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Nitrile-tolerant Iridium-catalysed Hydrogen Isotope Exchange

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Isotopically labelled molecules are vital tools within drug discovery and are used extensively to assess a given candidate's absorption, distribution, metabolism, excretion, and toxicity (ADMET) profile. Related to this, transition metal-catalyzed hydrogen isotope exchange (HIE) has become a prominent technique for the rapid and selective late-stage installation of a deuterium or tritium label. Despite having a generally wide applicability, the current state-of-the-art in this specific field is limited when particularly co-ordinating motifs are present within a given molecule to be labelled. For example, the exceptional binding strength and sterically unencumbered nature of the nitrile functionality leads to inhibition of catalyst turnover, and has hindered the development of efficient methods for the HIE of nitrile-containing molecules. Herein, *in silico* solvent binding energy parameter approaches have been disclosed which have facilitated the discovery of uniquely tolerant neutral iridium catalyst species that demonstrate a significantly lower binding strength with nitrile functionality. In turn, we describe the first effective nitrile-tolerant HIE methodology enabled *via ortho*-directed C(sp^2)–H activation using air- and moisture-stable iridium pre-catalysts of the type Ir(COD)(NHC)Cl under an atmosphere of deuterium gas. This methodology proceeds under mild and practically accessible reaction conditions with a range of directing groups, including heterocycles, ketones, and amines, with this class of catalyst also shown to be applicable towards bioactive molecules, resulting in products with high levels of isotopic labelling.

Incorporation of hydrogen isotopes, deuterium and tritium, into a molecule facilitates several unique applications.[1] Specific advantages of deuterium isotopologues include the ability to exploit the increased C–D bond strength in kinetic isotope effect studies,[2] as well as the capacity to fine-tune a drug's pharmacokinetic profile. The latter is demonstrated by the first FDA-approved deuterated drug Deutetrabenazine (Austedo),[3] which displays a prolonged plasma half-life and allows for lower drug dosing than its non-deuterated analogue. Moreover, medicinal chemists have now expanded beyond the deuterium switch approach, with the use of deuterium now becoming integral to the drug discovery process,[4] and as exemplified by Deucravacitinib[5] as the first example of a *de novo* deuterated FDA-approved drug. At least as importantly, through the increased mass of deuterium and the radioactivity of tritium, the incorporation of hydrogen isotopes provides a readily identifiable molecular tag. This facilitates the use of deuterated compounds as stable isotopically labelled internal standards (SILS),[6] while tritiated compounds are unique for their utility in radioligand binding assays,[7] and other *in-vitro* or *in-vivo* ADMET studies.[8]

In a preparative sense, hydrogen isotope exchange (HIE) is a technique of increasing importance and can enable the rapid and efficient incorporation of deuterium or tritium atoms into late-stage intermediates, or final molecular targets themselves, avoiding the expensive and time consuming multistep synthesis of isotopically labelled compounds.[9,10] Within this HIE field, *ortho*-directed transition metal-catalyzed methods have emerged as robust and flexible processes that enable site-selective labelling under mild reaction conditions *via* C–H activation and functionalization.[9,11] In this regard, homogeneous iridium-based catalysts have come to dominate this field (Figure 1A),[9,12] from the use of monodentate, cationic, complexes such as Crabtree's catalyst **1**[13] and the catalysts emerging from our own laboratory (*e.g.* **2**),[14] to the application of bidentate species such as those developed by Tamm,[15] Pfaltz and Muri,[16] Burgess,[17] and ourselves[18] (**3**–**6**, respectively). Application of such iridium-based species has allowed an array of Lewis basic directing groups (DGs) to be applicable within HIE processes, including heterocycles, ketones, amides, carboxylic acids, esters, sulfur-based moieties, and the nitro unit, with complex (multifunctional) starting substrates displaying a wide functional group tolerance. Having stated this, the presence of nitrile functionality remains largely incompatible with homogeneous transition metal-catalyzed HIE. This limitation remains apparent despite the prominence of nitrile units in pharmaceutical candidates, where their linear nature can offer enhanced binding affinity to the target, as well as bringing improved bioavailability and prolonged half-life *via* the metabolic stability and non-toxic nature of this functional group

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(Figure 1B).[19] The key challenge with respect to the tolerance of the nitrile unit within HIE catalysis is attributed to the high coordination strength of this functionality likely (and irreversibly) outcompeting the requisite complexation of the directing group to the metal centre.[14b,20]

Nitrile incompatibility in HIE has been independently reported within the works of Heys,[21] Hesk,[13a] and Muri,[16] where otherwise functional group tolerant catalysts prove to be significantly inhibited by nitrile units or, indeed, completely shut down. As shown in Figure 1C, Muri and co-workers demonstrated in a single example that increased catalyst loading could overcome inhibition; however, 105 mol% of Pfaltz-type species **4** was required to achieve worthy levels of incorporation.[16] Further, Heys *et al.* reported the use of 190 mol% loading of $[Ir(COD)(dppe)]BF_4$ in an urea-directed C(sp^2)–H tritiation example of a nitrile-containing compound.[22] Unfortunately, the increased cost, poor atom economy, and potential for unwanted (tritiated) waste makes such elevated catalyst loading approaches an impractical general solution for the labelling of nitrile containing compounds.[23] Muri and coworkers did demonstrate a potential solution, whereby the use of tris(pentafluorophenyl)borane (1.1 eq.) as an additive facilitated an 88% deuteration of 4-acetylbenzonitrile using 5.0 mol% of a Pfaltz-derived iridium bidentate-*N,P* complex, albeit with the requirement of a 90 °C reaction temperature in PhCl for 18 h;[16] *NB*, this 88% incorporation was averaged over both the desired *ortho*-aryl position and the sp^3 methyl site. In this area, it is also important to highlight the work of Pieters *et al.*, whereby multiple site isotope incorporation can be achieved *via* the *in-situ* formation of iridium nanoclusters.[24] This protocol exhibits a high functional group tolerance, and the presence of the nitrile motif (in a single example) did not pose a limitation on this multiple site labelling system. Despite these latter described examples, it is clear that a general homogeneous catalysis strategy for the selective placement of isotopic substituents within nitrile-containing scaffolds remains elusive and would be of significant value within related drug discovery endeavours. In efforts to further widen the scope and utility of iridium catalysts for hydrogen isotope exchange, we report herein highly effective homogeneous catalytic labelling protocols that can readily accommodate the nitrile motif for the first time.

In line with recent studies from our laboratory on catalyst design and application within the field of HIE, our approach within this programme was importantly underpinned by the use of computational methods. In relation to this, a range of our previous preparative outputs have been complemented by DFT studies when exploring, for example, reaction mechanism, catalyst structure, substrate binding affinity, or binding enthalpies of solvent molecules.[14b,d,e,j] More specifically, in 2020 we reported the computationally-guided design of a novel chelated iridium(I) system capable of enabling the previously challenging aryl sulfone directing group to facilitate HIE.[18a] Key to this development was the use of the substrate binding energy (E_{Bind}) parameter[25] to assess, *in silico*, the potential of an array of putative catalyst species.[14l,18a] Aligned to this and with a view to considering the competition between substrate and solvent coordination to the active catalytic species, research within our laboratory has most recently involved mapping the binding affinity of an expanded and diverse array of reaction media to the active species across a full range of our developed iridium complexes. As related to this and as aligned directly with the work divulged herein, a key preliminary finding was that acetonitrile displays significantly distinct binding energy (E_{Bind}) values when comparing catalysts of the type Ir(COD)(NHC)Cl[26] with our more established cationic $[Ir(COD)(NHC)(PR_3)]X$ series. As shown in Figure 2, considering the coordinated derivatives of the known HIE-facilitating solvent ethyl acetate,[14c,27] comparison of the $[Ir(IMes^{Me})(PBn_3)(Solvent)_2H_2]^+$ complex **5** with the $Ir(IMes^{Me})(Cl)(Solvent)_2H_2$ species **6**[28] resulted in analogous E_{Bind} values. This contrasts significantly with the 16.1 kcal mol^{-1} difference in binding strengths observed between complexes **5** and **6** with acetonitrile as the solvent. Indeed, the large value of −45.2 kcal mol^{-1} for **5** (MeCN) emphasizes the significant (and catalyst-inhibiting) binding strength of the nitrile functionality, whilst species **6** (MeCN) displays a much more favourable E_{Bind} value of −29.1 kcal^{-1}, and aligns closely with the EtOAc binding

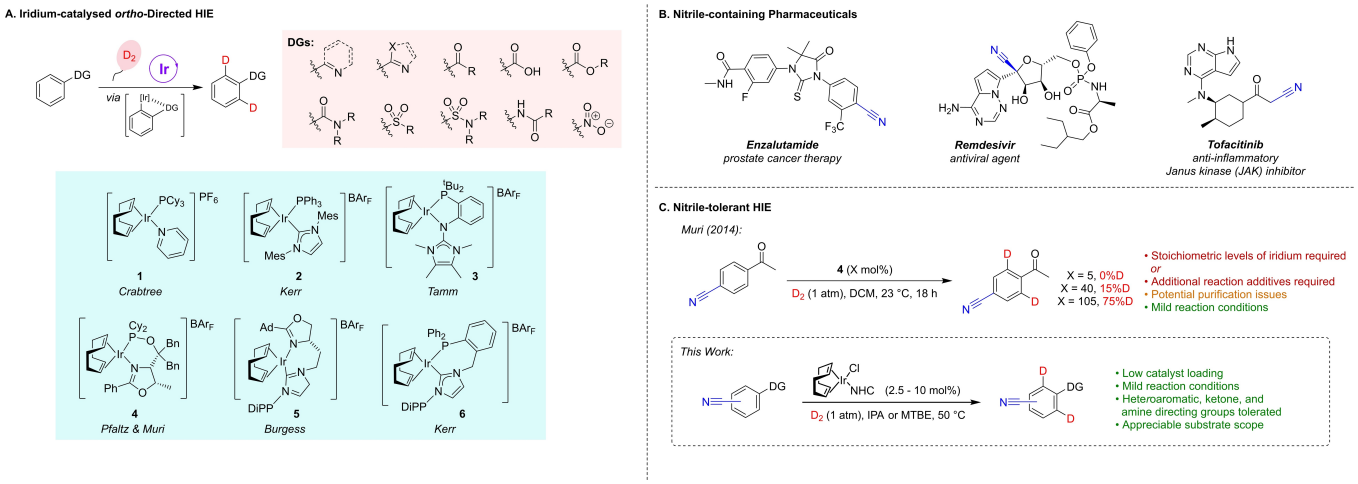


Figure 1. A) Iridium-catalysed *ortho*-directed HIE. B) Nitrile-containing pharmaceuticals. C) Nitrile-tolerant HIE.

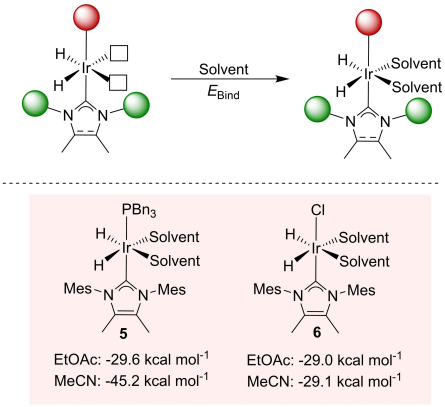
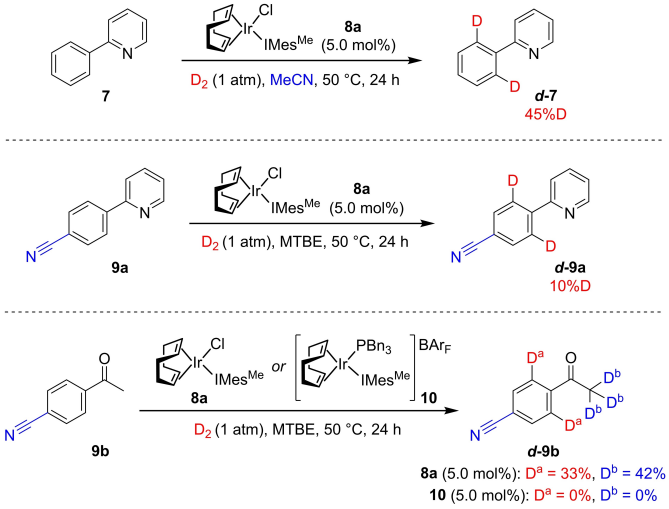


Figure 2. Calculated E_{Bind} values for ethyl acetate and acetonitrile bound species [Ir(IMes^{Me})(PBn$_3$)(Solvent)$_2$H$_2$] and Ir(IMes^{Me})(Cl)(Solvent)$_2$H$_2$.



Scheme 1. Initial results in the development of nitrile-tolerant HIE.

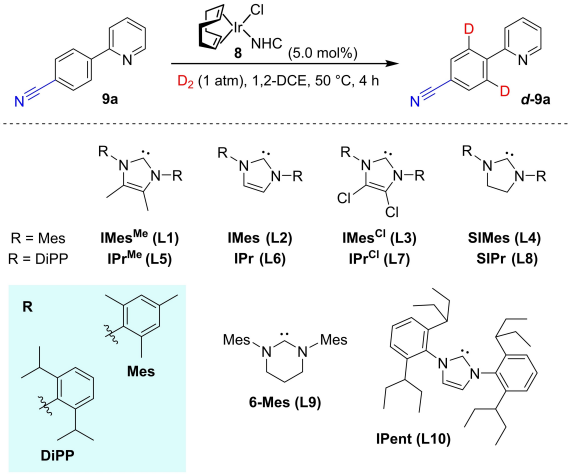
energies. These binding energy values can be rationalized by a consideration of electronic and steric effects. Electronically, moving from the cationic species **5** to the neutral complex **6** results in a naturally more electron-rich catalyst system, reducing the resultant binding affinity of the varying Lewis basic solvents. However, in a steric sense, moving from complex **5** to **6** represents an opening of the co-ordination sphere, with the large tribenzylphosphine ligand being replaced by a smaller chloride. In the case of EtOAc as solvent, it is proposed that these two effects are balanced, resulting in the similar binding energies observed with both **5** and **6**. In the case of acetonitrile, however, its linear and sterically undemanding geometry means that only the decreased binding affinity plays an appreciable role on moving to the more open ligand sphere of **6**. Nonetheless, given the agreeable E_{Bind} value for **6** (MeCN), it was hypothesized that Ir(COD)(NHC)Cl catalysts may offer successful HIE using MeCN as the reaction solvent, and, moreover, provide the foundations of an effective catalyst class with regards a more general nitrile-tolerant HIE protocol.

With this computational backdrop, in our first experiment 2-phenylpyridine **7** was reacted under hydrogen isotope exchange conditions using Ir(COD)(IMes^{Me})Cl **8a** (5.0 mol%) in MeCN as solvent at 50 °C under an atmosphere of D_2 gas (Scheme 1, top). Pleasingly, this resulted in a notable 45% deuterium incorporation after 24 h. The ability to perform *ortho*-directed HIE in acetonitrile supports our computational binding energy findings (*vide supra*) and now expands the solvent applicability of this catalyst type beyond that previously reported to include a highly polar aprotic solvent likely capable of solubilising key drug molecules. Taking advantage of the tolerance of catalyst **8a** to acetonitrile, the possibility of HIE on nitrile-containing molecules was examined. As such, 4-(2-pyridyl)benzonitrile **9a** was reacted with **8a** and D_2 gas in anticipation of pyridine-directed exchange in methyl *tert*-butyl ether (MTBE), with this medium employed based on the emerging efficacy of this solvent in such HIE processes, including recently established labelling methodologies.[14c,d,k,l,27,29] We were pleased to observe a modest 10% *ortho* deuterium incorporation within this process (Scheme 1, middle), providing a foundation for the ensuing optimization. As an additional substrate, 4-acetylbenzonitrile **9b** was similarly subjected to these HIE conditions, furnishing a higher 33% deuterium incorporation at the *ortho*-site (Scheme 1, bottom). Notably, concurrent methyl deuteration (adjacent to the ketone functionality) was observed with an appreciable 42% incorporation at this site. While this demonstrates a loss of selectivity, it does present the opportunity to access d_5-4-acetylbenzonitrile. To exemplify the challenge associated with nitrile functionality in the HIE domain, we also attempted to label 4-acetylbenzonitrile **9b** using a traditional cationic, and more generally highly effective, HIE catalyst from our laboratory, **10**. Deuteration was completely inhibited within this system and no labelled material was obtained, again highlighting the novel and potentially unique reactivity of species such as **8a**.

With these preliminary results in hand, assessment of the catalyst system *via* a ligand screen was envisaged with a view to establishing the optimal catalyst species to enable a nitrile-tolerant HIE methodology. As a prelude to this, it was also important to consider the somewhat unanticipated relative directing group effectiveness observed between the pyridine- and ketone-directed processes, as detailed within Scheme 1. More specifically, comparison of directing groups in homogeneous iridium-catalyzed HIE consistently reports the increased strength of the pyridine directing unit as compared to other functionalities, including the carbonyl-based ketone moiety.[30] Accordingly, this observed outcome was attributed to the MTBE solvent choice, where it is envisaged that such a weakly coordinating solvent would be less able to overcome strong pyridine (or nitrile) coordination, which is ultimately required to release the deuterated product, and, concordantly, limiting catalyst turnover. As such, prior to the assessment of the possible catalyst scope, a small range of alternative solvents were tested (for full details, see the *Supporting Information, Table S1*). To this end, 1,2-DCE was introduced as the reaction medium, which also provides advantages in terms of solvent volatility with a boiling point appreciably greater than 50 °C.

Indeed, such a chlorinated solvent (DCM) has prevailed as the reaction medium of choice for Ir(COD)(NHC)Cl species in previous studies,[26] providing the requisite balance of solvent ligation versus decomplexation as part of the catalytic cycle. Employing the standard substrate 4-(2-pyridyl)benzonitrile **9a** (Table 1), we were pleased to obtain a modest, but improved, 22% *ortho*-deuterium incorporation with catalyst **8a** after 4 h reaction time (entry 1). Varying the methyl substituents on the backbone of the NHC ligand to H (**L2**) or Cl (**L3**) atoms resulted in a reduction in the level of labelling in both cases, suggesting that lowering the steric bulk of the catalyst, or reducing the electron density of the NHC, is detrimental to the HIE of nitrile-containing compounds (Table 1, entries 2 and 3). In contrast, modifying to an iridium catalyst with the saturated SIMes NHC (**L4**) furnished a further modest increase to 32% incorporation, potentially due to the subtle shift in conformation of the saturated NHC (Table 1, entry 4). Unfortunately, catalysts with the bulkier di-*iso*-propylphenyl *N*-substituent (Table 1, entries 5–8) did not lead to any improvement in the effectiveness of this methodology, while the complex with the ring expanded NHC, 6-Mes (**L9**), was almost completely inactive (Table 1, entry 9). The breakthrough catalyst for this transformation employed the highly bulky IPent ligand (**L10**), which provided an excellent 96% deuterium incorporation (Table 1 entry 10). The activity of the iridium complex with the **L10** catalyst was further exemplified whereby a reduction to 2.5 mol% catalyst loading provided maintenance of high levels of labelling activity, although utilising only 1 mol% catalyst led to only 20% incorporation (Table 1, entries 11 and 12). Lastly, it was realised that the solvent could be exchanged from 1,2-DCE to *iso*-propyl alcohol (IPA), as recommended by the CHEM21 solvent selection guide,[31] while maintaining a low 2.5 mol% catalyst loading to deliver an excellent 93% deuterium labelling level (Table 1, entry 13).

Table 1. Catalyst optimization for the HIE of 4-(2-pyridyl)benzonitrile **9a**. Results shown are an average of two reaction runs.

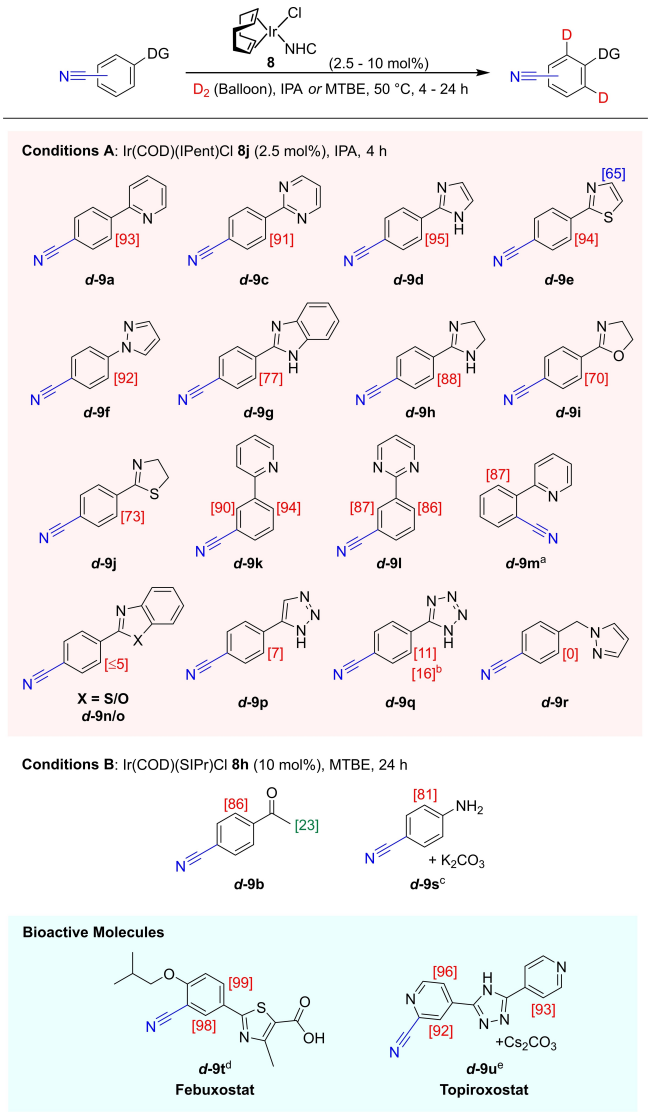


Entry	NHC	Catalyst	Deuterium Incorporation (%)
1	$IMes^{Me}$ (**L1**)	**8a**	22
2	IMes (**L2**)	**8b**	13
3	$IMes^{Cl}$ (**L3**)	**8c**	13
4	SIMes (**L4**)	**8d**	32
5[a]	IPr^{Me} (**L5**)	**8e**	25
6	IPr (**L6**)	**8f**	8
7	IPr^{Cl} (**L7**)	**8g**	8
8	SIPr (**L8**)	**8h**	8
9	6-Mes (**L9**)	**8i**	2
10	IPent (**L10**)	**8j**	96
11[b]	IPent (**L10**)	**8j**	96
12[c]	IPent (**L10**)	**8j**	20
13[d]	IPent (**L10**)	**8j**	93

[a] Single reaction performed. [b] 2.5 mol% catalyst loading. [c] 1.0 mol% catalyst loading. [d] 2.5 mol% catalyst loading; solvent: IPA.

With these favorable optimized conditions in hand, the directing group scope was explored (Scheme 2). Pleasingly, in addition to pyridine **9a**, pyrimidine **9c** also proved to be a very effective directing group resulting in 91% deuterium incorporation. Furthermore, a variety of 5-membered *N*-heteroaromatics proved to be highly efficient directors, including the imidazole **9d**, thiazole **9e**, and pyrazole **9f** units, each of which resulted in $\geq$92% deuteration at the desired position. Interestingly, the thiazole **9e** also exhibited an unexpected 65% deuteration in the α-*N* position. Increasing the bulk of the directing group resulted in a relatively modest drop in deuterium incorporation, as shown with benzimidazole **9g** which furnished 77% labelling. Moving from 5-membered aromatic directing groups to their more saturated *N*-heterocyclic analogues also resulted in similar deuterium incorporation efficiencies, albeit still delivering at very good levels of labelling with the imidazoline **9h**, oxazoline **9i**, and thiazoline **9j** units. *meta*-Positioning of the directing group and nitrile functionality (**9k** and **9l**) resulted in appreciable levels of labelling affinity and only moderately lower than their *para*-positioned equivalents. *ortho*-Configuration of the directing group and nitrile functionality, as demonstrated with pyridine **9m**, required an extension of the reaction time to 16 h to furnish an excellent 87% deuterium incorporation. Unfortunately, inactivity was observed with benzothiazole **9n**, despite the excellent 94% deuterium incorporation observed with the corresponding thiazole **9e**, and a similar outcome was observed with benzoxazole **9o**. Further selected directing groups that did not prove amenable to this HIE procedure included 1,2,3-triazole **9p** and tetrazole **9q**. With regards the latter, Cs_2CO_3 was added in attempts to induce a base-assisted protocol but to no avail; the addition of base to such iridium-catalyzed systems has previously been shown to promote labelling with substrates containing, for example, unprotected tetrazoles[14h] or carboxylic acids[14k] as the directing group (albeit with cationic catalysts such as **2**). Pyrazole **9r** was also subjected to the optimized reaction conditions to probe the efficacy of HIE from increasingly distal directing groups; however, this substrate failed to deliver any desired deuterium incorporation.

To fully assess the scope of this system, we further applied this methodology towards non-heterocyclic functional units. This required additional system optimization using the model



Scheme 2. Nitrile-tolerant hydrogen isotope exchange *via* a selection of common directing groups using either Ir(COD)(IPent)Cl **8j** or Ir(COD)(SIPr)Cl **8h**. Results shown are an average of at least two reaction runs. [a]The reaction time was increased to 16 h. [b]Cs_2CO_3 (0.5 eq.) added. [c]K_2CO_3 (1 eq.) added; single reaction run. [d]Ir(COD)(SIPr)Cl **8h** (10 mol%), 1,2-DCE, D_2 (1 atm), 50 °C, 24 h. [e]Ir(COD)(IPent)Cl **8j** (2.5 mol%), Cs_2CO_3 (0.5 eq.), IPA, D_2 (1 atm), 50 °C, 4 h.

substrate 4-acetylbenzonitrile **9b** (for full details, see *Supporting Information*, *Tables S4, S5, & S6*). In this case, the non-polar solvent MTBE was identified as the most favorable reaction medium, presumably due to the subtle balance of solvent coordination strength and directing group complexation. Furthermore, the large, sterically encumbered, IPent ligand **L10** was not required, with the di-*iso*-propylphenyl substituents in catalysts **8e**, **8g**, and **8h** leading to, at least, equally good levels of labelling performance. Indeed, moving from Ir(COD)(IPent)Cl to Ir(COD)(SIPr)Cl (catalyst **8h**) resulted in an active system for substrates **9b** and **9s**, albeit at 10 mol% catalyst loading over 24 h to furnish highly deuterated products. Specifically, 4-acetylbenzonitrile **9b** was deuterated to a very good level of 86% at the desired sp^2 position, with now only a modest 23% concurrent methyl labelling observed (*cf.* Scheme 1, bottom, as well as the previously published methods[16]). Pleasingly, and as inspired by the HIE of anilines reported by Yan and co-workers,[32] the addition of 1 eq. of K_2CO_3 to the reaction of **9s** enabled HIE to deliver an appreciable 81% selective incorporation adjacent to the aniline NH_2 unit.

The efficiency of the developed system was then scrutinized by extension to a selection of bioactive molecules, including the xanthine oxidase (XO) inhibitors, Febuxostat[33] **9t** and Topiroxostat[34] **9u** used in the treatment of gout. Pleasingly, the sterically hindered Febuxostat **9t** was deuterated to an almost quantitative level over both aromatic positions through the thiazole directing group, using a slight modification to Conditions B. Furthermore, our developed approach also facilitated the excellent deuteration of Topiroxostat **9u** with three distinct aromatic positions labelled to 92% or greater. This is despite the presence of two pyridine moieties, in addition to the nitrile functionality, that could compete for complexation to the catalyst in a non-productive manner. To note, in this example, the addition of Cs_2CO_3 was key to the delivery of highly labelled material, with the base likely facilitating a pathway via deprotonation of the triazole, in accordance with our previous studies with tetrazoles.[14h]

To fully exemplify the significance and impact of this newly developed nitrile tolerant protocol, the Ir(COD)(NHC)Cl catalysed HIE system was compared against our established, and normally highly capable, catalyst $[Ir(COD)(IMes)(PPh_3)]BAr_F$ **2** with both the benchmark substrate **9a** and the marketed drug, Topiroxostat, **9u** (for full details, see the *Supporting Information*, Section 2.3.8). As expected, considering the published precedent, only low levels of deuterium incorporation (<20%) were observed in each case, demonstrating the unique applicability of the neutral chlorocarbene-based iridium catalyst species as developed as part of this study.

In summary, we have disclosed catalysts of the type Ir(COD)(NHC)Cl as the first reported species capable of facilitating effective homogeneous catalytic processes for *ortho*-directed HIE in the presence of the pharmaceutically-relevant nitrile functionality. High levels of isotope incorporation have been achieved across an array of molecular contexts, including within multi-functional drug compounds, with low catalyst loadings and under mild reaction conditions. It is envisaged that the characteristics of our developed protocols will be of widespread value to pharmaceutical partners in the field of drug design and labelling science, including potential translation to tritiation endeavours, as well as the wider preparative community within both academia and industry.

Supporting Information Summary

The authors have cited additional references within the Supporting Information.[35–75]

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Hydrogen isotope exchange · Iridium · C–H activation · Nitriles · *N*-heterocyclic carbenes

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