was agitated for 12 h at room temperature and then drained. The resin was washed with DMF (5 × 5 mL) and CH_2Cl_2 (5 × 5 mL). To the resin **27** was added a solution of 30% trifluoroacetic acid in CH_2Cl_2, and the solution was stirred for 2 h at room temperature. The solution was filtered through Celite, and the resin residue was rinsed with CH_2Cl_2. The filtrate was concentrated in vacuo to yield target peptoid **23** in quantitative yield (53 mg, 98%) and high purity (95%, measured by HPLC). IR (thin film) 3477, 2985, 2942, 2629, 2477, 2240, 1641, 1593 cm^{-1}; ^{1}H NMR ($CDCl_3$, crude **23** (major) + rotamer (minor)) δ 8.80 (s, 1H, rotamer), 8.72 (s, 1H), 7.53 (s, 1H, rotamer), 7.50 (s, 1H), 7.40 (s, 1H, rotamer), 7.38 (s, 1H), 4.23−3.90 (m, 4H), 3.49 (s, 2H), 3.40−3.30 (m, 2H), 2.46 (m, 4H), 2.09, (m, 1H), 1.94 (m, 1H); HPLC 95% purity. HRMS (FAB) calcd for $C_{12}H_{19}N_4O_4$ $[M + H]^+$: 283.1406. Found: 283.1405.

***N*,*N*-Dimethyl-2-[(pyridin-2-ylmethyl)amino]acetamide.** To a solution of 2-(aminomethyl)pyridine (4.66 mL, 45.0 mmol) in DMF (10 mL) was added a solution of 2-bromo-*N*,*N*-dimethylacetamide (1.0 g, 6.0 mmol) in DMF (9 mL) dropwise at room temperature. After being stirred

for 10 h, the reaction solution was concentrated in vacuo to remove excess 2-(aminomethyl)pyridine and DMF. The crude residue was washed with H_2O, extracted with CH_2Cl_2 (3 × 50 mL), and concentrated. The residue was purified by flash column chromatography using 2% MeOH in CH_2Cl_2 as eluent to afford pure acetamide (1.04 g, 90%) as a colorless oil. $R_f = 0.53$ (1:1, MeOH/CH_2Cl_2); IR (thin film) 3325, 3009, 2928, 1652, 1591 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.54 (m, 1H), 7.64 (dt, J = 1.8, 7.5 Hz, 1H), 7.39 (d, J = 7.5 Hz, 1H), 7.15 (m, 1H), 3.97 (s, 2H), 3.47 (s, 2H), 2.97 (s, 3H), 2.93 (s, 3H), 2.67 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 170.4, 159.5, 148.9, 136.2, 121.8, 121.6, 55.0, 49.7, 35.9, 35.4. HRMS (FAB) calcd for $C_{10}H_{15}N_3O$ [M]$^+$: 193.1215. Found: 193. 1217.

3-(Dimethylcarbamoylmethylpyridin-2-ylmethylcarbamoyl)-5,6-dihydro-[1,4]dithiine-2-carboxylic Acid (24). To a solution of *N*,*N*-dimethyl-2-[(pyridin-2-ylmethyl)amino]-acetamide (1.0 g, 5.18 mmol) in DMF (15 mL) were added pyridine (1.23 mL, 15.5 mmol) and 2,3-dihydro[1,4]dithiino-[2,3-*c*]furan-5,7-dione (0.975 g, 5.18 mmol) at room temperature. After being stirred for 12 h, the reaction mixture was concentrated. The residue was purified by flash column chromatography using deactivated silica gel and 10% MeOH in CH_2Cl_2 (containing 2% NEt_3) as eluent to afford dimethylamide **24** as the triethylammonium salt (pale-yellow sticky solid, 2.12 g, 85%). $R_f = 0.33$ (1:1, MeOH/CH_2Cl_2); IR (thin film) 2983, 2466, 2232, 1644, 1557 cm^{-1}; ^{1}H NMR ($CDCl_3$, major) δ 8.49 (m, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.69−7.61 (m, 1H), 7.16 (m, 1H), 4.83 (s, 2H), 4.23 (s, 1H), 3.84 (s, 1H), 3.19 (s, 4H), 2.94 (s, 3H), 2.86 (s, 3H); ^{1}H NMR ($CDCl_3$, rotamer (minor)) δ 8.49 (m, 1H), 7.77 (d, J = 8.6 Hz, 1H), 7.69−7.61 (m, 1H), 7.23 (m, 1H), 4.91 (s, 2H), 4.28 (s, 2H), 3.19 (s, 4H), 2.92 (s, 3H), 2.90 (s, 3H); ^{13}C NMR ($CDCl_3$, major) δ 169.1, 166.6, 165.7, 156.6, 148.2, 136.2, 129.1, 124.7, 123.0, 121.9, 55.1, 45.5, 36.1, 35.2, 27.6, 27.4; Rotamer (minor): δ 169.1, 167.2, 166.1, 156.9, 147.7, 136.4, 128.2, 125.4, 122.3, 121.5, 50.8, 48.9, 36.3, 35.3, 27.7, 27.4. HRMS (FAB) calcd for $C_{16}H_{20}N_3O_4S_2$ [M + H]$^+$: 382.0895. Found: 382.0893.

***N*,*N*-Dimethyl-2-[(pyridin-3-ylmethyl)amino]acetamide.** To a solution of 3-(aminomethyl)pyridine (6.91 mL, 67.8 mmol) in DMF (15 mL) was added a solution of 2-bromo-*N*,*N*-dimethylacetamide (1.5 g, 9.04 mmol) in DMF (15 mL) dropwise at room temperature. After being stirred for 10 h, the reaction solution was concentrated in vacuo to remove excess 3-(aminomethyl)pyridine and DMF. The crude residue was washed with H_2O, extracted with CH_2Cl_2 (3 × 60 mL), and concentrated. The residue was purified by flash column chromatography using 2% MeOH in CH_2Cl_2 as eluent to afford pure acetamide (1.67 g, 95%) as a colorless oil. $R_f = 0.48$ (1:1, MeOH/CH_2Cl_2); IR (thin film) 3318, 3029, 2929, 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.57 (m, 1H), 8.50 (dd, J = 1.8, 4.8 Hz, 1H), 7.72 (m, 1H), 7.25 (ddd, J = 0.6, 4.8, 7.8 Hz, 1H), 3.83 (s, 2H), 3.40 (s, 2H), 2.98 (s, 3H), 2.92 (s, 3H), 2.34 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 170.4, 149.5, 148.3, 135.6, 135.2, 123.2, 50.9, 49.4, 35.9, 35.4. HRMS (FAB) calcd for $C_{10}H_{15}N_3O$ [M]$^+$: 193.1215. Found: 193. 1211.

***N*-Dimethylcarbamoylmethyl-6-hydroxy-*N*-pyridin-3-ylmethylphthalamic Acid (25).** To a solution of *N*,*N*-dimethyl-2-[(pyridin-3-ylmethyl)amino]acetamide (1.01 g, 5.23 mmol) in DMF (15 mL) were added pyridine (1.27 mL, 15.7 mmol) and 3-hydroxyphthalic anhydride (0.86 g, 5.23 mmol) at room temperature. After being stirred for 12 h, the reaction mixture was concentrated. The residue was purified by flash column chromatography using deactivated silica gel and 20% MeOH in CH_2Cl_2 (containing 2% NEt_3) as eluent to afford dimethylamide **25** as the triethylammonium salt (colorless sticky solid, 2.08 g, 87%). $R_f = 0.42$ (1:1, MeOH/CH_2Cl_2); IR (thin film) 3477, 2985, 2942, 2629, 2477, 2240, 1641, 1593 cm^{-1}; ^{1}H NMR ($CDCl_3$, **III-137**/rotamer (∼1.1:1)) δ 8.82 (d, J = 1.8 Hz, 1H), 8.56 (d, J = 2.1 Hz, 1H), 8.48 (dd, J = 1.5, 4.8 Hz, 1H), 8.46 (dd, J = 1.5, 4.8 Hz, 1H), 7.93 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.32−7.17 (m, 4H), 6.91−6.85 (m, 3H), 6.67 (dd, J = 0.9, 7.5 Hz, 1H), 5.63 (d, J = 15.6 Hz, 1H), 4.85 (d, J = 15.6 Hz, 1H), 4.62 (d, J = 15.6 Hz, 1H), 4.36 (d, J = 15.9 Hz, 2H), 4.02 (d, J = 16.8 Hz, 1H), 3.59 (d, J = 16.8 Hz, 1H), 3.49 (d, J = 16.2 Hz, 1H), 2.95 (s, 3H), 2.92 (s, 3H), 2.82 (s, 3H), 2.51 (s, 3H); ^{13}C NMR ($CDCl_3$, **III-137**) δ 173.0, 172.3, 167.3, 161.6, 149.2, 147.8, 138.1, 135.6, 132.7, 131.4, 122.73, 116.7, 115.9, 115.2, 47.7, 45.7, 35.8, 35.1; ^{13}C NMR (rotamer) δ 173.1, 172.0, 167.1, 161.8, 149.4, 148.3, 138.4, 135.9, 131.9, 131.6, 122.68, 116.6, 116.5, 115.4, 50.8, 43.7, 36.0, 35.2. HRMS (FAB) calcd for $C_{18}H_{20}N_3O_5$ [M + H]$^+$: 358.1403. Found: 358.1406.

2-(3-Imidazol-1-ylpropylamino)-*N*,*N*-dimethylacetamide (26). To a solution of 1-(3-aminopropyl)imidazole (8.09 mL, 67.8 mmol) in DMF (15 mL) was added a solution of 2-bromo-*N*,*N*-dimethylacetamide (1.5 g, 9.04 mmol) in DMF (15 mL) dropwise at room temperature. After being stirred for 24 h, the reaction solution was concentrated in vacuo to remove excess 1-(3-aminopropyl)imidazole and DMF. The crude residue was washed with H_2O, extracted with CH_2Cl_2 (3 × 60 mL), and concentrated. The residue was purified by flash column chromatography using 10% MeOH in CH_2Cl_2 as eluent to afford pure acetamide **26** (1.67 g, 87%) as a colorless oil. $R_f = 0.28$ (1:1, MeOH/CH_2Cl_2); IR (thin film) 3315, 3106, 2935, 1649, 1508 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.48 (s, 1H), 7.02 (s, 1H), 6.94 (t, J = 1.2 Hz, 1H), 4.07 (t, J = 6.9 Hz, 2H), 3.36 (s, 2H), 2.96 (s, 3H), 2.94 (s, 3H), 2.57 (t, J = 6.6 Hz, 2H), 2.19 (bs, 1H), 1.94 (qn, J = 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 170.2, 136.7, 128.7, 118.4, 49.9, 45.9, 44.1, 35.5, 35.1, 31.0. HRMS (FAB) calcd for $C_{10}H_{18}N_4O$ [M]$^+$: 210.1481. Found: 210.1482.

***N*-Dimethylcarbamoylmethyl-6-hydroxy-*N*-(3-imidazol-1-ylpropyl)phthalamic Acid (27) + *N*-Dimethylcarbamoylmethyl-3-hydroxy-*N*-(3-imidazol-1-yl-propyl)phthalamic Acid (28).** To a solution of 2-(3-imidazol-1-ylpropylamino)-*N*,*N*-dimethylacetamide (**26**) (0.82 g, 3.90 mmol) in DMF (10 mL) were added pyridine (0.95 mL, 11.7 mmol) and 3-hydroxyphthalic anhydride (0.64 g, 3.90 mmol) at room temperature. After being stirred for 12 h, the reaction mixture was concentrated. The residue was purified by flash column chromatography using deactivated silica gel and 50% MeOH in CH_2Cl_2 (containing 2% NEt_3) as eluent to afford a mixture of dimethylamide **27** (major) and regioisomer **28**

(minor) as the triethylammonium salt (pale-yellow sticky solid, 1.29 g, 70%). $R_f = 0.34$ (7:3, MeOH/CH_2Cl_2); IR (thin film) 3295, 3115, 2985, 2944, 2475, 2240, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, **27** (major)) δ 8.14 (s, 1H), 7.22−7.14 (m, 2H), 7.06 (s, 1H), 6.88−6.78 (m, 2H), 6.55 (dd, $J = 1.5$, 7.5 Hz, 1H), 4.32−4.21 (m, 1H), 4.06 (d, $J = 17.1$ Hz, 1H), 3.93 (m, 1H), 3.70 (d, $J = 17.1$ Hz, 1H), 3.36−3.16 (m, 2H), 2.81 (s, 3H), 2.60 (s, 3H), 2.20−1.87 (m, 2H); ^1H NMR ($CDCl_3$, **28** (regioisomer, minor)) δ 8.09 (s, 1H), 7.21 (d, $J = 3.3$ Hz, 1H), 7.11−7.00 (m, 2H), 6.93−6.79 (m, 2H), 6.65 (dd, $J = 1.2$, 7.2 Hz, 1H), 4.91 (d, $J = 15.9$ Hz, 1H), 4.32−4.21 (m, 1H), 3.93 (m, 1H), 3.77 (m, 1H), 3.58 (d, $J = 15.9$ Hz, 1H), 3.30 (m, 1H), 3.04 (s, 3H), 3.00 (s, 3H), 2.20−1.89 (m, 2H); ^1H NMR ($CDCl_3$, rotamer (minor)) δ 7.49 (s, 1H), 7.26 (d, $J = 7.2$ Hz, 1H), 7.11−7.00 (m, 2H), 6.87−6.79 (m, 2H), 6.70 (dd, $J = 1.2$, 7.2 Hz, 1H), 4.46−4.37 (m, 2H), 4.32−4.21 (m, 2H), 3.34−3.26 (m, 2H), 3.02 (s, 3H), 2.97 (s, 3H), 2.20−1.89 (m, 2H); ^{13}C NMR ($CDCl_3$, **27** (major)) δ 173.2, 172.0, 167.5, 161.7, 138.4, 136.4, 131.5, 124.9, 119.4, 116.8, 115.7, 115.1, 48.8, 44.7, 41.9, 35.9, 35.3, 28.3; ^{13}C NMR ($CDCl_3$, **28** (regioisomer, minor)) δ 172.2, 172.1, 167.6, 161.8, 139.8, 136.5, 131.7, 127.3, 118.5, 116.6, 115.8, 115.3, 47.1, 46.3, 44.4, 36.2, 35.4, 29.1; ^{13}C NMR ($CDCl_3$, rotamer (minor)) δ 172.8, 161.4, 136.1, 131.1, 125.3, 117.0, 116.2, 45.2, 44.3, 35.5, 30.6. HRMS (FAB) calcd for $C_{18}H_{23}N_4O_5$ $[M + H]^+$: 375.1668. Found: 375.1667.

5-Isopropyl-3,8-dimethylazulene-1-carboxylic Acid 4 Nitrophenyl Ester (29). To a solution of guaiazulene (1.2 g, 6.05 mmol) in toluene was added a solution of phosgene (20% in toluene, 30 mL, 60.5 mmol) at room temperature. After the mixture was stirred for 2 h, excess phosgene and toluene were removed in vacuo and then the residue was dissolved in THF. To this solution were added a solution of 4-nitrophenol (1.69 g, 12.1 mmol) in THF and pyridine (5.9 mL, 72.6 mmol) at room temperature, and the mixture was stirred overnight. The residue was purified by flash column chromatography using 10% ethyl acetate in hexanes as eluent to afford pure guaiazulenyl 4-nitrophenyl ester **29** (0.568 g, 26%) as a purple solid. $R_f = 0.32$ (1:4, EtOAc/hexane); IR (thin film) 2961, 1719, 1519, 1406, 1344, 1173 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.31 (d, $J = 2.1$ Hz, 1H), 8.27 (m, 2H), 8.20 (s, 1H), 7.61 (dd, $J = 2.4$, 10.8 Hz, 1H), 7.40 (m, 3H), 3.16 (sep, $J = 6.9$ Hz, 1H), 3.06 (s, 3H), 2.62 (d, $J = 0.6$ Hz, 3H), 1.39 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 162.5, 156.6, 148.3, 145.6, 144.6, 142.2, 141.2, 138.6, 136.5, 134.7, 132.4, 125.0 (2C), 124.5, 122.5 (2C), 113.3, 38.1, 28.5, 24.6 (2C), 13.0. Anal. Calcd for $C_{22}H_{21}NO_4$: C, 72.73; H, 5.79; N, 3.86. Found: C, 72.96; H, 5.90; N, 3.90.

Library Synthesis. Solid-phase combinatorial library synthesis was performed with aminomethyl-PS resin (0.95 mmol/g, 500−550 μm, Rapp polymere, item polystyrene AM-NH_2, order no. H500560.02.) using peptide synthesis vessels. To the resin (3.0 g, 2.85 mmol) were added a solution of bromoacetic acid (53.4 mL, 0.8 M, 42.75 mmol) in DMF and DIC (6.7 mL, 42.75 mmol). The reaction mixture was agitated for 3 h at room temperature and drained, and the resulting resin was washed with DMF (3 × 5 mL). The reaction was repeated. Resin-bound bromoacetamide was split into nine pools and washed with DMSO (2 × 5 mL). Nine individual ^{19}F tags, **14a**−**22a** (3.17 mmol, 0.7 M in DMSO), were added to each pool (0.317 mmol), and the nine reaction mixtures were agitated for 2 days at room temperature. The nine resin-bound amines were bromoacetylated with bromoacetic acid (5.9 mL, 0.8 M, 4.75 mmol) in DMF with DIC (0.7 mL, 4.75 mmol). The nine resin-bound bromoacetamides were washed with DMF (3 × 5 mL) and DMSO (2 × 5 mL) and then displaced by the addition of the nine individual amines as a solution in DMSO (3.17 mmol, 1.0 M, 12 h, room temperature). The resin in the nine pools was washed with DMF (3 × 5 mL) and then pooled and mixed thoroughly. The resins were split into 10 pools (0.285 mmol for each pool). Individual 10 anhydrides in DMF (2.85 mmol, 1.0 M) and pyridine (0.23 mL, 2.85 mmol) were added to the 10 pools, and the reaction mixtures in 10 pools were agitated for 12 h at room temperature. The resins in each pool were washed with DMF (3 × 5 mL) and THF (2 × 5 mL). TBAF (2.85 mL, 1.0 M in THF, 2.85 mmol) was added to each pool, and the reaction mixtures were agitated for 10 h at room temperature. The resins were washed with THF (3 × 5 mL) and MeOH (3 × 5 mL) to give 90 resin-bound peptoids (9 compounds (each pool) × 10 pools = 90 compounds). The 10 pools were kept separate in the dark for screening.

Solid-Phase Binding Assay. The solid-phase substrate library was prepared by the encoded split synthesis in 10 pools as described above. Each pool contained nine different peptoids corresponding to the combination of nine amines and one specific anhydride. To screen the substrate library, 90 beads (10 beads per compound) from each pool were transferred to a 2-dram vial and the solution for assay (Cu^{2+}, Fe^{3+}, Co^{2+}, or **29**) was added to the vial (total of 10 vials). The mixtures were agitated on a wrist action shaker for 48 h at room temperature. The concentration of the solution was increased from 0.1 mM until stained beads were observed (more concentrated solution was displaced after several washings with the same solution). The resin-bound bromoacetamide **31** was used as a control to ensure that the binding (or acylation) was specific for the peptoid in question.

Cu(II) Binding. After agitation with 4.0 mM $Cu(OTf)_2$ in CH_3CN for 48 h at room temperature, ∼10% of the beads in only one pool (no. 6) were found to be stained sky-blue. Ten sky-blue beads in pool 6 were picked by hand using a Pasteur pipette and transferred to a 1-dram vial. The selected beads were washed with THF thoroughly and then subjected to photochemical cleavage as described below.

Fe(III) Binding. After agitation with 5.0 mM Fe(2-ethylhexanoate)$_3$ in THF at room temperature, the beads in only one pool (no. 10) were stained from dark-red to orange-yellow. The colored beads in pool 10 were washed with THF thoroughly and then stratified into 4 groups based on gradation of color intensity (dark-red, red, red-orange, and orange-yellow). The beads in each group were subjected to photochemical cleavage as described below.

Co(II) Binding. After agitation with 2.0 mM Co(2-ethylhexanoate)$_2$ in THF at room temperature, 10−60% of the beads in all 10 pools were stained dark-purple. The colored beads were picked, washed with THF, and irradiated as described below.

Acylation with 29. After agitation with 20.0 mM guaiazulenyl ester **29** in THF in the presence of pyridine (20.0 mM) at room temperature, 10−60% of the beads in all 10 pools were stained purple. The colored beads were picked out, washed with THF, and irradiated as described below.

Tag Cleavage and ^{19}F NMR Analysis. Stained beads were picked up from each reaction vial with the aid of a Pasteur pipette and placed in another clean vial (1 dram). The selected beads were washed with THF (3 × 2 mL), and the vial was filled with 1.8 mL of THF and capped tightly under argon. The vial was irradiated at 350 nm for 12 h with vigorous stirring using a Rayonet photochemical reactor. The reaction mixture was concentrated and diluted with $CHCl_3$. The solution was filtered through a syringe filter (0.2 mm), transferred to a V vial (1 mL), and concentrated. The released tags were dissolved in 12 μL of $CDCl_3$ containing a small amount of fluorobenzene as an internal standard. The solution was transferred very carefully to a capillary NMR tube (8 μL/cm) to fill 1.5 cm of the tube. The capillary NMR tube was held by a Teflon holder placed inside a normal 5 mm NMR tube that already contained 0.6 mL of D_2O. The tags released from the selected beads by photochemical reaction were analyzed by ^{19}F NMR (20−25 min acquisition).

Spectrophotometric Titration with Cu(II). A solution of peptoid **24** in 2 mL of CH_3CN (0.05 mM) was placed into the sample cuvette, which contained a small stirring bar. The reference cuvette contained the solvent, CH_3CN, and a small stirring bar. A baseline of peptoid against solvent was recorded from 340 to 450 nm. Aliquots (7 μL) of $Cu(OTf)_2$ solution in CH_3CN (0.05 mM) were added to both sample and reference cuvettes, and the solutions were stirred for 2 min to allow the samples to reach equilibrium. A scan from 340 to 450 nm was taken after the addition of each aliquot of Cu^{2+}. The resulting difference spectra were analyzed by plotting the absorbance maximum (390 nm) against the volume of Cu^{2+}.

Spectrophotometric Titration with Fe(III). A solution of peptoid **25** in 2 mL of CH_3CN (0.06 mM) was placed into the sample cuvette, which contained a small stirring bar. The reference cuvette contained the solvent, THF/CH_3CN (v/v, 2:1), and a small stirring bar. A baseline of peptoid against solvent was recorded from 390 to 600 nm. Aliquots (40 μL) of Fe(2-ethylhexanoate)$_3$ solution in THF/CH_3CN (v/v, 2:1) (0.32 mM) were added to both sample and reference cuvettes, and the solutions were stirred for 2 min to allow the samples to reach equilibrium. A scan from 390 to 600 nm was taken after the addition of each aliquot of Fe^{3+}. The resulting difference spectra were analyzed by plotting the absorbance maximum (485 nm) against the volume of Fe^{3+}. For the mixture of peptoids **27** and **28**, a scan from 380 to 600 nm was taken and the maximum absorbance was found at 469 nm.

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Supporting Information Available. Figures S1 and S2 showing encoding of cobalt binding for the peptoid library and the titration curve for Figure 3, respectively. This material is available free of charge via the Internet at http://pubs.acs.org.

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