JOC Notes

Microwave-Assisted Preparation of Fused Bicyclic Heteroaryl Boronates: Application in One-Pot Suzuki Couplings

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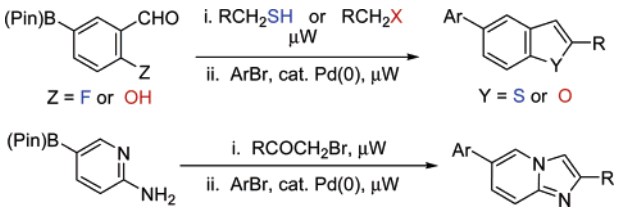
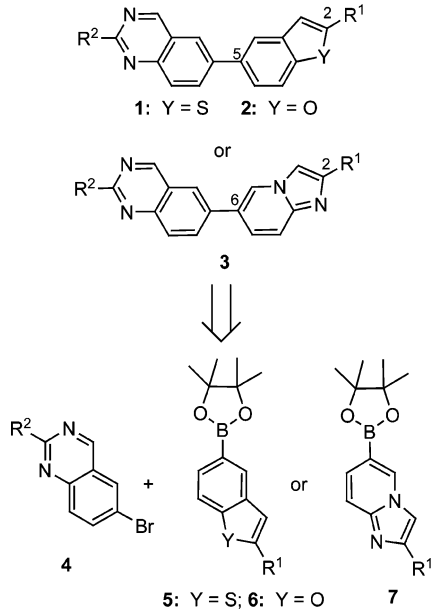


The rapid and efficient synthesis of various disubstituted 5,6-fused heterocycles using a microwave-assisted one-pot cyclization−Suzuki coupling approach is described. This work highlights the tolerance of the boronic ester functional group to a variety of reaction conditions and the utility of functionalized boronates as penultimate intermediates in the synthesis of diverse compound libraries.

The broad utility of Suzuki−Miyaura coupling reactions is widely appreciated in the synthetic community.[1] Consequently, the establishment of new routes to functionalized boronic acid and boronic ester precursors is an ongoing effort in several research groups.[2] Substituted 5,6-fused heterocycles can be found in many types of synthetic and naturally occurring medicinal substances.[3] The exploration of convenient synthetic routes to these compounds is a priority in drug discovery and the benefits of microwave-assisted approaches are becoming increasingly evident.[4]

To expand the scope of our small molecule drug discovery programs, we wished to identify practical and general microwave-assisted synthetic routes to access a variety of 2,5-disubstituted benzo[*b*]thiophenes,[5] benzo[*b*]furans,[6] and 2,6-disubstituted imidazo[1,2-*a*]pyridines,[7] exemplified by quinazolines of general structures **1**−**3**. We sought divergent routes that would allow for easy variation of the aryl group at C5/C6 and the R^1 group at C2. Thus, we set out to prepare small libraries of 2-substituted (benzo[*b*]thiophen-5-yl)boronates (**5**), (benzo[*b*]furan-5-yl)boronates (**6**), and imidazo[1,2-*a*]pyridine-6-boronates (**7**), each of which could be coupled under Suzuki conditions to a variety of bromoquinazolines (**4**) in order to obtain a diverse set of target libraries **1**−**3** (Scheme 1). An alternative strategy to libraries **1**−**3** would involve reversing the Suzuki coupling partners. The drawback of this route lies in the requirement for the preparation, purification and storage of multiple quinazoline boronates derived from bromides **4**. In our hands, such derivatives were difficult to isolate owing to their insolubility in organic solvents and instability to silica gel chromatography. Also, this approach would require that R^2 be compatible with the reaction conditions necessary for the formation of the boronate from **4**.

SCHEME 1. Retrosynthetic Routes to Target Libraries 1−3



Our initial efforts were focused on identifying convenient routes to boronates **5** or **6** toward target libraries **1** and **2**. The most obvious synthetic route to compounds such as **6** involves the conversion of 5-halobenzofurans (**9**) to boronic esters or acids using Pd(0) catalysis or lithiation−substitution (Scheme 2). A major limitation with this approach is that R^1 must be compatible with the reaction conditions required for the formation of the boronate. Furthermore, for library generation or

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† University of Pennsylvania.

(1) (a) For a review, see: Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (b) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419−2440.

(2) (a) Zenk, R.; Partzsch, S.; *Chimica Oggi* **2003**, *21*, 70−73. (b) Tyrrell, E.; Brookes, P. *Synthesis* **2003**, *4*, 469−483.

(3) (a) Jones, G., Ed. *Comprehensive Heterocyclic Chemistry. II. Volume 8: Fused Five-and Six-Membered Rings with Ring Junction Heteroatom*; Pergamon: Oxford, 1996. (b) Ramsden, C. A., Ed. *Comprehensive Heterocyclic Chemistry. II. Volume 7: Fused Five-and Six-Membered Rings without Ring Junction Heteroatom*; Pergamon: Oxford, 1996.

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(5) For a review on the synthesis of benzo[*b*]thiophenes, see: Rayner, C. M.; Graham, M. A. *Sci. Synth.* **2001**, *10*, 155−184.

(6) For a review on the synthesis of benzo[*b*]furans, see: Dell, C. P. *Sci. Synth.* **2001**, *10*, 11−86.

(7) For a review on the synthesis of azaindolizines (including imidazopyridines), see: Hajos, G.; Riedl, Z. *Sci. Synth.* **2002**, *12*, 613−678.

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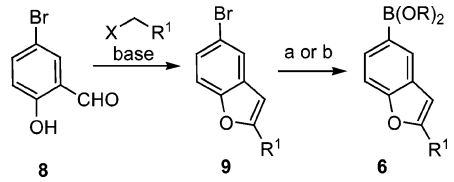
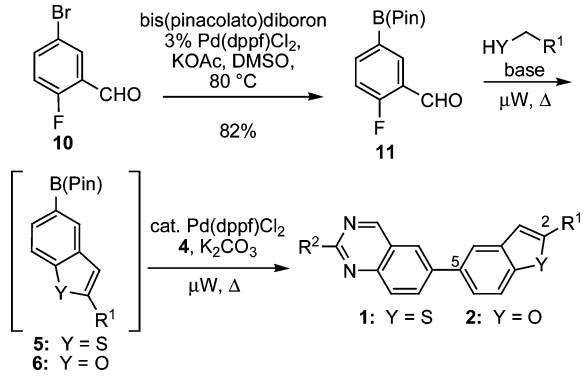
SCHEME 2. Common Route to (Benzo[*b*]furan-5-yl)boronates[a]



[a] Key: (a) (i) BuLi, (ii) $B(OMe)_3$, (iii) HCl; (b) cat. Pd(0), bis(pinacolato)diboron, KOAc, Δ.

SCHEME 3. Route A to Target Libraries 1 and 2



medicinal chemistry applications, it would be preferable to introduce the diversity element R^1 later in the reaction sequence. Recently, derivatization of functionalized arylboronic acids has been accomplished using a solid-phase resin immobilization strategy.[8] Similarly, there have been several reports of derivatization of functionalized arylboronic esters.[9] The most recently developed method for the formation of 2-substituted (benzo[*b*]-furan-5-yl)boronate esters **6** from functionalized aryl boronic esters is lengthy and low yielding.[9c]

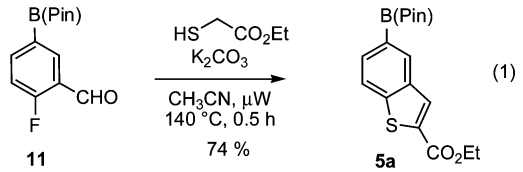
We first examined the reaction of α-activated alcohols or thiols with 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (**11**) followed by coupling of the boronate intermediates **5** or **6** with 6-bromoquinazolin-2-amine (**4a**, $R^2 = NH_2$) (route A, Scheme 3). Although **11** can be obtained by the reaction of pinacol and 4-fluoro-3-formylphenylboronic acid as previously demonstrated,[9a] we prepared **11** in 82% yield directly from commercially available **10** using the method of Miyaura et al.[10] For formation of **5** or **6**, the desired transformation is an S_NAr with concomitant condensation and cyclization. The activating group R^1 on the alcohol/thiol should be aryl, ester, amide, NO_2, CN, etc., such that the basicity and nucleophilicity of the alcohol/thiol is somewhat attenuated and the methylene hydrogens are rendered acidic. Although route A is an atypical method for the preparation of benzofurans, similar methodology has been employed in the prepartion of benzo[*b*]thiophenes.[11,12] Furthermore, **11** has been used as a substrate for nucleophilic aromatic substitutions.[9a]

TABLE 1. One-Pot Preparation of 5 and Conversion to 1: (Step 1)[a] 11 + $HSCH_2R^1$ (Step 2)[b] 5 + 4a

entry	1	R^1	T[b] (°C)	t[b] (h)	% yield
1	**1a**	CO_2Et	90	0.5	57
2	**1b**	CO_2i-Pr	90	1.0	60
3[c]	**1c**	CO_2H	95	1.0	24
4[d]	**1d**	CONHPh	90	1.0	41
5	**1e**	CONHMe	95	1.5	17

[a] Step 1: 1.0 equiv of **11**, 1.1 equiv of $HSCH_2R^1$, 1.0 equiv of K_2CO_3, μW, CH_3CN, 140 °C, 0.5 h. [b] Step 2: 0.8 equiv of **4a**, 0.13 equiv of $Pd(dppf)Cl_2$, 1.6 equiv of K_2CO_3, H_2O/CH_3CN (1:3); μW, T and t as reported. [c] Step 1: $CH_3CN/EtOH$ (1:1), 1 h. Step 2: 1.0 equiv of K_2CO_3, 0.3 equiv of $Pd(dppf)Cl_2$, $H_2O/CH_3CN/EtOH$ (1:2:1). [d] Step 2: 1.5 equiv of **4a**, 0.3 equiv of $Pd(dppf)Cl_2$.

The reaction of **11** and ethyl mercaptoacetate was examined in the microwave using a variety of organic solvents and bases. Optimal conditions for the preparation of 2-ethylcarboxylate-(benzo[*b*]thiphen-5-yl)boronate (**5a**) in 74% yield were quickly identified (eq 1).



We then determined that crude **5a**, prepared in this manner, can be *used directly without workup, in a subsequent microwave-assisted Suzuki coupling* to bromoquinazoline **4a**. Likewise, 2-mercaptoacetic acid and derivatives were condensed with **11**, and the resulting crude boronates were coupled with **4a** to prepare target compounds **1a**−**e** (Table 1). Attempts to condense benzylmercaptan boronates (R^1 = Ar) with **11** were unsuccessful.[13] In these cases, the S_NAr intermediates, observed by LCMS, were reluctant to cyclize to the benzothiophenes, presumably because of the decreased acidity of the α-protons.

Despite numerous attempts, no conditions were identified to prepare the analogous 2-ethyl carboxylate−(benzo[*b*]furan-5-yl)-boronate intermediate **6a** in acceptable yield from **11** and ethyl 2-hydroxyacetate.[14] As anticipated, the required S_NAr reaction is significantly slower with the alkoxide nucleophile than with the thiolate. Route A for target library **2** was therefore abandoned.

Next, we investigated the reaction of α-activated halides with 2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (**12**) (route B, Scheme 4). While this method is commonly employed in the synthesis of 2-substituted benzo-[*b*]furans,[15] it has not been demonstrated in the presence of a

(8) Gravel, M.; Thompson, M. Z.; Berube, C.; Hall, D. G. *J. Org. Chem.* **2002**, *67*, 3−15.

(9) (a) Holland, R.; Spencer, J.; Deadman, J. J. *Synthesis* **2002**, 2379−2382. (b) Spencer, J.; Burd, A.; Goodwin, C. A.; Metrette, S. A. M.; Scully, M. F.; Adatia, T.; Deadman, J. J. *Tetrahedron* **2002**, *58*, 1551−1556. (c) McKierman, G. J.; Hartley, R. C. *Org. Lett.* **2003**, *5*, 4389−4392. (d) Bois-Choussy, M.; Cristau, P.; Zhu, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4238−4241. (e) Kaiser, M.; Siciliano, C.; Assfalg-Machleidt, I.; Groll, M.; Milbradt, A. G.; Moroder, L. *Org. Lett.* **2003**, *5*, 3435−3437. (f) Schulz, M. J.; Coats, S. J.; Hlasta, D. J. *Org. Lett.* **2004**, 6, 3265−3268. (g) Lautens, M.; Mancuso, J. *J. Org. Chem.* **2004**, *69*, 3478−3487. (h) Moore, J. E.; York, M.; Harrity, J. P. A. *Synlett* **2005**, 860−862. (i) Moore, J. E.; Davies, M. W.; Goodenough, K. M.; Wybrow, R. A. J.; York, M.; Johnson, C. N.; Harrity, J. P. A. *Tetrahedron* **2005**, *61*, 6706−6714. (j) Zhang, H.; Vogels, C. M.; Wheaton, S. L.; Baerlocher, F. J.; Decken, A.; Westcott, S. A. *Synthesis* **2005**, 2739−2743.

(10) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508−7510.

(11) (a) Patel, M.; Rohde, J. J.; Kolasa, T. *Tetrahedron Lett.* **2003**, *44*, 6665−6667. (b) Bridges, A. J.; Lee, A.; Schwartz, C. E.; Towle, M. J.; Littlefield, B. A. *Bioorg. Med. Chem.* **1993**, *1*, 403−410. (c) Bridges, A. J.; Lee, A.; Maduakor, E. C.; Schwartz, C. E. *Tetrahedron Lett.* **1992**, *33*, 7499−7502. (d) Osuga, H.; Suzuki, H.; Tanaka, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 891−897.

(12) To the best of our knowledge, there have been no prior reports of this cyclization in the presence of boronic ester or acid functionality.

(13) Conditions examined: 4-chloro or 4-methoxybenzylmercaptan, various bases, μW, Δ.

(14) Best conditions identified: DMA, K_2CO_3, MS 4Å, 130 °C, 30 min, μW.; 50% conversion.

SCHEME 4. Route B to Target Library 2

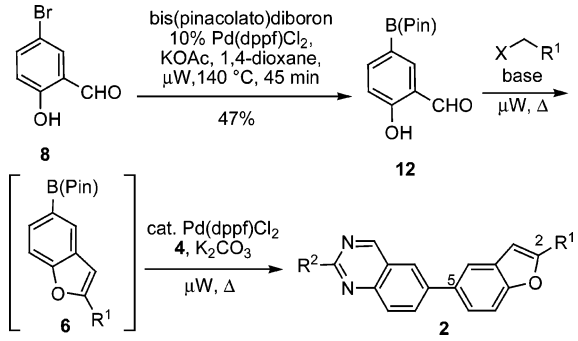


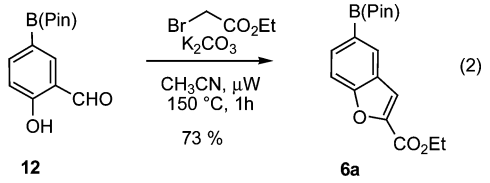
TABLE 2. One-Pot Preparation of 6 and Conversion to 2: (Step 1)[a] 12 + XCH_2R^1 (Step 2)[b] 6 + 4a

entry	2	R^1	X	T[a] (°C)	% yield
1	**2a**	CO_2Et	Br	150	33
2	**2b**	CONHPh	Cl	140	40
3	**2c**	CO(morpholine)	Cl	140	55
4	**2d**	COPh	Br	150	74
5	**2e**	CO*t*-Bu	Br	150	72

[a] Step 1: 1.0 equiv of **12**, 1.1 equiv of XCH_2R^1, 2.0 equiv of K_2CO_3, CH_3CN, μW, T as reported, 1 h. [b] Step 2: 0.8 equiv of **4a**, 0.13 equiv of $Pd(dppf)Cl_2$, 1.6 equiv of K_2CO_3, H_2O/CH_3CN (1:3); μW, 90 °C, 0.5 h.

boronic ester functionality. Microwave conditions for the one-step preparation of **12** from **8** were rapidly developed. Previously reported conditions for the synthesis of **12** from **8** involve a three-step protecting group strategy.[9c]

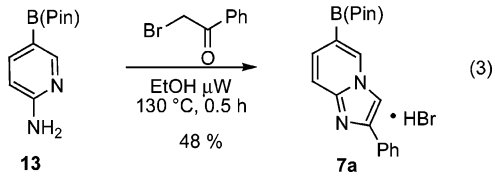
The reaction of **12** and ethyl 2-bromoacetate was examined in the microwave using a variety of organic solvents and bases. Optimal conditions for the preparation of 2-ethyl carboxylate−(benzo[*b*]furan-5-yl)boronate (**6a**) in 73% yield were identified (eq 2).



As observed for the benzothiophene series, crude **6a**, prepared in this manner, can be *used directly without workup, in a subsequent microwave-assisted Suzuki coupling* to bromoquinazoline **4a**. A brief substrate scope analysis of this one-pot cyclization−Suzuki coupling protocol (Table 2) served to validate route B as a suitable strategy to access target library **2**.

Having met with success in the microwave-assisted preparation of benzothiophenes **1** and benzofurans **2**, we set out to extend the methodology and target compound libraries to include quinazoline imidazopyridines of general structure **3** via route C (Scheme 5).

Optimal conditions for the microwave preparation of 2-phenylimidazo[1,2-*a*]pyridine 6-boronate (**7a**) from **13** and 2-bromo-1-phenylethanone were identified (eq 3).[12]



SCHEME 5. Route C to Target Library 3

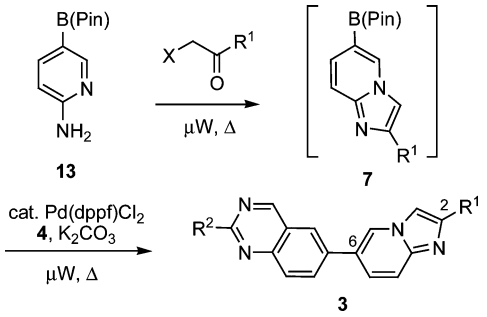


TABLE 3. One-Pot Preparation of 7 and Conversion to 3: (Step 1)[a] 13 + $BrCH_2COR^1$ (Step 2)[b] 7 + 4a

entry	3	R^1	% yield
1	**3a**	Ph	26
2	**3b**	2-OMe-C_6H_4	43
3	**3c**	3-OMe-C_6H_4	42
4	**3d**	4-OMe-C_6H_4	36
5	**3e**	3-thiophene	50
6	**3f**	5-benzo[*d*][1,3]dioxole	27
7	**3g**	Et	26
8	**3h**	*t*-Bu	54

[a] Step 1: 1.0 equiv of **13**, 1.1 equiv of $BrCH_2COR^1$, EtOH, μW, 130 °C, 0.5 h. [b] Step 2: 0.8 equiv of **4a**, 0.13 equiv of $Pd(dppf)Cl_2$, 3.0−3.6 equiv of K_2CO_3, H_2O/EtOH (1:3); μW, 90 °C, 0.5 h.

General conditions for the one-pot, two-step cyclization−Suzuki coupling to access disubstituted imidazopyridines of target library **3** were developed in short order (Table 3).

Further work is underway to extend target libraries **1**−**3** and to employ our microwave-assisted one-pot cyclization−Suzuki approach in the synthesis of other disubstituted 5,6- and 6,6-fused heterocycles. This work highlights the tolerance of the boronic ester functional group to a variety of reaction conditions. Owing to the wealth of commercially available aryl halides, these methods should allow for the rapid preparation of other modular target libraries from a single commercial or readily available aryl boronate building block.

Experimental Section

Ethyl 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzo-[*b*]thiophene-2-carboxylate (5a). To a 10−20 mL microwave reaction vessel were added **11** (0.500 g, 2.00 mmol), ethyl 2-mercaptoacetate (0.241 mL, 2.20 mmol), K_2CO_3 (0.276 g, 2.00 mmol), and CH_3CN (5.0 mL). The vessel was sealed, and the system was purged with N_2. The mixture was heated in the microwave for 30 min at 140 °C and then allowed to cool to room temperature, filtered, and concentrated. The crude product was purified by MPLC (SiO_2, eluent: 100% CH_2Cl_2) to afford the title compound (0.492 g, 1.48 mmol, 74%) as an off-white solid: LCMS (ESI, pos ion) *m*/*z* 333.1 [M + 1]; HRMS calcd for $[C_{17}H_{22}BO_4S]^+$ 333.13264, found 333.13335; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.33 (s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 4.42 (q, J = 8.0 Hz, 2H), 1.40 (t, J = 8.0 Hz, 3H), 1.39 (s, 12H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.9, 144.1, 138.3, 133.1,

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132.8, 132.0, 131.1, 122.5, 83.9, 61.5, 24.7, 14.1 (*C−B signal not observed up to 40 mg/mL*).

Ethyl 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-2-carboxylate (6a). To a 10−20 mL microwave reaction vessel were added **12** (0.200 g, 0.806 mmol), ethyl bromoacetate (0.098 mL, 0.886 mmol), K_2CO_3 (0.223 g, 1.61 mmol), and CH_3CN (2.0 mL). The vessel was sealed, and the system was purged with N_2. The mixture was heated in the microwave for 60 min at 150 °C and then allowed to cool to room temperature, transferred to round-bottom flask with CH_3CN, and concentrated. The crude product was purified by MPLC (SiO_2, eluent: 100% CH_2Cl_2) to afford the title compound (0.187 g, 0.590 mmol, 73%) as an off-white solid: LCMS (ESI, pos ion) *m*/*z* 317.0 [M + 1]; HRMS calcd for $[C_{17}H_{22}BO_5]^+$ 317.15548, found 317.15580; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 7.85 (s, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 4.43 (q, J = 8.0 Hz, 2H), 1.38 (t, J = 8.0 Hz, 3H), 1.38 (s, 12H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.6, 156.9, 145.3, 133.5, 130.5, 126.6, 114.2, 111.7, 83.8, 61.3, 24.7, 14.1.

2-Phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*H*-imidazo[1,2-*a*]pyridine Hydrobromide (7a). To a 10−20 mL microwave reaction vessel were added **13** (0.200 g, 0.909 mmol), 2-bromoacetophenone (0.199 g, 1.00 mmol), and EtOH (2.0 mL). The vessel was sealed, and the system was purged with N_2. The mixture was heated in the microwave for 30 min at 130 °C. After cooling to room temperature, the precipitate was collected using a membrane Buchner filtration apparatus and washed with EtOH to afford the title compound (0.177 g, 0.440 mmol, 48%) as a white solid: HPLC complete hydrolysis to boronic acid on LC column, 99.4%; LCMS (ESI, pos ion) complete hydrolysis to boronic acid on LC column, *m*/*z* 239.1 [M + 1]; HRMS calcd for $[C_{19}H_{22}BN_2O_2]^+$ 321.17688, found 321.17792; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.88 (s, 1H), 8.06−8.03 (m, 4H), 7.72−7.64 (m, 4H), 1.45 (s, 12H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 141.2, 136.4, 135.9, 134.9, 130.4, 129.5, 126.6, 126.2, 112.0, 111.2, 84.8, 73.5, 24.7.

General Method A: Preparation of Benzothiophene Quinazolines (1). To a 10−20 mL microwave reaction vessel were added **11** (0.200 g, 0.800 mmol), the *thiol* (0.880 mmol), K_2CO_3 (0.111 g, 0.800 mmol), and CH_3CN (2.0 mL). The vessel was sealed, and the system was purged with N_2. The mixture was heated in the microwave for 30 min at 140 °C then cooled to room temperature and unsealed. To the reaction vessel were added **4a** (0.149 g, 0.667 mmol), Pd(dppf)Cl_2 (0.082 g, 0.100 mmol), K_2CO_3 (0.184 g, 1.33 mmol), CH_3CN (2.0 mL), and water (1.3 mL). The vessel was sealed, and the system was purged with N_2. The mixture was heated in the microwave for 0.5−1.5 h at 90 °C and then allowed to cool to room temperature, transferred to a round-bottom flask with CH_3CN, and concentrated. The initial crude product was first purified by a MeOH wash. The solid was then further purified by MPLC (SiO_2, gradient eluent: 20 to 40% 90:10:1 (CH_2Cl_2/CH_3OH/NH_4OH) in CH_2Cl_2).

General Method B: Preparation of Benzofuran Quinazolines (2). To a 10−20 mL microwave reaction vessel were added **12** (0.200 g, 0.806 mmol), the *halide* (0.886 mmol), K_2CO_3 (0.223 g, 1.61 mmol), and CH_3CN (2.0 mL). The vessel was sealed, and the system was purged with N_2. The mixture was heated in the microwave for 1 h at 140−150 °C and then cooled to room temperature and unsealed. To the reaction vessel were added **4a** (0.150 g, 0.670 mmol), Pd(dppf)Cl_2 (0.082 g, 0.101 mmol), K_2CO_3 (0.185 g, 1.34 mmol), CH_3CN (2.0 mL), and water (1.3 mL). The vessel was sealed, and the system was purged with N_2. The mixture was heated in the microwave for 30 min at 90 °C then allowed to cool to room temperature, transferred to a round-bottom flask with CH_3CN, and concentrated. The initial crude product was first purified by a CH_3OH wash. The solid was then further purified by MPLC (SiO_2, gradient 0 to 40% 90:10:1 (CH_2Cl_2/CH_3OH/NH_4OH) in CH_2Cl_2).

General Method C: Preparation of Imidazopyridine Quinazolines (3). To a 10−20 mL microwave reaction vessel were added **13** (0.200 g, 0.909 mmol), the *bromo ketone* (1.00 mmol), and EtOH (2.0 mL). The vessel was sealed, and the system was purged with N_2. The mixture was heated in the microwave for 30 min at 130 °C and then cooled to room temperature and unsealed. To the reaction vessel were added **4a** (0.170 g, 0.758 mmol), Pd(dppf)Cl_2 (0.093 g, 0.114 mmol), K_2CO_3 (0.356 g, 2.58 mmol), EtOH (2.0 mL), and water (1.3 mL). The vessel was sealed, and the system was purged with N_2. The mixture was heated in the microwave for 30 min at 90 °C then allowed to cool to room temperature, transferred to a round-bottom flask with EtOH, and concentrated. The initial crude product was first purified by a CH_3OH wash. The solid was then further purified by MPLC (SiO_2, gradient eluent: 20 to 40% 90:10:1 (CH_2Cl_2/CH_3OH/NH_4OH) in CH_2Cl_2).

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Supporting Information Available: General experimental considerations. New methods for preparing **4a**, **11**, and **12**. Experimental details and analytical data for libraries **1**−**3**. ^{1}H and ^{13}C NMR spectral data of boronates **5a**, **6a**, and **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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