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Rh(III)-catalyzed double C–H activation of aldehyde hydrazones: a route for functionalized 1*H*-indazole synthesis†

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A novel and straightforward strategy for functionalized 1*H*-indazoles is realized by the Rh(III)-catalyzed double C–H activation and C–H/C–H cross coupling of readily available aldehyde phenylhydrazones. The reaction is scalable and various 1*H*-indazoles could be afforded in moderate to high yields with good functional-group compatibility. Mechanism experiments and DFT calculations suggest the distinctive Rh(III)-catalyzed C–H/C–H cross coupling reaction underwent a cascade C(aryl)–H bond metalation, C(aldehyde)–H bond insertion and reductive elimination process.

Introduction

Hydrazones are particularly attractive as building blocks in synthetic organic chemistry because of their easy availability and versatile reactivity.¹ As well as enjoying the features of carbonyl compounds, the most unique property of aldehyde hydrazone is its ability to react with active electrophiles as a neutral acyl anion equivalent, which represents an important method for the C(sp²)-H functionalization of aldehyde hydrazones.² However, the demand of limited strong electrophilic reagents such as acyl chloride and the subsequent problem in terms of functional-group tolerance have restricted its widespread application. Hence the development of effective and general methodologies for the C(sp²)-H functionalization of aldehyde hydrazones is highly desired. A recent breakthrough in this area is the transition metal (Cu, Pd) or visible light catalytic strategies for the C(sp²)-H functionalization of aldehyde hydrazones (Scheme 1a).³ Mechanism experiments as well as theoretical calculations in our previous report^{3b} support an electron transfer induced aminyl radical-polar crossover (ARPC) process, in which the key activating unit, the N–N bond, plays a crucial role. From another point of view, the N–N bond, a Lewis basic functional unit, often appears as a directing group

in transition metal-catalyzed C–H activation reactions. To complement these radical-type strategies, we have recently initiated a project to exploit the directing group strategy for the C(sp²)-H bond functionalization of aldehyde hydrazones.

1*H*-Indazole, a privileged pharmacophore in pharmaceuticals, is widely incorporated in multiple drugs such as anti-HIV, anti-inflammatory and anti-cancer drugs.⁴ The efficient synthesis of functionalized 1*H*-indazole has particularly attracted the increased attention of organic synthetic chemists.^{5,6} In the past few years, transition metal-catalyzed C–H activation has emerged with significant advantages toward the synthesis of a diverse array of heterocycles.⁷ Among them, Pd-,^{6a} Fe-,^{6b} Cu-,^{6c,e} and Rh-^{6d,f} catalyzed C–H activation strategies have been applied to the synthesis of 1*H*-indazoles (Scheme 1b), which

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a) Previous work on C(sp²)-H functionalization of aldehyde hydrazones



b) Previous work on 1*H*-indazole synthesis via C–H activation



c) This design



Scheme 1 Strategy design for 1*H*-indazole synthesis from aldehyde hydrazones.



Table 2 Scope of the intramolecular C–H/C–H cross coupling of aldehyde hydrazones^{a,b}

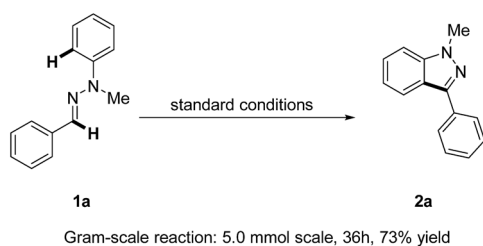


^a Standard conditions. ^b Yields of isolated products.

oxidative C–H/C–H cross coupling reaction.⁹ Importantly, hetero-aldehyde derived aldehyde hydrazones such as furan and thiophene also exhibit good reactivity, providing the expected products in moderate to good yields (**2q–s**).

Unfortunately, the aliphatic aldehyde-derived or alkyl-substituted alkenyl aldehyde hydrazones decomposed and failed to give the desired product under our reaction conditions. The broad substrate scope of this reaction was further illustrated by altering the substitution patterns on the aryl-hydrazine unit (**2u–x**). When *meta*-substituted substrates underwent the oxidative coupling reaction, the C–H activation occurred at both positions with moderate regioselectivities (**2u–v**).

Remarkably, a gram-scale reaction of **1a** could still be transformed into the product **2a** in a good yield (73%) under standard reaction conditions, thus making our strategy for 1*H*-indazole synthesis more attractive and robust (Scheme 2).



Scheme 2 Gram-scale synthesis of 1*H*-indazole **2a**.

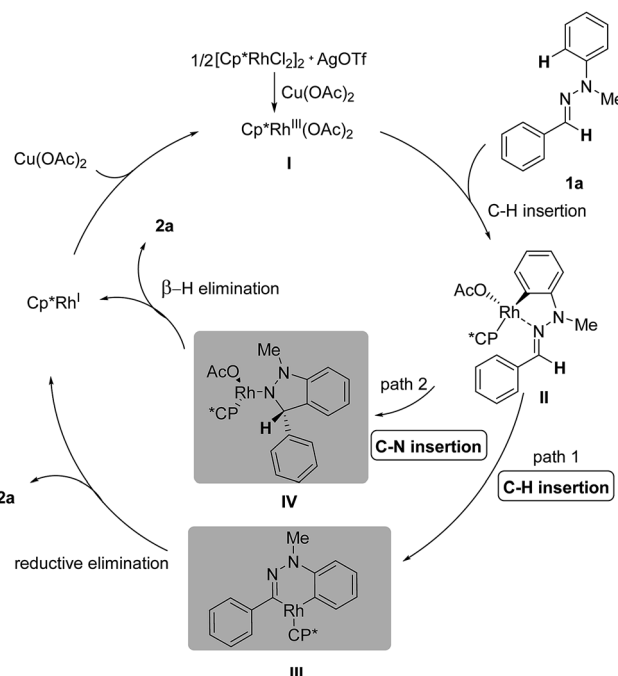
Table 3 Representative synthesis of the bioactive fused polycyclic 1*H*-indazole skeleton^{a,b}



^a Standard conditions. ^b Yield of isolated products.



Scheme 3 Deuterium labeling experiment.



Scheme 4 Proposed mechanism.



To further demonstrate the unique advantages of our reaction, we applied our synthetic strategy to the rapid synthesis of certain significant and bioactive 1*H*-indazole scaffolds (Table 3), which show special 5-HT₄/5-HT₃ receptor antagonist activity.¹⁰ With readily available tetrahydroquinoline and benzo[*b*][1,4]oxazine as starting materials, a simple four-step sequence including *N*-nitrosation, reduction, condensation with aldehyde and Rh(III)-catalyzed intramolecular oxidative C–H/C–H cross coupling could concisely furnish the desired 1*H*-indazole scaffolds in moderate overall yields. It is worth mentioning that this kind of 1*H*-indazole scaffold could not be accessed *via* previous

reported synthetic strategies. The X-ray single-crystal structure analysis of the 1*H*-indazole **4f** is shown in Table 3.

To gain insight into this Rh(III)-catalyzed oxidative C–H/C–H cross coupling reaction, a deuterium labeling experiment with **1j-d₃** was carried out (Scheme 3). Deuterium losses both in the product and reclaimed substrate were observed, suggesting the process involved an initial reversible C–H bond metalation. In addition, the identification of C–H bond deuteration at the *ortho*-position of the C-aryl rings (both product and substrate) provides an evidence for the initial two competitive coordination sites with the C=N–N system as the directing group.

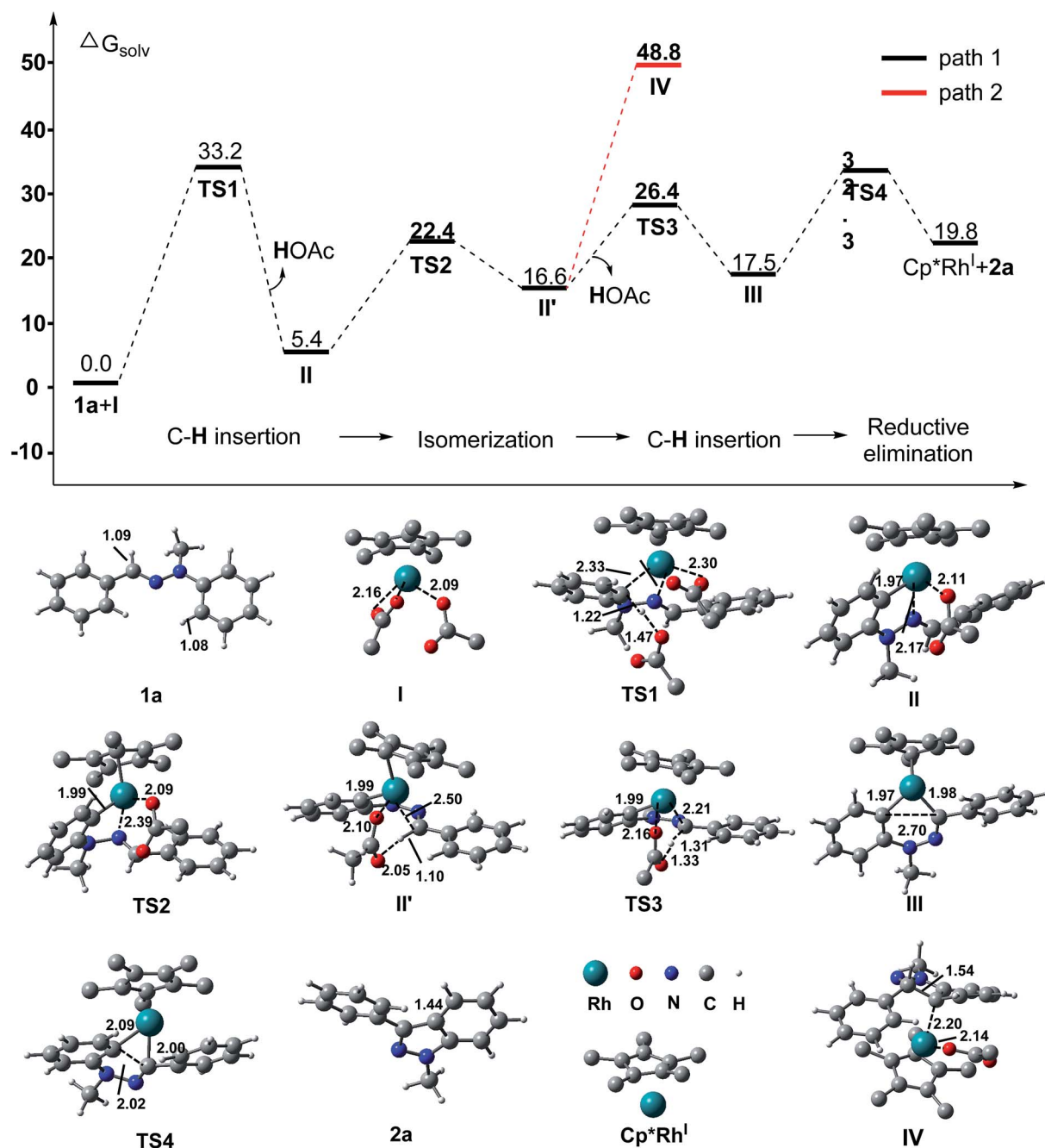


Fig. 1 Computed Gibbs free energy (in kcal mol⁻¹) profile for the reaction between the hydrazone **1a** and active catalyst **I** in the solvent (1,2-dichloroethane). Distances are in Å.



However, valuable and convincing KIE data for this intramolecular double C–H activation process can be obtained with difficulty *via* experiments to study the rate-limiting process.

Based on the preliminary studies, the mechanism of this Rh(III)-catalyzed oxidative C–H/C–H cross coupling is proposed in Scheme 4. In the presence of catalytic AgOTf and an equivalent of Cu(OAc)₂, Rh(III)Cp*⁺(OAc)₂ **I** is generated *in situ* as an active catalyst. The transformation is initiated through the coordination of the nitrogen atom of the C=N bond to the cationic Rh center and subsequent C(aryl)–H activation, generating the five-membered rhodacyclic complex **II**.⁸ Then the active intermediate serves as a reactive linkage for the second C(sp²)–H bond insertion,¹¹ resulting in the six-membered rhodacyclic complex **III** (path 1). Final reductive elimination will give the desired 1*H*-indazole **2a** and Rh(I), which can be oxidized by Cu(II) to regenerate the active Rh(III) catalyst. However, another mechanism, which involves C=N bond insertion¹² rather than C–H bond insertion, is also possible at this stage (path 2). The resulting polar C(aryl)–Rh bond in the first step can serve as a nucleophilic aryl source and undergo nucleophilic addition to the C=N bond, forming the N–Rh species **IV**. Under the basic conditions, the N–Rh species then undergoes β-H elimination to furnish the desired product **2a**.

Furthermore, density functional theory (DFT) calculations were performed to investigate the detailed mechanism of this Rh(III)-catalyzed oxidative C–H/C–H cross coupling reaction; two possible reaction pathways are proposed in Scheme 4, and the free energy profiles are shown in Fig. 1 (see ESI† for details). The active catalyst **I** and hydrazone **1a** were chosen as the model system. First, the coordination of the nitrogen atom of the C=N bond in **1a** to the Rh center and subsequent C(aryl)–H activation⁸ generates the five-membered rhodacyclic intermediate **II** *via* **TS1**, with a barrier of 33.3 kcal mol^{−1}. The formation of intermediate **II** is endothermic by 5.4 kcal mol^{−1}, which is consistent with the deuterium labeling experiment (a reversible C–H bond metalation). Then, the N–N bond rotation of intermediate **II** forms the rotation isomer **II'** *via* **TS2**, with a barrier of 22.4 kcal mol^{−1}. Subsequently, the second C(aldehyde)–H bond activation of the **II'** intermediate assisted by an acetate yields the 16-electron six-membered rhodacyclic complex **III** *via* **TS3** (with a barrier of 26.4 kcal mol^{−1}), releasing an acetic acid molecule. Finally, the reductive elimination of the intermediate **III** gives the desired 1*H* indazole (**2a**) and Rh(I) intermediate (Cp*⁺Rh(I)) *via* **TS4**, with a barrier of 32.3 kcal mol^{−1} (path 1, black lines). The generation of Cp*⁺Rh(I) and **2a** is endothermic by 19.8 kcal mol^{−1} (with respect to the active catalyst **I** and reactant **1a**). This result is consistent with the observed fact that the stoichiometric amount of oxidant (Cu(OAc)₂) and base (K₂CO₃) were required for promoting this reaction. In addition to path 1, path 2 which involves the nucleophilic addition of the C–Rh bond to the C=N bond of species **II'**¹¹ is also possible at this stage (as shown in Scheme 4, path 2). However, all attempts that tried to locate the transition state of the intramolecular nucleophilic addition (or C=N insertion) failed. Nevertheless, we performed a relaxed potential energy scan by fixing the C–C distance at a series of values to estimate the approximate barrier (as shown in Fig. S1†). The generation of the C=N bond

insertion intermediate **IV** is endothermic by 48.8 kcal mol^{−1} (path 2, red lines), which suggests that path 2 can be excluded. Therefore, path 1 which involves the C(aryl)–H metalation/C(aldehyde)–H insertion/reductive elimination sequence is more responsible for the Rh(III)-catalyzed C–H/C–H cross coupling reaction.

Conclusions

In conclusion, an intramolecule directing group strategy has been successfully applied for the C(aldehyde)–H functionalization of aldehyde hydrazones for the first time. Highly functionalized 1*H*-indazoles could be directly accessed from easily available aldehyde phenylhydrazones *via* Rh(III)-catalyzed oxidative C–H/C–H cross coupling. The reaction is scalable and various 1*H*-indazoles can be afforded in moderate to high yields with good functional-group compatibility. A mechanism study indicates this distinctive C–H/C–H cross coupling was enabled by a C(aryl)–H metalation/C(aldehyde)–H insertion/reductive elimination sequence. We believe this new strategy for the C(sp²)–H functionalization of aldehyde hydrazones will be extended to the concise synthesis of other important heterocyclic skeletons.

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