Are Rate and Selectivity Correlated in Iridium-Catalysed Hydrogen Isotope Exchange Reactions?

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Are rate and selectivity correlated in iridium-catalysed hydrogen isotope exchange reactions?‡§

Daria S. Timofeeva, David M. Lindsay,* William J. Kerr,* and David J. Nelson*

Herein we examine the relationship between reaction rate and reaction selectivity in iridium-catalysed hydrogen isotope exchange (HIE) reactions directed by Lewis basic functional groups. We have recently developed a directing group scale that allows semi-quantitative predictions of Lewis base directed selectivity in HIE, formally ranking ‘relative rates’ determined from a structured set of competition experiments. Here, we show that selectivity and rate are in fact not correlated, but that different types of behaviour emerge in competition experiments and that the observed behaviour can be predicted from our established selectivity scale.

Introduction

Hydrogen isotope exchange (HIE) is a crucial tool in many areas of chemistry, including in drug discovery, where it is critical in enabling the selective incorporation of $^2$H (D) and $^3$H (T) into drug molecules for pharmacokinetic studies, and in mechanistic studies, via measurement of kinetic isotope effects (KIE). An ideal HIE process should be general, operationally simple, and lead to high and predictable incorporation of the isotopic atom. Reactions catalysed by iridium complexes, which rely on a C-H activation step directed by a Lewis base, have emerged as reliable methods that fulfil these criteria (Figure 1). Numerous iridium complexes have been developed, but commercial Crabtree’s catalyst [Ir(COD)(PCy$_3$)][PF$_6$] and Kerr’s catalysts, such as [Ir(COD)(IL)(PPh$_3$)][PF$_6$] (X = PF$_6$ or BAr$_{24}$), are amongst the most widely used (COD = 1,5-cyclooctadiene; IMes = 2,6-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene; Cy = cyclohexyl; py = pyridine; BAr$_{24}$ = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate). Homogeneous iridium-catalysed HIE reactions using D$_2$ (or T$_2$) gas have proved to be highly efficient for the selective labelling of compounds at the ortho-position next to directing groups such as ketones, amides, esters, nitroarenes, and sulfonamides, as well as various heterocycles such as pyridines, pyrimidines, pyrazoles, imidazole(1)nes, thiazole(1)nes, oxazole(1)nes and their benzo-fused analogues.

No systematic kinetic investigation has, however, been carried out to determine the rates of iridium-catalysed hydrogen isotope exchange. Absolute rates for the deuteration (kD) of acetophenone, an arylsulfonamide and methyl phenylacetate, and for the hydrogenation of corresponding deuterated species (kH), were determined in the course of the kinetic isotope effect (KIE) measurements for these reactions. In other examples, reactions were monitored by sampling at time points to build reaction profiles, but in such cases no rate constants were determined.

We have recently constructed an empirical directing group scale that can be used to predict the selectivity of iridium-catalysed HIE reactions in substrates with multiple directing groups. This scale was obtained by conducting a structured series of competition experiments using representative HIE catalysts [Ir(COD)(IL)(PPh$_3$)][BAR$_{24}$] and [IrCl(COD)(IMes)].

‡ Electronic Supplementary Information (ESI) available: procedures and kinetic data.

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§ Electronic Supplementary Information (ESI) available: procedures and kinetic data.
Results and Discussion

The HIE reactions (Scheme 2) was therefore monitored by the withdrawal of aliquots from reaction mixtures at time intervals which were then analysed by $^1$H NMR spectroscopy (see the Supporting Information for full details).\textsuperscript{16} Reactions were carried out in chloroform-$d$ to enable the direct analysis of samples after quenching with a few drops of acetonitrile. We collected real-time quantitative information about the extent of isotopic labelling under representative laboratory conditions of D$_2$ pressure (using a balloon), temperature, and stirring.\textsuperscript{1} Using this method we were able to monitor the HIE reactions of representative substrates chosen from the spectrum of established directing group strengths.

This quantitative reactivity scale is formally ordered according to relative rate constants $k_{obs}$ and ranks nineteen commonly used directing groups, including various pharmacologically relevant, nitrogen-containing heterocycles, and can be used for semi-quantitative regioselectivity predictions in hydrogen isotope exchange reactions of complex molecules. However, these data cannot tell us why selectivity differences exist. The proposed catalytic cycle for these reactions proceeds via binding of a substrate via its directing group, followed by steps that break and form C-H/D and H-H/D-D bonds (Scheme 1).

In each case, the rate of HIE for the more reactive directing group in each pair (Ph-DG$_1$) was similar to that from the corresponding single substrate reaction. The rate of the reaction of the second (less strongly directing) substrate (Ph-DG$_2$) decreased.

Additionally, we monitored the reactions of a selection of substrates with multiple directing groups (Scheme 3 (b)) to understand whether the same behaviour is observed in intermolecular competition systems.

In each case, the rate of HIE for the more reactive directing group in each pair (Ph-DG$_1$) was similar to that from the corresponding single substrate reaction. The rate of the reaction of the second (less strongly directing) substrate (Ph-DG$_2$) decreased.

A plot of the concentration of unlabelled substrate and deuterium incorporation (%D) of the substrate versus time shows clear pseudo-first order kinetic behaviour for the representative examples of acetophenone, nitrobenzene, and 2-phenyloxazoline (Figure 2(a)). The expected linearity of the log [substrate] versus time plot was observed with a gradient of $-k_{obs}$ (Figure 2(b)). Rate constants ($k_{obs}$) are quoted in Table 1 and showed a high degree of reproducibility in duplicate experiments. These rate constants cover a very small range (ca. four-fold) and show very little correlation with the reactivity scale obtained from competition experiments ($k_{rel}$). The difference between the reaction rates observed for ketone, nitro and ester groups were found to be much smaller compared to heterocyclic systems.\textsuperscript{17} Pyridine is at least 15-fold more strongly directing than acetophenone according to competition experiments, and yet there is an inverted difference in reactivity (1:2.6) when $k_{obs}$ are compared.

We then studied selected two-substrate kinetic experiments (Scheme 3 (a)). The reactions were conducted under the same conditions to those for single substrate kinetics, but using 1 mol% of the catalyst in total to allow reaction rates and selectivity to be monitored for both substrates in these intermolecular competition systems.

In each case, the rate of HIE for the more reactive directing group in each pair (Ph-DG$_1$) was similar to that from the corresponding single substrate reaction. The rate of the reaction of the second (less strongly directing) substrate (Ph-DG$_2$) decreased.

Additionally, we monitored the reactions of a selection of substrates with multiple directing groups (Scheme 3 (b)) to understand whether the same behaviour is observed in intramolecular competition experiments. Three general scenarios were observed: i) the two substrates react in parallel, but at different rates; ii) the two substrates react in series, with

Scheme 1. Mechanism of HIE catalysed by iridium complexes.

Scheme 2. HIE reaction kinetic monitoring.

The HIE reactions of acetophenone performed in CDCl$_3$ ($k_{obs}$ (50°C) = 3.93 × 10$^{-4}$ s$^{-1}$) showed no significant solvent effect when compared to data obtained in DCM.\textsuperscript{6} The use of CDCl$_3$ as a reaction solvent allows for a wider temperature range and minimises the number of operations required after the withdrawal of the aliquot.

To simplify the practical aspects of the kinetic analysis of the HIE reactions, we have used D$_2$ gas in excess. Therefore, the concentration of D$_2$ is effectively constant throughout the reactions, resulting in pseudo-first-order kinetics. For [D$_2$]$_0$ ≫ [substrate]$_0$, the rate of consumption of substrate can be expressed as $-d$[substrate]/$dt$ = $k_{obs}$[substrate].

A plot of the concentration of unlabelled substrate and deuterium incorporation (%D) of the substrate versus time shows clear pseudo-first order kinetic behaviour for the representative examples of acetophenone, nitrobenzene, and 2-phenyloxazoline (Figure 2(a)). The expected linearity of the log [substrate] versus time plot was observed with a gradient of $-k_{obs}$ (Figure 2(b)). Rate constants ($k_{obs}$) are quoted in Table 1 and showed a high degree of reproducibility in duplicate experiments. These rate constants cover a very small range (ca. four-fold) and show very little correlation with the reactivity scale obtained from competition experiments ($k_{rel}$). The difference between the reaction rates observed for ketone, nitro and ester groups were found to be much smaller compared to heterocyclic systems.\textsuperscript{17} Pyridine is at least 15-fold more strongly directing than acetophenone according to competition experiments, and yet there is an inverted difference in reactivity (1:2.6) when $k_{obs}$ are compared.
the second substrate undergoing labelling once a significant proportion of the first substrate has labelled; iii) one substrate reacts and the other does not. Figure 4 shows the representative examples for each scenario, including concentration versus time profiles for intra- and intermolecular competition kinetics and single substrate kinetics.

**Scenario 1.** This is represented by the HIE reaction with competing ketone and nitro groups. As discussed above, the single substrate kinetic experiments gave comparable rates from these substrates. When the labelling reaction of acetophenone and nitrobenzene was carried out in the same flask, the rate of deuterium incorporation for both substrates decreased by ca. 2 and 3 times, respectively, with their reactions proceeding in parallel with approximately constant selectivity at each time point. The same scenario was observed for the following directing group combinations: pyrazole versus pyridine, oxazoline versus thiazoline, and oxazoline versus pyridine.

**Scenario 2.** This is represented by the competition between ketone and ester directing groups. As can be deduced from the intramolecular competition kinetics, the ketone group inhibits the isotopic labelling ortho to the ester group in the initial phases of the reaction. When the reaction reaches relatively high conversion (labelling) ortho to the ketone group, ester directed labelling begins to occur, albeit with a significantly lower rate \((k_{obs} \sim 10^{-5} \text{ s}^{-1})\) compared to the corresponding single substrate experiment \((k_{obs} \sim 10^{-4} \text{ s}^{-1})\). Similar observations showed that the combinations of nitro versus ester and \(N\)-methyl-imidazole versus pyridine demonstrated similar behaviour.

**Scenario 3.** This is obtained for pairs of directing groups with large differences in reactivity. The representative example of the competition between thiazoline and nitro showed that the latter is fully inhibited by the more reactive thiazoline group and almost no deuterium labelling was observed ortho to the nitro group. Similar behaviour was obtained for competition reactions between oxazoline and ketone, pyridine and ketone, \(N\)-methylimidazole and ketone, \(N\)-methylimidazole and benzothiazole, and oxazoline and benzothiazole.

For a given substrate pair, the same qualitative behaviour is obtained in both intermolecular competition experiments with two different substrates and intramolecular competition experiments with a single bifunctional substrate. However, in some cases the profiles from these experiments are somewhat different in quantitative terms. For example, in the competition between the ethyl ester and the methyl ketone (Figure 4, Scenario II), the sequential nature of labelling is far more pronounced for the intermolecular competition experiment than it is for the labelling of ethyl (4-acylbenzoate). There may be a pathway for the exchange of binding site without substrate
dissociation, and computational studies to explore this are currently underway.

As shown for various directing group combinations (Figure 4, right), the ratios of $k_{rel}$ for the corresponding directing groups from our directing group power scale can predict which coordinating groups can inhibit otherwise productive catalytic reactions:

**Scenario 1.** This is observed when the ratio of $k_{rel}$ from our directing group scale is less than ca. 3. The directing groups are of broadly similar strength and the reactions occur in parallel at similar rates.

**Scenario 2.** This is observed when the ratio of $k_{rel}$ of the two groups lies between ca. 3 and 10. In these situations, one of the directing groups is clearly stronger than the other. The
substrate bearing the more strongly directing Lewis basic group inhibits the reaction of that with the less strongly directing group in the initial phases of the reaction. The second substrate undergoes labelling subsequently.

Scenario 3. This is observed when the ratio of $k_{rel}$ for the two directing groups is greater than ca. 10, and so one directing group is overwhelmingly more strongly directing than the other. The substrate bearing more strongly directing Lewis basic group fully inhibits the reaction of the other substrate.

To further probe whether the reactions are guided by the binding abilities of the directing group, we conducted the HIE reaction of acetophenone in the presence of pyridine (0.50 mmol). No isotope labelling ortho to the ketone was observed, because the binding of the more Lewis basic pyridine to the iridium centre completely inhibits acetophenone binding. This is consistent with our observations in systems where acetophenone and 2-phenylpyridine compete (ratio of $k_{rel} = 16.7$ in favour of pyridine).

Conclusions

In summary, we have systematically studied the kinetic behaviour of iridium-catalysed hydrogen isotope exchange reactions using a sampling method. The reactions fit a pseudo-first order reaction model quite well, allowing us to obtain the rate constants ($k_{obs}$) for a range of directing groups that are both heterocyclic and non-heterocyclic. Surprisingly, the obtained rates do not show significant differences and do not correlate with previously determined $k_{rel}$ values from competition experiments. Instead, the two-substrate kinetic profiles showed that reactions occur in parallel with different rates for the substrates with very close directing group abilities, and one substrate inhibits the reaction of the other via competitive binding for the directing groups with bigger differences in reactivity. The ratio of the $k_{rel}$ of the directing groups can be used to predict the behaviour of reactions in which there are multiple directing groups, whether these be on discrete molecules or on one bifunctional substrate. This allows us to predict scenarios where, despite the presence of two directing groups, labelling will only occur at one site. Further studies are underway within our laboratories to understand this process in more detail.

Author Contributions

DST: data curation; formal analysis; investigation; methodology; writing - original draft.
DML: conceptualisation; funding acquisition; project administration; supervision; writing – review & editing.
WJK: conceptualisation; funding acquisition; resources; supervision.
DJN: conceptualisation; funding acquisition; methodology; project administration; resources; supervision; writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

† Representative procedure: Reactions were carried out in 30 mL microwave vials with septum-fitted caps. The vessel was kept at a constant temperature (thermostat/Drysyn block), and a balloon containing D$_2$ was connected to the flask to maintain a constant supply (and excess) of D$_2$. To calculate the concentration of the unlabelled substrate, the residual proton signal from the site of incorporation (ortho to the directing group) was compared against that of a site where deuterium incorporation did not occur.

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Initial attempts to monitor reactions in situ using an NMR tube with a J. Young valve were unsuccessful. These reactions are very slow, presumably due to the very small
interfacial area between the deuterium gas and the reaction solution. See the supporting information for full details.

17. The reactions of a series of para-substituted acetophenone substrates were monitored with the aim of examining a Hammett correlation. Unfortunately, the very small differences between the observed rates precluded such an analysis (see the supporting information).
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1. General Experimental Details

General

For the synthetic procedures, standard Schlenk techniques using an inert gas atmosphere (Ar or N\textsubscript{2}) were used, unless otherwise stated. Materials obtained from commercial sources (all acetophenones, ethylbenzoate, nitrobenzene, 2-phenylpyridine, 1-phenylpyrazole, 2-phenylloxazoline, 2-phenylbenzothiazole, 4-nitrobenzoate) were used without further purification. All glassware was flame dried and cooled under a stream of nitrogen.

Materials

(1,3-bis-(2,4,6-trimethylphenyl)imidazolium chloride\textsuperscript{51} phenylthiazoline,\textsuperscript{52} 2-(4-nitrophenyl)-4,5-dihydrothiazole,\textsuperscript{52} and 1-methyl-2-phenylimidazole\textsuperscript{53} were synthesised according to literature procedures. 2-(4-Acetyl)phenyloxazoline and 2-(4-(pyridin-2-yl)phenyl)-4,5-dihydrooxazole were obtained from the reaction between corresponding aryl nitriles and amino alcohols catalysed by [Cu(Cl)(IPr)].\textsuperscript{54} Anhydrous Na[BAr\textsubscript{24}] (BAr\textsubscript{24} = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) was obtained following Bergman’s synthesis,\textsuperscript{55} followed by recrystallising the crude Na[BAr\textsubscript{24}]·x(solvent) prior to drying. Phosphine/NHC monodentate complex [Ir(COD)(IMes)(PPh\textsubscript{3})][BAr\textsubscript{24}] was synthesised from [IrCl(COD)(IMes)][BAr\textsubscript{24}] in a procedure adapted from that published before for preparation of corresponding complexes with BF\textsubscript{4} and OTf counterions.\textsuperscript{58}

Flash column chromatography was carried out using silica gel (230-400 mesh). Thin layer chromatography (TLC) was performed using Merck silica plates coated with fluorescent indicator and visualised by UV light (254 nm).

Analysis

\textsuperscript{1}H (400 MHz) and \textsuperscript{13}C{\textsuperscript{1}H} (101 MHz) NMR spectra were obtained on a Bruker AV3-400 instrument with a liquid nitrogen Prodigy cryoprobe. The chemical shifts (δ) are reported in ppm relative to the residual protonated solvent for \textsuperscript{1}H NMR or the solvent signal for \textsuperscript{13}C{\textsuperscript{1}H} NMR (CDCl\textsubscript{3}: δ\textsubscript{H} 7.26 ppm and δ\textsubscript{C} 77.16 ppm).\textsuperscript{59} Coupling constants (J) are reported in Hz and refer to \textsuperscript{3}J_{H-H} couplings, unless otherwise stated. Multiplicities are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad signal). If no multiplicity is given for \textsuperscript{13}C{\textsuperscript{1}H} NMR data, the signal is a singlet. NMR assignments were made using additional 2D NMR experiments where necessary.
**Figure S1.** Scope of the substrates used in the study.

**a) For individual kinetics**

![Chemical structures for individual kinetics](image)

**b) For intramolecular competition kinetics**

![Chemical structures for intramolecular competition kinetics](image)
2. Synthesis and Characterisation

2-(4-nitrophenyl)-4,5-dihydrothiazole

Potassium carbonate (0.77 g, 5.56 mmol) was added to an ethanol solution (30 ml) of 4-cyanonitrobenzene (0.50 g, 3.37 mmol), and cysteamine hydrochloride (0.57 g, 5.05 mmol) at room temperature. The reaction was then heated at reflux overnight (20 h). The reaction mixture was cooled to room temperature before the ethanol was removed under reduced pressure. The residue was dissolved in ethyl acetate (10 mL) and water (10 mL) was added. The layers were separated and the aqueous layer was then extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over MgSO₄, filtered, and the solvent was removed under vacuum to give the crude product, which was purified by column chromatography (20 – 50% ethyl acetate in hexane) to afford the title compound as a yellow solid (209 mg, 1.01 mmol, 30%).

^1H NMR (400 MHz, CDCl₃) δ = 8.28 – 8.22 (m, 2H, Ar-H), 8.03 – 7.94 (m, 2H, Ar-H), 4.51 (t, J = 8.5 Hz, 2H, CH₂), 3.49 (t, J = 8.5 Hz, 2H, CH₂).

^13C{^1H} NMR (101 MHz, CDCl₃) δ = 166.7, 149.4, 138.9, 129.4, 123.8, 65.7, 34.4.

NMR data are consistent with the literature.  

Ethyl 4-acetylbenzoate

A solution of 4-acetylbenzoic acid (3.0 g, 18.3 mmol) in ethanol (35 mL) was stirred at 0°C in an ice bath. Concentrated H₂SO₄ (0.2 mL, 3.65 mmol) was slowly added and the mixture was heated to 80 °C for 3 h. The the reaction mixture was cooled to room temperature before the ethanol was removed under reduced pressure. The residue was dissolved in ethyl acetate (10 mL) and water (10 mL) was added. The layers were separated and the aqueous layer was then extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over MgSO₄, filtered, and the solvent was removed under vacuum to give the crude product, which was purified by column chromatography (9% ethyl acetate in hexane) to afford the title compound as a white solid (1.40 g, 7.28 mmol, 38%).

^1H NMR (400 MHz, CDCl₃) δ = 8.17 – 8.08 (m, 2H, Ar-H), 8.05 – 7.95 (m, 2H, Ar-H), 4.41 (q, J = 7.1 Hz, 2H, CH₂CH₃), 2.64 (s, 3H, COCH₃), 1.41 (t, J = 7.1 Hz, 3H, CH₂CH₃).

^13C{^1H} NMR (101 MHz, CDCl₃) δ = 197.7, 165.9, 140.3, 134.4, 129.9, 128.3, 61.6, 27.0, 14.4.

NMR data are consistent with the literature.
Spectral details for unlabeled substrates used in this work:

Substrates with single directing groups

Acetophenone

\[^1\text{H NMR} (400 \text{ MHz, CDCl}_3) \delta = 7.99 – 7.93 \text{ (m, 2H, H-3)}, 7.60 – 7.53 \text{ (m, 1H, H-1), 7.51 – 7.42 \text{ (m, 2H, H-2), 2.61 (s, 3H, H-4).}}
\]

Incorporation expected at $\delta$ 7.99 – 7.93 ppm (H-3)

Determined against integral at $\delta$ 2.61 ppm (H-4)

Ethylbenzoate

\[^1\text{H NMR} (400 \text{ MHz, CDCl}_3) \delta = 8.08 – 8.02 \text{ (m, 2H, H-3), 7.58 – 7.52 \text{ (m, 1H, H-1), 7.47 – 7.40 \text{ (m, 2H, H-2), 4.38 (q, J = 7.1 Hz, 2H, CH}_2), 1.40 \text{ (t, J = 7.1 Hz, 3H, CH}_3).}}
\]

Incorporation expected at $\delta$ 8.07 – 8.03 ppm (H-3)

Determined against integral at $\delta$ 4.38 ppm (OC\text{CH}_2\text{CH}_3)

Nitrobenzene

\[^1\text{H NMR} (400 \text{ MHz, CDCl}_3) \delta = 8.26 – 8.20 \text{ (m, 2H, H-3), 7.73 – 7.66 \text{ (m, 1H, H-1), 7.58 – 7.51 \text{ (m, 2H, H-2).}}
\]

Incorporation expected at $\delta$ 8.26 – 8.20 ppm (H-3)

Determined against integral at $\delta$ 7.73 – 7.66 ppm (H-1)

2-phenylpyridine

\[^1\text{H NMR} (400 \text{ MHz, CDCl}_3) \delta = 8.73 – 8.67 \text{ (m, 1H, H-4), 8.02 – 7.98 \text{ (m, 2H, H-3), 7.78 – 7.70 \text{ (m, 2H, H-6 and H-7), 7.51 – 7.45 \text{ (m, 2H, H-2), 7.45 – 7.39 \text{ (m, 1H, H-1), 7.25 – 7.21 \text{ (m, 1H, H-5).}}}
\]

Incorporation expected at $\delta$ 8.02 – 7.98 ppm (H-3)

Determined against integral at $\delta$ 8.73 – 8.67 ppm (H-4) or at $\delta$ 7.78 – 7.70 (H-6+H-7) depending on the competition partner.

1-phenylpyrazole

\[^1\text{H NMR} (400 \text{ MHz, CDCl}_3) \delta = 7.92 \text{ (d, J = 2.2 Hz, 1H, H-6), 7.75 – 7.68 \text{ (m, 3H, H-3 and H-4), 7.48 – 7.43 \text{ (m, 2H, H-2), 7.32 – 7.26 \text{ (m, 1H, H-1), 6.49 – 6.45 \text{ (m, 1H, H-5).}}}
\]

Incorporation expected at $\delta$ 7.75 – 7.68 ppm (H-3)

Determined against integral at $\delta$ 7.92 ppm (H-6)

2-phenyloxazoline

\[^1\text{H NMR} (400 \text{ MHz, CDCl}_3) \delta = 7.97 – 7.93 \text{ (m, 2H, H-3), 7.50 – 7.44 \text{ (m, 1H, H-1), 7.43 – 7.37 \text{ (m, 2H, H-2), 4.43 (t, J = 9.5 Hz, 2H, H-4), 4.06 (t, J = 9.5 Hz, 2H, H-5).}}
\]

Incorporation expected at $\delta$ 7.97 – 7.93 ppm (H-3)

Determined against integral at $\delta$ 4.43 ppm (H-4)

2-phenylthiazoline

\[^1\text{H NMR} (400 \text{ MHz, CDCl}_3) \delta = 7.86 – 7.81 \text{ (m, 2H, H-3), 7.48 – 7.37 \text{ (m, 3H, H-1 and H-2), 4.46 (t, J = 8.3 Hz, 2H, H-4), 3.41 (t, J = 8.3 Hz, 2H, H-5).}}
\]

Incorporation expected at $\delta$ 7.86 – 7.81 ppm (H-3)

Determined against integral at $\delta$ 4.46 ppm (H-4)

2-phenylbenzothiazole
2-(4-nitrophenyl)-4,5-dihydrothiazole

Substrates with multiple directing groups

4-nitroacetophenone

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \delta = 8.14 – 8.06 \text{ (m, 3H, H-3 and H-4), 7.91 (d, } J = 8.0 \text{ Hz, } 1H, \text{ H-7), 7.53 – 7.48 \text{ (m, 4H, H-2 and H-5), 7.41-7.37 (m, 1H, H-6).} \]

Incorporation expected at δ 8.14 – 8.06 ppm (H-3)
Incorporation determined against δ 7.91 ppm (H-7)

1-methyl-2-phenylimidazole

\[ ^1H \text{ NMR (400 MHz, CDCl}_3 \delta = 7.65 – 7.60 \text{ (m, 2H, H-3), 7.47 – 7.34 (m, 3H, H-1 and H-2), 7.12 (d, } J = 1.2 \text{ Hz, } 1H, \text{ H-5), 6.97 (d, } J = 1.2 \text{ Hz, } 1H, \text{ H-4), 3.19 (s, 3H, H-6).} \]

Incorporation expected at δ 7.65 – 7.60 ppm (H-3)
Incorporation determined against δ 7.12 ppm (H-5)

4-nitroacetophenone

\[ ^1H \text{ NMR (400 MHz, CDCl}_3 \delta = 8.33 – 8.30 \text{ (m, 2H, H/D}_a, \text{ 8.13 – 8.09 (m, 2H, H/D}_b), 2.68 (s, 3H, CH}_3). \]

Deuteration expected at δ (H\(_a\)) = 8.13 – 8.09 ppm and δ (H\(_b\)) = 8.33 – 8.30 ppm.
Deuterated against integral at δ = 2.68 ppm.

Ethyl 4-nitrobenzoate

\[ ^1H \text{ NMR (400 MHz, CDCl}_3 \delta = 8.30 – 8.26 \text{ (m, 2H, H/D}_a, \text{ 8.23 – 8.18 (m, 2H, H/D}_b), 4.43 (q, } J = 7.1 \text{ Hz, } 2H, \text{ CH}_2), 1.42 (t, } J = 7.1 \text{ Hz, } 3H, \text{ CH}_3). \]

Deuteration expected at δ (H\(_a\)) = 8.30 – 8.26 ppm and δ (H\(_b\)) = 8.23 – 8.18 ppm.
Deuterated against integral at δ = 4.43 ppm.

Ethyl 4-acetylanisate

\[ ^1H \text{ NMR (400 MHz, CDCl}_3 \delta = 8.17 – 8.08 \text{ (m, 2H, Ar-H/D}_a, \text{ 8.05 – 7.95 (m, 2H, H/D}_b), 4.41 (q, } J = 7.1 \text{ Hz, } 2H, \text{ CH}_2CH_3), 2.64 (s, 3H, COCH}_3), 1.41 (t, } J = 7.1 \text{ Hz, } 3H, \text{ CH}_2CH_3). \]

Deuteration expected at δ (H\(_a\)) = 8.17 – 8.08 ppm and δ (H\(_b\)) = 8.05 – 7.95 ppm.
Deuterated against integral at δ = 4.41 ppm.

2-(4-acetyl)phenoxazoline

\[ ^1H \text{ NMR (400 MHz, CDCl}_3 \delta = 8.06 – 8.01 \text{ (m, 2H, H}_a, \text{ 8.01 – 7.96 (m, 2H, H}_b), 4.47 (t, } J = 9.6 \text{ Hz, } 3H, \text{ CH}_2), 4.10 (t, } J = 9.6 \text{ Hz, } 2H, \text{ CH}_2), 2.62 (s, 3H, CH}_3). \]

Deuteration expected at δ (H\(_a\)) = 8.06 – 8.01 ppm and δ (H\(_b\)) = 8.01 – 7.96 ppm.
Deuterated against integral at δ = 4.47 ppm.

2-(4-nitropheryl)-4,5-dihydrothiazole

\[ ^1H \text{ NMR (400 MHz, CDCl}_3 \delta = 8.28 – 8.22 \text{ (m, 2H, H}_a, \text{ 8.03 – 7.94 (m, 2H, H}_b), 4.51 (t, } J = 8.5 \text{ Hz, } 2H, \text{ CH}_2), 3.49 (t, } J = 8.5 \text{ Hz, } 2H, \text{ CH}_2). \]

Deuteration expected at δ (H\(_a\)) = 8.28 – 8.22 ppm and δ (H\(_b\)) = 8.03 – 7.94 ppm.
Deuterated against integral at δ = 4.51 ppm.
2-(4-(Pyridin-2-yl)phenyl)-4,5-dihydrooxazole

$^1$H NMR (400 MHz, C$_6$D$_6$) δ = 8.56 – 8.51 (m, 1H, Ar-H), 8.36 – 8.32 (m, 1H, H$_A$), 8.17 – 8.11 (m, 2H, H$_B$), 7.25 – 7.21 (m, 1H, Ar-H), 7.11 – 7.04 (m, 1H, Ar-H), 6.66 – 6.61 (m, 1H, Ar-H), 3.77 – 3.69 (m, 2H, CH$_2$), 3.67 – 3.59 (m, 2H, CH$_2$).

Deuteration expected at δ (H$_A$) = 8.36 – 8.32 ppm and δ (H$_B$) = 8.17 – 8.11 ppm.

Determined against integral at δ = 3.77 – 3.69 ppm.
3. Kinetic Data

3.1. NMR Kinetics

Preparation of Solution 1 (Substrate + catalyst). 2-Phenylpyridine (0.15 mmol, 23.3 mg) and [Ir(COD)(IMes)(PPh3)][BArF24] (6.5 mg, 0.004 mmol) were added to a 1.00 mL volumetric flask. CDCl3 was then added to the 1 ml mark. The final concentrations were [Substrate] = 0.15 M, [Ir] = 0.004 M.

Preparation of Internal Standard (trimethoxybenzene) Solution. Trimethoxybenzene (0.30 mmol) was added to a 3.00 mL volumetric flask. CDCl3 was then added to the 3 ml mark. The final concentrations were [Internal Standard] = 0.10 M.

A J. Young NMR tube was charged with 0.20 ml of Solution 1 and 0.3 mL of Internal Standard Solution by syringe ([substrate]₀ = 0.06 M). The NMR tube was inserted into the NMR probe, which had been pre-equilibrated to 50 °C, and then after locking and shimming the sample the initial spectrum was acquired. The tube was removed from the magnet, the solution was cooled in an acetone/dry ice bath and the headspace of the tube was evacuated and then refilled with deuterium gas (1 atm) from a balloon. After 3 vacuum/deuterium cycles, the tube was removed from the cooling bath and placed back into the magnet. Automated data acquisition was then started. The kinetics experiment was initiated after reacquiring a lock to CDCl3, but without shimming or tuning. Arrays of 1H NMR spectra were collected at 600 MHz. Kinetics experiments (arrays of spectra) were implemented using standard Topspin software. Typical experiment: 16 scans per spectrum. The first spectrum was recorded ca. 10 min after D₂ was added, with each new spectrum collected in 17 min increments (80 total spectra). The total acquisition time was approximately 22 hours.

The residual proton signal from the site of incorporation (ortho to DG) was compared against that of a site where incorporation did not happen and to the peaks of the internal standard. The concentration decay (2-phenylpyridine) over time is shown below for 20 data points each 17 mins and additional 12 data points each 85 mins. The expected linearity of ln [substrate] vs. time plots was observed with a gradient of – k_{obs}. 

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S8
$y = -4E-05x - 2.7549$

$R^2 = 0.9938$
3.2. Standard Kinetics Protocol for Reaction Monitoring by Sampling Method

Ph-DG (0.50 mmol) and the iridium(I) pre-catalyst (0.005 mmol) were weighed into small vials. The solids were directly transferred to the reaction vial; any liquid substrates were first dissolved in a small amount of CDCl₃, the vial was washed with solvent, and the washings were transferred to the reaction vial. The reaction mixture was diluted using 2.5 mL (in total) of CDCl₃ ([Ph-DG]₀ = 0.20 mol/L). An aliquot was withdrawn to measure the initial spectrum and the vial was capped.

The solution was cooled in an acetone/dry ice bath and the headspace of the vial was evacuated and then refilled with deuterium gas (1 atm) from the balloon. After 3 vacuum/deuterium cycles, the reaction vial was removed from the cooling bath and placed in an aluminum block or thermostat-controlled water bath that had been preheated to 50 °C and the timer was started. The reaction mixture was then stirred vigorously (860 rpm) at 50 °C for 1-2 mins, allowing for catalyst activation and temperature equilibrium before the first aliquot was taken. The deuterium balloon was left in place for the duration of the reaction to ensure a continuous supply (and an excess) of D₂.

The aliquots (0.04 mL) of reaction mixture were removed at the specified intervals throughout the reaction via syringe to an NMR tube and diluted with 0.5 mL of CDCl₃.

The concentrations of the Ph-DG substrate (starting material) were determined by ¹H NMR analysis. The residual proton signal from the site of incorporation (ortho to DG) was compared against that of a site where incorporation did not happen.

To simplify the practical aspects of the kinetic analysis of the HIE reactions, we have used D₂ gas in excess. Therefore, the concentrations of D₂ can be considered almost constant throughout the reactions, resulting in pseudo-first-order kinetics. For [D₂]₀ ≫ [Substrate]₀ the rate of disappearance of substrate can be expressed as -d[substrate]/dt = k_{obs}[Substrate].

Plots of concentration of unlabeled substrate vs. time show clear pseudo-first order kinetic behavior. The expected linearity of ln [substrate] vs. time plots was observed with a gradient of - k_{obs}. All the kinetics with single substrate were run in duplicate and the averaged positive values of this gradient are shown in the manuscript (Table 1).
3.3. Kinetic data from single substrate experiments

**Table S1.** Rate monitoring for the deuteration of acetophenone (run 1)

Following the General Kinetic Protocol using 60.1 mg of acetophenone, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|---------|----------------|----------------|---------------|
| 0     | 0       | 2.00           | 0.200          | -1.61         |
| 1     | 300     | 1.80           | 0.180          | -1.71         |
| 2     | 600     | 1.63           | 0.163          | -1.81         |
| 3     | 900     | 1.45           | 0.145          | -1.93         |
| 4     | 1500    | 1.14           | 0.114          | -2.17         |
| 5     | 2100    | 0.87           | 0.087          | -2.44         |
| 6     | 2700    | 0.69           | 0.069          | -2.67         |
| 7     | 3300    | 0.59           | 0.059          | -2.83         |
| 8     | 3900    | 0.51           | 0.051          | -2.98         |
| 9     | 6300    | 0.39           | 0.039          | -3.24         |
| 10    | 9900    | 0.38           | 0.038          | -3.27         |

\[ k_{\text{obs}} = 3.88 \times 10^{-4} \text{ (s}^{-1} \text{)} \]
Table S2. Rate monitoring for the deuteration of acetophenone (run 2)
Following the General Kinetic Protocol using 60.1 mg of acetophenone, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|--------|----------------|----------------|---------------|
| 0     | 0      | 2.00           | 0.200          | -1.61         |
| 1     | 300    | 1.73           | 0.173          | -1.75         |
| 2     | 600    | 1.51           | 0.151          | -1.89         |
| 3     | 900    | 1.32           | 0.132          | -2.02         |
| 4     | 1200   | 1.16           | 0.116          | -2.15         |
| 5     | 1800   | 0.98           | 0.098          | -2.32         |
| 6     | 2400   | 0.82           | 0.082          | -2.50         |
| 7     | 3000   | 0.73           | 0.073          | -2.62         |
| 8     | 3600   | 0.64           | 0.064          | -2.75         |
| 9     | 5400   | 0.56           | 0.056          | -2.88         |
| 10    | 7200   | 0.54           | 0.054          | -2.92         |
| 11    | 10800  | 0.50           | 0.050          | -3.00         |

\[ k_{\text{obs}} = 3.98 \times 10^{-4} \, (s^{-1}) \]
**Table S3.** Rate monitoring for the deuteration of nitrobenzene (run 1)

Following the General Kinetic Protocol using 61.5 mg of nitrobenzene, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|---------|----------------|----------------|---------------|
| 0     | 0       | 2.00           | 0.200          | -1.61         |
| 1     | 300     | 1.83           | 0.183          | -1.70         |
| 2     | 600     | 1.68           | 0.168          | -1.78         |
| 3     | 1200    | 1.39           | 0.139          | -1.97         |
| 4     | 1800    | 1.15           | 0.115          | -2.16         |
| 5     | 2400    | 1.00           | 0.100          | -2.30         |
| 6     | 3000    | 0.90           | 0.090          | -2.41         |
| 7     | 3600    | 0.81           | 0.081          | -2.51         |
| 8     | 5700    | 0.64           | 0.064          | -2.75         |
| 9     | 7200    | 0.56           | 0.056          | -2.88         |
| 10    | 9000    | 0.52           | 0.052          | -2.96         |
| 11    | 10800   | 0.48           | 0.048          | -3.04         |
| 12    | 12600   | 0.47           | 0.047          | -3.06         |

\[ k_{\text{obs}} = 2.70 \times 10^{-4} \text{ (s}^{-1}) \]
Table S4. Rate monitoring for the deuteration of nitrobenzene (run 2)

Following the General Kinetic Protocol using 61.5 mg of nitrobenzene, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|---------|----------------|----------------|---------------|
| 0     | 0       | 2.00           | 0.200          | -1.61         |
| 1     | 300     | 1.83           | 0.183          | -1.70         |
| 2     | 600     | 1.69           | 0.169          | -1.78         |
| 3     | 900     | 1.58           | 0.158          | -1.85         |
| 4     | 1200    | 1.45           | 0.145          | -1.93         |
| 5     | 1800    | 1.26           | 0.126          | -2.07         |
| 6     | 2400    | 1.11           | 0.111          | -2.20         |
| 7     | 3000    | 1.00           | 0.100          | -2.30         |
| 8     | 3600    | 0.89           | 0.089          | -2.42         |
| 9     | 5400    | 0.71           | 0.071          | -2.65         |
| 10    | 7200    | 0.59           | 0.059          | -2.83         |
| 11    | 10800   | 0.52           | 0.052          | -2.96         |

\[ k_{\text{obs}} = 2.36 \times 10^{-4} \text{ (s}^{-1} \text{)} \]

![Graph 1](image1)

\[ y = -2.36E-04x - 1.61 \]

\[ R^2 = 9.94E-01 \]

![Graph 2](image2)
Table S5. Rate monitoring for the deuteration of ethyl benzoate (run 1)

Following the General Kinetic Protocol using 75.1 mg of ethyl benzoate, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|--------|----------------|----------------|----------------|
| 0     | 0      | 2.00           | 0.200          | -1.61          |
| 1     | 600    | 1.67           | 0.167          | -1.79          |
| 2     | 1200   | 1.40           | 0.140          | -1.97          |
| 3     | 1800   | 1.17           | 0.117          | -2.15          |
| 4     | 2400   | 1.02           | 0.102          | -2.28          |
| 5     | 3000   | 0.91           | 0.091          | -2.40          |
| 6     | 3600   | 0.82           | 0.082          | -2.50          |
| 7     | 7200   | 0.64           | 0.064          | -2.75          |
| 8     | 10800  | 0.58           | 0.058          | -2.85          |
| 9     | 14400  | 0.55           | 0.055          | -2.90          |
| 10    | 18000  | 0.52           | 0.052          | -2.96          |

\[ k_{\text{obs}} = 2.65 \times 10^{-4} \text{ (s}^{-1}) \]

\[ y = -2.65E-04x - 1.61 \]
\[ R^2 = 9.88E-01 \]
Table S6. Rate monitoring for the deuteration of ethyl benzoate (run 2)

Following the General Kinetic Protocol using 75.1 mg of ethyl benzoate, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|---------|----------------|----------------|----------------|
| 0     | 0       | 2.00           | 0.200          | -1.61          |
| 1     | 300     | 1.78           | 0.178          | -1.73          |
| 2     | 600     | 1.63           | 0.163          | -1.81          |
| 3     | 1200    | 1.38           | 0.138          | -1.98          |
| 4     | 1800    | 1.22           | 0.122          | -2.10          |
| 5     | 2400    | 1.06           | 0.106          | -2.24          |
| 6     | 3000    | 0.97           | 0.097          | -2.33          |
| 7     | 3600    | 0.90           | 0.090          | -2.41          |
| 8     | 7200    | 0.75           | 0.075          | -2.59          |
| 9     | 10800   | 0.72           | 0.072          | -2.63          |

\[ k_{\text{obs}} = 2.61 \times 10^{-4} \text{ (s}^{-1}) \]
Table S7. Rate monitoring for the deuteration of 2-phenylpyridine (run 1)

Following the General Kinetic Protocol using 77.6 mg of 2-phenylpyridine, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|---------|----------------|----------------|---------------|
| 0     | 0       | 2.00           | 0.200          | -1.61         |
| 1     | 300     | 1.95           | 0.195          | -1.63         |
| 2     | 600     | 1.88           | 0.188          | -1.67         |
| 3     | 1200    | 1.72           | 0.172          | -1.76         |
| 4     | 1800    | 1.58           | 0.158          | -1.85         |
| 5     | 2400    | 1.44           | 0.144          | -1.94         |
| 6     | 3600    | 1.23           | 0.123          | -2.10         |
| 7     | 4800    | 1.00           | 0.100          | -2.30         |
| 8     | 6000    | 0.93           | 0.093          | -2.38         |
| 9     | 7200    | 0.80           | 0.080          | -2.53         |
| 10    | 9000    | 0.73           | 0.073          | -2.62         |
| 11    | 10800   | 0.65           | 0.065          | -2.73         |

\[ k_{obs} = 1.32 \times 10^{-4} \text{ (s}^{-1}) \]
Table S8. Rate monitoring for the deuteration of 2-phenylpyridine (run 2)

Following the General Kinetic Protocol using 77.6 mg of 2-phenylpyridine, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|---------|----------------|----------------|---------------|
| 0     | 0       | 2.00           | 0.200          | -1.61         |
| 1     | 600     | 1.92           | 0.192          | -1.65         |
| 2     | 1200    | 1.77           | 0.177          | -1.73         |
| 3     | 1800    | 1.67           | 0.167          | -1.79         |
| 4     | 2400    | 1.58           | 0.158          | -1.85         |
| 5     | 3000    | 1.48           | 0.148          | -1.91         |
| 6     | 3600    | 1.40           | 0.140          | -1.97         |
| 7     | 7200    | 1.10           | 0.110          | -2.21         |
| 8     | 10800   | 0.89           | 0.089          | -2.42         |
| 9     | 14400   | 0.71           | 0.071          | -2.65         |

\[ k_{\text{obs}} = 9.90 \times 10^{-5} \text{ (s}^{-1}) \]

![Graph showing the relationship between time and substrate concentration](image1)

![Graph showing the relationship between time and ln(substrate concentration)](image2)
Table S9. Rate monitoring for the deuteration of 2-phenylbenzothiazole (run 1)

Following the General Kinetic Protocol using 105.6 mg of 2-phenylbenzothiazole, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|---------|----------------|----------------|---------------|
| 0     | 0       | 2.00           | 0.200          | -1.61         |
| 1     | 300     | 1.89           | 0.189          | -1.67         |
| 2     | 600     | 1.74           | 0.174          | -1.75         |
| 3     | 1200    | 1.55           | 0.155          | -1.86         |
| 4     | 1800    | 1.33           | 0.133          | -2.02         |
| 5     | 2400    | 1.16           | 0.116          | -2.15         |
| 6     | 3000    | 1.01           | 0.101          | -2.29         |
| 7     | 3600    | 0.92           | 0.092          | -2.39         |
| 8     | 5400    | 0.70           | 0.070          | -2.66         |
| 9     | 7200    | 0.57           | 0.057          | -2.86         |
| 10    | 9000    | 0.54           | 0.054          | -2.92         |
| 11    | 10800   | 0.56           | 0.056          | -2.88         |
| 12    | 12600   | 0.57           | 0.057          | -2.86         |

\[ k_{\text{obs}} = 2.24 \times 10^{-4} \text{ (s}^{-1}\text{)} \]

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\[ y = -2.22E-04x - 1.61 \]

\[ R^2 = 9.98E-01 \]
Table S10. Rate monitoring for the deuteration of 2-phenylbenzothiazole (run 2)

Following the General Kinetic Protocol using 105.6 mg of 2-phenylbenzothiazole, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|---------|----------------|----------------|---------------|
| 0     | 0       | 2.00           | 0.200          | -1.61         |
| 1     | 300     | 1.88           | 0.188          | -1.67         |
| 2     | 600     | 1.71           | 0.171          | -1.77         |
| 3     | 900     | 1.63           | 0.163          | -1.81         |
| 4     | 1200    | 1.49           | 0.149          | -1.90         |
| 5     | 1800    | 1.32           | 0.132          | -2.02         |
| 6     | 2400    | 1.16           | 0.116          | -2.15         |
| 7     | 3000    | 1.02           | 0.102          | -2.28         |
| 8     | 3600    | 0.95           | 0.095          | -2.35         |
| 9     | 7200    | 0.68           | 0.068          | -2.69         |
| 10    | 10800   | 0.53           | 0.053          | -2.94         |
| 11    | 14400   | 0.50           | 0.050          | -3.00         |

\[ k_{\text{obs}} = 2.20 \times 10^{-4} \text{ (s}^{-1}) \]
Table S11. Rate monitoring for the deuteration of 1-phenylpyrazole (run 1)

Following the General Kinetic Protocol using 72.1 mg of 1-phenylpyrazole, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|--------|---------------|----------------|---------------|
| 0     | 0      | 2.00          | 0.200          | -1.61         |
| 1     | 300    | 1.88          | 0.188          | -1.67         |
| 2     | 600    | 1.60          | 0.160          | -1.83         |
| 3     | 900    | 1.42          | 0.142          | -1.95         |
| 4     | 1200   | 1.24          | 0.124          | -2.09         |
| 5     | 1500   | 1.05          | 0.105          | -2.25         |
| 6     | 1800   | 0.93          | 0.093          | -2.38         |
| 7     | 2400   | 0.81          | 0.081          | -2.51         |
| 8     | 3000   | 0.73          | 0.073          | -2.62         |
| 9     | 3600   | 0.61          | 0.061          | -2.80         |
| 10    | 4200   | 0.60          | 0.060          | -2.81         |
| 11    | 4800   | 0.56          | 0.056          | -2.88         |
| 12    | 5400   | 0.56          | 0.056          | -2.88         |
| 13    | 6600   | 0.52          | 0.052          | -2.96         |
| 14    | 7800   | 0.49          | 0.049          | -3.02         |
| 15    | 9000   | 0.47          | 0.047          | -3.06         |

\[ k_{\text{obs}} = 3.97 \times 10^{-4} \text{ (s}^{-1}) \]
Table S12. Rate monitoring for the deuteration of 1-phenylpyrazole (run 2)

Following the General Kinetic Protocol using 72.1 mg of 1-phenylpyrazole, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|---------|----------------|----------------|----------------|
| 0     | 0       | 2.00           | 0.200          | -1.61          |
| 1     | 300     | 1.71           | 0.171          | -1.77          |
| 2     | 600     | 1.43           | 0.143          | -1.94          |
| 3     | 900     | 1.18           | 0.118          | -2.14          |
| 4     | 1200    | 1.03           | 0.103          | -2.27          |
| 5     | 1500    | 0.91           | 0.091          | -2.40          |
| 6     | 1800    | 0.82           | 0.082          | -2.50          |
| 7     | 2400    | 0.72           | 0.072          | -2.63          |
| 8     | 3000    | 0.65           | 0.065          | -2.73          |
| 9     | 3600    | 0.61           | 0.061          | -2.80          |
| 10    | 6000    | 0.57           | 0.057          | -2.86          |

$k_{obs} = 4.84 \times 10^{-4} \text{ (s}^{-1})$
**Table S13.** Rate monitoring for the deuteration of 2-phenylthiazoline (run 1)

Following the General Kinetic Protocol using 81.6 mg of 2-phenylthiazoline, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|---------|----------------|---------------|---------------|
| 0     | 0       | 2.00           | 0.200         | -1.61         |
| 1     | 300     | 1.86           | 0.186         | -1.68         |
| 2     | 1200    | 1.55           | 0.155         | -1.86         |
| 3     | 1800    | 1.39           | 0.139         | -1.97         |
| 4     | 2400    | 1.25           | 0.125         | -2.08         |
| 5     | 3000    | 1.13           | 0.113         | -2.18         |
| 6     | 3600    | 1.06           | 0.106         | -2.24         |
| 7     | 7200    | 0.77           | 0.077         | -2.56         |
| 8     | 10800   | 0.74           | 0.074         | -2.60         |

\[
k_{\text{obs}} = 1.96 \times 10^{-4} \text{ (s}^{-1})
\]
Table S14. Rate monitoring for the deuteration of 2-phenylthiazoline (run 2)

Following the General Kinetic Protocol using 81.6 mg of 2-phenylthiazoline, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|---------|----------------|----------------|----------------|
| 0     | 0       | 2.00           | 0.200          | -1.61          |
| 1     | 300     | 1.81           | 0.181          | -1.71          |
| 2     | 600     | 1.67           | 0.167          | -1.79          |
| 3     | 1200    | 1.43           | 0.143          | -1.94          |
| 4     | 1800    | 1.22           | 0.122          | -2.10          |
| 5     | 2400    | 1.11           | 0.111          | -2.20          |
| 6     | 3000    | 1.00           | 0.100          | -2.30          |
| 7     | 3600    | 0.94           | 0.094          | -2.36          |
| 8     | 5400    | 0.85           | 0.085          | -2.47          |
| 9     | 7200    | 0.78           | 0.078          | -2.55          |

\[ k_{\text{obs}} = 2.47 \times 10^{-4} \text{ (s}^{-1}) \]
Table S15. Rate monitoring for the deuteration of 2-phenyloxazoline (run 1)

Following the General Kinetic Protocol using 73.6 mg of 2-phenyloxazoline, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|---------|----------------|---------------|----------------|
| 0     | 0       | 2.00           | 0.200         | -1.61          |
| 1     | 300     | 1.66           | 0.166         | -1.80          |
| 2     | 600     | 1.37           | 0.137         | -1.99          |
| 3     | 900     | 1.06           | 0.106         | -2.24          |
| 4     | 1200    | 0.87           | 0.087         | -2.44          |
| 5     | 1800    | 0.64           | 0.064         | -2.75          |
| 6     | 2400    | 0.56           | 0.056         | -2.88          |
| 7     | 3000    | 0.51           | 0.051         | -2.98          |
| 8     | 3600    | 0.50           | 0.050         | -3.00          |
| 9     | 5400    | 0.49           | 0.049         | -3.02          |
| 10    | 7200    | 0.48           | 0.048         | -3.04          |

$k_{obs} = 6.57 \times 10^{-4} \, (s^{-1})$

\[ y = -6.57E-04x - 1.61 \quad R^2 = 9.93E-01 \]
Table S16. Rate monitoring for the deuteration of 2-phenyloxazoline (run 2)

Following the General Kinetic Protocol using 73.6 mg of 2-phenyloxazoline, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|---------|----------------|----------------|----------------|
| 0     | 0       | 2.00           | 0.200          | -1.61          |
| 1     | 300     | 1.64           | 0.164          | -1.81          |
| 2     | 600     | 1.43           | 0.143          | -1.94          |
| 3     | 900     | 1.21           | 0.121          | -2.11          |
| 4     | 1200    | 1.05           | 0.105          | -2.25          |
| 5     | 1800    | 0.83           | 0.083          | -2.49          |
| 6     | 2400    | 0.74           | 0.074          | -2.60          |
| 7     | 3000    | 0.65           | 0.065          | -2.73          |
| 8     | 3600    | 0.63           | 0.063          | -2.76          |
| 9     | 5400    | 0.60           | 0.060          | -2.81          |
| 10    | 7200    | 0.57           | 0.057          | -2.86          |
| 11    | 10800   | 0.54           | 0.054          | -2.92          |

\[ k_{\text{obs}} = 5.16 \times 10^{-4} \text{ (s}^{-1}) \]

\[
y = -5.16E-04x - 1.61 \\
R^2 = 9.92E-01
\]
Table S17. Rate monitoring for the deuteration of 1-methyl-2-phenylimidazole (run 1)

Following the General Kinetic Protocol using 79.1 mg of 1-methyl-2-phenylimidazole, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|---------|----------------|----------------|---------------|
| 0     | 0       | 2.00           | 0.200          | -1.61         |
| 1     | 120     | 1.86           | 0.186          | -1.68         |
| 2     | 240     | 1.72           | 0.172          | -1.76         |
| 3     | 360     | 1.64           | 0.164          | -1.81         |
| 4     | 480     | 1.53           | 0.153          | -1.88         |
| 5     | 600     | 1.41           | 0.141          | -1.96         |
| 6     | 900     | 1.22           | 0.122          | -2.10         |
| 7     | 1200    | 1.04           | 0.104          | -2.26         |
| 8     | 1800    | 0.80           | 0.080          | -2.53         |
| 9     | 2400    | 0.62           | 0.062          | -2.78         |
| 10    | 3000    | 0.52           | 0.052          | -2.96         |
| 11    | 3600    | 0.48           | 0.048          | -3.04         |
| 12    | 4800    | 0.44           | 0.044          | -3.12         |
| 13    | 6000    | 0.42           | 0.042          | -3.17         |

\[ k_{\text{obs}} = 5.10 \times 10^{-4} \text{ (s}^{-1}) \]
**Table S18.** Rate monitoring for the deuteration of 1-methyl-2-phenylimidazole (run 2)

Following the General Kinetic Protocol using 79.1 mg of 1-methyl-2-phenylimidazole, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|--------|----------------|----------------|---------------|
| 0     | 0      | 2.00           | 0.200          | -1.61         |
| 1     | 120    | 1.87           | 0.187          | -1.68         |
| 2     | 240    | 1.74           | 0.174          | -1.75         |
| 3     | 360    | 1.67           | 0.167          | -1.79         |
| 4     | 480    | 1.54           | 0.154          | -1.87         |
| 5     | 600    | 1.49           | 0.149          | -1.90         |
| 6     | 900    | 1.28           | 0.128          | -2.06         |
| 7     | 1200   | 1.15           | 0.115          | -2.16         |
| 8     | 1800   | 0.88           | 0.088          | -2.43         |
| 9     | 2400   | 0.74           | 0.074          | -2.60         |
| 10    | 3000   | 0.66           | 0.066          | -2.72         |
| 11    | 3600   | 0.63           | 0.063          | -2.76         |
| 12    | 5400   | 0.56           | 0.056          | -2.88         |
| 13    | 7200   | 0.54           | 0.054          | -2.92         |

\[ k_{obs} = 4.69 \times 10^{-4} \text{ (s}^{-1}) \]

\[
\begin{align*}
\text{y} &= -4.69\times 10^{-4}\times t - 1.61 \\
R^2 &= 9.97\times 10^{-1}
\end{align*}
\]
3.4. Kinetic Data from two substrates kinetic experiments (Intermolecular competition)

Following the Standard Kinetics Protocol, the competing isotope labeling of Ph-DG\(^1\) (0.50 mmol) and Ph-DG\(^2\) (0.50 mmol) using 1 mol % of the Ir-catalyst (0.005 mmol, 8.7 mg) with respect to both substrates were monitored at 50 °C in CDCl\(_3\) by the sampling method and analysed by \(^1\)H NMR spectroscopy.

The concentrations of the Ph-DG substrates (starting materials) were determined by \(^1\)H NMR analysis. The residual proton signal from the site of incorporation (ortho to DG) was compared against that of a site where incorporation did not happen.

The tables and plots below combine the obtained concentration over time data.
Table S19. Rate monitoring for the competing deuteration of acetophenone vs nitrobenzene

| Entry | Time, min | acetophenone integral (H/D) | nitrobenzene integral (H/D) |
|-------|-----------|----------------------------|----------------------------|
|       |           | [Ph-DG$_1$]                | [Ph-DG$_2$]                |
| 0     | 0         | 2.00                       | 2.00                       |
| 1     | 10        | 1.73                       | 1.99                       |
| 2     | 20        | 1.45                       | 1.89                       |
| 3     | 30        | 1.26                       | 1.77                       |
| 4     | 40        | 1.13                       | 1.63                       |
| 5     | 50        | 1.04                       | 1.50                       |
| 6     | 60        | 0.98                       | 1.38                       |
| 7     | 90        | 0.87                       | 1.15                       |
| 8     | 120       | 0.83                       | 0.98                       |
| 9     | 150       | 0.78                       | 0.88                       |

![Graph showing the decrease in substrate concentration over time](image)
Table S20. Rate monitoring for the competing deuteration of 1-phenylpyrazole vs 2-phenylpyridine

| Entry | Time, min | integral (H/D) | [Ph-DG\(^1\)] | integral (H/D) | [Ph-DG\(^2\)] |
|-------|-----------|----------------|----------------|----------------|----------------|
| 0     | 0         | 2.00           | 0.200          | 2.00           | 0.200          |
| 1     | 10        | 1.63           | 0.163          | 1.83           | 0.183          |
| 2     | 20        | 1.45           | 0.145          | 1.69           | 0.169          |
| 3     | 30        | 1.33           | 0.133          | 1.55           | 0.155          |
| 4     | 40        | 1.23           | 0.123          | 1.43           | 0.143          |
| 5     | 50        | 1.19           | 0.119          | 1.34           | 0.134          |
| 6     | 60        | 1.12           | 0.112          | 1.26           | 0.126          |
| 7     | 90        | 0.82           | 0.082          | 0.87           | 0.087          |
| 8     | 120       | 0.69           | 0.069          | 0.62           | 0.062          |
| 9     | 150       | 0.64           | 0.064          | 0.48           | 0.048          |
Table S21. Rate monitoring for the competing deuteration of 2-phenyloxazoline vs 2-phenylthiazoline

| Entry | Time, min | integral (H/D) | [Ph-DG^1] | integral (H/D) | [Ph-DG^2] |
|-------|-----------|----------------|------------|----------------|------------|
| 0     | 0         | 2.00           | 0.200      | 2.00           | 0.200      |
| 1     | 5         | 1.83           | 0.183      | 1.88           | 0.188      |
| 2     | 10        | 1.74           | 0.174      | 1.76           | 0.176      |
| 3     | 20        | 1.59           | 0.159      | 1.57           | 0.157      |
| 4     | 30        | 1.40           | 0.140      | 1.39           | 0.139      |
| 5     | 40        | 1.32           | 0.132      | 1.28           | 0.128      |
| 6     | 50        | 1.20           | 0.120      | 1.18           | 0.118      |
| 7     | 60        | 1.16           | 0.116      | 1.13           | 0.113      |
| 8     | 120       | 1.14           | 0.114      | 1.02           | 0.102      |
| 9     | 180       | 1.03           | 0.103      | 0.97           | 0.097      |

(empty circles used as most of the data points overlapped)
Table S22. Rate monitoring for the competing deuteration of 2-phenyloxazoline vs 2-phenylpyridine

| Entry | Time, min | integral (H/D) | [Ph-DG\(^1\)] | integral (H/D) | [Ph-DG\(^2\)] |
|-------|-----------|----------------|----------------|----------------|----------------|
| 0     | 0         | 2.00           | 0.200          | 2.00           | 0.200          |
| 1     | 10        | 1.71           | 0.171          | 1.93           | 0.193          |
| 2     | 20        | 1.51           | 0.151          | 1.86           | 0.186          |
| 3     | 30        | 1.39           | 0.139          | 1.77           | 0.177          |
| 4     | 40        | 1.3            | 0.130          | 1.68           | 0.168          |
| 5     | 50        | 1.25           | 0.125          | 1.56           | 0.156          |
| 6     | 60        | 1.21           | 0.121          | 1.5            | 0.150          |
| 7     | 90        | 1.17           | 0.117          | 1.34           | 0.134          |
| 8     | 120       | 1.15           | 0.115          | 1.22           | 0.122          |
| 9     | 150       | 1.12           | 0.112          | 1.18           | 0.118          |

![Graph showing the rate monitoring data with time on the x-axis and substrate concentration on the y-axis.](image-url)
Table S23. Rate monitoring for the competing deuteration of 2-phenyloxazoline vs 2-phenylpyridine*

| Entry | Time, min | integral (H/D) 2-phenyloxazoline | [Ph-DG$^1$] | integral (H/D) 2-phenylpyridine | [Ph-DG$^2$] |
|-------|-----------|----------------------------------|-------------|----------------------------------|-------------|
| 0     | 0         | 2.00                             | 0.200       | 2.00                             | 0.200       |
| 1     | 5         | 1.33                             | 0.133       | 1.83                             | 0.183       |
| 2     | 10        | 1.10                             | 0.110       | 1.77                             | 0.177       |
| 3     | 15        | 0.94                             | 0.094       | 1.65                             | 0.165       |
| 4     | 20        | 0.82                             | 0.082       | 1.49                             | 0.149       |
| 5     | 30        | 0.74                             | 0.074       | 1.28                             | 0.128       |
| 6     | 40        | 0.67                             | 0.067       | 1.02                             | 0.102       |
| 7     | 50        | 0.63                             | 0.063       | 0.88                             | 0.088       |
| 8     | 60        | 0.58                             | 0.058       | 0.73                             | 0.073       |
| 9     | 90        | 0.57                             | 0.057       | 0.50                             | 0.050       |
| 10    | 120       | 0.49                             | 0.049       | 0.39                             | 0.039       |
| 11    | 150       | 0.42                             | 0.042       | 0.30                             | 0.030       |

*Reaction performed in the 100 mL Schlenk flask (i.e. with higher excess of D$_2$) showed higher conversion.
Table S24. Rate monitoring for the competing deuteration of nitrobenzene vs ethyl benzoate

| Entry | Time, min | integral (H/D) [Ph-DG^1] | integral (H/D) [Ph-DG^2] |
|-------|-----------|--------------------------|--------------------------|
| 0     | 0         | 2.00                     | 2.00                     |
| 1     | 10        | 1.85                     | 1.99                     |
| 2     | 20        | 1.48                     | 1.97                     |
| 3     | 30        | 1.31                     | 1.94                     |
| 4     | 40        | 1.18                     | 1.89                     |
| 5     | 50        | 1.08                     | 1.84                     |
| 6     | 60        | 1.00                     | 1.81                     |
| 7     | 90        | 0.83                     | 1.68                     |
| 8     | 120       | 0.76                     | 1.56                     |
| 9     | 180       | 0.7                      | 1.36                     |
| 10    | 240       | 0.68                     | 1.23                     |

![Graph showing the rate monitoring for the competing deuteration of nitrobenzene vs ethyl benzoate](image-url)
**Table S25.** Rate monitoring for the competing deuteration of acetophenone vs ethyl benzoate

| Entry | Time, min | Integral (H/D) [Ph-DG$_1$] | Integral (H/D) [Ph-DG$_2$] |
|-------|-----------|----------------------------|----------------------------|
| 0     | 0         | 2.00                       | 2.00                       |
| 1     | 10        | 1.66                       | 1.98                       |
| 2     | 20        | 1.35                       | 1.98                       |
| 3     | 30        | 1.14                       | 1.96                       |
| 4     | 40        | 0.96                       | 1.94                       |
| 5     | 50        | 0.85                       | 1.92                       |
| 6     | 60        | 0.77                       | 1.89                       |
| 7     | 120       | 0.71                       | 1.61                       |
| 8     | 180       | 0.74                       | 1.35                       |
**Table S26.** Rate monitoring for the competing deuteration of 1-methyl-2-phenylimidazole vs 2-phenylpyridine

| Entry | Time, min | integral (H/D) [1-methyl-2-phenylimidazole] | [Ph-DG\(^1\)] | integral (H/D) [2-phenylpyridine] | [Ph-DG\(^2\)] |
|-------|-----------|---------------------------------------------|----------------|-----------------------------------|----------------|
| 0     | 0         | 2.00 | 0.200 | 2.00 | 0.200 |
| 1     | 10        | 1.33 | 0.133 | 1.98 | 0.198 |
| 2     | 20        | 1.04 | 0.104 | 1.88 | 0.188 |
| 3     | 30        | 0.88 | 0.088 | 1.75 | 0.175 |
| 4     | 40        | 0.76 | 0.076 | 1.62 | 0.162 |
| 5     | 50        | 0.73 | 0.073 | 1.49 | 0.149 |
| 6     | 60        | 0.70 | 0.070 | 1.38 | 0.138 |
| 7     | 90        | 0.69 | 0.069 | 1.13 | 0.113 |
| 8     | 120       | 0.68 | 0.068 | 0.98 | 0.098 |
| 9     | 180       | 0.59 | 0.059 | 0.86 | 0.086 |
Table S27. Rate monitoring for the competing deuteration of 2-phenyloxazoline vs 2-phenylbenzothiazole

| Entry | Time, min | integral (H/D) | [Ph-DG²] | integral (H/D) | [Ph-DG²] |
|-------|-----------|----------------|----------|----------------|----------|
| 0     | 0         | 2.00           | 0.200    | 2.00           | 0.200    |
| 1     | 10        | 1.39           | 0.139    | 1.97           | 0.197    |
| 2     | 20        | 1.10           | 0.110    | 1.96           | 0.196    |
| 3     | 30        | 0.92           | 0.092    | 1.96           | 0.196    |
| 4     | 40        | 0.67           | 0.067    | 1.98           | 0.198    |
| 5     | 50        | 0.58           | 0.058    | 1.97           | 0.197    |
| 6     | 60        | 0.53           | 0.053    | 1.97           | 0.197    |
| 7     | 90        | 0.50           | 0.050    | 1.96           | 0.196    |
| 8     | 150       | 0.50           | 0.050    | 1.95           | 0.195    |
Table S28. Rate monitoring for the competing deuteration of 1-methyl-2-phenylimidazole vs acetophenone

| Entry | Time, min | integral (H/D) | [Ph-DG$^1$] | integral (H/D) | [Ph-DG$^2$] |
|-------|-----------|----------------|-------------|----------------|-------------|
| 0     | 0         | 2.00           | 0.200       | 2.00           | 0.200       |
| 1     | 10        | 1.39           | 0.139       | 1.97           | 0.197       |
| 2     | 20        | 1.10           | 0.110       | 1.96           | 0.196       |
| 3     | 30        | 0.92           | 0.092       | 1.96           | 0.196       |
| 4     | 60        | 0.67           | 0.067       | 1.98           | 0.198       |
| 5     | 90        | 0.58           | 0.058       | 1.97           | 0.197       |
| 6     | 120       | 0.53           | 0.053       | 1.97           | 0.197       |
| 7     | 180       | 0.50           | 0.050       | 1.96           | 0.196       |
Table S29. Rate monitoring for the competing deuteration of 1-methyl-2-phenylimidazole vs 2-phenylbenzothiazole

| Entry | Time, min | integral (H/D) | [Ph-DG$^1$] | integral (H/D) | [Ph-DG$^2$] |
|-------|-----------|---------------|-------------|---------------|-------------|
| 0     | 0         | 2.00          | 0.200       | 2.00          | 0.200       |
| 1     | 10        | 1.39          | 0.139       | 1.97          | 0.197       |
| 2     | 20        | 1.10          | 0.110       | 1.96          | 0.196       |
| 3     | 30        | 0.92          | 0.092       | 1.96          | 0.196       |
| 4     | 60        | 0.67          | 0.067       | 1.98          | 0.198       |
| 5     | 90        | 0.58          | 0.058       | 1.97          | 0.197       |
| 6     | 120       | 0.53          | 0.053       | 1.97          | 0.197       |
| 7     | 180       | 0.50          | 0.050       | 1.96          | 0.196       |
| 8     | 240       | 0.5           | 0.050       | 1.95          | 0.195       |

![Graph of substrate concentration over time](image-url)
**Table S30.** Rate monitoring for the competing deuteration of 2-phenylthiazoline vs nitrobenzene

| Entry | Time, min | integral (H/D) | [Ph-DG\(^1\)] | integral (H/D) | [Ph-DG\(^2\)] |
|-------|-----------|----------------|----------------|----------------|----------------|
| 0     | 0         | 2.00           | 0.200          | 2.00           | 0.200          |
| 1     | 10        | 1.91           | 0.191          | 1.98           | 0.198          |
| 2     | 20        | 1.79           | 0.179          | 1.96           | 0.196          |
| 3     | 30        | 1.63           | 0.163          | 1.97           | 0.197          |
| 4     | 40        | 1.49           | 0.149          | 1.96           | 0.196          |
| 5     | 50        | 1.33           | 0.133          | 1.96           | 0.196          |
| 6     | 60        | 1.22           | 0.122          | 1.96           | 0.196          |
| 7     | 160       | 0.78           | 0.078          | 1.98           | 0.198          |
| 8     | 260       | 0.68           | 0.068          | 1.96           | 0.196          |
Table S31. Rate monitoring for the competing deuteration of 2-phenylpyridine vs acetophenone

| Entry | Time, min | integral (H/D) | [Ph-DG]$^1$ integral (H/D) | [Ph-DG]$^2$ |
|-------|-----------|----------------|-----------------------------|-------------|
| 0     | 0         | 2.00           | 0.200                       | 2.00        |
| 1     | 10        | 1.90           | 0.190                       | 1.99        |
| 2     | 20        | 1.69           | 0.169                       | 1.98        |
| 3     | 30        | 1.58           | 0.158                       | 1.99        |
| 4     | 40        | 1.39           | 0.139                       | 1.97        |
| 5     | 50        | 1.27           | 0.127                       | 1.98        |
| 6     | 60        | 1.16           | 0.116                       | 1.96        |
| 7     | 90        | 0.88           | 0.088                       | 1.97        |
| 8     | 120       | 0.75           | 0.075                       | 1.96        |
| 9     | 180       | 0.66           | 0.066                       | 1.94        |
3.5. Kinetic Data for substrates with two directing groups (Intramolecular competition)

Following the Standard Kinetics Protocol, the intramolecular competing isotope labeling of the substrate bearing both directing groups $\text{DG}^1$ and $\text{DG}^2$ (0.50 mmol) using 1 mol % of the Ir-catalyst (0.005 mmol, 8.7 mg) were monitored at 50 °C in CDCl₃ by the sampling method and analysed by $^1$H NMR spectroscopy.

The residual proton signal from the site of incorporation ($\text{ortho}$ to DG) was compared against that of a site where incorporation did not happen. The tables and plots below combine the obtained integral change of the protons ($H_A$ and $H_B$) $\text{ortho}$ to the directing groups over time.
Table S32. Rate monitoring for the competing deuteration of 4-nitroacetophenone

| Entry | Time, min | $\text{H}_\text{A} (\text{COCH}_3)$ | $\text{H}_\text{B} (\text{NO}_2)$ |
|-------|-----------|----------------------------------|----------------------------------|
| 0     | 0         | 2.00                             | 2.00                             |
| 1     | 10        | 1.52                             | 1.90                             |
| 2     | 20        | 1.31                             | 1.76                             |
| 3     | 30        | 1.15                             | 1.55                             |
| 4     | 40        | 1.07                             | 1.40                             |
| 5     | 50        | 1.01                             | 1.27                             |
| 6     | 60        | 0.97                             | 1.16                             |
| 7     | 90        | 0.44                             | 0.71                             |
| 8     | 120       | 0.27                             | 0.43                             |
| 9     | 180       | 0.21                             | 0.29                             |
| 10    | 240       | 0.15                             | 0.23                             |
| 11    | 300       | 0.11                             | 0.15                             |
| 12    | 360       | 0.10                             | 0.12                             |

![Graph showing the integral of $\text{H}_\text{A}$ to $\text{H}_\text{B}$ over time](image-url)
Table S33. Rate monitoring for the competing deuteration of ethyl 4-nitrobenzoate

| Entry | Time, min | $H_A$ (NO$_2$) | $H_B$ (CO$_2$Et) |
|-------|-----------|----------------|-----------------|
| 0     | 0         | 2.00           | 2.00            |
| 1     | 10        | 1.64           | 1.80            |
| 2     | 20        | 1.47           | 1.63            |
| 3     | 30        | 1.36           | 1.51            |
| 4     | 60        | 1.10           | 1.19            |
| 5     | 90        | 0.96           | 1.03            |
| 6     | 120       | 0.91           | 0.93            |
| 7     | 180       | 0.85           | 0.88            |
| 8     | 240       | 0.83           | 0.85            |

![Graph showing the rate monitoring of the competing deuteration of ethyl 4-nitrobenzoate](image)
Table S34. Rate monitoring for the competing deuteration of ethyl 4-acetylbenzoate

| Entry | Time, min | $H_A$ (COCH$_3$) | $H_B$ (CO$_2$Et) |
|-------|-----------|------------------|------------------|
| 0     | 0         | 2.00             | 2.00             |
| 1     | 5         | 1.49             | 1.97             |
| 2     | 10        | 1.26             | 1.91             |
| 3     | 20        | 1.05             | 1.62             |
| 4     | 30        | 0.93             | 1.38             |
| 5     | 40        | 0.82             | 1.20             |
| 6     | 50        | 0.79             | 1.03             |
| 7     | 60        | 0.72             | 0.92             |
| 8     | 90        | 0.61             | 0.67             |
| 9     | 120       | 0.44             | 0.51             |
| 10    | 150       | 0.33             | 0.38             |
| 11    | 180       | 0.29             | 0.31             |
**Table S35.** Rate monitoring for the competing deuteration of 2-(4-acetyl)phenyloxazoline

| Entry | Time, min | $H_A$ (oxazoline) | $H_B$ (COCH$_3$) |
|-------|-----------|-------------------|------------------|
| 0     | 0         | 2.00              | 2.00             |
| 1     | 10        | 1.46              | 2.00             |
| 2     | 20        | 1.12              | 2.00             |
| 3     | 30        | 0.96              | 1.99             |
| 4     | 60        | 0.69              | 1.98             |
| 5     | 90        | 0.57              | 1.98             |
| 6     | 120       | 0.52              | 1.99             |
| 7     | 180       | 0.50              | 1.98             |
| 8     | 240       | 0.51              | 1.98             |

[Graph showing the integral $H_A$/H$_B$ over time]
Table S36. Rate monitoring for the competing deuteration of 2-(4-nitrophenyl)-4,5-dihydrothiazole

| Entry | Time, min | $H_A$ (thiazoline) | $H_B$ (NO$_2$) |
|-------|-----------|-------------------|----------------|
| 0     | 0         | 2.00              | 2.00           |
| 1     | 5         | 1.93              | 2.00           |
| 2     | 10        | 1.89              | 1.99           |
| 3     | 20        | 1.77              | 1.99           |
| 4     | 30        | 1.69              | 1.99           |
| 5     | 40        | 1.60              | 1.99           |
| 6     | 50        | 1.52              | 1.99           |
| 7     | 60        | 1.42              | 1.99           |
| 8     | 90        | 1.25              | 1.99           |
| 9     | 120       | 1.09              | 1.99           |
| 10    | 180       | 0.81              | 1.99           |
| 11    | 240       | 0.65              | 1.99           |
| 12    | 300       | 0.53              | 1.99           |
| 13    | 360       | 0.42              | 1.99           |
Table S37. Rate monitoring for the competing deuteration of 2-(4-(Pyridin-2-yl)phenyl)-4,5-dihydrooxazole

| Entry | Time, min | $H_A$ (oxazoline) | $H_B$ (pyridine) |
|-------|-----------|------------------|------------------|
| 0     | 0         | 2.00             | 2.00             |
| 1     | 5         | 1.74             | 1.96             |
| 2     | 10        | 1.54             | 1.94             |
| 3     | 20        | 1.36             | 1.89             |
| 4     | 30        | 1.18             | 1.78             |
| 5     | 40        | 1.06             | 1.66             |
| 6     | 50        | 1.03             | 1.60             |
| 7     | 60        | 1.01             | 1.54             |
| 8     | 120       | 0.98             | 1.26             |
| 9     | 180       | 0.96             | 1.14             |
| 10    | 240       | 0.94             | 1.11             |
3.6. Hammett plot

Table S38. Rate constants for deuteration of substituted acetophenones and Hammett parameters

| X    | $k_{obs}$ (s$^{-1}$) | log ($k_X/k_H$) | $\sigma_p$ | $\sigma_{p-}$ | $\sigma_{p+}$ |
|------|---------------------|-----------------|------------|---------------|---------------|
| H    | $3.93 \times 10^{-4}$ | 0.00            | 0          | 0.00          | 0             |
| OMe  | $8.06 \times 10^{-4}$ | 0.31            | -0.27      | -0.26         | -0.78         |
| Br   | $8.52 \times 10^{-4}$ | 0.34            | 0.23       | 0.25          | 0.15          |
| F    | $8.46 \times 10^{-4}$ | 0.33            | 0.54       | 0.65          | 0.61          |
| CF$_3$ | $9.34 \times 10^{-4}$ | 0.38            | 0.06       | -0.03         | -0.07         |
| NO$_2^a$ | $2.93 \times 10^{-4}$ | -0.13           | 0.78       | 1.27          | 0.79          |
| CO$_2$Et$^a$ | $8.11 \times 10^{-4}$ | 0.31            | 0.45       | 0.75          | n/a           |

$^a$Approx. $k_{obs}$ calculated from intramolecular kinetics data (see Tables S30 and S32)

![Graphs showing Hammett plots for different substitutions](image-url)
**Table S39.** Rate monitoring for the deuteration of p-methoxy acetophenone

Following the General Kinetic Protocol using 75.1 mg of p-methoxy acetophenone, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|---------|----------------|----------------|----------------|
| 0     | 0       | 2.00           | 0.20           | -1.61          |
| 1     | 300     | 1.51           | 0.15           | -1.89          |
| 2     | 600     | 1.15           | 0.12           | -2.16          |
| 3     | 1200    | 0.72           | 0.07           | -2.63          |
| 4     | 1800    | 0.50           | 0.05           | -3.00          |
| 5     | 2400    | 0.41           | 0.04           | -3.19          |
| 6     | 3000    | 0.36           | 0.04           | -3.32          |
| 7     | 3600    | 0.36           | 0.04           | -3.32          |
| 8     | 5400    | 0.36           | 0.04           | -3.32          |
| 9     | 9000    | 0.32           | 0.03           | -3.44          |

\[ k_{\text{obs}} = 8.06 \times 10^{-4} \text{ (s}^{-1}) \]
Table S40. Rate monitoring for the deuteration of $p$-bromo acetophenone

Following the General Kinetic Protocol using 99.5 mg of $p$-bromo acetophenone, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D), | [Substrate], M | ln [Substrate] |
|-------|---------|----------------|----------------|----------------|
| 0     | 0       | 2.00           | 0.20           | -1.61          |
| 1     | 300     | 1.51           | 0.15           | -1.89          |
| 2     | 600     | 1.20           | 0.12           | -2.12          |
| 3     | 900     | 0.90           | 0.09           | -2.41          |
| 4     | 1200    | 0.74           | 0.07           | -2.60          |
| 5     | 1800    | 0.58           | 0.06           | -2.85          |
| 6     | 2400    | 0.52           | 0.05           | -2.96          |
| 7     | 3000    | 0.48           | 0.05           | -3.04          |
| 8     | 3600    | 0.45           | 0.05           | -3.10          |

$k_{obs} = 8.52 \times 10^{-4} \text{ (s}^{-1})$

![Graph showing substrate concentration vs time and ln(substrate) vs time with linear fit equations and R^2 values]
Table S41. Rate monitoring for the deuteration of \( p \)-fluoro acetophenone

Following the General Kinetic Protocol using 69.1 mg of \( p \)-fluoro acetophenone, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|---------|----------------|----------------|----------------|
| 0     | 0       | 2.00           | 0.20           | -1.61          |
| 1     | 300     | 1.38           | 0.14           | -1.98          |
| 2     | 600     | 1.00           | 0.10           | -2.30          |
| 3     | 900     | 0.85           | 0.09           | -2.47          |
| 4     | 1200    | 0.72           | 0.07           | -2.63          |
| 5     | 1800    | 0.59           | 0.06           | -2.83          |
| 6     | 2400    | 0.53           | 0.05           | -2.94          |
| 7     | 3000    | 0.50           | 0.05           | -3.00          |
| 8     | 3600    | 0.50           | 0.05           | -3.00          |

\[ k_{\text{obs}} = 9.34 \times 10^{-4} \text{ (s}^{-1}) \]

\[
y = -9.34 \times 10^{-4} x - 1.61 \\
R^2 = 0.63 \\
\]
Table S42. Rate monitoring for the deuteration of \( p \)-trifluoromethyl acetophenone

Following the General Kinetic Protocol using 94.1 mg of \( p \)-trifluoromethyl acetophenone, 8.7 mg of Ir-catalyst.

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|---------|----------------|----------------|----------------|
| 0     | 0       | 2.00           | 0.20           | -1.61          |
| 1     | 300     | 1.44           | 0.14           | -1.94          |
| 2     | 600     | 1.16           | 0.12           | -2.15          |
| 3     | 900     | 0.92           | 0.09           | -2.39          |
| 4     | 1200    | 0.76           | 0.08           | -2.58          |
| 5     | 1800    | 0.60           | 0.06           | -2.81          |
| 6     | 2400    | 0.53           | 0.05           | -2.94          |
| 7     | 3000    | 0.52           | 0.05           | -2.96          |
| 8     | 3600    | 0.48           | 0.05           | -3.04          |

\( k_{\text{obs}} = 8.46 \times 10^{-4} \text{ (s}^{-1}) \)

\( y = -8.46 \times 10^{-4} x - 1.61 \)
\( R^2 = 9.90 \times 10^{-1} \)
Table S43. Rate monitoring for the deuteration of $\rho$-nitro acetophenone
(for all data points see Table S30)

| Entry | Time, s | Integral (H/D) \([\text{Substrate}]\), M | ln [Substrate] |
|-------|--------|---------------------------------|----------------|
| 0     | 0      | 2.00                           | -1.61          |
| 1     | 600    | 1.52                           | -1.88          |
| 2     | 1200   | 1.31                           | -2.03          |
| 3     | 1800   | 1.15                           | -2.16          |
| 4     | 2400   | 1.07                           | -2.23          |
| 5     | 3000   | 1.01                           | -2.29          |
| 6     | 3600   | 0.97                           | -2.33          |
| 7     | 5400   | 0.44                           | -3.12          |

$k_{\text{obs}} = 3.31 \times 10^{-4} \text{ (s}^{-1})$
Table S44. Rate monitoring for the deuteration of $p$-CO$_2$Et acetophenone
(for all data points see Table S30)

| Entry | Time, s | Integral (H/D) | [Substrate], M | ln [Substrate] |
|-------|---------|----------------|----------------|----------------|
| 0     | 0       | 2.00           | 0.20           | -1.61          |
| 1     | 300     | 1.49           | 0.15           | -1.90          |
| 2     | 600     | 1.26           | 0.13           | -2.07          |
| 3     | 1200    | 1.05           | 0.11           | -2.25          |
| 4     | 1800    | 0.93           | 0.09           | -2.38          |
| 5     | 2400    | 0.82           | 0.08           | -2.50          |
| 6     | 3000    | 0.79           | 0.08           | -2.54          |
| 7     | 3600    | 0.72           | 0.07           | -2.63          |
| 8     | 5400    | 0.61           | 0.06           | -2.80          |

$k_{obs} = 8.11 \times 10^{-4}$ (s$^{-1}$)

![Graph showing the relationship between time and substrate concentration](image)

$y = -8.11E-04x - 1.61$

$R^2 = 9.76E-01$
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