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

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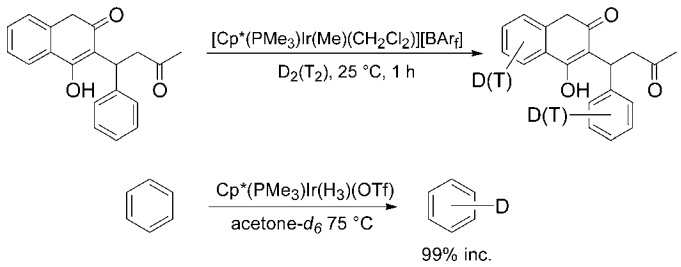
ABSTRACT



Ir(III) complex [Cp*(PMe$_3$)IrMe(CH$_2$Cl$_2$)][BAr$_f$] (1) was used to introduce deuterium stoichiometrically into substituted naphthalene/benzene templates and several "druglike" entities. The exchange process is tolerant of a wide array of functional groups. Labeling of warfarin using subatmospheric pressures of T_2 led to specific activities and total activities rivaling current functional group directed tritium labeling methods. When paired with the appropriate deuterium donor, Cp*(PMe$_3$)Ir(H$_3$)OTf (4) was found to deuterate a number of organic compounds catalytically.

The aggressive goals of drug development require fast and efficient isotopic labeling in the early stages of the drug discovery process. Heys made significant progress toward these demands when he implemented an Ir(I) catalyst that can label druglike substrates with high specific activity tritium gas.[1] Unfortunately, this method is limited to substrates that have certain coordinating functionalities on the aromatic ring (e.g., amides).[1−3]

The C−H bond activation of simple organic substrates with cationic Ir(III) complexes has been extensively studied;[4−14] however, these complexes have not yet been applied to tritium labeling.[15] Deuterium labeling reactions have been previously reported but require either exceptionally low temperature[12] or a water-soluble substrate.[13] We report here the use of cationic Ir(III) species for tritium labeling of

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(2) Hesk, D.; Das, P. R.; Evans, B. *J. Labelled Compd. Radiopharm.* **1995**, *36*, 497−502.
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(4) Alaimo, P. J.; Bergman, R. G. *Organometallics* **1999**, *18*, 2707−2717.
(5) Tellers, D. M.; Bergman, R. G. *J. Am. Chem. Soc.* **2000**, *122*, 954−955.
(6) Tellers, D. M.; Yung, C. M.; Arndtsen, B. A.; Adamson, D. R.; Bergman, R. G. *J. Am. Chem. Soc.* **2002**, *124*, 1400−1410.
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(9) Buchanan, J. M.; Stryker, J. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 1537−1550.
(10) Arndtsen, B. A.; Bergman, R. G. *Science* **1995**, *270*, 1970−1973.
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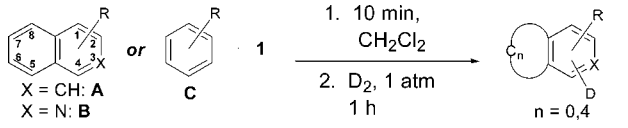
"druglike" compounds and catalytic H/D exchange with deuterated organic solvent at moderate temperature.

The stoichiometric H/D(T) exchange reactivity of the Ir(III) complex [Cp*(PMe_3)Ir(Me)(CH_2Cl_2)][BAr_f] (**1**) was investigated first. Deuterium gas was initially employed to facilitate characterization while examining functional group tolerance. Table 1 summarizes the reaction of **1** with a variety of organic substrates.[16] All of the reactions give a product mixture consisting of a combination of deuterated and nondeuterated substrates (e.g., entry 1 was 27% d_0, 41% d_1, 25% d_2, and 7% d_3 by mass spectrometry). These results reveal some interesting isotopic substitution patterns and functional group compatibilities. Moieties such as sulfonyl, amide, ether, nitro, phenoxy, carboxylic acid, and tertiary amine are tolerated reasonably well (entries 1−7, 10), whereas alcohols bearing an α-H undergo oxidation and side reactions occur with aliphatic amines and isolated double bonds.[13] Thioethers and heterocyclic nitrogen compounds do not exchange because of their irreversible binding to the Ir center. Similarly, addition of coordinating solvent leads to a significant reduction in exchange reactivity (entries 8 and 9). Although typically these Ir(III) complexes are very sensitive to the steric environment in the substrate,[6,11] there is significant labeling *ortho* to phenoxy groups (entries 1 and 3). This is most likely caused by coordination of the phenoxy group to the Ir metal, directing the activation of *ortho* positions in analogy to previously reported methods.[1−3]

The H/D exchange of druglike compounds was investigated to extend the application of these Ir(III) complexes to templates frequently encountered in the pharmaceutical industry (Table 2). Labeling efficiencies ranged from good to excellent. As expected, most of the H/D exchange occurred in aromatic positions. However, the *N*-methyl and *O*-methyl moieties of entries 1 and 4 were activated to a modest extent. It is noteworthy that aliphatic secondary amines (and primary amines by extension) can be protected as carbamates to make them amenable to this labeling procedure (entry 1).

Warfarin was used to test the feasibility of the Ir(III) exchange process with tritium gas. The tritiation produced 8.37 mCi of [^{3}H]warfarin at 2.82 Ci/mmol using 194 mCi (3.31 μmol) of T_2 gas. ^{3}H NMR spectroscopy confirmed that all tritium atoms were incorporated into the aromatic position.

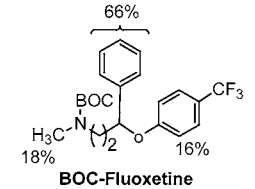
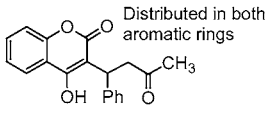
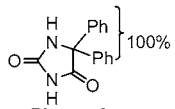
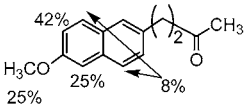
Table 1. Deuteration of Naphthyl and Phenyl Substrates



entry	substrate	R	D position[a]	D equiv[b]
1	**A**	1-OH	2 (19%) 3 (23%) 6, 7 (58%)	1.10
2	**C**	NHAc	3, 5 (58%) 4 (42%)	1.00
3	**C**	1,3-OH	2,4,6 (46%) 5 (21%)	0.84
4	**A**	1-OCH_3	3, 4, 6, 7	0.83
5	**A**	1-CO_2H	3, 6 (46%) 7 (54%)	0.80
6	**A**	1-NO_2, 2-CH_3	6 (41%) 7 (59%)	0.79
7	**C**	SO_2CH_3	3, 5 (66%) 4 (33%)	0.64
8[c]	**C**	SO_2CH_3		0.62
9[d]	**C**	SO_2CH_3		0.20
10	**A**	1-$N(CH_3)_2$	Ar and/or CH_3	0.47
11[e]	**A**	1-$CH_2N(CH_3)_2$	NCH_2D	0.28
12[f]	**A**	1-$CH(OH)CH_3$	unknown	0.77
13[g]	**A**	1-$CH_2CH{=}CH_2$	unknown	0.22
14	**C**	1-Br, 4-NO_2	aromatic	0.05
15	**A**	2-SCH_3	n/a	n/a
16	**B**	2-CH_3	n/a	n/a

[a] Location percentage in parentheses determined by ^{2}H NMR. [b] Deuterium equivalents based on mass spec isotopic envelope (i.e., number of protons exchanged, max = 1.1). [c] 110 Torr D_2. [d] 14% dioxane/CH_2Cl_2. [e] Majority of product was demethylated amine bound to Ir. [f] Majority of substrate converted to ketone (1-acetonaphthone). [g] Substrate bound to Ir; byproducts formed during reaction (including oxidized $C_{13}H_{10}O$ compound).

Table 2. Deuteration of Commercial Pharmaceuticals[16]

entry	substrate and D location[a]	D equiv.[b]
1	 **BOC-Fluoxetine**	1.1
2	 **Warfarin**	0.87
3	 **Phenytoin**	0.49
4	 **Nabumetone**	0.40

[a] Location percentage in parentheses determined by ^{2}H NMR. [b] Deuterium equivalents based on mass spec isotopic envelope (i.e., number of protons exchanged, max = 1.1).

(13) Klei, S. R.; Golden, J. T.; Tilley, T. D.; Bergman, R. G. *J. Am. Chem. Soc.* **2002**, *124*, 2092−2093.

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(16) Generally, 4.5−7 μmol of Ir complex and $NaBAr_f$ (both 1.1 equiv) were weighed in a small round-bottom flask (2.3−2.5 mL), dissolved in 150 μL of CH_2Cl_2, and stirred for 10 min. A solution of the substrate (4−6 μmol, 1 equiv) was then added, and the reaction mixture was stirred for 20 min, followed by exposure to 1 atm D_2 gas for 1 h unless otherwise indicated. All manipulations were performed in a N_2 drybox.

It is interesting to note that a scale-up to 1.1 Ci of T_2 (conventional limit for a tritiation, with no H_2 dilution) would produce 48.4 mCi at a specific activity of 16.2 Ci/mmol.[17] This is comparable and in some cases superior to the current Ir(I)-H/T exchange technology.[6,18,19]

Unfortunately, the precursor of **1**, Cp*(PMe$_3$)Ir(Me)OTf, suffers from thermal and air instability, necessitating its storage under an inert atmosphere at −40 °C. However, the thermally and air-stable complex Cp*(PMe$_3$)Ir(Me)Cl (**2**)[9] was determined to be equally capable of forming **1** when mixed with NaBAr$_f$. When this compound was applied to the deuteration of warfarin, 0.94 equiv of deuterium were incorporated. This is comparable to the activity of **1** (Table 2, entry 2) and therefore demonstrates the utility of **2** as a robust replacement for Cp*(PMe$_3$)Ir(Me)OTf.

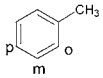
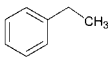
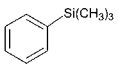
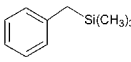
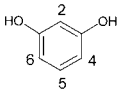
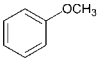
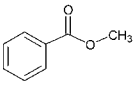
To extend the above methods to catalytic H/D exchange reactions, Cp*(PMe$_3$)IrCl$_2$ (**3**) and Cp*(PMe$_3$)Ir(H$_3$)OTf (**4**) were investigated as catalysts. A variety of deuterated solvents were screened as deuterium sources, and THF and benzene were used as model substrates. Reactions with **3** performed in organic solvents gave little to no deuterium incorporation. Exchange reactions into THF with D_2O gave comparable results with both complexes. Methanol-d_1 gave no deuterium incorporation into benzene with either catalyst, but surprisingly, high incorporation (95%) was observed in methanol-d_4 with catalyst **4**. The CH_3OH signal in ^{1}H NMR spectrum grew during the course of this reaction, rather than the CH$_3$O*H* signal, suggesting the involvement of a C−H bond activation step in the catalytic cycle rather than acid-catalyzed exchange reaction. Acetone-d_6 provides even higher deuterium incorporation (99%) into benzene at 135 °C.

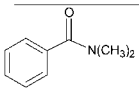
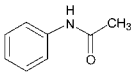
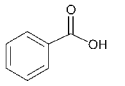
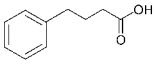
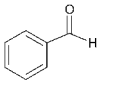
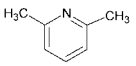
The aromatic compounds shown in Table 3 were then screened for H/D exchange using **4** and acetone-d_6. Most of the substrates showed satisfactory deuterium incorporation. The catalyst tolerated various functionalities, such as hydroxy, alkoxy, amide, carboxylic acid, and ester groups. Steric hindrance lowered deuterium incorporation into the *ortho* position, and coordination of Lewis bases to the Ir center shut down reactivity. However, sterically hindered bases such as 2,6-lutidine exhibited satisfactory deuterium incorporation into the methyl groups and the aromatic positions. Benzaldehyde showed low deuterium incorporation under the reaction conditions because cleavage of the aldehydic C−H bond by the iridium species followed by decarbonylation led to the formation of [Cp*(PMe$_3$)IrPh(CO)][OTf], shutting down the H/D exchange pathway.

When the H/D exchange reaction with **4** and acetone-d_6 was monitored carefully, >99% incorporation into benzene was achieved in less than 4 h at 135 °C. At 75 °C, the rate of the reaction was slower, but deuterium incorporation was comparable to reactions at 135 °C (Table 3). Even at 25 °C, 83% incorporation was observed in benzene after 1 week. Lowering the catalyst loading to 1 mol % gave 79% deuterium incorporation into benzene after 3 d at 75 °C.

Table 3. Substrate Screen with Catalyst **4**

R-H $\xrightarrow[\text{acetone-}d_6,\ 20\ h]{5\ \text{mol\% Cp*PMe}_3\text{Ir(H}_3\text{)OTf}}$ R-D

substrate	% D$_{inc}$ 135 °C	% D$_{inc}$ 75 °C
	99	99
	o: 57 m: 98 p: 97 CH$_3$: 50	o: 32 m: 93 p: 94 CH$_3$: 11
	o: 10 m: 99 p: 99 CH$_2$: 0 CH$_3$: 38	o: 9 m: 99 p: 99 CH$_2$: 0 CH$_3$: 23
	o: 5 m, p: 95 CH$_3$: 0	o: 16 m,p: 98 CH$_3$: 0
	o, p: 4 m: 99 CH$_2$: 0 CH$_3$: 0	o, p: 19 m: 92 CH$_2$: 0 CH$_3$: 0
	o, p: 96 m: 96 OH: 99	o, p: 98 m: 99 OH: 99
	5: 98 2, 4, 6: 96 OH: 99	5: 96 2, 4, 6: 96 OH: 99
	o, p: 96 m: 97 CH$_3$: 41	o, p: 97 m: 98 CH$_3$: 35
	o: 36 m: 72 p: 80 CH$_3$: 19	o: 47 m: 81 p: 89 CH$_3$: 16

substrate	% D$_{inc}$ 135 °C	% D$_{inc}$ 75 °C
	Ar: 43 Me: 32	Ar: 22 Me: 18
	o: 78 m: 97 p: 97 CH$_3$: 85	o: 44 m: 87 p: 89 CH$_3$: 27
	o: 72 m: 35 p: 26 COOH: 99	o: 12 m: 18 p: 11 COOH: 99
	Ar: 62 CH$_2$: 0 COOH: 99	Ar: 44 CH$_2$: 0 COOH: 99
	o: 72 m: 35 p: 26 CHO: 61	o: 21 m: 24 p: 21 CHO: 25
	0	0
	m: 67 p: 95 CH$_3$: 93	m: 31 p: 28 CH$_3$: 27
	98	96

In summary, we have developed methods for fast and efficient stoichiometric D(T) incorporation in pharmaceutical compounds and catalytic H/D exchange into aromatic compounds in acetone-d_6 at moderate temperature. Further experiments directed at understanding the selectivity of these reactions are in progress.

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Supporting Information Available: Experimental details for new compounds and information about deuterium/tritium incorporation. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) A full 1.1 Ci of T_2 was utilized in the labeling of a proprietary drug candidate, resulting in 79 mCi of pure product at 21.9 Ci/mmol.

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