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Rhodium-Catalyzed Intramolecular Cascade Sequence for the Formation of Fused Carbazole-Annulated Medium-Sized Rings by Cleavage of C(sp^2)–H/C(sp^3)–H Bonds

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The rhodium(III)-catalyzed intramolecular annulation of alkyne-tethered 3-(indol-3-yl)-3-oxopropanenitriles for the synthesis of fused carbazolescaffolds *via* C–H activation has been developed. A series of six-, seven-, and eight-membered hydroazepino[3,2,1-*jk*]carbazoles were achieved. This reaction proceeded under mild reaction conditions and with a broad substrates scope. The reaction involved sequential cleavage of C(sp^2)–H/C(sp^3)–H bonds and annulation with the tethered alkyne.

The indole skeletons are found in many biologically active natural products and are useful moieties in functional materials and drug design.[1] Among them, fused polycyclic indoles such as carbazoles, which are also the constituents of a large amount of important skeleton for many bioactive natural products, photorefractive materials, and organic dyes (Figure 1).[2] In addition, corresponding medium-sized-ring analogues are also the constituents of numerous natural products and pharmaceutical agents.[3] This class of compounds possesses a functionalized medium-sized ring bridged to the N1- and C3-positions of the carbazoles. Therefore, it is of great significance for the construction of these scaffolds. Few methods have been reported for the synthesis of azaheterocyclo[3,2,1-*jk*]carbazoles (Scheme 1).[4] So, the development of a general method for the rapid construction of their analogue library remains a challenge.

Recent years have witnessed an explosive growth of synthetic transformations relying on transition-metal catalyzed C–H bond activation processes.[5] Owning to its high efficiency, functional-group tolerance, and selectivity, rhodium(III) catalysis has emerged as a powerful tool in C–H activation in recent decades. Rh(III)-catalyzed C(sp^2)–H activation with

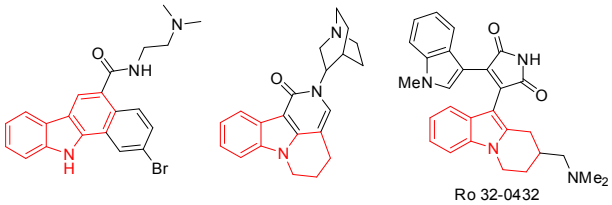
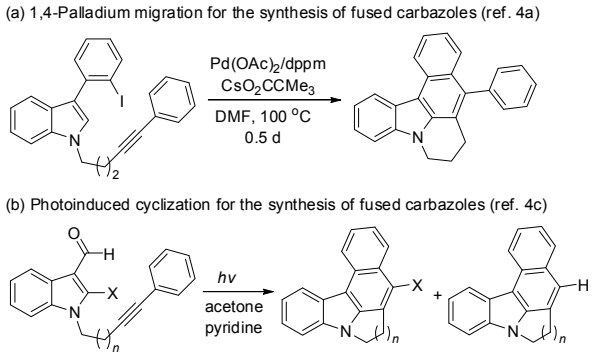


Figure 1 Biologically active compounds containing carbazole or 1,2-fused indoline moieties.



Scheme 1 Synthesis of azaheterocyclo[3,2,1-*jk*]carbazoles.

subsequent cross-coupling with alkynes or alkenes is a rapidly evolving research field. In 2010, Miura and Satoh,[6a] Rovis,[6b] and Li[6c] independently reported rhodium(III)-catalyzed oxidative C–H/N–H functionalization of benzamides in the coupling with alkynes. In 2012, we reported the annulation of benzoylacetonitrile with internal alkynes to get substituted naphtho[1,8-*bc*]pyrans.[6x] In 2016, we also reported Rh(III)-catalyzed carbocyclization reactions of 3-(indolin-1-yl)-3-oxopropanenitriles with alkynes and alkenes.[6q] However, the intermolecular reactions showed low regioselectivity with unsymmetrical alkynes, especially for the unsymmetrical dialkylalkynes. Consequently, intramolecular reactions are highly attractive on account of regioselectivity, high efficiency, and versatility for fused heterocyclic compounds. The rhodium-catalyzed intramolecular C–H activation reactions also have been reported recent years,[7] but most of them are

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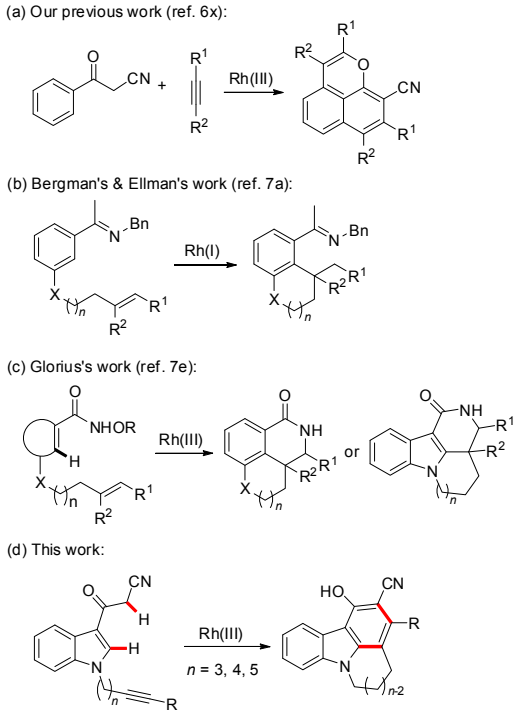
limited to Rh(III)-catalyzed C(sp^2)–H activation with hydroarylation of alkene tethers, Rh(III)-catalyzed C(sp^2)–H/C(sp^3)–H activation of the intramolecular reactions with N-tethered alkene have never been reported. Based on the pioneering works (Scheme 2), we became interested in the Rh(III)-catalyzed intramolecular reaction of alkyne-tethered indol-3-yl-propanenitrile. Herein we report the rhodium-catalyzed intramolecular annulation of alkynes *via* a C–H bond activation pathway to efficiently construct fused carbazoles (Scheme 2d).

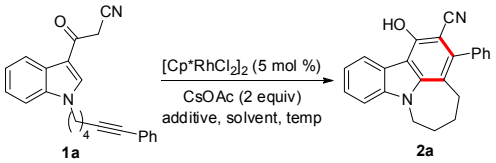


Scheme 2 Rhodium-catalyzed activation and annulation.

We initiated our studies by investigating the reaction of indole-derived propanenitrile (**1a**) as model substrate. When the reaction was performed in the presence of $[Cp^*RhCl_2]_2$ (5 mol %), CsOAc (0.4 mmol, 2 equiv), and $Cu(OAc)_2{\cdot}H_2O$ (0.4 mmol, 2 equiv) in MeCN at 120 °C for 12 h under Ar atomosphere (entry 1, Table 1), to our delight, the desired product **2a** was obtained in 50% isolated yield. Changing the solvent, oxidant, and temperature (entries 2–10), the yield was improved to 92% when DMF as the solvent and TEMPO as the oxidant in 100 °C (entry 9). Without catalyst no reaction was occurred (entry 11). In the absence of oxidant **2a** was obtained in 21% yield (entry 12). Different catalysts were also tested (entries 13–16), $[Cp^*RhCl_2]_2$ got the highest yield.

With the optimal conditions in hand, we surveyed various substrates to determine the scope of the reaction. When *n* = 4, the reaction proceeded smoothly to give a series of fused carbazoles in moderate to excellent yields. Ignoring the substituted groups at the 4-, 5-, 6-, or 7-position, both the electron-donating and electron-withdrawing groups could proceed smoothly to afford the corresponding carbazoles in synthetically useful yields (Table 2, **2a–n**). The molecular structure of **2a** was confirmed by its ^1H and ^{13}C NMR spectra, mass spectra, and single-crystal X-ray diffraction analysis (Figure 2). Then, the electronic effects of aryl groups attached to the alkyne were examined, which were all available for this intramolecular annulation reaction, affording the corresponding products in good yields (Table 2, **2o–r**). 2-Naphthalene group could be accommodated in the reaction, giving product **2s** in 67% yield. Compound **2t** with an oxazepino-7-membered ring was also produced in 53% yield by this method. Satisfyingly, the intramolecular reaction could be extended to generate fused carbazoles **2u** and **2v** with 6- and 8-membered rings in 89% and 44% yields, respectively.

Table 1 Optimization of reaction conditions[a]



Entry	Solvent	Oxidant	T/°C	Yield (%)[b]
1	CH_3CN	$Cu(OAc)_2{\cdot}H_2O$	120	50
2	DMF	$Cu(OAc)_2{\cdot}H_2O$	120	55
3	DCE	$Cu(OAc)_2{\cdot}H_2O$	120	trace
4	*t*-AmOH	$Cu(OAc)_2{\cdot}H_2O$	120	47
5	DMF	Ag_2CO_3	120	15
6	DMF	AgOAc	120	18
7	DMF	DDQ	120	trace
8	DMF	DTBP	100	trace
9	**DMF**	**TEMPO**	**100**	**92**
10	DMF	TEMPO	80	85
11[c]	DMF	TEMPO	100	n.r.
12	DMF	-	100	21
13[d]	DMF	TEMPO	100	45
14[e]	DMF	TEMPO	100	43
15[f]	DMF	TEMPO	100	trace
16[g]	DMF	TEMPO	100	51

[a]Reaction conditions: **1a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (5.0 mol %), CsOAc (0.4 mmol, 2.0 equiv), additive (0.4 mmol), solvent (1 mL), 100 °C, 12 h. [b]Isolated yield. [c]Without $[Cp^*RhCl_2]_2$, [d]$[Cp^*IrCl_2]_2$ (5.0 mol %), [e]$Cp^*Rh(CH_3CN)_3(SbF_6)_2$ (5.0 mol %), [f]$Cp^*Co(CO)I_2$ (5.0 mol %), [g]$[(p\text{-cymene})RuCl_2]_2$ (5.0 mol%).

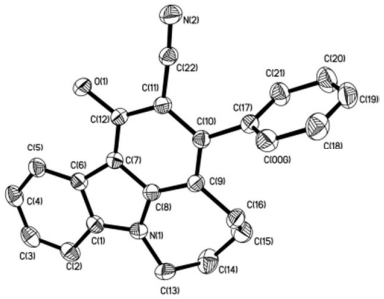


Figure 2 Molecular structure of **2a**

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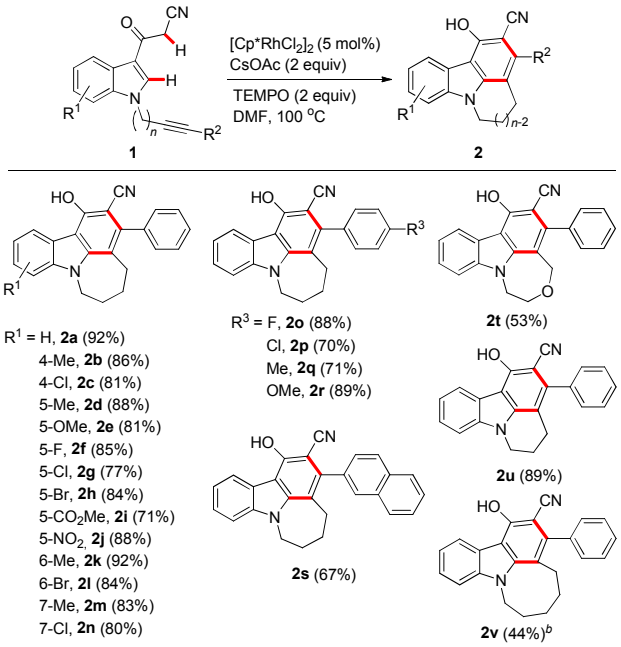
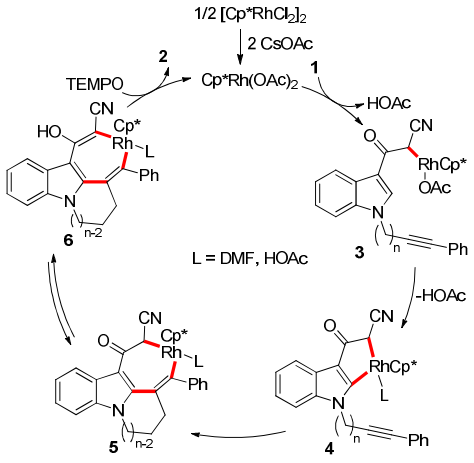
Table 2 Rh(III)-catalyzed intramolecular cyclization to fused carbazoles[a]



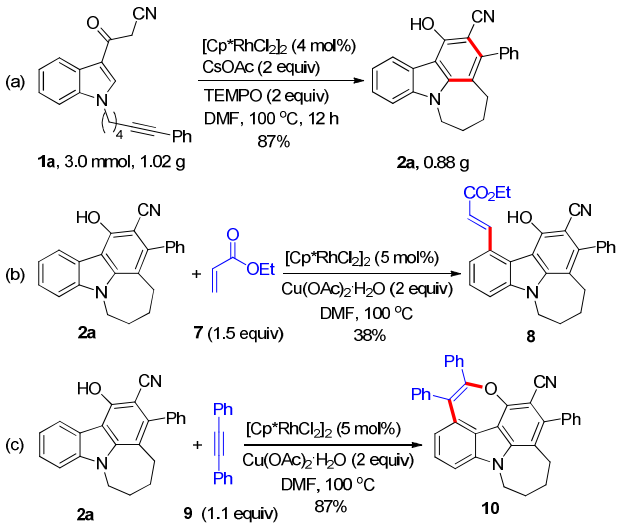
[a]Reaction conditions: **1a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (5.0 mol %), CsOAc (0.4 mmol, 2.0 equiv), TEMPO (0.4 mmol, 2.0 equiv), DMF, 100 °C, 12 h, isolated yield.[b]$Cp^*Rh(CH_3CN)_3(SbF_6)_2$ (5 mol%).

Based on the literature work,[6f] a possible mechanism for this rhodium-catalyzed cascade reaction is proposed as shown in Scheme 3. The first step is likely to be the acidic C(sp^3)–H bond activation process affording intermediate **3**, then C(sp^2)–H bond activation through the CMD mechanism gives a five-membered rhodacycle **4**. The coordination and insertion of the tethered alkyne leads to the six, seven or eight-membered rhodacycle intermediate **5**. After ketone enolization intermediate **6** is formed and undergoes reductive elimination to afford product **2a** and Cp*Rh(I). Cp*Rh(I) is oxidized by TEMPO to afford $Cp^*Rh(OAc)_2$ for the next catalytic cycle.



Scheme 3 Proposed mechanistic pathway of the annulation reaction

Synthetic applications of this protocol have been demonstrated (Scheme 4). Fused carbazole **2a** was synthesized in 89% yield on a gram scale even under reduced catalyst loading (Scheme 4, eqn (a)). Furthermore, the hydroxyl group of **2a** can act as an efficient directing group for further rhodium(III)-catalyzed C–H functionalization at the 9-position of the fused carbazole derivatives. Reactions of **2a** with ethyl acrylate and diphenylacetylene gave the corresponding olefination product **8** and fused carbazoles **10** in 38% and 87% yields, respectively (Scheme 4, eqn (b) and (c)).



Scheme 4 Gram-scale synthesis and derivatization reactions of carbazole

In summary, we have developed a mild and efficient method for the synthesis of fused carbazoles, based on a rhodium(III)-catalyzed C–H bond activation and subsequent intramolecular oxidative annulation of the tethered alkynes by cleavage of C(sp^2)–H/C(sp^3)–H bonds. This reaction has high selectivity and a broad substrate scope, contributing to the formation of heterocyclic scaffolds of utmost importance in agrochemistry or medicinal chemistry. Further applications of this method in the synthesis of other targets are in progress.

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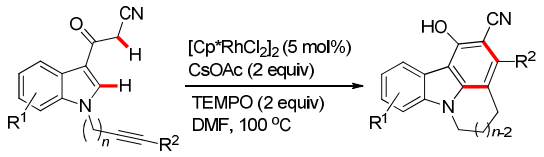

Rhodium-Catalyzed Intramolecular Cascade Sequence for the Formation of Fused Carbazole-annulated Medium-Sized Rings by Cleavage of $C(sp^2)$–H/$C(sp^3)$–H Bonds

The rhodium(III)-catalyzed intramolecular annulation of alkyne-tethered 3-(indol-3-yl)-3-oxopropanenitriles for the synthesis of fused carbazole scaffolds via C–H activation has been developed. A series of six-, seven-, and eight-membered hydroazepino[3,2,1-*jk*]carbazoles were achieved.