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Research Article

Ligand effects upon deuterium exchange in arenes mediated by $[Ir(PR_3)_2(cod)]^+.BF_4^-$

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Summary

A series of complexes of general form $[Ir(PR_3)_2(cod)]^+$ has been prepared and used, without isolation, to mediate deuteration of a range of model substrates. The data suggest that, with many substrates, basicity of the phosphine ligands bound to iridium is an important factor influencing substrate selectivity and the efficiency of deuteration. In addition, the spectrum of activity of iridium complexes bearing pure donor ligands is different in many cases to that of complexes where the ligands are known to be π-acids. Copyright © 2003 John Wiley & Sons, Ltd.

Key Words: iridium complexes; isotope exchange; *ortho*-deuteration; ligand effects

Introduction

Metal complex-mediated exchange of isotopic hydrogen is a method already used for the preparation of drug candidates labeled with tritium, without the need for lengthy precursor syntheses.[1] The technique could also be used in the preparation of deuterium-labeled molecules if its efficiency and reproducibility could be improved. Recent work from these laboratories includes some examples where better than 95% *ortho*-hydrogen exchange was observed,[2–5] raising the possibility that the technique might be applicable to the preparation of deuterated drug candidates for use as mass spectrometric standards. That pre-catalysts can be prepared and used without isolation is an added advantage, since this technique requires no more than minimal precautions

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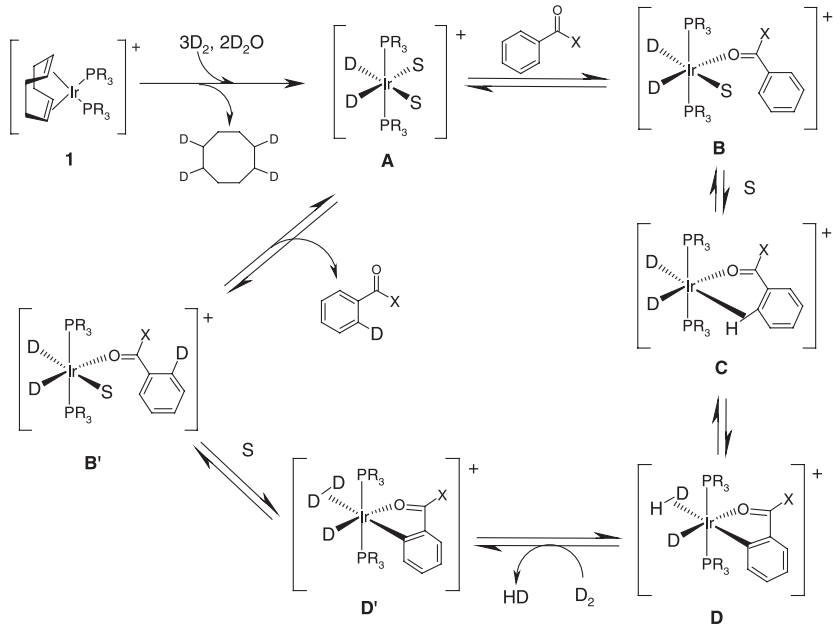
for protection of the complex and substrate from the atmosphere. Similar observations have been reported by Salter *et al.*[6]

In this work, we examine the effect of ligand stereoelectronic properties on the efficiency of isotope exchange with different substrates mediated by $[Ir(PR_3)_2(cod)]^+.BF_4^-$ (**1**). Steric demand, σ-donicity, and π-acidity and basicity of ligands at the iridium centre can all be expected to play a part in determining substrate selectivity for a given complex. However, the situation is unlikely to be simple, since exchange is a multi-step process and ligands favoring one step may inhibit others. Moreover, in coordinating to the metal centre, different substrate types will themselves affect the environment at the metal centre in different ways. Consequently, no one complex is likely to mediate optimum levels of exchange in all substrates. However, ligand variation allows the creation of a panel of catalysts with differing characteristics, which should be reflected in a range of substrate selectivities. From this premise, we set out to determine whether any relationship existed between ligand properties and the efficiency of exchange for each model substrate, in the expectation that this might guide us toward more effective catalysts.

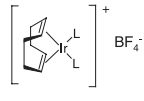
Results and discussion

The accepted mechanistic scheme for deuterium exchange (Scheme 1)[7] involves a series of octahedral iridium(III) species, in which the bulky phosphine ligands are mutually *trans*. Exposure of **1** to hydrogen is known to form a dihydride complex in the first instance,[8] and subsequent hydrogenolysis of the cyclooctadiene ligand is expected to give a catalytically active species **A** (where S is coordinated solvent, which may be adventitious water). Substrate binding to form intermediate **B** will depend upon the electron density at the metal centre (an electron-rich substrate may be expected to bind efficiently to an electron-deficient metal centre and *vice versa*), and upon the degree of steric congestion around the metal. Subsequent agostic interaction (intermediate **C**) and cyclization to form **D** will again be dependent upon ligand stereoelectronic properties. In particular, this process could be impeded by excessive congestion around the metal centre. Exchange of bound HD in this fluxional intermediate with the deuterium atmosphere (to form **D′**) is critical to the exchange process, and it is unclear to what extent this exchange can be promoted by ligand effects. Finally, for the process to proceed effectively, the preceding steps must be reversed, and substrate liberated from intermediate **B′** to re-form active catalyst **A**. If an exchanged substrate is bound too tightly, it may not be recovered.

The basicity of a complexed metal centre is known to be influenced strongly by ligand basicity,[9] and there are therefore a number of points at which ligand properties can influence the process for better or for worse, and so it is difficult



a. L = $P(OPh)_3$ **b**. L = $P(p\text{-}C_6H_4Cl)_3$ **c**. L = $P(p\text{-}C_6H_4F)_3$
d. L = $PhP(OMe)_2$ **e**. L = Ph_2POMe **f**. L = PPh_3
g. L = $P(o\text{-Tolyl})_3$ **h**. L = $P(m\text{-Tolyl})_3$ **i**. L = $P(OEt)_3$
j. L = $P(p\text{-Tolyl})_3$ **k**. L = $P(p\text{-anisyl})_3$ **m**. L = PPh_2Me
n. L = PBn_3 **o**. L = $PPhMe_2$ **p**. L = P-*i*-Bu_3
q. L = PBu_3 **r**. L = P(cyclohexyl)$_3$ **s**. L = P-*i*-Bu_3



Scheme 1. Proposed catalytic cycle for deuterium exchange using pre-catalysts 1

to predict the overall effect of a change in ligand properties in any given case. However, the electronic properties of a directing functionality should correspond to an optimum combination of ligand properties and, given the disparity between functionalities, a range of such optima are to be expected.

A number of parameters have been used to quantify the stereoelectronic properties of phosphine ligands in particular. The Tolman cone angle, θ,[10] is widely accepted as a measure of steric demand, while the spectroscopically derived parameters, ν and χ,[10] are claimed to be most representative of the overall interaction between ligand and metal. Alternatives include the solvatochromic parameters, E and C,[11] the enthalpy of protonation (ΔH_{HP}) of the ligand,[12] and ligand pK_a. Giering and co-workers[13] have found that both pK_a and χ are reasonable measures of ligand σ-donicity, although pK_a is limited in that the interaction between a soft phosphorus and a proton cannot be entirely predictive of that between a phosphorus and a soft metal centre. In addition, pK_a takes no account of ligand π-basicity or acidity, although the

same workers have been successful in distinguishing π-acidic and π-basic phosphines from pure σ-donors.

Using the methodology described previously,[4] we prepared a range of complexes **1**, and evaluated their effectiveness as mediators of deuterium exchange, using a range of substrates in which exchange would proceed *via* a five-membered metallacycle. Table 1 summarizes the results obtained upon deuterium exchange of a range of simple substrates with complexes **1**. As expected, variation of the ligands at the iridium centre does result in catalysts with a range of substrate selectivities. Indeed, better than 75% incorporation was observed, using at least one complex, with substrates of general form ArC(R)=*X*. In contrast, only modest levels of isotopic exchange were observed with methyl phenyl sulfoxide and benzenesulfonamide, and deuteration of methyl phenyl sulfone was never observed. It appears that complexes **1** are not well suited to mediate exchange in these substrates. With other substrates, slightly higher levels of exchange would be expected, had the isolated complexes been used; nevertheless, the present data are valid as a guide to the relative efficacy of different complexes as isotope exchange catalysts.

*Steric effects in exchange mediated by complexes **1***

Amongst the systems examined, only **1s** has a poor activity profile that could be attributed to steric reasons. Although this complex has not been reported

Table 1. Results from deuteration of simple substrates with complexes 1[a]

	Phosphine	θ (°)	pK_a	PhCOMe	Oxime	PhCOOMe	PhS(O)Me	$PhSO_2NH_2$
1a	$P(OPh)_3$	128	−2.0	1.0	0.0	0.0	0.5	0.8
1b	$P(p\text{-}C_6H_4Cl)_3$	145	1.0	1.6	1.5	0.2	0.4	0.3
1c	$P(p\text{-}C_6H_4F)_3$	145	2.0	0.8	1.4	0.8	0.3	0.3
1d	$PhP(OMe)_2$	115	2.6	1.5	0.7	0.1	0.0	0.0
1e	Ph_2POMe	132	2.7	0.4	0.0	0.0	0.0	0.5
1f	PPh_3	145	2.7	1.6	1.2	1.2	0.2[b]	0.1
1g	$P(o\text{-Tolyl})_3$	194	3.1	1.3	1.3	0.1	0.3	0.5
1h	$P(m\text{-Tolyl})_3$	145	3.3	1.7	1.3	1.3	0.4[b]	0.3
1i	$P(OEt)_3$	109	3.3	0.0	0.0	0.0	0.3	1.6
1j	$P(p\text{-Tolyl})_3$	145	3.8	1.1	1.0	0.0	[c]	0.5
1k	$P(p\text{-Anisyl})_3$	145	4.6	1.8	0.6	0.0	0.0	0.0
1m	PPh_2Me	136	4.6	1.5	1.6	1.1	0.3	0.0
1n	PBn_3	165	6.0	1.8	1.4	0.0	0.0	0.7
1o	$PPhMe_2$	122	6.5	1.7	1.6	0.0	0.4[b]	0.1
1p	$P\text{-}i\text{-}Bu_3$	143	8.0	1.5	1.8	0.0	0.4	0.4
1q	PBu_3	132	8.4	1.7	1.7	1.3	0.2	0.0
1r	PCy_3	170	9.7	1.7	1.0	0.1	0.1	0.6
1s	$P\text{-}t\text{-}Bu_3$	182	11.4	0.0	0.0	0.0	0.1	0.1

[a] Figures quoted are the number of *ortho* deuterium atoms per molecule of substrate, as determined by mass spectrometry.
[b] Some reduction observed to thioanisole.
[c] Entirely reduced to thioanisole (1.1D).

previously, the rhodium complex $Rh(P\text{-}t\text{-}Bu_3)_2(CO)Cl$ is known and the steric demand of the phosphine ligands is believed to be the cause of its tetrahedral, rather than square planar, structure,[14] so it is entirely possible that the geometry of the dihydride species corresponding to **1s** is substantially distorted also. However, a range of substrates undergoes comparatively efficient exchange mediated by the most sterically demanding complex **1g**, so the behavior observed with **1s** may be more a consequence of the high basicity of tri-*tert*-butylphosphine.

Steric hindrance at the metal centre in Crabtree's complex, $[Ir(cod)(Py)(PCy_3)]^+.PF_6^-$ (**2**), does not prevent this being an efficient mediator of deuteration,[2] but in this case steric bulk is reflected in an intolerance toward *meta*-substituents in even the better substrates. In view of this experience, the exchange of a selection of *meta*-substituted acetophenones was examined (Table 2), and it is clear that *meta*-substituents do not significantly impede the exchange process, even with **1g**. In practice, then, the steric effect of ligands upon the exchange process mediated by complexes **1** appears to be minor.

*Electronic effects on exchange mediated by complexes **1***

Of the electronic parameters mentioned above, we found essentially no correlation of the degree of exchange with E_b, C_b, or ν for any substrate. Nevertheless, limited relationships between deuterium incorporation and ligand pK_a are apparent for many substrates. With acetophenone, exchange proceeded consistently to between 75 and 90% of the theoretical maximum. The principal exceptions to this generalization are phosphite complexes **1a** and **1i**, and the very basic **1s**. Essentially the same pattern is observed using χ as the electronic parameter which, given the reported close correlation between χ and pK_a,[13] is to be expected. A very similar pattern is also observed for the *O*-methyloxime derived from acetophenone with, once again, **1a**, **1i** and **1s** having the poorest activity. In this case, the maximum achievable incorporation was 1.9D. Since the oxime used contained ca. 5% of the *Z* isomer, which would not be expected to undergo exchange.[5] Nevertheless, there is no trend

Table 2. Deuteration of 3-*X*-substituted acetophenones with selected complexes 1[a]

Catalyst	**1f**		**1g**		**1r**	
θ	145		194		170	
	H2	H6	H2	H6	H2	H6
X = H	0.8	0.8	0.65	0.65	0.85	0.85
Cl	0.95	0.95	0.5	0.5	0.85	0.85
OMe	0.85	0.85	0.5	0.5	0.85	0.85

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

that could guide one to a complex **1** with better activity towards either acetophenone or its oxime than those assayed so far.

Ethyl benzoate is expected to be a poorer donor ligand than either acetophenone or *N,N*-dimethylbenzamide. Consequently, the observation that complexes with π-acidic phosphine ligands mediate only low levels of exchange is not surprising. It was expected that complexes with more basic ligands would be the most efficient catalysts for exchange in this case and, indeed, most complexes with ligands of pK_a 2–10 mediate deuteration of ethyl benzoate. However, the incorporations obtained are generally modest, the results do not follow a consistent trend, and the best catalysts (**1f**, **1h** and **1q**) cover a considerable range of ligand basicity.

A number of substrates are able to undergo deuteration adjacent to an amide or pyridine-like nitrogen, as well as at *ortho*-sites, and results for these are presented in Table 3. The first of these is dimethylbenzaminde, in which case there is a general trend, with a few notable exceptions (Figure 1), where the degree of exchange increases as the ligands become less basic. This is broadly consistent with improved initial binding of the more electron-rich (relative, at least, to acetophenone) substrate to the metal centre as the latter becomes more electron-deficient. The results obtained using **3** (80% *ortho*-deuteration),[2] where the metal centre will be more electron-deficient again, are in line with this observation, and it appears that complexes **1** are not the ideal

Table 3. Multi-site deuteration of selected substrates with complexes 1[a]

	Substrate	$PhCONMe_2$							
Catalyst	Phosphine	C2/C6	NMe_2	C2′/6′	C3	C2′/6′	C6	NMe_2	C6
1a	$P(OPh)_3$	1.3	0.4	0.0	0.0	0.5	0.1	0.9	0.7
1b	$P(p\text{-}C_6H_4Cl)_3$	1.8	1.2	0.6	0.0	0.7	0.1	2.8	0.6
1c	$P(p\text{-}C_6H_4F)_3$	1.0	3.1	0.1	0.0	1.0	0.0	4.5	0.3
1d	$PhP(OMe)_2$	0.9	0.0	1.2	0.0	1.9	0.3	0.0	0.2
1e	Ph_2POMe	0.0	0.0	0.5	0.0	0.6	0.1	0.0	0.2
1f	PPh_3	1.1	4.3	1.7	0.1	1.4	0.5	4.2	0.8
1g	$P(o\text{-Tolyl})_3$	0.9	0.2	1.3	0.0	1.2	0.1	1.5	0.1
1h	$P(m\text{-Tolyl})_3$	1.1	3.6	0.3	0.0	0.8	0.4	0.0	0.2
1i	$P(OEt)_3$	0.6	0.0	1.0	0.0	0.7	0.4	0.5	0.0
1j	$P(p\text{-Tolyl})_3$	0.3	0.3	0.0	0.0	0.4	0.1		
1k	$P(p\text{-Anisyl})_3$	1.7	5.5	1.1	0.1	1.0	0.2	3.3	0.7
1m	PPh_2Me	1.5	4.9	1.3	0.1	0.8	0.1	3.5	0.7
1n	PBn_3	0.8	0.5	0.7	0.5	1.3	0.0	3.0	0.5
1o	$PPhMe_2$	0.7	0.2	1.5	0.2	0.9	0.2	2.8	0.0
1p	$P\text{-}i\text{-}Bu_3$	0.7	0.7	0.5	0.0	0.7	0.1	3.2	0.2
1q	PBu_3	0.7	0.0	1.2	0.2	0.2	0.0	1.1	0.2
1r	PCy_3	0.5	0.0	0.4	0.0	0.0	0.5	1.5	0.5
1s	$P\text{-}t\text{-}Bu_3$	0.0	0.0	0.1	0.0	0.4	0.1	0.1	0.3

[a] Figures quoted are the number of deuterium atoms in specified positions, as determined by mass spectrometry.

mediators of exchange for this type of substrate. Ligand pK_a does seem to be an important influence upon exchange into *N*,*N*-dimethylbenzamide, although it is not the only one, and process must also be affected by the previously observed capacity of this substrate to act as an efficient ligand for its own deuteration.[4] There is no general correlation between levels of exchange at *ortho* sites and into dimethylamino groups; nevertheless, the two complexes that give higher than expected incorporation into the arene ring also give the highest levels of incorporation into the *N*-methyl groups, suggesting that there is some link between the processes. However, hydrogens attached to an *N*-methyl group are in a very different electronic environment to those at an *ortho* position, so that the same complex would not necessarily favour cyclometalation to an *ortho* position and to an *N*-methyl group.

In principle, a similar situation arises with iridium-mediated exchange into 1-phenylpyrazole, which incorporates 1.2 D in the absence of any additional coordinating ligand.[4] Since 1-phenylpyrazole is expected to be a more tightly bound ligand than is *N,N*-dimethylbenzamide, the influence of phosphine pK_a upon exchange is therefore be limited by this factor, so the absence of a relationship between ligand basicity and the level of exchange for 1-phenylpyrazole is no surprise. Moreover, the best incorporations achieved by complexes **1** remain less than the complete exchange already observed using **3**,[2] so the presence of two phosphine ligands could be said to impede exchange in this instance. 1-Phenylpyrazole is also able to incorporate deuterium at C3 of the heterocyclic ring, but the extent to which this occurs is generally slight, and does not appear to be related to the simultaneous *ortho* exchange.

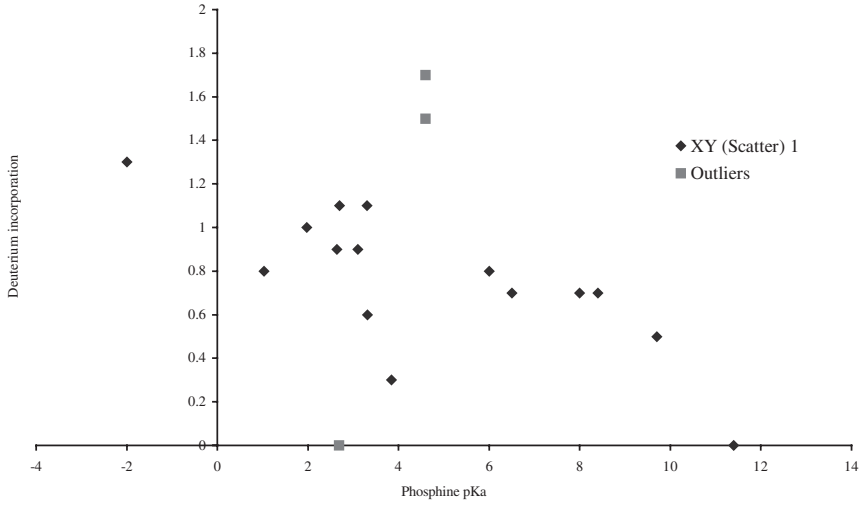


Figure 1. Deuterium incorporation as a function of phosphine pK_a in the *ortho*-deuteration of *N,N*-dimethylbenzamide

The recently reported isolation of a cyclometalated iridium species from 2-dimethylaminopyridine[15] provides good evidence that, as postulated previously,[2] exchange at these sites proceeds by cyclometalation in the same manner as *ortho*-exchange. It was therefore gratifying to observe that with both 2-phenylpyridine and 2-dimethylaminopyridine, complexes with pure σ-donor ligands become generally better mediators of *ortho*-deuteration as the phosphine pK_a decreases. Exceptions to this trend (Figure 2), are the phosphonate and phosphinate complexes **1e** and **1h**, and sterically encumbered **1g**. This is consistent with improved initial binding of the substrate to the metal as the latter becomes more electrophilic and, as with *N,N*-dimethylbenzamide, **3** promotes complete exchange into 2-phenylpyridine.[2] The four complexes with π-acidic ligands give generally poorer activity than pure donor ligands of similar basicity, and do not fit the correlation for either substrate.

The mechanism of exchange adjacent to a pyridine-like nitrogen is of some interest also, and it was hoped that some pattern could be discerned from the data for exchange at C6 of 2-phenylpyridine and of 2-dimethylaminopyridine. However, not only did these results prove to be entirely independent of ligand basicity but, beyond the fact that **1f** mediates the highest incorporation at C6 of both pyridine substrates, no relationship could be detected between the levels of exchange into the two substrates. If this process involved initial coordination of the pyridine nitrogen to the metal as previously proposed,[2] exchange at C6 should follow a similar general trend to that just described for *ortho* exchange. It is therefore more likely that reduction/reoxidation of a carbon–nitrogen double bond follows π-coordination *via* a η^6 species, or a η^2

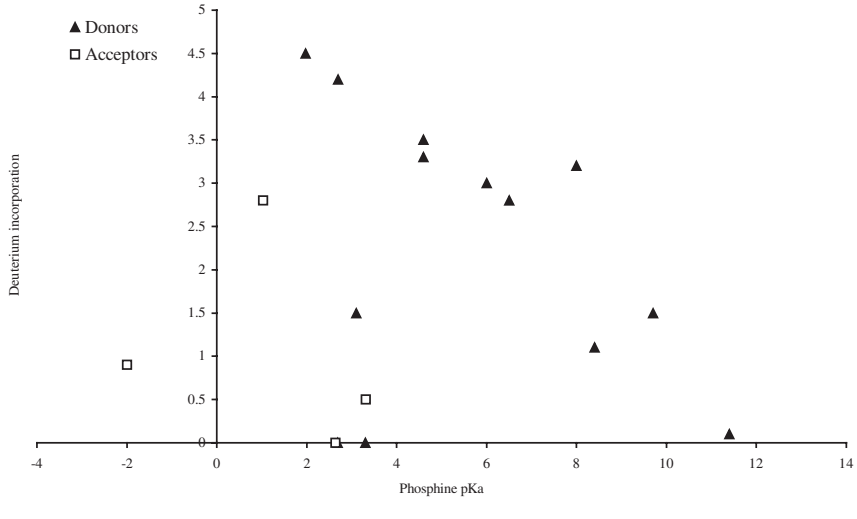
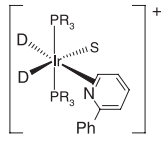


Figure 2. Deuterium incorporation as a function of phosphine pK_a in the *N*-methyl deuteration of 2-(dimethylamino)pyridine

intermediate such as **4**. In such cases, there is some evidence in the literature that the rate-determining step is hydrogen transfer to the substrate.[16]



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In conclusion, we have demonstrated that ligand stereoelectronic properties have a detectable effect upon the efficiency of iridium complex-mediated isotope exchange in a number of substrates and, amongst these, there are several where a definite correlation is observed between ligand pK_a and deuterium incorporation. Nevertheless, such correlations never account fully for the observations and, in many cases, the best levels of incorporation are obtained with complexes that do not fit the correlation. There are further cases where incorporation is entirely independent of ligand pK_a, including most of the substrates previously identified as capable of acting as effective ligands for exchange in the absence of any added phosphine.

Experimental

Gas chromatographic and NMR conditions, substrate preparations, and the general exchange procedure were as described previously.[2,4] Based on reported kinetic data,[4] exchange was carried out using a standard protocol with 20 μmol of substrate and 10 μmol of complex/1 ml of solution (to eliminate concentration as a possible variable), and was allowed to proceed for 64–68 h at room temperature (18–21°C) in all cases, to ensure that equilibrium had been reached. *Bis*(1,5-cyclooctadiene)diiridium(I) dichloride (Strem) and phosphines were obtained from commercial suppliers.

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References

1. Shu AYL, Heys JR. *J Organomet Chem* 1996; **524**: 87; Chen W, Garnes KT, Levinson SH, Saunders D, Senderoff SG, Shu AYL, Villani AJ, Heys JR. *J Label Compd Radiopharm* 1997; **39**: 291; Shu AYL, Heys JR. *Tetrahedron Lett* 2000; 41: 9015; Hesk D, Das PR, Evans B. *J Label Compd Radiopharm* 1995; **36**: 497.
2. Ellames GJ, Gibson JS, Herbert JM, McNeill AH. *Tetrahedron* 2001; **57**: 9487.
3. Ellames GJ, Gibson JS, Herbert JM, Kerr WJ, McNeill AH. *Tetrahedron Lett* 2001; **41**: 6413.
4. Cross PWC, Ellames GJ, Gibson JS, Herbert JM, Kerr WJ, McNeill AH, Mathers TW. *Tetrahedron* 2003; **59**: 3349.
5. Gibson JS, Herbert JM. *J Label Compd Radiopharm* 2003; **46**: 531.

6. Salter R, Chappelle M, Morgan A, Ackermann P, Moenius T, Studer M, Spindler F, Togni A. Advances in homogeneous metal catalysed H/D exchange. In *Synthesis and Applications of Isotopically Labelled Compounds*, vol. 7, Pleiss U, Voges R (eds). Wiley: New York, 2001; 63.
7. Shu AYL, Heys JR. Organoiridium mediated hydrogen isotope exchange: observable intermediates in the cyclometalation of $[(cod)Ir(PPh_3)_2]BF_4$ with benzophenone. In *Synthesis and Applications of Isotopically Labelled Compounds*, vol. 6, Heys JR, Melillo DG (eds). Wiley: New York, 1998; 223.
8. Crabtree R. *Acc Chem Res* 1979; **12**: 331.
9. Jessop PG, Morris RH. *Coord Chem Revs* 1992; **121**: 155.
10. Tolman CA. *Chem Rev* 1977; **77**: 313.
11. Joerg S, Drago RS, Sales J. *Organometallics* 1998; **17**, 589.
12. Angelici RJ. *Acc Chem Res* 1995; **28**: 51.
13. Golovin MN, Rahman MM, Belmonte JE, Giering WP. *Organometallics* 1985; **4**: 1981; Rahman MM, Liu H-Y, Eriks K, Prock A, Giering WP. *Organometallics* 1989; **8**: 1.
14. Harlow RL, Westcott SA, Thorn DL, Baker RT. *Inorg Chem* 1992; **31**: 323.
15. Lee D-H, Chen J, Faller JW, Crabtree RH. *Chem Commun* 2001; 213.
16. Herrera V, Fuentes A, Rosales M, Sanchez-Delgado RA, Bianchini C, Meli A, Vizza F. *Organometallics* 1997; **16**: 2465.

