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Research Article

An improved bidentate complex of iridium as a catalyst for hydrogen isotope exchange

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Summary
Iridium(I) complexes **1**, containing bidentate phosphines, and **3**, with arsine ligands, are generated *in situ*. These species mediate hydrogen isotope exchange in a variety of aromatic substrates including benzyl ketones. Although the catalytic activities of complexes **1** and **3** are generally unexceptional, a logical step leads to the use of [ethylene-1,2-*bis*(diphenylarsine)](cyclooctadiene)iridium(I) tetrafluoroborate (**5**), which is an efficient catalyst for both aryl and benzyl ketones, and mediates exchange to a substantial extent in other substrates also. Copyright © 2005 John Wiley & Sons, Ltd.

Key Words: iridium complexes; deuterium exchange; isotope exchange

Introduction
The majority of the iridium complexes developed as catalysts for *ortho*-hydrogen isotope exchange are effective only where the directing heteroatom in the substrate is separated from the arene by a single carbon. Thus, aryl ketones, benzoate esters, benzamides, and a number of arylheterocycles can be exchanged with reasonable efficiency.[1–4] In principle, exchange in homologous species such as phenylacetone or derivatives of phenylacetic acid should be possible but, in practice, complexes of simple phosphines do not mediate such processes readily, although exchange with acetanilide and its derivatives does occur in some cases.[3,4]

Substrates such as ethyl phenylacetate are, in fact, exchanged by bidentate phosphine complexes such as **1a**.[5] This observation can be rationalised by considering the mechanism of exchange (Scheme 1). The adduct **A** is believed

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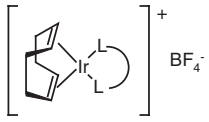
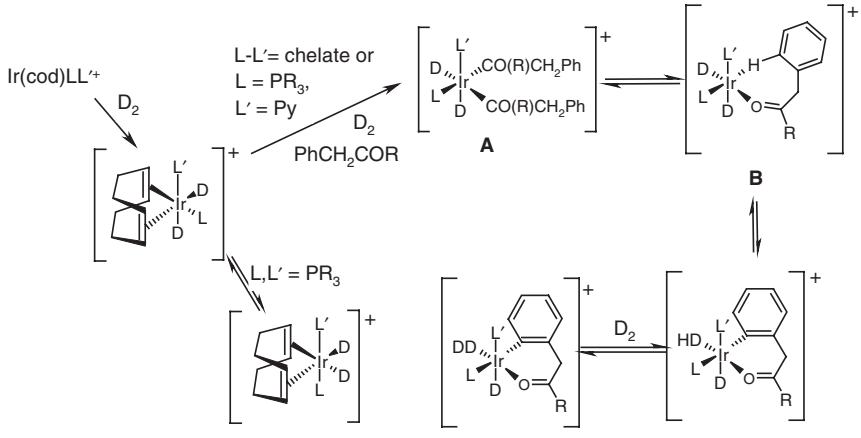


1

L-L	*L-L*
a. $Ph_2PCH_2CH_2PPh_2$	b. $Ph_2PCH_2CH_2CH_2PPh_2$
c. $Ph_2PCH_2PPh_2$	d. *o*-$C_6H_4(PPh_2)_2$
e. 2,2′-bis(diphenylphosphinyl)-1,1′-binaphthyl) [(±)-BINAP]	f. 1,1′-bis(diphenylphosphino)-ferrocene (dppf)
g. 9,9-dimethyl-4,5-bis(diphenyl-phosphino)xanthene [Xantphos]	h. $Cy_2PCH_2CH_2PCy_2$



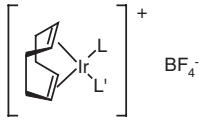
Scheme 1. Partial Mechanism for Deuterium Exchange in Phenylacetone or Ethyl Phenylacetate

to undergo cyclometalation *via* the agostic complex **B**: there is evidence for the formation of such agostic species and of the corresponding metallacycles from earlier work by Crabtree and co-workers.[6] However, the same work also describes deuterium exchange in both benzo[h]quinoline, which forms a metallacycle with iridium species, and with 8-methylquinoline where the iridium complex clearly contained an agostic bond from a methyl hydrogen to the metal, but cyclometalation did not occur. It is therefore unclear whether the cyclometalation step is essential to the exchange process in all cases, or whether exchange may simply follow weakening of a carbon–hydrogen bond by agostic interaction. It must also be uncertain whether cyclometalation absolutely has to be preceded by an agostic M–H interaction since, in principle, the proximity of *ortho* hydrogens to the metal centre in a species such as **A** must facilitate oxidative addition of the C–H bond to some extent.

Shu and Heys[5] suggested that because the coordinating centres in **1a** were constrained to lie *cis*, the corresponding active intermediates were less congested and better able to accommodate a six-membered metallacycle than were species where two simple phosphine ligands are *trans*-disposed. An improved explanation is that agostic interaction effectively forms a ring in

intermediate **B**, and the larger seven-membered ring can only be accommodated if the phosphine ligands are constrained by chelate formation. In either case, this rationale also explains the activity of Crabtree's catalyst, $Ir(cod)(Py)(PCy_3)^+.PF_6^-$ (**2**), as an exchange catalyst for phenylacetone and acetanilide,[3,4] since hydrogenation of **2** gives species in which the tricyclohexylphosphine and pyridine ligands have also been found to lie *cis*.[7]

In the course of an initial survey of the activity of simple phosphine complexes, we found that the monophosphine complex $Ir(cod)(MePPh_2)^+$, where it is assumed that the vacant fourth coordination is occupied either by adventitious water or the substrate, mediated complete *ortho* exchange in acetanilide.[2] However, analogues of this complex have much poorer activity, apparently degrading to form iridium metal within 24 h of exposure to deuterium. The most electron-rich complex of this series, $Ir(cod)(P\text{-}t\text{-}Bu_3)^+$, is more active than most toward phenylacetone, but even in this case exchange proceeds only to 20% of the theoretical maximum. In view of the reaction kinetics discussed later in this publication, it seems likely that it is the solution stability of these systems that limits their activity. We also found that the triphenylarsine complex **3a** had an interesting spectrum of activity,[2] mediating some incorporation into phenylacetone whereas the corresponding phosphine complex **4** did not. Since the bond radius of arsenic is greater than that of phosphorus,[8] this was also expected to result in less congestion at the metal centre. Our efforts to improve incorporation into phenylacetone, in particular, have therefore been focused in two areas: complexes with arsine ligands and with bidentate ligands.



3. (a) L,L′ = $AsPh_3$; (b) L,L′ = $As(p\text{-}C_6H_4F)_3$; (c) L,L′ = $As(p\text{-}C_6H_4Cl)_3$; (d) L,L′ = $MeAsPh_2$ (e) L,L′ = $As(p\text{-}C_6H_4OMe)_3$; (f) L,L′ = $AsEt_3$; (g) L = $AsPh_3$, L′ = PPh_3.

4. L,L′ = PPh_3.

Results and discussion

Our initial results using **1a**, formed *in situ*, to mediate deuterium exchange into phenylacetone were unexceptional. It had been assumed by ourselves and by previous workers,[5] that the kinetics of exchange with complexes **1** would be comparable to those of complexes such as **2** and **4**, where exchange is largely complete within 24 h.[2,4] However, this assumption proves to have been incorrect. Not only is exchange using **1a** comparatively slow (Figure 1), but exchange into phenylacetone is very much slower than into acetophenone. This observation prompted us to re-examine the kinetics of exchange with the dppp complex (**1b**; Figure 2) and of the *bis*(triphenylarsine) complex (**3a**; Figure 3). In these cases also, exchange is slower than with **4**. The differences

between exchange processes with these catalysts are equally interesting. Exchange of acetophenone with **3a** follows the pattern observed previously with **4**, in that after an initial induction period, which will correspond to hydrogenolysis of the cyclooctadiene ligand, exchange is rapid for a short period. Nevertheless, the process effectively stops within 12 h, possibly as a

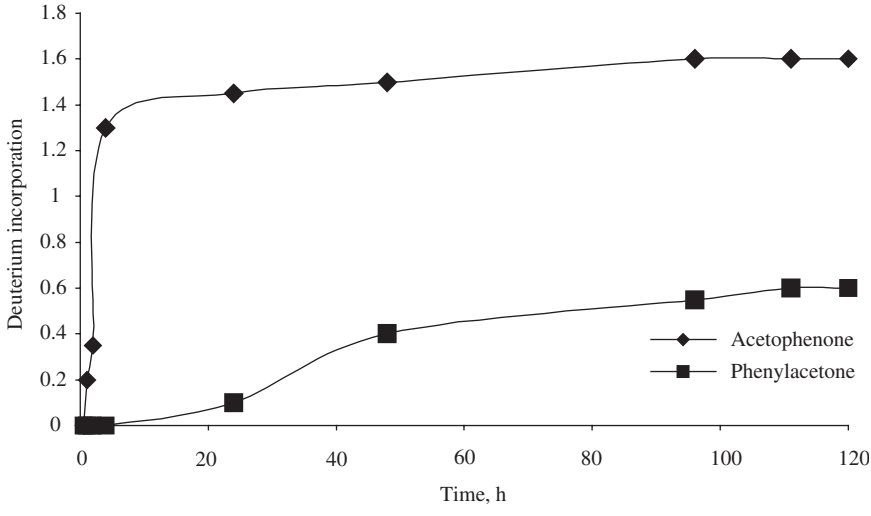


Figure 1. Variation of incorporation over time (2:1 substrate/catalyst) for *ortho*-deuteration of acetophenone and phenylacetone with complex 1a

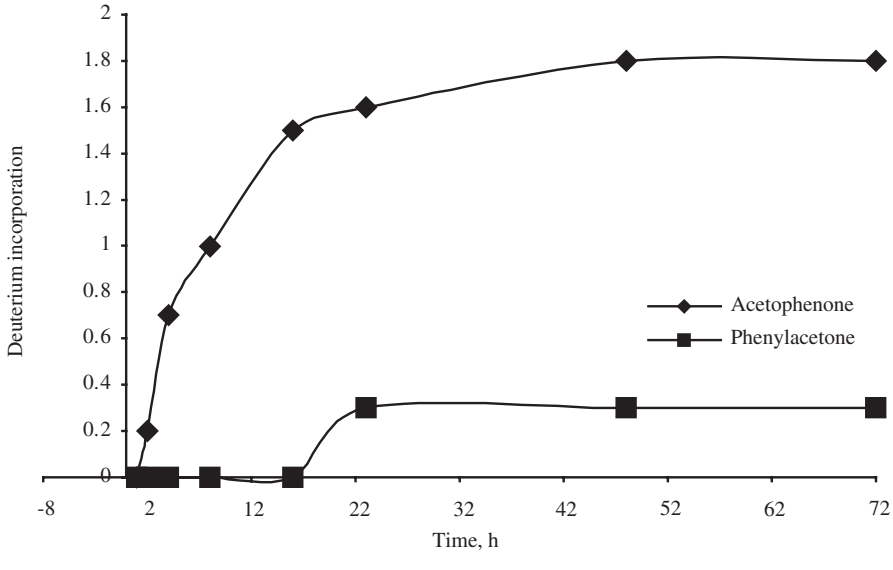


Figure 2. Variation of incorporation over time (2:1 substrate/catalyst) for *ortho*-deuteration of acetophenone and phenylacetone with complex 1b

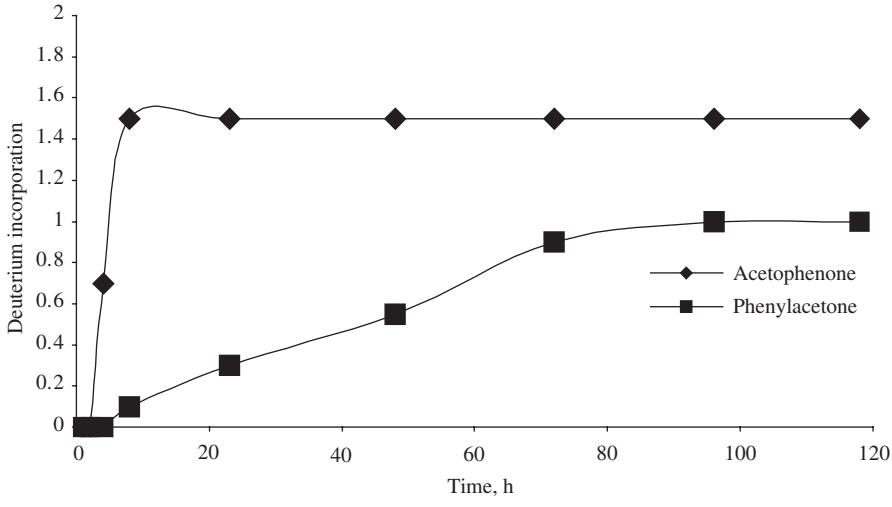


Figure 3. Variation of incorporation over time (2:1 substrate/catalyst) for *ortho*-deuteration of acetophenone and phenylacetone with complex 3a

result of catalyst inactivation. With phenylacetone, as already observed, the exchange is slower and reaches equilibrium after approximately 96 h. On the other hand, with both **1a** and **1b**, exchange into acetophenone does not plateau after the initial period of rapid exchange, but continues at a slower rate until equilibrium is eventually reached. Unlike acetophenone, initial exchange into phenylacetone with complexes **1** is very slow, significant deuterium incorporation being observed only after around 24 h. Even after this period, the catalysts display different kinetics, with the process mediated by **1a** continuing until it reaches equilibrium after approximately 96 h, while that in the presence of **1b** is faster, but plateaus after only a brief additional time. This latter behaviour cannot be due to loss of activity on the part of the catalyst, since exchange into acetophenone continues for some time thereafter. It is unclear why there is such a long induction period before exchange into phenylacetone is observed, but the difference between systems where exchange continues for a longer period, and those where exchange levels out within 24 h, may be one of complex stability; even where the complex involved is the same, it may be that different substrates are able to stabilise the active species to different extents. Nevertheless, based on these observations, it was apparent that an extended period of exchange is desirable when using complexes **1** or **3**, and the results that follow were all obtained after exposure times of around 120 h.

Exchange using complexes **1**

Deuteration of simple substrates using complexes **1** was examined in the manner described previously,[2] but comparing homologous pairs of substrates,

so that acetophenone was compared with phenylacetone and *N,N*-dimethylbenzamide with acetanilide and *N,N*-dimethylphenylacetamide. To ensure comparability, all experiments were carried out at the same catalyst loading (50 mole %) and at the same concentration (catalyst concentration 10 mM). The results are summarised in Table 1.

Assuming that reduced steric demand in complexes **1** is indeed critical to their ability to mediate isotope exchange *via* six-membered metallacycles, it is reasonable to expect that both the size of the ligand and the distance between the phosphorus centres (reflected in the ligand bite angle[9]) would be important factors influencing the activity of a complex. Electronic effects will also be different to those observed in complexes of simple phosphines; the distortion caused by chelate formation increases the basicity of the metal centre,[10] this effect increasing as the size of the chelate ring decreases. Since iridium complexes of the most basic phosphines are of limited value,[11] it was expected that the best results would be obtained using complexes with *bis*(phosphines) of moderate basicity. Indeed, the results presented in Table 1 are broadly in line with this expectation. Taking **1a** as a benchmark, the smaller chelate ring in **1c** results in a generally poorer profile (although this may not be an electronic effect), as does the use of a more basic ligand in complex **1h**. Complexes where the phosphorus centres are less basic are less effective for exchange in ketones, but the observed exchange in amides is not greatly affected either by small changes in ligand basicity or in chelate ring size. The best activity profiles overall are obtained with **1a**, and with the BINAP complex, **1e**, which is related to the series of complexes already examined by Salter and co-workers.[12] Increasing the chelate size a little further gives a complex (**1f**) of generally modest activity, while the extreme case (**1g**) is completely inactive. Nevertheless, the incorporation into both phenylacetone and *N,N*-dimethylphenylacetamide is consistently less than 50% of the theoretical maximum, and the prospect of finding a significantly improved catalyst within this series does not appear bright.

Table 1. Deuteration Mediated by Complexes 1 (50% loading)[a]

Complex **1**	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**	**1h**
- *ligand bite angle*	85	91	72	83	92	96	111	
Substrate								
Acetophenone	1.7	1.5	1.1	0.6	1.8	1.3	0.0	1.2
Phenylacetone	0.6	0.3	0.0	0.2	0.6	0.2	0.0	1.0
N,N-Dimethylbenzamide	1.8	1.6	0.7	1.1	1.6	0.9	0.0	1.2
N,N-Dimethylphenylacetamide	0.7	0.6		0.3	0.6	0.5		0.7
Acetanilide	2.0	1.6	1.3	1.5	1.7	1.0	0.0	1.3

[a] Figures are the average number of deuterium atoms incorporated per molecule of substrate, as determined by mass spectrometry. Exchange was carried out over 120 h in all cases.

Exchange using complexes **3**

Exchange reactions with complexes **3** were carried out exactly as described above for complexes **1**, the results being summarised in Table 2. We have already demonstrated that the effect of the phosphine cone angle in **2** and its analogues is small so that, in this series, the principal effect of changing the nature of the arsine ligand should be electronic.[11] However, exchange into phenylacetone in the presence of complexes **3** was not improved by modifying the ligands, systems other than **3a** mediating no more than 25% of the theoretical maximum level of exchange.

By comparison, deuterium incorporation into dimethylbenzamide and acetanilide was generally more efficient than into the ketones, and the extent of exchange into the two amides was comparable using any given catalyst. Complexes **3** therefore appear better suited for use with amides rather than with ketones, but still fail to reach the desired level of activity into either class of substrate. In addition, it appears that longer iridium–arsenic bond is not, in itself, sufficient to reduce steric demand to a point where formation of the required six-membered metallacycle is an efficient process. An interesting comparison can also be made with complex **3g**, where replacement of one of the arsine ligands of **3a** by triphenylphosphine results in a complex whose activity toward acetophenone and *N,N*-dimethylbenzamide is improved at the expense of activity toward phenylacetone in particular. In this respect, **3g** behaves more like the phosphine complex **4** than like **3a**.

Exchange using complex **5**

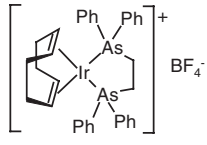
Given the limitations observed with **1** and **3**, a logical next step was the use of a bidentate arsine complex such as **5**. In this case, the enforced *cis*-relationship of the coordinating centres, the longer Ir–As bond length, and the increased effect on complex basicity resulting from chelate formation combine to favour exchange into the ketone substrates. Consequently, high levels of exchange are observed into both acetophenone and phenylacetone. At the same time, exchange into other substrates using **5** remains respectable (Table 2). In

Table 2. Deuteration mediated by Complexes 3 and 5

Complex **1**	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**[b]	**5**
Substrate								
Acetophenone	1.5	1.7	1.0	1.4	1.6	1.0	1.8	1.9
Phenylacetone	1.0	0.5	0.2	0.3	0.3	0.0	0.5	1.7
N,N-Dimethylbenzamide	1.8	1.5	1.4	0.6	0.3	1.4	1.6	1.4
Acetanilide	1.6	1.4	1.7	0.8	0.6	1.4	1.4	1.5

[a] Figures are the average number of deuterium atoms incorporated per molecule of substrate, as determined by mass spectrometry; [b] Using isolated complex.

particular, **5** mediates 50% *ortho*-deuteration (1.0 D) into *N,N*-dimethylphenylacetamide, this being the highest incorporation we have observed with this substrate. An additional interesting feature of this system is that exchange into phenylacetone occurs without the long induction period observed with complexes **1** (Figure 4), although the process still requires in excess of 96 h to reach equilibrium. Complex **5** therefore represents an important new lead for the development of improved promoters of isotope exchange in benzyl ketones and related substrates.



5

In summary, although bidentate complexes **1** are capable of mediating limited exchange into homologous substrates such as phenylacetone, the usefulness of complexes **3**, with simple arsine ligands, for this purpose, is very limited. However, complex **5**, which combines enforced *cis*-disposition of the coordinating centres with a comparatively long metal-arsenic bond, is a promising new lead for isotopic exchange into a reasonable range of substrates. The wider applicability of this complex, and the preparation of analogues, is under investigation.

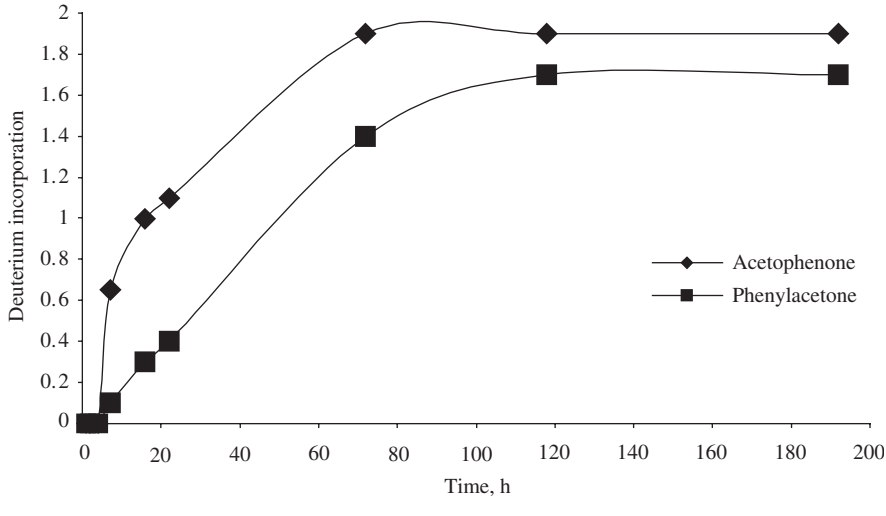


Figure 4. Variation of incorporation over time (2:1 substrate/catalyst) for *ortho*-deuteration of acetophenone and phenylacetone with complex 5

Experimental

NMR spectra were recorded using a Bruker DRX-500 instrument. GC-MS conditions and the general exchange procedure were as described previously,[2] except that exchange was allowed to proceed for a minimum of 100 h in all cases, to ensure that equilibrium had been reached. *Bis*(1,5-cyclooctadiene)-diiridium(I) dichloride, *bis*(1,5-cyclooctadiene)iridium tetrafluoroborate (Strem), phosphines, and ethylene-1,2-*bis*(diphenylarsine) (Aldrich) were obtained from commercial suppliers. Phenylacetone[4] and (1,5-cyclooctadiene)(triphenylarsine)(triphenylphosphine)iridium(I) hexafluorophosphate (**3g**)[8] were prepared as described previously.

Triarylarsines were prepared by the dropwise addition of arsenic(III) chloride to 10 molar equivalents of the appropriate Grignard reagent under nitrogen at −10°C.[13] Thus obtained were *tris*(4-fluorophenyl)arsine (90%), m.p. 73–73.6°C (lit.[14] m.p. 74°C), $\delta_H(CD_3SOCD_3)$ 7.23 (6H, dd, $J = 11.1$, 10.2 Hz), 7.29 (6H, $J = 10.2$, 7.2 Hz), *m/z* 360 ($M^{+\cdot}$), 170 (100%, 4-$FC_6H_4As^{+\cdot}$); *tris*(4-chlorophenyl)arsine (100%), m.p. 103–106°C (lit.[15] m.p. 104–107°C), $\delta_H(CDCl_3)$ 7.19 (6H, d, $J = 8.2$ Hz), 7.30 (6H, d, $J = 8.2$ Hz), *m/z* 408, 410, 412 ($M^{+\cdot}$), 186, 188 (100%, 2:1, 4-$ClC_6H_4As^{+\cdot}$); *tris*(4-methoxyphenyl)arsine (100%), m.p. 155–158°C (lit.[16] m.p. 156–158°C), $\delta_H(CD_3SOCD_3)$ 3.73 (9H, s), 6.92 (6H, d, $J = 8.1$ Hz), 7.15 (6H, d, $J = 8.1$ Hz), *m/z* 396 ($M^{+\cdot}$), 182 (100%, 4-$MeOC_6H_4As^{+\cdot}$). Diphenylmethylarsine was prepared as described by Doak and Freedman.[17] $\delta_H(CD_2Cl_2)$ 1.48 (3H, s), 7.29–7.34 (6H, m), 7.42 (4H, dd, $J = 7.5$, 2.0 Hz), *m/z* 244 ($M^{+\cdot}$), 154 (100%, $PhAsH_2^{+\cdot}$).

Representative exchange procedure

A solution of *bis*(1,5-cyclooctadiene)iridium tetrafluoroborate and ligand (1 mol. equiv.) in DCM was stirred for 5 min under nitrogen, then diluted with DCM, to give a 5 μmol/ml solution of **1** or **5**. This solution (2 ml) was added to the substrate (20 μmol) in a 10 ml flask; the system was degassed and flushed with deuterium (corresponding to at least 20 molar equivalents, or 10 molar equivalents per exchange site), then sealed and stirred for 120 h. After this time most of the volatiles were evaporated and the crude product was extracted with ethyl acetate. Exchange runs using complexes **3** or **4** were carried out using the procedure described previously for generation of the catalyst from *bis*(1,5-cyclooctadiene)diiridium(I) dichloride.[2]

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