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Borane-catalysed C2-selective indole reductive functionalisation†

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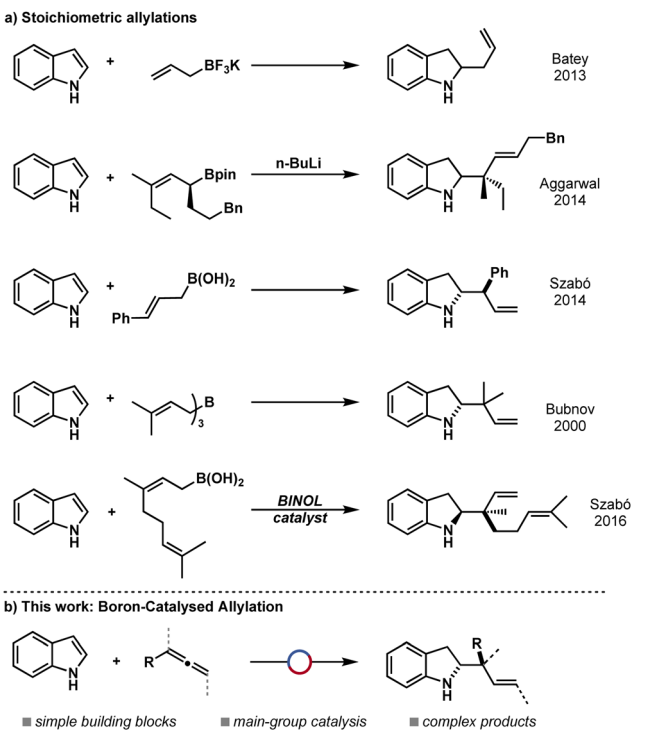
Indolines are common motifs within pharamceuticals and natural products. Boron catalysis enables the chemoselective allylation of indoles to give allylic indolines in excellent diastereoselectivity. Mechanistic studies revealed *in situ* formation of the allylic borane, allylation of the imine tautomer of the indole and B–N/B–H transborylation for catalytic turnover.

Indolines are useful building blocks in organic synthesis as their derivatives are widely found throughout pharmaceuticals and natural products, thus the development of facile functionalisation is a worthwhile pursuit.[1] Indoles are commonly used as nucleophiles in C3 selective Friedel–Crafts-type acylation[2] and alkylation reactions,[3] although electrophilic functionalisation[4] at other positions including C2,[5] C4,[6] C5,[7] C6[8] and C7[9] has been reported.[10] The reaction of an indole as the electrophile is less developed.[11] Stoichiometric, reductive allylation to give allylic indolines has been reported, though is limited to pre-functionalised substrates, telescope reactivity, and often requires the use of indoles bearing electron-donating groups.[12] A notable catalytic example is Szabó's use of enantioenriched diol catalysts and allylic boronic acids for C2 reductive allylation (Scheme 1a).[12j]

The electrophilic reactivity of indoles is proposed to proceed through an imine tautomer at the C2 position.[12a] The imine has been trapped using allylic boronic acids and esters in stoichiometric studies (Scheme 1a), with these pre-functionalised substrates typically prepared by transition metal catalysts.[13] Allylic boranes have not been as widely used due to their reduced stability[14] compared to boronic acids and esters, however, they can be readily prepared by allene hydroboration[15] and are more reactive than the boronic ester equivalents. Stoichiometric reaction of an indole with an allylic borane gives a B–N bond of the indoline, which is cleaved upon work-up and the borane destroyed. Recently, transborylation (boron exchange) catalysis has been developed to achieve catalytic turnover at B–heteroatom bonds.[16]

Here we sought to develop a catalytic, reductive allylation of unprotected indoles using allenes and boron catalysis. The C2 allylation of indoles faces several challenges, firstly unwanted reductive dimerisation of indoles must be avoided.[17] To achieve high diastereoselectivity in the product indoline, strict control of the diastereoselectivity in forming the allylic borane reagent and (*E*)/(*Z*)-isomerisation of the allylborane is required. This is



Scheme 1 (a) Existing functionalisations of indoles at C2 position. (b) This work: boron catalysed allylation of indoles.

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particularly relevant for dialkyl allylic boranes as both (*E*) and (*Z*) diastereomers exists in equilibrium with rapid interchange.[15d] Chemoselectivity must also be considered to prevent (nucleophilic) C3 functionalisation. Finally, direct reduction of the indole to indoline,[16c] and hydroboration of the indole[18] must be negated both of which have been reported using boron catalysis.

Inspired by our previous studies on borane-catalysed allylation reactions,[16g] H-*B*-9-borabicyclo[3.3.1]nonane, [H-*B*-9-BBN]$_2$, was tested as a catalyst for the reductive allylation of indole with cyclohexylallene using HBpin as the turnover reagent. [H-*B*-9-BBN]$_2$ (10 mol%) was found to be the optimal catalyst when the reaction was carried out under reflux in THF for 16 hours to give 2-(1-cyclohexylallyl)indoline **3a** in excellent yield (81%), diastereoselectivity (>95 : 5 d.r.) and as a single (C2) regioisomer. Indole reductive dimerisation,[17] hydroboration,[18] reduction to the indoline[16c] or C3 functionalisation were not observed. The anticipated *anti*-indoline product was observed presumably due to reaction of the (*E*)-allylic borane – formed by *syn* hydroboration and isomerisation[15a] – through a Zimmerman–Traxler-type transition-state structure. The use of other solvents including hexane, toluene and CH_2Cl_2 gave reduced yields, likely due to the poor solubility of the indole substrate. Decreasing the reaction temperature and catalyst loading resulted in reduced yields, while increasing reaction time did not result in a significant yield enhancement with no effect on diastereoselectivity in each case. Application of this catalytic system to other N-heterocycles including pyrrole, quinolone, isoquinoline, benzoimidazole, benzoxazole, and benzothiazole was unsuccessful as was reaction of benzofuran and benzothiophene.

Having optimised the reaction conditions the catalytic protocol was applied to a diverse scope of indoles and allenes (Fig. 1). 2-(1-Cyclohexylallyl)indoline was isolated in good yield and excellent d.r. **3a** (82% yield, >95 : 5 d.r.). Other allenes were tested to expand the scope of allylation with good yields and excellent diastereoselectivities including chloro-containing allene **3b** (46% yield, >95 : 5 d.r.), alkyl allene **3c** (62% yield, >95 : 5 d.r.) and reaction of penta-3,4-dienyl-benzene to give **3d** (53% yield, >95 : 5 d.r.). Previous stoichiometric studies showed limited substitution about the indole, often limited to only alkyl[12a,12d] or methoxy[12c] groups. The only stoichiometric example of a reductive allylation of halide substituted indole resulted in poor d.r.[12e] This catalytic protocol was applied to numerous halo-indoles including chloro-**3e** (77% yield, >95 : 5 d.r.) **3f** (83% yield, >95 : 5 d.r.) and bromo-**3g** (58% yield, >95 : 5 d.r.) exhibiting good yields and excellent diastereoselectivities in all cases. This clearly demonstrates the benefits of this protocol over the stoichiometric counterparts by enabling wider functional group tolerance and orthogonal reactivity. Other substituents on the indole including methyl **3h** (64% yield, >95 : 5 d.r.) and trifluoromethyl **3i** (65% yield, 73 : 27 d.r.) were reacted in good yields and selectivity, the latter being especially interesting as previous studies often required the use of electron-donating groups on the arene. Ester groups were tolerated under the standard reaction

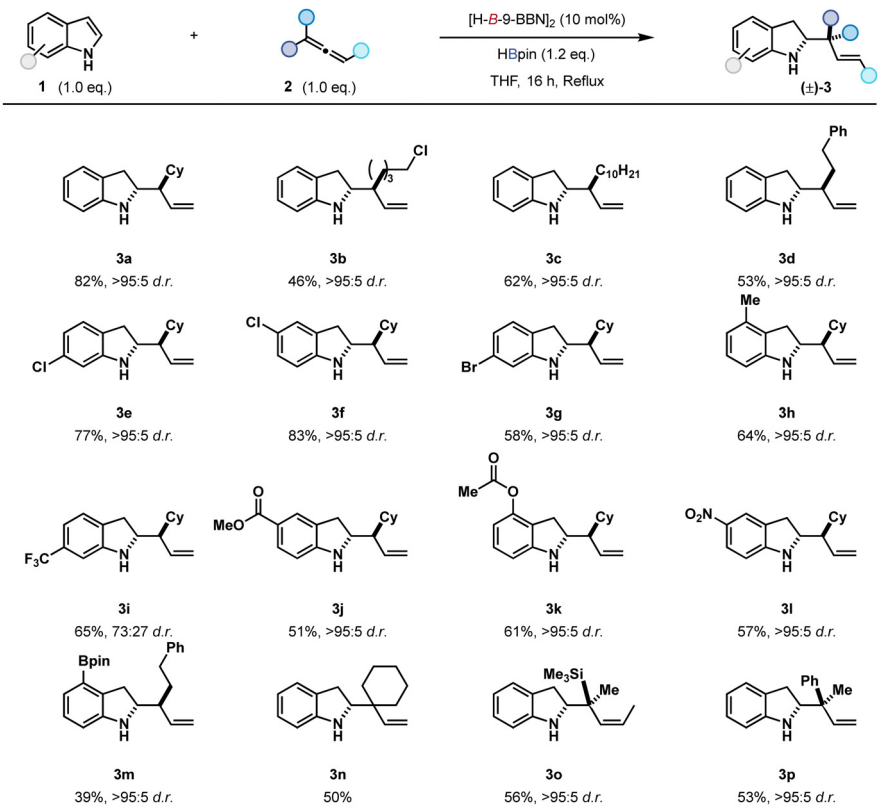
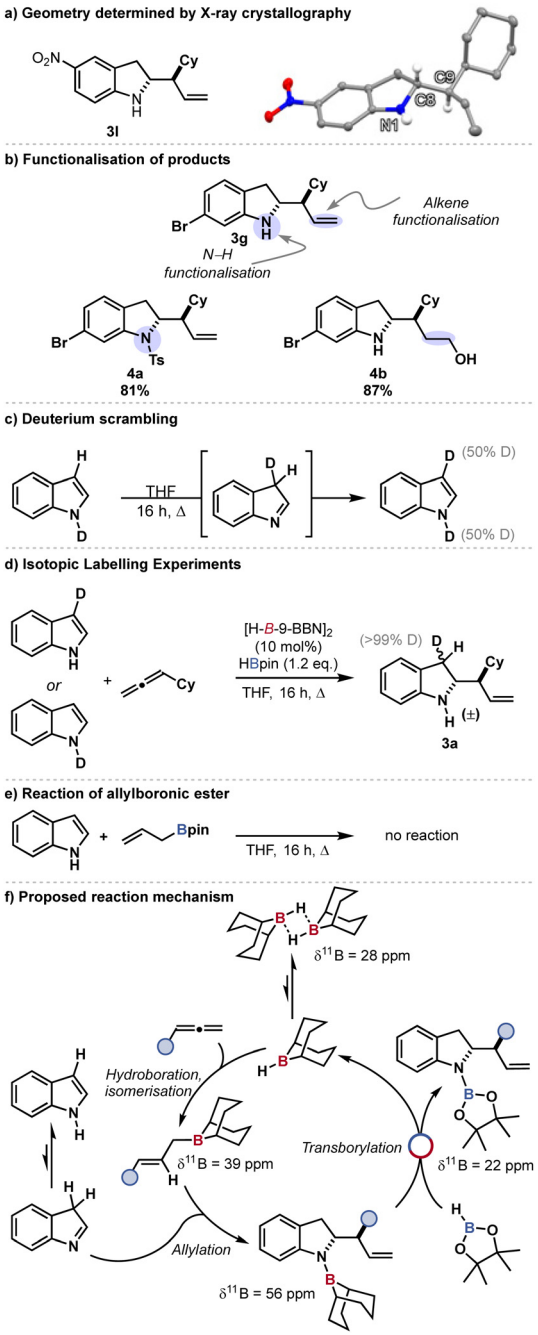


Fig. 1 Reaction conditions: Indole (0.5 mmol), allene (0.5 mmol), [H-*B*-9-BBN]$_2$ (10 mol%), HBpin (0.6 mmol), THF (1 mL), reflux, 16 h; reaction cooled to r.t. and quenched with SiO_2. d.r. measured by ^{1}H NMR spectroscopy of crude reaction mixture.



Scheme 2 (a) Crystal structure of allyl indoline **3l**. Grey = carbon, blue = nitrogen, white = hydrogen. All other H atoms omitted for clarity. (b) Derivatisation of allylindoline **3g**. **4a** synthesised by reaction of the indoline **3g** with tosylchloride at room temperature in CH_2Cl_2/pyridine. **4b** synthesised by hydroboration/oxidation of **3g** with H-*B*-9-BBN then hydrogen peroxide and sodium hydroxide. (c) Deuterium scrambling under reaction conditions in the absence of catalyst and allene (d) isotopic labelling experiments. (e) Reaction of allylboronic ester (f) proposed catalytic cycle.[21]

conditions **3j** (51% yield, >95 : 5 d.r.) **3k** (61% yield, >95 : 5 d.r.), in contrast to stoichiometric studies which gave only trace yield for these substrates.[12e] An indole bearing a nitro group underwent chemoselective allylation giving good yield and excellent diastereoselectivity **3l** (56%, >95 : 5 d.r.), again showing reactivity beyond stoichiometric allylations where this substrate resulted in only trace product.[12e] X-ray crystallography of this indoline product allowed assignment as the *anti* diastereomer (Scheme 2a). Bpin-bearing indole was reacted to give the allyl indoline in good yield and diastereoselectivtiy **3m** (39% yield, >95 : 5 d.r.) with no observed protodeboronation or boron exchange of the aryl Bpin. Vinylidenecyclohexane **3n** (55% yield) was successfully reacted with indole to give the product in good yield. Trisubstituted allene gave indoline **3o** (56% yield, >95 : 5 d.r.) in good yield and diastereoselectivity. 1-Methyl-1-phenylallene was also reacted with indole to provide a further example of allylation **3p** (53% yield, >95 : 5 d.r.) and the generation of a quaternary stereocenter.

The synthetic utility of the indoline products was demonstrated through onward reaction of bromoindoline **3g**;. *N*-tosylation[19] **4a** proceeded smoothly as did chemoselective alkene hydroboration–oxidation[20] **4b** (Scheme 2b).

Indoles have been proposed to react through an aldimine intermediate for C2 C–C bond forming reactions where the indole acts as an electrophile.[12a] To investigate if such an intermediate was involved in this catalysis, *N*-D-indole-d_1 was subject to catalytic conditions (reflux, THF, 16 h) in the absence of catalyst and allene. The 3-D-indole-d_1 was observed indicating that indole tautomerisation was possible under reaction conditions. Catalytic reaction of *N*-D-indole-d_1 or 3-D-indole-d_1 similarly resulted in the same deuteroproduct 3-D-allylic indoline **3a**-d_1. Reaction of allyl pinacol bornic ester (allyl-Bpin) with indole under reaction conditions gave no observed indoline product, indicating the reaction proceeds through an allyllic-*B*-9-BBN intermediate and that transborylation (boron-boron exchange) occurs exclusively at nitrogen (N–B/B–H exchange).[16a–d] A catalytic cycle was thus proposed whereby: 1. The dialkylborane catalyst reacts with the allene to give an allylic borane which isomerises to the (*E*)-allylborane; 2. The allylic borane reacts with the imine tautomer of the indole at the C2 position to give an *N*-*B*-9-BBN-2-allylic indoline.[12a] 3. B–N/B–H transborylation of the *N*-*B*-9-BBN-allylic indoline with HBpin regenerates the catalyst (H-*B*-9-BBN) and gives a *N*-boronic ester, *N*-Bpin-2-allylic indoline.

In summary a catalytic protocol for the reductive allylation of indoles has been developed. The reaction was successfully applied to a broad substrate scope of indoles and allenes, and, significantly, greatly expanded on the reactivity and functional group tolerance of the (previously reported) stoichiometric reactions. The reaction proceeded in excellent diastereoselectivity to give allylic indoline products which could be derivatised through synthetic handles thus allowing onward reactivity. Mechanistic studies indicated that the catalysis proceeds through a key indole-imine tautomerisation and B–N/B–H transborylation for catalytic turnover.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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