JOURNAL OF combinatorial CHEMISTRY

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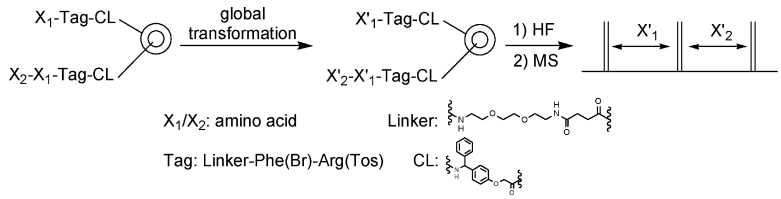
J. Comb. Chem., **2008**, 10 (2), 333-342• DOI: 10.1021/cc700165s • Publication Date (Web): 09 January 2008



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Global Transformation of OBOC Combinatorial Peptide Libraries into OBOC Polyamine and Small Molecule Libraries

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Received October 12, 2007

In "one-bead-one-compound" (OBOC) combinatorial chemistry, a compound-bead library with hundreds of thousands to millions of diversities can be rapidly generated such that each bead displays only one chemical entity. The highly efficient "libraries-from-libraries" approach involves the global transformation of a peptide library into many small molecule solution-phase mixture libraries, but this approach has never been successfully applied to OBOC libraries. Here we report a novel approach that allows us to combine these two enabling technologies to efficiently generate OBOC encoded small molecule bead libraries. By using a topologically segregated bilayer bead and a "ladder-synthesis" method, we can prepare peptide libraries with the peptide on the bead surface and a series of peptide ladders in the bead interior. Various global transformation reactions can then be employed to transform the starting peptide library into a variety of peptidomimetic libraries. During the transformation reactions, the peptide ladders in the bead interior are also transformed in a predictable manner. As a result, individual compound bead can be decoded by analyzing the hydrogen fluoride-released encoding tags with matrix-assisted laser desorption ionization Fourier transform mass spectrometry. Using this novel approach, a random encoded dipeptide library was prepared and subsequently transformed into polyamine and poly-*N*-acetylamine sublibraries. Random beads isolated from these sublibraries were reliably decoded.

Introduction

Combinatorial chemistry describes the rapid synthesis of large numbers of structurally similar molecules and, in conjunction with high-throughput screening strategies, offers a convenient way to identify ligands with high-binding affinities.[1–7] In the "one-bead-one-compound" (OBOC) method,[8] a "split-mix" synthetic approach[8–10] is used to prepare thousands to millions of compounds on individual beads, each of which contains a single chemical entity. On-bead screening assays against various biological targets of interest are then used to identify positive beads which can then be removed for decoding. OBOC libraries have been used to identify ligands for different biological targets including protein kinase substrates and inhibitors,[11,12] protease substrates and inhibitors,[13–17] cell surface receptors,[18–23] and artificial enzymes.[24,25]

Structural determination of hit compounds from fully deprotected, α-amino acid-containing peptide and peptoid OBOC libraries is straightforward by direct Edman microsequencing which sequentially identifies the constituent amino acid residues of the molecule. This technique restricts the composition of library compounds to α-amino acid building blocks, thus other decoding strategies are required for non-α-amino acid-containing peptides, branched peptides, peptidomimetics, and small molecules. For these nonsequenceable libraries, chemical encoding methods are often used in which a coding tag provides a record describing the synthetic history of each bead. We have reported chemical encoding strategies based on Edman microsequencing and mass spectrometry (MS) for nonsequenceable libraries.[26–29]

In chemically encoded OBOC libraries, at least two compounds are present on each bead, the coding tags and the target (testing) compound. In biological screening assays, the interaction between receptors and resin-bound ligands occurs at the bead surface. To minimize interference from the coding tags, it is preferable to prepare beads with a homogeneous outer layer containing only the testing compound and segregate the coding tags in the inner layers where the binding receptors do not penetrate. Thus, a key aspect of our encoding strategies is the use of topologically segregated bilayer beads. Two methods have been developed that are routinely used in our laboratory for this purpose. The first of these methods is the "partial amine-protection"

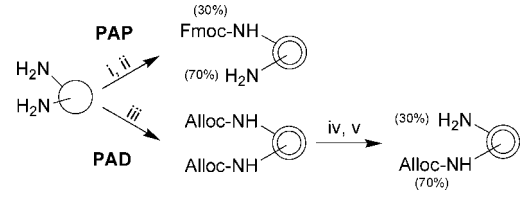

Figure 1. PAP and PAD bilayer bead synthetic approaches. Reagents and conditions: (i) swell in water for 24 h; (ii) Fmoc-OSu (0.3 equiv), DIEA (0.6 equiv), DCM–Et_2O (55:45), 30 min; (iii) Alloc-OSu (3 equiv), DIPEA (6 equiv), 1 h; (iv) swell in water for 5 h; (v) $Pd(PPh_3)_4$ (0.24 equiv), $PhSiH_3$ (20 equiv), DCM, 9 min.

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10.1021/cc700165s CCC: $40.75
Published on Web 01/09/2008

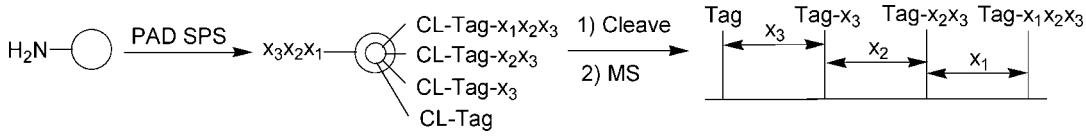


Figure 2. Mass spectrometry-based sequencing with the PAD synthesis method.

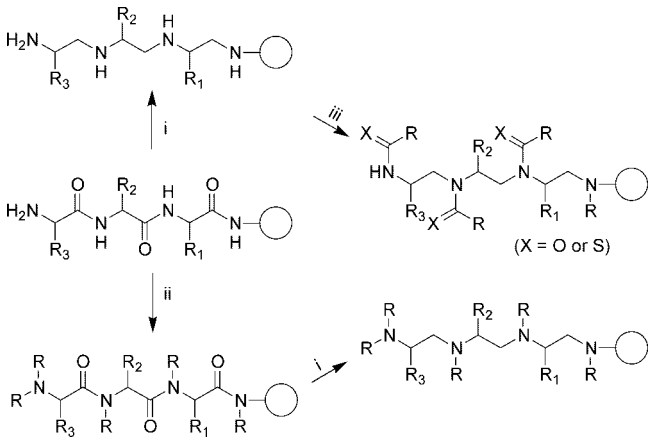
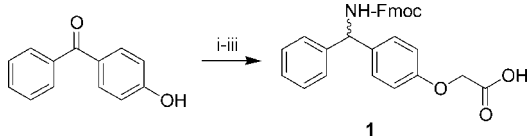


Figure 3. Global transformations of resin-bound peptides to generate peptidomimetic libraries from libraries. Reagents and conditions: (i) BH_3–THF; (ii) Li-*t*BuO, R-X; (iii) RNCX.

Scheme 1. Synthesis of Cleavable Linker **1**[a]



1

[a] Reagents and conditions: (i) Br-CH_2-CO_2H, K_2CO_3, acetone, reflux, 8 h; (ii) $NaBH_4$, EtOH–*i*PrOH–H_2O (2.5:2.5:1.0), 0 °C, 1 h then 0 to 20 °C, 1 h; (iii) Fmoc-NH_2, AcOH, TsOH, 20 °C, 12 h.

(PAP) bilayer approach.[27] Using Tentagel resin, biphasic solvent conditions are used to selectively protect the amino functionalities on the outer layer of the beads, while the inner core remains underivitized (Figure 1). "Partial alloc-deprotection" (PAD) is another approach for making bilayer beads.[29] In this method, resin beads with alloc group protection are swollen in water and then treated with $Pd(Ph_3)_4$/$PhSiH_3$ for a certain amount of time, resulting in deprotection of the outer-layer amino groups (Figure 1).

The ability to generate bilayer beads at any step in a reaction sequence allows for the possibility of using a "ladder-synthesis" encoding approach. Ladder synthesis using the PAD method has been used to encode OBOC libraries.[29] A cleavable linker (CL) is first inserted on the inner layer of the beads, and a multicomponent MS tag is assembled on the linker. Peptide synthesis with repetitive PAD cycles is used to assemble the peptide and corresponding ladders. The ladders are chemically cleaved, and the mass difference between each of the ladders is used to decode the compound structure (Figure 2).

A powerful technique for expanding the potential of combinatorial chemistry is the "libraries-from-libraries" method.[30,31] This concept describes the transformation of resin-bound amino acids, peptides, and peptidomimetics into low molecular weight heterocyclic and acyclic compounds. Global transformation reactions (reduction, oxidation, alkylation, and acylation) are performed on a parent library, modifying a particular functional group, to generate a sublibrary. This process can be repeated in turn so that a series of diverse libraries can be rapidly synthesized from the parent library. Figure 3 illustrates these possibilities starting from resin-bound tripeptide library. Exhaustive reduction of the peptide backbone yields a polyamine library, which treated with isocyanates or isothiocyanates generates a polyurea (X = O) or polythiourea (X = S) library, respectively. Alternatively, peralkylation of tripeptide generates a peptidomimetic library, which gives a polyamine sublibrary after reduction. In addition to these acyclic sublibraries, the libraries-from-libraries approach has been used to prepare low molecular weight heterocycles.

Methodology to access to peptidomimetic and small molecules is an important tool for drug discovery. Although peptides can be routinely synthesized and have high binding specificity, they are limited as drug candidates because of a lack of in vivo stability, susceptibility to proteolysis, and poor bioavailability.[32–36] In contrast, compounds synthesized with the libraries-from-libraries approach have vastly different physiochemical properties with respect to the original peptide library offering a means for discovering ligands more likely suited for drug development. This paper describes our efforts to combine the inherent power of the OBOC method with the libraries-from-libraries concept using chemical encoding as a means for discovering high-affinity drug-like ligands.

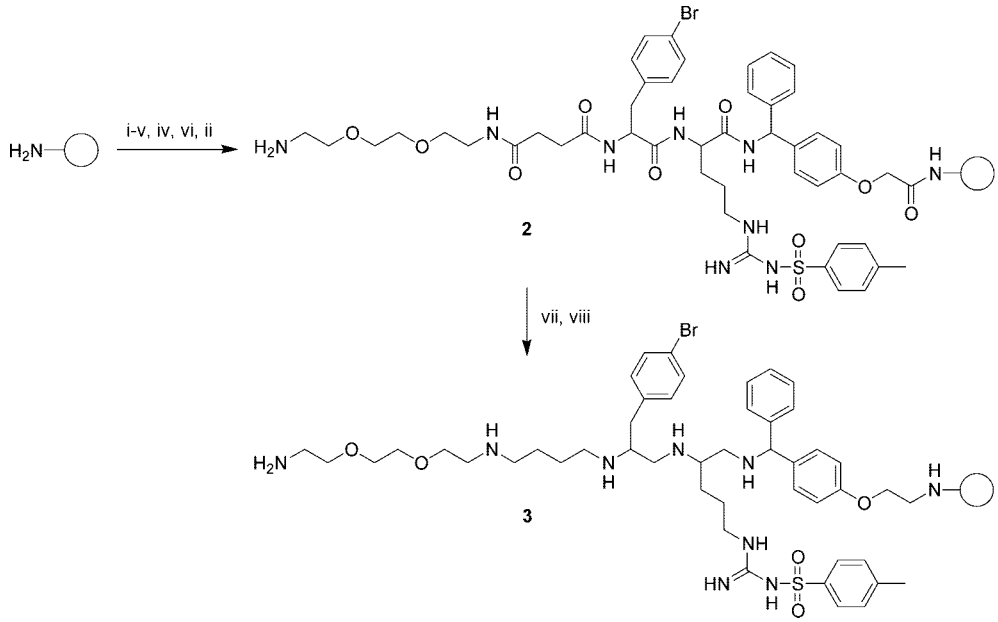
Results and Discussion

MS-based chemical encoding strategies require an additional step, in which the coding molecules are removed from the solid support for analysis. A cleavable linker facilitates this process and is chosen or designed for a particular synthesis according to the following criteria: it should be (i) selectively cleavable, (ii) stable to the conditions of the library synthesis, and (iii) capable of facilitating MS analysis and peak identification. We based our cleavable linker on the MBHA resin, and a literature search revealed *N*-tertbutoxy-carbonyl-aminomethyl(α-phenyl) phenoxy acetic acid,[37] the Boc group version of compound **1**, as an ideal choice.

Linker **1** was synthesized based on literature precedents[38–40] in a three-step procedure (Scheme 1). 4-Hydroxybenzophenone was alkylated with α-bromoacetic acid and, after reduction of the ketone intermediate, displacement with 9-fluorenylmethylcarbamate (Fmoc-NH_2) provided protected linker **1**.

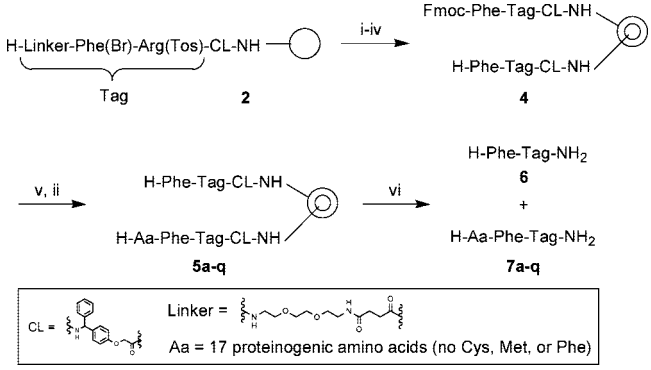
Linker **1** was used in conjunction with our previously described multicomponent MS-coding tag,[41] which is composed of the amino acids arginine, 4-bromophenylalanine, and 2,2′-ethylenedioxybis(ethylamine)monosuccinamide (Ebes).[42] The rationalization for each of these components is (i) Arg provides a protonation site to help generate a strong MS signal, (ii) Phe(4-Br) generates a distinctive isotopic

Scheme 2. Synthesis and Reduction of the Mass Spectrometry Coding Tag on Tentagel Beads[a]



[a] Reagents and conditions: (i) **1**, DIC, HOBt, DMF; (ii) 25% piperidine/DMF; (iii) Boc-Arg(Tos)-OH, DIC, HOBt, DMF; (iv) TFA–DCM (1:1), 30 min; (v) Boc-Phe(4-Br)-OH, DIC, HOBt, DMF; (vi) *N*-Fmoc-2,2′-ethylenedioxy-bis(ethylamine) monosuccinamide, DIC, HOBt, DMF; (vii) $B(OH)_3$, $B(OCH_3)_3$, 1 M BH_3–THF, 65 °C, 72 h; (viii) piperidine, 65 °C, 16 h.

Scheme 3. Synthesis and Cleavage of a Model Parallel Dipeptide Library[a]



[a] Reagents and conditions: (i) Fmoc-Phe-OH, DIC, HOBt, DMF; (ii) 25% piperidine−DMF; (iii) swell in H_2O, 5 h; (iv) Fmoc-OSu (0.4 equiv), DIEA (0.8 equiv), DCM–Et_2O (55:45), 30 min; (v) Fmoc-Aa-OH, DIC, HOBt, DMF; (vi) anisole vapors then HF, 20 °C, 2 h.

pattern allowing easy identification of relevant peaks, and (iii) Ebes is a hydrophilic spacer, which facilitates post cleavage extraction and provides additional mass so the peaks of interest will be pushed beyond the matrix region of the spectrum. The coding tag was assembled as illustrated in Scheme 2. Linker **1** was coupled to Tentagel resin, and following Fmoc deprotection, the coding tag elements were coupled in sequential order to give resin **2**. A single bead of **2** was treated with hydrogen fluoride (HF) gas to release the coding tag, which was easily detected by MALDI-TOF MS (Figure 4A). In anticipation of library synthesis, the coding tag was treated with diborane to generate polyamine resin **3**. Single-bead HF cleavage revealed the reduced coding tag (Figure 4B).

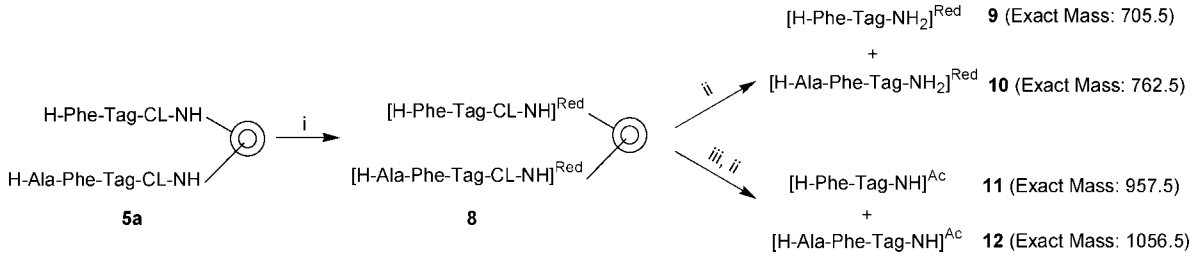
After the establishment of a single-bead HF cleavage protocol using linker **1**, a series of model-encoded peptides incorporating the above system was synthesized as a test of our ability to observe peptide ladders cleaved from single Tentagel beads (Scheme 3). Resin **2** was acylated with Fmoc-Phe-OH and, after Fmoc deblocking, vigorously shaken in water then reacted with 0.4 equiv of Fmoc-OSuc to generate the bilayer resin **4** in which the inner-layer Phe was unprotected. A series of Fmoc-protected amino acids were coupled to resin **4**, followed by Fmoc deblocking, to give the dipeptide ladder resins **5a**−**q**. A single bead from resins **5a**−**q** was treated with HF, and the crude cleavage products were analyzed by MALDI-MS. The results are summarized in Table 1. In each case, the expected masses of **7a**−**q** were easily observed in the respective spectrums. Figure 5 shows a representative example, in which the Ala−Phe (**7a**) and Phe (**6**) ladders were cleaved from resin **5a**.

To preview the global transformation chemistry we planned to use, resin **5a** was chosen as model system and was reacted under diborane reduction conditions to provide polyamine resin **8** (Scheme 4). Treatment of **8** with anisole then HF to cleave the polyamine ladders **9** and **10** revealed only a small signal for the Phe polyamine **9**, in addition to an unknown impurity with a *m*/*z* of 698.5 (Figure 6A). Because an amine-resin linkage is more stable and thus harder to cleave than the corresponding amide linkage it was proposed to extend the time of HF exposure of **7** to improve the cleavage yield and MS signaling. However, the same result was obtained when extending the cleavage time to 7h.

Alternatively, treatment of **8** with acetic anhydride and then anisole/HF was attempted to provide poly-*N*-acylamines **11** and **12**. The MS spectrum shows both of the expected products at 960.5 and 1059.6 *m*/*z* respectively (Figure 6B). Also present are two peaks (918.5 and 1017.6 *m*/*z*), which are 42 mass units less than **11** and **12**, respectively, indicating either incomplete acetylation or incomplete reduction.

OBOC library **13** (Scheme 5) was prepared to test the cleavage/decoding method on a completely random library. The synthesis used the same procedure as that for **5a**−**q** except

Scheme 4. Ladder synthesis of Ala−Phe-based peptidomimetics[a]



[a] Reagents and conditions: (i) $B(OH)_3$, $B(OCH_3)_3$, 1 M BH_3–THF, 65 °C, 72 h then piperidine, 65 °C, 16 h; (ii) anisole vapors, 5 h then HF, 20 °C, 2 h; (iii) Ac_2O, DIEA, DMF. Superscripts indicate the peptide has been globally modified: Red = reduced, Ac = acetylated.

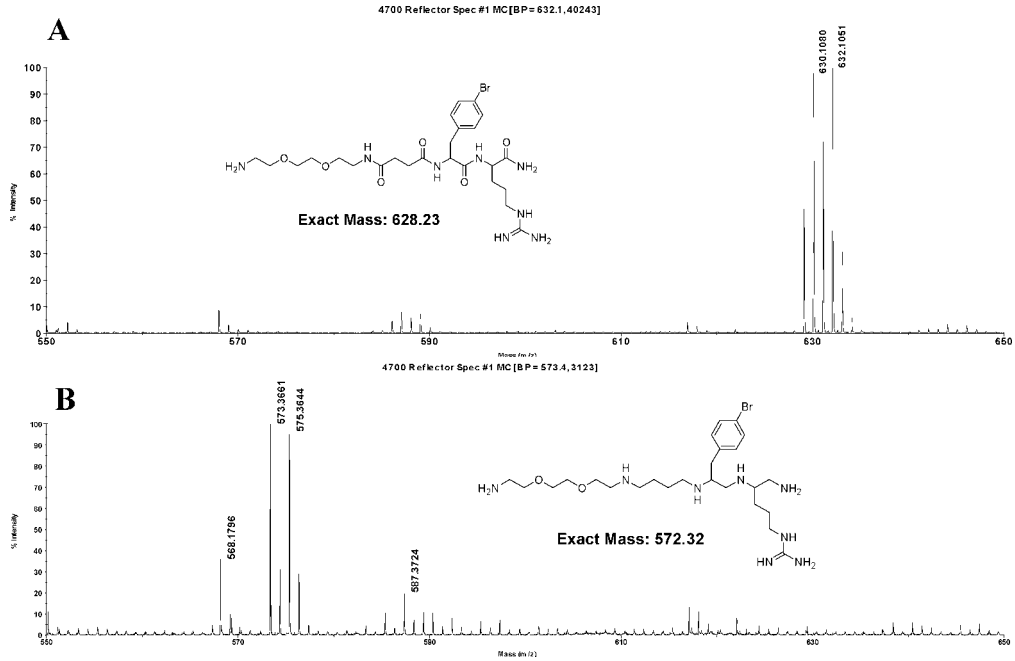


Figure 4. (A) Mass spectrum of the coding tag generated from cleavage of a single bead of resin **2** with gaseous HF. (B) Mass spectrum of the reduced coding tag generated from cleavage of a single bead of resin **3** with gaseous HF.

both Aa_1 and Aa_2 were randomized with 19 proteinogenic amino acids (Cys was not used) to give a dipeptide library with 361 permutations. After the library was synthesized, 20 beads were picked and subjected to the HF cleavage procedure. Following extraction with ACN–H_2O (1:1; 20 μL), the crude residue generated from each of the beads was analyzed by MALDI-TOF MS. Table 2 summarizes the results of the MS data. Each of the beads, with one exception (Table 2, entry 1), was decoded unambiguously by matching the spectrum peaks with the expected masses of the potential products.

Sublibraries of **13** were prepared (Scheme 6) using the same modifications used to make Ala−Phe dipeptide mimetics **10** and **12**. Exhaustive diborane reduction generated sublibrary **14**, which in turn was used to make the poly-*N*-acetylamine sublibrary **15**. For each of the sublibraries, 20 beads were chosen for cleavage/decoding.

The MS data for the 20 polyamine, sublibrary **14** beads are illustrated in Table 3. Nine of the beads were fully decoded, and eight of the beads were nonsequenceable. In addition, three of the beads were partially decoded so that one of the amino acids could be determined. Although nonideal, this reduces the potential pool of products from 361 to 19 and thus makes resynthesis a practical possibility. As mentioned in regards to the model Ala−Phe-based polyamine model **7**, difficulty in analyzing these beads may be a result of the additional stability afforded to the amino product-linker bond. To improve the reliability of decoding polyamine beads, single beads were acetylated immediately prior to cleavage in an attempt to increase the lability of the anchoring bond. The decoding results for 20 beads are illustrated in Table 4. In this case, only one bead was totally nondecodable, and three were partially decoded; 80% were fully decoded, a significant improvement with respect to the nonacetylated resin **14**.

Polyamine sublibrary **14** was used in turn to generate poly-*N*-acetylamine sublibrary **15**. Twenty randomly selected beads were cleaved and analyzed by MS. Table 5 summarizes the decoding data from these 20 beads. Eighteen of the beads were fully decoded, and two (entries 5 and 14) were partially decoded. This percentage is a significant improvement with respect to the source polyamine library **13** and confirms that the difficulty in decoding polyamines is caused by the cleavage step and is not a shortcoming of the chemical synthesis.

Conclusion

The ability to chemically encode globally transformed OBOC combinatorial libraries has been demonstrated. Ran-

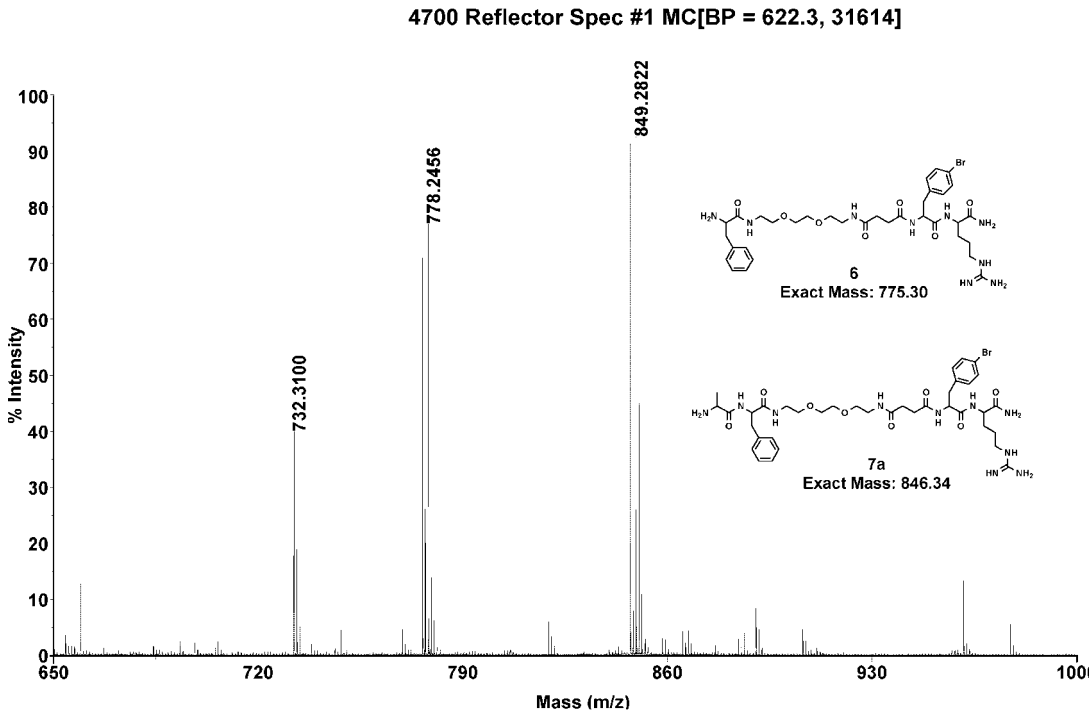


Figure 5. Mass spectrum of the cleavage products **6** and **7a** generated by treatment of resin **5a** with gaseous HF.

Table 1. MALDI-TOF Analysis of Crude, Single-Bead HF Cleavage Products from Model Parallel Dipeptide Library Resins **5a**−**q**

resin	Aa	calcd mass of **6a**−**q**[a]	observed mass of **6a**−**q**[a]
5a	Ala	849.3	849.3
5b	Arg	934.4	934.3
5c	Asn	892.3	892.4
5d	Asp	893.3	893.3
5e	Glu	907.3	907.3
5f	Gln	906.3	906.3
5g	His	915.4	915.4
5h	Ile	891.4	891.4
5i	Leu	891.4	891.5
5j	Lys	906.4	906.4
5k	Pro	875.3	875.4
5l	Ser	865.3	865.3
5m	Thr	879.3	879.4
5n	Trp	964.4	964.4
5o	Tyr	941.4	941.4
5p	Val	877.3	877.4
5q	Gly	835.3	835.3

[a] Values listed refer to the respective ^{81}Br isotopes.

dom beads from OBOC dipeptide and OBOC-dipeptide-derived polyamine and poly-*N*-acetylamine libraries were fully decoded with the following respective success rates: 95, 45, and 90%. In the case of polyamine beads, single-bead acetylation prior to cleavage improved the decoding success rate to 80%. Future goals include synthesis of peptidomimetic libraries incorporating higher degrees of diversity, application of this methodology to make OBOC heterocyclic libraries, and use of bead-screening assays to identify cancer-targeting ligands and tyrosine kinase inhibitors.

Experimental Section

Materials and General Methods. All reactions were performed at 20 °C unless stated otherwise. Polypropylene syringes fitted with polypropylene frits were used for solid-phase reactions and obtained from Torviq. HF cleavages were performed using the gaseous reaction apparatus available from Torviq. MALDI-MS was performed on an Applied Biosystems 4700 (Foster City, CA) instrument using α-cyano-4-hydroxycinnamic acid (CHCA) as sample matrix. TentaGel S NH_2 (0.28 mmol/g, 90 μm particle size) was purchased from Rapp Polymere. All chiral amino acids used were of the L configuration. Fmoc-protected amino acids were from CPC Scientific or GL Biochem Ltd. and Boc-protected amino acids were from Chem-Impex. DMF was purchased from VWR and dried over 4 Å molecular sieves prior to use. Other solvents and reagents were obtained from Sigma-Aldrich and were used without further purification. Fmoc deprotections were accomplished by treating the resin with 25% piperidine/DMF (2 × 5 min; 1 × 10 min) and then washing with DMF 8 × 0.5 min, MeOH 4 × 0.5 min, DCM 4 × 0.5 min, and DMF 4 × 0.5 min. Boc deprotections were accomplished by treating the resin with TFA–DCM (1:1) for 30 min then washing with DCM 4 × 0.5 min, 5% DIEA/DCM 4 × 0.5 min, MeOH 4 × 0.5 min, DCM 4 × 0.5 min, and DMF 4 × 0.5 min. Side-chain deprotections prior to HF cleavage were accomplished by treating the resin with TFA–anisole–DCM (50:5:45) for 30 min and then washing with DMF 8 × 0.5 min and MeOH 4 × 0.5 min. Analytical HPLC was performed using a Waters XTerra MS C18 reversed-phase column (4.6 × 150 mm) on a Waters 2525 Binary Gradient Module instrument with a 2996 photodiode array detector. Linear gradients of 0.1% aqueous TFA and 0.1% TFA in CH_3CN were run at 1.0 mL/min flow rate from 100:0 to 0:100 over 20 min.

General Procedure for Single Bead Gaseous HF Cleavage. A small aliquot of fully deprotected beads from a particular library or synthesis was placed in a small Petri dish and diluted with methanol. Individual beads to be cleaved were selected under a microscope with a micropipette

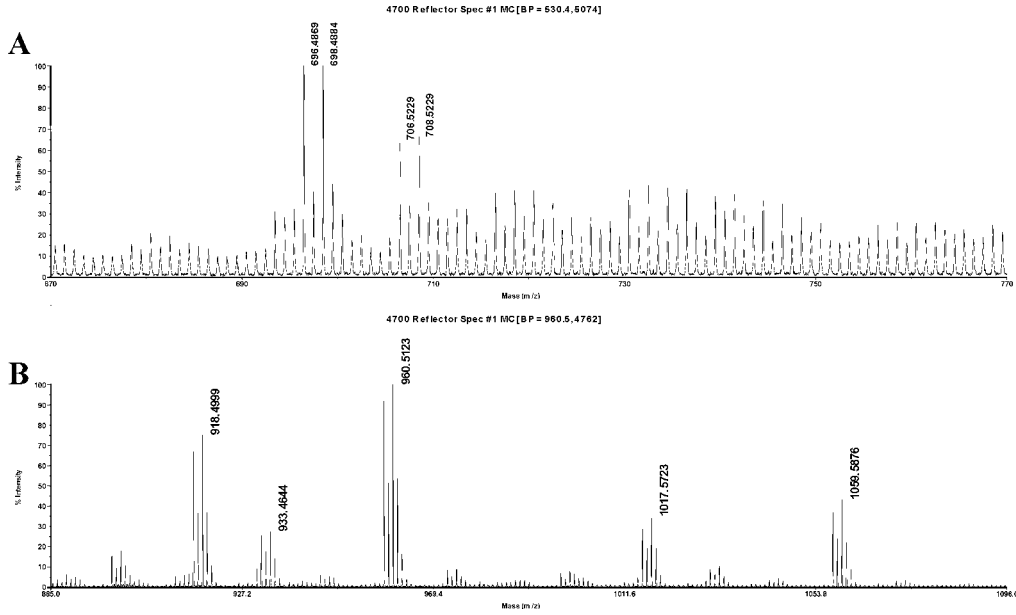
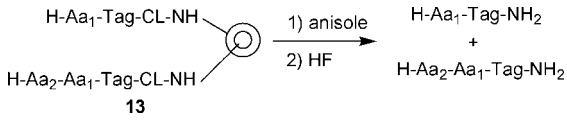


Figure 6. MALDI-MS of Ala-Phe-based peptidomimetics. All products were generated from HF treatment of a single bead of the respective starting resins. (A) **9** and **10** or (B) **11** and **12**.

Scheme 5. Single-Bead Cleavage of an OBOC Dipeptide Ladder Library



Aa_1 / Aa_2 = 19 proteinogenic amino acids (no Cys)

and placed into wells of a 96-well polypropylene plate. The wells were allowed to air-dry in a vacuum hood and then placed under high vacuum overnight. The 96-well plates were enclosed for 2−5 h in the cleavage apparatus reaction chamber in the presence of an open Petri dish containing 10 mL of anisole. The anisole was removed, and the reaction chamber was connected to the control panel. Evacuation and introduction of HF gas to the reaction chamber was performed according to the standard operational protocol provided by the manufacturer. The plates were exposed to gaseous HF for 2 h, and after the chamber was purged of HF, an open Petri dish filled with KOH was enclosed with the plates for 12 h. The cleavage products were extracted from the bead interior with ACN–H_2O (1:1; 20 μL) for at least one hour.

General Procedure for the Exhaustive Reduction of Resin-Bound Peptides. This procedure is essentially the same as described by Pinilla et al.[43] A portion of resin and boric acid (15 equiv per amide bond) were added to a screw-cap culture tube. Trimethyl borate (15 equiv per amide bond) was added to the tube, followed by careful addition of 1 M borane-THF (40 equiv per amide bond). The tube was purged with nitrogen, and the reaction mixture was heated at 65 °C for 72 h. MeOH was carefully added to quench the reaction, and the resin was washed with MeOH (4 × 0.5 min), THF (4 × 0.5 min), and piperidine (4 × 0.5 min). The resin was transferred to a culture tube and heated in piperidine at 65 °C for 12 h and then washed with DMF (4 × 0.5 min), MeOH (4 × 0.5 min, and DCM (4 × 0.5 min).

9-Fluorenylmethyl derivative of *p*-[Amino-methyl(phenyl)] phenoxyacetic acid (1). A solution of 4-hydroxybenzophenone (7.00 g, 35.3 mmol), bromoacetic acid (9.81 g, 70.1 mmol), and anhydrous K_2CO_3 (22.3 g, 211.9 mmol) in dry acetone (275 mL) was refluxed for 15 h and then concentrated. The residue was taken up in a mixture of H_20 (2000 mL) and concentrated aqueous dibasic sodium phosphate (200 mL), dissolved with heating and then acidified to pH 1 with 6 N HCl. After the mixture was cooled in an ice bath, the precipitate was collected, washed with water, and dried in vacuo under P_2O_5 providing 4-benzoyl-phenoxy acetic acid as a white powder (6.2 g, 69%). R_f = 0.39 [hexanes−ethyl acetate−AcOH (2:8:0.1)]; HPLC, t_R = 12.6 min (100%). Next, $NaBH_4$ (3.32 g, 87.8 mmol) was added in 6 portions over 30 min to a solution of 4-benzoyl-phenoxy acetic acid (5.00 g, 19.5 mmol) in EtOH–*i*PrOH–H_2O (2.5:2.5:1.0; 120 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 12 h. After it was carefully quenched with AcOH, the solution was acidified to pH 3 with 1 N H_2SO_4 and then concentrated to about 1/3 volume. The mixture was diluted with H_2O (300 mL) and EtOAc (150 mL), and the aqueous layer was extracted with EtOAc (4 × 100 mL). The organic extracts were combined and washed with H_2O (1 × 100 mL), 1 N HCl (2 × 100 mL), and brine (1 × 100 mL), then dried over $MgSO_4$, concentrated, and dried under vacuum to give the crude alcohol intermediate as a clear oil (3.18 g, 63%). TsOH (0.23 g, 1.23 mmol), Fmoc-NH_2 (3.24 g, 13.6 mmol), and AcOH (135 mL) were added to the alcohol. After the mixture was stirred for 12 h, the solution was diluted with H_2O (150 mL), and the resulting precipitate was collected by vacuum filtration. To remove unreacted Fmoc-NH_2, the crude product was refluxed in hexane–EtOAc (2:3; 150 mL) for 15 min, and after it was cooled to room temperature, the mixture was filtered and washed with hexane–EtOAc (2:3; 3 × 50 mL). The precipitate was dried in vacuo to provide the title compound as a white solid (3.66 g, 62%). R_f = 0.39

Table 2. MALDI-TOF Analysis of 20 Crude Single-Bead Cleavage Products from Resin **13**

entry	obsd mass 1[a]	Aa_1 (calcd mass)[a]	obsd mass 2[a]	Aa_2 (calcd mass)[a]	Aa_2-Aa_1
1	759.4/778.3	Gln, Lys (759.3)/Phe (778.3)	896.4/915.4	His (896.4)/Arg, His (915.4)	His−Gln, His−Lys, Arg−Gln, Arg−Lys, Phe−His
2	728.3	Pro (728.3)	829.3	Thr (829.3)	Thr−Pro
3	702.3	Ala (702.3)	759.3	Gly (759.3)	Gly−Ala
4	702.2	Ala (702.3)	815.3	Ile, Leu (815.4)	Ile−Ala, Leu−Ala
5	778.3	Phe (778.3)	835.3	Gly (835.3)	Gly−Phe
6	718.2	Ser (718.3)	775.2	Gly (775.3)	Gly−Ser
7	759.3	Gln, Lys (759.3)	846.3	Ser (846.4)	Ser−Gln, Ser−Lys
8	787.5	Arg (787.3)	901.5	Asn (901.4)	Asn−Arg
9	702.4	Ala (702.3)	817.4	Asp (817.4)	Asp−Ala
10	787.4	Arg (787.3)	884.5	Pro (884.4)	Pro−Arg
11	732.3	Thr (732.3)	829.4	Pro (829.3)	Pro−Thr
12	746.3	Asp (746.3)	874.4	Gln, Lys (874.4)	Gln−Asp, Lys−Asp
13	759.3	Gln, Lys (759.3)	846.4	Ser (846.4)	Ser−Gln, Ser−Lys
14	688.3	Gly (688.3)	801.4	Ile, Leu (801.4)	Ile−Gly, Leu−Gly
15	745.3	Asn (745.3)	873.3	Gln, Lys (873.4)	Gln−Asn, Lys−Asn
16	746.2	Asp (746.3)	909.3	Tyr (909.3)	Tyr−Asp
17	794.3	Tyr (794.3)	851.3	Gly (851.3)	Gly−Asp
18	745.2	Asn (745.3)	874.3	Glu (874.3)	Glu−Asn
19	744.2	Ile, Leu (744.3)	801.2	Gly (801.3)	Gly−Ile, Gly−Leu
20	794.4	Tyr (794.3)	881.4	Ser (881.3)	Ser−Tyr

[a] Values listed refer to the respective ^{81}Br isotopes.

Scheme 6. Synthesis of Encoded OBOC SubLibraries[a]

13 $\xrightarrow{i}$ **14** (Polyamine sub-library) $\xrightarrow{ii}$ **15** (Poly-*N*-acetylamine sub-library)

[a] Reagents and conditions: (i) $B(OH)_3$, $B(OCH_3)_3$, 1 M BH_3–THF, 65 °C, 72 h then piperidine, 65 °C, 16 h; (ii) Ac_2O, DIEA, DMF.

[$CHCl_3$−MeOH−AcOH (90:8:2)]; HPLC, t_R = 16.5 min (94%); ESIMS calcd for $C_{30}H_{25}NO_5$ 479.5, found 480.0 [M + H]$^+$.

Synthesis of Coding Tags 2 and 3 on Tentagel Beads. Tentagel resin (0.50 g, 0.28 mmol/g) was swollen in DMF for 30 min. **1** (0.20 g, 0.42 mmol), Boc-Arg(Tos)-OH (0.18 g, 0.42 mmol), Boc-Phe(4-Br)-OH (0.14 g, 0.42 mmol), Fmoc-Ebes-OH (0.20 g, 0.42 mmol) were sequentially coupled using DIPCDI (65 μL, 0.42 mmol) and HOBt (0.07 g, 0.42 mmol) activation. The Fmoc group was removed providing resin **2**, and a single bead was cleaved with HF. MALDI-TOF-MS calcd for $C_{25}H_{41}BrN_8O_6$ 628.2, found 629.2 [M+H]$^+$ and 631.3 [M+H]$^+$. A portion of resin **2** (0.10 g, 0.028 mmol) and boric acid (0.13 g, 2.1 mmol, 75 equiv–15 equiv per amide bond) was added to a screw-cap glass culture tube. Trimethyl borate (0.23 mL, 2.1 mmol) was added to the tube, followed by careful addition of 1 M borane–THF (5.6 mL, 5.6 mmol–40 equiv per amide bond). The tube was purged with nitrogen and the reaction mixture was heated at 65 °C for 72 h. MeOH was carefully added to quench the reaction, and the resin was washed with MeOH (4 × 0.5 min), THF (4 × 0.5 min), and piperidine (4 × 0.5 min). The resin was transferred to a culture tube and heated in piperidine (10 mL) at 65 °C for 12 h to provide resin **3**. After it was washed with DMF (4 × 0.5 min), MeOH (4 × 0.5 min), and DCM (4 × 0.5 min), a single bead was picked and cleaved by HF. MALDI-TOF-MS calcd for $C_{25}H_{49}BrN_8O_2$ 572.3, found 573.4 [M + H]$^+$ and 575.4 [M + H]$^+$.

Synthesis of Model Parallel Dipeptide Library (5a−q). A solution of Fmoc-Phe-OH (0.16 g, 42 mmol) and HOBt (0.06 g, 0.42 mmol) in DMF (1 mL) was added resin **2** (0.50 g, 0.14 mmol), followed by DIPCDI (65 μL, 0.42 mmol). After 1 h, the resin was washed with DMF (4 × 15 s), MeOH

Table 3. MALDI-TOF Analysis of 20 Crude Single-Bead Cleavage Products from Resin **14** (Polyamine Sublibrary)

entry	obsd mass 1[a]	Aa_1 (calcd mass)[a,b]	obsd mass 2[a,b]	Aa_2 (calcd mass)[a,b]	Aa_2-Aa_1[b]
1		X		X	X−X
2	674.4	Leu, Ile (674.4)		X	X−Leu, X−Ile
3		X		X	X−X
4	708.5	Phe (708.4)	795.5	Thr (795.5)	Thr−Phe
5	675.5	Asn (675.4)		X	X−Asn
6	660.5/674.5	Val (660.4)/Leu, Ile (674.4)	759.6	Leu, Ile (759.5)/Val (759.5)	Val−Leu, Val−Ile, Leu−Val, Ile−Val
7	708.4	Phe (708.4)	791.5	Pro (791.5)	Pro−Phe
8		X		X	X−X
9		X		X	X−X
10	662.4	Thr (662.4)		X	X−Thr
11		X		X	X−X
12	660.4	Val (660.4)	802.5	Arg (802.5)	Arg−Val
13	708.4	Phe (708.4)	857.4	Tyr (857.5)	Tyr−Phe
14		X		X	X−X
15		X		X	X−X
16	676.5	Asp (676.4)	719.5	Gly (719.4)	Gly−Asp
17	724.5	Tyr (724.4)	809.5	Val (809.5)	Val−Tyr
18		X		X	X−X
19	660.4	Val (660.4)	777.5	Met (777.5)	Met−Val
20	724.4	Tyr (724.4)	857.5	Phe (857.5)	Phe−Tyr

[a] Values listed refer to the respective ^{81}Br isotopes. [b] X indicates an unknown (i.e., nonsequenceable) amino acid.

Table 4. MALDI-TOF Analysis of 20 Crude Single-Bead Cleavage Products from Resin **14** (Polyamine Sublibrary) Following Single-Bead Acetylation

entry	obsd mass 1[a]	Aa_1 (calcd mass)[a,b]	obsd mass 2[a,b]	Aa_2 (calcd mass)[a,b]	Aa_2-Aa_1[b]
1	910.5	Pro (910.5)		X	X−Pro
2	969.5	Arg (969.5)	1094.6	Pro (1094.7)	Pro−Arg
3	960.5	Phe (960.6)	1101.6	Ile, Leu (1101.7)	Ile−Phe, Leu−Phe
4	969.5	Arg (969.5)	1098.6	Thr (1098.7)	Thr−Arg
5	976.5	Tyr (976.5)	1141.6	His (1141.7)	His−Tyr
6	914.4	Thr (914.5)	1029.5	Ser (1029.6)	Ser−Thr
7	976.5	Tyr (976.5)	1141.6	His (1141.7)	His−Tyr
8	976.5	Tyr (976.5)	1118.6	Asn (1118.6)	Asn−Tyr
9	969.5	Arg (969.5)	1144.6	Phe (1144.7)	Phe−Arg
10	960.5	Phe (960.6)	1087.6	Val (1087.7)	Val−Phe
11	900.4	Ser (900.4)		X	X−Ser
12	976.4	Tyr (976.4)	1105.5	Thr (1105.6)	Thr−Tyr
13	927.5	Asn (927.4)	1042.6	Ser (1042.6)	Ser−Asn
14		X		X	X−X
15	976.4	Tyr (976.4)	1117.6	Ile, Leu (1117.7)	Ile−Tyr, Leu−Tyr
16	912.5	Val (912.5)	1054.6	Asn (1054.6)	Asn−Val
17	927.5	Asn (927.4)	1118.6	Tyr (1118.6)	Tyr−Asn
18	950.5	His (950.5)	1065.6	Ser (1065.6)	Ser−His
19	997.6	X	1096.6	Ala (1098.7)	Ala−X
20	912.5	Val (912.5)	1040.6	Thr (1041.6)	Thr−Val

[a] Values listed refer to the respective ^{81}Br isotopes. [b] X indicates an unknown (i.e., nonsequenceable) amino acid.

Table 5. MALDI-TOF Analysis of 20 Crude Single-Bead Cleavage Products from Resin **15** (Poly-*N*-acetylamine Sublibrary)

entry	obsd mass 1[a]	Aa_1 (calcd mass)[a,b]	obsd mass 2[a,b]	Aa_2 (calcd mass)[a,b]	Aa_2-Aa_1[a,b]
1	927.4	Asn (927.4)	1070.5	Asp (1070.5)	Asp−Asn
2	914.4	Thr (914.5)	1098.5	Arg (1098.6)	Arg−Thr
3	976.3	Tyr (976.5)	1118.4	Asn (1118.5)	Asn−Tyr
4	914.5	Thr (914.5)	1079.7	His (1079.5)	His−Thr
5	976.6	Tyr (976.5)		X	X−Tyr
6	926.5	Ile, Leu (926.5)	1025.6	Ala (1025.6)	Ala−Ile, Ala−Leu
7	928.5	Asp (928.5)	1112.6	Arg (1112.6)	Arg−Asp
8	914.5	Thr (914.5)	999.5	Gly (999.5)	Gly−Thr
9	900.4	Ser (900.4)	1075.5	Phe (1075.5)	Phe−Ser
10	928.4	Asp (928.5)	1027.4	Ala (1027.5)	Ala−Asp
11	926.4	Ile/Leu (926.5)	1085.4	Met (1085.6)	Met−Ile/Leu
12	928.6	Asp (928.5)	1043.6	Ser (1043.5)	Ser−Asp
13	928.5	Asp (928.5)	1119.7	Tyr (1119.6)	Tyr−Asp
14	927.5	Asn (927.4)	1139.7	X	X−Asn
15	976.5	Tyr (976.5)	1118.6	Asn (1118.6)	Asn−Tyr
16	926.5	Ile, Leu (926.5)	1101.7	Phe (1101.6)	Phe−Ile, Phe−Leu
17	969.5	Arg (969.5)	1112.6	Asp (1112.6)	Asp−Arg
18	914.4	Thr (914.5)	1043.5	Thr (1043.5)	Thr−Thr
19	928.4	Asp (928.5)	1087.5	Met (1087.5)	Met−Asp
20	969.4	Arg (969.5)	1084.5	Ser (1084.6)	Ser−Arg

[a] Values listed refer to the respective ^{81}Br isotopes. [b] X indicates an unknown (i.e., nonsequenceable) amino acid.

(4 × 15 s), DCM (4 × 15 s), and DMF (4 × 15 s). After Fmoc deblocking, the resin was shaken vigorously in H_2O for 5 h. A solution of Fmoc-OSu (18 mg, 0.06 mmol, 0.4 equiv) in DCM–Et_2O (55:45, 40 mL) was added to the resin, followed by DIEA (20 μL, 0.11 mmol, 0.8 equiv), and then the reaction vessel was capped. These operations were performed as rapidly as possible. The reaction mixture was vigorously shaken for 30 min, and then the resin was washed with DCM–Et_2O (55:45, 4 × 15 s), MeOH (4 × 15 s), DCM (4 × 15 s), and DMF (4 × 15 s). The resin was taken up in DMF (17 mL) and then split into 17 reaction vessels. The DMF was then drained. A 3-fold excess containing solutions of amino acids [Fmoc-Ala-OH (14 mg), Fmoc-Arg(Pmc)-OH (29 mg), Fmoc-Asn(Trt)-OH (26 mg), Fmoc-Asp(O*t*Bu)-OH (18 mg), Fmoc-Glu(O*t*Bu)-OH (19 mg), Fmoc-Gln(Trt)-OH (27 mg), Fmoc-His(Trt)-OH (27 mg), Fmoc-Ile-OH (16 mg), Fmoc-Leu-OH (16 mg), Fmoc-Lys(Boc)-OH (21 mg), Fmoc-Pro-OH (15 mg), Fmoc-Ser(O*t*Bu)-OH (17 mg), Fmoc-Thr(O*t*Bu)-OH (18 mg), Fmoc-Trp(Boc)-OH (23 mg), Fmoc-Tyr(O*t*Bu)-OH (23 mg), Fmoc-Val-OH (15 mg), Fmoc-Gly OH (13 mg)] was prepared in DMF (250 μL). A 3-fold excess of HOBt was added to each of the amino acid solutions by equal distribution of a solution of HOBt (117 mg) in DMF (4.5 mL). The amino acid/HOBt solutions were added to the respective resins, followed by the addition of DIPCDI (7 μL). The resins were shaken for 2 h and then washed with sufficient amounts of DMF, MeOH, DCM, and DMF. Single beads from each of the 17 resins were placed into discrete wells of a 96-well plate. The individual wells (all single-bead manipulations were performed under microscope) were treated with piperidine–DMF (1:3, 100 μL, 2 × 10 min), washed with DMF (2 × 150 μL), MeOH (2 × 150 μL), and DCM (2 × 150μL), and then dried under a stream of air. Wells containing amino acids with side-chain protection were treated with TFA–anisole–DCM (50:5:45, 150 μL) for 30 min, concentrated under an air stream, and washed with MeOH–DIEA (95:5, 1 × 250 μL) and MeOH (1 × 250 μL). The wells were evaporated to dryness under an air stream and then placed under vacuum. HF cleavage and MS analysis was then performed. The MS results are listed in Table 1.

Synthesis of Ala-Phe-Based Peptidomimetics 10 and 12. Reduced Ala-Phe resin **8** was prepared from resin **5a** (100 mg, 0.28 mmol/g) using boric acid (0.16 g, 2.5 mmol, 90 equiv–15 equiv per amide bond), trimethyl borate (0.28 mL, 2.5 mmol), 1 M borane−THF (6.7 mL, 6.7 mmol–40 equiv per amide bond) according to the procedure described for the synthesis of resin **3**. A single bead was picked and cleaved by HF. **9**: MALDI-TOF-MS calcd for $C_{34}H_{60}BrN_9O_2$ 705.4, found 706.5 $[M + H]^+$ and 708.5 $[M + H]^+$. **10** was not observed. A portion of **8** (10 mg) was treated with DMF–Ac_2O (9:1, 1 mL) for 30 min then washed with DMF (4 × 15 s), DCM (4 × 15 s), and MeOH (4 × 15 s). A single bead was picked and cleaved by HF. **11**: MALDI-TOF-MS calcd for $C_{46}H_{72}BrN_9O_8$ 957.5, found 958.5 $[M + H]^+$ and 960.5 $[M+H]^+$. **12**: MALDI-TOF-MS calcd for $C_{51}H_{81}BrN_{10}O_9$ 1056.5, found 1057.6 $[M + H]^+$ and 1059.6 $[M + H]^+$.

Synthesis of OBOC Dipeptide Library (13). Resin **2** (0.50 g, 0.28 mmol) was split into 19 reaction vessels. Coupling of the respective amino acids (19 proteinogenic amino acids, no Cys) was performed as described in the synthesis dipeptide library (**5a**−**q**). The resins were combined and washed with DMF (4 × 0.5 min), MeOH (4 × 0.5 min), DCM (4 × 0.5 min), and DMF (4 × 0.5 min). The Fmoc group was removed, and bilayer formation performed as described in the synthesis dipeptide library (**5a**−**q**). A second split−mix cycle using the same 19 amino acids was performed. A small aliquot of this resin (∼5 mg) was treated with 20% piperidine/DMF then TFA–DCM–anisole (50:45:5, 1 mL) for 30 min. Twenty beads were picked, cleaved by HF, and analyzed by MS. The MS results are listed in Table 2.

Synthesis of OBOC Dipeptide Sublibraries (14 and 15). A portion of resin **13** (0.10 g, 0.028 mmol/g) was reduced as described for the synthesis of resin **3** to give resin **14**. Twenty of these beads were picked, cleaved by HF, and analyzed by MS. The MS results are listed in Table 3. A portion of resin **14** (10 mg) was acetylated with DMF–Ac_2O (9:1, 1 mL) for 30 min to give resin **15**. After they were washed with DMF (4 × 15 s), DCM (4 × 15 s), and MeOH (4 × 15 s), 20 beads were picked, cleaved by HF, and analyzed by MS. The MS results are listed in Table 5.

Acknowledgment. The authors wish to thank Dr. William Jewell at the UC Davis mass spectrometry facilities for assistance with MALDI-TOF MS and Dr. Viktor Krchňák for assistance with the Torviq gaseous cleavage apparatus. Funding sources: NSF CH 0302122, NIH/NCI NCDDG U19 CA113298, NIH/NCI R01CA115483, and NIH 1P41 GM076151.

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CC700165S