Article

Iridium-Catalysed ortho-Directed Deuterium Labelling of Aromatic Esters—An Experimental and Theoretical Study on Directing Group Chemoselectivity

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Abstract: Herein we report a combined experimental and theoretical study on the deuterium labelling of benzoate ester derivatives, utilizing our developed iridium N-heterocyclic carbene/phosphine catalysts. A range of benzoate esters were screened, including derivatives with electron-donating and -withdrawing groups in the para-position. The substrate scope, in terms of the alkoxy group, was studied and the nature of the catalyst counter-ion was shown to have a profound effect on the efficiency of isotope exchange. Finally, the observed chemoselectivity was rationalized by rate studies and theoretical calculations, and this insight was applied to the selective labelling of benzoate esters bearing a second directing group.

Keywords: hydrogen isotope exchange; deuterium; iridium; esters; C–H activation; DFT
1. Introduction

The ability to incorporate an isotopic label into a biologically-active molecule is of profound importance in the drug discovery process. Such a radioactive “tag” or “label” can be used to provide vital information on a compound’s absorption, distribution, metabolism, excretion, and toxicological (ADMET) properties. As a result of these uses, isotopic labelling is the gold standard method by which early stage drug discovery processes can be optimised.

Research into deuterium ($^2$H or D) and tritium ($^3$H or T) labelling is more substantial than for other isotopes, and has been developed on a number of fronts over the past 60 years [1–10]. Further to this, key developments in synthetic strategies and analytical techniques for tritium labelling over the past three decades now makes this the preferred technique for many ADMET studies [5]. In one particularly active branch of such labelling research, hydrogen isotope exchange (HIE) is employed to deliver either deuterium or radioactive tritium to pharmaceutical drug candidates in one synthetic step. As well as circumventing the requirement for isotopically-enriched starting materials in preparing tritiated drug candidates [1,5], HIE can also provide analogous deuterated compounds for use as internal standards for mass spectrometry [11,12], for kinetic isotope studies [13,14], and for the alteration of reaction pathways in total synthesis [15].

Over recent years, research in our laboratory has focused on the development of iridium(I) $N$-heterocyclic carbene (NHC)-ligated precatalysts of the type 1, and their application in HIE via ortho-directed C–H activation protocols ($2 \rightarrow 4$ via $3$, Scheme 1) [6,16–22]. Despite the growing list of compatible directing groups, we [23] and others [24–27] have found these developed C–H activation methods less applicable in the labelling of aromatic esters under ambient conditions. Herein, we report the extension of our methodology to encompass the labelling of weakly coordinating benzoate ester derivatives under mild conditions.

Scheme 1. General method for Ir-catalysed ortho-HIE via a C–H activation pathway.

2. Results and Discussion

2.1. Catalyst Screening and Comparisons with Crabtree’s Catalyst

Until recently, Crabtree’s catalyst, [(COD)Ir(PCy3)(py)]PF$_6$, 5, was the most widely applied iridium-based HIE catalyst for labelling applications within an industrial setting [24,28]. As such, any
studies which evaluate our developed catalysts in the labelling of aromatic esters should also compare them against the ability of 5 to mediate the same catalytic labelling reactions under identical conditions [19,29]. To this end, and to initiate this research programme, the labelling of a series of para-substituted ethyl benzoate derivatives 6 was examined, using our standard labelling protocol (5 mol % [Ir], 1 atm D2, 1 h) with Crabtree’s catalyst 5 (Scheme 2, blue bars) and our developed catalyst systems 1b and 1a (Scheme 2, red and green bars, respectively). With the exception of the p-chloro and p-methoxy esters (6d and 6e), Crabtree’s catalyst 5, proved relatively ineffective in the deuteration of these ester substrates, with incorporations as low as 10% being observed with the electron-withdrawing p-CF3 ester 6c. On assessing the larger and more electron-rich variant of our catalyst series, 1b, a significant improvement in labelling esters 6c (X = CF3) and 6d (X = Cl) was observed, whereas the other esters 6a, 6b and 6e were labelled less efficiently relative to Crabtree’s catalyst. Only on employing our more Lewis acidic catalyst, 1a, did we observe the most efficient and encouraging improvement in ester labelling across all examples tested, with the exception of the parent ethyl benzoate 6a. We hypothesize that the more flexible Lewis acidity of 1a vs. 5 or 1b partially diminishes the importance of the ester coordination event and negative Hammett σp values,[30] and simultaneously enhances the effect of positive σm in relation to a more facile C–H activation event. For example, compare the order of substrate reactivity for catalyst 5 (OMe > Cl > Me > H > CF3) vs. 1a (OMe–Cl > CF3 > Me > H). In the absence of more detailed reaction monitoring, we acknowledge that the observed results cannot be directly related to the kinetically-derived Hammett values. Nonetheless, the hypothesis remains feasible.

Scheme 2. Comparative labelling of ethyl benzoates 6 using catalysts 5, 1b, and 1a.
2.2. Applicable Substrate Scope with Catalyst 1a

2.2.1. Para-Substituted Methyl Benzoates

Using the most efficient of the three catalysts tested, catalyst 1a, we investigated the possibility of labelling methyl esters under the same conditions employed for the ethyl analogues 6 (Table 1). While methyl esters 8d and 8e were labelled with high levels of deuterium incorporation, the other methyl esters in the series proved more capricious. Specifically, substrates 8a, 8b and 8c were repeated multiple times, with individual deuterium incorporations ranging from 27% to 52% (see Experimental Section for full details).

\textbf{Table 1.} Labelling of methyl benzoates 8 using catalyst 1a.

| Entry | X   | Substrate | %D |
|-------|-----|-----------|----|
| 1     | H   | 8a        | 52 |
| 2     | CH₃ | 8b        | 42 |
| 3     | CF₃ | 8c        | 32 |
| 4     | Cl  | 8d        | 93 |
| 5     | OMe| 8e        | 89 |

\(\text{a \%D incorporation is the average of two runs and was determined by} \, ^1\text{H-NMR spectroscopy.}\)

2.2.2. Scope of O-Alkyl Substitution with Electron-Rich Benzoate Esters

Beyond methyl and ethyl benzoates, we also examined the applicability of larger \(O\)-alkyl ester substituents using our labelling method (Table 2). We pursued this line of enquiry for \(p\)-methoxybenzoate derivatives only, in order to minimise potential substrate coordination issues associated with the aryl substituent. Whilst the \(n\)-propyl, 2,2,2-trifluoroethyl, and tert-butyl benzoate derivatives 10a, 10b and 10c unfortunately proved to be less applicable, \(iso\)-propyl and benzyl esters 10d and 10e could be labelled with appreciable levels of deuterium incorporation.

\textbf{Table 2.} Labelling of electron-rich benzoate esters using catalyst 1a.

| Entry | R    | Substrate | %D |
|-------|------|-----------|----|
| 1     | \(n\)-Pr | 10a       | 28 |
| 2     | CH₂CF₃ | 10b       | 8  |
| 3     | \(t\)-Bu | 10c       | 10 |
| 4     | \(i\)-Pr | 10d       | 73 |
| 5     | Bn   | 10e       | 62 |

\(\text{a \%D incorporation is the average of two runs and was determined by} \, ^1\text{H-NMR spectroscopy.}\)
2.3. Reaction Optimisation for Efficient Labelling of Challenging Benzoate Ester Substrates

2.3.1. Temperature Effects

Due to the application of this hydrogen isotope exchange method in related tritiation chemistries [6], significant effort is usually made to maintain ambient reaction conditions during the optimization of ortho-deuteration processes. Having stated this, the use of slightly raised reaction temperatures need not be completely discounted from such investigations. We therefore revisited the labelling of the most challenging methyl and ethyl benzoate derivatives, using a moderately increased reaction temperature of 40 °C (Scheme 3). Pleasingly, dramatic improvements in deuterium incorporation were observed across all substrates examined, 6a–c and 8a–c, whilst the short reaction times were maintained (see Experimental Section 3.4).

Scheme 3. Temperature effects on deuterium labelling of previously problematic benzoate esters.

2.3.2. Catalyst Counterion Effects

We recently reported the improved activity and broad-spectrum solubility resulting from replacement of the PF$_6$ counterion in catalyst 1a with tetrakis[bis-3,5-trifluoromethylphenyl]borate, BArF, to give complex 1d [18]. Applying improved catalyst 1d to the labelling of larger ester derivatives 10a–e under otherwise identical conditions, significant and more usable levels of deuterium incorporation were observed across all examples (Scheme 4). Importantly, this counter-ion switch demonstrates an alternative means by which ester labelling efficiency can be improved, should ambient temperature conditions be required.
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2.4. Exploring Chemoselectivity Issues in Ester Labelling

2.4.1. Experimental Observations

From the outset of our studies, it was clear that the main challenge in labelling aromatic esters would be the weak coordinating ability of this functional group. To understand this issue in more detail, we conducted a series of intramolecular competition studies where multiple potential directing groups can compete for coordination (and subsequent C–H activation) at the iridium centre. To this end, we first investigated the labelling of ethyl $p$-nitrobenzoate, 12, under the optimised ambient reaction conditions. Interestingly, we observed an approximate 1.4:1 selectivity for labelling via the nitro rather than the ester directing group (Scheme 5). This chemoselectivity was eroded entirely on changing the ester to a tertiary amide in 13 (1:1 nitro:amides), and reversed by replacing the ester with a ketone in 14 (3:1 in favour of the ketone).
Focusing on the extreme substrate cases, with substrates 12 and 14, 1 mol % of catalyst 1a was employed to allow reaction rates and labelling selectivities to be monitored over time (Scheme 6). In the case of substrate 12, and the labelling of the positions ortho- to the ester vs. the nitro, the difference in reaction rate, and thus product selectivity, remains largely constant throughout the course of the reaction. Conversely, with substrate 14, the relative rate of labelling ortho- to ketone vs. nitro is higher at lower conversions, and decreases rapidly over time.

Scheme 6. Rate and product selectivity studies for 12 (top) and 14 (bottom).
2.4.2. Theoretical Analysis

In previous C–H activation studies, we rationalised observed directing group chemoselectivity using density functional theory (DFT) calculations (see Supplementary Materials for details) to model the relative energies of the binding conformers and subsequent C–H activation pathways [20]. We have now extended this approach to the analysis of the labelling reactions of 12 and 14 (Scheme 7). In agreement with previous findings, we qualitatively predicted that the most stable binding isomer should also be the most reactive. If Curtin-Hammett kinetics are assumed [31], the calculated ΔΔG‡ (and thus product selectivity) from equilibrium and activation parameters is predicted to be higher for the ketone in 14 vs. the nitro group in 12 (5.5 vs. 1.4 kcal/mol, respectively). However, the current model does not account for the barrier to interconversion of binding conformations (ketone to nitro, ester to nitro, and vice versa for each case). Considering these points in the context of the experimentally-determined product selectivity vs. time (vide supra), only substrate 12 (showing little variation in selectivity over time) appears to show rapid equilibrium between the binding isomers. Conversely, the labelling of 14 via the ketone may be interpreted as being faster than the rate of interconversion between binding conformers as well as possessing a lower barrier to C–H activation.

Scheme 7. Density functional theory (DFT) analyses on the C–H activation step in labelling substrates 12 and 14 with 1a.
2.4.3. Practical Exploitation of Directing Group Chemoselectivity

The fundamental analysis of intramolecular directing group chemoselectivity served to show that observed labelling patterns are, in part, dependent on the relative catalyst binding affinities of each directing group. With this new understanding in hand, we questioned if it would be possible to control the direction of labelling using the inherent reactivity of a given multi-functional substrate. Pleasingly, using substrate 14 as a proof-of-concept substrate, minimal optimisation was required to show that judicious choice of catalyst loading and reaction temperature allowed control of the labelling pattern (Scheme 8). Specifically, labelling ortho- to the ketone group could be achieved with a 5 mol % catalyst loading of 1a at room temperature to give 18, whereas the globally-labelled product 19 could be obtained by employing 5 mol % of 1a at 40 ºC. In turn, the previously elusive nitro-selective product, 20, was accessed by a retro-labelling strategy (employing H2 in place of D2) conducted on the globally-labelled product 19.

Scheme 8. Condition-dependent flexible access to alternatively deuterated forms of 18.

3. Experimental Section

3.1. General Considerations

All reagents were obtained from commercial suppliers (Sigma-Aldrich, Gillingham, UK; Alfa Aesar, Heysham, UK; or Strem, Newton, UK) and used without further purification, unless otherwise stated. Dichloromethane was obtained from a PureSolv SPS-400-5 Solvent Purification System (Innovative Technology, Inc., Galway, Ireland), and deoxygenated by bubbling argon through for a minimum of ten minutes. Thin layer chromatography was carried out using Camlab silica plates coated with fluorescent indicator UV254 (Sigma-Aldrich), and were visualized using a Mineralight UVGL-25 lamp (Fisher Scientific UK Ltd., Loughborough, UK) or developed using vanillin solution. Catalysts 1a [20], 1b [16], and 1d [18] were prepared according to literature procedures. Esters 6c [32], 10a [33], 10b [34], 10c [35], 10d [36], 10e [37], and 13 [38] were prepared according to the corresponding literature procedures. 1H-NMR spectra were recorded on a Bruker DPX 400 spectrometer (Bruker, Coventry, UK) at 400 MHz. Chemical shifts are reported in ppm and coupling constants are reported in Hz. All coupling constants are 3JH-H unless otherwise stated.
3.2. General Procedures

3.2.1. Deuteration of Substrates Using Iridium(I) Complexes 1a, 1b, 1d and 5

A three-necked round bottom flask was fitted with two stopcock side arms and a rubber septum, and then flame-dried. To this flask was added the iridium(I) complex and substrate. The solvent, DCM (2.5 mL, unless stated otherwise), was added, rinsing the inner walls of the flask, and the rubber septum was replaced with a greased glass stopper. The solution was placed under an atmosphere of Ar and stirred whilst being cooled to −78 °C in a dry ice/acetone bath. The flask was evacuated then refilled with argon and this process repeated. Upon a third evacuation, an atmosphere of deuterium gas was introduced to the flask. After sealing the flask, the cold bath was removed and the flask heated in an oil bath to the desired temperature. The reaction mixture was stirred for the allotted reaction time before removing the deuterium atmosphere and replacing with air. The resulting solution was washed with DCM and transferred to a single-necked flask before removing the solvent under reduced pressure. The catalyst was triturated from the remaining residue by addition of diethyl ether (3 × 5 mL). The solution was filtered through a short plug of silica before the solvent was removed in vacuo to deliver the crude product for analysis of the deuterium incorporation.

The level of deuterium incorporation in the substrate was determined by 1H-NMR spectroscopy. The integrals were calibrated against a peak corresponding to a position not expected to be labelled. Equation (1) was then used to calculate the extent of labelling:

\[
\% \text{ Deuteration} = 100 - \left( \frac{\text{residual integral}}{\text{number of labelling sites}} \right) \times 100
\]  

(1)

3.2.2. Deuteration of Substrates for Rate Studies

A three-necked round bottom flask fitted with one stopcock side arm and two rubber septa was flame-dried. To this flask was added the iridium(I) complex, and substrate. The solvent, DCM (25 mL), was added, rinsing the inner walls of the flask, and one rubber septum was replaced with a greased glass stopper. The solution was placed under an atmosphere of argon and stirred whilst being cooled to −78 °C in a dry ice/acetone bath. The flask was evacuated then refilled with argon and this process repeated. Upon a third evacuation, an atmosphere of deuterium gas was introduced to the flask via a balloon. The balloon was left in place for the duration of the reaction to ensure a continuous supply of deuterium. The cold bath was removed and the flask heated in an oil bath to the desired temperature. The reaction mixture was then stirred for the allotted reaction time. An aliquot (1 mL) of the reaction mixture was removed at intervals throughout the reaction (10, 20, 30, 40, 50, 60 min, 2 h, and 18 h). Each aliquot was transferred to a vial containing diethyl ether. After removal of solvent in vacuo, the residue was analysed by 1H NMR spectroscopy. The integrals were calibrated against a peak corresponding to a position not expected to be labelled. The extent of labelling was determined using Equation (1).
3.3. Labelling Studies

3.3.1. Deuteration of Ethyl benzoate 6a with Complex 5

![Image of 6a structure]

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 8.05 (d, $J = 7.1$ Hz, 2H, CH$_3$), 7.54 (t, $J = 7.3$ Hz, 1H, CH$_1$), 7.43 (t, $J = 7.9$ Hz, 2H, CH$_2$), 4.38 (q, $J = 7.2$ Hz, 2H, CH$_2$), 1.39 (t, $J = 7.1$ Hz, 3H, CH$_3$). Incorporation expected at $\delta$ 8.05. Determined against integral at $\delta$ 1.39. Following General Procedure A, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation.

Run 1: (a) 6a, 0.032 g, 0.215 mmol; (b) 5, 8.04 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 17%.
Run 2: (a) 6a, 0.032 g, 0.215 mmol; (b) 5, 8.04 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 22%

3.3.2. Deuteration of Ethyl 4-methylbenzoate 6b with Complex 5

![Image of 6b structure]

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.91 (d, $J = 8.0$ Hz, 2H, CH$_3$), 7.21 (d, $J = 7.9$ Hz, 2H, CH$_2$), 4.34 (q, $J = 7.1$ Hz, 2H, CH$_2$), 2.38 (s, 3H, CH$_3$), 1.36 (t, $J = 7.1$ Hz, 3H, CH$_3$). Incorporation expected at $\delta$ 7.91. Determined against integral at $\delta$ 2.38. Following General Procedure A, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation.

Run 1: (a) 6b, 0.035 g, 0.215 mmol; (b) 5, 8.04 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 36%.
Run 2: (a) 6b, 0.035 g, 0.215 mmol; (b) 5, 8.04 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 41%

3.3.3. Deuteration of Ethyl 4-(trifluoromethyl)benzoate 6c with Complex 5

![Image of 6c structure]

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 8.12 (d, $J = 8.3$ Hz, 2H, CH$_2$), 7.67 (d, $J = 8.3$ Hz, 2H, CH$_1$), 4.38 (q, $J = 7.2$ Hz, 2H, CH$_2$), 1.38 (t, $J = 7.1$ Hz, 3H, CH$_3$). Incorporation expected at $\delta$ 8.12. Determined against integral at $\delta$ 1.38. Following General Procedure A, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation.

Run 1: (a) 6c, 0.044 g, 0.215 mmol; (b) 5, 8.04 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 8%
Run 2: (a) 6c, 0.044 g, 0.215 mmol; (b) 5, 8.04 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 11%
3.3.4. Deuteration of Ethyl 4-chlorobenzoate 6d with Complex 5

![Image of Ethyl 4-chlorobenzoate 6d]

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.95 (d, $J = 8.8$ Hz, 2H, CH$_2$), 7.38 (d, $J = 8.8$ Hz, 2H, CH$_1$), 4.34 (q, $J = 7.3$ Hz, 2H, CH$_3$), 1.36 (t, $J = 7.3$ Hz, CH$_3$). Incorporation expected at $\delta$ 7.95. Determined against integral at $\delta$ 1.36. Following General Procedure A, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation.

Run 1: (a) 6d, 0.039 g, 0.215 mmol; (b) 5, 8.04 mg; 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 50%

Run 2: (a) 6d, 0.039 g, 0.215 mmol; (b) 5, 8.04 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 59%

3.3.5. Deuteration of Ethyl 4-methoxybenzoate 6e with Complex 5

![Image of Ethyl 4-methoxybenzoate 6e]

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.98 (d, $J = 9.1$ Hz, 2H, CH$_3$), 6.89 (d, $J = 9.0$ Hz, 2H, CH$_2$), 4.30 (q, $J = 7.0$ Hz, 2H, CH$_3$), 3.83 (s, 3H, CH$_3$), 1.35 (t, 1H, CH$_3$). Incorporation expected at $\delta$ 7.98. Determined against integral at $\delta$ 3.83. Following General Procedure A, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation.

Run 1: (a) 6e, 0.038 g, 0.215 mmol; (b) 5, 8.04 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 89%

Run 2: (a) 6e, 0.038 g, 0.215 mmol; (b) 5, 8.04 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 71%

3.3.6. Deuteration of Esters 6a–e Using Catalysts 1b and 1a

For the results relating to catalysts 1b and 1a in Scheme 2, please refer to the spectroscopic data from Sections 3.3.1–3.3.5 for the analysis of the deuterated esters 6a–e. As catalyst type and amount used are the only variables changed, General Procedure A was followed with the results tabulated in Table 3.

3.3.7. Deuteration of Methyl Benzoate 8a with Complex 1a

![Image of Methyl Benzoate 8a]

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 8.04 (d, $J = 7.0$ Hz, 2H, CH$_3$), 7.56 (t, $J = 7.4$ Hz, 1H, CH$_3$), 7.44 (t, $J = 7.9$ Hz, 2H, CH$_2$), 3.92 (s, 3H, CH$_3$). Incorporation expected at $\delta$ 8.04. Determined against integral at $\delta$ 3.92. Following General Procedure A, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation.
Run 1: (a) 8a, 0.032 g, 0.215 mmol; (b) 1a, 10.1 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 52%
Run 2: (a) 8a, 0.032 g, 0.215 mmol; (b) 1a, 10.1 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 51%

Table 3. Deuteration of Esters 6a–e.

| Entry | Substrate | Catalyst | %D (run 1) | %D (run 2) |
|-------|-----------|----------|------------|------------|
| 1     | 6a        |          | 10         | 10         |
| 2     | 6b        |          | 15         | 23         |
| 3     | 6c        | 1b (10.5 mg) | 62         | 50         |
| 4     | 6d        |          | 85         | 93         |
| 5     | 6e        |          | 65         | 59         |

| Entry | Substrate | Catalyst | %D (run 1) | %D (run 2) |
|-------|-----------|----------|------------|------------|
| 6     | 6a        |          | 6          | 40         |
| 7     | 6b        |          | 53         | 83         |
| 8     | 6c        | 1a (10.1 mg) | 74         | 79         |
| 9     | 6d        |          | 95         | 95         |
| 10    | 6e        |          | 96         | 96         |

3.3.8. Deuteration of Methyl 4-methylbenzoate 8b with Complex 1a

![8b](image)

$^{1}H$-NMR (400 MHz, CDCl3): $\delta$ 7.99 (d, $J = 8.0$ Hz, 2H, CH3), 7.21 (d, $J = 8.0$ Hz, 2H, CH3), 3.89 (s, 3H, CH3), 2.39 (s, 3H, CH3). Incorporation expected at $\delta$ 7.99. Determined against integral at $\delta$ 2.39. Following General Procedure A, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation.

Run 1: (a) 8b, 0.035 g, 0.215 mmol; (b) 1a, 10.1 mg, 0.01 mmol; (c) 1 h, d) 25 °C; and (e) 35%
Run 2: (a) 8b, 0.035 g, 0.215 mmol; (b) 1a, 10.1 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 48%

3.3.9. Deuteration of Methyl 4-(trifluoromethyl)benzoate 8c with Complex 1a

![8c](image)

$^{1}H$-NMR (400 MHz, CDCl3): $\delta$ 8.14 (d, $J = 8.8$ Hz, 2H, CH2), 7.70 (d, $J = 8.8$ Hz, 2H, CH2), 3.94 (s, 3H, CH3). Incorporation expected at $\delta$ 8.14. Determined against integral at $\delta$ 3.94. Following General Procedure A, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation.

Run 1: (a) 8c, 0.044 g, 0.215 mmol; (b) 1a, 10.1 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 27%
Run 2: (a) 8c, 0.044 g, 0.215 mmol; (b) 1a, 10.1 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 36%
3.3.10. Deuteration of Methyl 4-chlorobenzoate \(8d\) with Complex \(1a\)

\[
\begin{align*}
\text{1H-NMR} \ (400 \text{ MHz, CDCl}_3): \ & \delta \ 7.93 \ (d, J = 8.9 \text{ Hz, 2H, CH}_2), \ 7.36 \ (d, J = 8.9 \text{ Hz, 2H, CH}_3), \ 3.90 \ (s, 3\text{H, CH}_3) . \text{ Incorporation expected at } \delta \ 7.93. \text{ Determined against integral at } \delta \ 3.90. \text{ Following } \text{General Procedure A, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation.}
\end{align*}
\]

Run 1: (a) \(8d\), 0.039 g, 0.215 mmol; (b) \(1a\), 10.1 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 91%

Run 2: (a) \(8d\), 0.039 g, 0.215 mmol; (b) \(1a\), 10.1 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 94%

3.3.11. Deuteration of Methyl 4-methoxybenzoate \(8e\) with Complex \(1a\)

\[
\begin{align*}
\text{1H-NMR} \ (400 \text{ MHz, CDCl}_3): \ & \delta \ 7.96 \ (d, J = 9.0 \text{ Hz, 2H, CH}_3), \ 6.89 \ (d, J = 9.0 \text{ Hz, 2H, CH}_2), \ 3.85 \ (s, 3\text{H, CH}_3), \ 3.82 \ (s, 3\text{H, CH}_3) . \text{ Incorporation expected at } \delta \ 7.96. \text{ Determined against integral at } \delta \ 3.82. \text{ Following } \text{General Procedure A, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation.}
\end{align*}
\]

Run 1: (a) \(8e\), 0.038 g, 0.215 mmol; (b) \(1a\), 10.1 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 87%

Run 2: (a) \(8e\), 0.038 g, 0.215 mmol; (b) \(1a\), 10.1 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 90%

3.3.12. Deuteration of \(n\)-Propyl 4-methoxybenzoate \(10a\) with Complex \(1a\)

\[
\begin{align*}
\text{1H-NMR} \ (400 \text{ MHz, CDCl}_3): \ & \delta \ 8.00 \ (d, J = 9.2 \text{ Hz, 2H, CH}_3), \ 6.92 \ (d, J = 9.2 \text{ Hz, 2H, CH}_2), \ 4.25 \ (t, J = 6.8 \text{ Hz, 2H, CH}_4), \ 3.86 \ (s, 3\text{H, CH}_3), \ 1.82–1.73 \ (m, 2\text{H, CH}_2), \ 1.02 \ (t, J = 7.3 \text{ Hz, 3H, CH}_3) . \text{ Incorporation expected at } \delta \ 8.00. \text{ Determined against integral at } \delta \ 3.86. \text{ Following } \text{General Procedure A, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation.}
\end{align*}
\]

Run 1: (a) \(10a\), 0.042 g, 0.215 mmol; (b) \(1a\), 10.9 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 28%

Run 2: (a) \(10a\), 0.038 g, 0.215 mmol; (b) \(1a\), 10.9 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 27%
3.3.13. Deuteration of 2,2,2-Trifluoroethyl 4-methoxybenzoate 10b with Complex 1a

1H-NMR (400 MHz, CDCl3): δ 8.06 (d, J = 9.3 Hz, 2H, CH3), 6.97 (d, J = 9.3 Hz, 2H, CH2), 4.69 (q, J_H-F = 8.5 Hz, 2H, CH2), 3.90 (s, 3H, CH3). Incorporation expected at δ 8.06. Determined against integral at δ 3.90. Following General Procedure A, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation.

Run 1: (a) 10b, 0.050 g, 0.215 mmol; (b) 1a, 10.9 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 9%
Run 2: (a) 10b, 0.050 g, 0.215 mmol; (b) 1a, 10.9 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 7%

3.3.14. Deuteration of t-Butyl 4-methoxybenzoate 10c with Complex 1a

1H-NMR (400 MHz, CDCl3): δ 7.94 (d, J = 8.7 Hz, 2H, CH3), 6.89 (d, J = 8.9 Hz, 2H, CH2), 3.85 (s, 3H, CH3), 1.58 (s, 9H, CH3). Incorporation expected at δ 7.94. Determined against integral at δ 3.85. Following General Procedure A, results are reported as (a) amount of substrate, (b) amount of catalyst, (c) reaction time, (d) reaction temperature, and (e) level of incorporation.

Run 1: (a) 10c, 0.045 g, 0.215 mmol; (b) 1a, 10.9 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 10%
Run 2: (a) 10c, 0.045 g, 0.215 mmol; (b) 1a, 10.9 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 9%

3.3.15. Deuteration of Iso-propyl 4-methoxybenzoate 10d with Complex 1a

1H-NMR (400 MHz, CDCl3): δ 7.97 (d, J = 9.0 Hz, 2H, CH3), 6.89 (d, J = 9.0 Hz, 2H, CH2), 5.20 (septet, J = 6.3 Hz, 1H, CH3), 3.84 (s, 3H, CH3), 1.33 (d, J = 6.5 Hz, 6H, CH3). Incorporation expected at δ 7.97. Determined against integral at δ 3.84. Following General Procedure A, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation.

Run 1: (a) 10d, 0.042 g, 0.215 mmol; (b) 1a, 10.9 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 79%
Run 2: (a) 10d, 0.042 g, 0.215 mmol; (b) 1a, 10.9 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 66%
3.3.16. Deuteration of Benzyl 4-methoxybenzoate \(10e\) with Complex \(1a\)

![Chemical Structure](image)

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.04 (d, \(J = 9.0\) Hz, 2H, CH\(_3\)), 7.45–7.43 (m, 2H, CH\(_3\)), 7.40–7.37 (m, 2H, CH\(_6\)), 7.35–7.32 (m, 1H, CH\(_7\)), 6.92 (d, \(J = 9.0\) Hz, 2H, CH\(_2\)), 5.34 (s, 2H, CH\(_4\)), 3.90 (s, 3H, CH\(_3\)). Incorporation expected at \(\delta\) 8.04. Determined against integral at \(\delta\) 3.90. Following General Procedure \(A\), results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation.

**Run 1:** (a) \(10e\), 0.052 g, 0.215 mmol; (b) \(1a\), 10.9 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 73%

**Run 2:** (a) \(10e\), 0.052 g, 0.215 mmol; (b) \(1a\), 10.9 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 51%

3.4. Temperature Effects

For the results relating to Scheme 3, readers are directed to the spectroscopic data in the relevant parts of Section 3.3 for the analysis of the corresponding deuterated esters \(6a–c\) and \(8a–c\). As catalyst type and amount used are the only variables changed, the remaining results are tabulated below. In all cases, 0.215 mmol of substrate was employed with 10.1 mg of catalyst \(1a\) (0.01 mmol, 5 mol %) and the reactions run at 40 °C, otherwise following General Procedure \(A\), and the results shown below in Table 4.

**Table 4.** Deuteration of Esters \(6a–c\) and \(8a–c\) at 40 °C.

| Entry | Substrate | %D (run 1) | %D (run 2) |
|-------|-----------|------------|------------|
| 1     | \(6a\)    | 85         | 86         |
| 2     | \(6b\)    | 89         | 91         |
| 3     | \(6c\)    | 95         | 96         |
| 4     | \(8a\)    | 75         | 76         |
| 5     | \(8b\)    | 96         | 95         |
| 6     | \(8c\)    | 92         | 93         |

3.5. Catalyst Counterion Effects

3.5.1. Deuteration of \(n\)-Propyl 4-methoxybenzoate \(10a\) with Complex \(1d\)

Following General Procedure \(A\), results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation.

(a) \(10a\), 0.042 g, 0.215 mmol; (b) \(1d\), 18.6 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 89%

3.5.2. Deuteration of 2,2,2-Trifluoroethyl 4-methoxybenzoate \(10b\) with Complex \(1d\)

Following General Procedure \(A\), results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation.
3.5.3. Deuteration of t-Butyl 4-methoxybenzoate 10c with Complex 1d

Following General Procedure A, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation.
(a) 10c, 0.045 g, 0.215 mmol; (b) 1d, 18.6 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 41%

3.5.4. Deuteration of iso-Propyl 4-methoxybenzoate 10d with Complex 1d

Following General Procedure A, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation.
(a) 10d, 0.042 g 0.215 mmol; (b) 1d, 18.6 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 94%

3.5.5. Deuteration of Benzyl 4-methoxybenzoate 10e with Complex 1d

Following General Procedure A, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation.
(a) 10e, 0.052 g, 0.215 mmol; (b) 1d, 18.6 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 89%

3.6. Chemoselectivity Studies

3.6.1. Deuteration of Ethyl 4-nitrobenzoate 12 with Complex 1a

1H-NMR (400 MHz, CDCl3): δ 8.27 (d, J = 9.0 Hz, 2H, CH1), 8.19 (d, J = 8.3 Hz, 2H, CH2), 4.42 (q, J = 7.5 Hz, 2H, CH23), 1.41 (t, J = 7.5 Hz, 3H, CH34). Incorporation expected at δ 8.27 and 8.19. Determined against integral at δ 1.41. Following General Procedure A, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation at position 1 and position 2.
Run 1: (a) 12, 0.042 g, 0.215 mmol; (b) 1a, 10.1 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 1: 72%, 2: 49%
Run 2: (a) 12, 0.042 g, 0.215 mmol; (b) 1a, 10.1 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 1: 72%, 2: 52%

3.6.2. Deuteration of N,N-Diethyl 4-nitrobenzamide 13 with Complex 1a

1H-NMR (400 MHz, CDCl3): δ 8.28 (d, J = 8.9 Hz, 2H, CH1), 7.57 (d, J = 8.9 Hz, 2H, CH2), 3.17–3.53 (m, 4H, CH23), 1.25 (br s, 6H, CH34). Incorporation expected at δ 8.28 and 7.57. Determined
against integral at $\delta$ 1.25. Following *General Procedure A*, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation at position 1 and position 2.

*Run 1:* (a) 13, 0.047 g, 0.215 mmol; (b) 1a, 10.1 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 1: 89%, 2: 93%.

*Run 2:* (a) 13, 0.047 g, 0.215 mmol; (b) 1a, 10.1 mg, 0.01 mmol; (c) 1 h, d) 25 °C, and (e) 1: 94%, 2: 93%.

3.6.3. Deuteration of 4-Nitroacetophenone 14 with Complex 1a

\[
\begin{array}{c}
\text{O}_2\text{N} \\
1 \quad 2 \quad 3
\end{array}
\]

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 8.32 (d, $J = 8.9$ Hz, 2H, CH$_1$), 8.11 (d, $J = 8.9$ Hz, 2H, CH$_2$), 2.69 (s, 1H, CH$_3$). Incorporation expected at $\delta$ 8.32 and 8.11. Determined against integral at $\delta$ 2.69. Following *General Procedure A*, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation at position 1 and position 2.

*Run 1:* (a) 14, 0.0467 g, 0.215 mmol; (b) 1a, 10.1 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 1: 28%, 2: 97%

*Run 2:* (a) 14, 0.0467 g, 0.215 mmol; (b) 1a, 10.1 mg, 0.01 mmol; (c) 1 h; (d) 25 °C; and (e) 1: 33%, 2: 85%

3.7. Rate Studies

3.7.1. Deuteration of Ethyl 4-nitrobenzoate 12 with Complex 1a

\[
\begin{array}{c}
\text{O}_2\text{N} \\
1 \quad 2 \quad 3 \quad 4
\end{array}
\]

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 8.27 (d, $J = 9.0$ Hz, 2H, CH$_1$), 8.19 (d, $J = 8.3$ Hz, 2H, CH$_2$). 4.42 (q, $J = 7.5$ Hz, 2H, CH$_2$), 1.41 (t, $J = 7.5$ Hz, 3H, CH$_3$). Incorporation expected at 1: $\delta$ 8.27 and 2: $\delta$ 8.19. Determined against integral at $\delta$ 1.41. Following *General Procedure B*, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation at position 1 and 2 at each time interval.

**Labelling at Position 1:** (a) 12, 0.399 g, 2.15 mmol; (b) 1a, 2.17 mg, 0.0215 mmol; (c) 18 h; (d) 25 °C; and (e) 21% (10 min), 37% (20 min), 47% (30 min), 56% (40 min), 61% (50 min), 64% (1 h), 73% (2 h), and 76% (18 h).

**Labelling at Position 2:** (a) 12, 0.399 g, 2.15 mmol; (b) 1a, 2.17 mg, 0.0215 mmol; (c) 18 h; (d) 25 °C; and (e) 2: 14% (10 min), 24% (20 min), 33% (30 min), 37% (40 min), 41% (50 min), 43% (1 h), 52% (2 h), and 56% (18 h).
3.7.2. Deuteration of 4-Nitroacetophenone 14 with Complex 1a

\[ \text{1H-NMR (400 MHz, CDCl}_3\text{): } \delta 8.32 (d, J = 8.9 \text{ Hz, } 2\text{H, CH}_1), 8.11 (d, J = 8.9 \text{ Hz, } 2\text{H, CH}_2), 2.69 \text{ (s, } 1\text{H, CH}_3\text{). Incorporation expected at } \delta 8.32 \text{ and } 8.11. \text{ Determined against integral at } \delta 2.69. \]

Following General Procedure B, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation at position 1 and 2 at each time interval.

**Labelling at Position 1:** (a) 14, 0.355 g, 2.15 mmol; (b) 1a, 2.12 mg, 0.021 mmol; (c) 18 h; (d) 25 °C; and (e) 8% (10 min), 13% (20 min), 19% (30 min), 26% (40 min), 29% (50 min), 33% (1 h), 65% (2 h), 69% (18 h).

**Labelling at Position 2:** (a) 14, 0.0467 g, 2.15 mmol; (b) 1a, 2.12 mg, 0.01 mmol; (c) 18 h; (d) 25 °C; and (e) 54% (10 min), 75% (20 min), 82% (30 min), 84% (40 min), 85% (50 min), 85% (1 h), 91% (2 h), 95% (18 h).

3.8. Practical Exploitation of Directing Group Chemoselectivity

3.8.1. Deuteration of 4-Nitroacetophenone 14 with Complex 1a

\[ \text{1H-NMR (400 MHz, CDCl}_3\text{): } \delta 8.32 (d, J = 8.9 \text{ Hz, } 2\text{H, CH}_1), 8.11 (d, J = 8.9 \text{ Hz, } 2\text{H, CH}_2), 2.69 \text{ (s, } 1\text{H, CH}_3\text{). Incorporation expected at } \delta 8.32 \text{ and } 8.11. \text{ Determined against integral at } \delta 2.69. \text{ See the details within Section 3.6.3.} \]

3.8.2. Deuteration of 4-Nitroacetophenone 14 with Complex 1a

Following General Procedure A, results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time, (d) reaction temperature, and (e) level of incorporation at position 1 and position 2.

(a) 14, 0.035 g, 0.215 mmol; (b) 1a, 10.1 mg, 0.01 mmol; (c) 1 h; (d) 40 °C; and (e) 1: 97%, 2: 97%

3.8.3. Hydrogenation of 4-Nitroacetophenone-d4 19 with Complex 1a

Following General Procedure A (deuterium gas was replaced with hydrogen gas), results are reported as (a) amount of substrate; (b) amount of catalyst; (c) reaction time; (d) reaction temperature; and (e) level of incorporation of deuterium at position 1 and position 2.

(a) 19, 0.0363 g, 0.215 mmol; (b) 1a, 2.1 mg, 0.0021 mmol; (c) 1 h; (d) 25 °C; and (e) 1: 90%, 2: 12%.
4. Computational Details

DFT [39] was employed to calculate the gas-phase electronic structures and energies for all species involved in H/D exchange reactions. All structures have been optimised with the hybrid meta-GGA exchange correlation functional M06 [40]. The M06 density functional was used in conjunction with the 6-31G(d) basis set for main group non-metal atoms and the Stuttgart RSC [41] effective core potential along with the associated basis set for Ir. The participating transition states (TS) are located at the same level of theory. Harmonic vibrational frequencies are calculated at the same level of theory to characterize respective minima (reactants, intermediates, and products with no imaginary frequency) and first order saddle points (TSs with one imaginary frequency). The validity of using the 6-31G(d) basis set has previously been checked by comparative single point energy calculations employing the def2-TZVP basis set for all atoms on similar H/D exchange systems [20]. All calculations using the M06 functional have been performed using Gaussian 09 quantum chemistry program package (version A.02). Calculations were first carried out in the gas phase before reoptimising each structure at the same level of theory, implementing the Polarizable Continuum Model (PCM) for DCM as the solvent [42]. All coordinates provided are listed in Cartesian format, with charge and multiplicity of each system given at the top of the coordinate list (i.e., 0 1 = neutral singlet; 1 1 = 1 + charged singlet).

5. Conclusions

In summary, we have divulged novel iridium-catalysed methods for the ortho-deuteration of benzoate esters by the application of complexes emerging from our laboratory, possessing a bulky NHC/phosphine combination. Inherent variability in reproducibly labelling ester substrates to useable levels of D-incorporation was solved by two methods: (i) a mild increase in reaction temperature; and (ii) a switch in the catalyst anion from PF6 to BArF; this delivered good to excellent levels of deuterium incorporation adjacent to ester directing groups. Kinetic studies on intramolecular directing group chemoselectivity revealed that selectivity vs. time is substrate dependent, showing the possibility that different levels of binding conformer equilibria are possible. Supporting DFT analyses of the systems studied experimentally support previous findings that suggested the most stable binding conformer is also the most reactive. We have demonstrated that such knowledge can be exploited experimentally and, as such, we have shown that different modes of regioselective labelling is possible in a multifunctional substrate by simple variation of the reaction conditions. Overall, we believe that these methods further enhance the applicable substrate scope and wider utility of the iridium complexes at the centre of this study.

Supplementary Materials

Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/20/07/11676/s1.

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Author Contributions

The project was devised by W.J.K. and M.R. Experimental results were obtained by J.D. and T.J.D.M. Computational analysis was conducted by M.R. with consultation from T.T. The manuscript was prepared by D.M.L., M.R., and W.J.K.

Conflicts of Interest

The authors declare no conflict of interest.

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