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Mechanistic considerations on catalytic H/D exchange mediated by organometallic transition metal complexes

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ABSTRACT

The purpose of this review is to analyze the different reaction mechanisms of the H/D exchange on organic substrates catalyzed by transition metal complexes in homogeneous phase. The metal-catalyzed H/D exchange is a multifaceted reaction whose mechanism depends strongly on the reaction conditions and on the metal complex used as a catalyst. It is possible to group the different mechanisms into three main families depending on the "role" and behavior of the catalyst: (i) Lewis acid–base catalysis; (ii) C–H activation (iii) insertion/β-elimination. For each macro-group, several representative examples are discussed and critically evaluated in order to provide the reader with keys to the understanding of how the different catalytic systems act and how their modification may affect their performance in terms of activity and selectivity. This knowledge is fundamental for designing improved organometallic H/D catalysts for labeling organic products in greener conditions with more cost-effective processes.

1. Introduction

The selective isotopic labeling of organic molecules represents one of the major challenges in many areas of current scientific research and it requires a stimulating interaction between different areas of chemistry. In particular deuterium, one of the isotopes of hydrogen is quite abundant and easy to access and it possesses very distinct physical characteristics if compared to hydrogen. Such characteristics can be exploited for different purposes. In particular deuterium-labeled compounds are widely used as powerful tools in fundamental research as for example in the determination of mechanisms and kinetics of chemical reactions, the monitoring of drug metabolism or the structural analysis of biomacromolecules. However, deuterium-labeled compounds are also used for more practical purposes as the quantification of environmental pollutants and residual pesticides, as internal standard in mass spectrometry, as markers in diesel oil, for the synthesis of heavy drugs or for the production of innovative polymers [1].

The study of the H/D exchange reaction is indirectly useful for the development of methods to label organic compounds with tritium (T). In fact, deuterium and tritium have the same chemical characteristics, therefore it is possible to optimize the labeling of organic molecules using deuterium sources (e.g., D_2, D_2O), which are safe and

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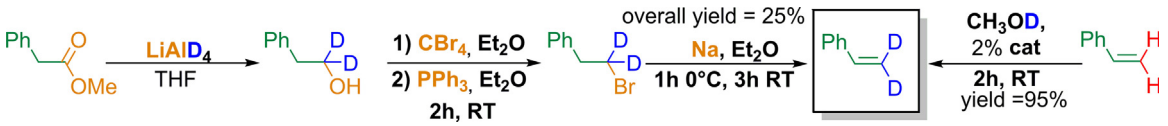


Scheme 1. (Color online.) H/D exchange reaction vs. classical synthesis (**cat** = [RhClH(κ^2O,N-C_9H_6NO)(IPr)] see [4]).

cheap, and to apply these methods to the T/H exchange using the same tritiated sources (e.g., T_2, T_2O). The H/T exchange reaction plays an important role in the pharmaceutical industries where it is carried out routinely to produce radio-labeled bioactive compounds that are extremely useful for monitoring drug metabolism [2]. In this review, we discuss only about the reaction mechanism of H/D exchange, which is extensively studied, but since D and T have the same electronic characteristics, these mechanistic considerations can be extended to the H/T exchange reaction.

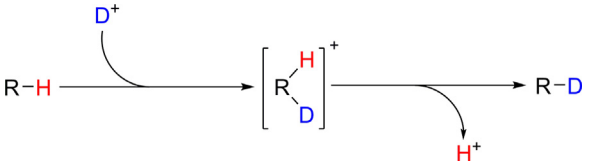
The incorporation of deuterium into an organic molecule can be achieved by two principal ways, the classical multistep synthesis [1i,3] or by a direct H/D exchange reaction. This last reaction involves an exchange of a hydrogen atom bonded to carbon by its heavier isotope without any structural modification. The H/D exchange reaction is normally more efficient and cost-effective with respect to the classical multistep synthesis. In Scheme 1, the synthesis of the β,β-dideuterostyrene by classical synthesis (left to right) and by catalyzed H/D exchange (right to left) is reported as an example [1i,4].

In general, H/D exchange reactions could require harsh conditions since the substrate is deuterated directly from the deuterated solvent [5]. But, in most cases, the H/D exchange of the substrate is not achieved, even under extreme conditions. For this reason, a series of catalytic systems able to catalyze this reaction have been developed. There are four main type of catalysts used in this type of reaction: acid catalysts, base catalysts or those based on homogeneous/heterogeneous metal catalysts.

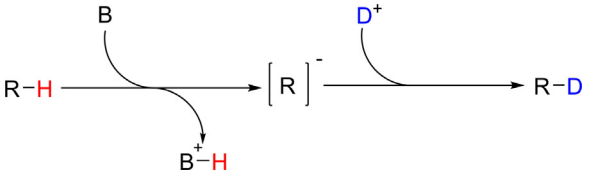
Acid-mediated H/D exchange is initiated by the acid addition of a deuterium resource to the substrates (Scheme 2). Typically, this reaction finds application with aromatic or hetero-aromatic substrates, even though other electron-rich substrates (e.g., alkenes) have been employed successfully. A prototypic reaction is the acid-catalyzed deuterium exchange of benzene, introduced as a valuable synthetic method several decades ago [6].

Another option is the use of a base as promoter for H/D exchange transformations. In contrast to acidic conditions, the use of a base represents a general viable option for the H/D exchange of sufficiently acidic protons. A general description is reported in Scheme 3. The substrates that can be deuterated by this method typically contain relatively acidic protons, as for example the terminal alkynes, or, alternatively, it may bear an electron-withdrawing group that can stabilize the formation of deprotonated species, such as in the case of carbonyl compounds [7].

The H/D exchange reaction catalyzed by acids or bases is only applicable in a few special cases in which the substrate can be protonated or deprotonated, without any decomposition due to the harsh reaction conditions. To solve these problems, other kinds of catalytic systems have



Scheme 2. (Color online.) H/D exchange under acidic conditions.

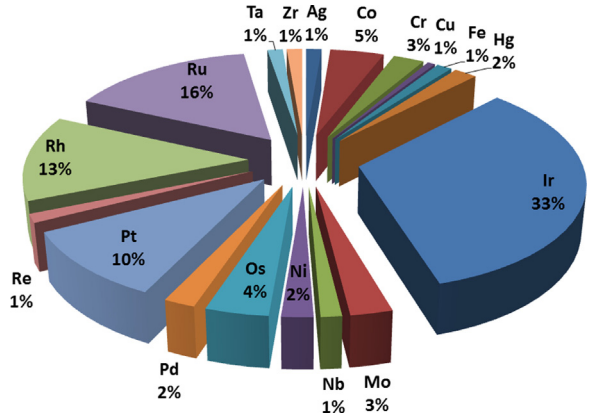


Scheme 3. (Color online.) General scheme of H/D exchange in basic conditions.

been developed, in particular homogeneous and heterogeneous catalytic systems based on transition metals [8]. These systems usually offer three main advantages with respect to the other methodologies described before:

- *mild reaction conditions* that prevent the decomposition of the substrate and decrease the cost of the deuteration process;
- *broad scope*, in fact a wide range of substrates can be treated by tuning the composition of the catalytic system (type of metal or ligands) and the deuterium source (D_2O, D_2 or organic deuterated solvent) in order to allow the highest compatibility with the reaction conditions and with high tolerance toward the principal functional groups involved;
- *regio- and stereo-selectivity*, using a catalytic system properly modified is possible to deuterate a substrate only in a specific position.

The homogeneous catalysts present the advantage of a more accurate tunability with respect to the heterogeneous ones [9]. The modification of stereo-electronic properties of the metal allows for an increase in the catalytic activity and selectivity. Moreover, such systems are easy to monitor by experimental and theoretical techniques that can help to elucidate the catalytic mechanism. Such information is of fundamental importance to precisely modify the catalytic system in order to solve specific synthetic problems. Several reviews have been published dealing with catalytic H/D exchange reactions of organic substrates [2a,e,8e,10]. Taking into account the importance of the issue, in this account we will review and analyze the different mechanistic pathways by which transition metal-based catalysts act in homogeneous phase.



Scheme 4. (Color online.) H/D exchange catalyst for organic substrates classified by metal (data based on the references of this review).

2. Organometallic catalysts for the H/D exchange reaction

The first studies in this field date back to 1967–1969 and were carried out by the research groups of Garnett [11] and Shilov [12]. After these pioneering studies, a plethora of transition metal-based homogeneous catalytic systems for H/D exchange have been developed for different X–H moieties (X=O, N, Si, B) and varied aliphatic, aromatic, vinylic and acetylenic C–H substrates (Scheme 4). Due to space restrictions, only C–H deuteration has been analyzed and the authors redirect the reader to the literature for other X–H/D exchanges [13].

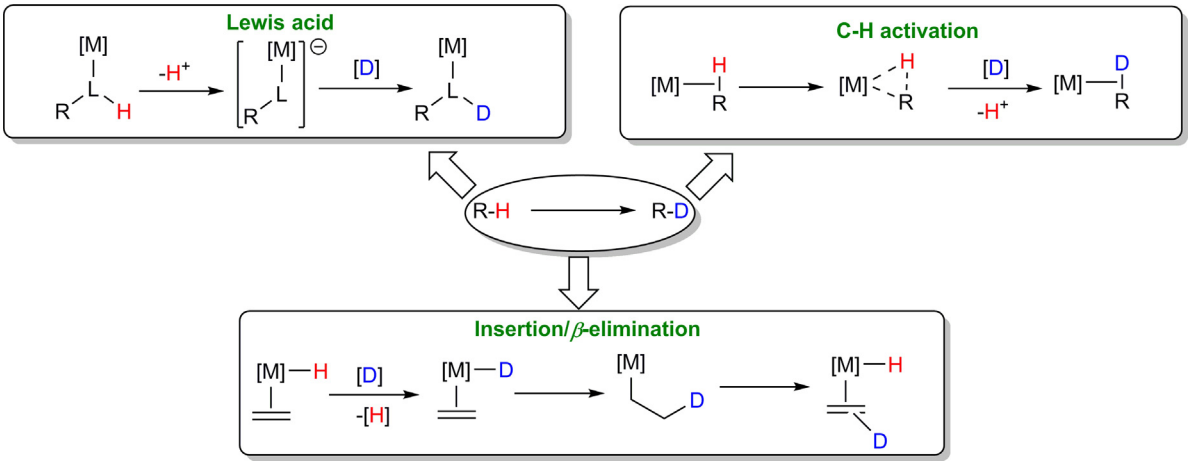
The H/D exchange reaction, mediated by organometallic catalysts, is a multifaceted reaction with regard to its mechanistic pathways. Each catalytic system, represented by an organometallic complex using an appropriate deuterium source, proceeds with a different way of reaction, but we can regroup all these systems in macrogroups on the basis of their mechanism: (1) Lewis acid–base catalysis; (2) C–H activation; (3) insertion/β-elimination (Scheme 5). In this account, we will especially focus on the aspects of the structure of the catalyst intimate related to its catalytic properties.

3. Lewis acid catalysts

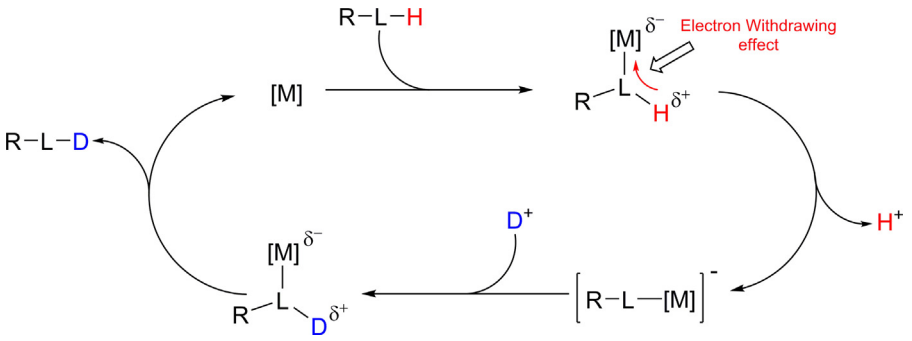
The organometallic complexes used as catalysts in the H/D exchange reaction of organic compounds can follow a Lewis acid-type mechanism as showed in Scheme 6. In the first step of this mechanism, the substrate binds to an appropriate site of coordination of the metal center. Within this complex, the metal acts as a Lewis acid that withdraws electron density from the L group, which in turn acidifies the hydrogen attached to it. This effect enables the exchange of this "activated" H with the deuterium from the solvent through the metal-stabilized anion intermediates.

The catalyst that proceeds via this mechanism must contain a powerful electron-withdrawing metal. Typical organometallic active species in this reaction include: Hg^{2+}, Ag^{+}, Co^{3+}, Cr^{3+}, Pt^{2+} [14]. Nitrogenated compounds such as azoles or purines are clear examples of substrates that function through this mechanism [14f,p]. Among these compounds, one of the most studied is 2-methylimidazole. Buncel et al. showed that various metals are able to bind this substrate activating the hydrogen on the C(2) position to the exchange with a D atom of the solvent (D_2O) by a simple acid–base exchange (Scheme 7) [14j,m,p,q].

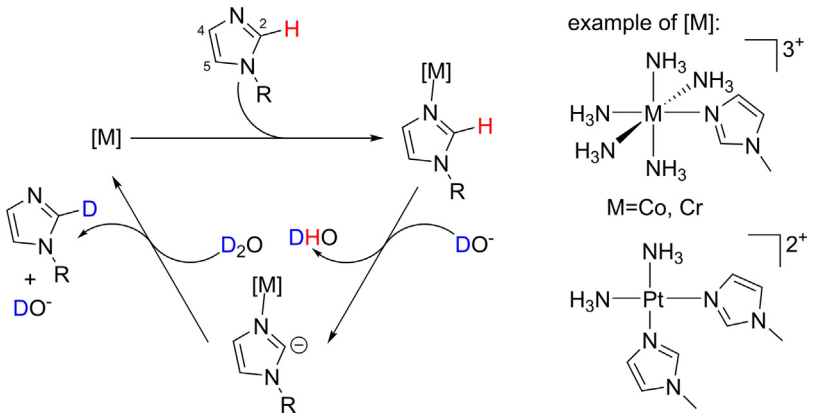
Metal complexes have been found to increase the rate of C2–H exchange by ca. 10^3–10^6 orders of magnitude with respect to the exchange in neutral heterocyclic species, the so-called metal activation factor (maf) [14f]. In particular, the order of metal ion catalytic effectiveness is Cr(III) > Co(III) > Pt(II). This is probably due to the different electronic properties of the three different metals, which produces a different effect on the ligand. In particular, Cr(III) presents predominantly a simple σ-withdrawing electrostatic effect, while other metals such as Co(III) and Pt(II) act through a combination of σ + π covalent interaction. In this latter case, it is possible to think that the back donation of these two metals probably increases the electron density in the imidazole ring, decreasing the acidity and therefore the rate of H/D exchange. Two key factors determine the selectivity of the H/D exchange in a specific position, the efficiency of the transmission of the electrostatic effect from the metal and the relative stability



Scheme 5. (Color online.) General reaction mechanism for the metal-catalyzed H/D exchange of organic substrates.



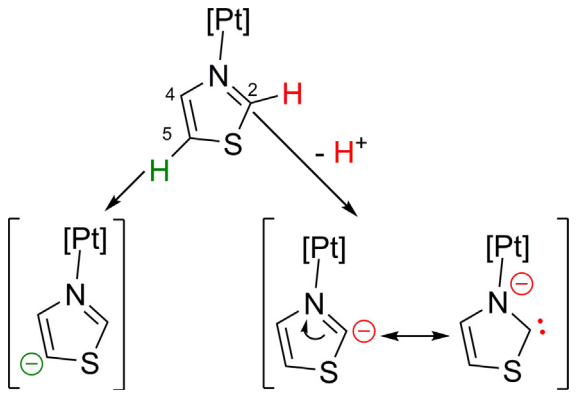
Scheme 6. (Color online.) General scheme of H/D exchange catalyzed by Lewis acid transition metal complexes.



Scheme 7. (Color online.) H/D exchange of 2-substitued imidazole catalyzed by Lewis acid transition metal complexes.

of the formed carbanion. The faster H/D exchange of C(2)–H versus C(5)–H of thiazole mediated by Pt(II) complexes is a clear example [14k]. The close proximity of C(2)–H to the metal increases the σ-withdrawal effect on it. In addition, the anion resulting from the deprotonation of C(2)–H is stabilized by a resonance carbene intermediate, absent in the case of the deprotonation of C(5)–H (Scheme 8).

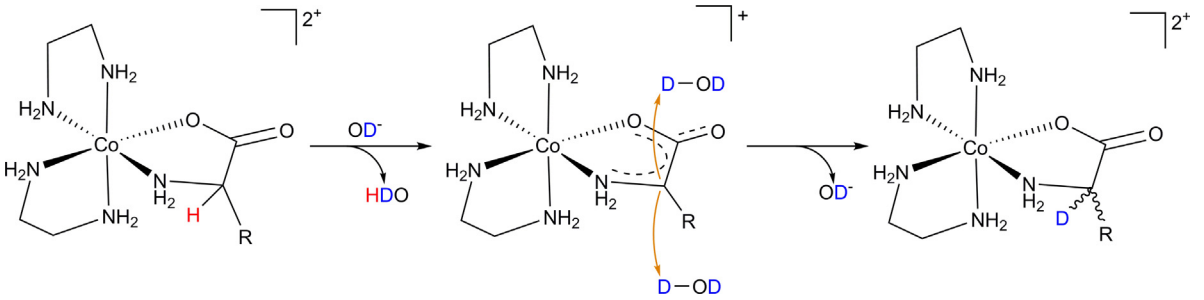
The stabilization of the carboanion resulting from the deprotonation of the substrate is also a key factor in the H/D exchange of the α-hydrogen of amino acids mediated by Co(III) complexes. Buckingham et al. have elegantly demonstrated with kinetic data that this reaction occurs



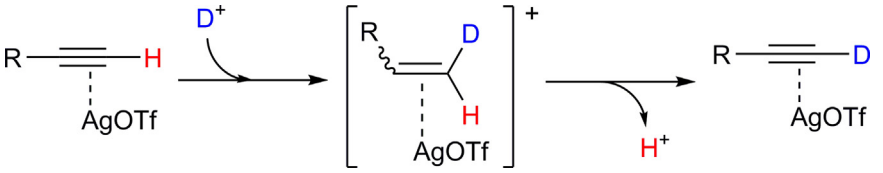
Scheme 8. (Color online.) Resonance stabilization of the intermediated formed upon abstraction of C(2)–H or C(5)–H.

via a stepwise S_E1 mechanism type, in which the α-hydrogen is abstracted by a base and then the substrate is re-protonated by the deuterated solvent (Scheme 9) [14a,i]. In this system, the Co complex acts by acidifying the α-proton and especially stabilizing the resulting anion by helping the delocalization of the charge onto the electronegative atoms of the molecule. The formation of the proposed planar intermediate species (structure in the center of Scheme 9) is also in accordance with the concomitant reaction of epimerization.

Molecules containing coordinating heteroatoms are not the only possible substrates of the Lewis acid–base catalyst for H/D exchange. Thus, unsaturated hydrocarbons can bind to the metal center that acidifies the substrate in specific positions suitable for H/D exchange. An example of this type of catalysts can be found in the work of Lewandos, in which the reaction of H/D exchange of terminal alkynes mediated by complexes of Ag(I) was studied [14g]. In this work, the authors show that AgOTf is able to catalyze the H/D exchange of the terminal alkynes in CD_3NO_2 using acetic acid-d_8 as deuterium source. In this case, the D incorporation is reported to be 10^5 times faster compared to the uncatalyzed reaction. The authors exclude the possible formation of silver-acetylide intermediates, which are formed more slowly (days) than the deuterium exchange process (minute). The formation of a π-adduct between the alkyne and the metal is proposed and then a direct electrophilic attack of D^+ take place (Scheme 10).



Scheme 9. α-Deuterium labeling of amino acid-mediated by the (ethylenediamine)Co(III) complex.



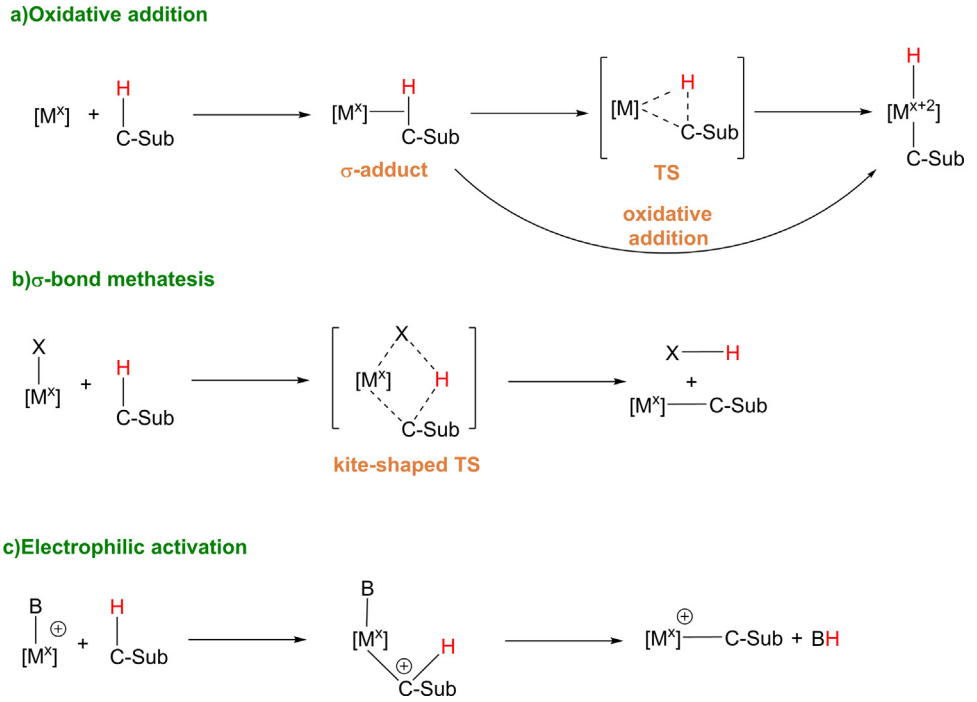
Scheme 10. Possible intermediates in the H/D exchange of terminal alkynes substrate with acetic acid-d_8 mediated by Ag^+.

4. C–H activation based catalysts

The direct C–H bond functionalization of organic substrates mediated by transition metal catalysts is one of the best tools nowadays available for the synthesis of products with high added value. These types of catalysts provide the huge advantage of working directly on the substrates without any prior step of modification. It allows a very high atom economy and improves the "greenness" of the global catalytic process. For these reasons, the direct C–H bond functionalization has gained enormous attention from the scientific community, leading it to be also called the "holy grail of catalysis" [15]. It is one of the hot topics in chemistry and for this reason, we assisted to the development of many catalytic systems based on organometallic complexes that act according to this mechanism [16].

The H/D exchange reaction is one of the most studied reactions in the field of C–H activation, since it represents a powerful method for evaluating the potential of a catalyst for the cleavage and formation of a C–H bond [1f]. Since the pioneering work of Garnett in the 1967, a large number of catalytic systems based on the C–H activation have been developed and deeply studied from the point of view of their mechanistic aspects. Substrate, solvent, additives, and the transition metal and ligand in the active ML_n species significantly influence the catalytic outcome. For this reason, in some cases the mechanism of reaction is not clearly understood and the interpretation of the different experimental and theoretical data often can lead to different conclusions. Since the purpose of this review is to provide an overview of the different mechanisms by which organometallic catalysts proceed in H/D exchange, and given the huge number of articles and the complexity of this subject, here we will concentrate on some of the most significant examples of important catalytic systems based on the C–H activation, and call upon the reader to the many reviews available on the specific topic [16a–g,i,k,l].

The principal mechanisms by which the organometallic complexes activate the C–H bond of the substrates are three: oxidative addition, σ-bond metathesis and electrophilic activation. Oxidative addition is the most common mechanism for C–H activation mediated by late transition metal as Re, Fe, Ru, Os, Rh, Ir or Pt. The first step of this mechanism consists in the metal [M^x] interaction with the C–H bond of a substrate leading to a σ-adduct. This adduct evolves towards the cleavage of the C–H bond and the formation of a new organometallic compound of the type H-[M^{x+2}]–C, which involves the formal transfer of two electrons to the H and C atoms from the metal (which therefore is oxidized), with the concomitant change in its coordination geometry to accommodate the two new ligands (Scheme 11a). The C–H activation could be achieved through another type of mechanism known as the σ–bond metathesis [17]. Catalytic systems that act by this mechanism are typically hydride or an alkyl (X) complexes of early transition metal with d^0 configuration from group 3, 4 and 5, but late metal complexes bearing a ligand able to extract a H from the substrate are also operative. These compounds react via a one-step transformation through a kite-shaped transition state in which simultaneous C–H cleavage and X–H and M–C bond formation occur (Scheme 11b). Differently from the previous mechanism, the formation of the σ-adduct is not critical, and in particular no change of oxidation state or coordination geometry are observed on the metal center. The last mechanism is the electrophilic activation in which formally an electron-rich carbon atom is attacked by the electrophilic metal species and a base extract a proton (Scheme 11c). The product of this reaction is the result of the formal substitution of a H^+ with the electrophilic $[M]^+$; for this reason this mechanism is also known as electrophilic substitution. This type of mechanism is very common for catalytic system based on late- and post-transition metals, generally in strong polar medium as water or strong acid. When the base is a ligand of the complex, the electrophilic attack and the H^+



Scheme 11. (Color online.) Transition metal-mediated C–H bond activation: (a) oxidative addition (b) σ-bond metathesis (c) electrophilic activation.

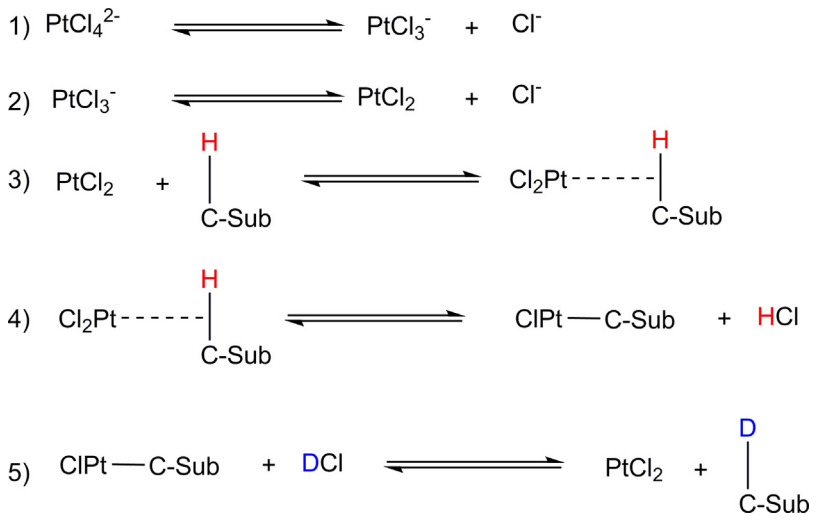
extraction is often a concerted reaction with a transition state formally equivalent to σ-bond metathesis, for this reason in some case there is a divergent of opinion, among the different authors, in the interpretation of this step of C–H activation.

The C–H activation of the substrate is the fundamental step by which the catalysts of this category work, but in order to achieve the final goal of this reaction, the exchange of H by D atom in the substrate, several other steps must take place. These other steps change considerably depending on the type of substrate (aliphatic, vinylic, aromatic or heteroatom-containing substrates as alcohols, esters, etc.), deuterium sources (D_2, D_2O or deuterated organic solvents as C_6D_6, CD_3OD, etc.) and complexes used as catalysts. In particular, several organometallic species operating with this mechanism and containing metal such as Nb [18], Ta [18], Cu [19], Ru [20], Pt [11a,21], Os [20g,h,22], Sc [23], Pd [24], Re [25], Mo [26], Ni [27], Rh [20a,28], Zr [18b], have been used and above all Ir represents the most prevalent metal for the catalytic H/D exchange reactions [20a,29]. The analysis of some of these systems lets us understand the mechanistic issues in catalytic H/D exchange.

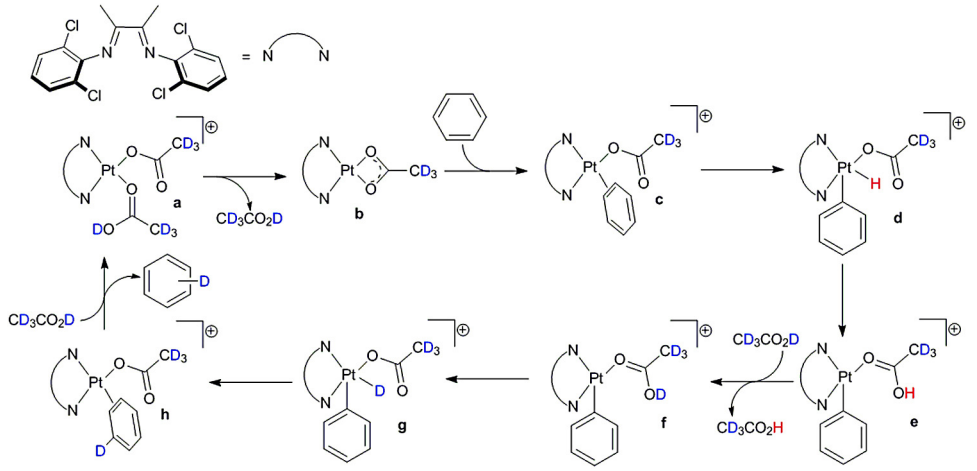
The first catalytic system for the H/D exchange of aromatic compounds was developed in 1967 and it is known as the Garnett and Hodges system. It is composed of a simple K_2PtCl_4 as the precatalyst, D_2O as the solvent and deuterium source under acidic conditions in order to obtain a homogeneous solution and avoid the deactivation of the catalyst by disproportionation of the Pt salt [11]. This study was extended by Shilov to the deuteration of more inert substrates as the alkenes. A deuterium incorporation of 2.5% was achieved for methane by heating a solution of 30% CH_3CO_2D in D_2O acidified with 30% HCl at 100 °C for 6 h whereas a 26% of D incorporation into ethane was observed after 9 h at 150 °C [12]. These systems, which also catalyze the oxidation of light alkenes, have been profusely studied and the proposed mechanism is described in Scheme 12.

A series of computational studies have tried to shed light onto the detailed mechanism of the Shilov system. Taking a *trans*-$[Pt(Cl)_2(H_2O)_2]$ as model system for DFT calculations, Siegbahn determined that the C–H activation reaction takes place in two steps [30]. In the first step, the substitution of a water ligand by methane occurs, with an energy cost of 10 kcal·mol^{-1}. In the second step, proton transfer produces Pt–CH_3 and HCl. This part has been described as a σ-bond metathesis process, in which one H of methane is transferred to a chlorido ligand, or as an ambiphilic metal–ligand activation (AMLA), in which a lone pair from the chloro atom participates in hydrogen migration [31,32]. This reaction has an energy barrier of 16.5 kcal·mol^{-1} with an overall activation energy of 27 kcal·mol^{-1}, in good agreement with the experimental value. In order to an in-depth understanding of the mechanism of the benzene deuteration by the Pt(II) CD_3CO_2D/D_2O system (Garnett system), Chen has studied the behavior of a well-defined cationic Pt(II)–diimine complex by ESI–MS and kinetic analysis (Scheme 13) [21e].

In this study, Chen has proved that the resting state of the reaction is a cationic Pt(II)–acetato complex bearing a coordinated acetic acid (**a**). This molecule is lost in the first step, leading the formation of a κ^2-acetato complex **b**. The authors showed that the next step, the opening of the acetate, followed by the coordination of benzene, represents the rate-determining step of the reaction. Based on



Scheme 12. (Color online.) Mechanism for deuterium exchange of alkenes in acidic medium catalyzed by the Pt(II) catalyst.

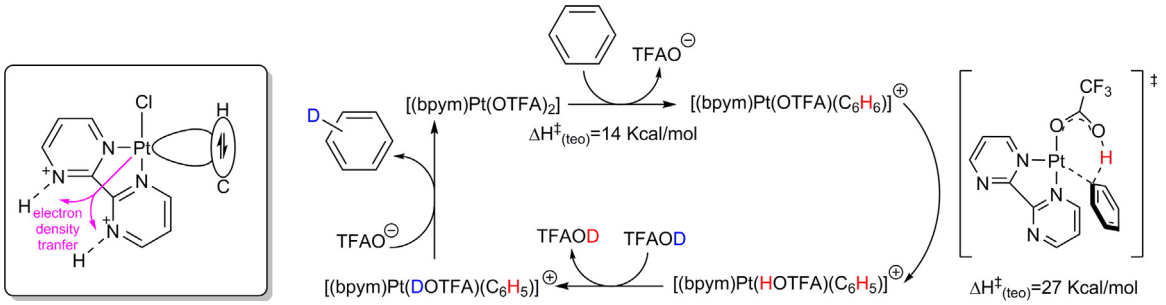


Scheme 13. Mechanism for H/D exchange catalyzed by Chen's catalyst.

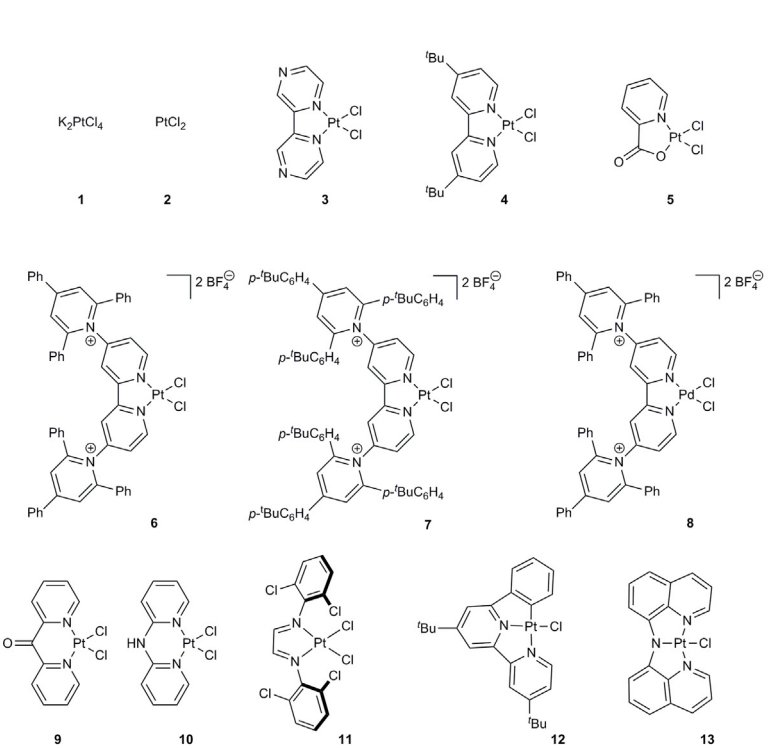
the DFT calculation on related Pt(II) complex [33], the authors suggested the formation of the Pt(IV)–H intermediate (**d**) instead of a direct abstraction of the proton from the acetate ligand, which, in fact, acts as a H/D shuttle deprotonating the Pt(IV)–H complex **d** and deutering the Pt(II) complex **f**, after exchange with deuterated acetic acid.

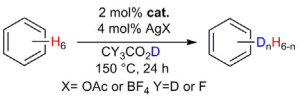
An important improvement in the world of the electrophilic catalytic systems was the development achieved by Periana's group in the catalytic system for the oxidation of CH_4 to CH_3OSO_3, named the Catalytica system [34]. This system is composed by a $[Pt(Cl)_2(bpym)]$ (bpym=bypirimidine) complex and H_2SO_4 that play the role of both, solvent and oxidant. The bypirimidine ligand is fundamental for this catalytic system; in fact it helps us to avoid the metal decomposition in the harsh acidic conditions and enhance the electrophilicity of the metal. In the strong acidic conditions of the reaction media, the bpym is protonated, and in this situation the ligand removes electron density from the metal center, leading to a lower energy metal-based LUMO that facilitates the interaction with the low C–H HOMO (box in Scheme 14). It is possible to use this system as a catalyst for H/D exchange of hydrocarbons by using a deuterated acid that does not behave as an oxidant, such as CF_3CO_2D (TFA). The mechanism relative to the H/D exchange of benzene with TFA catalyzed by $[Pt(bpym)(TFA)_2]$ is reported in Scheme 14. In this case it is important to remark that the C–H cleavage in this reaction occurs through a six-membered transition state in which the TFAO ligand assists the reaction by taking the proton from the substrate [21f]. According to Periana, this step is well described as an electrophilic substitution proceeding via addition of the Pt center to the arene ring.

Since the development of the Catalytica system, a plethora of other catalysts with similar structures have been developed. In a very interesting work, Sanford et al. have developed a protocol to compare the reactivity (turn over number, TON) of different complexes in H/D exchange reaction of benzene (as assay for C–H activation) with



Scheme 14. (Color online.) Periana's catalyst (in the box). Deuteration of benzene by [Pt(bpym)Pt(OTFA)$_2$] and TFA-d_1 (right).



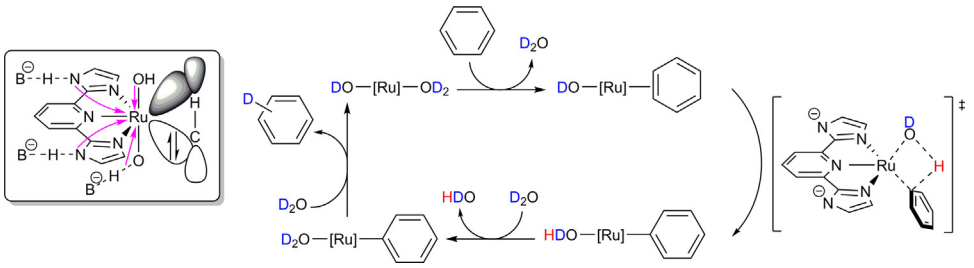


Entry	Catalyst	TON CF_3CO_2D[a]	TON CD_3CO_2D[b]
1	1	45	8
2	2	44	0
3	3	202	94
4	4	181	144
5	5	120	131
6	6	---	242
7	6	---	136[c]
8	7	---	241
9	7	---	167[c]
10	8	---	241
11	8	---	57[c]
12	9	142	241
13	10	200	65
14	11	207	224
15	12	53	---
16	13	46	---

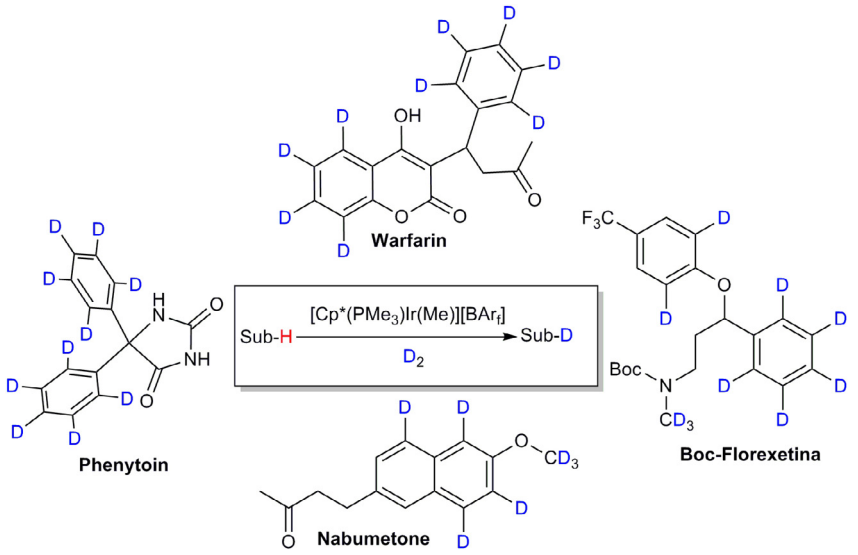
[a] Reaction conditions: [Benzene] = 0.26 mmol in 0.5 mL of TFA-d_1 (25 eq. relative to benzene) with 10 μmol (2 mol %) of catalyst and 10 μmol of AgOAc at 150°C for 24 h. The statistical maximum TON corrected for the background reaction is 207 under these conditions. Standard deviation is not shown [b] Reaction conditions: [Benzene] = 0.26 mmol in 0.37 mL of acetic acid-d_4 (25 eq. relative to benzene) with 10 μmol (2 mol %) of catalyst and 10 μmol of $AgBF_4$ at 150°C for 24h. The statistical maximum TON corrected for the background reaction is 241 under these conditions. Standard deviation is not shown [c] Reaction temperature 100°C.

Scheme 15. Comparison of the catalytic activity of the different complexes **1**–**13.**

deuterium sources as CD_3CO_2D or CF_3CO_2OD [21h]. As showed in Scheme 15, the results obtained can be very different depending on the type of complex and of the deuterium source. However, there are two discernible trends in the data reported herein. The inorganic catalyst **1** and **2** showed the lowest catalytic activity. In fact, a rapid formation of a black precipitate was observed suggesting the decomposition of the catalysts. The tridentate complexes **12** and **13** displayed lower activities with regard to the bidentate complexes **3**–**11** more likely for the highly unfavorable $\Delta H^{\ddagger}$ associated with the C–H activation reaction as suggested by Goddard and Periana [21g]. It is more difficult to rationalize the catalytic performances exhibited by the other complexes. From the experimental data it is revealed that the dicationic complexes **6**–**8** are the more performant; in fact they reach the maximum TON attainable (entries 6, 8, and 10). At lower reaction temperatures, it can be appreciated that the three catalysts actually have different activities (entries 7, 9, and 11), in particular the complex with the Pd instead of Pt is the less active. This set of catalysts [21] was designed in order to have the following three characteristics. Firstly, a bidentate N-donor ligand similar to the bypyrimidine used in the Catalytica system allows a direct comparison with this important system. Secondly, they contain an electro-withdrawing quaternized nitrogen substituent, which makes the coordinated metal center highly electrophilic. Finally, the quaternized nitrogens are not susceptible to decomposition in the reaction media, which makes the complex more resistant.



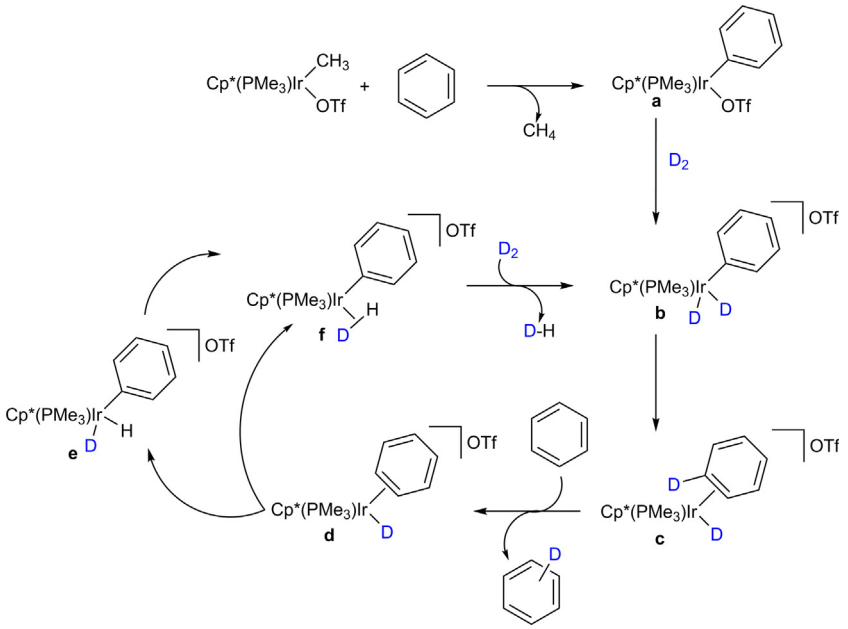
Scheme 16. (Color online.) Base stimulated C–H cleavage for the complex [(IPI)Ru(OH)(H_2O)] (in the box). Proposed catalytic cycle for the H/D exchange reaction of aromatic substrate mediated by [(IPI)Ru(OH)(H_2O)].



Scheme 17. (Color online.) Commercial pharmaceutical products deuteration catalyzed by [Cp*Ir(Me)(PMe_3)][BAr_F].

One of the most relevant problems of the electrophilic C–H activation systems is their inhibition by coordinating species such as H_2O through the formation of stabilized ground states that prevent substrate coordination [35]. This problem can be circumvented by the use of completely opposite nucleophilic catalytic systems. The prototype of this system consists in electron-rich good π-donor metals bearing strong electron donor ligands. With this idea in mind, Periana et al. have developed a catalytic system in which the interaction with the reaction media enhances the activity of the catalyst. In particular, in a similar way as with the Catalytica system, which is activated by *protonation* of the ligand by acid solvents, which accelerates electrophilic CH cleavage, a catalytic system in which reversible ligand *deprotonation* by basic solvents may accelerate nucleophilic C–H cleavage has been designed [21j]. The deprotonation of the ligand of a complex increases the electron density on the metal center and enhances the π-nucleophilicity by raising the energy of its HOMO. This effect facilitates the interaction with the high lying antibonding orbitals of the C–H bond of the substrate lowering the barrier for the cleavage of this bond (Scheme 16). Among several systems investigated, the tridentate Ru(III) complex (IPI)$RuCl_3$ (IPI = 2,6-diimidazoylpyridine) was selected. This complex provides the putative species $LRu(II)(OH)_n(H_2O)_m$ in situ by treatment with Zn in an aqueous solution of KOH by chloride displacement and deprotonation of the IPI ligand. This catalytic system resulted to be an interest catalyst for the H/D exchange of water-soluble aromatic compounds in a KOD/D_2O solution. The catalytic cycle is showed in Scheme 16. Based on the results reported for other nucleophilic systems, the authors proposed a 4-centered transition state where the basic hydroxo group assists the cleavage of the C–H bonds of the substrate [36].

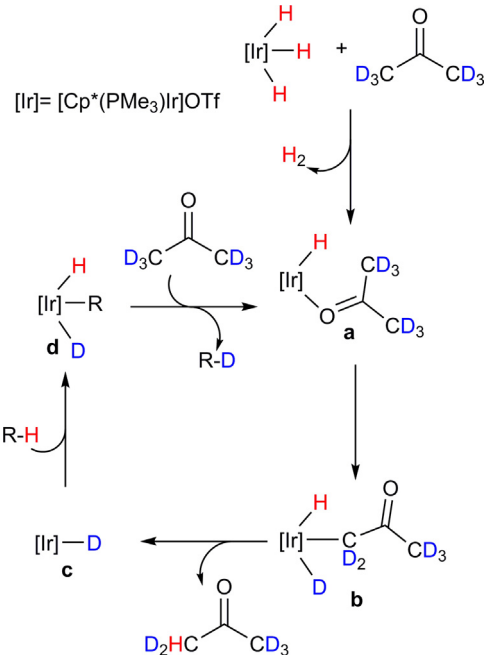
The catalytic systems analyzed previously are active only in strong acidic or basic conditions, which are allowed only for very resistant substrates as alkenes or simple aromatic compounds. Thus, a wide range of catalysts that work under milder conditions using simple deuterium source (D_2, D_2O, C_6D_6 or CD_3OD) have been developed. For example, Bergman et al. reported that the complex [Cp*Ir(Me)(PMe_3)][BAr_F] (Cp* = pentamethyl(cyclopentadienyl); BAr_F = tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate) results to be an excellent catalyst for the H/D exchange reaction of a wide range of organic compounds, including interesting pharmaceutical commercial products, using D_2 as deuterium source in dichloromethane as solvent (Scheme 17) [29p].



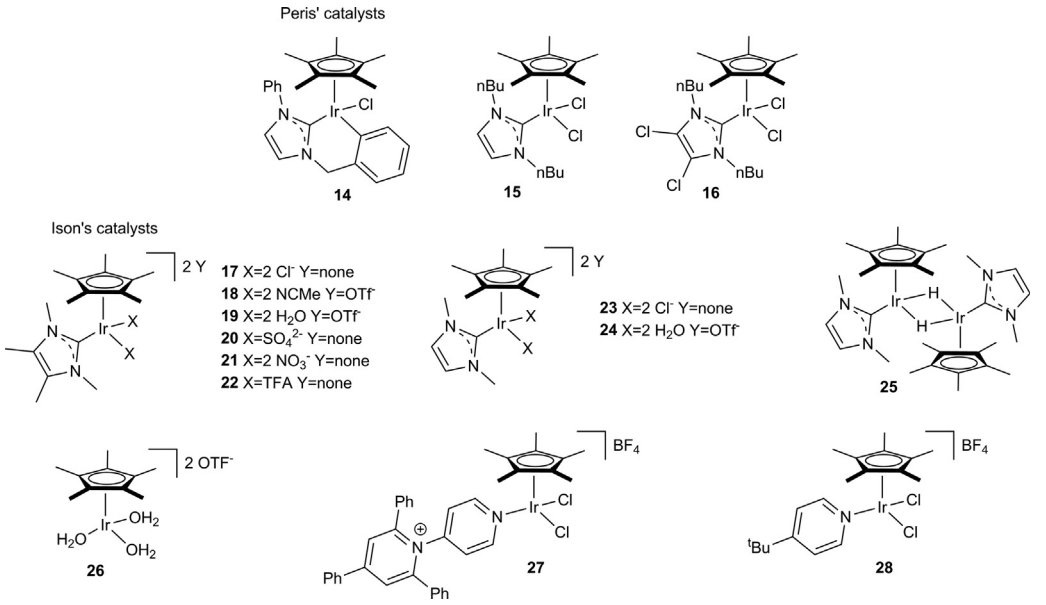
Scheme 18. (Color online.) Catalytic cycle for the deuteration of benzene with D_2 catalyzed by [Cp*Ir(Me)(PMe_3)][BAr_F].

Bergman's group demonstrated that this catalyst acts though a reversible elimination and re-addition of the aryl ligand and the different steps of the reaction may occur via oxidative addition or σ-bond metathesis (Scheme 18) [29r]. In the first step of the process the precatalyst reacts with the aromatic substrate via a C–H activation leading to the Ir(III) complex (**a**) bearing the aryl ligand through a σ-bond. Subsequent reaction with D_2 results in the formation of dihydride Ir(V) species **b**. Within **b** a carbon-deuterium reductive elimination takes place, yielding the Ir(III)–D complex **c,** which coordinates a deuterated η^2-arene that can be released by exchange with protiated benzene to form **d**. At this point, C–H activation takes place to form the aryl-η^2–HD complex **f** by two possible pathways: (i) oxidative addition to form **e** and subsequent reductive elimination, or (ii) direct σ-bond metathesis. Then, HD can exchange with D_2 regenerating the active species **b** and restarting the catalytic cycle.

The group of Bergman have also studied the use of the complex [Cp*(PMe_3)IrH_3][OTf] (OTf = trifluoromethanesulfonate) as a precatalyst and have extended the scope of the reaction to other substrates. They have showed a good activity using solvents as D_2O, CD_3OD and especially acetone-d_6 that allows a 99% deuteration yield of benzene in 20 h. A mechanism that reflects these experimental evidences is showed in Scheme 19. In the reaction medium, [Cp*(PMe_3)IrH_3][OTf] can coordinate a molecule of acetone-d_6 after the loss of H_2, leading to the Ir(III) complex **a** as observed by ^{1}H-NMR. The H/D exchange of the complex **a** to give **c** occurs through an oxidative addition of the C–D bond of the solvent that leads to the Ir(V)–D specie **b**, which subsequently loses acetone-d_5 by reductive elimination. This species can bind the substrate and promote a C–H activation that leads to complex **d**, which finally suffers from reductive elimination, leading to the deuterated substrate and regenerating the active species **a**. This catalytic system is effective for a varied set of aromatic compounds and alcohols (which will be discussed later) with different grade of selectivity depending on the substituents in the aromatic ring. In particular, lower levels of deuterium incorporation were observed in *ortho* position of the substrate as toluene or phenyltrimethylsilane, probably due to the steric hindrance in the key C–H activation step.



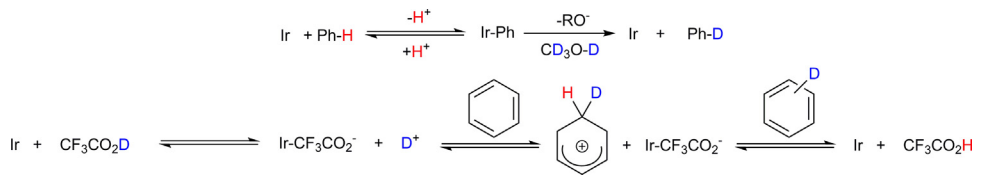
Scheme 19. (Color online.) Reaction pathway for the catalytic system [Cp*Ir(PMe_3)H_3][OTf]/acetone-d_6.



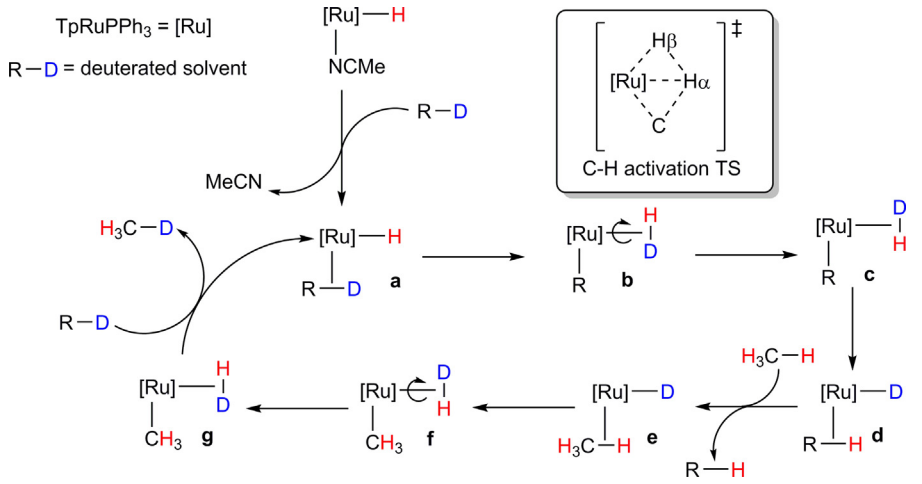
Scheme 20. (Color online.) Complexes containing the fragment [Cp*Ir(III)] synthetized by Peris' [29v] and Ison's [29ad,af] research groups.

The modification of a ligand can change dramatically the catalytic properties of a complex. Peris at first and Ison later have extended the work of Bergman synthesizing similar complexes containing the fragment [Cp*(L)Ir] (Scheme 20) [29v,ad,af]. In particular, both groups studied the effect of the substitution of the phosphine with a better σ-donor ligand such as an *N*-heterocyclic carbene (NHC) that have showed in many cases an improvement in the catalytic activity for various types of reactions, including C–H activation [4,16n,37]. In a similar way, complexes **14**–**16** bearing an NHC ligand showed a significantly higher catalytic activity with regard to the their phosphine analog [Cp*(PMe_3)$IrCl_2$] (Scheme 20). For all the experiments, the monodentate complex **15** showed higher activity with respect to the chelate complex **14**, probably because of the blocking of one active coordination site in the latter. The only case in which the catalytic activity of [Cp*(PMe_3)$IrCl_2$] is comparable with a Ir-NHC catalyst is complex **16**, in which the incorporation of two chloride substituents in the imidazole ring strongly decreases the σ-donation to the metal, thus decreasing its catalytic activity. The reaction conditions include the use of AgOTf in order to activate the catalyst by removing chlorido ligands. Alternatively, Ison showed the effect of these ancillary groups (and of the reaction solvent) on the catalytic activity of complexes **17–28** for the H/D exchange in benzene in standard conditions (developed by Sanford [21i]). Using CD_3OD as the solvent and deuterium source, the catalyst that has showed the better performances is complex **18**. The differences in the reactivity can be attributed to the ability of the ancillary group to dissociate from the metal center in order to allow the coordination and activation of the substrate. For this reason, the complex containing a more labile ligand as acetonitrile is the best catalyst.

Complexes lacking of an electron-rich ligand are also active in H/D exchange reactions (complexes **26–28** in Scheme 20). Similarly to Periana's catalyst, its high electrophilicity does not allow the easy exchange of ligands, thus they are much less active in a good nucleophilic solvent such as methanol. Instead, using TFA-d_1 as a deuterium source increases their catalytic activity up to 30 times. Through kinetic measurements, Ison has showed that the difference in the reactivity is due to a change in the reaction mechanism (Scheme 21). When methanol is used as deuterium source the proposed mechanism involves the activation of the Ph–H bond by the metal, to generate an Ir–Ph species. Then the Ir–Ph intermediate reacts with the deuterated solvent to form the deuterated product and regenerate the starting metal complex. In the case of TFA, the mechanism is totally different. In fact, in this case, the authors suggested a mechanism of electrophilic aromatic substitution (Ar–S_E) in which the metal reacts with the acid leading to a M(TFA)–D^+ species, which interacts with benzene producing the elimination of Ar–S_E H^+ and the release of Ph–D.



Scheme 21. (Color online.) Proposed mechanism for the H/D exchange of benzene by Ison's complexes in methanol (top) and TFA (bottom).

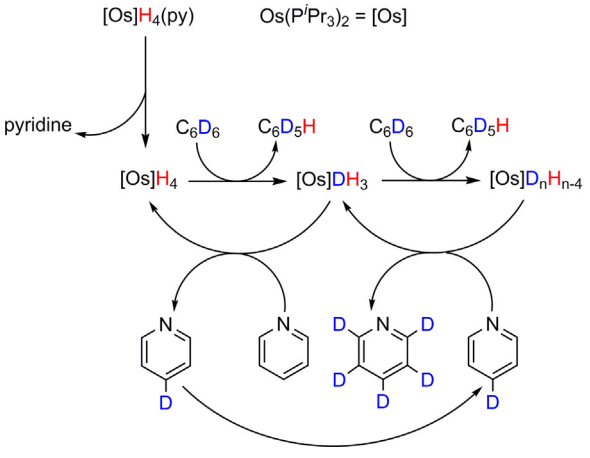


Scheme 22. [RuTp(H)(PPh$_3$)(CH$_3$CN)] catalyze CH_4 H/D exchange whit C_6D_6 as deuterium source, mechanism and TS of the C–H activation step (in box).

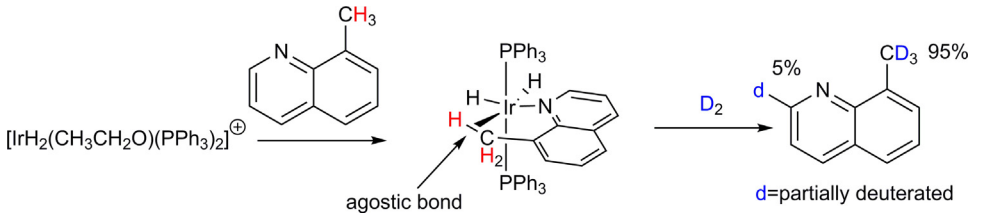
As previously stated, an alternative mechanism for C–H activation is σ-bond metathesis. Generally, the catalysts proceeding via this pathway include hydride or alkyl complexes of early transition metal with d^0 electronic configuration. A clear example is the complex $(Cp^*)_2ScD$. Miller has showed that this complex is able to catalyze the H/D exchange of the pentamethylcyclopentadiene (Cp*H), using C_6D_6 as deuterium source, with levels of deuterium incorporation of 95–96% in 4–5 weeks at 150 °C [23]. Also complexes containing d^4–d^8 metal can react through this mechanism, and in this case a σ-adduct could be observed before the σ-bond metathesis step. In some circumstances, the metal may facilitate the process by a weak interaction with the C–H proton, which is named "complex-assisted metathesis" (CAM) [38]. A clear example was showed by Jia et al., who demonstrated that the complex [RuTp(H)(PPh$_3$)(CH$_3$CN)] is able to catalyze the H–D exchange between CH_4 and deuterated organic solvents as tetrahydrofuran (THF), Et_2O, and benzene [39]. DFT theoretical calculations of a B3LYP level were carried out to understand the catalytic pathway of this reaction (Scheme 22). Transitions **a**–**b**, **c**–**d**, **e**–**f** and **g**–**h** are better described as σ-CAM processes. The rotation steps **b**–**c** and **f**–**g** are essential as they afford the exchange between H and D, leading to the desired deuterated substrate. From a careful analysis of the calculated TS of the C–H step, the authors have found that the distance between the Ru and the Hα is shorter with respect to the calculated TS for a classic σ-bond metathesis. This geometry is in agreement with a Ru(IV) complex; for this reason the authors described this process as oxidatively added transition state (OATS) (Figure 22 in box).

[Ru(II)–H] is a very useful fragment to synthetize a homogeneous catalyst for C–H activation [40]. Leitner has showed that the nonclassical hydride complex [Ru(dtbpmp)(η^2–H_2)H_2] (dtbpmp = 2,6-bis((di-*tert*-butylphosphino)methyl)pyridine) was an efficient and selective catalyst for the H/D exchange of aromatic substrates using the cheapest deuterium source (D_2O) under unprecedented mild conditions [20e]. A catalytic cycle similar to the one described above involves the reaction of the complex with D_2O, leading to a Ru–D, the subsequent activation of benzene via σ-CAM and the final elimination of the deuterated substrate. This system, as the previously described [Cp*(PMe$_3$)IrH$_3$][OTf], is very sensitive to the substituents of the aromatic substrate. For example, the reaction with *ortho* xylene is selective for the aromatic protons and particularly, distant protons to the methyl groups are preferentially deuterated compared to proximal ones. In order to understand the reason of this selectivity, theoretical calculations for the C–H activation of toluene were carried out. This study showed that the $\Delta G^{\ddagger}$ for the activation of the *meta* and *para* C–H positions are very similar (12.1 and 13.1 kcal·mol^{-1}, respectively), but that the one corresponding to the *ortho* position is higher (17.9 kcal·mol^{-1}).

A similar result was encountered by Esteruelas et al. in the H/D exchange of pyridine and 3- and 4-picoline with C_6D_6 using [OsH$_4$(Rpy)(P^{i}Pr$_3$)$_2$] (Rpy = pyridine or 3-picoline or 4-picoline) as a catalyst [22]. The catalytic cycle of this system reported in Scheme 23 shows an interesting result. In fact, the catalytic active species [OsH$_4$(P^{i}Pr$_3$)$_2$]



Scheme 23. (Color online.) H/D exchange of pyridine catalyzed by [OsH$_4$(Rpy)(P^{i}Pr$_3$)$_2$] (Rpy = pyridine, 3-picoline or 4-picoline) complexes.



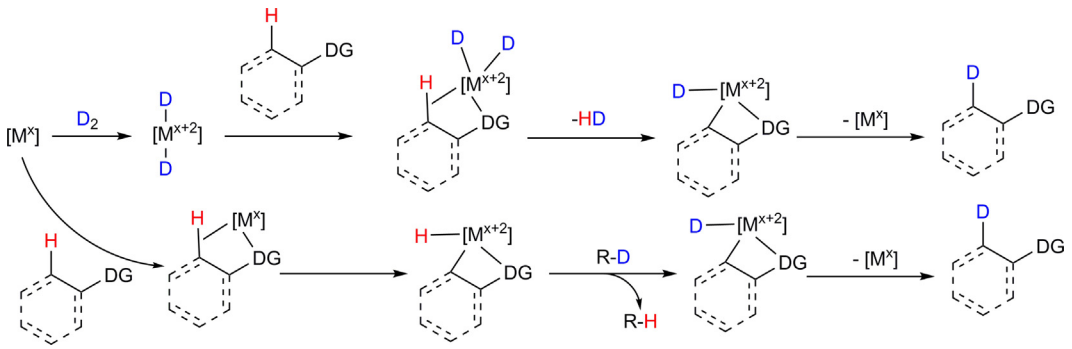
Scheme 24. Selective H/D exchange of 8-methylquinoline catalyzed by $[IrH_2(Me_2CO)(PPh_3)_2]BF_4$.

reacts with C_6D_6, generating the monodeuterated complex $[OsDH_3(P^iPr_3)_2]$ that selectively reacts with the *para* C–H of pyridine, giving 4-deuteropyridine. After the deuteration of the position 4 of the pyridine, $[OsDH_3(P^iPr_3)_2]$ reacts with another molecule of deuterated benzene, giving the species $[OsDnH_{4-n}(P^iPr_3)_2]$, which is responsible for the deuteration of the position 3,5 and 2,6 of the 4-deuteropyridine. The kinetic data confirmed the deuteration rate order $k[OsDH_3(P^iPr_3)_2] \approx k$ (4–Dpyr) $> k[OsD_2H_2(P^iPr_3)_2] > k[OsD_3H(P^iPr_3)_2] > k[OsD_4(P^iPr_3)_2] \approx k$ (3,5–Dpyr) $> k$ (2,6–Dpyr). According to the experimental data, theoretical calculations showed that the activation (via oxidative addition) of the C(4)–H has the lower TS (24.9 kcal·mol^{-1}), followed by the TS for the activation of the C(3,5)–H (25.4 kcal·mol^{-1}). The highest TS resulted to be the one for the activation of the C(2,6)–H (27.2 kcal·mol^{-1}). As described for the $[Cp^*(PMe_3)IrH_3][OTf]$ and $[Ru(dtbpmp)(\eta^2\text{–}H_2)H_2]$, the substituent in the aromatic substrate (in this case, pyridine) hinders the H/D exchange. For example, the H/D exchange in 4-picoline is slower with respect to that of pyridine and the proton proximal to the methyl group is deuterated more slowly, giving $k_{3,5} < k_{2,6}$.

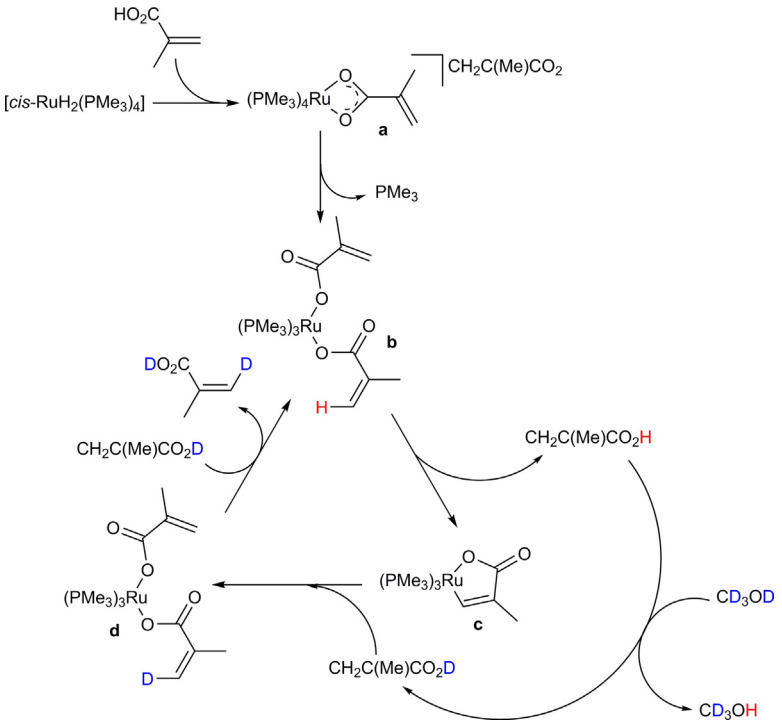
One of the most important advantages of metal-catalyzed H/D exchange is the regio- and chemoselectivity. The understanding of the mechanistic reasons that governs selectivity is essential in order to develop catalytic systems with higher performances. The C–H *ortho* position in substituted aromatic compounds for the system $[Cp^*(PMe_3)IrH_3][OTf]$/acetone-d_6 presents a low rate. However, in the case of phenol and anisole, the *ortho* position is deuterated in the same manner than *meta* and *para* ones. In the case of benzoic acid, the deuteration level of the *ortho* position is as high as 78%, while the *meta* and *para* ones are only 35 and 26%, respectively. This is due to the presence of a substituent containing heteroatoms (oxygen in this case) able to coordinate to the catalyst and directing the reaction into a determinate position of the substrate (normally close to the substituent). These substituents are usually known as *directing groups*. In the last years, there has been an incredible rise in the development of new selective catalytic systems based on the presence of these groups [16f,h,n,o,41].

The first example of this type of catalytic system applied to H/D exchange was evidenced in the years 1982–1984 by Lockley [20a,28a]. A few years later, Crabtree showed that the catalyst $[IrH_2(Me_2CO)(PPh_3)_2]BF_4$ using D_2 as the deuterium source was able to catalyze the selective H/D exchange of the 8-methylquinoline (mq) in the methyl position in 8 h with selectivity greater than 95% (Scheme 24) [29a]. The authors have showed that this selectivity is due to the in situ formation of complex $[IrH_2(mq)(PPh_3)_2]BF_4$, in which, as demonstrated by NMR and X-ray diffraction analysis, an intramolecular agostic bond between a C–H bond of the methyl group and the iridium is formed. This resting state probably favors the activation of the C–H bond on the methyl moiety, which subsequently exchanges with the deuteride bonded to the metal, formed from the H/D exchange reaction of Ir–H_2 with D_2.

After these works, a great amount of interesting research in the application in H/D exchange of several directing groups such as pyridines, pyrazoles, imidazoles, sulfonamide, sulfoxide, oxime, isoxazole, thiazole, anilide, ureas, esters, amines, amides, carboxylic acid, ketones, nitro groups, have appeared [19,20b,21c,d,j,28c,d,29a-h,29l,n,o,q,s–u,x,ab,ac,ae,ag–al]. A general mechanism of H/D exchange in aromatic substrates containing a directing group is showed in Scheme 25 [28d,29c,aj]. As we can see, the metal binds to the directing group of the substrate, activates the appropriate C–H moiety, which, after the exchange of a hydride with a deuteride from the deuterium source, leads to the deuterated substrate after reductive elimination.



Scheme 25. (Color online.) Generic H/D exchange of substrates containing a directing group (DG).

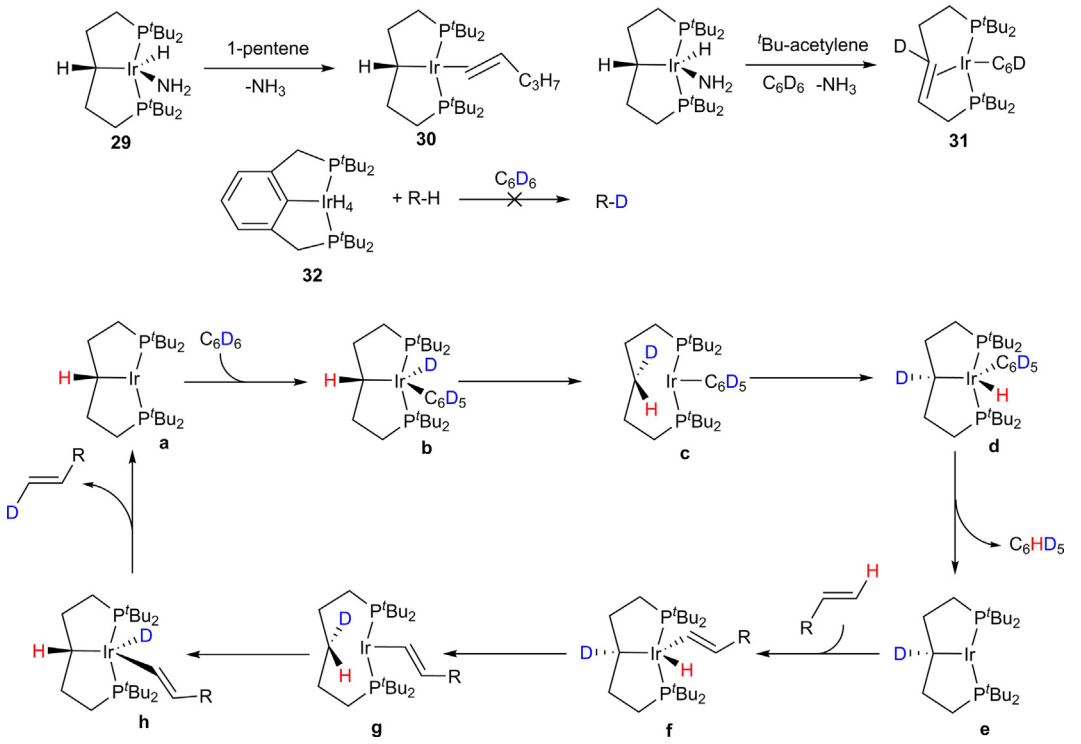


Scheme 26. (Color online.) Selective H/D exchange of metacrylic acid-catalyzed by [*cis*-$RuH_2(PMe_3)_4$] in CD_3OD.

Olefins are among the most problematic substrates for catalytic systems based on C–H activation. In fact, under the standard reaction conditions used for H/D exchange, these substrates can decompose in different ways such as polymerization or isomerization; therefore, the selective deuteration in vinylic position is a very challenging goal. In the 2005, Fels showed that the complex [IrCOD(acac)] (acac = acetylacetonate) is able to catalyze the regioselective H/D exchange of a few olefins conjugated with carbonyl groups as crotonil acid, trans-2,3-dimethoxycinnamic acid and 3 benzoacrylic acid, using D_2O as a deuterium source [28c]. Another similar example was showed recently by Kerr in the selective β-labeling of conjugated enones with Ir^I–NHC complexes using D_2 as a deuterium source [29al]. Hirano et al. have demonstrated the potential of [*cis*-$RuH_2(PMe_3)_4$] to catalyze the H/D exchange of metacrylic acid and of some derivatives in CD_3OD with 63 to 86% yield, with a very high selectivity for the β-*cis* hydrogen of the carboxylic acid [20j]. In the catalytic cycle (Scheme 26), the author proposed the in situ formation of the cationic monocarboxilato Ru(II) complex **a**, which after the loss of a PMe_3 leads to the dicarboxilato complex **b**. Then, a ruthenolactone **c** is formed by C–H activation, whose acidolysis with a deuterated CH_2CMe-CO_2D gives in situ **d**, in which D is incorporated in *cis* to the carboxyl group. After a final exchange between deuterated metacrilate and a new substrate, Z-CHD=C(Me)CO_2D is released.

One of the greatest results in this field was the catalytic system developed by Hartwig, which is able to catalyze selectively the H/D exchange reaction of olefins without isomerization or other decomposition reaction [29y]. The catalyst used was the pincer [(dtbpp)Ir(H)(NH_2)] (dtbpp = 1,5-bis(di-*tert*-butylphosphino)pentan-3-yl) (**29** in Scheme 27) in C_6D_6 as a solvent and a deuterium source. Different class of olefins including terminal and aromatic substituted compounds are deuterated, operating under mild conditions (room temperature to 60 °C). One of the most interesting results is the first example of regioselective deuteration of the β-*trans* vinyl C–H obtained with substrates as *tert*-butyl ethylene and pentene. Monitoring the H/D reaction of 1-pentene by ^{31}P-NMR, the authors demonstrated that [(dtbpp)Ir(1-pentene)] (**30** in Scheme 27) was formed via reductive elimination of NH_3. When *tert*-butylacetylene was used as a substrate, the complex [{($^tBu)_2PCH_2CH_2CH{=}CHCH_2P(^t$-$Bu)_2$}IrPh] (**31** in Scheme 27) containing an olefin in the backbone of the pincer ligand was obtained. This complex presents a deuterium atom at the olefinic position that was originally the central carbon atom of the backbone of the complex [(dtbpp)Ir(H)(NH_2)]. This observation led the authors to propose that the methine position of the backbone is fundamental in the mechanism, acting as H/D shuttle during the reaction. This observation was confirmed by the total inactivity of an aromatic pincer catalyst (**32** in Scheme 27).

Based on experimental evidences, the authors proposed the catalytic cycle showed in Scheme 27. The active species is the Ir(I) complex **a** obtained from **29** by reductive elimination of NH_3. This unsaturated compound reacts with C_6D_6 by activation of the C–D bond by oxidative addition leading to Ir–D complex **b**. Three subsequent reductive elimination-oxidative addition-reductive elimination steps result in the formation of complex **e**, the

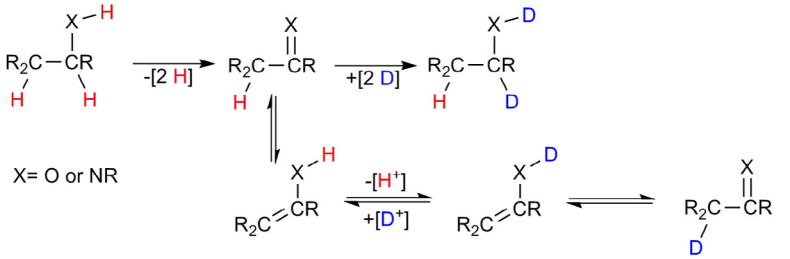


Scheme 27. (Color online.) Catalytic cycle of H/D exchange of olefins by the [(dtbpp)Ir(H)(NH_2)] catalyst with C_6D_6.

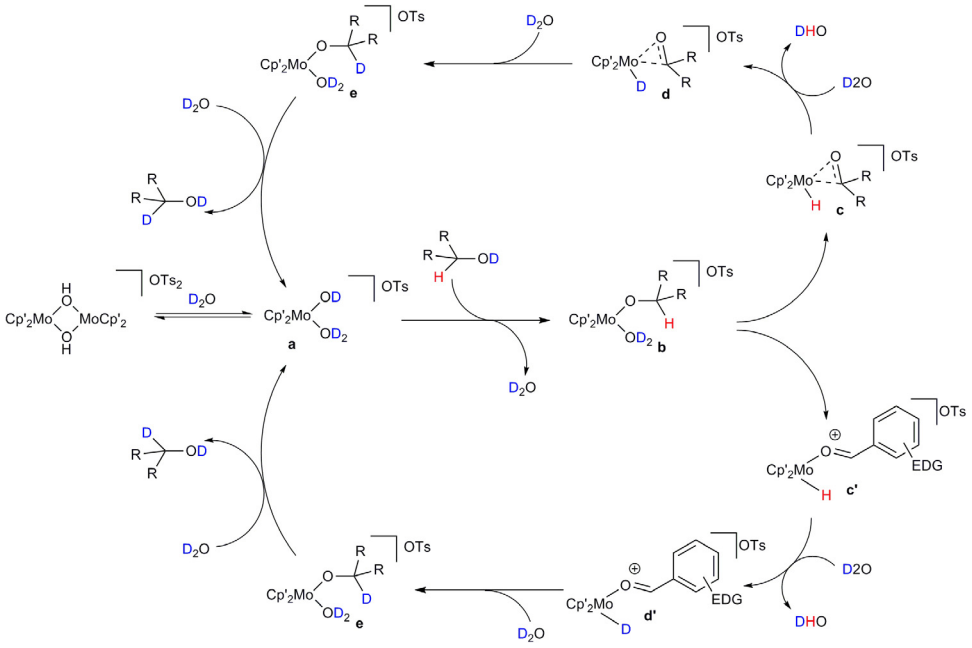
deuterated analog of **a**. Complex **e** lead to the formation of the deuterated substrate through oxidative addition on the C–H of the olefin (**e**–**f**) [42] followed by internal H/D scrambling (**f**–**g**) and finally reductive elimination of the deuterated alkenyl fragment. This mechanism could explain the selectivity observed in the H/D exchange of 1-pentene, in which only the β-*trans* vinyl C–H is deuterated. In fact, in steps **e**–**f**, it is reasonable to think that the activation of the C–H of the olefin is produced on the most accessible position, leading to the most stable and with less steric hindrance product.

In the group of the catalytic systems that work through a C–H activation step, an important place is occupied by the deuteration of alcohols and amines. These types of substrates are very important, especially for biomedical applications, so the development of systems able to effectively catalyze their H/D exchange is a priority to the chemistry labelling research. The moieties R–OH or R_3-N provide really different properties to these substrates with respect to other hydrocarbons. In particular, the α and β C–H moieties can be activated by a catalytic system though the assistance of the heteroatom (Scheme 28). In particular, many organometallic complexes are efficient catalysts for the dehydrogenation of alcohols and amines to carbonyl compound or imines, respectively. The desired α-deuterated alcohol or amine is achieved by the formal re-hydrogenation of the unsaturated compound by deuterium. As previously mentioned, also the β-C–H position can be activated through the mediation of the heteroatom; in fact, the carbonyl compound and the imine are in equilibrium with their enolic/enaminic forms that help with the functionalization of the β-C–H moiety.

Various catalytic systems have been developed for this reaction, using complexes containing different metals such as Zr, Nb, Ta, Mo, Ir, Pt, Os and mostly Ru, solvents as water, alcohols or C_6D_6 and in some case co-catalyst as KOH [18b,20f,h,i,l,26b–d,29k,r,v]. The catalytic mechanisms of the different systems vary depending on their composition and for this reason, we describe in this review some of the most representative.



Scheme 28. (Color online.) Generic H/D exchange of alcohol and amine in α and β positions.

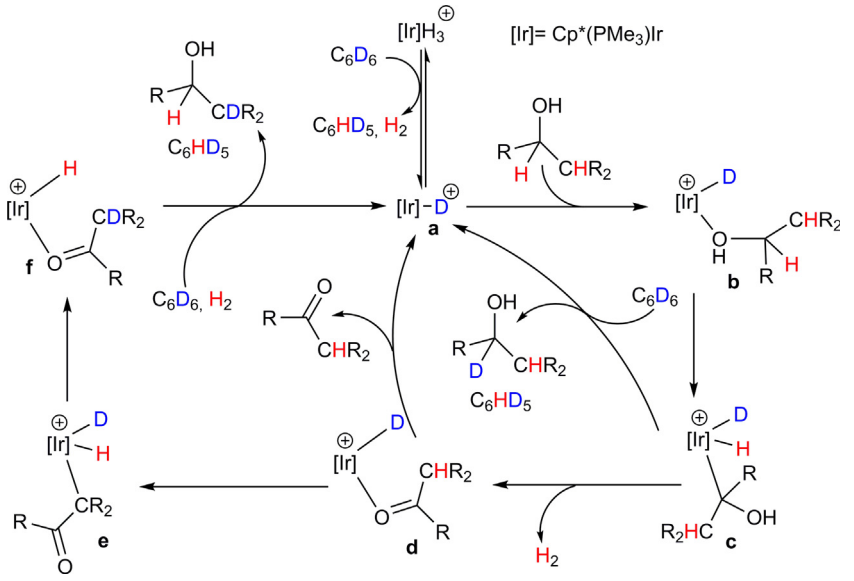


Scheme 29. (Color online.) Selective α deuteration of primary alcohols with D_2O mediated by $[Cp'_2Mo(\mu\text{-}OH)]_2(OTs)_2$.

One of the first examples of homogeneous catalytic systems able to catalyze the H/D exchange of alcohols was reported by Nugent et al. in the 1986 [18b]. In this work the authors used ethoxides of Nb, Zr and Ta as catalysts, and they studied the H/D exchange of CH_3CH_2OD, detecting the selective deuteration of the terminal methyl. This result was justified by the in situ formation of reversible carbonyl products, which, thanks to the keto-enolic tautomerism, led to the deuteration of the β-CH of ethanol. From this pioneering work, various other systems has been developed and studied. One of the most important and very well characterized is the system developed by Tyler et al. [26b–d]. In this work, the primary alcohols are selectively deuterated in α-position by a catalytic system composed by the dimeric Mo complex $[Cp'_2Mo(\mu\text{-}OH)]_2(OTs)_2$ (Cp′ = methylcyclopentadienyl, OTs = *p*-toluenesulfonate) and D_2O as both the solvent and the deuterium source. The catalytic cycle of this reaction is showed in Scheme 29. In the reaction media, the dimeric Mo complex is in equilibrium with the monomeric complex **a**, which represents the effective catalyst in this reaction. In the first step, a molecule of the substrate reacts with the OD moiety of the complex, giving the alcoxo compound **b**. This complex gives a η^2-keto hydride complex through the C–H activation of the α-C–H. Detailed mechanistic studies show that this represents the rate-determining step. In addition, they have demonstrated that the presence of an electron-donating group (EDG) induces C–H bond activation by β–hydride transfer, leading to the η^1-keto hydride complex **c**′ [26d]. Complex **c**, via a dissociative mechanism, changes an H^+ with a D^+ of the solvent, giving the deuterated complex **d**. Finally, the deuterated alcoxo complex **e** was formed by an insertion of the carbonyl moiety into the deuteride, and the exchange with a molecule of D_2O leads to the release of the α-deuterated alcohol.

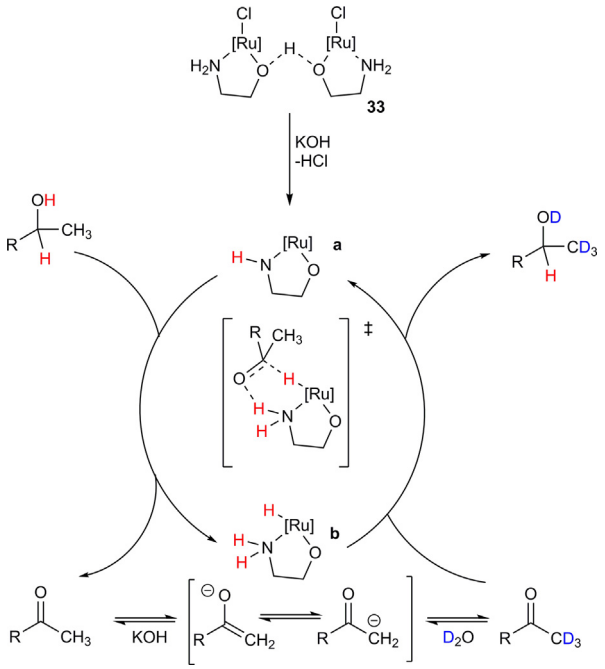
Bergman showed that the catalyst $[Cp^*(PMe_3)Ir\text{-}H_3][OTf]$, in the presence of C_6D_6 as a deuterium source, is active also in the deuteration of alcohols. This catalytic system provides the selective H/D exchange in the α and β positions of the primary alcohol, without any deuteration in γ-position. This experimental result has been explained with the cycle showed in Scheme 30. The loss of H_2 followed by the deuteration of the hydride by solvent lead to **a**, that binds the alcohol providing **b**. The activation of the α-C–H provides the Ir(V) intermediate **c**. Complex **c** can release the α-deuterated alcohol by reductive elimination or, alternatively, it can provide the keto-complex **d** by loss of H_2, which is responsible for the deuteration on the β-position of the alcohol.

After showing a system able to catalyze selectively the H/D exchange of the alcohol in α position (Tyler's system), and the Bergmann system able to catalyze both α and β C–H, a catalytic system designed to obtain the selective deuteration of the β-position will be described. Using a Ru(II) complex prepared from the reaction of $[\{(p\text{-cymene})RuCl_2\}_2]$ with ethanolamine, Jia et al. showed that it is possible to catalyze the selective β–H/D exchange of a large number of primary and secondary alcohols [20f]. The key point of this system is the use of KOH as a co-catalyst. In fact, it is known that Ru complexes are able to catalyze the reversible dehydrogenation of alcohols, thus combining this catalyst with a base, that enhance the enolization of the carbonyl compound generated, it is possible obtain, in D_2O, the deuteration of the β-hydrogen of the alcohols. The proposed catalytic cycle is showed below (Scheme 31).



Scheme 30. (Color online.) H/D exchange of alcohol in α and β position catalyzed by $[Cp^*(PMe_3)IrH_3][OTf]$ using C_6D_6.

From the reaction of $[\{(p\text{-cymene})RuCl_2\}_2]$ with ethanolamine in basic conditions, complex **33** was obtained. Under these reaction conditions, this complex gives the effective alkoxyamido catalyst **a**. Complex **a** reacts with the substrate, providing the hydride complex **b** and a carbonyl compound (ketone or aldehyde) through the known six-membered cyclic transition state for hydrogen transfer reactions. The carbonyl compound exchanges the β–H with D from D_2O in basic medium through keto-enol tautomerization. Finally, the deuterated ketone or aldehyde is reduced by complex **b** regenerating the complex **a** and releasing the β-deuterated alcohol.



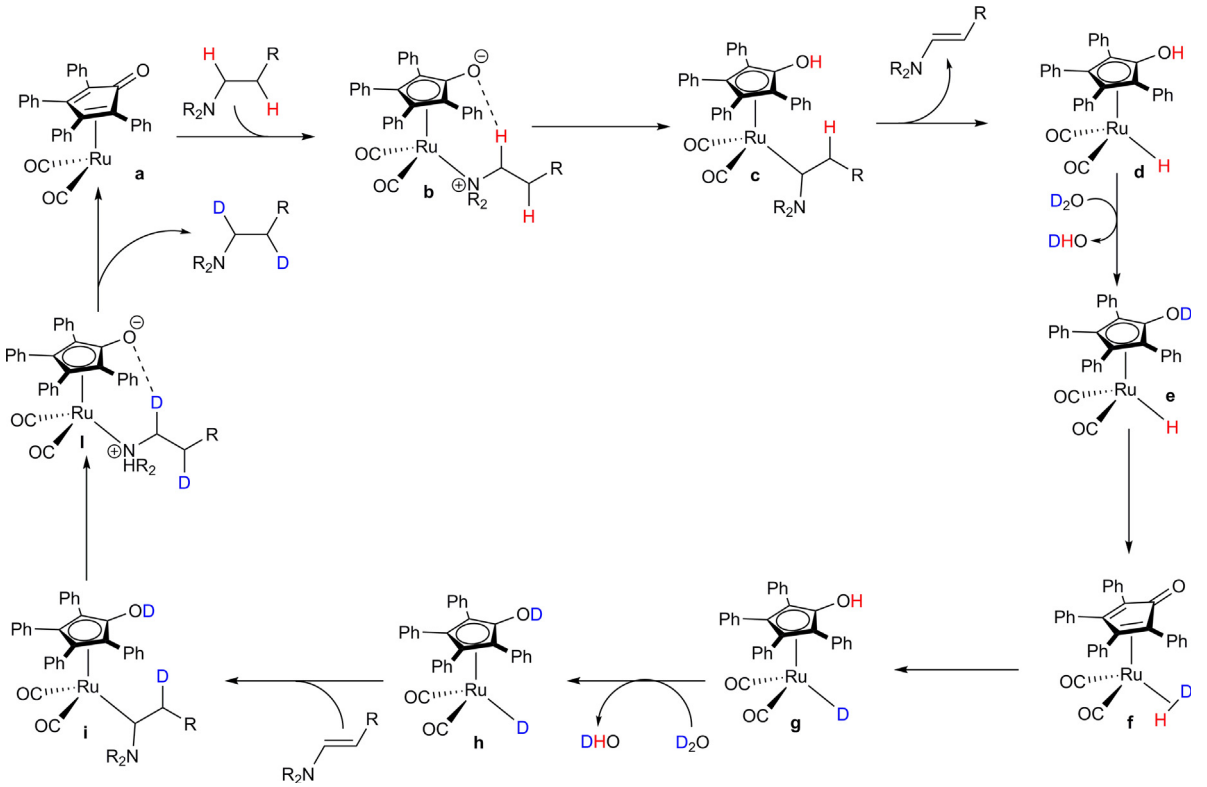
Scheme 31. (Color online.) Selective α H/D exchange of alcohols with D_2O mediated by Jia's catalyst and KOH.

As showed, various catalytic systems for the H/D exchange of alcohols have been developed, but in the case of amines only few works have been published [20c,d,i]. In a recent publication, Beller et al. have showed that Shvo's catalyst [43] is able to catalyze the H/D exchange of tertiary amines, including market drug compounds, using protic deuterated solvent as alcohols or water as deuterium source [20i]. Contrary to the case of the alcohols previously described, the tertiary amine used as a substrate in this work cannot form an imine as intermediate. For this reason, the author proposed a catalytic cycle in which the key step is the formation of a reactive enamine (Scheme 32).

In solution, the dimeric Shvo catalyst dissociates into two unequal complexes: one contains both hydrogen atoms from the dimer, and the other becomes coordinatively unsaturated. The second one (**a**) is the active species in this reaction. Complex **a** can coordinate a molecule of substrate (**b**) and extract the α-hydrogen of the amine by the alcoxide moiety on the cyclopentadienyl ligand (**c**). Through β-elimination, the enamine was released and the hydrogenated monomeric Shvo's complex is obtained. The H/D exchange of complex **d** is obtained by reaction with D_2O through formation of the intermediates **e**, **f**, and **g**. The deuterated Shvo's **h** can now react through an insertion of the Ru–H on the double bond of the enamine (previously obtained), giving complex **i**. Finally, protonation mediated by the OD moiety of the ligand leads to the formation of the α and β deuterated amines, and the catalytic active species **a** is regenerated.

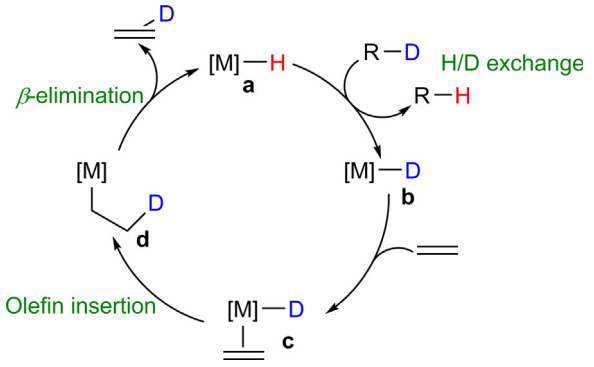
5. Insertion/β-elimination

As previously discussed, one of the most challenging catalytic processes in the field of H/D exchange is the



Scheme 32. (Color online.) Selective deuteration of amines by Shvo's catalyst.

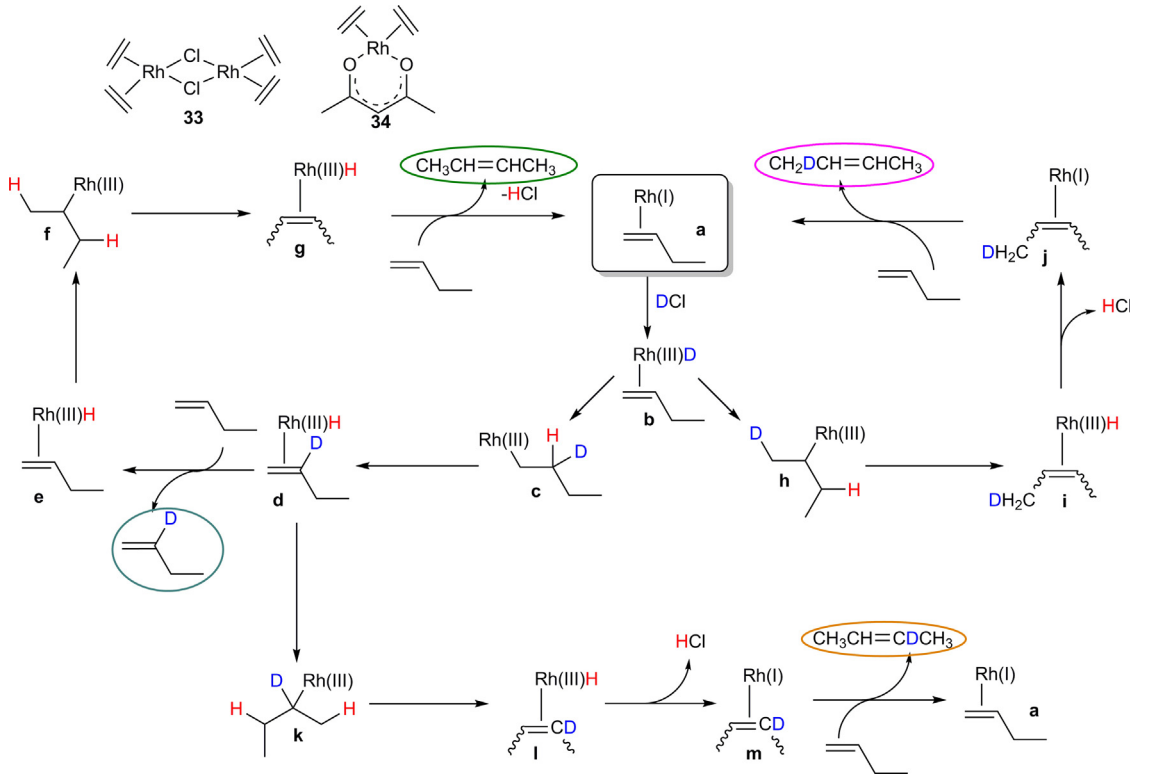
selective H/D scrambling of olefins, especially in the presence of aromatic compounds. A feasible alternative mechanism for these substrates has been developed. It could be defined as *insertion/β-elimination* mechanism from the name of the two principal processes involved in the reaction (Scheme 33) [4,20c,44]. A *necessary but not sufficient* (as we will see later) condition for a system to proceed according to this mechanism is the presence of a metal–hydride complex or a complex able to generate a metal–hydride species in the reaction medium. In the first step of the reaction, the deuterium source exchange the hydride of complex **a** to metal-deuteride to form **b**. Then, after coordination of the olefin (**c**), the second important step is the insertion of the C=C moiety into the M–D bond,



Scheme 33. (Color online.) General mechanism of ethylene deuteration by a metal–hydride catalyst.

giving the metal-alkyl intermediate **d**. The subsequent β-elimination of the alkyl ligand gives rise to the deuterated olefin and to the initial metal–hydride species.

One of the first examples of this type of catalytic system was showed by Cramer in 1966 [44a]. In this pioneering work, the author showed how a Rh(III)–H species generated in situ from a Rh(I) complex and HCl is able to isomerize olefins (terminal to internal and *cis* to *trans*), and they also found that, in the presence of CH_3OD, 1-butene suffers from H/D exchange. Data collected in this work suggest a strong connection between both isomerization and H/D exchange processes, which appear to be different aspects of the same reaction. In fact, in the products of the reaction of 1-butene, a mixture of different deuterated butenes (1-butene, and *cis* and *trans*-2-butene) and protiated 2-butene, resulting from isomerization, was obtained. In order to explain these results, the author proposed the reaction pathway described in Scheme 34. According to this mechanism, complexes **33** and **34** in the reaction medium exchange ethylene with 1-butene (**a**), then the oxidative addition of DCl (produced in situ by interaction of HCl with CH_3OD) leads to the Rh(III) complex **b**. At this point, the olefin may insert into the Rh–D bond with two orientations. 1,2 insertion results in the formation of linear anti-Markovnikov alkyl complex **c**, which after β-elimination of the proton in C(2), give rise to **d**. The exchange with fresh substrate produces the release of 2–D-1-butene and the formation of complex **e**, which formally represents the product of the oxidative addition of **a** with HCl. Within complex **e** only the Markovnikov-type

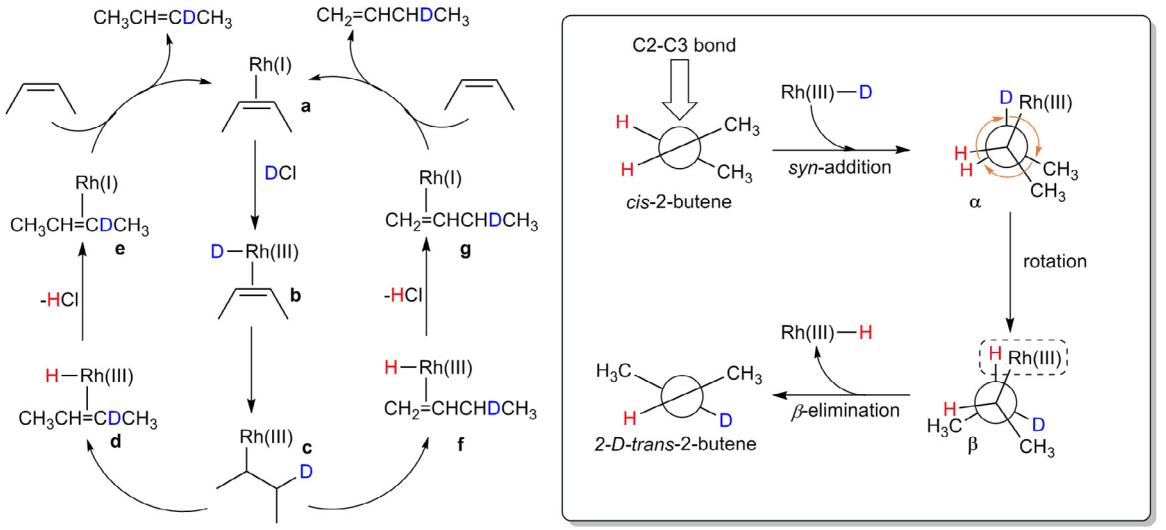


Scheme 34. (Color online.) Mechanism of isomerization–H/D exchange of 1-butene mediated by the in situ-produced Rh(III)–H catalyst.

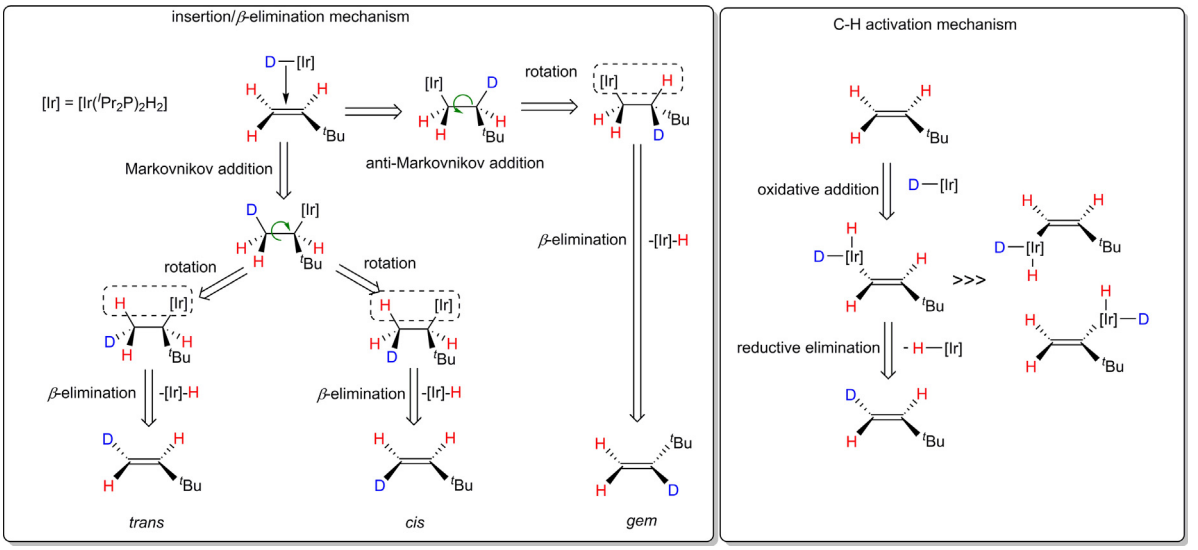
addition of the olefin in Rh–H is productive, leading to the formation of the branched alkyl complex **f**, which gives rise to a Rh(III)–H complex bonded to *cis* or *trans*-2-butene (**g**) by β-elimination of the internal C(3) hydrogen. Finally the exchange of 2-butene with 1-butene regenerates the active species **a**. This reaction pathway provides a route to the formation of both $CH_2{=}CDC_2H_5$ and $CH_3CH{=}CHCH_3$ in a one-to-one relationship as obtained experimentally. The other products found in the reaction medium were 2-butane, deuterated in positions 1 and 2. The former is the result of the 2,1 Markovnikov-type insertion within complex **b** to give the branched Rh-alkyl complex **h**, followed by *β*-elimination of the C(3) hydrogen (**i**). The final elimination of HCl (**j**) followed by exchange with fresh starting olefin provides $CH_2DCH{=}CHCH_3$ and regenerates **a**. Instead, $CH_3CH{=}CDCH_3$ was produced by Markovnikov addition within complex **d** through the formation of complexes **k**, **l**, and **m**. An interesting result that can be extracted from the analysis of the experimental results is that the 1,2 insertion is favored versus 2,1 insertion, as the amount of 2–D-1-butene and 2–D-2-butene is higher than that of 1–D-2-butene. Another remarkable fact is the absence of 1–D-1-butene, which could be rationalized by the preference for the β-elimination of the substituted C(3)–proton versus C(1)–H within complex **h**, in accordance with Zaitsev's rule [43]; therefore, the isomerized product prevails over the terminal deuterated olefin.

Another interesting result obtained by Cramer is the result of the isomerization–H/D exchange of *cis*-2-butene. In this case, the main products of the reaction are 2–D-*trans*-2-butene and 3–D-1-butene, without any significant amount of deuterated *cis*-2-butene. The formation mechanism of these products is very similar to the one described above for 1-butene (Scheme 35), but this pathway does not explain why the deuterated form of *cis*-2-butene is not obtained. The key steps to understand the origin of this stereo-selectivity is the addition of Rh(III)–D to the olefin (**b** to **c**) and the following β-elimination (**c** to **d**), which provide selectively the 2D-*trans*-2-butene derivative. The addition of the M–H to the unsaturated substrates is well known to be stereospecific and to provide the syn-addition product as **α** in Scheme 35 (in the box). In order to produce an effective H/D exchange, the Rh–alkyl moiety, bound to C(2), must rotate around the C(2)–C(3) bond to give the conformer **β**, in which a proton is located in the appropriate position for β-elimination, but also the methyl group has rotated. Therefore, the elimination step produces the deuterated form of *trans*-2-butane, resulting from both deuteration and isomerization.

As mentioned before, in the insertion/β-elimination mechanism, the presence of an M–H species is a fundamental requirement. However, not all the metal–hydride complexes catalyze the H/D exchange of olefins through this mechanism. For example, Faller has elegantly showed that the $[Ir(^iPr_3P)_2H_5]$ complex is able to catalyze the H/D exchange reaction of terminal aliphatic olefins through different mechanisms depending on the C–H position [45]. In the first step of the reaction the saturated Ir complex leads to the formation of the 14-electron

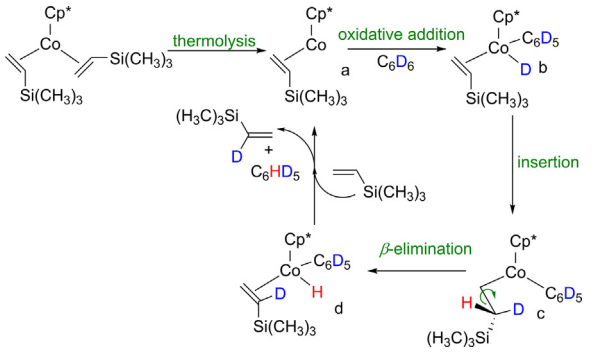


Scheme 35. (Color online.) Mechanism of isomerization–H/D exchange of *cis*-2-butene mediated by in situ-prepared Rh(III)–H catalyst. The figure in the box shows the stereochemistry of the addition of the Rh(III)–D moiety on the olefin.



Scheme 36. (Color online.) H/D exchange of ^{t}Bu-ethylene, insertion/β-elimination mechanism vs. C–H activation mechanism.

complex [Ir(^{i}Pr$_3$P)H$_3$] through the loss of a phosphine and the elimination of H_2 by reduction of an olefin molecule. This compound leads to the complex [Ir(d_5-Ph)(^{i}Pr$_3$P)DH$_3$] by recoordination of a phosphine and activation of the C–D bond of the solvent (C_6D_6), which provide the catalytic active species [Ir(^{i}Pr$_3$P)$_2$DH$_2$] via elimination of C_6D_5H. This Ir-D species could catalyze could catalyze the H/D exchange of olefins via the insertion/β-elimination mechanism. However, when ^{t}Bu-acetylene was used as a substrate, the composition of the H/D exchange products is not consistent with this mechanism. In fact, there is a clear preference for the deuteration of the terminal *versus* the internal position (8:1). Moreover, among the two terminal position, the *trans* C–H (to respect the ^{t}Bu) is deuterated in a 6:1 ratio with respect to the *cis* position. As showed in Scheme 36 (left), the mechanism of insertion/β-elimination accounts for the formation of the α-deuterated-^{t}Bu-acetylene (*gem*) through an anti-Markovnikov addition of the M–D in the double bond of the olefin, while the β-*trans* and β-*cis* derivatives are produced by Markovnikov addition. One would have expected that the anti-Markovnikov addition could be favored, as in the case discussed by Cramer, but the resulting *gem*-product is produced only in a 1:8 ratio as compared to the terminal deuterated product. On the other hand, in the case of the Markovnikov addition, both *trans* and *cis* β-deuterated products would be obtained in equal amounts, but experimentally it was observed that the deuteration in the *trans* position was six times faster. This experimental evidence points out that this complex does not catalyze



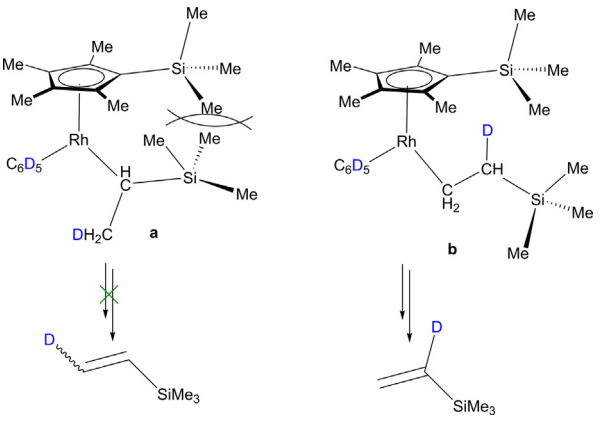
Scheme 37. (Color online.) Regioselective deuteration of trimethylsilylethylene in α-position by catalyst $Cp^*Co(CH_2{=}CHSi(CH_3)_3)_2$.

this reaction through the insertion/β-elimination mechanism, but more likely via the previously discussed C–H activation pathway (Scheme 36). In fact, with this mechanism, the more accessible position to the metal center is the one that is *trans* to the bulkiest substituent, which could explain the observed selectivity. However, the authors demonstrated that the deuteration of the hindered *gem*-position proceeds via an insertion/β-elimination mechanism.

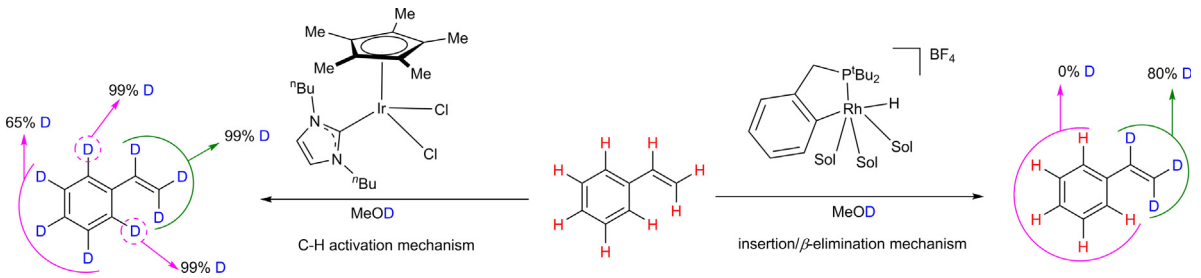
As we have showed above, metal–hydride complexes can catalyze the H/D exchange of olefins by a C–H activation mechanism instead of an insertion/β-elimination one. Indeed, it is also possible that a complex without hydride ligands, able to activate the C–H bond of an organic substrate, catalyzes the H/D exchange of olefins through an insertion/β-elimination mechanism. Typical examples of these catalysts are the half-sandwich complexes of the type $[Cp^RML^1L^2]$ that have been studied extensively as models for the C–H bond activation reaction [46]. A ligand could dissociate from these complexes, leading to an unsaturated species that can bind and activate the C–H bond of organic molecules to generate alkyl(aryl)–metal–hydride intermediates. If the complex activates the C–D bond of an appropriate deuterium source, it can generate an M–D complex potentially able to catalyze the H/D exchange of olefins through an insertion/β-elimination mechanism. A clear example of this type of reaction was presented for the first time in 1997 by Brookhart et al. [44h,j]. In this work, a $[Cp^*Co(CH_2{=}CH_2)_2]$ complex in C_6D_6 acting as both solvent and deuterium source was reported to catalyze the stoichiometric H/D exchange of the bonded ethylene. The use of an excess of ethylene suppresses completely the reaction, probably for the difficulty in losing an olefin to generate the 16-electron complex $[Cp^*Co(CH_2{=}CH_2)]$ able to start the reaction by C–D activation of the solvent. The use of a more labile olefin improves the reactivity of the system. In particular, the authors have showed that the complex $[Cp^*Co(CH_2{=}CH\text{-}Si(CH_3)_3)_2]$ favors the regioselective deuteration of trimethylsilylethylene in α-position (Scheme 37). In the proposed mechanism, the first step is the thermolysis of the $[Cp^*Co(CH_2{=}CHSi(CH_3)_3)_2]$ to produce the unsaturated complex **a**. Then the activation of the C–D bond of the solvent give rise to the in situ formation of the Co–D active species **b**. This compound reacts with the olefin for the formation of the most thermodynamically stable inserted anti-Markovnikov product (**c**), which is the key step for the regioselectivity of the catalytic outcome. In the last step, 2–D-trimethylsilylethylene is obtained by β-elimination on the alkyl ligand, and released by coordination exchange with a new olefin. The final reductive elimination of C_6D_5H permits the regeneration of the catalytic active species **a**.

In a similar fashion to the case of the Brookhart catalyst, other $[Cp^RML_2]$ systems have been studied with metals like Ir and Rh, showing in all cases the same reaction pattern [44i,o,s]. An interesting result was reported by Carmona et al. with their $[(\eta^5\text{-}C_5Me_4R)Rh(CH_2{=}CHSiMe_3)_2]$ (R = ^{t}But, 3,5-^{t}Bu$_2$C$_6$H$_3$, SiMe$_3$, SiMe$_2{}^t$Bu) complexes [44s]. In fact, the authors have found that these complexes are approximately by one order of magnitude more active in the H/D exchange of trimethylsilylethylene than the $[(\eta^5\text{-}C_5Me_5)Rh(CH_2{=}CHSiMe_3)_2]$. This result can be achieved thanks to the bulkier substituent in the Cp* ligand that enhance the rate of deuteration of the vinylic sites by increasing the dissociation of one olefin to form the unsaturated complex $[(\eta^5\text{-}C_5Me_4R)Rh(CH_2{=}CHSiMe_3)]$ that starts the H/D exchange reaction. The other interesting result is the increase in the α–β selectivity proportionally to the steric encumbrance of the Cp ligand (R = SiMe$_3$, SiMe$_2{}^t$Bu). The authors have proposed that this effect could be ascribed to the congested intermediate resulting from the Markovnikov addition (Scheme 38, **a**) due to the presence of bulky substituents in the Cp ligand that hinder the formation of the β-deuterated olefin.

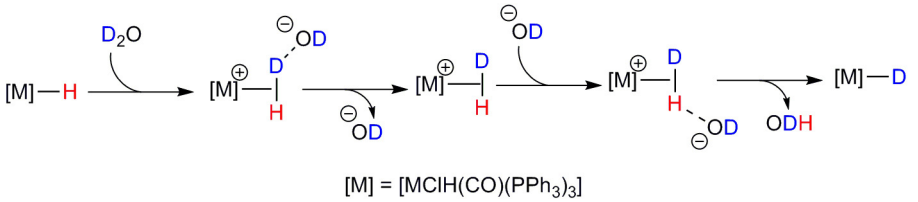
One of most interesting application of the catalytic system operating through the insertion/β-elimination mechanism is the H/D exchange of aromatic olefins. These types of substrates are very different from the aliphatic alkenes and often in the reaction medium can decompose or give oligomerization/polymerization products, which limits the use of catalytic systems that work in drastic conditions, like many catalysts operating through a C–H activation mechanism. Also, in some cases the presence of these types of substrates can poison the catalyst through a strong coordination with the metal, as observed by Nikonov with $[CpRu(P^iPr_3)H_3]$ [20k]. But the most important reason for choosing a catalyst that operates through



Scheme 38. (Color online.) Markovnikov (**a**) and anti-Markovnikov (**b**) insertion product of $[(\eta^5\text{-}C_5Me_4\ SiMe_3)Rh(C_6D_5)D]$ with $CH_2{=}CHSiMe_3$.



Scheme 39. (Color online.) H/D exchange of styrene mediated by a catalyst operating by C–H activation mechanism (left) or by insertion/β-elimination (right).



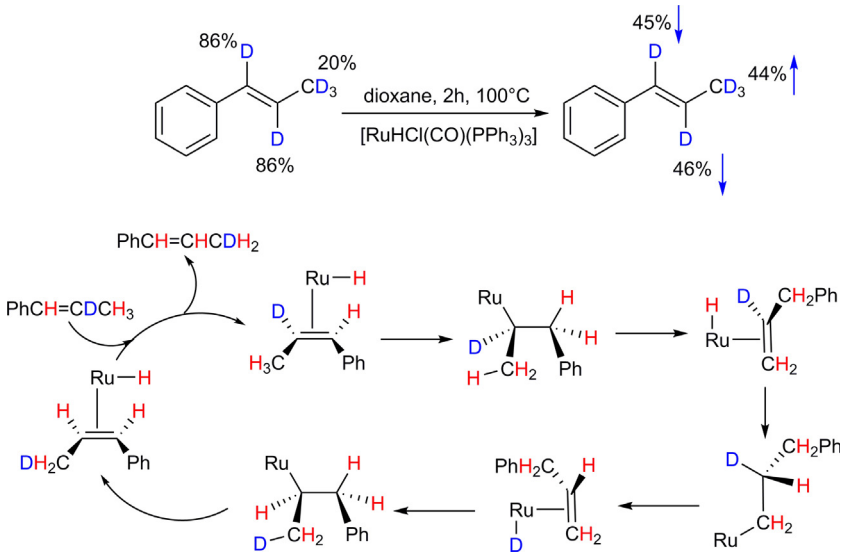
Scheme 40. (Color online.) Mechanism for the H/D exchange of [MHCl(CO)(PPh$_3$)$_3$] (M = Ru or Os).

an insertion/β-elimination mechanism instead of a C–H activation one is the selectivity for the vinylic deuteration, due to the fact that only an olefin moiety could insert into a metal–hydride bond. In fact, for the C–H activation mechanism the selectivity of the reaction depends on the activation energy of distinct C–H moieties, which is related to their dissociation energies. In the case of substrates with both aromatic and olefinic groups, where the C–H bond dissociation energy is comparable, the selective activation of the vinylic protons is problematic, as reported using the catalyst [Cp*IrCl$_2$(I$^{n\text{Bu}}$)] (Scheme 39, left part) [29v]. On the contrary, the use of metal–hydride species that proceed by the insertion/β-elimination mechanism, which is not operative for aromatic protons, can allow the selective vinylic deuterium labeling, as demonstrated in 2003 by Milstein (Scheme 39, right part) [44n].

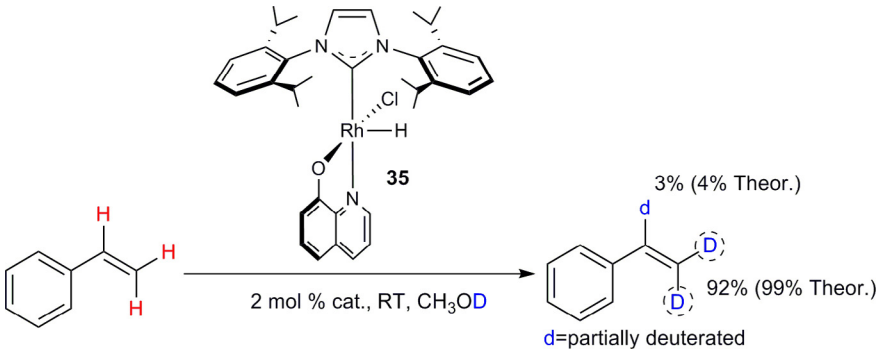
Jia et al. have recently extended this work by studying the H/D exchange of aromatic (and aliphatic) olefins with D_2O mediated by various M–H complexes containing Rh, Os or Ru [44t]. The authors have showed that complexes [RuHCl(CO)(PPh$_3$)$_3$] and [OsHCl(CO)(PPh$_3$)$_3$] are the most active catalysts in the selective H/D exchange of the vinyl portion of styrene, giving a percentage of deuterium incorporation close to the maximum value possible in the selected reaction conditions. These complexes exchange their hydride with the deuterium of the solvent to generate an M–D compound. The proposed mechanism for the deuteration of these saturated 18-electron complexes involves the formation of a dihydrogen, as observed for similar compounds (Scheme 40) [47].

The deuterated complexes showed in Scheme 40 catalyze the complete H/D exchange reaction of the vinylic portion of the styrene by cyclic steps of insertion and β-elimination, like the other systems showed above. Complex [RuHCl(CO)(PPh$_3$)$_3$] was also tested as a catalyst for the H/D exchange of other aromatic olefins, proving in every case to be totally selective for the vinylic hydrogens, giving excellent results for olefins lacking strong coordinating groups. This system is also active with the more inert internal alkenes as *cis*-stilbene. In this case, the complete deuteration of the olefinic hydrogen proceeds together with the isomerization of the double bound producing the d_2-*trans*-stilbene obtained probably through a mechanism similar to that already explained for the catalytic system studied by Cramer [44a]. Further experiments also demonstrated that the protons of the alkyl chain linked to a double bond could undergo an H/D exchange with D_2O as in the case of the *E*-β-methylstyrene, in which the terminal methyl was completely deuterated. In order to understand the mechanism of this transformation, a partially deuterated sample β-methylstyrene was treated with [RuHCl(CO)(PPh$_3$)$_3$] in dioxane at 100 °C without any additional deuterium source. The results of this experiment show that there is a shift of deuterium (and H) from the more enriched position to the other one (Scheme 41, top). The mechanism of this transformation, named by the authors 1,2-deuterium shift, consists in a simple series of insertion and β-elimination that allow the shift of a D (and H) along the olefinic carbon chain (Scheme 41, bottom).

One of the best advantages of the homogeneous catalysis is the possibility of obtaining a finely tuning of the system in order to get better catalytic performances in terms of activity, and especially selectivity. As showed above, Milstein and after Jia have demonstrated that Rh(III)–H complexes are able to catalyze the selective H/D exchange of the olefinic moiety of styrene with a protic deuterium source. In a recent work, Oro et al. showed that a Rh(III)–H complex bearing a bulky and strong σ-electron donor NHC as the IPr (IPr = 1,3-bis-(2,6-diisopropylphenyl)imidazol-2-carbene) and a chelating quinolinolate ligand are able to catalyze the same reaction with outstanding activity and a surprising selectivity for the β-vinyl protons of α-olefins (Scheme 42) [4,44u]. A similar selectivity was also reported by Bargon using RuH$_2$(PPh$_3$)$_4$,



Scheme 41. (Color online.) An example of 1,2-deuterium shift between C2–D and C3–H in β-methylstyrene mediated by [RuHCl(CO)(PPh_3)$_3$].



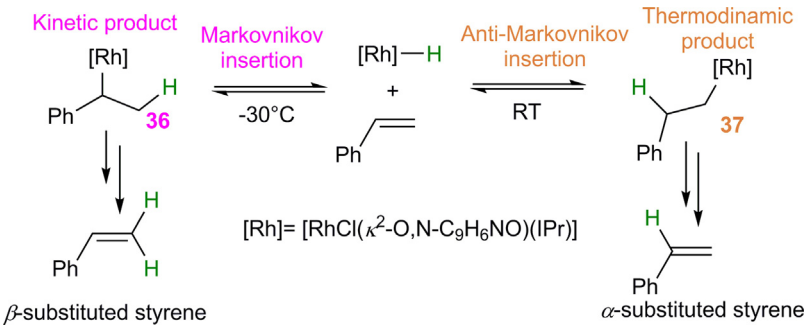
Scheme 42. (Color online.) Selective β-vinylic deuteration of styrene catalyzed by [RhClH(κ^2-O,N-C_9H_6NO)(IPr)] with CH_3OD. The deuteration percentage related to the maximum that is achievable in these reaction conditions is indicated in parentheses.

D_2 as deuterium source, and CO to inhibit the formation of the reduction of styrene [44k]. However, there are no reported data on the activity or selectivity of the system, nor any mechanistic explanation of the origin of the selectivity.

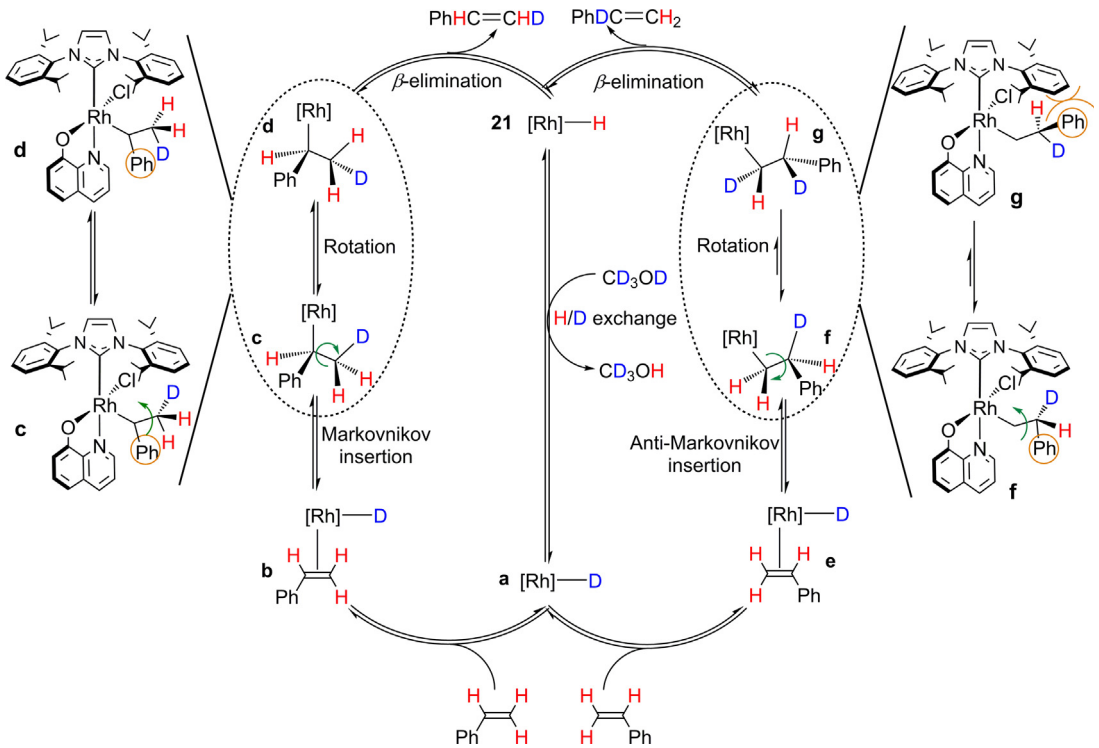
In order to understand the origin of the selectivity, both experimental and computational studies were carried out. The stoichiometric addition of styrene to **35** at −30 °C reveals the formation of a pair of diastereoisomers bearing a branched alkyl ligand generated by the Markovnikov insertion of styrene into the rhodium–hydride bond (Scheme 43, **36**). The same sample warmed at room temperature gives a new complex, the linear alkyl derivative from the anti-Markovnikov insertion (Scheme 43, **37**). This experiment provides two important results:

- the branched product obtained from the Markovnikov addition of the olefin in the Rh–H bond is obtained under kinetic control, whereas the linear product is thermodynamically favored;
- there is an equilibrium between the linear and branched product that allows their easy interconversion probably due to a series of β-elimination and insertion steps, connected by the Rh–H complex **35**.

The DFT calculation of this process agrees with the experimental results. In fact, the $\Delta E^{\ddagger}$ value of the 2,1 insertion is lower than that corresponding to the 1,2 insertion (6.8 and 9.2 kcal/mol, respectively), thus the Markovnikov addition is kinetically favored. However, the liner alkyl complex is much more stable with respect to the branched alkyl (−20.6 and −13.1 kcal/mol, respectively); therefore the anti-Markovnikov addition is thermodynamically preferred. It is important to remark that this two insertion complexes, in the presence of a deuterium source, are responsible for the production of the β-deuterated styrene from the branched Markovnikov complex and the α-deuterated styrene from the anti-Markovnikov insertion product. These observations suggest that in the reaction conditions (25 °C), in which the linear insertion product **37** is mainly present, the α-deuterated olefin should be obtained predominantly. This data could explain the selectivity showed by other similar M–H catalytic systems, but are in contrast with the



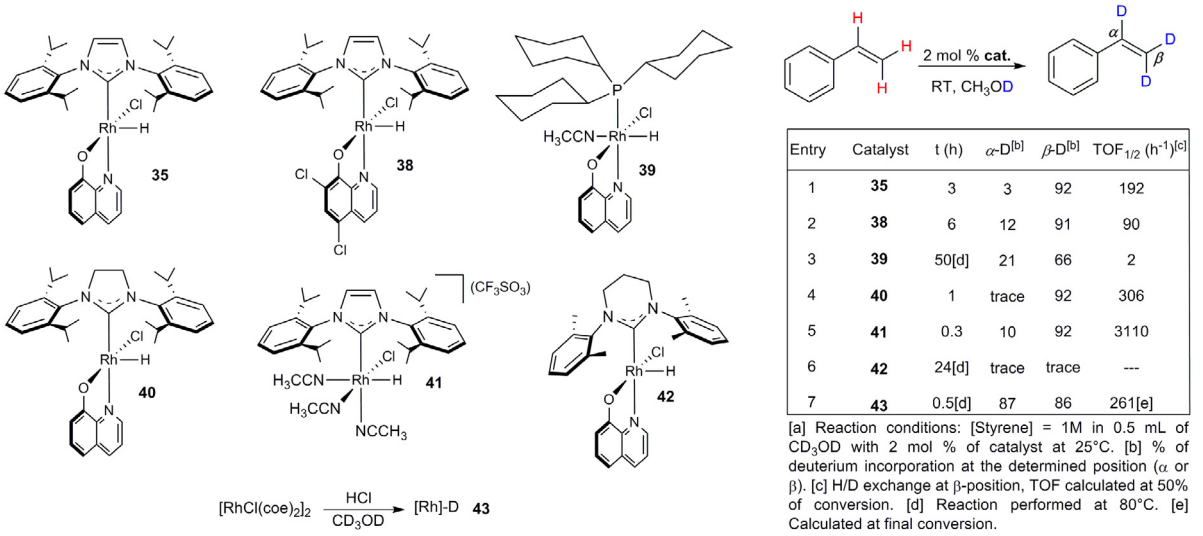
Scheme 43. (Color online.) Products of styrene insertion on [RhClH(κ^2-O,N-C_9H_6NO)(IPr)] at variable temperatures monitored by ^{1}H-NMR.



Scheme 44. (Color online.) Mechanism of H/D exchange of styrene catalyzed by [RhClH(κ^2-O,N-C_9H_6NO)(IPr)] with CD_3OD.

observed selective β-vinyl deuteration obtained with [RhClH(κ^2-O,N-C_9H_6NO)(IPr)].

The mechanism presented in Scheme 44 explains the observed selectivity. In the first step, the H/D exchange of the [Rh]–H by the solvent leads to the formation of the deuterated [Rh]–D species **a**. The experimental data show that the exchange takes place only between the complex and the protic deuterium atom of the methanol; in fact, the use of CH_3OD instead of CD_3OD leads to the same results. This evidence, combined with the observation of the quick deuteration of the hydride of the complex when it is in a d_4-methanol solution, suggests that deuteration occurs through a fast acid–base reaction between methanol and the hydride [48]. Complex **a** can now bind and insert an olefin, giving the branched product **c** by Markovnikov insertion or the linear complex **f** from the anti-Markovnikov insertion. The key step of this mechanism is the rotation around the bond C(1)–C(2), which is required to exchange the H and D position prior to H/D substitution. In the case of **f**, the steric hindrance imposed by the substituents of the NHC ligand restricts this rotation due to repulsion with the isopropyl–phenyl group of the alkyl ligand (**g**). For this reason, even if a deuterium atom can enter the benzyl position of the styrene, the hydride cannot easily leave. The transition state for this rotation is highly energetic and could not be determined by DFT calculations. Instead, the Markovnikov insertion process leads to a CH_2D terminal group (**c**) for which rotation around the C(1)–C(2) axis is not problematic as showed by the DFT calculation that provide a $\Delta E^{\ddagger}$ of the rotation of only 3.5 kcal·mol^{-1}. For this reason, the exchange between proton and deuterium orientations is easily achievable and the subsequent β-elimination produces the elimination of the deuterated styrene at the β-position in either a *cis* or *trans* position,



Entry	Catalyst	t (h)	α-D[b]	β-D[b]	TOF1/2 (h-1)[c]
1	**35**	3	3	92	192
2	**38**	6	12	91	90
3	**39**	50[d]	21	66	2
4	**40**	1	trace	92	306
5	**41**	0.3	10	92	3110
6	**42**	24[d]	trace	trace	---
7	**43**	0.5[d]	87	86	261[e]

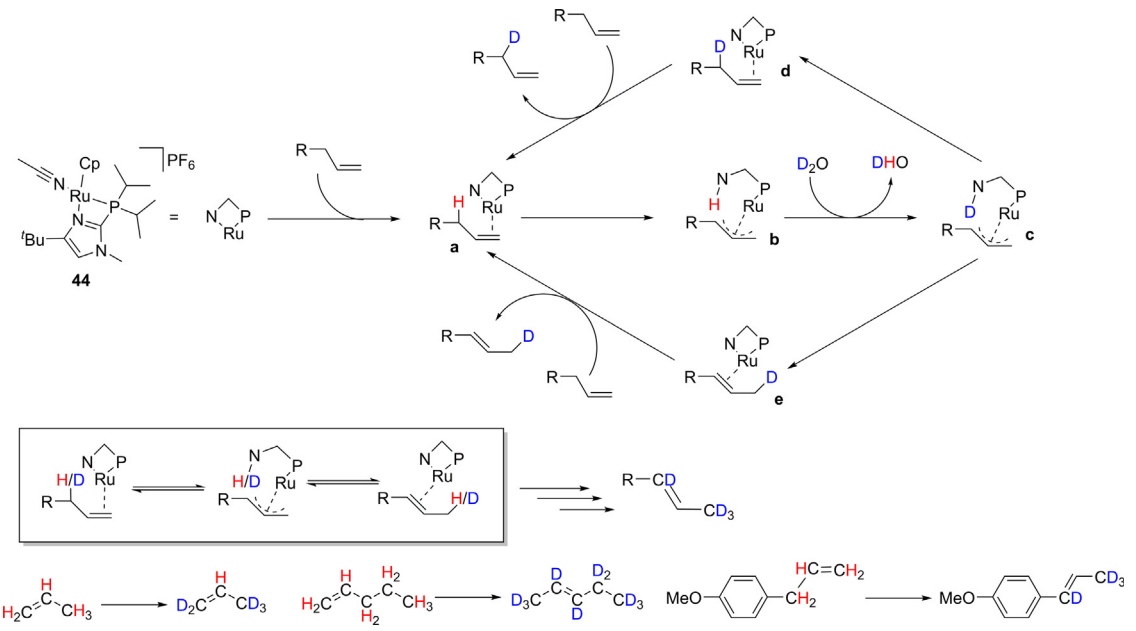
[a] Reaction conditions: [Styrene] = 1M in 0.5 mL of CD_3OD with 2 mol % of catalyst at 25°C. [b] % of deuterium incorporation at the determined position (α or β). [c] H/D exchange at β-position, TOF calculated at 50% of conversion. [d] Reaction performed at 80°C. [e] Calculated at final conversion.

Scheme 45. (Color online.) H/D exchange of styrene with CD_3OD mediated by various Rh–H complexes.

thereby explaining the similar rate observed for H/D exchange for both *cis* and *trans* protons.

In a recent work, we have studied the influence of the various ancillary ligands within a [Rh–H] framework in the catalytic H/D exchange of styrene with CD_3OD [44u]. In particular, we selected ligands having well-defined electronic and steric properties in order to establish a relationship between the structure of the complex and its catalytic activity in the H/D exchange of styrene. These studies have showed that the modifications in the rhodium coordination sphere lead to a deep change in the activity and selectivity of the catalyst. A selection of the most important results is showed in Scheme 45. One of the most interesting results is that the presence of a bulky and strong σ-donor ligand as the NHCs is fundamental for both activity and selectivity. In fact, the catalytic system **43**, a "naked" Rh–H species, catalyzes the H/D exchange of the vinylic part of the styrene without any selectivity between the α or β position (entry 7). Replacing a NHC with a basic phosphine such as the PCy_3, the activity of the catalyst falls down probably for the weaker electron donor ability of this ligand (complex **39**, entry 3). Also, α/β selectivity decreases, probably for the geometry of the phosphine in which the substituent pointing out of the coordination plane, in contrast with the NHC in which the substituent adopts an umbrella-like arrangement that increases the steric hindrance on the metal. Decreasing the electron density provided from the 8-quinolinolate ligand (complex **38**, entry 2) results also in a slight decrease in activity and selectivity. The substitution of the IPr ligand (complex **35**, entry 1) by the similar SIPr (1,3-bis-(2,6-diisopropylphenyl)imidazolidin-2-carbene) (complex **40**, entry 4) that is a stronger electron-donating ligand increases the activity of the catalytic system and in our reaction conditions proved to be completely selective for the H/D exchange of the β-position. A very bulky and good σ-donor ligand as 2,6-(dimethylphenyl)tetrahydropyrimidin-2-carbene (SPXyl) makes complex **42** totally inactive (entry 6). Our experimental data showed that the hydride ligand bonded to **42** does not undergoes H/D exchange in CD_3OD, most probably for the excessive steric hindrance that this ligand provides. Finally, complex **41** that does not contain the chelate 8-quinolinolate ligand showed an outstanding catalytic activity that is more than by one order of magnitude higher than **35**. The excellent catalytic activity of this complex could be related to the presence of labile acetonitrile ligands that facilitate olefin coordination and insertion processes, but the same effect leads to a loss of the selectivity (10% of α-deuteration).

As we have just showed, the ligands bonded to the metal center play a fundamental role in the modulation of the catalytic performances of the complexes, changing both the electron density and the steric hindrance on the metal. In some cases, the ligand could have also a more "active" role, directly participating in various steps of the reaction mechanism. A paradigmatic case was showed by Grodjahn et al., who developed a catalytic system based on a Ru complex (**44**) able to catalyze the deuteration/isomerization of olefins with D_2O (Scheme 46) [44q,r]. In the proposed catalytic cycle (Scheme 46), after coordination of the alkene (**a**), the chelated ligand acts as an internal base, deprotonating the allylic proton of the olefin, and leading to the allyl complex **b**. The acid/base exchange with the deuterated solvent allows the deuteration of the N–H (**c**) that can re-protonate the C(3), giving **d** or C(1), leading to **e**. Exchange with other olefins generates the 3-deuterated alkene, or the isomerized product of deuteration in C(1) position. The isomerization process described in the box of Scheme 46 is responsible for the complete deuteration of the hydrogen of the allyl moiety, and for the generation of the final internal olefin. This catalytic pathway is totally consistent with the deuterated product obtained as showed at the bottom of Scheme 46. In the case of symmetric propene, 1,3-trideutero-propene is obtained without any deuteration in C(2). Also, for 4-allylanisol, the H/D exchange occurs only in the C(1) and C(3), but in this case the final product is the isomerized trans-anethole. Finally, 1-pentene was fully deuterated, presumably



Scheme 46. (Color online.) Ligand-assisted isomerization and deuteration of alkenes.

η^3-allyl intermediates formed along the chain, allowing all positions to become allylic through isomerization.

6. Concluding remarks

Transition metal complexes can be very effective for the labelling of organic molecules with high regio- and stereoselectivity under mild conditions. A complete understanding of the mechanism of H/D exchange of organic substrates is crucial for the development of more effective catalysts. Three main mechanisms of reaction for H/D exchange catalyzed by complexes of transition metals are operative: (a) Lewis acid–base catalysis; (b) C–H activation; (c) insertion/β-elimination. For each one of these mechanisms, the various reaction steps have been explained, underlining the critical points that determine the rate and selectivity of the reaction. In particular, the fundamental role of the catalyst used has been showed, as well as how the choice of the metal influences the type of reaction mechanism, and thus the final products. Finally, it has been showed that a careful choice of the ligands, which influences the stereo-electronic characteristics of the complex, is essential for a fine tuning of the catalytic performance. The better understanding of these different processes and of the factors that govern them can lead to a future rational design of an array of organometallic catalysts able to provide deuterated compounds *à la carte* as a function of needs.

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