H/D Exchange

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The Renaissance of H/D Exchange

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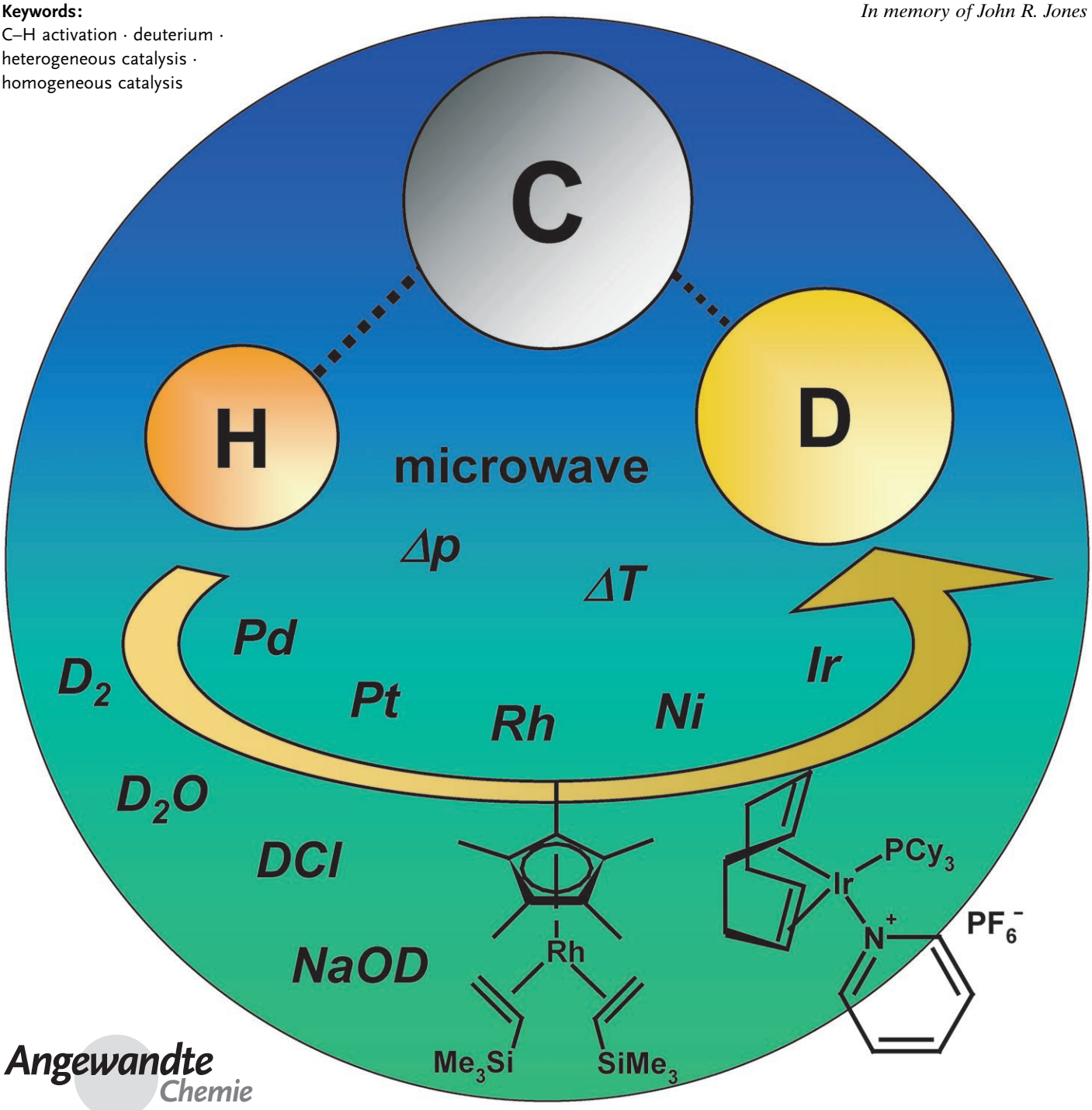
C–H activation · deuterium · heterogeneous catalysis · homogeneous catalysis

In memory of John R. Jones



The increasing demand for stable isotopically labeled compounds has led to an increased interest in H/D-exchange reactions at carbon centers. Today deuterium-labeled compounds are used as internal standards in mass spectrometry or to help elucidate mechanistic theories. Access to these deuterated compounds takes place significantly more efficiently and more cost effectively by exchange of hydrogen by deuterium in the target molecule than by classical synthesis. This Review will concentrate on the preparative application of the H/D-exchange reaction in the preparation of deuterium-labeled compounds. Advances over the last ten years are brought together and critically evaluated.

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1. Introduction

H/D-exchange reactions at carbon centers[1] are of interest in many respects, whether it be for the preparation of isotopically labeled compounds, in basic research on C–H bond activation,[2] or in mechanistic investigations on catalysts and reaction pathways.[3]

A period of intensive research in the 1960s and 1970s was followed by a much quieter time in the field of H/D-exchange reactions. It was not until the mid-1990s that the area experienced a renaissance as a result of the growing interest in catalytic C–H bond activation and the increasing demand for isotopically labeled compounds as reference materials in mass spectrometry.

The use of isotopically labeled internal standards is of particular advantage in the investigation of environmental, animal, and human samples in which matrix effects[4] can interfere with the quantification of toxins. This is because these effects can be almost totally excluded by the physical and chemical similarity of the substance under investigation and the standard. These compounds generally display the same retention and ionization behavior in LC/MS, but differ on account of their mass difference. If this mass difference is selected to be large enough to keep signal overlap, as a result of the natural isotope pattern, as low as possible, quantitative determination is possible.[5]

Furthermore, as a consequence of the rapid development of higher performance mass spectrometers and their widespread use, the demand for isotopically labeled internal standards has risen. Basically, two strategies are followed for the synthesis of isotopically labeled compounds. Thus, starting from commercially available, stable isotopically labeled precursors, both ^{2}H-, as well as ^{13}C- and ^{15}N-labeled compounds, can be prepared by conventional synthesis. The latter are also useful for in vivo studies, where deuterium-labeled compounds cannot be used because of the possibility of a different metabolism in comparison with the parent compound, or possible metabolic loss of deuterium.[6] However, long synthetic routes and the high costs of ^{13}C- and ^{15}N-labeled starting materials must often be taken into account. In contrast, a molecule can be labeled considerably more rapidly and cost effectively by the direct exchange of a hydrogen atom (bonded to a carbon atom) by a deuterium atom. Since these exchange reactions can often be carried out directly on the target molecule or a late intermediate in the synthesis, and deuterium-containing reagents such as D_2O or D_2 gas can be used as the deuterium source, this method is particularly efficient for the synthesis of deuterated organic compounds. Deuterium can be inserted into a molecule by halogen/deuterium exchange[7] or by reductive deuteration,[8] although suitable precursors must frequently first be prepared. In recent years, the introduction of automated parallel synthesis and the further development of laboratory microwave apparatus have resulted in a plethora of studies on the preparation of deuterated substances by H/D exchange. The commercial interest in these approaches is evident from a series of patents.[9]

In addition to the deuteration of organic molecules, exchange reactions have also been employed for the introduction of tritium (^{3}H, T). Here, H/D-exchange reactions are frequently used as models for synthesis optimization for tritiation. Radio-labeled pharmaceutical candidates of this type are used, for example, for pharmacokinetic and metabolic studies as part of drug development.[10]

The known methods for H/D exchange are divided into two classes: 1) pH-dependent H/D exchange and 2) metal-catalyzed H/D exchange (homogeneous/heterogeneous catalysis; Figure 1).

2. pH-Dependent H/D Exchange

H/D-exchange reactions that are pH-dependent count amongst the oldest methods used in this area.[11] From a mechanistic point of view, acid- or base-catalyzed enolization forms the basis of these reactions, for which reason H/D

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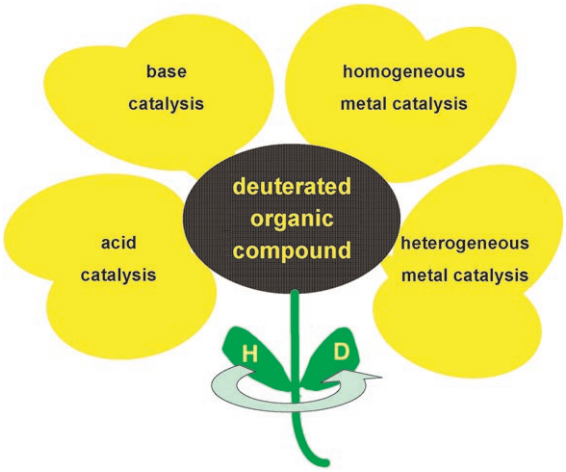
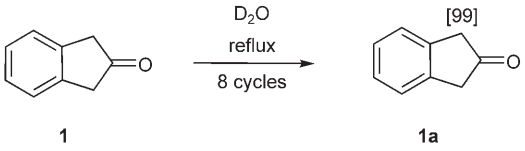


Figure 1. Methods for H/D exchange.

exchange at activated positions in particular can be achieved by the use of deuterated Brønsted acids or bases. Since the reverse exchange of deuterium for hydrogen can of course take place, further chemical steps are often necessary to achieve deactivation.

2.1. H/D Exchange without the Addition of Acid or Base

H/D-exchange reactions without the addition of acids and bases are characterized by the acidic CH position being deuterated simply by the use of deuterium oxide, which, because of its autoprotylic equilibrium can act as either an acid or a base. Thus, for example, in the synthesis of [1,1,3,3-D_4]2-indanone (**1a**) a high degree of deuteration was achieved simply by repeated heating in D_2O (Scheme 1).[11c]



Scheme 1. H/D exchange of 2-indanone (**1**) in D_2O. The number in brackets gives the percentage fraction of deuterium [% D].[12]

In other cases, H/D exchange was achieved under drastic conditions with very high selectivity. Thus Werstiuk and Ju reported that pyridine derivatives in D_2O incorporated several deuterium atoms without the addition of acid or base.[13] In the H/D exchange with 2-hydroxypyridine (**2**) or 2-mercaptopyridine (**3**), for example, the exchange was highly regioselective and the hydrogen atoms in positions C3, C5, and C6 were exchanged preferentially in both compounds (Scheme 2). The reactions were carried out in sealed vessels at temperatures between 200 and 260 °C.

A further variant is the H/D exchange in supercritical media. Junk and Catallo showed that different arenes were accessible by exchange reactions with D_2O in autoclaves at 380–430 °C. Thus, an almost complete incorporation of deuterium was achieved (> 98 % D) in the exchange reaction

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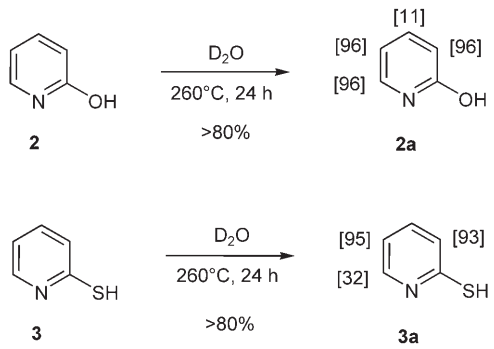
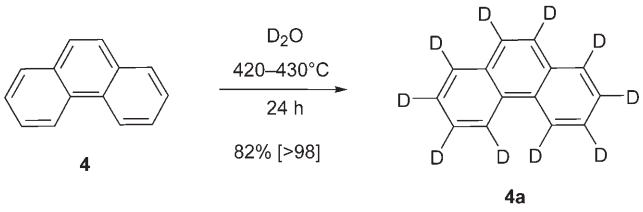


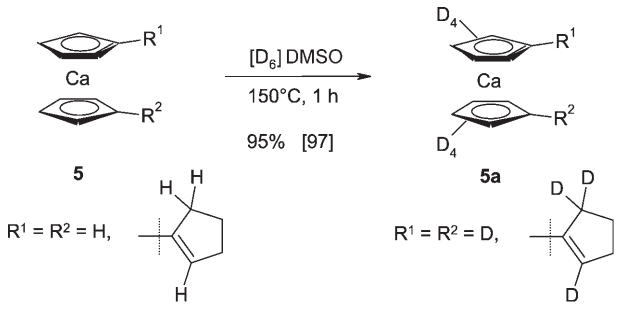
Scheme 2. H/D exchange of pyridine derivates in D_2O.

of phenanthrene (**4**, Scheme 3). In many cases, the reaction was repeated several times to achieve the reported deuterium content. However, whereas this method gave good results in the case of 1-methylnaphthalene, *n*-butylbenzene, and aniline, only decomposition products were obtained with benzothiazole, azobenzene, and phenylacetic acid.[14]



Scheme 3. H/D exchange of phenanthrene (**4**) under supercritical conditions.

Shapiro et al. have described an efficient method for the deuteration of cyclopentadienyl (Cp) ligands in unbridged calcocenes **5**. The hydrogen atoms of substituted and nonsubstituted Cp ligands **5** could be almost completely (97% D) exchanged for deuterium in [D_6]DMSO in a closed vessel at 150°C. Furthermore, it was possible to deuterate substituents on the Cp ring at those positions that are π-conjugated with the cyclopentadiene moiety through a fulvene tautomer (Scheme 4).[15] This method is an alternative to the acid-catalyzed H/D exchange at Cp ligands[16] (Section 2.2), since the deuterated Cp rings in **5a** can be transferred to other transition metals (for example, iron) without loss of deuterium.



Scheme 4. Noncatalyzed H/D exchange of calcocenes in [D_6]DMSO.

More recently, microwaves have been increasingly used in exchange reactions since, compared to conventional heating conditions, higher or comparable degrees of deuteration can be achieved, often with shorter reaction times. Thus, for example, several MS standards of the glycopeptide bleomycin A2 were prepared by two-minute heating in D_2O at 165°C.[17] Furthermore, several physicochemical contributions have appeared in which the kinetics of uncatalyzed H/D exchange have been discussed and energetic investigations carried out.[18]

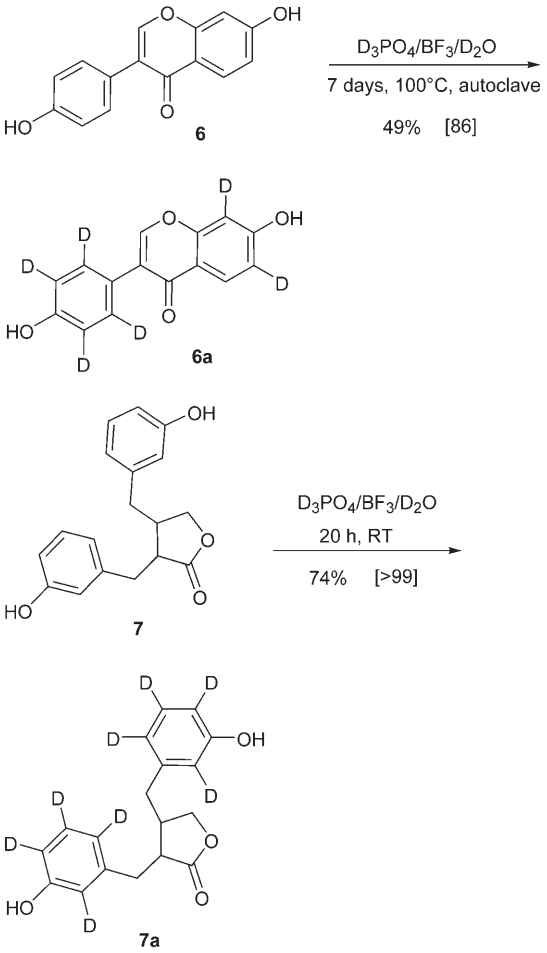
2.2. Acid-Catalyzed Methods

Strong deuterated Brønsted acids or alternatively Lewis acids, in combination with a deuterium source, are used for the incorporation of deuterium into aromatic compounds. The research group of Wähälä described a combination of both deuteration methods for polyphenolic substrates such as flavonoids, isoflavonoids, and lignans, in which a mixture of D_3PO_4, BF_3, and D_2O[19] are used.[20] After several reaction cycles over a period of one to four days at temperatures between 20 and 55°C, good yields and high degrees of deuteration are achieved at activated positions in the arene.[20a–c] Positions that are less readily accessible for an electrophilic aromatic substitution show a lower tendency for exchange under these conditions. However, it has been demonstrated in the case of daidzein (**6**) that, under more drastic conditions of 100°C in an autoclave, these positions can also be deuterated.[20d] In the case of enterolactone (**7**), complete exchange (> 99% D) of all protons on the aromatic ring took place in good yields even at room temperature, including the unactivated *meta* positions. In contrast, the hydrogen atoms of the aliphatic residues did not exchange under acidic conditions (Scheme 5).[20e]

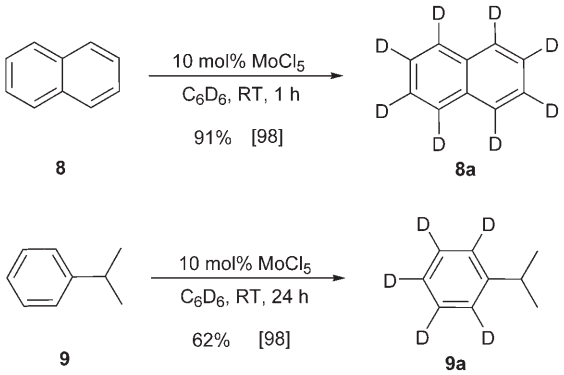
H/D-exchange reactions in the presence of Lewis acids such as $AlBr_3$, $EtAlCl_2$, or $MoCl_5$ are, in contrast, restricted to nonpolar arenes (for example, naphthalene (**8**) or isopropylbenzene (**9**)). However, with [D_6]benzene as the deuterium source, complete exchange of all hydrogen atoms on the aromatic rings is observed for these substrates (Scheme 6). In contrast, arenes such as phenol, anisole, aniline, benzaldehyde, or benzoic acid are not amenable to H/D exchange—to the extent that they inhibit the deuteration of other arenes through the complexation of the Lewis acid.[21]

Heinkele and Mürdter used a 50- to 100-fold excess of pyridinium deuterochloride in a melt at 220°C for H/D exchange. With the example of dextromethorphan (**10**; Scheme 7), it was demonstrated that a better yield and a higher degree of deuteration could be obtained in shorter reaction times than with D_2SO_4. As a result of concomitant O-demethylation, dextrorphan (**11**) was obtained in good yields with high deuterium content at the aromatic positions.[22]

Catalytic amounts of D_2SO_4 in D_2O have been used in the deuteration of imidazole and 2-methylimidazole. Thus, after four hours at 200°C in a pressure vessel and two reaction cycles, both the aromatic positions and the methyl substituent were more than 90% deuterated.[23] The use of catalytic



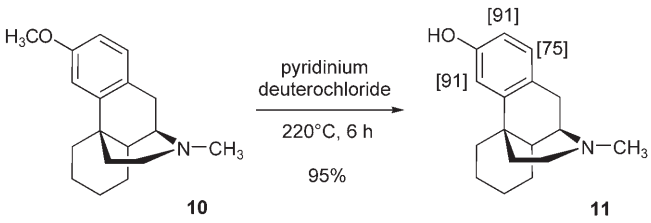
Scheme 5. H/D exchange of the polyphenols **6** and **7** with $D_3PO_4/BF_3/D_2O$ according to Wähälä et al.[20]



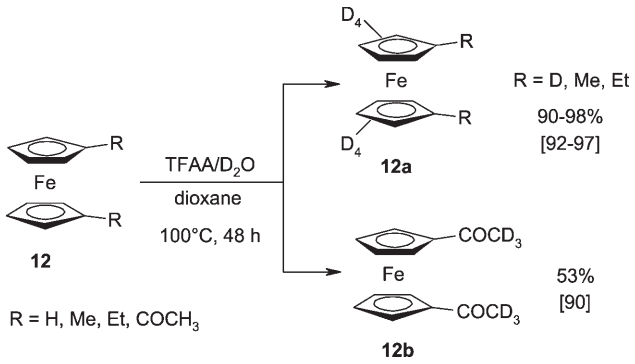
Scheme 6. H/D exchange of nonpolar arenes catalyzed by Lewis acids.

amounts of deuterosulfuric acid significantly restricted the extent of undesirable electrophilic aromatic sulfonation.

In most acid-catalyzed H/D-exchange reactions, a modest regioselectivity is observed. The influence of substituents on the regioselectivity was investigated in the acidic H/D exchange on ferrocenes (**12**) with trifluoroacetic anhydride (TFAA) in D_2O (Scheme 8). Whereas alkyl substituents favored the electrophilic aromatic deuteration of the cyclopentadienyl rings, enolization of the ketone resulted in



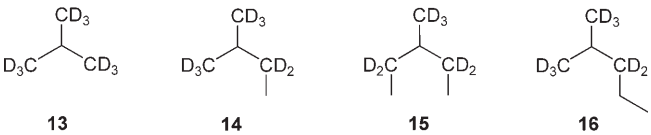
Scheme 7. H/D exchange and O-demethylation of dextromethorphan (**10**).



Scheme 8. Regioselectivity in the acid-catalyzed H/D exchange of ferrocenes **12**.

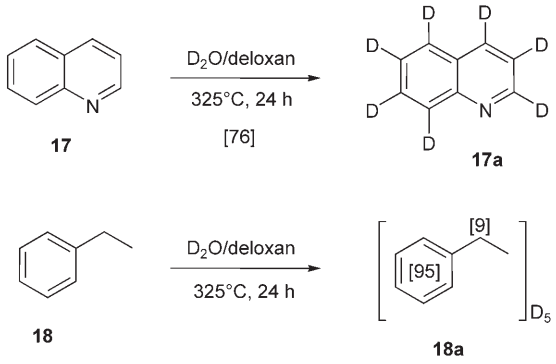
selective and complete exchange of all three hydrogen atoms of the acyl residue.[16a] The TFAA/D_2O system is a better method for the deuteration of ferrocene than earlier methods in which the use of $Ca(OD)_2$[16b] led to considerable decomposition, or the use of D_3PO_4,[16c] which required more than two reaction cycles. The deuteration agent is simply prepared in situ by mixing the two reagents in an open reaction vessel.[16a,d]

As part of their investigations into C–H bond activation of hydrocarbons, Sommer et al. described a series of isotope-exchange reactions with D_2O-treated support-bound reagents, such as zeolites or sulfated zirconium dioxide. These acid catalysts were first activated with dry nitrogen at 500 °C before the reaction. The conversion of short-chain (and mainly gaseous) alkanes then took place over one hour with 3 mol% of D_2O in N_2 at 25–200 °C.[24] In agreement with the results of Otvos et al.[25] for the H/D exchange of the selected isoalkanes **13**–**16** with D_2SO_4, regioselective isotope



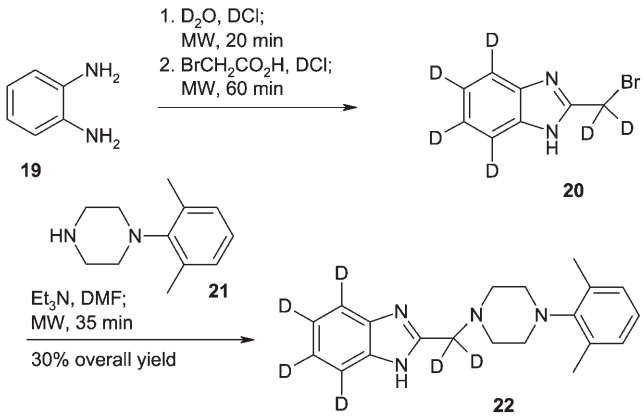
exchange was also observed with support-bound acids. Under the conditions described, those hydrogen atoms connected to carbon atoms that were situated near a tertiary center were exchanged most rapidly. In contrast, H/D-exchange reactions with linear hydrocarbons required higher temperatures (>200 °C). The advantage of support-bound acids over the liquid sulfuric acid lies in the prevention of oligomerization.

Boix and Poliakoff reported polymer-bound sulfonic acids (deloxan), which they used for the deuteration of aromatic compounds. Thus in the reaction of quinoline (**17**) or ethylbenzene (**18**), excellent deuterium incorporations were obtained in supercritical D_2O at 325 °C (Scheme 9).[26]



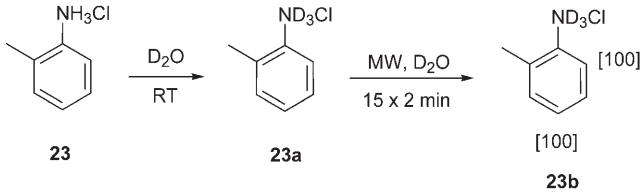
Scheme 9. H/D exchange of the arenes **17** and **18** under acid-catalyzed, supercritical conditions.

Acid-catalyzed H/D exchange may be greatly accelerated by microwave irradiation. In a few cases, when compared with conventional heating, the reaction time can be shortened from days to a few minutes with comparable deuterium incorporation.[27] Hence in aromatic rings, protons in the positions *ortho* or *para* to electron donors can be exchanged by electrophilic aromatic substitution. This method was used in the stable isotope labeling of the dopamine agonist ABT-724 (**24**, Scheme 10).[27d]



Scheme 10. Microwave (MW) assisted, acid-catalyzed H/D exchange in the synthesis of the dopamine agonist ABT-724 (**22**).

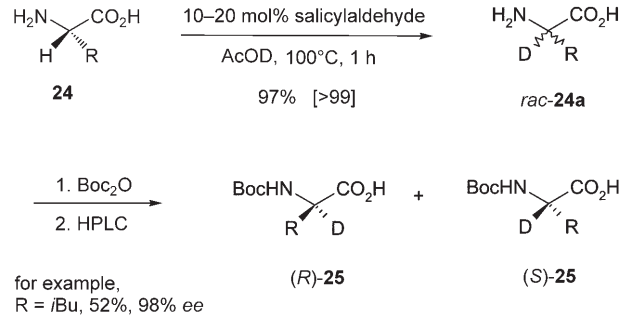
Deuterated Brønsted acids such as DCl, D_2SO_4, AcOD, CF_3CO_2D, or their mixtures find frequent use as deuteration agents in microwave-assisted, acid-catalyzed exchange reactions. One variant, which uses only D_2O during the deuteration process, was demonstrated by Jones and co-workers[28] with the hydrochloride salt of 2-methylaniline (**23**) (Scheme 11). The method was also subsequently applied to aminopyridine derivatives.[29] To avoid any simultaneous competing proton sources, the labile hydrogen atoms bound



Scheme 11. Microwave-supported H/D exchange of 2-methylaniline hydrochloride (**23**).

to the nitrogen atom were exchanged by prior treatment with D_2O. Deuteration was complete within a few minutes and, depending on the substrate, a high deuterium content was achieved at the positions *ortho* and *para* to the amino group.

Lämmerhofer et al. exploited the readily achieved racemization of α-amino acids (**24**; for example, alanine, leucine, phenylalanine) for acid-catalyzed deuteration. With an excess of [D_1]acetic acid and catalytic amounts of aldehyde, the reactions take place in good yields with a deuterium incorporation of more than 95% via the corresponding Schiffs Base (Scheme 12). After conversion into the *tert*-butoxycarbonyl (Boc) protected derivative **25**, the resulting enantiomeric mixture *rac*-**24a** was separated by preparative HPLC on a chiral stationary phase.[30]

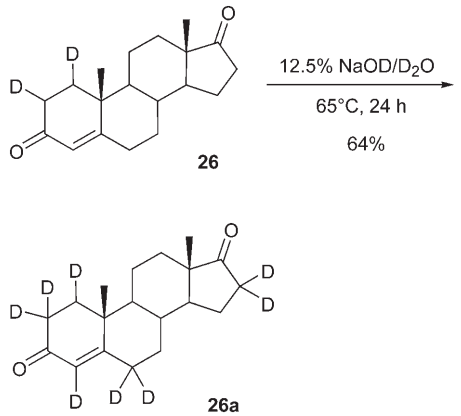


Scheme 12. Acid-catalyzed deuteration of α-amino acids.

2.3. Base-Catalyzed Methods

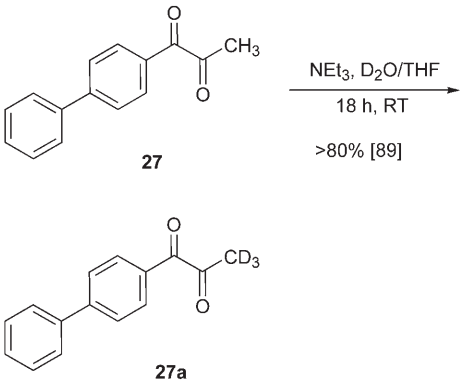
Base-catalyzed H/D-exchange reactions also provide a facile method for the exchange of acidic hydrogen atoms for deuterium by means of keto–enol equilibria. In carbonyl compounds such as ketones,[31] aldehydes,[32] esters,[33] and carboxylic acids,[34] the acidic C–H hydrogen atoms are exchanged with high selectivity (> 90% D) and yield. The γ hydrogen atoms in α,β-unsaturated ketones are also accessible for isotope exchange through conjugation, as was demonstrated on the steroid framework of androstendione (**26**; Scheme 13), testosterone, and cortisone. The conversions were carried out with alkali deuteroxides in D_2O at temperatures between 25 and 100 °C. In instances that required an anhydrous medium, sodium methoxide in MeOD proved to be a viable alternative.[33a,35]

Berthelette and Scheigetz have achieved good success in the deuteration of the methyl group of aryl methyl ketones[31d] and aryl methyl sulfones[36] with the use of tertiary amines as basic catalysts. Here, the efficiency and rate of exchange



Scheme 13. Aqueous base-catalyzed deuteration of androstenedione (**26**).

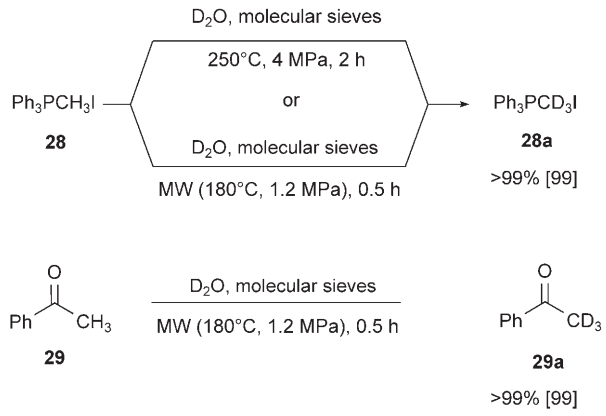
depended greatly upon the base, the substrate, and the solvent. With high conversion rates the incorporation of deuterium with both classes of compounds lay between 89 and 100% with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). In most cases, a lower deuterium uptake was achieved in the corresponding H/D exchange with triethylamine. However, it was possible to deuterate the methyl group of the base-sensitive ketone **27** without decomposition by the addition of triethylamine (Scheme 14).



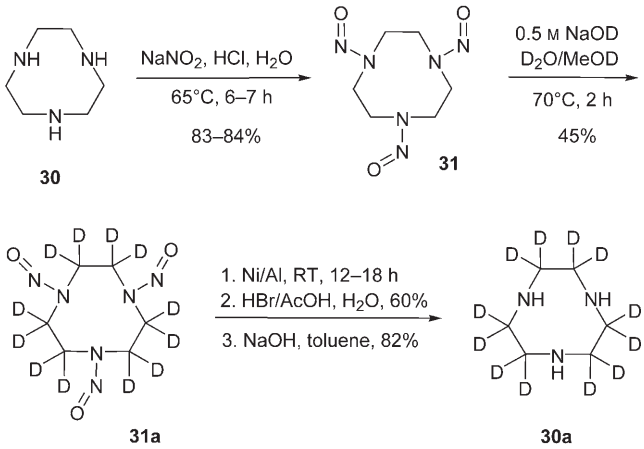
Scheme 14. Deuteration of the base-sensitive diketone **27**.

An interesting extension of the methodological spectrum of H/D exchange is the addition of molecular sieves, as described by Matsubara and co-workers. They demonstrated that the α positions of Wittig salts (**28**) and acetophenone (**29**) are quantitatively exchanged when molecular sieves are added to the aqueous medium. Reaction times can be significantly reduced by microwave activation (Scheme 15).[37]

A simple approach to the deuteration of the α position of secondary amines has been described by Cornia and co-workers. Nitrosation of the three amine groups of 1,4,7-triazacyclononane (**30**) increased the acidity of the α-methylene hydrogen atoms to such an extent that they could be exchanged for deuterium by base catalysis (Scheme 16). The low yield is attributed to decomposition of the nitrosated macrocycle **31**/**31a** in alkaline solution. Subsequent denitrosation with Raney nickel generated in situ can also be carried



Scheme 15. Molecular-sieve-mediated exchange of phosphanes and ketones in D_2O.



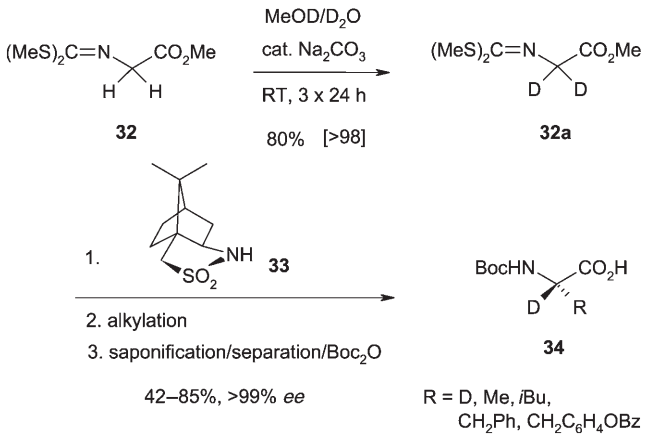
Scheme 16. Base-catalyzed deuteration of the azacrown ether **30**.

out without isolation of **31a** by the direct addition of Ni–Al alloy to the alkaline reaction solution, when the perdeuterated azacrown ether **30a** was obtained with a deuterium content of 90%.[38]

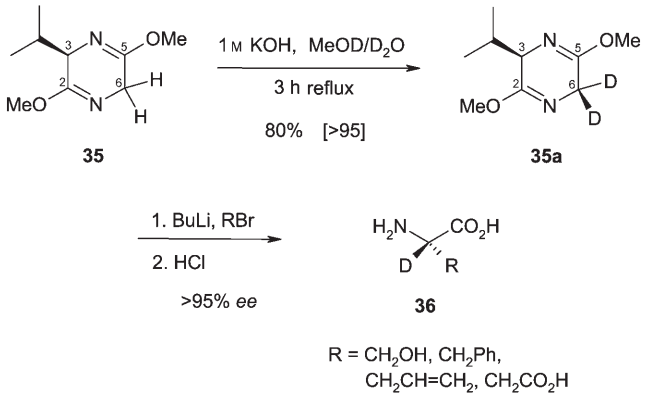
Base-catalyzed methods for the synthesis of enantiomerically pure α-deuterated amino acids are frequently based on the use of glycine or glycine derivatives, which are first subjected to a basic H/D exchange. The desired side chains of the amino acids are then inserted stereoselectively with the aid of chiral auxiliaries.[40,43,44]

Elemes and Ragnarsson deuterated the glycine derivative **32** with MeOD/D_2O using catalytic amounts of Na_2CO_3 as a base, and after three reaction cycles they obtained a deuterium content of greater than 98% D. The deuterated intermediate **32a** was reacted with the Oppholzer sultam (**33**)[39] to provide a substrate for the subsequent stereoselective alkylation. After cleavage of the auxiliary, the chiral Boc-protected amino acids **34** (glycine, alanine, leucine, phenylalanine, *O*-benzyltyrosine) were isolated almost enantiomerically pure (>99% *ee*) in high yield (Scheme 17).[40]

Based on the bislactim ether method of Schöllkopf et al.,[41] Gani and co-workers developed a base-catalyzed deuteration of the C6-position of the dihydropyrazine **35** in boiling MeOD/D_2O (Scheme 18). As expected, no H/D



Scheme 17. Synthesis of α-deuterated amino acids **34** with the Oppholzer sultam (**33**). Bz = benzoyl.

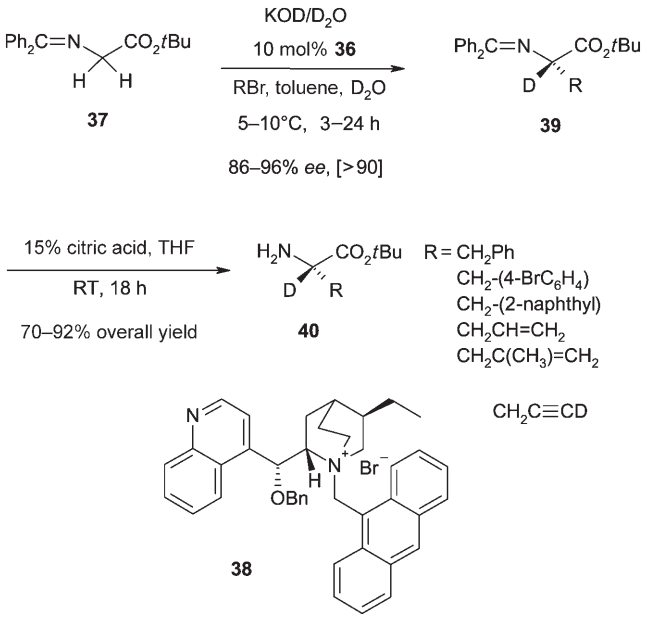


Scheme 18. Synthesis of α-deuterated amino acids **36** with the Schöllkopf bislactim ether.

exchange was observed at the C3-position owing to steric shielding by the isopropyl group in the transition state. The [6-D_2]isotopologue[42] **35a** was then alkylated stereoselectively at the C6-position, thereby giving access to a series of α-deuterated α-amino acids **36** (serine, phenylalanine, allylglycine, aspargic acid) in moderate to good yields with high degrees of deuteration and enantiomeric excesses (> 95 %).[43]

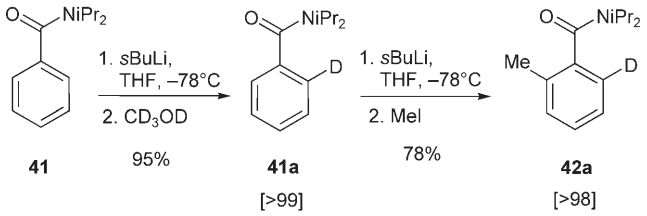
A further enantioselective synthesis of α-deuterated l-α-amino acids (Scheme 19) takes place by asymmetric alkylation of the activated glycine **37** with the aid of the chiral phase-transfer catalyst **38**. The H/D exchange with KOD in D_2O and the introduction of the respective amino acid side chain were thereby carried out in a single reaction step. After mild hydrolysis of the imine **39**, the *tert*-butyl esters of the amino acids **40** were isolated in good overall yields and with a deuterium incorporation of more than 90 %.[44]

In addition to H/D exchange based on keto-enol tautomerism, the deuterolysis of an organometallic compound can also be employed for the synthesis of deuterated compounds. Here, the intermediate organometallic species is generated by deprotonation with strong bases (for example, Grignard



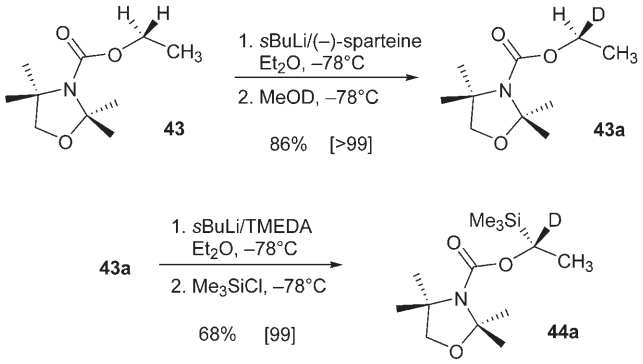
Scheme 19. Enantioselective synthesis of α-deuterated amino acids **40** with the chiral phase transfer catalyst **38**. Bn = benzyl.

reagents or alkyl–lithium compounds) and subsequently deuterated with electrophiles such as D_2O, MeOD, or AcOD; this corresponds formally to an H/D exchange.[45] In this way, Clayden et al.[45c] achieved complete *ortho*-deuteration of aromatic amides, such as **41**, and aromatic carbamates. Furthermore, they were able to show that with a sufficiently large kinetic isotope effect (KIE), deuterium functioned as a protecting group for the carbon center, and thus the regioselectivity of subsequent lithiations can be controlled (Scheme 20).

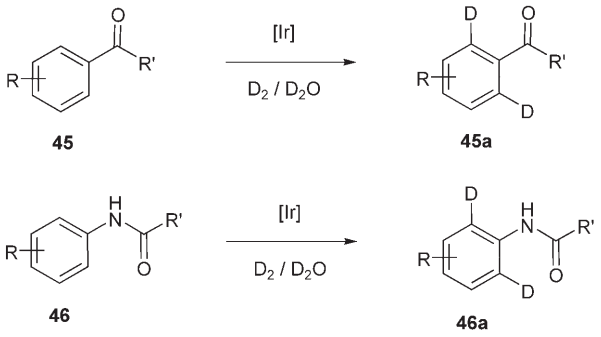


Scheme 20. Regioselective H/D exchange on aromatic amides.

Thanks to intensive research into the selective lithiations of numerous organic compounds,[46] diastereoselective and enantioselective deuterations are also now possible by Li/D exchange. For example, Hoppe et al.[47] achieved an enantioselective deuteration (> 99 % D) of **43** by sparteine-mediated lithiation. The large KIE permitted formation of the enantiomerically pure (> 95 % *ee*) and stereospecifically labeled alcohol derivative **44a** by renewed deprotonation and silylation (Scheme 21). Such stereospecifically monodeuterated compounds are of use for the elucidation of mechanistic problems.



Scheme 21. Stereodivergent, enantioselective H/D exchange according to Hoppe et al.[47] TMEDA = *N*,*N*,*N*',*N*'-tetramethylethylenediamine.



Scheme 22. Iridium-mediated *ortho* deuteration of arylketones **45** and acetanilides **46**.

3. H/D Exchange by Homogeneous Metal Catalysis

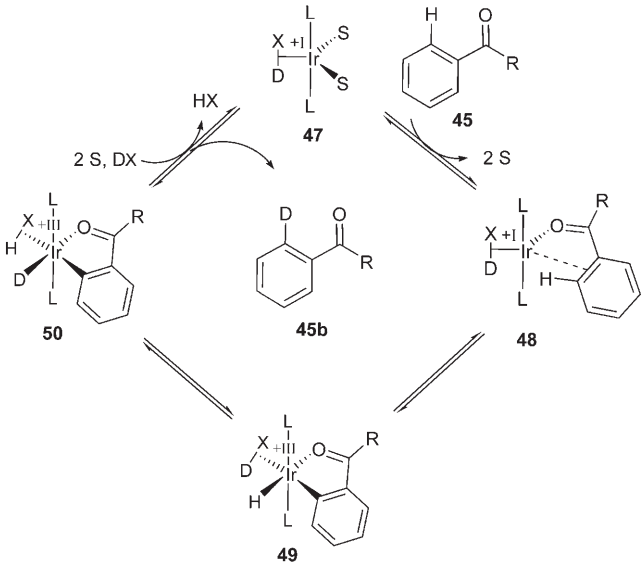
Transitional-metal-mediated H/D-exchange reactions with soluble catalyst complexes offer many advantages over other methodologies: of note here are the comparably mild reaction conditions and the high tolerance towards a number of functional groups through which undesirable side reactions, such as dehalogenation, deuterium addition to multiple bonds, hydrolysis, epimerization, or the cleavage of protecting groups, can usually be avoided. Moreover, very efficient deuterium incorporation with concomitant high regioselectivity can often be achieved with these catalytic systems, for which reason they are in principle also suitable for the incorporation of tritium. In addition to the use of deuterium gas and deuterium oxide as deuterium sources, deuterated solvents such as [D_6]acetone or [D_6]benzene are also suitable, which allows H/D exchange on less polar substrates.

Since the fundamental studies of the research groups of Garnett[48] and Shilov[49] in the late 1960s and early 1970s on H/D exchange by homogeneous catalysis, many efficient methods have been developed which allow a high degree of deuteration in both aromatic and aliphatic substrates. In the following Section, a number of selected iridium-mediated methods will be highlighted and the mechanistic considerations will also be illustrated. Exchange reactions based on other soluble transition-metal complexes will be described in Section 3.2.

3.1. Iridium-Catalyzed H/D Exchange

Cationic iridium complexes are particularly suited for the activation of C–H bonds,[50] for which reason iridium-mediated H/D-exchange reactions make up by far the greatest number of published examples in the area of homogeneous metal catalysis. The most investigated area is the *ortho*-deuteration of aryl ketones **45** and acetanilides **46** (Scheme 22). Commencing with the studies of the research groups of Heys[51] and Hesk,[52] many studies have been concerned with the effects of complex ligands,[53] the deuterium source,[54] the solvent,[54a,55,56] the addition of bases,[53c] of the amount of catalyst,[55] the temperature, and the duration of the reaction[53f,54] on the degree of deuteration and the substitution pattern in the substrate.

In the postulated mechanism (Scheme 23), the iridium(III) complex **49** is the pivotal intermediate for the explanation of the *ortho* regioselectivity. Commencing with coordination of the substrate **45** to the cationic iridium(I) catalyst **47** to form the complex **48**, oxidative insertion can only take place to form the five-membered metallacycle **49**. Subsequent H/D exchange with the deuterium source provides the intermediate **50**, which then, by reductive elimination, leads to regeneration of the catalyst **47** and to the labeled product **45b**. With acetanilides **46**, the intermediate metallacycle has only to be expanded by a nitrogen atom and is thus six-membered.



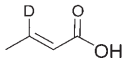
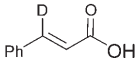
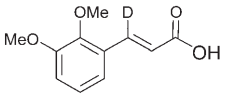
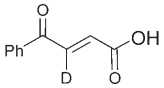
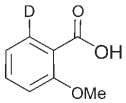
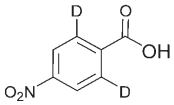
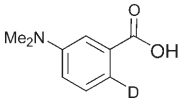
Scheme 23. Postulated mechanism of the *ortho* deuteration of arylketones **45** (XD = D_2 or D_2O, L = ligand, S = solvent molecule).[51b,54a,55]

Whereas the complete 2,6-deuteration of acetophenone, frequently used as model substrate, is achieved without difficulty, because of steric and electronic effects, the degree of deuteration with substituted derivatives can be reduced. In addition to acetophenone, a high degree of deuteration may be achieved with benzamides, benzoic acid derivatives,

acetanilides and 2-phenylpyridines, often with the commercial Crabtree catalyst $[Ir(cod)(PCy_3)(py)]PF_6$ (cod = 1,5-cyclooctadiene, Cy = cyclohexyl, py = pyridine).[51–56]

More recently Fels and co-workers demonstrated that α,β-unsaturated carbonyl compounds are also suitable substrates, which react through a similar mechanism.[54a] As shown in Table 1 (**51a**–**57a**), β-hydrogen atoms can be exchanged for deuterium with generally good results.

Table 1: Deuteration of α,β-unsaturated and aromatic carboxylic acids in the β and *ortho* positions according to Fels and co-workers.[54a]

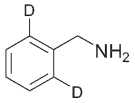
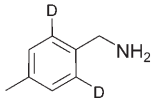
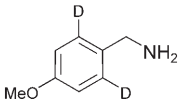
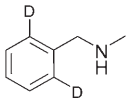
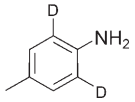
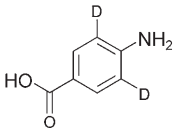
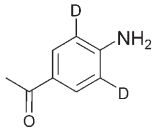
	Product[a]	Degree of deuteration[b] [%]
51a		69[c]
52a		17
53a		75
54a		75
55a		98
56a		99
57a		45

[a] Reaction conditions: [Ir(cod)(acac)] (4 mol%), D_2O, *N*,*N*-dimethylacetamide (DMA), 90 °C, 2 h. [b] Deuterium uptake relative to the labeled position(s). [c] After 4 h.

Fels and co-workers point out that by using [Ir(cod)(acac)] (acac = acetylacetonate), the regioselectivity of the labeling is dependent upon the deuterating agent. Thus in the case of 2-methoxybenzoic acid (**55**) they observed a 45% deuterium incorporation solely in the position *para* to the carboxy group when D_2 gas was used instead of D_2O. One explanation for this observation is provided by the reduction of the ligand with concomitant formation of elemental iridium, which precipitates from the reaction solution and then acts as a heterogeneous catalyst to bring about the unusual selectivity.[54a]

These observations are in accord with the findings of Lockley and co-workers, who have extended the substrate spectrum to anilines and benzylamines (Table 2).[57] By using [Ir(cod)(acac-F6)] (acac-F6 = hexafluoroacetylacetonate) and gaseous deuterium, an exclusively *ortho* H/D exchange relative to the position of the amino or methylamino group was found. 4-Aminobenzoic acid (**63**) and 4-aminoacetophenone (**64**) are particularly interesting here, because they show reversed selectivity with gaseous D_2 compared with D_2O.

Table 2: Deuteration of benzylamines and anilines according to Lockley and co-workers.[57]

	Product[a]	Degree of deuteration[b] [%]
58a		70
59a		69
60a		55
61a		94
62a		77
63a		80
64a		72

[a] Reaction conditions: [Ir(cod)(acac-F6)] (25 mol%), D_2, DMF or DMA, RT, 4 h. [b] Deuterium uptake relative to the labeled position(s).

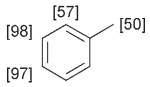
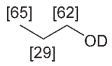
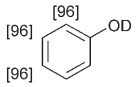
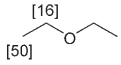
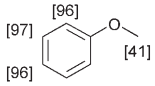
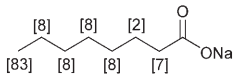
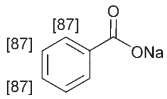
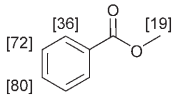
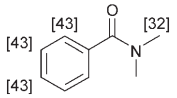
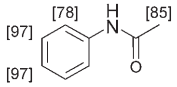
Since the anilines are unable to form a five-membered metallacycle intermediate, an alternative mechanism in which a small amount of acid generated during the induction phase may be responsible for the observed deuteration.

Depending on the reaction conditions, *N*-alkylbenzamides[53e,55,58] and acetophenone[53c,54a] increasingly incorporate deuterium into the aliphatic parts of the molecule by the same mechanism as for aromatic exchange, only the geometry of the metal complex is slightly different.

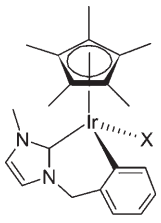
Bergmann and co-workers, who are developing catalysts for C–H bond activation,[50] have demonstrated that soluble iridium complexes are also suitable for the specific deuteration of aliphatic and nonfunctionalized aromatic substrates, depending on the ligand. They obtained a very high degree of deuteration with certain hydrocarbons, alcohols, phenols, ethers, carboxylic acids, esters, and amides with D_2O, [D_6]acetone, or [D_6]benzene (Table 3).[59]

Peris and co-workers also observed efficient H/D exchange with, amongst others, diethyl ether, ethyl methyl ketone, isopropanol, and styrene with the N-heterocyclic iridium–carbene complexes **77** (X = Cl, I) and **78** (R = H, Cl) in [D_4]methanol.[60] The continuing development of homogeneous iridium catalysts for C–H bond activation[61] should broaden even further the range of substrates amenable to high levels of deuterium incorporation.

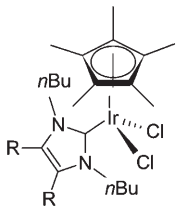
Table 3: Deuteration of aliphatic and aromatic substrates according to Bergman and co-workers.[59]

Method[a]		Product[b]
A	**65a**	
A[c]	**66a**	
B	**67a**	
B	**68a**	
A	**69a**	
B	**70a**	
A	**71a**	
B	**72a**	
B	**73a**	
A	**74a**	
A	**75a**	
A	**76a**	

[a] Method A: $[Cp^*(PMe_3)Ir(H_3)]OTf$ (5 mol%, $Cp^* = C_5Me_5$, OTf = trifluoromethane sulfonate), $[D_6]$acetone, 135 °C, 20 h; Method B: $[Cp^*(PMe_3)IrCl_2]$ 5 mol%, D_2O, 135 °C, 40 h. [b] Deuterium uptake relative to the respective position(s). [c] $[D_6]$Benzene as deuterium source.



77

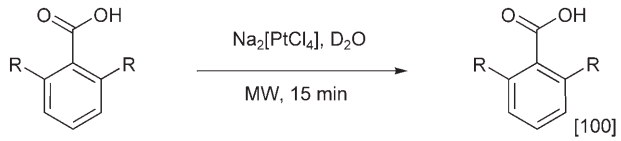


78

More recent publications describe the immobilization of catalysts on a polymer support,[62] reaction acceleration in microwave synthesis apparatus,[53d,63] the use of ionic liquids as cosolvents,[56] and the use of Raman spectroscopy for monitoring isotope exchange in real time.[64] The use of soluble iridium complexes for H/T exchange has also been described.[54b,58,65]

3.2. Homogeneous Catalytic H/D Exchange with other Transition Metals

Since the pioneering work of the research groups of Garnett[48a–b,66] and Shilov,[49a–b] with few exceptions,[67] homogeneous catalytic H/D exchange with platinum has been restricted to tetrachloridoplatinate(II) salts. Thus far, these have mainly been used for the deuteration of arenes.[68] The reactions are usually carried out with D_2O/AcOD as the deuterium source and solvent in a closed vessel at 80–130 °C. The pH-dependent stability and the activity of the catalyst complex necessitate acidic reaction conditions. In contrast, the significantly reduced reaction times caused by activation of the catalyst system with microwave irradiation allow acid-free deuteration of arenes. Thus, Jones and co-workers achieved a quantitative H/D exchange in the position *meta* to the carboxy group in the benzoic acid derivatives **79** with an aqueous $Na_2[PtCl_4]$ solution as shown in Scheme 24.[28]

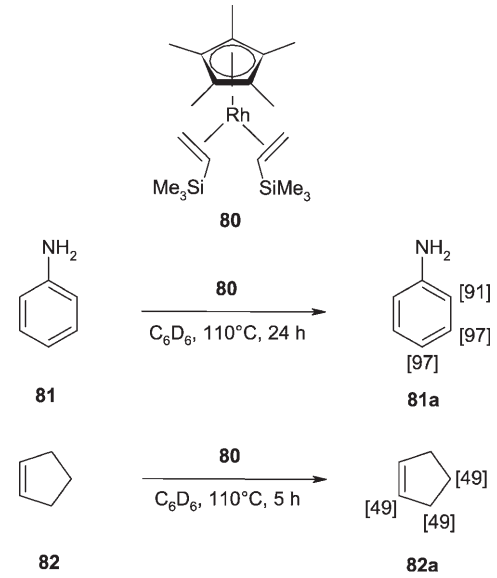


79 **79a**

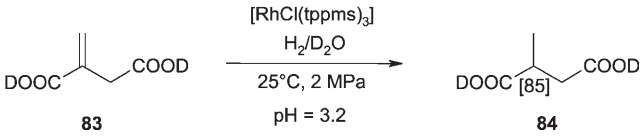
Scheme 24. Microwave-assisted homogeneously catalyzed H/D exchange with platinum according to Jones and co-workers.[28]

Soluble rhodium complexes are equally suitable for H/D exchange, as was demonstrated by Garnett and co-workers with the incorporation of deuterium into arenes.[48d] However, since this study, only a few further procedures with rhodium catalysts have been developed. Brookhart and co-workers achieved, for example, a high degree of deuteration with substrates such as aniline (**81**) and a moderate incorporation with cyclopentene (**82**; Scheme 25) with the rhodium–olefin complex **80**.[69] Joó and co-workers used water-soluble rhodium–phosphane complexes for the investigation of H/D exchange between H_2 and D_2O, and D_2 and H_2O.[70] With the addition of itaconic acid (**83**), they observed a reduction of the double bond and a high degree of H/D exchange exclusively at the C2 atom, depending on the pH of the reaction solution (Scheme 26).

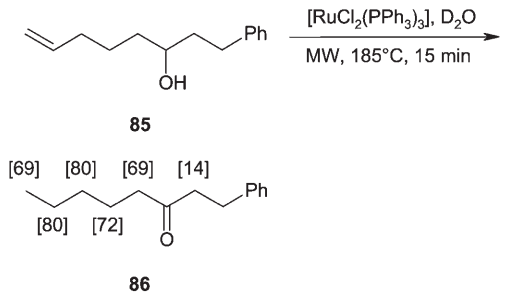
In recent years, the use of homogeneous ruthenium catalysts in preparative H/D exchange has been more frequently investigated.[71] Thus, Matsubara and co-workers demonstrated that substrates with electron donors such as double bonds, hydroxy groups, or amino groups may be efficiently deuterated in this way. As exemplified in Scheme 27, alkenols such as **85** are deuterated in good yields in D_2O by ruthenium-mediated migration of the double bond and isomerization to ketones.[72] Under similar



Scheme 25. Deuteration reactions with the olefin–rhodium complex **80** according to Brookhart and co-workers.[69]

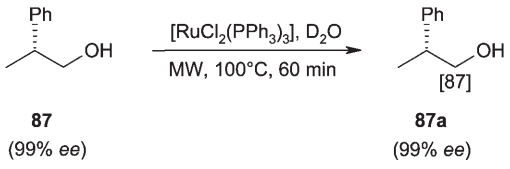


Scheme 26. Reduction and deuteration of itaconic acid (**83**) according to Joó and co-workers.[70] TPPMS = triphenylphosphane *meta*-monosulfonate sodium salt.



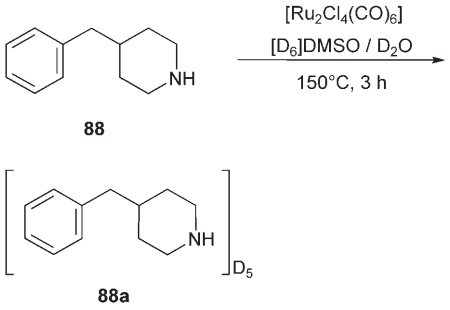
Scheme 27. Ruthenium-mediated deuteration of **85** with double-bond migration according to Matsubara and co-workers.[72]

conditions, primary alcohols and amines are deuterated selectively in the α position. In the case of **87**, the configuration of the stereocenter in the β position remained unaffected as long as the temperature did not exceed 100 °C (Scheme 28).[73]



Scheme 28. α-Deuteration of the primary alcohol **87** according to Matsubara and co-workers.[73]

Lockley and co-workers investigated soluble ruthenium complexes in the deuteration of piperidines, piperazines, and dialkylamines. In the case of 4-benzylpiperidine (**88**) with $[Ru_2Cl_4(CO)_6]$ as catalyst, an incorporation of an average of five deuterium atoms per molecule was observed, but their positions were not precisely specified (Scheme 29).[74]



Scheme 29. Deuteration of 4-benzylpiperidine (**88**) according to Lockley and co-workers.[74]

The use of other metals such as manganese, rhenium, chromium, and mercury, or their complexes, has been mentioned,[75] but thus far they have had little significance in homogeneously catalyzed H/D exchange.

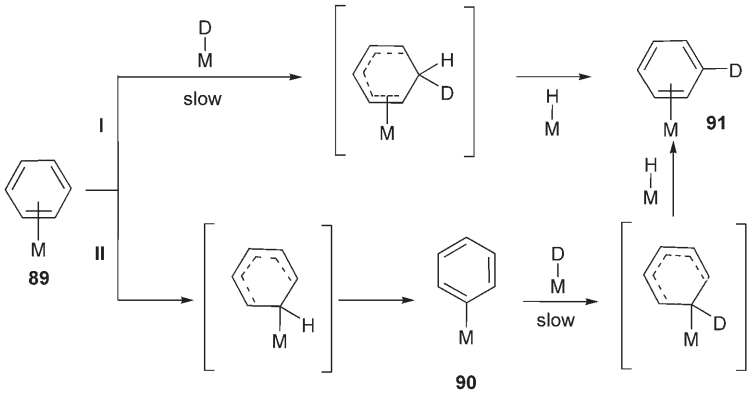
4. H/D Exchange by Heterogeneous Metal Catalysis

An important technical advantage of heterogeneous over homogeneous catalysis is the possibility to remove the catalyst by simple filtration at the end of the reaction. Moreover, in exchange processes that occur without side reactions, no further work-up steps are necessary.[76] However, the formation of dehalogenation, hydrogenation, and hydrolysis products as well as, under harsh conditions, epimerization and racemization must be frequently anticipated in heterogeneously catalyzed processes.[77] Adjustment and optimization of the reaction conditions for each substrate is usually unavoidable, in spite of the methodological improvements of recent years. High activity for H/D exchange has been found with palladium, platinum, rhodium, nickel, and cobalt catalysts.[78] On the other hand, no particular exchange activity has been observed in heterogeneous reaction procedures with either the metals iridium and ruthenium which are used with success in homogeneous catalysis, or with iron or osmium.[78c,d] In addition to gaseous deuterium[79], D_2O[80] and deuterated protic solvents that transfer their labile deuterium to the substrate[81] have been used as deuterium sources. Current techniques use, for example, the following combinations of catalyst and deuterium source: Pd/C–D_2,[87–94] Pd/C–$H_2(D_2)$/D_2O(DCl),[98–110,112–113] Pd/C–DCO_2K,[111] PtO_2–D_2–D_2O,[114–127] Rh/SiO_2–D_2,[128–129] and Raney-Ni–D_2O.[131–139]

After a short discussion about mechanisms in Section 4.1, the most important methods of heterogeneously catalyzed H/D exchange will be described, arranged according to the transition-metal catalysts (Section 4.2–4.6).

4.1. The Mechanism of the Heterogeneously Catalyzed H/D Exchange for Arenes

Since deuterium transfer in high yield is frequently only observed for substrates that contain a double bond or aromatic ring system, Garnett and co-workers postulated that a π-complex mechanism had to be involved in heterogeneously catalyzed H/D exchange.[82] Kinetic investigations indicated that, in addition to an associative mechanism **I**, a competing dissociative π-complex mechanism **II** was also involved.[83] The notable difference between these two reaction pathways is that, in the associative mechanism **I**, direct substitution of a hydrogen atom by a deuterium atom bound to the metal center takes place (Scheme 30), whereas



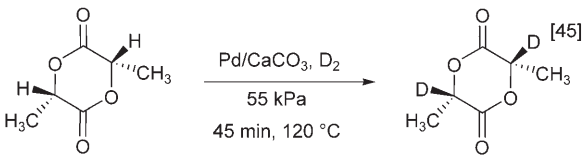
Scheme 30. Associative (**I**) and dissociative mechanism (**II**) of the heterogeneous H/D exchange of aromatic substrates.

in the dissociative mechanism **II**, a proton of the initially formed π complex **89**[84] is substituted by the metal atom. The intermediate phenyl radical **90** is then formed.[85] Only in the second step does substitution of the metal atom by a deuterium atom take place to form the product **91**. Apparently, both mechanisms are involved to different extents in the formation of the product, depending on the transition metal. In the case of platinum, a greater involvement of the dissociative mechanism is proposed; for palladium, the associative mechanism predominates; whereas in the case of rhodium, both mechanisms are involved equally.[86] Aliphatic compounds are deuterated only under forcing conditions (see Section 4.2). No mechanism has thus far been proposed.

4.2. Palladium-Catalyzed H/D Exchange

In early studies on heterogeneously catalyzed deuteration, gaseous deuterium was frequently used in combination with Pd catalysts.[87] In the method developed by Azran et al.,[88] the catalyst surface (10% Pd/C) was freed from adsorbed hydrogen and protic compounds before use by repeated purging with deuterium gas. Benzylic hydrogen atoms could be substituted selectively within an hour at room temperature with this catalyst and, again deuterium transfer was influenced by the solvent, the substrate structure, and the catalyst/substrate ratio. Under comparable reaction conditions, a reduction in deuterium incorporation through competing H/D exchange was observed in the hydrogenation of chromene derivatives.[89]

The HSCIE (high-temperature solid-state catalytic isotope exchange) method developed by Myasoedov and co-workers[90] is based on the action of gaseous deuterium or tritium on a solid, highly dispersed mixture of the substrate with the transition-metal catalyst. This isotope exchange proved to be highly efficient in the selective deuteration and tritiation of amino acids and peptides.[91] Vert and co-workers used this method for the selective deuteration of lactides[92] and glycolides,[93] which were used as starting compounds in the synthesis of isotopically labeled biocompatible absorbable poly-α-hydroxy acids. A value close to the melting point of the substrate was recommended as the optimal reaction temperature. The H/D exchange of l-lactide (**92**; Scheme 31) at 120 °C with a $Pd/CaCO_3$ catalyst gives only incomplete deuterium incorporation, but takes place without epimerization, and was equally suitable for the incorporation of tritium.[94]



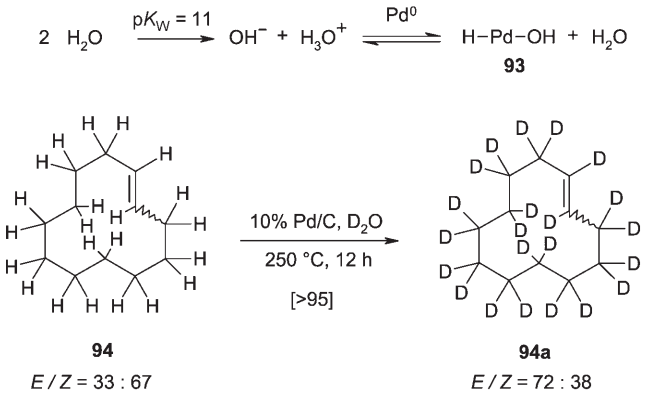
92 92a

Scheme 31. HSCIE method for the selective deuteration of l-lactide (**92**).

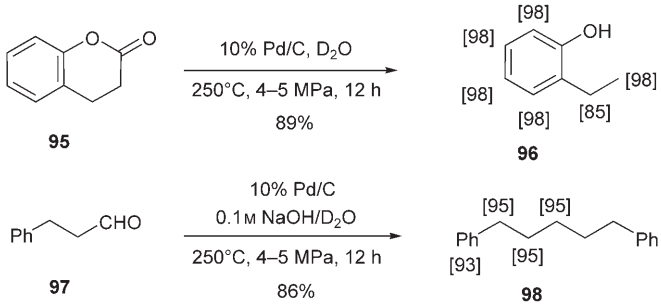
Möbius and Schaaf[95] have reported a hydrothermal method for deuteration of aliphatic hydrocarbons by catalyzed H/D exchange at temperatures up to 290 °C. A wire basket containing the catalyst was placed in the autoclave above the compound to be deuterated and the compound was subjected to a D_2/D_2O atmosphere up to a pressure of around 25 Mpa. Water dissociates a thousand times more rapidly under hydrothermal conditions than at room temperature[96] so that the Pd^0 can insert oxidatively into the H–OH bond with the formation of a Pd^{II} species.[97] The resulting palladium hydride **93** can interact with organic substrates so that H/D exchange can take place with the use of D_2O. For example, a high degree of deuteration (> 95% D) was observed with cyclodecene (**94**) (Scheme 32).[98]

According to Matsubara et al., completely deuterated aromatic or aliphatic hydrocarbons were formed under hydrothermal reaction conditions by decarboxylation of carboxylic acids. For example, the lactone **95** in D_2O afforded the phenol derivative **96** with a high degree of deuteration in the presence of 10% Pd/C (5 mol%) at 250 °C and a pressure of 4–5 Mpa (Scheme 33).[99]

It was postulated that the mechanism described by Schleyer and co-workers[100] of reductive decarboxylation via a alkylidene-palladium species with subsequent elimination of CO_2 at the metal surface is followed in this case,



Scheme 32. H/D exchange of cyclodecene (**94**) and considerations of the mechanism under hydrothermal reaction conditions.

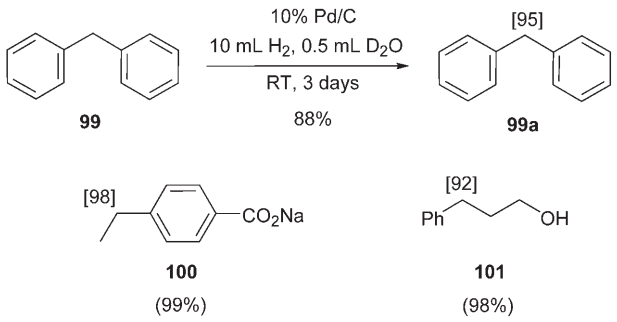


Scheme 33. Deuteration of a lactone (**95**) and an aldehyde (**97**) under hydrothermal reaction conditions.

whereas a hydride transfer from an intermediate acyl–palladium complex formed after direct C–H bond insertion has been discussed for the similarly observed decarbonylation of aldehydes. In the presence of a base, hydrocinnamic aldehyde (**97**) was transformed into deuterated diphenylpentane (**98**) as the result of sequencial aldol reaction, decarbonylation, and reduction. A complete deuteration of 4-aminobenzoic acid, which took place under somewhat milder reaction conditions (200 °C) without decarboxylation, formed the basis of a synthesis of folic acid derivatives.[101]

Hardacre et al. used a catalyst that was previously activated by hydrogen reduction for the deuteration of substituted imidazoles and imidazole salts. The substrate dissolved in D_2O was then added and the reaction mixture degassed by several cooling/thawing cycles.[102]

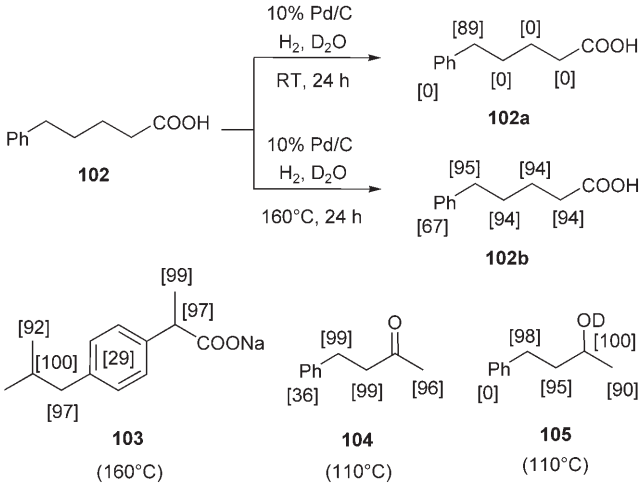
The principle of catalyst activation by initial occupancy of the catalyst surface with hydrogen has been known for some time in exchange reactions,[103] and was taken up by Hirota and Sajiki and developed into a one-pot method[104] in which an in situ activation of the Pd/C catalyst by hydrogen is carried out.[105] Consistent with this, no H/D exchange took place with the model compound diphenylmethane (**99**) in a hydrogen-free atmosphere with 10 wt % Pd/C (10 % Pd) in D_2O (Scheme 34). In contrast, the catalyst activity increased so dramatically in a hydrogen atmosphere that the benzylic positions of **99** achieved a deuterium content of 95 % within 3 days, even at room temperature. The method tolerated differently substituted benzyl substrates such as sodium



Scheme 34. H/D exchange of benzylic hydrogen atoms at room temperature with preactivated Pd catalysts.

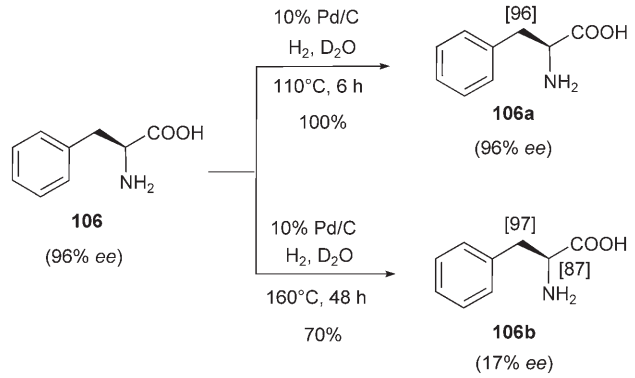
4-ethylbenzoate (**100**) and 3-phenylpropanol (**101**). It was notable that the exchange reactions described took place effectively without side reactions, and thus no chromatographic purification was necessary to obtain spectroscopically pure products. The deuterium uptake was influenced by the amount of hydrogen present and achieved a maximum in the presence of catalytic amounts (0.45 equiv) of H_2 gas.

Further investigations by Sajiki et al. on 5-phenylvaleric acid (**102**) found a considerable influence of reaction temperature on the regioselectivity and deuterium incorporation in H/D exchange.[106] The benzylic hydrogen atoms were selectively deuterated at room temperature, whereas as at 160 °C the less reactive positions were also involved, so that multiply deuterated products were formed. The reaction conditions described were compatible with numerous functional groups such as carboxy (**103**), keto (**104**) or hydroxy groups (**105**, Scheme 35), but the process remained restricted to substrates with aryl-linked side chains.



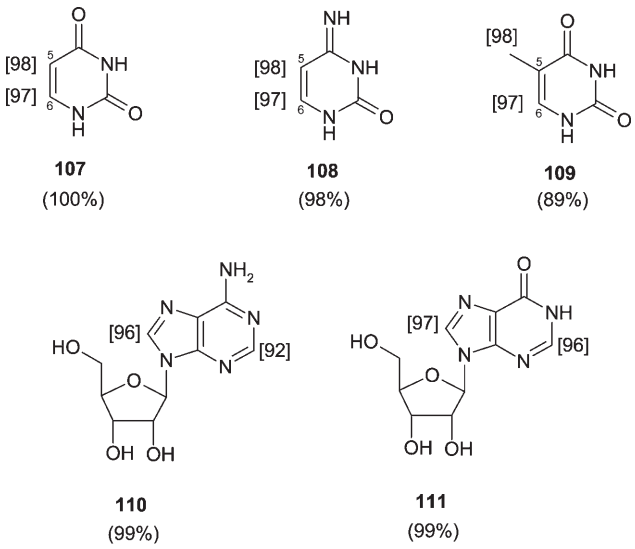
Scheme 35. Influence of the reaction temperature on the deuterium uptake and regioselectivity of the H/D exchange.

A preparatively useful application of this Pd/C–H_2/D_2O system is the selective deuteration of the β position of l-phenylalanine (**106**) shown in Scheme 36, which takes place at 110 °C (6 h, 96 % D) without racemization.[107] At 160 °C the α position is also accessible for H/D exchange, but under these conditions racemization occurs (17 % *ee*). Pyr-



Scheme 36. Deuteration of l-phenylalanine (**106**): influence of the reaction temperature on deuterium uptake and the stereochemical course of the H/D exchange.

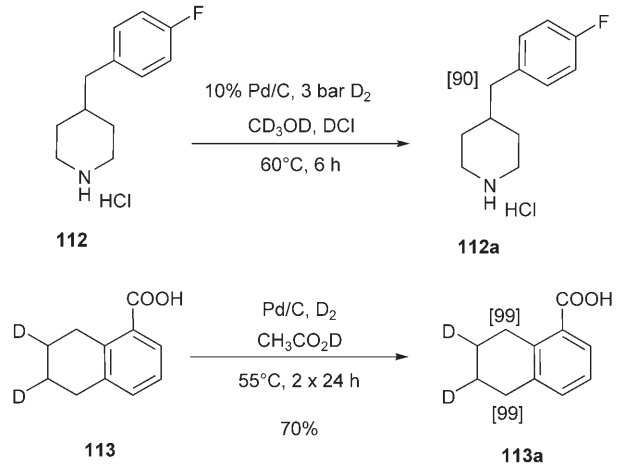
imidine bases such as uracil (**107**) or cytosine (**108**) could also be deuterated selectively in the 5- and 6-positions under comparable conditions (Scheme 37).[108] The 5-methyl group in thymine (**109**) was also completely deuterated at 110 °C, in



Scheme 37. H/D exchange of pyrimidine bases and nucleosides according to the research group of Sajiki.[108,109]

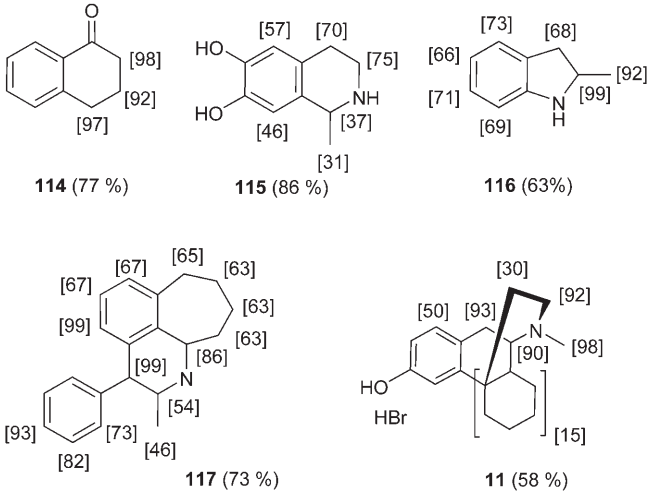
addition to the 6-position, without side reactions. Purine nucleosides such as adenosine (**110**) and inosine (**111**) were deuterated chemoselectively in the 2- and 8-positions.[109]

Significantly lower exchange rates were observed for the pyrimidine bases and nucleoside investigated with CD_3OD as solvent and deuterium source than with D_2O. In contrast, Faigl and co-workers achieved a significantly higher exchange efficiency for the benzylic hydrogen atoms of the piperidine derivative **112** with Pd/C–H_2–D_2O in the presence of deuterated alcohols and DCl.[110] Stock and Ofosu-Asante used deuterated acetic acid as the deuterium sources with Pd/C in a D_2 atmosphere for the selective benzylic deuteration of the tetrahydronaphthalene carboxylic acid **113** (Scheme 38).[111]



Scheme 38. H/D exchange of the piperidine derivate **112** and of the tetrahydronaphthalene carboxylic acid **113**.

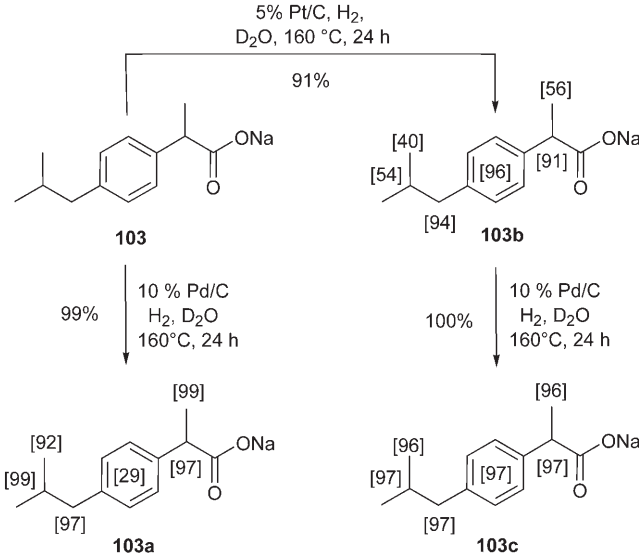
A method introduced by Derdau and Atzrodt used sodium borodeuteride for the in situ activation of the catalyst.[112,113] The avoidance of gaseous reactants makes this method (see also reference [78c,d]) particularly suitable for high-throughput and microwave applications. Thus, the long reaction times of 18 hours with conventional heating (130 °C) could be reduced to 60–90 minutes (140 °C) by microwave irradiation with a similar degree of deuteration. Palladium salts such as $PdCl_2$ or $Pd(OH)_2$, and also $RhCl_3$, have been used as catalysts in addition to Pd/C.[113] Both carbocyclic compounds such as 1-tetralone (**114**) and substituted heterocycles such as the isoquinoline derivative **115**, the indole derivative **116**, or the highly substituted piperidine derivative **117** are suitable as substrates (Scheme 39). These methods were also used for the preparation of deuterated dextrorphan (**11**), which was used for the investigation of the selective enzyme inhibition of cytochrome P450 2D6 in drug development.



Scheme 39. H/D exchange of 1-tetralone (**114**), isoquinoline derivative **115**, indole derivative **116**, piperidine derivative **117**, and dextrorphan (**11**).

4.3. Platinum-Catalyzed H/D Exchange

Fundamentally similar reaction and activation principles apply to platinum-catalyzed exchange processes as for palladium-catalyzed H/D exchange.[114] Current methods differ frequently in respect to substrate selectivity, rate of exchange, and reaction conditions. In a comparative study, Sajiki et al. were able to establish that platinum catalysts generally have a higher tendency towards the deuteration of aromatic positions, whereas palladium catalysts preferentially deuterated aliphatic positions.[115] The deuteration of phenol was achieved almost quantitatively with 5% Pt/C even at room temperature; in contrast, the palladium-catalyzed reaction had to be heated to 180°C for realization of a comparable degree of deuteration. On a preparative scale, the different selectivity of the two metals was used for the stepwise deuteration of ibuprofen (**103**) shown in Scheme 40, which led to an almost completely labeled product. Initially, all protons on the aromatic ring were exchanged with 5% Pt/C, followed by the remaining protons on the aliphatic residue with 10% Pd/C.

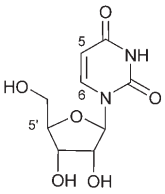
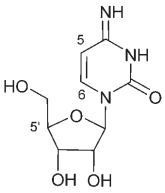


Scheme 40. Palladium- and platinum-catalyzed H/D exchange of ibuprofen (**103**).

Palladium and platinum can also be used as a mixed catalyst system for the deuteration of sterically hindered aromatic positions. For example, the deuterium incorporation for the H/D exchange of the *ortho* position of **102** with the addition of palladium (10% Pd/C) alone is only 14%, and with platinum (5% Pt/C) only 19%. However, if a combination of both catalyst systems is used in the same reaction, almost complete deuteration (97% D) of the *ortho* position is achieved. Since no comparably high degree of deuteration is achieved by stepwise deuteration of the molecules as described above, a synergistic effect of the palladium and platinum complexes was postulated, the mechanism of which is, however, still unexplained.[116]

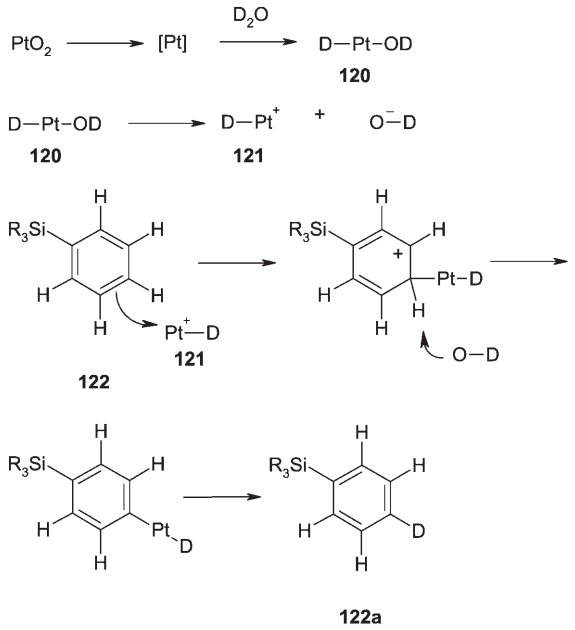
The development of methods for the activation of platinum[117] or palladium[118] in H/D exchange has been the subject of numerous fundamental investigations. Apart from the activation of platinum catalysts by prior hydrogenation[78c–d,119] or by initial occupation of the catalyst surface with oxygen[120] after reduction and oxidation cycles, catalyst activation is also possible by reduction with organic compounds such as benzene.[103,120] Moreover, PtO_2 was also activated by irradiation with ultraviolet light or by γ-radiation;[121] for example, after activation with D_2, PtO_2 was used for the selective deuteration of nucleosides.[122] However, deuterium incorporation was more highly dependent upon the amount of catalyst than with palladium,[108,109] and an almost stoichiometric amount of PtO_2 was recommended.[123] In contrast, however, the effect of reaction temperature appeared to be less significant; correspondingly, the C5-positions in uridine (**118**) and cytidine (**119**) were completely deuterated at 30°C (Table 4). Why significantly less deuterium was incorporated into the C6-position has not been fully explained, even after several comparative experiments.[108,109]

Table 4: Platinum-catalyzed H/D exchange of **118** and **119** at 100°C in relation to the catalyst/substrate ratio.

Compound	Cat./substrate	% D	
		C5	C6
 **118**	1:5.5	100	41
	1:2.2	100	70
	1:1.1	100	90
 **119**	1:5.5	100	33
	1:2.2	100	64
	1:1.1	100	83

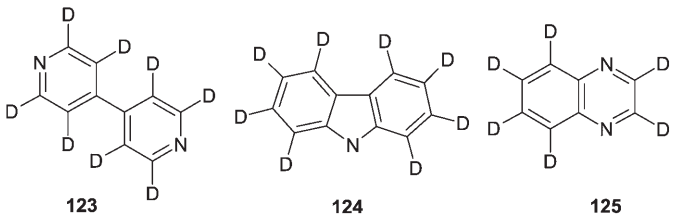
Strong dependency of the exchange selectivity upon the number and steric demand of the substituents on the nitrogen atom has been observed for the exchange of α-hydrogen atoms of aliphatic amines and amino acids with Adam's catalyst ($PtO_2 \cdot H_2O$). In this case, it is assumed that the nitrogen atom binds to the surface of the catalyst. The exchange efficiency decreases in the series tertiary > secondary > primary.[124]

The difference in chemoselectivity between palladium and platinum catalysts under hydrothermal reaction conditions has also been confirmed by Matsubara and co-workers (see also Section 4.1).[125] For example, aryl silanes **122** could be selectively deuterated at the aromatic ring in this process, in which exchange at the *ortho* position was restricted because of steric hindrance (Scheme 41).[126]



Scheme 41. Mechanistic considerations of the hydrothermal H/D exchange of arylsilanes **122**.

It has been postulated that, under hydrothermal conditions, metallic platinum forms during an inductive phase and then inserts into D_2O.[126] The resulting D–Pt–OD complex **120** dissociates with formation of the cationic $D–Pt^+$ species **121**, which interacts with the aryl ring in **122** and finally results in H/D exchange. Electron-rich arenes exchanged most efficiently in this reaction, in agreement with this mechanism. Accordingly, high degrees of deuteration could be achieved both for substituted arenes such as dibenzo[18]crown-6, triphenylphosphane, and ferrocene, but also for the heteroarenes such as 4,4′-dipyridine (**123**), carbazole (**124**) and quinoxaline (**125**), as shown in Scheme 42.[127]



Scheme 42. Platinum-catalyzed hydrothermal H/D exchange of 4,4′-dipyridine (**123**), carbazole (**124**), and quinoxaline (**125**).

Microwave-aided reactions were found to proceed with significantly shorter reaction times, with fewer side reactions.[28] Depending on the electronic nature of the substituent, arenes were deuterated selectively in the *meta* (for example, benzoic acid) or in the *ortho* position (for example, aniline).

4.4. Rhodium-Catalyzed H/D Exchange

At the end of the 1980s, a series of ground-breaking methods for rhodium-catalyzed H/D exchange were developed,[128] of which, however, only a few have received attention in the last ten years. The catalytic activity of rhodium is influenced by the particle size, the preparation, and the pre-treatment of the catalyst and the support material. Thus the ion pair generated from $RhCl_3$ and Aliquot 336 (methyltrioctylammonium chloride) is suitable for the catalytic deuteration of arenes in an organic/aqueous two-phase system.[129] Lockley and co-workers developed a method in which rhodium or ruthenium in the presence of D_2 gas was used for the regioselective *ortho* deuteration of substituted N-heterocycles such as pyridine, quinoline, and phthalazine derivatives. The reactions were carried out in THF at room temperature and after just two hours afforded respectable values for deuterium incorporation.[130]

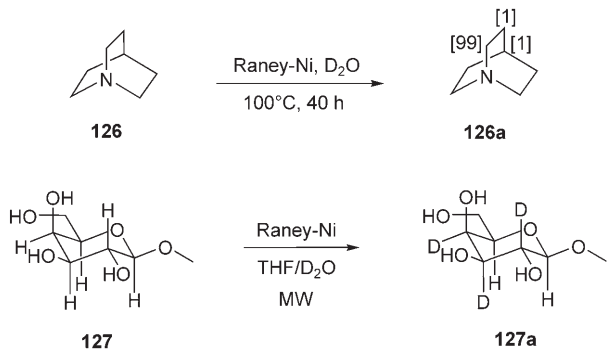
4.5. Nickel-Catalyzed H/D Exchange

Since the first applications developed by Lauer and Errede,[131] as well as Bonner,[132] H/D-exchange reactions catalyzed by Raney nickel have been used mainly for the deuteration of aromatic substrates.[133] Whereas only the hydrogen atoms on the aliphatic residue were exchanged by heating phenylacetic acid in D_2O in a sealed ampoule, the fully deuterated product was formed with a deuterium content of 97% after the addition of Raney nickel.[134] A high degree of deuteration was achieved by the use of D_2O or deuterated protic solvents. In contrast, specific positions could be deuterated selectively in tryptophan analogues with Raney nickel in $[D_6]$acetone, $[D_3]$acetonitrile or $[D_1]$chloroform.[135] The different nucleophilicity of these positions and, in particular, the orientation of the indole ring on the catalyst surface influenced by the solvent were suggested as influencing the differences in selectivity.

In microwave-assisted H/D exchange, all the hydrogen atoms in *N*-methylindole were involved in the isotope exchange in protic solvents such as D_2O or CD_3OD, whereas only the C4-position was deuterated in nonprotic solvents such as $CDCl_3$. Similar solvent effects had previously been observed in the ultrasound-activated deuteration with Raney nickel.[29,136]

In the case of Raney nickel catalyzed H/D exchange, only the hydrogen atoms at the α-carbon atoms were selectively deuterated in quinuclidine (**126**) with conventional heating (D_2O, 100 °C, 40 h, 2 reaction cycles; ≥ 99.7% D), whereas less than 1% D was incorporated into the β and γ positions (Scheme 43).[137]

The ultrasound activation of Raney nickel, as described by Cioffi and Prestegard,[138] allowed a microwave-assisted deuteration of nonreducing carbohydrates with retention of configuration (Scheme 43).[139] The model compound 1-*O*-methyl-β-d-galactopyranoside (**127**) was thus heated sequentially for 15-second intervals up to 36 times in a modified domestic microwave oven, whereupon deuterium incorporation took place without epimerization or decomposition.



Scheme 43. Raney-Ni-catalyzed H/D exchange of quinuclidine (**126**) and 1-*O*-methyl-β-d-galactopyranoside (**127**).

4.6. Copper- and Cobalt-Catalyzed H/D Exchange

Unlike Raney nickel, copper–aluminum alloys show little or only slight catalytic activity for H/D exchange.[140] Thus, in the reductive dehalogenation with Raney copper, only the halogen atoms of the aromatic substrate were selectively substituted by deuterium, whereas additional H/D-exchange processes took place with Raney nickel.[141] However, microwave-induced decarboxylation of aromatic carboxylic acids gave somewhat higher degrees of deuteration with a $CuCO_3$/$Cu(OH)_2$ catalyst system in the presence of quinoline.[142]

High levels of incorporation of deuteration at the benzylic positions of arenes were achieved with the use of Raney cobalt in 20% Na_2CO_3/D_2O solution.[143]

5. Summary and Outlook

The developments of the past years in the areas of "classical" acid- and base-catalyzed methods and in particular in metal-catalyzed reactions have enriched the methodological repertoire for H/D exchange. A central component of the methodological developments was the investigations into catalyst activation. The ever-improving understanding of the processes of the catalyst during C–H activation, especially in reactions of non-activated hydrocarbons, gives rise to expectations of exchange reactions under even milder conditions in the future. This development would allow a wider applicability of the H/D-exchange reaction to a wide range of sensitive classes of substances, including natural products. Microwave techniques have also led to new methods for H/D exchange. All methods of H/D exchange profit from microwave techniques by way of shorter reaction times, frequently with the formation of fewer by-products. Known methods for H/D exchange were investigated for their applicability under microwave conditions and optimized, and further improvements are to be expected. The deepening of mechanistic knowledge permits better prediction of chemo- and regioselectivity of exchangeable hydrogen atoms for many organic molecules.

The considerable attention of authorities to the toxicity and environmentally damaging properties of commercial chemical products leads to expectations of an increasing demand for reliable methods for the analysis of these substances. It can thus be assumed that the demand for analytical standards for chemical substances that have not yet been fully tested for their toxicology will grow further. Further methodological improvements and applications for H/D-exchange reactions are thus predicted.

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