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COMMUNICATION

Synthesis of Isoquinolones via Rh-Catalyzed C–H Activation of Substituted Benzamides Using Air as the Sole Oxidant in Water.

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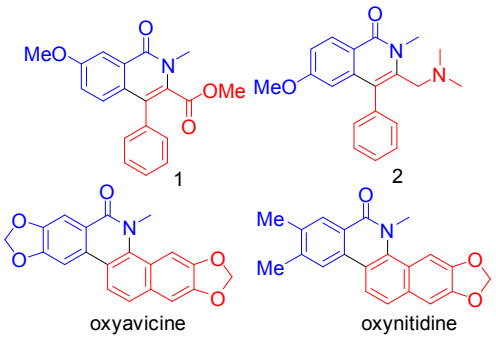
Most of the metal-catalyzed C–H activation/annulation reaction were carried out in organic solvent using expensive oxidant such as Cu(II) and Ag(I) salts. Here, we reported a new approach for highly regioselective synthesis of isoquinolones from *N*-alkyl benzamides and alkynes using Rh(III) catalyst and inexpensive oxygen as the sole oxidant in aqueous medium. In the reaction, water gave the highest product yield among the solvents used. In addition, at the end of reaction the isoquinolone product directly precipitated out from the aqueous solution. The methodology can be applied to a gram scale synthesis. This Rh(III)-catalyzed reaction shows interesting *meta* selectivity with the meta substituted benzamide and shows various regioselectivity with different substituted alkynes. Moreover, the methodology can be applied to the preparation of biologically active compounds having the isoquinolone core.

Transition metal-catalyzed oxidative C–H bond activation and annulation has attracted considerable attention because the catalytic reaction does not require pre-functionalization of the substrate and is highly regioselective. In the past several years, Rh-catalyzed oxidative annulation reactions were mostly carried out in the presence of an organic solvent and an expensive metal based oxidant.[1,2,3] For the catalytic reaction to be practical, expensive organic solvent and metal-based oxidant are better avoided. Water is the most abundant compound on the earth surface which is a non-flammable, nontoxic green solvent. Oxygen is the third-most abundant element in the universe and has good solubility in water, and is the cheapest and renewable source of oxidant. Reactions carried out in water via aerobic oxidation are generally more ecology and environment-friendly and have fascinated many synthetic chemists. A few Rh-catalyzed oxidative annulation reactions were known to proceed in organic solvents using inexpensive oxygen as the oxidant or in water using metal-based oxidant for the metal-catalyzed C–H activation/annulation reaction.[4] Our continuous interest[5,6,7] in the metal-catalyzed C-H bond activation reactions prompted us to explore the possibility of metal-catalyzed C-H bond activation and annulation in water using dioxygen as the oxidant. In this report, we demonstrate an efficient Rh-catalyzed environmentally friendly synthetic route for the synthesis of isoquinolone derivatives from *N*-alkyl benzamides and alkynes in water using dioxygen (or air) as the oxidant. The rhodium and rhuthinium-catalyzed annulations of benzamide and alkynes to give the corresponding isoquinolones in *t*-amyl alcohol as the solvent using $Cu(OAC)_2.H_2O$ as the oxidant have been reported by of Rovis',[8] Ackermann's[9] groups, respectively. Isoquinolone is an important structural unit which is present in various natural products, biologically active molecules and pharamaceuticals.[10] The structures of some of the alkaloids and biologically active compounds are shown in Scheme 1. The present methodology using water as the solvent and oxygen (or air) as the oxidant is compatible with a wide-range of substituent on the benzamide and alkyne substrates. Excellent regioselcetivity is obtained with unsymmetrical alkynes. In addition, we also demostrated the utility of this new less expensive green methodology in the one pot synthesis of an anti-cardiac arrhythmias agent, 3-((dimethylamino)methyl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2H)-one.[11]



Scheme 1. Natural and bioactive compounds containing isoquinolone core.

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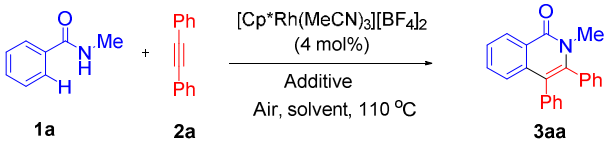
Table 1. Optimization studies for the reaction of *N*-methylbenzamide with 2-diphenylethyne[a]



1a 2a 3aa

Entry	Additive	Solvent	Yield [%][b] 3aa
1	-	H_2O	38
2	$NaHCO_3$	H_2O	46
3	NaPiv	H_2O	56
3	K_2CO_3	H_2O	58[c]
4	K_2CO_3	H_2O	94 (92)
5	K_2CO_3	H_2O	94[d]
6	NaOH	H_2O	65
7	NH_4OAc	H_2O	33
8	KOH	H_2O	52
9	Na_2CO_3	H_2O	47
10	NaOAc	H_2O	72
11	K_2CO_3	t-AmOH	51
12	K_2CO_3	MeOH	65
13	K_2CO_3	DMF	7
14	K_2CO_3	toluene	0
15	K_2CO_3	-	5

[a] Unless otherwise mentioned, all reactions were carried out using *N*-methylbenzamide **1a** (0.40 mmol), 1,2-diphenylethyne **2a** (0.50 mmol), $[Cp^*Rh(MeCN)_3][BF_4]_2$ (4.0 mol%), additive (0.20 mmol), oxygen balloon (1 atm, ~ 1.5 L)) and solvent (2.0 mL) at 110°C for 16 h. [b] Yields were measured by ^1H NMR, using mesitylene as an internal standard. The value in the parenthesis is isolated yield. [c] 0.10 mmol of K_2CO_3 was used. [d] Air was used instead of oxygen.

The rhodium-catalyzed synthesis of isoquinolones via oxidative annulation of *N*-alkyl benzamides with alkynes is known to depend greatly on the reaction conditions.[2,6,8,12] To understand the nature of this reaction and to find the optimized reaction conditions, the effect of solvent and base was examined using *N*-methyl-benzamide **1a** and diphenyl acetylene **2a** as the substrates in the presence of 4.0 mol% of $[Cp^*Rh(MeCN)_3][BF_4]_2$, a base and solvent at 110 °C for 16 h.

First, the reaction of **1a** and **2a** in water in the presence of oxygen but without Rh complex and base was carried out; no product **3aa** was observed. In the presence of $[Cp^*Rh(MeCN)_3][BF_4]_2$, but without a base, the reaction gave **3aa** in 38 % yield (entry 1). The use of base greatly improves the product yield. Among the bases examined (entries 2- 10), K_2CO_3 is most effective furnishing **3aa** in 92 % yield. Other bases such as NaOAc, and NaOH are also active affording product **3aa** in 72 and 65% yields, respectively. Product **3aa** was thoroughly characterized by its ^1H and ^{13}C NMR and mass spectral analysis and the structure was further confirmed by the result of single-crystal X-ray diffraction.[13]

The choice of solvents is also vital to the catalytic reaction. To our surprise, of the solvent examined, water was found to be most effective for the reaction of **1a** and **2a** affording **3aa** in 92% yield (Table 1, entry 4). In addition, at the end of reaction and upon cooling of the reaction, **3aa** directly precipitated out from the aqueous solution. Other solvents such as *t*-amyl alcohol, methanol also effective giving **3aa** in 51 and 65 % yields, respectively. DMF, and toluene were ineffective for the catalytic reaction (entries 13-14). Notably, when the reaction was carried out without solvent, product **3aa** was formed in 5% yield (entry 15).

To evaluate the scope of the present reaction, we examined the reaction of various *N*-alkyl benzamides (**1a-1e**) with **2a** under the optimized reaction conditions (Table 1). Thus, *N*-methyl (**1a**), *N*-ethyl (**2b**), *N*-phenyl (**2c**), and *N*-benzyl (**2d**) benzamide and *N*-phenyl *p*-methoxybenzamide (**1e**) reacted with **2a** to afford the corresponding Isoquinolones **3aa-3ea**, respectively, in 75-92 % yields.

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† Electronic Supplementary Information (ESI) available: Experimental procedures, Compound characterization, and copies of ^1H and ^{13}C NMR spectra. See DOI: 10.1039/x0xx00000x

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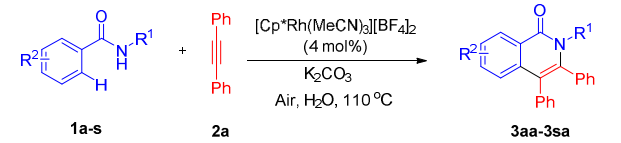
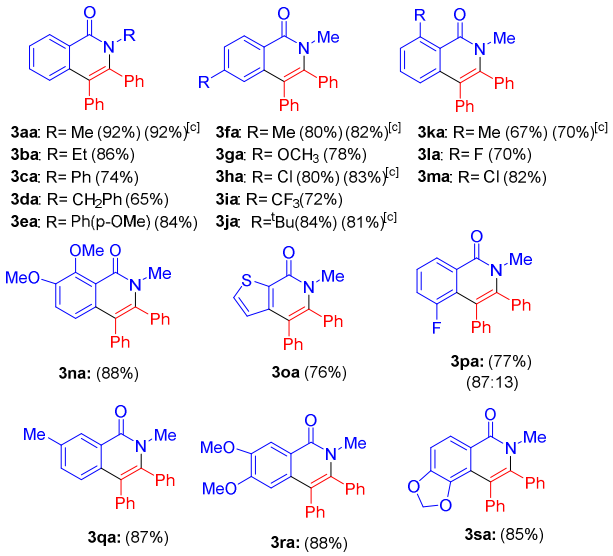
Table 2. Scope of Rh-catalyzed reaction of benzamide with **2a** in water.



1a-s **2a** **3aa-3sa**



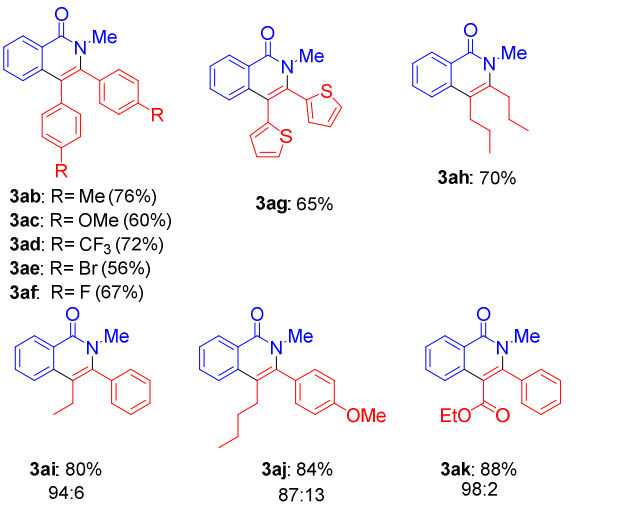
[a] Unless otherwise mentioned, all reactions were carried out using benzamide **1a-s** (0.40 mmol), 1,2-diphenylethyne **2a** (0.50 mmol), $[Cp^*Rh(MeCN)_3][BF_4]_2$ (4.0 mol%), K_2CO_3 (0.20 mmol), air (or oxygen) balloon (1 atm, ~ 1.5 L) and water (2.0 mL) at 110°C for 16 h. [b] isolated yield. [c] O_2 was used instead of air.

It is noteworthy that we have tested some of the reactions using dioxygen and using air and in most cases, the products yield are close (see Table 2).

Next we tested the substituent effect of *N*-methyl benzamides on the reaction with **2a**. Thus, benzamide derivatives bearing 4-methyl (**1f**), 4-methoxy (**1g**), 4-chloro (**1h**), 4-triflurometyl (**1i**) and 4-*t*-butyl (**1j**) on the benzene ring reacted with **2a** effectively under the standard conditions to provide the corresponding products (**3fa-3ja**) in 72-84 % yields. The reactions of *ortho* substituted *N*-methyl benzamide (**1k-1m**) with **2a** also proceeded smoothly to afford **3ka-3ma**, but in slightly lower yields compared with the corresponding *para*-substituted products. Further, 2,3-dimethoxybenzamide **1n** gives the expected product **3na** in 88 %. Extension of this reaction to thiophene-2-carboxamide **1o** was also successful giving **3oa** in 76 % yield.

To know the regioselectivity of *meta*-substituted *N*-methyl benzamides, we investigated the reactions of **1p** and **1q** with **2a**. To our surprise, *N*-methyl 3-flurobenzamide (**1p**) reacted with **2a** efficiently to afford **3pa** with the C–H bond activation and annulation occurring majorly at the 2-position of the benzene ring. In contrast, for *N*-methyl 3-methylbenzamide (**1q**), the C–H bond activation occurred at the 6-position. This selectivity is caused by effective steric shielding of such group, in a similar fashion, 3,4-dimethoxy-*N*-methylbezamide (**1r**) gives the expected product **3ra** in 86%, whereas *N*-methylbenzo[d][1,3]dioxole-5-carboxamide (**1s**) reacted with **2a** to give annulated product **3sa** in 85 % yield in which C–H activation also take place at the hindered side C2. Whereas when we tested primary benzamide ($PhC(O)NH_2$) with **2a** under the standard conditions, we observed twofold coupled alkyne product **3ta** in 7%. The reaction is slow compared with *N*-substituted benzamides (See more details in P. S13, Supporting Information).

Table 3. Scope of Rh Catalyzed reaction of alkyne in water.



After screening different benzamides, we also tested different alkynes with **1a**. Thus, symmetrical diarylalkynes including 4-methyl (**2b**), 4-methoxy (**2c**), **4**-trifluoromethyl (**2d**), 4-bromo (**2e**), and 4-fluro (**2f**) substituted diarylalkynes reacted with **1a** smoothly to give products **3ab-f**, respectively. The reaction of di(2-thienyl)alkyne, **2g** and 4-octyne (**2h**) also provided the corresponding Isoquinolones (**3ag-h**) in good yields, whereas unsymmetrical alkynes **2i** and **2j** gave highly regioselective products **3ai** and **3aj**, respectively, with the insertion of the aryl substituted carbon attached to 3-position. Unsymmetrical alkyne carrying an electron withdrawing group such as ethyl 3-phenylpropiolate (**2k**) reacts with **1a** to product **3ak**, of which the structure were further confirmed by single-crystal X-ray diffraction.[13] Unfortunately, terminal alkyne such as phenyl acetylene does not undergo the expected annulation on reaction with **1a**.

Moreover, we conducted intermolecular competition experiment between electron rich (**1f**) and deficient benzamide (**1g**). Interestingly, we found electron-rich benzamide is more reactive than electron-deficient benzamide in the reaction with alkyne **2a**. In contrast to the observation, electron more deficient alkyne **2a** is more reactive than the electron rich 4-octyne (**2h**) in the reaction with benzamide **1a** to give the corresponding isoquinolones.

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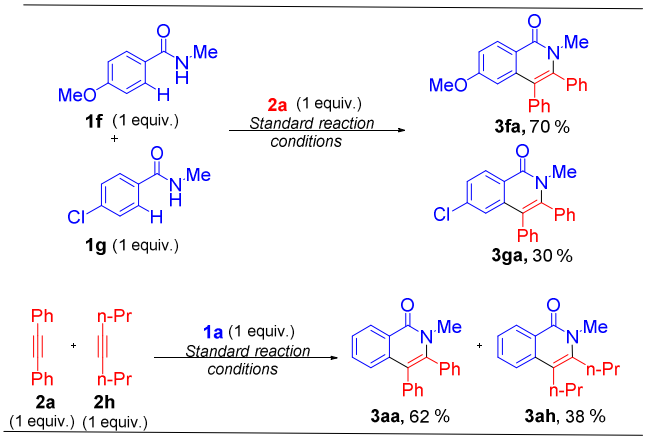
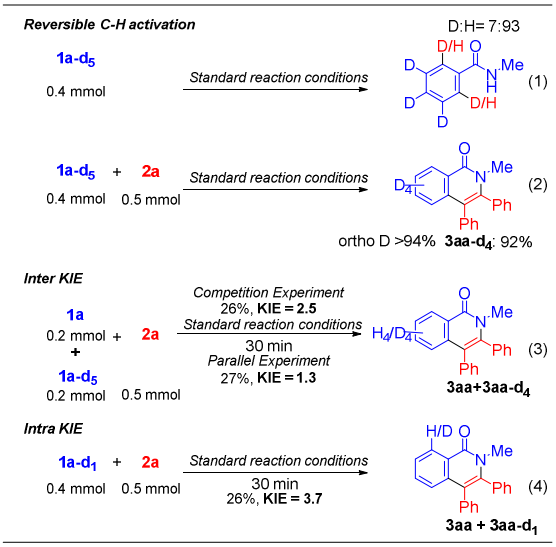


Scheme 2 Intermolecular Competition Experiment.

To understand the mechanism of the catalytic reaction, we studied *ortho* H/D exchange of **1a-d$_5$** with H_2O by heating the substrate in H_2O at 110°C in the absence of **2a** (Scheme 3, eq 1).[14] The ^{1}H NMR spectrum of **1a-d$_5$** after reaction revealed extensive D/H exchange showing D : H = 7 : 93 at both ortho positions of the phenyl ring indicative of reversible C-H activation in the absence of alkyne.

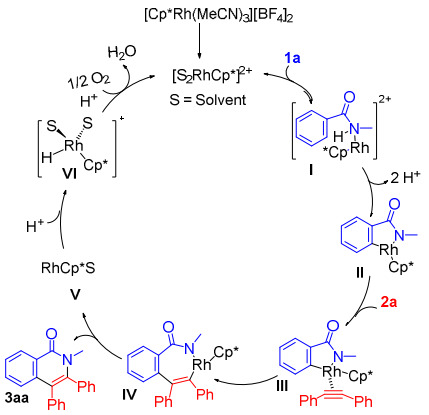


Scheme 3. Mechanistic studies.

In contrast, when the reaction of **1a-d$_5$** with **2a** was performed in H_2O, no hydrogen was incorporated into the ortho benzo group of the product (Scheme 3, eq.2). The results suggest that alkyne insertion is much faster than the reverse C–H activation step. In addition we carried out intermolecular competition and parallel experiments for the reaction of equimolar amount of **1a-d$_5$** and **1a** with **2a** for 30 min (eq.3). The experiment gave an intermolecular kinetic isotope effect (k_H/k_D) of 2.5 and 1.3 for competition and parallel experiments, respectively, measured by ^{1}H NMR Integration. We also carried out the intramolecular competition of the reaction of **1a-d$_1$** with **2a**. A k_H/k_D of 3.7 (eq 4) was observed. The small kinetic isotope effects of parallel experiment suggests that the *ortho* C-H bond cleavage is involved but is likely not the rate limiting step.[14]

On the basis of the metal-catalyzed cyclization reaction and synthesis of heterocyclic compounds, a possible reaction mechanism is proposed in Scheme 4 to account for the present catalytic reaction.[7,8] By using **1a** and **2a** as the substrates, the catalytic reaction starts with the coordination of **1a** to the rhodium center to form intermediate **I**. NH deprotonation and CH activation provides a five membered rhodacycle **II**. Further coordination of alkyne **2a**, followed by insertion (**IV**) and reductive elimination affords the final product **3aa** and a Rh(I) species (**V**). The latter is protonated (**VI**) and then oxidized by dioxygen to regenerate the catalytically active Rh(III) species.

To find further support this proposed mechanism, we carried out the catalytic reaction of **1a** with **2a** under the standard reaction conditions except that D_2O is the solvent and the rhodium catalyst $[Cp^*Rh(MeCN)_3][BF_4]_2$ is increased to 10 mol% to ensure the detection of the rhodium species. The ^{1}H NMR measurements of the catalytic reaction show that only $Cp^*Rh(S)_3]^{2+}$is present in the catalytic solution, where S are solvent and MeCN. The results indicate that Rh(III) species $Cp^*Rh(S)_3]^{2+}$ are the resting state of rhodium catalyst during the catalytic reaction. Therefore, further reaction of this rhodium species with **1a** likely determines the turnover rate of this catalytic reaction.[14] A possible rate-limiting step is the coordination of **1a** via the NHMe group to $Cp^*Rh(S)_3]^{2+}$replacing one of the solvent molecule to give intermediate **I**. With the weak basicity of the electron lone pair on the nitrogen atom of **1a**, the coordination is likely weak and dissociation should occur readily in a reversible manner. This reversible coordination of **1a** likely keeps the concentration of intermediate **I** relative to $Cp^*Rh(S)_3]^{2+}$ at low ratio.



Scheme 4. Proposed catalytic cycle.

The significance of this Rh-catalyzed annulation reaction is demonstrated by its application to the one-pot synthesis of 3-dimethylaminomethyl-6-methoxy-2-methyl-4-phenyl-isoquinolin-1(2H)-one (ISQ-1),[11] an anti-cardiac arrhythmias used for treatment of cardiac atrial fibrillation. Thus the reaction of 4-methoxy *N*-methyl benzamide with *N,N*-dimethyl-3-phenyl prop-2-yn-1-amine, **2l**, under standard conditions provided the isoquinolone derivative **3fl** in 82 % yield in a highly regioselective manner; no other isomer

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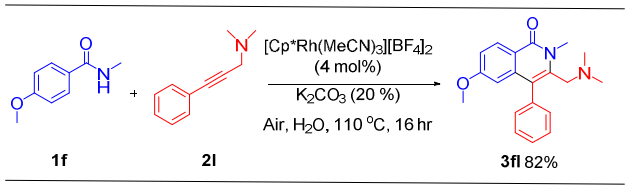
was detected in this catalytic reaction. The regiochemistry of product **3fl** was confirmed by NOE experiments and the structure was further confirmed by the results of single crystal X-ray diffraction. It is noteworthy that the regiochemistry of the insertion of alkyne **2l** is in contrast to that of alkynes **2i** and **2j** (see Table 3) and we speculate that the nitrogen of substrate **2l** is coordinated to rhodium in intermediate (**III**) prior to insertion leading to opposite regioselectivity for insertion and product **3fl**. The unusual regiocontrol by a directing group built in the alkyne substrate was known before.[15]



Scheme 5. Synthesis of 3-dimethylaminomethyl-6-methoxy-2-methyl-4-phenyl-2H isoquinolin-1-one.

Importantly, the methodology can be carried out on a gram scale reaction, and **3aa** was isolated in 86 % yield. We have evaluated the green chemistry metrics[16] for the synthesis of isoquinolones (**3aa**) on preparative scale with *E* factor of 10.5, 99.4% atom economy, 85.5% atom efficiency, 100% carbon efficiency, and 85.8% reaction mass efficiency, which are better than existing methods[8a] (see more details in P. S10, Supporting Information).

In conclusion, we have developed the first rhodium catalyzed oxidative annulation reaction of alkynes and benzamides through C-H bond activation in water using oxygen as the sole oxidant. It is interesting to note that water is the most effective solvent in this catalytic reaction giving much higher catalytic activity than organic solvents. The catalytic reaction proceeds with high regioselectivity and is accomplished through N–H and C–H bond cleavage, and C–C and C–N bond formation. Moreover, the applications of this methodology is successfully applied to the total synthesis of bioactive compound 3-((dimethylamino)methyl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2H)-one, **3fl** with 82 % excellent yield. Further studies towards inexpensive oxidant to catalyzed oxidative C-H bond functionalization are underway in our laboratory by using metal and water as a medium.

Acknowledgement

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