One-Pot, Three-Component, Domino Heck-aza-Michael Approach to Libraries of Functionalized 1,1-Dioxido-1,2-benzisothiazoline-3-acetic Acids

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A sequential three-component synthesis of functionalized benzisothiazoline-3-acetic acid 1,1-dioxides utilizing a domino Heck-aza-Michael pathway is reported. This one-pot procedure rapidly assembles functionalized benzylsulfonamides, which undergo a palladium-catalyzed, domino, Heck-aza-Michael transformation in an experimentally straightforward manner. This attractive protocol has been utilized to synthesize three combinatorial sublibraries (**I**−**III**) comprising a total of 95 compounds in high purities (≥95% for 75 compounds), yield and quantities.

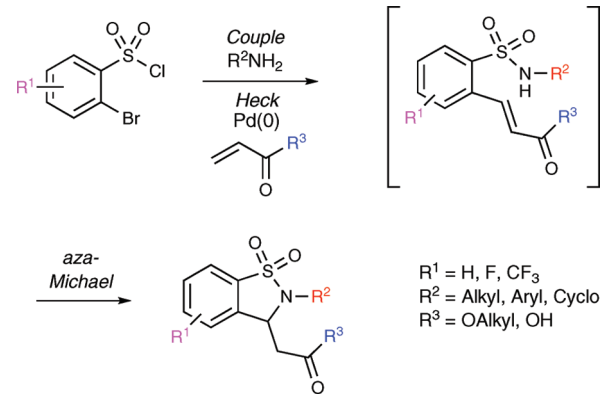
Introduction

Advances in high-throughput screening and the need for new pharmaceutical leads have prompted the development of new protocols to generate diverse libraries of drug-like compounds. In recent years, a number of facilitated protocols that utilize both solid-phase and solution-phase chemistry have emerged to meet this challenge. Despite success in this area, there are limited examples of protocols that take advantage of cross-reaction functionality to allow domino/tandem processes to occur in a multicomponent one-pot procedure.[1]

Recently, we reported a one-pot, sequential three-component approach toward the synthesis of 1,2-benzisothiazoline-3-acetic acid 1,1-dioxides (Scheme 1).[2] The key step in this protocol was the utilization of a domino Heck-aza-Michael (HaM) reaction for both the mode of cyclization and as a pathway for the incorporation of an additional point of diversification.

A small proof of concept demonstrative library, created utilizing the (HaM) protocol, of 1,2-benzisothiazoline-3-acetic acid 1,1-dioxides and subsequent derivatives was reported.[3] Building on this work, the application of a domino, HaM protocol in the synthesis of three combinatorial sublibraries (**I**−**III**) utilizing a variety of reaction platforms (Figure 1) is herein reported. Additionally a wider range of coupling partners was utilized to ultimately afford structural diversity around the central core. To maximize their potential drug-like properties, the subsequent libraries feature a multifaceted design scheme, as well as in-silico screening against Lipinski's rule of five criteria. The in-silico data ranges include a molecular weight range under 500 g/mol, no more than 5 hydrogen bond donors or 10 hydrogen bond acceptors, and a partition coefficient log *P* (clogP) less than 5.0.[3] Overall, the application of a domino Heck-aza-Michael (HaM) allows for rapid incorporation of functionality via the manipulation of the three individual components, allowing for the design of a library of diverse drug-like small molecules.

Scheme 1. Sequential Three-Component Domino Heck-aza-Michael



Sultams (cyclic sulfonamide analogues) have emerged as important targets in drug discovery because of their extensive

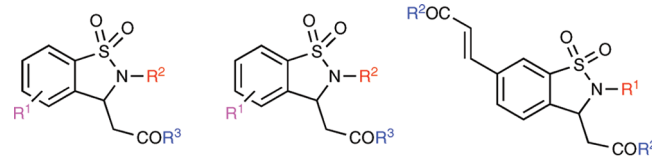


Figure 1. Overview of the prepared libraries.

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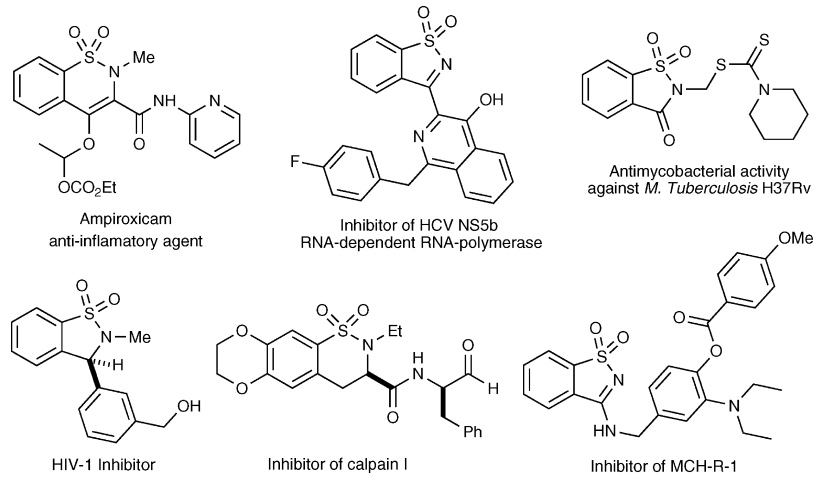


Figure 2. Representative biologically active sultams.

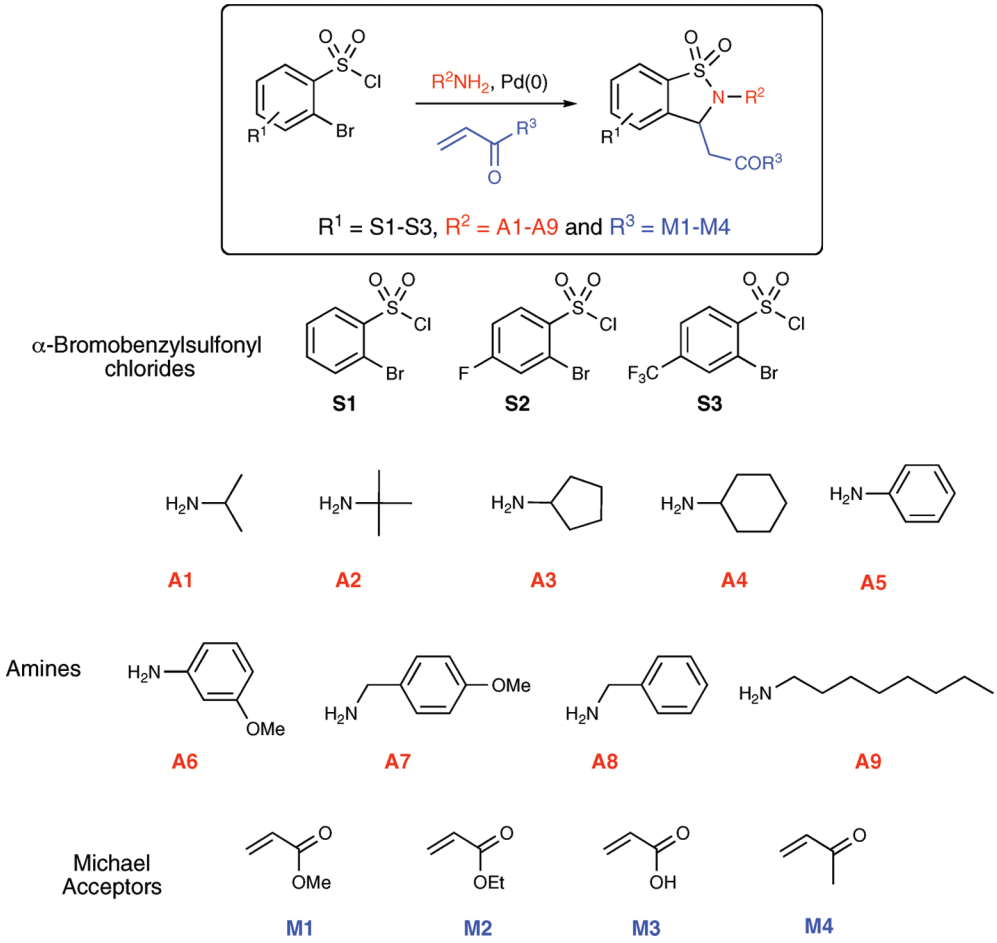


Figure 3. Representative coupling partners for Heck-aza-Michael.

chemical and biological profiles.[4] Though not found in nature, a number of benzofused sultams have recently surfaced in the literature, which display potent activity across a variety of biological targets. Such reports include inhibition of a variety of enzymes, including COX-2 (Ampiroxicam),[5,6] HCV NS5b RNA-dependent RNA-polymerase,[7] HIV integrase,[8] cysteine proteases involved in the progression of maleria,[9] and lipoxygenases.[10] In addition, sultams have also shown antimycobacterial activity against *Mycobacterium tuberculosis*[11] and inhibition of melanin-concentrating hormone [MCH] (Figure 2).[12]

This aforementioned biological profile is augmented by a number of inherent chemical properties possessed by both sultams and their sulfonamide precursors, including facile coupling/allylation pathways for sulfonamide and sultam formation, hydrolytic stability, polarity and their crystalline nature. Traditionally, sultams have been synthesized utilizing a variety of classical cyclization protocols such as Friedel−Craft,[13] dianion,[14] [3+2]-cycloadditions,[15] Diels−Alder reaction,[16] and recently the application of an oxa/aza-Michael reaction.[17] However, recently there have been a number of transition metal-catalyzed protocols reported utilizing ring-

closing methathesis (RCM),[18] Heck,[19] as well as Au-,[20] Cu-,[21] and Rh-catalyzed[22] cyclization protocols for the generation of diverse sultams.

Results and Discussion

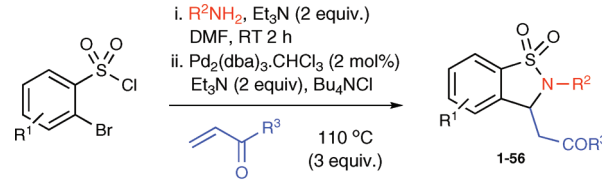
A 56-member library **I** was initially designed to expand on the prototype library previously reported,[2] demonstrating the capability of the HaM protocol in a library format. The method allows for the generation of sultams with three points of diversification starting from commercially available α-bromobenzenesulfonyl chlorides coupled with a range of aromatic, cyclic, and alkyl amines (Figure 3).[23,19]

Specific combinations of the three-components were chosen to evaluate the robustness of this protocol to peripheral functionality. In addition, Lipinski's rule of five also guided in silico efforts in the selection of combinations. On the basis of previous work, it was anticipated that these substrates would be well tolerated under the reaction conditions, carrying out the preparation of library **I** in 1-dram vials on an aluminum reaction block.[24] To this effect, α-bromobenzylsulfonyl chlorides (**S1**−**3**) were coupled with amines (**A1**−**9**) and stirred for 2 h at room temperature. After such time, Et_3N, Bu_4NCl, $Pd_2(dba)_3 \cdot CHCl_3$ and the corresponding Michael acceptors (**M1**−**4**) were added to the reaction mixture, which was heated to 110 °C and subjected to workup after 14 h. Workup consisted of removal of DMF, suspension of the crude reaction mixture in EtOAc and filtration through a SiO_2 SPE to remove inorganic salts and spent palladium. The crude material was analyzed by HPLC (UV 214 nm) and submitted to purification by mass-directed fractionation (MDF) to yield the anticipated products in modest to good yield and high purity (Table 1).[25]

Overall, a total of 56 reactions afforded product in variable yield and purity, validating the scope and economy of the HaM strategy. Specifically, out of the 56 reactions carried out, 44 had a final purity of 95% or greater with reactions yielding good overall mass recovery.[25] Having established the viability of the HaM protocol in the generation of libraries, we set out to design a library (Library **II**) of 1,2-benzisothiazoline-3-acetic acid 1,1-dioxides utilizing the Bohdan MiniBlock platform. Under this premise, a library of compounds was prepared in parallel using a 26-member Bohdan MiniBlock. In an attempt to design more drug-like molecules a new collection of amines (**A10**−**15**) was employed (Table 2). In addition, reactions were carried out using stock solutions to streamline the process thereby granting it the potential for future automation. As with sublibrary **I**, crude compounds were analyzed by HPLC (UV 214 nm) and submitted to purification by MDF.

Overall, with the exception of compounds **60** and **81**, all reactions worked with good yield and high purity. Notably, 20 out of the 24 reactions had a final purity of 95% or greater. Having validated the methodology, the protocol was implemented for the generation of 1,2-benzisothiazoline-3-acetic acid 1,1-dioxides **84**−**95** bearing both saturated and unsaturated side chains as previously reported (Table 3). The addition of one more point of diversification was accomplished by utilizing commercially available 2,5-dibromosulfonyl chloride. In this regard, 12 parallel reactions were carried out in a Radley Carousel, utilizing stock solutions for the quick generation of the desired products in a

Table 1. Summary of Library **I** Results[a,b,c]

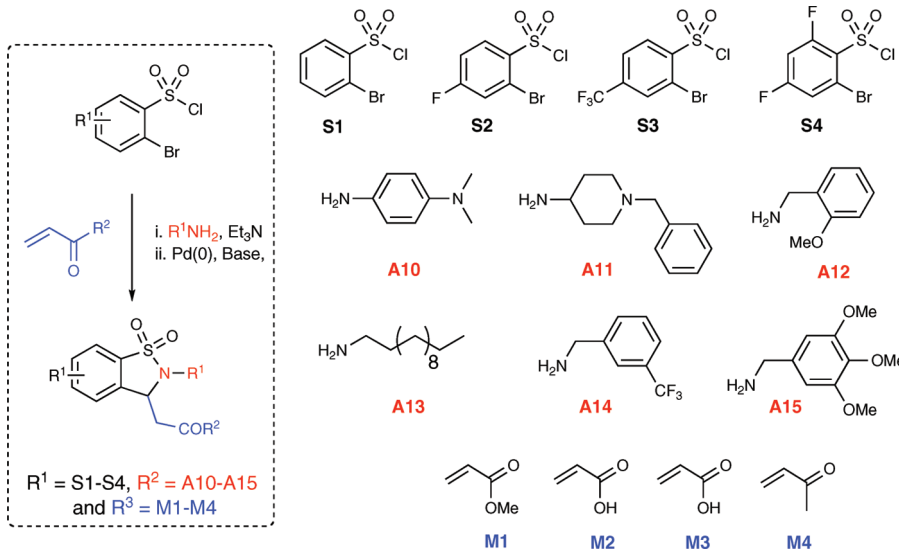


R^1 = S1-S3, R^2 = A1-A9 and R^3 = M1-M4

entry	R^1	R^2NH_2	R^3	yield (%)	purity (%)	product
1	S1	A1	M1	44	100	**1**
2	S1	A6	M1	48	97	**2**
3	S1	A7	M1	53	98	**3**
4[d]	S1	A5	M2	22	98	**4**
5[d]	S1	A6	M2	22	95	**5**
6	S1	A7	M2	74	100	**6**
7	S1	A3	M3	57	100	**7**
8	S1	A4	M3	64	100	**8**
9[d]	S1	A5	M3	35	100	**9**
10[d]	S1	A6	M3	34	95	**10**
11	S1	A7	M3	60	98	**11**
12	S1	A3	M4	42	100	**12**
13[d]	S1	A4	M4	29	92	**13**
14	S1	A5	M4	40	99	**14**
15	S1	A6	M4	57	90	**15**
16	S2	A1	M1	12	99	**16**
17	S2	A2	M1	30	99	**17**
18	S2	A5	M1	40	90	**18**
19[d]	S2	A7	M1	25	96	**19**
20	S2	A8	M1	75	93	**20**
21	S2	A9	M1	69	90	**21**
22	S2	A1	M2	28	100	**22**
23	S2	A2	M2	46	96	**23**
24	S2	A3	M2	87	94	**24**
25	S2	A4	M2	57	95	**25**
26	S2	A5	M2	56	98	**26**
27	S2	A6	M2	40	94	**27**
28	S2	A7	M2	69	97	**28**
29	S2	A8	M2	72	97	**29**
30	S2	A9	M2	54	96	**30**
31	S2	A3	M3	58	100	**31**
32	S2	A4	M3	64	97	**32**
33[d]	S2	A5	M3	13	93	**33**
34[d]	S2	A7	M3	54	100	**34**
35[d]	S2	A8	M3	50	99	**35**
36[d]	S2	A9	M3	45	100	**36**
37[d]	S3	A1	M1	25	96	**37**
38[d]	S3	A2	M1	21	97	**38**
39	S3	A3	M1	53	99	**39**
40	S3	A4	M1	51	100	**40**
41	S3	A7	M1	52	99	**41**
42[d]	S3	A8	M1	31	91	**42**
43	S3	A9	M1	42	96	**43**
44	S3	A1	M2	50	95	**44**
45[d]	S3	A3	M2	5	100	**45**
46[d]	S3	A4	M2	7	100	**46**
47[d]	S3	A6	M2	5	87	**47**
48[d]	S3	A7	M2	6	97	**48**
49[d]	S3	A8	M2	9	96	**49**
50[d]	S3	A9	M2	9	93	**50**
51[d]	S3	A2	M3	27	97	**51**
52[d]	S3	A3	M3	42	93	**52**
53[d]	S3	A4	M3	46	95	**53**
54[d]	S3	A7	M3	35	92	**54**
55	S3	A8	M3	44	92	**55**
56	S3	A9	M3	40	99	**56**

[a] Reaction conditions: **1** (0.273 mmol), $Pd_2(dba)_3.CHCl_3$ (2 mol %), methyl acrylate (0.82 mmol), Bu_4NCl (0.273 mmol) in DMF at 110 °C for 14 h. [b] Purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy). [c] Purity was determined by HPLC with peak area (UV) at 214 nm. [d] When repeated in single reaction formation, good yields (50−80%) were achieved as predicted.

Table 2. Representative Components and Products Synthesized Using Bohdan MiniBlock Platform[a,b,c]



entry	R^1	R^2NH_2	R^3	yield (%)	purity (%)	product
1	S1	A10	M1	92	98	**57**
2	S1	A11	M4	12	98	**58**
3	S1	A12	M3	44	100	**59**
4	S1	A13	M4	6	100	**60**
5	S1	A14	M2	56	100	**61**
6	S1	A15	M2	68	100	**62**
7	S2	A10	M1	93	99	**63**
8	S2	A10	M4	82	99	**64**
9	S2	A11	M3	16	100	**65**
10	S2	A12	M1	84	90	**66**
11	S2	A12	M3	16	97	**67**
12	S2	A15	M2	82	100	**68**
13	S3	A10	M1	40	100	**69**
14	S3	A10	M3	32	95	**70**
15	S3	A10	M4	52	100	**71**
16	S3	A11	M3	18	91	**72**
17	S3	A12	M1	36	92	**73**
18	S3	A12	M4	20	100	**74**
19	S3	A13	M1	30	100	**75**
20	S3	A13	M3	34	93	**76**
21	S3	A13	M4	16	100	**77**
22	S4	A10	M1	32	100	**78**
23	S4	A11	M1	30	99	**79**
24	S4	A11	M3	24	97	**80**
22	S4	A12	M3	8	100	**81**
23	S4	A13	M1	22	100	**82**
24	S4	A13	M4	16	100	**83**

[a] Reaction conditions: **1** (0.136 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (2 mol %), Michael acceptor (0.40 mmol), Bu_4NCl (0.136 mmol) in DMF at 110 °C for 14 h. [b] Purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy). [c] Purity was determined by HPLC with peak area (UV) at 214 nm.

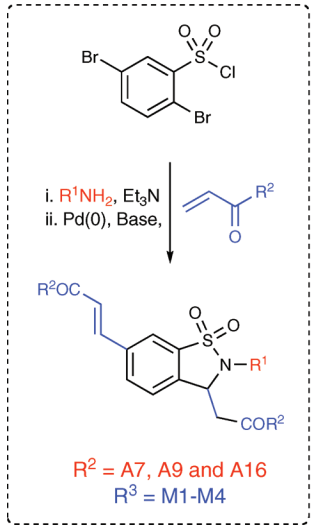
sequential three-component coupling. Crude material was analyzed via HPLC (UV 214 nm) and submitted to purification by MDF. As expected, all reactions resulted in good yields and high purities yielding the desired compounds with good mass recovery.

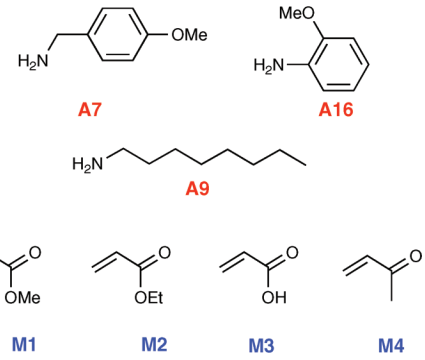
In conclusion, the successful demonstration of a sequential three-component synthesis of functionalized benzisothiazoline-3-acetic acid 1,1-dioxides utilizing a domino Heck-aza-Michael pathway has been accomplished. This one-pot, three-step procedure, rapidly assembles functionalized benzylsulfonamides, which undergo a palladium-catalyzed domino Heck-aza-Michael transformation in an experimentally straightforward manner. This protocol was demonstrated on a variety of platforms (Reaction blocks, Bohdan MiniBlock and Radley Carousel) producing overall three combinatorial sublibraries (**I**−**III**) comprising a total of 95 pure compounds in high purities (≥95% for 75 compounds) and good quantities. The evaluation of biological activities of the compounds reported herein in high-throughput screens is currently underway. Future efforts will continue to focus on the development of new methodology for the synthesis of diverse, functionalized libraries and their biological evaluation.

Experimental Section

General Procedures. All air and moisture sensitive reactions were carried out in flame- or oven-dried glassware under argon atmosphere using standard gastight syringes, cannula, and septa. Stirring was achieved with oven-dried, magnetic stir bars. CH_3CN was purified by passage through the Solv-Tek purification system employing activated

Table 3. Representative Components and Products Synthesized Using the Radley Carousel Platform[a,b,c]





entry	R^2NH_2	R^3	yield (%)	purity (%)	compound
1	A7	M1	18	100	**84**
2	A7	M2	45	93	**85**
3	A7	M3	62	90	**86**
4	A7	M4	86	100	**87**
5	A9	M1	69	100	**88**
6	A9	M2	90	100	**89**
7	A9	M3	86	99	**90**
8	A9	M4	59	100	**91**
9	A16	M1	78	100	**92**
10	A16	M2	81	100	**93**
11	A16	M3	60	100	**94**
12	A16	M4	90	90	**95**

[a] Reaction conditions: **1** (0.136 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (2 mol %), methyl acrylate (0.40 mmol), Bu_4NCl (0.136 mmol) in DMF at 110 °C for 14 h. [b] Purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy). [c] Purity was determined by HPLC with peak area (UV) at 214 nm.

Al_2O_3.[25] Et_3N was purified by passage over basic alumina and stored over KOH. Flash column chromatography was performed with SiO_2 from Sorbent Technology (30930M-25, Silica Gel 60A, 40−63 um). Thin layer chromatography was performed on silica gel 60F254 plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 NMR spectrometer operating at 400 and 100 MHz respectively; or a Bruker Avance operating at 500 and 125 MHz respectively. High-resolution mass spectrometry (HRMS) and FAB spectra were obtained in one of two manners: (i) on a VG Instrument ZAB double-focusing mass spectrometer and (ii) on a LCT Premier Spectrometer (Micromass UK Limited) operating on ESI (MeOH). All library syntheses using block technology were performed using a 24-position Mettler-Toledo Bohdan MiniBlock XT under an argon atmosphere in oven-dried Autochem 17 × 100 mm round-bottom tubes. Parallel evaporations were performed using a GeneVac EZ-2 plus evaporator. Automated preparative reverse-phase HPLC purification was performed using a Waters 2767 Mass-Directed Fractionation system (2767 sample manager, 2525 Binary Pump, 515 Make-up pump) with a Waters ZQ quadrapole spectrometer and detected by UV (270 nm, Waters Xterra MS C-18 column, 19 × 150 mm, elution with the appropriate gradient of CH_3CN in pH 9.8 buffered aqueous ammonium formate at 18 mL min^{-1} flow rate). Purity was determined by reverse-phase HPLC with peak area (UV) at 214 nm using a Waters Alliance 2795 system (Waters Xterra MS C-18 column, 4.6 × 150 mm, elution with a linear gradient of 5% CH_3CN in pH 9.8 buffered aqueous ammonium formate to 100% CH_3CN at 1.0 mL/min flow rate).

General Procedure A for the Synthesis of Library I (1−56) on Reaction Blocks in 1-dram Vials. Into a 1-dram vial was added amine (0.237 mmol), Et_3N (0.546 mmol), and dry DMF (0.60 mL), and the reaction was stirred at rt for 15 min. After such time, α-bromobenzenesulfonyl chlorides (0.237 mmol) were added and the reaction was stirred for 2 h. To the reaction vial was added Et_3N (0.546 mmol), Bu_4NCl (0.237 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (2 mol %), and dry DMF (1.4 mL). After the mixture was stirred for 5 min at RT, Michael acceptor (0.819 mmol) was added, and the reaction vial was placed immediately into a preheated reaction block. The reaction was stirred at 110 °C for 14 h, after which time the reaction was cooled and concentrated under reduced pressure. The crude was suspended in EtOAc, filtered through a SiO_2 SPE, and analyzed by HPLC (UV 214 nm). Crude material with purity below 90% was submitted to purification by MDF.

General Procedure B for the Synthesis of Library II (57−83) in a Bohdan MiniBlock. Into a MiniBlock reaction tube was added a stock solution of amine (0.136 mmol) in dry DMF (0.10 mL), followed by Et_3N (0.273 mmol) in dry DMF (0.10 mL), and the reaction mixture was stirred at rt for 15 min. A stock solution of α-bromobenzenesulfonyl

chloride (0.136 mmol) in dry DMF (0.10 mL) was added, and the reaction mixture was stirred for 2 h. After such time, a stock solution of Et_3N (0.273 mmol), Bu_4NCl (0.136 mmol), and $Pd_2(dba)_3 \cdot CHCl_3$ (2 mol %) in dry DMF (0.7 mL) was added to the reaction mixture. The MiniBlock was then heated to 110 °C, and the Michael acceptor (0.410 mmol) was added. After the mixture was stirred at 110 °C for 14 h, the crude reaction mixture was cooled to rt and concentrated under reduced pressure. The crude was suspended in EtOAc, filtered through a SiO_2 SPE, and analyzed by HPLC (UV 214 nm). Crude material with purity below 90% was submitted to purification by MDF.

General Procedure C for the Synthesis of Library III (84−95) in a Radleys Carousel. Into a reaction tube contained within a 12-port Radley Carousel was added a stock solution of amine (0.136 mmol) in dry DMF (0.10 mL), followed by Et_3N (0.273 mmol) in dry DMF (0.10 mL), and the reaction mixture was stirred at rt for 15 min. A stock solution of α-bromobenzenesulfonyl chloride (0.136 mmol) in dry DMF (0.10 mL) was added, and the reaction was stirred for 2 h. After such time, a stock solution of Et_3N (0.273 mmol), Bu_4NCl (0.136 mmol), and $Pd_2(dba)_3 \cdot CHCl_3$ (2 mol %) in dry DMF (0.7 mL) was added to the reaction mixture. The MiniBlock was then heated to 110 °C; after which, the Michael acceptor (0.410 mmol) was added. After it was stirred at 110 °C for 14 h, the crude reaction mixture was cooled to rt and concentrated under reduced pressure. The crude was suspended in EtOAc, filtered through a SiO_2 SPE, and analyzed by HPLC (UV 214 nm). Crude material with purity below 90% was submitted to purification by mass-directed fractionation (MDF).

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Supporting Information Available. Experimental procedures, tabulated results for all libraries, and full characterization data for representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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