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Article

N-Methylation of Amines with Methanol Catalyzed by Iridium(I) Complexes Bearing an N,O-Functionalized NHC Ligand

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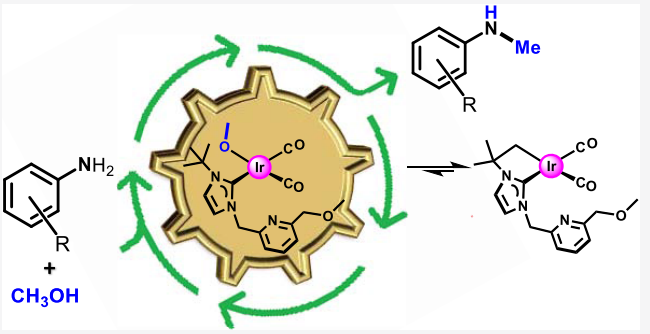
ABSTRACT: A set of neutral [IrBr(L$_2$)-(κC-^{t}BuImCH$_2$PyCH$_2$OMe)] and cationic [Ir(L$_2$)-(κ^2C,N-^{t}BuImCH$_2$PyCH$_2$OMe)]PF$_6$ (L$_2$ = cod, (CO)$_2$) Ir(I) compounds featuring a flexible lutidine-derived polydentate ligand having NHC and −OMe as donor functions have been evaluated as catalyst precursors for the *N*-methylation of aniline using methanol both as a reducing agent and a C1 source. The carbonyl complexes are somewhat more active than the related diene compounds with the neutral compound [IrBr(CO)$_2$(κC-^{t}BuImCH$_2$PyCH$_2$OMe)] being the more active. A range of aromatic primary amines, including heterocyclic amines, have been selectively transformed into the corresponding *N*-methylamino derivatives using this catalyst at a low catalyst loading (0.1 mol %) and substoichiometric amounts of Cs_2CO_3 (half equiv) as a base, in methanol at 423 K. For aliphatic primary amines, selective *N*,*N*-dimethylation was achieved under the same catalytic conditions. The unselective deprotonation of the methylene linkers in [IrBr(CO)$_2$(κC-^{t}BuImCH$_2$PyCH$_2$OMe)] affords two isomeric neutral complexes featuring a coordinated dearomatized pyridine core, which were converted into [Ir(OMe)(CO)$_2$(κC-^{t}BuImCH$_2$PyCH$_2$OMe)] upon addition of methanol. This compound undergoes thermal activation of a C−H bond of the tert-butyl group to give the cyclometalated iridium(I) complex [Ir(CO)$_2${κ^2C,C-(-CH$_2$Me$_2$C-ImCH$_2$PyCH$_2$OMe)}] featuring a bidentate *C*,*C*-coordinated NHC ligand. Mechanistic investigations support a borrowing hydrogen mechanism proceeding through iridium(I) intermediates with the methoxo complex as the catalytic active species and the cyclometalated complex as the catalyst resting state. Deuterium labeling experiments have demonstrated that both species are in equilibrium under catalytic conditions, which is consistent with the exhibited catalytic activity of the cyclometalated complex.



INTRODUCTION

The development of efficient and environmentally friendly catalytic strategies for the easy formation of carbon−nitrogen bonds is an important goal in organic chemistry. *N*-substituted amines, and in particular *N*-methylamines, play an important role as key intermediates and building blocks in synthetic organic chemistry, agrochemicals, and materials.[1] In addition, many medicinal drugs contain one or multiple *N*-methylated amino subunits in their core structures that perform important functions in the regulation of biological and pharmaceutical properties.[2]

Traditional synthetic methodologies to produce *N*-methylated molecules require toxic and hazardous stoichiometric reagents such as methyl halides, dimethyl sulfate, or diazomethane, which produce large amounts of waste and generally exhibit low selectivities as a result of the formation of overalkylated products.[3] Therefore, the development of new synthetic strategies to reduce environmental impact is a topical challenge for both chemical and pharmaceutical industries.[4] The reductive amination involving formic acid, formaldehyde, or carbon dioxide, and the use of dimethyl carbonate,[4b,5] dimethyl sulfoxide (DMSO),[6] CH_3NO_2,[7] or Me_3NBH_3[8] as methylating agents are more sustainable alternatives that have been intensively studied in the last decade. Nonetheless, some of them still suffer from low atom economy and require harsh reaction conditions or an excess of reducing agents.[4b,9] Methanol has been actively investigated as a hydrogen source,[10] C1 reagent for catalytic organic transformations,[11,12] and energy applications,[13] and has emerged as a greener approach in the methylation of amines[14] and nitroarene derivatives.[15] In this regard, methanol is a convenient methyl source because it is less hazardous, cheap, and available from

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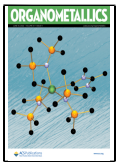
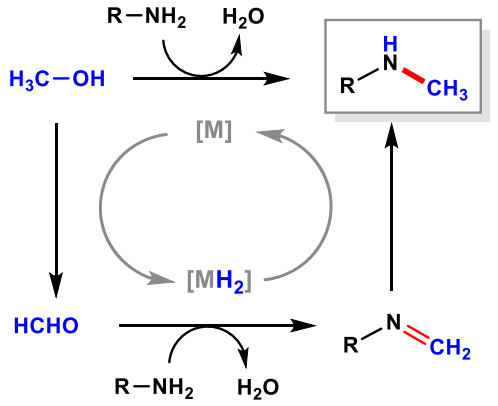


many plentiful sources, and it only produces water as a byproduct in the methylation processes.

Transition-metal-catalyzed *N*-alkylation of amines by alcohols based on hydrogen autotransfer or borrowing hydrogen methodology[16−18] has attracted considerable attention. Particularly, *N*-methylation of amines with methanol is a powerful atom-economical catalytic strategy that has been significantly expanded during the last few years[14,19] after the pioneering reports by Grigg,[20] Porzi,[21] Watanabe,[22] and Jenner[23] in the 1980s. Under borrowing hydrogen conditions, formaldehyde is formed by hydrogen transfer dehydrogenation of methanol and the *N*-methylamine product is obtained by hydrogenation of the in situ generated methanimine intermediate by metal hydride species (Scheme 1). The main challenge of this

Scheme 1. Borrowing Hydrogen Mechanism for the *N*-Methylation Amines Using Methanol as a C1 Source (MH_2 Results from the Formal Abstraction of Two Hydrogen Atoms by the Catalyst)



methodology is to overcome the high energy demand of methanol dehydrogenation (*i.e.*, for methanol ΔH = 84 kJ·mol^{-1} *vs* 68 kJ·mol^{-1} for ethanol).[24] A number of homogeneous and heterogeneous transition-metal-based catalysts have been developed, with ruthenium[14a,25] and iridium[14b,e,26] catalysts being the most active. In addition, some examples of catalysts based on non-noble metals—cobalt,[27] iron,[11c,28] or manganese[11b,29]—among others, have also been reported recently.

N-heterocyclic carbenes (NHCs) have emerged as powerful ligands to enhance catalytic activity, due to their strong coordination ability and tunable electronic and steric properties, in a wide range of catalytic transformations.[30] However, only a few Ir-NHC catalysts efficient in the *N*-methylation of amines have been reported to date (Figure 1). Crabtree and co-workers reported efficient cationic bis-NHC iridium(I) catalysts for the selective monomethylation of substituted anilines under microwave irradiation and high catalyst loading conditions.[31] Fujita reported the selective *N,N*-dimethylation of aliphatic primary amines and *N*-monomethylation using Cp*Ir(NHC)-based catalysts at low catalyst and base loadings. Interestingly, the *N,N*-dimethylation of aromatic primary amines was also achieved with a related catalyst in the absence of base.[32] Recently, Hou et al. showed that the introduction of 2-arylbenzo[*d*]oxazole-functionalized benzyimidazol-2-ilydene ligands improves the catalyst performance in the *N*-methylation of ortho-substituted aromatic amines, thereby broadening the substrate scope.[26f] In addition, the related bimetallic bis-NHC Cp*Ir complex reported by Hou and Li

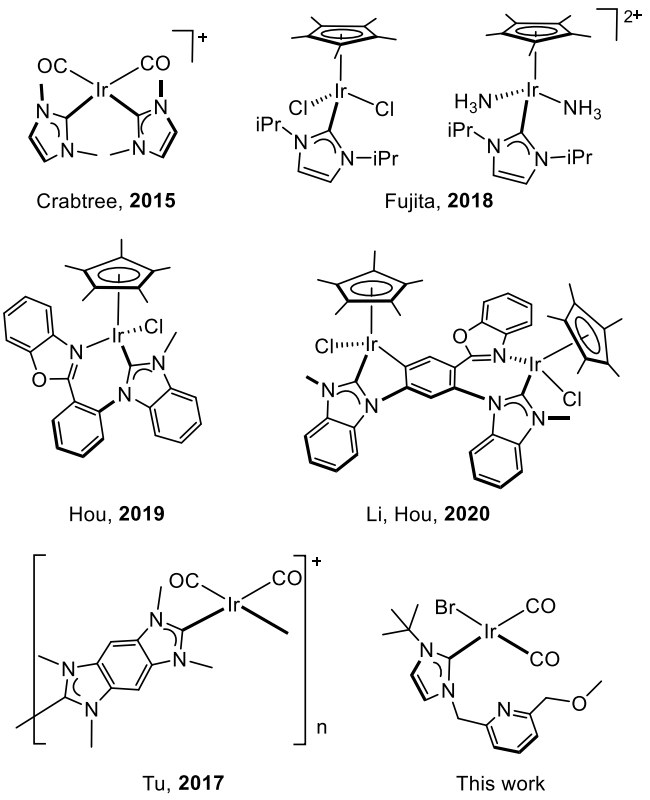


Figure 1. Ir-NHC catalysts for the *N*-methylation of Amines with Methanol.

showed significantly higher activity than the monometallic analogues.[26b] Moreover, using the "self-supporting" strategy,[33] a series of NHC-metal coordination assemblies have been developed. Among them, the NHC-Ir coordination assembly shown in Figure 1 was successfully applied as solid molecular recyclable catalysts in the selective mono-*N*-methylation of amines.[26h]

Iridium(I) complexes bearing NHC ligands with O/N-donor functions have been revealed as efficient catalysts for the *β*-alkylation of alcohols and *N*-alkylation of amines with alcohols via a borrowing hydrogen mechanism.[18] The incorporation of *O*- and *N*-functional groups as wingtips in NHC ligands usually results in enhanced catalytic performance probably due to their ability to assist the metal center in catalytic transformations. In this context, we have recently shown that [IrBr(CO)$_2$(*κC*-tBuImCH$_2$PyCH$_2$OMe)] (Figure 1) featuring a flexible lutidine-derived polydentate ligand, having NHC and −OMe as donor functions, efficiently catalyzes the selective *N*-monomethylation of a range of nitroarenes using methanol as both the reducing agent and the C1 source.[15a] Herein, we report on the catalytic activity in the *N*-methylation of amines of a series of neutral and cationic iridium(I) complexes derived from this pyridine/OMe-functionalized NHC ligand and their application in the *N*-methylation of a range of anilines and alkyl amines. In addition, reactivity and mechanistic studies have been performed to shed light on the operating mechanism of this tandem transformation.

RESULTS AND DISCUSSION

Synthesis and Structure of Iridium(I) Complexes Bearing an N,O-Functionalized NHC Ligand. The

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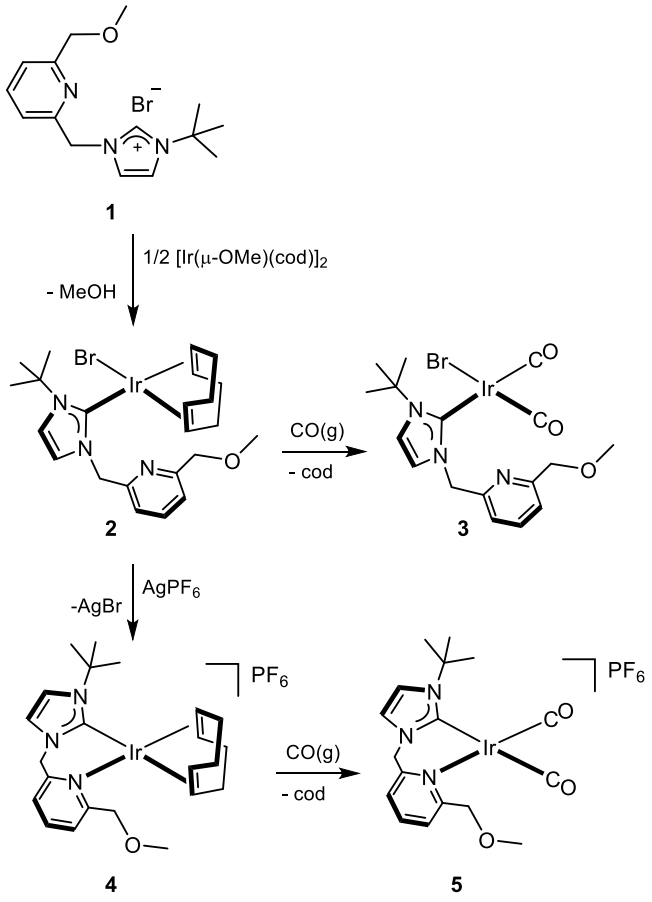
imidazolium salt [^{t}BuImHCH$_2$PyCH$_2$OMe]Br (**1**), precursor for the N,O-functionalized NHC ligand, was prepared from the commercially available 2,6-bis(bromomethyl)pyridine in two steps following the synthetic procedure recently reported by us.[15a,34] Deprotonation of **1** by the methoxo bridging ligands of [Ir(μ-OMe)(cod)]$_2$ gave the iridium(I) diene complex [IrBr(cod)(κC-^{t}BuImCH$_2$PyCH$_2$OMe)] (**2**), which was carbonylated in dichloromethane to afford [IrBr(CO)$_2$(κC-^{t}BuImCH$_2$PyCH$_2$OMe)] (**3**). The reaction of complex **2** with silver hexafluorophosphate (1:1) in CH_2Cl_2 resulted in the precipitation of AgBr and the formation of a yellow solution of the cationic complex [Ir(cod)(κ^2C,N-^{t}BuImCH$_2$PyCH$_2$OMe)][PF$_6$] (**4**) which was isolated as a yellow solid in 87% yield. Carbonylation of **4** in CH_2Cl_2 led to the release of the cod ligand with concomitant formation of the complex [Ir(CO)$_2$(κ^2C,N-^{t}BuImCH$_2$PyCH$_2$OMe)][PF$_6$] (**5**), which was isolated as a yellow solid in 79% yield (Scheme 2).

Scheme 2. Synthetic Pathway for the Preparation of Neutral and Cationic Ir(I)/(^{t}BuImCH$_2$PyCH$_2$OMe) Complexes



The high-resolution mass spectra (ESI+) in methanol for complexes **4** and **5** showed peaks at m/z 560.2241 and 508.1208, respectively, that match the mass of the corresponding cations. Furthermore, the measured conductivity in nitromethane of approximately 80 Ω^{-1} cm^2 mol^{-1} for both compounds is in agreement with that of 1:1 electrolytes. It is noticeable that as a consequence of the conformational restriction imposed by the coordination of the pyridine fragment to the metal center, the protons of both methylene linkers are diastereotopic and consequently were observed as four well-separate doublets (**4**) or two AB quartets (**5**) in the ^{1}H NMR spectra which contrast with the singlet resonance observed for the protons of the CH$_2$-OMe moiety in the neutral complexes **2** and **3**. On the other hand, the resonances of the CH$_2$-Im linker in **4** are high-field shifted with respect to **2**, reasonably as a consequence of the coordination of the pyridine fragment (see the Supporting Information).[35] The existence of two carbonyl ligands in a *cis* disposition in **5** was confirmed by two strong stretching ν(CO) bands at 2069, 1994 cm^{-1} in the attenuated total reflectance-infrared (ATR-IR) spectrum and two resonances at δ 179.2 and 171.7 ppm in the ^{13}C{^{1}H} spectra.

The κ^2C,N coordination mode of the lutidine-based NHC/OMe ligand in complexes **4** and **5** (vide infra, Figure 2), in contrast to the κC of the parent compounds, was established by single-crystal X-ray diffraction analysis.

The crystal structures of **4** and **5** show a slightly distorted square-planar environment for the iridium center. In both complexes, the NHC-lutidine ligand exhibits a κ^2C,N coordination mode rendering the six-membered metalacycle Ir-C1-N2-C6-C7-N8 (Figure 2). The visual inspection of this cycle as well as the corresponding Cremer−Pople puckering parameters[36] (**4**, q 0.9876 Å, θ 99.51°, φ 1.4116°; **5**, q 1.0482 Å, θ 78.08°, φ 177.4009°) clearly indicate a boat conformation featuring the iridium center and the C6 atom in the out-of-plane positions. The bite angle C1-Ir-N8 of the NHC-lutidine ligand is slightly smaller in **4** [81.4(2)°] than in **5** [83.87(11)°] reasonably as a consequence of steric hindrance of the cod ligand. In both cases, the NHC moiety and the pyridine fragment deviate from the least sterically hindered arrangement perpendicular to the coordination plane, i.e., Ir-C1-N8-CT01-CT02, **4**, or Ir-C1-N8-C20-C22, **5**, each ring forming angles between 50° and 70° with the corresponding coordination plane (**4**, NHC 59.0°, pyridine 67.7°; **5**, NHC 51.8°, pyridine 54.3°). This behavior should be the consequence of the constraint imposed by the above-mentioned κ^2C,N coordination mode. In this connection, it is worth mentioning that the NHC deviates significantly from the ideal arrangement with respect to the Ir-C1 bond (**4**: pitch 2.6°, yaw 15.0°; **5**: pitch 0.6°, yaw 13.8°),[37] whereas a minor deviation is observed for the pyridine ring with respect to the Ir-N8 bond (**4**: pitch 6.1°, yaw 5.0°; **5**: pitch 0.1°, yaw 3.1°).

The remaining coordination sites at the metal center are occupied by one cyclooctadiene ligand (**4**) or two carbonyl ligands (**5**). It is worth mentioning that in **4** the NHC group exerts a higher trans influence than the pyridine moiety. As a matter of fact, the Ir-CT01 distance [2.0641(3) Å] −trans to NHC− is longer than the Ir-CT02 one [2.0186(3) Å], and accordingly, the C20−C21 bond length [1.384(8) Å] is shorter than the C24−C25 one [1.420(8) Å]. As for **5**, reasonably the strong π-acceptor character of the carbonyl ligands blurs the different *trans* influence of the NHC and pyridine moieties, which results in the fact that the C20−O21 [1.136(4) Å] and C22−O23 [1.137(4) Å] bond lengths are similar, whereas the Ir-C20 bond length [1.886(4) Å] is minimally longer than the Ir-C21 one [1.850(4) Å].

Finally, Figure 2c shows the overlay of the crystal structures of **4** and **5** demonstrating that the overall arrangements of the N,O-functionalized NHC ligand in both complexes are similar except for the conformation of the methoxymethyl substituent at the 6-position of the pyridine moiety (N8-C9-C17-O18,

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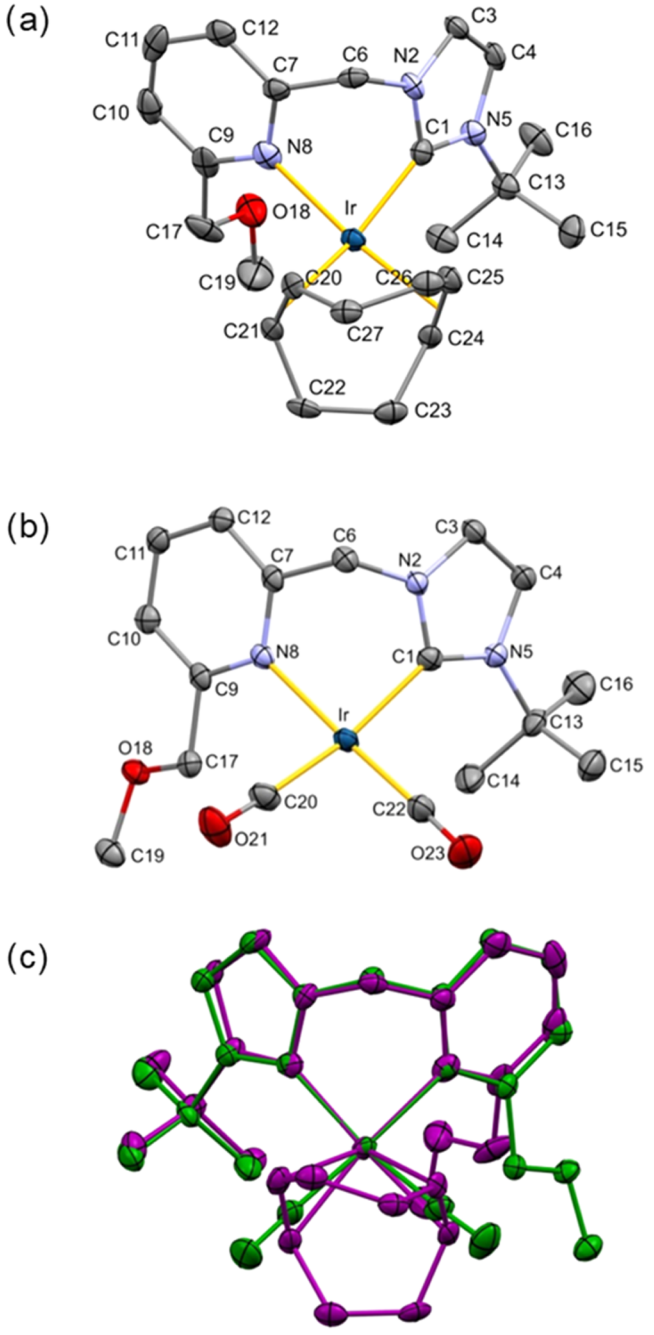

Figure 2. ORTEP view of the cation of (a) compound **4**, (b) compound **5**, and (c) overlay of the crystal structure of **4** (purple) and **5** (green). Ellipsoids are at 50% probability; hydrogen atoms and the hexafluorophosphate anion are omitted for clarity. Selected bond lengths (Å) and angles (°) are: **4**, Ir-C1 2.054(6), Ir-N8 2.122(5), Ir-CT01 2.0641(3), Ir-CT02 2.0186(3), C20-C21 1.384(8), C24-C25 1.420(8), C1-Ir-N8 81.4(2), CT01-Ir-CT02 86.314(13); **5**, Ir-C1 2.082(3), Ir-N8 2.122(3), Ir-C20 1.886(4), Ir-C22 1.850(4), C20-O21 1.136(4), C22-O23 1.137(4), C1-Ir-N8 83.87(11), C20-Ir-C22 89.68(16). CT01 and CT02 are the centroids of the C20 and C21 atoms, and of the C24 and C25 atoms, respectively.

−79.0(7)° **4**, 166.1(3)° **5**), which may be the consequence of the solid state packing.

***N*-Methylation of Amines with Methanol Catalyzed by Iridium(I) Complexes.** The neutral and cationic Ir(I) complexes **2**−**5** bearing an N,O-functionalized NHC ligand have been evaluated as catalysts for the *N*-methylation of amines using aniline as model substrate and methanol as C1 source under the following standard reaction conditions: [aniline] = 0.33 M, 1 mol % of catalyst, 50 mol % of Cs_2CO_3 as a base, and 1.5 mL of MeOH at 383 K for 5 h (Table 1). The four catalysts showed comparable activity giving conversions greater than 30% with complete selectivity to *N*-methylaniline. In contrast, low conversion was attained with the iridium dimer $[Ir(\mu\text{-Cl})(cod)]_2$ under the same reaction conditions to give a mixture of the mono- and dimethylated products (entry 2). The carbonyl compound $[IrBr(CO)_2(IMe)]$,[38] with an unfunctionalized 1,3-dimethylimidazol-2-ylidene ligand, afforded only a 5% conversion to *N*-methylaniline (entry 3). However, the related compound $[IrBr(CO)_2(\kappa C\text{-MeImCH}_2Py)]$ bearing a pyridine-functionalized NHC ligand, prepared by carbonylation of the diene compound, gave a 22% of conversion to *N*-methylaniline (entry 4), lower than that attained with complexes **2**−**5**. In general, the carbonyl complexes **3** and **5** were found to be more active than the parent diene complexes **2** and **4** (entries 4−7) being compound $[IrBr(CO)_2(\kappa C\text{-}^t\text{BuImCH}_2\text{PyCH}_2\text{OMe})]$ (**3**) the most active catalyst with a 40% conversion to *N*-methylaniline in 5 h. Although the cationic compound **5** is only slightly less active than **3**, the latter has been chosen for the optimization process due to its easy synthesis.

The close performance of cod and carbonyl catalysts might suggest the formation of similar catalytic active species. In fact, methanol decarbonylation under catalytic conditions could transform compound **2** into **3** in a multistage process involving C−H activation of formaldehyde.[39] However, the infrared spectrum of the reaction mixture resulting from the reaction of **2** with methanol in the presence of Cs_2CO_3 at 403 K did not show the presence of Ir-CO species ruling out the transformation between both types of compounds under these conditions.

Optimization of the reaction conditions, including base, base/substrate ratio, temperature, and catalyst loading, was carried out for the benchmark reaction of *N*-methylation of aniline with methanol using catalyst **3** (see the Supporting Information). Several organic and inorganic bases such as KHMDS, NaOMe, KOtBu, NaH, NaOH, KOH, K_2CO_3, and Cs_2CO_3, have been investigated under the standard conditions. The best catalytic performance was attained with Cs_2CO_3 as a base using a minimum amount of 50 mol %. The temperature has a strong influence on the catalytic activity. Indeed, a progressive increase in conversion to *N*-methylaniline from 40% at 383 K to 100% at 423 K was observed. Interestingly, the catalyst loading can be lowered up to 0.5 mol % at 423 K affording a 97% conversion to *N*-methylaniline. Based on these results, the optimized reaction conditions are as follows: 0.5 mol % of **3**, 50 mol % of Cs_2CO_3, methanol (1.5 mL), and 423 K for a reaction time of 5 h. Finally, a catalytic test in the presence of mercury (4 equiv), under the optimized catalytic conditions, gave similar results, confirming that the catalytic reaction proceeds in a homogeneous phase.[40]

To explore the substrate scope of this catalytic system, the *N*-methylation of a range of substituted anilines and alkyl amines with methanol was carried out under the optimized reaction conditions (Table 2). In general, good conversions with complete selectivity to mono-*N*-methylation products were attained with aniline derivatives. Aniline derivatives with electron-donating groups in para position were quantitatively transformed into the corresponding *N*-methyl derivatives **6b** and **6c** and isolated in yields higher than 90%. Both derivatives

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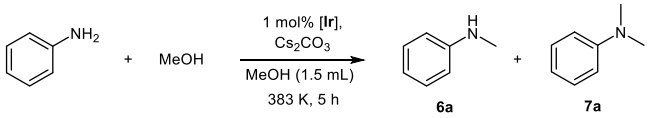
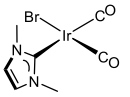
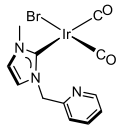
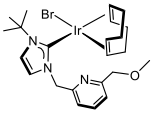
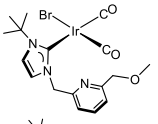
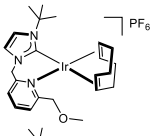
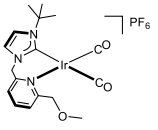
Table 1. Catalysts Evaluation for the *N*-Methylation of Aniline with Methanol[a]



	Catalyst		Conversion (%)	Selectivity (%)[b]	
				6a	7a
1	-		0	0	0
2	[Ir(μ-Cl)(cod)]$_2$		13	89	11
3			5	100	-
4			22	100	-
5		**2**	34	100	-
6		**3**	40	100	-
7		**4**	33	100	-
8		**5**	38	100	-

[a]Reaction conditions: aniline (0.5 mmol), catalyst (0.005 mmol, 1.0 mol %), Cs_2CO_3 (0.25 mmol, 50 mol %) in methanol (1.5 mL) at 383 K for 5 h. [b]Conversion of aniline and selectivity determined by gas chromatography (GC) using mesitylene as the internal standard.

are more reactive than aniline. In fact, additional catalytic experiments performed at 2.5 h showed 88% of conversion for the *N*-methylation of 4-methoxyaniline to 4-methoxy-*N*-methylaniline (**6c**), whereas a 79% conversion was attained in the *N*-methylation of aniline to **6a**. Also, para-substituted anilines with weak electron-withdrawing groups, such as 4-chloroaniline and 4-bromoxyaniline, were selectively transformed into the corresponding *N*-methyl derivatives **6d** and **6e**, respectively, which were isolated in yields higher than 95%. In contrast, substrates with a strong electron-withdrawing group, such as 4-(trifluoromethyl)aniline, proved to be less reactive as only a 50% conversion was achieved in 5 h with total selectivity to 4-(trifluoromethyl)-*N*-methylaniline (**6f**). Increasing the reaction time to 15 h resulted in a slight improvement in conversion up to 61%, but selectivity decreased significantly to 55% due to the formation of methyl 4-aminobenzoate and methyl 4-(methylamino)benzoate as byproducts. In this regard, methanolysis of the $-CF_3$ group in basic media[41] gives rise to the aminobenzoate derivative, which is subsequently methylated to give the product 4-(methylamino)benzoate. Increasing the catalyst loading to 2 mol % and decreasing the temperature to 383 K resulted in a 93% conversion in 48 h although the selectivity to **6f** was only 43%.

Regarding ortho- and meta-substituted methoxyaniline derivatives, longer reaction times and/or higher catalyst loadings were necessary to achieve selectivities above 90% for the desired *N*-methylanilines **6g** and **6h** (Table 2). Particularly, the *o*-anisidine derivative is by far the least reactive, requiring a catalyst load of 3 mol % and 48 h to achieve complete conversion to 2-methoxy-*N*-methylaniline (**6g**). On the other hand, *m*-anisidine is slightly less reactive than *p*-anisidine with full conversion to **6h** in 8 h. The negative influence of the substitution at both ortho positions on the reactivity was evident with 2,6-dimethylaniline since no reaction was observed even using a 2 mol % catalyst loading and 100 mol % of base after 48 h. Catalyst **3** is also efficient in the *N*-methylation of the heterocyclic amines such as 4-aminopyridine. Although the reaction is slower than with aniline, *N*-methylpyridin-4-amine (**6j**) was selectively obtained in 15 h. Therefore, the observed decrease in reactivity appears to be a consequence of the electron-poor character of the heterocycle rather than the inhibition of the catalysis by coordination of the pyridine fragment to the metal center.

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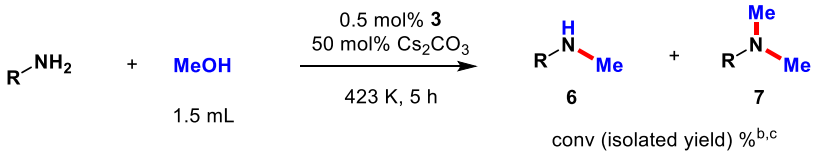
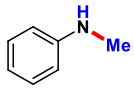
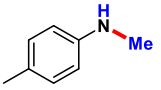
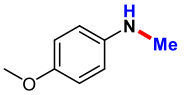
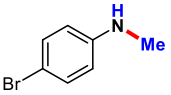
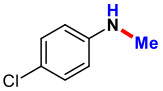
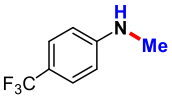
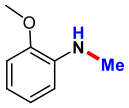
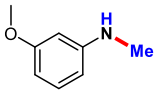
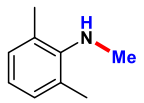
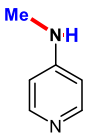
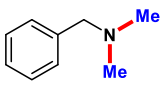
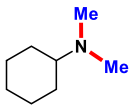
Table 2. *N*-Methylation of Aromatic and Aliphatic Amines with Methanol Catalyzed by $[IrBr(CO)_2(\kappa C\text{-}^tBuImCH_2PyCH_2OMe)]$ (3)[a]



 **6a**	 **6b**	 **6c**	 **6d**
2.5 h, 79% 5 h, 97% (92)	5 h, 100% (92)	2.5 h, 88% 5 h, 100% (93)	5 h, 100% (96)
 **6e**	 **6f**	 **6g**	 **6h**
5 h, 100% (97)	0.5 mol% **3**, 5 h, 50% 0.5 mol% **3**, 15 h, 61%[d] 2 mol% **3**, 48 h, 93%[d,e,f]	0.5 mol% **3**, 5 h, 30% 1 mol% **3**, 15 h, 42% 2 mol% **3**, 24 h, 62% 3 mol% **3**, 48 h, 100% (98)	5 h, 86% 8 h, 100% (86)
 **6i**	 **6j**	 **7k**	 **7l**
0.5 mol% **3**, 5 h, 0% 2 mol% **3**, 48 h, 0%[g]	5 h, 78% 15 h, 100%[f]	5 h, 75% 15 h, 100%[f]	0.5 mol% **3**, 5 h, 30% 1 mol% **3**, 15 h, 56%[h] 1 mol% **3**, 48 h, 100%[f,h]

[a]Reaction conditions: amine (0.5 mmol), Cs_2CO_3 (0.25 mmol, 50 mol %) in methanol (1.5 mL) at 423 K. [b]Conversion based on the amine. Selectivity determined by GC using mesitylene as the internal standard. [c]Isolated yield (%) in parentheses after purification by column chromatography. [d]Selectivity to **6f** of 55 and 43%, respectively. [e]383 K. [f]Not isolated. [g]100 mol % of Cs_2CO_3. [h]Selectivity to **7l** of 65 and 86%, respectively.

On the other hand, the *N*-alkylation of aliphatic amines selectively affords *N*,*N*-dimethylated amines which is in agreement with previous results.[25−27] Thus, benzylamine was selectively transformed in *N*,*N*-dimethyl-1-phenylmethanamine (**7k**) in 15 h. However, *N*-methylation of cyclohexylamine required a higher catalyst loading and longer reaction time to achieve complete conversion to the *N*,*N*-dimethylcyclohexanamine product (**7l**). In this case, it was possible to observe the formation of the monomethylated intermediate product, *N*-methylcyclohexanamine (**6l**), which is the major product at very low conversions, and its transformation to **7l** at higher conversions. In general, *N*-methylated amines are isolated in good yields, except when byproducts are formed, e.g., 4-trifluotomethyl-aniline, or when double methylation occurs.

Reactivity of $[IrBr(CO)_2(\kappa C\text{-}^tBuImCH_2PyCH_2OMe)]$ (3). Metal−ligand cooperation, MLC, based on the dearomatization of pyridine-based pincer complexes has provided a new paradigm for bond activation and homogeneous catalysis. Particularly, Ru(II)-dearomatized five-coordinate lutidine-derived PNP and PNN pincer complexes heterolytically activate polar and nonpolar chemical bonds.[42] Metal complexes based on lutidine-derived CNC, CNP, and CNN pincer ligands (C stands for an NHC moiety) have also received considerable attention in recent years.[43] Although deprotonation of asymmetric lutidine-derived pincer ligands can take place in both methylene arms, selective deprotonation of one of the arms has generally been observed.[44]

In this context, to determine the ability of the N,O-functionalized NHC ligand in $[IrBr(CO)_2(\kappa C\text{-}^tBuImCH_2PyCH_2OMe)]$ (**3**) to undergo dearomatization−aromatization processes of relevance in cooperative catalysis, the acidic nature of the methylene protons linking the pyridine moiety has been investigated. The ^1H NMR spectrum of a solution of **3** in methanol-d_4 in the presence of an excess of Cs_2CO_3 (5 equiv) evidenced the initial formation of the d_3-methoxo $[Ir(OCD_3)(CO)_2(\kappa C\text{-}^tBuImCH_2PyCH_2OMe)]$ (**8-*d***). Compound **8-*d*** undergoes progressive H/D exchange at the CH_2-Im linker that is completed after 20 h at room temperature (see the Supporting Information). The ^2H NMR spectrum of this species in tetrahydrofuran showed two broad ^2H-singlets at δ 5.88 and 4.33 ppm, which correspond to the CD_2-Im fragment and the CD_3O ligand.

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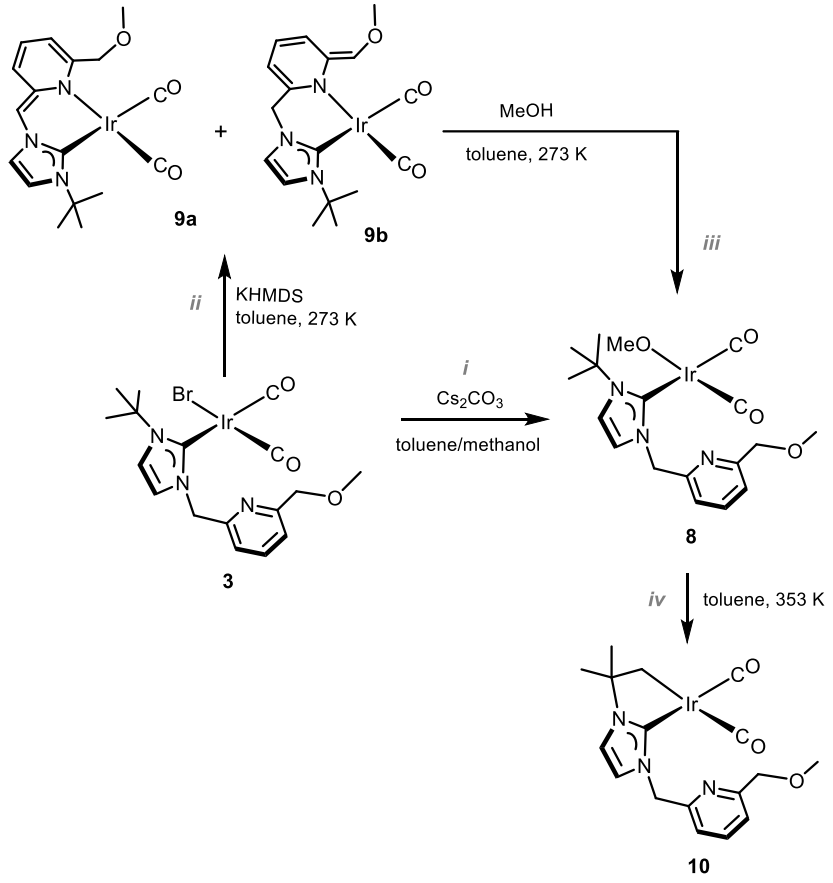
Scheme 3. Reactivity of 3: Synthetic Routes for the Preparation of Compounds 8 and 10



Compound [Ir(OMe)(CO)$_2$(κC-^{t}BuImCH$_2$PyCH$_2$OMe)] (**8**) was prepared by reaction of **3** with Cs_2CO_3 (5 equiv) in toluene/methanol and isolated as a pale-yellow solid in 68% yield (Scheme 3i). The ^{1}H NMR spectrum of **8** in toluene-d_8 showed two doublets, at δ 6.11 and 5.47 ppm, and a singlet at δ 4.48 ppm for the protons of the CH$_2$-Im and CH$_2$-OMe linkers, respectively, which is in agreement with a κC coordination mode of the N,O-functionalized NHC ligand. Moreover, the methoxo ligand was observed at δ 4.69 and 66.6 ppm in the ^{1}H and ^{13}C{^{1}H} NMR spectra, respectively. Finally, the presence of two carbonyl ligands in a cis configuration was confirmed by the two strong stretching ν(CO) bands at 2045, 1959 cm^{-1} in the IR spectrum, and the two resonances at δ 183.3 and 174.2 ppm in the ^{13}C{^{1}H} NMR spectrum.

The addition of a moderate excess of potassium bis(trimethylsilyl)amide (KHMDS) (5 equiv) to a yellow suspension of **3** in toluene-d_8 at 273 K afforded a dark-yellow suspension due to the formation of KBr. The ^{1}H NMR spectrum evidenced the formation of two dearomatized species in a 1:1 ratio, **9a** and **9b**, resulting from the nonselective deprotonation of the two methylene linkers (Scheme 3ii) (see the Supporting Information). According to the NMR information, [Ir(CO)$_2$(κ^2C,N-^{t}BuImCHPy'CH$_2$OMe)] (**9a**) is formed by deprotonation of the CH$_2$-Im linker, whereas deprotonation of the CH$_2$-OMe linker results in the formation of [Ir(CO)$_2$(κ^2C,N-^{t}BuImCH$_2$Py'CHOMe)] (**9b**). Thus, the methine group of **9a** was observed as a singlet at δ 6.00 ppm, whereas the protons of the CH$_2$-OMe linker appeared now as a second order AB quartet centered at δ 4.36 ppm. However, the methine group and the protons of the CH$_2$-Im linker in **9b** were observed as two singlets at δ 4.56 and 4.54 ppm, respectively.

We hypothesized that the rigidity imparted by the methine group in the dearomatized ligand framework could stabilize penta-coordinated structures derived from the coordination of the −OMe moiety. However, density functional theory (DFT) calculations have shown that the hypothetical trigonal bipyramidal structures in which the dearomatized ligand adopts a tridentate pincer coordination are 20.0 and 24.3 kcal·mol^{-1} less stable than the proposed square-planar structures (Figure 3). This energy difference could be attributed to conformational constraints imposed by the fused metallocycles that prevent the =CH bridge to adopt a planar disposition (see the Supporting Information).

The mixture of dearomatized compounds has the ability to activate methanol. In fact, the addition of methanol (5 equiv) to a solution of **9** generated in situ in toluene-d_8 at 273 K resulted in the clean formation of [Ir(OMe)(CO)$_2$(κC-^{t}BuImCH$_2$PyCH$_2$OMe)] (**8**) (Scheme 3iii).

The easy substitution of the bromide ligand in **3** prompted us to attempt the preparation of the key amido complex [Ir(NMePh)(CO)$_2$(κC-^{t}BuImCH$_2$PyCH$_2$OMe)] likely involved as an intermediate in the *N*-alkylation catalytic reaction. With this aim, **3** was reacted with potassium methyl(phenyl)amide, prepared in situ by reaction of *N*-methylaniline and KHMDS in toluene-d_8, at 353 K for 2 h. The ^{1}H NMR of the reaction mixture showed the formation of an unexpected compound and the presence of methyl(phenyl)amine. This compound has been identified as a square-planar iridium(I)

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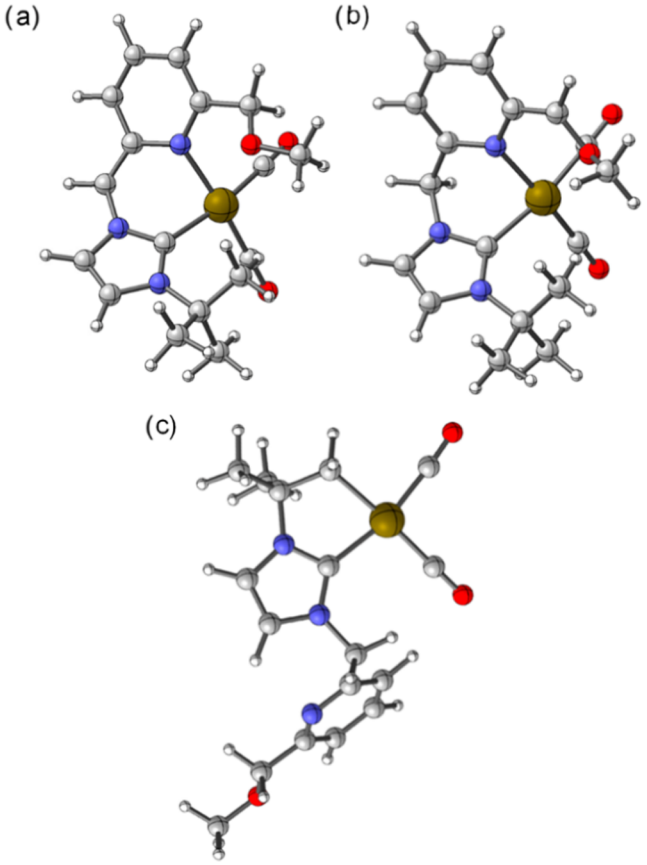

Figure 3. DFT-optimized structures of (a) [Ir(CO)$_2$(κ^2*C*,*N*-^{t}BuImCHPy'CH$_2$OMe)] (**9a**), (b) [Ir(CO)$_2$(κ^2*C*,*N*-^{t}BuImCH$_2$Py'CHOMe)] (**9b**), and (c) [Ir(CO)$_2${κ^2*C*,*C*-(-CH$_2$Me$_2$C-ImCH$_2$PyCH$_2$OMe)}] (**10**).

complex [Ir(CO)$_2${κ^2*C*,*C*-(-CH$_2$Me$_2$C-ImCH$_2$PyCH$_2$OMe)}] (**10**) featuring a bidentate *C*,*C*-coordinated NHC ligand due to the activation of a C−H bond of the tert-butyl group. On the other hand, the reaction of **3** with a moderate excess of lithium methyl(phenyl)amide in toluene-d_8 under milder conditions, 273 K, gave the dearomatized compound **9**. Interestingly, heating a solution of **8** in toluene-d_8 at 353 K for 3 h showed the clean formation of **10** and methanol. The transformation of **8** into **10** in methanol-d_4 under the same conditions evidenced that both compounds undergo facile H/D exchange at the CH$_2$-Im linker (see the Supporting Information).

Compound **10** was prepared by heating a solution of **8** in toluene at 353 K for 3 h and was isolated as a reddish-purple solid in 69% yield (Scheme 3iv). The compound has been fully characterized by mass spectrometry, IR, and NMR spectroscopy (see the Supporting Information). The HRMS (ESI+) in CH$_3$CN showed a peak at *m*/*z* of 480.1281 corresponding to the molecular fragment [M − CO + H]$^+$. The ^{1}H NMR spectrum in toluene-d_8 showed a new resonance at δ 2.39 ppm for the methylene group formed after the C−H activation of the *t*-butyl group which correlates with the resonance at δ 40.3 ppm in the ^{13}C{^{1}H} NMR spectra. In addition, the infrared spectrum of **10** in toluene showed two ν(CO) bands at 2026 and 1949 cm^{-1}, which are characteristic of square-planar iridium(I) compounds having two carbonyl ligands in cis disposition. The inequivalent carbonyl ligands were observed at δ 190.4 and 187.7 ppm in the ^{13}C{^{1}H} NMR spectrum. Interestingly, both methylene linkers in the ligand framework were observed as singlets at δ 5.04 and 4.33 ppm in the ^{1}H NMR spectrum which suggest the noncoordination of the pyridine moiety to the iridium center which agrees with DFT calculations. On the other hand, the Ir-CH$_2$ resonance showed cross-peaks with the carbonyl carbon atoms in the ^{1}H/^{13}C-HMBC spectrum that strongly support the proposed structure. The DFT-optimized structure of **10** is shown in Figure 3.

A number of examples of cyclometalation reactions via intramolecular C−H activation of I^{t}Bu or IMes with reactive iridium(I) centers have been described.[45] In our case, the cyclometallation reaction likely proceeds by a concerted intramolecular C−H activation involving the deprotonation of the methyl group in the *t*-butyl moiety by the methoxo ligand acting as an internal base. In fact, the bromo compound **3** remains unchanged after heating in toluene at 353 K for 5 h which supports the proposed mechanism.

Mechanistic Studies. The reaction profile of the **3**-catalyzed *N*-methylation of aniline monitored by GC under the optimized conditions showed a rapid decrease in aniline concentration along with the formation of *N*-methylaniline with a conversion above 20% after 20 min of reaction (Figure 4). Hydrogen transfer reduction of the putative intermediate

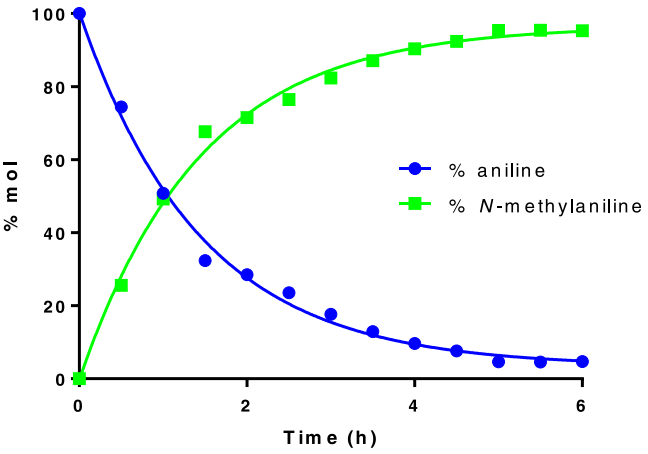

Figure 4. Reaction profile of the *N*-methylation of aniline with methanol monitored by GC. Reaction conditions: aniline (0.5 mmol), **3** (0.0025 mmol, 0.5 mol %) and Cs$_2$CO$_3$ (0.25 mmol, 50 mol %) in methanol (1.5 mL) at 423 K.

N-methylidenaniline should be fast since it was not detected throughout the reaction, indicating that the reduction of the imine intermediate product is not the limiting step of the overall process (Scheme 1).

Formation of N-Methylidenaniline. The possible influence of the iridium catalyst on the formation of the *N*-methylidenaniline intermediate was investigated by studying the condensation step between formaldehyde and aniline (Table 3). It should be noted that the study was performed in wet toluene since commercial formaldehyde was supplied as an aqueous solution (37 wt %) with 10−15% methanol as a stabilizer. When the condensation reaction was carried out in the absence of a catalyst, a 22% aniline conversion was attained in 30 min (entry 1) to afford a white solid corresponding to the condensation product *N*-methylidenaniline (**11**), insoluble in the reaction medium, or more precisely to the cyclic compound 1,3,5-triphenylhexahydro-1,3,5-triazine, which is in equilibrium with **11** (Scheme 4i.3) and is the predominant species at low temperature.[46] In addition, gas chromatog-

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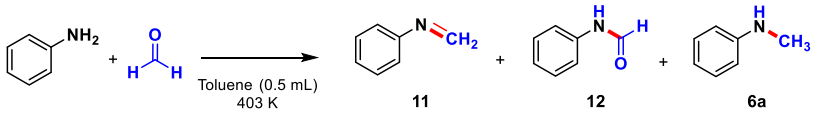
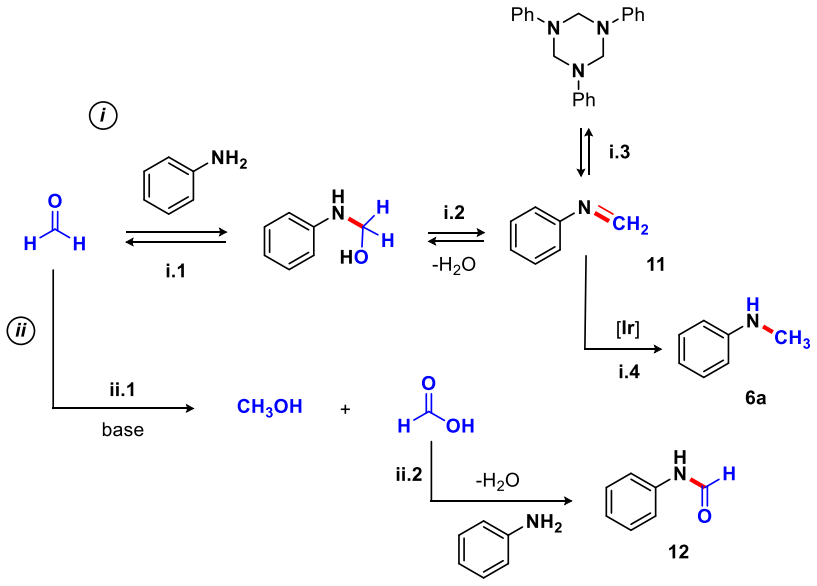
Table 3. Formaldehyde and Aniline Condensation Experiments: Influence of the Iridium Catalyst on the Formation of *N*-Methylidenaniline[a]



	catalyst	t (h)	conversion (%)[a]	selectivity (%)[a] 11	12	6a
1	no catalyst[b]	0.5	22	√	√	-
2	3, 2.5 mol %	0.5	25	-	35	65
3	3, 2.5 mol %	2	53	-	12	88

[a]Conversion and selectivity determined by GC (mesitylene as internal standard) referenced to aniline. Reaction conditions: aniline (0.5 mmol), formaldehyde (0.5 mmol, 37 wt % in water, with 10−15% methanol as stabilizer) and Cs_2CO_3 (0.375 mmol, 75%), in toluene (0.5 mL) at 403 K for 30 min. [b]A mixture of *N*-methylidenaniline/1,3,5-triphenyl-1,3,5-triazine and *N*-phenylformamide was obtained.

Scheme 4. Reaction Pathways for the Formation of *N*-Phenylformamide (12) and *N*-Methylidenaniline (11)



raphy−mass spectrometry (GC-MS) analysis of the solution revealed the formation of *N*-phenylformamide (**12**). However, when the condensation reaction was performed in the presence of catalyst **3** (2.5 mol %) under the same conditions, a mixture of *N*-phenylformamide (**12**) and *N*-methylaniline (**6a**), was initially obtained with a 25% aniline conversion and a 65% selectivity to **6a** (entry 2). The aniline conversion increased to 53% after 2 h with a selectivity to **6a** of 88% (entry 3).

To better understand the condensation reaction in the absence of a catalyst, additional experiments using methanol as a solvent have been carried out. A solution of aniline (0.25 mmol) and formaldehyde (0.5 mmol) in methanol-d_4 was heated at 403 K for 15 min in a reinforced glass reactor. The ^{1}H NMR of the reaction mixture evidenced the formation of 1,3,5-triphenyl-1,3,5-triazine. This species showed a set of resonances in the aromatic region and a characteristic resonance at δ 4.82 (s, 6H) ppm, that correlates with the signal at δ 68.6 ppm in the two-dimensional ^{1}H-^{13}C HSQC spectrum, which is assigned to the >CH_2 protons of the central cycle (see the Supporting Information).[47] The presence of *N*-methylidenaniline was discarded by the absence of the imidic carbon at δ 157.0 ppm in the ^{13}C{^{1}H}-NMR.[48] On the other hand, the addition of Cs_2CO_3 (0.375 mmol) to the reaction mixture and heating at 403 K for 15 min resulted in the disappearance of the white precipitate and a color change of the solution from pale yellow to brown. GC-MS analysis of the solution allowed the detection of *N*-phenylformamide (m/z = 121) and *N*-methylidenaniline (m/z = 105)[49] in a relative ratio of 85:15. Finally, in an additional experiment, if after the formation of 1,3,5-triphenylhexahydro-1,3,5-triazine, Cs_2CO_3 (0.375 mmol) and **3** (0.0125 mmol) are added, and the reaction mixture is heated to 403 K for 15 min, a brown solution containing *N*-phenylformamide and *N*-methylaniline (m/z = 107) in a similar relative ratio of 88:12 (GC-MS analysis) was obtained.

These results suggest that under noncatalytic conditions in the presence of base two competitive pathways could be operative: (i) the formation of *N*-methylidenaniline in equilibrium with the cyclic trimer form as a result of the condensation reaction and (ii) the formation of *N*-phenylformamide (Scheme 4). Specifically, the formation of *N*-methylidenaniline may occur by dehydration of the hemiaminal, (phenylamino)methanol, catalyzed by a base (Scheme 4i.2). The imine is in equilibrium with the 1,3,5-triphenyl-1,3,5-triazine trimeric form, an equilibrium that is shifted toward the cyclic form at low temperatures (Scheme 4i.3). On the other hand, the formation of *N*-phenylformamide may occur through the Cannizzaro reaction by disproportionation

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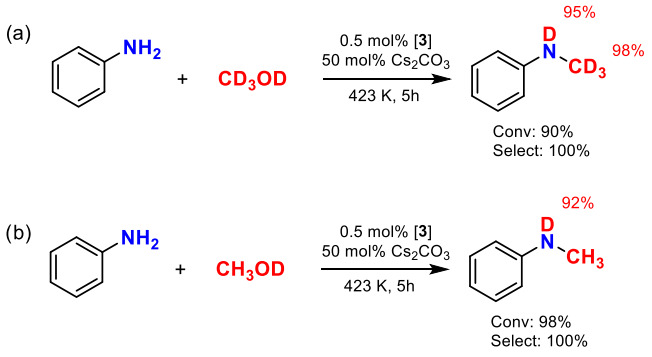
of formaldehyde in the presence of a base to give to methanol and formic acid (Scheme 4ii.1). Subsequently, the condensation between formic acid generated *in situ* and aniline afforded *N*-phenylformamide and water (Scheme 4ii.2). Finally, the formation of *N*-methylaniline and the disappearance of *N*-methylidenaniline in the presence of **3** confirm the efficiency of this catalyst in the transfer hydrogenation of the imine (Scheme 4i.4).

The absence of *N*-phenylformamide under the optimized catalytic reaction conditions could be explained by the low concentration of formaldehyde under catalytic conditions and the fast hydrogenation of the imine by **3** that drives the equilibrium along this path, inhibiting the Cannizzaro reaction. Furthermore, the formation of significant amounts of *N*-methylidenaniline in the absence of **3** under mild conditions practically rules out that the condensation reaction between aniline and formaldehyde occurs in the coordination sphere of the metal center. This result contrasts with the theoretical studies, carried out by our research group, on the mechanism of *N*-alkylation of amines with alcohols in which the Ir(I)-NHC catalyst is involved in the condensation step.[18b]

Deuterium Labeling Experiments. To gain insight into the reaction mechanism, deuterium labeling experiments using methanol-d_4 or methanol-d_1 as solvents have been carried out (Scheme 5). *N*-methylation of aniline catalyzed by **3** in methanol-d_4 (≥99.8% D) resulted in the formation of *N*-methylaniline with a degree of deuteration greater than 95% in both the methyl and N−H groups indicating that all of the methanol atoms, except for the oxygen atom which is eliminated as water after the condensation reaction, are incorporated into the final product. Furthermore, when methanol-d_1 (≥99.5% D) was used, the deuterium is incorporated only in the N−H moiety, which confirms that the deuterium of the −OD group is exclusively transferred to the nitrogen atom of the amine (see the Supporting Information). The ^{1}H NMR kinetic study comparing the reaction rate for the *N*-methylation of aniline with methanol and methanol-d_4 catalyzed by **3** under the optimized reaction conditions gave a kinetic isotopic effect (KIE) of 4.47 ± 0.28 (see the Supporting Information). This value suggests that the formation of the Ir-H species should occur in the rate-determining step in accordance with the low concentration of formaldehyde under catalytic conditions.[50]

Scheme 5. Deuterium Labeling Experiments in the *N*-Methylation of Aniline Catalyzed by 3 Using Methanol-d_1 and Methanol-d_4 as Solvents



IR Spectroscopy Studies. To identify possible species involved in the mechanism, the catalytic reaction was monitored by IR spectroscopy. The reaction of *N*-methylation of aniline (0.5 mmol) was performed in methanol (1.5 mL) in the presence of Cs_2CO_3 (50 mol %) using [Ir(OMe)-(CO)$_2$(κC-^{t}BuImCH$_2$PyCH$_2$OMe)] (**8**) as a catalyst (10 mol %) at 423 K. The IR spectra of reaction aliquots (1.5 mL) taken at 1 and 2 h, for which aniline conversion determined by GC was 35 and 92%, respectively, showed two strong stretching ν(CO) bands at 2026 and 1949 cm^{-1}, which correspond to the cyclometalated iridium(I) compound [Ir(CO)$_2${κ^2*C*,*C*-(-CH$_2$Me$_2$C-ImCH$_2$PyCH$_2$OMe)}] (**10**). The spectra also show two absorptions at 1979 and 1906 cm^{-1}, which can be tentatively attributed to a *cis*-dicarbonyl iridium(I) intermediate (see the Supporting Information).

Mechanistic Proposal. The IR experiments suggest that the catalytic reaction likely proceeds through iridium(I) intermediates featuring two carbonyl ligands in cis-arrangement. The role of **10** in the catalytic reaction is a matter of debate, as it could be considered both the active species and the catalyst resting state. In principle, if the cyclometalated compound **10** were involved in the mechanism the reaction should proceed through 18 e$^-$ penta-coordinated anionic iridium(I) intermediates, which is highly unlikely. Therefore, it is very plausible that the methoxo compound **8** is the catalytically active species and that β−H elimination in **8** leading to the key hydride intermediate [IrH-(CO)$_2$(κC-^{t}BuImCH$_2$PyCH$_2$OMe)] is favored over the formation of **10** under catalytic conditions. However, deuterium labeling experiments have demonstrated that **8** and **10** are in equilibrium under catalytic conditions. Thus, heating of a solution of **10** in methanol-d_4 at 423 K for 1 h resulted in deuterium incorporation into the Ir-CH$_2$-C(Me$_2$)-N fragment of the cyclometalated moiety, as well as in the CH$_2$-Im linker and the nearest-neighbor meta proton of the pyridine ring (Figure 5).

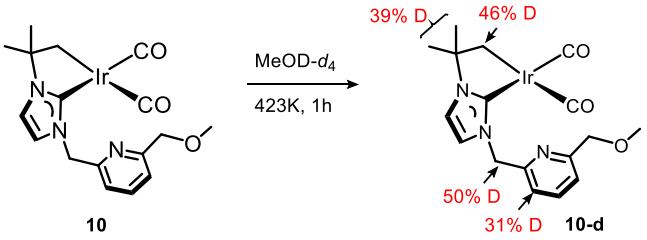


Figure 5. Deuteration of **10** with methanol-d_4 after heating at 423 K for 1 h.

Accordingly, compound **10** catalyzed the *N*-methylation of aniline under optimized conditions affording a 78% conversion to *N*-methylaniline in 5 h. The lower catalytic performance of **10** compared to that of **3** (97% conversion in 5 h) is consistent with the expected lower concentration of the active species **8**. Interestingly, the ^{1}H NMR of a solution of **10** in methanol after heating at 423 K for 1 h showed two tiny resonances at δ 8.55 and −18.50 ppm (see the Supporting Information). Both resonances are ascribed to formaldehyde, which is formed by β−H elimination in the methoxo complex **8** (not observed) in equilibrium with **10**, and tentatively to the resulting iridium(I) hydride intermediate [IrH(CO)$_2$(κC-^{t}BuImCH$_2$PyCH$_2$OMe)] (**13**). These observations support the methoxo complex **8** as the catalytic active species and **10** as the catalyst resting state in the *N*-methylation reaction.

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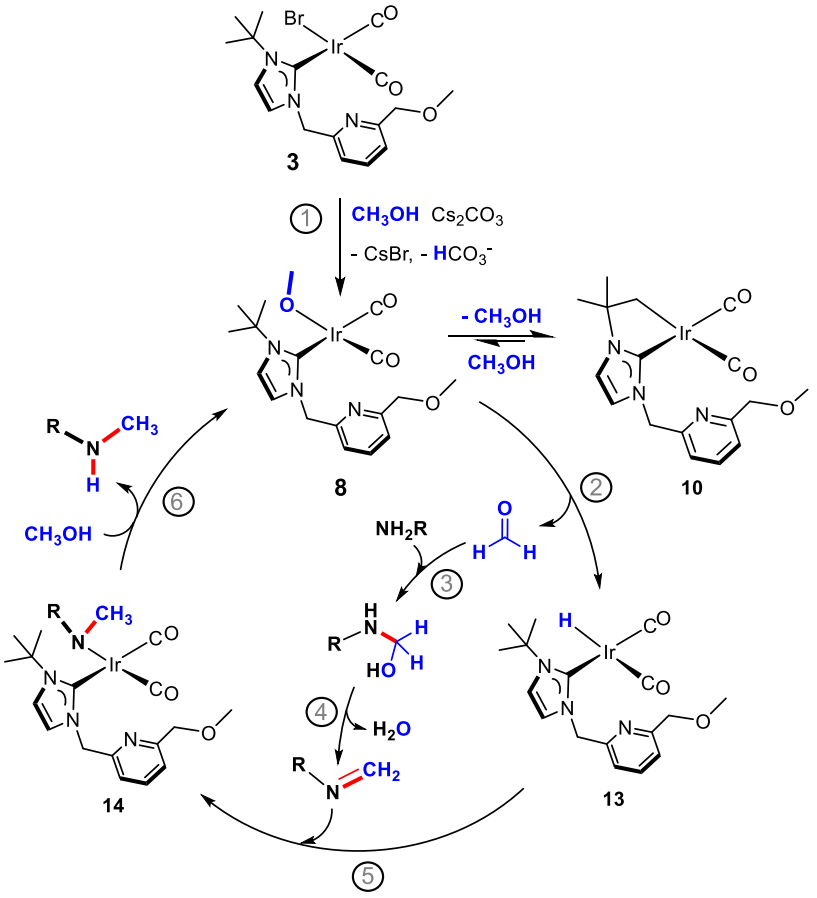
Scheme 6. Proposed Mechanism for the *N*-Methylation of Amines with Methanol Catalyzed by [IrBr(CO)$_2$(κC-^{t}BuImCH$_2$PyCH$_2$OMe)] (3)



On the basis of the experimental observations, the proposed mechanism for the *N*-methylation of amines with methanol catalyzed by **3** is depicted in Scheme 6. The mechanism involves the rapid formation of the methoxo complex **8** (step 1) and subsequent *β*−H elimination to give the iridium(I) hydride intermediate **13** releasing formaldehyde as the rate-determining step (step 2). Formaldehyde condenses with the amine yielding the corresponding imine outside the coordination sphere of the metal (step 3). Then, imine coordination followed by insertion into the Ir−H bond affords the amido intermediate **14** (step 4). Finally, methanolysis of the Ir−N bond results in the formation of the *N*-methylamine product regenerating the catalytically active species **8**.[18b] Although the role of the pyridine fragment in the sketched mechanism is not evident, the positive influence of a functionalized NHC ligand on the catalytic activity in the *N*-methylation reaction becomes evident when comparing the performance of compounds [IrBr(CO)$_2$(IMe)] and [IrBr(CO)$_2$(κC-MeImCH$_2$Py)], featuring an unfunctionalized and a pyridine-functionalized NHC ligands, respectively (Table 1). Therefore, the possible stabilizing role of the pyridine fragment, through the transient formation of pentacoordinate species, as responsible for the improved catalytic performance cannot be ruled out. On the hand, the role of the remote flexible methoxymethyl fragment in **3** could be related to its ability to facilitate the *β*−H elimination reaction as it has been found in related catalytic systems with improved activity in hydrogen transfer reactions.[51]

CONCLUSIONS

Neutral and cationic iridium(I) compounds featuring a flexible lutidine-derived polydentate ligand having NHC and −OMe as donor functions have been revealed as efficient catalyst precursors for the *N*-methylation of amines with methanol. Catalyst screening has shown that carbonyl complexes are more active than related diene compounds, with the neutral compound [IrBr(CO)$_2$(κC-^{t}BuImCH$_2$PyCH$_2$OMe)] being the more active in the *N*-methylation of aniline. This catalyst has been applied for the *N*-methylation of a variety of aromatic and aliphatic primary amines. A range of functionalized anilines having both electron-withdrawing and electron-rich substituents, including heterocyclic primary amines, have been selectively converted into the corresponding *N*-methylamine derivatives in excellent yields at low catalyst loading and substoichiometric amounts of cesium carbonate as a base. In contrast, *N*,*N*-dimethylamine derivatives were selectively obtained with aliphatic primary amines.

Reactivity studies have shown that compound [IrBr(CO)$_2$(κC-^{t}BuImCH$_2$PyCH$_2$OMe)] undergoes deprotonation of the functionalized NHC ligand with KHMDS to afford two isomeric neutral complexes featuring a coordinated dearomatized pyridine core that result from the unselective deprotonation of the methylene linkers. Rearomatization of the complexes with methanol selectively gives compound [Ir(OMe)(CO)$_2$(κC-^{t}BuImCH$_2$PyCH$_2$OMe)]. Interestingly, this methoxo compound, which is also accessible directly from the bromo-complex in methanol in basic medium, undergoes

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thermal activation of a C−H bond of the tert-butyl group to give the cyclometalated iridium(I) complex [Ir(CO)$_2${κ^2*C*,*C*-(-CH_2Me_2C-ImCH_2PyCH_2OMe)}] featuring a bidentate *C*,*C*-coordinated NHC ligand.

Deuterium labeling studies have demonstrated that the *N*-methylation of amines catalyzed by [IrBr(CO)$_2$(κ*C*-^{t}BuImCH_2PyCH_2OMe)] proceeds through a borrowing hydrogen mechanism. On the other hand, independent reactivity studies have shown that the condensation step between aniline and formaldehyde occurs without the intervention of the iridium catalyst. Experimental observations support the methoxo complex as the catalytic active species and the cyclometalated iridium(I) complex as the catalyst resting state in the *N*-methylation reaction. Deuterium labeling experiments have demonstrated that both species are in equilibrium under catalytic conditions which is consistent with the exhibited catalytic activity of the cyclometalated complex. The proposed mechanism involves the β−H elimination in the methoxo compound to give a square-planar iridium(I) hydride intermediate, which has been observed spectroscopically, and formaldehyde which condenses with the amine to afford the intermediate imine compound. Imine insertion into the Ir−H bond affords an amido intermediate from which the *N*-methylamine product is released by methanolysis, thus regenerating the methoxo catalytically active species.

EXPERIMENTAL SECTION

General Considerations. All experiments were carried out under an atmosphere of argon using Schlenk techniques or in a dry box. Solvents were distilled immediately prior to use from the appropriate drying agents or obtained from a Solvent Purification System (Innovative Technologies). Oxygen-free solvents were employed throughout. $CDCl_3$, benzene-d_6, and toluene-d_8 were dried using activated molecular sieves. Methanol-d_4 and methanol-d_1 (<0.02% D_2O) were purchased from Eurisotop and used as received. The neutral compounds [IrBr(cod)(κ*C*-^{t}BuImCH_2PyCH_2OMe)] (**2**) and [IrBr(CO)$_2$(κ*C*-^{t}BuImCH_2PyCH_2OMe)] (**3**) were prepared following the procedure recently reported by us.[15a] The organic substrates were obtained from common commercial sources and used as received, or recrystallized or distilled prior to use depending on their purity.

Scientific Equipment. C, H, and N analyses were carried out in a PerkinElmer 2400 Series II CHNS/O analyzer. Infrared spectra were recorded on an FT-PerkinElmer Spectrum One spectrophotometer using Nujol mulls between polyethylene sheets. ^{1}H NMR spectra were recorded on a Bruker Avance 300 (300.128 MHz) or Bruker Avance 400 (400.130 MHz). NMR chemical shifts are reported in ppm relative to tetramethylsilane and are referenced to partially deuterated solvent resonances. Coupling constants (*J*) are given in hertz. Spectral assignments were achieved by a combination of ^{1}H−^{1}H COSY, ^{13}C APT, ^{1}H−^{13}C HSQC, and ^{1}H−^{13}C HMBC experiments. High-resolution electrospray ionization mass spectra (HRMS-ESI) were recorded using a Bruker MicroToF-Q equipped with an API-ESI source and a Q-ToF mass analyzer, which leads a maximum error in the measurement of 5 ppm, using sodium formate as reference. Conductivities were measured in ca. 5 × 10^{-4} M nitromethane solutions of the complexes using a Philips PW 9501/01 conductimeter. The catalytic reactions were analyzed on an Agilent 4890D system equipped with an HP-INNOWax capillary column (0.4 μm film thickness, 25 m × 0.2 mm i.d.) using mesitylene as the internal standard. Organic compounds were identified by gas chromatography−mass spectrometry (GC/MS) using an Agilent 6890 GC system with an Agilent 5973 MS detector equipped with an HP-5MS polar capillary column (0.25 μm film thickness, 30 m × 0.25 mm i.d.).

*Synthesis of [Ir(cod)(κ^2C,N-^{t}BuImCH$_2$PyCH$_2$)]PF$_6$ (**4**).* $AgPF_6$ (79 mg, 0.313 mmol) was added to a solution of [IrBr(cod)(^{t}BuImCH_2PyCH_2OMe)] (**2**) (200 mg, 0.313 mmol) in dichloromethane (5 mL). The suspension was stirred at room temperature for 30 min, and the silver bromide formed was removed by filtration through celite and washed with dichloromethane (2 × 5 mL). The resulting solution was brought to dryness under vacuum to give an orange oil, which was disaggregated by stirring with cold diethyl ether. The yellow solid was washed with diethyl ether (2 × 5 mL) and dried under vacuum. Yield: 192 mg, 87%. Anal. calcd for $C_{23}H_{33}F_6N_3OPIr$: C, 39.20; H, 4.72; N, 5.96. Found: C, 38.98; H, 4.57; N, 5.83. HRMS (ESI+, MeOH, *m*/*z*): calcd for $C_{23}H_{33}N_3OIr$, 560.2253; found, 560.2241 [M]$^+$. Λ_M (nitromethane, 5.0 × 10^{-4} M) = 84 Ω^{-1} cm^2 mol^{-1}. ^{1}H NMR (298 K, 300 MHz, $CDCl_3$): δ 7.94−7.82 (m, 2H, H$_m$ and H$_p$, Py), 7.50−7.45 (m, 2H, H$_m$ Py and =CH Im), 7.02 (d, J_{H-H} = 2.1, 1H, =CH Im), 6.07 (d, J_{H-H} = 15.0, 1H, CH_2Im), 6.67 (d, J_{H-H} = 15.0, 1H, CH_2Im), 4.92 (d, J_{H-H} = 12.6, 1H, CH_2OMe), 4.59 (d, J_{H-H} = 12.6, 1H, CH_2OMe), 4.01−3.88 (m, 2H, =CH cod), 4.86−4.72 (m, 2H, =CH cod), 3.56 (s, 3H, OCH_3), 2.50−2.35 (m, 2H, >CH_2 cod), 2.25−1.84 (m, 4H, >CH_2 cod), 1.67 (s, 9H, ^{t}Bu), 1.64−1.50 (m, 2H, >CH_2 cod). ^{31}P{^{1}H} NMR (298 K, 121.4 MHz, $CDCl_3$): δ −144.2. ^{13}C{^{1}H} NMR (298 K, 75 MHz, $CDCl_3$): δ 173.1 (C$_{NCN}$), 159.1, 154.0 (C$_o$ Py), 139.7 (C$_p$ Py), 125.7, 125.1 (C$_m$ Py), 122.8, 118.8 (=CH Im), 84.9 (=CH cod), 75.8 (CH_2OMe), 75.6 (=CH cod), 61.8 (=CH cod), 59.5 (OMe), 58.2 (C ^{t}Bu), 56.9 (=CH cod), 56.4 (CH_2Im), 32.8 (>CH_2 cod), 32.5 (>CH_2 cod), 32.3 (CH_3 ^{t}Bu), 30.0 (>CH_2 cod), 29.3 (>CH_2 cod).

*Synthesis of [Ir(CO)$_2$(κ^2C,N-^{t}BuImCH$_2$PyCH$_2$OMe)]PF$_6$ (**5**).* Carbon monoxide was bubbled through a solution of [Ir(cod)(κ^2*C*,*N*-^{t}BuImCH_2PyCH_2)]PF_6 (**4**) (100 mg, 0.142 mmol) in dichloromethane (5 mL) for 5 min at room temperature to give a yellow solution. The solution was brought to dryness under vacuum to give an oily residue, which was disaggregated by stirring with cold *n*-hexane. The pale-yellow solid was washed with *n*-hexane (2 × 5 mL) and dried under vacuum. Yield: 73 mg, 79%. Anal. calcd for $C_{17}H_{21}F_6N_3O_3PIr$: C, 31.29; H, 3.24; N, 6.44. Found: C, 31.61; H, 3.79; N, 6.15. HRMS (ESI+, MeOH, *m*/*z*): calcd for $C_{17}H_{21}N_3O_3Ir$, 508.1212; found, 508.1208 [M]$^+$; 480.1254 [M − CO]$^+$. IR (ATR, cm^{-1}): 2069, 1994 (ν_{CO}). Λ_M (nitromethane, 5.0 × 10^{-4} M) = 80 Ω^{-1} cm^2 mol^{-1}. ^{1}H NMR (298 K, 300 MHz, $CDCl_3$): δ 8.12−8.01 (m, 2H, H$_p$ and H$_m$ Py), 7.72 (d, J_{H-H} = 7.5, 1H, H$_m$ Py), 7.61 (d, J_{H-H} = 2.6, 1H, =CH Im), 7.25 (d, J_{H-H} = 2.1, 1H, =CH Im), 5.75 (ABq, δ_A = 5.79, δ_B = 5.71, J_{A-B} = 5.0, 2H, CH_2Im), 4.79 (ABq, δ_A = 4.88, δ_B = 4.70, J_{A-B} = 4.0, 2H, CH_2OMe), 3.53 (s, 3H, OCH_3), 1.78 (s, 9H, ^{t}Bu). ^{31}P{^{1}H} NMR (298 K, 121.4 MHz, $CDCl_3$): δ −144.2. ^{13}C{^{1}H} NMR (298 K, 75 MHz, $CDCl_3$): δ 179.2 and 171.7 (CO), 168.8 (C$_{NCN}$), 160.7, 154.7 (C$_o$ Py), 142.6 (C$_p$ Py), 126.8, 125.8 (C$_m$ Py), 123.4, 120.6 (=CH Im), 76.2 (C$\underline{H}_2$OMe), 59.8 (C ^{t}Bu), 59.5 (OMe), 55.9 (CH_2Im), 32.2 (CH_3 ^{t}Bu).

Synthesis of [IrBr(CO)$_2$(κC-MeImCH$_2$Py)]. Carbon monoxide was bubbled through a solution of [IrBr(cod)(κ*C*-MeImCH_2Py)][S1b] (50 mg, 0.142 mmol) in tetrahydrofuran (5 mL) for 5 min at room temperature to give an orange solution, which was stirred under CO atmosphere for 2 h. The solvent was removed by bubbling of CO, and the residue washed with cold hexane (3 × 5 mL). Finally, the solvent residue was removed under a CO stream. The compound was obtained as an air-sensitive orange solid. Yield: 30 mg, 66%. HRMS (ESI+, CH_3CN, *m*/*z*): calcd for $C_{11}H_{11}N_3OIr$, 394.0526; found, 394.0537 [M−Br−CO]. IR (ATR, cm^{-1}): 2051, 1967 (ν_{CO}). ^{1}H NMR (400 MHz, CD_2Cl_2, 253 K): δ 8.69 (d, J_{H-H} = 5.1, 1H, H$_{o\text{-}Py}$), 7.81 (ddd, J_{H-H} = 7.5, 7.5, 1.6, 1H, H$_{p\text{-}Py}$), 7.58 (d, J_{H-H} = 7.5, 1H, H$_{m\text{-}Ph}$), 7.34 (dd, J_{H-H} = 7.5, 5.1, 1H, H$_{m\text{-}Py}$), 7.37 and 7.09 (both d, J_{H-H} = 1.4, 2H, =CHN), 5.62 (br, 2H, CH_2Im), 3.89 (s, 3H, Me). ^{13}C{^{1}H} NMR (298 K, 100 MHz, CD_2Cl_2): δ 182.4 and 168.7 (CO), 172.3 (C$_{NCN}$), 154.9, 151.9 (C$_o$ Py), 138.0 (C$_p$ Py), 123.9, 123.7 (C$_m$ Py), 123.1, 122.5 (=CH Im), 55.6 (CH_2Py), 38.5 (Me).

*Synthesis of [Ir(OMe)(CO)$_2$(κC-^{t}BuImCH$_2$PyCH$_2$OMe)] (**8**).* Cs_2CO_3 (66 mg, 0,20 mmol) was added to a solution of [IrBr(CO)$_2$(κ*C*-^{t}BuImCH_2PyCH_2OMe)] (**3**) (30 mg, 0.051 mmol) in toluene/methanol (1:1). The yellow solution was stirred at room temperature for 10 min and then brought to dryness under vacuum to give a solid residue. Compound **8** was extracted with toluene (1 mL),

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and the solution was brought to dryness under vacuum to give an oily residue, which was disaggregated by stirring with cold *n*-hexane. The pale-yellow solid was washed with *n*-hexane (2 × 5 mL) and dried under vacuum. Yield: 17 mg, 68%. HRMS (ESI+, MeOH, *m*/*z*): calcd for $C_{18}H_{24}N_3O_4Ir$, 539.1396 [M]; found, 508.1203 $[M-OCH_3]^+$, 480.1253 $[M-OCH_3-CO]^+$, 452.1304 $[M-OCH_3-2CO]^+$. IR (ATR, cm^{-1}): 2045, 1959 (ν_{CO}). ^1H NMR (298 K, 300 MHz, toluene-d_8): δ 7.50 and 7.20 (both m, 2H, $H_{m\text{-}Py}$), 7.12 (m, 1H, $H_{p\text{-}Py}$), 6.53 and 6.36 (both d, $J_{H\text{-}H}$ = 2.0, 2H, =CH Im), 5.83 (ABq, δ_A = 5.91, δ_B = 5.75, J_{A-B} = 14.7, 2H, CH_2Im), 4.69 (s, 3H, Ir-OMe), 4.48 (s, 2H, C$\underline{H}_2$OMe), 3.20 (s, 3H, OMe), 1.57 (s, 9H, ^{t}Bu).$^{13}C\{^1H\}$-APT NMR (298 K, 75.0 MHz, toluene-d_8,): δ 183.3 and 174.2 (CO), 177.2 (C_{NCN}), 158.5 and 155.2 (C_q Py), 136.9 (C_p Py), 121.6 and 119.8 (both C_m Py), 119.5 and 118.6 (=CH Im), 75.3 (C$\underline{H}_2$OMe), 66.6 (Ir-OMe), 58.9 (C_q-^{t}Bu), 58.0 (OMe), 57.9 (s, CH_2Im), 31.6 (CH_3 ^{t}Bu).

*Dearomatization of [IrBr(CO)$_2$(κC-^{t}BuImCH$_2$PyCH$_2$OMe)] (**3**): In Situ Formation of **9**.* KHMDS (3.7 mg, 0.019 mmol) was added to a solution of [IrBr(CO)$_2$(κC-^{t}BuImCH$_2$PyCH$_2$OMe)] (**3**) (10 mg, 0.017 mmol) in toluene-d_8 at 273 K to give a dark-yellow suspension. The ^1H NMR of the solution after centrifugation evidenced the formation of two compounds, [Ir(CO)$_2$(κ^2*C*,*N*-^{t}BuImCHPy'CH$_2$OMe)] (**9a**) and [Ir(CO)$_2$(κ^2*C*,*N*-^{t}BuImCH$_2$Py'CHOMe)] (**9b**), in an approximately 1:1 ratio. NMR data for **9a** (significant resonances): ^1H NMR (273 K, 500 MHz, toluene-d_8): δ 6.26 (s, 2H, =CH Im), 6.00 (s, 1H, =CH), 4.36 (ABq, δ_A = 4.40, δ_B = 4.32, J_{A-B} = 5.0, 2H, CH_2OMe), 3.12 (s, 3H, OMe), 1.72 (s, 9H, ^{t}BuIm). $^{13}C\{^1H\}$ NMR (273 K, 125 MHz, toluene-d_8): δ 123.2, 118.1 (=CH Im), 75.8 (CH_2OMe), 58.1 (OMe), 44.7 (=CH), 31.6 (CH_3 ^{t}Bu). NMR data for **9b** (significant resonances): ^1H NMR (273 K, 500 MHz, toluene-d_8): δ 6.66 (s, 1H, =CH Im), 6.15 (s, 1H, =CH Im), 4.56 (s, 1H, =CH), 4.54 (m, 2H, CH_2Im), 3.25 (s, 3H, OMe), 1.45 (s, 9H, ^{t}BuIm). $^{13}C\{^1H\}$ NMR (273 K, 125 MHz, toluene-d_8): 125.2, 114.8 (=CH Im), 75.7 (CH_2OMe), 58.1 (OMe), 39.6 (=CH), 30.5 (CH_3 ^{t}Bu).

*Reaction of **9** with Methanol: Formation of [Ir(OMe)(CO)$_2$(κC-^{t}BuImCH$_2$PyCH$_2$OMe)] (**8**).* A suspension of the dearomatized compound **9** (0.017 mmol), prepared in situ by the reaction of **3** with KHMDS in toluene-d_8, was treated with methanol (3.4 μL, 0.085 mmol) to give a yellow suspension. The ^1H NMR of the solution after centrifugation evidenced the formation **8**.

*Synthesis of [Ir(CO)$_2${κ^2*C*,*C*-(-CH$_2$Me$_2$C-ImCH$_2$PyCH$_2$OMe)}] (**10**).* A solution of **3** (50 mg, 0.085 mmol) in toluene/methanol 1:1 (5 mL) was treated with Cs_2CO_3 (138 mg, 0.425 mmol) and stirred for 30 min at room temperature. The solvent was removed under vacuum, and the residue was extracted with toluene (5 ml) and filtered through Celite to give a yellow solution of compound **8**. The solution was heated at 353 K for 3 h to give a pale-yellow solution. The concentration of the solution and the slow addition of cold hexane induced the precipitation of a reddish-purple solid, which was washed with hexane (3 × 4 mL) and dried in vacuo. Yield: 30.0 mg (69%). HRMS (ESI+, CH_3CN, *m*/*z*): calcd for $C_{17}H_{20}N_3O_3Ir$, 507.1134 [M]; found, 480.1281 $[M - O + H]^+$. IR (toluene, cm^{-1}): 2026, 1949 (ν_{CO}). ^1H NMR (300 MHz, toluene-d_8, 298 K): δ 7.15 and 7.03 (both m, 3H, P_y), 6.48 and 6.22 (both d, $J_{H\text{-}H}$ = 2.0, 2H, = CH Im), 5.14 (s, 2H, CH_2-Im), 4.43 (s, 2H, CH_2OMe), 3.17 (s, 3H, OCH_3), 2.39 (s, 2H, Ir-CH_2), 1.25 (s, 6H, CH_3).$^{13}C\{^1H\}$-APT NMR (75.0 MHz, toluene-d_8, 298 K, 298 K): δ 190.4 and 187.7 (both CO), 183.5 (Ir-NCN), 159.2 ($\underline{C}_q$ Py CH_2OMe), 155.1 ($\underline{C}_q$ Py CH_2Im), 137.5 (C_p Py), 121.2 and 117.8 (both =CH Im), 120.5 and 120.2 (both C_m Py), 75.5 (CH_2OMe), 67.5 (C_q ^{t}Bu), 58.3 (OCH_3), 56.4 (CH_2Im), 40.3 (Ir-CH_2) 33.6 (CH_3).

General Experimental Procedure for the Catalytic *N*-Methylation of Amines with Methanol. The catalytic reactions were carried out under an argon atmosphere in thick glass reaction tubes fitted with a greaseless high-vacuum stopcock. In a typical experiment, the reactor was charged inside a glovebox with the catalyst (0.0025 mmol) and base (0.25 mmol). After that, under argon, methanol (1.5 mL), amine (0.5 mmol), and mesitylene as an internal standard (0.25 mmol) were added. The resulting mixture was stirred at room temperature until complete dissolution of the catalyst and base and then placed in a thermostated oil bath at the required temperature, typically 423 K, for the required time. Conversions and selectivities were determined by gas chromatography analysis under the following conditions: column temperature 353 K (4 min) to 523 K at a heating rate of 20 °C min^{-1} using ultrapure He as a carrier gas.

Time dependence studies on the *N*-methylation of aniline catalyzed by **3** under the optimized reaction conditions were carried out by performing a series of identical experiments in parallel, following the outlined procedure, to avoid the adverse effects derived from the opening of the system.

Isolation of *N*-Methylated Amines. The reaction mixture obtained from catalytic reactions of *N*-methylation of amines was cooled to room temperature, and then silica gel was added. The mixture was dried under vacuum, and the residue was transferred to a silica gel column and then eluted using the appropriate eluent (see the Supporting Information).

Crystal Structure Determination. Single crystals of **4** and **5** suitable for the X-ray diffraction studies were grown by slow diffusion of diethyl ether into a concentrated solution of the complexes in acetone. X-ray diffraction data were collected at 100(2) K on a Bruker APEX SMART CCD diffractometer with graphite-monochromated Mo−Kα radiation (λ = 0.71073 Å) using <1° ω rotations. Intensities were integrated and corrected for absorption effects with SAINT−PLUS[52] and SADABS[53] programs, both included in APEX2 package. The structures were solved by the Patterson method with SHELXS-97[54] and refined by full-matrix least squares on F^2 with SHELXL-2014,[55] under WinGX.[56]

Crystal Data and Structure Refinement for 4. $C_{23}H_{33}F_6IrN_3OP$, 704.69 g·mol^{-1}, triclinic, $P\bar{1}$, a = 9.7213(14) Å, b = 11.4046(17) Å, c = 12.2121(18) Å, α = 104.185(2)°, β = 104.386(2)°, γ = 100.718(2)°, V = 1226.8(3) $Å^3$, Z = 2, D_{calc} = 1.908 g/cm^3, μ = 5.575 mm^{-1}, F(000) = 692, yellow prism, 0.160 × 0.070 × 0.020 mm^3, theta min/max 1.909/25.682°, index ranges $-11 \le h \le 11$, $-13 \le k \le 13$, $-14 \le l \le 14$, reflections collected/independent 11933/4618 [R(int) = 0.0515], max./min. transmission 0.6750/0.4750, data/restraints/parameters 4618/0/320, GooF(F^2) 1.029, R_1 = 0.0367 [$I > 2\sigma(I)$], wR_2 = 0.0707 (all data), largest diff. peak/hole 1.300/−1.302 e·$Å^{-3}$. CCDC deposition number 2069275.

Crystal Data and Structure Refinement for 5. $C_{17}H_{21}F_6IrN_3O_3P$, 652.54 g·mol^{-1}, monoclinic, $P21/n$, a = 8.5979(6) Å, b = 9.2848(7) Å, c = 26.8856(19) Å, β = 96.0480(10)°, V = 2134.3(3) $Å^3$, Z = 4, D_{calc} = 2.031 g·cm^{-3}, μ = 6.407 mm^{-1}, F(000) = 1256, yellow prism, 0.280 × 0.180 × 0.160 mm^3, theta min/max 2.322/28.676°, index ranges $-11 \le h \le 11$, $-12 \le k \le 11$, $-34 \le l \le 34$, reflections collected/independent 23340/5144 [R(int) = 0.0344], max./min. transmission 0.2791/0.2034, data/restraints/parameters 5144/0/284, GooF(F^2) 1.028, R_1 = 0.0248 [$I > 2\sigma(I)$], wR_2 = 0.0579 (all data), largest diff. peak/hole 1.134/−0.683 e·$Å^{-3}$. CCDC deposition number 2069277.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.2c00125.

^1H and ^{13}C NMR spectra of the organometallic compounds and *N*-methylated amines, catalyst screening and optimization, isotopic labeling experiments, and DFT-optimized structures (PDF)

Coordinates (XYZ)

Accession Codes

CCDC 2069275 and 2069277 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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