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Hydrogen isotope exchange with highly active iridium(I) NHC/phosphine complexes: a comparative counterion study

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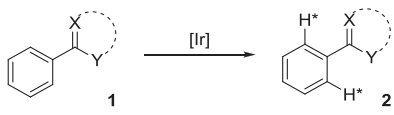
Herein, we present a range of substrates that undergo hydrogen isotope exchange with an iridium(I) *N*-heterocyclic carbene/phosphine complex bearing the less coordinating tetrakis[3,5-bis(trifluoromethyl)phenyl]borate counterion and compare these with labelling using the equivalent, more established hexafluorophosphate complex. The changes in reactivity and selectivity of these complexes in a series of solvents are examined. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords: *ortho*-hydrogen isotope exchange; *N*-heterocyclic carbene; deuteration; iridium

Introduction

The exchange of hydrogen in a C–H bond by deuterium or tritium, through the process of hydrogen isotope exchange (HIE), represents a direct and economical method of generating isotopically labelled molecules.[1] Furthermore, because of the growing demand for deuterium-labelled and tritium-labelled compounds for use in determining the pharmacokinetics of active pharmaceutical ingredients and in mechanistic studies, there has been increased focus on the development of catalysts capable of facilitating HIE in a mild and efficient manner.[2] Although a wide variety of metals can catalyse the HIE process, iridium complexes are the most widely utilised for directing group-assisted *ortho*-HIE (Scheme 1).[3]

Historically, this iridium-catalysed, directed HIE process has been commonly performed using Crabtree's catalyst.[4] However, the necessity for a high, and, indeed, often stoichiometric, catalyst loading has led to attention being turned to the use of alternative catalyst species in recent years. In this regard, studies within our laboratory have delivered a series of iridium(I) complexes that are highly effective HIE catlaysts,[5] and which have proven applicable with a wider array of functional groups and reaction solvents than Crabtree's catalyst.[6] A key breakthrough in this latter regard was the synthesis of cationic *N*-heterocyclic carbene (NHC)/phosphine complexes bearing alternative counterions to the traditional hexafluorophosphate (e.g. complex **3**). Specifically, improved catalyst activity and more general solvent applicability was observed with Ir(I) NHC/phosphine complex **4**, containing the BArF (tetrakis[3,5-bis (trifluoromethyl)phenyl]borate) counterion (Scheme 2).[6b] Herein, we further expand upon this initial application of catalyst **4** and extend the comparison of the PF_6 and BArF counterions, with particular attention to the selectivity within the HIE processes reported.



Scheme 1. Iridium-catalysed *ortho*-HIE.

Experimental

For full details on all experimental procedures, including catalyst syntheses and HIE processes, refer to the Supporting Information.

Results and discussion

Our studies commenced with a comparison of our commercially available catalyst **3**, bearing the PF_6 counterion, with the equivalent catalyst **4**, bearing the bulky, less coordinating BArF unit. The labelling of a range of substrates, featuring a variety of different directing groups (DG), was evaluated with low loadings of catalysts **3** and **4** (Figure 1). From our previous work, we had observed that both complexes performed excellently with a simple ketone DG (substrate **5**).[6b] Pleasingly, upon extending these studies to the weaker ester DG in **6**, high levels of deuterium incorporation were, again, observed with both catalysts. The

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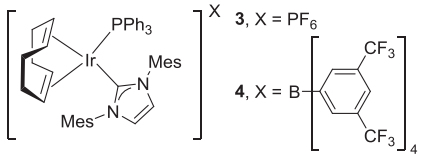
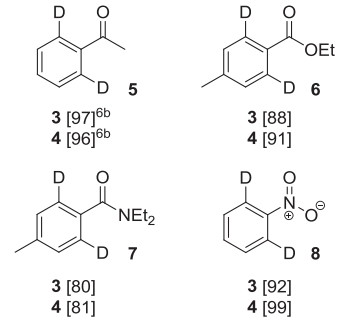


Scheme 2. Ir(I)-NHC/phosphine complexes for HIE.



[a]Substrate (0.215 mmol), catalyst (0.01075 mmol; 5 mol%), DCM (1 mL), D_2, 1 h, 25 °C; [b]Isotope incorporation was determined by ^{1}H NMR spectroscopy; [c]Incorporation values are the average of two runs.

Figure 1. *ortho*-HIE with a series of directing groups.[a,b,c]

amide DG in compound **7** delivered similar levels of HIE with both complexes **3** and **4**.

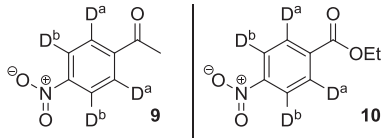
Importantly, nitrobenzene **8**, which is known not to undergo HIE with Crabtree's catalyst,[4b] performed excellently with both complexes, giving near quantitative incorporation with catalyst **4**.

We have previously reported on the utility of complexes **3** and **4** in a range of solvents.[6a,b] During these studies, in a single example of a substrate containing two competing DGs, a solvent-dependent variation in the selectivity of labelling was observed. To further develop and understand this behaviour, a number of multi-functional aromatic compounds were selected for study, based upon our earlier substrate scope. Firstly, we applied 4-nitroacetophenone **9** under our previously utilised conditions with complexes **3** and **4**, in dichloromethane (DCM), THF and toluene (Figure 2). In DCM, both complexes performed similarly, with excellent levels of deuterium incorporation observed *ortho* to the ketone DG and low levels observed *ortho* to the nitro unit. Lower overall incorporation was observed in THF following the same regioselectivity trend. Complex **4** also delivered the same general ratio of labelling in toluene. However, a change in selectivity was observed in this solvent with catalyst **3**. Specifically, enhanced levels of labelling were now observed adjacent to the nitro DG, indicating that, with the combination of a less coordinating solvent and the less electrophilic catalyst **3**, both DGs bind effectively, resulting in exchange at both sites.

Ethyl 4-nitrobenzoate **10** was next examined under the same protocol. In accordance with our earlier substrate scope study, elevated levels of deuterium incorporation were observed with complex **4** in DCM, with a slight preference for HIE *ortho* to the nitro DG with both catalysts. Notably, using THF as the solvent significantly reduced HIE at both positions, presumably because of the solvent versus substrate competitive binding with these more weakly coordinating DGs.[6a,b] In toluene, a low incorporation was observed with complex **3**; however, complex **4** proved more effective in this case, delivering moderate levels of HIE.

Next, we examined diethyl 4-nitrobenzamide **11** under the same reaction conditions. High levels of incorporation were observed at both positions, with complex **3** delivering a slightly increased deuterium incorporation compared with **4** (Figure 3). However, upon changing the solvent to THF, the selectivity for HIE *ortho* to the amide DG was significantly increased with both **3** and **4**. In toluene, moderate to good levels of deuterium incorporation were observed, with lowered selectivity relative to THF.

Finally, we applied this developed understanding to labelling of the antiandrogen drug, nilutamide **12**. With complex **3** in DCM, complete labelling *ortho* to the nitro DG, via a five-membered metallacyclic intermediate (5-mmi) was observed, in addition to a small amount of labelling directed by the amide through a 6-mmi. Pleasingly, the use of complex **4** suppressed this latter pathway, resulting in almost exclusive labelling *ortho* to the nitro DG. However, with THF as the solvent, the level of incorporation was negligible in all positions, in accordance with earlier observations that THF binds preferentially to the catalyst in place of weakly directing substrates. In toluene, very low levels of labelling were observed; however, this is mainly attributed to the poor solubility of **12** in this solvent.



DCM
3 - D^a [88], D^b [18]
4 - D^a [89], D^b [23]

THF
3 - D^a [45], D^b [8]
4 - D^a [37], D^b [8]

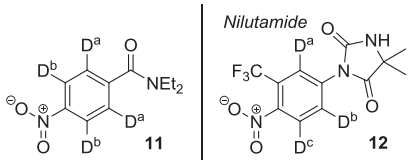
Toluene
3 - D^a [86], D^b [52]
4 - D^a [87], D^b [14]

DCM
3 - D^a [29], D^b [41]
4 - D^a [52], D^b [66]

THF
3 - D^a [6], D^b [7]
4 - D^a [7], D^b [6]

Toluene
3 - D^a [6], D^b [16]
4 - D^a [23], D^b [49]

Figure 2. HIE on bifunctional substrates **9** and **10**.



DCM
3 - D^a [85], D^b [85]
4 - D^a [76], D^b [76]

THF
3 - D^a [61], D^b [22]
4 - D^a [73], D^b [19]

Toluene
3 - D^a [60], D^b [37]
4 - D^a [61], D^b [54]

DCM
3 - D^a [5], D^b [11], D^c [99]
4 - D^a [3], D^b [3], D^c [99]

THF
3 - D^a [3], D^b [2], D^c [4]
4 - D^a [4], D^b [4], D^c [1]

Toluene
3 - D^a [4], D^b [2], D^c [9]
4 - D^a [5], D^b [3], D^c [14]

Figure 3. HIE on bifunctional substrates **11** and **12**.

Conclusions

The studies reported herein have provided further evidence that complex **4**, bearing the less coordinating BArF counterion, is more reactive than catalyst **3** with less coordinating DGs but that the combination of counterion and solvent is vital in delivering a site-selective HIE process. In conclusion, both catalysts **3** and **4** show excellent reactivity, with the specific choice of catalyst and solvent dependent upon the substrate in question and the required position of isotope incorporation.

Acknowledgements

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Supporting information

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