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An Alkyne Diboration-δElectrocyclization Strategy to Pyridine Boronic Acid Derivatives**

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Abstract: We report a new and efficient synthesis of pyridine-based heteroaromatic boronic acid derivatives via a novel diboration-δ-electrocyclization strategy. This method delivers a range of functionalized heterocycles from readily available starting materials.

Nitrogen based heterocyclic compounds constitute important building blocks for organic synthesis since they are found in many pharmaceutical and agrochemical targets. In this regard, heteroaromatic boronic acid derivatives are one of the most valuable classes of intermediates in synthetic chemistry.[1] Their value lies in their unique combination of high stability and rich reactivity, allowing them to participate in a wide range of functionalization reactions. Traditional approaches to these compounds relied on elaboration of pre-formed scaffolds through C-X or C-H borylation.[2] Complementary strategies such as cycloaddition reactions[3] and annelative borylations[4] have become more established quite recently, and allow functionalized aromatic boronic acid scaffolds to be made available in a direct manner.

The synthesis of pyridines via δ-electrocyclization reactions represents an interesting and alternative means for the bespoke synthesis of this class of heterocyclic intermediates, and the reaction is compatible with a range of common functional groups such as esters, aldehydes and ethers.[5,6] Importantly, in the context of boronic acid derivatives, we envisaged that we could take advantage of catalytic diboration methodology[7] to transform readily available yne-ene-oximes into pyridine boronic esters. As shown in Scheme 1, central to our objective was the activation of the alkyne substrate towards electrocyclization whilst simultaneously incorporating useful functionality.

Moreover, we expected that this process would selectively eliminate only one of the two boronic ester moieties; thereby obviating the common problem of differentiating between the two boronate units generated by diboration chemistry.[8]

The substrates for this study were readily prepared in two steps from 2-bromo aryl aldehydes by Sonogashira coupling and condensation with O-methylhydroxylamine.[9] To our delight, all substrates underwent smooth diboration under Pt-catalysis to deliver the corresponding products in good to excellent yields (Scheme 2). The scope of the chemistry was found to be quite general with a range of substituents tolerated on the alkyne and aryl rings. A relatively high catalyst loading was used in our scoping studies so that the reactions were complete in 30 min. However, we found it possible to lower the catalyst loading to 3 mol% and this had only a minor effect on the reaction yield over a slightly increased reaction time of 2.5 h.

Scheme 1. The diboration-δ-electrocyclization strategy.

Scheme 2. Diboration of 2-alkynyl aryl oximes. [a] Reaction conducted with 3 mol% Pt-catalyst over 2.5 h.
With a range of 1-azatrienes in hand, we turned our attention to the pyridine forming 6π-electrocyclization step. α-DCB (ortho-dichlorobenzene) proved to be the optimal solvent to perform this transformation and a reaction temperature of 200 °C led to complete conversion within 16 h. Pleasingly all substrates underwent the key cyclisation step giving rise to a large number of functionalized isoquinoline derivatives after elimination of MeOBpin. We observed that the silyl-substituted triene 1 required the use of slightly lower temperatures to avoid protodesilylation, and the free alcohol bearing substrate 3 required protection as a TBS-ether to avoid protodeboronation during the electrocyclisation process. Notably, chemoselective electrocyclization was observed in the reactions of 15 and 16, and the corresponding naphthalenes were not observed via the potentially competing 6π-cyclization in these cases (Scheme 3).

We next decided to explore the suitability of ketoximes to deliver more substituted heterocyclic products. As shown in Scheme 5, condensation of 27 with O-methylhydroxylamine provided a 4:1 mixture of oxime isomers E/Z-28 that could be separated by chromatography. The major isomer was assigned as E-28 on the basis of comparative 1H NMR spectroscopy and the propensity of acetophenone oximes to adopt the E-configuration. We decided to subject the individual oxime isomers to the diboration-electrocyclization sequence. In the event, E-28 underwent efficient conversion to the azatriene E-29 which was smoothly converted into isoquinoline 30 in high yield. In contrast, Z-28 provided the corresponding diboration product Z-29 in low yield. Moreover, to our surprise, this substrate was found to be inert to electrocyclization.

The dependence of oxime stereochemistry on the efficiency of electrocyclization of azatrienes is intriguing and has not been documented to the best of our knowledge. The reason could be steric in nature and related to the lower reactivity of Z-1-substituted butadienes in Diels-Alder reactions. Further
investigations as to the underlying causes of this phenomenon are currently underway.

The potential of the heterocyclic boronic esters to be further exploited for synthesis was next investigated by employing two representative organoboron transformations. Specifically, as highlighted in Scheme 6, compound 14 was oxidized to the corresponding phenol 31 and converted to the azido product 32 in good yield in both cases.

Scheme 6. Representative functionalization reactions of 14.

In conclusion we report a new and efficient synthesis of pyridine-based heteroaromatic boronic acid derivatives via a novel diboration-electrocyclization pathway. This strategy allows rapid access to bicyclic pyridines, although the suitability of this method to access monocyclic heterocycles will likely require further method development. Moreover, this method has raised an intriguing result that the cyclization of oxime derived trienes appears to depend on the substrate stereochemistry. Further studies to establish the generality of this observation together with the underlying causes are underway and will be reported in due course.

Experimental Section

Typical diboration-electrocyclization procedure as exemplified by the formation of 14: BpinO (640 mg, 2.5 mmol) was added to a stirred solution of (E)-2-(2-cyclopropylethynyl)benzaldehyde O-methyl oxime (456 mg, 2.3 mmol) in toluene (15 mL). Then Pt(PPh3)4 (132 mg, 0.12 mmol, 5 mol%) was added and the reaction was stirred at 120 °C for 1 h. The reaction mixture was allowed to cool to room temperature and 1,2-Cl2C6H4Br was added (30 mL). The reaction mixture was stirred at 200 °C for a further 16 h. The solution was allowed to cool to room temperature and was filtered through a pad of silica gel. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) and ethyl acetate to afford 3-cyclopropyl-4-(4,5,5-tetramethyl-1,3-dioxaborolan-2-yl)isoquinoline 14 (480 mg, 71%) as an orange oil.

1H NMR (400 MHz, CDCl3) δ = 9.09 (s, 1H), 8.11 (dd, J = 8.5, 1.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.62 (dd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.45 (dd, J = 8.0, 7.0, 1.0 Hz, 1H), 6.21 – 2.54 (m, 1H), 1.49 (s, 12H), 1.22 – 1.18 (m, 2H), 0.92 – 0.96 (m, 2H); 13C NMR (101 MHz, CDCl3) δ = 160.7, 135.8, 139.5, 130.4, 128.0, 126.3, 126.1, 125.5, 84.3, 25.0, 16.6, 9.9; 11B NMR (128 MHz, CDCl3) δ = 32.8 (br); FTIR: v = 2978 (m), 1619 (m), 1562 (m), 1495 (m), 1235 (s), 1134 (s) cm⁻¹. HRMS calculated for C18H23BNO2: m/z 295.1853, found: 295.1856.

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[9] Further details are contained within the supporting information.
Get in the ring! [β-Alkynyl α,β]-unsaturated oximes undergo a sequential alkyne diboration-6π electrocyclization sequence to deliver a range of pyridine boronic acid derivatives. The scope of this chemistry to deliver useful heterocyclic products is described.