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Deuterium exchange mediated by an iridium-phosphine complex formed in situ

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Abstract—Bis(triorganophosphine)(cyclooctadiene)iridium(I) tetrafluoroborates, 2, are readily generated in situ and utilised for the exchange of deuterium into a variety of aromatic substrates. The efficiencies of deuterium exchange using 2 formed in this way are comparable to those observed in exchange processes where the isolated pre-catalysts were used. © 2001 Elsevier Science Ltd. All rights reserved.

A number of reports have appeared describing the use of iridium complexes to mediate incorporation of tritium and deuterium into arenes at positions ortho to a directing group such as a carbonyl,¹⁻⁴ the isotopic hydrogen thereby being incorporated at a position where it is essentially inert in metabolic or uncatalysed exchange processes, as illustrated in general form in Scheme 1. A small number of such catalysts, including complexes 1² and 2a,³ are commercially available, while others, such as the bis(triphenylphosphine) complex, **2b**,⁴ are relatively simple to prepare. We were interested in investigating the possibility that complexes bearing different ligands at the iridium centre might offer a range of different substrate selectivities and, rather than attempt the preparation and isolation of a wide variety of complexes, an attractive option was to examine the formation of complexes in situ. In addition, the deuteration of substrates such as ethyl benzoate mediated by isolated 2b gave inconsistent results; these were attributed to degradation of the complex on standing, and it was hoped that complexes formed in situ would



Scheme 1. Generalised form of deuterium exchange mediated by iridium complexes.

be of a more consistent quality. This preliminary disclosure of results in this area is occasioned by the recent presentation of similar work by Salter et al.⁵



Since pre-catalysts 2a and 2b have been reported as efficient mediators of the deuteration of a variety of aromatic substrates,^{2,3} these were chosen for comparative studies. Deuterium exchange of a range of substrates was examined using pre-formed complexes, and also using the corresponding species prepared by variations on two in situ methods.

Three approaches were examined for the generation of catalytically active iridium species in situ. In the preferred procedure (Method A), the readily available chloro-1,5-cyclooctadieneiridium(I) dimer was treated with phosphine (4 molar equivalents) and silver tetra-fluoroborate (2 molar equivalents) in dichloromethane. After filtration to remove silver salts, the solution was diluted to a concentration of 10 μ mol/ml and this solution added to the substrate, which was then exposed to deuterium gas. Alternatively, the complex could be generated in the presence of the substrate, and the mixture exposed to deuterium without removal of

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Table 1.	Com	parison	of	results	from	deuterium	exchange	mediated	by	2 ^a
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Substrate	2a		2b			
	Isolated complex	Method A	Isolated complex	Method A	Method B	Method C
COCH3	1.8	1.5	1.8	1.6	1.4 (1.6 ^b)	1.2
	1.8	1.1	1.2°	1.2	0.0	0.0
	1.6	1.5	1.1	1.1	0.2	0.7
S(O)Me	0.4	0.3	0.2	0.2		
\mathbb{A}	1.1	0.8	1.8	1.4	1.4	0.6
	0.9	0.7			1.0	0.6
Ac N-0	1.8	1.6	1.7	1.7	1.7	0.3
N S	1.5	1.3	1.2	1.7	1.3	1.2
NHAC	1.6	1.6	0.3	0.6	0.1	0.5
	0.1	0.1	0.1	0.1		
	1.9 ^d	0.5	0.4	0.4	0.1	0.0

^a figures presented are the average number of *ortho*-deuterium atoms incorporated per molecule, as measured by mass spectrometry.

^b sodium carbonate added.

[°] not reproducible.

^d recovered as aniline.

the silver salts (Method B). In either case, TLC of the solution formed indicated rapid formation of complex **2**. Where they were not removed, it was clear that silver salts were often reduced during the course of the exchange to give metallic silver so, aside from the possibility that sensitive substrates might be oxidised, it was very probable that the reduction of silver(I) involved concomitant oxidation of deuterium to form deuterons. These may protonate basic substrates (and thereby reduce their ligating ability), exchange at labile sites (which was indeed observed with ketone sub-

strates) and possibly promote degradation of the catalyst. Consequently, where silver salts were not removed from the system, it was desirable to add two molar equivalents of sodium carbonate as a mild base. Alternatively (Method C), the presence of silver salts could be avoided entirely by treatment of commercially available bis(1,5-cyclooctadiene)iridium tetrafluoroborate with triphenylphosphine (2 molar equivalents) in the presence of a substrate and deuterium gas. Clearly, in the last case, coordination of phosphines will not occur until after removal of a cyclooctadiene ligand, and it is entirely possible that exposure of the mixture to deuterium might result in the formation of a mixture of iridium complexes.

Based on experiments with the isolated complex 2b, it was found that, as observed previously with 1.6^{6} a 2:1 substrate/catalyst ratio gave reasonable results with the majority of substrates, although it must be stressed that this ratio often did not correspond to the optimum for maximum exchange; this ratio was used in most cases throughout this study. Exchange processes carried out using the in situ methods proceeded at rates comparable to those observed using the isolated complex, and were essentially complete within a matter of a few hours. Again, as observed with 1,⁶ the degree of deuteration is affected considerably by the removal of samples during the exchange process. For example, where timed deuterations of acetophenone with 2b were conducted as separate experiments, complete deuteration occurred within 2.5 h. In contrast, removal of samples from a single exchange reaction over a short period resulted in loss of catalytic activity, so that exchange remained incomplete and the eventual degree of deuteration was only around half of that observed otherwise. This may be due to nothing more than loss of deuterium or ingress of air through the rubber septum and, as a consequence, all-glass systems were used for the deuterations which followed.

Selected results obtained upon deuterium exchange of a selection of substrates with 2a and 2b, and with the corresponding species formed in situ, are presented in Table 1. In all cases, the principal measurement of deuterium incorporation was by mass spectrometry, with NMR spectra being acquired for representative samples to confirm that incorporation had occurred only at the ortho-sites, as expected.⁶ Method A gives results which are both reproducible and reasonably consistent with the results obtained using the isolated pre-catalyst. As a rule, slightly lower levels of deuterium incorporation were observed using the complexes formed in situ than was observed using the isolated complexes, but the former is a consistently good guide to the latter. Notable exceptions are the deuteration of acetanilide mediated by 2b, where the in situ method is the more efficient, and the deuteration of nitrobenzene mediated by 2a. In the latter case, the

Table 2. Comparison of different iridium/triphenylphosphine ratios (Method B)^a

Substrate	Using [Ir(cod)Cl] ₂ -4PPh ₃ - 2AgBF ₄	Using [Ir(cod)Cl] ₂ -2PPh ₃ - 2AgBF ₄
Acetophenone	1.6	1.5
2-Phenylpyridine	1.4	1.3
1-Phenylpyrazole	1.0	1.0
5-Acetyl-3-phenyl- isoxazole	1.7	1.5

^a Figures presented are the average number of *ortho*-deuterium atoms incorporated per molecule, as measured.

process promoted by the pre-formed catalyst results in reduction to aniline, with concomitant 95% orthodeuteration. Since aniline itself incorporated only 5% of deuterium under the same conditions, it is entirely possible that deuterium exchange in this instance occurs at an intermediate stage, or prior to the reduction process.

In line with the concerns mentioned above over the homogeneity of the catalytic species involved in Method C, the results using this method are also poorer than those from Method A. The reduced efficiency of Method B compared to Method A may be the result of degradation of the catalyst, either by acid or by silver(I)-mediated oxidation of the phosphine ligand; certainly, significant quantities of phosphine oxides were detectable in the mixtures formed from exchange reactions conducted without removal of the silver salts.

That said, in situ catalytic exchange is surprisingly robust. Complexes 2 are air-sensitive but, whereas isolated 2b was not stable to storage even under an inert atmosphere, filtered solutions of the same complex retained catalytic activity for at least 7 days when stored under nitrogen at room temperature. In contrast, solutions of 2a lost much of their activity over the same period, even when stored under nitrogen at -20° C; the loss of catalytic activity was accompanied by disappearance of the characteristic ruby-red colour to give a pale yellow solution characteristic of inactive oligomeric species such as those characterised previously.⁷ As one might reasonably expect, formation of the complex using an excess of phosphine ligand generates a coordinatively saturated species which is catalytically inactive, but a deficiency of phosphine ligand does not result in a significant loss of catalytic activity (Table 2).

In summary, we have demonstrated that it is feasible to generate pre-catalysts 2 in situ and that the method provides a comparatively robust means of assaying the activity of different iridium catalysts towards a variety of substrates. The method is presently being applied to the development of a panel of complexes in order to facilitate the selection of catalysts for the tritiation of drug development candidates; further details of the process and of the evaluation of other iridium–phosphine complexes will be described in future publications.

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