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Conditions for deuterium exchange mediated by iridium complexes formed in situ

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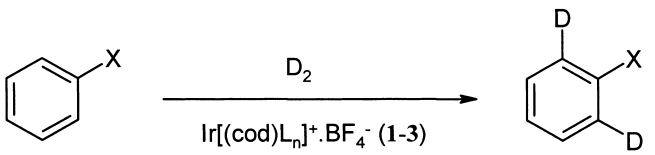
Abstract—A series of iridium-based complexes formed in situ, containing pyridine, phosphines, triphenylarsine, triphenylstibine, and triphenylamine as ligands, has been screened for ability to mediate *ortho*-exchange of hydrogen in a series of model substrates. Improved incorporation into a number of substrate classes has been achieved. The electronic properties and number of ligands at the metal centre are instrumental in determining which catalysts are best suited to exchange in any given substrate. © 2003 Published by Elsevier Science Ltd.

1. Introduction

Over the past decade, a number of groups have reported iridium complex-mediated hydrogen isotope exchange at relatively unactivated carbon centres.[1–5] Such methodology is of considerable potential value for the preparation of tritiated organic molecules in a minimal number of radiolabelled steps, but the efficiency of exchange remains insufficient for application to the preparation of deuterated species. Where the latter are to be used as internal standards for mass spectrometry, better than 99% exchange is desirable and, at present, this level of incorporation is not achievable by iridium-mediated exchange.

In a recent communication,[6] we described the generation of bis(phosphine)(cyclooctadiene)iridium(I) tetrafluoroborates, exemplified by the complexes formed with triphenylphosphine and methyldiphenylphosphine, and the in situ use of these pre-catalysts to mediate hydrogen isotope exchange adjacent to a heteroatom-containing functional group. More importantly, we demonstrated that the results obtained upon deuterium exchange using



X = Ac, CH_2Ac, COOMe, $CONH_2$, $CONMe_2$, SO_2NH_2, $NHSO_2Me$, NHAc, C(=NOMe)Me, 2-pyridinyl, 4-thiazolyl, 5-acetyl-3-isoxazolyl, 1-pyrazolyl, 4-pyrimidinyl, 2-amino-4-thiazolyl, CH_2OH, CH_2NH_2, CH_2NMe_2, S(O)Me, SO_2Me, NH_2, NO_2

$[IrL_2(cod)]^+.BF_4^-$ **1** $[IrL_3(cod)]^+.BF_4^-$ **2** $[IrL(cod)]^+.BF_4^-$ **3**

a. L = pyridine; **b**. L = PPh_3; **c**. L = $MePPh_2$; **d**. L = $P(C_6F_5)_3$; **e**. L =P(2-furyl)$_3$
f. L = $P(c\text{-}C_6H_{11})_3$; **g**. $P(NMe_2)_3$; **h**. L = $AsPh_3$; **i**. L = $SbPh_3$; **j**. L = NPh_3; **k**. L = P-*t*-Bu_3

Scheme 1. Generalised form of isotopic exchange using complexes **1**–**3**.

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complexes generated and used without isolation were, at worst, only slightly inferior to those obtained using the isolated complexes. This approach has enabled us to evaluate different ligands and stoichiometries (Scheme 1) without isolating the pre-catalysts, and also gives us the option of using catalysts whose isolation would be difficult.

Altering the nature and number of ligands at a metal centre can be expected to result in complexes with different properties, which raises the prospect of altering the characteristics of the iridium complex in order to optimise isotopic exchange for any given substrate. In what follows, we describe our initial attempts to explore the conditions necessary for maximising exchange, using a series of complexes **1**–**3** with a range of simple model substrates.

2. Discussion

2.1. Establishment of initial and optimised experimental protocols

Before considering ligand effects, it was necessary to establish robust experimental conditions. The effects of reaction time, catalyst loading, and of the presence of acid or base, were therefore examined using the readily available isolated complex $Ir(cod)(PPh_3)_2^+.BF_4^-$ (**1b**). The first thing to note is that variation of substrate/catalyst ratio (Table 1) has a different effect depending on the substrate. The process with acetophenone (entry 1) and 2-phenylpyridine (entry 11), in particular, is unaffected by loading. In contrast, where the directing group was a π-excessive heterocycle (entries 8–10), deuteration was efficient with less than 20% of catalyst, and an increased percentage of catalyst actually resulted in less exchange. Where a 1:1 ratio of catalyst to substrate was used, the recovery of such substrates was generally poor. Having stated all of this, in most cases deuteration became more efficient as the catalyst/substrate ratio was increased up to approximately 1:2. This catalyst loading was used in the work that followed, although just as this 1:2 ratio is by no means the optimum for all substrates, it may not be ideal for all of the complexes tested.

The most convenient means found for generation of **1b** in situ involved treatment of readily available bis(1,5-cyclooctadiene)diiridium(I) dichloride with the phosphine (4 M equiv.) and silver tetrafluoroborate (2 M equiv.).[6] When complexation was carried out in $CDCl_3$, within 5 min TLC and ^1H NMR of the solution formed were identical to those of the isolated complex.[7]

When the in situ catalyst generation technique was employed and the resulting species used in labelling reactions, in some cases it appeared that silver(I) was reduced in parallel with the exchange process, forming a silver mirror on the inside of the reaction flask.[6] It was therefore likely that sensitive substrates or more electron-rich phosphines would be oxidised using this protocol. Additionally, it was highly probable that deuterium was also being oxidised. Importantly, any acid formed as part of this latter process could promote degradation and inactivation of the iridium catalyst,[8] or alter the overall labelling profile. Indeed, with regard to this latter point, acid-mediated deuterium incorporation was observed in the methyl group of acetophenone. As shown in Table 2, this exchange could be suppressed by adding 1 equiv. of a mild inorganic base, of which a number were tested. It can be seen that sodium carbonate was the most satisfactory additive, in that it allowed aryl exchange to continue to a high level, whilst preventing any deuterium incorporation on the methyl unit. With respect to the other basic additives employed, the suppression of overall deuterium exchange by excess pyridine was not surprising, since this will bind competitively to the metal centre (while addition of more than 25% of 1,8-bis(dimethylamino)naphthalene completely suppressed deuterium exchange). Triethylamine removed all methyl exchange whilst still delivering relatively good levels of arene labelling.

If complexation was carried out in the absence of a silver salt, the resulting species had a different, and generally poorer, range of activity. It was therefore not practical to omit silver salts from the complexation step. Additionally and despite the knowledge that the addition of sodium carbonate could be advantageous, we felt that the overall process should not be complicated by the addition of a base. In this respect, we considered it preferable to filter off insoluble silver salts from the solution of **1a** before addition of the substrate; this last method was used in all subsequent work.

We had established previously that deuterium exchange mediated by Crabtree's catalyst, $[Ir(Py)(PCy_3)cod]^+.PF_6^-$, was not impeded by the presence of water.[4] However, it is worth noting that where wet silver tetrafluoroborate was used to promote formation of **1b** (and related complexes),

Table 1. Deuteration with different percentages of pre-formed **1b**

Entry	Substrate	10%	20%	50%	1 equiv.
1	Acetophenone	1.8	1.8	1.8	1.8
2	Benzamide	0.1	0.1	0.3	0.4
3	*N*,*N*-Dimethylbenzamide	0.6	–	1.4	1.8
4	Benzylamine	0.0	–	0.1	0.1
5	*N*,*N*-Dimethylbenzylamine	0.4	–	0.5	0.3
6	Benzyl alcohol	–	0.4	0.3	0.9
7	Acetanilide	0.2	–	0.7	0.7
8	1-Phenylpyrazole	1.4	–	1.0	0.7
9	4-Phenylthiazol-2-amine	1.7	0.4	0.3	–
10	5-Acetyl-3-phenylisoxazole	1.9	–	1.7	1.0
11	2-Phenylpyridine	1.7	–	1.7	1.7
12	4-Phenylpyrimidine	0.1	–	0.1	0.4
13	Phenylpyrazine	0.0	–	0.1	0.6

Figures quoted are the number of deuterium atoms per molecule of substrate, as determined by mass spectrometry.

Table 2. Effect of base upon the deuteration of acetophenone mediated by **1b**

Base	Deuterium in arene ring	Deuterium in methyl group
None	1.4	0.2
$NaHCO_3$	1.1	0.0
Na_2CO_3	1.6	0.0
Pyridine	0.3	0.1
Triethylamine	1.2	0.0

Figures quoted are the number of deuterium atoms per molecule of substrate, as determined by mass spectrometry.

Table 3. Comparison of NMR and MS data for 3-substituted acetophenones after deuteration mediated by **1b**

Acetophenone	Deuteration at C-2	Deuteration at C-6	Deuteration at C-4	Total (from NMR)	Total (from MS)
3-chloro-	0.95	0.95	–	1.9	1.9
3-bromo-	0.9	1.0	–	1.9	1.9
3-nitro-	0.9	0.9	0.75	2.55	2.6
3-methoxy-	0.85	0.85	–	1.7	1.7
3-methyl-	0.9	1.0	–	1.9	2.0

Figures quoted are the number of deuterium atoms incorporated per molecule of substrate.

there was a significant reduction of catalytic activity. Presumably, hydration reduces the solubility of the silver salt in dichloromethane. Since silver tetrafluoroborate is deliquescent, the use of other silver salts was considered. In this regard, silver hexafluorophosphate could be used in place of silver tetrafluoroborate, but silver(I) carbonate, methanesulfonate and trifluoroacetate all proved to be very poor substitutes.

At this stage it is also worth noting that, in contrast to isolated complex, solutions of **1b** retained the same activity toward exchange with acetophenone, even after a week of storage under nitrogen at room temperature (despite the ruby red colour of the original solution having faded significantly). The catalyst solution was therefore suitably robust (and certainly more so than the isolated complex), which augured well for the preparation of potentially more sensitive complexes. Nevertheless, the results presented here were obtained using freshly prepared catalyst solutions and, where it was necessary to store solutions, they were kept at −20°C under nitrogen.

2.2. Analysis of the levels and rates of labelling

In view of the number of experiments we intended to perform, it was of interest to compare the means by which deuterium incorporation was evaluated. Although NMR spectra were obtained for deuterated products, it was more convenient, in many cases, to determine the degree of deuteration simply by comparison of the averaged masses of key peak clusters in the mass spectra of labelled and unlabelled substrates. This method gives figures that agree well with those obtained from NMR spectra of the same deuterated products, as exemplified in Table 3 for a series of 3-substituted acetophenones.

In order to ensure that sufficient time was allowed for exchange runs to reach equilibrium, the kinetics of the deuteration of acetophenone mediated by **1b**, formed in situ, were examined (Fig. 1). As observed previously with $[Ir(Py)(PCy_3)cod]^+.PF_6^{-4}$, there is an induction period of a few minutes before any exchange is observed, corresponding to the time required for removal of the cyclooctadiene ligand from a significant proportion of the pre-catalyst (for

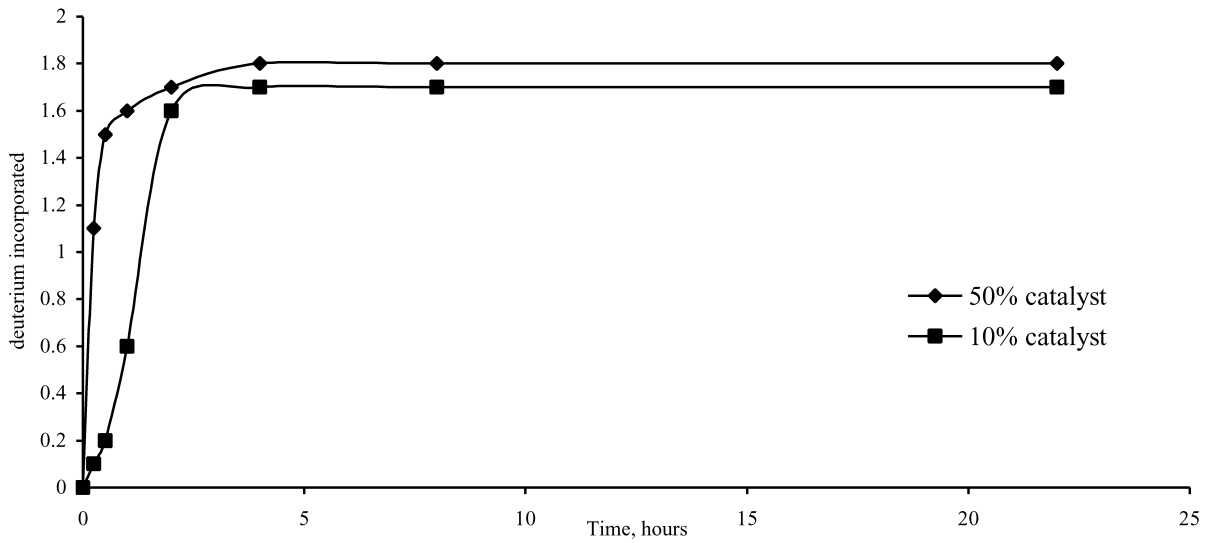
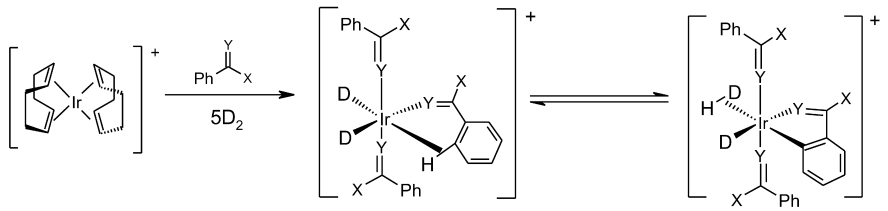


Figure 1. Deuterium incorporation into acetophenone, mediated by **1b**, as a function of time.



Scheme 2. Partial scheme for exchange without added coordinating ligands.

Table 4. Deuterium incorporation in the presence of $[Ir(cod)_2]^+ \cdot BF_4^-$ (no additional ligand)

	Substrate	Deuterium incorporated
1	Acetophenone	0.4
2	Phenylacetone	0.0
3	Ethyl benzoate	0.0
4	*N*,*N*-Dimethylbenzamide	1.9
5	Acetanilide	1.7
6	Benzenesulfonamide	0.0
7	*N*-Phenyl-methanesulfonamide	0.0
8	Aniline	0.9
9	Methyl phenyl sulfone	0.0
10	Methyl phenyl sulfoxides	0.0
11	1-Phenylpyrazole	1.2
12	4-Phenylthiazole	0.2
13	5-Acetyl-3-phenylisoxazole	1.4
14	2-Phenylpyridine	0.2
15	Acetophenone *O*-methyl oxime	1.4
16	Nitrobenzene	0.0

Figures quoted are the number of deuterium atoms per molecule of substrate, as determined by mass spectrometry; in all cases, 50% catalyst loading was used.

example, formation of a mixture of deuterated cyclooctanes was observed by GC/MS during this time). Subsequent exchange is rapid, being more so where a greater quantity of catalyst is used, then slows and reaches an equilibrium level after 3–4 h.[4] It should be noted that, even when using only 10% of catalyst, 1.8 atoms of deuterium per molecule were eventually incorporated after 48 h. Accordingly, in practice, deuteration runs were carried out over a period of at least 48 h to allow for the possibility that some complexes might promote, or that some substrates might undergo, slower exchange than others.

2.3. Exploration of the scope and limitations of ligands in IR-mediated exchange processes

One of the initial points for consideration is that, by definition, if a substrate undergoes iridium-mediated hydrogen isotope exchange, it must bind to iridium and can be considered a ligand. Consequently, it seemed perfectly possible that exchange might occur even if the only species bound to the metal centre were the substrate, solvent, and deuterium (Scheme 2). Therefore, in order to establish a set of baseline figures (in the absence of any additional coordinating ligand), each substrate was treated with deuterium in the presence of half an equivalent of bis(cyclooctadiene)iridium tetrafluoroborate. As shown in Table 4, where a substrate contains an sp^2 nitrogen (entries 10–14) capable of binding to the metal, some exchange is observed, while the levels of deuterium incorporation observed with amides are surprisingly high (entries 4 and 5). In these latter cases at least, lower levels of exchange with phosphine-containing complexes (see Table 1; 50% catalyst usage) could be interpreted as reflecting inhibition of the process by phosphine ligands. However, from a practical viewpoint, the significant drawback of self-promoted exchange by substrates is that the recovery is poor. More specifically, while substrate recovery in other cases is typically better than 75%, the recovery of material in the absence of added ligands is rarely better than 30%. In all of these cases, varying quantities of a black precipitate, assumed to be iridium(0), separated within the first 24 h; it is therefore not surprising that exchange is observed principally with substrates that could be expected to bind efficiently to the metal centre.

One implication of the results in Table 4 is that tertiary amides or *N*-heterocycles could be suitable ligands for iridium-mediated deuteration of, at least, some substrates. In order to test this possibility, the same set of substrates was exposed to deuterium in the presence of complexes prepared from $[Ir(cod)Cl]_2$ with one, 2 or 3 equiv. of dimethylacetamide (DMA) or pyridine (Table 5). Once again, a precipitate of what appeared to be iridium metal was observed shortly after exposure to deuterium in all cases (although the precipitate was only slight in the case of the pyridine complexes). This suggests that the ligating power of DMA and, to a lesser extent, pyridine is insufficient to stabilise the reduced complex, with the result that the iridium–dimethylacetamide complexes, irrespective of stoichiometry, are essentially inactive as catalysts for deuterium exchange. Nevertheless, for a few substrates, amongst which methyl phenyl sulfoxide is the most notable, the iridium–pyridine complexes were effective catalysts. In fact, the bis-pyridine complex **1a** is the most efficient mediator found for exchange into methyl phenyl sulfoxide and benzenesulfonamide. The latter observation is interesting in view of the results obtained with less electron-rich phosphine complexes (see later). However, the pyridine

Table 5. Deuterium-exchange mediated by iridium complexes of DMA and pyridine

Ligand	Dimethylacetamide (mol ligand/mol Ir^+)			Pyridine (mol ligand/mol Ir^+)		
	1	2	3	1	2	3
Substrate						
N,*N*-Dimethylbenzamide	0.0	0.0	0.0	0.0	0.5	0.0
Benzenesulfonamide	0.0	0.4	0.0	0.0	1.7	0.0
Methyl phenyl sulfoxide	0.0	0.0	0.0	1.6	1.8	1.3
Acetophenone *O*-methyl oxime	1.5	1.0	0.6	0.0	0.0	0.7
2-Phenylpyridine	0.6	0.0	1.0	0.7	0.7	1.7
1-Phenylpyrazole	1.0	1.2	0.4	0.3	0.3	0.0
4-Phenylthiazole	1.3	0.0	0.2	0.0	0.0	0.6
Aniline	0.0	0.0	0.0	1.7	0.0	1.5
Acetanilide	0.1	0.0	0.0	0.0	0.5	0.0

Figures quoted are the number of deuterium atoms per molecule of substrate, as determined by mass spectrometry. Acetophenone, ethyl benzoate, and 5-acetyl-3-phenylisoxazole were not deuterated under any of these conditions.

Table 6. Results from deuterium-exchange mediated by iridium complexes of triphenylphosphine (**b**) and methyldiphenylphosphine (**c**)

Complex no.	**3b** (mol ligand/ mol Ir^+)	**3c** (mol ligand/ mol Ir^+)	**1b**[a] (mol ligand/ mol Ir^+)	**1c**[a] (mol ligand/ mol Ir^+)	**2b** (mol ligand/ mol Ir^+)	**2c** (mol ligand/ mol Ir^+)
	1		2		3	
Substrate						
Acetophenone	1.5	1.7	1.6 (1.8)	1.5 (1.8)	2.0	1.7
Phenylacetone	0.3	0.1	0.0	0.2	0.2	0.5
Ethyl benzoate	0.0	0.0	1.2 (1.2)	1.1 (1.8)	0.0	0.6
Dimethylbenzamide		1.5	1.1 (1.4)	1.5 (1.5)	0.2	0.8
Benzenesulfonamide	0.4	0.9	0.1	0.0	0.3	1.3
Methyl phenyl sulfoxide	0.2	0.0	0.2	0.3 (0.4)	0.0	0.4
Acetophenone *O*-methyl oxime	1.7	0.8	1.7	1.6	1.7	1.4
2-Phenylpyridine	1.3	0.6	1.4 (1.8)	0.8 (1.1)	0.4	0.2
1-Phenylpyrazole	1.0	0.6	1.0	0.7 (0.9)	0.9	0.5
5-Acetyl-3-phenyl-isoxazole	1.5	0.8	1.7 (1.7)	1.6 (1.8)	1.0	1.0
4-Phenylthiazole	1.2	0.8	1.7 (1.2)	1.3 (1.5)	0.3	0.6
Acetanilide	0.4	2.0	0.6	1.6 (1.6)	0.4	1.0

Figures quoted are the number of deuterium atoms per molecule of substrate, as determined by mass spectrometry.
[a] Figures obtained using pre-formed complex are shown in parentheses.

complexes were of limited value in mediating exchange into 2-phenylpyridine, by comparison with results obtained previously.[5,6]

To date, the majority of iridium complexes reported to mediate deuterium exchange have borne either two phosphine ligands, or one phosphine and one pyridine ligand. However, in view of our earlier findings,[6] we were interested in the possibility that phosphine complexes with different stoichiometries might have different activities as pre-catalysts. As has been reported already,[6] addition of 4 mol of phosphine ligand per mole of iridium generated a catalytically inactive complex, but reducing the ratio of phosphine to iridium to as little as 1:1 still gave an active exchange catalyst. The results obtained by treatment of a panel of substrates with complexes formed in situ from $[Ir(cod)Cl]_2$ with triphenylphosphine and methyldiphenylphosphine are summarised in Table 6; the results from exchange mediated by the isolated complexes **1b** and **1c** are included for comparison. From these results, complexes containing 1, 2 and 3 M equiv. of phosphine ligand per iridium do have substantially different properties, consistent with the involvement of different active intermediates in each case.

In many cases, the level of exchange achieved approaches 90% of the theoretical maximum (or better). For example, complete *ortho*-exchange was observed in the case of acetophenone, using catalyst **2b** and in acetanilide, using catalyst **3c**. Additionally, ethyl benzoate, acetophenone *O*-methyl oxime, 2-phenylpyridine, 5-acetyl-3-phenylisoxazole, and acetanilide are all labelled very effectively with various complex types. On the other hand, benzenesulfonamide and methyl phenyl sulfoxide are both exchanged more efficiently using iridium-pyridine complexes (see Table 5), while dimethylbenzamide and phenylazoles in general are exchanged much more efficiently using $[Ir(Py)(PCy_3)cod]^+.PF_6^-$.[4] At this point, why particular complexes are efficacious in specific cases is unclear. Nonetheless, use of the in situ catalyst preparation methods has allowed us to (i) rapidly assess how a series of substrates perform with iridium–phosphine complexes of varying stoichiometries, and (ii) move towards choosing the most effective complex type for a given substrate class.

Table 7. Results from deuterium-exchange mediated by iridium complexes of tris(pentafluorophenyl)phosphine (**d**) and tris(2-furyl)phosphine (**e**)

Complex	**3d** (mol ligand/ mol Ir^+)	**3e** (mol ligand/ mol Ir^+)	**1d** (mol ligand/ mol Ir^+)	**1e** (mol ligand/ mol Ir^+)	**2d** (mol ligand/ mol Ir^+)	**2e** (mol ligand/ mol Ir^+)
	1		2		3	
Substrate						
Acetophenone	0.5	0.5	0.4	1.6	0.7	
Phenylacetone	1.0	0.3	0.0	0.0	0.5	0.3
Ethyl benzoate	0.0	0.0	0.0	0.0	0.3	0.0
Dimethylbenzamide	0.3	0.8	0.2	1.5	0.3	0.3
Benzenesulfonamide	0.5	0.7	1.1	0.1	0.7	0.4
2-Phenylpyridine	1.5	0.8	1.4	0.6	0.5	0.9
1-Phenylpyrazole	0.3	1.1	1.5	0.8	1.2	1.5
5-Acetyl-3-phenyl-isoxazole	0.0	1.3	1.7	1.4	1.5	1.1
4-Phenylthiazole	0.3	1.2	0.2	1.2	1.3	1.5
Acetanilide	0.4	0.3	0.0	0.5	0.8	1.0

Figures quoted are the number of deuterium atoms per molecule of substrate, as determined by mass spectrometry.

Table 8. Results from deuterium-exchange mediated by iridium complexes of tricyclohexylphosphine (**f**) and HMPT (**g**)

Complex	**3f** (mol ligand/ mol Ir^+)	**3g** (mol ligand/ mol Ir^+)	**1f** (mol ligand/ mol Ir^+)	**1g** (mol ligand/ mol Ir^+)	**2f** (mol ligand/ mol Ir^+)	**2g** (mol ligand/ mol Ir^+)
	1		2		3	
Substrate						
Acetophenone	1.8	0.1	1.7	0.7	0.3	0.0
Phenylacetone	0.0	0.0	0.0	0.0	0.0	0.0
Ethyl benzoate	0.0	0.0	0.1	0.0	0.0	0.0
Dimethylbenzamide	1.3	0.5	0.5	0.1	0.3	0.0
Benzenesulfonamide	0.5	0.0	0.6	0.0	0.0	
2-Phenylpyridine	1.6	0.7	0.0	0.6	0.7	
1-Phenylpyrazole	1.3	0.8	0.2	1.3	0.8	0.6
5-Acetyl-3-phenyl-isoxazole	1.4		–[a]	0.0	1.3	
4-Phenylthiazole	–[a]	0.5	0.4	1.2	0.5	1.2
Acetanilide	1.0		0.5	0.2	0.3	0.4

Figures quoted are the number of deuterium atoms per molecule of substrate, as determined by mass spectrometry.
[a] Substrate not recovered.

Additionally, from these observations one can envisage how minor changes to the electronic properties of the phosphines might also be expected to enable optimisation of exchange within certain substrates.

In an effort to extend the range of usable ligands, we examined deuterium labelling of a similar range of substrates with complexes formed using the relatively electron-poor tris(pentafluorophenyl)phosphine and tris(2-furyl)phosphine (Table 7), and the more electron-rich tricyclohexylphosphine and hexamethylphosphorous triamide (HMPT) (Table 8). We also examined the activity profiles of analogous complexes containing triphenylarsine, triphenylstibine, and triphenylamine (Table 9). In all cases, with the exceptions of 1-phenylpyrazole and (in one example) phenylacetone, complexes with these ligands are poorer mediators of deuteration than those described above. Moving down group V, the organic derivatives are expected to become poorer σ-donors, and it appears that, in most cases, phosphines represent an optimum σ-donicity. In view of the similar poor σ-donicity of tri-2-furylphosphine and tris(pentafluorophenyl)phosphine, it appears that, for the majority of substrates, poorer σ-donor ligands significantly reduce the efficiency of the complex. On the other hand, the very electron-rich tricyclohexylphosphine and HMPT form even less generally useful complexes. Therefore, for substrates such as ketones and amides, there appears to be an optimum range of σ-donicity, into which triphenylphosphine and dimethylphenylphosphine both fall.

Beyond the general observations just made, there are some definite trends in the efficiencies of complexes containing different phosphines. The exchange of acetophenone appears comparatively robust and, for complexes **1** at least, the electronic character of the phosphine seems to have little general influence upon the degree of exchange. However, acetophenone is unique in this respect. 2-Phenylpyridine and the phenylazoles appear to be most poorly deuterated by complexes of the most electron-rich phosphines and, in general, phosphine complexes are less efficient mediators of the deuteration of this group of substrates than is $[Ir(Py)(PCy_3)cod]^+.PF_6^-$.[4] The highest level of exchange into phenylacetone (albeit only 50% of the theoretical maximum) is observed using complex **3d**. It may be that a single tris(pentafluorophenyl)phosphine provides a balance of limited σ-donicity as well as limited steric demand, so that the complex is able to accommodate a six-membered metallacycle.[9] However, much more work remains to be done in order to develop an efficient system for exchange in this type of substrate.

Table 9. Results from deuterium-exchange mediated by iridium complexes with triphenylarsine (**h**), triphenylstibine (**i**) and triphenylamine (**j**)

Complex	**3h** (mol ligand/ mol Ir^+)	**3i** (mol ligand/ mol Ir^+)	**1h** (mol ligand/ mol Ir^+)	**1i** (mol ligand/ mol Ir^+)	**1j** (mol ligand/ mol Ir^+)	**2h** (mol ligand/ mol Ir^+)	**2i** (mol ligand/ mol Ir^+)
	1		2			3	
Substrate							
Acetophenone	1.1	0.0	1.3	1.3	0.0	0.3	0.6
Phenylacetone	0.0	0.0	0.2	0.0	0.0	0.0	0.0
Ethyl benzoate	0.7	0.0	0.4	1.4	0.0	0.0	0.0
Dimethylbenzamide	1.6	0.0	1.1	0.1	0.2	0.2	0.2
Benzenesulfonamide	0.6	0.0	1.2	0.0	0.0	0.4	0.0
2-Phenylpyridine	1.2	0.0	0.7	0.5	0.0	0.2	0.0
1-Phenylpyrazole	0.7	0.0	0.9	0.8	0.0	1.3	0.0
5-Acetyl-3-phenyl-isoxazole	0.8		0.6		0.0	0.2	0.0
4-Phenylthiazole[a]	1.2	0.1	1.1		0.8	0.8	0.0
Acetanilide	1.7		0.6	0.0	0.2	0.3	0.4

Figures quoted are the number of deuterium atoms per molecule of substrate, as determined by mass spectrometry.
[a] 10% catalyst.

Deuteration of benzenesulfonamide in the presence of **1d** or **1h** occurs at a level comparable to that mediated by **2c**. However, all of these are inferior to the bis-pyridine complex **1a** (Table 5, column 5) which, at this point, is the best lead candidate complex for mediating exchange in sulfonamides. None of the phosphine complexes were at all effective in mediating isotopic exchange into methyl phenyl sulfoxides, although up to 90% *ortho*-deuteration was achieved with this substrate with this substrate by use of **1a** (Table 5, column 5); **3a** (column 4) and **2a** (column 6) also perform well with methyl phenyl sulfoxide. The data at this point are insufficient to draw any definite conclusion, but it is possible that this is a consequence of hard/soft interactions between the complex and substrate. The nitrogen centre in pyridine is likely to be a harder σ-donor than a phosphine or an arsine, although the absence of exchange using **1j** is unexpected on this basis. Nevertheless, it would be reasonable to expect binding of the electron-rich (but very hard) oxygen of a sulfoxide to be promoted by hard ligands at the metal centre, whereas softer ligands, even where their σ-donicity is poor, may not perform the same function.

2.4. NMR analysis of complexes prepared in situ

We considered it important to examine the nature of the complexes present either as pre-catalysts or as active species in the exchange process. Complex **1b** is well-characterised;[7,10] ^{1}H and ^{31}P NMR spectra of the species formed in situ are identical to those of the isolated complex, and the two have comparable activities as exchange catalysts. The same applies in the case of **1c**,[10,11] while the ^{1}H NMR spectra of **1e** and that of the known complex **1h**[12] follow the same pattern. In the case of **1e**, however, the signal due to the vinylic protons of cyclooctadiene is shifted downfield by ca. 0.6 ppm, relative to the corresponding signal in **1b**. Tri-2-furylphosphine is known to be a strong π-acceptor,[13] and this deshielding of the vinylic protons reflects a significant reduction in electron density at the metal centre. There is no such downfield shift of the corresponding signal in the ^{1}H NMR spectrum of known complex **1h**; triphenylarsine is expected to be a poorer σ-donor than triphenylphosphine but, considering reported Ir–As bond lengths,[12] it is not expected to be a strong π-acceptor.

Deshielding (or downfield shifts) of the vinylic protons in these cases, therefore, appears to be indicative of a particularly electron-deficient metal centre. In the case of **1d**, the vinylic resonances are completely split, with the furthest downfield signal being observed at δ 5.24. Since tris(pentafluorophenyl)phosphine is again reported not to have significant π-acceptor character,[14] it is possible that the steric bulk of the ligand (cone angle 184°)[15] results in distortion of the complex with, for example, the Ir–P bond lengths being different. As a result, the vinylic protons would be shielded to different extents. In this context, it is worth noting that tri-*tert*-butylphosphine (cone angle 182°)[15] gives a complex (**1k**) whose ^{1}H NMR spectrum indicates no such distortion.

Addition of a third equivalent of phosphine results in complexes **2** which, from NMR data, can be formulated as $[IrL_3(cod)]^+ \cdot BF_4^-$ in line with previous reports.[11,16] Interestingly, ^{31}P NMR of this latter type of species contains only one signal, with a shift very similar to that for the bound phosphines in **1b** and **1c**. The phosphine ligands in **2b** and **2c** are therefore magnetically equivalent. Nevertheless, ^{1}H NMR signals due to the phosphine-methyl group in **2c** are split, with only a 3H doublet observed clear of the aliphatic multiplet. It appears that rotation around Ir–P bonds in this complex is severely restricted, even by comparison to **2b**, reflecting the very congested nature of the metal centre in complexes **2** generally.

Complexes **3b** and **3c**, formed from a 1:1 ratio of phosphine to iridium, can be formulated nominally as $[Ir(cod)L]^+$. However, both ^{1}H and ^{31}P NMR data for **3b** suggest the presence of more than one species in solution, while the spectra of **3c** are more complex still. In the former case, the multiplets due to the aliphatic protons of the cyclooctadiene moiety are very much broadened by comparison to the corresponding signals in the spectrum of **1b** or **2b**; ^{31}P NMR data for **3b** are consistent with the presence of two closely related complexes in a ratio of approximately 9:1. The more complex situation with **3c** is most apparent in the presence, in the ^{1}H NMR spectrum, of four different signals due to the phosphine methyl group, with two markedly different values for $^2J_{PH}$. Meanwhile, the ^{31}P NMR spectrum contains three different resonances in a ratio of approximately 8:1:1. Nevertheless, ^{31}P NMR shifts for the ligands in pre-catalysts **3b** and **3c** are in environments that are electronically similar to those in the corresponding complexes **1** and **2**. In addition, vinylic resonances in complexes **3b** and **3c** are observed around δ 4.2 in accord with expectations.

An additional consideration is that it is possible that, at the point of preparation, complexes **3b** and **3c** contain adventitious water as an additional ligand, and that the multiplicity of NMR signals reflects the presence of isomeric hydrates. The similarity of the ^{31}P NMR shifts to those for complexes **1b–c** and **2b–c** suggests that the major species present are monomeric, but we have not characterised these species any further. In the presence of a suitable substrate, it is expected that any of complexes **3** could be converted into a complex of general form $[Ir(PR_3)(cod)L]^+$, which would have different catalytic activity from the complexes discussed already. Indeed, although the activity of putative pre-catalyst $[Ir(MePPh_2)(cod)]^+$ **3c** toward most substrates is poorer than that of **1c**, it is unexpectedly effective in the deuteration of acetanilide, as mentioned above, and both **2c** and **3c** are significantly more effective than **1c** in the exchange of benzenesulfonamide. In contrast, **3b** has an activity profile similar to that of **1b**.

Overall, the electronic environment of phosphorus in cationic complexes **1–3** appears to change very little whether the complex contains one, two or three bound phosphines. The phosphines are therefore likely to be in electronically very similar environments across this range of complexes, and so it is to be expected that the iridium centre should become considerably more electron-rich (and by implication less electrophilic) as the number of phosphine ligands increases.

3. Conclusion

The establishment and investigation of methods for the formation of iridium-based catalysts, and their use to mediate exchange in situ, has allowed a series of complexes to be screened rapidly. Consequently, we have identified potential avenues for improving incorporation into a number of substrate classes. Moreover, we have found evidence that the electronic properties and number of ligands at the metal centre are instrumental in determining which catalysts are best suited to exchange in any given substrate. Depending upon the substrate concerned, hydrogen isotope exchange may be promoted most efficiently by a pre-catalyst containing 2 or 3 mol of pyridine, phosphine or arsine ligand per mole of iridium. Complexes containing a single ligand were of generally lesser value; although the observation that complex **3c** mediates essentially quantitative exchange into acetanilide is worthy of further investigation. At this point, tertiary amine and stibine complexes do not appear to mediate exchange to any useful extent. Further investigations into the effect of ligand stereoelectronic properties will be reported in due course.

4. Experimental

4.1. General

Gas chromatography was performed using a Hewlett–Packard chromatograph (HP 5890) fitted with a mass-selective detector (HP 5972MSD) on a capillary column (HP1, 30 m×0.25 mm; 0.25 μm layer); the injector temperature was 250°C and the oven temperature was increased, after an initial 2 min delay, either from an initial 70 to 200°C at 5°C/min, or from an initial 100 to 240°C at 10°C/min. ^{1}H NMR spectra were recorded using Jeol GSX-270 and Bruker 500 instruments; all spectra reported were recorded of solutions in deuterochloroform. Bis(1,5-cyclooctadiene)diiridium(I) dichloride was obtained from Strem and Fluka; **1c** was obtained from Aldrich Chemicals, and **1b** was prepared according to the published procedure.[7] Substrates were obtained commercially, or were prepared as described previously.[4] Key spectrometric data which permitted the determination of deuteration levels have been reported already.[4]

4.1.1. Typical exchange procedure. Bis(1,5-cyclooctadiene)diiridium(I) dichloride (67 mg, 0.1 mmol) was weighed into a 25 ml flask. To this was added the phosphine (0.2/0.4/0.6 mmol), followed by silver tetrafluoroborate (39–43 mg, 0.20–0.22 mmol). DCM (10 ml) was added, a nitrogen atmosphere was established, and the mixture was stirred for 20–30 min, giving a dark brown/black suspension. This solution was filtered through Celite and the pad was washed through with DCM until the filtrates became clear. The filtrate was made up to a total of 20 ml with DCM, to give a 10 μmol/ml solution of the iridium complex. This solution (1 ml/20 μmol) was added to the substrate; the system was degassed and flushed with deuterium, then sealed and stirred, typically for 48–72 h. After this time volatiles were evaporated and the residue was extracted with ether or ethyl acetate (5 ml) as appropriate. The extract was evaporated to give crude deuterated substrate; where readily exchangeable protons were present, the product was redissolved in methanol and evaporated, and this last process repeated before analysis.

Data obtained in the best case with each substrate are summarised below.

Exchange of acetophenone (2.4 μl, 20 μmol) in the presence of **2b** (10 μmol) gave [2,6-$^2H_2$]-acetophenone, *m*/*z* 122 ($M^{+\cdot}$), 107 ($PhCO^+$; average fragment mass 107.06, vs. 105.08 for unlabelled material).

Exchange of 3-bromoacetophenone (8.5 μl, 64 μmol) in the presence of **1b** (32 μmol) gave [2-$^2H_{0.6}$,6-$^2H_{0.9}$]-3-bromoacetophenone (13 mg). δ_H (270 MHz, $CDCl_3$) 2.58 (3H, s), 7.35 (1H, d, *J*=9 Hz, H5), 7.65–7.7 (1.1H, m, H2/4); *m*/*z*(EI) 202, 201, 200, 199 ($M^{+\cdot}$), 187, 186, 185, 184 ($[M-CH_3]^+$).

Exchange of 3-chloroacetophenone (8.3 μl, 64 μmol) in the presence of **1b** (32 μmol) gave [2-$^2H_{0.9}$,6-^2H]-3-chloroacetophenone (13 mg). δ_H (270 MHz, $CDCl_3$) 2.56 (3H, s), 7.37 (1H, d, *J*=8 Hz, H5), 7.50 (1H, d, *J*=8 Hz, H4), 7.79 (0.05H, d, *J*=8 Hz, H6), 7.89 (0.05H, s, H2); *m*/*z*(EI) 154, 156 ($M^{+\cdot}$), 139, 141 ($[M-CH_3]^+$).

Exchange of 3-methoxyacetophenone (8.8 μl, 64 μmol) in the presence of **1b** (32 μmol) gave [2,6-$^2H_{1.7}$]-3-methoxyacetophenone (7 mg). δ_H (270 MHz, $CDCl_3$) 2.57 (3H, s), 3.84 (3H, d, s), 7.09 (1H, d, *J*=9 Hz, H4), 7.3–7.4 (1H, m, H5), 7.47 (0.l5H, s, H2), 7.52 (0.15H, d, *J*=7.5 Hz, H6); *m*/*z*(EI) 152, 151 ($M^{+\cdot}$), 147, 146 ($[M-CH_3]^+$).

Exchange of 3-methylacetophenone (7.1 μl, 64 μmol) in the presence of **1b** (32 μmol) gave [2-$^2H_{0.9}$,6-^2H]-3-methylacetophenone (7 mg). δ_H (270 MHz, $CDCl_3$) 2.39 (3H, s), 2.56 (3H, s), 7.3–7.4 (2H, m), 7.75 (0.lH, s, H2); *m*/*z*(EI) 136, 135 ($M^{+\cdot}$), 121, 120 ($[M-CH_3]^+$).

Exchange of 3-nitroacetophenone (9.0 mg, 64 μmol) in the presence of **1b** (32 μmol) gave [2-$^2H_{0.9}$,6-^2H]-3-methylacetophenone (9 mg). δ_H (270 MHz, $CDCl_3$) 2.68 (3H, s), 7.67 (1H, m, H5), 8.27 (0.05H, d, *J*=7 Hz, H6), 8.41 (0.25H, d, *J*=9 Hz, H4), 8.77 (0.1H, s, H2); *m*/*z*(EI) 165 ($M^{+\cdot}$), 150 ($[M-CH_3]^+$).

Exchange of phenylacetone (7.2 μl, 50 μmol) in the presence of **2b** (25 μmol) gave [2,6-$^2H_{0.5}$]-phenylacetone (6 mg) as a colourless oil. δ_H ($CDCl_3$) 2.14 (3H, s), 3.69 (2H, s), 7.19 (1.5H, br d, *J*=7.0 Hz, H2/6), 7.25–7.28 (1H, m, H4), 7.30–7.36 (2H, m, H3/5). *m*/*z* 135, 134 ($M^{+\cdot}$), 92, 91 (100%).

Exchange of ethyl benzoate (3.0 μl, 20 μmol) in the presence of **2b** (isolated complex; 9.1 mg, 10 μmol) gave [benzoic acid-2,6-$^2H_{1.8}$]-ethyl benzoate, *m*/*z* 152, 151 ($M^{+\cdot}$), 107, 106 ($PhCO^+$; average fragment mass 106.89, vs 105.08 for unlabelled material).

Exchange of *N*,*N*-dimethylbenzamide (12 mg, 80 μmol) in the presence of bis(cyclooctadiene)iridium(I) tetrafluoroborate

(28 mg, 40 μmol) gave [2,6-$^2H_{1.9}$]-*N*,*N*-dimethylbenzamide (2 mg), δ_H (500 MHz, 70°C, CD_3SOCD_3) 2.94 (6H, s), 7.36–7.39 (2H, m), 7.40–7.43 (1.1H, m); *m/z* 152, 151, 150, 149 ($M^{+\cdot}$/$[M-H]^+$), 107, 106 ($PhCO^+$; average fragment mass 106.99, vs 105.08 for unlabelled material).

Exchange of benzenesulfonamide (12 mg, 76 μmol) in the presence of **1a** (40 μmol) gave [2,6-$^2H_{1.7}$]-benzenesulfonamide (8 mg). δ_H (500 MHz, 70°C, CD_3SOCD_3) 7.28–7.34 (3H, m, H4/NH_2), 7.53–7.60 (2H, m, H3/5), 7.82 (0.3H, br d, *J*=8.0 Hz, H2/6); *m/z* 157 ($M^{+\cdot}$), 77 ($C_6H_5^+$).

Exchange of methyl phenyl sulfoxide (6 mg, 43 μmol) in the presence of **1a** (20 μmol) gave [2,6-$^2H_{1.8}$]-methyl phenyl sulfoxide. δ_H (500 MHz, 70°C, CD_3SOCD_3) 3.70 (3H, s), 7.45–7.53 (3H, m), 7.63 (0.2H, br d, *J*=7.3 Hz); *m/z* 142, 141 ($M^{+\cdot}$), 127, 126 ($[M-CH_3]^+$).

Exchange of acetophenone *O*-methyl oxime (12 mg, 80 μmol) in the presence of **1b**, (40 μmol) gave [2,6-$^2H_{1.7}$]-acetophenone *O*-methyl oxime (10 mg). δ_H (270 MHz, $CDCl_3$) 2.25 (3H, s), 4.01 (3H, s), 7.35–7.40 (3H, m, H3/4/5), 7.60–7.70 (0.3H, m, H2/6); *m/z* 151, 150 ($M^{+\cdot}$).

Exchange of 2-phenylpyridine (3.1 mg, 20 μmol) in the presence of **2b** (isolated complex; 9.1 mg, 10 μmol) gave [2,6-$^2H_{1.8}$]-2-phenylpyridine (3 mg). δ_H (500 MHz, CD_3SOCD_3) 7.34 (1H, ddd, *J*=7.4, 4.9, 1.2 Hz, H5), 7.42 (1H, m, H4′), 7.46–7.50 (2H, m, H3′/5′), 7.86 (1H, ddd, *J*=8.0, 7.4, 1.8 Hz, H4), 7.94 (1H, ddd, *J*=8.0, 1.2, 1.1 Hz, H3), 8.07 (0.2H, d, *J*=8.0 Hz, H2′/6′), 8.66 (1H, ddd, *J*=4.9, 1.8, 0.9 Hz, H6); *m/z*(EI) 157, 156 ($M^{+\cdot}$), 129, 128 ($[M-HCN]^+$).

Exchange of 1-phenylpyrazole (5.6 mg, 40 μmol) in the presence of **1d** (20 mmol) gave [2,6-$^2H_{1.5}$]-1-phenylpyrazole (4 mg). δ_H (500 MHz, CD_3SOCD_3) 6.53 (1H, dd, *J*=2.3, 2.0 Hz, H4), 7.29 (1H, m, H4′), 7.46–7.51 (2H, m, H3′/5′), 7.73 (1H, dd, *J*=2.0, 0.6 Hz, H5), 7.83 (0.5H, br d, *J*=8.6 Hz, H2′/6′), 8.47 (1H, dd, *J*=2.3, 0.6 Hz, H3); *m/z* 146, 145, 144 ($M^{+\cdot}$), 118, 117, 116 ($[M-HCN]^+$).

Exchange of 5-acetyl-3-phenylisoxazole (3.7 mg, 20 μmol) in the presence of **1c** (10 μmol) gave [2,6-$^2H_{1.8}$]-5-acetyl-3-phenylisoxazole, *m/z* 189, 188, 187 ($M^{+\cdot}$), 146, 145, 144 ($[M-CH_3CO]^+$; average fragment mass 94.98, vs 144.16 for unlabelled material).

Exchange of 4-phenylthiazole (3.2 mg, 20 μmol) in the presence of **1b** (10 μmol) gave [2,6-$^2H_{1.7}$]-4-phenylthiazole, *m/z* 163, 162 ($M^{+\cdot}$; average molecular ion mass 162.87, vs. 161.19 for unlabelled material), 136, 135 (average fragment ion mass 135.85, vs 134.17 for unlabelled material).

Exchange of acetanilide (2.7 mg, 20 μmol) in the presence of **3c** (10 μmol) gave [2,6-$^2H_2$]-acetanilide, *m/z* 137 ($M^{+\cdot}$), 95 ($PhNH_2^{+\cdot}$; average fragment ion mass 94.98, vs 92.99 for unlabelled material).

4.1.2. NMR experiment. Preparation of Ir(cod)$(PPh_3)^+$. BF_4^- (3b). A suspension of silver tetrafluoroborate (5 mg) in deuterochloroform (0.5 ml) containing bis(1,5-cyclooctadiene)diiridium(I) dichloride (6.5 mg, 10 μmol) and triphenylphosphine (5.3 mg, 20 μmol) was stirred for 20 min, then filtered through Celite. The filter cake was washed through with a little additional deuterochloroform, and the yellow filtrate was transferred to an NMR tube. δ_H ($CDCl_3$) 1.9–2.0 (4H, m), 2.2–2.6 (4H, m), 4.19 (4H, br s), 7.3–7.75 (15H, m); δ_P ($CDCl_3$) 18.55, 20.51 (ca. 9:1).

This general technique, with appropriate changes in ligand stoichiometry, was also used to prepare: Ir(cod)$(MePPh_2)^+$. BF_4^- (**3c**) as a yellow solution. δ_H ($CDCl_3$) 1.70 (1H, d, *J*=6.2 Hz, P–CH_3), 1.8–2.5 (8H, m), 2.00 (0.5H, d, *J*=6.2 Hz, P–CH_3), 2.06 (1H, d, *J*=12.5 Hz, P–CH_3), 2.37 (0.5H, d, *J*=12.5 Hz, P–CH_3), 3.46 (2H, br s), 4.23 (2H, br s), 7.15–7.75 (10H, m); δ_P ($CDCl_3$) 3.07, 37.37, 51.93 (ca. 8:1:1).

Ir(cod)$(PPh_3)_2^+$.BF_4^- (**1b**) as a ruby red solution.[8,9] δ_H ($CDCl_3$) 1.55–2.12 (4H, m), 2.30–2.54 (4H, m), 4.19 (4H, br s), 7.25–7.70 (30H, m); δ_P ($CDCl_3$) 18.58.

Ir(cod)$(MePPh_2)_2^+$.BF_4^- (**1c**) as a ruby red solution.[9,10] δ_H ($CDCl_3$) 1.70 (6H, d, *J*=6.2 Hz, P–CH_3), 1.95–2.05 (4H, m), 2.25–2.35 (4H, m), 4.21 (4H, br s), 7.30–7.60 (20H, m); δ_P ($CDCl_3$) 3.05.

Ir(cod)$[P(C_6F_5)_3]_2^+$.BF_4^- (**1d**) as a ruby red solution. δ_H ($CDCl_3$) 1.86 (4H, m), 2.34 (4H, m), 3.48 (1H, m), 3.74 (1H, m), 4.03 (1H, br s), 5.24 (1H, m).

Ir(cod)$(P\text{-2-furyl}_3)_2^+$.BF_4^- (**1e**) as a ruby red solution. δ_H ($CDCl_3$) 1.56–1.67 (4H, m), 2.28–2.37 (4H, m), 4.81 (4H, br s), 6.47–6.49 (6H, m), 6.69–6.71 (6H, m), 7.59 (6H, br s).

Ir(cod)$[P(c\text{-}C_6H_{11})_3]_2^+$.$BF_4^-$ (**1f**) as a ruby red solution. δ_H ($CDCl_3$) 1.10–2.05 (66H, m), 2.10–2.30 (4H, m), 4.24 (2H, br s), 4.80–4.85 (2H, m).

Ir(cod)$(AsPh_3)_2^+$.BF_4^- (**1h**) as a ruby red solution.[11] δ_H ($CDCl_3$) 1.50–1.90 (4H, m), 2.15–2.45 (4H, m), 3.55 (2H, br s), 4.36 (2H, br s), 7.25–7.35 (12H, m), 7.35–7.50 (18H, m).

Ir(cod)$(P\text{-}t\text{-}Bu_3)_2^+$.$BF_4^-$ (**1k**) as a ruby red solution. δ_H ($CDCl_3$) 1.46 (54H, s), 1.60–1.64 (4H, m), 2.20–2.30 (4H, m), 4.25 (4H, br s).

Ir(cod)$(PPh_3)_3^+$.BF_4^- (**2b**) as a ruby red solution. δ_H ($CDCl_3$) 1.90–1.95 (4H, m), 2.3–2.4 (4H, m), 4.03 (2H, br s), 4.19 (2H, br s), 7.25–7.70 (45H, m); δ_P ($CDCl_3$) 18.56.

Ir(cod)$(MePPh_2)_3^+$.BF_4^- (**2c**) as a ruby red solution. δ_H ($CDCl_3$) 1.71 (3H, d, *J*=6.2 Hz), 1.60–2.50 (14H, m), 4.22 (4H, br s), 7.20–7.60 (30H, m); δ_P ($CDCl_3$) 3.04.

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