Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information for:

Iridium-catalysed *ortho*-H/D and -H/T Exchange under Basic Conditions: C-H Activation of Unprotected Tetrazoles

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Contents

1. General

1.1 General Experimental Considerations

All reagents were obtained from commercial suppliers (Aldrich, Alfa Aesar, or Strem) and used without further purification, unless otherwise stated. Solvents were purchased as anhydrous, and stored over molecular sieves (4 Å) under an argon atmosphere.

^{1}H NMR spectra were recorded on Bruker spectrometers, at 300, 400 or 500 MHz. ^{13}C, ^{11}B, ^{19}F, and ^{31}PNMR spectra were recorded on a Bruker DPX 400 spectrometer at 100 MHz, 128 MHz, 376 MHz, and 162 MHz, respectively. Chemical shifts are reported in ppm. Coupling constants are reported in Hz and refer to $^{3}J_{H\text{-}H}$ couplings, unless otherwise stated.

The distribution of hydrogen isotopes in the products was determined by one of two liquid chromatography-mass spectrometry (LC-MS) systems:

System 1: using a Symmetry Shield RP18 column, 3.9 mm × 150 mm with 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 (0.75 mL).
Flow rate: 0.6 mLmin^{-1}.
Detection: UV (254 nm and 210 nm).

System 2: using a Dionex Summit LC System with a DAD, coupled to a Thermo MSQ+ single quad MS. The LC column used was a Phenomenex Luna C18(2), 3 µm particle size, 100 Å pore size, 4.6 mm × 150 mm.

mobile phase A: water (900 mL), acetonitrile (100 mL), formic acid (1 mL).
mobile phase B: water (100 mL), acetonitrile (900 mL), formic acid (0.75 mL).
Flow rate: 0.6 mLmin^{-1}.

Detection: UV (254 nm and 210 nm).

For **system 2**, prior to mass detection, eluted LC samples were mixed with a 2.5% (v/v) solution of aqueous ammonia in order to form anionic entrants to the MS system.

High resolution mass spectrometry (HRMS) data were acquired in positive or negative ESI mode and the method is specifically stated for each compound. Data were obtained from the EPSRC UK National Mass Spectrometry Service Centre (NMSSC) at Swansea University. Alternatively, HRMS was provided by Sanofi (Frankfurt, Germany) via a Bruker micro-TOF-QII in positive ESI mode. Calibration was achieved against a sodium formate injection. A Dionex Ultimate 3000 RSLC system was used as an inlet to the MS, employing a flow of 0.5 $mLmin^{-1}$ of 0.044 % TFA in 50% acetonitrile (aq.). Use of this system is stated where necessary.

1.2 General Procedure – Deuteration Procedure Using Carousel

All reactions were carried out using a Radley 12-chamber carousel. The water inlet for the carousel reflux system was turned on prior to any further reaction set up. To a 25 mL oven-dried carousel tube was added the requisite tetrazole substrate (0.086 mmol, unless otherwise stated), base (0.043 mmol), and iridium(I) precatalyst (0.0043 mmol, 5 mol%, unless otherwise stated) under air. The requisite solvent (1 mL, unless otherwise stated) was added, rinsing the inner walls of the tube. The tube was then sealed at the screw cap (with gas inlet tap left open to air) and reconnected to the carousel rack. After charging all carousel tubes with their reactants, the air in the tubes was replaced with argon before cooling the base of the tubes in the rack to 0 ºC using an ice/water cooling bath. Separately, the carousel heating block was set to the desired reaction temperature. Whilst in the cooling rack, the cooled flasks were evacuated and flushed with deuterium *via* a balloon, and this cycle repeated one further time. The carousel tube gas inlets were then closed, creating a sealed atmosphere of deuterium. After sealing the flasks, the rack of tubes was transferred back to the heating block and the reaction timer was started. The reaction mixture was stirred for the allotted time before removing excess deuterium and replacing with air. At the end of each reaction time, a 2 µL sample was removed for LC-MS analysis. The reaction solution was then transferred to a single-necked flask, using DCM to wash in any residues in the reaction tube, before removing the solvent under reduced pressure. The remaining residue was partitioned between water (5 mL) and 2-MeTHF (5 mL) in a separating funnel. The organic phase was washed with 0.1 M HCl (5 mL), then dried over anhydrous Na_2SO_4 before filtering and concentrating *in vacuo*. The product was then analysed directly *via* ^{1}H NMR spectroscopy. The integrals were calibrated against a peak corresponding to a position not expected to be labelled.

NOTE: it is imperative that the reaction mixture be cooled *prior* to the introduction of deuterium. Heating the basified reaction mixture before adding D_2 was found to degrade the catalyst before the reaction began.

2. Reaction Optimisation for *ortho*-HIE with N-H Tetrazoles

Table S1 is a reprint of **Table 1** of the main text, provided for convenience. The general procedure for deuteration using the reaction carousel, as described in **Section 1.2**, was followed. Relevant spectroscopic and spectrometric data are provided in **Section 3** (substrate scope).

Table S1

Entry[a]	Catalyst	Base	*t* / h	*T* / ºC	%D[b]
1	**2**	Et_3N	1	25	7
2	**2**	Cs_2CO_3	1	25	6
3	**3**	Cs_2CO_3	1	25	10
4	**2**	Et_3N	2	37.5	10
5	**2**	Cs_2CO_3	2	37.5	15
6	**3**	Et_3N	2	37.5	0
7	**3**	Cs_2CO_3	2	37.5	66
8	**2**	Et_3N	3	50	5
9	**2**	Cs_2CO_3	3	50	83
10	**2**	Cs_2CO_3	1	50	72
11	**3**	Cs_2CO_3	1	50	80
12	**3**	**Cs_2CO_3**	**3**	**50**	**85**
13[c]	**3**	Cs_2CO_3	3	50	81
14	**3**	-	3	50	<5

[a] Standard reagent quantities: D_2 (1 atm), **1** (0.086 mmol, 13.8 mg), Cs_2CO_3 (0.043 mmol, 14.0 mg) or Et_3N (0.043 mmol, 0.006 mL), **2** (5 mol%, 4.4 mg) or **3** (5 mol%, 7.4 mg).
[b] D incorporation determined by ^1H NMR spectroscopy.
[c] Reaction carried out using 2.5 mol% of catalyst **3**.

3. Substrate Scope for Tetrazole *ortho*-HIE Protocol

3.1 Notes

1. In the ^{1}H NMR spectroscopic data reported for the tetrazoles, the *N*-H protons are not visible and are thus not reported.

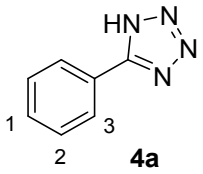
2. Literature references are provided for the characterisation data of known compounds.

3. For each substrate, an overlay is shown of the ^{1}H NMR spectra of both the starting tetrazole (green, top spectrum) and the labelled material (black, bottom spectrum). The integrals used to determine the level of incorporation on the labelled material are shown on the corresponding spectrum. Please note that only the ^{1}H NMR spectrum of the labelled material is aligned with the x-axis (ppm).

4. In all reactions reported for the substrate scope (**Scheme 2**, main text), catalyst **3** (7.4 mg, 0.0043 mmol, 5 mol%) was employed. All reactions in **Scheme 2** used 1 mL from a stock solution of Cs_2CO_3 (0.043 mM in methanol) as the combined source of solvent and base, and all reactions employed a temperature of 50 °C. Following the general procedure, results are reported as a) amount of substrate, b) reaction time, and c) level of deuterium incorporation.

3.2 Tetrazole Substrate Scope

5-Phenyl-1H-tetrazole ***4a***[1]



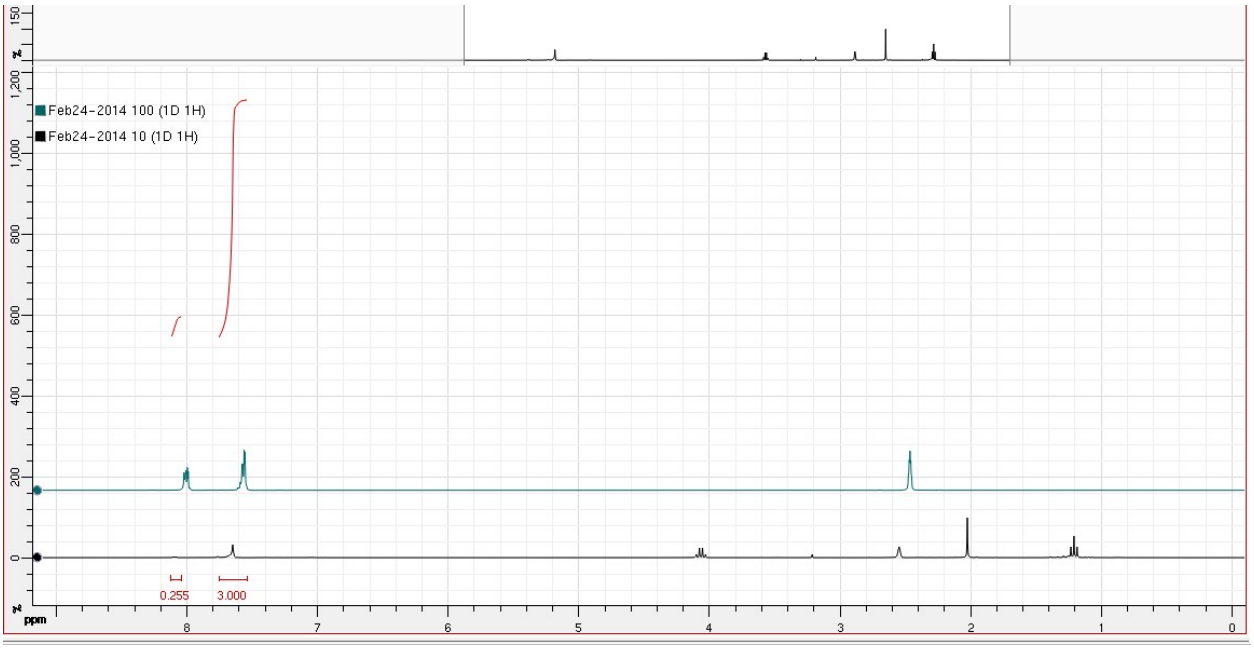
4a

Chemical Formula: $C_7H_6N_4$
Molecular Weight: 146.15

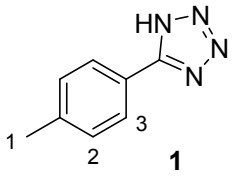
^{1}H NMR (300 MHz, DMSO-d_6): δ 8.05–8.02 (m, 2H, ArH^3), 7.63–7.58 (m, 3H, ArH^1 + ArH^2). Incorporation expected at δ 8.05–8.02. Determined against integral at δ 7.63–7.58.

HRMS (positive ESI): m/z calculated for $C_7H_5D_2N_4^+$ $[M\text{-}d_2+H]^+$: 149.0796; found: 149.0791.

a) 12.6 mg, 0.086 mmol, b) 3 h and c) 87% D.



5-(4'-Methylphenyl)-1H-tetrazole ***1***[2]



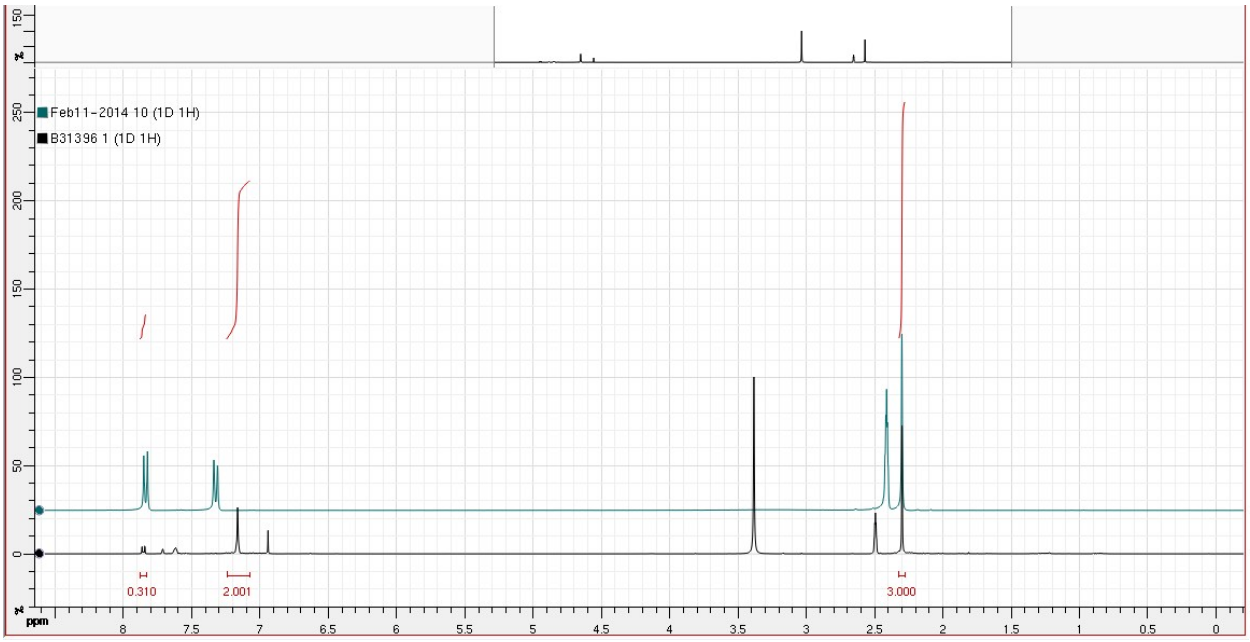
1

Chemical Formula: $C_8H_8N_4$
Molecular Weight: 160.18

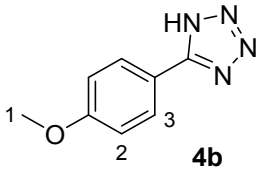
^{1}H NMR (300 MHz, DMSO-d_6): δ 7.92 (d, 2H, *J* = 8.1 Hz, ArH^3), 7.40 (d, 2H, *J* = 8.1 Hz, ArH^2), 2.38 (s, 3H, $ArCH_3$[1]). Incorporation expected at δ 7.92. Determined against integral at δ 2.38.

HRMS (positive ESI): m/z calculated for $C_8H_7D_2N_4^+$ $[M\text{-}d_2+H]^+$: 163.0947; found: 163.0946.

a) 13.8 mg, 0.086 mmol, b) 3 h, and c) 85% D.



5-(4'-Methoxyphenyl)-1H-tetrazole ***4b***[3]



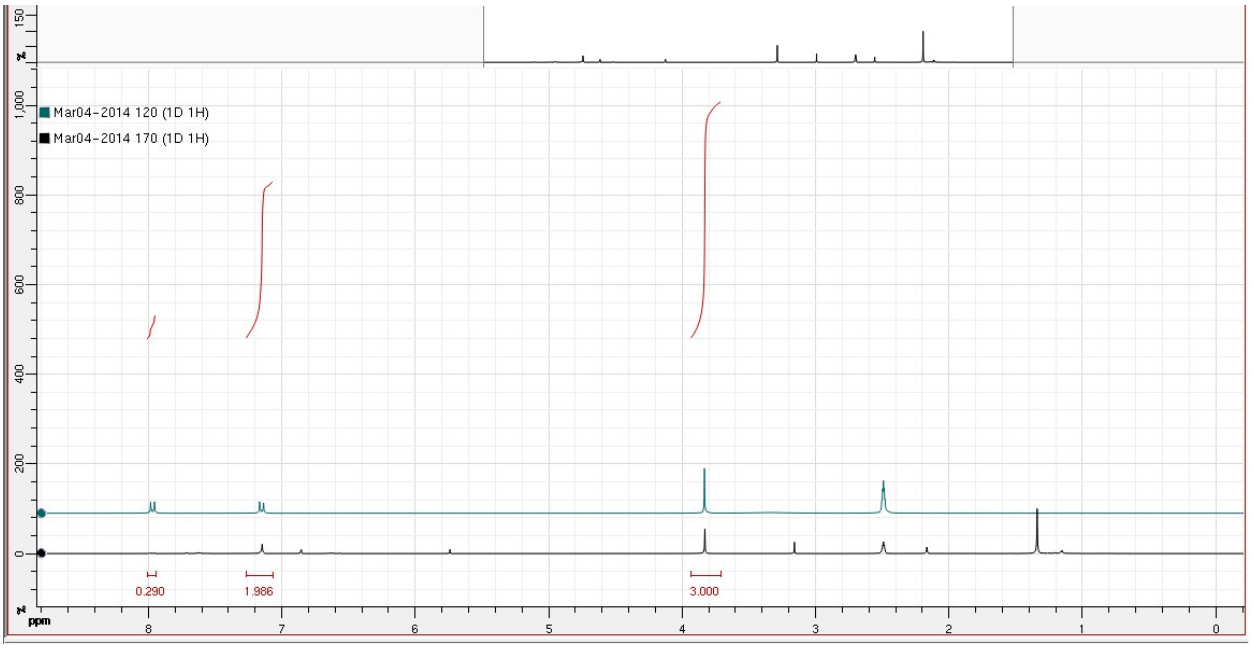
4b

Chemical Formula: $C_8H_8N_4O$
Molecular Weight: 176.18

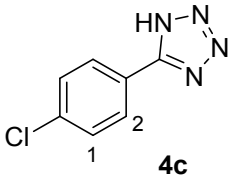
^{1}H NMR (300 MHz, DMSO-d_6): δ 7.97 (d, 2H, *J* = 8.8 Hz, ArH^3), 7.15 (d, 2H, *J* = 8.8 Hz, ArH^2), 3.83 (s, 3H, OCH_3^{1}). Incorporation expected at δ 7.97. Determined against integral at δ 3.83.

HRMS (positive ESI): m/z calculated for $C_8H_7D_2N_4O^+$ $[M\text{-}d_2+H]^+$: 179.0896; found: 179.0895.

a) 15.2 mg, 0.086 mmol, b) 3 h, and c) 86% D.



5-(4'-Chlorophenyl)-1H-tetrazole ***4c***[4]



4c

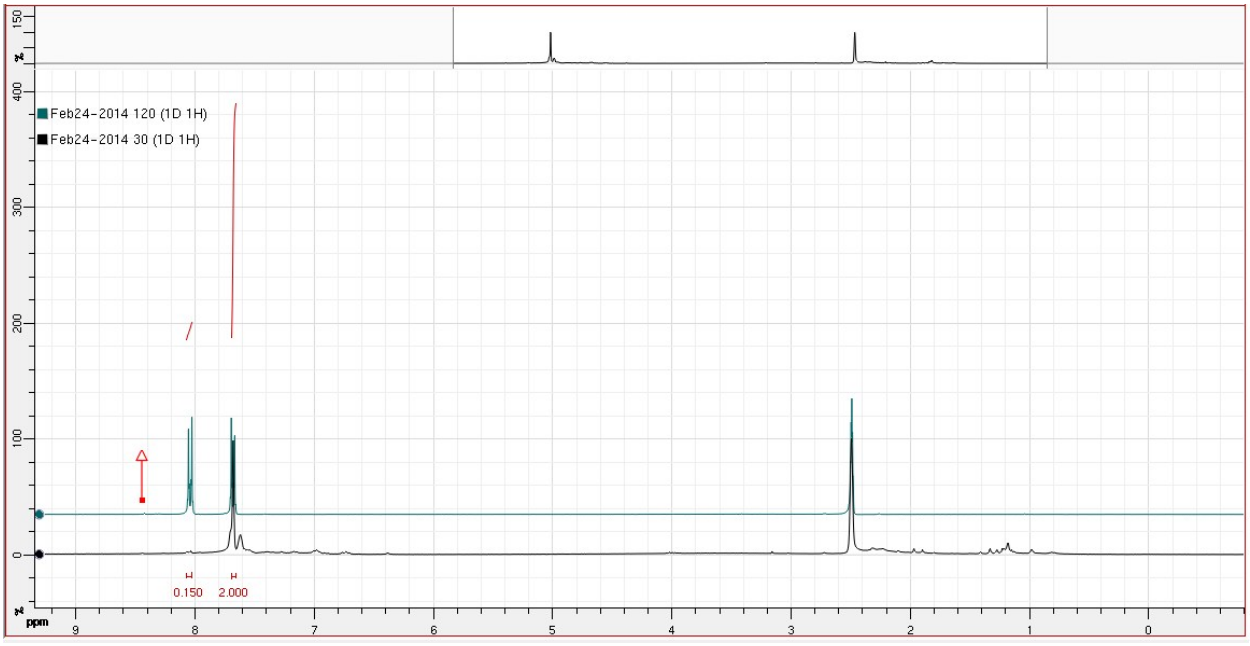
Chemical Formula: $C_7H_5ClN_4$
Molecular Weight: 180.60

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.04 (d, 2H, *J* = 8.6 Hz, ArH^2), 7.68 (d, 2H, *J* = 8.6 Hz, ArH^1). Incorporation expected at δ 8.04. Determined against integral at δ 7.68.

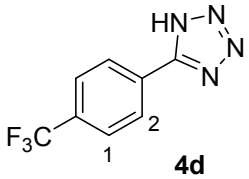
HRMS (positive ESI): m/z calculated for $C_7H_4D_2{}^{35}ClN_4{}^+$ $[M\text{-}d_2+H]^+$: 183.0407; found: 183.0398.

HRMS (positive ESI): m/z calculated for $C_7H_4D_2{}^{37}ClN_4{}^+$ $[M\text{-}d_2+H]^+$: 185.0377; found: 185.0372.

a) 15.5 mg, 0.086 mmol, b) 3 h, and c) 93% D.



5-(4'-Trifluoromethylphenyl)-1H-tetrazole ***4d*** [5]



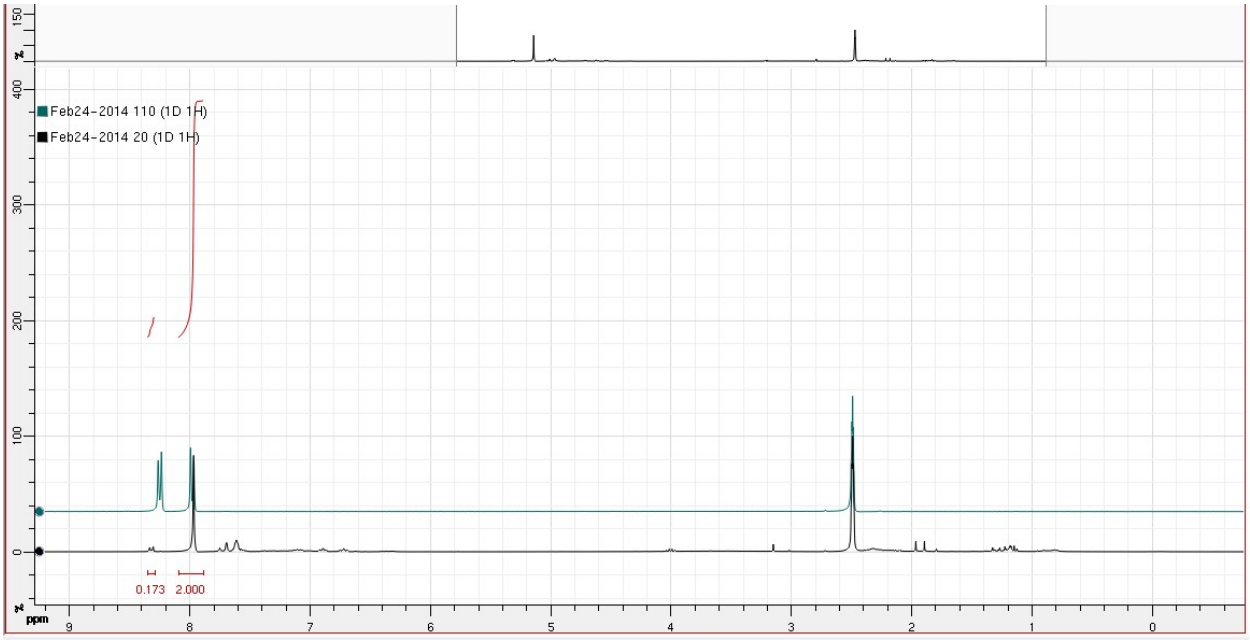
4d

Chemical Formula: $C_8H_5F_3N_4$
Molecular Weight: 214.15

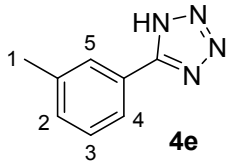
^{1}H NMR (300 MHz, DMSO-d_6): δ 8.25 (d, 2H, *J* = 8.3 Hz, ArH^2), 7.98 (d, 2H, *J* = 8.3 Hz, ArH^1). Incorporation expected at δ 8.25. Determined against integral at δ 7.98.

HRMS (positive ESI): m/z calculated for $C_8H_4D_2F_3N_4^+$ $[M\text{-}d_2+H]^+$: 217.0670; found: 217.0665.

a) 18.4 mg, 0.086 mmol, b) 3 h, and c) 91% D.



5-(3-Methylphenyl)-1H-tetrazole ***4e***[6]



4e

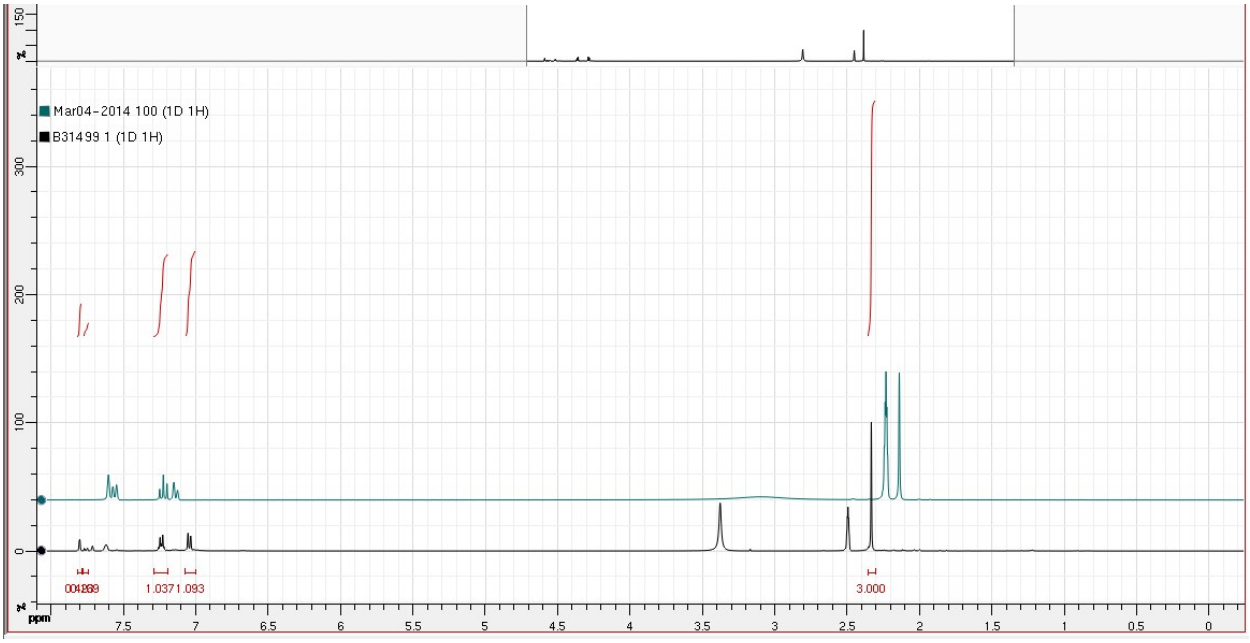
Chemical Formula: $C_8H_8N_4$
Molecular Weight: 160.18

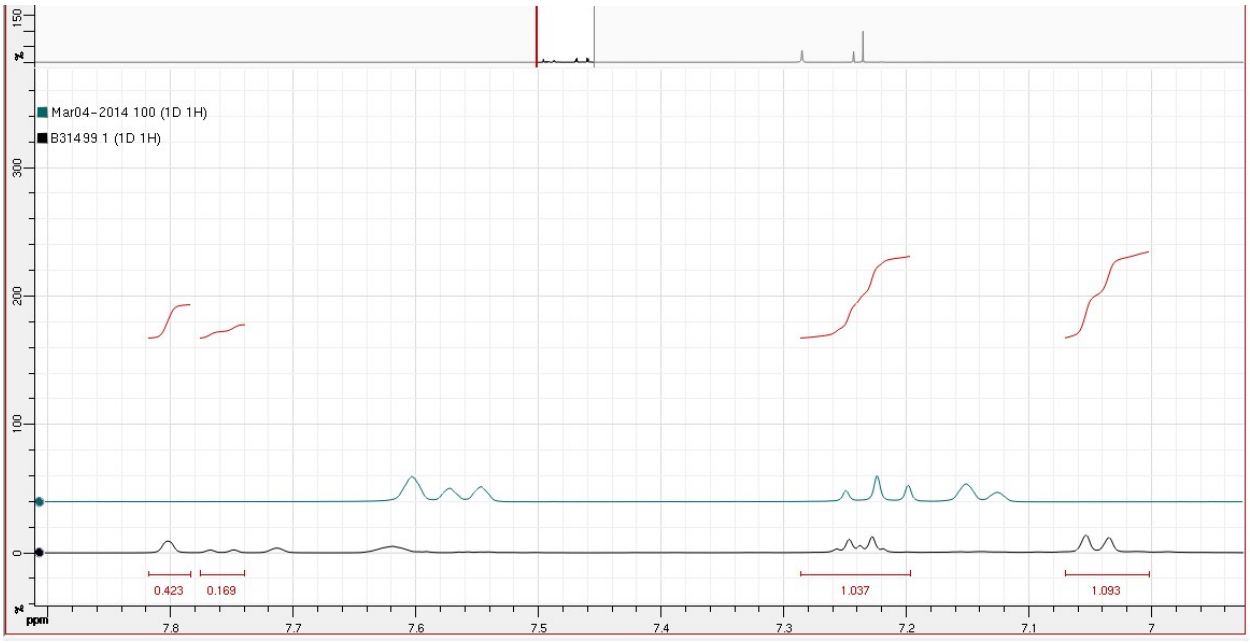
^{1}H NMR (300 MHz, DMSO-d$_6$): δ 7.86 (s, 1H, ArH^5), 7.82 (d, 1H, *J* = 7.7 Hz, ArH^4), 7.48 (t, 1H, *J* = 7.7 Hz, ArH^3), 7.41–7.39 (m, 1H, ArH^2), 2.40 (s, 3H, ArCH$_3$). Incorporation expected at δ 7.86 and 7.82. Determined against integral at δ 2.40.

HRMS (positive ESI): m/z calculated for $C_8H_7D_2N_4^+$ $[M\text{-}d_2+H]^+$: 163.0947; found: 163.0946.

HRMS (positive ESI): m/z calculated for $C_8H_8DN_4^+$ $[M\text{-}d_1+H]^+$: 162.0884; found: 162.0884.

a) 13.8 mg, 0.086 mmol, b) 3 h, and c) 83% D (ArH^4), 58% D (ArH^5).

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B31499 1 (1D 1H)
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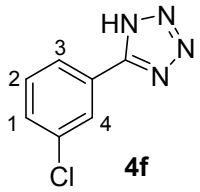
1.037
1.093
ppm

5-(3-Chlorophenyl)-1H-tetrazole ***4f*** [7]



4f

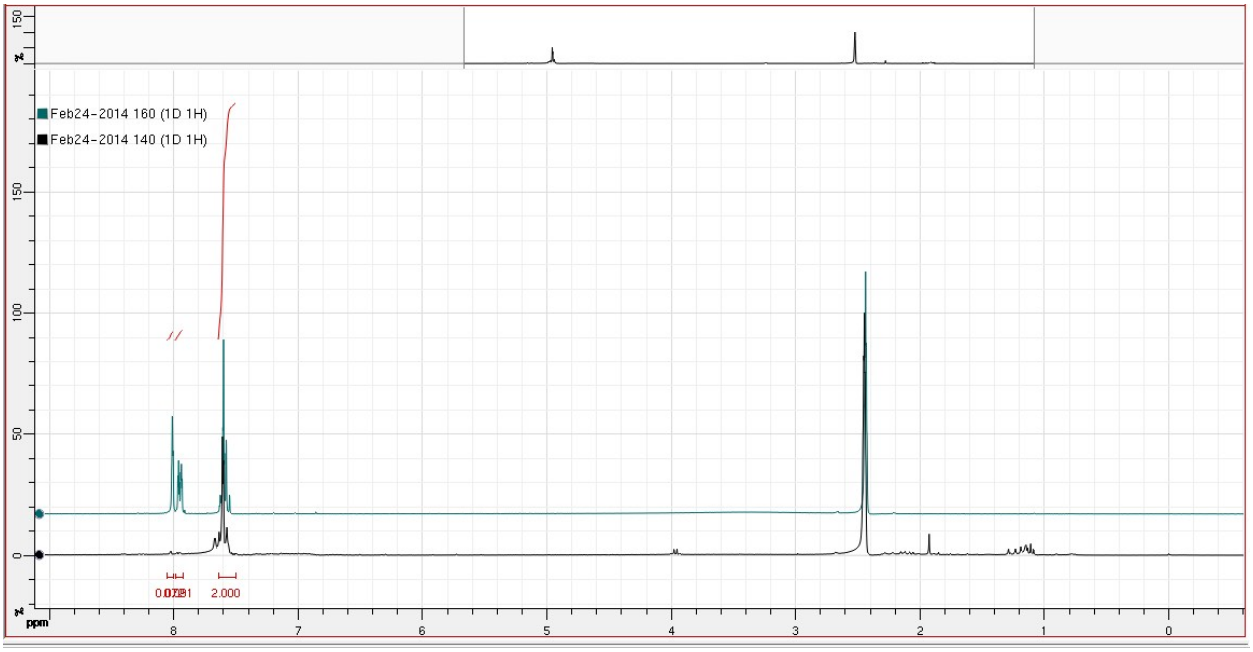
Chemical Formula: $C_7H_5ClN_4$
Molecular Weight: 180.60

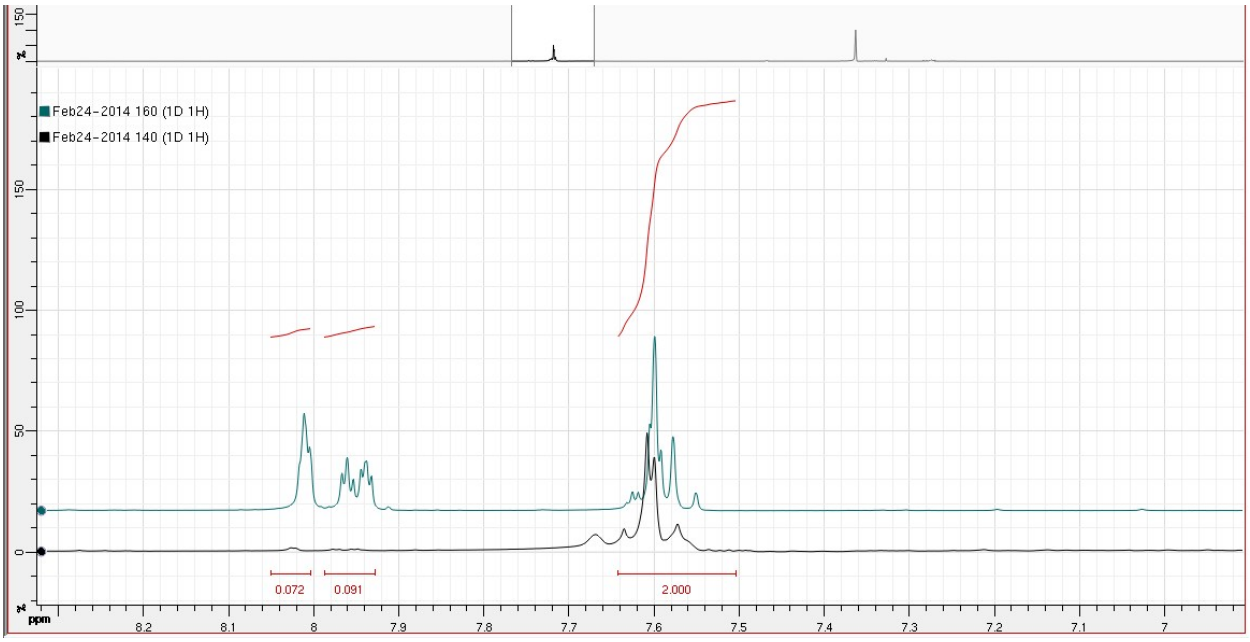
^{1}H NMR (300 MHz, DMSO-d_6): δ 8.07–8.06 (m, 1H, ArH^4), 8.02–7.98 (m, 1H, ArH^3), 7.68–7.60 (m, 2H, ArH^1 + ArH^2). Incorporation expected at δ 8.07–8.06 and 8.02–7.98. Determined against integral at δ 7.68–7.60.

HRMS (positive ESI): m/z calculated for $C_7H_4D_2{}^{35}ClN_4{}^+$ $[M\text{-}d_2+H]^+$: 183.0407; found: 183.0403.

HRMS (positive ESI): m/z calculated for $C_7H_4D_2{}^{37}ClN_4{}^+$ $[M\text{-}d_2+H]^+$: 185.0377; found: 185.0372

a) 15.5 mg, 0.086 mmol, b) 3 h, and c) 91% D (ArH^3), 93% D (ArH^4).




Feb24-2014 160 (1D 1H)
Feb24-2014 140 (1D 1H)
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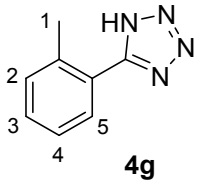
0.091
2.000
ppm

5-(2-Methylphenyl)-1H-tetrazole ***4g***[2]



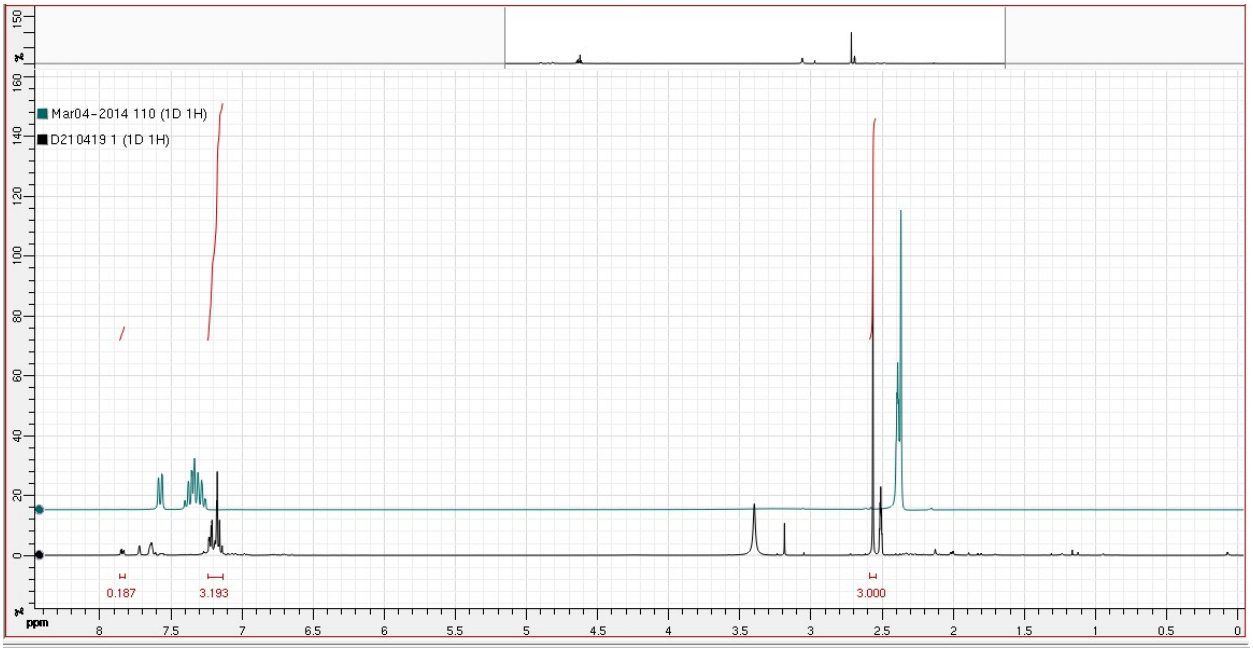
4g

Chemical Formula: $C_8H_8N_4$
Molecular Weight: 160.18

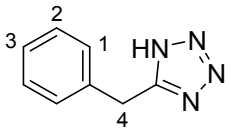
^{1}H NMR (300 MHz, DMSO-d_6): δ 7.92 (d, 1H, *J* = 7.6 Hz, ArH^5), 7.50–7.36 (m, 3H, ArH^{2-4}), 2.43 (s, 3H, ArCH_3^1). Incorporation expected at δ 7.92. Determined against integral at δ 2.43.

HRMS (positive ESI): m/z calculated for $C_8H_8DN_4^+$ $[M\text{-}d_1+H]^+$: 162.0890; found: 162.0884.

a) 13.8 mg, 0.086 mmol, b) 16 h, and c) 81% D.



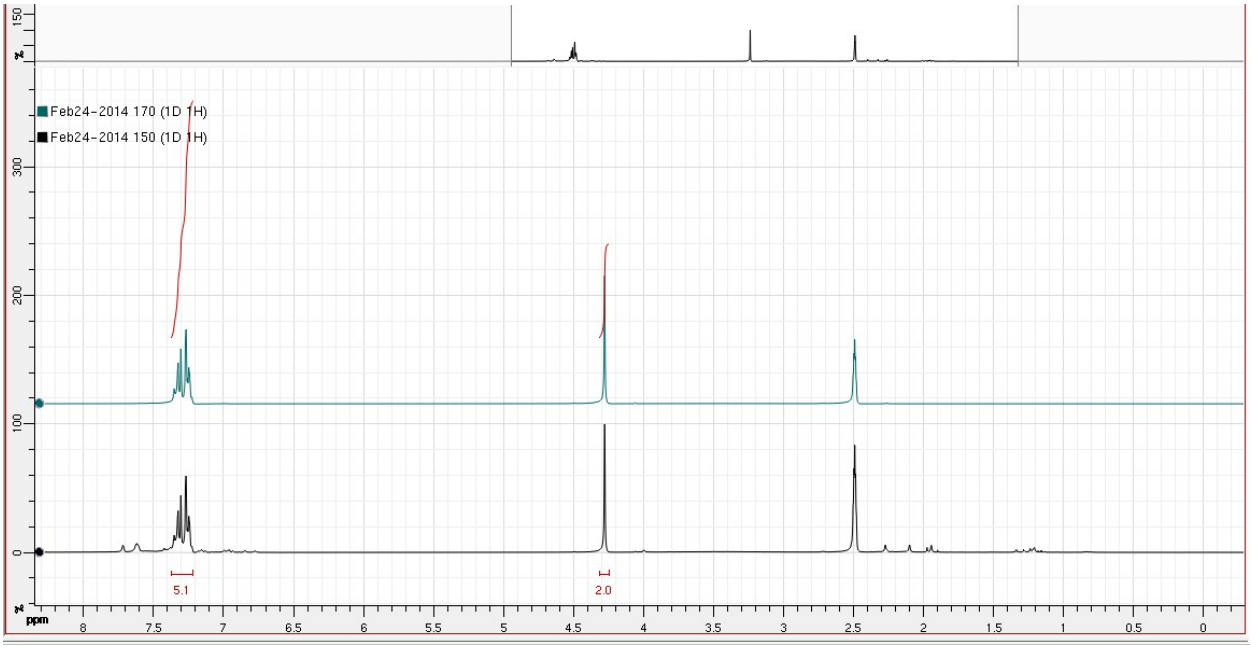
5-Benzyl-1H-tetrazole[1] (Not shown in Scheme 2 but discussed in the manuscript text)



Chemical Formula: $C_8H_8N_4$
Molecular Weight: 160.18

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.35–7.25 (m, 5H, ArH^{1-3}), 4.28 (s, 2H, $PhCH_2^4$). Incorporation expected at δ 7.35–7.25. Determined against integral at δ 4.28.

a) 13.8 mg, 0.086 mmol, b) 3 h, and c) 0% D.



4. Isotope Labelling of Valsartan

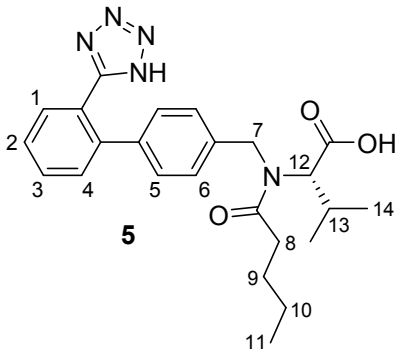
4.1 Deuteration of Valsartan

The deuterium labelling reaction was carried out in a Heidolph Synthesis 1 Liquid 16 device. **NOTE**: compared to the Radley carousel, the Heidolph system possesses smaller reaction tubes (10 mL *versus* 25 mL). This results in an overall reduced excess of deuterium gas.

Following the general procedure, no work-up of the sample was carried out. Results adjacent to spectroscopic data are reported as: a) amount of **5**, b) amount of **3**, c) amount of Cs_2CO_3, d) amount of MeOH, e) reaction temperature, f) reaction time, and g) %D.

It has been reported in the literature that Valsartan **5** exists in solution as a pair of rotamers, due to hindered rotation around the amide bond.[8] In light of these complications, full ^{1}H NMR spectroscopic analysis of **5** is not provided. Instead, partial analysis of the aromatic and stereogenic protons is given, along with the LC-MS trace showing the predominance of **5**-d_1.

*Valsartan **5***



5

Chemical Formula: $C_{24}H_{29}N_5O_3$
Molecular Weight: 435.52

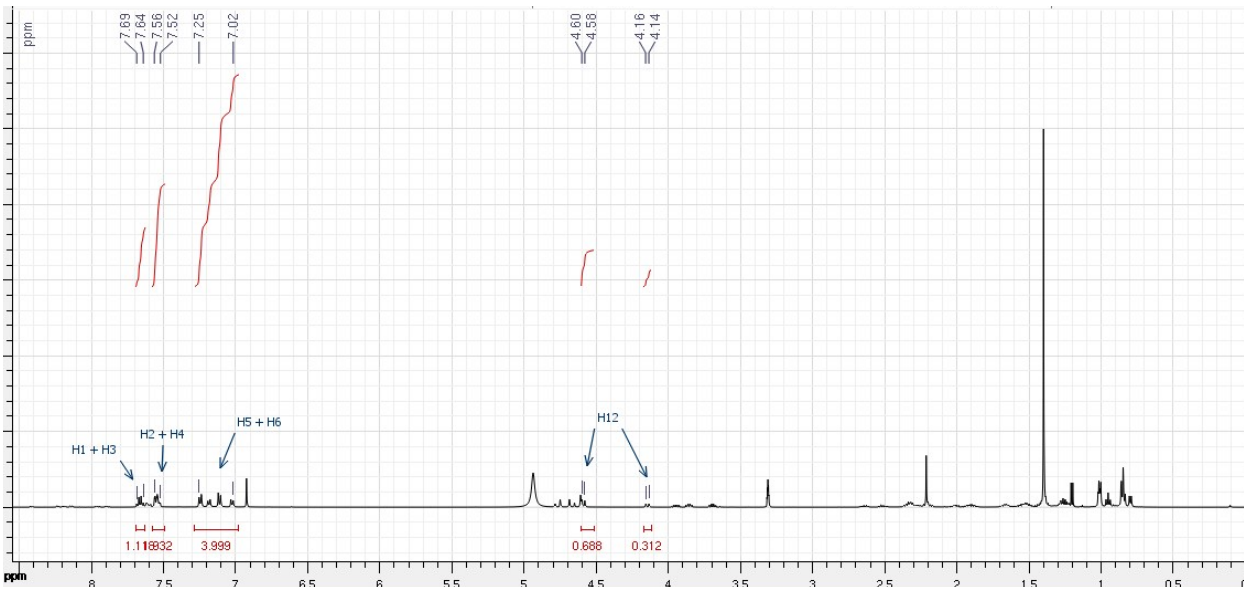
^{1}H NMR (500 MHz, DMSO-d_6): δ 7.69–7.64 (m, 2H, ArH^1 + ArH^3), 7.56–7.52 (m, 2H, ArH^2 + ArH^4), 7.25–7.02 (2 × d, with each d split in the ratio 2:1 according to the presence of two rotamers, 4H in total, both d share J = 8.3 Hz, ArH^5 + ArH^6), 4.59 and 4.15 (1 × d split in the ratio 2:1 according to the presence of two rotamers, 1H in total,

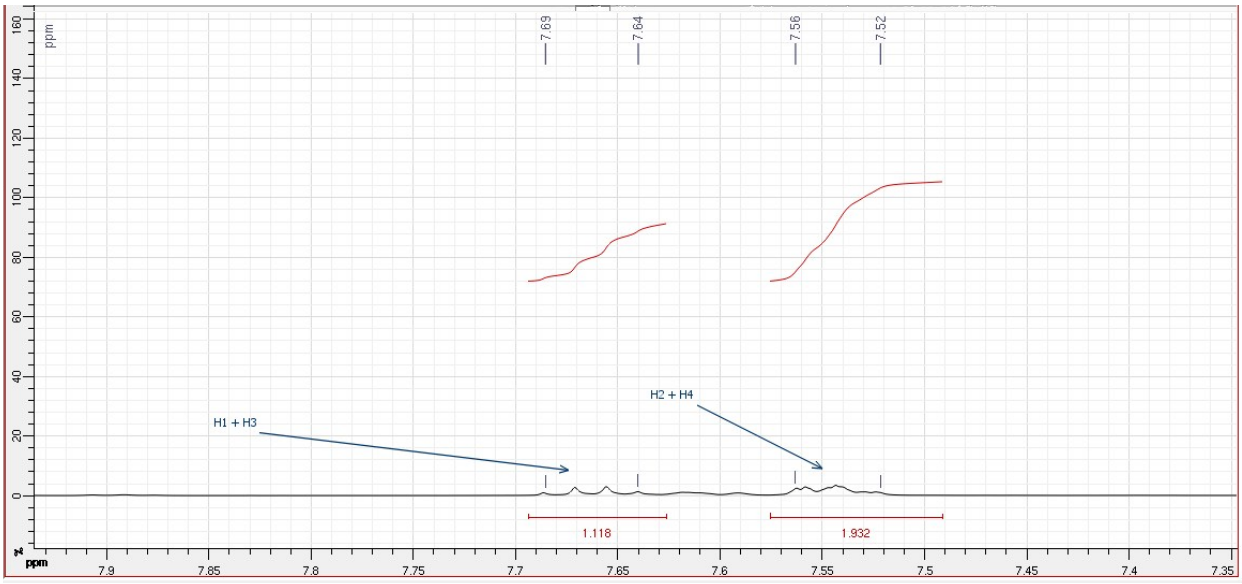
both d share J = 10.6 Hz, CH^{12}). Incorporation expected at δ 7.69–7.64. Determined against integral at δ 7.25–7.02.

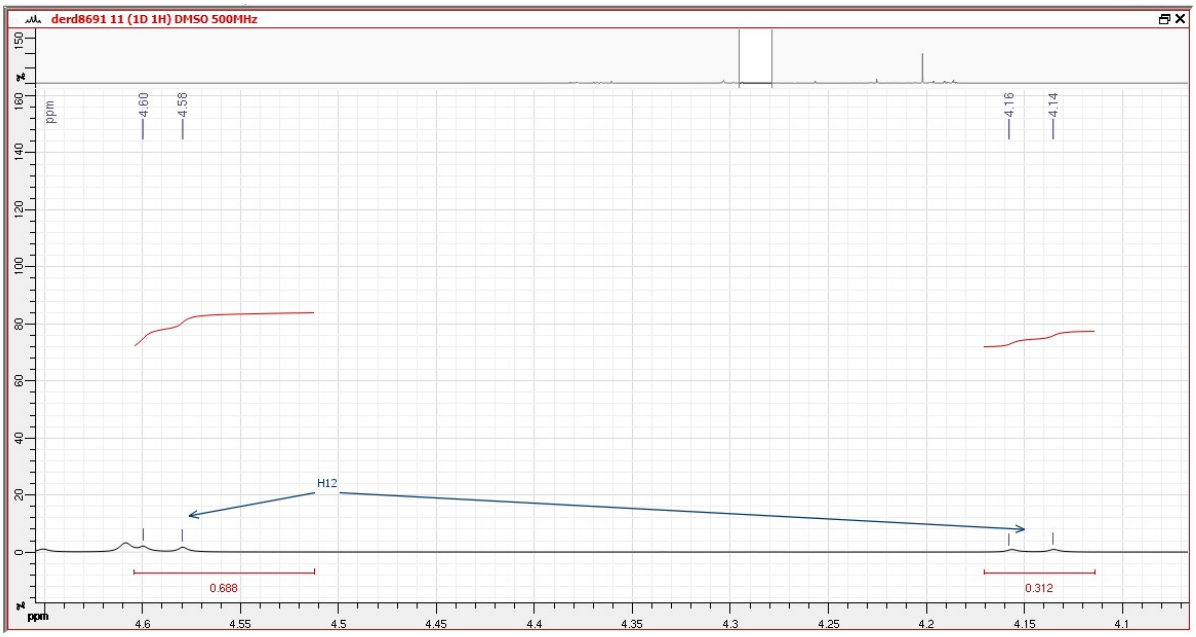
HRMS (positive ESI): m/z calculated for $C_{24}H_{29}DN_5O_3^+$ $[M\text{-}d_1+H]^+$: 437.2412; found: 437.2406.

a) 18.5 mg, 0.043 mmol, b) 3.7 mg, 0.002 mmol, 5 mol%, c) 14.0 mg, 0.043 mmol, d) 1mL, e) 50 °C, f) 6 h, and g) 88% D.

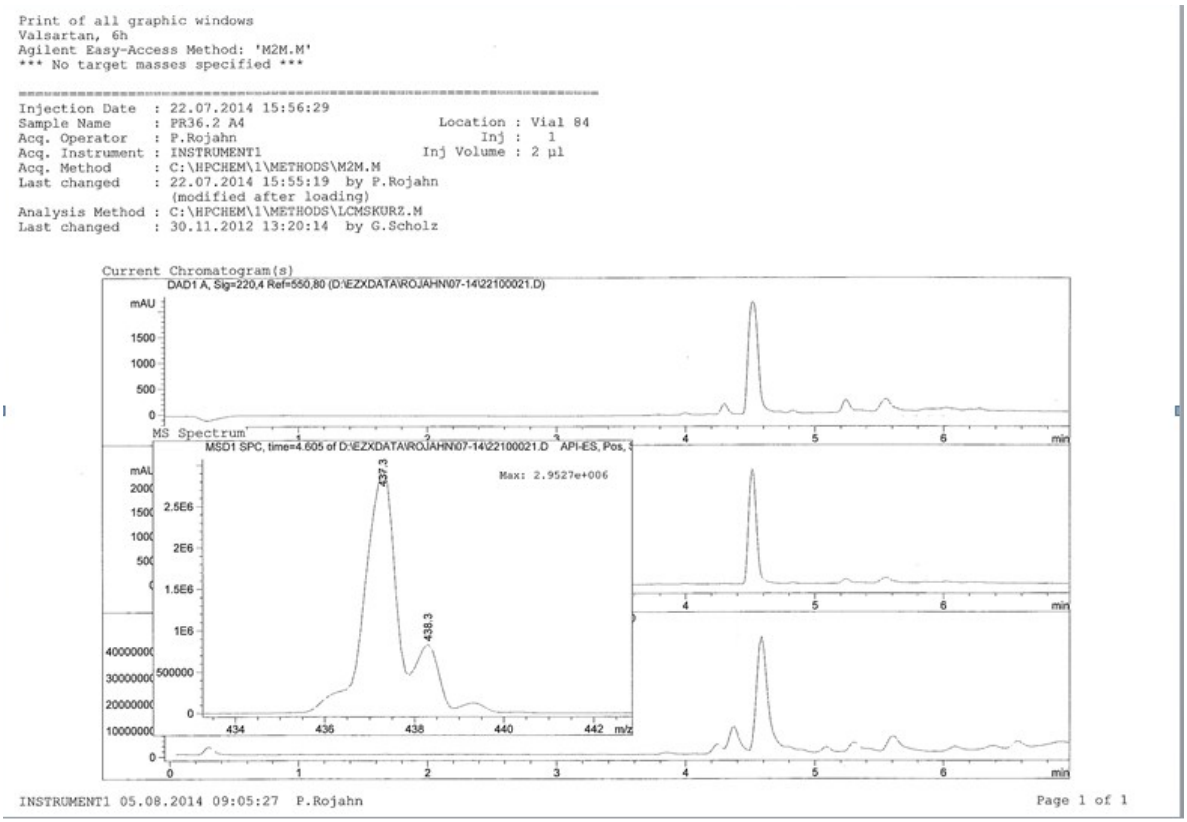
The ^1H NMR spectrum of deuterium labelled Valsartan **5** is shown below, followed by expansions of the 7.4–7.9 ppm and 4.1–4.6 ppm regions, respectively. From this, it can be seen that the stereogenic proton, H^{12}, remains largely unchanged, with an estimated total integration of ~1H:




ppm
7.69
7.64
7.56
7.52
H1 + H3
H2 + H4
1.118
1.932
7.9
7.85
7.8
7.75
7.7
7.65
7.6
7.55
7.5
7.45
7.4
7.35


derd8691 11 (1D 1H) DMSO 500MHz
ppm
4.60
4.58
4.16
4.14
H12
0.688
0.312
4.6
4.55
4.5
4.45
4.4
4.35
4.3
4.25
4.2
4.15
4.1

LC-MS (System 1) supports the presence of **5**-d_1 as the major product:



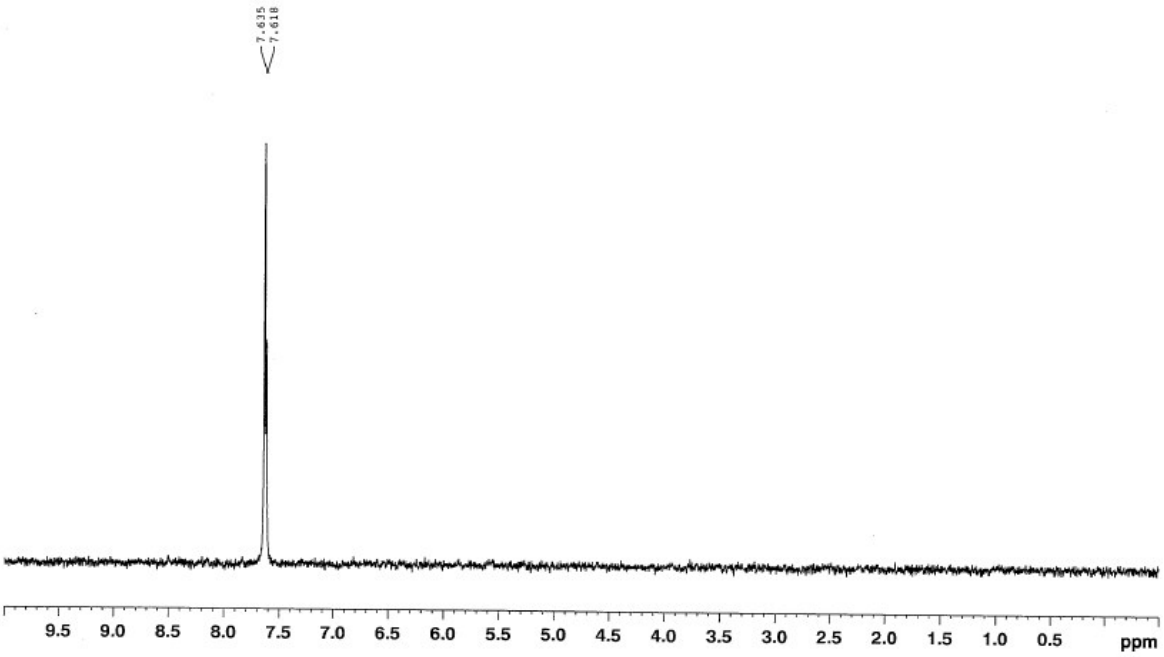
4.2 Tritiation of Valsartan

The tritiation of Valsartan **5** was carried out at Sanofi (Frankfurt) using a standard Tritec® tritium manifold. Valsartan **5** (3.5 mg, 8.0 μmol), Cs_2CO_3 (2.62 mg, 8.0 μmol, 1 eq.), and catalyst **3** (0.7 mg, 8.0 μmol, 6.7 mol%) were dissolved in MeOH (0.7 mL) in a 1.0 mL reaction flask before being connected to the manifold. The solution was frozen in liquid nitrogen and the flask was evacuated, then charged with tritium (1.5 Ci, 212–370 mbar). The reaction mixture was then allowed to warm to room temperature over 15 min before stirring at r.t. for a further 30 min (212 mbar pressure). The reaction mixture was then heated to 50 °C (370 mbar pressure) and stirred for 45 min before cooling again to r.t. and stirring for a final 2 h. Purification and isolation *via* HPLC gave the tritiated product (0.91 mg, **5**-T_1, 98.9% radiochemical purity). Radiochemical purity was established by comparison of the activity of the product-containing CH_3CN/H_2O fraction following HPLC purification (1168.7 MBq), with the activity of **5**-T_1 (15 Ci/mmol), which was measured by TOF-MS.

^{3}H NMR (533 MHz, DMSO-d_6): δ 7.63 (d, 1H, $^3J_{H\text{-}T}$ = 9.1 Hz, ArH^1)
HRMS (positive ESI): m/z calculated for $C_{24}H_{29}TN_5O_3^+$ $[M\text{-}t_1+H]^+$: 438.2431; found: 438.2502.

The ^{3}H NMR spectrum, below, shows tritium incorporation *ortho* to the tetrazole only:

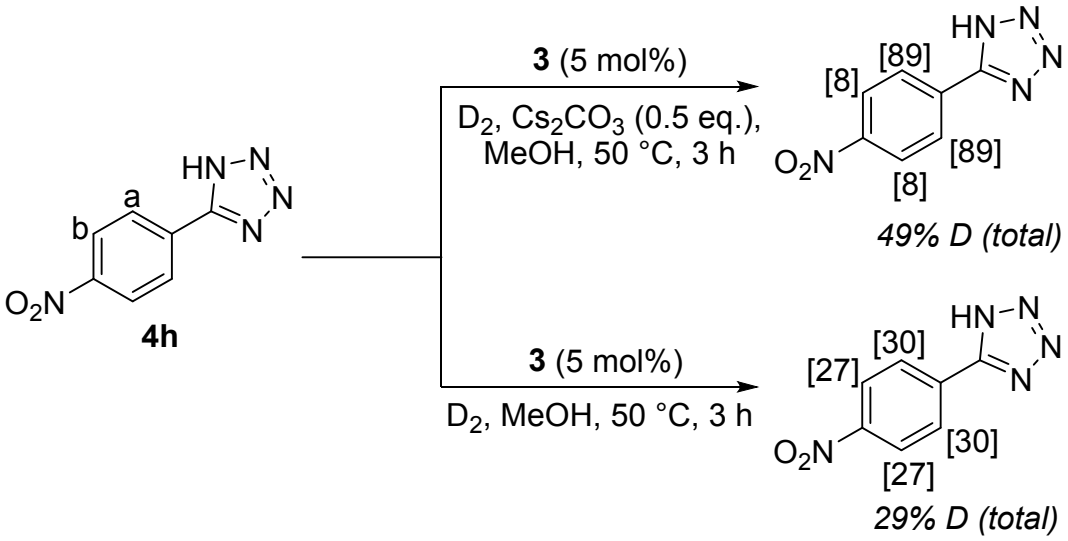
533MHz 3H/T Dr.De Valsartan-T FFC.URA.055.1 0.05mg ; DMSO-d6
zg3h1Hig



5. Investigating Nitro versus Tetrazole Labelling

In both studies, substrate **4h** (16.4 mg, 0.086 mmol) was employed with catalyst **3** (7.4 mg, 0.0043 mmol, 5 mol%). The basic reaction (**Table S2**, entry 1) employed base from a stock solution of Cs_2CO_3 (1 mL, 0.043 mM in MeOH) as the combined source of solvent and base. The base-free reaction (**Table S2**, entry 2) used MeOH (1 mL) as the solvent rather than the stock base solution. The general labelling procedure for the optimized deuteration conditions was followed otherwise, and no work-up was used before analysis. The results are summarised in **Table S2**.

Table S2

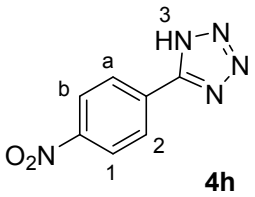


Entry	Conditions	%D[a]	%D[b]
1[a]	basic	89	8
2[b]	base-free	30	27

[a] Conditions: **4h** (16.4 mg,), Cs_2CO_3 (1 mL, 0.043 mM in MeOH), **3** (5 mol%), 3 h, 50 °C.

[b] Conditions: **4h** (16.4 mg), MeOH (1 mL), **3** (5 mol%), 3 h, 50 °C.

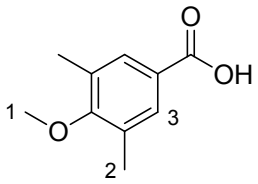
5-(4-Nitrophenyl)-1H-tetrazole ***4h***[9]



4h

Chemical Formula: $C_7H_5N_5O_2$
Molecular Weight: 191.15

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.42 (d, 2H, *J* = 8.8 Hz, ArH^1), 8.29 (d, 2H, *J* = 8.8 Hz, ArH^2). Incorporation expected at all positions. For the base-free reaction, incorporation at positions ArH^1 and ArH^2 was measured against an equimolar quantity of the following internal standard (15.5 mg, 0.086 mmol):



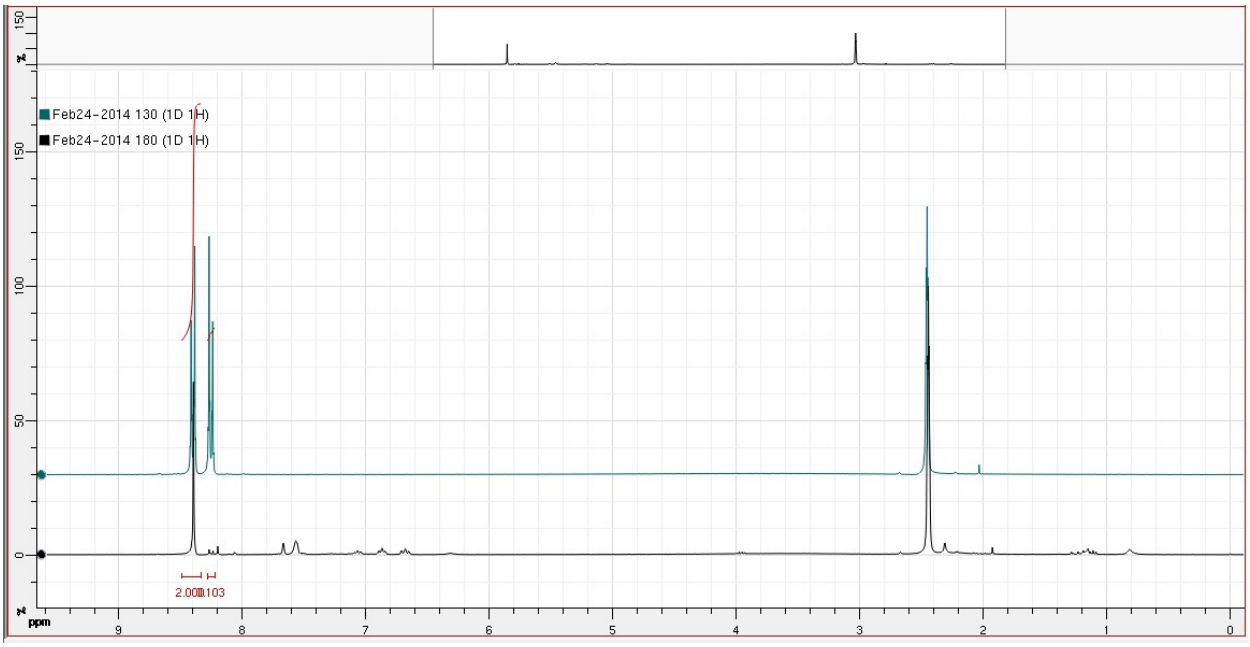
Chemical Formula: $C_{10}H_{12}O_3$
Molecular Weight: 180.20

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.61 (s, 2H, ArH^3), 3.67 (s, 3H, ArOCH_3^1), 2.23 (s, 6H, ArCH_3^2). Signal at δ 3.67 used to calibrate the extent of integrals in labelled **4i**.

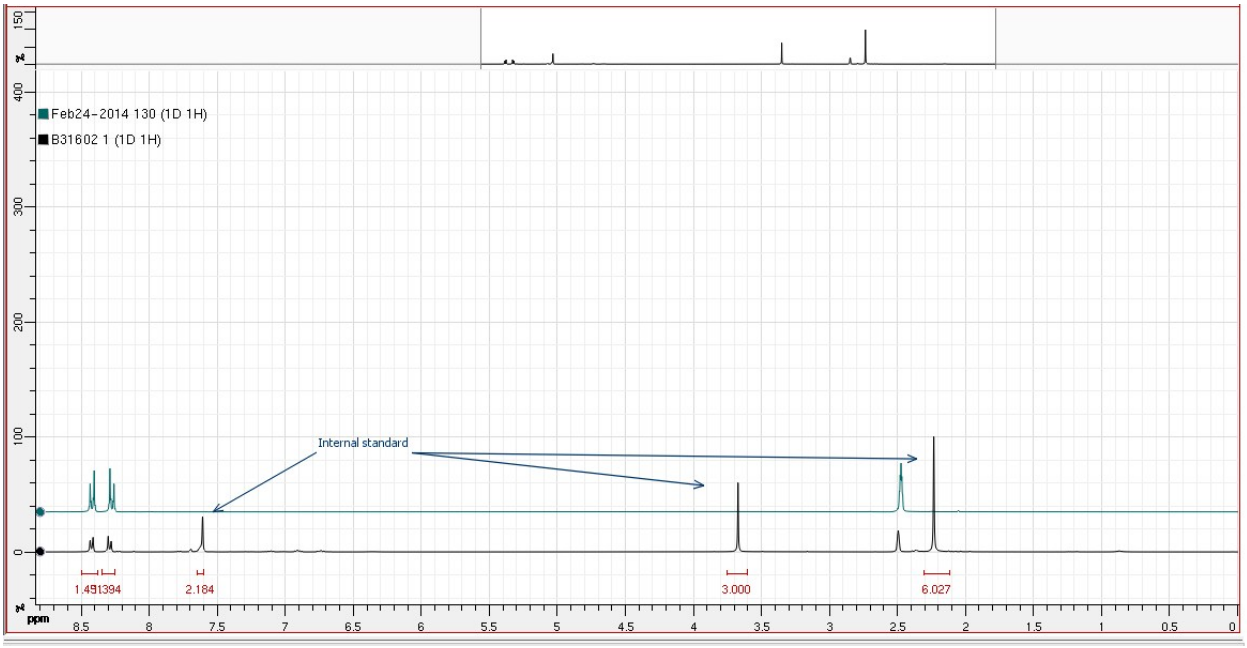
For the base-mediated reaction, the ratio of ^{1}H NMR spectrum signals in the product was compared to HRMS data in order to estimate the %D adjacent to each directing group. Specifically, a ^{1}H NMR spectrum residual peak ratio of 1:0.095 b:a (*i.e.* favouring tetrazole labelling) was compared to HRMS peaks $[M\text{-}d_n+H]^+$ (*n* = 1, 2, 3) in the ratio 7.4:85.0:7.6 (d_1:d_2:d_3). This translates to approximately 89% D^a and 8% D^b.

HRMS (positive ESI): m/z calculated for $C_7H_4D_2N_5O_2^+$ $[M\text{-}d_2+H]^+$: 194.0647; found: 194.0655.

With base:



Without base:



6. Mechanistic Studies

6.1 Investigating the pH of the Reaction and Likely State of the Tetrazole

Methyl red indicator test

As described in the results section (main text), substrate **4d** was used in repeat experiments of the conditions from **Table 1**, Entries 12 and 14. In the first instance, these two reactions were compared visually (after the 3 h reaction time) without the addition of indicator (top, **Figure S1**). Separately, two more reactions were carried out, and a similar visual comparison made *after* the addition of a spatula-tip of methyl red into each carousel flask (bottom, **Figure S1**). See **Figure S1** below for a comparison of the reactions with and without indicator; left flask – without base; and right flask – with base.

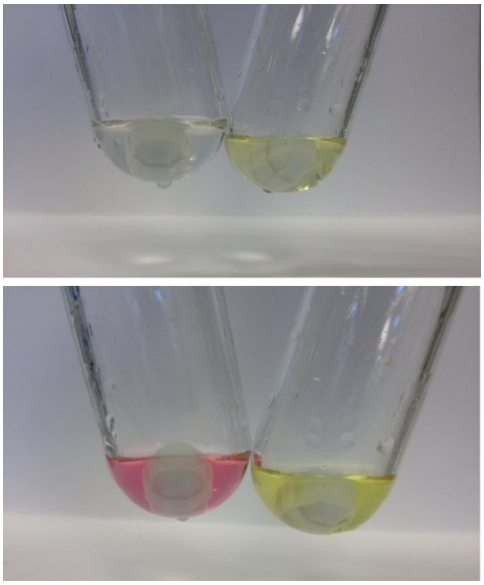
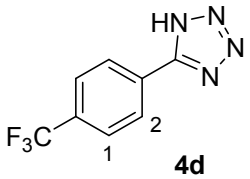


Figure S1. The nature of the substrate versus reaction basicity.

*^{19}F NMR studies of substrate **4d***

NOTE: all NMR studies in this section were carried out separately from the methyl red experiments. The following NMR data relates to the right-hand side of **Figure 1** in the main text.

The relevant data for substrate **4d** in methanol-d_4 are provided below:



4d

Chemical Formula: $C_8H_5F_3N_4$
Molecular Weight: 214.1512

^{1}H NMR (400 MHz, Methanol-d_4): δ 8.24 (d, 2H, *J* = 8.6 Hz, ArH^2), 7.89 (d, 2H, *J* = 8.6 Hz, ArH^1).
^{19}F NMR (376 MHz, Methanol-d_4): δ −64.6 (CF_3).

To assess the effects of the basic reaction conditions on tetrazole **4d**, the substrate (18.4 mg, 0.086 mmol), catalyst **3** (7.4 mg, 0.0043 mmol), and Cs_2CO_3 (14.0 mg, 0.043 mg) were dissolved in methanol-d_4 (1 mL) and added to an oven-dried NMR tube. After sealing the tube with a rubber septum, D_2 was bubbled through the tube for 30 min prior to NMR spectroscopic analysis at 300 K.

Similarly, for assessing the base-free conditions, a sample identical to that above, *minus* the addition of Cs_2CO_3, was prepared in a separate NMR tube.

Comparative ^{1}H NMR spectrum resonances (not shown in the main text) are provided below. In addition, all peak positions and relevant integrations are listed in **Table S3**, below the spectra.

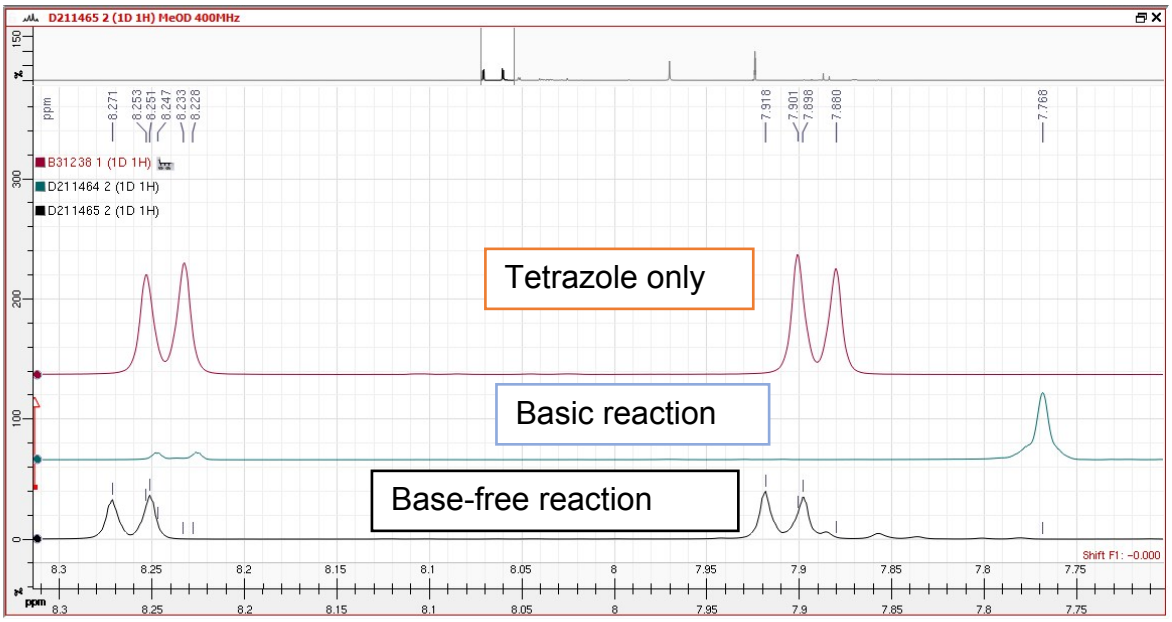


Table S3

Entry	Conditions	^{19}F NMR / ppm	^{1}H NMR / ppm[a]	Integral ratio (ArH^2:ArH^1)
1	Tetrazole only	-64.6	8.24, 7.89	2.0 : 2.0
2[b]	Basic reaction	-64.2	8.24, 7.77	0.3 : 2.0
3	Base-free reaction	-64.6	8.26, 7.91	1.8: 2.0

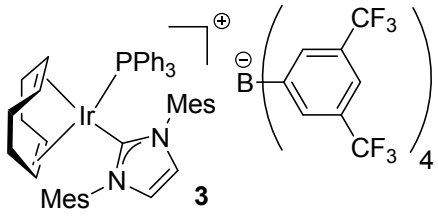
[a] Position of each resonance stated only (no coupling given).

[b] Significant deuterium labelling observed in *ortho*-positions.

6.2 ^{31}P NMR Spectroscopic Study of the Catalyst with Various Components of the Tetrazole Labelling Method

The relevant spectroscopic analyses of complex **3** in methanol-d_4 are given below. **NOTE**: the complex is only sparingly soluble in methanol-d_4 and has to be shaken vigorously to obtain a red solution.

*η^4–Cycloocta-1,5-diene(1,3-dimesitylimidazol-2-ylidene)(triphenylphosphine)iridium(I) tetrakis[(3,5-trifluoromethylphenyl)]borate **3***[10]



3

Chemical Formula: $C_{79}H_{63}BF_{24}IrN_2P$
Molecular Weight: 1730.35

^{1}H NMR (400 MHz, methanol-d_4): δ 7.74 (s, 2H, NCH=CHN), 7.61–7.59 (m, 12H, ArH_{BArF}), 7.52–7.48 (m, 3H, ArH), 7.38–7.33 (m, 6H, ArH), 7.24–7.19 (m, 6H, ArH), 7.13 (s, 2H, ArH), 6.76 (s, 2H, ArH), 4.48–4.45 (m, 2H, COD CH), 3.39–3.36 (m, 2H, COD CH), 2.37 (s, 6H, $ArCH_3$), 2.17 (s, 6H, $ArCH_3$), 1.83 (s, 6H, $ArCH_3$), 1.76–1.52 (m, 6H, COD CH_2), 1.34–1.29 (m, 2H, COD CH_2).

^{31}P NMR (162 MHz, methanol-d_4): δ 16.2 (PPh_3).

^{19}F NMR (376 MHz, methanol-d_4): δ −64.3 (BAr^F $ArCF_3$). These spectral details were largely unchanged between 300 K and 318 K.

Triphenylphosphine

^{31}P NMR (162 MHz, methanol-d_4): δ −5.94 (PPh_3).

Triphenylphosphine oxide

^{31}P NMR (162 MHz, methanol-d_4): δ 32.1 (Ph_3P=O).

A $^{31}P\{^{1}H\}$ NMR spectroscopic study of the catalyst in methanol-d_4 under various conditions revealed an intriguing variation in the phosphine-containing species present in solution. A single peak at 16.2 ppm was visible for the precatalyst, **3**, in the absence of any other reagent. Interestingly, whether mixing either **3** with H_2, or **3** with Cs_2CO_3, complete conversion to a peak at 32.3 ppm, corresponding to $Ph_3P{=}O$, was observed in both cases. Only when **3**, Cs_2CO_3, and H_2 were mixed together, were distinct peaks at 14.2 and 13.3 ppm observed, corresponding to the active catalyst, with both signals persisting in the presence of tetrazole **4d**. **Figure S2** below shows the $^{31}P\{^{1}H\}$ NMR spectroscopic study of complex **3** with various components of the tetrazole labelling method. The specific details of each entry (1 – 7) are detailed following the image.

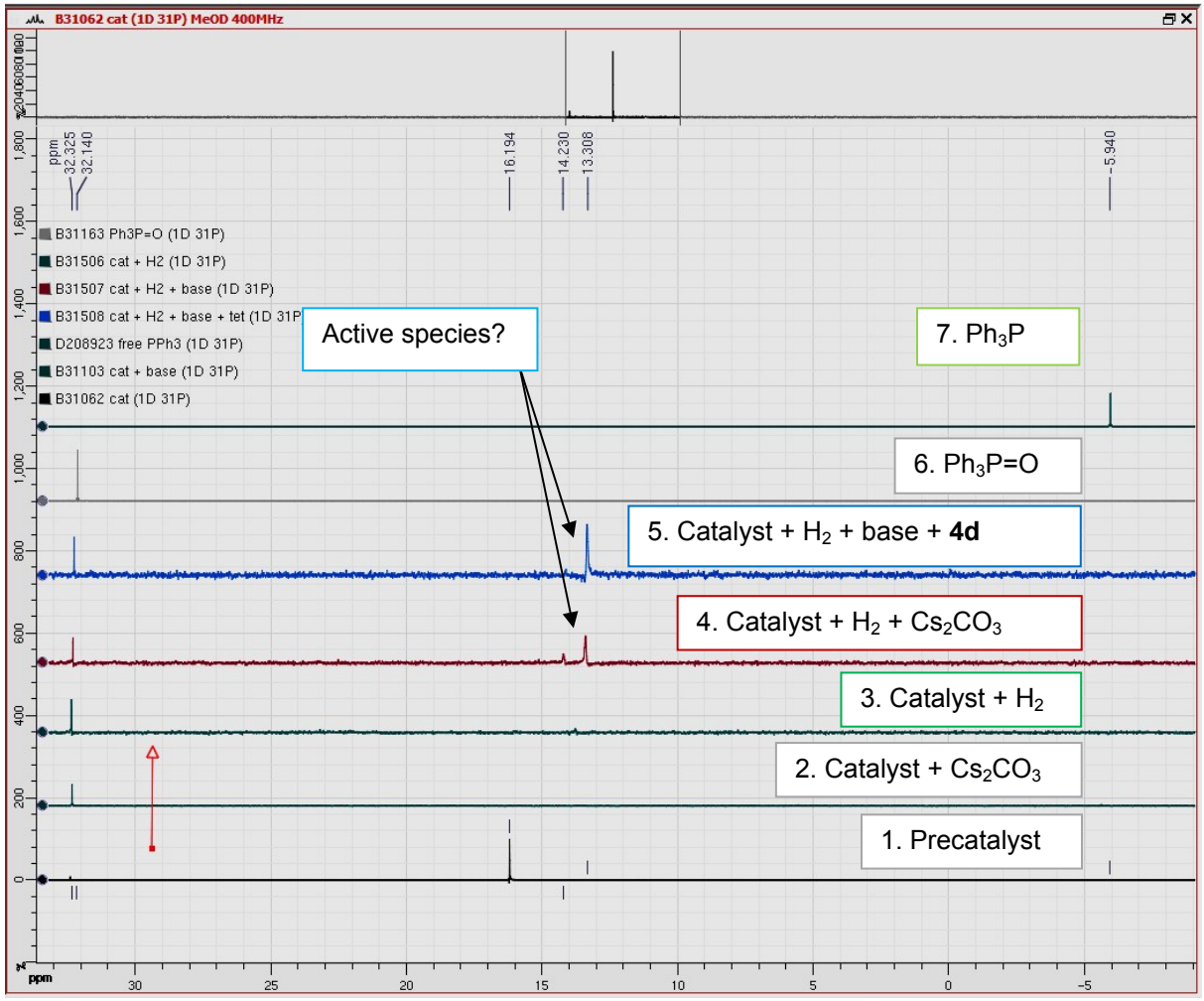
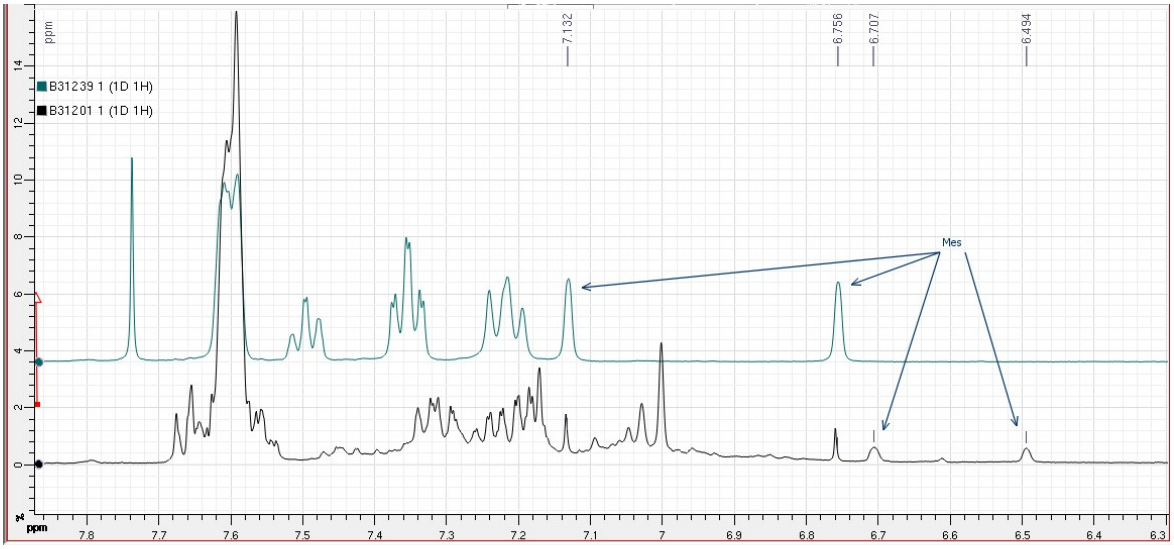


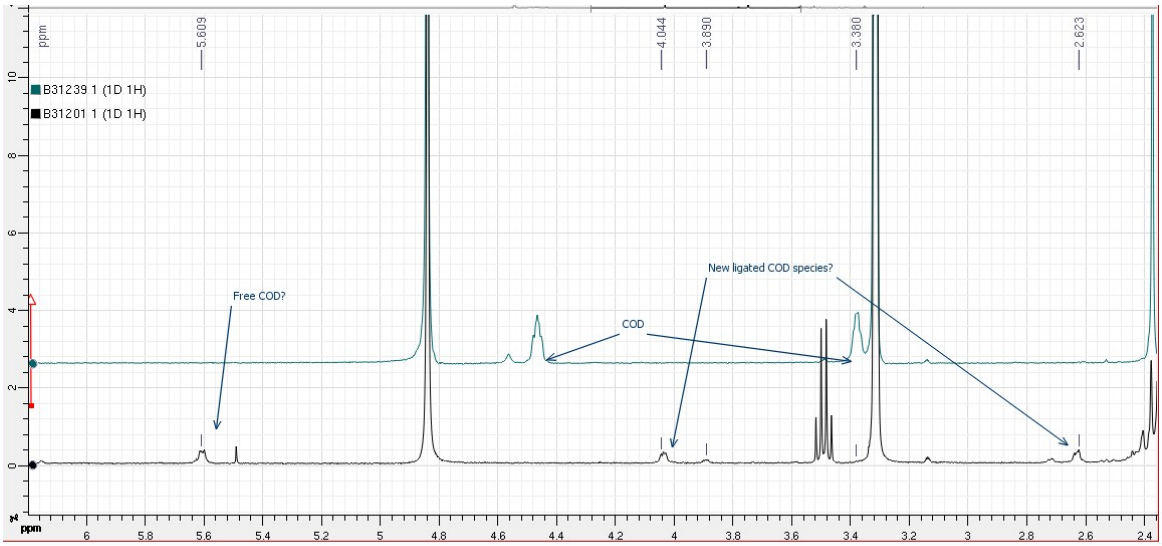
Figure S2. $^{31}P\{^{1}H\}$ NMR study of complex **3**.

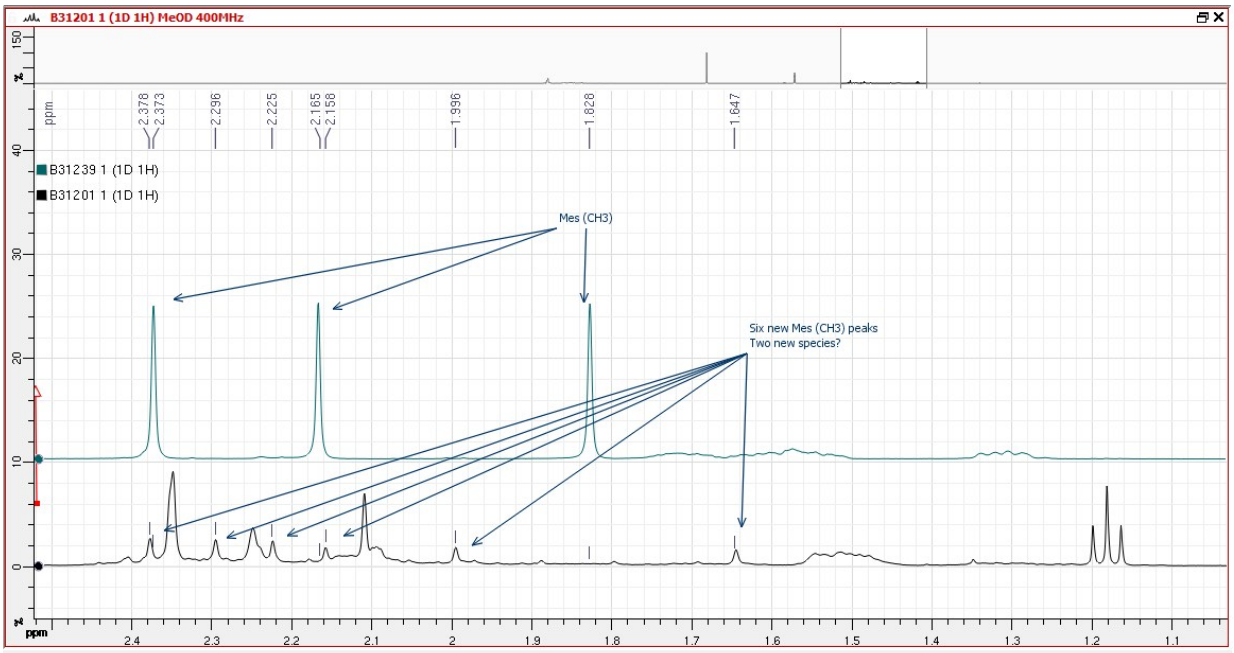
*Analysis of Catalyst **3** + Cs_2CO_3*

Catalyst **3** (7.4 mg, 0.0043 mmol) and Cs_2CO_3 (2.8 mg, 0.0086 mmol, 2.0 eq.) were dissolved in methanol-d_4 (1 mL) in an NMR tube, which was then sealed under an argon atmosphere. The contents of the tube were shaken vigorously for 10 min, causing a red to yellow colour change. NMR spectroscopic analysis of the sample at 300 K is provided (primarily ^{31}P). Additional spectral overlays are provided for ^{1}H NMR spectroscopic data (relative to catalyst **3**) where formal peak assignment is not yet possible.

^{31}P NMR (162 MHz, methanol-d_4): δ 32.3 (unknown).
^{19}F NMR (376 MHz, methanol-d_4): δ −64.3 (BAr^F $ArCF_3$).
^{1}H NMR (400 MHz, methanol-d_4): overlayed with **3** (green) below (7.8–6.3 ppm, 6.2–2.4 ppm and 2.4–1.0 ppm regions, respectively).







Similar results were obtained with only 1 eq. of Cs_2CO_3 (14.0 mg, 0.043 mmol) under otherwise identical conditions.

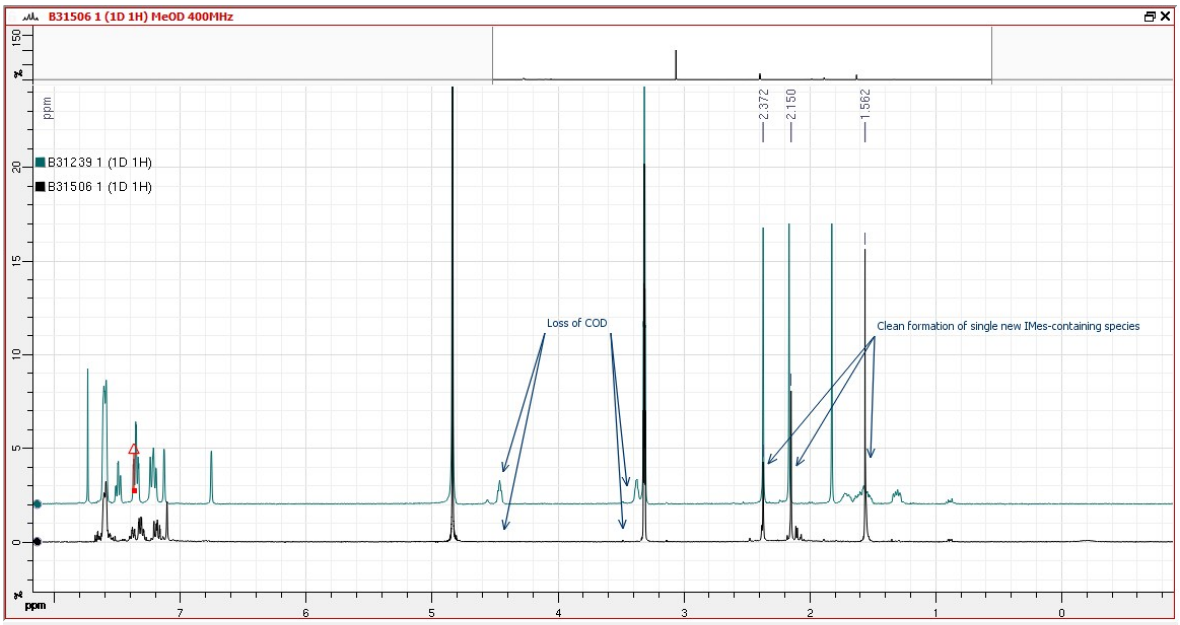
*Analysis of Catalyst **3** + H_2*

Catalyst **3** (7.4 mg, 0.0043 mmol) was placed in methanol-d_4 (1 mL) in an NMR tube, which was then sealed using a rubber septum. Hydrogen gas was bubbled through the mixture with shaking, dissolving the precatalyst and giving a clear yellow solution.

^{31}P NMR (162 MHz, methanol-d_4): δ 32.4 (unknown).

^{19}F NMR (376 MHz, methanol-d_4): δ −64.3 (BAr^F $ArCF_3$).

^{1}H NMR (400 MHz, methanol-d_4): overlayed with **3** (green).



No hydride signals (δ < 0 ppm) were observed. This is presumably due to exchange with methanol-d_4.

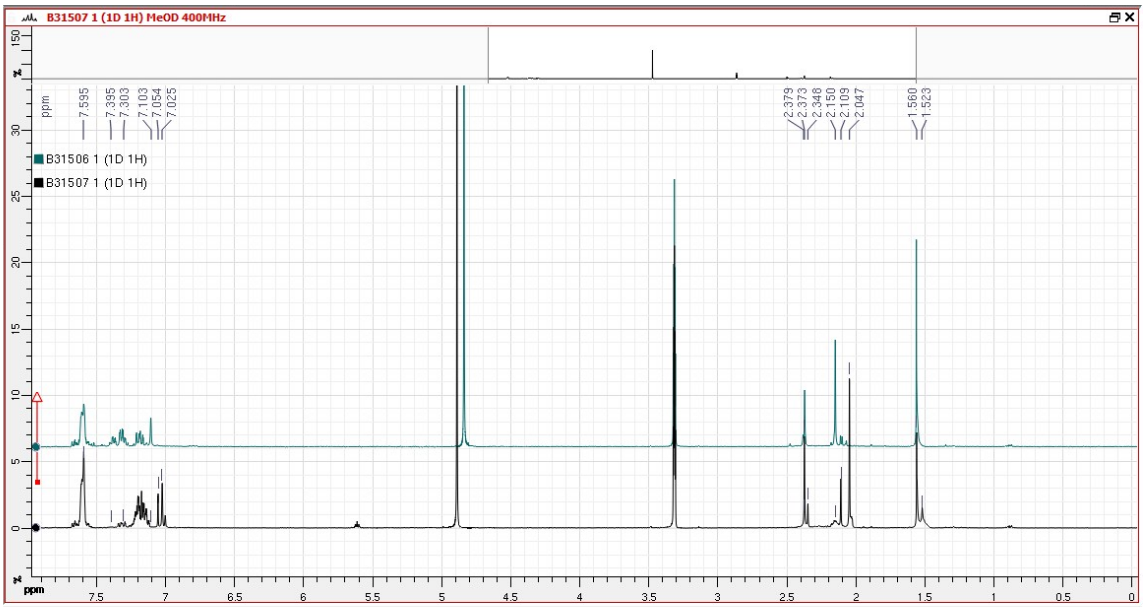
*Analysis of Catalyst **3** + H_2 + Cs_2CO_3*

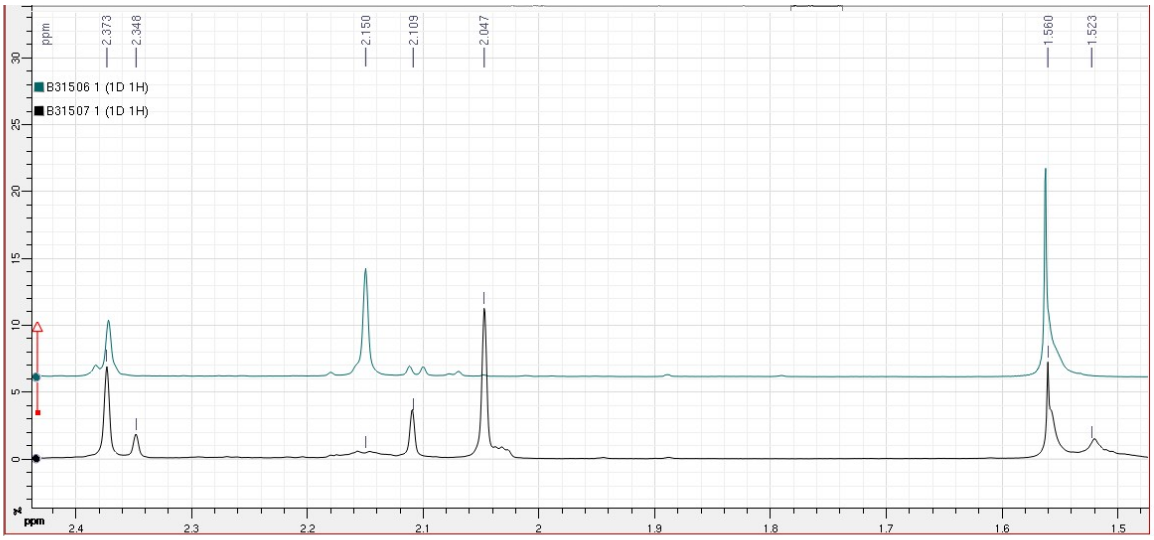
Catalyst **3** (7.4 mg, 0.0043 mmol) and Cs_2CO_3 (14.0 mg, 0.043 mmol) were dissolved in methanol-d_4 (1 mL) in an NMR tube, which was then sealed using a rubber septum. Hydrogen gas was then bubbled through the mixture, producing a clear yellow solution.

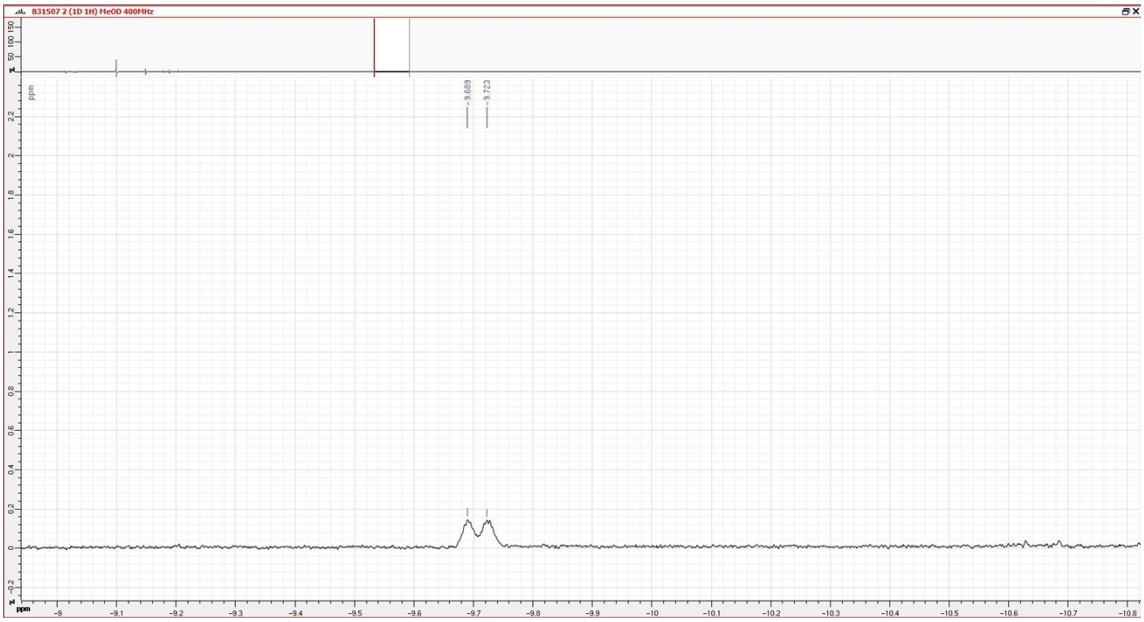
^{31}P NMR (162 MHz, methanol-d_4): δ 32.3, 14.2, 13.3 (unknown).

^{19}F NMR (376 MHz, methanol-d_4): δ −64.3 (BAr^F $ArCF_3$).

^{1}H NMR (400 MHz, methanol-d_4): The overlap provided shows the current experiment (black) *versus* the previous experiment (green), where catalyst **3** was mixed only with H_2. Analysis of the aliphatic region shows the formation of at least two distinct patterns of mesityl substitution. Analysis of the hydride region shows a trace doublet (−9.7 ppm) with a suspected $^{3}J_{H\text{-}P}$ = 13.6 Hz, consistent with a *cis*-ligated phosphine relative to at least one hydride ligand.




ppm
2.373
2.348
2.150
2.109
2.047
1.560
1.523
B31506 1 (1D 1H)
B31507 1 (1D 1H)


B31507 2 (1D 1H) MeOD 400MHz
-9.689
-9.723
ppm

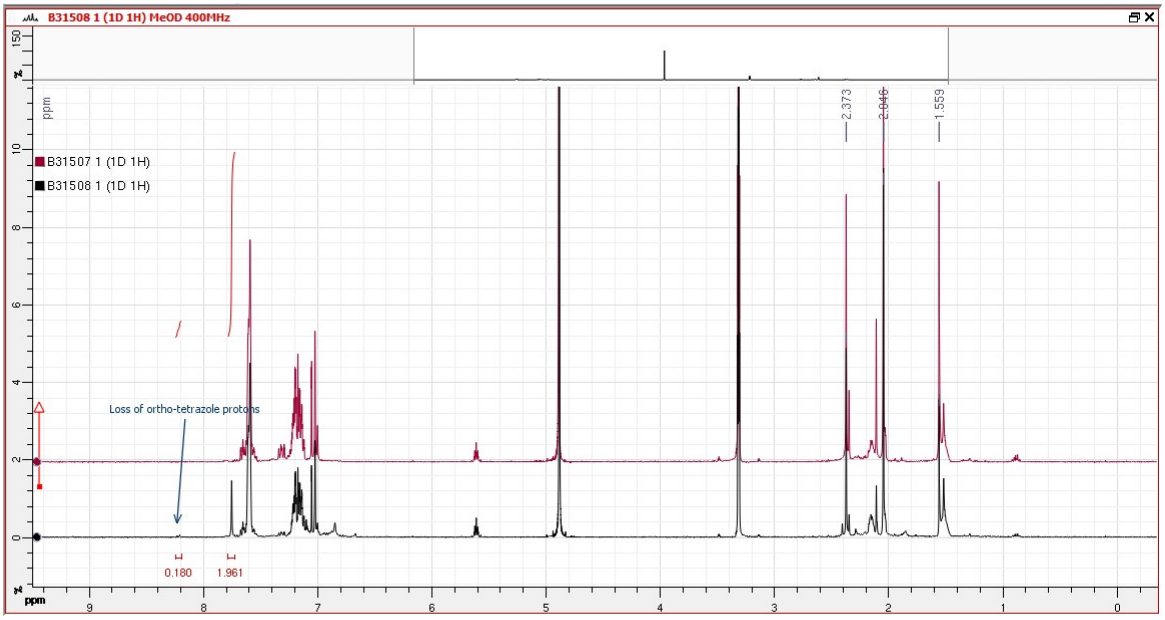
*Analysis of Catalyst **3** + H_2 + Cs_2CO_3 + tetrazole **4d***

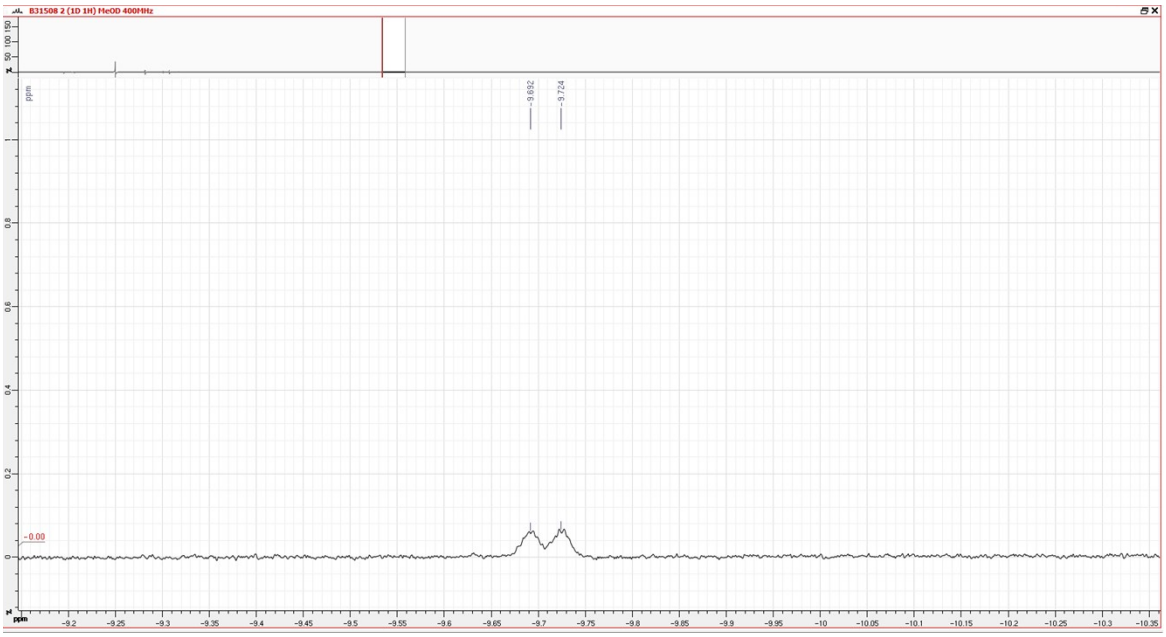
Catalyst **3** (7.4 mg, 0.0043 mmol), Cs_2CO_3 (14.0 mg, 0.043 mmol) and tetrazole **4d** (1.1 mg, 0.0086 mmol) were dissolved in methanol-d_4 (1 mL) in an NMR tube, which was then sealed using a rubber septum. Hydrogen gas was bubbled through the mixture, producing a clear yellow solution.

^{31}P NMR (162 MHz, methanol-d_4): δ 32.3, 14.3 (trace), 13.5 (unknown).

^{19}F NMR (376 MHz, methanol-d_4): δ -64.3 (BAr^F $ArCF_3$), -64.2 (tetrazole CF_3).

^{1}H NMR (400 MHz, methanol-d_4): The overlay provided shows the current experiment (black) *versus* the previous experiment (red), where the tetrazole was absent. Firstly, it appears that similar species are formed in solution in the presence or absence of tetrazole **4d**. Most interestingly, however, complete exchange of the *ortho*-protons was observed, *despite the fact that H_2 has been used in place of D_2*. The use of a 1:2 mixture of **3**:**4d** does not allow definitive conclusions to be drawn regarding the catalytic reactions. Nonetheless, this may indicate a favorable exchange between H (in the H_2) and D (in methanol-d_4), mediated by iridium. Analysis of the hydride region allowed observation of the same trace doublet (−9.7 ppm) with a suspected $^{3}J_{H\text{-}P}$ = 12.8 Hz, consistent with a *cis*-ligated phosphine relative to at least one hydride.




B31508 2 (1D 1H) MeOD 400MHz
ppm
9.692
9.724
0.00

6.3 Investigating the Effect of Substrate Electronics in Ir-catalysed Tetrazole Labelling

Following the general labelling procedure, tetrazoles **1** and **4a**–**4d** were subjected to the optimised labelling conditions as reported above for the reaction scope. The only change was in the reaction time (now 5 min rather than 3 h). For brevity, readers are directed to the spectroscopic data and reagent stoichiometries reported in **Section 3.2**. For construction of the Hammett plot, the %D values for substrates manifesting <30% D incorporation after 5 min (X = H, Me, and OMe) were used as reaction rate surrogates. These values are shown below, in **Table S4**.

Table S4

Entry	X	Substrate	%D	$\%D_X/\%D_H$	$\log_{10}(\%D_{X/H})$	F[b]	R[b]	σ_P[c]
1	H	**4a**	26	1.00	0.00	0.00	0.00	0.00
2	Me	**1**	14	0.54	−0.27	0.01	−0.18	−0.17
3	OMe	**4b**	10	0.38	−0.41	0.29	−0.56	−0.26
4[a]	Cl	**4c**	73	2.81	-	-	-	
5[a]	CF_3	**4d**	67	2.58				

[a] Not considered in the Hammet analysis.

[b] Field (F) and resonance (R) values obtained from the literature.[11]

[c] $\sigma_P = a.F + b.R$ such that σ_P produces a straight line of $R^2 = 1$ when plotted against $\log_{10}(\%D_{X/H})$. Here, $a = 1.00$ and $b = 0.98$. In other words, field and resonance effects are almost balanced.

The graph in **Figure S3** shows the ρ value calculated from **Table S4**:

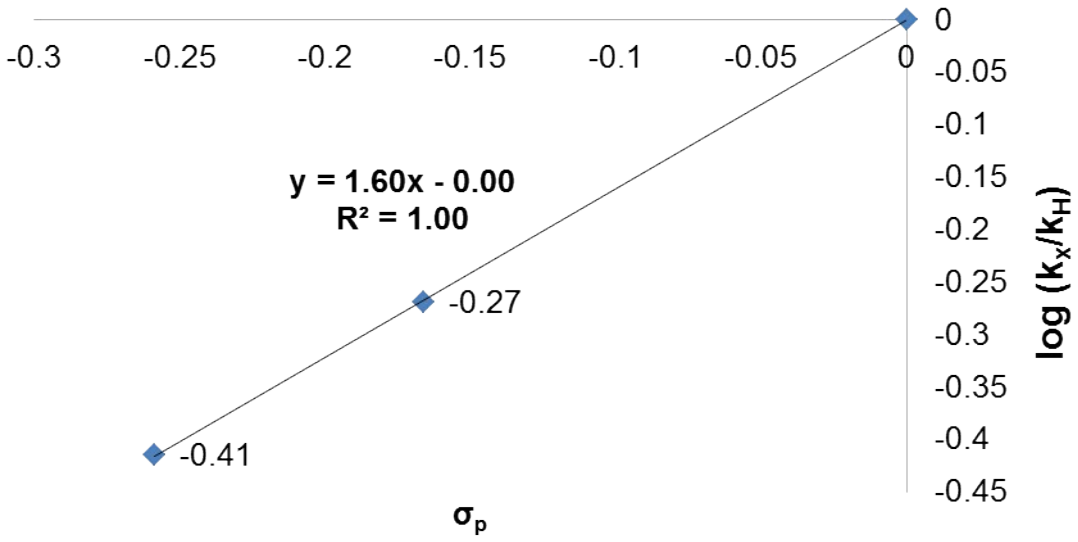
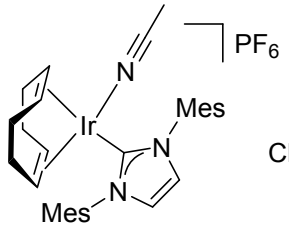


Figure S3. Pseudo-Hammett values for **1**, **4a** and **4b**.

6.4 Investigating the Role of the PPh_3 Ligand in Ir-catalyzed Tetrazole Labelling

*Synthesis of η^4–cycloocta-1,5-diene(1,3-dimesitylimidazol-2-ylidene)(acetonitrile)iridium(I) hexafluorophosphate **6***

The yellow complex [(COD)Ir(IMes)Cl] (0.250 g, 0.389 mmol, 1 eq.),[12] was dissolved in dry THF (10 mL) in a flame-dried round-bottom flask, fitted with a stopcock sidearm. After all the solids had dissolved, $AgPF_6$ (0.098 g, 0.389 mmol, 1 eq.) was added, affording a yellow to opaque orange colour change and formation of a precipitate. The reaction mixture was stirred for 15 min at r.t. before filtration through Celite under argon. Addition of dry acetonitrile (0.020 mL, 0.016 g, 0.389 mmol, 1 eq.) to the clear orange solution resulted in the immediate appearance of a bright red colour. After stirring for 16 h at r.t., the THF solution was reduced to a quarter of its original volume and the residue triturated using cold hexane, to afford the product as an orange solid (0.241 g, 78% yield).



6

Chemical Formula: $C_{31}H_{39}F_6IrN_3P$
Molecular Weight: 790.86

Appearance: orange/yellow solid.

m.p.: >175 °C (dec.).

FTIR (neat): 2980, 2935, 2920, 2885, 1607, 1495, 1335, 1240 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (s, 2H, NCH=CHN), 7.08 (bs, 4H, ArH), 4.03–4.01 (m, 2H, COD CH), 3.46–3.44 (m, 2H, COD CH), 2.48 (s, 3H, CH_3CN), 2.41 (s, 6H, $ArCH_3$), 2.18 (s, 12H, $ArCH_3$), 1.89–1.82 (m, 2H, COD CH_2), 1.75–1.66 (m, 2H, COD CH_2), 1.61–1.51 (m, 4H, COD CH_2).

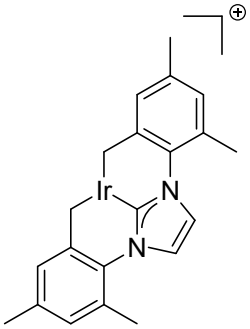
^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 140.0, 135.0, 134.9, 129.3, 125.1, 124.2, 82.7, 65.8, 32.8, 29.0, 21.1, 18.3, 3.44.

^{13}C JMOD NMR (100 MHz, $CDCl_3$): δ 140.0 ($CH_3\underline{C}N$, inverted), 135.0 (inverted), 134.9 (inverted), 129.3, 125.1 (inverted), 124.2, 82.7 (inverted), 65.8 (inverted), 32.8 (inverted), 29.0 (inverted), 21.1, 18.3, 3.44 ($\underline{C}H_3CN$, inverted).

^{31}P NMR (162 MHz, $CDCl_3$): δ −144.4 (septet, $^1J_{P\text{-}F}$ = 711.8 Hz, PF_6).

^{19}F NMR (376 MHz, $CDCl_3$): δ −73.2 (d, $^1J_{P\text{-}F}$ = 711.8 Hz, PF_6).

HRMS (positive ESI): No mass ion was observed nor was expected, based on literature precedent.[13] Suspected fragment (structure shown below) m/z calculated for $[M - PF_6 - COD - MeCN - 2H]^+$: 495.1412; found: 495.1402.

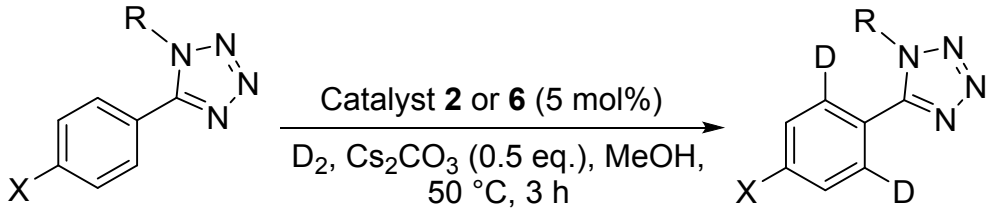


Chemical Formula: $C_{21}H_{22}IrN_2$
Molecular Weight: 494.6380

*Application of NHC/Acetonitrile Catalyst **6** in Tetrazole Labelling*

Following the general procedure (page S5), tetrazoles **1**, **4a** – **4d**, and **4i** were subjected to identical labelling conditions as reported earlier for the reaction scope. The only change was in the catalyst (**2** and **6**, rather than **3**). The comparison of catalysts here was chosen in order to maintain the same counterion whilst comparing the phosphine/NHC and acetonitrile/NHC combinations. For brevity, readers are directed to the spectroscopic data and reagent stoichiometries reported in **Section 3.2**. The data for catalysts **2** versus **6** are shown in **Table S5** below. Spectroscopic data for substrate **4i** are also provided.

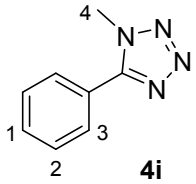
Table S5



Entry	Substrate	X	R	%D (catalyst **2**)[a]	%D (catalyst **6**)[b]
1	**4a**	H	H	83	20
2	**1**	Me	H	83	6
3	**4b**	OMe	H	89	11
4	**4c**	Cl	H	78	37
5	**4d**	CF_3	H	93	28
6	**4i**	H	Me	17 (29)[c]	22

[a] Conditions: Substrate (0.086 mmol), Cs_2CO_3 (1 mL from 0.043 mM solution in MeOH), **2** (4.3 mg, 0.0043 mmol, 5 mol%).
[b] Conditions: Substrate (0.086 mmol), Cs_2CO_3 (1 mL from 0.043 mM solution in MeOH), **6** (3.4 mg, 0.0043 mmol, 5 mol%).
[c] The reaction in parenthesis was carried out in the absence of base.

*5-Phenyl-N-methyltetrazole **4i***[14]



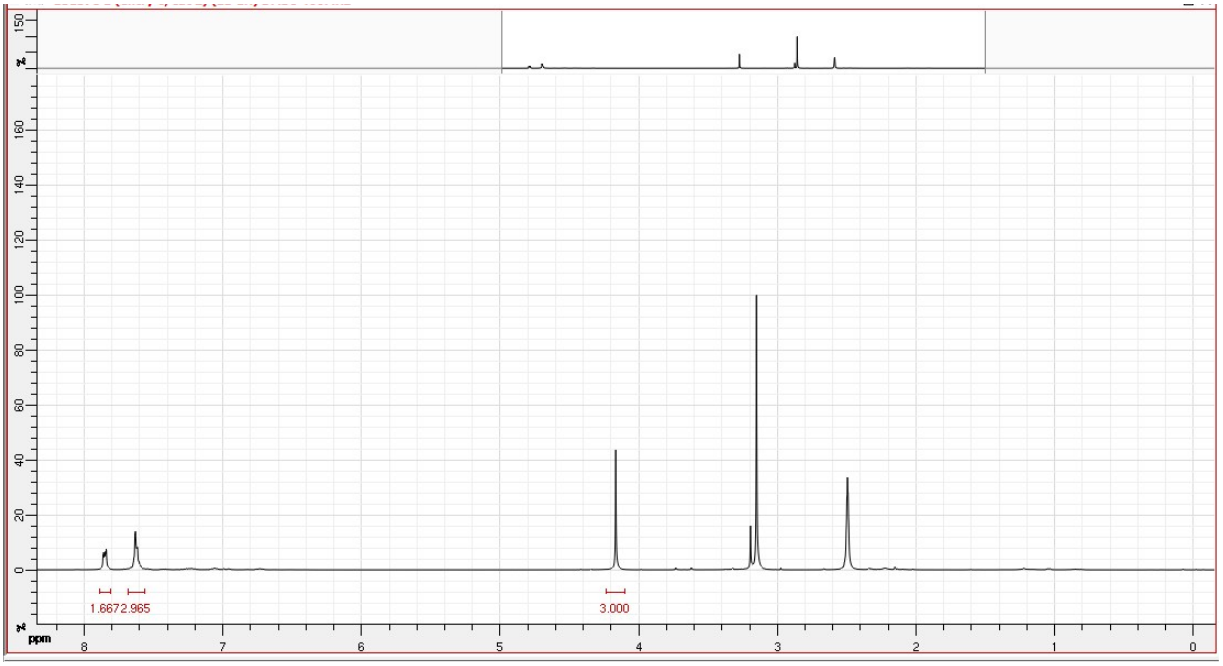
4i

Chemical Formula: $C_8H_8N_4$
Molecular Weight: 160.18

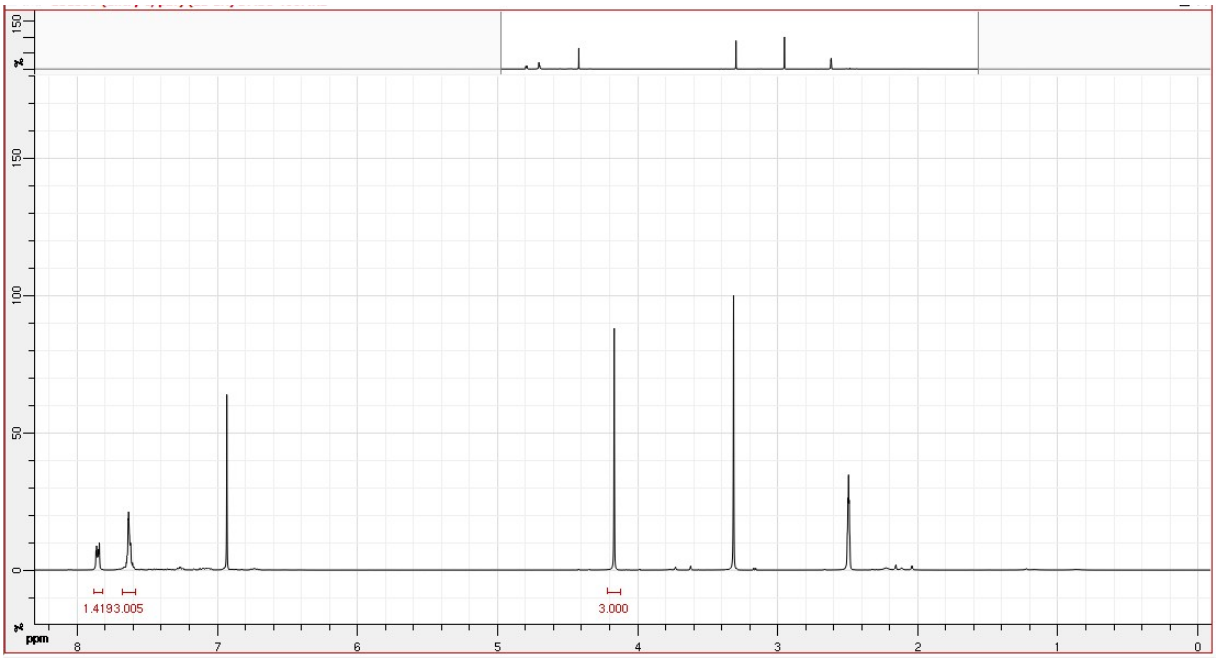
^{1}H NMR (300 MHz, Methanol-d_4): δ 7.85–7.82 (m, 2H, ArH^3), 7.68–7.61 (m, 3H, ArH$^{1-2}$), 4.21 (s, 3H, NCH_3^{4}). Incorporation expected at δ 7.85–7.82. Determined against integral at δ 4.21.

13.8 mg, 0.086 mmol of substrate **4i** were employed.

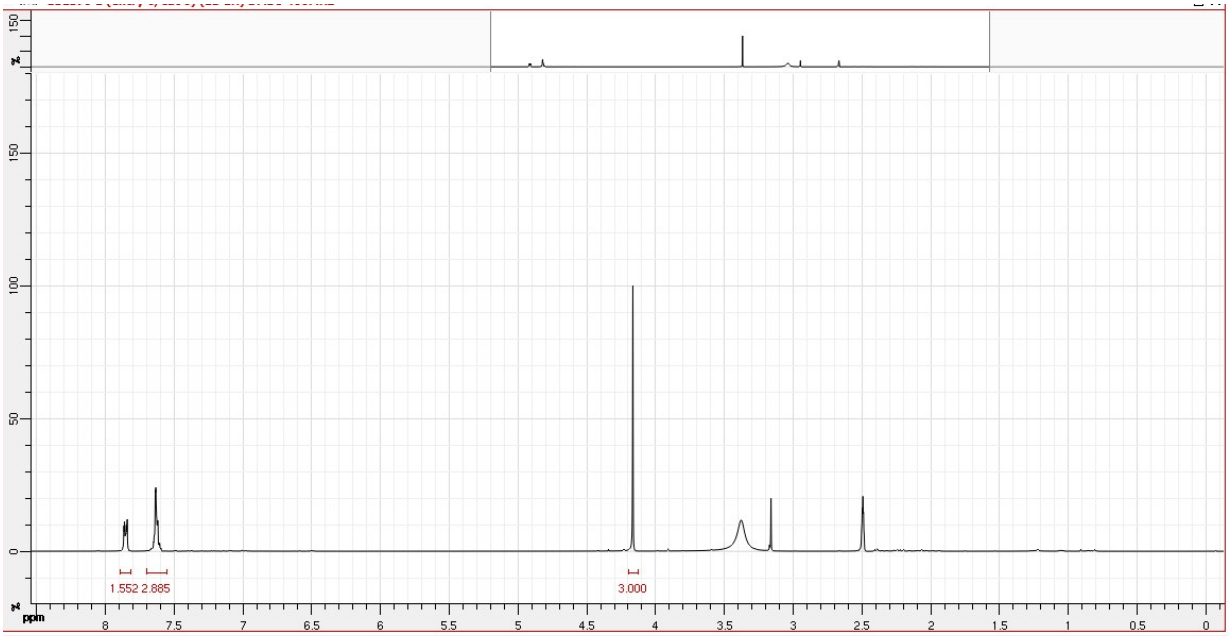
Entry 6, catalyst **2**:



Entry 6, catalyst **2** (parenthesis):



Entry 6, catalyst **6**:



6.5 Investigating the Importance of N-H Tetrazoles and Changes in the Active Catalyst – Additional Reactions Not in the Main Text

In reaction both with and without base, substrate **4i** (13.8 mg, 0.086 mmol) was employed with catalyst **3** (7.4 mg, 0.0043 mmol, 5 mol%). The base-free reaction (**A**, below) used MeOH (1 mL) as the solvent rather than the stock base solution. The basic reaction (**B**, below) employed base from a stock solution of Cs_2CO_3 (1 mL, 0.043 mM in MeOH) as the combined source of solvent and base. The general labelling procedure for the optimised deuteration conditions was followed otherwise, and no work-up was used before analysis. As for similar reactions employing catalyst **2** (**Table S5**), the *N*-protected tetrazole gave only low levels of deuterium incorporation under the reaction conditions (**Table S6**, below), showing again that the method is selective for unprotected tetrazoles.

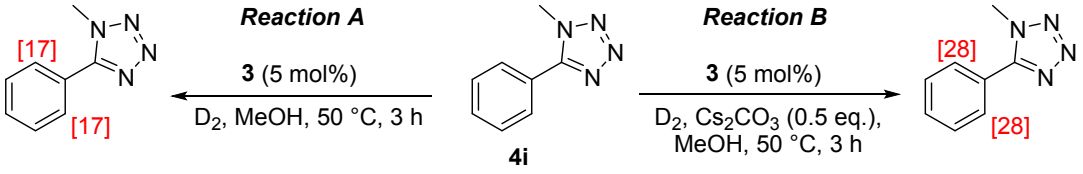


Table S6

Entry	*Conditions*	*% D*
1[a]	basic	28
2[b]	base-free	17

[a] Conditions: **4i** (13.8 mg, 0.086 mmol), Cs_2CO_3 (1 mL, 0.043 mM in MeOH), **3** (5 mol%).
[b] Conditions: **4i** (13.8 mg, 0.086 mmol), MeOH (1 mL), **3** (5 mol%).

6.6 Probing the Deuterium Source in Ir-catalysed Tetrazole Labelling

*Labelling of Substrate **1** in Methanol-d_4 in the Absence of D_2*

Following the general labelling procedure, tetrazole **1** (13.8 mg, 0.086 mmol), Cs_2CO_3 (14.0 mg, 0.043 mmol), and catalyst **3** (7.4 mg, 0.0043 mmol) were dissolved in methanol-d_4 (1 mL) and added to an oven-dried carousel tube under an argon atmosphere. Here, no cooling was carried out as no D_2 was introduced to the system. The reaction tube was heated to 50 °C (as before) and the solution stirred for 3 h. The solvent was removed *in vacuo* and the product analysed directly *via* ^{1}H NMR spectroscopy (8% D incorporation). See **Section 3.2** for the spectroscopic data relating to **1**.

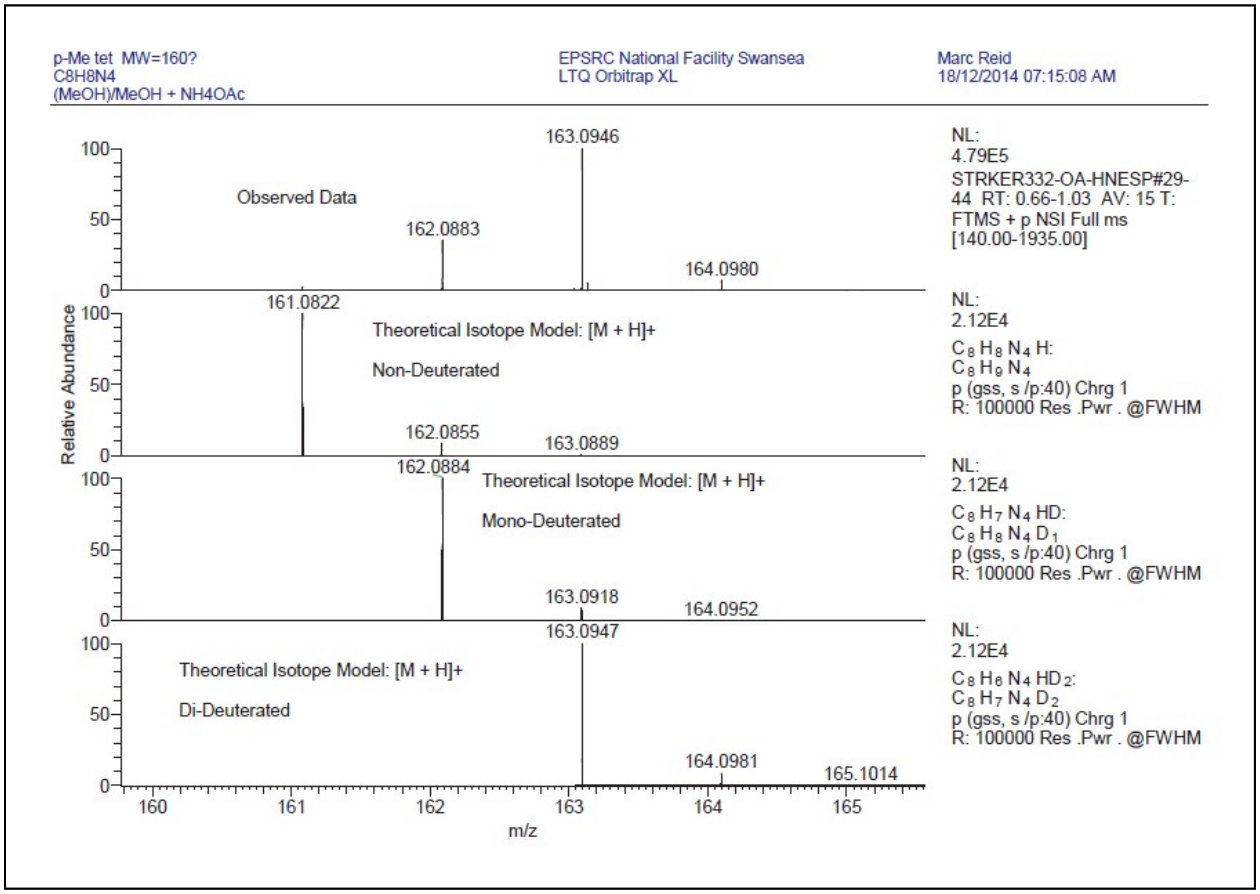
*Labelling of Substrate **1** in Methanol-d_4 in the Presence of D_2*

Following the general labelling procedure, tetrazole **1** was subjected to identical labelling conditions as reported in **Section 3.2** for the reaction scope, but replacing MeOH with methanol-d_4. The concentrated reaction mixture was analysed directly *via* ^{1}H NMR spectroscopy (98% D incorporation). See **Section 3.2** for the spectroscopic data relating to **1**.

7. Additional HRMS Data

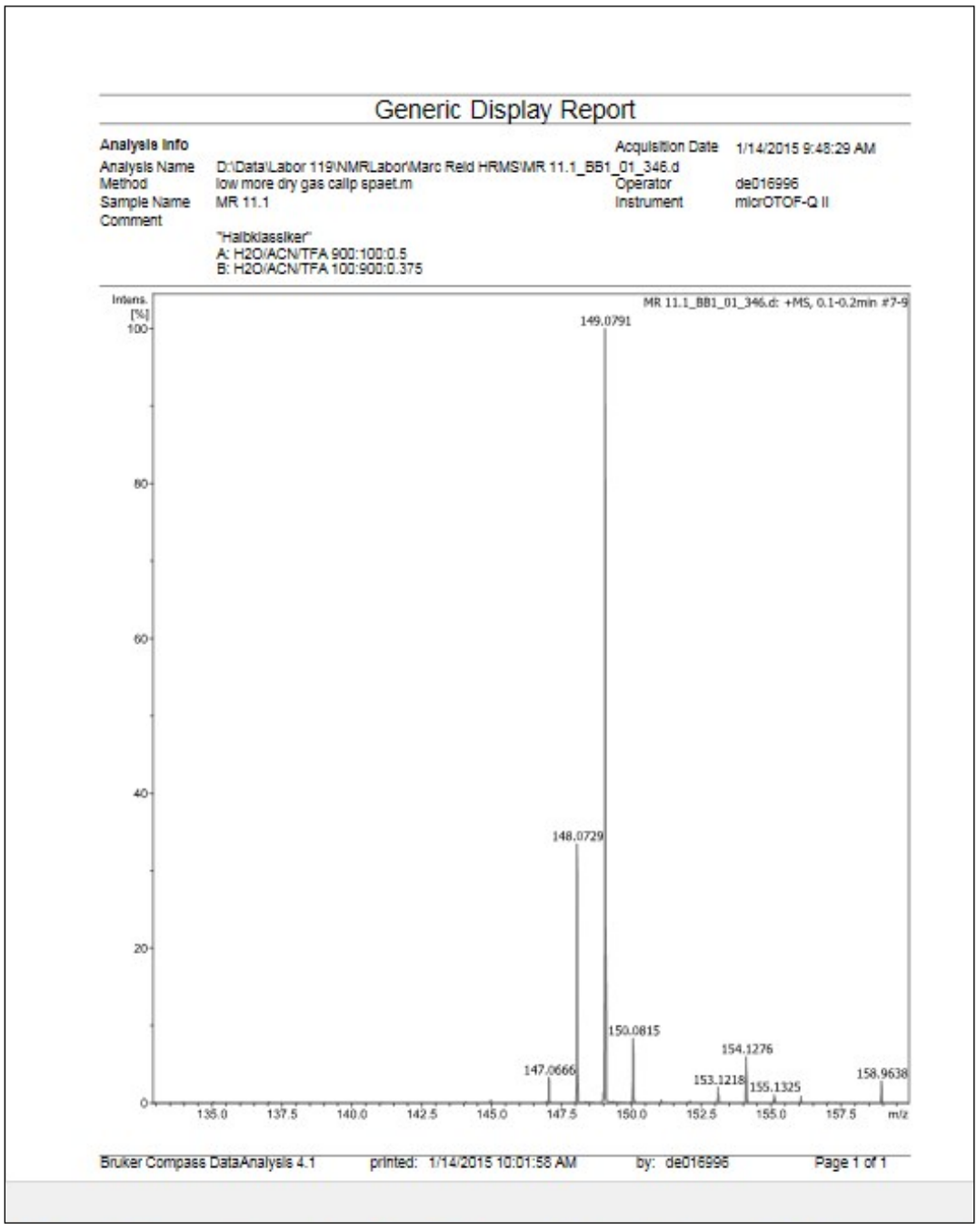
Tetrazole **1**

HRMS (positive ESI; NMSSC):



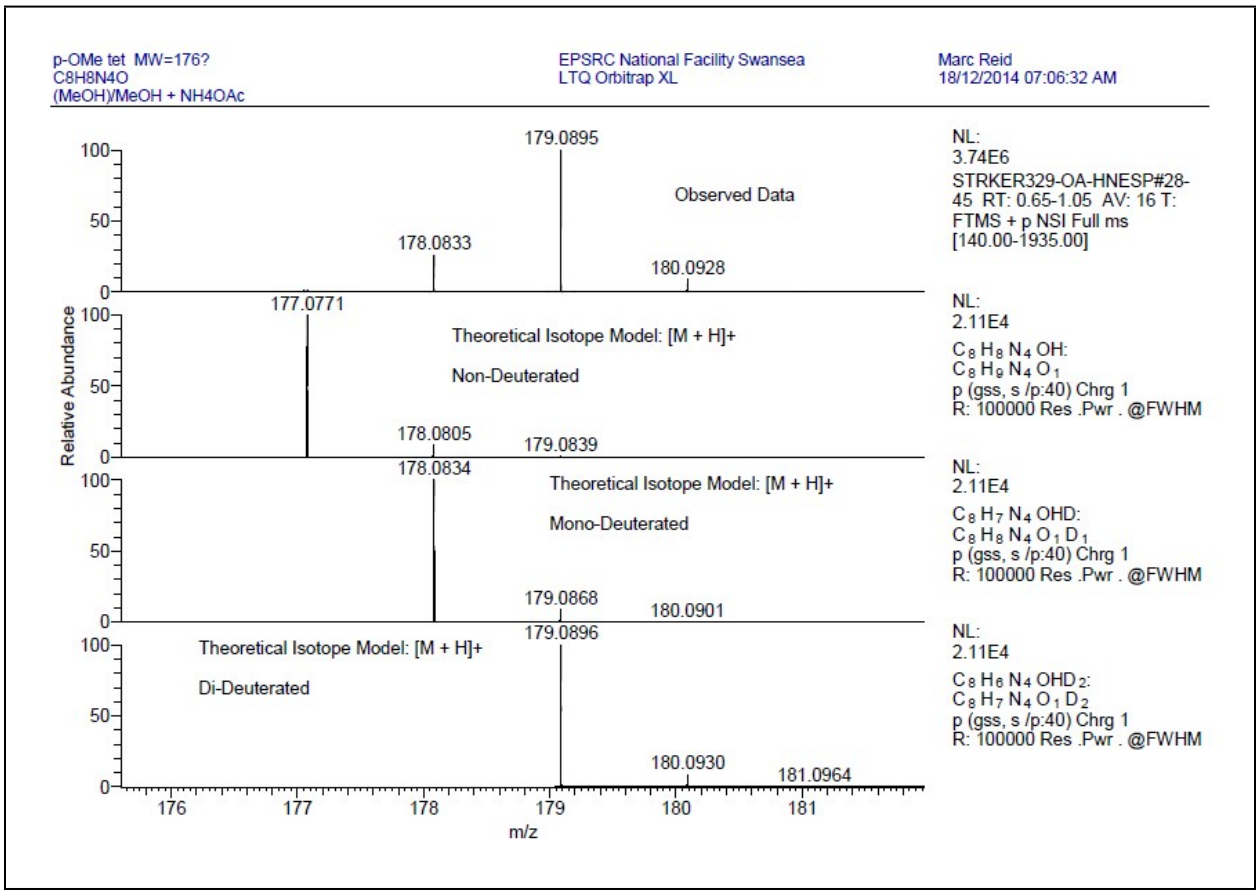
Tetrazole **4a**

HRMS (positive ESI; Sanofi):



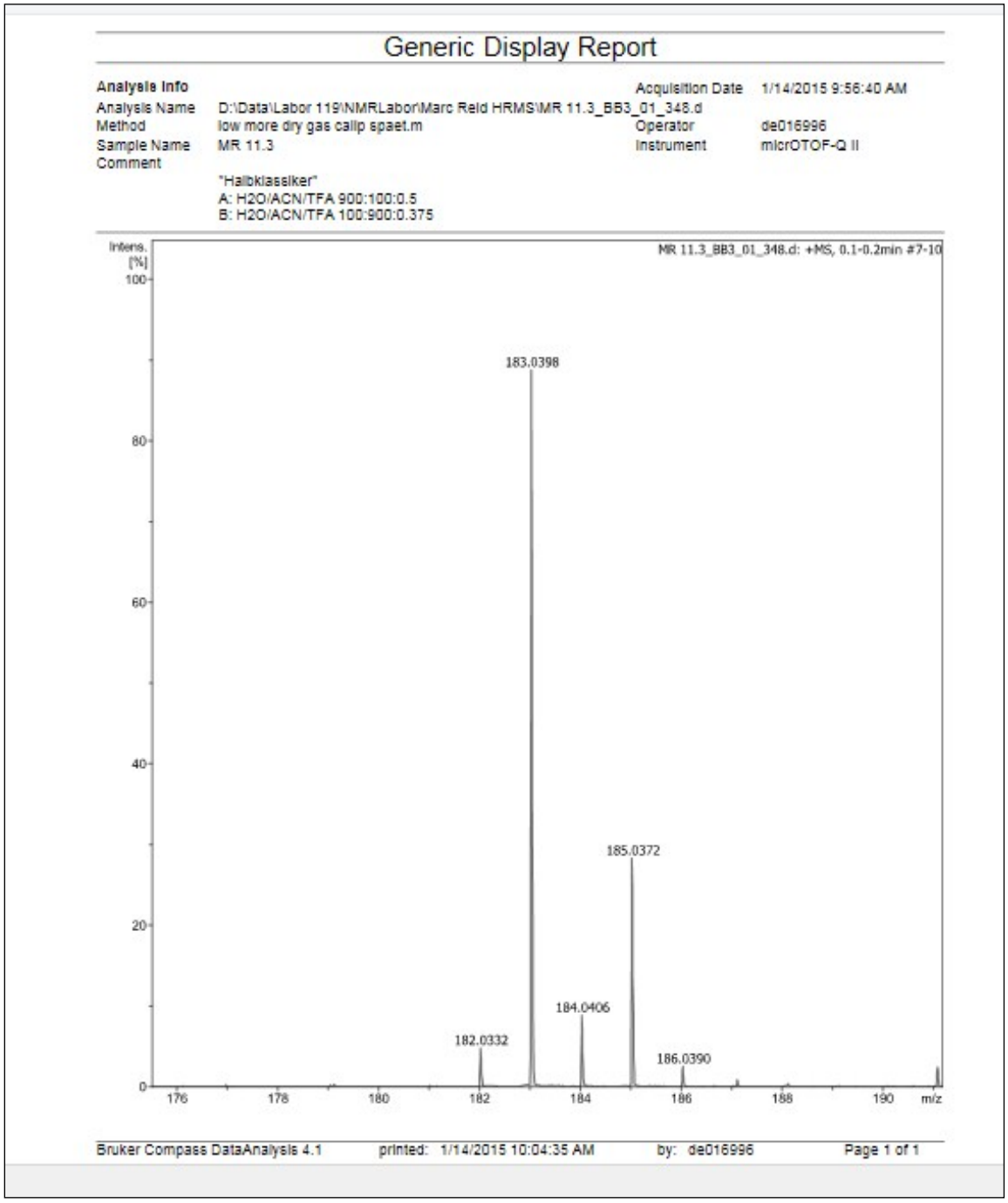
Tetrazole **4b**

HRMS (positive ESI; NMSSC):



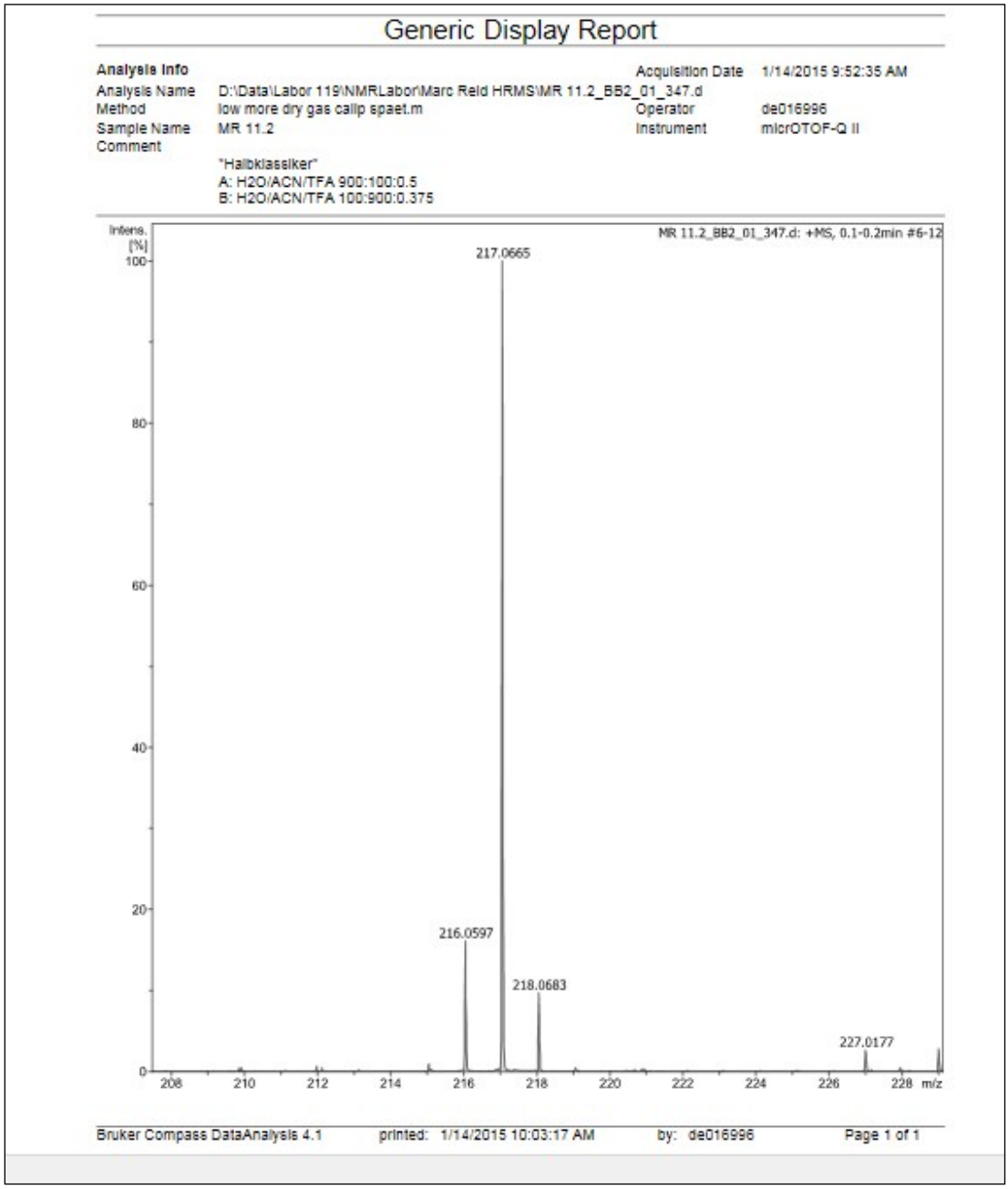
Tetrazole **4c**

HRMS (positive ESI; Sanofi):



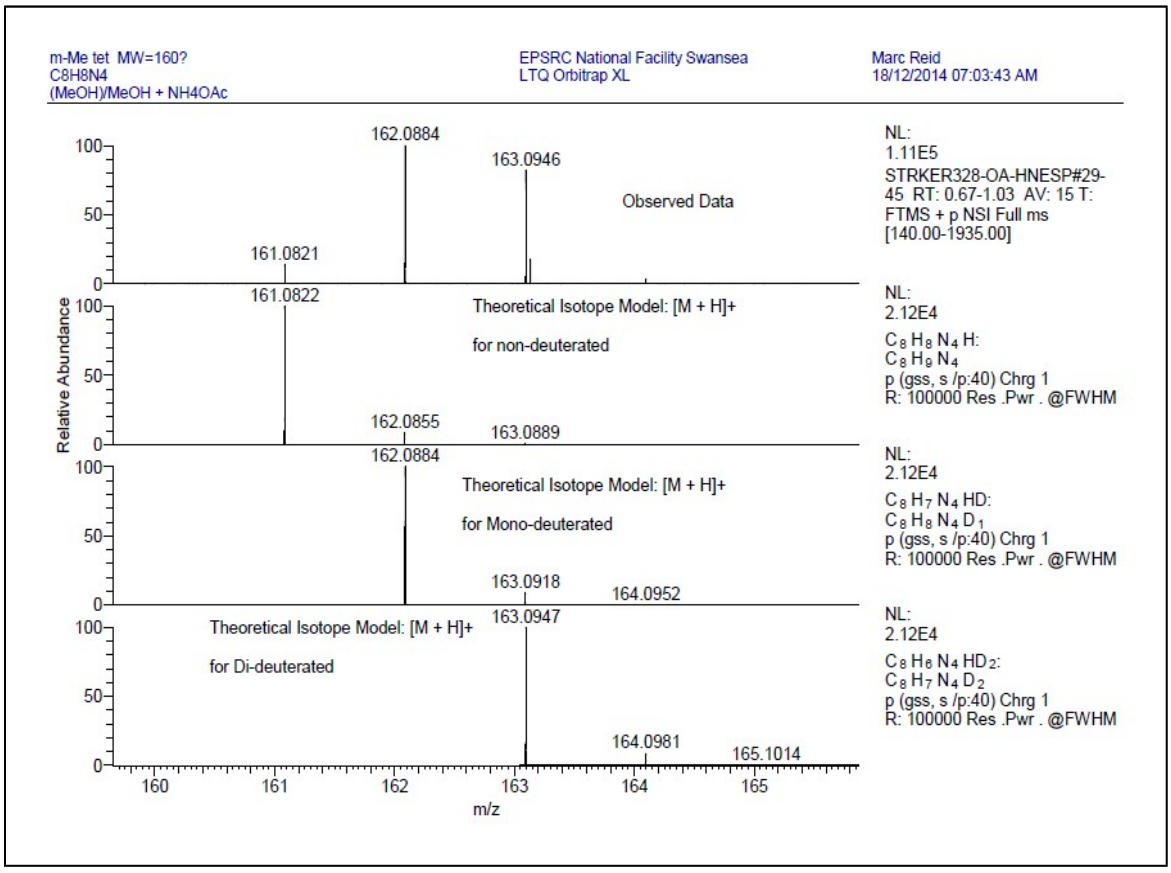
Tetrazole **4d**

HRMS (positive ESI; Sanofi):



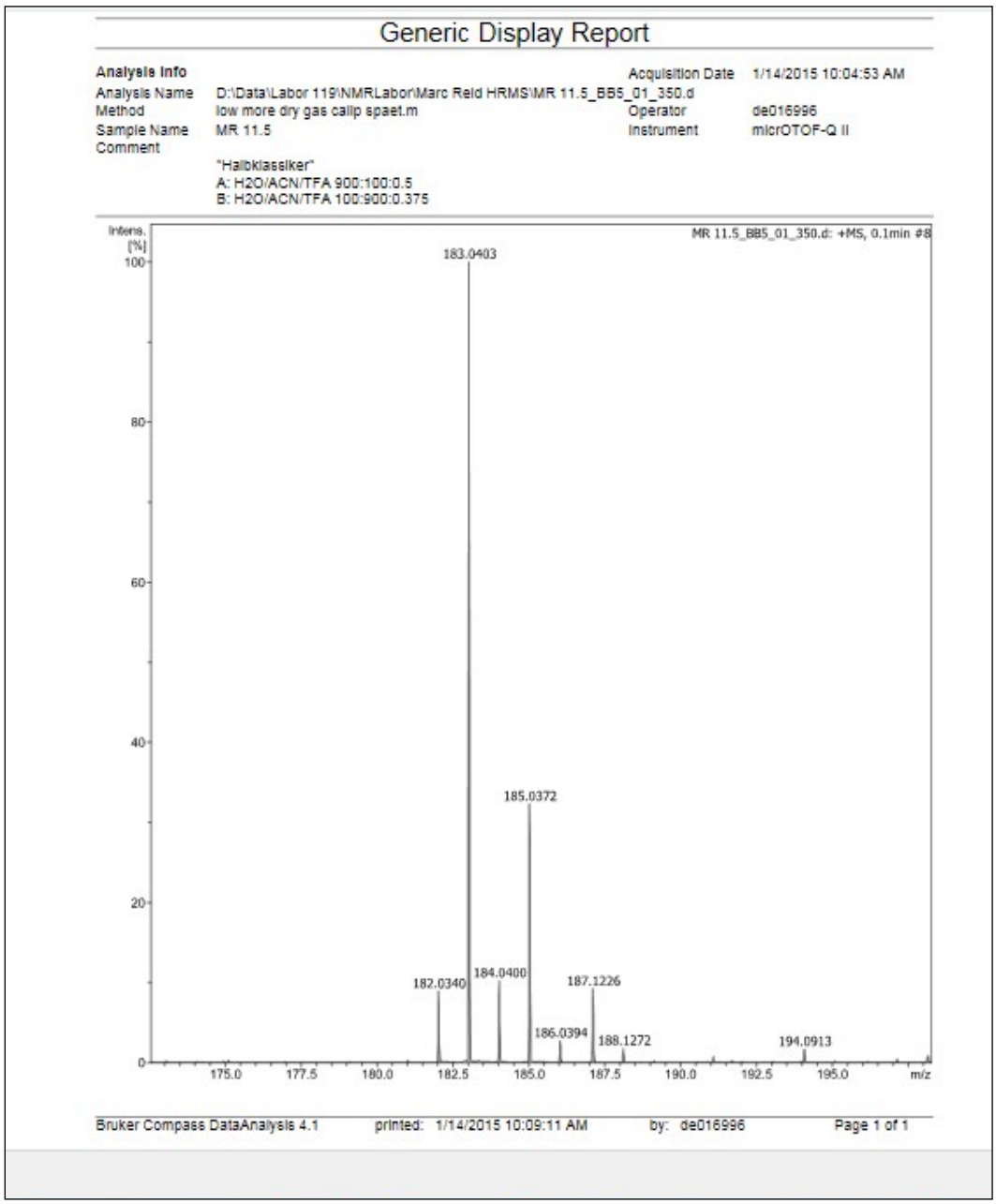
Tetrazole **4e**

HRMS (positive ESI; NMSSC):



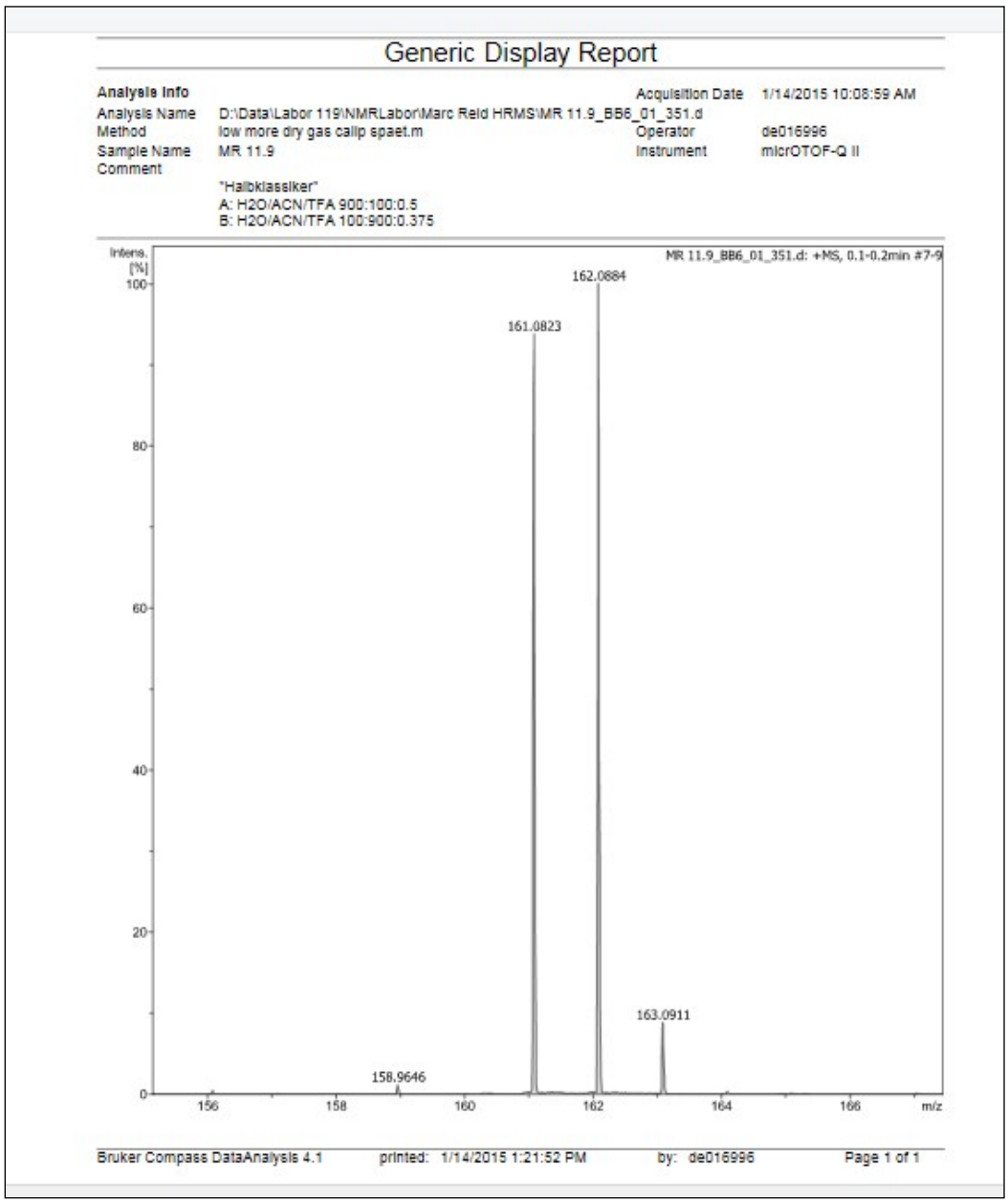
Tetrazole **4f**

HRMS (positive ESI; Sanofi):



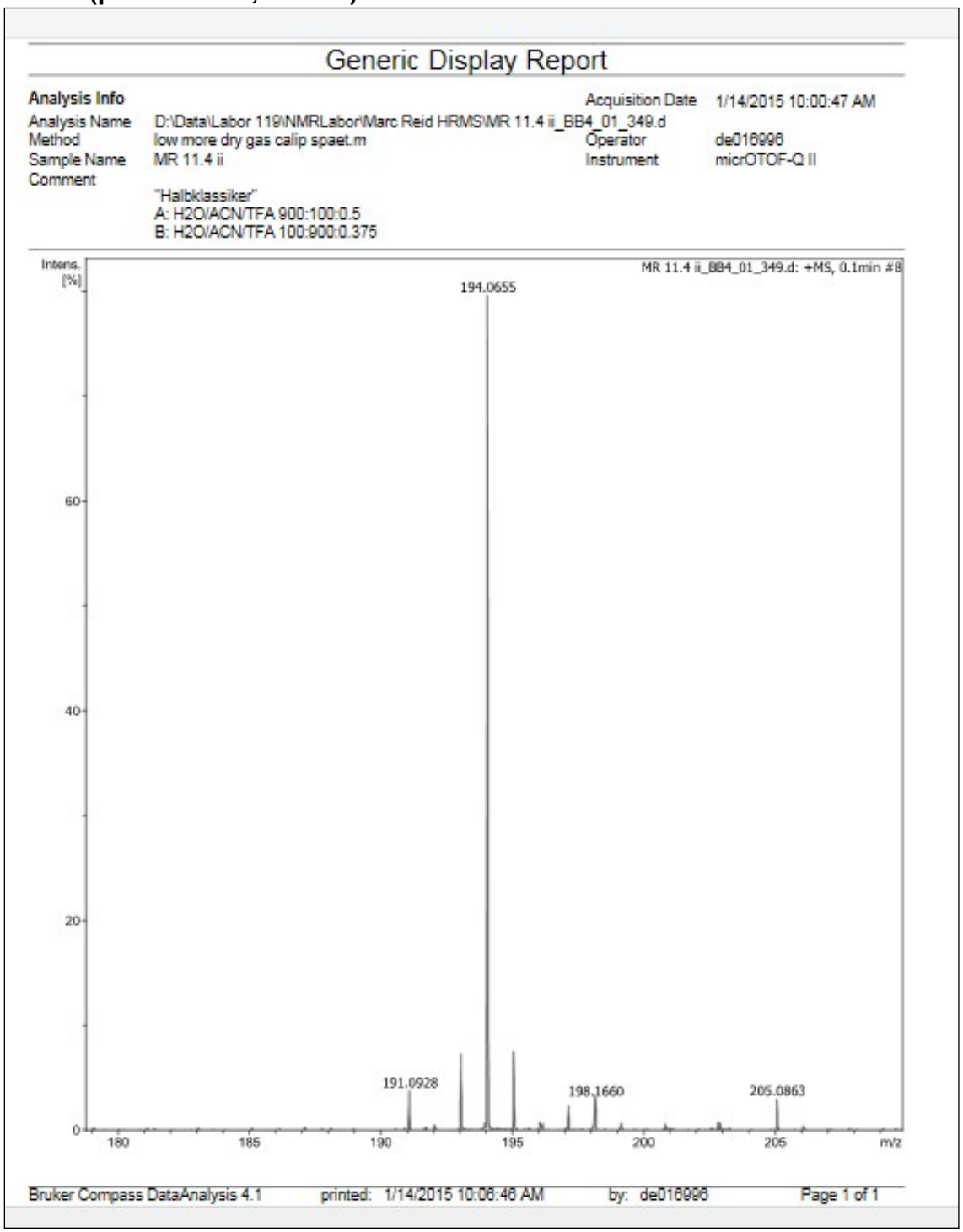
Tetrazole **4g**

HRMS (positive ESI; Sanofi):



Tetrazole **4i** (base-mediated)

HRMS (positive ESI; Sanofi):

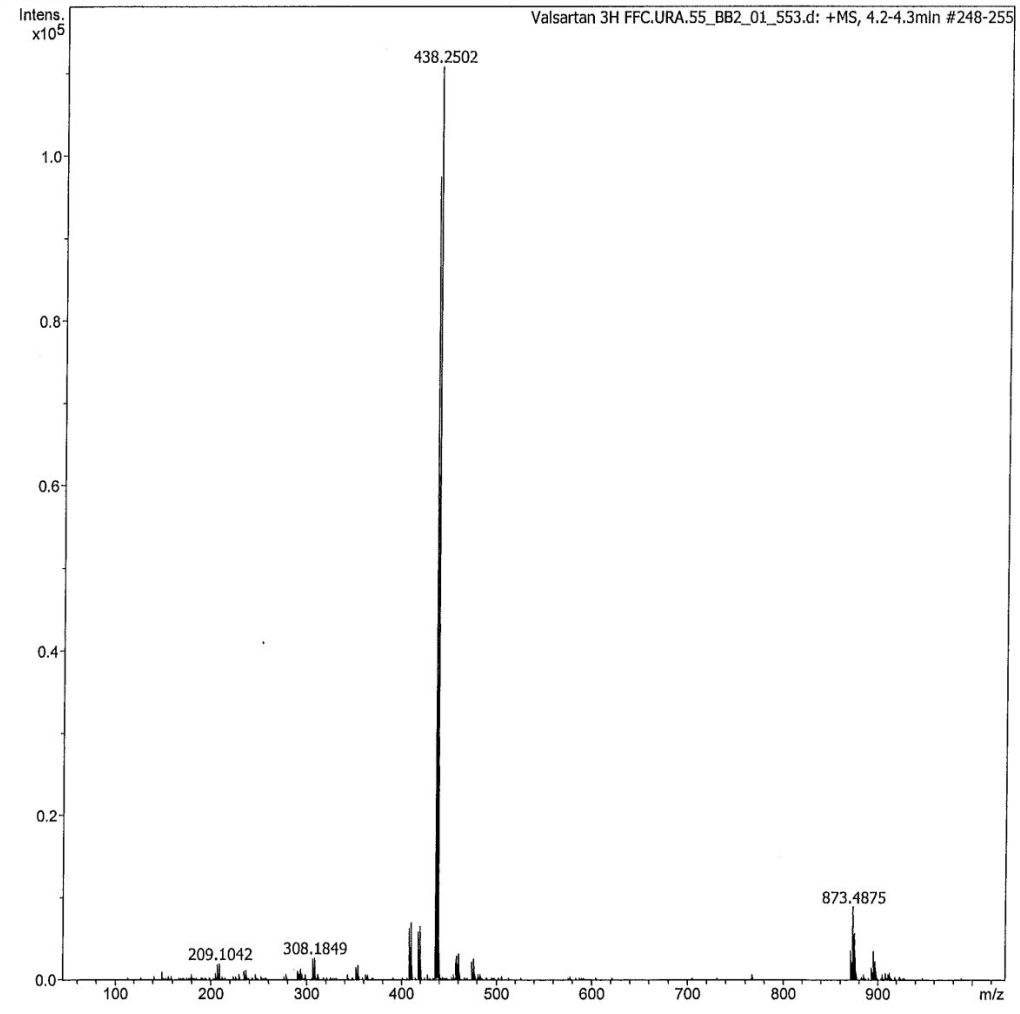


Tritiated Valsartan **5**-t

Generic Display Report

Analysis Info

Analysis Name	D:\Data\Labor 119\NMRLabor\Derd8757\Valsartan 3H FFC.URA.55_BB2_01_553.d	Acquisition Date	2/19/2015 3:22:03 PM
Method	low more dry gas.m	Operator	de016996
Sample Name	Valsartan 3H FFC.URA.55	Instrument	micrOTOF-Q II
Comment	"Halbklassiker" A: H2O/ACN/TFA 900:100:0.5 B: H2O/ACN/TFA 100:900:0.375 XBridge BEH C18 XP 2.1x50mm, 2.5 um XB18XP-1		

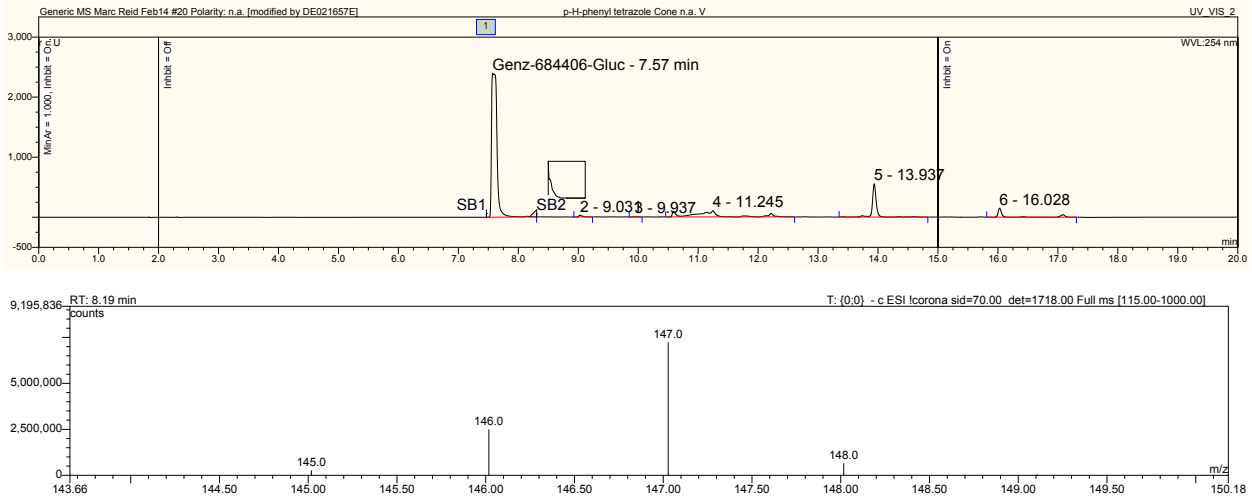


Bruker Compass DataAnalysis 4.1 printed: 2/19/2015 3:56:59 PM by: de016996 Page 1 of 1

8. Additional LC-MS Data

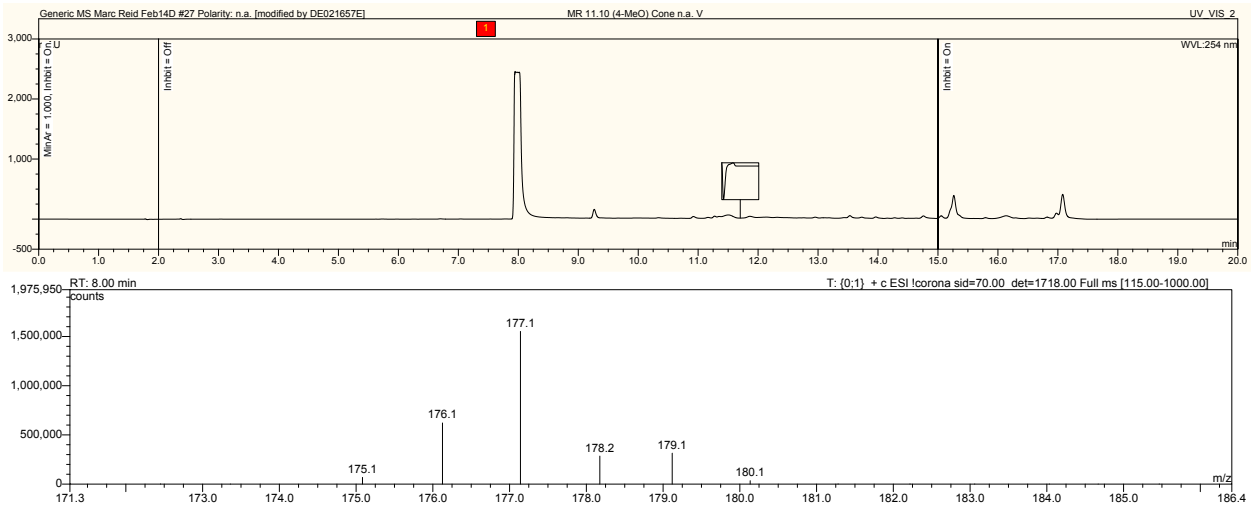
Tetrazole **4a**

LC-MS(System 2):



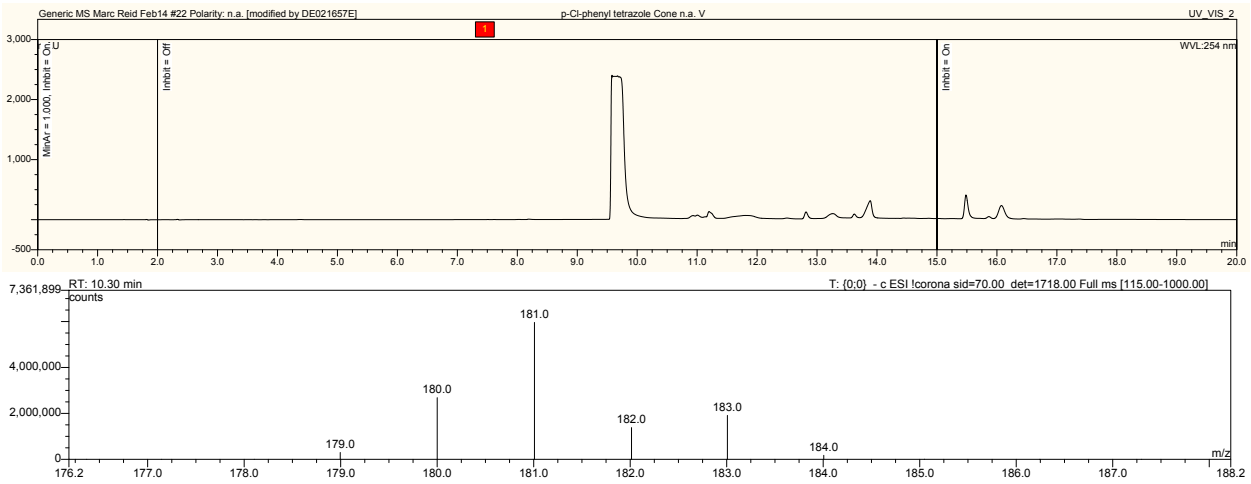
Tetrazole **4b**

LC-MS(System 2):



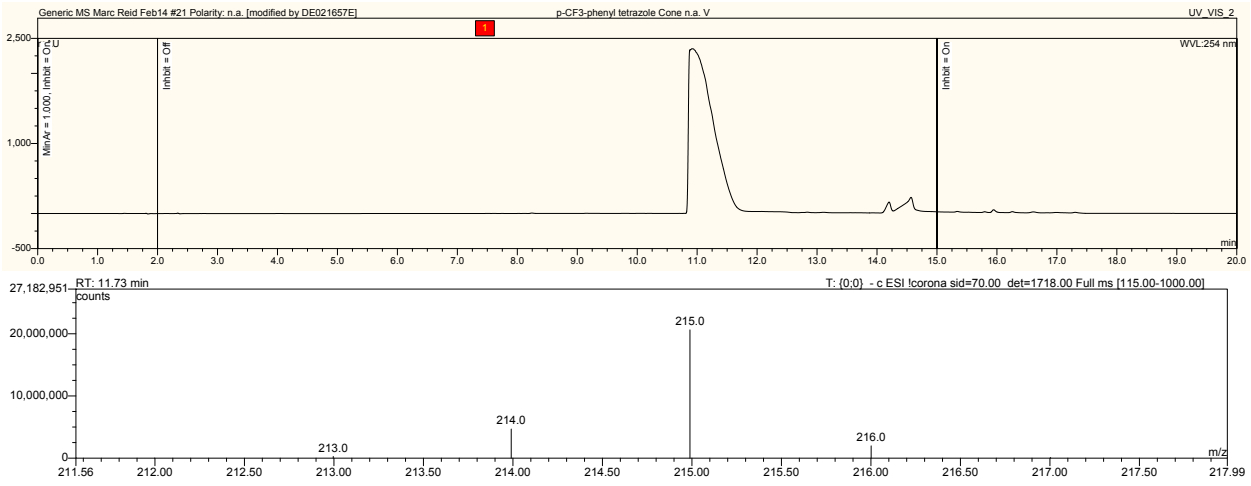
Tetrazole **4c**

LC-MS(System 2):



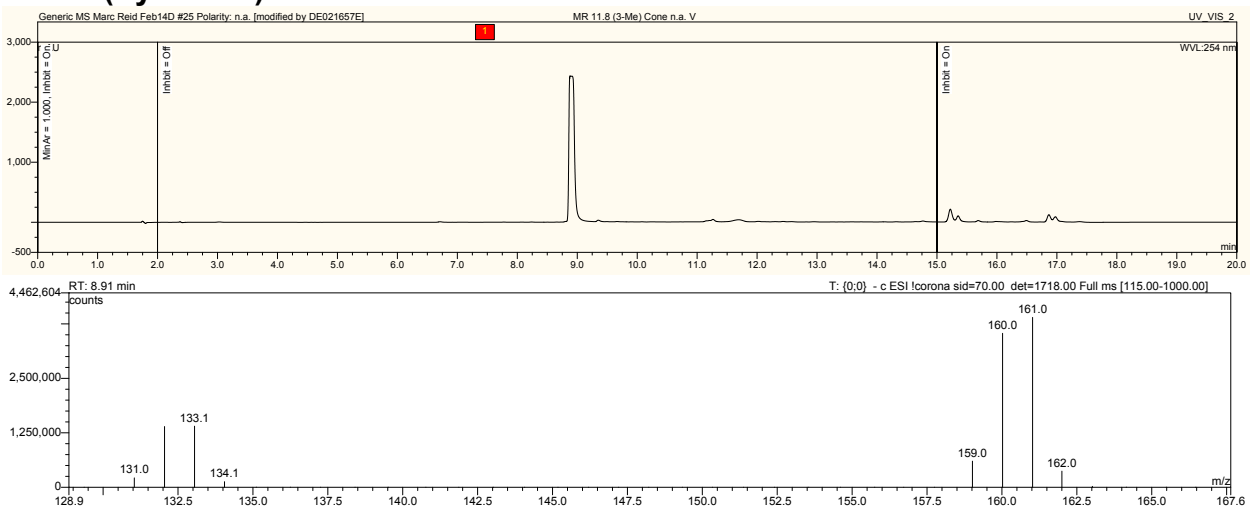
Tetrazole **4d**

LC-MS(System 2):



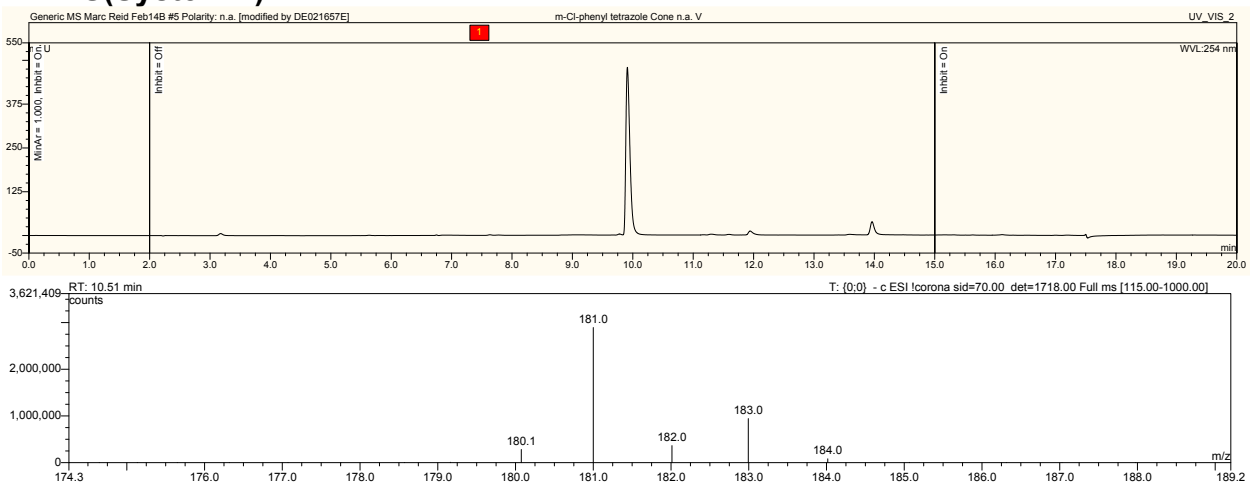
Tetrazole **4e**

LC-MS(System 2):



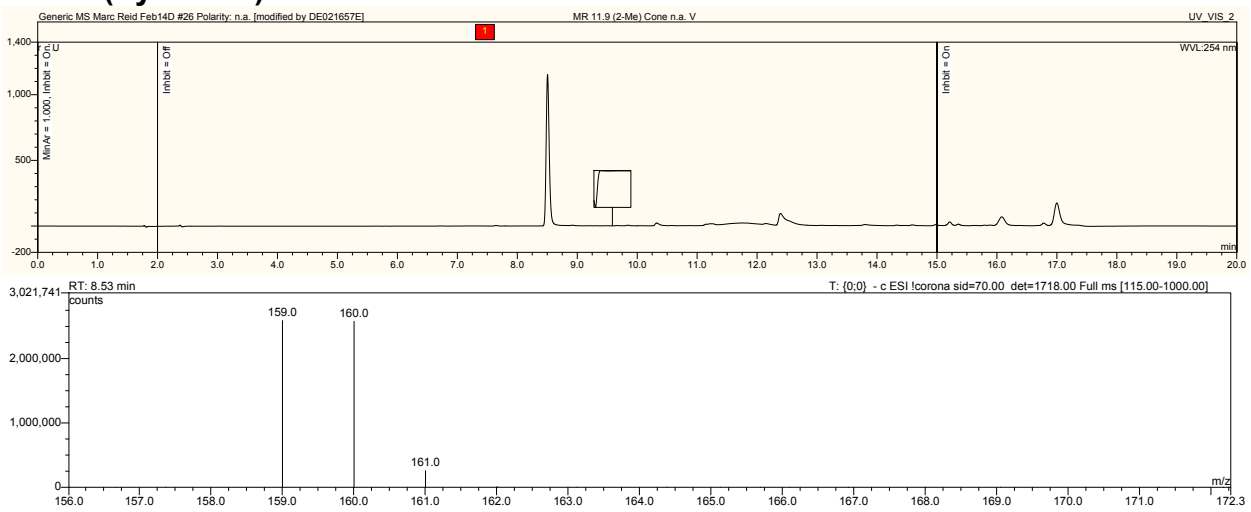
Tetrazole **4f**

LC-MS(System 2):



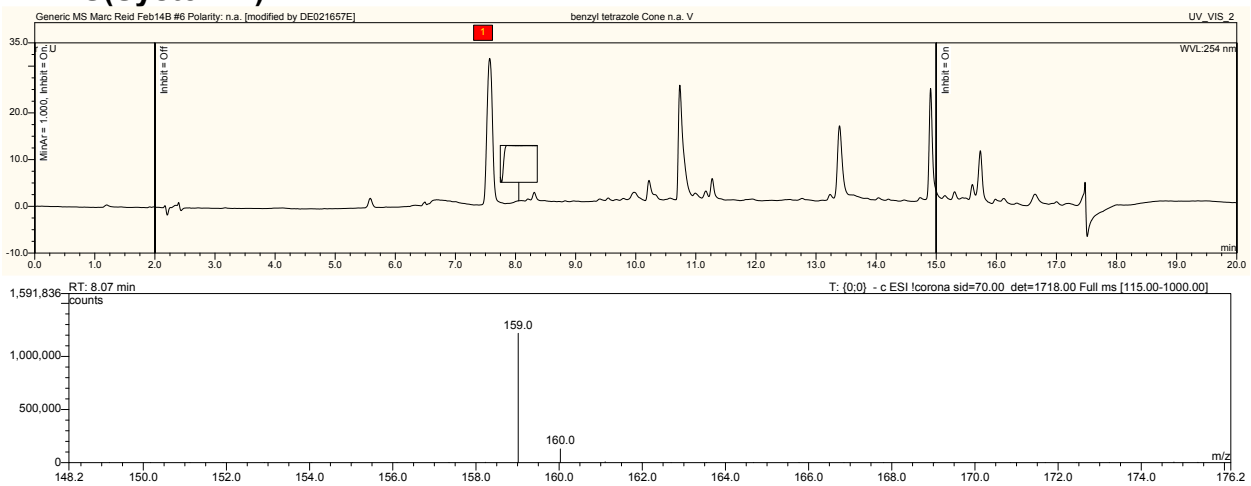
Tetrazole **4g**

LC-MS(System 2):



5-Benzyl-1*H*-tetrazole

LC-MS(System 2):



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