

ARTICLE

Practically Convenient and Industrially-aligned Methods for Iridium-catalysed Hydrogen Isotope Exchange Processes

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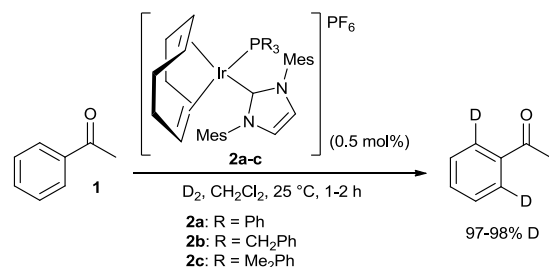
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The use of alternative solvents in the iridium-catalysed hydrogen isotope exchange reaction with developing phosphine/NHC Ir(I) complexes has identified reaction media which are more widely applicable and industrially acceptable than the commonly employed chlorinated solvent, dichloromethane. Deuterium incorporation into a variety of substrates has proceeded to deliver high levels of labelling (and regioselectivity) in the presence of low catalyst loadings and over short reaction times. The preparative outputs have been complemented by DFT studies to explore ligand orientation, as well as solvent and substrate binding energies within the catalyst system.

Introduction

With attrition rates in the drug development process at such an elevated level,¹ identification of any failing attributes of potential drug candidates at an early stage constitutes a strategy of appreciable focus within the pharmaceutical industry. Associated with this, the isotopic labelling of such molecules provides a fast and efficient method of incorporating a tracer into compounds of interest, enabling various metabolic, stability, and toxicity studies to be performed.² In this regard, hydrogen isotope exchange (HIE) potentially provides the most direct method of achieving such a labelling procedure in one preparative step. Accordingly, the development of methods and catalyst species which mediate hydrogen isotope exchange processes continues to be the subject of appreciable research focus, with these techniques, as well as alternative labelling strategies, being the subject of recent special issues and review articles.³

Although a number of transition metal species have been shown to catalyse H-D exchange,³⁻⁷ Crabtree's catalyst [Ir(COD)(PCy₃)(py)]PF₆^{8a,b} has been regarded as the optimal complex to facilitate this transformation. Having stated this, it is often found that high levels of incorporation can only be achieved in the presence of (super-)stoichiometric quantities of this Ir complex and after extended periods of time.^{8b-g} Research within our own laboratory has focused on the synthesis and use of highly active complexes of the type [Ir(COD)(PR₃)(IMes)]PF₆ **2**, which display high activity in the isotopic labelling of a number of substrates classes.⁹ Furthermore, such complexes are readily handled and deliver



Scheme 1 Isotopic labelling with Ir(I) complexes **2**.

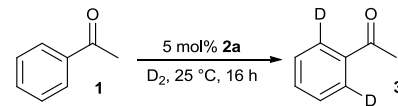
excellent levels of incorporation at low catalyst loadings and over short reaction times (Scheme 1). Despite the efficiency that has been evidenced to date with catalysts **2**, a drawback of the developed system relates to the use of dichloromethane (DCM) as the reaction medium. From an industrial perspective, the employment of this chlorinated solvent is deemed unfavourable due to its associated hazards, including suspected carcinogenicity and high vaporisability. Indeed, pharmaceutical companies are now driving specifically towards the replacement of DCM with solvents that are believed to be more industrially acceptable.¹⁰ Furthermore, the identification of suitable alternatives to DCM would have further and not inconsiderable benefits within medicinal chemistry research endeavours due to the low solubility of numerous potential drug candidates in this reaction medium. To date, various research groups have examined the application of solvents other than DCM in the field of hydrogen isotope exchange, however, with varying success.^{6q,8c-e,11} In view of these considerations, the study presented herein describes our most recent endeavours to

further develop the efficiency and applicability of our emerging catalysts **2** within HIE reactions, whilst striving to enhance the wider practical utility of these methods.

Results and Discussion

Our initial investigations involved the screening of a number of solvents using the otherwise standard conditions developed within our laboratory. As illustrated by the results displayed in Table 1, the isotopic labelling of the simple substrate acetophenone **1**, using 5 mol% of complex **2a** (R = Ph) over a 16 h reaction time, proceeded to varying degrees of deuteration in the selected reaction media. The first attempt to mediate HIE in an alternative solvent, Et₂O, delivered the isotopically-enriched product **3** in a level of deuterium incorporation comparable to that obtained previously in DCM (*cf.* Scheme 1)^{9a} Such a high degree of isotope exchange was maintained upon moving to the more sterically hindered and less volatile *t*-BuOMe. Unfortunately, but perhaps somewhat expectantly, the reaction performed in acetone produced only a moderate deuterium loading of 43%. Finally, the use of 2-MeTHF as an alternative reaction medium for HIE reactions was examined. The use of this solvent has increased greatly within the pharmaceutical industry over recent years and following its identification as a potential replacement for DCM in other areas of preparative chemistry, due to its high polarity but low miscibility with water.¹² Pleasingly, the use of this solvent in H-D exchange reactions proceeded without incident, furnishing the desired product with an excellent 95% level of deuteration.

Table 1 Solvent Screening

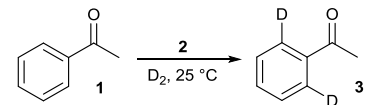


Entry	Solvent	% D ^{a)}
1	Et ₂ O	94
2	<i>t</i> -BuOMe	91
3	acetone	43
4	2-MeTHF	95

a) Average incorporation into the positions shown over two separate reaction runs; the percentage given refers to the level of D incorporation over the total number of positions possible, e.g. 94% for the two possible positions in **3** indicates 1.88D incorporation.

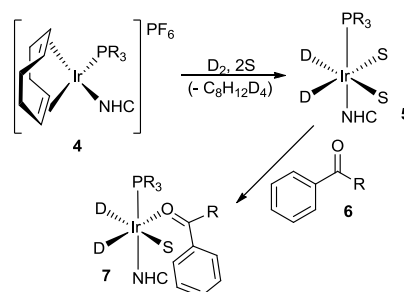
In view of these findings, Et₂O, *t*-BuOMe, and 2-MeTHF were selected for further investigation. As mentioned, our Ir(I) complexes display excellent levels of activity in HIE reactions performed in DCM (Scheme 1).^{9a} It was therefore of interest to determine if such an efficient catalytic procedure would be retained in systems utilising the described alternative solvents. Following a short series of optimisation studies, the most effective conditions for the isotopic labelling of acetophenone **1** were identified for complexes **2a** and **2b** (Table 2), with excellent levels of deuterium incorporation being observed over relatively short reaction times.

Table 2 Optimised conditions for HIE in alternative solvents



Entry	Solvent	Complex (PR ₃)	Mol%	Time (h)	% D
1	Et ₂ O	2a (PPh ₃)	3	2	92
2	Et ₂ O	2b (PBn ₃)	3	1	97
3	<i>t</i> -BuOMe	2a (PPh ₃)	5	2	91
4	<i>t</i> -BuOMe	2b (PBn ₃)	5	2	94
5	2-MeTHF	2a (PPh ₃)	3	2	95
6	2-MeTHF	2b (PBn ₃)	3	1	96

At this stage and, importantly, to gain further insight into our observations regarding the performance of complexes of class **2** in HIE reactions, both in a general sense and as conducted in the alternative solvents, a series of theoretical studies were undertaken.¹³ In accordance with the proposed mechanism by which isotope exchange occurs, as reported by Heys,¹⁴ it was assumed that following activation of our Ir(I) complexes through loss of d₄-cyclooctane, the resulting coordinatively unsaturated Ir species may be stabilised by the coordination of two solvent (S) molecules (**5**, Scheme 2).



Scheme 2 Complex activation and solvent coordination.

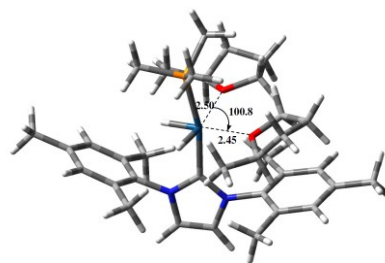


Fig. 1 Optimised structure of the Ir species with two solvent molecules (2-MeTHF) coordinated (distances are in Å and angles in degrees).

In line with the pathway proposed, we have located stable bi-solvent complexes for the five different solvents investigated (the optimised structure of 2-MeTHF coordinated to the iridium complex is shown in Figure 1; coordinates of all optimised structures are provided in the Electronic Supplementary Information). In all cases, the optimised structures illustrated that the phosphine and NHC ligands align in a *trans*-

configuration around the metal centre within the activated species. Further and in order for the reaction to progress, the dissociation of the solvent molecules from the metal centre must constitute a favourable process to enable subsequent coordination of the incoming substrate molecule (Scheme 2, 5→7). We therefore examined the explicit binding enthalpies of the solvent molecules (ΔH_{sol}), as illustrated in Scheme 3.¹⁵



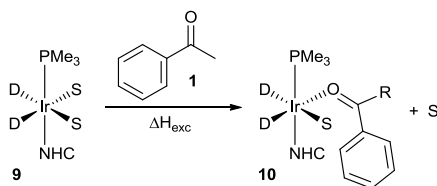
Scheme 3 Calculation of solvent binding enthalpy (ΔH_{sol}).

For each solvent investigated, the binding enthalpies (ΔH_{sol}) were found to be exothermic (Table 3). The variation in the degree of deuteration between different solvents can be affected by the strength of the interaction between the solvent molecule and the iridium centre, with a larger binding enthalpy potentially having an undesirable effect on % D. Of the solvents investigated, DCM was found to have the lowest binding enthalpy. The most weakly coordinating of the ethereal reaction media was found to be *t*-BuOMe, followed by Et₂O, and then 2-MeTHF, with acetone displaying the highest binding enthalpy. Accordingly, it is proposed that the binding enthalpy calculated for the more strongly coordinating acetone lies beyond the acceptable values required to favour dissociation of the solvent and, in turn, effective catalysis.

Table 3 Calculated solvent binding enthalpies (ΔH_{sol} , kcal/mol) for five different solvents.

Entry	Species	ΔH_{sol}
1	Ir(D) ₂ (PMe ₃)(IMes)(DCM) ₂	-13.1
2	Ir(D) ₂ (PMe ₃)(IMes)(<i>t</i> -BuOMe) ₂	-17.5
3	Ir(D) ₂ (PMe ₃)(IMes)(Et ₂ O) ₂	-26.8
4	Ir(D) ₂ (PMe ₃)(IMes)(2-MeTHF) ₂	-33.0
5	Ir(D) ₂ (PMe ₃)(IMes)(acetone) ₂	-38.6

As presented in Scheme 2, the second step of the reaction mechanism is the exchange of one solvent molecule with a substrate unit at the metal centre. We were therefore interested in determining the corresponding binding enthalpies (ΔH_{exc}) associated with such a substitution (Scheme 4). As anticipated, the substrate binding enthalpies follow the reverse order to that observed previously for the solvent binding (Table 4).



Scheme 4 Calculation of substrate binding enthalpy (ΔH_{exc}).

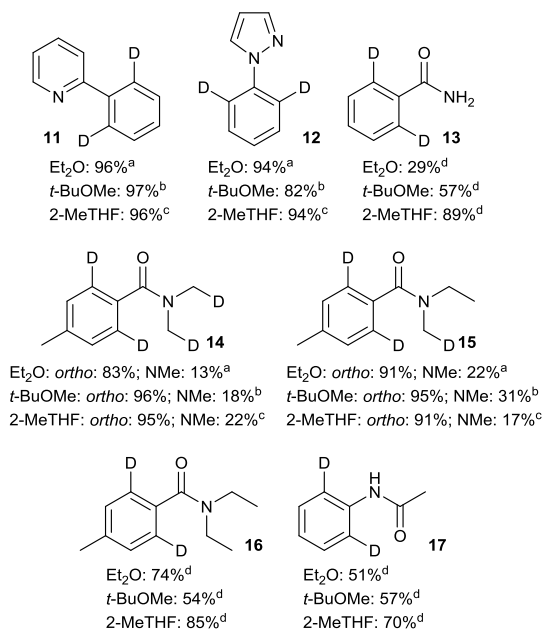
Table 4 Calculated binding enthalpies (ΔH_{exc} , kcal/mol) associated with the exchange of one solvent molecule with acetophenone.

Entry	Species	ΔH_{exc}
1	Ir(D) ₂ (PMe ₃)(IMes)(PhCOMe)(DCM)	-13.3
2	Ir(D) ₂ (PMe ₃)(IMes)(PhCOMe)(<i>t</i> -BuOMe)	-12.8
3	Ir(D) ₂ (PMe ₃)(IMes)(PhCOMe)(Et ₂ O)	-7.3
4	Ir(D) ₂ (PMe ₃)(IMes)(PhCOMe)(2-MeTHF)	-3.7
5	Ir(D) ₂ (PMe ₃)(IMes)(PhCOMe)(acetone)	0.3

More specifically, systems in which solvent molecules bind least strongly to the Ir centre are, consequently, stabilised to the highest degree by the exchange of the solvent molecule with the substrate, and *vice versa*. Importantly, the calculation of ΔH_{exc} provides a much clearer indication of the solvents that will support deuteration of the substrate. The substitution of DCM or ethereal solvent molecules by acetophenone occurs in an exothermic reaction (i.e. the equilibrium is shifted towards the substrate coordinated complex, which is then able to undergo deuteration). Conversely, the exchange of acetone with a substrate molecule occurs in a thermo-neutral (slightly endothermic) reaction. As such, the substrate bound complex will be present in appreciably lowered proportions, resulting in decreased deuterium incorporation. The difference in the direction of the equilibrium, as shown by the calculated ΔH_{exc} , in the presence of acetone in contrast with the other four solvents aligns with the difference between the levels of H-D exchange observed in the reactions. This delicate balance between solvent and substrate binding enthalpies is clearly important in determining the ability of the reaction to occur. However, once bound, the solvent may also affect the activity of the catalyst through polarising the medium in which the reaction occurs. These more subtle effects of the solvent on the reaction mechanism may further account for the differences in deuteration levels observed between DCM and the ethereal solvents investigated within this study.

Having established the optimum conditions for H-D exchange reactions performed in alternative reaction media, their application in the isotopic labelling of a range of substrates was explored with complex **2b** (Figure 2). In a number of instances, such as the labelling of heterocyclic compounds **11** and **12**, and methyl-substituted amides **14** and **15**, the use of lower catalyst loadings and shorter reaction times in the three solvents under investigation delivered high levels of isotope incorporation, as compared to those obtained previously in DCM.^{9a} With regards to substrates **13**, **16**, and **17**, marginally more elevated conditions catalyst loadings (5 mol%) and longer reaction times (16 h), were required to furnish increased levels of deuterium exchange. Of particular interest was the isotopic labelling of notoriously more demanding substrates, benzamide **13** and acetanilide **17**. While reactions run in Et₂O and *t*-BuOMe failed to reach deuterium incorporations which were comparable to those attained in DCM,^{9a} the use of 2-MeTHF with these systems greatly improved the degree of deuteration achieved;

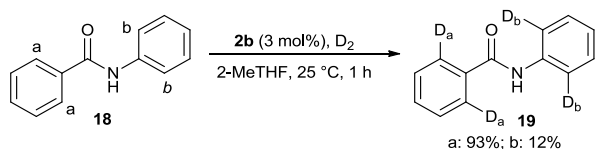
with regards to benzamide **13** an excellent 89% was recorded, the highest D loading obtained so far for this substrate using complexes of this type.



^a3 mol%, 1 h; ^b5 mol%, 2 h; ^c3 mol%, 1 h; ^d5 mol%, 16 h.

Fig. 2 Widening substrate scope with complex **2b**.

In further extending the substrates investigated, application of benzamide **18** allows the selectivity scope of the labelling processes in an ethereal solvent medium to be probed.^{9a} As shown in Scheme 5, following only 1 h reaction in 2-MeTHF with complex **2b** (3 mol%), an appreciable degree of preference was shown for H-D exchange *via* a five-membered metallocyclic intermediate (5-mmi, site a) over a six-membered metallocyclic intermediate (6-mmi, site b). Such levels of regioselective isotope incorporation could provide significant value in the directed labelling of more complex drug-like molecules under the mild and more practically acceptable conditions developed here.



Scheme 5 Selective deuteration of benzamide.

Additional success was revealed in the isotopic labelling of Pfizer's anthelmintic, Niclosamide **20**. As illustrated in Table 5, reactions employing **2b** with DCM as the solvent gave rise to only moderate levels of labelling in each of the four positions at which exchange is possible, with no significant site selectivity between being observed. A low preference for the position of exchange was also apparent in HIE reactions conducted in

Et₂O; however, in this instance, the extent of isotope incorporation was somewhat higher than with DCM as the reaction medium. The deuteration of **20** in the presence of *t*-BuOMe and 2-MeTHF delivered significantly improved overall levels of labelling and up to 97% D loading. In addition, results from the latter reactions indicated a clear preference for H-D exchange which occurs through the more favourable 5-mmi (site d) versus a 6-mmi (site c), implying that a high degree of selectivity could be attained in the labelling of alternative compounds that possess such competing possible sites. Further, in this specific example, the elevated levels of isotope incorporation observed in the alternative solvents is proposed to be due to the higher solubility of **20** in the more polar reaction media. Such results therefore reinforce the importance of the ability to perform HIE reactions in media other than DCM, and, in particular, those solvents which are capable of solubilising more polar drug molecules.

Table 5 Isotopic labelling of Niclosamide

Entry	Solvent	Mol%	Time	% D			
				a	b	c	d
1	DCM	5	1	55	44	40	58
2	Et ₂ O	3	1	75	70	63	76
3	<i>t</i> -BuOMe	5	2	83	48	37	87
4	2-MeTHF	3	1	89	55	28	97

Conclusions

Overall, we have illustrated that exceptional levels of deuteration can be maintained when employing the recently developed complexes **2** in more widely acceptable ethereal solvents. Furthermore, only low levels of catalyst loading are required with the desired labelled products being delivered over short reaction times to provide more generally convenient and applicable preparative protocols. In addition to this, investigation of the binding enthalpies associated with both the mono- and di-solvent complexes for five different reaction media has provided emerging insight into the reactivity of the Ir(I) catalyst in the various solvents aligned with the level of isotopic labelling observed.

Experimental Section

General

All solvents were purified prior to their use. Dichloromethane and 2-methyltetrahydrofuran were dried by heating to reflux over calcium hydride, and then distilled under nitrogen. Diethyl ether was dried by heating to reflux over sodium wire, and then distilled under nitrogen. Acetone and *tert*-butylmethyl ether

were dried by heating to reflux over calcium sulfate, and then distilled under nitrogen. Acetanilide, benzamide, and benzanilide were purified by recrystallisation from ethanol.

Standard Procedure for Hydrogen Isotope Exchange

To a flame-dried, 100 mL, three necked round bottomed flask, fitted with two stopcock valves and a suba seal, was added the iridium(I) complex, substrate, and dry solvent. The suba seal was replaced with a glass stopper, fitted with a Teflon sleeve, and the solution was placed in a dry ice/acetone slurry bath and cooled to -78 °C. The flask was evacuated three times, filled with nitrogen in the first two instances, and with deuterium in the third. The flask was then removed from the slurry bath and placed in a water bath set at 25°C. (NOTE: the glass stopper must be physically restrained as the reaction mixture warms to room temperature). The solution was then stirred vigorously for the allotted reaction time. The flask was evacuated to remove excess deuterium from the system. The contents of the flask and washings were then transferred to a single necked flask, and concentrated *in vacuo*. The catalyst was precipitated from the residue by addition of diethyl ether (~10 mL) and the solution filtered through a short plug of silica. The solvent was then removed under reduced pressure. The level of isotope incorporation achieved was determined by ¹H NMR analysis of the reaction products. As such, the relevant integral for the residue proton signal from the site of incorporation was compared against that of a site where exchange would not be expected to occur.

Theoretical Methods^{13,15}

All structures have been optimised at the M06/[6-31G(d,p) for H, C, O, N, P, Cl + Stuttgart RECP and associated basis set for Ir level of theory in Gaussian 09. Frequency calculations were also performed at this level of theory to fully characterise the stationary states as minima and to determine the thermodynamic parameters.

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Notes and references

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Electronic Supplementary Information (ESI) available: Full experimental details and associated data are provided. See DOI: 10.1039/b000000x/

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