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N-Methylation of Amines with Methanol Catalyzed by a Cp*Ir Complex Bearing a Functional 2,2′-Bibenzimidazole Ligand

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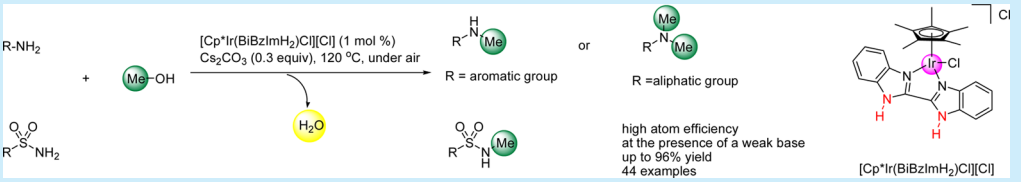
Supporting Information

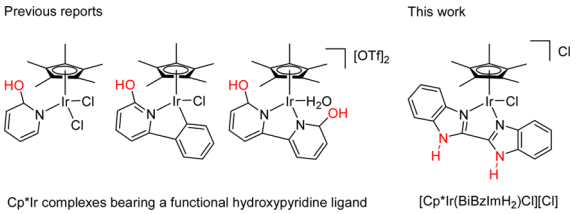


ABSTRACT: A new type of Cp*Ir complex bearing a functional 2,2′-bibenzimidazole ligand was designed, synthesized, and found to be a highly effective and general catalyst for the *N*-methylation of a variety of amines with methanol in the presence of a weak base (0.3 equiv of Cs_2CO_3).

The *N*-methylation of amines represents one of the most important C−N bond-forming reactions and is widely utilized for the synthesis of numerous fine chemicals, natural products, and pharmaceuticals.[1] Such transformations are traditionally performed using methyl iodide, dimethyl sulfate, or diazomethane as methylating agents in the presence of a stoichiometric amount of base. These procedures suffer from the use of highly toxic and carcinogenic methylating reagents, low selectivity of reaction, and the generation of excess waste. In recent years, considerable attention has been devoted to transition-metal-catalyzed *N*-methylation of amines with methanol as a methylating agent based on hydrogen autotransfer (or hydrogen-borrowing) processes[2] using ruthenium,[3] iridium,[4] or manganese complexes as catalysts.[5] In this process, methanol is initially dehydrogenated to afford formaldehyde and metal hydride species, followed by the condensation between the resulting formaldehyde and amines to afford unsaturated imines, which undergo transfer hydrogenation by the metal hydride species generated in the dehydrogenative step of methanol to produce *N*-methylamines. This method is highly attractive because methanol is an abundant and renewable C1 source[6] with high atom efficiency and environmental friendliness due to the formation of water as the only side product. Although significant advances have been made, these procedures usually require high temperature, long reaction time, and/or extra addition of phosphorus ligands due to a relatively high energy for the dehydrogenation of methanol compared with higher alcohols, such as ethanol (DH = +84 vs +68 kJ mol^{-1}, respectively).[7] Moreover, the presence of a strong base (KOtBu, LiOtBu, or NaOH) is necessary for all reported catalytic systems, and thus, the scope of substrates and synthetic potential are highly restricted. Recently, Seayad and co-workers reported a $[RuCp^*Cl_2]_2$/dpePhos/LiOtBu system that could catalyze the *N*-methylation of amines with methanol under relatively mild conditions (100 °C).[8] From both synthetic and environmental points of view, the development of a new type of organometallic catalyst for the *N*-methylation of amines with methanol in the presence of a weak base is highly desirable.

Very recently, Fujita, Yamaguchi, and co-workers developed a series of Cp*Ir complexes bearing a functional *α*-hydroxypyridine ligand, which exhibited high activity for the acceptorless dehydrogenation of alcohols based on the concept of "ligand-promoted dehydrogenation" (Scheme 1, left).[9] More recently,

Scheme 1. Cp*Ir Complexes Bearing a Functional Ligand



we have demonstrated that such complexes are highly effective catalysts for the activation of alcohols for the N-alkylation of sulfonamides[10] and the dehydrogenative cyclization for the construction of quinazolinones.[11] A mechanistic investigation revealed that protic hydrogens of OH units in the bpy ligand are crucially important for the catalytic activity, and thus, such complexes are metal−ligand bifunctional catalysts for the hydrogen autotransfer process. As part of our continuing interest in the development of iridium catalysts,[12] we herein describe the design, synthesis, and characterization of a new type of Cp*Ir complex bearing a 2,2′-bibenzimidazole ligand that contains protic hydrogens and a tautomerism structure like hydroxypyridine (Scheme 1, right). Furthermore, such a complex was found to be a highly effective and general catalyst for the *N*-methylation of a variety of amines with methanol.

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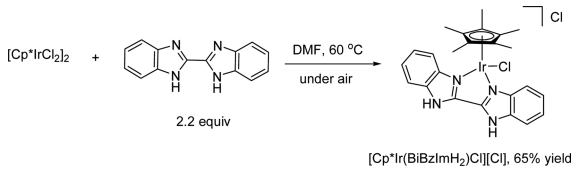
The Cp*Ir catalyst used in this study was prepared as shown in Scheme 2. The reaction of $[Cp^*IrCl_2]_2$ with 2,2′- bibenzimidazole was carried out at 60 °C for 12 h and was allowed to cool to ambient temperature. This complex is stable to air and moisture. Suitable crystals for X-ray crystallography were obtained. Clearly, 2,2′-bibenzimidazole as a ligand is coordinated to the iridium center in a bisdentate-N,N fashion (see the Supporting Information).

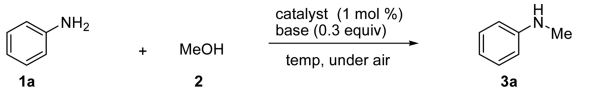
Scheme 2. Synthesis of $[Cp^*Ir(BiBzImH_2)Cl][Cl]$



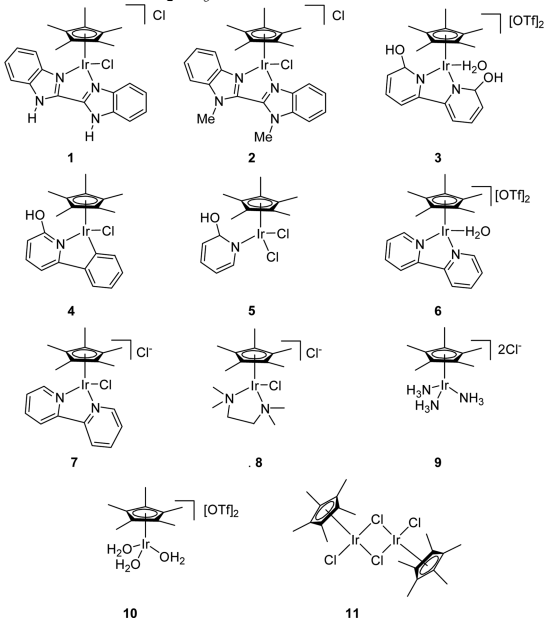
With this new type of Cp*Ir complex in hand, we next examined its catalytic activity for the *N*-methylation of aniline (**1a**) with methanol (**2**). The reaction was performed in the presence of $[Cp^*Ir(BiBzImH_2)Cl][Cl]$ (cat. **1**) (1 mol %) and Cs_2CO_3 (0.3 equiv) at 120 °C for 12 h to give the N-monomethylated product **3a** in >98% NMR yield (Table 1, entry 1). When $[Cp^*Ir(BiBzImMe_2)Cl][Cl]$ (cat. **2**) was used as an alternative catalyst, only 16% yield was obtained (Table 1, entry 2). Using Cp*Ir complexes bearing a functional α-hydroxypyridine ligand, such as $[Cp^*Ir(6,6'\text{-}(OH)_2bpy)(H_2O)][OTf]_2$ (cat. **3**), Cp*Ir[2-(2-(OH)py)phenyl]Cl (cat. **4**), and $[Cp^*(2\text{-}(OH)py)]Cl_2$ (cat. **5**) as a catalyst, the product **3a** was obtained in 47−90% yields (Table 1, entries 3−5). When other Cp*Ir complexes, including $[Cp^*Ir(bpy)(H_2O)][OTf]_2$ (cat. **6**), $[Cp^*Ir(bpy)Cl)][Cl]$ (cat. **7**), [Cp*Ir(2-phenylpyridine-*k*C,N)]Cl (cat. **8**), $[Cp^*Ir(H_2O)_3][OTf]_2$ (cat. **9**), $[Cp^*Ir(NH_3)_3][Cl]_2$ (cat. **10**), and $[Cp^*IrCl_2]_2$ (cat. **11**), were examined, the product **3a** could be obtained in ≤19% yield (Table 1, entries 6−11). Obviously, the number of NH or OH units in the ligand has a significant effect on the catalytic activity of a Cp*Ir complex. $[Cp^*Ir(BiBzImH_2)Cl][Cl]$ was chosen as the catalyst for further research. Attempts to decrease the reaction temperature, reduce the amount of Cs_2CO_3, or use K_2CO_3 and Na_2CO_3 as an alternative base resulted in relatively low yields (Table 1, entries 12−15). The yield of **2a** remained at 95% when the amount of methanol was reduced to 0.5 mL (Table 1, entry 6).

Encouraged by the promising results (Table 1, entry 1), the *N*-methylation of a variety of aromatic amines **1** with methanol **2** was evaluated, and these results are summarized in Scheme 3. Reactions of halogenated anilines gave the corresponding products **3b−g** in 83−94% yields. When anilines bearing an electron-withdrawing group, such as methylsulfonyl and trifluoromethoxy, were used as substrates, the desired products **3h** and **3i** were obtained in 92% and 95% yields, respectively. Sensitive functional groups, such as cyano, acetyl, and ester, were tolerated, and reactions afforded the desired products **3j−l** in 78−92% yields. Transformations of anilines containing an electron-donating group proceeded smoothly to give the corresponding products **3m−o** in 85−94% yields. This catalytic system was also applied to naphthylamine, aminopyridine, aminopyrazine, and aminoisoquinoline, affording the desired products **3p−t** in 84−95% yields. It was also found that only N-exo-substituted products **3u−w** were generated as sole products

Table 1. *N*-Methylation of Aniline with Methanol under Various Conditions[a]



entry	catalyst	base	temp (°C)	*x* (equiv)	yield[b] (%)
1	**1**	**Cs_2CO_3**	**120**	**0.3**	**>98 (94[c])**
2	**2**	Cs_2CO_3	120	0.3	16
3	**3**	Cs_2CO_3	120	0.3	90
4	**4**	Cs_2CO_3	120	0.3	53
5	**5**	Cs_2CO_3	120	0.3	47
6	**6**	Cs_2CO_3	120	0.3	19
7	**7**	Cs_2CO_3	120	0.3	16
8	**8**	Cs_2CO_3	120	0.3	<5
9	**9**	Cs_2CO_3	120	0.3	<5
10	**10**	Cs_2CO_3	120	0.3	40
11	**11**	Cs_2CO_3	120	0.3	33
12	**1**	Cs_2CO_3	120	0.1	81
13	**1**	Cs_2CO_3	110	0.3	52
14	**1**	K_2CO_3	120	0.3	84
15	**1**	Na_2CO_3	120	0.3	79
16	**1**	Cs_2CO_3	120	0.3	95[d]



[a]Reaction conditions: **1a** (0.5 mmol), **2** (1 mL), catalyst (1 mol %), base (*x* equiv), 12 h. [b]Yield was determined on the basis of the ^1H NMR spectrum of the crude reaction mixture. [c]Isolated yield. [d]**2** (0.5 mL).

in the regioselective *N*-methylation of amino-azoles using methanol as the methylating agent.

Furthermore, the *N*-methylation of a series of aliphatic amines **4** was then investigated (Scheme 4). Reactions of primary amines, such as *n*-octylamine, cyclohexanamine, amantadine, phenylethylamine, and 1,6-hexanediamine, afforded the corresponding N,N-dimethylated products **5a−e** in 78−94% yields.[13] Obviously, aliphatic amines are more nucleophilic than aromatic amines, and thus, *N*,*N*-dimethylated products were generated. Secondary aliphatic amines, such as 1,2,3,4-tetrahydroisoquinoline, piperazine, and 4-(3-(piperidin-4-yl)propyl)piperidine, could be converted to the desired *N*-methylated products **5f−i** in 78−83% yields.

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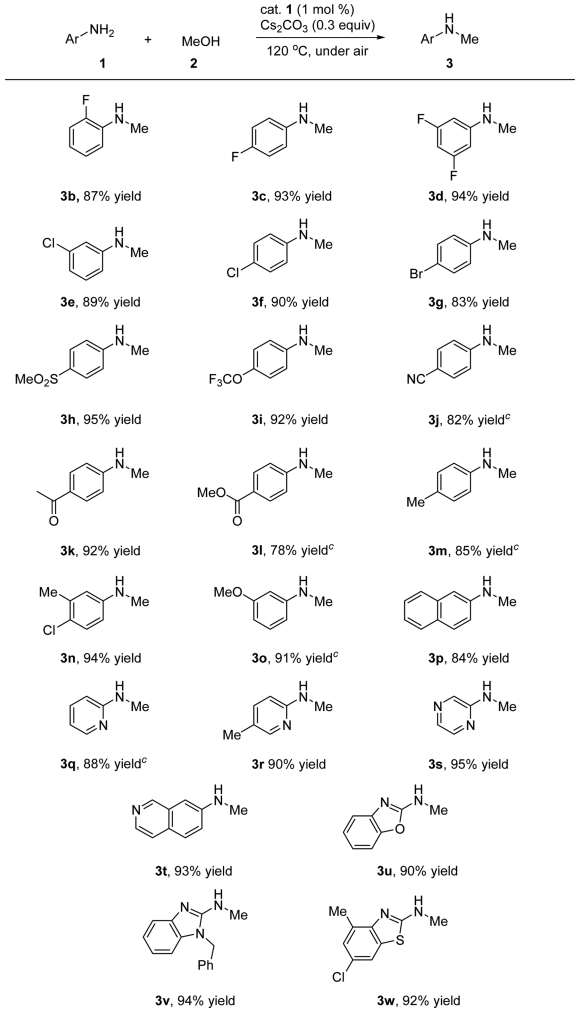
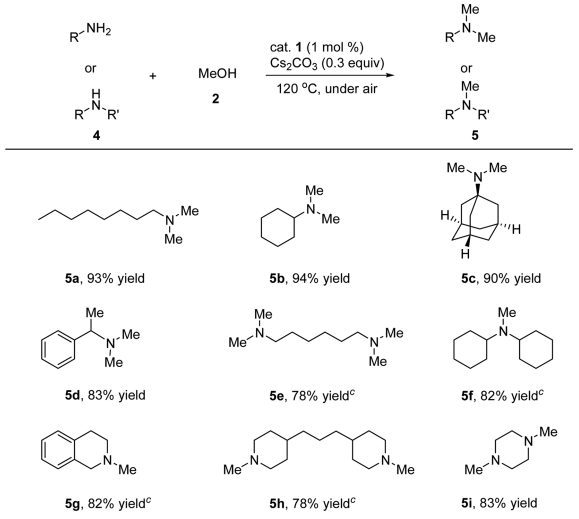
Scheme 3. *N*-Methylation of Various Aromatic Amines with Methanol Catalyzed by [Cp*Ir(BiBzImH$_2$)Cl][Cl]^{a,b}



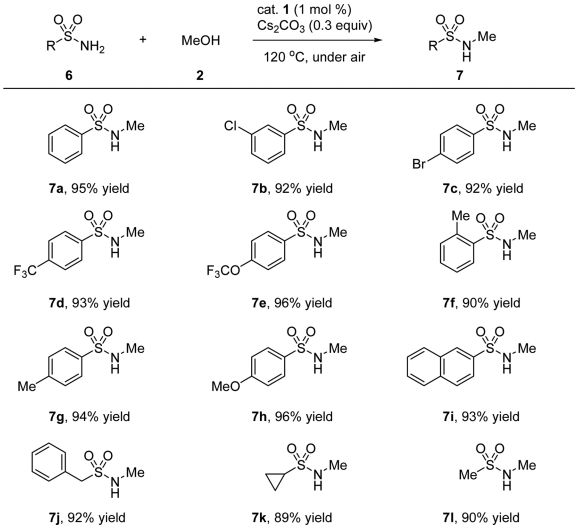
[a]Reaction conditions: **1** (0.5 mmol), **2** (1 mL), [Cp*Ir(BiBzImH$_2$)Cl][Cl] (1 mol %), Cs_2CO_3 (0.3 equiv), 120 °C, 12 h. [b]Isolated yield. [c]Cs_2CO_3 (0.5 equiv).

Scheme 4. *N*-Methylation of a Series of Aliphatic Amines with Methanol Catalyzed by [Cp*Ir(BiBzImH$_2$)Cl][Cl]^{a,b}



[a]Reaction conditions: **4** (0.5 mmol), **2** (1 mL), [Cp*Ir(BiBzImH$_2$)Cl][Cl] (1 mol %), Cs_2CO_3 (0.3 equiv), 120 °C, 12 h. [b]Isolated yield. [c]Cs_2CO_3 (0.5 equiv).

Scheme 5. *N*-Methylation of a Range of Sulfonamides with Methanol Catalyzed by [Cp*Ir(BiBzImH$_2$)Cl][Cl]^{a,b}



[a]Reaction conditions: **6** (0.5 mmol), **2** (1 mL), [Cp*Ir(BiBzImH$_2$)Cl][Cl] (1 mol %), Cs_2CO_3 (0.3 equiv), 120 °C, 12 h. [b]Isolated yield.

The *N*-methylation of a range of poorly nucleophilic sulfonamides **6** with methanol was then investigated (Scheme 5). Reactions of benzenesulfonamide, and benzenesulfonamides bearing an electron-withdrawing or electron-donating group, gave the corresponding products **7a**–**h** in 90–96% yields. In the case of naphthalenesulfonamide, the corresponding product **7i** was isolated in 93% yield. The catalytic system is suitable for aliphatic sulfonamides, affording the desired products **7j**–**l** in 89–92% yields.

A plausible mechanism is proposed to account for the *N*-methylation of amines with methanol catalyzed by [Cp*Ir(BiBzImH$_2$)Cl][Cl] (Scheme 6). The initial step of the reaction involved the formation of an unsaturated species **A** by the reaction of [Cp*Ir(BiBzImH$_2$)Cl][Cl] with Cs_2CO_3.[14] Furthermore, the ligand accepted a proton in the step of the activation of methanol, resulting in the generation of methoxy iridium species **B**, which underwent β-hydrogen elimination to afford an iridium hydride species **C** and formaldehyde.[15] The condensation between the resulting formaldehyde and amines gave unsaturated imines as intermediates. Accompanied by simultaneous transfer of the hydride on iridium and the proton on the 2,2′-bibenzimidazole of species **C** to the C=N bond of imine intermediates, *N*-methylamines were released as desirable products, and the catalytic species **A** were regenerated. A similar mechanism for the simultaneous delivery of hydride and proton to ketones or imines has been proposed in metal–ligand bifunctional catalysts, such as Shvo's catalyst[16] and Ru-TsDPEN systems.[17]

The present catalytic system was also applied to the synthesis of a biologically active molecule (an inhibitor of troponin I interacting kinase, TNNI3K)[18] (Scheme 7). The reaction of 3-bromobenzenesulfonamide **8** with methanol was performed in the presence of [Cp*Ir(BiBzImH$_2$)Cl][Cl] (1 mol %)/Cs_2CO_3 (0.3 equiv) at 120 °C for 12 h to afford the key intermediate **9** in 83% yield. Subsequently, Cu-catalyzed Ullmann-type ammonia-

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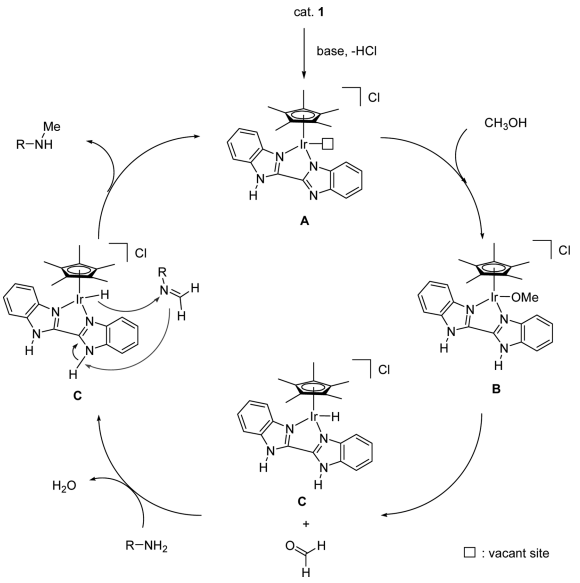
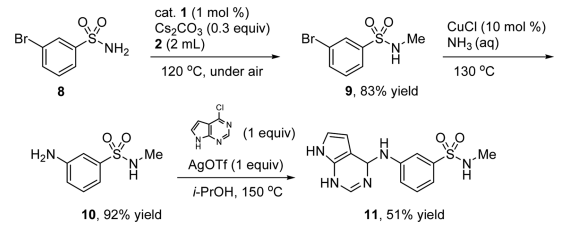
Scheme 6. Proposed Reaction Mechanism



Scheme 7. Synthesis of a Biologically Active Molecular



tion of **9** afforded the product **10**, which was further converted to the desired product **11** via SNAr reaction.

In summary, we have demonstrated the design and synthesis of a new type of Cp*Ir complex bearing a 2,2′-bibenzimidazole ligand and developed it as a highly effective and general catalyst for the *N*-methylation of a variety of amines with methanol in the presence of a weak base (0.3 equiv of Cs_2CO_3).

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data, and a CIF file giving crystallographic data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02723.

Experimental procedures and characterization data (PDF)

X-ray data for the Cp*Ir catalyst (CIF)

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Notes

The authors declare no competing financial interest.

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(13) As one of the reviewers suggested, reactions of **7a–e** with **2** were performed at lower temperature (60 °C). It was found that products were generated in <10% yields.

(14) The stoichiometric reaction of cat. **1** with a base (Cs_2CO_3) was performed in 120 °C for 12 h to afford an unidentifiable mixture by the analysis of ^{1}H NMR spectra. It was supposed that species **A** with a vacant site is not stable.

(15) A peak (δ −11.45) of [Ir-H] (species **C**) was observed in the ^{1}H NMR spectrum in the reaction of cat. **1** with **2**. It was speculated to be a characteristic signal of [Ir-H] (species **C**), see the Supporting Information.

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