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Rhodium-catalyzed annulation of hydrazines with vinylene carbonate to synthesize unsubstituted 1-aminoindole derivatives†

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Herein, we describe rhodium-catalysed C–H bond activation for [3 + 2] annulation using hydrazide and vinylene carbonate, providing an efficient method for synthesising unsubstituted 1-aminoindole compounds. Characterised by high yields, mild reaction conditions, and no need for external oxidants, this transformation demonstrates excellent regioselectivity and a wide tolerance for various functional groups.

Indole scaffolds,[1] among the most important N-heterocycles, have a wide range of applications, from pharmaceuticals and agrochemicals to renewable energy.[2] Particularly, 1-aminoindoles[3] serve as core components of numerous bioactive molecules, such as commercial drugs like besipirdine[4b] and indapamide,[4c] as well as antidepressant and receptor modulators (Fig. 1). Traditional synthetic methods[5] for these moieties are often complex, involving most synthetic routes requiring multiple steps and electrophilic *N*-amination. The necessity for strong bases, less secure *N*-aminating reagents, and harsh reaction conditions have limited their synthetic utility and practicality. Consequently, developing more efficient and economically viable synthetic strategies for the 1-aminoindole moiety has attracted significant attention.

Over the past two decades, transition metal-catalysed C–H bond activation[6] has emerged as a valuable approach for constructing complex molecular scaffolds. Rh(III) complexes,[7] in particular, have been instrumental in catalysing annulation reactions.[8] However, only a few studies have been conducted on the synthesis of 1-aminoindole skeletons *via* directed C–H bond activation. Glorius *et al.*[8a] developed an Rh(III)-catalysed oxidative annulation method using aryl-substituted diazene carboxylates and alkenes, producing C2, C3-disubstituted 1-aminoindoles (Scheme 1a, eqn (1)). Liu *et al.*[8b] achieved the oxidative annulation of hydrazines with alkynes using 1,3-dinitrobenzene as an oxidant (Scheme 1a, eqn (2)). However, these methods require stoichiometric oxidants.

The coupling of arenes with carbene precursors[9] in a redox-neutral manner has introduced important alternatives to oxidative annulation reactions. Wang's group[10a] realized Rh(III)-catalyzed tandem annulation of arylhydrazines with diazo compounds as carbene precursors to yield 1-aminoindole products (Scheme 1b, eqn (3)). Zhu *et al.*[10b] successfully used this strategy to synthesise *N*-aminoindoles *via* *N*-Boc cleavage (Scheme 1b, eqn (3)). Cui's group[10c] he synthesis of 1-aminoindoles through a three-component cyclisation using *in situ*-formed hydrazones as guiding groups (Scheme 1b, eqn (3)). Owing to their relatively higher safety and stability, sulfoxonium ylides[11] have been demonstrated as carbene surrogates for diazo compounds. Xie[12a] and Zhang[12b] independently described a rhodium-catalyzed redox-neutral reaction involving arylhydrazines and sulfoxonium ylides to create C2-substituted 1-aminoindole derivatives (Scheme 1b, eqn (4)). Recently, Li and his colleagues[13] reported an Rh(III)-catalyzed C–H bond activation reaction of arylhydrazines using iodonium ylides as a carbene precursor (Scheme 1b, eqn (5)). Despite the considerable progress with respect to the synthesis of 1-aminoindole derivatives, the synthesis of C2, C3-unsubstituted 1-aminoindoles through directed C–H bond activation remains underexplored (Scheme 1c, eqn (6)).

Vinylene carbonate[14] is a stable and readily available substance that can be produced on an industrial scale. In 2019,

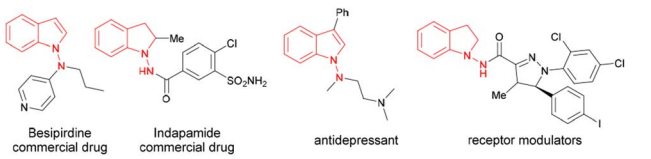

Fig. 1 Representative bioactive compounds containing 1-aminoindole skeletons.

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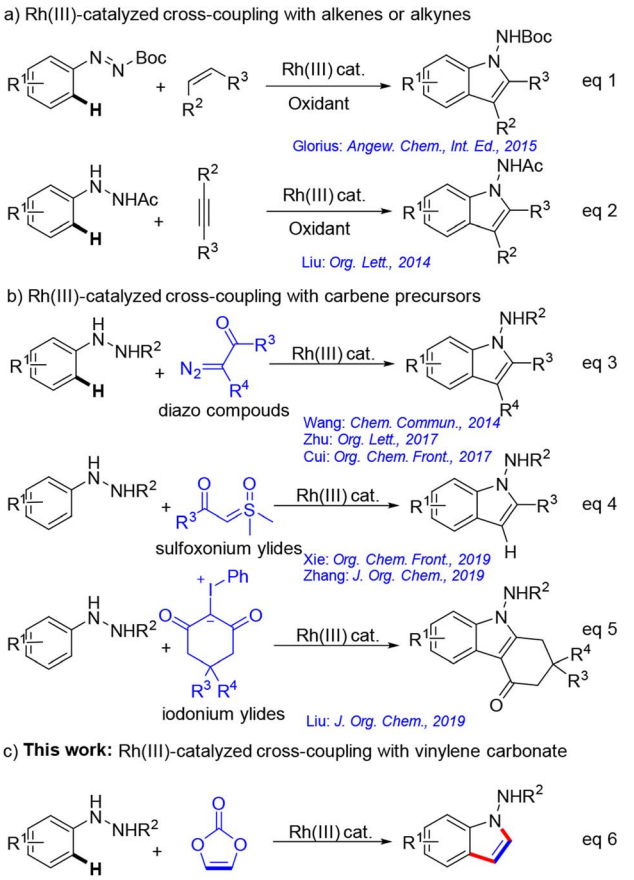
‡ Y. Chen and Z. Lu contributed to this work equally.

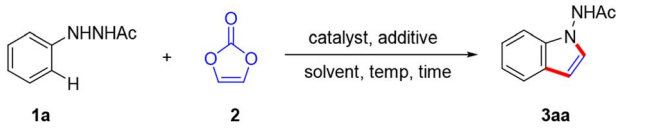


Scheme 1 Synthesis of 1-aminoindole compounds by C–H bond activation.

Miura's group[15] pioneered the use of vinylene carbonate as an acetylene surrogate strategy in C–H functionalization and cascade annulations. Building upon this concept, the facile synthesis of various heterocycles, such as isoquinolines, isocoumarins, quinazolines, quinoline quinolone, pyrazolidinones, cinnolines, and indoles using vinylene carbonate have been realized.[16] In line with our ongoing interest in heterocycle synthesis, we introduce a novel method for synthesising crucial C2, C3-unsubstituted 1-aminoindoles derivatives. This approach involves Rh(III)-catalyzed C–H bond activation and cascade annulation from arylhydrazines and vinylene carbonate (Scheme 1c).

To initiate our investigation of this reaction, we selected 1*N*′-phenylacetohydrazide (**1a**) and vinylene carbonate (**2a**) as the model substrates for the coupling reaction (Table 1). We were pleased to discover that the desired 1-aminoindole product **3aa** was obtained in 66% yield in the presence of a catalytic combination of $[Cp^*RhCl_2]_2$ and $Zn(OAc)_2$ in DMF (Table 1, entry 1). NMR spectroscopy and high-resolution mass spectrometry confirmed the structure of **3aa**, which was further validated *via* X-ray crystallographic analysis[17] (Fig. 2). A control experiment demonstrated the necessity of the Rh(III) catalyst; alternative catalysts such as $Cp^*Co(CO)I_2$, $[Cp^*IrCl_2]_2$ and $[p$-cymeneRuCl$_2]_2$ did not facilitate the reaction (Table 1, entries 3–5). The use of the cationic catalyst $[Cp^*Rh(MeCN)_3](SbF_6)_2$ resulted in a decreased yield (Table 1, entry 2). Various additives were screened, but it was disappointing that no reaction occurred when NaOAc or KOAc was used (Table 1, entries 7 and 8). A range of solvents was tested, including *t*-BuOH, MeCN, DME, DCE, dioxane, TAA, toluene and CH_3OH, with *t*-BuOH proving to be the optimal solvent, achieving a 94% yield of the target product **3aa** (Table 1; entry 9). When CH_3OH was used as the solvent, the reaction did not proceed (Table 1, entry 16). The reaction efficiency was negatively affected by both increments and decrements in reaction temperature (Table 1, entries 17 and 18). Altering the reaction duration to 12 or 20 h resulted in a reduced yield (Table 1, entries 19 and 20).

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Additive	Solvents	Yield[b] (%)
1	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$	DMF	66
2	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	$Zn(OAc)_2$	DMF	41
3	$Cp^*Co(CO)I_2$	$Zn(OAc)_2$	DMF	nd
4	$[Cp^*IrCl_2]_2$	$Zn(OAc)_2$	DMF	nd
5	$[p$-CymeneRuCl$_2]_2$	$Zn(OAc)_2$	DMF	nd
6	None	$Zn(OAc)_2$	DMF	nd
7	$[Cp^*RhCl_2]_2$	NaOAc	DMF	nd
8	$[Cp^*RhCl_2]_2$	KOAc	DMF	nd
9	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$	*t*-BuOH	94
10	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$	MeCN	91
11	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$	DME	86
12	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$	DCE	85
13	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$	Dioxane	80
14[c]	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$	TAA	76
15	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$	Toluene	70
16	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$	CH_3OH	nd
17[c]	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$	*t*-BuOH	66
18[d]	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$	*t*-BuOH	80
19[e]	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$	*t*-BuOH	90
20[f]	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$	*t*-BuOH	90

[a] **1a** (0.20 mmol), **2a** (0.40 mmol), catalyst (5 mol%), additive (20 mol%), solvent (2.0 mL), N_2, 80 °C, 16 h. [b] Isolated yield. [c] 60 °C. [d] 100 °C. [e] For 12 h. [f] For 20 h.

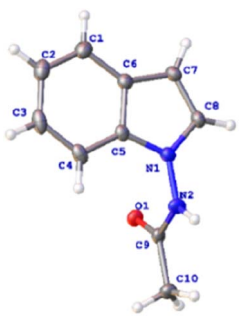
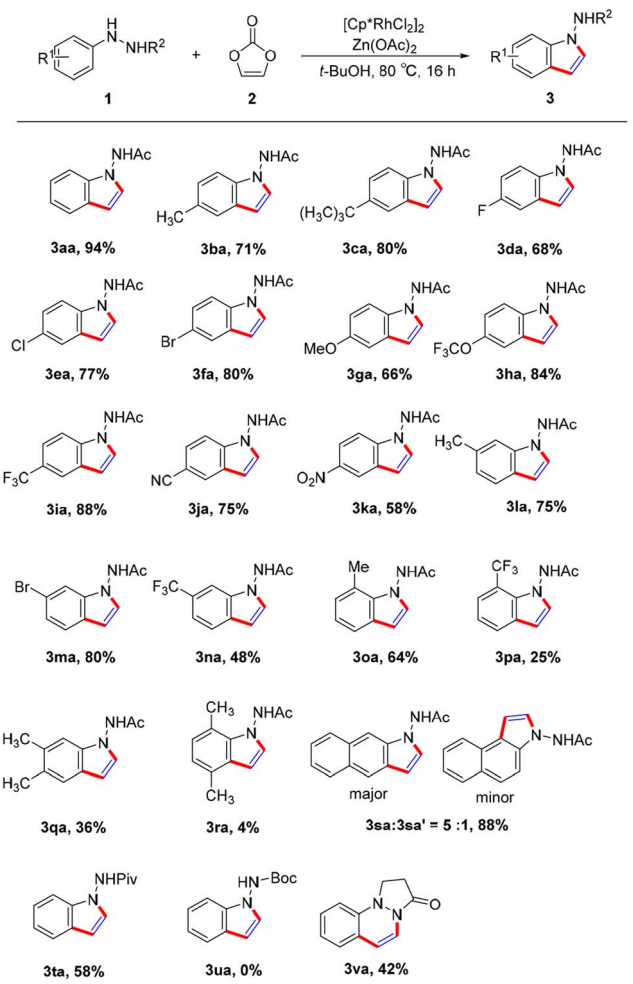


Fig. 2 Molecular structure of **3aa**.

With the optimized conditions established, we explored the substrate scope of 1-acetyl-2-phenylhydrazine (Scheme 2). The transformation exhibited a broad substrate scope, accommodating 2-acetyl-1-arylhydrazines with various substituents. 2-Acetyl-1-arylhydrazines, whether bearing electron-donating group (*e.g.*, Me, OMe, and OCF_3) or electron-withdrawing groups (*e.g.*, CF_3, CN, NO_2) at the para position, all reacted effectively with vinylene carbonate, yielding the corresponding products (**3ba–3ka**) in moderate to good yields. This functional group compatibility proves highly beneficial for synthesizing complex molecules. Furthermore, substrates with halogen substituents (*e.g.* F, Cl and Br) at different positions were well-tolerated, enabling further derivatisation through coupling reactions. This transformation demonstrated excellent regioselectivity, with coupling occurring at the less hindered position for *meta*-substituted substrates (**3la–3na**). The reaction seems to be sensitive to steric hindrance, as *ortho*-substituted phenylacetohydrazines (**1m–1o**) exhibited limited reactivity (**3oa–3ra**). When disubstituted derivatives were used in the reaction with vinylene carbonate, the product yield was reduced (**3qa**, **3ra**).



Scheme 2 Substrate scope for hydrazines.[a] [a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $Zn(OAc)_2$ (20 mol%), *t*-BuOH (2 mL), 80 °C, under N_2 for 16 h. Isolated yields after column chromatography.

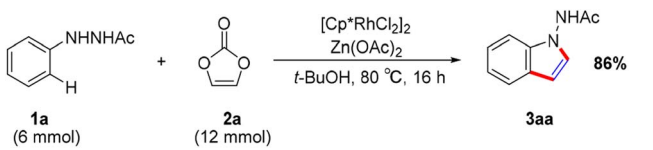
Moreover, when *N*′-(naphthalen-2-yl)acetohydrazide (**1s**) was used, the C–H bond at the 3-position, with less steric hindrance was preferred to be functionalized (**3sa : 3sa**′ = 5 : 1, 88%).

Our investigation also included hydrazines with different substitutions at the R^2 position. A pivaloyl (Piv) group led to the formation of 1-aminoindole derivatives (**3ta**) in 58% yield, while an *N*-Boc substituent failed to produce the desired product (**3ua**). Additionally, disubstituted hydrazine **1v** was also explored and the corresponding product (**3va**) could be isolated in 42% yield.

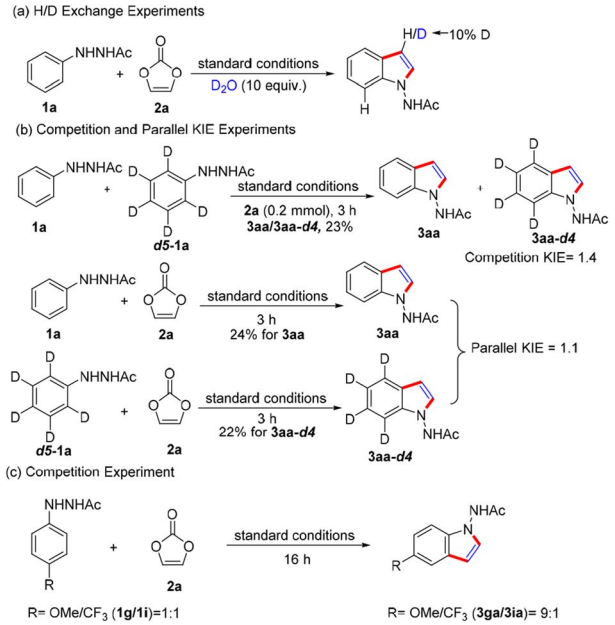
To demonstrate the synthesis utility of our catalytic system, we performed a scaled-up reaction with 6 mmol of hydrazine (**1a**), obtaining product **3aa** in 86% yield (Scheme 3).

A series of experiments was conducted to investigate the reaction mechanism (Scheme 4). Initially, an H/D exchange study was carried out under standard conditions in the presence of D_2O. Only 10% deuterium was incorporated at the C3 position of **3aa** but not at other positions (Scheme 4a). The results indicate a protonation process was possibly involved in the transformation. Furthermore, a kinetic isotope effect (KIE) experiment was investigated. An intermolecular competitive KIE experiment using equivalent substrates **1a** and **1a-d5** was implemented, revealing a KIE value of 1.4 (Scheme 4b). Moreover, a KIE value of 1.1 was detected based on parallel experiments (Scheme 4b). These results suggested that the C–H bond cleavage might not be involved in the rate-determining step of the overall reaction. Additionally, an intermolecular competition reaction between **1g** and **1i** was carried out in a one-pot fashion under the optimized reaction conditions, and the products were isolated in a 9 : 1 ratio (**3ga**/**3ia**), demonstrating higher reactivity for the electron-rich substrate (Scheme 4c).

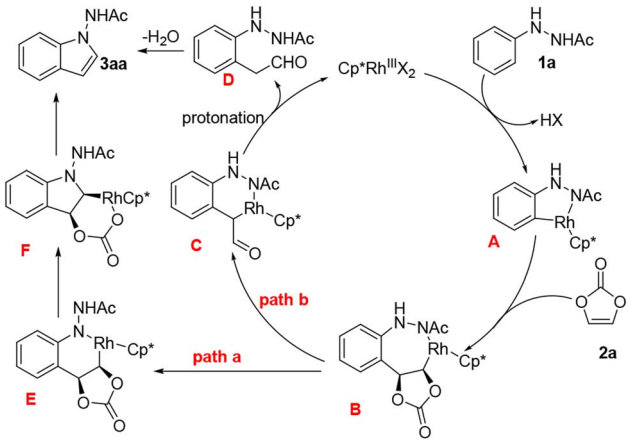
Based on the aforementioned experiments and previous reports,[18] we propose two possible catalytic cycle pathways (Scheme 5, path a and path b). The cycle begins with the activation of a C–H bond, catalysed by rhodium(III), leading to the formation of a five-membered rhodacycle intermediate **A**. Subsequently, intermediate **A** coordinates with vinylene carbonate and undergoes migratory insertion of vinylene carbonate into the Rh–C bond, resulting in the formation of a seven-membered metallacycle complex **B**. Rhodacycle **B** may further undergo intramolecular amide attack towards Rh, yielding the six-membered **E** (path a). This is followed by C–N reductive elimination, which is succeeded by the formation of a bond into the adjacent C–O bond, giving rise to intermediate **F**. Formal β-oxygen elimination is affected to liberate the desired product (**3aa**) along with the regenerated catalyst, and the extrusion of CO_2 (path a).



Scheme 3 Gram-scale synthesis.



Scheme 4 Mechanistic studies.



Scheme 5 Proposed mechanism.

An alternative possibility is that 1,2-Rh–C bond migration and decarboxylation may occur from intermediate **B**, resulting in the formation of intermediate **C** (path b). Subsequently, a protonolysis process generates the corresponding aldehyde intermediate **D**, along with the regeneration of the Cp*Rh(III). After eliminating water through intramolecular condensation, the final product **3aa** is formed.

Conclusions

In summary, we developed a new method for the step-economical synthesis of C2, C3-unsubstituted 1-aminoindole derivatives. This method involves rhodium-catalysed annulation of hydrazines with vinylene carbonate and is scalable to a gram-scale level without substantial yield loss. This protocol showcases a broad substrate scope and exceptional tolerance for various functional groups.

Conflicts of interest

There are no conflicts to declare.

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