JOC The Journal of Organic Chemistry

ARTICLE

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One-Pot Reductive Amination and Suzuki−Miyaura Cross-Coupling of Formyl Aryl and Heteroaryl MIDA Boronates in Array Format

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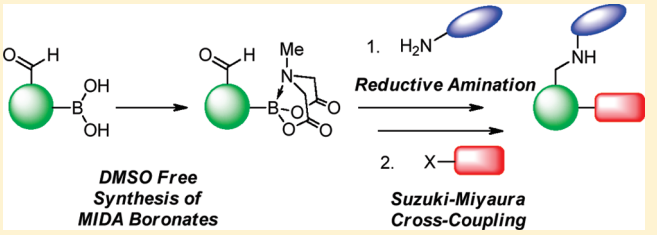
Supporting Information

ABSTRACT: Formyl-substituted aryl and heteroaryl MIDA boronates were prepared by a DMSO-free method and used in the first reported one-pot reductive amination−Suzuki−Miyaura cross-coupling sequence. This sequence was then carried out in parallel array format, using microwave-assisted *in situ* release cross-coupling of MIDA boronates to generate a library with diversity along two axes, affording rapid and convenient access to an array of druglike molecules.



INTRODUCTION

Lead optimization efforts in drug discovery programs often require development of structure−activity relationships (SAR) by the stepwise incorporation of diversity elements into a fixed scaffold or related set of scaffolds. Oftentimes this has been a node in the drug discovery process where the preparation of targeted libraries using parallel synthesis techniques has enhanced efficiency. These libraries have most commonly been prepared employing very robust and well-established synthetic methodologies, varying only a single moiety late in the synthetic sequence for analogue preparation.[1] Our laboratory has been focusing on developing chemistry to enable parallel synthesis based preparation of analogues where the diversity elements are introduced at the strategically most meaningful step(s) in the synthesis as opposed to where most technically feasible. While there are several known multicomponent reactions that accomplish this efficiently, many suffer from limited availability of diversity elements and/or reliance on formation of a single specific heterocyclic ring system, thereby limiting their broader applicability.[2] We sought to develop multistep sequences that would allow introduction of readily available diversity elements at each step, beginning with investigation of reactions commonly utilized in the practice of medicinal chemistry. One such widely used reaction is the Suzuki−Miyaura (SM) cross-coupling,[3] noted both for its broad functional group tolerance and substrate scope, and consequently, the SM cross-coupling has historically been one of the most prevalent transformations in drug discovery parallel synthesis.[1] Exciting new advances in cross-coupling of boron-functionalized building blocks have allowed use of this powerful reaction in conceptually novel ways.[4] In particular, the possibility to perform complexity building reactions in the presence of a boronic acid or a derivative thereof and thereby obviate the need to install a boronic acid in a complex molecule. Once constructed, these complex boronic acids are expected to participate in SM cross-coupling establishing a strategic two-stage sequence (Figure 1). This approach enables more efficient

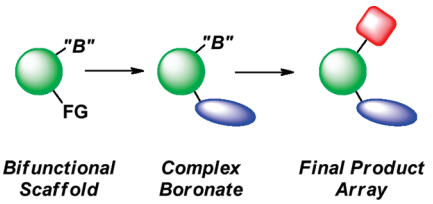


Figure 1. Strategic construction of complex boronic acid derivatives.

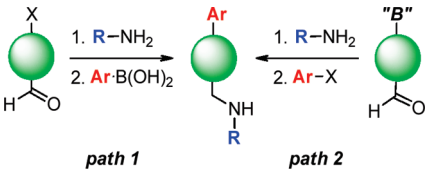


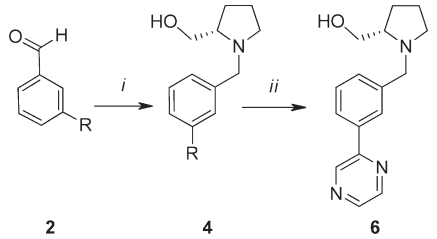
Figure 2. Reductive amination−SM cross-coupling reaction sequences from different starting points.

disconnections in the planning of complex molecule synthesis and has already been applied successfully to the synthesis of a number of polyene natural products.[5]

As an application of this approach, we chose to investigate the feasibility of reductive amination as the complexity building step depicted in Figure 1, due to the clear potential for the rapid buildup of complexity, the control over the disposition of installed diversity elements, and the broad scope of both the reductive amination and the SM cross-coupling. Traditionally, the "default" bifunctional arene core suitable for such a telescoped sequence would be a haloarylcarboxaldehyde, which would be combined with amine and boronic acid diversity elements (path 1 in Figure 2). While this would be reasonably effective at achieving diversity, our present

Received: March 18, 2011
Published: April 28, 2011

Table 1. One-Pot Reductive Amination−SM Cross-Coupling Sequence with Various Boronic Acid Derivatives



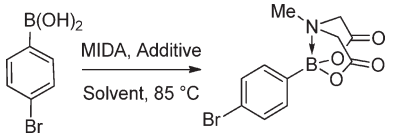
2 4 6

i) (*S*)-Prolinol **3**, $Na(OAc)_3BH$, THF 25 °C. *ii)* 2-Bromopyrazine **5**, PEPPSI-IPr, $K_2CO_{3(aq)}$, MeCN, μW 150 °C[a].

boronate	yield (%)[b]
R = BF_3K	54
R = Bpin	64
R = BMIDA	78

[a] Biotage Initiator microwave. [b] Isolated yield.

Table 2. Optimization of the Preparation of MIDA Boronates



entry	solvent	additive	yield (%)[a]
1	2-butanone	4 Å MS	42
2	1,2-DCE	4 Å MS	33
3	CH_3CN	4 Å MS	46
4	1,4-dioxane	4 Å MS	13
5	DMSO	4 Å MS	60
6	DMF	4 Å MS	62
7	DMF	4 Å MS[b]	83
8	DMF	*p*-TSA	>95
9	DMF	silica gel	44
10	DMF	$MgSO_4$	65
11	DMF	none	>95 (94[c])

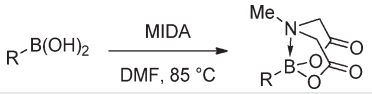
[a] Determined by UV-HPLC. [b] Reaction run at 100 °C. [c] Isolated yield.

approach utilizing a boron-functionalized aryl aldehyde offers distinct advantages in that the breadth of readily available aryl halides as coupling partners would be expected to lead to far greater diversity accessible by this reaction sequence (path 2 in Figure 2).

RESULTS AND DISCUSSION

Although there have been very limited reports of reductive amination in the presence of boronic acid derivatives, these methods are either prohibitively narrow in scope or require the use of inefficient multistep procedures.[6,7] We tested three classes of boronates expected to be tolerant of the proposed one-pot procedure in a reductive amination−SM reaction sequence with the somewhat challenging substrates of amino alcohol **3** and heterocyclic halide **5** in order to assess the feasibility in a context appropriately representative of the more broadly targeted diversity library rather than a "loaded case". For all the boronates tested, clean conversion to intermediate **4** was observed by HPLC-MS. After quenching with aqueous base, the resultant boronates **4** were directly subjected to microwave-assisted SM

Table 3. Scope of the DMSO-Free Synthesis of MIDA Boronates



boronic acid (**1**)[a]	product (**2**)	yield[b] (purity[c]) (%)
3-CHO-Ph	**2a**	100 (>95)
4-CHO-Ph	**2b**	75 (>95)
2-CHO-Ph	**2c**	0
2-F, 5-CHO-Ph	**2d**	81 (>95)
2-Me, 4-CHO-Ph	**2e**	93 (>95)
5-CHO, 3-thienyl	**2f**	84 (>95)
4-CHO, 2-furyl	**2g**	85 (>95)
2-F, 4-CHO-Ph	**2h**	70 (>95)
3-CF_3, 4-CHO-Ph	**2i**	78 (>95)
3-F, 4-CHO-Ph	**2j**	74 (>95)
2-Cl, 5-CHO-Ph	**2k**	89 (>95)
2,4-di-F, 3-CHO-Ph	**2l**	73 (>95)
3-CHO, 4-F-Ph	**2m**	60 (>95)
2-OMe, 5-CHO-Ph	**2n**	81 (>95)
3-Cl, 4-CHO-Ph	**2o**	72 (>95)
2-OMe, 3-CHO-Ph	**2p**	96 (>95)
2-Cl, 3-pyridyl	**2q**	88 (>95)
2-Br, 3-quinolinyl	**2r**	76 (91)

[a] For the purposes of this table the boron bearing carbon is counted as position 1. [b] Isolated yield. [c] Determined by UV-HPLC after scavenge with Si-carbonate.

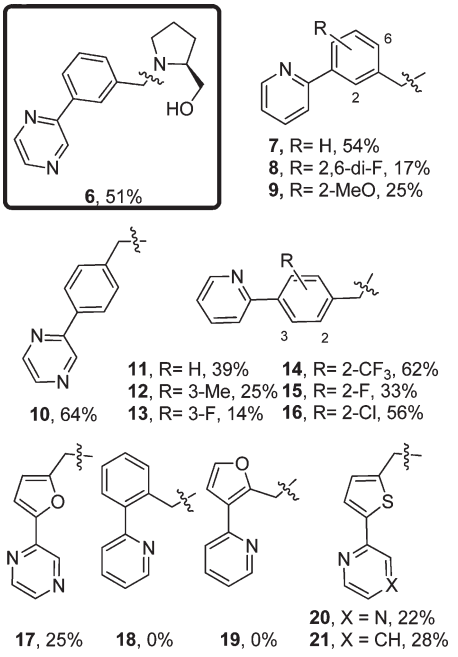
cross-coupling with 2-bromopyrazine **5** using the *N*-heterocyclic carbene derived PEPPSI-IPr catalyst system.[8] While each of the boronate derivatives were effective coupling partners in this one-pot sequence, the MIDA boronate was most efficient (Table 1). This protocol accomplished both the deprotection of the MIDA boronate and the subsequent cross-coupling reaction affording the desired compound **6** in 78% overall yield from **2**.[9] This is the first reported example of a one-pot reductive amination SM cross-coupling and furthermore is also the first reported demonstration of *in situ* release SM cross-coupling of MIDA boronates promoted by microwave irradiation.

The success of the MIDA boronates was particularly encouraging, and aside from their efficiency in the aforementioned reaction sequence, a number of other aspects of MIDA boronate chemistry led to our interest to further evaluate their potential in this application. In particular, their compatibility with other functional group transformations,[5] their ease of isolation, stability to a great variety of reagents, and their ability to participate in slow release cross-couplings[10] make these attractive tools to employ in the present targeted sequence, as well as in other potential one-pot sequences to rapidly build complex molecules.

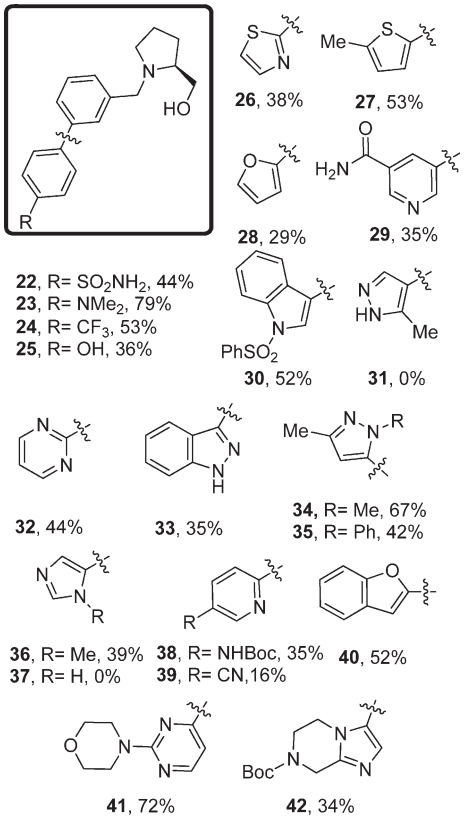
While the aforementioned features of MIDA boronates have been clearly demonstrated, the known methods for their synthesis suffer from drawbacks stemming from the use of DMSO as a reaction cosolvent and the requirement for azeotropic removal of water by Dean−Stark distillation.[11] These two factors led us to investigate alternative procedures for the synthesis of MIDA boronates that would further enable convenient access to a wide variety of protected bifunctional boron-containing building blocks (Table 2).[12] Included in our survey of conditions to effect this protection were procedures that omitted the use of any

dx.doi.org/10.1021/jo2005928 |*J. Org. Chem.* 2011, 76, 4930–4940

Scheme 1. Yields for Reductive Amination SM Cross-Coupling with Formyl Boronate Cores



Scheme 2. Yields for Reductive Amination SM Cross-Coupling with Variation of Aryl Substituents



means of water removal, as we reasoned that the hydrolytic stability of the MIDA boronates might allow their formation in the presence of the small amounts of water generated under the reaction conditions, obviating the need for its azeotropic removal. In practice, our investigations revealed that optimal conditions (entry 11, Table 2) involved simply heating MIDA together with the boronic acid, providing the desired MIDA boronate in 94% isolated yield, without employing special apparatus or dehydrating additives.

Using these optimized conditions the scope and generality of the condensation reaction was explored on a range of boronic acids. To enable rapid evaluation of these conditions and to further underscore the convenience of this approach, we undertook this investigation in a small parallel synthesis library format (Table 3). By this method, MIDA boronates were isolated in good to excellent yields and high purity after scavenging with alkyl ammonium carbonate functionalized silica gel (Si-carbonate). Of particular interest was the success of the somewhat unstable boronyl heterocycles **2f** and **2g** and the fact that this is also a viable method to prepare halogen containing MIDA boronates (**2q** and **2r**), which are useful building blocks for iterative cross-couplings. It bears mentioning that *o*-formyl boronates exemplified by **2c** failed to participate in the condensation reaction. Plausible explanations for this include steric constraints and the proximal location of two electrophilic centers, and this is currently under further investigation. Overall the convenience of this procedure represents an improvement in the preparation of MIDA boronates and should become the method of choice for the preparation of these important building blocks on both laboratory and commercial scale.[13]

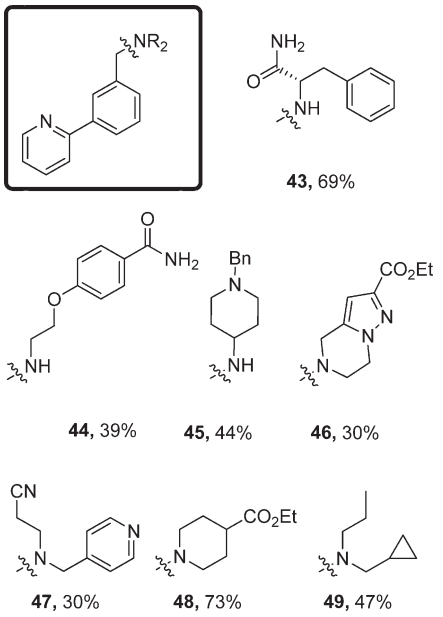
We next set out to evaluate the scope of the one-pot reductive amination SM cross-coupling reaction sequence. As with the MIDA boronate synthesis itself, we chose to carry out this investigation in array format both for the opportunity to quickly establish the scope of the reaction as well as to demonstrate the potential of this sequence in applications targeting diversity oriented synthesis. The library was designed to establish the scope of all three reaction components (boronyl aldehyde, aryl and heteroaryl halide, and amine), thus affording expedient and convenient access to diversity points along two axes. For this evaluation we selected monocyclic phenyl and heteroaryl cores. Amines and aryl halides were chosen with the aim of incorporating a range of functionality. The results obtained in preparation of this library are summarized according to building block types (Schemes 1−3). These data were collected in two libraries (a small pilot library of 10 members and a larger production library of 48 members). All yields are of HPLC-purified material and are reported over the two steps of the reaction sequence relative to the formyl MIDA boronate **2**, and yields were not optimized independently.[14]

Library members containing phenyl cores were accessed in yields ranging from adequate to moderate, while heterocyclic cores (**17**, **20**, and **21**) participated in the reaction sequence albeit in low overall yield due to incomplete conversion in the reductive amination step. The scope of bifunctional cores applicable to the reaction sequence is limited mainly by the failure of *o*-boronyl aldehydes (**18** and **19**) to participate in the reductive amination step.

While investigating the scope of aryl components (Scheme 2), we observed examples with good yields for both electron-rich **23** and electron-deficient **24** haloarenes. Of even greater significance was the breadth of successful heteroaryl halides, with examples spanning wide variation of electronics, ring size, and functionality, as these moieties are representative of fragments ubiquitously used in the practice of medicinal chemistry.[15] The only class of heteroaryl halides that failed to participate in the SM cross-coupling was the five-membered heterocycles with a free N−H bond such as a

dx.doi.org/10.1021/jo2005928 |*J. Org. Chem.* 2011, 76, 4930–4940

Scheme 3. Yields for Reductive Amination SM Cross-Coupling with Variation of Amine Substituents



pyrazole or imidazole (**31** and **37**). These N−H azoles are known to be difficult substrates for SM cross-coupling without resorting to the use of phase transfer conditions.[16]

Amine building blocks provided a convenient handle to assess the performance of this reaction sequence on a range of functionality (Scheme 3). The amines furnished products containing amino acid derivatives (**43**), ethers (**44**), esters (**46** and **48**), and heterocycles (**45**−**48**), all in serviceable yields for the multistep sequence. The relative success of the amine variants, along with the positive results of the aryl halides and the boronyl aldehydes establish a reaction sequence that operates with broad scope and represents an effective and highly efficient approach to the preparation of a diverse set of chemical matter.

CONCLUSION

We have developed an approach for installing diversity along multiple axes in a single library operation. Our methodology allows rapid and efficient assembly of complex drug-like molecules, affords full control over the disposition of diversity elements in chemical space, and is applicable to a broad variety of scaffolds. This method is enabled by (1) the development of a convenient and effective synthesis of MIDA boronates; (2) the development of the first one-pot reductive amination−Suzuki−Miyaura cross-coupling sequence; and (3) further facilitation by the use of microwave irradiation to effect the *in situ* release cross-coupling of MIDA boronates. We are currently investigating other strategic combinations of reactions allowing for the derivatization and *in situ* release SM cross-coupling of MIDA boronates, and those results will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Procedures. Parallel synthesis was carried out in 2 dram septum-capped round-bottom vials, and reactions were mixed by orbital shaking. Organic solutions were concentrated via rotary evaporation under reduced pressure with a bath temperature of 35−40 °C or using a centrifugal evaporator system. Reactions were monitored by analytical HPLC-MS using either Waters Sunfire OBD C-18, 3 μm, 4.6 × 50 mm column (A: water + 0.1% TFA; B: MeCN; flow rate: 2.1 mL/min; gradient: 95% A to 95% B over 5 min) or Phenomenex Gemini C-18, 3 μm, 4.6 × 50 mm column (A: 5 mM aqueous NH_4OH; B: MeCN; flow rate: 2.1 mL/min; gradient: 95% A to 95% B over 5 min). Carbonate scavenging was performed using tetraalkylammonium carbonate functionalized silica gel Si-Carbonate cartridges (SIR-R66030 B-06S, 6 mL, 1 g loading = 0.7 mmol of carbonate/gram). Preparative HPLC was performed using either Waters Sunfire OBD C-18, 5 μm, 19 × 100 mm column (A: water + 0.1% TFA; B: MeCN + 0.1% TFA; flow rate: 30 mL/min) or Phenomenex Gemini C-18, 5 μm, 21.2 × 100 mm column (A: water (5 mM NH_4OH); B: MeCN (5 mM NH_4OH); flow rate: 30 mL/min); gradient conditions and collection wavelengths were determined on a per sample basis. Microwave reactions were carried out in a Biotage Initiator microwave. Temperature was measured using an external IR sensor.

Synthesis of MIDA Boronates. *General Procedure for the Synthesis of MIDA Boronates.* To a 2 dram round-bottom vial was added *N*-methyliminodiacetic acid (49 mg, 0.33 mmol) and a boronic acid (0.3 mmol). DMF (1 mL) was added, and the vial was sealed and heated at 85 °C for 18 h. The reaction was allowed to cool to ambient temperature and was transferred to a Si-carbonate column (1 g, 6 mL carbonate loading = 0.7 mmol/g), the column was eluted with acetonitrile (7 mL), and the solvents were removed using a centrifugal evaporation system.

*3-Formylphenylboronic Acid MIDA Ester (**2a**).* The general procedure was followed using 3-formylphenylboronic acid (45 mg, 0.3 mmol), *N*-methyliminodiacetic acid (49 mg, 0.33 mmol), and DMF (1 mL) affording desired product (78 mg, 100% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.04 (s, 1 H), 7.94−8.02 (m, 1 H), 7.91 (d, J = 7.58 Hz, 1 H), 7.78 (d, J = 7.58 Hz, 1 H), 7.60 (t, J = 7.33 Hz, 1 H), 4.37 (d, J = 17.18 Hz, 2 H), 4.17 (d, J = 17.18 Hz, 2 H), 2.53 (s, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 193.6, 169.3, 138.6, 135.5, 133.9, 129.9, 128.5, 62.0, 47.7; HRMS (ESI-TOF) $[M + NH_4]^+$ for $C_{12}H_{12}BNO_5$ calculated: 279.1152 found: 279.1153.

*4-Formylphenylboronic Acid MIDA Ester (**2b**).* The general procedure was followed using 4-formylphenylboronic acid (45 mg, 0.3 mmol), *N*-methyliminodiacetic acid (49 mg, 0.33 mmol), and DMF (1 mL) affording desired product (59 mg, 75% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.04 (s, 1 H), 7.89 (d, J = 8.08 Hz, 2 H), 7.68 (d, J = 8.08 Hz, 2 H), 4.38 (d, J = 17.18 Hz, 2 H), 4.16 (d, J = 17.18 Hz, 2 H), 2.50 (s, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 193.4, 169.2, 136.5, 133.1, 128.5, 62.0, 47.7; HRMS (ESI-TOF) $[M + NH_4]^+$ for $C_{12}H_{12}BNO_5$ calculated: 279.1152 found: 279.1152.

*2-Formylphenylboronic Acid MIDA Ester (**2c**).* The general procedure was followed using 2-formylphenylboronic acid (45 mg, 0.3 mmol), *N*-methyliminodiacetic acid (49 mg, 0.33 mmol), and DMF (1 mL) affording no desired product.

*2-Fluoro-5-formylphenylboronic Acid MIDA Ester (**2d**).* The general procedure was followed using 2-fluoro-5-formylphenylboronic acid (50 mg, 0.3 mmol), *N*-methyliminodiacetic acid (49 mg, 0.33 mmol), and DMF (1 mL) affording desired product (68 mg, 81% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.01 (s, 1 H), 8.08 (dd, J = 6.57, 2.02 Hz, 1 H), 8.00 (d, J = 2.02 Hz, 1 H), 7.35−7.41 (m, 1 H), 4.45 (dd, J = 17.18, 1.01 Hz, 2 H), 4.14 (dd, J = 17.18, 1.01 Hz, 2 H), 2.66 (s, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 192.1, 169.0 (d, J = 250.8 Hz), 169.0, 137.1 (d, J = 11.74 Hz), 133.7 (d, J = 11.00 Hz), 132.5, 116.2 (d, J = 26.41 Hz), 62.5, 47.6; HRMS (ESI-TOF) $[M + NH_4]^+$ calculated for $C_{12}H_{11}BFNO_5$: 297.1058 found: 297.1063.

*2-Methyl-4-formylphenylboronic Acid MIDA Ester (**2e**).* The general procedure was followed using 2-methyl-4-formylphenylboronic acid (49 mg, 0.3 mmol), *N*-methyliminodiacetic acid (49 mg, 0.33 mmol),

dx.doi.org/10.1021/jo2005928 |*J. Org. Chem.* 2011, 76, 4930–4940

and DMF (1 mL) affording desired product (77 mg, 93% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.99 (s, 1 H), 7.70 (d, J = 8.03 Hz, 1 H), 7.67 (s, 1 H), 7.59 (d, J = 7.53 Hz, 1 H), 4.40 (d, J = 17.07 Hz, 2 H), 4.21 (d, J = 17.07 Hz, 2 H), 2.53 (s, 3 H), 2.44 (s, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 193.4, 169.3, 143.0, 136.5, 134.7, 131.3, 125.8, 62.7, 47.7, 22.4; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{13}H_{14}BNO_5$: 276.1043 found: 276.1046.

*5-Formylthiophen-3-ylboronic Acid MIDA Ester (**2f**).* The general procedure was followed using 5-formylthiophen-3-ylboronic acid (47 mg, 0.3 mmol), *N*-methyliminodiacetic acid (49 mg, 0.33 mmol), and DMF (1 mL) affording desired product (67 mg, 84% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.95 (s, 1 H), 8.13 (s, 1 H), 8.06 (s, 1 H), 4.37 (d, J = 17.07 Hz, 2 H), 4.15 (d, J = 17.07 Hz, 2 H), 2.62 (s, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 184.5, 169.1, 144.1, 142.4, 141.1,61.7, 47.5; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{10}H_{10}BNO_5S$: 268.0451 found: 268.0445.

*4-Formylfuran-2-ylboronic Acid MIDA Ester (**2g**).* The general procedure was followed using 4-formylfuran-2-ylboronic acid (42 mg, 0.3 mmol), *N*-methyliminodiacetic acid (49 mg, 0.33 mmol), and DMF (1 mL) affording desired product (64 mg, 85% yield; purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.92 (s, 1 H), 8.74 (d, J = 0.95 Hz, 1 H), 6.91 (s, 1 H), 4.39 (d, J = 17.07 Hz, 2 H), 4.14 (d, J = 17.07 Hz, 2 H), 2.65 (s, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 185.7, 168.9, 156.4, 128.5, 114.1, 61.5, 47.2; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{10}H_{10}BNO_6$: 252.0679 found: 252.0679.

*2-Fluoro-4-formylphenylboronic Acid MIDA Ester (**2h**).* The general procedure was followed using 2-fluoro-4-formylphenylboronic acid (50 mg, 0.3 mmol), *N*-methyliminodiacetic acid (49 mg, 0.33 mmol), and DMF (1 mL) affording desired product (55 mg, 70% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.02 (d, J = 2.02 Hz, 1 H), 7.76−7.80 (m, 1 H), 7.70−7.76 (m, 1 H), 7.62 (dd, J = 8.59, 1.00 Hz, 1 H), 4.45 (d, J = 17.18 Hz, 2 H), 4.14 (d, J = 17.18 Hz, 2 H), 2.65 (s, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 192.3, 168.9, 165.7 (d, J = 243.70 Hz), 139.4 (d, J = 7.32 Hz), 135.9 (d, J = 8.78 Hz), 125.3, 114.8 (d, J = 25.61 Hz), 62.6, 47.6; HRMS (ESI-TOF) $[M + NH_4]^+$ calculated for $C_{12}H_{11}BFNO_5$: 297.1058 found: 297.1059.

*4-Formyl-3-(trifluoromethyl)-phenylboronic Acid MIDA Ester (**2i**).* The general procedure was followed using 4-formyl-3-(trifluoromethyl)-phenylboronic acid (65 mg, 0.3 mmol), *N*-methyliminodiacetic acid (49 mg, 0.33 mmol), and DMF (1 mL) affording desired product (77 mg, 78% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.30 (d, J = 2.01 Hz, 1 H), 8.09 (d, J = 7.53 Hz, 1 H), 7.93−8.01 (m, 2 H), 4.41 (d, J = 17.57 Hz, 2 H), 4.21 (d, J = 17.57 Hz, 2 H), 2.59 (s, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 189.9, 169.3, 137.4, 133.7, 130.1, 130.1, 130.0, 129.6, 127.6, 127.3, 125.3, 122.6, 62.3, 47.9; HRMS (ESI-TOF) $[M + NH_4]^+$ calculated for $C_{13}H_{11}BF_3NO_5$: 347.1023 found: 347.1039.

*3-Fluoro-4-formylphenylboronic Acid MIDA Ester (**2j**).* The general procedure was followed using 3-fluoro-4-formylphenylboronic acid (50 mg, 0.3 mmol), *N*-methyliminodiacetic acid (49 mg, 0.33 mmol), and DMF (1 mL) affording desired product (62 mg, 74% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.25 (s, 1 H), 7.83 (t, J = 7.28 Hz, 1 H), 7.46 (d, J = 7.53 Hz, 1 H), 7.40 (d, J = 12.05 Hz, 1 H), 4.39 (d, J = 17.07 Hz, 2 H), 4.18 (d, J = 17.07 Hz, 2 H), 2.57 (s, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 188.1 (d, J = 5.87 Hz), 169.2, 162.9 (d, J = 258.23 Hz), 128.9 (d, J = 2.93 Hz), 128.4 (d, J = 1.47 Hz), 123.9 (d, J = 8.07 Hz), 120.2 (d, J = 18.34 Hz), 62.1, 47.7; HRMS (ESI-TOF) $[M + NH_4]^+$ calculated for $C_{12}H_{11}BFNO_5$: 297.1055 found: 297.1069.

*2-Chloro-5-formylphenylboronic Acid MIDA Ester (**2k**).* The general procedure was followed using 2-chloro-5-formylphenylboronic acid (55 mg, 0.3 mmol), *N*-methyliminodiacetic acid (49 mg, 0.33 mmol), and DMF (1 mL) affording desired product (79 mg, 89% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.03 (s, 1 H), 8.15 (d, J = 2.02 Hz, 1 H), 7.92 (dd, J = 8.08, 2.02 Hz, 1 H), 7.66 (d, J = 8.08 Hz, 1 H), 4.46 (d, J = 17.18 Hz, 2 H), 4.21 (d, J = 17.68 Hz, 2 H), 2.70 (s, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 192.6, 169.1, 143.9, 137.0, 134.1, 131.8, 130.8, 63.9, 48.2; HRMS (ESI-TOF) $[M + NH_4]^+$ calculated for $C_{12}H_{11}BClNO_5$: 313.0763 found: 313.0767.

*2,4-Difluoro-3-formylphenylboronic Acid MIDA Ester (**2l**).* The general procedure was followed using 2,4-difluoro-3-formylphenylboronic acid (56 mg, 0.3 mmol), *N*-methyliminodiacetic acid (49 mg, 0.33 mmol), and DMF (1 mL) affording desired product (65 mg, 73% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.2 (s, 1 H), 7.8 (dd, J = 15.56, 7.03 Hz, 1 H), 7.2−7.3 (m, 1 H), 4.4 (d, J = 17.57 Hz, 2 H), 4.1 (d, J = 17.57 Hz, 2 H), 2.7 (s, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 185.3−185.5 (m), 168.9, 166.8−167.0 (m), 164.3 (dd, J = 12.47, 5.13 Hz), 162.3−162.3 (m), 161.6 (d, J = 6.60 Hz), 141.6−141.9 (m), 113.2−113.5 (m), 112.4 (dd, J = 19.81, 3.67 Hz), 62.5, 47.6; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{12}H_{10}BF_2NO_5$: 298.0698 found: 298.0707.

*4-Fluoro-3-formylphenylboronic Acid MIDA Ester (**2m**).* The general procedure was followed using 4-fluoro-3-formylphenylboronic acid (50 mg, 0.3 mmol), *N*-methyliminodiacetic acid (49 mg, 0.33 mmol), and DMF (1 mL) affording desired product (50 mg, 60% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR(400 MHz, DMSO-d_6) δ ppm 10.26 (s, 1 H), 7.94 (dd, J = 7.58, 2.02 Hz, 1 H), 7.81 (ddd, J = 8.34, 5.81, 2.02 Hz, 1 H), 7.39 (dd, J = 11.12, 8.08 Hz, 1 H), 4.36 (d, J = 17.18 Hz, 2 H), 4.16 (d, J = 17.18 Hz, 2 H), 2.55 (s, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 188.3 (d, J = 5.12 Hz), 169.2, 162.8, 141.1 (d, J = 9.51 Hz), 134.0, 123.0, 116.0 (d, J = 19.76 Hz), 62.1, 47.7; HRMS (ESI-TOF) $[M + NH_4]^+$ calculated for $C_{12}H_{11}BFNO_5$: 297.1058 found: 297.1051.

*5-Formyl-2-methoxyphenylboronic Acid MIDA Ester (**2n**).* The general procedure was followed using 5-formyl-2-methoxyphenylboronic acid (54 mg, 0.3 mmol), *N*-methyliminodiacetic acid (49 mg, 0.33 mmol), and DMF (1 mL) affording desired product (71 mg, 81% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.90 (s, 1 H), 8.03 (d, J = 2.51 Hz, 1 H), 7.95 (dd, J = 8.53, 2.51 Hz, 1 H), 7.18 (d, J = 8.53 Hz, 1H), 4.41 (d, J = 17.07 Hz, 2 H), 4.07 (d, J = 17.07 Hz, 2 H), 3.85 (s, 3 H), 2.62 (s, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 191.8, 169.3, 166.9, 135.6, 133.9, 129.1, 110.7, 63.3, 55.7, 47.3; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{13}H_{14}BNO_6$: 292.0992 found: 292.0988.

*3-Chloro-4-formylphenylboronic Acid MIDA Ester (**2o**).* The general procedure was followed using 3-chloro-4-formylphenylboronic acid (55 mg, 0.3 mmol), *N*-methyliminodiacetic acid (49 mg, 0.33 mmol), and DMF (1 mL) affording desired product (64 mg, 72% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.36 (s, 1 H), 7.86 (d, J = 8.03 Hz, 1 H), 7.64 (d, J = 1.20 Hz, 1 H), 7.59 (dd, J = 8.03, 1.20 Hz, 1 H), 4.39 (d, J = 17.57 Hz, 2 H), 4.19 (d, J = 17.57 Hz, 2 H), 2.58 (s, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 190.1, 169.2, 135.8, 134.5, 132.2, 131.8, 128.8, 62.2, 47.8; HRMS (ESI-TOF) $[M + NH_4]^+$ calculated for $C_{12}H_{11}BClNO_5$: 313.0759 found: 313.0762.

*3-Formyl-2-methoxyphenylboronic Acid MIDA Ester (**2p**).* The general procedure was followed using 3-formyl-2-methoxyphenylboronic acid (54 mg, 0.3 mmol), *N*-methyliminodiacetic acid (49 mg, 0.33 mmol), and DMF (1 mL) affording desired product (84 mg, 96% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.26 (s, 1 H), 7.84 (dd, J = 7.53, 2.01 Hz, 1 H), 7.81 (dd, J = 7.53, 2.01 Hz, 1 H), 7.34 (t, J = 7.03 Hz, 1 H), 4.42 (d, J = 17.07 Hz, 2 H), 4.08 (d, J = 17.07 Hz, 2 H), 3.80 (s, 3 H), 2.57 (s, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 190.2, 169.2, 166.2, 141.0, 131.2, 128.3, 124.3, 65.3,

62.9, 47.7; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{13}H_{14}BNO_6$: 292.0992 found: 292.0989.

*2-Chloro-pyridin-3-ylboronic Acid MIDA Ester (**2q**).* The general procedure was followed using 2-chloropyridine-3-boronic acid (65.6 mg, 0.4 mmol), *N*-methyliminodiacetic acid (65.4 mg, 0.44 mmol), and DMF (1.3 mL) affording desired product (99.4 mg, 88% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.41 (dd, J = 2.0 Hz, 4.5 Hz, 1 H), 8.00 (dd, J = 2.0 Hz, 7.5 Hz, 1 H), 7.44 (dd, J = 5.0 Hz, 7.5 Hz, 1 H), 4.46 (d, J = 17.6 Hz, 2 H), 4.20 (d, J = 17.6 Hz, 2 H), 2.72 (s, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 169.1, 154.2, 150.4, 145.6, 122.6, 63.9, 48.1; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{10}H_{10}BClN_2O_4$: 269.0495 found: 269.0502.

*2-Bromo-quinolin-3-ylboronic Acid MIDA Ester (**2r**).* The general procedure was followed using 2-bromoquinoline-3-boronic acid (101 mg, 0.4 mmol), *N*-methyliminodiacetic acid (65.4 mg, 0.44 mmol), and DMF (1.3 mL) affording desired product (120.7 mg, 76% yield, purity >91% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.54 (s, 1 H), 8.09 (d, J = 7.0 Hz, 1 H), 7.96 (d, J = 8.0 Hz, 1 H), 7.85 (td, J = 1.5 Hz, 7.0 Hz, 1 H), 7.68 (td, J = 1 Hz, 7.0 Hz, 1 H), 4.51 (d, J = 17.6 Hz, 2 H), 4.27 (d, J = 17.1 Hz, 2 H), 2.81 (s, 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 169.2, 148.0, 146.7, 145.6, 131.3, 128.5, 127.4, 127.3, 126.3, 64.2, 48.7; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{14}H_{12}BBrN_2O_4$: 363.0146 found: 363.0157.

General Procedure for the Library Synthesis. *Aryl Halide Diversity.* To a set of 2 dram round-bottom vials were added suspensions (THF) of 3-formylphenyl MIDA boronate (0.4 M, 0.5 mL, 0.2 mmol, 1 equiv), sodium triacetoxyborohydride (0.8 M, 0.5 mL, 0.4 mmol, 2 equiv), and a solution of (*S*)-prolinol (0.8 M, 0.5 mL, 0.4 mmol 2 equiv), and the reactions were shaken at ambient temperature for 18 h. To the vials was added a solution of $K_2CO_{3(aq)}$ (2 M, 1 mL, 2 mmol, 10 equiv). The reactions were then transferred to a set of 2−5 mL microwave vials containing preweighed amounts of the aryl halide diversity reagents (0.4 mmol, 2 equiv). To these vials was added a solution of PEPPSI-IPr (0.1 M, 10 μmol, 0.05 equiv in MeCN), and the vials were irradiated in a microwave reactor at 150 °C for 20 min, followed by analysis by HPLC-MS.

Amine Diversity. To a set of 2 dram round-bottom vials were added either suspensions or solutions of the amines (0.8 M in THF, 0.5 mL, 0.4 mmol, 2 equiv) followed by suspensions (THF) of 3-formylphenyl MIDA boronate (0.4 M, 0.5 mL, 0.2 mmol, 1 equiv) and sodium triacetoxyborohydride (0.8 M, 0.5 mL, 0.4 mmol, 2 equiv). The reactions were shaken at ambient temperature for 18 h. To the vials was added a solution of $K_2CO_{3(aq)}$ (2 M, 1 mL, 2 mmol, 10 equiv). The reactions were then transferred to a set of 2−5 mL microwave vials. To these vials was added a solution of 2-chloropyridine (1 M, 0.4 mL, 0.4 mmol, 2 equiv) as well as PEPPSI-IPr (0.1 M, 10 μmol, 0.05 equiv in MeCN), and the vials were irradiated in a microwave reactor at 150 °C for 20 min, followed by analysis by HPLC-MS.

Formyl Boronate Diversity. To a set of 2 dram round-bottom vials were added neat formyl boronates (0.2 mmol, 1 equiv) followed by a solution of (*S*)-prolinol (0.8 M in THF, 0.5 mL, 0.4 mmol, 2 equiv) and a suspension of sodium triacetoxyborohydride (0.8 M in THF, 0.5 mL, 0.4 mmol, 2 equiv). The reactions were shaken at ambient temperature for 18 h. To the vials was added a solution of $K_2CO_{3(aq)}$ (2 M, 1 mL, 2 mmol, 10 equiv). The reactions were then transferred to a set of 2−5 mL microwave vials. To these vials was added a solution of either 2-chloropyridine or 2-bromopyrazine (1 M, 0.4 mL, 0.4 mmol, 2 equiv) as well as PEPPSI-IPr (0.1 M, 10 μmol, 0.05 equiv in MeCN), and the vials were irradiated in a microwave reactor at 150 °C for 20 min, followed by analysis by HPLC-MS.

General Procedure for the Library Workup. To the microwave vials was added DCM and water, and the resulting biphasic mixture was transferred to hydrophobic phase separators. Organic phases were collected and evaporated using a centrifugal evaporation system.

General Procedure for the Library Purification. Library compounds were purified by prep-HPLC using a gradient of acetonitrile and water with either 0.1% TFA (Sunfire 19 × 100 mm column) or 5 mM NH_4OH (Gemini 21.2 × 100 mm column) as modifier. Gradients and collection wavelengths were determined for each compound and are indicated below.

*Gram Scale Procedure. (S)-(1-(3-(Pyrazin-2-yl)benzyl)pyrrolidin-2-yl)methanol (**6**).* To a suspension of 3-formylphenylboronic acid MIDA ester (1 g, 3.83 mmol) in THF 4 mL) was added (*S*)-prolinol (0.775 mg, 7.66 mmol, 2 equiv) and sodium triacetoxyborohydride (1.624 g, 7.66 mmol). The reaction was stirred at room temperature for 1 h at which point the reaction was judged to be complete (LC/MS). To the reaction mixture was added, $K_2CO_{3(aq)}$ (9.58 mL, 4 M, 38.3 mmol, 10 equiv), MeCN (10 mL), 2-bromopyrazine (1.218 g, 7.66 mmol, 2 equiv) and PEPPSI-IPr (0.130 g, 0.192 mmol 0.05 equiv), and the reaction mixture was heated at 80 °C for 18 h. The reaction mixture was concentrated by half and diluted with water and dichloromethane. The organic phase was separated and concentrated to afford the crude product. The crude material was purified by column chromatography (1−15% DCM/MeOH) to afford product (596 mg, 58% yield, purity >95% HPLC at UV 254 nm).

*Boronyl Aldehyde Diversity. (S)-(1-(3-(Pyrazin-2-yl)benzyl)pyrrolidin-2-yl)methanol (**6**).* The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 2-bromopyrazine. The reaction was purified by prep-HPLC (21−61% MeCN/water 5 mM NH_4OH collected at 246 nm) affording product (28 mg, 51% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, MeOD) δ ppm 9.13 (s, 1 H), 8.68 (s, 1 H), 8.53 (d, J = 3.01 Hz, 1 H), 8.09 (s, 1 H), 7.99 (d, J = 4.02 Hz, 1 H), 7.45−7.56 (m, 2 H), 4.20 (d, J = 13.05 Hz, 1 H), 3.57−3.69 (m, 1 H), 3.47−3.58 (m, 2 H), 2.89−3.02 (m, 1 H), 2.74 (d, J = 5.02 Hz, 1 H), 2.35 (d, J = 7.53 Hz, 1 H), 1.99 (dd, J = 8.78, 4.27 Hz, 1 H), 1.70 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ ppm 153.9, 145.7, 144.3, 143.3, 138.0, 135.2, 132.7, 130.6, 129.7, 128.0, 68.2, 63.4, 60.0, 55.7, 28.3, 23.4; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{16}H_{19}N_3O$: 270.1606 found: 270.1617.

*(S)-(1-(3-(Pyridin-2-yl)benzyl)pyrrolidin-2-yl)methanol (**7**).* The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 2-chloropyridine. The reaction was purified by prep-HPLC (27−67% MeCN/water 5 mM NH_4OH collected at 246 nm) affording product (28 mg, 54% yield, purity >95% HPLC at 254 nm): ^{1}H NMR (400 MHz, MeOD) δ ppm 8.68−8.57 (m, 1 H), 7.99−7.79 (m, 4 H), 7.50−7.41 (m, 2 H), 7.36 (ddd, J = 1.8, 5.1, 6.8 Hz, 1 H), 4.19 (d, J = 12.6 Hz, 1 H), 3.62 (dd, J = 4.5, 6.1 Hz, 1 H), 3.57−3.46 (m, 2 H), 2.95 (dt, J = 3.3, 6.2 Hz, 1 H), 2.72 (dd, J = 4.5, 8.6 Hz, 1 H), 2.42−2.27 (m, 1 H), 2.06−1.91 (m, 1 H), 1.79−1.63 (m, 3 H); ^{13}C NMR (101 MHz, MeOD) δ ppm ^{13}C NMR (101 MHz, MeOD) δ 159.1, 150.4, 141.0, 140.6, 139.1, 131.4, 130.0, 129.3, 127.2, 123.9, 122.8, 66.7, 65.4, 60.7, 55.9, 29.2, 23.8; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{17}H_{20}N_2O$: 269.1654 found: 269.1652.

*(S)-(1-(2,6-Difluoro-3-(pyridin-2-yl)benzyl)pyrrolidin-2-yl)methanol (**8**).* The general procedure was followed using (*S*)-prolinol, 2,4-difluoro-3-formylphenyl MIDA boronate, and 2-chloropyridine. The reaction was purified by prep-HPLC (27−67% MeCN/water 5 mM NH_4OH collected at 238 nm) affording product (11 mg, 17% yield, purity >95% HPLC at UV 254 nm): HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{17}H_{18}F_2N_2O$: 305.1465 found: 305.1480.

*(S)-(1-(2-Methoxy-3-(pyridin-2-yl)benzyl)pyrrolidin-2-yl)methanol (**9**).* The general procedure was followed using (*S*)-prolinol, 2-methoxy-3-formylphenyl MIDA boronate, and 2-chloropyridine. The reaction was purified by prep-HPLC (30−70% MeCN/water 5 mM NH_4OH collected at 220 nm) affording product (15 mg, 25% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, MeOD) δ ppm 8.65 (d, J = 4.02 Hz, 1 H), 7.89−7.98 (m, 1 H), 7.79−7.88 (m, 1 H), 7.48−7.62 (m, 2 H), 7.38−7.48 (m, 1 H), 7.22−7.36 (m, 1 H), 4.27−4.53 (m, 1 H), 3.78−3.91 (m, 1 H), 3.63−3.76 (m, 2 H), 3.42 (s, 3 H), 3.09−3.28

(m, 2 H), 2.73−2.95 (m, 1 H), 2.00−2.23 (m, 1 H), 1.71−1.98 (m, 3 H); ^{13}C NMR (101 MHz, MeOD) δ ppm 158.3, 157.5, 150.2, 138.7, 136.8, 134.6, 134.4, 133.6, 126.3, 125.5, 124.1, 62.1, 55.7, 54.6, 28.3, 25.3, 23.5, 20.6; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{18}H_{22}N_2O_2$: 299.1760 found: 299.1759.

*(S)-(1-(4-(Pyrazin-2-yl)benzyl)pyrrolidin-2-yl)methanol (**10**).* The general procedure was followed using (*S*)-prolinol, 4-formylphenyl MIDA boronate, and 2-bromopyrazine. The reaction was purified by prep-HPLC (26−66% MeCN/water 5 mM NH_4OH collected at 250 nm) affording product (33 mg, 64% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, MeOD) δ ppm 9.09 (s, 1 H), 8.66 (s, 1 H), 8.51 (d, *J* = 2.53 Hz, 1 H), 8.04 (d, *J* = 8.08 Hz, 2 H), 7.52 (d, *J* = 8.08 Hz, 2 H), 4.15 (d, *J* = 13.14 Hz, 1 H), 3.61 (dd, *J* = 10.61, 4.55 Hz, 1 H), 3.44−3.55 (m, 2 H), 2.89−3.00 (m, 1 H), 2.71 (dd, *J* = 8.59, 4.55 Hz, 1 H), 2.26−2.38 (m, 1 H),1.91−2.06 (m, 1 H), 1.63−1.80 (m, 3 H); ^{13}C NMR (101 MHz, MeOD) δ ppm 154.2, 145.6, 143.9, 143.1, 142.6, 136.3, 131.1, 128.0, 66.6, 65.3, 60.2, 55.7, 29.1, 23.6; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{16}H_{19}N_3O$: 270.1606 found: 270.1610.

*(S)-(1-(4-(Pyridin-2-yl)benzyl)pyrrolidin-2-yl)methanol (**11**).* The general procedure was followed using (*S*)-prolinol, 4-formylphenyl MIDA boronate, and 2-chloropyridine. The reaction was purified by prep-HPLC (27−67% MeCN/water 5 mM NH_4OH collected at 278 nm) affording product (21 mg, 39% yield, purity >95% HPLC at UV 254 nm): HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{17}H_{20}N_2O$: 269.1654 found: 269.1641.

*(S)-(1-(3-Methyl-4-(pyridin-2-yl)benzyl)pyrrolidin-2-yl)methanol (**12**).* The general procedure was followed using (*S*)-prolinol, 2-methyl-4-formylphenyl MIDA boronate, and 2-chloropyridine. The reaction was purified by prep-HPLC (29−69% MeCN/water 5 mM NH_4OH collected at 220 nm) affording product (14 mg, 25% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, MeOD) δ ppm 8.61 (d, *J* = 4.0 Hz, 1 H), 7.90−7.97 (m, 1 H), 7.48−7.53 (m, 1 H), 7.42 (dd, *J* = 7.5, 5.0 Hz, 1 H), 7.39 (s, 1 H), 7.35 (s, 2 H), 4.33 (d, *J* = 12.0 Hz, 1 H), 3.71−3.85 (m, 1 H), 3.61−3.68 (m, 2 H),3.04−3.20 (m, 2 H), 2.61−2.82 (m, 1 H), 2.32 (s, 3 H),2.02−2.17 (m, 1 H), 1.69−1.96 (m, 3 H); ^{13}C NMR (101 MHz, MeOD) δ ppm 160.6, 149.7, 141.3, 138.7, 137.5, 136.1, 133.3, 130.9, 128.6, 126.0, 123.8, 67.9, 67.4, 59.8, 55.6, 28.3, 23.4, 20.2; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{18}H_{22}N_2O$: 283.1810 found: 283.1804.

*(S)-(1-(3-Fluoro-4-(pyridin-2-yl)benzyl)pyrrolidin-2-yl)methanol (**13**).* The general procedure was followed using (*S*)-prolinol, 2-fluoro-4-formylphenyl MIDA boronate, and 2-chloropyridine. The reaction was purified by prep-HPLC (28−68% MeCN/water 5 mM NH_4OH collected at 242 nm) affording product (8 mg, 14% yield, purity >95% HPLC at UV 254 nm): HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{17}H_{19}FN_2O$: 287.1560 found: 287.1566.

*(S)-(1-(4-(Pyridin-2-yl)-2-(trifluoromethyl)benzyl)pyrrolidin-2-yl)methanol (**14**).* The general procedure was followed using (*S*)-prolinol, 3-trifluoromethyl-4-formylphenyl MIDA boronate, and 2-chloropyridine. The reaction was purified by prep-HPLC (5−45% MeCN/water 0.1% TFA collected at 250 nm) affording product as a TFA salt (53 mg, 62% yield, purity >95% HPLC at UV 254 nm): HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{18}H_{19}F_3N_2O$: 337.1528 found: 337.1515.

*(S)-(1-(2-Fluoro-4-(pyridin-2-yl)benzyl)pyrrolidin-2-yl)methanol (**15**).* The general procedure was followed using (*S*)-prolinol, 3-fluoro-4-formylphenyl MIDA boronate, and 2-chloropyridine. The reaction was purified by prep-HPLC (29−69% MeCN/water 5 mM NH_4OH collected at 248 nm) affording product (19 mg, 33% yield, purity >95% HPLC at UV 254 nm): HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{17}H_{19}FN_2O$: 287.1560 found: 287.1565.

*(S)-(1-(2-Chloro-4-(pyridin-2-yl)benzyl)pyrrolidin-2-yl)methanol (**16**).* The general procedure was followed using (*S*)-prolinol, 3-chloro-4-formylphenyl MIDA boronate, and 2-chloropyridine. The reaction was purified by prep-HPLC (5−45% MeCN/water 0.1% TFA collected at 284 nm) affording product as a TFA salt (44 mg, 56% yield, purity >95% HPLC at UV 254 nm): HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{17}H_{19}ClN_2O$: 303.1259 found: 303.1260.

*(S)-(1-((5-(Pyrazin-2-yl)furan-2-yl)methyl)pyrrolidin-2-yl)methanol (**17**).* The general procedure was followed using (*S*)-prolinol, 5-formylfuran MIDA boronate, and 2-bromopyrazine. The reaction was purified by prep-HPLC (17−57% MeCN/water 5 mM NH_4OH collected at 290 nm) affording product (13 mg, 25% yield, purity >95% HPLC at UV 254 nm): HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{14}H_{17}N_3O_2$: 260.1399 found: 260.1408.

*(S)-(1-(2-(Pyridin-2-yl)benzyl)pyrrolidin-2-yl)methanol (**18**).* The general procedure was followed using (*S*)-prolinol, 2-formylphenyl MIDA boronate, and 2-chloropyridine affording no product.

*(S)-(1-((3-(Pyridin-2-yl)furan-2-yl)methyl)pyrrolidin-2-yl)methanol (**19**).* The general procedure was followed using (*S*)-prolinol, 2-formylfuran-3-yl MIDA boronate, and 2-chloropyridine affording no product.

*(S)-(1-((5-(Pyrazin-2-yl)thiophen-2-yl)methyl)pyrrolidin-2-yl)methanol (**20**).* The general procedure was followed using (*S*)-prolinol, 5-formylthiophen-2-yl MIDA boronate, and 2-bromopyrazine. The reaction was purified by prep-HPLC (22−62% MeCN/water 5 mM NH_4OH collected at 292 nm) affording product (11 mg, 22% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, MeOD) δ ppm 9.00 (s, 1 H), 8.50 (s, 1 H), 8.38 (d, *J* = 2.53 Hz, 1 H), 7.70 (d, *J* = 3.54 Hz, 1 H), 7.07 (d, *J* = 3.54 Hz, 1 H), 4.26 (d, *J* = 14.15 Hz, 1 H), 3.84 (d, *J* = 14.65 Hz, 1 H), 3.57−3.65 (m, 1 H), 3.49−3.56 (m, 1 H), 3.04−3.15 (m, 1 H), 2.80 (br. s., 1 H),2.47 (q, *J* = 8.42 Hz, 1 H), 1.90−2.04 (m, 1 H), 1.60−1.82 (m, 3 H); ^{13}C NMR (101 MHz, MeOD) δ ppm 150.3, 145.5, 143.1, 141.4, 129.1, 127.4, 66.0, 65.4, 55.5, 54.2, 29.1, 23.8; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{14}H_{17}N_3OS$: 276.1171 found: 276.1166.

*(S)-(1-((5-(Pyridin-2-yl)thiophen-2-yl)methyl)pyrrolidin-2-yl)methanol (**21**).* The general procedure was followed using (*S*)-prolinol, 5-formylthiophen-2-yl MIDA boronate, and 2-chloropyridine. The reaction was purified by prep-HPLC (25−65% MeCN/water 5 mM NH_4OH collected at 310 nm) affording product (15 mg, 28% yield, purity >95% HPLC at UV 254 nm); HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{15}H_{18}N_2OS$: 275.1218 found: 275.1222.

*Aryl Halide Diversity. (S)-3′-((2-(Hydroxymethyl)pyrrolidin-1-yl)methyl)biphenyl-4-sulfonamide (**22**).* The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 4-bromobenzenesulfonamide. The reaction was purified by prep-HPLC (23−63% MeCN/water 5 mM NH_4OH collected at 254 nm) affording product (31 mg, 44% yield, purity >95% HPLC at UV 254 nm); HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{18}H_{22}N_2O_3S$: 347.1429 found: 347.1432.

*(S)-(1-((4′-(Dimethylamino)biphenyl-3-yl)methyl)pyrrolidin-2-yl)methanol (**23**).* The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 4-bromo-*N*,*N*-dimethylaniline. The reaction was purified by prep-HPLC (5−45% MeCN/water 0.1% TFA collected at 252 nm) affording product as a TFA salt (67 mg, 79% yield, purity >95% HPLC at UV 254 nm): HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{20}H_{26}N_2O$: 311.2126 found: 311.2122.

*(S)-(1-((4′-(Trifluoromethyl)biphenyl-3-yl)methyl)pyrrolidin-2-yl)methanol (**24**).* The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 4-trifluoromethyl-bromobenzene. The reaction was purified by prep-HPLC (12−52% MeCN/water 0.1% TFA collected at 252 nm) affording product as a TFA salt (47 mg, 53% yield, purity >95% HPLC at UV 254 nm): HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{19}H_{20}F_3NO$: 336.1575 found: 336.1579.

*(S)-3′-((2-(Hydroxymethyl)pyrrolidin-1-yl)methyl)biphenyl-4-ol (**25**).* The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 4-bromophenol. The reaction was purified by prep-HPLC (5−45% MeCN/water 0.1% TFA collected at 254 nm) affording product as a TFA salt (28 mg, 36% yield, purity >95% HPLC at

UV 254 nm): HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{18}H_{21}NO_2$: 284.1651 found: 284.1652.

(S)-(1-(3-(Thiazol-2-yl)benzyl)pyrrolidin-2-yl)methanol (**26**). The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 2-bromothiazole. The reaction was purified by prep-HPLC (29−69% MeCN/water 5 mM NH_4OH collected at 290 nm) affording product (21 mg, 38% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, MeOD) δ ppm 8.07 (s, 1 H), 7.96 (d, *J* = 7.03 Hz, 1 H), 7.90 (d, *J* = 3.01 Hz, 1 H), 7.65 (d, *J* = 3.51 Hz, 1 H), 7.46−7.61 (m, 2 H), 4.48 (d, *J* = 13.05 Hz, 1 H), 3.97 (d, *J* = 11.54 Hz, 1 H),3.60−3.75 (m, 2 H), 3.11−3.28 (m, 2 H), 2.87 (br. s., 1 H),2.13 (ddd, *J* = 13.30, 7.78, 7.53 Hz, 1 H),1.76−2.05 (m, 3 H); ^{13}C NMR (101 MHz, MeOD) δ ppm 169.5, 144.6, 135.2, 133.0, 130.8, 129.2, 127.7, 121.3, 68.6, 62.4, 59.6, 55.6, 28.0, 23.4; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{15}H_{18}N_2OS$: 275.1218 found: 275.1217.

(S)-(1-(3-(5-Methylthiophen-2-yl)benzyl)pyrrolidin-2-yl)methanol (**27**). The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 2-bromo-5-methylthiophene. The reaction was purified by prep-HPLC (5−45% MeCN/water 0.1% TFA collected at 284 nm) affording product as a TFA salt (42 mg, 53% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, MeOD) δ ppm 7.65 (s, 1 H), 7.52−7.61 (m, 2 H), 7.46−7.51 (m, 1 H), 7.34 (d, *J* = 5.02 Hz, 1 H), 6.97 (d, *J* = 5.02 Hz, 1 H), 4.69 (d, *J* = 13.05 Hz, 1 H), 4.29 (d, *J* = 13.05 Hz, 1 H), 3.63−3.86 (m, 3 H), 3.36−3.51 (m, 1 H), 2.33 (s, 3 H), 2.25 (br. m., 1 H), 2.25 (br. m., 1 H), 2.11 (br. m., 1 H), 1.94 (br. m., 2 H); ^{13}C NMR (101 MHz, MeOD) δ ppm 137.5, 137.5, 135.1, 132.4, 132.3, 131.5, 130.7, 130.5, 125.2, 70.1, 60.7, 59.5, 55.7, 27.3, 23.2, 15.0; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{17}H_{21}NOS$: 288.1422 found: 288.1421.

(S)-(1-(3-(Furan-2-yl)benzyl)pyrrolidin-2-yl)methanol (**28**). The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 3-bromofuran. The reaction was purified by prep-HPLC (5−45% MeCN/water 0.1% TFA collected at 254 nm) affording product as a TFA salt (22 mg, 29% yield, purity >95% HPLC at UV 254 nm); HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{16}H_{19}NO_2$: 258.1494 found: 258.1503.

(S)-5-(3-((2-(Hydroxymethyl)pyrrolidin-1-yl)methyl)phenyl)nicotinamide (**29**). The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 5-bromonicotinamide. The reaction was purified by prep-HPLC (14−54% MeCN/water 5 mM NH_4OH collected at 252 nm) affording product (22 mg, 35% yield, purity >95% HPLC at UV 254 nm): HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{18}H_{21}N_3O_2$: 312.1712 found: 312.1709.

(S)-(1-(3-(1-(Phenylsulfonyl)-1H-indol-3-yl)benzyl)pyrrolidin-2-yl)methanol (**30**). The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 1-benzenesulfonyl-3-bromoindole. The reaction was purified by prep-HPLC (59−99% MeCN/water 5 mM NH_4OH collected at 254 nm) affording product (45 mg, 52% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, MeOD) δ ppm 8.1 (d, *J* = 8.53 Hz, 1 H), 8.0 (d, *J* = 7.03 Hz, 2 H), 7.9 (s, 1 H), 7.8−7.9 (m, 2 H), 7.8 (d, *J* = 7.53 Hz, 1 H), 7.6−7.7 (m, 2 H), 7.5−7.6 (m, 3 H), 7.4 (t, *J* = 7.78 Hz, 1 H), 7.3 (t, *J* = 7.53 Hz, 1 H), 4.7 (d, *J* = 13.05 Hz, 1 H), 4.3 (d, *J* = 13.05 Hz, 1 H), 3.8−3.8 (m, 1 H), 3.7−3.8 (m, 2 H), 3.4−3.5 (m, 1 H), 3.3−3.4 (m, 1 H), 2.2−2.3 (m, 1 H), 2.1 (dd, *J* = 7.78, 4.77 Hz, 1 H), 1.9−2.0 (m, 2 H); ^{13}C NMR (101 MHz, MeOD) δ ppm 141.0, 139.3, 137.0, 135.4, 134.3, 130.7, 130.6, 130.0, 130.0, 129.8, 128.0, 127.8, 126.1, 125.6, 125.0, 124.5, 121.6, 115.0, 66.7, 65.4, 60.7, 55.8, 29.1, 23.6; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{26}H_{26}N_2O_3S$: 447.1742 found: 447.1740.

(S)-(1-(3-(5-Methyl-1H-pyrazol-4-yl)benzyl)pyrrolidin-2-yl)methanol (**31**). The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 4-bromo-3-methyl-1*H*-pyrazole. The reaction was purified by prep-HPLC (5−45% MeCN/water 0.1% TFA collected at 220 nm) affording no product.

(S)-(1-(3-(Pyrimidin-2-yl)benzyl)pyrrolidin-2-yl)methanol (**32**). The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 2-chloropyrimidine. The reaction was purified by prep-HPLC (35−75% MeCN/water 5 mM NH_4OH collected at 250 nm) affording product (23 mg, 44% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, MeOD) δ ppm 8.84 (d, *J* = 5.05 Hz, 2 H), 8.39 (s, 1 H), 8.30 (d, *J* = 7.58 Hz, 1 H), 7.48−7.54 (m, 1 H), 7.42−7.49 (m, 1 H), 7.36 (t, *J* = 5.05 Hz, 1 H), 4.18 (d, *J* = 12.63 Hz, 1 H), 3.59−3.66 (m, 1 H), 3.48−3.57 (m, 2 H), 2.91−3.00 (m, 1 H), 2.68−2.79 (m, 1 H), 2.36 (d, *J* = 7.58 Hz, 1 H), 1.92−2.05 (m, 1 H),1.65−1.79 (m, 3 H); ^{13}C NMR (101 MHz, MeOD) δ ppm 165.9, 158.8, 148.6, 139.0, 133.1, 130.3, 129.8, 128.3, 125.6, 120.9, 66.7, 65.4, 60.7, 55.8, 29.2, 23.8; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{16}H_{19}N_3O$: 270.1606 found: 270.1616.

(S)-(1-(3-(1H-Indazol-3-yl)benzyl)pyrrolidin-2-yl)methanol (**33**). The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 3-chloroindazole. The reaction was purified by prep-HPLC (5−45% MeCN/water 0.1% TFA collected at 302 nm) affording product as a TFA salt (29 mg, 35% yield, purity >95% HPLC at UV 254 nm); HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{19}H_{21}N_3O$: 308.1763 found: 308.1766.

(S)-(1-(3-(1,3-Dimethyl-1H-pyrazol-5-yl)benzyl)pyrrolidin-2-yl)methanol (**34**). The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 5-bromo-1,3-dimethyl-1*H*-pyrazole. The reaction was purified by prep-HPLC (5−45% MeCN/water 0.1% TFA collected at 244 nm) affording product as a TFA salt (54 mg, 67% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, MeOD) δ ppm 7.65 (s, 1 H), 7.63−7.56 (m, 3 H), 6.22 (s, 1 H), 4.71 (d, *J* = 12.5 Hz, 1 H), 4.32 (d, *J* = 13.1 Hz, 1 H), 3.81 (s, 3 H), 3.78 (dd, *J* = 2.8, 10.8 Hz, 1 H), 3.76−3.67 (m, 2 H), 3.47−3.39 (m, 1 H), 3.32 − 3.26 (m, 1H), 2.29−2.22 (m, 1 H), 2.26 (s, 3 H), 2.18−2.09 (m, 1 H), 2.01−1.82 (m, 2 H); ^{13}C NMR (101 MHz, MeOD) δ ppm 149.0, 145.2, 132.9, 132.6, 132.1, 132.1, 131.3, 130.9, 107.0, 70.2, 60.6, 59.2, 55.7, 37.3, 27.3, 23.2, 13.2; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{17}H_{23}N_3O$: 286.1919 found: 286.1913.

(S)-(1-(3-(3-Methyl-1-phenyl-1H-pyrazol-5-yl)benzyl)pyrrolidin-2-yl)methanol (**35**). The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole. The reaction was purified by prep-HPLC (5−45% MeCN/water 0.1% TFA collected at 250 nm) affording product as a TFA salt (39 mg, 42% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, MeOD) δ ppm 7.57−7.40 (m, 4 H), 7.40−7.37 (m, 2 H), 7.34 (s, 1 H), 7.27 (dd, *J* = 2.0, 8.0 Hz, 2 H), 6.48 (s, 1 H), 4.56 (d, *J* = 13.1 Hz, 1 H), 4.13 (d, *J* = 13.1 Hz, 1 H), 3.79−3.68 (m, 1 H), 3.68−3.60 (m, 1 H), 3.56−3.46 (m, 1 H), 3.17−3.07 (m, 1 H), 3.00−2.87 (m, 1 H), 2.35 (s, 3 H), 2.20−2.08 (m, 1 H), 2.07−1.95 (m, 1 H), 1.95−1.79 (m, 2 H); ^{13}C NMR (101 MHz, MeOD) δ ppm 151.1, 144.8, 141.1, 132.7, 132.5, 132.2, 132.1, 132.0, 131.3, 130.8, 130.4, 129.2, 127.2, 108.9, 69.7, 60.6, 58.7, 55.2, 27.1, 23.0, 13.3; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{22}H_{25}N_3O$: 348.2076 found: 348.2082.

(S)-(1-(3-(1-Methyl-1H-imidazol-5-yl)benzyl)pyrrolidin-2-yl)methanol (**36**). The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 5-bromo-1-methyl-1*H*-imidazole. The reaction was purified by prep-HPLC (17−57% MeCN/water 5 mM NH_4OH collected at 260 nm) affording product (20 mg, 39% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, MeOD) δ ppm 7.62 (s, 1 H), 7.44−7.54 (m, 3 H), 7.16 (s, 1 H), 7.02 (s, 1 H), 4.15 (d, *J* = 13.14 Hz, 1 H), 3.76 (s, 3 H), 3.45−3.63 (m, 3 H), 2.95 (br. m., 1 H), 2.73 (br. m., 1 H), 2.34 (br. m., 1 H), 1.98 (br. m., 1 H), 1.63−1.80 (m, 3 H); ^{13}C NMR (101 MHz, MeOD) δ ppm 149.1, 140.8, 131.4, 131.2, 130.9, 129.7, 128.8, 128.2, 124.0, 66.5, 65.3, 60.3, 55.7, 34.8, 29.1, 23.7; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{16}H_{21}N_3O$: 272.1763 found: 272.1776.

(S)-(1-(3-(1H-Imidazol-5-yl)benzyl)pyrrolidin-2-yl)methanol (**37**). The general procedure was followed using (*S*)-prolinol, 3-formylphenyl

MIDA boronate, and 5-bromoimidazole. The reaction was purified by prep-HPLC (20−60% MeCN/water 5 mM NH_4OH collected at 262 nm) affording no product.

*(S)-tert-Butyl 2-(3-((2-(hydroxymethyl)pyrrolidin-1-yl)methyl)phenyl) pyridin-4-ylcarbamate (**38**).* The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 6-bromo-3-Boc-aminopyridine. The reaction was purified by prep-HPLC (6−46% MeCN/water 0.1% TFA collected at 254 nm) affording product as a TFA salt (35 mg, 35% yield, purity >95% HPLC at UV 254 nm); HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{22}H_{29}N_3O_3$: 384.2287 found: 384.2293.

*(S)-2-(3-((2-(Hydroxymethyl)pyrrolidin-1-yl)methyl)phenyl)isonicotinonitrile (**39**).* The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 6-bromonicotinonitrile. The reaction was purified by prep-HPLC (5−45% MeCN/water 0.1% TFA collected at 290 nm) affording product (13 mg, 16% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, MeOD) δ ppm 9.00 (d, J = 1.5 Hz, 1 H), 8.34 (s, 1 H), 8.29−8.20 (m, 2 H), 8.13 (d, J = 8.5 Hz, 1 H), 7.72−7.61 (m, 2 H), 4.78 (d, J = 18.6 Hz, 1 H), 4.33 (d, J = 12.0 Hz, 1 H), 3.83 − 3.80 (m, 1 H), 3.78−3.67 (m, 2 H), 3.48−3.36 (m, 1 H), 3.35−3.24 (m, 1 H), 2.36−2.21 (m, 1 H), 2.30−2.10 (m, 1 H), 2.04−1.83 (m, 2 H); ^{13}C NMR (101 MHz, MeOD) δ ppm 160.5, 153.7, 142.0, 139.8, 133.8, 132.9, 131.1, 131.0, 129.9, 121.8, 117.7, 109.9, 70.2, 60.7, 59.4, 55.6, 27.2, 23.2; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{18}H_{19}N_3O$:294.1606 found: 294.1601.

*(S)-(1-(3-(bBenzofuran-2-yl)benzyl)pyrrolidin-2-yl)methanol (**40**).* The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 2-bromobenzofuran. The reaction was purified by prep-HPLC (9−49% MeCN/water 0.1% TFA collected at 290 nm) affording product as a TFA salt (44 mg, 52% yield, purity >95% HPLC at UV 254 nm); HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{20}H_{21}NO_2$: 308.1651 found: 308.1630.

*(S)-(1-(3-(4-Morpholinopyrimidin-2-yl)benzyl)pyrrolidin-2-yl)methanol (**41**).* The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 4-(4-bromopyrimidin-2-yl) morpholine. The reaction was purified by prep-HPLC (5−45% MeCN/water 0.1% TFA collected at 248 nm) affording product as a TFA salt (67 mg, 72% yield, purity >95% HPLC at UV 254 nm); HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{20}H_{26}N_4O_2$: 355.2134 found: 355.2120.

*(S)-tert-Butyl-3-(3-((2-(hydroxymethyl)pyrrolidin-1-yl)methyl)phenyl)-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate (**42**).* The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and *tert*-butyl 3-bromo-5,6-dihydroimidazo[1,2-*a*]pyrazine-7(8*H*)-carboxylate. The reaction was purified by prep-HPLC (34−74% MeCN/water 5 mM NH_4OH collected at 262 nm) affording product (28 mg, 34% yield, purity >95% HPLC at UV 254 nm); HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{23}H_{32}N_4O_3$: 413.2553 found: 413.2548.

*Amine Diversity. (S)-3-Phenyl-2-(3-(pyridin-2-yl)benzylamino)propanamide (**43**).* The general procedure was followed using (*S*)-2-amino-3-phenylpropanamide, 3-formylphenyl MIDA boronate, and 2-chloropyridine. The reaction was purified by prep-HPLC (5−45% MeCN/water 0.1% TFA collected at 288 nm) affording product as a TFA salt (62 mg, 69% yield, purity 85% HPLC at 254 nm); HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{21}H_{21}N_3O$: 332.1763 found: 332.1760.

*4-(2-(3-(Pyridin-2-yl)benzylamino)ethoxy)benzamide (**44**).* The general procedure was followed using 4-(2-aminoethoxy)benzamide, 3-formylphenyl MIDA boronate, and 2-chloropyridine. The reaction was purified by prep-HPLC (23−63% MeCN/water 5 mM NH_4OH collected at 247 nm) affording product (27 mg, 39% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, MeOD) δ ppm 8.61 (d, J = 5.02 Hz, 1 H) 7.95 (s, 1 H), 7.79−7.94 (m, 5 H), 7.44−7.51 (m, 2 H), 7.37 (t, 1 H), 7.00 (d, J = 9.03 Hz, 2 H), 4.17 (t, J = 5.27 Hz, 2 H), 3.95 (s, 2 H) 3.03 (t, J = 5.27 Hz, 2 H); ^{13}C NMR (101 MHz, MeOD) δ ppm 172.0, 163.3, 158.9, 150.3, 141.2, 140.7, 139.0, 130.7, 130.5, 130.1, 128.4, 127.2, 127.1, 123.8, 122.8, 115.2, 68.2, 54.2, 48.4 HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{21}H_{21}N_3O_2$: 348.1712 found: 348.1712.

*1-Benzyl-N-(3-(pyridin-2-yl)benzyl)piperidin-4-amine (**45**).* The general procedure was followed using 1-benzyl-4-aminopiperidine, 3-formylphenyl MIDA boronate, and 2-chloropyridine. The reaction was purified by prep-HPLC (47−87% MeCN/water 5 mM NH_4OH collected at 246 nm) affording product (31 mg, 44% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, MeOD) δ ppm 8.61 (1 H, d, J = 5.0 Hz), 7.95 (1 H, s), 7.83−7.94 (3 H, m), 7.42−7.52 (2 H, m), 7.34−7.40 (1 H, m), 7.31 (4 H, d, J = 4.5 Hz), 7.22−7.29 (1 H, m), 3.92 (2 H, s), 3.51 (2 H, s), 2.92 (2 H, d, J = 12.5 Hz), 2.57−2.69 (1 H, m), 2.00−2.10 (2 H, m), 1.97 (2 H, d, J = 12.5 Hz), 1.51 (2 H, dd, J = 11.5, 3.5 Hz); ^{13}C NMR (101 MHz, MeOD) δ ppm 158.7, 150.3, 140.8, 140.4, 139.0, 138.4, 130.8, 130.6, 130.2, 129.3, 128.54, 128.51, 127.3, 123.9, 122.7, 63.8, 55.4, 53.2, 51.0, 32.0; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{24}H_{27}N_3$: 358.2283 found: 358.2284.

*Ethyl 5-(3-(pPyridin-2-yl)benzyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylate (**46**).* The general procedure was followed using ethyl 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-2-carboxylate, 3-formylphenyl MIDA boronate and 2-chloropyridine. The reaction was purified by prep-HPLC (35−75% MeCN/water 5 mM NH_4OH collected at 220 nm) affording product (22 mg, 30% yield, purity 90% HPLC at 254 nm); HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{21}H_{22}N_4O_2$: 363.1821 found: 363.1828.

*3-((3-(pPyridin-2-yl)benzyl)(pyridin-4-ylmethyl)amino)propanenitrile (**47**).* The general procedure was followed using 3-(pyridin-4-ylmethylamino)-propanenitrile, 3-formylphenyl MIDA boronate, and 2-chloropyridine. The reaction was purified by prep-HPLC (31−71% MeCN/water 5 mM NH_4OH collected at 248 nm) affording product (20 mg, 30% yield, purity >95% HPLC at UV 254 nm); HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{21}H_{20}N_4$: 329.1766 found: 329.1763.

*Ethyl 1-(3-(Pyridin-2-yl)benzyl)piperidine-4-carboxylate (**48**).* The general procedure was followed using ethyl piperidine-4-carboxylate, 3-formylphenyl MIDA boronate, and 2-chloropyridine. The reaction was purified by prep-HPLC (5−45% MeCN/water 0.1% TFA collected at 284 nm) affording product as a TFA salt (64 mg, 73% yield, purity 85%); HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{20}H_{24}N_2O_2$: 325.1916 found: 325.1909.

*N-(Cyclopropylmethyl)-N-(3-(pyridin-2-yl)benzyl)propan-1-amine (**49**).* The general procedure was followed using *N*-(cyclopropylmethyl)propan-1-amine, 3-formylphenyl MIDA boronate, and 2-chloropyridine. The reaction was purified by prep-HPLC (5−45% MeCN/water 0.1% TFA collected at 286 nm) affording product as a TFA salt (37 mg, 47% yield, purity >95% HPLC at UV 254 nm): ^{1}H NMR (400 MHz, MeOD) δ ppm 8.69 (d, J = 5.02 Hz, 1 H), 8.15 (s, 1 H), 8.08 (d, J = 7.53 Hz, 1 H), 7.91−8.04 (m, 2 H), 7.58−7.71 (m, 2 H), 7.42−7.51 (m, 1 H), 4.53 (d, J = 14.05 Hz, 2 H), 3.17−3.26 (m, 2 H), 3.13 (d, J = 6.53 Hz, 2 H), 1.95 − 1.70 (br. m, 2H), 1.13−1.24 (m, 1 H), 0.99 (t, J = 7.28 Hz, 3 H), 0.79 (d, J = 8.03 Hz, 2 H), 0.41 (br. m., 2 H); ^{13}C NMR (101 MHz, MeOD) δ ppm 157.4, 150.1, 141.1, 139.8, 132.9, 131.1, 131.9, 130.9, 129.8, 124.6, 123.1, 59.0, 58.2, 55.3, 18.2, 11.2, 6.6, 5.1; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{19}H_{24}N_2$: 281.2018 found: 281.2020.

*Other Library Members Not Referenced Above. (S)-(1-(6-Chloro-3-(pyrazin-2-yl)benzyl)pyrrolidin-2-yl)methanol (**50**).* The general procedure was followed using (*S*)-prolinol, 3-formyl-6-chlorophenyl MIDA boronate, and 2-bromopyrazine. The reaction was purified by prep-HPLC (37−77% MeCN/water 5 mM NH_4OH collected at 248 nm) affording product (38 mg, 65% yield, purity >95% HPLC at UV 254 nm). ^{1}H NMR (400 MHz, MeOD) δ ppm 9.12 (d, J = 1.52 Hz, 1 H), 8.72−8.64 (m, 1 H), 8.54 (d, J = 2.53 Hz, 1 H), 8.13 (d, J = 1.52 Hz, 1 H), 8.03−7.95 (m, 1 H), 7.69 (d, J = 8.08 Hz, 1 H), 4.21 (d, J = 14.15 Hz, 1 H), 3.68 (d, J = 13.64 Hz, 1 H), 3.65−3.59 (m, 1 H), 3.57−3.49 (m, 1 H), 3.06−2.94 (m, 1 H), 2.85−2.73 (m, 1 H),

2.42−2.30 (m, 1 H), 2.07−1.92 (m, 1 H), 1.81−1.64 (m, 3 H); ^{13}C NMR (101 MHz, MeOD) δ ppm 152.8, 145.9, 144.6, 143.2, 140.1, 138.0, 136.1, 133.1, 129.0, 126.4, 66.9, 65.5, 57.3, 56.0, 29.2, 24.1; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{16}H_{18}ClN_3O$: 304.1217 found: 304.1223.

*(S)-(1-((4-(Pyridin-2-yl)thiophen-2-yl)methyl)pyrrolidin-2-yl)methanol (**51**).* The general procedure was followed using (*S*)-prolinol, 5-formylthiophen-3-yl MIDA boronate, and 2-chloropyridine. The reaction was purified by prep-HPLC (23−63% MeCN/water 5 mM NH_4OH collected at 232 nm) affording product (16 mg, 28% yield, purity >95% HPLC at UV 254 nm). HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{15}H_{18}N_2OS$: 275.1218 found: 275.1213.

*(S)-(1-(3-(Pyrimidin-5-yl)benzyl)pyrrolidin-2-yl)methanol (**52**).* The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 5-bromopyrimidine. The reaction was purified by prep-HPLC (17−57% MeCN/water 5 mM NH_4OH collected at 252 nm) affording product (22 mg, 40% yield, purity >95% HPLC at UV 254 nm). ^{1}H NMR (400 MHz, MeOD) δ ppm 9.17−9.12 (m, 1 H), 9.09 (s, 2 H), 7.79 (s, 1 H), 7.70 (d, J = 7.0 Hz, 1 H), 7.60−7.48 (m, 2 H), 4.35 (d, J = 13.1 Hz, 1 H), 3.75 (d, J = 11.5 Hz, 1 H), 3.69−3.56 (m, 2 H), 3.14−2.91 (m, 2 H), 2.61 (s, 1 H), 2.07 (td, J = 8.5, 4.5 Hz, 1 H), 1.93−1.70 (m, 3 H); ^{13}C NMR (101 MHz, MeOD) δ ppm 158.0, 156.2, 135.8, 135.6, 131.6, 130.8, 129.6, 127.7, 67.6, 63.9, 60.1, 55.7, 28.5, 23.5; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{16}H_{19}N_3O$: 270.1606 found: 270.1611.

*(S)-5-(3-((2-(Hydroxymethyl)pyrrolidin-1-yl)methyl)phenyl)nicotinamide (**53**).* The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and 5-bromonicotinamide. The reaction was purified by prep-HPLC (14−54% MeCN/water 5 mM NH_4OH collected at 252 nm) affording product (22 mg, 35% yield, purity >95% HPLC at UV 254 nm). HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{18}H_{21}N_3O_2$: 312.1712 found: 312.1709.

*(S)-Methyl-2-(3-((2-(hydroxymethyl)pyrrolidin-1-yl)methyl)phenyl)-6-methylisonicotinate (**54**).* The general procedure was followed using (*S*)-prolinol, 3-formylphenyl MIDA boronate, and methyl 2-bromo-6-methylisonicotinate. The reaction was purified by prep-HPLC (5−45% MeCN/water 0.1% TFA collected at 248 nm) affording product as a TFA salt (27 mg, 30% yield, purity >95% HPLC at UV 254 nm). ^{1}H NMR (400 MHz, MeOD) δ ppm 8.24 (s, 1 H), 8.20 (s, 1 H), 8.17 (dt, J = 2.0, 4.5 Hz, 1 H), 7.78 (d, J = 1.0 Hz, 1 H), 7.70−7.59 (m, 2 H), 4.76 (d, J = 13.1 Hz, 1 H), 4.36 (d, J = 15.1 Hz, 1 H), 3.98 (s, 3 H), 3.86−3.65 (m, 3 H), 3.50−3.37 (m, 1 H), 3.37−3.33 (m, 1 H), 2.68 (s, 3 H), 2.34−2.21 (m, 1 H), 2.13 (dd, J = 4.5, 8.0 Hz, 1 H), 2.02−1.86 (m, 2 H); ^{13}C NMR (101 MHz, MeOD) δ ppm 167.0, 161.3, 158.2, 141.1, 140.5, 132.7, 132.6, 130.9, 130.5, 129.7, 122.6, 118.3, 70.2, 60.7, 59.5, 55.7, 53.3, 27.3, 24.4, 23.2 HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{20}H_{24}N_2O_3$: 341.1865 found: 341.1866.

*4-(3-(Pyrazin-2-yl)benzyl)morpholine (**55**).* The general procedure was followed using morpholine, 3-formylphenyl MIDA boronate, and 2-bromopyrazine. The reaction was purified by prep-HPLC (22−62% MeCN/water 5 mM NH_4OH collected at 254 nm) affording product (17 mg, 34% yield, purity >95% HPLC at UV 254 nm). ^{1}H NMR (400 MHz, MeOD) δ ppm 9.11 (s, 1 H), 8.67 (s, 1 H), 8.53 (d, J = 2.53 Hz, 1 H), 8.07 (s, 1 H), 8.03−7.94 (m, 1 H), 7.54−7.45 (m, 2 H), 3.74−3.66 (m, 4 H), 3.63 (s, 2 H), 2.51 (t, 4 H); ^{13}C NMR (101 MHz, MeOD) δ ppm 152.8, 145.8, 144.2, 143.3, 139.7, 137.8, 132.5, 130.3, 129.4, 127.3, 67.9, 64.3, 54.8; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{15}H_{17}N_3O$: 256.1450 found: 256.1451.

*1-Cyclopropyl-N-(3-(pyrazin-2-yl)benzyl)methanamine (**56**).* The general procedure was followed using cyclopropylmethylamine, 3-formylphenyl MIDA boronate, and 2-bromopyrazine. The reaction was purified by prep-HPLC (32−72% MeCN/water 5 mM NH_4OH collected at 248 nm) affording product (14 mg, 31% yield, purity >95% HPLC at UV 254 nm). ^{1}H NMR (400 MHz, MeOD) δ ppm 9.12 (s, 1 H), 8.68 (s, 1 H), 8.53 (d, J = 2.53 Hz, 1 H), 8.08 (s, 1 H), 7.99 (d, J = 6.06 Hz, 1 H), 7.55−7.45 (m, 2 H), 3.89 (s, 2 H), 2.50 (d, J = 7.07 Hz, 2 H), 1.00 (br. m., 1 H), 0.51 (q, 2 H), 0.16 (q, 2 H); ^{13}C NMR (101 MHz, MeOD) δ ppm 154.4, 145.8, 144.2, 143.4, 141.8, 137.8, 131.5, 130.4, 128.3, 127.1, 55.1, 54.2, 11.5, 4.2; HRMS (ESI-TOF) $[M + H]^+$ calculated for $C_{15}H_{17}N_3$: 240.1501 found: 240.1500.

■ ASSOCIATED CONTENT

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

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■ ACKNOWLEDGMENT

The authors wish to acknowledge Ruben Tommasi for his contributions to the development of parallel synthesis infrastructure at Novartis in Cambridge. We are also grateful to Michael McKinnon and Guangxiang Wu for carrying out high resolution mass spectrometry.

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