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RESEARCH ARTICLE

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Microwave-Mediated Synthesis of an Arylboronate Library

John Spencer,*[,†] Christine B. Baltus,[†] Hiren Patel,[†] Neil J. Press,[‡] Samantha K. Callear,[§] Louise Male,[§] and Simon J. Coles[§]

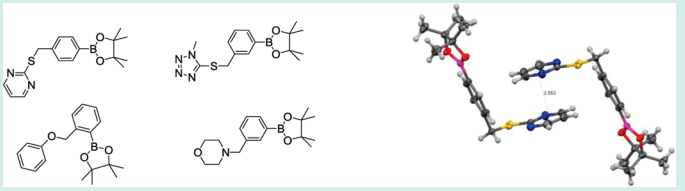
[†]School of Science at Medway, University of Greenwich, Chatham, ME4 4TB, U.K.

[‡]Novartis Pharmaceuticals U.K., Horsham, Sussex, RH12 5AB, U.K.

[§]UK National Crystallography Service, School of Chemistry, University of Southampton, Highfield, Southampton. SO17 1BJ, U.K.

Supporting Information

ABSTRACT: A series of arylboronates has been synthesized from the reaction of 2-(2-, (3-, or (4-(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **1**{*1*−*3*} respectively with a range of N-, S-, and O-nucleophiles, using microwave-mediated chemistry. For the synthesis of N- and S-substituted boronates, a supported base, PS-NMM, was employed, and many reactions were complete within 15 min. With O-nucleophiles, a mixture of tetrabutylammonium bromide, potassium carbonate, and sodium hydroxide was employed. The resulting aminomethyl, mercaptomethyl, or alkoxy-/phenoxymethyl-arylboronates were subjected to microwave-mediated Suzuki Miyaura coupling reactions to afford a range of biaryls in moderate to good yields. The X-ray structures of five boronates were determined.



KEYWORDS: Suzuki coupling, microwave, boronic acid, nucleophilic substitution, biaryls, supported reagents

INTRODUCTION

The biaryl motif is found in many natural and synthetic products and as a privileged scaffold in medicinal chemistry, notably in a variety of inhibitors of enzymes, transporter proteins, and GPCR ligands as well as in herbicides,[1] fungicides,[2] chiral ligands in catalysis,[3] liquid crystals,[4] and novel materials (organic conductors, organic electric wires) (Figure 1).[5−7]

The palladium-catalyzed Suzuki−Miyaura (SM) coupling reaction is one of the most important and efficient strategies for the construction of biaryls. This reaction involves the coupling of organic halides, typically a bromide with organoboron compounds, in the presence of a base and a catalytic amount of palladium complex.[8] Arylboronic acids are often synthesized by a low-temperature transmetalation reaction and can be difficult to modify or isolate. They are often purchased (many are expensive) for use in SM couplings, which limits the scope of the parallel synthetic process.[8]

We[9a,b] and others[9c] have advocated the deployment of pinacol-ester-protected arylboronic acids (ArBPin) **1** in biaryl synthesis, given their ease of synthesis, purification, and stability compared with their acid precursors. Moreover, **1** can be functionalized, in parallel, by the use of a simple S_N2 reaction with S- and N-nucleophiles, which can lead to a variety of analogs **3**. By introducing a high degree of diversity on the ArBPin coupling partner at an early stage,[9a,10] not only is the scope of the synthetic process increased and the range of biphenyls **5** to be synthesized widened, but also the ArBPin compounds may have interesting structural properties in their own right or applications such as enzyme inhibitors or in molecular recognition (Scheme 1).[8,11]

Our previously published preliminary attempted SM coupling reactions on a few analogs **3** were unsuccessful, yielding protodeboronated species,[9a] although we have recently found that the use of MAOS (microwave assisted organic synthesis) can lead to biaryl compounds,[12d] notably employing literature conditions.[12] The aim of the current study was to extend the synthetic scope of the S_N2 reaction leading to a library of ArBPin using a variety of N-, S-, and O-nucleophiles and to investigate SM couplings to afford biphenyl products.

RESULTS AND DISCUSSION

The S_N2 reaction of the pinacol ester **1**{*1*} with a piperazine derivative **2**{*1*} was initially investigated with a view to reducing the reaction time to minutes for it to be amenable to parallel synthesis: previously, **1**{*1*} was found to react at room temperature overnight with S-nucleophiles or at reflux for several hours with N-nucleophiles.[9a] For this to be feasible, we attempted microwave-mediated reactions, and using a rapid screen, the best results were obtained when a supported base was employed as base (PS-NMM) as opposed to potassium carbonate or excess nucleophile. When required, supported scavengers, PS-trisamine and PS-isocyanate, were used to remove unreacted bromide or amine, respectively, and in general, yields of product

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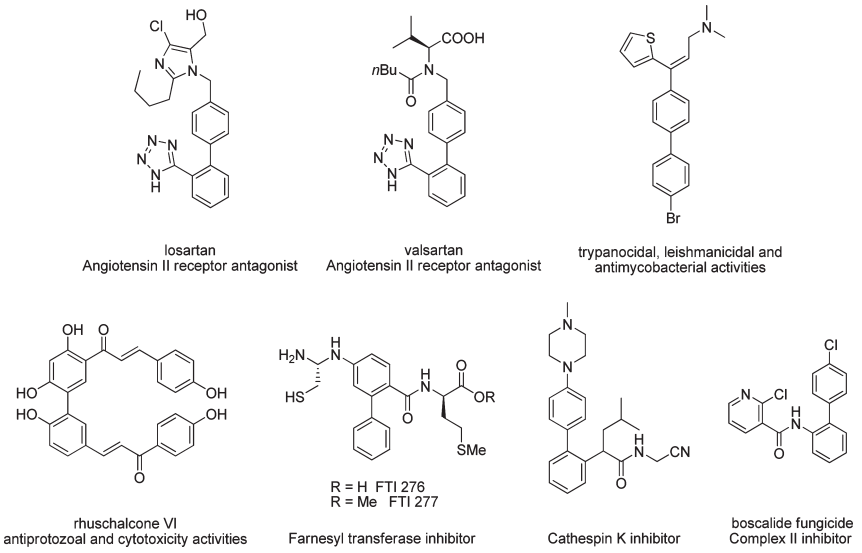
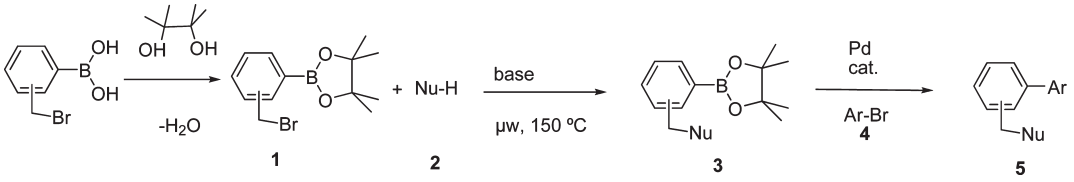


Figure 1. Examples of important biologically active biphenyls.

Scheme 1. Boronate and Biaryl Synthesis



were good to excellent (Table 1, Figure 2). In one case, we were able to react a protected valine analogue (Table 1, entry 15) to yield a precursor to valsartan (vide supra). The reaction of other primary amines, including benzylamine as well as tautomerizable heterocycles such as imidazoles, often led to a mixture of products, presumed to result from mono- or disubstitution reactions, and these were not investigated further in the present study.

Next, we focused our attention to thiols as nucleophiles. Hence, heteroaromatic thiols, such as 2-mercaptopyrimidine, afforded the thioether derivatives **3**{*2,8*} and **3**{*3,8*} in excellent yields using the standard conditions, although in some cases, reaction times were slightly longer; cooled reaction mixtures were assessed by TLC after 15 or 30 min reaction time, and if incomplete, the reaction was extended an additional 15−30 min (see Table 1). Aliphatic thiols were found to be unreactive when employing a supported base; however, when treated with sodium hydride prior to the microwave mediated reaction, an excellent yield of thioether **3**{*2,13*} was recorded (Figure 3). Sodium thiomethoxide proved to be an effective nucleophile in the synthesis of **3**{*1,12*} and **3**{*3,12*}.

The use of modified literature conditions enabled us to synthesize ether containing boronates.[13] Sodium hydride was effective as base, although a combination of potassium carbonate, sodium hydroxide, and tetrabutylammonium bromide gave moderate to good yields; for example, **3**{*3,16*} and **3**{*3,14*}. Limited success was achieved with an aliphatic alcohol as nucleophile **3**{*3,17*}.

To investigate the structures of the arylboronates in the solid state, X-ray structure determinations on compounds **1**{*2*}, **3**{*2,10*}, **3**{*3,8*}, **3**{*1,6*}, and **3**{*3,3*} were carried out and are shown in Figure 4 and in Figure S1 in the Supporting Information.

The geometry of the arylboronate rings in all five molecules is very similar (Table S2 of the Supporting Information). The rings are twisted in every case, with the angle between the least-squares planes drawn through atoms B1, O2, and O3 and those drawn through atoms O2, C3 and C4 ranging from 21.4° to 24.5° (Table S2). In three out of five cases, **1**{*2*}, **3**{*2,10*}, and **3**{*3,3*}, the least-squares plane drawn through atoms B1, O2, O3, and C10 is almost parallel to the plane of the phenyl ring C10−C15, with the angle between the least-squares planes ranging from 4.2° to 5.0° (Table S2). This angle is larger in structures **3**{*1,6*} and **3**{*3,8*}: 21.3° and 16.3°, respectively.

Structure **3**{*1,6*} has two substituents of the phenyl ring that are in ortho positions, and it is thought that the steric hindrance caused by this configuration is the reason for the twisting of the plane of the phenyl ring away from the B1, O2, O3, C10 plane. Structure **3**{*3,8*} is the only one of the five structures in which a $\pi-\pi$ stacking interaction is formed, with the distance between the least-squares planes drawn through the two pyrimidine rings (C18, C20−C22, N19, N23) involved being 3.6 Å (see Figure S1, Supporting Information).

SUZUKI COUPLINGS

Selected members of the arylboronate library were subjected to SM couplings under microwave conditions. Good to excellent yields were obtained for the coupling of *meta*-and *para*-ArBPin derivatives. Excellent yields were observed for aryl halide coupling

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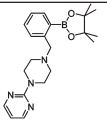
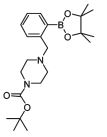
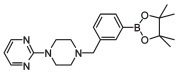
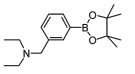
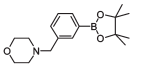
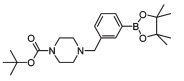
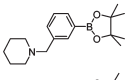
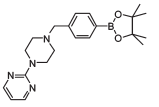
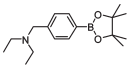
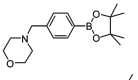
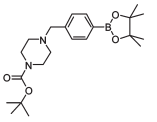
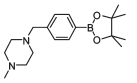
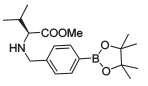
Table 1. Amine-Substituted Arylboronates

Entry	NuH **2**	Time (min)	Product **3**	IsolatedYield (%)
1	*{1}*	15		100
2	*{2}*	15		63
3	*{3}*	15		100
4	*{6}*	15		100
5	*{1}*	15		100
6	*{2}*	15		100
7	*{3}*	15		98
8	*{6}*	15		75
9	*{4}*	30		100
10	*{1}*	30		93
11	*{2}*	15		100
12	*{3}*	40		99
13	*{6}*	45		95
14	*{5}*	35		100
15[b]	*{7}*	120		72

[a] Microwave, PS- NMM base. [b] Two equivalents of (L)-Val(OMe), 140 °C.

partners substituted with electron-withdrawing groups (e.g. **5**{*2,3,4*}), as opposed to moderate yields for aryl halides substituted with electron-rich groups (e.g. 37% yield obtained for **5**{*2,4,5*}). Tetrakis(triphenylphosphine)palladium(0) is a very efficient precatalyst for the SM cross-coupling process[8] and was effective in the presence of sodium carbonate as base, a toluene/ethanol/water solvent system, under microwave conditions[9b] to afford, for example, **5**{*3,1,14*} in good yields (Figure 5).

These coupling conditions do not appear to be appropriate for either S- or ortho-substituted arylboronic acid pinacol ester coupling partners. In these two cases, protodeborylation products, starting materials, or both were observed. An O-substituted compound gave a moderate yield of 38% of the expected biphenyl **5**{*3,14,3*}.

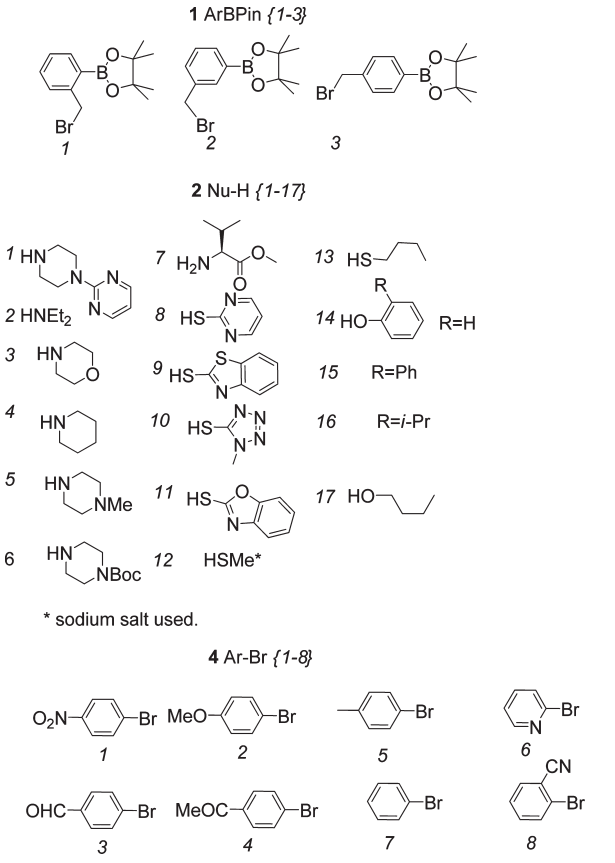


Figure 2. Building blocks used.

Finally, we investigated the coupling reaction in the synthesis of a precursor to valsartan, an antihypertensive.[14,15] The known compound **7**{*3,7,1*},[14d] synthesized from **3**{*3,7*}, was coupled with both bromobenzene and 2-bromobenzonitrile in acceptable yields (Scheme 2). The biphenyl derivative **8**{*3,7,1,8*} is a known intermediate in the synthesis of valsartan.[14e,15] The ^{1}H NMR spectra of the compounds showed the presence of rotamers as noted in other publications; for **7**{*3,7,1*}, increasing the temperature (and changing the solvent to DMSO-d_6) led to coalescence (see Experimental Procedures).

A previous synthesis of **8**{*3,7,1,8*} employed a reductive amination of 2-cyano-4′-formylbiphenyl (formed from a decarboxylative coupling in 80% yield) with a protected valine derivative followed by treatment with valeroyl chloride, in an overall yield of around 70%.[14e] Analog **7**{*3,7,1*} has been shown to undergo direct SM couplings with phenyltetrazole halides under thermal conditions. Our attempts using protected and unprotected phenyltetrazole chlorides or bromides under microwave conditions gave unsatisfactory yields.

Current studies are aimed at expanding the scope of the SM coupling reaction involving the arylboronate library as coupling partners, especially in regard to the use of thioether or ortho-substituted ArBPin, and will be reported in due course.

CONCLUSION

A library of N- and S-substituted arylboronates can be synthesized using MAOS coupled with supported reagents to ease workup.

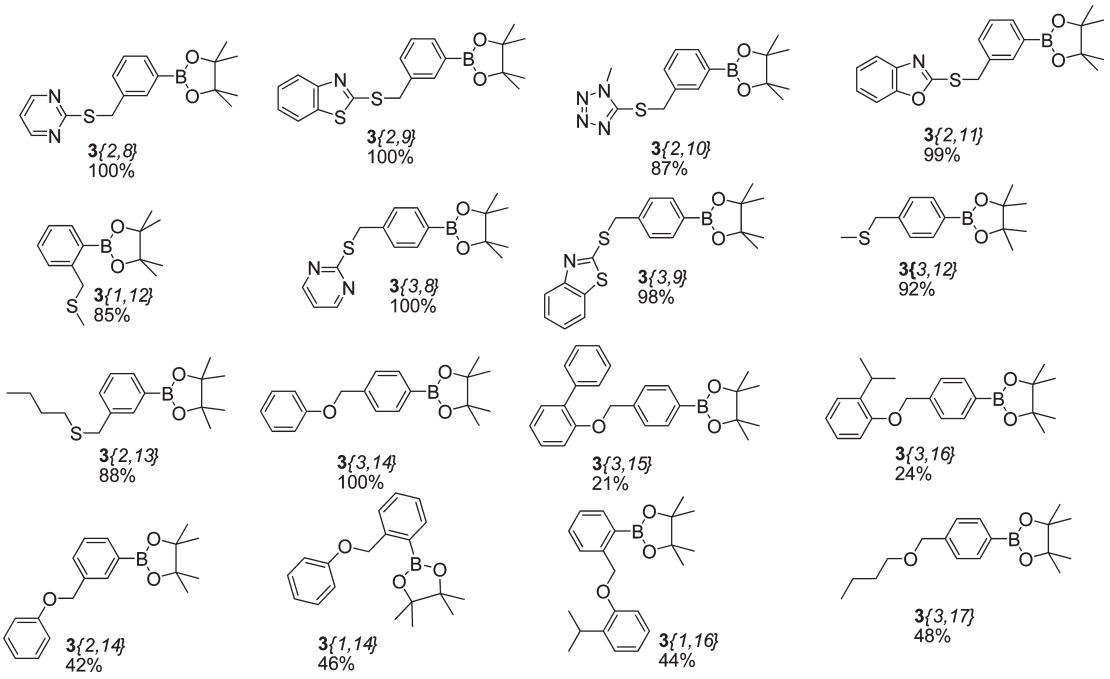


Figure 3. *S*- and *O*-boronate library.

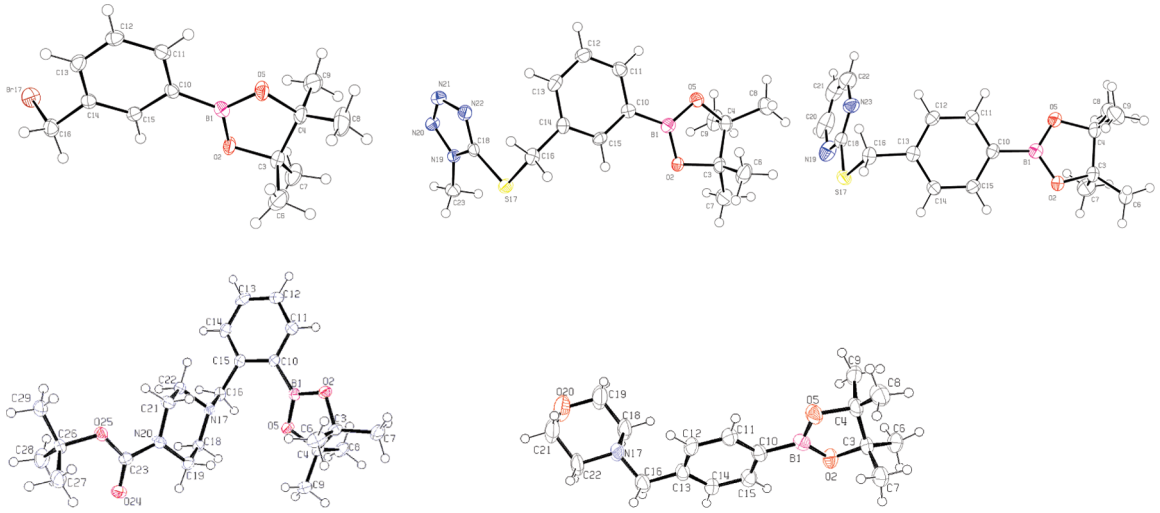


Figure 4. Solid state structure of ArBPin analogs.

O-substituted analogues were formed under solventless conditions. SM coupling reactions of the arylboronates with aryl halides led to a library of biphenyls.

EXPERIMENTAL PROCEDURES

All reactions were carried out in air, and commercial grade solvents and materials were used except where specified. Supported reagents PS-NMM, -trisamine, and -isocyanate were purchased from Biotage or Novabiochem. NMR spectra were measured on a Jeol EX270 spectrometer at 270 MHz (^{1}H) and 75 MHz (^{13}C) in $CDCl_3$. Microwave reactions were performed in a CEM Discover unit. Elemental analyses were performed on a CE Instruments apparatus. Chromatographic purification was carried out on an ISCO purification unit using Redisep silica gel columns. Purities of compounds were assessed by inspection of their NMR spectra, and a large number of solid compounds were analyzed by combustion analysis. General procedures are given below, and analytical data for compounds can be found in the Supporting Information.

General Procedure for the Synthesis of 3 . *2-(4-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazin-1-yl) Pyrimidine, 3{1,1}.* Compound **1**{*1*} (0.5 mmol, 149 mg), 1-(2-pyrimidyl)piperazine **2**{*1*} (0.7 mmol, 0.1 mL), PS-NMM (0.75 mmol, 2.28 mmol g^{-1}, 329 mg), and THF (2 mL) were mixed in a microwave vial. The mixture was stirred under microwave irradiation at 150 °C for 20 min. The mixture was cooled to room temperature and filtered. The filtrate was concentrated under

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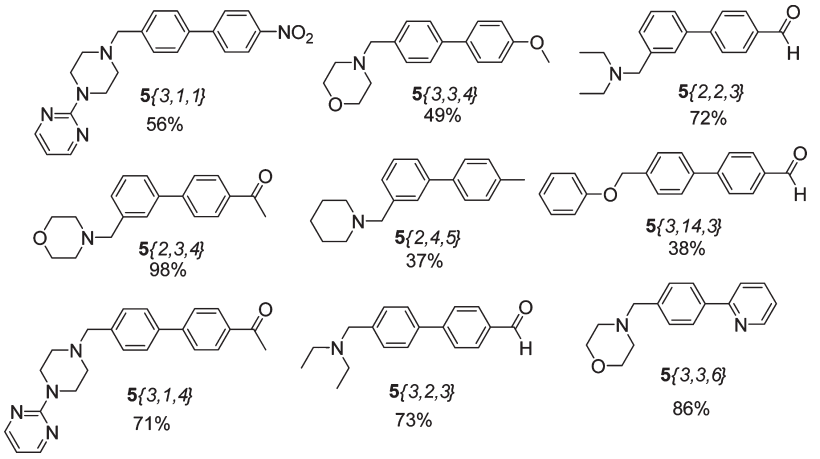
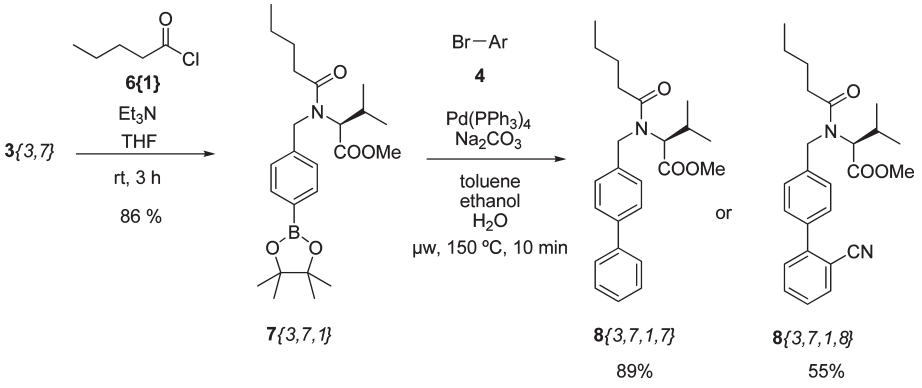


Figure 5. Biphenyls synthesized.

Scheme 2. Synthesis of a Precursor to Valsartan



reduced pressure to afford 229 mg of a yellow oil, which contained unreacted **2**{*1*}, observed by TLC and ^{1}H NMR analysis. The oil was treated with PS-trisamine (0.1 mmol, 3.34 mmol g^{-1}, 30 mg) and PS-isocyanate (0.2 mmol, 1.58 mmol g^{-1}, 127 mg) in THF under microwave irradiation at 150 °C for 5 min, cooled to room temperature, and filtered. The filtrate was concentrated under reduced pressure to give 210 mg of the expected product as a beige solid in 100% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.22 (d, 2H, J = 4.8 Hz), 7.65 (d, 1H, J = 7.3 Hz), 7.20−7.35 (m, 3H), 6.40 (dd, 1H, J = 4.8 Hz), 3.68 (m, 6H), 2.42 (m, 4H), 1.28 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 157.7 (2C), 135.1, 130.9, 130.0, 129.3, 128.8, 126.5, 125.5, 109.7, 83.4 (2C), 62.1, 52.8 (2C), 43.5 (2C), 25.1 (4C). HRMS-ES (m/z) found, 381.2462; calcd for $[C_{21}H_{29}O_2N_4B + H]^+$, 381.2456. Elemental analysis CHN (%) found: C, 66.0, H, 7.7, N, 14.3. Calcd for $C_{21}H_{29}O_2N_4B$: C, 66.3; H, 7.7; N, 14.7.

(S)-Methyl-3-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylamino) Butanoate 3{3,7}. [Note: Stench for thiols and thiomethoxides.] Compound **1**{3} (0.89 mmol, 264 mg), L-valine methyl ester (1.79 mmol, 234 mg), PS-NMM (1 mmol, 250 mg), and THF (3 mL) were mixed in a microwave vial and stirred under microwave irradiation at 130 °C for 2 h. The mixture was cooled to room temperature, filtered, and concentrated to give 417 mg of a yellow oil, which was purified by chromatography on silica gel, hexane/EtOAc from 0% to 20% of EtOAc, to give 222 mg of the expected product as a pale yellow oil in 72% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.76 (d, 2H, J = 7.7 Hz), 7.35 (d, 2H, J = 8.1 Hz), 3.86 (d, 1H, J = 13.2 Hz), 3.72 (s, 3H), 3.58 (d, 1H, J = 13.2 Hz), 2.99 (d, 1H, J = 6.2 Hz), 1.90 (sex, 1H, J = 7.0 Hz), 1.80 (m, 1H, NH), 1.34 (s, 12H), 0.93 (2d, 6H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 175.8, 143.3, 134.8 (3C), 127.6 (2C), 83.7 (2C), 66.4, 52.5, 51.4, 31.7, 24.8 (4C), 19.3, 18.6. HRMS-ES (m/z) found, 347.2378; calcd for $[C_{19}H_{30}O_4NB + H]^+$, 347.2377.

4,4,5,5-Tetramethyl-2-(2-(methylthiomethyl)phenyl)-1,3,2-dioxaborolane 3{1,12}. Compound **1**{*1*} (1 mmol, 297 mg), sodium thiomethoxide (1 mmol, 70 mg), and THF (3 mL) were mixed in a microwave vial. The mixture was stirred under microwave irradiation at 150 °C for 20 min. THF was removed under reduced pressure. The product was diluted in water and CH_2Cl_2, extracted by CH_2Cl_2, washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give 225 mg of the expected product as a pale yellow oil in 85% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.77 (d, 1H, J = 7.3 Hz), 7.34 (dd, 1H, J = 8.4 Hz), 7.18−7.30 (m, 2H), 3.97 (s, 2H), 1.93 (s, 3H), 1.34 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 149.4, 145.3, 136.1, 130.5, 129.4, 126.1, 83.6 (2C), 37.4, 24.9 (4C), 14.7.

2-(3-(Butylthiomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 3{2,13}. n-Butylthiol (1 mmol, 107 μL, 0.842 g mL^{-1}), sodium hydride (1 mmol, 40 mg), and THF (2 mL) were mixed in a microwave vial and stirred at room temperature for

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15 min, then a solution of **1**{*2*} (1 mmol, 297 mg) in THF (2 mL) was added. The mixture was stirred under microwave irradiation at 150 °C for 15 min. THF was removed under reduced pressure. The product was diluted in water and CH_2Cl_2, extracted by CH_2Cl_2, washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give 270 mg of the expected product as a pale yellow liquid in 88% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.70 (s, 1H), 7.65 (d, 1H, J = 7.3 Hz), 7.42 (d, 1H, J = 7.7 Hz), 7.30 (dd, 1H, J = 7.3 Hz), 3.69 (s, 2H), 2.39 (t, 2H, J = 7.3 Hz), 1.53 (m, 2H), 1.36 (m, 5H), 1.32 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 137.9, 135.1 (2C), 133.3, 131.7, 127.9, 83.8 (2C), 36.2, 31.3, 31.1, 24.9 (4C), 22.0, 13.6.

General Procedure for O-Nucleophiles. *4,4,5,5-Tetramethyl-2-(2-(phenoxymethyl)phenyl)-1,3,2-dioxaborolane 3{1,14}.* Compound **1**{*1*} (1.00 mmol, 298 mg), phenol (1.03 mmol, 97 mg), sodium hydroxide (1.13 mmol, 45 mg), potassium carbonate (4.00 mmol, 552 mg), and tetrabutylammonium bromide (0.10 mmol, 32 mg) were mixed in a microwave vial. The mixture was stirred under microwave irradiation at 110 °C for 5 min. The mixture was cooled to room temperature, diluted with EtOAc and water, extracted with EtOAc, washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give 269 mg of a brown oil. The crude product was purified by chromatography on silica gel, hexane/EtOAc 9:1, to give 144 mg of the expected product as a yellow oil in 46% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.84 (d, 1H, J = 7.3 Hz), 7.53 (d, 1H, J = 7.7 Hz), 7.44 (dd, 1H, J_1 = 1.5 Hz, J_2 = 7.3 Hz), 7.34−7.23 (m, 3H), 6.97 (d, 2H, J = 8.8 Hz), 6.91 (d, 1H, J = 7.3 Hz), 5.34 (s, 2H), 1.33 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 159.1, 143.4, 136.4, 135.9, 131.1, 129.3 (2C), 127.4, 127.0, 120.5, 114.8 (2C), 83.7 (2C), 69.4, 24.8 (4C).

2-(4-(Butoxymethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 3{3,17}. *n*-Butanol (1 mmol, 91 μL, 0.811 g.mL^{-1}), sodium hydride (2 mmol, 80 mg), and THF (3 mL) were mixed in a microwave vial and stirred at room temperature for 15 min, then **1**{*3*} (1 mmol, 297 mg) was added, and the mixture was stirred under microwave irradiation at 150 °C for 15 min. THF was removed under reduced pressure. The product was diluted in water and CH_2Cl_2, extracted by CH_2Cl_2, washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give 247 mg of a colorless oil. The product was purified by chromatography on silica gel, CH_2Cl_2, to give 139 mg of the expected product as a colorless oil in 48% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.77 (d, 2H, J = 8.1 Hz), 7.32 (d, 2H, J = 8.4 Hz), 4.50 (s, 2H), 3.43 (t, 2H, J = 6.6 Hz), 1.60 (m, 2H), 1.35 (m, 2H), 1.32 (s, 12H), 0.89 (t, 3H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 142.0, 134.8 (3C), 126.7 (2C), 83.7 (2C), 72.7, 70.2, 31.8, 24.9 (4C), 19.4, 13.9.

General Procedure for $Pd(OAc)_2$ Mediated SM Couplings. *2-(4-((4′-Nitrobiphenyl-4-yl)methyl)piperazin-1-yl)pyrimidine 5{3,1,1}.* 2-[4-(1-(4-(2-Pyrimidyl)piperazine)methyl)phenyl]-4,4,5,5-tetramethyl-1,3-dioxaborolane **3**{*1,1*} (0.5 mmol, 190 mg), 1-bromo-4-nitrobenzene **4**{*1*} (0.5 mmol, 101 mg), palladium-(II) acetate (0.005 mmol, 1 mg), sodium carbonate (1 mmol, 106 mg), tetrabutylammonium bromide (0.5 mmol, 161 mg), and water (2 mL) were mixed in a microwave vial. The mixture was stirred under microwave irradiation at 150 °C for 10 min. The mixture was cooled and diluted with EtOAc and water. The separated organic layer was washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give 105 mg of the expected product as a brown solid in 56% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.27 (2d, 4H), 7.73 (d, 2H, J = 8.8 Hz), 7.59 (d, 2H, J = 8.4 Hz), 7.51 (d, 2H, J = 8.4 Hz), 6.46 (dd, 1H, J = 4.8 Hz), 3.83 (m, 4H), 3.59 (s, 2H), 2.52 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 161.7, 157.7 (2C), 147.4, 147.0, 139.2 (2C), 129.8 (2C), 127.6 (2C), 127.3 (2C), 124.1 (2C), 109.8, 62.6, 53.0 (2C), 43.6 (2C). HRMS-ES (m/z) found, 376.1770; calcd for $[C_{21}H_{21}O_2N_5 + H]^+$, 376.1768. Elemental analysis CH (%) found: C, 65.2; H, 5.7. Calcd for $C_{21}H_{21}O_2N_5 \cdot 0.17CH_2Cl_2$: C, 65.2; H, 5.5.

General Procedure for $Pd(PPh_3)_4$-Mediated SM Couplings. *1-[4′-(4-Pyrimidin-2-yl-piperazin-1-ylmethyl)-biphenyl-4-yl]-ethanone 5{3,1,4}.* 2-{4-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazin-1-yl}-pyrimidine **3**{*3,1*} (0.3 mmol, 115 mg), 4-bromobenzophenone (0.35 mmol, 70 mg), tetrakis-(triphenylphosphine)palladium(0) (0.01 mmol, 12 mg), sodium carbonate (0.9 mmol, 95 mg), toluene (1 mL), ethanol (1 mL), and water (1 mL) were mixed in a microwave vial. The mixture was stirred under microwave irradiation at 150 °C for 10 min then cooled to room temperature, diluted with EtOAc and water, and extracted with EtOAc. The separated organic layer was washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give a crude product, which was purified by chromatography on silica gel, CH_2Cl_2/EtOAc 1:1, to give 79 mg of the expected product as a white solid in 71% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.31 (d, 2H, J = 4.8 Hz), 8.04 (d, 2H, J = 8.8 Hz), 7.70 (d, 2H, J = 8.4 Hz), 7.61 (d, 2H, J = 8.1 Hz), 7.46 (d, 2H, J = 8.4 Hz), 6.48 (dd, 1H, J = 4.8 Hz), 3.85 (m, 4H), 3.61 (s, 2H), 2.65 (s, 3H), 2.55 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 197.7, 161.7, 157.7 (2C), 145.5, 138.8, 138.2, 135.8, 129.8 (2C), 128.9 (2C), 127.2 (2C), 127.1 (2C), 109.8, 62.7, 53.0 (2C), 43.7 (2C), 26.6. HRMS-ES (m/z) found, 373.2023; calcd for $[C_{23}H_{24}ON_4 + H]^+$, 373.2023. Elemental analysis CHN (%) found: C, 73.6; H, 6.4; N, 14.2. Calcd for $C_{23}H_{24}O_1N_4 \cdot 0.34$EtOAc: C, 73.6; H, 6.7; N, 14.3.

(S)-Methyl-3-methyl-2-(N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-l)benzyl) Pentanamido)butanoate 7{3,7,1}. Compound **3**{*3,7*} (2.06 mmol, 714 mg), valeroyl chloride (4.12 mmol, 0.995 g mL^{-1}, 0.50 mL), triethylamine (2.10 mmol, 0.726 g mL^{-1}, 0.31 mL), and THF (10 mL) were mixed and stirred at room temperature for 3 h. THF was removed, and the mixture was diluted with EtOAc, washed with water and a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated to give 1.006 g of a yellow oil which was purified by chromatography on silica gel, hexane/EtOAc from 0 to 20% of EtOAc to give 763 mg of the expected product as a yellow oil in 86% yield. ^{1}H NMR mixture of rotamers ($CDCl_3$) δ (ppm): 7.76 and 7.69 (2d, 2H, J = 8.1 Hz), 7.17 and 7.14 (2d, 2H, J = 8.1 Hz), 5.00 and 4.91 (2d, 1H, J_{d1} = 10.4 Hz, J_{d2} = 15.3 Hz), 4.63 (s, 1.5H), 4.32 (d, 0.25H, J = 15.4 Hz), 4.03 (d, 0.25H, J = 10.6), 3.44 and 3.37 (2s, 3H), 2.65−2.11 (m, 3H), 1.79−1.53 (m, 2H), 1.49−1.17 (m + s, 14H), 0.96 (d, 3H, J = 6.2 Hz), 0.88 (d, 3H, J = 7.0 Hz), 0.84 (t, 3H, J = 7.3 Hz). ^{13}C NMR mixture of rotamers ($CDCl_3$) δ (ppm): 174.7, 174.1, 171.0, 170.3, 141.3, 140.5, 135.1, 134.6 (2C), 126.8, 125.0 (2C), 83.8 (2C), 66.0, 61.6, 51.7, 51.6, 48.3, 45.8, 33.3, 27.8, 27.6, 27.4, 24.8 (4C), 22.4, 19.8, 18.7, 13.8. HRMS-ES (m/z) found, 431.2947; calcd for $[C_{24}H_{38}O_5N^{10}B + H]^+$, 431.2952.

Coalescence was observed at higher temperature ^{1}H NMR (DMSO-d_6, 400 MHz, 373 K) δ (ppm): 7.63 (d, 2H, J = 7.4 Hz),

7.19 (d, 2H, J = 7.5 Hz), 4.69 (m, 1H), 4.60−4.30 (m, 2H), 3.44 (s, 3H), 2.45−2.15 (m, 3H), 1.60−1.40 (m, 2H), 1.31 (s, 12H), 1.40−1.20 (m, 2H), 0.94 (d, 3H, J = 6.5 Hz), 0.89 (t, 3H, J = 7.4 Hz), 0.82 (d, 3H, J = 6.9 Hz).

(S)-Methyl-2-(N-(biphenyl-4-ylmethyl)pentanamido)-3-methylbutanoate 8{3,7,1,7}. Compound 7{3,7,1} (0.37 mmol, 160 mg), bromobenzene (0.44 mmol, 1.491 g mL^{-1}, 46 μL), sodium carbonate (1.11 mmol, 118 mg), tetrakis(triphenylphosphine)-palladium(0) (0.01 mmol, 12 mg), toluene (1 mL), EtOH (1 mL), and water (0.5 mL) were mixed in a microwave vial and stirred under microwave irradiation at 150 °C for 10 min. The mixture was cooled to room temperature, diluted with EtOAc and water, and extracted three times with EtOAc. The separated organic layer was washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil which was purified by chromatography on silica gel, hexane/EtOAc 8:2, to give 126 mg of the expected product as a pale yellow oil in 89% yield. ^{1}H NMR mixture of rotamers ($CDCl_3$) δ (ppm): 7.61−7.52 (m, 3H), 7.52−7.30 (m, 4H), 7.30−7.18 (m, 2H), 4.97 (2d, 1H, J = 10.3 Hz), 4.66 (s, 1.3H), 4.29 (d, 0.3H, J = 15.3 Hz), 4.05 (d, 0.3H, J = 10.9 Hz), 3.45 and 3.36 (2s, 3H), 2.67−2.20 (m, 3H), 1.82−1.54 (m, 2H), 1.50−1.20 (m, 2H), 0.99 (d, 3H, J = 6.5 Hz), 0.95−0.80 (d + t, 6H, J_d = 7.0 Hz, J_t = 7.3 Hz). ^{13}C NMR mixture of rotamers ($CDCl_3$) δ (ppm): 174.6, 171.2, 140.5, 140.2, 136.4, 128.8, 128.7, 128.1, 127.4, 127.3, 127.0 (2C), 126.8, 126.4, 65.9, 61.8, 51.6, 48.2, 45.4, 33.4, 27.9, 27.4, 22.5, 19.9, 18.8, 13.8. HRMS-ES (m/z) found, 382.2375; calcd for $[C_{24}H_{31}O_3N_1 + H]^+$, 382.2377.

■ ASSOCIATED CONTENT

Supporting Information. Analytical data (^{1}H, ^{13}C spectra, MS, elemental analysis) for compounds are provided, as well as X-ray crystallography experimental details for **1**{*2*}, **3**{*1,6*}, **3**{*2,10*}, **3**{*3,3*}, and **3**{*3,8*}.This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +44 2083318215. Fax: +44 2083319805. E-mail: j.spencer@gre.ac.uk.

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