Solution Phase Combinatorial Synthesis of Biaryl Libraries Employing Heterogeneous Conditions for Catalysis and Isolation with Size Exclusion Chromatography for Purification

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A convenient and effective approach to the solution phase synthesis of biaryl libraries from iodoarenes is described enlisting 10% Pd−C as an inexpensive and readily available supported catalyst. Isolation and purification of small library mixtures, individual library members, and intermediates in the multistep sequence by a combination of liquid−liquid and liquid−solid extractions and size exclusion chromatography are detailed.

Introduction

Ligand-induced dimerization or oligomerization has been established as a general mechanism for the activation of certain cell surface receptors.[1] Important examples of this, where hormone antagonists or agonists would be of pharmacological significance, include tyrosine kinase receptors[2] and cytokine receptors.[3] Accumulating evidence that such receptor dimerization events may be driven by hormone binding involving only a relatively small cluster of residues,[4] accompanied by stabilizing inter-receptor interactions, has driven the search for small molecule hormone antagonists and agonists. Peptide[5] as well as nonpeptide[6] agonists promoting receptor homodimerization have recently been identified through the random screening of compound libraries. Complementary to such approaches, solution phase combinatorial chemistry[7] provides a unique potential for generating C_2-symmetrical diversity through the synthetic convergent dimerization of combinatorially assembled building blocks. We have recently developed such solution phase approaches which utilized amide bond formation,[8,9] optionally in combination with olefin metathesis reactions,[10] to produce multimilligram quantities of library mixtures or individual compounds in multistep sequences. Typically, liquid−liquid or liquid−solid extractive purification was used to reliably produce libraries of high purity for screening purposes. As a complement to these structurally flexible libraries, we have extended the convergent, solution phase dimerization strategy to the preparation of more rigid and densely functionalized systems. On the basis of considerations related to target compound shape and size as well as library deconvolution, biaryl formation was selected as one of the primary strategies. However, since the approach would constitute a rare example of solution phase combinatorial synthesis based on carbon−carbon bond formation under conditions where extractive purification is precluded, a concern was the development of reaction conditions and purification methods allowing reliable production of highly pure biaryl mixtures.[11] Herein, we disclose studies which address these concerns

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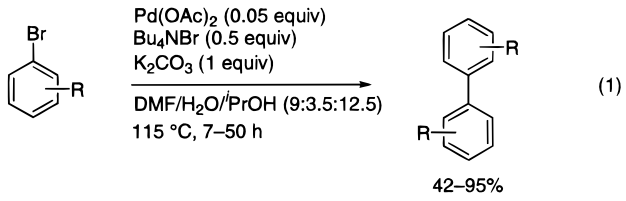
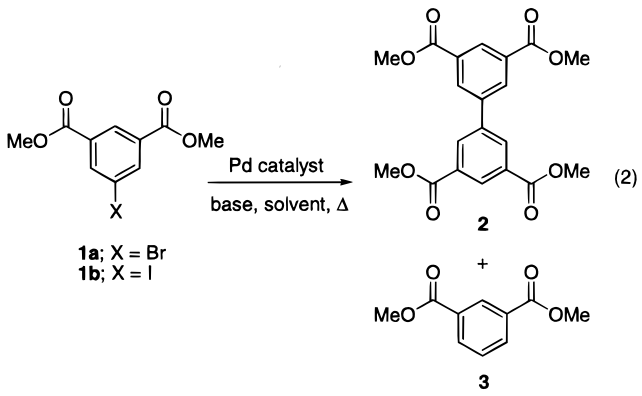
using a representative set of 5-haloisophthalic acid derivatives as coupling partners.

Results and Discussion

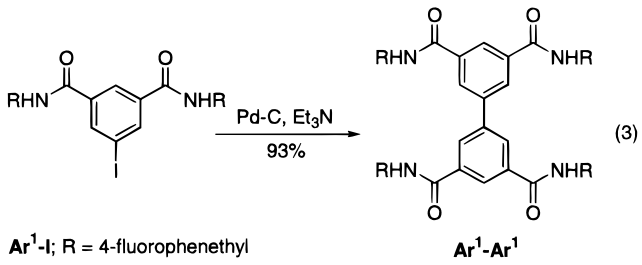
Reaction Conditions. Anticipating coupling mixtures of 5-haloisophthalamides in which the variations in the *N*-substituents would not strongly affect the coupling rate, the commercially available haloesters **1a** and **1b** were chosen as prototypical model substrates. Our starting point for reaction optimization was a recent communication by Lemaire and co-workers,[12] in which biaryls and bipyridyls were obtained through homocoupling of aromatic bromides or iodides in the presence of $Pd(OAc)_2$ and Bu_4NBr. In these studies, the highest coupling yields resulted from reactions performed in a DMF, H_2O, 2-propanol, K_2CO_3 mixture (eq 1). However, since basic aqueous conditions typically are not compatible with hydrolyzable functional groups, and therefore potentially unreliable for combinatorial biaryl formation, modifications to the published procedure were examined (eq 2).





Using the bromide **1a**, reaction in DMF in the presence of Bu_4NBr (0.5 equiv), Et_3N (1 equiv), and $Pd(OAc)_2$ (0.1 equiv) provided a 2:1 mixture of coupled product **2** and reduced product **3** with complete consumption of starting material after 16 h at 115 °C. In efforts to simplify product isolation, heterogeneous catalysts were examined, and replacing $Pd(OAc)_2$ with *palladium on carbon* (10% Pd−C) was productive,[13] although the total consumption of **1a** required treatment with 0.2 equiv of Pd−C for 24 h at 100 °C and provided a slightly less favorable 1−2:1 mixture of the products **2** and **3**. Further examination of the reaction conditions showed that the Bu_4NBr could be excluded with no effect on the reaction outcome, that the amount of Et_3N was an important variable since increasing its concentration provided a faster reaction rate, and that K_2CO_3 did not support the reaction in anhydrous DMF. A range of substrate concentrations were examined (0.1−1 M), and the more dilute reaction mixtures provided greater amounts of competitive reduction.

Although the coupling results with the aryl bromide **1a** were modest, the iodide **1b** provided a very efficient and selective route to the biaryl **2** under our modified conditions. At concentrations ranging from 0.2−1.0 M in DMF, **1a** afforded the homocoupling product **2** very cleanly using 0.1 equiv of Pd−C and 1.5 equiv of Et_3N with only a trace of **3** detected by NMR. Applying these conditions to a diamide representative of the library building blocks, *N*,*N*′-bis(4-fluorophenethyl)-5-iodoisophthalamide[14] (**Ar^1-I**, see below) established that the heterogeneous catalytic protocol was effective for homocoupling of such substrates. By using 0.1 equiv of Pd−C and 1.5 equiv of Et_3N at 100 °C for 16 h (0.5 M in DMF), the desired biaryl (**Ar^1-Ar^1**) was isolated in 93% yield (eq 3).



Similar reactions performed on several 5-iodoisophthalamides provided good to excellent yields of the biaryls with only traces of reduction products observed by NMR and/or HPLC. Subsequent experiments performed in order to assess the rates of the homocoupling reactions indicated that complete consumption of the starting iodide required as little as 1−2 h. For mixture syntheses, however, the overnight reaction time was retained to ensure complete conversion since no appreciable degradation of the products could be detected.

Preparation of Combinatorial Libraries: Synthesis. The building blocks for the mixture syntheses were prepared in good yields from commercially available **1b** as shown in Scheme 1. A stock solution of the diacid dichloride was portioned into solutions of the appropriate amine and Hünig's base in either CH_2Cl_2 or THF. Isolation of the pure diamides (**Ar-I**) was accomplished either by liquid−liquid extractive workup or precipitation from dilute hydrochloric acid, and they were stored as stock solutions in DMF. The amine entries included in the prototypical libraries discussed herein (Scheme 1) were chosen to sample functional groups that would highlight the generality of the procedure, and to span a range of polarities[15] allowing reasonable separation on HPLC. Thus, primary and secondary amines containing oxidizable (alcohol) and hydrolytically labile (carbamate, acetal) functionality were included. For identification purposes, the corresponding reduction byproducts (**Ar-H**) were prepared analogously from commercially available isophthaloyl dichloride. Enlisting the protocol for preparing homodimers discussed above, the mixed cou-

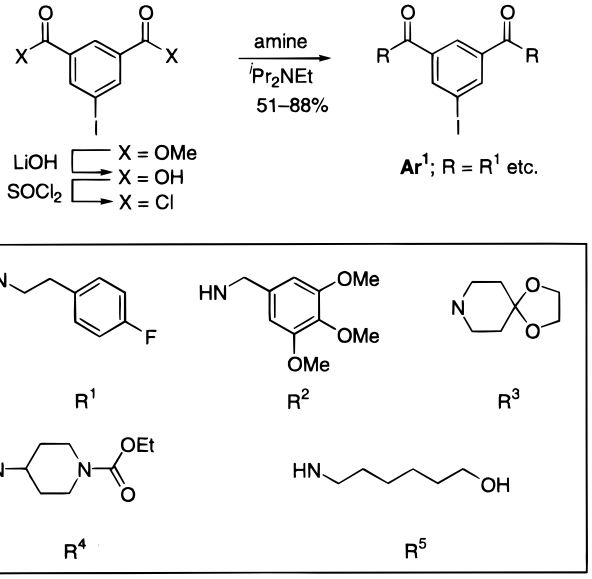
(12) Penalva, V.; Hassan, J.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron Lett.* **1998**, *39*, 2559. For the use of $Pd(OAc)_2$ in neat Et_3N (100 °C), see: Clark, F. R. S.; Norman, R. O. C.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. 1* **1975**, 121.

(13) For an early example of the use of PdBC in Heck arylations, see: Hallberg, A.; Westfelt, L.; Andersson, C.-M. *Synth. Commun.* **1985**, *15*, 1131.

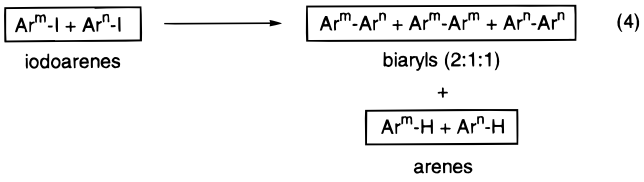
(14) Although the corresponding bromide also provided the desired homodimer under identical conditions, the iodide was preferred due to a faster conversion and much lower propensity for competitive reduction.

(15) Aryl iodides **Ar^1-I** through **Ar^5-I** showed R_f values between 0.1 and 0.8 in EtOAc.

Scheme 1



pling reactions were examined. Employing the iodides **Ar¹-I** through **Ar⁵-I** in a pairwise fashion as described generically in eq 4, the reaction afforded the expected



2:1:1 ratio of hetero- and homodimers. A typical HPLC trace of a crude product mixture obtained after extractive workup (see below) is shown in Figure 1. The yields varied from 75−95% depending on the scale and workup procedure used (see below), but the ratio between heterodimers, homodimers, and reduction products was invariant, illustrating that the iodide reactivities were not influenced by the nature of the amide substituents.

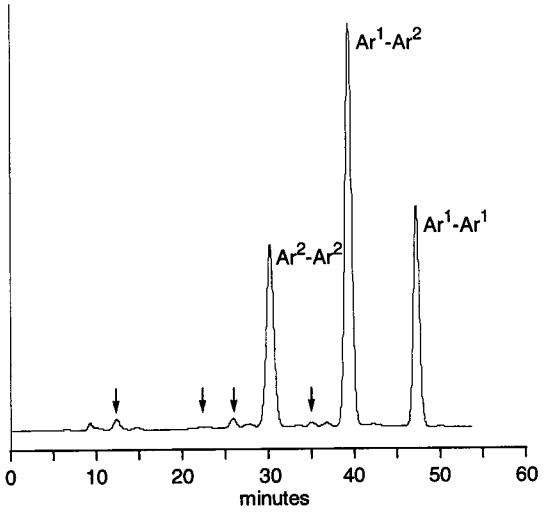


Figure 1. HPLC trace (254 nm) of the crude reaction mixture obtained from homocoupling of **Ar¹-I** and **Ar²-I**. Reduction products (Ar-H) and starting iodides (Ar-I) appear at 12 and 26 min, and 22 and 35 min, respectively (arrows). See Experimental Section for HPLC conditions.

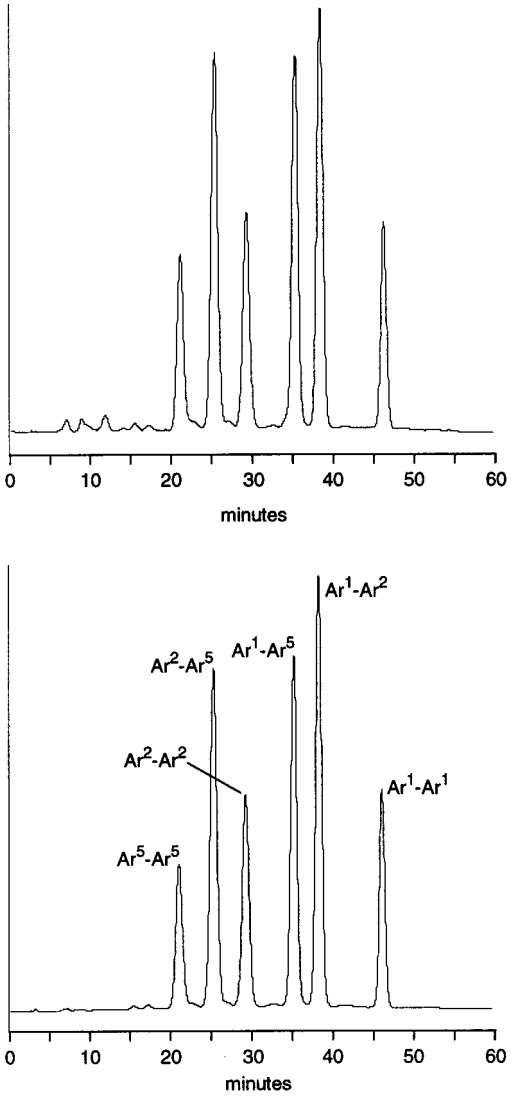


Figure 2. (a) HPLC trace (254 nm) of the crude reaction mixture obtained from homocoupling of **Ar¹-I**, **Ar²-I**, and **Ar⁵-I** (2:2:2:1:1:1 mixture of unsymmetrical and symmetrical biaryls). Reduction products and starting iodides appear at 7, 12, and 26 min and 15, 22, and 35 min, respectively. (b) HPLC trace (254 nm) of the purified product mixture obtained from homocoupling of **Ar¹-I**, **Ar²-I**, and **Ar²-I**.

The statistical dimerization of *n* building blocks (**Ar-I**) should deliver a mixture of $[n(n + 1)]/2$ products. According to the present protocol, the product mixture should further consist of *n* homodimers **Arᵐ-Arᵐ** and $[[n(n + 1)]/2] - n$ heterodimers **Arⁿ-Arᵐ** in relative, individual molar ratios of 1:2. Thus, increasing the number of building blocks favors the relative concentration of the heterodimers. Increasing the mixture complexity to six compounds by reacting three iodides still allowed good separation by HPLC, and the mixture resulting from homocoupling of **Ar¹-I**, **Ar²-I**, and **Ar⁵-I** serves well to illustrate this. The composition of the mixture was qualitatively consistent with the expected statistical distribution (Figure 2a) and deviations from the theoretical 2:2:2:1:1:1 ratio observed upon integration of the peaks (actual values were 2.0:2.2:2.4:1.0:1.3:1.0) were presumably derived from slight differences in extinction coefficients of the products at 254 nm. The mixture represented in Figure 2 was obtained in quantitative yield on a 75 μmol scale (32 mg). Similar results

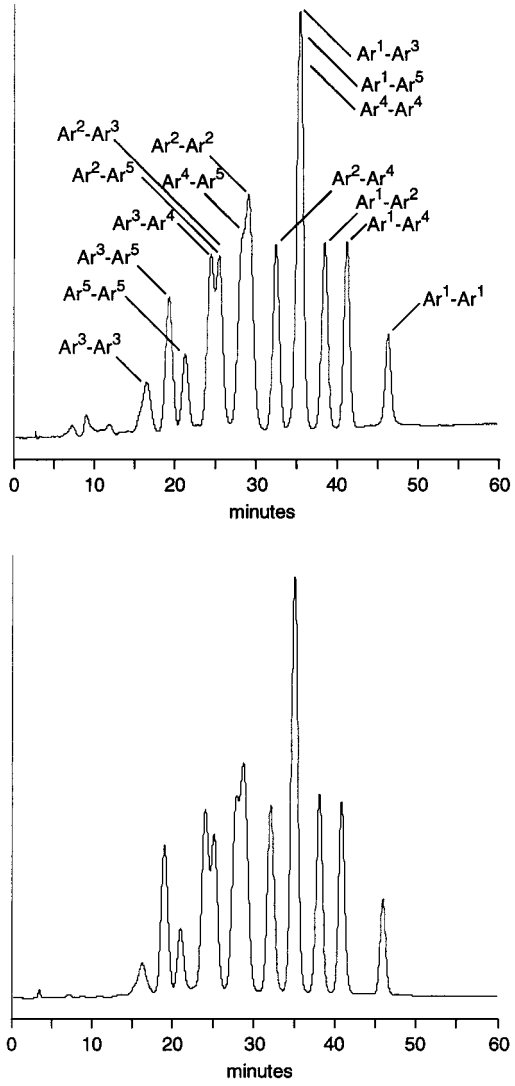


Figure 3. (a) HPLC trace (254 nm) of the crude mixture of 15 biaryls **Ar¹-Ar¹**−**Ar⁵-Ar⁵**(2:2:2:2:2:2:2:2:2:2:1:1:1:1:1) obtained from homocoupling of **Ar¹**⁻⁵**-I**. Identification of components was accomplished using HPLC-MS. (b) HPLC trace (254 nm) of the purified mixture of biaryls **Ar¹-Ar¹**−**Ar⁵-Ar⁵**.

were observed upon expanding the library size, although chromatographic analysis becomes increasingly difficult. The mixture of 15 biaryls produced by reacting all five iodides **(Ar¹-I**−**Ar⁵-I)** was characterized by HPLC−MS, which confirmed the presence of all the expected coupling products (Figure 3a), and integration of well-resolved peaks was consistent with a statistical product distribution.

Isolation. Three different methods have been employed for the isolation of the individual coupling products or biaryl mixtures. The heterogeneous reaction conditions provided for convenient filtration removal of the catalyst, leaving only removal of polar reaction byproducts (triethylammonium iodide and excess Et_3N) and solvent. Although the latter was readily accomplished through liquid−liquid extraction using EtOAc and 10% aqueous hydrochloric acid, liquid−solid extraction procedures[8] have proven especially useful. In addition, dilution of the reaction mixture followed by filtration through a short pad of silica gel has been used with good results, but might present complications with mixtures containing components of highly dissimilar polarity.[15]

Table 1. Molecular Weights of Biaryls Prepared

	Ar^1	Ar^2	Ar^3	Ar^4	Ar^5
Ar^1	814.9	931.0	822.9	881.0	770.9
Ar^2		1047.1	939.0	979.0	887.0
Ar^3			830.9	889.0	778.9
Ar^4	weighted avg.			947.0	837.0
Ar^5	842.6				726.9

Therefore, we routinely utilize ion-exchange resins (liquid−solid extraction) for the isolation of mixtures in order not to compromise their original composition. Thus, the mixtures disclosed herein and related larger libraries were isolated by diluting the crude reaction mixtures with $CHCl_3/CH_3OH$, brief stirring with a mixture of acidic and basic ion-exchange resins, filtration, and evaporation. The biaryl mixtures were generally isolated as yellow oils which solidified on standing using this technique.

Purification. Transition metal-catalyzed homo- or cross-coupling reactions are frequently accompanied by reduction of the substrates.[16] Although the levels of reduction products we observed with the 5-iodoisophthalamides were not a significant concern, more extensive reduction has been observed with other substrates and could become a limiting factor in extending the methodology. Recognition that the dimerization inherently doubles the molecular size of the library components irrespective of the linkage strategy suggested purification via size exclusion chromatography. The product biaryls **Ar-Ar** possess molecular weights of 726.9−1047.1 (Table 1), whereas the starting materials **Ar-I** and reduction byproducts **Ar-H** spanned molecular weights of 490.4−650.5 and 354.5−524.6, respectively. A proper grouping of diversity entries should readily produce similar or better size characteristics for virtually any library constructed according to similar principles. We have found that simple gravity size exclusion chromatography is an effective method for purifying such biaryl libraries. This technique allows the use of a variety of polar protic and aprotic solvents in combination with a very robust and reusable polymeric stationary phase. A comparison of the HPLC traces reproduced in Figures 2 and 3 illustrates the effectiveness of the technique (examples used THF as the mobile phase). Removal of lower molecular weight impurities occurred without complications due to the differences in polarity of the mixture components, and the separation was sufficiently good to allow simple filtration collection of only a few large (10 mL) fractions. Similar separations have been successfully conducted with mixtures containing higher levels of reduction byproducts and with larger mixtures of compounds. Importantly, the stoichiometric integrity of the desired combinatorial biaryl mixture was unaltered by size exclusion chromatography, making it especially useful for purifying diverse mixtures, for which standard adsorption or partition-based chromatography would be more difficult.

Conclusions

Biaryl libraries may be prepared in high yields and under mild conditions through the solution phase, and palladium-catalyzed homocoupling of iodoarene mixtures and palladium on carbon may be used as a convenient

(16) See: Hassan, J.; Penalva, V.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron* **1998**, *54*, 13793.

and inexpensive supported catalyst for these reactions. The direct convergent solution phase dimerization of combinatorially assembled iodoarene building blocks provides an effective and rapid route to symmetrical and unsymmetrical structures that would be precluded by typical solid-phase techniques where the combining components would typically be on mutually exclusive solid-phases. Purification of such library mixtures based on molecular size allows for mixture purification with complete conservation of the product mixture composition.

Experimental Section

General. ^{1}H NMR spectra were recorded at 250 MHz in DMSO-d_6, and chemical shifts were determined using residual solvent protons set to 2.50 ppm as reference. HRMS was performed using the FAB technique. Mixtures were characterized using electrospray ionization. HPLC analyses were performed on a Bondapak C_{18}, 125 Å column (3.9 × 300 mm) using a flow rate of 1 mL/min. A gradient going from 50% to 80% CH_3OH in 0.07% aqueous trifluoroacetic acid over 40 min was employed. DMF and CH_3OH were HPLC grade. Palladium on carbon (10% Pd−C) was purchased from Aldrich, Bio-Beads S-X8 resin was purchased from Bio-Rad Laboratories, and dimethyl 5-iodoisophthalate was purchased from Trans World Chemicals.

Building Blocks. Dimethyl 5-iodoisophthalate (5.6 g) was dissolved in a mixture of CH_3OH (50 mL) and H_2O (20 mL). $LiOH·H_2O$ (3.0 g) was added, and the mixture was stirred overnight. Addition of H_2O (200 mL) and extraction with EtOAc followed by acidification (HCl) and filtration gave 5-iodoisophthalic acid as a moist white solid (6.4 g). Without drying, the acid (2.5 g) was dissolved in $SOCl_2$ (20 mL) containing one drop of DMF. After the initial foaming had ceased, the mixture was warmed at reflux for 4 h. The $SOCl_2$ was removed by rotary evaporation followed by concentration from anhydrous toluene twice. Removal of residual solvent under vacuum provided 2.47 g of an oil (lit. mp 43−44 °C)[17] which was dissolved in 10 mL of anhydrous toluene and refrigerated. The following procedures are representative for the preparation of 5-iodoisophthalamides (**Ar-I**) or isophthalamides (**Ar-H**).

***N,N′*-Bis[2-(4-fluorophenyl)ethyl]-5-iodoisophthalamide (Ar^1-I).** A mixture of 4-fluorophenethylamine (1.5 mmol, 209 mg) and *i*-Pr_2NEt (1.5 mmol, 194 mg, 0.26 mL) in anhydrous CH_2Cl_2 (10 mL) was treated with 0.7 mL (0.5 mmol) of a stock solution of 5-iodoisophthaloyl chloride (exothermic). A precipitate was observed after reaction overnight. EtOAc (50 mL) was added, and the solution was washed sequentially with 10% aqueous HCl (2H), 5% aqueous K_2CO_3, and saturated aqueous NaCl. Drying (Na_2SO_4) and evaporation afforded the title diamide as a white solid (0.24 g, 88%).

***N,N′*-Bis(6-hydroxyhexyl)-5-iodoisophthalamide (Ar^5-I).** A mixture of 6-aminohexan-1-ol (1.8 mmol, 210 mg) and *i*-Pr_2NEt (1.73 mmol, 0.3 mL) in 10 mL of anhydrous CH_2Cl_2 was treated with 0.7 mL (0.5 mmol) of 5-iodoisophthaloyl chloride in toluene. After stirring overnight, the product was isolated through addition of 20 mL of 10% aqueous HCl and filtration. The solid was washed with H_2O and dried in vacuo to give 0.13 g (51%).

Ar^1-I: ^{1}H NMR 8.75 (t, 2H, J = 5.5 Hz), 8.24 (s, 3H), 7.25 (m, 4H), 7.10 (m, 4H), 3.43 (m, 4H), 2.81 (t, 4H, J = 7.2 Hz); HRMS calcd for $C_{24}H_{21}F_2IN_2O_2$ 666.9670 (M + Cs^+), found 666.9652.

Ar^2-I: ^{1}H NMR 9.16 (t, 2H, J = 5.7 Hz), 8.38 (d, 1H, J = 1.4 Hz), 8.36 (d, 2H, J = 1.4 Hz), 6.65 (s, 4H), 4.41 (d, 4H, J = 5.7 Hz), 3.75 (s, 12H), 3.62 (s, 6H); HRMS calcd for $C_{28}H_{31}IN_2O_8$ 783.0180 (M + Cs^+), found 783.0206.

Ar^3-I: ^{1}H NMR 7.83 (d, 2H, J = 1.4 Hz), 7.46 (t, 1H, 1.4 Hz), 3.90 (s, 8H), 3.64 (br s, 4H), 1.62 (br s, 8H). Remaining protons were obscured by the H_2O signal at 3.3 ppm; HRMS calcd for $C_{22}H_{27}IN_2O_6$ 674.9968 (M + Cs^+), found 674.9987.

Ar^4-I: ^{1}H NMR 8.53 (d, 2H, J = 7.5 Hz), 8.28 (m, 3H), 4.04 (q, 4H, J = 7.1 Hz), 3.97 (br m, 6H, partially overlapping with q), 2.91 (br m, 4H), 1.80 (br m, 4H), 1.42 (br m, 4H), 1.18 (t, 6H, J = 7.1 Hz); HRMS calcd for $C_{24}H_{33}IN_4O_6$ 733.0499 (M + Cs^+), found 733.0525.

Ar^5-I: ^{1}H NMR 8.65 (t, 2H, J = 5.5 Hz), 8.28 (s, 3H), 4.35 (t, 2H, J = 5.2 Hz), 3.38 (m, 4H), 3.24 (m, 4H), 1.56−1.20 (m, 16H); HRMS calcd for $C_{20}H_{31}IN_2O_4$ 491.1407 (M + H^+), found 491.1393.

Synthesis of Homodimers. The preparation of **Ar^1-Ar^1** is typical: a vial containing Et_3N (20 μL, 0.15 mmol) and 10% Pd−C (10.6 mg, 0.01 mmol) was treated with a solution of **Ar^1-I** (53.4 mg, 0.1 mmol) in DMF (0.2 mL). The vial was capped and stirred at 100 °C (oil bath) for 16 h.

Extractive Workup. The reaction mixture was diluted with 50 mL of EtOAc and filtered into a separatory funnel. The organic layer was washed with 10% aqueous HCl (50 mL), H_2O (50 mL), and saturated aqueous NaCl (25 mL), dried (Na_2SO_4), and concentrated to afford 38 mg (93%) of **Ar^1-Ar^1** as a yellow oil, which gave off-white crystals upon trituration with CH_3OH.

Workup Using Silica Gel Filtration. The crude reaction mixture was diluted with 4 mL of an EtOAc/CH_3OH mixture (95/5). The solution was filtered through 0.7 g of silica gel in a pasteur pipet, which was rinsed with an additional 15 mL of the solvent mixture. Evaporation of the solvents afforded a 75% yield of the biaryl as a pale oil.

Workup Using Ion Exchange Resins. The reaction mixture was diluted to 10 mL using a $CHCl_3$/CH_3OH mixture (1/1). Strongly acidic (Dowex 50WX8-200, 1 g) and strongly basic (Amberlite IRA-400, 0.5 g) ion-exchange resins were added, and the mixture was stirred for a few minutes. Filtration and additional washing of the resins and catalyst followed by concentration gave an 82% yield of the biaryl as a yellow oil.

Ar^1-Ar^1: ^{1}H NMR 8.89 (t, 4H, J = 5.5 Hz), 8.32 (s, 6H), 7.32 (m, 8H), 7.13 (m, 8H), 3.53 (m, 8H), 2.88 (t, 8H, J = 7.2 Hz); HRMS calcd for $C_{48}H_{42}F_4N_4O_4$ 947.2197 (M + Cs^+), found 947.2228. The presence of minor amounts (<5%) of the reduction product (**Ar^1-H**) was evident from diagnostic peaks at 8.25 (d), 7.91 (dd) and 7.54 (t). HPLC analysis confirmed a high purity of the biaryl product (47 min retention time) with only trace peaks accounting for reduction product (26 min) and starting material (35 min).

General Procedure for the Generation of Combinatorial Mixtures. The synthesis of the mixture of six biaryls (Figure 2) is representative: a 4 mL vial equipped with a stir bar was charged with 10% Pd−C (7.5 mg, 0.1 equiv) and Et_3N (15 μL, 0.11 mmol, 1.5 equiv). The iodides (**Ar^1-I**, **Ar^2-I**, and **Ar^5-I**) were added via syringe (125 μL of 0.2 M stock solutions in DMF, 25 μmol each), the vial was capped and warmed with stirring at 100 °C for 16 h. After cooling, the reaction mixture was diluted with 10 mL of a $CHCl_3$/CH_3OH mixture (1/1) and transferred to a 20 mL vial containing ion-exchange resins (0.75 g of Dowex 50WX8-200 and 0.38 g of Amberlite IRA-400). After stirring for 5 min, filtration and evaporation afforded 32 mg (quantitative yield based on the weighted average molecular weight of 845 g/mol) of a yellow oil. HPLC analysis (see Figure 2) indicated the presence of six biaryl products in a distribution reflecting a statistical dimerization.

Similarly, the mixture coupling of all five iodides provided a statistical mixture of 15 biaryls. HPLC-MS analysis of the product mixture confirmed its integrity; a Bondapak C_{18}, 125 Å column (3.9 × 300 mm) was used with a flow rate of 1 mL/min and a gradient of 50% to 80% CH_3OH in 0.07% aqueous trifluoroacetic acid over 40 min (Figure 3); ESMS pos: t = 14.8 min, M + H^+ 831 (**Ar^3-Ar^3**); t = 17.2 min, M + H^+ 779 (**Ar^3-Ar^5**); t = 19.1 min, M + H^+ 727 (**Ar^5-Ar^5**); t = 22.3 min, M + H^+ 939 (**Ar^2-Ar^3**); t = 23.5 min, M + H^+ 887 (**Ar^2-Ar^5**); t = 25.9 min, M + H^+ 889 (**Ar^3-Ar^4**); t = 26.8 min, M + H^+ 837 (**Ar^4-Ar^5**); t = 28.0 min, M + H^+ 1047 (**Ar^2-Ar^2**); t = 30.4 min, M + H^+ 997 (**Ar^2-Ar^4**); t = 33.1 min, M + H^+ 771 (**Ar^1-Ar^5**) and 823 (**Ar^1-Ar^3**); t = 34.1 min, M + H^+ 947 (**Ar^4-Ar^4**); t = 36.6 min, M + H^+ 931 (**Ar^1-Ar^2**); t = 39.9 min, M + H^+ 881 (**Ar^1-Ar^4**); t = 44.2 min, M + H^+ 815 (**Ar^1-Ar^1**).

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Size Exclusion Chromatography. A standard flash column charged with 100 g of Bio-Beads SX-8 resin was used for mixture purification. The column was typically washed with 10−50 mL of HPLC grade THF before the sample (5−25 mg dissolved in 1 mL of THF) was loaded via syringe. Additional THF was introduced on top of the resin and the column connected to a THF reservoir using standard Teflon tubing. Elution under gravity conditions gave a flow rate of about 2 mL/min. The first 100 mL of eluent were recirculated, and then five 10 mL fractions were collected. The most concentrated fraction (invariably the second 10 mL fraction in our case) was selected (by spotting on a TLC plate and visually estimating UV absorption) and concentrated under a stream of N_2. HPLC analysis of the main fraction as well as subsequent fractions showed efficient removal of reduction byproducts and traces of starting materials. Typical HPLC traces are reproduced in Figures 2 and 3.

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Supporting Information Available: ^{1}H NMR spectra of **Ar^n-I** and **Ar^1-Ar^1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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