

Multiple Deuterium Atom Transfer Perdeuteration of Unactivated Alkenes under Base-Assisted Cobalt/Photoredox Dual Catalysis

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Abstract: A radical approach for hydrogenative perdeuteration of unactivated alkenes under cobalt/photoredox dual catalysis is described. The addition of a suitable base plays a key role in controlling two competing pathways by switching the catalytic performance of cobalt/photoredox catalysis. Base-assisted cobalt/photoredox dual catalysis promoted a hydrogen isotope exchange reaction of alkenes to afford deuterated alkenes via multiple repeating deuterium atom transfer/hydrogen atom abstraction processes, while consecutive reductive deuteration of alkenes proceeded in the absence of a base to afford polydeuterated alkanes. One-pot hydrogenative perdeuteration and perdeutero-arylation were also developed, providing access to various polydeuterated aliphatic compounds.

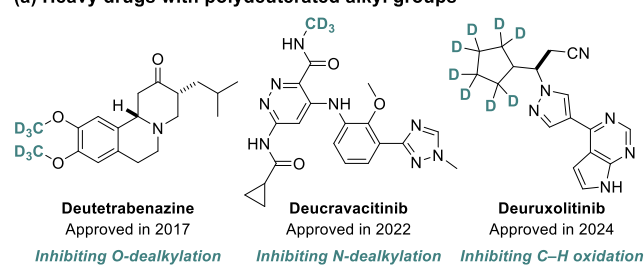
Introduction

Nearly a century has passed since the discovery of deuterium,^[1] and deuterium-labeled compounds play an indispensable role in various scientific areas.^[2] Significant attention has recently focused on the introduction of deuterium atoms into drug candidates for modification of their absorption, distribution, metabolism, and excretion (ADME) properties.^[3] In some occasions, the deuterium kinetic isotope effect (DKIE) in the cleavage of C–H/C–D bonds could slow down the metabolic reactions of deuterium-labeled pharmaceuticals, leading to a longer half-life, reduced toxicity, and other beneficial effects. Additionally, highly deuterated analogs of pharmaceuticals serve as quantitative tracers for studies of drug metabolism and as tags for Raman imaging and quantitative ²H-MRI imaging.^[2d–f, 4] In this background, the development of new deuterium-labeling methodologies has witnessed significant advances in modern synthetic organic chemistry.^[5–7]

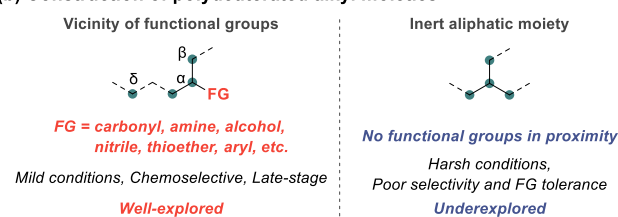
Among these compounds, drug candidates with perdeuterated alkyl groups often exhibit enhanced tolerance against oxidative metabolism, like deutetrabenazine and deucravacitinib, both approved by the US Food and Drug Administration (FDA) (Scheme 1a).^[3] Very recently, deuruxolitinib (ruxolitinib-*d*₈, CTP-543) bearing a

polydeuterated cyclic alkyl group was also approved by FDA as an oral treatment for alopecia areata.^[3i] The success of these deuterated pharmaceuticals has inspired the development of various methods to introduce multiple deuterium atoms into organic compounds, mainly through hydrogen isotope exchange (HIE) of C(sp³)–H bonds using acid, base, and metal catalysts.^[8] In recent years, site-selective deuteration of pharmaceutical alkyl moieties targeting the vicinity of functional groups^[9] such as amines,^[10] carboxylic acids,^[11] and alcohols^[12] have been explored intensively (Scheme 1b, left), especially with the rise of photocatalytic^[9f–g, 10i–n] and electrocatalytic^[7c, 10q] methods. Alkylating reagents for facile introduction of a methylene-*d*₂ unit into drug molecules have also been reported.^[13] On the other hand, the construction of polydeuterated aliphatic moieties without such functional groups in proximity at a late stage of synthesis remains challenging (Scheme 1b, right).^[14] Thus, efficient synthetic methodologies for polydeuterated alkanes would accelerate further studies on deuterium-labeled drugs.

(a) Heavy drugs with polydeuterated alkyl groups

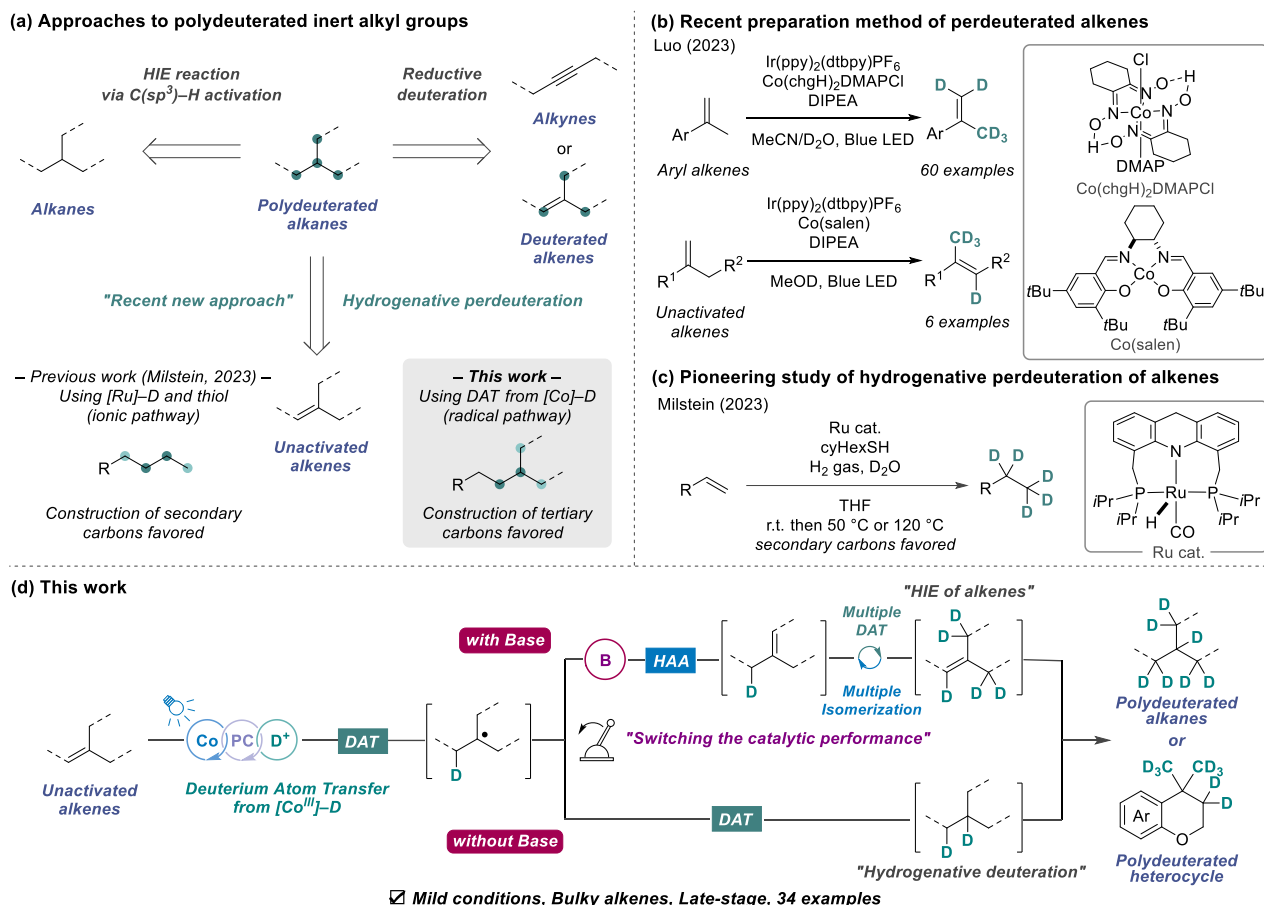


(b) Construction of polydeuterated alkyl moieties



Scheme 1. Polydeuterated alkyl moieties and their synthetic methods.

As one of the pioneering catalytic methods for constructing perdeuterated alkyl groups, Sajiki reported HIE reactions of



Scheme 2. Approaches to polydeuterated inert alkyl groups and recent methods of multiple deuteration of alkenes.

simple alkanes using heterogeneous transition metal catalysts (Scheme 2a);^[15] these reaction conditions, however, are comparatively harsh for activating inert C(sp³)-H bonds. Moreover, under such harsh conditions, C(sp²)-H bonds are also activated, making chemoselective deuterium incorporation difficult. Another approach to accessing polydeuterated alkyl groups is reductive deuteration of alkynes^[16] or perdeuterated alkenes (Scheme 2a). The construction of polydeuterated alkanes with tertiary carbons is, however, impossible through the reduction of alkynes. The preparation of multiply deuterated alkenes is also challenging. Recently, Luo and co-workers reported an HIE reaction of alkenes using cobalt/photoredox dual catalysis (Scheme 2b).^[17] The reaction proceeded through H/D exchange via deprotonation of the cobalt hydride species by bases and re-deuteration. Luo's protocol was applicable to broad styrene derivatives, but the scope of unactivated alkenes investigated was still limited (six examples). Milstein and co-workers reported the groundbreaking hydrogenative perdeuteration of various styrenes and unactivated alkenes using a ruthenium pincer complex, thereby providing access to broad perdeuterated alkanes (Scheme 2c).^[18] The method is efficient, but still requires a high temperature when applied to unactivated alkenes. Moreover, the efficiency of deuterium incorporation was reduced for an alkane with a tertiary carbon, likely due to steric hindrance. Therefore, the development of a complementary synthetic method enabling access to sterically

hindered polydeuterated inert alkanes under mild conditions is highly desirable.

To address the challenge of how to access deuterium-rich tertiary alkanes, we selected a radical approach based on metal-catalyzed deuterium atom transfer (DAT) catalysis. Metal-hydride hydrogen atom transfer (HAT)-mediated hydrofunctionalization of alkenes stands out as one of the most reliable and useful transformations frequently employed for the synthesis of sp³-carbon-rich complex molecules, including natural products.^[19] The HAT reaction of alkenes is characterized by its mild conditions, high functional group tolerance, and unique stepwise mechanism. In recent years, we^[20] and others^[21] have reported cobalt-catalyzed HAT hydrogenation and hydrofunctionalization reactions based on the reductive catalytic cycle combined with photochemical and/or electrochemical conditions,^[22] representing a new approach distinct from traditional oxidative conditions for the HAT process.^[19] We also previously developed a photocatalytic DAT deuteration of electron-deficient alkenes using ascorbic acid-d₄ as an inexpensive and readily available deuterium source.^[20c] In our previous report, selective di-deuteration^[23] occurred with electron-deficient alkenes. Preliminary trials with unactivated alkenes, however, gave totally different results; *i.e.* isomerization to the terminal alkenes proceeded concurrently and deuterium-shuffled alkanes with a moderate degree of labeling were obtained.^[20c, 24] Based on the preliminary results with unactivated alkenes, we assumed that precise control of

two competing pathways, DAT/isomerization to afford deuterated alkenes via HIE and DAT/hydrogenation to afford deuterated alkanes, is required to establish efficient polydeuterated alkane synthesis from unactivated alkenes. Herein, we report the full details of our efforts toward this goal. The addition of a suitable base plays a key role in controlling two competing pathways by switching the catalytic performance of cobalt/photoredox dual catalysis (Scheme 2d). Base-assisted cobalt/photoredox dual catalysis promoted an HIE reaction of alkenes to afford deuterated alkenes via multiple DAT and hydrogen atom abstraction (HAA) processes, while the consecutive reductive deuteration of alkenes proceeded in the absence of base to afford polydeuterated alkanes.

Results and Discussion

Our previous preliminary result with model substrate **1a** under cobalt/photoredox dual catalysis^[25] is shown in entry 1, Table 1.^[20c,24] Under hydrogenative deuteration conditions

optimized for electron-deficient alkenes, *i.e.* the **Co-1** catalyst, Ru(bpy)₃Cl₂ as a photocatalyst (PC) with excess ascorbic acid-*d*₄^[26] (3.0 equiv.) in MeCN/D₂O at 25 °C, alkane **3a** was obtained in 74%. NMR analysis indicated that deuterium-shuffling occurred and more than two deuterium atoms were incorporated in **3a** (2.51D, entry 1).^[24] To increase the deuterium labeling efficiency, we assumed it necessary to accelerate the DAT/isomerization pathway, which would lead to multiple repeating DAT and HAA processes, affording deuterated alkene **1a-d_n** rather than alkane **3a**. For that purpose, we screened Brønsted bases **base-1** to **base-5** (entries 2–6). In the presence of the Brønsted bases, the hydrogenation pathway leading to alkane **3a** was efficiently suppressed (entries 2–6: **3a**, 0%–9% vs entry 1: **3a**, 74%) and alkene **1a** was recovered together with its isomer (**2a**). The H/D-exchange efficiency, however, changed drastically depending on the base used. 2,6-Lutidine (**base-2**) afforded **1a-d_n** (D^A: 65%, D^B: 61%) and **2a-d_n** (D^C: 73%, D^D: 52%) (entry 2). Although it was difficult to determine the deuterium incorporation level at the D^E position of **2a-d_n** due to

Table 1. Optimization of HIE reaction of unactivated alkenes.^[a]

(PMP = *p*-methoxyphenyl)

entry	deviation from above	1a-d_n (%) ^[b]	D ^A (%) ^[c]	D ^B (%) ^[c]	2a-d_n (%) ^[b]	D ^C (%) ^[c]	D ^D (%) ^[c]	3a (%) ^[b]
1	ascorbic acid- <i>d</i> ₄ (3.0 equiv.), without base	0	—	—	0	—	—	74 (2.51D) ^[d]
2	base-2 instead of base-1	74	65	61	23	73	52	5
3	none	69	73	76	25	82	71	9
4	base-3 instead of base-1	82	18	21	20	20	11	4
5	base-4 instead of base-1	94	—	—	<5	—	—	<5
6	base-5 instead of base-1	>95	—	—	0	—	—	0
7	acetone/D ₂ O instead of MeCN/D ₂ O	65	90	90	17	88	89	21
8	acetone/D ₂ O instead of MeCN/D ₂ O, 5 °C	63	91	89	17	89	91	16
9	without Ru(bpy) ₃ Cl ₂	>95	—	—	0	—	—	0
10	without Co-1	>95	—	—	0	—	—	0
11	without ascorbic acid- <i>d</i> ₄	>95	—	—	0	—	—	0
12	under dark	>95	—	—	0	—	—	0

Ru(bpy)₃Cl₂

Co-1 (prepared from ascorbic acid and D₂O in gram scale)

ascorbic acid-*d*₄

base-1

base-2

base-3

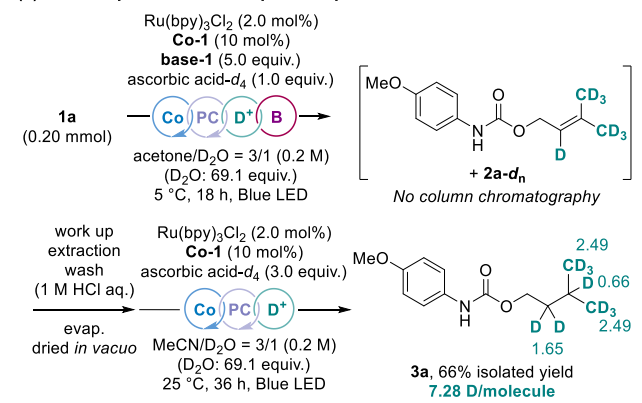
base-4

base-5

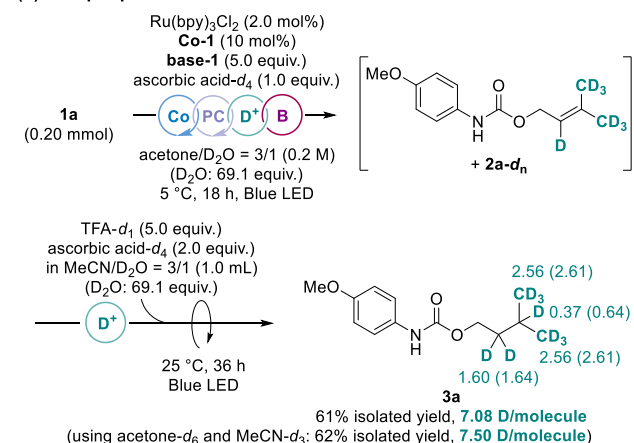
[a] The reaction was carried out with **1a** (0.10 mmol), Ru(bpy)₃Cl₂ (2.0 μmol, 2.0 mol%), **Co-1** (10 μmol, 10 mol%), **base** (0.50 mmol) and ascorbic acid-*d*₄ (0.10 mmol) in solvent (0.5 mL) under blue LED irradiation for 18 h. [b] Yields were determined from the crude reaction mixture by ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. Combined yields of **1a-d_n**, **2a-d_n**, and **3a** in Table 1 somewhat exceed 100%, but within experimental error in ¹H NMR analysis. [c] Deuterium incorporation level was determined by ¹H NMR analysis of isolated mixture of **1a-d_n**, **2a-d_n**, and **3a** after purification by preparative TLC. [d] Total number of deuteriums incorporated per molecule (see section 3-1 of Supporting Information for details).

overlapped ^1H NMR signals, overall H/D-exchange efficiency was evaluated based on those at D^{A} , D^{B} , D^{C} , and D^{D} positions. More basic 2,4,6-collidine (**base-1**) resulted in somewhat higher deuterium incorporation, affording **1a-d_n** (D^{A} : 73%, D^{B} : 76%) and **2a-d_n** (D^{C} : 82%, D^{D} : 71%) (entry 3). On the other hand, deuterium incorporation decreased when using bulky 2,6-di-*t*Bu-pyridine (**base-3**), giving **1a-d_n** (D^{A} : 18%, D^{B} : 21%) and **2a-d_n** (D^{C} : 20%, D^{D} : 11%) in entry 4. Amine base (**base-4**) and DBU (**base-5**) suppressed the catalytic activity, resulting in the recovery of alkene **1a** with only trace, if any, deuterium incorporation (entries 5, 6). Using acetone as a co-solvent for D_2O improved the H/D-exchange efficiency, giving **1a-d_n** (D^{A} : 90%, D^{B} : 90%) and **2a-d_n** (D^{C} : 88%, D^{D} : 89%) (entry 7). Finally, at 5 °C, the amount of alkene **3a** was somewhat decreased, but good deuterium incorporation efficiency was maintained (entry 8). Thus, entry 8 was selected as optimum for the HIE process. Control experiments in entries 9–12 revealed that the H/D exchange did not occur in the absence of the photocatalyst, cobalt catalyst, ascorbic acid- d_4 , or light irradiation. Thus, all reaction components and light irradiation are essential to promote HIE process.

With the optimized HIE conditions in hand, we next investigated hydrogenative DAT perdeuteration of **1a** into polydeuterated alkane **3a** (Scheme 3). After the first HIE reaction of **1a** with **base-1**, **base-1** was removed by washing the crude reaction mixture with aq. HCl. The crude mixture of **1a-d_n** and **2a-d_n** was used for the next DAT deuteration in the absence of **base-1**, yielding the desired polydeuterated alkane (**a**) General protocol of multiple DAT perdeuteration



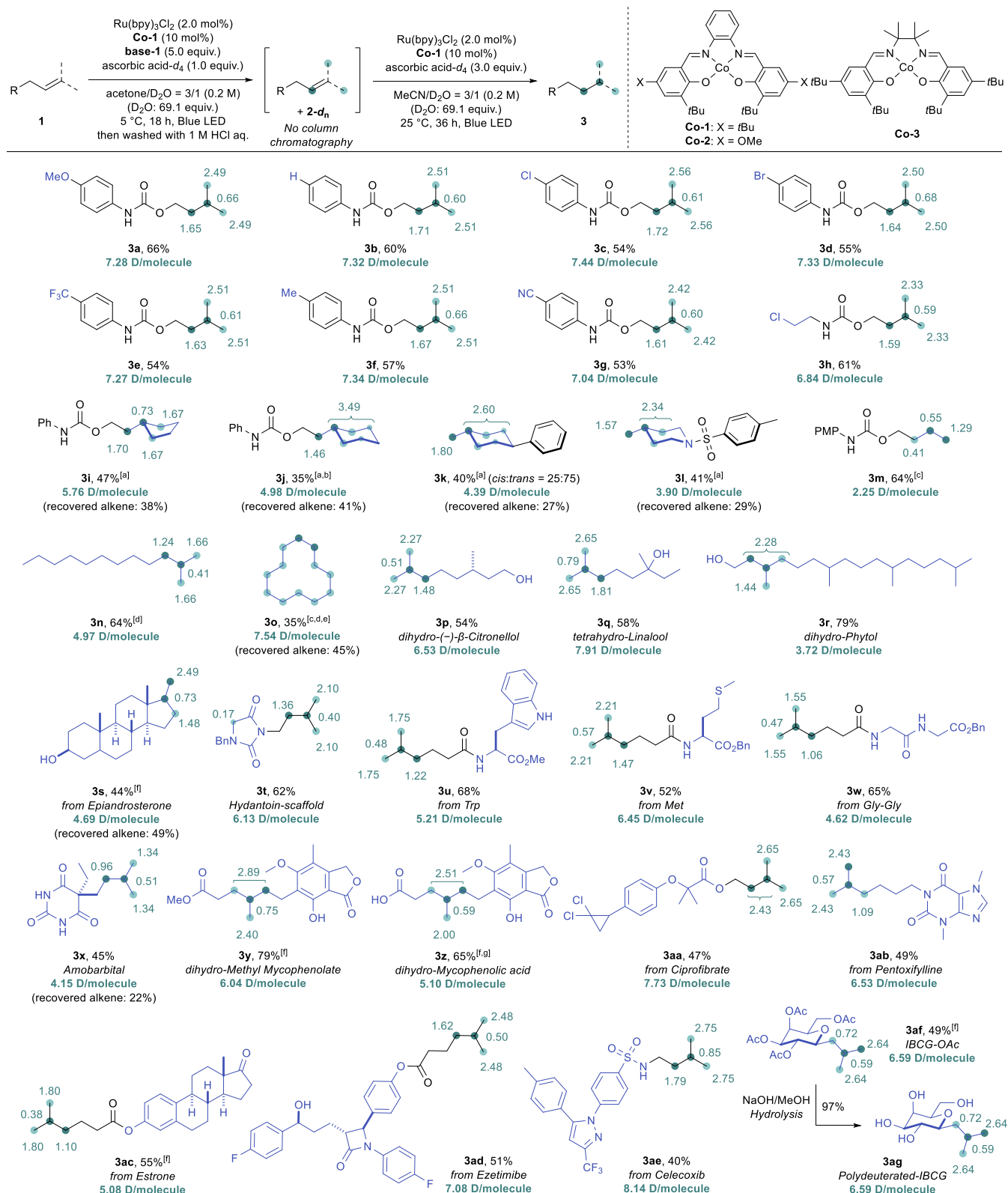
(b) One-pot procedure



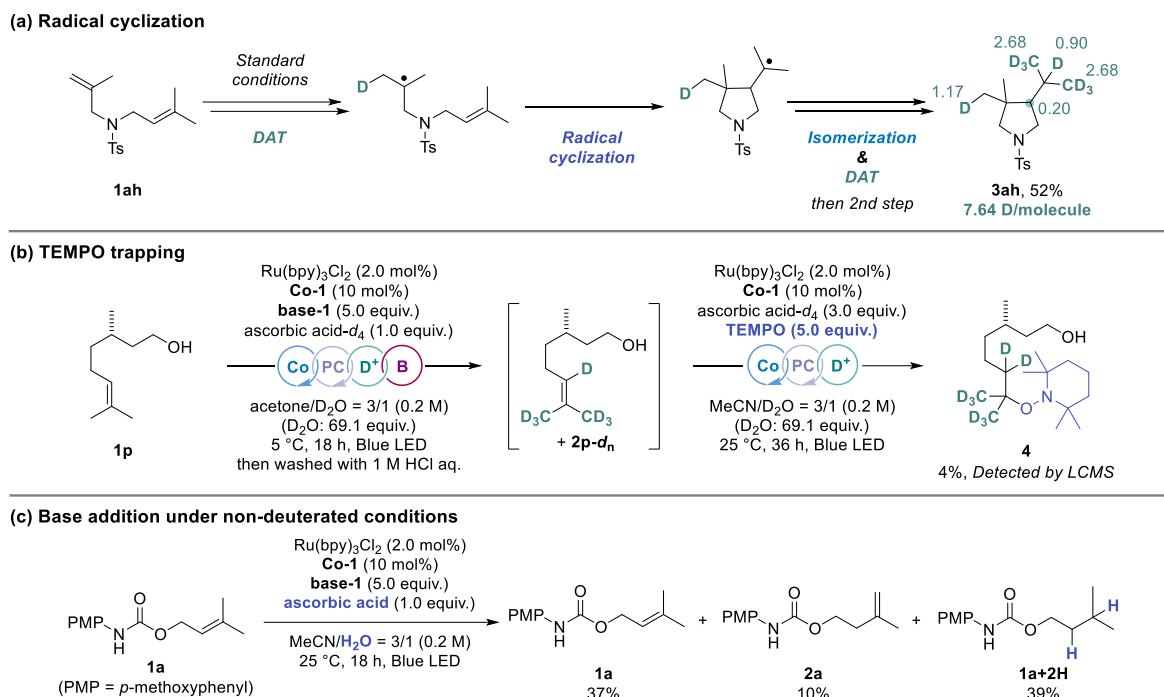
Scheme 3. Protocols of multiple deuterium atom transfer perdeuteration.

3a in 66% isolated yield with 7.28 D/molecule (Scheme 3a). In addition to consecutive DAT perdeuteration reactions of **1a**, a one-pot DAT perdeuteration without work-up/extraction was also possible. Following the first HIE reaction with **base-1**, TFA- d_1 in acetonitrile/ D_2O and additional ascorbic acid- d_4 were added directly to the reaction vial to neutralize the base. After stirring for 36 h under light irradiation, polydeuterated alkane **3a** was obtained in 61% isolated yield with 7.08 D/molecule (Scheme 3b). The number of deuterium incorporated somewhat increased to 7.50 deuteriums when all solvents were changed to deuterated solvents.

We next investigated the substrate scope of the hydrogenative perdeuteration of unactivated alkenes (Scheme 4). The hydrogenative DAT perdeuteration of trisubstituted inert alkenes containing various functional groups proceeded smoothly under mild conditions (**3a–3h**). $\text{C}(\text{sp}^2)\text{--X}$ ($\text{X} = \text{Cl}, \text{Br}$) bonds of haloarenes (**3c**, **3d**) and a $\text{C}(\text{sp}^3)\text{--Cl}$ bond of alkyl halide (**3h**) were well-tolerated under the reaction conditions and chemoselective perdeuteration of alkenes proceeded with good deuterium incorporation. Both electron-rich arenes with a methoxy or methyl group (**1a**, **1f**) and electron-deficient arenes with a trifluoromethyl or cyano group (**1e**, **1g**) were compatible and polydeuterated products **3a**, **3e–3g** were obtained with good degrees of deuteration (>7.0 D/molecule). In contrast to the previous method,^[18] sterically more hindered cyclic substrates, such as five-membered (**1i**) or six-membered cyclic alkenes (**1j**, **1k**) and a piperidine derivative (**1l**), were also applicable under the present Co/photoredox dual catalysis, and the desired polydeuterated alkanes **3i–3l** were obtained in moderate yields, along with the recovery of polydeuterated alkenes. We assume that these bulky substrates were applicable because the sterically less crowded planar cobalt salophen complex (**Co-1**) was used. Perdeuteration of an exocyclic alkene afforded *trans*-isomer (**3k**) in major, consistent with the thermodynamically controlled diastereoselectivity observed in the HAT hydrogenation.^[19, 20a] For a less sterically hindered monosubstituted terminal alkene **1m**, further optimization studies were required (see, section 3-5 of Supporting Information for details). Product **3m** was obtained with moderate degree of deuteration (2.25 D/molecule) when **Co-3** and **Co-2** were used in each step. The result with **1m** indicated that a relatively stable secondary alkyl cobalt species generated by the DAT reaction^[19g, 21r–u], along with the low reactivity of the di-substituted internal alkene produced by HAA, would reduce the efficiency of the H/D exchange process. The differences in the deuterium incorporation efficiency depending on the number of substituents on alkenes implied that our radical approach is complementary to the previously reported transition metal-catalyzed process.^[18] DAT perdeuteration of alkene **1n** without polar functional groups also proceeded, but the deuterium incorporation rate somewhat decreased (**3n**, 4.97 D/molecule). The DAT/HAA processes proceeded several times for a simple cyclic alkene **1o** without a tertiary carbon, affording the desired product **3o** with 7.54 D/molecule incorporation albeit in moderate yield. Given that trisubstituted alkenes are frequently found in terpenoids and steroids, we next investigated the perdeuteration of these analogs. (–)- β -



Scheme 4. Substrate scope of multiple deuterium atom transfer perdeuteration of unactivated alkenes using base-assisted cobalt/photoredox dual catalysis. Reaction conditions (unless otherwise noted): [1st step] **1** (0.20 mmol), $\text{Ru}(\text{bpy})_3\text{Cl}_2$ (4.0 μmol , 2.0 mol%), **Co-1** (20 μmol , 10 mol%), **base-1** (1.0 mmol), and ascorbic acid- d_4 (0.20 mmol) in acetone/ D_2O = 3:1 (1.0 mL) at 5 °C for 18 h under blue LED irradiation (supplied by Kessil). [2nd step] $\text{Ru}(\text{bpy})_3\text{Cl}_2$ (4.0 μmol , 2.0 mol%), **Co-2** (20 μmol , 10 mol%), and ascorbic acid- d_4 (0.60 mmol) in MeCN/ D_2O = 3:1 (1.0 mL) at 25 °C for 36 h under blue LED irradiation (supplied by Kessil). The yields of **3** were determined after purification by silica gel column chromatography. Deuterium incorporation level was determined by ^1H NMR analysis or ^2H NMR analysis of isolated product, and dark green circles mark the original double-bond positions. [a] 1st step was performed at 25 °C for 36 h. [b] 2nd step was performed for two cycles. [c] 1st step was performed at 25 °C for 36 h using **Co-3** and $\text{Ir}(\text{ppy})_2(\text{dtbpy})\text{PF}_6$ as a photoredox catalyst. 2nd step was performed using **Co-2** and $\text{Ir}(\text{ppy})_2(\text{dtbpy})\text{PF}_6$ as a photoredox catalyst. [d] 2nd step was performed in acetone/ D_2O = 3:1 (1.0 mL). [e] Deuterium incorporation level was estimated by HRMS(EI) analysis of isolated product. [f] 1st step was performed at 25 °C. [g] Isolated after treatment with trimethylsilyldiazomethane.



Scheme 5. Mechanistic studies. (a) detection of radical intermediate by radical cyclization; (b) by TEMPO trapping; (c) base effect under non-deuterated conditions.

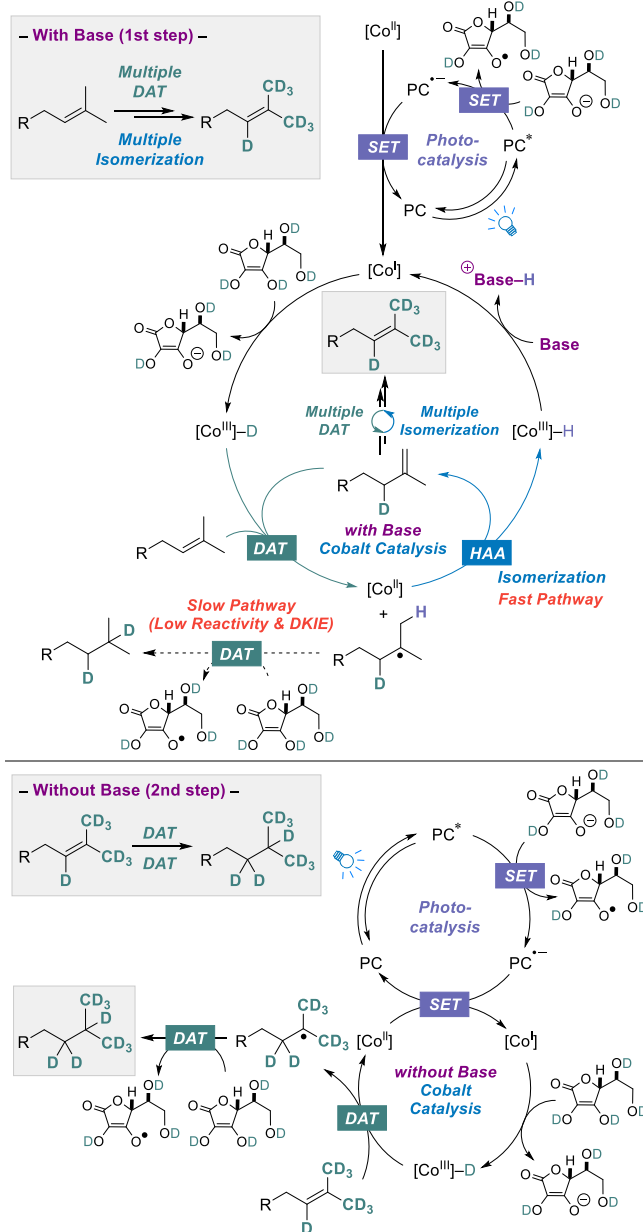
Citronellol (**1p**), dihydrolinalool (**1q**), phytol (**1r**), and epiandrosterone derivative (**1s**) were polydeuterated, affording the desired products **3p–3s** in modest yield with 3.72–7.91 D/molecule under the standard conditions. Amino acid and dipeptide derivatives **1t–1w** were also successfully perdeuterated, further demonstrating the utility of our method. A non-protected indole unit of tryptophan derivative (**3u**) and a thioether unit of methionine derivative (**3v**) were compatible. Because the reaction showed good tolerance for a variety of functional groups, we next examined late-stage perdeuteration of bioactive molecules useful as potential quantitative tracers as well as heavy drugs. The perdeuteration protocol was applicable to amobarbital with a urea skeleton (**3x**), although some polydeuterated alkenes were recovered. An immunosuppressant, mycophenolic acid methyl ester with a trisubstituted internal alkene was perdeuterated to furnish the desired product **3y** in 79% yield with 6.04 D/molecule. Additionally, mycophenolic acid with free carboxyl and phenol groups was also compatible with the present conditions and the polydeuterated product **3z** was obtained in 65% yield with 5.10 D/molecule, as determined in a methyl ester form after treatment with trimethylsilyldiazomethane. Substrates derived from ciprofibrate (**1aa**) and pentoxifylline (**1ab**) bearing *gem*-dichlorocyclopropane and xanthine groups, respectively, were also applicable. Chemoselective perdeuteration proceeded for an estrone derivative **1ac** containing a ketone group. Furthermore, ezetimibe derivative (**1ad**) and celecoxib derivative (**1ae**) gave polydeuterated products **3ad** and **3ae** with 7.08 D and 8.14 D/molecule, respectively. We finally applied our method for the synthesis of polydeuterated isobutyl- β -C-galactoside (IBCG), which is known as a gene inducer.^[27] Acetyl-protected dehydro-IBCG (**1af**) gave **3af** in

49% yield with good deuterium incorporation (6.59 D/molecule). Subsequent hydrolysis of **3af** gave polydeuterated IBCG (**3ag**) in 97% yield without loss of any deuteriums.

To gain insight into the present perdeuteration, we conducted mechanistic studies (Scheme 5). First, unconjugated diene **1ah** was treated under the standard conditions and the reductive polydeuterated cyclized product **3ah** was obtained in 52% yield with 7.64 D/molecule (Scheme 5a). We also added a radical trapping agent, TEMPO, to the second step for the reaction of **1p**, and polydeuterated TEMPO adduct **4** was observed by LCMS analysis of the reaction mixture. The yield of **4** was determined to be 4% by ¹H NMR analysis (Scheme 5b). These results confirmed the formation of alkyl radical intermediates through deuterium atom transfer from cobalt deuteride to unactivated alkenes in both the first and second steps. In Scheme 5c, **base-1** was added for the reaction with non-deuterated ascorbic acid in H₂O instead of ascorbic acid-*d*₄ in D₂O. Interestingly, the alkene/alkane ratio changed in Scheme 5c, and the alkane **1a+2H** was obtained in a similar amount with recovered alkenes **1a** and **2a**. The results indicated that DKIE at the O–D bond cleavage of ascorbic acid-*d*₄ partially contributed to enhancing the desirable H/D exchange process via multiple repeating DAT/isomerization processes over a simple hydrogenation process.

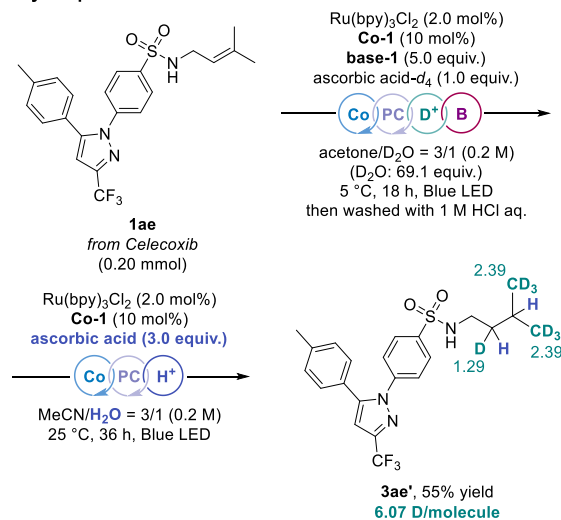
Based on previous reports and our own investigation,^[20,21] a plausible mechanism is shown in Scheme 6. The photoredox catalyst Ru(bpy)₃Cl₂ is excited by visible light and oxidizes deuterated-ascorbate to afford the corresponding radical ions of PC and the deuterium-labeled ascorbic acid radical. The reduction of cobalt(II) with the reduced PC generates cobalt(I), which is converted to cobalt(III) deuteride, [Co^{III}]-D, upon deuteriation. Deuterium atom transfer (DAT) from the

cobalt(III) deuteride to an unactivated alkene should regenerate the cobalt(II) catalyst and afford an alkyl radical, which is in equilibrium with alkyl-cobalt species. In the presence of **base-1**, the reactivity of the acidic deuteron of ascorbic acid-*d*₄ is relieved, thereby slowing the alkane formation via a second DAT. DKIE at the O–D bond cleavage of ascorbic acid-*d*₄ also contributed as discussed in Scheme 5c. Thus, the hydrogen atom abstraction (HAA)-mediated alkene isomerization is favorable instead. We assume that **base-1** would assist in the conversion of the cobalt(III) hydride [Co^{III}]-H, produced by the HAA process to [Co^{III}]-D. Deprotonation of [Co^{III}]-H by the base, followed by deuteration with ascorbic acid-*d*₄ regenerates [Co^{III}]-D. The DAT/isomerization processes are then repeated to afford perdeuterated alkenes in the first step in the presence of base. On the other hand, in the absence of the base (2nd step), DAT from [Co^{III}]-D followed by further DAT from ascorbic acid-*d*₄ to the resulting alkyl radical affords polydeuterated alkanes.

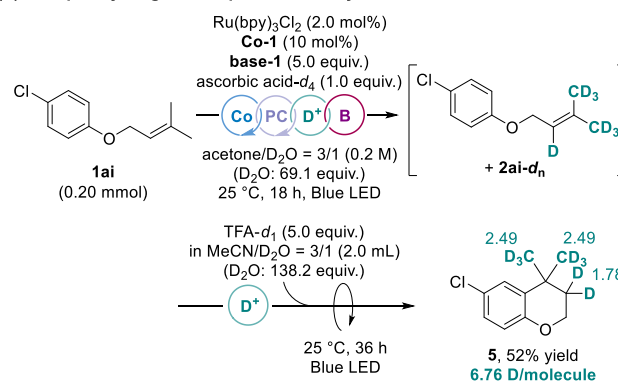


Scheme 6. Proposed mechanism.

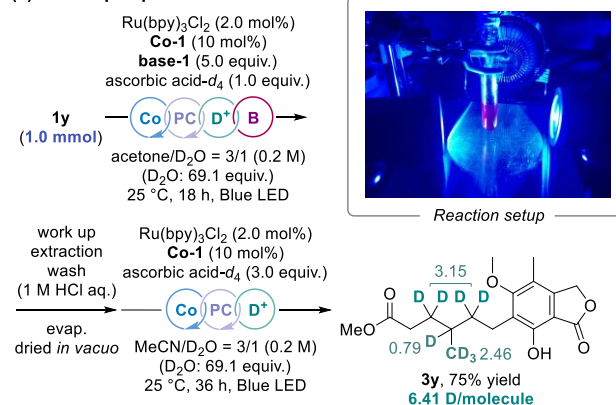
(a) Dihydro-perdeuteration



(b) One-pot hydrogenative perdeutero-arylation



(c) Scale-up experiment



Scheme 7. Synthetic applications.

With the mechanistic understanding in mind, we subsequently investigated the synthetic application of this method. We further applied the unique characteristic of this method, stepwise switching of the reaction conditions with or without base. As shown in Scheme 7a, dihydro-perdeuteration of unactivated alkene was conducted. After treatment of celecoxib derivative **1ae** under the 1st step conditions with **base-1**, the second step was conducted with ascorbic acid in H₂O instead of ascorbic acid-*d*₄ in D₂O, giving dihydro-polydeuterated alkane derived from celecoxib in 55% yield (**3ae'**). Only trace, if any, deuterium was incorporated at the

tertiary carbon in **3ae**'. The site-selective hydrogen and deuterium incorporation demonstrated in Scheme 7a is potentially useful in metabolic studies, such as investigations of metabolic switch effects.^[28] One-pot perdeutero-arylation of unactivated alkene **1ai** was also demonstrated, yielding polydeuterated heterocyclic product **5** with a quaternary carbon in 52% yield with 6.76 D/molecule (Scheme 7b). The result indicates that the base-assisted cobalt/photoredox dual catalysis has the potential to provide a wide variety of polydeuterated aliphatic compounds. Scale-up reaction was also performed as shown in Scheme 7c. The perdeuteration of methyl mycophenolate (**1y**) proceeded smoothly in a 1.0 mmol scale, giving **3y** in 75% yield with 6.41 D/molecule.

Conclusion

In conclusion, we developed a protocol for the hydrogenative perdeuteration of unactivated alkenes under base-assisted cobalt/photoredox dual catalysis. Our radical approach proceeded under mild conditions and efficiently introduced multiple deuteriums into substrates with tertiary carbons, thus complementing the previous hydrogenative perdeuteration method.^[18] The protocol showed good functional group compatibility and was applicable to terpenoids, amino acids, and pharmaceutical derivatives, suggesting its potential utility for synthesizing multiply deuterium-labeled complex compounds. Additionally, perdeutero-arylation of an alkene was demonstrated, giving polydeuterated alkane with a quaternary carbon.

Supporting Information

The authors have cited additional references within the Supporting Information.^[20a–c, 21i, 27a, 29–41]

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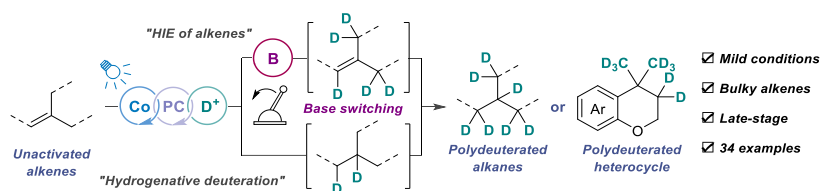
Keywords: perdeuteration • deuterium atom transfer • late-stage functionalization • cobalt • photocatalysis

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A radical approach for hydrogenative perdeuteration of unactivated alkenes under cobalt/photoredox dual catalysis was developed. The addition of a suitable base plays a key role in controlling two competing pathways by switching the catalytic performance of cobalt/photoredox catalysis. A perdeutero-arylation was also demonstrated, giving a polydeuterated heterocyclic compound with a quaternary carbon.

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