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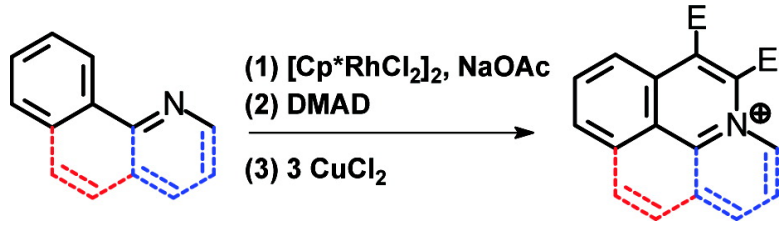

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An Efficient Low-Temperature Route to Polycyclic Isoquinoline Salt Synthesis via C−H Activation with $[Cp^*MCl_2]_2$ (M = Rh, Ir)

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Abstract: Bi-, tri-, and tetracyclic isoquinoline salts were readily synthesized in excellent yields at room temperature from readily available starting materials after three reaction steps. Aromatic C−H activation was first promoted by sodium acetate with $[Cp^*MCl_2]_2$ (M = Rh, Ir) at room temperature to form cyclometalated compounds. Dimethylacetylenedicarboxylate was then found to insert into the metal−carbon bonds of the cyclometalated compounds. Finally, the insertion compounds underwent oxidative coupling to form the desired isoquinoline salts and regenerate $[Cp^*MCl_2]_2$. All of the intermediate compounds following C−H activation, alkyne insertion, and oxidative coupling were fully characterized, including the determination of X-ray structures in several cases, and the results shed light on the overall mechanism. Moreover, it was possible to synthesize the isoquinoline salts from readily available starting materials using one-pot procedures; thus, this work provides a novel, efficient method for metal-mediated synthesis of heterocycles.

Introduction

Aromatic C−H activation mediated by transition metals has been widely exploited because of its potential for use in both industrial and pharmaceutical applications that produce heterocycles.[1−7] We have previously discovered metal-catalyzed routes to heterocycles such as indoles and quinolines that involve cyclometalations of unactivated C−H bonds.[8−10] Isoquinoline has been recognized as the structural backbone in naturally occurring alkaloids and is broadly used industrially in dyes, paints, insectides, and antifungals and pharmaceutically in anesthetics, antihypertension agents, disinfectants, and vasodilators. Traditional routes to isoquinolines such as the Bischler−Napieralski reaction[11−13] and the Pomeranz−Fritsch reaction[14,15] require strong acid at the ring-closure step, while the Pictet−Spengler reaction[16−19] requires making complicated substituted phenylethylamines.

Several transition-metal-mediated processes have been developed for isoquinoline ring systems. In particular, stoichimetric cyclopalladated compounds have been exploited for the isoquinoline ring closure. One early example started from the reaction of a cyclopalladated imine with acrylonitrile,[20] but the second step required thermolysis via heating to at least 180 °C in order to generate the isoquinoline. A palladium-mediated synthetic procedure for preparing a 1,2,3,4-tetrahydroisoquinolinium salt employed five reaction steps; however, the overall yield was less than 10%, and the final product was unstable upon exposure to air.[21] Perhaps the best effort to synthesize isoquinolines to date is that reported by Heck and co-workers,[22] in which aryl aldimines were cyclopalladated using silver tetrafluoroborate to activate the C−H bond of the aldimine, after which slow addition of dialkyl/aryl alkyne at 100 °C (rapid addition produced cyclotrimers) gave 3,4-disubstituted isoquinolinium salts in yields as high as 80%. Use of functionalized alkynes such as dimethylacetylenedicarboxylate (DMAD) gave poor yields (25%). Another example, in which cyclopalladated aromatic imines and vinyl ethers were used to synthesize isoquinolines,[23] was also limited by high temperatures and low yields for cyclization, rendering the methodology of limited synthetic utility. Isoquinoline derivatives have also been syn-

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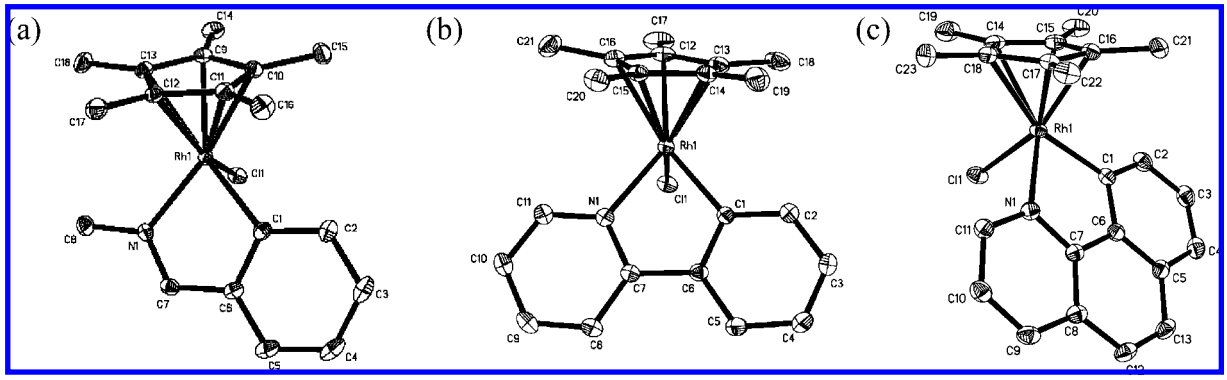


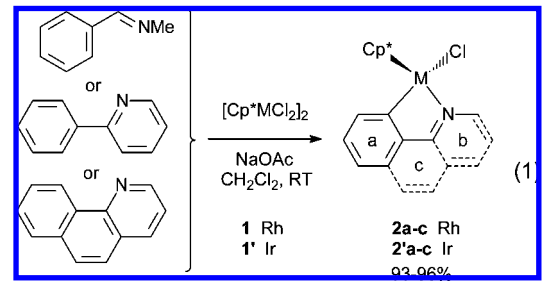
Figure 1. Molecular structures and atom-numbering schemes for (a) **2a**, (b) **2b**, and (c) **2c** with 50% displacement ellipsoids. H atoms have been omitted for clarity.

thesized by a nickel(0)-catalyzed [2 + 2 + 2] cocyclization at room temperature in good yields;[24] however, the cyclization is very sensitive to steric hindrance, and with disubstituted alkynes in place of acetylene, no cyclized isoquinoline products were afforded. Recently, several palladium-catalyzed coupling reactions of alkynes having moderate to good yields that involve heteroannulation of alkynes with prefunctionalized *o*-bromo- or *o*-iodophenylimines without C−H activation have also been reported.[25−28]

Despite the recent advances, new, efficient metal-catalyzed routes to isoquinolines, especially ones that require very mild conditions and proceed in high yields, are still in demand because of the number of broad biological applications. In this paper, we provide a new, efficient route to isoquinoline salts at room temperature in excellent yields from readily available arylaldimine starting materials. Noting the formation of nitrogen-containing metallocycles reported by the Davies group,[29−32] we became interested in the examination of *N*-benzylidenemethylamine, 2-phenylpyridine, and benzo[*h*]quinoline under analogous reaction conditions, and the expected cyclometalated compounds were obtained. Several unsaturated molecules, such as DMAD, were employed in order to expand the metallocycles, in which clean monoinsertion products were obtained in high yields (DMAD insertion into palladium−aryl and nickel−aryl is known and oftentimes gives multiple-insertion adducts[33−36]). The inserted products finally were oxidatively cleaved from the metal using anhydrous $CuCl_2$ at room temperature to obtain the expected heterocyles in high yields, and the final rhodium product $[Cp^*RhCl_2]_2$ was regenerated. In addition, after the use of a one-pot procedure for the sequential reactions in which all of the commercially available starting materials were mixed at room temperature, the desired isoquinoline derivatives were isolated simply by washing with hexane to remove the excess substrates and alkynes, thus avoiding the tremendous separation problems and product loss that occurred in most of the previous procedures. Consequently, we have developed a more efficient method for synthesizing isoquinoline derivatives from readily available starting materials under more mild conditions than in traditional synthetic routes.

Results and Discussion

By analogy to Davies work with similar substrates,[32] *N*-benzylidenemethylamine, 2-phenylpyridine, and benzo[*h*]quinoline were reacted with $[Cp^*MCl_2]_2$ [M = Rh (**1**), Ir (**1′**)] in dichloromethane at room temperature in the presence of NaOAc, producing metallocycles **2a**, **2′a**, **2b, 2′b**, **2c**, and **2′c** in good yields (eq 1). Single-crystal X-ray structures of **2a**, **2′a**, **2b, 2′b**, **2c**, and **2′c** were obtained, and the rhodium examples are shown in Figure 1a-c. Selected bond lengths and angles are summarized in Table S-1 in the Supporting Information.



The structures of **2a**, **2′a**, **2b, 2′b**, **2c**, and **2′c** show the expected piano-stool type geometry, and the bond lengths and bond angles are very similar except that the Ir−N bonds for **2′a** and **2′b** are unexpectedly slightly shorter than the Rh−N bonds of **2a** and **2b**, implying stronger σ donation from N to Ir. The C(1)−M(1)−N(1) angle is larger when the substrate is more bulky, as expected. It is worth noticing that the C−H activation is faster for the same substrate with $[Cp^*IrCl_2]_2$ than with $[Cp^*RhCl_2]_2$. Also, the reactions with *N*-benzylidenemethylamine are faster than those with 2-phenylpyridine or benzo[*h*]quinoline because of the electron-donating methyl group on nitrogen, which is consistent with electrophilic C−H activation as proposed earlier by the Davies group.[32]

DMAD was reacted with all of the cyclometalated complexes at room temperature in methanol, similar to its widespread use in palladium and nickel analogs.[33−36] In all cases, pure insertion

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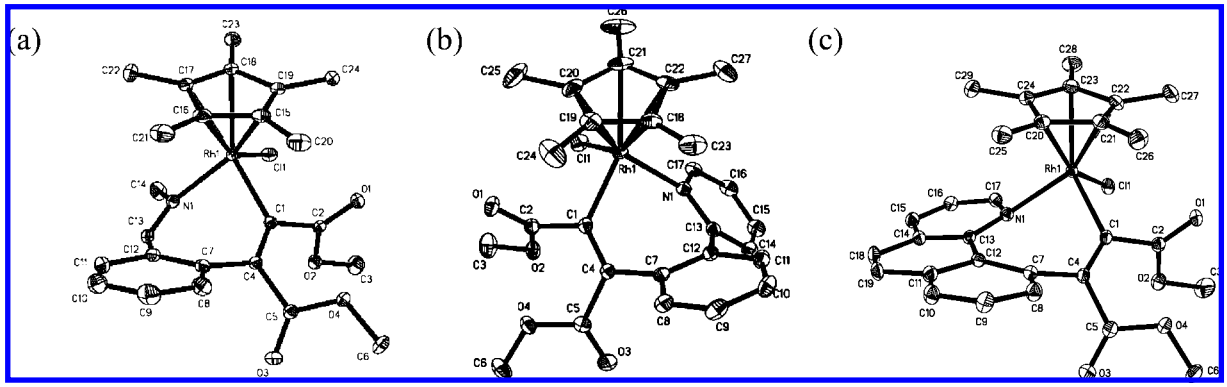
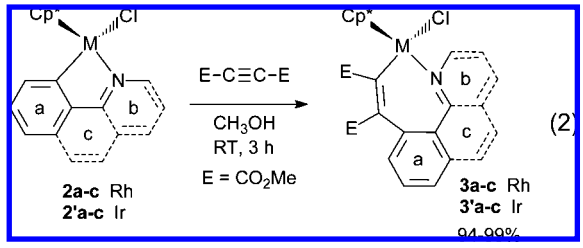


Figure 2. Molecular structures and atom-numbering schemes for (a) **3a**, (b) **3b**, and (c) **3c** with 50% displacement ellipsoids. H atoms have been omitted for clarity.

compounds were obtained in high yields following washing with hexane to remove excess DMAD (eq 2). In addition, only a single alkyne insertion was observed, instead of multiple insertions as seen in palladium and nickel analogs.



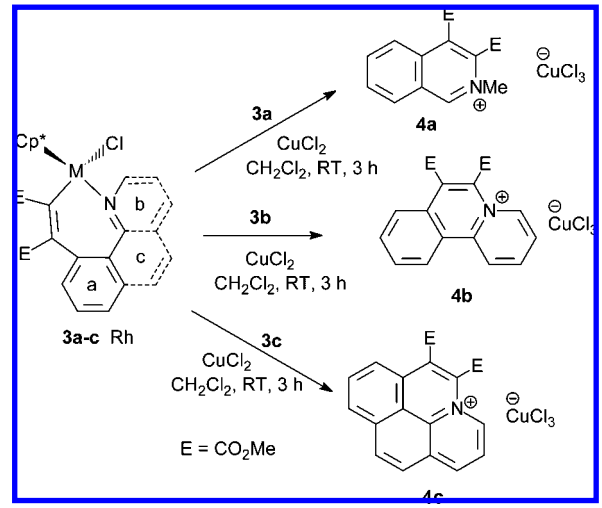
The single-crystal X-ray structures of **3a**, **3′a**, **3b, 3′b**, **3c**, and **3′c** were determined, and those for the rhodium series are shown in Figure 2a−c. Selected bond lengths and bond angles are summarized in Table S-2 in the Supporting Information. It is noteworthy that the Ir−N distance in **3′a** is longer than the Rh−N distance in **3a**. Also, for all of the compounds except **3a**, the M−Cl and M−N bonds after insertion are much longer than the bonds before insertion.

Several oxidants were examined for reaction with **3a**, **3b**, and **3c** to induce oxidative coupling of the C−N bond in order to liberate the isoquinoline derivatives.[37] It was found that upon addition of 3 equiv of anhydrous copper dichloride, quantitative liberation of rhodium dimer **1** was observed and an isoquinoline heterocycle was produced, as shown in Scheme 1.

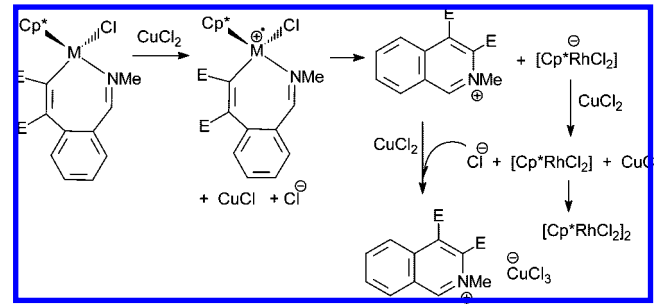
Both **1** and the isoquinoline salts can be recognized and characterized by ^{1}H NMR and ^{13}C NMR spectroscopy. When the same reaction was performed on **3a** with only 1 equiv of $CuCl_2$, a mixture of the starting complex **3a** and the isoquinoline salt **4a** was obtained, indicating that a full 3 equiv of $CuCl_2$ is required in order to complete the oxidative-coupling reaction. Scheme 2 shows how 3 equiv of $CuCl_2$ might be required in the reaction, using **3a** as an example.

While the $CuCl_3^-$ salts were not isolated, the isoquinoline structures were confirmed by adding 2 equiv of $AgBF_4$ into the reaction mixtures to allow isolation of the BF_4^- salts. The X-ray structures of the isoquinoline salts with the BF_4 anion (**5a** and **5c**) were determined (Figure 3a,b), as well as that of the byproduct $\{[RhCp^*]_2(\mu\text{-}Cl)_3\}[BF_4]$ arising from chloride abstraction from $[Cp^*RhCl_2]_2$ by Ag^+. Compounds **3′a**, **3′b**, and

Scheme 1



Scheme 2[a]



[a] M = Rh.

3′c were also treated with 3 equiv of $CuCl_2$, but no reaction was observed at ambient temperature.

The sequential reaction of all three steps in one pot (eq 3) was also examined, and the expected isoquinoline derivative was formed in 85% yield. Interestingly, in the stepwise reactions described above, dichloromethane was used in the first and third steps, but the second step required a more-polar solvent such as methanol or acetonitrile. Use of 2% acetonitrile in dichloromethane was also found to be adequate for carrying out the second step. For the one-pot reaction, the first step was carried out in dichloromethane. Next, 2% acetonitrile was added along with the DMAD to effect the second step. Finally, addition of $CuCl_2$ produced the isoquinoline in the oxidative-coupling step. Since the reaction is very solvent-dependent in that the insertion

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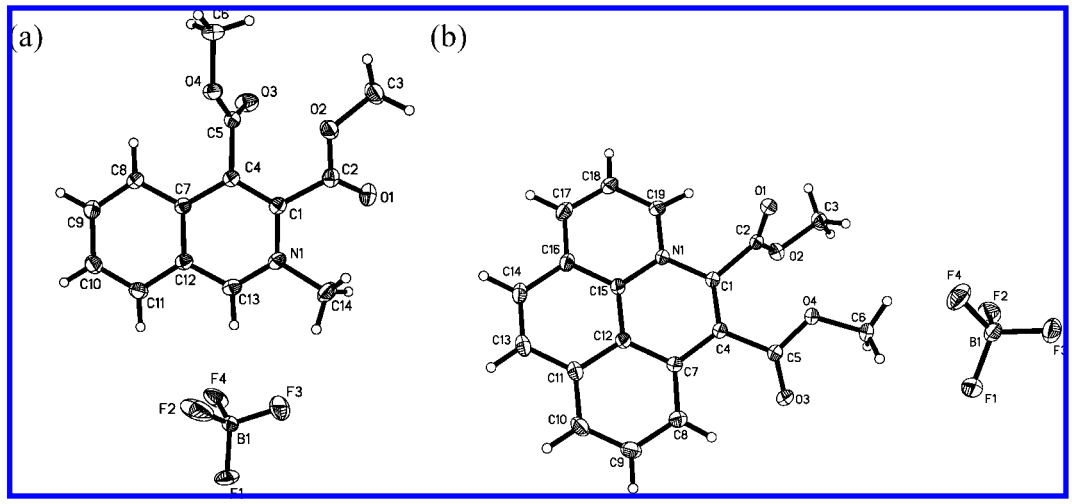
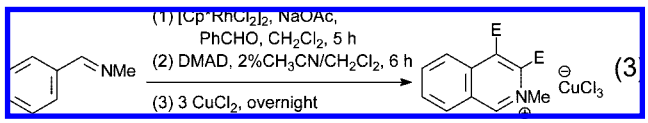


Figure 3. Molecular structures and atom-numbering schemes for (a) **5a** and (b) **5c** with 50% displacement ellipsoids. Selected bond lengths (Å) and angles (deg) for **5a**: C(1)−N(1), 1.3884(14); C(13)−N(1), 1.3230(15); N(1)−C(14), 1.4893(14); C(1)−C(4), 1.3685(14); C(4)−C(7), 1.4267(14); C(12)−C(13), 1.4049(15); C(1)−N(1)−C(13), 120.66(9); N(1)−C(1)−C(4), 119.92(10); C(1)−C(4)−C(7), 120.96(9); N(1)−C(13)−C(12), 122.39(10). For **5c**: C(1)−N(1), 1.4119(15); C(1)−C(4), 1.3583(16); C(4)−C(7), 1.4475(16); N(1)−C(1)−C(4), 121.84(10); N(1)−C(1)−C(2), 114.15(9); C(2)−C(1)−C(4), 123.91(10); C(1)−C(4)−C(7), 120.54(10); C(4)−C(7)−C(12), 116.96(10).

step requires a more-polar solvent while the oxidative-coupling step requires a less-polar solvent, it is hard to find reaction conditions that favor both steps. As shown in eq 3, even if 2% CH_3CN is added, the oxidative-coupling step is much slower than in pure dichloromethane. The reaction was tried using catalytic amounts of rhodium but found to be very slow, even though it proceeds to completion after a long time.



In summary, this paper reports a new synthesis of polycyclic isoquinoline salts under very mild conditions. The insertion of unsaturated molecules into the M−C bonds (M = Rh, Ir) of cyclometalated complexes combined with the oxidative liberation of the resulting N-containing organic compounds provides a new, efficient tool for the metal-mediated synthesis of heterocycles. Further studies of the scope of the electrophilic C−H activation and of the insertion of unsaturated molecules are currently under investigation.

Experimental Section

General Information. $RhCl_3 \cdot 3H_2O$ and $IrCl_3 \cdot 3H_2O$ were purchased from Pressure Chemical Co., and their dimers [Cp*RhCl$_2$]$_2$ and [Cp*IrCl$_2$]$_2$ were prepared by literature methods.[38] Methanol, dichloromethane, and acetonitrile were dried and distilled before use. Benzo[*h*]quinoline was purchased from Alfa Aesar, anhydrous copper chloride from Fisher, and *N*-benzylidenemethylamine, 2-phenylpyridine, and dimethyl acetylenedicarboxylate from Aldrich; all were used as supplied. All of the reactions were carried out under nitrogen. However, once the reactions were completed, subsequent workups were done without precaution, as the compounds are air-stable. All of the NMR spectra were recorded on a Bruker AMX400, AVANCE 400, or AVANCE 500 spectrometer in $CDCl_3$ (δ 7.26) unless otherwise specified. Elemental analyses were performed by Desert Analytics (Tucson, Arizona).

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Preparation of 2a. A mixture of [Cp*RhCl$_2$]$_2$ (50.0 mg, 0.081 mmol), NaOAc (40.0 mg, 0.49 mmol), *N*-benzylidenemethylamine (21.4 mg, 0.18 mmol), and benzaldehyde (trace) was stirred at room temperature (RT) in 20 mL of dichloromethane for 5 h. The mixture was filtered through Celite and evaporated to dryness. The solid obtained was washed with hexane to remove excess ligand. Cyclometalated compound **2a** was isolated as a red-orange solid (59.2 mg, 93%). Anal. Calcd for $C_{18}H_{23}ClNRh$: C, 55.19; H, 5.92; N, 3.58. Found: C, 54.61; H, 5.75; N, 3.83. ^{1}H NMR: δ 8.06 (dd, 1H, J = 3.8, 1.3 Hz, HC=N), 7.80 (d, 1H, J = 7.6 Hz, C_6H_4), 7.40 (dd, 1H, J = 7.4, 1.2 Hz, C_6H_4), 7.21 (ddd, 1H, J = 7.5, 7.4, 1.3 Hz, C_6H_4), 7.00 (dd, 1H, J = 7.4, 0.9 Hz, C_6H_4), 3.82 (d, 3H, J = 1.2 Hz, NMe), 1.69 (s, 15H, C_5Me_5). ^{13}C NMR: δ 183.47 (d, J = 91.1 Hz, Rh−C), 172.99 (HC=N), 145.45, 135.85, 130.47, 127.80, 122.42 (5 C's of C_6H_4), 95.78 (d, J = 24.2 Hz, C_5Me_5), 48.67 (NMe), 9.42 (s, C_5Me_5). IR: ν(C=N), 1575 cm^{-1}.

Preparation of 2′a. The reaction was carried out as for **2a**, using [Cp*IrCl$_2$]$_2$ (50.0 mg, 0.063 mmol), NaOAc (32.0 mg, 0.39 mmol), *N*-benzylidenemethylamine (17.0 mg, 0.14 mmol), and benzaldehyde (trace) in 20 mL of CH_2Cl_2 at RT for 5 h. Cyclometalated compound **2′a** was isolated as a yellow-orange solid (56.2 mg, 93%). Anal. Calcd for $C_{18}H_{23}ClNIr$: C, 44.95; H, 4.82; N, 2.91. Found: C, 45.05; H, 4.82; N, 3.03. ^{1}H NMR: δ 8.26 (d, 1H, J = 1.3 Hz, HC=N), 7.79 (d, 1H, J = 7.6 Hz, C_6H_4), 7.50 (dd, 1H, J = 7.4, 1.2 Hz, C_6H_4), 7.15 (ddd, 1H, J = 7.5, 7.4, 1.3 Hz, C_6H_4), 6.97 (dd, 1H, J = 7.4, 0.9 Hz, C_6H_4), 3.90 (d, 3H, J = 1.4 Hz, NMe), 1.73 (s, 15H, C_5Me_5). ^{13}C NMR: δ 175.17 (Ir−C), 168.50 (HC=N), 146.30, 134.70, 131.24, 127.81, 121.71 (5 C's of C_6H_4), 88.63 (C_5Me_5), 49.38 (NMe), 9.16 (C_5Me_5). IR: ν(C=N), 1579 cm^{-1}.

Preparation of 2b. The reaction was carried out as for **2a**, using [Cp*RhCl$_2$]$_2$ (50.0 mg, 0.081 mmol), NaOAc (40.0 mg, 0.49 mmol), and 2-phenylpyridine (28.2 mg, 0.18 mmol) in 20 mL of CH_2Cl_2 at RT overnight. Cyclometalated compound **2b** was isolated as a red-orange solid (64.6 mg, 93%). Anal. Calcd for $C_{21}H_{23}ClNRh$: C, 58.97; H, 5.42; N, 3.27. Found: C, 59.12; H, 5.51; N, 3.29. ^{1}H NMR: δ 8.72 (d, 1H, J = 5.3 Hz, HC=N), 7.80 (d, 1H, J = 7.5 Hz), 7.74 (d, 1H, J = 7.8 Hz), 7.69 (dd, 1H, J = 7.6, 7.5 Hz), 7.59 (d, 1H, J = 7.6 Hz), 7.23 (d, 1H, J = 7.3 Hz), 7.11 (dd, 1H, J = 6.5, 6.0 Hz), 7.05 (d, 1H, J = 7.3 Hz), 1.61 (s, 15H, C_5Me_5). ^{13}C NMR: δ 178.71 (d, J = 86.8 Hz, Rh−C), 165.38, 151.30 (HC=N), 143.72, 137.08, 136.88, 130.42, 123.46, 122.74, 121.98, 119.05, 95.95 (d, J = 25.2 Hz, C_5Me_5), 9.19 (s, C_5Me_5).

Preparation of 2′b. The reaction was carried out as for **2a**, using $[Cp^*IrCl_2]_2$ (50.0 mg, 0.063 mmol), NaOAc (32.0 mg, 0.39 mmol), and 2-phenylpyridine (21.8 mg, 0.14 mmol) in 20 mL of CH_2Cl_2 at RT overnight. Cyclometalated compound **2′b** was isolated as a yellow-orange solid (61.8 mg, 95%). Anal. Calcd for $C_{21}H_{23}ClNIr$: C, 48.78; H, 4.48; N, 2.71. Found: C, 48.47; H, 4.51; N, 2.74. ^{1}H NMR: δ 8.70 (d, 1H, J = 1.5 Hz, HC═N), 7.82 (d, 2H, J = 7.7 Hz), 7.67 (dd, 1H, J = 7.8, 7.0 Hz), 7.65 (ddd, 1H, J = 7.8, 7.7, 1.2 Hz), 7.20 (ddd, 1H, J = 7.4, 7.3, 1.2 Hz), 7.06 (m, 2H), 1.68 (s, 15H, C_5Me_5). ^{13}C NMR: δ 167.32 (Ir−C), 163.34, 151.31 (HC═N), 144.09, 136.99, 135.80, 131.00, 123.84, 122.30, 122.04, 118.89, 88.51 (C_5Me_5), 8.93 (C_5Me_5).

Preparation of 2c. The reaction was carried out as for **2a**, using $[Cp^*RhCl_2]_2$ (50.0 mg, 0.063 mmol), NaOAc (40.0 mg, 0.49 mmol), and benzo[*h*]quinoline (33.0 mg, 0.18 mmol) in 20 mL of CH_2Cl_2 at RT overnight. Cyclometalated compound **2c** was isolated as a yellow-orange solid (68.6 mg, 94%). Anal. Calcd for $C_{23}H_{23}ClNRh$: C, 61.14; H, 5.13; N, 3.10. Found: C, 60.73; H, 4.99; N, 2.78. ^{1}H NMR: δ 9.00 (d, 1H, J = 4.5 Hz, HC═N), 8.17 (dd, 1H, J = 8.0, 1.1 Hz), 8.06 (d, 1H, J = 7.0 Hz), 7.78 (d, 1H, J = 8.7 Hz), 7.64 (dd, 1H, J = 7.6, 7.3 Hz), 7.56 (d, 1H, J = 7.5 Hz), 7.55 (d, 1H, J = 8.7 Hz), 7.49 (dd, 1H, J = 8.0, 5.2 Hz), 1.68 (s, 15H, C_5Me_5). ^{13}C NMR: δ 175.97 (d, J = 134.0 Hz, Rh−C), 155.16, 149.11 (HC═N), 140.55, 135.53, 133.75, 133.55, 129.97, 129.60, 127.12, 122.99, 121.37, 120.92, 95.75 (d, J = 25.2 Hz, C_5Me_5), 9.35 (s, C_5Me_5).

Preparation of 2′c. The reaction was carried out as for **2a**, using $[Cp^*IrCl_2]_2$ (50.0 mg, 0.063 mmol), NaOAc (32.0 mg, 0.39 mmol), and benzo[*h*]quinoline (24.8 mg, 0.14 mmol) in 20 mL of CH_2Cl_2 at RT overnight. Cyclometalated compound **2′c** was isolated as a yellow-orange solid (65.2 mg, 96%). Anal. Calcd for $C_{23}H_{23}ClNIr$: C, 51.06; H, 4.28; N, 2.59. Found: C, 50.44; H, 4.46; N, 2.54. ^{1}H NMR: δ 8.95 (dd, 1H, J = 5.3, 1.1 Hz, HC═N), 8.13 (dd, 1H, J = 8.0, 1.1 Hz), 8.06 (dd, 1H, J = 7.1, 0.6 Hz), 7.81 (d, 1H, J = 8.4 Hz), 7.62 (dd, 1H, J = 7.7, 7.2 Hz), 7.55 (d, 2H, J = 8.6 Hz), 7.46 (dd, 1H, J = 8.0, 5.4 Hz), 1.74 (s, 15H, C_5Me_5). ^{13}C NMR: δ 160.86 (Ir−C), 157.37, 149.00 (HC═N), 141.93, 135.75, 134.00, 132.49, 130.64, 130.01, 127.04, 123.07, 121.50, 120.10, 88.34 (C_5Me_5), 9.10 (C_5Me_5).

Preparation of 3a. A mixture of **2a** (50.0 mg, 0.13 mmol) and DMAD (20.0 μL, 0.16 mmol) in 20 mL of methanol was stirred at RT for 3 h. The solution was evaporated to dryness, and the yellow solid was washed with hexane to remove excess DMAD. **3a** was isolated as a yellow-orange solid (63.9 mg, 94%). Anal. Calcd for $C_{24}H_{29}ClNO_4Rh$: C, 54.00; H, 5.47; N, 2.62. Found: C, 53.74; H, 5.43; N 2.47. ^{1}H NMR: δ 8.60 (s, 1H, HC═N), 7.45 (dd, 1H, J = 7.6, 7.4 Hz, C_6H_4), 7.35 (dd, 1H, J = 7.6, 7.4 Hz, C_6H_4), 7.29 (d, 1H, J = 7.6 Hz, C_6H_4), 7.28 (d, 1H, J = 7.6 Hz, C_6H_4), 3.83 (s, 3H, NMe), 3.71 (s, 3H, COOMe), 3.66 (s, 3H, COOMe), 1.31 (s, 15H, C_5Me_5). ^{13}C NMR: δ 176.01 (d, J = 131.2 Hz, Rh−C), 174.27 (HC═N), 170.47, 167.55 (C═O), 138.62 (C−COOMe), 133.06, 132.57, 132.46, 132.04, 130.55, 126.74 (6 C's of C_6H_4), 96.60 (d, J = 26.0 Hz, C_5Me_5), 55.97 (MeOOC), 51.91 (MeOOC), 50.40 (NMe), 8.52 (s, C_5Me_5). IR: ν(C═N), 1578 cm^{-1}.

Preparation of 3′a. The reaction was carried out as for **3a**, using **2′a** (50.0 mg, 0.10 mmol) and DMAD (18.0 μL, 0.15 mmol) in 20 mL of methanol at RT for 3 h. **3′a** was isolated as a yellow solid (60.9 mg, 94%). Anal. Calcd for $C_{24}H_{29}ClNO_4Ir$: C, 46.24; H, 4.69; N, 2.25. Found: C, 46.09; H, 4.59; N 2.32. ^{1}H NMR: δ 8.65 (d, 1H, J = 1.1 Hz, HC═N), 7.44 (ddd, 1H, J = 7.6, 1.2 Hz, C_6H_4), 7.33 (ddd, 1H, J = 7.6, 7.4, 1.0 Hz, C_6H_4), 7.23 (d, 1H, J = 7.4 Hz, C_6H_4), 7.21 (d, 1H, J = 7.3 Hz, C_6H_4), 3.89 (s, 3H, NMe), 3.73 (s, 3H, COOMe), 3.66 (s, 3H, COOMe), 1.34 (s, 15H, C_5Me_5). ^{13}C NMR: δ 176.16 (Ir−C), 170.59 (HC═N), 169.09, 163.03 (C═O), 134.30 (C−COOMe), 139.81, 133.00, 132.57, 131.95, 130.61, 126.59 (6 C's of C_6H_4), 88.98 (C_5Me_5), 56.63 (MeOOC), 51.82 (MeOOC), 50.18 (NMe), 8.24 (C_5Me_5). IR: ν(C═N), 1575 cm^{-1}.

Preparation of 3b. The reaction was carried out as for **3a**, using **2b** (50.0 mg, 0.12 mmol) and DMAD (20.0 μL, 0.16 mmol) in 20 mL of methanol at RT for 3 h. The solution was evaporated to dryness, and the yellow solid was washed with hexane to remove excess DMAD. **3b** was isolated as a yellow-orange solid (63.9 mg, 96%). Anal. Calcd for $C_{27}H_{29}ClNO_4Rh$: C, 56.91; H, 5.13; N, 2.46. Found: C, 55.71; H, 5.33; N 2.21. ^{1}H NMR: δ 9.50 (d, 1H, J = 5.1 Hz, HC═N), 7.78 (dd, 1H, J = 7.7, 1.5 Hz), 7.50 (d, 1H, J = 7.3 Hz), 7.45 (ddd, 1H, J = 7.7, 7.3, 1.2 Hz), 7.34 (d, 1H, J = 7.6 Hz), 7.33 (d, 1H), 7.24 (m, 2H), 3.69 (s, 3H, COOMe), 3.66 (s, 3H, COOMe), 1.29 (s, 15H, C_5Me_5). ^{13}C NMR: δ 177.16 (d, J = 140.0 Hz, Rh−C), 174.60, 167.16 (C═O), 162.85, 154.74 (HC═N), 139.34, 138.06, 137.99, 133.61, 132.98, 131.53, 128.79, 127.34, 126.70, 123.45, 96.51 (d, J = 26.4 Hz, C_5Me_5), 51.71 (MeOOC), 50.20 (MeOOC), 8.51 (s, C_5Me_5).

Preparation of 3′b. The reaction was carried out as for **3a**, using **2′b** (50.0 mg, 0.097 mmol) and DMAD (18.0 μL, 0.15 mmol) in 20 mL of methanol at RT for 3 h. **3′b** was isolated as a yellow solid (63.7 mg, 98%). Anal. Calcd for $C_{27}H_{29}ClNO_4Ir$: C, 49.20; H, 4.43; N, 2.12. Found: C, 49.11; H, 4.52; N 2.03. ^{1}H NMR: δ 9.40 (dd, 1H, J = 5.9, 1.0 Hz, HC═N), 7.75 (ddd, 1H, J = 8.0, 7.8, 1.7 Hz), 7.49 (dd, 1H, J = 7.9, 1.3 Hz), 7.42 (dd, 1H, J = 7.9, 1.3 Hz), 7.30 (dd, 1H, J = 7.9, 1.3 Hz), 7.27 (dd, 1H), 7.17 (m, 2H), 3.67 (s, 3H, COOMe), 3.64 (s, 3H, COOMe), 1.27 (s, 15H, C_5Me_5). ^{13}C NMR: δ 176.26 (Ir−C), 168.74, 163.91 (C═O), 163.41, 155.13 (HC═N), 140.80, 138.43, 138.23, 134.28 (C−COOMe), 133.51, 131.48, 128.76, 127.44, 126.38, 124.01, 88.84 (C_5Me_5), 51.59 (MeOOC), 49.95 (MeOOC), 8.20 (C_5Me_5).

Preparation of 3c. The reaction was carried out as for **3a**, using **2c** (50.0 mg, 0.11 mmol) and DMAD (20.0 μL, 0.16 mmol) in 20 mL of methanol at RT for 3 h. **3c** was isolated as an orange solid (65.5 mg, 99%). Anal. Calcd for $C_{29}H_{29}ClNO_4Rh$: C, 58.65; H, 4.92; N, 2.36. Found: C, 58.33; H, 4.93; N 2.27. ^{1}H NMR: δ 10.24 (dd, 1H, J = 5.4, 1.5 Hz, HC═N), 8.20 (dd, 1H, J = 7.8, 1.6 Hz), 7.88 (dd, 1H, J = 7.8, 1.2 Hz), 7.82 (d, 1H, J = 8.6 Hz), 7.73 (dd, 1H, J = 7.7, 7.5 Hz), 7.62 (d, 1H, J = 8.6 Hz), 7.57(dd, 1H, J = 7.8, 1.4 Hz), 7.53 (dd, 1H, J = 7.8, 5.4 Hz), 3.81 (s, 3H, COOMe), 3.55 (s, 3H, COOMe), 0.99 (s, 15H, C_5Me_5). ^{13}C NMR: δ 174.41 (C═O), 173.08 (d, J = 131.6 Hz, Rh−C), 167.87 (C═O), 155.74 (HC═N), 149.14, 137.61, 137.54, 136.71, 134.65 (C−COOMe), 131.54, 129.86, 129.42, 128.26, 127.98, 127.04, 125.66, 122.71, 96.54 (d, J = 26.4 Hz, C_5Me_5), 51.77 (MeOOC), 50.48 (MeOOC), 8.25 (s, C_5Me_5).

Preparation of 3′c. The reaction was carried out as for **3a**, using **2′c** (50.0 mg, 0.092 mmol) and DMAD (18.0 μL, 0.15 mmol) in 20 mL of methanol at RT for 3 h. **3′c** was isolated as a yellow solid (60.6 mg, 96%). Anal. Calcd for $C_{29}H_{29}ClNO_4Ir$: C, 50.99; H, 4.28; N, 2.05. Found: C, 51.67; H, 4.52; N 2.00. ^{1}H NMR: δ 10.24 (dd, 1H, J = 5.5, 1.5 Hz, HC═N), 8.17 (dd, 1H, J = 7.8, 1.5 Hz), 7.83 (dd, 1H, J = 7.5, 1.2 Hz), 7.81 (dd, 1H, J = 8.4, 1.2 Hz), 7.72 (dd, 1H, J = 7.6, 7.5 Hz), 7.59 (d, 1H, J = 8.6 Hz), 7.51 (dd, 1H, J = 7.5, 1.2 Hz), 7.48 (dd, 1H, J = 7.8, 5.5 Hz), 3.81 (s, 3H, COOMe), 3.54 (s, 3H, COOMe), 1.00 (s, 15H, C_5Me_5). ^{13}C NMR: δ 176.20 (Ir−C), 169.47, 161.10 (C═O), 156.11 (HC═N), 149.88, 144.66 (C−COOMe), 139.31, 137.44, 136.81, 131.54, 129.81, 129.49, 128.37, 127.57, 127.52, 125.28, 122.95, 88.79 (C_5Me_5), 51.58 (MeOOC), 50.19 (MeOOC), 8.20 (C_5Me_5).

Preparation of 4a. A brown suspension of **3a** (53.4 mg, 0.10 mmol) and anhydrous copper(II) chloride (43.0 mg, 0.32 mmol) in 20 mL of dichloromethane was stirred at RT for 3 h. The mixture was filtered through Celite and evaporated to dryness. **4a** and **1** were produced in a ratio of ~2:1 (NMR) as a red-orange solid (68.9 mg, 92%). ^{1}H NMR for **4a**: δ 10.70 (s, 1H, HC═N), 8.95 (d, 1H, J = 8.1 Hz, C_6H_4), 8.47 (d, 1H, J = 8.6 Hz, C_6H_4), 8.35 (dd, 1H, J = 8.2, 7.6 Hz, C_6H_4), 8.20 (dd, 1H, J = 7.3, 7.2 Hz, C_6H_4), 4.75 (s, 3H, NMe), 4.13 (s, 3H, OMe), 4.11 (s, 3H, OMe). ^{13}C NMR (CD_2Cl_2) for **4a**: δ 162.97 (C═O), 162.22 (HC═N), 160.81 (C═O), 141.92 140.86, 136.15, 135.93, 134.16, 130.56, 129.95, 126.70, 58.08 (NMe), 55.57 (MeOOC), 54.84 (MeOOC).

Preparation of 5a. To the reaction mixture for **4a** after 3 h at RT was added 2 equiv of $AgBF_4$ (39.0 mg, 0.20 mmol), and the reaction mixture was stirred for additional 3 h. The mixture was filtered through Celite and evaporated to dryness. **5a** and {[RhCp*]$_2$(μ-Cl)$_3$}[BF$_4$][39] were produced in a ratio of ~2:1 (64.1 mg, 94%). **5a** is a colorless solid after crystallization from CH_2Cl_2/pentane. ^{1}H NMR for **5a**: δ 10.11(s, 1H, HC═N), 8.66 (d, 1H, J = 8.3 Hz, C_6H_4), 8.38 (d, 1H, J = 8.5 Hz, C_6H_4), 8.28 (dd, 1H, J = 8.2, 7.3 Hz, C_6H_4), 8.07 (dd, 1H, J = 7.7, 7.6 Hz, C_6H_4), 4.60 (s, 3H, NMe), 4.08 (s, 3H, OMe), 4.07 (s, 3H, OMe). ^{13}C NMR (CD_2Cl_2) for **5a**: δ 163.01 (C═O), 160.36 (C═O), 155.55 (HC═N), 139.48, 135.58, 133.74, 133.17, 132.50, 129.68, 127.96, 125.72, 54.90 (MeOOC), 54.29 (MeOOC), 48.24(NMe).

Preparation of 4b. The reaction was carried out as for **4a**, using **3b** (57.0 mg, 0.10 mmol) and anhydrous copper(II) chloride (43.0 mg, 0.32 mmol) in 20 mL of CH_2Cl_2 at RT for 3 h. **4b** and **1** were produced in a ratio of ~2:1 as a red-orange solid (68.3 mg, 88%). ^{1}H NMR for **4b**: δ 9.36 (d, 1H, J = 7.1 Hz, HC═N), 8.97 (dd, 1H), 8.90 (d, 1H), 8.42 (d, 1H, J = 7.5 Hz), 8.31 (br, 1H), 8.16 (d, 1H, J = 7.7 Hz), 7.91 (dd, 1H, J = 7.5 Hz), 7.85 (dd, 1H, J = 7.7, 7.5 Hz), 4.01 (s, 3H, OMe), 3.97 (s, 3H, OMe). ^{13}C NMR for **4b**: δ 163.66 (C═O), 161.96 (C═O), 154.76 (HC═N), 152.74, 145.13, 135.25, 134.58, 134.18, 131.59, 128.92, 128.61, 128.54, 124.20, 85.04, 84.18, 59.39 (MeOOC), 57.55 (MeOOC).

Preparation of 5b. The reaction was carried out as for **5a**, using 2 equiv of $AgBF_4$ (39.0 mg, 0.20 mmol). **5b** and {[RhCp*]$_2$(μ-Cl)$_3$}[BF$_4$] were produced in a ratio of ~2:1 (66.0 mg, 92%). ^{1}H NMR for **5b**: δ 9.28 (d, 1H, J = 6.5 Hz, HC═N), 8.84 (dd, 1H, J = 7.6, 7.3 Hz), 8.74 (d, 1H, J = 7.9 Hz), 8.33 (d, 1H, J = 7.3 Hz), 8.19 (d, 1H, J = 7.2 Hz), 8.18 (dd, 1H, J = 7.2, 5.8 Hz), 7.88 (dd, 1H, J = 7.3, 6.8 Hz), 7.83 (ddd, 1H, J = 7.8, 7.4, 1.0 Hz), 4.00 (s, 3H, OMe), 3.99 (s, 3H, OMe). ^{13}C NMR for **5b**: δ 163.55 (C═O), 161.78 (C═O), 153.94 (HC═N), 149.76, 143.01, 134.98, 133.80, 133.06, 131.27, 127.90, 126.57, 124.43, 121.65, 84.86, 83.31, 56.50 (MeOOC), 55.70 (MeOOC).

Preparation of 4c. The reaction was carried out as for **4a**, using **3c** (59.4 mg, 0.10 mmol) and anhydrous copper(II) chloride (43.0 mg, 0.32 mmol) in 20 mL of CH_2Cl_2 at RT for 3 h. **4c** and **1** were produced in a ratio of ~2:1 as a red-orange solid (72.2 mg, 90%). ^{1}H NMR for **4c**: δ 10.21 (d, 1H, J = 6.7 Hz, HC═N), 9.41 (d, 1H, J = 7.9 Hz), 8.82 (dd, 1H, J = 7.8, 6.8 Hz), 8.73 (d, 1H, J = 7.7 Hz), 8.65 (d, 1H, J = 7.7 Hz), 8.56 (d, 1H, J = 8.6 Hz), 8.55 (dd, 1H, J = 7.9, 7.8 Hz), 8.49 (d, 1H, J = 8.6 Hz), 4.30 (s, 3H, OMe), 4.21 (s, 3H, OMe). ^{13}C NMR (CD_2Cl_2) for **4c**: δ 163.53 (C═O), 161.07 (C═O), 146.10 (HC═N), 142.64, 137.37, 133.54, 133.38, 132.16, 131.72, 131.14, 130.40, 129.57, 127.27, 126.97, 126.30, 124.54, 119.29, 55.72 (MeOOC), 54.48 (MeOOC).

Preparation of 5c. The reaction was carried out as for **5a**, using 2 equiv of $AgBF_4$ (39.0 mg, 0.20 mmol). **5c** and {[RhCp*]$_2$(μ-Cl)$_3$}[BF$_4$] were produced in a ratio of ~2:1 (68.2 mg, 92%). **5c** is a colorless solid after recrystallization from CH_2Cl_2/pentane. ^{1}H NMR for **5c**: δ 10.20 (d, 1H, J = 6.6 Hz, HC═N), 9.33 (d, 1H, J = 7.9 Hz), 8.82 (dd, 1H, J = 7.6, 7.5 Hz), 8.69 (d, 1H, J = 7.7 Hz), 8.63 (d, 1H, J = 7.4 Hz), 8.53 (dd, 1H, J = 7.8 Hz), 8.51 (d, 1H, J = 9.0 Hz), 8.43 (d, 1H, J = 9.0 Hz), 4.30 (s, 3H, OMe), 4.19 (s, 3H, OMe). ^{13}C NMR (CD_2Cl_2) for **5c**: δ 163.54 (C═O), 160.97 (C═O), 142.66 (HC═N), 137.72, 133.54, 133.38, 132.01, 131.56, 130.79, 129.52, 127.49, 126.20, 124.69, 124.08, 124.00, 121.07, 119.20, 55.26 (MeOOC), 54.38 (MeOOC).

X-ray Crystal Structure Determinations. Data were collected on a Bruker SMART APEX II CCD Platform diffractometer at 100.0(1) K. The data collection was carried out using Mo Kα radiation. The intensity data were corrected for absorption. The structure was solved using SIR 97 and refined using SHELXL-97. All of the non-hydrogen atoms were refined with anistropic displacement parameters. All of the hydrogen atoms were found from the difference Fourier map and refined independently from the carbon atoms with individual isotropic displacement parameters. Selected bond lengths and angles are included in Tables S-1 and S-2 in the Supporting Information.

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Supporting Information Available: Tables of selected bond lengths and angles and structural data for **2a**−**c**, **2′a-c**, **3a**−**c**, **3′a**−**c**, **5a**, and **5c**; thermal ellipsoid drawings of **2′a**−**c** and **3′a**−**c**; and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org. The structures are available in the Cambridge Crystallographic Database as CCDC 683543–683556.

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