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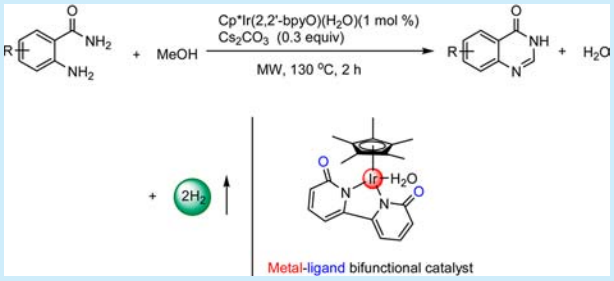
# Acceptorless Dehydrogenative Coupling of *o*-Aminobenzamides with the Activation of Methanol as a C1 Source for the Construction of Quinazolinones

Feng Li,*[†,‡] Lei Lu,[†] and Pengcheng Liu[†]

[†]School of Chemical Engineering, Nanjing University of Science & Technology, Nanjing 210094, China
[‡]State Key Laboratory of Fine Chemicals, Dalian University of Technology, Dalian 116024, China

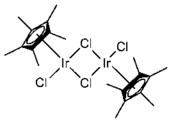
S *Supporting Information*

**ABSTRACT:** A strategy for the synthesis of quinazolinones via acceptorless coupling of *o*-aminobenzamides with methanol has been accomplished in the presence of the metal–ligand bifunctional catalyst [Cp*Ir(2,2′-bpyO)($H_2O$)]. Notably, this research exhibited the potential of transition-metal-catalyzed activation of methanol as a C1 source for the construction of heterocycles.



With increasing environmental awareness, the development of catalytic reactions with high atom economy using readily available materials is an important task for modern organic synthesis.[1] Methanol is an abundant and renewable source because it can be efficiently produced from a wide variety of sources including fossil fuels (natural gas, coal, oil shale, etc.), agricultural products, municipal waste, varied biomass, and carbon dioxide from the atmosphere. Although methanol has been widely used as a chemical feedstock, fuel, and energy storage media, catalytic transformations involving the dehydrogenative activation of methanol is still underdeveloped. It is also speculated that a relatively high energy is required for the dehydrogenation of methanol compared with higher alcohols, such as ethanol (DH = +84 vs +68 kJ $mol^{-1}$, respectively).[2] Very recently, transition-metal-catalyzed reactions with the activation of methanol have emerged and attracted great interest.[3−7] However, only a few examples are restricted to the production of hydrogen in the presence of water,[3] C−N bond-forming reactions,[4] C−C bond-forming reactions,[5] and functionalization of allenes[6] and indoles.[7] Despite the significant importance, the utilization of methanol as a C1 source for the construction of heterocycles remained unexplored.

We have developed a series of iridium-catalyzed environmentally friendly reactions.[8] As part of our continuing effort in this field, we are interested in the exploration of the acceptorless dehydrogenative coupling of *o*-aminobenzamides with methanol to quinazolinones, which are very important structural scaffolds of many naturally occurring alkaloids[9] and are generally synthesized via the condensation between *o*-aminobenzoic acids (or their esters) and formamide with the generation of high-molecular-weight byproduct under drastic conditions.[10,11]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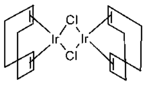
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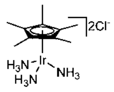

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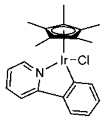
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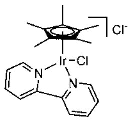

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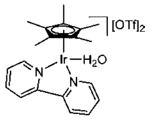

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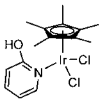
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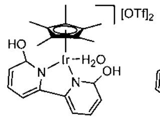

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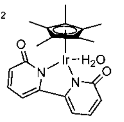
cat. 9

Initially, the coupling of *o*-aminobenzamide (**1a**) with methanol (**2**) as the reagent and solvent was selected as a model to explore the feasibility of the reaction. In the presence of $[Cp^*IrCl_2]_2$ (Cp* = pentamethylcyclopentadienyl) (catalyst **1**) (1 mol %) and $Cs_2CO_3$ (0.3 equiv), the reaction of **1a** with **2** was carried out at 150 °C for 12 h to afford quinazolinone **3a** in only 13% yield (Table 1, entry 1). When other iridium complexes, including $[Ir(cod)Cl]_2$ (cod = 1,5-cyclooctadienyl) (**2**), $[Cp^*Ir(NH_3)_3][Cl]_2$ (**3**), [Cp*Ir(2-phenylpyridine-*k*C,N)]Cl (**4**), [Cp*Ir(bpy)Cl)][Cl] (**5**), or $[Cp^*Ir(bpy)(H_2O)][OTf]_2$ (**6**), were used as the catalyst, product **3a** was obtained in ≤10% yield (Table 1, entries 2−6). Furthermore, metal−ligand bifunctional catalysts, such as $[Cp^*Ir(2\text{-}(OH)py)]Cl_2$ (**7**), $[Cp^*Ir(6,6\text{-}(OH)_2bpy)(H_2O)][OTf]_2$ (**8**), and [Cp*Ir(2,2′-bpyO)($H_2O$)] (**9**), were screened for this model reaction (Table 1, entries 7−9).[12,13] The presence of functional units in the ligand is crucially important for the improvement of catalytic activity of catalysts.

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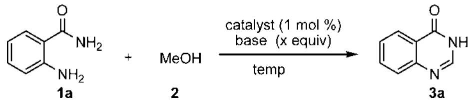
**Table 1. Coupling of *o*-Aminobenzamide (1a) with Methanol (2) under Various Conditions[a]**



| entry | catalyst | base | temp (°C) | time (h) | x | yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | cat. **1** | $Cs_2CO_3$ | 150 | 12 | 0.3 | 13 |
| 2 | cat. **2** | $Cs_2CO_3$ | 150 | 12 | 0.3 | n.d. |
| 3 | cat. **3** | $Cs_2CO_3$ | 150 | 12 | 0.3 | n.d. |
| 4 | cat. **4** | $Cs_2CO_3$ | 150 | 12 | 0.3 | n.d. |
| 5 | cat. **5** | $Cs_2CO_3$ | 150 | 12 | 0.3 | 10 |
| 6 | cat. **6** | $Cs_2CO_3$ | 150 | 12 | 0.3 | n.d. |
| 7 | cat. **7** | $Cs_2CO_3$ | 150 | 12 | 0.3 | 26 |
| 8 | cat. **8** | $Cs_2CO_3$ | 150 | 12 | 0.3 | 62 |
| 9 | cat. **9** | $Cs_2CO_3$ | 150 | 12 | 0.3 | 66 |
| 10 | cat. **9** | $Cs_2CO_3$ | 150 | 12 | 1.0 | 70 |
| **11** | **cat. 9** | $\mathbf{Cs_2CO_3}$ | **130 (MW)** | **2** | **0.3** | **88** |
| 12 | cat. **9** | $Cs_2CO_3$ | 130 (MW) | 2 | 0.2 | 80 |
| 13 | cat. **9** | $Cs_2CO_3$ | 120 (MW) | 2 | 0.3 | 78 |
| 14 | cat. **9** | $K_2CO_3$ | 130 (MW) | 2 | 0.3 | 83 |
| 15 | none | $Cs_2CO_3$ | 130 (MW) | 2 | 0.3 | 0 |
| 16 | cat. **9** | none | 130 (MW) | 2 | 0.3 | 0 |

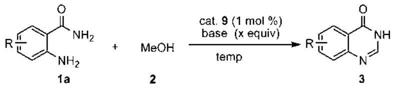
[a] Reactions conditions: **1a** (0.5 mmol), **2** (1 mL), catalyst (1 mol %), base (*x* equiv). [b] Isolated yield.

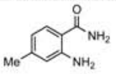
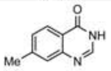
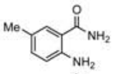
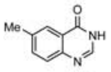
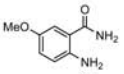
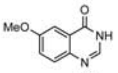
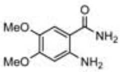
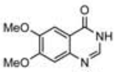
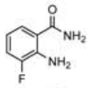
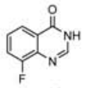
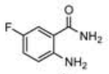
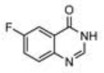
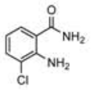
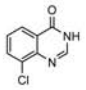
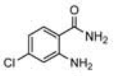
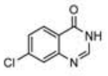
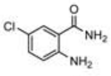
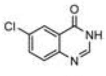
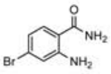
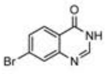
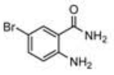
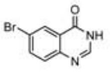
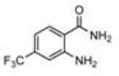
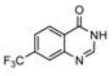
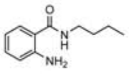
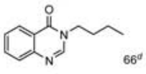
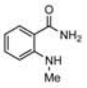
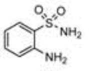
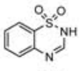
Among them, **9** exhibited the highest catalytic activity, and product **3a** was isolated in 66% yield. Increasing the amount of $Cs_2CO_3$ had no obvious effect on the yield of **3a** (Table 1, entry 10). The yield of **3a** could be enhanced to 88% when the reaction was carried out for 2 h at 130 °C in a focused, single-mode microwave synthesizer (Discover CEM, USA, 300 W) (Table 1, entry 11). Attempts to decrease the reaction temperature, reduce the amount of $Cs_2CO_3$, or use $K_2CO_3$ as an alternative base resulted in low yields (Table 1, entries 12–14). It was also observed that no reaction occurred in the individual presence of **9** and $Cs_2CO_3$ (Table 1, entries 15 and 16).

With the optimal conditions in hand (Table 1, entry 11), we investigated the coupling of a range of *o*-aminobenzamides (**1**) with methanol, and the results are summarized in Table 2. Transformations of *o*-aminobenzamides bearing one or two electron-donating groups (**1b**–**1e**) gave the corresponding products **3b**–**3e** in 86–91% yields (Table 2, entries 1–4). When *o*-aminobenzamides bearing a fluoride or chloride atom (**1f**–**1j**) were utilized, the desired products **3f**–**3j** were isolated in 68–77% yields (Table 2, entries 5–9). Couplings of bromated *o*-aminobenzamides (**1k**–**1l**) proceeded smoothly to give the corresponding products **3k** and **3l** in 80 and 82% yields, respectively (Table 2, entries 10 and 11). Furthermore, highly catalytic activity was found in the reaction of *o*-aminobenzamides bearing a stronger electron-withdrawing trifluoromethyl group (**1m**) (Table 2, entry 12). In the case of *o*-aminobenzamide bearing a steric hindrance on the N atom of an amido group (**1n**), corresponding product **3n** was successfully obtained in 66% yield, although stronger reaction conditions were required (Table 2, entry 13). However, none of product was found when *o*-aminobenzamide bearing an alkyl group on the N atom of an amino group (**1o**) was used a substrate (Table 2, entry 14). This catalytic system was also proven to be effective for *o*-aminobenzenesulfonamide (**1p**), affording the desired product **3p** in 76% yield (Table 2, entry 15).

A plausible mechanism is proposed to account for the present acceptorless dehydrogenative coupling of *o*-aminobenzamides with methanol for the construction of quinazolinones (Scheme 1). In cycle I, the bipyridonate ligand accepted a proton in the step of the activation of methanol to give methoxy iridium species **B**, which underwent *β*-hydrogen elimination to afford iridium hydride species **C** and formaldehyde. Companied by simultaneous transfer from the hydroxyl proton on the bpy ligand and the hydride on the iridium, hydrogen gas was released and catalytic species **A** was regenerated. Furthermore, the condensation between *o*-aminobenzamides and formaldehyde occurred to gave 2,3-dihydroquinazolinones. In cycle II, reaction of the resulting 2,3-dihydroquinazolinones and species **A**

**Table 2. Coupling of a Range of *o*-Aminobenzamides (1) with Methanol (2)[a]**



| entry | *o*-aminobenzamide | product | yield (%)[b] |
|---|---|---|---|
| 1 |  **1b** |  **3b** | 87 |
| 2 |  **1c** |  **3c** | 90 |
| 3 |  **1d** |  **3d** | 91 |
| 4 |  **1e** |  **3e** | 86 |
| 5 |  **1f** |  **3f** | 72 |
| 6 |  **1g** |  **3g** | 77 |
| 7 |  **1h** |  **3h** | 68[c] |
| 8 |  **1i** |  **3i** | 70[c] |
| 9 |  **1j** |  **3j** | 77 |
| 10 |  **1k** |  **3k** | 80 |
| 11 |  **1l** |  **3l** | 82 |
| 12 |  **1m** |  **3m** | 78 |
| 13 |  **1n** |  **3n** | 66[d] |
| 14 |  **1o** | — | |
| 15 |  **1p** |  **3p** | 76 |

[a] Reactions conditions: **1** (0.5 mmol), **9** (1 mol %), $Cs_2CO_3$ (0.3 equiv), MeOH (0.5 mL), MW, 130 °C, 2 h. [b] Isolated yield. [c] $Cs_2CO_3$ (1.0 equiv). [d] MeOH (1 mL).

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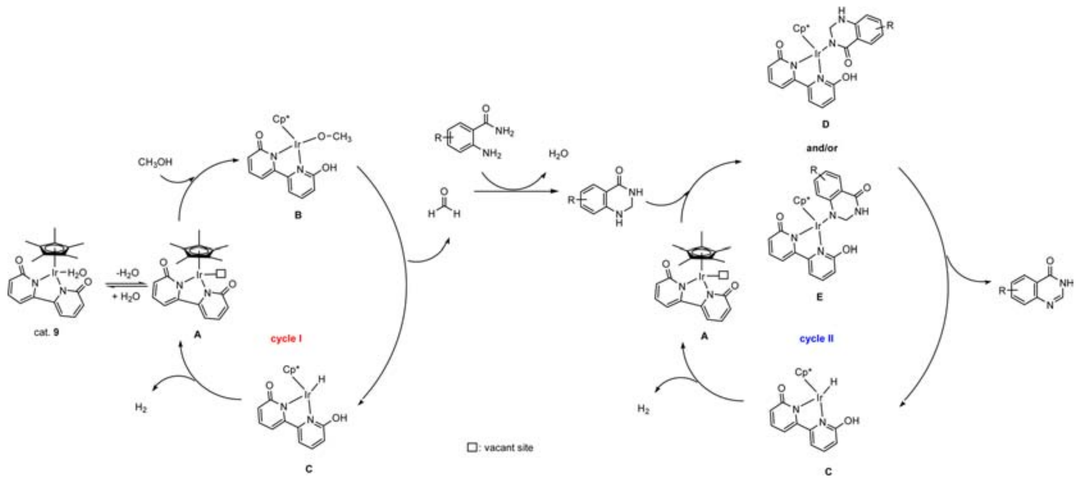
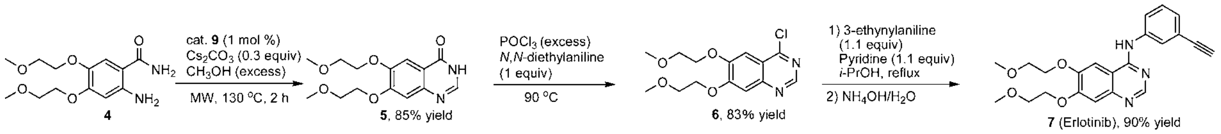
**Scheme 1. Proposed Reaction Mechanism**



**Scheme 2. Synthesis of Biologically Active Molecules**



afforded amino iridium species **D** and/or **E**, which underwent $\beta$-hydrogen elimination to afford iridium hydride species **C** with the liberation of quinazolinones as products. Similar to the case of cycle I, catalytic species **A** was regenerated and hydrogen gas was released, accompanied by ligand-promoted hydrogen transfer.

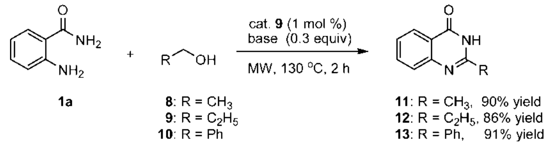
The liberation of gas in the coupling of **1a** with **2** (Table 1, entry 9) was collected by a gas buret by water displacement, and this gas was confirmed to be hydrogen gas by GC analysis and calculated to be 61% yield (283.15 K, 102 600 Pa, 14 mL). Additionally, the coupling of **1a** with paraformaldehyde was undertaken. In the presence of **9** (1 mol %) and $Cs_2CO_3$ (0.3 equiv), the reaction was carried out at 130 °C for 2 h under microwave irradiation to afford product **3a** in 82% yield. These results supported the proposed mechanism shown in Scheme 1.

Furthermore, synthesis of a biologically active molecule Erlotinib (the tyrosine kinase inhibitor, **7**)[14] was represented to demonstrate the practicality of the present methodology (Scheme 2). The reaction of 2-amino-4,5-bis(3-methoxypropyl)-benzamide (**4**) with methanol was performed under established conditions (Table 1, entry 11) to afford the key intermediate **5** in 85% yield. Subsequently, chlorination of **5** with phosphorus oxychloride gave product **6**, which was further converted to **7** (Erlotinib) via the amination with 3-ethynylaniline according to the reported methods.[15]

The present catalytic system was also expanded to acceptorless dehydrogenative coupling of *o*-aminobenzamide with other alcohols. As outlined in Scheme 3, reactions of **1a** with **8**−**10** afforded the desired products **11**−**13** in 86−91% yields.

In summary, we have demonstrated a novel and efficient strategy for the synthesis of quinazolinones via acceptorless coupling of *o*-aminobenzamides with methanol catalyzed by metal−ligand bifunctional catalyst [Cp*Ir(2,2′-bpyO)($H_2O$)]. Notably, this research exhibited the potential of transition-metal-catalyzed activation of methanol as a C1 source for the construction of heterocycles.

**Scheme 3. Acceptorless Dehydrogenative Coupling of *o*-Aminobenzamide with Other Alcohols**



## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00925.

> Experimental procedures and characterization data for all products (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: fengli@njust.edu.cn.

### Notes

The authors declare no competing financial interest.

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