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Rh-Catalyzed Sequential Oxidative C−H and N−N Bond Activation: Conversion of Azines into Isoquinolines with Air at Room Temperature

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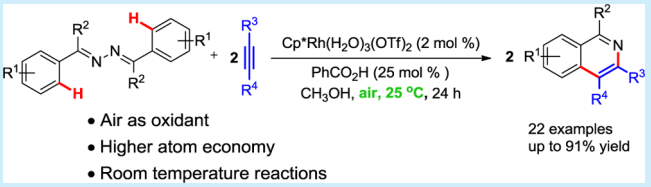
Supporting Information

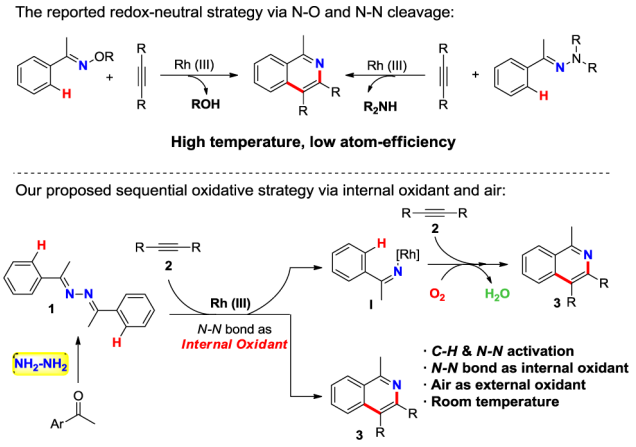
ABSTRACT: A rhodium-catalyzed sequential oxidative C−H annulation reaction between ketazines and internal alkynes has been developed via C−H and N−N bond activation with air as an external oxidant, which led to an efficient approach toward isoquinolines with high atom efficiency at rt. Utilizing the distinctive reactivity of this catalysis, both N-atoms of the azines could be efficiently incorporated to the desired isoquinolines under very robust and mild reaction conditions.



Transition-metal-catalyzed C−C bond coupling reactions via direct C−H bond activation under relatively mild reaction conditions compared to traditional synthetic methods[1] have exemplified the construction advantage of heterocyclic compounds. Among many of them, Rh-catalyzed C−H activation/oxidative coupling reactions are notable for their excellent catalytic efficiency, good functional group tolerance, and value of applications.[2] However, most approaches require the use of superstoichiometric amounts of external oxidants, especially metal salts, to sustain the catalytic turnover, which indisputably results in lower atom efficiency by producing undesired waste byproduct and off-cycle side reactions.[3] To avoid the use of external oxidants, a new strategy employing an internal multifunctional group that acts as both a directing group and an oxidant to regenerate the catalyst has been developed.[4] These remarkable procedures, while taking a large step toward eliminating the need for external oxidants, still require prefunctionalized substrates and suffer from low atom economy since these oxidizing moieties contained in the substrates have never been incorporated to the desired products (Scheme 1). Herein, we report the realization of this goal in the Rh-catalyzed oxidative C−H annulation with ketazines and internal alkynes for synthesizing diverse isoquinolines via sequential C−H and N−N bond activation at rt,[5] wherein the N−N bond was reductively cleaved and both N-atoms of the azines were efficiently incorporated to the desired isoquinolines under mild reaction conditions.

Among the plentiful N−N bond containing compounds, azines ($R_2C{=}N{-}N{=}CR_2$) are very useful compounds. The N−N bond could be reductively cleaved by a redox-active metal complex via metal−ligand cooperation, in which the N−N bond acted as an internal oxidant.[6] This unique feature, coupled with our success in Rh-catalyzed C−H activation/annulation with molecular oxygen as a sole oxidant,[7] led us to envision the possibility of establishing a sequential oxidative catalytic system for the synthesis of isoquinolines[8] by using the N−N bond of azines as an internal oxidant and molecular oxygen as an external oxidant, respectively. We postulated that, in the presence of a catalytic Rh^{III}-complex, a diverse range of ketazines **1**, readily prepared via the reaction of ketone and hydrazine, would first react with one molecule of internal alkyne **2** to afford one molecule of isoquinoline along with a Rh-imide complex via C−H and N−N bond activation. Facile C−H activation and subsequent alkyne insertion/reductive elimination, which leads to the sandwich type Rh^{I}-bond isoquinoline complex, would ideally take place.[7] Oxygen mediated reoxidation of the Rh^{I}-

Scheme 1. A New Strategy for Synthesis of Isoquinolines via C−H and N−N Bond Activation



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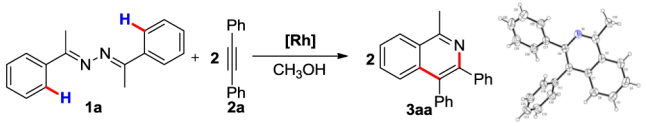
complex in the presence of acid would reconstitute the Rh^{III}-catalyst and deliver the other molecule of the desired isoquinoline product. On the basis of this mechanistic assumption, we recognized that consuming one molecule of azine would give rise to two molecules of isoquinoline and only water was produced as the byproduct in this sequential oxidative C−H and N−N bond activation.

As an initial attempt, the reaction between ketazine **1a** and 1,2-diphenylethyne **2a** in methanol was chosen as the model reaction for optimization of the reaction conditions (Table 1). Because

Table 1. Optimization of the Reaction Conditions[a]



entry	[Rh]	[O]	HX (equiv)	t (°C)	yield (%)
1[b]	$Cp^*Rh(H_2O)_3(OTf)_2$	–	HOAc (1.0)	120	15
2	$Cp^*Rh(H_2O)_3(OTf)_2$	O_2	HOAc (1.0)	120	66
3	$Cp^*Rh(H_2O)_3(OTf)_2$	O_2	HOAc (1.0)	25	56
4	$Cp^*Rh(H_2O)_3(OTf)_2$	O_2	PivOH (1.0)	25	57
5	$Cp^*Rh(H_2O)_3(OTf)_2$	O_2	HOTf (1.0)	25	17
6	$Cp^*Rh(H_2O)_3(OTf)_2$	O_2	$PhCO_2H$ (1.0)	25	65
7	$Cp^*Rh(H_2O)_3(OTf)_2$	O_2	$PhCO_2H$ (0.5)	25	66
8	$Cp^*Rh(H_2O)_3(OTf)_2$	O_2	–	25	27
9	$Cp^*Rh(CH_3CN)_3(OTf)_2$	O_2	$PhCO_2H$ (0.5)	25	61
10	$Cp^*Rh(H_2O)_3(OTf)_2$	air	$PhCO_2H$ (0.5)	25	65
11[b]	$Cp^*Rh(H_2O)_3(OTf)_2$	–	$PhCO_2H$ (0.5)	25	28
12[c]	$Cp^*Rh(H_2O)_3(OTf)_2$	air	$PhCO_2H$ (0.25)	25	70
13[c,d]	$Cp^*Rh(H_2O)_3(OTf)_2$	air	$PhCO_2H$ (0.25)	25	71
14[c,e]	$Cp^*Rh(H_2O)_3(OTf)_2$	air	$PhCO_2H$ (0.25)	25	75

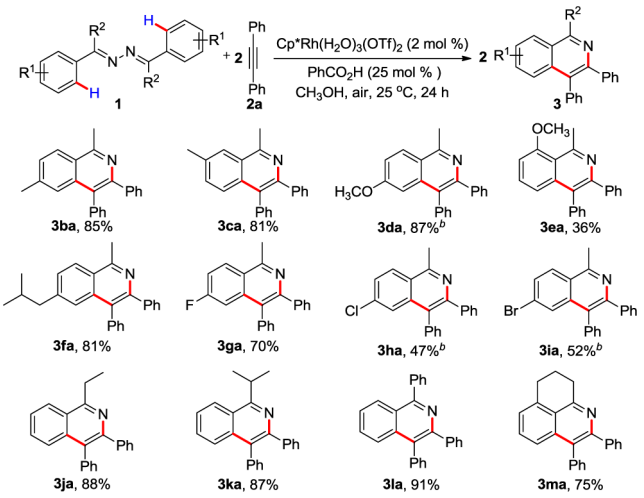
[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.625 mmol), [Rh] (0.01 mmol), HX based on the amount of **1a**, CH_3OH (2 mL), O_2 (1 atm), 24 h, yield of isolated product and based on the amount of ketimine unit. [b]Under vacuum. [c]With **1a** (0.3 mmol) and **2a** (0.5 mmol), [Rh] (0.01 mmol), HX and yield based on the amount of **2a**. [d][Rh] (0.015 mmol). [e]CH_3OH (4 mL).

$Cp^*Rh(H_2O)_3(OTf)_2$ has shown to be highly effective for the oxidative C−H activation/annulation of phenylpyridines and alkynes,[7] we initially focused on exploring conditions using this readily available catalyst at 120 °C. The desired 1-methyl-3,4-diphenylisoquinoline **3aa** was obtained in 15% yield (based on the amount of ketimine unit),[9] when the reaction was conducted in the absence of an external oxidant. This result indicated that our proposed internal oxidative C−H activation/annulation between the ketazine **1a** and internal alkyne **2a** was indeed possible.

To achieve a higher yield, molecular oxygen was introduced into the reaction system under the same reaction conditions and the yield dramatically increased to 66% in the presence of HOAc (1.0 equiv) (Table 1, entry 2). Temperature screening indicated that when the reaction was ran at 25 °C instead of 120 °C, the product was still obtained in 56% yield. We next examined the optimal acids (Table 1, entries 4−8), and the best result (65% yield, Table 1, entry 6) was obtained using benzoic acid. Fortunately, the yield was maintained when the dosage of acid was lowered to 0.5 equiv (Table 1, entry 7).[10] A control reaction in the absence of $PhCO_2H$ failed to give the desired product in high yield (Table 1, entry 8), indicating that the acid is crucial to promoting the molecular oxygen to oxidize Rh^I to regenerate active Rh^{III}.[3a,b,7] Another cationic Rh^{III} species $Cp^*Rh(CH_3CN)_3(OTf)_2$, an efficient catalyst precursor in the C−H activation reaction, gave a slightly lower yield (Table 1, entry 9) under the same reaction conditions. To our great delight, when we performed the reaction under an air atmosphere instead of oxygen, a good yield still resulted (Table 1, entry 10). Further control experimentation demonstrated that only a lower yield of the desired product **3aa** was obtained in the absence of oxygen or air (Table 1, entry 11) under otherwise identical reaction conditions, indicating the crucial role of oxygen in the Rh catalytic cycle and the oxidative efficiency of air. Furthermore, when the ratio of **2a**/**1a** decreased from 5/2 to 5/3, the yield of product **3aa** slightly increased to 70% (based on the amount of **2a**, Table 1, entry 12). Increasing the catalyst loading could not enhance the reaction efficiency obviously (Table 1, entry 13). Finally, lowering the concentration of the reaction could improve the yield to 75% (Table 1, entry 14) owing to the poor solubility of **1a** in methanol.

Encouraged by the optimized results, we started to investigate the substrate scope of this new protocol (Scheme 2). The

Scheme 2. Substrate Scope of Ketazines[a]



[a]General conditions: **1** (0.3 mmol), **2a** (0.5 mmol), $Cp^*Rh(H_2O)_3(OTf)_2$ (0.01 mmol, 2 mol %), $PhCO_2H$ (0.125 mmol, 25 mol %), CH_3OH (4 mL), air, 25 °C, 24 h. Yield of isolated product and based on the amount of **2a**. [b] CH_3OH/CH_2Cl_2 = 1:1 (4 mL).

optimized reaction conditions were compatible to a broad range of ketazines derived from substituted acetophenones. For the reactions of acetophenone azines, having electron-donating groups at the *para* position of the phenyl ring (e.g., methyl, methoxy, isobutyl), with **2a**, the desired products were afforded (**3ba**, **3da**, and **3fa**) in good yields (81%−87%). The *meta* methyl substituted substrate also gave a regioselective product in good yield (**3ca**). However, the *ortho* methoxy substituted substrate led to a rather lower yield. This was plausibly ascribed to the steric hindrance of the *ortho* position (**3ea**). Electron-withdrawing groups (e.g., F, Cl, Br) at the same positions resulted in lower yields (**3ga**−**3ia**), which might result from their poor

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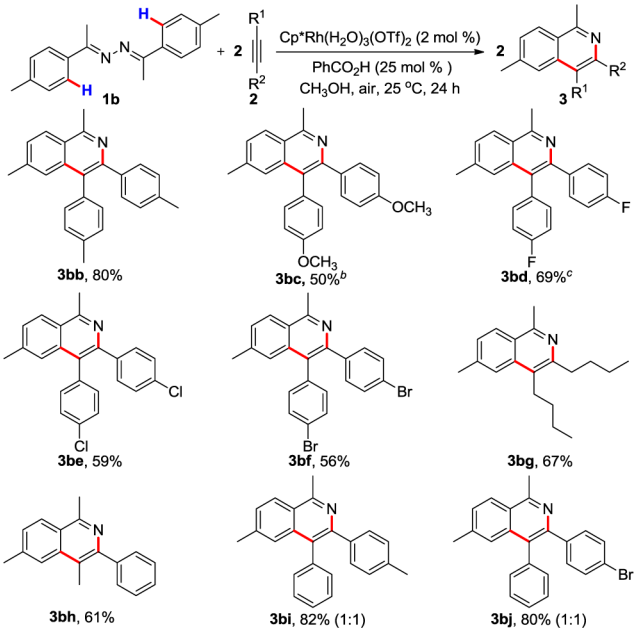
solubility in methanol. In addition to acetophenone derived ketazines, alkyl aryl ketones such as benzophenone and α-tetralone derived ketazines (**3ja**−**3ma**) also proceeded well to give the corresponding products in good to excellent yields (75−91% yields) under the standard reaction conditions.

After investigating the scope of substitution features of the ketazines, the scope of this sequential oxidative C−H activation/annulation with respect to the alkynes was also surveyed. As summarized in Scheme 3, the annulation reaction of 4-

Scheme 3. Substrate Scope of Alkynes[a]



[a]General conditions: **1b** (0.3 mmol), **2** (0.5 mmol), Cp*Rh-$(H_2O)_3(OTf)_2$ (0.01 mmol, 2 mol %), $PhCO_2H$ (0.125 mmol, 25 mol %), CH_3OH (4 mL), air, 25 °C, 24 h. Yield of isolated product and based on the amount of **2**. [b] Cp*Rh$(H_2O)_3(OTf)_2$ (0.02 mmol, 4 mol %), 36 h. [c] CH_3OH/CH_2Cl_2 = 1:1 (4 mL).

methylacetophenone azine with alkynes catalyzed by the Cp*Rh$(H_2O)_3(OTf)_2$ was found to be general with diaryl alkynes bearing a variety of substituents (**3bb**−**3bf**). Typical functional groups, such as methoxy and halide groups, were compatible with the reaction conditions, which offered an opportunity for subsequent transformation via transition-metal catalysis. An aliphatic internal alkyne was also compatible under the standard reaction conditions, achieving the expected product **3bg** in 67% yield. An aryl alkyl alkyne, such as prop-1-ynylbenzene, was also suitable for this reaction, affording the expected product **3bh** in moderate yield with excellent regioselectivity. Furthermore, the reactions of unsymmetric substituted diaryl alkynes were also investigated. Mono 4-methyl and 4-Br substituted diphenylacetylenes gave the corresponding isoquinolines in 82% and 80% yields with lower regioselectivities.

A possible mechanism for the present sequential oxidative C−H and N−N bond activation/annulation is shown in Figure 1. Initial coordination of ketazine **1a** to Cp*Rh$(H_2O)_3(OTf)_2$ and *ortho* arene C−H bond activation take place, generating the five-membered rhodacycle complex **I**. After ligand exchange to form intermediate **A**, insertion of the alkyne into the Rh−C bond of **A** gives the seven-membered rhodacycle intermediate **B**. Subsequent reductive elimination and N−N bond cleavage release a five-membered rhodacycle complex **II** and give the desired

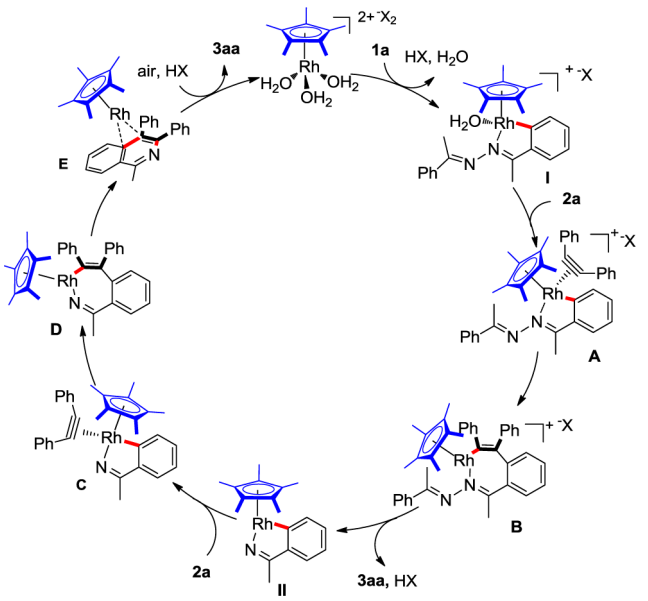


Figure 1. Proposed mechanism.

product **3aa**. Then the other molecule of **2a** coordinates to complex **II** followed by insertion into the Rh−C bond of complex **C**, affording the seven-membered rhodacycle complex **D**. Finally reductive elimination from **D** gives rise to the sandwich type Rh^{I}-complex **E**, which is reoxidized by air in the presence of acid to release the other molecule of **3aa** and regenerate the active catalyst for the next catalytic cycle.

Further strong evidence for supporting the above mechanism was stemmed from the ESI-MS studies (see Supporting Information). After stirring the mixture of the ketazine **1a** and Cp*Rh$(H_2O)_3(OTf)_2$ (10 mol %) in methanol at 60 °C under a nitrogen atmosphere for 2.5 h, the unreacted ketazine **1a** was removed by filtration and the resulting solution was analyzed by HRMS analysis. A strong peak at m/z = 473.1463 was observed, which could be attributed to the corresponding rhodacycle complex [**I**−X]. Furthermore, two peaks of m/z = 356.0889 and 534.1678 were successfully detected when alkyne **2a** was introduced into the above reaction mixture at rt under a nitrogen atmosphere. These two peaks could be assigned as [**II**+H] and [**D**+H] or [**E**+H], respectively.

In summary, we have successfully developed a novel simple method for the assembling of ketone, alkyne, and hydrazine via a Rh-catalyzed C−H and N−N bond activation, which led to establishing an efficient approach toward isoquinolines. Utilizing the distinctive reactivity of this catalysis, both N-atoms of the ketazine could be efficiently incorporated to the desired isoquinolines under very mild reaction conditions. The method is very simple and can be efficiently performed in an open vessel at rt without the addition of external co-oxidants, which is among the mildest reaction conditions for the reported oxidative C−H activation reactions.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, structural assignment, and NMR spectra for all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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