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# Immobilized and recyclable catalysts for deuterium labelling: recent developments and emerging strategies†

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Deuterated compounds have become indispensable across a wide range of applications in medicinal chemistry and materials science, driving interest in the development of efficient and sustainable synthetic methodologies. In particular, there is a growing emphasis on greener approaches that enable deuteration under mild conditions which typically necessitate the use of catalytic systems. While homogeneous catalysts are often employed due to their high activity, their limited recoverability can lead to inefficiencies, waste generation, and potential product contamination. To address these challenges, increasing attention has been directed toward the use of immobilized and recyclable catalysts, which offer enhanced sustainability and operational advantages. Such systems not only facilitate catalyst recovery and reuse but also enable integration with continuous flow technologies, providing a promising route toward scalable and environmentally responsible deuteration processes. In this review, we survey recent advances (since June 2024) in the application of immobilized and recyclable catalysts for deuteration, with a focus on innovative materials, catalytic strategies, and emerging trends that are shaping the future of this field.

### Sustainability spotlight

Materials in which protium (H) is selectively replaced by its heavier isotope, deuterium (D), have attracted growing interest due to the expanding applications of deuterated compounds. Accordingly, significant research has focused on developing efficient and sustainable synthetic strategies for deuterated molecules. This review summarizes recent advances in this field, with particular emphasis on immobilized and recyclable catalysts employed in both batch and continuous-flow systems. These strategies promote United Nations SDG 12 by enhancing resource efficiency, reducing waste, and promoting sustainable production practices. Such factors are especially important in deuterium labelling, which depends on specialized catalysts, scarce deuterated reagents, and highly reproducible methodologies. The importance of reporting turnover numbers and green metrics for newly developed recyclable catalysts is also highlighted.

## 1. Introduction

### 1.1. Deuterium (D)-labelled compounds

D-Labelled drugs gained prominence in 2017 with the U.S.A. Food and Drug Administration (FDA) approval of the first deuterated drug, deutetrabenazine (**1a**), used for the treatment of Huntington's Disease (Fig. 1).

Compared with tetrabenazine (**1b**), deutetrabenazine (**1a**) has increased metabolic stability due to the C–D bonds which have a slightly higher bond energy compared with C–H bonds (a difference of 1.4 kcal $mol^{-1}$) and a lower reaction rate compared with C–H. This results from lower zero-point energy of C–D as compared to C–H, and the effect is known as the primary deuterium kinetic isotope effect. Since then, eight drugs have been approved for commercial usage by regulatory bodies in different countries and fifteen more are in clinical trials.[6,7] D-Labelled compounds are also finding use in functional materials where the D enables higher stability as well as improved performance metrics *e.g.*, as fluorescence probes with enhanced stability against photodegradation such as **3**,[2] solar cells where D incorporation can lead to enhanced up-conversion efficiency *e.g.*, **4**;[3] Organic Light-Emitting Diodes (OLEDs) with enhanced light emission and extended operational lifetime, *e.g.*, **5**,[4] and catalysts stabilized against deactivation, *e.g.*, **6**.[5] Deuteration is also valuable in the analysis of biomolecules and fabricated devices wherein the D enables critical structural elucidation *via* neutron studies (neutron scattering, reflectometry) due to the contrasting coherent scattering lengths of protium compared with D.[8,9] Examples include developing an understanding of the changes that occur during the operation of OLEDs[10] and organic photovoltaic systems;[11] investigating dynamic processes across

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† We dedicate this review to Emeritus Professor Slovenko Polanc.

a range of polymer-based systems, such as reactions involving polymer catalyst supports[12] and the performance of lithium–sulfur batteries using deuterated polyelectrolytes;[13] and elucidating the structure of biopolymers, including polysaccharides,[14–19] proteins[20–23] (including membranes,[24–26]), and lipids.[27–29] Neutron studies involving deuterated biomacromolecules have also enabled insights into mechanisms of action, for example in SARS-CoV-2 (ref. 30–32) and enzyme catalysis.[33,34]

The expanding applications of deuterated materials create a corresponding need to develop efficient and sustainable strategies for their preparation. The development of approaches which involve the use of immobilized and/or recyclable catalysts to accomplish this in both batch and continuous flow chemistry processes forms the focus of this mini review.

#### 1.1.1. Preparation of D-labelled compounds.

The synthetic approach used to label a compound with D depends on the chemical structure of the compound to be deuterated and whether this compound needs to be perdeuterated,[35–38] polydeuterated,[36,39] or selectively mono- or di-deuterated.[40] Each of these outcomes has utility in specific applications. Additionally, with increased demand for novel D-labelled compounds, there is an urgent need to develop synthetic methods that are both efficient and sustainable to address the United Nations Sustainable Development Goals, especially no. 12: "ensuring sustainable consumption and production patterns", the Stockholm Declaration on Chemistry for the Future,[41] and the European Green Deal.[42]

The use of more sustainable Earth Abundant (EA) metal catalysis, organocatalysis, photocatalysis, electrocatalysis, and

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**Ross D. Jansen-van Vuuren**

*Ross D. Jansen-van Vuuren completed his PhD at the University of Queensland (UQ) in 2012 under the mentorship of Prof. Paul L. Burn (organic electronics). This was followed by postdoctoral research at UQ (developing phosphorescent polymers for OLEDs) and Queen's University, Canada: $CO_2$-switchable polymers (Philip Jessop), and directed* ortho *metalation/deuteration (Victor Snieckus). In 2021, he was awarded a EUTOPIA Science and Innovation Fellowship, which led Ross to Slovenia, where he developed immobilized, recyclable catalysts for deuterium-labelling. He has since secured funding from IIS-CED, ARIS, and CELSA (with KU Leuven) to advance sustainable synthetic methods for the preparation of deuterated organic compounds.*

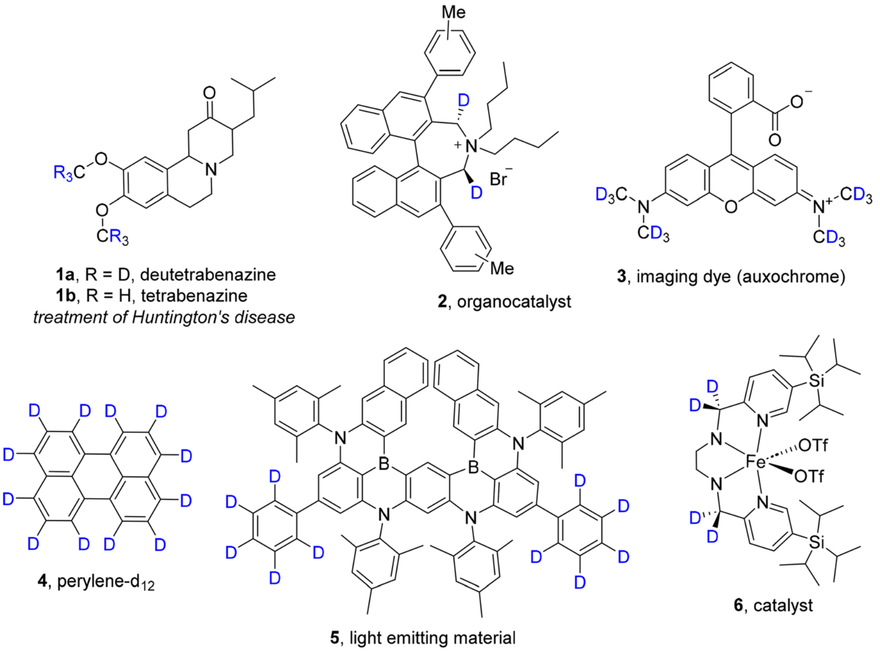


Fig. 1 Chemical structures of deutetrabenazine **1a** and tetrabenazine **1b**, organocatalyst **2**,[1] tetradeuteromethylrhodamine **3**,[2] perylene-$d_{12}$ **4**,[3] deuterated photoemitter for OLED applications **5**,[4] and iron complex used as catalyst, deuterated at the benzyl positions **6**.[5]

biocatalysis are reasonable approaches. However, in many cases, the catalyst used is still not recovered and reused.[43,44] For catalysts used in stoichiometric quantities *e.g.*, some organocatalysts, prepared or isolated using time- and resource-consuming processes, this is unsustainable. One approach to make the process more sustainable involves designing the process so that the catalyst is fully recyclable *i.e.*, it is recoverable and can be reused in subsequent reactions. Aside from being less wasteful, this has practical advantages, namely: it can avoid leaching and contamination of the product with catalyst (and consequent catalyst deactivation)[45–47] and it can be economically favourable since it reduces the need to purchase fresh catalyst.[48–52] Although we agree with the concerns shared by Hübner *et al.*[53] that research sometimes focuses too much on catalyst recyclability and not the catalyst turnover number/frequency (TON/TOF), we maintain that catalyst recycling is a valuable strategy to improve catalyst productivity (including TON/TOF). We agree that researchers in this field ought to compare the TON/TOF of the recyclable catalyst with that of the homogeneous catalyst, and we have tried to highlight this throughout the review. Recyclable catalysts are more useful if the catalyst is not so sensitive to deactivation and/or does not produce contaminants or side-products upon deactivation.[54]

One strategy to create a recyclable catalyst involves immobilizing the catalyst on a soluble or insoluble support, ensuring its removal, recovery, and reuse (*i.e.*, its recyclability) post-reaction. Catalyst immobilization (or heterogenization) also facilitates the use of such catalysts in continuous flow chemistry,[55,56] recognized to be a safer and greener approach to chemistry than batch systems due to lower reaction volumes, better control of reaction variables (especially important for deuteration involving $D_2$ gas), better product selectivity, and reduced waste generation.[57–60]

This mini review highlights advances made with developing immobilized and recyclable catalysts for deuteration or hydrogen/deuterium (H/D) exchange (in both batch and flow systems) since a prior similar review published in June 2024 (ref. 61) (Fig. 2). Since the publication of this review, there has been an increase in interest in developing electrocatalytic, photocatalytic and homogeneous earth abundant (EA) metal catalytic systems.

By contrast, there has been a decrease in the development of heterogeneous catalysts (both for EA and precious metal (PM)-based systems), homogeneous PM catalysts (down from 11% to 3%), biocatalytic systems (from a significant 25% to 0%), and organocatalysts (no immobilized/recyclable organocatalysts were reported over the past $1\frac{1}{2}$ years), while new concepts have arisen in the form of porous carbon catalysts and bimetallic catalytic systems (five papers over the past year). The porous catalyst was prepared from biomass, and we expected an increase in the development of similar catalysts in the years to come, contributing to the circular economy.[62,63]

**1.1.2. Strategies for developing recyclable catalysts.** There are several strategies which can be used to develop recyclable catalysts: one approach involves the use of multiphasic systems in which catalysts can be separated from the reaction products based on differing solubility and phase separation.[64] Another strategy includes the immobilization of homogeneous catalysts by anchoring the catalyst to soluble supports like dendrimers, polymers, polyethylene oligomers, or ionic liquids, enabling recovery through dialysis or nanofiltration.[65,66] Homogeneous catalysts can also be heterogenized through immobilization on insoluble supports such as polymers, gels, magnetically retrievable materials, or silica, allowing catalyst recovery through filtration or centrifugation.[53] The rational design of active sites is increasingly allowing heterogeneous catalysts to

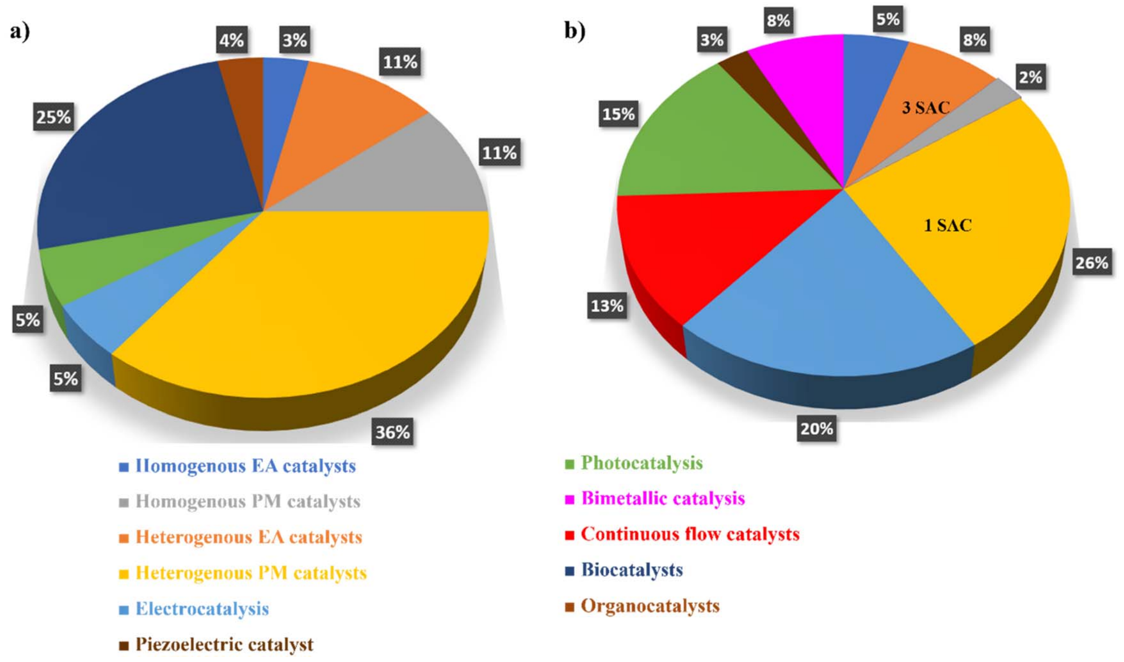


Fig. 2 Pie chart showing the types of catalysts immobilized: (a) as reviewed in our first paper (up until May 2024)[61] compared to (b) within this mini review (June 2024 – current). SAC = Single Atom Catalyst paper(s).

achieve selectivity on par with their homogeneous counterparts.[67] Colloidal nanoparticle (NP) catalysts, often positioned between homogeneous and heterogeneous catalysis, offer another avenue for the development of recyclable catalysts, with supported or encapsulated NPs enabling stability, recovery, and reuse, especially in continuous flow reactors (CFR).[68]

In this mini review, we examine reports of recyclable (or immobilized) catalysts which have been used in the synthesis of deuterated organic compounds. The paper is organized as follows. Firstly, we consider recyclable homogeneous EA and PM-containing catalysts, before discussing heterogeneous catalysts comprising both EA and PM systems. We then review recent reports on bimetallic, piezoelectric, electro-, and photocatalytic approaches (in this order) for the synthesis of D-labelled compounds. Finally, we highlight recent developments in immobilized catalysts designed for CFR applications.

## 2. Recyclable catalysts for the synthesis of D-labelled compounds

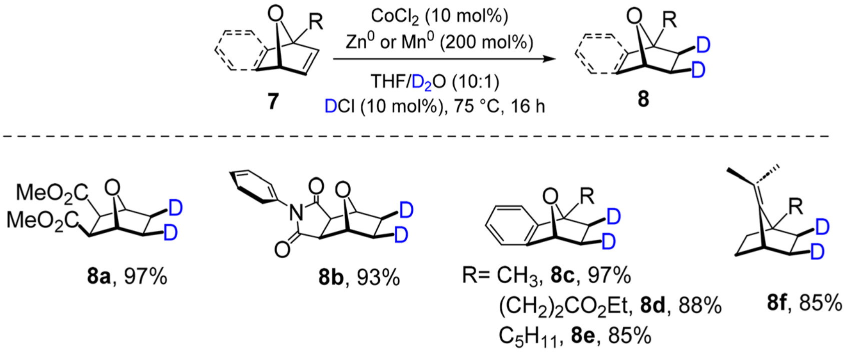
### 2.1. Homogeneous catalysts

**2.1.1. Earth abundant metal-based homogeneous catalysts.** Pounder *et al.*[69] reported a recyclable cobalt catalyst for the deuteration of bicyclic alkenes **7** utilizing $D_2O$ as the source of D, with $Zn^0$ or $Mn^0$ as reductants and DCl (10 mol%) as an additive in a THF/$D_2O$ (10 : 1, v/v) solvent system to afford products **8** (Scheme 1).

Selected bicyclic alkenes, exemplified by the structures **7a–f**, were deuterated in excellent 88–97% yields and high isotopic purity (~90%). Following the deuteration reaction, the *in situ* formed cobalt catalyst could be isolated by a simple magnetic separation, due to the ferromagnetic nature of the cobalt particles. However, the recovered cobalt catalyst exhibited poor performance in subsequent recycling experiments in terms of poor product yield with recovery of >90% of starting material, likely attributed to oxygen passivation of the metal surface hindering catalytic activity. No attempts to recover the catalyst under controlled inert conditions has been reported by the author.

In another example, Li *et al.*[70] demonstrated reductive deutero-amination of simple keto acids/esters with amines using a calcium(II) catalyst and pre-prepared $d_2$-Hantzsch ester **HE1-d$_2$** as the D source, to synthesize α-deuterated amino acid motifs with a remarkable deuteration efficiency, >99 D incorporation. This chemistry was demonstrated for a range of useful substrates including amino acids **9a-d$_1$**, peptides **9b-d$_1$**, and modified drug molecules/natural products **9c-d$_1$**, as demonstrated with select examples in Scheme 2.

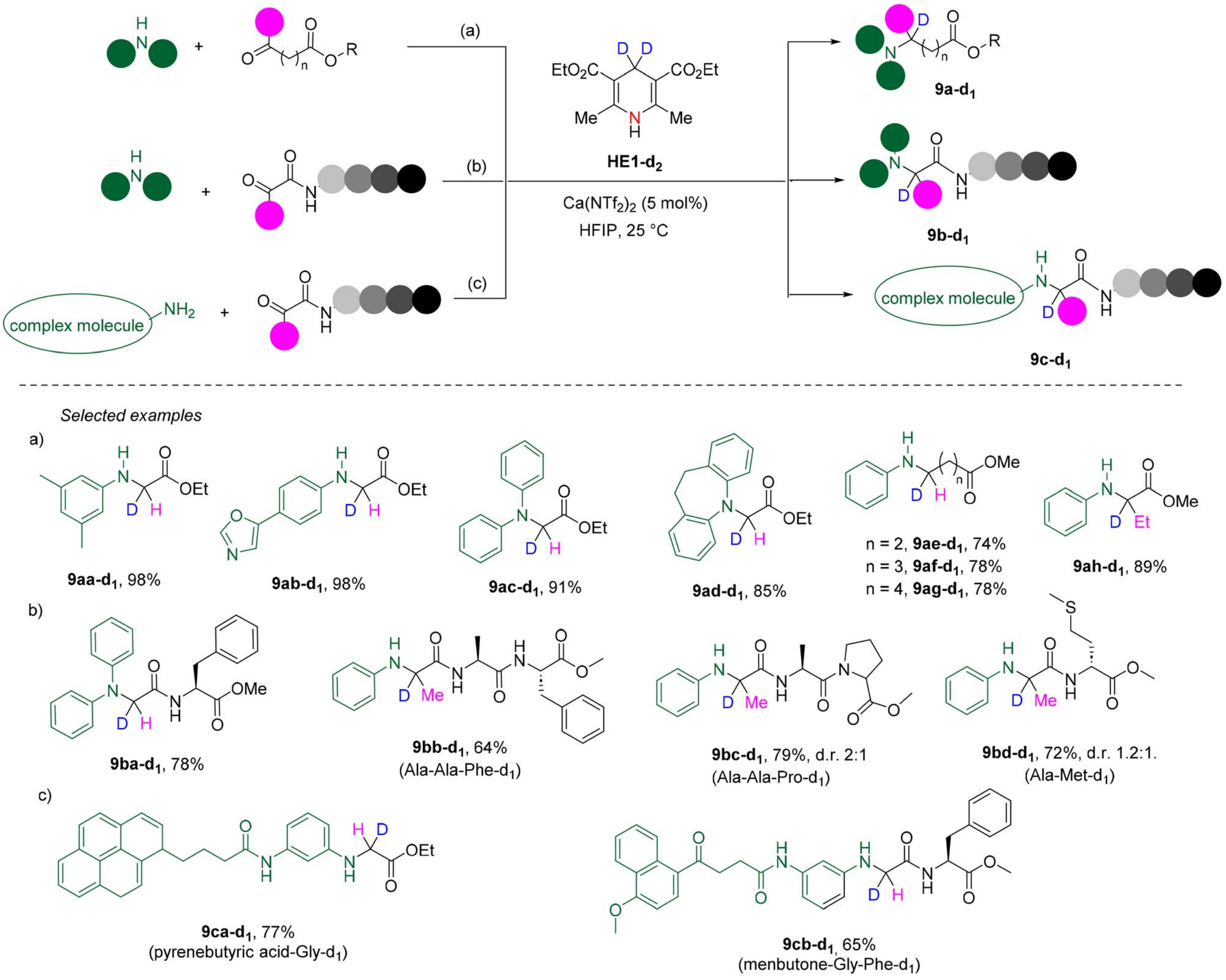
Inspired by biological reductive amination and recognizing the notable performance of the calcium(II)-catalysed system, particularly with the incorporation of hexafluoroisopropanol (HFIP), the researchers proposed a modular three-component reductive deuteration amination protocol. In this approach, the natural H-bond donor and reducing agent NADH was replaced by the Ca(II)/HFIP catalytic system and **HE2-d$_2$**. Exposing an amine and a ketoester or ketoacid to the active $Ca(NTf_2)_2$-HFIP catalytic system resulted in the formation of an iminium intermediate which underwent reductive deutero-amination with **HE2-d$_2$**. This process enabled the modular synthesis of diverse deuterated amino acids (and even peptides) in high yields and excellent levels of % D incorporation at the α-position to the nitrogen. This synthetic protocol allows the catalyst to be recovered by simple extraction from the reaction mixture into water. The catalyst was reused in up to eight consecutive runs, with a decrease from 94% to 71% of isolated



Scheme 1 Deuteration of bicyclic alkenes **7** using cobalt catalyst with $D_2O$ as source of D. Adapted from Pounder *et al.*[69] with permission from Wiley-VCH GmbH copyright © 2024.

yield on the 8th run, demonstrated with different amine substrates and drug molecules (Fig. 3). Although the recovery of HFIP was not mentioned in this paper, this is possible by distillation.[71]

**2.1.2. Precious metal-based homogeneous catalysts.** Navarro *et al.*[72] reported the ruthenium catalysed transfer dideuteration of heteroaromatics **10** in $D_2O$ into **11** (Scheme 3). The reaction involves the use of deuterated formic acid/sodium formate as D-source and catalyst, cat = $[RuCl(cym)(dmbpy)]BF_4$



Scheme 2 Reductive deutero-aminations of various substrates: (a) synthesis of deuterated amino acids and their derivatives (**9a-d$_1$**), (b) synthesis of peptide derivatives (**9b-d$_1$**) and (c) late-stage functionalization of complex molecules, to form **9c-d$_1$**. The yields are isolated yields. >99% Deuteration was obtained in all cases. Scheme adapted from Li *et al.*[70] licensed under CC BY 4.0. Springer Nature Copyright © 2025.

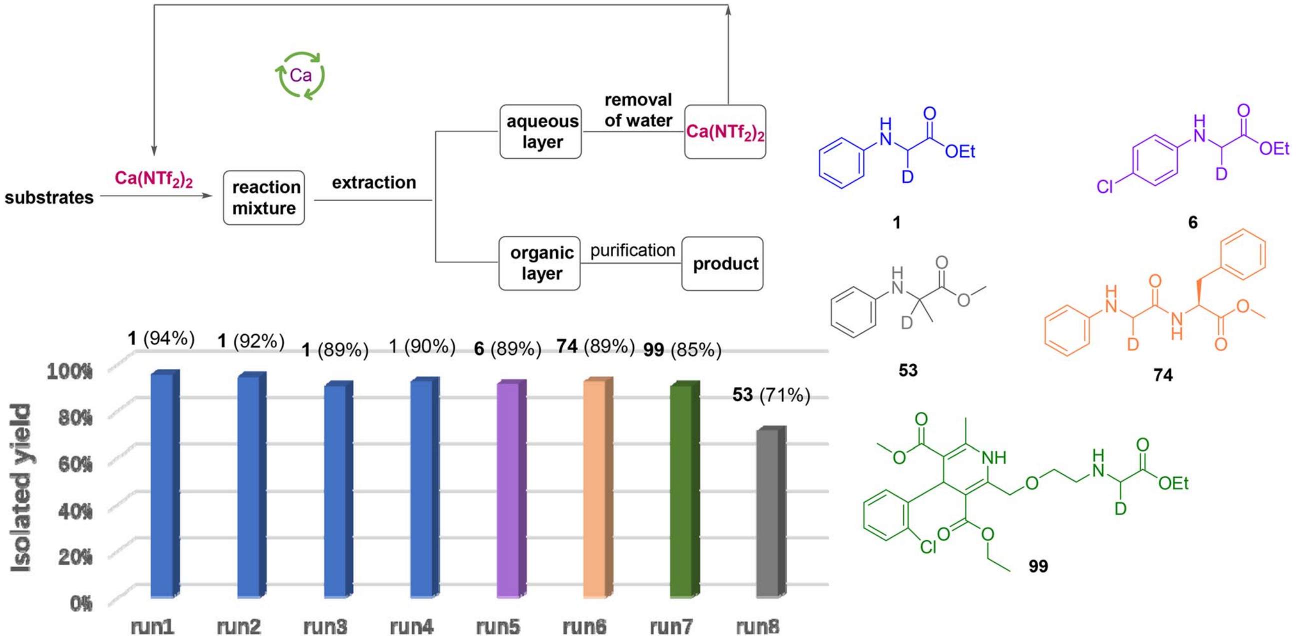
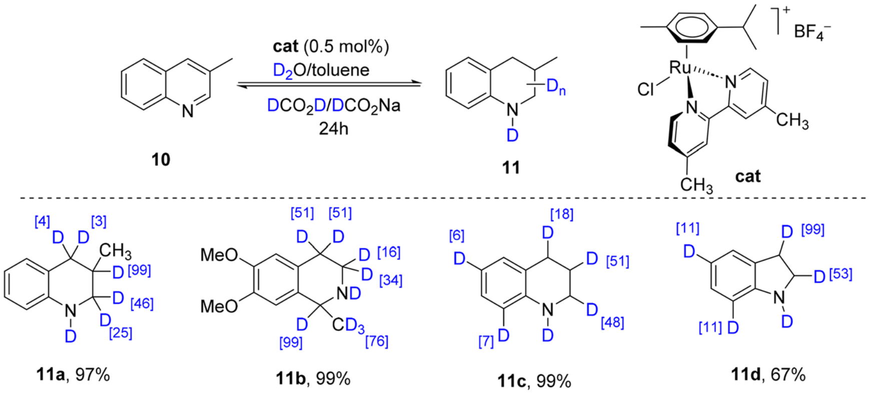


Fig. 3 Recovery and reuse of $Ca(NTf_2)_2$. Adapted from Li *et al.*[70] licensed under CC BY 4.0. Springer Nature Copyright © 2025.



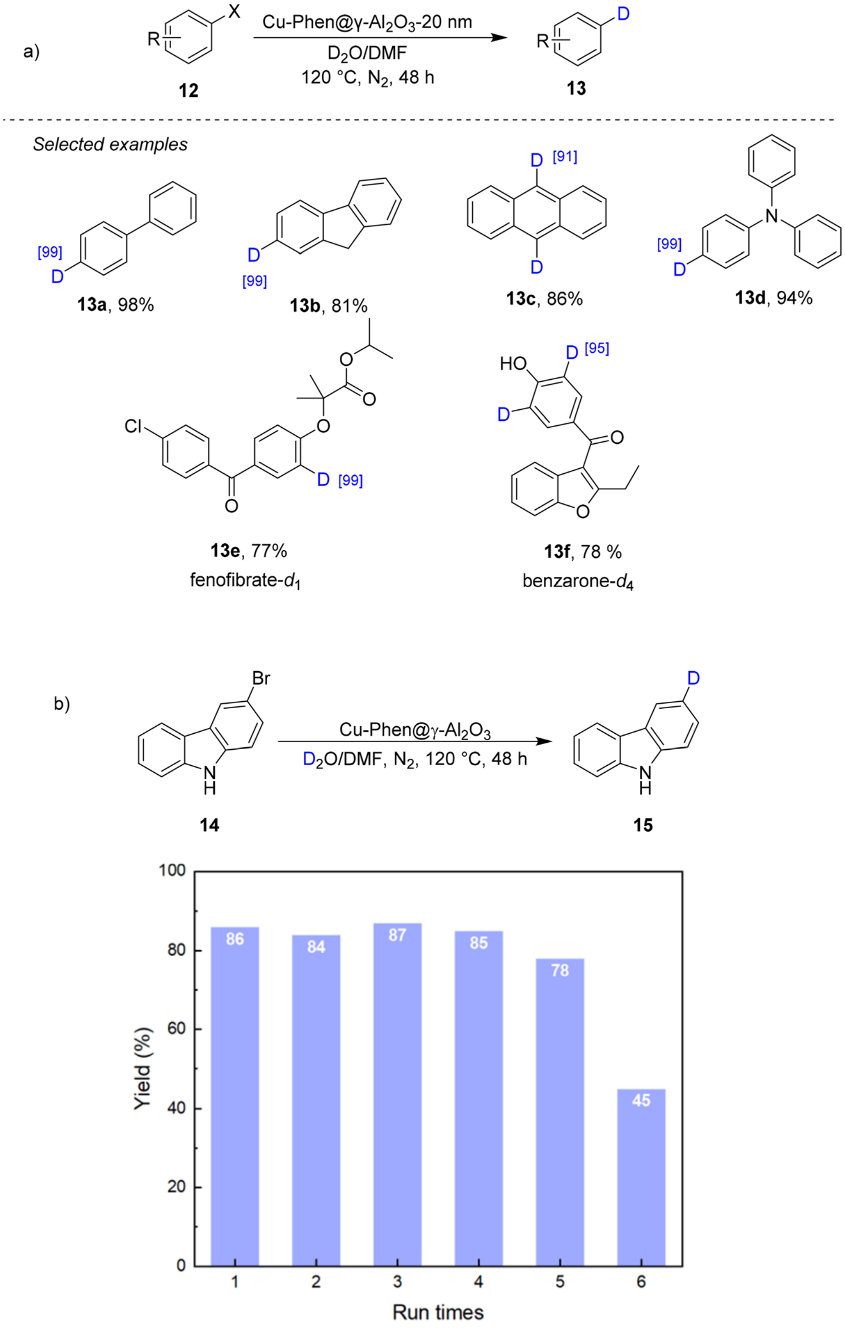
Scheme 3 D-labelling of N-heterocyclic compounds **10** *via* transfer deuteration. % D incorporation is provided within square brackets at the corresponding C–D bond and D incorporation on N atoms are not reported. Adapted from Navarro *et al.*[72] licensed under CC BY 4.0. Wiley-VCH GmbH Copyright © 2024.

(cym = *p*-cymene, dmbpy = 4,4′-dimethyl-2,2′-bipyridine). The reactions were conducted in a biphasic $D_2O$/toluene medium on several quinoline, acridine derivatives, enabling effective catalyst recycling (demonstrated with the hydrogenation reaction) while facilitating a straightforward work-up procedure. The recycling procedure involved quenching the reaction after the first catalytic cycle by cooling it in an ice-water bath before allowing the reaction mixture to warm to room temperature (r.t.). Once the mixture reached r.t., the organic phase was separated using Pasteur pipettes. Fresh substrate, toluene, and either 2 or 4 equivalents of $DCO_2D$ were then added to the aqueous phase, and a new catalytic cycle was initiated. This process was repeated for four catalytic cycles to evaluate the recyclability of the system. It was found that the catalyst activity was stable, achieving conversions >97% for each cycle when 4 equiv. of formic acid were added to ensure prior deuteration for efficient transfer hydrogenation to occur.

### 2.2. Heterogeneous catalysts

Now, we present recent reports of recyclable heterogeneous EA metal and PM catalysts used in the deuteration of organic molecules.

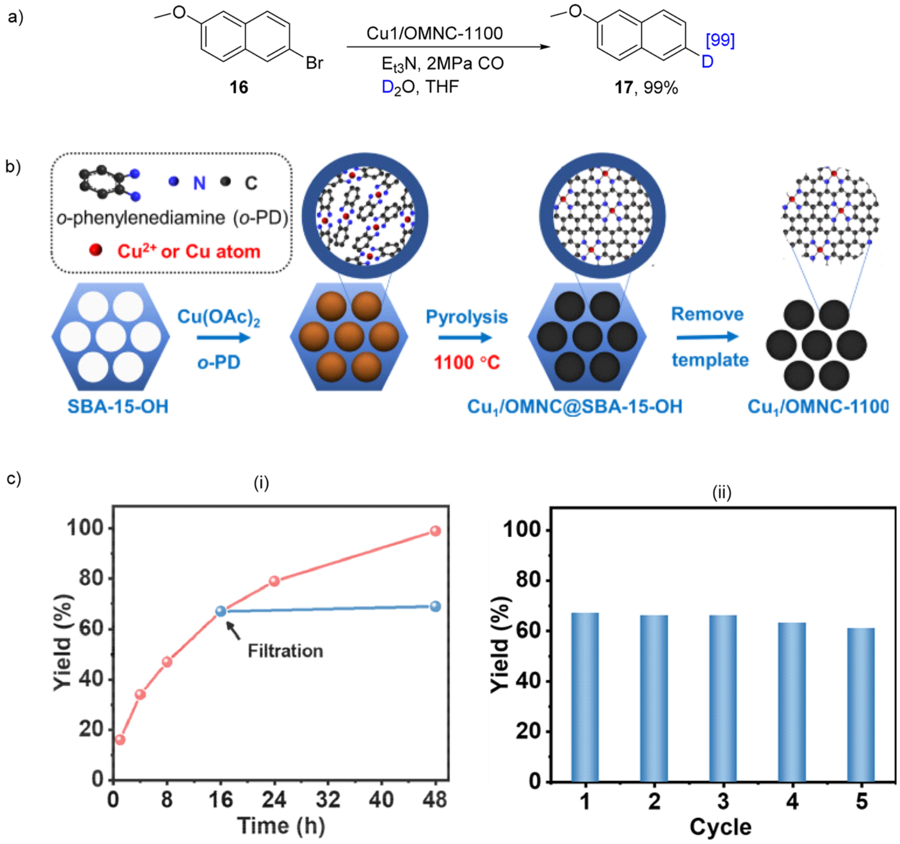
**2.2.1. Earth abundant metal-based heterogeneous catalysts.** Using a heterogeneous copper catalyst, Yang *et al.*[73] demonstrated a novel methodology for the deuterodehalogenation of aromatic halides **12** employing $D_2O$ as the D source and *N*,*N*-dimethylformamide (DMF) as both the solvent and a CO surrogate (Scheme 4). The latter acted as the reductant for the generation of active species for the dehalogenation. The copper catalyst, Cu-Phen@γ-$Al_2O_3$, was prepared by



Scheme 4 (a) Deuterodehalogenation of aromatic halides using heterogeneous copper catalyst. Adapted from Yang *et al.*[73] licensed under CC BY 4.0 (b) the catalyst recycling study using 3-bromo-9*H*-carbazole **14** as a model substrate. Adapted from Yang *et al.*[73] licensed under CC BY 4.0. Elsevier Copyright © 2025.

impregnating γ-$Al_2O_3$ with copper(II) acetate and 1,10-phenanthroline, followed by pyrolysis at 800 °C. The optimal deuteration conditions involved heating the substrate with 16 mol% of the catalyst per mole of substrate, 0.5 mL of $D_2O$, and 1.5 mL of DMF under 10 bar $N_2$ at 120 °C for 48 hours. The Cu catalyst demonstrated high efficiency, achieving quantitative yields and high >80% D incorporation to yield **13** for most compounds. Selected examples are shown in Scheme 4a. It also showed good functional group tolerance and could be reused up to five times with minimal loss of activity for the first four cycles and then approximately 50% loss of activity (from 86% to 45%) in the fifth cycle. The catalyst was recovered by simple filtration followed by washing with ethanol and acetone (Scheme 4b).

In another study, Xie *et al.*[74] developed a novel Cu single atom-catalyst (SAC) for the selective dehalogenative deuteration of 2-bromo-6-methoxynaphthalene **16** (Scheme 5a). Heterogeneous SACs *i.e.*, atomically dispersed metal atoms on a support material (*cf.* clustered together), have become more popular recently due to their high catalytic activity, selectivity, and cost-effectiveness, even for PMs.[75] The Cu SAC (abbreviated Cu1/

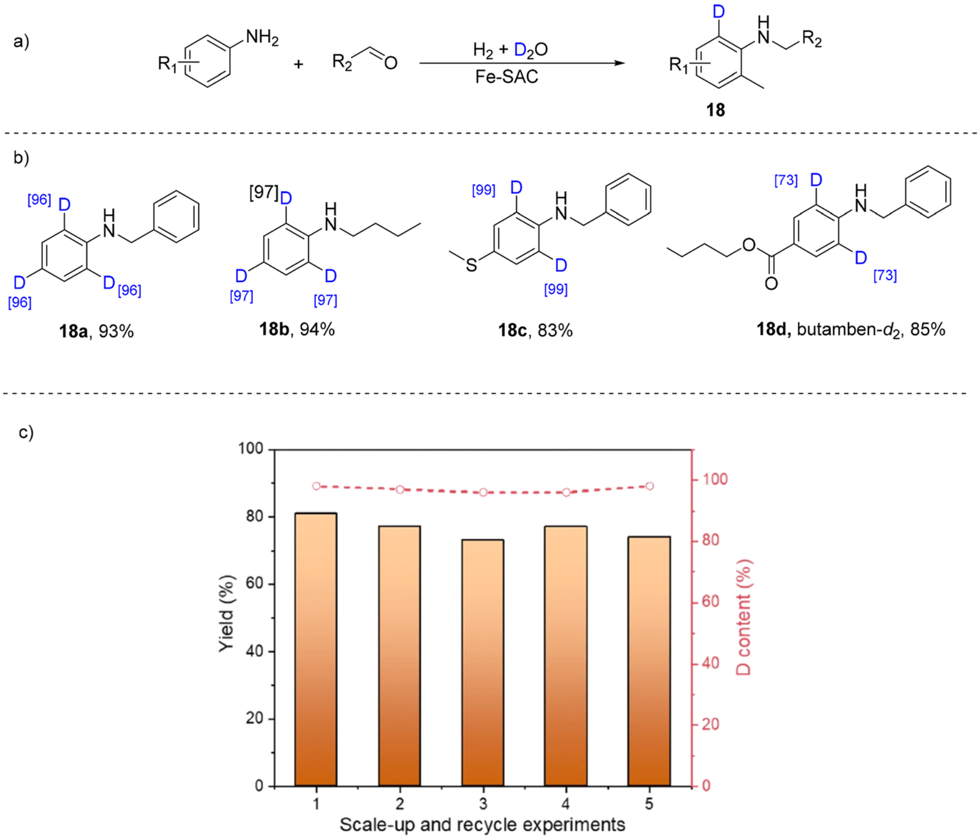


Scheme 5 (a) Synthesis of the SAC. (b) Selective dehalogenative deuteration of 2-bromo-6-methoxynaphthalene **16**. (c) Recycling experiments on SAC. Adapted from Xie *et al.*[74] with permission from American Chemical Society Copyright © 2025.

OMNC-1100) was anchored within an ordered mesoporous N-doped carbon matrix with a high atomic utilization efficiency and unique electronic properties, crucial for achieving high selectivity and catalytic activity. The Cu1/OMNC-1100 catalyst was synthesized *via* an '*o*-phenylenediamine-assisted *in situ* mesopore confinement method', involving pyrolysis at 1100 °C, to form a stable Cu–$N_4$ coordination environment (Scheme 5b). The catalyst exhibited excellent recyclability and stability, maintaining high performance over five reaction cycles, as demonstrated with 2-bromo-6-methoxynaphthalene as the substrate, $D_2O$ as the D source, and $Et_3N$ as the base under relatively mild conditions (80 °C and 2 MPa of CO) (Scheme 5c). Key features of this research include high (99%) yield and % D incorporation (73–99%), mild reaction conditions, broad substrate compatibility in various types of hetero aryl bromide, scalability for gram-scale reactions, and the importance of regulating the coordination environment of single-atom catalysts.

For both above examples, it would be interesting to perform a green metric analysis on the whole process, considering the impact of the synthesis of the catalyst. Precedent analyses can be found in the literature,[76–78] and provide examples of what should be applied to similar studies to quantitatively demonstrate an improvement in the greenness and sustainability of the recyclable catalyst.

Iron-based catalysts are also being studied for deuteration of organic compounds. Beller's and Hutchings' groups collaboratively demonstrated a phosphorus-doped Fe-based SAC (Fe-SAC) capable of reductive amination–deuteration in amines, drugs and complex biomolecules with efficient reactivity and regioselectivity.[79,80] Compared with previous reports of iron catalysts performing reductive amination and deuteration separately with heavy loading of iron content (∼20 mol%),[39] the Fe-SAC developed is a dual functional catalyst which effectively enables both reductive amination and deuteration in a one pot reaction (without multi-step purification) using $H_2$ as a reducing agent and inexpensive $D_2O$ as D source. Additionally, the metal is applied in catalytic amounts (0.2 mol%) and demonstrated a moderate TOF of 115 $h^{-1}$ compared to an Fe NP catalyst with high Fe loading (4.9 wt%) with a TOF of 4.5 $h^{-1}$. The reaction efficacy was improved upon P-doping with 91% yield with 98% deuteration content. The tandem reductive amination and deuteration of various amino-substituted (hetero)arenes and aldehyde into **18** were conducted under a reaction condition of 0.25 mmol amino-substituted (hetero) arenes, 0.25 mmol aldehydes, 0.2 mol% Fe-SAC, 90 equiv. $D_2O$ (405 μL) was used for the deuteration in 1 mL toluene and 40 bar $H_2$. The reaction was performed at 140 °C for 24 h (Scheme 6). The heterogeneous Fe-SAC were successfully recycled by a simple separation from the reaction system by centrifugation.



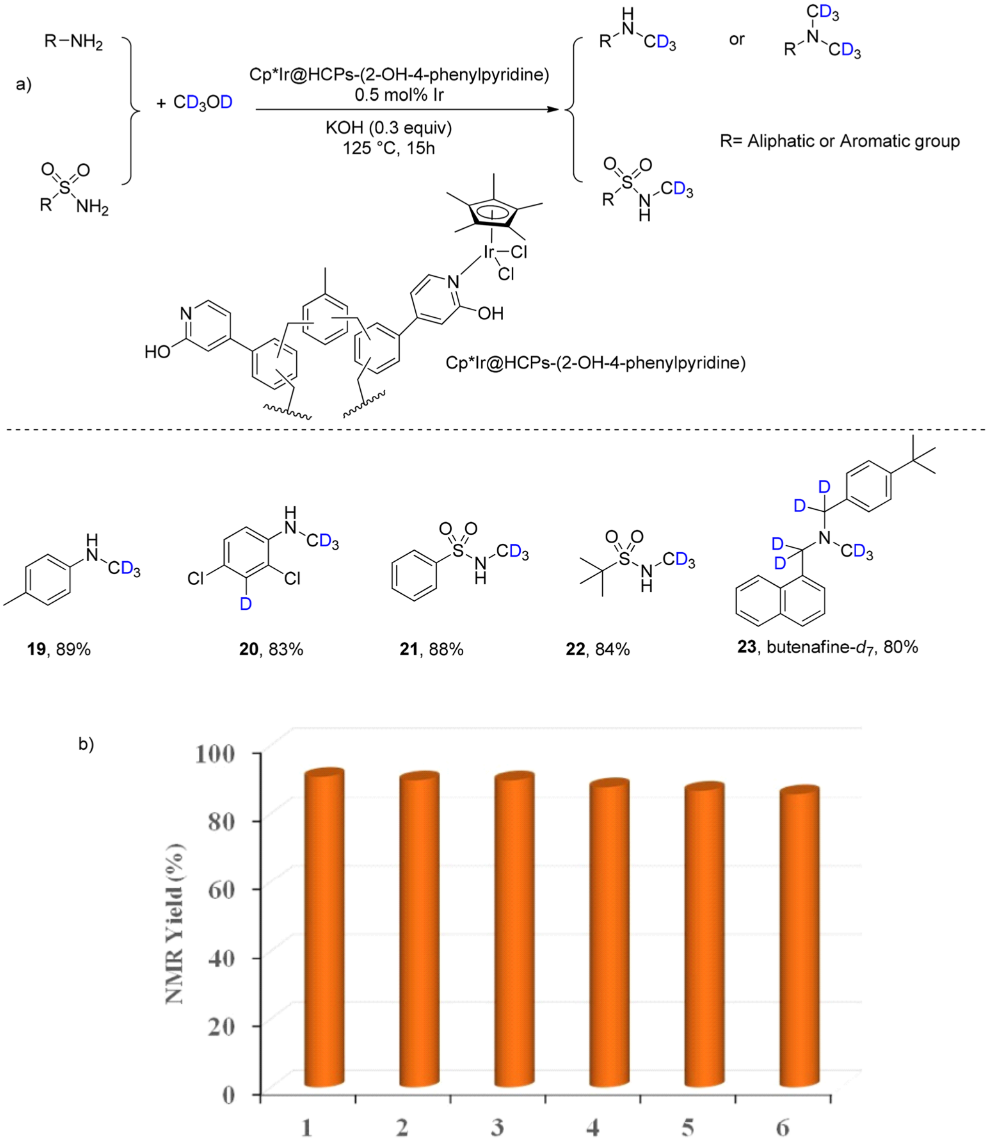
Scheme 6 (a) Catalytic reductive amination and deuteration using dual-functional Fe SAC. (b) Tandem reductive amination and deuteration of different amino substituted (hetero)arenes and aldehydes. (c) Scale-up and recycling experiments. Adapted from Qi *et al.*[79] licensed under CC BY 4.0. Springer Nature Copyright © 2025.

The collected catalyst was then successively washed by ethanol (3 × 50 mL) and dried at 80 °C for 2 h before being used in the next reaction, the catalyst-maintained activity up to five cycles, maintaining deuteration of 80% as shown in Scheme 6c.

**2.2.2. Precious metal-based heterogeneous catalysts.** Since PM catalysts still offer desirable catalytic activity in low loadings and under mild conditions compared to their non-PM counterparts, there is still significant interest in their usage, academically and industrially. We have reviewed several recently reported heterogeneous PM-based catalysts.

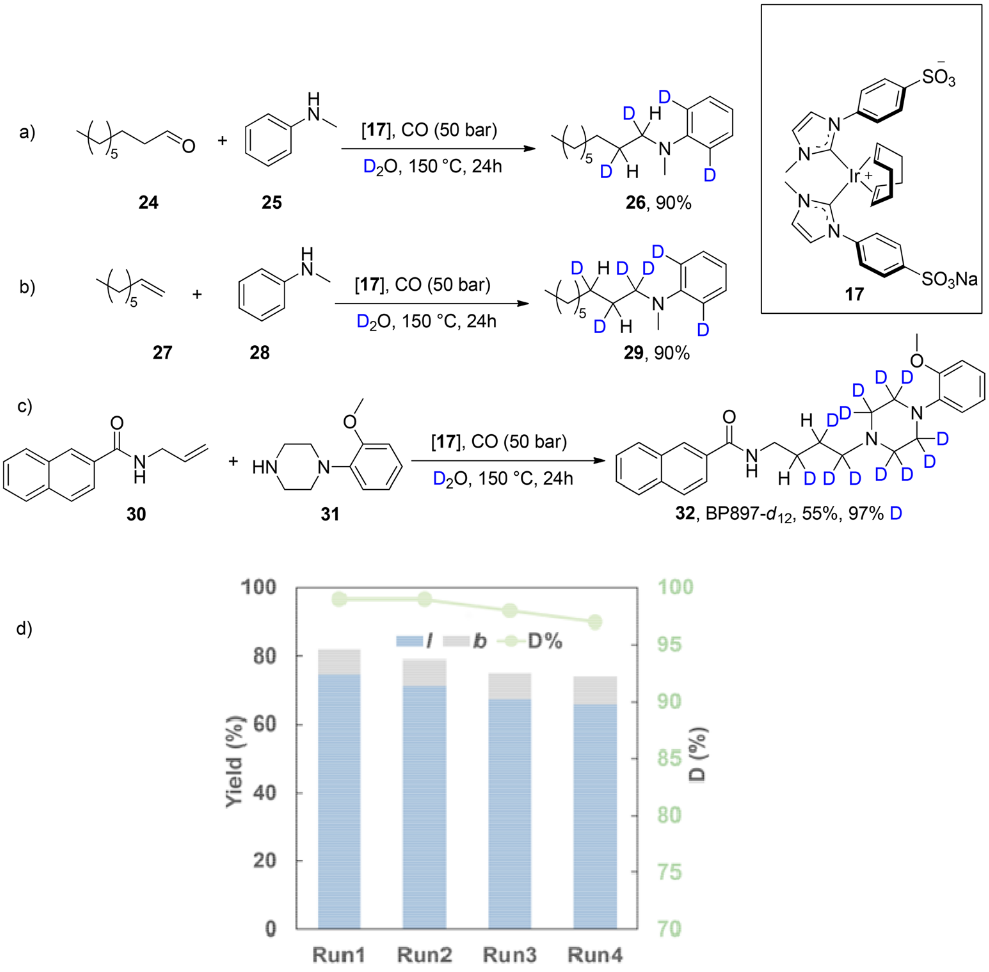
Iridium (Ir) is a key PM used for H/D exchanges; due to its high cost, there has been a shift towards the development of heterogeneous, recyclable Ir catalysts. In 2025, Chen *et al.*[81] reported a heterogeneous Ir(0) catalyst, CpIr@HCPs-(2-OH-4-phenylpyridine), synthesized *via* the coordinative immobilization of [$CpIrCl_2$] on a hyper-cross-linked polymer functionalized with 2-OH-4-phenylpyridine ligands (Scheme 7). This catalytic system was applied for the *N*-trideuteromethylation of amines using $CD_3OD$ as the D source under borrowing hydrogen (or D) conditions. The reaction operates optimally at 125 °C for 15 hours in the presence of 0.5 mol% Ir catalyst and 0.3 equivalents of KOH (Scheme 7a). Under these conditions, a wide array of aromatic and aliphatic amines, including electronically and sterically diverse sulfonamides, underwent smooth conversion to the corresponding *N*-trideuteromethylated products in yields up to 92%. Mechanistic investigations support a metal–ligand bifunctional mechanism involving dehydrogenation of $CD_3OD$, condensation to imines, and subsequent reduction *via* Ir–D and ligand OD delivery, regenerating the active species. The key highlight of the work is the demonstration of recyclability and robustness of the catalyst. Six consecutive cycles of the model transformation (aniline to its trideuteromethylated derivative) were carried out with the catalyst retaining high activity (≥86% yield in each cycle) (Scheme 7b). Post-reaction analysis revealed minimal loss of iridium (from 3.35 wt% to 3.07 wt%) and preserved morphology, as confirmed by scanning electron microscopy (SEM) and energy-dispersive X-ray spectroscopy (EDS) mapping. This stability is attributed to the strong coordination between Ir and the ligand in the polymer matrix and the porous framework's ability to retain metal centres. Overall, the study effectively addresses the challenges of iridium catalyst recyclability in H/D exchange reactions by anchoring a functionally critical ligand into a thermally stable porous polymer network, setting a precedent for future heterogeneous systems in isotope labelling chemistry.

In a recent study, Huo *et al.*[82] reported an additive-free hydroaminomethylation of long chain olefins in water with hydrophilic Ir-containing N-heterocyclic carbene (NHC) complexes as recyclable catalyst. When the reaction was carried out using $D_2O$ instead of $H_2O$ under standard conditions,



Scheme 7 (a) $N$-Trideuteromethylation of amines and sulfonamides. The percentage of D incorporation was not reported. (b) Recyclability of Cp*Ir@HCPs-(2-OH-4-phenylpyridine) for the $N$-trideuteromethylation of amines with $CD_3OD$. Adapted from Chen *et al.*[81] with permission from American Chemical Society Copyright © 2025.

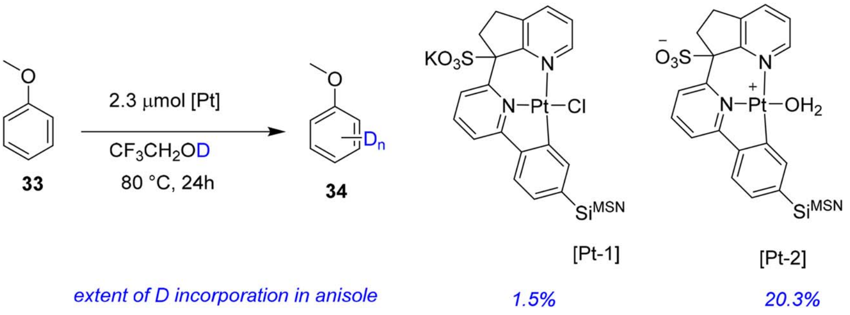
deuteroaminomethylated products were obtained in excellent yields and with a high (~90–97%) D incorporation (Scheme 8). In this system, $H_2O$ or $D_2O$ functions not only as the solvent but also as H/D source, with CO promoting *in situ* $H_2/D_2$ generation *via* the water–gas shift reaction (WGSR). The catalytic cycle proceeds through Ir-catalysed hydroformylation of the olefin to an aldehyde intermediate, followed by reductive amination with the amine, as confirmed by the isolation of reaction intermediates. Deuteration studies revealed selective incorporation at both benzylic and aromatic positions, affording products such as **26** and **29** in high yields, while kinetic isotope effect measurements (KIE ≈ 3.0) identified D release from WGSR as the rate-determining step. The catalyst recovery involves a simple liquid–liquid extraction of the water-soluble iridium catalyst into the aqueous phase from reaction mixture. The recovered aqueous phase containing catalysts was directly reused for the next run without additional activation and the recycling experiments demonstrated up to 99% D incorporation in initial cycles, with only minor erosion (to ~97%), after four cycles due to the gradual accumulation of hydrogen-containing water formed during the reaction, and the subsequent water–gas shift reaction, a small amount of hydrogen-containing gas was generated which declined the percentage deuteration (Scheme 8c). Notably, this methodology extends to complex substrates, exemplified by the direct synthesis of the deuterated dopamine receptor ligand **32**, BP897-$d_{12}$, in a single step. Collectively, these results highlight a mechanistically well-defined and sustainable strategy for site-selective isotopic labelling, with implications for both mechanistic studies and



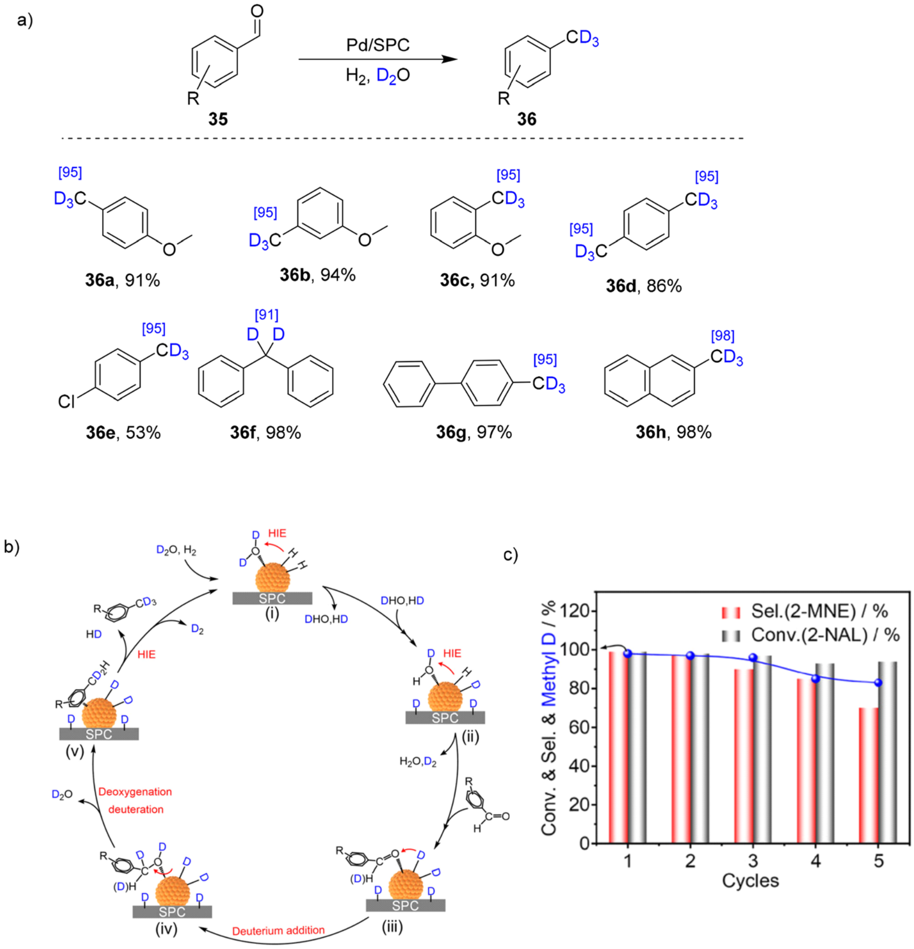
Scheme 8 Deuteroaminomethylation of (a) 1-nonanal **24** and *N*-methylaniline **25**, (b) 1-octene **27** and *N*-methylaniline **28**, and (c) **30** and **31** in the synthesis of deuterated analogue of BP897. (d) Recyclability study on **27** reacting with **28** (shown in (b) above). Adapted from Huo *et al.*[82] with permission from Wiley-VCH GmbH Copyright © 2025.

the preparation of metabolically stabilized pharmaceutical analogues.

Kramer *et al.*[83] developed novel Pt complexes for catalytic hydrogen/deuterium (H/D) exchange reactions of aromatic substrates (Scheme 9). The Pt(II) aqua complex (Pt-1 and Pt-2) is anchored to mesoporous silica NPs MSNs *via* a rigid $SiO_3$ tether, an immobilization strategy designed to enhance robustness and recyclability by preventing deactivation through intraparticle and interparticle coordination The primary reaction investigated is the H/D exchange of C($sp^2$)–H bonds in aromatic substrates using a Pt(II) aqua complex immobilized on MSNs. The catalyst facilitates the exchange of hydrogen atoms in the aromatic substrates with D atoms from deuterated solvents, such as $D_2O$-2,2,2-trifluoroethanol-d$_1$ (TFE-d$_1$) or $CD_3CO_2D$. The reactions were typically carried out at 80 °C using a mixture of $D_2O$ and TFE-d$_1$ as the D source, while reactions using $CD_3CO_2D$ required



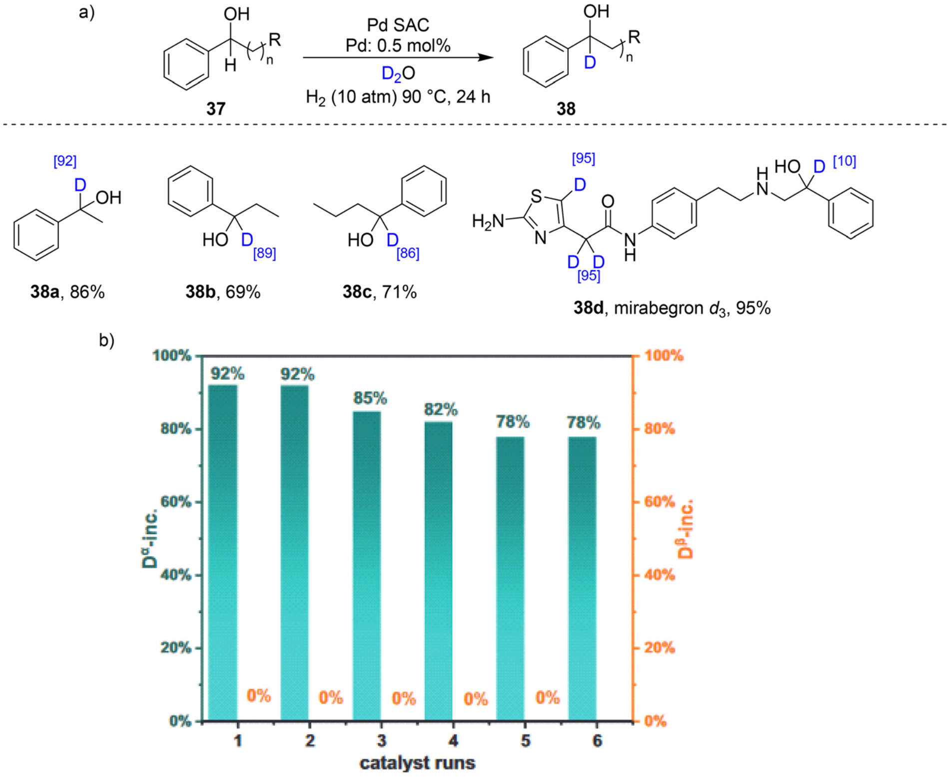
Scheme 9 Pt complexes catalysed H/D exchange reactions of anisole. Adapted from Kramer *et al.*[83] with permission from American Chemical Society Copyright © 2025.



Scheme 10 (a) Selective deoxygenative deuteration of aldehydes **35** by PD/SPC and (b) proposed mechanism. (c) Recyclability study using 2-naphthaldehyde as model substrate. Adapted from Wu *et al.*[84] with permission from Wiley-VCH GmbH Copyright © 2025.

higher temperatures of up to 120 °C (Scheme 9). The immobilized Pt(II) catalyst exhibited higher activity and chemical robustness than the parent Pt(II) complexes, with TON values 2–10 times greater than the parent complex. Additionally, the immobilized catalyst was able to maintain its activity over multiple recycling cycles without significant loss of activity. Additionally, the catalyst proved versatile, effectively facilitating H/D exchange reactions with both $D_2O$-TFE-$d_1$ and $CD_3CO_2D$, the latter being a more readily available and cost-effective D source. Furthermore, the innovative use of a rigid $SiO_3$ tether for immobilization on MSNs significantly enhanced the catalyst's performance and recyclability, making it a promising candidate for deuteration of organic compounds.

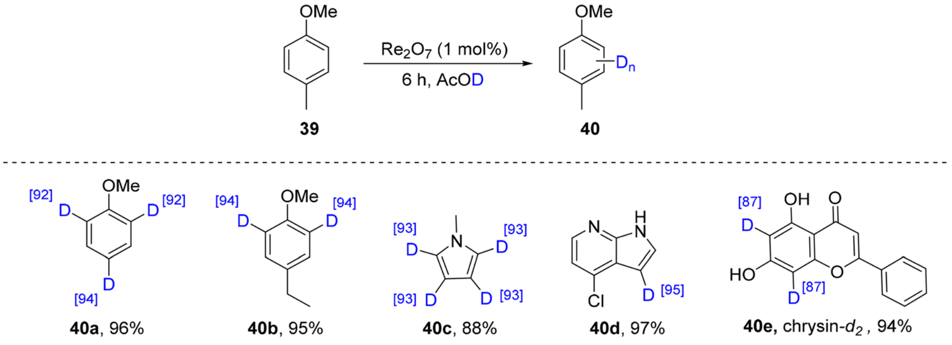
In 2025, Wu *et al.*[84] reported the deoxygenative deuteration of aldehydes **35** using a heterogeneous porous 'superwetting' carbon-supported palladium catalyst (Pd/SPC) for the synthesis of aromatic compounds with deuterated methyl groups (Scheme 10). The catalytic performance of the heterogeneous Pd/SPC catalyst was attributed to the combined influence of surface wettability and the electron-rich character of the palladium metal centre. The mechanistic studies also revealed a stepwise deuteration process, involving H/D exchange, D addition, and subsequent deoxygenative deuteration under cost-effective $D_2O$/$H_2$ reaction conditions. In this sequence, $D_2$ formed *in situ* through H/D exchange between $H_2$ and $D_2O$, was efficiently captured by the electron-rich Pd centres. These Pd sites then promoted the deuterogenolysis of C–O bonds *via* deuterated alcohol intermediate. The average yield of deoxygenative deuteration of aldehydic products exceeded 90%, with the methyl D content reaching ≥95%, indicating that the deoxygenative deuteration of aldehydes were well-tolerated by electron-donating substituents. In contrast, for substrates bearing electron-withdrawing groups, competitive reduction pathways diminished the selectivity toward $CD_3$-labeled products during the deoxygenative deuteration of aldehydes. The Pd/SPC displayed recyclability of up to five cycles using 2-naphthaldehyde as a model substrate to give 2-methylnaphthalene-$d_3$ (**36h**) as the product. In five successive catalytic cycles, the D content and selectivity gradually decreased from 98% to 90%, while the conversion rate remained constant (Scheme 10c). A visible agglomeration of Pd NPs in the spent Pd/SPC catalyst after five cycles was not observed. However, the number of $Pd^{2+}$ species visibly increased on the catalyst surface after the 1st and 5th cycles.



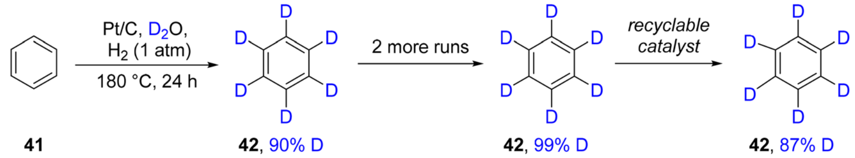
Scheme 11 (a) Catalytic α-site-selective H/D exchange of benzylic alcohols **37** by Pd single-atom catalyst (Pd-SAC) and (b) catalyst recyclability studies (using 1-phenylethanol as a model compound), the orange axis shows the percentage of deuteration of β hydrogen in the substrate. Adapted from Li *et al.*[85] with permission from Wiley-VCH GmbH Copyright © 2025.

Li *et al.*[85,86] reported catalytic α-site-selective H/D exchange of benzylic alcohols by a Pd single-atom catalyst (Pd-SAC). Pd-SAC enabled exceptional activity and selectivity in H/D exchange, providing up to 95% D incorporation at the α-position while suppressing undesired pathways such as α,β-multisite deuteration (exemplified by **37a–d**) (Scheme 11a). Mechanistic studies indicated that the Pd SAC facilitates site-selective H/D exchange through two distinct surface pathways: (i) a previously unreported direct C–H bond activation mechanism,[87,88] and (ii) a modified borrowing hydrogen process, wherein high-pressure hydrogen suppresses keto–enol tautomerization, thereby significantly reducing the occurrence of α,β-multisite deuteration (Scheme 11b, denoted in orange colour axis). The Pd-SAC catalyst could be reused in several runs, albeit with slight decreases in % D incorporation after the second cycle, as demonstrated using 1-phenylethanol as model substrate to yield **38a** (Scheme 11b). After the reaction, the spent Pd SAC was washed three times with a 1 : 1 mixture of deionized water and ethanol (3 × 30 mL), before being dried at 80 °C. The dried Pd-SAC was finely ground and subsequently calcined in a muffle furnace at 400 °C for 2 hours followed by reduction in a 10 vol% $H_2$/He atmosphere at 150 °C for 2 hours and then used for cycle experiments.

Meng *et al.*[89] reported the deuteration of $P^V$-substituted naphthalene derivatives using commercially available and recyclable Pd/$Al_2O_3$ catalyst with $D_2$ gas as D source. Naphthalene was deuterated under a $D_2$ atmosphere and ≥95% D



Scheme 12 C–H deuteration of (hetero)arenes catalysed by recyclable rhenium catalyst $Re_2O_7$. Adapted from Hu *et al.*[90] with permission from American Chemical Society Copyright © 2025.



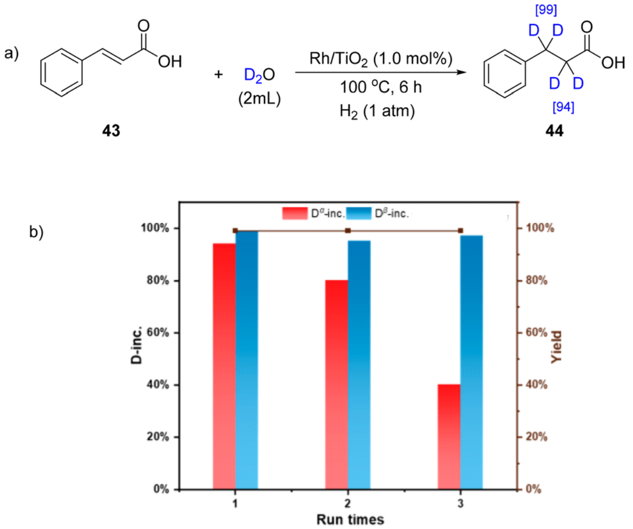
Scheme 13 Deuteration of benzene using Pt/C/$D_2O$ according to Sadjadi *et al.*[94]

incorporation was reported at all four positions (C1–C4) of the naphthalene ring. In contrast, no D was observed in the product when the reaction was conducted in deuterated methanol under $H_2$, confirming that molecular D ($D_2$) rather than the solvent serves as the exclusive D source. Further analysis of site-specific D incorporation revealed that the deuterium atoms at C1 and C2 were introduced exclusively *via cis* addition, with deuteration levels of 96 and 95%, respectively. No D was observed in a *cis* orientation at C2 relative to the phosphinoyl group. At C3 and C4, 85% of D was incorporated in the *trans*-positions relative to the phosphinoyl group, while 13% was found in the *cis* positions. Catalyst recyclability was demonstrated with the hydrogenation reaction only: the reaction mixture was centrifuged, then the catalyst was separated from the reaction mixture by pipetting out the supernatant and the left-over catalyst was washed thrice by methanol, and the reaction was repeated by introducing fresh substrate and solvent into the washed catalyst. This process was repeated five times and no decrease in catalyst activity was observed.

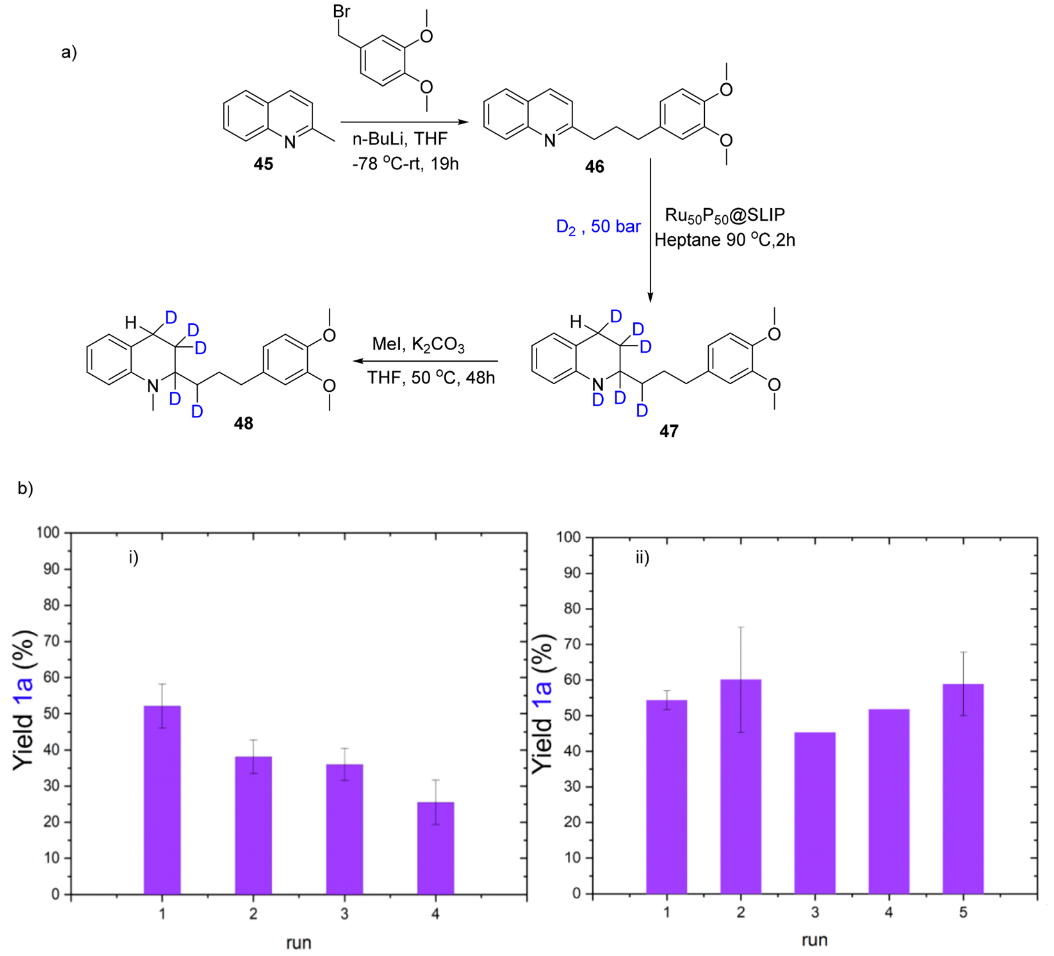
Hu *et al.*[90] reported a late C–H deuteration *via* D-bonding catalysed by a rhenium complex $Re_2O_7$ (Scheme 12). Rhenium complexes have gained widespread attention in organic transformation due to their versatile reactivity that results from their hard and soft Lewis acidity.[91] There were previous reports demonstrating that hydrogen bonding between $Re_2O_7$ and a weakly acidic solvent such as HFIP significantly enhanced the catalyst's efficiency in activating hydroxy groups, electronically deactivated alkenes, and cyclopropanes across various challenging transformations.[92,93] Hu *et al.*[90] reported that the weak acid AcOD can be effectively utilized in selective arene C–H deuteration when paired with $Re_2O_7$ catalysis. In this system, AcOD functions both as a D bonding donor and as an inexpensive D source. This method displayed a markedly broader substrate scope compared to prior strategies that employed deuterated strong acids like $D_2SO_4$, DCl, or TfOD. The reactions were performed with variety of arenes (including heterocyclecs, biomolecules) (1.0 equiv), AcOD (0.25 M), $Re_2O_7$ (1 mol%) at 120 °C for 6 h (Scheme 12). The enhanced reactivity is attributed to a proposed D bonding interaction between $ReO_4^-$ and AcOD, a hypothesis supported by both $^1H$ NMR studies and DFT calculations. A substrate recycling experiment was carried out under standard reaction conditions with 1,4-dimethoxybenzene. On the first run an 84% D incorporation was found. After a simple recycling protocol, it was found that a second run further improved the D incorporation to as high as 95%. Regrettably, no reason was provided for this.

Sadjadi *et al.*[94] reported a practical and recyclable heterogeneous system for the synthesis of benzene-$d_6$ using commercially available 5 wt% Pt/C and $D_2O$ as the deuterium source (Scheme 13). The reaction was carried out in a reactor under 1 atm of $H_2$ at 180 °C, using 20 wt% Pt/C relative to benzene and a $D_2O$-to-benzene volumetric ratio of 34 : 1. Under these conditions, approximately 90% deuterium incorporation was achieved in a single 24 h run. Repeating the exchange for three consecutive cycles under identical conditions increased the level of deuteration to 99.6%. The catalyst could be readily recovered by simple filtration and reused; a recycled batch provided 87% deuterium incorporation, indicating good retention of catalytic activity after one reuse. The authors noted that the catalyst's recyclability justifies its relatively high cost. However, only a single recycle attempt was demonstrated, without detailed analysis of potential metal leaching or catalyst morphology after reuse, which falls short of the multi-cycle stability typically desirable for industrial applications. Additional reuse tests and post-reaction characterisation would further substantiate the claimed robustness. In comparison, the homogeneous $CF_3CO_2D$ protocol examined as a benchmark required ten days at 110 °C and a large excess of acid to achieve comparable isotopic purity, with limited opportunities for reagent recovery. Overall, Pt/C represents a cleaner, recyclable, and operationally simple option for H/D exchange using $D_2O$, though its long-term reusability remains to be more thoroughly validated.

Rhodium metal-based catalysts have also been reported in H/D exchange reactions. Asif *et al.*[95] reported an atomically dispersed Rh/$TiO_2$ catalyst for tandem hydrogenation and H/D exchange of cinnamic acid **43** using $D_2O$ (~500 equivalents)



Scheme 14 (a) One-pot tandem hydrogenation and H/D exchange of cinnamic acid catalysed by atomically dispersed Rh catalyst. (b) Catalyst recycling experiment for the conversion of **43** to **44**. Adapted from Asif *et al.*[95] licensed under CC BY 4.0. MDPI Copyright © 2025.



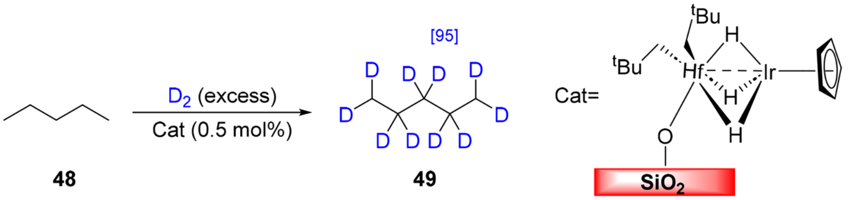
Scheme 15 (a) The synthesis of a deuterated analogue of cuspareine. (b) Recycling experiments of selective hydrogenation of quinoline **45**: (i) catalyst washing with heptane; (ii) catalyst washing with ethanol. Adapted from Zahedi *et al.*[96] licensed under CC BY 4.0. American Chemical Society Copyright © 2025.

as the D source, achieving exceptional D-incorporation (94% at the α- and 99% at the β-position, respectively) (Scheme 14), markedly outperforming Rh NPs (control study done on commercial sample) and homogeneous Rh complexes. The work elegantly demonstrated that single-atom catalysis, where Rh–O interfacial sites enabled otherwise challenging α-C–H activation. This indicates that the active single-atom configuration is metastable under the reaction conditions, compromising the practical reusability of the system. Mechanistic experiments revealed α-C–H activation as the rate-limiting step and underscoring the role of Rh–O interfacial coordination, yet the work lacks in-depth kinetic isotope or *in situ* spectroscopic evidence to substantiate the proposed pathway. Further, the study exposes key limitations regarding catalyst recyclability and structural robustness: while no Rh leaching was detected post catalysis, rapid aggregation of Rh single atoms into NPs during reuse led to a significant loss of α-deuteration efficiency (from 95% to 40% within two cycles as shown in Scheme 14c).

In a recent study, Zahedi *et al.*[96] reported hydrogenation of heteroarenes using ruthenium phosphide nanoparticles on imidazolium-based supported ionic liquid phases (SLIP), $Ru_{50}P_{50}$@SILP, as catalysts. Using the same catalyst, the authors reported the synthesis of a deuterated analogue of cuspareine, a natural tetrahydro-quinoline, in 98% yield, using $D_2$ as the deuterium source (Scheme 15a). The recyclability of $Ru_{50}P_{50}$@SILP catalyst was evaluated on batch-wise recycling using the hydrogenation of quinoline as a model reaction. The recyclability was demonstrated by washing $Ru_{50}P_{50}$@SILP catalyst using heptane and ethanol and recycled up to four and five cycles respectively as shown in Scheme 15b.

## 2.3. Bimetallic catalysts

Although heterogeneous catalysts are widely recognized for their ease of preparation and separation, they often encounter significant limitations such as slow reaction rates and low D source utilization, primarily due to multistep reactions.[97,98] To overcome these challenges and enhance catalytic performance, modulating the active centre of the catalyst presents a promising avenue for improvement, which can be achieved using heterobimetallic systems involving a combination of two transition metal atoms from opposite sides of the d-block within a single molecule. Such mixtures can lead to highly polarized metal–metal interactions, often resulting in asymmetrical

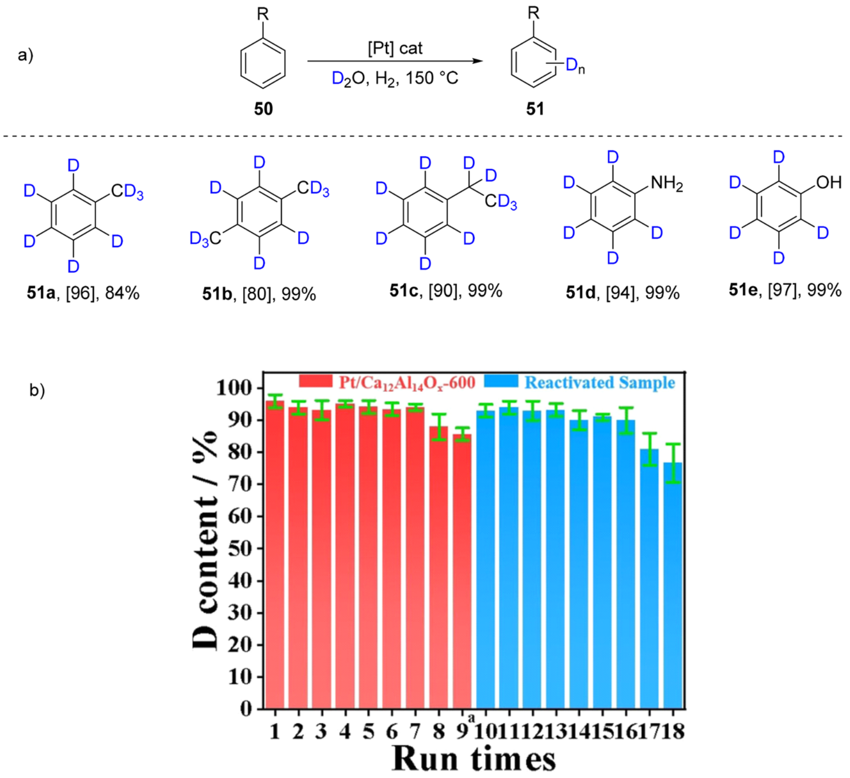


**Scheme 16** The reaction of *n*-pentane with $D_2$ in the presence of the catalysts (0.5 mol%) upon heating yielding deuteropentanes. Adapted from Pichugov *et al.*[100] licensed under CC BY 4.0. Wiley-VCH GmbH Copyright © 2024.

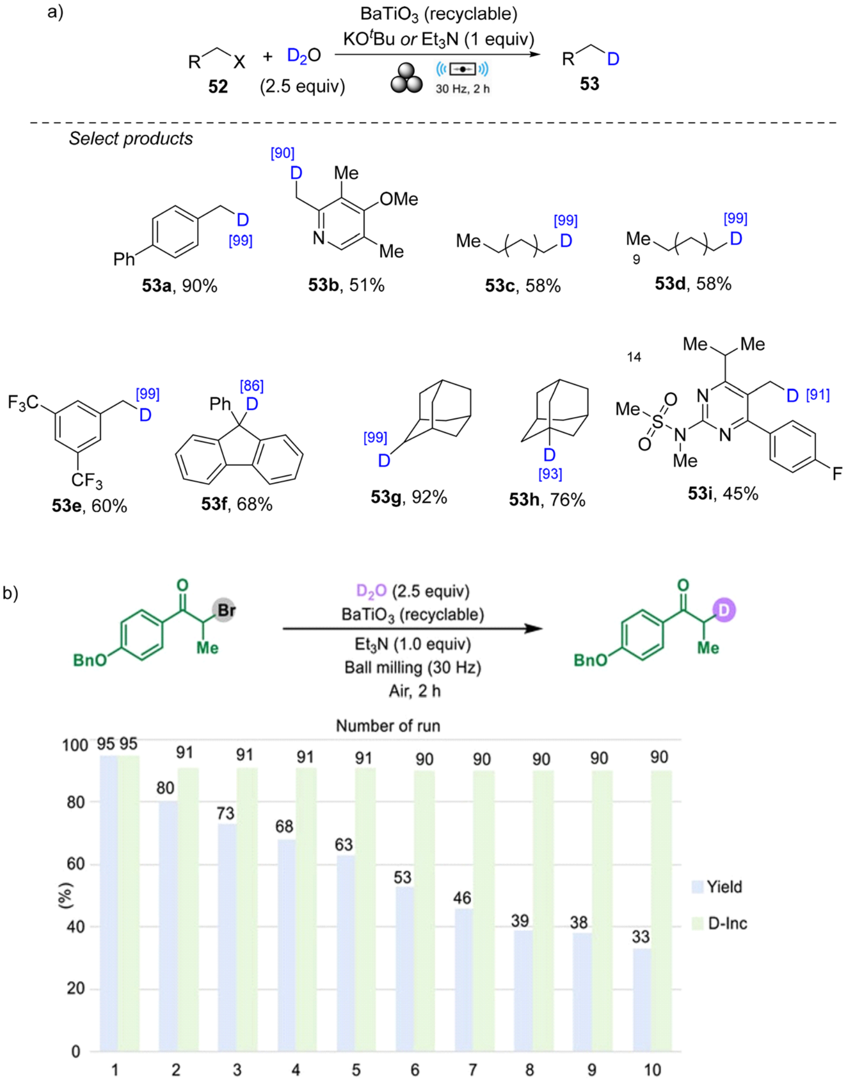
interactions with substrates, which can be harnessed to promote heterolytic cleavage of C–H bonds.[99]

Pichugov *et al.*[100] reported perdeuteration of *n*-pentane **48** *via* H/D exchange, catalysed by a silica-supported hafnium–iridium (Hf–Ir) bimetallic complex. The novel, well-defined, hafnium–iridium catalyst immobilized on silica was prepared *via* a surface organometallic chemistry approach featuring well-defined $[\cdots SiOHf(CH_2{}^tBu)_2(\mu\text{-}H)_3IrCp^*]$ surface site, which treats the surface of the catalyst support as a ligand and aims at directing its reactivity toward molecular precursors such as organometallic or coordination complexes.[101] The Hf–Ir analogue was highly efficient and selective for the perdeuteration of alkanes with $D_2$, exemplified using *n*-pentane (<2% at 95% conversion) (Scheme 16). The reaction proceeded without any substantial deuterogenolysis, as compared to the $SiO_2$ supported monometallic Hf and Ir catalysts, which promote *n*-pentane deuterogenolysis, under the same experimental conditions. The Hf–Ir/$SiO_2$ catalyst demonstrated notable robustness by maintaining a steady activity and selectivity over three consecutive catalytic runs. After each cycle, the gas phase was evacuated, fresh portions of *n*-pentane and $D_2$ were introduced into the reactor, and the reaction was conducted under identical experimental conditions, showing no degradation in performance. It would have been interesting to continue the recycling experiment until the catalyst showed signs of degradation/loss of activity.

Adopting a similar strategy, Pichugov *et al.*[102] reported deuteration of *n*-pentane using a silica-supported tantalum–cobalt heterobimetallic catalyst $[Ta(CH_2{}^tBu)_2(\mu\text{-}CH{}^tBu)_2CoCp^*]$. After each catalytic cycle, the gas phase was evacuated and fresh *n*-pentane and $D_2$ were introduced under identical reaction conditions (room temperature, <1 bar $D_2$, 1 mol% cat.). The catalyst retained the same activity across all runs (79% D incorporation after 3 h in the first cycle, compared to 75% and 72% in the second and third cycles, respectively).



**Scheme 17** (a) Deuteration of arenes using Pt catalyst under reaction condition: substrates (0.35 mmol), [Pt] catalyst (7 mol%), $D_2O$ (1.75 mL), $H_2$ at 150 °C for 4 h. The average percentage of D incorporation is given within square brackets, followed by the average yield. (b) Recycling experiment for hydrogen isotope exchange with toluene. Adapted from Jiang *et al.*[98] with permission from Wiley-VCH GmbH Copyright © 2023.



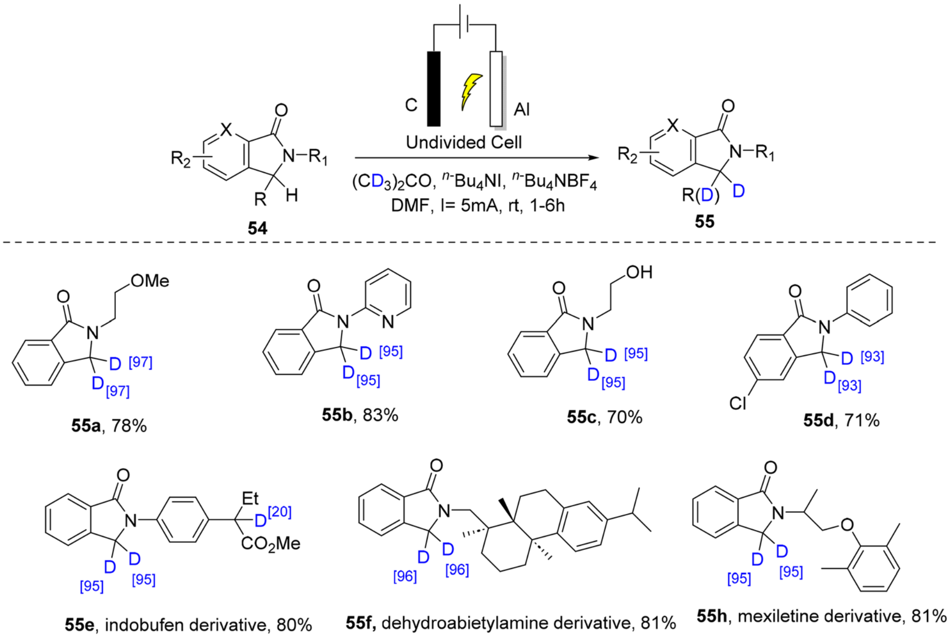
Scheme 18 (a) Select examples of substrates which could undergo mechanochemical dehalogenative deuteration. (b) Recycling experiments of $BaTiO_3$. Adapted from Qu *et al.*[103] licensed under CC BY 4.0 Wiley-VCH GmbH Copyright © 2025.

Jiang *et al.*[98] reported a calcium aluminate induced platinum system, which was used for H/D exchange reactions in arenes using deuterium oxide. A complex valence $Pt/Ca_{12}Al_{14}O_x$ catalyst was successfully developed for the deuteration of toluene and other arenes using cost-effective $D_2O$ as the source. A remarkably high deuteration efficiency with 96% deuteration of arenes was achieved within just 4 hours, 14% higher than the widely used Pt/C catalyst as shown in Scheme 17.

The catalyst can be reactivated and recycled, with the reactivation process though not a green technique, it involves calcination in air at 400 °C for 10 min, before cooling to r.t. in an inert atmosphere. The catalyst maintained its activity for up to nine cycles and was then reactivated to continue the reaction for another seven cycles (Scheme 17b). Various characterization techniques revealed that the interaction between Pt and $Ca_{12}Al_{14}O$ results in the co-existence of platinum in two different oxidation state, $Pt(\delta^+)$ and Pt(0), which work synergistically to promote oxidation and elimination reactions. This unique complex valence of Pt enhances the processes necessary for H/D exchange, significantly improving both the reaction rate and the stability of the hydrogen isotope exchange (HIE) system.

## 2.4. Piezoelectric catalysts

Qu *et al.*[103] developed a mechanochemical approach to the deuteration of both activated and unactivated alkyl halides **52** (X = Cl, Br, and I) using $D_2O$ as the D source and $BaTiO_3$ as the piezoelectric material (a substance that generates an electric charge when subjected to mechanical stress) (Scheme 18). This method facilitates the dehalogenative deuteration of a range of primary *e.g.*, **53a–e**, secondary (**53g**), and tertiary (**53f, 53h**) alkyl halides as well as drug molecule analogs *e.g.*, **50i**, a derivative of Rosusastatin calcium (commonly used to lower blood cholesterol levels), using only stoichiometric amounts of $D_2O$ (See select substrate scope, shown in Scheme 18a). The catalyst, $BaTiO_3$, could easily be recovered by a physical separation and then reused in nine subsequent experiments, as demonstrated



Scheme 19 Synthesis of deuterated isoindolinones 51, including late-stage modification of select pharmaceutical molecules. Adapted from Gao *et al.*[106] with permission from the Royal Society of Chemistry Copyright © 2023.

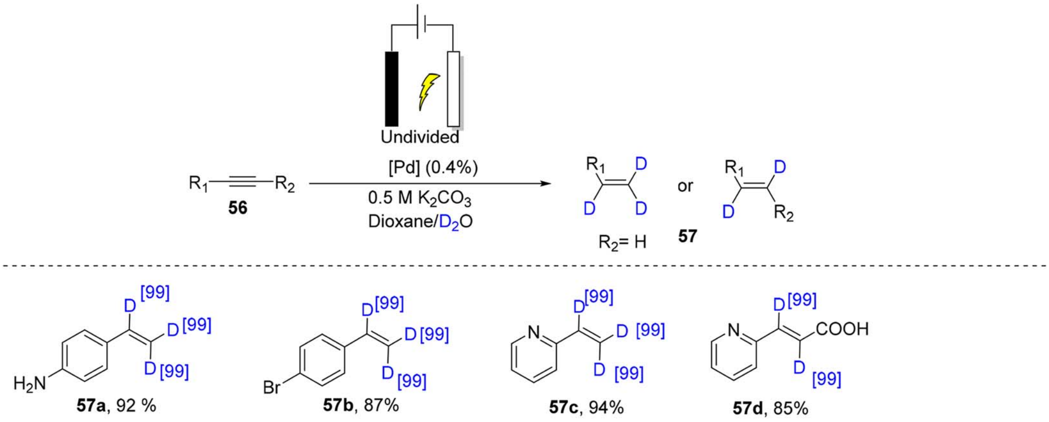
with 1-(4-(benzyloxy)phenyl)-2-bromopropan1-one (Scheme 18b). However, although the more important parameter, the % D, was maintained at a high level (91%), the yield dropped with each consecutive cycle, from 95% to 80% after the first reaction and then a drop to 33% by the 9th run.

### 2.5. Electrocatalysts

Electrochemistry represents an environmentally benign strategy in organic synthesis,[104,105] reliant on redox reactions using an electric current. Deuteration of organic compounds has been achieved using electrocatalysis. Gao *et al.*[106] reported the electroselective C($sp^3$)–H deuteration of isoindolinones **54** (the first deuteration of isoindolinones *via* H/D exchange). This electrochemical approach offered an efficient way to synthesize deuterated isoindolinones **55** under mild, neutral conditions. With a total of 39 substrates, the method delivered above 90% D incorporation including various pharmaceutical molecules (Scheme 19, **55a–d**). The electrochemical reactor was equipped with graphite rod as anode and aluminium or zinc rod as cathode, and $(CD_3)_2CO$ was used as the D source. Optimized reaction conditions (5 mA current at r.t.) enabled 96% D-incorporation with isoindolinone as the substrate. To demonstrate the synthetic utility of the methodology, the modification of pharmaceutical molecules was also reported, indobufen derivative **55e**, dehydroabietylamine derivative **55f**, mexiletine derivative **55h**, deacetyl linezolid derivative and cholesterol derivative were efficiently transformed into their deuterated forms.

Similarly, Wang *et al.*[107] reported the electrocatalytic alkyne semi-hydrogenation and deuteration of using a polyaniline-functionalized palladium catalyst (Pd/PANI) supported on nickel foam. The Pd/PANI was immobilized on nickel foam (NF) using a cyclic voltammetry electrodeposition process. The resulting $Pd_{0.3}$/PANI-NF materials demonstrated excellent selectivity and activity for electrocatalytic alkyne semi-hydrogenation (deuteration) reactions under ambient conditions: both terminal and internal alkynes **56** with various functional groups were efficiently converted into their corresponding alkenes **57** with yields up to 92%, using $D_2O$ as D source (Scheme 20). This was achieved with low Pd loading (0.4 mol%), while maintaining a high faradaic efficiency of 88%, meaning the electrocatalyst effectively utilized the electrons into the deuteration reaction with minimal wasted current. The catalyst also showed excellent stability, enabling six cycles under CF for gram-scale alkene synthesis (demonstrated only for hydrogenation). With TOF of up to 88 $h^{-1}$ and TONs exceeding 2100, this system outperformed previous reported non-recyclable catalysts.[108]

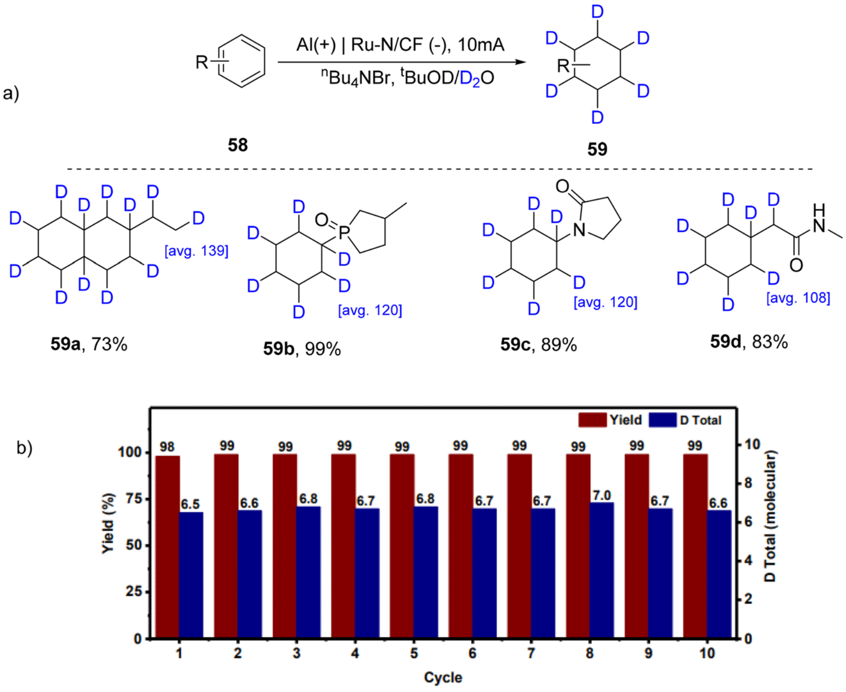
He *et al.*[109] reported a robust Cu–Pd bimetallic electrocatalytic system that address the persistent challenge of low faradaic efficiency (FE) in dehalogenative deuteration reactions due to the competitive $D_2$ evolution reaction (DER). A $CuPd_{0.52}$ nanowire array electrocatalysts was designed with forming positively charged Cu (denoted as $Cu^{\delta+}$) sites to enhance the adsorption and activation of aryl iodides, thereby improving mass transfer and reaction kinetics. Complementing the catalyst design, the study employed 18-crown-6 ether as an electrolyte additive to reconfigure the interfacial $D_2O$ environment. This dual strategy effectively promoted the selective generation of deuterated products by not only increasing substrate–catalyst interaction but also suppressing DER. Under optimized conditions ($-100$ mA $cm^{-2}$, 0.5 M $K_2CO_3$ in acetonitrile/$D_2O$ electrolyte), the system achieved an FE of 84% for the deuterodehalogenation of 4-iodoaniline, a significant improvement over conventional Cu-based catalysis.[110] The study further



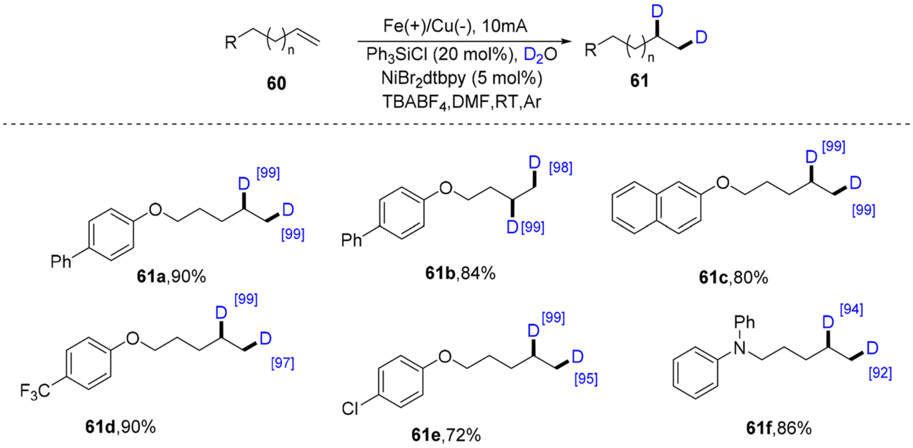
Scheme 20 Substrate scope for the electrocatalytic semi-deuteration of alkynes with $D_2O$ and $Pd_{0.3}$/PANI-NF catalyst. The percentage of D incorporation is given within square brackets, followed by the average yield. Adapted from Wang *et al.*[107] Licensed under CC BY 4.0 Elsevier Copyright © 2024.

explored the mechanism underlying the enhanced performance using *in situ* spectroscopies, DFT calculations, and electrochemical kinetics. The presence of $Cu^{\delta+}$ sites lowered the activation energy for C–I bond cleavage and facilitated substrate diffusion, while the crown ether disrupted the hydration shell of $K^+$ ions and modulated hydrogen bonding with interfacial $D_2O$, thus retarding water dissociation and DER. Although no long-term recyclability tests were explicitly presented, the system exhibited stable performance over multiple substrate types, including aryl bromides and alkyl chlorides, and tolerated reducible functional groups such as nitriles, alkynes, and carboxylic acids.

Bu *et al.*[111] reported a recyclable ruthenium (Ru) electrode for scalable reductive deuteration of (hetero)arenes and polyfluoroarenes. Utilizing $D_2O$ as the D source, the method enabled the preparation of over 120 selectively deuterated building blocks and 13 model drugs with excellent D incorporation (>92%). Preliminary tests were done with common heterogeneous catalysts (Pd/C, Ir/C, Pt/C, Rh/C, and Ru/C) for the reductive hydrogenation of 3,5-di-*tert*-butyl-1,1′-biphenyl using $H_2O$, and it resulted in minimal activity. In contrast, the nitrogen-doped Ru electrode (Ru-N/CF) achieved a 99% yield (Scheme 21a). Replacing $H_2O$ with $D_2O$ produced a deuterated product with 7.2 D atoms per molecule. Control experiments



Scheme 21 (a) Scalable reductive deuteration of (hetero)arenes and polyfluoroarenes using a recyclable Ru electrode. (b) Recycling experiment of electrochemical reductive deuteration of *N*-methylbenzamide to **59d** catalysed by Ru-N/CF. Adapted from Bu *et al.*[111] with permission from Springer Nature Copyright © 2024.



Scheme 22 Scope of electroreductive deuteration on unactivated alkenes, Adapted from Wang *et al.*[104] Licensed under CC BY 4.0 Springer Nature Copyright © 2024.

inferred that both N doping and Ru metal were essential for high reactivity, as alternatives like Ru/CF, N/CF, and other metal-doped electrodes (Pd-N/CF, Pt-N/CF, Rh-N/CF) showed little to no activity. This highlights the selectivity and efficiency of the Ru-N/CF electrode for reductive deuteration. The cell was equipped with a carbon felt anode and N doped carbon felt supported Ru cathode and $^{n}Bu_4NBr$, $^{n}Bu_4NCl$ and NaF were used as electrolytes in electrochemical reductive deuteration. The yield and total D number had almost no change up to ten cycles of arene electroreduction, which indicated that the catalytic activity of the Ru-N/CF was very stable (Scheme 21b). Further ICP-OES results also indicated that only a trace amount (0.006–0.128 ppm) of Ru leached after using different substrates and recycling experiments. To further demonstrate the utility of the electrocatalyst, the researchers undertook preparation of several existing deuterated drug molecules such as D-labelled hypoglycaemia drug glipizide, D-labelled expectorant bromhexine, D-labelled apixaban and D-labelled antithrombotic drug cilostazol, using standard reaction conditions.

Wang *et al.*[104] reported a simple electroreduction (deuteration) of unactivated alkenes **60** using $D_2O$ as D source. The electrocatalysis involved the use of a Fe as anode, Cu as cathode and with a constant current of 10 mA. Silicon derivative ($Ph_3SiCl$) was used as additive for the catalysis, the catalytic amounts of Si-additive work as a D-carrier from $D_2O$ to generate a highly active silane species *in situ* under CF electrochemical conditions, resulting in desired deuterated products in good yields with excellent D-incorporation (up to >99%) (Scheme 22).

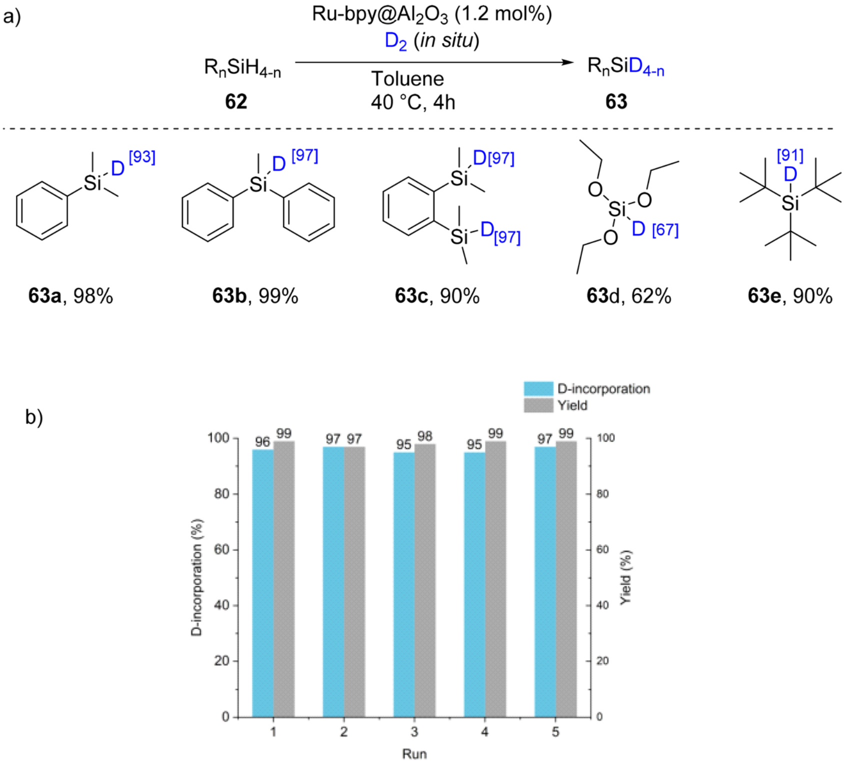
The notable highlights of this strategy include the use of a simple and low-cost catalytic amount of chlorosilane as a D-carrier in the reaction system, use of $D_2O$ as D-source, a low-cost Fe based electrocatalyst, high chemo- and regioselectivity, and the scope late-stage deuteration of naturally occurring compounds and drug derivatives. These findings underscore the practical viability of use of the organic electrocatalysis as an efficient and low-cost tool in the preparation of deuterated compounds, further extending its scope in the development of D-labelled pharmaceuticals.

In another study, Wang *et al.*[112] demonstrated the synthesis of deuterated silanes **62**, a versatile source of D for organic synthesis, using Ru NPs. In this study, an effective method for H/D exchange of silanes using Ru-bpy@γ-$Al_2O_3$ NPs was reported where $D_2$ gas, generated *in situ* from the electrolysis of $D_2O$, served as the D source (Scheme 23). The catalysts were successfully recovered from the reaction mixture by centrifuging. The recyclability tests were run on a model substrate and the yield **63a** and % deuteration remained consistently high at 99% and 97%, respectively, up to five cycles (Scheme 23b).

Bu *et al.*[113] developed an electrocatalytic system for alkene hydrogenation and deuteration employing Rh- and Ru-decorated nitrogen-doped graphite felt (NGF) electrodes, where $H_2O$ or $D_2O$ acts as the sole hydrogen/deuterium source. The process efficiently reduced a wide range of mono-, di-, tri-, and tetra-substituted alkenes—including bioactive and drug-like substrates—achieving high yields (>90%) and excellent D incorporation (70–95%) (Scheme 24). According to the proposed mechanism, the alkene **64** is first adsorbed on metal NPs I and generates intermediate II. Then, $D_2O$ is reduced on modified electrodes to form M–D species III. Next, the adsorbed alkene is reduced by M–D to produce C–M species IV, which is further reduced by another D* to produce the deuterated alkane b. Meanwhile, the oxygen evolution reaction (OER) occurs on the anode.

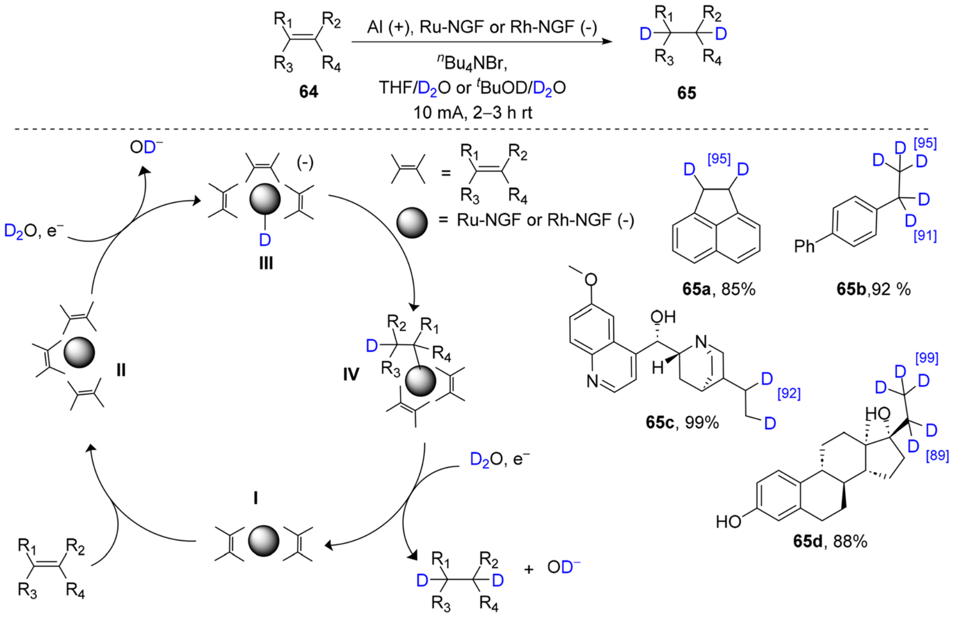
## 2.6. Photocatalysts and photoredox catalysts

Radical chemistry has made notable advancements in organic synthesis, extending up to isotope exchange organic transformations. Light assisted organic reactions are green, environmentally benign, and highly efficient. The photocatalyst (PC) and light source are the key components that facilitates these transformations by enabling efficient generation of reactive radical intermediates under mild conditions. Some recent organic transformation involving light assisted catalysis for deuteration of organic compounds are halogen exchanges, decarboxylation, synthesis of α-deuterated α-amino acid derivatives.

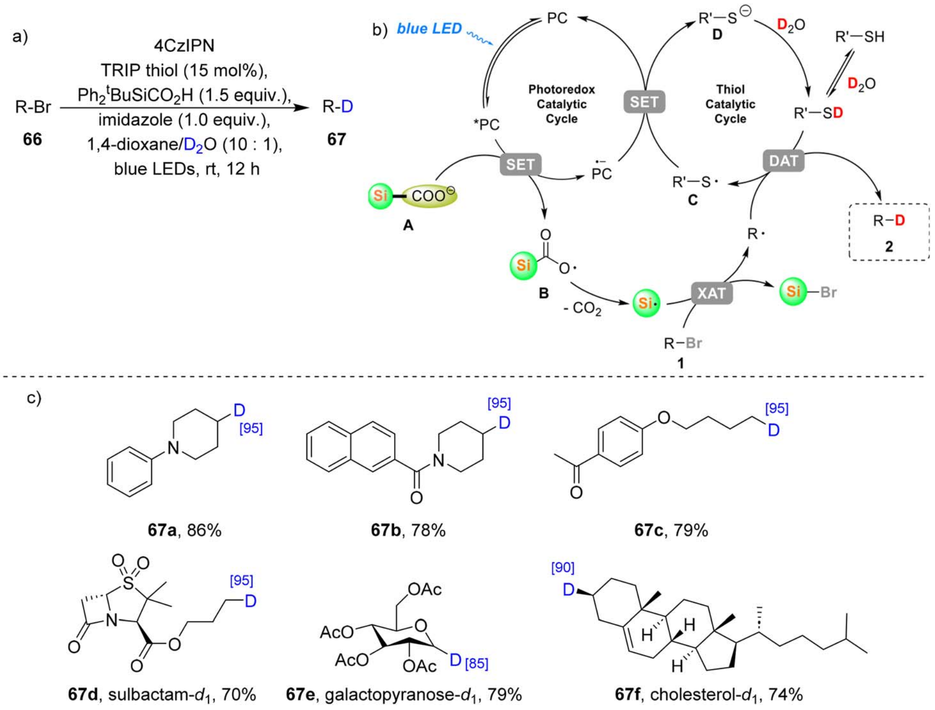


Scheme 23 (a) H/D exchange of silanes using Ru-bpy@γ-Al$_2$O$_3$ NPs. (b) Recyclability experiment on dimethyl phenyl silane to yield **63a**. Adapted from Wang *et al.*[112] with permission from the Royal Society of Chemistry Copyright © 2025.

Hu *et al.*[114] reported a visible light-assisted organo-photocatalytic approach for the dehalogenative deuteration of a wide variety of alkyl bromides **66** (Scheme 25a). Two primary mechanisms are involved in the dehalogenative deuteration (Scheme 25b): (1) firstly, a silyl radical-induced halogen atom transfer, followed by: (2) a thiol-facilitated D atom transfer. Silacarboxylic acids, which readily generate silyl radicals under visible light irradiation in the presence of a PC, were used as efficient halogen atom transfer reagents to cleave the C–Br bond of organic bromides due to the strong Si–Br bonds. The reaction condition involves 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene as the PC, TRIP thiol, Ph$_2{}^t$BuSiCO$_2$H,



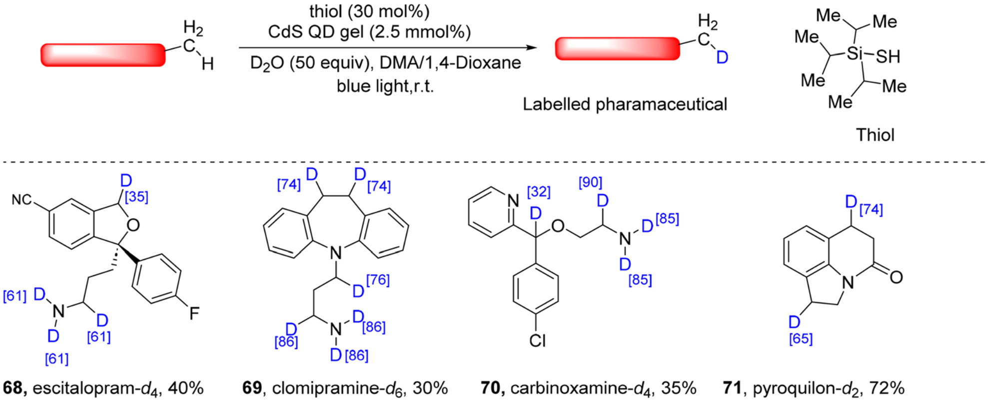
Scheme 24 Electrocatalytic deuteration (select example shown) and proposed mechanism, Adapted from Bu *et al.*[113] with permission from American Chemical Society Copyright © 2025.



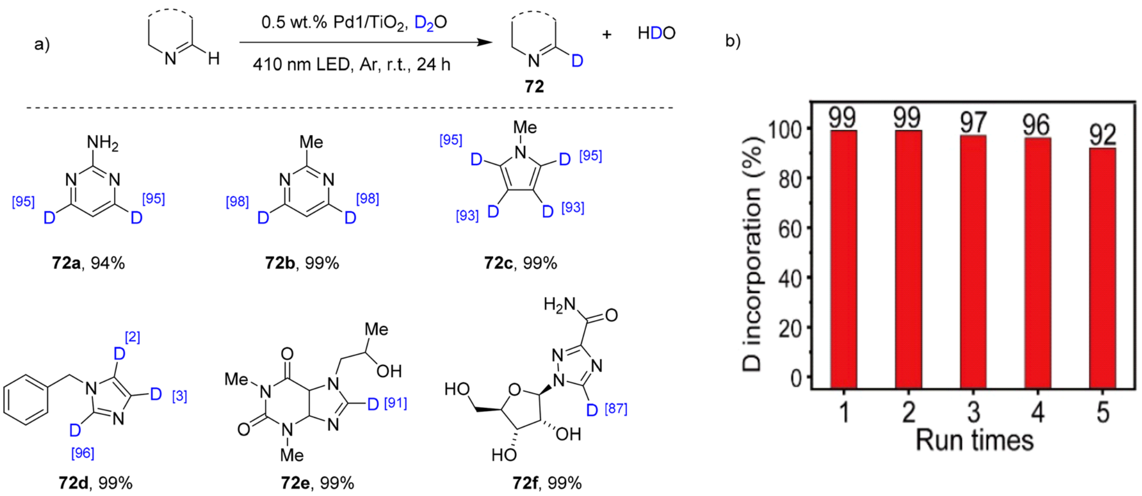
Scheme 25 (a) Visible-light-mediated dehalogenative deuteration of alkyl bromides **66** *via* an organo-photocatalytic approach. (b) Proposed mechanism for the dehalogenative deuteration. (c) Examples of substrates that can undergo this transformation. Adapted from Hu *et al.*[114] with permission from the Royal Society of Chemistry Copyright © 2024.

imidazole, 1,4-dioxane/$H_2O$ (solvent), under irradiation of blue LEDs. The generated carbon radical was deuterated with $D_2O$ *via* D-atom transfer in the presence of a thiol catalyst. Several bromo-substituted pharmaceutical derivatives were tested under the standard conditions for dehalogenative deuteration. For example, deuterated derivatives of cholesterol, sulbactam, glucopyranose, were achieved in good yields (70–79%) (Scheme 25c).

Maity *et al.*[115] recently reported H/D exchange in pharmaceutical compounds *via* a dual HIE pathway using CdS quantum dot (QD) as a heterogeneous PC. The dual pathway involves isotopic exchange both in solution and surface phase, making simultaneous multiple site hydrogen exchange on complex pharmaceuticals practical. In brief, the photoredox deuteration incorporation was conducted using deuterated thiol as hydrogen atom transfer catalyst, CdS as the PC, $D_2O$ as the D source and blue LED light source at r.t. (Scheme 26). The light on/off experiment showed that D-labelling increased only when the light was on, indicating that the HIE reaction is a light-driven process. The CdS gel QD photocatalytic systems involves two parallel HIE pathways: one in solution and the other on the catalyst surface, allowing simultaneous isotopic labelling at different molecular sites. In solution, photoexcitation of CdS generates radical intermediates *via* single-electron transfer (SET), which react with a solution-phase hydrogen atom transfer catalyst, such as deuterated thiols, for D transfer. Meanwhile, the CdS surface stabilizes radicals and adsorbed D atoms, facilitating



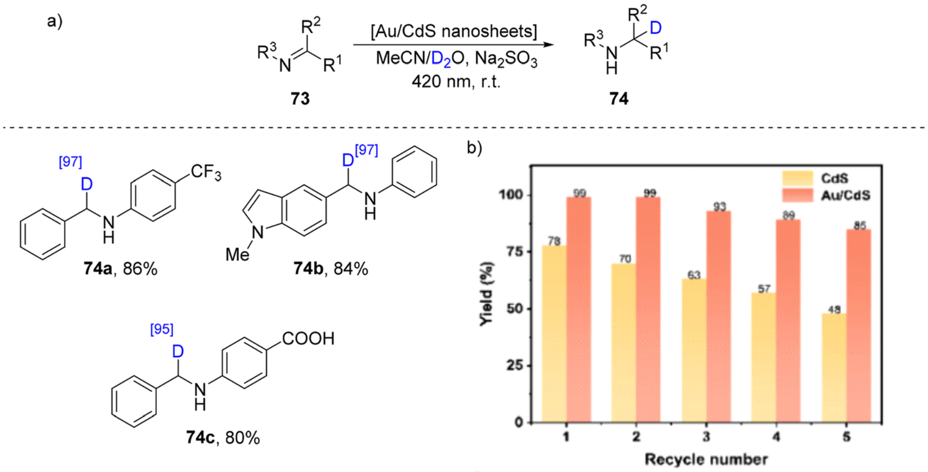
Scheme 26 Light driven H/D exchange transformation of pharmaceuticals using CdS QD gel. Adapted from Maity *et al.*[115] with permission from American Chemical Society Copyright © 2024.



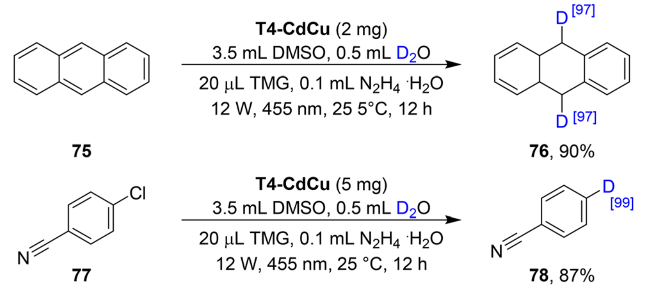
Scheme 27 (a) Photo-assisted H/D exchanges on N-heteroaromatic scaffolds using a Pd/$TiO_2$ photocatalyst. (b) Recyclability studies of $Pd_1/TiO_2$ using **72a** as a model substrate. Adapted from Xu *et al.*[116] with permission Springer Nature Copyright © 2026.

their transfer to surface-bound intermediates. These complementary pathways enable precise and efficient labelling of sites like benzylic and α-amino groups, while the CdS surface further stabilizes reactive intermediates such as secondary amines, cyclic ethers, and allylic or vinylic radicals, enhancing HIE reactions in the synthesis of deuterated pharmaceutical. The CdS catalysts were recovered and reused without change in morphology or catalytic activity up to three cycles.

Xu *et al.*[116] reported single atom photocatalysis for deuteration of N-heteroarenes. The heterogeneous catalysis was carried out using $Pd_1/TiO_2$ as the PC with $D_2O$ at r.t. under 410 nm irradiation and an inert atmosphere. Deuteration of 2-aminopyrimidine using heavy water was chosen as the model reaction to explore the photocatalytic deuteration using single atom palladium/$TiO_2$ denoted as $Pd_1/TiO_2$ in batch-mode autoclave photoreactors (Scheme 27a). The HIE selectively occurred at the $C(sp^2)$–H positions adjacent to heteroatoms of 2-aminopyrimidine based on $^1H$ NMR analysis. The control tests (not containing PC or Pd, not exposed to light, or in air) did not show any deuteration, which revealed that the deuteration of N-heteroarenes was intrinsically driven only *via* the single atom photocatalysis. External heating failed to initiate H/D reactions in the dark. The increased HDO (0.34 mmol) in $D_2O$ after photocatalysis confirmed that H/D exchange occurred between 2-aminopyrimidine and $D_2O$. Notably, $TiO_2$-PC with other PMs like Pt, Ru, Rh, Ir, or Au showed no activity. Similarly, various Pd-deposited semiconductors (*e.g.*, rutile $TiO_2$, $In_2O_3$, $Nb_2O_5$, $SrTiO_3$, SiC, BiOCl, $BiVO_4$, and $Bi_2WO_6$) and commercial 10 wt% Pd/C failed to drive deuteration under mild conditions. These findings suggest that single-atom Pd might serve as the key active site for photocatalytic HIE of N-heteroarenes in $D_2O$, rather than PM NPs. This protocol successfully afforded satisfactory deuteration of 46 N-heteroarenes. According to the mechanistic investigation it was found that the partially reduced single-atom Pd species, *in situ* generated under light irradiation, were active sites for photocatalytic HIE of the N-heteroaromatic substrates. Recyclability of the PC was achieved, on 2-aminopyrimidine substrate, by centrifuging the



Scheme 28 (a) Photo-assisted reduction C=N bond using Au/CdS nanosheets PC and (b) recycling experiment. Adapted from Wang *et al.*[117] with permission from American Chemical Society Copyright © 2025.



Scheme 29 Deuteration of substrates anthracene **75** and 4-chlorobenzonitrile **77** using the semiconductor cluster **T4-CdCu**. Adapted from Ma *et al.*[118] with permission from Wiley-VCH GmbH Copyright © 2025.

suspension to obtain the used PC which could be reused for three catalytic cycles with (99–97% of D incorporation) and loss of catalytic efficiency after 4/5th cycle D incorporation dropping down to 92% (Scheme 27b).

In another recent study, Wang *et al.*[117] reported recyclable Au/CdS nanosheets capable of catalysing the photoreductive deuteration of C=N bonds in **70** to prepare α-deuterated amines **71**, using $D_2O$ as the D source (Scheme 28a). The photocatalytic reaction demonstrated broad substrate scope which includes aliphatic aldimines, aromatic aldimines and ketimines. This approach leverages photocatalytic water splitting under mild conditions (r.t., 420 nm light, MeCN/$D_2O$ solvent mixture) to generate active D species (*D), which are then used to selectively reduce imines to α-deuterated amines. The Au/CdS nanosheets catalyst demonstrates significantly enhanced charge separation and transfer compared to pristine CdS, due to strong Au–S interactions that also suppress photo corrosion. This not only stabilizes the semiconductor structure but also improves photocatalytic performance. The recycling experiment (carried out using *N*-benzylideneaniline as the model compound) demonstrated that the Au/CdS catalyst not only increased reaction activity than CdS nanosheets but also retained its catalytic efficiency after five cycles (Scheme 28b).

Ma *et al.*[118] reported that a light-driven copper-based metal chalcogenide super-tetrahedral semiconductor cluster, ($[Cd_3CuIn_{16}S_{35}]^{15-}$ (**T4-CdCu**)), catalyses the dearomatization of nonactivated arenes and the reductive dehalogenation of challenging aryl/alkyl chlorides and aryl fluorides, as well as arylation and amination, under visible-light irradiation with high functional-group tolerance (Scheme 29). The catalyst also enabled deutero-reduction in D-labelling studies, reducing anthracene **75** to give a deuterated product in 90% yield with 97% D incorporation. In addition, it promoted the deuterohalogenation of 4-chlorobenzonitrile **77** to form benzonitrile-4-$d_1$ **78** in 87% yield with 99% D incorporation. However, the recyclability of catalysts was only demonstrated on a non-deuteration reaction. In brief, after the reaction, an equal volume of DCM was added to the reaction mixture and the **T4-CdCu** catalyst was precipitated while the reaction product remained in the supernatant. The supernatant was separated from the precipitate by centrifugation, then extracted with ethyl acetate and dried to obtain the reaction product. The precipitate was dried to recover **T4-CdCu**, which could be redispersed in $N_2H_4 \cdot H_2O$ for subsequent cycles under the same conditions.

Xu *et al.*[119] reported a deuterated reductive amination process based on thiol-mediated H/D exchange and $D_2O$ as both the reductant and deuteration source using a recyclable conjugated microporous polymer-based PC (Fig. 4).

In this case, the PC was a polymeric derivative of 4CzIPN, 4DPAIPN, or 5CzBN, prepared according to a procedure originally developed by Zhang *et al.*,[120] involving oxidative coupling polymerization of the carbazole–cyanobenzene monomers using $FeCl_3$ in trichloroethane. The mechanism of the photocatalytic deuteration (Fig. 4b and c), proceeded as follows: the radical $RS^\bullet$ is generated in the presence of the PC. The $RS^\bullet$ then reacts with formic acid salt *via* hydrogen atom transfer (HAT) to form $CO_2^{\bullet-}$ while regenerating thiol (RSH), which can then undergo H/D exchange with $D_2O$ to form RSD. Single-electron transfer (SET) occurs between $CO_2^{\bullet-}$ and imine ion (I) (formed from the amine substrate), resulting in the formation of radical (II) and $CO_2$. Subsequent D atom transfer (DAT) *via* RSD enables radical (II) to abstract a D atom, forming intermediate (III). This intermediate then undergoes HDE of its α-amino C–H bonds, ultimately yielding a multiply deuterated amine product.

The researchers demonstrated a broad substrate scope using this photocatalysis, and recyclability of the heterogeneous PC (Fig. 4d). The catalyst retained its activity (reaction yield and % D incorporation in subsequent substrates) over four cycles, although a slight decrease was observed. The stability of the PC was confirmed using Fourier transform infrared spectroscopy analysis before and after the reaction (Fig. 4e). This technique is not the most sensitive to changes in the solid state: perhaps X-ray powder diffraction would have been preferable. Additionally, the authors did not compare the TON or TOF of the polymeric PC with the homogeneous version, which would have provided useful information related to the activity of the catalyst.

## 3. Immobilized catalysts used in continuous flow chemistry systems

Continuous flow (CF) provides an efficient and scalable approach, also offering enhanced safety, productivity, and catalyst longevity compared to conventional batch processes. The effectiveness of these systems depends on the development of immobilized and recyclable catalytic beds that maintain activity and structural integrity during prolonged operation. Recent advances have focused on both supported metal catalysts and emerging metal-free porous materials, representing complementary strategies for robust flow deuteration.

There are several reports on the use of CF chemistry for deuteration reactions.[57,58,61,121] Recently, Minya *et al.*[122] reported the use of commercially available RANEY® (RaNi) catalyst for deuteration of N-heterocycles and pharmaceuticals *via* CF approach that boasts compatibility with a wide spectrum of N-heterocycles and pharmaceutical compounds. In brief the flow experiments were carried out in the HCube® Pro hydrogenation reactor, with $D_2O$ instead of $H_2O$, which could electrochemically

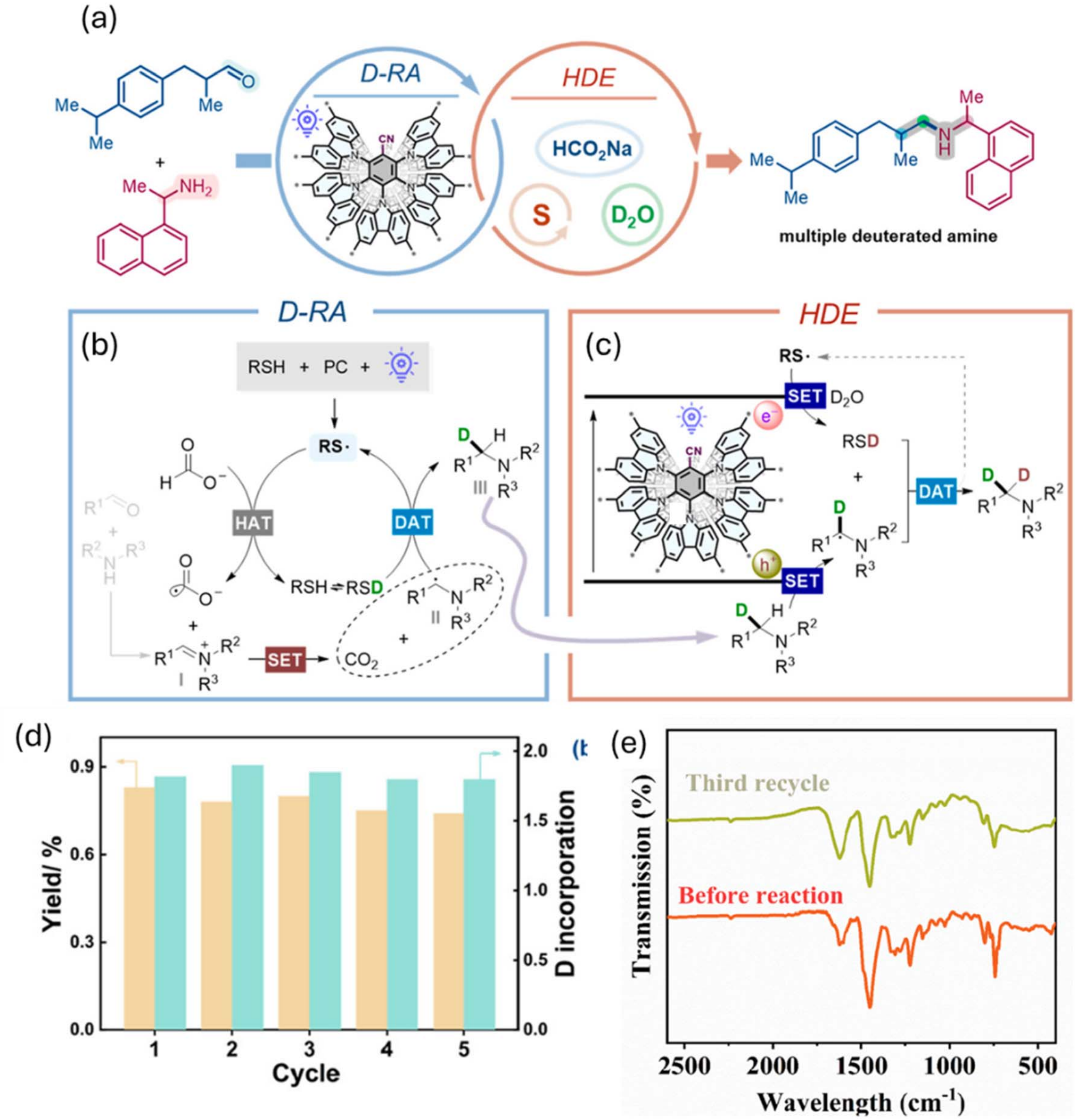
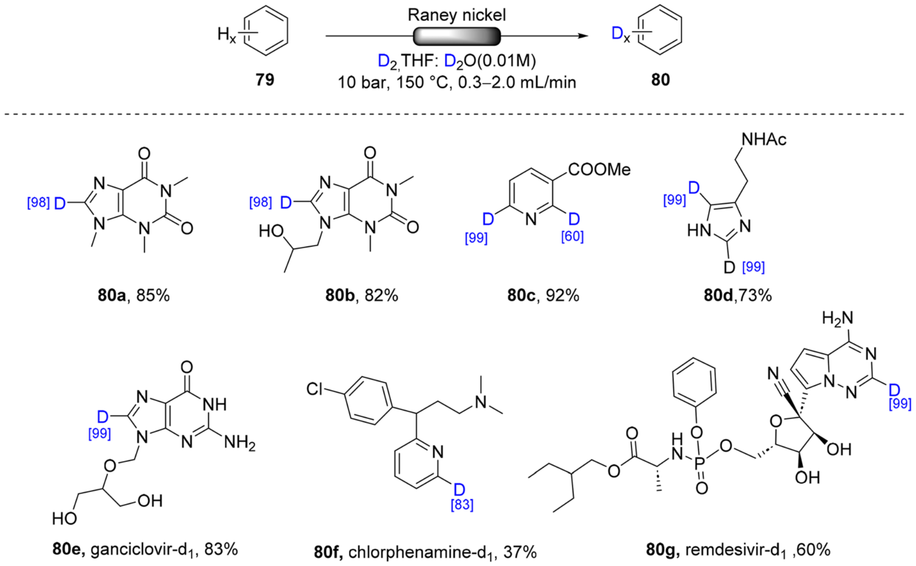


Fig. 4 (a) Schematic showing general photocatalysed RA for multiple deuteration of amines, while (b) and (c) show the proposed mechanism for the process (HDE = hydrogen–deuterium exchange). (d) Recycling experiments using *N*-benzylideneaniline as the model substrate. (e) FT-IR spectrum of PC (Poly-5CzBN) before and after the photocatalytic reaction. Adapted from Xu *et al.*[119] with permission from American Chemical Society Copyright © 2025.

generate $D_2$ gas for the HIE reactions. The reaction was conducted at 150 °C and a pressure of 10 bar, and the flow was maintained at 0.3–2.0 mL $min^{-1}$. A typical 30 mm cartridge contained around 490 mg RaNi. A single catalyst cartridge was used for the HIE of multiple substrates on a 0.3–2.1 mmol scale. After every cycle the RaNi catalyst was freshly pre-treated with caffeine. The deuteration was successfully demonstrated on several N-heterocycles such as purine and pyridine-type substrates, imidazoles, and pharmaceuticals. A few examples are shown in Scheme 30.

The control experiments with methyl imidazole carboxylate as a model substrate and utilizing 50 mol% RaNi, provided crucial insights into the role of RaNi and the reaction conditions in the H/D exchange process. Notably, the batch reactions yielded only monodeuterated products even after prolonged durations. The flow reaction achieved nearly twice the D incorporation in a much shorter timeframe, highlighting the kinetic advantages of CF systems (Scheme 30).

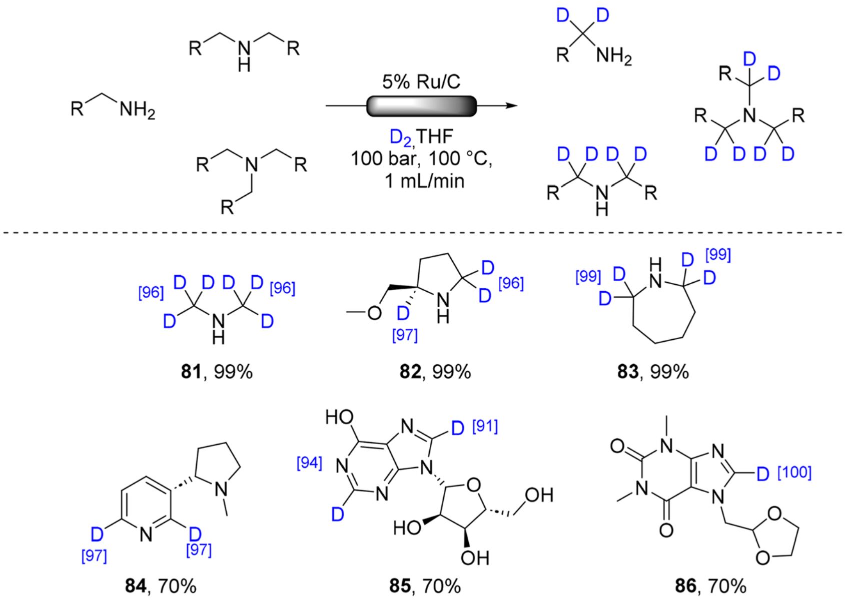
Ru-catalysed D-incorporation has also been reported. Sakurada *et al.*[124] reported a site- and stereo-selective D labelling protocol for carbohydrates using a Ru/C catalyst under continuous flow conditions. The D labelling efficiency was improved by increasing the void fraction within the catalyst cartridge used in the flow reactor, whilst maintaining high selectivity. In brief, the catalyst cartridge (*ø*: 3.0 mm, *L*: 200 mm) was packed with 130 mg of 10% Ru/C (no diluent). A solution of methyl-α-D-glucopyranoside in $D_2O$ (0.125 M) was introduced in up-flow at a flow rate of 0.05 mL $min^{-1}$, along with hydrogen gas at 0.8



Scheme 30 Deuteration of N-heterocycles using RaNi (using a CFR). Adapted from Minya *et al.*[122] with permission from Wiley-VCH GmbH Copyright © 2024.

mL min$^{-1}$. The reaction was carried out at 80 °C for 4 hours under CF conditions. Under optimized flow conditions, selective deuterium incorporation occurred at the C2, C3, C4, and C6 positions of methyl-α-D-glucopyranoside, yielding multi-deuterated methylglycoside-$d_5$ without cartridge clogging. Notably, the catalytic activity was sustained over 150 h of continuous deuteration of the carbohydrate, methyl-α-D-glucopyranoside, achieving >90% D incorporation for the tetraacetate derivative of methyl-α-D-glucopyranoside-$d_5$ and a TON of 1021 (Fig. 5). Compared with conventional batch processes, this approach offered significant benefits, including enhanced sustainability by reducing energy, chemicals, and minimal waste, whilst conserving Ru, a PM.

Tatoueix *et al.*[123] advanced CF H/D exchange by introducing an iterative recirculation strategy employing a commercial Ru/C catalyst packed in stainless-steel CatCart® cartridges within an H-Cube® reactor (Scheme 31). The H-Cube® instrument generates $D_2$ gas *in situ* by electrolysis of $D_2O$, ensuring safe operation without external gas cylinders, and is designed to enable reactions at elevated temperatures and pressures under precisely controlled flow conditions. The recirculation loop developed by the authors allowed repeated passage of the reaction mixture through the catalyst bed, thereby maximising isotopic



Scheme 31 Ru-catalysed flow deuteration of aliphatic amines and APIs. Adapted from Tatoueix *et al.*[123] Licensed under CC BY 4.0 Springer Nature Copyright © 2025.

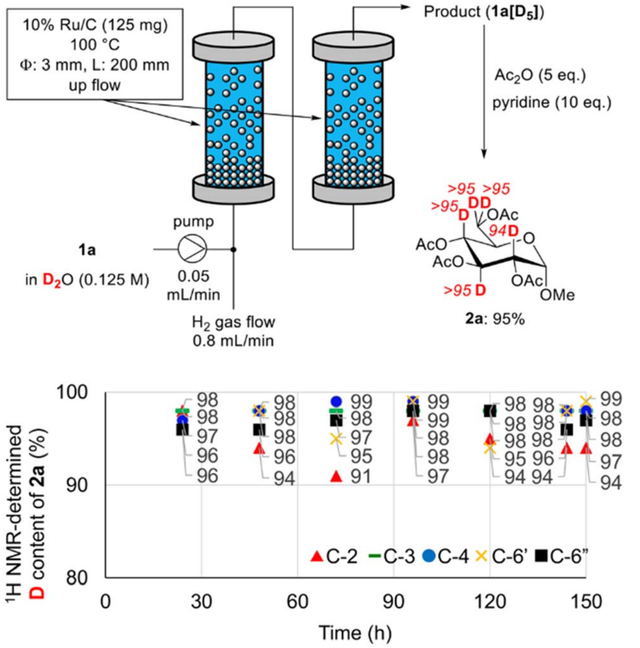
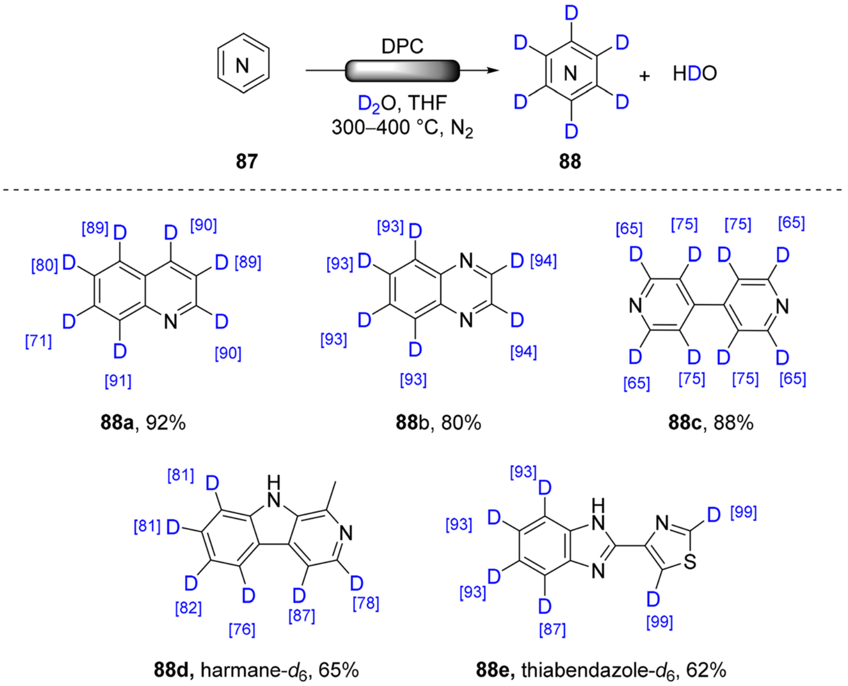


Fig. 5 Long run continuous flow deuteration of methyl-α-D-glucopyranoside **1a**. Adapted from Sakurada *et al.*[124] with permission from the Royal Society of Chemistry Copyright © 2025.

enrichment across all exchangeable positions. The reactions were performed mainly in THF, which provided good substrate solubility and compatibility with the flow system, while $D_2O$ served exclusively as the D source *via* electrolysis. Only when substrates were poorly soluble in THF was $D_2O$ used directly as the reaction (co)solvent. Under these conditions, a wide range of aliphatic amines, N-heterocycles, and active pharmaceutical ingredients (APIs) underwent efficient exchange, affording either selective α-deuteration or complete perdeuteration by adjusting the temperature (up to 100 °C) and pressure (up to 100 bar). Isotopic incorporations above 95% were routinely achieved in quantitative yields without the need for purification.

The Ru/C cartridge showed high robustness under flow conditions, retaining its activity over at least 15 successive cycles with no significant deactivation. When combined with the safe, on-demand generation of $D_2$ and the ability of the H-Cube® reactor to operate at elevated temperature and pressure, this highlights the suitability of immobilized Ru catalysts for isotope labelling in flow. The protocol was readily scalable, enabling the synthesis of azepane-d$_4$ on the gram scale (5.7 g, 98% yield) within six hours, corresponding to a productivity of 0.95 g h$^{-1}$ and substantially outperforming typical batch processes. The increased efficiency is attributed to enhanced mass transfer and continuous renewal of reactive $D_2$ under recirculating flow. Overall, Ru/C in continuous flow emerges as a durable and efficient platform for scalable H/D exchange with high isotopic fidelity and improved operational safety.

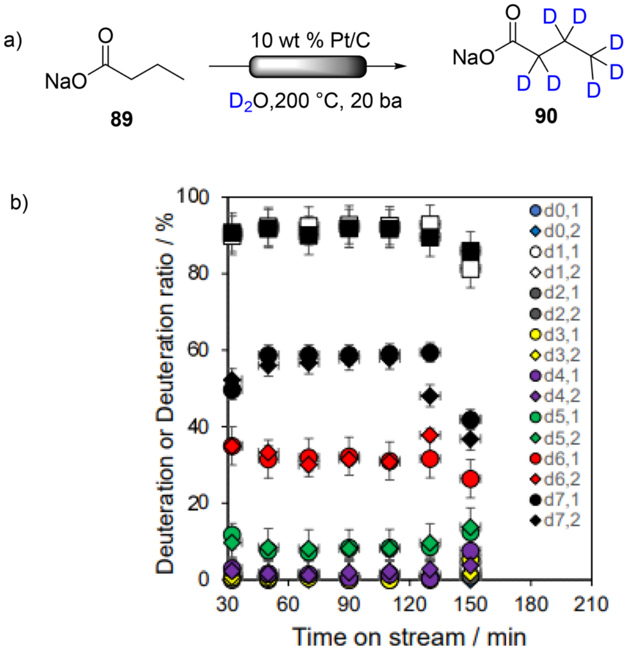
Complementary to the metal-supported systems described above, Gao *et al.*[125] demonstrated that high isotopic efficiency in flow can also be achieved using metal-free, defect-engineered catalysts. Their study introduced a defective porous carbon (DPC) framework derived from cellulose as a heterogeneous and stable platform for the perdeuteration of (hetero)arenes **87** using $D_2O$ as both solvent and isotopic source (Scheme 32). The catalyst – an oxygen-doped, vacancy-rich amorphous carbon with a high surface area (BET ≈ 1151 m$^2$ g$^{-1}$), was prepared by pyrolysis at 1000 °C and packed into a quartz flow reactor.



Scheme 32 Flow deuteration of heteroarene using porous carbon. Adapted from Gao *et al.*[125] with permission from Wiley-VCH GmbH Copyright © 2025.

Under an inert atmosphere at 400–450 °C, a broad range of aromatic and heteroaromatic substrates underwent efficient H/D exchange, typically achieving >95% D incorporation. Remarkably, sensitive functionalities such as halides and nitriles tolerated the harsh conditions. Notably, the protocol also proved compatible with pharmaceutical molecules including non-steroidal anti-inflammatory drugs and xanthine derivatives, highlighting the potential of the method for late-stage isotope labelling of drug-like scaffolds. The DPC bed operated continuously for over 50 hours with only modest activity loss (~10–20%) and was successfully scaled up to 95 g of perdeuterated product, demonstrating its mechanical integrity and resistance to fouling. Post-reaction analyses identified coke deposition and partial pore collapse as the main causes of mild deactivation, while spectroscopic and computational studies revealed that hole-type carbon defects adsorb $D_2O$ to generate reactive OD species mediating exchange *via* a cationic arene intermediate confined within the lattice.

Although discrete recycling cycles were not reported, the excellent CF stability and structural robustness of DPC position it as a sustainable alternative to metal-based catalysts. In contrast to Ru/C, the carbon material is inexpensive, non-toxic, and free from metal-leaching concerns, aligning with the broader movement towards greener isotope-labelling technologies. Together, the Ru/C and DPC systems exemplify the evolution of immobilized catalysts for flow H/D exchange – from durable, commercially accessible metal-supported platforms towards metal-free architectures that preserve high isotopic fidelity while advancing sustainability and cost-efficiency.



Scheme 33 (a) Deuteration of sodium butyrate under flow conditions. (b) Reproducibility of H/D exchange for sodium butyrate in continuous flow. Reaction conditions: 5 g sodium butyrate in 50 mL $D_2O$, $T = 220$ °C, $P = 20$ bar, 550 mg 10 wt% Pt/C. % D (white square), selectivity ($d_7$ – black, $d_6$ – red, $d_5$ – green, $d_4$ – purple, $d_3$ – yellow, $d_2$ – grey, $d_1$ – white, $d_0$ – blue). Adapted from Mensah *et al.*[126] licensed under CC BY 4.0 American Chemical Society Copyright © 2026.

Mensah *et al.*[126] reported the deuteration of sodium butyrate using platinum group metal as catalyst in continuous flow system. An optimized reaction condition of 10 wt% Pt/C achieved 93% deuterium incorporation and 98% isolated yield of sodium butyrate-$d_7$ in 90 min time-on-stream under $H_2$-free conditions (20 bar $D_2O$, 220 °C) in a single phase. While the flow deuteration afforded high selectivity to -$d_7$ (60%) and -$d_6$ (32%) isotopologues and favored the formation of thermodynamically stable isotopologues at elevated temperatures. The catalyst reusability tests were performed, after each reaction, the post-reaction catalyst was thermally activated *in situ* for 60 min at 220 °C. The observed deuterium incorporation levels and isotopologue formation were highly reproducible, exhibiting standard deviations of <±5% D across separate experimental runs as shown in Scheme 33.

## 4. Conclusions & future implications

In this work, we have reviewed recent literature (since June 2024) featuring recyclable and/or immobilized catalysts that have been investigated for the synthesis of deuterated organic compounds. These catalysts occurred in various forms: homogeneous and heterogeneous catalysts, bimetallic catalysts, electrocatalysts, photoredox catalysts, organocatalysts, and biocatalysts. Compared to our previous mini-review, only two papers reported the use of immobilized catalysts in CF chemistry systems. Additionally, over the past year, no examples of immobilized biocatalysts for deuteration were reported.

We also observed that only four reports included calculation and comparison of the TON/TOF of the recyclable catalyst with its non-recyclable counterpart (including the use of the catalyst in subsequent cycles). Similarly, there is no evidence to show the use of green metrics in demonstrating how the use of immobilized/recyclable catalysts shows an improvement in the environmental nature of the process compared to the status quo (in which the catalyst is not recycled).[127,128] We strongly recommend that researchers take these extra steps in analysis of their newly developed catalysts to go beyond the rhetoric and provide quantitative evidence for the advantages of their newly developed process.

We anticipate the following developments in this field:

- Immobilization of biocatalysts, considering the recent advances in the field.[129]
- The use of biopolymer-supported catalysts/biocatalysts (valorising biopolymers such as chitosan and lignin), yet to be demonstrated for deuteration reactions, whether in batch or flow.
- The use of 3D printing to create porous monoliths containing anchored catalysts for use in batch and CF reactors. Depending on the process used, it might be more economical to use an EA catalyst. For example, selective laser printing requires a large batch of powdered catalyst (>60 g, of which a % of this can be the actual catalyst) is required for the 3D printing,[130] whereas aerosol[131] and printing[132] is more suited to PM based catalysts as it requires far less material.

- Innovations enabling recycling of reagents and/or biocatalysts (including microbial and yeast cells) would enable greener and more efficient chemoenzymatic deuteration processes.[133,134]
- The use of magnetically recoverable catalysts for deuteration has not yet been explored, despite the potential for this in immobilization of metal NPs such as Ir NPs,[135] which would be useful considering their toxic nature but utility in selective H/D exchange.[136–138]
- New designs of Covalent Organic Frameworks (COFs) and metal Organic Frameworks (MOFs) (multivariate/tailored ligands) that both stabilize catalytically active sites and enable multiple reuse cycles,[139–141] including COFs/MOFs engineered for CFRs. Neither COFs nor MOFs have been explored as supports for catalysts enabling deuteration chemistry.
- The use of "click-heterogenisation" – covalent/orthogonal linking of homogeneous catalysts to solid supports as a strategy to heterogenise highly active homogeneous catalysts *e.g.*, Kerr's catalyst, *via* click-type chemistry so you retain activity while immobilizing the catalyst on the walls of a CFR.[142] Possible future avenues might include making the catalyst trivially separable and reusable from the support.[143,144]
- Currently, mainly heterogeneous EA SACs have been developed for deuteration (Section 2.2.1) with one example of a PM SAC (Pd SAC, see Section 2.2.2). We anticipate the development of PM SACs in the future.

In conclusion, we hope that this mini review will be both informative and instructive for practitioners of isotope labelling and catalysis (particularly those looking into the implementation of greener and more sustainable practice) as well as medicinal chemists and material scientists.

## Conflicts of interest

There are no conflicts to declare.

## Abbreviations

| | |
|---|---|
| CFR | Continuous flow reactor |
| D | Deuterium |
| DAT | D atom transfer |
| DER | $D_2$ evolution reaction |
| DPC | Defective porous carbon |
| EA | Earth abundant |
| EDS | Energy-dispersive X-ray spectroscopy |
| FDA | Food and Drug Administration |
| FE | Faradaic efficiency |
| H/D | Hydrogen/deuterium |
| HAT | Hydrogen atom transfer |
| HFIP | Hexafluoroisopropanol |
| HIE | Hydrogen isotope exchange |
| NGF | Nitrogen-doped graphite felt |
| NF | Nickel foam |
| NP | Nanoparticle |
| OER | Oxygen evolution reaction |
| OLEDs | Organic light-emitting diodes |
| PC | Photocatalyst |
| PM | Precious metal |
| QD | Quantum dot |
| SAC | Single atom-catalyst |
| SEM | Scanning electron microscopy |
| SET | Single-electron transfer |
| TON | Turnover number |
| TOF | Turnover frequency |
| WGSR | Water–gas shift reaction |

## Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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