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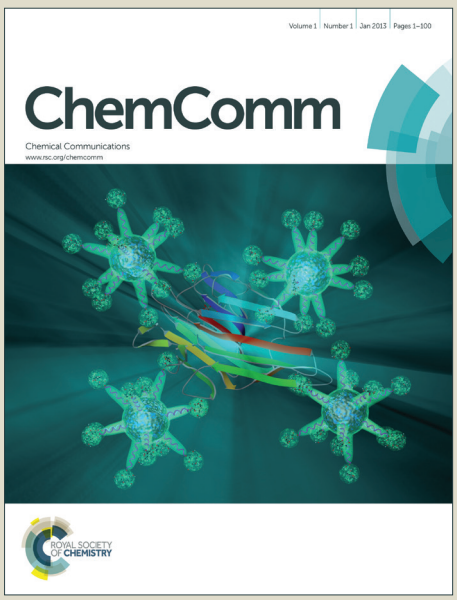

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Rh-Catalyzed Oxidative C-H Activation/Annulation: Converting Anilines to Indoles with Molecular Oxygen as Sole Oxidant

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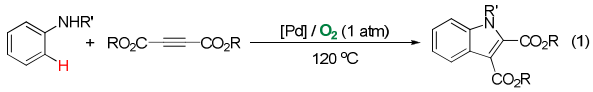
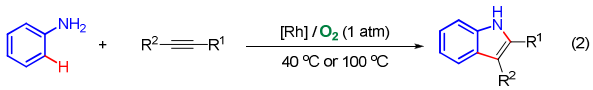
A practical and efficient Rh(III)-catalyzed aerobic C-H activation has been developed for the facile synthesis of a broad range of indoles from simple anilines and alkynes. The protocol could be conducted at mild conditions and used environmentally friendly oxygen as the sole clear oxidant.

Substituted indoles exsit widely as pharmaceuticals, agrochemicals, natural products, organic functional materials and are also useful intermediates in synthetic organic chemistry.[1] As a result, considerable recent effort has focused on the development of new synthetic methods for the generation of indole motif.[2] Among them, transition-metal-catalyzed direct oxidative coupling of commercially available arylamines and alkynes via C-H activation are of particular interest due to its sustainable and environmentally friendly features.[3] However, stoichiometric oxidants, such as $Cu(OAc)_2$, AgOAc, $PhI(OAc)_2$, TBHP, are generally required to maintain the catalytic cycle, resulting in the generation of undesired waste.[4] One attractive method to solve this problem is using O_2 as the sole oxidant, in which only water is produced as a by-product.[5] Indeed, by using O_2 as the sole oxidant, Jiao and co-workers have successfully developed an elegant process for synthesis of indoles from anilines and alkynes with $Pd(OAc)_2$ as catalyst.[3d] However, only electron-deficient alkynes (dialkyl acetylenedicarboxylate) could be tolerated in this system (Scheme 1, Eq 1), thereby limiting the potential scope of this environmentally benign transformation.

Previous work:



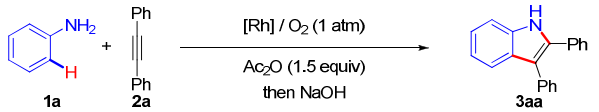
This work:



Scheme 1 Methods for conversion of anilines to indoles by using molecular oxygen as sole oxidant.

We have recently demonstrated that molecuar oxygen has enough ability to oxidize Rh(I) to Rh(III) in the presence of acid. Based on this discovery, our group successfully developed an efficient Rh/O_2 catalytic system for highly efficient oxidative C-H activation.[6] Inspired by these results and in connection with our interests in the aerobic C-H activation, herein we report a practical and efficient approach to indoles from simple arylamines and a broad range of alkynes via rhodium catalyzed aerobic C-H activation with oxygen as the sole oxidant (Scheme 1, Eq 2).

Table 1. Optimization of the reaction conditions[a]



1a 2a 3aa

Entry	[Rh]	T/°C	Solvent	Yield (%)
1	$Cp^*Rh(H_2O)_3(OTf)_2$	40	*t*-AmOH	70
2	$Cp^*Rh(H_2O)_3(OTf)_2$	40	*t*-BuOH	18
3	$Cp^*Rh(H_2O)_3(OTf)_2$	40	CH_3OH	<5
4	$Cp^*Rh(H_2O)_3(OTf)_2$	40	DMF	<5
5	$Cp^*Rh(H_2O)_3(OTf)_2$	40	acetone	49
6	$Cp^*Rh(H_2O)(OAc)_2$	40	*t*-AmOH	<5
7	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	40	*t*-AmOH	<5
8	$[Cp^*RhCl_2]_2$	40	*t*-AmOH	0
9	$Cp^*Rh(H_2O)_3(OTf)_2$	60	*t*-AmOH	80
10	$Cp^*Rh(H_2O)_3(OTf)_2$	80	*t*-AmOH	79
11	$Cp^*Rh(H_2O)_3(OTf)_2$	100	*t*-AmOH	84
12	$Cp^*Rh(H_2O)_3(OTf)_2$	120	*t*-AmOH	81
13	$Cp^*Rh(H_2O)_3(OTf)_2$	25	*t*-AmOH	44
14[b]	$Cp^*Rh(H_2O)_3(OTf)_2$	100	*t*-AmOH	<5

[a] General conditions: **1a** (0.6 mmol), **2a** (0.4 mmol), [Rh] (0.02 mmol), Ac_2O (0.6 mmol), solvent (2.0 mL), O_2 (1 atm), for 24 h. Then NaOH (1.2 mmol), CH_3OH (2.0 mL), RT for 1 h. Isolated yield, unless otherwise noted. [b] Under nitrogen.

Our initial investigation focused on the direct synthesis of indole **3aa** from the reaction of aniline **1a** and 1,2-diphenylethyne **2a** under 1 atm of O_2 with *t*-AmOH as solvent at 40 °C. On the basis of our experience with Rh-catalyzed aerobic oxidative C-H activation/annulation,[6] we chose $Cp^*Rh(H_2O)_3(OTf)_2$ as a catalyst and Ac_2O as an additive, since one molecular of HOAc (which can facilitate the oxidation of Rh(I) to Rh(III)) would be simultaneously produced in the reaction of Ac_2O with aniline **1a**. Under these conditions, the desired product 2,3-diphenylindole **3aa** was isolated in 70% yield after hydrolysis in situ in the presence of NaOH (Table 1, entry 1). Other solvents, such as *t*-BuOH, CH_3OH, DMF and acetone did not improve the reactivity (Table 1, entries 2-5). Further investigation of the rhodium catalyst precursors revealed that the reactivity was affected by the nature of the counterion cationic, and the best result was achieved with $Cp^*Rh(H_2O)_3(OTf)_2$ as the catalyst precursor. The best yield of **3aa** was obtained when the reaction conducted at 100 °C whereas no appreciable increase in yield was obtained at higher temperature. It was noteworthy that the reaction still worked well even at room temprature and **3aa** was obtained in moderate yield under other identical reaction

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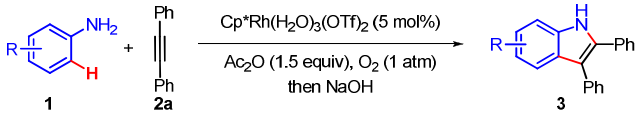
conditions (Table 1, entry 13). Finally, control reactions demonstrated that only trace amount of annulation product **3aa** was obtained under nitrogen atmosphere. Taken together, we can conclude that the annulation was carried out by stirring *t*-AmOH solution of aniline, 1,2-diphenylethyne, 5 mol% of $Cp^*Rh(H_2O)_3(OTf)_2$, and 1.5 equiv of Ac_2O at 100°C under 1 atm of O_2 for 24 h to give the product in the best yield.

Table 2. Substrate scope of anilines[a]



1 2a 3

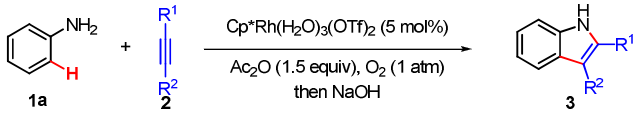
Entry	R	Yield (%)
1	H	**3aa**, 84 (70)[b]
2	4-CH_3	**3ba**, 93 (76)[b]
3	3-CH_3	**3ca**, 71
4	4-*t*-Bu	**3da**, 92
5	3-*t*-Bu	**3ea**, 84
6	4-CH_3O	**3fa**, 90 (61)[b]
7	3,5-$(CH_3O)_2$	**3ga**, 61
8	3,4-$(CH_3O)_2$	**3ha**, 76
9	4-CF_3O	**3ia**, 78
10	4-F	**3ja**, 76
11	4-Cl	**3ka**, 90 (80)[b]
12	3-Cl	**3la**, 49[c]
13	4-Br	**3ma**, 90 (71)[b]
14	4-CN	**3na**, 31
15	4-$COOCH_3$	**3oa**, 60
16	1-Naphthyl	**3pa**, 62

[a] General conditions: **1** (0.6 mmol), **2a** (0.4 mmol), Ac_2O (0.6 mmol), $Cp^*Rh(H_2O)_3(OTf)_2$ (5 mol%), *t*-AmOH (2.0 mL), O_2 (1 atm), at 100 °C for 24 h. Then NaOH (1.2 mmol), CH_3OH (2.0 mL), RT for 1 h. Isolated yield. [b] At 40 °C. [c] Ratios of regioisomers was determined by ^1H NMR analysis (1.08:1).

With the optimized conditions in hand, the scope of this reaction with various arylamines was investigated. As shown in Table 2, the reactions of arylamines **1** bearing an electron-donating or electron-withdrawing group at the *ortho*, *meta*, or *para* position of the phenyl ring proceeded smoothly to give the corresponding products **3aa-3oa** in 31-93% yields. An obvious steric hindrance effect on the reactivity was observed, which was demonstrated by the reactivities of **1b** *vs* **1c**, **1d** *vs* **1e** and **1k** *vs* **1l**. Besides, when a *meta*-substituent is present, the reaction is preferred at the more sterically accessible position (**3ca**, **3ea**, **3ha** and **3la**). It is worth noting that the tolerance of halogen, cyano and ester groups on the aromatic ring in this protocol offers an opportunity for subsequent transformations, which facilitates expedient synthesis of complex indoles. In addition to substituted anilines, naphthyl-substituted amine was also compatible with this process, furnishing the desired product **3pa** in good yield. Notably, some arylamines could be transformed into the corresponding indoles at 40 °C in moderate to good yields, which could increase the practicality of our reaction process dramatically (**3aa**, **3ba**, **3fa**, **3ka** and **3ma**).

Furthermore, the scope of the alkynes was also explored and the results are shown in Table 3. Symmetrical diarylalkynes containing electron-rich or -deficient functional groups reacted smoothly to give the corresponding products in high yields. The unsymmetrical alkynes, such as **2f** and **2g** were also successfully transformed into the corresponding products in high yields with lower regioselectivity. However, when **2h** was employed as the coupling partner, only isomer **3ah** was obtained in 77% yield. The observed excellent regioselectivity for this substrate may stem from the strong electron-withdrawing ability of trifluoromethyl group attached here. Although dimethyl acetylenedicarboxylate and dialkyl alkynes did not react with amines under these conditions, the aryl alkyl alkynes such as **2i** and **2j** are suitable for this reaction, affording the corresponding products **3ai** and **3aj** in moderate yields with high regioselectivities, respectively.

Table 3. Substrate scope of alkynes[a]



1a 2 3

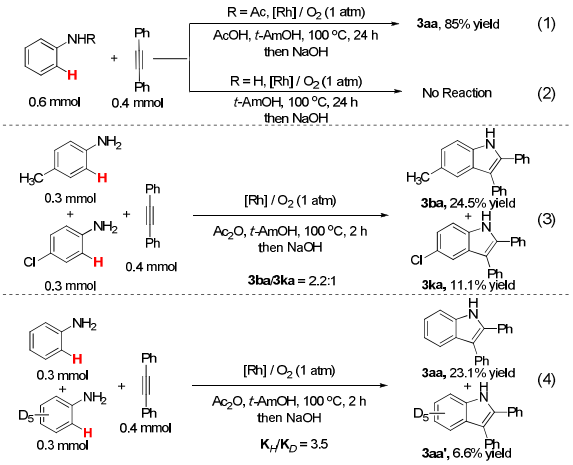
Entry	R^1	R^2	Yield (%)
1	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	**3ab**, 81 (58)[b]
2	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	**3ac**, 85
3	4-FC_6H_4	4-FC_6H_4	**3ad**, 76
4	4-BrC_6H_4	4-BrC_6H_4	**3ae**, 75 (37)[b]
5	4-$CH_3C_6H_4$	C_6H_5	**3af**, 79 (1.14:1)[c] (65)[b]
6	4-BrC_6H_4	C_6H_5	**3ag**, 62 (1:1)[c]
7	3,5-$(CF_3)_2C_6H_4$	C_6H_5	**3ah**, 77 (56)[b]
8	C_6H_5	CH_3	**3ai**, 52
9	C_6H_5	Bn	**3aj**, 50 (12:1)[c]
10	*n*-Bu	*n*-Bu	**3ak**, 0

[a] General conditions: **1a** (0.6 mmol), **2** (0.4 mmol), Ac_2O (0.6 mmol), $Cp^*Rh(H_2O)_3(OTf)_2$ (5 mol%), *t*-AmOH (2.0 mL), O_2 (1 atm), at 100 °C for 24 h. Then NaOH (1.2 mmol), CH_3OH (2.0 mL), RT for 1 h. Isolated yield. [b] At 40 °C. [c] Ratios of regioisomers were determined by ^1H NMR analysis. Major isomers are shown.

To gain insight into the reaction mechanism, several control experiments were conducted under the standard conditions (Scheme 2). Initially, acetanilide served as a substrate to react with **2a** under the modified conditions, the product **3aa** was obtained in 85% yield. However, aniline could not be transformed into the product at all under the same reaction conditions. These results indicated that the acetanilide might be involved in the present reaction (Eq 1-2). Then intermolecular competition experiments were carried out between the arylamine **1b** (4-CH_3) and **1k** (4-Cl). The result that product **3ba** was preferentially formed demonstrated that the C-H activation step might go through an electrophilic rhodation rather than the concerted metalation deprotonation (CMD) process (Eq 3). Moreover, intermolecular kinetic isotope effect experiments were carried out under the standard conditions. The observed significant isotopic effects (K_H/K_D = 3.5) demonstrated that the C-H bond of aniline cleavage might be involved in the rate-determining step (Eq 4).

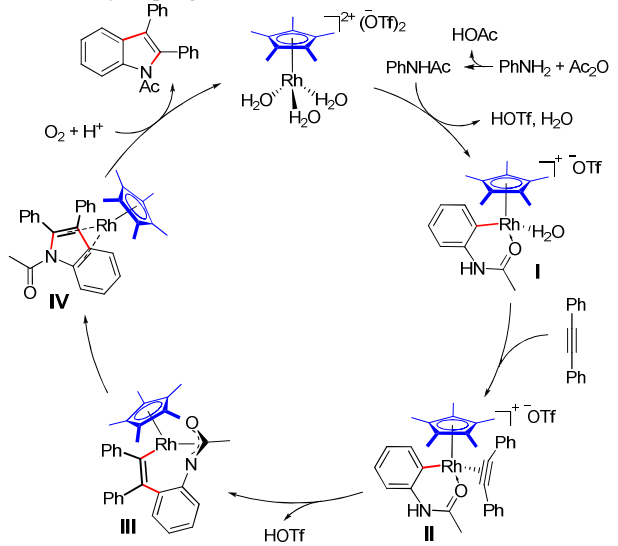
On the basis of the results we obtained here and previous reports,[6] a plausible mechanism for the present process can be proposed as shown in Scheme 3. In this scenario, initial coordination of acetanilide generated *in situ* from acetic anhydride and aniline to $Cp^*Rh(H_2O)_3(OTf)_2$ gave the six-membered rhodacycle intermediate **I** via *ortho* C-H bond activation. After species **II** was formed by ligand exchange, regioselective insertion of the alkyne into the Rh-C bond of **II** gained the rhodacycle intermediate **III**. Subsequent reductive elimination releases complex **IV**, which is reoxidized by O_2 in

the presence of acid to regenerate the active catalyst for the next catalytic cycle and give rise to the indole product.



Scheme 2 Preliminary mechanistic studies.

In summary, we have developed an efficient Rh/O_2 catalytic system that allows the direct formation of indoles from commercially available anilines and alkynes via C-H activation under the aerobic conditions. The method is compatible with a variety of functional groups and can be used to prepare a range of 1,2-disubstituted indoles. This study together with our previous studies provides strong evidences that the molecular oxygen has enough ability to oxidize the Rh(I) to Rh(III) species in the presence of appropriate acid. Further investigations to gain a detailed mechanistic understanding as well as application of this aerobic oxidative catalytic system to other oxidative C-H activation reactions are currently in progress.



Scheme 3 Proposed catalytic cycle.

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7 CCDC 974194 (**3na**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The

Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.