

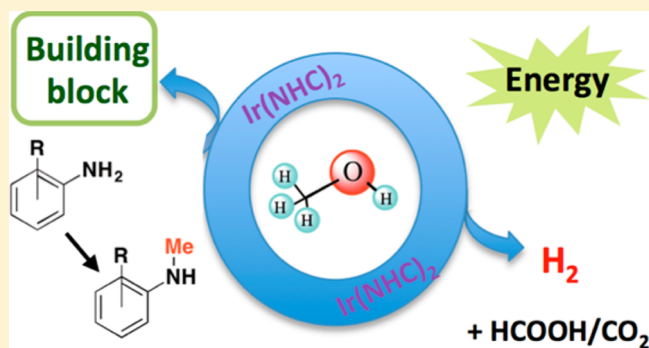
Methanol Dehydrogenation by Iridium N-Heterocyclic Carbene Complexes

Jesús Campos,[†] Liam S. Sharninghausen,[†] Michael G. Manas, and Robert H. Crabtree*

Chemistry Department, Yale University, 225 Prospect Street, New Haven, Connecticut 06520, United States

S Supporting Information

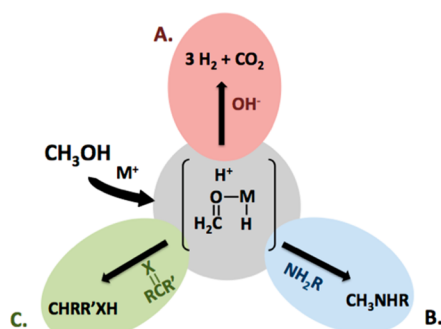
ABSTRACT: A series of homogeneous iridium bis(N-heterocyclic carbene) catalysts are active for three transformations involving dehydrogenative methanol activation: acceptorless dehydrogenation, transfer hydrogenation, and amine monoalkylation. The acceptorless dehydrogenation reaction requires base, yielding formate and carbonate, as well as 2–3 equivalents of H₂. Of the few homogeneous systems known for this reaction, our catalysts tolerate air and employ simple ligands. Transfer hydrogenation of ketones and imines from methanol is also possible. Finally, N-monomethylation of anilines occurs through a “borrowing hydrogen” reaction. Notably, this reaction is highly selective for the monomethylated product.



INTRODUCTION

Methanol, produced from natural gas, coal, or biomass,¹ is an abundant and cheap resource with many applications.^{2–4} It has even been suggested as a future energy carrier and synthetic feedstock in the “methanol economy”.⁵ Methanol can be activated by catalyzed conversion to the more reactive H₂C=O, with formation of metal hydrides or the release of H₂ (Scheme 1).^{6,7} The carbonyl group can then undergo

Scheme 1. Methanol Activation by Initial Dehydrogenation



nucleophilic attack with or without metal mediation. With OH[−] as a nucleophile, formate and a second molecule of H₂ can be produced, and {formate + H⁺} can be subsequently dehydrogenated to CO₂ (path A in Scheme 1).⁸ If the nucleophile is an amine, an imine intermediate can lead to methylation of the amine in a “borrowing hydrogen” (BH) reaction (path B in Scheme 1).^{6,7,9,10} Alternatively, the hydrogen borrowed from methanol could be transferred to a second molecule containing a C=X (X = C, N, O) bond by

hydrogen transfer (path C in Scheme 1).^{6,11} However, no single catalyst has so far been proven to be capable of accomplishing all of these reactions under relatively mild conditions.^{6,8} In this paper, we apply our new family of homogeneous iridium bis(N-heterocyclic carbene) (bis-NHC) catalysts to these reactions.

Methanol can serve as an excellent storage reservoir for hydrogen,^{1,8,12} which can, in turn, generate electricity via a fuel cell.¹³ Liquid organic hydrogen carriers such as methanol have garnered much recent attention,^{1,14,15} in part because such fuels would be compatible with the current gasoline-based infrastructure.¹⁶ Methanol is especially attractive because of its low cost, high energy density (up to 3 H₂ per MeOH, or 12.6 wt % H), and the fact that no C–C bond cleavage is required for hydrogen release.¹ A major current challenge lies in developing catalysts that completely and selectively release all H₂ from methanol under mild conditions.^{1,8}

Traditional heterogeneous methanol dehydrogenation catalysts convert methanol to CO₂ and H₂ but often require high temperature (>200 °C) and pressure, produce unwanted CO (a poison for most fuel-cell catalysts), and can be pyrophoric.^{1,17} Early homogeneous catalysts based on ruthenium did produce H₂ without CO contamination but suffered from low activity [turnover frequency (TOF) < 4 h^{−1}] and limited reactivity, releasing only a single H₂ per MeOH.¹⁸

Some new homogeneous acceptorless dehydrogenation catalysts involve ruthenium complexes with cooperative chelating ligands (Figure 1, 1–5).^{19–23} Beller and co-workers

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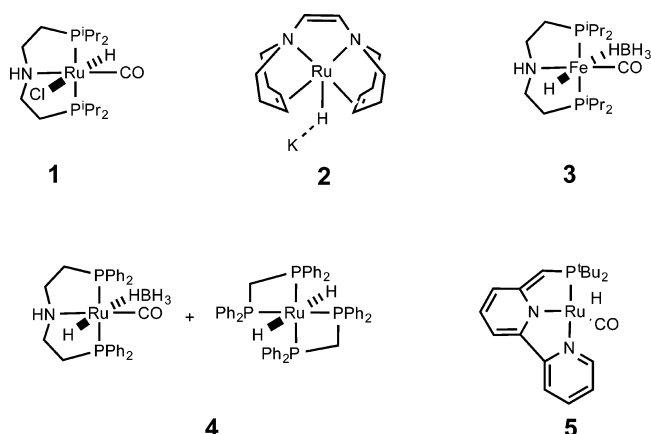


Figure 1. Recent homogeneous catalysts for methanol dehydrogenation.

found that Ru(PNP) pincer, **1**, has high activity (TOF = 4780 h⁻¹) and selectivity for releasing 3 H₂ per (MeOH + H₂O) even at modestly elevated temperature (91 °C), although it still requires strongly basic conditions.¹⁹ Grützmacher's less active ruthenium catalyst, **2**, functions at neutral pH.²⁰ The proposed reaction sequence (Scheme 1, path A) goes via CH₂O and HCOOH.^{8,19,20} Three additional systems (**3–5**) were subsequently described.^{21–23}

In the related transfer hydrogenation reaction (TH, Scheme 1, path C), the catalyst abstracts H₂ from an alcohol (typically as {H⁺ + H⁻}) and directly transfers it to reduce a C=X (X = C, O, N) multiple bond,^{6,11,24} thus avoiding free H₂. Despite the abundance and low cost of methanol, there are few examples of its use in TH. These include the reduction of C–C multiple bonds in α,β -unsaturated carbonyls, alkenes, and alkynes with iridium and nickel complexes.²⁵ Smith and Maitlis performed TH from methanol to aliphatic and aromatic ketones with RuCl₂(PPh₃)₃ at 150 °C, forming the corresponding alcohols in moderate yields.²⁶

In a future methanol economy, MeOH would also serve as a C1 building block for chemical synthesis. Dehydrogenative activation of methanol in the presence of an amine can result in N-methylation to prepare desirable secondary amines (Scheme 1, path B)^{10a–f,27,28} without the need for environmentally harmful alkylating agents. These reactions are generally catalyzed by ruthenium and iridium compounds.^{10a–f,28} Methanol is a challenging substrate because of the difficulty of the initial dehydrogenation step, and currently there are only a few catalysts that can use it to selectively monomethylate anilines, by either BH^{28,29} or otherwise.³⁰

Previously, we reported a series of iridium bis-NHC compounds, which are very active catalysts for TH of ketones³¹ as well as the acceptorless dehydrogenation of glycerol³² and sugar alcohols,³³ to form lactic acid. Here, we show that these complexes catalyze the dehydrogenative activation of methanol and can mediate acceptorless dehydrogenation, TH, and aniline monomethylation reactions.

RESULTS AND DISCUSSION

Methanol Dehydrogenation and H₂ Production. We first screened a library of iridium precatalysts for methanol dehydrogenation using a modified version of our reported conditions for glycerol dehydrogenation (0.004 mol % iridium, neat MeOH, 6.7 M KOH, reflux; Table 1). Methanol dehydrogenation was quantified by the integration of formate

Table 1. Catalyst Screening for Acceptorless Methanol Dehydrogenation^a

entry	compound	TON (15 h) ^b
1	1a : L ¹ = L ² = IMe, n = 1	880
2	1b : L ¹ = pyridine, X ² = Cl, n = 0	128
3	1c : L ¹ = L ² = IBu, n = 1	388
4	1d : L ¹ = IMe, X ² = Cl, n = 0	21
5	1e : L ¹ = L ² = pyridine, n = 1	104
6	1f : L ¹ = IMe, L ² = pyridine, n = 1	38
7	2a : L ¹ = L ² = pyridine, m = 0, n = 1	125
8	2b : L ¹ = IMe, L ² = pyridine, m = 1, n = 1	24
9	2c : L ¹ = L ² = IMe, m = 1, n = 1	88
10	3a : R = Me	1430
11	3b : R = Et	377
12	3c : R = n-Bu	347
13	4a : R = Me	1680
14	4b : R = Et	481
15	4c : R = n-Bu	322
16	[Cp*IrCl ₂] ₂	124
17	IrCl ₃	47
18	IrO ₂	11
19	Ir ⁰ nanoparticles ^c	78
20	Ir ⁰ nanoparticles + Hg ⁰	23
21	none	15

^aReactions were run with 3 μ mol [Ir] (0.004 mol %) and 1.34 g of KOH (15% H₂O by mass, 20 mmol) in 3 mL of degassed MeOH at reflux under a N₂ atmosphere for 15 h. The reflux temperature of the 6.7 M KOH solution was measured to be 91 °C. ^bTON for formate production calculated by ¹H NMR spectroscopy using sodium acetate as an internal standard (subsequent dehydrogenation to CO₂ is not considered in this calculation). ^c2–3 nm.³⁵

and carbonate signals obtained by ¹H and ¹³C{¹H} NMR spectroscopy (see the Supporting Information, SI). The results were confirmed by gas buret measurements (>94% agreement; see Figure 2 and the SI for details). Unlike many prior systems, our catalysts predominantly yield formate rather than CO₂, although they are also active for the conversion of sodium formate to CO₂ in water [CO₂ trapped as carbonate, 172 turnover number (TON) over 15 h with **4a**; see the SI for details]. Because carbonate was a minor product (<5% in representative cases, the catalyst performance in our initial screenings was assessed based on formate production only. In analogy with our previous studies, precatalysts bearing two NHC ligands gave the highest activity of those tested, and among the bis-NHC complexes, those stabilized by CO ligands (**4a–4c**) were generally superior to others containing a Cp* (1a and 1c) or cyclooctadiene ligand (**3a–3c**; Table 1, entries 1, 3, and 10–15). In addition, smaller wingtips on the NHC ligands improved the performance, with the bis-IR complexes (IR = 1,3-dialkylimidazol-2-ylidene) giving higher activity in the order R = n-Bu < Et < Me. The same trend was previously seen in our sugar alcohol dehydrogenation studies,³³ where we

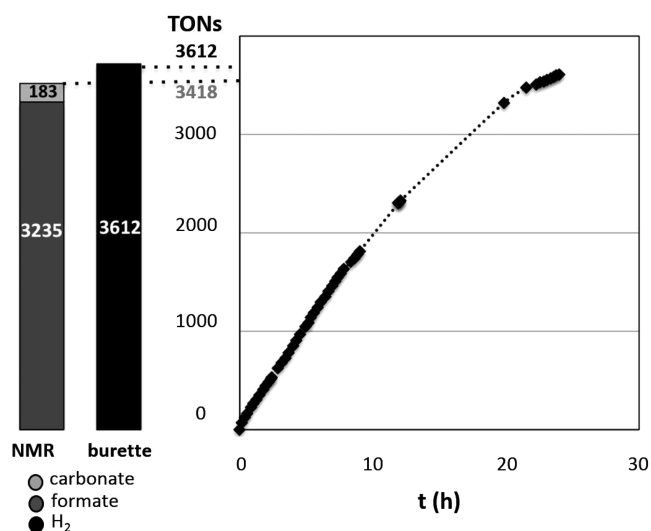


Figure 2. Reaction profile for methanol dehydrogenation with complex **4a**.

postulated a catalyst deactivation pathway based on a Hofmann elimination reaction that is only applicable to R = Et and *n*-Bu. Under our experimental conditions, compound **4a** gave the best activity, with 1680 turnovers over 15 h. As discussed in a prior work,^{31b} the considerably higher activity of **1e** (880 TON) versus other Cp*-based precatalysts (21–128 TON) and the improved performance of the related cyclooctadiene (**3a**) and CO (**4a**) analogues is consistent with the idea that Cp* is released during catalysis.³⁴ Cp* loss has been shown for compound **1a** in TH reactions,^{31b} and thus **1a**, **3a**, and **4a** may share one or several common catalytically active species. Poisoning studies are consistent with the homogeneous character of the active species (see the SI).

We next focused on optimization of the reaction conditions with precatalysts **1a** and **4a** (Table 2). The reaction proceeds in methanol/water solutions in place of neat methanol but at decreased rates (entries 2 and 3). The lower rates in these cases are partly a result of the lower methanol concentration and lower reflux temperature. With dry methanol as the solvent, the performance increased considerably (entries 1 and 10). Among the bases tested, NaOH and LiOH·H₂O were significantly less effective than KOH, likely because of their lower solubility in methanol (entries 4 and 5). Additionally, the reactions were highly dependent on both the KOH concentration and temperature (entries 6–8), with high temperature and base concentration required for effective catalysis. Interestingly, compound **4a** gave similar activity both in air and under an inert atmosphere (entries 9 and 10). TONs as high as 8000 were achieved by lowering the catalyst loading to 1 μmol (0.001 mol %) and extending the reaction time to 40 h (entry 12). Our previous work on glycerol dehydrogenation showed that iridium bis-NHC precatalysts form dimer and cluster deactivation products in a way that is highly dependent on the precatalyst concentration.^{32,36} CO impurities in the product H₂ gas were found to be <8 ppm, similar to other homogeneous methanol dehydrogenation catalysts¹⁹ (see the SI).

A 24 h reaction profile was generated for compound **4a** by following H₂ evolution with a gas buret (Figure 2). Gas generation is nearly linear for the first 20 h under our experimental conditions. While the TOF of ~200 h⁻¹ falls short

Table 2. Screening of the Conditions for Acceptorless Methanol Dehydrogenation^a

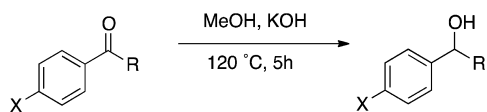
entry	catalyst	solvent	base	base concn (M)	temp (°C)	TON (15 h) ^g
1	1a	MeOH (dry) ^b	KOH	6.7	91 ^c	1255
2	1a	9:1 MeOH/H ₂ O	KOH	6.7	85 ^c	374
3	1a	1:1 MeOH/H ₂ O	KOH	6.7	83 ^c	241
4	1a	MeOH	NaOH	6.7	83 ^c	115
5	1a	MeOH	LiOH·H ₂ O	6.7	69 ^c	26
6	1a	MeOH	KOH	6.7	65	42
7	1a	MeOH	KOH	3.4	65	13
8	1a	MeOH	KOH	0.8	65	7
9	4a	MeOH (dry) ^b	KOH	6.7	91 ^c	1950
10 ^d	4a	MeOH (dry) ^b	KOH	6.7	91 ^c	1930
11	4a^e	MeOH (dry) ^b	KOH	6.7	91 ^c	2900
12 ^f	4a^e	MeOH (dry) ^b	KOH	6.7	91 ^c	8000

^aReactions were run with 3 μmol of catalyst (0.004 mol %) and KOH (15% H₂O by mass, 20 mmol) in 3 mL of degassed MeOH (3 mL) under a N₂ atmosphere for 15 h. ^bDirectly purchased in a 100 mL Sure/Seal bottle and stored over 4 Å molecular sieves. ^cThe reaction was run under reflux. ^dThe reaction was prepared in air and run connected to an oil bubbler. ^eThe reaction was run with 1 μmol of catalyst. ^fThe reaction was run for 40 h. ^gTON for formate production calculated by ¹H NMR spectroscopy using sodium acetate as an internal standard (subsequent dehydrogenation to CO₂ is not considered in this calculation).

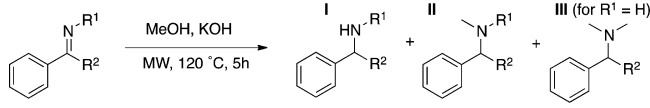
of those of some of the recently reported systems,^{19,21–23} our catalysts are notable for working in the presence of air and for using simpler and less expensive ligands than in previously described methanol dehydrogenation catalysts.⁸ In addition, they are the first single-component iridium catalysts to achieve this transformation.

The bar graph of Figure 2 shows a comparison of TONs calculated from formate (dark gray) and carbonate (light gray) in a reaction vessel by ¹H and ¹³C{¹H} NMR spectroscopy with TONs calculated from gas evolution measured in a gas buret (black). The reaction was run with 3 μmmol of **4a** (0.004 mol %) and 1.34 g of KOH (15% H₂O by mass, 20.0 mmol) in 3 mL of dry, degassed MeOH at reflux in a gas buret (see the SI for details).

Transfer Hydrogenation. We next explored the related TH reaction using MeOH as a source of reducing equivalents. While iridium TH catalysts are common, few effective systems use MeOH as the H₂ donor.^{25,26} Several aromatic ketones and primary and secondary imines were screened for TH using 5 mol % **4a** and 1–5 equiv of KOH versus substrate (Table 3). It was found that microwave (MW) irradiation greatly improved yields compared to conventional heating at the same temperature (entry 1), so all subsequent experiments were carried out under MW irradiation. Benzophenones (entries 1–3) gave generally good yields of the reduced benzhydrols, and the reactions were tolerant of a variety of substitutions at the 4 position of the aromatic ring. As expected, the electron-withdrawing –CF₃ group favored reduction of the ketone, whereas the electron-donating –OMe group disfavored the

Table 3. Transfer Hydrogenation of Ketones and Imines with 4a and Methanol under Microwave Irradiation


entry	R	X	yield (%) ^a
1	Ph	H	70 ^b > 95 ^c 70 ^{c,e} 15 ^{b,d}
2	Ph	OMe	49, ^b 61 ^c
3	Ph	CF ₃	>95 ^b
4	Me	H	30 ^b
5	Me	OMe	28 ^b
6	Me	CF ₃	70 ^b



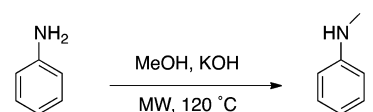
entry	R ¹	R ²	yield I ^a	yield II ^a	yield III ^a
7	Ph	H	>95 ^b	<1 ^b	
8	Bn	H	15 ^b	70 ^b	
9	Me	H	<1 ^b	63 ^b	
10	<i>n</i> -Bu	H	<1 ^b	50 ^b	
11	H	Ph	20 ^b	34 ^b	20 ^b

Experiments were run under MW irradiation (120 °C, 5 h) with **4a** (6.5 μmol, 5 mol %), substrate (0.13 mmol), KOH (0.13–0.65 mmol), and dry and degassed MeOH (0.5 mL) in sealed MW tubes. ^aYields determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. ^bThe reaction was run with 0.13 mmol of KOH (1 equiv vs substrate). ^cThe reaction was run with 0.65 mmol of KOH (5 equiv vs substrate). ^dThe reaction was heated at 120 °C in an oil bath instead of MW. ^eIsolated yield.

reaction. In contrast, acetophenones gave generally poorer yields of 1-phenylethanols (entries 4–6) due to competing methylation of the α-CH₃ group (see the SI, Figure S3). This reactivity was recently shown for simple iridium compounds such as [Cp*IrCl₂]₂, which selectively methylate ketones.³⁷ Next, N-heterocycles were explored as substrates. Acridine was selectively reduced to 9,10-dihydroacridine in >95% yield (5 mol % **4a**, 5 equiv of KOH versus substrate, 0.5 mL of MeOH, MW, 120 °C). However, quinoxaline and quinaldine showed no reduction (see the SI). Among the representative imines tested, *N*-benzylideneaniline was cleanly reduced to the corresponding amine (entry 7); however, imines without the *N*-phenyl motif (R¹ ≠ Ph) showed both reduction and N-methylation (entries 8–11). Background KOH-catalyzed TH was below 6% in most representative cases, with a maximum of 14% for TH of benzophenone with 5 equiv of KOH versus substrate (see the SI).

N-Methylation. The N-methylation reaction was further explored for anilines, which are difficult substrates for BH reactions. Bis-Ime complexes **1a**, **3a**, and **4a** selectively converted aniline to *N*-methylaniline with <5% dimethylated side product (Table 4, entries 1–3). As expected, complex **4a** gave superior activity compared to the Cp* (**1a**) and cod (**3a**) complexes. Full conversion (>95%) was achieved using 5 mol % loading of **4a** and 1 equiv of KOH versus substrate under MW heating at 120 °C for 5 h (entry 6), while lowering the loading of the catalyst or base led to decreased yields (entries 7 and 8). MW irradiation significantly improved yields, as was observed for TH reactions (entries 3 and 4).

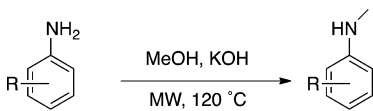
Several substituted anilines were screened under our optimized reaction conditions, and the system was found to

Table 4. Catalyst Screening and Optimization of Reaction Conditions for Aniline Methylation


entry	catalyst	catalyst loading (mol %)	KOH/aniline ratio	time (h)	yield (%) ^b
1	1a	5	1	1	26
2	3a	5	1	1	33
3	4a	5	1	1	40
4 ^a	4a	5	1	1	9
5	4a	5	1	2	72
6	4a	5	1	5	>95, 88 ^c
7	4a	1	1	5	50
8	4a	5	0.33	5	60
9	None		1	5	<5

Experiments were run under MW irradiation (120 °C) with an iridium catalyst (1–5 mol %), aniline (0.13 mmol), KOH (0.043–0.13 mmol), and dry and degassed MeOH (0.5 mL). ^aThe reaction was heated at 120 °C in an oil bath instead of MW. ^bYields were determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. ^cIsolated yield.

be tolerant of a range of functional groups (Table 5). Yields were lower for substrates with ortho substituents (entries 6–8),

Table 5. Microwave-Assisted Monomethylation of Substituted Anilines Catalyzed by 4a


entry	substrate	yield (%) ^a
1	4-methoxyaniline	>95 ^b
2	4-bromoaniline	>95 ^b
3	4-nitroaniline	60 ^b
4	4-(trifluoromethyl)aniline	14 ^b
5	4-aminoaniline	>95 ^b
6	2-aminoaniline	54, ^b 91 ^c
7	2-methylaniline	29, ^b 45 ^c
8	2,6-dimethylaniline	<1 ^c

The experiments were run under MW irradiation (120 °C, 5 h) with **4a** (6.5 μmol, 5 mol %), aniline (0.13 mmol), KOH (0.13–0.65 mmol), and dry and degassed MeOH (0.5 mL). ^aYields determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. ^bReaction run with 0.13 mmol KOH (1 equiv vs substrate). ^cReaction run with 0.65 mmol KOH (5 equiv vs substrate).

as has been observed in other systems.^{28c,29c} Notably, 2-aminoaniline, previously difficult to methylate,^{28c} was converted to the alkylated product in 91% yield using 5 equiv of KOH versus substrate (entry 6). In contrast to the trend seen for TH (Table 3), the presence of electron-withdrawing substituents such as –NO₂ and –CF₃ hindered the reaction (entries 3 and 4), likely because the electron-withdrawing group lowers the nucleophilicity of the amine.

CONCLUSION

We have applied our family of iridium bis-NHC catalysts to three challenging reactions involving the activation of methanol, namely, acceptorless dehydrogenation, TH, and

selective amine N-monoalkylation. MW heating proved highly beneficial in the TH and N-alkylation reactions. The value of our catalysts thus extends well beyond the dehydrogenation of glycerol and other polyols.

EXPERIMENTAL SECTION

General Procedures. Reactions were carried out under a N₂ atmosphere using degassed solvents unless otherwise noted. NMR spectra were recorded using Agilent DD2-400 and -500 or Bruker AMX-500 spectrometers. Reactions under MW irradiation were carried out in a Biotage initiator microwave synthesizer with a Robot Eight automated sampler.

General Procedure for Acceptorless Methanol Dehydrogenation. A Schlenk tube attached to a condenser and equipped with a stir bar or a reactor vessel (Radleys Carousel 12 Place Reaction Station, RR98030) was charged with iridium catalyst (0.001–0.004 mol %), potassium hydroxide (85% by mass, 1.34 g, 20 mmol), and degassed MeOH (3 mL) under a N₂ atmosphere. The resulting solution was heated at 115 °C for 15–40 h. Upon cooling, deuterium oxide (2 mL) was added, along with sodium acetate (34.5 mg, 0.420 mmol) as an internal standard for NMR. Methanol dehydrogenation was quantified by integration of formate and carbonate signals obtained by ¹H and ¹³C{¹H} NMR spectroscopy (see the SI for details). TON was calculated based on the amount of H₂ produced (2 times the amount of formate and 3 times the amount of carbonate).

General Procedure for TH and N-Methylation Reactions. To a Biotage microwave vial (size 2–5 mL) were added iridium catalyst (1.5–6.5 μmol, 1–5 mol %) and potassium hydroxide (0.043–0.65 mmol, 0.33–5 equiv vs substrate). The vial was purged with N₂, then MeOH (0.5 mL) and substrate (0.13 mmol) were added, and the vial was sealed and heated under MW irradiation (120 °C, 5 h). After cooling to room temperature, CD₂Cl₂ (0.5 mL) and trimethoxybenzene (5 mg, 0.030 mmol, NMR internal standard) were added. The products were identified by a comparison of ¹H NMR spectra with those of authentic samples (all products were either commercially available or previously reported). Yields were quantified by ¹H NMR spectroscopy.

ASSOCIATED CONTENT

Supporting Information

Details of the quantitation of carbonate, H₂, and CO, as well as homogeneity studies, other control reactions, and NMR data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

*E-mail: robert.crabtree@yale.edu.

Author Contributions

[†]These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

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