Communication

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An Efficient Rh/O_2-Catalytic System for Oxidative C-H Activation/Annulation: Evidence for Rh(I) to Rh(III) Oxidized by Molecular Oxygen

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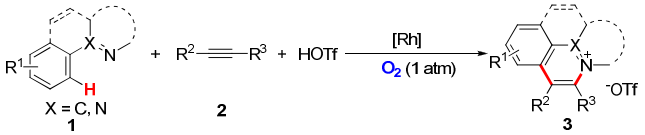
Supporting Information Placeholder

ABSTRACT: A novel and efficient Rh/O_2-catalytic system has been developed and shown to catalyze highly efficient oxidative C-H activation/annulation reactions, producing a broad range of isoquinolinium salts in high TON (740). Mechanistic studies provide evidence to strongly support that molecular oxygen could facilely oxidize the Rh (I) to Rh(III) facilitated by acid.

Transition-metal-catalyzed oxidative C-H bond functionalization has emerged as a powerful tool for the step-economical construction of C-C bonds in modern organic chemistry. Mechanistically, the metal-mediated oxidative C-H functionalization is usually initiated from higher oxidation state of the metal catalyst and ended in lower oxidation state.[1] As a result, stoichiometric oxidants are generally required to sustain the catalytic cycle. Consequently, varieties of oxidants, such as peroxide, metal oxidant are used in such process, thus resulting in the generation of undesired waste, especially when metal oxidants are used. One attractive approach to circumvent this problem is using O_2 as a sole oxidant, in which only water is produced as a co-product.[2] Indeed, O_2 has been successfully used as a sole oxidant for some transition metal catalyzed C-H activation reactions.[2-3] However, to the best of our knowledge, the Rh-catalyzed oxidative C-H functionalization with O_2 as a sole oxidant has never been reported.[4]

Isoquinolinium salts are one of the most valuable backbones in natural alkaloids and widely utilized in industrial field, such as dyes, paints, insecticides, as well as pharmaceuticals.[5] Although a number of methods are available for the synthesis of such compounds, many are limited by the lack of generality, functional group tolerance and lengthy synthetic steps.[6] In 2008, Jones developed a novel reaction towards this kind of compounds with 2-phenylpyridine, *N*-benzylidenemethylamine and DMAD via Rh-mediated C-H activation, in which a stoichiometric amount of [{Cp*RhCl$_2$}$_2$] was required.[7] Inspired by this work, the catalytic oxidative coupling of alkynes with in situ formed *N*-benzylidenemethylamines has been established in the presence of catalytic amount of rhodium or ruthenium (5-10 mol%).[8] However, the stoichiometric amount of silver salts and copper salts were still required to sustain the catalytic cycle, which led to lower atom economy and reduced the appeal of rhodium-catalyzed oxidative couplings and hindered large-scale applications. Hence, efficient method enables O_2 as a sole oxidant to sustain the Rh-catalytic cycle would circumvent the need for stoichiometric metal oxidant, and thereby provide an important C-H functionalization protocol for synthesis of isoquinolinium salts. Herein, we describe a novel Rh/O_2 catalytic system that is efficient for the oxidative coupling of 2-aryl pyridines and alkynes. Mechanistic studies have disclosed that oxygen acts as a sole oxidant in the present reaction to efficiently promote the Rh(I) to Rh(III).

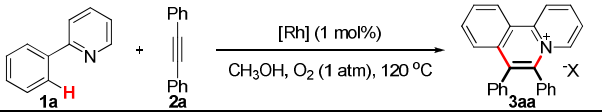
Scheme 1. Rh-catalyzed Oxidative Annulation under Molecular Oxygen



With these considerations in mind, an annulation reaction between 2-phenylpyridine **1a** and 1,2-diphenylethyne **2a** in CH_3OH at 120 °C was chosen as the model reaction to investigate the optimized reaction conditions. [{Cp*RhCl$_2$}$_2$] was firstly used as catalyst precursor for searching the optimal oxidant (Table 1, entries 1-7). The combined oxidants system consisted of stoichiometric Cu(OTf)$_2$ and catalytic amount of AgOTf (4 mol%) could readily promote the reaction to afford the desired product **3aa** in high yield under argon atmosphere (Table 1, entry 1). The structure of **3aa** was confirmed to contain a pyridoisoquinolinium cation and an OTf anion by single-crystal X-ray analysis.[9] With stoichiometric AgOTf alone, the reaction could also give high yield (Table 1, entry 2). These results suggested that both Cu(OTf)$_2$ and AgOTf were suitable as oxidants for this C-H functionalization. However, the reaction virtually stopped with stoichiometric Cu(OTf)$_2$ as oxidant, which indicated that the reaction was most likely initiated with the cationic Cp*Rh(III) species formed *in situ* by reaction of [{Cp*RhCl$_2$}$_2$] with AgOTf. To our delight, almost quantitative yield (99% yield) was obtained when O_2 was served as terminal oxidant and the reaction was conducted in the presence of one equivalent of HOTf with catalytic amount of AgOTf as an additive (Table 1, entry 4). Similar good results were observed when reactions were conducted in the presence of CF_3CO_2Ag/TFA and

AgOTs/HOTs under aerobic conditions, respectively (Table 1, entries 6-7). Further investigation of the rhodium catalyst precursors demonstrated that the cationic Rh(III) species were effective for this reaction and the best results could be achieved with $Cp^*Rh(H_2O)_3(OTf)_2$ as the catalyst in the presence of one equivalent of acid under the aerobic conditions (Table 1, entries 8-11). Control reactions demonstrated that only trace amount of the annulation product **3aa** was obtained in the absence of acid, indicating the importance of acid (Table 1, entry 12). Finally, when the catalyst loading was lowered from 1 to 0.2 mol%, the reaction still worked well and gave the identical high yield of the annulation product (Table 1, entry 13). Further decreasing the catalyst loading to 0.1 mol%, the desired product **3aa** was obtained with 74% yield in prolonged reaction time under other identical conditions. Notably, this result represents a TON of 740, which is among the highest reported for oxidative C-H activation reaction.[10]

Table 1. Optimization of Reaction Conditions [a]

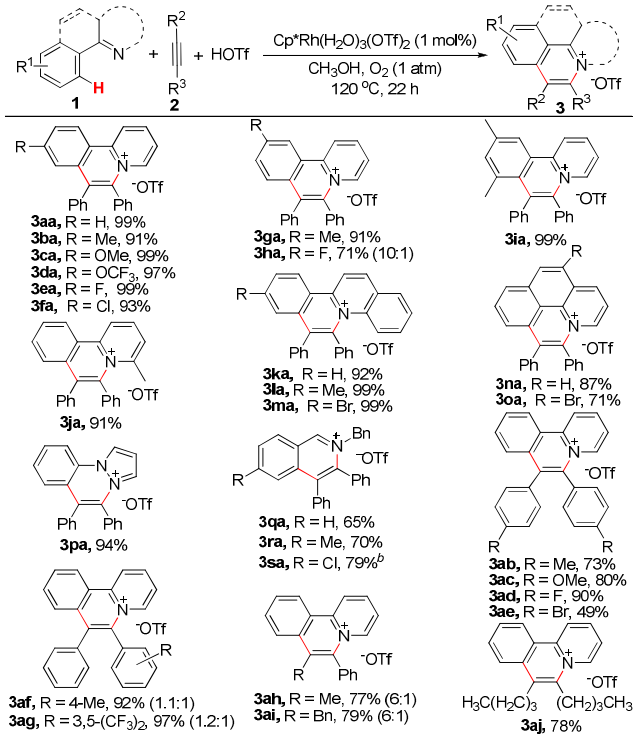


Entry	[Rh]	MX (equiv)	HX	Yield (%)
1	$[\{RhCp^*Cl_2\}_2]$	AgOTf (0.04)/$Cu(OTf)_2$ (1)	-	91[b]
2	$[\{RhCp^*Cl_2\}_2]$	AgOTf (1)	-	96[c]
3	$[\{RhCp^*Cl_2\}_2]$	$Cu(OTf)_2$ (1)	-	<5[d]
4	$[\{RhCp^*Cl_2\}_2]$	AgOTf (0.04)	HOTf	99
5	$[\{RhCp^*Cl_2\}_2]$	AgOAc (0.04)	HOAc	<5
6	$[\{RhCp^*Cl_2\}_2]$	CF_3CO_2Ag (0.04)	TFA	75
7	$[\{RhCp^*Cl_2\}_2]$	AgOTs (0.04)	HOTs	99
8	$Cp^*Rh(H_2O)_3(OTf)_2$	-	HOTf	99
9	$Cp^*Rh(CH_3CN)_3(OTf)_2$	-	HOTf	95
10	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	-	HOTf	84
11	$Cp^*Rh(H_2O)_3(OTf)_2$	-	HOTs	94
12	$Cp^*Rh(H_2O)_3(OTf)_2$	NaOTf (1)	-	8
13	$Cp^*Rh(H_2O)_3(OTf)_2$	-	HOTf	99[e]
14	$Cp^*Rh(H_2O)_3(OTf)_2$	-	HOTf	74[f]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), catalyst (0.005 mmol), HX (0.5 mmol), CH_3OH (2.0 mL), O_2 (1 atm), 120 °C for 22 h, isolated yield, unless otherwise noted. [b] AgOTf (0.02 mmol), $Cu(OTf)_2$ (0.5 mmol), under argon atmosphere. [c] AgOTf (0.5 mmol), under argon atmosphere. [d] $Cu(OTf)_2$ (0.5 mmol), under argon atmosphere. [e] $Cp^*Rh(H_2O)_3(OTf)_2$ (0.2 mol%), 4 days. [f] $Cp^*Rh(H_2O)_3(OTf)_2$ (0.1 mol%), 8 days.

With these results in hand, we next investigated the substrate scope of this transformation. As shown in Table **2**, for 2-phenylpyridines, a series of functional groups, such as methyl, methoxyl, trifluoromethoxyl, fluoro and chloro, contained in the phenyl-ring were compatible with the present Rh/O_2 catalytic system, and the desired products were isolated in excellent yields (**3aa-3ia**), which indicated that the present reaction had a good functional-group tolerance. The reaction of 2-*meta*-tolylpyridine **1g** and 1,2-diphenylethyne afforded a single regioisomer **3ga**. However, the reaction of 2-(3-fluorophenyl)pyridine **1h** afforded **3ha** as a mixture of regioisomers in a ratio of 10:1. These results suggest that the rhodium attacks selectively the sterically less hindered C-H bond of the phenyl ring. In addition to phenylpyridine, the reactions of phenylquinolines also proceeded well, affording the corresponding products in good to excellent yields (**3ka-3ma**). The electron-donating and electron-withdrawing groups contained in the phenyl ring were tolerated well. Furthermore, when benzo[h]quinoline and 5-bromobenzo[h]quinoline were subjected to this procedure, 87% and 71% yield of the annulation products were isolated, respectively (**3na**, **3oa**), which revealed that the quinoline could functionalize as useful direction group for this C-H activation. Moreover, 1-phenyl-1H-pyrazole could also provide the desired product **3pa** in excellent yield under the standard conditions. It is worth noting that *N*-benzylidene-1-phenylmethanamine derivatives are usable for the present reaction, affording the corresponding products **3qa-3sa** in decent yields as well.

Table 2. Substrate Scope of Rh-catalyzed annulation [a]



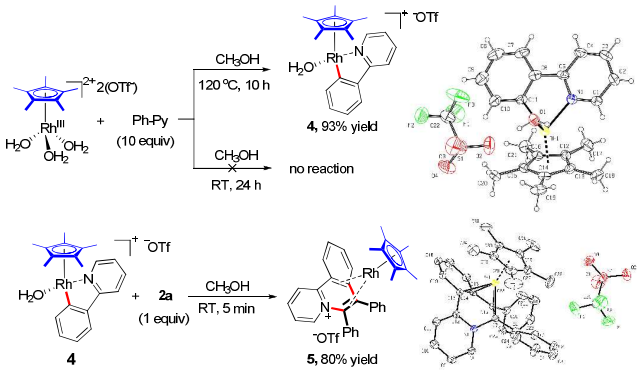
[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), HOTf (0.5 mmol), $Cp^*Rh(H_2O)_3(OTf)_2$ (1 mol%), CH_3OH (2.0 mL), O_2 (1 atm), at 120 °C for 22 h. Isolated yield. Ratios of regioisomers are given within parentheses and were determined by NMR analysis. Major isomers are shown. [b] $Cp^*Rh(H_2O)_3(OTf)_2$ (2 mol%), 36 h.

On the other hand, diarylalkynes containing various electron-rich and electron-deficient functional groups reacted smoothly to give the corresponding products in high yields (**3ab-3ag**). Typical functional groups such as methoxyl and halide groups were compatible with the reaction conditions. The aryl alkyl alkynes such as **2h-2i** were also suitable for this reaction, affording the corresponding products (**3ah-3ai**) in high yields. Furthermore, the challenging dialkyl alkyne **2j** successfully underwent this annulation reaction to provide the desired product **3aj** in 78% yield. The unsymmetrical alkynes gave the desired products in high yields with moderate regioselectivity (**3af-3ai**), revealing that the rhodium selectively attacked the less hindered position of alkynes.

To gain insight into the reaction mechanism, several experiments for forming cyclometalated rhodium complexes were conducted. The desired five-membered cyclometalated Rh(III) complex **4** was isolated in almost

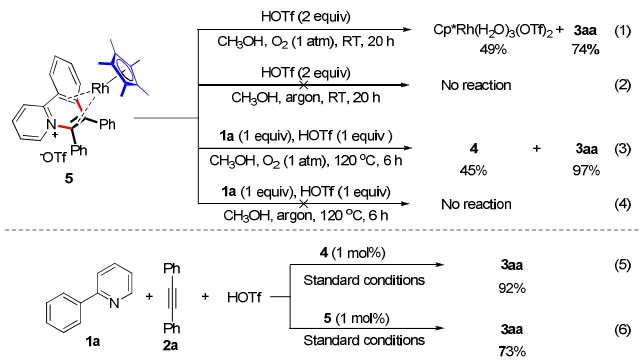
quantitative yield, when treating $Cp^*Rh(H_2O)_3(OTf)_2$ with ten equivalents of **1a** in CH_3OH at 120 °C for 10 hours (Scheme 2, top). The structure of **4** was characterized by X-ray crystallography[9] and high-resolution mass spectrometry (see the Supporting Information). However, no any desired rhodium complex was detected when the same reaction conducted at room temperature for 24 hours. These results indicate that high temperature is required for the cleavage of C-H bond of the phenyl ring. Further reaction of **4** with 1,2-diphenylalkyne at room temperature could quickly lead to formation of air stable complex **5** in five minutes (Scheme 2, bottom). The unique sandwich structure of **5** was confirmed by X-ray crystallography,[9] in which the pyridoisoquinolinium moiety are bound to the rhodium-center through η^4-coordination. These results indicate that the Rh(III)-Rh(I)-Rh(III) catalytic cycle was most likely involved in the present catalytic reaction.

Scheme 2. Synthesis of Complex 4 (top) and complex 5 (bottom)



After confirming that **4** could be facilely converted to **5**, we proceeded to execute a set of experiments for elucidating the catalytic cycle of the present reaction. As shown in Scheme **3**, the final product **3aa** together with $Cp^*Rh(H_2O)_3(OTf)_2$ were obtained when the sandwich type Rh(I)-complex **5** was treated with HOTf in CH_3OH under O_2 atmosphere at room temperature for 20 hours (Scheme 3, Eq 1). However, the reaction was virtually stopped when the same reaction was conducted in the absence of O_2 (Scheme 3, Eq 2). In addition, the complex **5** quantitatively converted to the desired product **3aa** with formation of **4** in 6 hours by reaction with one equivalent of **1a** and HOTf under the aerobic conditions.

Scheme 3. Preliminary Mechanistic Studies



No reaction occurred when the same reaction was performed in the absence of O_2 (Scheme 3, Eqs 3-4). These trials provided evidences that O_2 has the ability to oxidize the sandwich type Rh(I) species to the Rh(III) species in presence of acid even at room temperature. The higher activity of **5** that is prone to be oxidized by molecular oxygen in the present aerobic oxidation is partially attributed to the special sandwich structure, in which the redox potential of the corresponding Rh(I) can be increased by the η^4-coordination. Finally, both **4** and **5** could catalyze the aerobic C-H activation/annulation between **1a** and **2a** to give **3aa** in high yield under the standard conditions, suggesting the plausible intermediacy of **4** and **5** in the catalytic cycle (Scheme 3, Eqs 5-6).

On the basis of the results described above and the precedented reports,[4n, 7] a tentative reaction mechanism for this aerobic C-H activation/annulation reaction is exemplified in Figure **1**. The initial coordination of 2-phenylpyridine to the $Cp^*Rh(H_2O)_3(OTf)_2$ and the *ortho* C-H bond activation take place to generate the five-membered rhodacycle complex **4,** which is the rate-limiting step of the reaction.[11] After ligand exchange to form **A**, the regioselective insertion of alkyne into the rhodium-carbon bond of intermediate **A** gives the seven-membered rhodacycle intermediate **B**. The subsequent reductive elimination of **B** releases the complex **5**, which is re-oxidized by molecular oxygen in the presence of HOTf to regenerate the active catalyst for the next catalytic cycle and give rise to the desired product **3aa**.

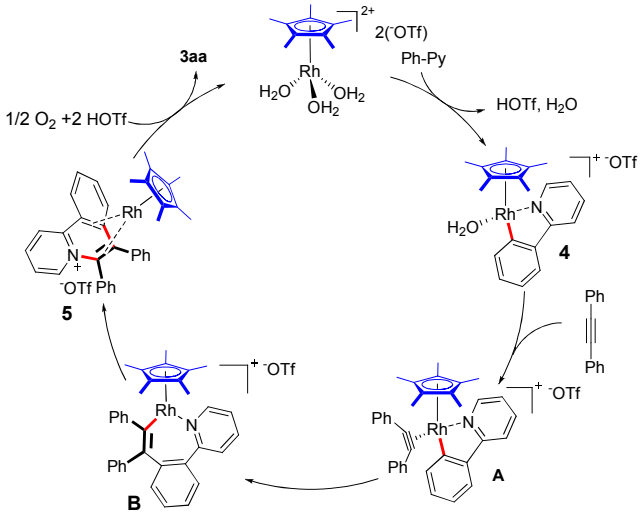


Figure 1. Proposed Reaction Pathway

In summary, we have successfully developed a new and efficient rhodium-catalyzed protocol for synthesis of isoquinolinium salts from the reaction between arenes and alkynes through oxidative C-H bond activation and annulation. Notably, this rhodium-catalyzed aerobic oxidative C-H activation exhibits high reactivity (up to 740 TON), which represents the first Rh/O_2 catalytic system for highly efficient oxidative C-H activation with lower catalyst loading. Furthermore, the discovery of the facile oxidation of Rh(I) to Rh(III) with molecular oxygen would pave the way for establishing some new and efficient Rh-catalyzed oxidative C-H activation reactions. Further investigations on application of the Rh/O_2 system in other oxidative C-H activation reactions are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information. Experimental details and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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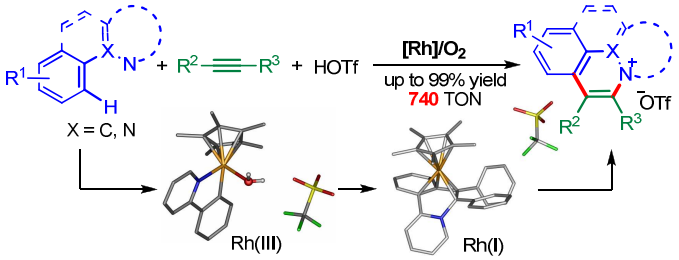
(9) CCDC 932849 (**3aa**), 932850 (**5**) and 932851 (**4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(10) Highest TON of 762 was obtained in Pd-catalyzed oxidative Heck reaction. see: Dams, M.; DeVos, D. E.; Celen, S.; Jacobs, P. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3512.

(11) The kinetic isotope effects observed in both intramolecular (k_H/k_D=4.1) and intermolecular (k_H/k_D=4.2) competition experiments together with the results of stoichiometric reactions (Scheme 3) suggested that the C-H cleavage was most likely involved in the rate-limiting step. See Supporting Information for details.


X = C, N
+ HOTf
[Rh]/O2
up to 99% yield
740 TON
OTf
Rh(III)
Rh(I)