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Authors: Yejin Chang, Tanner Myers, and Masayuki Wasa

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VERY IMPORTANT PUBLICATION

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$B(C_6F_5)_3$-Catalyzed α-Deuteration of Bioactive Carbonyl Compounds with D_2O

Yejin Chang,[a] Tanner Myers[a] and Masayuki Wasa[a]*

[a] Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, United States. Email: wasa@bc.edu.

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Dedicated to Professor Eric N. Jacobsen on the occasion of his 60th birthday.

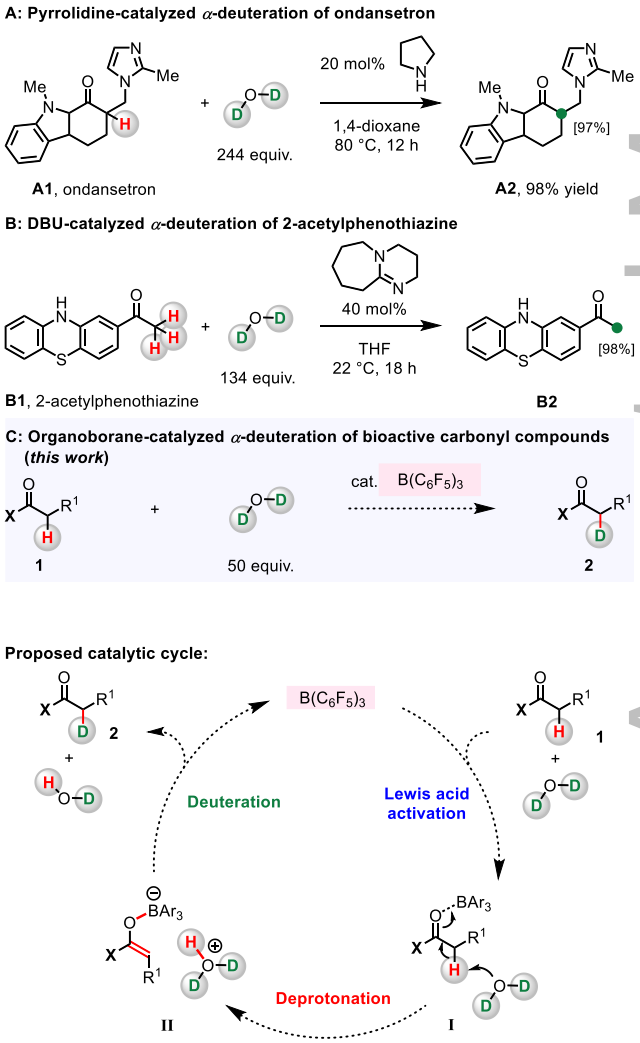
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.

Abstract. An efficient deuteration process of α-C–H bonds in various carbonyl-based pharmaceutical compounds has been developed. Catalytic reactions are initiated by the action of Lewis acidic $B(C_6F_5)_3$ and D_2O, converting a drug molecule into the corresponding boron–enolate. Ensuing deuteration of the enolate by in situ-generated D_2O^+–H then results in the formation of α-deuterated bioactive carbonyl compounds with up to >98% deuterium incorporation.

Keywords: Deuterated drug; Frustrated Lewis pair; Late-stage functionalization; Cooperative catalysis

Exchanging the hydrogen atoms contained in a bioactive compound by deuterium may improve its properties.[1-4] A deuterated drug could have significantly lower rates of metabolism relative to the original molecule because of the kinetic isotope effect, and hence a longer half-life.[1-3] In particular, hydrogen isotope exchange (HIE) reaction targeting α-C–H bonds of bioactive carbonyl compounds is in high demand because of their tendency to undergo deprotonation in vivo and also due to their prevalence in pharmaceuticals.[3a,5-6] α-Deuteration of bioactive ketones have previously been achieved through Lewis base-catalyzed conversion of these molecules into enamine or enol intermediates.[6] Representative methods include α-C–H deuteration of ondansetron (**A1**) by pyrrolidine and D_2O (Scheme 1A).[6b] 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)-catalyzed α-deuteration process represents a notable strategy for isotopic labelling of 2-acetylphenothiazine (**B1**) and two other structurally related drugs (Scheme 1B).[6a] Still, development of a catalyst system for α-deuteration of carbonyl-based drugs that cannot be readily deprotonated by Lewis base catalysts and/or those containing base-sensitive functional groups stands as a significant challenge.[6-8]

We began by contemplating a method for α-deuteration of bioactive carbonyl compounds (**1**) by utilizing a Lewis acidic organoborane that can activate **1** towards deprotonation by D_2O (Scheme 1C; **I** to **II**).[9-10] A potential complication of this approach is that the Lewis acid may form stable acid–base adducts with D_2O as well as Lewis basic functional groups that may be contained in **1**.[11-14] The application of frustrated Lewis pairs (FLPs), consisting of strongly Lewis acidic and hindered $B(C_6F_5)_3$ and various Lewis bases, has emerged as an attractive strategy for overcoming undesired acid–



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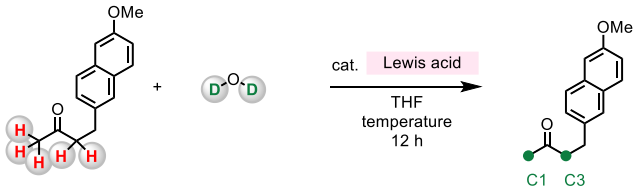
Scheme 1. *α*-Deuteration of bioactive carbonyl compounds

base complexation.[9,12-14] We envisioned that $B(C_6F_5)_3$ could activate **1**,[9] thereby facilitating deprotonation by D_2O to generate a boron–enolate and D_2O^+–H (**I** to **II**).[11-12] Ensuing deuteration of the enolate by D_2O^+–H would afford desired product **2**. An alternative mechanistic scenario may entail the in situ formation of Brønsted acidic D_2O–$B(C_6F_5)_3$ which deuterates the carbonyl unit of **1**. Ensuing D_2O-catalyzed deprotonation of deuterated **1** affords an enol and D_2O^+–H which could then undergo *α*-deuteration to give **2** (See the SI for details). Here, we report $B(C_6F_5)_3$-catalyzed and protecting group free method for *α*-deuteration of various bioactive carbonyl compounds.

We first set out to identify the reaction conditions for *α*-deuteration of nabumetone **1a**. We probed the ability of $B(C_6F_5)_3$ and D_2O to catalyze the reaction between nabumetone **1a** and D_2O, generating **2a** (Table 1). Treatment of **1a** and D_2O with 10 mol% $B(C_6F_5)_3$ and 50 equivalent of D_2O at 60, 80 or 100 °C afforded **2a** in >95% yield (THF, 12 h); while only 6% of *α*-C–H bonds were converted to C–D bonds at 60 °C, *d*-incorporation could be improved to 89-95% at 80 and 100 °C (entries 1–3). When the reaction mixture was heated at 100 °C for 6 hours, **2a** was generated with 82% and 83% deuterium incorporation (entry 4). Deuterium incorporation diminished to 75% and 77% with 5.0 mol% of $B(C_6F_5)_3$ (entry 5). With 10 mol% of $B(C_6F_5)_3$ and 10 equivalent of D_2O there was only 76% and 79% of *d*-incorporation (entry 6). Less than 7% of labelling occurred without $B(C_6F_5)_3$ or when less Lewis acidic

Table 1. Evaluation of Reaction Parameters [a,b,c]



1a, **nabumetone** 0.1 mmol — 50 equiv. — **2a**, >95% yield

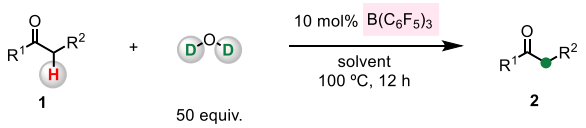
entry	Lewis acid (mol%)	temperature (°C)	*d*-incorporation (%) [C1]	[C3]
1	$B(C_6F_5)_3$ (10)	60	6	6
2	$B(C_6F_5)_3$ (10)	80	89	89
3	$B(C_6F_5)_3$ (10)	100	93	95
4[d]	$B(C_6F_5)_3$ (10)	100	82	83
5	$B(C_6F_5)_3$ (5.0)	100	75	77
6[e]	$B(C_6F_5)_3$ (10)	100	76	79
7	none	100	0	0
8	BPh_3 (10)	100	7	<5
9	BF_3•OEt_2 (10)	100	62	77

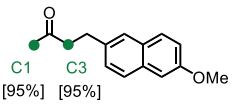
[a] Conditions: nabumetone (**1a**, 0.1 mmol), D_2O (50 equiv.), Lewis acid (5.0 or 10 mol%), THF (0.2 mL), 100 °C, 12 h. [b] Yield and deuterium incorporation level was determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. [c] Green label indicates sites that undergo deuteration. [d] The reaction mixture was allowed to stir for 6 h. [e] D_2O (10 equiv.) was used.

BPh was used (entries 7–8). Less hindered BF_3•OEt_2 was found to be a potent catalyst, however **2a** was obtained with lower level of *d*-incorporation (62% and 77%). These findings support the notion that strongly Lewis acidic and hindered $B(C_6F_5)_3$ together with D_2O constitute the most effective combination.[10]

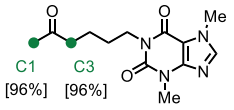
An array of acyclic and cyclic bioactive ketones (**1a**–**1h**) underwent efficient deuteration (Table 2). This protocol was found to be compatible with compounds that contain an array of Lewis acid-sensitive functional groups. In addition to the ketone units of **1a**–**1h**, methoxy (**1a**), theobromine (**1b**),

Table 2. Deuteration of Bioactive Ketones [a,b,c]

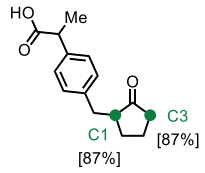




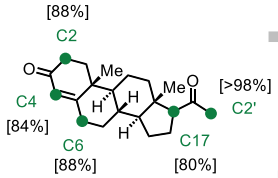
2a, **nabumetone**
(nonsteroidal anti-inflammatory)
>95% yield



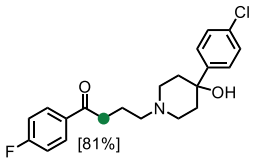
2b, **pentoxifylline**
(treats muscle pain/cramping)
95% yield



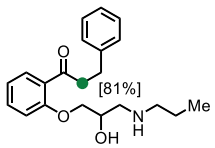
2c, **loxoprofen**
(nonsteroidal anti-inflammatory drug)
>95% yield



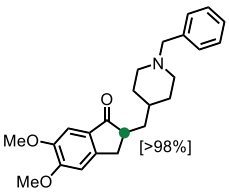
2d, **progesterone**
(endogenous steroid)
84% yield



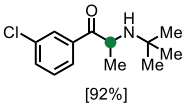
2e, **haloperidol**
(antipsychotic)
>95% yield



2f, **propafenone**[d]
(anti-arrhythmic)
46% yield



2g, **donepezil**
(treats Alzheimer's disease)
>95% yield

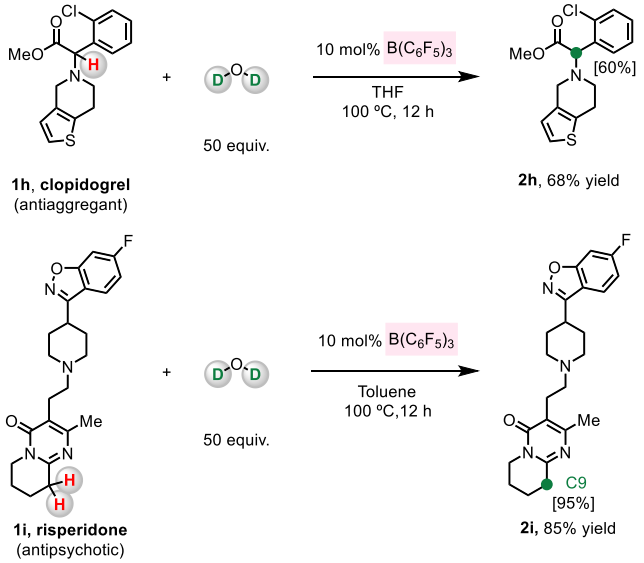


2h, **bupropion**[d,e]
(antidepressant)
71% yield

[a] Conditions: ketone (**1**, 0.2 mmol), D_2O (50 equiv.), $B(C_6F_5)_3$ (10 mol%), solvent (0.4 mL), 100 °C, 12 h. For the detailed conditions, see the SI. [b] Yield of isolated and purified product. Deuterium incorporation level was determined by ^1H NMR analysis of the isolated and purified product. [c] Green label indicates sites that undergo deuteration. [d] The substrate was used as the corresponding HCl salt. For the detailed conditions, see the SI. [e] The reaction mixture was allowed to stir for 1 h at 80 °C.

carboxylic acid (**1c**), *N*-alkylamine (**1e**, **1f**, **1g**, **1h**), and hydroxyl (**1e**, **1f**) moieties were tolerated to give the deuteration products **2a**–**2h** in 46 to >95% yield after purification by silica gel chromatography. Labeling took place with high regioselectivity for α-ketone C–H bonds. No deuterium incorporation at less acidic α-carboxylic acid C–H bond of loxoprofen (**1c**) was observed. In addition, progesterone which possesses acidic allylic C(6)–H bonds also underwent efficient deprotonation/deuteration at C(6); ensuing deuteration of the resulting enolate at C(4) affords **2d**.

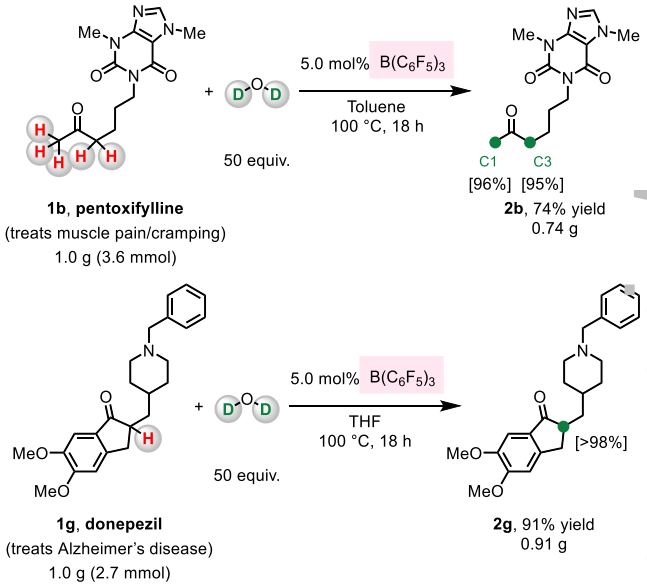
Next, we investigated possible labeling of pharmaceuticals that contain α-ester or α-imino C–H bonds (Scheme 2; **1h**–**1i**). *a*-Deuteration of clopidogrel **1h** gave **2h** in 68% yield and 60% *d*-incorporation. With risperidone **1i**, acidic C(9)–H bonds of 2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one underwent efficient deuteration to give **2i**. These results further demonstrate the tolerance of this deuteration protocol to Lewis acid-sensitive heterocycles such as 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**1h**) and benzo[*d*]isoxazole (**1i**).



Scheme 2. α-Deuteration of bioactive carbonyl compounds

The method is readily scalable. Reaction of 1.0 g of pentoxifylline **1b** (3.6 mmol) or donepezil **1g** (2.7 mmol) with D_2O afforded **2b** and **2g** in 74% yield (0.74 g, >95% *d*-incorporation) and 91% yield (0.91 g, >98% *d*-incorporation), respectively (Scheme 3; 5.0 mol% $B(C_6F_5)_3$, 50 equiv. D_2O, 18 h, 100 °C).

The kinetic profile of α-deuteration of donepezil **1g** was monitored through the ^1H NMR spectroscopic analysis (Figure 1, see the SI for experimental details). While only 30% of α-carbonyl C–H bonds were converted to C–D bonds when the reaction mixture was allowed to react in the NMR machine for 1 hour, *d*-incorporation level gradually increased to 90% in 12 hours.



Scheme 3. Gram-scale α-deuteration of bioactive ketones

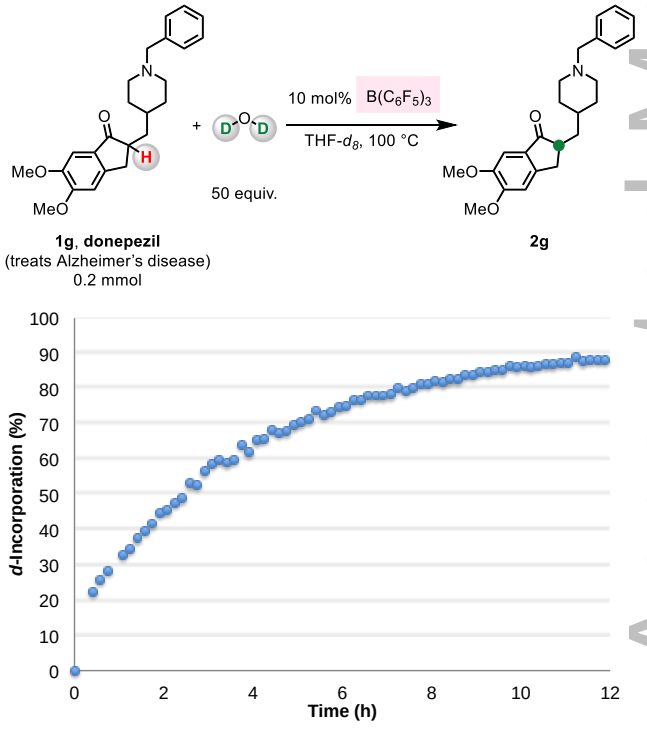


Figure 1. Kinetic profile of α-deuteration of donepezil **1g**

In summary, we have designed an efficient and regioselective deuterium labeling protocol of carbonyl C–H bonds in a series of pharmaceuticals. By implementing the cooperative catalytic function of $B(C_6F_5)_3$ and D_2O, we show that it is possible to convert a carbonyl-based drug to the corresponding boron–enolate, and that the same catalyst system can

generate a labeling agent from D_2O. The principles outlined herein, entailing conversion of carbonyl containing drugs into enolates and its reaction with an in situ generated electrophilic partner, provide a new rational framework for late-stage modification of a drug candidate. Studies along these lines are in progress.

Experimental Section

General Procedure for the Synthesis of 2a

To a 15 mL oven-dried pressure vessel was added nabumetone **1a** (0.2 mmol), $B(C_6F_5)_3$ (10 mol%), THF (0.4 mL), and D_2O (10 mmol). The reaction mixture was allowed to stir for 12 hours at 100 °C. Upon completion, the reaction mixture was concentrated *in vacuo*. After purification by column chromatography (Et_2O:hexanes = 1:9), **2a** was obtained as a white solid (45 mg, >95% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.5 Hz, 2H), 7.53 (s, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.15 – 7.07 (m, 2H), 3.89 (d, *J* = 2.0 Hz, 3H), 3.00 (s, 2H), 2.83 – 2.74 (m, 0.10H, 95%D), 2.13 – 2.08 (m, 0.14H, 95%D); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.22, 157.26, 157.21, 136.06, 133.06, 132.99, 129.03, 128.87, 128.86, 127.47, 126.92, 126.86, 126.19, 118.76, 105.62, 55.24, 44.58, 44.43, 44.29, 29.60, 29.55; **IR** (neat) 2931, 1703, 1633, 1604, 1484, 1461, 1391, 1246, 1232, 1161, 1030, 853, 817 cm^{-1}; **HRMS** (DART) Calcd for $C_{15}H_{12}D_5O_2$ (MH+): 234.1537; found: 234.1547.

Acknowledgements

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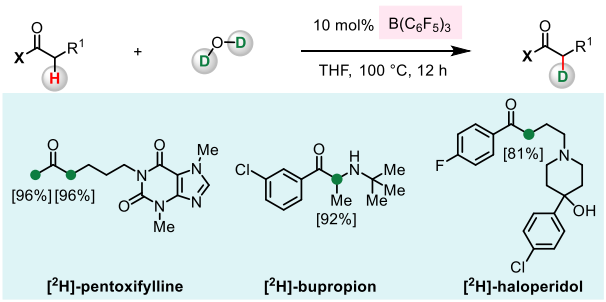
COMMUNICATION

$B(C_6F_5)_3$-Catalyzed α-Deuteration of Bioactive Carbonyl Compounds with D_2O



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