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Published on: 12 Mar 2018 - Angewandte Chemie (Angew Chem Int Ed Engl)

Topics: Hydrogen and Deuterium

C–H Functionalization for Hydrogen Isotope Exchange

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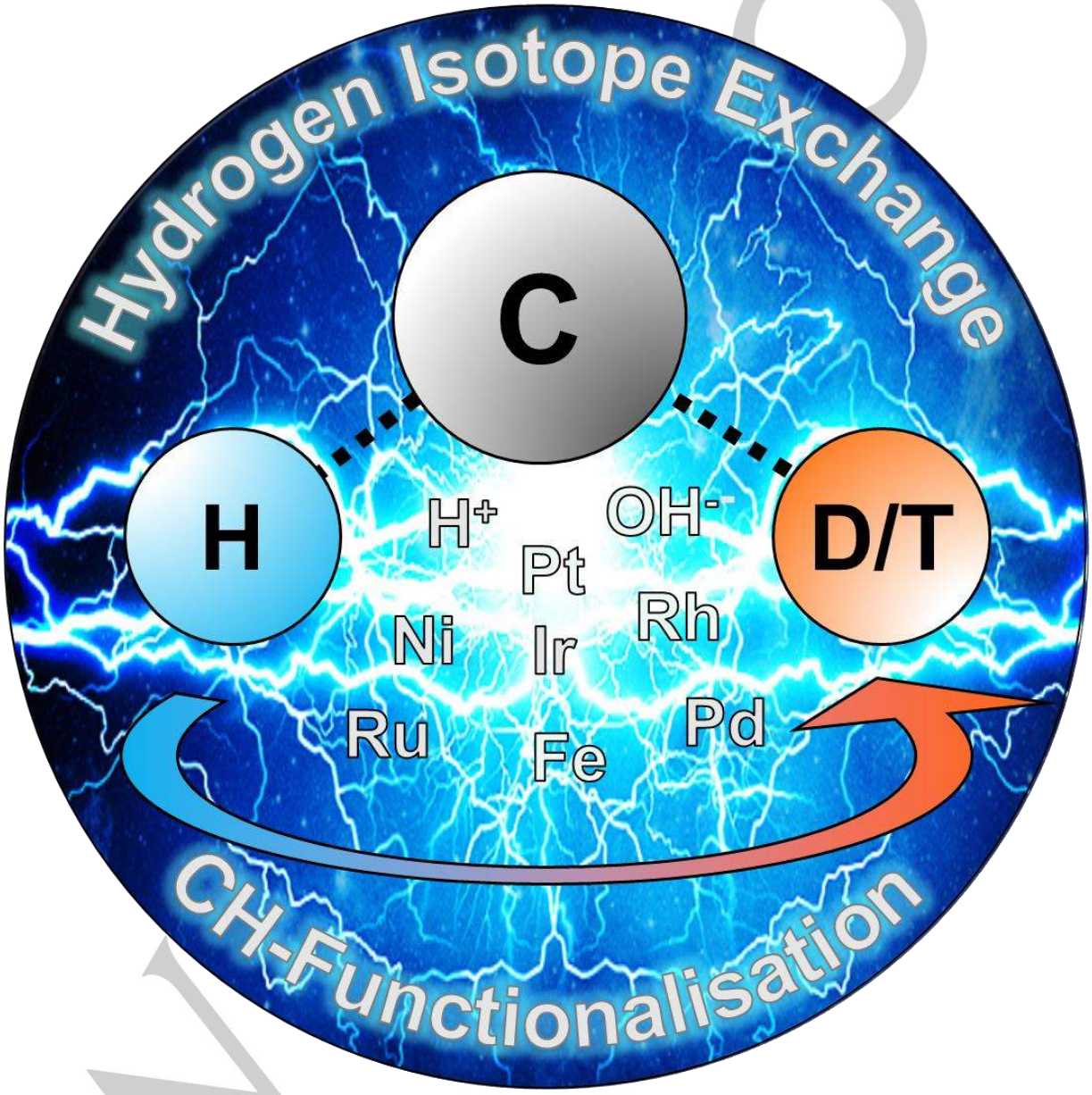

Abstract: The varied applications of hydrogen isotopes (deuterium, D, and tritium, T) in the physical and life sciences demands a range of methods for their installation in an array of molecular architectures. In this review, we describe recent advances in synthetic C–H functionalization for hydrogen isotope exchange.

Jens Atzrodt studied chemistry in Jena and obtained his PhD in 1999 with Prof. R. Beckert before joining Aventis Pharma Germany (today Sanofi) as laboratory head and later as section head in the Medicinal Chemistry department (Sanofi) responsible for Isotope Chemistry & Metabolite Synthesis (ICMS). Today he is the head of the Hub Management Office at Sanofi Frankfurt. From 2018 he will become President of the International Isotope Society and is presently a member of the advisory board of the Journal of Labeled Compounds and Radiopharmaceuticals (Wiley).

Volker Derdau studied chemistry in Münster and Braunschweig and obtained his PhD in 1999 with Prof. Sabine Laschat. He went for a one year DAAD funded Post-Doc in Prof. Victor Snieckus group (Kingston, Canada) before he started at Aventis Pharma Germany (today Sanofi) as laboratory head. Today he is section head in the Medicinal Chemistry department (Sanofi) responsible for Isotope Chemistry & Metabolite Synthesis (ICMS), senior lecturer at the University of Applied Sciences (Darmstadt), and European Associate Editor of the Journal of Labeled Compounds and Radiopharmaceuticals (Wiley).

Billy Kerr studied at the University of Strathclyde, gaining his PhD in 1986 with Prof. Peter Pauson and Dr David Billington. Following postdoctoral research at Brandeis University (Waltham, MA, USA) with Prof. Myron Rosenblum, and Imperial College (London, UK) with Professor Steven Ley, he returned to Strathclyde in 1989 as a Lecturer in Organic Chemistry. Following Senior Lectureship, he was promoted to a Professorial Chair in 2002. He now holds the endowed Chair of 1919 Professor of Organic Chemistry and is Deputy Associate Principal at Strathclyde. He was elected as a Fellow of the Royal Society of Edinburgh (FRSE) in 2014, and in 2015 was the recipient of the Melvin Calvin Award for outstanding contributions to Isotope Chemistry.

Marc Reid earned his PhD (2015) in organic and computational chemistry (w/ Prof. William J. Kerr and Dr Tell Tuttle) from the University of Strathclyde. Recently, he completed postdoctoral studies at the University of Edinburgh (w/ Prof. Guy Lloyd-Jones, FRS). In 2016, he was selected for the SciFinder Future Leaders program, and in 2017, he was selected to be among the Young Observers for the IUPAC World Chemistry Leadership Meeting. Marc is currently pursuing independent research at Strathclyde as a Leverhulme Fellow and GSK-funded Early Career Academic, where his research interests include transition metal catalysis, kinetics, and cheminformatics.

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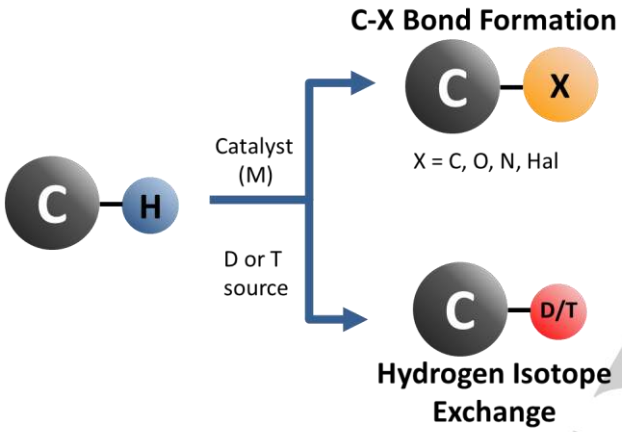
1. Introduction

The catalytic activation of C–H bonds has been in the spotlight of research for several decades.[1,2] In addition to the numerous investigations on C–H functionalization towards C–C,[3] C–X,[4] C–N,[5] or C–O[6] bond formation, hydrogen isotope exchange (HIE)[7, 8] for selective installation of C–D[9] and C–T[10] bonds is also of appreciable practical importance. Generally, the overall process can be understood as catalytic replacement of a C–H bond (mainly by transition metals) followed by a substitution either by carbon, halogen, oxygen or nitrogen atoms, or hydrogen isotopes (HIE) (see Scheme 1). Therefore, the HIE reaction can be considered as the most fundamental of all C–H functionalization processes.



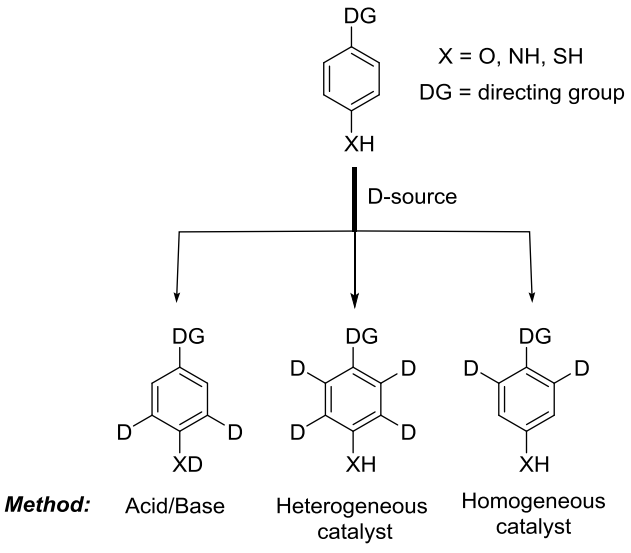
Scheme 1. A principle method of C-H functionalization to form C-D/T or C-X (C, N, O) bonds.

Incorporation of deuterium or tritium into an organic molecule can be achieved by two principle routes, either by a conventional multistep synthesis or by direct HIE. Depending on the complexity of the chemistry, the chemical structure of the target molecule, and the labeling position, a classical synthesis approach, starting from appropriate commercially available labeled precursors, can be very time and resource consuming. Alternatively, the HIE reaction enables a direct deuterium or tritium labeling of the desired target molecule and, thus, may circumvent the need for additional synthetic steps (e.g. precursor synthesis or multi-step routes from isotopically-labeled building blocks). If carried out directly on the target molecule, or an advanced intermediate thereof, the HIE labeling approach bears appreciable potential for time and cost savings and, thus, has become a desireable strategy for the delivery of deuterium or tritium into organic molecules.[11]

However, after a period of intensive research in the 1960s and 1970s, it took until the mid-1990s before the HIE approach experienced another resurgence; accordingly, our 2007 review was entitled "*The Renaissance of H/D Exchange*".[7] Since then, the need for stable isotopically labeled compounds (and, to a lesser extent, their radiolabeled analogues) has further escalated. This is largely due to the rapid development of high performance mass spectrometry and the enhanced application of liquid chromatography-mass spectrometry (LC-MS)-based analysis. The ability for precise measurement of isotope ratios promotes a dynamic view on biosynthetic pathways, protein turnover, and systems-wide metabolic networks and, thus, has paved the way for a number of scientific breakthroughs in biomedical research.[12] Additionally, in medicinal chemistry, replacement of hydrogen by deuterium has recently received much attention as a way to alter ADME properties of existing drug candidates.[13] Associated with all of this, C–H functionalization continues to be a hot topic for late stage elaboration of complex molecules.[2a]

In relation to the synthesis of labeled compounds, the last decade has seen a shift in research focus from hetero- to homogeneous catalytic HIE method development. Having stated this, both classes of labeling approach have complementary applications and are both used regularly. Typically, heterogeneous metal-catalyzed HIE results in relatively unspecific incorporation of numerous deuterium atoms into a molecular substrate (Scheme 2, centre). Accordingly, heterogeneous metal-catalyzed H/D exchange tends to be the method of choice for preparation of stable isotopically labeled internal standards (SILS) for LC-MS/MS investigations. For SILS applications, the overlap of the mass signals for the unlabeled analyte relative to the signals for the internal standard should be as low as reasonably feasible. As a consequence, heterogeneous exchange methods have been optimized to incorporate 3 – 5 deuterium atoms in the case of small molecules without chlorine, bromine, or sulfur-containing functionalities and where the remaining amount of unlabeled (D_0) is negligible.[14] In contrast, homogeneous metal catalyzed HIE methods are typically much more selective, incorporating deuterium only at specific positions in the molecule (e.g. next to a directing group; Scheme 2, right). Therefore, these methods are of particular importance for tritium incorporation *via* H/T exchange.[10,11]

Acid/base-mediated labeling methods are still used. The selectivity of these methods largely depends on innate electronic activation within the target molecule (e.g. for electrophilic aromatic substitution; Scheme 2, left).



Scheme 2. Illustration of various selectivities available by distinct HIE methods.

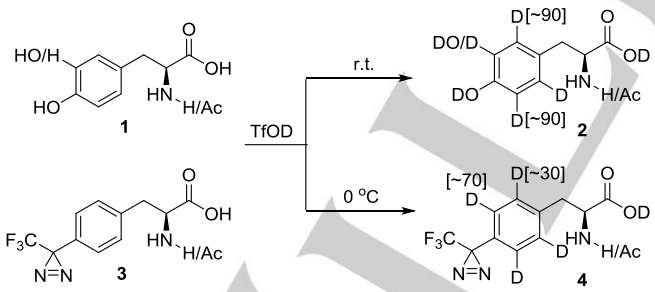
In this review, we describe current progress and remaining challenges in synthetic HIE methods published since 2007. The review complements our sister review, "*Applications of Hydrogen Isotopes in the Life Sciences*", which details the expansive application areas for deuterium and tritium isotopes in both the physical and life sciences.[15]

2. Acid/Base-mediated Labeling

Even though pH-dependent H/D-exchange reactions are amongst the oldest methods used to mediate such labeling, there are still new applications and examples being reported. While simple Brönsted acids such as DCl[16] or D_2SO_4[17] are mostly used to introduce deuterium into activated aromatic compounds, bases like NaOD/D_2O,[18] DMAP/D_2O,[19] Na_2CO_3/D_2O[20] or even near-supercritical D_2O[21] are convenient reagents with which to introduce the hydrogen isotope into aliphatic CH-positions. Due to the fact that the isotope source is used in high excess there are only a few acid/base-catalyzed protocols known to introduce tritium.[11] Most of these examples are of older provenance, with no new application having been reported in the last ten years, most probably due to the development of more effective alternative tritiation methods.

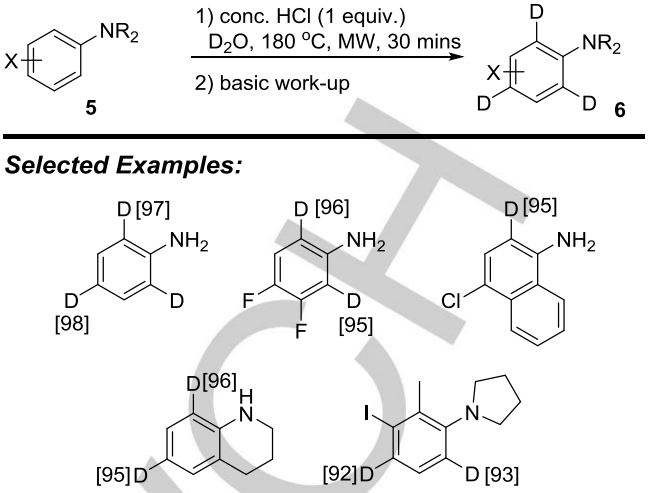
2.1 Acid-mediated labeling

As peptides have become increasingly important in pharmaceutical research, there has also been a significant increase of reported methods to prepare deuterium-labeled amino acids or peptides. For example, Hashimoto *et al.* reported the deuteration of α-amino acids derivatives by triflic acid (trifluoromethanesulfonic acid) with high deuterium content (**1**→**2** and **3**→**4**; Scheme 3).[22] In one example, a pentapeptide was deuterated at room temperature in 9 hours with up to 8 deuterium atoms introduced at the aromatic positions.[23]



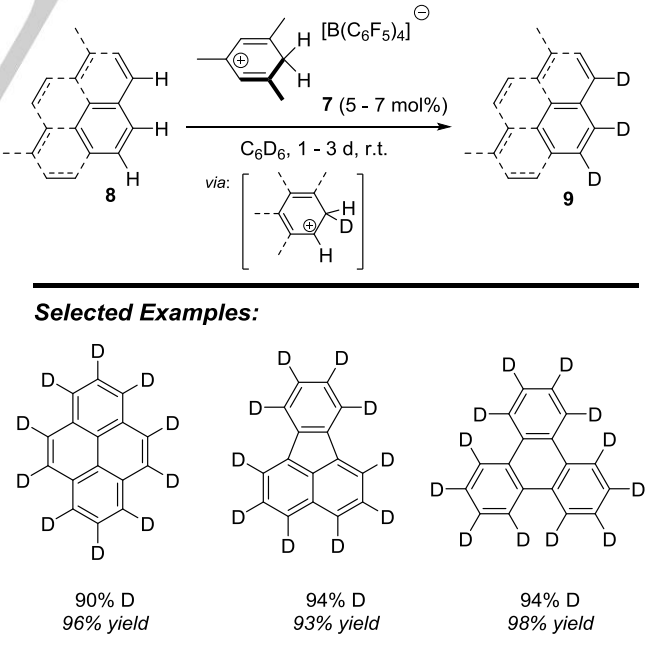
Scheme 3. Acid-mediated labeling of amino acid derivatives.

Martins and Lautens have also devised a quick and effective method for deutering anilines under microwave conditions.[16d] DCl was generated *in situ* from D_2O and HCl, mediating H/D exchange *via* electrophilic aromatic substitution (**5**→**6**; Scheme 4).



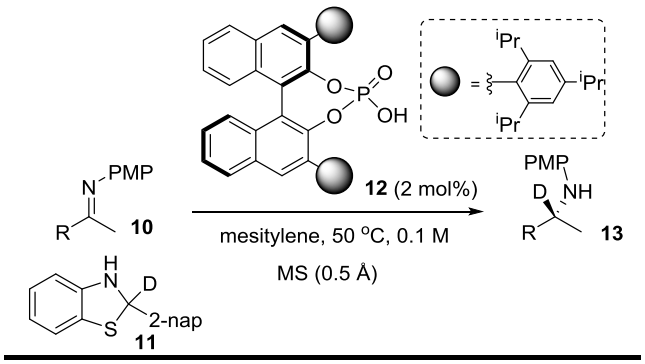
Scheme 4. Microwave-assisted deuteration of anilines under acidic conditions.

The arenium acid, **7** [mesitylene−H]$^+$ was demonstrated to be an extraordinarily active H/D exchange catalyst for the perdeuteration of polycyclic aromatic hydrocarbons (**8**→**9**; Scheme 5). Using ambient temperatures and C_6D_6 as the deuterium source, high isolated yields and excellent degrees of deuterium incorporation were achieved with the substrates p-terphenyl, fluoranthene, pyrene, triphenylene, and corannulene. More generally, the concept of pairing a cationic proton donor with a weakly coordinating anion has enabled the development of strong Brønsted acids that lack the nucleophilic and oxidative properties of traditionally used reagents such as H_3PO_4 or H_2SO_4.[24]

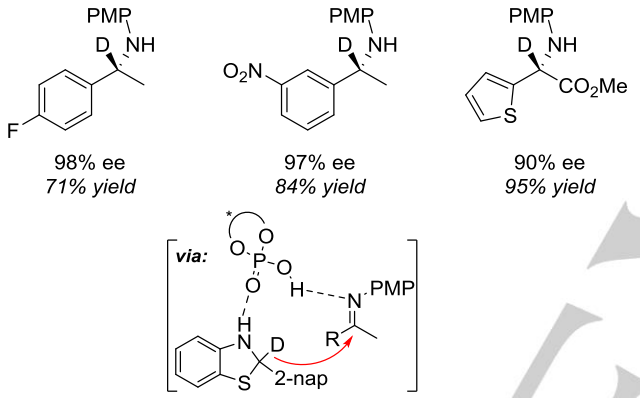


Scheme 5. Arenium acid-catalyzed deuteration of extended aromatic systems.

Another recently reported pathway to access α-deuterated amino acids (**13**) is *via* enantioselective transfer deuteration of ketimines (**10**) with chiral phosphoric acid (**12**) and by use of benzothiazoline (**11**) as deuterium donor (**10**+**11**+**12**→**13**; Scheme 6).[25]



Selected Examples:

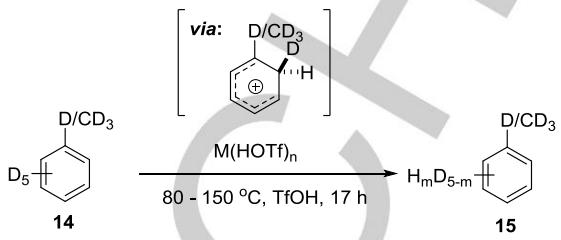


Scheme 6. Phosphoric acid-catalyzed asymmetric reductive deuteration of imines. D-incorporation is assumed to be quantitative.

In summary, acid-mediated HIE is most powerful (and practicable) when harnessing the innate reactivity of electronically-activated aromatics and unsaturated molecules. It is most useful for structurally simple molecules, where the chance of degrading complex functionalities within the molecule is minimal. Indeed, the cost-efficiency of such labeling methods continues to make acid-mediated labeling an attractive option. As in Scheme 6, and beyond using acids solely as part of the isotope source, further developments where acids are used a supramolecular director of reactivity have the potential to expand the toolbox for enantioselective labeling.

2.2 Lewis acids & frustrated Lewis pairs

The H/D exchange of arenes in acidic media by transition-metal and main-group-metal complexes, as well as common inorganic salts has been studied intensively by Goddard and Gunnoe *et al.* (**14**→**15**; Scheme 7).[26] As part of this, the influence of Lewis acidity, anions, charge, and ligands have been evaluated, leading to the conclusion that the determination of H/D exchange activity in acidic media was not related to the formation of metal−carbon bonds (i.e. *not* C−H functionalization *via* an oxidative addition mechanism). The experimental data (regioselectivity, activation energy, kinetics, and isotope and solvent effects) and density functional theory (DFT) calculations supported a proton catalysis mechanism and, consequently, highly Lewis acidic metal compounds, such as aluminum(III) triflate, were extraordinarily active in the H/D exchange reactions.

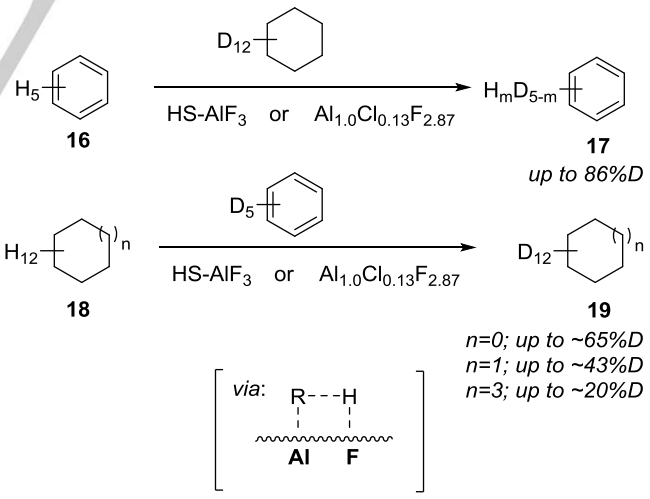


Lewis Acid Catalyst Activity:

$Al^{3+} > Fe^{3+} > Cu^{2+} > Bi^{3+} > (PhCN)_2Pd^{2+} > Zn^{2+} > Fe^{2+} > (NHC)_2Pt^{2+} > Ir^{+} > Rh^{+} > Au^{+} \sim Au^{3+} \sim Tl^{+} \sim Ag^{+}$

Scheme 7. Lewis acid-assisted labeling in acidic media.

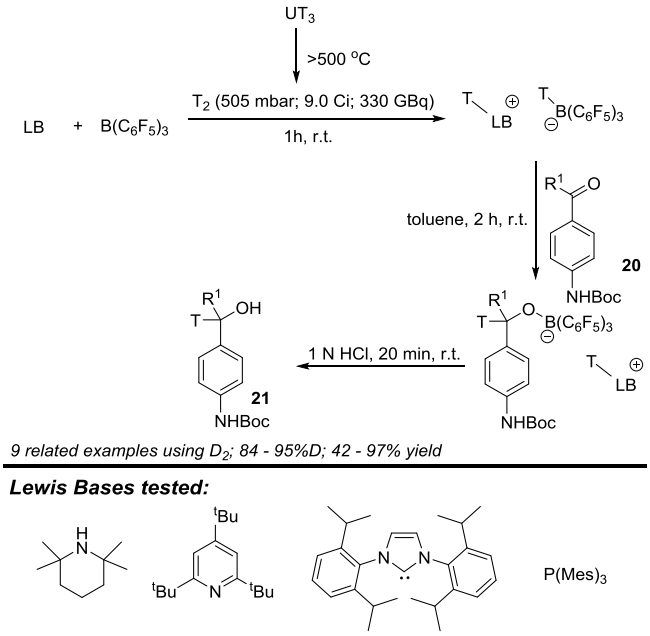
Kemnitz and Braun *et al.* described a new catalytic method for efficient H/D exchange reactions at aromatic and aliphatic C–H/C–D bonds (**16**→**17** and **18**→**19**; Scheme 8).[27] Solid nanoscopic Lewis acids, like aluminium chlorofluoride, and high-surface aluminium trifluoride (HS-AlF_3) were used as catalysts to deliver deuterated benzene and alkanes at mild to moderate temperatures (40 °C to 110 °C).



Scheme 8. Aliphatic H/D exchange using high surface-AlF_3.

A further area gaining increased attention in the context of hydrogen isotope exchange reactions is the application of Frustrated Lewis acid/base pairs (FLPs).[28] There are already some examples demonstrating that H/D exchange in the gas phase takes place.[29] In another example, a series of Lewis base/borane mixtures were used in the reduction of imines,[30] or

carbonyl groups (for example, **20**→**21**; Scheme 9).[31] An equivalent H/D or H/T exchange reaction on hydrocarbons has yet to be realised.



Scheme 9. Frustrated Lewis pairs in HIE.

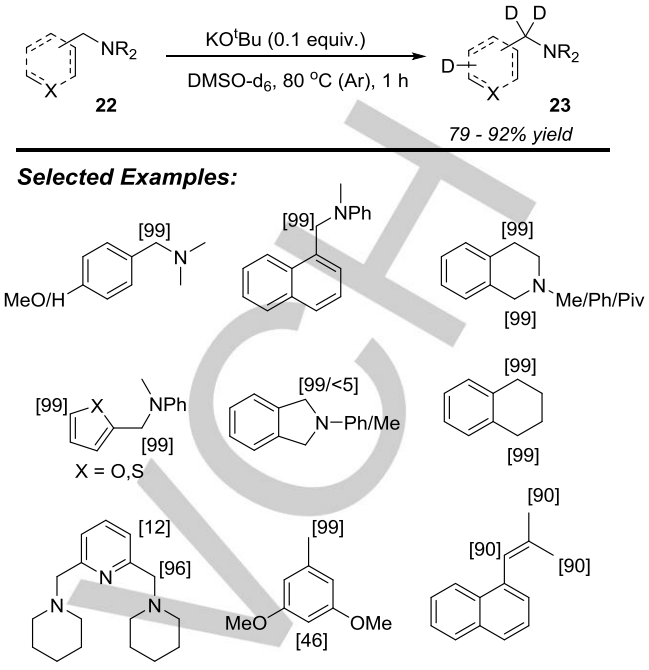
As with the section 2.1, the methods described in section 2.2 are most appropriate for structurally simple molecules, or molecules in which there is a targeted, reducible functionality. Using Lewis acids in combination with isotopic media, future challenges lie in understanding how such methods can catalyze or mediate labeling at lower temperatures.

2.3 Base-mediated labeling

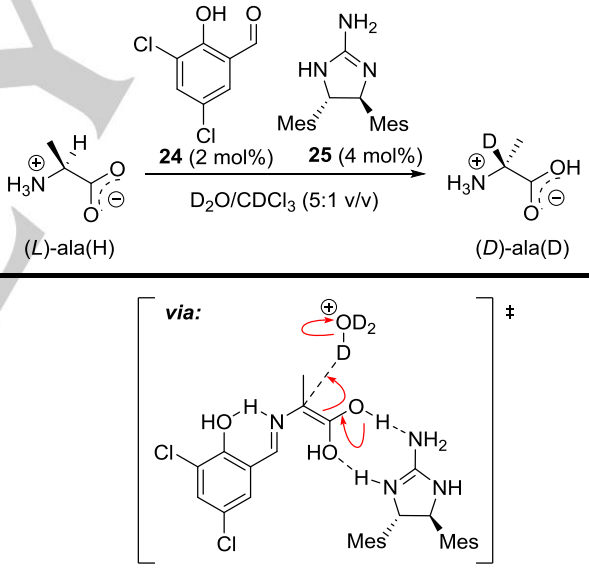
A convenient way to synthesize deuterium labeled amines and nitrogen-containing heterocycles was reported by Zhang and Yan *et al.* (**22**→**23**; Scheme 10).[32] Utilizing a base and DMSO-d_6, a free radical deuteration mechanism has been postulated, starting by deprotonation of DMSO. Best deuteration results were achieved with NaH and KO^{t}Bu.

In another approach to deuterate amino acids, L-alanine was catalytically transformed into deuterated D-alanine by reaction with an aldehyde **24** and a chiral base **25** in 67%ee, without any use of protecting groups (Scheme 11).[33] When L-alanine was reacted for 3 days instead of 4 h, the D/L ratio of deuterated alanine changed to 1:1. The drop in the D/L ratio (5:1 to 1:1) was considered to be due to catalytic racemization of deuterated D-alanine. This system could also be used for catalytic deuteration of D-alanine with retention of stereochemistry to give deuterated D-alanine.

In conjunction with labeling phenols, Xie and Chen *et al.* developed a highly effective method using NaOH as a catalyst and D_2O as the deuterium source under microwave irradiation at 180 °C (**26**→**27**; Scheme 12).[34] High degrees of both regioselectivity and deuterium incorporation for the *ortho*- and/or



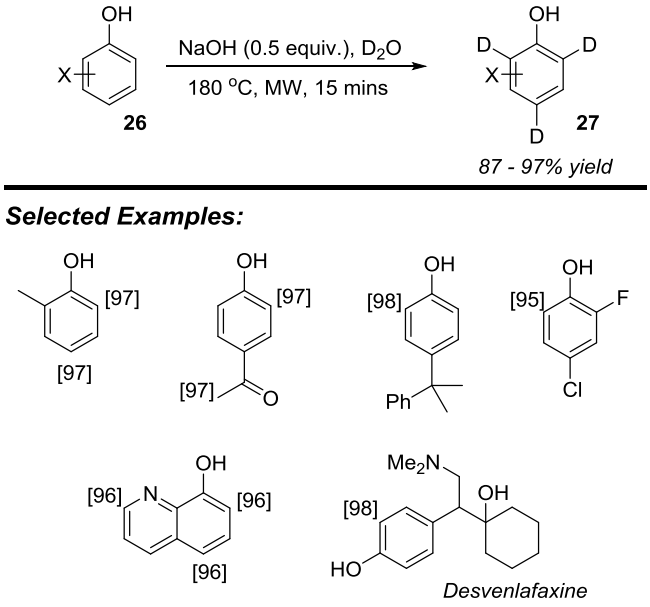
Scheme 10. Base-mediated labeling of benzylamines.



Scheme 11. Enantioselective deuteration of amino-acids.

para-hydrogens relative to the oxygen atom were achieved. The method showed a relatively high functional group tolerance and allowed the deuteration of complex pharmaceutically interesting substrates, such as Desvenlafaxine (Scheme 12).

Finally, it can be summarized that the field of acid/base-catalyzed H/D exchange is slowly progressing with some very convenient new approaches and methods emerging. Accordingly, further attention to this developing area is advised.



Scheme 12. Base-medated HIE with Phenols.

3. Heterogeneous Catalysis

In homogeneous catalysis, selectivity is one of the major objectives, while in heterogeneous catalysis, the high catalyst reactivity, which can be fine-tuned by activation of the catalyst surface, is a more prominent advantage. The reasons for needing different types of labeling selectivity depend on the end application of the labeled molecule, and this is discussed in full in our sister review, "*Applications of Hydrogen Isotopes in the Life Sciences*".[15] Generally, heterogeneous catalysis is applied if several deuterium/tritium atoms are required to be introduced. Therefore, this method is mainly applied to prepare deuterated MS standards for LC-MS/MS analysis. Another technical advantage of heterogeneous catalysis is the possibility to remove the catalyst by simple filtration on reaction completion. Moreover, in exchange processes that occur without side reactions or decomposition, no further purification step is necessary. However, due to the generally low levels of selectivity there is always the possibility of unwanted dehalogenation, hydrogenation, hydrolysis, or, under more harsh conditions, epimerization and racemization. Additionally and in spite of the methodological improvements in recent years, adjustment and optimization of the reaction conditions for each substrate are usually unavoidable.

High activity for H/D exchange by heterogeneous approaches has been found with palladium, platinum, rhodium, nickel, cobalt, and, more recently, ruthenium catalysts. On the other hand, no particular exchange activity has been observed in heterogeneous reaction procedures with either iridium or iron, which are used with success in homogeneous catalysis (see next section). Regarding the isotope source, gaseous deuterium or tritium, deuterium- or tritium-oxide, and deuterated protic solvents that transfer their labile deuterium to the substrate have all been used as isotopic hydrogen sources.[7, 8] The most recent method developments and trends of heterogeneously catalyzed HIE reactions are now described, below.

3.1 Transition metal-catalyzed HIE reactions

Palladium is amongst the most common transition metals applied in C–H functionalization, and there are many recent applications of such heterogeneously catalyzed HIE reactions reported.[8e, 35, 36, 37, 38, 39, 40, 41] In principle, Pd/C is one of the most widely used heterogeneous catalysts in organic synthesis, as typically applied in hydrogenation reactions. Many different catalyst variations are commercial available, generating a complex portfolio of hydrogenation reactivity measured in turn-over-number (TON) and turnover-frequency (TOF) of different model reactions. Pd/C has also proven its usefulness in HIE reactions. However, detailed descriptions of the catalyst (supplier, batch, etc.) are essential to fully reproduce published results.

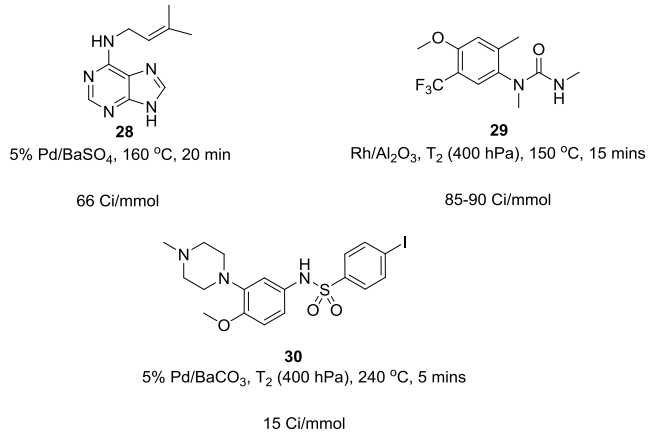
In relation to isotope incorporation, a comprehensive investigation of the scope of the Pd/C–H_2-D_2O has been accomplished over the last ten years. More specifically, aliphatic secondary alcohols and ketones have been deuterated with high deuterium contents of >90% in redox processes; interestingly, the ketones reached higher levels of deuterium incorporation compared to the alcohols.[35] Furthermore, kinetic investigation of Pd-catalyzed D_2O and H_2 reactions have been performed, TON for such processes were calculated, and investigations performed for hydride catalyst activation.[36, 37, 38]

Pd/C has also been applied to introduce tritium into molecules (for applications, see our sister review).[15] In a recent example, the HIE reaction of sodium 4-phenylbenzoate in a diluted tritium atmosphere was accomplished generating the labeled product with a low specific activity of 0.8 ± 0.2 Ci/mmol)[39, 40] (29.2 Ci/mmol[11] = 100% tritium at a C–H position). However, heterogeneous catalyzed H/T-exchange reactions remain a relatively neglected field of research.

Another approach to influence the activity of the heterogeneous catalyst is to adjust the Pd/C activity by modification of the catalyst surface in combination with organic bases. This has been extensively studied in hydrogenation reactions of CBz- or benzyl-protected ethers or amines.[42] In a HIE reaction with the catalyst Pd/C–ethylenediamine complex [Pd/C(en)], for example, only deuterium exchange at the benzylic positions took place. The benzylic site of 1-benzyloxy-3-phenylpropane was deuterated at 50 °C using 5% Pd/C(en) without the hydrogenolysis of the benzyl ether (yield 90%), while the use of Pd/C alone caused a significant deprotection of the *O*-benzyl group to afford the benzyl ether in only 36%.[43] Finally, it should be noted that other organic support materials have been applied in successful deuterations, e.g. Pd/BN (BN=boron nitride)[44] or Pd/PVP (PVP = poly(*N*-vinyl-2-pyrrolidone), demonstrating a broad acceptance of different carrier materials.[45]

Besides organic catalyst support, the effect of inorganic catalyst carriers in HIE reactions has also been studied intensively. One major field is the high-temperature solid-state catalytic isotope exchange (HSCIE) method developed by Myasoedov *et al.*, which is based on the action of gaseous deuterium/tritium on a solid, highly dispersed mixture of the substrate and the transition-metal catalyst (mostly applying an inorganic carrier e.g. $CaCO_3$, $BaSO_4$, etc.) without any solvent at high temperatures (130-180 °C).[46, 47, 48] This isotope exchange method proved to be highly efficient in the selective,

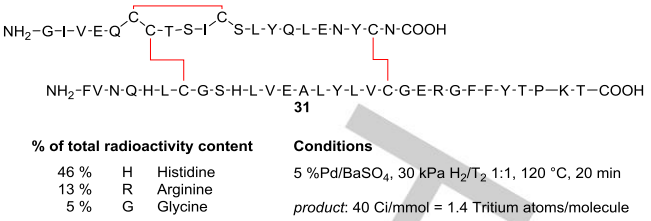
racemization-free deuteration/tritiation of amino acids and peptides.



Scheme 13. Recent applications of heterogeneous Pd- or Rh-catalyzed HIE for tritiation. Labeling position not specified.

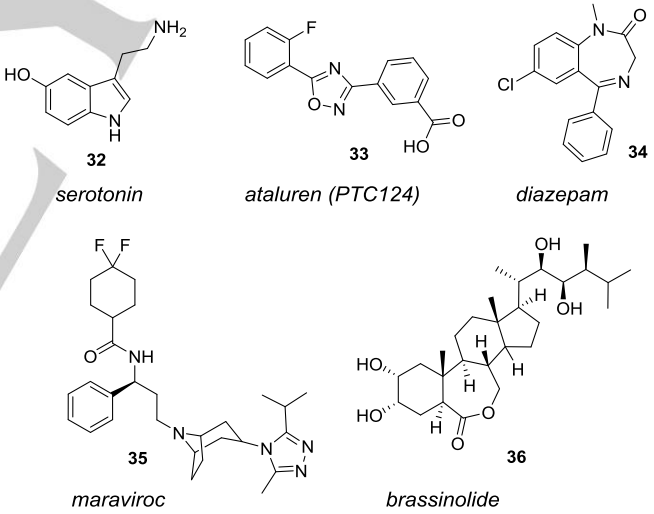
Some recent examples have further broadened the scope of this method in recent years (Scheme 13). For example, the effect of catalyst and temperature on the HSCIE reaction of isopentenyladenine **28** was studied; this substrate was required for investigation of the specific binding with the AHK4 cytokinin receptor. Applying the standard procedure at 160 °C and Pd on $BaSO_4$ or $CaCO_3$ for 20 minutes afforded tritiated isopentenyladenine in moderate yields.[47] If non-diluted tritium gas was applied, higher specific activities were reached as reported in the HSCIE reaction of methylurea **29**. After reaction of **29** with PdO/$BaSO_4$ at 150 °C for 15 min under a tritium atmosphere, the tritiated analogue was isolated in 30-35% yield and with high specific activity.[48] In another example, SB258585 **30** was tritium labeled without loss of the iodine moiety. This outcome is considered to be quite remarkable as these reaction conditions are the standard procedures for iodine/tritium exchange in solution. SB258585 **30** is an antagonist of the 5-HT-6 receptor and exhibits antidepressant, nootropic, and anxiolytic properties. The compound is considered to be a promising structure for the treatment of schizophrenia, cognitive disorders, or Alzheimer's disease.[49] Most interestingly, the Myasoedov method has been successfully applied to label larger peptides, like insulins. Recombinant insulin **31** was subjected to HSCIE reaction (5% Pd/$BaSO_4$, 30 kPa T_2/H_2, 20 min, 120 °C) with a hydrogen–tritium 1:1 mixture to produce the ^{3}H-insulin with a specific activity of 40 Ci/mmol and an overall radioactivity amount of 3 mCi being isolated (Scheme 14). After digestion and MS analysis, the percentage of ^{3}H-labeling for each amino acid was determined. Histidine (46%), arginine (13%), and glycine (5%) were identified as the amino acids with the highest tritium content. However, around 36% of the total radioactivity was distributed unselectively within the other amino acids.[50]

Zolotarev *et al.* examined the HSCIE reaction under the action of spillover hydrogen[51] on amino acids or peptides as applied on alumina oxide. Activation energies for hydrogen isotope exchange with tritium and deuterium in glycine and α-aminoisobutyric acidwere measured experimentally and calculated using a quantum chemical approach. The activation



Scheme 14. Pd-catalyzed tritium labeling of insulin.

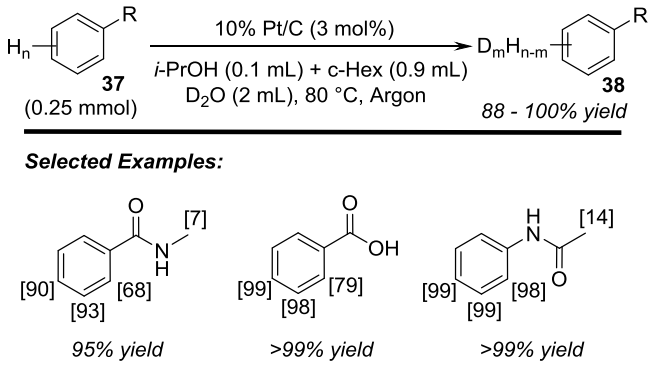
energies for H/T and H/D exchange in all measured amino acids were very close, with the hydrogen isotopes reacting at virtually the same rate. It was shown that for the solid-state reaction studied, with deuterium and tritium the kinetic isotopic effect was 1.2−1.4, which is several times smaller than the kinetic isotopic effect in hydrogen transfer reactions in the liquid phase. Using the HSCIE reaction, it becomes possible to substitute hydrogen for deuterium or tritium almost quantitatively in a series of amino acids without racemization.[52] This method has also been applied in the tritiation of GABA and L-DOPA,[53] brassinolide,[54] ataluren (PTC124),[55] druglike glutamate and dopamine ligands,[56] maraviroc, a new generation agent for HIV treatment blocking chemokine receptors CCR-5,[57] D-ribose,[58] serotonin (5-methoxytryptamine), and diazepam (see, for example, **32**-**36**, Scheme 15).[59]



Scheme 15. Applications of high temperature solid-state catalytic isotope exchange (HSCIE).

In addition to palladium, platinum also plays an appreciable role in heterogeneous catalyzed HIE reactions. Platinum has especially proven to be very efficient for aromatic C–H positions, with much higher deuterium incorporation compared to aliphatic C–H positions. For example, Sajiki *et al.* reported an effective deuteration method for aromatic rings using the Pt/C–D_2O–H_2 system. They demonstrated the complete labeling of phenol at room temperature; additionally, other electron-rich aromatic nuclei were efficiently deuterated under mild conditions.[60] However, the use of hydrogen gas for catalyst activation can be

avoided within this general Pt-catalyzed approach. Recently, a method for deuteration of several arenes under Pt/C-^{i}PrOH-D_2O conditions was reported (**37**→**38**; Scheme 16). Remarkably, the activation of the metal surface was performed by *in situ* generated hydrogen/deuterium through transfer hydrogenation from *iso*-propanol. This developed external hydrogen gas-free method could, therefore, be used on process scale or for substrates where undesired Pt-H_2-reductions were otherwise likely.[61]

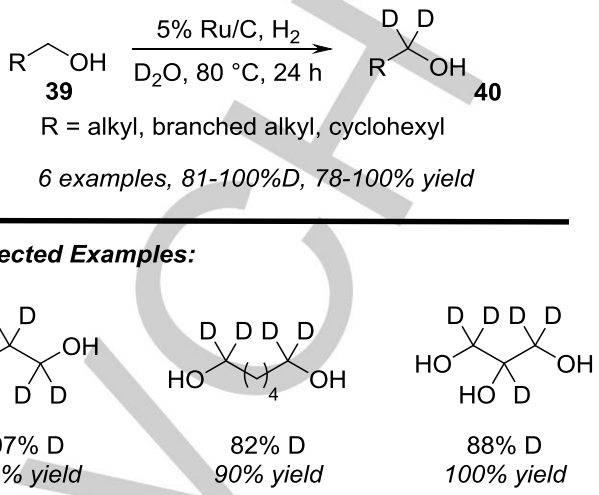


Scheme 16. Global deuteration using Pt/C.

There have also been several cases where the design and structure of the heterogeneous catalysts has been studied and ways in which to optimize reactivity and efficiency in the hydrogenation or HIE reaction have been found. In one example Nakamura *et al.* have demonstrated high durability in ten catalytic cycles of a simple HIE reaction with hydrogen and deuterium using a nitrogen-doped graphite surface. The applied ion bombardment enhanced extensively the durability of deposited Pt clusters for H_2−D_2 exchange reactions.[62]

The difficulty in finding a suitable method for the deuteration of unactivated hydrocarbons was addressed in 2008 by applying Rh/C–H_2-D_2O as catalytic system. At 160 °C linear alkanes were deuterated with grades higher than 90% deuterium at each carbon atom. In the case of *n*-octacosane ($C_{28}H_{58}$), full deuteration with up to 58 exchanged deuterium atoms was determined. The method was also successfully applied to a number of cyclic hydrocarbons, such as α-cholestane or cyclopentadecane, with moderate to high deuterium incorporation.[63, 64]

One of the major improvements in this general field over the past 10 years has been the application of ruthenium in heterogeneous catalyzed HIE reactions. While ruthenium catalysts have been used in selective homogeneous HIE reactions for many years, heterogeneous ruthenium catalysts on support have been appreciably neglected. In a first example, a regioselective deuteration of carbinol carbons was achieved by the combination of ruthenium on carbon (Ru/C), hydrogen gas, and deuterium oxide (D_2O). The reaction proceeded with high deuterium efficiency and regioselectivity at the position α to the hydroxy unit, with hydrogen exchange of either one deuterium atom for secondary or two deuterium atoms for primary alcohols, respectively (**39**→**40**; Scheme 17). Testing 2-(*S*)-hydroxynonane (97%ee) under the reaction conditions with H_2 rather than D_2, it was found that the α-hydroxy position was completely racemized (1.8%ee). This method is applicable to the deuteration of various aliphatic alcohols, including diol and triol derivatives.[65]



Scheme 17. Heterogeneous Ru-catalyzed α-deuteration of alcohols.

The same general method was further explored in the deuteration of various sugars. Several pyranosides, such as 1-deoxy-D-glucopyranoside, β-D-galactopyranoside, D-(+)-trehalose,β-D-ribofuranoside, and D-(+)-saccharose were successfully deuterated with up to 100% deuterium at the 2-, 3-, 4-, and 6-position without any loss of stereoinformation.[66] By using protected sugars, a site-selective deuteration allowed the synthesis of the various deuterated sugars in a regio- and stereoselective fashion. Nearly quantitative deuterated sugars could be obtained following simple work-up processes, such as filtration of the heterogeneous Ru/C catalyst and extraction (**41**→**42**; Scheme 18).[67] It was proposed that the ring strain that would be induced by oxidising (dehydrogenating) the hydroxyl groups to the corresponding carbonyl group en route to epimerisation allows for kinetically competitive and stereo-retentive oxidative addition into the C-H bonds. Thus, unlike the acyclic example discussed above (Scheme 17), no epimerisation occurs during C–H cleavage in labeling the cyclic sugars.

Scheme 18. Ru-catalyzed deuteration of sugar derivatives.

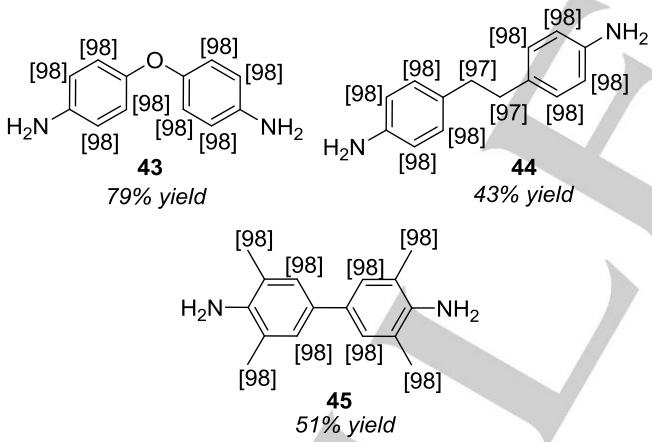
Cobalt and iron were also examined in an HIE reaction of D_5-1-pentene under standard Fischer-Tropsch conditions. A significant inhibition of the catalyst in the presence of carbon monoxide was observed.[68, 69] In material science, the study of

HIE in understanding hydrogen storage and dissociation processes is of fundamental importance. In one example, HIE was studied in polycrystalline tungsten at 320 and 450 K. It was concluded that hydrogen does not freely diffuse through hydrogen saturated layers. The transport of hydrogen is a chain of trapping, de-trapping, and diffusion events.[70] Furthermore, the results reported by Rai *et al.* indicate that graphite (carbon surface) also may have a significant influence on HIE processes.[71] Assiociated with all of this and into the future, understanding of the physical processes in heterogeneous catalysis is expected to improve the HIE applications in general.

3.2 HIE reactions with catalyst mixtures

Where individual heterogeneous catalyst systems have found applications in HIE in their own right, more recent advances have been made using *combinations* of catalysts to produce labeling strategies complementary to those of either catalyst on its own. The fundamental reasons for these observed effects remain an unknown in this area of applied synthesis.

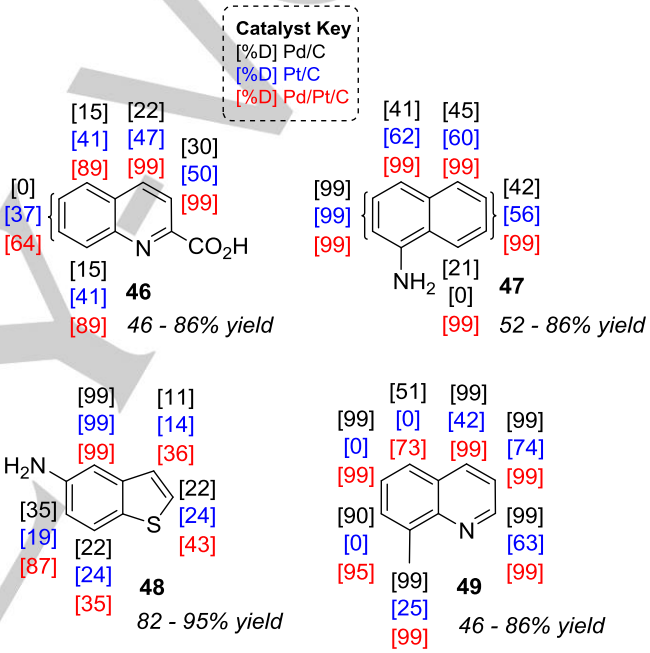
In 2006, Sajiki *et al.* made the first report of a synergistic effect when using catalyst mixtures of Pd/C and Pt/C for H/D exchange reactions (Pd-Pt-D_2O-H_2).[72] Since then this principle has been demonstrated successfully on several occasions. In a specific example, Pd/C and Pt/C catalyst mixtures revealed an almost quantitative deuteration of a number of bisanilines. With this method, benzylic and aromatic positions were deuterated very effectively (**43** – **45**; Scheme 19).[73]



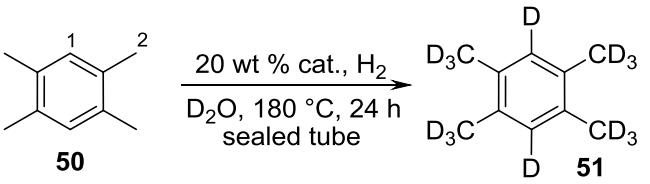
Scheme 19. Synergic Pd/Pt-catalyzed HIE with bisanilines.

In another example reported by Derdau and Atzrodt, the synergistic effect was proven after $NaBD_4$-activation of the catalyst mixture resulting in significantly higher deuterium incorporations compared to those obtained with the single catalysts induced H/D exchange of heterocycles (see Scheme 20).[74] More specifically, a significant synergistic effect could be observed for quinoline-2-carboxylic acid **46**, aminonaphthalene **47**, and 5-aminobenzothiophene **48**. For 8-methylquinoline **49**, an almost complete deuteration was achieved with the Pd/Pt/C catalyst mixture and, in contrast to Pd/C alone, a representative mass peak at M+9 could also be identified and, thus, the material could be used as precursor for internal MS standard preparation.

In the same year, similar results were reported by Sajiki *et al.* with bimetallic Pt/Pd/C catalysts produced by various reducing agents.[75] Depending on the reducing agent, the activity of the *in situ* prepared active bimetallic catalysts differed. Interestingly, the $NaBH_4$ reduced catalyst showed the highest overall catalytic activity for the deuteration of 1,2,4,5-tetramethylbenzene and was even superior than the species reduced by H_2 alone (**50**→**51**, Scheme 21). Recently the mixed catalyst 10% Pd/C (10 wt %) and 10% Pt/C (25 wt %) was utilized for deuteration of Mesalamine at 145 °C, using D_2O as the deuterium source under a hydrogen atmosphere.[76]



Scheme 20. Synergistic effect in the $NaBD_4$ activated microwave-induced H/D exchange.



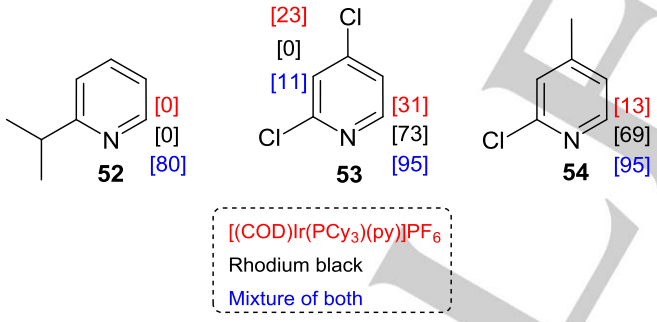
	D-content (%)		*Yield (%)*
	C_1	C_2	
$Pd/Pt/C + NaBH_4$	[95]	[94]	quant.
Pd/C +Pt/C	[96]	[75]	76
Pd/C (10 %)	[97]	[13]	96
Pt/C (5%)	[93]	[75]	92

Scheme 21. H/D exchange with bimetallic platinum/palladium-on carbon catalysts.

In order to establish a suitable approach for the large scale synthesis (1-12 g scale) of deuterated arylamines which demonstrate a great potential for use in optoelectronic devices, the deuteration of diphenylamine, *N*-phenylnaphthylamine, *N*-phenyl-*o*-phenylenediamine, and 1-naphthylamine (*via* H/D exchange in D_2O at 80 °C, catalyzed by Pt/C and Pd/C) was examined. While primary and secondary aromatic amines showed high overall deuteration incorporation (88-96%), tertiary amines failed completely.[77]

Mixtures of heterogeneous Pt/C and Rh/C have been applied in deuteration of alkanes in a mixture of *i*-PrOD-d_8 and D_2O.[78] The reported multi-deuteration was initiated by the transition metal-catalyzed dedeuteration of *i*-PrOD-d_8 (Oppenauer oxidation) to produce D_2, and the subsequent CH bond activation of the alkanes catalyzed by the catalyst mixture complex. This method was used to deuterate a wide variety of linear, branched, and cyclic alkanes at relatively moderate temperatures (120 °C) with deuterium contents from 14-39% (α-cholestane) up to 92-97% (pentadecane).

In another case, rhodium black was combined with the homogeneous Crabtree catalyst, $[(COD)Ir(PCy_3)(py)]PF_6$, resulting in improved deuterium incorporation into aromatic heterocycles and anilines compared to rhodium alone, delivering labeling levels of up to 95% (**52**-**54**; Scheme 22).[79] The reactions were performed under deuterium atmosphere at room temperature. Schou showed that the catalytic system was generally independent of the solvent used (THF, DCM, EtOAc). With other rhodium sources, such as Rh/C or Rh/alumina, the synergistic effect of the homo-/heterogeneous catalyst combination was limited and, thus, only minor differences were observed.



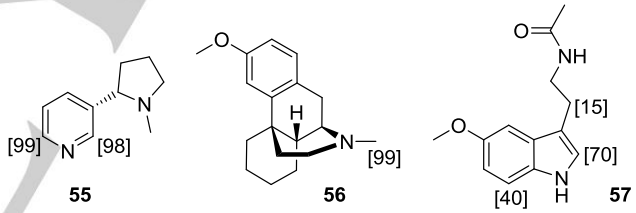
Scheme 22. Combined homo- and heterogeneous catalysts in HIE.

3.3 HIE reactions with nanoparticles

The use of nanoparticles[80] can be described as existing on the borderline between homogeneous and heterogeneous catalysis. These nanoparticles are fully dispersed in an aqueous or organic matrix and invisible by human eye, however, they are still formally heterogeneous catalysts. Therefore, the critical reaction parameter continues to be the surface of the activated catalyst. Nevertheless, nanoparticles have shown very interesting reactivities and selectivities in a number of examples of HIE reactions.

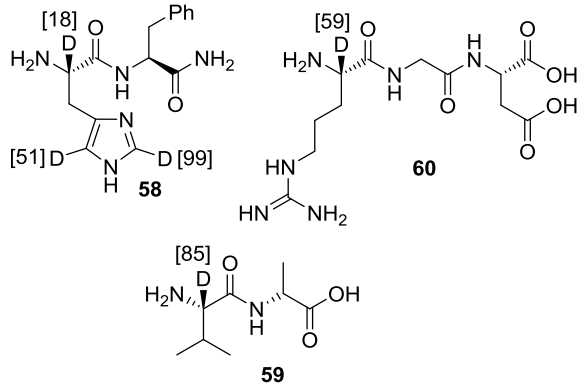
In an early example Sullivan *et al.* prepared Pd nanoparticles (with a mean diameter of 3.4 nm) through BH_4 reduction of Na_2PdCl_4 in the presence of 4-dimethylaminopyridine (DMAP).[81] The particles were stable in solution for up to six months and were used for a selective H–D exchange at the 2,6-positions of pyridines in D_2O. Oxidised Pd(II) complex species also present, as dissolved in the nanoparticle dispersion, played no part in the exchange. However, attempts to extend this activity and selectivity to other related molecules have shown that the presence of other functional groups (e.g. hydroxyl, amino) within the substrate of interest can have detrimental consequences for both the activity and the selectivity of the reaction.

Pieters *et al.* reported an efficient H/D exchange method allowing the selective deuteration α to the nitrogen atom position in pyridines, quinolines, indoles, and alkyl amines with D_2 in the presence of RuNP@PVP nanoparticles (**55**-**57**; Scheme 23). Enantiomeric purity was conserved in the labeled compounds, where labeling took place in the vicinity of the stereogenic center.[82] These results were further extended by applying the same Ru@PVP nanoparticles in the selective deuteration of amino acids and peptides (**58**-**60**; Scheme 24).[83] More specifically, an enantiospecific C–H activation reaction followed by deuterium incorporation at stereogenic centers was demonstrated. Mechanistic studies suggested that the selectivity for the α-position of the directing heteroatom results from a four membered dimetallacycle as the key intermediate. These results clearly demonstrate the potential of nanoparticles for the effective catalysis of C–H bond activation and pave the way for new enantiospecific C–H functionalization reactions.



Conditions: RuNP@PVP (3 mol%), 55 °C, D_2 (1-2 bar), THF, 36 h

Scheme 23. Ru-nanoparticle-mediated HIE.



Conditions: RuNP@PVP (5-6 mol%), 55 °C, D_2 (2 bar), D_2O, 36 h

Scheme 24. Ru-nanoparticle-mediated HIE with conservation of stereochemistry.

In a further example, Ru/PVP nanoparticles were applied in the H/D exchange of phenyl rings in phenyl- or phenyl alkylphosphines, including diphosphines. This enables the comprehension of how different phosphorus ligands coordinate to the nanoparticle surface as analyzed by ^{31}P-NMR techniques.[84] Recently, Jackson *et al.* have reported the application of electroactivated ruthenium particles, which are supported by an activated carbon cloth (Ru/ACC), that enables stereoretentive C–H activation at sp^3 C–H sites bearing amine or alcohol groups.[85]

Generally the applications of nanoparticles show different reactivity or selectivity compared to the already known homogeneous or heterogeneous HIE reaction systems. It is, therefore, anticipated that advances in material science will also enrich the armory of HIE reaction methods in the future.

3.4 Conclusion

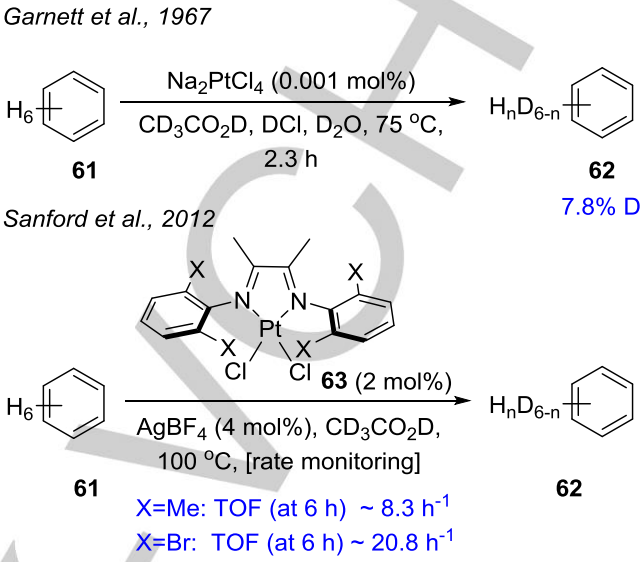
Currently known techniques for heterogeneous labeling with deuterium/tritium atoms use the following representative combinations of catalyst and hydrogen isotope sources: Pd/C–D_2 or Pd/C–T_2, Pd/C–(H_2/D_2)-D_2O(DCl), Pd/C-Et_3SiD-*i*PrOH-D_8, Pd/C(en)-D_2, Pd/PVP-D_2, Pt/C–D_2, PtO_2–D_2–D_2O, Rh/C, or Rh black-D_2, Ru/C–D_2, and, more rarely, cobalt or nickel metal. Generally, significant improvements have been made by applying the synergistic effect of catalyst mixtures to deliver higher deuterium contents. Nanoparticles have been identified as a new class of HIE catalyst, providing promise for further improvements in deuteration efficiency and selectivity.

4. Homogeneous Catalysis

As homogeneous catalysts are often single molecule species, their catalytic properties can be tuned by judicious manipulation of the ligands bound to the reactive metal centre. Furthermore, this mode of catalysis often leads to very mild, widely applicable and, indeed, industrially attractive reaction conditions. Therefore, parallel to advances in heterogeneous catalysis (*vide supra*), acid/base-mediated HIE, and even organocatalytic HIE methods (see section 2), homogeneous catalysis dominates modern research in HIE.[8a, 10a,c, 86, 87, 88, 89, 90, 91, 92] Additionally, isotopic labeling remains in regular use for the measurement of KIEs[93, 94, 95, 96, 97, 98] and metal-ligand cooperativity[99, 100, 101, 102, 103, 104, 105, 106, 107, 108] in various applications of homogeneous transition metal catalysis. These latter mechanistic applications of homogeneous HIE fall outside the scope of the current organic synthesis focused discussion.

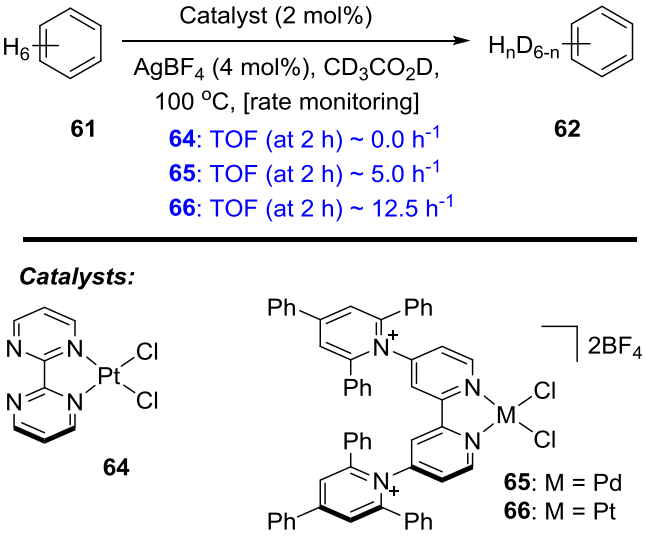
4.1. Platinum

In 1967, Garnett and Hodges reported one of the first examples of HIE employing homogeneous catalysts.[109] Using Pt(II) salts, in the presence of deuterated acetic acid, water, and hydrochloric acid, various arenes were labeled, albeit in a non-regioselective manner (**61**→**62**; Scheme 25, top). Many years later, Sanford and co-workers explored a similar deuterium labeling strategy using diimine-ligated Pt(II) catalysts, **63** (Scheme 25, bottom).[110, 111, 112, 113] It was found that a bromo- rather than methyl-substituted ligand provided the most active catalyst, with this being hypothesized to originate from the greater propensity of the bromine to coordinate to and stabilize the metal centre. Related developments with Rh(I) bis-imine complexes have also been reported.[114]



Scheme 25. Global aromatic HIE *via* homogeneous Pt(II) catalysis.

The study of homogeneous palladium complexes in HIE processes has often been compared to analogous platinum complexes. Indeed, this was the case in the earlier of Sanford's aforementioned deuterium labeling studies, where cationic bipyridine ligands were employed to produce advantageously Lewis acidic catalysts, **65** and **66** (versus **64**), for the deuterium labeling of benzene in the presence of CD_3CO_2D (Scheme 26).[110, 111, 112] Although both metals produced highly active HIE catalysts compared to the parent catalyst of the study (**64**), Pt was more useful than Pd, as Pt provided the most highly acidic catalyst.

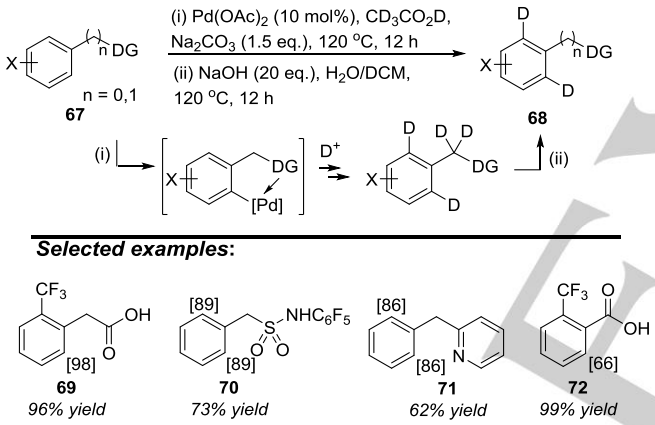


Scheme 26. Palladium versus platinum in global homogeneous HIE.

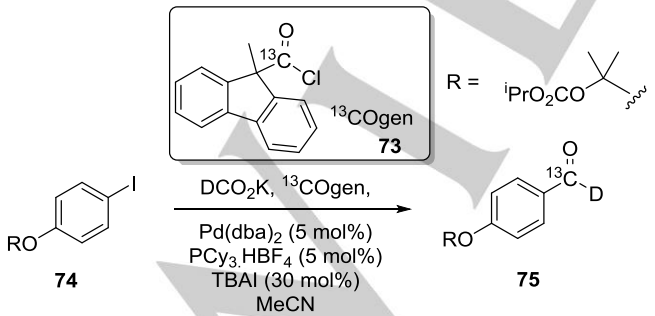
4.2 Palladium

Homogeneous palladium catalysis has also been explored more fully in its own right for HIE processes. Recently, Yu and co-workers demonstrated that Pd(II)-catalysis can be effectively employed in *ortho*-directed HIE processes.[115] Using $Pd(OAc)_2$ under basic conditions in the presence of CD_3CO_2D, various weakly coordinating functionalities were able to affect *ortho*-deuterium labeling in moderate to excellent yield (**67**→**68**; Scheme 27). More weakly coordinating directing groups proved to be most reactive (for example, **69** *versus* **71**). Furthermore, labeling *via* a six-membered metallocyclic intermediate (6-mmi) was found to be more efficient than the analogous 5-mmi (for example, **69** *versus* **72**, Scheme 27).

Skrydstrup and co-workers have developed a fundamentally different method for labeling organic molecules using Pd catalysis. With a two-chamber system, COgen, **73**, was employed as a synthetically convenient CO source in the reductive carbonylation of aryl iodides (**74**→**75**; Scheme 28).[116, 117] In this manner, a range of isotopically-enriched aromatic aldehydes could be accessed without the necessity to label the aromatic C–H positions.



Scheme 27. Pd-catalyzed *o*-directed HIE with aromatic compounds.

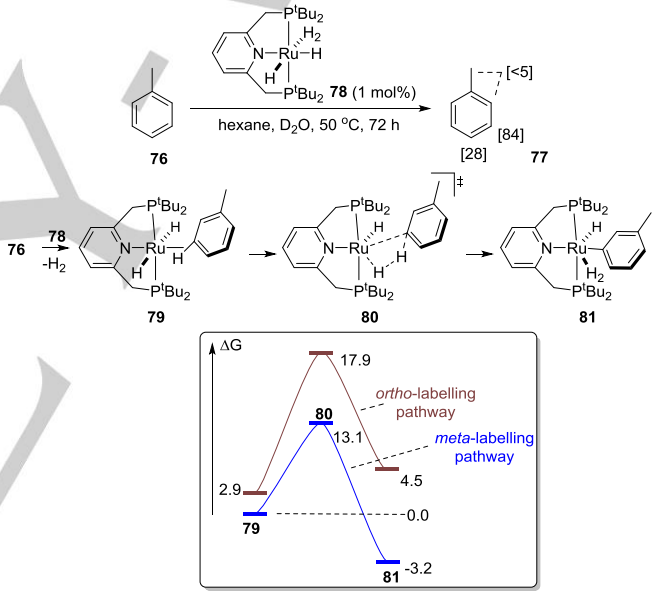


7 examples reported; various combinations of C and H isotopes
69-86% yield

Scheme 28. Dual ^{13}C and D-labeling of aryl iodides.

4.3 Ruthenium

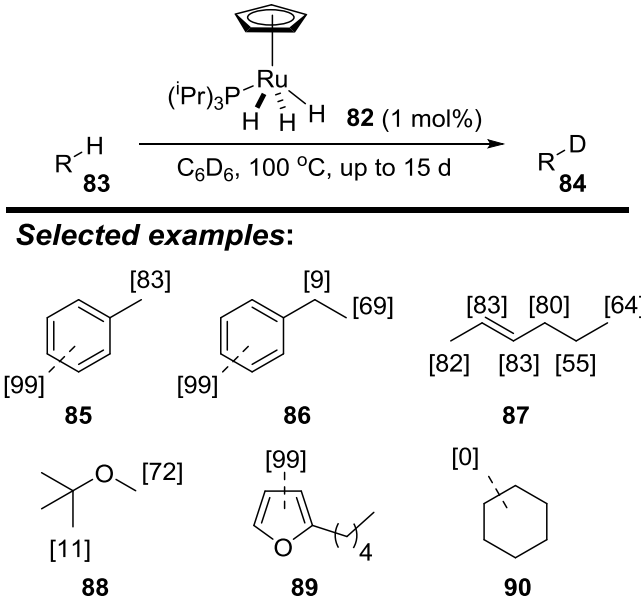
Since 2007, Ru-derived HIE methods have been developed on several fronts.[87] A number of methods have been developed to affect the deuterium labeling of molecules which lack strong coordinating functionalities. Among these, Leitner has reported the D-labeling of benzene derivatives (**76**→**77**, for example) and heteroaromatic compounds using the Ru(II) pincer complex, **78**, under relatively mild, albeit time-consuming, conditions (Scheme 29, top).[118] A combined experimental and computational study revealed that site selectivity in labeling was largely based on steric effects. Mechanistically, after the loss of the dihydrogen ligand and agostic coordination of the unlabeled substrate (**79**, Scheme 29) the key step in the mechanism was reported to involve a σ-bond metathesis between the substrate C–H and a hydride ligand on Ru(II) (**79**→**81** *via* **80**). DFT-calculated energies showed that *ortho*-labeling was disfavoured both thermodynamically and kinetically (as shown *versus* *meta*-labeling in the potential energy surface (PES); Scheme 29).



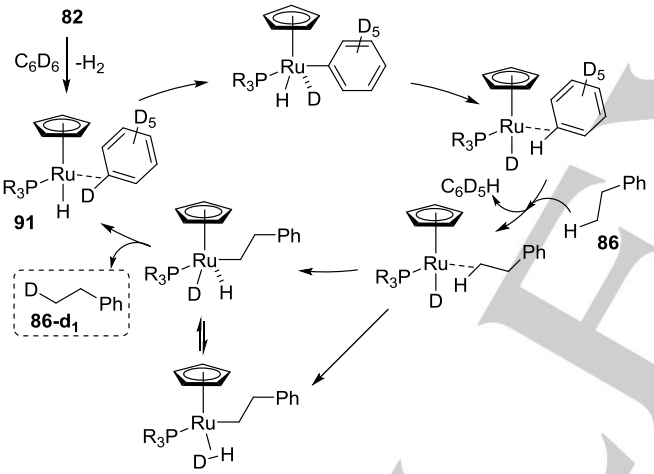
Scheme 29. Sterically-selective labeling of toluene using Leitner's Ru(II) pincer catalyst.

In a related but less selective approach, Gorelsky and Nikonov reported the use of Ru(IV) trihydride precatalyst, **82**, in the Ru(II)-catalyzed labeling of unactivated molecules, using C_6D_6 (Scheme 30).[119] In all cases, aryl and heteroaryl positions were labeled fastest (**85**, **86**, and **89**). In alkyl species, the extent of labeling varied markedly depending on the exact nature of the molecule, and required at least some weakly coordinating functionality to operate at all (for example, **90** *versus* **87** and **88**). Potential reaction mechanisms were studied by DFT (Scheme 31). Reductive loss of H_2 rather than phosphine dissociation was found to be the most likely source of precatalyst initiation (**82**→**91**).

Periana and co-workers investigated Ru-catalyzed perdeuteration using a conceptually distinct approach.[120] Base-sensitive Ru(III) precatalyst **92** was shown to produce active



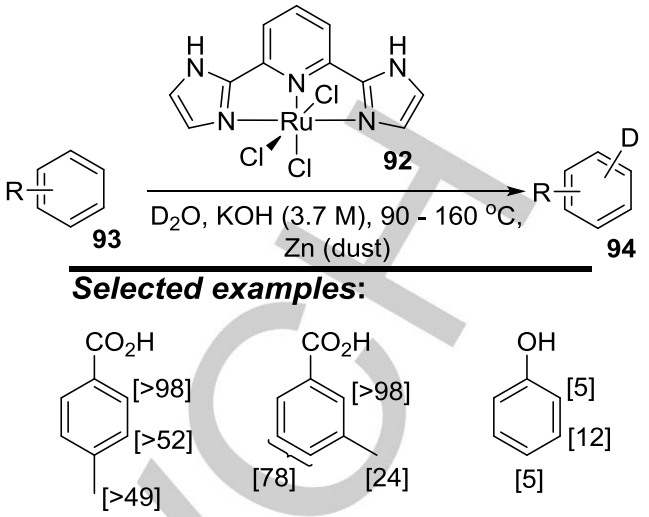
Scheme 30. Ru-catalyzed HIE with aryl and alkyl groups using C_6D_6.



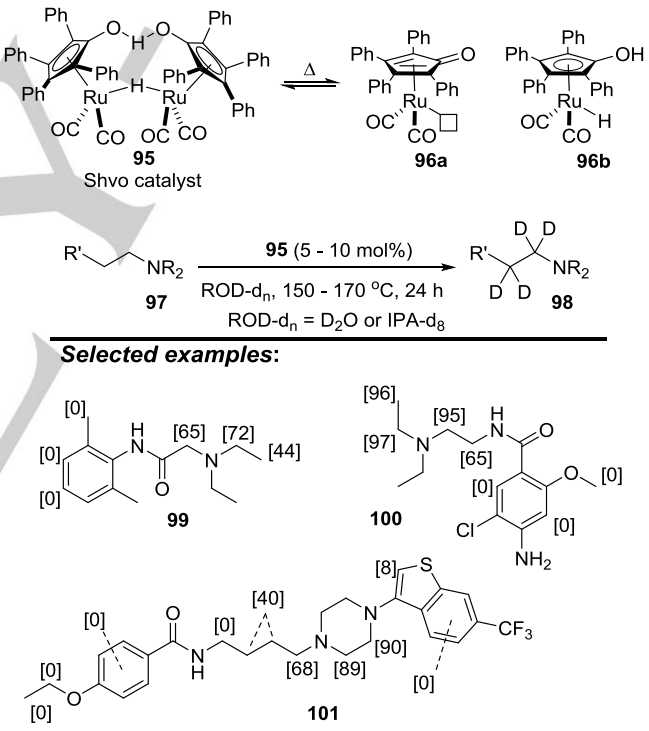
Scheme 31. Proposed mechanism for Ru(II)-catalyzed HIE with **82**.

nucleophilic Ru(II) catalyst(s) *in situ*. The deuterium labeling of several water-soluble organic substrates showed that more electron-deficient molecules could be labeled most efficiently (**93**→**94**; Scheme 32). It is also worth noting the slight preference for labeling adjacent to the (presumably) *ortho*-directing carboxylate.

Beller and co-workers were able to exploit the unusual and so-called Shvo catalyst,[121] **95**, in the α,β-deuteration of biologically-relevant amine molecules (**97**→**98**; Scheme 33).[122] On heating, the Shvo catalyst dimer breaks down into two distinct, catalytically active monomers: the dehydrogenated form **96a**, and the hydrogenated form, **96b**. Together, they catalyze the reaction of **97** to **98** using various deuteratium sources (including IPA-d_8 and D_2O). This method was applied to a host of drug-type molecules, including **99** - **101**.



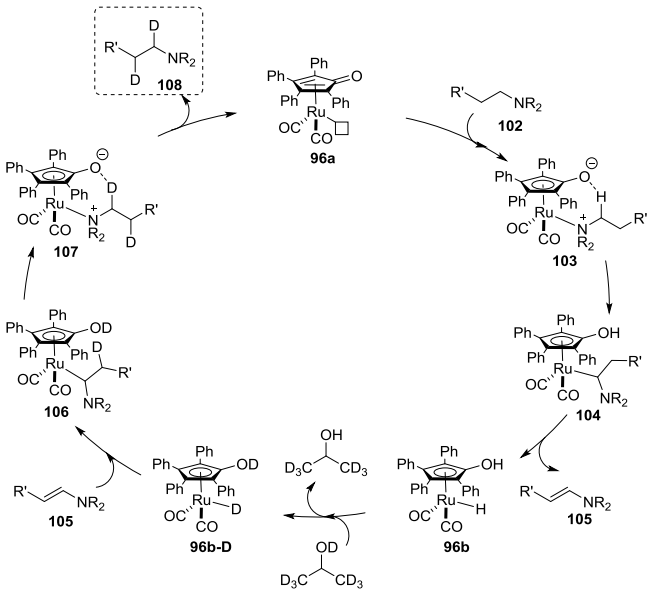
Scheme 32. Perdeuteration of organic molecules under nucleophilic Ru(II) catalysis.



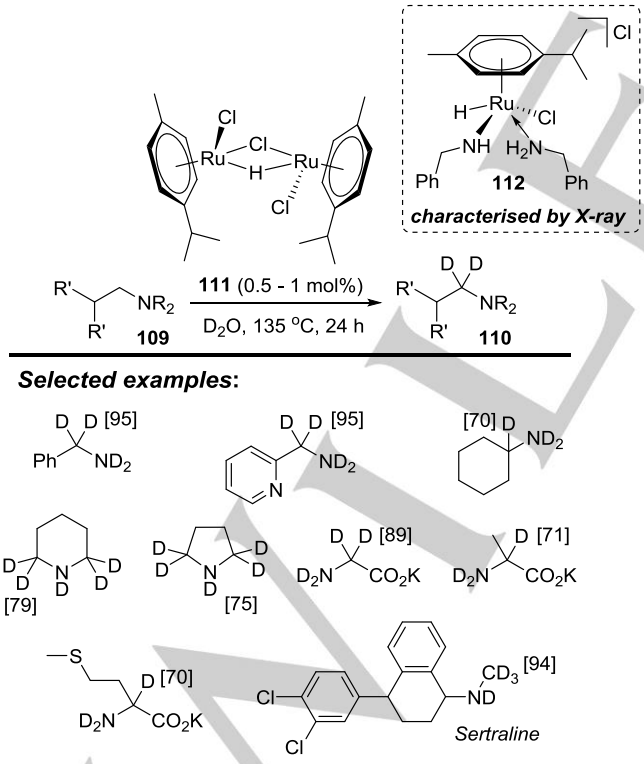
Scheme 33. Ru-catalyzed α,β-deuteration of biologically-relevant amines.

The full significance of both monomeric forms of the Shvo catalyst becomes fully apparent in the reaction mechanism proposed by the authors (Scheme 34). Amine substrate, **102**, first coordinates to the dehydrogenated catalyst monomer, **96a**, producing the zwitterion, **103**. In a ligand-assisted step, the amine is deprotonated, thus switching from a nitrogen- to carbon-centred coordination mode in **104**. Subsequent β-hydride elimination produces enamine **105** and the hydrogenated form of the Shvo catalyst, **96b**. In this form, isotope exchange with IPA-d_8 gives the deuterated catalyst, **96b-D**. The aforementioned enamine, **105**, undergoes migratory insertion with **96b-D** to

deliver the β-label in intermediate **106**. Deprotonation of the cyclopentadienyl ligand by the metalled amine gives **107**, installing the α-label in the final product amine, **108**, and recycling **96a**.



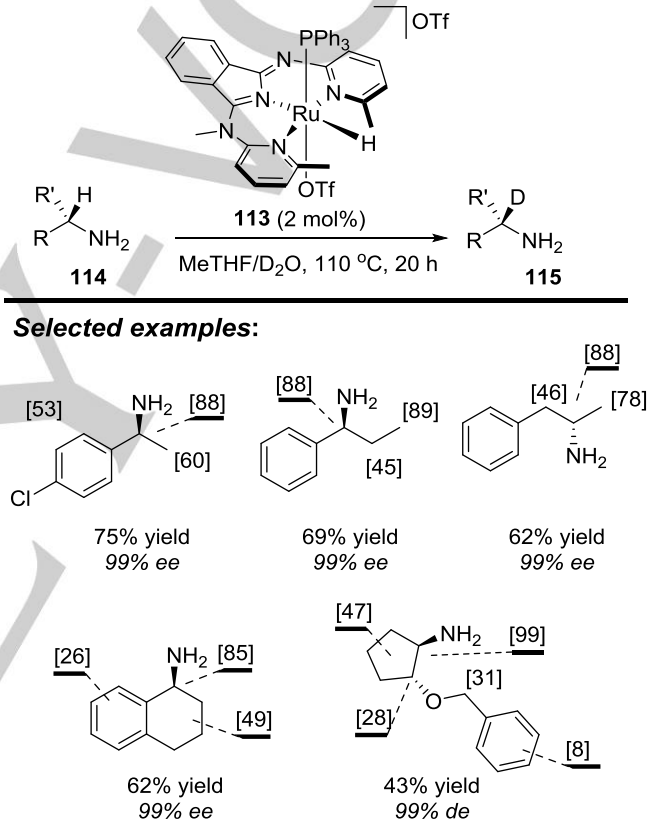
Scheme 34. Proposed mechanism for α,β-deuteration of amines with the Shvo catalyst.



Scheme 35. Ru-catalyzed α-selective labeling of amines.

In 2016, Gunanathan and coworkers published a ruthenium-catalyzed α-selective deuteration of amines, using D_2O as the isotope source under basic consitions.[123] This method suitably complements Beller's α,β-selective method, proceeding *via* amine N–H activation and amide-ligated ruthenium deuteride intermediates (**109**→**110**; Scheme 35). The mechanistic hypothesis was supported by isolation of mixed amine/amide complex, **112**, from **111**.

At a similar time, Szymczak and Hale reported the selective and stereoretentive deuteration of α-chiral amines (**114**→**115**; Scheme 36).[124] This was achieved using judiciously selected electron-deficient Ru(II) catalysts (such as **113**), bearing a rigidified ligand framework, promoting strong substrate binding and fast isotope exchange, thus, minimizing racemization *via* dissociation of planar imine intermediates.

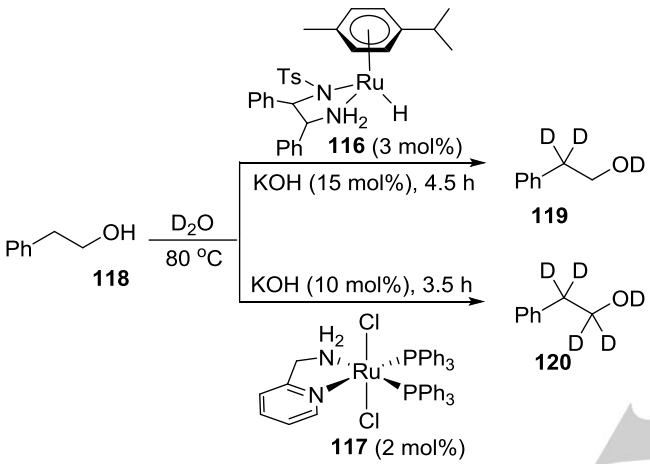


Scheme 36. Regioselective and stereoretentive deuteration of α-chiral amines.

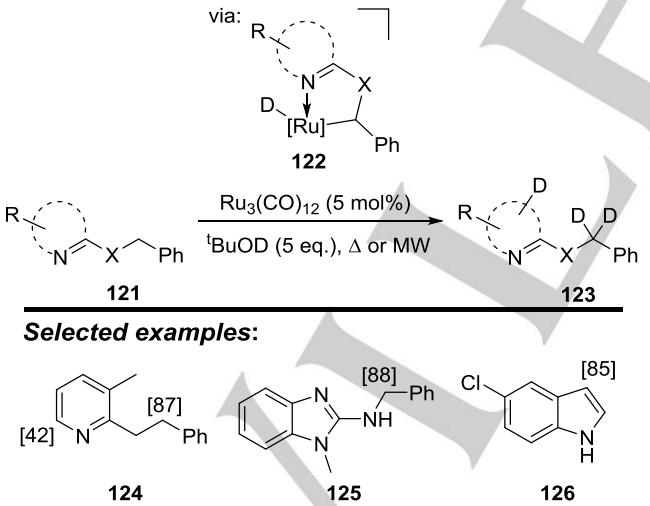
Beyond amines, ruthenium-derived catalysts have been explored for the regioselective labeling of aliphatic alcohols. Recently, Lin and Jia reported complementary precatalysts **116** and **117**, for the β- and α,β-labeling of alcohols with D_2O, respectively (Scheme 37).[125] Computations showed that precatalyst **117** produces hydrides that exchange with D_2O more readily than for **116**, leading to labeling of **118** at the α-position to give **120**. Conversely, β-labeling to give **119** and **120** was facilitated by enolisation of aldehyde intermediates.

Regioselective Ru-catalyzed HIE processes have also been exploited in the labeling of *N*-heteroaromatic substrates. In 2012, Schnürch and co-workers reported the regioselective deuteration of *N*-heterocycles using the Ru(0) cluster, $Ru_3(CO)_{12}$,

and ^{t}BuOD as the deuterium source (**121**→**123**, *via* **122**).[126] In some substrates, deuteration occurred at aromatic and benzylic positions accessible *via* nitrogen coordination, favouring the latter when both were available (molecules **124** and **125**, Scheme 38). Conversely, indole-derived structures were deuterated at the electron-rich 3-position (**126**, Scheme 38). No in-depth mechanistic analysis was carried out by the authors. However, it was speculated that labeling of substrates like **124** or **125** is likely to occur *via* a deuterated ruthenacycle, such as **122**. The mechanism for the labeling of indoles such as **126** remains altogether unclear.

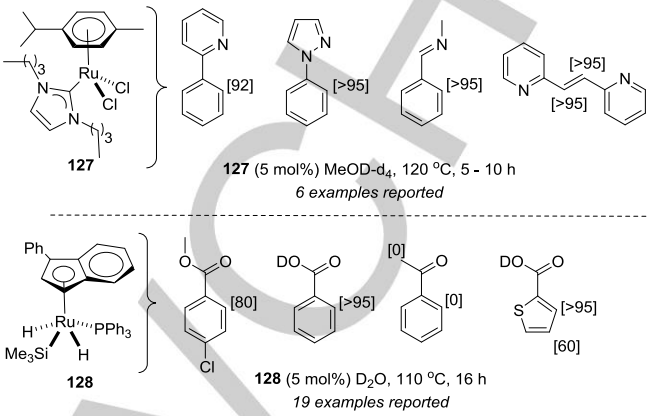


Scheme 37. Complementary labeling strategies for aliphatic alcohols.



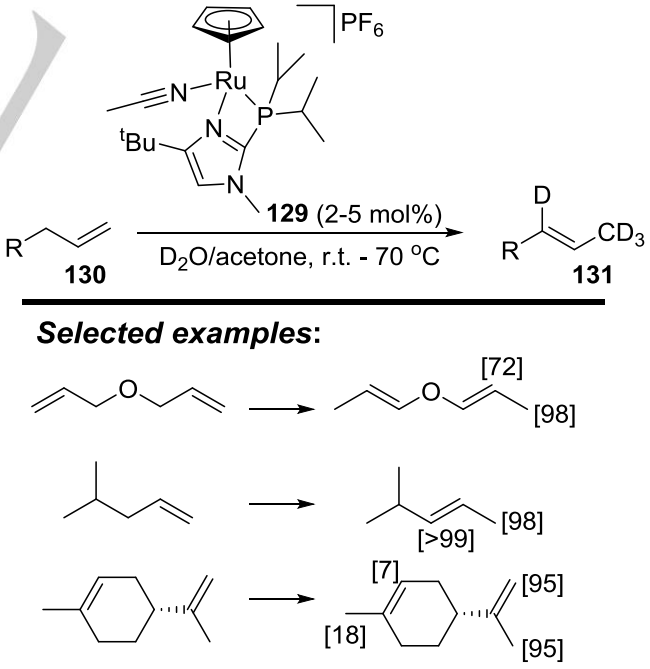
Scheme 38. Ru-catalyzed directed HIE with *N*-heterocycles.

Additional developments in *ortho*-directed HIE reactions using Ru catalysts have emerged in recent years. In the first of two key examples, Peris and co-workers showed that Ru(II) NHC complex, **127**, could efficiently catalyze the *ortho*-directed deuteration of various N-heterocycles in the presence of MeOD (Scheme 39, top).[127] Similarly, Nolan and co-workers recently divulged the directed deuteration of a significantly broader range of coordinating functionalities using the Ru(IV) phosphine complex **128** and D_2O as the key main isotope source (Scheme 39, bottom).[128]



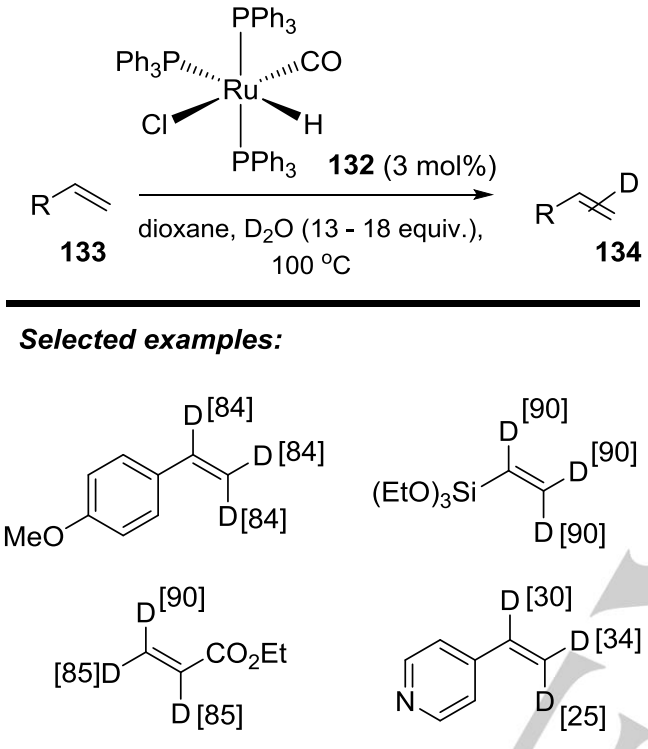
Scheme 39. Directed *o*-HIE with various Ru(II) catalysts.

Ru catalysis has also been applied to chemoselective HIE with alkenes. Grotjahn and co-workers applied bifunctional alkene zipper catalyst **129** to the isomerisation and deuterium labeling of various alkenes, producing selective vinyl and allyl labeling (**130**→**131**, Scheme 40).[129] This process requires only very mild conditions and was purported to proceed *via* a series of allyl anion intermediates.



Scheme 40. Chemoselective labeling of olefins *via* isomerization using a bifunctional Ru(II) precatalyst.

In a complementary study, Lin and Jia reported the Ru(II)-catalyzed labeling of vinyl functionalities of varying degrees of substitution using complex **132** (**133**→**134**; Scheme 41).[130] The report includes impressive examples of labeling of homoaryl derivatives, as well as vinyl silanes and acrylates, but is, otherwise, limited in the presence of the one pyridyl example described.

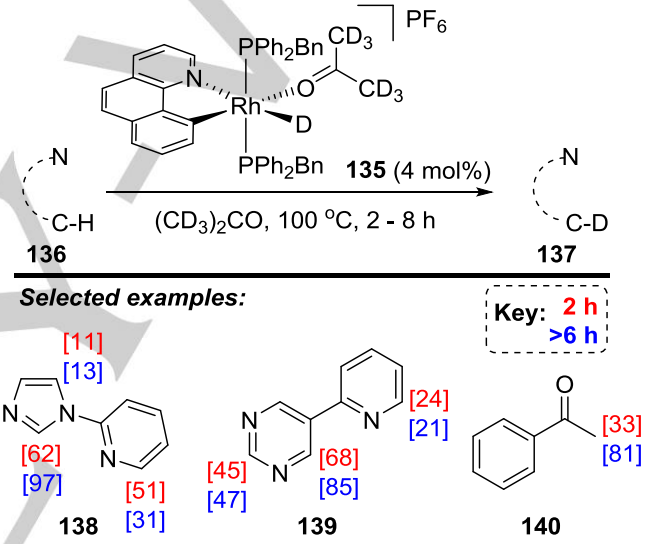


Scheme 41. Ru(II)-catalyzed deuterium labeling of vinyl groups.

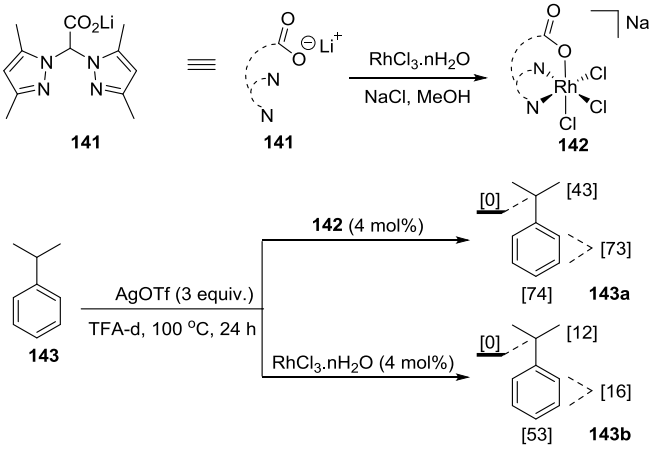
4.4 Rhodium

The rich history of homogeneous Rh-catalyzed hydrogen isotope exchange[131, 132, 133, 134, 135, 136, 137] has continued to evolve over the last decade. The principles of directed HIE originally developed by Lockley, Hesk, and Jones[132, 133, 134, 135, 136] have been applied by Li and co-workers using a bis-phosphine, chelation-assisted Rh(III) catalyst series, led by **135**, in the directed labeling of various *N*-heterocycles (**136**→**137**; Scheme 42).[138] The catalyst structure was optimized by simple screening of available phosphine ligands. In general, more electron-donating phosphines provided more active catalysts, with **135** being optimal. Excessively large phosphines were less active and thought to hinder necessary coordination of substrate to Rh. Intriguingly, only those labeling sites most easily accessed *via* a metal-coordinating atom were found to have significantly increased D-incorporation with longer reaction times (**138** and **139**). Some base-sensitive sites were subject to *decreased* D-incorporation. This demonstrated an element of thermodynamic selectivity rarely encountered in HIE catalysis. The alkaline nature (and ultimate limitation) of Li's catalysts was demonstrated in labeling acetophenone, **140**, where only the acid-sensitive alkyl sites were exchanged.

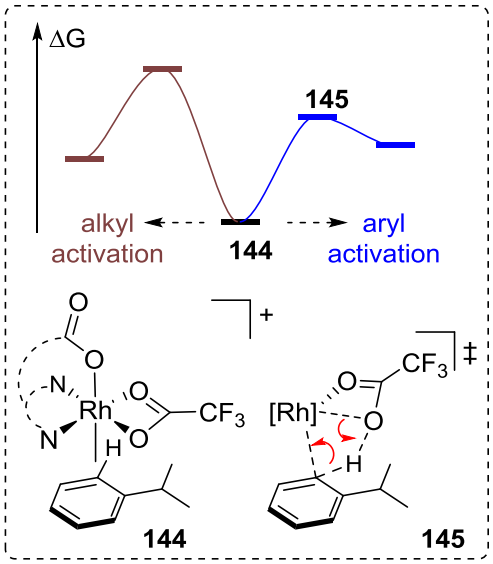
The $RhCl_3$ catalyst was used as a precursor to an active species with complementary reactivity to that previously divulged by Lockley.[132, 133, 134] More specifically, the bis(3,5-dimethylpyrazol-1-yl) acetate (bdmpza) ligand, **141**, delivered an anionic Rh(III)-centred pre-catalyst, **142**, that was able to deuterate both aryl and β-alkyl positions of substrates bearing no strong directing group (**143**→**143a**; Scheme 43).[139] Under identical conditions, the parent $RhCl_3.H_2O$ was more selective for aryl deuteration (**143**→**143b**). A combined experimental and DFT investigation into the operative reaction mechanism using**142** revealed that aryl labeling was kinetically favoured over alkyl labeling by 9.0 kcal/mol, *via* the shared catalyst resting state, **144**. Additionally, C–H bond breaking was postulated to occur *via* a trifluoroacetate-assisted and redox neutral, concerted metalation-deprotonation (CMD) transition state **145** (Scheme 44).[139]



Scheme 42. Directed HIE with *N*-heterocycles using basic chelation-assisted Rh(III) catalysts.

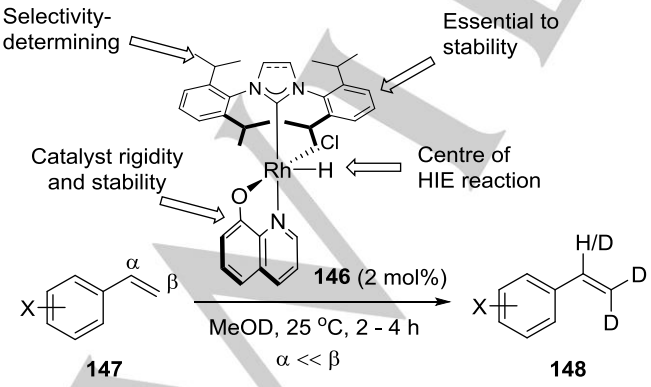


Scheme 43. Rh(III)-catalyzed HIE *via* CMD in the absence of directing groups.

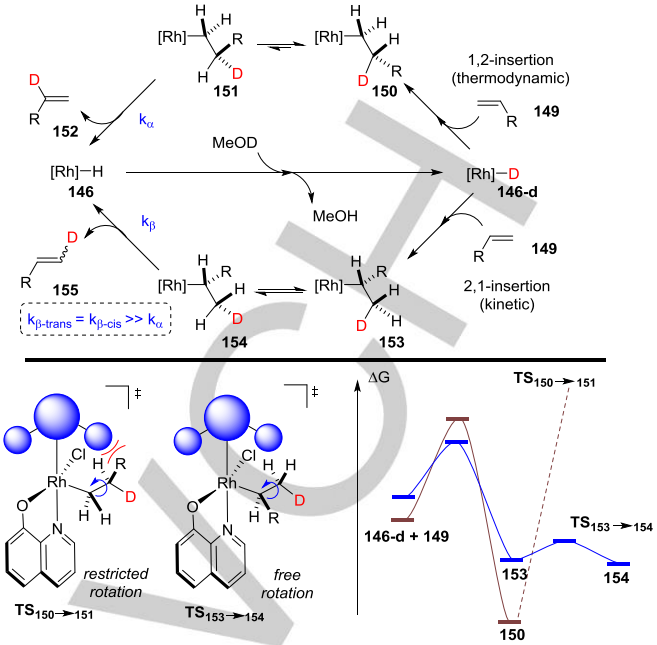


Scheme 44. Rationale for aryl over alkyl labeling emplying Rh catalyst **142**.

Complementary to the work of Grotjahn (*vide supra*), Castarlenas and Oro reported a beautifully detailed method for the β-selective deuteration of styrenes (**147**→**148**) using *N*-heterocyclic carbene (NHC) and 8-quinolinol-derived ligands within catalysts, such as **146** (Scheme 45).[140, 141] The reaction mechanism merits discussion, as detailed studies revealed the essential role played by all ligands bound to the Rh centre (Scheme 46).[141] From synthesised precatalyst, **146**, exchange with MeOD gives the active catalyst, **146-d**. Subsequently, the styrene, **149**, can undergo migratory insertion across the Rh–D bond in one of two directions. Thermodynamic 1,2-insertion gives **150**, but suffers from a high barrier to rotation towards **151**, ultimately retarding the formation of α-labeled product **152** *via* β-hydride elimination. Alternatively, kinetically-favoured 2,1-insertion of **149** across **146-d** gives intermediate **153** which, crucially, can freely rotate toward intermediate **154** to finally deliver the observed β-labeled product **155**. This analysis is further summarised by DFT-calculated energetics (Scheme 46, bottom).

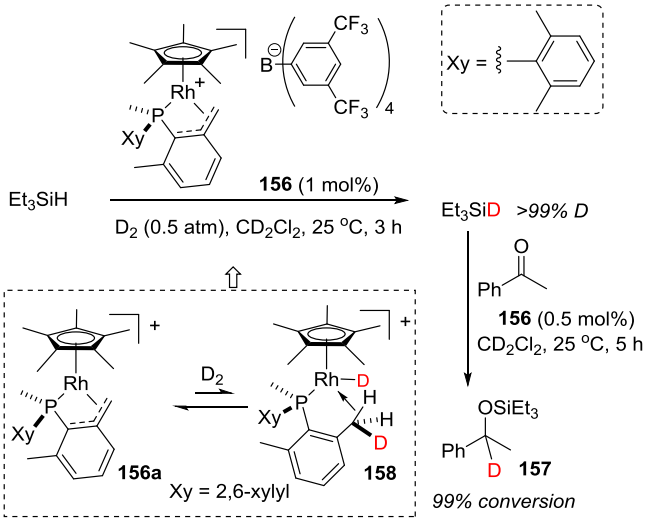


Scheme 45. Rh(III)-catalyzed β-selective deuteration of styrenes.



Scheme 46. Mechanistic analysis for Rh(III)-catalyzed β-selective deuteration of styrenes.

Labeling heteroatom X–H bonds can deliver valuable intermediates *en route* to labeling more complex organic molecules. Most notably, Carmona and co-workers have explored this concept for tandem silane deuteration/deuterosilylation protocols.[142, 143] Employing an unusual cyclometallated phosphine complex, **156**, silane labeling was achieved under extremely mild conditions for mono-, di-, and trisilanes using D_2 or T_2 as the isotope source (for example, see Et_3SiH→Et_3SiD, Scheme 47).



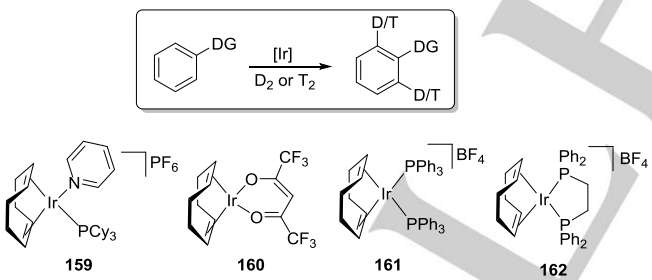
Scheme 47. Rh(III)-catalyzed deuteration of silanes and application in deuterosilylation.

In an impressive application of this work, the deuterated silanes were later employed with the same catalyst as starting materials in the large-scale production of α-deuterated silyl protected alcohols and amines (for example, **157**). With observable solution-phase ligand fluxionality in **156**, and its recovery unchanged after catalysis, D_2 (or T_2) gas was proposed to be activated by the ligand and metal together (**156a**→**158**). This example of metal-ligand cooperation to shuttle an isotopic label is complementary to that reported by Brookhart.[131]

4.5 Iridium

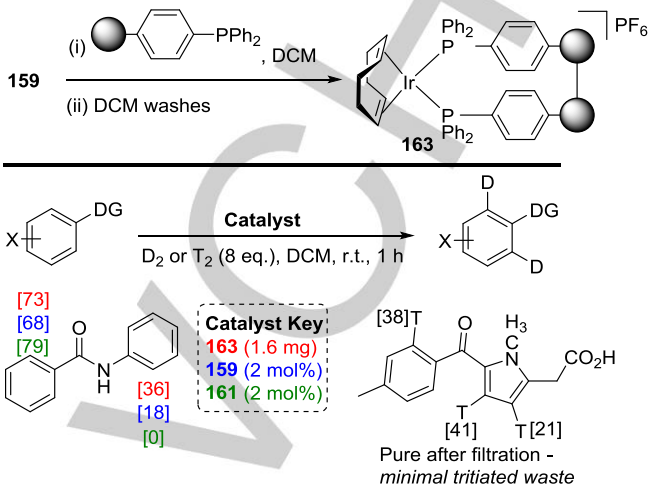
Among all transition metals employed in homogeneous HIE methods, iridium is arguably the most widely studied [86, 88, 90, 91, 144, 145, 146]. This is, in part, due to the vast and ever-expanding literature precedent in related hydrogenation reactions.[147, 148, 149] Despite interesting alternative Ir-catalyzed HIE methods (*vide infra*), such as for silanes,[150, 151] boranes,[152] alkenes,[153] and global aryl labeling,[139, 151, 154, 155, 156, 157] there is a clear dominance of *ortho*-directed HIE in the published literature.[7, 10a, 88, 90, 144, 146, 158] In this sub-field of Ir-catalyzed HIE, several catalysts (**159** – **162**) were used extensively in the period up to 2007, using D_2 or T_2 as the main isotope source (Scheme 48). Although these catalysts remain in use,[159, 160, 161] focus has been placed on improved systems that have emerged within the past decade.

Amongst these more recent studies, much emphasis has been placed in improving on the original design of Crabtree's catalyst, **159**, in labeling and alkene hydrogenation.[149] Despite its widely reported success, **159** is known to suffer from thermal deactivation *via* the formation of inactive, hydride-bridged, iridium clusters.[148] Similar effects have been documented for other iridium-based complexes.[162]

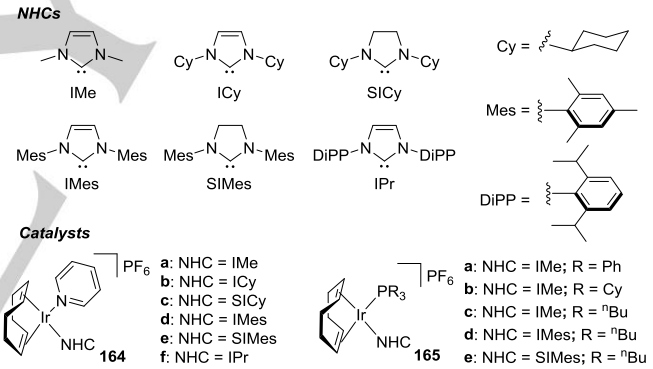


Scheme 48. Popularised Ir(I) *ortho*-HIE precatalysts in use between 1995 and 2007.

In a notably singular crossover between Crabtree's catalyst and bis-phosphine catalysts, Hickey and co-workers developed**163**, a polymer-supported variant of Heys' bis-phosphine catalyst, **161**, which showed comparable *ortho*-HIE activity to **159** and **161**, but with the practical benefit of simple catalyst filtration at the end of the reaction (Scheme 49).[146, 163] From 2001 – 06, separate investigations by Nolan[164] and Buriak[165, 166] towards improved thermal stability and predictable chemoselectivity of Crabtree-like *hydrogenation* catalysts resulted in a series of electron-rich, NHC-ligated complexes (Scheme 50). Such species were first applied in *ortho*-HIE processes by Powell and co-workers.[167] In their study, complexes **159** and **164a** – **164c** were employed under stoichiometric (classical 'tritiation-like') conditions, with the most active variant, **164c**, shown to be superior to Crabtree's catalyst (**159**) across the substrate range investigated.



Scheme 49. Polymer-supported Ir catalyst in *ortho*-HIE.

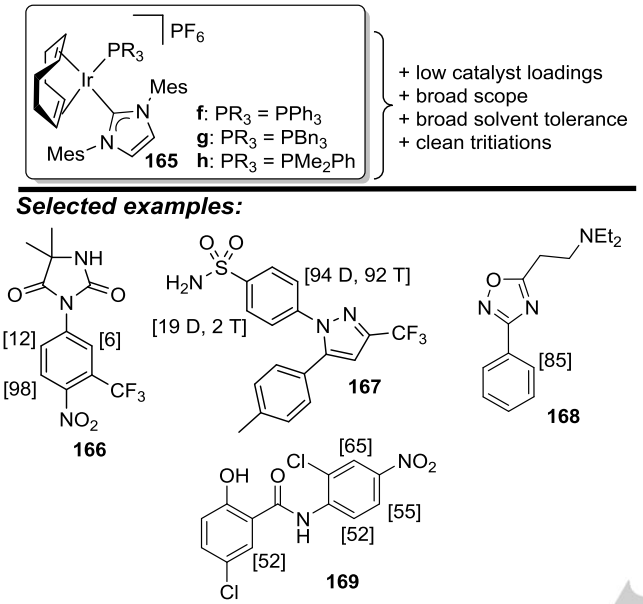


Scheme 50. The first NHC-ligated Ir hydrogenation catalysts explored in HIE.

In extension, Kerr and co-workers studied the *catalytic* activity of complexes **164b – 164f**, showing most active complex, **164e**, to be highly active over an appreciable substrate scope (5 mol% [Ir], 16 h, r.t.), and displaying a higher turnover frequency (TOF) than Heys' bis-phosphine catalyst, **161**.[168] Interestingly, the smaller complexes in the series studied by Kerr (**164b** and **164c**) were catalytically inactive in HIE (unlike the case reported above where these complexes were successfully employed in a stoichiometric fashion). Similar investigations by the same group later led to the discovery that small NHC/phosphine complexes such as **165a** were also inactive as HIE catalysts, but larger variants **165d** and **165e** were active across a limited substrate scope.[169]

The exploration of NHC-ligated Ir HIE catalysts had revealed promising (proof-of-concept) developments beyond the popular and established works of Hesk and Heys. Accordingly, Kerr and co-workers developed a synthesis of previously unattainable complexes **165f** – **165h**, bearing large phosphine *and* NHC

ligands in the same ligand sphere (Scheme 51, top).[169, 170] These complexes have proven seminal within the *ortho*-HIE domain, and have among the highest activity,[144, 170] substrate/solvent scope,[159, 169, 170, 171, 172, 173, 174] and tritiation reaction cleanliness[88, 175] of any such catalyst reported to date (see drug examples **166** -**169**, Scheme 51, bottom).

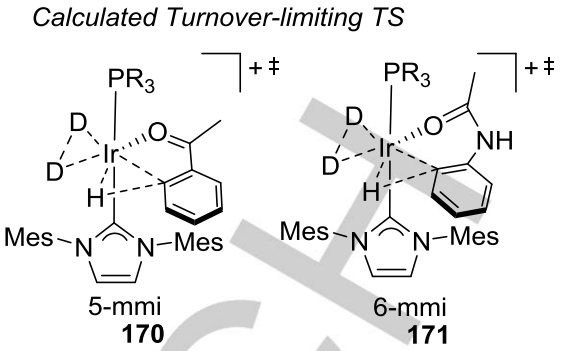


Scheme 51. Highly-active NHC/phosphine Ir *ortho*-HIE catalysts.

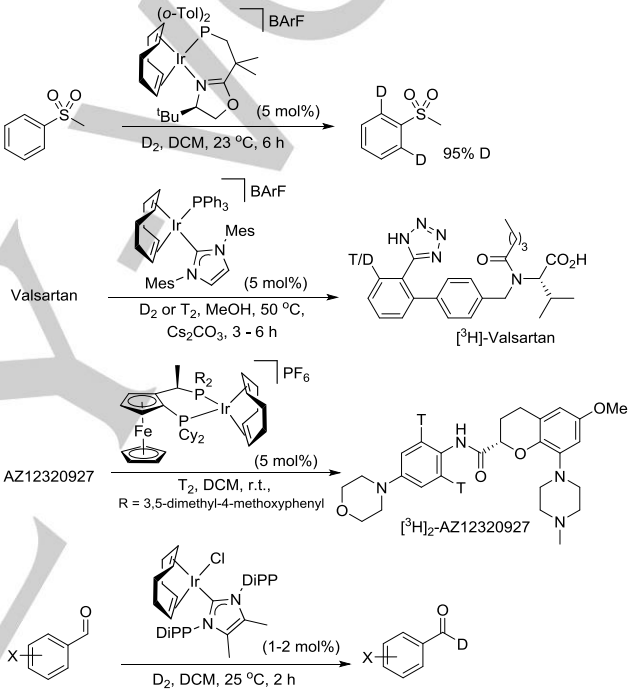
Additionally, *ortho*-HIE processes with these complexes have been studied experimentally and computationally,[170, 176] strengthening the case for an Ir(III)-based reaction mechanism, akin to that proposed by Heys.[91, 146, 177, 178] More specifically, kinetic isotope effect (KIE) measurements[170, 176] revealed that C–H bond cleavage was turnover-limiting in the reaction, and detailed NMR studies revealed the *trans*-geometry of the ancillary ligands.[170] The same study was also able to reveal the origins of the selective reactivity of such catalysts for 5- over 6-mmi substrates, citing dual kinetic and thermodynamic favourability for the 5-mmi (**170** *versus* **171**, Scheme 52).

Ir(III)-catalyzed *ortho*-HIE has continued to flourish, with recent contributions from Salter,[146] Muri,[179] Kerr,[176, 180, 181, 182] Derdau and Atzrodt,[183,184] Tamm,[184] and others,[172] leading to improved applicability of a broader scope of drug-related molecules and *ortho*-directing functionalities (Scheme 53).

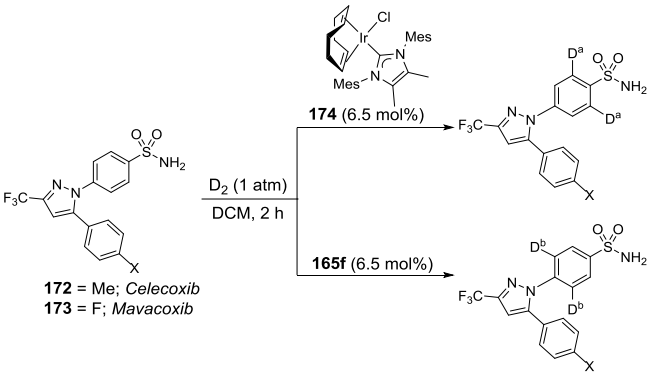
Among recent advances, whilst developing a rare method for labeling primary sulfonamides, Kerr and coworkers considered directing group chemoselectivity in detail.[176] It was observed that the sulfonamide *versus* pyrazole selectivity in *Celecoxib* (**172**) and *Mavacoxib* (**173**) varied dramatically with catalyst choice (Scheme 54). Whereas encumbered NHC/phosphine catalysts, such as **165f**, facilitated labeling adjacent to the pyrazole moiety, NHC/Cl catalysts, such as **174**, facilitated selective sulfonamide labeling for the first time. Accompanying DFT studies revealed that the substrate binding event was likely to be product-determining, even though C–H activation remained rate-limiting (for example, see **175a** *versus* **175b,** Scheme 55).[176] Similar computational evidence was derived for



Scheme 52. Calculated σ-CAM C–H activation step in Ir-catalyzed *o*-HIE.



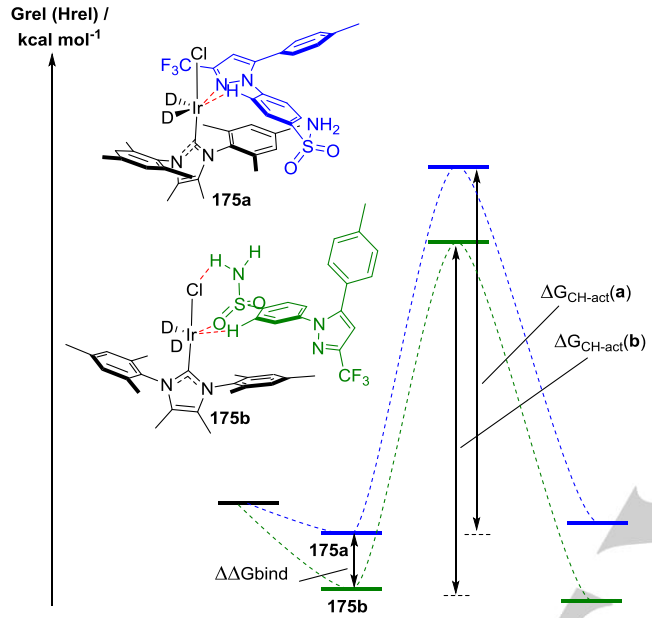
Scheme 53. Ir-catalyzed *o*-HIE with challenging substrates.



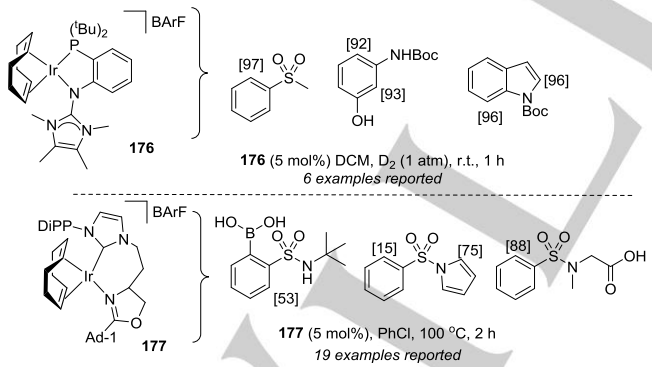
Scheme 54. Catalyst-controlled site-selective labeling of sulfonamide drugs.

the formyl-selective labeling of aldehydes (Scheme 53, last example), where a smaller catalyst ligand sphere promoted formyl agostic C–H binding over the carbonyl oxygen.[185]

Further in recent interesting developments, Derdau and Tamm divulged a series of P,N-bidentate ligated Ir(I) precatalysts, such as **176** and **177**, able to *ortho*-deuterate previously troublesome substrate classes such as *N*-Boc-protected amines, sulfones, and encumbered sulfonamides (Scheme 56).[183, 184]



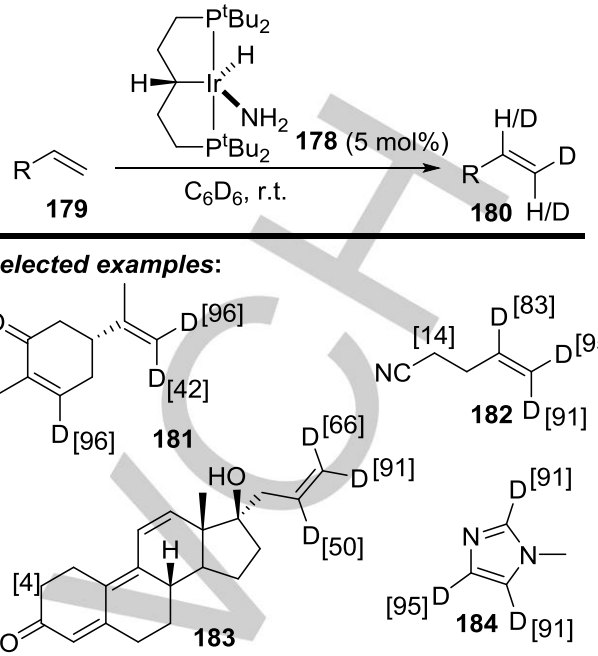
Scheme 55. DFT-calculated rationale for directing group selectivity using catalyst **165f** and sufonamide drug **172**.



Scheme 56. New Ir(I) precatalysts bearing bidentate ligands.

Labeling organic molecules *via* homogeneous Ir-catalysis has also advanced beyond *ortho*- and formyl-selective HIE. Several non-directed C–H deuteration strategies similar to those described for other metals (*vide supra*) have been reported,[103, 139, 154, 155, 156, 157, 186] but are not discussed here in detail.

Chemoselective labeling of alkenes has also been explored using iridium. In 2008, Hartwig reported a method complementary to those of Grotjahn, and Castarlenas and Oro



Scheme 57. Ir-catalyzed deuteration of alkenes.

(*vide infra*), where pincer complex **178** was able to label vinyl C–H positions with selectivity largely dependent on the specific steric environment of the substrate, albeit under air and moisture sensitive conditions (**179**→**180**, Scheme 57).[153] Notably, this method was applied to a series of both simple and complex organic molecules (see **181** – **184**, Scheme 57). This method could be applied to global labeling of aromatic and heteroaromatic substrates.

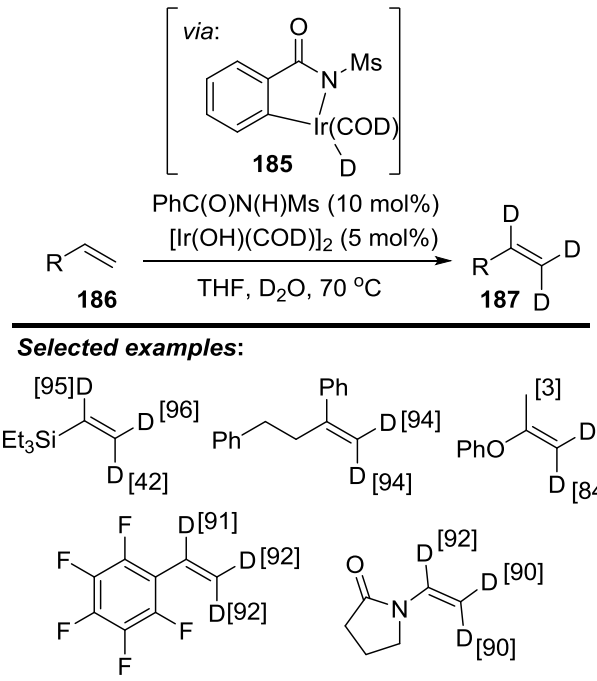
A more practical variant of this method was divulged by Nishimura and co-workers.[187] Using an *in situ* derived Ir(III) monohydride, **185**, and D_2O as the isotope source, an attractive range of mono-substituted alkenes could selectively deuterated at the vinyl or methylidene positions (**186**→**187**; Scheme 58).

Some of the most recent developments in isotopic labeling employing Ir catalysis have been applied to X–H moieties. Specifically, Nolan and Grubbs have independently reported on silane labeling.[150, 151] Grubbs studied catalyst **188**, while Nolan investigated **189a** and **189b** in Si–H and B–H labeling, respectively (Scheme 59).[152]

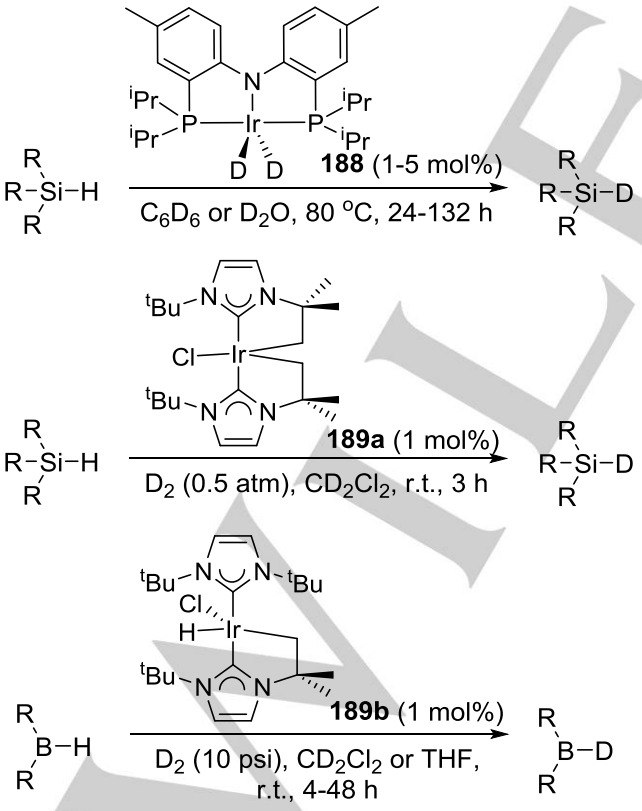
4.6 Latest Developments

As shown for *ortho*-HIE, selective functionalization within evermore complex molecules remains a worthy challenge in the broader realm of C–H activation. Furthermore, selective methods complementary to those already available are highly prized. A fine example of these goals was recently demonstrated by Chirik, Hesk, and co-workers,[188] who reported the Fe-catalyzed tritiation of pharmaceutical substrates under mild (albeit air/moisture-sensitive) conditions (**190**→**193**, *cf.* Ir-catalyzed **190**→**192**; Scheme 60). In addition to employment of a sustainable base metal, Chirik's method showed direct complementarity to *ortho*-HIE methods employing iridium, and

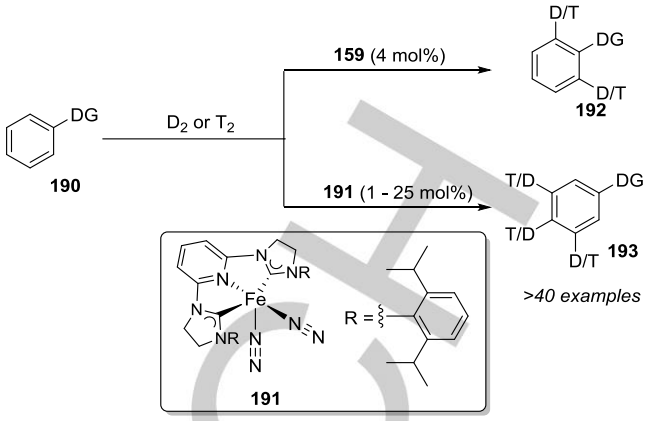
has been applied across a noteable range of drug-like substrates (Schemes 60 and 61).



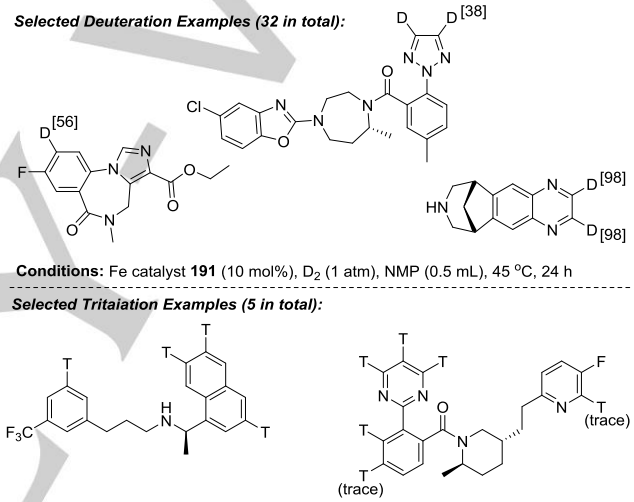
Scheme 58. Ir-catalyzed deuteration of alkenes with an *in situ* derived catalyst.



Scheme 59. Heteroatom labeling employing homogeneous Ir catalysts.



Scheme 60. Fe-catalyzed sterically-controlled HIE complementary to *ortho*-HIE.



Scheme 61. Examples of deuterium and tritium labeling from Chirik and Hesk.

4.7 Conclusions

Homogeneous metal-catalyzed HIE dominates current efforts to achieve labeling in complex molecules by late-stage C–H functionalization. Indeed, a broad range of directing groups and functionalities are now amenable to these selective labeling methods, and often by more than one class of catalyst or metal. Associated with this, the most attractive methods remain those where conditions are mild and most practicable, and where catalysts are readily handled within routine preparative reaction protocols. Accordingly, as researchers strive to establish more advanced methods, air and moisture stable techniques for broad adoption should be the target of future developments in the field. For directed labeling techniques, broadening the drug-like functionalities that can be used as directing groups should remain an additional and prominent focus.

5. Conclusions & Outlook

Owing to the broad significance of hydrogen isotopes, both historically and in modern chemical, biological, and ecological sciences, HIE method development remains highly relevant and vibrant. Associated with this, as a low-cost, easily handled radioisotope, tritium is spearheading modern radiochemistry and pharmacokinetic studies, adding further to the importance of HIE method development.

The wide range of applications involving hydrogen isotopes makes their installation an important and continuing challenge to synthetic chemists. Despite the apparent simplicity of the transformation, hydrogen isotope exchange requires a continually evolving preparative toolbox in order to satisfy the escalating regio-, chemo-, and stereoselectivity demands set by practicing isotope chemists. Indeed, we have deliberately avoided any ranking of the synthetic methods described herein, since it is the increasing breadth of methods that is, and will remain, most important in tackling the incalculable variation in the necessary HIE approaches required within different drug design projects, as part of selective labeling of substrates for mechanistic studies, and beyond. It is envisaged that these requirements will continue to drive developments in homogeneous, heterogeneous, and acid/base-catalysis in order to expand on the existing methods available for isotope incorporation. The widespread use of embedded deuterium and tritium units makes efforts towards the further development of these fundamental synthetic transformations increasingly valued. Moreover, and of even more widespread resonance for preparative chemistry, the evolving synthetic developments in late-stage hydrogen isotope exchange provides increasing data resources with which to understand the fundamental nature of various C–H functionalization methodologies. For selective labeling protocols, a key synthetic challenge for future developments will be to further consider directing group chemoselectivity and innate regioselectivity in increasingly complex drug-like architectures. Additionally, further escalation of catalyst activity and selectivity is required in order to expand beyond the established array of sp^2 functionalization methods towards the challenging goal of more widely successful sp^3 labeling.

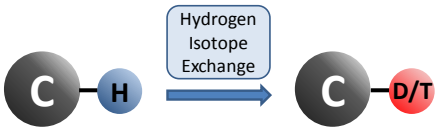
We hope that this review will provide a strong starting point for understanding the demands and applications within synthetic and biochemical processes across a wide range of disciplinary areas, and that the content will prove useful to chemists, biologists, and analytical scientists alike.

Acknowledgements

We are grateful to the Leverhulme Trust for the provision of an Early Career Fellowship (MR) and to GlaxoSmithKline (GSK) for further financial support.

Keywords: C–H functionalization • hydrogen isotope exchange • catalysis • drug discovery

REVIEW



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C–H Functionalization for Hydrogen Isotope Exchange

Hydrogen Isotope Exchange (HIE), the most fundamental of all C–H functionalization processes, is a key tool for installation of C-D and C-T bonds. In this review, an array of recent advances in synthetic C-H functionalization for hydrogen isotope exchange is described.

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