Construction of Indole and Benzofuran Systems on the Solid Phase via Palladium-Mediated Cyclizations[1]

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Molecular diversity in the area of nonpeptide, small organic molecules has been receiving considerable attention in the chemical community. Herein, we report new solid-phase methodology for the rapid generation of such small-molecule libraries by simultaneous-parallel or combinatorial synthesis. We have adapted a palladium-mediated, intramolecular Heck-type reaction, a mild and versatile method for carbon−carbon bond formation, to the solid phase. This has been applied to the synthesis of diverse indole and benzofuran derivatives, such as **8**, **15**, and **28**, in good to excellent yields.

Over the past few years, molecular diversity in the area of nonpeptide, small organic molecules has attracted widespread attention.[2] The rapid generation of such small-molecule libraries can be executed effectively by employing combinatorial or simultaneous-parallel synthesis on solid supports. From the standpoint of advantages, the solid-phase approach facilitates organization of the chemistry, allows reactions to be driven to completion with an excess of reagents, and provides single products or planned mixtures in a relatively clean state. Given the central role of carbon−carbon bond-forming reactions in organic synthesis, it would seem of particular importance to develop such reactions as powerful tools for producing organic compound libraries. Indeed, several solution-phase carbon−carbon bond-forming reactions, such as Suzuki, Stille, and Heck coupling, as well as enolate alkylation, have been transported to the solid-phase environment.[3] In this respect, our interest was sparked in adapting the palladium-mediated intramolecular Heck-type reaction to solid-phase synthesis because this reaction has proven to be a versatile method for the synthesis of natural and unnatural products. Herein, we report the successful application of Heck-type cyclization for the solid-phase assembly of indole and benzofuran derivatives.[4]

Results and Discussion

Indole Synthesis. The Heck-type cyclization of *N*-allyl-substituted *o*-haloanilines affords indole ring systems.[5] The method has been used to synthesize *N*-Ac- and *N*-Boc-indole-3-acetic acid derivatives in 8−68% yield.[6] As a model in the solution phase, we chose to study the palladium-mediated cyclization of commercially available methyl 4-(2-bromoanilino)-2-butenoate (**1**). Thus, **1** was treated with a catalytic amount (10 mol %) of bis(triphenylphosphine)palladium(II) chloride in the presence of tetrabutylammonium chloride and water. Both tetrabutylammonium chloride[7] and water[8] have been reported to accelerate palladium-mediated Heck-type coupling reactions. Although the desired indole **2** was obtained from the reaction, the yield was poor (about 25%). Since an aromatic iodide is more reactive than bromide in Heck couplings, **3** was prepared from 2-iodoaniline via either alkylation with methyl 4-bromocrotonate or reductive alkylation with fumaraldehydic acid methyl ester in the presence of sodium triacetoxyborohydride. Under the conditions used for converting **1** into **2**, **3** underwent cyclization much more smoothly to afford **2** in 80% isolated yield (Scheme 1). No cyclized product with an exocyclic double bond was observed, indicating that β-hydridopalladium elimination of σ-organopalladium adduct was followed by readdition of PdH to form a new σ-adduct, thereby effecting double-bond migration[9] to form the thermodynamically more stable indole derivative.

The successful conditions from the solution-phase reaction were then tested on the solid phase. Hydrolysis of ester **3** afforded acid **4**, which was then coupled with Rink amide AM resin (deprotected with 20% piperidine in DMF) by using DCC/HOBt to yield resin-bound cyclization precursor **5**, which was confirmed by cleavage

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(1) (a) This paper was presented in part at the 212th National Meeting of the American Chemical Society, Orlando, FL, 25−29 Aug 1996, Abstr. ORGN-185. (b) Nonstandard abbreviations used: DCC = dicyclohexylcarbodiimide, DIC = 1,3-diisopropylcarbodiimide, TFA = trifluoroacetic acid, HOBt = *N*-hydroxybenzotriazole.

(2) For reviews, see: (a) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527−4554. (b) Früchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17−42. (c) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135−8173. (d) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555−600.

(3) (a) Backs, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11171−11172. (b) Frenette, R.; Friesen, R. W. *Tetrahedron Lett.* **1994**, *35*, 9177−9180. (c) Yu, K.-L.; Deshpande, M. S.; Vyas, D. M. *Tetrahedron Lett.* **1994**, *35*, 8919−8922. (d) Deshpande, M. S. *Tetrahedron Lett.* **1994**, *35*, 5613−5614. (e) Forman, F. W.; Sucholeiki, I. *J. Org. Chem.* **1995**, *60*, 523−528. (f) Hiroshige, M; Hauske, J. R.; Zhou, P. *Tetrahedron Lett.* **1995**, *36*, 4567−4570. (g) Hiroshige, M; Hauske, J. R.; Zhou, P. *J. Am. Chem. Soc.* **1995**, *117*, 11590−11591. (h) Guiles, J. W.; Johnson, S. G.; Murray, W. V. *J. Org. Chem.* **1996**, *61*, 5169−5171.

(4) During the course of our study, a paper describing the solid-phase synthesis of substituted peptoid 1(2*H*)-isoquinolinones by palladium-mediated intramolecular coupling reaction was published. See: Goff, D. A.; Zuckermann R. N. *J. Org. Chem.* **1995**, *60*, 5748−5749.

(5) (a) Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, H. S. *J. Org. Chem.* **1980**, *45*, 2709−2710. (b) Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291−5294.

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(8) (a) Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324−4330. (b) Zhang, H.-C.; Daves, G. D., Jr. *Organometallics* **1993**, *12*, 1499−1500. (c) Jeffery, T. *Tetrahedron Lett.* **1994**, *35*, 3051−3054.

(9) Zhang, H.-C.; Daves, G. D., Jr. *J. Org. Chem.* **1993**, *58*, 2557−2560 and references cited therein.

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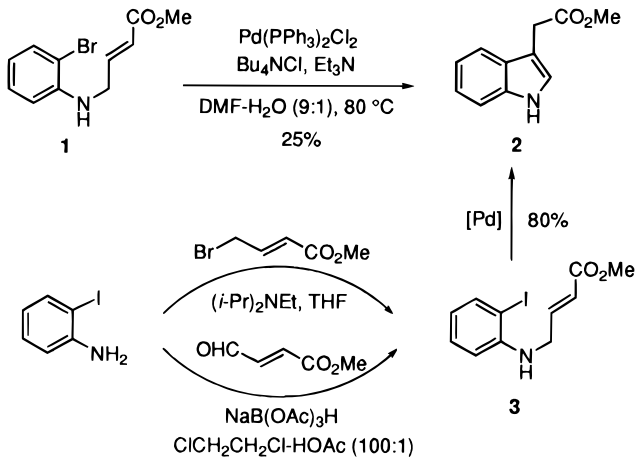
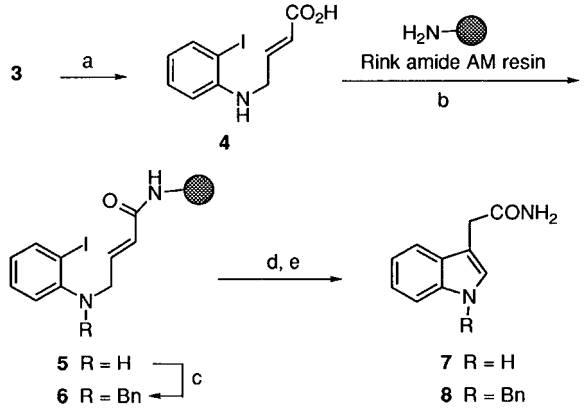
Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (a) $(Bu_3Sn)_2O$, toluene, 90 °C, 2 d; (b) DCC, HOBt, DMF, rt, 24 h; (c) BnBr, $(i\text{-}Pr)_2NEt$, DMF, 80 °C, 20 h; (d) $Pd(PPh_3)_2Cl_2$, Bu_4NCl, Et_3N, DMF−H_2O (9:1), 80 °C, 24 h; (e) 30% TFA in CH_2Cl_2, rt, 2 h.

with 30% TFA in CH_2Cl_2. Palladium-mediated cyclization of **5**, by using the conditions described for conversion of **3** to **2**, was followed by TFA cleavage. TLC and ^1H NMR analysis of the cleaved product indicated that the reaction was more complex than the one in solution. Although the desired indole **7** was observed in the crude product, the yield was modest (less than 60%) and other unidentified products were present. Since TFA is reported[10] to induce the dimerization of indole-3-acetic acid, or its methyl ester, we reasoned that N1-alkylated indole might be more stable under the TFA-cleavage conditions. Therefore, the free NH in **5** was alkylated with benzyl bromide and *N*,*N*-diisopropylethylamine to give **6**, which was then subjected to palladium-mediated cyclization and TFA cleavage. Analysis by TLC, ^1H NMR, and MS showed that indole **8** was the predominant product, formed in 88% yield from **5** (Scheme 2). In analogy to the cyclization of **3** in solution phase, no exocyclic isomer was observed.

Resin-bound intermediates **5** and **6** were obtained by loading prefabricated cyclization precursor **4** onto the Rink amide AM resin. To increase the diversity around the benzene ring of the indole, it was necessary to prepare a resin-bound reagent before introducing that benzene ring. As mentioned in the solution-phase model study, the cyclization precursor could be prepared through direct alkylation or reductive alkylation of 2-iodoaniline; thus, the resin-bound reagents **10** were planned. Coupling of γ-bromocrotonic acid (**9a**)[11] with Rink amide AM or Rink amide resin in the presence of DIC provided resin-bound alkylating agent **10a**,[4] which was confirmed by TFA cleavage. However, an attempt to load fumaraldehydic acid (**9b**; prepared from oxidation of γ-bromocrotonic acid with *N*-methylmorpholine *N*-oxide[12]) or its activated ester **9c** onto Rink amide AM resin under various conditions failed. Alkylation of the substituted 2-iodoanilines **11a**−**c**[13] with **10a** (Rink amide resin) gave **12a**−**c**, respectively. The intermediates **12a**−**c** were further alkylated separately with different substituted benzyl bromides, **13**, in the presence of *N*,*N*-diisopropylethylamine to afford the resin-bound cyclization precursors **14**. Palladium-mediated cyclization of **14** proceeded smoothly under the conditions described above and, after TFA cleavage, the desired indoles **15** were obtained in good to excellent purified yields (Scheme 3 and Table 1). In the crude cleaved products, a certain amount of Et_3N−TFA salt was normally observed by ^1H NMR, but this could easily be removed by dissolving the products in ethyl acetate and then washing with water. The resulting crude products were usually obtained in 80−90% purity as determined

Scheme 3

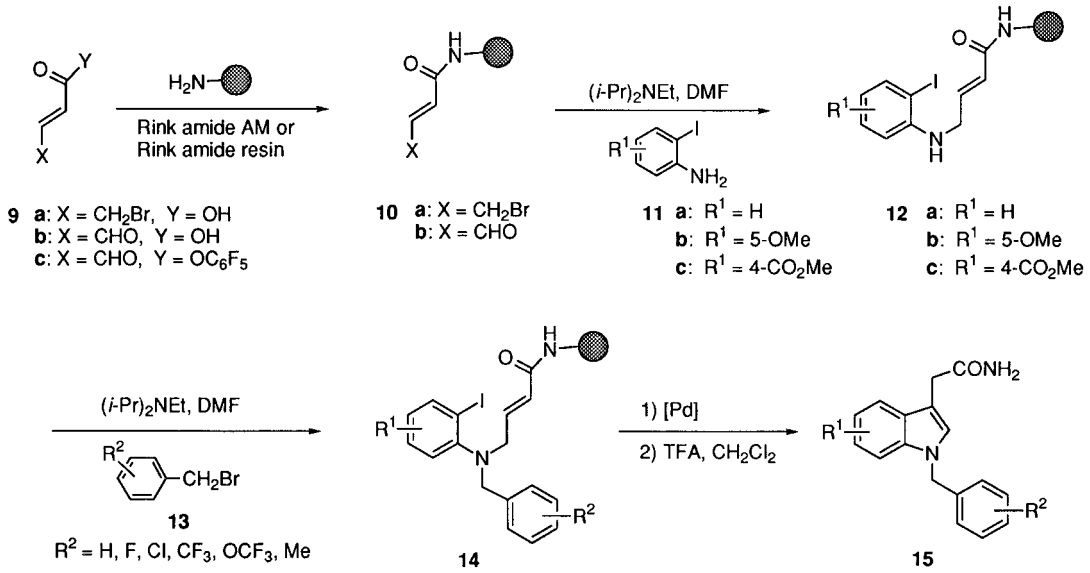


Table 1. Indole Derivatives 15[a]

product	R^1	R^2	yield[b] (%)
15a[c]	H	H	80
15b	H	4′-F	85
15c	H	4′-CF_3	74
15d	H	4′-Me	78
15e	6-OMe	4′-F	74
15f	6-OMe	2′-Cl	72
15g	6-OMe	4′-OCF_3	67
15h	6-OMe	4′-Me	69
15i	5-CO_2Me	H	88
15j	5-CO_2Me	4′-F	81
15k	5-CO_2Me	4′-CF_3	70
15l	5-CO_2Me	4′-Me	77

[a] Conditions for palladium-mediated cyclization: resin **14** (0.05−0.07 mmol), Bu_4NCl (1.5 equiv), Et_3N (3 equiv), $Pd(PPh_3)_2Cl_2$ (0.1 equiv), DMF−H_2O (9:1, 3−4 mL), 80 °C, 6−8 h. [b] Purified yields for four steps, based on the loading level of **10a**. [c] Same product as **8**.

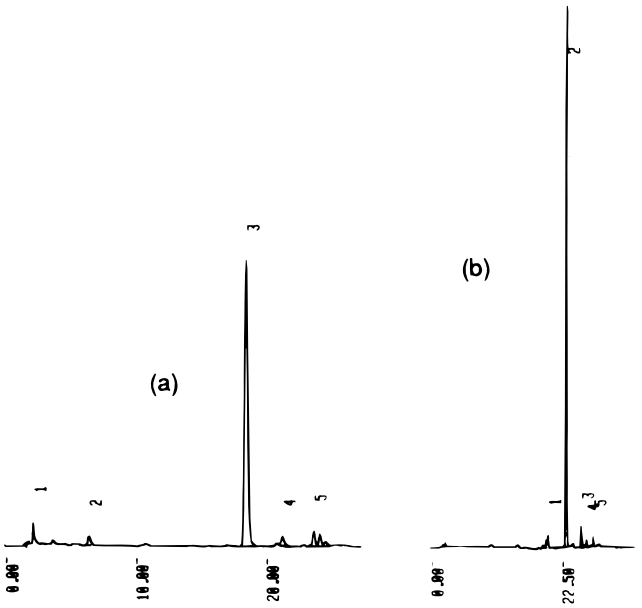
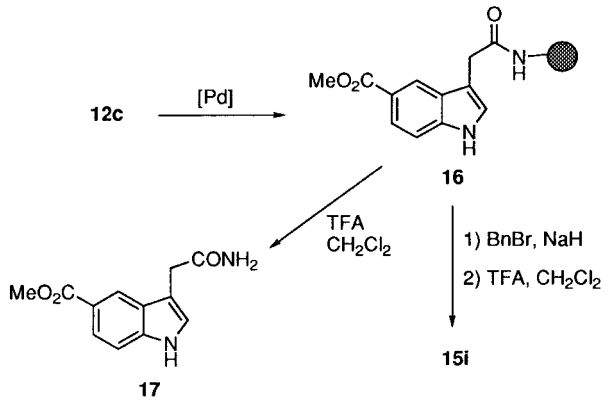


Figure 1. Reversed-phase HPLC traces. Panel a: crude **15c**. Analytical conditions: 2 mL/min 7:3 H_2O:CH_3CN (0.2% TFA), linear gradient to 5:95 in 30 min (254-nm detection). Panel b: crude **28b**. Analytical conditions: 2 mL/min 9:1 H_2O:CH_3CN (0.2% TFA), linear gradient to 5:95 in 30 min (254 nm detection).

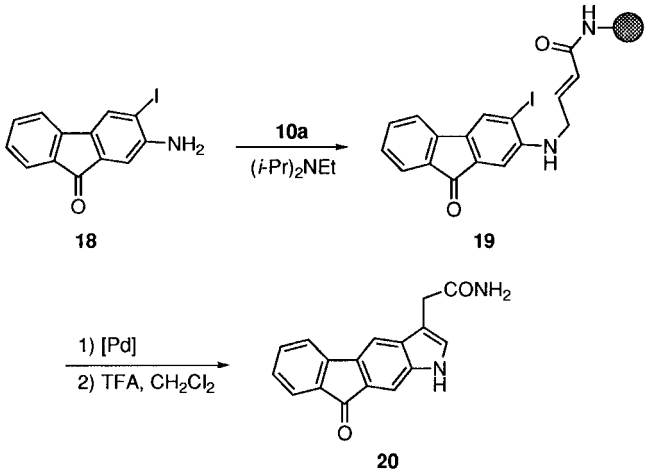
by reversed-phase HPLC analysis. To illustrate this point, a representative HPLC trace of crude material is provided in Figure 1a.

The examples shown in Table 1 demonstrate that solid-phase palladium-mediated indole formation works quite well for the systems containing various substituents. It is noteworthy that intermediate **12c**, which contains a free NH and an electron-deficient ring system, underwent palladium-mediated cyclization and TFA cleavage smoothly to afford the corresponding indole **17** in 79% yield (Scheme 4). The NH of the resulting resin-bound indole **16** could be alkylated before TFA cleavage by using benzyl bromide and NaH in DMF to give **15i** (83%), the same product that we had garnered from the cyclization of N-alkylated **14** (R^1 = 4-CO_2Me, R^2 = H).

Scheme 4



Scheme 5



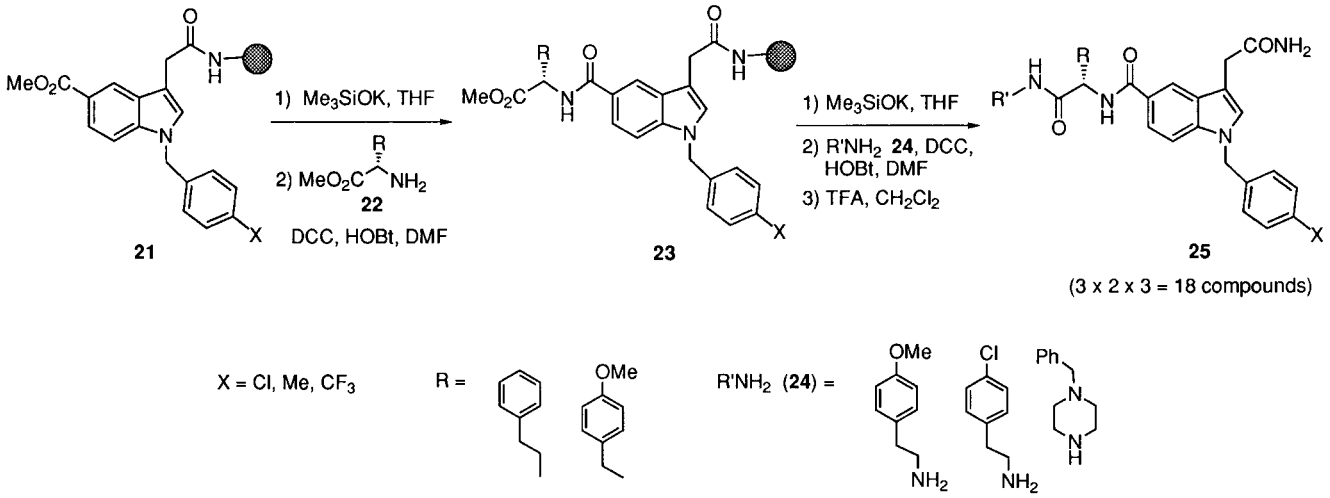
The process was subsequently extended to a disubstituted iodoaniline system. For example, the commercially available 2-amino-3-iodo-9-fluorenone (**18**) was loaded onto resin **10a**. The resulting resin-bound intermediate **19** was cyclized under palladium catalysis conditions and then cleaved with 30% TFA in CH_2Cl_2 to provide **20** in 76% isolated yield (Scheme 5).

To extend the utility of this solid-phase indole synthesis, a side chain was built from the 5-position of the resin-bound palladium-mediated cyclized products **21** (Scheme 6). Such indole compounds, having a carboxylic function at the 5-position, are not well known. Thus, compounds **21** were treated with potassium trimethylsilanolate[14] to afford the corresponding acids, which were coupled with L-homoPhe-OMe and L-Tyr(Me)-OMe,[15] respectively, to furnish **23**. Hydrolysis of the methyl ester of **23** with potassium trimethylsilanolate, followed by coupling with various amines **24** and cleavage with TFA, provided indoles **25**. For illustrative purposes, a minilibrary of 18 compounds of type **25** was prepared via simultaneous-parallel synthesis for biological evaluation.

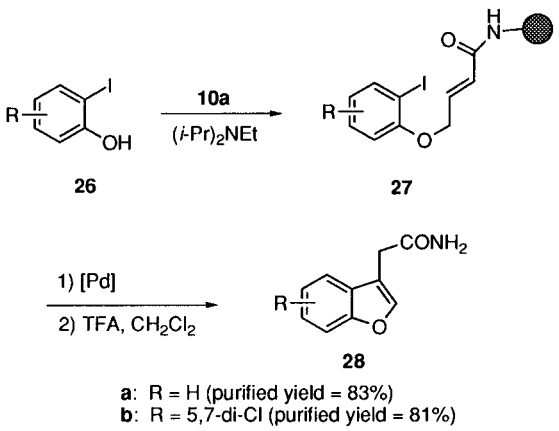
Benzofuran Synthesis. The methodology developed for solid-phase indole formation was successfully extended to the construction of benzofurans.[16] Alkylation

(10) Bergman, J.; Koch, E.; Pelcman, B. *Tetrahedron Lett.* **1995**, *36*, 3945−3948.
(11) Salomon, C. J.; Mata, E. G.; Mascarett, O. A. *Tetrahedron Lett.* **1991**, *32*, 4239−4242.
(12) Griffith, W. P.; Jolliffe, J. M.; Ley, S. V.; Springhorn, K. F.; Tiffin, P. D. *Synth. Commun.* **1992**, *22*, 1967−1971.
(13) Compound **11b** was prepared from 4-iodo-3-nitroanisole by using N_2H_4/$FeCl_3$/MeOH. See: Sakamoto, T.; Kondo, Y.; Uchiyama, M.; Yamanaka, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1941−1942.
(14) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831−5834.
(15) L-Tyr(Me)-OMe was prepared from L-Tyr(Me)-OH by using Me_3SiCHN_2.
(16) An example of this type of benzofuran formation in solution phase was reported; see: Larock, R. C.; Stinn, D. E. *Tetrahedron Lett.* **1988**, *29*, 4687−4690.

Scheme 6



Scheme 7



of the substituted 2-iodophenol **26a**,**b** with **10a** gave the resin-bound cyclization precursors **27a**,**b**, respectively. Palladium-mediated intramolecular cyclization of **27a**,**b** followed by cleavage with 30% TFA in CH_2Cl_2 afforded the desired benzofuran derivatives **28a**,**b** with excellent yields and purity (Scheme 7). Figure 1b shows a reversed-phase HPLC trace of crude product **28b**.

Related Solid-Phase Heck-Type Reactions. Goff and Zuckerman published a paper on the solid-phase synthesis of peptoid 1(2*H*)-isoquinolinones involving palladium-mediated intramolecular carbon−carbon coupling.[4] A Heck-type macrocyclization on the solid phase was also reported recently by Hiroshige et al.[3g] Very recently, after our work was completed,[1a] Yun and Mohan published a related solid-phase indole synthesis.[17] They attached a 3-amino-4-bromophenol derivative to TentaGel resin via an acid-labile linker. The resulting resin-bound *o*-bromoaniline was acylated with acid chlorides, and alkylated with allylic bromides, then subjected to palladium-mediated cyclization with the agency of 50 mol % of tetrakis(triphenylphosphine)palladium(0) to give indoles in 65−94% crude yield, with 48−93% purity. Our solid-phase indole synthesis provides an approach to diversity around the benzene ring of the indole. Also, generally speaking, the Rink resins employed in our studies can provide greater loading compared with TentaGel resins.

Conclusion. We have successfully applied the palladium-mediated intramolecular Heck-type coupling reaction to the construction of indole and benzofuran backbones on the solid phase. By using this chemistry, we have also conducted simultaneous-parallel synthesis, which should have wider implications for the generation of heterocycle-based chemical libraries.

(17) Yun, W.; Mohan, R. *Tetrahedron Lett.* **1996**, *37*, 7189−7192.

Experimental Section

General Procedures. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Methyl 4-(2-bromoanilino)-2-butenoate, methyl 4-amino-3-iodobenzoate, 2-amino-3-iodo-9-fluorenone, 4-iodo-3-nitroanisole, and 2,4-dichloro-6-iodophenol were purchased from Aldrich Chemical Co. Fumaraldehydic acid methyl ester was purchased from TCI. Rink amide and Rink amide AM resin were purchased from Novabiochem. NMR spectra were recorded on a Bruker AC 300 B (300 MHz) or a Bruker DMX 600 (600 MHz) spectrometer with Me_4Si as an internal standard (s = singlet, d = doublet, t = triplet). APCI-MS and ES-MS were recorded on a VG Platform II mass spectrometer. Accurate mass measurements were obtained by using a VG ZAB 2-SE spectrometer in the FAB mode. TLC was performed with Whatman 250-μm silica plates. Preparative TLC was performed with Analtech 1000-μm silica gel GF plates. Flash chromatography was done with flash-column silica gel (40−63 μm). Analytical reversed-phase HPLC was carried out on a Waters 600 and using μBondapak C18 column (10 μm, 125 Å, 3.9 × 300 mm); detection was at 254 nm with a Waters 481 UV detector. Microanalysis was performed by Roberston Microlit Laboratories, Inc.

4-[(2-Iodophenyl)amino]but-2-enoic Acid Methyl Ester (3). Method A. To a solution of 2-iodoaniline (2.19 g, 10.0 mmol) and *N*,*N*-diisopropylethylamine (2.58 g, 20.0 mmol) in THF (50 mL) was added dropwise methyl 4-bromocrotonate (1.79 g, 10.0 mmol). The reaction mixture was stirred at 60 °C for 6 h and then cooled to room temperature and diluted with ethyl acetate (130 mL). The solution was washed with water (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give 3.10 g of the crude product. A portion of the crude product (100 mg) was purified by preparative TLC using hexane:ethyl acetate (5:1) to afford 85 mg (83%) of **3** as a colorless viscous oil: ^{1}H NMR ($CDCl_3$) δ 3.73 (s, 3 H), 4.03 (m, 2 H), 4.46 (m, 1 H), 6.02 (ddd, J = 1.9, 15.7 Hz, 1 H), 6.45−6.51 (m, 2 H), 7.04 (ddd, J = 4.5, 15.7 Hz, 1 H), 7.19 (dd, J = 7.5 Hz, 1 H), 7.67 (dd, J = 1.5, 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 44.8, 51.5, 85.3, 110.6, 119.2, 121.5, 129.4, 139.0, 144.8, 146.1, 166.5; MS *m*/*z* 318 (MH^+). Anal. Calcd for $C_{11}H_{12}INO_2$: C, 41.66; H, 3.81; N, 4.42. Found: C, 41.38; H, 3.66; N, 4.22.

Method B. A solution of 2-iodoaniline (11 mg, 0.050 mmol) and fumaraldehydic acid methyl ester (5.2 mg, 0.046 mmol) in $ClCH_2CH_2Cl$−HOAc (100:1, 0.5 mL) was stirred at room temperature for 20 min, and then to the solution was added

sodium triacetoxyborohydride (25 mg, 0.12 mmol) in one portion. The resulting mixture was stirred at room temperature for 3 h, at which time TLC showed that the reaction was complete. Acetone (1 mL) was added to the reaction mixture. After being stirred for another hour, the mixture was diluted with ethyl acetate (20 mL), and the solution was washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting crude product was purified by preparative TLC using hexane:ethyl acetate (5:1) to afford 11.5 mg (79%) of **3**.

Indole-3-acetic Acid Methyl Ester (2). To a solution of 4-[(2-iodophenyl)amino]but-2-enoic acid methyl ester (**3**) (22 mg, 0.069 mmol), tetrabutylammonium chloride (29 mg, 0.10 mmol), and triethylamine (40 mg, 0.40 mmol) in DMF−H_2O (9:1, 2 mL) was added bis(triphenylphosphine)palladium(II) chloride (5.0 mg, 0.007 mmol). The resulting mixture was stirred under nitrogen at 80 °C for 2 days, and then the volatiles were removed under vacuum. The residue was separated by preparative TLC using hexane:ethyl acetate (2:1) to afford 10.5 mg (80%) of **2** as a colorless viscous solid: ^{1}H NMR ($CDCl_3$) was identical with an authentic sample: MS *m*/*z* 190 (MH^+).

4-[(2-Iodophenyl)amino]but-2-enoic Acid (4). A solution of the crude **3** (1.5 g; see preparation of **3**) and bis(tributyltin) oxide (8.46 g, 14.2 mmol) in toluene (50 mL) was stirred at 90 °C for 2 days. The solvent was then removed *in vacuo*, and the residue was partitioned between hexane (60 mL) and 1 N aqueous NaOH (40 mL). The aqueous layer was separated, and the organic layer was extracted with 1 N aqueous NaOH (3 × 40 mL). The combined aqueous extracts were acidified with 3 N aqueous HCl to pH = 4 and then extracted with ethyl acetate (60 mL × 3). The combined organic extracts were washed with brine (30 mL × 2), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography using CH_2Cl_2:MeOH (9:1) to give 0.85 g of **4** (58% for 2 steps) as a colorless solid: ^{1}H NMR (CD_3OD) δ 4.04 (dd, J = 1.4, 3.7 Hz, 2 H), 5.89 (d, J = 15.8 Hz, 1 H), 6.42 (dd, J = 7.3 Hz, 1 H), 6.51 (d, J = 8.1 Hz, 1 H), 6.99 (ddd, J = 4.3, 15.7 Hz, 1 H), 7.17 (ddd, J = 1.0, 7.6 Hz, 1 H), 7.64 (dd, J = 1.0, 7.6 Hz, 1 H); ^{13}C NMR (CD_3OD) δ 45.5, 85.2, 112.1, 119.9, 122.7, 130.4, 140.4, 147.5, 148.4, 169.9; MS *m*/*z* 304 (MH^+). Anal. Calcd for $C_{10}H_{10}INO_2$: C, 39.63; H, 3.33; N, 4.62. Found: C, 39.22; H, 3.20; N, 4.43.

2-(1-Benzyl-1*H*-indol-3-yl)acetamide (8). Rink amide AM resin (1.0 g, 0.49 mmol/g, 0.49 mmol) was treated with 20% piperidine in DMF (20 mL) at room temperature for 2.5 h and then washed with DMF (3×), MeOH (3×), and CH_2Cl_2 (3×) to give the deprotected resin, 0.87 g. Deprotected resin (435 mg, 0.245 mmol) was suspended in DMF (10 mL) and then treated with acid **4** (120 mg, 0.40 mmol) followed by HOBt (108 mg, 0.80 mmol) and DCC (165 mg, 0.80 mmol). The resulting mixture was stirred at room temperature for 24 h and then filtered and washed sequentially with DMF, MeOH, CH_2Cl_2, and Et_2O to provide 504 mg of resin-bound indole derivative **5**. To a mixture of resin **5** (70 mg, 0.034 mmol) and *N*,*N*-diisopropylethylamine (110 mg, 0.85 mmol) in DMF (3 mL) was added benzyl bromide (149 mg, 0.85 mmol). The mixture was stirred at 80 °C for 20 h, at which time TLC indicated that the benzylation reaction was complete. (An aliquot was taken, filtered, washed, cleaved with 30% TFA in CH_2Cl_2, and checked by TLC). The reaction mixture was then filtered and washed sequentially with DMF, MeOH, and CH_2Cl_2 to give the resin-bound cyclization precursor **6**. Resin **6** was suspended in DMF−H_2O (9:1, 4 mL), and to the suspension were added tetrabutylammonium chloride (14 mg, 0.051 mmol), triethylamine (27 mg, 0.27 mmol), and bis(triphenylphosphine)palladium(II) chloride (3.6 mg, 0.005 mmol). After being stirred at 80 °C for 24 h, the reaction mixture was filtered, washed with DMF, MeOH, and CH_2Cl_2, and cleaved with 30% TFA in CH_2Cl_2 at room temperature for 2 h to afford 7.9 mg (88%, based on **5**) of the cleaved product **8** as a light yellow solid: ^{1}H NMR (CD_3OD) δ 3.66 (s, 2 H), 5.34 (s, 2 H), 7.02−7.30 (m, 9 H), 7.58 (d, J = 7.7 Hz, 1 H); ^{13}C NMR (CD_3OD) δ 33.4, 50.7, 109.7, 111.0, 119.8, 120.3, 122.8, 128.0, 128.5, 128.8, 129.4, 129.7, 138.2, 139.5, 177.7; MS *m*/*z* 265 (MH^+); FAB-HRMS calcd for $C_{17}H_{16}N_2O$ + H^+ 265.1341, found 265.1325.

Solid-Phase Synthesis of Indole Derivatives 15 via Palladium-Mediated Cyclization. A. 2-[1-[4-(Trifluoromethyl)benzyl]-1*H*-indol-3-yl]acetamide (15c). The procedure described here for **15c** is representative. Rink amide resin (7.5 g, 0.48 mmol/g, 3.6 mmol) was deprotected with 20% piperidine in DMF (100 mL) at room temperature for 1.5 h and then filtered and washed with DMF, MeOH, and CH_2Cl_2. The deprotected resin was suspended in DMF (36 mL) and treated with DIC (2.73 g, 21.6 mmol), followed by γ-bromocrotonic acid (**9a**, 3.56 g, 21.6 mmol). The mixture was stirred at room temperature for 30 min, and then filtered, washed with CH_2Cl_2 and DMF. The resulting resin was retreated with DMF (36 mL), DIC (21.6 mmol), and **9a** (21.6 mmol) at room temperature for 30 min and then washed with DMF, MeOH, CH_2Cl_2, and Et_2O and dried *in vacuo* to give 7.41 g of resin **10a** with a loading level of 0.32 mmol/g, which was determined by cleaving an aliquot with 30% TFA in CH_2Cl_2 at room temperature for 80 min. Resin **10a** (1.2 g, 0.38 mmol) was suspended in DMF (10 mL) and treated with *N*,*N*-diisopropylethylamine (387 mg, 3.0 mmol) followed by 2-iodoaniline (420 mg, 1.9 mmol). The reaction mixture was stirred at 80 °C for 18 h and then filtered, washed with CH_2Cl_2, MeOH, and CH_2Cl_2, and dried *in vacuo* to give 1.25 g of **12a**. A mixture of resin **12a** (230 mg, 0.070 mmol), *N*,*N*-diisopropylethylamine (90 mg, 0.70 mmol), and α′-bromo-α,α,α-trifluoro-*p*-xylene (167 mg, 0.70 mmol) in DMF (2.5 mL) was stirred at 80 °C for 22 h and then filtered, washed sequentially with MeOH and CH_2Cl_2, and dried *in vacuo* to give **14** (R^1 = H, R^2 = 4′-CF_3). (Note: For the alkylation of **12c**, double treatments with alkylating agents were required for the complete conversion.) The resulting resin was then suspended in DMF−H_2O (9:1, 4 mL) and treated with tetrabutylammonium chloride (29 mg, 0.11 mmol), triethylamine (21 mg, 0.21 mmol), and bis(triphenylphosphine)palladium(II) chloride (4.9 mg, 0.007 mmol). The suspension was stirred at 80 °C for 8 h, at which time TLC indicated that the reaction was complete. The dark brown reaction mixture was filtered, washed sequentially with CH_2Cl_2, MeOH, and CH_2Cl_2, and then dried *in vacuo*. The resulting resin was cleaved with 30% TFA in CH_2Cl_2 (8 mL) at room temperature for 1.5 h. The crude cleaved product obtained was dissolved in ethyl acetate (25 mL), and the solution was washed with water (5 mL), to remove contaminated Et_3N−TFA salt, and then brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting product showed 85% purity by reversed-phase HPLC (2 mL/min, 7:3 H_2O/CH_3CN (0.2% TFA), linear gradient to 5:95 in 30 min; R_f = 18.5 min). After purification by preparative TLC using ethyl acetate−methanol (95:5), 17.2 mg (74% yield for four steps, based on the loading level of **10a**) of **15c** was obtained as a colorless solid: ^{1}H NMR (CD_3OD) δ 3.67 (s, 2 H), 5.46 (s, 2 H), 7.06 (t, J = 7.0 Hz, 1 H), 7.13 (t, J = 7.2 Hz, 1 H), 7.25−7.31 (m, 4 H), 7.56−7.61 (m, 3 H); ^{13}C NMR (CD_3OD) δ 33.4, 50.3, 110.3, 111.0, 120.1, 120.7, 123.2, 125.8 (q, J_{CF} = 271.9 Hz), 126.7, 128.6, 128.9, 129.6, 130.8 (q, $^2J_{CF}$ = 32.3 Hz), 138.2, 144.4, 177.7; MS *m*/*z* 333 (MH^+); FAB-HRMS calcd for $C_{18}H_{15}F_3N_2O$ + H^+ 333.1215, found 333.1165. Anal. Calcd for $C_{18}H_{15}F_3N_2O$·1.3H_2O: C, 60.77; H, 4.99; N, 7.87; F, 16.02. Found: C, 60.45; H, 4.22; N, 7.79; F, 16.57.

B. 2-[1-(4-Fluorobenzyl)-1*H*-indol-3-yl]acetamide (15b): ^{1}H NMR (CD_3OD) δ 3.66 (s, 2 H), 5.33 (s, 2 H), 6.97−7.20 (m, 6 H), 7.22 (s, 1 H), 7.29 (d, J = 8.1 Hz, 1 H), 7.58 (d, J = 7.7 Hz, 1 H); ^{13}C NMR (CD_3OD) δ 33.3, 50.0, 109.9, 110.9, 116.2, 116.4, 119.9, 120.4, 122.9, 128.7, 129.4, 129.9, 130.0, 135.5, 138.0, 163.6 (d, J_{CF} = 244.3 Hz), 177.7; MS *m*/*z* 283 (MH^+); FAB-HRMS calcd for $C_{17}H_{15}FN_2O$ + H^+ 283.1247, found 283.1310.

C. 2-[1-(4-Methylbenzyl)-1*H*-indol-3-yl]acetamide (15d): ^{1}H NMR (CD_3OD) δ 2.27 (s, 3 H), 3.65 (s, 2 H), 5.29 (s, 2 H), 7.01−7.13 (m, 6 H), 7.19 (s, 1 H), 7.29 (d, J = 8.1 Hz, 1 H), 7.57 (d, J = 7.8 Hz, 1 H); ^{13}C NMR (CD_3OD) δ 21.1, 33.4, 50.5, 109.6, 111.0, 119.8, 120.2, 122.8, 128.1, 128.7, 129.4, 130.2, 136.4, 138.1, 138.3, 177.7; MS *m*/*z* 279 (MH^+); FAB-HRMS calcd for $C_{18}H_{18}N_2O$ + H^+ 279.1497, found 279.1515.

D. 2-[1-(4-Fluorobenzyl)-6-methoxy-1*H*-indol-3-yl]-acetamide (15e): ^{1}H NMR (CD_3OD) δ 3.61 (s, 2 H), 3.75 (s, 3 H), 5.29 (s, 2 H), 6.72 (dd, J = 2.1, 8.7 Hz, 1 H), 6.80 (d, J = 2.0 Hz, 1 H), 6.98−7.04 (m, 2 H), 7.08 (s, 1 H), 7.16−7.21 (m, 2 H), 7.44 (d, J = 8.7 Hz, 1 H); MS m/z 313 (MH^+); FAB-HRMS calcd for $C_{18}H_{17}FN_2O_2 + H^+$ 313.1352, found 313.1322.

E. 2-[1-(2-Chlorobenzyl)-6-methoxy-1*H*-indol-3-yl]-acetamide (15f): ^{1}H NMR (CD_3OD) δ 3.62 (s, 2 H), 3.75 (s, 3 H), 5.41 (s, 2 H), 6.72−6.76 (m, 3 H), 7.08 (s, 1H), 7.15 (t, J = 7.3 Hz, 1 H), 7.25 (t, J = 7.3 Hz, 1 H), 7.46 (m, 2 H); ^{13}C NMR (CD_3OD) δ 33.6, 48.4, 56.1, 94.3, 110.4, 110.7, 120.8, 123.8, 127.7, 128.5, 129.8, 130.2, 130.7, 133.8, 136.9, 139.1, 158.3, 177.7; MS m/z 329 (MH^+); FAB-HRMS calcd for $C_{18}H_{17}ClN_2O_2 + H^+$ 329.1057, found 329.1069.

F. 2-[6-Methoxy-1-[4-(trifluoromethoxy)benzyl]-1*H*-indol-3-yl]acetamide (15g): ^{1}H NMR (CD_3OD) δ 3.62 (s, 2 H), 3.75 (s, 3 H), 5.34 (s, 2 H), 6.72 (dd, J = 2.1, 8.5 Hz, 1 H), 6.80 (d, J = 2.0 Hz, 1 H), 7.10 (s,1 H), 7.17−7.26 (m, 4 H), 7.46 (d, J = 8.7 Hz, 1 H); MS m/z 379 (MH^+); FAB-HRMS calcd for $C_{19}H_{17}F_3N_2O_3 + H^+$ 379.1270, found 379.1235.

G. 2-[6-Methoxy-1-(4-methylbenzyl)-1*H*-indol-3-yl]-acetamide (15h): ^{1}H NMR (CD_3OD) δ 2.28 (s, 3 H), 3.60 (s, 2 H), 3.75 (s, 3 H), 5.24 (s, 2 H), 6.71 (dd, J = 2.1, 8.7 Hz, 1 H), 6.80 (d, J = 2.0 Hz, 1 H), 7.04−7.22 (m, 5 H), 7.43 (d, J = 8.7 Hz, 1 H); MS m/z 309 (MH^+); FAB-HRMS calcd for $C_{19}H_{20}N_2O_2 + H^+$ 309.1603, found 309.1549.

H. 1-Benzyl-3-(carbamoylmethyl)-1*H*-indole-5-carboxylic acid methyl ester (15i): ^{1}H NMR (CD_3OD) δ 3.70 (s, 2 H), 3.89 (s, 3 H), 5.40 (s, 2 H), 7.20−7.40 (m, 7 H), 7.81 (d, J = 8.8 Hz, 1 H), 8.37 (s, 1 H); MS m/z 323 (MH^+); FAB-HRMS calcd for $C_{19}H_{18}N_2O_3 + H^+$ 323.1396, found 323.1434.

I. 3-(Carbamoylmethyl)-1-(4-fluorobenzyl)-1*H*-indole-5-carboxylic acid methyl ester (15j): ^{1}H NMR (CD_3OD) δ 3.70 (s, 2 H), 3.89 (s, 3 H), 5.38 (s, 2 H), 7.02−7.22 (m, 4 H), 7.34 (s,1 H), 7.40 (d, J = 8.7 Hz, 1 H), 7.82 (d, J = 8.6 Hz, 1 H), 8.37 (s, 1 H); MS m/z 341 (MH^+); FAB-HRMS calcd for $C_{19}H_{17}FN_2O_3 + Na^+$ 363.1121, found 363.1156.

J. 3-(Carbamoylmethyl)-1-[4-(trifluoromethyl)benzyl]-1*H*-indole-5-carboxylic acid methyl ester (15k): ^{1}H NMR (CD_3OD) δ 3.72 (s, 2 H), 3.90 (s, 3 H), 5.51 (s, 2 H), 7.32−7.39 (m, 4 H), 7.58−7.61 (m, 2 H), 7.83 (d, J = 8.8 Hz, 1 H), 8.38 (s, 1 H); MS m/z 391 (MH^+).

K. 3-(Carbamoylmethyl)-1-(4-methylbenzyl)-1*H*-indole-5-carboxylic acid methyl ester (15l): ^{1}H NMR (CD_3OD) δ 2.28 (s, 3 H), 3.69 (s, 2 H), 3.89 (s, 3 H), 5.33 (s, 2 H), 7.06−7.13 (m, 4 H), 7.31 (s,1 H), 7.39 (d, J = 8.7 Hz, 1 H), 7.81 (d, J = 8.3 Hz, 1 H), 8.36 (s, 1 H); MS m/z 337 (MH^+); FAB-HRMS calcd for $C_{20}H_{20}N_2O_3 + H^+$ 337.1552, found 337.1623.

3-(Carbamoylmethyl)-1*H*-indole-5-carboxylic Acid Methyl Ester (17). Resin **12c** (180 mg, 0.39 mmol/g, 0.070 mmol) was subjected to palladium-mediated intramolecular cyclization using the conditions as described for **14** at 80 °C for 18 h to give 178 mg of the resin-bound cyclized product **16** (Note: when NaOAc was used as base instead of Et_3N, cyclization was complete within 3 h at 80 °C). **16** (78 mg, 0.031 mmol) was cleaved with 30% TFA in CH_2Cl_2 (5 mL) at room temperature for 80 min, and the crude cleaved product was purified by flash column chromatography to give **17** (5.7 mg, 79% from **10a**) as a colorless solid: ^{1}H NMR (CD_3OD) δ 3.69 (s, 2 H), 3.90 (s, 3 H), 7.29 (s,1 H), 7.40 (d, J = 8.6 Hz, 1 H), 7.81 (d, J = 8.8 Hz, 1 H), 8.35 (s, 1 H); MS m/z 233 (MH^+); FAB-HRMS calcd for $C_{12}H_{12}N_2O_3 + Na^+$ 255.0746, found 255.0783.

Preparation of 15i from 16. Resin **16** (95 mg, 0.037 mmol) was suspended in DMF (1.5 mL) and treated with NaH (60% dispersion in mineral oil, 27.6 mg, 0.19 mmol) and benzyl bromide (33 mg, 0.19 mmol). The suspension was stirred at room temperature for 5 h and then filtered and washed with MeOH and CH_2Cl_2. The resulting resin was cleaved with 30% TFA in CH_2Cl_2 (5 mL) at room temperature for 1.5 h, and the crude product was purified by preparative TLC using ethyl acetate−methanol (95:5) to give 10.2 mg (83% from **10a**) of **15i** as a colorless solid.

2-(9-Oxo-1,9-dihydroindeno[1,2-*f*]indol-3-yl)acetamide (20). 2-Amino-3-iodo-9-fluorenone (**18**) (24 mg, 0.077 mmol) was alkylated with **10a** (134 mg, 0.043 mmol) in DMF (2 mL) in the presence of *N*,*N*-diisopropylethylamine (27 mg, 0.21 mmol) at 80 °C for 18 h. The resulting resin (**19**) was then subjected to palladium-mediated cyclization followed by cleavage with TFA and purification with preparative TLC (see general procedure used for the synthesis of **15c**) to afford 9.0 mg (76% from **10a**) of **20** as a yellow solid: ^{1}H NMR (CD_3OD) δ 3.67 (s, 2 H), 7.20 (t, J = 7.5 Hz, 1 H), 7.35 (s, 1 H), 7.45−7.63 (m, 4 H), 7.76 (s, 1 H); MS m/z 277 (MH^+); FAB-HRMS calcd for $C_{17}H_{12}N_2O_2 + H^+$ 277.0977, found 277.1011.

General Procedure for Simultaneous-Parallel Synthesis of 25. The suspensions of the resin-bound cyclized products **21** (X = Cl, Me, CF_3, 0.34 mmol for each resin) in THF (0.014 M) were treated with potassium trimethylsilanolate (10 equiv), respectively. The mixtures were stirred at room temperature for 40 h and then filtered, washed with THF, MeOH, and CH_2Cl_2, and dried *in vacuo*. The resulting resins were split equally, suspended in DMF (0.024 M), and coupled with L-homoPhe-OMe and L-Tyr(Me)-OMe (5 equiv), respectively, in the presence of DCC (5 equiv) and HOBt (5 equiv) to give **23**. Methyl esters **23** were hydrolyzed again with potassium trimethylsilanolate in THF. The resulting acids were further split, and each portion was suspended in DMF (3 mL) and coupled with 100 μL of 2-(4-chlorophenyl)ethylamine, 4-methoxyphenethylamine, and 1-benzylpiperazine, respectively, in the presence of DCC (0.4 mmol) and HOBt (0.4 mmol). The resin-bound coupled products were then cleaved with 30% TFA in CH_2Cl_2 to afford **25** (total 18 products). All products were confirmed by MS and by representative ^{1}H NMR spectra. For example, for **25** (X = Cl, R = $PhCH_2CH_2$, R′ = *p*-$MeOC_6H_4CH_2CH_2$): ^{1}H NMR (CD_3OD) δ 1.70−2.20 (m, 2 H), 2.60−2.80 (m, 4 H), 3.56 (s, 2 H), 3.65−3.82 (m, 5 H), 4.50 (m, 1 H), 5.40 (s, 2 H), 6.68 (d, J = 8.6 Hz, 2 H), 7.07−7.41 (m, 13 H), 7.65 (m, 1 H), 8.19 (s, 1 H); MS m/z 637 (MH^+).

2-(Benzofuran-3-yl)acetamide (28a). 2-Iodophenol (**26a**) (88 mg, 0.40 mmol) was alkylated with **10a** (250 mg, 0.080 mmol) in DMF (2.5 mL) in the presence of *N*,*N*-diisopropylethylamine (83 mg, 0.64 mmol) at 80 °C for 5 h. The resulting resin **27a** was then subjected to palladium-mediated cyclization followed by cleavage with TFA and purification with preparative TLC (see general procedure used for the synthesis of **15c**) to afford 11.6 mg (83% from **10a**) of **28a** as a colorless solid: ^{1}H NMR (CD_3OD) δ 3.62 (s, 2 H), 7.21−7.32 (m, 2 H), 7.45 (d, J = 8.1 Hz, 1 H), 7.61 (d, J = 7.9 Hz, 1 H), 7.68 (s, 1 H); ^{13}C NMR (CD_3OD) δ 31.5, 112.2, 115.7, 120.8, 123.6, 125.5, 129.0, 144.4, 156.8, 175.9; MS m/z 176 (MH^+).

2-(5,7-Dichlorobenzofuran-3-yl)acetamide (28b). Similarly, **28b** was obtained from 2,4-dichloro-6-iodophenol (**26b**). The crude product showed 90% purity by reversed-phase HPLC (2 mL/min, 9:1 H_2O:CH_3CN (0.2% TFA), linear gradient to 5:95 in 30 min; R_f = 23.3 min); the purified yield was 81%: ^{1}H NMR (CD_3OD) δ 3.61 (s, 2 H), 7.37 (d, J = 1.9 Hz, 1 H), 7.61 (d, J = 1.8 Hz, 1 H), 7.84 (s, 1 H); MS m/z 244 (MH^+); FAB-HRMS calcd for $C_{10}H_7Cl_2NO_2 + H^+$ 243.9932, found 243.9884.

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Supporting Information Available: NMR spectra for the new compounds and representative ^{1}H NMR and all MS spectra for compounds **25** (46 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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