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REVIEW

Recent Advance in Electrochemical Dehalogenative Deuteration

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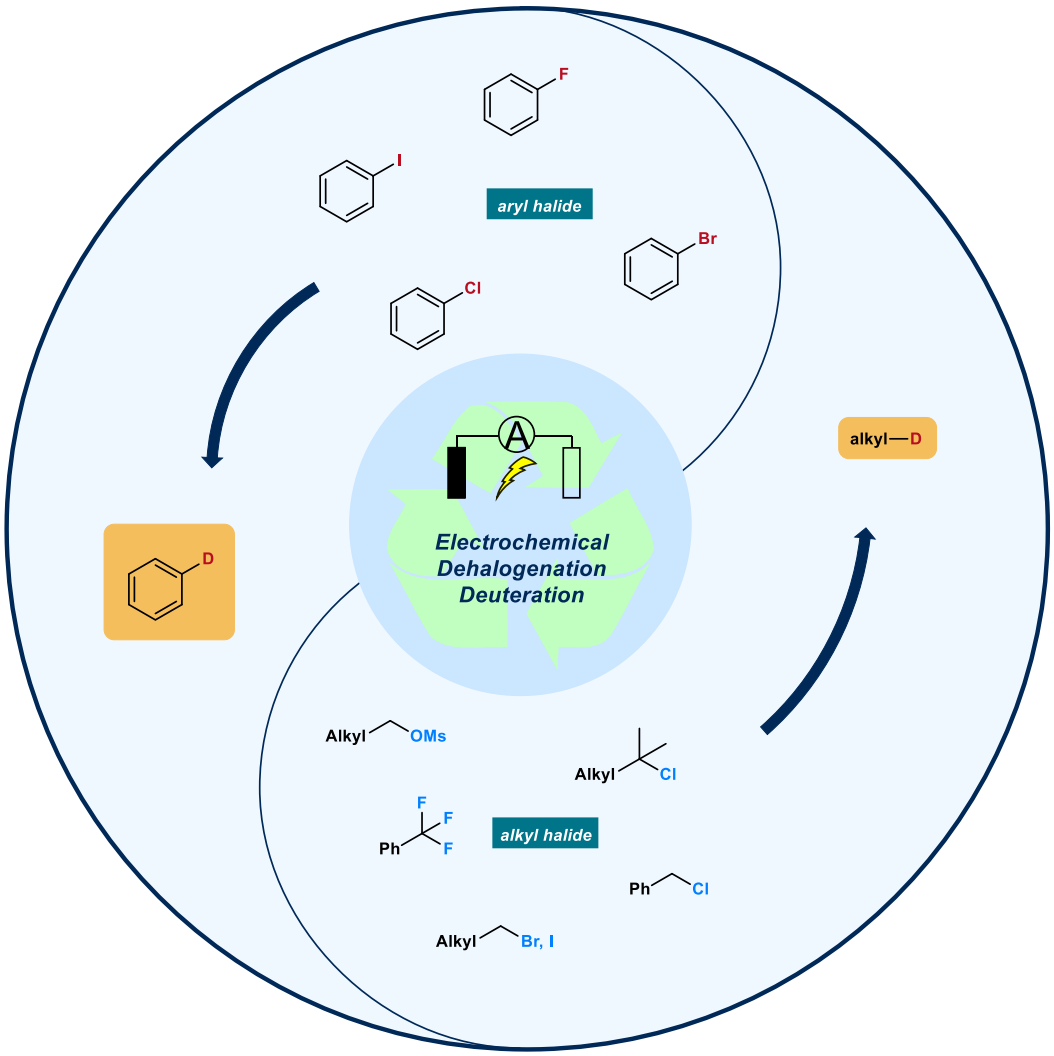

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Abstract

In recent years, the incorporation of deuterium atoms into organic compounds has emerged as a vital focus in the development of pharmaceutical molecules. This trend is driven by the increasing recognition of the significance of compounds containing deuterium atoms across various domains, including materials and biopharmaceuticals, where they have found widespread applications in mechanistic studies within the realms of chemistry and biology. Meanwhile, organic electrochemistry, as a relatively environmentally friendly catalytic mode with broad adaptability to redox reactions, has emerged as a crucial alternative to traditional halogen-deuterium exchange in the context of the reduction deuteration of halides. This approach circumvents the uses of transition metal catalysts and toxic deuterated reagents which are commonly employed in traditional methods. Notably, electrocatalytic dehalogenation with deuterium incorporation typically relies on heavy water as the deuterium source, ensuring high yields and significant deuterium incorporation. In recent years, electrochemically dehalogenative deuteration of halides has made substantial progress, providing critical support for the synthesis and development of deuterated compounds. This article offers a comprehensive overview of the latest advancements in electrochemical reductive deuteration of both aromatic and alkyl halides, categorizing the progress according to the type of halide and delving into the underlying reaction mechanisms.

Keywords: Electrochemistry; Deuteration; Halide; Deuterium oxide; Dehalogenation

1. Introduction

Deuterium, a stable isotope of hydrogen found in nature, has one more neutron than hydrogen and twice the weight of a hydrogen atom. Therefore, activation of C−D bonds requires higher activation energy than C−H bonds [1]. In recent years, a greater emphasis has been placed on incorporating deuterium into molecular scaffolds for drug development [2,3]. In 2017, the first deuterated drug deutetrabenazine, has been approved by FDA [4]. These deuterated molecules are significant because the incorporation of deuterium atoms into bioactive compounds can dramatically affect their metabolic and pharmacokinetic properties [5,6]. Importantly, deuterated labeled molecules are widely used as standards for high-resolution mass spectrometry and measurements of kinetic isotope effect (KIE) in the field of reaction mechanism investigation [7,8]. As a result, the development of robust and bio-friendly deuterated protocols is in vast demand in numerous fields.

Although direct hydrogen isotope exchange (HIE) has been regarded as the most favorable approach, it often requires the uses of precious metal catalysts and strong bases/acids to activate the resilient C−H bonds, leading to uncontrollable deuteration locations and low deuterium incorporation rates [9−14]. In contrast, dehalogenation deuteration of halides offers excellent site-selectivity and higher deuterium incorporation rates. These traditional methods of halide dehalogenation deuteration predominantly rely on the use of organometallic reagents, such as Grignard reagents, organolithium reagents, or organotin reagents [15]. Nevertheless, these rigorous reaction conditions significantly curtail their practical applicability.

Meanwhile, redox reactions with single-electron transfer (SET) via electrocatalysis have emerged as a powerful synthetic tool over the past few years [16−24]. A range of electrochemical methods for forging new chemical bonds have been well established, including C−C [25−29], C−N [21,30−33], and hydrogenation of unsaturated bonds [24,34−38]. Notably, within this repertoire, the electrochemical dehalogenation facilitating functionalization has introduced novel prospects for the deuteration of halides [26,39−42]. Recently, there have been sustained growth and significant progress in achieving efficient electrochemical dehalogenation and deuteration (Fig. 1). In this review, we have summarized the advance of electrochemical deuteration of halides, with the substrate scopes, reaction characteristics, and plausible mechanisms discussed.

2. Electrochemical deuteration of aryl halides

2.1. Direct organic electrosynthesis

Organic electro-synthesis can be classified into two types: direct organic electro-synthesis and

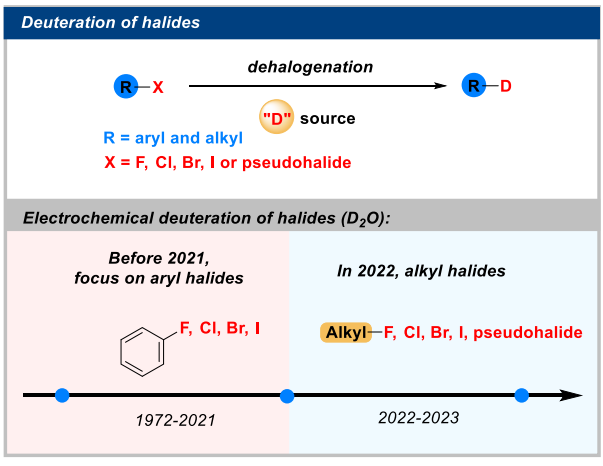

Fig. 1. Electrochemical deuteration of halides.

indirect organic electro-synthesis, based on the electrode's role in the reaction process. Direct electro-synthesis involves electrochemical reactions occurring directly on the electrode's surface. In this process, reactants gain or lose electrons on the electrode surface, forming free radical intermediates [43,44]. These intermediates then participate in homogeneous reactions, producing different products or intermediates. Due to the direct generation of reaction intermediates from substrates on the electrode surface, direct electro-synthesis is considered the most effective method for redox reactions. It is pertinent to highlight that the dehalogenation process of halides under electrochemical conditions can be systematically classified into two distinct mechanisms: concerted dissociative electron transfer (DET) process and stepwise dissociative electron transfer [45,46]. The choice between these mechanisms is contingent upon the structural and chemical attributes of the substrate. Unless otherwise specified, the dehalogenation processes discussed in this review typically follow the stepwise DET mechanism. In this mechanism, the halide initially accepts an electron to form a radical anion, and followed by the cleavage of the C−X bond to produce an aryl radical and a halide anion.

The deuteration of aryl halides in direct organic electrocatalysis can be traced back to Murray's early report in 1972 [47](Fig. 2), which focused on the electrochemical dehalogenation deuteration of electron-rich aryl compounds. This work demonstrated that aryl iodide with methoxyl as the electron donor group could undergo dehalogenation deuteration to produce the desired product under an electrocatalytic system. Ortho, meta, and para-substituted methoxy groups are all able to achieve high deuterium exchange rates upon replacement. Notably, with D_2O as the only deuterium source, and $LiClO_4$ as the electrolyte, the anode and cathode are lead sheet and graphite, respectively. In 1974, Renaud group reported the electroreduction deuteration of halogenated naphthalene under the similar conditions [48], when the solvent was changed to dioxane, and found that it was compatible with chlorine, bromine, and iodine substituted aryl. In addition, Sawaki reported the reduction of polyhalogenated aryl halides in 1990 [49], but suggested that only alkoxy-substituted halogenated hydrocarbons can produce deuteration products.

The previous work referred to above was limited in terms of the range of substrates that could be utilized. It was not until 2020 that the Lei group reported a more versatile electrocatalytic reduction of deuterium halides using a platinum sheet as the

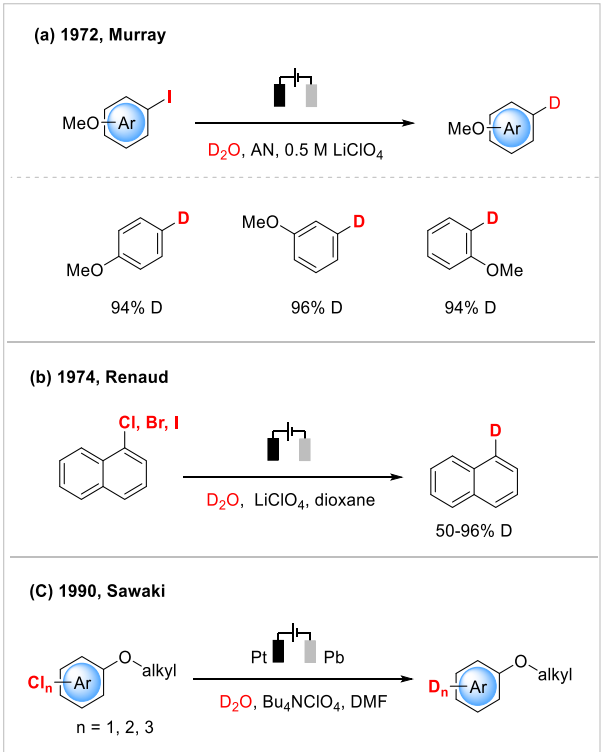

Fig. 2. Early electrochemical dehalogenation deuteration efforts.

anode, lead sheet as the cathode, and triphenyl phosphorus as the anode sacrificial reagent [50] (Fig. 3). Importantly, the reaction can efficiently reduce a wide range of halogenated aromatic compounds, including chloro-, bromo-, and iodo-substituted compounds, as well as heterocyclic compounds, while tolerating various functional groups such as alkyl, cyano, indole, etc. Moreover, for polyhalogenated aromatic rings, deuterium atoms can selectively replace halogen atoms with lower reduction potentials. Lei's group also proposed a clear reaction mechanism combining cyclic voltammetry experiments and EPR experiments, where aryl radicals and deuterium radicals are generated by the reduction of halogenated aromatic compounds and D_2O at the cathode, respectively. Deuterated aromatic compounds are then produced through radical coupling. During the electrocatalytic reduction process, bromide ions are oxidized at the anode to form bromine radicals, which are then captured by triphenylamine to form triphenylammonium bromide.

In the same year, Zhang's research group pioneered the uses of copper nanowire arrays (Cu NWAs) as the cathode material of the electrode, and nickel phosphide as the anode material to realize the highly selective deuteration of halogenated aromatic hydrocarbons [51] (Fig. 4). This method demonstrated strong functional group

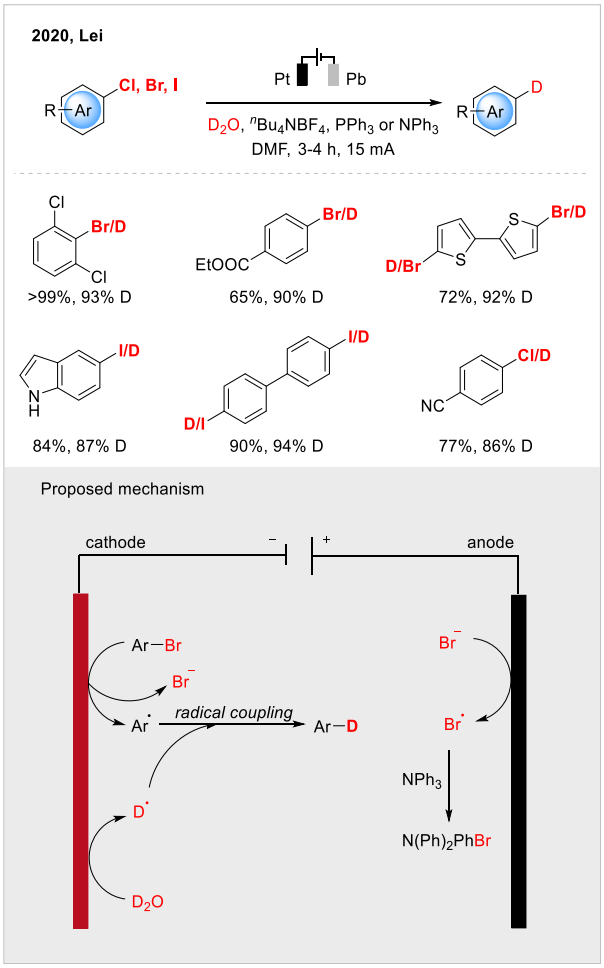

Fig. 3. Electrochemical dehalogenation deuteration of aryl halides.

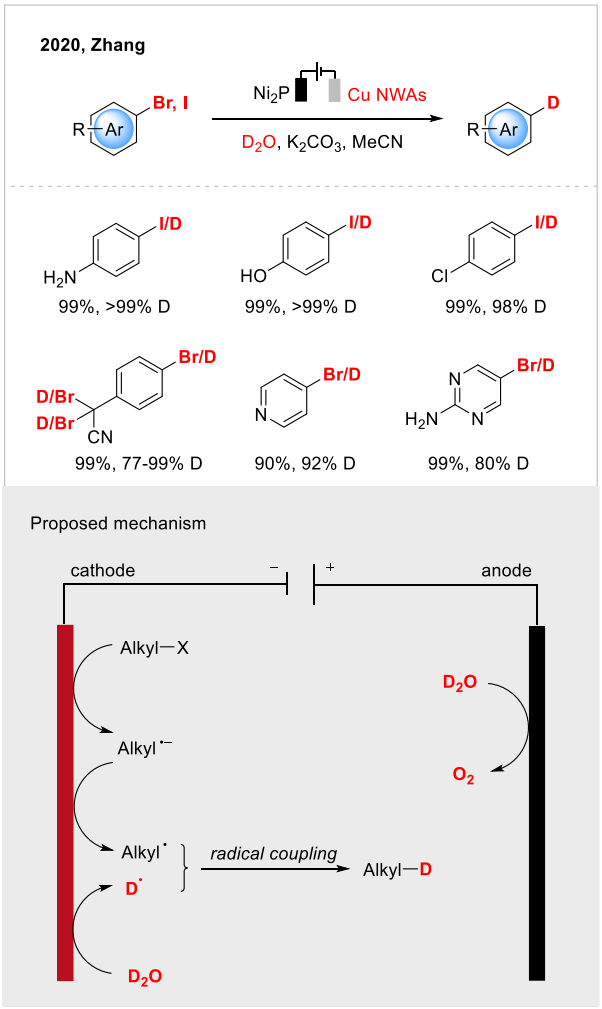

Fig. 4. Electrochemical dehalogenation deuteration with Cu NWAs as the cathode.

tolerance, hydroxyl groups, amino groups, halogen atoms, and heterocyclic halogenated hydrocarbons on the benzene ring were all compatible. Notably, benzyl bromides and allyl bromides also undergo deuteration under these reaction conditions.

2.2. *Indirect organic electrosynthesis*

Indirect organic electro-synthesis involves a substance other than the reactant transferring electrons with the electrode, known as a mediator [17,52,53]. The mediator is initially oxidized or reduced on the electrode surface, and then reacts chemically with substrate to yield the product. After the product separates, the mediator is regenerated at the anode or cathode in the electrolysis cell and participates in the next reaction step. This cycle continues until the electrolysis is complete. In the electrochemical reaction system, the mediator mainly acts as an "electron carrier" with catalytic effects. Compared with the limitations caused by the high overpotential in direct electrosynthesis, the use of a mediator in indirect electrosynthesis has been widely used to reduce the activation potential of the substrate. A lower potential can reduce energy consumption, improve reaction selectivity, and promote greater compatibility with various functional groups. It is noteworthy that, under the influence of specific electrode materials, cathodic reduction can engender hydrogen radicals, thereby initiating the cleavage of the C—X bond [54]. However, it is imperative to underscore that this reaction process remains unexplored in the studies encompassed by this review.

The aforementioned studies were achieved through direct electrochemical oxidation and reduction. In contrast, in 2013 [55] (Fig. 5), Suga reported such a novel approach to reduce halogenated aromatic hydrocarbons under electrochemical conditions that involves the use of anthraquinone as an electron transfer mediator. This method has achieved a breakthrough in the electrochemical reduction of deuteration of aryl fluoride, and obtained extremely high D-labeling level product smoothly under standard conditions.

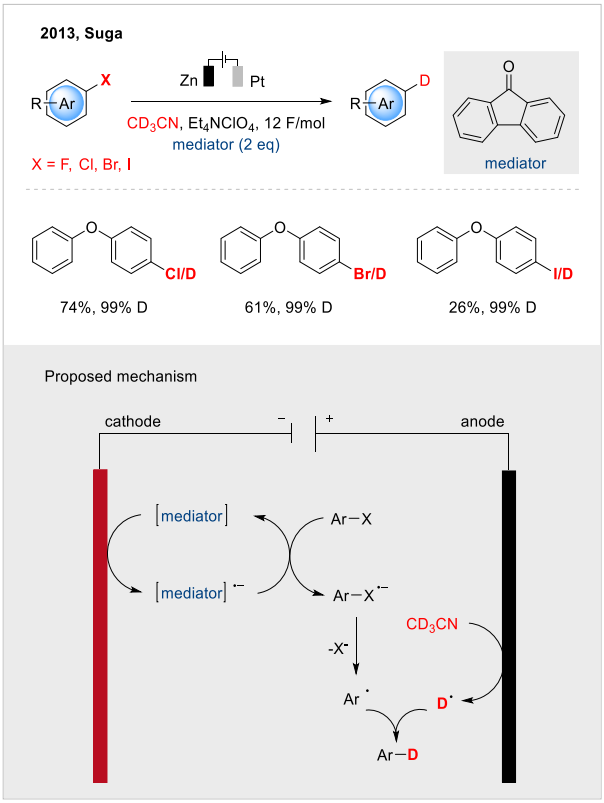

Fig. 5. Electrochemical dehalogenation deuteration promoted by organic mediator.

The difference is that the scheme uses a sacrificial anode strategy, and the expensive deuterium acetonitrile as the deuterium source reduces the application ability of the reaction.

In 2021, Su and co-workers reported a strategy for the deuteration of heavy water by utilizing a palladium-catalyzed electrochemical method [56] (Fig. 6). This approach offers a broad substrate scope and functional group tolerance, allowing the efficient deuteration of diverse organic molecules. In this study, palladium serves as the key metal catalyst and combines with halides to generate Intermediate I through a series of electrochemical processes. Meanwhile, the palladium catalyst undergoes reduction from a divalent to a zero-valent state at the cathode and participates in the reduction of D_2O to produce deuterium ions. The generated deuterium radicals then react with Intermediate I to form Intermediate II, which subsequently undergoes an elimination process to afford deuterated benzene.

3. Electrochemical deuteration of alkyl halides

In recent years, the electrochemical reduction of unactivated alkyl halides has received widespread attention [57,58]. In contrast to aryl halides, alkyl halides manifest diminished reduction potentials,

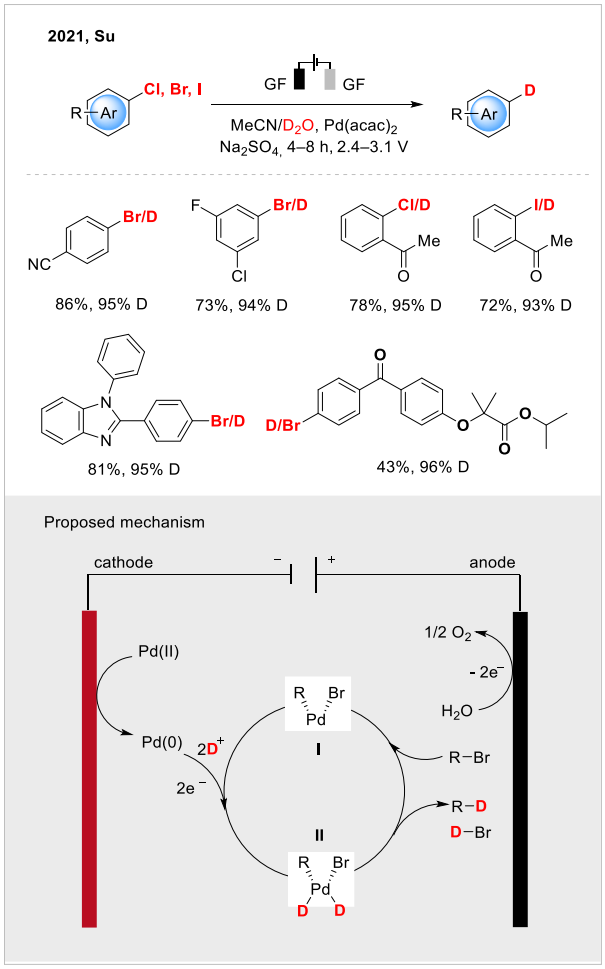

Fig. 6. Palladium-catalyzed electrochemical dehalogenation deuteration.

rendering them more susceptible to dehalogenation within electrochemical settings. Nevertheless, the regulation of the subsequent directed conversion process following dehalogenation presents a formidable challenge. This complexity arises from the facile occurrence of alkyl radicals, which readily undergo homocoupling or β-hydrogen elimination, resulting in the formation of byproducts under reducing conditions. Consequently, the achievement of selectively electrochemical deuteration for alkyl halides remains a substantial undertaking. Furthermore, with regard to the dehalogenation mechanism, while aryl halides typically adhere to a stepwise DET process, alkyl halides undergo either stepwise DET or concerted DET, contingent upon the molecular characteristics of the substrate.

3.1. Unactivated alkyl halides

Dehalogenation deuteration of alkyl halides is one of the important methods to introduce deuterium atoms into alkanes. With the rapid

development of electrochemistry in recent years, the dehalogenation deuteration of electrocatalytic alkyl halides was reported by Qiu Group in 2022 [59] (Fig. 7). The reaction takes graphite felt or carbon felt as the anode, lead sheet as the cathode, DIPEA as the anode sacrificial reagent, and D_2O as the deuterium source. Under the current condition of 30 mA, alkyl halides can be reduced smoothly to form alkyl radicals. Importantly, the reaction has strong functional group tolerance, and some complex drug molecular structures can also be well-compatible. Surprisingly, under the current of 500 mA, it only takes 15 minutes to obtain very high D-incorporation products. Some necessary mechanism experiments and cyclic voltammetry tests can conclude that this is a continuous single-electron transfer process at the cathode, and finally the deuterium-doped alkane is generated through the attack of carbon anions.

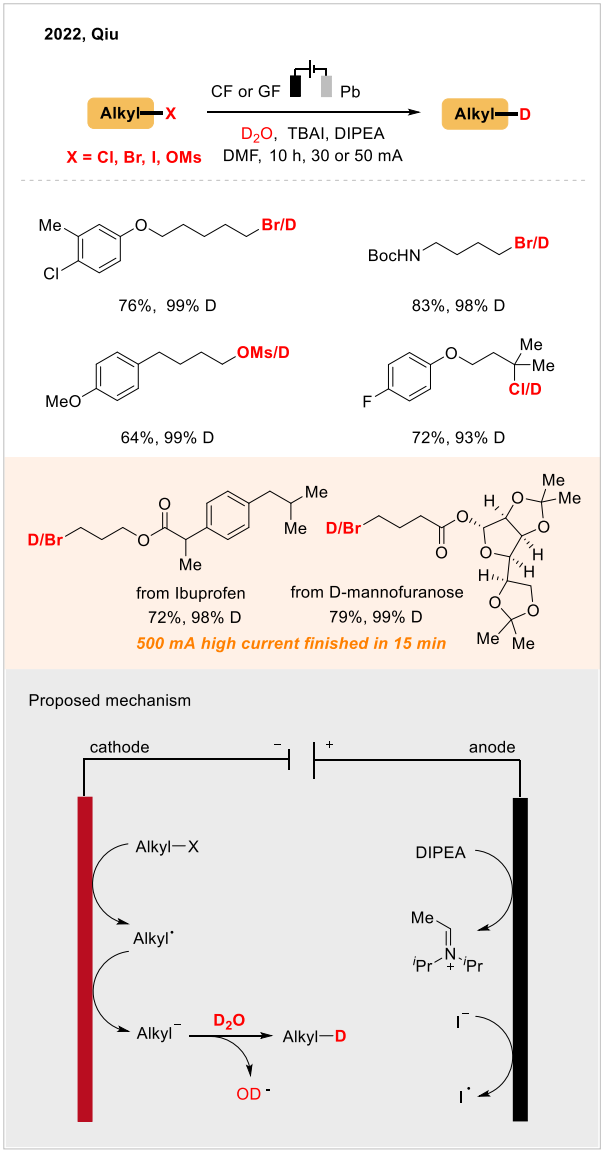

Fig. 7. Electrochemical dehalogenation deuteration of unactivated alkyl halides.

3.2. *Activated halides*

Compared to unactivated alkyl halides, halides with reactive functional groups at the α-position exhibit lower reduction potentials and higher reactivity. Therefore, for some challenging-to-reduce C−X bonds, such as C−Cl and C−F bonds, installing functional groups at their α-positions can significantly alter the reaction outcomes.

In 2023, Lin and co-workers reported on the highly selective deuteration of benzyl halides using D_2O as the deuterium source [60] (Fig. 8). To

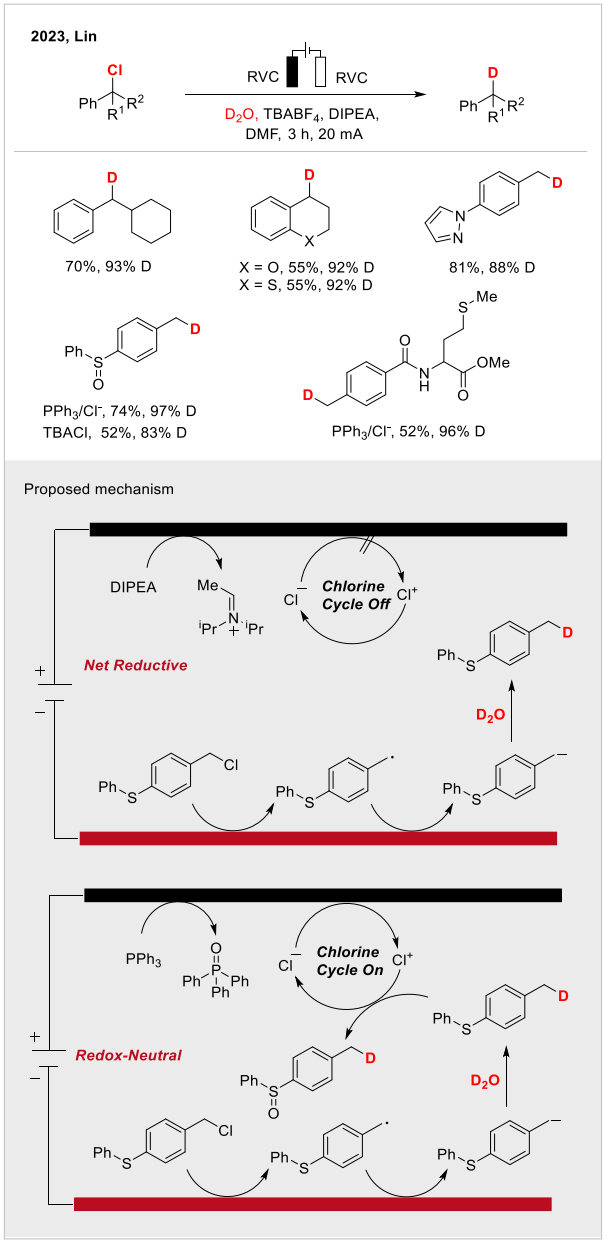

Fig. 8. Electrochemical dehalogenation deuteration of benzyl halide.

accommodate for a wider range of active functional groups, they employed two different electrochemical reduction conditions, sacrificial reductant or anodic metals. Interestingly, using triphenylphosphine and tetra-n-butylammonium chloride as sacrificial reductants at the anode could convert substrates with thioethers to sulfoxides, while using DIPEA could preserve the thioether. The success of this reaction is primarily attributed to the carbon anions produced through the two reduction processes of halides at the cathode.

While progress has been made in the electrochemical reduction deuterodehalogenation of alkyl halides, addressing the electrochemical reduction deuterodehalogenation of highly polar C—F bonds remains a formidable challenge. In order to tackle this issue, in 2022, the Xia group achieved the selective deuterodefluorination of trifluoroacetamides under electrochemical conditions, controlled by organic boron reagents (Fig. 9) [61]. It is worth noting that the chemical selectivity of this reaction is achieved by using different organic boron sources. In this electrocatalytic approach, both mono-deuterated and di-deuterated trifluoroacetamides can be obtained with moderate yields and high deuterium incorporation rates. Through mechanistic studies and Density Functional Theory (DFT) calculations, the authors propose that the key step in deuterodefluorination involves the generation of a gem-difluoroalkenyl boronate complex at the cathode. This complex then reacts with deuterium cations to produce mono-deuterated or multiply deuterated products.

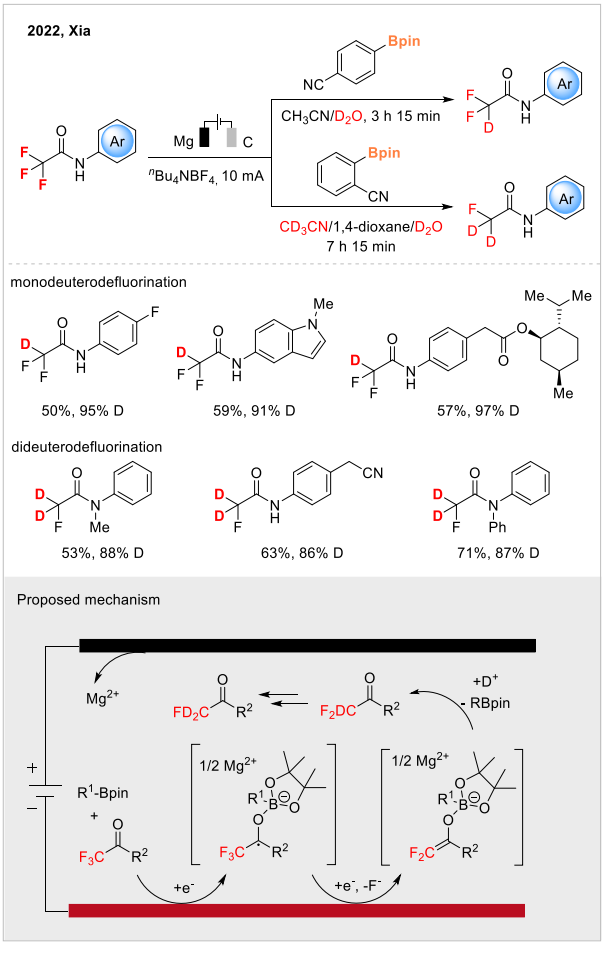

Fig. 9. Organoboron reagent-controlled selective deuterodefluorination.

The Ar—CD_3 group is widely found in medicinal compounds to enhance their pharmacokinetic performance, such as deutetrabenazine, SD-560, and AVP 786 [62—64]. Recently, the Cheng group has developed an electrochemical method for the conversion of Ar—CF_3 to Ar—CD_3 under D_2O as the sole source of deuterium [65] (Fig. 10). This method allows for the preparation of Ar—CD_3 compounds tolerant of various functional groups, including electron-rich aromatics. Mechanistic studies have demonstrated that the trifluoromethyl substrate is reduced at the cathode, liberating fluoride ions to form a difluoromethyl radical. The difluoromethyl radical subsequently undergoes reduction at the cathode to produce the intermediate Ar—CF_2D through a reaction with D_2O. Then, two successive deuterofluorination steps are employed to yield the final product.

4. Outlooks

Deuterated compounds play a crucial and indispensable role in the field of medicine,

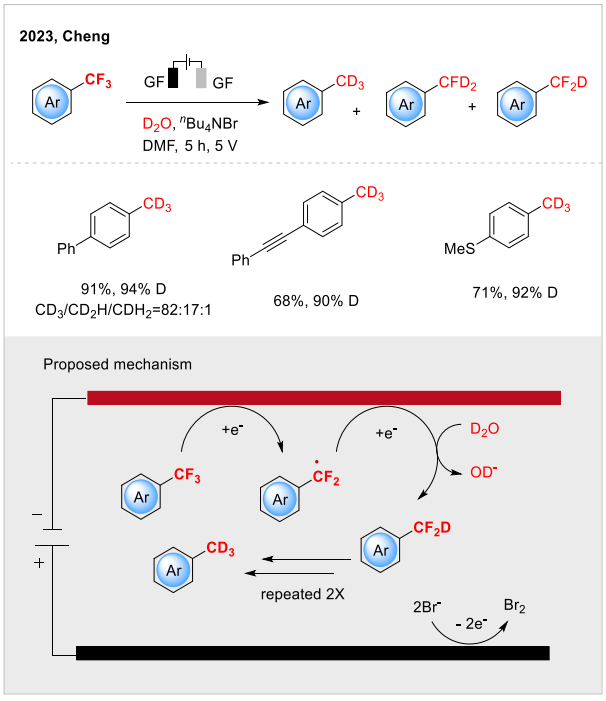

Fig. 10. Electrochemical defluorination deuteration of trifluoromethylbenzene.

especially with the continuous emergence of deuterated drugs in recent years. This phenomenon has notably advanced the methodologies employed for effecting deuteration in organic compounds. Organic electro-synthesis, as a green, efficient, and highly selective synthetic approach, provides a vital method for the deuteration of organic compounds. This review primarily focuses on the electrochemical dehalogenative deuteration of halides, but there are still many electrochemical deuteration methods worthy of further exploration. i) The conversion of C−H bonds to C−D bonds is undoubtedly one of the most effective deuteration methods. This approach can significantly enhance atom economy and avoid structural modifications in complex drug molecules. For such reactions, new reaction strategies should be designed, such as using alternating current catalysis or photoelectrocatalysis to achieve efficient electrochemical hydrogen-deuterium exchange. ii) Chiral carbon centers are widely presented in organic molecules, and achieving the asymmetric construction of C−D bonds via electrochemical means remains a significant challenge. Leveraging the advantages of electrochemical methods, introducing suitable metal catalysts and chiral ligands in electrocatalytic systems, or employing chiral amino acids and chiral NHC catalysts may assist in achieving asymmetric C−D bond formation. iii) To overcome the limitations of electrochemical development, there are other aspects worthy of investigation. In organic electro-synthesis, electrode materials play a crucial role but have not received sufficient attention from organic chemists. The development and application of novel electrode materials tailored for specific organic electrochemical systems may help address these issues and even lead to the discovery of new reactions. Through this concise review, we hope to inspire further inquiry into the development of novel and more effective deuterium incorporation approaches in the future.

Conflict of interest

The authors declare no competing financial interest.

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电化学脱卤氘化研究进展

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摘要

近年来，含有氘原子的化合物在包括材料和生物医药在内的各个领域中的重要性日益增加，被广泛应用于化学和生物学的机制研究中，将氘原子引入有机化合物已经成为药物分子发展的重要方向之一。同时，在非生物活性物质的活体内氘标记的化合物也发挥了重要作用。自美国食品药品监督管理局（FDA）批准的第一种用于临床治疗的氘化药物问世以来，氘标记的化合物就迅速成为人们关注的焦点，各种有机化合物的氘化方法被广泛开发。其中，卤化物的还原氘化具有高选择性的优势，但是大部分反应策略受到氘源和催化模式的限制。有机电合成作为一种相对绿色的催化模式以及其对氧化还原反应的广泛适应性，电化学卤化物的还原氘化成为替代传统卤-氘原子交换的重要方法之一，它避免了传统方法中过渡金属催化剂、金属试剂及昂贵氘代试剂的使用。近年来卤化物的电化学脱卤氘化得到很快的的发展，电化学脱卤氘化通常仅需要重水作为最廉价易得的氘源就能高效得到高氘代掺入率的产物，这为氘代化合物的合成与发展提供了重要的支撑。本文根据卤化物的类型，综述了电化学条件下芳基卤化物和烷基卤化物还原氘化的最新进展以及其反应机制，有望为未来更为广泛的氘代方法研究以及氘代化合物的研究提供一定的基础.

关键词：电化学；氘化；卤化物；氘水；脱卤反应