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Catalytic Deuterium Incorporation within Metabolically Stable β-Amino C—H Bonds of Drug Molecules

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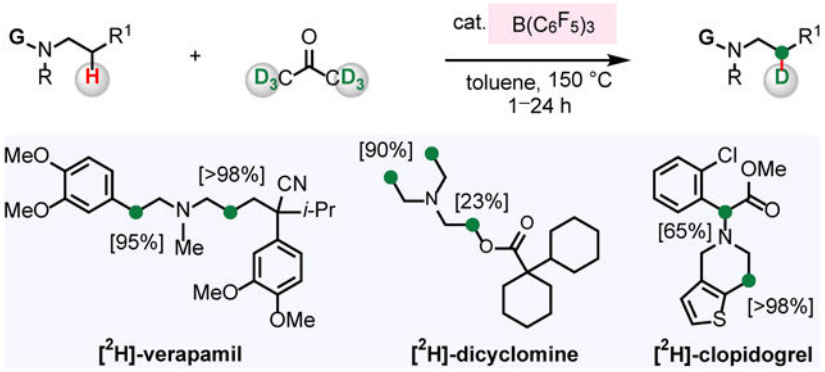
Abstract

An efficient deuteration process of β-amino C—H bonds in various *N*-alkylamine-based pharmaceutical compounds has been developed. Catalytic reactions begin with the action of Lewis acidic $B(C_6F_5)_3$ and Brønsted basic *N*-alkylamine, converting a drug molecule into the corresponding enamine. The acid/base catalysts also promote the dedeuteration of acetone-d_6 to afford a deuterated ammonium ion. Ensuing deuteration of the enamine then leads to the formation of β-deuterated bioactive amines with up to 99% deuterium incorporation.

Graphical Abstract



Deuterium-labeled pharmaceuticals are pivotal diagnostic tools in research aimed at determination of the corresponding biological outcomes and metabolites.[1-6] Drugs containing C—D bonds have been prepared through multistep synthesis involving the reduction of unsaturated or halogenated intermediates.[3] However, innovations in organometal-catalyzed C—H activation have enabled direct hydrogen isotope exchange (HIE) at C—H bonds for deuterium.[4-6] In particular, HIE reaction targeting C(sp^3)—H bonds of pharmaceuticals that contain an *N*-alkylamine unit is in high demand because these

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Supporting Information Available: Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge *via* the Internet at http://pubs.acs.org.

entities constitute over 50% of the top-selling commercial drugs.[7] The state-of-the-art processes include Beller's α- and β-amino C—H deuteration of metoclopramide (**A1**) and two other structurally related drug molecules promoted by Ru-based Shvo catalyst (Figure 1A).[5] MacMillan's photoredox-mediated α-deuteration and α-tritiation represents a notable strategy for isotopic labelling of a range of *N*-alkylamine-based drugs (Figure 1B).[6] Still, development of methods for regioselective deuteration of poorly reactive β-amino C(sp^3)—H bonds of drugs containing Lewis acid- and base-sensitive functional groups with an inexpensive deuterium source and promoted by non-precious metal-based catalysts is a significant challenge.[8,9] Regioselective deuteration of metabolically stable β-amino C—H bonds (vs more labile α-amino C—H bonds) is particularly attractive as it minimizes the loss of the label due to exchange.[1-3]

We began by contemplating a possible way to design a method for deuteration of biologically active compounds that contain an *N*-alkylamine unit (**1**) with readily available acetone-d_6 **2** as a source of deuterium (Figure 1C). We considered utilizing a combination of Lewis acid and Brønsted base catalysts that would function cooperatively.[10-12] We envisioned that $B(C_6F_5)_3$ could receive a hydride from an amine (**1**), generating a borohydride and an iminium ion (**I**).[13-19] Subsequently, a Brønsted basic amine catalyst would deprotonate **I**, furnishing enamine **II**.[13-16] Concurrently, the *N*-alkylamine could dedeuterate $B(C_6F_5)_3$-activated acetone-d_6 **2**, generating an enolate and a deuterated ammonium ion (**III**).[20] Ensuing deuteration (**IV**) of the enamine **II** by **III** gives an iminium ion; subsequent borohydride reduction would afford β-deuterated product **3**. Here, we report the development of a catalyst system for β-amino C—H deuteration of bioactive amines.

We first set out to identify a desirable combination of catalysts. We probed the ability of $B(C_6F_5)_3$ and various Brønsted bases to catalyze the reaction between verapamil **1a** and acetone-d_6 **2** (6.8 equivalent), generating **3a** (Table 1). Treatment of **1a** and **2** with 5.0 mol% $B(C_6F_5)_3$ and 10 mol% NEt_3, NBn_3, or 1,2,2, 6,6-pentamethylpiperidine (PMP) afforded **3a** in >90% yield (toluene, 125 °C, 1 h); 16-34% of β-amino C—H bonds were converted to C—D bonds (entries 1–3). With more Brønsted basic 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), no labeling was observed (entry 4). When the transformation was performed without a Brønsted base co-catalyst, **3a** was generated with 35% and 21% deuterium incorporation (entry 5), suggesting that *N*-alkylamines **1a** and/or **3a** can promote deprotonation of the iminium ion (**I**, Figure 1C; NR_3 = **1a** and/or **3a**). Deuterium incorporation diminished to <10% with 5.0 mol% of $B(C_6F_5)_3$ and reaction temperature of 100 °C (entry 6), but when the reaction mixture was heated at 150 °C, **3a** was obtained with >80% labeling (entry 7). With 10 mol% $B(C_6F_5)_3$ there was only minor improvement (entry 8, 88% and 92%). However, by reacting **1a** with two batches of 5.0 mol% of $B(C_6F_5)_3$ and **2** (6.8 equivalent), we were able to obtain **3a** with >95% deuterium incorporation (entry 9). There was no labeling without $B(C_6F_5)_3$ or when the less hindered BF_3 or the less Lewis acidic BPh_3 were used (entries 10–12). These findings support the notion that strongly acidic $B(C_6F_5)_3$ together with sterically demanding and electron-rich *N*-alkylamine constitute the most effective combination.[10]

Acyclic β-amino C—H bonds in a number of pharmaceuticals (**1a**–**1j**) 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 *N*-alkylamine units of **1a**–**1j**, cyano (**1a**), ester (**1b**), amide (**1d**, **1e**, **1f**) and ketone (**1j**) were tolerated to give the deuteration products **3a**–**3j** in 77 to >95% yield after purification by silica gel chromatography. Labeling took place with high regioselectivity for β-amino C—H bonds. In addition, drug molecules that possess acidic α-carbonyl C—H bonds also underwent efficient deuteration (**3d**, **3j**) based on analysis of ^{1}H NMR spectra of unpurified mixtures. Nonetheless, in case of **3d**, α-carbonyl C—D bonds of indolin-2-one underwent H—D exchange during purification.

For substrates that possess electronically and sterically disparate β-amino C—H bonds (**1a**, **1b**, **1c**, **1d**, **1g**, **1j**), deuterium labeling occurred at varying levels. With verapamil **1a**, benzylic C2—H and non-benzylic C4—H bonds were converted to C—D bonds in >95%, but deuteration of non-benzylic C4—H bonds was more efficient (Table 1, entries 5-9). With dicyclomine **1b**, while 90% of C2'—H bonds of *N*-ethyl groups was deuterated, only 23% of C1—H bonds adjacent to an ester group were converted to C—D bonds. Similar reactivity was observed with clomiphene **1c**: 90% of C2'—H bonds were converted into C2'—D bonds, but 15% of α-aryloxy C1—H bonds were deuterated. Ropinirole **1d** was labeled at benzylic C1—H bonds (63%), and C2'—H bonds of *N*-propyl group (86%).

Although the catalytic protocol tolerates an array of functional groups, isotopic labeling was more efficient with substrates bearing a protecting group. For instance, 80% of β-C—H bonds of lidocaine **1e**, which possesses acidic amide N—H bonds, was converted to C—D bonds to give **3e**. However, deuteration of *N*-benzyl-protected lidocaine **1f** proceeded more efficiently to afford **3f** with 96% d-incorporation; in addition, deuteration of α-carbonyl C—H bonds was also observed (9%). Cinacalcet **1g** containing a secondary amine moiety was a compatible substrate to provide **3g** (63% [C2] and 8% [C2']), and *N*-benzyl-protected cinacalcet **3h** was obtained with >98% of β-amino C2—H bonds selectively converted into C—D bonds. With less sterically hindered secondary amines nortriptyline **1i** and propafenone **1j**, their reaction with acetone-d_6 may inhibit labeling. However, with an *N*-benzhydryl group installed, **3i** and **3j** could be readily generated. Silyl protection of the secondary alcohol proved to be effective in the case of propafenone **1j**, giving **3j** (76% [C2] and 0% at more sterically hindered [C2']).

Next, we investigated possible labeling of various pharmaceuticals that contain cyclic β-amino C—H bonds (Table 3; **1k**–**1s**). A variety of Lewis acid-sensitive heterocycles such as piperidine (**1k**–**1q**), 1,4-diazepane (**1r**), piperazine (**1s**), thiophene (**1k**, **1l**), indanone (**1m**), benzodioxole (**1o**, **1p**), benzothiophene (**1q**), as well as benzoimidazole (**1r**) were tolerated to give the corresponding deuteration products in 85 to >95% yield. With clopidogrel **1k**, prasugrel **1l**, and donepezil **1m**, both β-amino C—H bonds and enolizable α-carbonyl C—H bonds underwent efficient deuteration to give **3k**–**3m**, but acidic α-keto C—D bond of **3l** was converted to C—H bond during purification. Less acidic α-amide C—H bond of bupivacaine **1n** was not deuterated. With bupivacaine **1n** and raloxifene **1q** that contain acyclic and cyclic β-amino C—H bonds, labeling of the cyclic C—H bond was more efficient (>90% vs ≤29% for the acyclic C—H). *N*-Benzyl (**1o**) and *N*-benzhydryl (**1p**)-protected paroxetine gave **3o** and **3p**, respectively. The level of labeling for the more

hindered **3p** (94%) was superior to **3o** (76%). Furthermore, deuteration of the C5—H bond occurred selectively, while the tertiary C3—H bond remained intact. Deuteration of emedastine **1r** was found to take place at C2—H (33%) and C6—H (60%) bonds. All eight C—H bonds of piperazine ring of *O*-TBS-protected dropropizine **1s** underwent deuteration to afford **3s** (>86%). Using this protocol, α-amino C—H deuteration occurred only when these bonds were also alpha to a carbonyl group (**3f**) or beta to a N atom (**3s**).

The method is scalable. Treatment of 1.4 g (3.0 mmol) of verapamil **1a** with 5.0 mol% $B(C_6F_5)_3$, 20 mmol of acetone-d_6 (toluene, 12 h, 150 °C), followed by filtration through a pad of silica gel and repeating the aforementioned procedure afforded **3a** in 95% yield (2.9 mmol, 1.3 g) and >93% deuterium incorporation (Scheme 1).

To summarize, we have designed an efficient and regioselective deuterium labeling of β-amino C—H bonds in various bioactive molecules, provided that sufficient steric congestion is present around the reacting amine. By implementing the cooperative action of $B(C_6F_5)_3$ and *N*-alkylamine catalyst system, we show that it is possible to convert an *N*-alkylamine-based pharmaceutical compound to the corresponding enamine, and that the same catalyst system can generate a labeling agent from acetone-d_6. The principles outlined herein, entailing conversion of amine containing drugs into enamines and its reaction with 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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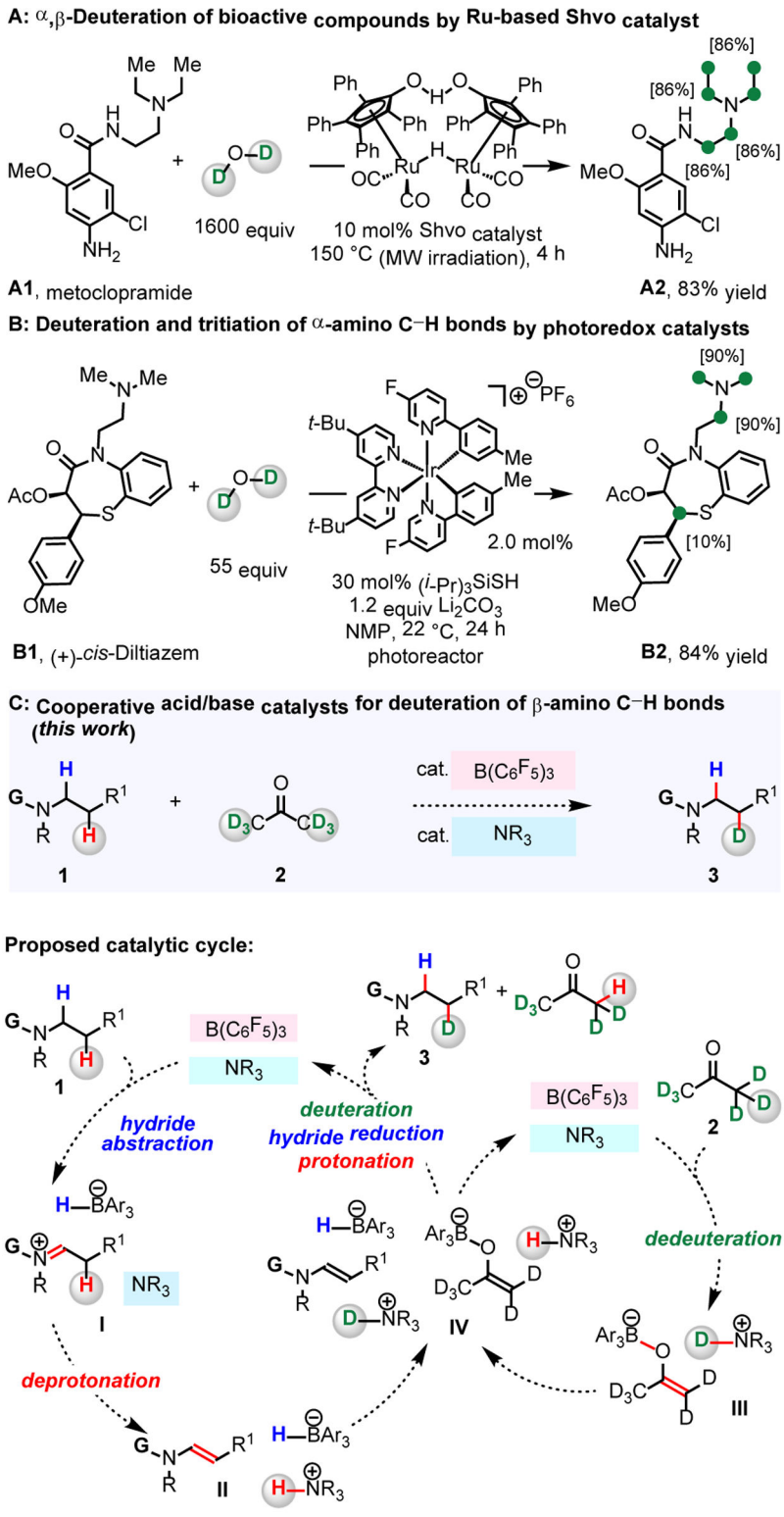
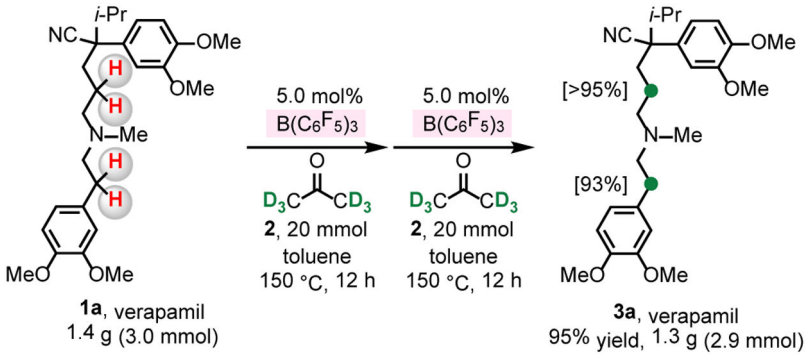


Figure 1.

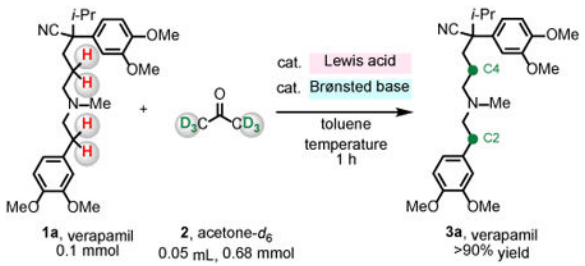
Amino C—H deuteration of biologically active molecules.



Scheme 1.
Scale-up experiment

Table 1.

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



entry	Lewis acid (mol%)	Brønsted base (mol%)	temperature (°C)	*d*-incorporation (%) [C2]	[C4]
1	$B(C_6F_5)_3$ (5.0)	NEt_3 (10)	125	17	26
2	$B(C_6F_5)_3$ (5.0)	NBn_3 (10)	125	20	34
3	$B(C_6F_5)_3$ (5.0)	PMP (10)	125	16	26
4	$B(C_6F_5)_3$ (5.0)	DBU (10)	125	0	0
5	$B(C_6F_5)_3$ (5.0)	none	125	21	35
6	$B(C_6F_5)_3$ (5.0)	none	100	<5	7
7	$B(C_6F_5)_3$ (5.0)	none	150	80	85
8	$B(C_6F_5)_3$ (10)	none	150	88	92
9[c]	$B(C_6F_5)_3$ (5.0 x 2)	none	150	95	>98
10	none	none	150	0	0
11	BF_3•OEt_2 (5.0)	none	150	0	0
12	BPh_3 (5.0)	none	150	0	0

[a] Conditions: verapamil (**1a**, 0.1 mmol), acetone-d_6 (**2**, 0.68 mmol), organoborane, Brønsted base, toluene (0.4 mL), under N_2, 1 h.

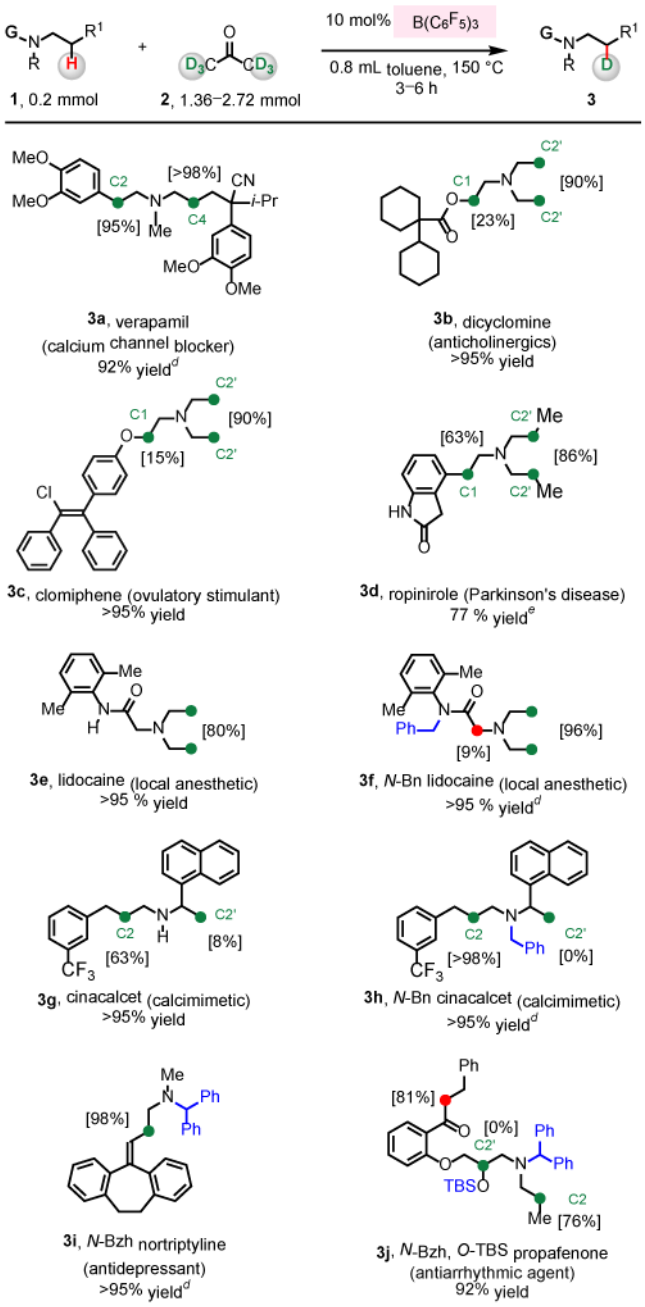
[b] Yield and deuterium incorporation level was determined by ^{1}H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard.

[c] Conditions: verapamil (**1a**, 0.2 mmol), acetone-d_6 (**2**, 1.4 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), under N_2, 150 °C, 1 h. Isolated and purified **3a** was reacted with acetone-d_6 (**2**, 1.4 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), under N_2, 150 °C, 1 h.

[d] Green label indicates sites that are beta to N.

Table 2.

Deuteration of Acyclic *β*-Amino C—H Bonds [a,b,c]



[a]Conditions: *N*-alkylamine (**1**, 0.2 mmol), acetone-d_6 (**2**, 1.36 mmol), $B(C_6F_5)_3$ (10 mol%), toluene (0.8 mL), under N_2, 150 °C, 3 h.

[b]Yield of isolated and purified product. Deuterium incorporation level was determined by ^1H NMR analysis of the isolated and purified product.

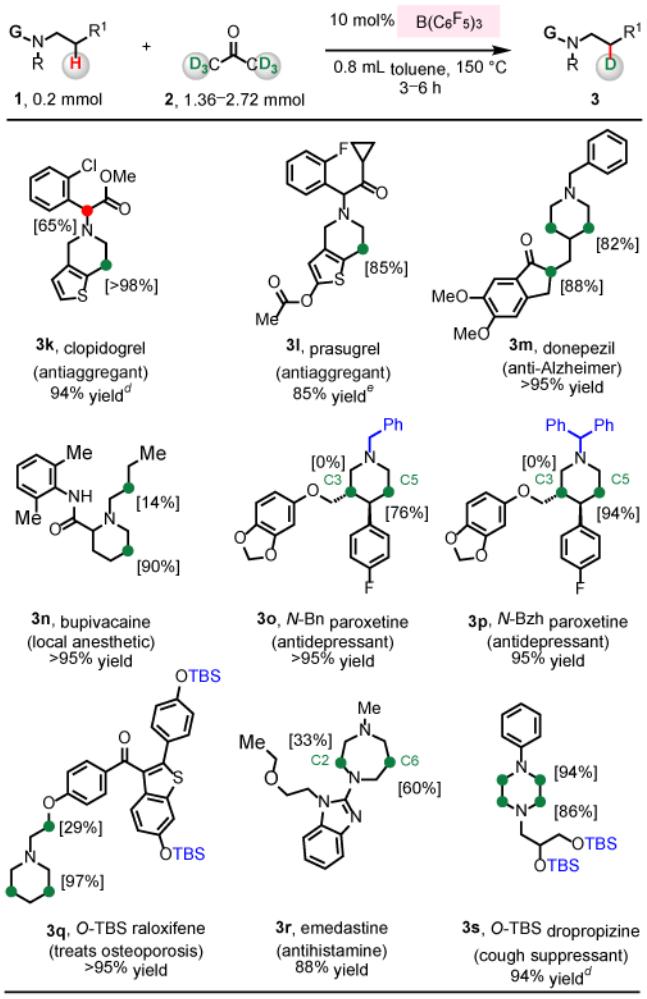
[c]Green label indicates sites that are beta to N. Red label is used for any other sites that undergo deuteration.

[d]Conditions: *N*-alkylamine (**1**, 0.2 mmol), acetone-d_6 (**2**, 1.4 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), under N_2, 150 °C, 3 h. After the filtration of the crude reaction mixture through a pad of silica gel and removal of volatiles, acetone-d_6 (**2**, 1.4 mmol), $B(C_6F_5)_3$ (5.0 mol%), and toluene (1.0 mL) were added under N_2, and then heated at 150 °C, 3 h.

[e]The reaction was carried out in two batches, using 10 mol% of $B(C_6F_5)_3$ in the first batch, and 5.0 mol% in the second. For details, see the SI.

Table 3.

Deuteration of Cyclic Amino C—H Bonds [a,b]



[a]Conditions: *N*-alkylamine (**1**, 0.2 mmol), acetone-d_6 (**2**, 1.36 mmol), $B(C_6F_5)_3$ (10 mol%), toluene (0.8 mL), under N_2, 150 °C, 3 h.

[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 are beta to N. Red label is used for any other sites that undergo deuteration.

[d]Conditions: *N*-alkylamine (**1**, 0.2 mmol), acetone-d_6 (**2**, 1.4 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (0.8 mL), under N_2, 150 °C, 3 h. After the filtration of the crude reaction mixture through a pad of silica gel and removal of volatiles, acetone-d_6 (**2**, 1.4 mmol), $B(C_6F_5)_3$ (5.0 mol%), and toluene (1.0 mL) were added under N_2, and then heated at 150 °C, 3 h.

[e]The reaction was carried out in two batches, using 10 mol% of $B(C_6F_5)_3$ in the first batch, and 5.0 mol% in the second. For details, see the SI.