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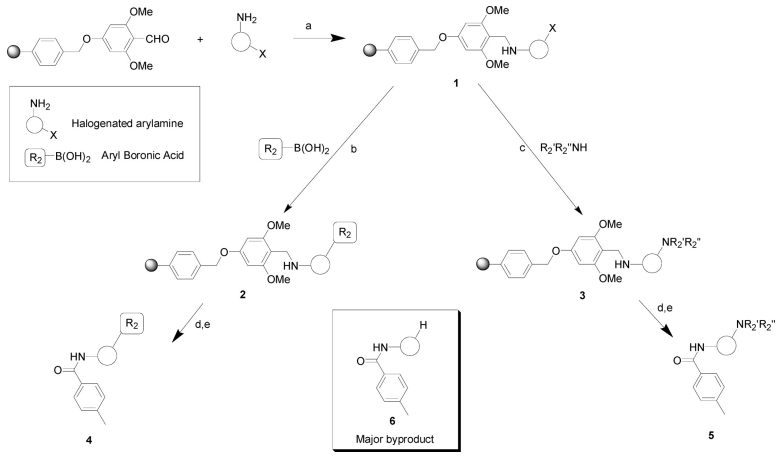

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Combinatorial Synthesis of Substituted Biaryls and Heterocyclic Arylamines

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In this paper, we report very general conditions that enable palladium-mediated coupling reactions on the solid support. A wide variety of biaryls and arylamines (including pyrimidines) have been synthesized using this protocol. The chemistry facilitates a combinatorial approach to the production of large numbers of medicinally relevant heterocyclic structures.

Introduction

The sequencing of the human genome has created huge opportunitites for the discovery of new therapeutics.[1] Given the potentially large numbers of molecular targets, chemical genomics can provide a way to discover lead compounds while simultaneously validating those targets for further drug discovery. Synthesis of diverse pools of small drug-like molecules using combinatorial chemistry is an integral part of a chemical genomic approach when coupled with the appropriate screening platform.[2] Our current research efforts focus on the production of large combinatorial mixture libraries enabled by the development of general and robust chemical synthesis methodologies.

The biaryl template has recently received wide attention in the pharmaceutical industry as a privileged substructure.[3] Molecules incorporating the unique structure of this scaffold have demonstrated activity across many therapeutic classes, including antinflammatory, antirheumatic, and antitumor agents.[4] In addition, some ortho-substituted biphenyl analogues have been proposed as potential mimetics of a protein α helix.[5] Suzuki or Stille coupling conditions represent the most general synthetic route to these type of molecules.[6] The synthesis of arylamine compounds has received considerable attention as well.[7] Buchwald/Hartwig coupling conditions can be employed to generate diverse sets of these structures.[8] Recently, solid-phase approaches to biaryls and arylamines have been explored in order to simplify their purification and provide a large number of molecules in a short period of time.[9,10] To this end, we have developed general palladium-mediated coupling conditions on the solid support for the combinatorial synthesis of both biaryl or arylamine compounds with relatively high yield and purity.

Our solid-phase protocol is described in Scheme 1. Halogenated arylamines were chosen as the template, which can be attached to the solid support via reductive amination[11] to an acid-cleavable aldehyde linker. The halogen can then be replaced with either an aromatic ring or an amine through palladium-catalyzed cross-coupling reactions to produce compounds of type **2** and **3**. Acylation of these intermediates followed by TFA mediated cleavage from the resin afforded the desired products **4** and **5**. Although the reactions were set up under an inert atmosphere by using an AtmosBag, the actual chemical transformations were carried out in 48-position Bohdan MiniBlock synthesizers without the need for special drying or other handling procedures. To accommodate larger numbers of reactions during a parallel synthesis run, a stock solution of the catalyst and ligand is required. A solution of the catalyst can quickly become deactivated in the absence of ligand. However, when the catalyst is added to a ligand solution (or suspension) under argon, it maintains activity during the course of the addition to the reaction blocks. After screening a variety of ligand systems,[8,12] we have found that dppf and tri-*tert*-butylphosphine tetrafluoroborate in conjunction with base (K_3PO_4 or NaOtBu) provided the best results. The tri-*tert*-butylphosphine tetrafluoroborate ligand yielded compounds of higher purity and was found to be more broadly applicable across various classes of substrates (Table 1).

Under our optimized reaction conditions, both pyridine and benzene systems worked well as halogenated arylamine templates (R_1, Table 1). A pyrazole template also gave satisfactory results (Table 1, entry **4c**). Generally, activated halopyridine templates furnished products of higher purity. The major impurity observed in these reactions is the reduced halogen byproduct **6**. One of the factors affecting this byproduct formation is temperature. While lowering the reaction temperature helps to suppress this byproduct, it increases the risk of an incomplete cross-coupling reaction. This impurity was more prevalent (∼30%) by HPLC-ELSD (evaporative light scattering detector) with the amination protocol than with the Suzuki coupling pathway (Table 1, entries **5l**−**5p**, **5s**). Use of hindred amines can lead to the formation of byproduct **6** as well (Table 1, entry **5p**). We have observed that most Suzuki coupling reactions go to completion at room temperature, and the amination reactions proceeded at temperatures as low as 55 °C. However, some reactions were incomplete under these conditions. Optimal temperatures for the widest range of reactants were found to be 45 °C for the Suzuki coupling and 70 °C for the

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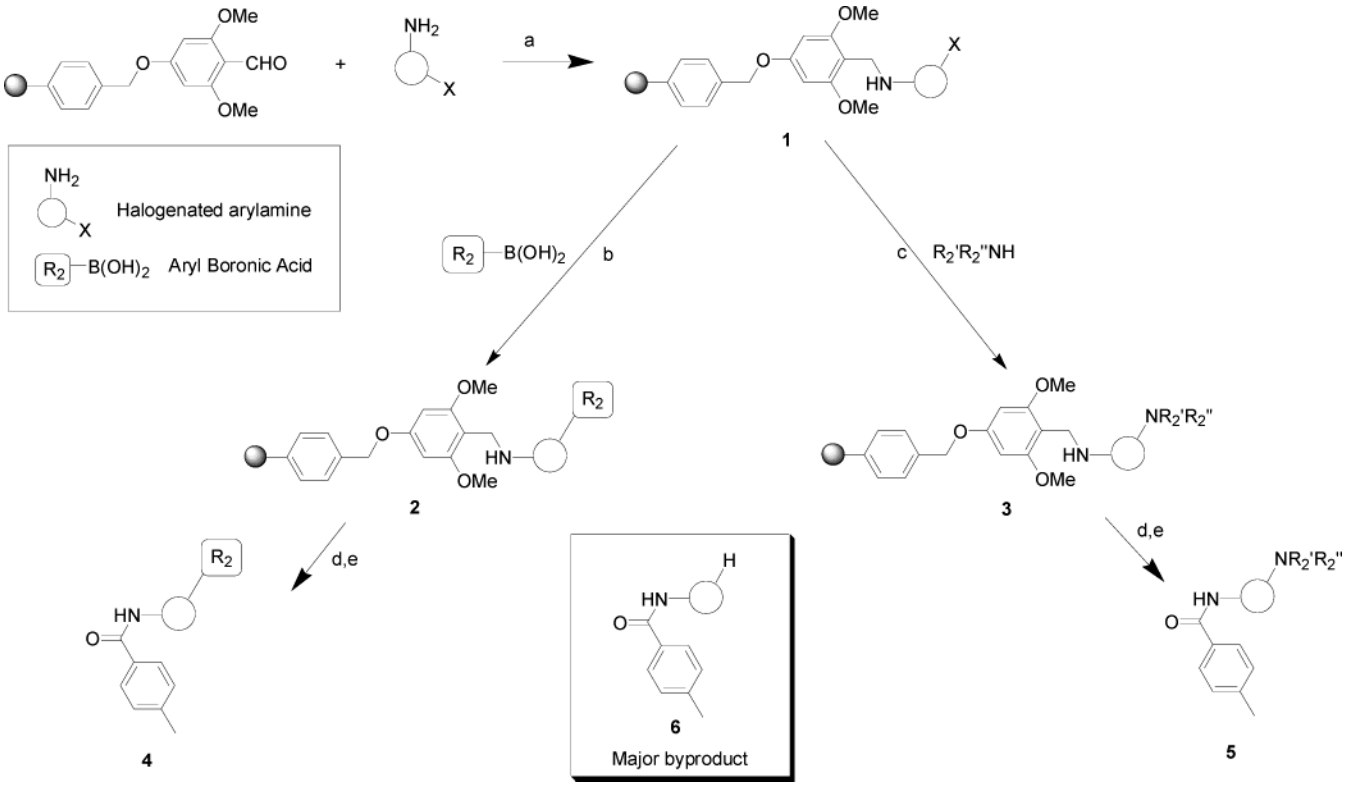
Scheme 1



[a] 5% AcOH in DCE, $NaBH(OAc)_3$, 36 h. [b] 20% $Pd_2(dba)_3$, 50% *t*-Bu_3P-HBF_4, 10 equiv of K_3PO_4, 10 equiv of $R_2B(OH)_2$, 45 °C. [c] 20% $Pd_2(dba)_3$, 50% *t*-Bu_3P-HBF_4, 10 equiv of NaO*t*-Bu, 10 equiv of $R_2'R_2''NH$, 70 °C. [d] 5 equiv of *p*-toluoyl chloride, 5 equiv DIPEA, DCM. [e] 95:5 TFA/H_2O, 1h.

Table 1. Suzuki Coupling or Amination of Aryl Halides (Formation of **4** and **5**)

entry	halogenated arylamine (R_1)	aryl boronic acid (R_2) for **4**	amine (R_2) for **5**	*m/z* (found)[a]	purity (%)[b]	yield (%)[c]
4a	5-amino-2-bromo-3-picoline	phenylboronic acid		303	85	85
4b	5-amino-2-bromobenzo-trifluoride	phenylboronic acid		356	80	55
4c	3-(3-aminophenyl)-4-bromo-1-methyl-pyrazole	phenylboronic acid		368	85	99
4d	3-bromo-4-(trifluoromethoxy)-aniline	phenylboronic acid		372	80	50
4e	2-amino-6-bromopyridine	phenylboronic acid		289	90	99
4f	3-bromoaniline	3-fluoro-6-methoxyphenyl-boronic acid		336	90	90
4g	3-bromoaniline	3-fluoro-4-methylboronic acid		320	90	75
4h	3-bromoaniline	3-chloro-6-methoxyphenyl-boronic acid		352/354	65[d]	90
4i	3-bromoaniline	benzo[*b*]thiophene-3-boronic acid		344	85	45
4j	2-bromo-4-fluoroaniline	phenoxathiin-4-boronic acid		428	85	45
4k	2-bromo-4-fluoroaniline	2-methoxy-5-pyridine-boronic acid		337	45[e]	60
5l	3-bromoaniline		piperidine	295	45[e]	55
5m	2-amino-3-bromo-5-methyl-pyridine		piperidine	310	50[e]	75
5n	2-amino-5-bromo-3-methyl-pyridine		piperidine	310	75[e]	60
5o	4-bromoaniline		piperidine	295	60[e]	65
5p	2-amino-6-bromopyridine		2-phenylpyrrolidine	358	50[e]	60
5q	2-amino-6-bromopyridine		*N*-ethylpiperazine	325	80	99
5r	2-amino-6-bromopyridine		2-(1-piperazinyl)pyrimidine	375	90	99
5s	2-amino-6-bromopyridine		L-proline *tert*-butyl ester	326	70[e]	95
5t	2-amino-6-bromopyridine		*N*-methylbenzylamine	332	85	90

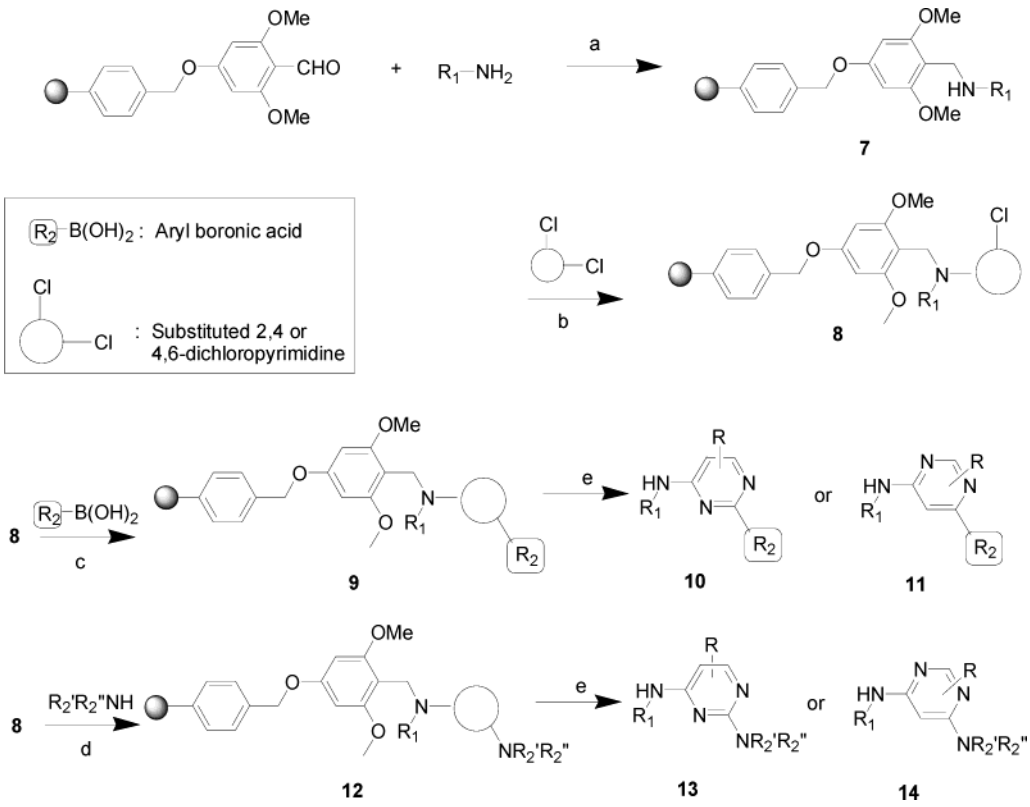
[a] MH^+ from LC/MS. [b] As determined by both ELSD and UV spectra of the desired ion. [c] Isolated yield after cleavage and concentration. [d] Major impurity is bis-Suzuki coupling product. [e] Major impurity is the reduced halogen byproduct **6**.

amination. As expected, a bis-Suzuki coupling product was observed when a chloroboronic acid was used under these conditions (Table 1, entry **4h**).

It was found that after the palladium-mediated reaction, using a solution of 1 M lithium tetrafluoroborate in MeCN helps remove some of the solid support color (presumably from palladium byproducts) without damaging the attached products. As a result, we utilized this wash protocol to clean the beads after all palladium-mediated coupling steps. Under these optimized conditions, no postcleavage purification was necessary to validate building blocks for a combinatorial synthesis of the title structures. Using the split−pool synthesis method,[13] libraries covering a combination of 36 halogenated anilines and 45 boronic acids or 33 halogenated anilines and 74 amines have been produced.

Since aminopyrimidines are poor substrates for reductive amination and halopyrimidines are particularly reactive in S_NAr reactions, we applied a slightly different strategy for the elaboration of these templates, as shown in Scheme 2.[3b]

Scheme 2



[a] 5% AcOH in DCE, $NaBH(OAc)_3$, 36 h. [b] *n*-Butanol, 5 equeiv DIPEA, 5 equiv of dichloropyrimidine, 90 °C. [c] 20% $Pd_2(dba)_3$ 50% *t*-bu_3P-HBF_4, 10 equiv of K_3PO_4, 10 equiv of $R_2B(OH)_2$, 45 °C. [d] 20% $Pd_2(dba)_3$, 50% *t*-Bu_3P-HBF_4 10 equiv of NaO*t*-Bu, 10 equiv of $R_2'R_2''NH$, 70 °C. [e] 1:1 DCM/TFA, 2 h.

Although the Suzuki coupling conditions were similar to those used in Krueger's investigation,[3c] in our study, the coupling step was performed only once, and no postsynthesis purification was necessary. As shown in Scheme 2, reductive amination to tether a primary amine to the resin was followed by a thermal reaction of the amine with a variety of 2,4- or 4,6-dichloropyrimidines to give compounds of type **8**. The second chloride could be replaced by either an aryl group or an amine, as in Scheme 1. TFA-mediated cleavage gave products of type **10** and **11** or **13** and **14** (Table 2). The chloride displacement reaction was conducted either in NMP (1-methyl-2-pyrrolidone) at room temperature or in *n*-butanol at 90 °C, with the latter producing better purity for most substrates. When DMF was used as a solvent, a trace of *N*,*N*′-(dimethylamino)-substituted byproduct was observed, as well. Compared to the products generated from Scheme 1, dehalogenation is considerably attenuated for these templates. According to the literature, the first nucleophilic substitution takes place primarily at the 4-position of the 2,4-dichloropyrimidine templates.[3b,3c] After the Suzuki coupling or amination reactions of 2,4-dichloropyrimidine templates, two sets of signals were observed in the ^1H NMR spectra (Table 2, entries **10a**, **10c**−**10g**, **13k**) of the cleaved products. These correspond to two peaks of the same mass found in most cases in their LC/MS chromatograms.These regioisomers are present in ratios varying from 3:1 to 10:1. The 2,4-dichloro-6,7-dimethoxyquinazoline template predominantly produced a single regioisomer, as evidenced by the LC/MS chromatograms and ^1H NMR spectra (Table 2, entries **10b** and **13l**). After building block validation, the sequence in Scheme 2 was used to produce libraries covering a combination of 14 substituted dichloropyrimidines and 47 boronic acids or 14 substituted dichloropyrimidines and 168 amines.

In summary, we have fully adapted two important palladium-mediated coupling reactions for use on solid support. We have also validated the robust operation of these types of reactions with a wide variety of diverse reactants by using a Bohdan Miniblock synthesizer (48 position) in an inert atmosphere. Reaction conditions described herein can be employed as a very general synthetic protocol for solid-phase Suzuki coupling or amination without the need for post-cleavage purification in most cases. These methods have been utilized in our lab to synthesize combinatorial libraries of thousands of heterocyclic compounds in mixture or discrete formats.

Experimental Section

StratoSpheres PL-FDMP (loading 1.5 mmol/g, Lot No. 13720PI) resin was used as the solid support for all described reactions and was purchased from Aldrich. Tris(dibenzylideneacetone)dipalladium (0) was purchased from Aldrich. Tri-*tert*-butylphosphonium tetrafluoroborate was purchased from Strem Chemicals, Inc. All NMR spectra were taken in CD_3COCD_3, with a 400-MHz Varian NMR Spectrometer. LC/MS data were obtained using an Agilent 1100 Binary HPLC instrument coupled to a mass spectrometer (Micromass Quattro LC or Agilent MSD). The mass spectra were recorded in positive electrospray mode. All acquired data were processed using Chemstation (Agilent) or MassLynx (Micromass) software. UV spectra were recorded at a

Table 2. Suzuki Coupling or Amination of Dichloropyrimidine (Formation of **10**, **11**, **13,** and **14**)

entry	R_1	dichloropyrimidine	aryl boronic acid (R_2) for **10** or **11**	amine ($R_2'R_2''NH$) for **13** or **14**	*m/z* (found)[a]	purity (%)[b]	yield (%)[c]
10a	4-$MeOC_6H_4NH_2$	2,4-dichloropyrimidine	phenylboronic acid		278	95	90
10b	4-$MeOC_6H_4NH_2$	2,4-dichloro-6,7-dimethoxy-quinazoline	phenylboronic acid		388	95	60
10c	4-$MeOC_6H_4NH_2$	2,4-dichloropyrimidine	4-methoxyphenylboronic acid		308	95	85
10d	4-$MeOC_6H_4NH_2$	2,4-dichloropyrimidine	benzothiophene-2-boronic acid		334	75[d]	40
10e	4-$MeC_6H_4CH_2NH_2$	2,4-dichloropyrimidine	benzofuran-2-boronic acid		316	95	99
10f	4-$MeC_6H_4CH_2NH_2$	2,4-dichloropyrimidine	(2-phenoxyphenyl)-boronic acid		368	95	99
10g	4-$MeC_6H_4CH_2NH_2$	2,4-dichloropyrimidine	dibenzothiophene-4-boronic acid		382	90	65
11h	4-$MeOC_6H_4NH_2$	4,6-dichloropyrimidine	phenylboronic acid		278	95	95
11i	4-$MeOC_6H_4NH_2$	fenclorim (4,6-dichloro-2-phenylpyrimidine)	phenylboronic acid		354	95	75
11j	4-$MeC_6H_4CH_2NH_2$	4,6-dichloro-*N*,*N*-dimethyl-2-pyrimidinamine	phenylboronic acid		319	95	70
13k	4-$MeOC_6H_4NH_2$	2,4-dichloropyrimidine		morpholine	287	95	90
13l	4-$MeOC_6H_4NH_2$	2,4-dichloro-6,7-dimethoxy-quinazoline		morpholine	397	95	55
14m	4-$MeOC_6H_4NH_2$	4,6-dichloro-2-(methylthio)-pyrimidine		morpholine	333	95	65
14n	4-$MeOC_6H_4NH_2$	4,6-dichloropyrimidine		morpholine	287	95	85
14o	4-$MeC_6H_4CH_2NH_2$	4,6-dichloro-*N*,*N*-dimethyl-2-pyrimidinamine		morpholine	328	85	65
14p	4-$MeC_6H_4CH_2NH_2$	4,6-dichloropyrimidine		dipropylamine	299	95	99
14q	4-$MeC_6H_4CH_2NH_2$	4,6-dichloropyrimidine		2-phenylpyrrolidine	345	95	90
14r	4-$MeOC_6H_4NH_2$	4,6-dichloropyrimidine		1-(2-fluorophenyl)piperazine	380	85	70
14s	4-$MeOC_6H_4NH_2$	4,6-dichloropyrimidine		2,6-difluorobenzylamine	343	80	80
14t	4-$MeOC_6H_4NH_2$	4,6-dichloropyrimidine		2-methoxyethylamine	273	90	80

[a] MH^+ from LC/MS. [b] As determined by ELSD-HPLC spectra of the desired ion, which covers possible regioisomers for the unsymmetrical dichloropyrimidine templates. [c] Isolated yield after cleavage and concentration. [d] Major impurity is the unreacted starting material.

wavelength of 254 nm. Palladium coupling reactions were conducted in a Bohdan Miniblock synthesizer (48 position). The reactions were set up under argon using an AtmosBag purchased from Aldrich. The aforementioned library mixtures were synthesized through the resin split−pool method.

Representative Procedure for the Preparation of Compounds 4 and 5, Preparation of 4e and 5q. (A) Reductive Amination, **Resin 1.** To 0.1 mmol Stratospheres PL-FDMP resin (1.5 mmol/g) in a 4-mL Bohdan tube was added 2-amino-6-bromopyridine (0.5 mmol, 87 mg) in 1.25 mL of 5% AcOH in DCE. The reactions were sealed and shaken at room temperature (rt) for 3 h. Sodium triacetoxyborohydride (0.5 mmol, 106 mg) was then added. The reactions were sealed and shaken at rt for 1 h. They were then vented, and they were shaken at rt for an additional 36 h. MeOH (0.5 mL) was added, and the resins were filtered and then washed with MeOH, DMF, IPA, and DCM (3×). The resins were dried under vacuum for 5+ h.

(B) Suzuki Coupling Reaction, **Resin 2e.** A solution of phenylboronic acid was made at a concentration of 0.625 M in dioxane (76 mg/mL). A stock solution (or suspension) of the ligand, *t*-Bu_3P-HBF_4, was made at a concentration of 0.0625 M in dioxane (18 mg/mL) using a sonicator if necessary. To resin **1** (0.05 mmol) in a 4-mL Bohdan tube was added K_3PO_4 (0.5 mmol, 106 mg), followed by the phenylboronic acid solution (0.5 mmol, 0.8 mL). In an argon-purged AtmosBag, catalyst $Pd_2(dba)_3$ was added to the ligand stock solution (1:2.5 equiv for catalyst/ligand, 23 mg/mL). The mixture was shaken well before use. The catalyst/ligand stock solution (0.4 mL, 0.01 mmol catalyst, 0.025 mmol ligand) was added to the reaction. The reaction tube was then sealed. The Bohdan block was removed from the AtmosBag and shaken at 45 °C for 24 h. The resin was filtered and washed with 1:1 DME/H_2O, 1:1 AcOH/DCM, toluene, DMF, IPA, and DCM (3×) and dried under vacuum for 2+ h.

(C) Amination Reaction, **Resin 3q.** A solution of *N*-ethylpiperazine was made at a concentration of 0.625 M in dioxane (71 mg/mL). A stock solution (or suspension) of the ligand, *t*-Bu_3P-HBF_4, was made at a concentration of 0.0625 M in dioxane (18 mg/mL), using a sonicator if necessary. To resin **1** (0.05 mmol) in a 4-mL Bohdan tube was added NaOtBu (0.5 mmol, 48 mg), followed by the *N*-ethylpiperazine solution (0.5 mmol, 0.8 mL). In an argon-purged AtmosBag, catalyst $Pd_2(dba)_3$ (1:2.5 equiv. for catalyst/ligand, 23 mg/mL) was added to the ligand solution. The mixture was shaken well before use. The catalyst/ligand stock solution (0.4 mL, 0.01 mmol catalyst, 0.025 mmol ligand) was added to the reaction. The reaction tube was then sealed. The Bohdan block was removed from the AtmosBag and shaken at 70 °C for 24 h. The resin was filtered and washed with 1:1 DME/H_2O, 1:1 AcOH/DCM, toluene, DMF, IPA, and DCM (3×) and dried under vacuum for 2+ h.

(D) Treatment of Resin after Palladium Coupling Reaction. To each resin **2e** or **3q** (0.05 mmol) was added a mixture of THF and H_2O (0.5 mL THF + 10 μL of H_2O) and 1 M $LiBF_4$ in MeCN (0.5 mL). The mixture was shaken at rt for 1 h. The resin was filtered, washed with THF, H_2O, DMF, IPA, and DCM (3×) and dried under vacuum for 5+ h.

(E) Acylation of Resin 2e or 3q with *p*-Toluoyl Chloride. To resin **2e** or **3q** (0.05 mmol) in DCM (1 mL) was added DIPEA (0.25 mmol, 44 μL), followed by *p*-toluoyl chloride (0.25 mmol, 33 μL). The mixture was shaken at rt

overnight. The resin was filtered and washed with DCM, DMF, IPA, and DCM (3×) and dried under vacuum for 1 h.

(F) Cleavage of the Resin, **4e or 5q.** To resin **4e** or **5q** (0.05 mmol) in a 4-mL Bohdan tube was added 1 mL of 95:5 TFA/H_2O. The resin was agitated at rt for 1 h. The resin was filtered and washed with 1 mL of acetonitrile. Evaporation of the combined filtrates under vacuum gave a residue, which was redissolved in 1 mL of acetonitrile, diluted with 1 mL of water, and lyophilized to give **4e** or **5q**.

Representative Procedure for the Preparation of Compounds 11 and 14, Preparation of 11h and 14r. (G) Reductive Amination, **Resin 7.** Procedure A was followed, using *p*-anisidine as the amine building block.

(H) Chloro Displacement, **Resin 8.** To resin **7** (0.05 mmol) in a 4-mL Bohdan tube was added *n*-butanol (0.5 mL), followed by DIPEA (0.25 mmol, 44 μL) and 4,6-dichloropyrimidine (0.25 mmol, 41 mg) in *n*-butanol (0.5 mL). The mixture was sealed and shaken overnight at 90 °C. It was then cooled to ambient temperature, and the resin was washed with DMF, IPA, and DCM (3×) and dried under vacuum for 2+ h.

(I) Suzuki Coupling Reaction, **Resin 9h.** Procedure B was followed, using resin **8** in place of resin **1**.

(J) Amination Reaction, **Resin 12r.** Procedure C was followed, using resin **8** in place of resin **1**.

(K) Treatment of Resins 9h and 12r after Palladium Coupling Reaction. The protocol described in Procedure D was followed to treat these resins.

(L) Cleavage of the Resin, **11h or 14r.** To resin **9h** or **12r** (0.05 mmol) in a 4-mL Bohdan tube was added 1 mL of 1:1 TFA/DCM. The resin was agitated at rt for 2 h., then filtered and washed with 1 mL of acetonitrile. Evaporation of the combined filtrates under vacuum gave a residue, which was redissolved in 1 mL of acetonitrile, diluted with 1 mL of water, and lyophilized to give **11h** or **14r**.

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Supporting Information Available. ^{1}H NMR spectra of representative compounds **4e**, **4f**, **5q**, **5s**, **10a**, **10b**, **11h**, **13k**, **13l**, and **14r** and LC/MS spectra for all compounds listed in Tables 1 and 2 are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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