

## Synthetic Methods

Deutsche Ausgabe: DOI: 10.1002/ange.201601084  
Internationale Ausgabe: DOI: 10.1002/anie.201601084An Alkyne Diboration/ $6\pi$ -Electrocyclization Strategy for the Synthesis of Pyridine Boronic Acid Derivatives

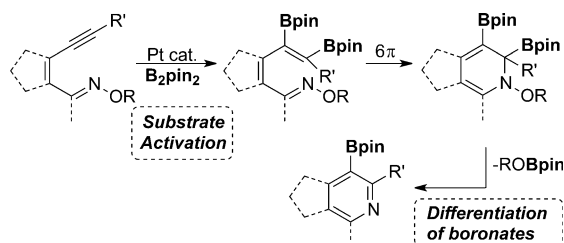
Helena Mora-Radó, Laurent Bialy, Werngard Czechtizky, María Méndez, and Joseph P. A. Harrity\*

**Abstract:** A new and efficient synthesis of pyridine-based heteroaromatic boronic acid derivatives is reported through a novel diboration/ $6\pi$ -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.<sup>[1]</sup> 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 preformed scaffolds through C–X or C–H borylation.<sup>[2]</sup> Complementary strategies, such as cycloaddition reactions<sup>[3]</sup> and annelative borylations,<sup>[4]</sup> have become more established, and allow functionalized aromatic boronic acid scaffolds to be made available in a direct manner.

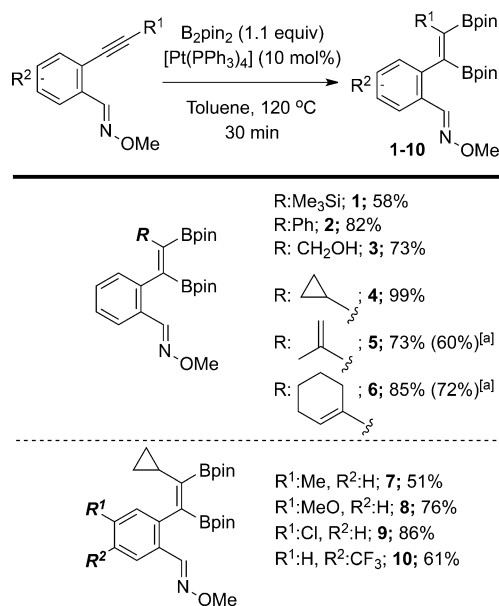
The synthesis of pyridines through  $6\pi$ -electrocyclization reactions represents an interesting and alternative means for the bespoke synthesis of this class of heterocyclic intermediates, and the reaction is compatible with a range of common functional groups such as esters, aldehydes, and ethers.<sup>[5,6]</sup> Importantly, in the context of boronic acid derivatives, we envisaged that we could take advantage of catalytic diborylation methodology<sup>[7]</sup> 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.<sup>[8]</sup>

The substrates for this study were readily prepared in two steps from 2-bromo aryl aldehydes by Sonogashira coupling



**Scheme 1.** The diboration/ $6\pi$ -electrocyclization strategy.  $B_2pin_2$  = (bispinacolato)diboron.

and condensation with *O*-methylhydroxylamine.<sup>[9]</sup> To our delight, all substrates underwent smooth diborylation 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 (10 mol %) was used when investigating the scope of the reaction method so that the reactions were complete in 30 min. However, we found that it was possible to lower the catalyst loading to 3 mol % and that this had only a minor effect on the reaction yield over a slightly increased reaction time of 2.5 h.

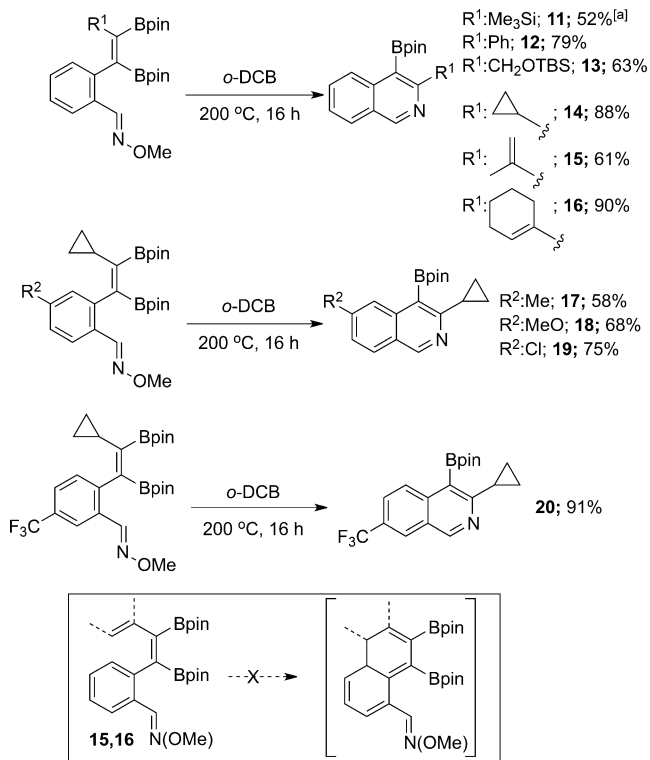


**Scheme 2.** Diboration of 2-alkynyl aryloximes. [a] Reaction conducted with 3 mol % Pt catalyst over 2.5 h.

[\*] H. Mora-Radó, Prof. J. P. A. Harrity  
Department of Chemistry, University of Sheffield  
Sheffield, S3 7HF (UK)  
E-mail: j.harrity@sheffield.ac.uk  
Dr. L. Bialy, Dr. W. Czechtizky, Dr. M. Méndez  
Sanofi, Industrial Park Hoechst  
65926 Frankfurt am Main (Germany)

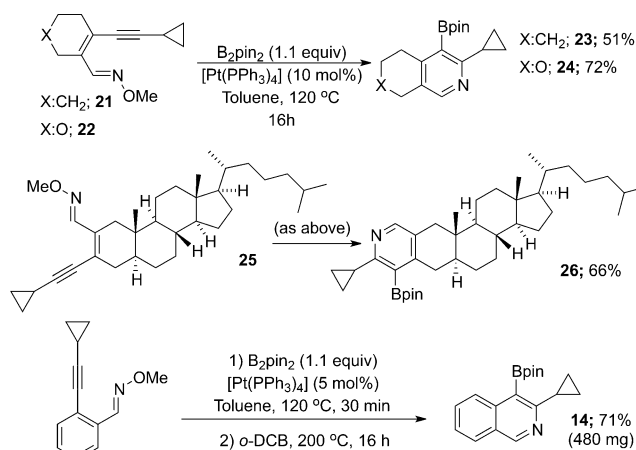
Supporting information for this article can be found under:  
<http://dx.doi.org/10.1002/anie.201601084>.

With a range of 1-azatrienes in hand, we turned our attention to the pyridine-forming  $6\pi$ -electrocyclization step. *o*-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 (Scheme 3). 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** (yielding compound **11**) required the use of slightly lower temperatures to avoid protodesilylation, and the free alcohol bearing substrate **3** required protection as a TBS-ether<sup>[9]</sup> to avoid protodeborylation during the electrocyclization process to form compound **13**. Notably, chemoselective electrocyclization was observed in the reactions of **15** and **16**, and the corresponding naphthalenes were not detected through the potentially competing  $6\pi$ -cyclization in these cases.

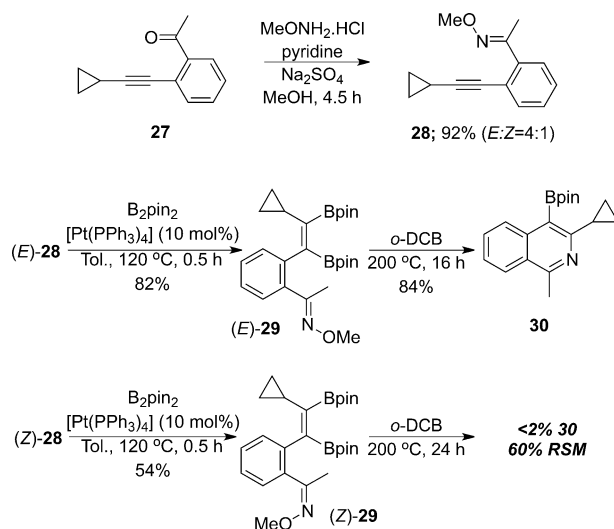
We were able to extend our studies to include aliphatic 1-azatrienes and our results are shown in Scheme 4. Substrates **21**, **22**, and **25** were prepared in a similar manner as before,<sup>[9]</sup> and the *O*-methyl oximes were subjected to  $B_2pin_2$  in the presence of the Pt catalyst. In each of these cases, however, we were unable to isolate the intermediate diborylation products, and instead these reactions directly furnished the cyclized pyridine boronates **23**, **24**, and **26** in good yields at 120 °C. The one-pot diboration/electrocyclization observed in substrates **21**, **22**, and **25** reflects the increased reactivity of aliphatic substrates towards pyridine formation. Nonetheless,



**Scheme 4.** One-pot diboration/electrocyclization.

a similar sequence could also be achieved with aryloximes. Specifically, isoquinoline **14** could be prepared directly from the corresponding alkyne on circa 0.5 g scale by utilizing a telescoped diboration/electrocyclization sequence.

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

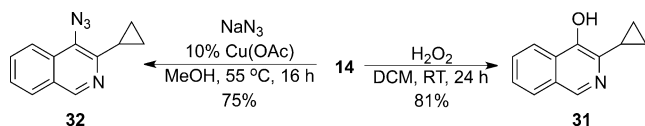


**Scheme 5.**  $6\pi$ -electrocyclization of (*E/Z*)-oxime isomers. Tol. = toluene.

assigned as (*E*)-**28** on the basis of comparative <sup>1</sup>H NMR spectroscopy<sup>[9]</sup> and the propensity of acetophenone oximes to adopt the (*E*)-configuration.<sup>[10]</sup> We decided to subject the individual oxime isomers to the diboration/electrocyclization sequence. In the reaction, (*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 diborylation product (*Z*)-**29** in low yield. Moreover, and to our surprise, this substrate was found to be inert to electrocyclization.

The dependence of oxime stereochemistry on the efficiency of electrocyclicization of azatrienes is intriguing and has not been documented to our knowledge. The reason could be steric in nature and related to the lower reactivity of (*Z*)-1-substituted butadienes in Diels–Alder reactions.<sup>[11]</sup> 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** or could be converted into azido product **32** in good yield in both cases.



**Scheme 6.** Representative functionalization reactions of **14**. DCM = CH<sub>2</sub>Cl<sub>2</sub>.

In conclusion we report a new and efficient synthesis of pyridine-based heteroaromatic boronic acid derivatives through a novel diboration/6 $\pi$ -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**: B<sub>2</sub>pin<sub>2</sub> (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(PPh<sub>3</sub>)<sub>4</sub>] (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-Cl<sub>2</sub>C<sub>6</sub>H<sub>4</sub> 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 v/v) and ethyl acetate to afford 3-cyclopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinoline **14** (480 mg, 71 %) as an orange oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.09 (s, 1H), 8.11 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.62 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.45 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 2.61–2.54 (m, 1H), 1.49 (s, 12H), 1.22–1.18 (m, 2H), 1.02–0.96 ppm (m, 2H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 160.7, 153.8, 139.5, 130.4, 128.0, 126.3, 126.1, 125.5, 84.3, 25.0, 16.6, 9.9 ppm; <sup>11</sup>B NMR (128 MHz, CDCl<sub>3</sub>):  $\delta$  = 32.8 ppm (br); FTIR:  $\nu$  = 2978 (m), 1619 (m), 1562 (m), 1495 (m), 1235 (s), 1134 (s) cm<sup>−1</sup>.

HRMS ESI calculated for C<sub>18</sub>H<sub>22</sub>BNO<sub>2</sub>: *m/z* 295.1853, found: 295.1856.

**Keywords:** boronic esters · diboration · electrocyclic reactions · nitrogen heterocycles · synthetic methods

**How to cite:** *Angew. Chem. Int. Ed.* **2016**, 55, 5834–5836  
*Angew. Chem.* **2016**, 128, 5928–5930

- [1] *Boronic Acids: Preparation and Applications in Organic Synthesis Medicine and Materials*, Vol. 1, 2nd ed. (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2011**.
- [2] For selected examples, see: a) T. Ishiyama, M. Murata, N. Miyaoura, *J. Org. Chem.* **1995**, 60, 7508; b) I. A. I. Mkhaliid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, 110, 890; c) A. Del Grosso, P. J. Singleton, C. A. Muryn, M. J. Ingleson, *Angew. Chem. Int. Ed.* **2011**, 50, 2102; *Angew. Chem.* **2011**, 123, 2150.
- [3] a) S. P. J. T. Bachollet, J. F. Vivat, D. C. Cocker, H. Adams, J. P. A. Harrity, *Chem. Eur. J.* **2014**, 20, 12889; b) D. F. P. Crépin, J. P. A. Harrity, J. Jiang, A. J. H. M. Meijer, A.-C. M. A. Nassoy, P. Raubo, *J. Am. Chem. Soc.* **2014**, 136, 8642; c) V. Gandon, D. Leboeuf, S. Amslinger, K. P. C. Vollhardt, M. Malacria, C. Aubert, *Angew. Chem. Int. Ed.* **2005**, 44, 7114; *Angew. Chem.* **2005**, 117, 7276; d) G. Hilt, K. I. Smolko, *Angew. Chem. Int. Ed.* **2003**, 42, 2795; *Angew. Chem.* **2003**, 115, 2901; e) Y. Yamamoto, J.-i. Ishii, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2004**, 126, 3712; f) H. Wang, C. Grohmann, C. Nimphius, F. Glorius, *J. Am. Chem. Soc.* **2012**, 134, 19592.
- [4] a) D. J. Faizi, A. Issaian, A. J. Davis, S. A. Blum, *J. Am. Chem. Soc.* **2016**, 138, 2126; b) E. Chong, S. A. Blum, *J. Am. Chem. Soc.* **2015**, 137, 10144; c) A. J. Warner, J. R. Lawson, V. Fasano, M. J. Ingleson, *Angew. Chem. Int. Ed.* **2015**, 54, 11245; *Angew. Chem.* **2015**, 127, 11397; d) J. Huang, S. J. F. Macdonald, J. P. A. Harrity, *Chem. Commun.* **2010**, 46, 8770.
- [5] a) S. J. Markey, W. Lewis, C. J. Moody, *Org. Lett.* **2013**, 15, 6306; b) T. Hosokawa, N. Shimo, K. Maeda, A. Sonoda, S.-I. Murahashi, *Tetrahedron Lett.* **1976**, 17, 383; c) T. Kumemura, T. Choshi, A. Hirata, M. Sera, Y. Takahashi, J. Nobuhiro, S. Hibino, *Chem. Pharm. Bull.* **2005**, 53, 393.
- [6] For related examples involving in situ generation of unsaturated oximes, see: a) D. A. Colby, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, 130, 3645; b) S. Liu, L. S. Liebeskind, *J. Am. Chem. Soc.* **2008**, 130, 6918; c) K. Parthasarathy, M. Jeganmohan, C.-H. Cheng, *Org. Lett.* **2008**, 10, 325; d) R. M. Martin, R. G. Bergman, J. A. Ellman, *J. Org. Chem.* **2012**, 77, 2501.
- [7] T. Ishiyama, N. Matsuda, N. Miyaoura, A. Suzuki, *J. Am. Chem. Soc.* **1993**, 115, 11018.
- [8] a) S. D. Brown, R. W. Armstrong, *J. Am. Chem. Soc.* **1996**, 118, 6331; b) H. Prokopcová, J. Ramírez, E. Fernández, C. O. Kappe, *Tetrahedron Lett.* **2008**, 49, 4831.
- [9] Further details are contained within the Supporting Information.
- [10] G. J. Karabatsos, N. Hsi, *Tetrahedron* **1967**, 23, 1079.
- [11] We thank a reviewer for this suggestion. For an example of comparative Diels–Alder reactions of *E/Z*-1-substituted butadienes, see: H. Adams, J. C. Anderson, R. Bell, D. N. Jones, M. R. Peel, N. C. O. Tomkinson, *J. Chem. Soc. Perkin Trans. I* **1998**, 3967.

Received: January 30, 2016

Revised: February 19, 2016

Published online: April 5, 2016