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A Highly Active Bifunctional Iridium Complex with an Alcohol/Alkoxide-Tethered N-Heterocyclic Carbene for Alkylation of Amines with Alcohols

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Abstract: A series of new iridium(III) complexes containing bidentate N-heterocyclic carbenes (NHC) functionalized with an alcohol or ether group (NHC–OR, R = H, Me) were prepared. The complexes catalyzed the alkylation of anilines with alcohols as latent electrophiles. In particular, biscationic Ir^{III} complexes of the type $[Cp^*(NHC\text{-}OH)Ir(MeCN)]^{2+}2[BF_4^-]$ afforded higher-order amine products with very high efficiency; up to >99% yield using a 1:1 ratio of reactants and 1–2.5 mol% of Ir, in short reaction times (2–16 h) and under base-free conditions. Quantitative yields were also obtained at 50 °C, although longer reaction times (48–60 h) were needed. A large variety of aromatic amines have been alkylated with primary and secondary alcohols. The reactivity of structurally related iridium(III) complexes was also compared to obtain insights into the mechanism and into the structure of possible catalytic intermediates. The Ir^{III} complexes were stable towards oxygen and moisture, and were characterized by NMR, HRMS, single-crystal X-ray diffraction, and elemental analyses.

Keywords: amines · carbene ligands · iridium · bifunctional catalyst · synthetic methods

Introduction

N-Heterocyclic carbenes (NHCs) are a very important family of ligands for the synthesis of stable transition-metal complexes.[1] The robustness of metal complexes with NHCs can be attributed to the strong σ-donation ability and steric properties of these ligands. The strong metal–NHC bond often makes carbene complexes more thermally, oxygen, and moisture stable, and, in some instances, more active than those containing phosphane ligands.[1] Another advantage of NHCs is their straightforward synthesis, which allows easy access to multiple structures that are modified in a desired fashion. A special group of NHCs are those that are functionalized with an extra donor moiety. Such modification introduces a stabilizing chelating effect.[2] Depending on the nature of the donor functionality, bidentate NHCs may behave as hemilabile ligands and are thus able to create vacant coordination sites easily.[3] A special group among donor-functionalized NHCs is those having proton donor/acceptor capability. Ligands having such donor moieties are capable of protonating/deprotonating reactants and intermediates, which may have a beneficial influence in catalytic reactions involving hydrogen transfer. This metal–ligand cooperation is called bifunctional catalysis.[4,5,6] Additionally, secondary interactions between the ligand and the substrate or ligand and catalyst by formation of hydrogen bonds may enhance the reaction rate and/or improve selectivity.[7] A number of complexes containing NHCs functionalized with alcohol,[8] alkoxide,[9] phenoxide,[10] ether,[11] *N*-heteroaryl,[12,13] oxazoline,[9] amino,[14] and amido,[15] and other donor groups have been reported.[9] In several cases, potential hemilability or metal–ligand bifunctionality has been proposed.[11b,c,13b,f,g,14b,d,e,g–i,8i]

Among the methods available for amine bond formation,[16] the catalytic redox condensation reaction between alcohols and amines to give higher-order amines and water is an attractive approach.[17,18,19] A wide variety of inexpensive alcohols are commercially available and water is the sole by-product of the reaction, making it an atom economical and environmentally friendly synthetic method. The reaction is catalyzed by complexes of Ru, Ir, Pd, and other metals.[17] The first examples with discrete catalysts[18] were described independently by Grigg[20] and Watanabe[21] in the 1980's and, since then, a number of very successful examples have been reported by the groups of Fujita,[22] Williams,[23]

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Beller,[24] Kempe,[25] Madsen,[26] Yus,[27] Peris,[28] and others.[17,29] Our own group has used this reaction in the synthesis of aminosugars and aminoferrocenes.[30] This transition-metal-catalyzed reaction proceeds through a hydrogen transfer mechanism, which consists of three steps, namely: 1) oxidation of an alcohol with concomitant formation of a metal hydride; 2) formation of an imine from the resulting carbonyl compound and the amine substrate, and 3) rehydrogenation of the imine and catalyst regeneration.[17,31] Transition-metal complexes with NHC ligands have also been used in the alkylation of amines with alcohols.[14b,28a,32]

As a part of our ongoing research in the synthesis of efficient homogeneous[33] and heterogenized[34] transition-metal complexes, we aimed towards the preparation of novel bifunctional metal complexes for reactions involving hydrogen transfer. Most of the cooperative catalytic systems incorporate amine/amide[4,6] or aromatic hydroxyl/dearomatized enone[5] functionalities. In contrast, to the best of our knowledge, no alcohol/alkoxide bifunctional system has ever been tested in hydrogen transfer reactions or hydrogenations.[35] Herein, we report the preparation of iridium(III) complexes having hydroxy-, ether-, and alkoxide-functionalized NHC ligands, and their catalytic activity in the alkylation of amines with alcohols. The most active complex (**1a**) contains a hydroxyl-functionalized NHC [NHC–alcohol], and can be synthesized in high yields in a few steps from commercially available starting materials. The [NHC–alcohol]Ir^{III} complex **1a** (Figure 1) was found to have excellent catalytic activity;

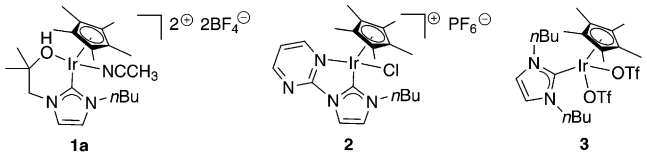


Figure 1. Structure of complexes **1a**, **2** and **3**.

it combines the best characteristic of complexes **2**[13b] and **3**,[28a] reported previously by Crabtree and Peris, respectively (Figure 1). A low catalyst loading of iridium (**1a**) affords excellent yields in the alkylation of amines with alcohols in short reaction times. No excess of alcohol substrate is required to reach full conversions, and the reactions proceed without addition of base. Furthermore, **1a** allows, for the first time, amines to be alkylated with alcohols at temperatures as low as 50 °C.

Results and Discussion

Ligand design: Carbene ligand **A** (NHC–alcohol; Figure 2) was designed to include the following properties: 1) A chelate effect that would provide higher stability; 2) a potentially labile OH group that could dissociate during the catalytic cycle, creating a vacant coordination site on iridium; 3) coordination of the hydroxyl group that could help in the release of the amine product, which has been proposed to be a turnover-limiting step,[36] and 4) the corresponding alkoxide formed after deprotonation might act as proton acceptor, which could play an important role in the catalytic cycle (bifunctional catalysis).

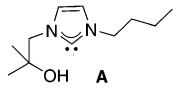
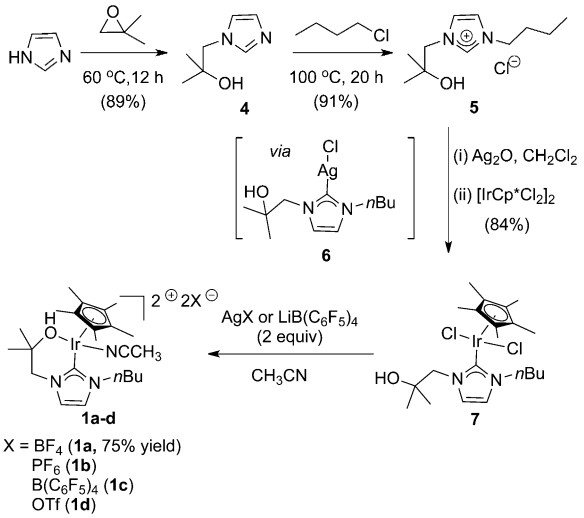


Figure 2. Carbene ligand **A**.

Syntheses of complexes: Complexes **1a–d** were synthesized by following the short reaction sequence depicted in Scheme 1. Salt **5** was prepared in three steps starting from



Scheme 1. Synthesis of complexes **1a–d**.

imidazole in an overall yield of 81 %.[37] To obtain iridium complex **7**, the corresponding silver carbene complex (**6**) was first prepared by addition of Ag_2O to a solution of **5** in CH_2Cl_2 under light-free conditions. Formation of **6** was confirmed by NMR spectroscopic analysis, which showed the characteristic Ag–$C_{carbene}$ signal at $\delta = 180.4$ ppm in the ^{13}C NMR spectrum, and the imidazole backbone proton signals at $\delta = 7.21$ and 6.95 ppm in the ^{1}H NMR spectrum. Complex **7** was prepared by transmetallation of the carbene ligand on **6** to $[IrCp^*Cl_2]_2$. The presence of the OH proton was confirmed by an exchange experiment with D_2O (disappearance of the signal at $\delta = 4.5$ ppm in the ^{1}H NMR spectrum upon addition of D_2O), as well as by IR spectroscopic analysis. Single crystal X-ray diffraction analysis of **7** (Figure 3) confirmed the structure of the complex, and revealed that the OH group of the ligand was not coordinated to the iridium center. Full characterization of complex **7** is given in the Supporting Information.

Dicationic iridium complexes **1a–d** were prepared by addition of two equivalents of AgX (X = BF_4, PF_6, OTf; for complexes **1a**, **1b** and **1d**, respectively) or $LiB(C_6F_5)_4$ (for **1c**) to a solution of **7** in CH_3CN (Scheme 1). Complex **1a** was characterized by ^{1}H and ^{13}C NMR spectroscopy, two-dimensional ^{1}H-^{13}C (HSQC) correlation spectra, and HRMS analysis. The presence of the acidic OH proton was further

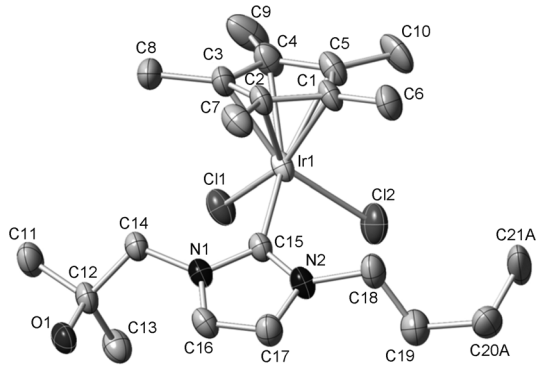


Figure 3. Molecular structure of **7** with displacement ellipsoids shown at 30% probability. Selected bond lengths (Å) and angles (deg): Ir(1)–C(15) 2.040(7), Ir(1)–Cl(1) 2.425(2), Ir(1)–Cl(2) 2.414(2), C(15)-Ir(1)-Cl(1) 92.1(2), C(15)-Ir(1)-Cl(2) 90.2(2), Cl(1)-Ir(1)-Cl(2) 84.8(8).

confirmed by an exchange experiment with D_2O (disappearance of the signal at $\delta = 7.02$ ppm in the ^1H NMR spectrum upon addition of D_2O), as well as by IR spectroscopic analysis. In addition, the structure of complex **1a** was characterized by single crystal X-ray diffraction analysis (Figure 4). In

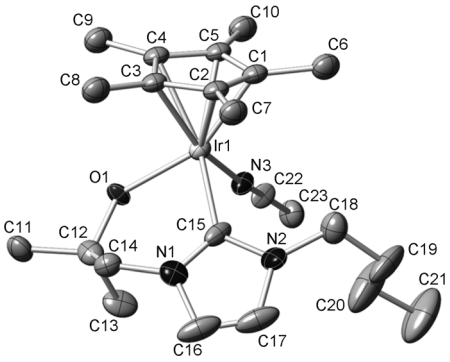
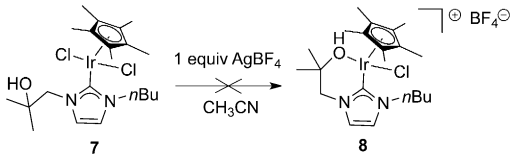


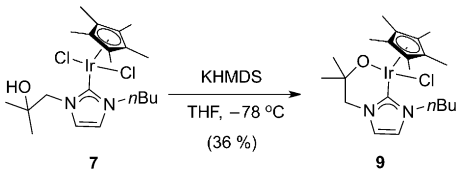
Figure 4. Molecular structure of **1a** with displacement ellipsoids shown at 30% probability. The crystal structure includes two symmetry-independent complexes (**1a**-A and **1a-**B, only one shown here) in the asymmetric unit with only small differences in bond distances and bond angles. Selected bond lengths (Å) and angles (deg): **1a**-A: Ir(1)–C(15) 2.03(2), Ir(1)–O(1) 2.15(1), Ir(1)–N(3) 2.08(1), C(15)-Ir(1)-O(1) 84.2(6), C(15)-Ir(1)-N(3) 86.3(6), O(1)-Ir(1)-N(3) 85.7(5). **1a**-B: Ir(2)–C(38) 2.11(2), Ir(2)–O(2) 2.18(1), Ir(1)–N(6) 2.07(1), C(38)-Ir(2)-O(2) 86.3(7), C(38)-Ir(2)-N(6) 89.2(6), O(2)-Ir(2)-N(6) 86.4(5).

contrast to complex **7**, the hydroxyl group in **1a** is coordinated to iridium. The average Ir–$C_{carbene}$ (2.07 Å) and Ir–O distances (2.17 Å), are both in the expected range.[38] Single crystal X-ray diffraction of **1a** also revealed the presence of intermolecular hydrogen bonds between the alcohol proton and the tetrafluoroborate anion.[39]

To understand the influence of the functionalized carbene moiety on the catalytic activity, we also synthesized the structurally similar complexes **9**, **13**, and **14**. We initially attempted to synthesize the monocationic complex **8**, which is a structural intermediate between complexes **7** and **1** (Scheme 2). Despite multiple attempts to prepare **8** by treatment of **7** with $AgBF_4$ (1 equiv), a mixture of different complexes was always formed. Because the acidic proton of **8** (as well as those of **1a–d**) is expected to be abstracted under the reaction conditions (see below), we instead prepared complex **9**, which is a deprotonated version of **8**. The reaction of complex **7** with KHMDS (potassium bis(trimethylsilyl)amide) at low temperature afforded alkoxide **9**, albeit in low yield (Scheme 3). After recrystallization from a mixture of pentane and dichloromethane, **9** could be characterized by NMR spectroscopy, HRMS, and single crystal X-ray diffraction analysis (Figure 5).



Scheme 2. Attempted synthesis of **8**.



Scheme 3. Synthesis of **9**.

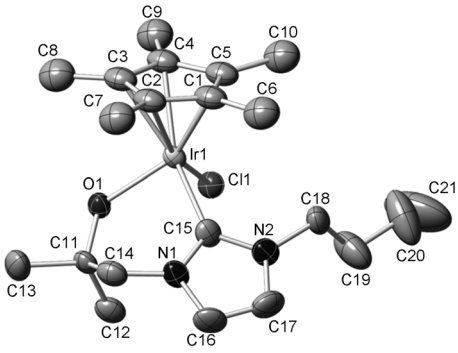
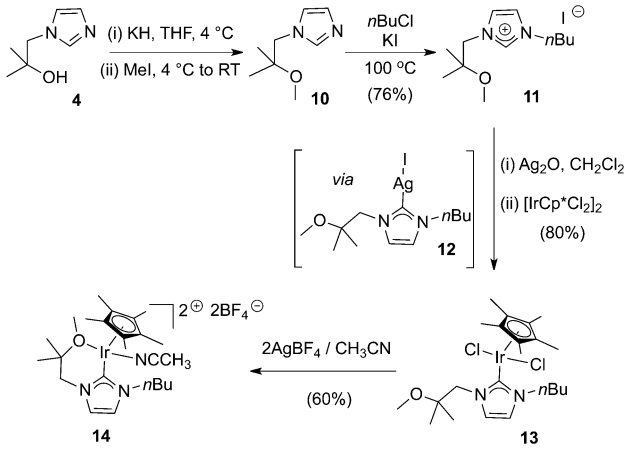


Figure 5. Molecular structure of **9** with displacement ellipsoids shown at 30% probability. Selected bond lengths (Å) and angles (deg): Ir(1)–C(15) 2.04(1), Ir(1)–O(1) 2.071(9), Ir(1)–Cl(1) 2.432(3), C(15)-Ir(1)-O(1) 87.6(5), C(15)-Ir(1)-Cl(1) 91.1(4), O(1)-Ir(1)-Cl(1) 85.9(3).

In addition, complexes **13** and **14**, containing a methoxy group in the pendant chain, were synthesized (Scheme 4). The precursor imidazolium salt **11** was prepared by treatment of **4** with MeI under basic conditions in tetrahydrofuran (THF), followed by reaction with *n*-butyl chloride. Complexes **13** and **14** were obtained following a synthetic route similar to that used for the preparation of **7** and **1** (i.e., through transmetallation of carbene from silver to iridium followed by chloride abstraction). In the crystal structures (see Figure S1 and S2 in the Supporting Information), the

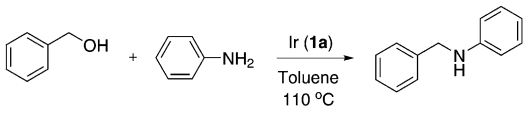


Scheme 4. Synthesis of complexes **13** and **14**.

methoxy group is not coordinated to iridium in the case of neutral complex **13**, whereas in biscationic complex **14**, the ether group is bound to the metal.

Catalytic activity and optimization of reaction conditions: Preliminary studies of the catalytic activity of NHC–iridium complexes **1**, **7**, **9**, and **14** were performed to explore their potential application in the N-alkylation of amines with alcohols; for comparison, we also tested $[IrCp^*Cl_2]_2$. The coupling of aniline with benzyl alcohol was investigated as a model reaction (Table 1). All reactions were carried out with 1.0 mol% catalyst loading in toluene under an argon atmosphere, by using a 1:1 ratio of amine/alcohol, in the absence of base.

Table 1. N-Alkylation of aniline with benzyl alcohol. Catalyst screening.[a]



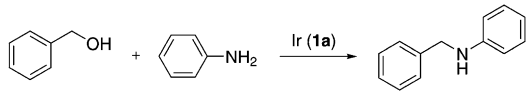
Entry	Catalyst	Time [h]	Yield [%][b]
1	none	14	0
2	$[IrCp^*Cl_2]_2$	14	12
3	$[IrCp^*Cl_2]_2/2AgBF_4$	14	5
4	**7**	2/14	11/47
5	**1a**	1/2	76/>99
6	**1b**	1/2	78/>99
7	**1c**	1/2	78/>99
8	**1d**	2/5	50/>99
9	**9**	2/14	33/>99
10[c]	**9** + $AgBF_4$	1	>99
11[d]	**14**	2	72

[a] Reagents and conditions (unless otherwise noted): BnOH (1.0 mmol), $PhNH_2$ (1.0 mmol), [Ir] (1 mol%, 0.01 mmol), toluene (0.5 mL), 110 °C. [b] Yield of the *N*-benzylaniline determined by ^1H NMR spectroscopic analysis using 1,4-di-*tert*-butylbenzene as internal standard. [c] The active catalyst was prepared in situ from **9** and $AgBF_4$ (1 equiv) in CH_2Cl_2 (0.1 mL), AgCl was separated by centrifugation and the remaining solution was used in the reaction. [d] 1.5 mol% Ir was used. When the reaction was performed with 1.0 mol%, 10% conversion was obtained (monitored from 2 to 24 h).

The reaction was not successful in the absence of any catalyst (Table 1, entry 1), and with $[IrCp^*Cl_2]_2$ only a small amount of product was formed (Table 1, entry 2).[40] The combination of $[IrCp^*Cl_2]_2$ with $AgBF_4$ resulted in a very low yield (Table 1, entry 3), suggesting the importance of the carbene ligand for catalytic activity (see below, Table 1, entry 5). The yield of *N*-benzylaniline was improved when complex **7** was used (Table 1, entry 4). A dramatic increase in the catalytic activity was obtained when the chloride ligands in **7** were substituted by less coordinating counterions such as BF_4 (**1a**), PF_6 (**1b**), $B(C_6F_5)_4$ (**1c**), and OTf (**1d**) (Table 1, entries 5–8, respectively). The best results were obtained with catalysts **1a–c** with BF_4, PF_6, and $B(C_6F_5)_4$ anions, namely 76, 78 and 78% yield after 1 h, respectively. Complex **1d**, having a more coordinating anion (OTf), required slightly longer reaction time to reach high yields (Table 1, entry 8). Monochloride complex **9** gave a slightly better yield than dichloride **7** (Table 1, entry 9 vs. 4), but was inferior to catalysts **1a–d** (Table 1, entries 5–8). This suggests that the more electrophilic the character of the iridium catalyst, the higher the activity. When alkoxide complex **9** was used together with 1 equiv of $AgBF_4$, the reaction was completed in only 1 h, indicating that the alkoxide complex might be the active intermediate in the reaction (Table 1, entry 10). Finally, the activity of complex **14**, containing a methyl ether moiety, was worse than that of catalyst **1a**, with a hydroxyl group (both with BF_4^- as the counterion, Table 1, entry 11). Furthermore, catalyst **14** was less stable than catalysts **1a–d** and its loading had to be increased from 1 to 1.5 mol% to reach high conversion levels. These results indicate that the presence of the acidic proton increases the reaction rate. Importantly, complexes **1a–d** and **14** showed higher catalytic activity than the structurally related complex **3** (Figure 1),[28a] which points to a possible stabilization of coordinatively unsaturated catalytic intermediates as well as minimization of product inhibition by the hemilabile donor group in **1a**.

Complex **1a** was chosen for further optimization studies (catalyst loading and temperature) due to its high reactivity, better accessibility, and lower cost (Table 2). An attempt to lower the catalyst loading below 1 mol% resulted in a drastic decrease of the catalytic activity (Table 2, entry 1 vs. 2). We evaluated the possibility of generating the active catalyst **1a** in situ from the more stable precursor **7** (Table 2, entry 3), avoiding the requirement for additional, low-yielding purification. After mixing **7** with $AgBF_4$ in acetonitrile and filtering off the precipitated AgCl, the catalyst solution was used directly in the reaction.[41] Such a procedure afforded the N-alkylated product in excellent yield in the same reaction time as when the isolated catalyst **1a** was used (Table 2, entry 1 vs. 3, respectively). The temperature of the reaction was found to have a strong impact on the reaction rate (Table 2, entries 4–8). The temperature could be lowered to 90 °C, but longer reaction time was needed to obtain high conversion (6 h, 93% conv., Table 2, entry 5). However, when the acetonitrile used to prepare the catalyst stock solutions was replaced by a noncoordinating solvent (CH_2Cl_2),

Table 2. N-Alkylation of aniline with benzyl alcohol. Reaction temperature and catalyst loading screening.[a,b]



Entry	Cat [mol%]	Temp [°C]	Time [h]	Yield [%][b]
1	1	110	2	>99
2	0.5	110	6	21
3[c]	1	110	2	>99
4	1	100	6	>99
5	1	90	6	93
6[d]	2	80	3	>99
7[d]	1	80	36	92
8[d]	2	60	24	95
9[d]	2	50	48	>99

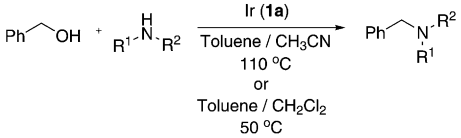
[a] Reaction conditions: BnOH (1.0 mmol), $PhNH_2$ (1.0 mmol), toluene (0.5 mL). [b] Yield of the N-benzylaniline determined by ^1H NMR spectroscopic analysis using 1,4-di-*tert*-butylbenzene as internal standard. [c] **1a** was prepared in situ from **7** and $AgBF_4$ (2 equiv) in MeCN and used in the reaction after filtration through Celite to remove AgCl. The reaction was carried out in a mixture of MeCN/toluene (1:2). [d] The active catalyst was prepared in situ from **7** and $AgBF_4$ (2 equiv) in CH_2Cl_2 and used in the reaction after filtration through Celite to remove AgCl. The reaction was carried out in a mixture of CH_2Cl_2/toluene (1:4).

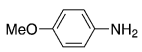
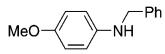
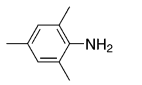
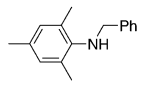
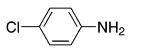
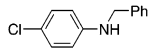
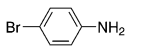
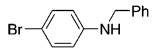
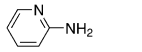
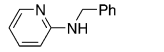
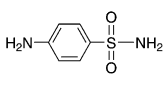
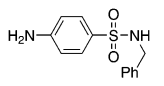
the temperature could be decreased to 50°C (Table 2, entries 6–9) without diminishing the yields, albeit requiring longer reaction times and catalyst loadings of 2 mol%. To the best of our knowledge, this is first time that the alkylation of amines with alcohols has been performed at temperatures below 70°C.[25e,f]

Substrate scope: The optimized conditions involving in situ generation of the active catalyst (1 mol% at 110°C, Table 2, entry 3) were applied to the coupling of various amines and alcohols (Tables 3 and 4). In some cases, an increase in catalytic loading from 1 to 1.5 or 2.5 mol% was necessary to reach full conversion. Anilines with either electron-donating or electron-withdrawing substituents on the aromatic ring were successfully alkylated with benzyl alcohol in high yields (Table 3, entries 1–5). Sterically hindered 2,4,6-trimethylaniline could also be used, although longer reaction time was necessary to obtain high conversion (Table 3, entry 3). No cleavage of halogen atoms was observed when *p*-bromo- or *p*-chloro-substituted substrates were used (Table 3, entries 4 and 5). Moreover, the heteroaromatic moiety in 2-aminopyridine was also well-tolerated (Table 3, entry 6). *N*-Alkyl-*N*-arylamines reacted efficiently under similar conditions in 15–16 h (Table 3, entries 7 and 8). Reaction of benzyl alcohol with 4-amino-*N*-benzylbenzenesulfonamide resulted in selective alkylation of the sulfonamide group (Table 3, entry 9).[42] The most reactive anilines could be alkylated with benzyl alcohol at 50°C, albeit with longer reaction times (Table 3, entries 1 and 4). The corresponding higher-order amines were formed in quantitative yields.

The catalytic system has also been tested with aliphatic amines such as benzyl amine, *n*-hexylamine, and cyclohexylamine but, in all cases, conversions of less than 10% were observed. The low activity obtained with aliphatic amines compared with aromatic amines might be due to the higher nucleophilicity of the former. Strong coordination of the more nucleophilic aliphatic amines blocks the empty coordination site on iridium, preventing coordination of the alcohol substrate, which results in deactivation of the complex. On the other hand, various primary or secondary alcohols could be coupled with aniline, producing monoalkylated amines in high yields (Table 4). Primary aliphatic alcohols (Table 4, entries 1, 2, and 6), *sec*-alcohols with alkyl and aryl substituents (Table 4, entries 3 and 4), and benzylic alcohols (Table 4, entry 5, and Table 3, entry 1), afforded the corresponding higher-order amines in excellent yields. When 1,5-pentanediol was reacted with aniline, the cyclic 1-phenylpiperidine was obtained as the major product, which was isolated in 75% yield (Table 4, entry 2). The most reactive alcohol could be reacted with aniline at 50°C (Table 4, entry 5) giving the product in 95% yield.

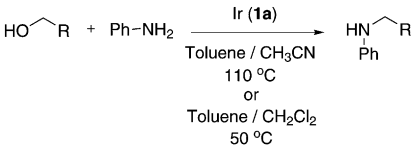
Table 3. Amine scope; N-alkylation of amines with benzyl alcohol catalyzed by **1a**.[a]

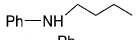
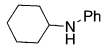
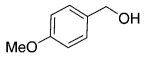
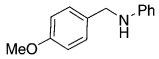
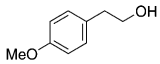
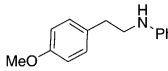


Entry	Amine	Amine product	Time [h]	Conv. [%][b]	Yield [%][c]
1			2/48[d]	>99	92/>99[d]
2[e]			5	>99	93
3[e]			12	>99	71
4			2.5/60[d]	>99	85/>99[d]
5			3	>99	86
6[e]			16	>99	88
7[e]			16	>99	74
8[e]			15	>99	84
9[f]			16	95	80

[a] Reagents and conditions (unless otherwise noted): benzyl alcohol (1.0 mmol), amine (1.0 mmol), **1a** (0.01 mmol, 1 mol%), toluene (0.3 mL), 110°C. **1a** was prepared in situ as described in Table 2, entry 3. [b] Conversion of the alcohol substrate was determined by ^1H NMR spectroscopic analysis. [c] Isolated yield after flash chromatography. [d] The active catalyst was prepared in situ from **7** and $AgBF_4$ (2 equiv) in CH_2Cl_2 and used in the reaction (Ir = 2 mol%) after filtration through Celite to remove AgCl. The reaction was carried out in a mixture of CH_2Cl_2/toluene (1:4) at 50°C. The yield was determined by ^1H NMR spectroscopic analysis using naphthalene as an internal standard. [e] Ir (1.5 mol%). [f] Ir (2.5 mol%).

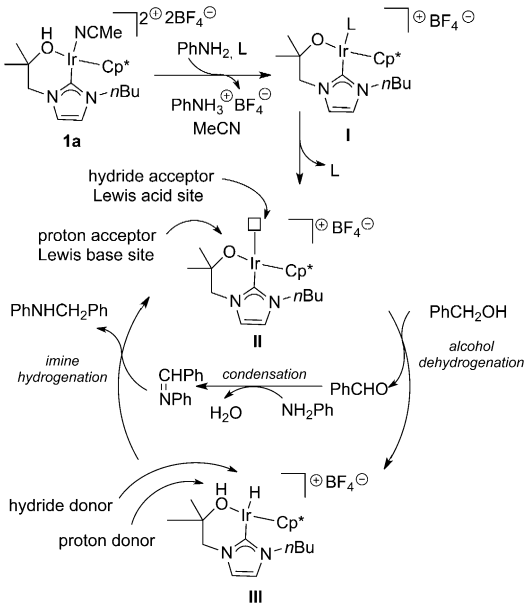
Table 4. Alcohol scope; N-alkylation of aniline with alcohols catalyzed by **1a.**[a]



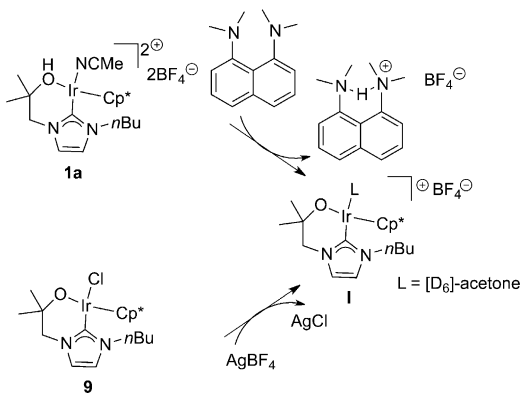
Entry	Alcohol	Amine product	Time [h]	Conv. [%][b]	Yield [%][c]
1[d]			4	>99	84
2[d]			5	80	75
3[d]			16	>99	87
4[d]			18	>99	83
5[e]			2/60[f]	97	91/95[f]
6[e]			8	>99	88

[a] Reagents and conditions (unless otherwise noted): alcohol (1.0 mmol), aniline (1.0 mmol), **1a** (0.01 mmol, 1 mol%), toluene (0.3 mL), 110°C. **1a** was prepared in situ as described in Table 2, entry 3. [b] Conversion of alcohol substrate was determined by ^{1}H NMR spectroscopic analysis. [c] Isolated yield after flash chromatography. [d] 2.5 mol% Ir. [e] 1.5 mol% Ir. [f] The active catalyst was prepared in situ from **7** and $AgBF_4$ (2 equiv) in CH_2Cl_2 and used in the reaction (Ir = 2 mol%) after filtration through Celite to remove AgCl. The reaction was carried out in a mixture of CH_2Cl_2/toluene (1:4) at 50°C. The yield was determined by ^{1}H NMR spectroscopic analysis using naphthalene as internal standard.

Reaction mechanism: Based on the results presented in Table 1, we propose the general mechanism depicted in Scheme 5. To become catalytically active, complex **1a** must undergo a two-step activation. First, the acidic OH proton is abstracted by the amine substrate, which is present in abundance in the reaction mixture. The acidity of this proton is increased due to coordination to the metal center, making possible its deprotonation by the moderately basic aromatic amine, forming intermediate **I**. The weakly bound acetonitrile ligand can be exchanged by other potential ligands present in the reaction mixture, such as amine or alcohol. In the second activation step, the weakest bound ligand L (L = acetonitrile, aniline, alcohol, solvent) dissociates, forming a bifunctional 16e$^-$ complex (**II**). The importance of generating a vacant coordination site was demonstrated by the low catalytic activity of complexes **7** and **9** (Table 1, entries 4 and 9, respectively), containing strongly bound chloride ligands. Interestingly, the fact that **9** is a significantly better catalyst than **7** may indicate that the chelating oxygen-containing arm in the former complex can temporarily dissociate upon protonation, creating unsaturation. Furthermore, the higher electrophilicity of the Ir center in monocationic complex **9** may facilitate coordination of the alcohol substrate. To further support our assumption that **1a** can be deprotonated by aniline during the reaction, producing the active alkoxide complex **I**, we wanted to study the deprotonation step by ^{1}H NMR spectroscopy. Unfortunately, titration of **1a** with aniline, which is the base and the substrate used in the reaction, resulted in a complex NMR spectra that was difficult to interpret due to equilibria between the reactants (see the Supporting Information). Instead, **1a** could be successfully deprotonated with proton sponge (*N*,*N*,*N*′,*N*′-tetramethylnaphthalene-1,8-diamine), which is a non-nucleophilic amine (Scheme 6). Upon addition of 0.5 equiv of proton sponge to a solution of **1a**, the ^{1}H NMR spectrum showed immediate formation of **I** (0.5 equiv, L = [D$_6$]acetone) together with protonated amine and remaining unreacted **1a** (0.5 equiv; see the Supporting Information). All the signals were sharp, indicating that there is no fast equilibrium between the reactants. After addition of another 0.5 equiv of proton sponge, all starting material (**1a**) was transformed into **I**. Thus, this experiment shows that indeed the OH proton of **1a** is acidic enough to



Scheme 5. Possible mechanism of alkylation of amines with alcohols through metal–ligand bifunctional catalytic intermediates **II** and **III**.



Scheme 6. Two methods for the generation of intermediate complex **I**.

become deprotonated under the reaction conditions (the pK_a of the coordinated OH group is several units lower than usual tertiary alcohols; the reported pK_a of proton sponge in water is 12.1[43]).

Intermediate **I** was also prepared by an alternative method from complex **9** and $AgBF_4$, and could be fully characterized by NMR spectroscopic and HRMS analyses. The ^1H NMR spectrum of **I** obtained in this way was identical to that obtained by reacting **1a** with proton sponge. Furthermore, when intermediate **I** was used as the catalyst, the reaction time decreased from 2 to 1 h (Table 1, entry 10). This suggests that alkoxide complex **I** may be an intermediate in the reaction cycle.

Bifunctional complex **II** contains basic (oxygen) and acidic (iridium) sites. Thus, **II** is capable of accepting a proton and a hydride, producing complex **III** (Scheme 5). The exact mechanism of the dehydrogenation step is unknown at this stage of the investigation. Both an outer-sphere type (proceeding without coordination of the alcohol to the metal center) and an inner-sphere type (involving direct coordination of the alcohol to iridium and β-hydride elimination) may be possible. The aldehyde produced during the dehydrogenation step condenses with the amine, forming an imine intermediate. Bifunctional complex **III**, which contains both hydride and proton-donating sites, subsequently rehydrogenates the imine, closing the catalytic cycle. Similar to the dehydrogenation, the imine hydrogenation step may also proceed through inner- or outer-sphere mechanisms.

It is important to mention that the relatively high catalytic activity of complex **14** (Table 1, entry 11), containing a methyl substituent on the oxygen atom, indicates that this complex operates through a different mechanism in which the proton-accepting capability is not crucial for catalysis.

Conclusion

We have synthesized new N-heterocyclic carbene ligands containing a hydroxyl moiety that allow, for the first time, the preparation of iridium complexes with chelating [NHC–alcohol] ligands. The unique properties of the complexes account for their high catalytic activity in the N-alkylation of amines with alcohols. The best catalyst displays a broad substrate scope and is one of the most active catalysts known to date; it can be used to catalyze the reaction at temperatures as low as 50 °C. A reaction mechanism involving complex **1a** has been proposed. Key intermediates are a bifunctional iridium alkoxide complex (**II**), which was prepared and characterized, and bifunctional iridium hydride complex **III**.

Encouraged by these results, we are currently investigating the mechanism further and developing a solid-supported version of this catalyst. Our results will be communicated in due course.

Experimental Section

Preparation of complex 7: A mixture of $[IrCp^*Cl_2]_2$ (119 mg, 0.15 mmol) and silver carbene **6** (101.4 mg, 0.3 mmol, 0.3 M in CH_2Cl_2) was stirred at 35 °C for 4 h. The reaction mixture was filtered through Celite and the solvent was removed under vacuum. After purification by column chromatography (SiO_2; CH_2Cl_2/MeOH, 90:10), **7** (149.7 mg, 84% yield) was obtained as a yellow powder. ^1H NMR ($CDCl_3$): $\delta = 7.44$ (d, $J = 2$ Hz, 1H; C$H_{\text{imidazol backbone}}$), 7.02 (d, $J = 2$ Hz, 1H; C$H_{\text{imidazol backbone}}$), 5.11 (d, $J = 14.0$ Hz, 1H; NCHHC$(CH_3)_2$OH), 4.77 (dt, $J = 12.2$, 5.3 Hz, 1H; CHH$_{n\text{-butyl}}$), 3.81 (dt, $J = 12.2$, 5.3 Hz, 1H; CH$H_{n\text{-butyl}}$), 3.66 (d, $J = 14.0$ Hz, 1H; NCHHC$(CH_3)_2$OH), 3.06 (br s, 1H; OH), 2.13–1.97 (m, 1H; CHH$_{n\text{-butyl}}$), 1.81–1.65 (m, 1H; CH$H_{n\text{-butyl}}$), 1.57–1.40 (m, 2H; C$H_{2n\text{-butyl}}$), 1.58 (s, 15H; $C_5(CH_3)_5$), 1.40 (s, 3H; C$(CH_3)_2$OH), 1.39 (s, 3H; C$(CH_3)_2$OH), 0.99 ppm (t, $J = 7.4$ Hz, 3H; C$H_{3n\text{-butyl}}$); ^{13}C NMR ($CDCl_3$): $\delta = 156.0$ (Ir–C), 122.8 (C$H_{\text{imidazol backbone}}$), 121.1 (C$H_{\text{imidazol backbone}}$), 88.8 ($C_5(CH_3)_5$), 70.1 (NCH$_2C$-$(CH_3)_2$O), 59.1 (NC$H_2C(CH_3)_2$O), 50.7 (C$H_{2n\text{-butyl}}$), 34.0 (C$H_{2n\text{-butyl}}$), 28.7 ((C$H_3$)$_2$OH), 27.8 ((C$H_3$)$_2$OH), 20.2 (C$H_{2n\text{-butyl}}$), 14.0 (C$H_{3n\text{-butyl}}$), 9.0 ppm ($C_5(CH_3)_5$); HRMS (ESI+): m/z calcd for $C_{21}H_{35}ClIrN_2O$: 559.2062 $[M-Cl]^+$; found: 559.2085; elemental analysis calcd (%) for $C_{21}H_{37}Cl_2IrN_2O$: C 42.27, H 6.25, Cl 11.88, N 4.70; found: C 42.07, H 5.87, Cl 11.16, N 4.33.

Preparation of complex 1a: A solution of $AgBF_4$ (28.8 mg, 0.15 mmol) in anhydrous and degassed MeCN (0.25 mL) was added to an oven-dried sealed microwave tube containing complex **7** (44.6 mg, 0.075 mmol) in acetonitrile (0.5 mL) under an argon atmosphere. The reaction mixture was stirred for 15 min at RT, then the resulting crude solution was filtered through Celite and the solvent was evaporated. After precipitation from a CH_2Cl_2/pentane solution, complex **1a** (41.6 mg, 75% yield) was obtained as a yellow powder. ^1H NMR ([D$_6$]acetone): $\delta = 7.71$ (d, $J = 2.1$ Hz, 1H; C$H_{\text{imidazol backbone}}$), 7.65 (d, $J = 2.1$ Hz, 1H; C$H_{\text{imidazol backbone}}$), 7.02 (br s, 1H; OH), 4.40 (d, $J = 15.0$ Hz, 1H; NCHHC$(CH_3)_2$OH), 4.37 (ddd, $J = 13.3$, 10.7, 6.5 Hz, 1H; CHH$_{n\text{-butyl}}$), 4.18 (ddd, $J = 13.3$, 10.7, 6.5 Hz, 1H; CHH$_{n\text{-butyl}}$), 3.89 (d, $J = 15.0$ Hz, 1H; NCHHC$(CH_3)_2$OH), 2.80 (s, 3H; CH_3CN), 2.14–1.80 (m, 2H; C$H_{2n\text{-butyl}}$), 1.85 (s, 15H; $C_5(CH_3)_5$), 1.61 (s, 3H; C$(CH_3)_2$OH), 1.59–1.47 (m, 2H; C$H_{2n\text{-butyl}}$), 1.03 (t, $J = 7.5$ Hz, 3H; C$H_{3n\text{-butyl}}$), 0.98 ppm (s, 3H; C$(CH_3)_2$OH); ^{13}C NMR ([D$_6$]acetone): $\delta = 152.8$ (Ir–C), 126.8 (C$H_{\text{imidazol backbone}}$), 126.4 (C$H_3$CN), 122.3 (C$H_{\text{imidazol backbone}}$), 93.6 ($C_5(CH_3)_5$), 77.1 (NC$H_2C(CH_3)_2$O), 58.8 (NC$H_2C(CH_3)_2$O), 51.1 (C$H_{2n\text{-butyl}}$), 33.5 (C$H_{2n\text{-butyl}}$), 27.3 ((C$H_3$)$_2$OH), 22.7 ((C$H_3$)$_2$OH), 20.6 (C$H_{2n\text{-butyl}}$), 14.1 (C$H_{3n\text{-butyl}}$), 9.4 ($C_5(CH_3)_5$), 3.8 ppm (C$H_3$CN); IR (NaCl, selected bands): $\tilde{\nu} = 3625$–3500 (br), 1000–1100 cm^{-1} (two bands overlapping, s); HRMS (ESI+): m/z calcd for $C_{21}H_{34}IrN_2O$: 523.2295 $[M]^+$; found: 523.2312.

General procedure for the alkylation of amines with alcohols catalyzed by 1a: A solution of $AgBF_4$ (28.8 mg, 0.15 mmol) in anhydrous and degassed MeCN (0.25 mL) was added to an oven-dried sealed tube containing pre-catalyst **7** (45 mg, 0.075 mmol) in MeCN (0.5 mL) under an argon atmosphere. The reaction mixture was stirred for 15 min at RT, then the resulting solution was filtered by using a cannula under an argon atmosphere and used as the stock solution for catalysis. The solution containing the catalyst (0.1–0.25 mL) was added to a solution of alcohol (1 mmol) and amine (1 mmol) in anhydrous and degassed toluene (0.4 mL) under an argon atmosphere. The reaction mixture was stirred at 110 °C for the time indicated in Tables 3 and 4. After completion, the mixture was cooled, filtered, and concentrated. The products were purified by column chromatography (SiO_2; pentane/CH_2Cl_2 = 90:10 to 80:20; or pentane/EtOAc = 100:0 to 70:30). For those reactions that were run at 50 °C, the active catalyst was prepared in situ from **7** and $AgBF_4$ (2 equiv) in CH_2Cl_2 and used in the reaction (Ir = 2 mol%) after filtration through Celite to remove AgCl. The reaction was carried out in a mixture of CH_2Cl_2/toluene (1:4) for the time indicated in Tables 3 and 4.

X-ray crystallography: Crystallographic data and refinement are provided in Table 1 in the Supporting Information. CCDC-867806 (**1a**), CCDC-867807 (**7**), CCDC-868525 (**9**), CCDC-881979 (**13**), and CCDC-868780 (**14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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