ChemComm

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/d1cc01512e

Received 19th March 2021,
Accepted 20th April 2021

DOI: 10.1039/d1cc01512e

rsc.li/chemcomm

A one-pot "back-to-front" approach for the synthesis of benzene ring substituted indoles using allylboronic acids†

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Synthesis of only benzene ring functionalized indoles and poly-substituted carbazoles is reported *via* a one-pot triple cascade benzannulation protocol. Usage of differently substituted and readily accessible allylboronic acids as a 3-carbon annulating partner enables diverse aliphatic and aromatic substitution patterns, which is still a daunting task. This scalable synthetic protocol tolerates broad scope, thus enabling further downstream modifications. As an application, carbazole based natural products glycozoline and glycozolinol were synthesized.

The chemistry of π-excessive heterocycle indoles is extensive due to their wide-spread presence in natural products, alkaloids, amino acids, neurotransmitters, plant hormones such as serotonin and melatonin, bacterial metabolites, agro-chemicals and various FDA approved medicines (Fig. 1).[1] Recent studies have shown that the functionalization at the benzene ring of active pharmaceutical ingredients (APIs) leads to better pharmacological properties and is closely responsible for their druglikeness, shape, and structural complexity.[2] However, the general trends show predominance of a certain substitution pattern in these with a particular set of reactions being used exhaustively. This inaccessibility to other sites is mostly due to the lack of a well-defined method or often needs extra synthetic maneuvers. Functionalization at the C2/C3-position of an indole nucleus is quite straightforward due to the embedded nucleophilic character, however defining a suitable substitution pattern at the benzene ring is found to be quite challenging and cumbersome while leaving the C2 and C3-positions un-substituted (Fig. 1).[3] Substitutions at the C4, C5, and C7 positions are generally installed by transition metal catalyzed C–H bond functionalization, Fischer indole synthesis, Bartoli indole synthesis, *etc.* (Fig. 1). They are often plagued by prefunctionalized starting materials, extra installation and removal steps, regiochemical issues, low functional group tolerance, strong acidic conditions, and diminished yields.[4] In contrast, functionalization at the C6-position is scarcely reported as it is remotely located from the nearby directing groups, and has low intrinsic reactivity towards electrophiles.[5] Apart from this, in general, installation of multiple linear as well as branched aliphatic substitutions of choice on the benzene ring of indole without regiochemical ambiguity while still keeping C2 and C3-positions free is still arduous since most of the methods are known to react with "activated electrophiles". In 2015, Baran *et al.* developed a ligand controlled C6 borylation of a tryptophan derivative under Ir-catalysis along with its C5-regioisomer (Scheme 1a).[5e] Recently, Shi *et al.* reported a copper catalyzed C6 functionalization under Cu(II)-catalysis, applicable to arylation only (Scheme 1b).[5f] A much less explored benzannulation on the pyrrole to forge a benzene ring represents a complementary method due to no substrate pre-functionalization and no regiochemical ambiguity. It can be sub-categorized such as transition metal catalyzed cyclization,[6] [4+2] cycloaddition,[7] 6π-electrocyclization,[8] and Brønsted and Lewis acid catalyzed transformations.[9] Although development in this area has gained substantial traction in recent years, development of more general

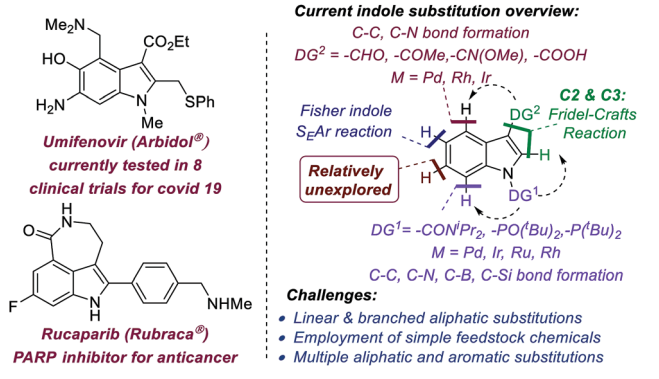

Fig. 1 FDA approved drugs containing an indole nucleus and current indole ring substitution overview.

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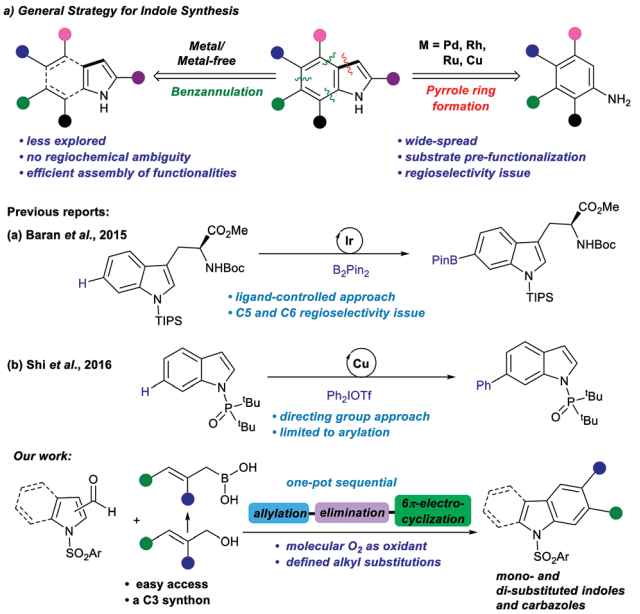
† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1cc01512e



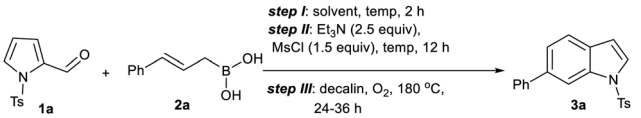
Scheme 1 Literature reports and our work.

and sustainable methods from cheaper feedstock chemicals using step-economic pathways is still elusive. In this direction, metal catalyst free organic synthesis has evolved as contemporary pathway due to its various advantages.[10] Recently, allylboronic acids have emerged as a powerful allylating reagent due to their easy access from the corresponding allyl alcohol, geometrical stability, and high reactvity.[11] In line with our ongoing research towards functionalization of indole and pyrrole,[12] we herein report a one-pot triple cascade protocol for the synthesis of functionalized indoles and carbazoles by employing allyl alcohol based allylboronic acids as a 3-carbon annulating partner.

At the outset of the optimization, we chose *N*-tosyl-pyrrole-2-carboxaldehyde **1a** and cinnamyl boronic acid **2a** as a coupling partner (Table 1). In $CHCl_3$, the reaction provided 45% isolated yield of product **3a** using decalin as a solvent for the final electrocyclization and O_2 as a terminal oxidant (entry 1). Changing the solvent to other protic and aprotic ones shows that CH_2Cl_2 is the best one providing **3a** in 76% yield (entries 2–7). Changing the terminal oxidant to DDQ provided comparable yields (entry 8), so we have chosen O_2 for its shear abundance and environment friendly nature. Changing the organic base to DIPEA or DABCO for the elimination step diminished the yields (55–62%, entries 9 and 10). Screening of the temperature showed that increasing the temperature to 80 °C by different combinations for the first two steps is detrimental on the outcome (65–72% yields, entries 11–13). To check the compatibility of the other allylating-agents, though, a zinc mediated allylation using cinnamyl bromide was not fruitful as the reaction did not proceed further after the first step (entry 14), cinnamyl-BPin provided 52% of **3a** by employing 10 mol% of diphenyl phosphate as a catalyst (entry 15).

Having the optimized conditions in hand, we set out to investigate the generality of the reaction first by synthesizing several benzene ring substituted indoles employing

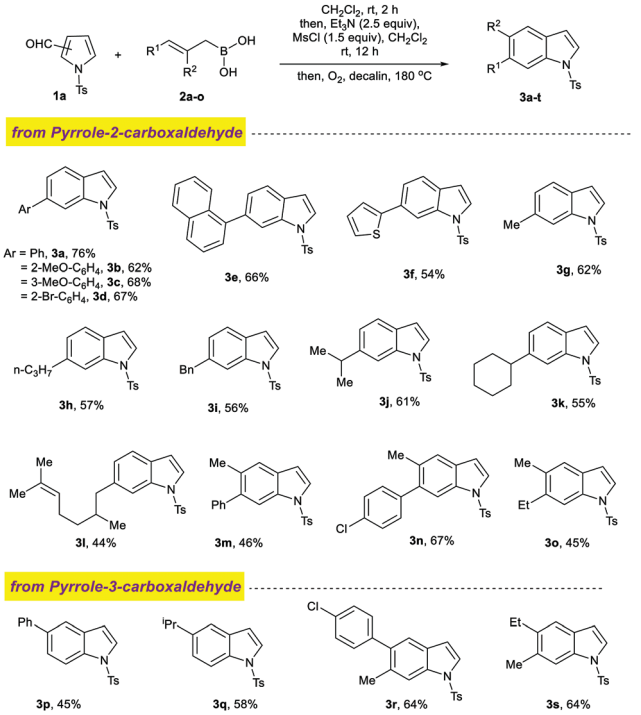
Table 1 Optimization of the reaction conditions[a]



Entry	Solvent	Temp [°C] (step I/II)	Yield of **3a**[b] (%)
1	$CHCl_3$	r.t./r.t.	45
2	THF	r.t./r.t.	54
3	DCE	r.t./r.t.	41
4	Toluene	r.t./r.t.	35
5	EtOAc	r.t./r.t.	55
6	MeCN	r.t./r.t.	46
7	**CH_2Cl_2**	r.t./r.t.	**76**
8	CH_2Cl_2	r.t./r.t.	75[c]
9	CH_2Cl_2	r.t./r.t.	62[d]
10	CH_2Cl_2	r.t./r.t.	55[e]
11	CH_2Cl_2	80/r.t.	70
12	CH_2Cl_2	r.t./80	72
13	CH_2Cl_2	80/80	65
14	CH_2Cl_2	r.t./r.t.	—[f]
15	CH_2Cl_2	r.t./r.t.	52[g]

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), solvent (2.0 mL), r.t., Ar; Et_3N (0.5 mmol), MsCl (0.3 mmol), r.t., Ar; decalin (2.0 mL). [b] Isolated yield. [c] Step III was carried out in the presence of DDQ instead of O_2. [d] DIPEA was used as a base. [e] DABCO was used as a base. [f] Cinnamyl zinc (0.3 mmol) was used as an allylating agent. [g] Cinnamyl-BPin (0.24 mmol) was used as an allylating agent.

pyrrole-2-carboxaldehydes and a wide range of allylboronic acids (Scheme 2). Incorporating an electron donating methoxy group at the C2- and C3-positions of the benzene ring shows mild variation in the yields and the products **3b–3c** were



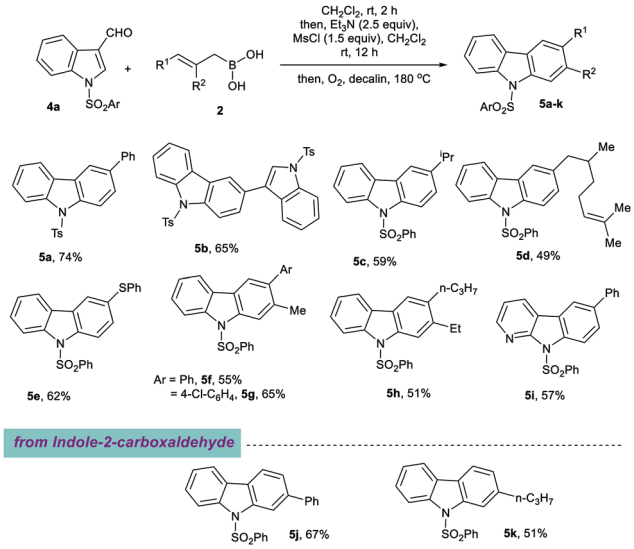
Scheme 2 Scope of indoles. Reaction conditions: step I: **1a** (0.2 mmol), **2** (0.3 mmol), CH_2Cl_2 (2 mL), r.t.; step II: Et_3N (0.5 mmol), MsCl (0.3 mmol), r.t.; step III: decalin (2.0 mL), 180 °C; isolated yield.

isolated in 62–68% yields. Gratifyingly, bromine substitution at the C2-position of the benzene ring, which can act as a template for further synthetic manipulations, was well tolerated under the optimized conditions providing the corresponding C6-substituted indole **3d** in 67% yield. Similarly, naphthyl substituted indole **3e** was also synthesized in 66% yield. The thiophene moiety is a key building block and precursor to various functional groups. To check whether such heteroaromatics can be incorporated or not, (*E*)-(3-(thiophen-2-yl)allyl)boronic acid **2f** was used as an allylating partner and to our joy, indole **3f** was isolated in 54% yield. Incorporation of linear as well as branched alkyl chains onto the benzene nucleus of indole is extremely challenging. To check whether this newly developed method can solve this long-standing issue, we screened several γ-alkyl substituted allylboronic acids. Simple linear aliphatic chains such as methyl, propyl, and benzyl groups were readily introduced using this sequential protocol, providing **3g–3i** in 56–62% yield. Similarly, the reaction allowed us to incorporate sterically encumbered branched aliphatic groups such as isopropyl and cyclohexyl moieties also at the C6 position, providing **3j–3k** in 55–61% yields. The synthetically challenging citronellal moiety was also introduced with no alkene isomerization despite the high reaction temperature, thus providing the corresponding indole **3l** in 44% yield. Next several aromatic as well as aliphatic groups containing β,γ-disubstituted boronic acids **2m–2o** were screened for their compatibility and pleasingly di-substituted indoles **3m–3o** were isolated in 45–67% yields. This is in particular remarkable since simultaneously C5 and C6 functionalized indoles can be synthesized in a one-pot operation.

To scrutinize whether the complimentary regiodivergence can be achieved using the same allyl boronic acids by only changing the allyl acceptor, we next choose *N*-Ts-pyrrole-3-carboxaldehyde, and screened several aromatic, aliphatic, and di-substituted boronic acids. Pleasingly this one-pot sequential protocol also provided indoles **3p–3s** in 45–64% yields.

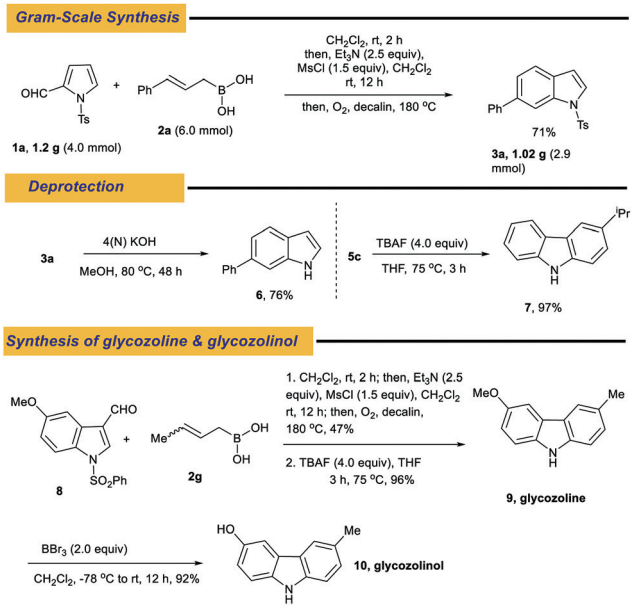
After investigating the scope of indoles, we next switched our attention toward extrapolating this approach to the synthesis of substituted carbazoles (Scheme 3). Screening of aromatic and heteroaromatic substituted boronic acids shows that they can be easily incorporated at the C3-position of carbazole, thus providing carbazoles **5a–5b** in 65–74% yields. To our joy, branched as well as linear alkyl chains were also installed under the reaction conditions furnishing **5c–5d** in 49–59% yields. To install a –SPh group directly at the C3-position of carbazole, –SPh substituted boronic acid **2q** was reacted under the optimized conditions and the corresponding carbazole **5e** was isolated in 62% yield. Next, screening of di-substituted boronic acids enables 2,3-di-alkyl and aryl substituted carbazoles **5f–5h** in 51–65% yields. Lastly, α-carboline **5i** was synthesized from the corresponding 7-azaindole derivative in 57% yield. Upon implementing regio-isomeric indole 2-carboxaldehyde, C2-aryl and -alkyl substituted carbazoles **5j–5k** were isolated in 51–67% yields which are extremely difficult to prepare *via* traditional cross-coupling approaches as the corresponding carbazole precursors are difficult synthetic tasks.

To check the scalability of the developed protocol, a gram scale reaction was performed on **1a** (4.0 mmol, 1.2 g) using **2a**

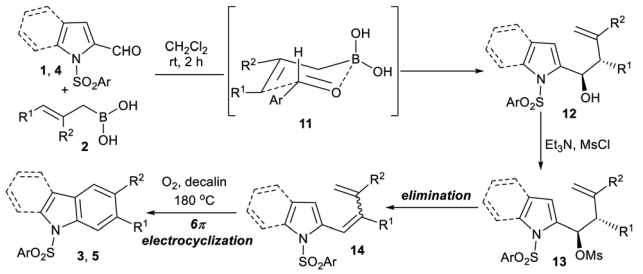


Scheme 3 Scope of carbazoles. Reaction conditions: step I: **4a** (0.2 mmol), **2** (0.3 mmol), CH_2Cl_2 (2 mL), r.t.; step II: Et_3N (0.5 mmol), MsCl (0.3 mmol), r.t.; step III: decalin (2.0 mL), 180 °C; isolated yield.

and the product **3a** was isolated in 1.02 g (71% yield, Scheme 4). To check further applicability of the synthesized indoles and carbazoles, **3a** was first deprotected under methanolic KOH conditions to give **6** in 76% yield. In this line, **5c** was also deprotected using TBAF at 75 °C to furnish **7** in 97% yield. As a synthetic application, two carbazole based natural products glycozoline and glycozolinol were targeted. Treatment of N-protected indole **8** with crotyl boronic acid **2g** under standard conditions, and finally deprotection resulted in glycozoline **9** in 45% overall yield over two steps. Treatment of glycozoline with BBr_3 resulted in glycozolinol **10** in 92% yield.



Scheme 4 Scalability and synthetic applications.



Scheme 5 Plausible mechanism.

Based on the obtained results, we have postulated a plausible mechanism (Scheme 5). At first, boronic acid reacts *via* a six-membered chair-like transition state **11** to provide homoallylic alcohol **12**. Next, mesylation of the benzylic alcohol followed by Et_3N mediated E2 elimination furnished conjugated alkene **14**. Next, 6π-electrocyclization under thermal conditions and subsequent aromatization accomplished indoles and carbazoles **3–5** in one-pot.

In conclusion, a one-pot sequential triple cascade protocol was developed for the synthesis of functionalized indoles and carbazoles based on the benzannulation approach. Allyl alcohol based allylboronic acids were utilized as a 3-carbon annulating partner. The easy access and high reactivity of the allylboronic acid facilitates a wide range of substitution patterns, especially the aliphatic functionality. The reaction was amenable to gram scale and two carbazole based natural products were synthesized. We believe that this approach provides a solution to access this structurally diverse set of N-heterocycles.

M. S. M. gratefully acknowledges SERB, Department of Science and Technology, India (Sanction No. CRG/2018/000317) for funding. G. K. and S. S. thank CSIR, India for fellowships.

Conflicts of interest

There are no conflicts to declare.

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