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Rh(III)-Catalyzed dual C–H functionalization of 3-(1*H*-indol-3-yl)-3-oxopropanenitriles with sulfoxonium ylides or diazo compounds toward polysubstituted carbazoles†

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A rhodium-catalyzed annulation of 3-(1*H*-indol-3-yl)-3-oxopropanenitriles with sulfoxonium ylides or diazo compounds has been developed, leading to a series of polysubstituted carbazoles in moderate to good yields. This procedure proceeded with formal Rh(III)-catalyzed (4 + 2) cycloaddition, with the functionalization of 2-C–H bonds of indole in a step-economical procedure. Additionally, this reaction could also be conducted under acidic conditions when diazo compounds were employed as the reaction partners, which was a complement to the annulation of sulfoxonium ylides under weak basic conditions.

Carbazoles are important structural scaffolds of many bioactive natural products,¹ light-emitting materials² and organic dyes.³ Moreover, they show antimalarial⁴ and antitumor activities.⁵ For example, rebeccamycin and its analogues such as NSC655649 have been permitted into clinical trials for treatment of cancer.⁶ Carbazoles also serve as building blocks of functional materials, such as conjugated polymers, which possess light-emitting properties that allow for the detection of diverse chemicals.⁷

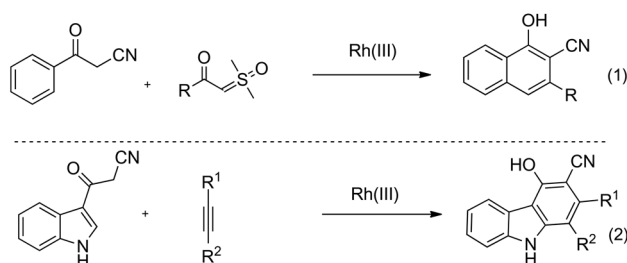
As such, great attention has been paid to the synthesis of such frameworks. There are two general pathways based on the construction of a ring in carbazoles. One is the construction of a middle pyrrole ring *via* the intramolecular C–N bond formation in the *ortho*-substituted biphenyl starting material.⁸ Alternatively, the other involves the construction of a new aromatic ring toward benzo-indole, namely carbazole *via* benzanulation.⁹ From the diversity and complexity of the product point of view, this version attracted increasing interest of organic chemists.

Recently, phenyl 3-oxopropanenitriles were well developed in the annulation with diazo compounds^{10,11} and sulfoxonium

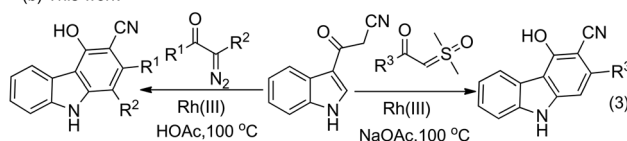
ylides¹² as a C4 synthon leading to naphthalene frameworks (Scheme 1, eqn (1)).^{13,14} In 2017, Wang and co-workers reported a pioneering work for the synthesis of carbazoles from the cascade reaction of 3-(1*H*-indol-3-yl)-3-oxopropanenitriles with alkynes catalyzed by rhodium (Scheme 1, eqn (2)).¹⁵ We herein report an efficient strategy to access polysubstituted carbazoles *via* Rh(III)-catalyzed C–H activation with sulfoxonium ylides or diazo compounds (Scheme 1, eqn (3)).

We initiated our work *via* exploring the reaction of 3-(1*H*-indol-3-yl)-3-oxopropanenitriles **1a** (0.1 mmol) and sulfoxonium ylide **2a** (0.12 mmol) in the presence of [Cp*Rh(MeCN)₃] (SbF₆)₂ (5 mol%), and NaOAc (0.2 mmol) as the additive in DCE at 100 °C for 12 h (Table 1). To our delight, the annulation product **3** was isolated in 31% yield (entry 1). [Cp*Co(CO)I₂] and Pd(OAc)₂ resulted in no reaction (entries 2 and 3). In contrast, [Cp*IrCl₂]₂, [Cp*Rh(OAc)₂]₂ and [Cp*RhCl₂]₂

(a) Previous works



(b) This work



Scheme 1 The annulation of aryl 3-oxopropanenitriles toward fused aromatics.

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Table 1 Screening the optimal conditions^a

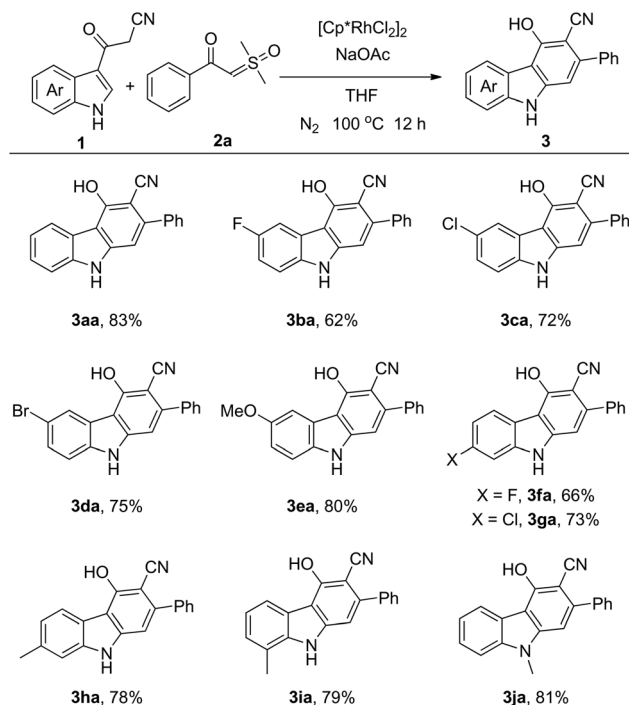
Entry	Catalyst	Additive	Solvent	Yield ^b (%)
1	[Cp*Rh(MeCN) ₃](SbF ₆) ₂	NaOAc	DCE	31
2	[Cp*Co(CO)I ₂]	NaOAc	DCE	n.r.
3	Pd(OAc) ₂	NaOAc	DCE	n.r.
4	[Cp*IrCl ₂] ₂	NaOAc	DCE	46
5	[Cp*Rh(OAc) ₂] ₂	NaOAc	DCE	49
6	[Cp*RhCl ₂] ₂	NaOAc	DCE	55
7	[Cp*RhCl ₂] ₂	NaOAc	MeCN	69
8	[Cp*RhCl ₂] ₂	NaOAc	DMF	73
9	[Cp*RhCl ₂] ₂	NaOAc	EtOH	41
10	[Cp*RhCl ₂] ₂	NaOAc	THF	70 ^c , 83, 77 ^d
11	[Cp*RhCl ₂] ₂	LiOAc	THF	72
12	[Cp*RhCl ₂] ₂	CsOAc	THF	78
13	[Cp*RhCl ₂] ₂	HOAc	THF	n.r.
14	[Cp*RhCl ₂] ₂	Cu(OAc) ₂	THF	<10
15	[Cp*RhCl ₂] ₂	AgOAc	THF	n.r.

^a Reaction conditions: 3-(1H-indol-3-yl)-3-oxopropanenitriles **1a** (0.1 mmol), sulfoxonium ylide **2a** (0.12 mmol), [Cp*RhCl₂]₂ (5 mol%), additive (0.2 mmol), solvent (2.0 mL), N₂ (1.0 atm), at 100 °C for 12 h, in a sealed Schlenk tube. ^b Isolated yield. ^c **1a** (0.1 mmol), **2a** (0.1 mmol). ^d **1a** (0.1 mmol), **2a** (0.15 mmol).

increased the yields to 46%, 49% and 55%, respectively (entries 4–6). During solvent screening, THF (83%) was superior to DCE (55%), MeCN (69%), DMF (73%) and EtOH (41%, entries 7–10). Changing the ratio of **1a** and **2a** to 1 : 1 or 1 : 5 decreased the reaction efficiency (entry 10). NaOAc was the best additive in the transformation (entries 11 and 12) while HOAc, Cu(OAc)₂, and AgOAc inhibited the reaction (entries 13–15). Finally, the optimized reaction conditions were selected as follows: **1** (0.1 mmol), **2** (0.12 mmol), [Cp*RhCl₂]₂ (5 mol%), and NaOAc (0.2 mmol) in THF (2.0 mL) at 100 °C for 12 h under an inert atmosphere (N₂).

With the optimized reaction conditions identified, the scope and limitation of 3-(1H-indol-3-yl)-3-oxopropanenitriles were studied, as shown in Scheme 2. Generally, this procedure was compatible with 3-(1H-indol-3-yl)-3-oxopropanenitriles bearing both electron-donating and withdrawing groups in the phenyl ring in moderate to good yields (62–83%, **3aa–ja**). Notably, the analogues bearing functional groups such as fluoro, chloro, bromo, methyl, and methoxy worked well with sulfoxonium ylides for the regioselective construction of carbazoles. Typically, 3-(1-methyl-1H-indol-3-yl)-3-oxopropanenitrile **1j** could also react with **2a** smoothly to generate the corresponding product **3ja** in 81% yield.

Next, various substituted sulfoxonium ylides were examined (Scheme 3). Once again, the reaction efficiency was not sensitive to the electronic properties of the groups on the sulfoxonium ylides (**3ab–am**, 56–78%). Notably, sulfoxonium ylides with the phenyl ring substituted with methyl at the *ortho*, *meta*, and *para* positions worked well to afford **3ae**, **3af** and

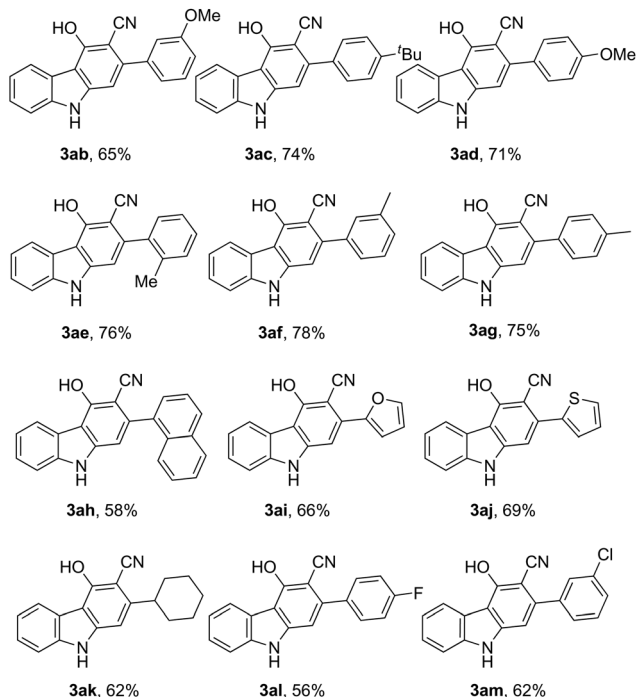
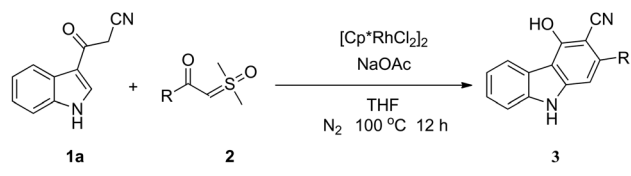


Scheme 2 Scope of substituted 3-(1H-indol-3-yl)-3-oxopropanenitriles. Reaction conditions: 3-(1H-indol-3-yl)-3-oxopropanenitriles **1** (0.1 mmol), sulfoxonium ylide **2a** (0.12 mmol), [Cp*RhCl₂]₂ (5 mol%), additive (0.2 mmol), solvent (2.0 mL), N₂ (1.0 atm), at 100 °C for 12 h, in a sealed Schlenk tube.

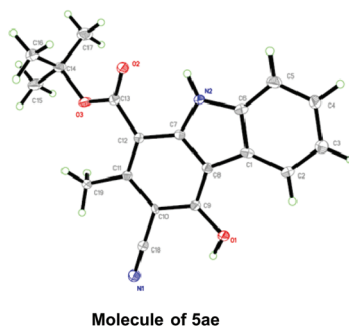
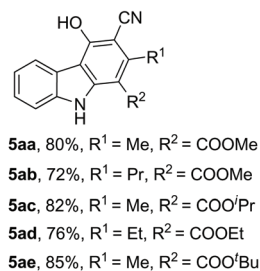
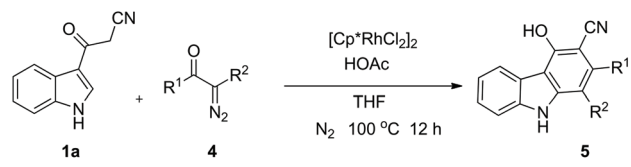
3ag in 76%, 78% and 75% yields, respectively. Moreover, sulfoxonium ylides possessing a cyclohexyl group or fused heterocyclic ring were also investigated, which provided the corresponding carbazoles in acceptable yields (**3ah–ak**, 58–69%). Notably, some reactive groups, such as fluoro (**3al**) and chloro (**3am**) groups, which are suitable for further potential functionalization, survived well in these reactions.

This procedure was also applicable to diazo compounds by slightly changing the reaction parameters as follows: [RhCp*Cl₂]₂ (5 mol%) and HOAc (2.0 equiv.) at 100 °C in THF under the atmosphere of N₂ (Scheme 4). Generally, it was found that diazo compounds bearing different substituents could afford their corresponding products in good yields (**5aa–ae**, 72–85%). The structure of **5ae** was further confirmed by X-ray crystallography (Scheme 4).¹⁶ In this case, the reaction was performed under acidic conditions, which was a complement to the aforementioned Rh-catalyzed annulation of sulfoxonium ylides under weak basic conditions.

In conclusion, we have developed a novel and step-economical method to access substituted carbazoles from readily accessible indoles and sulfoxonium ylides or diazo compounds through a formal Rh(III)-catalyzed (4 + 2) cycloaddition. The scope of 3-(1H-indol-3-yl)-3-oxopropanenitriles and sulfoxonium ylides was found to be broad. Further applications of this method will be investigated in the synthesis of related fused structures.



Scheme 3 Scope of substituted sulfoxonium ylides. Reaction conditions: 3-(1H-Indol-3-yl)-3-oxopropanenitriles **1a** (0.1 mmol), sulfoxonium ylides **2** (0.12 mmol), $[\text{Cp}^*\text{RhCl}_2]_2$ (5 mol%), additive (0.2 mmol), solvent (2.0 mL), N_2 (1.0 atm), at 100 °C for 12 h, in a sealed Schlenk tube.



Scheme 4 Scope of substituted diazo compounds. Reaction conditions: 3-(1H-Indol-3-yl)-3-oxopropanenitriles **1a** (0.1 mmol), diazo compounds **4** (0.12 mmol), $[\text{Cp}^*\text{RhCl}_2]_2$ (5 mol%), additive (0.2 mmol), solvent (2.0 mL), N_2 (1.0 atm), at 100 °C for 12 h, in a sealed Schlenk tube.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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- 16 Crystallographic data for **5ae** (CCDC 1848812†).