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C–H Activation and Hydrogen Isotope Exchange of Aryl Carbamates Using Iridium(I) Complexes Bearing Chelating NHC-Phosphine Ligands

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Hydrogen isotope exchange (HIE) via C–H activation constitutes an efficient method for the synthesis of isotopically-enriched compounds, which are crucial components of the drug discovery process and are extensively employed in mechanistic studies. A series of iridium(I) complexes, bearing a chelating phosphine-*N*-heterocyclic carbene ligand, was designed and synthesized for application in the catalytic HIE of challenging *N*- and *O*-aryl carbamates. A broad range of substrates were labeled efficiently, and applicability to biologically-relevant systems was demonstrated by labeling an L-tyrosine-derived carbamate with excellent levels of deuterium incorporation. Combined theoretical and experimental studies unveiled intriguing mechanistic features within this process, in comparison to C–H activation and hydrogen isotope exchange catalyzed by monodentate Ir(I) NHC/phosphine complexes.

Introduction

The development of catalytic C–H activation protocols for the functionalization of organic compounds enables rapid access to sophisticated molecular architectures. In recent years, various catalytic methods, employing a range of metals, such as Ru, Pd, Rh, Pt, and Ir, have been reported within this overarching area.[1] Related to this, the activation of C–H bonds is of particular interest for hydrogen isotope exchange (HIE).[2] This process is frequently employed to generate labelled molecules for the assessment of pharmacological properties of new drug candidates through absorption, distribution, metabolism, and excretion (ADME) studies;[3] and in the synthesis of deuterated compounds for the elucidation of reaction mechanisms.[4] In the realm of directed HIE, iridium complexes are often employed as catalysts owing to their functional group tolerance and compatibility with a vast range of directing groups.[2d] Over a number of years, we have reported a suite of Ir(I) *N*-heterocyclic carbene/phosphine complexes[5,6] for the C–H activation and HIE of aryl substrates bearing a range of Lewis basic directing groups (Figure 1a).

Despite the broad applicability of current *ortho*-directed metal-catalyzed HIE methods, substrates possessing sterically hindered, poorly coordinating directing groups represent a challenge to such HIE protocols.[7] Specifically, aryl carbamates constitute an important example of this class of substrate. Associated with this, application of previously developed and more generally broadly applicable catalysts **1a-b** to the labelling of *N*-Boc-*p*-toluidine **2a** led to only low levels of deuterium incorporation, Figure 1b[8] (N.B. catalysts such as **1a** provide >90% D at r.t. with a range of less encumbered directing units,[5e,h,j] *e.g.* acetophenone, Figure 1c). Nonetheless, as a result of their ubiquitous use as

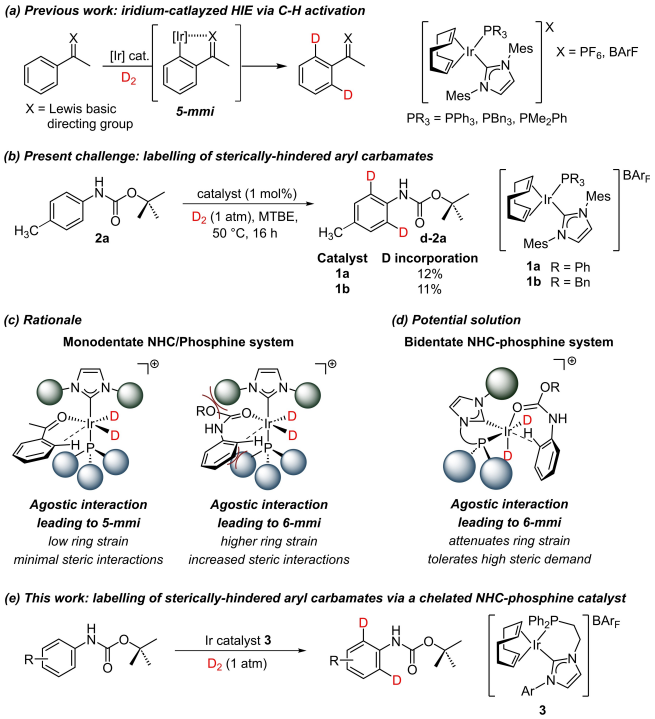

Figure 1. Hydrogen Isotope Exchange and the challenge of sterically-encumbered directing groups.

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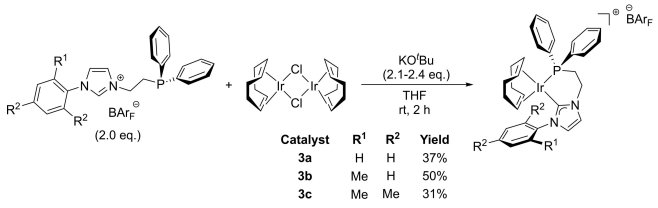
protecting groups[9] and the presence of such protected (aryl) amines in pharmaceutically relevant compounds,[10] an effective protocol for the HIE of aryl carbamates is highly desirable. In this regard, it is envisaged that any successful catalytic system must overcome two important challenges: i) the sterically hindered nature of the Boc group; and ii) a C–H activation process that leads to a more sterically-congested, and less energetically favourable, 6-membered metallacyclic intermediate (6-mmi), *cf.* substrates that lead to a more kinetically accessible 5-mmi.[5d,11] The challenging nature of this C–H activation, compared to simpler substrates such as an aryl ketone, is illustrated in Figure 1c.

Unsurprisingly, few systems capable of performing isotope exchange on hindered aryl carbamates have been reported. Despite an earlier report describing the labelling of a small selection of Boc-protected anilines (as well as other substrates),[12] we were motivated to conduct an in-depth study of carbamate-directed labelling; to probe the mechanism of the HIE process; and to also investigate related *O*-aryl carbamate labelling.

Based on the perceived challenges associated with the Boc carbamate directing group, as discussed above, and as evidenced by the low levels of labelling observed with complexes **1 a-b** (Figure 1b), we hypothesized that the use of a chelating NHC-phosphine ligand would reduce the steric hindrance around the iridium centre (Figure 1d), conferring higher stability to a resulting 6-mmi, thus facilitating the C–H activation process and subsequent HIE in carbamates. Specifically, having recently reported an iridium(I) complex bearing a chelating NHC-phosphine (NHC–P) ligand for use in the HIE of the sterically encumbered and weakly directing arylsulfone moiety,[13] we were interested in evaluating related NHC–P chelated motifs as alternatives to our established monodentate NHC/phosphine complexes in the labelling of *N*-Boc aryl carbamates (Figure 1e). Indeed, in the case of sulfone labelling, binding energy calculations demonstrated the remarkably enhanced coordination of methyl phenyl sulfone with a chelate catalyst ($E_{bind} = -23.1$ kcal mol^{-1}) vs the PF_6 analogue of complex **1 a** ($E_{bind} = -15.3$ kcal mol^{-1}).[13]

Results and Discussion

With this backdrop, we prepared a series of iridium complexes **3 a–c**, bearing NHC–P chelating ligands (Scheme 1), from their corresponding phosphino-imidazolium salts,[8] with a view to evaluating their catalytic activity in the labelling of Boc-protected anilines.



Catalyst	R^1	R^2	Yield
3a	H	H	37%
3b	Me	H	50%
3c	Me	Me	31%

Scheme 1. Synthesis of NHC-Phosphine chelate catalysts **3 a–c**.

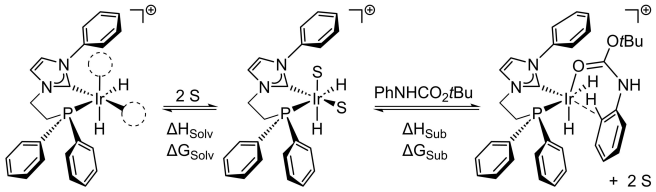
In order to establish an effective labelling protocol, the selection of an appropriate solvent is considered to be critical for the success of HIE processes.[5c,e,g,j,13] If the solvent has appreciably better ligating properties than the (carbamate) substrate, the equilibrium for dissociative ligand exchange would strongly favour the solvent-bound complex. Conversely, if substrate ligation severely dominates the displacement equilibria, turnover of the substrate would be inhibited, given the relative lower abundance of the substrate (*cf.* the solvent). Hence, a subtle balance between solvent and substrate binding is required for the development of an efficient catalytic HIE process. Accordingly, as detailed in Table 1, we first undertook an *in silico* screening of solvents covering a spectrum of physical properties, employing the catalyst **3 a** (using hydride ligands as a proxy for deuteride) and the Boc carbamate of aniline in order to assess displacement equilibria.

The outcome of this *in silico* screen revealed some interesting trends. Firstly, solvation enthalpies are in qualitative agreement with the σ- and π-donor abilities of the selected solvents. Secondly, considering the difference in free energies in relation to both solvent association and substrate binding (ΔG_{Solv} and ΔG_{Sub}, respectively), relatively weakly ligating ethereal solvents, di-*iso*-propyl ether, methyl *tert*-butyl ether (MTBE), and diethyl ether (Table 1, Entries 3–5), appeared as promising candidates due to their ability to compete with substrate, whilst slightly favouring coordination of the carbamate. Notably, the less effective coordinating capacity of the carbamate strongly favours solvent association when the less sterically-hindered ether, THF, and ester, *iso*-propyl acetate, are considered, with 2-MeTHF, methanol, and *iso*-propanol exhibiting similar profiles. Conversely, weakly coordinating solvents, CH_2Cl_2 and toluene, are likely to inhibit substrate turnover based on the calculated negative ΔH_{Sub} values (Table 1, Entries 1–2). Overall, this screening led us to select MTBE as the solvent for our initial investigations. Based on the calculations, MTBE should provide steric protection of reactive intermediates whilst enabling reversible coordination of substrate.

We next screened catalysts **3 a–c** in the labelling of model carbamate **2 a**, employing MTBE as the reaction solvent (Scheme 2). Pleasingly, good to excellent levels of deuterium incorporation were observed in reactions conducted with all three iridium complexes, with 1 mol% of catalyst giving very good levels of incorporation in all three cases at 50 °C in MTBE for 16 h. Notably, the excellent activity of complex **3 c** allowed elevated levels of deuterium incorporation to be maintained when conducting experiments at 1 mol% catalyst loading and over a shorter reaction time of 4 h.[8] Further, the use of MTBE was also pleasing given that broad applicability of this solvent was not evidenced in related previous studies, with chlorinated media being more generally applied.[12]

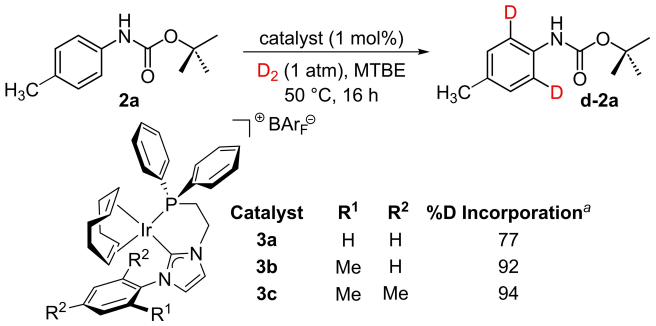
Having established the high activity of chelated complex **3 c**, we sought to evaluate the substrate scope for HIE with a range of *N*-aryl carbamates, as depicted in Scheme 3. Notably,

Table 1. Computational screening of potential solvents.



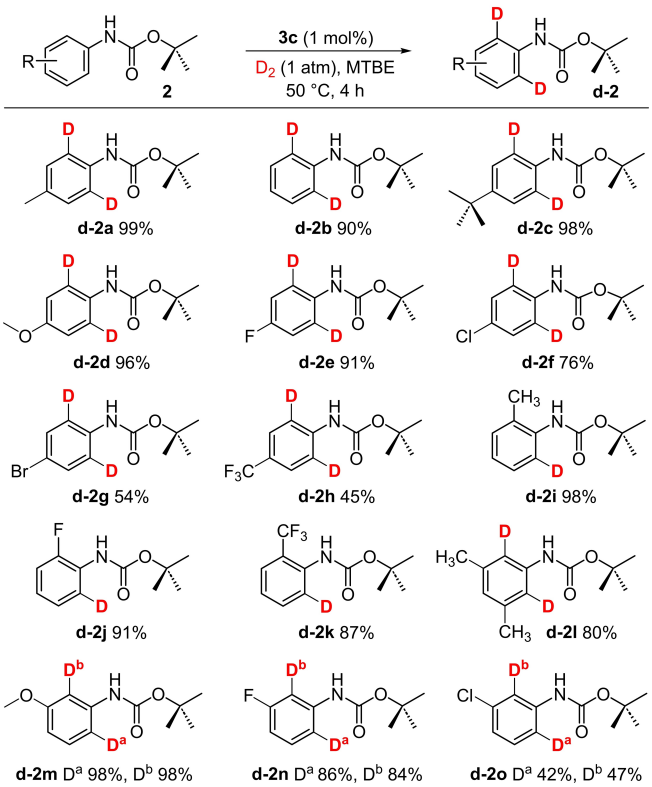
Entry	Solvent, S	ΔH_{Solv}	ΔG_{Solv}	ΔH_{Sub}	ΔG_{Sub}
1	CH_2Cl_2	−25.8	−0.9	−9.9	−17.5
2	Toluene	−33.0	−6.1	−2.7	−12.3
3	*i*Pr_2O	−38.1	−8.7	2.4	−9.7
4	MTBE	−45.4	−14.5	9.6	−3.9
5	Et_2O	−43.5	−16.6	7.7	−1.9
6	MeOH	−45.3	−23.7	9.6	5.3
7	2-MeTHF	−53.8	−26.0	18.0	7.6
8	THF	−56.1	−28.8	20.3	10.3
9	*i*PrOH	−55.5	−29.6	19.7	11.2
10	$MeCO_2$*i*Pr	−57.2	−31.8	21.5	13.4

Energies given in kcal mol^{-1}; $_{Solv}$ = solvent coordination event; $_{Sub}$ = substrate complexation event.



Catalyst	R^1	R^2	%D Incorporation[a]
3a	H	H	77
3b	Me	H	92
3c	Me	Me	94

Scheme 2. Chelate catalyst screening. Reaction conditions: Carbamate **2a** (0.1 mmol) and catalyst (1 mol%) in methyl *tert*-butyl ether (MTBE, 2.0 mL) were reacted at 50 °C under an atmosphere of D_2 (1 atm) for 16 h. [a]Determined by ^{1}H NMR spectroscopy as the average of 3 reaction runs.

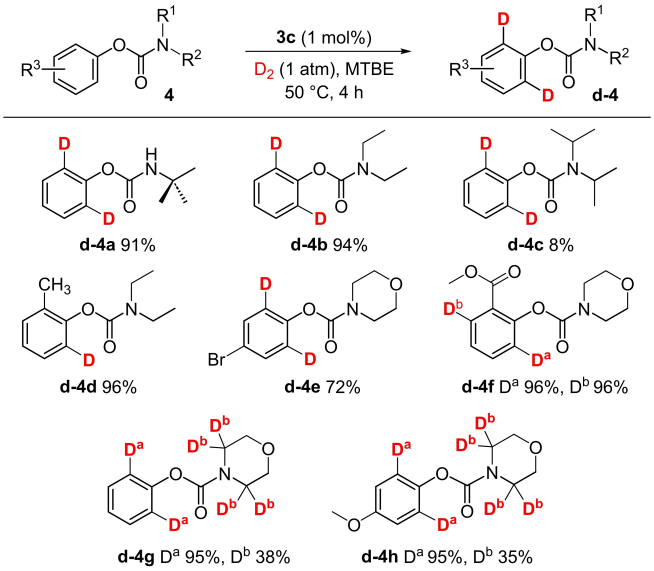


Scheme 3. HIE of *N*-aryl carbamates.

care was taken to ensure the carbamate substrates were of high purity, as any free aniline has the potential to bind strongly to the catalyst and inhibit turnover. In addition to the parent aniline derivative **2b**, *para*-substituted alkyl, halide, and ether functionalities (**2a**, **2c–h**) were well tolerated, with good to excellent levels of deuterium incorporation generally being observed. With substrate **2g**, steric interactions between the ligand set and the large *p*-Br substituent may slightly disfavour the bound complex, resulting in the reduced levels of labelling observed. In the case of **2h**, the strongly electron-withdrawing CF_3 group may reduce the effectiveness of substrate binding. Substitution *ortho* to the directing group had no detrimental effect, with excellent levels of incorporation observed at the remaining *ortho*-position in substrates **2i–k**. With 3,5-dimethyl-substituted substrate **2l**, bearing sterically hindered *ortho*-activation sites, good levels of incorporation were maintained, evidencing the high tolerance of catalyst **3c** to sterically congested labelling environments. The carbamate derivative of 3-methoxyaniline, **2m**, was also labelled to appreciably high levels in the two distinct *ortho*-positions. Interestingly, *m*-fluoroaniline derivative **2n** also labelled to very good

levels in both distinct *ortho* sites. However, in contrast, labelling under the same conditions was significantly lower with *m*-chloro derivative **2o**, perhaps again due to steric interactions in the substrate-bound complex. Notably, the labelled Boc carbamates can also be deprotected to give the corresponding deuterated anilines with no loss of isotopic integrity.[8]

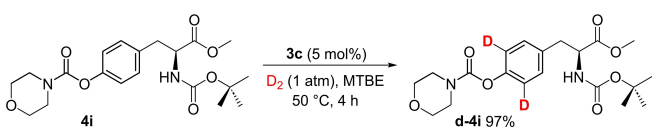
This success in the HIE of *N*-aryl carbamates led us to speculate that the emerging iridium catalyst system would also be suitable for the C–H activation of the corresponding *O*-aryl analogues. A range of *O*-aryl carbamates **4** were thus evaluated in novel HIE processes with catalyst **3c**, with the chosen substrates also possessing a series of differing *N*-substituents. As detailed in Scheme 4, good to excellent levels of incorporation were, again, observed for *O*-aryl carbamates, with the exception of *N*,*N*-di-*iso*-propyl-containing substrate **4c**, where, presumably, the severe steric hindrance imposed by the *iso*-propyl substituents results in low levels of labelling. Notably, in the case of substrate **4f**, a carbamate derived from methyl salicylate, the ester[5h] is as competent a directing group as the carbamate, with excellent levels of deuterium incorporation observed at both potential labelling sites. In the case of morpholino-carbamates **4g-h**, both C(sp^2)–H and C(sp^3)–H bonds were activated, resulting in deuterium incorporation α to nitrogen within the morpholine ring in addition to the expected aryl labelling. Whilst not the focus of the present work,[14] the activation of the less reactive alkyl C–H bonds[15] demonstrates potential application of these novel iridium catalysts to the HIE of a broader range of organic substrates. In the substrates where C(sp^3)–H HIE is not observed, we attribute this to entropic disfavouring of the corresponding Csp^3–H agostic or subsequent cyclometallated species (for substrates **4b** and **4d**), or to inductively-withdrawing substituents facilitating the formation of a more favourable C(sp^2)–H agostic or cyclometallated intermediate (for substrates **4e** and **4f**).



Scheme 4. HIE of *O*-aryl carbamates.

To further investigate the applicability of our protocol to more elaborated scaffolds of biological relevance, *N*-Boc-L-tyrosine methyl ester was converted to the morpholino *O*-aryl carbamate **4i** and subjected to HIE with 5 mol% of catalyst **3c** (Scheme 5). Under these conditions, an excellent 97% deuterium incorporation was achieved.

With an effective carbamate directed HIE process established, we next investigated the mechanism of labelling with catalyst **3c**. In this regard, although extensive mechanistic data is available for HIE processes catalyzed by heteroleptic iridium complexes bearing monodentate ligands,[5d,f,h,k,6b–c] no such studies have been communicated for these emerging systems bearing chelating NHC–P ligands. Using our previous work on the mechanism of these iridium-catalyzed HIE processes as a basis,[5d,h,k,6b–c] DFT studies were initiated in order to probe the reaction pathway involving chelated catalyst **3c**. The potential energy surface shown within Figure 2 begins with complex **5**, which is anticipated to form upon the displacement of two solvent molecules by the *tert*-butyl *p*-tolylcarbamate substrate **2a**. The resulting bound aryl carbamate substrate can then undergo C–H activation *via* a σ-bond metathesis process to deliver the 6-mmi complex **7**. With a ΔΔG of 20.9 kcal mol^{-1}, the C–H activation barrier is notably low for a sterically-encumbered directing group leading to a 6-mmi. For example, in the 6-mmi C–H activation of acetanilide using the PF_6 counter-ion analogue of monodentate catalyst **1a**,[5d] a $\Delta H^{\ddagger}$ (not expected to be significantly different from $\Delta G^{\ddagger}$ in the C–H activation process) of 23.04 kcal mol^{-1} was calculated. From complex **7**, to position a deuteride in the requisite arrangement for C–D bond formation, it would be expected that intermediate **7** would undergo hydride fluxionality, similar to that proposed within the original monodentate catalyst HIE mechanistic pathway.[5d] However, despite multiple attempts, this H–D fluxionality step could not be established computationally. Instead, it is proposed that the H–D molecule formed upon C–H activation may dissociate, in a barrierless process, to deliver complex **8**, where the vacant coordination site resulting from H–D extrusion is stabilized through the formation of an agostic interaction with an *ortho*-methyl C–H bond from the mesityl unit within the NHC moiety. Subsequent association of a D_2 molecule then delivers complex **9**, which is now primed to facilitate C–D bond formation within the aryl carbamate substrate *via* another σ-bond metathesis process. This then delivers complex **11**, in which the monodeuterated aryl carbamate substrate is bound to the catalyst. The all Ir(III) catalytic cycle can then turn over *via* displacement of the labelled product by another molecule of starting material or by solvent, or by rotation of the aryl C–N



Scheme 5. HIE of a tyrosine derivative.

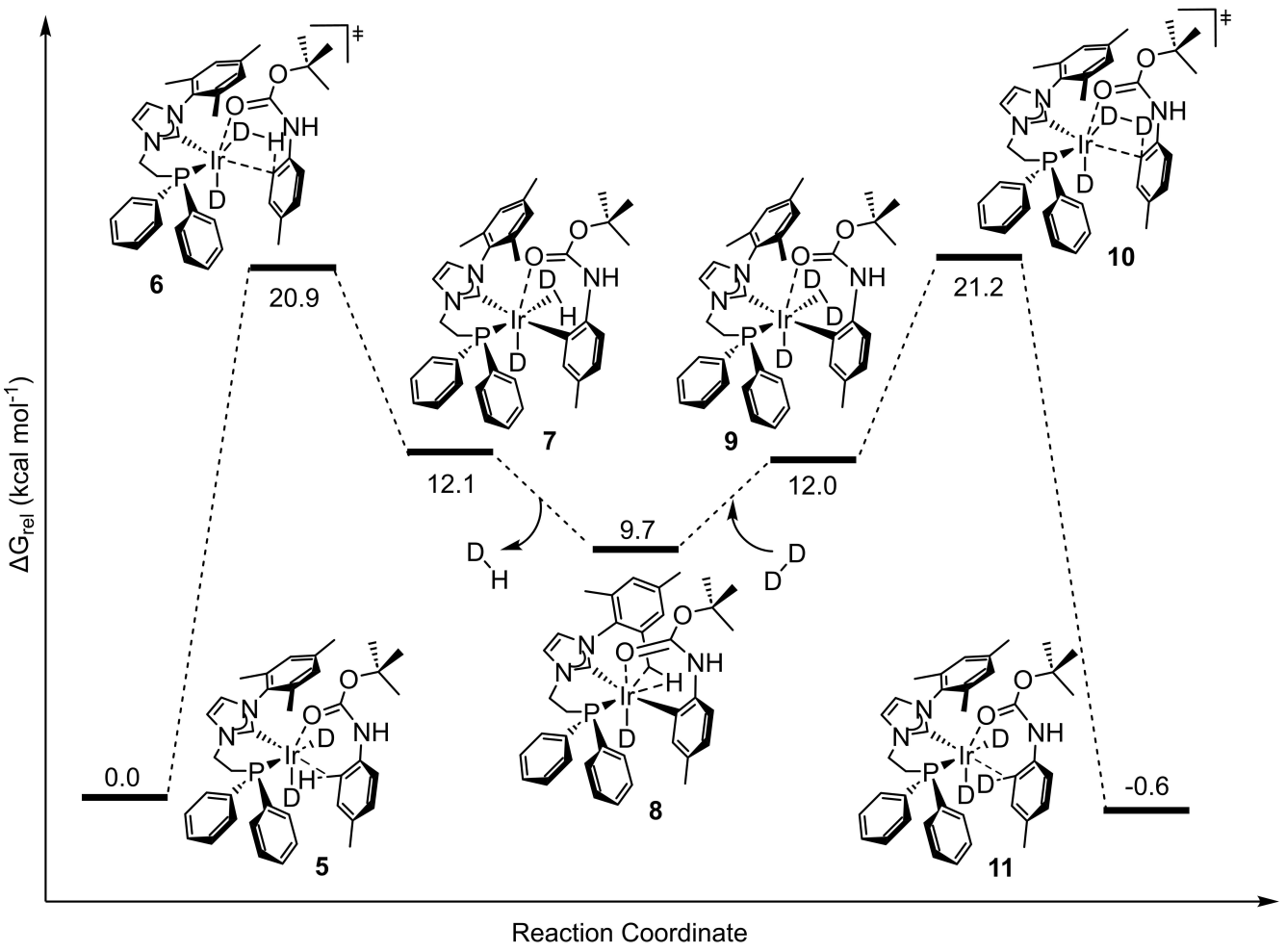
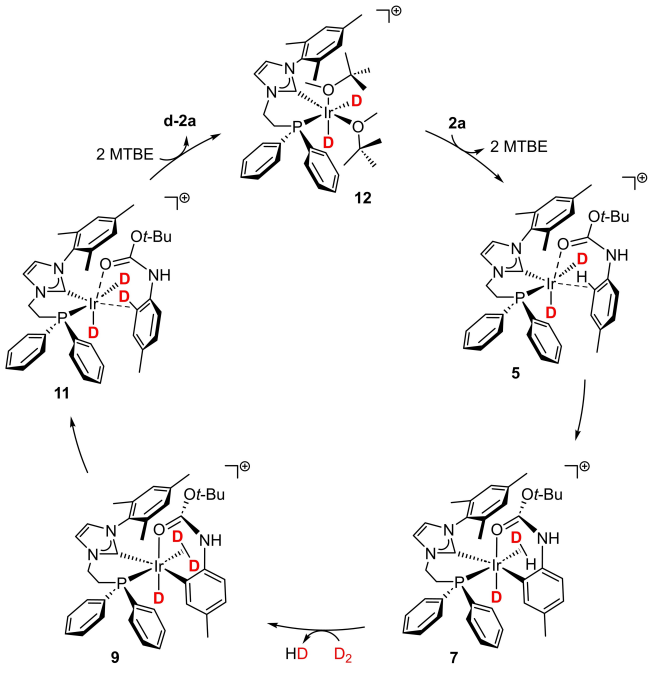


Figure 2. Potential energy surface for the carbamate-directed HIE using catalyst **3 c**. All structures depicted relate to the cationic Ir(III) species. Calculations were carried out using M06 L/6-31G(d) and the Stuttgart RSC ECP for iridium.

bond, resulting in direct incorporation of a second deuterium atom into the substrate.

Based on this potential energy surface, the catalytic cycle is outlined in Scheme 6. Upon exposure of pre-catalyst **3 c** to D_2, and subsequent reduction of coordinated cyclooctadiene, the catalytically active iridium complex **12** is formed. Displacement of solvent by substrate then ensues to afford **5**, which engages in C–H activation through a σ-bond metathesis process[16] leading to the 6-mmi complex **7**. Ligand exchange with deuterium then delivers complex **9**, which undergoes C–D bond formation leading to **11**. Finally, displacement of the deuterated product by the solvent reforms complex **5** and restarts the catalytic cycle. Notably, and in contrast to that proposed for the monodentate Ir system,[5d] in the C–H activation step, the H being cleaved forms part of the neutral H–D ligand (i.e. a σ-complex-assisted metathesis process),[16] as opposed to being bound to the iridium as a hydride; additionally, the C–D bond formation takes place with D from the, subsequently installed, D_2 ligand, as opposed to a deuteride bound to iridium. These differences are a result of the change in relative configurations of the bound substrate and deuteride



Scheme 6. Proposed catalytic cycle.

ligands, enforced by the NHC and P ligands being *cis* in the chelated system, as opposed to *trans* with the monodentate ligand species.

Finally, we further investigated the catalytic cycle experimentally, by measuring the kinetic isotope effect (KIE) via the rate of HIE of **2a** to **d-2a** alongside the reverse process (Scheme 7). Interestingly, a KIE of 1.49 was obtained, indicating that the C–H activation event does not dominate the turnover limiting step of this process.[4b–c] This observation is in contrast to previously reported Ir-catalyzed processes for HIE of C(sp^2)–H bonds, where typical KIE values of 3.2–3.7 were found.[5d,f,6b] We propose here that the steric hindrance of the *O-tert*-butyl carbamate directing group inhibits the usually rapid co-ordination/turnover of the substrate, such that this process becomes competitive with C–H activation as the turnover-limiting step of the overall reaction, leading to a considerably reduced KIE for the labelling in this case.

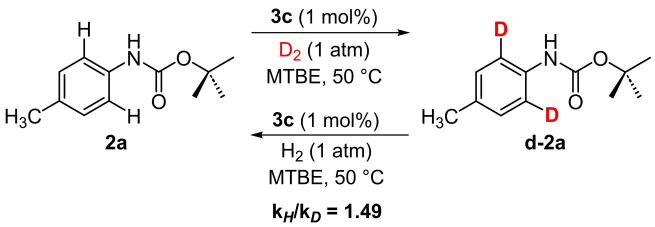
Conclusions

In conclusion, we have developed a novel catalytic process with a range of iridium(I) complexes **3a–c** bearing bidentate *N*-heterocyclic carbene/phosphine ligands, and have demonstrated the appreciable activity of these species in the HIE of *N*- and *O*-aryl carbamates. The applicability to biologically relevant systems was also demonstrated by the deuterium labelling of an analogue of L-tyrosine. Combined theoretical and experimental mechanistic studies have also revealed an interesting dynamic behaviour relating to the C–H activation step, which was found to proceed with a relatively low activation barrier, and a subtle kinetic interplay between substrate co-ordination and C–H activation as aligned specifically with this chelated catalyst/sterically-hindered substrate combination. Expansion of the applicability of these novel catalyst systems to a broader variety of weakly coordinating directing functionalities is currently under way in our laboratories.

Experimental Section

Full experimental details and compound characterization data are provided in the Supporting Information.

General Procedure for hydrogen isotope exchange (HIE) of carbamates in a flask. To a flame-dried 100 mL round-bottom flask fitted with a glass stopper, two side stopcocks, and a stirrer bar, were added the iridium catalyst and the desired carbamate under a constant stream or argon. The atmosphere was then evacuated and carefully replenished with argon. Methyl *tert*-butyl ether (MTBE) was then added, the resulting mixture was thoroughly stirred at room temperature and subsequently immersed in a dry ice-acetone bath at −78 °C under an atmosphere of argon. A balloon of D_2 was connected to one of the side stopcocks, then the atmosphere was evacuated and replenished with D_2, and this process was repeated a further two times at −78 °C. After the third gas exchange cycle, both stopcocks were firmly closed, the flask was immediately transferred to an oil bath heated to 50 °C, and the glass stopper was restrained to prevent leakage of gases and solvent due to the increase in pressure inside the vessel. After the allocated reaction time, one of the stopcocks was opened to the atmosphere, the solution was filtered through a small pipette containing a plug of silica gel, the filtrate was collected, and the solids were washed with Et_2O (2×2.5 mL). The combined filtrates were evaporated under reduced pressure to afford the deuterated carbamate. Deuterium incorporation was determined by ^{1}H NMR spectroscopy of the products thus obtained. The calibration of integrals was performed against a peak corresponding to a position in which deuterium incorporation was not expected, and the percent deuterium incorporation was calculated according to the following expression: %Deuterium Incorporation = 100 − [(residual integral/number of labelling sites)×100].



Scheme 7. Kinetic isotope effect study in the labeling of **2a** with catalyst **3c**.

Supporting Information Summary

The authors have cited additional references within the Supporting Information.[17–52]

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: C–H functionalization · Hydrogen isotope exchange · Iridium · *N*-Heterocyclic carbene

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