Novel Solution Phase Strategy for the Synthesis of Chemical Libraries Containing Small Organic Molecules

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Received September 5, 1995[⊗]

Abstract: A simple, versatile, and general approach to the solution phase, parallel synthesis of chemical libraries conducted on a generalized or universal template, which allows the preparation of multi-milligram quantities of each individual member, is described. In each step of the sequence, the reactants, unreacted starting material, reagents and their byproducts are removed by simple liquid/liquid or liquid/solid extractions providing the desired intermediates and final compounds in high purities (95% average) irrespective of the reaction yields and without deliberate reaction optimization.

The generation and use of combinatorial chemical libraries for the identification of novel chemical leads or for the optimization of a promising lead candidate has emerged as a potentially powerful method for the acceleration of the drug discovery process.[1−4] Initially explored with peptide or oligonucleotide libraries and related oligomeric structures,[2,5−13] more recent efforts have been directed at exploiting the greater diversity and range of useful properties embodied in small molecule libraries.[11−17]

A wide range of approaches to the generation of chemical libraries have been disclosed including split or mixed,[18] encoded,[19] indexed,[20] or parallel and spatially addressed synthesis on pins,[5,15] beads,[21] chips,[22] and other solid supports,[23] while solution phase synthesis has not been widely embraced as a viable alternative.[20,24,25] In a large measure, this may be due to both the natural extension of the methodology from solid phase peptide and oligonucleotide synthesis where supported phase synthesis has emerged as the medium of choice for their repetitive coupling reactions as well as its two key advantages of product isolation and sample manipulation. In addition to other merits of solid phase synthesis, the resin bound product isolation by simple filtration permits the use of large reagent

[⊗] Abstract published in *Advance ACS Abstracts,* March 1, 1996.

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excesses to effect high yield conversions required for each of the repetitive steps. However, its scale is generally restricted by the amount of required solid support and its loading capacity[26] and the production of multi-milligram quantities of each library member can be cumbersome and expensive.[27] Its use also requires functionalized substrates and solid supports,[23] compatible spacer linkers, orthogonal attachment and detachment chemistries often with the release of spectator functional groups, specialized protocols for monitoring the individual steps of a multistep synthesis[28] including orthogonal capping strategies for blocking unreacted substrate, and does not permit the purification of resin-bound intermediates. This latter feature necessarily produces the released product of a multistep sequence in an impure state and requires that each reaction on each substrate proceed with an unusually high efficiency. For a modest criterion of final product purity of 85%, this would require that each step of a two-step reaction sequence proceed in 92% yield on each substrate or that each step of a three-step reaction sequence proceed in 95% yield on each substrate. Our experience has been that such generalized reaction efficiencies are not routinely obtainable and require an extensive investment in reaction optimization and/or a purification of the released solid phase product.[29]

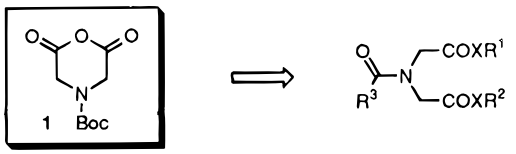

Figure 1.

An important complement to adapting solution phase chemistry to solid phase combinatorial synthesis is the development of protocols for solution phase combinatorial synthesis. Given that solution and solid-phase sample manipulation are both convenient and easily automated, the limitation to the solution phase parallel synthesis of chemical libraries is the isolation or purification of the library members. If the advantages of sample isolation characteristic of solid phase synthesis may be embodied in a solution phase synthesis, its nonlimiting scale, expanded repertoire of chemical reactions, direct production of soluble intermediates and final products for assay or purification, and the lack of required linking, attachment/detachment, or capping strategies make solution phase combinatorial synthesis an attractive complement. A number of potential techniques are available for such purposes, and one of the most attractive is liquid/liquid or solid/liquid extraction. Herein, we detail a high-purity solution phase parallel synthesis of chemical libraries employing a general template which implements one such simple purification protocol at each step. The recently disclosed but not yet detailed[24] single-step parallel synthesis of individual compounds using reliable solution chemistry as well as recent reports of solution phase, single step amide, ester, or carbamate condensations in the preparation of library mixtures[20] have provided the incentive for us to disclose our efforts.

The template **1**, which is representative of a series of anhydride-based templates that have been examined, consists of a densely functionalized core which imposes little structural or conformational bias which might limit its use.[30] The added pendant groups provide the molecular diversity and, as such, libraries built upon **1** may prove applicable to many biological targets. Its symmetrical structure contains three positions which can be controllably functionalized with nucleophiles or an acylating agent enabling the synthesis of libraries with up to three variable regions (Figure 1). As an anhydride, the starting template is activated for the first functionalization which upon reaction liberates its second functionalization site ($-CO_2H$). Thus, no orthogonal protecting groups are required for the template functionalization and only four chemical steps are required for the N^3 diversification (Scheme 1). At each step, the same released functionality may be used for both the isolation and purification of the intermediates and expected products from the starting material, reactants, reagents, and their reaction byproducts by simple liquid/liquid or solid/liquid extraction providing highly pure materials ($\geq 90-95\%$) regardless of the reaction efficiencies.

To illustrate the library constructions with **1**, herein we provide full details of our initial efforts which were conducted without prior optimization and that provided a fully characterized 27 member library constructed as a $3 \times 3 \times 3$ matrix affording 39 unique components in individual vessels (Scheme 2, Figure 2). Including enantiomer and diastereomer mixtures, 51 unique

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(27) For a 10 000 member library (three-step synthesis at 95% yield/step) to obtain 50 mg of each component (MW = 500 g/mol) on Merrifield resin with a typical loading of 1 mmol/g requires 1.166 kg of solid support, which equals $2499/library; on Wang resin with loading of 0.7 mmol/g, 1.666 kg of solid support is required, or $8331/library.

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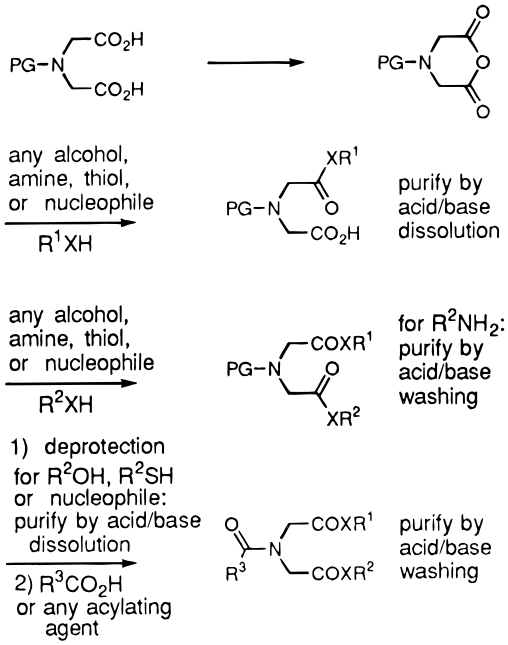
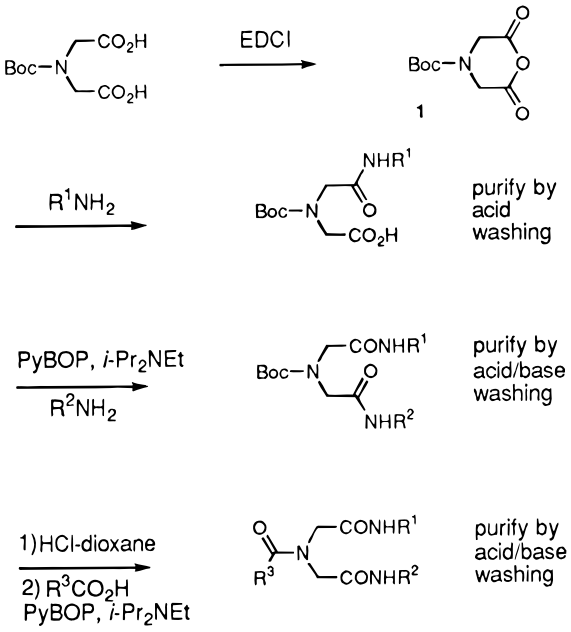
(29) For example, see: Wang, G. T.; Li, S.; Wideburg, N.; Krafft, G. A.; Kempf, D. J. *J. Med. Chem.* **1995**, *38*, 2995.

(30) Related, conformationally restricted templates including a general dipeptidomimetic template have been developed and serve as useful secondary libraries for subsequent examination. Efforts with such templates will be disclosed in due course.

Scheme 1



Scheme 2



entities were contained in the chemical library. Although this has been subsequently expanded to much larger library generations and more carefully optimized, the disclosure of its initial implementation serves to highlight a number of the advantages of the approach and is representative of the more extensive efforts. The most notable is that each of the expected library members was obtained in a purified form (≥90−100% pure)[31] irrespective of the reaction efficiencies in amounts ranging from 5 to 60 mg without prior optimization. In situ closure of *N*-BOC-iminodiacetic acid to the anhydride **1** (1 equiv of 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI), DMF, 25 °C, 1 h) followed by treatment with one of three R^1NH_2 (1 equiv, DMF, 25 °C, 20 h, 84−86%) cleanly afforded the monoamides which were purified by simple acid extraction to remove unreacted R^1NH_2, EDCI, and its reaction

(31) ^{1}H NMR spectra of all intermediates and final library members of the 3 × 3 × 3 matrix synthesis are provided in the supporting information, and the HPLC purity of the final products is summarized in Table 1.

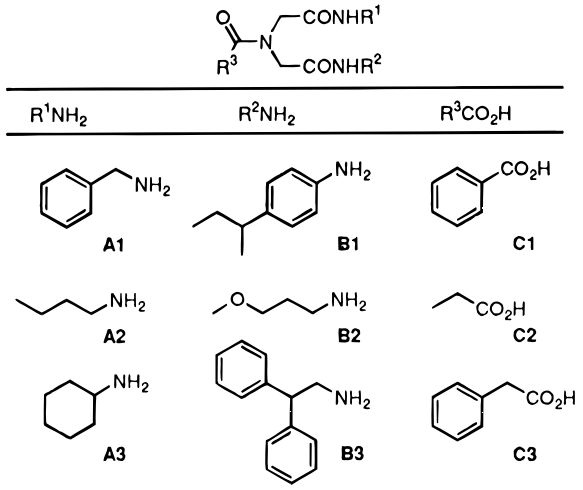


Figure 2.

byproducts. Both primary and secondary aliphatic or aryl amines were found to work well, and the first derivatization of **1** with an amine proved sufficiently effective that the deliberate aqueous base dissolution of the desired product was not required for isolation of pure product. In the instances of the use of a neutral nucleophile (R^1OH, R^1SH, R^1Met) in this first functionalization, the purification may be effectively accomplished by removal of the coupling reagent (EDCI) and its byproducts by dissolution in 10% aqueous HCl, extraction of the product carboxylic acid into 10% aqueous NaOH for the removal of neutral reactants, and reacidification and extraction into EtOAc or CH_2Cl_2 for product isolation. The three monoamides were each partitioned into three portions with one smaller portion being retained for archival purposes. Each of the equal three portions were treated with three R^2NH_2 (1 equiv) and PyBOP (1 equiv, 2 equiv of *i*-Pr_2NEt, DMF, 20 °C, 25 h, 65−99%) to afford nine diamides which were effectively purified by acid and base extractions of the unreacted R^2NH_2, PyBOP, and its reaction byproducts. Although this is illustrated in Scheme 2 with a primary amine, secondary amines as well as aryl amines could also be employed without difficulty. In the instances of the use of neutral nucleophiles (R^2OH, R^2SH, R^2Met) in this second functionalization, the further purification of the neutral reactants from the desired products may be readily accomplished upon *N*-BOC deprotection and aqueous acid extraction of the resulting secondary amine. Following the second functionalization and *N*-BOC deprotection (4 N HCl, dioxane, 25 °C, 45 min), reaction of three equal portions of each amine with three R^3CO_2H (1 equiv) in the presence of PyBOP (1 equiv, 3 equiv of *i*-Pr_2NEt, DMF, 25 °C, 20 h, 16−100%) provided 27 agents which were purified by aqueous acid and base extractions to remove unreacted starting materials, reagents, and their reaction byproducts. Overall yields for the 27 components ranged from 9 to 84% with an average overall yield of 61% for the three derivatizations. Importantly and irrespective of individual yields, all intermediates and final products were ≥90% pure and the average purity was 95.3% (Table 1, Experimental Section).[31] Without optimization and in these first efforts, most of the final library products were obtained in 20−60 mg quantities as individual identified samples at this exceptional level of purity suitable for direct use in screening efforts without further purification.

Without further optimization, subsequent extensions of these efforts to the preparation of a similarly characterized 125 member library constructed as a 5 × 5 × 5 matrix affording 155 unique compounds in individual vessels (Figure 3) provided comparable observations. Each library member was obtained

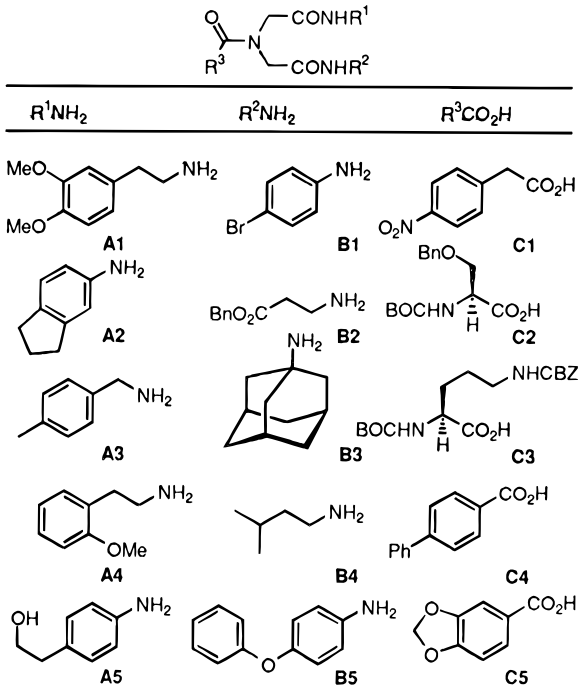


Figure 3.

as an individual entity in 30−100 mg quantities in pure form (>90%, generally ≥95% pure) in overall yields ranging from 32 to 85% (64% average).

One of the largest libraries addressed to date by manual manipulation of the reactions is a 960 member library constructed in a 6 × 8 × 20 matrix affording 1014 final components in individual vessels including intermediates constituting a library of 1158 compounds including diastereomers/enantiomers (Figure 4). Each library member was obtained in final sample sizes of 10−148 mg in overall yields ranging from 10 to 71% (52% average).

Conclusions. Complementary to the emerging solid phase synthesis of combinatorial libraries, a method for the rapid and simple multistep, solution phase, parallel synthesis of chemical libraries in which each component is produced as an individual compound in unlimited quantities (typically 30−150 mg) for extensive or broad screening purposes has been developed. In each step of the sequence, intermediates and final products were subjected to simple purification by liquid/liquid or liquid/solid extraction to remove reactants, unreacted starting material, reagents, and their byproducts providing the library members in high purities (≥90−98%) irrespective of the reaction yields and without deliberate reaction optimization. The template **1** on which this technology was illustrated is unusually flexible possessing one to three functionalization sites for diversification and little inherent structural or conformational bias which might limit its use. Although the initial examples described above enlist conventional liquid/liquid extractions, similar results employing solid-supported resins, columns, or pads have been used to effect solid/liquid extractions by simple batch, column, or filtration protocols. The one secondary amine protecting group may be easily altered to accommodate its sensitivity to selected liquid/liquid or liquid/solid extraction protocols used to remove starting materials and reaction byproducts. Although not illustrated herein, the strategy is not limited to the parallel synthesis of individual compounds but is also applicable to split or mixed synthesis employing limiting amounts of variable units and excess template to construct combinatorial libraries of compound mixtures subject to subsequent compound identification by repeat parallel synthesis or recursive deconvolution.

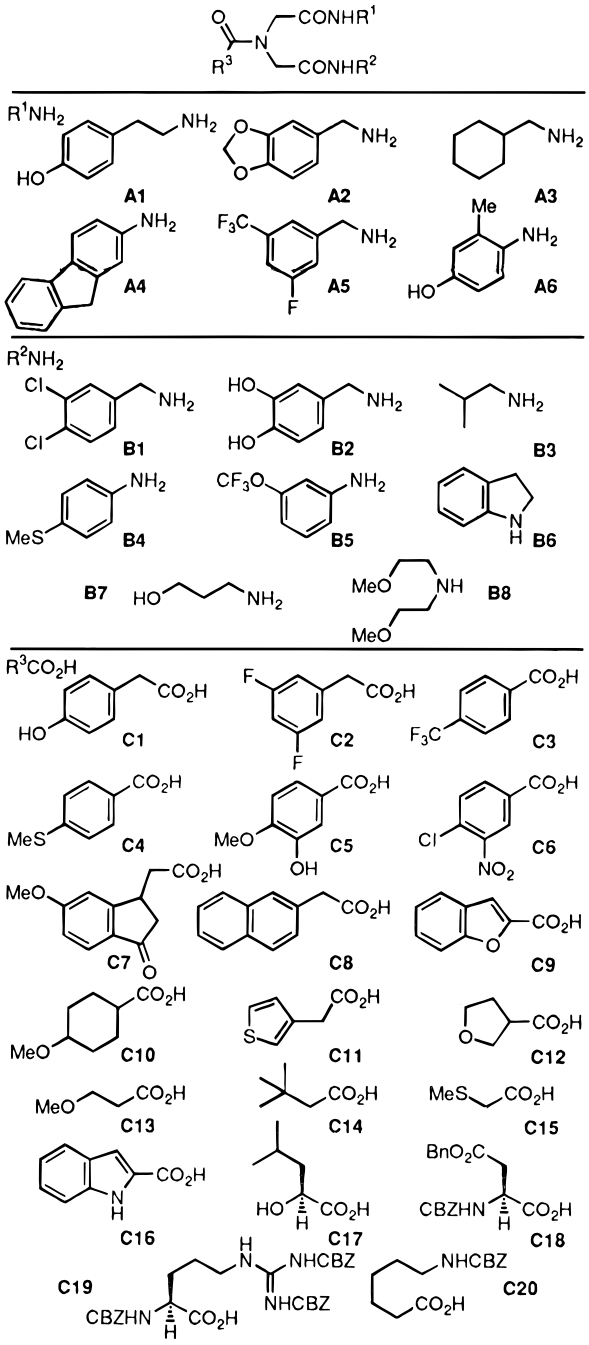


Figure 4.

Studies employing larger targeted libraries with matrix characterization of each reaction type, their adaptation to automation, and the development of related library templates, as well as additional approaches to the solution phase synthesis of chemical libraries, will be disclosed in due time.[31]

Experimental Section

General Procedure for the Preparation of *N*-((*tert*-Butyloxy)-carbonyl)iminodiacetic Acid Monoamides. A solution of *N*-((*tert*-butyloxy)carbonyl)iminodiacetic acid (0.349 g, 1.50 mmol) in DMF (15 mL) was treated with EDCI (0.294 g, 1.54 mmol) at 25 °C. The mixture was stirred at 25 °C for 1 h before the amine (R^1NH_2, 1 equiv) was added, and the solution was stirred for 20 h at 25 °C. The reaction mixture was poured into 10% aqueous HCl (60 mL) and extracted with EtOAc (100 mL). The organic phase was washed with 10% HCl (40 mL) and saturated aqueous NaCl (2 × 50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to yield the pure *N*-((*tert*-butyloxy)carbonyl)-iminodiacetic acid monoamides.

***N*-((*tert*-Butyloxy)carbonyl)-*N*′-benzyliminodiacetic Acid Monoamide:** 417 mg (86%); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.28 (m, 5H), 4.40 (br s, 2H), 4.04, 4.01, 3.98 and 3.93 (four s, total 4H), 1.40 and 1.32 (two s, total 9H); FABHRMS (NBA) *m/e* 323.1615 (M + H$^+$, $C_{16}H_{23}N_2O_5$ requires 323.1607).

***N*-((*tert*-Butyloxy)carbonyl)-*N*′-(*n*-butyl)iminodiacetic Acid Monoamide:** 362 mg (84%); ^{1}H NMR (CD_3OD, 300 MHz) δ 4.04 and 4.00 (two s, total 2H), 3.92 and 3.89 (two s, total 2H), 3.22 (m, 2H), 1.55−1.31 (m, 4H), 1.42 (s, 9H), 0.95−0.89 (m, 3H); FABHRMS (NBA) *m/e* 289.1769 (M + H$^+$, $C_{13}H_{25}N_2O_5$ requires 289.1763).

***N*-((*tert*-Butyloxy)carbonyl)-*N*′-cyclohexyliminodiacetic Acid Monoamide:** 402 mg (85%); ^{1}H NMR (CD_3OD, 300 MHz) δ 4.03 and 3.99 (two s, total 2H), 3.90 and 3.87 (two s, total 2H), 3.68 (m, 1H), 1.90−1.20 (m, 10H), 1.42 (s, 9H); FABHRMS (NBA) *m/e* 315.1928 (M + H$^+$, $C_{15}H_{27}N_2O_5$ requires 315.1920).

General Procedure for the Second Derivatization. Each of the *N*-((*tert*-butyloxy)carbonyl)iminodiacetic acid monoamides was dissolved in anhydrous DMF (20 mL/mmol) and was divided into three equal portions in three separate vials. Each solution was treated with one of three amines (R^2NH_2, 1 equiv), diisopropylethylamine (2 equiv), and PyBOP (1 equiv). The solution (20 mL DMF/mmol) was stirred at 25 °C for 20 h. The mixture was poured into 10% aqueous HCl and extracted with EtOAc. The organic phase was washed with 10% aqueous HCl, saturated aqueous NaCl, 5% aqueous $NaHCO_3$, and saturated aqueous NaCl. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to yield the diamides (65−99%).

***N*-((*tert*-Butyloxy)carbonyl)-*N*″-(4-*sec*-butylphenyl)-*N*′-cyclohexyliminodiacetic Acid Diamide:** 198 mg (99%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.60 (m, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.61 and 5.80 (two m, total 1H), 4.03 and 3.95 (two s, total 2H), 3.90 and 3.84 (two s, total 2H), 2.57 (m, 1H), 2.0−1.55 (m, 8H), 1.45 and 1.41 (two s, total 9H), 1.22 (d, J = 6.9 Hz, 3H), 0.82 (t, J = 7.2 Hz, 3H); FABHRMS (NBA) *m/e* 446.3005 (M + H$^+$, $C_{25}H_{40}N_3O_4$ requires 446.3019).

***N*-((*tert*-Butyloxy)carbonyl)-*N*′-cyclohexyl-*N*″-(3-methoxypropyl)iminodiacetic Acid Diamide:** 135 mg (88%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.98 (m, 1H), 6.99 and 6.82 (two m, total 1H), 3.84 and 3.79 (two s, total 4H), 3.47 (t, J = 5.9 Hz, 2H), 3.43−3.39 (m, 2H), 3.34 (s, 3H), 1.92−1.15 (m, 10H), 1.43 (s, 9H); FABHRMS (NBA−CsI) *m/e* 518.1647 (M + Cs$^+$, $C_{19}H_{35}N_3O_5Cs$ requires 518.1631).

***N*-((*tert*-Butyloxy)carbonyl)-*N*′-cyclohexyl-*N*″-(2,2-diphenylethyl)iminodiacetic Acid Diamide:** 197 mg (82%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90 and 6.85 (two t, total 1H), 7.78 and 6.78 (two d, total 1H), 7.26 (m, 10H), 4.26 (m, 1H), 3.95, 3.94, 3.93 and 3.91 (four s, total 4H), 3.72 and 3.70 (two s, total 2H), 3.15 (m, 1H), 1.92−1.61 (m, 4H), 1.40 and 1.33 (two s, total 9H), 1.29−1.21 (m, 6H); FABHRMS (NBA−CsI) *m/e* 626.2023 (M + Cs$^+$, $C_{29}H_{39}N_3O_4Cs$ requires 626.1995).

***N*-((*tert*-Butyloxy)carbonyl)-*N*′-benzyl-*N*″-(4-*sec*-butylphenyl)iminodiacetic Acid Diamide:** 180 mg (99%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.43 (br s, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.30 (br s, 5H), 7.13 (d, J = 8.2 Hz, 2H), 6.60 (t, 1H), 4.52 and 4.50 (two s, total 2H), 4.01, 3.95 and 3.89 (three s, total 4H), 2.56 (m, 1H), 1.57 (m, 2H), 1.40 and 1.36 (two s, total 9H), 1.21 (d, J = 6.8 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H); FABHRMS (NBA−CsI) *m/e* 586.1662 (M + Cs$^+$, $C_{26}H_{35}N_3O_4Cs$ requires 586.1682).

***N*-((*tert*-Butyloxy)carbonyl)-*N*′-benzyl-*N*″-(3-methoxypropyl)iminodiacetic Acid Diamide:** 141 mg (90%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.82, 7.85, 7.58 and 6.90 (four br s, total 2H), 7.30 (m, 5H), 4.49 and 4.47 (two s, total 2H), 3.90 and 3.86 (two s, total 2H), 3.84 and 3.81 (two s, total 2H), 3.46 (t, J = 5.8 Hz, 2H), 3.32 (s, 3H), 3.14 (m, 2H), 1.80 (m, 2H), 1.42 and 1.35 (two s, total 9H); FABHRMS (NBA−CsI) *m/e* 526.1335 (M + Cs$^+$, $C_{20}H_{31}N_3O_5Cs$ requires 526.1318).

***N*-((*tert*-Butyloxy)carbonyl)-*N*′-benzyl-*N*″-(2,2-diphenylethyl)iminodiacetic Acid Diamide:** 212 mg (99%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.50, 7.78 and 6.50 (three br s, total 2H), 7.33−7.21 (m, 15H), 4.47 and 4.45 (two s, total 2H), 3.93−3.89 (m, 2H), 3.72−3.67 (m, 2H), 3.15 (m, 1H), 1.32 (s, 9H); FABHRMS (NBA−CsI) *m/e* 634.1664 (M + Cs$^+$, $C_{30}H_{35}N_3O_4Cs$ requires 634.1682).

***N*-((*tert*-Butyloxy)carbonyl)-*N*′-(*n*-butyl)-*N*″-(4-*sec*-butylphenyl)iminodiacetic Acid Diamide:** 137 mg (99%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.60 (br s, 1H), 7.61, 7.52, 7.13 (three d, J = 8.2 Hz, total 4H), 6.32 (br s, 1H), 4.02, 3.95, 3.91 and 3.86 (four s, total 4H), 3.32 (m, 2H), 2.56 (m, 1H), 1.81−1.48 (m, 6H), 1.43 and 1.40 (two s, total 9H), 1.22 (m, 3H), 0.93 (t, J = 7.3 Hz, 3H), 0.81 (t, J = 7.2 Hz, 3H); FABHRMS (NBA−CsI) *m/e* 552.1823 (M + Cs$^+$, $C_{23}H_{37}N_3O_4Cs$ requires 552.1838).

***N*-((*tert*-Butyloxy)carbonyl)-*N*′-(*n*-butyl)-*N*″-(3-methoxypropyl)iminodiacetic Acid Diamide:** 75 mg (65%); ^{1}H NMR (CD_3OD, 300 MHz) δ 3.90 and 3.88 (two s, total 4H), 3.43 (m, 2H), 3.31 and 3.29 (two s, total 3H), 3.22 (m, 2H), 1.86−1.74 (m, 4H), 1.41 (s, 9H), 0.93 (m, 3H); FABHRMS (NBA−CsI) *m/e* 492.1461 (M + Cs$^+$, $C_{17}H_{33}N_3O_5Cs$ requires 492.1475).

***N*-((*tert*-Butyloxy)carbonyl)-*N*′-(*n*-butyl)-*N*″-(2,2-diphenylethyl)iminodiacetic Acid Diamide:** 155 mg (99%); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.27−7.15 (m, 10H), 4.30 (t, J = 7.7 Hz, 1H), 3.86 and 3.83 (two s, total 2H), 3.81 and 3.77 (two s, total 2H), 3.30 (m, 2H), 3.21 (t, 6.8 Hz, 2H), 1.56−1.42 (m, 2H), 1.37 and 1.30 (two s, total 9H), 0.96 and 0.95 (two t, J = 7.2 Hz, total 3H): FABHRMS (NBA−CsI) *m/e* 600.1821 (M + Cs$^+$, $C_{27}H_{37}N_3O_4Cs$ requires 600.1838).

General Procedure for the Third Derivatization. Each of the *N*′-((*tert*-butyloxy)carbonyl)-*N*,*N*-disubstituted iminodiacetic acid diamides was dissolved in 4 N HCl−dioxane (32 mL/mmol), and the mixture was stirred at 25 °C for 45 min. the solvent was removed in vacuo, and the residue was dissolved in anhydrous DMF (28 mL/mmol) and was divided into three equal portions and placed in three separate vials. The solution was treated with one of three carboxylic acids (R^3CO_2H, 1 equiv) followed by diisopropylethylamine (3 equiv) and PyBOP (1 equiv). The solution was stirred for 20 h at 25 °C. The mixture was poured into 10% aqueous HCl and extracted with EtOAc. The organic phase was washed with 10% aqueous HCl and extracted with EtOAc. The organic phase was washed with 10% aqueous HCl, saturated aqueous NaCl, 5% aqueous $NaHCO_3$, and saturated aqueous NaCl. The organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo to yield the final products (16−100%).

***N*-(Benzylcarbonyl)-*N*′-cyclohexyl-*N*″-(2,2-diphenylethyl)iminodiacetic Acid Diamide:** 47 mg (86%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.10 and 8.75 (two m, total 1H), 7.50−7.05 (m, 15H), 6.10 and 5.95 (two m, total 1H), 4.40 and 4.18 (two t, J = 8.4 Hz, total 1H), 3.91 (m, 2H), 3.82 and 3.73 (two s, total 2H), 3.61 and 3.58 (two s, total 2H), 3.21 (br s, 2H), 1.93−1.14 (m, 10H); FABHRMS (NBA) *m/e* 512.2907 (M + H$^+$, $C_{32}H_{38}N_3O_3$ requires 512.2913).

***N*-Benzoyl-*N*′-cyclohexyl-*N*″-(2,2-diphenylethyl)iminodiacetic Acid Diamide:** 37 mg (69%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.18 and 6.40 (two br s, total 1H), 8.35 and 6.05 (two m, total 1H), 7.38−7.21 (m, 15H), 4.48 and 4.22 (two t, J = 8.4 Hz, total 1H), 3.99 (m, 2H), 3.89−3.84 (m, 2H), 3.13 (m, 2H), 2.04−1.20 (m, 10H); FABHRMS (NBA) *m/e* 498.2759 (M + H$^+$, $C_{31}H_{36}N_3O_3$ requires 498.2756).

***N*-(Ethylcarbonyl)-*N*′-cyclohexyl-*N*″-(2,2-diphenylethyl)iminodiacetic Acid Diamide:** 39 mg (81%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.27 and 6.05 (two t, total 1H), 8.80 and 5.87 (two d, J = 7.3 Hz, total 1H), 7.37−7.15 (m, 10H), 4.38 and 4.16 (two t, J = 8.4 Hz, total 1H), 3.89 and 3.84 (two s, total 2H), 3.76 and 3.62 (two s, total 2H), 3.15 (m, 2H), 2.25 (q, J = 7.3 Hz, 2H), 1.95−1.07 (m, 10H), 0.88 (t, J = 7.4 Hz, 3H); FABHRMS (NBA) *m/e* 450.2749 (M + H$^+$, $C_{27}H_{36}N_3O_3$ requires 450.2756).

***N*-(Benzylcarbonyl)-*N*′-benzyl-*N*″-(3-methoxypropyl)iminodiacetic Acid Diamide:** 28 mg (76%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.61 and 8.71 (two t, total 1H), 7.12−7.37 (m, 10H), 6.89 and 6.85 (two t, total 1H), 4.43−4.40 (m, total 2H), 4.04 and 4.00 (two s, total 2H), 3.89 and 3.84 (two s, total 2H), 3.64 and 3.58 (two s, total 2H), 3.42 (t, J = 6.7 Hz, 2H), 3.30 (s, 3H), 3.13 (t, J = 3.5 Hz, 2H), 1.82−1.72 (m, 2H); FABHRMS (NBA) *m/e* 412.2231 (M + H$^+$, $C_{23}H_{30}N_3O_4$ requires 412.2236).

***N*-Benzoyl-*N*′-benzyl-*N*″-(3-methoxypropyl)iminodiacetic Acid Diamide:** 24 mg (67%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.35 and 8.46 (two br s, total 1H), 7.42−7.20 (m, 10H), 6.98 (br s, 1H), 4.49 (d, J = 5.7 Hz, 2H), 4.00 (m, 4H), 3.47−3.31 (m, 5H), 3.13 (m, 2H), 1.80 (m, 2H); FABHRMS (NBA) *m/e* 398.2077 (M + H$^+$, $C_{22}H_{28}N_3O_4$ requires 398.2079).

***N*-(Ethylcarbonyl)-*N*′-benzyl-*N*″-(3-methoxypropyl)iminodiacetic Acid Diamide:** 15 mg (48%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.75 and 8.90 (two t, total 1H), 7.30−7.26 (m, 5H), 6.85 and 6.65 (two t, total 1H), 4.47 and 4.46 (two d, J = 17.8 Hz, 2H), 4.03 and 4.00 (two

s, total 2H), 3.94 and 3.88 (two s, total 2H), 3.48−3.34 (m, 2H), 3.32 and 3.31 (two s, total 3H), 3.16 (m, 2H), 2.26 (m, 2H), 1.86−1.74 (m, 2H), 1.07 (m, 3H); FABHRMS (NBA) *m/e* 350.2054 (M + H^+, $C_{18}H_{28}N_3O_4$ requires 350.2079).

***N*-(Benzylcarbonyl)-*N*′-benzyl-*N*″-(2,2-diphenylethyl)iminodiacetic Acid Diamide:** 52 mg (88%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.38 and 9.00 (two t, total 1H), 7.32−7.18 (m, 20H), 6.42 and 5.98 (two t, total 1H), 4.44−4.36 (m, 2H), 3.95−3.84 (m, 2H), 3.82 and 3.72 (two s, total 2H), 3.62 and 3.55 (two s, total 2H), 3.20 (s, 2H), 3.16−3.11 (m, 2H); FABHRMS (NBA) *m/e* 520.2606 (M + H^+, $C_{33}H_{34}N_3O_3$ requires 520.2600).

***N*-Benzoyl-*N*′-benzyl-*N*″-(2,2-diphenylethyl)iminodiacetic Acid Diamide**: 49 mg (86%); ^{1}H NMR (CD_3OD, 300 MHz) δ 9.00 (m, 1H), 7.36−7.14 (m, 20H), 6.75 (m, 1H), 4.45 (br s, 2H), 4.05−3.83 (m, 4H), 3.30 (m, 2H); FABHRMS (NBA) *m/e* 506.2448 (M + H^+, $C_{32}H_{32}N_3O_3$ requires 506.2443).

***N*-(Ethylcarbonyl)-*N*′-benzyl-*N*″-(2,2-diphenylethyl)iminodiacetic Acid Diamide:** 45 mg (87%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.50 and 9.25 (two t, total 1H), 7.35−7.16 (m, 15H), 6.95 and 6.30 (two t, total 1H), 4.46 (m, 2H), 4.36 and 4.15 (two t, J = 8.4 Hz, total 1H), 3.94 and 3.82 (two s, total 2H), 3.75 and 3.68 (two s, total 2H), 3.15 (m, 2H), 2.20 (q, J = 7.2 Hz, 2H), 1.02 and 0.87 (two t, J = 7.2 Hz, total 3H); FABHRMS (NBA) *m/e* 458.2439 (M + H^+, $C_{28}H_{32}N_3O_3$ requires 458.2443).

***N*-(Benzylcarbonyl)-*N*′-(4-*sec*-butylphenyl)-*N*″-cyclohexyliminodiacetic Acid Diamide:** 57 mg (99%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.38 and 8.50 (m, total 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.26−7.04 (m, 7H), 6.45 (m, 1H), 4.13 and 4.02 (two s, total 2H), 3.98 and 3.89 (two s, total 2H), 3.68 and 3.64 (two s, total 2H), 3.14 (m, 2H), 2.56 (m, 1H), 1.86−1.12 (m, 15H), 0.81 (t, J = 7.2 Hz, 3H); FABHRMS (NBA) *m/e* 464.2893 (M + H^+, $C_{28}H_{38}N_3O_3$ requires 464.2913).

***N*-Benzoyl-*N*″-(4-*sec*-butylphenyl)-*N*′-cyclohexyliminodiacetic Acid Diamide:** 55 mg (98%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.78 and 8.00 (m, total 1H), 7.05−7.66 (m, 9H), 4.15 and 4.10 (two s, total 2H), 4.04 and 4.00 (two s, total 2H), 3.78 (m, 2H), 2.55 (m, 1H), 1.16−1.81 (m, 14H), 0.81 (t, J = 7.4 Hz, 3H); FABHRMS (NBA) *m/e* 450.2748 (M + H^+, $C_{27}H_{36}N_3O_3$ requires 450.2756).

***N*-(Ethylcarbonyl)-*N*″-(4-*sec*-butylphenyl)-*N*′-cyclohexyliminodiacetic Acid Diamide:** 54 mg (99%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.30 and 9.56 (two br s, total 1H), 8.52 and 6.57 (two d, J = 7.6 Hz, total 1H), 7.65, 7.58, 7.13 and 7.07 (four d, J = 8.5 Hz, total 4H), 4.15 and 4.07 (two s, total 2H), 4.06 and 3.96 (two s, total 2H), 2.55 (m, 1H), 2.33 (m, 1H), 1.90−1.14 (m, 17H), 1.09 (t, J = 7.2 Hz, 3H), 0.80 (t, J = 7.2 Hz, 3H); FABHRMS (NBA) *m/e* 402.2747 (M + H^+, $C_{23}H_{36}N_3O_3$ requires 402.2756).

***N*-(Benzylcarbonyl)-*N*′-benzyl-*N*″-(4-*sec*-butylphenyl)iminodiacetic Acid Diamide:** 50 mg (99%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.40 and 9.00 (two br s, total 1H), 7.58−7.04 (m, 14H), 4.38 and 4.36 (two s, total 2H), 4.07 and 4.02 (two s, total 2H), 3.91 and 3.88 (two s, total 2H), 3.63 and 3.54 (two s, total 2H), 2.55 (m, 1H), 1.55 (m, 2H), 1.21 and 1.18 (two d, J = 6.8 Hz, total 2H), 0.80 (t, J = 7.1 Hz, 3H); FABHRMS (NBA) *m/e* 472.2603 (M + H^+, $C_{29}H_{34}N_3O_3$ requires 472.2600).

***N*-Benzoyl-*N*′-benzyl-*N*″-(4-*sec*-butylphenyl)iminodiacetic Acid Diamide:** 47 mg (97%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.60 and 8.95 (two br s, total 1H), 8.70 (m, 1H), 7.44−7.12 (m, 14H), 4.48−4.10 (m, 4H), 3.59 (q, J = 7.0 Hz, 2H), 1.58 (m, 2H), 1.19 (m, 3H), 0.80 (t, J = 5.6 Hz, 3H); FABHRMS (NBA) *m/e* 458.2436 (M + H^+, $C_{28}H_{32}N_3O_3$ requires 458.2443).

***N*-(Ethylcarbonyl)-*N*′-benzyl-*N*″-(4-*sec*-butylphenyl)iminodiacetic Acid Diamide:** 41 mg (95%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.40 and 9.20 (two t, total 1H), 7.64, 7.42, 7.12, 7.05 (four d, J = 8.5 Hz, total 4H), 7.26 (br s, 5H), 4.46 (m, 2H), 4.09 and 4.05 (two s, total 2H), 4.03 and 3.98 (two s, total 2H), 1.20 (m, 3H), 1.07 and 1.01 (two t, J = 7.5 Hz, total 3H), 0.80 and 0.79 (two t, J = 7.4 Hz, total 3H); FABHRMS (NBA) *m/e* 410.2429 (M + H^+, $C_{24}H_{32}N_3O_3$ requires 410.2443).

***N*-(Benzylcarbonyl)-*N*′-(*n*-butyl)-*N*″-(4-*sec*-butylphenyl)iminodiacetic Acid Diamide:** 34 mg (98%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.14 and 8.57 (two t, total 1H), 7.61, 7.43, 7.10, 7.06 (four d, J = 8.2 Hz, total 4H), 7.22 (m, 5H), 4.13 and 4.05 (two s, total 2H), 3.99 and 3.91 (two s, total 2H), 3.69 and 3.65 (two s, total 2H), 3.23 (m, 2H), 2.55 (m, 1H), 1.59−1.14 (m, 6H), 1.20 (t, J = 6.9 Hz, 3H), 0.88 (d, J = 7.2 Hz, 3H), 0.81 (t, J = 7.2 Hz, 3H); FABHRMS (NBA) *m/e* 438.2762 (M + H^+, $C_{26}H_{36}N_3O_3$ requires 438.2756).

Table 1. HPLC Purity of 3 × 3 × 3 Library Intermediates and Final Products

agent	purity (%)	agent	purity (%)
A1	100	A1B3C3	95.6
A2	95.6	A2B1C1	100
A3	100	A2B1C2	90.1
A1B1	100	A2B1C3	95.2
A1B2	95.6	A2B2C1	93.6
A1B3	94.8	A2B2C2	nd[a]
A2B1	96.5	A2B2C3	95.6
A2B2	97.5	A2B3C1	92.6
A2B3	100	A2B3C2	91.3
A3B1	100	A2B3C3	93.7
A3B2	nd[a]	A3B1C1	97.5
A3B3	97.5	A3B1C2	96.1
A1B1C1	94.0	A3B1C3	96.8
A1B1C2	91.3	A3B2C1	94.3
A1B1C3	96.2	A3B2C2	nd[a]
A1B2C1	93.5	A3B2C3	96.7
A1B2C2	95.3	A3B3C1	90.7
A1B2C3	90.6	A3B3C2	96.1
A1B3C1	91.2	A3B3C3	91.4
A1B3C2	92.9		

[a] Not determined, no UV active chromophore.

***N*-Benzoyl-*N*′-(*n*-butyl)-*N*″-(4-*sec*-butylphenyl)iminodiacetic Acid Diamide:** 30 mg (89%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.10 and 8.85 (two br s, total 1H), 7.70−7.12 (m, 9H),6.31 (m, 1H), 4.13−4.06 (m, 4H), 3.32 (m, 2H), 3.15−3.12 (m, 2H), 2.58 (m, 1H), 1.54 (m, 2H), 1.19 (m, 3H), 0.92 (t, J = 7.0 Hz, 3H), 0.82 (t, J = 7.2 Hz, 3H); FABHRMS (NBA) *m/e* 424.2607 (M + H^+, $C_{25}H_{34}N_3O_3$ requires 424.2600).

***N*-(Ethylcarbonyl)-*N*′-(*n*-butyl)-*N*″-(4-*sec*-butylphenyl)iminodiacetic Acid Diamide:** 30 mg (100%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.33 and 9.30 (two br s, total 1H), 8.78 and 6.63 (two br s, total 1H), 7.66, 7.46, 7.14, 7.07 (four d, J = 8.2 Hz, total 4H), 4.15, 4.07 and 3.98 (three s, total 4H), 3.27 (m, 2H), 3.15 (m, 1H), 2.54 (m, 1H), 2.34 (m, 2H), 1.83 (m, 1H), 1.59−1.25 (m, 6H), 1.19 (t, J = 7.2 Hz, 3H), 1.09 (t, J = 7.7 Hz, 3H), 0.89 (m, 3H), 0.80 (m, 3H); FABHRMS (NBA) *m/e* 376.2588 (M + H^+, $C_{21}H_{34}N_3O_3$ requires 376.2600).

***N*-(Benzylcarbonyl)-*N*′-cyclohexyl-*N*″-(3-methoxypropyl)iminodiacetic Acid Diamide:** 20 mg (60%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.93 and 6.12 (two d, total 1H), 8.82 and 6.60 (two t, total 1H), 7.30−7.22 (m, 5H), 4.00 (s, 2H), 3.85 (s, 2H), 3.66 and 3.65 (two s, 2H), 3.48−3.38 (m, 2H), 3.32 (s, 3H), 3.16 (m, 1H), 1.86−1.10 (m, 10H); FABHRMS (NBA) *m/e* 404.2550 (M + H^+, $C_{22}H_{34}N_3O_4$ requires 404.2549).

***N*-Benzoyl-*N*′-cyclohexyl-*N*″-(3-methoxypropyl)iminodiacetic Acid Diamide:** 14 mg (43%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.68 (m, 1H), 7.46−7.26 (m, 5H), 6.78 and 6.35 (two m, 1H), 3.98 (s, 2H), 3.95 (s, 2H), 3.52−3.34 (m, 2H), 3.33 (s, 3H), 3.14 (m, 1H), 1.90−1.10 (m, 12H); FABHRMS (NBA) *m/e* 390.2364 (M + H^+, $C_{21}H_{32}N_3O_4$ requires 390.2392).

***N*-(Ethylcarbonyl)-*N*′-cyclohexyl-*N*″-(3-methoxypropyl)iminodiacetic Acid Diamide:** 6 mg (21%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.00 and 3.98 (two s, 2H), 3.87 (br s, 2H), 3.85−3.36 (m, 5H), 3.34 (s, 3H), 3.16 (m, 2H), 2.30 (q, J = 7.2 Hz, 2H), 1.88−1.18 (m, 12H), 1.11 (t, J = 7.2 Hz, 3H); FABHRMS (NBA) *m/e* 342.2407 (M + H^+, $C_{17}H_{32}N_3O_4$ requires 342.2392).

***N*-(Benzylcarbonyl)-*N*′-(*n*-butyl)-*N*″-(2,2-diphenylethyl)iminodiacetic Acid Diamide:** 38 mg (89%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.05 and 8.90 (two t, total 1H), 7.29−7.18 (m, 15H), 6.20 and 6.10 (two t, total 1H), 4.38 and 4.16 (two t, J = 7.7 Hz, total 1H), 3.92 (br s, 2H), 3.82 and 3.72 (two s, total 2H), 3.61 (s, 2H), 3.25−3.12 (m, 2H), 1.51−1.32 (m, 4H), 0.94 and 0.93 (two t, J = 7.2 Hz, 3H); FABHRMS (NBA) *m/e* 486.2765 (M + H^+, $C_{30}H_{36}N_3O_3$ requires 486.2756).

***N*-Benzoyl-*N*′-(*n*-butyl)-*N*″-(2,2-diphenylethyl)iminodiacetic Acid Diamide:** 34 mg (80%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.05 and 8.50

(two br s, total 1H), 7.37−7.14 (m, 15H), 6.50 and 6.30 (two br s, total 1H), 4.44 and 4.22 (two t, J = 7.7 Hz, total 1H), 3.97 (m, 2H), 3.87 and 3.83 (two s, total 2H), 3.30 (q, J = 6.2 Hz, 2H), 1.53−1.35 (m, 4H), 0.94 (t, J = 7.1 Hz, 3H): FABHRMS (NBA) *m/e* 472.2581 (M + H^+, $C_{29}H_{34}N_3O_3$ requires 472.2600).

***N*-(Ethylcarbonyl)-*N′*-(*n*-butyl)-*N″*-(2,2-diphenylethyl)iminodiacetic Acid Diamide:** 32 mg (86%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.21 and 9.00 (two t, total 1H), 7.33−7.16 (m, 10H), 6.18 and 6.12 (two t, total 1H), 4.38 and 4.19 (two t, J = 7.7 Hz, total 1H), 3.91 and 3.84 (two s, total 2H), 3.76 and 3.65 (two s, total 2H), 3.27 (m, 2H), 3.15 (m, 1H), 2.26 (q, J = 7.3 Hz, 2H), 1.87−1.81 (m, 4H), 1.56−1.32 (m, 4H), 1.09 (t, J = 7.3 Hz, 3H), 0.87 (t, J = 7.3 Hz, 3H); FABHRMS (NBA) *m/e* 424.2578 (M + H^+, $C_{25}H_{34}N_3O_3$ requires 424.2600).

***N*-(Benzylcarbonyl)-*N′*-(*n*-butyl)-*N″*-(3-methoxypropyl)iminodiacetic Acid Diamide:** 15 mg (70%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.10 and 8.71 (two t, total 1H), 7.32−7.22 (m, 5H), 6.58 and 6.32 (two t, total 1H), 4.01 (s, 2H), 3.88 and 3.85 (two s, total 2H), 3.66 (s, 2H), 3.49−3.34 (m, 2H), 3.33 (s, 3H), 3.25−3.15 (m, 2H), 1.82−1.76 (m, 2H), 1.52−1.30 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H); FABHRMS (NBA) *m/e* 378.2406 (M + H^+, $C_{20}H_{31}N_3O_4$ requires 378.2392).

***N*-Benzoyl-*N′*-(*n*-butyl)-*N″*-(3-methoxypropyl)iminodiacetic Acid Diamide:** 10 mg (49%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.95 and 8.50 (two br s, total 1H), 7.46−7.38 (m, 5H), 6.72 and 6.52 (two br s, total 1H), 3.98 (s, 4H), 3.47−3.42 (m, 2H), 3.33 and 3.31 (two s, total 3H), 3.16 (m, 1H), 1.85−1.79 (m, 2H), 1.70 (br s, 2H), 1.60−1.25 (m, 6H), 0.94 (t, J = 7.7 Hz, 3H); FABHRMS (NBA) *m/e* 364.2236 (M + H^+, $C_{19}H_{30}N_3O_4$ requires 364.2236).

***N*-(Ethylcarbonyl)-*N′*-(*n*-butyl)-*N″*-(3-methoxypropyl)iminodiacetic Acid Diamide:** 3 mg (16%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.00 (br s, 2H), 3.87 (br s, 2H), 3.85−3.38 (m, 6H), 3.34 (s, 3H), 2.16 (q, J = 7.2 Hz, 2H), 1.70−1.23 (m, 6H), 1.12 (t, J = 7.3 Hz, 1H), 0.91 (t, J = 6.6 Hz, 3H); FABHRMS (NBA) *m/e* 316.2245 (M + H^+, $C_{15}H_{30}N_3O_4$ requires 316.2236).

Supporting Information Available: ^{1}H NMR spectra of the 3 × 3 × 3 matrix library intermediates and final products (38 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, can can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA9530681