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Letter

Synthesis and Stabilities of 3-Borylated Indoles

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Abstract We report herein that 3-pinacol boronic esters undergo facile protodeborylation in the presence of palladium catalysts and base, and this contributes significantly to the generation of nonborylated indole byproducts in the B_2Pin_2 -mediated palladium-catalysed borylative cyclization of 2-alkynylanilides. Suginome's reagent provides an alternative method to access 3-borylated indoles as these compounds are less susceptible to protodeborylation.

Key words palladium, cyclisation, indoles, boronic ester, protodeborylation

Aromatic and hetereoaromatic boronic acid derivatives are widely employed in synthetic chemistry because of their versatile reactivity, allowing them to be successfully elaborated by carbon-carbon bond-forming processes or by changing the C–B bond to an alternative functional group (e.g., via oxidation or azidonation reactions).¹ We have been engaged in the investigation of benzannulation strategies to boronic acid derivatives and have found that cycloaddition reactions,² metal-templated cyclizations,³ and condensation processes⁴ all have the potential to construct the (hetero)aromatic nucleus while simultaneously installing the boronate moiety. In addition to these approaches, we became interested in a borylative cyclization strategy⁵ as we envisaged that it would allow access to scaffolds not easily obtained by the aforementioned methods. As shown in Scheme 1, we were able to prepare 3-borylated indoles 2 by this approach via the treatment of 2-alkynylanilides 1 with B₂Pin₂ under palladium catalysis.^{5a,6}

A common byproduct arising from the borylative cyclization was 3-*H* indole **3**, and we believed that this compound arose from a competing palladium-catalysed hy-



Scheme 1 Palladium-catalyzed borylative cyclization

droamination of the starting material.⁷ Moreover, the tendancy of **3** to co-elute with the desired boronic ester product **2** made separation quite challenging in some cases. In order to circumvent this side reaction, we wanted to explore alternative borylating agents in order to establish their compatibility with the borylative cyclization strategy. In this context, Suginome and co-workers described the synthesis of the diboron reagent BPin-Bdan,⁸ which offered the potential to generate stable indole boronamides as the less Lewis acidic Bdan group has a tendency to transfer in preference to the Bpin in borylation reactions.⁹ We report herein the realisation of this idea and the relative stabilities of the respective Bpin-Bdan indoles.

Before undertaking an investigation of the borylative cyclization reaction using the BPin-Bdan reagent, we wanted to establish that indole-Bdan compounds could be accessed and isolated using more traditional procedures. Accordingly, we prepared a small family of 3-iodoindoles following the method of Amjad and Knight.¹⁰ As shown in Scheme 2, the iodocyclisation methodology provided the requisite 3-iodoindoles in good to high yield under mild conditions. Moreover, this process was compatible with a broad selection of substituents and functional groups and offered adequate scope to investigate the subsequent borylation reaction.

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Our next step was to carry out the borylation of indole iodides **4–11**. In this respect, Xu and Li recently reported that aryl bromides and chlorides could be converted into the corresponding boronamides using the Suginome reagent.¹¹ Although these authors reported one example of an indole substrate, borylation was conducted at the benzene moiety (i.e., at C5). In the event, subjection of indoles **4–11** to BPin-Bdan in the presence of Pd₂dba₃ provided the corresponding masked boronates **12–19** in good to excellent yield, with the mass balance consisting of indole derived from protodeiodination–protodeborylation of the starting material/product, respectively. The products were isolated as crystalline solids, and **19** was further characterised by Xray crystallography (Scheme 3).

We next took the opportunity to explore the relative stability of indole-Bdan and indole-BPin compounds towards our established borylative cyclization conditions, and our results are shown in Scheme 4. In the event, subjecting **12** and the corresponding pinacol ester **20** to the catalyst and base under conditions typically used in the borylative cyclisation resulted in complete deborylation of **20**, while **12** was returned essentially untouched. Notably, however, subjection of **12** to these conditions over longer periods (>5 h) did result in significant protodeborylation also.

Taken together, these experiments highlight the propensity for borylated indoles to undergo protodeborylation in the presence of palladium catalysts. Pinacol esters are especially sensitive to this side reaction and, with respect to the palladium-catalyzed borylative cyclization of 2-alkyLetter



Scheme 3 Borylation of 3-iodoindoles. ^a Reaction run overnight using 10 mol% catalyst.





nylanilides developed in our labs (cf. Scheme 1), we believe that this is the major factor in the generation of nonborylated indole byproducts. Facile deborylation can also be implicated in the work of Kaila et al. They reported significant levels of reduction (to nonborylated indole byproducts) in their efforts to prepare 3-borylated indoles from the corresponding 3-bromoindoles under palladium catalysis with B_2Pin_2 .¹² In this respect, the employment of Knight's iodocyclization and borylation using Suginome's reagent offers an alternative approach.¹³

Finally, we decided to attempt the direct synthesis of indole-Bdan **12** via borylative cyclization, and our results are shown in Scheme 5. Subjection of 2-phenyl(ethynyl)anilide to our optimal catalyst in the presence of Suginome's reagent provided a mixture of three indole products **12**, **20**, and **21** (ca. 4:1:1), from which the desired indole-Bdan **12** could be isolated in 58% yield.



Scheme 5 Borylative cyclization using Suginome's reagent

In conclusion, we have found that indole 3-pinacol boronic esters undergo facile protodeborylation in the presence of palladium catalysts and base, resulting in the generation of nonborylated indole byproducts. Suginome's reagent provides an alternative method to access 3-borylated indoles as these compounds are less susceptible to deboronation. Efforts to extend the scope of this chemistry, in particular with respect to borylative cyclization and functionalization of the C–B bond, are ongoing and will be reported in due course.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561944.

References and Notes

- (1) Boronic Acids; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005.
- (2) For representative examples, see: (a) Bachollet, S. P. J. T.; Vivat, J. F.; Cocker, D. C.; Adams, H.; Harrity, J. P. A. *Chem. Eur. J.* 2014, *20*, 12889. (b) Crépin, D. F. P.; Harrity, J. P. A.; Jiang, J.; Meijer, A. J. H. M.; Nassoy, A.-C. M. A.; Raubo, P. *J. Am. Chem. Soc.* 2014, *136*, 8642. (c) Browne, D. L.; Taylor, J. B.; Plant, A.; Harrity, J. P. A. *J. Org. Chem.* 2009, *74*, 396. (d) Delaney, P. M.; Browne, D. L.; Adams, H.; Plant, A.; Harrity, J. P. A. *Tetrahedron* 2008, *64*, 866.
- (3) (a) Stalling, T.; Harker, W. R. R.; Auvinet, A.-L.; Cornel, E. J.; Harrity, J. P. A. *Chem. Eur. J.* **2015**, *21*, 2710. (b) Auvinet, A.-L.; Harrity, J. P. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 2769. (c) Auvinet, A.-L.; Harrity, J. P. A.; Hilt, G. J. Org. Chem. **2010**, *75*, 3893.

(d) Gandon, V.; Leboeuf, D.; Amslinger, S.; Vollhardt, K. P. C.; Malacria, M.; Aubert, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 7114. (e) Hilt, G.; Smolko, K. I. *Angew. Chem. Int. Ed.* **2003**, *42*, 2795.

- (4) Kirkham, J. D.; Edeson, S. J.; Stokes, S.; Harrity, J. P. A. Org. Lett. 2012, 14, 5354.
- (5) (a) Huang, J.; Macdonald, S. J. F.; Harrity, J. P. A. *Chem. Commun.* **2010**, 46, 8770. (b) Warner, A. J.; Lawson, J. R.; Fasano, V.; Ingleson, M. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 11245. (c) Chong, E.; Blum, S. A. J. Am. Chem. Soc. **2015**, *137*, 10144.
- (6) For alternative approaches to 3-borylated indoles, see:
 (a) Tasch, B. O. A.; Merkul, E.; Müller, T. J. J. *Eur. J. Org. Chem.* **2011**, 4532. (b) Merkul, E.; Schäfer, E.; Müller, T. J. J. *Org. Biomol. Chem.* **2011**, *9*, 3139. (c) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. Chem. Rev. **2010**, *110*, 890.
- (7) Cacchi, S.; Fabrizi, G. Chem. Rev. 2005, 105, 2873.
- (8) Iwadate, N.; Suginome, M. J. Am. Chem. Soc. 2010, 132, 2548.
- (9) Cid, J.; Carbó, J. J.; Fernández, E. Chem. Eur. J. 2014, 20, 3616.
- (10) Amjad, M.; Knight, D. W. Tetrahedron Lett. 2004, 45, 539.
- (11) Xu, L.; Li, P. Chem. Commun. 2015, 51, 5656.
- (12) Kaila, N.; Follows, B.; Leung, L.; Thomason, J.; Huang, A.; Moretto, A.; Janz, K.; Lowe, M.; Mansour, T. S.; Hubeau, C.; Page, K.; Morgan, P.; Fish, S.; Xu, X.; Williams, C.; Saiah, E. *J. Med. Chem.* **2014**, *57*, 1299.
 (13) Representative Procedure for the Borylation of N-Tosyl 3-
 - Iodo Indoles Synthesis of Indole 19 2-Cyclopropyl-3-iodo-1-tosyl-1H-indole (11, 200 mg, 0.455 mmol), Pd₂(dba)₃ (21 mg, 0.023 mmol), Cs₂CO₃ (297 mg, 0.910 mmol), PinB-Bdan (268 mg, 0.910 mmol) in MeOH (1 mL) was stirred at reflux under a nitrogen atmosphere for 2 h. The reaction mixture was allowed to cool to r.t., and EtOAc (10 mL) was added. The organic extract was washed with $H_2O(2 \times 5 \text{ mL})$ and brine (5 mL), dried over MgSO₄, and the solvents removed under reduced pressure to provide the crude product. Purification of the residue by flash chromatography on silica gel using a solvent gradient of PE-EtOAc (95:5), increasing in polarity to EtOAc gave the target compound 19 as a colorless solid (151 mg, 70%), mp 240-241 °C. ¹H NMR (400 MHz, CDCl₃): δ = 8.25 (d, *I* = 8.5 Hz, 1 H), 7.77 (d, *I* = 8.5 Hz, 2 H), 7.57 (d, *I* = 7.5 Hz, 1 H, ArH), 7.34-7.29 (m, 1 H, ArH), 7.25-7.20 (m, 3 H, ArH), 7.14 (dd, J = 8.0, 7.5 Hz, 2 H), 7.07 (dd, J = 8.5, 1.0 Hz, 2 H), 6.35 (dd, J = 7.0, 1.0 Hz, 2 H), 5.87 (s, 2 H), 2.39 (s, 3 H), 2.33 (tt, J = 8.5, 5.5 Hz, 1 H), 0.96 (dt, J = 8.5, 3.0 Hz, 2 H), 0.66–0.59 (m, 2 H). ¹³C NMR (101 MHz, $CDCl_3$): $\delta = 146.4$, 144.6, 140.8, 137.6, 137.0, 136.3, 132.2, 129.7, 127.6, 126.6, 124.3, 123.3, 120.7, 119.8, 117.9, 114.5, 105.9, 21.6, 10.3, 8.9. ¹¹B NMR (128 MHz, CDCl₃): δ = 30.9. FTIR: v_{max} = 3404, 3042, 2963, 2884, 1625, 1600 cm⁻¹. HRMS (ESI-TOF): m/z [M + Na]⁺ calcd for C₂₈H₂₄BN₃O₂S: 500.1580; found: 500.1561.

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