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# Synthesis and Stabilities of 3-Borylated Indoles

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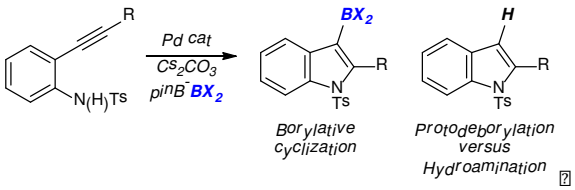


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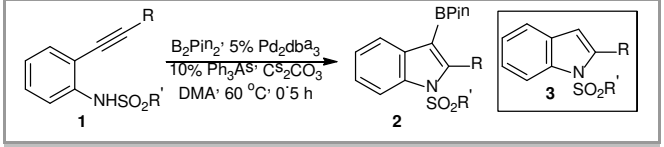
**Abstract** We report herein that 3-pinacol boronic esters undergo facile protodeborylation in the presence of Pd catalysts and base, and this contributes significantly to the generation of non-borylated indole by-products in the $B_2Pin_2$ mediated Pd-catalysed borylative cyclization of 2-alkynylanilides.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

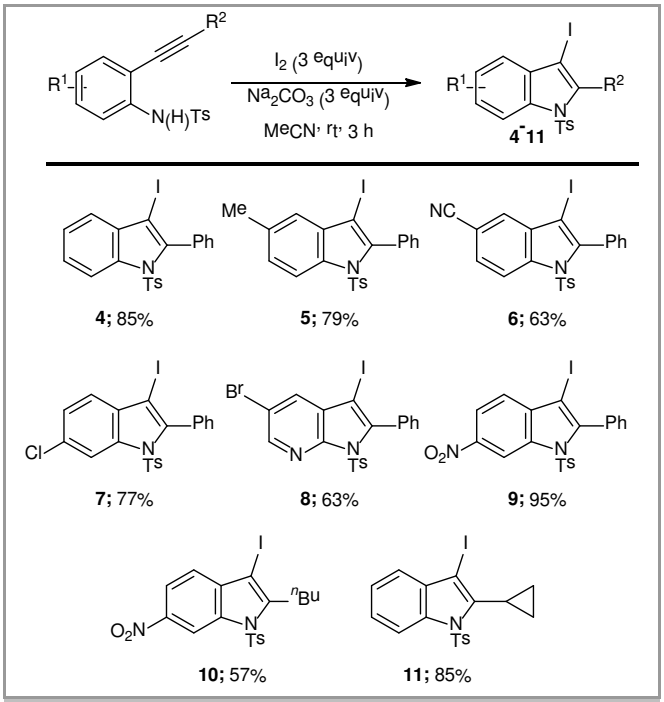
**Key words** Palladium, cyclisation, indoles, boronic ester, protodeborylation

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

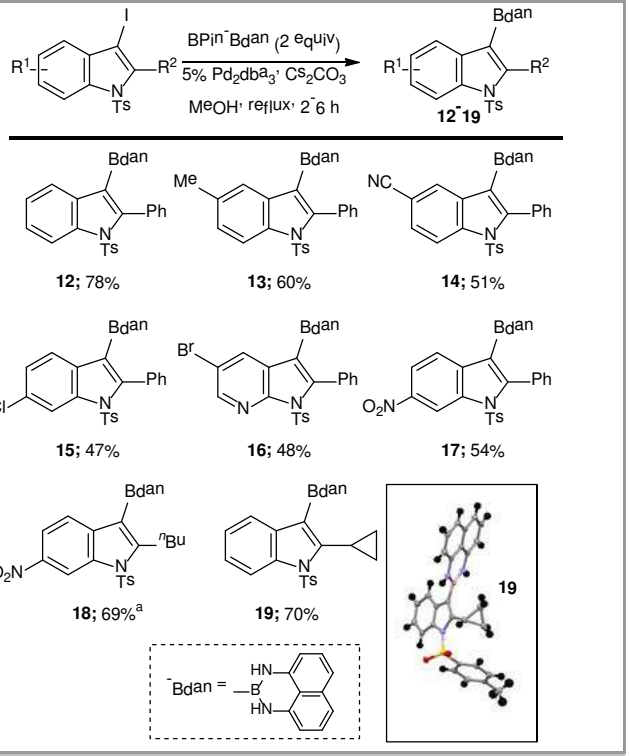



**Scheme 2** Iodocyclization of 2-alkynylanilines.

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.

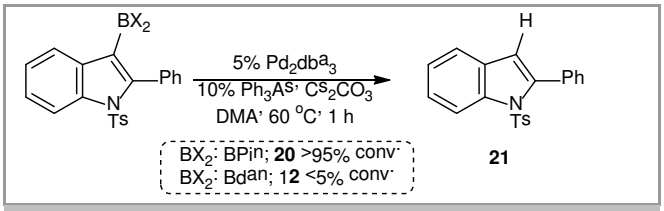
Before undertaking an investigation of the borylative cyclization reaction using the BPin-Bdan reagent, we wanted to establish that indole-Bdan compounds could be accessed and isolated using more traditional procedures. Accordingly, we prepared a small family of 3-iodoindoles following the method of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

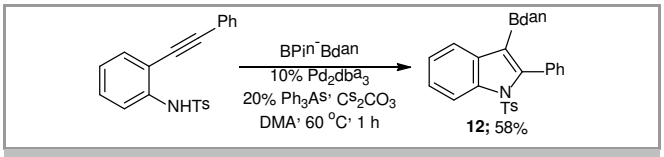
We next took the opportunity to explore the relative stability of indole-Bdan and indole-BPin compounds towards our established borylative cyclization conditions, and our results are shown in scheme 4. In the event, subjecting **12** and the corresponding pinacol ester **20** to the catalyst and base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

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## 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: $\nu_{max}$ 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.