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Meta-substituent effects on organoiridium-catalyzed *ortho*-hydrogen isotope exchange

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Reports in the literature appear to differ on the effects of some C3 substituents on the relative efficiencies of isotope exchange in the nonidentical C2- and C6-positions catalyzed by organoiridium complexes. Controlled experiments were conducted using a set of model substrates in attempts to clarify these effects. The results clearly showed that, in common with most previous findings, alkyl substituents at C3 reduced the rate of isotope incorporation into C2 relative to C6, as expected on steric grounds. In contrast, all substituents possessing electron lone pairs resulted in a lessening of the inhibition of C2-vs-C6 labeling or promoted C2 labeling to such a degree that it became faster than that at C6. NMR measurements on equimolar mixtures of active iridium complex with selected substrates revealed that the ratios of C2- and C6-iridacycles present in solution correlated with the relative rates of *ortho*-deuteration in the rate studies. The results of the two studies, taken together, suggest that conventional explanations for the origin of the positive *meta*-effect may not be adequate for the present system. An alternative hypothesis is advanced.

Keywords: Ir-catalyzed *ortho*-hydrogen exchange; deuteration; directing effect

Introduction

Heteroatom-directed intramolecular aryl C–H activation (*ortho-metallation*) by transition metal complexes has been widely investigated in organometallic chemistry, developed for new selective C–C bond-forming reactions in synthetic chemistry, and applied to hydrogen isotope labeling. For the last, the report of the Crabtree group that the hydrogens of the methyl group of 8-methylquinoline and the N3-methyl group of caffeine are rapidly exchanged with deuterium gas in the presence of $[Ir(H)_2(acetone)_2(PPh_3)_2]BF_4$[1] inspired us[2,3] and others[4] to investigate this and related iridium complexes for their ability to catalyze regioselective isotopic exchange labeling of compounds from deuterium or tritium gas sources. Since then, a variety of complexes have been found to be effective in different compound types, and organoiridium-catalyzed heteroatom-directed hydrogen isotope exchange (HDE) has become a commonly used method for the preparation of a wide variety of tritium- and deuterium-labeled compounds, especially for use as tracers in the life sciences.[5]

In aromatic compounds, this labeling method introduces isotopic hydrogen into positions *ortho* to the directing group, probably via an iridacyclic intermediate formed by coordination of the iridium center with the directing group and oxidative addition to the *ortho* C–H bond.[6] In *meta*-substituted substrates, the two *ortho*-positions are nonequivalent, and literature reports of the labeling of such compounds are not entirely in agreement as to the influence of these substituents on labeling. Although all reports are consistent in showing that *meta*-substituents of the alkyl and aryl types are associated with lower or no labeling at C2 relative to C6, results reported for compounds whose *meta*-substituents possess electron lone pairs are not. Some reports[2,6] indicate that compounds possessing alkoxyl and halo substituents at C3 are labeled to a greater extent at C2 than at C6, but others[7] indicate greater labeling at C6, while yet others[8] suggest a lack of discrimination between C2 and C6 labeling in such substrates.

As the abovementioned isotope labeling studies differed from one another in their objectives, experimental designs and in the ways the data were interpreted, the reasons for the differing conclusions are obscure. Our objective was to clarify the issue by investigating the effects of a range of *meta* (C3)-substituents on the exchange of the nonequivalent *ortho*-positions (C2 and C6) in a selected set of substrates, under conditions where confounding variables were excluded to the extent practicable. Two experimental protocols were used: One was designed to permit direct measurement of the relative rates of C2 and C6 deuteration in substrates with different substituents at C3; the other was to permit observation of the relative amounts of the two isomeric iridacycle intermediates that are obligatory intermediates in the isotope exchange at C2 and C6, respectively.

Results

In the first series of experiments, we determined the deuterium content of C2 and C6 in each substrate at various time points during deuteration reactions by mixing the substrate and a catalytic amount (0.2–5%) iridium complex in an NMR tube, purging the solution for a few seconds with deuterium gas, then

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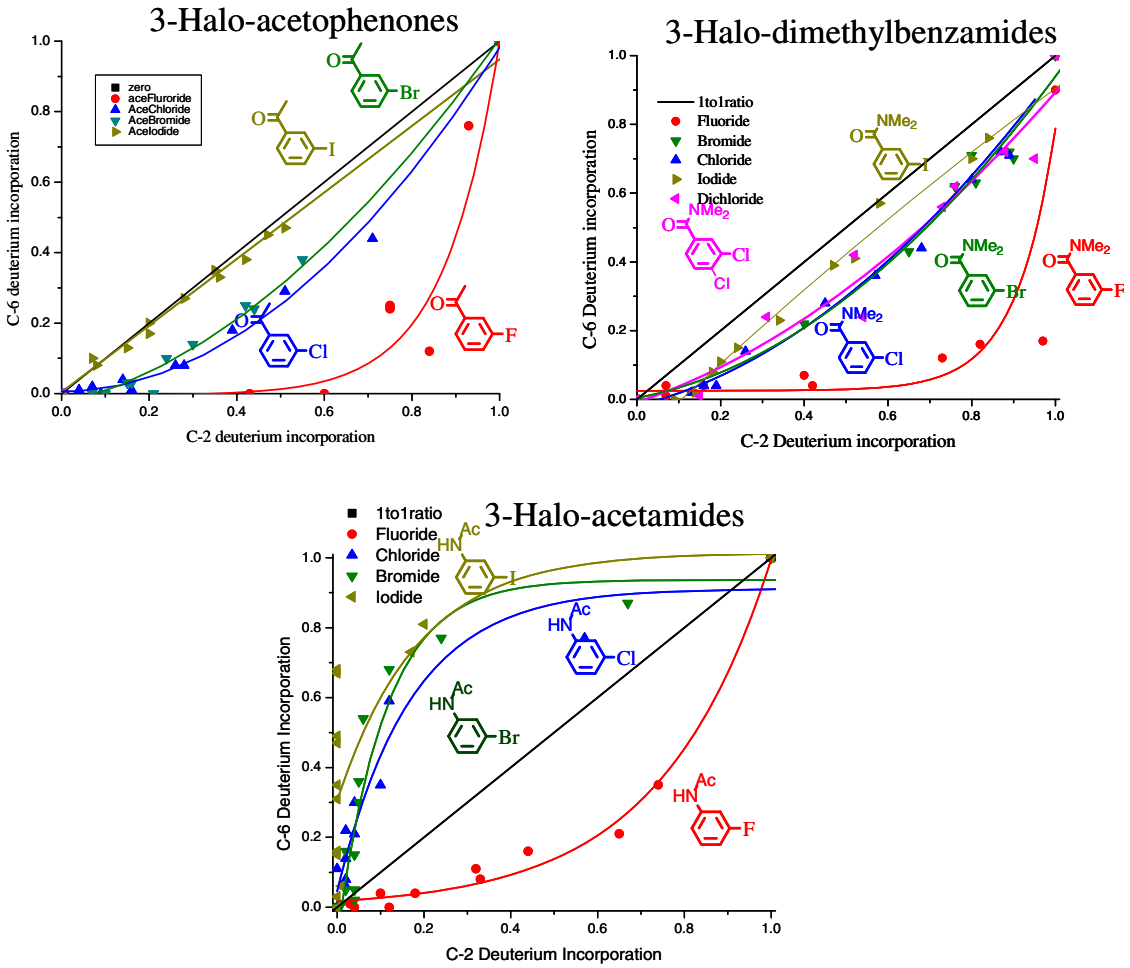
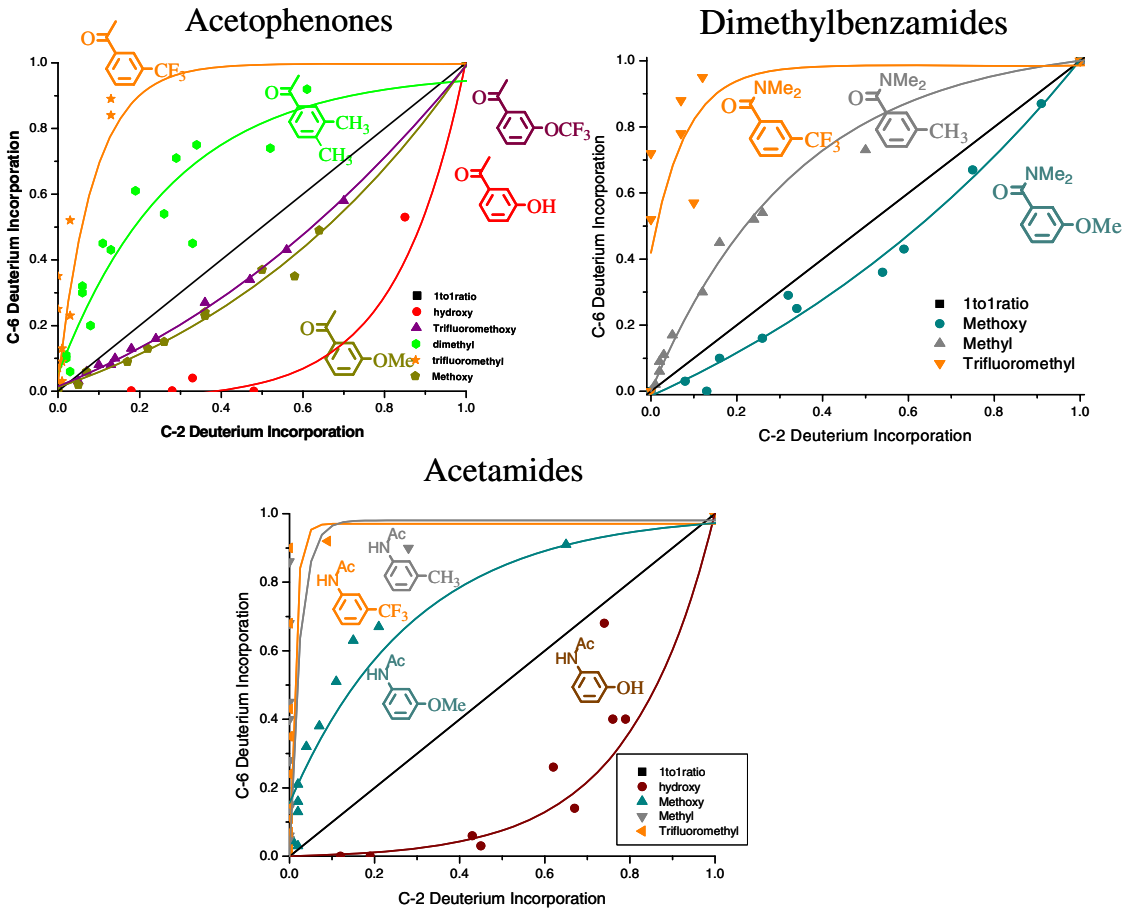
measuring the diminution of the ^{1}H NMR signals of C2 and C6 with time. As dichloromethane is the solvent of choice for such HDE reactions, we used CD_2Cl_2 as the solvent in most experiments in order to facilitate the NMR measurements. It has already been shown that, at least over the reaction times used here, hydrogen/deuterium from this solvent is not exchanged.[1,2] In cases where the NMR signals of interest were not resolved in CD_2Cl_2, reactions were run in CH_2Cl_2 and aliquots were withdrawn for NMR analysis (usually in $CDCl_3$ or D_6-DMSO). The complexes used in our study were the two most commonly used for HDE: $[(cod)Ir^{I}(PPh_3)_2]BF_4$ (**1**) and $[(cod)Ir^{I}(PCy_3)(py)]PF_6$ (**2**); they are reduced rapidly *in situ* by deuterium gas to produce the active catalyst forms $[Ir^{III(D)}{}_2S_2(PPh_3)_2]BF_4$ and $[Ir^{III}(D)_2S_2(PCy_3)(py)]PF_6$, respectively (S = loosely bound ligand such as solvent, substrate or adventitious water). Three substrate classes, typical of those commonly used as model substrates for HDE, were used: acetophenones, *N*,*N*-dimethylbenzamides and acetanilides. The *meta*-substituents included F, Cl, Br, I, CH_3 (or for acetophenone 3,4-dimethyl), CF_3, OCH_3, OH (for acetophenone and acetanilide) and OCF_3 (acetophenone only). In most cases, results from multiple experiments with the same substrate–catalyst combination were combined in order to give an adequate number of data points, as the rapid rate of exchange often permitted the acquisition of only a limited number of NMR measurements on a single sample.

The results are collected below in a set of graphs in which the extent of deuteration at C2 is plotted against the degree of deuteration at C6 at the same time point. In this way of presenting the data, identical rates of labeling C2 and C6 would give points along a straight line with slope = 1 (diagonal black line, added for reference). Faster labeling at C2 gives data points beneath the diagonal, and faster labeling at C6 above it. Curves were fitted to each substrate's data points using origin to calculate a curve using the non-linear best fit method. The farther a curve deviates from the diagonal and toward the corners, the greater the difference in the rate of exchange at the two sites. Thus, this mode of presentation gives a clear qualitative view of the results. The experimental procedure allows measurements of the progress of exchange in real time, and removes the effects of variables such as overall reaction rates, interexperimental differences in catalyst loading or quantity of deuterium gas and any confounding effects caused by ancillary sources of exchangeable hydrogen.

These graphs are immediately informative in several ways:

First, it is clear that in all three series, substrates with *meta*-CH_3 and -CF_3 undergo exchange at C2 much slower than at C6, and CF_3 has a stronger effect than CH_3. This behavior is consistent with expectations based on steric factors alone. Examination of the slopes of the curves from both substituents at early reaction stages shows that the rate of C6 deuteration is at least an order of magnitude faster than C2 deuteration.





Second, within each class of substrate, those with *meta*-substituents possessing electron lone pairs either undergo labeling at C2 *faster* than at C6, or the labeling at C2 is less retarded relative to that at C6 compared with those substituted with CH_3 and CF_3. This suggests the influence of a *meta*-effect opposing the steric effect.

Third, the positive effects of *meta*-substituents effects are most pronounced in the acetophenone series, less so in the dimethylbenzamide series and weakest in the acetanilide series.

Fourth, the rank order of substituent effects is similar for all three substrate classes. Their potency in facilitating C2 exchange increases in the order $I < Br < OCH_3$ (OCF_3) $\approx Cl < OH \approx F$. Where tested, OCF_3 is only slightly less potent than OCH_3. The effects of OH and F substituents are so strong that, as indicated by the slopes of the curves at early reaction stages, the rates of C2 deuteration are *faster* than those at C6 by at least an order of magnitude in the acetophenone and dimethylbenzamide series, and by a factor of at least five in the acetanilide series.

Data points acquired in comparable experiments with $[(cod)Ir(PPh_3)_2]BF_4$ (**1**) or $[(cod)Ir(PCy_3)(py)]PF_6$ (**2**) and acetophenone substrates possessing Cl, Br, I, OCH_3 and CF_3 fall nearly along the same curves: the two curves for 3-bromo-, 3-iodo- and 3-trifluoromethylacetophenone were indistinguishable from one another; those for 3-chloroacetophenone suggested that the effect with catalyst **2** was slightly greater than that with catalyst **1**, but those for 3-methoxyacetophenone were just the reverse. Therefore, data obtained with both catalysts are combined in the respective graphs.

In the second set of experiments, the fully deuterated precursor complex $[(cod)Ir\{P(C_6D_5)_3\}_2]BF_4$ (**3**) was used in order to permit unencumbered observation of the substrate-derived ^1H NMR signals in the aromatic region. Reaction mixtures consisting of 1:1 molar ratios of complex **3** and 3-fluoro-, 3-trifluoromethoxy-, 3-chloro- or 3-trifluoromethylacetophenone were stirred briefly under hydrogen gas to convert **3** into the active complex $[Ir(H)_2S_2\{P(C_6D_5)_3\}_2]BF_4$. ^1H and ^{19}F NMR analyses of reaction mixtures at this point showed only the signals of the intact *meta*-substituted acetophenone in the aromatic region. That is, the substrate was present as free compound or only coordinated to iridium at the carbonyl oxygen; all four ring-C–H signals were present and integrated as 1.0H in the spectra. The reaction mixtures were then briefly purged with nitrogen to remove H_2 and then heated at 80°C under a nitrogen atmosphere for 12 h. ^1H and ^{19}F NMR analyses of the crude reaction mixtures at this stage showed the presence of new signals, along with those of varying amounts of remaining intact *meta*-substituted acetophenone. In each case, complete assignments were made of the new NMR signals through the use of proton–proton couplings, Heteronuclear Multiple Quantum Coherence (HMQC) experiments and by comparison with the chemical shifts reported for the parent acetophenone iridacycle prepared by a similar method recently reported.[9] This allowed unambiguous identification of two iridacycles for each substrate, one fused to the acetophenone ring at C2 and the other at C6. A small peak at 7.5 ppm grew in

slowly with increasing reaction times but did not hinder data evaluation; this peak is attributed to slow exchange of H into the *ortho*-positions of the deuterated phosphine phenyl rings. The relative quantities of isomeric iridacycles obtained in these reactions are given in Table 1. These ratios of isomeric iridacycles correlate with the relative rates of C2-vs-C6 deuteration found for the same substrates in the first set of experiments.

Reexposure of solutions of these iridacycle mixtures to hydrogen and stirring for 10–90 min at room temperature (rt) converted them entirely, within the limits of NMR detection, back to the intact *meta*-substituted acetophenone form(s) (see also Reference 5).

Table 1. Ratio of Iridacycles formed with metasubstituted acetophenones

m-X-acetophenone	Ratio of C2/C6 iridacycles
Fluoro	5:1
Trifluoromethoxy	1.3:1
Chloro	1.6:1
Trifluoromethyl	1:>10

Discussion

The competing pathways to deuterium labeling at C2 and C6 can be depicted as shown in Figure 1. First, the carbonyl oxygen of the directing function (acetyl, dimethylaminocarbonyl or benzoyl) of the substrate (**4**) coordinates to the iridium center (step 1) to form intermediate **5**. Then, iridium oxidatively adds to the C2–H or the C6–H bond, cleaving it to form either an $\eta^2_{O,C2}$ metallacycle (**6a**) or an $\eta^2_{O,C6}$ metallacycle (**6b**). Subsequent ligand isomerization around the Ir(III) center rotates the C2- or C6-derived H out of the orientation *cis* to the Ir–C bond and replaces it with a D (**7a,b**). Finally, reductive elimination of iridium forms a C2–D or a C6–D bond, thence eventually free deuterium-labeled substrate [2-^{2}H]**4** or [6-^{2}H]**4**. Except for the presence of the isotope, steps 4a and 4b are the same in reverse as 2a and 2b, respectively, and decoordination steps 5a and 5b are the same in reverse as the first step.

The findings here of the retardation of C2 labeling in substrates with C3-methyl and -trifluoromethyl substituents are consistent with a large number of published observations, both in HDE and in related organometallic reactions, and are generally agreed to occur because the steric bulk of these

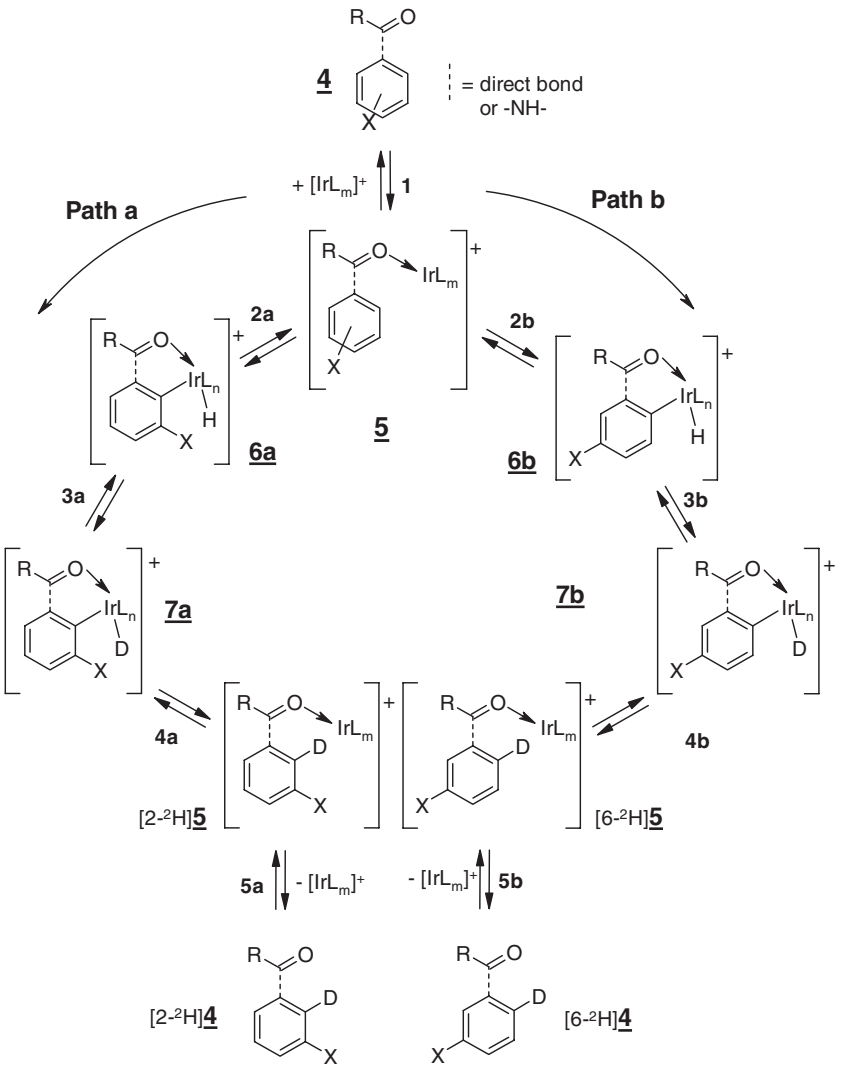


Figure 1. Proposed mechanistic routes leading to 2- and 6- deuterated products

substituents increases the congestion that occurs with the approach of the iridium center to the C2–H bond, thereby raising the activation energy of the metallacyclization. In the present system this diverts the labeling process from **Path a** to **Path b** of Figure 1 to give mainly C6-labeled product. Our data further show that the C3 halo and oxygen-containing substituents exert an opposite effect, partially or entirely offsetting the steric effect and toward **Path a**, and in some cases overriding it to make **Path a** predominant.

Positive *meta*-substituent effects such as these have been observed in a few other systems but have not been thoroughly investigated mechanistically.[10] A further example that is somewhat related to the present HDE system is the Murai chemistry,[11] in which silylolefins add to aromatic ketone substrates to give exclusively *ortho*-(silyl)alkyl products. This is illustrated in Figure 2 for a typical reaction between acetophenone and triethoxysilylethene catalyzed by $RuH_2(CO)(PPh_3)_3$. Most *meta*-substituents tested give addition only at C6, in accordance with expected effect of the higher steric congestion around C2. However, 3-fluoroacetophenone is preferentially alkylated at C2 (77:3 vs C6) and so is 3-methoxyacetophenone (83:10). No other halo derivatives were reported on. The rationale tentatively advanced was that this phenomenon results from (undefined) electronic interactions between ruthenium and the lone pair of electrons on the methoxy oxygen or the fluorine atom. In the Murai chemistry the rate-determining step is the carbon–carbon bond formation between the olefin and the aryl ring,[11] and cyclometallation is fast. Therefore, if it is true that electronic interaction between ruthenium and the *meta*-substituent facilitates substitution at C2, it must do so either by lowering the activation energy for the C_{alkyl}–$C2_{aryl}$ bond-formation step (relative to C_{alkyl}–$C6_{aryl}$ bond formation) or by providing thermodynamic stabilization of the $\eta^2_{O,C2}$ ruthenacycle (**7**) (relative to the $\eta^2_{O,C6}$ ruthenacycle, **6**) in a rapid preequilibrium.

The Orito group[12] revealed that some coordinating *meta*-functions exert moderate positive effects in the palladium-catalyzed carbonylation–cyclization of *N*-substituted benzylamines and phenethylamines ($Pd(OAc)_2$, $Cu(OAc)_2$, CO; Figure 3). The 3,4-methylenedioxy substituent was the most effective and the only substituent that gave predominately C2 products. This positive effect was stronger in the phenethylamine case (Y = $-CH_2CH_2-$, where the palladacyclic intermediate is a six-membered ring) than in the benzylamine case (Y = $-CH_2-$; five-membered palladacycle); this is the reverse of our findings, where the positive *meta*-effects in the acetanilide series (six-membered iridacycles) are weaker than in the other two series (five-membered iridacycles). The explanation offered by the Orito group is that chelation occurs between the C3-oxygen of 3,4-methylenedioxy group and the palladium(II) center during the transition state of the metallacycle ring closure at C2 (i.e. **8** → **9**). The fact that the 3-methoxy group of the 3,4-dimethoxy

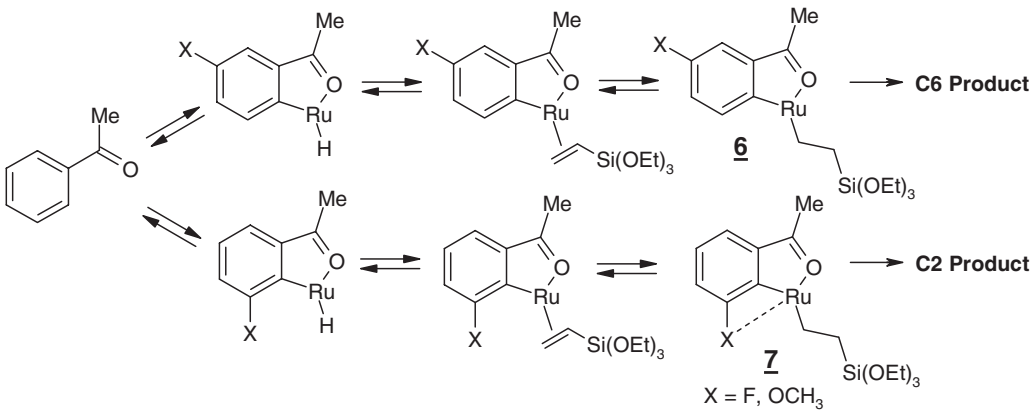


Figure 2. Murai ortho-substitution of 3-substituted acetophenones catalyzed by $RuH_2(CO)(PPh_3)_3$

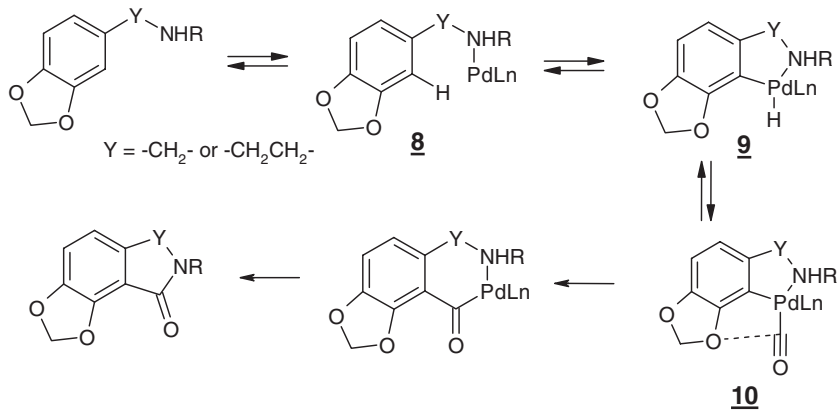


Figure 3. Meta effect on the palladiumcatalyzed carbonylation-cyclization of *N*-substituted benzylamines and phenethylamines with $Pd(OAc)_2$, $Cu(OAc)_2$, and CO

analog was not as effective in this role was attributed to its greater steric demand relative to methylenedioxy. However, in a separate set of experiments with the dimethoxy substrate, the rank order of C2/C6 product ratios obtained by varying the added ligand was in the order $PPh_3 > Cu(OAc)_2 >$ none. This trend is the reverse of that predicted by the explanation based on steric congestion. As no mechanistic analysis was presented for the overall transformation, the *meta*-effect in the Orito system may in reality be expressed in a different way or in another step. One possibility would be by assisting the migratory insertion of the carbonyl (electronic interaction indicated by the dotted line in structure **10**).

Recent reports that are highly relevant to our mechanistic speculations, but that highlight a more fundamental problem, are the selective *ortho* C–H activation of haloarenes and anisole by an iridium(I) complex.[13] In this chemistry, complex **11** reacts directly with the substrates to give the aryl hydrido complexes **12** (Figure 4).

After 1-h reaction times, mixtures of *ortho*-, *meta*- and *para*-halo or -methoxy complexes are observed, and after 24–48 h, most of the mixtures equilibrate toward the *ortho* isomer, whose substituent is coordinated to the iridium center (**13**). Table 2 summarizes the Milstein results.

These results clearly establish that the Kinetically preferred products are determined by the coordinative affinity of the iridium center with the aryl substituent. The order of affinity is $OCH_3 > Br > Cl > F$. This trend is in agreement with the earlier reported stability of *ortho*-haloaryl ligands of iridium complexes.[14] It is also consistent with predictions, based on C-halogen bond polarizabilities and σ-donor capacity, that the order of decreasing coordinative avidity toward a low-valent, late transition metal center such as Ir(I) should be $I > Br > Cl > F$.[15]

This is the *opposite* of the order of the power of halogens to facilitate C2-deuterium exchange in our studies, a serious problem for the hypothesis that direct coordination between *meta*-substituents and the iridium center can explain the positive *meta*-effects of these substituents.

The rate-determining step in our HDE sequence can be proposed with some degree of confidence. Initial coordination of substrates' directing atoms to iridium (**4** → **5** in Figure 1) is common to both **Paths a** and **b**, and the decoordination (labeled as **5a,b** → labeled as **4a,b**) is very *unlikely* to be the rate-determining step as it is rapid and reversible. The ligand isomerization step (**6a,6b** → **7a,7b**) is also unlikely to be rate-determining, as such rearrangements have been shown[16] to have low activation energies (< 5 kcal/mol). Our second set of experiments shows that the metallacycle forms (**6a**,**b** and **7a**,**b**) are thermodynamically less stable than the ring-opened forms (**5**). This conclusion comes from the fact that in the presence of H_2 the ring-opened forms predominate, and only upon removal of hydrogen and heating do the ring-closed forms predominate (Figure 5; see also Reference5). Therefore, it is likely that the ring closure (**5a** → **6a** and **5b** → **6b** in Figure 1) is rate-determining, and is the step through which the influence of *meta*-substituents is exerted on the relative rates of C2 and C6 deuteration. Once the **6a,b** structures are reached, either they revert to **5a,b** or proceed rapidly to isotopically labeled products.

How do OH, OCH_3, OCF_3, F, Cl, Br and I functions at C3 facilitate the iridacyclization of **5** to **6**? No conventional explanations seem to be able to account for our findings. If the effect involves coordination of the substituent lone electron pairs to the iridium center during iridacyclization, the order of potency should be very different from that observed, as discussed above. If it instead involves an inductive influence of the substituent, OCF_3 and CF_3 would be expected to produce C2/C6 deuteration ratios greater than OCH_3 and CH_3, respectively, but the opposite is found. Nor does an examination of mesomeric forms provide a credible explanation.

An alternative and novel possibility is that the influence of the coordinating *meta*-substituents might be exerted through intermediary atoms. Likely candidates for such a role are water and (isotopic) dihydrogen. Water (small amounts of which are always present adventitiously) is known to be a ligand in organoiridium complexes such as these.[17] The Crabtree group has reported[18] on new types of intramolecular hydrogen bonds in iridium complexes and associated hydrogen transfers involving such intermediaries, i.e. $Ir^{\delta+} \cdots H^{\delta-} \cdots H^{\delta+} \cdots X^{\delta-}$, where X is N or O. Either water or (isotopic) dihydrogen could play such a role in our system, as illustrated in Figure 6. Supporting these possibilities for indirect electronic interaction is the fact that H···halogen bond strengths increase in the order $I < Br < Cl < F$.

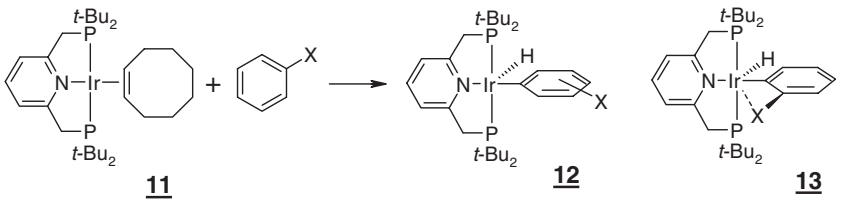


Figure 4. Insertion of Ir-complex 13 into Aryl C-H bond

Table 2.

	1 h			24–48 h		
	Ortho	*Meta*	*Para*	*Ortho*	*Meta*	*Para*
OCH_3	28	~1	~1	All	—	—
Br	7	2	1	All	—	—
Cl	4.6	2	1	All	—	—
F	2	2	1	1.8	—	1

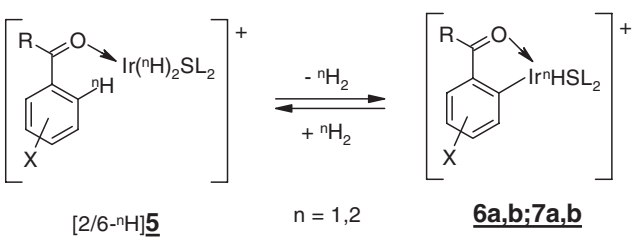


Figure 5. Proposed rate determining step in the HDE reaction

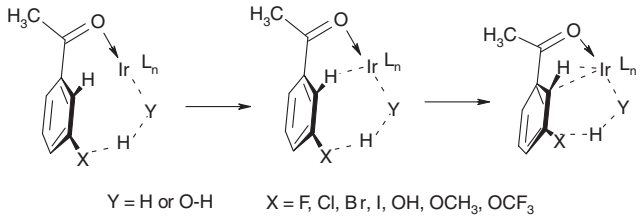


Figure 6. Proposed hydrogen bonding effect leading to a preference of ortho exchange in some substrates.

This is the only parameter that trends in the same direction as the observed effects of the substituents.

Experimental

General: *N*-(3-methylphenyl)acetamide, *N*-(3-trifluoromethylphenyl)-acetamide, *N*-(3-chlorophenyl)acetamide, *N*-(3-methoxyphenyl)acetamide, *N*-(3-bromophenyl)acetamide and *N*-(3-iodophenyl)acetamide were prepared in one step from the corresponding anilines. $[(cod)Ir(PCy_3)(py)]PF_6$ (Crabtree's catalyst) was obtained from Strem Chemical Company. $[(cod)Ir^{I}(PPh_3)_2]BF_4$ was prepared from $[(cod)Ir^{I}Cl]_2$ by treatment with PPh_3 as reported by Singleton.[19] Dichloromethane was obtained from Fisher Scientific and was used directly in reactions. Deuterium gas (ultrahigh purity, 99.95% D_2) was obtained from GT&S gas. The aromatic proton chemical shifts were assigned using a combination of NOESY and COSY. ^{1}H NMR spectra were recorded on an Avance 500 spectrometer and were referenced to residual solvent peak (7.26 for $CDCl_3$, 5.32 for CH_2Cl_2, 2.49 for D_6-DMSO and 7.20 for D_6-benzene). ^{19}F NMR were recorded on an Avance 500 spectrometer and were referenced externally to $CFCl_3$ (0 ppm).

Method A: *N, N-dimethyl 3-fluorobenzamide*: To a solution of 1.01 mg (6.0 μmol) of *N, N*-dimethyl 3-fluorobenzamide in 1 mL of CD_2Cl_2 in an NMR tube was added 16 μg (0.020 μmol) of Crabtree's catalyst in 20 μL of CD_2Cl_2. The solution was gently purged with D_2 for approx. 10 s, and the NMR tube capped. The tube was rocked back and forth 5 times and the ^{1}H NMR was taken immediately. A solution of 33 μg of Crabtree's catalyst in 40 μL of CD_2Cl_2 was added to the NMR tube and the solution purged with D_2 for approx. 10 s. The NMR tube was rocked gently back and forth and the ^{1}H NMR taken immediately. Additional aliquots of 50 and 67 μg in 60 and 80 μL of CD_2Cl_2, respectively, were added and the procedure repeated. For run B, 2.70 mg (16.3 μmol) of *N, N*-dimethyl 3-fluorobenzamide was treated as described above with four aliquots of Crabtree's catalyst (0.640, 1.4, 1.0 and 6.7 mg). ^{1}H NMR (500 MHz, CD_2Cl_2) δ ppm 2.97 (br. s., 3H), 3.09 (br. s., 3H), 7.12 (m, 2H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.37 (td, *J* = 7.9, 5.6 Hz, 1H).

		Run A				Run B			
	ppm	1	2	3	4	1	2	3	4
H-2	7.12	0.93	0.84	0.6	0.27	0.58	0.18	0.03	0
H-6	7.19	0.99	0.96	0.93	0.88	0.96	0.84	0.83	0.1

Method B: *N-(3-hydroxyphenyl)acetamide*: A solution of 8.74 mg (57.8 μmol) of *N*-(3-hydroxyphenyl)acetamide and 0.206 mg (0.256 μmol) of Crabtree's catalyst in 9 mL of CH_2Cl_2 was purged with D_2 for approx. 15 s and the vial was capped and rocked back and forth 5 times. After standing for 15 min, 0.5 mL was removed, concentrated to near dryness and a ^{1}H NMR was acquired on the residue. To the bulk material was added 0.206 mg (0.256 μmol) of Crabtree's catalyst and the solution purged with D_2 for approx. 15 s. The vial was capped and gently rocked back and forth 5 times. After standing for 15 min, 0.5 mL was removed, concentrated to near dryness and a ^{1}H NMR was acquired on the residue. This procedure was repeated with additions of 0.412 mg (0.512 μmol) and 0.825 mg (1.024 μmol) of Crabtree's catalyst. ^{1}H NMR (500 MHz, D_6-DMSO) δ ppm 2.01 (s, 3H), 6.41 (dd, *J* = 7.9, 1.8 Hz, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 7.03 (t, *J* = 7.9 Hz, 1H), 7.17(s, 1H), 9.73 (br. s., 1H), 9.27 (br. s., 1H).

		Run A					Run B				
	ppm	1	2	3	4	5	1	2	3	4	5
H-2	7.17	0.88	0.57	0.38	0.24	0.26	1.0	0.81	0.55	0.33	0.21
H-6	6.91	1.0	0.94	0.74	0.6	0.32	1.0	1.0	0.97	0.86	0.60

N-(3-fluorophenyl)acetamide: A total of 11.96 mg (0.0781 mmol) of *N*-(3-fluorophenyl)acetamide in 6 mL of CH_2Cl_2 was treated as described in method B with 0.206, 0.206, 1.24 and 1.24 mg of Crabtree's catalyst for run A and with 0.206, 0.412, 0.825, 1.65 and 2.27 mg of Crabtree's catalyst for run B. ^{1}H NMR (500 MHz, D_6-DMSO) δ ppm 2.05 (s, 3H), 6.84 (dt, *J* = 1.8, 8.2 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 1H), 7.31 (dt, *J* = 8.2, 6.7 Hz, 1H), 7.58 (d, *J* = 11.9 Hz, 1H), 10.10 (br. s., 1H).

		Run A						Run B				
	ppm	0	1	2	3	4	5	1	2	3	4	5
H-2	7.58	1.00	0.97	0.90	0.82	0.67	0.35	0.96	0.88	0.68	0.56	0.26
H-6	7.26	1.00	1.00	0.97	0.97	0.93	0.80	1.01	1.01	0.90	0.85	0.65

N-(3-methylphenyl)acetamide: A total of 9.84 mg (0.066 mmol) of *N*-(3-methylphenyl)acetamide in 6 mL of CH_2Cl_2 was treated as described in method B with 0.197, 0.295, 0.590 and 0.982 mg of Crabtree's catalyst for run A and 0.532, 1.064, 2.128, 4.256 and 15.623 mg of Crabtree's catalyst for run B. ^{1}H NMR (500 MHz, D_6-DMSO) δ ppm 2.02 (s, 3H), 2.26 (s, 3H), 6.83 (d, *J* = 7.6 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.40 (s, 1H), 9.79 (br. s., 1H).

		Run A						Run B					
	ppm	0	1	2	3	4	5	1	2	3	4	5	6
H-2	7.40	1.00	1.03	1.03	1.04	1.03	1.03	0.99	1.02	1.06	1.09	1.06	0.72
H-6	7.35	1.00	0.95	0.94	0.85	0.72	0.55	0.86	0.72	0.60	0.32	0.14	0.10

N-(3-trifluoromethylphenyl)acetamide: A total of 11.003 mg (0.054 mmol) of *N*-(3-trifluoromethylphenyl)acetamide in 6 mL of CH_2Cl_2 was treated as described in method B with 0.197, 0.295, 0.295, 0.590 and 0.982 mg of Crabtree's catalyst for run A and 0.532, 1.064, 2.128, 4.256 and 10.3 mg of Crabtree's catalyst for run B. ^{1}H NMR (500 MHz, D_6-DMSO) δ ppm 2.08 (s, 3H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 8.07 (s, 1H), 10.23 (br. s., 1H).

		Run A					Run B				
	ppm	1	2	3	4	5	1	2	3	4	5
H-2	8.07	0.98	0.99	1.00	1.01	1.03	1.00	1.01	1.03	1.03	1.03
H-6	7.76	0.98	0.93	0.85	0.76	0.65	0.89	0.76	0.57	0.32	0.10

N-(3-chlorophenyl)acetamide: A total of 10.05 mg (0.059 mmol) of *N*-(3-chlorophenyl)acetamide in 6 mL of CH_2Cl_2 was treated as described in method B with 0.197, 0.295, 0.590 and 0.982 mg of Crabtree's catalyst for run A and 0.532, 1.064, 2.128 and 4.256 mg of Crabtree's catalyst for run B. ^{1}H NMR (500 MHz, D_6-DMSO) δ ppm 2.05 (s, 3H), 7.07 (d, J = 7.6 Hz, 1H), 7.31 (t, J = 8.1 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.80 (s, 1H), 10.08 (br. s., 1H).

		Run A					Run B				
	ppm	1	2	3	4	5	1	2	3	4	5
H-2	7.80	0.98	0.98	0.98	0.96	0.90	1.00	0.98	0.96	0.88	0.43
H-6	7.41	0.94	0.92	0.86	0.79	0.65	0.89	0.78	0.70	0.41	0.23

N-(3-methoxyphenyl)acetamide: A total of 8.35 mg (0.051 mmol) of *N*-(3-methoxyphenyl)acetamide in 6 mL of CH_2Cl_2 was treated as described in method B with 0.197, 0.298, 0.590 and 0.982 mg of Crabtree's catalyst for run A and 0.197, 1.064, 1.064, 2.128 and 4.312 mg of Crabtree's catalyst for run B. ^{1}H NMR (500 MHz, D_6-DMSO) δ ppm 2.03 (s, 3H), 3.72 (s, 3H), 6.60 (dd, J = 8.2, 1.8 Hz, 1H), 7.10 (d, J = 8.2 Hz, 1H), 7.18 (t, J = 8.1 Hz, 1H), 7.28 (s, 1H), 9.86 (br. s., 1H).

		Run A					Run B					
	ppm	1	2	3	4	5	1	2	3	4	5	6
H-2	7.28	0.98	0.98	0.98	0.96	0.85	0.99	0.98	0.93	0.89	0.79	0.35
H-6	7.10	0.97	0.87	0.84	0.68	0.37	0.96	0.79	0.62	0.49	0.33	0.09

N-(3-bromophenyl)acetamide: A total of 7.7 mg of *N*-(3-bromophenyl)acetamide in 6 mL of CH_2Cl_2 was treated as described in method B with 0.187, 0.374, 0.748, 1.496, 1.87 and 2.9 mg of Crabtree's catalyst. ^{1}H NMR (500 MHz, D_6-DMSO) δ ppm 2.05 (s, 3H), 7.23 (d, J = 8.2 Hz, 1H), 7.25 (t, J = 8.1 Hz, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.93 (s, 1H), 10.06 (br. s., 1H).

		Run A						Run B					
	ppm	1	2	3	4	5	6	1	2	3	4	5	6
H-2	7.93	0.96	0.96	0.98	0.95	0.88	0.33	0.99	0.98	0.96	0.95	0.94	0.76
H-6	7.45	0.98	0.95	0.84	0.64	0.32	0.13	0.99	0.95	0.85	0.70	0.46	0.23

N-(3-iodophenyl)acetamide: A total of 8.30 mg (31.7 mmol) of *N*-(3-iodophenyl)acetamide in 6 mL of CH_2Cl_2 was treated as described in method B with 0.187, 0.374, 0.748, 1.496, 1.87 and 5.2 mg (10.1 mg for run B) of Crabtree's catalyst. ^{1}H NMR (500 MHz, D_6-DMSO) δ ppm 2.03 (s, 3H), 7.09 (t, J = 7.9 Hz, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 7.3 Hz, 1H), 8.08 (s, 1H), 9.98 (br. s., 1H).

		Run A						Run B					
	ppm	1	2	3	4	5	6	1	2	3	4	5	6
H-2	8.08	0.99	0.98	0.99	1.00	1.02	0.79	0.98	0.98	1.00	1.01	0.99	0.82
H-6	7.49	0.94	0.84	0.65	0.81	0.32	0.19	0.97	0.85	0.69	0.53	0.33	0.27

N, N-dimethyl 3-iodobenzamide: A total of 10.95 mg (39.8 μmol) of *N*, *N*-dimethyl 3-iodobenzamide in 6 mL of CH_2Cl_2 was treated as described in method B with five 0.433 mg additions of Crabtree's catalyst for run A and five 0.862 mg additions of Crabtree's catalyst for run B. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.88 (br. s., 3H), 2.96 (br. s., 3H), 7.24 (t, J = 7.8 Hz, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.73 (s, 1H), 7.80 (d, J = 7.9 Hz, 1H).

		Run A						Run B				
	ppm	1	2	3	4	5	6	1	2	3	4	5
H-2	7.73	0.91	0.86	0.82	0.76	0.66	0.48	0.8	0.53	0.42	0.20	0.16
H-6	7.41	1.0	0.98	0.92	0.85	0.77	0.59	0.89	0.61	0.43	0.30	0.24

N, N-dimethyl 3-trifluoromethylbenzamide: A total of 11.05 mg (50.9 μmol) of *N*, *N*-dimethyl 3-trifluoromethylbenzamide in 6 mL of CH_2Cl_2 was treated as described in method B with 0.090, 0.18, 0.18, 0.54, 0.90 and 0.90 mg of Crabtree's catalyst for run A and 0.045, 0.090, 0.090, 0.18, 0.18 and 1.8 mg of Crabtree's catalyst for run B. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.98 (br. s., 3H), 3.13 (br. s., 3H), 7.54 (t, J = 7.8 Hz, 1H), 7.61(d, J = 7.8 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.69 (s, 1H).

		Run A						Run B					
	ppm	1	2	3	4	5	6	1	2	3	4	5	6
H-2	7.69	1.00	1.00	1.00	1.00	1.00	0.96	1.00	1.00	1.00	1.00	1.00	0.89
H-6	7.61	0.99	0.96	0.86	0.75	0.61	0.18	0.99	0.98	0.96	0.89	0.67	0.20

N, N-dimethyl 3-methylbenzamide: A total of 7.10 mg (43.5 μmol) of *N*, *N*-dimethyl 3-methylbenzamide in 6 mL of CH_2Cl_2 was treated as described in method B with four aliquots of 0.433 mg of Crabtree's catalyst for run A and three aliquots of 0.862 mg and one of 1.72 mg of Crabtree's catalyst for run B. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.33 (s, 3H), 2.89 (br. s., 3H), 2.96 (br. s., 3H), 7.16 (d, J = 7.6 Hz, 1H), 7.19 (s, 1H), 7.24 (d, J = 7.3 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H).

		Run A						Run B			
	ppm	1	2	3	4	5	6	1	2	3	4
H-2	7.19	0.99	0.98	0.97	0.95	0.88	0.76	0.98	0.84	0.74	0.50
H-6	7.16	0.98	0.91	0.89	0.83	0.70	0.48	0.94	0.55	0.46	0.27

N, N-dimethyl 3-methoxybenzamide: A total of 1.703 mg (9.5 μmol) of *N*, *N*-dimethyl 3-methoxybenzamide in 0.75 mL of CD_2Cl_2 was treated as described in method B with 0.108, 0.138, 0.110, 0.087 and 0.119 mg of Crabtree's catalyst for run A and 2.188 mg (12.2 mmol) of *N*, *N*-dimethyl 3-methoxylbenzamide with 0.250, 0.375, 0.500, 0.750 and 1.0 mg of Crabtree's catalyst. ^{1}H NMR (500 MHz, D_6-DMSO) δ ppm 2.89 (br. s., 3H), 2.98 (br. s., 3H), 3.77 (s, 3H), 6.92 (d, J = 2.1 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 6.96 (dd, J = 8.2, 2.4 Hz, 1H), 7.34 (t, J = 7.9 Hz, 1H).

		Run A					Run B				
	ppm	1	2	3	4	5	1	2	3	4	5
H-2	6.92	0.87	0.92	0.74	0.68	0.46	0.84	0.66	0.41	0.25	0.09
H-6	6.93	1.0	0.97	0.84	0.71	0.64	0.90	0.75	0.57	0.33	0.13

N, N-dimethyl 3-bromobenzamide: A total of 2.23 mg (9.8 μmol) of *N*, *N*-dimethyl 3-bromobenzamide and 0.826 mg (3.5 μmol) of 2, 6-di-*t*-butylmethoxyphenol in 0.75 mL of CD_2Cl_2 were treated

as described in method A with 0.517, 0.471 and 0.953 mg of Crabtree's catalyst for run A and 2.26 mg (9.9 μmol) of *N, N*-dimethyl 3-bromobenzamide and 0.971 mg (4.1 μmol)of 2, 6-di-*t*-butylmethoxyphenol with 0.423, 0.517, 0.634 and 1.52 mg of Crabtree's catalyst. ^{1}H NMR (500 MHz, CD_2Cl_2) δ ppm 2.97 (br. s., 3H), 3.09 (br. s., 3H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.58 (s, 1H), 7.59 (d, *J* = 7.4 Hz, 1H).

		Run A			Run B			
	ppm	1	2	3	1	2	3	4
H-2	7.58	0.60	0.24	0.20	0.35	0.19	0.10	0.11
H-6	7.35	0.78	0.38	0.29	0.57	0.37	0.30	0.28

(the peak at 6.77 from the phenol was used as an internal standard for integration).

N, N-dimethyl 3, 4-dichlorobenzamide: A total of 1.985 mg (9.1 μmol) of *N, N*-dimethyl 3, 4-dichlorobenzamide in 0.75 mL of CD_2Cl_2 was treated as described in method B with 0.320, 0.573 and 0.797 mg of Crabtree's catalyst for run A and 6.471 mg (29.6 μmol) of *N, N*-dimethyl 3, 4-dichlorobenzamide with five aliquots of 0.514 mg of Crabtree's catalyst. ^{1}H NMR (500 MHz, CD_2Cl_2) δ ppm 2.98 (br. s., 3H), 3.08 (br. s., 3H), 7.30 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.55 (s, 1H).

		Run A			Run B					
	ppm	1	2	3	1	2	3	4	5	6
H-2	7.55	0.85	0.46	0.05	0.69	0.48	0.27	0.24	0.12	0
H-6	7.30	0.99	0.76	0.30	0.76	0.58	0.44	0.38	0.28	0.13

(the peak at 6.77 from the phenol was used as an internal standard for integration).

N, N-dimethyl 3-chlorobenzamide: A total of 6.258 mg (34.0 μmol) of *N, N*-dimethyl 3-chlorobenzamide in 5 mL of CH_2Cl_2 was treated as described in method B with five aliquots of 0.771 mg (0.96 μmol) of Crabtree's catalyst in 120 μL of CH_2Cl_2 for run A and 6.258 mg (34.0 μmol) of *N, N*-dimethyl 3-chlorobenzamide with five aliquots of 1.543 mg (1.9 μmol) of Crabtree's catalyst in 240 μL of CH_2Cl_2. ^{1}H NMR (500 MHz, C_6D_6) δ ppm 2.14 (br. s., 3H), 2.67 (br. s., 3H), 6.72 (t, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 7.28 (s, 1H).

		Run A					Run B				
	ppm	1	2	3	4	5	1	2	3	4	5
H-2	7.28	0.87	0.84	0.74	0.55	0.32	0.81	0.43	0.20	0.13	0.11
H-6	7.04	0.98	0.96	0.86	0.72	0.56	0.96	0.64	0.36	0.28	0.29

N, N-dimethyl 3-iodobenzamide: A total of 10.95 mg (39.8 μmol) of *N, N*-dimethyl 3-iodobenzamide in 6 mL of CH_2Cl_2 was treated as described in method B with five aliquots of 0.433 mg (0.54 μmol) of Crabtree's catalyst for run A and 10.95 mg (39.8 μmol) of *N, N*-dimethyl 3-iodomethylbenzamide with four aliquots of 0.862 mg of Crabtree's catalyst. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.88 (br. s., 3H), 2.96 (br. s., 3H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.73 (s, 1H), 7.80 (d, *J* = 7.9 Hz, 1H).

		Run A						Run B				
	ppm	1	2	3	4	5	6	1	2	3	4	5
H-2	7.73	0.91	0.86	0.82	0.76	0.66	0.48	0.8	0.53	0.42	0.20	0.16
H-6	7.41	1.0	0.98	0.92	0.85	0.77	0.59	0.89	0.61	0.43	0.30	0.24

1-(3-Fluorophenyl)ethanone: A total of 0.954 mg (6.9 μmol) of 1-(3-fluorophenyl)ethanone in 0.6 mL of CD_2Cl_2 was treated as described in method A with four aliquots of 0.116 mg (0.145 μmol) of Crabtree's catalyst for run A and 1.13 mg (8.2 μmol) of 1-(3-fluorophenyl)ethanone with two aliquots of 0.044 mg of Crabtree's catalyst. ^{1}H NMR (500 MHz, CD_2Cl_2) δ ppm 2.49 (s, 3H), 7.20 (td, *J* = 8.4, 1.8 Hz, 1H), 7.39 (td, *J* = 8.0, 5.6 Hz, 1H), 7.54 (ddd, *J* = 9.5, 1.7, 2.3 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H).

		Run A				Run B	
	ppm	1	2	3	4	1	2
H-2	7.54	0.57	0.40	0.16	0.18	0.25	0.07
H-6	7.66	1.0	1.0	0.88	1.0	0.75	0.24

1-(3-Hydroxyphenyl)ethanone: A total of 1.51 mg (12.0 μmol) of 1-(3-hydroxyhenyl)ethanone in 0.6 mL of CD_2Cl_2 was treated as described in method A with three aliquots of 0.014 mg (0.017 μmol) of Crabtree's catalyst for run A and 1.51 mg (12.0 μmol) of 1-(3-hydroxyphenyl)ethanone with three aliquots of 0.029 mg (0.036 μmol) of Crabtree's catalyst. ^{1}H NMR (500 MHz, CD_2Cl_2) δ ppm 2.47 (s, 3H), 6.97 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.27 (t, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 1.5 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H).

		Run A			Run B		
	ppm	1	2	3	1	2	3
H-2	7.32	0.89	0.82	0.67	0.79	0.72	0.15
H-6	7.43	1.0	1.0	0.96	1.0	1.0	0.47

1-(3, 4-Dimethylphenyl)ethanone: A total of 12.27 mg (82.3 μmol) of 1-(3, 4-dimethylphenyl)ethanone in 6 mL of CH_2Cl_2 was treated as described in method B with 0.086, 0.173, 0.173, 0.173, 0.173 and 0.173 mg (2.1 μmol) of Crabtree's catalyst for run A and 11.41 mg (7.70 μmol) of 1-(3, 4-dimethylphenyl phenyl)ethanone with 0.086, 0.173, 0.173, 0.173, 0.173 and 0.173 mg (2.1 μmol) of Crabtree's catalyst. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.29 (s, 6H), 2.53 (s, 3H), 7.28 (d, *J* = 7.9 Hz, 1H), 7.68 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.73 (s, 1H).

		Run A						Run B					
	ppm	1	2	3	4	5	6	1	2	3	4	5	6
H-2	7.73	0.97	0.98	0.94	0.89	0.81	0.66	0.98	0.92	0.94	0.87	0.71	0.39
H-6	7.68	0.94	0.90	0.7	0.55	0.39	0.25	0.89	0.80	0.68	0.57	0.29	0.08

1-(3-Chlorophenyl)ethanone: A total of 10.8 mg (69.9 μmol) of 1-(3-chlorophenyl)ethanone in 6 mL of CH_2Cl_2 was treated as described in method B with six aliquots of 0.208 mg (0.25 μmol) of Crabtree's catalyst for run A and 10.8 mg (69.9 μmol) of 1-(3-chlorophenyl)ethanone with five aliquots of 0.104 mg (0.13 μmol)

of Crabtree's catalyst. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.59 (s, 3H), 7.41 (t, J = 7.9 Hz, 1H), 7.53 (dd, J = 7.5, 1.7 Hz, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.92 (t, J = 2.0 Hz, 1H).

		Run A						Run B				
	ppm	1	2	3	4	5	6	1	2	3	4	5
H-2	7.92	0.93	0.86	0.74	0.61	0.49	0.29	0.99	0.96	0.91	0.84	0.72
H-6	7.83	0.98	0.96	0.92	0.82	0.71	0.56	1.0	0.99	1.0	0.99	0.92

1-(3-Bromophenyl)ethanone: A total of 12.3 mg (61.8 μmol) of 1-(3-bromophenyl)ethanone in 6 mL of CH_2Cl_2 was treated as described in method B with five aliquots of 0.102 mg (13 μmol) of Crabtree's catalyst for run A and 12.3 mg (61.8 μmol) of 1-(3-bromophenyl)ethanone with five aliquots of 0.203 mg (25 μmol) of Crabtree's catalyst. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.59 (s, 3H), 7.35 (t, J = 7.9 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 7.9 Hz, 1H), 8.08 (t, J = 1.7 Hz, 1H).

		Run A					Run B				
	ppm	1	2	3	4	5	1	2	3	4	5
H-2	8.08	0.93	0.90	0.84	0.76	0.56	0.85	0.79	0.70	0.58	0.45
H-6	7.87	1	1	0.97	0.9	0.76	0.97	1.0	0.86	0.75	0.62

1-(3-Iodophenyl)ethanone: A total of 15.5 mg (63.1 μmol) of 1-(3-iodophenyl)ethanone in 6 mL of CH_2Cl_2 was treated as described in method B with six aliquots of 0.207 mg (26 μmol) of Crabtree's catalyst for run A and 15.5 mg (63.1 μmol) of 1-(3-iodophenyl)ethanone with six aliquots of 0.414 mg (0.51 μmol) of Crabtree's catalyst. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.58 (s, 3H), 7.21 (t, J = 7.8, 1.7 Hz, H), 7. 87(dt, J = 7.8, 1.7 Hz, 1H), 7.90 (dt, J = 7.4, 1.7 Hz, 1H), 8.28 (t, J = 1.7 Hz, 1H).

		Run A						Run B					
	ppm	1	2	3	4	5	6	1	2	3	4	5	6
H-2	8.28	0.93	0.80	0.67	0.65	0.58	0.49	0.92	0.85	0.80	0.72	0.64	0.53
H-6	7.90	0.90	0.83	0.65	0.65	0.62	0.53	0.92	0.87	0.80	0.73	0.67	0.55

1-(3-Trifluomethylphenyl)ethanone: A total of 8.89 mg (47.2 μmol) of 1-(3-trifuoromethylphenyl)ethanone in 6 mL of CH_2Cl_2 was treated as described in method B with five aliquots of 0.327 mg (0.41 μmol) of Crabtree's catalyst for run A and 8.89 mg (47.2 μmol) of 1-(3-triflurometh ylphenyl)ethanone with five aliquots of 0.656 mg (0.82 μmol) of Crabtree's catalyst. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.65 (s, 3H), 7.61 (t, J = 7.8 Hz, 1H), 7.82 (d, J = 7.9 Hz, 1H), 8.14 (d, J = 7.9 Hz, 1H), 8.21 (s, 1H).

		Run A					Run B				
	ppm	1	2	3	4	5	1	2	3	4	5
H-2	8.21	0.99	1.0	0.99	1.0	1.0	0.99	1.0	1.0	1.0	0.99
H-6	8.14	0.96	0.94	0.87	0.75	0.65	0.97	0.95	0.94	0.90	0.85

1-(3-Trifluomethoxyphenyl)ethanone: A total of 13.8 mg (67.6 μmol) of 1-(3-trifluoromethoxyphenyl)ethanone in 6 mL of CH_2Cl_2 was treated as described in method B with six aliquots of 0.104 mg (0.13 μmol) of Crabtree's catalyst for run A and 13.8 mg (67.6 μmol) of 1-(3-triflurometh oxyphenyl)ethanone with five aliquots of 0.208 mg (0.26 μmol) of Crabtree's catalyst. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.61 (s, 3H), 7.42 (dd, J = 8.2, 1.2 Hz, 1H), 7.51 (t, J = 7.9 Hz, 1H), 7.80 (s, 1H), 7.88 (d, J = 7.6 Hz, 1H).

		Run A						Run B				
	ppm	1	2	3	4	5	6	1	2	3	4	5
H-2	7.80	0.95	0.93	0.87	0.82	0.53	0.44	0.90	0.86	0.76	0.64	0.30
H-6	7.88	0.97	0.94	0.92	0.87	0.66	0.57	0.92	0.90	0.84	0.73	0.42

1-(3-Methoxyphenyl)ethanone: A total of 8.87 mg (59.0 μmol) of 1-(3-methoxyphenyl)ethanone in 6 mL of CH_2Cl_2 was treated as described in method B with five aliquots of 0.102 mg (0.13 μmol) of Crabtree's catalyst for run A and 8.87 mg (59.0 μmol) of 1-(3-methoxyphenyl)ethanone with five aliquots of 0.204 mg (0.25 μmol) of Crabtree's catalyst. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.59 (s, 3H), 3.85 (s, 3H), 7.11 (dd, J = 8.2, 1.8 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.48 (m, 1H), 7.53 (d, J = 7.9 Hz, 1H).

		Run A					Run B				
	ppm	1	2	3	4	5	1	2	3	4	5
H-2	7.48	0.95	0.93	0.78	0.64	0.42	0.83	0.74	0.64	0.50	0.36
H-6	7.53	0.98	0.94	0.87	0.76	0.65	0.91	0.85	0.77	0.63	0.51

[(cod)Ir{$P(C_6D_5)_3$}$_2$]BF_4 (**3**) was prepared according to the procedure of Haines and Singleton.[19] A suspension of 750 mg (1.12 mmol) of [(cod)IrCl]$_2$ in 32 mL of EtOH was stirred at rt and 1 g (3.61 mmol) of tri(phenyl-d5)phosphine was added. The solids gradually went into solution. The reaction mixture was stirred overnight. A yellow precipitate was removed by filtration. A filtered solution of 766 mg (7.31 mmol) of ammonium tetrafluoroborate in 40 mL of EtOH was added. The flask was purged with N_2 and then stored at −20°C for 2 days. A red solid was collected by filtration, which gave 428 mg (42%) after drying overnight under high vacuum.

Reaction of [(cod)Ir{$P(C_6D_5)_3$}$_2$]BF_4 with (3-chlorophenyl)ethanone: A solution of 5.8 mg (6.1 mmol) of **3** and 0.93 mg (6.0 mmol) of (3-chlorophenyl)ethanone in 0.5 mL of D_6-acetone was prepared in an NMR tube. H_2 was bubbled through the solution for 1 min and the tube was then capped and parafilmed and heated at 80°C for 20 min and the ^{1}H NMR was taken. ^{1}H NMR (500 MHz, D_6-acetone) δ ppm 7.55 (t, J = 7.8 Hz, 1H), 7.65 (d, J = 7.0 Hz, 1H), 7.95 (m, 2H). The cap was then removed and the tube attached to an N_2 bubbler for 12 h. The ^{1}H NMR was again taken. ^{1}H NMR (500 MHz, D_6-acetone) δ ppm 6.69 (d, J = 7.9 Hz, 0.44H), 6.85 (t, J = 7.3 Hz, 0.73H), 6.93 (d, J = 7.6 Hz, 0.65H), 7.09 (s, 0.32H), 7.16 (d, J = 8.5 Hz, 0.35H), 7.19 (d, J = 7.6 Hz, 0.64H), 7.36 (m, 0.81H), 7.55 (t, J = 7.6 Hz, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.69 (d, J = 11.6 Hz, 0.30H), 7.95 (m, 1.3H). H_2 was again bubbled through the NMR tube and the tube capped and sealed with parafilm. After 30 min the NMR was acquired again. ^{1}H NMR (500, D_6-acetone) δ ppm 7.52 (m, 0.6H), 7.55 (t, J = 7.8 Hz, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.70 (d, J = 11.9 Hz, 0.3H), 7.95 (m, 1.6H)

Reaction of [(cod)Ir{$P(C_6D_5)_3$}$_2$]BF_4 with (3-triflurometh ylphenyl)-ethanone: The reaction was run as described for the reaction of (3-chlorophenyl)ethanone with **3** using 8.23 mg (8.6 mmol) of **3** and 1.44 mg (7.7 mmol) of (3-triflurometh ylphenyl)ethanone.

^{1}H NMR (500 MHz, D_6-acetone) δ ppm 7.79 (t, J = 7.8 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H), 8.26 (s, 1H), 8.28 (d, J = 7.9 Hz, 1H). ^{19}F NMR (471 MHz, acetone) δ ppm 25.48 (s, 4.2F), 25.54 (s, 1F), 114.13 (s, 5.9F). After heating under N_2: ^{1}H NMR (500 MHz, D_6-acetone) δ ppm 6.89 (d, J = 7.9 Hz, 1.8H), 7.32 (s, 1.8H), 7.39 (d, J = 7.6 Hz, 2.74H), 7.70 (d, J = 11.6 Hz, 0.3H), 7.79 (t, J = 7.6 Hz, 1H), 7.96 (d, J = 7.9 Hz, 1H), 8.26 (s, 1H), 8.28 (s, 1H). After bubbling H_2 through the solution: ^{1}H NMR (500 MHz, D_6-acetone) δ ppm 7.39 (br. s., 0.5H), 7.56 (d, J = 12.3 Hz, 0.19H), 7.66 (t, J = 7.6 Hz, 1H), 7.83 (d, J = 7.6 Hz, 1H), 8.13 (br. s., 1H), 8.15 (d, J = 7.9 Hz, 1H). There was no change to the ^{19}F NMRs of the later two samples.

Reaction of [(cod)Ir{P(C_6D_5)$_3$}$_2$]BF_4 with (3-fluorophenyl)ethanone: The reaction was run as described for the reaction of (3-chlorophenyl)ethanone with **3** using 11.4 mg (11.9 mmol) of **3** and 1.49 mg (10.8 mmol) of (3-fluorophenyl)ethanone. ^{1}H NMR (500 MHz, D_6-acetone) δ ppm 7.40 (td, J = 8.2, 2.3 Hz, 1H), 7.56 (m, 1H), 7.68 (dd, J = 9.8, 1.5 Hz, 1H), 7.84 (d, J = 7.0 Hz, 1H). ^{19}F NMR (471 MHz, acetone) δ ppm 25.5 (s, 1.6F), 25.6 (s, 7.3F), 63.1 (s, 1.3F), 63.4 (s, 1F). After heating under N_2: ^{1}H NMR (500 MHz, D_6-acetone) δ ppm 6.52 (t, J = 7.8 Hz, 1.24H), 6.58 (m, 0.17H), 6.84 (dt, J = 7.6, 4.9 Hz, 1.23H), 6.89 (m, 0.12H), 7.08 (d, J = 7.6 Hz, 1.28H), 7.15 (m, 0.14H), 7.23 (m, 0.07H), 7.40 (t, J = 8.4 Hz, 1H), 7.58 (m, 1H), 7.68 (d, J = 9.8 Hz, 0.66H), 7.84 (d, J = 7.6 Hz, 1H). ^{19}F NMR (471 MHz, acetone) δ ppm 25.54, (s, 22.6F), 25.59 (s, 6.7F), 63.1 (s, 1.4F), 63.4 (s, 3.1F), 84.6 (s, 1F), 84.7 (br. s., 4.2F). After H_2 bubbling: ^{1}H NMR (500 MHz, D_6-acetone) δ ppm 7.39 (m, 0.5H), 7.57 (d, J = 11.6 Hz, 0.2H), 7.66 (t, J = 7.6 Hz, 1H), 7.83 (d, J = 7.6 Hz, 1H), 8.13 (s, 1H), 8.15 (d, J = 7.9 Hz, 1H).

Reaction of [(cod)Ir{P(C_6D_5)$_3$}$_2$]BF_4 with (3-trifluromethoxyphenyl)ethanone: The reaction was run as described for the reaction of (3-chlorophenyl)ethanone with **3** using 6.37 mg (6.67 mmol) of **3** and 1.32 mg (6.44 mmol) of (3-trifluromethoxyphenyl)ethanone ^{1}H NMR (500 MHz, D_6-acetone) δ ppm 7.59 (d, J = 7.3 Hz, 1H), 7.68 (t, J = 7.9 Hz, 1H), 7.86 (s, 1H), 8.03 (d, J = 7.6 Hz, 1H). ^{19}F NMR (471 MHz, acetone) δ ppm 25.5 (s, 4F), 25.6 (s, 1F), 118.8 (s, 5F). After heating under N_2: ^{1}H NMR (500 MHz, D_6-acetone) δ ppm 6.68 (d, 3.3H), 6.73 (d, J = 7.3 Hz, 2.6H), 6.95 (t, J = 7.8 Hz, 2.3H), 7.04 (s, 2.2H), 7.15 (d, J = 7.9 Hz, 1.7H), 7.26 (d, J = 8.5 Hz, 3.3H), 7.35 (t, J = 5.3 Hz, 2H), 7.38 (t, J = 5.3 Hz, 2H), 7.60 (s, 1.4H), 7.70 (m, 3.9H), 7.86 (s, 1H), 8.03 (d, J = 7.6 Hz, 1H). ^{19}F NMR (471 MHz, acetone) δ ppm 25.45 (s, 5.4F), 25.5 (s, 1.1F), 118.6 (s, 1.8F), 118.8 (s, 3.5F), 121.3 (s, 1F). After H_2 bubbling: ^{1}H NMR (500 MHz, D_6-acetone) δ ppm 7.52 (t, J = 5.3 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.70 (m, 3.38H), 7.86 (s, 1H), 8.03 (d, J = 7.6 Hz, 1H). ^{19}F NMR (471 MHz, acetone) δ ppm 25.5 (s, 4F), 25.6 (s, 1F), 118.8 (s, 5F).

Conclusions

Our studies show unambiguously the effects of a variety of *meta*-substituents on the relative rates of deuterium exchange into the nonequivalent *ortho*-positions of three model substrate classes, catalyzed by two different organoiridium complexes commonly used in HDE. The *meta*-substituent effects are nearly the same (where tested) for both organoiridium complexes. The various *meta*-substituents produce similar effects, relative to one another, in all three substrate classes. Substituents lacking electron lone pairs strongly retard C2 labeling relative to that at C6, probably through steric blockade. In contrast, all substituents possessing electron lone pairs are associated either with faster C2 labeling or C2/C6 labeling rate ratios less unfavorable than those associated with substituents lacking electron lone pairs. The acceleration of C2 labeling by the more powerful substituents may be exploitable for regioselective labeling, especially if the progress of reactions is monitored (a noninvasive method for real-time monitoring of HDE reactions is available for certain substrates).[20] No definite mechanistic explanation is yet available to account for the positive influence of some C3 substituents on the rate of C2 hydrogen isotope exchange catalyzed by organoiridium complexes. Application of isotope studies, such as those presented here, may be useful in investigations into these mechanistic questions.

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