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Metal-Free Coupling of Saturated Heterocyclic Sulfonylhydrazones with Boronic Acids

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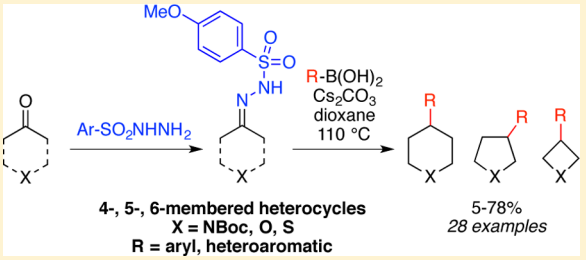
Supporting Information

ABSTRACT: The coupling of aromatic moieties with saturated heterocyclic partners is currently an area of significant interest for the pharmaceutical industry. Herein, we present a procedure for the metal-free coupling of 4-, 5-, and 6-membered saturated heterocyclic *p*-methoxyphenyl (PMP) sulfonylhydrazones with aryl and heteroaromatic boronic acids. This procedure enables a simple, two-step synthesis of a range of functionalized sp^2–sp^3 linked bicyclic building blocks, including oxetanes, piperidines, and azetidines, from their parent ketones.



INTRODUCTION

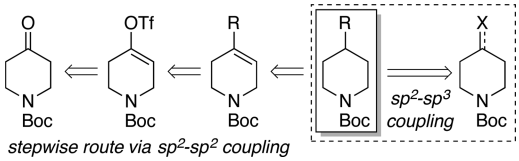
A recent analysis of the type of molecules within the pharmaceutical industry noted that there has been an increase in the proportion of "flat" molecules synthesized since the 1970s and that this correlates with the increased availability of chemistry facilitating sp^2–sp^2 coupling.[1] This trend has been driven, in particular, by the Suzuki reaction, which benefits from readily available and generally bench-stable boronates and boronic acids. In addition, the widespread availability of palladium catalysts and ligands allow coupling of even the most challenging heterocyclic halides.[2−6]

Within the industry, there is now a great deal of interest in increasing the three-dimensional character of synthesized molecules, and straightforward methods to directly form sp^2–sp^3 carbon–carbon bonds have therefore become highly desirable.[7] Although there have been significant recent advances in this field,[8−18] there are still several shortfalls in available methodologies.

One area that is particularly challenging is the coupling of saturated heterocycles such as oxetanes, azetidines and piperidines. For example, data from the Pfizer electronic laboratory notebook shows that for aryl-alkyl couplings of azetidines and oxetanes, only one-third of such reactions worked in yields greater than 0%, with one-quarter giving yields in excess of 20%.

Because of the challenging nature of these reactions, sp^2–sp^3 carbon–carbon bond construction in a pharmaceutical environment has typically been performed in a stepwise manner, incorporating the more viable sp^2–sp^2 coupling, followed by hydrogenation of the resulting alkene.[19,20] (Scheme 1). Clearly, a direct coupling to form the key bond is a more efficient approach, and there is significant interest in increasing the range of methodologies available to carry out this type of reaction.

Scheme 1. Direct and Indirect Routes to sp^2–sp^3 Carbon–Carbon Bond Formation



Gonzàlez-Bobes and co-workers recently reported a nickel-catalyzed Suzuki reaction with aliphatic halides (Scheme 2a).[17] The reported yields were good to excellent, but the scope of the reaction was largely limited to alkyl or cycloalkyl substrates. This reaction was applied to more pharmaceutically relevant substrates by Duncton et al., who report low to good yields (Scheme 2b).[18] A range of aromatic and heterocyclic boronic acids were found to be synthetically useful in the reaction, but drawbacks included the requirement for a toxic and carcinogenic nickel catalyst and the high cost of iodinated starting materials.

In 2009, Barluenga et al. described a metal-free reductive coupling between tosylhydrazones and alkyl, alkenyl and aryl boronic acids (Scheme 2c) in good to excellent yields.[21] This reaction bypassed the need for precious metal catalysts and highly air/moisture-sensitive or expensive coupling partners. However, the substrate scope was primarily limited to benzylic, α-heterocyclic and/or aldehyde-derived tosylhydrazones, with lower yields observed for substrates that deviated from these limiting parameters.[21,22] The scope was subsequently expanded by Nakagawa et al. (Scheme 2d), who applied the conditions to a protected 3-formylazetidine tosylhydrazone.[23] The reaction

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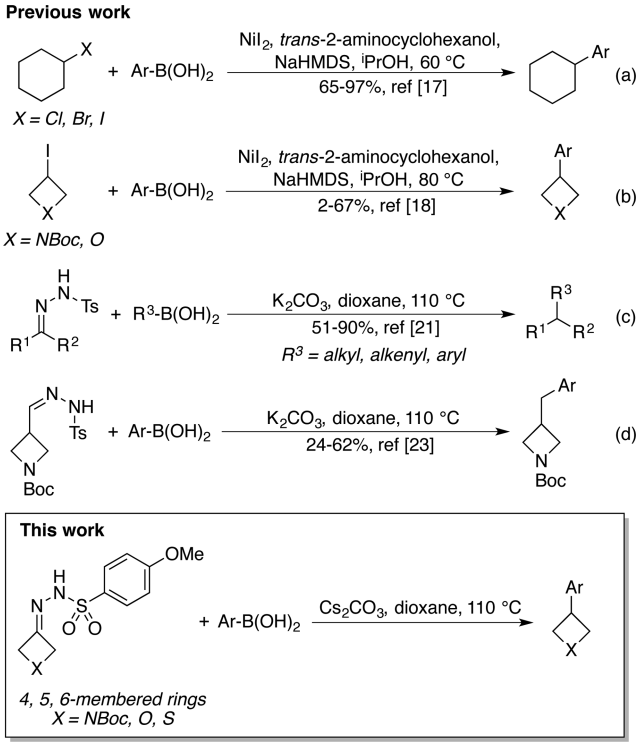
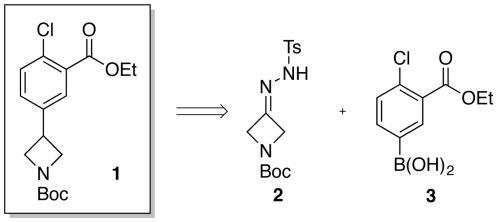
Scheme 2. Selected Studies in sp^2–sp^3 Carbon–Carbon Bond Formation



was shown to give low to good yields of bicyclic products, albeit with the rings separated by a methylene (CH_2) linker. We envisaged, therefore, that metal-free coupling of tosylhydrazones derived from heterocyclic ketones would give directly linked pharmaceutically relevant bicyclic products analogous to those synthesized by Duncton et al. (Scheme 2b), but without the requirement for metal catalysis, sensitive reagents or expensive starting materials.

A key target for our studies was the synthesis of compound **1**, which was identified as an important intermediate in an internal medicinal chemistry program (Scheme 3). This molecule

Scheme 3. Targeted Synthesis of Compound 1 by Metal-Free Coupling



presented a challenging bond formation between the aryl and azetidine rings, as well as some functional group incompatibility problems with current methods. It was found to be extremely difficult to synthesize in isolable yields using either the stepwise or direct coupling approaches discussed previously. Initial attempts to synthesize **1** using the described conditions for metal-free coupling gave similarly poor results, and we therefore began optimization studies.[21] Herein, we report a resolution to this problem and describe a general protocol for the metal-free coupling of a range of saturated heterocyclic sulfonylhydrazones with aromatic and heteroaromatic boronic acids.

RESULTS AND DISCUSSION

The piperidinone-derived tosylhydrazone **5a** was prepared from the corresponding tosylhydrazide **4a** and subjected to the previously reported conditions[21] with 4-chlorophenylboronic acid (Table 1, entry 1). The product **6a** was isolated in low yield (37%); consequently, this system was chosen as a model for optimization. The mechanism for this type of transformation has been proposed and discussed at length by Barluenga et al.,[21] and as such, our observations are made in line with their original proposals.

Initial experiments focused on modulating the electron density of the aromatic group in the sulfonylhydrazone moiety in order to influence the rate at which the free diazo compound is formed in the reaction. Electron-poor substituents on the sulfonylhydrazone were postulated to increase the rate of diazo formation by improving the leaving-group character of the corresponding arylsulfinic acid. Consistent with this hypothesis, replacement of the tosyl group with an electron-deficient *p*-nitrophenylsulfonyl (*p*-nosyl) moiety in compound **5c** led to total decomposition of the sulfonylhydrazone within 1 h; however, no coupled product was observed (Table 1, entry 2). Conversely, the electron-rich *p*-methoxyphenyl (PMP) analogue **5b** slowed the rate of starting material consumption relative to **5a**, providing a similar yield of coupled product with purification aided by the presence of fewer nonpolar impurities (Table 1, entry 3). The major byproducts observed in these reactions were derived from the breakdown of the sulfonylhydrazone starting material, either by β-elimination to an alkene, conversion back to the parent ketone or other dimerization or self-condensation products that have been previously reported.[22,24]

A base screen using PMP sulfonylhydrazone **5b** improved the yield of **6a** from 37 to 50% by replacement of K_2CO_3 with Cs_2CO_3 (Table 1, entry 14). Other bases gave lower yields of **6a** (Table 1, entries 6–13), with the exception of NEt^iPr_2 or Ag_2CO_3, which both decomposed the starting materials (Table 1, entry 4), and $CaCO_3$ or $CuCO_3$, which provided no conversion (Table 1, entry 5).

Lowering the temperature of the reaction to 90 °C provided an identical yield with a slightly longer reaction time, while a further reduction to 70 °C severely lowered the yield (Table 1, entries 15 and 16). Since the reaction was found to require temperatures in excess of 90 °C, a short screen of solvents with similar boiling points to dioxane was performed. This revealed significantly lower yields with nonpolar solvents such as toluene and 1,2-DCE and a marginally reduced yield in acetonitrile (Table 1, entries 17, 19–20). THF was also investigated, but the volatility of the solvent dictated that a lower temperature be used, which was postulated to be the prime cause of the low yield obtained (Table 1, entry 18).

The reaction was subsequently discovered to be insensitive to addition of further equivalents of base, boronic acid or both (Table 1, entries 21–23); however, a pronounced loss of yield was observed on the addition of 10 equiv of water (Table 1, entry 24). In light of this result, the reaction was performed using carefully dried glassware and dry, degassed dioxane, which improved the yield to 60% (Table 1, entry 25). However, upon further removal of trace water by azeotropic distillation of the starting materials with toluene (Table 1, entry 26), a lower yield was observed. The dependence of conversion on trace water is

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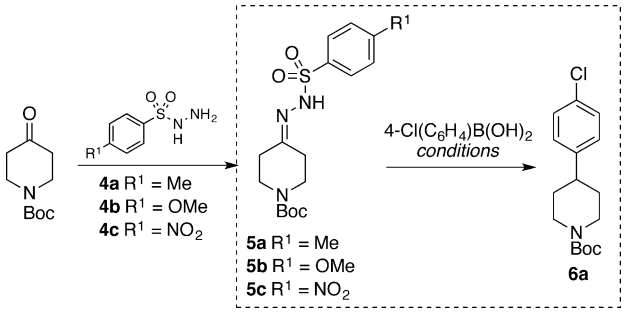
Table 1. Optimization of Reaction Conditions[a]



entry	5	base	solvent	T (°C)	[5] (M)	equiv of base	equiv of bor acid	conditions	t (h)	yield 6a (%)[b]
1	5a	K_2CO_3	dioxane	110	0.25	1.5	1.5	–	6	37
2	5c	K_2CO_3	dioxane	110	0.25	1.5	1.5	–	1	0
3	5b	K_2CO_3	dioxane	110	0.25	1.5	1.5	–	18	35
4	5b	NEt^iPr_2 or Ag_2CO_3	dioxane	110	0.25	1.5	1.5	–	18	0[c]
5	5b	$CaCO_3$ or $CuCO_3$	dioxane	110	0.25	1.5	1.5	–	18	0[d]
6	5b	TBAF	dioxane	110	0.25	1.5	1.5	–	18	18
7	5b	CsF	dioxane	110	0.25	1.5	1.5	–	18	22
8	5b	DBU	dioxane	110	0.25	1.5	1.5	–	18	29
9	5b	BEMP	dioxane	110	0.25	1.5	1.5	–	18	20
10	5b	^{t}BuOK	dioxane	110	0.25	1.5	1.5	–	18	44
11	5b	K_3PO_4	dioxane	110	0.25	1.5	1.5	–	18	10
12	5b	$CsHCO_3$	dioxane	110	0.25	1.5	1.5	–	18	41
13	5b	CsOH	dioxane	110	0.25	1.5	1.5	–	18	46
14	5b	Cs_2CO_3	dioxane	110	0.25	1.5	1.5	–	18	50
15	5b	Cs_2CO_3	dioxane	90	0.25	1.5	1.5	–	24	50
16	5b	Cs_2CO_3	dioxane	70	0.25	1.5	1.5	–	24	29
17	5b	Cs_2CO_3	toluene	110	0.25	1.5	1.5	–	18	17
18	5b	Cs_2CO_3	THF	70	0.25	1.5	1.5	–	24	19
19	5b	Cs_2CO_3	1,2-DCE	90	0.25	1.5	1.5	–	24	12
20	5b	Cs_2CO_3	MeCN	90	0.25	1.5	1.5	–	24	31
21	5b	Cs_2CO_3	dioxane	110	0.25	3.0	1.5	–	18	49
22	5b	Cs_2CO_3	dioxane	110	0.25	1.5	3.0	–	18	49
23	5b	Cs_2CO_3	dioxane	110	0.25	3.0	3.0	–	18	52
24	5b	Cs_2CO_3	dioxane	110	0.25	1.5	1.5	10 equiv of H_2O	18	12
25	5b	Cs_2CO_3	dioxane	110	0.25	1.5	1.5	dry solvent (DS)	18	60
26	5b	Cs_2CO_3	dioxane	110	0.25	1.5	1.5	DS, dried SMs	18	49
27	5b	Cs_2CO_3	dioxane	110	0.25	1.5	1.5	DS, reflux (110 °C)	18	49
28	5b	Cs_2CO_3	dioxane	110	0.25	1.5	1.5	DS, reflux, 4b added/8 h	18	39
29	5b	Cs_2CO_3	dioxane	110	1.0	1.5	1.5	DS	18	39
30	5b	Cs_2CO_3	dioxane	110	0.5	1.5	1.5	DS	18	49
31	5b	Cs_2CO_3	dioxane	110	0.125	1.5	1.5	DS	18	58
32	5b	Cs_2CO_3	dioxane	110	0.0625	1.5	1.5	DS	18	48
33	5b	Cs_2CO_3	dioxane	110	0.25	1.5	1.5	DS, 5 mol % $Pd(OAc)_2$	18	55
34	5b	Cs_2CO_3	dioxane	110	0.25	1.5	1.5	DS, 5 mol % $Rh_2(OAc)_4$	18	52
35	5b	Cs_2CO_3	dioxane	110	0.25	1.5	1.5	DS, 5 mol % $Cu(OTf)_2$	18	19

[a]Reaction conditions: 0.5 mmol of **4**, 0.75 mmol of base, 0.75 mmol of boronic acid, sealed tube. [b]Isolated yield. [c]Starting materials decomposed; no product isolated. [d]No conversion of starting materials. Abbreviations: BEMP, 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine; DS, dry solvent; SMs, starting materials.

presumably due to the requirement of water for protodeboronation[25] from the coupled intermediate to give the final product, in line with Barluenga's proposed mechanism.[21]

Azeotropic removal of water from the starting materials is likely to promote higher equilibrium boroxine concentration in the boronic acid. However, this was not envisaged to be completely detrimental, since reductive coupling of diazo compounds with boroxines is a known process.[26] Performing the reaction in an unsealed system at reflux was found to be detrimental to the yield, as was slow addition of **5b** to the same setup over 8 h (Table 1, entries 27 and 28). The reasons for these effects are currently unclear, although in our experience, any reaction performed in an unsealed system gave lower yields, and so this may be attributable to the increased pressure inside the vessel or more efficient exclusion of excess moisture. The concentration of the reactants was altered by adjustment of the volume of dioxane used and was found to be optimal between 0.125 and 0.25 M (Table 1, entries 29–32). The direct purification of the reaction residue without an aqueous workup revealed negligible loss of material, and so it was retained.

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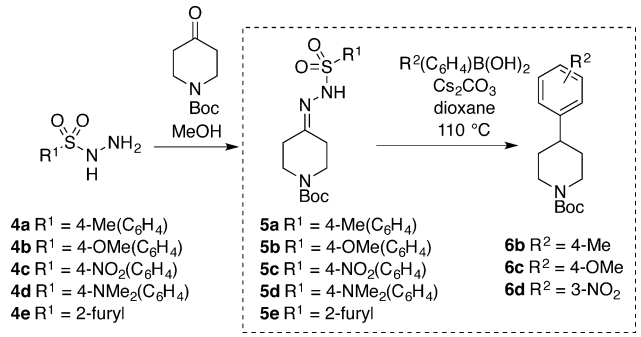
Finally, since sulfonylhydrazones are known to undergo a number of metal-catalyzed processes,[27] we evaluated the addition of 5 mol % of Pd^{II}, Rh^{II} or Cu^{II} salts to the reaction, to ensure that trace metal was not responsible for conversion. None of the metals tested were found to be beneficial in the reaction and in fact led to reduced yields (Table 1, entries 33–35).

With improved reaction conditions in hand, we explored the electronic scope of the reaction more fully by coupling sulfonylhydrazones and aryl boronic acids, each with a broader range of electron density (Table 2). As we observed previously,

Table 2. Effect of Substrate Electronics on Isolated Yield of 6 (%)



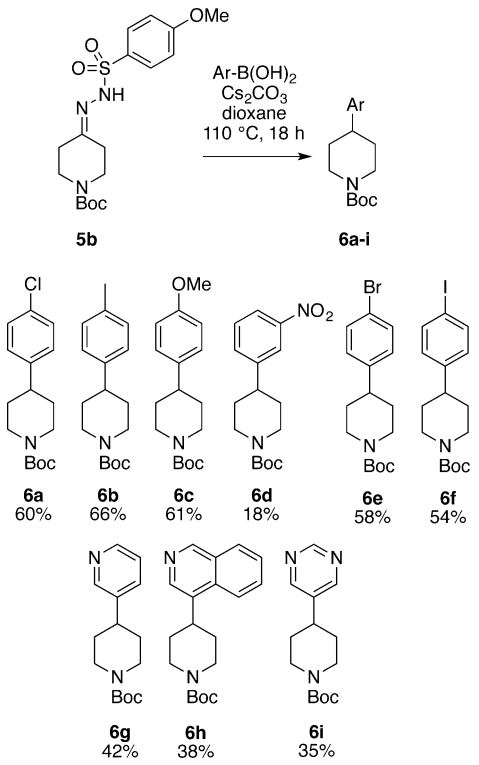
		R^2			
entry	5	4-Me	4-OMe	3-NO_2	t (h)
1	**5a**	59	27	15	6
2	**5b**	66	61	18	18
3	**5c**	0	0	0	1
4	**5d**	66	61	15	18
5	**5e**	59	53	13	18

the *p*-nosylhydrazone **5c** gave no coupled product in any instance (Table 2, entry 3). The reaction of tosylhydrazone **5a** with 4-toluneboronic acid proceeded in 59% yield, but was lower with both the highly electron-rich 4-methoxyphenyl- and highly electron-deficient 3-nitrophenyl-boronic acid substrates (Table 2, entry 1).

Use of PMP sulfonylhydrazone **5b** improved the yield of the coupling with the electron-rich substrate dramatically, while coupling to the electron-deficient boronic acid remained relatively low-yielding (Table 2, entry 2). We postulate that the low yields obtained from 3-nitrophenylboronic acid couplings is due to protodeboronation of the starting material prior to coupling, since a significant amount of nitrobenzene was consistently recovered as a byproduct. Further increases in the electron density of the sulfonylhydrazone moiety with 4-dimethylaminophenyl (**5d**) and 2-furyl (**5e**) analogues displayed no further improvement in yield (Table 2, entries 4 and 5). Since **5d** and **5e** were more synthetically challenging to prepare, **5b** was carried forward as the optimum sulfonylhydrazone substrate.

A range of boronic acids were then investigated for coupling to the optimized substrate **5b** (Scheme 4). As discussed previously, the reaction gives good yields with highly electron rich (**6c**), neutral (**6b**) and mildly electron-poor (**6a**) substrates, but performs less well on highly electron-deficient systems (**6d**). Importantly, the reaction works well with both brominated (**6e**) and iodinated (**6f**) boronic acids. This provides the capability for further structural elaboration from

Scheme 4. Isolated Yields from Metal-Free Coupling of 5b with a Range of Aromatic and Heterocyclic Boronic Acids



a functional handle that is challenging to introduce using the majority of current metal-based methodologies. The reaction also works for heteroaromatic boronic acids (**6g–6i**), allowing access to a range of pharmaceutically relevant bicyclic building blocks and demonstrating a potential area of synthetic application for this method.

In order to establish the scope of the sulfonylhydrazone coupling partner, tosyl- and PMP sulfonyl-hydrazones of a range of 4-, 5- and 6-membered saturated nitrogen-, oxygen- and sulfur-containing heterocyclic ketones were prepared (**2**, **5a–t**) and investigated in the reaction (Scheme 5). Yields using the PMP sulfonylhydrazones (shown in blue, Scheme 5) were consistently higher than the reactions performed with the equivalent tosylhydrazone (shown in red, Scheme 5). This disparity is more pronounced in couplings with the electron-rich 4-methoxyphenylboronic acid substrate (e.g., **6c**, **8b**, **9b**, Scheme 5). In some instances, no coupled product was isolated from the reaction with the tosylhydrazone, but a modest yield could be achieved by using the corresponding PMP sulfonylhydrazone (e.g., **9a**, **10a**, **13b**, Scheme 5). All examples yielded coupled products with the exception of those derived from tetrahydrothiophenes (**11a,b**) or thietanes (**14a,b**), where primarily olefinic thiol byproducts (**15**) were detected by crude ^{1}H NMR.

The same sulfonylhydrazones were also investigated for coupling to the highly electron-deficient substrate 3-nitrophenylboronic acid (Scheme 6). We postulated in earlier experiments that the poor yields observed in 3-nitrophenylboronic acid couplings were due to protodeboronation of the starting material. This trend proved to be consistent across all examples tested, with the reactions providing similarly low yields for both tosyl- and PMP sulfonyl-hydrazones and significant recovery of nitrobenzene in each instance. We

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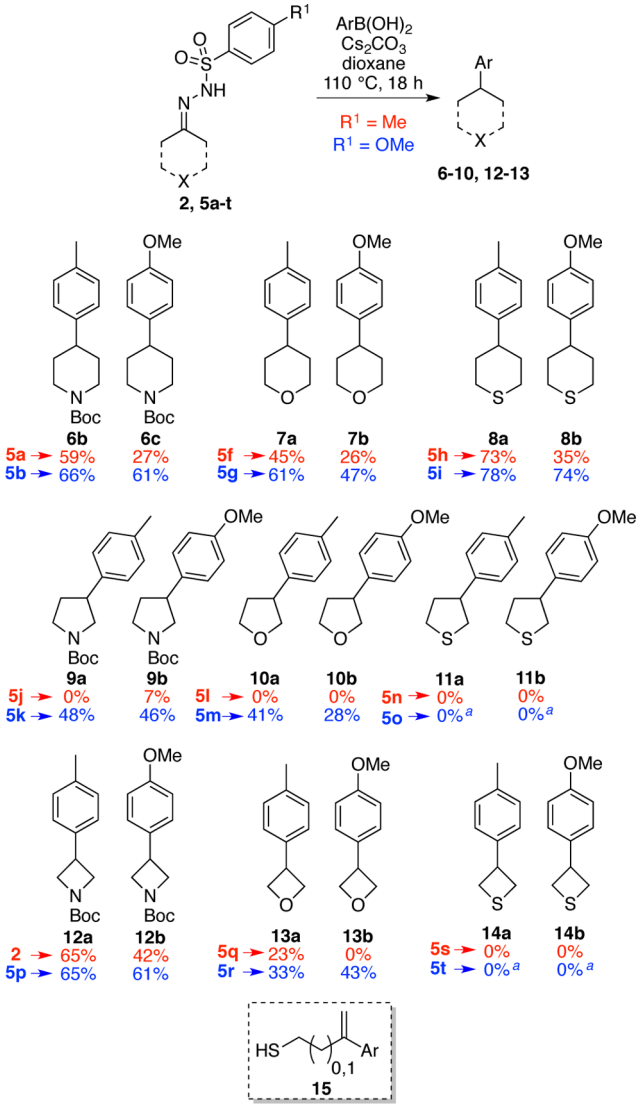
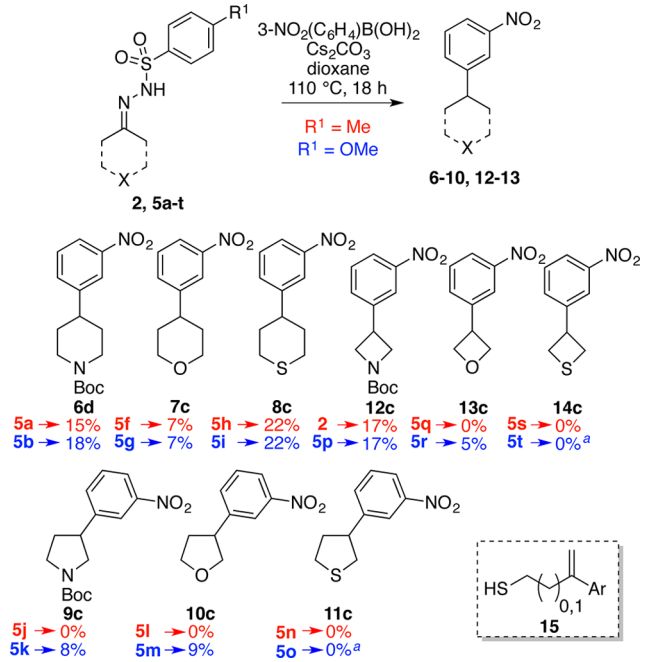
Scheme 5. Isolated Yields from Metal-Free Couplings of a Range of Saturated Heterocyclic Sulfonylhydrazones with Boronic Acids



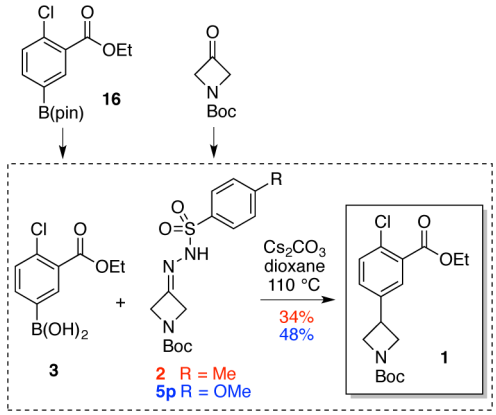
[a]No coupled products observed, only olefinic products of the general form **15** detected.

Scheme 6. Isolated Yields from Metal-Free Couplings of a Range of Saturated Heterocyclic Sulfonylhydrazones with 3-Nitrophenylboronic Acid



[a]No coupled products observed, only olefinic products of the general form **15** detected.

Scheme 7. Isolated Yields of Target Compound 1, Prepared by Metal-Free Coupling of 2 or 5p with 3



propose that these results restate the diminished influence of the sulfonylhydrazone moiety in these reactions due to an increased proportion of the boronic acid starting material undergoing protodeboronation prior to the coupling reaction occurring.

Since reactions using the Boc-azetidine sulfonylhydrazones **2** and **5p** had been demonstrated to give good yields of coupled products (Scheme 5, **12a**, **12b**), we applied our optimized reaction conditions to our target synthesis of compound **1** (Scheme 7).

Prior to our investigations, our initial attempts to perform this reaction using previously described conditions were unsuccessful.[21] Pleasingly, our improved conditions for metal-free coupling gave the desired product in 34% yield with tosylhydrazone **2** and 48% yield with PMP sulfonylhydrazone **1p**, thereby overcoming a major obstacle to the development of the project. In addition, this demonstrates a further example of the functional group tolerance of this reaction, since the ester moiety is retained in the product and is therefore a useful handle for further synthetic elaboration.

CONCLUSION

In summary, we present a procedure for metal-free coupling between saturated sulfonylhydrazones and aromatic boronic acids. This approach benefits from an electron-rich sulfonylhydrazone and modified reaction conditions to enable cross-couplings of a range of 4-, 5-, and 6-membered saturated heterocycles with aryl and heteroaromatic boronic acid substrates. The reaction tolerates functionality that is incompatible with many current methods and represents an improved procedure for the synthesis of these pharmaceutically relevant bicyclic building blocks.

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EXPERIMENTAL SECTION

General Experimental Methods. All reactions were conducted using standard Schlenk techniques. Analytical thin layer chromatography (TLC) was performed using silica gel 60 F_{254} precoated glass-backed plates and visualized by ultraviolet radiation (254 nm) and/or potassium permanganate as appropriate. Flash column chromatography was performed using silica gel (particle size 40−63 nm) under air pressure. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are reported in ppm with the resonance resulting from incomplete deuteration of the solvent as the internal standard ($CDCl_3$: 7.26 ppm, DMSO-d_6: 2.50 ppm). ^{13}C NMR spectra were recorded on a 100 MHz spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($^{13}CDCl_3$: 77.0 ppm, t or ^{13}C-DMSO-d_6: 39.5 ppm, septet). HRMS was performed using electrospray ionization with time-of-flight mass analysis. HRMS signals are reported to 4 decimal places and are within ±5 ppm of theoretical values. Infrared spectra were recorded neat as thin films and only selected peaks are reported.

General Procedure A: Preparation of Sulfonylhydrazides 4b−4e. Compounds were prepared according to a known procedure.[28] To a solution of sulfonyl chloride (1.0 equiv) in THF (0.2 M) at 0 °C was added hydrazine hydrate (2.5 equiv) dropwise. The reaction mixture was stirred at 0 °C until complete conversion was observed by TLC. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4 and solvents removed in vacuo to give the title compounds.

4-Methoxybenzenesulfonohydrazide (4b). Isolated as an off-white amorphous solid (9.52 g, 47.1 mmol, 94%) according to general procedure A: ^{1}H NMR ($CDCl_3$) δ 3.59 (2H, br), 3.88 (3H, s), 5.69 (1H, br), 7.02 (2H, d, J 8.8 Hz), 7.84 (2H, d, J 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 55.7, 114.5, 127.4, 130.5, 163.7; FTIR (υ_{max} cm^{-1}) 3377, 1153, 1093, 1012, 817, 671; R_f 0.05 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_7H_{11}N_2O_3S$ [M + H]$^+$ 203.0490, found 203.0481.

4-Nitrobenzenesulfonohydrazide (4c). Isolated as an off-white amorphous solid (1.57 g, 7.23 mmol, 72%) according to general procedure A: ^{1}H NMR (DMSO-d_6) δ 4.31 (2H, s), 8.03 (2H, d, J 8.2 Hz), 8.41 (2H, d, J 8.4 Hz), 8.74 (1H, s); ^{13}C NMR (DMSO-d_6) δ 124.7, 129.7, 144.7, 150.2; FTIR (υ_{max} cm^{-1}) 3375, 1522, 1351 1171, 843, 739; R_f 0.08 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_6H_8N_3O_4S$ [M + H]$^+$ 218.0230, found 218.0224.

4-(Dimethylamino)benzenesulfonohydrazide (4d). Isolated as a white amorphous solid (876 mg, 4.07 mmol, 70%) according to general procedure A:[29] ^{1}H NMR ($CDCl_3$) δ 3.07 (6H, s), 3.56 (2H, br), 5.42 (1H, s), 6.70 (2H, d, J 9.1 Hz), 7.71 (2H, d, J 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 40.1, 111.1, 120.3, 130.1; FTIR (υ_{max} cm^{-1}) 3348, 1333, 1318, 1144, 1094, 812; R_f 0.05 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_8H_{14}N_3O_2S$ [M + H]$^+$ 216.0807, found 216.0813.

Furan-2-sulfonohydrazide (4e). Isolated as a white amorphous solid (417 mg, 2.57 mmol, 83%) according to general procedure A:[30] ^{1}H NMR ($CDCl_3$) δ 3.74 (2H, br), 5.91 (1H, br), 6.57 (1H, ddd, J 3.5, 1.8, 0.9 Hz), 7.21 (1H, dt, J 3.5, 0.9 Hz), 7.64 (1H, dt, J 1.8, 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 111.6, 119.5, 145.0, 147.3; FTIR (υ_{max} cm^{-1}) 3368, 1336, 1155, 1121, 758; R_f 0.10 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_4H_7N_2O_3S$ [M + H]$^+$ 163.0177, found 163.0180.

General Procedure B: Preparation of Sulfonylhydrazones 2 and 5a−5t. General Procedure B1. To a solution of sulfonylhydrazide (1.0 equiv) in MeOH (0.5 M) was added ketone (1.0 equiv). The reaction mixture was stirred at room temperature until complete conversion was observed by TLC. Solvents were removed in vacuo to give the title compound.

General Procedure B2. A suspension of sulfonylhydrazide (1.0 equiv) and ketone (1.0 equiv) was heated to 110 °C in toluene (0.33 M) until complete dissolution was observed. After 5 min at reflux, a white precipitate formed. The reaction mixture was cooled to room temperature, and the precipitate was filtered and dried in vacuo to give the title compound.

General Procedure B3. A solution of sulfonylhydrazide (1.0 equiv) and ketone (1.0 equiv) in DMSO-d_6 (1.5 M) was heated to 60 °C until complete conversion was observed by ^{1}H NMR. The solution was cooled to room temperature and poured into stirring water, and the resulting white precipitate was filtered and dried in vacuo to give the title compound.

***tert*-Butyl 4-(2-tosylhydrazono)piperidine-1-carboxylate (5a).** Isolated as a white amorphous solid (3.67 g, 9.99 mmol, quant.) according to general procedure B1: ^{1}H NMR ($CDCl_3$) δ 1.44 (9H, s), 2.37 (4H, m), 2.43 (3H, s), 3.50 (4H, m), 7.31 (2H, d, J 8.0 Hz), 7.71 (1H, br), 7.83 (2H, d, J 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 21.6, 27.2, 28.4, 33.5, 43.2 (br), 80.2, 128.0, 129.6, 135.2, 144.1, 154.5, 158.0 (br); FTIR (υ_{max} cm^{-1}) 3246, 1701, 1160, 1034, 659; R_f 0.21 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{17}H_{26}N_3O_4S$ [M + H]$^+$ 368.1644, found 368.1655.

***tert*-Butyl 4-(2-((4-methoxyphenyl)sulfonyl)hydrazono) piperidine-1-carboxylate (5b).** Isolated as a white amorphous solid (7.65 g, 19.9 mmol, quant.) according to general procedure B1: ^{1}H NMR ($CDCl_3$) δ 1.44 (9H, s), 2.36 (4H, m), 3.48 (4H, m), 3.86 (3H, s), 6.98 (2H, d, J 9.0 Hz), 7.66 (1H, br), 7.88 (2H, d, J 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 27.2, 28.4, 33.6, 43.4 (br), 55.6, 80.2, 114.2, 129.7, 130.2, 154.5, 157.8 (br), 163.4; FTIR (υ_{max} cm^{-1}) 2974, 1686, 1595, 1579, 1497, 1416, 1366, 1330, 1305, 1257, 1154 (s), 1121, 1044, 1024, 912, 860, 832, 802, 770, 728, 684, 668 (m); R_f 0.14 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{17}H_{26}N_3O_5S$ [M + H]$^+$ 384.1593, found 384.1579.

***tert*-Butyl 4-(2-((4-nitrophenyl)sulfonyl)hydrazono)-piperidine-1-carboxylate (5c).** Isolated as an off-white amorphous solid (794 mg, 1.99 mmol, quant.) according to general procedure B1: ^{1}H NMR ($CDCl_3$) δ 1.44 (9H, s), 2.35 (2H, t, J 6.0 Hz), 2.39 (2H, t, J 6.1 Hz), 3.53 (4H, m), 7.71 (1H, br), 8.15 (2H, d, J 9.0 Hz), 8.37 (2H, d, J 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 27.2, 28.4, 33.6, 41.3 (br), 80.4, 124.2, 129.5, 143.7, 150.5, 154.5, 159.6 (br); FTIR (υ_{max} cm^{-1}) 3247, 1688, 1532, 1165, 854, 736, 688; R_f 0.18 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{16}H_{23}N_4O_6S$ [M + H]$^+$ 399.1338, found 399.1328.

***tert*-Butyl 4-(2-((4-(dimethylamino)phenyl)sulfonyl)-hydrazono)piperidine-1-carboxylate (5d).** Isolated as a white amorphous solid (1.19 g, 3.00 mmol, quant.) according to general procedure B1: ^{1}H NMR ($CDCl_3$) δ 1.43 (9H, s), 2.33 (2H, t, J 6.1 Hz), 2.36 (2H, t, J 6.1 Hz), 3.04 (6H, s, NMe_2), 3.47 (4H, m), 6.66 (2H, d, J 9.1 Hz), 7.76 (2H, d, J 9.1 Hz), 7.88 (1H, br); ^{13}C NMR ($CDCl_3$) δ 27.1, 28.4, 33.6, 40.1, 43.6 (br), 80.1, 110.7, 123.1, 129.8, 153.2, 154.6, 157.1; FTIR (υ_{max} cm^{-1}) 3210, 1596, 1147, 1098, 654; R_f 0.12 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{18}H_{29}N_4O_4S$ [M + H]$^+$ 397.1910, found 397.1908.

***tert*-Butyl 4-(2-(furan-2-ylsulfonyl)hydrazono)-piperidine-1-carboxylate (5e).** Isolated as an off-white amorphous solid (796 mg, 2.32 mmol, quant.) according to general procedure B1: ^{1}H NMR ($CDCl_3$) δ 1.44 (9H, s), 2.40 (4H, m), 3.52 (4H, m), 6.53 (1H, ddd, J 3.5, 1.8, 1.0 Hz), 7.20 (1H, dt, J 3.5, 1.0 Hz), 7.57 (1H, dt, J 1.8, 1.0 Hz), 8.03 (1H, br); ^{13}C NMR ($CDCl_3$) δ 27.4, 28.4, 33.6, 43.1 (br), 80.3, 111.6, 118.9, 146.4, 146.7, 154.5, 158.9 (br); FTIR (υ_{max} cm^{-1}) 3143, 1158, 1124, 728, 688; R_f 0.18 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{14}H_{22}N_3O_5S$ [M + H]$^+$ 344.1280, found 344.1283.

4-Methyl-*N*′-(tetrahydro-4*H*-pyran-4-ylidene)-benzenesulfonohydrazide (5f). Isolated as an off-white amorphous solid (1.34 g, 4.99 mmol, quant.) according to general procedure B1: ^{1}H NMR ($CDCl_3$) δ 2.37 (4H, m), 2.42 (3H, s), 3.67 (2H, t, J 5.7 Hz), 3.74 (2H, t, J 5.6 Hz), 7.30 (2H, d, J 8.1 Hz), 7.83 (2H, d, J 8.1 Hz), 8.15 (1H, br); ^{13}C NMR ($CDCl_3$) δ 21.6, 28.5, 35.3, 66.3, 68.1, 128.0, 129.6, 135.2, 144.1, 157.5; FTIR (υ_{max} cm^{-1}) 3232, 1327, 1164, 1093, 812, 685, 660; R_f 0.17 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{12}H_{17}N_2O_3S$ [M + H]$^+$ 269.0960, found 269.0952.

4-Methoxy-*N*′-(tetrahydro-4*H*-pyran-4-ylidene)-benzenesulfonohydrazide (5g). Isolated as a white amorphous solid (568 mg, 2.00 mmol, quant.) according to general procedure B1: ^{1}H NMR ($CDCl_3$) δ 2.38 (4H, app. q, J 5.8 Hz), 3.70 (2H, t, J 5.8 Hz), 3.76

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(2H, t, *J* 5.6 Hz), 3.87 (3H, s, 6.98 (2H, d, *J* 8.7 Hz), 7.88 (3H, d); ^{13}C NMR ($CDCl_3$) δ 28.4, 35.3, 55.6, 66.2, 68.1, 114.2, 129.7, 130.2, 157.3, 163.4; FTIR (υ_{max} cm^{-1}) 3240, 1157, 1088, 1017, 821, 802, 693, 681; R_f 0.14 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{12}H_{17}N_2O_4S$ $[M + H]^+$ 285.0909, found 285.0910.

4-Methyl-*N*′-(tetrahydro-4*H*-thiopyran-4-ylidene)-benzenesulfonohydrazide (5h). Isolated as a white amorphous solid (2.84 g, 9.99 mmol, quant.) according to general procedure B1: ^{1}H NMR ($CDCl_3$) δ 2.42 (3H, s), 2.55 (2H, t, *J* 5.8 Hz), 2.59 (2H, dd, *J* 7.3, 4.4 Hz), 2.66 (2H, t, *J* 5.7 Hz), 2.72 (2H, t, *J* 5.8 Hz), 7.30 (2H, d, *J* 8.1 Hz), 7.82 (2H, d, *J* 8.3 Hz), 8.19 (1H, br); ^{13}C NMR ($CDCl_3$) δ 21.6, 27.9, 29.4, 29.5, 36.8, 128.0, 129.6, 135.2, 144.2, 159.1; FTIR (υ_{max} cm^{-1}) 3238, 1161, 913, 676, 665; R_f 0.32 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{12}H_{16}N_2O_2S_2Na$ $[M + Na]^+$ 307.0545, found 307.0534.

4-Methoxy-*N*′-(tetrahydro-4*H*-thiopyran-4-ylidene)-benzenesulfonohydrazide (5i). Isolated as a white amorphous solid (901 mg, 3.00 mmol, quant.) according to general procedure B1: ^{1}H NMR ($CDCl_3$) δ 2.59 (4H, dd, *J* 7.1, 4.2 Hz), 2.70 (2H, app. q, *J* 6.2 Hz), 2.76 (2H, dd, *J* 7.2, 4.7 Hz), 3.88 (3H, s), 6.99 (2H, d, *J* 8.9 Hz), 7.48 (1H, br), 7.88 (2H, d, *J* 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 27.8, 29.2, 29.4, 36.8, 55.6, 114.1, 129.7, 130.3, 159.1, 163.4; FTIR (υ_{max} cm^{-1}) 3246, 1157, 1093, 819, 682; R_f 0.36 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{12}H_{17}N_2O_3S_2$ $[M + H]^+$ 301.0681, found 301.0681.

***tert*-Butyl 3-(2-tosylhydrazono)pyrrolidine-1-carboxylate (5j).** Isolated as a white amorphous solid (3.49 g, 9.87 mmol, 99%) according to general procedure B1: ^{1}H NMR ($CDCl_3$, 3:2 mixture of geometric isomers) δ 1.42 (9H, s), 2.43 (3H, s), 2.55 (1.2H, t, *J* 7.4 Hz), 2.66 (0.8H, t, *J* 7.5 Hz), 3.51 (0.8H, t, *J* 7.0 Hz), 3.59 (1.2H, t, *J* 7.4 Hz), 3.92 (0.8H, s), 3.97 (1.2H, s), 7.31 (2H, d, *J* 8.2 Hz), 7.83 (2H, d, *J* 8.2 Hz), 7.94 (0.4H, br), 8.09 (0.6H, br); ^{13}C NMR ($CDCl_3$) δ 21.6, 27.5 (br), 28.4, 28.8 (br), 43.9 (br), 49.5 (br), 80.2, 80.4, 128.0, 129.7, 135.1, 144.4, 154.1, 160.1 (br); FTIR (υ_{max} cm^{-1}) 3135, 1658, 1420, 1165, 1120, 680; R_f 0.09 and 0.13 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{16}H_{24}N_3O_4S$ $[M + H]^+$ 354.1488, found 354.1474.

***tert*-Butyl 3-(2-((4-methoxyphenyl)sulfonyl)-hydrazono)-pyrrolidine-1-carboxylate (5k).** Isolated as a white amorphous solid (1.85 g, 5.00 mmol, quant.) according to general procedure B1: ^{1}H NMR ($CDCl_3$, 3:2 mixture of geometric isomers) δ 1.42 (9H, s), 2.54 (1.2H, t, *J* 7.4 Hz), 2.67 (0.8H, t, *J* 7.4 Hz), 3.52 (0.8H, t, *J* 7.3 Hz), 3.59 (1.2H, t, *J* 7.3 Hz), 3.86 (3H, s), 3.92 (0.8H, s), 3.98 (1.2H, s), 6.98 (2H, d, *J* 8.8 Hz), 7.82 (0.4H, br), 7.88 (2H, d, *J* 8.8 Hz), 7.97 (0.6H, br); ^{13}C NMR ($CDCl_3$) δ 26.4 (br), 28.4, 30.6 (br), 43.9 (br), 46.5 (br), 49.6 (br), 55.6, 80.1, 80.3, 114.3, 129.6, 130.2, 154.1, 159.9, 163.5; FTIR (υ_{max} cm^{-1}) 3217, 1675, 1407, 1258, 1158, 726, 675; R_f 0.13 and 0.20 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{16}H_{24}N_3O_5S$ $[M + H]^+$ 370.1437, found 370.1444.

***N*′-(Dihydrofuran-3(2*H*)-ylidene)-4-methylbenzene-sulfonohydrazide (5l).** Isolated as an off-white amorphous solid (1.27 g, 4.99 mmol, quant.) according to general procedure B1: ^{1}H NMR ($CDCl_3$, 3:1 mixture of geometric isomers) δ 2.42 (3H, s), 2.48 (1.5H, t, *J* 6.9 Hz), 2.61 (0.5H, t, *J* 7.1 Hz), 3.93 (0.5H, td, *J* 7.0, 2.7 Hz), 3.99 (1.5H, td, *J* 6.9, 2.9 Hz), 4.16 (1.5H, s), 4.20 (0.5H, s), 7.32 (2H, d, *J* 8.1 Hz), 7.83 (2H, d, *J* 8.3 Hz), 8.05 (0.25H, br), 8.19 (0.75H, br); ^{13}C NMR ($CDCl_3$) δ 21.6, 28.4, 32.4, 66.2, 67.7, 67.8, 69.4, 128.0, 129.8, 135.1, 144.4, 162.2; FTIR (υ_{max} cm^{-1}) 3223, 1162, 808, 706, 672; R_f 0.10 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{11}H_{15}N_2O_3S$ $[M + H]^+$ 255.0803, found 255.0809.

***N*′-(Dihydrofuran-3(2*H*)-ylidene)-4-methoxybenzene-sulfonohydrazide (5m).** Isolated as an off-white amorphous solid (1.35 g, 4.99 mmol, quant.) according to general procedure B1: ^{1}H NMR ($CDCl_3$, 3:1 mixture of geometric isomers) δ 2.47 (1.5H, t, *J* 6.9 Hz), 2.63 (0.5H, t, *J* 6.8 Hz), 3.87 (3H, s), 3.95 (0.5H, t, *J* 7.0 Hz), 4.02 (1.5H, t, *J* 6.9 Hz), 4.19 (1.5H, s), 4.20 (0.5H, s), 6.99 (2H, d, *J* 9.0 Hz), 7.83 (0.75H, br), 7.88 (2H, d, *J* 8.9 Hz), 7.92 (0.25H, br); ^{13}C NMR ($CDCl_3$) δ 28.4, 32.4, 55.7, 66.1, 67.7, 67.8, 69.4, 114.3, 129.45, 129.53, 130.1, 130.2, 162.1, 163.5; FTIR (υ_{max} cm^{-1}) 3203, 1593, 1401, 1265, 1156, 1025, 691; R_f 0.10 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{11}H_{15}N_2O_4S$ $[M + H]^+$ 271.0753, found 271.0753.

***N*′-(Dihydrothiophen-3(2*H*)-ylidene)-4-methylbenzene-sulfonohydrazide (5n).** To a solution of dihydrothiophen-3(2*H*)-one (854 μL, 10.0 mmol, 1.0 equiv) in MeOH (30 mL) was added tosyl hydrazide (1.86 g, 10.0 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 0.5 h, during which time a white precipitate formed. The precipitate was filtered and dried in vacuo to give the title compound (2.02 g, 7.47 mmol, 75%) as a white amorphous solid, which was used without further purification: ^{1}H NMR ($CDCl_3$, 11:9 mixture of geometric isomers) δ 2.43 (3H, s), 2.57 (0.9H, t, *J* 6.9 Hz), 2.80 (2.2H, m), 2.94 (0.9H, t, *J* 6.8 Hz), 3.34 (1.1H, s), 3.44 (0.9H, s), 7.32 (2H, d, *J* 8.0 Hz), 7.84 (1H, d, *J* 8.4 Hz), 8.01 (0.45H, s), 8.04 (0.55H, s); ^{13}C NMR ($CDCl_3$) δ 21.7, 28.4, 29.4, 29.5, 30.5, 36.1, 37.2, 128.0, 129.7, 135.1, 144.4, 163.2; FTIR (υ_{max} cm^{-1}) 3210, 1334, 1165, 808, 663; R_f 0.25 and 0.33 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{11}H_{14}N_2O_2S_2Na$ $[M + Na]^+$ 293.0389, found 293.0384.

***N*′-(Dihydrothiophen-3(2*H*)-ylidene)-4-methoxy-benzenesulfonohydrazide (5o).** To a solution of dihydrothiophen-3(2*H*)-one (427 μL, 5.00 mmol, 1.0 equiv) in MeOH (15 mL) was added **4b** (1.01 g, 5.00 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 1 h, during which time a white precipitate formed. The precipitate was filtered and dried in vacuo to give the title compound (1.16 g, 4.05 mmol, 81%) as a white amorphous solid, which was used without further purification: ^{1}H NMR ($CDCl_3$, 11:9 mixture of geometric isomers) δ 2.57 (1.1H, t, *J* 6.8 Hz), 2.78 (1.8H, m), 2.92 (1.1H, t, *J* 6.8 Hz), 3.34 (0.9H, s), 3.43 (1.1H, s), 3.85 (3H, s), 6.97 (2H, d, *J* 8.9 Hz), 7.87 (2H, app. dd, *J* 8.9, 1.9 Hz), 8.08 (0.55H, br), 8.12 (0.45H, br); ^{13}C NMR ($CDCl_3$) δ 28.4, 29.47, 29.52, 30.5, 36.1, 37.2, 55.7, 114.30, 114.33, 129.5, 130.1, 130.2, 163.17, 163.22, 163.5; FTIR (υ_{max} cm^{-1}) 3201, 1337, 1255, 1162, 1027, 676; R_f 0.17 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{11}H_{15}N_2O_3S_2$ $[M + H]^+$ 287.0524, found 287.0525.

***tert*-Butyl 3-(2-tosylhydrazono)azetidine-1-carboxylate (2).** Isolated as a white amorphous solid (890 mg, 2.62 mmol, 87%) according to general procedure B2: ^{1}H NMR ($CDCl_3$) δ 1.42 (9H, s), 2.44 (3H, s), 4.53 (4H, app. dd, *J* 9.6, 3.2 Hz), 7.33 (2H, d, *J* 8.5 Hz), 7.81 (2H, d, *J* 8.3 Hz), 8.13 (1H, br); ^{13}C NMR ($CDCl_3$) δ 21.6, 28.2, 60.3 (br), 80.9, 128.0, 129.8, 134.8, 144.6, 155.9; FTIR (υ_{max} cm^{-1}) 3185, 1708, 1369, 1340, 1164, 1147, 1119, 1044, 765, 745, 666; R_f 0.38 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{15}H_{22}N_3O_4S$ $[M + H]^+$ 340.1331, found 340.1333.

***tert*-Butyl 3-(2-((4-methoxyphenyl)sulfonyl)-hydrazono)-azetidine-1-carboxylate (5p).** Isolated as a white amorphous solid (737 mg, 2.07 mmol, 73%) according to general procedure B3: ^{1}H NMR (DMSO-d_6) δ 1.34 (9H, s), 3.80 (3H, s), 4.47 (4H, d, *J* 13.3 Hz), 7.08 (2H, d, *J* 8.7 Hz), 7.76 (2H, d, *J* 8.8 Hz), 10.78 (1H, s); ^{13}C NMR (DMSO-d_6) δ 28.3, 56.0, 60.4 (br), 79.9, 114.7, 130.0, 130.9, 148.2, 156.1, 163.1; FTIR (υ_{max} cm^{-1}) 3193, 1711, 1367, 1335, 1159, 1145, 1025, 764, 745, 670; R_f 0.14 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{15}H_{21}N_3O_5SNa$ $[M + Na]^+$ 378.1100, found 378.1098.

4-Methyl-*N*′-(oxetan-3-ylidene)benzenesulfono-hydrazide (5q). Isolated as a white amorphous solid (620 mg, 2.58 mmol, 86%) according to general procedure B2: ^{1}H NMR ($CDCl_3$) δ 2.48 (3H, s), 5.20 (4H, d, *J* 1.4 Hz), 7.35 (2H, d, *J* 8.0 Hz), 7.80 (2H, d, *J* 8.4 Hz), 8.16 (1H, br); ^{13}C NMR ($CDCl_3$) δ 21.7, 79.8, 81.1, 127.9, 129.9, 134.6, 144.7, 153.9; FTIR (υ_{max} cm^{-1}) 3258, 1331, 1160, 950, 809, 660; R_f 0.17 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{10}H_{13}N_2O_3S$ $[M + H]^+$ 241.0647, found 241.0639.

4-Methoxy-*N*′-(oxetan-3-ylidene)benzenesulfono-hydrazide (5r). Isolated as a white amorphous solid (524 mg, 2.04 mmol, 68%) according to general procedure B3: ^{1}H NMR (DMSO-d_6) δ 3.83 (3H, s), 5.11 (4H, app. dd, *J* 6.5, 2.4 Hz), 7.11 (2H, d, *J* 8.4 Hz), 7.72 (2H, d, *J* 8.3 Hz), 10.76 (1H, s); ^{13}C NMR (DMSO-d_6) δ 56.2, 80.5, 114.9, 130.0, 130.8, 153.2, 163.1; FTIR (υ_{max} cm^{-1}) 3260, 1594, 1259, 1154, 1023, 742, 664; R_f 0.08 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{10}H_{13}N_2O_4S$ $[M + H]^+$ 257.0596, found 257.0598.

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4-Methyl-*N*′-(thietan-3-ylidene)benzenesulfono-hydrazide (5s). Isolated as a white amorphous solid (289 mg, 1.13 mmol, 88%) according to general procedure B2:[31] ^{1}H NMR ($CDCl_3$) δ 2.45 (3H, s), 3.97 (2H, t, *J* 2.4 Hz), 4.02 (2H, t, *J* 2.3 Hz), 7.34 (2H, d, *J* 8.0 Hz), 7.82 (2H, d, *J* 8.4 Hz), 8.13 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.7, 36.8, 39.1, 127.9, 129.9, 134.9, 144.6, 151.6; FTIR (υ_{max} cm^{-1}) 3208, 1336, 1165, 1047, 904, 808, 729, 661; R_f 0.35 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{10}H_{13}N_2O_2S_2$ [M + H]$^+$ 257.0418, found 257.0406.

4-Methoxy-*N*′-(thietan-3-ylidene)benzenesulfono-hydrazide (5t). Isolated as a white amorphous solid (218 mg, 0.800 mmol, 80%) according to general procedure B3:[31] ^{1}H NMR (DMSO-d_6) δ 3.82 (3H, s), 3.98 (2H, d, *J* 2.3 Hz), 4.03 (2H, d, *J* 2.4 Hz), 7.10 (2H, d, *J* 8.9 Hz), 7.72 (2H, d, *J* 8.9 Hz), 10.47 (1H, br); ^{13}C NMR (DMSO-d_6) δ 38.6, 39.4, 56.1, 114.8, 130.0, 131.1, 151.4, 163.0; FTIR (υ_{max} cm^{-1}) 3217, 1598, 1263, 1153, 743, 669; R_f 0.38 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{10}H_{13}N_2O_3S_2$ [M + H]$^+$ 273.0368, found 273.0380.

General Procedure C: Preparation of Coupled Compounds 1, 6a−i, 7−10a−c, and 12−13a−c. Compounds were prepared according to a modification of a known procedure.[21] Sulfonylhydrazone (0.5 mmol, 1.0 equiv), boronic acid (0.75 mmol, 1.5 equiv) and cesium carbonate (0.75 mmol, 1.5 equiv) were placed in an oven-dried tube in vacuo for 30 min. The tube was backfilled with argon, and dry, degassed 1,4-dioxane (2 mL, 0.25 M) was added. The tube was sealed and heated to 110 °C for 18 h before being cooled to room temperature, quenched with $NaHCO_3$ (2 mL of a saturated aqueous solution), and extracted with CH_2Cl_2 (3 × 5 mL). The organic phase was dried over $MgSO_4$, and solvents were removed in vacuo to give a residue, which was purified by flash column chromatography (10−30% EtOAc/hexane) to give the title compounds.

***tert*-Butyl 4-(4-chlorophenyl)piperidine-1-carboxylate (6a).** Isolated as a colorless oil (88.2 mg, 0.298 mmol, 60%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 1.57 (2H, app qd, *J* 12.7, 4.2 Hz), 1.78 (2H, br d, *J* 13.2 Hz), 2.61 (1H, tt, *J* 12.2, 3.6 Hz), 2.78 (2H, br t, *J* 12.4 Hz), 4.23 (2H, br), 7.12 (2H, d, *J* 8.6 Hz), 7.26 (2H, d, *J* 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 28.5, 33.1 (br), 42.1, 44.1 (br), 79.5, 128.1, 128.6, 131.9, 144.2, 154.8; FTIR (υ_{max} cm^{-1}) 2975, 1687, 1230, 1161, 1011; R_f 0.75 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{16}H_{23}NO_2Cl$ [M + H]$^+$ 296.1417, found 296.1406.

***tert*-Butyl 4-(*p*-tolyl)piperidine-1-carboxylate (6b).** Isolated as a colorless oil (91.5 mg, 0.332 mmol, 66%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 1.50 (9H, s), 1.61 (2H, app. qd, *J* 12.6, 4.1 Hz), 1.81 (2H, br d, *J* 15.1 Hz), 2.33 (3H, s), 2.61 (1H, tt, *J* 12.1, 3.5 Hz), 2.80 (2H, br t, *J* 12.3 Hz), 4.25 (2H, br), 7.10 (2H, d, *J* 8.3 Hz), 7.13 (2H, d, *J* 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.0, 28.5, 33.3, 42.3, 44.6 (br), 79.4, 126.6, 129.2, 135.8, 142.9, 154.9; FTIR (υ_{max} cm^{-1}) 2975, 1689, 1230, 1162, 861; R_f 0.85 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{17}H_{25}NO_2Na$ [M + Na]$^+$ 298.1778, found 298.1768.

***tert*-Butyl 4-(4-methoxyphenyl)piperidine-1-carboxylate (6c).** Isolated as a colorless oil (89.5 mg, 0.307 mmol, 61%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 1.58 (2H, app. qd, *J* 12.7, 4.2 Hz), 1.79 (2H, br d, *J* 13.2 Hz), 2.59 (1H, tt, *J* 12.2, 3.5 Hz), 2.79 (2H, br t, *J* 12.4 Hz), 3.79 (3H, s), 4.23 (2H, br), 6.85 (2H, d, *J* 8.5 Hz), 7.12 (2H, d, *J* 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 28.5, 33.4, 41.9, 44.2 (br), 55.3, 79.4, 113.9, 127.6, 138.0, 154.9, 158.1; FTIR (υ_{max} cm^{-1}) 2975, 1687, 1512, 1229, 1161, 764; R_f 0.79 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{17}H_{26}NO_3$ [M + H]$^+$ 292.1913, found 292.1912.

***tert*-Butyl 4-(3-nitrophenyl)piperidine-1-carboxylate (6d).** Isolated as a colorless oil (27.1 mg, 0.0885 mmol, 18%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 1.49 (9H, s), 1.65 (2H, app. qd, *J* 12.7, 4.0 Hz), 1.86 (2H, br d, *J* 13.2 Hz), 2.80 (3H, m), 4.28 (2H, br), 7.47 (1H, t, *J* 8.2 Hz), 7.54 (1H, d, *J* 7.8 Hz), 8.07 (2H, m); ^{13}C NMR ($CDCl_3$) δ 28.5, 32.9, 42.4, 43.9 (br), 79.8, 121.5, 121.8, 129.4, 133.1, 147.7, 154.8; FTIR (υ_{max} cm^{-1}) 2978, 1686, 1525, 1348, 1232, 1160, 736; R_f 0.68 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{16}H_{22}N_2O_4Na$ [M + Na]$^+$ 329.1477, found 329.1471.

***tert*-Butyl 4-(4-bromophenyl)piperidine-1-carboxylate (6e).** Isolated as a colorless oil (98.6 mg, 0.290 mmol, 58%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 1.47 (9H, s), 1.58 (2H, td, *J* 12.7, 4.3 Hz), 1.78 (2H, br d, *J* 13.1 Hz), 2.59 (1H, tt, *J* 12.2, 3.5 Hz), 2.78 (2H, br t, *J* 12.3 Hz), 4.23 (2H, br), 7.06 (2H, d, *J* 8.5 Hz), 7.41 (2H, d, *J* 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 28.5, 33.1 (br), 42.2, 44.2 (br), 79.5, 120.0, 128.5, 131.6, 144.7, 154.8; FTIR (υ_{max} cm^{-1}) 2974, 1686, 1162, 1007, 821; R_f 0.77 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{16}H_{22}NO_2{}^{79}BrNa$ [M + Na]$^+$ 362.0726, found 362.0717.

***tert*-Butyl 4-(4-iodophenyl)piperidine-1-carboxylate (6f).** Isolated as a colorless oil (105.2 mg, 0.272 mmol, 54%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 1.47 (9H, s), 1.57 (2H, td, *J* 12.6, 4.2 Hz), 1.77 (2H, br d, *J* 13.1 Hz), 2.58 (1H, tt, *J* 12.2, 3.5 Hz), 2.77 (2H, br t, *J* 12.3 Hz), 4.22 (2H, br), 6.94 (2H, d, *J* 8.4 Hz), 7.60 (2H, d, *J* 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 28.5, 33.0, 42.3, 44.3 (br), 79.5, 91.4, 128.9, 137.5, 145.4, 154.8; FTIR (υ_{max} cm^{-1}) 2975, 1686, 1161, 1003, 860; R_f 0.77 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{16}H_{22}NO_2INa$ [M + Na]$^+$ 410.0588, found 410.0585.

2g: *tert*-Butyl 4-(pyridin-3-yl)piperidine-1-carboxylate (6g). Isolated as a colorless oil (55.1 mg, 0.210 mmol, 42%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 1.45 (9H, s), 1.59 (2H, qd, *J* 12.7, 4.2 Hz), 1.80 (2H, br d, *J* 12.8 Hz), 2.65 (1H, tt, *J* 12.2, 3.6 Hz), 2.79 (2H, br t, *J* 12.2 Hz), 4.23 (2H, br), 7.21 (1H, dd, *J* 7.9, 4.8 Hz), 7.48 (1H, ddd, *J* 7.9, 2.1, 1.8 Hz), 8.43 (1H, dd, *J* 4.8, 1.4 Hz), 8.45 (1H, d, *J* 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 28.5, 32.8, 40.2, 44.0 (br), 79.6, 123.5, 134.0, 140.8, 147.8, 148.8, 154.8; FTIR (υ_{max} cm^{-1}) 2975, 1685, 1421, 1233, 1161, 730, 714; R_f 0.16 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{15}H_{23}N_2O_2$ [M + H]$^+$ 263.1760, found 263.1771.

***tert*-Butyl 4-(isoquinolin-4-yl)piperidine-1-carboxylate (6h).** Isolated as a colorless oil (59.6 mg, 0.191 mmol, 38%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 1.50 (9H, s), 1.83 (2H, qd, *J* 12.6, 4.1 Hz), 2.00 (2H, br d, *J* 13.0 Hz), 2.95 (2H, br t, *J* 13.3 Hz), 3.39 (1H, tt, *J* 12.0, 3.2 Hz), 4.34 (2H, br), 7.61 (1H, t, *J* 7.5 Hz), 7.75 (1H, t, *J* 8.0 Hz), 8.00 (1H, d, *J* 8.1 Hz), 8.05 (1H, d, *J* 8.6 Hz), 8.42 (1H, s), 9.14 (1H, s); ^{13}C NMR ($CDCl_3$) δ 28.5, 32.5, 36.4, 44.2 (br), 79.7, 121.9, 126.8, 128.4, 128.7, 130.4, 133.9, 134.1, 140.1, 151.5, 154.8; FTIR (υ_{max} cm^{-1}) 2974, 1683, 1235, 1161, 728; R_f 0.33 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{19}H_{25}N_2O_2$ [M + H]$^+$ 313.1916, found 313.1918.

***tert*-Butyl 4-(pyrimidin-5-yl)piperidine-1-carboxylate (6i).** Isolated as a pale yellow oil (46.3 mg, 0.176 mmol, 35%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 1.47 (9H, s), 1.65 (2H, qd, *J* 12.7, 4.2 Hz), 1.85 (2H, br d, *J* 12.5 Hz), 2.69 (1H, tt, *J* 12.3, 3.6 Hz), 2.82 (2H, br t, *J* 12.4 Hz), 4.28 (2H, br), 8.60 (2H, s), 9.09 (1H, s); ^{13}C NMR ($CDCl_3$) δ 28.4, 32.4, 38.2, 43.9 (br), 79.8, 138.2, 154.7, 155.5, 157.2; FTIR (υ_{max} cm^{-1}) 2975, 1684, 1411, 1238, 1159, 728; R_f 0.09 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{14}H_{22}N_3O_2$ [M + H]$^+$ 264.1712, found 264.1724.

4-(*p*-Tolyl)tetrahydro-2*H*-pyran (7a). Isolated as a colorless oil (53.9 mg, 0.306 mmol, 61%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 1.81 (4H, m), 2.34 (3H, s), 2.73 (1H, tt, *J* 11.4, 4.5 Hz), 3.54 (2H, td, *J* 11.3, 2.8 Hz), 4.09 (2H, m), 7.14 (4H, app. s); ^{13}C NMR ($CDCl_3$) δ 21.0, 34.1, 41.2, 68.5, 126.6, 129.2, 135.8, 142.9; FTIR (υ_{max} cm^{-1}) 2934, 1515, 1128, 1085, 1018, 895, 841, 806; R_f 0.85 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{12}H_{17}O$ [M + H]$^+$ 177.1274, found 177.1269.

4-(4-Methoxyphenyl)tetrahydro-2*H*-pyran (7b). Isolated as a colorless oil (44.9 mg, 0.234 mmol, 47%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 1.78 (4H, m), 2.71 (1H, tt, *J* 10.7, 5.3 Hz), 3.52 (2H, td, *J* 11.3, 3.2 Hz), 3.80 (3H, s), 4.08 (2H, m), 6.87 (2H, d, *J* 8.7 Hz), 7.15 (2H, d, *J* 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 34.2, 40.7, 55.3, 68.5, 113.9, 127.6, 138.1, 158.0; FTIR (υ_{max} cm^{-1}) 2934, 1512, 1242, 827, 765; R_f 0.73 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{12}H_{17}O_2^+$ [M + H]$^+$ 193.1229, found 193.1226.

4-(3-Nitrophenyl)tetrahydro-2*H*-pyran (7c). Isolated as a colorless oil (7.5 mg, 0.0362 mmol, 7%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 1.85 (4H, m), 2.89 (1H, tt, *J* 10.5, 5.3 Hz), 3.55 (2H, td, *J* 10.9, 3.5 Hz), 4.11 (2H, m), 7.49 (1H, t, *J* 7.8

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Hz), 7.56 (1H, d, *J* 7.7 Hz), 8.09 (2H, m); ^{13}C NMR ($CDCl_3$) δ 33.6, 41.3, 68.1, 121.5, 121.8, 129.5, 133.0, 147.1; FTIR (υ_{max} cm^{-1}) 2942, 1522, 1348, 1078, 803, 737, 686; R_f 0.56 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{11}H_{13}NO_3Na$ $[M + Na]^+$ 230.0788, found 230.0781.

4-(*p*-Tolyl)tetrahydro-2*H*-thiopyran (8a). Isolated as a white amorphous solid (75.0 mg, 0.390 mmol, 78%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 1.87 (2H, app. qd, *J* 12.7, 3.1 Hz), 2.15 (2H, dd, *J* 13.5, 2.8 Hz), 2.35 (3H, s), 2.51 (1H, tt, *J* 12.1, 3.1 Hz), 2.72 (2H, br d, *J* 13.9 Hz), 2.86 (2H, td, *J* 12.3, 2.3 Hz), 7.12 (2H, d, *J* 8.1 Hz), 7.15 (2H, d, *J* 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 21.0, 29.4, 35.3, 43.9, 126.7, 129.2, 135.8, 144.0; FTIR (υ_{max} cm^{-1}) 2922, 1514, 1109, 951, 816, 658; R_f 0.94 (30% EtOAc/hexane); HRMS (ESI +) calculated for $C_{12}H_{17}S$ $[M + H]^+$ 193.1045, found 193.1040.

4-(4-Methoxyphenyl)tetrahydro-2*H*-thiopyran (8b). Isolated as a white amorphous solid (77.5 mg, 0.372 mmol, 74%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 1.82 (2H, app. qd, *J* 12.7, 3.1 Hz), 2.12 (2H, dd, *J* 13.5, 2.8 Hz), 2.47 (1H, tt, *J* 12.1, 3.1 Hz), 2.69 (2H, br d, *J* 13.9 Hz), 2.84 (2H, m), 3.79 (3H, s), 6.85 (2H, d, *J* 8.5 Hz), 7.11 (2H, d, *J* 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 29.4, 35.5, 43.5, 55.3, 113.9, 127.6, 139.2, 158.0; FTIR (υ_{max} cm^{-1}) 2914, 1511, 1245, 1179, 1028, 821; R_f 0.88 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{12}H_{17}OS$ $[M + H]^+$ 209.0995, found 209.0987.

4-(3-Nitrophenyl)tetrahydro-2*H*-thiopyran (8c). Isolated as a white amorphous solid (24.7 mg, 0.111 mmol, 22%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 1.89 (2H, app. qd, *J* 12.7, 3.2 Hz), 2.17 (2H, dd, *J* 13.4, 2.9 Hz), 2.68 (3H, m), 2.86 (2H, td, *J* 13.1, 2.0 Hz), 7.52 (2H, m), 8.07 (1H, t, *J* 2.1 Hz), 8.24 (1H, d, *J* 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 29.0, 34.9, 44.0, 121.9, 123.5, 129.3, 133.1, 148.6; FTIR (υ_{max} cm^{-1}) 2915, 1511, 1246, 1180, 1029, 954, 821; R_f 0.68 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{11}H_{14}NO_2S$ $[M + H]^+$ 224.0740, found 224.0734.

***tert*-Butyl 3-(*p*-tolyl)pyrrolidine-1-carboxylate (9a).** Isolated as a colorless oil (63.0 mg, 0.241 mmol, 48%) according to general procedure C: ^{1}H NMR ($CDCl_3$, 1:1 mixture of rotamers at room temperature) δ 1.48 (4.5H, s), 1.49 (4.5H, s), 1.96 (1H, m), 2.23 (1H, m), 2.33 (3H, s), 3.33 (3H, m), 3.55 (0.5H, br t, *J* 8.7 Hz), 3.65 (0.5H, br t, *J* 8.7 Hz), 3.77 (0.5H, br t, *J* 8.4 Hz), 3.84 (0.5H, m), 7.13 (4H, app. s); ^{13}C NMR ($CDCl_3$) δ 21.0, 28.6, 32.5, 33.5, 43.0, 43.9, 45.7, 46.0, 51.9, 52.7, 79.3, 126.9, 129.3, 136.4, 138.4, 154.6; FTIR (υ_{max} cm^{-1}) 2975, 1693, 1390, 1366, 1159, 1109, 879, 805, 770; R_f 0.91 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{16}H_{23}NO_2Na$ $[M + Na]^+$ 284.1626, found 284.1634.

***tert*-Butyl 3-(4-methoxyphenyl)pyrrolidine-1-carboxylate (9b).** Isolated as a colorless oil (64.2 mg, 0.231 mmol, 46%) according to general procedure C: ^{1}H NMR ($CDCl_3$, 5:4 mixture of rotamers at room temperature) δ 1.47 (5H, s), 1.48 (4H, s), 1.94 (1H, m), 2.21 (1H, m), 3.21 (0.6H, t, *J* 9.9 Hz), 3.28 (1.4H, m), 3.38 (1H, m), 3.54 (0.4H, t, *J* 8.5 Hz), 3.63 (0.6H, t, *J* 8.6 Hz), 3.74 (0.6H, dd, *J* 10.2, 7.8 Hz), 3.79 (3H, s), 3.82 (0.4H, m), 6.86 (2H, d, *J* 8.7 Hz), 7.15 (2H, d, *J* 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 28.6, 32.6, 33.5, 42.6, 43.5, 45.6, 46.0, 52.0, 52.8, 55.3, 79.2, 114.0, 128.0, 133.4, 154.6, 158.4; FTIR (υ_{max} cm^{-1}) 2973, 1690, 1514, 1398, 1245, 1164, 1121, 1033, 828, 770; R_f 0.69 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{16}H_{23}NO_3Na$ $[M + Na]^+$ 300.1576, found 300.1563.

***tert*-Butyl 3-(3-nitrophenyl)pyrrolidine-1-carboxylate (9c).** Isolated as a colorless oil (8.8 mg, 0.0421 mmol, 8%) according to general procedure C: ^{1}H NMR ($CDCl_3$, 1:1 mixture of rotamers at room temperature) δ 1.48 (9H, s), 2.02 (1H, m), 2.33 (1H, br), 3.34 (3H, m), 3.59 (0.5H, br t, *J* 8.4 Hz), 3.67 (0.5H, br t, *J* 9.0 Hz), 3.83 (1H, m), 7.50 (1H, t, *J* 8.2 Hz), 7.56 (1H, d, *J* 7.7 Hz), 8.11 (2H, m); ^{13}C NMR ($CDCl_3$) δ 28.5, 32.4, 33.2, 43.0, 43.9, 45.5, 45.7, 51.7, 52.2, 79.7, 122.0, 122.1, 129.6, 133.3, 143.6, 148.5, 154.4; FTIR (υ_{max} cm^{-1}) 2975, 1688, 1529, 1399, 1346, 1162, 1122, 736; R_f 0.56 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{15}H_{20}N_2O_4Na$ $[M + Na]^+$ 315.1321, found 315.1335.

3-(*p*-Tolyl)tetrahydrofuran (10a). Isolated as a colorless oil (33.0 mg, 0.203 mmol, 41%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 2.01 (1H, dq, *J* 12.3, 8.2 Hz), 2.36 (4H, m), 3.38 (1H, quint., *J* 7.9 Hz), 3.71 (1H, t, *J* 8.1 Hz), 3.93 (1H, td, *J* 8.1, 7.3 Hz), 4.07 (1H, td, *J* 8.3, 4.5 Hz), 4.15 (1H, t, *J* 8.0 Hz), 7.14 (2H, d, *J* 8.4 Hz), 7.16 (2H, d, *J* 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 21.0, 34.7, 44.6, 68.5, 74.7, 127.1, 129.3, 136.1, 139.5; FTIR (υ_{max} cm^{-1}) 2971, 1515, 1055, 811, 770; R_f 0.92 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{11}H_{15}O$ $[M + H]^+$ 163.1117, found 163.1118.

3-(4-Methoxyphenyl)tetrahydrofuran (10b). Isolated as a colorless oil (24.6 mg, 0.138 mmol, 28%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 1.97 (1H, dq, *J* 12.3, 8.2 Hz), 2.34 (1H, dtd, *J* 12.2, 7.7, 4.6 Hz), 3.36 (1H, quint., *J* 7.9 Hz), 3.68 (1H, t, *J* 8.0 Hz), 3.80 (3H, s), 3.91 (1H, q, *J* 7.8 Hz), 4.06 (1H, td, *J* 8.4, 4.5 Hz), 4.12 (1H, t, *J* 8.0 Hz), 6.86 (2H, d, *J* 8.6 Hz), 7.17 (2H, d, *J* 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 34.7, 44.2, 55.3, 68.5, 74.7, 114.0, 128.2, 134.5, 158.2; FTIR (υ_{max} cm^{-1}) 2934, 1512, 1243, 1178, 1033, 827; R_f 0.77 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{11}H_{15}O_2$ $[M + H]^+$ 179.1072, found 179.1076.

3-(3-Nitrophenyl)tetrahydrofuran (10c). Isolated as a colorless oil (8.9 mg, 0.0461 mmol, 9%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 2.03 (1H, dq, *J* 12.5, 7.8 Hz), 2.46 (1H, dtd, *J* 12.6, 7.9, 4.7 Hz), 3.53 (1H, quint., *J* 7.5 Hz), 3.78 (1H, dd, *J* 8.7, 6.7 Hz), 3.95 (1H, q, *J* 8.1 Hz), 4.12 (1H, td, *J* 8.3, 4.6 Hz), 4.16 (1H, dd, *J* 8.6, 7.3 Hz), 7.49 (1H, t, *J* 7.9 Hz), 7.59 (1H, br d, *J* 7.7 Hz, C6), 8.09 (1H, ddd, *J* 8.1, 2.1, 1.0 Hz), 8.12 (1H, t, *J* 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 34.6, 44.6, 68.4, 74.3, 121.7, 122.2, 129.6, 133.5, 145.2, 148.5; FTIR (υ_{max} cm^{-1}) 2935, 1523, 1344, 735, 686; R_f 0.49 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{10}H_{11}NO_3Na$ $[M + Na]^+$ 216.0631, found 216.0626.

***tert*-Butyl 3-(*p*-tolyl)azetidine-1-carboxylate (12a).** Isolated as a colorless oil (80.4 mg, 0.325 mmol, 65%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 2.35 (3H, s), 3.70 (1H, tt, *J* 8.7, 6.2 Hz), 3.96 (2H, dd, *J* 8.4, 6.2 Hz), 4.31 (2H, t, *J* 8.6 Hz), 7.16 (2H, d, *J* 8.4 Hz), 7.20 (2H, d, *J* 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 21.0, 28.5, 33.2, 56.5 (br), 79.5, 126.7, 129.4, 136.6, 139.2, 156.5; FTIR (υ_{max} cm^{-1}) 2970, 1698, 1389, 1128, 811, 772; R_f 0.88 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{15}H_{22}NO_2$ $[M + H]^+$ 248.1645, found 248.1645.

***tert*-Butyl 3-(4-methoxyphenyl)azetidine-1-carboxylate (12b).** Isolated as a colorless oil (80.3 mg, 0.305 mmol, 61%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 1.46 (9H, s), 3.68 (1H, tt, *J* 8.7, 6.1 Hz), 3.80 (3H, s), 3.93 (2H, dd, *J* 8.5, 6.2 Hz), 4.30 (2H, t, *J* 8.6 Hz), 6.88 (2H, d, *J* 8.6 Hz), 7.23 (2H, d, *J* 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 28.4, 32.9, 55.3, 56.8 (br), 79.5, 114.1, 127.8, 134.3, 156.5, 158.6; FTIR (υ_{max} cm^{-1}) 2969, 1697 (s), 1514, 1390, 1246, 1129, 1033, 826; R_f 0.74 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{15}H_{21}NO_3Na$ $[M + Na]^+$ 286.1414, found 286.1402.

***tert*-Butyl 3-(3-nitrophenyl)azetidine-1-carboxylate (12c).** Isolated as a colorless oil (23.1 mg, 0.0830 mmol, 17%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 1.47 (9H, s), 3.84 (1H, tt, *J* 8.6, 5.8 Hz), 3.98 (2H, dd, *J* 8.6, 5.8 Hz), 4.39 (2H, t, *J* 8.7 Hz), 7.54 (1H, t, *J* 7.9 Hz), 7.67 (1H, d, *J* 7.7 Hz), 8.13 (1H, ddd, *J* 8.2, 2.2, 0.9 Hz), 8.17 (1H, t, *J* 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 28.4, 33.2, 56.3 (br), 80.0, 121.9, 122.1, 129.8, 132.9, 144.4, 148.5, 156.3; FTIR (υ_{max} cm^{-1}) 2976, 1697, 1529, 1130, 735, 684; R_f 0.46 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{14}H_{18}N_2O_4Na$ $[M + Na]^+$ 301.1164, found 301.1164.

3-(*p*-Tolyl)oxetane (13a). Isolated as a colorless oil (24.6 mg, 0.166 mmol, 33%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 2.36 (3H, s), 4.21 (1H, m), 4.77 (2H, dd, *J* 6.9, 6.1 Hz), 5.06 (2H, dd, *J* 8.4, 6.1 Hz), 7.19 (2H, d, *J* 7.7 Hz), 7.29 (2H, d, *J* 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.0, 40.0, 79.1, 126.7, 129.4, 136.7, 138.5; FTIR (υ_{max} cm^{-1}) 2961, 1606, 1515, 1116, 980, 810; R_f 0.86 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{10}H_{12}ONa$ $[M + Na]^+$ 171.0780, found 171.0778.

3-(4-Methoxyphenyl)oxetane (13b). Isolated as a colorless oil (35.5 mg, 0.216 mmol, 43%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 3.81 (3H, s), 4.19 (1H, m), 4.75 (2H, dd, *J* 6.8, 6.0 Hz), 5.05 (2H, dd, *J* 8.4, 6.0 Hz), 6.91 (2H, d, *J* 8.7 Hz), 7.33 (2H, d, *J* 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 39.7, 55.3, 79.3, 114.1, 127.9, 133.6, 158.6; FTIR (υ_{max} cm^{-1}) 2957, 1512, 1243, 1178, 977, 911, 826; R_f 0.64 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{10}H_{13}O_2$ $[M + H]^+$ 165.0910, found 165.0909.

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3-(3-Nitrophenyl)oxetane (13c). Isolated as a colorless oil (4.1 mg, 0.0229 mmol, 5%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 4.32 (1H, tt, J 8.3, 6.5 Hz), 4.76 (2H, app. t, J 6.4 Hz), 5.13 (2H, dd, J 8.3, 6.3 Hz), 7.56 (1H, t, J 8.0 Hz), 7.76 (1H, dddd, J 7.7, 1.7, 1.1, 0.6 Hz), 8.14 (1H, ddd, J 8.2, 2.3, 1.1 Hz), 8.25 (1H, t, J 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 40.0, 78.2, 121.9, 122.2, 129.9, 132.9, 143.7, 148.6; FTIR (υ_{max} cm^{-1}) 2966, 1524, 1347, 1161, 978, 735, 683; R_f 0.47 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_9H_9NO_3Na$ $[M + Na]^+$ 202.0475, found 202.0472.

Ethyl 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (16). A solution of bis(pinacolato)diboron (1.59 g, 6.25 mmol, 1.25 equiv), $PdCl_2$(1,1′-Bis(diphenylphosphino)-ferrocene)·CH_2Cl_2 (204 mg, 0.25 mmol, 5 mol %), 1,1′-Bis-(diphenylphosphino)-ferrocene (139 mg, 0.25 mmol, 5 mol %) and KOAc (1.47 g, 15.0 mmol, 3.0 equiv) in 1,4-dioxane (50 mL) was vacuum-argon purged (15 cycles) before addition of ethyl 5-bromo-2-chlorobenzoate (892 μL, 1.32 g, 5.0 mmol, 1.0 equiv) under argon. The mixture was heated to 80 °C for 22 h before being cooled to room temperature and concentrated in vacuo. The resulting residue was purified by flash column chromatography (10% EtOAc/hexane) to give the title compound (1.07 g, 3.45 mmol, 69%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.33 (12H, s), 1.39 (3H, t, J 7.1 Hz), 4.39 (2H, q, J 7.1 Hz), 7.42 (1H, d, J 8.0 Hz), 7.79 (1H, dd, J 8.0, 1.6 Hz), 8.18 (1H, d, J 1.6 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3, 24.8, 61.5, 84.3, 130.2, 130.3, 136.5, 137.3, 138.4, 165.9; FTIR (υ_{max} cm^{-1}) 2979, 1731, 1355, 1280, 1241, 1141, 1096, 852; R_f 0.59 (10% EtOAc/hexane); HRMS (ESI+) calculated for $C_{15}H_{21}BO_4Cl$ $[M + H]^+$ 311.1221, found 311.1233.

(4-Chloro-3-(ethoxycarbonyl)phenyl)boronic acid (3). According to a known procedure,[32] to a suspension of **16** (621 mg, 2.0 mmol, 1.0 equiv) in acetone (4 mL) and water (2 mL) were added NH_4OAc (462 mg, 6.0 mmol, 3.0 equiv) and $NaIO_4$ (462 mg, 6.0 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 19 h before being partitioned between EtOAc (25 mL) and water (25 mL). The aqueous phase was extracted with EtOAc (3 × 25 mL) and dried over $MgSO_4$, and solvents were removed in vacuo to give the title compound (428 mg, 1.87 mmol, 94%) as a white amorphous solid: ^{1}H NMR (DMSO-d_6) δ 1.32 (3H, t, J 7.1 Hz), 4.33 (2H, q, J 7.0 Hz), 7.56 (1H, d, J 8.0 Hz), 7.97 (1H, d, J 8.0 Hz), 8.17 (1H, s); ^{13}C NMR (DMSO-d_6) δ 14.5, 61.7, 130.0, 130.2, 130.4, 133.5, 135.9, 138.1, 166.1; FTIR (υ_{max} cm^{-1}) 3394, 1698, 1286, 1243, 1047, 832, 711, 668; R_f 0.39 (50% EtOAc/hexane); HRMS (ESI+) calculated for $C_9H_{11}BO_4Cl$ $[M + H]^+$ 229.0439, found 229.0440.

***tert*-Butyl 3-(4-chloro-3-(ethoxycarbonyl)phenyl)-azetidine-1-carboxylate (1).** Isolated as a colorless oil (81.9 mg, 0.241 mmol, 48%) according to general procedure C: ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, t, J 6.9 Hz), 1.45 (9H, s), 3.72 (1H, app. tt, J 8.6, 5.9 Hz), 3.92 (2H, dd, J 8.6, 5.9 Hz), 4.33 (2H, t, J 8.7 Hz), 4.39 (2H, q, J 7.1 Hz), 7.36 (1H, dd, J 8.3, 2.3 Hz), 7.41 (1H, d, J 8.3 Hz), 7.70 (1H, d, J 2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2, 28.4, 32.8, 56.4 (br), 61.7, 79.9, 129.6, 130.6, 130.8, 131.4, 132.0, 141.0, 156.3, 165.7; FTIR (υ_{max} cm^{-1}) 2976, 1697, 1390, 1127, 730, 668; R_f 0.75 (30% EtOAc/hexane); HRMS (ESI+) calculated for $C_{17}H_{22}NO_4ClNa$ $[M + Na]^+$ 362.1135, found 362.1135.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Walters, W. P.; Green, J.; Weiss, J. R.; Murcko, M. A. *J. Med. Chem.* **2011**, *54*, 6405−6416.
(2) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780−1824.
(3) Johansson-Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062−5085.
(4) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417−1492.
(5) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.
(6) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1470.
(7) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752−6756.
(8) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340−1341.
(9) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686−3687.
(10) Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788−7789.
(11) Strotman, N. A.; Sommer, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3556−3558.
(12) Vechorkin, O.; Proust, V.; Hu, X. *J. Am. Chem. Soc.* **2009**, *131*, 9756−9766.
(13) Wang, S.; Qian, Q.; Gong, H. *Org. Lett.* **2012**, *14*, 3352−3355.
(14) Deng, H.; Xing, Y.; Xia, C.; Sun, H.; Shen, Q.; Zhang, Y. *Dalton Trans.* **2012**, *41*, 11597−11607.
(15) Luo, R.; Li, K.; Hu, Y.; Tang, W. *Adv. Synth. Catal.* **2013**, *355*, 1297−1302.
(16) Presset, M.; Fleury-Brégeot, N.; Oehlrich, D.; Rombouts, F.; Molander, G. A. *J. Org. Chem.* **2013**, *78*, 4615−4619.
(17) Gonzàlez-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360−5361.
(18) Duncton, M. A. J.; Estiarte, M. A.; Tan, D.; Kaub, C.; O'Mahony, D. J. R.; Johnson, R. J.; Cox, M.; Edwards, W. T.; Wan, M.; Kincaid, J.; Kelly, M. G. *Org. Lett.* **2008**, *10*, 3259−3262.
(19) Mesaros, E. F.; Thieu, T. V.; Wells, G. J.; Zificsak, C. A.; Wagner, J. C.; Breslin, H. J.; Tripathy, R.; Diebold, J. L.; McHugh, R. J.; Wohler, A. T.; Quail, M. R.; Wan, W.; Lu, L.; Huang, Z.; Albom, M. S.; Angeles, T. S.; Wells-Knecht, K. J.; Aimone, L. D.; Cheng, M.; Ator, M. A.; Ott, G. R.; Dorsey, B. D. *J. Med. Chem.* **2012**, *55*, 115−125.
(20) Ghosh, S.; Kinney, W. A.; Gauthier, D. A.; Lawson, E. C.; Hudlicky, T.; Maryanoff, B. E. *Can. J. Chem.* **2006**, *84*, 555−560.
(21) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Nat. Chem.* **2009**, *1*, 494−499.
(22) The metal-free coupling reported by Barluenga *et al.* has also been performed in a continuous flow system on similar substrates: Kupracz, L.; Kirschning, A. *J. Flow Chem.* **2013**, *3*, 11−16.
(23) Nakagawa, S.; Bainbridge, K. A.; Butcher, K.; Ellis, D.; Klute, W.; Ryckmans, T. *ChemMedChem* **2012**, *7*, 233−236.
(24) Sha, Q.; Wei, Y. *Tetrahedron* **2013**, *69*, 3829−3835.
(25) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 17096−17098.
(26) Peng, C.; Zhang, W.; Yan, G.; Wang, J. *Org. Lett.* **2009**, *11*, 1667−1670.
(27) Barluenga, J.; Valdés, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 7486−7500.
(28) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.
(29) 4-(Dimethylamino)benzenesulfonyl chloride starting material for this reaction was prepared by a known procedure: Binisti, C.; Assogba, L.; Touboul, E.; Mounier, C.; Huet, J.; Ombetta, J. -E.; Dong,

C. J.; Redeuilh, C.; Heymans, F.; Godfroid, J. -J. *Eur. J. Med. Chem.* **2001**, *36*, 809−828.
(30) 2-Furansulfonyl chloride starting material for this reaction was prepared by a known procedure: Chan, M. F.; Kogan, T.; Verner, E. J.; Kois, A.; Balaji, V. N. Biphenylsulfonamides and Derivatives Thereof that Modulate the Activity of Endothelin. U.S. Patent US2002095041, July 18, 2002.
(31) 3-Thietanone starting material for this reaction was prepared by a known procedure: Burkhard, J. A.; Guérot, C.; Knust, H.; Roger-Evans, M.; Carreira, E. M. *Org. Lett.* **2010**, *12*, 1944−1947.
(32) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860−2863.