Fully Automated Flow-Through Synthesis of Secondary Sulfonamides in a Binary Reactor System

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A fully automated flow-through process for the production of secondary sulfonamides is presented. Primary sulfonamides were monoalkylated using a two-step "catch and release" protocol to generate library products of high purity. The automated flow synthesis platform incorporates four independent reactor columns and is able to perform automated column regeneration. A 48-member sulfonamide library was prepared as two 24-member sublibraries, affording library compounds in good yields and high purities without the need for further column chromatographic purification.

Introduction

A key objective within the pharmaceutical industry is the rapid production of high-quality libraries of compounds as a means of generating lead molecules with desirable biological activities.[1] However, the protracted workup and purification procedures associated with conventional solution-phase chemistry are unsuited to the increased demands of high-throughput synthesis. In contrast, solid-phase synthesis is a powerful tool, allowing the efficient preparation of large numbers of compounds. Yet, this approach also has some significant limitations.[2] For example, reaction monitoring and optimization of conditions is difficult, and incomplete conversions over a number of steps can lead to impure products being generated. Purification of the library is therefore usually required, which is a very costly and time-consuming exercise.

An alternative approach is the use of polymer-assisted solution-phase synthesis (PASP), for which a wide variety of supported scavengers and reagents have been developed.[3] This has the advantage over solid-phase techniques in that standard reaction monitoring and rapid optimization are possible using conventional analytical instrumentation. In addition, it benefits from simplified workup (filtration) and the ability to directly produce high-purity products by the judicious use of scavenger resins and catch and release techniques.[4]

PASP chemistry is well suited to implementation in flow reactor systems, and this introduces additional benefits such as high reproducibility, safety, and the opportunity for both scale up and scale out.[5] We have previously described the use of reusable, stoichiometric reactor cartridges as a component of a custom-built, fully automated flow-through system leading to the preparation of an array of heterocyclic thioethers.[6] Herein, as part of our ongoing efforts to develop automated flow-through processes that efficiently execute key bond-forming reactions that are widely exploited within medicinal chemistry, we describe the use of an automated system to generate a collection of monoalkylated sulfonamides via a two-step synthesis. The fully automated system described has the ability to rapidly generate an array of compounds with high levels of purity suitable for direct evaluation in a biological screen.

Sulfonamides represent an important chemotype for medicinal chemistry. Not only are they important in drugs in their own right, representing the largest class of antimicrobial agents,[7] but they also form the starting point for many classes of drugs including diuretics, antidiabetic drugs, and antihypertensives.[8] Simple alkylation of primary sulfonamides, however, often leads to varying amounts of bisalkylated material being formed. Similarly, acylation of primary amines commonly generates bis-sulfonyl derivatives as impurities.[9] PASP synthesis of sulfonamides has been achieved by the coupling of amines with sulfonyl chlorides in parallel batch-reaction systems.[10] However, purification of the reaction products was generally required. To circumvent these issues, an alternative synthetic strategy was adopted using a Boc-protected primary sulfonamide as the starting material that can only undergo monoalkylation prior to subsequent acid-mediated removal of the Boc-activating/blocking group (Scheme 1).[11]

To exploit this strategy to prepare a combinatorial library of sulfonamides, a resin catch and release strategy was utilized, whereby a set of Boc-protected sulfonamides are each "captured" in turn by a suitable reactor cartridge prior to sequential elution with a set of alkylating agents that promotes alkylative "release" of the intermediate monoalkylated adducts. In each case, the protected adduct was passed through a second reactor cartridge in an in-line process to remove the Boc group, prior to isolation and parallel evaporation to yield the discrete array products. The reactor cartridge was then regenerated, a different Boc-

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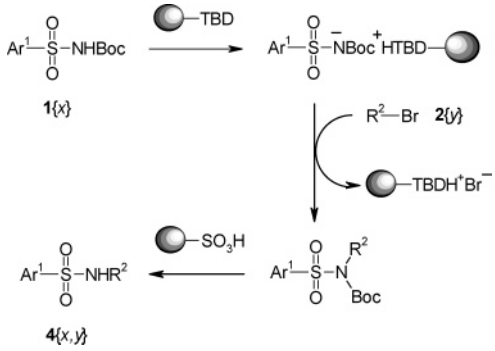
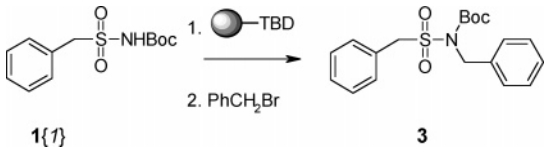
Scheme 1



Scheme 2. Capture and Alkylative Release of *N*-Boc Sulfonamide by PS-TBD Resin



sulfonamide was "captured" on the column, and the process was repeated.

Results and Discussion

Library Rehearsal Studies. Establishing Optimized Conditions for Sulfonamide Monoalkylation in Flow. The acidity of primary sulfonamides is increased by the presence of an *N*-Boc electron-withdrawing protecting group, and as such, Boc-protected sulfonamides are readily N-deprotonated and may be scavenged by polymer-supported bases, such as the immobilized guanidine base PS-TBD,[12] to form stable immobilized ionic complexes.[13] Preliminary studies examined how quickly the sulfonamide **1**{*1*} was captured from solution by PS-TBD to form a stable zwitterionic complex **2** and then subsequently underwent alkylative release upon the introduction of benzyl bromide to liberate **3**. The speed of both processes was observed to benefit from moderate heating. For example, Figure 1 contrasts the rapidity of the capture of the representative sulfonamide **1**{*1*} (0.5 mmol, 0.025M) by PS-TBD (5 equiv) in a batch system at 60 °C in three different solvents: *N*,*N*-dimethylformamide (DMF), acetonitrile (MeCN), and chloroform ($CHCl_3$).

Although the rate of capture was fastest in DMF, when the subsequent alkylative release step was studied using benzyl bromide, the product obtained suffered from disappointingly low purity.

This problem was resolved by switching to MeCN as the solvent of choice. An increase of the reaction temperature to 80 °C ensured that capture and release both went to completion in a short time period (<8 min in each case), suggesting that the analogous flow process should be viable within a relatively short residence time (Figure 2), particularly, if higher substrate concentrations are invoked. Importantly, no impurities were detected by LC-MS or NMR spectroscopy, implying that the process could deliver compounds directly with high levels of purity.

To study the reaction in a flow system, we first addressed the issue of determining functional loading. A glass reactor column was packed with PS-TBD (0.5 g × 1.4 mmol g^{-1} = 0.7 mmol) and flushed with MeCN. A solution of sulfonamide **1**{*1*} (0.5 mmol, 0.25 M) was eluted through the column at 0.1 mL min^{-1} (optimized by experimentation), and the column was subsequently washed with MeCN to elute any nonbound material. Substoichiometric solutions of the benzyl bromides **4**{*1*} and **4**{*2*} (0.033 mmol, 0.066 M each) were alternately eluted through the loaded column, also at 0.1 mL min^{-1}, and the resulting eluted material in each case was collected. This process was repeated for a total of 16 individual elutions, and the substituted sulfonamides obtained were individually analyzed by LC-MS and NMR to check both that cross contamination was not occurring

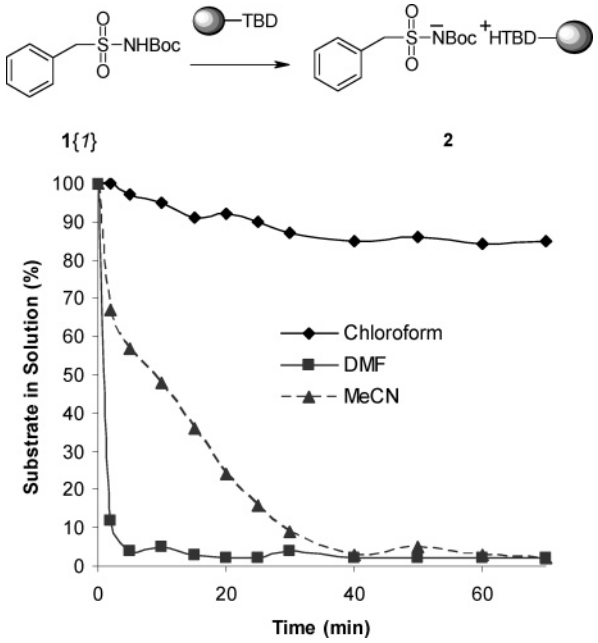


Figure 1. Capture of **1**{*1*} (0.5 mmol, 0.025M) by PS-TBD under batch conditions. Reagents and conditions: PS-TBD (5 equiv), **1**{*1*} (1 equiv, 0.025 M), 60 °C.

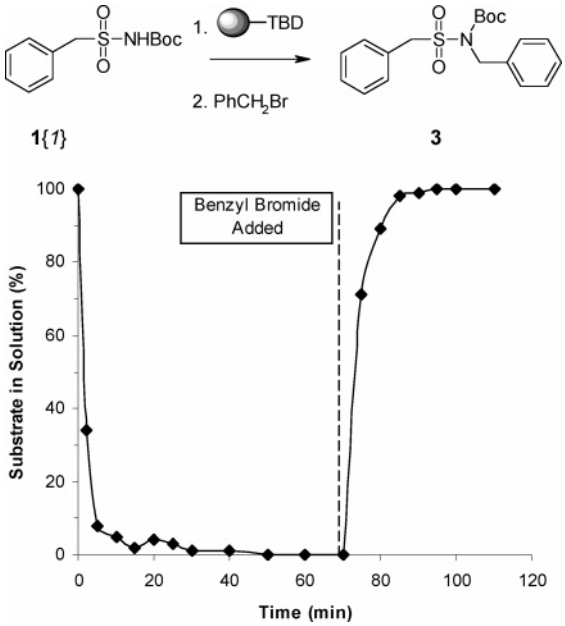


Figure 2. Capture of sulfonamide **1**{*1*} by PS-TBD and alkylative release with benzyl bromide in a batch reactor. Reagents and conditions: (i) PS-TBD (5 equiv), **1**{*1*} (1 equiv, 0.5 mmol, 0.025 M), MeCN, 80 °C; (ii) BnBr (1 equiv, 0.5 mmol), 80 °C.

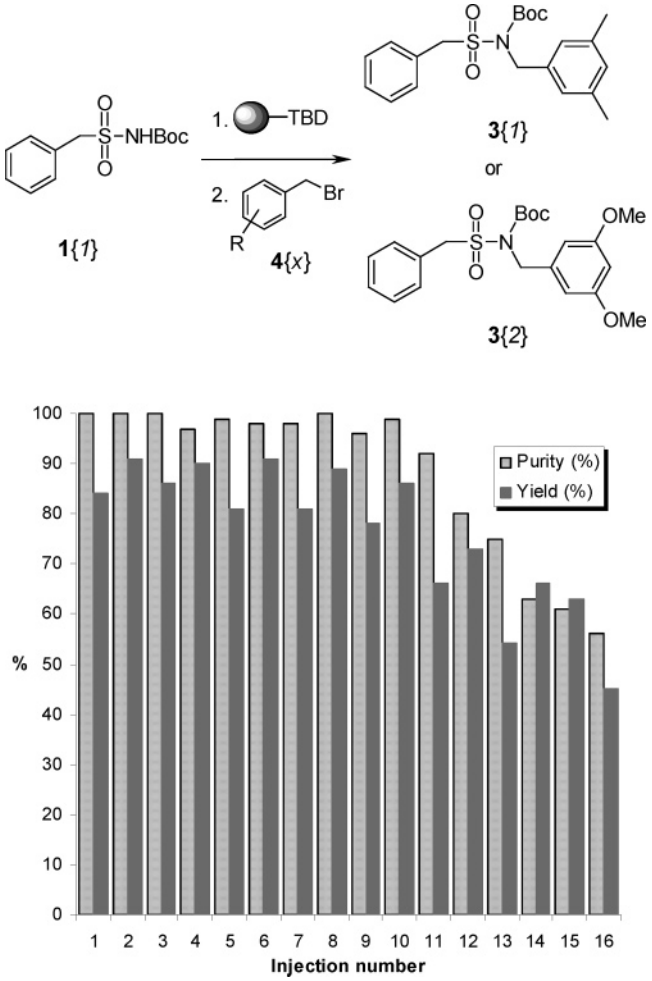


Figure 3. Purity and yield of successive flow-through alkylations.

and that complete reaction of the benzyl halide had occurred to afford *N*-alkyl sulfonamides **3**{*1*} or **3**{*2*}. We found it beneficial to load the column initially at a low flow rate (typically 0.1 or 0.05 mL min^{-1}), followed by a slightly increased rate of elution (typically 0.3 mL min^{-1} for 3−4 min) to disperse the subtrate throughout the column and finally a more rapid wash-off period to collect the reaction product (typically 1 mL min^{-1} for 9 min). This procedure results in a retention time range, but from observing the response of the UV detector at the outflow, the minimum retention time was observed to be approximately 5 min.

As shown in Figure 3, the first ten reactions proceeded with excellent conversion and in good yield. Conversion and yield rapidly decreased for subsequent reactions indicating that the viable functional loading of the PS-TBD column reactor was approx 0.33 mmol. Interestingly, it is apparent that the isolated yields achieved with bromide **4**{*2*} were routinely slightly lower than those with bromide **4**{*1*}. This was more likely attributable to the use of a generic UV threshold detection level on the fraction collector used than any significant difference in reactivity between the two substrates under the reaction conditions used.

At the end of this cycle, the column was first exhausted by elution with an excess of allyl bromide, an inexpensive and reactive alkylating agent, to remove any remaining unreacted sulfonamide. The column was then regenerated

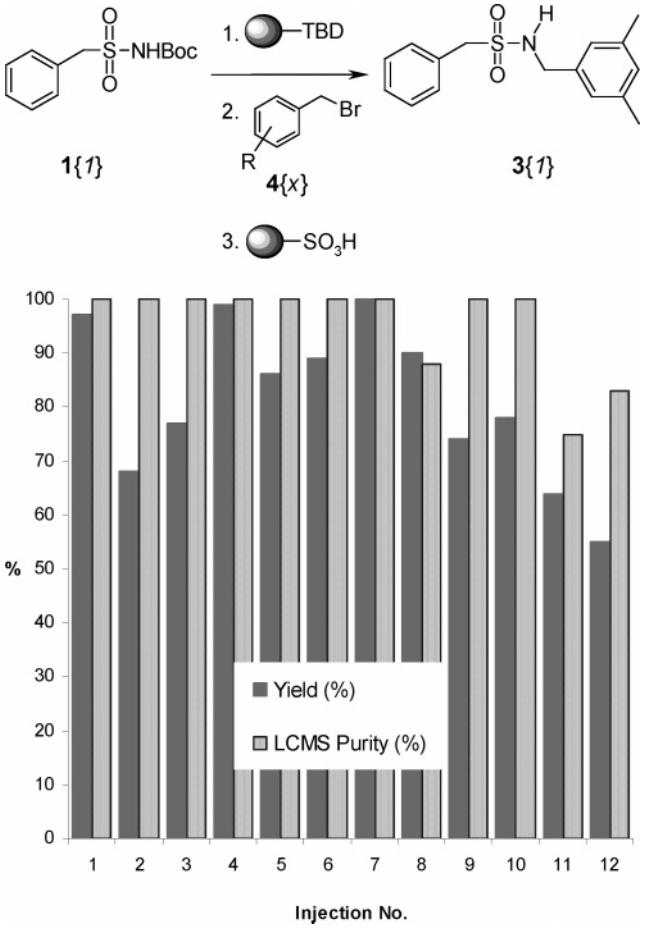


Figure 4. Purity and yield of successive flow-through alkylation and deprotection reactions affording sulfonamide **3**{*1*}.

by elution with a solution of the P_4-phosphazene base BEMP,[14] followed by a MeCN wash.

After regeneration of the PS-TBD column, a solution of sulfonamide **1**{*1*} was loaded onto the column, and the same sequence of alkylative release experiments could be repeated with high reproducibility. In fact, the PS-TBD column could be regenerated at least 6 times without any apparent loss in reactivity.

Establishing Optimized Conditions for Flow-Through Boc Removal. In the determination of suitable conditions for the flow-through removal of the sulfonamide *N*-Boc protecting group, it was important to recognize at the outset that conditions must be compatible with the preceding N-alkylation step. In this way, two reactor columns could be linked together to enable in-line alkylation and deprotection. Preliminary batch deprotection reactions were performed using the sulfonamide **3**{*1*}, and a silica-supported sulfonic acid (SCXII)[15] was identified as a suitable deprotection reagent to produce the secondary sulfonamide **5**{*1*}.

However, when SCXII was incorporated into a column, and a series of flow-through experiments were performed with various temperatures and flow rates, it was noted that the extent of Boc deprotection gradually decreased with time. Interestingly, this deterioration was not observed when MeCN was replaced with either tetrahydrofuran (THF) or $CHCl_3$. Unfortunately, neither of these alternative solvents was suitable for the preceding N-alkylation step. A compromise solution was identified when it was observed that

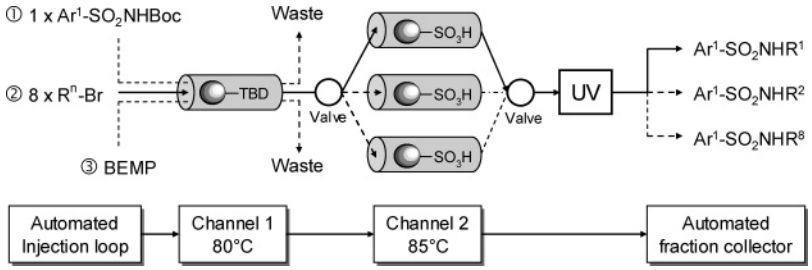


Figure 5. Schematic automated flow-through synthesizer configuration: (1) load channel 1 reactor column with Ar^1SO_2NHBoc (capture), (2) serial alkylative release and Boc deprotection of 8 × $Ar^1SO_2NHR^n$, (3) channel 1 reactor column regenerated with BEMP, and (4) repeat process for Ar^2SO_2NHBoc, then Ar^3SO_2NHBoc using a new reactor column in channel 2 in each case.

replacement of the silica-based SCXII column with the polystyrene-supported sulfonic acid Amberlyst H-15[16] resulted in a significantly lower rate of deterioration. As shown in Figure 4, it was established that by running the flow-through deprotection step using a column containing 1.4 g of H-15 resin at 85 °C with a flow rate of 0.6 mL/min it was possible to perform ten sequential deprotections each on the 33 μmol scale of the preceding flow-through N-alkylation step with high efficiency before the H-15 column became unviable and needed to be replaced.

These optimization experiments clearly demonstrated the potential to prepare arrays of sulfonamides in a sequential, fully automated flow-through process. On the basis of the observed functional capacity of the PS-TBD and Amberlyst H-15 columns, we elected to prepare a 48-member combinatorial library composed of two sublibraries of 24 members each, in which each sulfonamide was reacted in turn with each of eight alkyl halides and then underwent an in-line Boc deprotection on a 33 μmol scale before regeneration of the PS-TBD column and connection of a new Amberlyst H-15 column reactor.

Library Production. An automated flow reactor was assembled from commercial HPLC components as previously described (Figure 5).[6,17] Substrates, monomers, and array products were allocated positions on the bed of the liquid handler, which was used both to inject substrates into the flow stream, and as a fraction collector to collect the array products. A pair of syringe pumps was used both to take up samples and to elute reactants through the two columns. After it passed through the reactor cartridges, the flow stream passed through a UV detector so that UV threshold detection could be used to minimize the volume of solvent collected.

To maximize throughput, complete conversion must occur within a short time period. This was achieved by heating of the reactor columns to 80 °C and 85 °C, respectively, using a novel column heater module developed specifically for flow chemistry applications.[18] The device holds up to 4 reactor columns that may be independently heated or cooled using a circulating air current. Temperature equilibration occurs within a few minutes, and the unit will accurately and safely maintain temperatures up to 150 °C for several days. The temperature may be controlled through the same user interface that controls the HPLC modules. This unit allowed us to incorporate one PS-TBD and three Amberlyst H-15 reactor columns simultaneously.

Since the column regeneration protocol for the first step requires a strong base, it was necessary to fluidically isolate

Chart 1. Monomer Set A

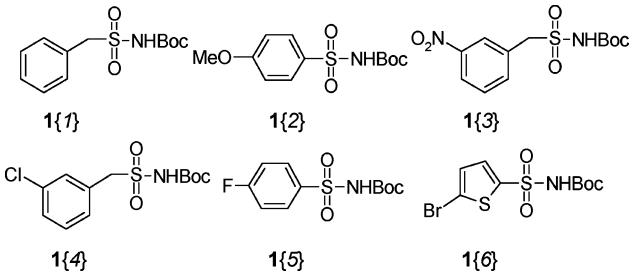
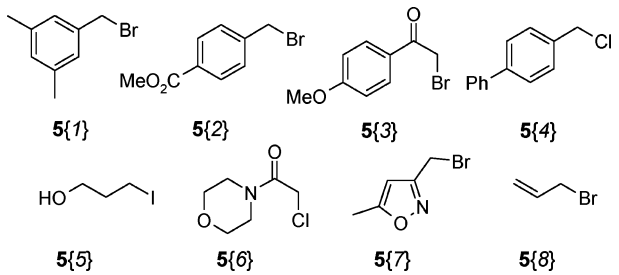


Chart 2. Monomer Set B



the acidic H-15 resin while the procedure took place. This was achieved using a 4-position electronic selection valve, also controlled through the system interface. This valve also allowed the output from the PS-TBD column to be directed independently to each of three separate H-15 reactor columns as the library synthesis required. Thus, a sulfonamide was loaded onto the PS-TBD-containing column, and this column eluted with a set of alkylating agents. The resulting adducts flowed through the first H-15 column. The PS-TBD column was then fluidically isolated from the second reactor while regeneration took place, and a second sulfonamide was then loaded. The products formed by alkylative release then flow through the second Amberlyst column prior to collection. Finally, this process was repeated for a third time. In this way, it was possible to generate a library of 24 compounds from three sulfonamides and eight alkylating agents in a fully automated fashion without the need for manual intervention.

A simple program was compiled to enable automated array synthesis consisting of a module to control column regeneration, the loading of a sulfonamide from monomer set A (Chart 1), and setting any associated system parameters, a module to control the introduction of an alkylating reagent from monomer set B (Chart 2) with product elution and collection, and modules to control the column temperature and position of the switching valve after the first column.

This program was used to prepare a 48-member 2D array from a set of sulfonamides A **1**{*1*−*6*} and a set of halides B

Table 1. Yields and Purities for Deprotected Alkylation Products

alkylating agent **5**{*y*}	yield (%) (purity (%))[a] **4**{*x*,*y*}: sulfonamide **1**{*x*}					
	1{*1*}	**1**{*2*}	**1**{*3*}	**1**{*4*}	**1**{*5*}	**1**{*6*}
5{*1*}	96 (97)	100 (97)	94 (98)	100 (97)	100 (95)	100 (94)
5{*2*}	100 (97)	100 (97)	96 (95)	100 (97)	100 (96)	100 (97)
5{*3*}	30 (91)	90 (93)	72 (89)	90 (91)	83 (63)	10 (68)
5{*4*}	76 (51)	88 (86)	62 (96)	100 (88)	100 (86)	100 (82)
5{*5*}	79 (95)	69 (94)	98 (94)	52 (96)	72 (92)	25 (71)
5{*6*}	48 (89)	41 (88)	59 (78)	45 (87)	61 (90)	56 (50)
5{*7*}	66 (84)	59 (96)	76 (96)	62 (95)	62 (96)	57 (84)
5{*8*}	92 (97)	79 (90)	64 (97)	62 (94)	62 (89)	100 (97)

[a] Purities were determined using a combination of LC-MS and ^{1}H NMR.

5{*1*−*8*}. The array was prepared in two runs of 24 compounds each (i.e., sublibraries **4**{*1*−*3*, *1*−*8*} and **4**{*4*−*6*, *1*−*8*}, respectively); the three H-15 reactor columns were replaced after the first 24 compounds.

All products were isolated by parallel evaporation and then analyzed by LC-MS and ^{1}H NMR spectroscopy. As shown in Table 1, without any further purification, 88% of the targeted array was obtained in excess of 80% purity. No cross-contamination was observed in any instance. Notably, in a few instances (e.g., **4**{*5*,*6*}), although a low isolated yield was obtained, the purity of the material was found to be high. This is most likely attributable to nonoptimal sample collection where the peak detection threshold was set too high for a weak UV chromaphore, which is a consequence of using a generic set of parameters to trigger the UV fraction collection.

Conclusion

A fully automated two-step flow-through process comprising a capture and release sulfonamide N-alkylation, followed by removal of a Boc-protecting/activating group, has been used to conveniently prepare a 48-member array **4**{*1*−*6*, *1*−*8*} of secondary sulfonamides. In this process, a PS-TBD reactor column, incorporating a commercially available polystyrene-supported reagent, was automatically regenerated using the P_4-phosphazene base BEMP. An integrated deprotection step was performed using a disposable Amberlyst H-15 reactor cartridge. The system ran unattended for 21 h to generate each set of 24 compounds, prior to replacement of the consumable H-15 reactor cartridges and repetition of the synthesis with a further set of sulfonamide starting materials. This strategy afforded compounds in good yields and high purities that were generally suitable for direct biological evaluation without the need for further purification.

Further work is currently underway in our laboratory with the objective of developing fully automated flow processes for bond-forming reactions that are widely exploited in medicinal chemistry and provide compounds directly in high purity. The results of these studies will be presented in due course.

Experimental Section

General. All starting materials, solvents, and reagents were commercially available and were used without further purification. ^{1}H NMR spectra were recorded on a Bruker AM-400 spectrometer at 400 MHz. The chemical shifts are in δ units relative to TMS ($\delta = 0$) using the indicated solvent as an internal standard. Multiplicities are indicated as s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublet; td, triplet of doublet; or br, broad. RP-HPLC was run on a Hewlett-Packard 1050 instrument. Column: Supelcosil ABZ$^+$PLUS column, 3.3 cm, 4.6 mm ϕ, 3 μm. Eluent: A water, 0.1% TFA; B acetonitrile 95%, water 5%, TFA 0.05%. Gradient: 10−95% B in A (1 mL min^{-1}) over 8 min. Detection: UV (diode array detector). LC-MS analyses were performed on a Waters Alliance 2795XE HT attached to a Micromass ZQ 2000 mass spectrometer using electrospray ionization in positive and negative modes. Column: Supelcosil ABZ$^+$PLUS, 3.3 cm, 4.6 mm ϕ, 3 μm. Eluent: A 10 mM solution of ammonium acetate in water, 0.1% formic acid; B acetonitrile 95%, water 5%, formic acid 0.05%. Gradient: 0−100% B in A (3 mL min^{-1}) over 3.5 min.

Automated Flow-Through Array Preparation. Column Preparation. Polystyrene-bound (2% crosslinked with DVB) 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PS-TBD, 930 mg × ∼2.6 mmol g^{-1}, ∼2.4 mmol) was transferred to a 150 mm Omnifit glass column (i.d. 6.6 mm). The column was then eluted with acetonitrile at 80 °C to obtain good swelling of the resin before a variable-length end piece was fitted and adjusted to remove solvent gaps and retain the resin beads under a slightly positive pressure.

Amberlyst H-15 (1.4 g) was transferred to a 150 mm Omnifit glass column (i.d. 6.6 mm). The column was then eluted with acetonitrile at 85 °C to obtain good swelling of the resin before a variable-length end piece was fitted and adjusted to remove solvent gaps and retain the resin beads under a slightly positive pressure.

Column Regeneration. 2-*tert*-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,2,3-diazaphosphorine (BEMP, 2.10 mL, 7.3 mmol) was diluted with anhydrous *N*,*N*-dimethylformamide (DMF, 6 mL). Two milliliters of this solution was injected at 0.3 mL min^{-1} in each regeneration step to deprotonate the PS-TBDH$^+$X$^-$ and regenerate the column reactor. The column was subsequently washed with acetonitrile.

Column Reloading. Solutions of each sulfonamide from monomer set A (0.50 mmol) were dissolved in acetonitrile (2 mL). In each reloading step, a single substrate solution was injected onto the reactor column (2 mL) to charge the column with 0.50 mmol of substrate.

Fraction Collector Wavelength. To compensate for significant variations in the molar absorptivities (ϵ) associated with products based on different heterocyclic core motifs and ensure that the UV detection threshold was set appropriately, the detector wavelength (λ) was varied for each core structure to a predetermined value at which the molar absorptivities were approximately the same.

substrate	**1**{*1*}	**1**{*2*}	**1**{*3*}	**1**{*4*}	**1**{*5*}	**1**{*6*}
λ (mm)	215	255	220	255	220	255

Alkylative Release. Stock solutions of alkylating agents **5**{*1*−*8*} from monomer set B were prepared in acetonitrile

(5 mL, 0.066 M) and introduced onto the reactor column as a single injection (500 μL, 33 μmol) for each alkylative release step. The monomer solution used for the ninth injection, to fully discharge the column prior to reloading with the next monomer A, was a 0.2 M solution of allyl bromide **5**{*8*} in acetonitrile.

Synthesizer Configuration. The system used was configured from a Gilson liquid handler (233XL), which was used both as an autoinjector and fraction collector, a dual syringe pump (402) fitted with a 1 mL and a 10 mL syringe, a variable-wavelength UV detector (UV119), and a Vapourtec R-4 column heater. One syringe pump (1 mL) was connected to the needle via the collection valve, and the other (10 mL) syringe was connected to the column via the injection valve. This setup made it possible to use the needle for an initial injection/elution, followed by elution and washing of the column using the 10 mL syringe pump, while a threshold triggered fraction was collected with the needle. A single-channel liquid handler was used to perform both substrate manipulation and fraction collection. The system solvent used was acetonitrile, and the whole setup was controlled using Gilson Unipoint, version 3.3.

Synthesis Control Program. The synthesizer was controlled by an operations file comprising two subroutines to control iteration and looping of common operations. The *N_alkylation control file* controlled column regeneration, reloading from monomer set A, and set the specified wavelength for the UV detector. The *Addmonomer control file* controlled the introduction of alkylating agents from monomer set B. A typical array synthesis run, with variables in brackets, is given below.

All operations allowed for 100 μL of dead volume between the injection port and the top of the PS-TBD column where appropriate.

***N*-Alkylation Control File. Regeneration.** The regeneration portion of the file included the following steps: set TBD column temperature to 80 °C, set valve to send TBD column outflow to waste, wash needle and injection port, inject 2 mL of a solution of BEMP in THF onto the column at 0.2 mL min^{-1}, elute column with 1 mL of MeCN at 0.3 mL min^{-1} (using 10 mL syringe pump), and wash column with 9 mL of MeCN at 1.0 mL min^{-1} (using 10 mL syringe pump).

Substrate Loading. The substrate loading portion of the file included the following steps: wash needle and injection port, inject 2 mL (0.25 M, 0.5 mmol) of [substrate] onto the column at 0.1 mL min^{-1}, elute the column with 1 mL at 0.3 mL min^{-1} (using 10 mL syringe pump), and wash the column with 9 mL at 1.0 mL min^{-1} (using 10 mL syringe pump).

Wavelength. The wavelength portion of the file included the following steps: set [wavelength], wash column with 5 mL at 1.0 mL min^{-1} (using 10 mL syringe pump), autozero UV channel.

Add Monomer Control File (Repeated 8x). Monomer Addition. The monomer addition portion of the file included the following steps: set Amberlyst column temperature to 85 °C, set selection valve to send PS-TBD column outflow to Amberlyst column, wash needle and injection port, inject 500 μL (0.066 M, 33 μM) of [monomer] onto the column at 0.05 mL min^{-1}, home needle, and wash needle.

Product Elution. The product elution portion of the file included the following steps: switch on the UV detector, set [peak level %], elute the column with 1 mL at 0.05 mL min^{-1} (using 10 mL syringe), elute the column with 9 mL at 0.6 mL min^{-1} (using 10 mL syringe), start collection by threshold, and stop collection.

Characterization Data For Library Products. 4{*1,1*}. Yield: 9.2 mg, 96% (97% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.30 (6H, s), 4.07 (2H, d, J = 6 Hz), 4.20 (2H, s), 4.32 (1H, t, J = 6 Hz), 6.87 (2H, s), 6.93 (1H, s), 7.29 (2H, m), 7.35 (3H, m). LC/MS (ESI): t_R = 3.10 min (*m*/*z* 290.4, MH$^+$).

4{*1,2*}. Yield: 12.8 mg, 100% (97% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.90 (3H, s), 4.15 (2H, d, J = 6 Hz), 4.23 (2H, s), 4.58 (1H, t, J = 6 Hz), 7.34 (7H, m), 7.98 (2H, d, J = 8 Hz). LC/MS (ESI): t_R = 2.84 min (*m*/*z* 320.4, MH$^+$).

4{*1,3*}. Yield: 3.2 mg, 30% (91% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.87 (3H, s), 4.24 (2H, d, J = 4 Hz), 4.32 (2H, s), 5.35 (1H, t, J = 4 Hz), 6.92 (2H, d, J = 9 Hz), 7.32 (3H, m), 7.41 (2H, m), 7.76 (2H, d, J = 9 Hz). LC/MS (ESI): t_R = 2.84 min (*m*/*z* 320.4, MH$^+$).

4{*1,4*}. Yield: 8.5 mg, 76% (51% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.17 (2H, d, J = 4 Hz), 4.25 (2H, s), 4.38 (1H, t, J = 4 Hz), 7.35 (5H, m), 7.46 (4H, m), 7.58 (5H, m). LC/MS (ESI): t_R = 3.31 min (*m*/*z* 336.4, (M − H)$^-$).

4{*1,5*}. Yield: 6.0 mg, 79% (95% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.68 (2H, tt, J = 6, 6 Hz), 3.11 (2H, td, J = 6, 6 Hz), 3.72 (2H, t, J = 6 Hz), 4.25 (2H, s), 4.55 (1H, brs), 7.38 (5H, m). LC/MS (ESI): t_R = 1.93 min (*m*/*z* 230.3, MH$^+$).

4{*1,6*}. Yield: 4.7 mg, 48% (89% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.09 (2H, t, J = 5 Hz), 3.52 (2H, d, J = 4 Hz), 3.57 (4H, t, J = 5 Hz), 3.66 (2H, t, J = 5 Hz), 4.30 (2H, s), 5.37 (1H, t, J = 4 Hz), 7.36 (3H, m), 7.42 (2H, m). LC/MS (ESI): t_R = 2.06 min (*m*/*z* 299.4, MH$^+$).

4{*1,7*}. Yield: 5.8 mg, 66% (84% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.39 (3H, d, J = 0.5 Hz), 4.10 (2H, d, J = 6 Hz), 4.29 (2H, s), 4.70 (1H, t, J = 6 Hz), 5.96 (1H, d, J = 0.5 Hz), 7.37 (5H, m). LC/MS (ESI): t_R = 2.45 min (*m*/*z* 267.4, MH$^+$).

4{*1,8*}. Yield: 6.4 mg, 92% (97% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.58 (2H, dddd, J = 1.5, 1.5, 6, 6 Hz), 4.11 (1H, t, J = 6 Hz), 4.25 (s, 2H), 5.18 (1H, tdd, J = 1.5, 1.5, 10 Hz), 5.19 (1H, tdd, J = 1.5, 1.5, 17 Hz), 5.76 (1H, tdd, J = 6, 10, 17 Hz), 7.39 (5H, m). LC/MS (ESI): t_R = 2.38 min (*m*/*z* 212.3, MH$^+$).

4{*2,1*}. Yield: 12.2 mg, 100% (97% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.23 (6H, s), 3.87 (3H, s), 4.03 (2H, d, J = 6 Hz), 4.57 (1H, t, J = 6 Hz), 6.76 (2H, s), 6.87 (1H, s), 6.96 (2H, d, J = 9 Hz), 7.79 (2H, d, J = 9 Hz). LC/MS (ESI): t_R = 3.11 min (*m*/*z* 306.4, MH$^+$).

4{*2,2*}. Yield: 11.9 mg, 100% (97% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.86 (3H, s), 3.89 (3H, s), 4.17 (2H, d, J = 6 Hz), 4.78 (1H, t, J = 6 Hz), 6.95 (2H, d,

J = 9 Hz), 7.27 (2H, d, J = 9 Hz), 7.79 (2H, d, J = 9 Hz), 7.93 (2H, d, J = 9 Hz). LC/MS (ESI): t_R = 2.86 min (*m*/*z* 336.4, MH^+).

4{***2,3***}**.** Yield: 10.0 mg, 90% (93% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.83 (3H, s), 3.86 (3H, s), 4.37 (2H, d, J = 5 Hz), 5.62 (1H, t, J = 5 Hz), 6.92 (2H, d, J = 9 Hz), 6.94 (2H, d, J = 9 Hz), 7.81 (4H, d, J = 9 Hz). LC/MS (ESI): t_R = 2.83 min (*m*/*z* 336.3, MH^+).

4{***2,4***}**.** Yield: 10.2 mg, 88% (86% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.85 (3H, s), 4.16 (2H, d, J = 6 Hz), 4.65 (1H, t, J = 6 Hz), 6.96 (2H, d, J = 9 Hz), 7.26 (2H, d, J = 9 Hz), 7.34 (1H, m), 7.42 (2H, m), 7.49 (2H, d, J = 9 Hz), 7.53 (2H, m), 7.81 (2H, d, J = 9 Hz). LC/MS (ESI): t_R = 3.34 min (*m*/*z* 354.4, MH^+).

4{***2,5***}**.** Yield: 5.6 mg, 69% (94% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.70 (2H, tt, J = 6, 6 Hz), 3.09 (2H, t, J = 6 Hz), 3.73 (2H, t, J = 6 Hz), 3.86 (3H, s), 6.97 (2H, d, J = 9 Hz), 7.79 (2H, d, J = 9 Hz). LC/MS (ESI): t_R = 2.03 min (*m*/*z* 246.3, MH^+).

4{***2,6***}**.** Yield: 4.2 mg, 41% (88% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.28 (2H, t, J = 5 Hz), 3.53 (2H, t, J = 5 Hz), 3.62 (4H, t, J = 5 Hz), 3.72 (2H, s), 3.86 (3H, s), 5.58 (1H, brs), 6.96 (2H, d, J = 9 Hz), 7.79 (2H, d, J = 9 Hz). LC/MS (ESI): t_R = 2.08 min (*m*/*z* 315.4, MH^+).

4{***2,7***}**.** Yield: 5.5 mg, 59% (96% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.36 (3H, d, J = 0.5 Hz), 3.86 (3H, s), 4.14 (2H, d, J = 6 Hz), 4.88 (1H, t, J = 6 Hz), 5.92 (1H, d, J = 0.5 Hz), 6.97 (2H, d, J = 9 Hz), 7.79 (2H, d, J = 9 Hz). LC/MS (ESI): t_R = 2.45 min (*m*/*z* 283.4, MH^+).

4{***2,8***}**.** Yield: 5.9 mg, 39% (90% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.57 (2H, dddd, J = 1.5, 1.5, 6, 6 Hz), 3.86 (3H, s), 4.34 (1H, t, J = 6 Hz), 5.10 (1H, tdd, J = 1.5, 1.5, 10 Hz), 5.16 (1H, tdd, J = 1.5, 1.5, 17 Hz), 5.72 (1H, tdd, J = 6, 10, 17 Hz), 6.97 (2H, d, J = 9 Hz), 7.79 (2H, d, J = 9 Hz). LC/MS (ESI): t_R = 2.49 min (*m*/*z* 228.3, MH^+).

4{***3,1***}**.** Yield: 10.4 mg, 94% (98% purity), cream solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.31 (6H, s), 4.15 (2H, d, J = 6 Hz), 4.21 (2H, s), 4.46 (1H, t, J = 6 Hz), 6.89 (2H, s), 6.96 (1H, s), 7.53 (1H, dd, J = 8, 8 Hz), 7.63 (1H, d, J = 8 Hz), 8.06 (1H, dd, J = 2, 2 Hz), 8.20 (1H, ddd, J = 1, 2, 8 Hz). LC/MS (ESI): t_R = 3.18 min (*m*/*z* 333.4, $(M - H)^-$).

4{***3,2***}**.** Yield: 11.5 mg, 96% (95% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.91 (3H, s), 4.25 (2H, s), 4.27 (2H, d, J = 6 Hz), 4.74 (1H, t, J = 6 Hz), 7.36 (2H, d, J = 8 Hz), 7.54 (1H, dd, J = 8, 8 Hz), 7.67 (1H, d, J = 8 Hz), 8.02 (2H, d, J = 8 Hz), 8.12 (1H, dd, J = 2, 2 Hz), 8.21 (1H, ddd, J = 1, 2, 8 Hz). LC/MS (ESI): t_R = 2.88 min (*m*/*z* 365.3, MH^+).

4{***3,3***}**.** Yield: 8.7 mg, 72% (89% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.89 (3H, s), 4.41 (2H, s), 4.46 (2H, d, J = 5 Hz), 5.33 (1H, t, J = 5 Hz), 6.95 (2H, d, J = 9 Hz), 7.55 (1H, dd, J = 8, 8 Hz), 7.81 (1H, d, J = 8 Hz), 7.83 (2H, d, J = 9 Hz), 8.19 (1H, ddd, J = 1, 2, 8 Hz), 8.29 (1H, dd, J = 2, 2 Hz). LC/MS (ESI): t_R = 2.86 min (*m*/*z* 365.4, MH^+).

4{***3,4***}**.** Yield: 7.8 mg, 62% (96% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.24 (2H, s), 4.28 (2H, d, J = 6 Hz), 4.58 (1H, t, J = 6 Hz), 7.37 (3H, m), 7.44 (2H, m), 7.54 (1H, dd, J = 8, 8 Hz), 7.60 (4H, m), 7.67 (1H, d, J = 8 Hz), 8.10 (1H, dd, J = 2, 2 Hz), 8.21 (1H, ddd, J = 1, 2, 8 Hz). LC/MS (ESI): t_R = 3.34 min (*m*/*z* 381.4, $(M - H)^-$).

4{***3,5***}**.** Yield: 7.4 mg, 98% (94% purity), pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.75 (2H, tt, J = 6, 6 Hz), 3.21 (2H, t, J = 6 Hz), 3.77 (2H, t, J = 6 Hz), 4.34 (2H, s), 4.95 (1H, brs), 7.58 (1H, dd, J = 8, 8 Hz), 7.77 (1H, d, J = 8 Hz), 8.23 (1H, ddd, J = 1, 2, 8 Hz), 8.26 (1H, dd, J = 2, 2 Hz). LC/MS (ESI): t_R = 2.02 min (*m*/*z* 275.4, MH^+).

4{***3,6***}**.** Yield 5.8 mg, 59% (78% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.26 (2H, t, J = 5 Hz), 3.61 (2H, t, J = 5 Hz), 3.68 (4H, t, J = 5 Hz), 3.82 (2H, d, J = 4 Hz), 4.41 (2H, s), 5.38 (1H, brs), 7.57 (1H, dd, J = 8, 8 Hz), 7.82 (1H, d, J = 8 Hz), 8.24 (1H, ddd, J = 1, 2, 8 Hz), 8.30 (1H, dd, J = 2, 2 Hz). LC/MS (ESI): t_R = 2.19 min (*m*/*z* 344.4, MH^+).

4{***3,7***}**.** Yield: 6.7 mg, 76% (96% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.43 (3H, d, J = 0.5 Hz), 4.26 (2H, d, J = 6 Hz), 4.39 (2H, s), 4.85 (1H, t, J = 6 Hz), 5.95 (1H, d, J = 0.5 Hz), 7.56 (1H, dd, J = 8, 8 Hz), 7.77 (1H, d, J = 8 Hz), 8.18 (1H, dd, J = 2, 2 Hz), 8.22 (1H, ddd, J = 1, 2, 8 Hz). LC/MS (ESI): t_R = 2.56 min (*m*/*z* 312.4, MH^+).

4{***3,8***}**.** Yield: 5.4 mg, 64% (97% purity), pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.67 (2H, dddd, J = 1.5, 1.5, 6, 6 Hz), 4.27 (1H, t, J = 6 Hz), 4.33 (2H, s), 5.22 (1H, tdd, J = 1.5, 1.5, 10 Hz), 5.27 (1H, tdd, J = 1.5, 1.5, 17 Hz), 5.81 (1H, tdd, J = 6, 10, 17 Hz), 7.59 (1H, dd, J = 8, 8 Hz), 7.77 (1H, d, J = 8 Hz), 8.25 (2H, m). LC/MS (ESI): t_R = 2.50 min (*m*/*z* 255.3, $(M - H)^-$).

4{***4,1***}**.** Yield: 10.7 mg, 100% (97% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.31 (6H, s), 4.11 (2H, d, J = 6 Hz), 4.12 (2H, s), 4.40 (1H, t, J = 6 Hz), 6.89 (2H, s), 6.96 (1H, s), 7.18 (2H, m), 7.27 (1H, dd, J = 8, 8 Hz), 7.32 (1H, dd, J = 2, 8 Hz). LC/MS (ESI): t_R = 3.34 min (*m*/*z* 324.4, MH^+).

4{***4,2***}**.** Yield: 14.3 mg, 100% (97% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.90 (3H, s), 4.16 (2H, s), 4.19 (2H, d, J = 6 Hz), 4.66 (1H, t, J = 6 Hz), 7.21 (1H, ddd, J = 2, 2, 8 Hz), 7.26 (1H, dd, J = 2, 2 Hz), 7.28 (1H, dd, J = 8, 8 Hz), 7.33 (3H, d, J = 8 Hz), 8.01 (2H, d, J = 8 Hz). LC/MS (ESI): t_R = 3.06 min (*m*/*z* 352.3, $(M - H)^-$).

4{***4,3***}**.** Yield: 10.5 mg, 90% (91% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.88 (3H, s), 4.28 (2H, s), 4.35 (2H, d, J = 5 Hz), 5.37 (1H, t, J = 5 Hz), 6.93 (2H, d, J = 9 Hz), 7.25 (1H, dd, J = 8, 8 Hz), 7.29 (2H, m), 7.42 (1H, dd, J = 2, 2 Hz), 7.80 (2H, d, J = 9 Hz). LC/MS (ESI): t_R = 3.05 min (*m*/*z* 354.4, MH^+).

4{***4,4***}**.** Yield: 13.1 mg, 100% (88% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.17 (2H, s), 4.22 (2H, d, J = 6 Hz), 4.46 (1H, t, J = 6 Hz), 7.22 (2H, m), 7.29 (1H, t, J = 7 Hz), 7.35 (3H, m), 7.44 (3H, m), 7.58 (4H, m). LC/MS (ESI): t_R = 3.48 min (*m*/*z* 370.4, $(M - H)^-$).

4{*4,5*}. Yield: 4.5 mg, 52% (96% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.71 (2H, tt, J = 6, 6 Hz), 3.15 (2H, brs), 3.74 (2H, t, J = 6 Hz), 4.21 (2H, s), 4.71 (1H, brs), 7.29 (1H, ddd, J = 2, 2, 8 Hz), 7.32 (1H, dd, J = 8, 8 Hz), 7.35 (1H, ddd, J = 2, 2, 8 Hz), 7.39 (1H, s). LC/MS (ESI): t_R = 2.28 min (*m*/*z* 264.3, MH^+).

4{*4,6*}. Yield: 4.9 mg, 45% (87% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.15 (2H, t, J = 5 Hz), 3.61 (4H, m), 3.63 (2H, d, J = 4 Hz), 3.68 (2H, t, J = 5 Hz), 4.27 (2H, s), 5.39 (1H, t, J = 4 Hz), 7.30 (1H, dd, J = 7, 7 Hz), 7.33 (1H, ddd, J = 2, 2, 7 Hz), 7.36 (1H, ddd, J = 2, 2, 7 Hz), 7.43 (1H, dd, J = 2, 2 Hz). LC/MS (ESI): t_R = 2.37 min (*m*/*z* 333.4, MH^+).

4{*4,7*}. Yield: 6.1 mg, 62% (95% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.41 (3H, d, J = 0.5 Hz), 4.17 (2H, d, J = 6 Hz), 4.25 (2H, s), 4.79 (1H, t, J = 6 Hz), 5.95 (1H, d, J = 0.5 Hz), 7.29 (2H, m), 7.33 (2H, m). LC/MS (ESI): t_R = 2.75 min (*m*/*z* 301.3, MH^+).

4{*4,8*}. Yield: 5.0 mg, 62% (94% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.62 (2H, dddd, J = 1.5, 1.5, 6, 6 Hz), 4.18 (1H, t, J = 6 Hz), 4.21 (2H, s), 5.19 (1H, tdd, J = 1.5, 1.5, 10 Hz), 5.24 (1H, tdd, J = 1.5, 1.5, 17 Hz), 5.78 (1H, tdd, J = 6, 10, 17 Hz), 7.28 (1H, ddd, J = 2, 2, 7 Hz), 7.32 (1H, dd, J = 7, 7 Hz), 7.35 (1H, ddd, J = 2, 2, 7 Hz), 7.39 (1H, dd, J = 2, 1 Hz). LC/MS (ESI): t_R = 2.74 min (*m*/*z* 246.3, MH^+).

4{*5,1*}. Yield: 10.2 mg, 100% (95% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.23 (6H, s), 4.07 (2H, d, J = 6 Hz), 4.71 (1H, t, J = 6 Hz), 6.74 (2H, s), 6.87 (1H, s), 7.15 (2H, dd, J = 9, 9 Hz), 7.85 (2H, dd, J = 5, 9 Hz). LC/MS (ESI): t_R = 3.17 min (*m*/*z* 294.4, MH^+).

4{*5,2*}. Yield: 11.2 mg, 100% (96% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.90 (3H, s), 4.21 (2H, d, J = 6 Hz), 4.90 (1H, t, J = 6 Hz), 7.16 (2H, dd, J = 9, 9 Hz), 7.26 (2H, d, J = 9 Hz), 7.86 (2H, dd, J = 5, 9 Hz), 7.93 (2H, d, J = 9 Hz). LC/MS (ESI): t_R = 2.89 min (*m*/*z* 324.3, MH^+).

4{*5,3*}. Yield: 8.8 mg, 83% (63% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.84 (3H, s), 4.34 (2H, d, J = 5 Hz), 5.62 (1H, t, J = 5 Hz), 6.87 (2H, d, J = 9 Hz), 7.10 (2H, dd, J = 9, 9 Hz), 7.76 (2H, d, J = 9 Hz), 7.84 (2H, dd, J = 5, 9 Hz). LC/MS (ESI): t_R = 2.87 min (*m*/*z* 324.3, MH^+).

4{*5,4*}. Yield: 11.2 mg, 100% (86% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.20 (2H, d, J = 6 Hz), 4.80 (1H, t, J = 6 Hz), 7.16 (2H, dd, J = 9, 9 Hz), 7.24 (2H, d, J = 8 Hz), 7.38 (1H, m), 7.43 (2H, m), 7.51 (4H, m), 7.88 (2H, dd, J = 5, 9 Hz). LC/MS (ESI): t_R = 3.37 min (*m*/*z* 340.4, $(M - H)^-$).

4{*5,5*}. Yield: 5.5 mg, 42% (92% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.71 (2H, tt, J = 6, 6 Hz), 3.12 (2H, t, J = 6 Hz), 3.74 (2H, t, J = 6 Hz), 7.18 (2H, dd, J = 9, 9 Hz), 7.88 (2H, dd, J = 5, 9 Hz). LC/MS (ESI): t_R = 2.00 min (*m*/*z* 234.4, MH^+).

4{*5,6*}. Yield: 6.1 mg, 61% (90% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.28 (2H, t, J = 5 Hz), 3.53 (2H, t, J = 5 Hz), 3.62 (4H, t, J = 5 Hz), 3.75 (2H, d, J = 4 Hz), 5.69 (1H, t, J = 4 Hz), 7.18 (2H, dd, J = 9, 9 Hz), 7.88 (2H, dd, J = 5, 9 Hz). LC/MS (ESI): t_R = 2.06 min (*m*/*z* 303.4, MH^+).

4{*5,7*}. Yield: 5.5 mg, 62% (96% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.36 (3H, d, J = 0.5 Hz), 4.18 (2H, d, J = 6 Hz), 5.06 (1H, t, J = 6 Hz), 5.90 (1H, d, J = 0.5 Hz), 7.17 (2H, dd, J = 9, 9 Hz), 7.87 (2H, dd, J = 5, 9 Hz). LC/MS (ESI): t_R = 2.48 min (*m*/*z* 271.3, MH^+).

4{*5,8*}. Yield: 4.4 mg, 62% (89% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.61 (2H, dddd, J = 1.5, 1.5, 6, 6 Hz), 4.44 (1H, t, J = 6 Hz), 5.11 (1H, tdd, J = 1.5, 1.5, 10 Hz), 5.16 (1H, tdd, J = 1.5, 1.5, 17 Hz), 5.71 (1H, tdd, J = 6, 10, 17 Hz), 7.19 (2H, dd, J = 9, 9 Hz), 7.88 (2H, dd, J = 5, 9 Hz). LC/MS (ESI): t_R = 2.51 min (*m*/*z* 216.2, MH^+).

4{*6,1*}. Yield: 12.7 mg, 100% (94% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.26 (6H, s), 4.14 (2H, d, J = 6 Hz), 4.73 (1H, t, J = 6 Hz), 6.79 (2H, s), 6.90 (1H, s), 7.03 (1H, d, J = 4 Hz), 7.32 (1H, d, J = 4 Hz). LC/MS (ESI): t_R = 3.42 min (*m*/*z* 362.2, MH^+).

4{*6,2*}. Yield: 13.7 mg, 100% (97% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.90 (3H, s), 4.27 (2H, d, J = 6 Hz), 5.01 (1H, t, J = 6 Hz), 7.04 (1H, d, J = 4 Hz), 7.32 (2H, d, J = 8 Hz), 7.33 (1H, d, J = 4 Hz), 7.96 (2H, d, J = 8 Hz). LC/MS (ESI): t_R = 3.13 min (*m*/*z* 390.2, $(M - H)^-$).

4{*6,3*}. Yield: 1.1 mg, 10% (68% purity), cream solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.88 (3H, s), 4.48 (2H, d, J = 4 Hz), 5.79 (1H, t, J = 4 Hz), 6.95 (2H, d, J = 9 Hz), 7.02 (1H, d, J = 4 Hz), 7.37 (1H, d, J = 4 Hz), 7.86 (2H, d, J = 9 Hz). LC/MS (ESI): t_R = 3.09 min (*m*/*z* 392.2, MH^+).

4{*6,4*}. Yield: 11.0 mg, 100% (82% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.27 (2H, d, J = 6 Hz), 4.84 (1H, t, J = 6 Hz), 7.04 (1H, d, J = 4 Hz), 7.30 (2H, d, J = 8 Hz), 7.34 (1H, d, J = 4 Hz), 7.35 (1H, m), 7.44 (2H, m), 7.55 (4H, m). LC/MS (ESI): t_R = 3.57 min (*m*/*z* 408.3, $(M - H)^-$).

4{*6,5*}. Yield: 2.0 mg, 25% (71% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.76 (2H, tt, J = 6, 6 Hz), 3.22 (2H, t, J = 6 Hz), 3.78 (2H, t, J = 6 Hz), 7.06 (1H, d, J = 4 Hz), 7.35 (1H, d, J = 4 Hz). LC/MS (ESI): t_R = 2.35 min (*m*/*z* 302.2, MH^+).

4{*6,6*}. Yield: 6.3 mg, 56% (50% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.33 (2H, t, J = 5 Hz), 3.57 (2H, t, J = 5 Hz), 3.63 (4H, t, J = 5 Hz), 3.83 (2H, d, J = 4 Hz), 5.79 (1H, brs), 7.06 (1H, d, J = 4 Hz), 7.36 (1H, d, J = 4 Hz). LC/MS (ESI): t_R = 2.37 min (*m*/*z* 371.2, MH^+).

4{*6,7*}. Yield: 4.0 mg, 57% (84% purity), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.39 (3H, d, J = 0.5 Hz), 4.25 (2H, d, J = 6 Hz), 5.10 (1H, t, J = 6 Hz), 5.95 (1H, d, J = 0.5 Hz), 7.06 (1H, d, J = 4 Hz), 7.37 (1H, d, J = 4 Hz). LC/MS (ESI): t_R = 2.78 min (*m*/*z* 339.2, MH^+).

4{*6,8*}. Yield: 11.7 mg, 100% (97% purity), pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.68 (2H, dddd, J = 1.5, 1.5, 6, 6 Hz), 4.61 (1H, t, J = 6 Hz), 5.16 (1H, tdd, J = 1.5, 1.5, 10 Hz), 5.22 (1H, tdd, J = 1.5, 1.5, 17 Hz), 5.76

(1H, tdd, $J = 6$, 10, 17 Hz), 7.06 (1H, d, $J = 4$ Hz), 7.35 (1H, d, $J = 4$ Hz). LC/MS (ESI): $t_R = 2.86$ min (*m*/*z* 284.2, MH^+).

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Supporting Information Available. ^{1}H NMR spectra for 20 representative library array compounds are reproduced. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Amberlyst 15 sulfonic acid resin was prewashed with methanol and dried before use.

(17) Commercial Gilson HPLC modules were used to construct the flow-through synthesizer, and the device was controlled using Unipoint, version 3.3 software (www.Gilson.com).

(18) R-4 Flow reactor module was developed in collaboration with Vapourtec (www.Vapourtec.co.uk).

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