Chapter 9
Metal Nanoparticles for Hydrogen Isotope Exchange

A. Palazzolo, J. M. Asensio, D. Bouzouita, G. Pieters, S. Tricard, and B. Chaudret

Abstract Since the mid-1990s Hydrogen Isotope Exchange (HIE), consisting in the direct exchange of protium with its isotopes, has witnessed an enormous development (Atzrodt et al. in Angew Chem Int Ed, 57:3022–3047, 2018, [1], Atzrodt in Angew Chem Int Ed, 46:7744–7765, 2007, [2]). HIE reactions can nowadays be performed on a plethora of organic compounds by using both homogeneous and heterogeneous catalysis. Molecular catalysts remain the most commonly used due to their high reliability (Atzrodt et al. in Angew Chem Int Ed, 57:3022–3047, 2018, [1]). However, metallic nanoparticles have started attracting the attention of the scientific community (Asensio et al. in Chem Rev, 120:1042–1084, 2020, [3]) because of their interesting characteristics such as:

1. their reactivity in between homogeneous and heterogeneous catalysts,
2. the possibility to deeply influence their chemical properties by varying the stabilizing agent,
3. the non-negligible advantages of (generally) simple workup procedures.

In this chapter, we will give an overview of the recent advances in HIE. First, we will describe the main applications of protium isotopes. Then, we will briefly discuss the main advances in catalytic HIE reactions in both homogeneous and heterogeneous phase. Finally, we will summarize the examples of HIE catalyzed by metallic nanoparticles that have been described in the literature.

Keywords Hydrogen Isotope Exchange · Catalytic deuteration · C-H activation · H-H activation · Metal nanoparticles

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9.1 Utilization of Protium Isotopes

Deuterium and tritium are nowadays employed in several research fields spanning drug development processes, material chemistry and fundamental mechanistic investigations [4]. Deuterium is a stable isotope of hydrogen that contains one proton, one electron and one neutron; thus, it is stated as both ^{2}H and D (IUPAC). Deuterium was discovered in 1931 by Urey et al. [5]. Its name was derived from the Greek *deuteros*, namely second [6]. Tritium is a radioactive isotope of hydrogen that contains one proton, one electron and two neutrons. Thus, it is stated as both ^{3}H and T (IUPAC). Firstly produced by Oliphant, Harteck and Rutherford bombarding deuterated inorganic salts with deuterium ions, [7] tritium has a half-life of 12.32 years and decays to ^{3}He emitting low-energy β^{-} particles [8]. One of the most important characteristics of hydrogen isotopes is their strong kinetic isotope effect (KIE). Primary KIE is defined as "the ratio between the kinetic constants of a chemical transformation when one of the atoms of a reactant is substituted by one of its isotopes" [9]. This phenomenon can be explained considering that "heavier" isotopes possess lower vibrational frequency and zero-point energy (ZPE) [10–12]. Although this explanation does not consider the influence of tunneling, it can be used as a valid approximation to explain several experimental observations. In the case of C-D and C-H bonds, there is an important energy difference at the ZPE which becomes almost inexistent at the transition state; such a difference is experimentally translated in a very important primary KIE (Fig. 9.1).

Moreover, different types of secondary KIE can emerge when a C-D bond breaking is not directly involved in the chemical transformation. Secondary KIEs often arise upon changing of hybridization or through the involvement of hyperconjugation. Nevertheless, they are much smaller in magnitude compared to primary KIE. The

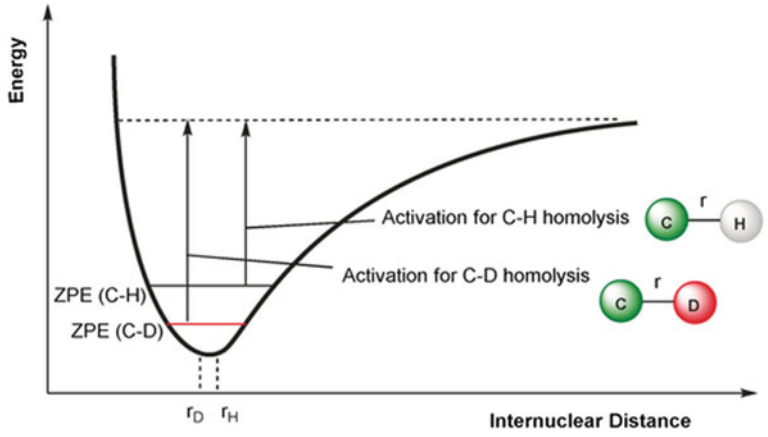


Fig. 9.1 Energetic profile for C-H and C-D bonds showing the difference in ZPE. Reprinted with permission from Ref. [4]. Copyright 2018 Wiley [4]

kinetic constant of a reaction at 25 °C that involves a C-H bond breaking is, theoretically, around 6.5 times faster than the same reaction involving a C-D bond breaking (Eq. 9.1).

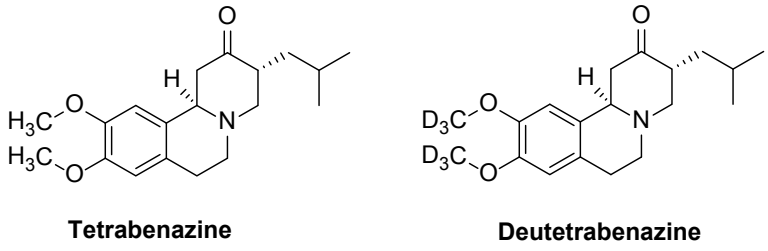
$$\frac{k_H}{k_D} = e^{\frac{hc(v_H - v_D)}{2kT}} \tag{9.1}$$

Equation **9.1**, $k_H - k_D$ kinetic constant for C-H and C-D bonds, h Planck's constant, c speed of the light, $v_H - v_D$ elongation frequencies for C-H and C-D bonds, k Boltzmann's constant, T temperature.

One of the most classical (or common) applications of deuterated compounds is their use as tools to understand reaction mechanisms. By observing the magnitudes of isotope effects, it is possible to deduce which site might contribute to the chemical mechanism of a reaction. Therefore, KIE can be used for:

1. determining the absolute rates in two parallel reactions,
2. distinguishing two chemical processes in competition experiments, when "labeled" and "unlabeled" compounds are placed in the same flask,
3. assessing the reactivity of two different C-H bonds within the same molecule.

These techniques are used to study inter/intramolecular organic transformations as well as enzymatic reactions [13–15] and organometallic processes. Additionally, deuterium can be incorporated into metabolized sites of bioactive compounds in order to alter their pharmacokinetic profiles [16–19]. Metabolic inactivation of drugs is one of the main reasons of discard during drug development processes, because it can potentially lead to the production of toxic metabolites, to the inactivation of the drug or to too low concentrations in blood. On the other hand, deuterated drugs may possess enhanced pharmacokinetic properties thanks to lower metabolic rates. Recently, FDA has allowed the first deuterated drug to reach the market [20]. Tetrabenazine is a vesicular monoamine transporter 2 (VMAT2) inhibitor, and it is used for the treatment of chorea associated with Huntington disease. The active metabolite, issue from the reduction of the carbonyl moiety, is rapidly oxidized on the cathecolic methoxy groups and thus excreted. The deuteration of these positions increases the half-life of tetrabenazine and permits reduction of the daily dose (Fig. 9.2).



Tetrabenazine **Deutetrabenazine**

Fig. 9.2 Chemical structures of tetrabenazine and deutetrabenazine

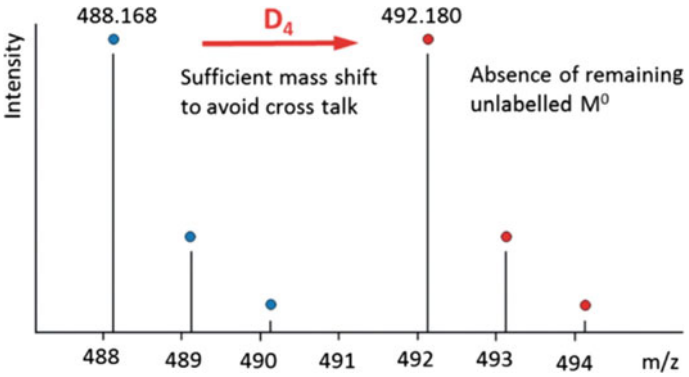


Fig. 9.3 Desired mass shift of deuterated internal standard to avoid signal overlapping [4]. Reprinted with permission from Ref. [4]. Copyright 2018 Wiley

Deuterated molecules are also routinely applied as internal standards for quantitative LC-MS/MS analysis. The precise quantification of a substance using MS may be difficult because of many factors (matrix effects, ion suppression). For this reason, the quantitative analysis of molecules in a complex matrix usually requires an internal standardization involving the use of stable isotope labeled internal standards (SILSs) [21−22]. The latter are particularly advantageous because they display the same chemical and physical properties of the analyte, but they possess different molecular weights. To be used as internal standard, a deuterated sample should have ideally the following specifications:

1. containing a negligible amount of unlabeled molecule (less than 1%),
2. possessing a deuterium content of 3–5 atoms to avoid signal superimposition (Fig. 9.3),
3. displaying an isotopic distribution as narrow as possible to increase the accuracy of the measurement.

In a common procedure, a known quantity of SILS is added to the biological sample containing the compound to be quantified. After purification, it is possible to calculate the initial quantity of the desired molecule by comparing the peaks of "labeled" standard and "unlabeled" molecule in the MS spectrum. SILS is also used to assess drug-drug interactions, to detect and quantify illegal drugs, [23−24] for anti-doping tests [25−26] and to test the presence of a variety of contaminants [27−28].

On the other hand, tritium-labeled compounds are widely applied during early drug development processes. For example, tritiated molecules are used in radioligand binding assays, which measure the interaction between two molecules, generally a ligand and a target. Such a use is due to two main factors:

1. tritium's high specific activity,
2. the fact that tritium labeling does not modify the interaction between the molecule of interest and its target (compared to other probing techniques).

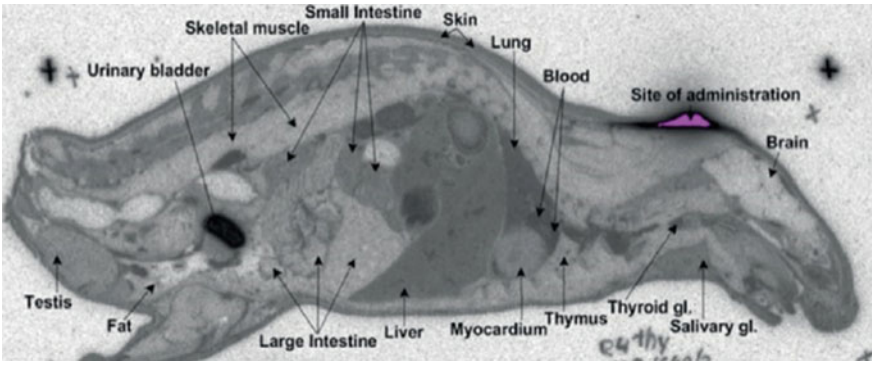


Fig. 9.4 Quantitative whole-body autoradiography (QWBA) showing the site of administration of a radioactive drug [4]. Reprinted with permission from Ref. [4]. Copyright 2018 Wiley

Receptor affinity can be easily measured by saturation experiments which provide the half maximal inhibitory concentration (IC_{50}) of the unlabeled molecule [29]. Tritiated compounds can also be used in later phases of drug development process such as adsorption, distribution, metabolism and excretion (ADME) studies. Among them, ex vivo imaging techniques such as whole-body autoradiography (WBA) can be used to determine the in situ localization of radiolabeled xenobiotics in laboratory animals (Fig. 9.4) [30].

9.2 Current Approach to the Synthesis of Deuterated and Tritiated Molecules

The synthesis of molecules labeled with hydrogen isotopes can be achieved throughout two pathways. First, one can envisage the use of isotopically labeled building blocks for the synthesis of the desired molecules. This approach is the most reliable one because of the high control on the site of the isotope incorporation and the high level of isotopic enrichment achievable. However, the necessity of reworking a synthetic pathway in order to incorporate a labeled fragment may be difficult, especially for complicated compounds such as biomolecules. Moreover, in the case of tritiations, high amounts of radioactive wastes are produced. In this context, direct exchange of hydrogen with its isotopes represents a fascinating alternative to classical synthesis. In fact, Hydrogen Isotope Exchange (HIE) is easier, cheaper and leads to less radioactive wastes because it can be done directly on the compound of interest (late stage functionalization) [31]. On the other hand, HIE methods are still under development, and not all functionalities are nowadays compatible. In the example reported in Fig. 9.5, [32] deuterated paroxetine was prepared through a five-step synthesis with an overall yield of 20%. The same molecule could be deuterated (on

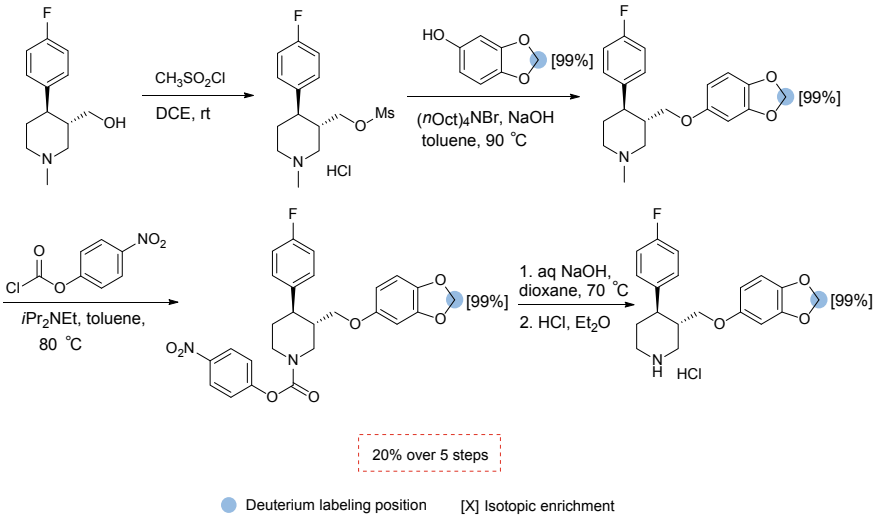


Fig. 9.5 Example of the synthesis of deuterated paroxetine [32]

other positions) with high isotopic enrichments in one step using HIE catalyzed by RuNPs (see—Fig. 9.17).

As stated in the introduction, molecular catalysts such as Crabtree's type iridium complexes are among the most widely employed systems for catalytic HIE reactions. Initially used as hydrogenation catalysts, [33] Ir(I) complexes were firstly explored in the context of HIE by Heys [34] in 1992. In this work, the labeling of different compounds containing functional groups such as amides or esters was examined. The hypothesized reaction mechanism envisages the initial activation of the Ir(I) to Ir(III) upon the oxidative addition of D_2 and further release of the cyclooctadiene ligand (Fig. 9.6). The rate-limiting step is the C-H activation which possesses a high energy barrier and leads to the formation of a metallacycle intermediate (**9-10**).

The second generation of iridium catalysts started in 2008, when Kerr reported a bulky cationic Ir(I) pre-catalyst able to promote ortho-HIE to different directing groups (Fig. 9.7). The bulkiness as well as the electron richness of the ligands played a fundamental role avoiding the formation of inactive iridium clusters and favoring both oxidative addition and reductive elimination [35]. Extensive theoretical investigations confirmed that the rate-limiting step of the reaction is the C-H activation.

In an extension of this work, Atzrodt showed that Kerr's catalyst can be successfully applied to the ortho-directed labeling of various heterocycles such as pyrimidine, imidazole, oxazole, thiazole and their benzofused analogs [36]. Recently, several efforts have been done in the direction of C(sp^3)-H activation [37]. Kerr showed that iridium-catalyzed HIEs can be easily achieved on aliphatic C-H bonds using mild conditions. Interestingly, the investigated catalyst tolerated the use of diverse DGs including pyridine, pyrimidine, quinoline, thiazole and benzothiazole.

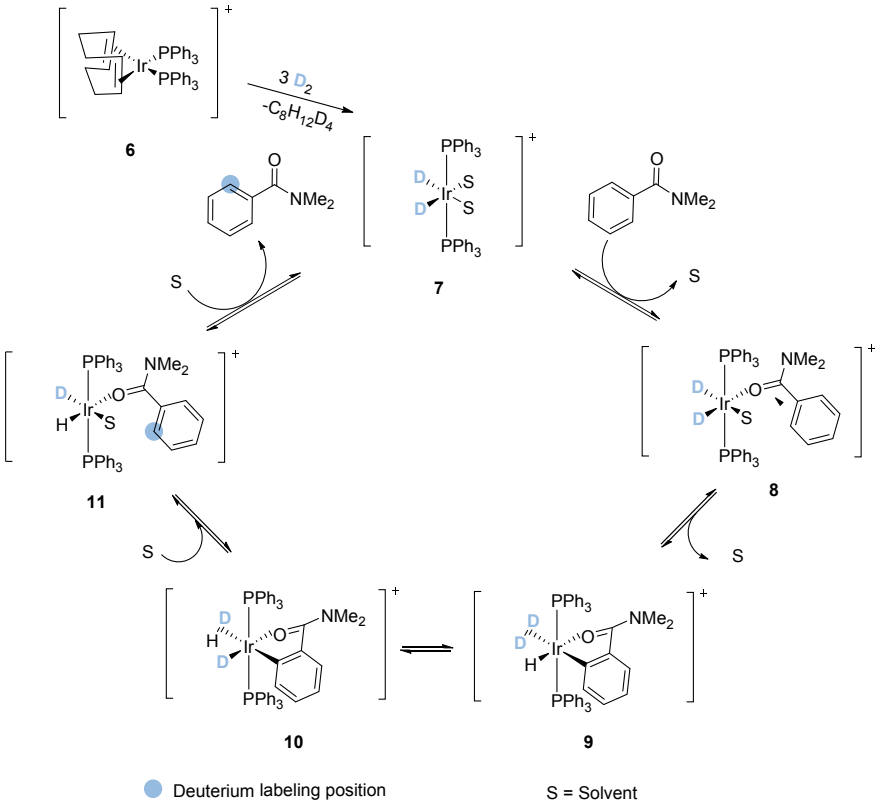


Fig. 9.6 Reaction mechanism proposed by Heys and co-workers for the Ir(III) catalyzed HIE of amides and esters [34]

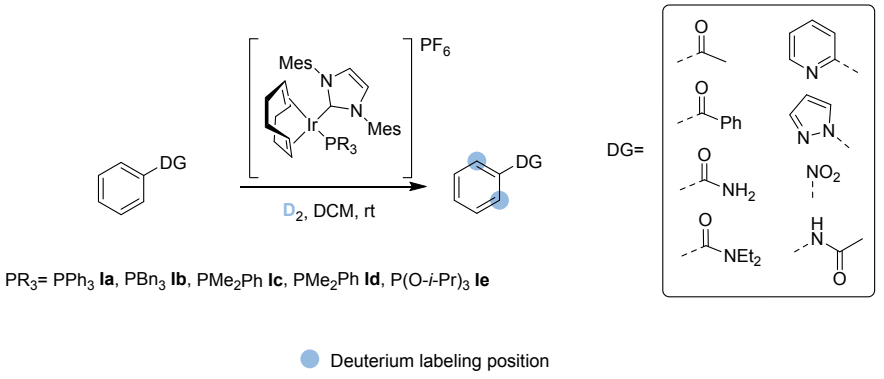


Fig. 9.7 Supported directing group by the first generation of Kerr catalysts [35]

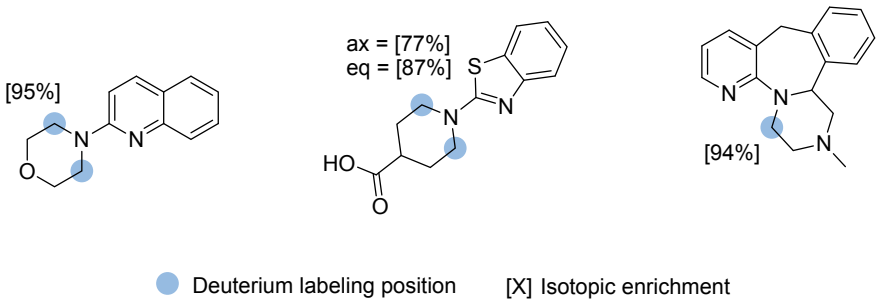


Fig. 9.8 Selected examples from Kerr and co-workers' labeling of aliphatic amines directed by nitrogen-containing heterocycles [38]

Cyclic aliphatic moieties such as morpholines, piperidines and piperazines can be labeled under mild conditions and with very low catalytic loadings (Fig. 9.8) [38].

Although less efficient than cationic catalysts, [39] neutral iridium catalysts have also been widely studied in HIE. In 2015, Kerr described a well-designed neutral iridium(I) complex bearing a chlorine substituent which allowed the labeling of primary sulfonamides [40]. In addition, the different reactivity of neutral and less hindered Ir(I) species has been confirmed by its use in the selective labeling of highly reactive moieties such as aldehydes [41].

Along with iridium, ruthenium possesses a chemical reactivity which makes it one of the most studied metals in HIE. For example, ruthenium is efficient for the labeling of molecules that lack strongly coordinating functional groups. Leitner and co-workers reported the deuterium labeling of benzene derivatives and heteroaromatics under mild conditions using Ru(II) pincer complexes and D_2O as isotopic source (Fig. 9.9). Theoretical calculations revealed that the isotopic uptake is governed by steric effects [42]. Recently, Szymczak and co-workers reported

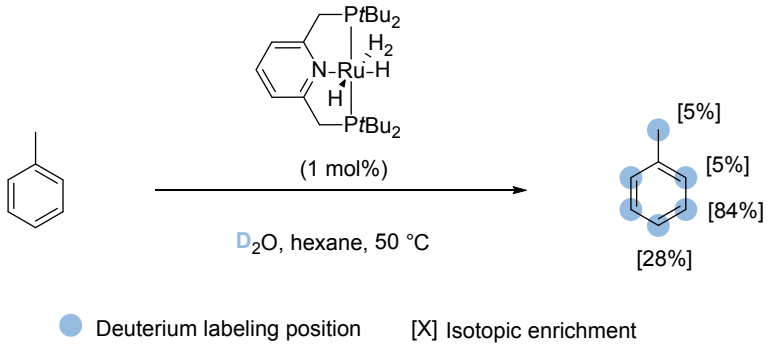


Fig. 9.9 Leitner and co-workers' deuteration of benzene derivatives in the absence of a directing group. The regioselectivity is ruled by steric effects [42]

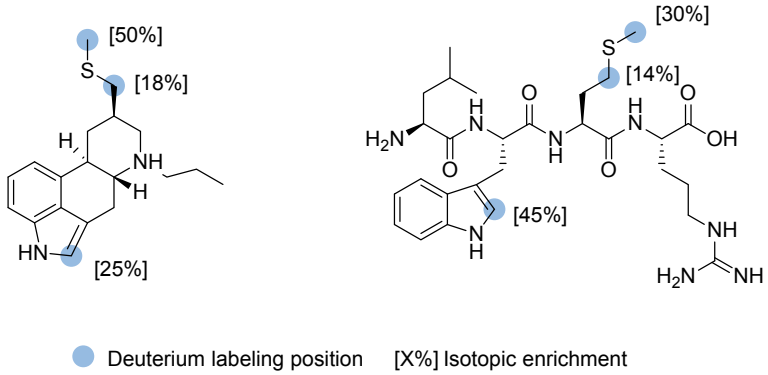


Fig. 9.10 Selected examples from Pieters et al. of deuteration of thioethers with Ru/C showing the high complexity of the substrates which can be labeled with this method [46]

H/D exchange catalyzed by an electron-poor Ru(II) cationic catalyst, which allows complete stereoretentive labeling of chiral amines using D_2O as isotopic source [43].

On the other hand, heterogeneous ruthenium catalysts are known to promote HIE on compounds containing hydroxyl groups. For instance, Sajiki reported a catalytic reaction involving Ru/C and D_2O as isotopic source under hydrogen atmosphere for the efficient labeling of linear, branched, cyclic, primary and secondary alcohols [44]. The same group reported subsequently the labeling of protected sugars with the same catalytic system [45]. Recently, Pieters and co-workers showed that Ru/C is capable of performing HIE directed by thioethers (Fig. 9.10) despite the fact that they are known to efficiently poison heterogeneous catalysts. By increasing the catalytic loading for this reaction, it was possible to label very complex molecules including peptides and drugs [46].

Palladium-based catalysts have also been widely explored in HIE chemistry. Homogeneous Pd catalysts are not much used because of the high stability of alkyl-palladated intermediates. Nevertheless, some examples of HIE catalyzed by Pd complexes have been reported. Reaction mechanisms involve the formation of cyclopalladated species, which are further hydrolyzed with acids [47] or D_2/T_2 [48]. On the other hand, heterogeneous Pd species have been largely employed in the field of HIE. In 2005, Sajiki et al. reported an interesting Pd/C catalyzed HIE protocol for the labeling of phenylalanine employing D_2O under H_2 atmosphere (1 bar). The reaction is highly selective for the benzylic position [49]. The same catalytic system also allowed the labeling of nucleobases derivatives with high isotopic enrichments but in harsh conditions (160–180 °C in a sealed tube), which limited its employability to very simple substrates [50]. Recent efforts on transition metal catalyzed C-H activation go strongly in the direction of the use of earth-abundant metals because of their lower cost and higher availability. In this field, Chirik described the first iron catalyzed synthesis of labeled drugs using D_2 or T_2 as isotopic source (Fig. 9.11). In contrast with the typical ortho-directed HIE of most transition metals, the iron catalyst activates the more electron-poor and accessible C-H bonds. Despite its high

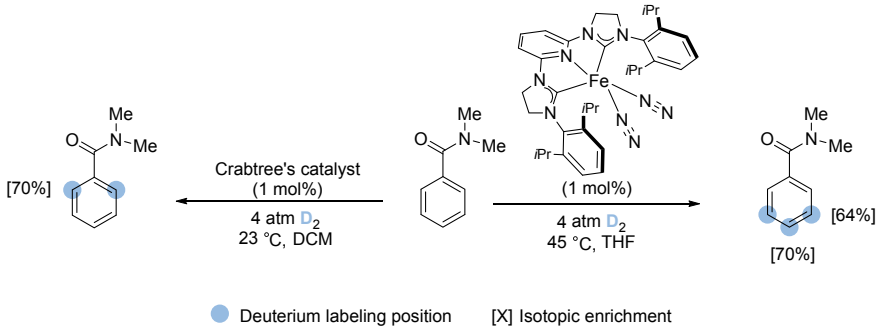


Fig. 9.11 Difference in regioselectivity between Crabtree and Chirik's iron catalysts [51]

sensitivity to oxygen, moisture and protic functionalities, this catalyst allows efficient tritiation of pharmaceuticals employing very low pressures of the isotopic gas source [51].

The same group recently developed cobalt and nickel diimine complexes for the labeling of benzylic sites and various azines and diazines [52–54]. However, with nickel, the formation of nickel nanoparticles or clusters under D_2 atmosphere cannot be excluded.

9.3 Nanoparticles for HIE

Recently, metallic nanoparticles (NPs) have become a prominent tool for the activation of C-H bonds, [55] yet their use in HIE chemistry has just recently been described. The first example of H/D exchange catalyzed by metal nanoparticles was reported by Ott et al. in 2005 [56]. In this work, Ir nanoparticles with a size of 2.1 ± 0.6 nm were prepared in ionic liquids. These NPs catalyzed the H-D exchange on 1-butyl-3-methylimidazolium, not only on the imidazolium cation, but also on the alkyl chain. The high deuteration percentage at position 2 of the cycle was explained by the coordination of imidazolium on the surface of the NPs. This work opened the field to the stabilization of NPs by "N-Heterocyclic Carbene" (NHC) ligands. Later on, Sullivan et al. synthesized DMAP-stabilized Pd nanoparticles with a mean diameter of 3.4 ± 0.5 nm via reduction of Na_2PdCl_4 in water by sodium borohydride, which were used in the deuteration of pyridines (Fig. 9.12) [57]. Control experiments revealed that the starting Pd(II) was not active in H/D exchange reaction. After supporting the Pd NPs on thiol-modified carbon nanotubes, an enhancement in their catalytic activity in H/D exchange on various pyridines was observed. However, low deuteration degrees were obtained on substrate carrying hydroxyl groups. In addition, deuteration degree was higher in the ortho positions in respect of the hydroxyl group, which suggests that coordination of 4-hydroxypyridyl through the O atom to the surface of the NPs atom

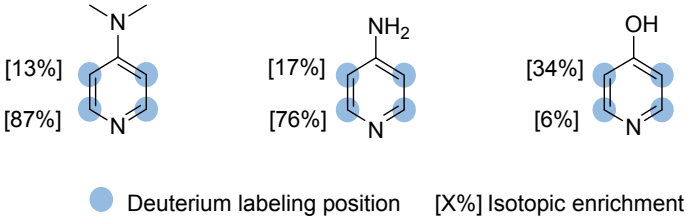


Fig. 9.12 Molecules deuterated by Sullivan et al. through PdNP catalysis [57]

took place preferentially. Shapley also reported the deuteration of various nitrogen-containing heterocycles catalyzed by Pd NPs stabilized by polyvinylpyrrolidone (PVP). The latter are prepared by thermal decomposition of $Pd(OAc)_2$ and possess a mean diameter of 4.5 nm. These catalysts were stable colloidal dispersions for months and promoted the α deuteration of various N-containing heterocycles using D_2O as isotopic source [58].

A different approach for the preparation of metallic NPs consists in the controlled decomposition of organometallic precursors under mild conditions. This "organometallic" approach has been widely employed by our research groups to synthesize Ru NPs. For example, [Ru(COD)(COT)] can be decomposed to yield Ru NPs with a mean size of 1.1 nm in the presence of a stabilizing agents such as polymeric polyvinylpyrrolidone (PVP) and hydrogen (Fig. 9.13) [59].

As this approach limits the production of surface contaminants, it grants a higher control on the surface species and a potentially higher catalytic activity. In 2005, Pery et al. investigated the presence of mobile hydrides at the surface of Ru NPs/HDA (HDA = hexadecylamine) using solid state ^2H MAS NMR. Surface hydrides were rapidly exchanged by deuterides putting the Ru NPs/HDA under deuterium gas atmosphere (1 bar). In this work, the authors observed by ^2H NMR analysis that Ru NPs promote H/D exchange at the HDA ligands at low D_2 pressures and low temperatures (Fig. 9.14). Thus, this work constituted the proof of concept that Ru NPs can be used as catalysts to perform HIE reactions under mild conditions [60].

Breso-Femenia et al. studied the deuteration of phosphorus compounds by Ru/PVP NPs and more precisely on three different phosphines: triphenylphosphine,

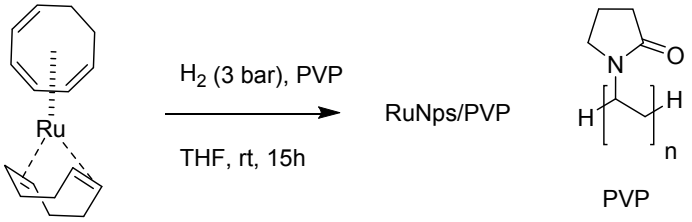


Fig. 9.13 Synthesis of Ru NPs/PVP by decomposition of organometallic [Ru(COD)(COT)] [59]

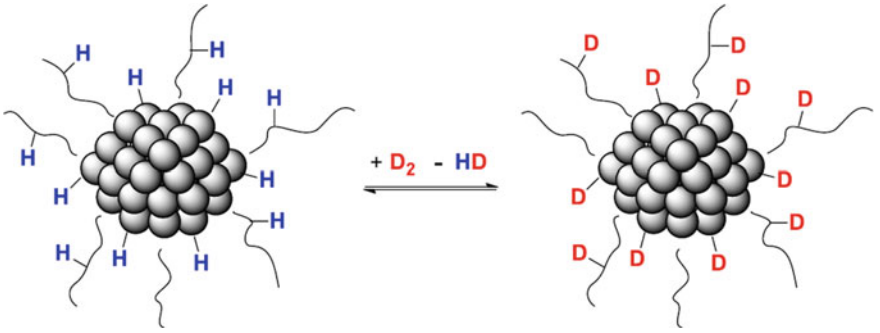


Fig. 9.14 H/D exchange promoted by RuNPs/HDA in the presence of D_2 gas [60]

triphenylphosphine oxide and triphenyl phosphite [61]. In the case of triphenylphosphine, a selective deuteration of the ortho position of the aromatic ring was observed with an incorporation of 1-6 deuterium atoms depending on the reaction time without detection of products from the aromatic ring reduction. Nevertheless, the Ru/PVP NPs were not able to deuterate the aliphatic groups of phosphines. Concerning triphenylphosphine oxide, an incorporation of deuterium was observed under the same conditions but with a reduction of the aromatic rings even at low temperatures, which can be explained by a π-coordination of the substrate through the aromatic ring. Then, for triphenyl phosphite, no deuteration took place under the same conditions. The authors proposed that the presence of O increases the distance between the surface of the nanoparticles and the aromatic ring, which disadvantages the H/D exchange (Fig. 9.15).

Later on, Pieters et al. demonstrated that Ru NPs/PVP were indeed able to deuterate diverse nitrogen-containing aromatic and aliphatic compounds using D_2 as isotopic source [62]. Thus, activation of either $C(sp^3)$- or $C(sp^2)$-H bonds next to a nitrogen atom under very mild conditions and with high regioselectivity was

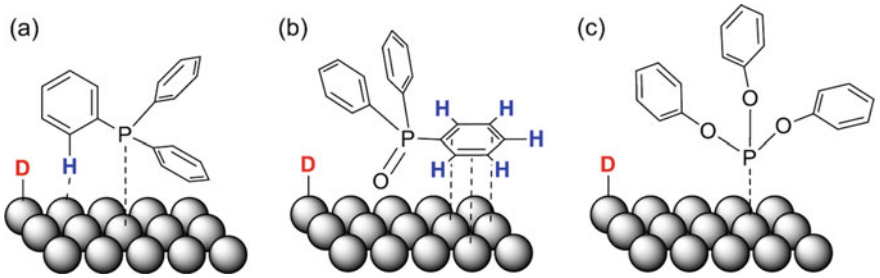


Fig. 9.15 Ru@PVP NPs catalyze H/D exchange on phosphines. Selectivity depends on the coordination mode of the ligand. **a** PPh_3 is deuterated in the ortho of the phenyl substituent. **b** $OPPh_3$ is not able to coordinate through the P atom. Thus, π-coordination leads to the reduction of the phenyl substituents. **c** In the case of $P(OPh)_3$, the distance between the ligand and the NPs surface inhibits the deuteration of the phosphine [3]

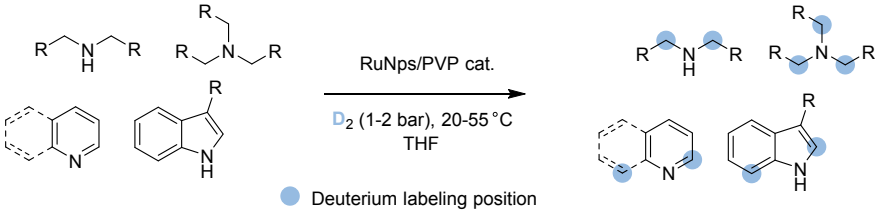


Fig. 9.16 Common nitrogen heterocyclic scaffolds which can be labeled under mild conditions using Ru NPs/PVP catalysis and deuterium gas as isotopic source [62]

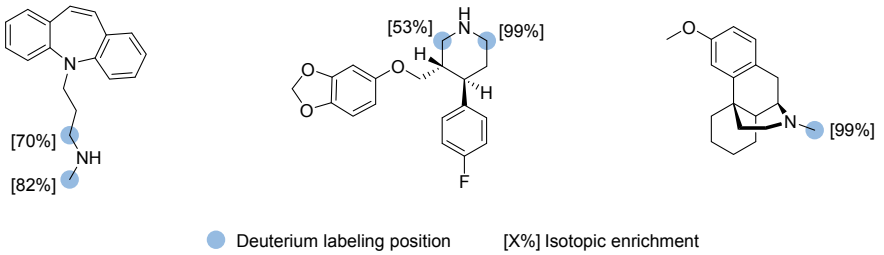


Fig. 9.17 Selected examples from the work Pieters et al. using Ru NPs/PVP and showing the high molecular complexity of the drugs successfully labeled [62]

achieved for several molecules such as pyridines, quinolines, indoles and alkyl amines (Fig. 9.16). Remarkably, RuNps/PVP catalysis granted access to a series of complex labeled drugs with high deuterium incorporation (Fig. 9.17).

Thereafter, Ru NPs/PVP were used to catalyze the deuteration of amino acids and peptides in D_2O. This work constitutes the first general method permitting stereoretentive C-H deuteration [63]. The reaction is very regioselective to the α position of the amino group of the amino acids, and it does not require any protection of the carboxylic acid moiety. High deuterium uptake was observed for amino acids containing aliphatic, amido, amino and hydroxyl side chains, with the latter being stereoretentively labeled as well. Moreover, this method was successfully applied to biologically relevant di-, tri- and tetra-peptides (Fig. 9.18).

DFT calculations confirmed that the less energetic pathway starts with the coordination of the amine to the nanoparticle, followed by a C-H activation through oxidative addition onto a Ru surface atom [63]. The C-H bond breaking is the rate-limiting step, which proceeds via a 4-membered dimetallacycle intermediate (Fig. 9.19). The formation of this intermediate explains just partially the chiral outcome of the investigated transformation. In fact, the stereoretentivity needs also to be attributed to the fact that the H/D exchange is happening at the surface of the nanoparticle thanks to the high mobility of deuteride species. It is noteworthy to say that molecular catalysts can generally form only a monometallacycle; thus, their effectiveness in the C-H activation process strongly relies on a defined geometry. On the other hand,

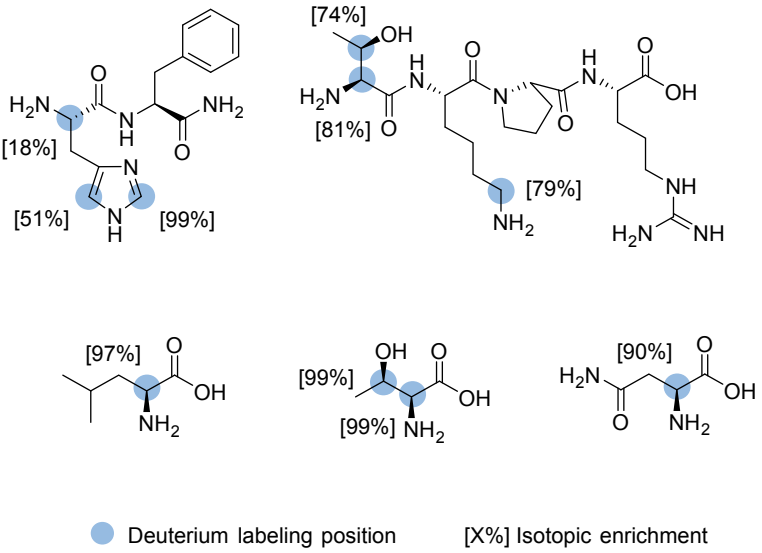


Fig. 9.18 Selected examples from Taglang et al. deuteration of aminoacids and peptides using RuNPs/PVP [63]

given the polyatomic nature of NPs surface, a larger diversity of key intermediates can be formed when they are used as catalysts for C-H bond activations.

One of the advantages of NHCs is that it is possible to play with the substituents and thus modulate their solubility. Water-soluble Ru NPs stabilized by NHC ligands functionalized with a sulfonate group were synthesized by Martínez-Prieto et al. in 2017 [64]. The selective H/D exchange on L-lysine at different pHs was studied (Fig. 9.20). At a pH of 10.4, two positions are selectively deuterated (α and ε) with low deuteration in the γ position (12.5%). The reaction efficiency decreases when reducing the pH value, with virtually no reactivity at a pH of 2.2. This loss of reactivity is understandable since under these conditions, the NH_2 groups are protonated, which disadvantages the coordination of the substrate on the surface of the NPs. On the contrary, at basic pH (13.4), a higher deuterium incorporation is observed. This incorporation is facilitated by the coordination of the two amine groups on the surface of the NPs and thus leads to an almost complete deuteration of positions α, β and γ (99%, 98.5% and 89.5%, respectively). The coordination of the substrate on the surface of the NPs was demonstrated by a chemical shift perturbation-nuclear magnetic resonance (CSP-NMR) study.

Ru NPs were also used by Bhatia et al. in H/D exchange of aminoacids by electrocatalysis [65]. The authors used Ru NPs supported on activated carbon (RuNPs/ACC). The described method allowed the deuteration of amines and alcohols in D_2O with a power supply. The platinum anode acts as a counter electrode, and the reaction takes place on the cathode made up of RuNPs/ACC. A better incorporation

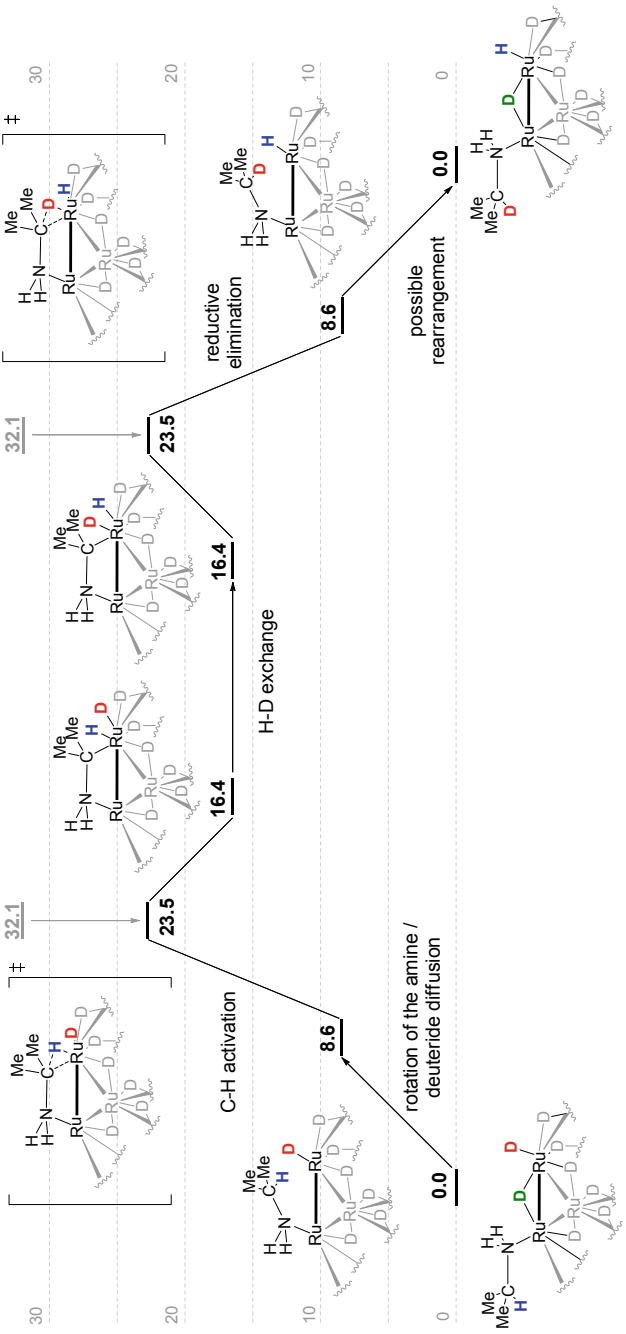
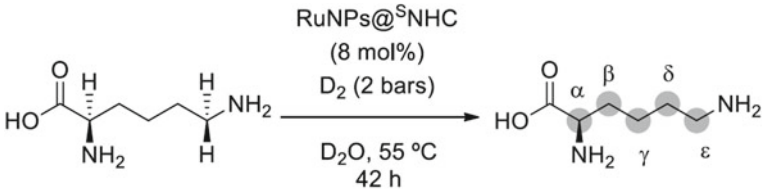


Fig. 9.19 DFT calculations showing the key 4-membered di ruthenacycle intermediates [63]



pH	α (%)	ε (%)	γ (%)	β (%)	δ (%)
2.2	6	2	-	-	-
6.9	95	70	-	-	-
8.4	97	92	-	-	-
10.4	99	98.5	12.5	-	-
11.0	99	98.5	45	-	-
13.2	99	98.5	89.5	10	-
13.8	76	98	31.5	-	-

Fig. 9.20 Activities of RuNPs@NHC on enantiospecific deuteration of L-lysine as a function of Ph [64]

of deuterium was observed on alcohols at the OH group's α position compared to amines. A mechanism similar to that proposed by Taglang et al. was presented.

The influence of introduction of Pt atoms at the surface of Ru NPs was studied by Bouzouita et al. [66]. In this work, the authors prepared several RuPt NPs (Fig. 9.21) and studied the influence of the Pt precursor on the surface composition and therefore on the catalytic reactivity of the NPs. The exchange of Ru atoms by Pt led to a decrease in the reaction rate of the H/D exchange in the α position of L-lysine

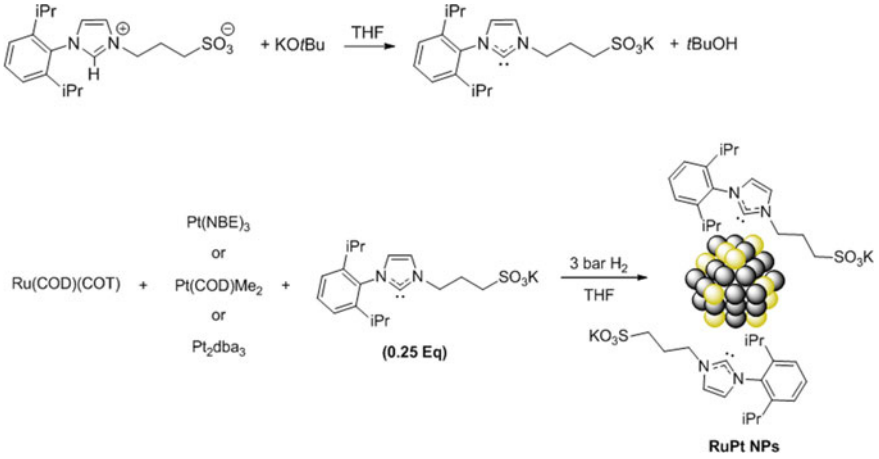


Fig. 9.21 Water-soluble Ru-Pt nanoparticles synthesis [66]. Reprinted with permission from Ref. [66]. Copyright 2019 Royal Society of Chemistry

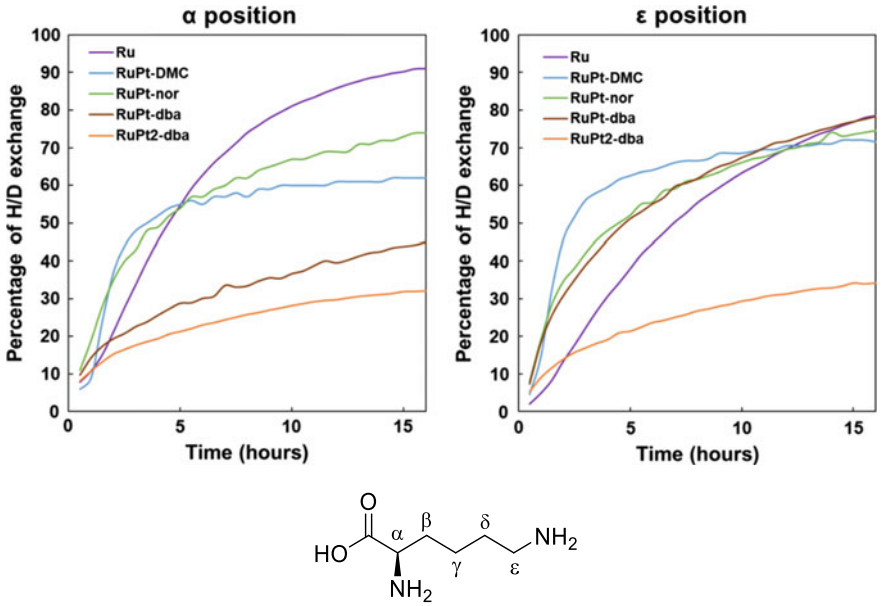


Fig. 9.22 Kinetic study of H/D exchange with different catalysts on the α and ε positions of L-lysine [66]. Reprinted with permission from Ref. [66]. Copyright 2019 Royal Society of Chemistry

without significant modification of the reactivity on the ε position (Fig. 9.22). To explain these effects, the authors proposed that a chelate effect involving the amine and acid groups of L-lysine would result in stronger adsorption of the groups near Cα at the surface of the RuPt. Thus, introduction of Pt at the surface would result in stronger coordination of carboxylate with a concomitant decrease in catalytic activity toward deuteration at Cα.

Palazzolo et al. have recently used Ru NPs@NHC to ameliorate HIE reactions of nucleobases derivatives. Indeed, in this case, Ru NPs/PVP were efficiently used in the deuteration of several biomolecules (nucleosides, nucleotides, xanthines) and drugs, but they were less efficient when more challenging conditions had to be adopted in the case of tritiation of drugs or deuteration of high molecular weight oligonucleotides. Indeed, the use of a more organosoluble stabilizing agent such as the carbene "ICy" (N,N-dicyclohexylimidazol-2-ylidene) deeply modified the reactivity of Ru NPs, which became more efficient toward C(sp^2)-H activation. The latter permitted the high specific activity in drugs tritiation in organic solvents. On the other hand, in the case of the deuteration of oligonucleotides, the use of water-soluble carbene "PriPr" [3-(2,6-diisopropylphenyl)-1-(3-sulfonatopropyl)-1H-imidazol-3-ium-2-ylidene] permitted the synthesis of an oligonucleotide biomolecule which could be used as internal standard for quantification in mass spectrometry (Fig. 9.23) [67].

The reactivity of Ru NPs in HIE reactions can be applied to light alkanes that do not contain directing groups. Rothermel, et al. prepared Ru NPs stabilized by

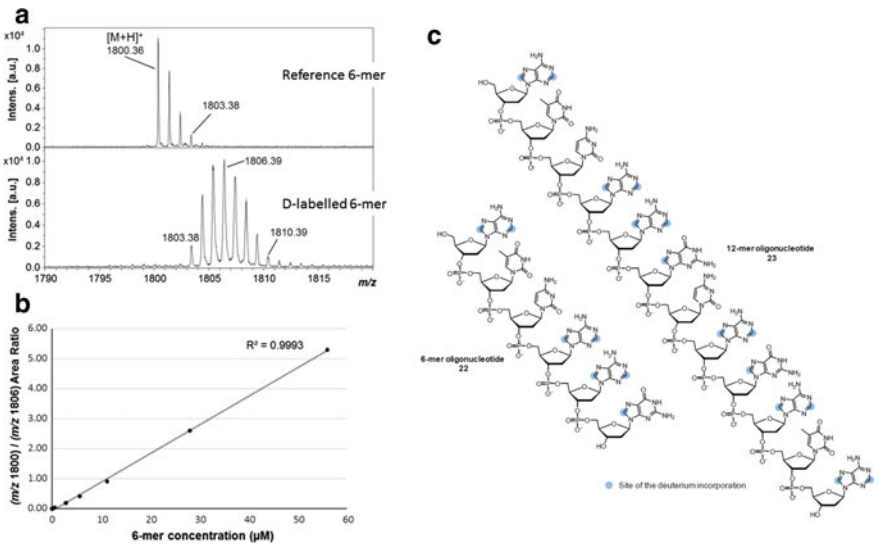


Fig. 9.23 **a** MALDI-TOF mass spectra of native and deuterium-labeled 6-mer oligonucleotide. Non-overlapping isotope massifs were observed after D-labeling. **b** Calibration curve obtained for the native 6-mer from 0.56 to 56 μM, using a deuterium-labeled 6-mer concentration set at a constant value of 280 μM (overall concentration). Most intense isotopes were used for native and D-labeled species (m/z 1800.36 and m/z 1806.39, respectively). **c** Structures of the labeled oligonucleotides [67]. Reprinted with permission from Ref. [67]. Copyright 2019 Wiley

bis(diphenylphosphino)butane (dppb) ligands, which were used in the deuteration of cyclohexane and cyclopentane [68]. The reactions were carried out in the neat substrate (1 or 2 mL) using gaseous D_2 as isotopic source (6 bar) at 60 °C. H/D exchange was much higher for cyclopentane (See Scheme 9), and the uptake of up to 4 D atoms was observed in this case, whereas cyclohexane only incorporated 1 D atom (Fig. 9.24). The reason of such a different reactivity was difficult to determine, but several hypotheses were considered. First, it was proven that the presence of ligands at the surface was not enough to explain the difference in reactivity. Then, thermodynamic explanations were discarded as cyclohexane and cyclopentane have similar bond cleavage energies (400 kJ/mol and 395-403 kJ/mol, respectively). Thus, the authors concluded that reactivity came from a specific recognition of the Ru surface for cyclopentane, the origin of which has not yet been determined.

9.4 Conclusions and Perspectives

HIE has attracted the attention of the catalysis community as deuterated compounds possess interesting applications in several fields. Although catalytic HIE has been traditionally performed by homogeneous complexes, recent studies have proved that

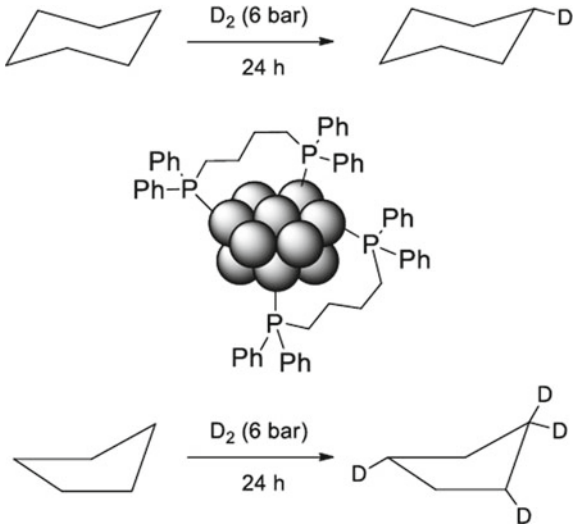


Fig. 9.24 Higher deuterium incorporation for cyclopentane than for cyclohexane with Ru NPs stabilized by dppb under mild conditions [68]

metallic NPs stabilized by polymers or ligands are powerful catalysts that permit us to selectively obtain high degrees of deuteration in a wide variety of substrates with high interest. However, until nowadays, the efforts have been focused on Ru NPs, which have demonstrated to be very active catalysts under mild conditions. Mechanistic studies pointed out that the reaction elapses through the σ-bond activation of the C-H bond by surface Ru. Nevertheless, there are no examples in the literature of NPs composed of other metals that have been traditionally used in HIE such as Ir, Pd and Ni. In addition, different reaction mechanisms may be involved in the reaction when changing the nature of the active metal (i.e., σ-bond metathesis or heterolytic cleavage), which surely will influence reaction selectivity. Thus, we believe that new efforts in HIE will be focused on exploring new compositions of metallic NPs, which may permit us to modulate the selectivity of the reaction and to broaden the scope of substrates. In any case, thanks to the level reached today on the synthesis and overall comprehension of HIE catalyzed by metallic NPs, it is possible to solve historical issues of HIE such as high molecular complexity or deuteration of compounds containing poisoning moieties (i.e., sulfur-containing compounds). These advantages will surely attract the attention of researchers in the field to the utilization of metallic NPs as catalysts for HIE reactions in solution.

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