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B(C₆F₅)₃-Catalyzed α -Deuteration of Bioactive Carbonyl Compounds with D₂O

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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(C₆F₅)₃ and D₂O, converting a drug molecule into the corresponding boron–enolate. Ensuing deuteration of the enolate by in situ-generated D₂O⁺–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 D₂O (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 D₂O (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 D₂O 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(C₆F₅)₃ and various Lewis bases, has emerged as an attractive strategy for overcoming undesired acid–base complexation.^[9,12–14] We envisioned that B(C₆F₅)₃ could activate **1**,^[9] thereby facilitating deprotonation by D₂O to generate a boron–enolate and D₂O⁺–H (**I** to **II**).^[11–12] Ensuing deuteration of the enolate by D₂O⁺–H would afford desired product **2**. An alternative mechanistic scenario may entail the in situ formation of Brønsted acidic D₂O–B(C₆F₅)₃ which deuterates the carbonyl unit of **1**. Ensuing D₂O-catalyzed deprotonation of deuterated **1** affords an enol and D₂O⁺–H which could then undergo α -deuteration to give **2** (See the SI for details). Here, we report B(C₆F₅)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(C₆F₅)₃ and D₂O to catalyze the reaction between nabumetone **1a** and D₂O, generating **2a** (Table 1). Treatment of **1a** and D₂O with 10 mol% B(C₆F₅)₃ and 50 equivalent of D₂O 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(C₆F₅)₃ (entry 5). With 10 mol% of B(C₆F₅)₃ and 10 equivalent of D₂O there was only 76% and 79% of d -incorporation (entry 6). Less than 7% of labelling occurred without B(C₆F₅)₃ or when less Lewis acidic BPh was used (entries 7–8). Less hindered BF₃•OEt₂ 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(C₆F₅)₃ together with D₂O 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**), 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**). α -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**).

The method is readily scalable. Reaction of 1.0 g of pentoxifylline **1b** (3.6 mmol) or donepezil **1g** (2.7 mmol) with D₂O 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(C₆F₅)₃, 50 equiv. D₂O, 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.

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(C₆F₅)₃ and D₂O, 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 D₂O. 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(C₆F₅)₃ (10 mol%), THF (0.4 mL), and D₂O (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 (Et₂O:hexanes = 1:9), **2a** was obtained as a white solid (45 mg, >95% yield).

¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 C₁₅H₁₂D₅O₂ (MH⁺): 234.1537; found: 234.1547.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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A: Pyrrolidine-catalyzed α -deuteration of ondansetron **B: DBU-catalyzed α -deuteration of 2-acetylphenothiazine** **C: Organoborane-catalyzed α -deuteration of bioactive carbonyl compounds (this work)** **Proposed catalytic cycle:**

Scheme 1.
 α -Deuteration of bioactive carbonyl compounds

Scheme 2.
 α -Deuteration of bioactive carbonyl compounds

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

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

Table 1.

Evaluation of Reaction Parameters ^[a,b,c]

entry	Lewis acid (mol%)	Temperature (°C)	<i>d</i> -incorporation (%)	
			[C1]	[C3]
1	B(C ₆ F ₅) ₃ (10)	60	6	6
2	B(C ₆ F ₅) ₃ (10)	80	89	89
3	B(C ₆ F ₅) ₃ (10)	100	93	95
4 ^d	B(C ₆ F ₅) ₃ (10)	100	82	83
5	B(C ₆ F ₅) ₃ (10)	100	75	77
6 ^e	B(C ₆ F 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), D₂O (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] D₂O (10 equiv.) was used.

Table 2.

Deuteration of Bioactive Ketones ^[a,b,c]

^[a] Conditions: ketone (**1**, 0.2 mmol), D₂O (50 equiv.), B(C₆F₅)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.