Organic LETTERS

Letter

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Acceptorless Dehydrogenative Cyclization of *o*-Aminobenzyl Alcohols with Ketones to Quinolines in Water Catalyzed by Water-Soluble Metal–Ligand Bifunctional Catalyst [Cp*(6,6′-$(OH)_2$bpy)(H_2O)][OTf]$_2$

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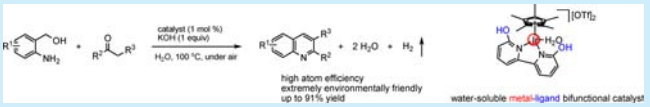
Supporting Information

ABSTRACT: The strategy for acceptorless dehydrogenative cyclization of *o*-aminobenzyl alcohols with ketones to quinolines in water has been accomplished. In the presence of [Cp*Ir(6,6′-$(OH)_2$bpy)(H_2O)][OTf]$_2$, a series of desirable products were obtained in high yields. Notably, this research exhibits the potential for the construction of heterocycles via acceptorless dehydrogenative reactions in water catalyzed by water-soluble metal–ligand bifunctional catalysts.



Quinolines are an important class of nitrogen-containing heterocycles that occur in various natural products, especially in alkaloids.[1] They also exhibit a wide range of biological activities. Recent examples include micromolar inhibitors of nicotinamide adenine dinucleotide (NAD)-hydrolyzing accomplished by catalyzing enzyme CD38,[2a] DNA cytosine deaminases APOBEC3G inhibitors,[2b] multitarget-directed ligands against Alzheimer's disease,[2c] and positron emission tomography (PET) radioligands for translocator protein (18 kDa).[2d] Given the importance of quinolines, a number of classical annulation reactions, such as Skraup, Doebner–von Miller, Conrad–Limpach, Pfitzinger, and Friedlaeder syntheses, have been developed over the past few decades.[3] Among these methods, Friedlander synthesis, namely, base- or acid-promoted cyclization of *o*-aminobenzaldehydes with ketones to quinolines, is considered to be the simplest approach, although its potential is highly restricted due to the fact that *o*-aminobenzaldehydes are unstable and easily prone to self-condensation.[4] In recent years, considerable effort has been devoted to the development of the oxidative cyclization of *o*-aminobenzyl alcohols with ketones to quinolines catalyzed by Ru,[5] Pd,[6] Ir,[7] or other transition metal catalysts[8] (e.g., modified Friedlander quinoline synthesis). However, these procedures require large excesses of ketones, unsaturated olefine (1-dodecene or 1-decene), or oxygen gas as a sacrificial hydrogen acceptor to generate in situ *o*-aminobenzaldehydes from *o*-aminobenzyl alcohols via transfer hydrogenation. Moreover, these procedures were performed in organic solvents, which might cause environmental pollution.

Recently, significant attention has been paid to the development of transition metal-catalyzed acceptorless dehydrogenation reactions with the liberation of hydrogen gas, such as acceptorless dehydrogenation of alcohols[9] and *N*-containing heterocycles.[10] Such methodologies provide the clearest and most atom-economical processes as alternatives to traditional oxidation reactions. More recently, Kawahara and co-workers reported a water-soluble Cp*Ir complex bearing a functional bipyridine ligand [Cp*Ir(6,6′-$(OH)_2$bpy)(H_2O)][OTf]$_2$, which exhibits high activity for the acceptorless dehydrogenation of alcohols in water based on the concept of "ligand-promoted dehydrogenation".[11] We have demonstrated that such a complex is a highly effective metal–ligand bifunctional catalyst for the *N*-alkylation of sulfonamides with alcohols in water via the "hydrogen autotransfer process".[12] As part of our continuing effort in the development of iridium-catalyzed reactions,[12,13] we are herein interested in the exploration of acceptorless dehydrogenative cyclization of *o*-aminobenzyl alcohols with ketones to quinolines in water catalyzed by a water-soluble iridium complex.

Our initial investigation focused on the cyclization of *o*-aminobenzyl alcohol (**1a**) with acetophenone (**2a**) in water. As shown in Table 1, a series of water-soluble Cp*Ir complexes, including cationic [Cp*Ir(bpy)Cl]Cl (bpy = 2,2′-bipyridine) (cat. **1**) and [Cp*Ir($Me_2NCH_2CH_2NMe_2$)Cl]Cl (cat. **2**), Cp*Ir complex bearing three ammonia ligands [Cp*Ir$(NH_3)_3$][Cl]$_2$ (cat. **3**), Cp*Ir complexes bearing one or more aqua ligands such as [Cp*Ir$(H_2O)_3$][OTf]$_2$ (cat. **4**), [Cp*Ir(bpy)(H_2O)][OTf]$_2$ (cat. **5**), [Cp*Ir(6,6′-$(OMe)_2$bpy)(H_2O)][OTf]$_2$ (cat. **6**), and [Cp*Ir(6,6′-$(OH)_2$bpy)(H_2O)][OTf]$_2$ (cat. **7**), were assayed for their ability to catalyze the model reaction. In the presence of catalyst (1 mol %) and KOH (1 equiv), the reaction was carried out in water at 100 °C under a sealed nitrogen atmosphere for 12 h. The reaction afforded product **3aa** in 43–58% yields when cat. **1**–**6** were used as the catalyst (entries 1–6). To our delight, cat. **7** exhibited high

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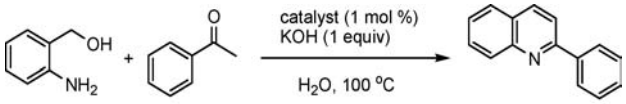
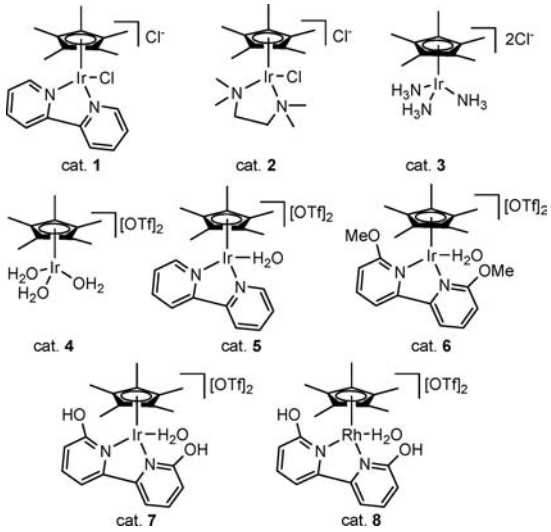
Table 1. Cyclization of *o*-Aminobenzyl Alcohol (1a) and Acetophenone (2a) under Various Conditions[a]



1a 2a 3aa

entry	catalyst[b]	base	atmosphere	*x*	yield (%)[c]
1	cat. **1**	KOH	sealed N_2	1	43
2	cat. **2**	KOH	sealed N_2	1	51
3	cat. **3**	KOH	sealed N_2	1	58
4	cat. **4**	KOH	sealed N_2	1	54
5	cat. **5**	KOH	sealed N_2	1	43
6	cat. **6**	KOH	sealed N_2	1	56
7	cat. **7**	KOH	sealed N_2	1	75
8	cat. **8**	KOH	sealed N_2	1	52
9	**cat. 7**	**KOH**	open air	**1**	**89**
10	cat. 7	Cs_2CO_3	open air	1	44
11	cat. 7	K_2CO_3	open air	1	33
12	cat. 7	KOH	open air	0.5	77
13		KOH	open air	1	n.d.

[a]Reactions conditions: **1a** (1 mmol), **2a** (1.2 mmol), catalyst (1 mol %), base (x equiv), H_2O (1 mL), 100 °C, 12 h. [b]Catalyst structures:

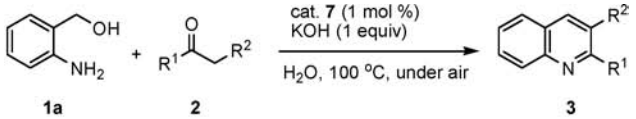


[c]NMR yield.

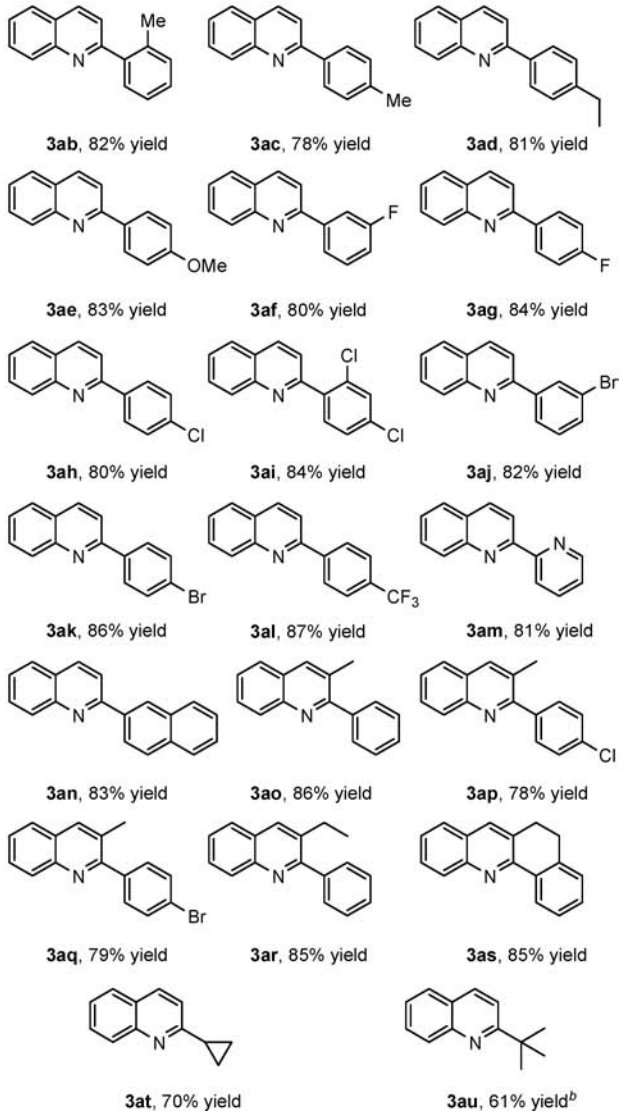
catalyst activity, and product **3aa** was obtained in 75% yield, indicating the unique potential of a water-soluble metal−ligand bifunctional iridium catalyst (entry 7). Using an analogous rhodium complex as an alternative catalyst, the reaction gave product **3aa** in 52% yield (entry 8). The yield of **3aa** could be enhanced to 89% yield in the presence of cat. **7** under an open-air atmosphere (entry 9).[14] Attempts to use Cs_2CO_3 or K_2CO_3 as a base, or to reduce the amount of KOH, resulted in low yield of product (entries 10−12). It was also found that no reaction occurred in the presence of KOH alone (entry 13).

Having established the optimal conditions (Table 1, entry 9), the scope of the reaction with respect to ketones was examined, and the results are shown in Scheme 1. Treatments of acetophenones bearing an electron-donating substituent gave the corresponding products **3ab**−**3ae** in 78−83% yields. Similarly, reactions of acetophenones bearing one or two halogen atoms proceeded smoothly to afford the desired products **3af**−**3ak** in 80−86% yields. The even stronger

Scheme 1. Cyclization of *o*-Aminobenzyl Alcohol (1a) with a Range of Ketones (2) in Water[a]



1a 2 3



[a]Reactions conditions: **1a** (1 mmol), **2** (1.2 mmol), cat. **7** (1 mol %), KOH (1 equiv), H_2O (1 mL), 100 °C, under air, 12 h. Isolated yield. [b]Sealed tube.

electron-withdrawing trifluoromethyl group was also tolerated, and the corresponding product **3al** was obtained in 87% yield. Furthermore, 1-(pyridin-2-yl)ethanone and 1-(naphthalen-2-yl)ethanone were successfully converted to desired products **3am** and **3an** in 81 and 83% yields, respectively. Nonmethyl ketones were proven to be suitable substrates, and desired products **3ao**−**3as** were obtained in 78−86% yields.

In the case of aliphatic ketones, such as cyclopropylethanone and 3,3-dimethyl-2-butanone, the corresponding products **3at** and **3au** could be obtained, albeit in moderate yields.

For the scope of reaction to be expanded further, transformation with respect to *o*-aminobenzyl alcohols was conducted (Scheme 2). Reactions of *o*-aminobenzyl alcohols

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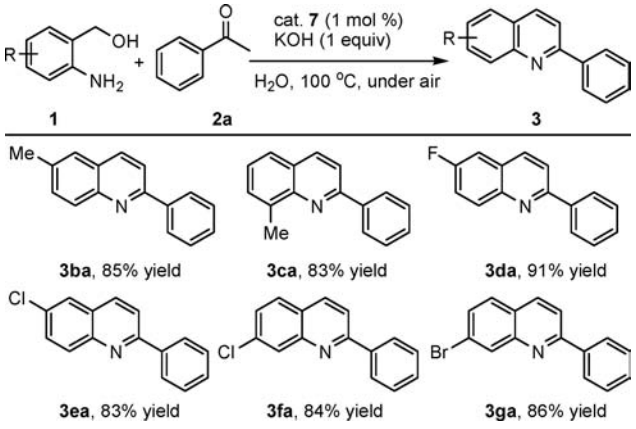
Scheme 2. Cyclization of a Series of *o*-Aminobenzyl Alcohols (1) with Acetophenone (2a) in Water[a]



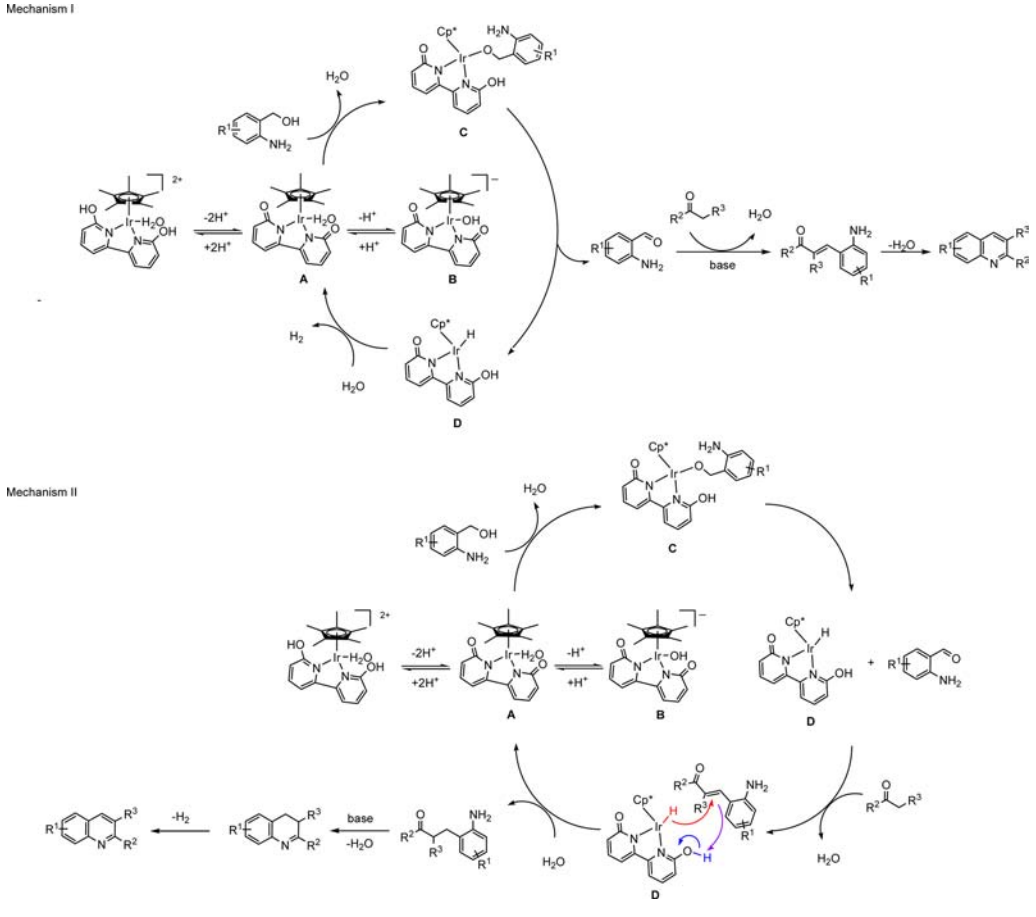
[a]Reactions conditions: 1 (1 mmol), 2a (1.2 mmol), cat. 7 (1 mol %), KOH (1 equiv), H_2O (1 mL), 100 °C, under air, 12 h. Isolated yield.

bearing an electron-donating substituent gave corresponding products **3ba** and **3ca** in 85 and 83% yields, respectively. Furthermore, *o*-aminobenzyl alcohols bearing an electron-withdrawing substituent were converted to desired products **3da**–**3ga** in 83–91% yields.

It should be noted that, differing from traditional Friedlander synthesis, no self-condensation side-products of *o*-aminobenzaldehydes were found. One possible explanation is that *o*-aminobenzaldehydes are generated in situ and their concentration would be much smaller than that of ketones, which suppresses self-condensation.

Two possible simultaneous mechanisms for the present acceptorless dehydrogenative cyclization of *o*-aminobenzyl alcohols with ketones to quinolines are presented (Scheme 3). In the presence of an excess amount of strong base, cat. **7** could be transformed to neutral complex [Cp*Ir(2,2′-bpyO)-(H_2O)] (**A**) and anionic complex [Cp*Ir(2,2′-bpyO) (OH)]$^-$ (**B**) via multiple deprotonations.[15] Accompanied by the activation of alcohols, the ligand accepted a proton to afford alkoxy iridium species **C**, which then underwent *β*-hydrogen elimination to give iridium hydride species **D** and aldehydes.[16] In mechanism I, the ligand-promoted simultaneous hydrogen transfer from the hydroxy proton on the bpy ligand and the hydride on the iridium resulted in the liberation of hydrogen gas and regeneration of catalytic species **A**.[17] A base-promoted cross-aldol condensation between the resulting *o*-aminobenzaldehyde and ketones occurred to give *α,β*-unsaturated ketones, which were further converted to quinolines via intramolecular cyclodehydration. In mechanism II, after the condensation between the resulting aldehydes and ketones, the hydride on the iridium and hydroxy proton on the ligand of species **D** were simultaneously transferred to the C=C bond of *α,β*-unsaturated ketones; thus, catalytic species **A** was regenerated, and *α*-alkylated ketones were produced.[18] Finally, the resulting *α*-alkylated ketones underwent sequential intramolecular cyclodehydration/dehydrogenation to afford quinolines.[19,20]

Scheme 3. Proposed Reaction Mechanisms



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In summary, we have demonstrated the first examples of acceptorless dehydrogenative cyclization of *o*-aminobenzyl alcohols with ketones to quinolines in water. Notably, this research exhibits the potential for the construction of heterocycles via acceptorless dehydrogenative reactions in water catalyzed by water-soluble metal−ligand bifunctional catalysts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01518.

Experimental procedures, and ^{1}H NMR and ^{13}C NMR spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

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(14) The enhancement of yield is probably due to the fact that the produced hydrogen gas was removed away from the reaction system under air-open conditions compared to that with a sealed nitrogen atmosphere, which facilitates the reaction process.

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(16) Although a *ß*-H elimination mechanism has been widely accepted, Wang and co-workers proposed another possible mechanism for the acceptorless dehydrogenation catalyzed by various catalysts based on DFT computational studies: dehydrogenation via the metal−ligand bifunctional active site takes place more favorably than *ß*-H elimination, see: (a) Li, H.; Lu, G.; Jiang, J.; Huang, F.; Wang, Z. X. *Organometallics* **2011**, *30*, 2349. (b) Li, H.; Jiang, J.; Lu, G.; Huang, F.; Wang, Z. X. *Organometallics* **2011**, *30*, 3131. (c) Li, H.; Wang, X.; Huang, F.; Lu, G.; Jiang, J.; Wang, Z. X. *Organometallics* **2011**, *30*, 5233. (d) Qu, S.; Dang, Y.; Song, C.; Wen, M.; Huang, K. W.; Wang, Z. X. *J. Am. Chem. Soc.* **2014**, *136*, 4974.

(17) Kawahara and co-workers have confirmed the ligand-promoted dehydrogenation of alcohols with the liberation of hydrogen gas, see ref 11.

(18) We have confirmed the ligand-promoted transfer hydrogenation of the C═C bond of an *α,β*-unsaturated ketone with an alcohol as the hydrogen catalyzed by [Cp*Ir(2,2′-bpyO)(H_2O)], see ref 13f.

(19) Fujita and co-workers have demonstrated the dehydrogenation of C−C and C−N bonds of *N*-heterocycles catalyzed by iridium complexes bearing a functional bipyridonate ligand, see: Fujita, K.; Tanaka, Y.; Kobayashi, M.; Yamaguchi, R. *J. Am. Chem. Soc.* **2014**, *136*, 4829.

(20) For support of the proposed mechanisms, the liberation of hydrogen gas in the process of the cyclization of **1a** with **2a** was confirmed, see the Supporting Information.

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