



This is a repository copy of *An alkyne diboration/6 π -electrocyclization strategy for the synthesis of pyridine boronic acid derivatives.*

White Rose Research Online URL for this paper:
<http://eprints.whiterose.ac.uk/152820/>

Version: Accepted Version

Article:

Mora-Radó, H., Bialy, L., Czechtizky, W. et al. (2 more authors) (2016) An alkyne diboration/6 π -electrocyclization strategy for the synthesis of pyridine boronic acid derivatives. *Angewandte Chemie*, 128 (19). pp. 5928-5930. ISSN 0044-8249

<https://doi.org/10.1002/ange.201601084>

This is the peer reviewed version of the following article: H. Mora-Radó, L. Bialy, W. Czechtizky, M. Méndez, J. P. A. Harrity, An Alkyne Diboration/6 π -Electrocyclization Strategy for the Synthesis of Pyridine Boronic Acid Derivatives, *Angewandte Chemie* 2016, 128 (19), pp 5928-5930, which has been published in final form at <https://doi.org/10.1002/ange.201601084>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.

Reuse

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

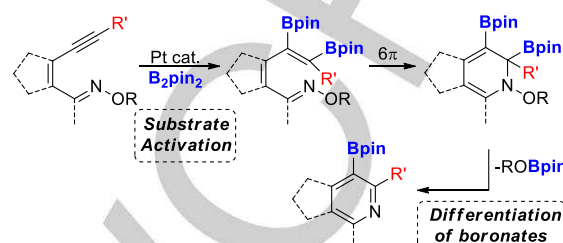
An Alkyne Diboration-6 π -Electrocyclization Strategy to Pyridine Boronic Acid Derivatives**

Helena Mora-Radó,^[a] Laurent Bialy,^[b] Werngard Czechtizky,^[b] María Méndez^[b] and Joseph P. A. Harrity*^[a]

Abstract: We report a new and efficient synthesis of pyridine-based heteroaromatic boronic acid derivatives via a novel diboration-6 π -electrocyclization strategy. This method delivers a range of functionalized heterocycles from readily available starting materials.

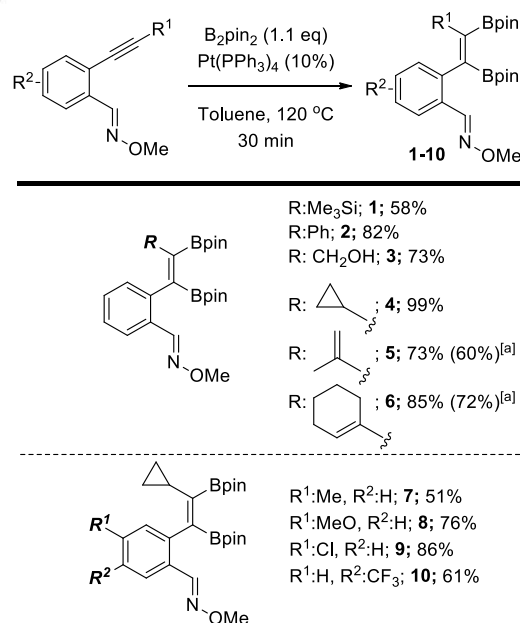
Nitrogen based heterocyclic compounds constitute important building blocks for organic synthesis since they are found in many pharmaceutical and agrochemical targets. In this regard, heteroaromatic boronic acid derivatives are one of the most valuable classes of intermediates in synthetic chemistry.^[1] 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 annulative 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 6 π -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 diborylation 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 alkynes 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]



Scheme 1. The diboration-6 π -electrocyclization strategy.

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

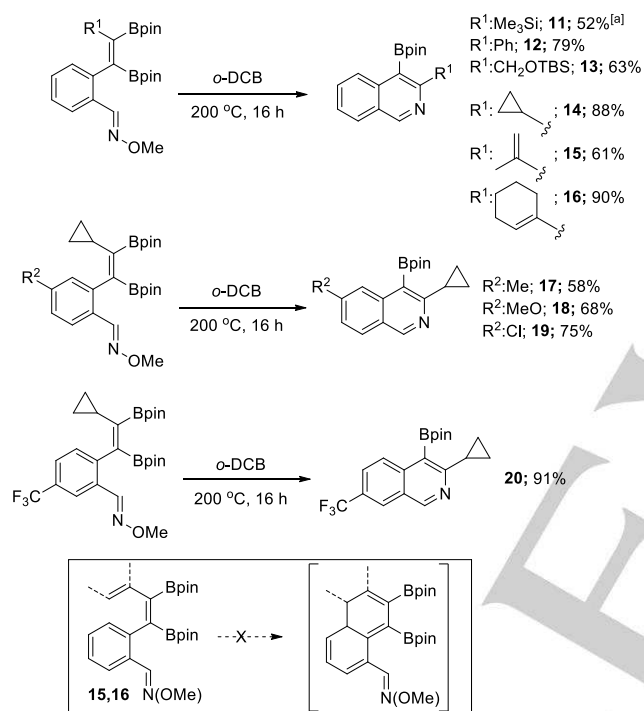
[a] H. Mora Radó, Prof. J. P. A. Harrity
Department of Chemistry
University of Sheffield
Sheffield, S3 7HF (U.K.)
E-mail: j.harrity@sheffield.ac.uk

[b] Dr. L. Bialy, Dr. W. Czechtizky, Dr. M. Méndez
Sanofi
Industrial Park Hoechst, D-65926, Frankfurt am Main, Germany

[**] This work was supported by the FP7 Marie Curie Actions of the European Commission via the ITN COSSHNET network.

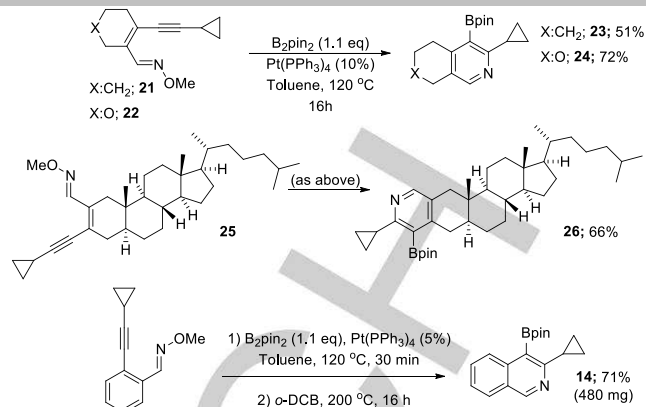
Supporting information for this article is given via a link at the end of the document.

With a range of 1-azatrienes in hand, we turned our attention to the pyridine forming 6π -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. 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^[9] to avoid protodeborylation 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).



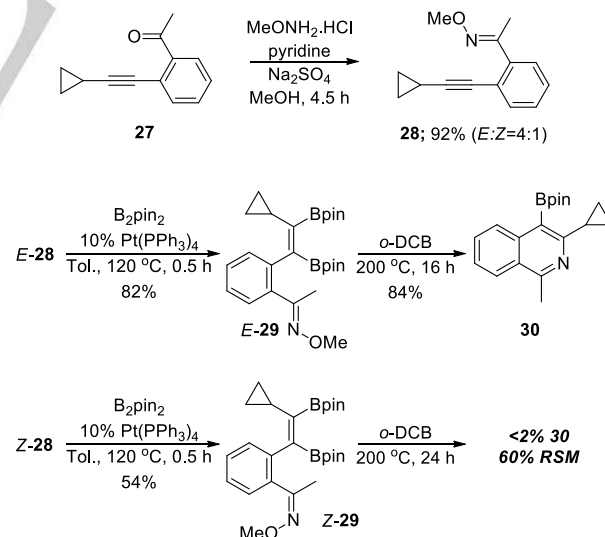
Scheme 3. 6π -electrocyclization to isoquinolines. [a] Reaction conducted at 180 °C for 16 h. *o*-DCB: 1,2-dichlorobenzene.

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,^[9] and the *O*-methyl oximes were subjected to B₂pin₂ 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 yield 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, a similar sequence could also be achieved with aryloximes. Specifically, isoquinoline **14** could be prepared directly from the corresponding alkyne on ~ 0.5 g scale by utilizing a telescoped diboration-electrocyclization sequence.



Scheme 4. One-pot diboration-electrocyclization.

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^[9] and the propensity of acetophenone oximes to adopt the *E*-configuration.^[10] We decided to subject the individual oxime isomers to the diboration-electrocyclization sequence. In the event, *E*-**28** underwent efficient conversion to the aza-triene *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.

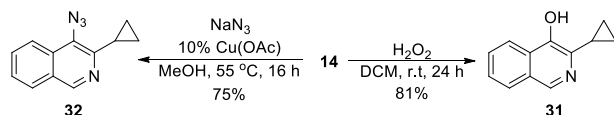


Scheme 5. 6π -electrocyclization of *E/Z*-oxime isomers.

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.^[11] 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-6 π -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:** B₂pin₂ (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-Cl₂C₆H₄ 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-(4,4,5,5-tetramethyl-1,3,2-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 (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 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ = 160.7, 153.8, 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: ν = 2978 (m), 1619 (m), 1562 (m), 1495 (m), 1235 (s), 1134 (s) cm⁻¹. HRMS calculated for C₁₈H₂₂BNO₂: m/z 295.1853, found: 295.1856.

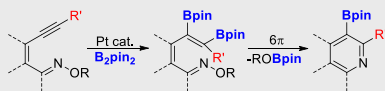
Received: ((will be filled in by the editorial staff))

Published online on ((will be filled in by the editorial staff))

Keywords: diboration • electrocyclization • pyridine • boronic ester

- [1] Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials, 2nd ed.; D. G. Hall, WILEY-VCH, Weinheim, 2011; Vol. 1.
- [2] For selected examples see: a) T. Ishiyama, M. Murata, N. Miyauro, 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. **2011**, 123, 2150; Angew. Chem. Int. Ed. **2011**, 50, 2102.
- [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. **2005**, 117, 7276; Angew. Chem. Int. Ed. **2005**, 44, 7114. d) G. Hilt, K.I. Smolko, Angew. Chem. **2003**, 115, 2901; Angew. Chem. Int. Ed. **2003**, 42, 2795; 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. **2015**, 137, DOI: 10.1021/jacs.5b12989; 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. **2015**, 127, 11397; Angew. Chem. Int. Ed. **2015**, 54, 11245; 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. Jegannathan, 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. Miyauro, 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. 1 **1998**, 3967.

COMMUNICATION



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.

Helena Mora-Radó, Laurent Bialy,
Werngard Czechtizky, María Mendez
Perez, Joseph P. A. Harrity*

Page No. – Page No.

**An Alkyne Diboration- 6π -
Electrocyclization Strategy to
Pyridine Boronic Acid Derivatives**