Heterocycles

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Oxalyl Boronates Enable Modular Synthesis of Bioactive Imidazoles

*C. Frank Lee, Aleksandra Holownia, James M. Bennett, Jonathan M. Elkins, Jeffrey D. St. Denis, Shinya Adachi, and Andrei K. Yudin**

Abstract: *Described herein is the preparation of oxalyl boronate building blocks and their application for the construction of heterocycles. The oxalyl unit, readily accessible through commercially available starting materials, enables a modular approach for the synthesis of imidazoles. A variety of aromatic, heteroaromatic, and alkyl carboxaldehydes were condensed with oxalyl boronates to afford substituted boryl imidazoles in a regiocontrolled fashion. Subsequent palladium-catalyzed cross-coupling with haloarenes furnished the desired trisubstituted imidazole scaffolds. To demonstrate the utility of these scaffolds, potent inhibitors of the serine/threonine-protein kinase STK10 were synthesized.*

Rapid access to small organic molecules continues to attract the attention of synthetic chemists and chemical biologists.[1] Approaches that utilize readily accessible reagents are deemed particularly useful. In this regard, cross-coupling reactions offer a versatile path to generate collections of diverse compounds[2] in which rotatable bonds serve as connectors between variously substituted building blocks. The ultimate goal of these endeavors is to deliver molecules capable of productive interactions with the binding pockets on protein surfaces. The nature of small molecule/protein interactions ranges from hydrophobic contacts to hydrogen bonds.[3] The most useful molecules are often based on either linear (e.g. Gleevec, Figure 1) or "hub" scaffolds (e.g. Celebrex, Figure 1). The hub systems are especially attractive because rotatable bonds emanating from the central ring offer different vectors to interact with the grooves on protein surfaces and in binding sites. However, the construction of hub scaffolds, particularly azacycles, in a regiochemically controlled fashion continues to be a challenge, one that often requires elaborate precursors and harsh reaction conditions.[4] We became interested in creating a flexible approach to the synthesis of hub architectures. Herein, we highlight oxalyl MIDA (*N*-methyliminodiacetic acid) boronates in the synthesis of hub-based scaffolds, and demonstrate their utility for the design of orphan kinase inhibitors.

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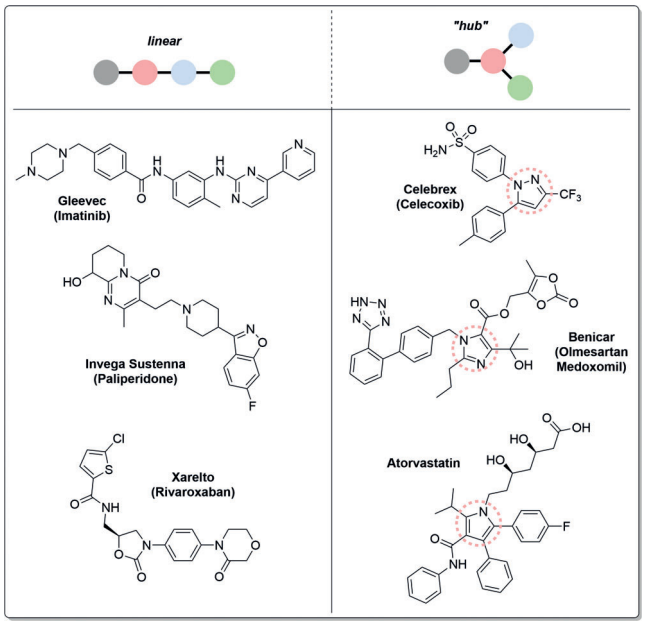

Figure 1. Select therapeutic agents with linear and "hub" topologies.[5]

Imidazoles have found widespread application in medicinal chemistry as a central heterocyclic unit for biologically active small molecules, pharmaceuticals, natural products, and application in materials chemistry.[6] A wide variety of classical methods for constructing the imidazole scaffold have been reported.[4e,7] Given the role of 1,2-dicarbonyl compounds in synthesis, we became interested in merging the boronate and diketone functionalities in the same molecule. Treatment of vinyl MIDA boronates (**2a**–**h**) with catalytic OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) afforded dihydroxylated MIDA boronates (**3a**–**h**) in high yields (Table 1).[8] 1,2-Boryl alcohols are typically unstable motifs because of the facile borono-Peterson-type elimination that is commonly observed.[9] However, the stability of **3** is attributed to the MIDA ligand on the boron atom, thus shielding the empty p-orbital from the elimination pathway.

The oxidation of **3** with Dess–Martin periodinane (DMP) after 1 hour furnished the desired oxalyl boronates (**4a**–**h**) in good to excellent yields as bench-stable solids (Table 1). This route is not only amenable to electron-rich (**4g**,**h**), electron-poor aromatics (**4f**), and alkyl (**4a**–**c**) derivatives, but also highly scalable as the reactions were performed on a 1.0–5.0 gram scale without significant effect on product yields.

We investigated the synthetic utility of oxalyl boronates in the synthesis of imidazoles. In the presence of NH_4OAc and benzaldehyde, phenyl oxalyl boronate (**4d**) smoothly converted into the corresponding 2,4,5-trisubstituted borylated

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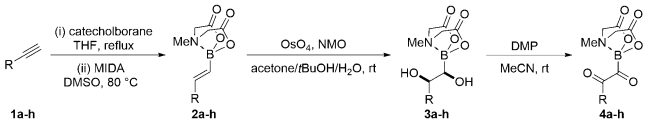
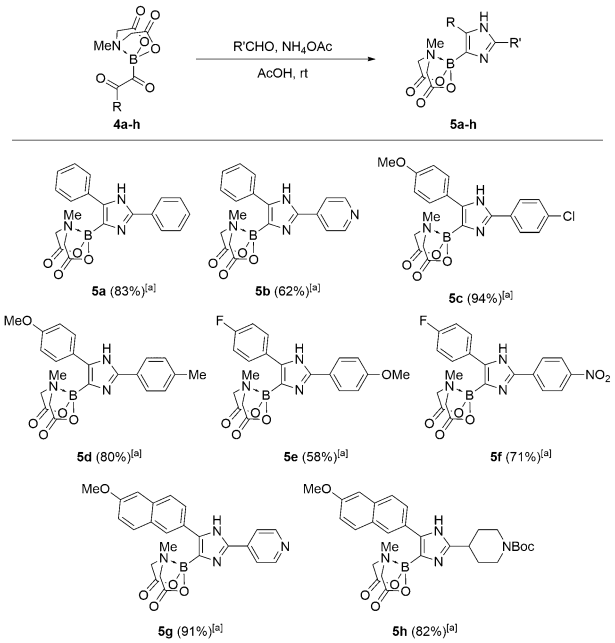
Table 1: Synthesis of oxalyl MIDA boronates.[a]



Alkyne	R	*cis*-Diol	Yield [%][b]	Oxalyl boronate	Yield [%][b]
1a	cyclohexyl	**3a**	76	**4a**	36
1b	cyclopropyl	**3b**	78	**4b**	84[c]
1c	phenethyl	**3c**	83	**4c**	90[c]
1d	phenyl	**3d**	92	**4d**	72
1e	1-naphthyl	**3e**	63	**4e**	51
1f	4-FC_6H_4	**3f**	84	**4f**	50
1g	4-$OMeC_6H_4$	**3g**	91	**4g**	67
1h	6-$OMeC_{10}H_6$	**3h**	65	**4h**	58

[a] Reactions were carried out using 1.0 equiv of alkyne, 1.5 equiv of catecholborane in tetrahydrofuran (THF: 0.5 M) at 65 °C for 24 hours; 1.5 equiv of *N*-methyliminodiacetic acid (MIDA) in dimethylsulfoxide (DMSO: 0.1 M) at 80 °C for 1–5 hours. Dihydroxylation was achieved using 1–2 mol% of osmium tetroxide (4 wt% in H_2O) and 1.5 equiv of *N*-methylmorpholine *N*-oxide (NMO) in an 18:1:1 solvent ratio of acetone/*tert*-butanol/water (0.05 M). Oxidations were executed using 2.2 equiv of Dess–Martin periodinane (DMP) in acetonitrile (MeCN: 0.1 M) at room temperature for 1 hour. [b] Yield is that of product isolated after silica gel chromatography. [c] Products were unstable towards column chromatography. Yield determined by NMR analysis using trimethoxybenzene as the internal standard. DMSO = dimethylsulfoxide, THF = tetrahydrofuran.

imidazole in a highly regioselective fashion (**5a**; Scheme 1). Contrary to classical Debus conditions,[7d,10] our modified method of utilizing AcOH as the reaction medium allowed the reaction to occur at room temperature as the borylated imidazole product was formed after 1–2 hours without any decomposition or oxazole byproduct formation.[11] This allowed us to modularly control the C2 position on the heterocycle, wherein a wide variety of aldehydes, including alkyl *N*-Boc protected aldehydes (**5h**), were well tolerated in the synthesis without any observed deprotected material or oxazole byproducts. Electron-rich (**5d**, **5e**), electron-poor (**5c**, **5f**), and heterocyclic carboxaldehydes were all tolerated, thus yielding bis-heterocyclic hub-like scaffolds (**5b**, **5g**). This regioselective route towards borylated imidazoles enables the heterocycle to become a hub of controlled functionalization, where each spoke is introduced in one step. In addition, the boryl imidazole products are intensely colored, thus highlighting the potential utility of these compounds in photophysical/chemical applications.[12]



Scheme 1. Scope of borylated imidazoles. Reactions were carried out using 1.0 equiv of oxalyl boronate, 1.1 equiv of aldehyde (R′CHO), and 15 equiv of ammonium acetate (NH_4OAc) in acetic acid (AcOH: 0.1 M) at room temperature for 1–2 hours. [a] Yield is that of product isolated after silica gel chromatography. Boc = *tert*-butyloxycarbonyl.

Finally, with the C2 and C5 positions functionalized, the resulting borylated imidazoles were subjected to standard cross-coupling conditions with aryl bromides to complete a facile method for generating densely functionalized imidazoles. Unfortunately, employing cross-coupling conditions for MIDA boronates (variations of Buchwald precatalysts)[13] led to quantitative formation of the undesired protodeboronation product and trace amounts of the desired product by LC/MS analysis (see the Supporting Information). The boryl imidazole scaffold, similar to the analogous 2-boryl pyridine system, is notoriously prone to protodeboronation under cross-coupling conditions because of the electronic nature of the heterocycle and the position of the boronic acid/ester group on the ring.[14] Employing the slow-release method developed by Burke, et al.[15] also led to exclusive protodeboronation product. An improved product ratio, as indicated by LC/MS analysis, was observed with a modified slow-release method. Furthermore, switching to [Pd(dppf)Cl_2] and sodium carbonate in a 10:1 mixture of DMF/H_2O led to the best product ratio (see the Supporting Information) where the products were isolated by reverse-phase column chromatography (Scheme 2).

To highlight the versatility of our approach, we decided to use this method to tackle the kinase STK10, a serine/threonine-protein kinase highly expressed in lymphocytes and involved in regulating lymphocyte migration,[16] for the discovery of a chemical probe. STK10 and the related kinase SLK are involved in regulating PLK1 (polo-like kinase 1).[17] PLKs are critical regulators of cell-cycle progression, mitosis, cytokinesis, and DNA damage response.[18] Kinases are well-known drug targets because of their roles in the regulation of cellular physiology and pathology,[19] and as of January 2016 there were 28 FDA-approved drugs that target kinases.[20] With more than 500 protein kinases in the human genome, many of which have strong links to fundamental cellular processes, there is a strong need for efficient methods of elaborating kinase inhibitors. After analyzing the co-crystal structures of SB-633825 and SB-440719 (Figure 2) where SB-633825 inhibited STK10 to 44% maximal activity at 100 nM,[21] we were prompted to use oxalyl boronates to rapidly generate a series of STK10 inhibitors by varying the substituent at C2 of the heterocycle. This series would allow the optimization of modulating hydrogen-bond interactions with either amino-acid residues or the protein backbone.

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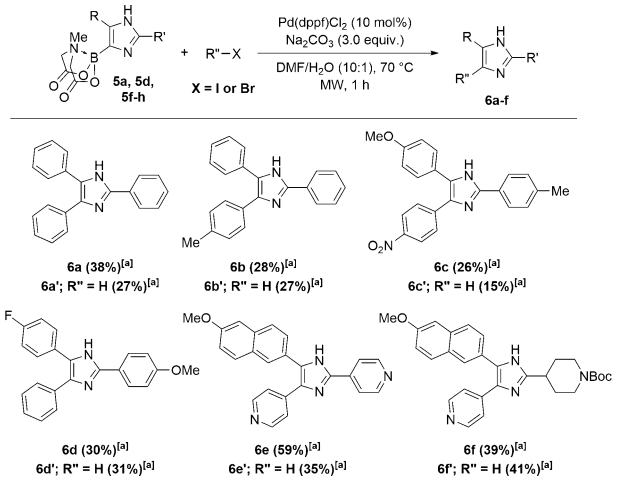

Scheme 2. Suzuki–Miyaura cross-coupling of borylated imidazoles. Reactions were achieved using 1.0 equiv of boryl imidazole, 1.5 equiv of R″X, 10 mol% of Pd(dppf)Cl_2, 3.0 equiv of sodium carbonate (Na_2CO_3) in a 10:1 solvent mixture of dimethylformamide (DMF), and water at 70 °C for 1 hour in a Biotage microwave reactor. [a] Yield is that of isolated product after reverse-phase silica gel chromatography. dppf = 1,1′-bis(diphenylphosphino)ferrocene, MW = microwave.

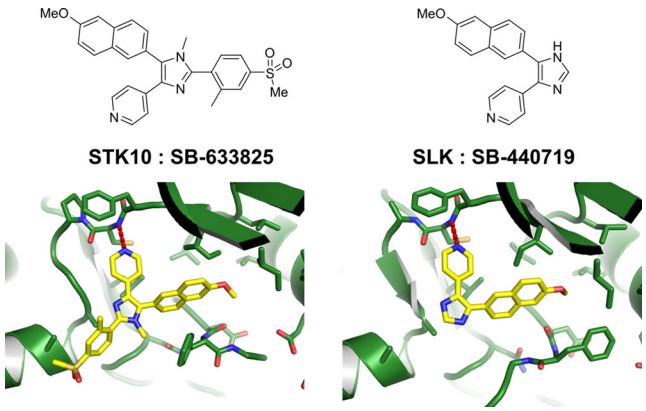

Figure 2. X-ray co-crystal structures of STK10:SB-633825 (PDB 4USD, left) and SLK:SB-440719 (PDB 4USF, right)[21] that were used for compound design.

The compounds **6e** and **7** (Scheme 3) were tested against STK10 and SLK. Preliminary results have shown that **6e** and **7** exhibited K_i values of 250 nM and 130 nM, respectively, against STK10, and 340 nM and 180 nM, respectively, against SLK (Figure 3; see the Supporting Information). The introduction of a heteroatom at C2 (**6e**) lowered the K_i value, presumably because of an increase in hydrogen-bond interactions. However, swapping the pyridyl group with an *N*-acyl piperidyl group (**7**) resulted in an improved K_i value. With the added flexibility of the saturated heterocycle (**7**) compared to a flat aromatic group (**6e**), it may allow the molecule to adopt a more optimal geometry in the binding pocket. With the ease of modifying the groups on the imidazole core, efforts to generate a more comprehensive library of compounds are currently ongoing.

Scheme 3. Synthesis of *N*-acyl piperidine derivative. Reaction was carried out using 1.0 equiv of imidazole **6f** and 20 equiv of trifluoroacetic acid (TFA) in dichloromethane (0.1 M) at room temperature for 1 hour. Followed by 1.0 equiv of Amberlite® IRA-67 resin and 1.5 equiv of acetic anhydride (Ac_2O) in acetonitrile (MeCN: 0.1 M) at room temperature for 30 minutes. [a] Yield is that of product isolated after reverse-phase silica gel chromatography.

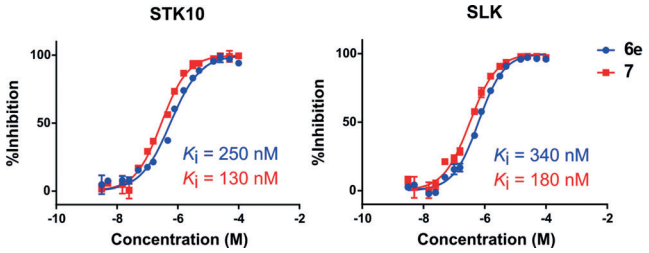

Figure 3. Percentage inhibition for compounds **6e** and **7** against STK10 and SLK as measured in a binding–displacement assay. Each measurement was measured in duplicate and repeated on a subsequent day. One example of each duplicate is shown.

In summary, we have developed a modular approach towards the construction of densely functionalized imidazole scaffolds through our oxalyl boronate technology. The use of a multicomponent double condensation reaction with a wide range of aldehydes followed by a cross-coupling of MIDA-boryl imidazoles provided an efficient method to regioselectively vary the groups on the central heterocycle. Current investigations are aimed at leveraging oxalyl boronates to provide further insight into the physiological significance of novel imidazole inhibitors and target validation of the protein kinase STK10.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

Keywords: biological activity · boron · cross-coupling · heterocycles · synthetic methods

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Communications

Heterocycles

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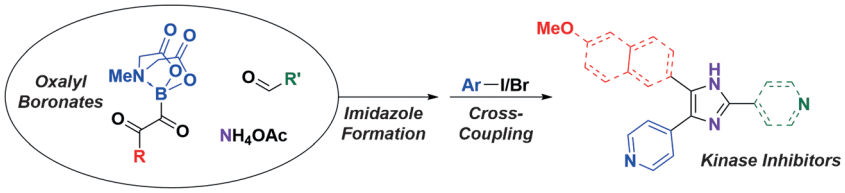
Oxalyl Boronates Enable Modular Synthesis of Bioactive Imidazoles



A variety of aromatic, heteroaromatic, and alkyl carboxaldehydes were condensed with oxalyl boronates to afford substituted boryl imidazoles in a regiocontrolled fashion. Subsequent palladium-catalyzed cross-coupling with haloarenes furnished the desired trisubstituted imidazole scaffolds. To demonstrate the utility of these scaffolds, potent inhibitors of the serine/threonine-protein kinase STK10 were synthesized.

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