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Condensation-Driven Assembly of Boron-Containing Bis(Heteroaryl) Motifs Using a Linchpin Approach

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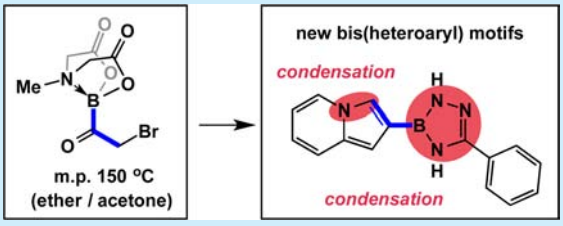
Supporting Information

ABSTRACT: Herein, we describe the bromomethyl acyl boronate linchpin—an enabling reagent for the condensation-driven assembly of novel bis(heteroaryl) motifs. This building block is readily accessible from commercially available starting materials. A variety of 2-amino- and 2-methylpyridines were reacted with MIDA-protected bromomethyl acylboronate to afford 2-boryl imidazo[1,2-*a*]pyridine and 2-boryl indolizine derivatives, respectively, in excellent yields. Subsequent condensation with hydroxyamidines and hydrazonamides converted the intermediate heterocycles into novel boron-containing bis(heteroaryl) units characterized by high thermal stability.



Contemporary approaches to drug discovery emphasize the need to access diverse and underexplored chemical space to ensure the novelty of new chemical entities (NCEs). One way to address this challenge is to produce complex organic molecules and synthetically manipulate their skeletons. While this strategy has many attractive features at the drug *development* stage,[1] it may not be easily transferable to the *discovery* of bioactive molecules due to high C-sp^3 content in many natural product-inspired frameworks. This is the reason why fragment-based discovery approaches emphasize relatively small, sp^2-rich scaffolds that enable the discovery of promising molecules with high ligand efficiency.[2] To be relevant in drug discovery, such strategy is likely to rely on heteroaromatics, a well-established modality that is known to deliver drug candidates.[3]

We have pursued synthetic tools to rapidly build novel bis(heterocycle) chemotypes with unusual connectivity between the two components. We felt that such strategy must (a) have its origin in a readily accessible amphoteric linchpin and employ simple starting materials and (b) deliver privileged structural end points while simultaneously facilitating access to hitherto unexplored chemotypes. In the present manuscript, we report a successful realization of this concept using bromomethyl acylboronate and its use in the condensation-based synthesis of novel bis(heteroaryl) motifs.[4]

Pyridine is second to only benzene as the most frequently used ring system found in the FDA's Orange Book of Small Molecule Drugs.[5] It is for this reason that synthetic chemists have shown tremendous interest in the synthesis of pyridine-containing compounds. Fused derivatives of pyridine, such as imidazo[1,2-*a*]pyridines and indolizines, are present in a wide range of bioactive molecules.[6,7] Many of these molecules have been extensively exploited in drug discovery and, as defined by Evans, are often called "privileged scaffolds" based on their ability to bind multiple protein targets.[8] It was our hope to develop a chemoselective process toward novel privileged scaffolds with substitution patterns that cannot be easily accessed using alternative means. We also sought to use this technology to generate entirely new bis(heterocycle) motifs that would accommodate boron as an integral part of the new ring system.

To initiate our studies, we aimed to synthesize the doubly electrophilic parent bromomethyl acylboronate building block **3**,[9] which was unattainable using our previous methodology.[9d] Starting from commercially available 2-MIDA (*N*-methylimino-diacetic acid) boryl[10,11] oxirane **1**,[10b] the epoxide was regioselectively ring-opened with lithium bromide in the presence of acetic acid. The crude α-bromomethyl alcohol **2** was directly subjected to Dess–Martin oxidation, which afforded the bromomethyl acylboronate **3** in 65% overall yield in just two steps (Scheme 1). This synthesis involves only one purification step and can also be performed on gram scale.

Having secured a short and scalable route to **3**, we pursued heterocycle synthesis via a condensation/substitution reaction sequence. We first experimented with 2-aminopyridine **4a** (Table 1). The reaction mixture of **3** with **4a** in acetonitrile was

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Scheme 1. Synthesis of Bromomethyl Acylboronate 3

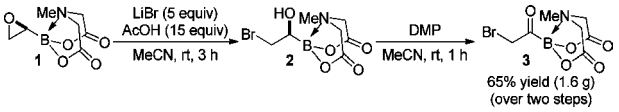
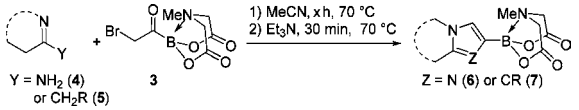
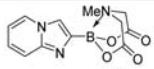
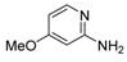
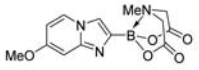
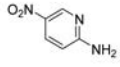
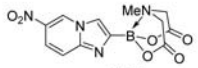
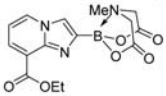
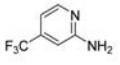
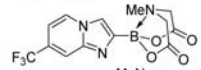
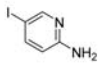
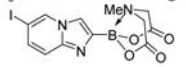
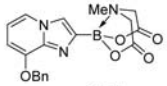
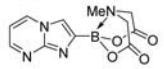
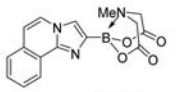
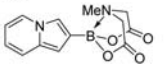
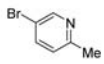
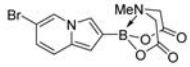
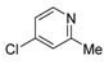
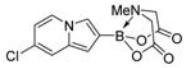
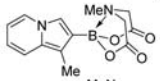
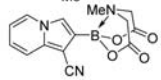
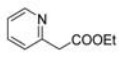
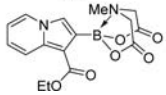


Table 1. Synthesis of 2-MIDA Boryl Imidazo[1,2-*a*]pyridines and Indolizines[a]



entry		pyridine	x (h)		product	yield (%)
1	**4a**		0.5	**6a**		90
2	**4b**		1	**6b**		>99
3	**4c**		60 24[b]	**6c**		87 42
4	**4d**		60	**6d**		97
5	**4e**		60 24[b]	**6e**		85 73
6	**4f**		48	**6f**		98
7	**4g**		24	**6g**		97
8[c]	**4h**		24	**6h**		97
9[c]	**4i**		12	**6i**		89
10[d]	**5a**		3	**7a**		82
11[d]	**5b**		21	**7b**		84
12[d]	**5c**		21	**7c**		77
13[d]	**5d**		2	**7d**		60
14[e]	**5e**		3	**7e**		80
15[e]	**5f**		3	**7f**		65

[a]Unless otherwise noted the reaction was carried out under the following conditions: bromomethyl acylboronate **3** (0.10−0.48 mmol, 1.0 equiv), **4** or **5** (1.0 equiv), Et_3N (3.0 equiv), MeCN, 70 °C. [b]Reaction was performed at 80 °C. [c]Amberlite IRA-67 was used instead of Et_3N. [d]1.2 equiv **3** was used. [e]2.0 equiv **5** were used.

stirred at 70 °C for 30 min, followed by the addition of triethylamine. After aqueous workup and silica gel chromatography, 2-MIDA boryl imidazo[1,2-*a*]pyridine **6a** was isolated in excellent yield (entry 1). The scope of this synthesis was explored with a range of substituted 2-aminopyridines. The reaction with 2-amino-4-methoxypyridine afforded the corresponding product in high yield (**6b**, entry 2). Aminopyridines containing electron-withdrawing substituents at the 3-, 4-, or 5-position, such as trifluoromethyl, nitro, and ester groups (**4c−e**), were tolerated in this process, but required longer reaction times (entries 3−5). We found that increasing the temperature to 80 °C allowed for a reduction of reaction time without substantially compromising the yield of **6e**. Unfortunately, the yield of **6c** was nearly halved under the same conditions. 5-Iodo- and 3-benzyloxy-2-aminopyridines **4f,g** also furnished the corresponding products in high yields (**6f,g**, entries 6−7). The reaction of 2-aminopyrimidine **4h** proceeded to full conversion, however, the product **6h** decomposed during aqueous workup. We were able to circumvent aqueous workup by replacing triethylamine with Amberlite IRA-67, which furnished the desired product **6h** in high yield after chromatography (entry 8). The reaction of 1-aminoisoquinoline **4i** with the bromomethyl acylboronate was also performed in the presence of Amberlite IRA-67 (entry 9).

With our success in isolating previously inaccessible 2-borylated imidazo[1,2-*a*]pyridines, we focused our attention on the synthesis of 2-substituted indolizines.[12] Expanding our methodology of condensation-based cyclizations with 2-alkylated pyridines was projected to furnish these difficult-to-access products with complete regioselectivity. The reaction of 2-methylpyridines **5a−c** and 2-ethylpyridine **5d** with bromomethyl acylboronate **3** using the same protocol as the one used with 2-aminopyridines afforded 2-MIDA boryl indolizines **7a−d** in good yields (entries 10−13). 2-Pyridylacetonitrile **5e** and ethyl-2-pyridylacetate **5f** were also used to produce the corresponding boryl indolizine **7e,f** in good yields, although an excess of the pyridine was required to achieve full conversion (entries 14 and 15).

To the best of our knowledge, 2-boryl derivatives of imidazo[1,2-*a*]pyridines and indolizines have not been reported in the literature. This can be attributed to the regioselectivity issues associated with conventional heterocycle borylation strategies.[13] Our condensation-based approach allows for exclusive access to 2-borylated heterocycles that can be further used for the construction of novel bis(aryl) motifs.

With the surging interest to incorporate boron into aromatic structures,[14] we aimed to adopt our linchpin approach toward the synthesis of boron-containing bis(heteroaryl) systems using condensation as *the sole synthetic operation*. The use of readily available hydroxyamidines **8** and hydrazonamide **9** serves a twofold purpose: (a) to act as a bidentate ligand to chelate boron[15,16] and (b) to fulfill the electronic requirements of Hückel's rule when chelated to boron to produce an aromatic heterocycle. Although 2-MIDA boryl imidazo[1,2-*a*]pyridines **6** were unsuitable for the reaction with **8** and **9** due to the competing protodeboronation process, the free boronic acids of indolizines **7a−f** reacted with **8** to successfully afford novel 2-indolizyl-oxadiazaboroles (IN-OZBs) **10** in high yields (Scheme 2). Benzohydrazonamide **9** was also reacted with indolizines **7a−c,e,f** to produce the corresponding 2-indolizyl-triazaboroles (IN-TZBs) **11** in good yields.

We were able to grow X-ray quality crystals of **10a** and **11a**.[17] The X-ray structure of **10a** and **11a** (Figures 1 and 2) revealed that the OZB and TZB rings are planar, further confirming their aromatic character. In IN-OZB **10a**, the OZB ring forms dihedral angles of 28.64(19)° with the phenyl ring and

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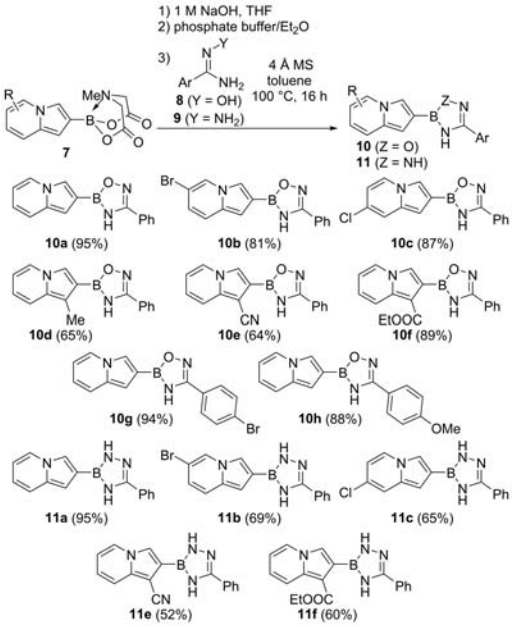
Scheme 2. Synthesis of IN-OZBs 10 or IN-TZBs 11



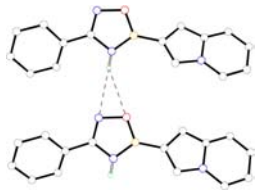


Figure 1. Contacts in the crystal structure of **10a**.

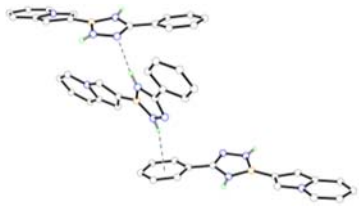


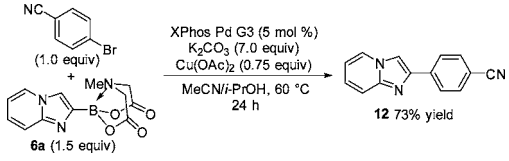
Figure 2. Contacts in the crystal structure of **11a**.

26.18(17)° with the indolizine ring system, while in IN-TZB **11a** the TZB ring forms dihedral angles of 14.41(6)° with the phenyl ring and 16.71(5)° with the indolizine ring system. In the crystal, molecules of IN-OZB **10a** are linked by weak bifurcated N---H···(N,O) hydrogen bonds to form chains along [010]. It is apparent that the N and O atoms each participate as hydrogen bond acceptors to the NH of a second equivalent of the molecule. In contrast, simply swapping the O atom in the OZB to an NH as in TZB **11a** introduces a second hydrogen bond donor in the molecule and completely changes the intermolecular contacts in the crystal structure. It is particularly intriguing that, of the two NH contacts on the boron atom, one is participating in a conventional N---H···N hydrogen bond to form chains along [010], while the other is participating in a weak N---H···π(arene) interaction to complete a two-dimensional network parallel to [001]. OZBs **10** may be viewed as BN analogues of oxazoles and isoxazoles, while the TZBs **11** may be perceived as BN isosteres of imidazoles and pyrazoles, all of which are frequently utilized components within bioactive compounds.

We ran additional experiments to further understand the stability profiles of our molecules. The melting points of **10a** and **11a** are 205 and 189 °C, respectively, indicating that IN-OZBs **10** and IN-TZBs **11** possess excellent thermal stability. When exposed to protic solvents such as d_6-DMSO/water or d_4-methanol, IN-OZBs **10** undergo partial solvolysis to hydroxyamidines **8**, as indicated by ^{1}H NMR experiments. In contrast, IN-TZBs **11** showed high resistance toward solvolysis under the same experimental conditions (see Supporting Information). Our ability to fine-tune the heterocycle stability based on the composition of the boron chelate may find application in self-healing boronic acid based materials, where pH based stability is the prevailing feature.[18]

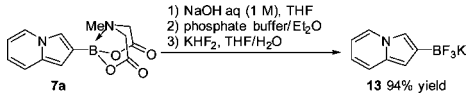
We also assessed the potential of borylated heterocycles in other applications. It is known that 2-boryl azacycles (e.g., 2-pyridyl boronic acid) are unfavorable substrates for cross-coupling due to their high propensity for protodeboronation.[10c] It was recently reported that the Suzuki-type reaction of MIDA-protected pyridyl boronic acids can be achieved in the presence of a Buchwald palladacycle and $Cu(OAc)_2$.[10c,19] We applied this methodology to successfully cross-couple our imidazo[1,2-*a*]pyridine **6a** with 4-bromobenzonitrile catalyzed by XPhos-G3-Palladacycle (XPhos Pd G3)[20] to produce biaryl **12** in 73% yield (Scheme 3).

Scheme 3. Suzuki-Type Cross-Coupling Reaction of 2-MIDA Boryl Imidazo[1,2-*a*]pyridine 6a



2-MIDA boryl indolizine **7a** was also transformed into the corresponding BF_3K salt **13** in 94% yield by deprotection of MIDA followed by treatment with KHF_2 (Scheme 4). Recently,

Scheme 4. Synthesis of 2-Indolizyl Potassium Trifluoroborate



Perrin and co-workers demonstrated that ^{18}F-labeled compounds could be used as small molecule tracers.[21] Our methodology offers a unique condensation-driven route toward new ^{18}F-labeled heterocyclic chemotypes.

In summary, we have outlined a strategy that applies the previously elusive bromomethyl acylboronate toward the construction of novel bis(heteroaryl) motifs. Our synthesis utilizes straightforward condensation processes, offering a rare example of a bottom-up synthesis of unexplored chemotypes. We also demonstrate how one can run consecutive condensation reactions using a boron-based linchpin and obtain heteroaromatic units that are linked by C−B bonds. This approach to build bis(heteroaryl) units leads to the installation of boron-based heterocycles that are difficult to procure using any other means. In addition, the condensation protocol we describe is governed by different regiochemistry rules compared to conventional heteroaromatic borylation reactions. We believe that our strategy will open access to novel

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IN-OZB and IN-TZB-based scaffolds and will be useful in fragment-based discovery and scaffold-hopping approaches because the intermolecular contacts furnished by OZB and TZB containing compounds are otherwise inaccessible in the carbon-based 1,2,4-triazoles and oxadiazoles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02741.

Experimental procedures and spectroscopic data for all new compounds (PDF)
Crystallographic data for **10a** (CIF)
Crystallographic data for **11a** (CIF)
Analytical data (PDF)
Analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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