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Indole Synthesis

Rhodium(III)-Catalyzed C–H Activation and Indole Synthesis With Hydrazone as an Auto-Formed and Auto-Cleavable Directing Group

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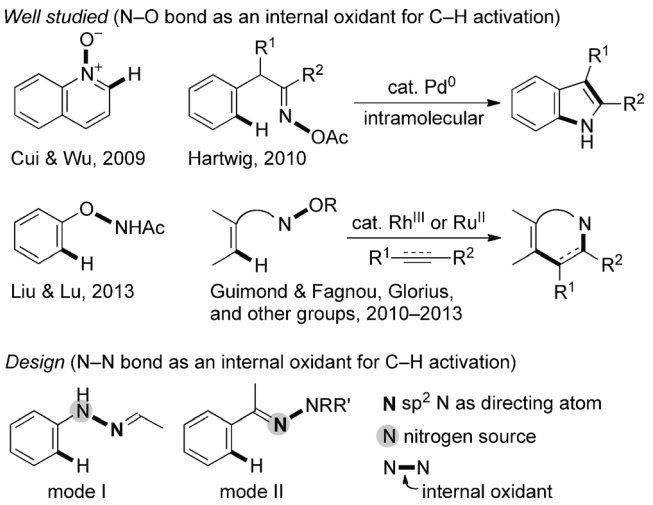
Abstract: An efficient, practical, and external-oxidant-free indole synthesis from readily available aryl hydrazines was developed, by using hydrazone as a directing group for Rh^{III}-catalyzed C–H activation and alkyne annulation. The hydrazone group was formed by in situ condensation of hydrazines and C=O source, whereas its N–N bond was served as an internal oxidant, for which we termed it as an auto-formed and auto-cleavable directing group (DG^{auto}). This method needs no step for pre-installation and post-cleavage of the directing group, making it a quite easily scalable approach to access unprotected indoles with high step economy. The DG^{auto} strategy was also applicable for isoquinoline synthesis. In addition, synthetic utilities of this chemistry for rapid assembly of π-extended nitrogen-doped polyheterocycles and bioactive molecules were demonstrated.

Introduction

Recently, C–H activation has emerged as a robust toolkit for rapid assembly of heterocycles,[1] including indole, a ubiquitous structural component in natural products and pharmaceuticals.[2–4] Since 2008, several synthetic strategies have been developed for indole synthesis by C–H activation using external oxidants.[5–8] In 2010, Hartwig reported a unique indole synthesis by Pd-catalyzed intramolecular amination, in which the N–O bond served as an internal oxidant (Scheme 1).[9] Afterwards, this strategy was widely extended to Rh^{III}- or Ru^{II}-catalyzed intermolecular cyclization, by using an N-O containing oxidizing directing group (DG^{ox}).[10–12] Nevertheless, design of an N–N containing DG^{ox} is still challenging.[13]

In 1883, E. Fischer discovered an indole synthesis by the acid-mediated rearrangement of arylhydrazone, with N–N cleavage and elimination of NH_3.[14] After that, hydrazones became a widely used class of compounds, and the N–N bond was tamed by chemists as a useful synthetic handle. Inspired by this, we designed two modes of hydrazone as multifunctional DG^{ox}, in which the two nitrogen atoms serve as the directing atom and the nitrogen source for heterocycle synthesis, whereas the N–N bond serves as a linkage as well as an internal oxidant (Scheme 1). Though nitrogen-containing groups such as pyridines and amides are well studied as directing groups or C–H activation, hydrazone, especially in mode I is rarely exploited.[15]



Scheme 1. C–H activation with internal oxidants.

In pioneering work, Fagnou and Stuart developed an elegant indole synthesis by Rh^{III}-catalyzed oxidative coupling of acetanilides and alkynes (Scheme 2).[6] Afterwards, Pd- and Ru-catalyzed indole syntheses were also developed by using 2-pyridyl, acetyl or 2-pyrimidyl as a directing group (DG).[7] In these methods, the DGs are pre-installed and removed after the synthesis, resulting in very low step economy. Recently, Huang developed a unique triazene DG for alkyne annulation to access unprotected indoles, in which the N=N bond of triazene DG is cleaved in the reaction.[8] However, the N=N bond does not serve as an internal oxidant for C–H activation, and stoichiometric $Cu(OAc)_2$ is needed as an external oxidant.

In the Fischer indole synthesis, hydrazones are usually formed by in situ condensation of hydrazines and aldehydes/

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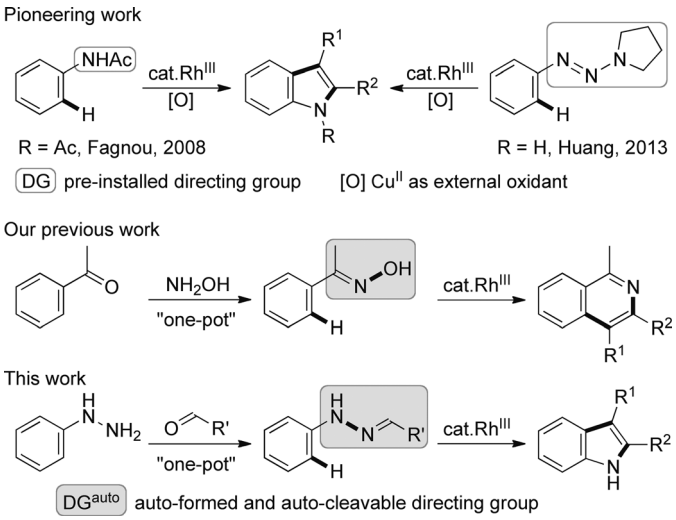


Scheme 2. Rh^{III}-Catalyzed alkyne annulation by C–H activation.

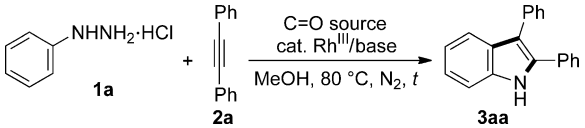
ketones. With this and our previous one-pot isoquinoline synthesis[16] in mind, we envisioned that a hydrazone could be formed in situ from hydrazines and serve as a DG^{ox} for Rh^{III}-catalyzed C–H activation and alkyne annulation (Scheme 2). In this way, the hydrazone group could be an auto-formed and auto-cleavable directing group, which we have termed as an auto-directing group (DG^{auto}),[17–19] leading to a one-pot synthesis with a high step economy. Herein, we disclose our design and development of a hydrazone DG^{auto} strategy for the rapid assembly of unprotected indoles in a practical and external-oxidant-free way.

Results and Discussion

We initiated our study employing phenylhydrazine hydrochloride (**1a**) and diphenylacetylene (**2a**) as substrates, and $[(Cp^*RhCl_2)_2]$ as a precursor of the Rh^{III} catalyst (Table 1). Acetone was used as the C=O source to generate corresponding hydrazone from **1a**. Excess KOAc was used as base to neutralize the hydrochloride and facilitate the generation of $[Cp^*Rh(OAc)_n]$ species as the active catalyst.[11,16] As expected, reaction at 60 °C for 24 h gave full conversion of **1a** to corresponding acetone hydrazone, but only 11% indole product **3aa** was obtained (Table 1, entry 1). Reaction with 2.0 equivalents of acetone in MeOH at 80 °C gave improved yield (Table 1, entries 2 and 3).

Considering that structure of the hydrazone group may have a great influence on the generation of the rhodacycle intermediate and reactivity of the N–N bond, we then focused on screening various C=O sources. Cyclic ketones gave improved yields (Table 1, entries 4 and 5), whereas benzaldehyde gave no desired product (Table 1, entry 9). For alkyl aldehydes $R_nCH_{3-n}CHO$, those with a 2° carbon connected to CHO ($n=2$, Table 1, entries 7 and 10) proved to be better C=O sources than those with a 1° carbon ($n=1$, Table 1, entry 6) or a 3° carbon ($n=3$, Table 1, entry 8).With isobutyraldehyde (*i*PrCHO) as a C=O source, other carboxylates such as NaOAc, CsOAc and CsOPiv were tested and gave similar or slightly lower yields (Table 1, entries 11–13). Reaction in other solvents such as MeCN, DCE, THF, and *t*-AmOH led low conversion and declined yield.

Table 1. Optimization of the reaction conditions.[a]



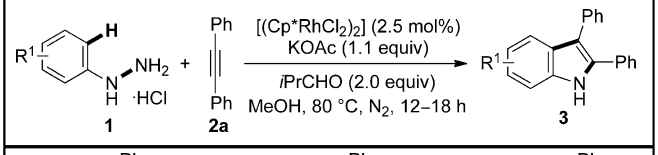
Entry[a]	C=O source (equiv)	Base (equiv)	*t* [h]	Yield [%][b]
1[c]	acetone ([d])	KOAc (2.0)	24	11
2[c]	acetone (2.0)	KOAc (2.0)	24	19
3	acetone (2.0)	KOAc (2.0)	24	28
4	cyclohexanone (2.0)	KOAc (2.0)	18	40
5	cyclopentanone (2.0)	KOAc (2.0)	18	51
6	*n*PrCHO (2.0)	KOAc (2.0)	18	64
7	*i*PrCHO (2.0)	KOAc (2.0)	18	73 (68)
8	*t*BuCHO (2.0)	KOAc (2.0)	18	24
9	PhCHO (2.0)	KOAc (2.0)	18	0
10	CyCHO[e] (2.0)	KOAc (2.0)	18	70
11	*i*PrCHO (2.0)	NaOAc (2.0)	18	72
12	*i*PrCHO (2.0)	CsOAc (2.0)	18	70
13	*i*PrCHO (2.0)	CsOPiv (2.0)	18	69
14	*i*PrCHO (2.0)	KOAc (1.5)	18	78
15	*i*PrCHO (2.0)	KOAc (1.1)	18	85
16	***i*PrCHO (2.0)**	**KOAc (1.1)**	**12**	**87 (83)**
17	*i*PrCHO (1.2)	KOAc (1.1)	12	70
18	-	KOAc (1.1)	12	0
19[f]	*i*PrCHO (2.0)	KOAc (1.1)	12	85
20[g]	*i*PrCHO (2.0)	KOAc (1.1)	12	<5

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.24 mmol), KOAc, and $[(Cp^*RhCl_2)_2]$ (2.5 mol%) in 1.0 mL MeOH at 80 °C under N_2 atmosphere. [b] Yield of **3aa** is based on GC by using n-$C_{24}H_{50}$ as internal standard; value in parentheses is isolated yield at 0.5 mmol scale. [c] 60 °C. [d] MeOH–acetone (4:1) as solvent. [e] Cy = cyclohexyl. [f] 5 mol% $[Cp^*Rh(MeCN)_3][SbF_6]_2$ was used. [g] 2.5 mol% $[\{Ru(p\text{-cymene})Cl_2\}_2]$ was used.

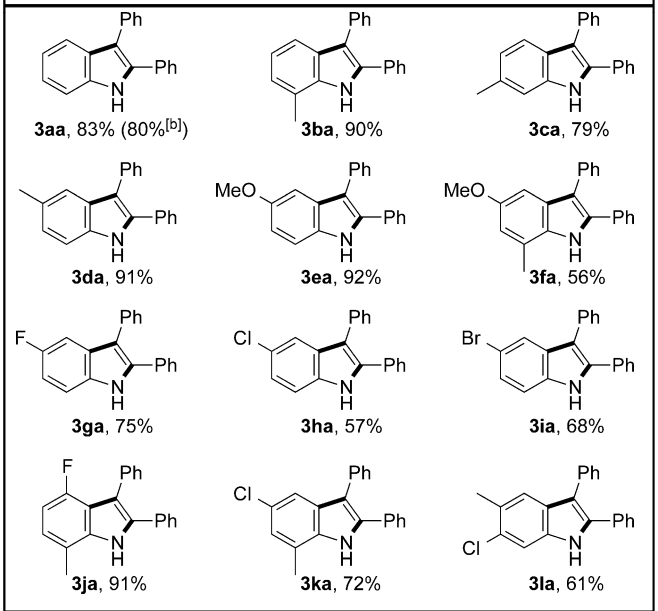
To our delight, simply reducing the amount of KOAc to 1.1 equiv gave a satisfactory yield (87% GC, 83% isolated) within a shorter reaction time (Table 1, entry 16). Reducing the amount of *i*PrCHO to 1.2 equiv gave a reduced yield (Table 1, entry 17) and reducing it to a catalytic amount led to much lower conversions. Further optimization focused on the development of a special C=O source for metal-organic cooperative catalysis[17] is ongoing. No **3aa** was detected without a C=O source (Table 1, entry 18), and no hydrohydrazination product of **2a** was detected in either entry, indicating the cyclization did not proceed by an alkyne hydrohydrazination followed by a Fischer indole synthesis.[20] The cationic Cp^*Rh^{III} complex showed similar catalytic activity with $[(Cp^*RhCl_2)_2]$ (Table 1, entry 19). The structurally analogous Ru^{II} complex,[12] which is active in some cases with N–O containing DG^{ox}, showed little catalytic activity in this reaction, and only a trace of **3aa** was detected by GC-MS (Table 1, entry 20).

With the optimized reaction conditions in hand, the generality of the one-pot synthesis of indoles was examined. By employing **2a** as the alkyne partner, various substituted aryl hydrazines were surveyed (Table 2). *o*-Methylphenylhydrazine gave an improved yield (**3ba**, 90%) and *m*-methylphenylhydrazine afforded **3ca** as a single regioisomer. Aryl hydrazines with an electron-donating group (EDG) as *para*-substituent showed

Table 2. Substrate scope of aryl hydrazines.[a]

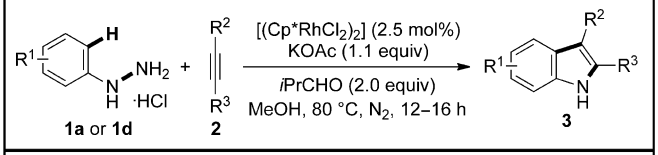


1 2a 3

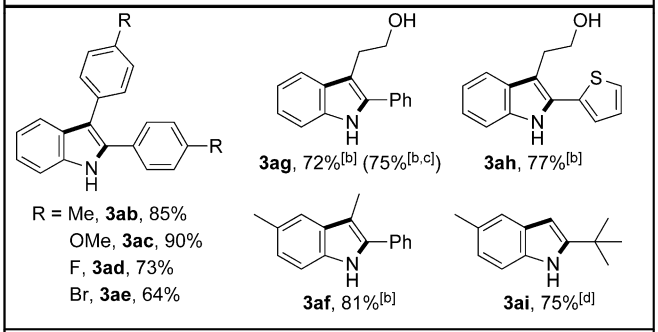


[a] Reaction conditions: **1** (0.50 mmol), **2a** (0.60 mmol), KOAc (0.55 mmol), and $[(Cp^*RhCl_2)_2]$ (2.5 mol%) in 2.5 mL MeOH at 80 °C under N_2 atmosphere. [b] 6 mmol scale.

Table 3. Substrate scope of alkynes.[a]



1a or 1d 2 3

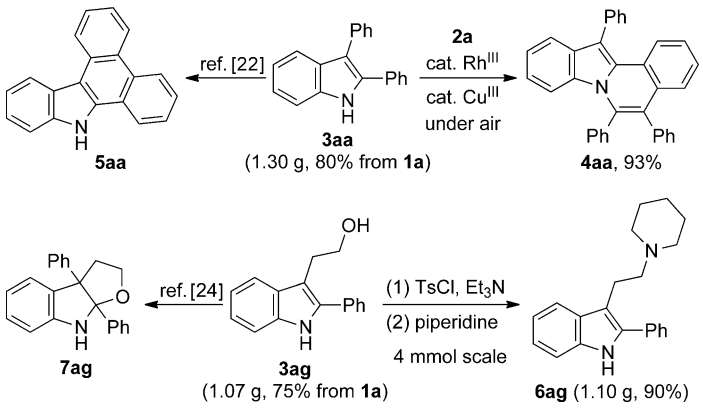


[a] Reaction conditions: **1** (0.50 mmol), **2** (0.60 mmol), KOAc (0.55 mmol), and $[(Cp^*RhCl_2)_2]$ (2.5 mol%) in 2.5 mL MeOH at 80 °C under N_2 atmosphere. [b] 1.4 equiv alkyne (0.70 mmol). [c] 6 mmol scale. [d] 2.0 equiv alkyne (1.0 mmol).

higher reactivity than those with an electron withdrawing group (EWG). Products with *p*-Me (**3da**) or *p*-OMe (**3ea**) were obtained in excellent yields (> 90%), whereas those with halogens (**3ga**–**ia**) were obtained in moderate yield. Notably, substrates with two substitutes reacted smoothly, giving rapid access to multiply substituted indoles (**3fa**, **3ja**–**la**).

The scope of alkynes was next investigated (Table 3). Diaryl alkynes with either EDGs (Me, OMe) or EWGs (F, Br) were tolerated to afford **3ab**–**ae**. Arylalkyl asymmetric alkynes reacted regioselectively to afford **3af**–**ah**. The regioselectivity was in accordance with other Rh^{III}-catalyzed alkyne annulations[6,11,16] and contrary to the Fischer indole synthesis.[20] Significantly, alkynes with a free hydroxyl group were tolerated for synthesis of **3ag** and **3ah**, whereas the hydroxyl group needs protection in the Fagnou indole synthesis.[6] This type of product (2-aryl tryptophol) are also quite challenging in the traditional Fischer indole synthesis.[14] Terminal alkyne *t*Bu≡H was also compatible to afford the 2-substituted indole **3ai**. It should be noted that terminal alkynes in Rh^{III}-catalyzed reactions are rare, expecially with Cu^{II} as an external oxidant, due to severe side reactions such as alkyne dimerization and oxidative homocoupling.[6,11]

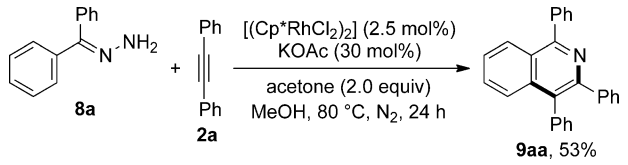
To probe the practical synthetic utility of our method, large scale reactions were carried out for **3aa** (1.30 g, 80%) and **3ag** (1.07 g, 75%) up to gram scale, facilitating further transformations of these products to valuable molecules (Scheme 3). Under Miura's conditions[21] with a modification, a fused product **4aa** was obtained by Rh^{III}-catalyzed alkyne annulation of **3aa** in 93% yield. **3aa** could also be converted to **5aa** by dehydrogenative coupling.[22] **4aa** and **5aa** are polyheterocycles with π-extended and nitrogen-doped conjugated systems,



Scheme 3. Derivatization of products to valuable molecules.

which are promising for organic semiconductors. 2-Aryl indole is a privileged structure for drug discovery.[3] Especially, 2-aryl tryptamines such as **6ag** are high-affinity selective h5-HT_{2A} antagonists.[23] We converted 2-phenyl tryptophol **3ag** to **6ag** by a simple tosylation-amination on a 4 mmol scale in excellent yield (1.10 g, 90%), which is much more efficient and scalable than previous method.[23] **3ag** could also be converted to **7ag** with a naturally occurring furoindoline skeleton.[24]

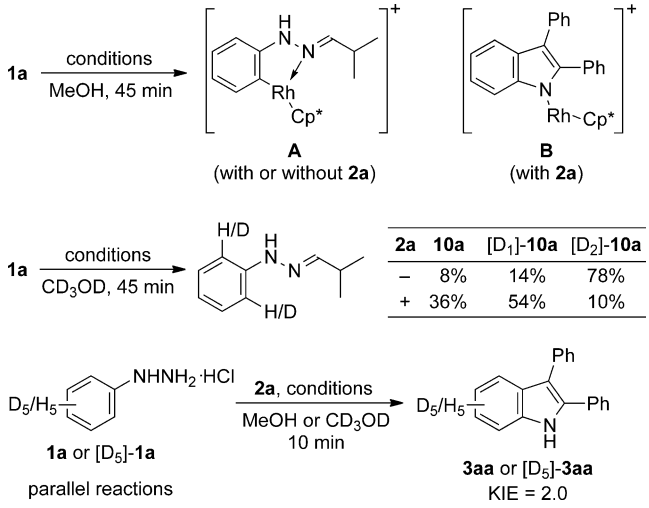
To test the versatility of DG^{auto} with N–N bond as an internal oxidant, we extended this strategy to isoquinoline synthesis with hydrazone mode II (Scheme 1). With benzophenone hy-



Scheme 4. Isoquinoline synthesis by hydrazone DG^{auto}.

drazone (**8a**) and **2a** as substrates, isoquinoline **9aa** was formed, as expected (Scheme 4), though the yield was only moderate (53%) due to low conversion (approx. 60%) of the alkyne annulation step. Interestingly, *i*PrCHO gave a much lower yield, indicating that the C=O source should be selected specifically for each type of substrates.

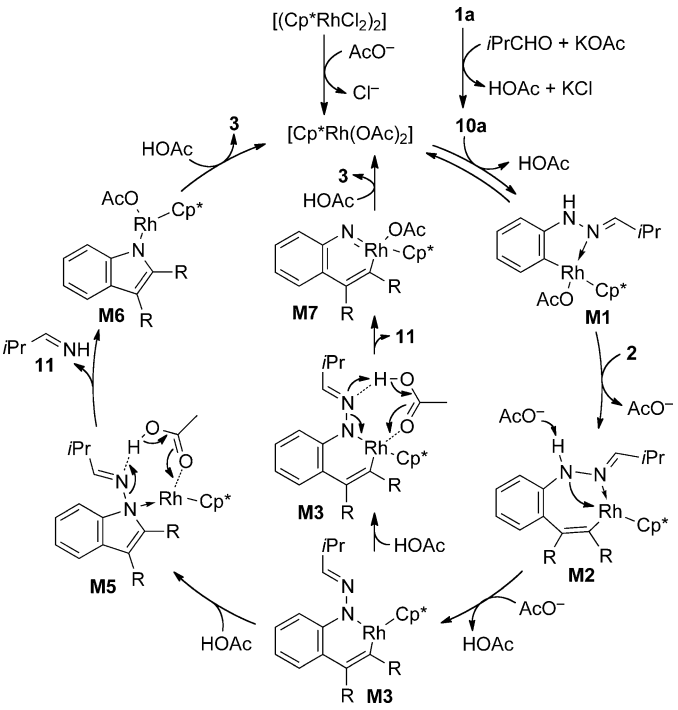
To gain a better understanding of the reaction mechanism, several experiments were carried out (Scheme 5). First, parallel reactions were performed under standard conditions for 45 min with or without adding alkynes. Remarkable HRMS sig-



Scheme 5. Mechanistic studies. Conditions: [(Cp*RhCl$_2$)$_2$] (2.5 mol%), KOAc (1.1 equiv), *i*PrCHO (2.0 equiv), 80 °C, N_2.

nals fitted with $[C_{20}H_{28}N_2Rh]^+$ and $[C_{30}H_{29}NRh]^+$ were observed, indicating the formation of complex **A** and **B**, respectively. In addition, **1a** gave >90% conversion to the hydrazone **10a** within 2 min, indicating that hydrazone is formed rapidly and can serve as an efficient DG. When these reactions were performed in deuterated methanol, deuteration at the *ortho* positions of **10a** was observed, indicating the cyclorhodation was reversible even with an alkyne.[6b] A modest kinetic isotope effect (KIE) of 2.0 was observed in the early stage by comparison of parallel reactions with **1a** and [D_5]-**1a**, indicating the C–H cleavage should be involved in turnover-controlling steps but may not be an exclusive step.[5d,25]

Based on these facts and previous mechanistic studies of N–O bond containing DG^{ox},[11,26] we propose the mechanism shown in Scheme 6. First, hydrazone **10a** was formed in situ from **1a** and *i*PrCHO rapidly, with the generation of 1 eqiuv HOAc. To initiate the catalytic cycle, **10a** undergoes reversible C–H activation to form rhodacycle **M1**. Alkyne insertion of **M1**



Scheme 6. Proposed mechanism.

affords a seven-membered rhodacycle **M2**, which rearranges to a more stable six-membered rhodacycle **M3**.[8] Reductive elimination of **M3** formed **M4**,[11b] which undergoes HOAc promoted N–N cleavage to form **M5**. Protonation of **M5** yields the indole product **3** and turnover of the Rh^{III} catalyst. For another possible pathway, **M3** might undergo N–N cleavage to afford Rh^{V} nitrene intermediate **M6**,[26,27] which could undergo reductive elimination to form **3**.

Conclusions

In summary, we have developed a novel C–H activation and annulation strategy with hydrazone as an auto-formed and auto-cleavable directing group (DG^{auto}) and its N–N bond as internal oxidant, which enables efficient and external-oxidant-free synthesis of unprotected indoles from readily available aryl hydrazines and alkynes. The synthetic utilities of this chemistry and extension of the strategy for isoquinoline synthesis were also demonstrated. We expect that more diverse transformations can be developed through rational design of DG^{auto}.

Experimental Section

Typical procedure for synthesis of indole 3: To a 25 mL tube equipped with a magnetic stirrer, phenylhydrazine hydrochloride (**1a**, 72.3 mg, 0.50 mmol), 1,2-diphenylacetylene (**2a**, 106.9 mg, 0.60 mmol, 1.2 equiv), [(Cp*RhCl$_2$)$_2$] (7.7 mg, 0.0125 mmol, 2.5 mmol%) and KOAc (54.0 mg, 0.55 mmol, 1.1 equiv) were added sequentially. The tube was evacuated and backfilled with nitrogen three times. Isobutyraldehyde (72.1 mg, 1.0 mmol, 2.0 equiv) was dissolved in MeOH (2.5 mL), and added under nitrogen atmos-

phere and the tube was sealed. The tube was immersed in an oil bath (80 °C) and stirred for 12 h. After removal of the solvent under reduced pressure, purification was performed by flash column chromatography on silica gel with petroleum ether/acetone (gradient mixture ratio from 100:0 to 80:20) as eluant to afford **3aa** (111.4 mg, 83%). For detailed reaction procedures for other compounds, see the Supporting Information.

Acknowledgements

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Keywords: C–H activation · hydrazones · indoles · N–N cleavage · rhodium catalysis

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