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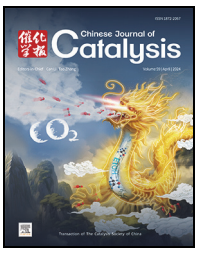

Article

Cobalt-catalyzed dehalogenative deuterations with D_2O

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ABSTRACT

The regioselective incorporation of deuterium to organic skeletons has gained ever-growing attention among scientific community. Herein, we present a robust and general protocol for site-specific deuteration through the cobalt catalyzed dehalogenative process. Using D_2O as the economical deuterium reagent, we achieved excellent substrate compatibility across a wide collection of organohalides or pseudo-halides, such as aryl, alkenyl, benzyl, allyl, or alkyl halides and propargyl acetates. Preliminary experimental evidences and related DFT calculation are also presented to support a mechanistic scenario involving a Co(I)-C(III)-Co(I) cycle. The generality and potential utilization of this moisture-insensitive catalysis have also been demonstrated by the selective deuterodehalogenation of drug-like candidates, concise synthesis of D-labeled pharmaceutical molecule, as well as the stepwise hydrogen isotope exchange of bioactive compounds.

1. Introduction

As a naturally occurring, stable and nonradioactive isotope of hydrogen, the deuterium has found widespread applications in chemistry and related fields, including the spectrometry studies, mechanistic elucidation and pharmaceutical research (Fig. 1(a)) [1–5]. Particularly, since the Austedo was approved by FDA in 2017, the deuterated compounds have attracted booming attention in discovery of drug candidates [6]. As a result, it is of great interest to develop practical and efficient protocols for highly selective deuteration of organic molecules [7,8]. In this regard, the direct hydrogen isotope exchange (HIE) process seems a theoretically straightforward procedure [9–22]. However, the poor selectivity and low functional group tolerance may obstruct the utilization of many established works, especially in those compounds rich in active C–H bonds [8,23]. Successful outputs often rely on structurally specific substrates. On the other hand, the organohalides are bench-stable and easily accessible chemicals. More importantly, the regio-selective halogenation reactions have been well exploited over the past years [24]. Hence the catalytic deuterodehalogenation of C–X bonds is becoming an appealing alternative route to construct C–D bonds, with which deuterium atoms can be incorporated at site-specific positions [25–29].

Several protocols have been reported and widely used to enable efficient dehalogenative deuteration. Different from the stoichiometric transformations employing excess strong bases, active metals, or toxic organometallic reagents [24,30,31]. The transition-metal-catalyzed deuterodehalogenation usually benefits from its good functional group tolerance and scale-up convenience (Fig. 1(b)). During the past years, reliable methods were developed to convert C(sp^2)–X bonds to C–D bonds under Pd- or Ni-catalysis [32–41]. Nevertheless, due to the difficulties arising from the sluggish oxidative addition of alkyl halides and

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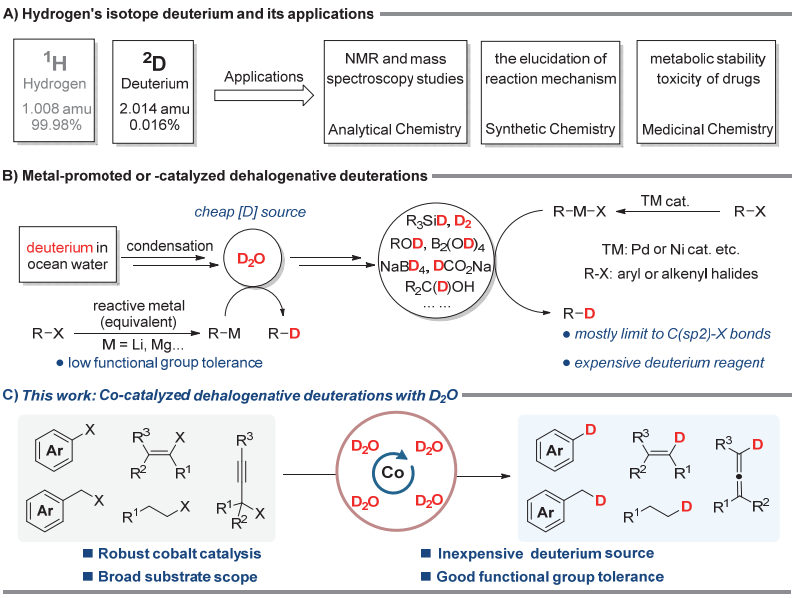


Fig. 1. Transition-metal-catalyzed deuterodehalogenation reactions. (A) Hydrogen's isotope deuterium and its applications. (B) Metal-promoted or -catalyzed dehalogenative deuterations. (C) This work: Co-catalyzed dehalogenative deuterations with D_2O.

the competing β-hydride elimination of alkyl–metal intermediates, the selective deuterodehalogenation of C(sp^3)–X bonds is still a challenging task [38]. Moreover, precedents with transition-metal catalyst were usually moisture-sensitive that obliges these reactions to use expensive deuterium reagents rather than cheaper D_2O (Fig. 1(B)) [34–37,39,42]. These long-standing limitations have compelled chemists to venture into reactions with special apparatus (photocatalysis or electrochemistry) [26–29,43–49]. Among them, efficient deuterations of a certain type of substrates (aryl or alkyl halides, respectively) could be achieved with D_2O. An improved substrate scope was achieved by Gong group which both aryl and alkyl chlorides could be applied under organophotocatalytic condition [27]. However, some special but useful substrates, such as propargyl pseudo-halides, were excluded in these existing protocols.

Cobalt is industrially and ecologically friendly because its earth-abundance and low toxicity [50,51]. Cobalt catalyst has shown good tolerance with H_2O and superior reactivity in activating either C(sp^2)–X or C(sp^3)–X bonds [52,53], which renders cobalt as an ideal catalyst in deuterodehalogenation of diversified organohalides with D_2O. As an extension of our continuous research in deuteration reactions [54], herein we report a robust and broadly applicable cobalt-catalysis for dehalogenative deuteration of organohalides (Fig. 1(C)). The foremost advantage of this strategy lies within the wide scope of substrates, such as aryl, alkenyl, benzyl, allyl, alkyl, and propargyl halides or pseudo-halides. With D_2O as an economical deuterium source, an array of halogenated candidates could be steadily converted with excellent D-incorporation in short reaction time.

2. Experimental

2.1. General

All the reagents were commercially available and were used without further purification unless otherwise stated. Solvents were treated prior to use according to the standard methods. ^1H NMR, ^2H NMR and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ on 400 MHz or 700 MHz instrument with tetramethylsilane (TMS) as internal standard. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, m = multiplet), coupling constant (Hz), and integration. Flash column chromatography was performed on commercially available silica gel (200–300 mesh). All reactions were monitored by TLC and NMR analysis.

2.2. General procedure for the synthesis of deuterated compounds (Fig. 3)

(Dppf was used as the ligand for **2a–2l**, **2r**, **8f** and **8g**. Bipyridine was used as the ligand for **2m–2q**, **4a–4e**, **6a–6e** and **8a–8e**.)

Organic halides (0.20 mmol), $CoBr_2$ (5.0 mol%), dppf (5.0 mol%)/bipyridine (5.0 mol%), manganese (0.30 mmol), ZnI_2 (0.30 mmol), D_2O (2.0 mmol) and CH_3CN (2.0 mL) were added to an oven-dried 15-mL Schlenk tube under nitrogen atmosphere. The resulting mixture was then stirred at 80 °C for 30 min. After the reaction completed, the crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate or pentane/dichloromethane) to afford the corresponding product.

2.3. General procedure for the synthesis of deuterated allenes (Fig. 4)

(Dppf was used as the ligand for **10a**, **10g–10l**. BINAP was used as the ligand for **10b–10f**, **10m–10q**.)

Proparyl acetate (0.20 mmol), $CoBr_2$ (5.0 mol%), dppf (5.0

mol%)/BINAP (5.0 mol%), manganese (0.30 mmol), ZnI_2 (0.30 mmol), D_2O (2.0 mmol) and CH_3CN (2.0 mL) were added to an oven-dried 15-mL Schlenk tube under nitrogen atmosphere. The resulting mixture was then stirred at 80 °C for 30 min. After the reaction completed, the crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate or pentane/dichloromethane) to afford the corresponding product.

2.4. General procedure for the synthesis of drug-like molecules and drugs (Fig. 5)

(Bipyridine was used as ligand for **12a**–**12f, 14**)(**12f**: 0.10 mmol scale, **12a**–**12e** and **14:** 0.20 mmol scale)

Drug-like molecule (0.10–0.20 mmol), $CoBr_2$ (5.0 mol%), bipyridine (5.0 mol%), manganese (0.30 mmol), ZnI_2 (0.30 mmol), D_2O (2.0 mmol) and CH_3CN (2.0 mL) were added to an oven-dried 15-mL Schlenk tube under nitrogen atmosphere. The resulting mixture was then stirred at 80 °C for 30 min. After the reaction completed, the crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate or pentane/dichloromethane) to afford the corresponding product.

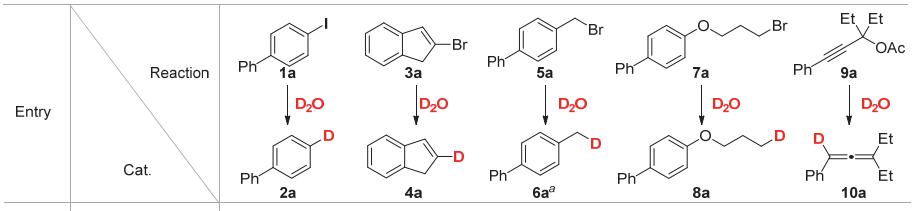
2.5. Scale-up reaction

Proparyl acetate **9a** (10.0 mmol), $CoBr_2$ (5.0 mol%), dppf (5.0 mol%), manganese (30.0 mmol), ZnI_2 (15.0 mmol), D_2O (100.0 mmol) and CH_3CN (20.0 mL) were added to an oven-dried Schlenk tube under nitrogen atmosphere. The resulting mixture was then stirred at 80 °C for 2 h. After the reaction completed, the crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate or pentane/dichloromethane) to afford the corresponding product.

Other detail experimental procedures refer to Supporting Information.

3. Results and discussion

To initiate the study, the generality of cobalt catalysis for representative organohalides—iodoarene (**1a**), alkenyl bromide (**3a**), benzyl bromide (**5a**), alkyl bromide (**7a**) and propargyl acetate (**9a**)—was examined simultaneously (Fig. 2). In 2021, Gosmini *et al.* [53] reported a Co-catalyzed dehalogenation using ^{i}PrOH as the proton source under strong acidic condition. Considering the employment of semi-equivalent of TFA will bring huge trouble for trying deuteration under such condition. Therefore, we chose ZnI_2 as the additive and D_2O as cheaper deuterium agent [55]. With $CoBr_2$ and PPh_3 as the catalyst combo, alkenyl bromide (**3a**) could be smoothly converted into dehalogenated product **4a** in 40% yield with good deuterium incorporation (88% D). Benzyl bromide **5a** and propargyl acetate **9a** also showed some reactivities under this condition. However, the reactions with iodobenzene **1a** and



Entry	Cat. \ Reaction	2a	4a	6a[a]	8a	10a
1	$CoBr_2$/PPh_3	trace	40%, 88% D	12%, >95% D	trace	26%, 93% D
2	$CoBr_2$/dppe	trace	51%, 86% D	35%, >95% D	35%, >95% D	19%, 95% D
3	$CoBr_2$/dppb	trace	60%, 92% D	8%, >95% D	8%, >95% D	20%, 92% D
4	$CoBr_2$/dppp	42%, >95% D	38%, 92% D	trace	trace	27%, 95% D
5	**$CoBr_2$/dppf**	**73%, >95% D**	**61%, 90% D**	**5%, >95% D**	**5%, 95% D**	**76%, 95% D**
6	$CoBr_2$/1,10-phen	35%, >95% D	trace	8%, >95% D	27%, >95% D	25%, 94% D
7	**$CoBr_2$/bipyridine**	**56%, >95% D**	**71%, 93% D**	**73%, >95% D**	**43%, >95% D**	**34%, 95% D**
8	$Pd_2(dba)_3$/dppf	20%, >95% D	7%, 92% D	32%, >95% D	trace	NR
9	$Pd_2(dba)_3$/bipyridine	11%, >95% D	6%, 91% D	21%, >95% D	trace	NR
10	$Ni(COD)_2$/dppf	trace	16%, 93% D	26%, >95% D	10%, >95% D	NR
11	$Ni(COD)_2$/bipyridine	trace	13%, 90% D	16%, >95% D	17%, >95% D	NR

Fig. 2. Optimization of reaction conditions. Reaction conditions: substrate (0.10 mmol), MLn (dimer 2.5 mol% or monomer 5 mol%), PPh_3 (10 mol%) or ligand (5 mol%), Mn (0.15 mmol), ZnI_2 (0.15 mmol), CH_3CN (1.0 mL), 80 °C, 30 min. Yield and deuterium incorporation were determined by ^{1}H NMR spectroscopy analysis with 1,3,5-trimethoxybenzene as the internal standard. [a]CH_3CN (0.5 mL).

alkyl bromide **7a** were completely unproductive (entry 1). By altering ligand to dppe or dppb, the alkyl bromide **7a** could become a feasible substrate (entries 2 and 3), whereas using dppp as the ligand choice could promote the formation of deuterated product **2a** in 42% yield (entry 4). Notably, under $CoBr_2$/dppf catalysis, the deuteration reactions of all the examined organohalides took place feasibly. Among them, the products **2a** and **10a** could be obtained in good yields (entry 5). To further improve the outputs of benzyl and alkyl substrates, we then investigated the performance of bidentate nitrogen ligands (entries 6 and 7). To our delight, a remarkable increasing of yields was observed for products **6a** and **8a** when reactions were conducted with bipyridine as the ligand (entry 7). Notably, replacing cobalt with palladium or nickel catalyst, the deuteration reactions all showed very limited efficiency and narrow substrate generalities with whether dppf or bipyridine as the ligand (entries 8–11). In addition, both palladium and nickel catalysis were not suitable for the conversion of propargyl acetate **9a**.

Having established the optimized reaction conditions, we then sought out to explore the generality of this robust Co catalysis (Fig. 3). The substituted iodobenzenes, no matter bearing electron-withdrawing or -donating groups at the *para*-position of phenyl ring, could successfully afford the D-labeled products in 52%–73% yields (**2a**–**2c**). By a slight adjustment of reaction condition (bipyridine as the ligand), product **2a** could also be obtained in 78% yield with phenyl bromide. Aryl bromides with benzo rings, such as coumarin,

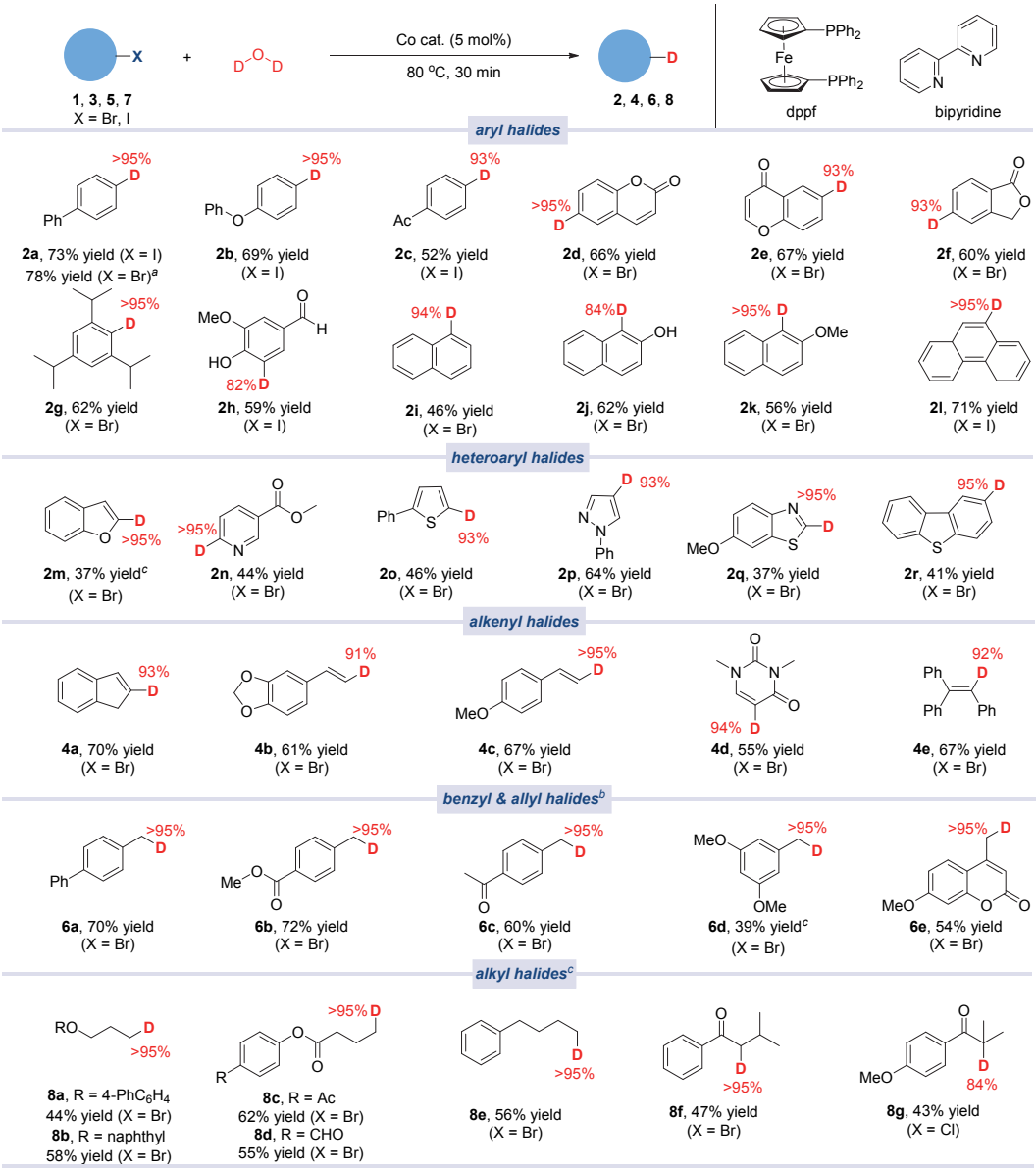


Fig. 3. Co-catalyzed deuterodehalogenation reactions with D_2O. Reaction conditions: Substrate (0.20 mmol), $CoBr_2$ (5 mol%), Ligand (5 mol%), Mn (0.30 mmol), ZnI_2 (0.30 mmol), D_2O (2.0 mmol), CH_3CN (2.0 mL), 80 °C, 30 min. Dppf was used as a ligand for aryl halides 1, bipyridine was used as a ligand for substrates 3, 5 and 7. Deuterium incorporation was determined by ^1H NMR spectroscopy analysis and isolated yields were reported for all cases. [a] DMF (1.0 mL) and bipyridine were used instead of CH_3CN and dppf. [b] CH_3CN (1.0 mL) was used as solvent for the synthesis of 6. [c] Extend the reaction time to 12 h.

chromone or phthalide-derived substrates, were all suitable candidates for current deuteration reactions (**2d**–**2f**). It was noteworthy that the sterically hindered substrate also steadily furnished the deuterated product **2g** in desirable yield without any loss of deuterium incorporation. Delightfully, synthetically useful but sensitive groups (–OH, –CHO), which were fragile under radical or basic process, could all remain intact (**2h**,**2j**). Replacing phenyl ring with naphthyl or phenanthryl group, the substrates were compatible for this conversion and gave the products **2i**–**2l** in 46%–71% yields. Moreover, the current cobalt catalysis could be applied to heteroaryl halides as well. The reactions with O-, N-, or S-containing arenes all proceeded smoothly with acceptable yields and high level of deuterium incorporations (**2m**–**2r**). Similarly, alkenyl bromides with internal or terminal C(sp^2)–Br bonds went through current reactions feasibly, giving the deuterated alkenes in satisfactory yields (**4a**–**4e**). Of particular importance is the trisubstituted alkenyl bromide, which could be also tolerated under current protocol (**4e**). For benzyl or allyl halides, the developed Co-catalysis also exhibited good tolerance, the deuterium atoms could be installed precisely at the benzylic or allylic positions (**6a**–**6e**). Remarkably, the reactions with inactivated alkyl bromides were productive and generated the corresponding products in decent yields. No competing β-hydride elimination was observed during these transformations, highlighting the unique applicability of this Co-catalysis. To our delight, secondary alkyl bromide and tertiary alkyl chloride were also reacted, delivering products **8f**, **8g** in 47% and 43% yields.

Allenes constitute an important class of bioactive compounds and usually serve as versatile building blocks in organic synthesis. The regio-specific deuteration of allenes plays an important role for the rapid assembly of target molecules and related mechanism investigation [56,57]. Therefore, we then shifted our efforts to the synthesis of D-labeled allenes (Fig. 4). Pleasingly, subjecting propargyl acetates to current Co-catalysis, the reactions afforded allene products with excellent regioselectivities and good D-incorporations. Substrates with the phenyl groups bearing electron-donating or -withdrawing substituents, regarding of their positions, were all applicable to give the terminal products in 21%–88% yields (**10a**–**10k**). Instead of the methyl group, the propargylic substituents could also be the benzyl (**10g**–**10k**), 4-thiopentamethylene (**10l**) and butyl (**10m**) groups. Trialkyl-substituted propargylic acetates have been examined as well. These substrates proceeded through the deuteration reactions successfully, albeit in somewhat decreased yields (**10n**–**10o**). No detectable side-product was found during these transformations. In addition to phenyl or alkyl groups, propargyl acetates having alkenyl and heterocyclic substituents were also compatible, resulting in 61% and 46% yields of D-labeled products respectively (**10p** and **10q**). Notably, the reaction with **9a** still worked well on a scale-up reaction and **10a** was delivered in 1.02 g with 59% yield.

To demonstrate the generality and potential utilization of this method in drug discovery, the selective deuteration of drug-like molecules containing carbon-halide bonds was subsequently performed. As depicted in Fig. 5, Andrist-derived compounds, no matter the hydroxy group was protected or not, all steadily went through the cleavage of C–I bonds, giving the

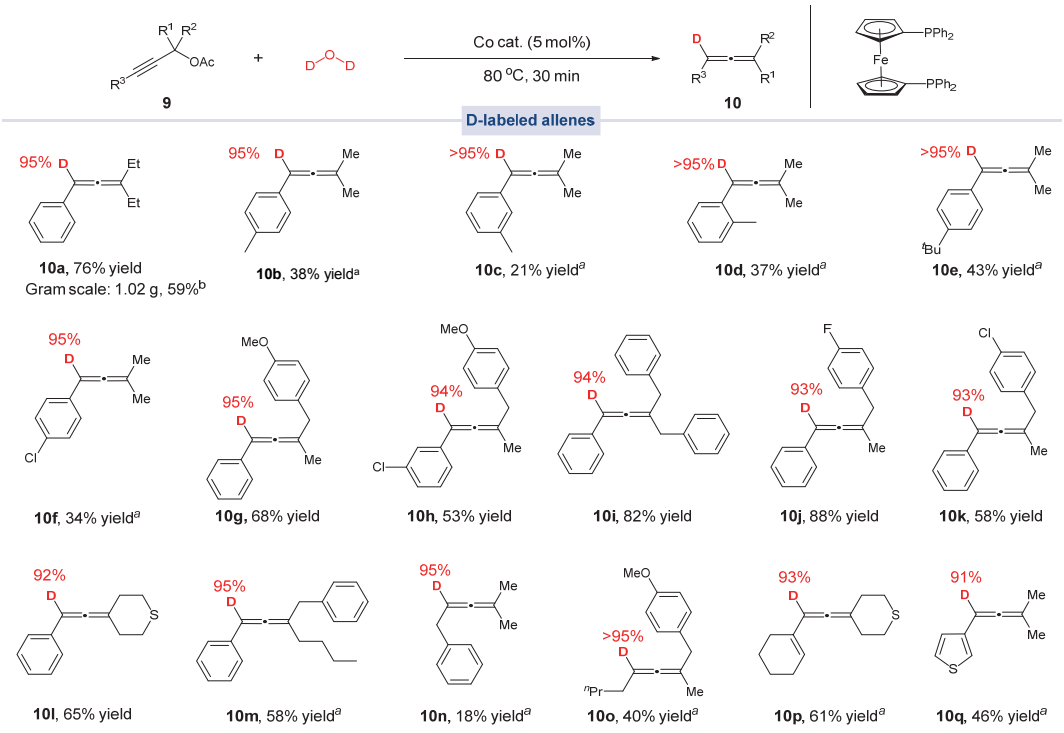


Fig. 4. Substrate scope of propargyl acetates. Reaction conditions: Substrate (0.20 mmol), $CoBr_2$ (5 mol%), dppf (5 mol%), Mn (0.30 mmol), ZnI_2 (0.30 mmol), D_2O (2.0 mmol), CH_3CN (2.0 mL), 80 °C, 30 min. Deuterium incorporation was determined by ^1H NMR spectroscopy analysis and isolated yields were reported for all cases. See the Supporting Information for full experimental details. [a] BINAP was used instead of dppf. [b]10 mmol scale, 2 h.

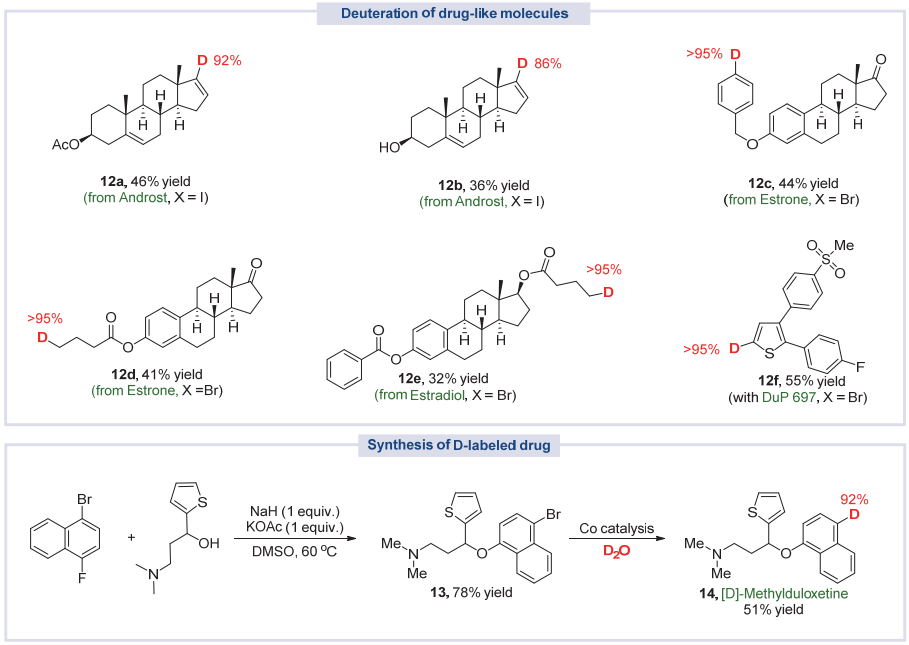


Fig. 5. Selective deuteration of drug-like molecules. Deuterium incorporation was determined by ^{1}H NMR spectroscopy analysis and isolated yields were reported for all cases. See the Supporting Information for full experimental details.

D-labeled products **12a** and **12b** in decent yields. The estrone-derived aryl bromide also complied with this deuterodehalogenation to afford the corresponding product **12c** in 44% yield. Apart from the C(sp^2)–X bonds, the bioactive molecules bearing C(sp^3)–X bonds were also accommodated, without any decrease of deuterated ratios (**12d** and **12e**). DuP-697, a thiophene ring having two vicinal phenyl substituents, exhibits multiple biological activities, such as antiproliferative, antiangiogenic and apoptotic effects [58]. Delightfully, such compound was also a feasible candidate in this dehalogenative reaction, leading to the desirable product **12f** in 55% yield. Duloxetine is a common antidepressant known as an inhibitor of serotonin reuptake (5-hydroxytryptamine; 5-HT) [59]. Through current Co-catalyzed dehalogenative deuteration, the deuterated methylduloxetine **14** could be concisely prepared with compound **13**, a brominated precursor that was easily synthesized via a simple nucleophilic substitution.

Hydrogen isotope exchange (HIE) of existing pharmaceutical molecules is an intriguing approach for the exploitation of potential drugs. However, the direct C–H deuteration often suffers from some undesired deuterium scrambling. Encouraged by the endeavors in regioselective C–H halogenation reactions [60–62], we imagined that a stepwise halogenation-deuterodehalogenation may be a site-specific protocol for controllable HIE process. With this vision in mind, a series of commercially available bioactive compounds was tested. As shown in Fig. 6, a bromination of tocopherol (**15a**) could be conducted easily in the presence of HBr with a good regioselective control. The naked ortho-hydroxy group did not trouble the following Co-catalyzed deuteration reaction (**16a**). Similar operations could also be applied successfully in the precise hydrogen isotope exchange of naproxen (**15b**) and xanthotoxin (**15c**). The reactive C–H bonds in the electron-rich furan ring remained untouched during this process (**15c**). For candidates bearing fragile C–Cl bonds, an iodination reaction could effectively avoid the undesired dechlorination side reaction (**16d** and **16e**). Notably, the reaction with nabumetone (**15f**) gave no excess deuteration over the activated methylene units adjacent to carbonyl group, highlighting the good utility of this stepwise hydrogen isotope exchange.

Comparing with the Co(II)/Zn catalytic system in which the reduction of Co(II) with Zn generally affords Co(I) species [63–65], the oxidation state of Co(II) precatalyst after reduction by Mn powder is comparably more complex. In 2020, Gosmini *et al.* [66] demonstrated that the reaction of Co(Bibpy)$_2$Br$_2$ and Mn in DMF could deliver both Co(I) and Co(0) complexes (Fig. 7(a)). To probe the real role of cobalt catalyst enrolled in current dehalogenated reactions, a series of mechanistic experiments were performed. Pleasingly, with a dose of commercially available (PPh$_3$)$_3$Co$^{\text{I}}$Cl, the reactions with **1a** or **7e** could successfully afford deuterated products in 54% and 24% yield, respectively (Fig. 7(b)). In contrast, the Co(0) precursor prepared from the reduction of (dppf)CoCl$_2$ with *p*-tolMgBr [67] failed to promote the deuterodehalogenation of **1a** and **7e** (Fig. 7(c)). Although the Co(I) species could undergo disproportionation to form cobalt(0) along with Co(II) [68], the existing solvent acetonitrile and ligand bipyridine may stabilize the formed Co(I) complex [69]. We could not exclude the possibility of the disproportionation of Co(I) complex, but such process seems prone to the off-cycle pathway based experimental studies.

Moreover, to evaluate the possible existence of radical intermediates, radical scavengers were subjected to the reactions with **1a** and **5a** respectively (Fig. 7(d)). It seems to suggest that no free organic radicals are present during the reaction, as in the presence of BHT (butylated hydroxytoluene) or 1,1-diphenylethylene the reactions still provided **2a** in

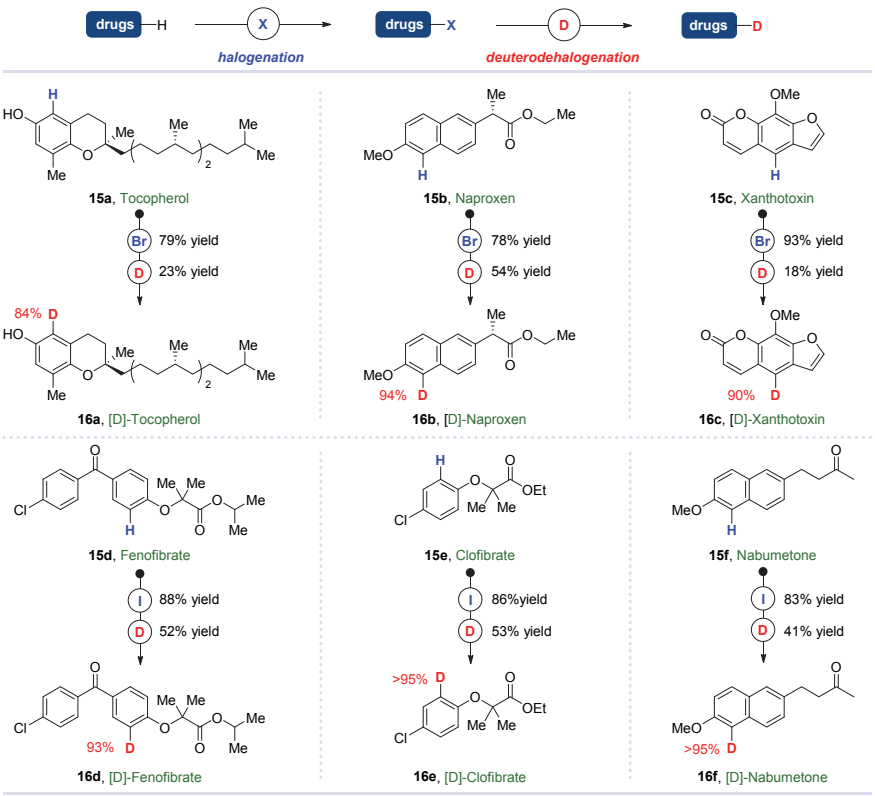


Fig. 6. Stepwise hydrogen isotope exchange for drug molecules. Deuterium incorporation was determined by ^{1}H NMR spectroscopy analysis and isolated yields are reported for all cases. See the Supporting Information for full experimental details.

64%–48% yields and **6a** in 34%–69% yields. We also did not observe the formation of any adducts from the BHT and 1,1-diphenylethylene in these transformations. The addition of TEMPO hindered the dehalogenated reactions, which probably resulted from be a consequence of catalyst deactivation. These above observations indicate that this deuterodehalogenation is likely to be launched by the Co(I) species. Therefore, a plausible reaction mechanism is proposed based on a Co(I)-C(III)-Co(I) cycle (Fig. 7(e)). Firstly, the reduction of Co(II) species with Mn and ZnI_2 gives the active Co(I) species **A**. The presence of ZnI_2 may facilitate the stabilization of generated Co(I) species through the formation of a bimetallic Co-Zn complex [55,70]. Then, an oxidation addition of **A** with organohalide generates the Co(III) intermediate **B**. Following a coordination with a deuterium oxide, the intermediate **C** yields the deuterated products via a four-centered transient state. Finally, Co(III) species was reduced to regenerate Co(I) species **A** by Mn.

To further examine the validity of proposed mechanism, a density functional theory (DFT) calculation of Co(I)-C(III)-Co(I) cycle was performed. As shown in Fig. 7(f), the oxidative addition step is predicted to have a much lower free energy cost of (7.2 kcal/mol, **TS1**). The coordination with a deuterium oxide can significantly improve the stability of Co(III). Notably, the rate determining step for the reaction may be the transfer of deuterium from the deuterium oxide to the aryl group, bearing an energy barrier of 23.8 kcal/mol (**TS2**). This result also indicates that the calculated process is very feasible under room temperature. The elevated temperature needed for the reaction may due to harsh condition demanding step of the reduction of the corresponding Co(III) species to Co(I) species. Corresponding calculation data are publicly available on Figshare at http://dx.doi.org/10.6084/m9.figshare.24587406.

4. Conclusions

In conclusion, a general and moisture-insensitive cobalt catalysis was established for the site-specific deuterodehalogenation reactions. With the cheap D_2O as the deuterium source, various types of organohalides or pseudo-halides, such as aryl, alkenyl, benzyl, allyl, or alkyl halides and propargyl acetates, all proceeded through the cleavage of C–X bonds efficiently, enabling the D-labeled products produced in excellent deuterated ratios. According to preliminary investigation of mechanistic experiments and related DFT calculation, we proposed a mechanism involving on a Co(I)-C(III)-Co(I) cycle. Encouraged by the broad substrate scope, this robust protocol was successfully applied in the selective deuterodehalogenation of drug-like candidates. A facile synthesis of D-labeled pharmaceutical molecule and the stepwise hydrogen isotope exchange of bioactive compounds were also developed to showcase the potential utilization, which would be of great interest to the chemists in both academic and industrial areas.

Acknowledgments

Author contributions: Q.-A. C. conceived and supervised the project. Q.-A. C., B.-Z. C., D.-W. J. and X.-P. H. designed the experiments. B.-Z. C., B.-C. Z., X.-Y. W., and H. L. performed the

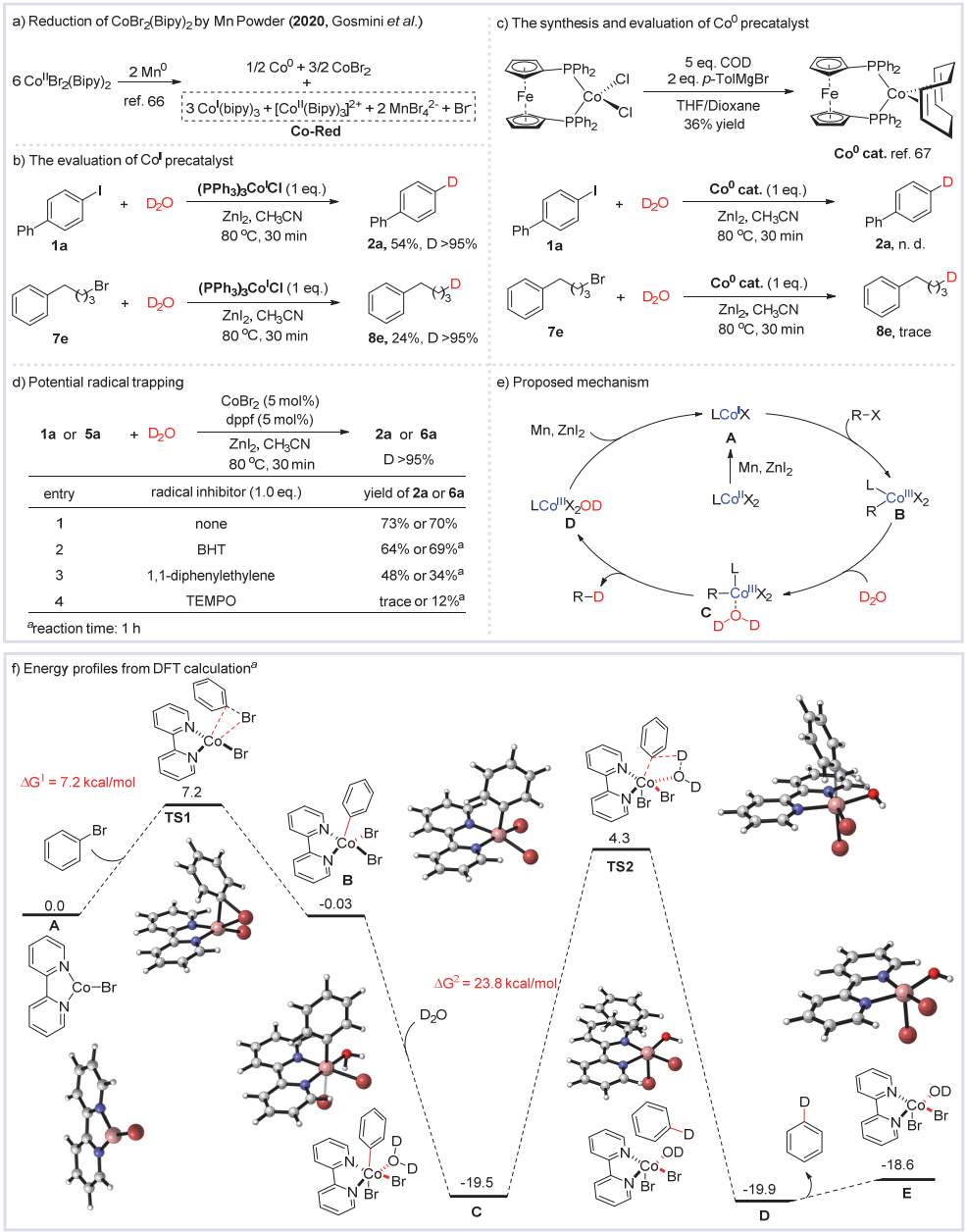


Fig. 7. Mechanistic studies and proposed mechanism. [a] DFT calculations were performed at the M06-L/6-311++G(2df,2p)-SDD(Co)/SMD(Acetonitrile)//M06-L/6-31G(d)-SDD(Co) level of theory.

experiments and analyzed the data. All authors discussed the results and commented on the manuscript.

Competing interests

Authors declare that they have no competing interests.

Electronic supporting information

Data relating to the characterization data of materials and products, general methods, experimental procedures, mass spectrometry, and NMR spectra in the Supplementary Information are available in the online version of this article.

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Graphical Abstract

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Cobalt-catalyzed dehalogenative deuterations with D_2O

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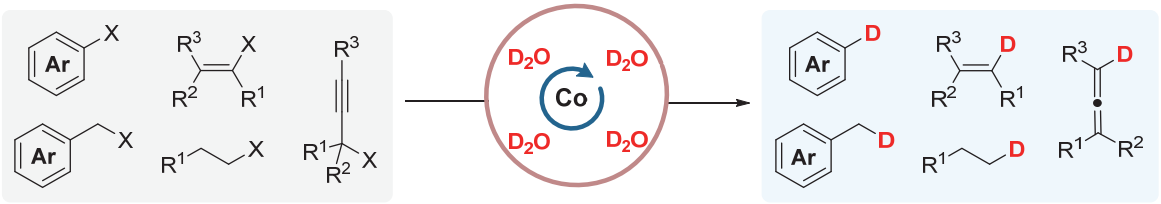

■ Robust cobalt catalysis ■ Inexpensive deuterium source ■ Broad substrate scope

A robust and general cobalt catalysis for site-specific deuteration through dehalogenative process has been developed. Using D_2O as the economical deuterium reagent, this protocol exhibits excellent substrate compatibility across a wide collection of organohalides or pseudo-halides.

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以重水为氘源的钴催化脱卤氘代反应

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摘要: 自2017年氘代丁苯那嗪获得美国食品药品监督管理局批准以来, 氘代化合物在药物开发领域的潜力受到越来越多的重视. 开发高效实用的有机分子选择性氘化方法成为有机和药物化学家的研究热点. 有机卤化物是性质稳定且来源广泛的化学品, 其脱卤氘代反应已经发展成为构建氘代化合物的有效策略. 然而, 已报道的制备方法普遍存在氘代试剂昂贵、底物适用范围较窄或需要使用特殊的反应设备(光催化或电化学)等诸多问题. 因此, 开发简单普适的廉价金属催化体系, 实现以廉价重水为氘源的脱卤氘代反应, 具有重要的研究意义.

相较于钯、铑等贵金属, 储量丰富且毒性较低的钴金属催化剂对水分敏感度较低, 且对C(sp^2)–X和C(sp^3)–X键活化都表现出较好的反应活性. 基于此, 本文开发了制备简单、普适性较好的钴催化体系, 实现了位点选择性氘代化合物的构建. 反应以锰金属为还原剂, 重水为氘源, 对各种类有机卤化物或类卤化合物, 如芳基、烯基、苄基、烯丙基或烷基卤化物, 均获得较好的收率和氘代率. 值得注意的是, 对于炔丙基乙酸酯类化合物, 该催化体系也展现出较好的适用性, 可以专一的选择性得到氘代联烯类化合物. 在此基础上, 成功将该方法应用于一系列药物类似物的选择性脱卤氘代. 利用简单的C–O偶联和脱溴氘代反应, 即可实现氘代的*N*-甲基度洛西汀的合成. 鉴于药物分子直接进行氢-氘同位素交换时位点选择性控制的挑战, 本文发展了卤代-氘代的两步策略. 该策略成功应用于生育酚、萘普生、黄毒素、萘丁美酮等多个药物分子的位点选择性氢-氘同位素交换, 充分展现出该催化合成方法在药物开发领域的应用潜力. 为了验证反应机理, 开展了一系列对照实验. 结果表明, 反应可能是由一价钴物种催化启动的. 此外, 自由捕获和抑制实验结果表明, 反应并非通过自由基反应过程进行. 基于以上实验结果提出了一个反应机理, 它涉及Co(I)到Co(III)再回到Co(I)的催化循环. 具体来说, 首先, 一价钴络合物与底物发生氧化加成生成三价钴络合物; 随后, 三价钴物种与重水络合, 并通过还原消除的方式生成氘代化合物和一价钴物种. 最后, 为了验证这一机理, 还利用密度泛函理论进行了计算, 结果进一步证明了该机理的合理性.

综上, 本文利用钴催化体系, 以廉价重水为氘源, 实现芳基、烯基、苄基、烯丙基或烷基等卤化物, 以及炔丙基乙酸酯类类卤化合物的选择性氘代反应. 该反应表现出较好的底物适用性, 为相关氘代有机化合物的制备提供了新思路.

关键词: 钴催化; 脱卤氘代; 位点选择性氘代; 有机卤代物; 氘代药物

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