A borylative cyclisation towards indole boronic esters†

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2-Alkynylaniline borylative cyclisations provide a direct means to access indole 3-boronic esters from simple precursors. The Pd-catalysed cyclisation can be merged with cross-coupling processes in the same reaction vessel, moreover, the products can be exploited in C–N bond forming reactions.

Increasing pressure on the Fine Chemicals Industry to produce novel therapeutics with an efficacious clinical profile but within a shorter timeframe has revolutionised medicinal chemistry over the last decade, and has been significantly promoted by the advent of high throughput synthesis techniques. A key element of this drug discovery process is the availability of starting compounds that bear useful functionality for further elaboration, such that a systematic investigation of the biological and physiochemical properties can be made. In this context, aromatic and heteroaromatic boronic acid derivatives represent one of the most valuable classes of synthetic intermediates in modern organic chemistry because they undergo a large variety of functional group interconversions as well as C–C bond forming reactions.[1] Approaches towards the synthesis of boronic acid derivatives largely falls into two categories: (1) Functionalisation of a pre-formed (hetero)-aromatic ring;[2] (2) Benzannulation strategies, whereby the boronate is installed by virtue of aromatic ring formation.[3] In the context of this latter approach, alkynylboronates have proven to be useful precursors to a range of heteroaromatic- and benzene based boronic acid derivatives *via* metal promoted[4] and pericyclic[5] cycloaddition processes.

Although the alkynylboronate cycloaddition approach has provided access to a reasonable selection of arylboronic ester compounds, exclusive use of alkyne cycloadditions as a vehicle for aromatic ring formation places an obvious limitation on the type of scaffold that can be prepared. There is therefore a clear need to expand the current paradigm beyond this method and we therefore envisaged an alternative sequence that employed a metal catalysed benzannulation process that was terminated by a boration reaction. In this context, the metal catalyzed cyclisation of *o*-alkynylaniline derivatives has become a well established method for the synthesis of indoles.[6] The substrates for this transformation are easily prepared by Sonogashira coupling of an appropriate alkyne and *o*-haloaniline. As well as providing 2-substituted indoles, Pd-catalysis allows this strategy to be expanded to permit the incorporation of substituents at the 3-position by additional metal catalysed coupling reactions.[7,8] Moreover, 3-halo- and 3-cyanoindoles can be accessed by Cu-catalysed cyclisations,[9] or *via* electrophilic iodination.[10] Our specific goal was to investigate the potential of *boronate incorporation within the indole cyclisation reaction*. This technique would have the potential to generate the heteroaromatic boronates in a single step from established indole precursors, and would provide the opportunity to generate azole boronates that are currently inaccessible by alkyne benzannulation strategies, thereby representing a powerful and complementary alternative. The traditional and proposed approaches to indole boronic acid derivatives are summarised in Fig. 1.

We initiated our studies by preparing the Ts-protected *o*-alkynylaniline substrate **1**,[11] and investigated the Pd-catalysed cyclisation in the presence of bis(pinacolato)diboron. Our results are summarised in Table 1. We screened a series of Pd(II) catalysts which are known to promote indole forming cyclisations and subsequent electrophile trapping reactions.[7a] In the event, whilst $PdCl_2$ catalysis efficiently promoted cyclisation at room temperature and provided the desired product **2a**, the major product of the reaction was the C3-protonated indole **2b** (entries 1 and 2). We next employed low valent Pd-catalysts but again were disappointed to find that desired product **2a** was only a minor component of the cyclised products (entries 3 and 4). In an effort to reduce reaction times, we attempted the cyclisations at elevated temperatures and were surprised to find an overall improvement in the ratio of **2a** : **2b** (compare entries 4 and 5). Further optimisation highlighted that DMA and Cs_2CO_3 gave marginal improvement (entries 6–8) but significantly, the introduction of Ph_3As proved to promote the borative cyclisation, thereby providing an effective means to deliver the desired 2-substituted indole 3-boronic esters. The superior ability of Ph_3As to promote this formation of **2a** over **2b** is intriguing but mirrors similar successes documented by Marinelli and co-workers.[7c]

In an effort to confirm that boronic ester formation occurred during cyclisation rather than after indole formation, we subjected **2b** to the optimised reaction conditions over 16 h and found $<5\%$ conversion to **2a** (Scheme 1). Moreover, **2a** was found to be quite stable towards protodeboronation under

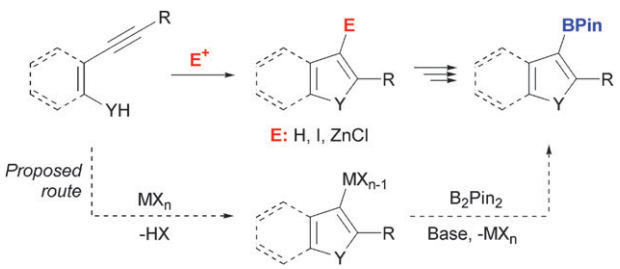

Fig. 1 Metal catalysed benzannulation–borylation sequence.

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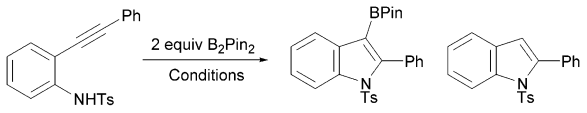
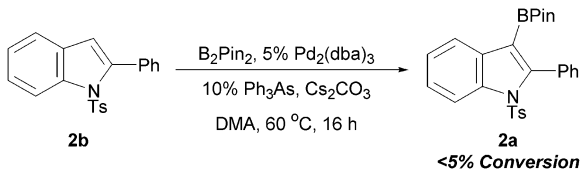
Table 1 Optimisation of the borylative cyclisation



1 2a 2b

Entry	Catalyst (mol%)	Base (2 equiv.)	Conditions	Yield % (**2a** : **2b**)
1	$PdCl_2$ (10)	K_2CO_3	DMF, rt, 16 h	83 (1 : 4.5)
2	$(PPh_3)_2$ $PdCl_2$ (10)	K_2CO_3	DMF, rt, 16 h	78 (1 : 3)
3	$Pd(PPh_3)_4$ (10)	K_2CO_3	DMF, rt, 16 h	76 (1 : 6)
4	$Pd_2(dba)_3$ (5)	K_2CO_3	DMF, rt, 16 h	92 (1 : 5.5)
5	$Pd_2(dba)_3$ (5)	K_2CO_3	DMF, 60 °C, 0.5 h	91 (1 : 2)
6	$Pd_2(dba)_3$ (5), PPh_3 (20)	Cs_2CO_3	DMA, 60 °C, 0.5 h	81 (1 : 1)
7	$Pd_2(dba)_3$ (5), $AsPh_3$ (20)	Cs_2CO_3	DMA, 60 °C, 0.5 h	88 (3.5 : 1)
8	$Pd_2(dba)_3$ (5), $AsPh_3$ (10)	Cs_2CO_3	DMA, 60 °C, 0.5 h	92 (3.5 : 1)

dba: dibenzylideneacetone.

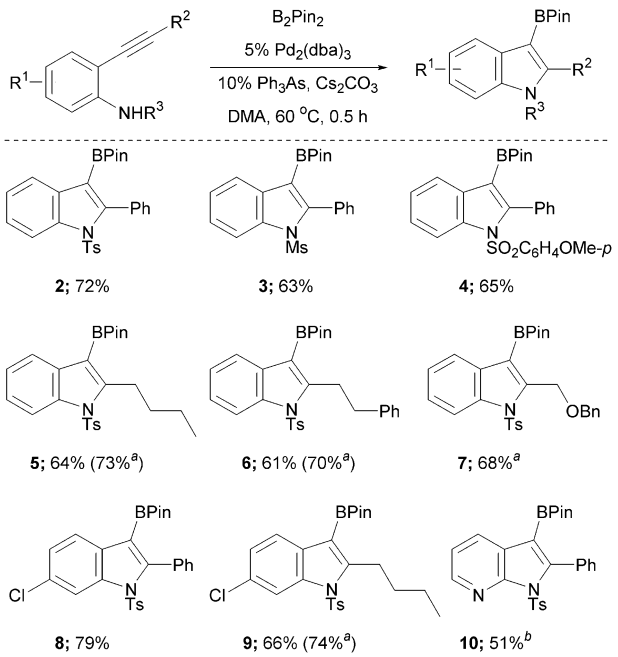


2b **2a** ***<5% Conversion***

Scheme 1

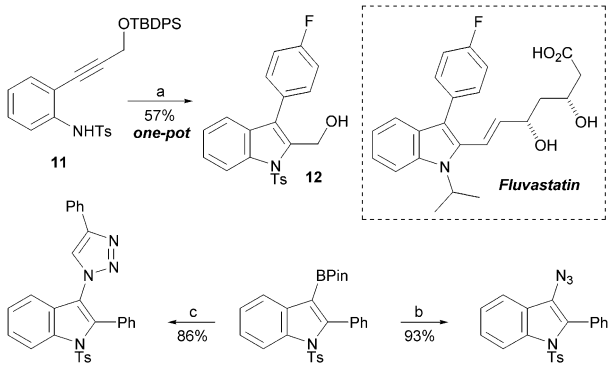
the reaction conditions, undergoing only 5–10% deborylation to **2b** over this extended period.

We next turned our attention to exploring the scope of the borative cyclisation and our results are depicted in Scheme 2. The methodology was found to be successful over a small series of sulfonamide based substrates (**2–4**), although all attempts to cyclise anilines bearing N-Boc or N-Bn substituents failed and starting material was returned in these cases. The chemistry was found to be tolerant of alkyl substituents (**5–7**), and bifunctional indoles **8** and **9** were also prepared in good yield. Finally, we found this methodology to be applicable to the synthesis of azaindoles and compound **10** was prepared in 51% yield.



Scheme 2 [a]Reaction conducted with 10% Pd_2dba_3, 40% Ph_3As. [b]Reaction conducted with 10% Pd_2dba_3, 20% Ph_3As.

In order to demonstrate the synthetic potential of these scaffolds we undertook some representative functionalisation reactions, these are highlighted in Scheme 3. We began these investigations with a Suzuki–Miyaura coupling reaction, as it represents the most heavily utilised synthetic manipulation of boronic acid derivatives.[12] Moreover, given that the indole boronic ester formation employs Pd-catalysis, we believed there to be an opportunity to conduct the cross-coupling reaction after benzannulation, thereby using a single Pd-catalyst to promote sequential cyclisation and C–C bond forming processes *in situ*. In the event, borative cyclisation of **11** followed by addition of 4-fluoro iodobenzene provided cross-coupled product **12** upon treatment with TBAF.[13] Compound **12** represents the core indole motif of fluvastatin, used in the treatment of hypercholesterolemia.[14] Boronic acid derivatives also offer the potential to construct carbon–heteroatom bonds and we explored the Cu-catalysed azide formation from **2**.[15] Pleasingly, compound **13** was generated in 93% yield, moreover, this procedure was found to be compatible with a one-pot azidation/click reaction and biheteroaryl product **14** was generated in good yield.



11 **12** **14** **2** **13**

Scheme 3 *Reagents and conditions*: (a) 5% $Pd_2(dba)_3$, 10% Ph_3As, Cs_2CO_3, B_2Pin_2, DMA, 60 °C, 0.5 h; 4-IC_6H_4F, DMA : H_2O (1 : 1), 60 °C, 16 h; TBAF, 60 °C , 6 h. (b) NaN_3, 10% $CuSO_4$, MeOH, rt, 2 h. (c) NaN_3, 10% $CuSO_4$, MeOH, rt, 2 h; phenylacetylene, sodium ascorbate, CH_2Cl_2 : H_2O (1 : 1).

In conclusion, we have developed a borative cyclisation strategy to indole 3-boronic esters. This technique employs readily available *o*-alkynylanilines whereby simply adding commercially available B_2Pin_2 to a typical catalyst mixture employed in indole formation, allows direct synthesis of the corresponding indole boronic esters, that would otherwise be generated after additional functionalisation steps. This process is amenable to one-pot cyclisation/cross-coupling protocols providing a versatile means for generating compound diversity in a practical manner. Studies towards investigating the scope of this technique for the synthesis of other heteroaromatic systems are underway and will be reported in due course.

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