Cobalt-catalyzed dehalogenative deuterations with D₂O

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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 D₂O 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(sp²)–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...
the competing β-hydride elimination of alkyl–metal intermediates, the selective deuterodehalogenation of C(\(sp^2\))−X bonds is still a challenging task [38]. Moreover, precedents with transition-metal catalysts were usually moisture-sensitive that obliges these reactions to use expensive deuterium reagents rather than cheaper D\(_2\)O (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\(_2\)O. 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\(_2\)O 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\(_2\)O. As an extension of our continuous research in deuteration reactions [54], herein we report a robust and broadly applicable cobalt-catalysis for dehalogenative deuterations of organohalides (Fig. 1(C)). The foremost advantage of this strategy lies within the wide scope of substrates, such as aryl, allenyl, benzyl, allyl, alkyl, and propargyl halides or pseudo-halides. With D\(_2\)O 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. \(^1\)H NMR, \(^2\)H 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 (\(\delta\)), 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\(_2\)O (2.0 mmol) and CH\(_3\)CN (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.)

Propargyl acetate (0.20 mmol), CoBr\(_2\) (5.0 mol%), dppf (5.0 mol%)}
mol%)/BINAP (5.0 mol%), manganese (0.30 mmol), ZnI2 (0.30 mmol), D2O (2.0 mmol) and CH3CN (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), CoBr2 (5.0 mol%), bipyridine (5.0 mol%), manganese (0.30 mmol), ZnI2 (0.30 mmol), D2O (2.0 mmol) and CH3CN (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), CoBr2 (5.0 mol%), dppf (5.0 mol%), manganese (30.0 mmol), ZnI2 (15.0 mmol), D2O (100.0 mmol) and CH3CN (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 iPrOH 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 ZnI2 as the additive and D2O as cheaper deuterium agent [55]. With CoBr2 and PPh3 as the catalyst combo, alkenyl bromide (3a) could be smoothly converted into dehalogenated product 4a in 40% yield with good deuteration incorporation (88% D). Benzyl bromide 5a and propargyl acetate 9a also showed some reactivities under this condition. However, the reactions with iodobenzene 1a and...
alkyl bromide 7a were completely unproductive (entry 1). By altering ligand to dppe or dpph, the alkyl bromide 7a could become a feasible substrate (entries 2 and 3), whereas using dppp as the ligand could promote the formation of deuterated product 2a in 42% yield (entry 4). Notably, under CoBr2/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 increase 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.

Fig. 3. Co-catalyzed deuterodehalogenation reactions with D2O. Reaction conditions: Substrate (0.20 mmol), CoBr2 (5 mol%), Ligand (5 mol%), Mn (0.30 mmol), ZnI2 (0.30 mmol), D2O (2.0 mmol), CH3CN (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. *DMF (1.0 mL) and bipyridine were used instead of CH3CN and dppf. †CH3CN (1.0 mL) was used as solvent for the synthesis of 6. ‡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, 2i).

Replacing phenyl ring with naphthyl or phenanthryl group, the substrates were compatible for this conversion and gave the products 2j–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, allenyl bromides with internal or terminal C(sp²)–Br bonds went through current reactions feasibly, giving the deuterated alkenes in satisfactory yields (4a–4e). Of particular importance is the trisubstituted allenyl bromide, which could be also tolerated under current protocol (4e). For benzylic or allylic 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 propargyl substituents could also be the benzyl (10g–10k), 4-thiopentamethylene (10l) and butyl (10m) groups. Trialkyl-substituted propargyl 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 allylic groups, propargyl acetates having allenyl 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), CoBr₂ (5 mol%), dpf (5 mol%), Mn (0.30 mmol), ZnCl₂ (0.30 mmol), D₂O (2.0 mmol), CH₃CN (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. *BINAP was used instead of dpf. †10 mmol scale, 2 h.](image-url)
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(sp²)–X bonds, the bioactive molecules bearing C(sp³)–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 methyl duloxetine 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 deutering 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(H)/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(Bipy)₂Br₂ 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 (PPh₃)₃CoICl, 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 [dpdf]CoCl₂ 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
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)-Co(III)-Co(I) cycle (Fig. 7(e)). Firstly, the reduction of Co(II) species with Mn 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 organohalides gives 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)-Co(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 D2O as the deuterium source, various types of organohalides or pseudo-halides, such as aryl, alkynyl, 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 a Co(I)-Co(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. B.-Z. C., B.-C. Z., D.-W. J. and X.-P. H. designed the experiments. B.-Z. C., B.-C. Z., X.-Y. W., and H. L. performed the
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.

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.

References

A robust and general cobalt catalysis for site-specific deuteration through dehalogenative process has been developed. Using D₂O as the economical deuterium reagent, this protocol exhibits excellent substrate compatibility across a wide collection of organohalides or pseudo-halides.
应以锰金属为还原剂，现出较好的反应活性。反”，实现了位点选择性氘代化合物的构建。

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摘要

本文通过钴催化体系，实现以廉价重水为氘源的脱卤氘代反应，该反应表现出较好的底物适用性，且对芳基、烯基、苄基、烯丙基或烷基等卤化物，都可以实现氘代，充分展现出该催化合成方法在药物开发领域的应用潜力。

关键词：选择性氢的挑战，联和脱溴氘代反应，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。

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，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。

相关于钯、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(sp3)–X和C(sp3)–X键活化都表现出较好的反应活性。基于此，本文开发了钴基催化体系。钴基催化体系，实现了位点选择性氘烷化物的构建。反应以金属钯为还原剂，重水为氘源，对多种有机卤化物或卤类化合物，如芳基、烯基、苯基、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，相比于钯、铑等贵金属催化剂，钴基催化体系具有良好的实用性和专一性，对复杂有机卤化物的氘代改性具有重要的研究价值。本文通过钴催化体系，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。