# Iridium-catalyzed Csp³-H Activation for Mild and Selective Hydrogen Isotope Exchange

William J. Kerr,*,[†] Richard J. Mudd,[†] Marc Reid,[†] Jens Atzrodt,[‡] and Volker Derdau[‡]

[†]Department of Pure & Applied Chemistry, WestCHEM, University of Strathclyde, Glasgow G1 1XL, Scotland, UK.

[‡]Integrated Drug Discovery, Isotope Chemistry, Sanofi-Aventis Deutschland GmbH, Industriepark Hoechst, Frankfurt, Germany.

**ABSTRACT:** The increasing demand for isotopically labeled compounds has provided appreciable impetus for the development of improved methods for the late stage introduction of isotopes of hydrogen (deuterium or tritium). Moreover, sp³-rich molecules are becoming increasingly common in the exploration of chemical space for drug design. Herein, we report an efficient iridium(I) catalysed C-H activation method for the hydrogen isotope exchange of sp³ C-H bonds. A wide range of substrates have been labeled, including active pharmaceutical ingredients, delivering excellent levels of isotope incorporation and predictable regiocontrol, with low catalyst loadings, in short reaction times, and under mild reaction conditions.

KEYWORDS: C-H activation, iridium, isotopes, homogeneous catalysis, heterocycles.

Transition metal-mediated C-H activation has received significant attention in recent years, and continues to produce prominent new methods for complex chemical synthesis.[1] Despite such widespread use, the majority of applications are aimed towards sp² C-H bonds, which are intrinsically more readily activated, with considerably fewer applications targeting the activation of sp³ C-H bonds. Furthermore, iridium-catalyzed sp³ C-H activation processes are rare,[1o,2,3] with reported catalytic applications focused upon alkylation,[3a,e] alkenylation,[3b,c] oxidation,[3d] and amidation.[3f] However, in the majority of these cases, high temperatures and extended reaction times are required. In relation to this, hydrogen isotope exchange (HIE) provides a fundamental basis for the investigation of new C-H activation processes, as well as providing a means of generating valuable, specifically deuterated molecular units for mechanistic studies.[4] Additionally, such flexible and direct methods of producing isotopically-labeled compounds are of appreciable importance for the pharmaceutical industry, especially within absorption, distribution metabolism, excretion, toxicity, and stability (ADMETS) studies of active pharmaceutical ingredients (APIs).[4a,5]

Inspired by the structural architecture of Crabtree's catalyst,[6,7] we developed a series of iridium(I) complexes of the type [(COD)Ir(IMes)(PR₃)]X, capable of delivering heavy isotopes of hydrogen (deuterium, D, and tritium, T) to aromatic and olefinic compounds via a directed sp² C-H activation process, under mild conditions and short reaction times with a plethora of directing groups (Scheme 1, (a)).[8-10] Complementary to the directing group approach, the growing interest in this area of research is further exemplified by recent reports detailing iron,[11a] cobalt,[11b] and photoredox[12] catalysis methods for the introduction of an isotopic label at sterically unencumbered aryl (sp²) and oxidatively active alkyl (sp³) positions, respectively (Scheme 1 (b) and (c)). Accordingly, a general method for the directed introduction of a hydrogen isotope at sp³ centers would deliver this previously unmet requirement, whilst also having the potential to provide further insight into sp³ C-H activation processes. Following the recent
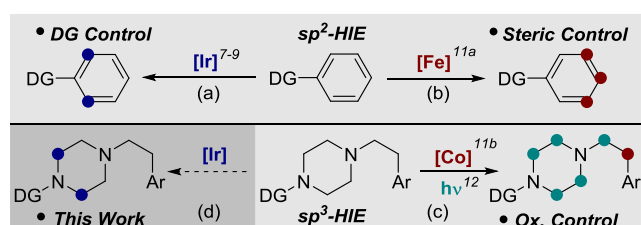


**Scheme 1. Complementary approaches to hydrogen isotope exchange.**

disclosure of methylene labelling in a range of amides,[3g] we now report the selective C-H activation and hydrogen isotope exchange on sp³ centers utilizing our developed iridium(I) NHC/phosphine complexes as directed by a range of pharmaceutically-relevant heterocyclic units, in turn expanding the utility of these catalysts and providing expedient access to a new range of important labeled chemical entities (Scheme 1 (d)).

Our studies commenced with the application of a range of developed iridium(I) complexes **1a-1e**, as well as Crabtree's catalyst **1f** and related BArF analogue **1g**, in a HIE reaction using commercially available 4-(pyridine-2-yl)morpholine **2**, as a typical, drug-like heterocyclic motif.[13] Pleasingly, when applying the NHC/phosphine complex **1a**, we observed selective D-incorporation at the four positions α to the morpholine nitrogen only (Table 1, Entry 1). This incorporation was improved to deliver excellent levels of labeling by utilizing complex **1b** bearing the less coordinating BArF counterion (Table 1, Entry 2).[8e,h,j] Further manipulation of the iridium complex by variation of the phosphine ligand resulted in a small decrease in D-incorporation (Table 1, Entries 3 and 4). Also, despite its reported use in sp² HIE,[9a-c] the neutral complex **1e** proved to be inactive for sp³ exchange under these conditions (Table 1, Entry 5). Similarly, the smaller ligand sphere of Crabtree catalysts **1f** and **1g** delivered only low levels of D-incorporation (Table 1, Entries 6 and 7). With catalyst **1b** selected for further exploration of reaction parameters, we

**Table 1. Screening of Catalysts 1a-g.**[a]
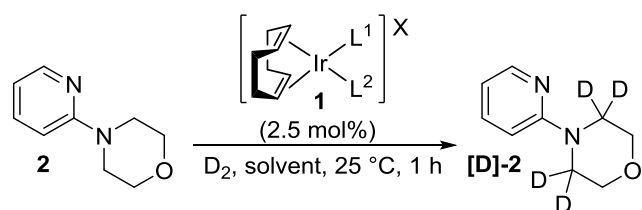


| Entry | L¹, L², X[b] | Catalyst | Solvent | %D[c] |
|-------|-------------|----------|---------|-------|
| 1 | IMes, PPh₃, PF₆ | **1a** | DCM | 79 |
| 2 | IMes, PPh₃, BAr^F | **1b** | DCM | 90 |
| 3 | IMes, PBn₃, BAr^F | **1c** | DCM | 85 |
| 4 | IMes, PMePh₂, BAr^F | **1d** | DCM | 78 |
| 5 | IMes, Cl | **1e** | DCM | 0 |
| 6 | Py, PCy₃, PF₆ | **1f** | DCM | 24 |
| 7 | Py, PCy₃, BAr^F | **1g** | DCM | 26 |
| 8 | IMes, PPh₃, BAr^F | **1b** | tAmylOH | 76 |
| 9 | IMes, PPh₃, BAr^F | **1b** | MTBE | 87 |
| 10 | IMes, PPh₃, BAr^F | **1b** | tBuOAc | 86 |

[a]Each entry displayed is the average of two reaction runs. Conditions: **2** (0.086 mmol), solvent (1 mL), catalyst (0.00215 mmol). [b]BAr^F = tetrakis(3,5-triflouromethylphenyl)borate. [c]Percentage deuterium incorporation calculated from LCMS, with the position confirmed by ¹H NMR spectroscopy.

examined the flexibility of the reaction medium, understanding that many APIs are not soluble in DCM. Encouragingly, the reaction could be performed in a range of alcohol, ether and ester-derived solvents, with only a slight reduction in D-incorporation when applying *t*-amyl alcohol, MTBE or *t*-BuOAc (Table 1, Entries 8-10) (see ESI for full range of solvents tested).

Subsequent investigations examined the reaction conditions thoroughly, applying a design of experiments (DoE) approach[14] to optimization of the labelling process using catalyst **1b** with substrate **2** in DCM. To this end, we applied a three-factor, two-level, full factorial design investigating the catalyst loading, reaction time, and reaction volume (see ESI for full details). This study clearly demonstrated that catalyst loading, and to a lesser extent reaction time, influenced the D-incorporation. Additionally, increasing the reaction volume was found to have a small positive effect upon the result, indicating that substrate complexation and subsequent product decomplexation influences the catalyst turnover,[15] in accordance with our mechanistic observations in sp²-HIE systems.[8d]

Following a detailed examination of the results garnered from the DoE, an optimized protocol using notably low catalyst loadings for sp³ C-H activation and HIE was developed (Scheme 2, Conditions A: **1b** (1 mol%), D₂, DCM (1 mL), 1

h), and applied to a range of saturated heterocyclic substrates (Scheme 2a). Initial studies focused on the influence that other *N*-heterocycles had when acting as a directing group for the C-H activation. Beyond previously applied pyridine substrate **2**, exchange was facilitated well with pyrimidine, quinoline, and isoquinoline directing groups, delivering ≥94% D-incorporation across the four specific C-H labeling sites of the morpholine ring in **3-5**. In addition to the sp³-exchange, D-incorporation was observed at positions *ortho* to the nitro and ester directing groups in **6** and **7**. Pleasingly, the sp³-exchange was preferred in the case of ester **7**, presumably because the greater Lewis basicity of the *N*-heterocyclic directing group favors coordination to the catalyst and subsequent sp³-exchange. This hypothesis is further supported by the example of *N*-acetyl morpholine **8**, where, under the optimized conditions, no D-incorporation was observed, and heating the reaction (5 mol% **1b**, D₂, MTBE, 50 °C, 3 h) resulted in only minimal incorporation.

Similar trends were observed within piperidine-derived substrates **9** and **11-15**, with consistently high D-incorporation being obtained (Scheme 2b). The level of labeling with thiazole **10** remained high despite the anticipated increase in ring strain present in the cyclometallated intermediate with this 5-membered directing heterocycle. Notably, compound **14** is insoluble in DCM, but the broad solvent compatibility of catalyst **1b** allowed this substrate to be labeled in 2-MeTHF, resulting in good levels of D-incorporation. In addition, where the axial and equatorial protons can be distinguished by ¹H NMR spectroscopy (**11-15**), the equatorial exchange is favored slightly, plausibly indicating a stronger agostic interaction between the catalyst and the equatorial C-H bond.

Following successful application to a range of morpholines and piperidines, we applied optimized Conditions A to piperazines (Scheme 2c), with initial results yielding lowered levels of D-incorporation (Conditions A, **16-20**). However, we observed that when the free amine was converted to an *N*-methyl unit, high incorporations were re-established (**19** vs **21**, and **20** vs **22**). Therefore, the decreased activity of these compounds clearly relates to an interaction between the free amine and catalyst, generating a different species from the active catalyst, as has been observed by ³¹P NMR spectroscopy (see ESI for full details).[16] However, since the exchange process still continues, albeit to a lesser degree, the unreactive complex is presumed to form reversibly.

With this information in hand, we applied a second DoE phase, this time utilizing 1-(pyridin-2-yl)piperazine **16** as a reference substrate, to develop conditions that would facilitate exchange without protection of the piperazine. This DoE approach returned a similar dependency upon catalyst loading, reaction time, and reaction volume (see ESI for full details), and provided a second protocol (Conditions B: 5 mol% **1b**, D₂, DCM (1 mL), 3 h). Pleasingly, under the newly developed conditions, high levels of D-incorporation were observed and, crucially, without protection of piperazines **16-20**.

Keen to develop a general protocol for the labeling of saturated *N*-heterocycles, we next considered the effect of changing the size of the ring being labeled (Scheme 2d). Under Conditions A, HIE occurs to deliver a moderate D-incorporation within both azepane **23** and pyrrolidine **24**, but with no incorporation in azetidine **25**. In contrast, by utilizing Conditions B, high levels of D-incorporation can be achieved
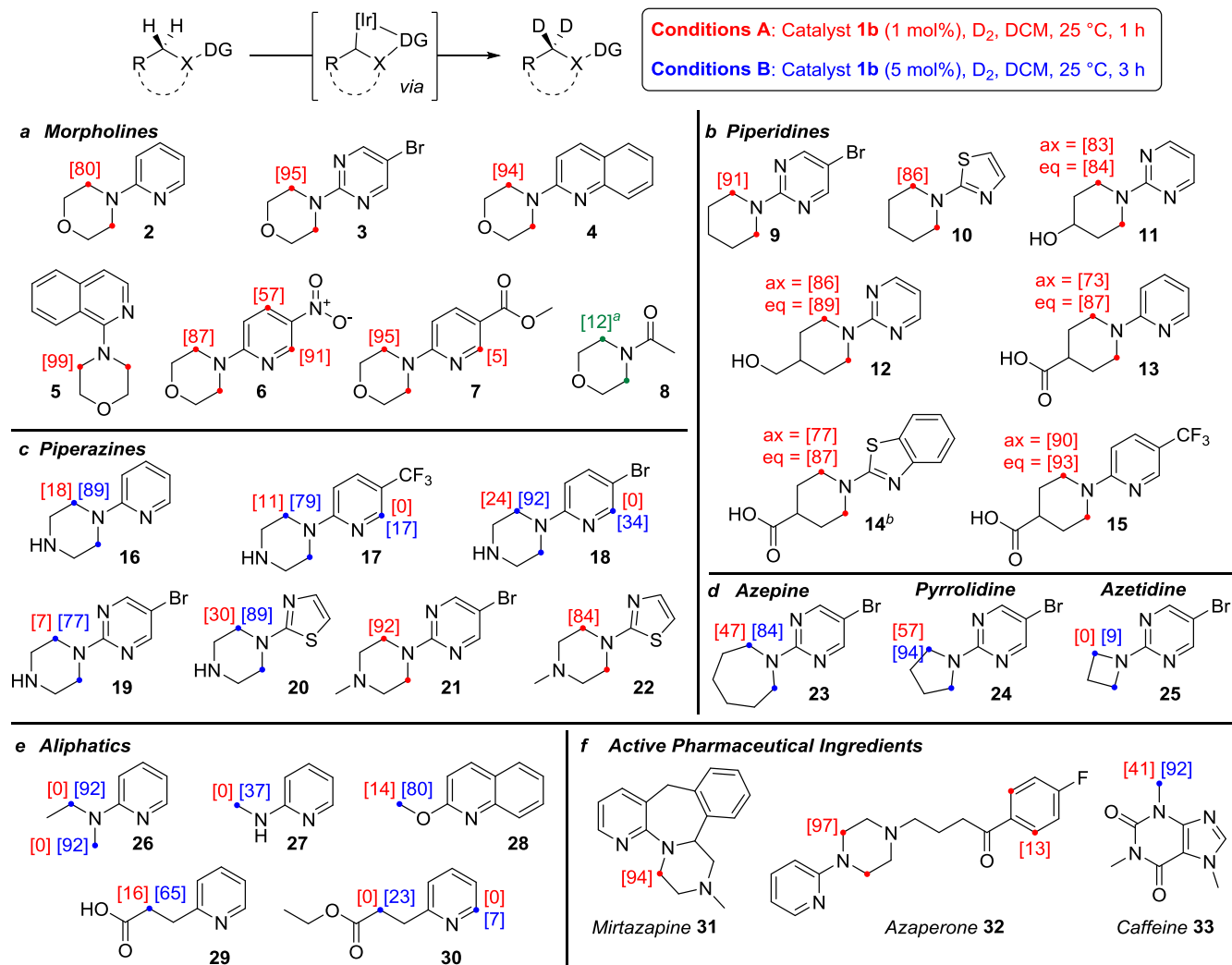
**Scheme 2. Hydrogen isotope exchange on saturated *N*-heterocycles.** Conditions A or B with substrate (0.086 mmol) in DCM (1 mL). Percentage deuterium incorporation at each site calculated by ^{1}H NMR spectroscopy. [a]1b (5 mol%), MTBE, 50 °C, 3 h. [b]Reaction performed in 2-MeTHF instead of DCM.

in **23** and **24**, and a small level of labelling is evolved in **25**. This series indicates that the heterocycle ring size can affect the efficiency of the HIE process, presumably by influencing the strain in the metallacyclic intermediate following C-H activation.

Following our success with saturated heterocycles, we next turned our attention to non-cyclic substrate components (Scheme 2e). Initial reactions with *N*-ethyl-*N*-methylpyridin-2-amine **26** and *N*-methylpyridin-2-amine **27** delivered no incorporation, and *O*-methylquinoline **28** showed only low levels of exchange on the *O*-methyl group. Accordingly, we turned to our second protocol, Conditions B, which gave high levels of incorporation at both the methyl- and methylene positions of **26**, and the *O*-methyl of **28**. In contrast, substrate **27** underwent only moderate levels of exchange, perhaps due to the unprotected secondary amine. Next, we examined several substrates with sp[3] C-H bonds which do not possess an α-heteroatom, but which instead are adjacent to acid and ester functionalities (**29-30**). Under Conditions B, somewhat more moderate levels of D-incorporation were observed at the site arising from C-H activation via a 5-membered metallocycle.

Having established the utility of our labelling process on a broad range of heterocycles and acyclic substrates, we applied the developed method to several commercially available drug compounds (Scheme 2f). The anti-depressant *Mirtazapine* **31** does not contain any sp[2] centers which could be labelled via directed HIE, however its pyridine nitrogen could direct sp[3] labelling. Applying conditions A, we were pleased to observe a high D-incorporation of 94% on the piperazine ring. Similarly, a high incorporation was obtained on the piperazine ring of the tranquilizer *Azaperone* **32**, and notably with excellent selectivity versus the *ortho* sp[2]-exchange directed by the ketone. Finally, application of conditions B to the stimulant *Caffeine* **33** resulted in a highly selective labelling at the 7-methyl position, directed by the imidazole nitrogen.

We next looked to investigate the mechanism through which the exchange occurs. Firstly, we confirmed a homogeneous catalysis process by continuation of the reaction in the presence of metallic mercury.[17] Secondly, a mechanism involving more than one molecule of catalyst during the rate determining step was discounted, by observing a first order rate dependence with respect to catalyst (see ESI for full details). Finally, by measuring the rate of reaction for both the

installation and removal of deuterium (Scheme 3), a kinetic isotope effect of 3.22 was established, which indicates an iridium-mediated C-H activation as the rate determining step.[18]
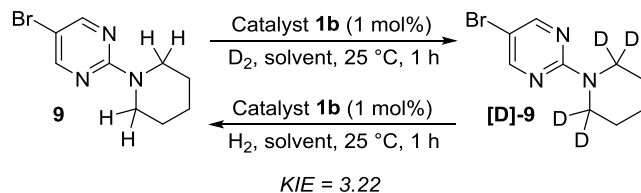


**Scheme 3. Kinetic isotope studies.**

Taken together, these pieces of experimental evidence are consistent with our mechanistic observations in the sp$^2$ C-H activation and hydrogen isotope exchange catalyzed by complexes of type **1a-e**.[8d,9b] As a result, it is plausible to propose a similar mechanistic pathway (Scheme 4), beginning with activation of the pre-catalyst **1** to the key iridium(III) dihydride intermediate **I**. Displacement of solvent and coordination of substrate, including the key agostic interaction with the exchange site, delivers **II**. Subsequent C-H insertion results in metallacycle **III**, followed by deuterium-hydrogen fluxionality affording complex **IV**. This intermediate can then undergo C-D bond formation to generate **V**, prior to product decomplexation and regeneration of active intermediate **I**.



S = loosely bound solvent or deuterium molecule.
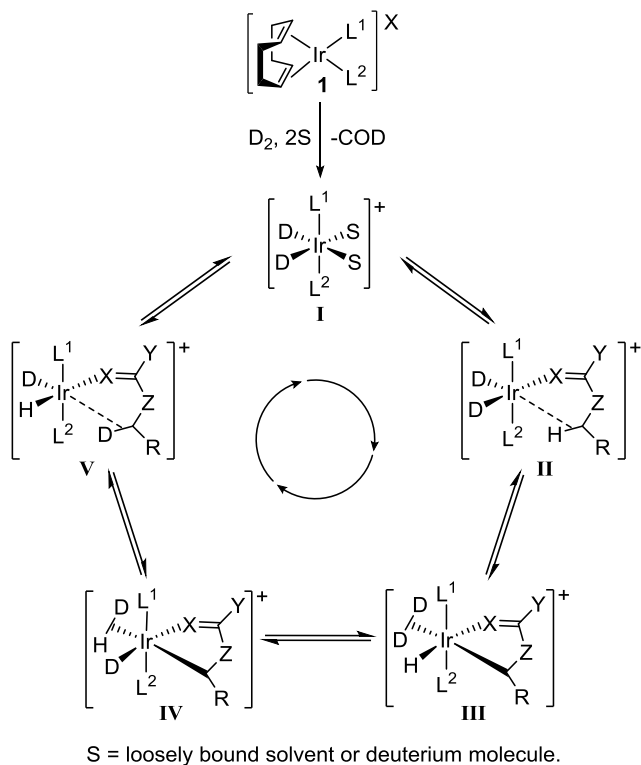
**Scheme 4. Proposed mechanism for sp$^3$-hydrogen isotope exchange.**

To conclude, we have developed new protocols for directed and selective hydrogen isotope exchange at sp$^3$ C-H centers, resulting in high levels of D-incorporation with low catalyst loadings and under mild reaction conditions. Exploration of a broad variety of substrates has shown the protocols to be efficient and reliable across a wide range of saturated het-erocycles and aliphatic units. Application of the labelling conditions to commercial drug compounds also results in high levels of exchange selective for sp$^3$ positions. Beyond the substrate scope, we have investigated the mechanism of this process, providing evidence for a pathway proceeding *via* sp$^3$-C-H activation as the rate determining step. Further work is underway in our laboratory to further explore the sp$^3$-HIE of complex molecules and these studies will be reported in due course.

## AUTHOR INFORMATION

### Corresponding Author
*Email: w.kerr@strath.ac.uk

### Notes
The authors declare no competing financial interest.

## ASSOCIATED CONTENT

Details of experimental procedures and computational methods can be found in the Electronic Supporting Information (ESI). This material is available free of charge via the Internet at http://pubs.acs.org.

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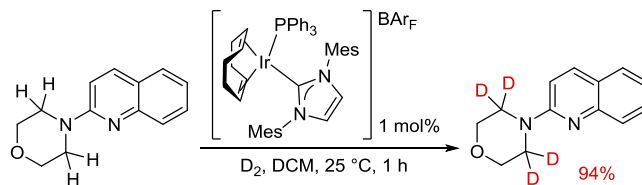


· High deuterium incorporation (up to 99%)
· Mild reaction conditions
· >30 examples (including drug compounds)
· Selectivity over aromatic labeling

**Supporting Information:**

# Iridium-catalyzed Csp$^3$-H Activation for Mild and Selective Hydrogen Isotope Exchange

William J. Kerr,[*,†] Richard J. Mudd,[†] Marc Reid,[†] Jens Atzrodt[‡] and Volker Derdau[‡]

[†]Department of Pure and Applied Chemistry, WestCHEM, University of Strathclyde, Glasgow, G1 1XL, Scotland, UK.

[‡]Integrated Drug Discovery, Isotope Chemistry, Sanofi-Aventis Deutschland GmbH, Industriepark Hoechst, Frankfurt, Germany
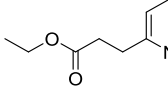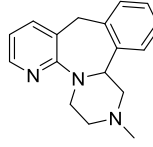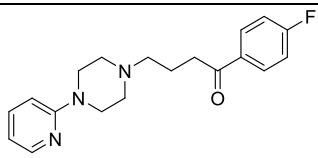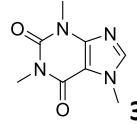
* w.kerr@strath.ac.uk

# Contents

# 1. General experimental information

All reagents were obtained from commercial suppliers (**Table S1**) and used without further purification, unless otherwise stated. Purification was carried out according to standard laboratory methods.

**Table S1**. Starting materials and suppliers.

| Entry | Structure | Supplier / Synthesis |
|-------|-----------|----------------------|
| 1 | **1a** | Strem |
| 2 | **1b** | Prepared according to reference [1] |
| 3 | **1c** | See ESI page S8 |
| 4 | **1d** | Prepared according to reference [2] |
| 5 | **1e** | Prepared according to reference [1] |
| 6 | **1f** | Strem |
| 7 | **1g** | Prepared according to reference [3] |
| 8 | **2** | Sigma-Aldrich |
| 9 | **3** | Combi-Blocks |
| 10 | **4** | Sigma-Aldrich |
| 11 | **5** | Sigma-Aldrich |
| 12 | **6** | Alfa-Aesar |
| 13 | **7** | Maybridge |
| 14 | **8** | Sigma-Aldrich |
| 15 | **9** | Fluorochem |

| | | |
|---|---|---|
| 16 | **10** | Fluorochem |
| 17 | **11** | Synchem |
| 18 | **12** | Maybridge |
| 19 | **13** | Fluorochem |
| 20 | **14** | Enamine |
| 21 | **15** | Fluorochem |
| 22 | **16** | Sigma-Aldrich |
| 23 | **17** | Fluorochem |
| 24 | **18** | Apollo Scientific |
| 25 | **19** | ABCR |
| 26 | **20** | Fluorochem |
| 27 | **21** | Apollo Scientific |
| 28 | **22** | Fluorochem |
| 29 | **23** | Fluorochem |
| 30 | **24** | Fluorochem |

| | | |
|---|---|---|
| 31 | **25** | Fluorochem |
| 32 | **26** | TCI |
| 33 | **27** | Sigma-Aldrich |
| 34 | **28** | Combi-Blocks |
| 35 | **29** | Fluorochem |
| 36 | **30** | Fluorochem |
| 37 | **31** | TCI |
| 38 | **32** | Sigma-Aldrich |
| 39 | **33** | ABCR |
| 40 | Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBArF) | Sigma Aldrich |
| 41 | Tribenzylphosphine (PBn$_3$) | Sigma Aldrich |

Hydrogen isotope exchange reactions were carried out on a Heidolph Synthesis 1 Liquid 16 device (**Figure S1**).



**Figure S1.** Heidolph synthesis 1 liquid 16 device.

$^1$H (300, 500 MHz) and $^{13}$C (75, 125 MHz) NMR spectra were obtained on Bruker spectrometers in the solvents indicated. Chemical shifts are reported in ppm. Coupling constants are reported in Hz and refer to $^3J_{\text{H-H}}$ couplings,

unless otherwise stated. ^{1}H NMR spectra of labeled products were obtained using a 10 second delay to allow full relaxation of all hydrogen environments (D1 = 10).

IR spectra were obtained on a Shimadzu IRAffinity-1 Spectrophotometer machine and values are reported in $cm^{-1}$, unless stated otherwise.

Thin layer chromatography was carried out using Camlab silica plates coated with fluorescent indicator $UV_{254}$. The plates were analysed using a Mineralight UVGL-25 lamp or developed using vanillin or $KMnO_4$ solution.

Flash column chromatography was carried out using Prolabo silica gel (230-400 mesh).

Mass spectrometry data was acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

The distribution of hydrogen isotopes in the products was determined by a liquid chromatography-mass spectrometry (LC-MS) system with a Symmetry Shield RP18 column, 3.9 x 150 mm, with a gradient program. LC column conditions were as follows:

Mobile phase A: water (900 mL), acetonitrile (100 mL), TFA (1 mL)

Mobile phase B: water (100 mL), acetonitrile (900 mL), TFA (1 mL)

Gradient program:      0-4 min: 5% A/95% B

                                   4-7 min: 10% A/90% B

Flow rate: 1.0 mL/min

Detection: UV 254 nm.

## 2. General procedure for exchange reactions using Heidolph synthesis 1 liquid 16 device.

The apparatus was evacuated then filled with argon, and the water condenser was turned on. To a carousel tube was added the substrate of choice (0.086 mmol), and iridium catalyst (0.00086 mmol (1 mol%) or 0.00215 mmol (2.5 mol%) or 0.0043 mmol (5 mol%)). The requisite solvent was then added, rinsing the inner walls of the tube. The tube was then sealed at the screw cap (with the gas inlet left open) under argon. The flask was then twice evacuated and refilled with deuterium *via* a balloon. The carousel gas inlet tube was then closed, creating a sealed atmosphere of deuterium, the carousel shaking motion was initiated (750 rpm) and the temperature set (25 °C unless otherwise stated). After starting the device, the timer was initiated and a rapid red/orange to clear/yellow colour change was observed. The reaction mixture was stirred for the allotted time (1 h or 3 h) before removing excess deuterium and replacing with air. The yellow solution was then prepared for analysis by LC-MS and $^1$H NMR spectroscopy.

The level and regioselectivity of deuterium incorporation in the substrate was determined by $^1$H 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.

$$\% \, Deuteration \; = 100 - [\left(\frac{residual \; integral}{number \; of \; exchangeable \; sites}\right) \times 100]$$

**Equation 1**

For example, in a substrate containing four possible positions of exchange, the percentage given refers to the level of deuterium incorporation over the total number of positions (see page S34 for an example of such a spectrum).

The incorporation of deuterium into each substrate was verified by LC-MS, observing a shift in the isotope distribution in the starting material (M) to show M+1 ($d_1$), M+2 ($d_2$), M+3 ($d_3$), etc.

Example LC-MS analysis of compound **2**:

~5 μL of the labelling reaction mixture was removed and diluted with 0.5 mL of MeCN, and the sample analysed by LC-MS. Data processing was performed using ADvion Mass express analysis software and the given formula:

| # of D atoms incorporated | D0 | D1 | D2 | D3 | D4 |
|---|---|---|---|---|---|
| Integral of MS peak | 0 | 0.2 | 0.23 | 1.2 | 1.3 |
| Percentage | 0% | 6.3% | 15.6% | 37.5% | 40.6% |

Total incorporation = (%D1 × 0.25) + (%D2 × 0.5) + (%D3 × 0.75) + (%D4 × 1)

Total incorporation = (6.3 × 0.25) + (15.6 × 0.5) + (37.5 × 0.75) + (40.6 × 1)

Total incorporation = (1.6) + (7.8) + (28.1) + (40.6) = 78.1%

## 3. Preparation of [(COD)Ir(IMes)(PBn₃)]BArF 1c

The catalyst was prepared according to a modified procedure from reference [1].
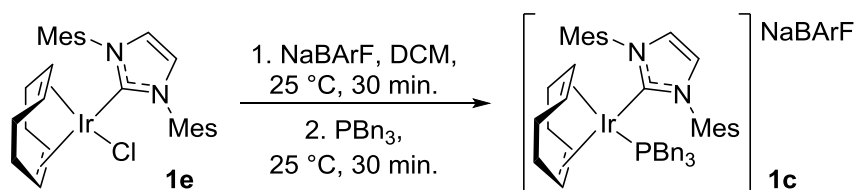


To a flame-dried, argon-cooled Schlenk tube was added IMes/chloride complex **1e**[1] (320 mg, 0.5 mmol, 1 eq), dry DCM (10 mL) and NaBAr$^F$ (443 mg, 0.5 mmol, 1 eq). After stirring at 25 °C for 30 min, tribenzylphosphine (152 mg, 0.5 mmol, 1 eq) was added slowly, initiating an orange to red colour change. Following a further 30 min stirring, the solvent was removed *in vacuo* leaving a red oily solid. The residue was purified by flash column chromatography, eluting with DCM/petroluem ether 40-60 °C (50/50). The isolated catalyst was dried in a vacuum oven (40 °C, 1 mbar) for 24 h, yielding **1c** as a deep red solid (762 mg, 86% yield).

**Melting Point (°C):** >175 (dec).

**FTIR (neat)**: (cm-1): 2978, 2361, 1495.

**¹H NMR** (400 MHz, CDCl₃): δ 7.79 (8H, t $^4J$ = 2.3 Hz, Ar-<u>H</u>), 7.58 (4H, s, Ar-<u>H</u>), 7.37-7.27 (13H, m, Ar-<u>H</u>), 7.25-7.21 (2H, m, Ar-<u>H</u>), 6.92-6.87 (6H, m, N-C<u>H</u> and Ar-<u>H</u>), 4.66-4.61 (2H, m, COD-C<u>H</u>), 3.31-3.27 (2H, m, COD-C<u>H</u>), 2.90 (6H, d $^2J$ = 8.7 Hz, P-C<u>H₂</u>-Ar), 2.51 (6H, s, Ar-CH₃), 2.50 (6H, s, Ar-CH₃), 2.33 (6H, s, Ar-CH₃), 1.86-1.73 (2H, m, COD-CH₂), 1.65-1.49 (4H, m, COD-CH₂), 1.43-1.32 (2H, m, COD-CH₂).

**¹³C NMR** (101 MHz, CDCl₃): δ 176.5 (d $^2J_{C-P}$ = 7.7 Hz), 161.2 (q $^1J_{C-B}$ = 49.5 Hz), 140.4, 135.6, 135.3, 134.3, 134.2, 132.2, 132.1, 130,0, 129.5, 129.33, 129.28, 128.4 (q $^2J_{C-F}$ = 32.9 Hz), 128.3, 127.1, 125.7, 124.1 (q $^1J_{C-F}$ = 269 Hz), 116.9, 86.1, 85.9, 75.5, 31.3, 31.0, 30.0, 29.7, 20.5, 19.6, 19.0.

**³¹P NMR (**162 MHz, CDCl₃): δ -7.98 (PBn₃).
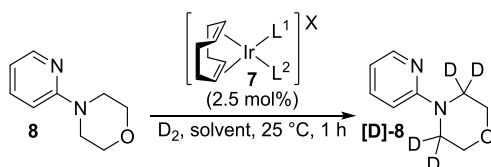
**¹⁹F NMR** (376 MHz, CDCl₃): δ -62.42 (BArF).

**¹¹B NMR** (128 MHz, CDCl₃): δ -6.65 (BArF).

**HRMS** (NSI): m/z calculated for C₅₀H₅₇IrN₂P [M]⁺: 607.3867; found: 607.3860.

See page S29 for spectra.

## 4. Screening of Catalysts 1a-1g and Extended Solvent Screen (Manuscript Table 1)



Reactions were carried out following the general procedure on page S7, using 4-(pyridin-2-yl)morpholine **2** (14.1 mg, 0.086 mmol, 1 eq), with catalyst (0.00215 mmol, 2.5 mol%) in 1 mL of solvent (0.086 M) under $D_2$ for 1 h at 25 °C. The full details are tabulated below in **Table S2**. Entries 11-15 are supplementary to the manuscript Table 1 entries.

Each reaction was performed in duplicate. The deuterium incorporation was analysed by LCMS and the deuterium distribution was confirmed by $^1$H NMR spectroscopy.

**Table S2**. Screening of Catalysts **1a**-**1g** and Extended Solvent Screen.

| Entry | Complex | mass (mg) of catalyst used | Solvent | Deuterium Incorporation (%D) | | |
| --- | --- | --- | --- | --- | --- | --- |
| | | | | Run 1 | Run 2 | Average |
| 1 | 1a | 2.2 | DCM | 76 | 81 | 79 |
| 2 | 1b | 3.7 | DCM | 88 | 92 | 90 |
| 3 | 1c | 3.8 | DCM | 85 | 84 | 85 |
| 4 | 1d | 3.5 | DCM | 75 | 81 | 78 |
| 5 | 1e | 1.4 | DCM | 0 | 0 | 0 |
| 6 | 1f | 1.7 | DCM | 26 | 22 | 24 |
| 7 | 1g | 3.3 | DCM | 25 | 26 | 26 |
| 8 | 1b | 3.7 | *t*-AmylOH | 76 | 75 | 76 |
| 9 | 1b | 3.7 | MTBE | 87 | 86 | 87 |
| 10 | 1b | 3.7 | *t*-BuOAc | 86 | 86 | 86 |
| 11 | 1b | 3.7 | MeOH | 65 | 67 | 66 |
| 12 | 1b | 3.7 | *i*-PrOH | 60 | 55 | 58 |
| 13 | 1b | 3.7 | 2-MeTHF | 64 | 73 | 69 |
| 14 | 1b | 7.4 | CPME | 83 | 83 | 83 |
| 15 | 1b | 3.7 | *i*-PrOAc | 80 | 72 | 76 |

# 5. Design of Experiment

## 5.1. Optimisation for Conditions A.

Experimental design was used to assess the effect of varying catalyst loading, reaction time, and reaction concentration [Conditions: **2** (14.1 mg, 0.086 mmol), **1b** (*catalyst loading*), DCM (*concentration*), $D_2$, 25 °C, (*reaction time*)]. As such, 'high' and 'low' values for each of these three variables were chosen. To generate a series of experiments to study optimal conditions within the variable ranges chosen, Design Expert™ software v9.0 (Stat_Ease Inc., Minneappolis, Mn) was used. This generated a *2 level, 3 factorial* design containing three centre points, giving 11 experiments in total. The deuterium incorporation of 4-(pyridin-2-yl)morpholine **2** was used as the response (**Table S3**).

**Table S3.** Design of Experiment: Optimisation for Protocol 1

| Run[a] | Variable A: Catalyst Loading (mol%) | Amount of 1b (mg (mmol)) | Variable B: Reaction Time (min) | Variable C: DCM Volume (mL) | Response: Incorporation (%D) |
|---|---|---|---|---|---|
| 1 (++-) | 1.5 | 2.2 (0.00129) | 40 | 0.5 | 52 |
| 2 (--+) | 0.5 | 0.7 (0.0043) | 20 | 2.5 | 24 |
| 3 (+++) | 1.5 | 2.2 (0.00129) | 40 | 2.5 | 94 |
| 4 (000) | 1.0 | 1.5 (0.00086) | 30 | 1.5 | 72 |
| 5 (-+-) | 0.5 | 0.7 (0.0043) | 40 | 0.5 | 45 |
| 6 (000) | 1.0 | 1.5 (0.00086) | 30 | 1.5 | 73 |
| 7 (---) | 0.5 | 0.7 (0.0043) | 20 | 0.5 | 30 |
| 8 (+--) | 1.5 | 2.2 (0.00129) | 20 | 0.5 | 51 |
| 9 (000) | 1.0 | 1.5 (0.00086) | 30 | 1.5 | 69 |
| 10 (-++) | 0.5 | 0.7 (0.0043) | 40 | 2.5 | 37 |
| 11 (+-+) | 1.5 | 2.2 (0.00129) | 20 | 2.5 | 70 |

[a] (+) = high value, (-) low value, and (0) = centre point of a variable. (-+-) = combination of low A, high B, and low C

Entries 4, 6, and 9 represent the centre points of the design. These were employed in order to:

(i) assess any curvature in the response of conversion changes in the variables; and
(ii) assess the repeatability of the hydrogen isotope exchange reaction.

A response surface was created in the same design program. This generated a half-normal plot (**Graph S1**), inferring that increasing the catalyst loading, reaction time, DCM volume, and the combination of catalyst loading and DCM volume have a positive impact upon the efficacy of the labeling reaction.
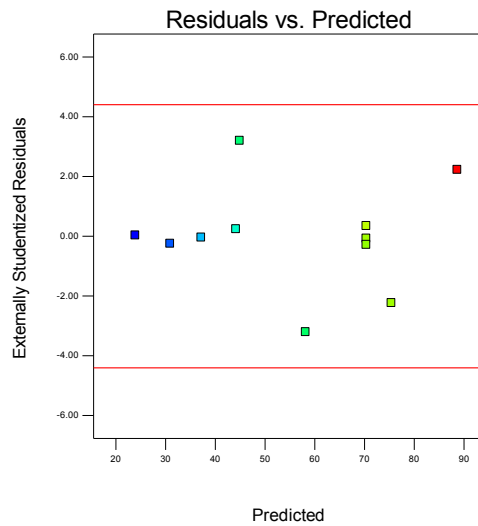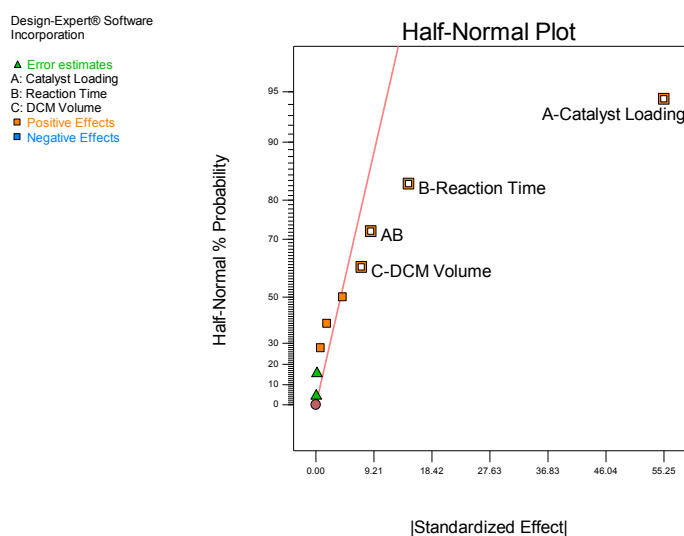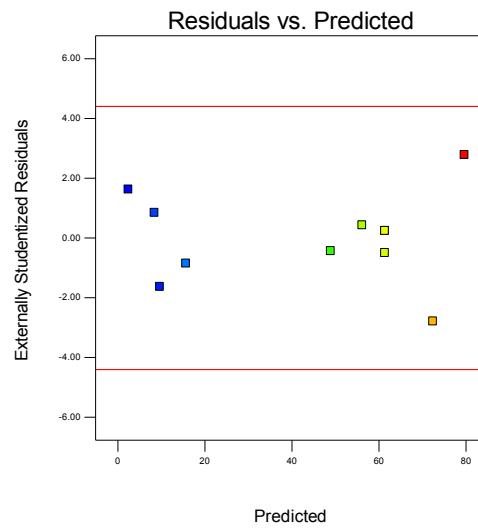
**Graph S1**

Finally, provided below is a graph of Residuals versus Predicted plot. This is a plot of the residuals versus the ascending predicted response values (lower conversion to higher conversion) and tests the assumption of constant variance in the data (**Graph S2**).



**Graph S2**

### 5.2. Optimisation for Conditions B

Experimental design was used to assess the effect of varying catalyst loading, reaction time, and reaction concentration [Conditions: **16** (14.0 mg, 0.086 mmol), **1b** (*catalyst loading*), DCM (*concentration*), D$_2$, 25 °C, (*reaction time*)]. As such, 'high' and 'low' values for each of these three variables were chosen. To generate a series of experiments to study optimal conditions within the variable ranges chosen, Design Expert$^{TM}$ software v9.0 (Stat_Ease Inc., Minneappolis, Mn) was used. This generated a *2 level, 3 factorial* design containing three centre points, giving 11 experiments in total. The deuterium incorporation of 4-(pyridin-2-yl)piperazine **16** was used as the response (**Table S4**).

**Table S4.** Design of Experiment: Optimisation for Protocol 2

| Run$^a$ | Variable A: Catalyst Loading (mol%) | Amount of 1b (mg (mmol)) | Variable B: Reaction Time (min) | Variable C: DCM Volume (mL) | Response: Incorporation (%D) |
|---|---|---|---|---|---|
| 1 (000) | 3.0 | 4.5 | 75 | 1.5 | 62 |
| 2 (+++) | 5.0 | 7.4 | 120 | 2.5 | 83 |
| 3 (+--) | 5.0 | 7.4 | 30 | 0.5 | 48 |
| 4 (--+) | 1.0 | 1.5 | 30 | 2.5 | 7 |
| 5 (000) | 3.0 | 4.5 | 75 | 1.5 | 62 |
| 6 (++-) | 5.0 | 7.4 | 120 | 0.5 | 69 |
| 7 (---) | 1.0 | 1.5 | 30 | 0.5 | 5 |
| 8 (-+-) | 1.0 | 1.5 | 120 | 0.5 | 10 |
| 9 (-++) | 1.0 | 1.5 | 120 | 2.5 | 14 |
| 10 (+-+) | 5.0 | 7.4 | 30 | 2.5 | 57 |
| 11 (000) | 3.0 | 4.5 | 75 | 1.5 | 64 |

$^a$ (+) = high value, (-) low value, and (0) = centre point of a variable. (-+-) = combination of low A, high B, and low C

Entries 1, 5, and 11 represent the centre points of the design. These were employed in order to:

(i) assess any curvature in the response of conversion changes in the variables; and

(ii) assess the repeatability of the hydrogen isotope exchange reaction.

A response surface was created in the same design program. This generated a half-normal plot (**Graph S3**), inferring that increasing the catalyst loading, reaction time, DCM volume, and the combination of catalyst loading and DCM volume have a positive impact upon the efficacy of the labelling reaction.



**Graph S3**

Finally, provided below is a graph of Residuals versus Predicted plot. This is a plot of the residuals versus the ascending predicted response values (lower conversion to higher conversion) and tests the assumption of constant variance in the data (**Graph S4**).



**Graph S4**

# 6. Substrate Scope (Manuscript Scheme 2)



Conditions A: Catalyst **1b** (1 mol%), D₂, DCM, 25 °C, 1 h

Conditions B: Catalyst **1b** (5 mol%), D₂, DCM, 25 °C, 3 h
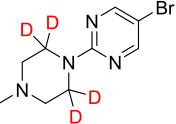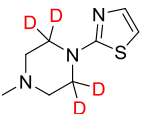
## Conditions A

Reactions were carried out following the general procedure on page S7, using substrate (0.086 mmol, 1 eq), with catalyst **1b** (1.5 mg, 0.00086 mmol, 1.0 mol%) in 1 mL of DCM (0.086 M) under D₂ for 1 h at 25 °C.
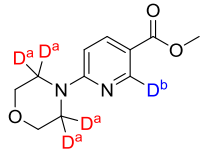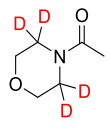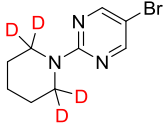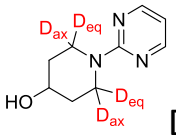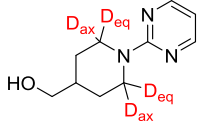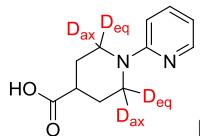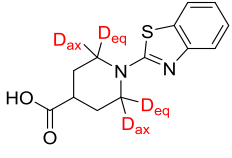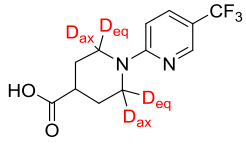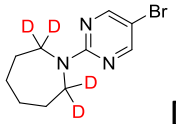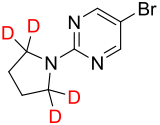
## Conditions B
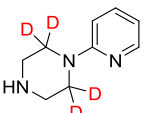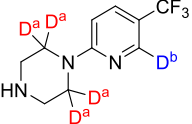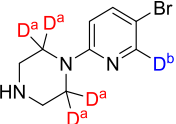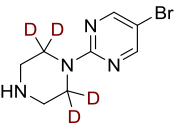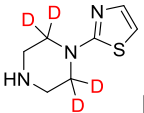
Reactions were carried out following the general procedure on page S7, using substrate (0.086 mmol, 1 eq), with catalyst **1b** (7.4 mg, 0.0043 mmol, 5.0 mol%) in 1 mL of DCM (0.086 M) under D₂ for 3 h at 25 °C.
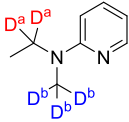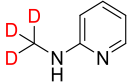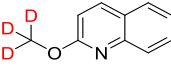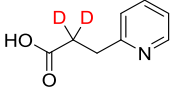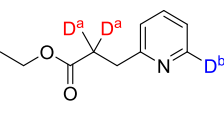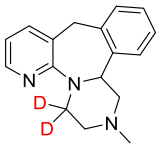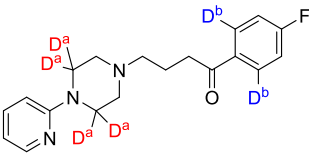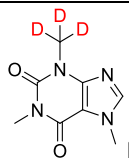
Each reaction was performed in duplicate. The extent and position of labeling was established using $^1$H NMR spectroscopy. The average deuterium incorporation for each molecule across all labeled positions was further confirmed by LCMS analysis. The details of the substrate scope described within the manuscript are given in **Table S5** below.

**Table S5.** Substrate Scope.
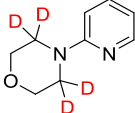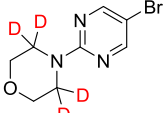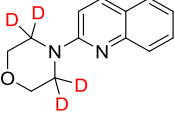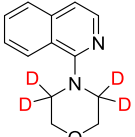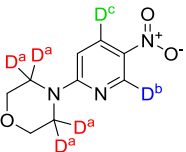
| Entry | Substrate | Mass of Substrate Used (mg) | Protocol | Deuterium Incorporation (%D) | | | $^1$H NMR Distribution |
|---|---|---|---|---|---|---|---|
| | | | | LC-MS | | | |
| | | | | Run 1 | Run 2 | Average | |
| 1 | [D]-2 | 14.1 | A | 82 | 78 | 80 | 80 |
| 2 | [D]-3 | 21.0 | A | 95 | 95 | 95 | 95 |
| 3 | [D]-4 | 18.4 | A | 85 | 91 | 88 | 94 |
| 4 | [D]-5 | 18.4 | A | 96 | 92 | 94 | 99 |
| 5 | [D]-6 | 18.0 | A | 85 | 86 | 86 | $D^a$ = 87; $D^b$ = 91; $D^c$ = 57 |

| # | Structure | | | | | | |
|---|---|---|---|---|---|---|---|
| 6 | [D]-7 | 19.1 | A | 82 | 83 | 83 | $D^a = 95$ |
| | | | | | | | $D^b = 5$ |
| 7 | [D]-8 | 11.1 | A | 0 | 0 | 0 | 0 |
| | | | B* | 11 | 13 | 12 | 12 |
| 8 | [D]-9 | 20.8 | A | 94 | 96 | 95 | 91 |
| 9 | [D]-10 | 14.5 | A | 78 | 82 | 80 | 86 |
| 10 | [D]-11 | 15.4 | A | 88 | 90 | 89 | $D_{ax} = 83$ |
| | | | | | | | $D_{eq} = 84$ |
| 11 | [D]-12 | 16.6 | A | 89 | 89 | 89 | $D_{ax} = 86$ |
| | | | | | | | $D_{eq} = 89$ |
| 12 | [D]-13 | 17.7 | A | 78 | 83 | 81 | $D_{ax} = 73$ |
| | | | | | | | $D_{eq} = 87$ |
| 13 | [D]-14 | 22.6 | A** | 83 | 81 | 82 | $D_{ax} = 77$ |
| | | | | | | | $D_{eq} = 87$ |
| 14 | [D]-15 | 23.6 | A | 95 | 89 | 92 | $D_{ax} = 90$ |
| | | | | | | | $D_{eq} = 93$ |

| Entry | Structure | Value | Cond. | | | | |
|---|---|---|---|---|---|---|---|
| 15 | [D]-16 | 14.0 | A | 17 | 18 | 18 | 18 |
| | | | B | 90 | 94 | 92 | 89 |
| 16 | [D]-17 | 19.9 | A | 11 | 12 | 12 | $D^a = 11$ / $D^b = 0$ |
| | | | B | 64 | 70 | 67 | $D^a = 79$ / $D^b = 17$ |
| 17 | [D]-18 | 20.8 | A | 24 | 25 | 25 | $D^a = 24$ / $D^b = 0$ |
| | | | B | 86 | 86 | 86 | $D^a = 92$ / $D^b = 34$ |
| 18 | [D]-19 | 20.9 | A | 7 | 8 | 8 | 7 |
| | | | B | 77 | 82 | 80 | 77 |
| 19 | [D]-20 | 14.6 | A | 24 | 19 | 22 | 30 |
| | | | B | 90 | 90 | 90 | 89 |
| 20 | [D]-21 | 22.1 | A | 87 | 94 | 91 | 92 |
| 21 | [D]-22 | 15.8 | A | 87 | 82 | 85 | 84 |
| 22 | [D]-23 | 22.0 | A | 47 | 47 | 47 | 47 |
| | | | B | 86 | 84 | 85 | 84 |
| 23 | [D]-24 | 19.6 | A | 58 | 56 | 57 | 57 |
| | | | B | 94 | 94 | 94 | 94 |

| # | Structure | | Cond. | | | | |
|---|---|---|---|---|---|---|---|
| 24 | [D]-25 | 18.4 | A | 0 | 0 | 0 | 0 |
| | | | B | 8 | 9 | 9 | 9 |
| 25 | [D]-26 | 11.7 | A | 0 | 0 | 0 | $D^a = 0$ |
| | | | | | | | $D^b = 0$ |
| | | | B | 96 | 95 | 96 | $D^a = 92$ |
| | | | | | | | $D^b = 92$ |
| 26 | [D]-27 | 9.3 | A | 0 | 0 | 0 | 0 |
| | | | B | 32 | 28 | 30 | 37 |
| 27 | [D]-28 | 13.7 | A | 13 | 15 | 14 | 14 |
| | | | B | 70 | 77 | 74 | 80 |
| 28 | [D]-29 | 13.0 | A | 16 | 19 | 18 | 16 |
| | | | B | 58 | 63 | 61 | 65 |
| 29 | [D]-30 | 15.4 | A | 0 | 0 | 0 | $D^a = 0$ |
| | | | | | | | $D^b = 0$ |
| | | | B | 25 | 21 | 23 | $D^a = 23$ |
| | | | | | | | $D^b = 7$ |
| 30 | [D]-31 | 22.8 | A | 95 | 94 | 95 | 94 |
| 31 | [D]-32 | 28.2 | A | 71 | 72 | 72 | $D^a = 97$ |
| | | | | | | | $D^b = 13$ |
| 32 | [D]-33 | 16.7 | A | 41 | 41 | 41 | 41 |
| | | | B | 93 | 91 | 92 | 92 |

\* Reaction conditions = substrate (0.086 mmol, 1 eq), with catalyst **1b**, (7.4 mg, 0.0043 mmol, 5.0 mol%) in 1 mL of MTBE (0.086 M) under $D_2$ for 3 h at 50 °C. \*\* Reaction conditions = substrate (0.086 mmol, 1 eq), with catalyst **1b**, (1.5 mg, 0.00086 mmol, 1.0 mol%) in 1 mL of 2-MeTHF (0.086 M) under $D_2$ for 1 h at 25 °C.

| Substrate | ¹H NMR data[4] |
|---|---|
| [D]-2 | **¹H NMR** (300 MHz, DMSO-d₆): δ 8.12 (1H, dd, $J$ = 5.1 Hz, $^4J$ = 1.5 Hz, Ar-<u>H</u>), 7.54 (1H, ddd, $J$ = 8.7 Hz, 7.1 Hz, $^4J$ = 1.5 Hz, Ar-<u>H</u>), 6.81 (1H, d, $J$ = 8.7 Hz, Ar-<u>H</u>), 6.66 (1H, dd, $J$ = 7.7 Hz, $^4J$ = 5.1 Hz, Ar-<u>H</u>), 3.72-3.64 (4H, m, O-C<u>H</u>₂), 3.44-3.37 (4H, m, N-C<u>H</u>₂).<br>Incorporation expected at δ 3.44-3.37.<br>Determined against integral at δ 6.66. |
| | *LCMS data* |
| | Retention time: 0.28 min; Mass ion: 165.1 (M+H)⁺ |

| | ¹H NMR data[5] |
|---|---|
| [D]-3 | **¹H NMR** (300 MHz, DMSO-d₆): δ 8.46 (2H, s, Ar-<u>H</u>), 3.70-3.60 (8H, m, C<u>H</u>₂).<br>Incorporation expected at δ 3.70-3.60.<br>Determined against integral at δ 8.46. |
| | *LCMS data* |
| | Retention time: 2.69 min; Mass ion: 244.1 (M+H)⁺ [using ⁷⁹Br] |

| | ¹H NMR data[6] |
|---|---|
| [D]-4 | **¹H NMR** (300 MHz, DMSO-d₆): δ 8.05 (1H, d, $J$ = 9.3 Hz, Ar-<u>H</u>), 7.70 (1H, d, $J$ = 7.9 Hz, Ar-<u>H</u>), 7.61-7.48 (2H, m, Ar-<u>H</u>), 7.28-7.18 (2H, m, Ar-<u>H</u>), 3.76-3.69 (4H, m, O-C<u>H</u>₂), 3.68-3.59 (4H, m, N-C<u>H</u>₄).<br>Incorporation expected at δ 3.68-3.59.<br>Determined against integral at δ 7.28-7.18. |
| | *LCMS data* |
| | Retention time: 0.49 min; Mass ion: 215.1 (M+H)⁺ |

| | ¹H NMR data[7] |
|---|---|
| [D]-5 | **¹H NMR** (300 MHz, DMSO-d₆): δ 8.15-8.08 (2H, m, Ar-<u>H</u>), 7.88 (1H, d, $J$ = 8.2 Hz, Ar-<u>H</u>), 7.75-7.66 (1H, m, Ar-<u>H</u>), 7.63-7.54 (1H, m, Ar-<u>H</u>), 7.39 (1H, d, $J$ = 5.7 Hz, Ar-<u>H</u>), 3.90-3.80 (4H, m, O-C<u>H</u>₂), 3.33-3.27 (4H, m, N-C<u>H</u>₂).<br>Incorporation expected at δ 3.33-3.27.<br>Determined against integral at δ 7.39. |
| | *LCMS data* |
| | Retention time: 0.80 min; Mass ion: 215.1 (M+H)⁺ |

| | ¹H NMR data[8] |
|---|---|
| [D]-6 | **¹H NMR** (300 MHz, DMSO-d₆): δ 8.96 (1H, d, $^4J$ = 2.8 Hz, Ar-<u>H</u>), 8.23 (1H, dd, $J$ = 9.6 Hz, $^4J$ = 2.8 Hz, Ar-<u>H</u>), 6.93 (1H, d, $J$ = 9.6 Hz, Ar-<u>H</u>), 3.81-3.59 (8H, m, C<u>H</u>₂).<br>Incorporation expected at δ Dᵃ 3.81-3.59, Dᵇ 8.96, Dᶜ 8.23.<br>Determined against integral at δ 6.93. |
| | *LCMS data* |
| | Retention time: 2.38 min; Mass ion: 210.1 (M+H)⁺ |

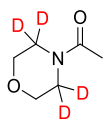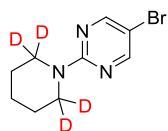| | $^1$H NMR data[9] |
|---|---|
| [D]-7 | $^1$**H NMR** (300 MHz, DMSO-d$_6$): δ 8.65 (1H, d, $^4J$ = 2.5 Hz, Ar-<u>H</u>), 7.96 (1H, dd, $J$ = 9.1 Hz, $^4J$ = 2.4 Hz, Ar-<u>H</u>), 6.87 (1H, d, $J$ = 9.2 Hz, Ar-<u>H</u>), 3.78 (3H, s, O-C<u>H$_3$</u>), 3.71-3.64 (4H, m, O-C<u>H$_2$</u>), 3.63-3.56 (4H, m, N-C<u>H$_2$</u>). Incorporation expected at δ D$^a$ 3.63-3.56, D$^b$ 8.65, D$^c$ 7.96. Determined against integral at δ 3.78. |
| | **LCMS data** |
| | Retention time: 2.00 min; Mass ion: 223.2 (M+H)$^+$ |

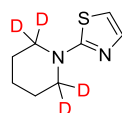| | $^1$H NMR data[10] |
|---|---|
| [D]-8 | $^1$**H NMR** (300 MHz, DMSO-d$_6$): δ 3.59-3.48 (4H, m, O-C<u>H$_2$</u>), 3.45-3.36 (4H, m, N-C<u>H$_2$</u>), 1.97 (3H, s, CO-C<u>H$_3$</u>). Incorporation expected at δ 3.45-3.36. Determined against integral at δ 1.97. |
| | **LCMS data** |
| | Retention time: 0.41 min; Mass ion: 130.1 (M+H)$^+$ |

| | $^1$H NMR data[11] |
|---|---|
| [D]-9 | $^1$**H NMR** (300 MHz, DMSO-d$_6$): δ 8.38 (2H, br s, Ar-<u>H</u>), 3.75-3.62 (4H, m, N-C<u>H$_2$</u>), 1.66-1.56 (2H, m, C<u>H$_2$</u>), 1.55-1.43 (4H, m, C<u>H$_2$</u>). Incorporation expected at δ 3.75-3.62. Determined against integral at δ 1.55-1.43. |
| | **LCMS data** |
| | Retention time: 3.54 min; Mass ion: 242.1 (M+H)$^+$ [using $^{79}$Br] |

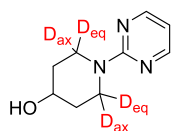| | $^1$H NMR data[12] |
|---|---|
| [D]-10 | $^1$**H NMR** (300 MHz, DMSO-d$_6$): δ 7.11 (1H, d, $J$ = 3.7 Hz, Ar-<u>H</u>), 6.75 (1H, d, $J$ = 3.6 Hz, Ar-<u>H</u>), 3.45-3.33 (4H, m, N-C<u>H$_2$</u>), 1.65-1.52 (6H, m, C<u>H$_2$</u>). Incorporation expected at δ 3.45-3.33. Determined against integral at δ 1.65-1.52. |
| | **LCMS data** |
| | Retention time: 0.67 min; Mass ion: 169.0 (M+H)$^+$ |

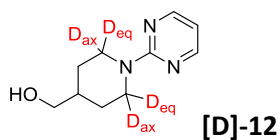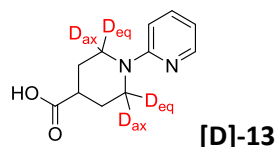| | $^1$H NMR data[13] |
|---|---|
| [D]-11 | $^1$**H NMR** (300 MHz, DMSO-d$_6$): δ 8.31 (2H, d, $J$ = 4.7 Hz, Ar-<u>H</u>), 6.55 (1H, t, $J$ = 4.7 Hz, Ar-<u>H</u>), 4.64 (1H, d, $J$ = 4.2 Hz, O-<u>H</u>), 4.24 (2H, ddd, $^2J$ = 13.0 Hz, $J$ = 5.6 Hz, 4.1 Hz, N-C<u>H$_2$</u>), 3.72 (1H, oct, $J$ = 4.2 Hz, O-C<u>H</u>), 3.24 (2H, ddd, $^2J$ = 13.0 Hz, $J$ = 9.1 Hz, 3.7 Hz, N-C<u>H$_2$</u>), 1.81-1.70 (2H, m, C<u>H$_2$</u>), 1.39-1.23 (2H, m, C<u>H$_2$</u>). Incorporation expected at δ 3.24 axial, 4.24 equatorial. Determined against integral at δ 1.39-1.23. |
| | **LCMS data** |
| | Retention time: 0.72 min; Mass ion: 180.1 (M+H)$^+$ |

## [D]-12

### $^1$H NMR data[14]

$^1$**H NMR** (300 MHz, DMSO-$d_6$): δ 8.30 (2H, d, $J$ = 4.7 Hz, Ar-<u>H</u>), 6.53 (1H, t, $J$ = 4.7 Hz, Ar-<u>H</u>), 4.70-4.58 (2H, m, N-C<u>H</u>$_2$), 4.40 (1H, t, $J$ = 5.3 Hz, O-<u>H</u>), 3.33-3.20 (2H, m, O-C<u>H</u>$_2$), 2.83 (2H, td, $J$ = 12.7 Hz, 2.7 Hz, N-C<u>H</u>$_2$), 1.77-1.55 (3H, m, CH$_2$-C<u>H</u> & C<u>H</u>$_2$), 1.14-0.95 (2H, m, C<u>H</u>$_2$).

Incorporation expected at δ 2.83 axial, 4.70-4.58 equatorial.

Determined against integral at δ 1.14-0.95.

### LCMS data

Retention time: 0.71 min; Mass ion: 194.1 (M+H)$^+$

## [D]-13

### $^1$H NMR data[15]

$^1$**H NMR** (300 MHz, DMSO-$d_6$): δ 12.15 (1H, br s, O-<u>H</u>), 8.08 (1H, dd, $J$ = 5.2 Hz, $^4J$ = 2.0 Hz, Ar-<u>H</u>), 7.49 (1H, ddd, $J$ = 8.7 Hz, 7.1 Hz, $^4J$ = 2.0 Hz, Ar-<u>H</u>), 6.80 (1H, d, $J$ = 8.7 Hz, Ar-<u>H</u>), 6.58 (1H, dd, $J$ = 7.1 Hz, 5.2 Hz, Ar-<u>H</u>), 4.16 (2H, ddd, $^2J$ = 13.3 Hz, $J$ = 4.3 Hz, 3.2 Hz, N-C<u>H</u>$_2$), 2.92 (2H, ddd, $^2J$ = 13.3 Hz, $J$ = 11.5 Hz, 2.9 Hz, N-C<u>H</u>$_2$), 2.52-2.42 (1H, m, C<u>H</u>), 1.91-1.79 (2H, m, C<u>H</u>$_2$), 1.61-1.40 (2H, m, C<u>H</u>$_2$).

Incorporation expected at δ 2.92 axial, 4.16 equatorial.

Determined against integral at δ 1.61-1.40.

### LCMS data

Retention time: 0.39 min; Mass ion: 207.1 (M+H)$^+$

## [D]-14
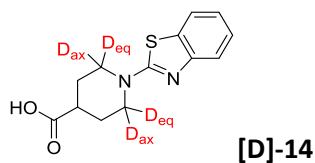
### $^1$H NMR data[16]

$^1$**H NMR** (300 MHz, CD$_3$CN): δ 9.05 (1H, br-s, O-<u>H</u>), 7.68 (1H, d, $J$ = 7.5 Hz, $^4J$ = 1.5 Hz, Ar-<u>H</u>), 7.44 (1H, d, $J$ = 7.5 Hz, Ar-<u>H</u>), 7.28 (1H, td, $J$ = 7.5 Hz, $^4J$ = 1.5 Hz, Ar-<u>H</u>), 7.07 (1H, td, $J$ = 7.5 Hz, $^4J$ = 1.5 Hz, Ar-<u>H</u>), 4.04 (2H, ddd, $^2J$ = 12.6 Hz, $J$ = 4.2 Hz, 4.1 Hz, N-C<u>H</u>$_2$), 3.25 (2H, ddd, $^2J$ = 12.6 Hz, $J$ = 11.4 Hz, 3.0 Hz, N-C<u>H</u>$_2$), 2.62 (1H, tt, $J$ = 11.1 Hz, 4.0 Hz, C<u>H</u>), 2.07-1.96 (2H, m, C<u>H</u>$_2$), 1.81-1.64 (2H, m, C<u>H</u>$_2$).

Incorporation expected at δ axial 3.25, equatorial 4.04.

Determined against integral at δ 1.81-1.64.

### LCMS data

Retention time: 2.49 min; Mass ion: 263.1 (M+H)$^+$

## [D]-15
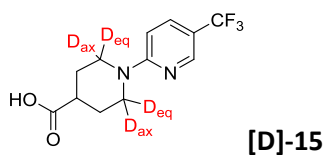
### $^1$H NMR data[17]

$^1$**H NMR** (300 MHz, DMSO-$d_6$): δ 12.11 (1H, br s, O-<u>H</u>), 8.37 (1H, br s, Ar-<u>H</u>), 7.74 (1H, dd, $J$ = 9.1 Hz, $^4J$ = 2.6 Hz, Ar-<u>H</u>), 6.93 (1H, d, $J$ = 9.1 Hz, Ar-<u>H</u>), 4.27 (2H, ddd, $^2J$ = 13.5 Hz, $J$ = 3.8 Hz, 3.8 Hz, N-C<u>H</u>$_2$), 3.08 (2H, ddd, $^2J$ = 13.5 Hz, $J$ = 11.2 Hz, 3.0 Hz, N-C<u>H</u>$_2$), 2.56 (1H, tt, $J$ = 11.0 Hz, 4.0 Hz, C<u>H</u>), 1.94-1.81 (2H, m, C<u>H</u>$_2$), 1.61-1.41 (2H, m, C<u>H</u>$_2$).

Incorporation expected at δ 3.08 axial, 4.27 equatorial.

Determined against integral at δ 1.61-1.41.

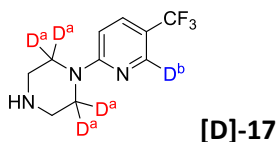### LCMS data

Retention time: 3.19 min; Mass ion: 275.1 (M+H)$^+$

## [D]-16
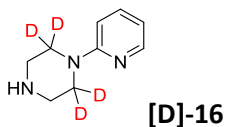
**¹H NMR** (300 MHz, DMSO-$d_6$): δ 8.08 (1H, dd, $J$ = 4.9 Hz, $^4J$ = 2.1 Hz, Ar-H), 7.49 (1H, ddd, $J$ = 8.7 Hz, 7.1 Hz, $^4J$ = 2.1 Hz, Ar-H), 6.75 (1H, d, $J$ = 8.7 Hz, Ar-H), 6.59 (1H, dd, $J$ = 7.1 Hz, 4.9 Hz, Ar-H), 3.43-3.32 (4H, m, N-CH₂), 2.81-2.70 (4H, m, NH-CH₂).
Incorporation expected at δ 3.43-3.32.
Determined against integral at δ 2.81-2.70.

### *LCMS data*
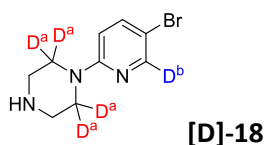
Retention time: 0.37 min; Mass ion: 164.0 (M+H)⁺

## [D]-17

*¹H NMR data*[19]

**¹H NMR** (300 MHz, DMSO-$d_6$): δ 8.37 (1H, br s, Ar-H), 7.73 (1H, dd, $J$ = 9.1 Hz, $^4J$ = 2.7 Hz, Ar-H), 6.88 (1H, d, $J$ = 9.1 Hz, Ar-H), 3.59-3.48 (4H, m, N-CH₂), 2.88-2.60 (4H, m, NH-CH₂).
Incorporation expected at δ D^a 3.59-3.48, D^b 8.37.
Determined against integral at δ 2.88-2.60.

### *LCMS data*
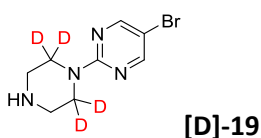
Retention time: 1.12 min; Mass ion: 232.3 (M+H)⁺

## [D]-18

*¹H NMR data*[20]

**¹H NMR** (300 MHz, DMSO-$d_6$): δ 8.40 (1H, br s, Ar-H), 7.77 (1H, dd, $J$ = 9.2 Hz, $^4J$ = 2.5 Hz, Ar-H), 6.92 (1H, d, $J$ = 9.4 Hz, Ar-H), 3.64-3.46 (4H, m, N-CH₂), 2.88-2.71 (4H, m, NH-CH₂).
Incorporation expected at δ D^a 3.64-3.46, D^b 8.40.
Determined against integral at δ 2.88-2.71.

### *LCMS data*

Retention time: 2.24 min; Mass ion: 242.1 (M+H)⁺ [using ⁷⁹Br]
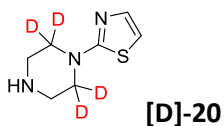
## [D]-19

*¹H NMR data*[21]

**¹H NMR** (300 MHz, DMSO-$d_6$): 8.46 (2H, br s, Ar-H), 3.89-3.75 (4H, m, N-CH₂), 2.90-2.78 (4H, m, NH-CH₂).
Incorporation expected at δ 3.89-3.75.
Determined against integral at δ 2.90-2.78.

### *LCMS data*

Retention time: 2.24 min; Mass ion: 243.1 (M+H)⁺ [using ⁷⁹Br]
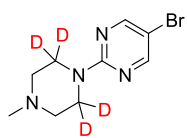
## [D]-20

*¹H NMR data*[22]

**¹H NMR** (300 MHz, DMSO-$d_6$): δ 7.14 (1H, d, $J$ = 3.6 Hz, Ar-H), 6.79 (1H, d, $J$ = 3.6 Hz, Ar-H), 3.36-3.26 (4H, m, N-CH₂), 2.83-2.73 (4H, m, NH-CH₂).
Incorporation expected at δ 3.36-3.26.
Determined against integral at δ 2.83-2.73.

### *LCMS data*

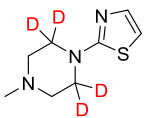Retention time: 0.29 min; Mass ion: 170.1 (M+H)⁺

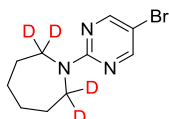|  | **¹H NMR data**[23] |
|---|---|
| | **¹H NMR** (300 MHz, DMSO-$d_6$): δ 8.42 (2H, s, Ar-<u>H</u>), 3.76-3.63 (4H, m, N-C<u>H</u>$_2$), 2.38-2.29 (4H, m, NMe-C<u>H</u>$_2$), 2.19 (3H, s, N-C<u>H</u>$_3$). Incorporation expected at δ 3.76-3.63. Determined against integral at δ 2.19. |
| | ***LCMS data*** |
| | Retention time: 0.41 min; Mass ion: 257.1 (M+H)$^+$ [using $^{79}$Br] |



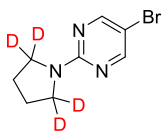|  | **¹H NMR data**[24] |
|---|---|
| | **¹H NMR** (300 MHz, DMSO-$d_6$): δ 7.15 (1H, d, $J$ = 3.6 Hz, Ar-<u>H</u>), 6.81 (1H, d, $J$ = 3.6 Hz, Ar-<u>H</u>), 3.43-3.33 (4H, m N-C<u>H</u>$_2$), 2.46-2.35 (4H, m, NMe-C<u>H</u>$_2$), 2.21 (3H, s, N-C<u>H</u>$_3$). Incorporation expected at δ 3.43-3.33. Determined against integral at δ 2.21. |
| | ***LCMS data*** |
| | Retention time: 0.29 min; Mass ion: 184.1 (M+H)$^+$ |



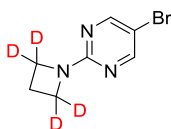|  | **¹H NMR data**[25] |
|---|---|
| | **¹H NMR** (300 MHz, DMSO-$d_6$): δ 8.39 (2H, br s, Ar-<u>H</u>), 3.73-3.60 (4H, m, N-C<u>H</u>$_2$), 1.77-1.61 (4H, m, C<u>H</u>$_2$), 1.54-1.39 (4H, m, C<u>H</u>$_2$). Incorporation expected at δ 3.73-3.60. Determined against integral at δ 1.54-1.39. |
| | ***LCMS data*** |
| | Retention time: 0.29 min; Mass ion: 256.1 (M+H)$^+$ [using $^{79}$Br] |



|  | **¹H NMR data**[26] |
|---|---|
| | **¹H NMR** (300 MHz, DMSO-$d_6$): δ 8.40 (2H, br s, Ar-<u>H</u>), 3.53-3.38 (4H, m, N-C<u>H</u>$_2$), 2.01-1.85 (4H, m, C<u>H</u>$_2$). Incorporation expected at δ 3.53-3.38. Determined against integral at δ 2.01-1.85. |
| | ***LCMS data*** |
| | Retention time: 2.85 min; Mass ion: 228.1 (M+H)$^+$ [using $^{79}$Br] |



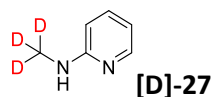|  | **¹H NMR data**[27] |
|---|---|
| | **¹H NMR** (300 MHz, DMSO-$d_6$): δ 8.40 (2H, br s, Ar-<u>H</u>), 4.02 (4H, t, $J$ = 7.5 Hz, N-CH$_2$), 2.30 (2H, quin, $J$ = 7.6 Hz, C<u>H</u>$_2$). Incorporation expected at δ D 4.02. Determined against integral at δ 2.30. |
| | ***LCMS data*** |
| | Retention time: 2.30 min; Mass ion: 214.0 (M+H)$^+$ [using $^{79}$Br] |



|  | **¹H NMR data**[28] |
|---|---|
| | **¹H NMR** (300 MHz, DMSO-$d_6$): δ 8.04 (1H, dd, $J$ = 4.9 Hz, $^4J$ = 2.1 Hz, Ar-<u>H</u>), 7.45 (1H, ddd, $J$ = 8.7 Hz, 7.1 Hz, $^4J$ = 2.1 Hz, Ar-<u>H</u>), 6.57 (1H, d, $J$ = 8.7 Hz, Ar-<u>H</u>), 6.50 (1H, dd, $J$ = 7.1 Hz, 4.8 Hz, Ar-<u>H</u>), 3.53 (2H, q, $J$ = 7.1 Hz, N-C<u>H</u>$_2$), 2.94 (3H, s, N-C<u>H</u>$_3$), 1.05 (3H, t, $J$ = 7.1 Hz, CH$_2$-C<u>H</u>$_3$). Incorporation expected at δ D$^a$ 3.53, D$^b$ 2.94. Determined against integral at δ 1.05. |
| | ***LCMS data*** |
| | Retention time: 0.30 min; Mass ion: 137.2 (M+H)$^+$ |

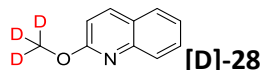| | |
|---|---|
| | ***¹H NMR data***[29] |
|  **[D]-27** | **¹H NMR** (300 MHz, DMSO-d$_6$): δ 7.96 (1H, dd, *J* = 5.0 Hz, ⁴*J* = 2.0 Hz, Ar-<u>H</u>), 7.34 (1H, ddd, *J* = 8.4 Hz, 7.0 Hz, ⁴*J* = 2.0 Hz, Ar-<u>H</u>), 6.50-6.37 (2H, m, Ar-<u>H</u>), 6.31 (1H, br s, N-<u>H</u>), 2.75 (3H, d, *J* = 4.9 Hz, NH-C<u>H</u>$_3$). Incorporation expected at δ 2.75. Determined against integral at δ 7.34. |
| | ***LCMS data*** |
| | Retention time: 0.25 min; Mass ion: 109.2 (M+H)$^+$ |

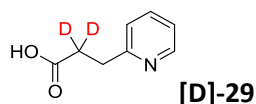| | |
|---|---|
| | ***¹H NMR data***[30] |
|  **[D]-28** | **¹H NMR** (300 MHz, DMSO-d$_6$): δ 8.21 (1H, d, *J* = 8.9 Hz, Ar-<u>H</u>), 7.86 (1H, dd, *J* = 7.8 Hz, ⁴*J* = 1.6 Hz, Ar-<u>H</u>), 7.78 (1H, d, *J* = 8.3 Hz, Ar-<u>H</u>), 7.65 (1H, ddd, *J* = 8.4 Hz, 7.0 Hz, ⁴*J* = 1.6 Hz, Ar-<u>H</u>), 7.42 (1H, ddd, *J* = 8.1 Hz, 6.9 Hz, ⁴*J* = 1.4 Hz, Ar-<u>H</u>), 7.00 (1H, d *J* = 8.9 Hz, Ar-<u>H</u>), 3.98 (3H, s, O-C<u>H</u>$_3$). Incorporation expected at δ 3.98. Determined against integral at δ 7.00. |
| | ***LCMS data*** |
| | Retention time: 3.00 min; Mass ion: 160.1 (M+H)$^+$ |

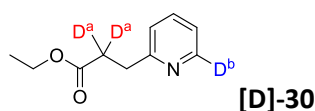| | |
|---|---|
| | ***¹H NMR data***[31] |
|  **[D]-29** | **¹H NMR** (300 MHz, DMSO-d$_6$): δ 12.10 (1H, br s, O-<u>H</u>), 8.46 (1H, dd, *J* = 5.1 Hz, ⁴*J* = 1.9 Hz, Ar-<u>H</u>), 7.68 (1H, dd, *J* = 7.7 Hz, ⁴*J* = 1.9 Hz, Ar-<u>H</u>), 7.26 (1H, d, *J* = 7.9 Hz, Ar-<u>H</u>), 7.19 (1H, dd, *J* = 7.7 Hz, 5.0 Hz, Ar-<u>H</u>), 2.96 (2H, t, *J* = 7.4 Hz, Ar-C<u>H</u>$_2$), 2.65 (2H, t, *J* = 7.4 Hz, CO-C<u>H</u>$_2$). Incorporation expected at δ 2.65. Determined against integral at δ 7.68. |
| | ***LCMS data*** |
| | Retention time: 0.29 min; Mass ion: 152.1 (M+H)$^+$ |

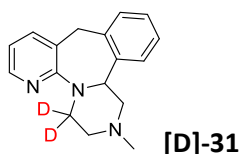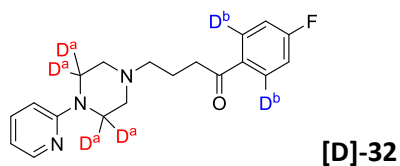| | |
|---|---|
| | ***¹H NMR data***[32] |
|  **[D]-30** | **¹H NMR** (300 MHz, DMSO-d$_6$): δ 8.45 (1H, d, *J* = 4.9 Hz, Ar-<u>H</u>), 7.68 (1H, td, *J* = 7.7 Hz, ⁴*J* = 1.8 Hz, Ar-<u>H</u>), 7.26 (1H, d, *J* = 7.5 Hz, Ar-<u>H</u>), 7.18 (1H, dd, *J* = 7.3 Hz, 4.8 Hz, Ar-<u>H</u>), 4.02 (2H, q, *J* = 7.2 Hz, O-C<u>H</u>$_2$), 2.99 (2H, t, *J* = 7.3 Hz, Ar-C<u>H</u>$_2$), 2.72 (2H, t, *J* = 7.3 Hz, CO-C<u>H</u>$_2$), 1.13 (3H, t, *J* = 7.2 Hz, CH$_2$-C<u>H</u>$_3$). Incorporation expected at δ D$^a$: 2.72, D$^b$: 8.45. Determined against integral at δ 1.13. |
| | ***LCMS data*** |
| | Retention time: 0.46 min; Mass ion: 180.2 (M+H)$^+$ |

| | *¹H NMR data*[33] |
|---|---|
| **[D]-31** | **¹H NMR** (300 MHz, DMSO-d$_6$): δ 8.08 (1H, dd, *J* = 4.9 Hz, *⁴J* = 1.9 Hz, Ar-H), 7.43 (1H, d, *J* = 7.3 Hz, Ar-H̲), 7.30-7.07 (4H, m, Ar-H̲), 6.77 (1H, dd, *J* = 7.3 Hz, 4.9 Hz, Ar-H̲), 4.39-4.19 (2H, m, N-CH̲ & Ar-CH̲$_2$), 3.67 (1H, d, *²J* = 13.5 Hz, Ar-CH̲$_2$), 3.48-3.36 (2H, m, N-CH̲$_2$), 2.84-2.66 (2H, m, NMe-CH̲$_2$), 2.52-2.45 (1H, m, NMe-CH̲$_2$), 2.36-2.19 (4H, m, N-CH̲$_3$ & NMe-CH̲$_2$). Incorporation expected at δ 3.48-3.36. Determined against integral at δ 3.67. |
| | *LCMS data* |
| | Retention time: 0.50 min; Mass ion: 266.3 (M+H)⁺ |

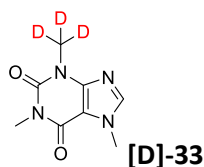| | *¹H NMR data*[34] |
|---|---|
| **[D]-32** | **¹H NMR** (300 MHz, DMSO-d$_6$): δ 8.15-7.91 (3H, m, Ar-H̲), 7.49 (1H, ddd, *J* = 8.5 Hz, 7.7 Hz, *⁴J* = 2.2 Hz, Ar-H̲), 7.39-7.24 (2H, m, Ar-H̲), 6.76 (1H, d, *J* = 8.6 Hz, Ar-H̲), 6.60 (1H, dd, *J* = 7.7 Hz, 4.8 Hz, Ar-H̲), 3.43-3.32 (4H, m, Ar-N-CH̲$_2$), 3.01 (2H, t, *J* = 7.0 Hz, N-CH̲$_2$), 2.45-2.27 (6H, m, CH̲$_2$ & N-CH̲$_2$), 1.90-1.77 (2H, m, CH̲$_2$). Incorporation expected at δ Dᵃ 3.43-3.32, Dᵇ 8.15-7.91. Determined against integral at δ 1.90-1.77. |
| | *LCMS data* |
| | Retention time: 0.38 min; Mass ion: 328.4 (M+H)⁺ |

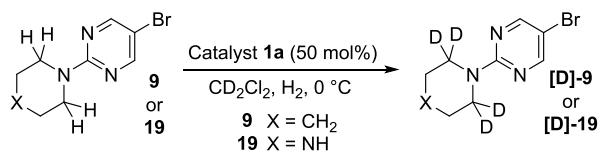| | *¹H NMR data*[35] |
|---|---|
| **[D]-33** | **¹H NMR** (300 MHz, DMSO-d$_6$): δ 7.98 (1H, s, Ar-H̲), 3.87 (3H, s, N-CH̲$_3$), 3.40 (3H, s, N-CH̲$_3$), 3.21 (3H, s, N-CH̲$_3$). Incorporation expected at δ 3.40. Determined against integral at δ 3.87. |
| | *LCMS data* |
| | Retention time: 0.92 min; Mass ion: 195.1 (M+H)⁺ |

## 7. NMR Studies Regarding Piperazine NH Binding



Experiments were run to determine the effect of secondary amines on the unactivated pre-catalyst, and activated catalyst species. Below, "Unactivated" refers to experiments run without catalyst activation with $H_2$, and "Activated" refers to experiments run after catalyst activation with $H_2$.

"Activated" protocol: In an oven dried NMR tube, substrate (**9**: 4.8 mg, 0.02 mmol or **19**: 4.9 mg, 0.02 mmol), catalyst **1a** (10 mg, 0.01 mmol) and DCM (0.5 mL) were added and the tube capped with a rubber septum. Hydrogen was bubbled through the solution at a constant rate for 5 min to activate the catalyst, and a red to yellow colour change was observed. Following the catalyst activation the NMR tube was cooled to 0 °C in an ice bath prior to injection into the NMR spectrometer. ^{31}P NMR experiments were run at 0 °C to allow observation of changes in the active catalytic species.

"Unactivated" protocol: This follows the above "Activated" protocol, but without the introduction of hydrogen gas.

^{31}P NMR data for the experiments are displayed below (**Fig. S2**).

The experiments reveal that when unactivated, the pre-catalyst remains unaffected by the substrate, showing the same shift of 18.3 ppm. Similarly, in the case of piperidine-containing substrate **9** a single catalytic species is formed, with a ^{31}P NMR shift of 24.9 ppm after activation. However, with piperazine containing substrate **19**, several signals are observed, with none appearing at 24.9 ppm, clearly indicating several different phosphine-containing species are being formed.
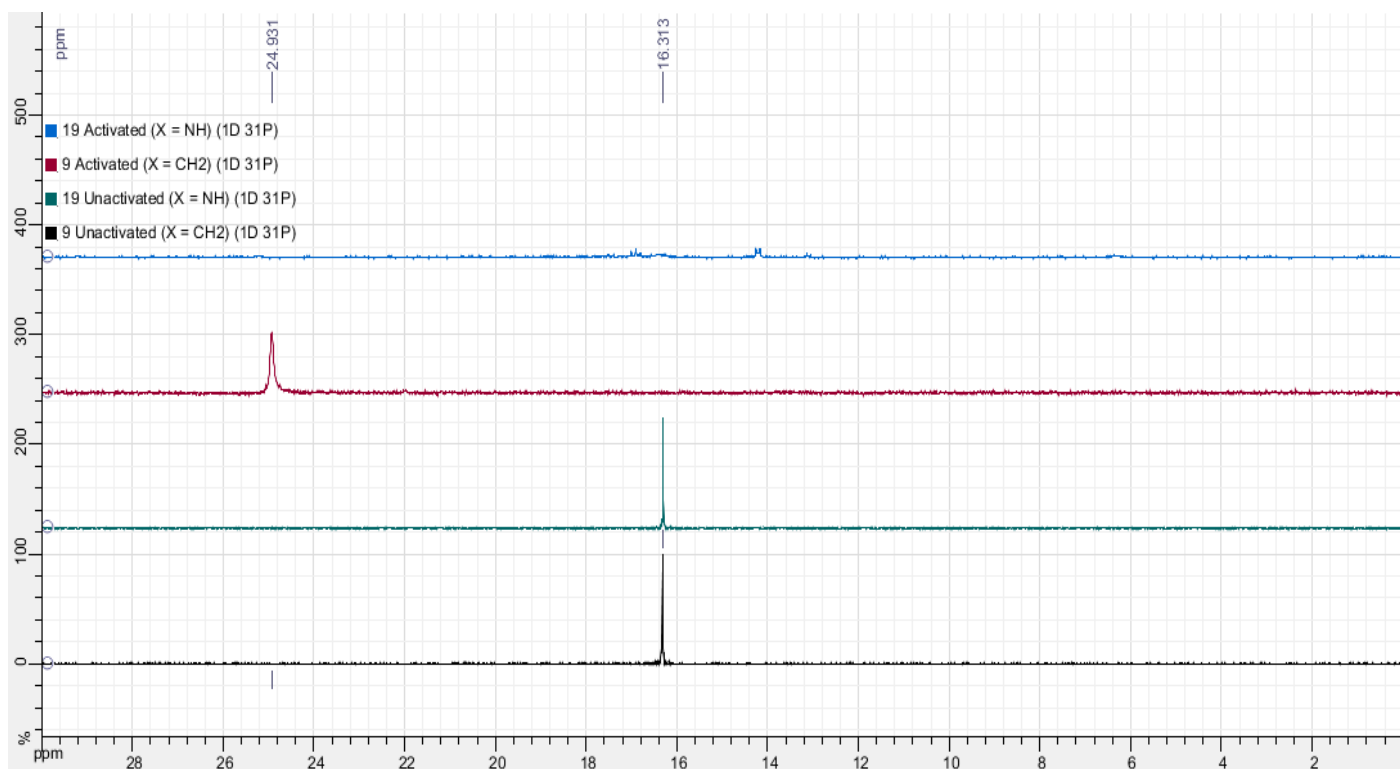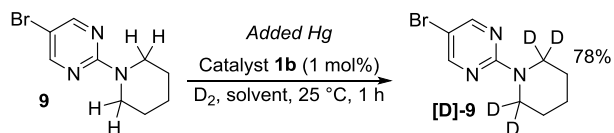


**Figure S2.**

# 8. Mechanistic Investigations

## 8.1. Mercury Nanoparticle Test



The reaction was carried out as described on page S7, except with the addition of a mercury drop prior to catalyst activation with $D_2$. The reaction proceeded to similarly high incorporation (78%) as without added mercury (91%), indicating that the reaction is homogeneous in nature, and is not catalysed by heterogeneous nanoparticles formed *in situ*.
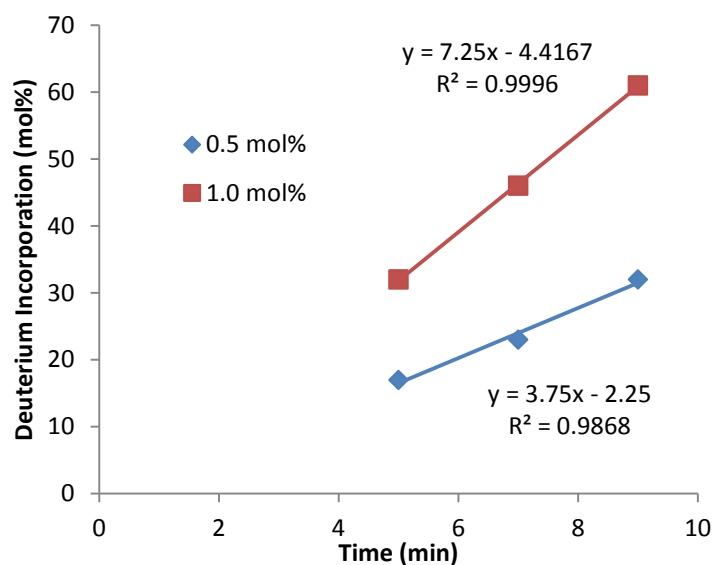
## 8.2. Order of Reaction
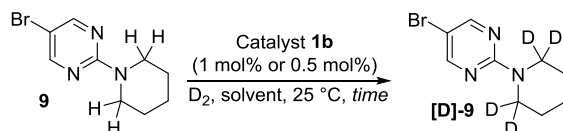


Reactions were carried out following the general procedure on page S7, using 5-bromo-2-(piperidin-1-yl)pyrimidine **9** (20.8 mg, 0.086 mmol, 1 eq), with catalyst **1b** (1.5 mg, 0.00086 mmol, 1.0 mol% or 0.7 mg, 0.00043 mmol, 0.5 mol%) in 1 mL of solvent (0.086 M) under an atmosphere of $D_2$ for the stated time at 25 °C. The deuterium incorporation was assigned by $^1$H NMR spectroscopy. The full incorporation data are given below in **Table S6**, and in **Graph S5**.

**Table S6.** Reactions carried out to determine the order of the reaction with respect to catalyst.

| Entry | Time (min) | Catalyst Loading (mol%) | Deuterium Incorporation (%D) |
|---|---|---|---|
| 1 | 3 | 0.5 | 8 |
| 2 | | 1.0 | 12 |
| 3 | 5 | 0.5 | 17 |
| 4 | | 1.0 | 32 |
| 5 | 7 | 0.5 | 23 |
| 6 | | 1.0 | 46 |
| 7 | 9 | 0.5 | 32 |
| 8 | | 1.0 | 61 |
| 9 | 11 | 0.5 | 39 |
| 10 | | 1.0 | 67 |



**Graph S5.** Rate study to determine the order of reaction with respect to catalyst.

The data points for 3 min were discarded as they could occur within the catalyst activation period. The data points for 11 min were discarded as product inhibition has been observed when the incorporation is >60%.

The gradient of the line is proportional to the reaction rate constant. Therefore, the rate increases by a factor of 1.93 (1.93 ≈ 2) in changing the catalyst loading from 0.5 to 1.0, indicating a first order rate dependence upon the catalyst.

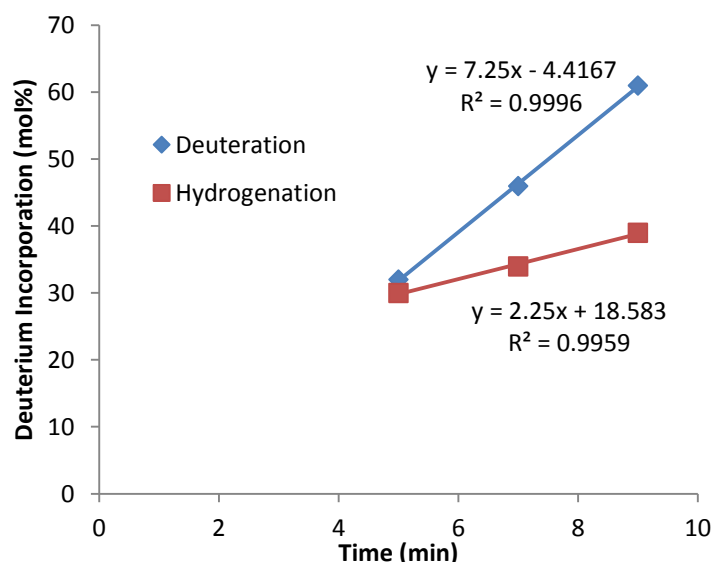## 8.3. Kinetic Isotope Effect



KIE = 3.22
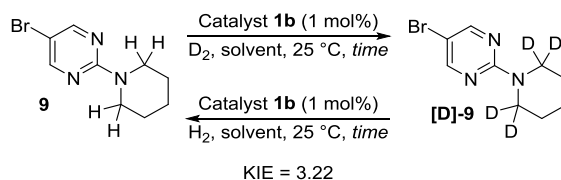
Reactions to incorporate deuterium were carried out following the general procedure on page S7, using 5-bromo-2-(piperidin-1-yl)pyrimidine **9** (20.8 mg, 0.086 mmol, 1 eq), with catalyst (0.00086 mmol, 1.0 mol%) in 1 mL of solvent (0.086 M) under an atmosphere of $D_2$ for the stated time at 25 °C.

Reactions to incorporate hydrogen were carried out following the general procedure on page S7, using 5-bromo-2-(2,2',6,6'-$d_4$-piperidin-1-yl)pyrimidine **[D]-9** (21.1 mg, 0.086 mmol, 1 eq), with catalyst (0.00086 mmol, 1.0 mol%) in 1 mL of solvent (0.086 M) under an atmosphere of $H_2$ for the stated time at 25 °C.

The deuterium/hydrogen incorporation was assigned by $^1H$ NMR spectroscopy. The full incorporation data are given below in **Table S7**, and **Graph S6**.

**Table S7.** Reactions carried out to determine the kinetic isotope effect.

| Entry | Time (min) | Substrate used | Isotope Introduced | Incorporation (%) |
|-------|-----------|---------------|-------------------|-------------------|
| 1 | 3 | **[D]-9** | H | 14 |
| 2 | | **9** | D | 7 |
| 3 | 5 | **[D]-9** | H | 30 |
| 4 | | **9** | D | 32 |
| 5 | 7 | **[D]-9** | H | 34 |
| 6 | | **9** | D | 46 |
| 7 | 9 | **[D]-9** | H | 39 |
| 8 | | **9** | D | 61 |
| 9 | 11 | **[D]-9** | H | 45 |
| 10 | | **9** | D | 67 |



**Graph S6.** Rate study to determine the kinetic isotope effect.

The data points for 3 min were discarded as they could occur within the catalyst activation period. The data points for 11 min were discarded as product inhibition has been observed when the incorporation is >60%. The gradient of the line is proportional to the reaction rate constant. Therefore, the kinetic isotope effect ($k_H/k_D$) is (7.25 / 2.25) 3.22.
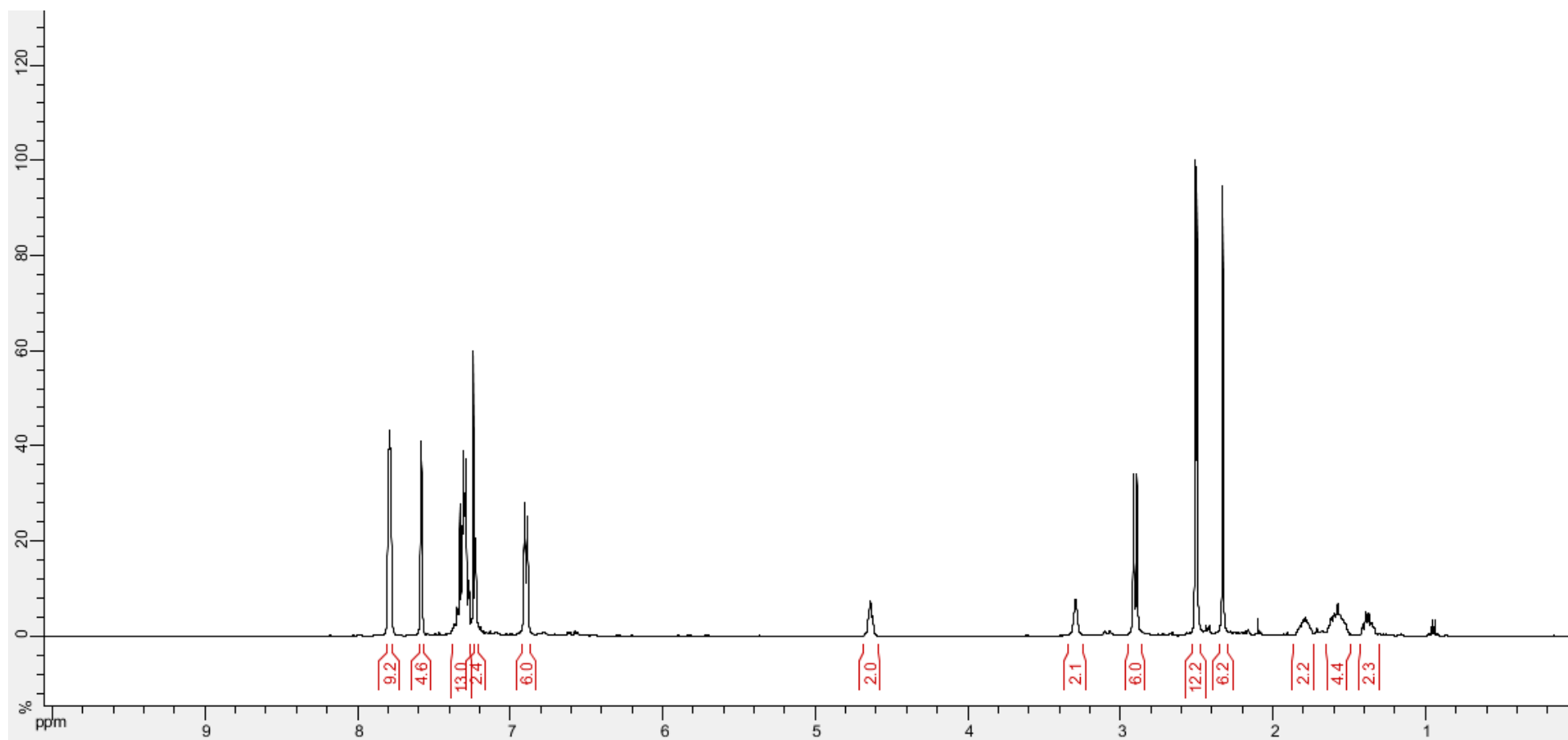
S28

# 9. Compound Spectra
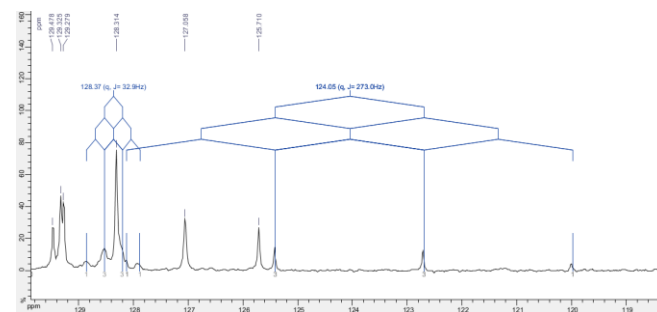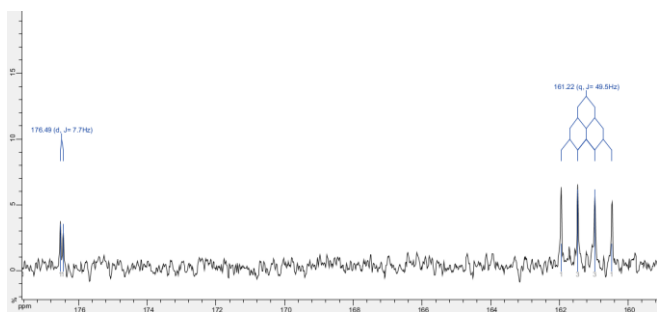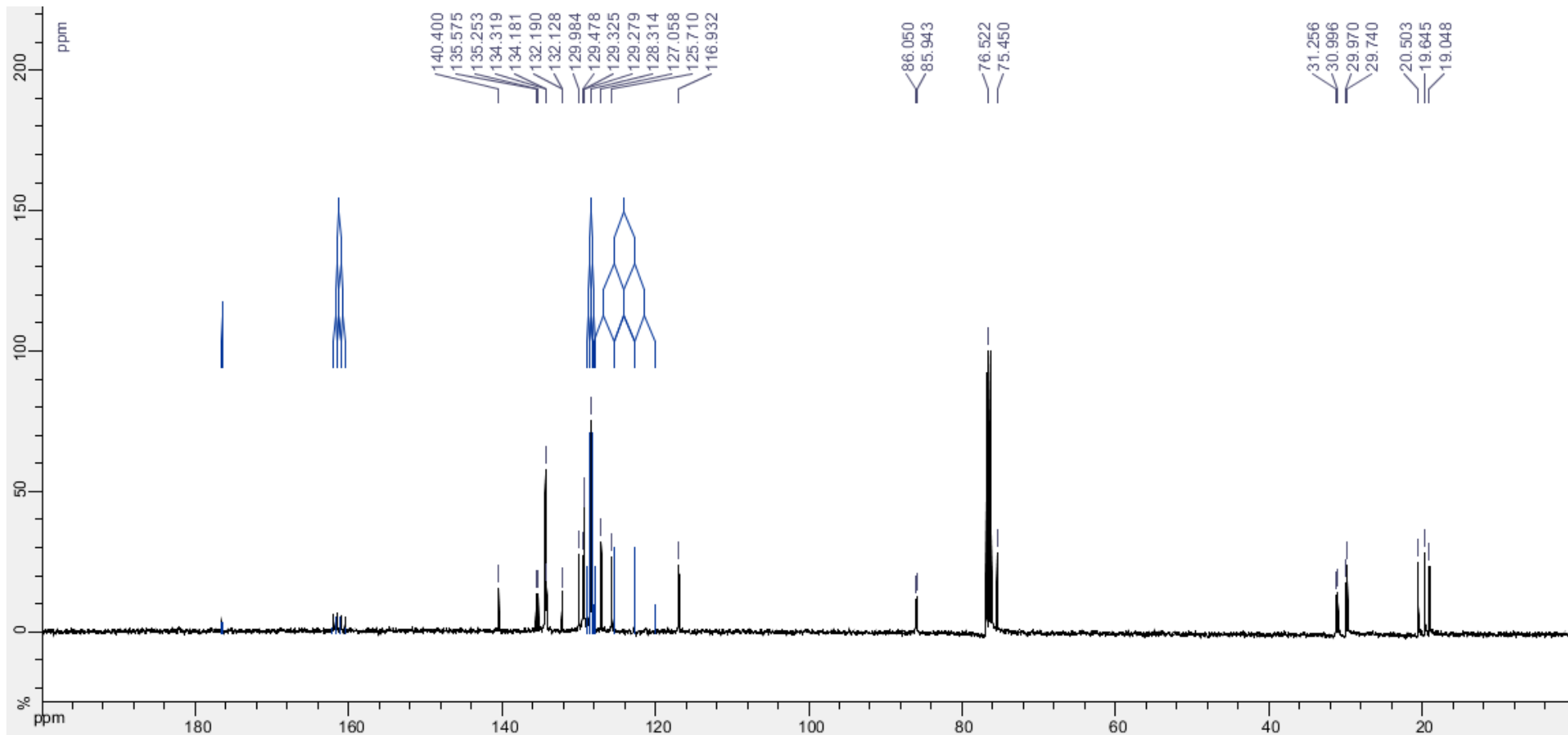
### 9.1. Catalyst [(COD)Ir(IMes)(PBn₃)]BArᶠ, 1c.
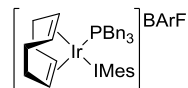
Chemical Formula: $C_{82}H_{69}BF_{24}IrN_2P$
Molecular Weight: 1772.43

**¹H NMR**

## <sup>13</sup>C NMR

**¹⁹F NMR**
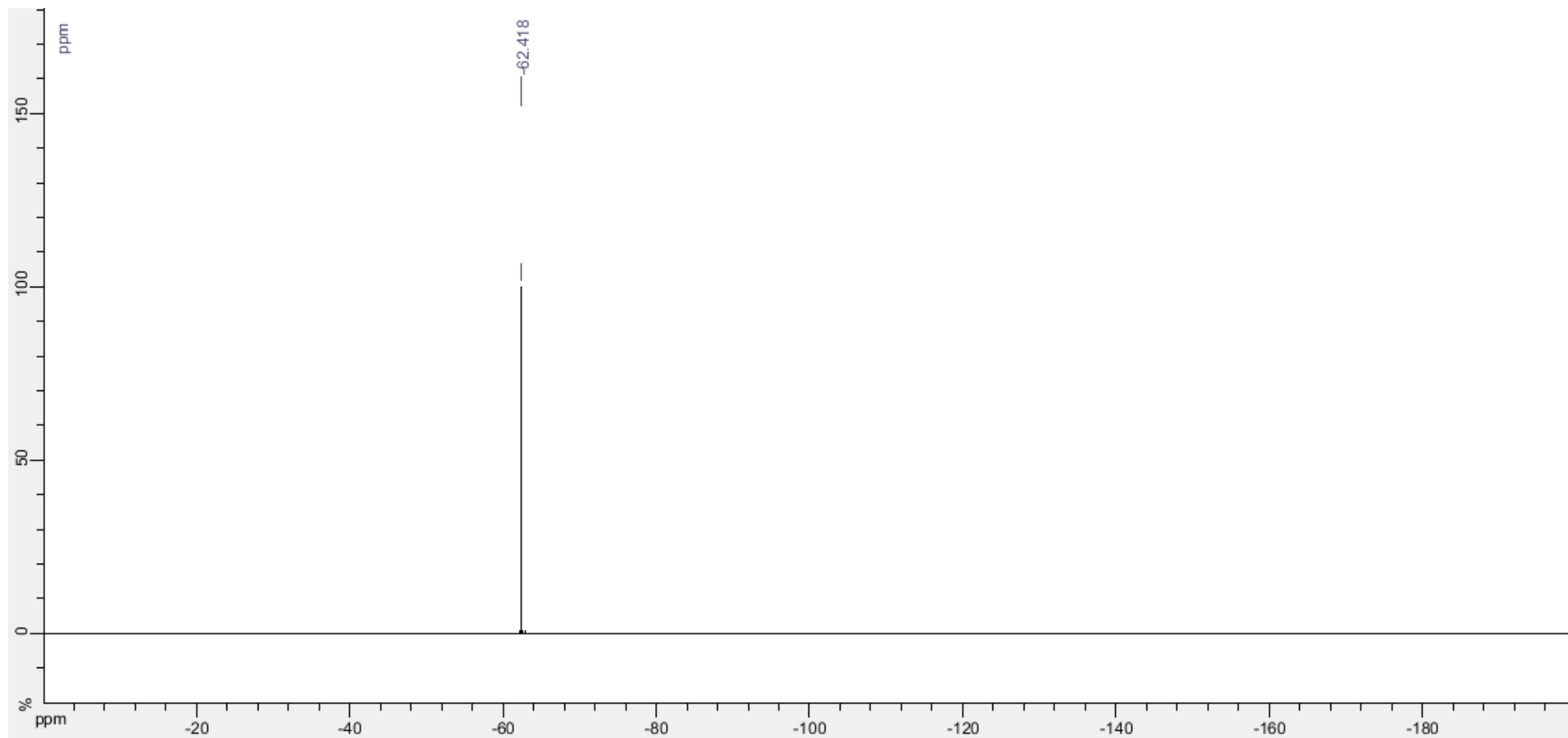
**³¹P NMR**
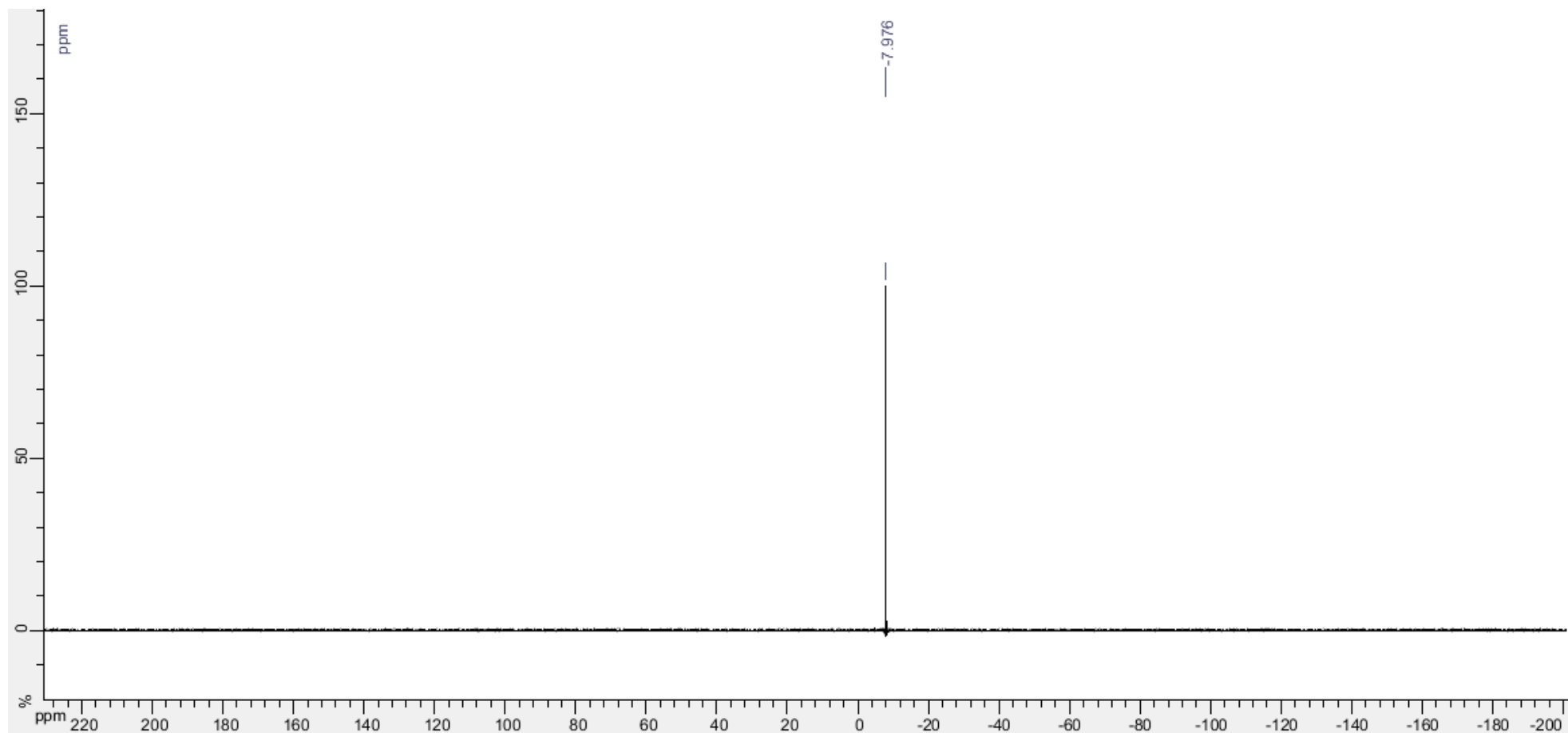
**¹¹B NMR**
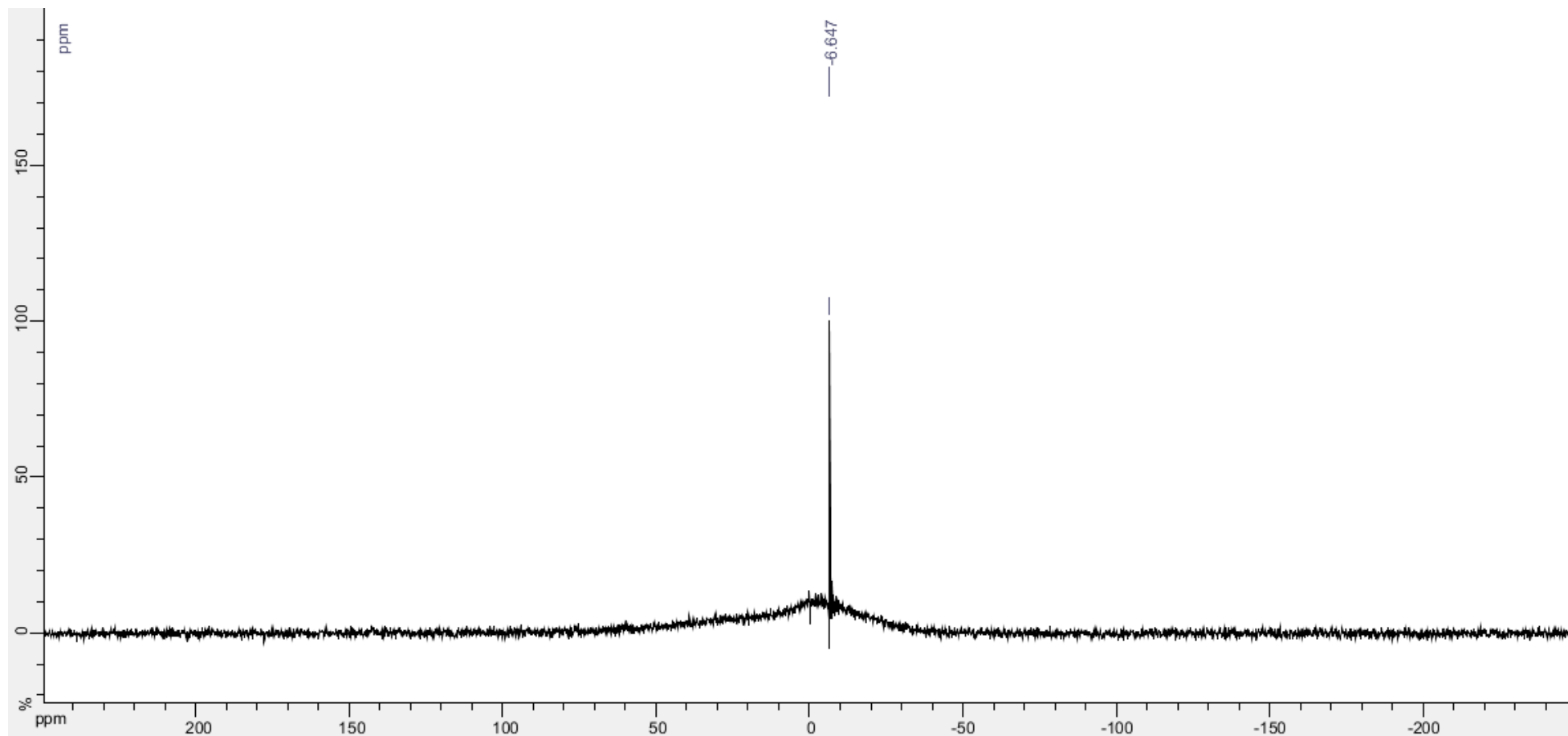
## 9.2. Example LC-MS and NMR data of unlabelled and labelled substrates (2 and [D]-2)

**2**

**[D]-2**
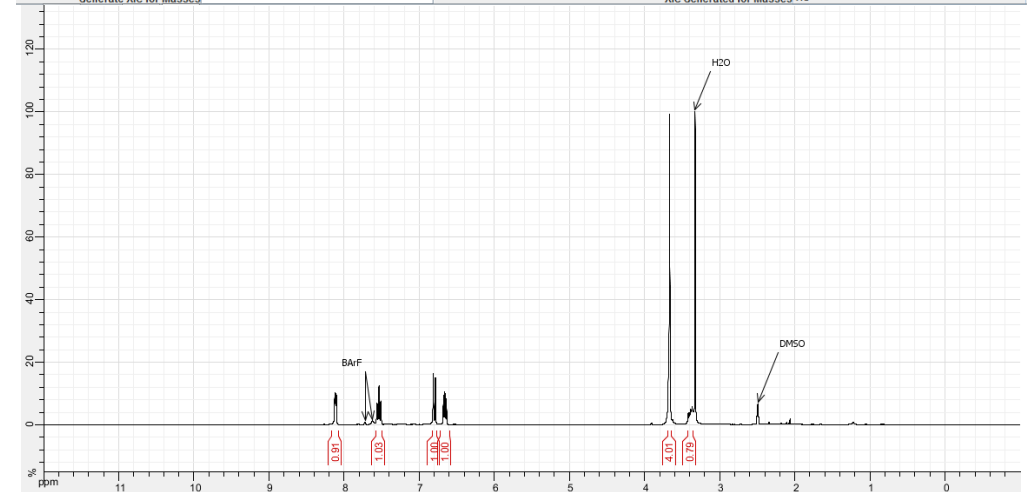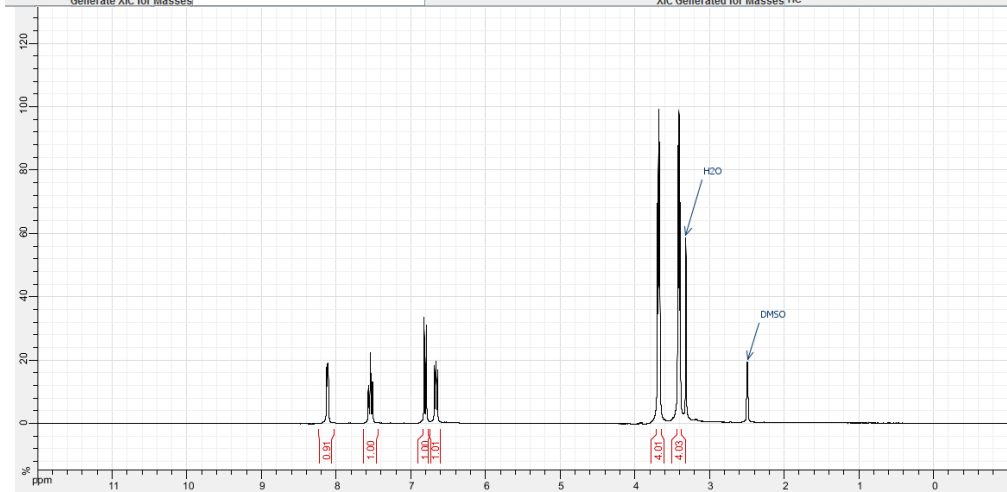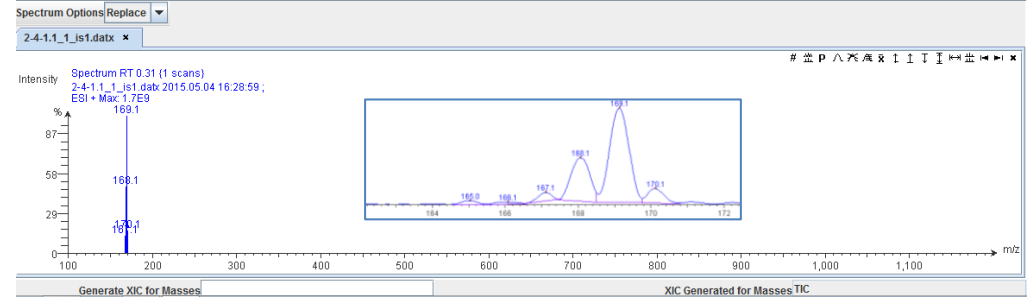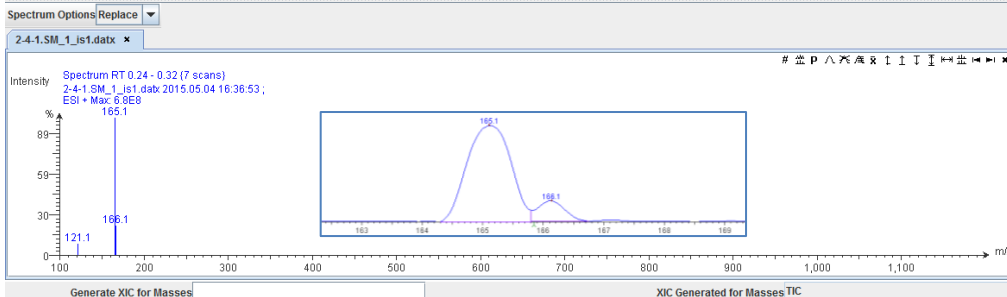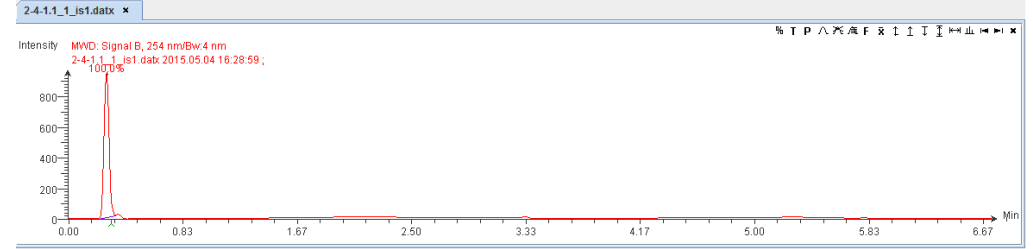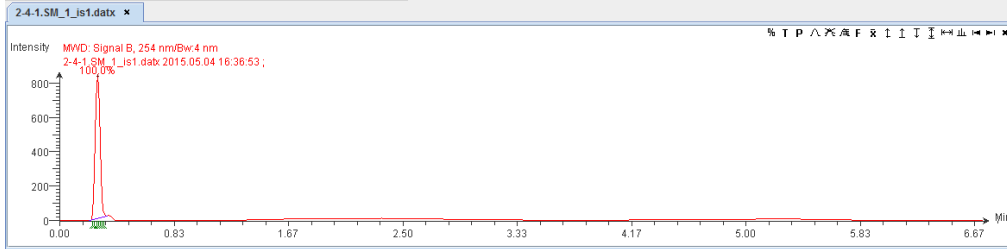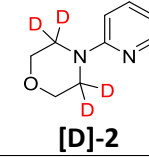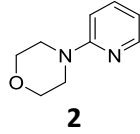
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