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C–H deuteration of organic compounds and potential drug candidates

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C–H deuteration has been intricately developed to satisfy the urgent need for site-selectively deuterated organic frameworks. Deuteration has been primarily used to study kinetic isotope effects of reactions but recently its significance in pharmaceutical chemistry has been discovered. Deuterium labelled compounds have stolen the limelight since the inception of the first FDA-approved deuterated drug, for the treatment of chorea-associated Huntington's disease, and their pharmacological importance was realised by chemists, although surprisingly very late. Various approaches were developed to carry out site-selective deuteration. However, the most common and efficient method is hydrogen isotope exchange (HIE). This review summarises deuteration methods of various organic motifs containing C(sp^2)–H and C(sp^3)–H bonds utilizing C–H bond functionalisation as a key step along with a variety of catalysts, and exemplifies their biological relevance.

1. Introduction

Over the past few years, synthetic organic chemistry has seen a broadening of its horizons by the flourishing field of C–H activation. This tool has been frequently harnessed by chemists to carry out C–H bond functionalisation in a highly regioselective manner and promises to facilitate the incorporation of a plethora of elements into a C–H bond.[1] Most organic architectures contain such C–H bonds and their activation and functionalisation often yields fascinating results which serve as foundations for the development of natural products and pharmacophores. Recently, this unique strategy has been utilized to carry out site-selective deuterations of organic frameworks to satisfy the urgent need for deuterated compounds in the pharmaceutical industry.[2] Deuterium labelled compounds have stolen the limelight since the inception of the first FDA-approved deuterated drug, used to treat chorea-associated Huntington's disease,[3] and their pharmacological importance was realised by chemists, although surprisingly very late. C–H bonds are the Achilles heel of drug candidates and their enzymatic degradation has been a long-standing problem which reduces the circulation time of drugs *in vivo*.[4] One ingenious solution could be to deuterate the C–H bonds,

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Gaurav Prakash

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thereby increasing the bioavailability of the drugs and delaying possible metabolic degradation pathways. This pragmatic approach has been effectively used for the development of various deuterated pharmacophores for enhanced biostability and ameliorated pharmacokinetics.[5] Hitherto, aromatic systems and N-heterocycles have been exploited as major pharmacophores and deuterium incorporation is able to generate a myriad of lead compounds and drug targets.[6] Deuterium labelled compounds can be synthesized using classical transformations in multistep synthesis such as treatment with D_2 gas,[7] or reaction with a metal deuteride.[8] However, all these strategies require prefunctionalised starting materials. Thus, the labelling of these organic motifs by conventional means is often accompanied by the ramifications of superfluous reaction steps and poor atom economy. A possible alternative is direct hydrogen–deuterium exchange through late-stage functionalisation of the desired molecule.[9] C–H activation not only serves to eliminate this problem by carrying out these reactions in a single step with outstanding yields, but it also enables late-stage functionalisation of drug targets.[10] The past few decades have seen a tremendous amount of effort put into functionalising organic substrates ranging from simple amino acids to complex natural products, and C–H activation has been utilized to carry out the daunting task of selectively activating the desired position in a moiety containing multiple possible functionalisation sites.[11] Therefore, this strategy is unparalleled when it comes to functionalising complex medicinally important scaffolds with precision, accuracy and excellent yields. Synthetic organic chemists working on the development of organometallic catalysis have endowed the scientific community with a wide range of catalysts which can aid C–H bond functionalisation.[12] Several defunctionalisation strategies have been designed to carry out complex syntheses.[13] Hence, the nascent C–H deuteration techniques enjoy the presence of such pre-existing metal catalysts which allow C–D bond formation to be carried out simply and without the need to design novel catalysts. C–H functionalisation has proven to be highly effective in incorporating a myriad of functionalities and therefore is a suitable strategy for deuteration. Various natural products have also been found to have deuterium as a constituent and total synthesis of these compounds requires efficient chemical strategies for its incorporation.[14] Mechanistic studies of reaction pathways[15] and medicinal chemistry[16] are the key domains which demand deuterated compounds. Deuteration also plays a critical role in the characterisation of organic structures by spectroscopic techniques such as NMR, IR and mass spectroscopy.[17] This review showcases the chemical strategies that have been designed for the deuteration of various organic motifs. Numerous methodologies have been developed for isotopic exchange of aromatic, heteroaromatic, vinylic, allylic, and aliphatic protons among others. These efforts using homogenous and heterogeneous catalysis are summarised below.

Gwyndaf A. Oliver

Gwyndaf A. Oliver received his MChem in 2019 from Magdalen College, University of Oxford. He completed his Masters research under the supervision of Prof. Michael C. Willis working with SO_2 surrogates. In October 2019 he joined the group of Prof. Daniel B. Werz at TU Braunschweig as a PhD candidate focussing on synthetic methodology using donor-acceptor cyclopropanes.

2. C–H deuteration of arenes

Arenes are ubiquitous moieties in drugs, natural products, agrochemicals *etc.* Thus, formation of their deuterated analogues might enhance their chemical properties, half lives, and

Daniel B. Werz

Daniel B. Werz received his diploma (2000) and PhD (2003, R. Gleiter) from the University of Heidelberg supported by a scholarship (Studienstiftung des deutschen Volkes). After a postdoctoral stay at the ETH Zurich (P. H. Seeberger), he began his independent research at the University of Göttingen in 2006 (mentor of the habilitation: L. F. Tietze). In 2013 he was appointed as associate professor of organic chemistry at TU Braunschweig where he was promoted to full professor in 2018. His research interests include donor-acceptor cyclopropanes, Pd catalysis, carbohydrates and organic dyes.

Debabrata Maiti

Debabrata Maiti received his PhD from Johns Hopkins University (USA) in 2008 under the supervision of Prof. Kenneth D. Karlin. After postdoctoral studies at Massachusetts Institute of Technology (MIT) with Prof. Stephen L. Buchwald (2008–2010), he joined the Department of Chemistry at IIT Bombay in 2011. His research interests are focused on the development of new and sustainable synthetic and catalytic methods.

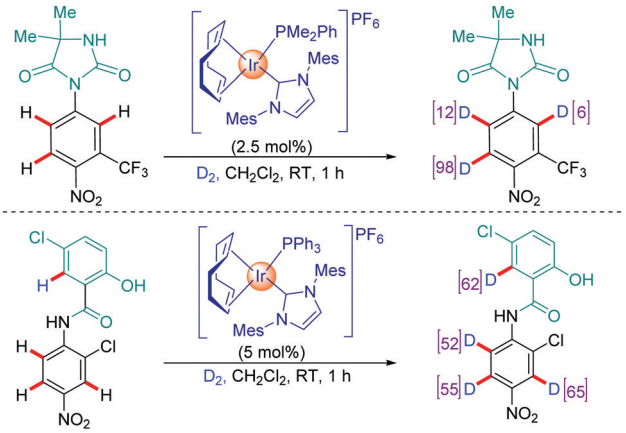
reduce their possible metabolic degradation. Scientists across the globe used various metals such as Ir, Pd, Rh, Ru, Co, and Ni for hydrogen isotope exchange (HIE) in arenes. Most widely used among these metals is iridium. Different positions of arenes were deuterated with good regioselectivity. *ortho*-C–H deuteration has been well explored over the years, however, *meta*- and *para*-C–H deuteration is underexplored.

2.1. *ortho*-C–H deuteration

Electron-donating substituents on arenes direct the electrophile to the *ortho*- and *para*-positions because of the positive mesomeric effect. However, there is always a compromise in selectivity *via* this approach; thus, a mixture of regioisomers is generated. A directing group approach solved this problem to a major extent. Directing groups such as pyridines, amides, and azoles, bind to the metal centre and deliver the metal to the vicinity of *ortho*-C–H bonds.[18] Subsequently, the metal functionalises the bond. Deuterium incorporations at the *ortho*-positions of arenes have been performed by various metals. Herein, we discuss deuterium incorporation in arenes by Ir, Pd, Rh, and Ru catalysis.

2.1.1 Ir-catalysed *ortho*-C(sp^2)–H deuteration. Iridium is the most versatile metal catalyst for HIE reactions (Fig. 1). Originally intended for the hydrogenation of olefinic double bonds, Crabtree's catalyst is by far the most used for HIE.[19] However, there are a number of factors which limit the use of Crabtree's catalyst. Dichloromethane (DCM) is the best suited solvent for this catalyst. Steric crowding in the vicinity of the target C–H bond prevents exchange. Inactive iridium dimers and trimers tend to form in solution when the complexation of the directing units is hampered. Some functional groups do not provide a good degree of exchange.

Additionally, to have efficient levels of exchange, a high loading of Crabtree's catalyst is often required to overcome unproductive competitive complexation arising from different functional groups present in the molecule. In 2010, Nilsson and Kerr synthesized a novel iridium catalyst decorated with both a novel phosphine and a bulky N-heterocyclic carbene (NHC) ligand, which delivered high levels of deuterium and tritium exchange in drug-like molecules.[20] The reaction conditions were mild and thus tolerated a range of functional groups. They performed isotopic labelling of niclosamide (Bayer AG antihelminthic agent) and nilutamide (Sanofi-Aventis anti-androgen) shown in Scheme 1.



Scheme 1 Ir-Catalysed deuterium exchange into drug-like molecules.

Peris and co-workers developed water-soluble Ir(III) NHC-based catalysts in 2011 and used them for the selective deuteration of aryl amines with D_2O (Scheme 2).[21] H/D exchanges are powerful processes to evaluate the potential of a catalyst for cleavage and formation of C–H bonds. D_2O is generally preferred as a deuterating agent over others due to its low cost and rather low toxicity.

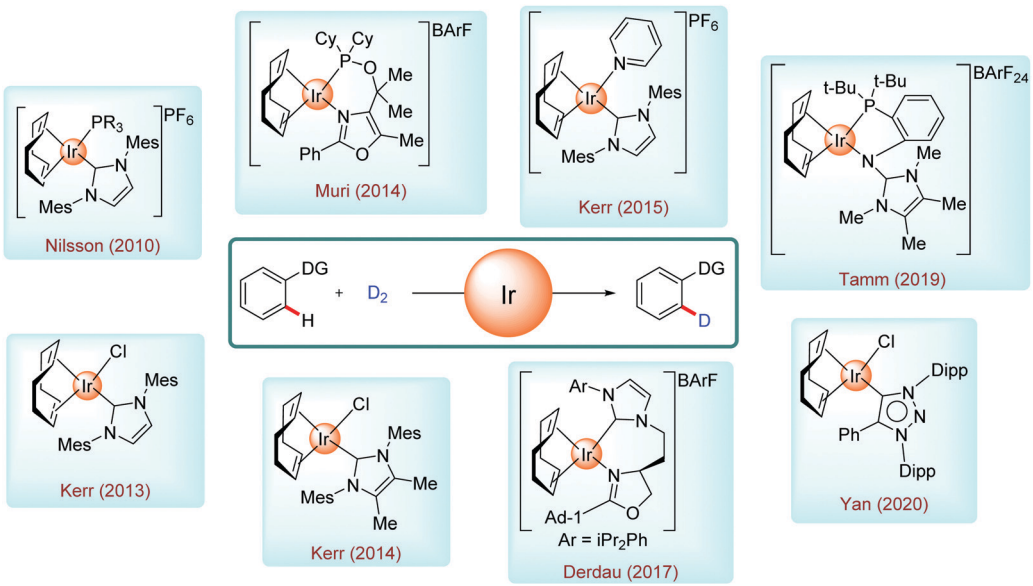
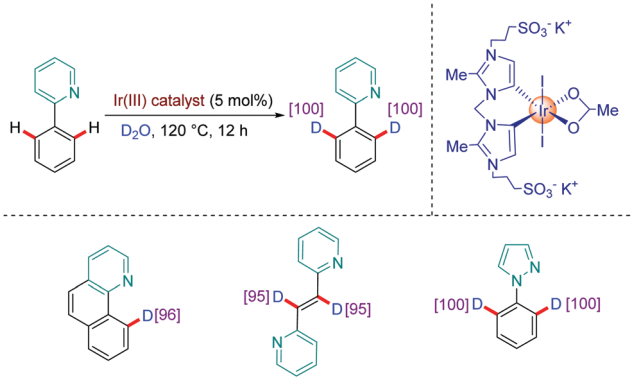
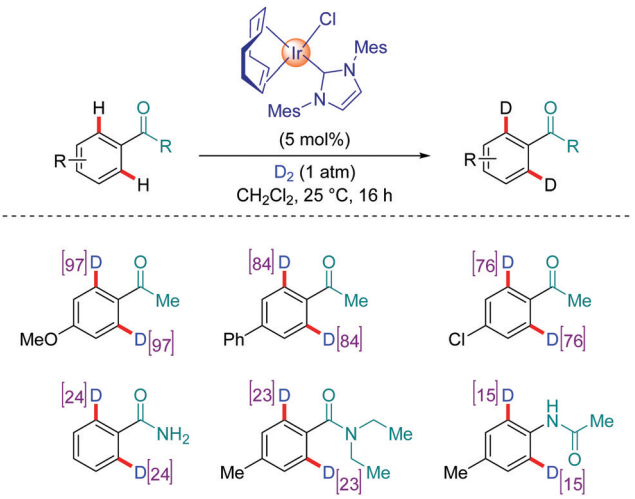


Fig. 1 Different Ir complexes developed over time for *ortho*-selective C–H deuterium labelling of arenes and heteroarenes.



Scheme 2 Deuteration of heterocycles containing arenes using an Ir(III) NHC catalyst.



Scheme 3 Ir-Catalysed deuteration of ketones and amides.

Notably, the reaction was carried out without the presence of any base or additive. Kerr and co-workers developed the NHC-phosphine based catalysts [(COD)Ir(NHC)Cl] for highly efficient *ortho*-directed HIE.[22] *ortho*-Deuteration of aryl ketones, amides and N-heterocyclic compounds were performed. This protocol makes use of deuterium gas as a deuterium source, DCM as solvent, and proceeds at room temperature. Aryl amides showed only a low degree of deuterium incorporation (Scheme 3). In 2014 the Muri group developed Ir-based complexes with different backbones and electronic properties for HIE reactions. Initially, they selected 15 chiral ligand systems containing both nitrogen (oxazoline, oxazole, imidazoline, or pyridine) and phosphorus moieties (diaryl or dialkyl phosphine or phosphinite). Among them, ThrePHOX, NeoPHOX, SimplePHOX and PHIM ligands were found to be the best choice for the catalyst, displaying good functional group tolerance and high proficiency (Fig. 2).[23]

A variety of substrates such as 2-phenylpyridine, acetophenone, acetanilide, and phenylbenzamide were chosen for *ortho*-directed HIE. High deuterium incorporation was observed in most of the tested substrates. Most of the Ir-catalysed HIE

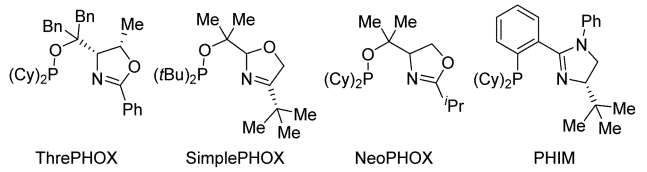
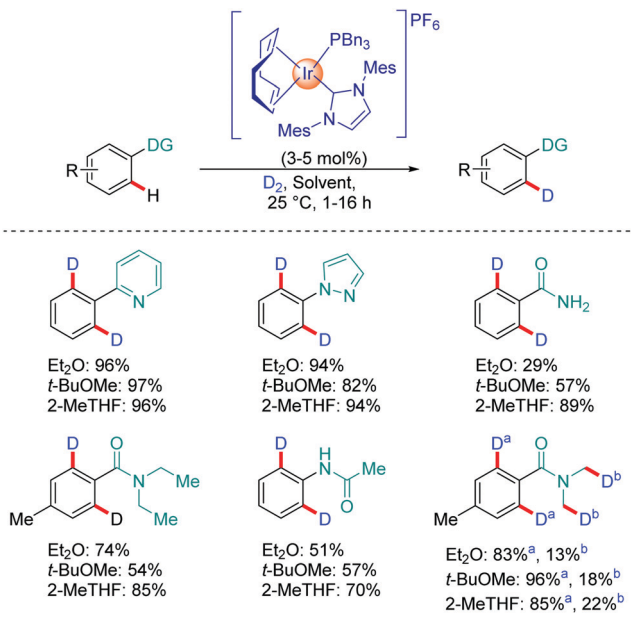
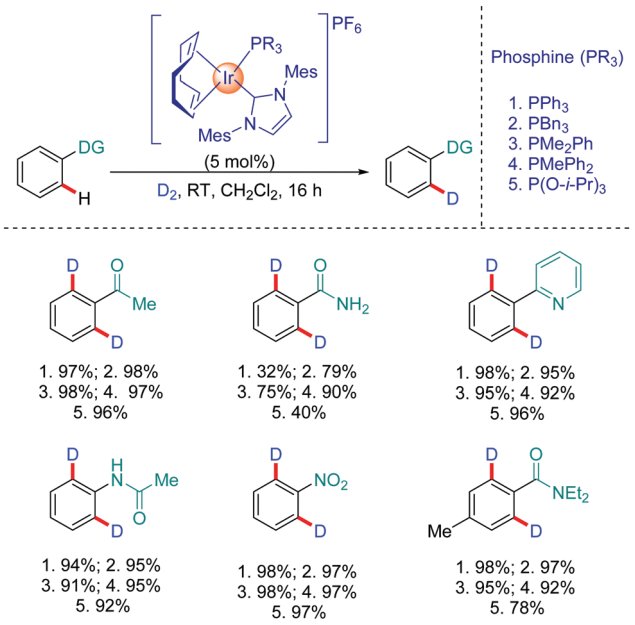


Fig. 2 Chiral ligand systems for high deuterium incorporation.

reactions occur in the presence of DCM as solvent. Since chlorinated solvents are undesirable from an industrial point of view because of hazards such as suspected carcinogenicity and high vaporisability, scientists searched for suitable replacements. In 2014, the Kerr group designed a method for *ortho*-C–H deuteration of arenes such as acetophenone, benzamide, and phenylpyridine using $[Ir(COD)(PBn_3)(IMes)]PF_6$ as catalyst (Scheme 4).[24] The reaction worked well in solvents such as Et_2O, ^{t}BuOMe, and 2-MeTHF. Isotopic labelling of niclosamide was successfully performed. They then calculated the binding enthalpies associated with solvent–Ir complexes in five different reaction media. The same group developed an alternate methodology for HIE processes by synthesising a series of NHC/phosphine-based Ir(I) complexes (Scheme 5).[25] Deuterium incorporation was performed in various substrates with low catalyst loadings and shorter reaction times. Moreover, DFT calculations were performed to find the possible reaction pathways. Mechanistic investigations suggested that the C–H activation process is the rate-determining step. The C–H activation step also determines the regioselectivity when there is the possibility of forming both five- and six-membered metallacycle intermediates. It was found that bulky groups on the Ir center provided excellent catalytic activity by preventing the formation of Ir clusters and restricting the catalyst to the active monomeric iridium species.



Scheme 4 Solvent effecting extent of deuterium incorporation.



Scheme 5 Effect of phosphine ligands on *ortho*-deuterium labelling of arenes.

Additionally, they performed tritiation of arenes which proceeded *via* a five-membered metallacycle intermediate. A plausible mechanism for the HIE reaction is shown in Scheme 6. Sulfonamide-containing drugs constitute a significant milestone in the generation of pharmaceuticals and have been developed to produce different antibiotics, diuretics, hypoglycemia and antihypertensive treatments since their emergence in 1935. Therefore, their deuterated analogues have been of great importance. In 2014, Kerr, Tuttle and co-workers synthesized a carbene-based iridium(I) chloride complex which acts as an active catalyst for the C–H activation.[26]

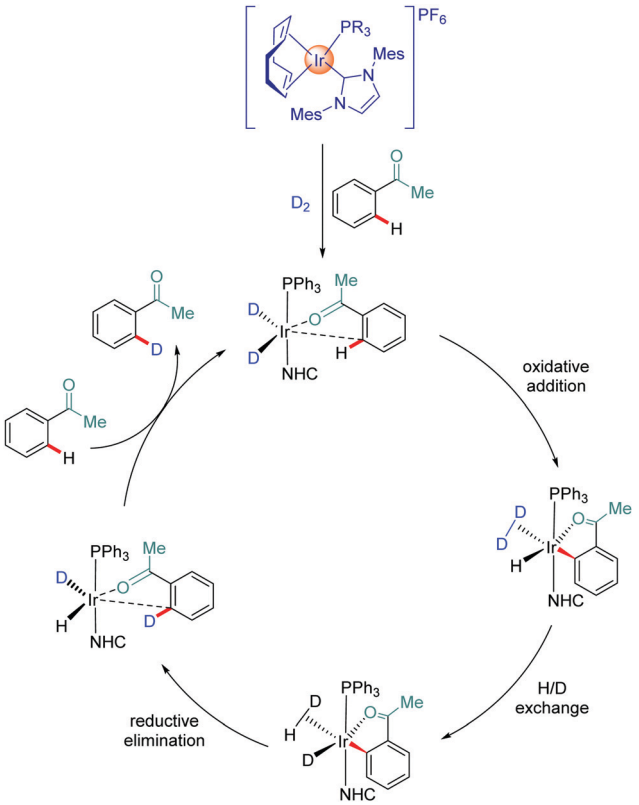
Labelling of primary sulfonamides was performed under mild reaction conditions (Scheme 7). A plausible catalytic cycle is depicted in Scheme 8.

Experiments revealed a primary kinetic isotope effect (KIE) with a value of approximately 3.2 demonstrating that the *ortho*-C–H bond activation is the rate-limiting step (Scheme 9).

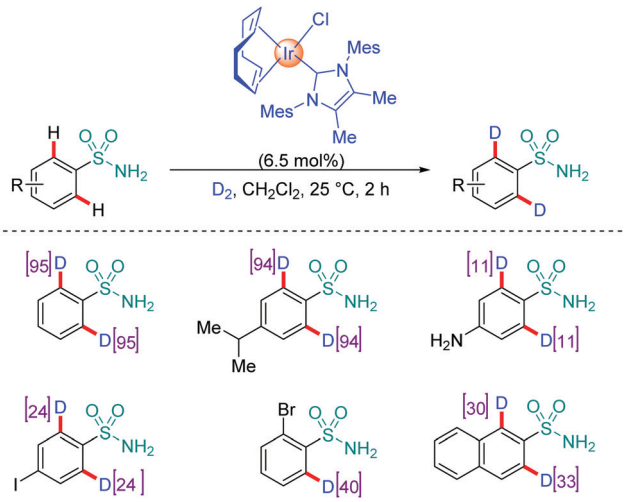
In particular, substrates with alkyl, halogen, methoxy, trifluoromethyl and naphthyl substituents at the *ortho*-, *meta*-, and *para*-positions were well tolerated. They also examined more complex drug molecules such as celecoxib and mavacoxib, which were first marketed as COX-2 inhibitors by Pfizer and achieved an impressive incorporation of deuterium.

Kerr and Derdau devised a methodology for the C–H deuteration of heteroaryl functionalised benzene derivatives under ambient conditions. The reaction occurred with 5 mol% catalyst loading, DCM as solvent and D_2 gas as the deuterium source at 25 °C (Scheme 10).[27] N-Heterocycles such as pyrimidine, imidazole, oxazoline, isoxazole, thiazole, benzimidazole, and benzothiazole containing pharmaceutical groups were deuterated with high levels of D-incorporation (Fig. 3).

The Kerr group designed the Ir complexes [(COD)Ir(NHC)(py)]PF_6 for the deuteration of ketone, amide, ester, pyrazole,

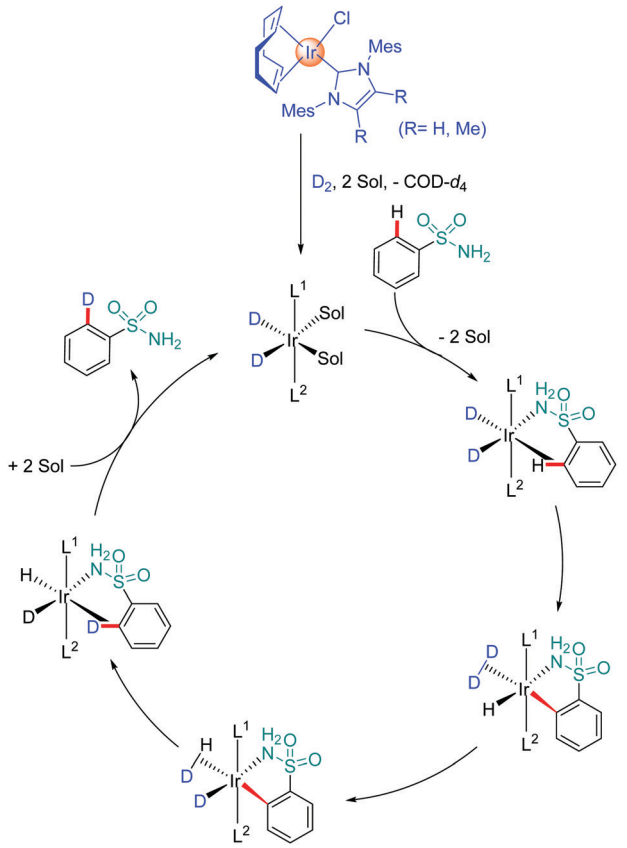


Scheme 6 Proposed catalytic cycle for the *ortho*-deuteration of arenes with an NHC/phosphine-based Ir(I) complex.

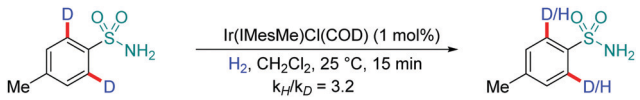


Scheme 7 Deuteration of sulfonamide derivatives.

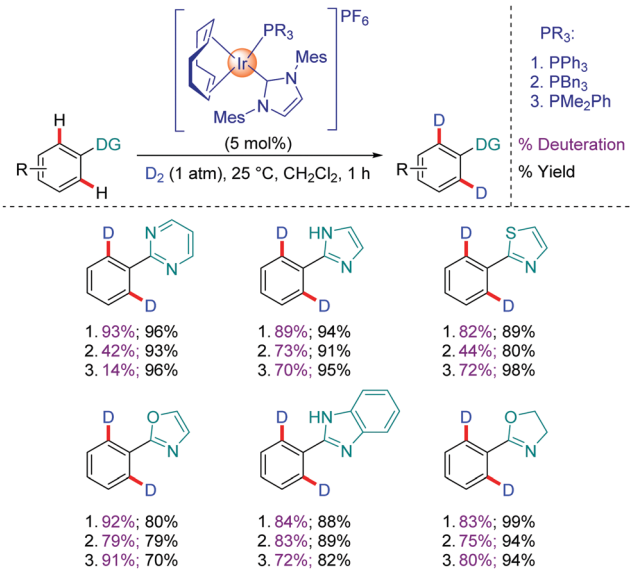
and imidazole containing arene systems (Scheme 11).[28] They synthesized three Ir catalysts by changing the substitution on the NHC group. The SIMes (R = 2,4,6-trimethylphenyl) substituted NHC catalyst was found to be the most versatile and provided a high degree of deuterium incorporation. Additionally, HIE of the pharmaceutical agent SR 121463 was demonstrated. Tetrazoles are a major azacyclic functional group in drug design and have been used successfully in a range of medical agents,



Scheme 8 Plausible mechanistic cycle for the *ortho*-deuteration of sulfonamides.



Scheme 9 Experiment to determine the kinetic isotope effect.



Scheme 10 N-Heterocycle assisted *ortho*-C–H deuteration of arenes.

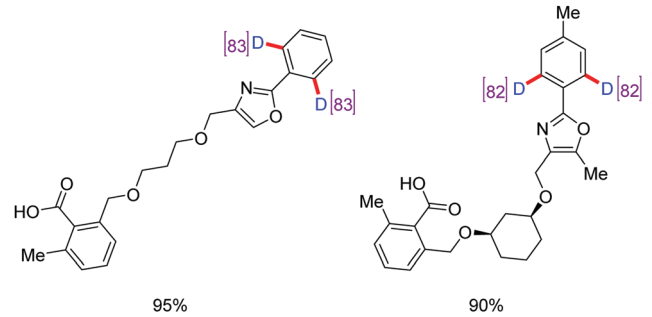
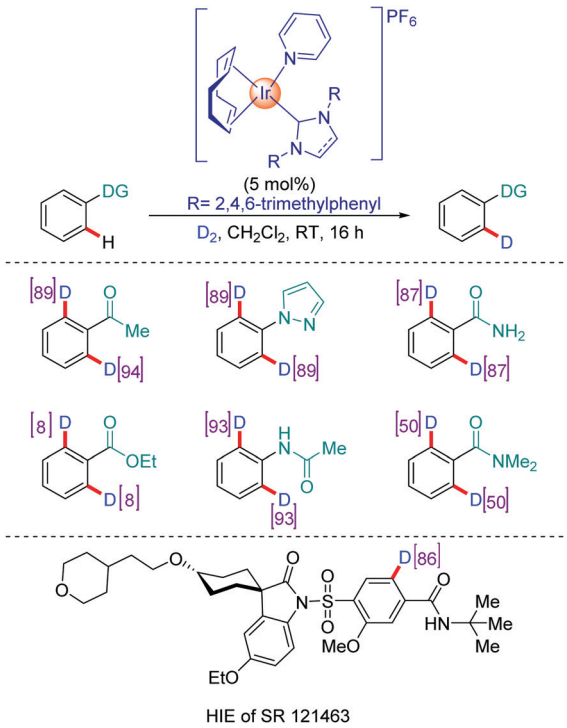


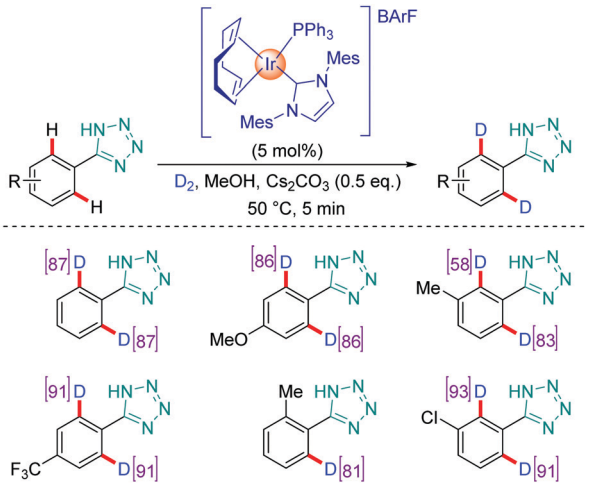
Fig. 3 Deuterium incorporation in drug-like heterocycles.



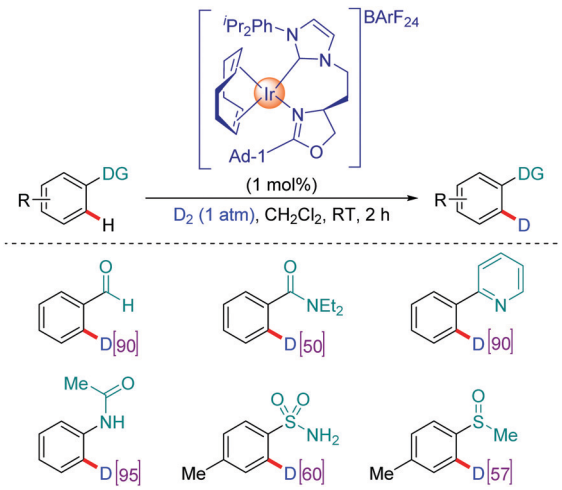
Scheme 11 Ketones, amides, and esters undergoing C–H deuteration.

including the sartan pharmaceutical class. In 2016, the Kerr group came up with a direct method for *ortho*-deuteration and -tritiation of pharmaceutically relevant unprotected aryl tetrazoles (Scheme 12).[29] Base was found to be crucial for the transformation. Mechanistic investigations supported a base-assisted concerted metalation deprotonation (CMD) type mechanism.

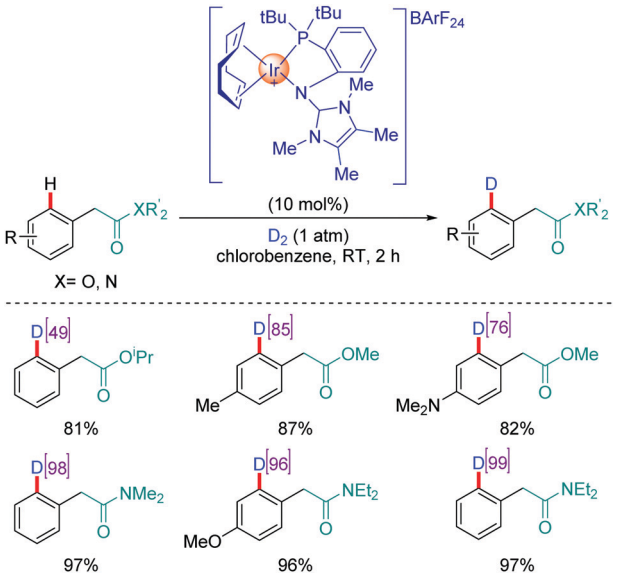
Most of the Ir catalysts known were monodentate Ir complexes limited to the deuteration of a particular type of substrates. Derdau and co-workers developed a bidentate Ir complex, Burgess' catalyst, which was used for selective *ortho*-deuteration of various types of arene containing moieties. Burgess' catalyst tolerated a wide range of functionalities such as ketones, imidazoles, aldehydes, pyridines, pyrazines and oxazoles affording deuterium incorporation of over 90% (Scheme 13).[30] This was also applicable for 2° and 3° sulfonamides and sulfonyl ureas. However, only moderate isotopic exchange occurred in substrates



Scheme 12 Tetrazole assisted *ortho*-C–H deuteration.



Scheme 13 *ortho*-C–H deuteration catalysed by Burgess' catalyst.



Scheme 14 Ir-Catalysed HIE in phenylacetic acid derivatives.

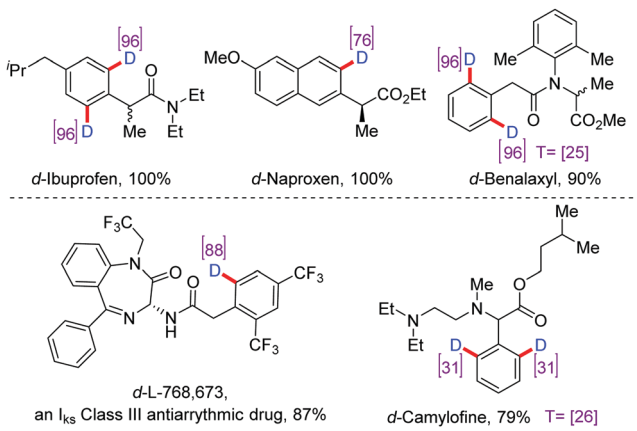


Fig. 4 Ir-Catalysed deuterium incorporation in drug molecules.

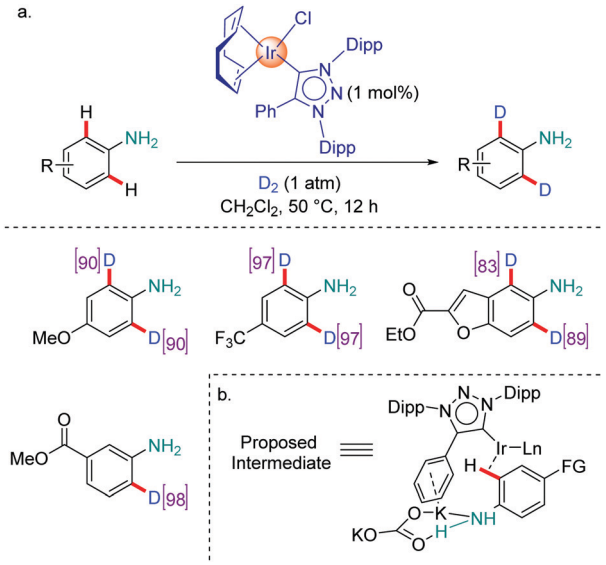
containing functional groups such as amines, amides, carboxylic acids, sulfoxides, and sulfones.

Derdau and Tamm were the first to perform Ir-catalysed HIE of phenylacetic acid derivatives under mild conditions (Scheme 14).[31] This was accomplished by using a bidentate phosphine-imidazolin-2-imine P,N ligand-based Ir complex. *ortho*-C–H deuteration of a series of phenylacetic acid esters was achieved in good yields with high selectivities. Similarly, for amide derivatives a high degree of deuterium incorporation was observed. Deuterium gas was used as the deuterium source and chlorobenzene as solvent.

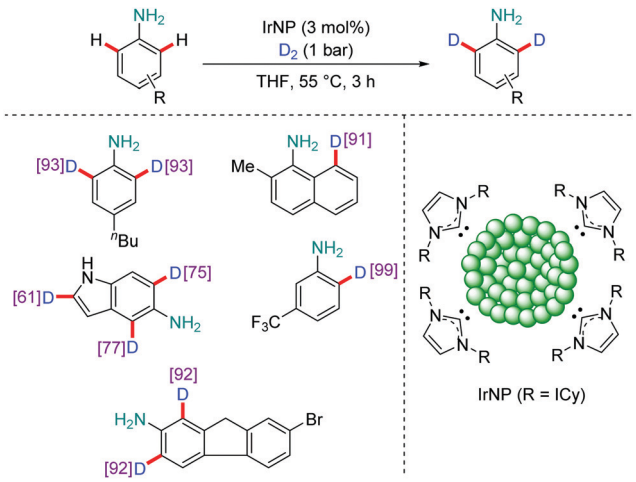
Furthermore, deuterium labelling was performed on drug molecules, namely ibuprofen (painkiller), naproxen (COX- and HSL-inhibitor), and camylofin (antimuscarinic), as well as the fungicide benalaxyl (Fig. 4). DFT studies suggested that a six-membered nonconjugated metallacycle is formed after *ortho*-C–H activation. Additionally, tritium labelling of Benalaxyl and Camylofin was demonstrated. Anilines are useful moieties in synthetic organic and pharmaceutical chemistry. So, in turn, deuterated anilines also attracted a lot of attention. Several groups tried to deuterate aniline derivatives but were only successful under harsh reaction conditions with poor selectivity.

Several transition metals such as Co, Ni, and Pt were evaluated, but resulted in poor deuterium incorporation. Due to the poor coordinating ability of the amino group to transition metals, *ortho*-C–H deuteration of anilines could not be achieved in the presence of other functionalities. In 2020, Yan and co-workers synthesized a mesoionic carbene (MIC)–Ir(I) complex which was used for *ortho*-C–H selective deuterium labelling of anilines with high deuterium incorporation (Scheme 15a).[32] Mesoionic carbenes enhance the σ-donating property of the ligand. This protocol was found to be superior for primary anilines whereas secondary and tertiary anilines resulted in low deuterium incorporation. It was proposed that the reaction proceeds *via* the metallacycle depicted in Scheme 15b.

Chaudret and co-workers demonstrated HIE reactions of anilines using NHC-stabilized Ir nanoparticles as catalyst



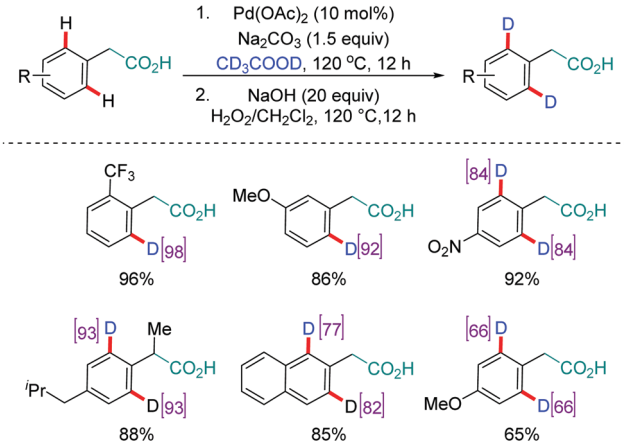
Scheme 15 Mesoionic carbene Ir(I) complex catalysed *ortho*-deuteration of anilines.



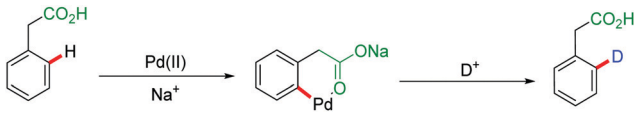
Scheme 16 Deuteration of anilines using NHC-stabilized Ir nanoparticles.

(Scheme 16).[33] These nanoparticles are air-stable, easy-to-handle, and show unique catalytic activity and efficient HIE of anilines using D_2 as a deuterium source. They also observed steric interactions as the major driving force for the Ir nanoparticle catalysed HIE reaction. Many functional groups such as halogens, phenols, esters, indoles and ketones were well tolerated without any influence on selectivity. This protocol was also effective on drugs, for example aminoglutethimide, sulfadimethoxine, and sulfamoxole, along with the sunscreening agent menthyl anthranilate, in which excellent selectivity and moderate to good HIE reactivity was observed.

2.1.2 Pd-catalysed *ortho*-C(sp^2)–H deuteration. Phenylacetic acid derivatives are prevalent in many medicinal molecules. Yu and co-workers devised a method for Pd-catalysed *ortho*-selective C–H deuteration of phenylacetic acid derivatives (Scheme 17).[34] Use of an inorganic base was crucial for this transformation which



Scheme 17 Pd-Catalysed *ortho*-deuteration of phenylacetic acids.

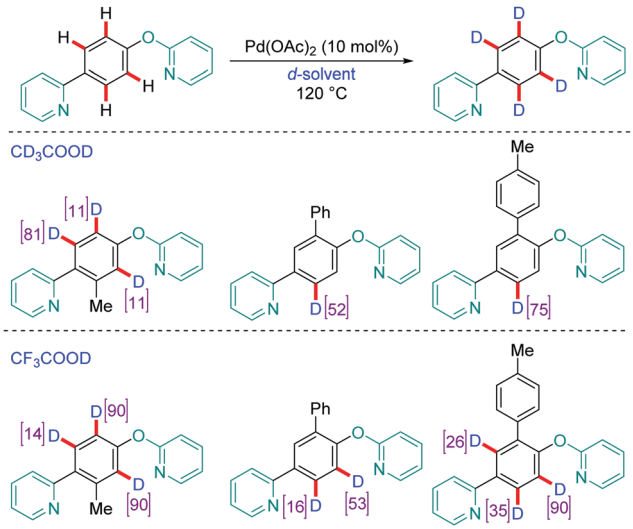


Scheme 18 Plausible catalytic cycle for the *ortho*-deuteration of phenylacetic acid and benzoic acid derivatives.

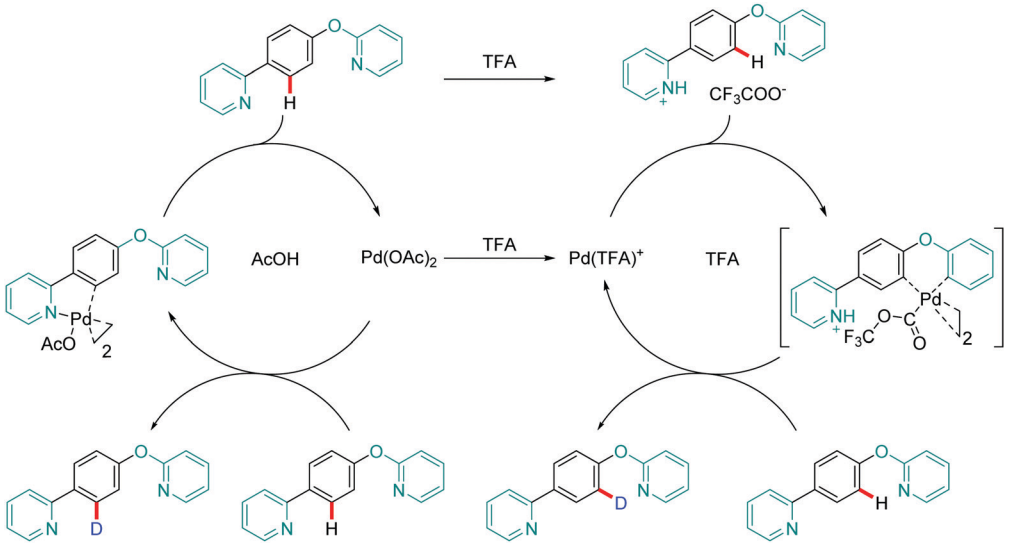
was consistent with previously reported reactions involving *ortho*-palladation of benzoic and phenylacetic acids.

The reaction proceeds *via* formation of an aryl–palladium(II) complex which reacts with the electrophile, D^+, generated from d_4-acetic acid, and forms the *ortho*-deuterated product (Scheme 18).

In 2018, the Liu group successfully demonstrated Brønsted acid-controlled regioselective Pd-catalysed C–H deuteration of molecules containing two pyridyl groups (Scheme 19).[35] Generally, N-heterocycles promote *ortho*-C–H activation *via* formation of five- and six-membered palladacycles through a



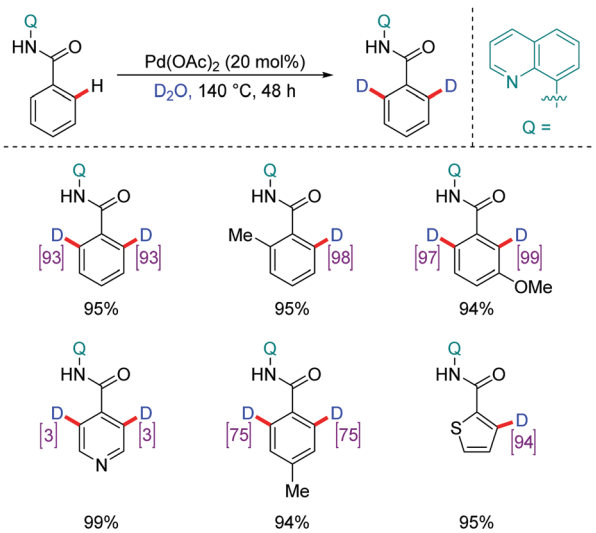
Scheme 19 Pd-Catalysed C–H deuteration of substrates containing two pyridyl groups.



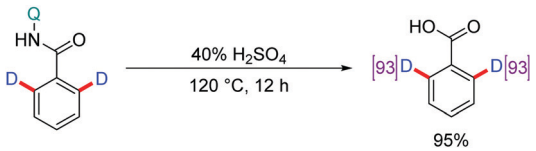
Scheme 20 Plausible catalytic cycle for the *ortho*- and *meta*-deuteration of molecules containing two pyridyl groups.

CMD mechanism. Both these intermediates have different reactivity profiles for any synthetic transformation. Utilizing this concept in their substrates containing two pyridine rings, where one is connected *via* an O-atom and can form a six-membered metallacycle, and the other pyridine ring is directly attached to the phenyl ring. Interestingly they found that by changing the acid used as a deuterium source, they were able to switch the selectivity. *ortho*-Deuterated molecules were synthesized by changing the deuterated solvent. The mechanism they elucidated is shown in Scheme 20.

Zhang, Yu, and co-workers synthesized *ortho*-selective deuterated aromatic acids through Pd-catalysed *ortho*-C–H deuteration using 8-aminoquinoline (8-AMQ) as the directing group and D_2O as deuterium source (Scheme 21).[36] 8-AMQ binds to the Pd centre in a bidentate fashion through both nitrogen atoms forming a five-membered metallacycle. Then, Pd(II)



Scheme 21 8-Aminoquinoline directed *ortho*-C–H deuteration.

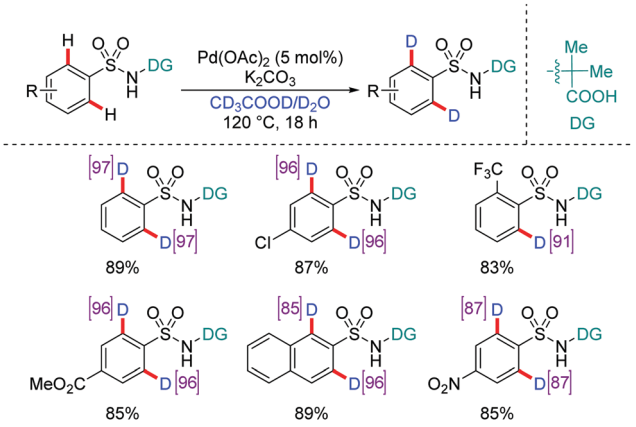


Scheme 22 Removal of aminoquinoline directing group.

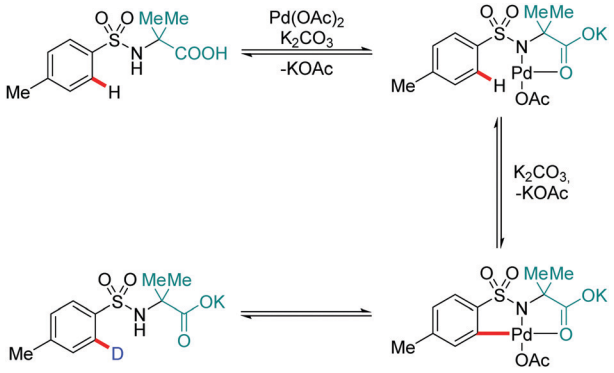
activates the C–H bond and subsequently H/D exchange takes place. However, the reaction conditions were not suitable for pyridine rings or nitro-containing benzamides. 8-AMQ can be cleaved and the corresponding *ortho*-deuterated benzoic acids were obtained (Scheme 22).

Ir catalysts such as Kerr's NHC catalyst, Burgess' catalyst, and Tamm's catalyst were reported for H/D exchange in sulfonamides through C–H activation, but these HIE processes have not been well explored in Pd catalysis. Ir catalysts do not perform well for substrates where competitive directing groups are present. In addition, Ir is quite expensive compared to Pd. Therefore, an alternative approach was required for site-selective deuteration of sulfonamides. In 2018, the Yan group published a method for *ortho*-selective deuterium incorporation in sulfonamides using amino acids as weakly coordinating directing groups (Scheme 23).[37]

Different functional groups containing arene substrates were well tolerated under the reaction conditions. The chelating coordination of palladium with an N–O auxiliary was responsible for the selectivity. Carbonate base (K_2CO_3) was also required; this fact suggests that a small amount of water being generated as a byproduct in the reaction between acetic acid and carbonate promotes the reaction. This in turn is also supported by the observation that the use of 3 Å molecular sieves leads to a drastic decrease in deuterium incorporation. Both electron-donating and -withdrawing groups were found to be well tolerated under the given reaction conditions. Mechanistic studies suggested that the reaction proceeds by formation of a



Scheme 23 Pd-catalysed *ortho*-C–H deuteration of sulfonamides.



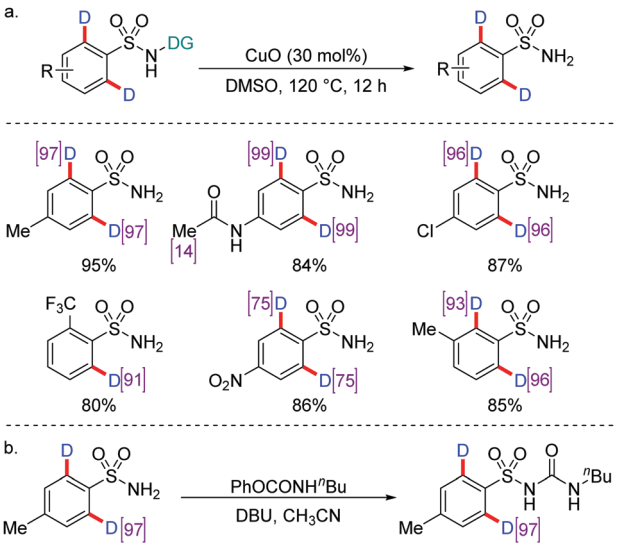
Scheme 24 Possible reaction mechanism for the *ortho*-deuteration of sulfonamide derivatives.

five-membered palladacycle *via* coordination to N and O atoms, then C–H activation takes place and subsequent depalladation by CD_3COOD affords the deuterium labelled sulfonamide (Scheme 24).

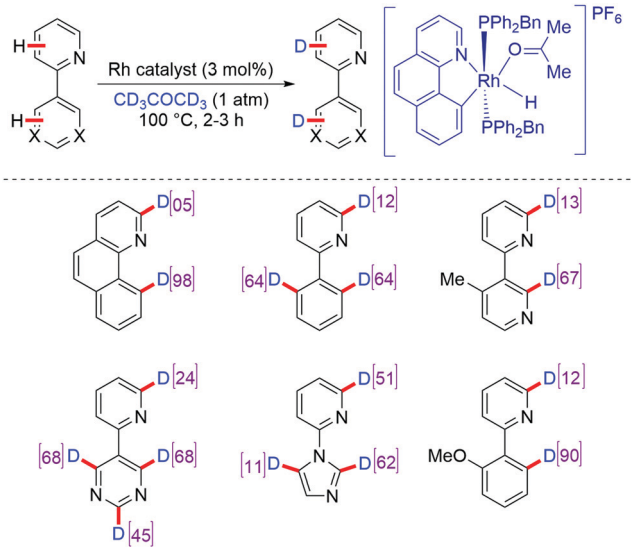
The amino acid auxiliary could be removed by treatment of the product with CuO in DMSO at 120 °C (Scheme 25a). The deuterated analogue of tolbutamide was also synthesized (Scheme 25b).

2.1.3 Rh-catalysed *ortho*-C(sp^2)–H deuteration. Rh complexes are known for regiospecific isotopic labelling of aromatic acids, amides, amines and heterocycles. In 1985, Lockley performed Rh(III) chloride catalysed deuterium labelling of anilides.[38] Following these initial results, Lockley, Jones and co-workers developed in 1990 an *ortho*-tritiation of aromatic carboxylic acids, amides and aralkylamines with moderate regioselectivity.[39] In 2008, Li and co-workers synthesized a range of Rh(III) hydride complexes and utilized them for HIE using d_6-acetone as the deuterium source (Scheme 26).[40] Rhodium complexes containing stronger electron-donating phosphines tend to increase the catalytic activity. The reaction proceeds *via* a chelation-assisted mechanism shown in Scheme 27.

2.1.4 Ru-catalysed *ortho*-C(sp^2)–H deuteration. Plietker and co-workers presented a method for orthogonal selective deuteration through variation of additives. This was a fine



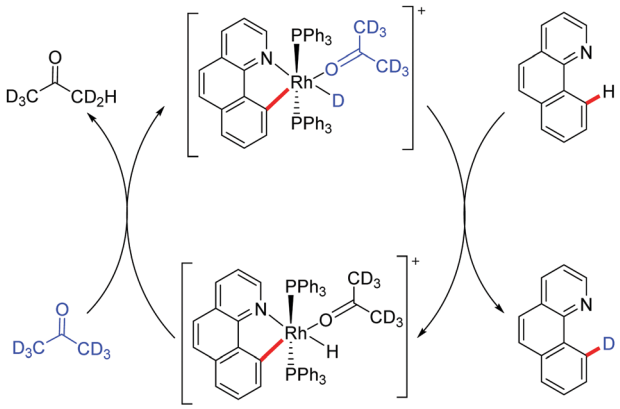
Scheme 25 Removal of the directing group.



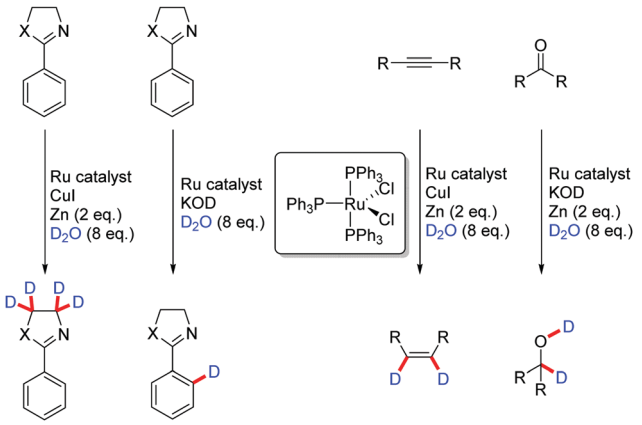
Scheme 26 Rh-Catalysed deuteration assisted by an *ortho* directing group.

example of Ru-catalysed deuteration of functional organic molecules using D_2O as a deuterium source under mild reaction conditions.[41] The role of additives was to convert the precatalyst $[RuCl_2(PPh_3)_3]$ into different Ru complexes which in turn act as active catalysts and perform chemoselective deuteration (Scheme 28). When CuI was used along with Zn as additives, alkyne reduction took place while carbonyl reduction was performed when KOD was used with Zn. H/D exchange took place at both sp^2 and sp^3 centres when the former conditions were used while the latter only led to sp^2 C–H deuteration.

Ackermann and co-workers developed a protocol for HIE at the *ortho*-position of benzoic acids, sulfonamides, and some pharmaceuticals.[42] This protocol makes use of a Ru(II) biscarboxylate complex as catalyst and D_2O as the most economic



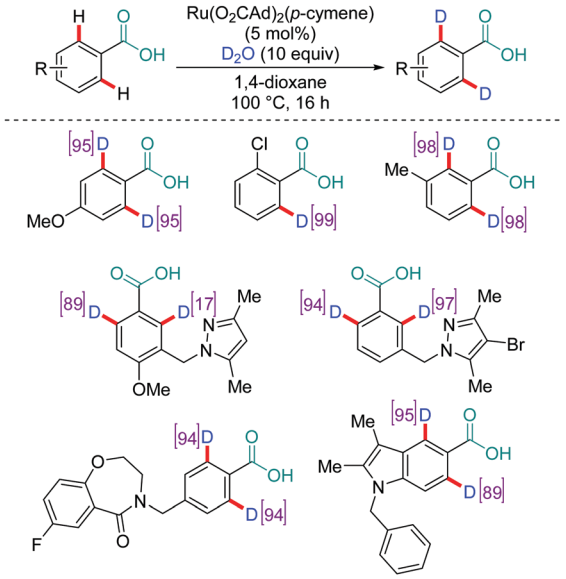
Scheme 27 Plausible catalytic cycle involving a Rh hydride complex.



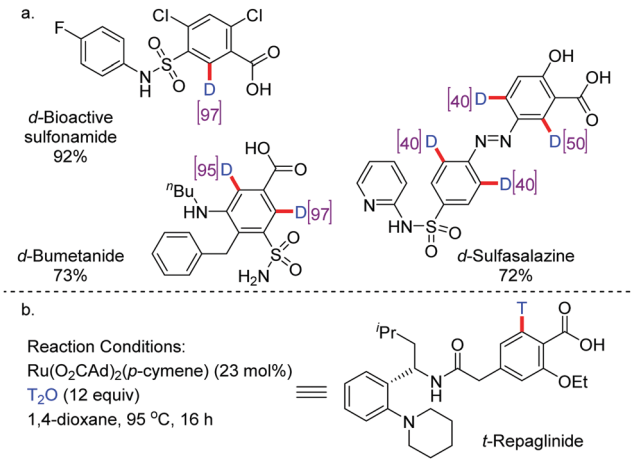
Scheme 28 Chemoselective deuteration of heterocycles, arenes, alkynes and ketones.

deuterium atom source. High-yielding and selective deuterations were observed at the *ortho*-position with respect to the carboxyl group. Heterocycles such as indoles, pyrazoles, and oxazepanes were tolerated under the standard reaction conditions (Scheme 29). Kinetic isotope experiments revealed a k_H/k_D value of about 2. Intermolecular competition experiments showed that substrates with more electron-donating substituents reacted preferentially suggesting that a base-assisted internal electrophilic substitution (BIES) may be associated with the mechanism. Late-stage modifications of drugs were also performed to showcase the robustness of the protocol. Tritium labelling of the pharmaceutical Repaglinide with T_2O as the tritium source was also performed under slightly modified reaction conditions (Scheme 30b).

The Yan group reported a method for *ortho*- and *meta*-C–H deuterium labelling using Ru with PPh_3 and AgOAc as additives and d_4-acetic acid as the deuterium source and solvent (Scheme 31).[43] Several nitrogen-containing heterocycles were used as directing groups. In the case of pyrazole as the directing group, it was found that substituents at the *para*-position had a superficial effect on *meta*-selectivity, but *ortho*-deuteration was almost unaffected by the presence of any substituents. In the case of 2-phenyl pyridine as directing group, electron-donating



Scheme 29 HIE at the *ortho*-position of benzoic acids, sulfonamides etc catalysed by Ru(II) biscarboxylate complex.

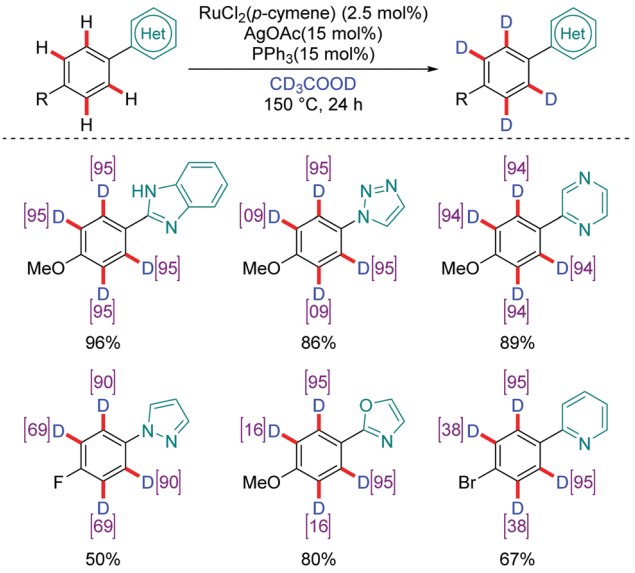


Scheme 30 Deuterium and tritium labelling of pharmaceutically important compounds using a Ru(II) biscarboxylate complex.

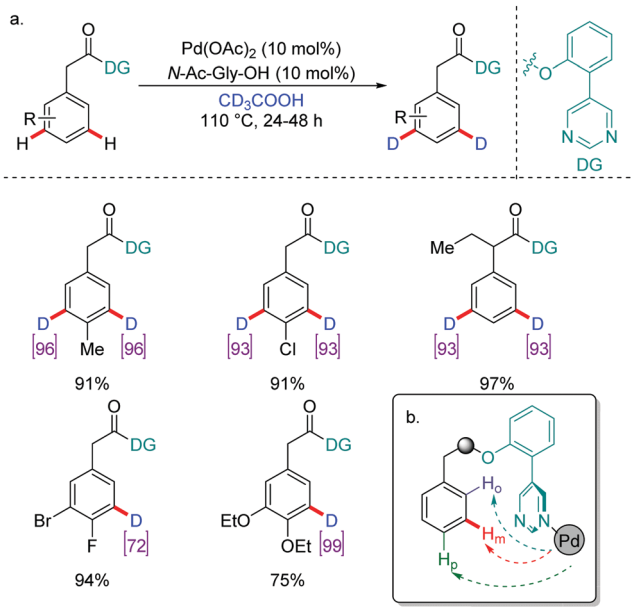
groups at the *para*-position yielded more than 90% *meta*-deuterium incorporation product. However, electron-withdrawing halide substituents resulted in lower deuteration rates. This methodology differs from traditional Ru-catalysed radical C–H activation pathways.

2.2 *meta*-C–H deuteration

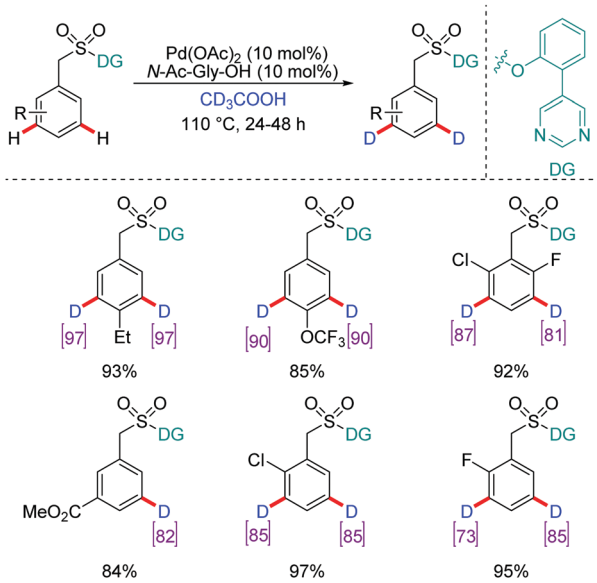
With the addition of deuterium to pharmaceutical motifs, the properties of current drug applicants can be changed and explored. A number of synthetic methods to install deuterium atoms in certain positions are necessary to broaden the scope of deuterium labelled compounds. Metal catalysed C–H activation has enabled direct HIE in the substrate. However, reaching the distal positions of arene rings has always been challenging. The problem has been addressed by the use of a directing group.[44] However, the directing group should be simple to



Scheme 31 *ortho*- and *meta*-C–H deuterium labelling using Ru.



Scheme 32 *meta*-C–H deuteration of phenyl acetic acids derivatives using a pyrimidine directing group.

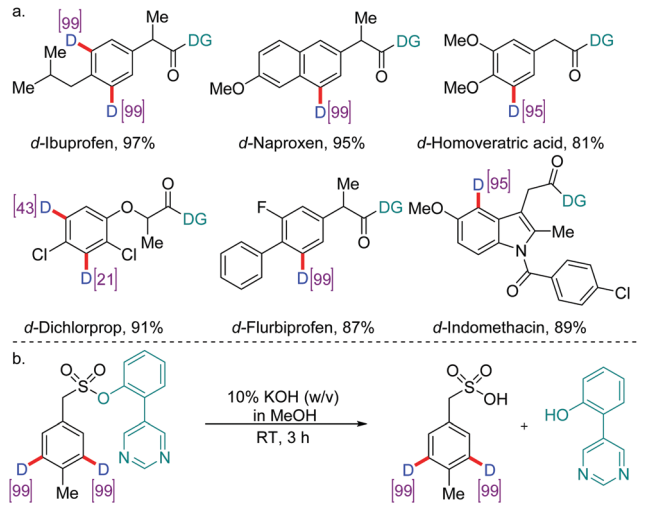


Scheme 33 *meta*-C–H deuteration of sulfones using a pyrimidine-based directing group.

install and remove for late-stage pharmaceutical and bioactive compound modification. Assisted by a directing group, metals such as Ir, Pd, Rh and Ru have been used for *ortho*-C–H deuteration. In 2012, the Yu group reported *meta*-C–H functionalisation of toluene and hydrocinnamic acids which proceeds with the assistance of a U-shaped directing group.[45] The overall transformation proceeds *via* a macrocyclic cyclophane-like transition state. Since then, many other groups have performed template-assisted *meta*- and *para*-C–H functionalisation such as olefination, arylation, acetoxylation, amination, alkynylation, ketonisation, silylation, germanylation, cyanation, and iodination. Nitrile-, pyrimidine- as well as pyridine-based directing groups have been used for these transformations. *meta*-Deuteration has not yet led to clear benefits in the properties of pharmaceuticals as they are difficult to synthesize. When our group reported *meta*-C–H cyanation with the help of a pyrimidine-based directing group using CuCN as the cyanating agent, it was found that k_H/k_D is almost equal to 1, implying that the C–H activation is not the rate-determining step. By utilizing this key finding, our group investigated the reversibility of the C–H activation step using d_4-acetic acid as the D^+ source under similar reaction conditions and observed deuterium incorporation at the *meta*-position.[46] Extensive optimizations were performed to achieve high deuterium incorporation.

A pyrimidine-based directing group (DG) was found to be best for this transformation in comparison to nitrile- and pyridine-based DGs. Only d_4-acetic acid was found to be suitable for deuterium labelling, whereas other sources such as D_2O and CD_3OD were unreactive. The final conditions were successfully applied to phenylacetic acids (Scheme 32) and sulfonyl ester derivatives (Scheme 33). In the case of electron-deficient substrates prolonged reaction time improved the degree of deuteration. The high *meta*-selectivity was attributed to a perpendicular orientation of substrate and directing group due to steric hindrance between the two six-membered rings of the heterobiphenyl unit as shown in Scheme 32b. Pd binds to a nitrogen atom of pyrimidine in its plane and the *meta*-C–H bond is the most proximal C–H bond. Thus, it is highly accessible in comparison to the *ortho*- and *para*-C–H bonds.

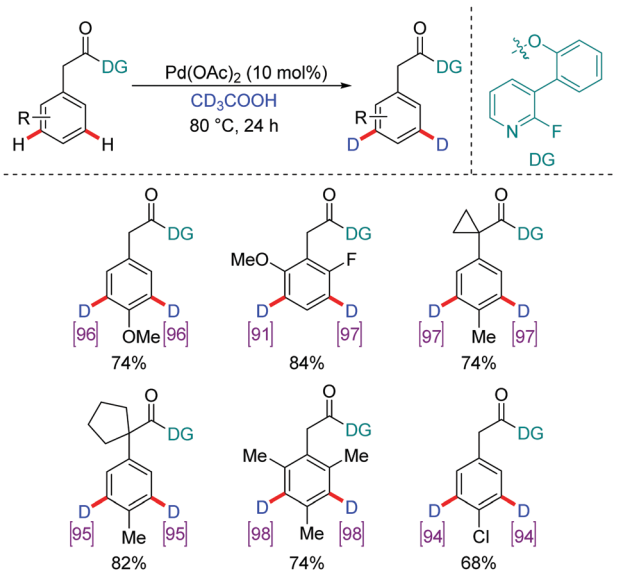
Five pharmaceuticals, namely ibuprofen, flurbiprofen (antipyretic and analgesic drug), naproxen, homoveratric acid (main metabolite of 3,4-dimethoxyphenylethylamine in urine), and indomethacin, as well as the herbicide dichlorprop were deuterated at the *meta*-position using this strategy (Scheme 34a). Moderate to excellent deuterium incorporation was observed



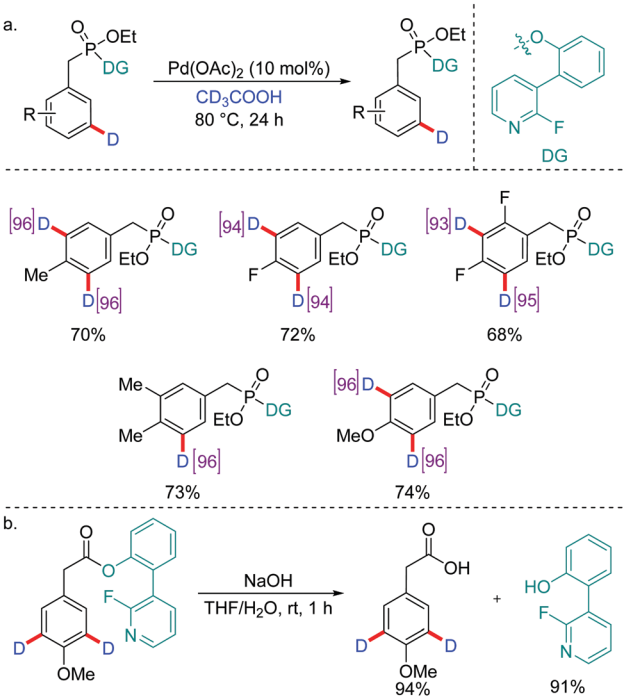
Scheme 34 a. Deuterium incorporation in phenylacetic acid based pharmaceuticals. b. Removal of the directing group.

in these cases. Removal and recovery of the pyrimidine-based directing group is possible under basic conditions (Scheme 34b).

In the same year, the Yu group used a pyridine containing directing group with phenylacetic acid derivatives to harness the coordinating ability of the nitrogen atom. As a linking moiety an ester group was used. It was found that the strong coordinating ability of pyridine with Pd(II) deactivated the catalyst and it was not suitable for the reaction. To regulate the coordinating ability, they substituted the pyridine ring with fluorine as an electron-withdrawing group which improved the yield and the selectivity of the reaction (Scheme 35).[47] Different deuterium sources such as D_2O, d_4-methanol, $CDCl_3$, and d_4-acetic acid were evaluated. Among these only d_4-acetic acid gave deuterated product. With optimized conditions in hand, they performed *meta*-C–H deuteration of phenylacetic acids,



Scheme 35 *meta*-C–H deuteration using a pyridine containing directing group.



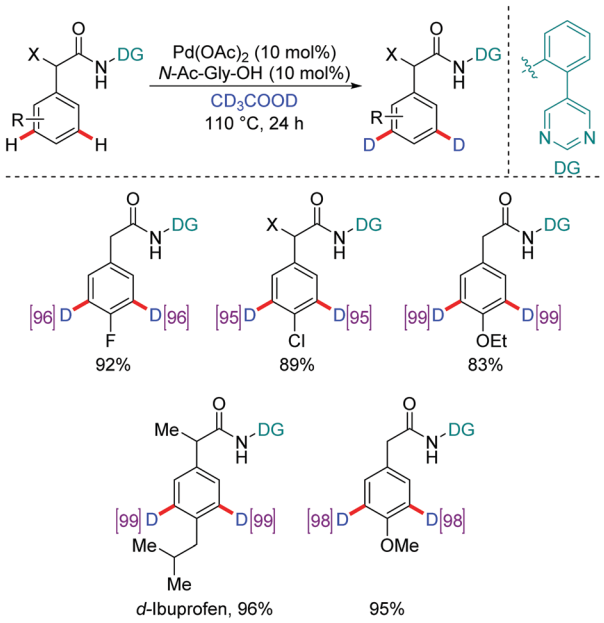
Scheme 36 a. Deuterium incorporation in benzylphosphonates. b. Removal of the directing group.

benzylphosphonates, benzylsulfonates and alcohols (Scheme 35 and 36a). The directing group can be removed and recovered by simple basic hydrolysis using NaOH (Scheme 36b). Benzamides are an important class of substrates in biologically active molecules. Therefore, their deuterated analogues should be explored for possible enhancement of pharmacokinetic properties. In 2020, Maiti and co-workers performed diverse *meta*-C–H functionalisation of amides overriding the *ortho*-directing ability of an amide group (Scheme 37).[48] They reported *meta*-allylation, cyanation, alkylation, alkynylation, and deuteration using the same previously used biphenyl pyrimidine scaffold as directing group. Regioselective *meta*-C–H deuterium incorporation was established with electron-deficient and electron-rich arenes, as well as in the drug ibuprofen.

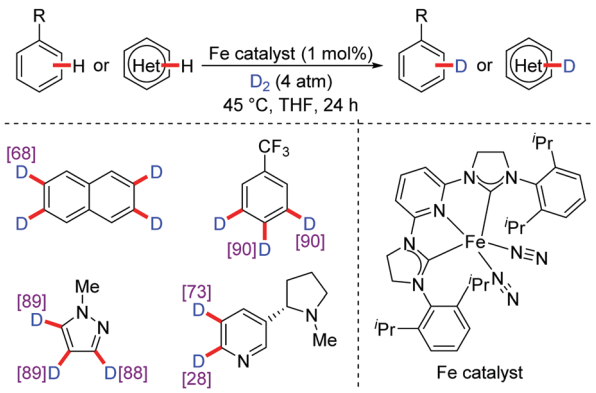
2.3 Non-directed C(sp^2)–H deuteration

In 2016, Chirik and co-workers proposed deuteration and tritiation of pharmaceuticals and pharmaceutically relevant organic compounds using an iron catalyst (Scheme 38).[49] This catalyst operates efficiently in polar aprotic solvents and at low pressure of deuterium and tritium gas. It was also established that electron-poor substrates undergo isotopic exchange faster than electron-rich ones and the site-selectivity of C–H bond activation occurs at the most sterically accessible C–H bonds. Many commercially available pharmaceuticals, namely varenicline, loratadine, cinacalcet, flumazenil *etc.* were deuterated successfully at the predicted sterically accessible sites (Fig. 5).

In 2019, the same group developed a nickel hydride dimer $[(^{ipr}ADI)Ni(\mu_2\text{-}H)]_2$ (^{ipr}ADI = *N*,*N*′-bis(2,6-diisopropylphenyl)-2,3-butanediimine) which is a very effective precatalyst for HIE in



Scheme 37 Deuterium incorporation at the *meta*-position of benzamides.



Scheme 38 Fe-Catalysed deuterium labelling of arenes and heteroarenes.

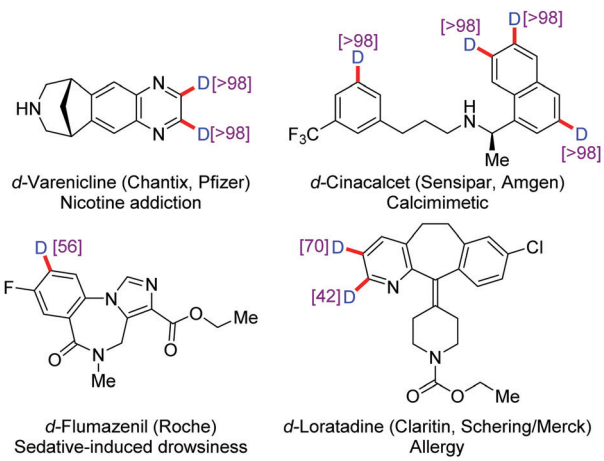
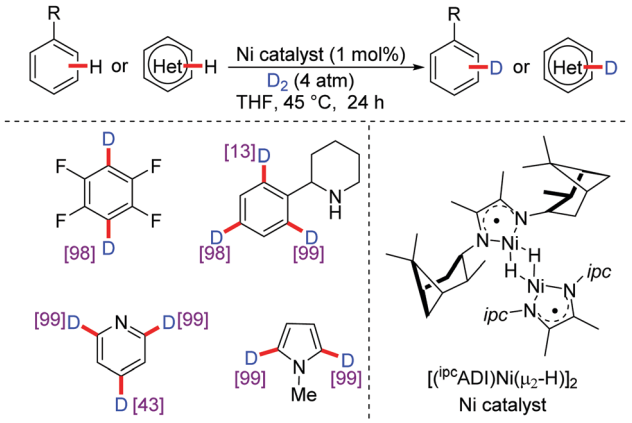
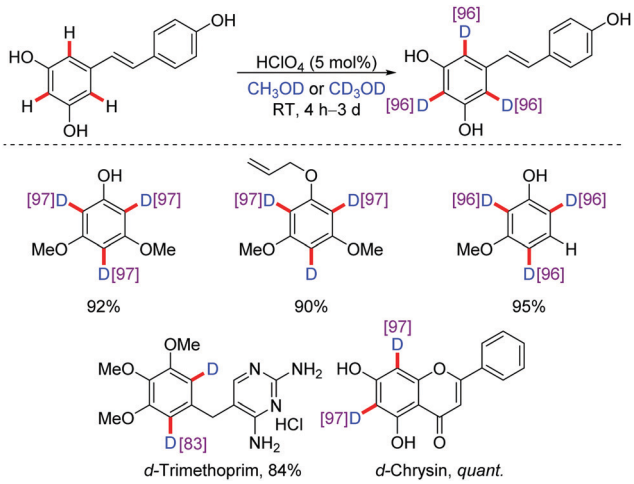


Fig. 5 Deuterium labelling of drug molecules using an Fe catalyst.



Scheme 39 Ni(I)–X complexes bearing a bulky α-diimine ligand catalysed hydrogen isotope exchange.

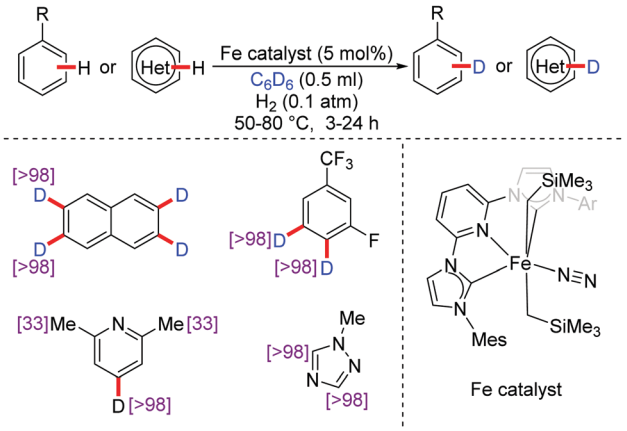


Scheme 40 Deuteration of arenes using Brønsted acid catalysis in deuterated methanol.

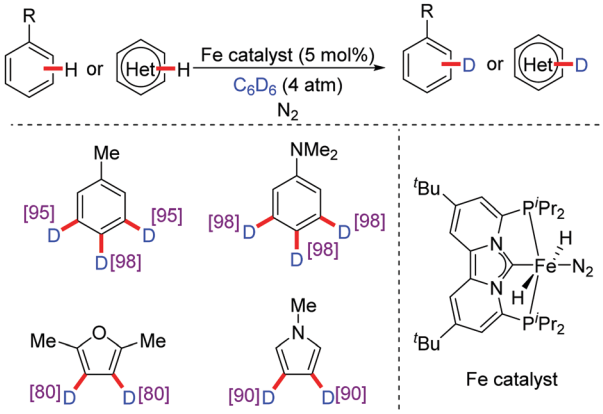
organic molecules (Scheme 39).[50] This strategy was effective for the exchange of multiple C(sp^2)–H sites in a diverse range of (hetero)arenes and pharmaceutical compounds with wide functional group compatibility.

Having multisite reactivity and high efficiency, this nickel precatalyst provides unprecedented high specific activities in radiolabelling, which meets the threshold required for radiolabelling binding assays. In 2020, Heinrich and co-workers carried out deuteration of electron-rich aromatic systems under mild acid catalysis by taking advantage of the 'differentiating effect' of methanol solvent (Scheme 40).[51] In this work, the authors showed that the differentiating effect of the solvent can be used to obtain some exceptional selectivities in protonation, and thereby deuteration of aromatic systems are strongly enhanced while highly acidic groups remain stable.

Here they introduced the concept of a 'differentiating effect' in which, by changing the solvent from water to methanol or acetic acid, the protonating strength of a strong acid such as hydrochloric acid or perchloric acid can be increased.



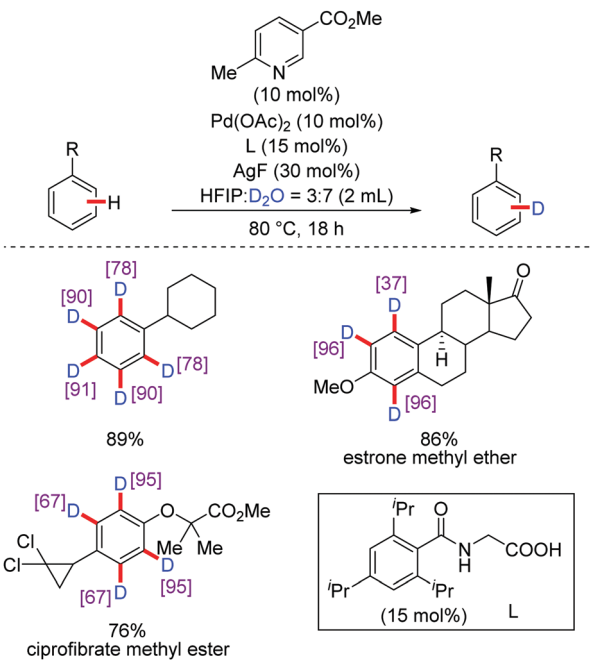
Scheme 41 Pyridine dicarbene iron dialkyl complex catalysed HIE of arenes and heteroarenes.



Scheme 43 Deuteration of (hetero)aromatic C–H bonds catalysed by an (NHC) iron complex.

This method allows access to complex deuterated aromatic compounds including natural products and pharmaceuticals. In 2020, the Chirik group again contributed towards deuteration of arenes and heteroarenes using pyridine dicarbene based iron dialkyl complexes and d_6-benzene as a deuterium source (Scheme 41).[52] Different arenes and heteroarenes were deuterated with good regioselectivity. They also studied the time dependence effect of hydrogen gas pressure on deuteration.

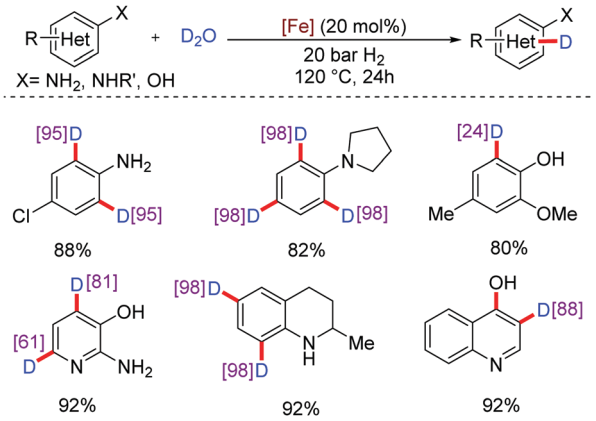
Pd-Catalysed non-directed late stage deuteration of arenes was described recently by van Gemmeren and co-workers (Scheme 42).[53] Using D_2O as a convenient and easily available deuterium source, this protocol enables a high degree of deuterium incorporation *via* a reversible C–H activation step which also features extraordinary functional group tolerance and deuteration of complex structures. The authors proposed two sets of conditions for the deuteration of arenes. Both electron-rich and electron-poor arenes were well tolerated using this dual-ligand based palladium catalyst. It is also noteworthy that besides the aromatic core, the α-keto position also underwent complete deuteration, presumably *via* an acid/base type mechanism. Ruiter and co-workers synthesized a rare *trans*-dihydride iron(II) dinitrogen complex which is based on a novel $PC_{NHC}P$ pincer type motif (Scheme 43).[54] This complex $[(PC_{NHC}P)Fe(H)_2N_2]$ is highly stable under N_2 atmosphere and reactive for HIE at (hetero)aromatic hydrocarbons under mild reaction conditions (50 °C, N_2). This complex tolerates easily reducible functional groups such as esters and amides which results in a wide substrate scope. However, substrates containing ketones such as acetophenone or cyclohexyl phenyl ketone are not susceptible to this catalytic H/D exchange reaction.



Scheme 42 Non directed late-stage C–H deuteration of arenes.

DFT studies suggest a complex assisted σ-bond metathesis pathway for $C(sp^2)$–H bond activation. Also, the robustness and stability of this complex holds great potential for other organic transformations that rely on hydride transfer or those that focus on small molecule activation. The Beller group devised a highly selective and scalable deuterium incorporation protocol for arenes and heteroarenes using a unique nanostructured heterogeneous iron catalyst synthesized by combining cellulose with $Fe(NO_3)_3 \cdot 9H_2O$ (Scheme 44).[55] This was widely applicable protocol for (hetero)arenes like anilines, phenols, indoles, and other heterocycles, including post synthetic labelling of drugs and bioactive moieties (Fig. 6). Inexpensive and safe deuterium source D_2O was used. The isotope incorporation improved in the presence of hydrogen gas which suggests the *in situ* reduction of iron oxides on the surface as proven by XPS analysis. The deuteration was performed even on the multi-gram or even kilogram scale using recycled catalyst.

Ritter and co-workers reported a hydrogen isotopic exchange of aryl thianthrenium salts using homogenous molecular palladium catalyst and deuterium and tritium gas (Scheme 45).[56] Utilizing this protocol, deuterium and tritium atoms were introduced to drug molecules with high isotopic purity without the need of rigorous dry and inert conditions. The plausible reaction pathway suggested is shown in Scheme 46.



Scheme 44 Nanostructured iron catalysed deuteration of (hetero)arenes.

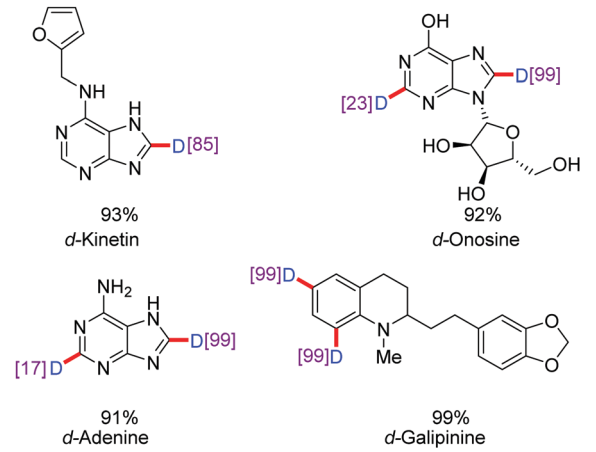
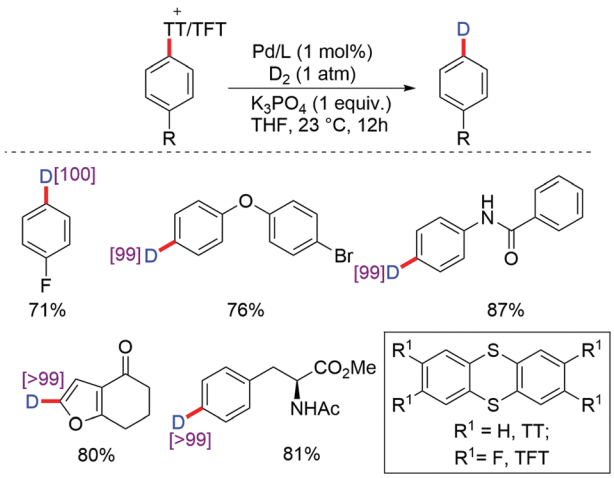


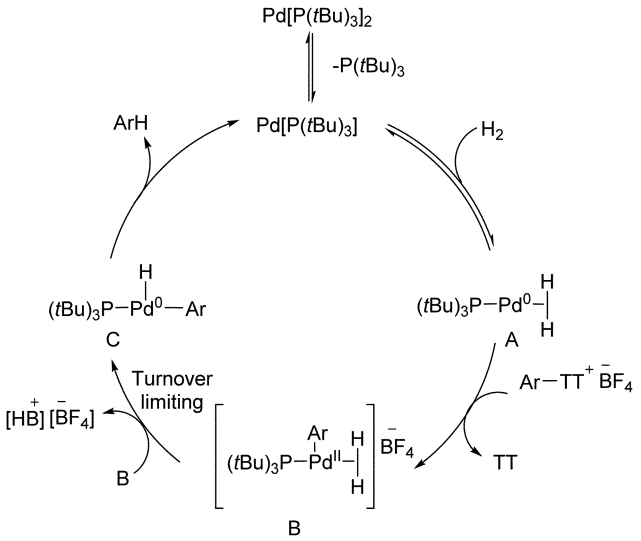
Fig. 6 Deuteration of (hetero)arenes using nanostructured Fe catalyst.



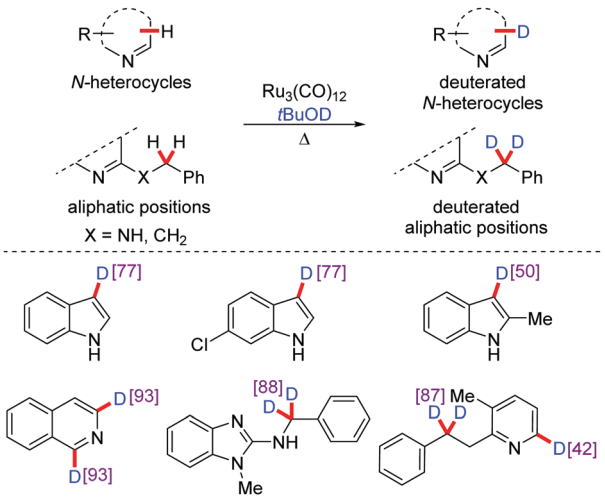
Scheme 45 Deuteration of aryl thianthrenium salts using molecular palladium catalyst.

3. C–H deuteration of heteroarenes

Nitrogen-containing heterocycles are of great interest because of their biological activities and also their occurrence in many



Scheme 46 Plausible mechanistic pathway for deuteration of aryl thianthrenium salts.



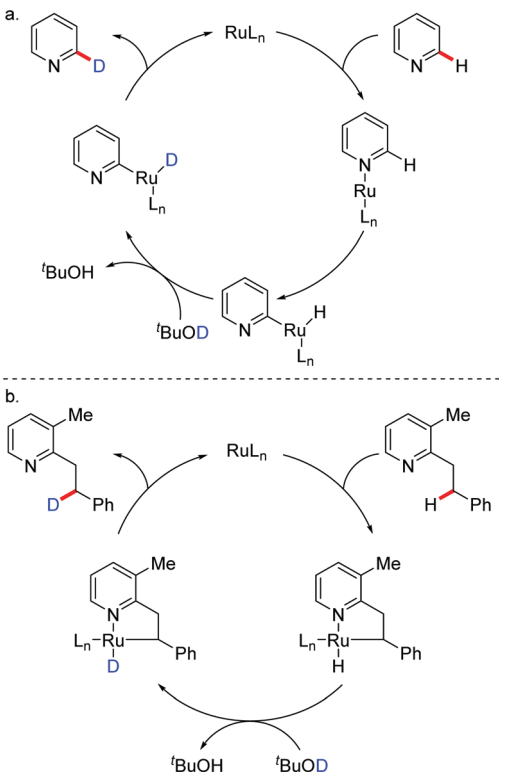
Scheme 47 Deuteration of nitrogen containing heterocycles using a Ru(0) catalyst.

natural products. Deuterated derivatives of these heterocycles are important because their use in mechanistic investigations leads to a better understanding of many synthetic transformations, leading to the development of much more efficient reaction conditions. Various methods for deuterium incorporation by activating C–H bonds using different metal catalysts have been reported. In 2012, the Schnürch group reported the deuteration of electron-rich and electron-poor nitrogen containing heterocycles using a Ru(0) catalyst (Scheme 47).[57]

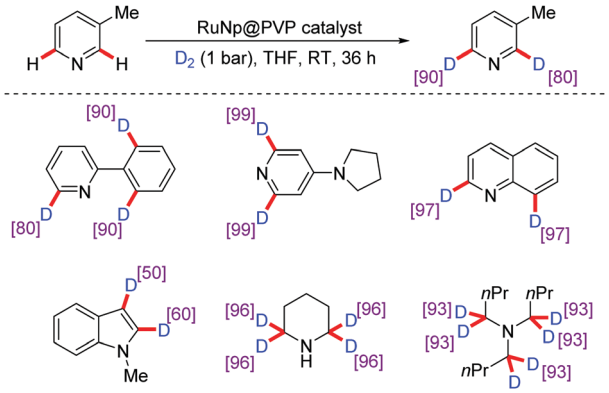
Here they used *t*BuOD as the deuterium source, whereas D_2O and MeOD were not as effective. In the case of indoles and isoquinolines, this procedure showed quite good deuteration degrees (DDs). However, introducing a methyl substituent to the indole 2-position led to lower DDs. This method worked well for both electron-rich and electron-poor substituents.

Notably, nitroindoles were the exception, where no deuterated products were isolated.

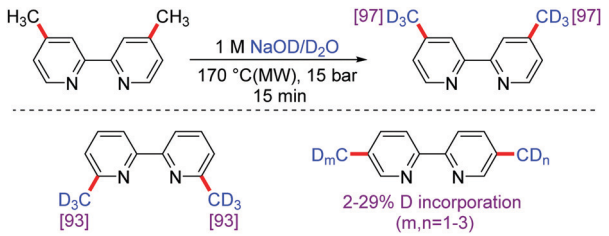
Here they also observed higher DDs by carrying out the deuteration protocol in repetitive cycles. In attempts to further broaden the substrate scope, they found that the benzylic position attached to the heterocycle could be deuterated with high DDs. However, formation of a five-membered ruthenacycle intermediate after the C–H activation was a critical prerequisite. They also showed a plausible mechanism for deuteration of the 2-position of pyridines, as well as the aliphatic position of pyridines (Scheme 48). In the case of pyridine, insertion takes place in the 2-position, whereas for the aliphatic substrates insertion takes place in the aliphatic position giving rise to a favourable five-membered ruthenacycle intermediate. Hydrogen is exchanged with deuterium from the solvent and finally reductive elimination takes place forming the desired compound. Later, Chaudret and co-workers used ruthenium nanoparticles for regioselective and stereospecific deuteration of bioactive nitrogen-containing compounds (Scheme 49).[58] These nanoparticles are attractive because their properties can be fine-tuned by surface ligand modification. RuNp@PVP (Np: nanoparticle, PVP: polyvinylpyrrolidone), which can be considered as 'Naked Particles', are used as catalysts to facilitate the interaction between substrates and the Ru surface. This catalyst showed deuteration of a diverse range of nitrogen-containing compounds such as pyridines, quinolines, indoles, and primary, secondary and tertiary amines. Pyridine derivatives were regioselectively deuterated with high isotopic enrichment, indoles also showed H/D exchange with high selectivity. Piperidines were labelled at both 2- and 6-positions with almost total replacement of four hydrogen atoms by four deuterium atoms. Subsequently, tributylamine was also deuterated in all the Cα positions with high deuterium incorporation. In 2015, Ramström and co-workers reported regioselective deuteration of dimethyl-2,2′-bipyridines *via* microwave assistance (Scheme 50).[59] The motivation behind this interest in deuteration of 2,2′-bipyridines is their further application in supramolecular systems.



Scheme 48 Proposed mechanism for the deuteration of N-heterocycles.



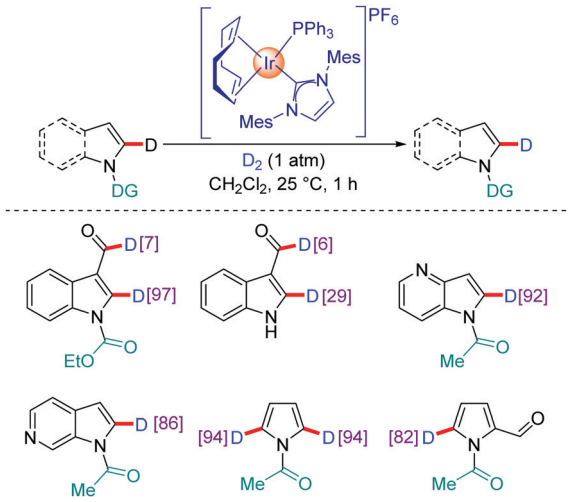
Scheme 49 Deuteration of nitrogen-containing compounds using Ru nanoparticles.



Scheme 50 Deuteration of dimethyl-2,2′-bipyridine *via* microwave assistance.

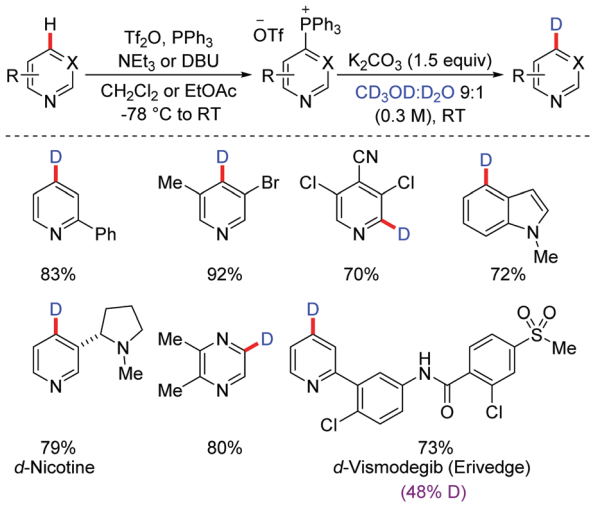
Deuteration of 4,4′-dimethyl-2,2′-bipyridine occurred readily within 15 min using microwave assistance, however, for both 5,5′-dimethyl-2,2′-bipyridine (5,5′-bpy) and 6,6′-dimethyl-2,2′-bipyridine (6,6′-bpy) it took 180 min for deuteration. Notably, in 5,5′-bpy a distribution of deuterated products was obtained with 5,5′-bpy-d_4 as the major product (29%), together with lower amounts of the deuterated products 5,5′-bpy-d_5 (23%), 5,5′-bpy-d_3 (19%), 5,5′-bpy-d_6 (14%), 5,5′-bpy-d_2 (10%), and 5,5′-bpy-d_1 (2%), respectively. Although several H/D exchange reaction conditions of 5,5′-bpy were considered by increasing temperature and/or time, fully deuterated product as in the case of 4,4′-dimethyl-2,2′-bipyridine or 6,6′-bpy was not observed.

Kerr and co-workers reported site-selective deuteration of N-heterocycles *via* Ir-catalysed HIE in 2017. They developed an Ir(I) phosphine catalyst, which delivered highly selective deuteration of indole, azaindole and pyrrole-like N-heterocycles, and was much more effective than Crabtree's catalyst (Scheme 51).[60] When 3-formylindole was protected with ethyl

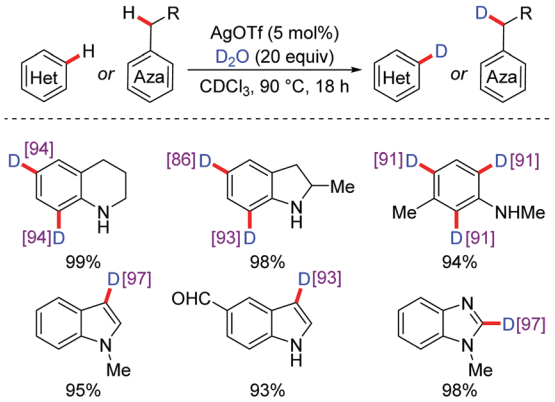


Scheme 51 Deuteration of N-heterocycles using an Ir(I) catalyst.

carbamate to give the product, deuterium incorporation at the C2 position was increased, with the level of aldehyde label remaining low. Also, in N-acetylazaindoles, varying the N-position had no effect on deuteration. Interestingly, when formyl pyrrole was subjected to deuteration, no decarbonylation or aldehyde labelling was observed, yielding a good amount of deuterated product. In 2018, McNally, Davies and co-workers introduced a strategy for site-selective incorporation of deuterium into pyridines, diazines and pharmaceuticals, resulting in high yields of deuterated products (Scheme 52).[61] Notably, deuterium is installed at the 4-position of pyridines, a different regioselectivity profile from current labelling methods and not reliant on halogenated precursors. They transformed pyridines and diazines into phosphonium salts and then envisioned a labelling process using an isotopic form of water and methanol. The D_2O component in the reaction medium is used to dissolve the carbonate base which increases the rate of deuterium incorporation. When the 4-position is blocked, the

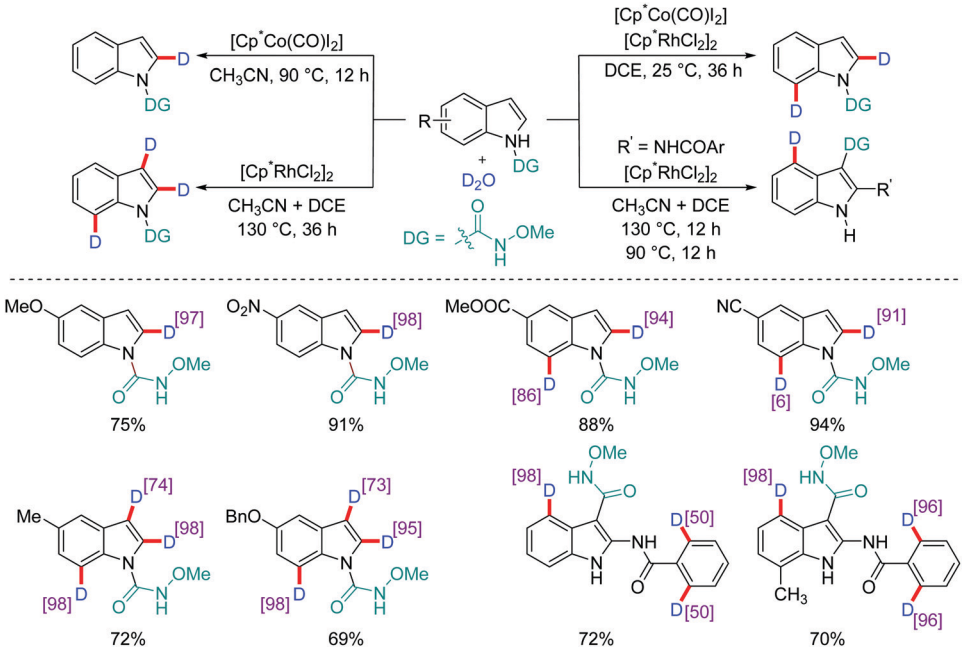


Scheme 52 Deuteration scope of azaarenes and pharmaceuticals.

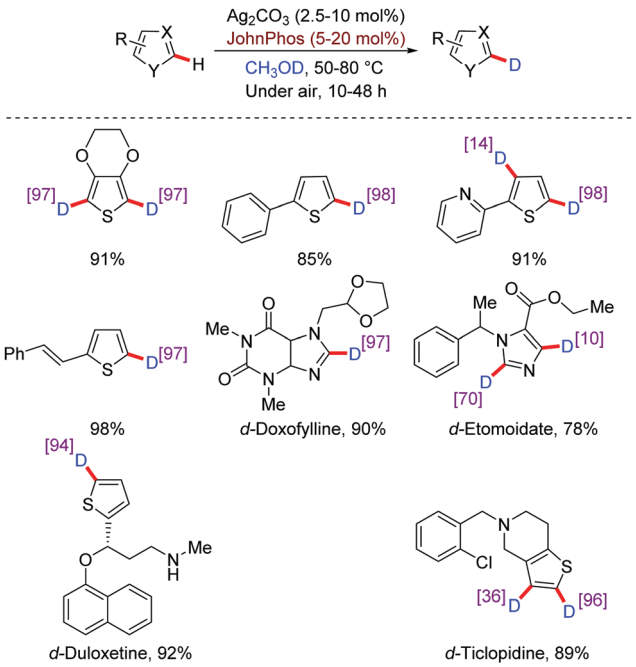


Scheme 53 Ag-Catalysed deuteration of heteroarenes and azaarenes.

2-position is deuterated. Pyridines with 3,5-substituents were also deuterated with high regioselectivity. In addition, this protocol afforded deuterated pharmaceuticals and biologically active compounds. In 2020, Hao and co-workers investigated silver catalysed regioselective deuteration of (hetero)arenes and α-deuteration of 2-alkyl azaarenes, utilizing D_2O as the deuterium source under mild conditions where additives are not needed (Scheme 53).[62] AgOTf showed a very good range of deuteration probably because of slow release of TfOH in the reaction. A broad range of electron-rich arenes were well tolerated in this catalytic system, resulting in good to excellent deuterium incorporation. Remarkably, electron-deficient azaarenes such as imidazole and benzimidazole were also readily deuterated in the C2 position with a high level of deuterium incorporation. In the same year, Zou and co-workers reported a highly effective regioselective direct C–H deuteration of indoles in D_2O using $Cp^*Co(CO)I_2$, $[Cp^*RhCl_2]_2$, or their combination as a catalyst. This protocol made available mono(C2)-, di(C2/C7)-, tri(C2/C3/C7)-, and even C4-deuterated products from various indole substrates (Scheme 54).[63] $Cp^*Co(CO)I_2$, a cheap and commercially available cobalt complex, deuterated the C2 position of indole, whereas the mixture of $Cp^*Co(CO)I_2$ and $[Cp^*RhCl_2]_2$ selectively deuterated the C2 and C7 positions of indole, which is the first example of synergistic transition-metal-catalysed deuteration. Apart from the mono- and di-deuterated indoles, using $[Cp^*RhCl_2]_2$ they also obtained the trideuterated (C2/C3/C7) indole product. Interestingly, introducing an electron-donating amido group in the C2 position, deuteration takes place at the C4 position, accompanied by migration of the directing group from N1 to C3 position. More recently, the Hartwig group described the identification of a catalytic system based on silver for site-selective C–H deuteration of medicinally relevant five-membered aromatic heterocycles. This method does not need any directing group and proceeds through commercially available silver catalysts, phosphine ligands and CH_3OD as a low-cost deuterium source (Scheme 55).[64] This method also shows broad functional group compatibility and enables the isotopic labelling of complex pharmaceutical ingredients to produce new isotopologues. Based on all the consistent data, the authors proposed an



Scheme 54 Versatile regioselective deuteration of indoles.

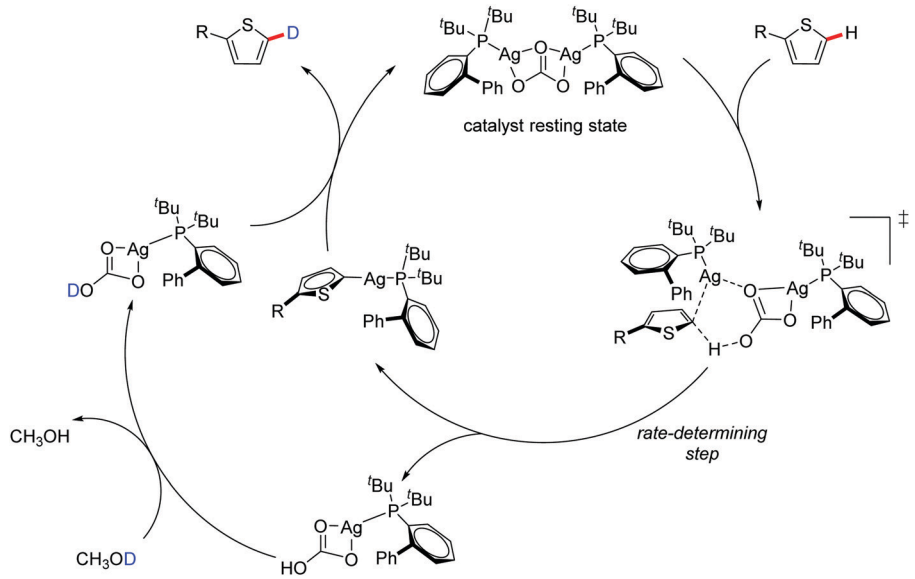


Scheme 55 Thiophenes undergo C–H deuteration by Ag catalysis.

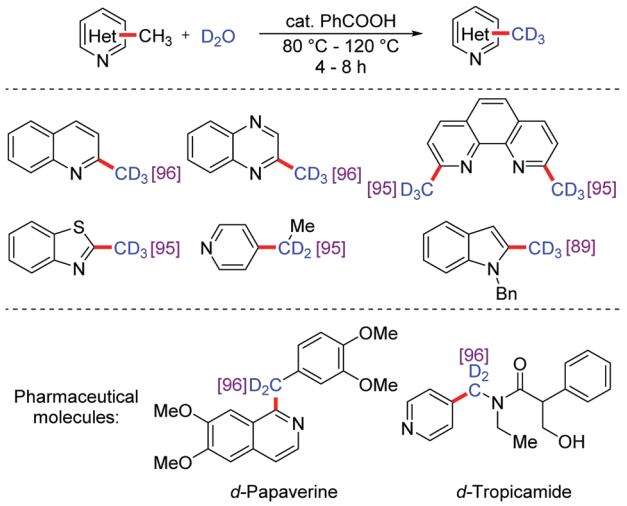
initial hypothesis for the silver-catalysed C–H bond deuteration. Mechanistic experiments support turnover-limiting C–H bond activation by a new phosphine ligated silver carbonate catalyst with a decisive carbonate-assisted CMD step (Scheme 56). Organocatalysis, that is the use of small organic molecules to catalyse organic transformations, has been among the most successful concepts in asymmetric catalysis, and it has been used for the enantioselective construction of C–C, C–N, C–O, C–S, C–P, and C–halogen bonds.[65] Drugs containing C–D bonds have been prepared through multistep syntheses involving reduction of unsaturated or halogenated derivatives. N-Heteroarylmethanes are present as a core unit in many natural products and pharmaceutical drugs. In 2017, Yin and co-workers proposed a facile acid catalysed deuteration at the methyl groups of N-heteroarylmethanes, which was achieved through an enamine intermediate under relatively mild conditions (Scheme 57).[66] Pyridines, benzothiazoles, indoles, imines and bioactive pharmaceutical molecules were efficiently deuterated at their methyl groups. 2-Methyl and 4-methyl groups in quinolines were also deuterated with high deuterium incorporation. Investigating the mechanism, the authors proposed that this H/D exchange reaction proceeds through an enamine intermediate (Scheme 58). The results show strong evidence to support the proposed mechanism of acid-mediated functionalisation of methyl groups in N-heteroarylmethanes.

In 2017 Werner and co-workers demonstrated a highly efficient protocol for the deuteration of electron-rich (hetero)-aromatic compounds using $B(C_6F_5)_3$ as a catalyst (Scheme 59).[67] This transition metal free deuteration was successfully applied to different substrates including natural neurotransmitters such as melatonin.

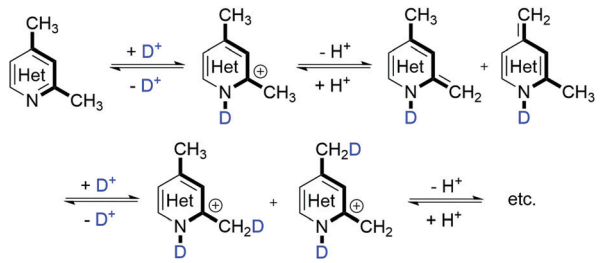
It was further investigated that weakening of the O–D bond in D_2O leads to the formation of a Lewis acid–base adduct which subsequently results in the formation of electrophilic D^+. This undergoes an electrophilic aromatic substitution which forms the deuterated product. A Ni-catalysed site-selective HIE of $C(sp^2)$–H bonds in nitrogen-containing heteroarenes was described by Chirik and co-workers in 2018 (Scheme 60).[68] This Ni catalyst shows high HIE activity under low D_2 pressure along with broad functional group tolerance including aryl chlorides,



Scheme 56 Possible mechanistic pathway for the site-selective C–H deuteration of five-membered heterocycles.

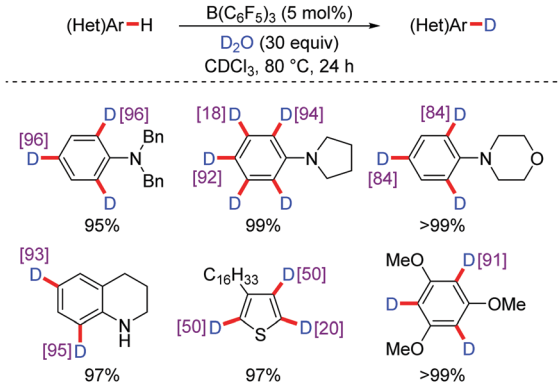


Scheme 57 Brønsted acid-catalysed deuteration at methyl groups of N-heteroarylmethanes and its application to bioactive pharmaceutical molecules.



Scheme 58 Proposed mechanism for isotopic exchange at the methyl groups of N-heteroarylmethanes.

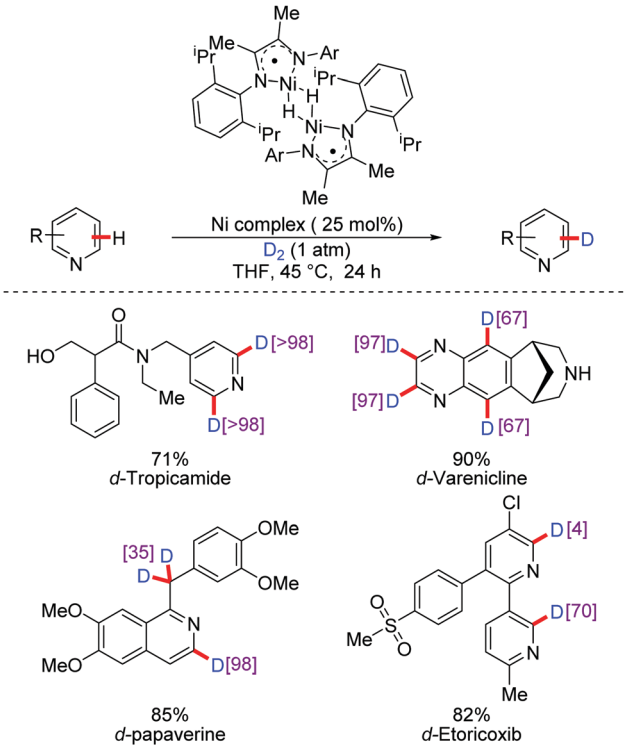
alcohols and secondary amides. This α-diimine nickel hydride complex mediates efficient HIE when employed as a single



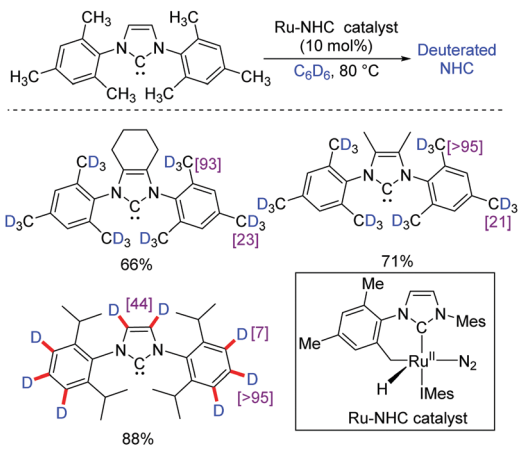
Scheme 59 $B(C_6F_5)_3$ catalysed H/D exchange of electron-rich (hetero)-aromatic compounds.

component precatalyst or generated *in situ* from readily available and air-stable metal and ligand precursors. Also, the authors proposed a pathway that involves C(sp^2)–H activation by an α-diimine nickel hydride monomer which is consistent with the experimentally measured relative rate constants for HIE with electronically disparate pyridines.

A catalytic method for the preparation of deuterated NHCs was proposed by Deng and co-workers in 2021 (Scheme 61).[69] The catalytic H/D exchange reaction takes place between NHCs and deuterated benzene using a coordinatively unsaturated Ru(II) NHC catalyst. This catalytic system enables selective deuteration of C(sp^3)–H bonds on NHCs by taking advantage of facile intramolecular C(sp^3)–H bond activation reactions of coordinatively unsaturated Ru NHC species. Also, this system facilitates deuteration of sterically unhindered C(sp^2)–H bonds on NHCs. 16 deuterium-labelled NHCs were prepared using this strategy that have a deuteration ratio on specified sites higher than 90%. The authors also showed mechanistic studies that reveal that the high regioselectivity toward those C(sp^3)–H



Scheme 60 Site-selective nickel-catalysed hydrogen isotope exchange in drug molecules.

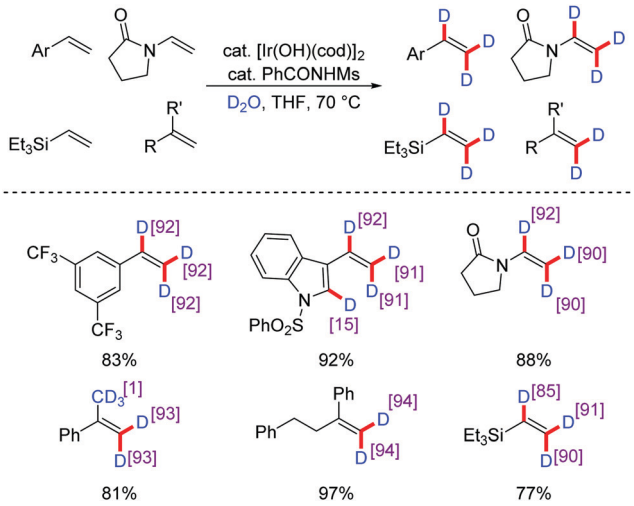


Scheme 61 Catalytic deuteration of NHCs.

bonds on NHCs originates from the regioselectivity of cyclometallation reactions of coordinatively unsaturated Ru NHC species.

4. C–H deuteration of alkenes

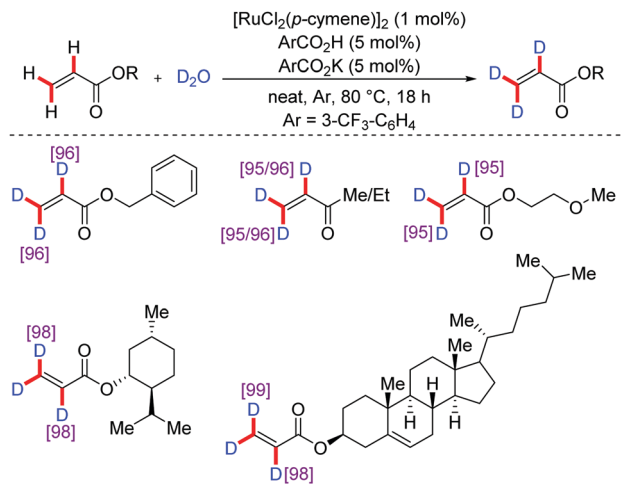
In 2016, Nishimura and co-workers reported selective H/D exchange of vinyl and methylidene groups with D_2O by an Ir catalyst which is generated *in situ* from a hydroxoiridium complex and *N*-mesylbenzamide (Scheme 62).[70] Vinyl arenes produced the deuterated alkenes in high yields with high deuterium incorporation. However, in the case of 3-vinyl-



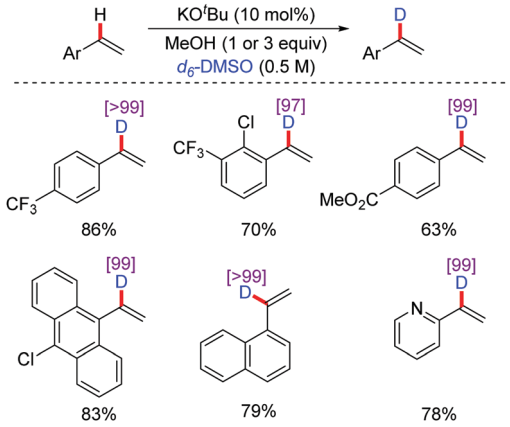
Scheme 62 Ir-Catalysed H/D exchange of vinyl and methylidene groups.

indole, a significant amount of deuteration was observed at the 2-position. *N*-Vinyl pyrrolidone, which is a useful monomer for some important synthetic materials, was also successfully deuterated using this protocol. In α-methylstyrene, the methylidene group was selectively deuterated with a very small amount of deuteration at the methyl position. Simple alkenes and isopropenyl ether were also deuterated at the methylidene groups with high regioselectivity.

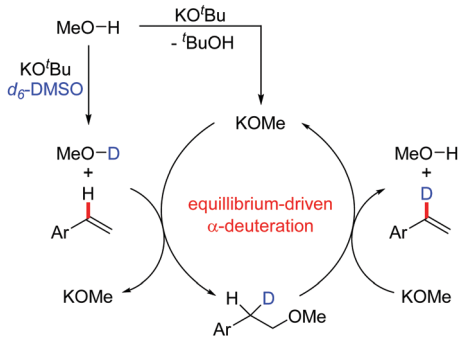
In 2019, Ackermann and co-workers reported Ru(II)-biscarboxylate catalysed HIE of acrylic C–H bonds with user-friendly D_2O as the deuterium source (Scheme 63).[71] This protocol is characterized by exceptional selectivity and broad functional group tolerance. It is noteworthy that in the late-stage modification of the cholesteryl scaffold no deuteration was observed at other positions of the steroid. Control experiments revealed that a significantly reduced catalyst loading (0.1 mol%) also led to quantitative deuterium incorporation occurring with turnover numbers (TON) greater than 1000. In the same year, Bandar and co-workers proposed a catalytic



Scheme 63 Ru-Catalysed deuteration of acrylic esters.



Scheme 64 α-Selective deuteration of styrene derivatives.



Scheme 65 Plausible deuteration pathway of styrene derivatives.

α-selective deuteration of styrene derivatives (Scheme 64).[72] This reaction proceeds *via* a base-catalysed reversible addition of methanol to styrenes in d_6-DMSO as solvent. MeOH plays an important role in this transformation.

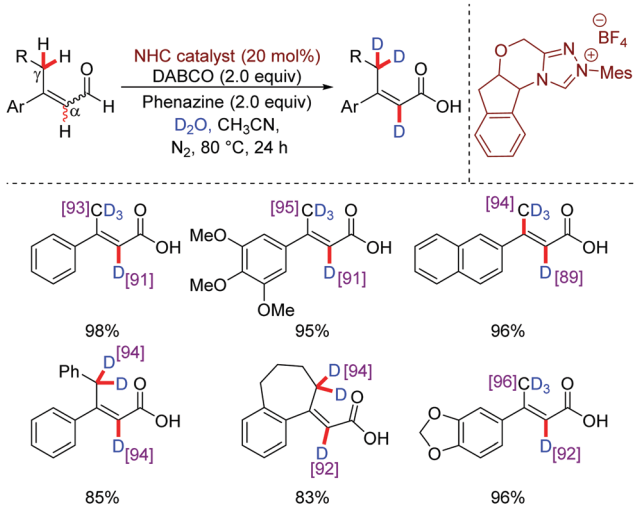
First, KO^{t}Bu catalyses MeO–H/D exchange with the deuterium source and forms KOMe, then it further undergoes nucleophilic addition to the styrene with concomitant deuteration of the developing benzylic anion by MeOD, forming partially deuterated β-phenylethyl ether. MeOH elimination catalysed by KOMe finally produces α-deuterated styrene (Scheme 65).

As deuterated allyl groups are very attractive in organic compounds to enhance pharmacokinetic properties, Chi and co-workers proposed a carbene-catalysed α,γ-deuteration of enals at allylic C(sp^3) and C(sp^2) centers under oxidative conditions in 2020 (Scheme 66).[73]

To achieve high deuterium incorporation, the carbene catalyst was added to the aldehyde moiety of enals to ensure the activation of α- and γ-carbon atoms. D_2O was used as the deuterium source in mild reaction conditions to achieve α,γ-deuterated-2-alkenoic acids with good to excellent yields and high deuterium incorporation.

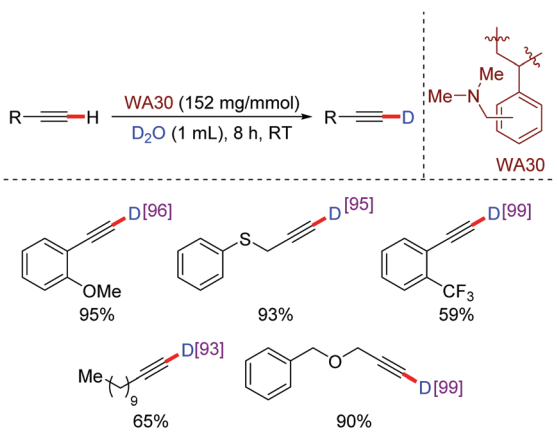
5. C–H deuteration of alkynes

Although the deuteration of terminal alkynes is not a "true" C–H activation process due to the slightly acidic nature of the

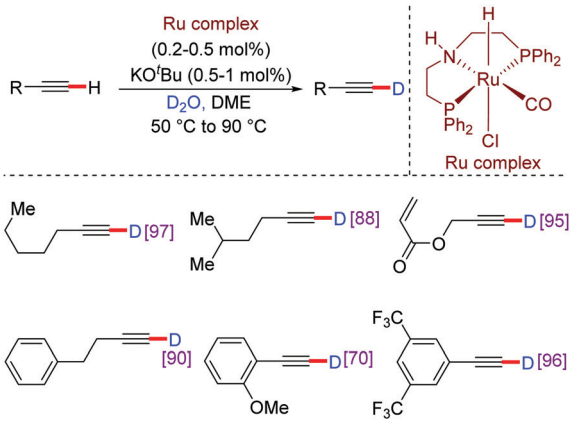


Scheme 66 Carbene-catalysed α,γ-deuteration of enals.

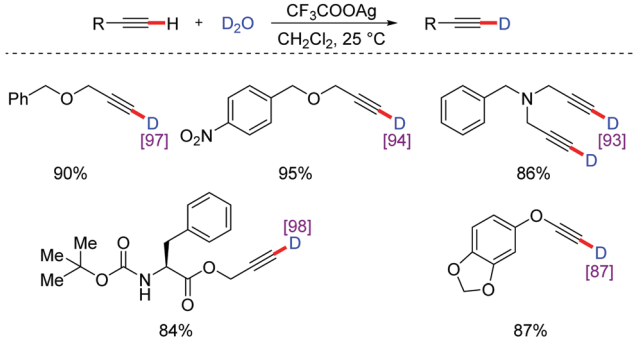
terminal alkyne proton, we would like to give a brief overview of this area. In 2015, Sajiki and co-workers reported a mild deuteration method of terminal alkynes in heavy water using a reusable basic resin.[74] Basic anion exchange resin, WA30, which is a polystyrene polymer bearing a tertiary amine residue on the aromatic system is used in the reported procedure (Scheme 67). Notably, WA30 could be easily removed using simple filtration and reused. It has been shown that WA30 can be used five times without any deactivation. Using this protocol various mono aryl- and alkyl-substituted alkynes were efficiently deuterated with quantitative deuterium incorporation. Deuterated terminal alkynes are often used as reliable probes in the mechanistic investigations of many chemical transformations. In 2016, Gunanathan and co-workers reported an efficient method for the synthesis of monodeuterated terminal alkynes using a Ru(II) pincer complex (Scheme 68).[75] This protocol shows very good functional group tolerance where both electron-donating and electron-withdrawing groups on the *meta*- and *para*-positions of aryl alkynes were well tolerated. Arene C–H bonds were not deuterated under these conditions.



Scheme 67 Deuteration of terminal alkynes using a basic resin.



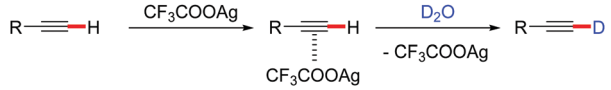
Scheme 68 Ru-Catalysed mono-deuteration of terminal alkynes.



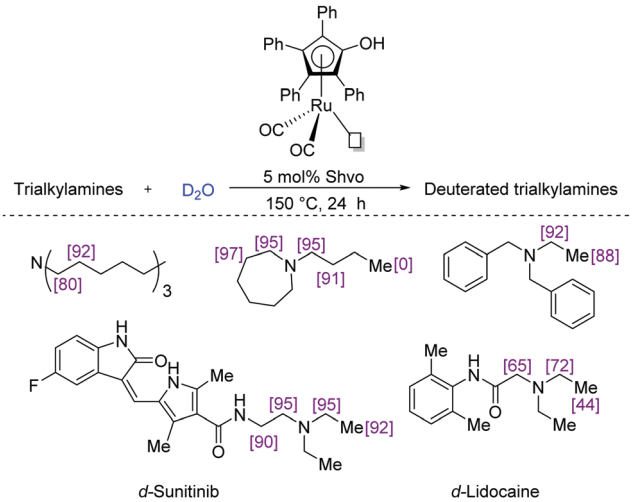
Scheme 69 Silver salt catalysed deuteration of terminal alkynes.

Aliphatic terminal alkynes were also efficiently deuterated using this protocol. It is noteworthy that this catalytic process is chemoselective and no undesirable side reactions were observed.

An H/D exchange method for selective deuteration of terminal alkynes using a silver salt as catalyst was reported by Liu and co-workers in 2021 (Scheme 69).[76] CF_3COOAg was used as catalyst at room temperature which affords the deuterated products with a high level of deuterium incorporation. This procedure shows excellent site-selectivity and promising functional group tolerance which enables it to deuterate pharmaceuticals and natural products. They also proposed a mechanistic pathway for this deuteration where the terminal C–H bond was first activated by the coordination of silver salt to the triple bond. H/D exchange between D_2O and the terminal alkyne then affords the deuterated terminal alkyne as shown in Scheme 70. Nucleotide derivatives, sesamol, and α-amino acids were deuterated from their corresponding terminal alkyne precursors using this catalytic process.



Scheme 70 Proposed mechanistic pathway for the deuteration of terminal alkynes.



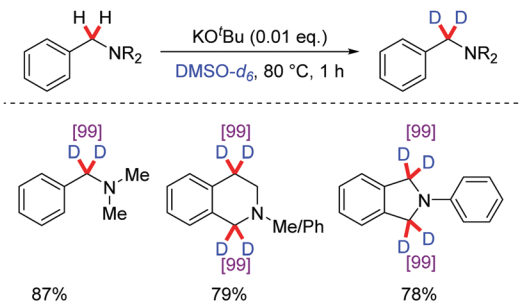
Scheme 71 Ru based Shvo catalysed deuteration of amines.

6. C–H deuteration of C(sp^3)–H bonds

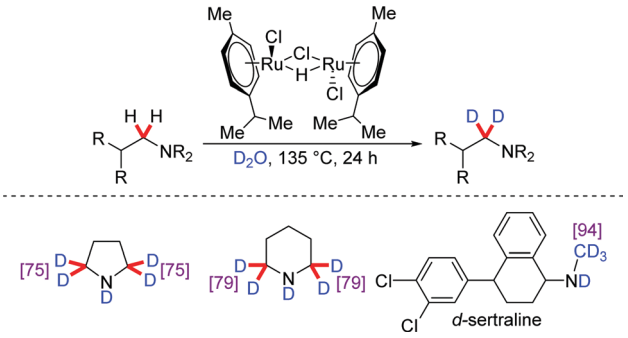
6.1 Deuteration of C(sp^3)–H bonds of amines and amides

Beller's group demonstrated the α,β-hydrogen-deuterium exchange of bioactive amines using a commercially available Shvo catalyst with excellent chemoselectivity (Scheme 71).[77] Different deuterated solvents were used as deuterium source. The authors suggested that the mechanism proceeds through hydrogen borrowing methodology. They also applied their protocol to deuterate marketed drugs containing a trialkyl moiety.

In 2015, Zhang and co-workers demonstrated by using a base (KO^{t}Bu) and a deuterating agent (d_6-DMSO), that amines and nitrogen-containing heterocycles can be easily deuterated (Scheme 72).[78] Exceptionally high deuterium incorporation (up to 99%) in the benzylic position has been observed using this protocol. The authors proposed a free radical deuteration mechanism for their observations. At first, DMSO is deprotonated by KO^{t}Bu to give a DMSO anion which further converts to a DMSO radical *via* single electron transfer (SET). This radical then abstracts an α–H from the benzylic position to give a radical intermediate which in turn produces the mono-deuterated product. A second radical deuteration to the mono-deuterated product yields the desired product.



Scheme 72 Base mediated deuteration of benzylamines.

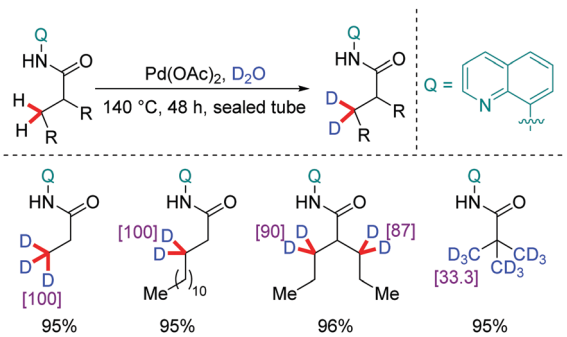


Scheme 73 Ru-Catalysed α-selective deuteration of amines.

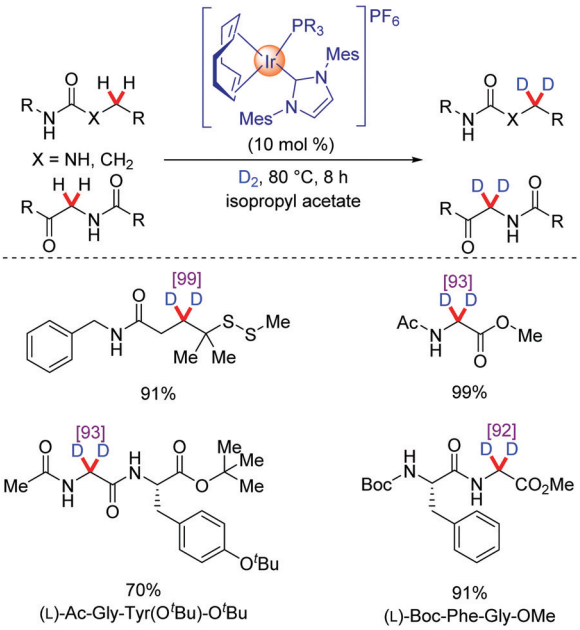
In 2016, Gunanathan and co-workers reported selective α-deuteration of amines using a Ru catalyst and D_2O as the deuterium source and found excellent deuterium incorporation (94%) at the sp^3-α-CH_2 protons (Scheme 73).[79] Experimental observations reveal that the reactions proceed through a Ru(IV) intermediate. They also proposed that the HIE reaction proceeds *via* an amine N–H activation by a cationic ruthenium complex and a subsequent 1,3-deuteride transfer to the *in situ* formed imine. High deuterium incorporation, exceptional selectivity and low loading of the Ru catalyst make this method very attractive and advantageous for both laboratory- and large-scale preparation of these deuterated amines.

Yu and co-workers developed in 2018 a palladium-catalysed H/D exchange reaction with 8-aminoquinoline as the directing group and D_2O as both deuterium source and solvent (Scheme 74).[80] Selective H/D exchange was achieved at the β-C–H positions of aliphatic amides. A plausible mechanism states that the reaction proceeds *via* a palladium amide or cyclometallation intermediate. The authors also mentioned that some *ortho*-deuterated benzoic acid and β-deuterated valproic acid were obtained upon removal of the directing group.

Derdau and co-workers reported a highly selective homogeneous Ir-catalysed H/D exchange of unactivated $C(sp^3)$ centers of aliphatic amides in 2018 (Scheme 75).[81] With this method, using the commercially available Kerr catalyst, H/D exchange of a series of common linker side chains of antibody–drug conjugates proceeds with high regioselectivity, high yields and deuterium incorporation of up to 99%.

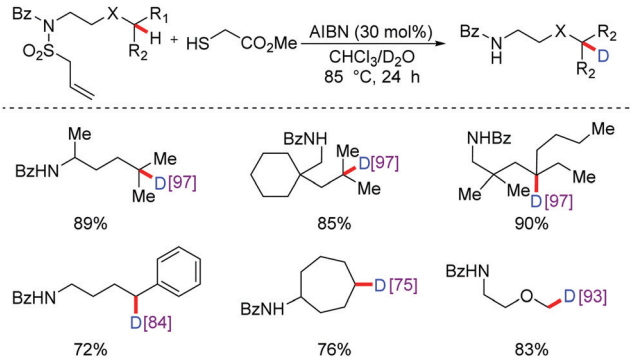


Scheme 74 Palladium catalysed H/D exchange reaction of aliphatic amides.



Scheme 75 HIE reaction with amides, amino acids and dipeptides.

Protecting groups enabled tunable selectivity in di- and tripeptides. The authors also investigated the energies of the transition states using DFT calculations and further explained the observed selectivity and the influence of protecting groups in amino acids. In recent years, Studer and co-workers reported a mild and environmentally benign metal-free method for the site-selective radical C–H monodeuteration of aliphatic C–H bonds in various amides using D_2O as the deuterium source (Scheme 76).[82] In this method the *N*-allylsulfonyl moiety is used as an N-radical precursor that generates the C-radical *via* site-selective 1,5- or 1,6-hydrogen atom transfer. Various unactivated and activated $C(sp^3)$–H bonds along with primary C–H bonds next to heteroatoms were selectively deuterated using this strategy. A wide range of functional group tolerances including successful deuteration of natural product derivatives and pharmaceutically relevant compounds clearly proves the impact of this strategy.



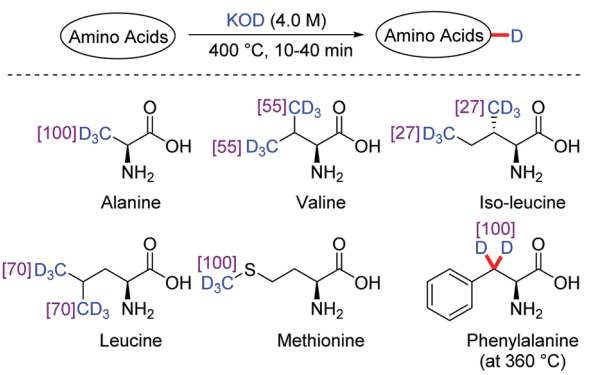
Scheme 76 Metal-free deuteration of aliphatic C–H bonds in various amides.

6.2 Deuteration of C(sp^3)–H bonds of amino acids

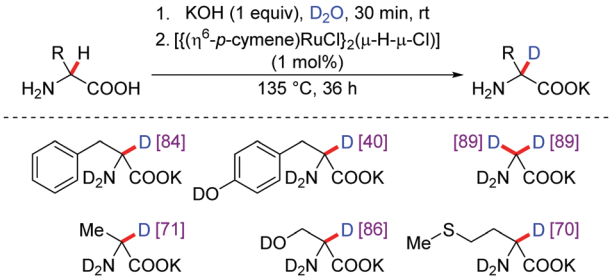
Deuterated amino acids are useful in biological systems as non-radioactive isotope tracers. Complex proton spectra of peptides containing amino acids can be simplified with the help of H/D exchange. Therefore, direct deuteration of amino acids is an important methodology. Considering the importance of these compounds, a number of methods has been reported over recent decades. Evilia and Yang developed deuteration of amino acids using a basic deuterium oxide solution in 1996 (Scheme 77).[83] A 4.0 M KOD solution was used as the source of deuterium at 400 °C for 5 to 40 min depending upon the substrate. Alanine, isoleucine, leucine, valine, methionine, glutamic acid, histidine, phenylalanine, tryptophan and tyrosine were all deuterated. Deuterium incorporation was observed at different sites depending upon the substrate. However, many amino acids such as arginine, cysteine, serine and threonine were not compatible with the reaction conditions and decomposed.

In 2013, Hashimoto and co-workers performed a detailed analysis of H/D exchange at the arene rings of α-amino acids and peptides utilizing deuterated trifluoromethanesulfonic acid (TfOD). Alanine, tyrosine and tryptophan were treated with TfOD at 0 °C and room temperature successively to study the temperature dependent deuteration and their corresponding mass spectra were analysed. They concluded that deuterium incorporation can be controlled by varying the amount of reagent, the reaction time and the temperature.[84] Later, in 2016, Gunanathan and co-workers performed Ru-catalysed, selective α-deuteration of amines and amino acids using deuterium oxide (Scheme 78).[85] A monohydrido-bridged dinuclear complex [{(η^6-*p*-cymene)RuCl}$_2$(μ-H-μ-Cl)] was used for facile selective α-deuteration of amino acids. Glycine, alanine, serine, and methionine displayed excellent H/D exchange at the α-position. Other amino acids showing facile deuterium incorporation included isoleucine, aspartic acid, valine, proline and the methyl ester of serine.

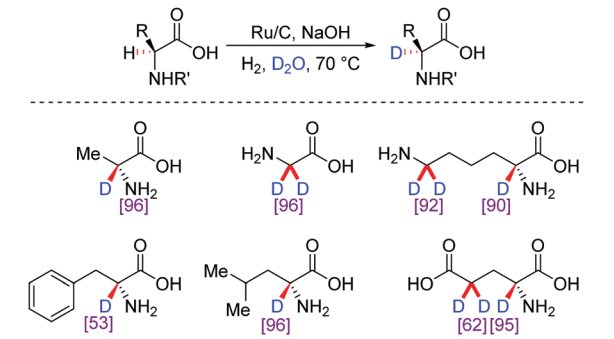
In 2017, chemists at Roche devised a methodology for stereoretentive deuteration of amino acids utilizing Ru on charcoal, H_2 gas at atmospheric pressure and deuterium oxide (Scheme 79).[86] This protocol avoids the use of an expensive or sensitive catalyst. Finally, deuterated product was obtained by a simple filtration process which makes this methodology attractive for industrial purposes.



Scheme 77 Deuteration of amino acids at supercritical temperatures.



Scheme 78 α-Deuteration of amino acids using a Ru complex.

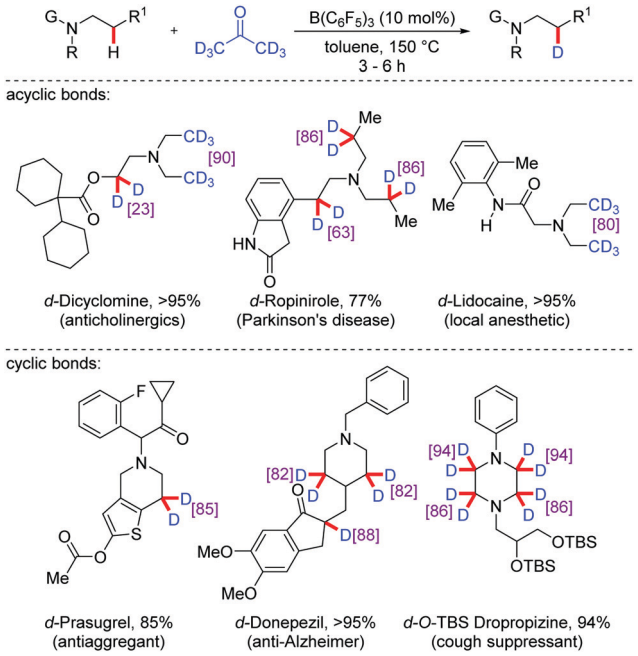


Scheme 79 Stereoretentive deuteration of amino acids at the α-positions.

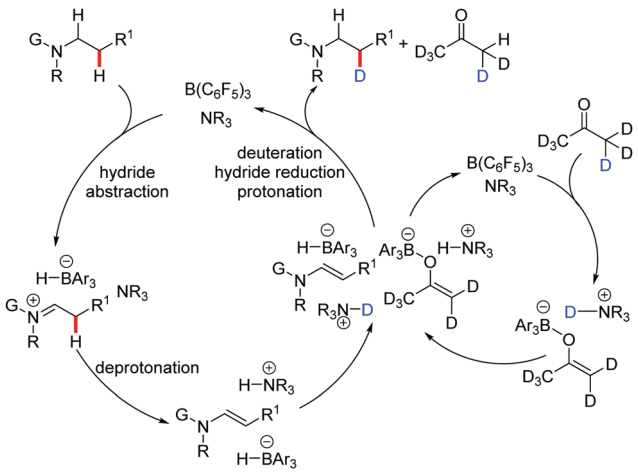
Wasa and co-workers proposed a catalytic deuterium incorporation of β-amino C–H bonds in various *N*-alkylamine-based pharmaceutical compounds. The reactions begin by the action of Lewis acidic $B(C_6F_5)_3$ and Brønsted basic *N*-alkylamine, which convert a drug molecule to its corresponding enamine (Scheme 80).[87]

The acid/base catalysts promote the dedeuteration of d_6-acetone to form deuterated ammonium ions, then deuteration of the enamine leads to the formation of β-deuterated bioactive amines with a high level of deuterium incorporation (Scheme 81).

This protocol was suitable for compounds that contain an array of Lewis acid-sensitive functional groups. Deuteration took place with high regioselectivity for β-amino C–H bonds. For the drug molecules that possess acidic α-carbonyl C–H bonds efficient deuteration was also observed. In recent years, visible-light mediated photoredox catalysis has been extended enormously as an ideal tool to access new organic transformations through SET processes.[88] Using available light sources, transition metal complexes or organic dyes are photoactivated to mediate electron transfer to organic substrates. The resulting radical cation and anion intermediates offer lower energy pathways for bond formation, enabling both the discovery of new reactions and the enhancement of classical transformations *via* improved reaction conditions. Excitation of photoredox catalysts is highly selective, with colorless organic substrates generally being inert to photoexcitation by visible light. As a result, undesirable radical side

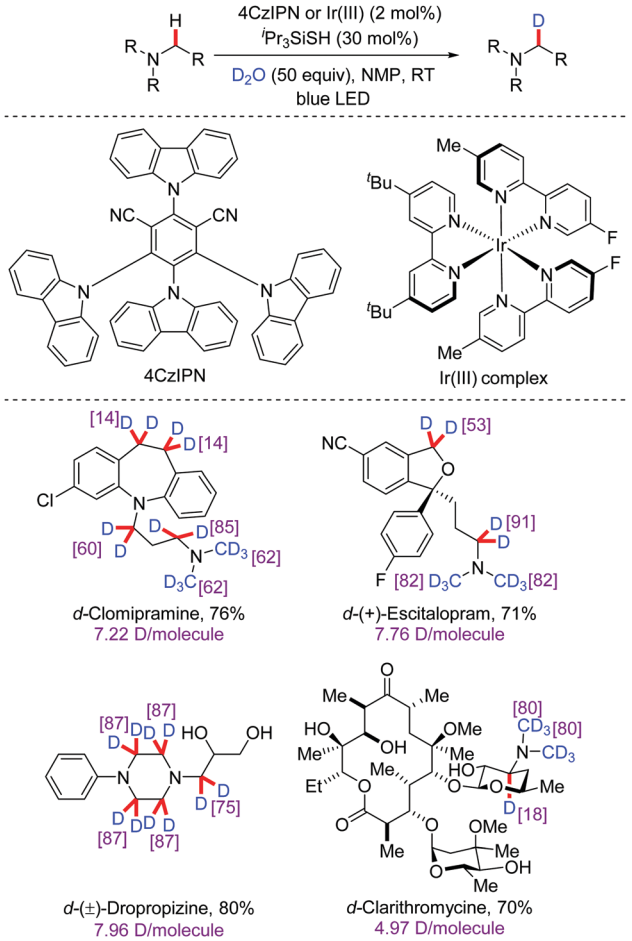


Scheme 80 Deuteration of acyclic and cyclic β-amino C–H bonds.

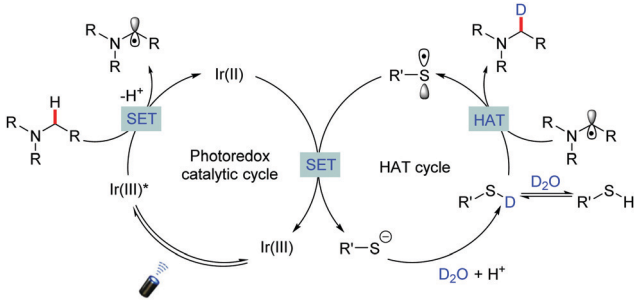


Scheme 81 Proposed catalytic cycle for the deuteration of β-amino C–H bonds in *N*-alkylamine-based pharmaceutical compounds.

reactions can be avoided, widening the substrate scope and improving yields. In 2017, MacMillan and co-workers reported a photoredox-catalysed deuteration of α-amino C(sp^3)–H bonds in a single step, which was applied for high deuterium incorporation into pharmaceutical compounds (Scheme 82).[89] A variety of commercially available drugs containing alkyl amine scaffolds were readily deuterated by the combination of 4-CzIPN or an Ir(III) complex along with a hydrogen atom transfer (HAT) catalyst, triisopropylsilanethiol, with D_2O in *N*-methyl-2-pyrrolidone (NMP) under the irradiation of either blue LEDs or an integrated photoreactor. This method has good functional group tolerance, and uses cheap, readily available D_2O as a deuterating agent. In this protocol, α-amino C(sp^3)–H bonds are deuterated without affecting the C(sp^2)–H ones.

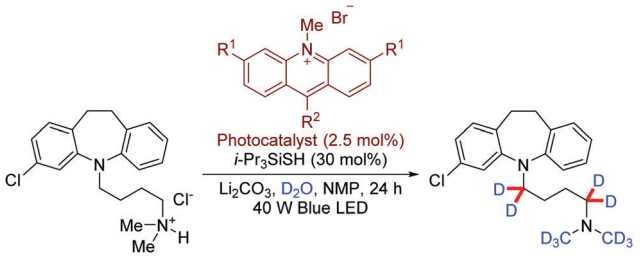


Scheme 82 Photocatalytic deuteration of α-amino C(sp^3)–H bonds.



Scheme 83 Proposed catalytic cycle for the deuteration reaction.

Notably, this method gave excellent deuterium incorporations on a large scale, with incorporation of more than 5 deuterium atoms per molecule and less than 0.1% of the unlabelled compound. They proposed a mechanism involving photoredox catalysis and a HAT process for the deuteration of α-amino C(sp^3)–H bonds as depicted in Scheme 83. Reductive quenching of excited Ir(III)* by the amine substrate forms the α-amino radical after deprotonation. Concurrently, the thiol HAT catalyst exchanges deuterium with D_2O to give the deuterated thiol which serves as the source of deuterium. Due to a



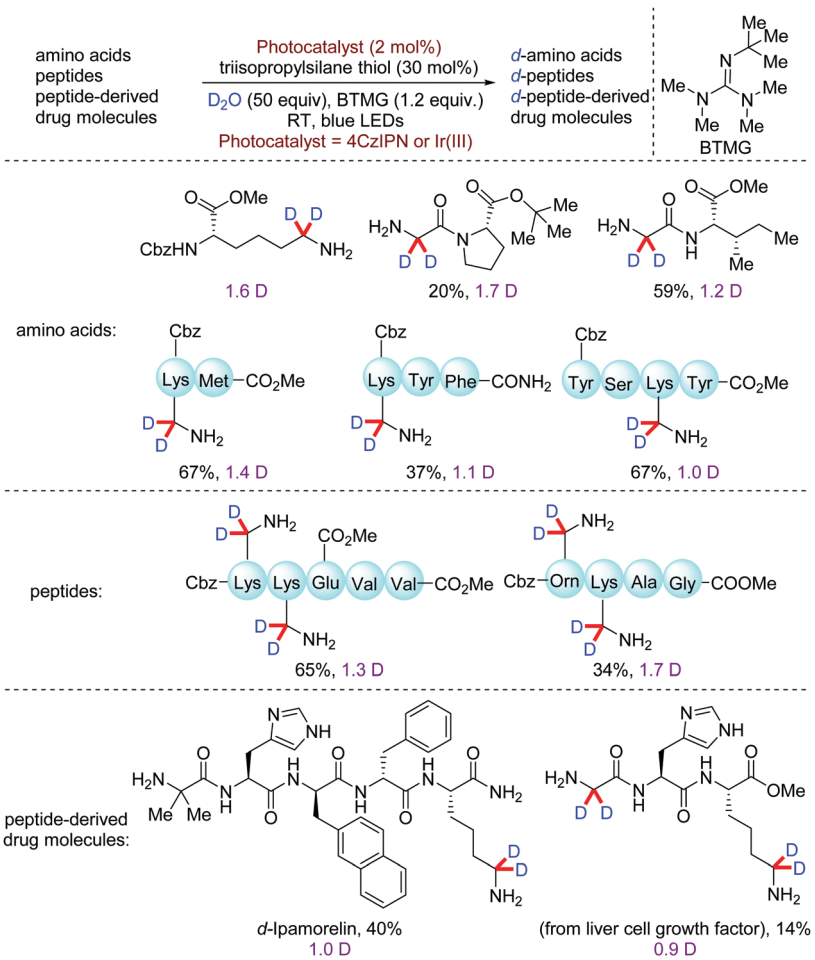
Scheme 84 Application of acridinium photocatalysts in the photocatalytic deuteration of clomipramine.

favourable polar effect and a difference in bond dissociation energy of α-amino C–H (BDE = 93 kcal mol^{-1}) and thiol S–H bonds (BDE = 87 kcal mol^{-1}), the nucleophilic α-amino radical abstracts deuterium from the deuterated thiol to produce the α-deuterated amine. Finally, SET from Ir(II) to the thiol radical regenerates the photocatalyst Ir(III). Following the work of Macmillan, Sparr and co-workers revealed a scalable synthesis of acridinium photocatalysts, which were further used as an efficient catalyst for the deuteration of α-amino C(sp^3)–H bonds of the pharmaceutically relevant amine clomipramine (Scheme 84).[90] Gratifyingly, a high selectivity for the aliphatic positions with an average of 4 deuterium atoms per molecule was observed using low catalyst loading. Employing similar conditions to those reported by MacMillan, in 2020 Derdau and co-workers reported photoredox-mediated deuteration reactions of amino acids, peptides and peptide-derived drugs (Scheme 85).[91]

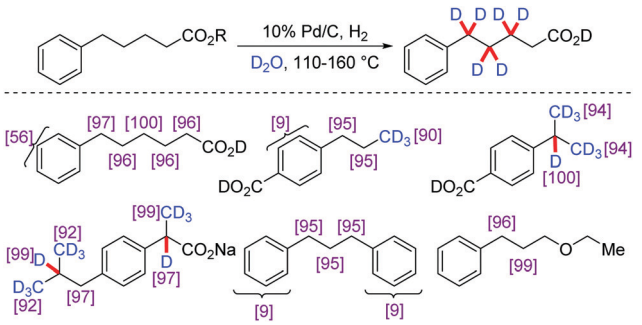
A variety of amino acids including lysine, proline, and glycine derivatives were efficiently deuterated at the C(sp^3)–H bond of the terminal amino moiety. Notably, lysine containing peptides with a chain length of 3 and higher were selectively deuterated at the α-position of the primary amino group of the lysine moiety with a reasonably good amount of deuterium incorporation. The efficiency of this protocol was further demonstrated by deuterium labelling of several known pharmaceuticals such as ipamorelin, a liver cell growth factor with deuterium incorporation of 0.5–2.5 D per molecule.

6.3 Deuteration of C(sp^3)–H bonds of arenes, esters, alkynes, (thio)ethers & ketones

Heterogeneous isotope exchange has been known for the past few decades, but in most of the protocols developed deuterium incorporation was not very high or it was not chemoselective. In 1994, heterogeneous catalytic HIE reactions of benzylic compounds were observed by Buchman and co-workers. This



Scheme 85 Photocatalytic deuteration of amino acids, peptides and peptide-derived drugs.

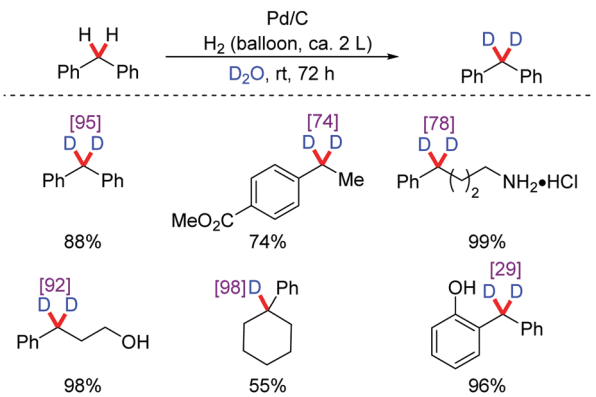


Scheme 86 C–H/C–D exchange reaction on the alkyl side chain of aromatic compounds.

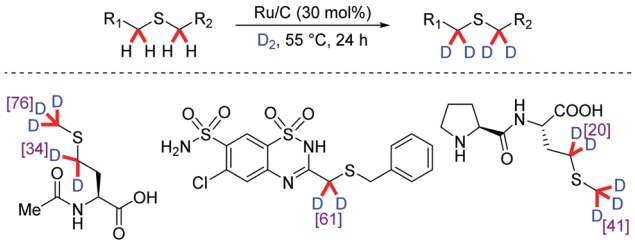
HIE reaction of bibenzyl and benzylic derivatives with D_2 gas was catalysed by 10% Pd/C and performed in solution.[92] This reaction strongly depends upon solvent. In aprotic solvents such as dioxane, ethyl acetate, 3.1 to 3.5 D atoms were incorporated under standard conditions, while in benzene one D atom was incorporated. In 2004, the Hirota and Sajiki group in Japan developed a heterogeneous catalytic method for deuterium labelling of unactivated C–H bonds present in the alkyl side chain of aromatic compounds (Scheme 86).[93] H/D exchange was observed using 10% Pd/C and H_2 in D_2O at elevated temperatures (around 160 °C). Deuterium incorporation drastically decreased when the reaction was performed under D_2 atmosphere instead of H_2 in dry EtOAc which led to the conclusion that D_2O was required for efficient deuteration.

In 2008, Sajiki and coworkers performed a Pd/C-catalysed regioselective deuteration reaction on the benzylic site using D_2O in the presence of a small amount of H_2 gas (Scheme 87).[94] This method affords the corresponding deuterium-labelled compounds with excellent deuterium incorporation efficiency. Using 10% Pd/C in the presence of a small amount of hydrogen gas can achieve high efficiency of H/D exchange with less expensive D_2O as the deuterium source.

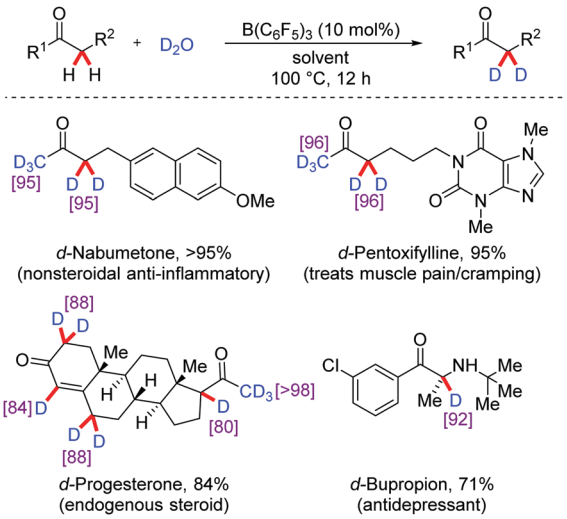
Also, under mild heating conditions (50 °C) the reaction is greatly accelerated which results in a shortening of the reaction time and broadening of the substrate scope. In 2018, Pieters and co-workers reported Ru-catalysed HIE of C(sp^3)–H bonds



Scheme 87 Heterogeneous palladium-catalysed regioselective deuteration at the benzylic position.



Scheme 88 Sulfur-directed Ru-catalysed HIE reaction.



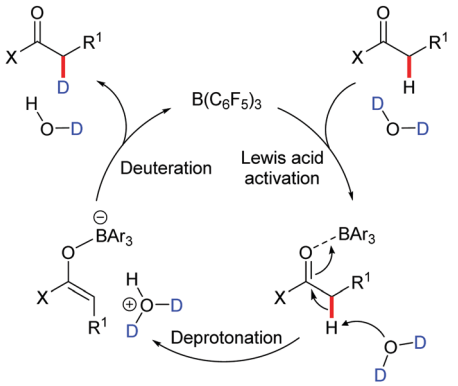
Scheme 89 α-Deuteration of bioactive carbonyl compounds.

directed by sulfur.[95] The transformation, which is catalysed by Ru/C, deuterated a variety of different thioether substructures in complex molecules (Scheme 88).

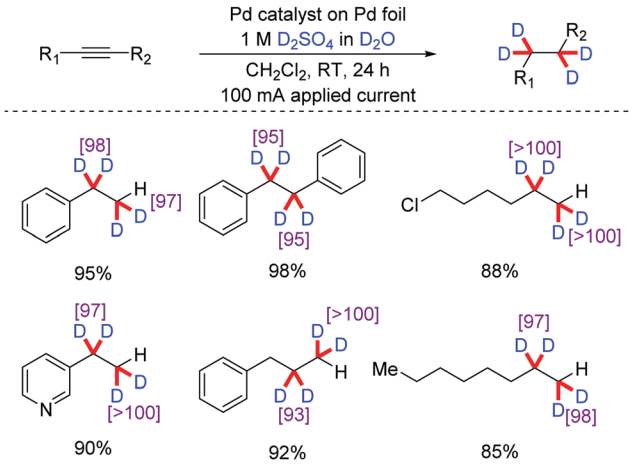
In 2020, the Wasa group developed a deuteration process for α-C–H bonds in various carbonyl-based pharmaceutical compounds (Scheme 89).[96] They implemented the cooperative catalytic function of $B(C_6F_5)_3$ and D_2O to show that it is possible to convert a carbonyl-based drug to its corresponding boron–enolate, and the same catalytic system can generate a labelling agent from D_2O.

An array of acyclic and cyclic bioactive ketones were efficiently deuterated with high regioselectivity. The authors proposed a catalytic cycle for the deuteration process, wherein they envisioned α-deuteration of bioactive carbonyl compounds by utilizing a Lewis acidic organoborane, $B(C_6F_5)_3$, that is able to activate the carbonyl compound towards deprotonation by D_2O to generate a boron enolate and D_2O^+–H. Deuteration of the enolate by D_2O^+–H generates the desired deuterated product (Scheme 90).

In 2020, Berlinguette and co-workers reported a site-selective reductive deuteration of alkynes to produce deuterated alkanes using a tandem electrochemical palladium membrane reactor (Scheme 91).[97] In this strategy in a palladium membrane reactor, deuterons from D_2O are reduced to deuterium atoms at a palladium membrane which travel through the membrane and deuterate the desired alkyne molecule.



Scheme 90 Proposed catalytic cycle for α-deuteration of carbonyl-based pharmaceutical compounds.



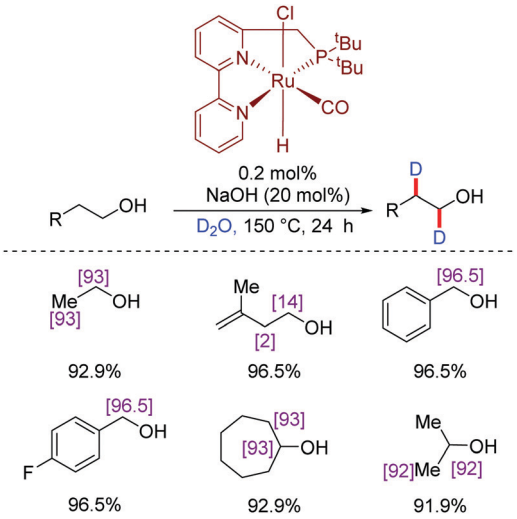
Scheme 91 Electrolytic deuteration of alkynes to deuterated alkanes using palladium membrane reactor.

Moreover, deuteration reaction rates and chemoselective formation of C(sp^2)–D or C(sp^3)–D bonds can be controlled by simply changing the current applied to the system. This electrocatalytic deuteration strategy proceeds with high functional group tolerance along with excellent deuteration and high site selectivity. Many precursors to valuable deuterated pharmaceuticals were developed using the palladium membrane reactor which highlights the utility of the reactor.

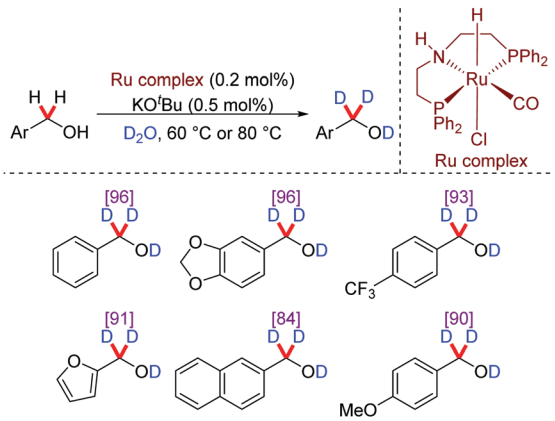
6.4 Deuteration of C(sp^3)–H bonds of alcohols

In 2013, Milstein and co-workers developed a protocol for deuteration of primary and secondary alcohols at α- and β-positions using heavy water (Scheme 92).[98] Both aliphatic primary and benzyl alcohols showed high degrees of deuterium incorporation at the α-position. Acyclic as well as cyclic secondary alcohols were deuterated at both α-and β-positions. However, deuteration of tertiary alcohols was ineffective under this protocol. The reaction does not require inert conditions and can be performed under air which shows the robustness of the catalyst used.

In 2015, Gunanathan and co-workers reported a highly selective Ru-catalysed α-deuteration of primary alcohols using



Scheme 92 α and β deuteration of primary and secondary alcohols.

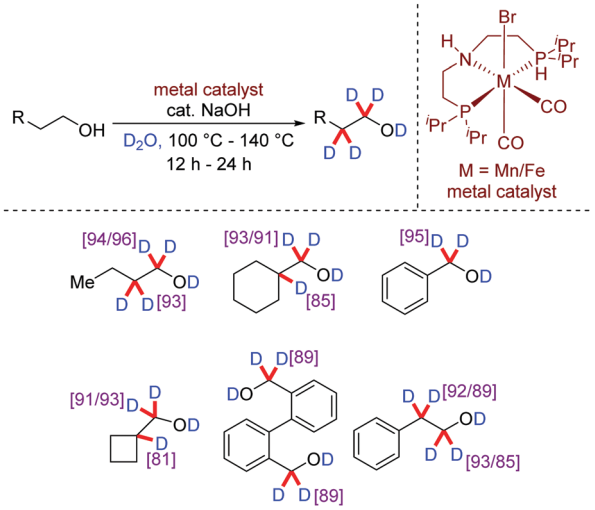


Scheme 93 Ru-Catalysed deuteration of aryl methanols.

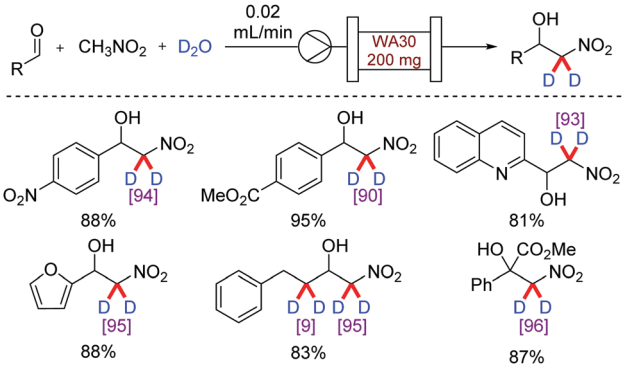
readily available D_2O (Scheme 93).[99] They used the same ruthenium catalyst as for the deuteration of terminal alkynes. A high level of selective deuterium incorporation along with mild experimental conditions and low loadings of the catalyst makes this protocol very attractive for both laboratory- and large-scale preparation.

The reaction proceeds *via* O–D activation of D_2O and alcohols by the Ru catalyst and subsequent alkoxide ligand dehydrogenation to the carbonyl compounds by amine-amide metal–ligand cooperation. Then, catalytic hydrogenation of the carbonyl motif affords the desired α-deuterated product. In another example, Prakash and co-workers reported a convenient and cost-effective regioselective deuteration of primary and secondary alcohols in D_2O catalysed by earth-abundant homogeneous first-row transition metal pincer complexes (Scheme 94).[100]

Here, Mn and Fe pincer complexes are used as catalysts which result in a high degree of deuterium incorporation at the α- and β-position (Mn) or exclusively at the α-position (Fe), for primary alcohols. The reason behind H/D exchange selectivity



Scheme 94 Mn- and Fe-catalysed deuteration of alcohols.



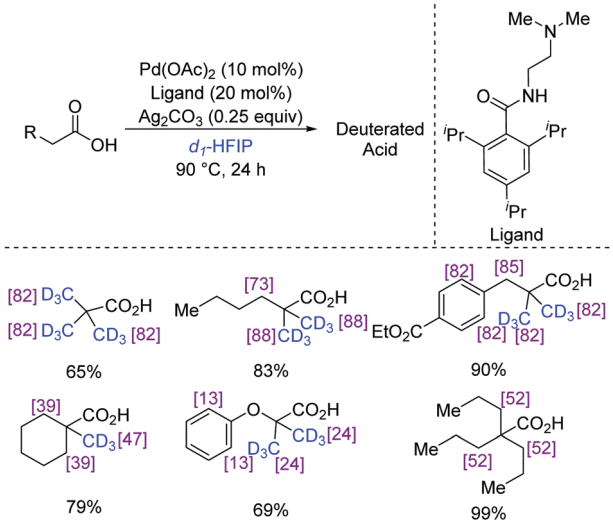
Scheme 95 Synthesis of deuterium labelled β-nitroalcohols catalysed by WA30.

differences between Mn and Fe pincer complexes is the different hydrogenation rates of the aldehyde species formed *in situ*. It was also predicted that metal–alkoxide and metal–deuteroxide species were involved in the catalytic cycle. In 2020, Sajiki and co-workers reported an efficient continuous-flow system for the synthesis of regioselective deuterium-labelled β-nitroalcohols using WA30. A variety of β-nitroalcohols were deuterated in moderate to excellent yields and high deuterium incorporation (Scheme 95).[101]

Also, cost-effective and environmentally friendly D_2O was used as the deuterium source. In the heterogeneously-catalysed continuous flow system, the substrate and reagent solutions are mixed well in the narrow flow channel and the mixture is continuously introduced into the prepacked cartridge containing the solid catalyst. The products are continuously obtained at the outlet of the cartridge in the mobile phase.

6.5 Deuteration of C(sp^3)–H bonds of carboxylic acids

The carboxyl group can act as a directing group and can bind with metal in κ^1 and κ^2 fashion. However, only the κ^1 mode is



Scheme 96 β-C(sp^3)–H deuteration of carboxylic acids.

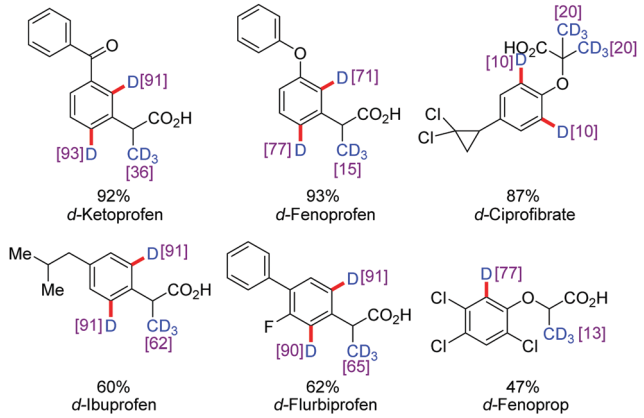


Fig. 7 Late-stage β-C(sp^3)–H deuteration of carboxylic acid containing drug molecules.

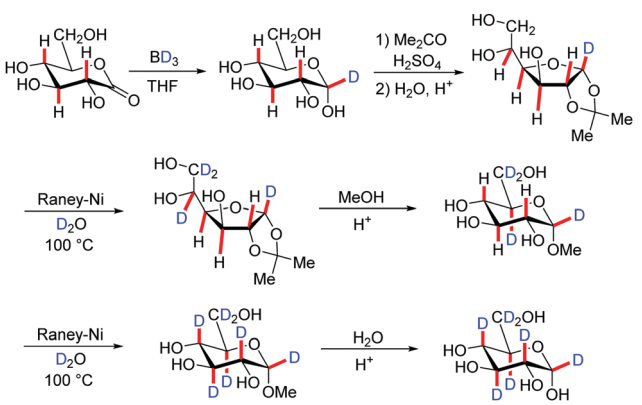
crucial for β- or γ-C–H activation which can be achieved in the presence of any alkali metal salt.[102]

Utilizing this concept, the groups of Yu, Maiti and van Gemmeren developed different C–H functionalisation reactions at the β and γ positions of the carboxyl group. Very recently the van Gemmeren group reported a β-C(sp^3)–H deuteration of aliphatic acids (Scheme 96).[103] d_1-HFIP as deuterium source and an ethylenediamine-based ligand were crucial for this transformation. This protocol also allowed deuteration of non-activated methylene β-C(sp^3)–H bonds. Late-stage deuteration of drug molecules such as ibuprofen, flurbiprofen, ketoprofen, fenoprofen, clofibric acid, ciprofibrate, clinofibrate, and bezafibrate were also realized under this protocol (Fig. 7).

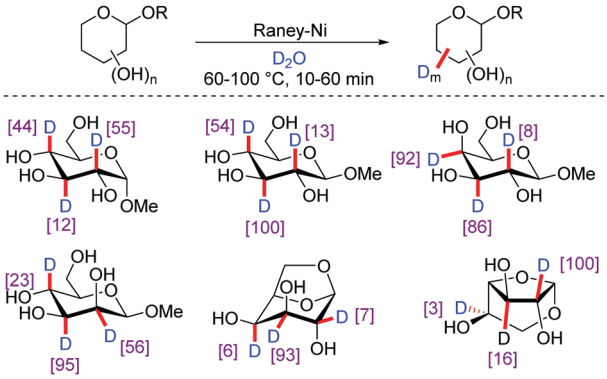
6.6 Deuteration of C(sp^3)–H bonds of carbohydrates

Although of immense interest for the investigation of biosynthetic pathways, the simplification of complex NMR spectra and the study of glycolipid dynamics in cell membranes,[104] C–H deuteration of carbohydrates has remained scarce. The

most prominent methods to generate deuterated carbohydrates are still biotechnological methods or stereoselective reductions by $NaBD_4$ of distinct carbonyl groups obtained by oxidation of the respective hydroxyl groups. For the latter method, most commonly, a distinct protecting group pattern is crucial. Nevertheless, already in the 1970s the first attempts were made to substitute C-bonded hydrogens in carbohydrates by deuterons. Based on the deuteration of primary and secondary alcohols using RANEY®-Ni, sugars were also deuterated.[105] Mechanistically, one assumes a dehydrogenation by Ni and a subsequent reduction by the deuterium in deuterated RANEY®-Ni. The deuterated RANEY®-Ni is easily available by the presence of D_2O. Commonly, only carbon atoms with free hydroxyl groups undergo such an exchange. Therefore, for methyl hexopyranosides the exchange rate at C1 and C5 is extremely slow. Surprisingly, the process generates almost no epimers, *i.e.* stereochemical information is not lost. All sugars stay in their native configuration. To explain the retention of configuration one assumes that the molecule is absorbed so strongly to the surface during the oxidation–reduction process that it is not able to alter its position. Free reducing sugars cannot be deuterated by this method because a reduction to alditols takes place. In addition, one should not use alditols for deuteration purposes since the less rigid molecules lead to a less preferred absorption on the surface and thus to more epimerization.[105] To access perdeuterated D-glucose *via* a chemical approach several synthetic steps were required (Scheme 97).[106] As starting material, D-glucono-1,5-lactone was used which was reduced by BD_3 providing deuterium at C1. This compound was transformed to the respective furanose in acetone with sulfuric acid as catalyst. Afterwards, weak acid cleaved the less stable isopropylidene protecting group at C5/C6. The obtained compound was subjected to RANEY®-Ni catalysis in deuterated water. During this process the hydrogens at C5 and C6 are exchanged by deuterium. Acidic cleavage of the isopropylidene in methanol afforded the methyl glucoside which is then further deuterated at the positions C4, C5 and C6. To cleave the anomeric methoxy group and to obtain the native sugar, acidic hydrolysis takes place in the final step. Since the mentioned



Scheme 97 Synthesis of perdeuterated glucose.



Scheme 98 Deuteration of carbohydrates by Ra–Ni in deuterated water.

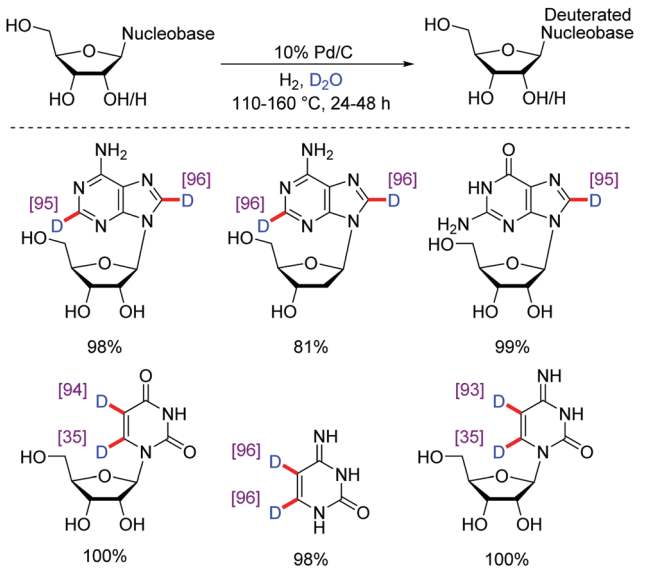
report is rather old, an in-depth study of the completeness of H/D exchange at the different positions was not conducted.

Later on, investigations with a variety of non-reducing methyl glycosides[107] and 1,6-anhydrosugars[108] were performed and showed that the rate of H/D exchange varies significantly between the different positions. As before, Ra-Nickel proved to be the best choice as catalyst, using deuterated water as both solvent and deuterium source. Scheme 98 shows that the exchange processes suffer from poor regioselectivity. How facile a C–H bond is converted into a C–D bond strongly depends on its accessibility. Several parameters are decisive and it is almost impossible to rationalize the specific outcome; of course, steric hindrance (*e.g.* the stereochemistry at the anomeric center) plays a major role, but also the existence of *syn*-axial hydroxyl groups besides a few other factors.[107] Even the type of RANEY®-Nickel seems to be very important. Commonly, the anomeric hydrogen is not touched and the methylene unit at the primary hydroxyl is only transformed to a minor extent. Later on, the method was extended by the use of a microwave oven leading to much shorter reaction times (Scheme 98).[109]

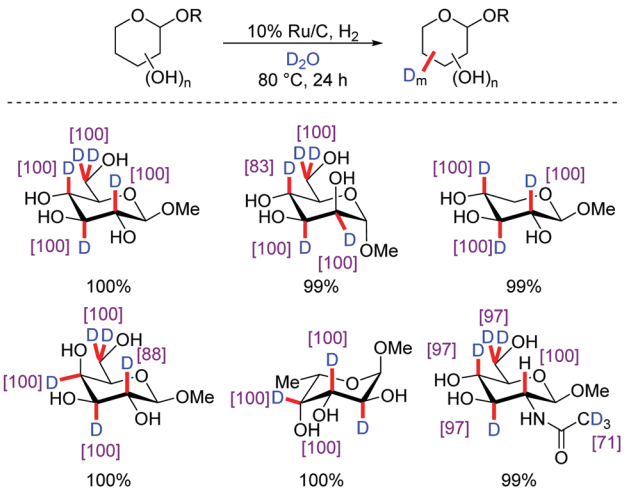
With such a procedure even a disaccharide such as sucrose was partially deuterated. However, problems with the regioselectivity remained. A more recent method to obtain partially deuterated carbohydrates was developed by the Sajiki lab.[110] It is based on heterogeneous Ru catalysis. This site-selective deuteration of non-reducing sugars allows access to various deuterated mono- and disaccharides.[111] Often quantitative deuterium incorporation was observed with 10% Ru on carbon, a hydrogen atmosphere and heavy water as deuterium source and solvent. The reaction runs for 24 h at 80 °C. Only C–H bonds geminal to hydroxyl groups are exchanged (Scheme 99). As the example of the fucoside shows methyl groups in 6-deoxy sugars remain untouched. This fact leads to the advantage that very selective deuterations were developed using a protecting group strategy. C–H bonds with geminal hydroxy groups being protected as isopropylidene acetals are not deuterated.[111] MOM groups and Me groups were also in use to hinder deuterations at the respective carbon atoms. The methodology uses, besides the conditions mentioned above, LiOH or NaOH as base. This method was applied to pentoses and hexoses in their furanose and their pyranose forms (Scheme 100).

7. C–H deuteration of nucleosides and (oligo)nucleotides

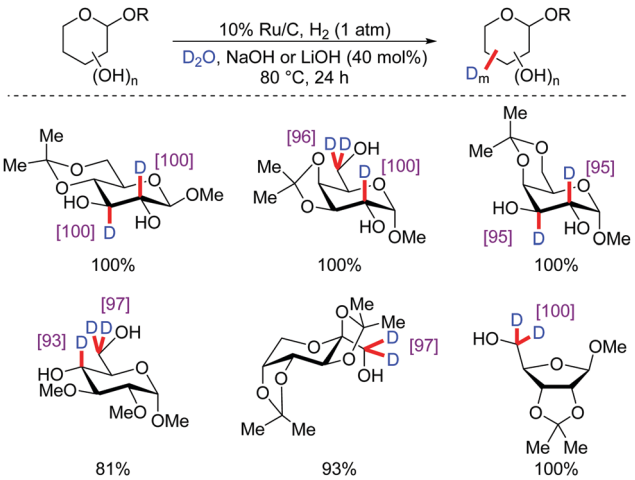
The Ru-based deuteration method shown in Scheme 99 for monosaccharides was also successfully employed to deuterate the ribose core of nucleosides.[111] To reach completely deuterated 2-deoxyribose one starts from ribose and later transforms the hydroxy group at position 2 into D by a Barton-McCombie deoxygenation using Bu_3SnD.[112] For H/D exchange reactions of the nucleobase different pathways were followed. Already in the 1960s a HIE at position 8 of purine derivatives took place. However, harsh acidic/basic conditions and temperatures of 80–110 °C were required.[113] A Pd-catalysed approach employing Pd on charcoal in D_2O also needs temperatures of 110-160 °C. Without touching the sugar part this procedure exchanges all carbon-bonded protons in the nucleobase in excellent yield. Adenine, guanine, cytosine, uracil and thymine derivatives were successfully converted (Scheme 101).[114]



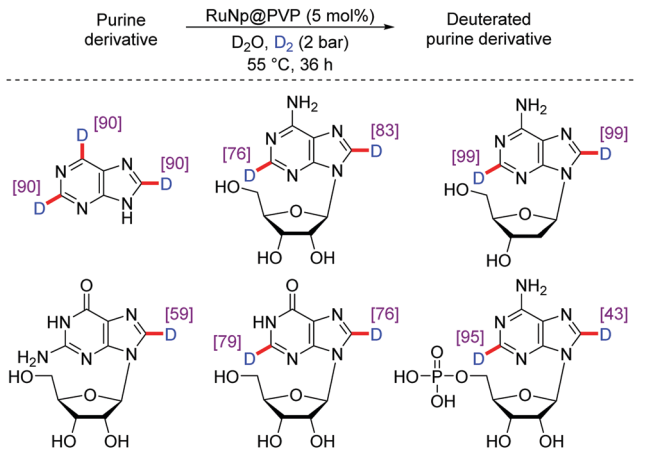
Scheme 101 H/D exchange of nucleotides using Pd catalysis under an atmosphere of H_2 in D_2.



Scheme 99 H/D exchange of methyl glycosides using Ru/C-H_2-D_2O.



Scheme 100 Regioselective H/D exchange of partially protected monosaccharides using Ru/C-H_2-D_2O.



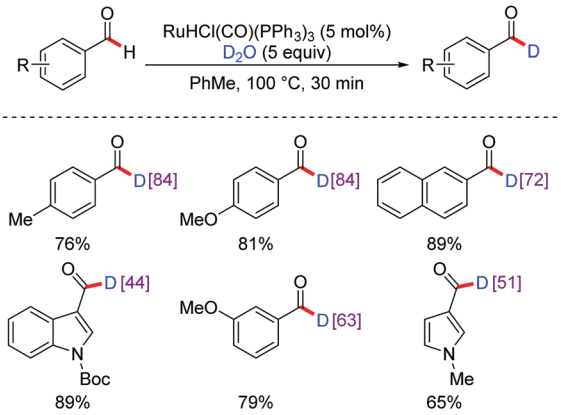
Scheme 102 H/D exchange of purine derivatives using Ru nanoparticles under an atmosphere of D_2 in D_2O.

A very recent and much milder method made use of ruthenium nanoparticles embedded in a PVP polymer matrix (RuNp@PVP) for the H/D-exchange of purine derivatives.[115] Under elevated pressure of deuterium gas in D_2O as solvent all positions α to a nitrogen atom were deuterated (Scheme 102).

Secondary reactions were not observed. The system not only worked for nucleosides, but also for nucleotides, cyclic phosphates, diphosphates and triphosphates. Even oligonucleotides such as 8- and 12-mers were converted. Pyrimidine-derived nucleobases were not affected; the deuterium incorporation took place solely in the purine nucleobases.

8. C–H deuteration of aldehydes

In 2017, the Newman group reported a catalytic deuteration of aldehydes using $RuHCl(CO)(PPh_3)_3$ as the catalyst (Scheme 103).[115]

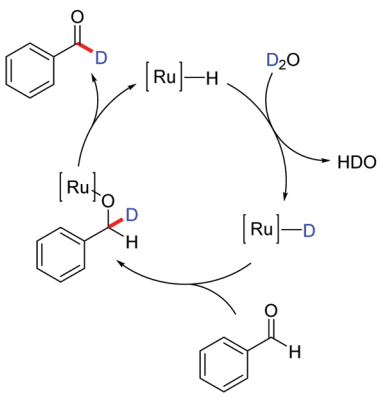


Scheme 103 Ru-catalysed deuteration of aromatic aldehydes.

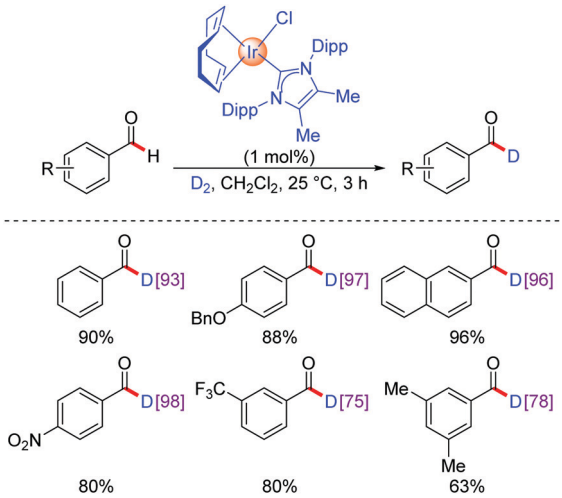
This catalyst was easily prepared from inexpensive $RuCl_3$. Deuteration of the formyl C–H bond of aldehydes was achieved within 30 min with moderate to good deuterium incorporation. Deuterium incorporation was increased to 90% when the deuterated product was resubjected to the reaction conditions.

The reaction proceeds through a very simple mechanism: first coordination of Ru followed by insertion takes place to generate a ruthenium alkoxide bearing one deuterium and one hydrogen atom on the alkoxide α-carbon. β-hydride elimination provides the deuterated aldehyde and regenerates the initial ruthenium hydride complex (Scheme 104).

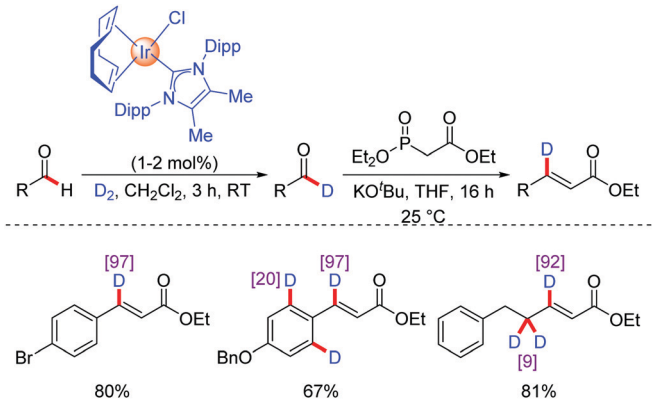
Tuttle and co-workers developed a mild and efficient methodology for a selective formyl C–H bond labelling utilizing an Ir carbene-based catalyst and D_2 gas as deuterium source (Scheme 105).[116] Various *para*-substituted benzaldehydes were subjected to this deuteration with good to excellent regioselectivities. However, in a few cases, aryl C–H labelling also occurred. The group further extended the work to the labelling of aliphatic aldehydes. They also demonstrated one-pot labelling followed by olefination of aldehydes (Scheme 106). DFT studies suggest a competitive reaction between two cycles, an Ir(III) catalytic cycle for the aryl C–H labelling and an Ir(III)/Ir(IV) cycle for the formyl C–H labelling with partial decarbonylation.



Scheme 104 Plausible mechanism for the deuteration of aromatic aldehydes.



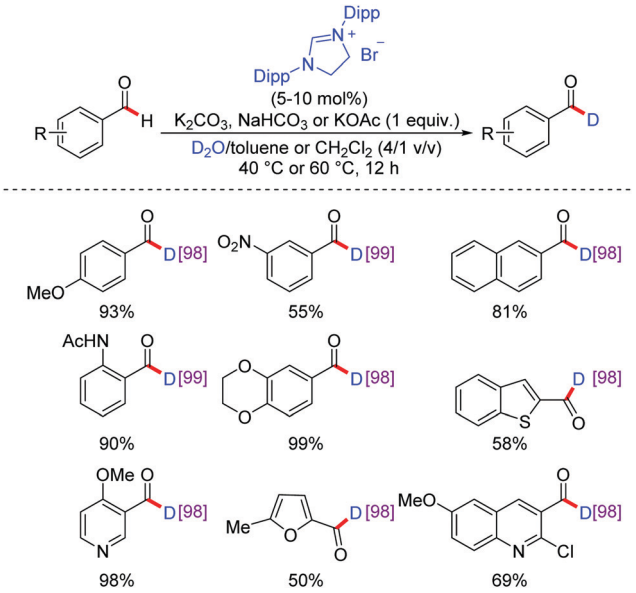
Scheme 105 Ir–NHC catalysed deuteration of benzaldehyde derivatives.



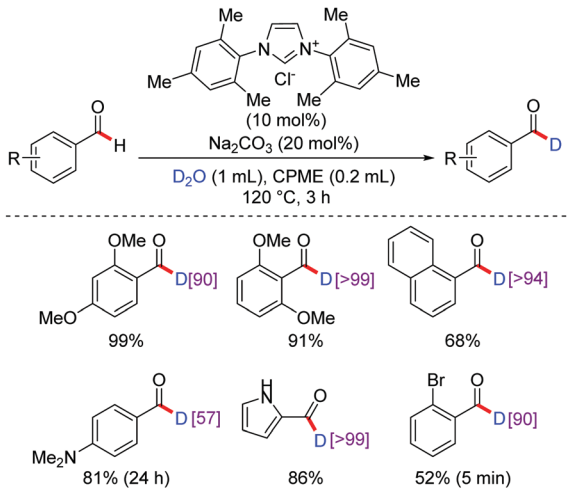
Scheme 106 One-pot formyl labelling and olefination of aldehydes.

Wang and Zhang later provided a new avenue to C–H deuteration of aldehydes. This protocol makes use of NHCs which promote reversible H/D exchange to produce C1 deuterated aldehydes (Scheme 107).[117] The organocatalytic methodology was applicable to aryl, alkyl and alkenyl aldehydes along with drug molecules and natural products, demonstrating more than 100 examples. This proves the robustness of the protocol. The NHC catalyst is known to produce the Breslow intermediate after activation of the formyl C–H bond of the aldehyde which is able to undergo self-benzoin condensation. However, the reaction of aldehyde with NHC catalyst was performed in D_2O which in turn produced deuterated Breslow intermediate reversibly which further reacts with D_2O to produce the desired deuterated analogue of the aldehyde with regeneration of the catalyst.

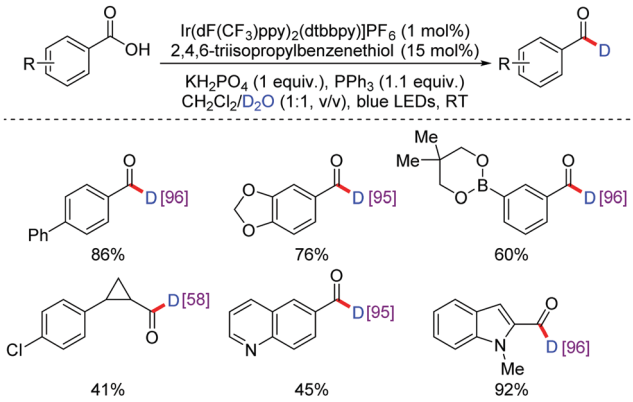
Following the above mentioned papers, the Sajiki group published a seminal work focussing on the direct deuteration of aldehydes by using an NHC catalyst, D_2O as deuterium source and process chemistry-friendly cyclopentyl methyl ether (CPME) as solvent (Scheme 108).[118] Substrates differed strongly in comparison with the previous report. They also achieved deuteration of the benzoin condensation by-product.



Scheme 107 Metal free NHC catalyst for deuteration of aromatic aldehydes.



Scheme 108 NHC-Catalysed formyl deuteration of aromatic aldehydes.



Scheme 109 Deoxygenative deuteration of carboxylic acids to produce deuterated aldehydes.

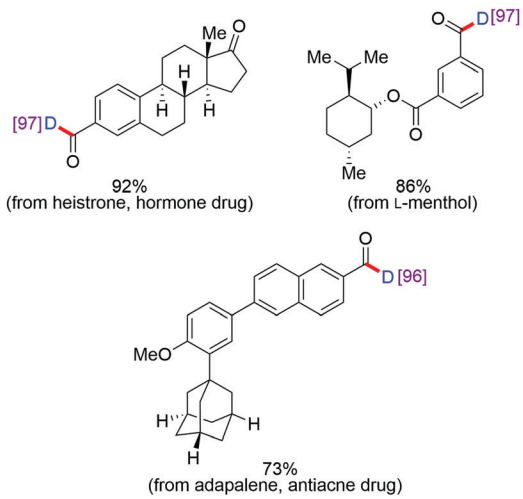
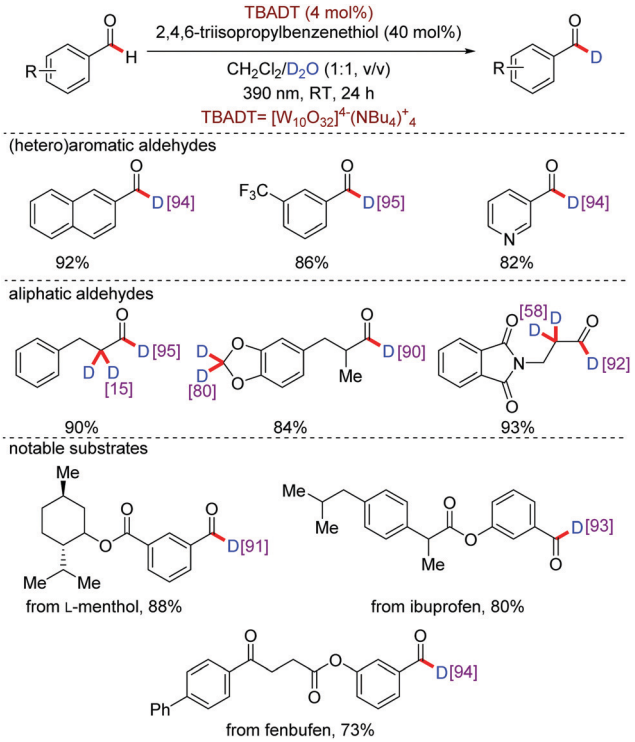


Fig. 8 Deoxygenative deuteration of complex biologically active molecules.

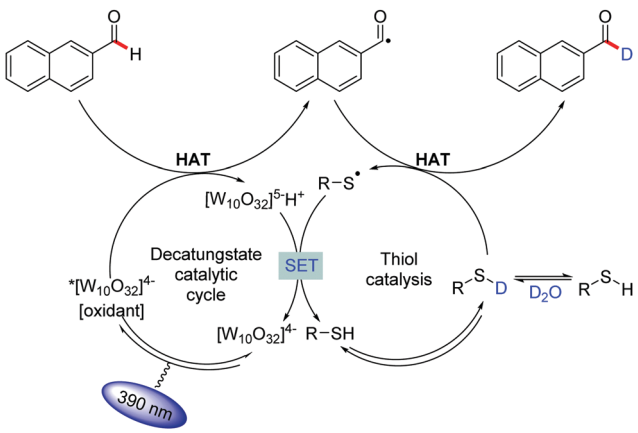
Deoxygenative deuteration of carboxylic acids to produce deuterated aldehydes was developed by Xie and co-workers (Scheme 109).[119] Ph_3P was used as an oxygen atom transfer reagent for deoxygenation of aromatic acids and Ph_2POEt for aliphatic acids. The reaction proceeds *via* an SET mechanism where $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ was used as photocatalyst, and 2,4,6-triisopropylbenzenethiol as the HAT catalyst. The methodology showed an excellent functional group tolerance which enabled the synthesis of complex deuterated aldehydes by late-stage functionalisation (Fig. 8).

In 2020, the Wang group demonstrated a formyl-selective deuteration of aldehydes with D_2O *via* a synergistic combination of light-driven, polyoxometalate-facilitated HAT and thiol catalysis (Scheme 110).[120] Upon combining the photocatalyst tetra(*n*-butyl)ammonium decatungstate (TBADT) and a thiol catalyst 2,4,6-triisopropylbenzenethiol, a wide range of aromatic as well as aliphatic aldehydes bearing different electronic and physical properties were selectively deuterated at the formyl $C(sp^2)$–H bond. High yields and excellent deuterium incorporation were achieved using D_2O under the irradiation of near UV light (390 nm). The proposed mechanistic cycle for the formyl-selective deuteration is shown in Scheme 111. Moreover, this protocol was effective for late-stage modification of several medicinally relevant aldehydes with high potency. It is worth mentioning that although linear and branched aliphatic aldehydes were susceptible to this deuteration procedure, deuteration also occurred at the α-position of the formyl group under these photocatalytic deuteration conditions. Aldehydes, being a versatile functional group, show plenty of organic transformations; thus, libraries of deuterated compounds were accessed using this protocol.

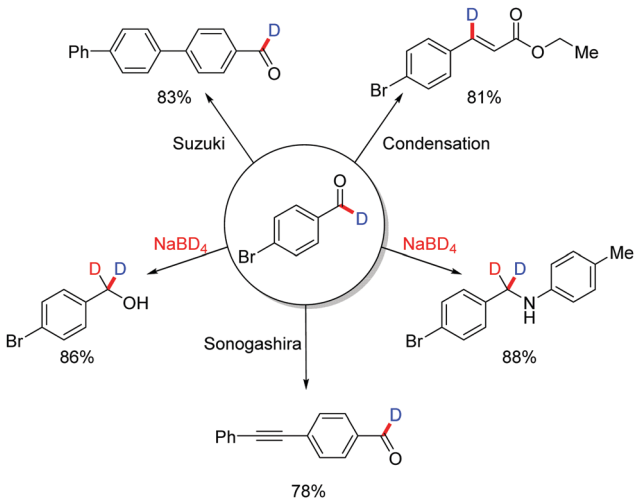
Deuterium labelled aldehydes underwent reduction, reductive amination and Horner–Wadsworth–Emmons olefination to produce deuterated alcohols, deuterated amines and β-deuterated α,β-unsaturated esters, respectively (Scheme 112).



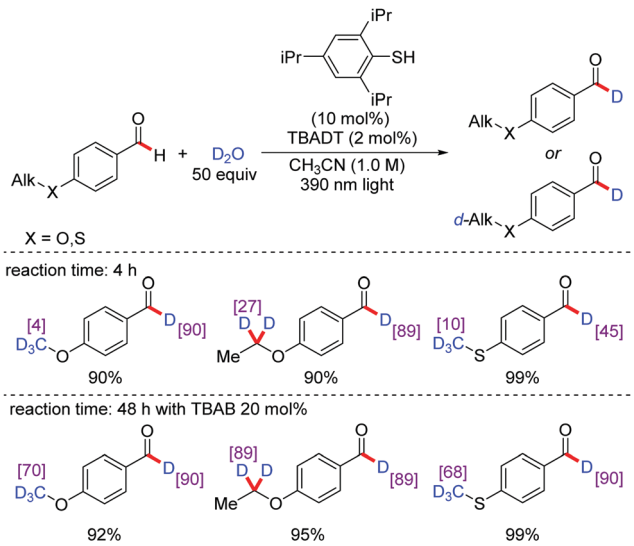
Scheme 110 Photoredox-catalysed deuteration of C(sp^2)–H bonds.



Scheme 111 Proposed mechanistic cycle for the formyl-selective deuteration.



Scheme 112 Transformations of a deuterated aldehyde.



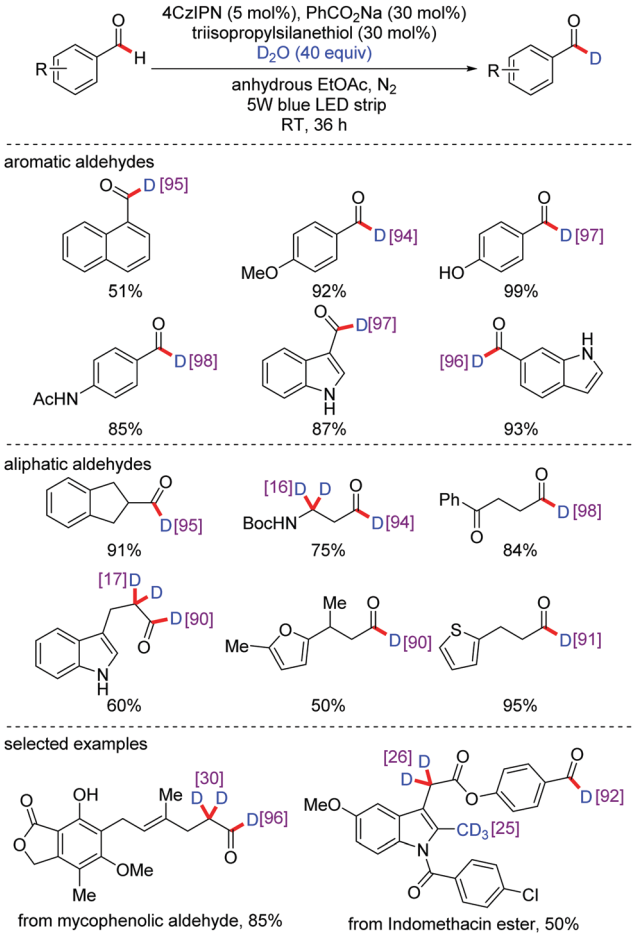
Scheme 113 Photocatalytic selective sequential deuteration of formyl C–H and hydridic C(sp^3)–H bonds.

Using a similar strategy to that designed by the Wang group, in 2020 Wu and co-workers demonstrated deuteration of formyl C–H bonds of aldehydes and other activated hydridic C(sp^3)–H bonds using the photocatalyst TBADT and the thiol catalyst 2,4,6-triisopropylbenzenethiol in acetonitrile with D_2O as the deuterium source (Scheme 113).[121] It is noteworthy that the reaction time was reduced to 4 h instead of 24 h in Wang's work.

The authors also reported that increasing the reaction time to 48 h together with the presence of TBAB (tetra(*n*-butyl)-ammonium bromide), hydridic C(sp^3)–H bonds such as α-oxy, α-thioxy and benzylic C(sp^3)–H bonds in aldehydes are also efficiently deuterated. Furthermore, the authors demonstrated late-stage deuteration of various pharmaceuticals and drug precursors. In the same year, the Wang group demonstrated deuteration of formyl C(sp^2)–H bonds *via* a photoredox catalytic, visible light-mediated neutral radical approach (Scheme 114).[122]

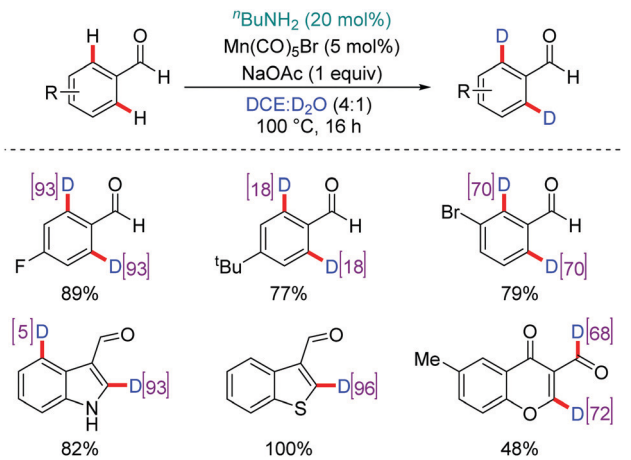
By the synergistic combination of the photoredox catalyst 4CzIPN and two HAT catalysts (sodium benzoate and triisopropylsilanethiol), a broad variety of substrates ranging from aromatic aldehydes to aliphatic aldehydes bearing different functionalities had been efficiently and selectively deuterated at the formyl group using D_2O as the deuterium source.

Complex pharmaceutically relevant structures were also successfully deuterated using this protocol. Distinct from the established transition metal catalysed ionic H/D exchange processes, this organophotoredox catalytic radical strategy was successfully employed.

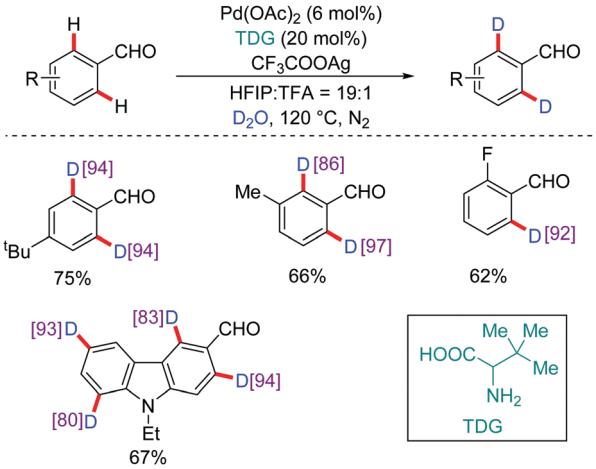


Scheme 114 Deuteration of formyl groups by an organophotoredox catalytic radical strategy.

Beller's group performed manganese catalysed *ortho*-selective deuteration of aromatic aldehydes using an amine as a transient directing group *via* C(sp^2)–H activation (Scheme 115).[123] 5 mol% of $Mn(CO)_5$ was found to be the optimum catalyst and a combination of DCE and D_2O was selected as solvent. Different



Scheme 115 Transient directing group assisted deuteration of aromatic aldehydes.



Scheme 116 *tert*-Leucine as a transient directing group for deuteration of benzaldehydes.

benzaldehyde derivatives and heterocycles were deuterated at the *ortho* position with high selectivity and good yield. Pd-catalysed *ortho*-selective deuteration of aromatic aldehydes by using a transient directing group was nicely described by Gao and co-workers in 2021 (Scheme 116).[124] α-Amino isobutyric acids were used as the transient directing group (TDG) in this strategy. Among various α-amino acids *tert*-leucine provided the best result giving 70% deuterium incorporation. Using the redox-neutral medium D_2O, aldehydes were well tolerated in these reaction conditions with good to excellent deuterium incorporation. The authors also proposed a reversible concerted metalation-deprotonation (CMD) pathway for the formation of the deuterated product.

9. Some deuterated drug molecules and their uses

Deuteration has been primarily used to study KIEs of reactions, but recently its significance in pharmaceutical chemistry has been realised. Bioactive organic structures/potential drugs are decorated with C–H bonds and these are highly prone to biological degradation which takes place mostly in the liver. This process hampers the activity and the half-lives of drugs. Deuteration of the C–H bonds has significantly slowed this possible degradation pathway and in turn has successfuly generated pharmacophores with enhanced bioactivity. The growing demand for new heavy drugs with improved half-lives has triggered the development of deuterium labelled pharmacophores. Here, a few common deuterated drugs commercialized in the market are discussed.

Deutetrabenazine

In 2017, the U.S. Food and Drug Administration (USFDA) first approved deutetrabenazine as a deuterated drug for the treatment of chorea associated with Huntington's disease (Fig. 9a). This drug has improved pharmacokinetic properties compared to its non-deuterated equivalent.[125] Tedious techniques such as

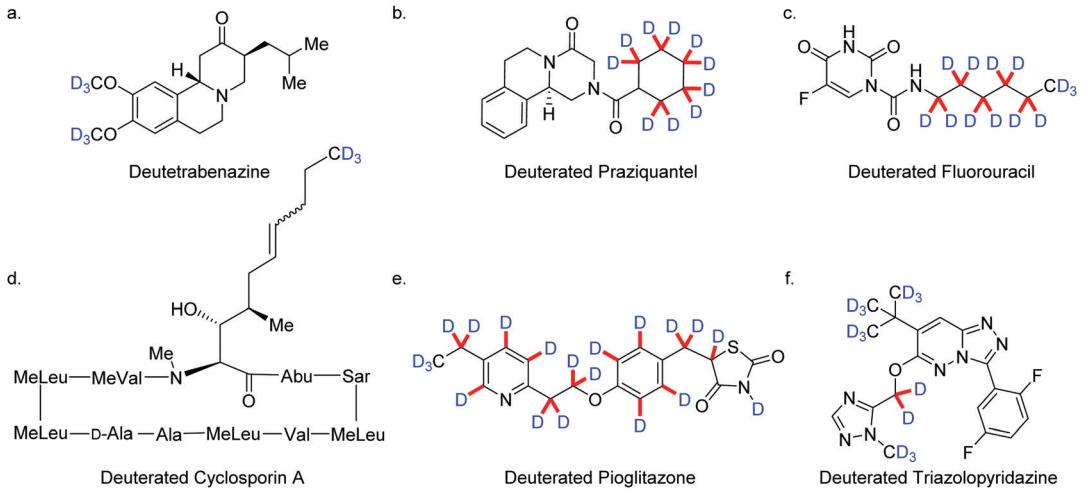


Fig. 9 Some representative deuterated drugs.

column chromatography and the use of genotoxic d_3-iodomethane were not associated with the preparation of deutetrabenazine.

Pyrazinoisoquinoline

Praziquantel, which is an analogue of pyrazinoisoquinoline compounds, is used as an antihelminthic, antitrematodal agent (Fig. 9b).[126] Deuterated analogues of praziquantel are used for the treatment of schistosomiasis, which is an infection by schistosoma worms. Single step, two step or multistep methods were used to synthesize praziquantel by the researchers. The intermediates and derivatives formed during the reaction were eco-friendly. These products had high efficacy in the treatment of infectious diseases such as schistosomes and liver flukes.

Fluorouracil

Deuterating 5-fluorouracil derivatives prevent their clearance by slowing cytochrome P450-dependent drug metabolism (Fig. 9c).[127]

Cyclosporine

Deuteration of cyclosporine molecules results in altered physicochemical and pharmacokinetic properties which are useful in the treatment of transplantation rejection, host *vs.* graft disease, psoriatic arthritis, aplastic anaemia and relapsing polychondritis (Fig. 9d). Deuterating the methyl groups of the cyclosporine molecule results in a slower rate of oxidation of the C–D bond compared to the non-deuterated C–H bond. Lower rates of oxidation, metabolism and clearance result in greater and more sustainable biological activity.[128] Deuteration is favourable at various sites of the cyclosporine molecule to increase the potency of the drug, reduce toxicity, and to improve the stability of the molecule.

Pioglitazone

Deuterated pioglitazone is used for treating diseases like diabetes mellitus type 2 or non-alcoholic steatohepatitis (Fig. 9e).[129] Deuterium-enriched pioglitazone can be achieved either by exchanging protons with deuterium or by synthesizing the molecule with deuterium enriched starting material.

Triazolopyridazine

Deuterated triazolopyridazine is useful in the treatment or prevention of diseases or disorders of the central nervous system including anxiety, convulsions, and also migraine associated pain (Fig. 9f).[130]

10. Conclusion and future prospects

As hydrogen isotopes are very significant in modern biological, chemical and ecological sciences, the development of HIE reaction methods are highly relevant and urgently required. Homogeneous metal catalysed HIE reactions have the greatest impact on the labelling of complex molecules by late-stage C–H functionalisation. In spite of simplicity of transformation, HIE needs a continually evolving preparative toolbox to satisfy the demand with regard to efficiency, selectivity and functional group tolerance. Deuteration in arenes has been well explored by 4d and 5d metals. However, deuteration using more abundant 3d transition metals are still rare. We are excited about new catalysts that will enable H/D exchange reactions under milder conditions, but we also expect the use of bioenzymatic catalysts that will play an important role in the synthesis of deuterated complex molecules. Selective deuteration at a distal position like the *para*-position in the case of arenes and γ- and δ-positions in the case of aliphatic systems is still elusive. New, sustainable approaches such as continuous flow, mechanochemical and electrochemical methods to synthesize deuterated materials will also help the medical and industrial community to synthesise pharmaceutically-relevant deuterated compounds at large scale in a cleaner and greener fashion. Late-stage H/D exchange provides increasing data resources which give a clearer idea about various C–H functionalisation methods. We hope this review will provide understanding of

the demands and applications of the synthetic methodologies, and that the content will prove useful to chemists and isotope scientists alike.

Conflicts of interest

There are no conflicts to declare.

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