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Base-promoted direct synthesis of functionalized *N*-arylindoles *via* the cascade reactions of allenic ketones with indoles†

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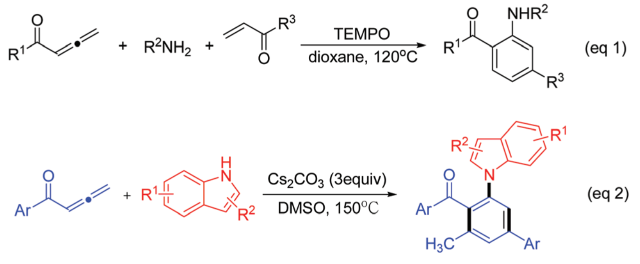
A convenient Cs_2CO_3-promoted cascade benzannulation reaction of allenic ketones with indoles was achieved for the synthesis of functionalized *N*-arylindole derivatives under transition-metal-free conditions. A series of readily available starting materials can undergo the process successfully. It represents a practical method for the construction of *N*-arylindole scaffolds with high atom economy.

Functionalized benzenes, especially carbonyl- or nitrogen-containing heterocyclic substituted benzenes, are attractive molecules as they are not only privileged structural motifs in natural products, pharmaceuticals, and functional organic materials,[1] but also the most widely applied precursors in organic synthesis.[2] Consequently, practical and convenient methods for the construction of polysubstituted benzene derivatives are of utmost importance and have been greatly investigated.[3] Traditionally, polysubstituted benzenes are prepared by the stepwise introduction of functional groups into simple aromatic starting materials through various functionalization reactions.[4] Over the past decades, metal-free or transition-metal-catalyzed tandem cyclization reactions have become particularly attractive because they enable facile construction of substituted benzenes from easily obtainable acyclic units with high atom economy.[5]

Recently, allenes have attracted great attention from organic chemists due to their rich reactivity and ready availability.[6] Among various allene derivatives, 1,2-allenic ketones are good electrophiles for tandem reactions with nucleophiles to prepare cyclic skeletons.[7] Although many efforts have been devoted to converting allenic ketones into cyclic compounds, reports on the fabrication of functionalized benzenes through the domino reactions of 1,2-allenic ketones are quite limited. For instance, Fan and co-workers reported a cascade reaction of 1,2-allenic ketones with cyanoacetate for the construction of highly substituted benzenes in 2011.[8] Subsequently, the same group also developed a convenient method for the selective synthesis of functionalized phenols through cascade reactions of 1,2-allenic ketones with β-diketones.[9] However, compared to the above-mentioned carbon nucleophiles in the benzannulation reactions of 1,2-allenic ketones, the use of nitrogen nucleophiles has rarely been reported. More recently, a one-pot three-component reaction of allenic ketones with amines and enones for the selective syntheses of 2-aminobenzophenones has been reported (Scheme 1, eqn (1)).[10]

In continuation of our interest in indole and allene chemistry,[11] herein we report a convenient method for the syntheses of both carbonyl and indole substituted benzenes from easily available allenic ketones and indoles promoted by Cs_2CO_3 in a highly atom economical manner (Scheme 1, eqn (2)).

At the outset of this investigation, 1-phenylbuta-2,3-dien-1-one **1a** and indole **2a** were chosen as the model substrates for this transformation to optimize the reaction conditions (Table 1). The effect of solvents and bases was initially evaluated (entries 1–11). To our delight, the benzannulation product **3a** was successfully obtained in DMSO with 3.0 equiv. of Cs_2CO_3 at 90 °C for 4 hours, albeit in a slightly low yield of 38% (entry 6). The good solubility of Cs_2CO_3 in dipolar aprotic solvents may be the main reason why the current reaction can



Scheme 1 Benzannulation of 1,2-allenic ketones with nitrogen nucleophiles.

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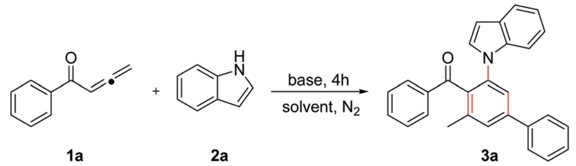
Table 1 Optimization of reaction conditions[a]



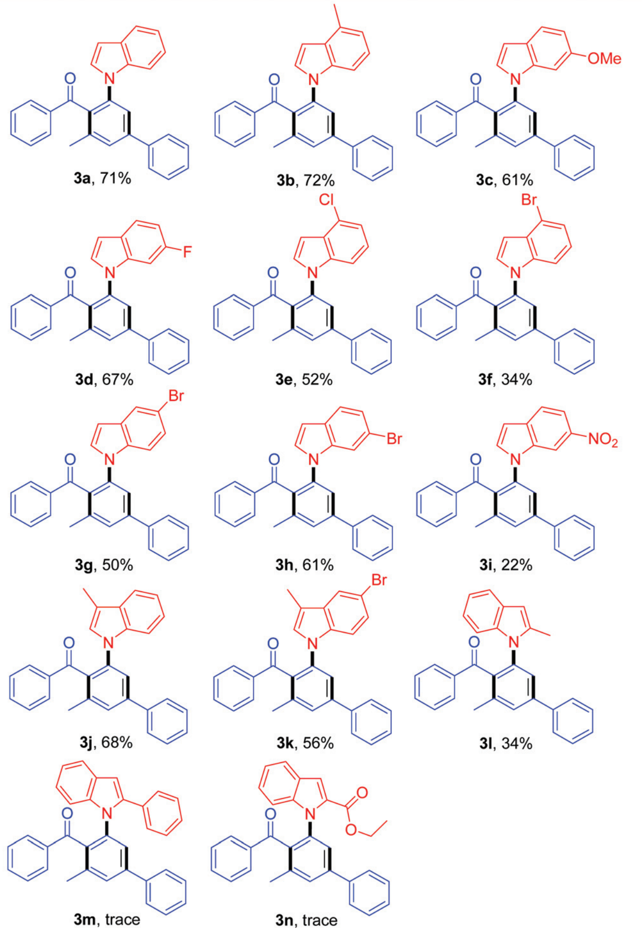
1a + **2a** → **3a**

Entry	Solvent	Base (equiv.)	T (°C)	Yield[b] (%)
1	Toluene	Cs_2CO_3 (3)	90	NR
2	THF	Cs_2CO_3 (3)	90	NR
3	MeCN	Cs_2CO_3 (3)	90	NR
4	DMF	Cs_2CO_3 (3)	90	NR
5	MeOH	Cs_2CO_3 (3)	90	NR
6	DMSO	Cs_2CO_3 (3)	90	38
7	H_2O	Cs_2CO_3 (3)	90	NR
8	DMSO	K_2CO_3 (3)	90	NR
9	DMSO	Et_3N (3)	90	NR
10	DMSO	*tert*-BuOK (3)	90	NR
11	DMSO	NaOH (3)	90	NR
12	DMSO	CsOAc (3)	90	NR
13	DMSO	CsF (3)	90	Trace
14	DMSO	CsCl (3)	90	Trace
15[c]	DMSO	Cs_2CO_3 (3)	150	56
16[d]	DMSO	Cs_2CO_3 (3)	150	41
17[e]	DMSO	Cs_2CO_3 (3)	150	71
18[e]	DMSO	Cs_2CO_3 (2)	150	52
19[e]	DMSO	Cs_2CO_3 (4)	150	65
20[e]	DMSO	Cs_2CO_3 (5)	150	63
21[e]	DMSO	Cs_2CO_3 (0.5)	150	27
22[e]	DMSO	HOTf (2)	150	0

[a] Reaction conditions: **1a** (0.22 mmol), **2a** (0.1 mmol) and base (3 equiv.) in 1.0 mL of solvent at the indicated temperature. [b] Yield of the isolated product after chromatography. [c] **1a** : **2a** = 3 : 1. [d] **1a** : **2a** = 2 : 1. [e] **1a** : **2a** = 4 : 1.

Table 2 Scope of substituted indole derivatives[a]

1a + **2a-n** → **3a-n**



3a, 71% **3b**, 72% **3c**, 61%

3d, 67% **3e**, 52% **3f**, 34%

3g, 50% **3h**, 61% **3i**, 22%

3j, 68% **3k**, 56% **3l**, 34%

3m, trace **3n**, trace

[a] Reaction conditions: **1a** (1.2 mmol), **2a–n** (0.3 mmol) and Cs_2CO_3 (3 equiv.) in 3.0 mL of DMSO at 150 °C and isolated yields were reported.

proceed smoothly.[12] Considering that only the target product is produced when cesium carbonate was used, several other cesium salts that are often employed in catalytic transformations were screened for this reaction. It was found that cesium salts such as CsOAc, CsF, or CsCl showed no conversions (entries 12–14). Next, the ratio of substrates as well as the reaction temperature was examined carefully. The results showed that the temperature of 150 °C and the optimum loading of **1a** of 4.0 equiv. gave the best yield (entry 17). We also examined the effects of different amounts of bases on the reaction and found that the yield of the reaction reduced upon increasing or decreasing the amount of Cs_2CO_3 (entries 18–20). When 0.5 equiv. of Cs_2CO_3 was employed, the yield of the product was only 27% (entry 21). For comparison, an acidic promoter (HOTf) instead of Cs_2CO_3 was employed in this reaction, and it was found that no desired product was formed under these conditions (entry 22). Finally, the conditions in entry 17 (Table 1) were identified as the optimal conditions.

With the optimized reaction conditions in hand, the substrate scope and limitation of the current benzannulation reaction using various indoles as substrates were examined. As depicted in Table 2, it was found that a number of substituted indoles successfully reacted to afford the desired products **3a**–**3l** in moderate to good yields. Specifically, methyl and methoxyl were well tolerated at the 4- and 6-position of the indole, affording the corresponding products **3b** and **3c** in 72% and 61% yields, respectively. In addition, the reaction was compatible with functional groups such as halides at the 4-, 5- or 6-position of indoles. Notably, with C6 halogen substituted indoles as the substrates, the corresponding products **3d** and **3h** were obtained in good yields. To our delight, a strong electron-withdrawing group, such as nitro, present at the 6-position of indole, could also be used in this reaction and afforded the corresponding product **3i**, albeit in 22% yield. Interestingly, C3 substituted indoles were also suitable substrates for this transformation to obtain the desired products **3j** and **3k** in good yields. However, it was found that the substrate bearing a substituent on the C2 position of indole, such as a methyl group, only gave a moderate yield of the product (**3l**), whereas the indole bearing a phenyl group failed to afford any product (**3m**). These results can be attributed to the steric effect of the indoles. Unfortunately, the substrate containing an ester group on the 2-position of the indole ring did not yield any desired product (**3n**). Finally, the structure of **3g** was unambiguously confirmed by X-ray crystallographic analysis (Fig. 1).[13]

Subsequently, we investigated the suitability of the allenic ketones in this domino benzannulation reaction in the presence of indole **2a** under optimal conditions (Table 3). Substrates bearing various electron-donating substituents on the phenyl ring proved to be reactive, affording moderate to good yields of the desired products **3o–3q**. However, substrates with a *para*-chloro substituted aromatic ring of R were inert for this transformation and only a trace amount of the product **3r** was detected. To our satisfaction, by replacing the phenyl group of R with the 2-naphthyl substituent, the cascade reaction was smoothly carried out to obtain the corresponding desired product **3s** in 61% yield. Moreover, heteroaryl allenic ketones were also found to be suitable reaction partners affording the desired products **3t** and **3u** in 68% and 64% yields. In the case when there is a strong electron-withdrawing group, such as *p*-CN, only a trace amount of the *N*-arylindole product was detected (**3v**). However, when an aliphatic substituted allenic ketone was used as the substrate, no desired product was detected (**3w**). It should be noted that the use of allenic ketones bearing substituents on the alpha-allene carbon or at the terminal position of the allenic moiety did not offer the products (**1k** and **1l**).

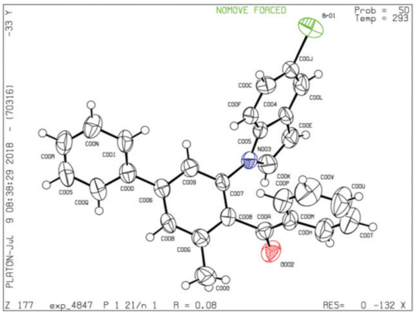
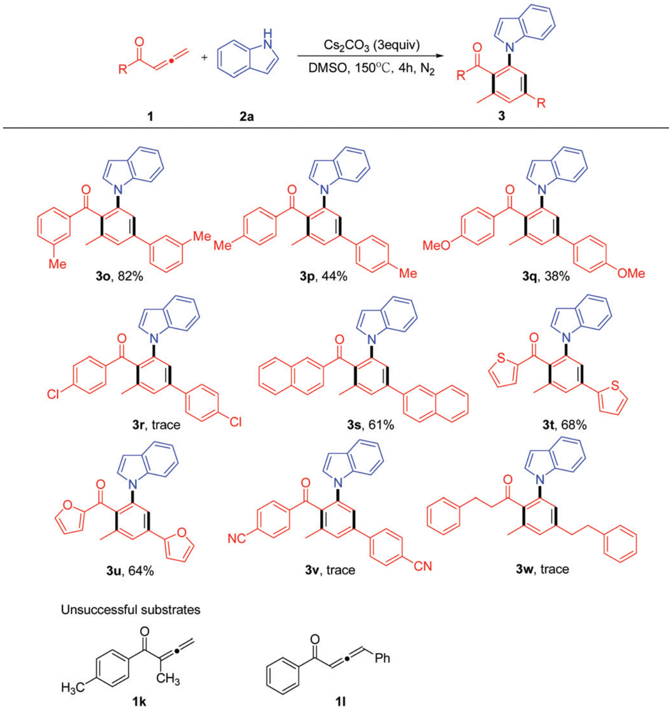


Fig. 1 X-Ray structure of **3g**.

Table 3 Scope of allenic ketone derivatives[a]

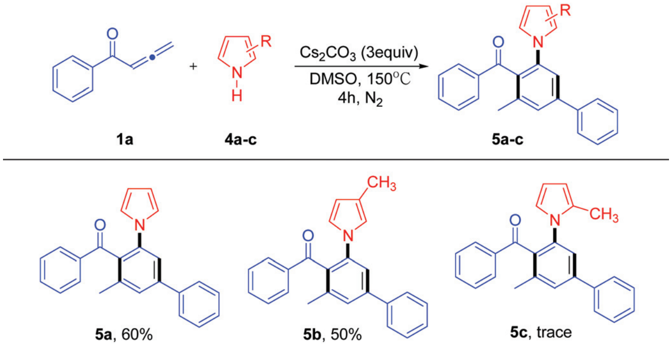


[a] Reaction conditions: **1b–l** (1.2 mmol), **2a** (0.3 mmol) and Cs$_2$CO$_3$ (3 equiv.) in 3.0 mL of DMSO at 150 °C and isolated yields were reported.

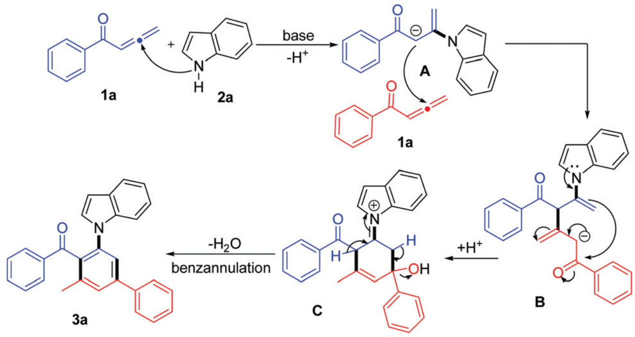
To further highlight the versatility of this methodology, we then investigated the reactivity of other nitrogen containing aromatic heterocycle sources by exchanging indole with pyrroles (Table 4). To our delight, the corresponding pyrrole substituted functionalized benzenes **5a** and **5b** were obtained in 60% and 50% isolated yields respectively under the best reaction conditions. However, increasing the steric hindrance further by using 2-methyl-1*H*-pyrrole resulted in a trace amount of the product **5c** being detected, probably due to the steric hindrance effect.

On the basis of the above results and related literature,[6i] a plausible pathway to account for the formation of **3a** by this Cs$_2$CO$_3$-promoted benzannulation reaction is proposed in Scheme 2. First, a Michael addition of indole **2a** to allenic ketone **1a** occurred with the aid of a base to afford the anion intermediate **A**, which then underwent a second Michael addition onto another allenic ketone **1a** leading to the formation of the anion intermediate **B**. Subsequently, an intramolecular cyclization of intermediate **B** accompanied by the

Table 4 The reaction of 1-phenylbuta-2,3-dien-1-one **1a** with pyrroles[a]



[a] Reaction conditions: **1a** (1.2 mmol), **4** (0.3 mmol) and Cs$_2$CO$_3$ (3 equiv.) in 3.0 mL of DMSO at 150 °C and isolated yields were reported.



Scheme 2 Proposed mechanism of the reaction.

protonation process gave the imine intermediate **C**. Finally, the corresponding product **3a** is generated through the benzannulation process of intermediate **C**.

In conclusion, we have developed a cascade reaction, thus allowing the selective benzannulation of the allenic ketone with an indole derivative leading to functionalized *N*-arylindoles promoted by Cs_2CO_3. This method has the advantages of atom and step economy, transition-metal-free conditions, wide scope of substrates and simple and readily available starting materials. Thus, the methodology developed herein is expected to find wide applications in the field of organic synthesis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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13 CCDC 1876682 (**3g**)† contains the supplementary crystallographic data for this paper.