Isotopic Labelling of Functionalised Arenes Catalysed by Ir(I) Species of the [(COD)Ir(NHC)(py)]PF_6 Complex Class

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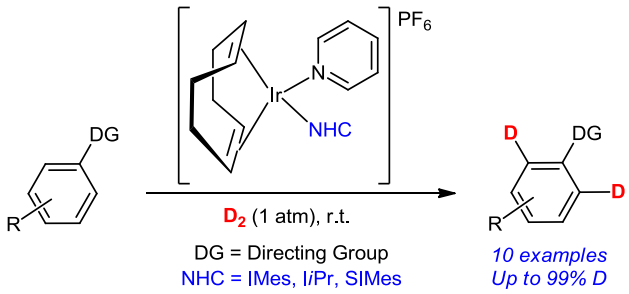
This paper is dedicated to Professor Steven V. Ley, with much gratitude and respect, on the occasion of his 70th birthday.



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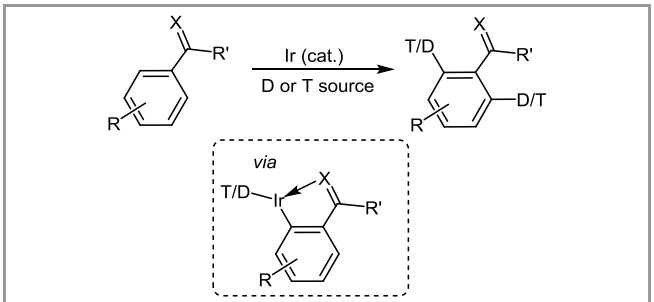
Abstract Ir(I) complexes of the type [(COD)Ir(NHC)(Py)]PF_6 have been exposed as efficient catalysts in the area of hydrogen isotope exchange. More specifically, *via* an *ortho*-directed C-H activation process, high levels of deuterium incorporation have been achieved using low levels of catalyst over a range of functionalised aromatic compounds. Additionally, the developed protocol has been extended to include a selected pharmacological target, where chemoselective labelling is observed within such a multifunctional substrate.

Key words iridium, C-H activation, hydrogen isotope exchange, deuteration

Isotopic labelling with heavy hydrogen isotopes (D_2 and T_2) is widely used as a means to monitor the biological fate of a potential drug molecule.[2] In relation to this, methods that deliver hydrogen isotope exchange (HIE) are of appreciable importance in accessing such isotopically-labelled species, whilst also being central to the provision of analogous deuterated compounds for use as internal standards as aligned with mass spectrometry,[3] for kinetic isotope studies,[4] and for the alteration of reaction pathways in total synthesis.[5] As such, direct, flexible, and selective means of introducing hydrogen isotopes continues to be the focus of considerable research attention. In this regard, studies from our laboratory have shown that a range of iridium complexes of the type [(COD)Ir(IMes)(PR_3)]X are very effective homogeneous catalysts which mediate the exchange of hydrogen with deuterium (or tritium) *via* an *ortho*-directed C-H activation process.[2c,6] The key to their applicability in this area lies with the ability of such complexes to selectively target unactivated C-H bonds, whilst simultaneously allowing convenient isotope incorporation with the use of, practically convenient, deuterium or tritium gas (Scheme 1). Our developing methodology in this domain allows exchange with high levels of incorporation using low levels of catalyst and encompasses a comprehensive range of substrates including ketone, amide, nitro, and a spectrum of heterocyclic functionality, and, most recently, primary sulfonamides[7] and esters,[6f] which were previously less accessible targets. Indeed, the developed series of iridium complexes have emerged to become some of the most active species now known in this area of labelling chemistry.



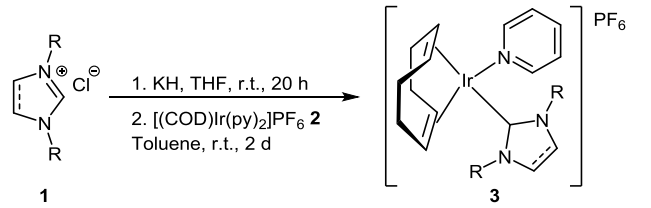
Scheme 1 Hydrogen isotope exchange process

In addition to an isotopic exchange process, our [(COD)Ir(IMes)(PR_3)]X complexes have been shown to perform as effective hydrogenation catalysts, delivering reduced products under notably mild reaction conditions.[8] In relation to this, studies by Nolan *et al.* have divulged that iridium species with the alternative specific combination of a bulky *N*-heterocyclic carbene (NHC) and a pyridine ligand represent appreciably robust complexes that are active within both alkene hydrogenation[9] and transfer hydrogenation protocols.[10] In view of these findings, and based on the knowledge that judicious and careful manipulation of the ligands supporting the iridium centre is critical for success within hydrogen isotope exchange processes, we turned our attention to the application of the general class of Ir(NHC)(py) complexes

within our developing HIE procedures. Herein, we report an assessment of iridium(I) complexes of the type [(COD)Ir(NHC)(py)]PF_6 as an additional series of C-H activation catalysts in the deuteration of a range of functionalised arene substrates.

Our initial investigations involved the preparation of catalysts **3a-c**[9,10] *via* the modified preparative procedure shown in Table 1. In this regard, the desired *N*-heterocyclic carbene was reacted with readily accessible [(COD)Ir(py)$_2$]PF_6, **2**,[11] *via* a simple ligand exchange reaction in toluene. Pleasingly, the desired complexes were obtained in very good chemical yield in every case. Moreover, this procedure allowed the preparation of these extremely stable catalyst species on gram scale.

Table 1 Preparation of Ir complexes **3a**-**c**[12]

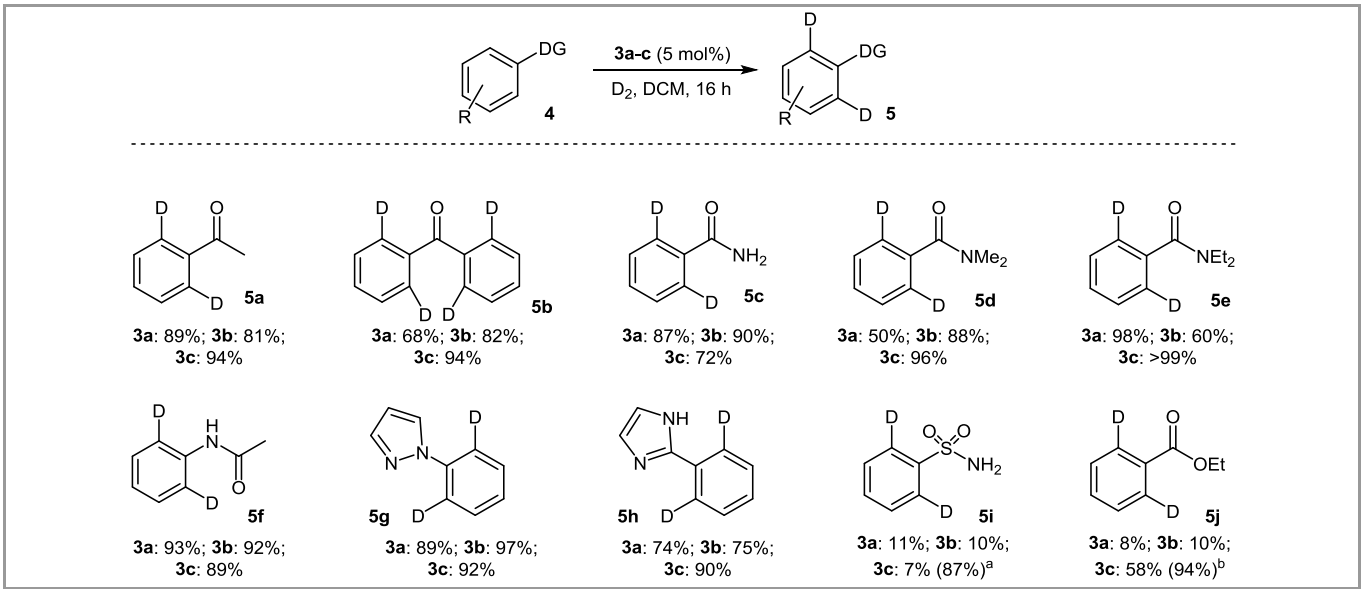


1 **3**

Entry	NHC	Catalyst	Yield (%)
1	IMes, R = 2,4,6-trimethylphenyl	**3a**	88
2	I*i*Pr, R = *iso*-propyl	**3b**	82
3	SIMes, R = 2,4,6-trimethylphenyl	**3c**	97

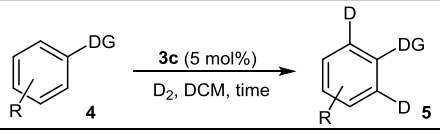
Having successfully prepared complexes **3a-c**, we looked to the standard HIE protocol developed within our laboratory for the labelling of a variety of substrates. As shown in Scheme 2, catalysts **3a-c** displayed very good levels of efficiency in our labelling protocol. Using only 5 mol% catalyst loading, high levels of deuterium incorporation at the expected *ortho*-positions were achieved for the selected substrates over 16 h. Ketones, amides, pyrazole, and imidazole functionalities were all viable within this system, with catalyst **3c**, derived from SIMes, proving the most active in the majority of cases. Notable examples include the labelling of benzamide, **4c**; despite this substrate previously requiring extremely high levels of catalyst and delivering variable results,[13a,b] complexes **3a-c** delivered consistently high isotope incorporations for this substrate within our study. The [(COD)Ir(NHC)(py)]PF_6 complex class was also able to deliver very good levels of deuteration with acetanilide, **4f**, facilitating isotope exchange in C-H bonds positioned five bonds away from the required coordinating functionality i.e. *via* a 6-membered metallacyclic intermediate (6-mmi). This process is believed to be energetically more demanding and, as such, often leads to lower levels of deuteration.[6a,d] Moreover, the delivery of deuterium labelled heterocyclic derivatives **5g** and **5h** displays additional versatility and illustrates the overall robustness of this catalytic system. Whilst we believe that the encumbered nature of the iridium centre within this wider catalyst series is key to the high levels of activity shown,[6] we were conscious that these same steric constraints may disfavour the initial coordination of larger and more tetrahedral directing functional units such as sulfonamides.[7] Having stated this, we were able to induce high levels of incorporation within compound **5i**, albeit by moving to a much higher catalyst loading of 50 mol%. Similarly, an increased loading of 10 mol% was required to more effectively deliver deuterated ester **5j** at a level of 94% D incorporation under ambient conditions; again, this was a pleasing outcome given the well-documented difficulties arising with such a weakly binding aromatic ester group.[6f,13]

At this point, it is important to reflect on the preparation and performance of this [(COD)Ir(NHC)(py)]PF_6 complex class and their new application as C-H activation catalysts, as compared to our existing and more well-established [(COD)Ir(IMes)(PR_3)]PF_6 series. In relation to this, both catalyst classes are readily accessible and provide stable and readily handled species for use in HIE processes. Indeed, access to the NHC/pyridine complexes described here is relatively



Scheme 2 HIE reaction scope.[14] 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 shown, e.g. 94% for the two possible positions in **5a** indicates 1.88 D incorporation. [a] Reaction run using 50 mol% catalyst. [b] Reaction run using 10 mol% catalyst.

Table 2 HIE time study using catalyst **3c**



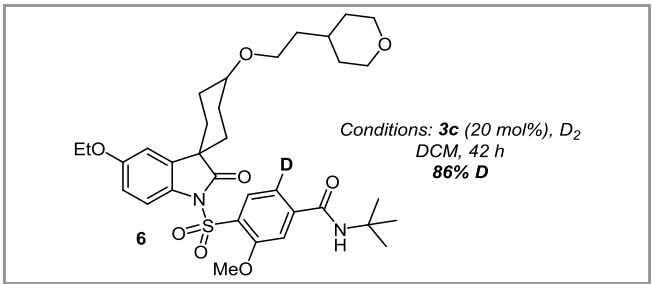
Entry	Product	% D after 30 min[a]	% D after 16 h[a]
1	**5a**	96	94
2	**5b**	89	94
3	**5c**	33	72
4	**5d**	90	96
5	**5e**	97	>99
6	**5f**	75	89
7	**5g**	89	92
8	**5h**	10	90
9	**5j**	30 (65)[b]	58 (94)[b]

[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 shown, e.g. 96% for the two possible positions in **5a** indicates 1.92 D incorporation. [b] Reaction run using 10 mol% catalyst.

more direct overall, notwithstanding the requirement for the use of a glove box technique at the outset of the preparative process.[12] With regards to catalyst performance within the described HIE processes, in an overall qualitative sense, the NHC/pyridine complexes generally compare well with our existing NHC/phosphine series, especially when considering, for example, substrates such as acetophenone (**4a**), benzophenone (**4b**), and 2-phenylpyrazole (**4g**).[6a,d] Additionally, this current set of catalysts delivered good levels of isotopically-labelled benzamide (**5c**) across the series, where the [(COD)Ir(IMes)(PR_3)]PF_6 complexes delivered somewhat more variable results with this primary amide substrate.[6a,d] Moreover and as described above, moving to slightly increased catalyst loading, **3c** was able to accommodate ester functionality at ambient temperatures, whereas our previous [(COD)Ir(IMes)(PR_3)]PF_6 systems employed moderately elevated temperatures to deliver similar levels of incorporation in ester containing compounds at lower catalyst loading.[6f]

Encouraged by the results obtained to this stage, we looked to more fully probe the reaction parameters in an attempt to explore the wider capability of the NHC/pyridine catalyst series within these HIE processes. As such, varying levels of catalyst loading were explored, as well as a study on the reaction rate. Despite lower quantities of catalyst being utilisable in the hydrogen isotope exchange of acetophenone, **4a**,[15] it was recognised that a reliable quantity of 5 mol% of the requisite iridium species was optimal over a range of substrates. In addition to these experiments, as shown within Table 2, we were pleased to realise that our developed labelling protocol was indeed more rapid than anticipated. As detailed, after only 30 minutes, using 5 mol% of SIMes catalyst **3c**, comparably high levels of incorporation were achieved with the majority of substrates tested as part of our studies. In contrast, at 30 minutes reaction time the more demanding substrates, benzamide **4c**, 2-phenylimidazole **4h**, and ethyl benzoate **4j** did not deliver the high levels of incorporation obtained over the more prolonged 16 h process.

In an extension of these studies and to further illustrate the capability of catalysts of type **3**, we applied the SIMes derived complex **3c** in the hydrogen isotope exchange of Sanofi-Synthélabo's pharmacological target, **6** (Scheme 3). The ability to label fully functionalised drug scaffolds is central to the application of HIE catalysis, especially as aligned to the endeavours of pharmaceutical partners. In this instance we were pleased to obtain 86% D incorporation using 20 mol% of catalyst, albeit over 42 h. Notably, the observed labelling was completely selective, with incorporation occurring at the least hindered site of the complex drug target and as directed by the adjacent amide functionality *via* a 5-mmi.



Scheme 3 HIE of a pharmaceutical agent, SR 121463.

In summary, we have revealed the escalated capability of complexes of the type [(COD)Ir(NHC)(py)]PF_6 within transition metal catalysis. Specifically, such complexes have been shown to perform within an *ortho*-directed C-H activation and hydrogen isotope exchange process, delivering high levels of deuterium incorporation over a series of functionalised aromatic substrates. The established system displays notable efficacy under mild reaction conditions and over short reaction times. From these studies, catalyst **3c** has proven to be the most versatile and broadly applicable of the series applied, and also providing high levels of selective isotopic labelling within a fully functional drug target. With HIE now a key procedure in the optimisation of the drug discovery process, the results presented in this study are of direct value and importance to pharmaceuticals partners. Indeed, ongoing studies within our laboratory have the goal of discovering catalysts that are compatible with increasingly complex organic molecules and alternative drug-like substrates, as well as in the establishment of alternative C–H activation processes in a wider sense.

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Supporting Information

NO (this text will be deleted prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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(12) **Typical Procedure for the Preparation of Catalysts 3a-c:** An oven dried Schlenk flask was charged with NHC salt **1** (2.49 mmol) and evacuated for 30 minutes. The flask was then transferred to a nitrogen filled glove box and isolated potassium hydride (2.49 mmol) was added. The flask was then attached to a Schlenk line (argon/vacuum), evacuated once, and filled with argon. Anhydrous THF (30 ml) was added and the slow evolution of hydrogen was observed. The resulting solution was then allowed to stir for 20 h at room temperature, after which time the reaction mixture was filtered through a dry filter stick into an oven dried Schlenk flask. The THF was evaporated and the resulting free carbene was extracted into anhydrous toluene (30 ml). The resulting toluene solution was filtered through another dry filter stick into a previously evacuated and oven dried Schlenk flask containing $[(COD)Ir(py)_2]PF_6$, **2**, (1.66 mmol). The reaction was allowed to stir for two days at room temperature under an argon atmosphere. After this time, the mixture was filtered to yield the desired iridium complex **3**.

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(14) **Representative Procedure for Isotopic Labelling:** *Acetophenone, **4a**, using catalyst **3c** (Scheme 2)*. A 100 mL, 3-necked round bottom flask was fitted with two stopcock valves and a suba seal, and was flame dried under vacuum. The flask was then placed under a nitrogen atmosphere and evacuated three times. The flask was then charged with catalyst **3c** (34 mg, 0.042 mmol) and DCM (5 mL), and then purged with nitrogen. The solution was allowed to stir under an atmosphere of nitrogen for 15 minutes prior to the addition of acetophenone (100 mg, 0.83 mmol). The suba seal was then replaced with a greased glass stopper and the solution was stirred whilst being cooled to -78°C in a dry ice/acetone slurry. The flask was twice evacuated and flushed with nitrogen. Upon a third evacuation, an atmosphere of deuterium gas was introduced *via* a balloon. The cold bath was removed and the flask was allowed to warm to room temperature. NOTE: the glass stopper was physically restrained as the reaction mixture warms. The resulting mixture was stirred vigorously for 16 h before removing excess deuterium gas and replacing with air. The reaction mixture and washings (DCM) were transferred to a single necked flask before removing the solvent under reduced pressure. The catalyst complex was then precipitated by the addition of petrol/ether (1:1, 10 mL) to the reaction residues. The catalyst was then removed by filtration through a plug of silica and the resulting filtrate was concentrated under reduced pressure. The level of deuterium incorporation in the substrate was determined by ^{1}H NMR to be 94%. The integrals were calibrated against a peak corresponding to a position not expected to be labelled. The equation below was used to calculate the extent of labelling:

% D = 100 – [(residual integral/no. of labelling sites) x 100]

*Acetophenone, **4a***: ^{1}H NMR (400 MHz, $CDCl_3$) δH 2.45 (s, 3H); 7.32 (t, 2H, *J* = 8.0 Hz); 7.41 (t, 1H, *J* = 8.0 Hz); 7.81 ppm (d, 2H, *J* = 8.0 Hz). Labelling expected at δH 7.81. Determined against integral at δH 2.45.

(15) In experiments using 2.5 mol% of catalysts **3a** or **3c** in DCM over 16 h at room temperature, 81% and 90% D incorporation was obtained, respectively, in the labelling of acetophenone (**4a**).