The Use of a Supported Base and Strong Cation Exchange (SCX) Chromatography to Prepare a Variety of Structurally-Diverse Molecular Libraries Prepared by Solution-Phase Methods

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Abstract: The preparation of molecular libraries of aminomethylbiaryls, allylic amines, and ethanolamines using solution-phase methodology is described. In particular, the use of a solid-supported base reagent (PTBD resin) and strong cation exchange(SCX) resin to effect 'catch and release' purification across these diverse libraries is highlighted.

INTRODUCTION

Combinatorial chemistry, which is perhaps better and more generally referred to as high throughput synthesis (HTPS) (sometimes also called high throughput organic synthesis or HTOS), is touted to be a means of dramatically shortening the process for discovering new materials, catalysts, and pharmaceutical agents [1]. Advances in high throughput biological screening (HTS), which triggered the development of HTPS, hastened the ability to assess accurately the efficacy of discrete compounds. Thus, a growing need developed for the preparation of large numbers of single compounds of good to high purity. In the earlier developmental stages of HTPS, compound purity of 50 percent or greater was deemed to be acceptable for performing bioassays. Later, the level of acceptable purity was increased to 80 percent purity for 80 percent of all unpurified compounds attempted in a library preparation [2]. This would constitute an acceptable or successful library synthesis for publication and screening purposes. Ideally of course, one would rather have libraries that are comprised of essentially pure compounds.

There are numerous difficulties associated with preparing large libraries of pure compounds. In light of the diversity that one is trying to achieve when preparing a library, the starting materials can react at significantly different rates for steric or electronic reasons (or both). As a consequence, the synthetic success rate will be variable across the reaction wells in a synthetic block.

Solid-phase organic synthesis (SPOS) has dealt with the purity issue, in part, by using mass action coupled with filtration [3]. Although once considered the method of choice to prepare molecular libraries, SPOS has a number of issues to contend with that are making it less attractive to use, at least to prepare libraries of 2000 compounds or less. Such reasons include long and tedious synthetic rehearsals and a limited number of reactions that have been reliably adapted for use on the solid-phase. Further, if reactions do not complete along the synthetic pathway, the same purity problem exists at the end of the sequence once the compound is cleaved from the support. Nonetheless, SPOS has proven to be effective despite these difficulties in library preparation, especially when coupled to encoding strategies [4].

Solution-phase library preparation, which is essentially traditional synthesis coupled to automation, is receiving increasing attention [5]. Solution-phase preparations neither have the long rehearsals associated with SPOS, nor involve the attachment and cleavage of material to a support. In general, the biggest problem with solution-phase library synthesis is reaction work-up and purification. This is especially true for HTPS. Automated liquid-liquid extraction is impractical at this stage of equipment development, and incomplete reactions (or reagent excesses) pose a major challenge to large-scale parallel purification.

In one-off synthesis, purification would be dealt with by traditional column chromatography or product re-crystallization. Purification of libraries on a large scale by re-crystallization is not feasible, but high throughput liquid chromatography (LC) stations have been developed for parallel, large scale purification of libraries [6]. The problem with this strategy is the growing solvent waste stream generated by large scale LC. Some companies have responded to this problem with the development of supercritical carbon dioxide separation (SFC) techniques [7]. However, the technique is still embryonic in its development, and the equipment is quite expensive.

A more practical, long-term solution for acceptable library purity is to improve the synthetic chemistry to minimize contaminating starting materials and reaction byproducts in the crude product so that high throughput purification is not necessary. Although this may not provide the near analytically pure material that would be obtained using LC purification, it would provide compounds of acceptable purity (>90%) for biological screens, and would minimize product handling and chromatography waste.

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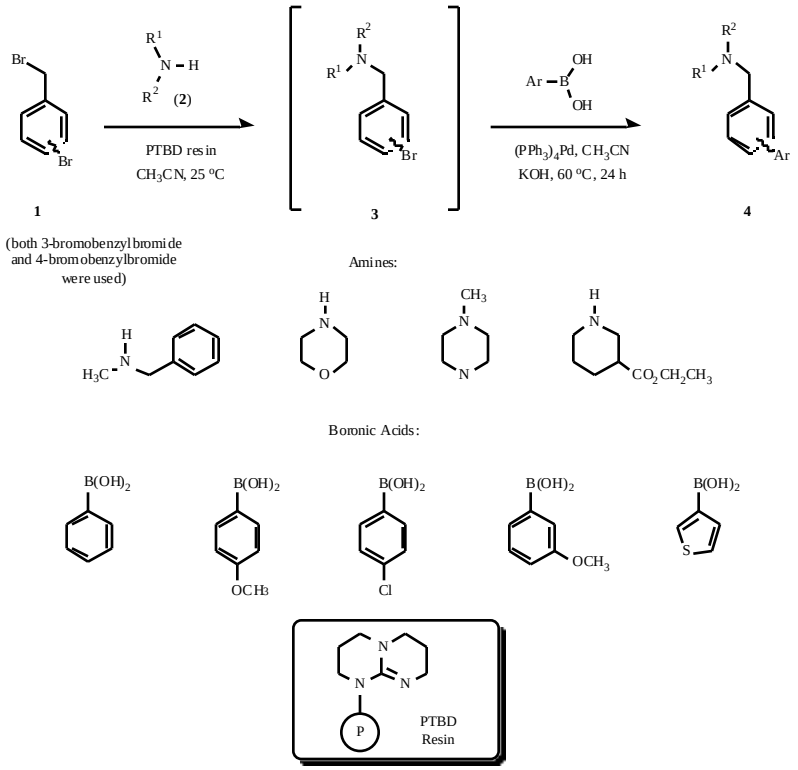
While our group develops both solid- and solution-phase strategies to prepare libraries, we prefer to use solution-phase approaches that take advantage of solid-supported reagents and 'catch-and-release' purification strategies [8]. These reagents and their by-products (including salts) are solid-supported thus they can be removed by filtration often eliminating the need for liquid-liquid extraction. Catch-and-release purification methods, be they covalent or ionic, are an effective means of dealing with excess starting materials and/or reaction byproducts[5]. Here it is important that the synthetic design allows for the selective sequestering of the desired material, be it the product or unreacted starting materials, onto the support to achieve separation of the desired product from the mixture by filtration. These scavenging resins act as chemical mops that try to clean up the products without resorting to large scale chromatography [9]. In this report we summarize the preparation of three structurally-diverse libraries using solution-phase methods, all of which use a solid-supported base to facilitate a key substitution step and strong cation exchange (SCX) chromatography to purify the products.

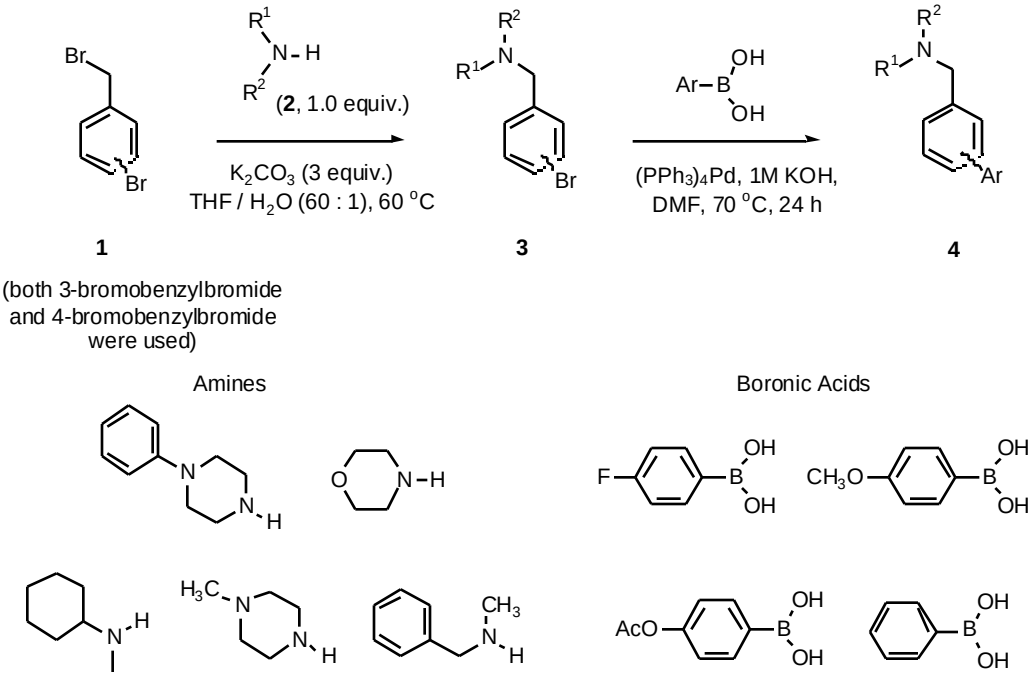
RESULTS

The most success to date for the production of large molecular libraries has been centered around established, robust reactions such as reductive amination and carboxylic acid derivatizations (e.g. amides, sulfonamides, ureas). In addition to being well studied, such reactions are typically very efficient even with 1:1 ratios of the starting materials. Thus, purification is relatively simple if it is necessary at all. However successful, such a narrow range of C-X bond-forming reactions limits synthetic flexibility, thus restricting the diversity of the targets approachable in a HTPS format. We are interested in expanding the range of chemical transformations for HTPS, while keeping the step count low and addressing purification. Our approach has been to incorporate late transition metal catalysts into parallel synthesis. Metals such as Pd coordinate and react selectively at soft binding sites, such as alkenes and alkynes. This largely eliminates the need for orthogonal protecting group strategies that increase the synthetic complexity and reduce the effectiveness of HTPS. An important issue in this approach is that C-C bond-formation can become a central part of the library design. Hence, C-X bond-forming reactions no longer need to be the final and major diversification step. This is demonstrated with the first class of compounds discussed below, i.e., aminomethylbiaryls, that we prepared using this methodology.

In addition to their interesting biological properties [10], biaryl compounds offered us a suitable target to test our metal-catalyzed reaction strategy in a solution-phase, parallel synthesis format. The original approach we devised is shown in Scheme 1. A 1:1 ratio of **1**:**2** in the presence of 1.05 equivalents of 1,3,4,6,7,8-hexahydro-2H-pyrimido [1,2-c] pyrimidine on polystyrene (PTBD resin) provided intermediate **3** very cleanly [11]. The supported guanidine salt was removed by in-line filtration and the filtrate was loaded directly into a second reaction vessel charged with the Suzuki coupling mixture [12]. When the reactions were complete, they were drained from the synthesizer through a short SCX column affixed to the bottom manifold of the reaction vessel and the compounds were collected in vials and evaluated. Overall yields ranged from 43 to 63 percent



Scheme 1.



Scheme 2.

and the average purity was 86 percent with all but two examples over 94 percent pure by HPLC (λ = 254 nm) [13].

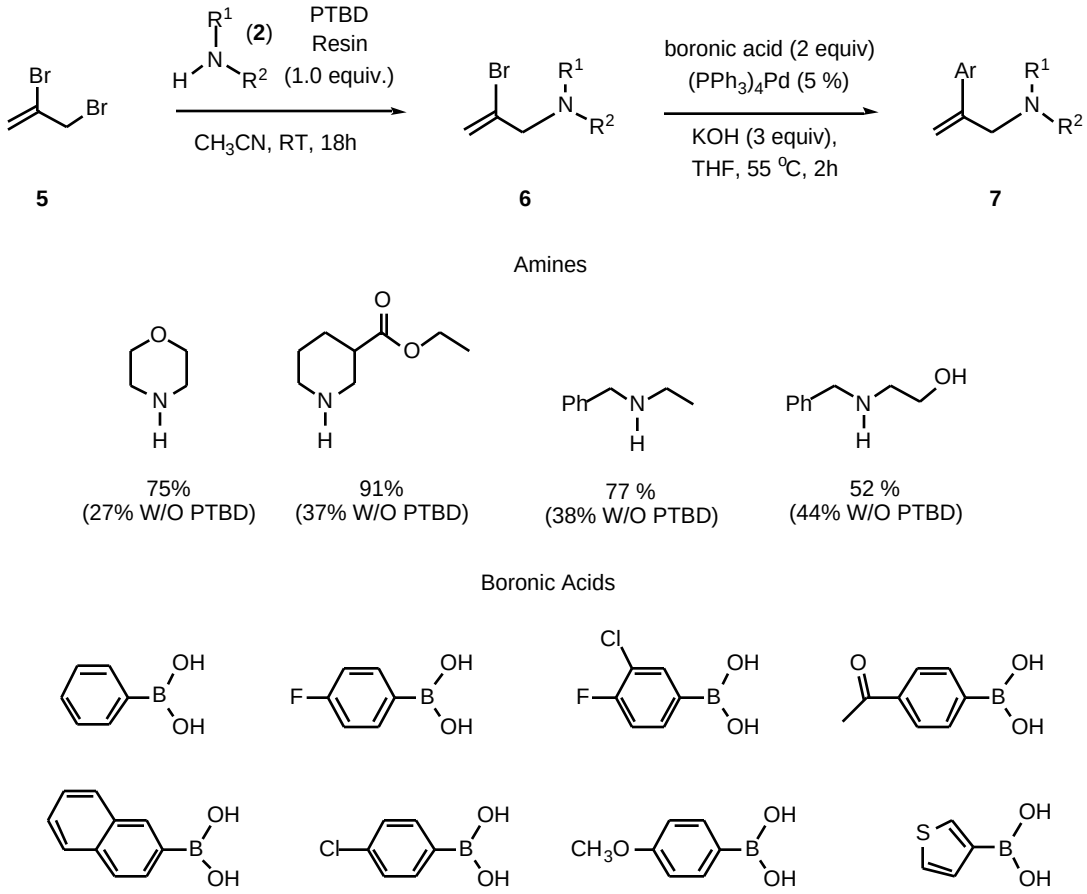
Due to the cost of PTBD resin [14], and other resin-supported bases [15], we sought an alternative method for the benzylic substitution that would still maintain the ease and reliability of the library purification [16]. We reasoned that excess potassium carbonate could serve as a proton sponge because the benzylic substitution should proceed smoothly without the activating guanidine base. Non-consumed base would be removed by filtration, although its presence would not affect the cross coupling step. The reaction proceeded smoothly in wet THF with heating (Scheme 2).

This procedure provided a sub-library of 10 benzylic amines (**3**, average yield, 96 percent) with no secondary amine visible in any of the crude ^{1}H NMR spectra (average purity, 97% by NMR spectroscopy). This material was then plated out into a single 96-well Robbins FlexChem® reactor block for the Suzuki coupling using DMF as solvent followed by SCX chromatography to provide 24 compounds in good yield (62% average) and purity (87% average by HPLC, λ = 254 and 280 nm) over the plate of aminomethylbiaryls **4** (Scheme 2) [17].

In a related study, a library of allylic amines was prepared using a similar strategy with PTBD base and SCX chromatography (Scheme 3, first step) [18]. In the initial pass, we reasoned that one equivalent of starting amine in the absence of any other base should be sufficient to effect the substitution. The tertiary amine product would be the most basic species and thus serve as the proton sponge for the transformation. However, it became apparent that this was not the case in practice as we identified significant quantities of various secondary amines that crystallized out as their HBr salts during the reaction resulting in very poor yields (the yields for reactions performed in the absence (W/O) of PTBD resin are given in brackets).

Thus, not only did the supported reagent facilitate the reaction with a simple filtration at the end, but it also provided significantly improved yields without having to resort to an excess of the secondary amine to drive the reaction to completion. This would have compromised the SCX chromatography. The intermediate amines (**6**) were then cross coupled with a variety of boronic acids (Scheme 3, second step) to provide a small array of 32 compounds with a minimum purity of 95 percent (by ^{1}H NMR spectroscopy) following SCX chromatography. Crude **6** could be used (i.e., without SCX chromatography) because the PTBD-promoted reactions were so efficient and clean.

Once again for cost considerations, we opted to prepare a larger library (1344-member) without the PTBD resin base (*vide supra*) [18]. Instead, we opted to use an excess of starting amine (2.0 equiv.) followed by liquid-liquid extraction to remove the secondary amine salt and we obtained excellent recovery of allylic amine **6** (average yield >80 percent). The intermediate obtained was essentially pure (i.e., there was no secondary amine visible in the crude NMR spectra) and we were able to use it further without purification. This result seems to confirm that the secondary amines are thermodynamically more basic than **6**, at least on the surface, which is not what one would have predicted *a priori*. One possible explanation is that the tertiary amines may be protonated as well and, like the secondary amines salts, can be extracted into the aqueous phase during liquid-liquid extraction which has ether in it to reduce the miscibility of the two phases. Proton transfer from the protonated tertiary amine to the secondary amine could be happening at the interface of the two phases. The secondary amine salts are less greasy than those derived from **6**, thus it



Scheme 3.

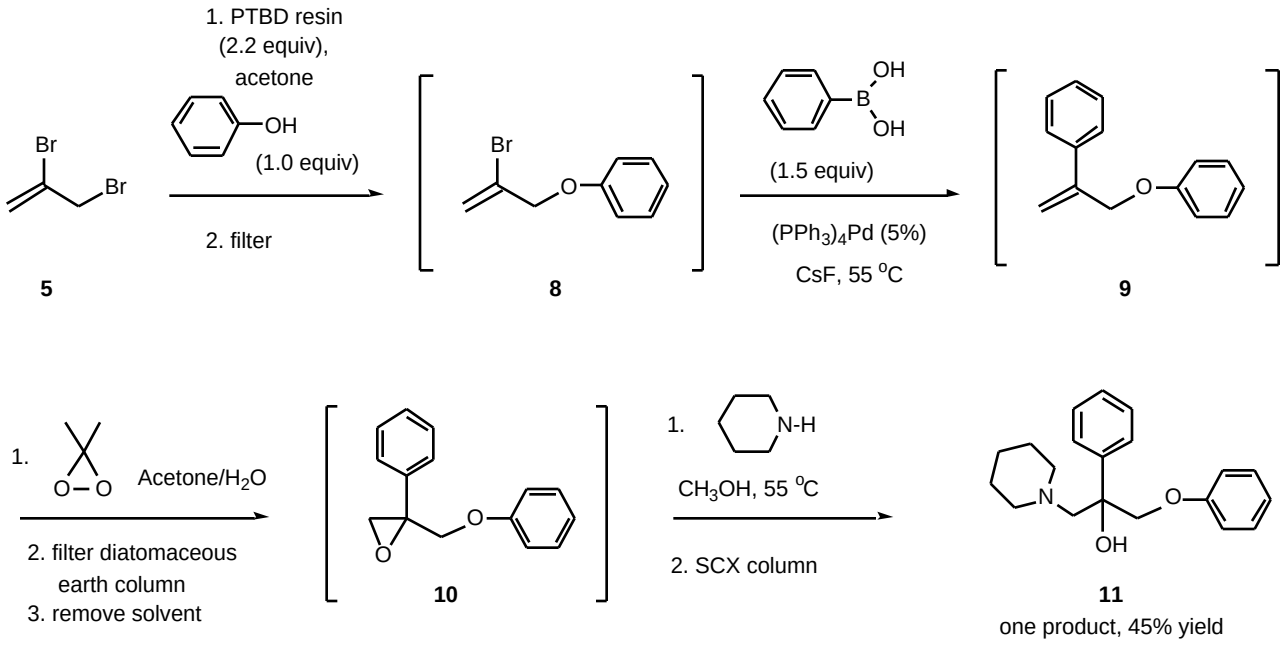
may be a solubility issue and not really a pKa issue that is pushing the equilibrium. In any case, a good recovery of essentially pure **6** was obtained using this method which indicates that it could be used more widely in the preparation of other libraries. Compounds **6** were then plated out into 96-well Robbins FlexChem® reactor blocks where the cross coupling proceeded smoothly providing **7** after SCX chromatography.

Olefin template **5** was also used to prepare a library of ethanolamines (**13**), the pharmacophore of which is quite different structurally from **7**, according to the same solid-supported base and SCX resin purification strategy. Once again, the efficacy of the chemistry and advances in automation allowed this whole synthetic sequence to be done in one overall operation. In a proof of concept experiment, compound **11** was prepared very cleanly and in good yield given the number of transformations along the way (Scheme 4) [12]. In truth, the percent conversion was higher, as it was for most of the reactions reported in this paper, but moderate recovery associated with SCX chromatography resulted in product loss. We have found that despite the manufacturer's suggested loading, the amount of the protonated amine ionically bound to the SCX resin was less than expected. Thus, much of the desired product came straight through the column during the loading step. However, what came off the column at the end was very clean demonstrating the usefulness and efficiency of this simple process. Of course, recovery can be improved by simply using more than the recommended amount of the resin. This would be a short-term, albeit expensive solution. However, the long-term solution resides in the development of more efficient ion-exchange resins.

A 20-member library (i.e., compounds **13**) was created using the first three steps of this sequence to prepare 4 epoxides (**12**) which were incubated with 5 amines that underwent an epoxide-opening aminolysis to provide an array of 20 ethanolamines (Scheme 5) [19]. These reactions where carried out using a Robbins FlexChem® reactor block. In this case, we opted to use methoxyethanol as the solvent to allow us to heat to 80 °C as reactions with some substrates were sluggish at 55 °C in methanol. We are presently working on expanding this route to produce a library of approximately one thousand ethanolamines for biological evaluation.

DISCUSSION

It can be said with certainty that solution-phase synthesis is being used increasingly to prepare combinatorial libraries.[5] The primary reason for this shift is the ability to perform chemistry directly without the need to adapt it to solid support that requires additional investigation. Solid-supported reagents and catalysts are essential for simplifying reaction work-up and purification and hence expand the range of approachable pharmacophores using solution-phase

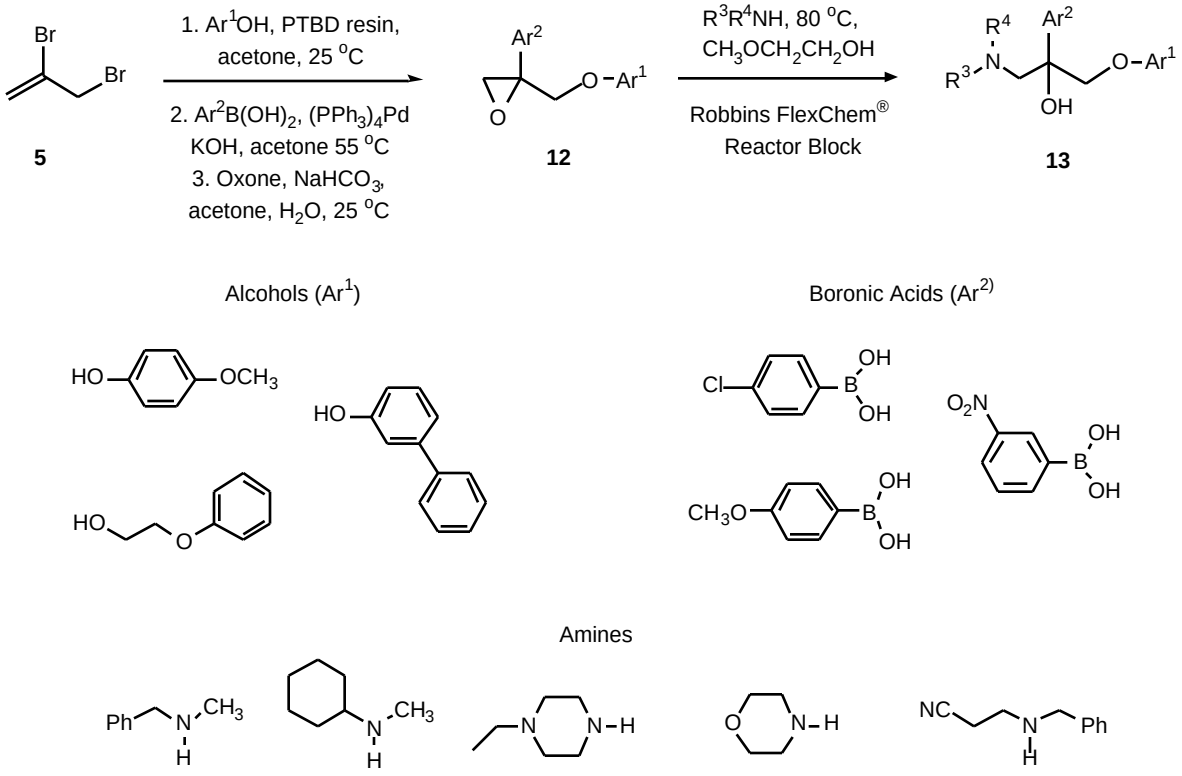


Scheme 4.

techniques. In this report we have illustrated the diverse use of PTBD resin, a supported guanidine base, to facilitate a variety of nucleophilic substitution reactions. In all cases, the reactions proceeded efficiently, typically out performing the same reaction when a homogeneous base was used.

In situations where excess reagents are required and a supported reagent or catalyst will not suffice, such as the cross-coupling reactions in this report, excellent purity was obtained using a 'catch and release' strategy with SCX resin. This chromatographic step is now essentially part of the synthetic strategy to prepare a library.

There are a couple of issues that, when addressed, will promote a wider acceptance of such supported reagents in solution-phase synthesis to prepare molecular libraries, and in particular large libraries (i.e., greater than 800 compounds). The efficiency of sequestering resins will



Scheme 5.

continue to be improved so that scavenging and catch-and-release techniques work with greater reliability [20]. This will ensure that product loss, such as that observed in this report following the suggested loading capacities of the commercial supplier, does not take place. Further, the price of these supported reagents and exchange resins makes their use by academic labs and smaller industrial companies difficult [21]. Presumably, continued research and development will aid in lowering the cost of production of polymer-supported reagents. Never-the-less, the future of solution-phase synthesis to prepare molecular libraries of increasing size with the aid of supported reagents, catalysts, and catch and release resins is certainly a promising one.

EXPERIMENTAL

All chemicals and solvents were purchased from Aldrich Chemical Company and used as received. The PTBD resin was purchased from Fluka. NMR spectra were acquired using a Bruker Avance 400 MHz Spectrometer. ChemElut and SCX resin (in 500 mg prepackaged cartridges) were purchased from Varian and Whatman, respectively. Mass spectra were obtained using a PE SCIEX API 200 triple quadrupole mass spectrometer with electrospray ionization. All mass spectra were full scan experiments (mass range 100 – 650 amu). The Shimadzu HPLC system consisted of an LC-8A pump and an SPD-10A VP UV-VIS system (λ = 254 nm). The Quest 210 Synthesizer (Argonaut Technologies), equipped with the Teflon male Luers on the lower manifold, was used to carry out the multi-step parallel syntheses. Parallel synthesis conducted in 96-well plates was done using Robbins 2 mL FlexChem® reactor blocks.

General procedure for the two-step preparation of biaryls (4) using PTBD resin as the base for the substitution reaction on an Argonaut Quest model 210 synthesizer:

Reaction vessel 1 in Bank A on the Quest 210 was charged with 4-bromobenzylbromide (**1**, 50 mg, 0.2 mmol) and 1,3,4,6,7,8-hexahydro-2H-pyrimido [1,2-c] pyrimidine on polystyrene (PTBD resin) (100 mg, 2.2 mmol/g, 0.22 mmol). N-benzylmethyl amine (**2**, 24 mg, 0.2 mmol) in 3 mL CH_3CN was then added and the reaction was agitated for 5 h at RT. At this time, TLC analysis (100% Et_2O) revealed the presence of a single product spot and the absence of both the amine (**2**) and the benzyl bromide (**1**) starting materials.

Reaction vessel 11 in Bank B was charged with 4-methoxyphenylboronic acid (48 mg, 0.4 mmol) and $(PPh_3)_4Pd$ (12 mg, 0.01 mmol). The contents of reaction vessel 1 (Bank A) were then transferred, via cannula, to the corresponding reaction vessel, i.e., 11, in Bank B. Filtration of the mixture during the transfer through a Teflon frit affixed to the bottom of the reaction vessel 1 in Bank A completely removed all solid material providing a clear solution entering Bank B. To this reaction mixture was added 1M KOH (0.6 mL, 0.6 mmol) and the resulting mixture was heated to 60 ^oC and agitated for 24 h.

Following the 24 h incubation period, the reaction vessel was allowed to cool and the solution diluted with CH_2Cl_2 (5 mL) and water (2 mL). The resulting biphasic mixture was then drained from the apparatus and passed through a column of Varian Chem-Elut hydromatrix. The hydromatrix was washed with CH_2Cl_2 (3 x 3 mL) with the combined eluent from the reaction being returned to a clean reaction vessel on the apparatus in Bank A. The reaction vessel was then fitted with an SCX cartridge (wetted with 5% HOAc/MeOH) via the Luer attachment. The solution was then slowly forced through the SCX cartridges by carefully controlling the metered nitrogen gas. When elution of the solution through the SCX cartridge was completed, the resin was washed several times (5 x 5 mL) with methanol. Final elution of **4** was achieved by washing the SCX with 2.0 M NH_3/MeOH (2 x 3 mL). Evaporation of the MeOH provided essentially clean product.

For HPLC analysis for the biaryl library, a Hypersil C_{18} column (50 mm x 2 mm) was used with a mobile phase consisting of 52 : 48 MeOH : H_2O, buffered with 0.1% HOAc/2 mM NH_4OAc or acetonitrile/H_2O with 0.1% TFA.

General procedure for the preparation of biaryl library (4) using potassium carbonate base for the substitution reaction and Suzuki-couplings that were carried out in a 96-well Robbins FlexChem® reactor block:

Alkylation of amines was performed on a Radleys 12-place PTFE carousel in conjunction with an IKALabortechnik magnetic stirring plate. To a solution of either 3- or 4-bromobenzyl bromide **1** (0.75 g, 3.0 mmol, 1.2 equiv.) in THF:H_2O (10 mL : 0.17 mL) and in a Radleys' reaction tube, were added K_2CO_3 (0.35 g, 2.5 mmol, 1 equiv.) and secondary amine **2** (2.5 mmol, 1 equiv.). The reaction mixture was heated to 50°C and stirred vigorously for 16 h. Upon cooling to RT, 7 mL of AcOH were added to adjust the pH from 10 to 3. The mixture was diluted with a 25 mL solution of MeOH : CH_2Cl_2 (4 : 1) and loaded on an SCX column (BondElut®, 5 g, 0.82 meq/g). The resin was then washed thoroughly with MeOH followed by CH_2Cl_2 until the eluent became colorless (to remove impurities). Elution with a 2M NH_3/MeOH solution (3x5 mL), followed by solvent removal *in vacuo* afforded either 3- or 4-bromobenzylamines **3** that were used in the Suzuki coupling without further purification.

The following procedure was repeated for each well of the Robbins FlexChem® reactor block. To a solution of bromobenzylamine **3** (50 mmol) in DMF (50 μL) was added a solution of boronic acid (100 mmol, 2 equiv.) in DMF (100 μL), a solution of KOH (150 mmol, 3 equiv.) in H_2O (125 μL) and a solution of $Pd(PPh_3)_4$ (2.5 mmol, 0.05 equiv.) in DMF (250 μL). The plate was agitated at 70 °C for 18 h. Upon cooling to RT, 0.4 mL of a 10% AcOH solution in MeOH/$CHCl_3$ (1:1) was added. The plate was filtered under vacuum and the reaction mixtures were collected into a 96-well plate (2 mL capacity); each well was rinsed with a 10% AcOH solution in MeOH/$CHCl_3$ (2 x 0.4 mL). The reaction mixtures were then loaded onto SCX columns (BondElut®, 500 mg, 0.69 meq/g). The columns were washed with MeOH (3x3 mL) to remove impurities. Elution (3 x 2 mL) with a 2M NH_3 solution in MeOH/$CHCl_3$ (1:1) and collection of the filtrates into round-bottom flasks was followed by evaporation of the solvent (*in vacuo*) to afford compounds **4**.

General procedure for allylic substitution of 2,3-dibromo-1-propene (5) with secondary amines (2) using PTBD resin as the base and subsequent non-plate Suzuki-couplings:

Into a 10 mL test tube was added 3 mL of acetonitrile followed by PTBD resin (0.5 g, 1.1 mmol), 2,3-dibromo-1-propene (**5**, 200 mg, 1 mmol), and ethyl nipecotate (**2**, 157 mg, 1 mmol) and the mixture was stirred. When the reaction was judged complete by TLC analysis (usually left for 18h), the mixture was filtered and the solvent removed *in vacuo.* The mass balance and crude ^{1}H NMR spectrum revealed full conversion and a 95% product recovery. Intermediate **6** was then used without purification in the Suzuki step.

Aqueous KOH (1M, 0.7 mL, 0.7 mmol) was added to a solution of phenylboronic acid (59 mg, 0.48 mmol) in THF (3 mL). A solution of the vinyl bromide **6** from the above procedure (50 mg, 0.24 mmol) in THF (1 mL) was then added. Finally, $(PPh_3)_4Pd$ (14 mg, 12 mmol) was added and the resulting solution was stirred at 55 ^oC for 14 h. Upon cooling to RT, water (2 mL) and CH_2Cl_2 (5 mL) were added. The organic layer was collected and the solvent removed *in vacuo.* The residue was taken up in 10% AcOH/MeOH and loaded onto an SCX column (Varian BondElut, 500 mg SCX resin / 3 mL column). The impurities were eluted with MeOH (3 x 2 mL). Then, the desired tertiary amine product was collected by eluting the SCX column with 2M NH_3/MeOH (3 x 2 mL). After removal of the solvent, the final product was obtained (39.5 mg, 81% yield).

General procedure for the preparation of allylic amine library (7) using excess secondary amine base for the substitution reaction and Suzuki-couplings that were carried out in a 96-well Robbins FlexChem® reactor block:

Morpholine (**2**, 0.75 g, 8.61 mmol) was added to a stirred solution of **5** (0.86 g, 4.31 mmol) in THF (15 mL). After 14 h, water (5 mL) and ether (2 mL) were added. The aqueous layer was separated and discarded. The organic layer was dried (anhydrous $MgSO_4$) and the solvent was removed *in vacuo* to obtain the amine-alkylated product **6** (818 mg, 92 % yield). This product was used in subsequent Suzuki reactions without purification.

The following procedure was repeated for each well of the Robbins FlexChem® reactor block. Aqueous KOH (1M, 0.3 mmol, 0.3 mL) was added to a solution of a boronic acid (0.2 mmol) in THF (0.2 mL). A solution of tertiary amine **6** (0.1 mmol) in THF (0.1 mL) was added. Finally, a solution of $(PPh_3)_4Pd$ (5 mmol) in THF (0.2 mL) was added. The mixture was agitated in a Robbins oven at 55 ^oC for 14 h. Upon cooling to RT, water (0.2 mL) and CH_2Cl_2 (0.7 mL) were added. The two-phase solution was filtered through a 96-well filter plate filled with Varian Hydromatrix, and the plate was rinsed with CH_2Cl_2 to ensure complete elution. The residue was concentrated and taken up in 10% AcOH/MeOH and the resulting solutions were filtered through a 96-well filter plate with 500 mg SCX per well,

using a 96-well plate vacuum manifold available from Varian. Product was eluted with 2M NH_3/MeOH. In general, no signals corresponding to reagents or intermediates were observed in the subset of ^{1}H NMR spectra examined.

General procedure for the preparation of ethanolamine library (13) using three-step sequence on the Argonaut Quest model 210 synthesizer to provide epoxides (12) that were opened with secondary amines (2) in a 96-well Robbins FlexChem® reactor block:

Reaction vessel 1 in Bank A on the Quest 210 was charged with 3 mL of acetone, **5** (75 mg, 0.38 mmol) and PTBD resin (190 mg, 2.2 mmol/g, 0.42 mmol). Twenty six mg of 4-(2-hydroxyethyl)phenol (0.19 mmol) were added and the reaction followed by TLC analysis.

Reaction vessel 11 in Bank B was charged with phenylboronic acid (22 mg, 0.18 mmol), CsF (55 mg, 0.36 mmol), and $(PPh_3)_4Pd$ (28 mg, 0.024 mmol) in 0.5 mL of acetone. The contents of reaction vessel 1 (Bank A) were then transferred, via cannula, to the corresponding reaction vessel, i.e., 11, in Bank B. Filtration of the mixture during the transfer through a Teflon frit affixed to the bottom of the reaction tube in Bank A completely removed all solid material providing a clear solution entering Bank B. The reaction mixture was heated to 60 ^oC and agitated for 24 h.

Reaction vessel 1 in Bank A (which had a fresh reaction vessel), was charged with oxone (1.17 g, 3.8 mmol), $NaHCO_3$ (623 mg, 7.5 mmol), Na_2EDTA (260 mg), acetone 2 mL, and 2 mL H_2O. This solution was allowed to stir at 0 ^oC for 15 min. to ensure that dimethyl dioxirane formation was well under way. At this time, the solution in Bank B vessel 11 was transferred into Bank A, vessel 1 via cannula and the mixture agitated at RT for 2 h. The mixture was further diluted with CH_2Cl_2, the organic layer separated and the solvent removed *in vacuo*. The ^{1}H NMR spectrum of the crude reaction mixture revealed that the steps had all gone to completion. The crude epoxides (**12**) were purified by flashing them through a short silica gel column.

The following procedure was repeated for each well of the Robbins FlexChem® reactor block. The four epoxide products (**12**) from the tandem sequence on the Quest were weighed and each dissolved in 1.0 mL of methoxyethanol. Two hundred μL of each stock solution were loaded into 4 rows of the reactor block (20 wells in total). Five stock solutions of secondary amines (**2**) were prepared by dissolving 0.5 mmol of the amine in 1.0 mL of methoxyethanol, and 0.9 equiv. of each amine were dispensed orthogonally to the epoxides (**12**) to complete the array. After sealing the Block, the mixtures were heated at 80 ^oC for 16 h. Upon cooling to RT, the residues were concentrated and taken up in 10% AcOH/MeOH. The resulting solutions were passed through a 96-well filter plate containing 500 mg of SCX resin per well and the products were eluted with 20% NH_3/MeOH. In general, no signals corresponding to reactants or byproducts were observed in the ^{1}H NMR spectra. The yield/recovery range for the 20 compounds was 30-60% and the average purity was over 86 percent (based on LC/MS data, λ = 254 and 280 nm).

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[12] Reactions were conducted on a Quest 210 personal synthesizer (Argonaut Technologies, see: http://www.argotech.com/) with parallel reaction chambers (banks) so that reactions can be transferred from 'bank-to-bank' via cannula without having to leave the instrument for successive transformations. See Experimental for full details.

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[14] The largest bottle of PTBD resin that can be purchased from Aldrich (from their catalogue) is 25 G and the material costs approximately $8.00 per gram.

[15] For example, polystyrene-supported morpholinomethyl resin is available from Advanced ChemTech at $4.50 per gram as a 25 G bottle.

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[21] The largest bottle of SCX resin listed in the Varian catalogue is 1 Kg at approximately $2.50 per gram.

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