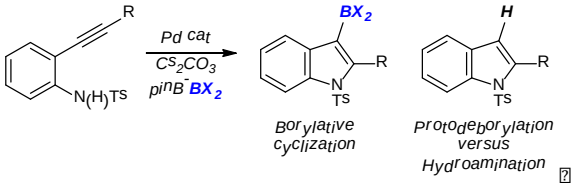
Synthesis and Stabilities of 3-Borylated Indoles

Muhannad A. E. Al-Saedy
Joseph P. A. Harrity*

Department of Chemistry, The University of Sheffield, Brook Hill, Sheffield. S3 7HF, U.K.

j.harrity@sheffield.ac.uk

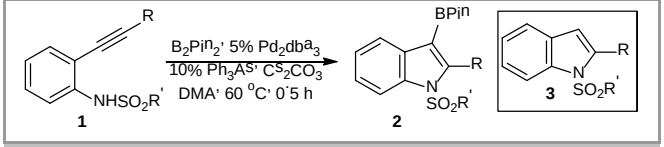


Received:
Accepted:
Published online:
DOI:

Abstract We report herein that 3-pinacol boronic esters undergo facile protodeborylation in the presence of Pd catalysts and base, and this contributes significantly to the generation of non-borylated indole by-products in the B_2Pin_2 mediated Pd-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.

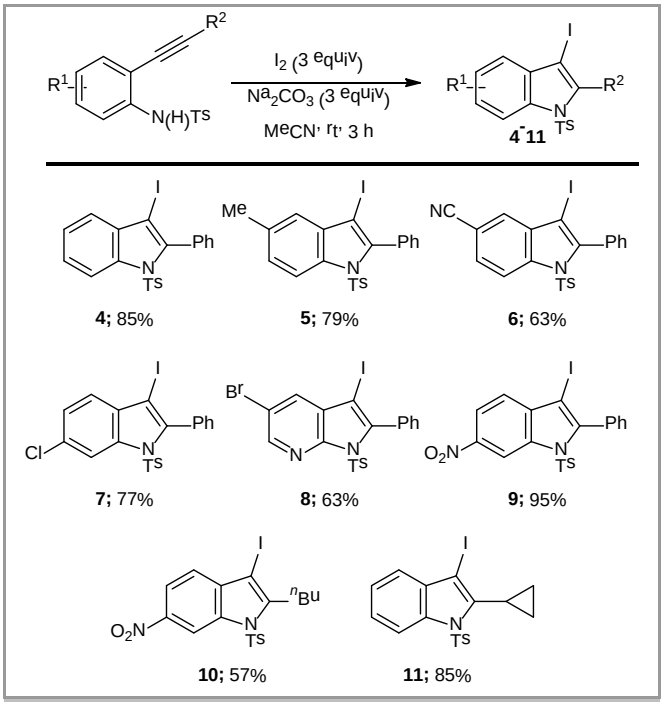
Key words Palladium, cyclisation, indoles, boronic ester, protodeborylation

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 processes[4] 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 strategy[5] 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 B_2Pin_2 under Pd-catalysis.[5(a),6]



Scheme 1 Pd-catalyzed borylative cyclization.

A common by-product arising from the borylative cyclization was 3-*H* indole **3**, and we believed that this compound arose from a competing Pd-catalysed hydroamination 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

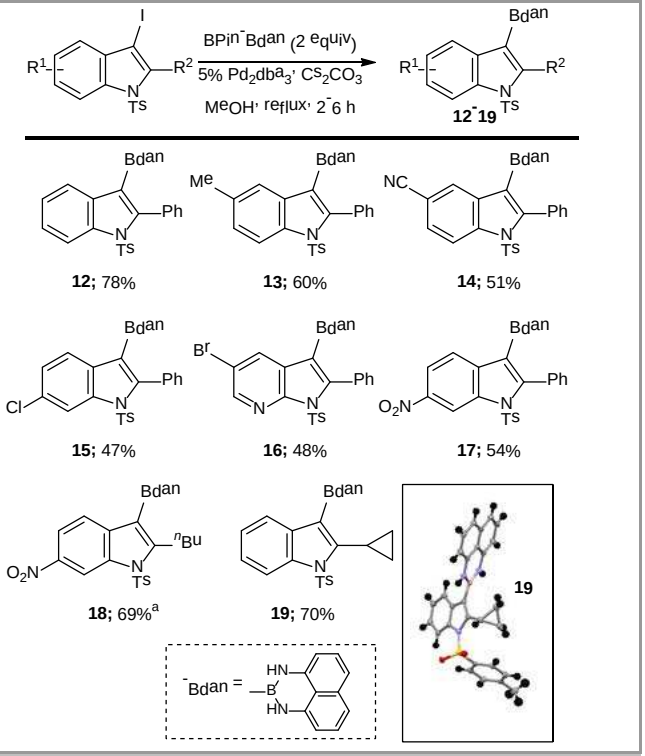


Scheme 2 Iodocyclization of 2-alkynylanilines.

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.

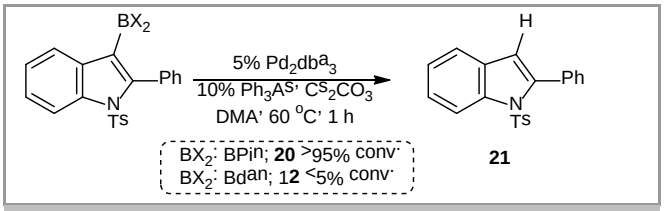
Before undertaking an investigation of the borylative cyclization reaction using the BPin-Bdan reagent, we wanted to establish that indole-Bdan compounds could be accessed and isolated using more traditional procedures. Accordingly, we prepared a small family of 3-iodoindoles following the method of 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.

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 to the corresponding boronamides using the Suginome reagent.[11] Although these authors reported 1 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 Pd_2dba_3 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 X-ray crystallography (Scheme 3).



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

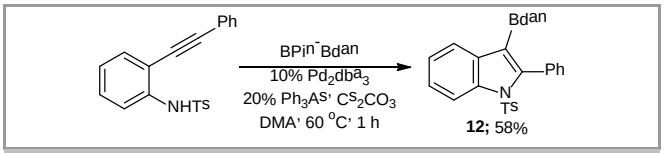
We next took the opportunity to explore the relative stability of indole-Bdan and indole-BPin compounds towards our established borylative cyclization conditions, and our results are shown in scheme 4. In the event, subjecting **12** and the corresponding pinacol ester **20** to the catalyst and base 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 (> 5h) did result in significant protodeborylation also.



Scheme 4 Stabilities of indole-Bdan versus –Bpin towards protodeborylation.

Taken together, these experiments highlight the propensity for borylated indoles to undergo protodeborylation in the presence of Pd-catalysts. Pinacol esters are especially sensitive to this side-reaction and, with respect to the Pd-catalyzed borylative cyclization of 2-alkynylanilides developed in our labs (c.f. Scheme 1), we believe that this is the major factor in the generation of non-borylated indole by-products. Facile deborylation can also be implicated in the work of Kaila et al. They reported significant levels of reduction (to non-borylated indole by-products) in their efforts to prepare 3-borylated indoles from the corresponding 3-bromoindoles under Pd 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** (~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 Pd catalysts and base, resulting in the generation of non-borylated indole by-products. 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.

Acknowledgment

We are grateful to The Iraqi Ministry of Higher Education and Scientific Research and Al-Mustansiriyah University for financial support.

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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(13) Representative procedure for borylation of *N*-tosyl 3-iodo indoles. Synthesis of indole **19**: 2-Cyclopropyl-3-iodo-1-tosyl-1*H*-indole **11** (200 mg, 0.455 mmol), Pd_2dba_3 (21 mg, 0.023 mmol), Cs_2CO_3 (297 mg, 0.910 mmol), PinB-Bdan (268 mg, 0.910 mmol) in methanol (1 mL) was stirred at 75 °C under a nitrogen atmosphere for 2 h. The reaction mixture was allowed to cool to room temperature and ethyl acetate (10 mL) was added. The organic extract was washed with H_2O (2 x 5 mL) and brine (5 mL), dried over $MgSO_4$ 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 petroleum ether/ethyl acetate (95:5), increasing in polarity to ethyl acetate gave the target compound **19** as a colorless solid (151 mg, 70%), M.p.: 240-241 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 7.5 Hz, 1H, ArH), 7.34-7.29 (m, 1H, ArH), 7.25-7.20 (m, 3H, ArH), 7.14 (dd, J = 8.0, 7.5 Hz, 2H), 7.07 (dd, J = 8.5, 1.0 Hz, 2H), 6.35 (dd, J = 7.0, 1.0 Hz, 2H), 5.87 (s, 2H), 2.39 (s, 3H), 2.33 (tt, J = 8.5, 5.5 Hz, 1H), 0.96 (dt, J = 8.5, 3.0 Hz, 2H), 0.66 – 0.59 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 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. ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.9. FTIR: ν_{max} 3404, 3042, 2963, 2884, 1625, 1600 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{28}H_{24}BN_3O_2S$ 500.1580, found 500.1561.