**Stoichiometric and Catalytic Deuterium and Tritium Labeling of “Unactivated” Organic
Substrates with Cationic Ir(III) Complexes**

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I. Procedures and Characterization Data for Stoichiometrically Labeled Compounds

General (Stoichiometric Reactions). The CH_2Cl_2 used for the stoichiometric deuterations/tritiations was purchased from J.T. Baker (BakerDRY™, catalog No. 9295-10) without further purification. Anhydrous dioxane (Aldrich) was degassed via freeze-pump-thaw (3 cycles). Most substrates were used “as is” from Aldrich, Fluka, or Mallinckrodt. 2-(Methylthio)naphthalene was purchased from Avocado Research Chemicals Ltd. (cat. #B22368). *N*-Methylnaphthalene-1-methylamine was purchased from Matrix Scientific (cat. #007083). The synthesis of *N*-BOC-fluoxetine has been described elsewhere.^{1,2} Mass spectrometer data were collected on a Fisons VG Platform single quadrupole (electrospray), a PerkinElmer Sciex API 150EX (electrospray), a Micromass GCT TOF using a DCI probe (EI, 70 eV), a Fisons Trio 2000 single quadrupole MS using a DCI probe (EI, 70 eV), or a VG 70SE double focusing magnetic sector MS using a direct insertion probe (EI, 70 eV). Thin-layer chromatography (Analtech scored glass 10 cm x 20 cm hard TLC plates, or plastic-backed neutral Al_2O_3) was used to assess Sep-Pak® purification conditions and to visualize the eluent UV profile. ^1H NMR spectra were obtained at 300 or 400 MHz (Bruker) and (where appropriate) are reported in parts per million relative to the incomplete deuteration signal from the NMR solvent. ^2H NMR spectra were obtained on a Bruker 500 MHz Avance NMR with a probe optimized for deuterium detection. Chemical shifts are reported in parts per million relative to signals associated with the natural abundance of deuterium in the reference solvent. Deuterium location (as reported in Tables 1 and 2) was performed by correlating deuterium signals with ^1H signals. Where applicable, this location was confirmed in the ^1H NMR by loss of signal (reduction in relative integration value). Location percentages (as reported in Tables 1 and 2) are approximate and are determined by integration of deuterium signals. HPLC analysis of 1-naphthyl-1-ethanol and 1-allylnaphthalene was performed on an Agilent 1100 LC system, using a Phenomenex Luna C-18(2) 4.6 × 250 mm column, UV=254 nm, flow= 1.0 ml/min. Radioactivity measurements for [^3H]warfarin were made on a Packard Tricarb 1900CA liquid scintillation analyzer.

General Procedure for Stoichiometric H/D exchanges. All manipulations prior to Trisorber manipulations were performed in an N₂ dry box. Cp*Ir(PMe₃)Me(OTf) or Cp*Ir(PMe₃)MeCl (4.5-7 μmol, 1.10 equiv) was added to an oven-dried 2.5 ml Trisorber flask with stir bar, then NaBAR_f (4.5-7 μmol, 1.10 equiv) was added. The dry mixture was solubilized in CH₂Cl₂ (approx. 150 μl), creating a dark orange solution. The flask was capped and stirred vigorously for 10 min. A solution of the substrate (4-6 μmol, 1 equiv) in CH₂Cl₂ (approx. 150 μl) was added to the Ir solution, and the total volume was brought to exactly 300 μl. The flask was fitted with an oven-dried 2-way glass stopcock valve (stopcock in closed position), and the reaction mixture was stirred for 20 min at 25 °C. The assembly was removed from the dry box and attached to an IN/US TriSorber® TS-1000 manifold (IN/US Systems Inc., Tampa, FL). The solution was degassed by freeze-pump-thaw (1 cycle). The sensitive volume (V_e, 3.61 ml) was loaded with 760 Torr D₂ (147 μmol). The sensitive volume was opened to the flask and the reaction was stirred vigorously for 1 h. The reaction mixture was frozen and the excess gas was removed under high vacuum. The apparatus was backfilled with He and removed from the TriSorber® manifold. The reaction mixture was transferred to a 4 ml vial with MeOH, and the solvents were removed under a steady stream of N₂. The residue was redissolved in EtOAc/Hexanes and purified by solid phase extraction (SPE) using Sep-Pak® SiO₂ classic cartridges (Waters, WAT051910) or, in the case of *N*-methylnaphthalene-1-methylamine, Sep-Pak® neutral Al₂O₃ classic cartridges (Waters, WAT051810).

Method for Determining Deuterium Content/Specific Activity of Labeled Molecules (Stoichiometric Reactions). The amount of deuterium incorporation was calculated by first measuring the peak heights in the isotopic envelope of the unlabelled substrate standard. An analogous routine was then performed on the purified labeled substrate. The isotopic envelope peak heights from the labeled substrate were then corrected by subtracting out the contribution from the standard (natural abundance). The corrected peak heights for the various isotopes (e.g. d₀, d₁, etc.) were then translated into a percent (peak height of isotope/sum of peak heights from isotopic

envelope), and these percentages are reported below. The “deuterium equivalents” in the manuscript were calculated by taking the percentage contribution from the individual isotopes, multiplying by the number of deuterium atoms per molecule, then summing the total. For example, for a reaction that gave 40% d₀, 40% d₁, and 20% d₂, the “deuterium equivalents” would be: (0.40 × 0) + (0.40 × 1) + (0.20 × 2) = 0.80 deuterium equivalents. This gives an estimate of the extent of H-D exchange. The measurement of specific activity was performed in an analogous fashion, where the fraction corresponding to the tritiated species was multiplied by the requisite maximum specific activity the tritiated molecule could have. For example, a reaction that gave product consisting of 40% t₀, 40% t₁, and 20% t₂ would have a specific activity of: (0.4 × 28.8 Ci/mmol) + (0.2 × 57.6 Ci/mmol) = 23 Ci/mmol.

[²H]-1-Naphthol (Table 1, entry 1). Addition of substrate to the Ir/NaBAr_f solution was accompanied by a color change from orange to black within 20 min. The color reverted back to orange upon exposure to D₂ gas. SPE solvent system: 20% EtOAc/Hexanes. Isotope distribution (Fisons VG MS): 27% d₀, 41% d₁, 25% d₂, 7% d₃. ²H NMR (CH₃OH, 77 MHz): δ 6.80, 7.25, 7.40.

[²H]-Acetanilide (Table 1, entry 2). Addition of substrate to the Ir/NaBAr_f solution was accompanied by a color change from dark orange to light orange within 20 min. The color changed to a light yellow-orange upon exposure to D₂ gas. SPE solvent system: 20% EtOAc/Hexanes. Isotope distribution (Fisons VG MS): 28% d₀, 38% d₁, 24% d₂, 10% d₃. Further fragmentation analysis on a VG70SE MS (EI, 70 eV) confirmed that most of the label was in the aromatic ring.

[²H]-Resorcinol (Table 1, entry 3). Addition of substrate to the Ir/NaBAr_f solution was accompanied by a color change from orange to orange-brown within 20 min. The color changed to a light yellow-orange upon exposure to D₂ gas. SPE solvent system: 40% EtOAc/Hexanes. Isotope distribution (Fisons VG MS): 42% d₀, 38% d₁, 13% d₂, 7% d₃. ²H NMR (CH₃OH, 77 MHz): δ 4.85, 6.25, 6.90.

[²H]-1-Methoxynaphthalene (Table 1, entry 4). Addition of substrate to the Ir/NaBAr_f solution was accompanied by a color change from orange to green-orange within 20 min. The color changed to a light yellow-orange upon exposure to D₂ gas. SPE solvent system: 40% EtOAc/Hexanes. Isotope distribution (Micromass GCT MS): 35% d₀, 39% d₁, 21% d₂, 5% d₃. ²H NMR (CH₂Cl₂, 77 MHz): δ 7.30-7.55.

[²H]-1-Napthoic acid (Table 1, entry 5). The solution was orange during the sequence of reactions. SPE solvent system: 30% EtOAc/Hexanes. Isotope distribution (Fisons VG MS): 41% d₀, 40% d₁, 17% d₂, 2% d₃. ²H NMR (CH₂Cl₂, 77 MHz): δ 7.58-7.72.

[²H]-2-Methyl-1-nitronaphthalene (Table 1, entry 6). Addition of substrate to the Ir/NaBAr_f solution was accompanied by a color change from orange to red-black within 20 min. The color changed to orange upon exposure to D₂ gas. SPE solvent system: 20% EtOAc/Hexanes. Isotope distribution (Fisons Trio MS): 38% d₀, 45% d₁, 17% d₂, 0% d₃. ²H NMR (CH₂Cl₂, 77 MHz): δ 7.64, 7.69.

[²H]-Methyl phenyl sulfone (Table 1, entry 7). Addition of substrate to the Ir/NaBAr_f solution produced no change in color (orange) within 20 min. The color changed to yellow upon exposure to D₂ gas. Isotope distribution (Fisons VG MS): 53% d₀, 34% d₁, 9% d₂, 4% d₃. ²H NMR (CH₂Cl₂, 77 MHz): δ 7.62, 7.71.

[²H]-N,N-Dimethylaminonaphthalene (Table 1, entry 10). The solution was orange during the sequence of reactions. SPE solvent system: 20% EtOAc/Hexanes. Isotope distribution (Fisons VG MS): 61% d₀, 30% d₁, 9% d₂, 0% d₃. Further fragmentation analysis on a VG 70SE MS (EI, 70 eV) proved inconclusive as to whether the label was exclusively located on the aromatic ring. There was a small amount (<10%) of by-product in the reaction which corresponded to *m/z* 188 (M+16) by MS, most likely an *N*-oxide or similar oxidized product.

Dimethyl(1-naphthylmethyl)amine. Formic acid (95-97%, 320 μ l) was added to a 5 ml flask containing *N*-methylnaphthalene-1-methylamine (343 mg, 2.00 mmol) and a stir bar. The mixture was stirred until the amine had completely dissolved (exothermic). Formaldehyde (120 mg, 4 mmol) was then added all at once and the solution was heated at 100 ° C with continued stirring. The solution bubbled vigorously for 1 min, and was stirred an additional 2 h at 90-100 °C. The reaction mixture was cooled and transferred to a 30 ml separatory funnel with 1.5 ml water. The solution was made basic with 6M NaOH, resulting in a white, turbid solution. The aqueous solution was extracted with Et₂O (2 $\times$ 10 ml). The organic extracts were combined and washed with 5 ml brine, then dried over MgSO₄. The solution was filtered through a 13 mm, 0.45 μ m acrodisk syringe filter to remove MgSO₄. Ether was evaporated to provide a slightly turbid orange oil. This oil was filtered again through a 0.2 μ m syringe filter, then dried on the high vacuum line to give a clear orange oil (322 mg, 87%). This was used for the deuteration without further purification. ¹H NMR (CDCl₃, 400 MHz) δ 2.30 (s, 6H), 3.81 (s, 2H), 7.38-7.43 (m, 2H), 7.45-7.55 (m, 2H), 7.77-7.79 (m, 1H), 7.84 (d, 8.5 Hz), 8.25 (d, 8.5 Hz). MS (Fisons VG, ESI): *m/z* 172 (M+H⁺, 57), 141 (M-2Me, 100).

[²H]-Dimethyl(1-naphthylmethyl)amine (Table 1, entry 11). Addition of substrate to the Ir/NaBAR_f solution was accompanied by a color change from orange to light green within 30 seconds, followed by a gradual return to an orange color within 20 min. There was no color change upon exposure to D₂ gas. SPE (Al₂O₃) solvent system: 40% EtOAc/Hexanes. Isotope distribution (Fisons VG, ESI): 76% d₀, 20% d₁, 4% d₂, 0% d₃. MS analysis also showed that approx. 50% of the crude reaction mixture was the fully demethylated Ir-bound complex (1-naphthylmethylamine bound to Cp*(PMe₃)Ir, *m/z* = 557/559). ²H NMR (CH₂Cl₂, 77 MHz): δ 2.30.

[²H]-1-Naphthyl-1-ethanol (Table 1, entry 12). Addition of substrate to the Ir/NaBAR_f solution was accompanied by a color change from orange to dark-green/black within 20 min. The color changed to yellow-orange upon exposure to D₂ gas. SPE solvent system: 40% EtOAc/Hexanes. The majority

(81% by HPLC, $t_r = 12.7$ min, 50% $\text{CH}_3\text{CN}:\text{H}_2\text{O}$) of the substrate was converted to the ketone (1-acetonaphthone), MS (VG70SE, EI, 70 eV) $m/z = 170$. The remainder of the reaction mixture (19% by HPLC, $t_r = 7.8$ min, 50% $\text{CH}_3\text{CN}:\text{H}_2\text{O}$) was labeled 1-naphthyl-1-ethanol: isotope distribution: 42% d_0 , 39% d_1 , 16% d_2 , 2% d_3 .

[^2H]-1-Allylnaphthalene (Table 1, entry 13). Addition of substrate to the Ir/NaBAr_f solution was accompanied by a color change from orange to yellow within 20 min. The color did not change upon exposure to D_2 gas. SPE solvent system: 30% EtOAc/Hexanes. The majority of the substrate (>90%) was transformed to more polar impurities. The most prominent impurity (~60% by HPLC, $t_r = 7.0$ min, 65% $\text{CH}_3\text{CN}:\text{H}_2\text{O}$) was identified as $\text{C}_{13}\text{H}_{10}\text{O}$ ($M+14$, most likely 1-acrylonaphthone) by HRMS (Micromass GCT, EI, 70 eV). Isotope distribution of isolated [^2H]-1-allylnaphthalene ($t_r = 16.8$ min, 65% $\text{CH}_3\text{CN}:\text{H}_2\text{O}$): 82% d_0 , 13% d_1 , 5% d_2 , 0% d_3 .

[^2H]-1-Bromo-4-nitrobenzene (Table 1, entry 14). Addition of substrate to the Ir/NaBAr_f solution was accompanied by a color change from orange to green within 20 min. The color changed to orange upon exposure to D_2 gas. SPE solvent system: 20% EtOAc/Hexanes. Isotope distribution (Fisons Trio, EI, 70 eV): 95% d_0 , 5% d_1 , 0% d_2 , 0% d_3 .

[^3H]Warfarin. The general procedure used for the other deuterated compounds was followed with the following changes. The sensitive volume (V_e , 3.08 ml) was loaded with 20 Torr T_2 (3.31 μmol) and the manifold volume (V_a) was filled with 144 Torr H_2 ; the two chambers were quickly mixed to give a pressure of 115 Torr in V_e (3.31 μmol T_2 and 15.7 μmol H_2). The manifold was opened to the reaction flask and the reaction mixture was stirred for 1.5 h at 25 $^\circ\text{C}$. Exchangeable tritium was removed by adding 0.5 ml EtOH and distilling the solvents under vacuum, providing 12.3 mCi of crude material and 65.9 mCi exchangeable tritium. The crude material was redissolved in 250 μl 30% EtOAc/Hexanes, and loaded onto 2 tandem SiO_2 Sep-Paks[®] (Waters, WAT051910). The majority of the activity eluted in the 7.5-11 ml fraction. This fraction was evaporated under an N_2 stream to give

8.37 mCi of [^3H]warfarin (98.3% pure by HPLC). The specific activity was determined by MS (*vide supra*, Sciex150, neg. ion, ESI).

II. Procedures and Characterization Data for Catalytically *d*-Labeled Compounds

General Procedure. Unless otherwise noted, reactions were manipulated in an inert atmosphere (N_2) glove box at 25 °C or using standard Schlenck techniques. Glassware was dried at 150 °C or higher for at least 12 h. All NMR spectra were obtained using Bruker AMX 400 MHz and DRX 500 MHz instruments and chemical shifts are reported in parts per million (ppm) relative to residual protiated solvent: acetone- d_6 (2.04). $^{31}\text{P}\{^1\text{H}\}$ NMR spectra were recorded at 162 MHz, and chemical shifts (δ) are reported relative to external 85% H_3PO_4 .

Material. Unless otherwise noted, reagents were purchased from commercial suppliers and used without further purification. Deuterated solvents (Cambridge Isotope Laboratories) were stored over 3 Å sieves, except D_2O , CH_3OD and CD_3OD . $\text{Cp}^*(\text{PMe}_3)\text{IrCl}_2$ ³ (**3**) and $\text{Cp}^*(\text{PMe}_3)\text{Ir}(\text{H})_3\text{OTf}^4$ (**4**) were prepared according to literature procedures.

Catalytic H/D Exchange Experiments. In a typical reaction, a NMR tube was charged with catalyst (**3**, 5.0 mg, 0.011 mmol or **4**, 6.0 mg, 0.011 mmol), substrate (see table below), solvent (0.5 mL) and an external standard capillary consisting of 1, 3, 5-trimethoxybenzene in CD_2Cl_2 .² The tube was attached to a Cajon adaptor, and brought out of the glovebox. The tube was put under slight vacuum (~500 Torr) on a high vacuum line, and then flame sealed. The tube was heated in a constant temperature oil bath and the reaction was monitored by ^1H NMR spectroscopy through the loss of intensity of the substrate resonance.⁵ Deuterium incorporation was verified by ^2H NMR analysis.

Reaction of 4 with benzaldehyde. The reaction was performed as described above. The organometallic product of the reaction (NMR yield: 82%) matched the NMR data of the independently synthesized $[\text{Cp}^*(\text{PMe}_3)\text{IrPh}(\text{CO})][\text{OTf}]$.⁶ ^1H NMR: (acetone- d_6 , 400 MHz) δ 7.09 (m, 5H, Ph), 2.03 (s, 15H, $\text{C}_5(\text{CH}_3)_5$), 1.79 (d, $\text{P}(\text{CH}_3)_3$, 11.2 Hz). $^{31}\text{P}\{^1\text{H}\}$ NMR: (acetone- d_6) δ -34.5.

Table S-1. Amount of substrate used in catalytic H/D exchange reactions.

substrate	amount used	mmol	substrate	amount used	mmol
20 μL	0.25		30 μL	0.24
20 μL	0.22		32 mg	0.22
25 μL	0.23		29 mg	0.22
30 μL	0.25		26 mg	0.22
40 μL	0.23		36 mg	0.22
45 μL	0.24		25 μL	0.25
20 mg	0.22		20 μL	0.25
24 mg	0.24		30 μL	0.26
25 μL	0.25		39 mg	0.22

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