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Anion Effects to Deliver Enhanced Iridium Catalysts for Hydrogen Isotope Exchange Processes†

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Synthesis of a series of iridium(I) complexes of the type [(COD)Ir(IMes)(PPh_3)]X (X = BF_4, OTf, and BArF) has been established. Application of these species in mild hydrogen isotope exchange processes revealed more efficient catalysis and, further, a wider solvent scope when employing larger, more weakly coordinating counterions.

Ionic transition metal complexes play a central role in catalysis and organic synthesis. Although it is more common to tune the properties of such catalysts *via* manipulation of the coordinated ligands on the transition metal cation, the past two decades have witnessed a significant increase in studies of the effects of changing the negatively charged counterion.[1] In most cases where the counterion plays a spectator role, moving to larger, more weakly coordinating counterions has evidenced a positive influence on catalyst efficiency across various methodologies, with examples spanning palladium,[2] rhodium,[3] and iridium[4] catalyses, among others.[1a,b] Having stated this, there also exist some cases in which the ability of the counterion to coordinate to the inner sphere of the transition metal cation is essential for overall structural stability.[5] Furthermore, changing the counterion has also been documented to completely alter reaction pathways in both transition metal complex synthesis[6] and organic synthesis.[7]

Our interest in this field stems from the development of cationic iridium(I) *N*-heterocyclic carbene (NHC)-phosphine complexes for pharmaceutically-relevant hydrogen isotope exchange (HIE) processes.[8,9] To date, we have reported on the development and application of several such complexes, all of which bear the hexafluorophosphate counterion.[8c,9] In this contribution, we report the syntheses and application in HIE of complexes **1b**-**d**, counterion variations of our flagship catalyst, **1a** (Fig. 1).[9,10] As has been demonstrated by Pfaltz and others in iridium-based catalysis,[4] we hypothesised that moving to larger counterions, such as tetrakis[3,5-bis(trifluoromethyl)phenyl] borate (BArF), would enhance the activity

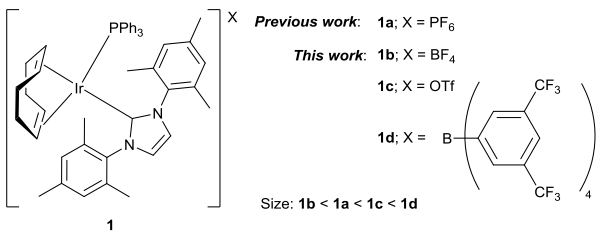


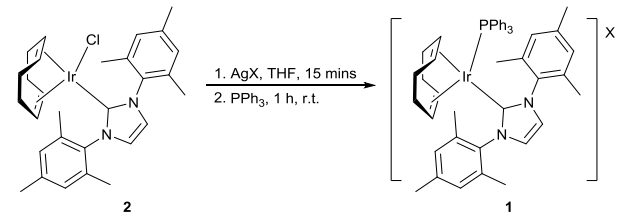
Fig. 1 HIE catalysts bearing different counterions.

and longevity of the proposed new Ir species at lower catalyst loadings. Furthermore, as wider preparative applications of HIE require catalysts operable in a more expansive array of solvent media,[8d,9b,11] we theorised that the more diffuse counterions would enhance the solvent scope of the catalyst beyond that which we have already reported.[9] To substantiate these proposals, it was necessary to study complexes bearing counterions both larger *and* smaller than for catalyst **1a**.

We began our studies with the syntheses of novel complexes **1b** and **1c**, using the general method shown in Table 1. Starting from the chloro-carbene complex, **2**,[12,13] the choice of silver salt used to the abstract the chloride ligand simultaneously delivered the counterion of choice (after addition of PPh_3). Both complexes were isolated in acceptable yields by simple trituration from ethyl acetate.

In turning our attention to the synthesis of complex **1d**, the lack of a commercially available source of AgBArF prompted the search for a silver-free synthetic route. In this regard, it was hypothesised that the chloro-carbene intermediate, **2**, may be circumvented if the parent imidazolium salt required to provide the NHC ligand was partnered with a large and weakly coordinating counterion such as BArF. Indeed, this approach has promising literature precedent relating to iridium complexes bearing a chelating carbene-phosphine ligand.[14] Accordingly and as detailed in Scheme 1, this approach was successfully realised for

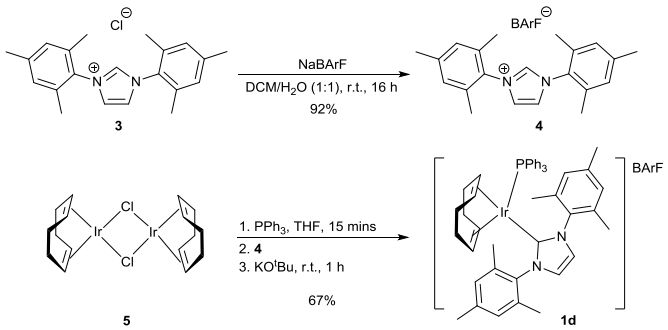
Table 1 General procedure for the syntheses of complexes **1b** and **1c**.



2 1

Entry	X	Catalyst	% Yield
1	BF_4	**1b**	80
2	OTf	**1c**	69

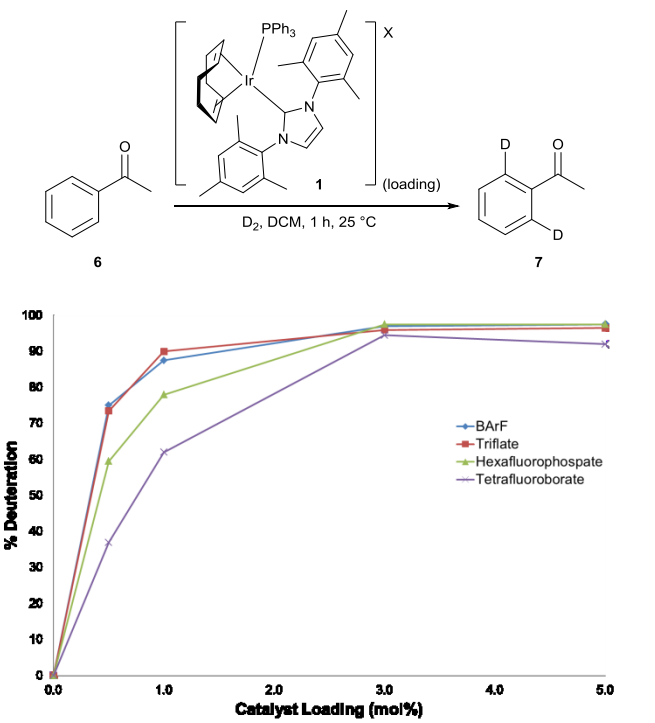
our monodentate NHC-phosphine ligand combination. Firstly, NHC precursor, **4**, was synthesised by salt metathesis from **3**. Following *in-situ* generation of [(COD)Ir(PPh_3)Cl] from **5** and PPh_3, **4** was added followed by base to yield the desired complex, **1d**, in good yield, and on gram scale.



Scheme 1 Silver-free synthesis of complex **1d**.

All novel compounds, **1b-d** and **4**, were characterised by NMR (^1H, ^{13}C, ^{31}P, ^{19}F, and ^{11}B), IR, melting point, HRMS, and X-ray crystallography. Of particular note is the X-ray structure determination of complex **1d**, which reveals the similar size of the BArF counterion relative to the cationic portion of the complex (Fig. 2).¶

To investigate the impact of the series of counterions in iridium-based HIE processes, model reactions employing acetophenone, **6**, as the substrate were undertaken. In particular, the effect of catalyst loading on the labelling efficacy of complexes **1a-d** was scrutinised. As shown in Scheme 2, the effect of changing the counterion was clearly drawn out at the most accessible and commonly applied reaction temperature of 25 ºC. As predicted, the relative efficiency of each catalyst increases in order of increasing counterion volume.[15] Catalysts **1c** and **1d**, bearing the OTf and BArF counterions, respectively, are more active than parent catalyst, **1a**, and the catalyst bearing the small BF_4 counterion, **1b**. Notably, the reactivity of the triflate catalyst, **1c**, contrasts with observations made by Pfaltz and co-workers during their study on the counterion effects in olefin hydrogenation using PHOX-type chelating ligands.[4b] Where these previous studies showed complete shutdown of catalytic activity using the triflate species, we have evidenced that both triflate and BArF counterions perform equally well (and, indeed, better than the parent catalyst, **1a**) at 25 °C within HIE processes. Presumably, this difference in the effectiveness of triflate across these two systems is related to the different orientations of the ancillary ligands in the active catalyst forms. For bidentate PHOX ligands, the coordinating groups adopt a *cis* configuration, allowing coordination of the dipolar triflate anion to the iridium centre. In catalyst series **1**, the bulky NHC and phosphine ligands are known to rest *trans* to one another in the active form.[9c] Therefore, triflate coordination may be blocked by the more effective combined steric bulk of a *trans* NHC-phosphine system relative to the more open *cis*-coordinated PHOX ligands.



Scheme 2 Assessment of counterion effects on catalyst efficiency.

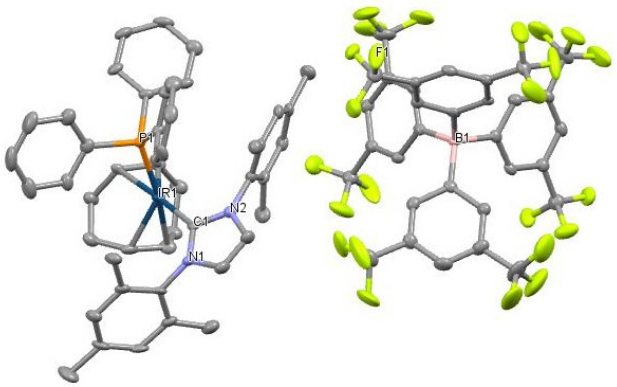


Fig. 2 Molecular structure of catalyst **1d** as determined by X-ray crystallography.

Next, we explored the effective solvent scope of catalyst **1** with different counterions. Previously, we have identified 2-MeTHF, MTBE, and Et_2O as viable alternatives to DCM using catalyst **1a**.[9b] Therefore, we compared the applicable solvent scope of **1a** *versus* the most non-polar derivative, **1d**, across a wider range of solvents than previously explored. Using the same reference reaction as shown in Scheme 2 (5 mol% catalyst, 25 °C), we screened a series of ethereal,

alcoholic, ester, chlorinated, and aromatic solvents. Firstly, we were encouraged to note that the more soluble catalyst, **1d**, was generally superior to parent catalyst, **1a**, within HIE for the range of ether and carbonate solvents tested (Fig. 3). For dioxane, MTBE, Et_2O, and 2-MeTHF both catalysts were shown to perform equally well, with the larger counterion of **1d** offering slight improvements to an already efficient deuteration system. However, more significant improvements were recorded on comparing the activities of **1a** and **1d** in $^{i}Pr_2O$, THF, and the recognised green solvents, CPME and dimethyl carbonate.[16]

Alcohol-derived solvents provided a more varied range of reaction efficiencies (Fig. 4). Notably, in all cases, catalyst **1d** displayed greater levels of activity and was more widely applicable than **1a**. The most significant reactivity from the alcoholic solvents shown was observed in the most sterically shielded (and presumably least coordinating) alcohol, ^{t}AmOH.

A similar pattern of reactivity was observed for ester solvents, and accompanied with higher overall levels of deuterium incorporation (Fig. 4). Again, the combination of catalyst **1d** and the most sterically encumbered solvent (^{i}PrOAc over EtOAc) proved most effective. Chlorinated solvents DCM and DCE evidenced no difference in catalysts **1a** and **1d**, with both producing almost quantitative D-incorporation. In contrast, a stark difference in deuterium labelling efficiency was recorded between **1a** and **1d** when using toluene as the solvent. Again, catalyst **1d** was superior to the less soluble catalyst, **1a**. Finally, it is also worth noting that more polar solvents DMSO and DMF were tested under the same reaction conditions with complex **1d**, however, only very low levels of deuteration in acetophenone were detected (see ESI for results).

As stated in the introduction, owing to the highly variable solubility profile of different drug classes, HIE processes with drug candidates require a flexible solvent choice. To explore the potential benefits of expanded solvent scope with catalyst **1d** over **1a**, we next turned our attention to the deuterium labelling of drug molecule, Niclosamide, **8**. Using catalyst **1a** or **1d** in DCM, similarly moderate to good deuterium incorporation was achieved across all four possible labelling sites (Table 2, Entries 1 and 2). This is presumed to be due to the relative insolubility of **8** in DCM. On moving to 2-MeTHF as an alternative solvent (able to fully solubilise all reactants), catalyst **1a** showed suppressed deuteration in positions *a-c*, and enhanced deuteration at position *d* (Entry 3).[17] Pleasingly and to excellently exemplify the effectiveness of the larger anionic counterion, especially with more demanding pharmaceutically-related substrates, catalyst **1d** in 2-MeTHF showed improved labelling in *all four positions* over all other conditions tested (Entry 4 *versus* 1-3).

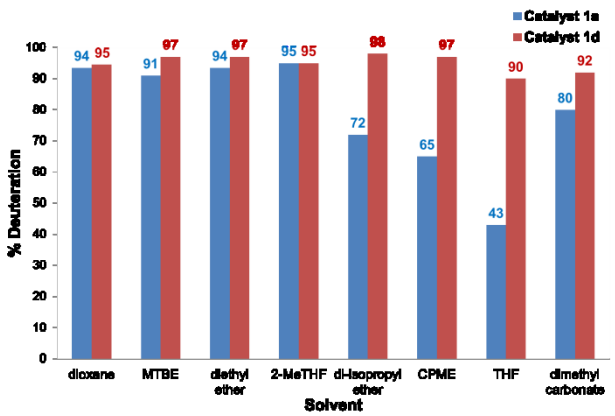


Fig. 3 Counterion influence on ether and carbonate solvent scope. Results are reported as an average of two runs.

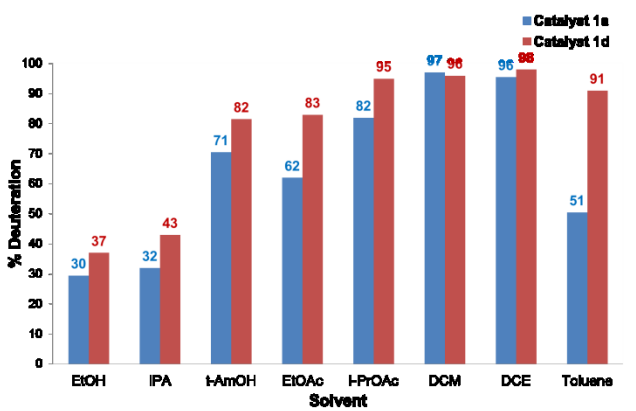
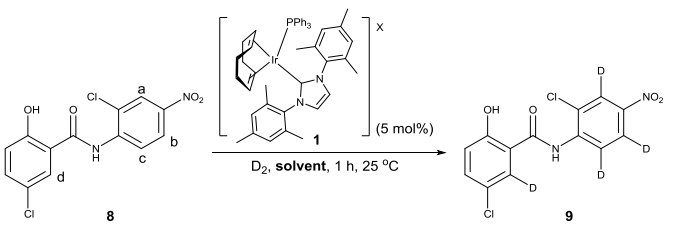


Fig. 4 Counterion influence on alcohol, ester, chlorinated, and aromatic solvent scope. Results are reported as an average of two runs.

Table 2 Improved deuterium labelling of Niclosamide with **1d**.[a]



Entry	Catalyst	X	Solvent	%D_a	%D_b	%D_c	%D_d
1	**1a**	PF_6	DCM	66	53	41	66
2	**1d**	BArF	DCM	71	57	18	73
3	**1a**	PF_6	2-MeTHF	51	11	4	98
4	**1d**	BArF	2-MeTHF	97	96	65	96

[a] Percent deuteration determined by ^{1}H NMR.

Conclusions

In summary, we have reported on the syntheses of three novel complexes of the type [(COD)Ir(IMes)(PPh_3)]X (X = BF_4, OTf, and BArF), with the BArF complex having been accessed by a modified and more direct preparative process. Application of these complexes as catalysts in hydrogen isotope exchange has demonstrated improved catalytic activity at lower catalyst loadings in the order X = BArF ≈ OTf > PF_6 > BF_4. Relative to the parent complex (**1a**, X = PF_6), **1d** (X = BArF) possesses a superior solubility profile and applicable solvent scope in HIE processes. This is of fundamental importance to the delivery of labelled drug candidates for use in absorption, distribution, metabolism, excretion, and toxicology (ADMET) studies. Accordingly, the complex **1d** now provides a catalyst system of wider potential applicability and effectiveness, in particular, within pharmaceutical settings. Further and in relation to this, the utility of improved solvent

scope has been demonstrated through improved global deuterium labelling of the drug molecule Niclosamide in 2-MeTHF. Our on-going efforts in this area are focused on the further application of optimal catalyst, **1d**, in labelling processes and to alternative C-H activation methodologies beyond HIE.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Details of all experimental procedures (catalyst syntheses and deuterium labelling) are provided. For crystallographic data in CIF or other electronic format, see DOI: 10.1039/c000000x/

¶ Crystallographic data (excluding structure factors) for the new complexes reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 1001847 (**1b**), 1001848 (**1c**), 1001849 (**1d**), and 1001850 (**4**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; email: deposit@ccdc.cam.ac.uk) or via *via* www.ccdc.cam.ac.uk/data_request/cif.

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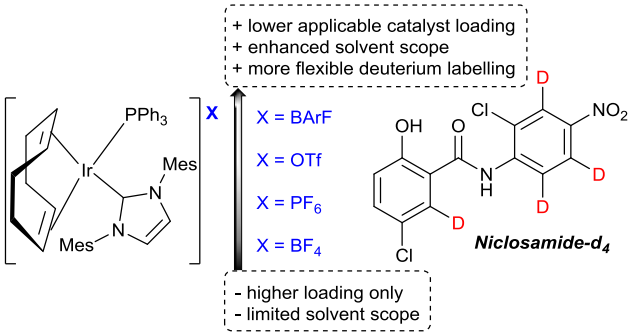
17 The increased selectivity for position *d* when using **1a** in 2-MeTHF may be based on the increased polarity of the solvent relative to DCM and the resultant increase in competition between substrate and solvent for coordination to iridium. Coordination of the amide carbonyl and labelling *via* a 5-membered metallacycle (position *d*) is more facile than *via* the 6-membered metallacycle (position *c*; see ref. 9 for details). Additionally, coordination through the nitro group (for labelling at *a* and *b*) is presumed to be weaker than for the amide. For a recent discussion on the use of coordinating additives to increase reaction chemoselectivity, see: R. M. Drost, T. Bouwens, N. P. van Leest, B. de Bruin and C. J. Elsevier, *ACS Catal*., 2014, **4**, 1349.


+ lower applicable catalyst loading
+ enhanced solvent scope
+ more flexible deuterium labelling
PPh3
Ir
Mes
N
Mes
N
X
X = BArF
X = OTf
X = PF6
X = BF4
OH
O
Cl
NO2
N
H
D
D
D
D
Cl
Niclosamide-d4
- higher loading only
- limited solvent scope