Convergent Solution-Phase Combinatorial Synthesis with Multiplication of Diversity through Rigid Biaryl and Diarylacetylene Couplings

Dale L. Boger,* Weiqin Jiang, and Joel Goldberg

Department of Chemistry and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Received April 16, 1999

The solution-phase synthesis of iminodiacetic acid diamide libraries linked to aryl iodides and their Pd-catalyzed dimerization are detailed. Mixtures containing 64 980 components are synthesized in only 4 steps from *N*-BOC-iminodiacetic acid anhydride (**1**) and 21 readily available starting materials, demonstrating the multiplication of diversity achievable by the convergent assembly of building blocks. Both biaryl formation and sequential Stille couplings with bis(tributylstannyl)-acetylene are utilized to dimerize the functionalized iminodiacetic acid diamide precursors resulting in product libraries with two sets of binding groups separated by variable length rigid linkers suitable for probing protein−protein interactions. Deconvolution libraries synthesized alongside the full mixtures allow for identification of active components.

Introduction

Ligand-induced receptor and protein dimerization or oligomerization has emerged as a general mechanism for signal transduction[1] and important members of many receptor superfamilies are activated by such a process.[2−5] Many of these receptors and proteins appear to bind their ligands using only a small cluster of residues for a majority of the binding interaction.[6,7] This has led to the expectation that small molecules may be capable of inducing their dimerization and activation, and recently peptide,[7,8] as well as nonpeptide,[9] agonists promoting receptor homodimerization have been identified through the random screening of compound libraries. Our interest in combinatorial chemistry rested on its potential to provide candidate leads for promoting receptor activation by dimerization. This, coupled with the potential of utilizing a single approach for the discovery of antagonists and their conversion to agonists, is an important element underlying our continued development[10,11] of solution-phase techniques (Figure 1).[12] Recently we disclosed an example of the convergent combination of a small number of monomers that is especially suited for the discovery of receptor antagonists and their derivitization into potential receptor dimerization agonists.[13] Mixture libraries containing 476 775 and 114 783 975 components were prepared by the dimerization of functionalized iminodiacetic acid diamides via the olefin metathesis reaction. Deconvolution of these mixtures can be accomplished by the complementary techniques of positional scanning[14] and deletion synthesis deconvolution.[13]

Complementary to our development of the olefin metathesis reaction to simultaneously join iminodiacetic acid derivatives and randomize the length of the linking tether, we have explored other methods of such convergent library synthesis. Herein we report the palladium-catalyzed dimerization of iodoarene-appended iminodiacetic acid diamide libraries (Figure 2). As in the olefin metathesis studies, these libraries were designed to contain binding groups of appreciable size to allow sufficient contact with target protein surfaces. In this investigation we explored dimerization methods which result in a rigid core from which the pendent binding groups are directed toward the target proteins. This may

(1) Hinterding, K.; Alonso-Diaz, D.; Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 688. Klemm, J. D.; Schreiber, S. L.; Crabtree, G. R. *Annu. Rev. Imunol.* **1998**, *16*, 569. Heldin, C.-H. *Cell* **1995**, *80*, 213.

(2) Ullrich, A.; Schlessinger, J. *Cell* **1990**, *61*, 203.

(3) Moutoussamy, S.; Kelly, P. A.; Finidori, J. *Eur. J. Biochem.* **1998**, *255*, 1.

(4) Massague, J.; Attisano, L.; Wrana, J. L. *Trends Cell Biol.* **1994**, *4*, 172. Lemmon, M. A.; Schlessinger, J. *Trends Biochem. Sci.* **1994**, *19*, 459.

(5) Smith, C. A.; Farrah, T.; Goodwin, R. G. *Cell* **1994**, *76*, 959.

(6) Wells, J. A. *Science* **1996**, *273*, 449. Reineke, U.; Schneider-Mergener, J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 769.

(7) Livnah, O.; Stura, E. A.; Johnson, D. L.; Middleton, S. A.; Mulcahy, L. S.; Wrighton, N. C.; Dower, W. J.; Jolliffe, L. K.; Wilson, I. A. *Science* **1996**, *273*, 464.

(8) Cwirla, S. E.; Balasubramanian, P.; Duffin, D. J.; Wagstrom, C. R.; Gates, C. M.; Singer, S. C.; Davis, A. M.; Tansik, R. L.; Mattheakis, L. C.; Boytos, C. M.; Schatz, P. J.; Baccanari, D. P.; Wrighton, N. C.; Barrett, R. W.; Dower, W. J. *Science*, **1997**, *276*, 1696. Kimura, T.; Kaburaki, H.; Miyamoto, S.; Katayama, J.; Watanabe, Y. *J. Biochem.* **1997**, 122, 1046,

(9) Tian, S.-S.; Lamb, P.; King, A. G.; Miller, S. G.; Kessler, L.; Luengo, J. I.; Averill, L.; Johnson, R. K.; Gleason, J. G.; Pelus, L. M.; Dillon, S. B.; Rosen, J. *Science* **1998**, *281*, 257. Kimura, T.; Kaburaki, H.; Tsujino, T.; Ikeda, Y.; Kato, H.; Watanabe, Y. *FEBS Lett.* **1998**, *428*, 250.

(10) Cheng, S.; Comer, D. D.; Williams, J. P.; Myers, P. L.; Boger, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 2567. Boger, D. L.; Tarby, C. M.; Myers, P. L.; Caporale, L. H. *J. Am. Chem. Soc.* **1996**, *118*, 2109. Cheng, S.; Tarby, C. M.; Comer, D. D.; Williams, J. P.; Caporale, L. H.; Myers, P. L.; Boger, D. L. *Bioorg. Med. Chem.* **1996**, *4*, 727. Boger, D. L.; Ducray, P.; Chai, W.; Jiang, W.; Goldberg, J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2339. Boger, D. L.; Ozer, R. S.; Andersson, C.-M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1903. Boger, D. L.; Chai, W. *Tetrahedron* **1998**, *54*, 3955. Boger, D. L.; Chai, W.; Ozer, R. S.; Andersson, C.-M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 463.

(11) Boger, D. L.; Goldberg, J.; Jiang, W.; Chai, W.; Ducray, P.; Lee, J. K.; Ozer, R. S.; Andersson, C.-M. *Bioorg. Med. Chem.* **1998**, *6*, 1347.

(12) For a recent review on solution-phase combinatorial chemistry, see: Merritt, A. T. *Comb. Chem. High Throughput Screening* **1998**, *1*, 57.

(13) Boger, D. L.; Chai, W.; Jing, Q. *J. Am. Chem. Soc.* **1998**, *120*, 7220.

(14) Dooley, C. T.; Houghten, R. A. *Life Sci.* **1993**, *52*, 1509. Pinilla, C.; Appel, J. R.; Blanc, P.; Houghten, R. A. *Biotechniques* **1992**, *13*, 901.

10.1021/jo990639p CCC: $18.00
Published on Web 08/21/1999

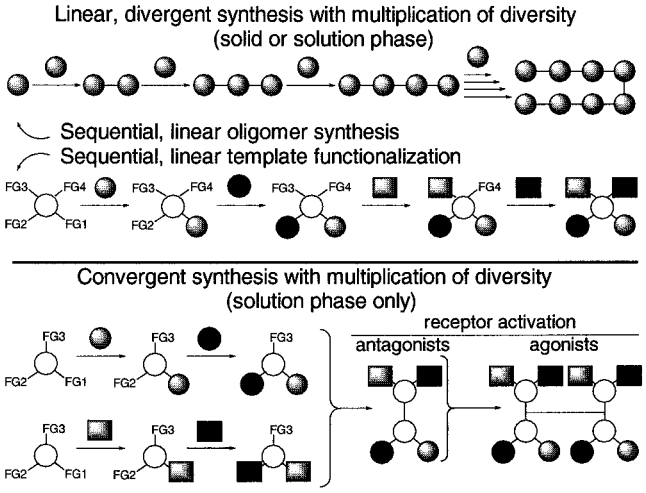


Figure 1.

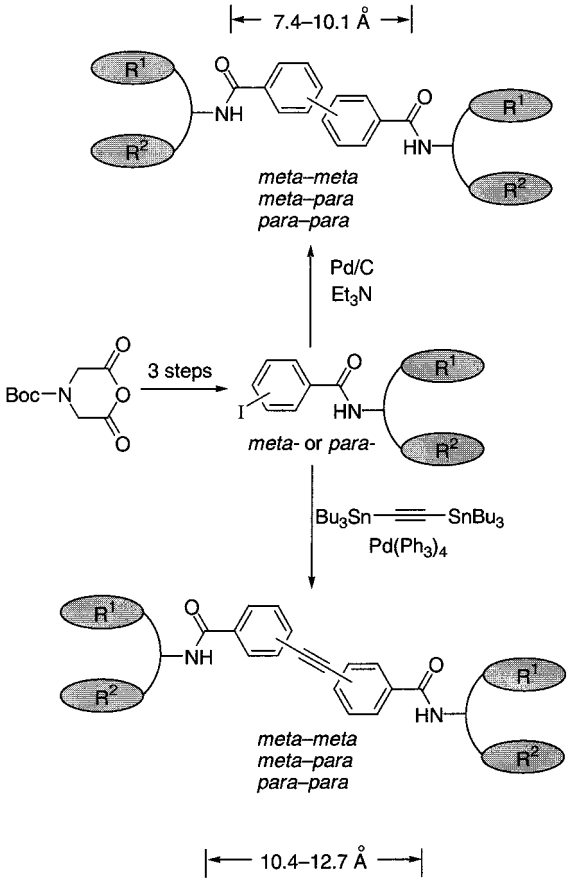
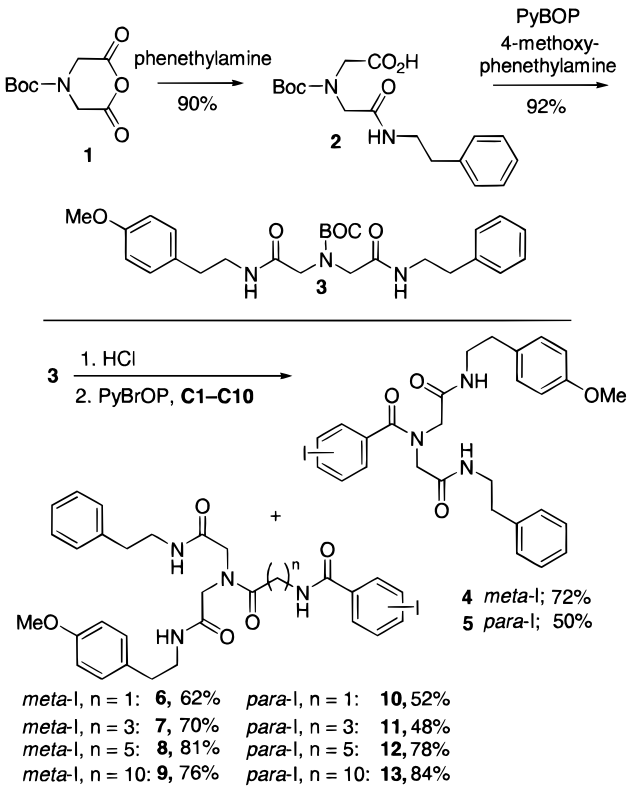


Figure 2. Dimerization via biaryl and diarylacetylene rigid linkages which position target binding groups R^1 and R^2.

be an especially important property for receptor dimerization agonist libraries considering recent studies which suggest receptor activation is achievable only by a precise

(15) Livnah, O.; Stura, E. A.; Middleton, S. A.; Johnson, D. L.; Jolliffe, L. K.; Wilson, I. A. *Science* **1999**, *283*, 987. Remy, I.; Wilson, I. A.; Michnick, S. W. *Science* **1999**, *283*, 990. Ballinger, M. D.; Wells, J. A. *Nature Struct. Biol.* **1998**, *5*, 938. Livnah, O.; Johnson, D. L.; Stura, E.; Farrell, F. X.; Barbone, F. P.; You, Y.; Liu, K. D.; Goldsmith, M. A.; He, W.; Krause, C. D.; Pestka, S.; Jolliffe, L. K.; Wilson, I. A. *Nature Struct. Biol.* **1998**, *5*, 993. Syed, R.; Reid, S. W.; Li, C.; Cheetham, J. C.; Aoki, K. H.; Liu, N.; Zhan, H.; Osslund, T. D.; Chirino, A. J.; Zhang, J.; Finer-Moore, J.; Elliott, S.; Sitney, K.; Katz, B. A.; Matthews, D. J.; Wendoloski, J. J.; Egrie, J.; Stroud, R. M. *Nature* **1998**, *395*, 511.

Scheme 1



(re)orientation of the membrane bound target proteins.[15] Two palladium-catalyzed dimerization protocols are described which link functionalized iodoarene precursors, biaryl formation by direct homocoupling, and diarylacetylene formation by sequential Stille couplings with bis(tributylstannyl)acetylene.

Developmental Studies. Initial efforts focused on the preparation of a modest library to validate the approach and allow for optimization of the reaction conditions (Scheme 1). *N*-BOC-iminodiacetic acid anhydride (**1**), formed in situ from the readily available dicarboxylic acid, was the starting point for the library synthesis.[10,11] Functionalization with phenethylamine provided monoamide **2** in 90% yield, and subsequent coupling (PyBOP) of the remaining carboxylic acid with 4-methoxyphenethylamine provided **3** in 92% yield. Simple liquid−liquid extractions provided pure products for both steps. The third functionalization of the iminodiacetic acid template involved the coupling to an iodoarene suitable for Pd-catalyzed dimerization. Variability in the chain-length connecting the iminodiacetic acid template to the dimerization center was included to allow the binding groups to span a variety of distances. Both meta and para substitution of the iodobenzamides were also chosen to increase the diversity of reaction products. *N*-BOC deprotection of **3** (HCl−dioxane) and PyBrOP coupling of the crude HCl salt with the 10 iodoarene-linked carboxylic acids **C1**−**C10** (Figure 3) provided the dimerization precursors **4**−**13** (48−84%). Regardless of the conversion, unreacted starting materials or reaction byproducts were easily removed by acidic and basic liquid−liquid extractions providing pure products.

With the model iodoarene precursors in hand, their symmetrical and unsymmetrical dimerizations were investigated[16] (Scheme 2). Initial experiments with the Stille coupling reaction between the iodoarenes (**4**−**13**)

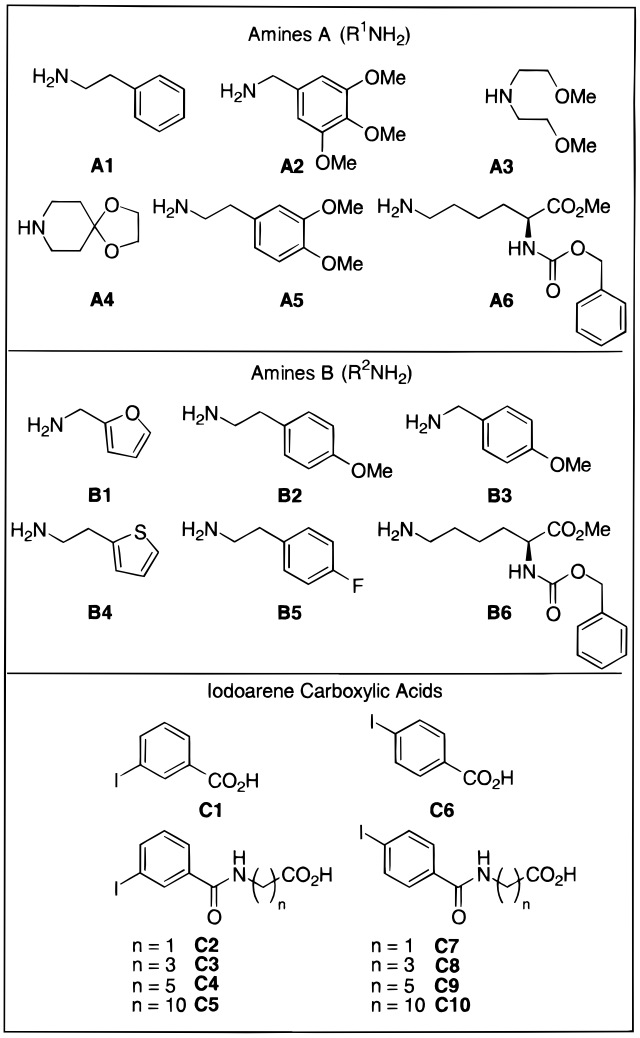
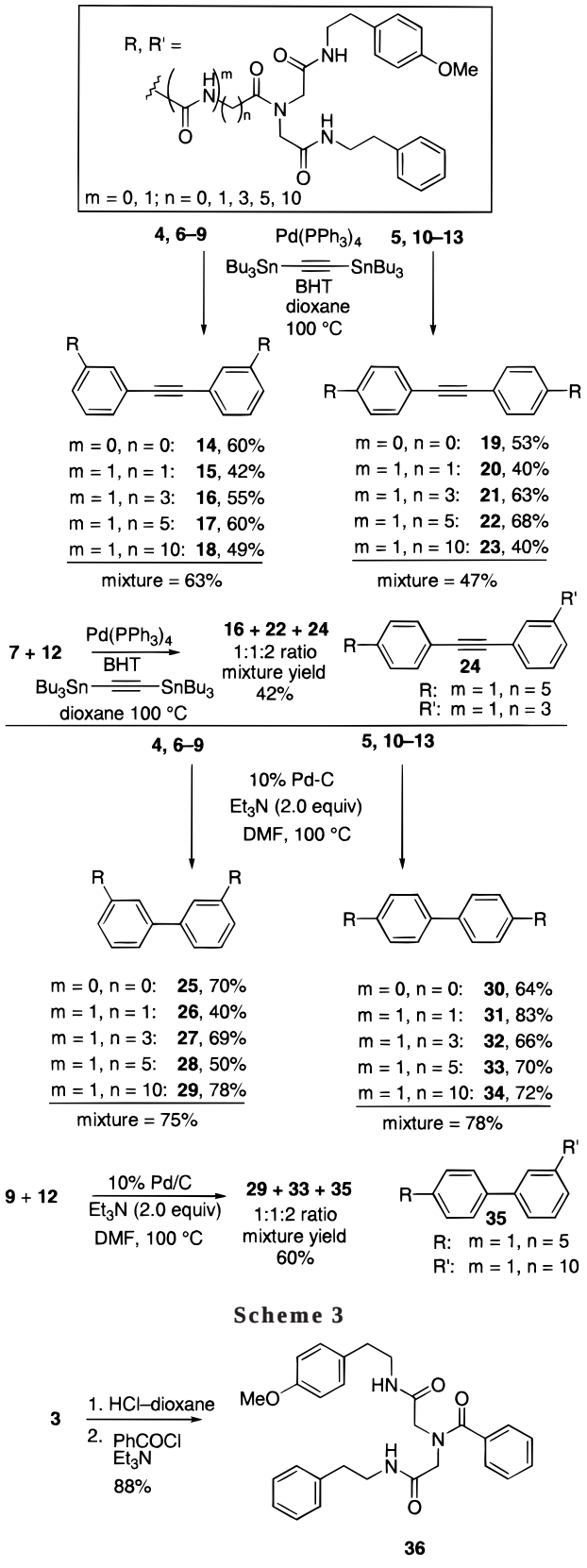


Figure 3. The 21 building blocks used to assemble both the biaryl and diarylacetylene libraries.

and bis(tributylstannyl)acetylene[17] suggested that the reactivities of the iodobenzamide derivatives were nearly identical regardless of the amide substitution (chain length) or site of substitution (meta or para). Optimum conditions were found to be reaction with bis(tributylstannyl)acetylene (0.5 equiv) and $Pd(Ph_3)_4$ (0.05 equiv) in dioxane at 100 °C for 4 h. Addition of a few crystals of BHT were found to improve the reaction yields which ranged from 40 to 68% for the homodimerizations **4**−**13** → **14**−**23**. Other additives such as LiCl[17] used in similar couplings were found to have no effect on these reactions. The iodides were completely consumed under these conditions, and no reduction or other byproducts (e.g., biaryl formation) were observable. The lack of these byproducts from **14** and **19** was further demonstrated by an independent synthesis of the biaryl products **25** and **30** and the reduction product **36** (Scheme 3). Comparison of these products by ^1H NMR spectroscopy and TLC to that of the crude Stille product confirmed their absence. Consequently, purification mainly involved the removal of catalyst and tin byproducts. This was accomplished by eluting the reaction mixtures from a short column of SiO_2. All impurities were found to be removable by this method, providing compounds judged clean by NMR spectroscopy.

Unsymmetrical couplings were first examined by reacting an equimolar mixture of the 5 *m*-iodobenzamide

Scheme 2



Scheme 3

(16) The corresponding aryl bromides were also tested and found to be either too unreactive or lead to unacceptable amounts of reduction byproduct in both the Stille and biaryl coupling reactions.

(17) For the use of bis(tributylstannyl)acetylene to synthesize diarylalkynes, see: Cummins, C. H. *Tetrahedron Lett.* **1994**, *35*, 857.

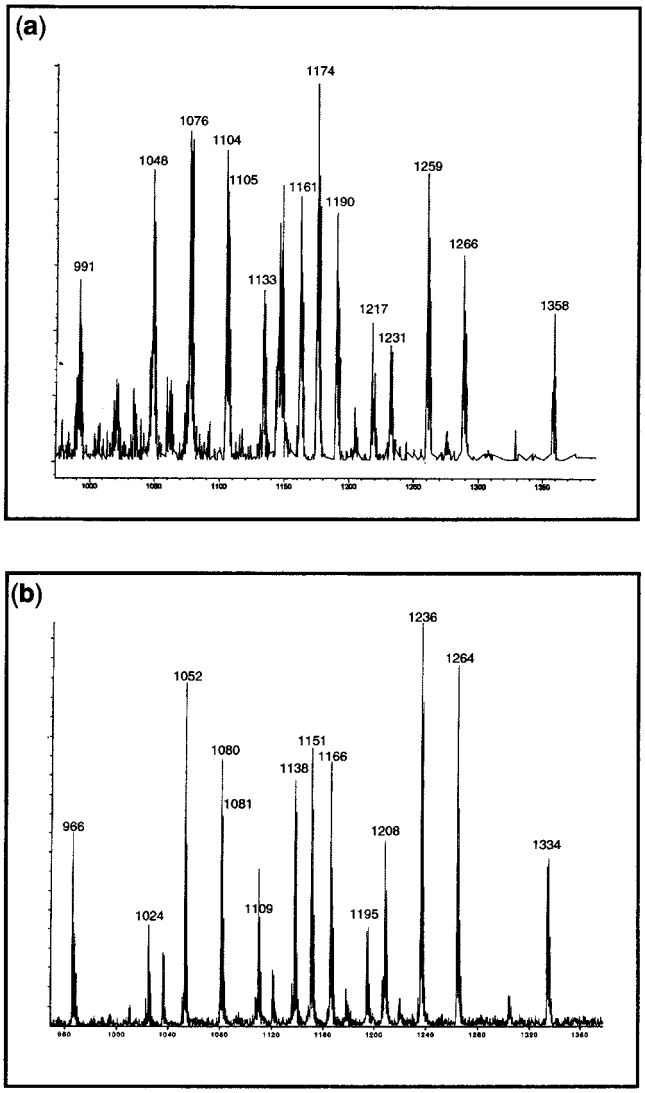


Figure 4. ESMS of the dimerization sublibraries synthesized from the couplings of a mixture of **4** and **6**−**9** by either (a) Stille coupling with bis(tributylstannyl)acetylene, $Pd(Ph_3)_4$ or (b) homocoupling with 10% Pd/C, Et_3N. Each product mixture consists of 15 components with 14 distinct molecular weights.

derivatives **4** and **6**−**9** in a single reaction vessel using the same reaction and purification conditions optimized for the individual compounds. The purified product mixture contained all 15 dimeric products[18] (63% yield) as confirmed by MS analysis of the product mixture (Figure 4a). Similarly a mixture of the *p*-iodobenzamide derivatives **10**−**13** were reacted providing the expected mixture of 9 products in comparable yield. The meta and para mixture couplings were investigated by reacting **7** and **12** in which a statistical 1:1:2 distribution of the two homo- and hetero-coupled products (**16**, **22**, and **24**) were observed, the mixture yield being 42%.

We have previously reported the synthesis of biaryl libraries by the Pd/C-catalyzed homocoupling of substituted iodoarenes.[19] This was extended to the same iodoarene-linked iminodiacetic acid diamides used in the Stille coupling reactions. The test reactions for biaryl synthesis (individual homocouplings of **4**−**13**, Scheme 2) worked effectively with the best conditions being 10% Pd/C (0.1 equiv) and Et_3N (2.0 equiv) in DMF at 100 °C, for 18 h. All starting materials were consumed, and the product biaryls were isolated in moderate to good yields for both the meta- and para-substituted iodobenzamides. A small amount of reduction byproduct (e.g., **36**) was observed even under these optimized conditions; however, conducting the reactions highly concentrated (0.2 M) kept this to a minimum (<10%). The biaryl products (**25**−**34**) were found to be chromatographically similar to one another and distinct from any reaction byproducts (including reduction products). Therefore, they could be similarly purified by eluting the crude product mixture from a short column of SiO_2.[20]

Unsymmetrical and mixture biaryl couplings were examined first by dimerizing a mixture of the 5 *m*-iodobenzamide derivatives **4** and **6**−**9**. The eluted product mixture contained all 15 predicted dimeric products (75% yield) demonstrated by MS analysis of the product mixture (Figure 4b). The *p*-iodobenzamide derivatives **5** and **10**−**13** were similarly reacted with analogous results. Mixed meta and para couplings were tested by subjecting a mixture of **9** and **12** to the 10% Pd/C, Et_3N, DMF conditions in which a statistical 1:1:2 distribution of the two homo- and hetero-coupled and products (**29**, **33**, and **35**) were formed in 60% yield.

Synthesis of Full Mixture and Deconvolution Libraries. With optimized conditions for both the homocoupling and Stille coupling reactions in hand, the synthesis of biaryl and diarylacetylene full matrix libraries was conducted (Scheme 4, Figure 3). Following the synthetic protocols used with the model substrates, two libraries containing 64 980 members each were assembled in a total of five steps. Functionalization of **1** with a mixture of six amines (**A1**−**A6**) provided **37** in 74% yield (Scheme 4). PyBOP coupling of the remaining carboxylic acid group with 6 amines (**B1**−**B6**) provided 36 compound mixture **38** (65%). This mixture was deprotected (HCl−dioxane) and coupled with the 10 iodoarene carboxylic acids (**C1**−**C10**) providing mixture **39** (360 components, 67%). After each coupling reaction in this sequence, the product mixtures were purified by acid and/or base extractions which effectively removed any unreacted starting materials or reaction byproducts without affecting the integrity of the product mixtures. The iodoarene mixture **39** was then subjected to each of our two palladium-catalyzed dimerization strategies. The reaction and purification conditions employed were the same as described for the smaller mixture models. The direct coupling was found to proceed in 90% yield based on the average product molecular weight, and the Stille coupling with bis(tributylstannyl)acetylene was in 76% yield resulting in iminodiacetic acid diamide dimer libraries with rigid biaryl and diarylacetylene cores. Each product library contains 64 980 components (360 homodimers and 64 620 heterodimers).

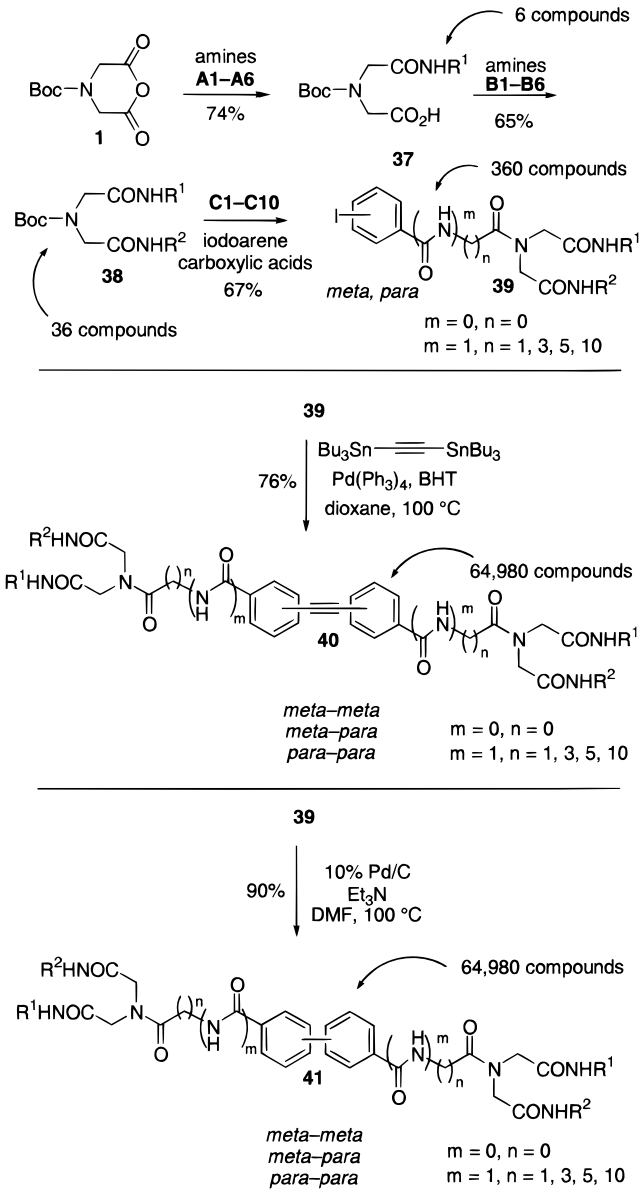
At the same time that the full mixture libraries were constructed, positional scanning[14] and deletion synthesis[13] deconvolution libraries were assembled (see Table 1). These sublibraries are designed to be synthesized and screened alongside the parent mixtures to allow identification of active components. For either process, decon-

(18) A statistical dimerization of *n* components results in a mixture of $n(n + 1)/2$ products.

(19) Boger, D. L.; Goldberg, J.; Andersson, C.-M. *J. Org. Chem.* **1999**, *64*, 2422.

(20) The product biaryls can also be purified by size exclusion chromatography using Bio-Beads S-X8 resin, THF eluent.

Scheme 4



volution of each library requires only 22 additional mixture syntheses. Each of the positional scanning sublibraries contains a single substitution at one location but the full mixtures at the other positions. For example, the mixture **40 scanA1** is the diarylalkyne product containing only **A1** in the first substitution position (R^1-NH_2), combined with **B1**−**B6** and **C1**−**C10**. The deletion synthesis deconvolution libraries are synthesized in a similar fashion, but in this case a single building block is omitted at one location and the full mixtures are used at the other positions. For example, **40 deleteA1** is the diarylalkyne product containing only **A2**−**A6** in the first substitution position (R^2NH_2), combined with **B1**−**B6** and **C1**−**C10**. Both of these deconvolution libraries are synthesized by the same synthetic procedure as the parent library (Scheme 4, Figure 3).

Conclusions

The combinatorial dimerization of iodoarene-linked iminodiacetic carboxamide libraries was conducted by both Pd-catalyzed homocoupling (biaryl formation) and Stille coupling with bis(tributylstannyl)acetylene (diarylalkyne formation) resulting in product libraries containing 64 980 components. Both deletion synthesis deconvolution and positional scanning sublibraries, synthesized alongside the parent mixtures, allow for rapid identification of active components. The examination of these libraries in receptor dimerization and other protein−protein interaction screens is in progress, and the results will be disclosed in due course.

Table 1. Yields (Calculated by the Average Product Molecular Weight) for the Synthesis of Scanning and Deletion Deconvolution Mixture Libraries[a]

Scanning Deconvolution

38	scanA1	65%	scanB1	61%				
	scanA2	77%	scanB2	66%				
	scanA3	58%	scanB3	65%				
	scanA4	49%	scanB4	58%				
	scanA5	60%	scanB5	86%				
	scanA6	77%	scanB6	85%				
39	scanA1	95%	**40**	scanA1	93%	**41**	scanA1	90%
	scanA2	88%		scanA2	78%		scanA2	87%
	scanA3	84%		scanA3	91%		scanA3	90%
	scanA4	82%		scanA4	95%		scanA4	71%
	scanA5	70%		scanA5	95%		scanA5	90%
	scanA6	84%		scanA6	95%		scanA6	95%
	scanB1	48%		scanB1	76%		scanB1	55%
	scanB2	65%		scanB2	84%		scanB2	79%
	scanB3	72%		scanB3	94%		scanB3	87%
	scanB4	55%		scanB4	67%		scanB4	80%
	scanB5	71%		scanB5	47%		scanB5	90%
	scanB6	78%		scanB6	71%		scanB6	90%
	scanC1	58%		scanC1	95%		scanC1	94%
	scanC2	36%		scanC2	95%		scanC2	88%
	scanC3	68%		scanC3	95%		scanC3	63%
	scanC4	71%		scanC4	95%		scanC4	91%
	scanC5	67%		scanC5	95%		scanC5	93%
	scanC6	69%		scanC6	95%		scanC6	80%
	scanC7	56%		scanC7	39%		scanC7	52%
	scanC8	62%		scanC8	91%		scanC8	79%
	scanC9	67%		scanC9	70%		scanC9	84%
	scanC10	61%		scanC10	69%		scanC10	85%

Deletion Deconvolution

38	deleteA1	48%	deleteB1	41%				
	deleteA2	56%	deleteB2	43%				
	deleteA3	64%	deleteB3	48%				
	deleteA4	42%	deleteB4	62%				
	deleteA5	52%	deleteB5	61%				
	deleteA6	48%	deleteB6	52%				
39	deleteA1	63%	**40**	deleteA1	77%	**41**	deleteA1	83%
	deleteA2	67%		deleteA2	75%		deleteA2	91%
	deleteA3	44%		deleteA3	95%		deleteA3	84%
	deleteA4	70%		deleteA4	72%		deleteA4	78%
	deleteA5	49%		deleteA5	80%		deleteA5	88%
	deleteA6	59%		deleteA6	78%		deleteA6	69%
	deleteB1	68%		deleteB1	88%		deleteB1	81%
	deleteB2	61%		deleteB2	71%		deleteB2	67%
	deleteB3	62%		deleteB3	88%		deleteB3	81%
	deleteB4	61%		deleteB4	64%		deleteB4	75%
	deleteB5	62%		deleteB5	86%		deleteB5	65%
	deleteB6	60%		deleteB6	66%		deleteB6	64%
	deleteC1	59%		deleteC1	81%		deleteC1	80%
	deleteC2	46%		deleteC2	88%		deleteC2	76%
	deleteC3	55%		deleteC3	95%		deleteC3	78%
	deleteC4	60%		deleteC4	95%		deleteC4	68%
	deleteC5	58%		deleteC5	93%		deleteC5	70%
	deleteC6	54%		deleteC6	96%		deleteC6	68%
	deleteC7	98%		deleteC7	85%		deleteC7	90%
	deleteC8	95%		deleteC8	83%		deleteC8	66%
	deleteC9	77%		deleteC9	86%		deleteC9	65%
	deleteC10	77%		deleteC10	95%		deleteC10	66%

[a] See text for an explanation of the structures and codes.

Experimental Section

***N*-((*tert*-Butyloxy)carbonyl)-*N*′-(2-(4-methoxyphenyl)-ethyl)-*N*″-(2-(phenyl)ethyl)iminodiacetic Acid Diamide (3).** Monoamide **2**[11] (0.41 g, 1.3 mmol) was dissolved in DMF (5.0 mL) and added to a flask containing *i*-Pr_2NEt (0.33 g, 2.6

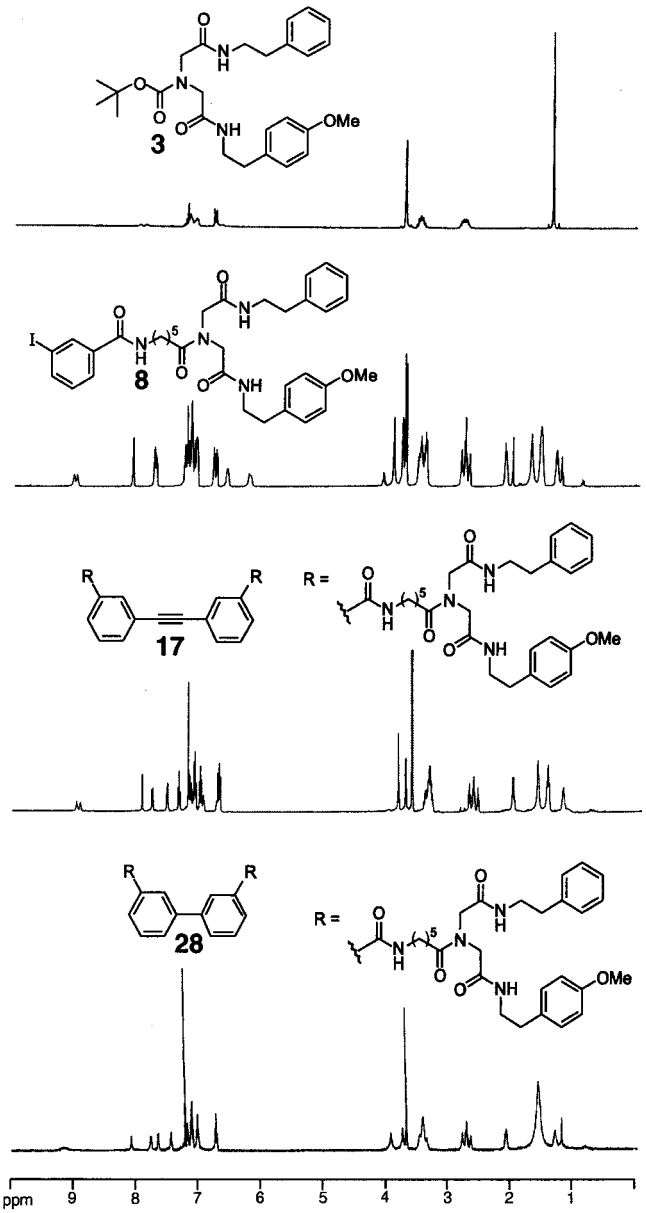


Figure 5. Comparison of the ^{1}H NMR ($CDCl_3$) spectra of **3**, **8**, **17**, and **28**.

mmol) and 4-methoxyphenethylamine (0.21 g, 1.42 mmol). PyBOP (0.74 g, 1.42 mmol) was added, and the reaction mixture was stirred for 16 h at 25 °C and then poured into a separatory funnel containing 50 mL of 10% aqueous HCl and extracted into EtOAc (3 × 50 mL). The combined organic phases were washed with 10% aqueous HCl (2 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), and saturated aqueous NaCl (50 mL), dried (Na_2SO_4), and concentrated to provide 0.55 g (94%) of **3** as a colorless oil (see Figure 5 for a comparison of ^{1}H NMR spectra): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.29−7.08 (m, 7H), 6.81 (d, 2H, J = 8.5 Hz), 3.74 (m, 7H), 3.50 (m, 4H), 2.80 (m, 4H), 1.38 (s, 9H); IR (film) ν_{max} 3243, 3066, 2974, 2932, 1700, 1652, 1558, 1513, 1456, 1394, 1367, 1247, 1175, 1140, 1033, 960, 894, 846, 751, 700 cm^{-1}; FABHRMS (NBA−NaI) m/z 470.2651 (M + H$^+$, $C_{26}H_{35}N_3O_5$ requires 470.2655).

General Procedure for the Third Diversification, Individual Components. Preparation of *N*-(3-iodobenzoyl)-*N*′-(2-phenylethyl)-*N*″-(2-(4-methoxyphenyl)ethyl)-iminodiacetic Acid Diamide (4). The BOC derivative **3** (71 mg, 0.15 mmol) was stirred in 4 N HCl−dioxane (1.0 mL) for 2 h. Solvent and excess acid were removed under a stream of N_2, and the remaining crude HCl salt was dissolved in DMF (1.5 mL) and treated with *m*-iodobenzoic acid (**C1**, 41.9 mg, 0.169 mmol), PyBrOP (79 mg, 0.169 mmol), and *i*-Pr_2NEt (88 μL, 0.507 mmol). After 18 h of stirring at 25 °C, the reaction mixture was diluted with EtOAc (50 mL) and washed with 10% aqueous HCl (3 × 50 mL), saturated aqueous $NaHCO_3$ (50 mL), and saturated aqueous NaCl (50 mL). Drying (Na_2SO_4) and concentration provided **4** as a white foam (63 mg, 68%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.75 (m, 2H), 7.28 (m, 6H), 7.18 (m, 2H), 7.10 (m, 1H), 6.85 (m, 2H), 3.86 (br s, 4H), 3.76 (s, 3H), 3.61 (m, 4H), 2.85 (m, 4H); IR (film) ν_{max} 3274, 3062, 2932, 2834, 1651, 1558, 1512, 1454, 1398, 1372, 1331, 1301, 1247, 1196, 1178, 1033, 1009, 958, 914, 803, 750, 735, 700 cm^{-1}; FABHRMS (NBA−CsI) m/z 732.0359 (M + Cs$^+$, $C_{28}H_{30}N_3O_4I$ requires 732.0335).

Characterization data for **5**−**13** may be found in Supporting Information.

General Procedure for the Synthesis of Individual Diarylacetylenes, Preparation of 14. Iodide **4** (14.4 mg, 0.024 mmol), bis(tributylstannyl)acetylene (7.24 mg, 0.012 mmol), and tetrakis(triphenylphosphine)palladium (1.38 mg, 0.0012 mmol) were dissolved in dioxane (0.2 mL). Three crystals of BHT (2,6-di-*tert*-butyl-4-methylphenol) were added, and the reaction mixture was stirred at 100 °C for 5 h. The solvent was evaporated and chromatography (SiO_2, 50% EtOH/EtOAc) afforded **14** as a colorless oil (7.0 mg, 60%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.90−6.95 (m, 22H), 6.75 (m, 4H), 3.90−3.40 (m, 22H), 3.20−2.60 (m, 8H); IR (film) ν_{max} 3274, 3064, 2933, 1652, 1558, 1539, 1512, 1456, 1398, 1301, 1246, 1178, 1112, 1087, 1033, 957, 806, 750, 699 cm^{-1}; FABHRMS (NBA−CsI) m/z 1101.3583 (M + Cs$^+$, $C_{58}H_{60}N_6O_8$ requires 1101.3527).

Characterization data for **15**−**23** may be found in Supporting Information.

Synthesis of a 15-Component Diarylacetylene Sublibrary. An equimolar solution of *m*-iodobenzamides **4** and **6**−**9** (0.004 mmol each, 0.020 mmol total) in 0.4 mL dioxane was treated with bis(tributylstannyl)acetylene (6.0 mg, 0.010 mmol), $Pd(PPh_3)_4$ (11.4 mg, 0.0010 mmol), and three crystals of BHT and stirred at 100 °C for 5 h. The solvent was evaporated and chromatography (SiO_2, 5−50% EtOH/EtOAc) afforded the sublibrary as a yellow oil (7.2 mg, 63%). The ^{1}H NMR spectrum was consistent with the desired product mixture, and the mass spectrum exhibited all predicted molecular ions (15 components which have 14 unique molecular weights): ESMS (M + Na$^+$) m/z 991, 1048, 1076, 1104, 1105, 1133, 1161, 1174, 1189, 1217, 1231, 1259, 1287, 1357.

The mixture Stille coupling of *p*-iodobenzamides **10**−**13** under identical conditions afforded the expected 10-component product mixture (9 unique molecular weights) in 47% yield: ESMS (M + Na$^+$ or M + H$^+$) m/z 1107, 1134, 1162, 1190, 1218, 1231, 1260, 1290, 1335.

Mixture Stille Coupling between Meta and Para Substrates (7 and 12). A solution of iodobenzamides **7** (4.0 mg, 5.85 μmol) and **12** (4.5 mg, 6.32 μmol) in dioxane (0.3 mL) was treated with bis(tributylstannyl)acetylene (3.7 mg, 6.1 μmol), $Pd(PPh_3)_4$ (0.7 mg, 0.61 μmol), and three crystals of BHT, and stirred at 100 °C for 5 h. The solvent was evaporated and chromatography (SiO_2, 5−50% EtOH/EtOAc) afforded the product mixture as a yellow oil (3.0 mg, 42%). The ^{1}H NMR spectrum was consistent with a 1:1:2 mixture of products **16**, **22**, and **24**, and MS analysis confirmed the presence of all three molecular ions: ESMS (M + Na$^+$) m/z 1161, 1189, 1218.

General Procedure for the Synthesis of Individual Biaryls, Preparation of 30. Iodide **5** (10.6 mg, 17.7 mmol) was mixed with 10% Pd/C (1.8 mg, 1.77 mmol) and Et_3N (3.2 μL, 25.8 mmol) in DMF (90 μL, 0.2 M) and stirred at 100 °C for 18 h. The solvent was evaporated and chromatography (SiO_2, 5−50% EtOH/EtOAc) afforded **30** as a pale yellow foam (5.4 mg, 64%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.48 (m, 4H), 7.38 (m, 4H), 7.25 (m, 10H), 7.18 (m, 4H), 6.86 (m, 4H), 3.89 (m, 8H), 3.75 (m, 6H), 3.55 (m, 8H), 2.85 (m, 8H); IR (film) ν_{max} 3281, 3063, 2930, 1650, 1565, 1512, 1454, 1400, 1301, 1246, 1178, 1087, 1032, 1000, 910, 834, 730, 699 cm^{-1}; FABHRMS (NBA−CsI) m/z 1077.3488 (M + Cs$^+$, $C_{56}H_{60}N_6O_8$ requires 1077.3527).

Characterization data for **25**−**29** and **31**−**34** may be found in Supporting Information.

Synthesis of a 15 Component Biaryl Library. An equimolar solution of *m*-iodobenzamides **4**, **6**−**9** (0.005 mmol each, 0.025 mmol total) in DMF (0.13 mL) was treated with 10% Pd/C (2.6 mg, 0.0025 mmol) and Et_3N (4.4 μL, 0.038 mmol) and stirred at 100 °C for 5 h. The solvent was evaporated and chromatography (SiO_2, 5−50% EtOH/EtOAc) afforded the library as a yellow oil (10.5 mg, 75%). The ^{1}H NMR spectrum was consistent with the desired product mixture, and the mass spectrum exhibited all predicted molecular ions (15 components which have 14 unique molecular weights): ESMS ($M + Cl^-$) *m*/*z* 980, 1036, 1065, 1093, 1094, 1122, 1150, 1163, 1178, 1206, 1220, 1248, 1276, 1346.

The mixture biaryl coupling of *p*-iodobenzamides **5** and **10**−**13** under identical conditions afforded the expected 15-component product mixture in 78% yield: ESMS ($M + Na^+$) *m*/*z* 966, 1024, 1053, 1081, 1082, 1110, 1138, 1151, 1166, 1194, 1209, 1236, 1264, 1335.

Mixture Biaryl Coupling between Meta and Para Substrates (9 and 12). A solution of iodobenzamides **9** (3.7 mg, 4.7 μmol) and **12** (3.4 mg, 4.7 μmol) was treated with 10% Pd/C (1.0 mg, 0.94 μmol) and Et_3N (1.7 μL, 14.1 μmol) and stirred in DMF (0.05 mL) at 100 °C for 5 h. The solvent was evaporated and chromatography (SiO_2, 5−50% EtOH/EtOAc) afforded the product mixture as a yellow oil (3.5 mg, 60%). The ^{1}H NMR spectrum was consistent with a 1:1:2 mixture of products **20**, **33**, and **35**, and MS analysis confirmed the presence of all three molecular ions: ESMS $(M - H)^-$ *m*/*z* 1170, 1240, 1310.

Full Library Synthesis: Procedure for the First Diversification, Synthesis of Mixture 37. A mixture of *N*-(*tert*-butyloxy)carbonyl)iminodiacetic acid (0.5 g, 2.14 mmol) and EDCI (0.413 g, 2.14 mmol) in DMF (5.0 mL) was stirred for 1 h at 25 °C. A stock solution was prepared by diluting a mixture of 0.5 mmol of each amine (**A1**−**A6**) to 3.0 mL in DMF. This stock solution (2.14 mL, 0.356 mmol of each amine) was added to the anhydride solution. The reaction mixture was stirred for 18 h at 25 °C before it was poured into 50 mL of 10% aqueous HCl. The mixture was extracted with EtOAc (3 × 50 mL), the combined organic phases were washed with 10% aqueous HCl (2 × 50 mL) and saturated aqueous NaCl (50 mL) dried (Na_2SO_4), and the solvent was removed in vacuo to afford 0.66 g (78%) of **37** as a viscous oil, whose ^{1}H NMR spectrum included all peaks observable with authentic individual materials.

Procedure for the Second Diversification, Synthesis of Mixture 38. Monoamide mixture **37** (51.2 mg, 0.13 mmol) was dissolved in DMF (1.3 mL) and treated with *i*-Pr_2NEt (0.045 mL, 0.26 mmol). A stock solution was prepared by diluting a mixture of 0.5 mmol of each amine (**B1**−**B6**) to 3.0 mL in DMF. This stock solution (0.13 mL, 0.0217 mmol of each amine) and PyBOP (67.6 mg, 0.13 mmol) were added to the monoamide solution and stirred at 25 °C for 16 h. The reaction mixture was poured into 50 mL of 10% aqueous HCl and extracted into EtOAc (50 mL). The organic phase was washed with 10% aqueous HCl (2 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), and saturated aqueous NaCl (50 mL), dried (Na_2SO_4), and concentrated to provide 62.5 mg (90%) of **38** as a viscous oil.

Procedure for the Third Diversification, Synthesis of Mixture 39. Mixture **38** (42.4 mg, 0.0795 mmol) was stirred in 4 N HCl−dioxane (0.1 mL) for 2 h, and then solvent and excess acid were removed in vacuo. A stock solution was prepared by diluting a mixture of 0.5 mmol of each iodoarene carboxylic acid (**C1**−**C10**) to 5.00 mL in DMF. This stock solution (0.079 mL, 0.0079 mmol of each acid) was added to a DMF solution (0.8 mL) of the crude amine hydrochloride salts, treated with PyBrOP (37.1 mg, 0.079 mmol) and *i*-Pr_2NEt (14 μL, 0.16 mmol), and stirred for 18 h at 25 °C. The reaction mixture was diluted with EtOAc (50 mL) and washed with 10% aqueous HCl (3 × 50 mL), saturated aqueous $NaHCO_3$ (50 mL), and saturated aqueous NaCl (50 mL). Drying (Na_2SO_4) and concentration provided 51.1 mg (81%) of **39** as pale yellow oil.

Synthesis of a 64 980-Component Diarylacetylene Library, 40. Mixture **39** (35.0 mg, 0.044 mmol), bis(tributylstannyl)acetylene (11.7 μL, 0.022 mmol), and $Pd(PPh_3)_4$ (2.5 mg, 0.0022 mmol) were dissolved in 1.1 mL of dioxane. Three crystals of BHT were added, and the reaction mixture was stirred at 100 °C for 5 h. The solvent was evaporated and chromatography (5−50% EtOH/EtOAc) afforded 24.3 mg (81%, based on average molecular weight) of **52** as a pale yellow oil.

Synthesis of a 64 980-Compound Biaryl Library, 41. Mixture **39** (6.4 mg, 8.11 μmol), 10% Pd/C (0.9 mg, 0.811 μmol), and Et_3N (1.4 μL, 16.2 μmol) were added to DMF (0.04 mL), and the reaction mixture was stirred at 100 °C for 18 h. The solvent was evaporated and chromatography (5−50% EtOH/EtOAc) afforded 4.8 mg (64%, based on average molecular weight) of **41** as a pale yellow oil.

Acknowledgment. This work was supported by the National Institutes of Health (CA78045), The R. W. Johnson Pharmaceutical Research Institute, and the award of a predoctoral fellowship (J.G., NDSEG, 1995−1998).

Supporting Information Available: Experimental procedures and characterization of **C2**−**C5** and **C7**−**C10**, characterization of **5**−**13**, **15**−**23**, **25**−**29**, and **31**−**34**, general procedures for the synthesis of the scanning and deletion deconvolution sublibraries, and ^{1}H NMR spectra of **C2**−**C5**, **C7**−**C10**, **4**−**23**, **25**−**34** and **36**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO990639P