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Research Article

The mediation of aryl ketone deuteration by $[Ir(PPh_3)_3(cod)]^+.BF_4^-$

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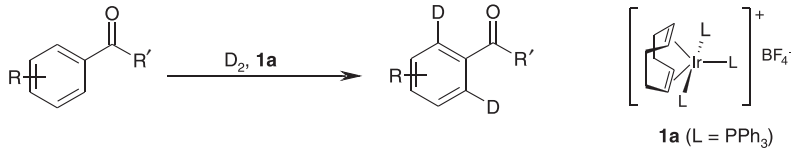
Summary

The usefulness of the hydrogen isotope exchange catalyst, $[Ir(PPh_3)_3(cod)]^+.BF_4^-$ (1), is explored. It appears that isotopic exchange mediated by **1** occurs via a series of complexes in which all three phosphine ligands are retained. The disadvantage of this system is that the catalytic intermediates are necessarily sterically hindered, with the result that the range of substrates for which the system is effective is small. Copyright © 2005 John Wiley & Sons, Ltd.

Key Words: iridium *tris*(phosphine) complexes; isotope exchange; ortho-deuteration

Introduction

In the process of establishing conditions for iridium-mediated hydrogen isotope exchange with a range of aromatic substrates, it was found that the putative pre-catalyst, (cyclooctadiene)*tris*(triphenylphosphine) iridium(I) tetrafluoroborate (**1**) was unexpectedly efficient in promoting exchange in acetophenone, resulting in essentially quantitative displacement of the *ortho*-protons (Scheme 1).[1] In the light of this result, further work was undertaken,



Scheme 1. *ortho*-Deuteration of aryl ketones in the presence of 1

both to examine the more general utility of this complex as a catalyst for isotope exchange in aryl ketones and in the hope of better understanding the

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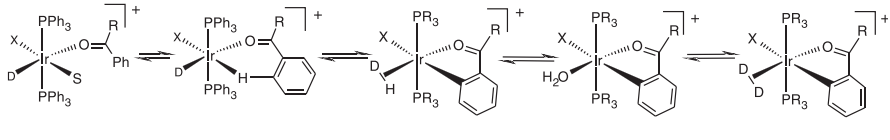
mechanism by which exchange works with this and other complexes. This work is the subject of this publication.

Results and discussion

Given the robustness of the catalyst formed from **1**, it is relevant to consider the mechanism by which it mediates exchange. When NMR spectra of a 1:1 mixture of **1** and acetophenone were recorded 1 h after exposure to hydrogen, the ^{1}H spectrum contained resonances consistent with the presence of cyclooctane and cyclooctene in a ratio of approximately 1:1.2. The substrate methyl protons gave rise to a broad singlet centred at δ 2.50, consistent with the presence of several closely related (and presumably isomeric) bound forms of acetophenone; there was no signal attributable to free acetophenone. The aromatic envelope was complex but did contain identifiable signals corresponding to the protons of variously bound forms of acetophenone. Even after 120 h, the spectrum was essentially unchanged, apart from the near-disappearance of peaks due to cyclooctene. Upfield signals were complex but occurred in two clear clusters around $\delta - 24$ and around $\delta - 11$, the former being very minor; these are consistent with metal hydride and metal dihydrogen species, respectively. Whereas the ^{31}P NMR spectrum of **1** contains only one signal,[1] due to rapid Berry pseudo-rotation as reported previously,[2] the corresponding hydrogenated acetophenone complex gives rise to a number of distinct resonances between $\delta - 1$ and $+22$. However, what is noticeably absent in the ^{31}P spectrum is any signal due to free triphenylphosphine (observed at $\delta - 3.83$ under the same conditions), all the signals observed being downfield of this point. The implication is that all of these signals correspond to metal-bound phosphines in different environments.

Possibly the most instructive feature of the NMR spectra is the predominance of signals (in the ^{1}H spectrum) arising from bound dihydrogen, rather than hydride. In the accepted mechanism of exchange using $Ir(cod)(PPh_3)_2^+.BF_4^-$ (**2**) and its analogues (Scheme 2),[3] the complex bears at least one hydride ligand at all stages. Since the various species formed upon hydrogenation of **1** in the presence of acetophenone appear to contain more bound dihydrogen than hydride, and free triphenylphosphine does not appear to be liberated, it appears likely that the mechanism operating is the same, but with a third phosphine in place of hydride in each intermediate (Scheme 2).



Scheme 2. Key intermediates in isotopic exchange mediated by 1 (X = PPh_3) and 2 (X = D)

Table 1. Deuteration of aryl ketones mediated by 1 and 2[a]

R	R′	**1** (C2/C6)	**2** (C2/C6)[1]
H	Me	1.0/1.0[1]	0.8/0.8
H	Ph	0.35/0.35	
3-Cl	Me	0.67/0.82	0.95/0.95
4-Cl	Et	0.90/0.90	
4-Br	Me	0.88/0.88	
3-Me	Me	0.54/0.59	0.9/1.0
4-Me	Pr	0.94/0.94	
3-OMe	Me	0.35/0.85	0.85/0.85
4-OMe	i-Pr	0.35/0.35	
4-cyclohexyl	Me	0.83/0.83	

[a] Figures are the number of deuterium atoms per molecule of substrate, at the positions indicated, as determined by ^{1}H NMR spectrometry.

The presence of very small quantities of a *bis*(triphenylphosphine) species, which could be the active intermediate, cannot be discounted entirely on the basis of the NMR data. However, indirect evidence that the active species retains all three phosphine ligands comes from efforts to examine the scope and limitations of **1** in exchange into a range of simple ketones (Table 1). Since the intermediates formed from **1** are sterically encumbered by comparison to those involved in the process mediated by **2**, it was expected that hindered ketones would be poorer exchange substrates. In exchange processes mediated by Ir(cod) (Py) (PCy3) + .PF6-(3), steric hindrance results most obviously in the blocking of exchange (in benzamides) between a directing group and a *meta*-substituent.[4] With **1**, not only does the same effect occur in the deuteration of *meta*-substituted ketones, but levels of exchange at C6 in these cases are reduced by comparison with those observed in *para*-substituted substrates. Moreover, even a bulky *para*-substituent reduces the extent of exchange slightly, as in the case of 4′-cyclohexylacetophenone. In contrast, exchange processes mediated by **2** are largely unaffected by *meta* substituents.[1] Moreover, the presence of any substituent α- to the directing carbonyl has an even greater disruptive effect on the exchange process; the tolerance of α-branching is very much poorer than with **3**, which mediates incorporation of 1.0D into 4-methoxyisobutyrophenone and 1.85D into desoxybenzoin. The range of substrate geometry over which **1** operates effectively is rather limited also: phenylacetone incorporates 0.2D, but 1-indanone, where formation of a geometrically constrained five-membered metallacycle would be required, is not exchanged at all.

In summary, exchange mediated by complex **1** results from a variation upon the accepted mechanism for such processes. The presence of a third phosphine results in stabilization of the hydrogenated complex in the absence of an excess of ligand, so that exchange proceeds to completion for sterically unencumbered substrates.

Experimental

Analytical methods were as described previously.[1,4] *Bis*(1,5-cyclooctadiene)-diiridium(I) dichloride was obtained from Strem. 4-Methoxyisobutyrophenone was prepared by Friedel-Crafts acylation of anisole.[5]

Typical exchange procedure

A suspension of silver tetrafluoroborate (20 mg) in DCM (10 ml) containing *bis*(1,5-cyclooctadiene)diiridium(I) dichloride (40 mg, 60 μmol) and triphenylphosphine (94 mg, 0.36 mmol), was stirred for 20–30 min under nitrogen, then filtered through Celite. The pad was washed through with DCM until the filtrates became clear, and the combined filtrates were made up to 12 ml with DCM, to give a 10 μmol/ml solution of **1**. This solution (1 ml/20 μmol) was added to the substrate; the system was degassed and flushed with deuterium, then sealed and stirred for 66–68 h. After this time most of the volatiles were evaporated and the product was isolated by preparative t.l.c on silica gel.

Selected product data are summarized below

Exchange of 1-(4-methylphenyl)-1-butanone (22 mg, 0.13 mmol) in the presence of **1** (0.06 mmol) gave [*benzene*-2,6-$^2H_2$]-1-(4-methylphenyl)-1-butanone (16 mg, 73%). $\delta_H(CDCl_3)$ 0.98 (3H, t, $J = 7.3$ Hz), 1.75 (2H, observed as sextet, $J = 7.3$ Hz), 2.39 (3H, s), 2.89 (2H, t, $J = 7.3$ Hz), 7.23 (2H, s), 7.84 (0.12H, d, $J = 8.3$ Hz); m/z 134, 133 (M^+), 105, 104 ([M-C_2H_5]$^+$).

Exchange of 1-(4-chlorophenyl)-1-propanone (17 mg, 0.1 mmol) in the presence of **1** (0.05 mmol) as above gave [*benzene*-2,6-$^2H_2$]-1-(4-chlorophenyl)-1-propanone (13 mg, 76%). $\delta_H(CDCl_3)$ 1.20 (3H, t, $J = 7.2$ Hz), 2.96 (2H, q, $J = 7.2$ Hz), 7.31 (1H, m), 7.41 (2H, s), 7.88 (0.12H, d, $J = 8.9$ Hz); m/z 172, 170 (M^+), 143, 141 (100%, [M-CH_3]$^+$).

Exchange of 3-chloroacetophenone (39 μl, 0.3 mmol) in the presence of **1** (0.15 mmol) gave [*benzene*-2,6-$^2H_2$]-3-chloroacetophenone (32 mg, 68%). $\delta_H(CDCl_3)$ 2.59 (3H, s), 7.53–7.57 (1H, m), 7.69 (1H, d, $J = 8.1$ Hz), 7.89 (0.33H, dd, $J = 7.6$, 1.2 Hz), 7.92–7.93 (0.18H, m); m/z 156, 155 (M^+), 142, 141, 140 (100%, [M-CH_3]$^+$).

Exchange of 3-methylacetophenone (40 μl, 0.3 mmol) in the presence of **1** (0.15 mmol) gave [*benzene*-2,6-$^2H_2$]-3-methylacetophenone (38 mg, 92%). $\delta_H(CDCl_3)$ 2.37 (3H, s), 2.55 (3H, s), 7.38–7.41 (1H, m), 7.44 (1H, d, $J = 7.3$ Hz), 7.74 (0.41H, d, $J = 7.4$ Hz), 7.76 (0.46 H, s); m/z 136, 135, 134 (M^+), 121, 120, 119 (100%, [M-CH_3]$^+$).

Exchange of 3-methoxyacetophenone (42 μl, 0.3 mmol) in the presence of **1** (0.15 mmol) gave [*benzene*-2,6-$^2H_2$]-3-methoxyacetophenone (29 mg, 64%).

$\delta_H(CDCl_3)$ 2.56 (3H, s), 3.81 (3H, s), 7.19 (1H, d, $J = 8.3$ Hz), 7.41–7.45 (1.15H, m), 7.54 (0.65 H, dd, $J = 7.5$, 0.8 Hz); m/z 152, 151 (M^+), 137, 136 (100%, $[M\text{-}CH_3]^+$).

Exchange of 4-bromoacetophenone (12 mg, 0.06 mmol) in the presence of **1** (0.03 mmol) gave [*benzene*-2,6-$^2H_2$]-4-bromoacetophenone (12 mg, 100%). $\delta_H(CDCl_3)$ 2.56 (3H, s), 7.59 (2H, s), 7.79 (0.24H, d, $J = 8.8$ Hz); m/z 199, 200, 201, 202 (M^+), 184, 185, 186, 187 ($[M\text{-}CH_3]^+$), 51 (100%, $[M\text{-}CH_3]^+$).

Exchange of 4-cyclohexylacetophenone (12 mg, 0.06 mmol) in the presence of **1** (0.03 mmol) gave [*benzene*-2,6-$^2H_2$]-4-cyclohexylacetophenone (8 mg, 66%). $\delta_H(CDCl_3)$ 1.22–1.44 (5H, m), 1.72–1.89 (5H, m), 2.52–2.56 (1H, m), 2.55 (3H, s), 7.28 (2H, s), 7.87 (0.34H, d, $J = 8.5$ Hz); m/z 203, 204, 205 (M^+), 188, 189 (100%, $[M\text{-}CH_3]^+$), 190.

NMR Experiment

A solution of **1** was prepared as described above, from *bis*(1,5-cyclooctadiene)diiridium(I) dichloride (20 mg, 30 μmol) and triphenylphosphine (47 mg, 180 μmol) in CD_2Cl_2 (1 ml). Acetophenone (3.6 μl, 30 μmol) was added to half the solution in an NMR tube, which was then degassed and flushed with hydrogen. Shaking the solution briefly resulted in discharge of the red colour, and NMR spectra were recorded after a further 1 h. $\delta_H(CD_2Cl_2)$ 1.47–1.49 (m, 8H of cyclooctene), 1.52 (s, cyclooctane), 2.10–2.15 (m, 4H of cyclooctene), 2.30–2.70 (br s, 3H of acetophenone), 5.61 (ddd, $J = 7.2$, 5.2, 2.0 Hz, 2H of cyclooctene), 6.83–7.39 (45H, m), 7.47 (2H, t, $J = 7.7$ Hz), 7.55–7.61 (1H, m), 7.85–7.93 (2H, m), upfield signals not being acquired; $\delta_P(CD_2Cl_2)$ −1.04, −0.57, 4.88, 5.00, 6.96, 7.92, 11.08, 11.85, 12.29, 14.90 (major), 18.32, 18.56, 21.20, 21.40. After 96 h, the hydrogen atmosphere was replaced by argon, and after a further 24 h, the spectrum was reacquired: $\delta_H(CD_2Cl_2)$ −25.0 to −24.0 (3 small multiplets, Ir-H), −23.5 to −23.0 (3 small multiplets, Ir-H), −22.2 to −21.4 (m, Ir-H), −12.2 to −10.8 (m, Ir-H_2), −8.7 to −8.1 (m, Ir-H_2), the remainder of the spectrum being as above.

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