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

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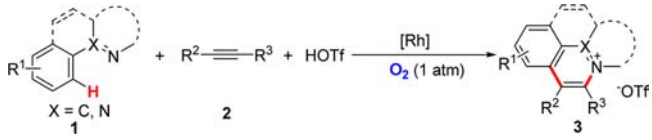
Supporting Information

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 with high turnover numbers (up to 740). Mechanistic studies provided strong evidence of facile oxidation of Rh(I) to Rh(III) by molecular oxygen 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, metal-mediated oxidative C−H functionalization is usually initiated from the higher oxidation state of the metal catalyst and ends with the metal in the lower oxidation state.[1] As a result, stoichiometric oxidants are generally required to sustain the catalytic cycle. A variety of oxidants have been used in this process, such as peroxide and metal oxidants, thus resulting in the generation of undesired waste, especially with metal oxidants. One attractive approach to circumvent this problem is to use O_2 as the sole oxidant, producing only water as a coproduct.[2] Indeed, O_2 has been successfully used as the sole oxidant for some transition-metal-catalyzed C−H activation reactions.[2,3] However, to the best of our knowledge, Rh-catalyzed oxidative C−H functionalization with O_2 as the sole oxidant has never been reported.[4]

Isoquinolinium salts are one of the most valuable backbones in natural alkaloids and are widely utilized as dyes, paints, and insecticides as well as pharmaceuticals.[5] Although a number of methods for the synthesis of such compounds are available, many are limited by the lack of generality, narrow functional group tolerance, and lengthy synthetic steps.[6] In 2008, Jones developed a novel reaction leading to these compounds using 2-phenylpyridine, *N*-benzylidenemethylamine, and dimethyl acetylenedicarboxylate (DMAD); the reaction proceeds via Rh-mediated C−H activation and requires a stoichiometric amount of [{Cp*$RhCl_2$}$_2$].[7] Inspired by this work, Cheng developed a catalytic oxidative coupling of alkynes with in situ-formed *N*-benzylidenemethylamines in the presence of a catalytic amount of rhodium or ruthenium (5−10 mol %).[8] However, stoichiometric amounts of silver salts and copper salts were still needed to sustain the catalytic cycle, leading to lower atom economy. This has reduced the appeal of Rh-catalyzed oxidative couplings and hindered large-scale applications. Hence, an efficient method enabling O_2 to be used as the sole oxidant to sustain the Rh catalytic cycle would circumvent the need for a stoichiometric metal oxidant, thereby providing an important C−H functionalization protocol for the synthesis of isoquinolinium salts. Herein we describe a novel Rh/O_2 catalytic system that is efficient for the oxidative coupling of 2-arylpyridines and alkynes (Scheme 1). Mechanistic studies disclosed that oxygen acts as the sole oxidant in the present reaction, efficiently promoting Rh(I) to Rh(III).

Scheme 1. Rh-Catalyzed Oxidative Annulation under O_2



With these considerations in mind, the annulation reaction between 2-phenylpyridine (**1a**) and 1,2-diphenylethyne (**2a**) in CH_3OH at 120 °C was chosen as the model reaction for optimization of the reaction conditions (Table 1). [{Cp*$RhCl_2$}$_2$] was first used as the catalyst precursor to search for the optimal oxidant (entries 1−7). The combined oxidant system consisting of stoichiometric Cu(OTf)$_2$ and a catalytic amount of AgOTf (4 mol %) readily promoted the reaction, affording the desired product **3aa** in high yield under an argon atmosphere (entry 1). Single-crystal X-ray analysis confirmed that the structure of **3aa** contains a pyridoisoquinolinium cation and an OTf anion.[9] With stoichiometric AgOTf alone, the reaction also gave a high yield (entry 2). These results suggested that both Cu(OTf)$_2$ and AgOTf are suitable as oxidants for this C−H functionalization. However, the reaction virtually stopped with stoichiometric Cu(OTf)$_2$ as the oxidant, indicating that the reaction is most likely initiated with the cationic Cp*Rh(III) species formed in situ by the reaction of [{Cp*$RhCl_2$}$_2$] with AgOTf. To our delight, an almost quantitative yield (99%) was obtained when O_2 was used as the terminal oxidant and the reaction was conducted in the presence of 1 equiv of HOTf with a catalytic amount of AgOTf as an additive (entry 4). Similar good results were observed when the reaction was conducted in the presence of CF_3CO_2Ag/trifluoroacetic acid (TFA) and AgOTs/HOTs under aerobic conditions (entries 6 and 7). Further

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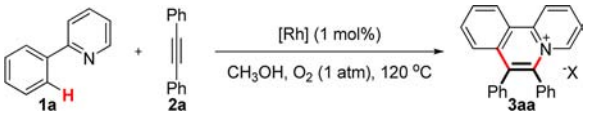
Table 1. Optimization of the Reaction Conditions[a]



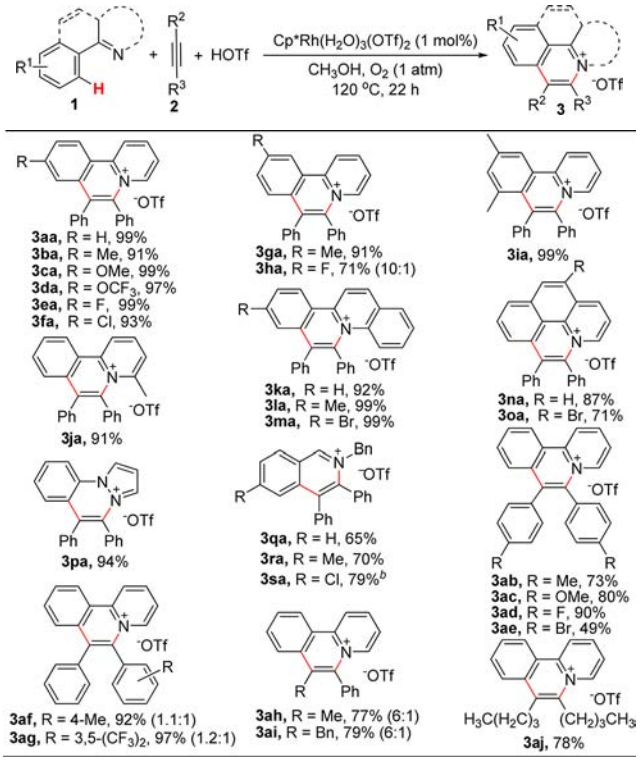
entry	[Rh]	MX(equiv)	HX	yield (%)
1	$[\{RhCp^*Cl_2\}_2]$	AgOTf (0.04)/ $Cu(OTf)_2$(1)	–	91[b]
2	$[\{RhCp^*Cl_2\}_2]$	AgOTf(1)	–	96[c]
3	$[\{RhCp^*Cl_2\}_2]$	$Cu(OTf)_2$(1)	–	<5[d]
4	$[\{RhCp^*Cl_2\}_2]$	AgOTf (0.04)	HOTf	99
5	$[\{RhCp^*Cl_2\}_2]$	AgOAc (0.04)	HOAc	<5
6	$[\{RhCp^*Cl_2\}_2]$	CF_3CO_2Ag (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, 22 h, unless otherwise noted. Isolated yields are shown. [b]AgOTf (0.02 mmol), $Cu(OTf)_2$ (0.5 mmol), under Ar atmosphere. [c]AgOTf (0.5 mmol), under Ar atmosphere. [d]$Cu(OTf)_2$ (0.5 mmol), under Ar 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.

investigation of the rhodium catalyst precursor demonstrated that cationic Rh(III) species were effective for this reaction, and the best results were achieved with $Cp^*Rh(H_2O)_3(OTf)_2$ as the catalyst in the presence of 1 equiv of acid under aerobic conditions (entries 8–11). A control reaction demonstrated that only a trace amount of the annulation product **3aa** was obtained in the absence of acid (entry 12), indicating the importance of acid. Finally, when the catalyst loading was lowered from 1 to 0.2 mol %, the reaction still worked well, giving the identical high yield of the annulation product (entry 13). When the catalyst loading was further decreased to 0.1 mol %, **3aa** was obtained in 74% yield with a prolonged reaction time under otherwise identical conditions (entry 14). Notably, this result represents a turnover number (TON) of 740, which is among the highest reported for oxidative C–H activation reactions.[10]

With these results in hand, we next investigated the substrate scope of this transformation. (Table 2). For 2-phenylpyridines, a series of functional groups on the phenyl ring (e.g., methyl, methoxy, trifluoromethoxy, fluoro, and chloro) were compatible with the present Rh/O_2 catalytic system, and the desired products were isolated in excellent yields (**3aa**–**3ia**). This indicated that the present reaction has good functional-group tolerance. The reaction of 2-(*m*-tolyl)pyridine (**1g**) and **2a** afforded **3ga** as a single regioisomer. However, the reaction of 2-(3-fluorophenyl)pyridine (**1h**) afforded **3ha** as a mixture of regioisomers in a 10:1 ratio. These results suggest that the rhodium selectively attacks the sterically less hindered C–H bond of the phenyl ring. In addition to phenylpyridines, phenylquinolines afforded the corresponding products in good to excellent yields (**3ka**–**3ma**). Electron-donating or -withdrawing groups on the phenyl ring were well-tolerated. Furthermore, when benzo[*h*]quinoline and 5-bromobenzo[*h*]-

Table 2. Substrate Scope of the 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), 120 °C, 22 h. Major isomers and isolated yields are shown. Ratios of regioisomers (given in parentheses) were determined by NMR analysis. [b]$Cp^*Rh(H_2O)_3(OTf)_2$ (2 mol %), 36 h.

quinoline were subjected to this procedure, the corresponding annulation products **3na** and **3oa** were isolated in yields of 87% and 71%, respectively, which revealed that the quinoline could function as a useful directing group for this C–H activation. Moreover, 1-phenyl-1*H*-pyrazole also provided the desired product **3pa** in excellent yield under the standard conditions. It is worth noting that *N*-benzylidene-1-phenylmethanamine derivatives could also be used in the present reaction, affording the corresponding products **3qa**–**3sa** in decent yields.

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

To gain insight into the reaction mechanism, several experiments to form cyclometalated rhodium complexes were conducted. The desired five-membered cyclometalated Rh(III) complex **4** was isolated in almost quantitative yield by treating $Cp^*Rh(H_2O)_3(OTf)_2$ with 10 equiv of **1a** in CH_3OH at 120 °C for 10 h (Scheme 2 top). The structure of **4** was characterized by X-ray crystallography[9] and high-resolution mass spectrometry (see the Supporting Information). However,

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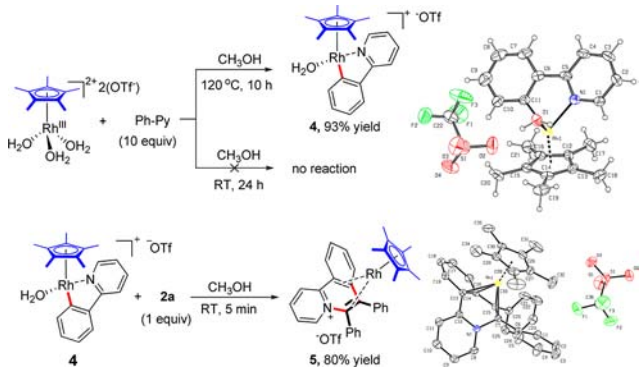
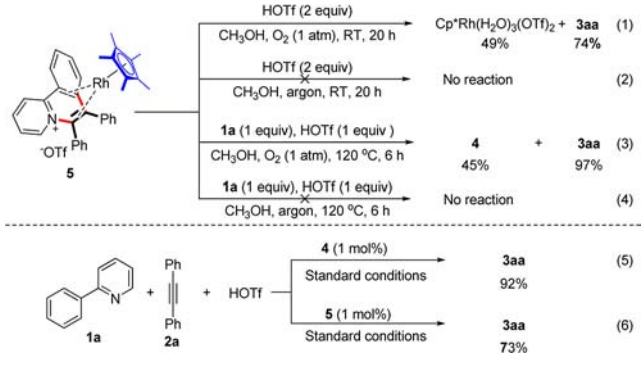
Scheme 2. Syntheses of (top) 4 and (bottom) 5



none of the desired rhodium complex was detected when the same reaction was conducted at room temperature for 24 h. These results indicate that high temperature is required for cleavage of the C−H bond of the phenyl ring. Further reaction of **4** with **2a** at room temperature quickly led to the formation of air-stable complex **5** in 5 min (Scheme 2 bottom). X-ray crystallography[9] confirmed the unique sandwich structure of **5**, in which the pyridoisoquinolinium moiety is bound to the Rh center through η^4 coordination. These results indicate that a Rh(III)−Rh(I)−Rh(III) catalytic cycle is most likely involved in the present catalytic reaction.

After confirming that **4** could be facilely converted to **5**, we proceeded to execute a set of experiments to elucidate the catalytic cycle of the present reaction (Scheme 3). The final

Scheme 3. Preliminary Mechanistic Studies



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 an O_2 atmosphere at room temperature for 20 h (Scheme 3, eq 1). However, the reaction was virtually stopped when conducted in the absence of O_2 (Scheme 3, eq 2). In addition, **5** was quantitatively converted to the desired product **3aa** with formation of **4** in 6 h by reaction with 1 equiv of **1a** and HOTf under aerobic conditions, but this reaction did not proceed in the absence of O_2 (Scheme 3, eqs 3 and 4). These trials provided evidence that O_2 has the ability to oxidize the sandwich-type Rh(I) species to the Rh(III) species in the presence of acid even at room temperature. The higher activity of **5**, which is prone to be oxidized by O_2 in the present aerobic oxidation, is partially attributed to the special sandwich structure, in which the redox potential of the corresponding Rh(I) is 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 and 6).

On the basis of the results described above and previous reports,[4n,7] a tentative reaction mechanism for this aerobic C−H activation/annulation reaction is shown in Figure 1. Initial

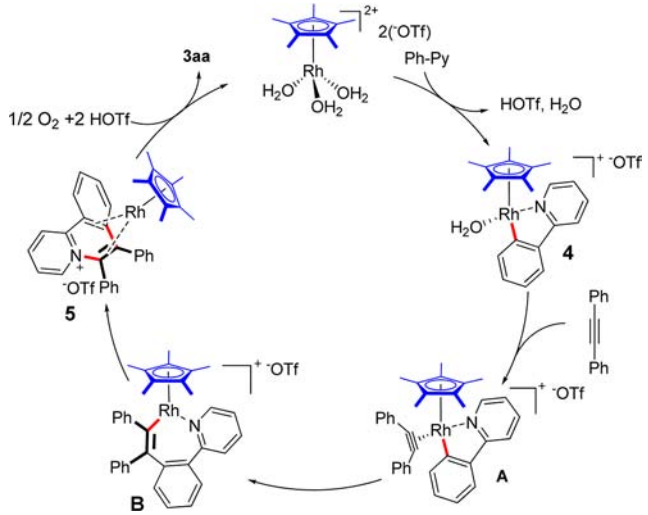


Figure 1. Proposed reaction pathway.

coordination of 2-phenylpyridine to $Cp^*Rh(H_2O)_3(OTf)_2$ and ortho C−H bond activation take place, generating the five-membered rhodacycle complex **4**; this is the rate-limiting step of the reaction.[11] After ligand exchange to form intermediate **A**, regioselective insertion of the alkyne into the Rh−C bond of **A** gives the seven-membered rhodacycle intermediate **B**. Subsequent reductive elimination from **B** releases complex **5**, which is reoxidized by O_2 in the presence of HOTf to regenerate the active catalyst for the next catalytic cycle and give rise to the desired product **3aa**.

In summary, we have successfully developed a new and efficient rhodium-catalyzed protocol for the 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 (TON of up to 740) and thus 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 O_2 should pave the way for establishing some new and efficient Rh-catalyzed oxidative C−H activation reactions. Further investigations on the application of the Rh/O_2 system to 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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Notes

The authors declare no competing financial interest.

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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.

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