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Stoichiometric and Catalytic H/D Incorporation by Cationic Iridium Complexes: A Common Monohydrido-Iridium Intermediate

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Abstract: A mechanistic study of the stoichiometric and catalytic H/D exchange reactions involving cationic iridium complexes is presented. Strong evidence suggests that both stoichiometric and catalytic reactions proceed via a monohydrido-iridium species. Stoichiometric deuterium incorporation reactions introduce multiple deuterium atoms into the organic products when aryliridium compounds $Cp^*PMe_3Ir(C_6H_4X)(OTf)$ (X = H, *o*-CH_3, *m*-CH_3, *p*-CH_3) react with D_2. Multiple deuteration occurs at the unhindered positions (*para* and *meta*) of toluene, when X = CH_3. The multiple-deuteration pathway is suppressed in the presence of an excess of the coordinating ligand, CH_3CN. The compound $Cp^*PMe_3IrH(OTf)$ (**1-OTf**) is observed in low-temperature, stoichiometric experiments to support a monohydrido-iridium intermediate that is responsible for catalyzing multiple deuteration in the stoichiometric system. When paired with acetone-d_6, $[Cp^*PMe_3IrH_3][OTf]$ (**4**) catalytically deuterates a wide range of substrates with a variety of functional groups. Catalyst **4** decomposes to $[Cp^*PMe_3Ir(\eta^3\text{-}CH_2C(OH)CH_2)][OTf]$ (**19**) in acetone and to $[Cp^*PMe_3IrH(CO)][OTf]$ (**1-CO**) in CH_3OH. The catalytic H/D exchange reaction is not catalyzed by simple H^+ transfer, but instead proceeds by a reversible C−H bond activation mechanism.

Introduction

Isotopically labeled compounds are often used to study reaction mechanisms.[1] In addition, labeled compounds are used in pharmacokinetics and metabolism studies for drug development.[2] Traditional methods for isotopic labeling of drug candidates involve incorporation of ^{13}C and ^{2}H labels into drug precursors in the early stages of drug synthesis. However, recent advances in rapid development of new drugs prompt a need for more efficient isotopic labeling methods. Toward this end, Heys[3] reported a fast and efficient way of labeling drug molecules using an Ir(I) catalyst to exchange hydrogen for tritium. This method is attractive, as the isotopic labels are introduced at the late stages of the drug discovery process with high specific activity, using tritium gas (T_2). However, this method is limited to aromatic substrates bearing directing groups, such as amides.[3−7]

Incorporation of deuterium or tritium atoms into a molecule using the iridium catalyst described above involves activation of C−H bonds in the molecules and subsequent exchange for the isotopic label. H/D exchange reactions have been reported with both early and late transition metal complexes, and these processes are believed to proceed via reversible C−H bond activation steps.[8−24] Activation of C−H bonds by transition metal complexes has been well studied by many research

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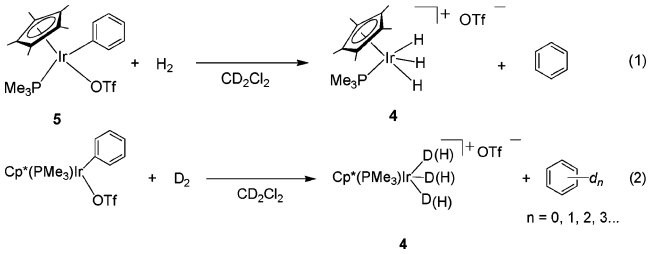
groups,[25−29] and our group has reported the activation of C−H bonds of various small organic molecules using cationic Ir(III) complexes.[30−39] In particular, we have made progress toward the use of Ir(III) complexes for catalytic H/D exchange reactions with organic molecules. At low temperature, [Cp*PMe_3IrH-($ClCD_2Cl$)][X] (**1-CD_2Cl_2**; X = $MeB(C_6F_5)_3$, Cp* = η^5-C_5Me_5) was observed to catalyze H/D exchange between C_6D_6 and a variety of organic molecules.[34] Incorporation of deuterium atoms into water-soluble substrates was achieved with Cp*PMe_3IrCl_2 (**2**) using D_2O as both the solvent and the deuterium source.[36,37]

Further developments in cationic iridium chemistry led to the use of [Cp*PMe_3IrMe($ClCH_2Cl$)][BAr_f] (**3**; BAr_f = B(3,5-C_6H_3-(CF_3)$_2$)$_4$) to stoichiometrically incorporate deuterium/tritium into druglike molecules with high specific activity.[40,41] As reported, some substrates contained a combination of d_0, d_1, and d_n (n > 1) isotopomers under reaction conditions, indicating that multiple deuterium atoms were incorporated into the substrates.[41] We have also reported catalytic H/D exchange between aromatic compounds and acetone-d_6 using [Cp*PMe_3IrH_3][OTf] (**4**; OTf = OSO_2CF_3).[41] The stoichiometric reactions that incorporated multiple deuterium atoms into a single molecule and the catalytic deuterium incorporation reactions described above are proposed to proceed via a monohydrido-iridium intermediate, [Cp*PMe_3IrH(L)]$^+$ (**1-L**). Low-temperature H/D exchange experiments showed that **1-L** could catalyze the incorporation of multiple deuterium atoms into a single molecule.[34] In this paper, we report mechanistic studies that elucidate the multiple deuteration of substrates in the stoichiometric reactions and provide insight into the mechanism of the catalytic H/D exchange reactions.

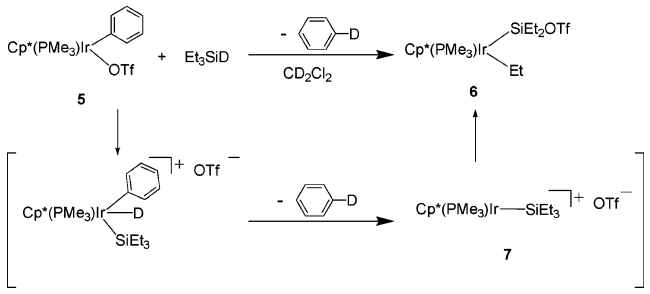
Results and Discussion

Stoichiometric Deuterium Labeling. A. Reaction of Cp*PMe_3IrPh(OTf) (5) with D_2. The compound Cp*PMe_3IrPh(OTf) (**5**) was chosen as a model compound for mechanistic studies of the stoichiometric labeling reaction. Complex **5** was treated with H_2 (600 Torr) in CD_2Cl_2 at 25 °C, generating the trihydride complex **4** and benzene in quantitative yield within seconds (eq 1). It was expected that when **5** was treated with D_2, only one atom of deuterium would be incorporated into benzene. However, ^{1}H NMR spectroscopy revealed that multiple deuteration had occurred. Benzene-d_1, along with benzene-d_n (n = 0, 2, 3...) were observed in the mass spectrum of the product mixture (eq 2). These results are consistent with findings on complex **3** and other aromatic substrates.[41] Both ^{1}H and ^{2}H NMR spectroscopy revealed that the iridium complex **4** resulting from the experiment with D_2 bears hydride and deuteride ligands (eq 2, vide infra).



B. Reaction of 5 with Et_3SiD. It can be difficult to quantify the amount of D_2 in solution, as the quantity of D_2 that is kinetically solvated often varies with the degree of agitation.[42] However, as silanes and H_2 have been shown to have similar reactivity toward organometallic complexes,[43,44] reaction of **5** with a deuterated silane (Et_3SiD) was used as a model substrate for D_2 to explore the effect of varying the number of equivalents of the deuterium source in solution. When **5** was treated with varying (1−20 equiv) equivalents of Et_3SiD, only one deuterium atom was incorporated into the resulting benzene product; no multiple deuteration in benzene was observed. The organometallic species resulting from the reaction was determined to be Cp*PMe_3Ir($SiEt_2$OTf)Et (**6**). Based on previous studies, we assume that Cp*PMe_3Ir($SiEt_3$)$^+$ (**7**) is formed by elimination of benzene-d_1, and this subsequently rearranges to yield **6** (Scheme 1).[30,45] Presumably, the formation of a hydrido-iridium

Scheme 1



intermediate is essential to the multiple deuteration of a substrate. Silyliridium intermediate **7** cannot further react with a second equivalent of Et_3SiD to form a deuterido-iridium intermediate; thus, incorporation of only one deuterium atom into benzene is observed. These results indicate that the deuteration of **5** with silanes differs from that of **5** with D_2, and that silane is not an effective model for deuterium incorporation by D_2.

C. Reactions of Cp*PMe_3Ir(R)OTf and D_2. To examine a wide range of deuteration patterns in the organic fragments resulting from hydrogenolysis, a variety of aryliridium complexes were prepared and treated with D_2. The 3,5-disubstituted

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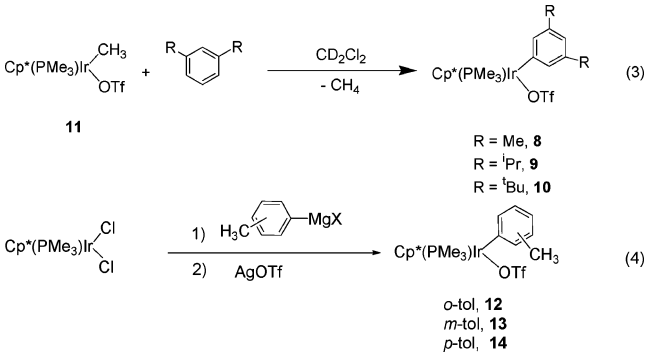
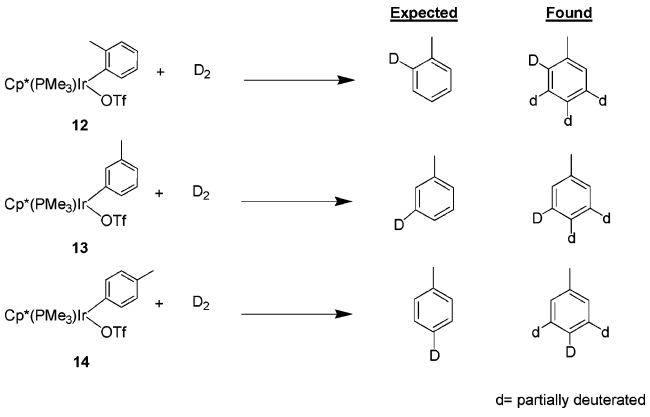
aryliridium complexes, Cp*PMe$_3$IrR(OTf) (**8**, R = 3,5-dimethylphenyl; **9**, R = 3,5-diisopropylphenyl; **10**, R = 3,5-di-*tert*-butylphenyl), were synthesized by treating Cp*PMe$_3$IrMe(OTf) (**11**) with the appropriate arene in CH_2Cl_2 (eq 3).[30] As previously reported, these reactions proceeded with high regioselectivity to form only 3,5-disubstitutited aryliridium complexes.[30] The isomers of Cp*PMe$_3$Ir(tolyl)(OTf) (**12**, *o*-tolyl; **13**, *m*-tolyl; **14**, *p*-tolyl) were prepared by treating Cp*PMe$_3$IrCl$_2$ (**2**) with a slight excess of the corresponding tolyl Grignard reagent,[46] followed by metathesis with AgOTf (eq 4).



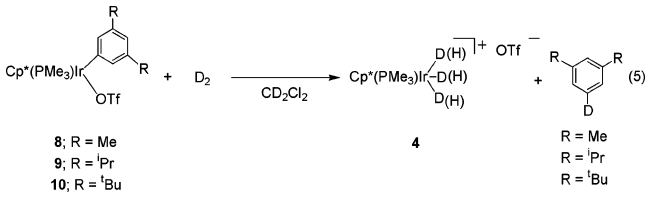
(3) (4)

When the disubstituted aryliridium complexes **8**, **9**, and **10** were treated with D_2 (600 Torr), only one deuterium atom was incorporated into the resulting arene (eq 5). However, treatment of **12** with D_2 yielded multiply deuterated toluene. Integration of the ^{1}H NMR spectrum of this toluene product revealed 0.81 *meta* protons and a total of 1.29 *ortho* and *para* protons. These integrations correspond to approximately 58% deuteration of the toluene aryl protons (roughly d_3-toluene). Similarly, the ^{1}H NMR integrations for the toluene product resulting from the reaction of **13** with D_2 revealed 0.71 *meta* protons and 2.18 *ortho* and *para* protons (42% deuteration of the toluene aryl protons; roughly d_2-toluene). The integrations from the reaction with **14** showed 0.62 *meta* protons, as well as 2.05 *ortho* and *para* protons (Scheme 2; 47% deuteration of the toluene aryl

Scheme 2



protons). In all the cases described above, the *ortho* and *para* protons could not be sufficiently resolved from each other to obtain accurate integrations of each, but the *ortho* signals were qualitatively the major peaks.

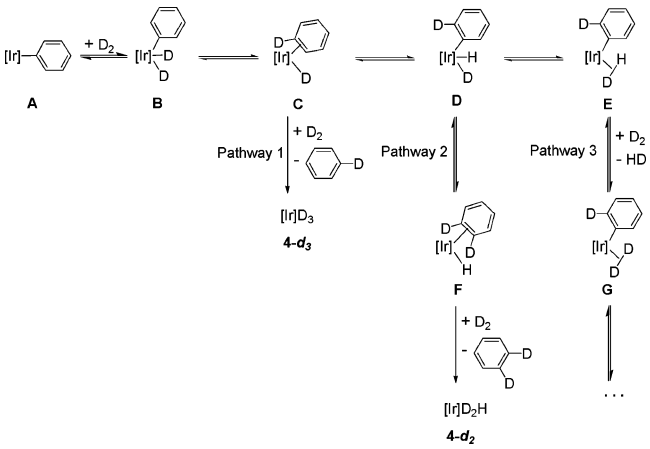


(5)

Steric hindrance appears to govern the regiochemistry of deuterium incorporation. Deuterium incorporation in the *ortho* position is observed when the substrate is bound to iridium at that location (**12**), undoubtedly resulting from hydrogenolysis of the Ir−C bond. However, in cases where the arene is bound to iridium at a *meta* or *para* position (**13**, **14**), little or no deuterium incorporation is observed in the *ortho* position. In contrast, some level of deuteration is always observed in the *meta* and *para* positions of the toluene products, regardless of the original point of bonding to iridium (**12**, **13**, **14**). These results indicate that, in addition to incorporating deuterium at the expected position (the carbon atom attached to the iridium center), the arene is also deuterated by an additional H/D exchange process that is sensitive to the steric environment of the arene.

We suggest that this process is reversible elimination and readdition of the aryl ligand (Scheme 3). These steps may occur

Scheme 3



via either oxidative addition or σ-bond metathesis mechanisms.[39] The first step involves addition of D_2 to the iridium center **A** to form the Ir(V) intermediate **B**. Next, C−D reductive elimination in **B** results in the formation of [Cp*PMe$_3$IrD(η^2-benzene-d_1)]-[OTf] (**C**). For intermediate **C**, benzene either coordinates to the iridium center through its π-bond (as drawn) or through its σ C−H bond.[46−57] In pathway 1, displacement of benzene-d_1

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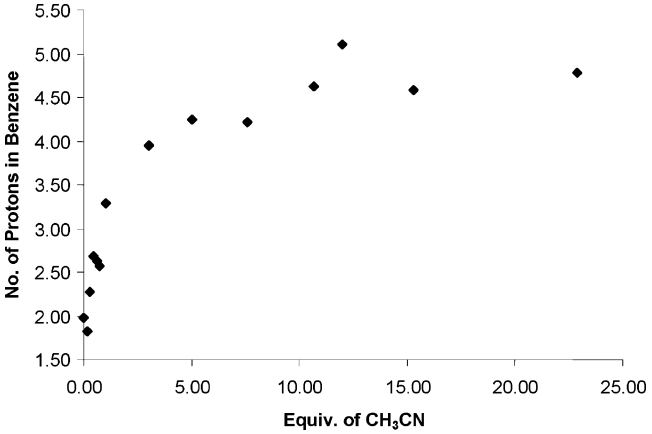


Figure 1. Plot of number of protons remaining in benzene vs equivalents of CH_3CN.

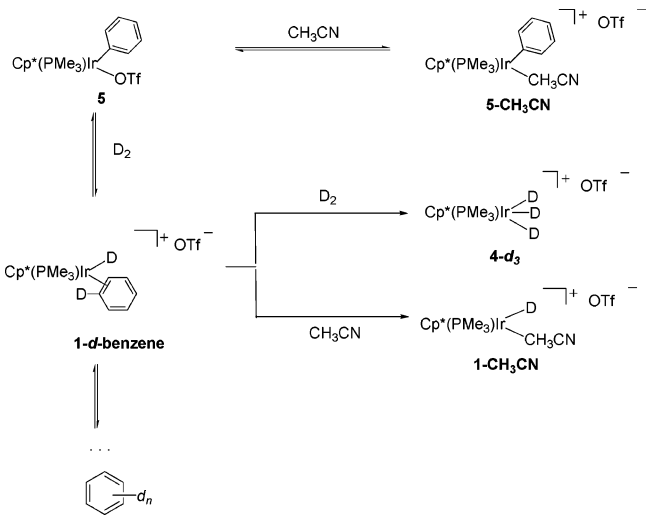
by a molecule of D_2 from **C** leads to the thermodynamic product, trihydride **4-*d*$_3$**. Alternatively (pathway 2), a second benzene C−H bond is activated in **C** to form Ir(V) species **D;** elimination from **D** incorporates a second deuterium atom into benzene to form benzene-d_2 complex **F**. An equivalent of D_2 displaces benzene-d_2 from **F** to form the thermodynamic product **4-*d*$_2$** with one hydride ligand on iridium center. In pathway 3, elimination of HD from **D** results in the nonclassical Ir−HD complex **E**.[58−60] An equivalent of D_2 displaces HD to form the D_2 complex **G**, and **G** incorporates additional deuterium atoms into benzene by processes similar to those described above. The proposed mechanism accounts for the hydride resonances observed in product **4** by ^{1}H NMR spectroscopy when **5** is treated with D_2, and for the results observed with silane. The lack of *ortho* deuteration observed in the product is consistent with previous observations with **1-CD$_2$Cl$_2$** and toluene.[34]

D. Trapping Experiments with CH_3CN. Treatment of phenyliridium triflate **5** with H_2 in the presence of CH_3CN required heating at 45 °C for 4 days to result in elimination of benzene. The resulting organometallic products consisted of a mixture of trihydride **4** and [Cp*PMe$_3$IrH(CH$_3$CN)][OTf] (**1-CH$_3$CN**); the ratio of products depended on the equivalents of CH_3CN in the reaction mixture. At 1 equiv of CH_3CN, the ratio of **4** to **1-CH$_3$CN** is 2:1. The ratios are 1:5 and 1:20 at 5 and 20 equiv, respectively. The generation of **1-CH$_3$CN** strongly supports the intermediacy of a monohydrido-iridium complex **1-L**.

When **5** was treated with both D_2 and CH_3CN (12 equiv), incorporation of only one deuterium atom was observed in the benzene product. Apparently, in the presence of a coordinating solvent the multiple deuteration pathway is inoperative. By varying the number of equivalents (0−23 equiv) of CH_3CN added to the reaction mixture, the number of deuterium atoms incorporated into the benzene can be varied. At a low number of equivalents of CH_3CN (<5), multiple deuteration into benzene was observed; with a large excess of CH_3CN, only one deuterium atom was incorporated per benzene molecule (Figure 1). Similarly, when *p*-tolyl complex **14** was treated with both D_2 and CH_3CN (12 equiv), only one deuterium atom was incorporated into the *para* position.

Observation of the reaction mixture by ^{1}H NMR spectroscopy revealed that prior to addition of D_2 to the reaction mixture, CH_3CN coordinates to the iridium center of **5** to form the CH_3CN adduct [Cp*PMe$_3$IrPh(CH$_3$CN)][OTf] (**5-CH$_3$CN**).[61] Presumably, triflate complex **5** is in equilibrium with **5-CH$_3$CN**, allowing **5** to react with D_2 to extrude benzene-d_n (Scheme 4).

Scheme 4



Once intermediate **1** is formed, it could further react to multiply deuterate benzene by the process depicted in Scheme 3. At a relatively low equivalency of CH_3CN, **1-benzene** could react either with D_2 to form trihydride **4** or with CH_3CN to form **1-CH$_3$CN**. At high CH_3CN equivalencies (>5 equiv), **1-CH$_3$CN** is formed rather than **4.** This result is attributed to the better donor ability of CH_3CN relative to that of H_2. In the presence of a large excess of CH_3CN, the proposed intermediate **1** is trapped efficiently to form **1-CH$_3$CN**, thus shutting down the multiple deuteration pathway.

E. Low-Temperature Experiments with 5 and D_2. When H_2 was added to a solution of **5** at −78 °C, the NMR spectrum of the reaction mixture at −80 °C showed only starting material. No reaction occurred when the reaction mixture was warmed in the probe to −40 °C. The NMR tube was taken out of the probe and shaken vigorously to ensure good transport of H_2 into the solution. After shaking, the ^{1}H NMR spectrum of the reaction mixture at −40 °C revealed four new sets of signals containing Cp* and PMe_3 ligands, along with starting material. One set of signals corresponds to trihydride **4**, while another set of signals corresponds to the previously reported bridging hydride species [(Cp*PMe$_3$IrH)$_2$H][OTf] (**15**).[34,62] The third set of resonances was identified as **1-CD$_2$Cl$_2$**, in which the OTf counterion has moved outersphere and CD_2Cl_2 coordinates to the iridium center.[34] The fourth set of resonances is closely related to those observed for **1-CD$_2$Cl$_2$**, and consists of a Cp* signal at 1.85 ppm, a PMe_3 resonance at 1.62 ppm, and a hydride resonance at −11.03 ppm. This set of signals was assigned to **1-OTf**, where the OTf ligand is covalently bound to iridium. At 50% conversion, the relative ratios of **4**:**15**:**1-CD$_2$Cl$_2$**:**1-OTf**

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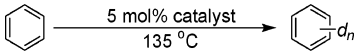
(62) Gilbert, T. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1985**, *107*, 3502.

Table 1. Solvent Screen for Catalytic H/D Exchange Reactions



		$Cp^*PMe_3IrCl_2$(**2**)		$[Cp^*PMe_3Ir(H)_3][OTf]$ (**4**)	
entry	solvent	% D_{inc}	(time)	% D_{inc}	(time)
1	D_2O	90	(5 d)	66	(17 h)
2	D_2O/CD_3OD (1:1)	97	(2 d)	75	(3 d)
3	CD_3OD	58	(2 d)	95	(3 d)
4	CH_3OD	0	(2 d)	0	(2 d)
5	DMSO-d_6	0	(5 d)	0	(2 d)
6	acetone-d_6	21	(2 d)	99	(20 h)

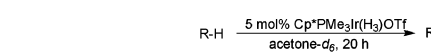
were 1:1:0.1:7. When D_2, instead of H_2, was added to **5** at low temperature, the same four iridium complexes were observed in the ^1H NMR spectrum in similar product ratios. When the reaction mixture was warmed to 25 °C with agitation, multiple deuteration was observed in the product benzene. Unfortunately, we were not able to observe the η^2-benzene complex **1-benzene** by NMR spectroscopy at low temperature, indicating that it remains a transient intermediate under these conditions. The same hydride species were observed in similar ratios at −40 °C when methyl complex **11** was used as the iridium source instead of **5**. When the reaction mixture was warmed to 25 °C, the methane formed from this reaction consisted of all isotopomers: CH_nD_{4-n} ($n = 0, 1, 2, 3, 4$). This final result indicates that multiple deuteration is not limited to reactions that involve aryl substituents bound to the iridium center. Deuterium incorporation into CH_4 is believed to proceed via a mechanism similar to that described by Jones et al.[63]

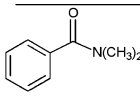
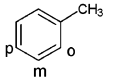
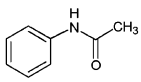
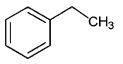
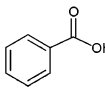
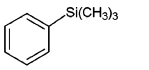
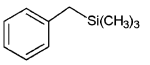
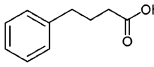
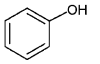
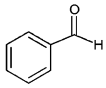
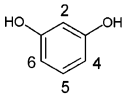
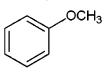
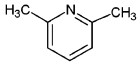
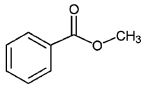
As reported previously, **1-CD_2Cl_2** decomposed to a mixture of **4** and **15** upon warming of the reaction mixture to above −20 °C.[34] The observation of **1-OTf** at low temperature provides strong evidence that the stoichiometric deuterium-labeling reaction described above proceeds via a monohydrido-iridium intermediate. This monohydride presumably catalyzes H/D exchange into substrates, as previously reported for **1-CD_2Cl_2**.[34]

Catalytic H/D Exchange. A. Solvent Screen. Dichloride complex **2** paired with D_2O,[36] and trihydride complex **4** paired with C_6D_6 in CD_2Cl_2,[34] have been previously reported to catalyze H/D exchange with organic substrates. To optimize the H/D exchange reactions with aromatic substrates, a variety of solvents were screened with both dichloride complex **2** and trihydride complex **4**. Benzene was used as the model substrate and Table 1 summarizes the results from this solvent screen. Complex **2** performed well in D_2O or mixed D_2O/CD_3OD (entries 1 and 2), but provided only modest-to-inadequate H/D exchange in organic solvents (entries 3−6: acetone-d_6, methanol-d_n, and DMSO-d_6). In contrast, **4** performed modestly in D_2O or mixed D_2O/CD_3OD, but gave excellent deuterium incorporation in CD_3OD and acetone-d_6. No deuterium exchange was observed with either catalyst in DMSO-d_6, presumably because this highly coordinating solvent shuts down the reaction. Importantly, for trihydride catalyst **4**, methanol-d_4 performs well as a deuterium source while methanol-d_1 is not an effective deuterium source. Of the solvents and catalysts tested, acetone-d_6 paired with **4** gave the highest level of deuterium incorporation into benzene and this system was used for subsequent H/D exchange reactions.

(63) Northcutt, T. O.; Wick, D. D.; Vetter, A. J.; Jones, W. D. *J. Am. Chem. Soc.* **2001**, *123*, 7257.

Table 2. Substrate Screen with $[Cp^*PMe_3Ir(H)_3][OTf]$



substrate	% D_{inc} 135 °C	% D_{inc} 75 °C	substrate	% D_{inc} 135 °C	% D_{inc} 75 °C
	99	99		Ar: 43 Me: 32	Ar: 22 Me: 18
	o: 57 m: 98 p: 97 CH_3: 50	o: 32 m: 93 p: 94 CH_3: 11		o: 78 m: 97 p: 97 CH_3: 85	o: 44 m: 87 p: 89 CH_3: 27
	o: 10 m: 99 p: 99 CH_2: 0 CH_3: 38	o: 9 m: 99 p: 99 CH_2: 0 CH_3: 23		o: 72 m: 35 p: 26 COOH: 99	o: 12 m: 18 p: 11 COOH: 99
	o: 5 m, p: 95 CH_3: 0	o: 16 m,p: 98 CH_3: 0			
	o, p: 4 m: 99 CH_2: 0 CH_3: 0	o, p: 19 m: 92 CH_2: 0 CH_3: 0		Ar: 62 CH_2: 0 COOH: 99	Ar: 44 CH_2: 0 COOH: 99
	o, p: 96 m: 96 OH: 99	o, p: 98 m: 99 OH: 99		o: 72 m: 35 p: 26 CHO: 61	o: 21 m: 24 p: 21 CHO: 25
	5: 98 2, 4, 6: 96 OH: 99	5: 96 2, 4, 6: 96 OH: 99		0	0
	o, p: 96 m: 97 CH_3: 41	o, p: 97 m: 98 CH_3: 35		m: 67 p: 95 CH_3: 93	m: 31 p: 28 CH_3: 27
	o: 36 m: 72 p: 80 CH_3: 19	o: 47 m: 81 p: 89 CH_3: 16		98	96

B. Substrate Scope. A variety of aromatic substrates were screened for H/D exchange using 5 mol % of the trihydride iridium catalyst **4** in acetone-d_6. Table 2 lists these substrates and their corresponding extents of deuterium incorporation (%D_{inc}). Most substrates showed satisfactory deuterium incorporation (>90% in aryl rings). The catalyst is tolerant of a wide range of functional groups, including hydroxy, ether, amide, carboxylic acid, and ester groups. It was found that the reaction temperature could be lowered to 75 °C without causing a significant decrease in the extent of deuterium incorporation relative to that observed in reactions run at 135 °C (Table 2).

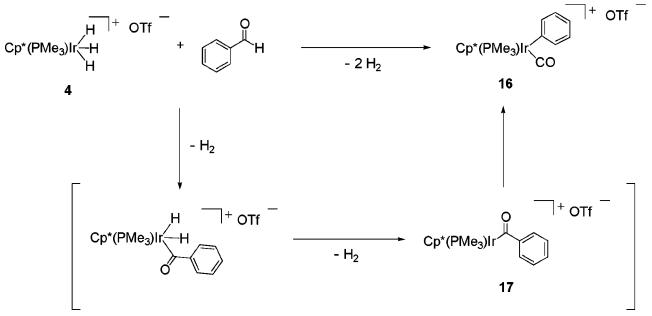
Performing the reactions at 75 °C with catalyst **4**, cyclic alkenes were found to be good substrates for H/D exchange. Cyclohexene gave deuterium incorporation of 95%, 83%, and 88% in the vinylic, allylic, and homoallylic positions, respectively. Similarly, cyclopentene gave 95%, 96%, and 90% deuterium incorporation into these positions. The 1-hexene gave an overall %D_{inc} of 18%, with most of the deuterium atoms incorporated into the vinylic position (26%). Deuterium was incorporated to a lesser extent into the internal methylene positions (23%), but not into the terminal methyl group. Isomerization of 1-hexene into internal alkene isomers was observed. Deuterium can be incorporated into some organometallic complexes, such as ferrocene and $CpRe(CO)_3$. However, attempted H/D exchange with other Cp-based organometallic substrates (e.g., Cp_2ZrCl_2, Cp_2TiCl_2, $CpMn(CO)_3$, and $[CpFe(CO)_2]_2$) led to decomposition of either the catalyst or the substrate. Unlike the system previously reported by our group,[34]

this system (**4** in acetone-d_6) was not active for exchange of deuteriums into Cp*$_2$Fe.

Lower levels of deuterium incorporation were observed in the *ortho* positions of the substrates with no directing group (e.g., toluene and phenyltrimethylsilane). This finding is probably due to steric hindrance, and it is consistent with our observations in the stoichiometric deuterium incorporation reactions described above. However, significant deuterium incorporation was observed with substrates bearing directing groups such as hydroxyls, esters, amides, and carboxylic acids. This is consistent with the H/D exchange observed with Crabtree's catalyst.[3−7] The unactivated sp^3-hybridized protons in 4-phenylbutanoic acid were not exchanged. This contrasts with our findings in the previously reported aqueous system catalyzed by **2**, which could H/D exchange into unactivated sp^3-hybridized protons.[36] However, using catalyst **4** in acetone-d_6, the protons on the sp^3-hybridized carbons in cyclic alkenes were exchanged with high levels of deuterium incorporation. Subsequent insertion and β-hydride elimination may result in the observed incorporation of deuterium atoms in the allylic and homoallylic positions of cyclic alkenes. Deuterium incorporation into the methylene position of 1-hexene and isomerization of terminal double bond supports this insertion and β-hydride elimination mechanism.[64]

Catalytic deuteration of benzaldehyde with **4** in acetone-d_6 resulted in low levels of deuterium incorporation (Table 2). The organometallic product [Cp*PMe$_3$IrPh(CO)][OTf] (**16**) was observed in this reaction mixture. This decarbonylation product is apparently catalytically inactive toward H/D exchange. It is assumed that complex **16** is formed via the mechanism depicted in Scheme 5. Benzaldehyde contains two classes of C−H bonds

Scheme 5

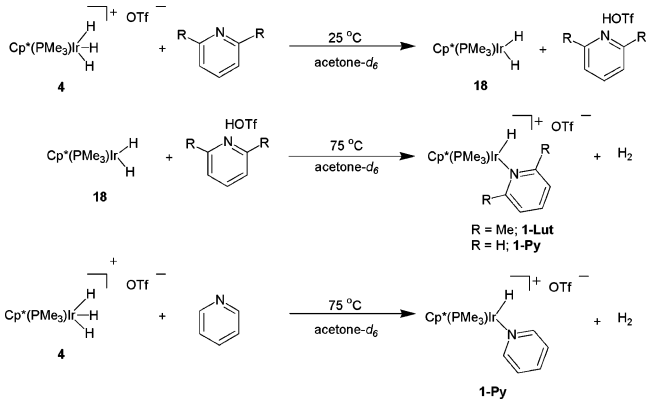


that can be activated by trihydride catalyst **4**: the aryl C−H bonds and the formyl C−H bond. If the formyl C−H bond is activated and this is followed by the loss of H_2, the acyl complex **17** is formed. Then, **17** could undergo decarbonylation to form **16**, thus shutting down the catalytic pathway.[31]

C. Reactions with Acids and Bases. The possibility that the H/D reactions with **4** in acetone-d_6 involve acid catalysis was explored (an acid catalyst may be generated in situ or the iridium species could act as a simple Lewis acid). When H/D exchange catalysis was attempted using B(C$_6$F$_5$)$_3$ or HOTf as catalysts in acetone-d_6, no deuterium incorporation into benzene was observed. Additionally, the H/D exchange reactions catalyzed by **4** were run with several base additives to scavenge any potential protons generated in situ. When the tertiary amines NEt$_3$ and N^{i}Pr$_2$Et were added to the reaction mixture, the levels of deuterium incorporation into benzene were only 37% and 7%, respectively. The catalyst in these cases decomposed to an intractable mixture of species, probably due to coordination of amine to the iridium center. However, when weakly coordinating bases, such as 2,2,6,6-tetramethylpiperidine, *N*,2,2,6,6-pentamethylpiperidine, and 2,6-lutidine, were added, >95% deuterium incorporation was observed in benzene. These results indicate that the H/D exchange reactions mediated by **4** do not proceed via acid catalysis.

The trihydride complex **4** can be deprotonated with an excess (5 equiv) 2,6-lutidine in acetone-d_6 at 25 °C to form Cp*PMe$_3$-IrH$_2$ (**18**) and 2,6-lutidinium triflate (LutHOTf; Scheme 6).

Scheme 6



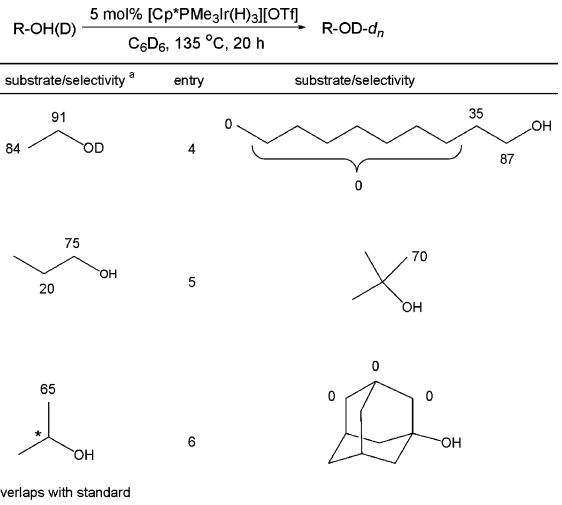
Independently, neither **18** nor LutHOTf catalyzed the H/D exchange reaction. However, the active catalyst can be generated by mixing **18** with excess LutHOTf (5 equiv). When **18** was treated with excess LutHOTf in the absence of any H/D exchange substrate, the resulting organometallic species was identified as [Cp*PMe$_3$IrH(2,6-lutidine)][OTf] (**1-Lut**) (Scheme 6). It is assumed that **1-Lut** is formed by reversible protonation of **18** by LutHOTf and loss of H_2, followed by coordination of 2,6-lutidine (Scheme 6).

Trihydride complex **4** can also be deprotonated by pyridine at 25 °C. Reversible protonation, followed by coordination of pyridine, was observed to form [CpPMe$_3$IrH(pyrdine)][OTf] (**1-Py**) when **4** was heated at 75 °C in acetone-d_6 with pyridine (Scheme 6). **1-Py** can also be synthesized by heating **18** in the presence of pyridinium triflate in acetone. Unlike the reaction mixture of **18** and LutHOTf, **1-Py** is catalytically inactive toward H/D exchange reactions, which we attribute to the strong coordination of pyridine to the iridium center. This result is consistent with the observed lack of H/D exchange into pyridine as a substrate (Table 1).

D. Reactions with Alcohols. As noted earlier, trihydride **4**-catalyzed H/D exchange occurs using CD$_3$OD, but not CH$_3$OD, as a source of deuterium. When monitoring these H/D exchange reactions by ^{1}H NMR spectroscopy in CD$_3$OD, the resonance for the C*H*$_3$OH protons grew in, rather than that corresponding to the CH$_3$O*H* proton. These results suggest that a C−H bond activation step is essential to the functioning of an alcohol-based deuterium source in the catalytic cycle. As such, CD$_3$CD$_2$OD was explored as the solvent/deuterium source in the H/D exchange reactions. At 135 °C, 98% deuterium incorporation was observed in benzene when the reaction was performed in CD$_3$CD$_2$OD. Proton resonances for both the

(64) *Fundamentals of Molecular Catalysis*; Kurosawa, H.; Yamamoto, A., Eds.; Elsevier: Amsterdam; Boston, 2003; Vol. 3.

Table 3. H/D Exchange into Alcohols

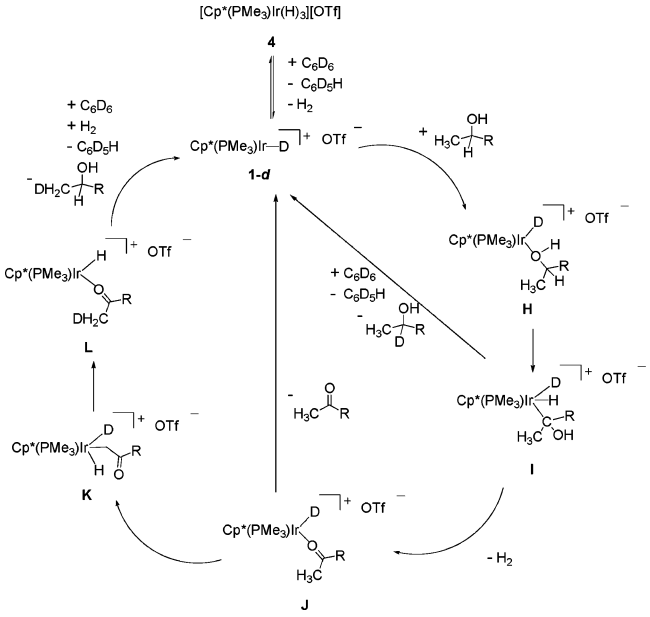


residual C*H*$_3$ and C*H*$_2$ protons in CD_3CD_2OD were observed to grow in the ^{1}H NMR spectrum as the reaction progressed.

To explore this process further, the reaction inverse to that described above was studied: protiated alcohols were used with C_6D_6 as the solvent to examine the deuteration pattern of the alcohols. The results of this study are summarized in Table 3. Only protons α and β to the oxygen atom of linear alcohols were observed to undergo H/D exchange: no deuterium incorporation was observed in the alkyl chain of 1-decanol or in the terminal CH_3 group of propanol. Under these reaction conditions, both formation of acetone (∼20%) and H/D exchange were observed when 2-propanol was used as a substrate. Deuterium incorporation was observed with *tert*-butyl alcohol, along with the dehydration product isobutene (∼30%). No deuterium was incorporated into 1-adamantanol.

In contrast to results obtained with the dichloride complex **2** as the catalyst in D_2O,[36,37] trihydride complex **4** does not incorporate deuterium atoms into the terminal positions of the alkyl chains of the alcohol in C_6D_6. Catalyst **4** behaves similarly to the molybdocene catalyst reported by Tyler and co-workers,[8,23,24] which promotes H/D exchange at the α-carbon of alcohols in D_2O. Unlike Tyler's mechanism, where deprotonation of the alcohol forms a metal alkoxide species to enter the catalytic cycle, activation of α C−H bond of the alcohol is thought to be the initial step of our iridium based cycle (Scheme 7). After loss of H_2 from **4** and activation of the C−D bond in C_6D_6, monodeutero iridium complex **1-*d*** is generated. Coordination of the alcohol substrate ($CH_3CH(OH)R$) leads to the alcohol complex **H**, followed by activation of the α C−H bond to form the Ir(V) intermediate **I**. Intermediate **I** loses $CH_3CD(OH)R$ to regenerate **1-*d***; alternatively, loss of H_2 results in the keto complex **J**. Loss of the ketone substrate ($CH_3C(O)R$) from **J** returns the active catalyst **1-*d***. In a different pathway, activation of a C−H bond from **J** leads to the Ir(V) intermediate **K**. Elimination of the C−D bond from **K** results in **L** with a deuterium atom incorporated into the ketone substrate. Addition of C_6D_6 to **L** releases $CH_2DCH(OH)R$ with a deuterium atom incorporated into its β position. This mechanism accounts for the incorporation of deuterium atoms in both the α and β positions of an alcohol, and it accounts the formation of acetone

Scheme 7



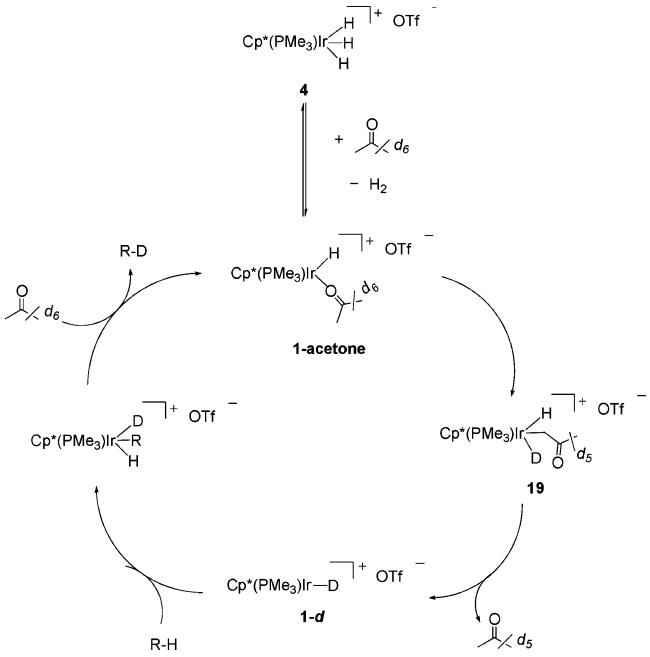
in the 2-propanol reaction. It also explains the lack of H/D exchange when CH_3OD is used as the deuterium source.

Deuterium incorporation in *tert*-butyl alcohol is assumed to occur via a dehydration reaction to form isobutene, followed by H/D exchange into the alkenic position, then hydration to regenerate *tert*-butyl alcohol. Dehydration of *tert*-butyl alcohol is favorable at the reaction temperature (135 °C) to form isobutene, and hydration is reversible under reaction conditions. Alkene formation by dehydration of 1-adamantanol is unfavorable, and so no deuterium is incorporated.

E. Catalytic Cycle and Decomposition Pathways. The fact that complex **1-Lut** is an active catalyst for H/D exchange suggests that the active catalyst in the reaction promoted by **4** could be a monohydride solvento species: [Cp*PMe$_3$IrH(solv)][OTf] (**1-solv**; solv = acetone-d_6, CD_3OD). A series of monohydride complexes stabilized by labile ligands had been prepared, for example, [Cp*PMe$_3$IrH(L)][X] (**1-CH_2CH_2**, L = CH_2CH_2, X = BF_4; **1-pentene**, L = 1-pentene, X = BAr_f; **1-vinyl ether**, L = CH_2=$CHOCH_2CH_3$; X = BAr_f). All these complexes are catalytically active toward H/D exchange in acetone-d_6, but, unlike **4**, they require a reaction temperature of 135 °C to achieve >90% deuterium incorporation in benzene. This result can be explained by the fact that olefin ligands are coordinated to iridium more tightly than either H_2 or acetone is. As such, olefin complexes based on **1** are not as active as **4**. As mentioned before, **1-Py** is catalytically inactive. These results demonstrate the importance of reversible ligand coordination for achieving high H/D exchange activity.

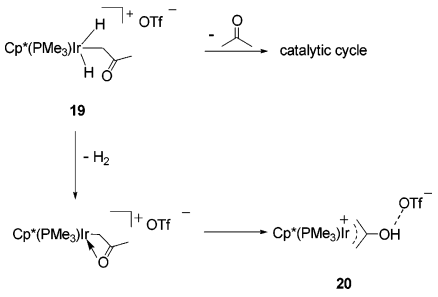
In acetone-d_6, H_2 dissociates from **4** and coordination of an acetone molecule forms **1-acetone**, which was observed by ^{1}H NMR spectroscopy. In the proposed catalytic cycle (Scheme 8), **1-acetone** oxidatively adds its C−D bond across the iridium center to form the Ir(V) intermediate **19**. Reductive elimination of acetone-d_5 from this intermediate generates monodeuteride iridium complex **1-*d***. We propose that intermediate **1-*d*** then oxidatively adds the C−H bond of a substrate to afford another Ir(V)-based intermediate. Subsequent reductive elimination affords the deuterated substrate.

Scheme 8



Acetone complex **1-acetone** could not be isolated due to its instability in solution. However, it was observed by NMR spectroscopy. In the presence of substrate, **1-acetone** is a competent catalyst for H/D exchange. In the absence of substrate, **1-acetone** reacts further to form [Cp*PMe_3Ir-(η^3-$CH_2C(OH)CH_2$)][OTf] (**20**), which is also observed as the decomposition product in the catalytic reactions (Scheme 9).

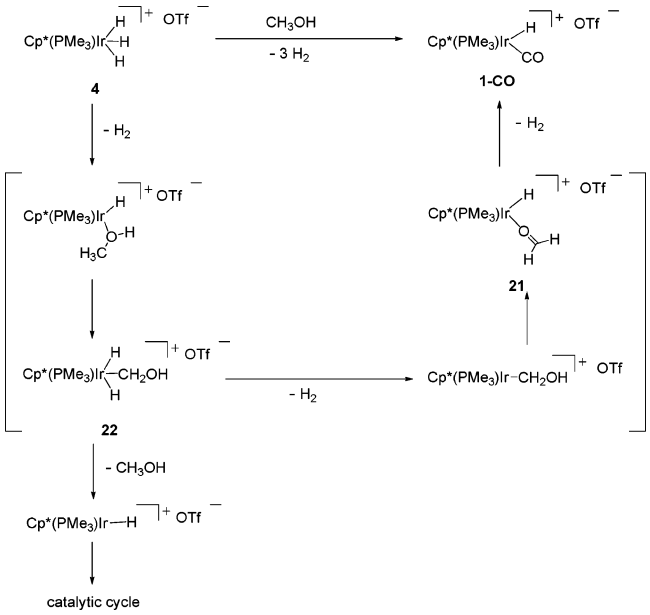
Scheme 9



As mentioned above, from **19**, the reductive elimination of acetone continues the catalytic cycle. However, if H_2 is lost instead, the resulting intermediate rearranges to form **20**. The formation of **20** from methyl triflate **11** and acetone is proposed to proceed via an intermediate similar to **19**.[65]

The H/D exchange reactions in CD_3OD are thought to proceed by the catalytic cycle similar to that described in Scheme 7. The major decomposition product observed in the CD_3OD reaction is [Cp*PMe_3IrD(CO)][OTf] (**1-*d*-CO**). To form this product, the iridium center is proposed to oxidize methanol to form a formaldehyde intermediate **21** via coordination of CH_3OH to the iridium center. Activation of the C−H bond leads to the Ir(V) intermediate **22**, which loses CH_3OH to enter the catalytic cycle. Intermediate **22** loses 2 equivalents of H_2 to form **21**. Activation of the C−H bond and loss of H_2, followed by decarbonylation, yields **1-CO** (Scheme 10).[31,36,37]

Scheme 10



In summary, more than one deuterium is incorporated into the organic fragment product when aryliridium complexes Cp*$(PMe_3)Ir(C_6H_4X)(OTf)$ (X = H, *o*-CH_3, *m*-CH_3, *p*-CH_3) are treated with D_2. Steric hindrance and the addition of a dative ligand, CH_3CN, both prevent multiple deuteration into the organic substrate extruded from the reaction. The observance of monohydride complex **1-OTf** at low temperature suggests that **1-OTf** is responsible for the multiple deuteration in the stoichiometric system. Trihydride complex **4**, when paired with acetone-d_6 or CD_3OD, is a competent catalyst for H/D exchange into aromatic substrates. Catalyst **4** decomposes to form [Cp*PMe_3Ir(η^3-$CH_2C(OH)CH_2$)][OTf] (**20**) in acetone and [Cp*PMe_3IrH(CO)][OTf] (**1- CO**) in CH_3OH. Evidence suggests that **1-L** (L = solvent) is the active species and reversible C−H bond activation steps are operative in the catalytic system.

Experimental Section

General Procedures. Unless otherwise noted, all reactions and manipulations were performed in an inert atmosphere (N_2) glovebox at 25 °C or using standard Schlenck techniques. Glassware was dried at a temperature of 150 °C or higher for at least 12 h prior to use. Unless otherwise noted, reagents were purchased from commercial suppliers and used without further purification. Deuterated solvents (Cambridge Isotope Laboratories) were degassed by freezing, evacuating, and thawing (3x). They were then dried over 3-Å sieves and stored under N_2. Merck silica gel, 60 Å, 230−400 mesh, grade 9385, was used in chromatography unless otherwise noted. Silylated silica gel (Silica Gel 60), 63−200 μm particle size, was obtained from EM Science. Diethyl ether, THF, hexanes, pentane, benzene, and CH_2Cl_2 were passed through activated alumina under N_2, then sparged with N_2 and stored over 4-Å molecular sieves.[66] The starting materials **1-CH_2CH_2,**[30] **1-pentene,**[32] **1-vinyl ether,**[38] **2,**[67] **4,**[68] **5,**[30] **11,**[30] Cp*PMe_3-Ir(*o*-tolyl)Br,[46] Cp*PMe_3Ir(*m*-tolyl)Cl,[46] Cp*PMe_3Ir(*p*-tolyl)Br,[46] and **18**[69] were synthesized according to literature procedures.

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Reactions with gases were performed by addition of a known pressure of gas from a high-vacuum line into the reaction vessel at 25 °C. The pressure was determined using a digital MKS Baratron gauge attached to the line. Elemental analyses were performed at the UC−Berkeley Microanalytical facility with a Perkin-Elmer 2400 Series II CHNO/S Analyzer. Gas Chromatograph−Mass Spectroscopy (GC−MS) data were obtained using an Agilent Technologies Instrument 6890N GC (column #HP-5MS, 30.0m × 250μm × 0.25 μm calibrated) and 5973N MS.

Unless otherwise indicated, NMR spectra were obtained using a Bruker AVQ-400 MHz spectrometer (400 MHz for ^{1}H, 162.1 MHz for ^{31}P{^{1}H}, 376.5 MHz for ^{19}F) or a DRX-500 MHz spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C{^{1}H}, 76.8 MHz for ^{2}H, 99 MHz for ^{29}Si{^{1}H}) at 25 °C. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual protiated solvent, coupling constants are reported in Hertz (Hz), and integrations are reported in number of protons. ^{19}F spectra are reported relative to $CFCl_3$ as the external standard and ^{31}P{^{1}H} spectra are reported relative to trimethyl phosphate as the external standard. Unless otherwise noted, samples for NMR analysis were prepared using CD_2Cl_2 as the solvent.

Synthesis of Cp*PMe$_3$Ir(SiEt$_2$OTf)Et (6). A 20-mL vial was charged with **5** (0.100 g, 0.160 mmol), Et_3SiH (0.028 g, 0.240 mmol), 5 mL CH_2Cl_2, and a stirbar. The reaction mixture was stirred at 25 °C for 5 min. The volatile materials were removed under vacuum to yield **6** as a pale yellow solid (0.105 g, 90%). ^{1}H NMR (500 MHz): δ 1.83 (d, 15H, $^4J_{P-H}$ = 2.0 Hz, C$_5$(C*H*$_3$)$_5$), 1.51 (d, 9H, $^2J_{P-H}$ = 10.0 Hz, P(C*H*$_3$)$_3$) 1.27 (m, 3H, Ir−CH$_2$C*H*$_3$), 1.17 (m, 4H, SiC*H*$_2$CH$_3$), 1.05 (m, 2H, Ir−C*H*$_2$CH$_3$), 1.02 (m, 6H, SiCH$_2$C*H*$_3$). ^{13}C{^{1}H} NMR: δ 96.7 (s, *C*$_5$(CH$_3$)$_5$), 21.1 (s, Ir−CH$_2$*C*H$_3$), 18.3 (d, $^1J_{P-C}$ = 37.5 Hz, P(*C*H$_3$)$_3$), 14.1 (s, SiC*H*$_2$CH$_3$), 13.1 (s, SiC*H*$_2$CH$_3$), 9.9 (s, C$_5$(*C*H$_3$)$_5$), 8.6 (s, SiCH$_2$*C*H$_3$), 8.5 (s, SiCH$_2$C*H*$_3$), −18.6 (d, $^2J_{P-C}$ = 6.3 Hz, Ir−C*H*$_2$-CH$_3$). ^{31}P{^{1}H} NMR: δ −45.1 (s). ^{19}F NMR: δ −76.8 (s). ^{29}Si{^{1}H} NMR: δ 70.4 (d, $^1J_{P-Si}$ = 23.9 Hz). Anal. Calcd for $C_{20}H_{39}F_3IrO_3PSSi$: C, 35.98; H, 5.89. Found: C, 35.60; H, 5.80.

Synthesis of Cp*PMe$_3$Ir(3,5-C$_6$H$_3$(CH$_3$)$_2$)OTf (8). A 20-mL vial was charged with **10** (0.100 g, 0.176 mmol), *m*-xylene (0.5 mL), 10 mL CH_2Cl_2, and a stirbar. The reaction mixture was stirred at 25 °C for 20 h. The volatile materials were removed under vacuum. The orange solid was crystallized from a concentrated Et_2O solution at −35 °C to yield orange crystals (0.092 g, 80%). ^{1}H NMR (400 MHz): δ 6.95 (s, 2H, Ir−(3,5-C$_6$*H*$_3$(CH$_3$)$_2$)), 6.57 (s, 1H, Ir−(3,5-C$_6$*H*$_3$(CH$_3$)$_2$)), 2.20 (s, 6H, Ir−(3,4-C$_6$H$_3$(C*H*$_3$)$_2$)), 1.64 (d, 15H, $^4J_{P-H}$ = 1.6 Hz, C$_5$(C*H*$_3$)$_5$), 1.47 (d, 9H, $^2J_{P-H}$ = 8.8 Hz, P(C*H*$_3$)$_3$). ^{13}C{^{1}H} NMR: δ 146.1 (s, *i*-C$_6$H$_3$(CH$_3$)$_2$), 136.8 (s, *C*$_6$H$_3$(CH$_3$)$_2$), 134.2 (s, C$_6$H$_3$(*C*H$_3$)$_2$), 126.3 (s, *C*$_6$H$_3$(CH$_3$)$_2$), 93.4 (s, *C*$_5$(CH$_3$)$_5$), 21.4 (s, C$_6$H$_3$(*C*H$_3$)$_2$), 14.5 (d, $^1J_{P-C}$ = 50 Hz, P(*C*H$_3$)$_3$), 9.4 (s, C$_5$(*C*H$_3$)$_5$). ^{31}P{^{1}H} NMR: δ −24.5 (s). ^{19}F NMR: δ −78.0 (s). Anal. Calcd for $C_{22}H_{33}F_3IrO_3PS$: C, 40.17; H, 5.06. Found: C, 39.90; H, 5.20.

Synthesis of Cp*PMe$_3$Ir(3,5-C$_6$H$_3$(CH(CH$_3$)$_2$)$_2$)OTf (9). A 20-mL vial was charged with **10** (0.100 g, 0.176 mmol), 1,3-diisopropylbenzene (0.5 mL), 5 mL CH_2Cl_2, and a stirbar. The reaction mixture was stirred at 25 °C for 20 h. The volatile materials were removed under vacuum. The orange solid was crystallized from a concentrated Et_2O solution at −35 °C to yield orange crystals (0.028 g, 24%). ^{1}H NMR (400 MHz): δ 6.94 (s, 2H, Ir−(3,5-C$_6$*H*$_3$(CH(CH$_3$)$_2$)$_2$)), 6.59 (s, 1H, Ir−(3,5-C$_6$*H*$_3$(CH(CH$_3$)$_2$)$_2$)), 2.76 (s, 2H, J_{H-H} = 6.8 Hz, Ir−(3,5-C$_6$H$_3$-(C*H*(CH$_3$)$_2$)$_2$)), 1.63 (d, 15H, $^4J_{P-H}$ = 2.0 Hz, C$_5$(C*H*$_3$)$_5$), 1.47 (d, 9H, $^2J_{P-H}$ = 10.8 Hz, P(C*H*$_3$)$_3$), 1.20 (d, 12H, J_{H-H} = 6.8 Hz, Ir−(3,4-C$_6$H$_3$(CH(C*H*$_3$)$_2$)$_2$)). ^{13}C{^{1}H} NMR: δ 147.8 (s, *C*$_6$H$_3$(CH(CH$_3$)$_2$)$_2$), 145.5 (s, $^2J_{P-C}$ = 13.8 Hz, *i*-C$_6$H$_3$(CH(CH$_3$)$_2$)$_2$), 131.9 (s, *C*$_6$H$_3$(CH-(CH$_3$)$_2$)$_2$), 119.8 (s, *C*$_6$H$_3$(CH(CH$_3$)$_2$)$_2$), 93.5 (s, $^2J_{P-C}$ = 3.8 Hz, *C*$_5$(CH$_3$)$_5$), 34.6 (s, C$_6$H$_3$(*C*H(CH$_3$)$_2$)$_2$), 24.4 (s, C$_6$H$_3$(CH(*C*H$_3$)$_2$)$_2$), 14.7 (d, $^1J_{P-C}$ = 37.5 Hz, P(*C*H$_3$)$_3$), 9.5 (s, C$_5$(*C*H$_3$)$_5$). ^{31}P{^{1}H} NMR: δ −24.0 (s). ^{19}F NMR: δ −78.0 (s). Anal. Calcd for $C_{26}H_{41}F_3IrO_3PS$: C, 43.75; H, 5.79. Found: C, 43.39; H, 5.90.

Synthesis of Cp*PMe$_3$Ir(3,5-C$_6$H$_3$(C(CH$_3$)$_3$)$_2$)OTf (10). A 20-mL vial was charged with **10** (0.100 g, 0.176 mmol), 1,3-di-*tert*-butylbenzene (0.5 mL), 5 mL CH_2Cl_2, and a stirbar. The reaction mixture was stirred at 25 °C for 20 h. The volatile materials were removed under vacuum. The orange solid was crystallized from a concentrated Et_2O solution at −35 °C to yield orange crystals (0.086 g, 66%). ^{1}H NMR (400 MHz): δ 7.11 (s, 2H, Ir−(3,5-C$_6$*H*$_3$(C(CH$_3$)$_3$)$_2$)), 6.93 (s, 1H, Ir−(3,5-C$_6$*H*$_3$(C(CH$_3$)$_3$)$_2$)), 1.62 (d, 15H, $^4J_{P-H}$ = 1.6 Hz, C$_5$(C*H*$_3$)$_5$), 1.49 (d, 9H, $^2J_{P-H}$ = 10.4 Hz, P(C*H*$_3$)$_3$), 1.34 (s, 18H, Ir−(3,4-C$_6$H$_3$-(C(C*H*$_3$)$_3$)$_2$)). ^{13}C{^{1}H} NMR: δ 149.4 (s, *C*$_6$H$_3$(C(CH$_3$)$_3$)$_2$), 144.4 (d, $^2J_{P-C}$ = 14 Hz, *i*-C$_6$H$_3$(C(CH$_3$)$_3$)$_2$), 131.1 (s, *C*$_6$H$_3$(C(CH$_3$)$_3$)$_2$), 116.3 (s, *C*$_6$H$_3$(C(CH$_3$)$_3$)$_2$), 93.6 (s, $^2J_{P-C}$ = 3 Hz, *C*$_5$(CH$_3$)$_5$), 34.9 (s, C$_6$H$_3$-(*C*(CH$_3$)$_3$)$_2$), 31.8 (s, C$_6$H$_3$(C(*C*H$_3$)$_3$)$_2$), 14.8 (d, $^1J_{P-C}$ = 38 Hz, P(*C*H$_3$)$_3$), 9.5 (s, C$_5$(*C*H$_3$)$_5$). ^{31}P{^{1}H} NMR: δ −24.0 (s). ^{19}F NMR: δ −78.0 (s). Anal. Calcd for $C_{28}H_{45}F_3IrO_3PS$: C, 45.33; H, 6.11. Found: C, 44.97; H, 6.10.

Synthesis of Cp*PMe$_3$Ir(*o*-C$_6$H$_4$(CH$_3$))OTf (12). A 20-mL vial was charged with Cp*PMe$_3$Ir(*o*-C$_6$H$_4$(CH$_3$))Br (0.091 g, 0.157 mmol), AgOTf (0.048 g, 0.188 mmol), 3 mL Et_2O, 2 mL C_6H_6, and a stirbar. The reaction mixture was stirred in the dark at 25 °C for 20 h. The reaction mixture was filtered through Celite, and the volatile materials were removed under vacuum. The orange solid was crystallized from a concentrated Et_2O solution at −35 °C to yield orange crystals (0.091 g, 90%). ^{1}H NMR (400 MHz): δ 7.17 (d, 1H, J_{H-H} = 8.5 Hz, Ir−(*o*-C$_6$*H*$_4$(CH$_3$))), 7.08 (d, 1H, J_{H-H} = 6.8 Hz, Ir−(*o*-C$_6$*H*$_4$(CH$_3$))), 6.85 (m, 2H, Ir−(*o*-C$_6$*H*$_4$(CH$_3$))), 2.20 (s, 3H, Ir−(*o*-C$_6$H$_4$(C*H*$_3$))), 1.62 (d, 15H, $^4J_{P-H}$ = 2.0 Hz, C$_5$(C*H*$_3$)$_5$), 1.55 (d, 9H, $^2J_{P-H}$ = 10.4 Hz, P(C*H*$_3$)$_3$). ^{13}C{^{1}H} NMR: δ 148.1 (d, $^2J_{P-C}$ = 12.5 Hz, *i*-C$_6$H$_5$(CH$_3$)), 144.1 (s, (*C*$_6$H$_4$(CH$_3$))), 138.5 (d, *J* = 6.3 Hz, *C*$_6$H$_4$(CH$_3$)), 130.8 (s, (*C*$_6$H$_4$(CH$_3$))), 124.6 (s, *C*$_6$H$_4$(CH$_3$)), 123.5 (s, *C*$_6$H$_4$(CH$_3$)), 93.7 (s, $^2J_{P-C}$ = 3.8 Hz, *C*$_5$(CH$_3$)$_5$), 25.7 (s, C$_6$H$_4$(*C*H$_3$)), 14.9 (d, $^1J_{P-C}$ = 36.3 Hz, P(*C*H$_3$)$_3$), 9.8 (s, C$_5$(*C*H$_3$)$_5$). ^{31}P{^{1}H} NMR: δ −21.4 (s). ^{19}F NMR: δ −77.6 (s). Anal. Calcd for $C_{21}H_{31}F_3IrO_3PS$: C, 39.18; H, 4.85. Found: C, 38.84; H, 4.76.

Synthesis of Cp*PMe$_3$Ir(*m*-C$_6$H$_4$(CH$_3$))OTf (13). A 20-mL vial was charged with Cp*PMe$_3$Ir(*m*-C$_6$H$_4$(CH$_3$))Cl (0.262 g, 0.494 mmol), AgOTf (0.152 g, 0.593 mmol), 6 mL Et_2O, 4 mL C_6H_6, and a stirbar. The reaction mixture was stirred in the dark at 25 °C for 20 h. The reaction mixture was filtered through Celite, and the volatile materials were removed under vacuum. The orange solid was crystallized from a concentrated Et_2O solution at −35 °C to yield orange crystals (0.123 g, 32%). ^{1}H NMR (400 MHz): δ 7.13 (s, 1H, Ir−(*m*-C$_6$*H*$_4$(CH$_3$))), 7.06 (d, 1H, J_{H-H} = 7.6 Hz, Ir−(*m*-C$_6$*H*$_4$(CH$_3$))), 6.96 (t, 1H, J_{H-H} = 7.6 Hz, Ir−(*m*-C$_6$*H*$_4$(CH$_3$))), 6.76 (d, 1H, J_{H-H} = 7.2 Hz, Ir−(*m*-C$_6$*H*$_4$-(CH$_3$))), 2.24 (s, 3H, Ir−(*m*-C$_6$H$_4$(C*H*$_3$))), 1.63 (d, 15H, $^4J_{P-H}$ = 2.0 Hz, C$_5$(C*H*$_3$)$_5$), 1.48 (d, 9H, $^2J_{P-H}$ = 10.4 Hz, P(C*H*$_3$)$_3$). ^{13}C{^{1}H} NMR: δ 146.9 (d, $^2J_{P-C}$ = 13.8 Hz, *i*-C$_6$H$_4$(CH$_3$)), 137.5 (s, (*C*$_6$H$_4$-(CH$_3$))), 132.8 (s, *C*$_6$H$_4$(CH$_3$)), 128.1 (s, (*C*$_6$H$_4$(CH$_3$))), 127.1 (s, *C*$_6$H$_4$-(CH$_3$)), 123.3 (s, *C*$_6$H$_4$(CH$_3$)), 93.6 (s, $^2J_{P-C}$ = 2.5 Hz, *C*$_5$(CH$_3$)$_5$), 21.6 (s, C$_6$H$_4$(*C*H$_3$)), 14.6 (d, $^1J_{P-C}$ = 38.8 Hz, P(*C*H$_3$)$_3$), 9.5 (s, C$_5$(*C*H$_3$)$_5$). ^{31}P{^{1}H} NMR: δ −24.1 (s). ^{19}F NMR: δ −77.4 (s). Anal. Calcd for $C_{21}H_{31}F_3IrO_3PS$: C, 39.18; H, 4.85. Found: C, 39.52; H, 4.73.

Synthesis of Cp*PMe$_3$Ir(*p*-C$_6$H$_4$(CH$_3$))OTf (14). A 20-mL vial was charged with Cp*PMe$_3$Ir(*p*-C$_6$H$_4$(CH$_3$))Br (0.296 g, 0.512 mmol), AgOTf (0.158 g, 0.614 mmol), 6 mL Et_2O, 4 mL C_6H_6, and a stirbar. The reaction mixture was stirred in the dark at 25 °C for 20 h. The reaction mixture was filtered through Celite, and the volatile materials were removed under vacuum. The orange solid was crystallized from a concentrated Et_2O solution at −35 °C to yield orange crystals (0.252 g, 77%). ^{1}H NMR (400 MHz): δ 7.13 (d, 2H, J_{H-H} = 8.0 Hz, Ir−(*p*-C$_6$*H*$_4$(CH$_3$))), 6.91 (d, 2H, J_{H-H} = 7.5 Hz, Ir−(*p*-C$_6$*H*$_4$(CH$_3$))), 2.29 (s, 3H, Ir−(*p*-C$_6$H$_4$(C*H*$_3$))), 1.64 (d, 15H, $^4J_{P-H}$ = 2.0 Hz, C$_5$(C*H*$_3$)$_5$), 1.48 (d, 9H, $^2J_{P-H}$ = 11.0 Hz, P(*CH*$_3$)$_3$). ^{13}C{^{1}H} NMR: δ 141.8 (d, $^2J_{P-C}$ = 15.0 Hz, *i*- C$_6$H$_4$(CH$_3$)), 136.3 (s, (*C*$_6$H$_4$(CH$_3$))), 132.0 (s, *C*$_6$H$_4$-(CH$_3$)), 129.1 (s, (*C*$_6$H$_4$(CH$_3$))), 93.5 (s, $^2J_{P-C}$ = 3.8 Hz, *C*$_5$(CH$_3$)$_5$), 20.7 (s, C$_6$H$_4$(*C*H$_3$)), 14.6 (d, $^1J_{P-C}$ = 37.5 Hz, P(*C*H$_3$)$_3$), 9.5 (s,

$C_5(CH_3)_5$). $^{31}P\{^1H\}$ NMR: δ −25.7 (s). ^{19}F NMR: δ −76.6 (s). Anal. Calcd for $C_{21}H_{31}F_3IrO_3PS$: C, 39.18; H, 4.85. Found: C, 38.86; H, 4.87.

Synthesis of [Cp*PMe$_3$IrH(NC$_5$H$_5$)][OTf] (1-py). A sealable glass vessel was charged with **4** (0.100 g, 0.180 mmol), pyridine (0.071 g, 0.900 mmol), and 5 mL acetone. The reaction mixture was heated at 75 °C for 2 days, and then the volatile materials were removed under vacuum. The yellow oil was crystallized from CH_2Cl_2 and pentane at −35 °C to yield a yellow solid (0.093 g, 82%). ^1H NMR (400 MHz): δ 8.65 (d, 2H, J_{H-H} = 4.8 Hz, Ir−*o*-NC_5H_5), 7.89 (t, 1H, J_{H-H} = 8.0 Hz, Ir−*p*-NC_5H_5), 7.33 (dd, 2H, J_{H-H} = 8.0 Hz, J_{H-H} = 4.8 Hz, Ir−*m*-NC_5H_5), 1.83 (d, 15H, $^4J_{P-H}$ = 1.6 Hz, $C_5(CH_3)_5$), 1.48 (d, 9H, $^2J_{P-H}$ = 10.4 Hz, $P(CH_3)_3$), −14.02 (d, 1H, $^2J_{P-H}$ = 39 Hz, Ir-*H*). $^{13}C\{^1H\}$ NMR: δ 159.9 (br s, Ir−*o*-NC_5H_5), 138.7 (s, Ir−NC_5H_5), 128.1 (s, Ir−NC_5H_5), 93.7 (s, $^2J_{P-C}$ = 2.5 Hz, $C_5(CH_3)_5$), 17.8 (d, $^1J_{P-C}$ = 40 Hz, $P(CH_3)_3$), 10.1 (s, $C_5(CH_3)_5$). $^{31}P\{^1H\}$ NMR: δ −37.1 (s). ^{19}F NMR: δ −77.8 (s). Anal. Calcd for $C_{19}H_{30}F_3IrO_3PSN$: C, 36.07; H, 4.78; N, 2.21. Found: C, 36.30; H, 4.62; N, 2.31.

Reaction of Cp*PMe$_3$IrPh(OTf) with H$_2$ or D$_2$. A typical experiment was performed as follows: A NMR tube was charged with **5** (0.010 g, 0.016 mmol) and ∼0.5 mL CD_2Cl_2. The tube was fitted with a Cajon adaptor and removed from the glovebox. To the NMR tube reaction was added D_2 (600 Torr) on a high vacuum line, and the tube was flame sealed. The NMR tube was shaken vigorously for 30 s, resulting in a color change from orange to pale yellow. Deuterium incorporation into the organic substrate was determined by integration of the ^1H NMR spectrum and comparison to the organometallic-species Cp* and PMe_3 peaks. Deuterium incorporation was verified by ^2H NMR spectroscopy. After the reaction was completed, the tube was cracked open, and the solution was passed through a short plug of silica gel before GC−MS analysis was carried out to verify deuterium incorporation.

Reaction of Cp*PMe$_3$IrPh(OTf) with Silane. A typical experiment was performed as follows: A NMR tube was charged with **5** (0.010 g, 0.016 mmol), Et_3SiD (13 μL, 0.080 mmol), and ∼0.5 mL CD_2Cl_2. The tube was fitted with a Cajon adaptor, removed from the glovebox, and flame sealed under slight vacuum (600 Torr). The NMR tube was shaken vigorously for 30 s, resulting in a color change from orange to pale yellow. Deuterium incorporation into the organic substrate was determined by integration of the ^1H NMR spectrum and comparison to the organometallic-species Cp* and PMe_3 peaks. Deuterium incorporation was verified by ^2H NMR spectroscopy. After the reaction was completed, the tube was cracked open, and the solution was passed through a short plug of silica gel before GC−MS analysis was carried out to verify deuterium incorporation.

Reaction of Cp*PMe$_3$IrPh(OTf) with D$_2$ at Low Temperature. A typical experiment was performed as follows: A NMR tube was charged with **5** (0.010 g, 0.016 mmol) and ∼0.5 mL CD_2Cl_2. The tube was fitted with a Cajon adaptor, and then was removed from the glovebox. To the NMR tube reaction was added D_2 (600 Torr) on a high vacuum line at −78 °C, and the tube was flame sealed. The tube was kept at −78 °C before being placed in a precooled (−80 °C) NMR probe. No reaction was observed at this temperature, so the probe was warmed to −40 °C. Because the reaction was still slow, the sample was ejected and shaken for 15 s to transfer D_2 from the headspace into solution, initiating the exchange reaction. The tube was quickly returned to the precooled NMR probe, and further monitored. Cp*PMe_3IrH-(OTf): ^1H NMR (500 MHz, CD_2Cl_2, 233 K) δ 1.85 ($C_5(CH_3)_5$), 1.62 ($P(CH_3)_3$, overlap with Cp* signal of starting material), −11.03 (d, $^2J_{P-H}$ = 39 Hz, Ir-*H*).

Reaction of Cp*PMe$_3$IrPh(OTf) D$_2$ and Added CH$_3$CN. A typical experiment was performed as follows: A NMR tube was charged with **5** (0.010 g, 0.016 mmol), CH_3CN (164 μL of 0.487 M solution in CD_2Cl_2, 0.080 mmol), and ∼0.5 mL CD_2Cl_2. The tube was fitted with a Cajon adaptor and removed from the glovebox. To the NMR tube was added D_2 (600 Torr) on a high vacuum line, and the tube was flame sealed. The NMR tube was shaken vigorously for 30 s, and then heated at 45 °C for 4 days. Deuterium incorporation into the organic substrate was determined by integration of the ^1H NMR spectrum and compared to the organometallic species Cp* and PMe_3 peaks. The organometallic species **1-CH$_3$CN** could not be isolated due to its instability under vacuum. ^1H NMR (400 MHz): 2.62 (s, 3H, CH_3CN), 1.95 (d, 15H, $^4J_{P-H}$ = 1.9 Hz, $C_5(CH_3)_5$), 1.66 (d, 9H, $^2J_{P-H}$ = 11 Hz, $P(CH_3)_3$), −14.7 (d, 1H, $^2J_{P-H}$ = 37 Hz, Ir−*H*). $^{31}P\{^1H\}$ NMR: δ −38.7 (s).

General Procedure for Catalytic H/D Exchange Experiments. In a typical reaction, a NMR tube was charged with catalyst, substrate, solvent, and an external standard capillary tube loaded with 1,3,5-trimethoxybenzene in CD_2Cl_2.[37] The tube was fitted with a Cajon adaptor, and then brought out of the glovebox. The tube was flame sealed under slight vacuum (∼600 Torr) on a high vacuum line. The reaction mixture was heated to 135 °C, and was monitored by ^1H NMR specctroscopy.[37] Deuterium incorporation was verified by ^2H NMR spectroscopy. After the reaction was completed, the tube was cracked open, and the solution was passed through a short plug of silica gel before GC−MS analysis was carried out.

Catalytic H/D Exchange Experiments with Added Base. In a typical reaction, a NMR tube was charged with **4** (0.006 g, 0.0108 mmol), C_6H_6 (20 μL, 0.224 mmol), 2,6-lutidine (10 μL, 0.086 mmol), acetone-d_6 (∼0.5 mL), and an external standard capillary tube loaded with 1,3,5-trimethoxybenzene in CD_2Cl_2.[37] The tube was fitted with a Cajon adaptor, and then brought out of the glovebox. The tube was flame sealed under slight vacuum (∼600 Torr) on a high vacuum line. The reaction mixture was heated to 135 °C, and was monitored by ^1H NMR spectroscopy.[37]

Catalytic H/D Exchange Reaction with 18 and LutHOTf. A NMR tube was charged with **18** (0.005 g, 0.0123 mmol), C_6H_6 (20 μL, 0.224 mmol), 2,6-lutidinium triflate (0.0160 g, 0.062 mmol), acetone-d_6 (∼0.5 mL), and an external standard capillary tube loaded with 1,3,5-trimethoxybenzene in CD_2Cl_2.[37] The tube was fitted with a Cajon adaptor, and then brought out of the glovebox. The tube was flame sealed under slight vacuum (∼600 Torr) on a high vacuum line. The reaction mixture was heated to 75 °C, and was monitored by ^1H NMR spectroscopy.[37]

Reaction of 18 and LutHOTf to Generate 1-Lut. A sealable glass vessel was charged with **18** (0.100 g, 0.247 mmol), 2,6-lutidinium triflate (0.266 g, 1.03 mmol), and 5 mL acetone. The reaction mixture was heated at 75 °C for 2 days, and then the volatile materials were removed under vacuum. The yellow oil was extracted with CH_2Cl_2. Crystallization with CH_2Cl_2/pentane diffusion removed most of the excess LutHOTf, but a small amount of LutHOTf (∼10%) remained. Crude yield: 0.143 g (88%), >85% pure by ^1H NMR spectroscopy. ^1H NMR (400 MHz): δ 7.51 (s, 3H, 2,6-$(CH_3)_2(NC_5H_3)$), 2.40 (s, 6H, 2,6-$(CH_3)_2(NC_5H_3)$), 1.88 (d, 15H, $^4J_{P-H}$ = 1.9 Hz, $C_5(CH_3)_5$), 1.37 (d, 9H, $^2J_{P-H}$ = 10.4 Hz, $P(CH_3)_3$), −16.9 (d, 1H, $^2J_{P-H}$ = 35.2 Hz, Ir−*H*). $^{31}P\{^1H\}$ NMR: δ −42.7 (s).

Catalytic H/D exchange Experiments with Benzaldehyde. A NMR tube was charged with **4** (0.006 g, 0.0108 mmol), PhCHO (25 μL, 0.246 mmol), acetone-d_6 (∼0.5 mL), and an external standard capillary tube loaded with 1,3,5-trimethoxybenzene in CD_2Cl_2. [37]The tube was fitted to a Cajon adaptor, and then brought out of the glovebox. The tube was flame sealed under slight vacuum (∼600 Torr) on a high vacuum line. The reaction mixture was heated to 135 °C and monitored by ^1H NMR spectroscopy.[37] The organometallic species **16** has the following NMR spectral features (aryl protons have been deuterated): ^1H NMR (400 MHz, acetone-d_6): 2.03 (d, 15H, $^4J_{P-H}$ = 1.6 Hz, $C_5(CH_3)_5$), 1.79 (d, 9H, $^2J_{P-H}$ = 11.2 Hz, $P(CH_3)_3$). $^{31}P\{^1H\}$ NMR: δ −34.5 (s).The species **16** was prepared independently according to a literature procedure,[31] and its spectral features are as follows: ^1H NMR (400 MHz, acetone-d_6): 7.65 (m, 2H, Ir(C_6H_5)) 7.33 (m, 1H, Ir(C_6H_5)), 7.09 (m, 2H, Ir(C_6H_5)), 2.03 (d, 15H, $^4J_{P-H}$ = 1.6 Hz, $C_5(CH_3)_5$), 1.79 (d, 9H, $^2J_{P-H}$ = 11.2 Hz, $P(CH_3)_3$). $^{31}P\{^1H\}$ NMR: δ −34.5 (s).

Reaction of 4 with Acetone. A vial was charged with **4** (0.100 g, 0.247 mmol) and 5 mL of acetone. The mixture was allowed to stand at 25 °C for 20 h, during which time it turned from colorless to yellow. The volatile materials were removed under vacuum to yield an oil. The **1-acetone** could not be purified, as it is unstable in solution; it decomposed to **20** during all attempts to crystallize it. By ^{1}H NMR spectroscopy, it contains ∼30% impurities, including **20**. The spectral features assigned to **1-acetone** are the following: ^{1}H NMR (400 MHz): 2.12 (s, 6H, Ir(OC(C*H*$_3$)$_2$)), 2.03 (d, 15H, $^4J_{P-H}$ = 2.0 Hz, C$_5$(C*H*$_3$)$_5$), 1.62 (d, 9H, $^2J_{P-H}$ = 10 Hz, P(C*H*$_3$)$_3$), −15.3 (d, 1H, $^2J_{P-H}$ = 33.2 Hz, Ir-*H*). ^{31}P{^{1}H} NMR: δ −47.5 (s). The spectral features of **20** are the following: ^{1}H NMR (400 MHz): 8.41 (s, 1H, Ir(η^3-CH$_2$C(O*H*)CH$_2$), lit. 8.95), 3.28 (m, 2H, Ir(η^3-C*H*$_2$C(OH)C*H*$_2$), lit. 3.26), 1.88 (d, 15H, $^4J_{P-H}$ = 1.6 Hz, C$_5$(C*H*$_3$)$_5$, lit. 1.87), 1.71 (m, 2H, Ir(η^3-C*H*$_2$C(OH)C*H*$_2$), lit. 1.73), 1.50 (d, 9H, $^2J_{P-H}$ = 10 Hz, P(C*H*$_3$)$_3$, lit. 1.39). ^{31}P{^{1}H} NMR: δ −38.5 (s, lit. −36.0).

Reaction of 4 and CD$_3$OD. A NMR tube was charged with **4** (0.006 g, 0.0108 mmol), and ∼0.5 mL of CD$_3$OD. The tube was fitted with a Cajon adaptor, and then brought out of the glovebox. The tube was flame sealed under slight vacuum (∼600 Torr) on a high vacuum line. The reaction mixture was heated at 135 °C for 20 h. The volatile materials were removed under vacuum, the resulting yellow solid (NMR yield > 95%) was redissolved in CD_2Cl_2. ^{1}H NMR of **1-CO** (400 MHz): 2.22 (d, 15H, $^4J_{P-H}$ = 1.6 Hz, C$_5$(C*H*$_3$)$_5$, lit. ^{34}2.22), 1.87 (d, 9H, $^2J_{P-H}$ = 10 Hz, P(C*H*$_3$)$_3$, lit. 1.84), −15.3 (d, 1H, $^2J_{P-H}$ = 33.2 Hz, Ir−*H*, lit. −15.3). ^{31}P{^{1}H} NMR: δ −41.1 (s, lit. −39.1).

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