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Effect of Processes Occurring in the Presence of Metal Catalysts on the Main Characteristics of the Hydrogen Isotope Labeled Organic Compounds Obtained

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Abstract—The main deuterium and tritium sources used for preparing hydrogen isotope labeled compounds are presented. The mechanisms of hydrogenation and isotope exchange in organic compounds in the presence of heterogeneous and homogeneous catalysts when using gaseous tritium (or deuterium) or tritium (or deuterium) water are considered. Examples of the participation of solvent protons in introduction of deuterium and tritium into organic compounds by dehalogenation are presented. The problem of selective hydrogenation and dehalogenation is briefly discussed. Particular attention is paid to isotope exchange with deuterium or tritium in the presence of homogeneous iridium catalysts.

Keywords: heterogeneous and homogeneous catalysis, iridium catalysts, sources of hydrogen isotopes, efficiency of deuterium and tritium labeling

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I. INTRODUCTION

Studies using isotope-substituted organic compounds were performed most frequently with deuterated and tritiated biologically active compounds [1–4]. Such compounds are used particularly actively in searching for candidate pharmaceuticals. Isotope exchange in this case is the preferable route, because it does not require labor-consuming synthesis of appropriate precursors. Deuterated compounds are also used as internal references for mass spectrometry [5, 6], in kinetic studies [7, 8], and for the development of new routes of chemical synthesis [9].

The main sites of deuterium or tritium incorporation in the structural formulas are marked with an asterisk. The asterisk in parentheses denotes only slight incorporation of hydrogen isotopes in this site.

I.1. Deuterium and Tritium Sources

The commonly used sources of hydrogen isotopes are gaseous deuterium (or tritium) and deuterium (or tritium) water. Other reagents containing hydrogen isotopes are used for deuterium or tritium labeling of organic compounds in the presence of catalysts more seldom. Irrespective of the source of hydrogen isotopes, it is necessary to take into account processes occurring in interaction both of the catalyst with hydrogen isotopes and of organic substrate molecules with active sites of the catalyst. This is associated with the possibility of large isotope effects in labeling, leading, as a rule, to a decrease in the deuterium or tritium incorporation into substrate molecules.

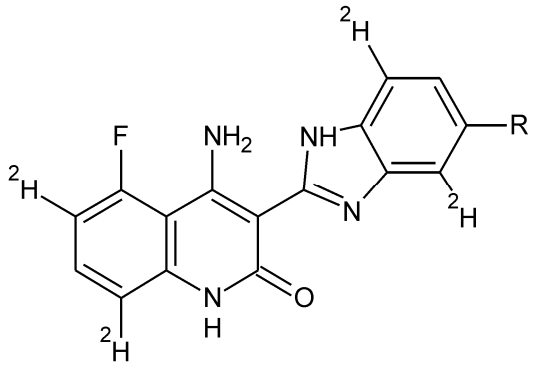
Hydrogen isotope labeling of organic compounds using gaseous deuterium or tritium can also be performed without catalyst, e.g., using the Wilzbach method. However, this method is of limited use, because the molar activities of the products obtained usually reach no more than 0.1–10 mCi $mmol^{-1}$ [10].

Labeling by isotope exchange with deuterium or tritium water can also be performed without catalyst. However, the substance in this case should be stable in media with pH higher than 11 or lower than 2 [11]. For example, such procedure was used for labeling of camptothecin, which stands heating for many days at 90°C in 98% sulfuric acid [11].

On heating *L*-histidine and *N*-methyl-*L*-histidine to 130°C in a mixture of hydrochloric acid and deuterium or tritium water, the label is incorporated in the aro-

matic fragment of the amino acid (5-position of the imidazole ring). When using tritium water, the molar activities were low, about 0.05–0.13 mCi mmol^{-1} [12].

If a substance stands microwave treatment, deuterophosphoric acid can catalyze the deuterium incorporation into sites differing in the reactivity. For example, deuterium was incorporated at 120°C in 60 min at four carbon atoms in a molecule containing several aromatic rings [13]:



The labeling of compounds in which the exchange of protons for tritium in the α-positions relative to the keto group is possible [14] occurs under milder conditions (solution in dimethylformamide in the presence of triethylamine, 64 h, 80°C). A series of labeled steroids were obtained by this procedure, but their molar activity did not exceed 1.5–3.5 mCi mmol^{-1} [14].

Isotope exchange with tritium water on heating occurs also in the presence of K_2PtCl_4 at low pH values [15].

Lewis acids are also convenient for increasing the efficiency of the isotope exchange with tritium water [16, 17]. $BF_3/Et_2O/^3H_2O$ and $BF_3/^3H_3PO_4$ mixtures allow incorporation of 40–60% tritium into aromatic compounds (relative to the molar radioactivity of tritium water) [17–20].

However, the efficiency of hydrogen isotope labeling of organic molecules can be considerably increased when using catalysts based on transition metals.

I.2. Hydrogen Isotope Labeling of Organic Compounds Using Gaseous Deuterium or Tritium

Reactions involving treatment of organic compounds with gaseous hydrogen are among the most studied catalytic reactions. In accordance with the modern views, the first obligatory step of a catalytic process is the chemisorption of the reactants on active sites of the catalyst. The reactants undergo further transformations in the chemisorbed state. Hence, the activity and selectivity of the catalyst should be primarily determined by the structure and properties of its active sites. Methods for directly studying the catalyst surface and adsorbed compounds on the molecular level have been developed by now. These methods include slow electron diffraction allowing characterization of the surface of the clean metal or adsorbed layer and electron-spectroscopic methods such as Auger electron spectroscopy, X-ray and UV photoelectron spectroscopy, electron energy loss spectroscopy, etc., allowing determination of the chemical composition of the surface and of the valence and nature of chemical bonds in adsorbed molecules, and also the EXAFS method [21].

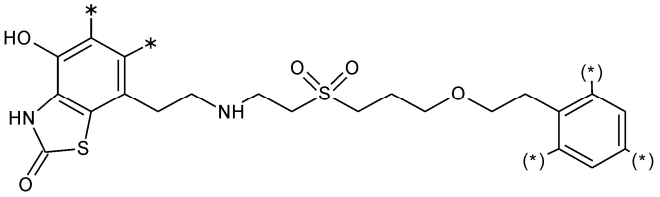
The most systematic studies were performed for Pt [22, 23]. Later similar conclusions were made for Ni, Pd, Rh, Ru, and other transition metals. The chemisorption of more than 20 compounds, and also hydrogenation, dehydrogenation, isomerization, hydrogenolysis, and isotope exchange on the surface of Pt crystals with different Miller indices were studied [22]. It has been shown that the limiting step of the H–^{2}H isotope exchange is not the proper chemisorption of the molecule on the active site, occurring with the energy close to zero, but the transfer of hydrogen molecules or atoms to this active site and between active sites.

I.3. Introduction of Hydrogen Isotopes into Organic Compounds Using Deuterium or Tritium Water

Isotope exchange with deuterium or tritium water can be performed using both homogeneous and heterogeneous catalysts. The molar activity of the labeled compounds was considerably increased when preparing tritium water in situ by reduction of palladium or platinum oxide with gaseous tritium. Such water had maximum possible activity, and it was used in the form of solutions in aprotic solvents to prevent the self-radiolysis of ^3H_2O and reduce to a minimum the radiolytic degradation of the desired product. Labeling reactions with 100% tritium water are usually performed using heterogeneous catalysts that are resistant to radiolysis and thus give rise to no additional problems in isolation of the labeled products from the reaction mixtures [24–32].

I.4. Other Sources of Hydrogen Isotopes, Used for Preparing Labeled Organic Compounds

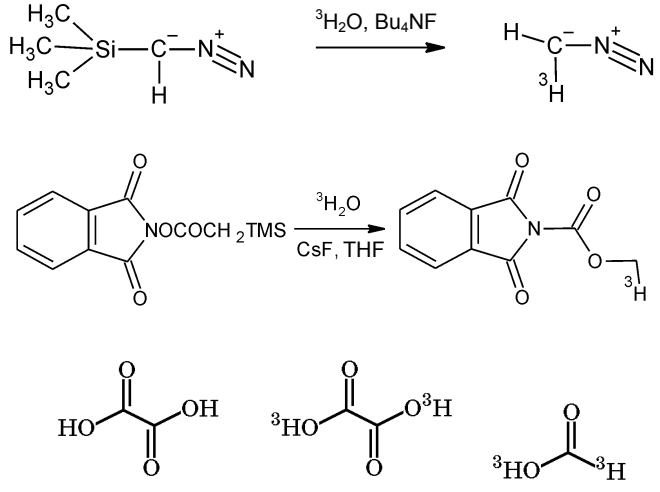
The majority of other sources of hydrogen isotopes are prepared using gaseous tritium and tritium water. For example, the use of a mixture of heptafluorobutyric anhydride and tritium water in an organic solvent allows isotope exchange with heptafluorobutyric acid to be performed without dilution of tritium with protium. Using 100% ^3H_2O, highly labeled compounds containing phenols, amines, and sulfur were perpared from tritium-labeled heptafluorobutyric acid [33–35]:



Molar activity 13–18 Ci mmol^{-1}

The use of tritium water allows synthesis of labeled diazomethane [36, 37] and of acetic and formic acids [38] with molar activities of the order of 20 Ci mmol^{-1}, 10 Ci mmol^{-1}, and 80 mCi mmol^{-1}, respectively (Scheme 1).

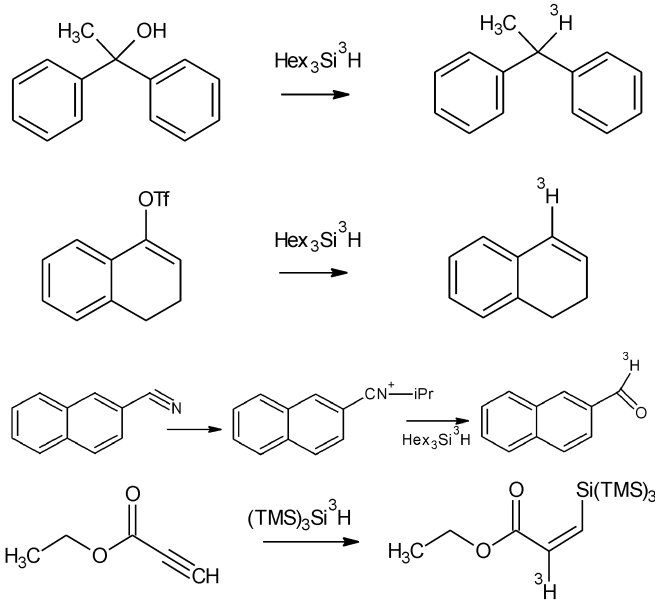
Treatment of R_3SiCl with lithium deuteride or tritide (THF, 23°C, 30 min) allows preparation of R_3Si^2H or R_3Si^3H.



^3H_2O (90.1 mCi mmol^{-1}), THF; 180°C, 3 days

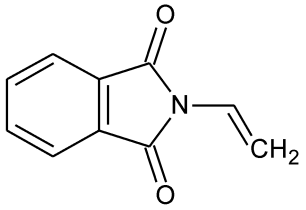
Scheme 1.

The use of these derivatives of silicon deuteride or tritide (R_3Si^3H) [39] allowed reduction of alcohols, conversion of nitriles to aldehydes, and reduction of triple bonds to double bonds (Scheme 2).

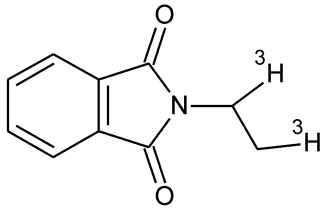


Scheme 2.

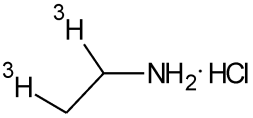
Tritium-labeled ethylamine can also be prepared from *N*-vinylphthalimide [40]:



$^3H_2$, 10% Pd/C, 23°C, 2 h. Ratio of the label amounts in the methyl and methylene groups 5 : 1.



HCl (6 M), ethanol–water (1 : 1), 12 h, refluxing.



Molar activity 48 Ci mmol^{-1}, $^3H_0$ 17%, $^3H_1$ 23%, $^3H_2$ 26%, $^3H_3$ 24%, $^3H_4$ 9%.

Some other reagents [^{3}HCHO, ^{3}HC^{3}HO, ^{3}HCON·$(CH_3)_2$, ^{3}HCOOCOCH$_3$, C^{3}H$_3$NH$_2$, *N*-trithioacetoxyphthalimide, ^{3}HN=N^{3}H] are also used for tritium labeling [41].

Complex metal tritides (usually sodium borotritide and lithium aluminotritide) and labeled methyl iodide are also used as sources of hydrogen isotopes [41]. These reagents are prepared by keeping the corresponding borohydride (of lithium, sodium, or potassium) in a tritium atmosphere at 270–500°C for 4–6 h or by treating butyllithium with gaseous tritium in the presence of *N*,*N*,*N*',*N*'-tetramethylethylenediamine to obtain lithium tritide, from which a set of complex metal tritides can be synthesized. For example, tri-*n*-butyltin tritide, which is an excellent reagent for dehalogenation, was prepared using lithium tritide [39].

The following compounds were prepared by the reduction of appropriate precursors (containing aldehyde, keto, carboxy groups, etc.) with the above-mentioned tritides: (2*E*,6*E*)-3,7,11-trimethyl-2,6,10-[10-^{3}H]dodecatrien-1-ol ([10-^{3}H]farnesol); (2*E*,6*E*)-3,7,11-trimethyl-2,6,10-[10-^{3}H]dodecatrien-1-al ([10-^{3}H]farnesal); (2*E*)-4-hydroxy-[4-^{3}H]nonen-1-al diethyl acetal; 2-vinyl[1,1,3-^{3}H]dihydrosphingosine 1-phosphate; 3-(*S*)-amino-4-hydroxy-5-[5,5,6,6-^{3}H]-tridecyl-1-phosphonium acid hydrochloride (phosphonate analog of sphinganine 1-phosphate); and also a series of ^{3}H-labeled steroids, vitamins, and derivatives of inositols. The molar activity of the products prepared using sodium borotritide was equal, as a rule, to 1/5 of the molar activity of sodium borotritide. The reaction was usually performed in ethanol-containing solvents for 0.5–72 h at 0 or 20°C. Then, excess borotritide was decomposed with a mineral acid, and the product was purified by chromatography.

Labeled methyl iodide was prepared by the reaction of HI with the corresponding precursor, which was prepared most frequently by the reduction of CO_2 with lithium aluminotritide or by dehalogenation of 4-Ph-C_6H_4COOCH$_2$Cl, C_6H_5SCH$_2$Cl, and 4-Ph-C_6H_4·$OCCl_3$ with gaseous tritium. Other methylating agents (methyl tosylate, methyl nosylate, C^{3}H$_3$MgI) were prepared using labeled methyl iodide. The procedures involving the use of C^{3}H$_3$I and its derivatives are well known [41]. The reactions are usually performed at 23–60°C in polar solvents (methanol, acetone, DMF, DMSO, etc.) in the presence of bases (Et_3N, *i*-Pr_2NEt, Ag_2O, K_2CO_3, NaOH, $NaHCO_3$, etc.) for the time from 5 min to several hours. Labeled derivatives of 5,7-pregnadiene, vitamin D_3, and 9-*cis*-retinoic acid were prepared by the reaction of C^{3}H$_3$MgI with the keto group [41].

II. INTRODUCTION OF HYDROGEN ISOTOPES INTO ORGANIC COMPOUNDS IN THE PRESENCE OF HETEROGENEOUS CATALYSTS

II.1. Mechanism of Hydrogenation and Isotope Exchange in Organic Compounds, Performed with Gaseous Tritium or Deuterium in the Presence of Heterogeneous Catalysts

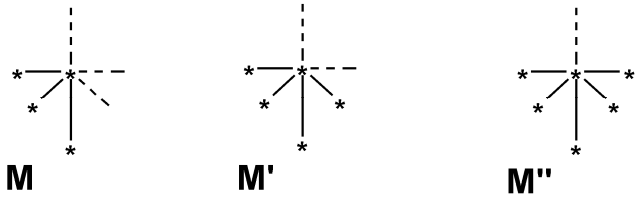
As noted above, the hydrogenation, isotope exchange, and other processes taking place in treatment of organic compounds with gaseous tritium in the presence of transition metals occur on active sites of the catalyst [22]. The capability of chemisorbed molecules for further transformations is determined by the type and strength of their bonds with the catalyst. The same molecule on the same adsorption sites can form several different adsorbed species. For example, more than ten kinds of species were identified in adsorption of ethylene on the platinum surface [42], including weakly bonded *p* complexes and covalently bonded species with linear (one-center) and bridging (two-center) adsorption modes, formed by both associative and dissociative mechanisms. For benzene, the number of such species is considerably larger [42, 43]; multicentered adsorption forms appear. Different species have different bonding energy with the catalyst and can transform into each other. The formation of weakly bonded species such as *p* complexes, transforming subsequently into linear species, always precedes the formation of more strongly bonded species. Not all the adsorbed species participate in this catalytic reaction; optimum bonding energy with the catalyst is required [44] (so-called energy matching principle clearly formulated for the first time by Balandin [45]).

Apparently, the probability of the formation of one or another adsorbed species even for structurally related compounds (e.g., benzodioxane derivatives) will significantly influence the distribution of the hydrogen isotope in the final labeled product [46].

Ample experimental and theoretical data on the hydrogen adsorption on various transition metals have been accumulated by now [47–50]. Quantum-chemical

calculations show that the hydrogen–metal bond energy is also determined by the structure of the active adsorption site, in particular, by the degree of participation of the *d* and *sp* states of the surface metal atoms in the hydrogen–metal bonding [51, 52].

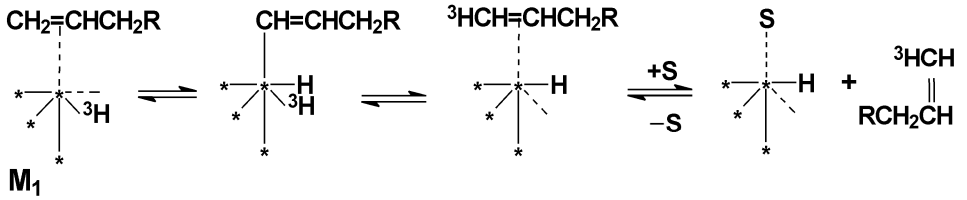
Dissolution of molecular hydrogen in metals is also a multistep process involving adsorption and dissociation of hydrogen [53]. Considering the processes that occur in interaction of hydrogen isotopes with active sites of the catalyst in the strongly simplified form and assuming that the adsorption sites differ only in the degree of coordination unsaturation, the active sites of the catalyst can be schematically presented by structures M, M', and M'' [54–57]:



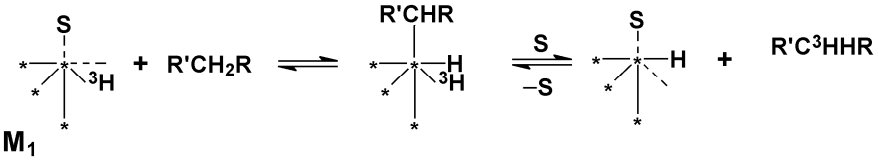
The maximal number of groups that an active site can bind is determined by its position in the lattice, is 6's complement (for the octahedral surrounding of the majority of platinum metals), and thus can take values of 1, 2, and 3. The difference between these sites in the reactivity strongly influences the hydrogenation, dehalogenation, selective hydrogenation and dehalogenation, and concurrent processes of isomerization (migration of double bonds, *cis–trans* isomerization) and isotope exchange.

According to the coordination model, interaction of an unsaturated compound molecule with an active site of a catalyst leads to the shift of the electron density in the carbon–metal system, with the hydrogen transfer from carbon to metal and vice versa becoming possible (Schemes 3–10).

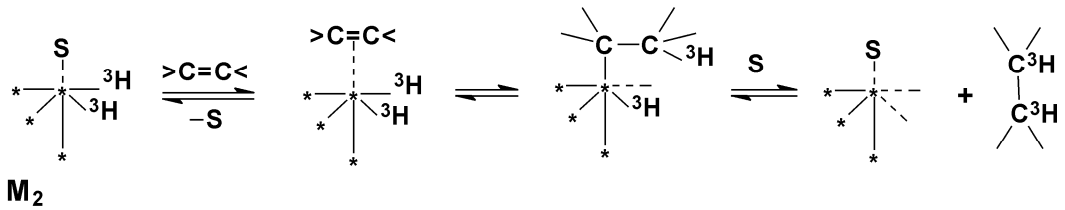
The adsorption of unsaturated compounds of ethylene type on transition metals can lead to the formation of intermediate ethylidene complexes like Ni=CH–CH_2R. The calculation results suggest that the limiting step is probably the turn of the CH_2 group. The presence of bound hydrogen decreases the energy barrier to the turn of this group from 3.16 to 0.36 eV. The possibility of the formation of a double bond between an alkene and a metal atom accounts for the label distribution and for the possibility of incorporation of more than two tritium atoms into the resulting alkane in hydrogenation of one double bond (Scheme 9) (Table 1).



Scheme 3. Label incorporation at dissociative mechanism of adsorption (via π complex).



Scheme 4. Label incorporation at dissociative mechanism of adsorption (via σ complex).

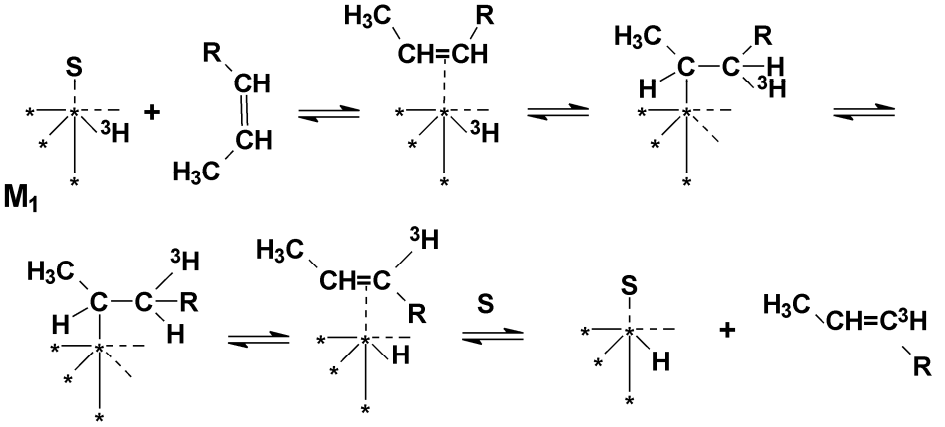


Scheme 5. Label incorporation via hydrogenation of double bonds.

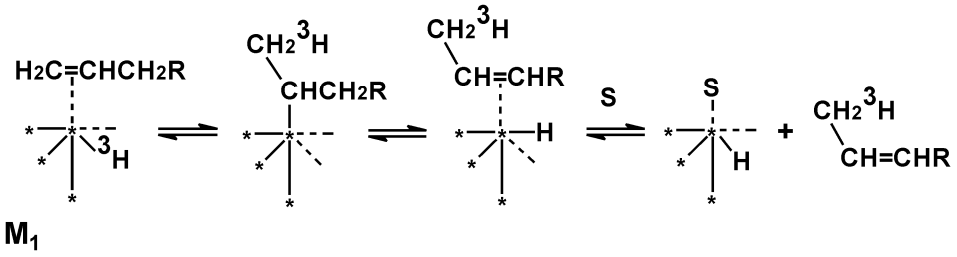
Table 1. Introduction of tritium label by hydrogenation of unsaturated compounds with gaseous tritium [59]

Starting compound	Reaction conditions	MA,[a] Ci mmol^{-1}
Methylundec-10-enoate	5% Pd/$BaSO_4$, 1 h, benzene	84.8
	The same, dioxane	45.9
	The same, ethyl acetate	41.6
	The same, chloroform	52.6
	The same, heptane	43.2
	The same, methanol	26.2
	10% Pd/C, 1 h, benzene	69.7
	5% PdO/Al_2O_3, 1 h, benzene	65.3
Picrotoxin	10% Pd/$BaSO_4$, 3 h, ethyl acetate	37.8
Dimethylallyl-3-chlorobutylammonium chloride	5% Pd/$BaSO_4$, 1 h, ethanol	13.5
2,2-Di(trifluoromethyl)-3,3-dicyanobicyclohept[2.2.1]ene-5	5% Pd/$BaSO_4$, 1.5 h, ethyl acetate	25.1
m,*m*'-Di-*tert*-butyl-*p*-coumaric acid	5% Pd/$BaSO_4$, 2 h, ethyl acetate	46.2

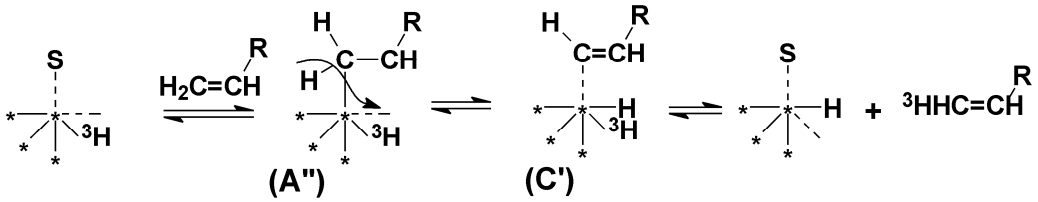
[a] Here and hereinafter, MA is the molar activity.



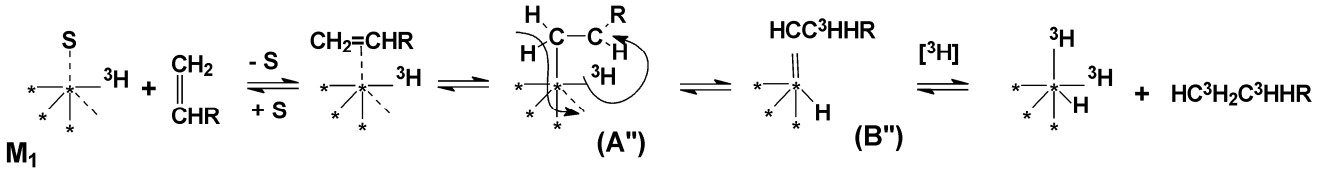
Scheme 6. Label incorporation accompanied by *cis–trans* isomerization of double bonds.



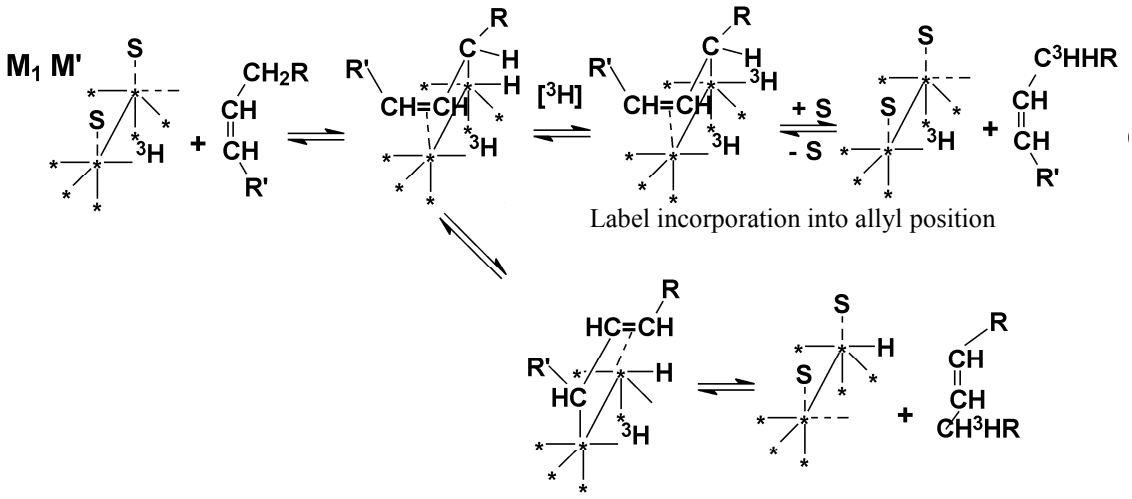
Scheme 7. Label incorporation accompanied by migration of double bonds.



Scheme 8. Label incorporation into terminal double bonds.



Scheme 9. Label incorporation via formation of metal–carbon multiple bonds.



Scheme 10. Label incorporation on a binuclear active site.

Thus, according to Scheme 9, elimination of two α-protons yields the complex Pd=CH–C^3HHR. If a β-proton is also eliminated, the complex Pd=C=C^3HR is formed. Hydrogenation of these complexes yields a saturated compound containing three and four hydrogen isotope atoms. For example, hydrogenation of the terminal double bond in fusicoccin with deuterium yielded a mixture of isotopomers containing dihydrofusicoccin with three (22%) and four (34%) D atoms [58].

Comparison of the C–C, Pd–Pd (in the crystal), H–C, H–Pd, and Pd–C bond lengths also counts in favor of the assumption that the hydrogenation, migration, and isomerization of double bonds and the isotope exchange (Schemes 3–8) occur on a single active site, whereas incorporation of the label into allyl position in formation of π-allyl complexes is determined by cooperative interactions on the surface of metal catalyst crystals. These features account for the fact that the migration of the terminal double bond in methyl undec-10-enoate mainly yields the *cis* isomer (Scheme 7) (Table 2), whereas the migration of the nonterminal double bond in molecules of methyl esters of unsaturated fatty acids yields the *trans* isomer (Scheme 10, Table 3), with the label mainly incorporated into the allyl positions and at the double bonds.

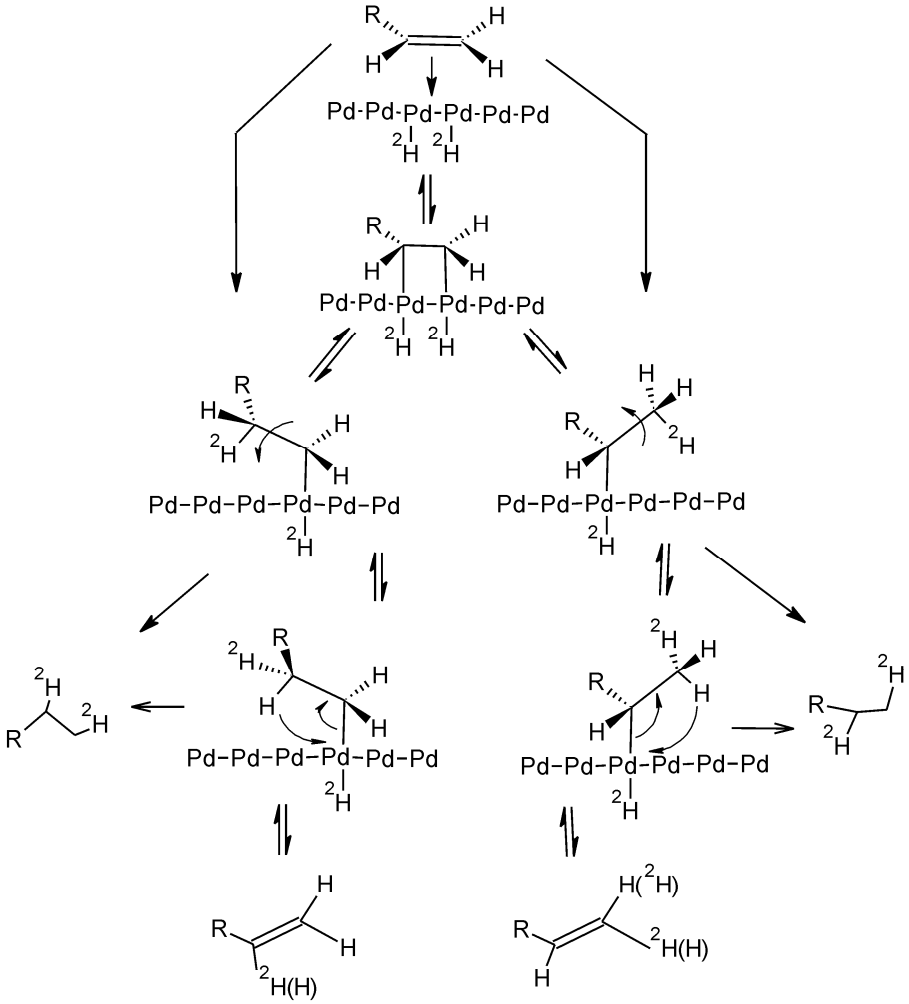
The possibility of the hydrogenation and isomerization of the double bonds and of the isotope exchange on a single active site was also demonstrated in experi-

Table 2. Analysis of reaction mixtures formed by hydrogenation of the double bond in methyl undec-10-enoate on 5% Pd/$BaSO_4$ in the presence of ethyl acetate (E), dioxane (D), and benzene (B)

Hydrogenation products	Time, min	Product content, %		
		E	D	B
Methyl undecanoate	10	44	46	48
	30	84	76	69
	60	100	93	82
Methyl *cis-iso*-undecenoate	10	14	13	13
	30	0	3	5
	60	0	0	1
Methyl *trans-iso*-undecenoate	10	2	5	0
	30	10	9	6
	60	0	5	8

Table 3. Distribution of ^{3}H (%) in fragments of molecules of fatty acids and prostaglandins (tritium introduction in the presence of Lindlar catalyst) [59]

Compound	Double bond	Carboxyl moiety	Alkyl moiety	Cyclopentane ring	Methyl arachidonate
Methyl arachidonate	14	–	47	–	39
Arachidonic acid	27	12	28	–	33
PGE_2	30	22	30	18	–
trans Isomer of PGE_2	54	12	23	11	–
trans Isomer of $PGF_{1\alpha}$	14	–	53	33	–
Methyl oleate	45	–	55	–	–
Oleic acid	54	23	23	–	–
trans Isomer of oleic acid	64	13	23	–	–



Scheme 11. Deuterium incorporation into a terminal double bond.

ments performed with homogeneous catalysts [60, 61]. This issue is described in more detail in Section III of this review.

Some authors suggest schemes in which the processes associated with the incorporation of hydrogen isotopes are interpreted as interaction of an organic compound with several atoms of the metal catalyst (Scheme 11) [62–65].

Table 4. Introduction of tritium label by heterogeneous catalytic isotope exchange [59, 69–74]

Compound	Reaction conditoins	Yield, %	MA, Ci mmol^{-1}
$PGF_{2\alpha}$ methyl ester	$^3H_2$, Lindlar catalyst, dioxane, 23°C, 1.5 h	75	0.05–0.07
$PGF_{2\alpha}$	$^3H_2$, 5% PdO/Al_2O_3, dioxane, 23°C, 1.5 h, 150 hPa	30	1.48–1.62
	$^3H_2$, $LaNi_5$, $LaNi_4Cr$, $LaNi_3Cu_2$, dioxane, 23°C, 22 h, 400 hPa	50–60	0.02–0.03
Eleutheroside B	$^3H_2$, 5% $Cu/CaCO_3$, dioxane, 23°C, 4 h, 400 hPa	40–45	0.18–0.19
Polyprenyl phosphate	$^3H_2$, 5% $Cu/CaCO_3$, dioxane, 23°C, 4 h, 400 hPa	30–35	0.005–0.008
6-Ketopalmitic acid	5% Pt/C, 160°C, 15 min	32	750.60
Hexadecane	5% Pt/C, 140°C, 15 min	80	472.50
Trichostatin	^3H_2O, 5% $Pd/BaSO_4$, dioxane–Et_3N, 140°C, 30 min	25–30	1.80
2-Amino-4-[β-hydroxyethylamino]anisole	^3H_2O, 115°C, 25 min, DMF	46	1.80
Pargyline	^3H_2O, 5% $Pd/BaSO_4$, dioxane–Et_3N, 23°C, 12 h	5	0.54
Dehydroabietic acid	^3H_2O (90 mCi mol^{-1}), PdO		0.013

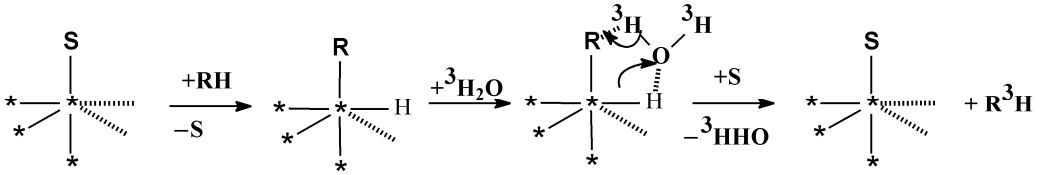
As seen from this scheme, the formation of products containing deuterium and double bonds simultaneously is possible along with the hydrogenation. If the C–Pd bond is formed via elimination of the terminal proton, the isotope exchange occurs at the nonterminal carbon atom, whereas in the case of the C–Pd bond formation via elimination of the nonterminal proton it occurs at the terminal carbon atom. In the latter case, deuterium is incorporated in the *trans* position relative to R. Thus, implementation of this scheme leads to the predominant formation of a definitely labeled product in accordance with the process described in Scheme 6. Incorporation of deuterium into the *cis* position relative to R is not considered in Scheme 11, but, according to Scheme 3, is associated with the label incorporation at dissociative mechanism of adsorption.

In some cases, when performing the reaction in solution at room temperature (introduction of tritium into aromatic compounds or compounds with possible keto–enol tautomerism), it becomes possible to obtain highly labeled compounds even by isotope exchange. For example, [1-^{3}H]glucose with the molar activity of 24 Ci mmol^{-1} [10] and purines and imidazole derivatives with the molar activity of 30–40 Ci mmol^{-1} [66, 67] were obtained by this method. The preparation of labeled aromatic compounds with the molar activity of 22–74 Ci mmol^{-1} and of aliphatic aldehydes with the molar activity of up to 20 Ci mmol^{-1} has been reported [68]. However, these data concern only compounds of specific structure. As a rule, isotope exchange between hydrogen isotopes and the majority of organic compounds at room temperature using solvents does not allow preparation of labeled products with the molar activity required for studying the reception and can be used only for preparing markers (Table 4).

Products with high molar activity can be prepared using procedures that do not involve solvents, which allows the reactions to be performed at high temperatures (Table 4).

Various methods were suggested for performing such reactions [75]. They mainly involve the spillover of activated hydrogen isotope species from the catalyst to the support and their reactions with substrate molecules adsorbed on the support surface. Some authors assume that activated hydrogen species can migrate to the support even through the gas phase [75]. It is also assumed in some papers that hydrogen spillover is possible only owing to defects on the catalyst surface and to the presence of impurities [76, 77]. Apparently, the latter conclusion does not take into account the possibility of the transfer of electrons from the metal catalyst to the support due, e.g., to tunneling effects. The possibility of the interaction of the electrons generated by catalyst active sites with the support and substrate does not contradict the results of studies of tunnelling effects in chemical reactions [78, 79]. In other words, the hydrogen spillover results from the spillover of electrons.

In particular, Prasittichai et al. [80] demonstrated the possibility of electron tunnelling through various insulators. The general conclusion that has been made is that the electrons, owing to the tunnelling effect, can cover long (on the microscopic scale) distances in migration over inorganic supports. This study shows that the tunnelling effects give rise to gradient of electrons



Scheme 12. Label incorporation on a catalyst untreated with gaseous tritium.

in the bulk of the insulator. It follows from these experimental studies that a part of electrons generated on catalyst active sites migrate to the support and become solvated on support atoms. Specifically this fact makes the migration of hydrogen cations from the metal to the support possoible. When the hydrogen cations and electrons getting onto the support surface owing to tunnelling effects form ion pairs (H^+,ē), which neutralize the negative charge on the support, the migration of a new portion of electrons from the catalyst active sites to the support becomes possible.

As a result, species activated on metal catalysts form clusters solvated on the support surface with different numbers of ion pairs of hydrogen isotopes and electrons. When the flow of electrons and activated tritium species reaches the substrate applied onto the support, clusters of solvated hydrogen cations and electrons start to form in the pool of the organic compound also. Different ability of even structurally similar compounds to solvate hydrogen cations and electrons may be responsible for significant differences in the efficiency of the incorporation of hydrogen isotopes into these compounds.

II.2. Mechanism of Introduction of Hydrogen Isotopes into Organic Compounds in the Presence of Heterogeneous Catalysts via Isotope Exchange with Tritium or Deuterium Water

When using heterogeneous catalysts (Schemes 3, 4) (Table 4), the efficiency of the isotope exchange of an organic compound with tritium or deuterium water using a traditional procedure (stirring at room temperature of a dioxane solution of a substrate with tritium water in the presence of a catalyst and triethylamine) is approximately the same as when using gaseous hydrogen isotopes (Scheme 12):

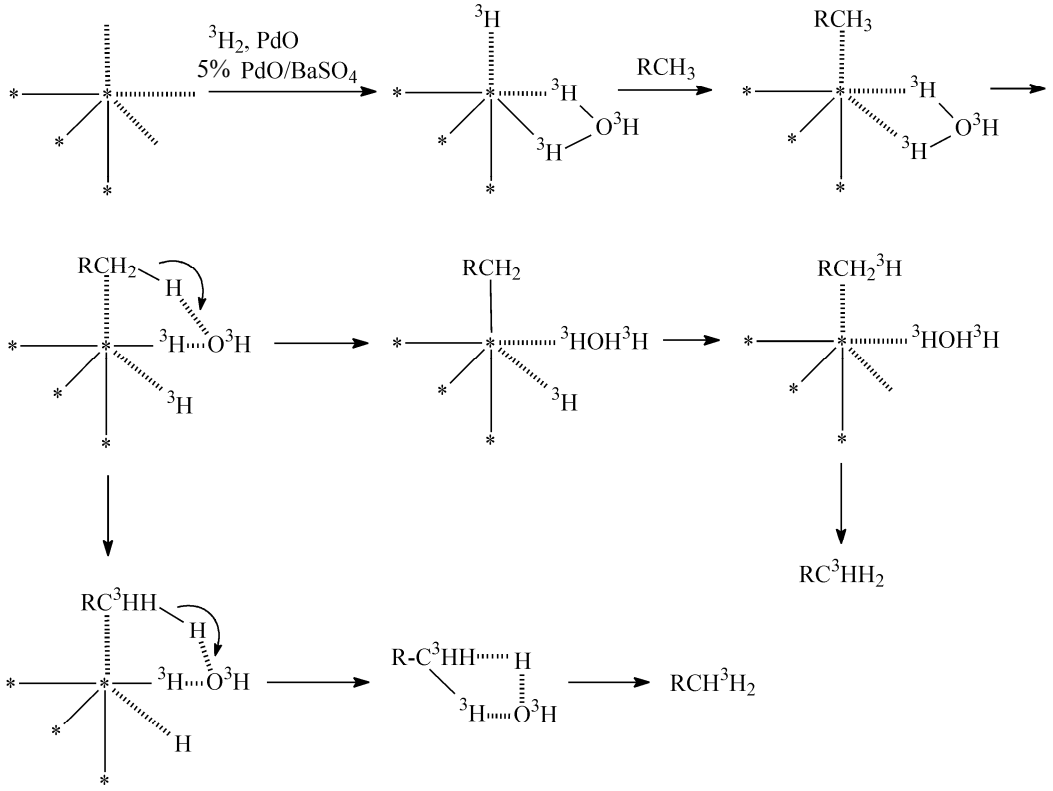
This is apparently associated with the fact that, when using heterogeneous catalysts, the first step of tritium incorporation coincides with the first step of the hydrogen isotope incorporation in the case when the label source is gaseous tritium, i.e., the first step involves dissociative adsorption of the substrate, in which the shift of the electron density in the carbon–metal system facilitates the protium transfer from carbon to the metal.

The isotope exchange efficiency can be enhanced by performing the reaction at 100–200°C with 100% ^3H_2O, prepared by the reduction of PdO in a gaseous tritium atmosphere, using the catalyst applied onto an inorganic support. As a result, the reaction ampule will contain, along with tritiuim water, also the catalyst which will contain activated tritium as a result of hydrogen spillover. After transferring a solution of a substrate in an aprotic solvent, to which Et_3N [14], $NaOCH_3$ [81], butyllithium [82–84], DBU, or 15% KOH [85] is usually added, into an ampule, the ampule is sealed and heated to a temperature optimum for each compound for the required time (Table 5). If the substance stands these conditions, then the optimum reaction time can be determined by monitoring the variation of the hydrogen isotope content in time (e.g., by the integral NMR signal) [86].

The enhancement of the isotope exchange efficiency in the presence of catalysts containing activated hydrogen isotope species can be accounted for by the appearance of acid sites $[^3H^+(^3H_2O)_n]$, where n is the number of water molecules in such clusters, on the catalyst surface [87]. Quantum chemical calculations of systems in which water clusters protonated with activated hydrogen, occurring on the catalyst surface, participate in the isotope exchange were performed for water clusters containing one to three water molecules [87]. The calculations show that the proton abstraction energy considerably increases with the water cluster size. As a result, the substrate complexation energy in interaction with the protonated water cluster $[^3H^+(^3H_2O)_n]$ decreases in the order n = 1, 2, 3 and approximately linearly correlates with energy of the proton abstraction from the corresponding water clusters.

Table 5. Introduction of tritium label by isotope exchange with tritium water [27, 70]

Compound	Reaction conditions	MA, Ci mmol^{-1}	Yield, %
Thiazofurin	PdO, 5% PdO/Al_2O_3, 0.5 h, 170°C, dioxane–Et_3N (10 : 1)	8.1	35
Alprazolam	PdO, 5% PdO/Al_2O_3, 1 h, 180°C, dioxane–Et_3N (10 : 1)	27.2	20
Zaleplon	PdO, 5% PdO/Al_2O_3, 0.7 h, 180°C, dioxane–Et_3N (9 : 1)	18.4	45
Methyl (*E*)-2-[6-cyanophenoxy)pyrimidin-4-yloxy]phenyl-3-methoxyacrylate	PdO, 23°C, 20 h, dioxane–Et_3N (9 : 1)	4.6	19
Ciprofloxacin	PdO, 5% PdO/Al_2O_3, 0.5 h, 150°C, dioxane–Et_3N (9 : 1)	35.1	7



Scheme 13. Isotope exchange with tritium water on a catalyst treated with gaseous tritium.

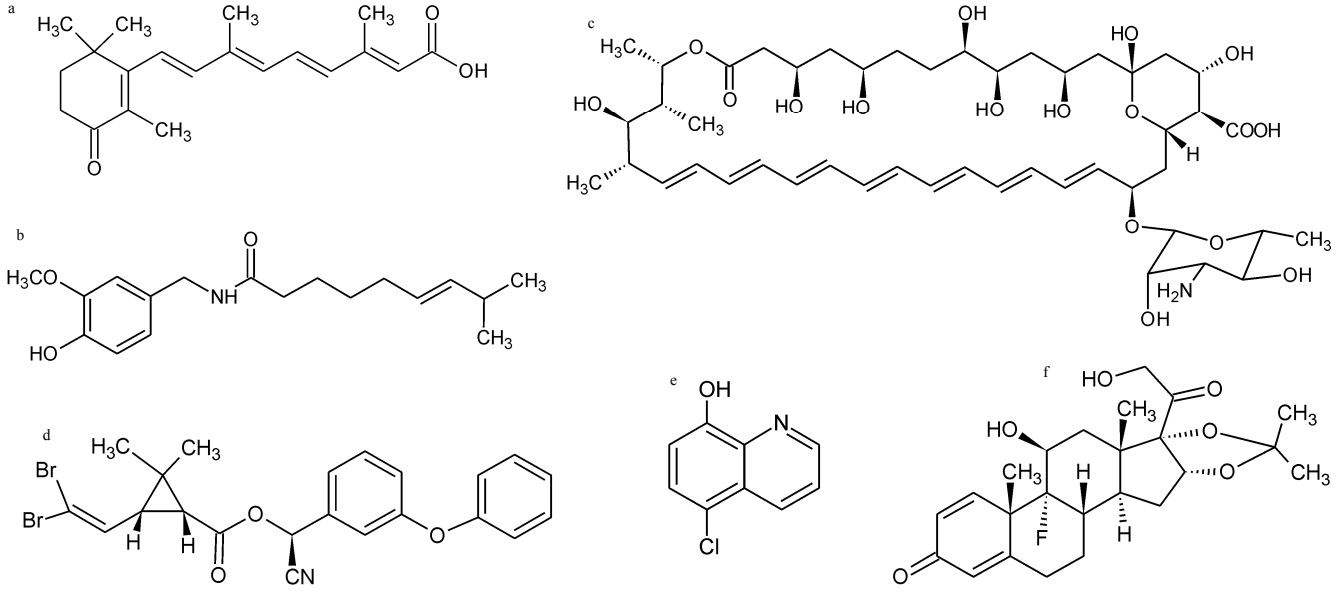
It follows from the calculation results that the complexation energy varies depending on the strength of acid sites, which strongly influences the isotope exchange efficiency. Thus, an increase in the concentration of tritium water in the solution not only leads to increased formation of radiolysis products, but also decreases the efficiency of the isotope exchange with organic substrate molecules. Scheme 13 illustrates the course of the isotope exchange under such conditions.

This modified labeling procedure appeared to be suitable for preparing highly unsaturated compounds with the molar activity sufficient for performing many biological experiments (Table 6).

It is known that molecular hydrogen can displace chemisorbed organic molecules and hence solvent and water molecules from active sites of the catalyst with high coordination unsaturation, on which isomerization, hydrogenolysis, hydrogenation, and isotope exchange occur most efficiently [88]. Hence, when using molecular hydrogen, n in the water cluster $[^3H^+(^3H_2O)_n]$ can be expected to decrease. As a result, the efficiency of the isotope exchange with deuterium or tritium water should increase. To check this assumption, isotope exchange with deuterium water was performed in the presence of gaseous protium whose participation in exchange reactions could lead only to a decrease in the deuterium incorporation. The results obtained fully confirmed the conclusions following from the quantum-chemical calculations: Under the action of gaseous protium, the probability of the isotope exchange

Table 6. Introduction of tritium label by isotope exchange with 100% ^3H_2O (solvent: dioxane or DMSO with Et_3N, palladium catalysts)

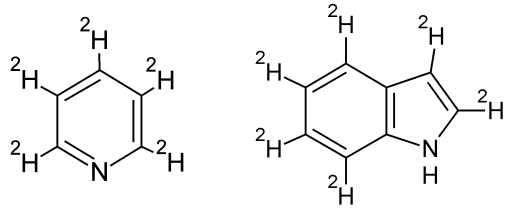
Compound	Reaction conditions	MA, Ci mmol^{-1}	Yield, %
Oxoretinoic acid[a]	30 min, 125°C, dioxane, PdO, 5% PdO/$BaSO_4$	1.8	28
Capsaicin[b]	30 min, 145°C, dioxane, PdO, 5% PdO/$BaSO_4$	7.0	30
Deltamethrin[c]	20 min, 140°C, dioxane, PdO, 5% Pd/$BaSO_4$	9.3	37
Amphotericin B[d]	30 min, 120°C, DMSO, PdO, 5% PdO/$BaSO_4$	18.2	36
5-Chloro-8-hydroxyquinoline[e]	35 min, 140°C, 5% Pd/$BaSO_4$, ^3H_2O, dioxane	3.8	80–90
Kenalog[f]	30 min, 140°C, dioxane, PdO, 5% PdO/$BaSO_4$	3.5	22



between deuterium water and organic compounds increased.

A series of organic compounds were perpared using this procedure (isotope exchange of a substrate with deuterium water in a gaseous protium atmosphere) [89–93].

For example, when performing isotope exchange with ^2H_2O in the presence of 10% Pd/C or 5% Rh/C in a protium atmosphere at 110–180°C for 12–24 h, deuterium was incorporated into both cyclic and linear alkanes [89] and into aromatic heterocycles [92]:

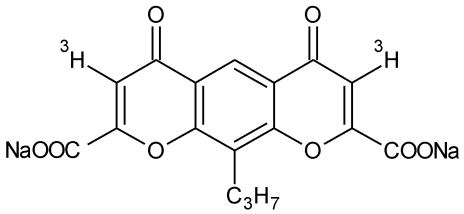


The yields appeared to be high. The only drawback of this method is that it is unsuitable for isotope exchange with unsaturated compounds. On the other hand, introduction of hydrogen isotopes into unsaturated compounds is one of the main reasons for performing isotope exchange with deuterium or tritium water. From the theoretical viewpoint, the results obtained give one more evidence for the dependence of the isotope exchange with deuterium or tritium water on the probability of the formation of water clusters protonated with activated hydrogen. Hence, the presence of activated hydrogen species on the catalyst indeed stimulates the isotope exchange and leads to the formation of products with high deuterium or tritium content.

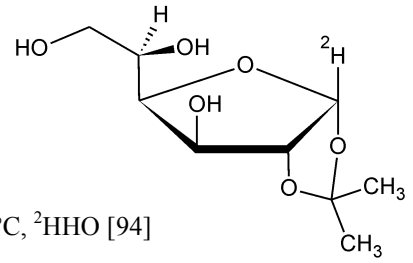
Thus, when considering the main methods for introducing the label in the presence of heterogeneous catalysts, it should be taken into account that the process occurs in a complex multicomponent system.

II.3. Examples of Using Heterogeneous Catalysts

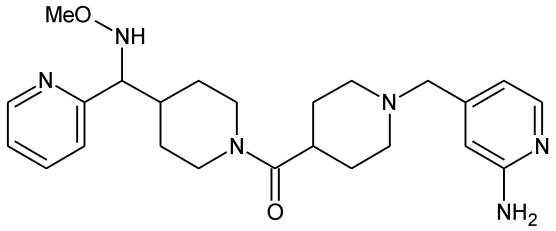
II.3.1. Isotope exchange. Isotope exchange with hydrogen isotopes was performed using 5% Ru/C, Raney catalyst, Rh or Pd black, 5% PdO/$BaSO_4$, and 5% Rh/Al_2O_3 (Scheme 14) [74, 89, 94–97].



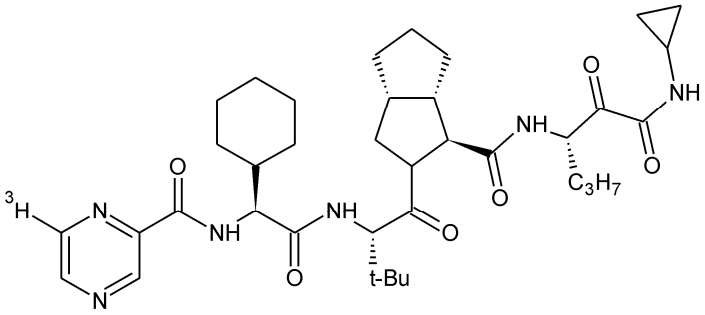
5% Ru/C, ^{3}HHO, DMF, 18 h [89]



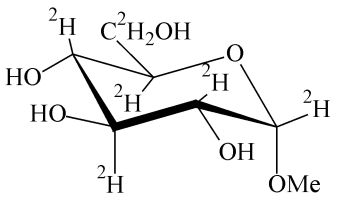
Raney nickel, 100°C, ^{2}HHO [94]



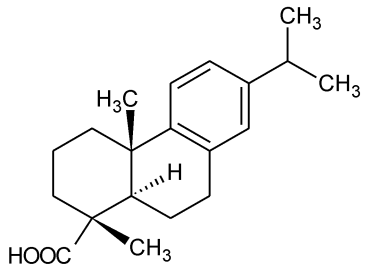
Raney nickel, tritium water (50 Ci mL^{-1}), molar activity 0.3 Ci mmol^{-1} (51% in 6-position of the 2-aminopyridine ring and 43% in the piperidine ring) [95]



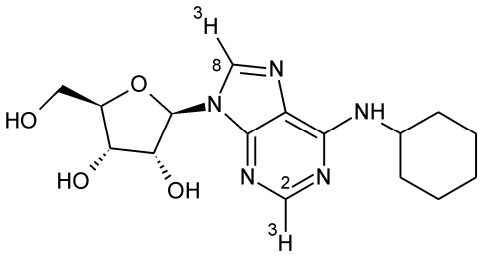
SCH D, Rh black, $^3H_2$, tetrahydrofuran (THF), 16 h, 15 Ci mmol^{-1} [96]



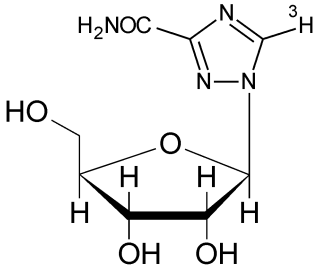
Raney nickel, 100°C, deuterium water [94]



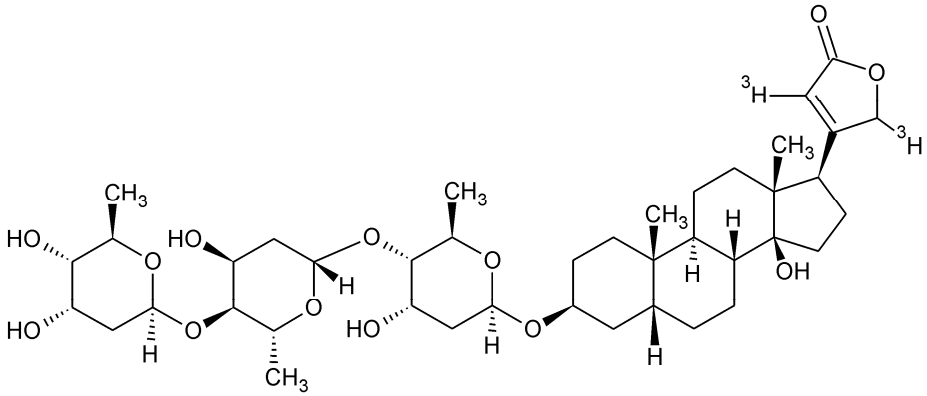
Dehydroabietic acid, Pd, [^{2}H]H_2O or [^{3}H]H_2O (90 mCi mmol^{-1} [^{3}H]H_2O), molar activity 12.6 mCi mmol^{-1} [74]



N^6-[2,8-^{3}H]Cyclohexyladenosine, 5% Rh/Al_2O_3, $^3H_2$, 0.1 M HCl, THF, 23°C, 16 h, 30.2 Ci mmol^{-1} [97]

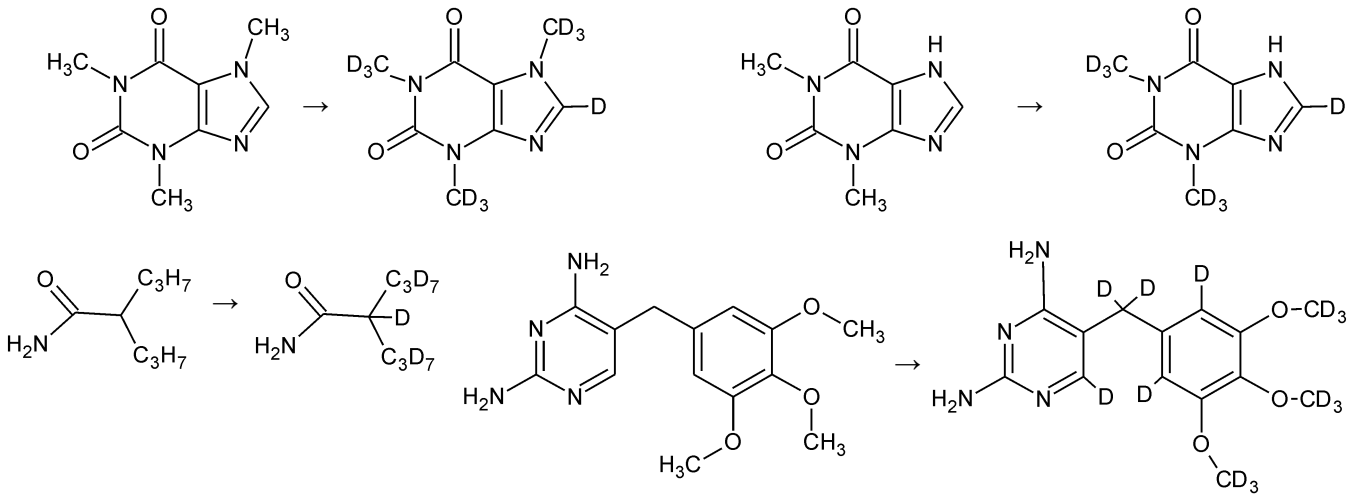


Ribavirin, 5% PdO/$BaSO_4$, 0.05 M K_2HPO_4, pH 9.3, $^3H_2$, 18 h, 24 Ci mmol^{-1} [96]



[^{3}H]Digitoxin, DMF, 5% Rh/Al_2O_3, 100 Ci of tritium water (58 Ci mmol^{-1}), 80°C, 48 h, 20–40 Ci mmol^{-1} [97]

Scheme 14. Types of compounds labeled with hydrogen isotopes by isotope exchange.



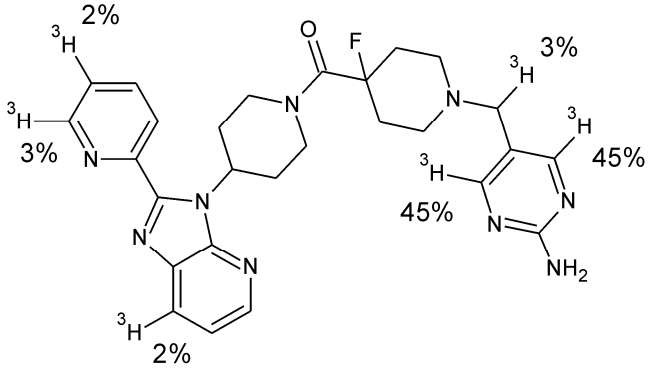
Scheme 15. Deuterium distribution upon isotope exchange performed using carbon as a support. Reaction conditions: 10% Pd/C (5% Pt/C, 10% Rh/C, 10% Ru/C, 10% Au/C), $^2H_2$, ^2H_2O, 90–180°C, 24–34 h.

As seen from these data, high molar activities are reached when using gaseous tritium. Isotope exchange with tritium water is efficient if about 100 Ci of tritium water with the molar activity close to the maximum possible value (58 Ci mmol^{-1}) is used.

Labeling of more thermally stable compounds can be performed under more severe conditions (Scheme 15) [98].

At 90–180°C, deuterium can undergo exchange with protium not only in aromatic and heteroaromatic fragments, but also at mono-, bi-, and trisubstituted carbon atoms.

The steps in which the hydrogen isotope is introduced can vary depending on the task. For example, when the reaction was performed directly with SCH C, the isotope was mainly incorporated into the pyrimidine ring (tritium water, dioxane, Raney catalyst, 110°C, 60 h). In this case, the molar activity of the product relative to that of water was approximately 40–60%, or 0.4–0.6 Ci mmol^{-1}:

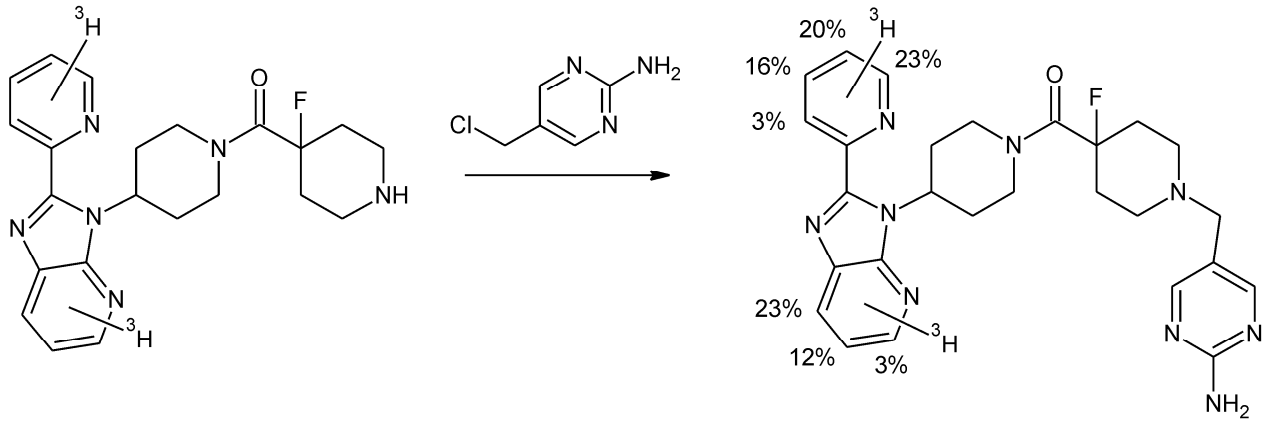


If it was necessary for boilogical studies to have tritium only in pyridine and imidazopyridine rings, the isotope was introduced into the corresponding precursor under the same conditions, which was followed by condensation with the pyrimidine constituent (Scheme 16).

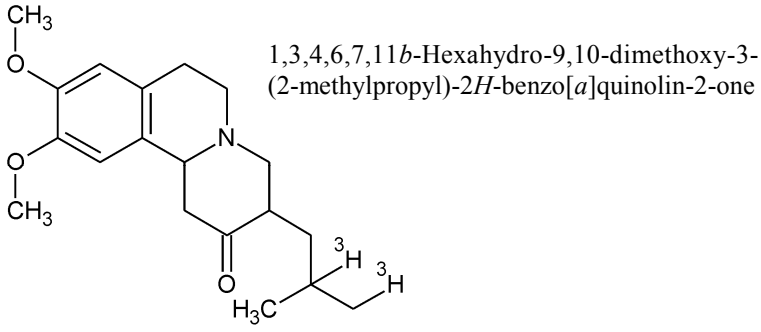
When using the second route, the tritium incorporation increased by a factor of approximately 1.7. This is apparentely associated with the fact that the tritium incorporation in the first route occurred only in interaction of the pyrimidine ring with the catalyst active site (at three carbon atoms), whereas in the second route the isotope exchange efficiently occurred in both imidazopyridine and pyridine rings (at seven carbon atoms) [96].

As noted above, the efficiency of the isotope exchange can be increased by performing reactions without using solvents (Table 4). This can be illustrated by the example of the synthesis of octarphin with the molar activity of 28 Ci mmol^{-1}. This compound after application of its aqueous solution onto alumina and evaporation of the suspension on a rotary evaporator was mechanically mixed with 5% Rh/Al_2O_3, and the mixture obtained was kept at 170°C for 20 min in a gaseous tritium atmosphere [99].

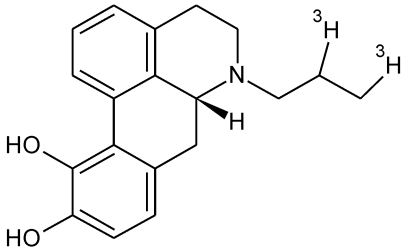
II.3.2. Hydrogenation. Reduction of unsaturated carbon–carbon bonds is a classical method for incorporation of hydrogen isotopes by hydrogenation. For example, tritium-labeled compounds with high molar activity were prepared by hydrogenation of precursors containing an allyl fragment [100, 101] (Scheme 17).



Scheme 16.



1,3,4,6,7,11*b*-Hexahydro-9,10-dimethoxy-3-(2-methylpropyl)-2*H*-benzo[*a*]quinolin-2-one



(–)*N*-*n*-[^{3}H]Propylnorapomorphine

Scheme 17.

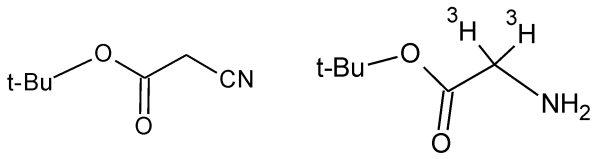
Numerous studies deal with the hydrogenation of unsaturated lipids [59, 75, 102–105].

For example, lecithin was hydrogenated in the presence of 5% Pd/$BaSO_4$ in dichloromethane at room temperature for 2 h (Scheme 18). In the process, tritium was incorporated not only at the carbon atoms initially involved in double bonding [106]. This result was attributed to the migration of double bonds in the course of hydrogenation (this process is shown in the generalized form in Scheme 19). This approach to interpretation of processes associated with the hydrogenation of unsaturated carbon–carbon bonds is similar to the approach presented in Schemes 7 and 10.

In this case, the new result is the higher mobility of double bonds in polyenoic acids compared to monoenoic acids. Therefore, in hydrogenation of polyenoic acids tritium becomes bonded to a larger number of carbon atoms.

The reduction of a nitrile group to an amine can serve as an example of the hydrogenation of unsaturated carbon–heteroatom bonds [101, 107] (Scheme 20).

Such reactions often are not successful. For example, in reduction on Raney catalyst in a tritium atmosphere in *i*-PrOH (0.5 h, 23°C), the molar activity of the product reached only 35 mCi mmol^{-1} [107]:

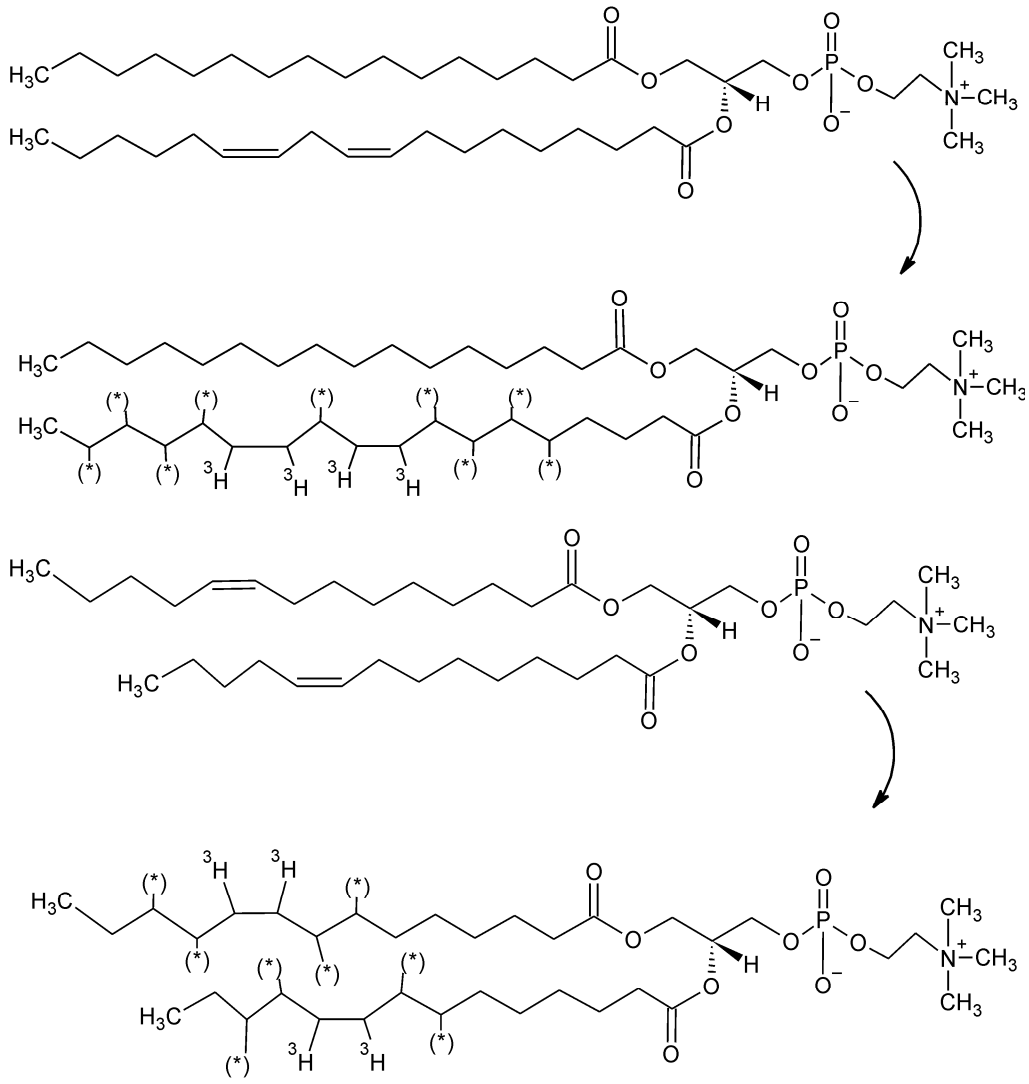


If the reduction of unsaturated carbon–heteroatom bonds or aromatic rings in a solvent is inefficient or a product with insufficient molar activity is formed, the process can be performed without solvent on heating. Saturated amines and acids were prepared by this procedure (Table 7).

For example, hydrogenation of 2-methylpropenoic acid, which was treated with gaseous tritium at 170°C on 5% Pd/C, yielded the labeled acid with the molar activity approximately three times higher than the level expected upon reduction of the double bond [108]. In reduction of benzylamine without solvent,

Table 7. Reduction of organic compounds without using solvents

Starting compound	Reaction conditions	MA, Ci mmol^{-1}	Yield, %
Benzylamine	5% Rh/Al_2O_3, 60°C, 3 h	210	45
2-Methylpropenoic acid	5% Pd/C, 170°C, 20 min	152	80
11-Cyanoundecanoic acid	5% Rh/C, 80°C, 3 h	55	51

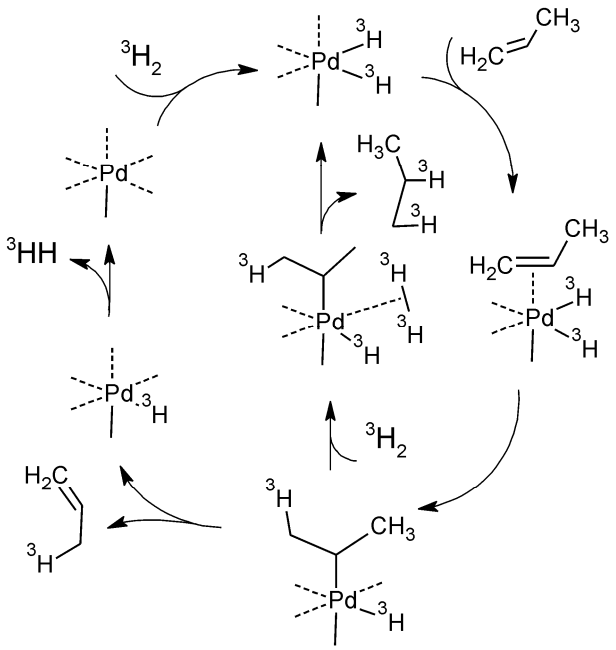


Scheme 18. Tritium distribution upon reduction of double bonds in phospholipids.

the molar activity appeared to be almost five times higher than that obtained when performing the reaction in a methanol–0.5 M HCl (20 : 1) mixture as a solvent [109].

II.3.3. Dehalogenation. The hydrogen–halogen catalytic exchange (or dehalogenation) is known for a long time [110], but the first reports on the use of this reaction for preparing tritium-labeled compounds appeared much later [111, 112]. Both polar and nonpolar solvents are used for catalytic dehalogenation in a gaseous tritium atmosphere. The tritium halide formed in the reaction should be neutralized, because it poisons the catalyst, which leads to the reaction deceleration [10]. If a substrate molecule contains several different halogens, it is possible to remove a stronger nucleophile without affecting the other halogen atoms. For example, when a molecule contains Cl in combination with I or Br, the heavier halogen is removed.

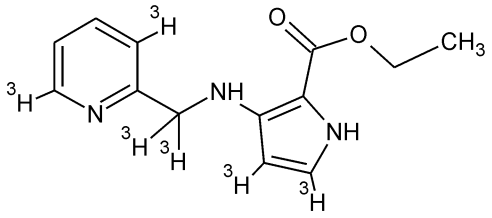
Dehalogenation is usually performed in the presence of hydrogenation catalysts (supported Pd in most



Scheme 19. Mechanism of the formation of the set of products in hydrogenation of unsaturated carbon–carbon bonds (the process occurs on Pd atoms with the degree of coordination unsaturation equal to 3).

cases). Pd supported on carbon is used for this purpose most frequently. With this catalyst, labeled 28-homocastasterone (5.8 Ci mmol^{-1}) [113, 114], (*S*)-4'-(2-(4-aminotetrahydro-2*H*-pyran-4-carboxamido)-2-cyanoethyl)-3-biphenyl-4-yl methanesulfonate (12.4 Ci mmol^{-1}) [115], AZD5069 (25.1 Ci mmol^{-1}) [116], TAK875 (16.2 Ci mmol^{-1}) [117], veratridine (4.48 Ci mmol^{-1}), and apomorphine (33 Ci mmol^{-1}) [101] were prepared. Some other catalysts were also used (Table 8) [101, 118–123].

It is intreresting that, in dehalogenation of ethyl 4,5-dibromo-3-(pyridin-2-ylmethylamino)-1*H*-pyrrole-2-carboxylate, the label was incorporated not only at the carbon atoms initially bearing bromine atoms, but also in other fragments of the molecule owing to isotope exchange:

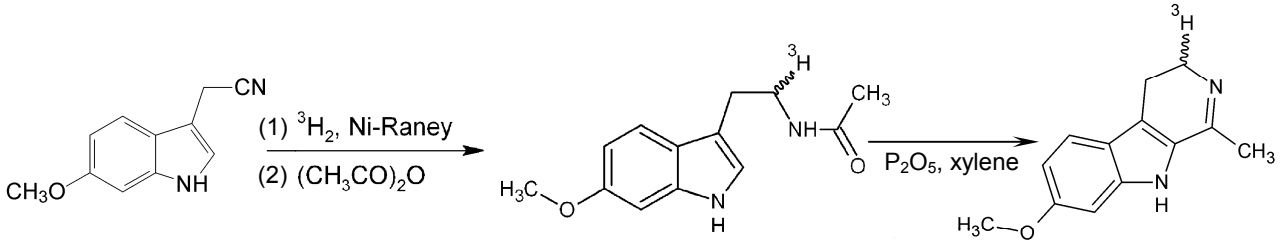


Available data show that the amount of deuterium or tritium incorporated upon dehalogenation is 1.5–2 times smaller than the amount of the halogen atoms removed. For example, debromination of a compound containing two bromine atoms yielded fully debrominated products containing both one and two deuterium atoms (Scheme 21). The ratio of these products depended on the reaction conditions (Table 9).

When using methanol, the percent ratio between the products with two and one deuterium atoms was 70 : 30. This may be due to the fact that a fraction of gaseous deuterium could exchange with labile methanol protons to form CH_3O^2H and ^2HH. When ^2HH participates in the dehalogenation, the compound formed contains one deuterium atom. Indeed, when using an aprotic solvent, the compound containing one deuterium atom was not formed, but the yield of the desired product was as low as ~5%. The product containing two deuterium atoms could be obtained in high yield using $C^2H_3O^2H$ as a solvent (Table 9).

[^{3}H]DPA-714 with the molar activity of 57 Ci mmol^{-1} was obtained using gaseous tritium and common methanol; i.e., tritium was incorporated in a larger amount than it could be expected if the ratio of the products with two and one tritium atoms remained 70 : 30.

The tritium distribution in the [^{3}H]DPA-714 molecule (25.3% 1^3H, 23.6% 2^3H, 15.9% 3^3H, 14.0% 4^3H,

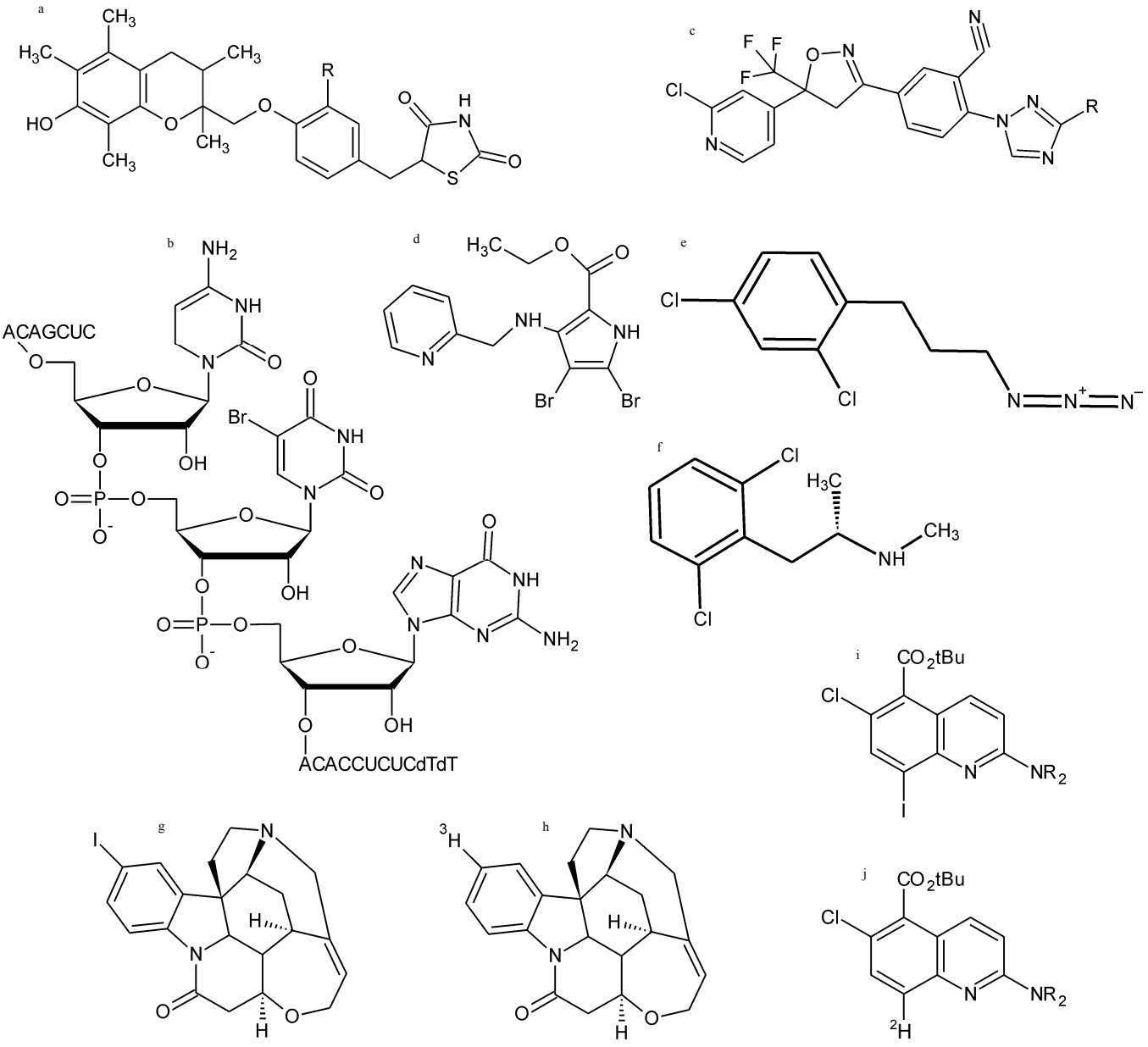


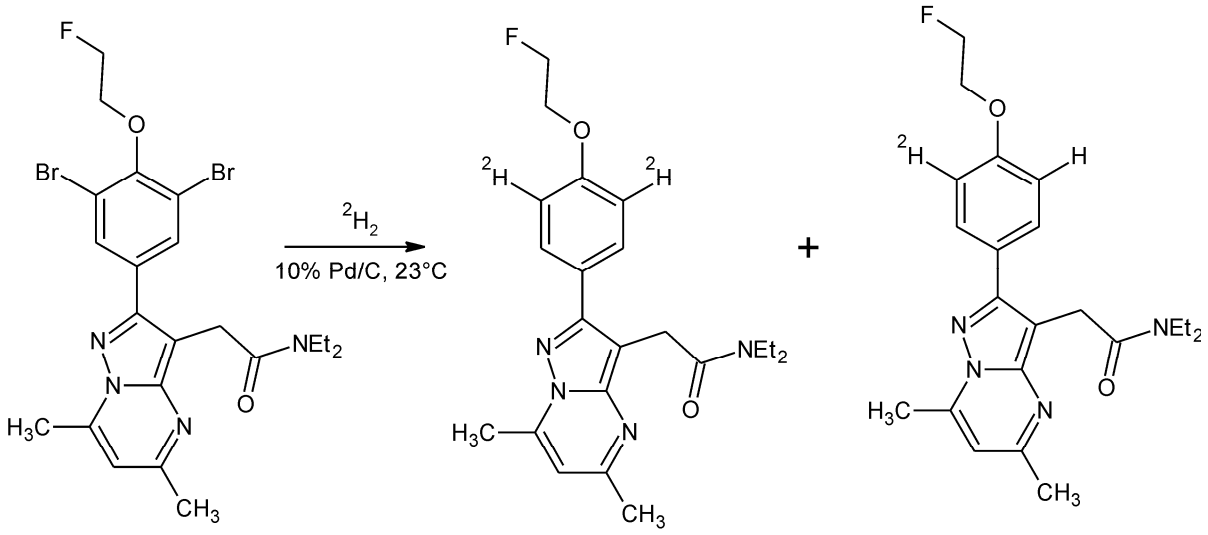
[^{3}H]Harmaline, 37 Ci mmol^{-1}

Scheme 20.

Table 8. Conditions of dehalogenation of organic compounds

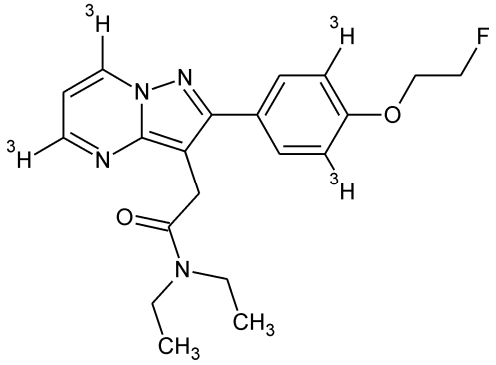
Compound	Reaction conditions	MA, Ci mmol^{-1}
Triglitazone[a] (R = I, [^{3}H]) [118]	10% Pd/$CaCO_3$, $^3H_2$, DMF, 320 hPa, 0°C, 2 h	23
RNAs[b] [119]	10% Pd/C, $^3H_2$, DMF–H_2O (80 : 20), (iPr)$_2$EtN, 170–270 hPa, 23°C, 6 h	1.9
[c], R = Br, then ^{3}H [120]	Lindlar catalyst, $^3H_2$, ethanol, 23°C, 4 days	29
Ethyl 4,5-dibromo-3-(pyridin-2-ylmethylamino)-1*H*-pyrrole-2-carboxylate[d] [121]	PdO, $^3H_2$, DMF, Et_3N, 807 hPa, 23°C, 12 h	43.2
(*S*)-(3,5-Dichlorophenyl)-2-propyl azide[e] [109]	10%Pd/C, Et_3N, THF–methanol (5 : 4), 5–12 h	30.1
(*S*)-2,6-Dichloromethamphetamine[f] [122]	20% Pd(OH)$_2$/C, Et_3N, THF–methanol (5 : 4), 5–12 h	38.3
Iodostrychnine[g] → [^{3}H]strychnine[h] [101]	$^3H_2$, 10% Pd/Al_2O_3, benzene, 23°C, 2 h	25.0
[i] → [j] [123]	Pd/C Et_3N, $^2H_2$	–





Scheme 21. Dehalogenation of a bromine-containing compound with deuterium ($^2H_2$ pressure 930 hPa, 20 min) [124].

4.3% 5^3H; reaction conditions: $^3H_2$, 10% Pd/C, 23°C, methanol, 20 min) [124] allowed the result obtained to be rationalized.



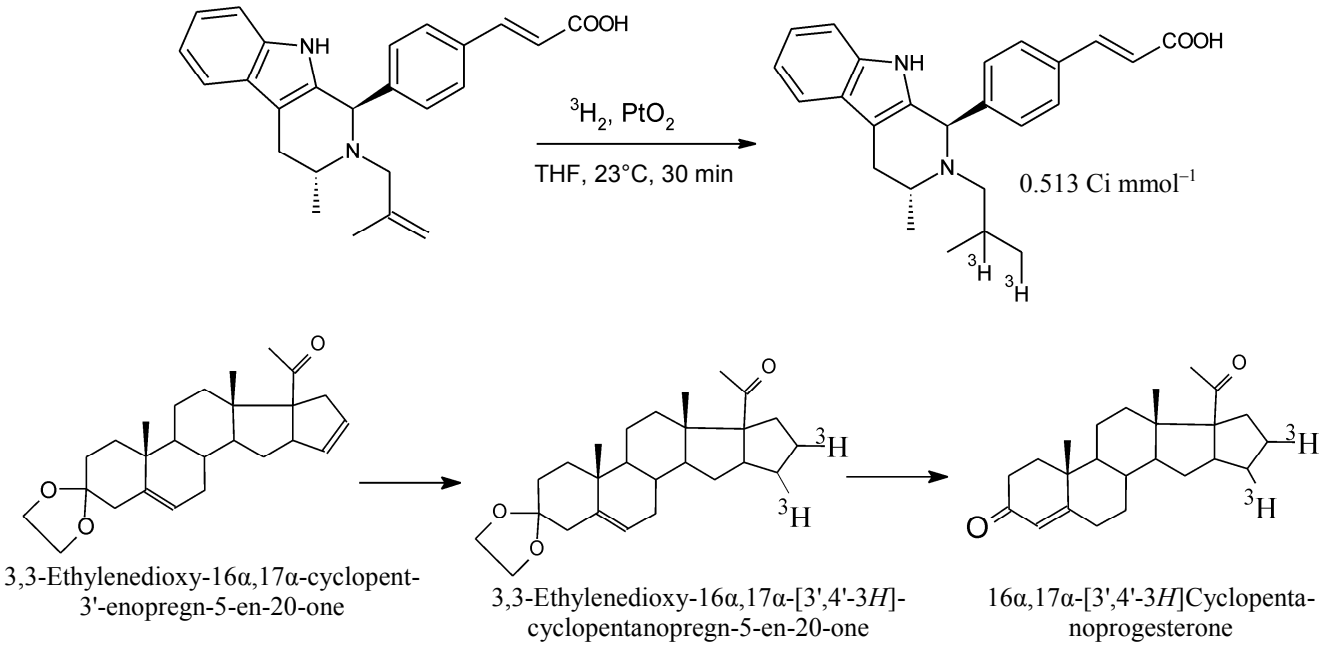
The data obtained show that the ratio of the products with two and one hydrogen isotopes approximately coincides with that obtained in treatment of the starting compound with deuterium. Both bromine atoms were replaced by tritium in 75% of cases, and one bromine atom was replaced by tritium and the other, by protium in 25% of cases. The remaining amount of tritium was incorporated into methyl groups by isotope exchange. Thus, the total amount of tritium incorporated into DPA-714 was about 2 atoms. Without isotope exchange, the mean amount of tritium would be no more than 1.8 atom per DPA-714 molecule.

Table 9. Yield of *N*,*N*-diethyl-2-(2-(4-(2-fluoroethoxy)phenyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidin-3-yl)acetamide (DPA-714) containing one and two deuterium atoms, reached using various solvents

Solvent	Reaction time	^2H (2 atoms)	^2H (1 atom)
CH_3OH	1 h	~70%	~30%
$C^2H_3O^2H$	30 min	~95%	~5%
Toluene	4 days	~5%	–

II.3.4. Selective hydrogenation and dehalogenation. Optimization of the conditions when performing selective hydrogenation consists in the choice of a catalyst for which the adsorption of the starting compound and reaction products on the active sites are appreciably different. As a result, the selective hydrogenation product leaves the reaction zone and can be isolated in preparative amounts. For example, hydrogenation of Ph–C≡C–C≡C–Ph in the presence of Pd on coal yields $Ph(C^3H_2)_4Ph$, whereas with Pd on $BaSO_4$ $PhC^3H_2C^3H{=}C^3HC^3H_2Ph$ is formed with the molar activity of 232.5 Ci mmol^{-1} [125].

Two cases are possible in selective hydrogenation of one of several double bonds. The first case is when the hydrogenation rates of these bonds differ significantly and it is possible, e.g., to hydrogenate with tritium the double bound in the oleic moiety of cholesteryl oleate leaving the double bond in the cholesterol moiety intact; i.e., it is sufficient to find conditions at which the difference in the hydrogenation rates will be maximal [66, 126, 127]. However, in this case the molar activity of the product can be low, as, e.g., in selective hydrogenation of (*E*)-3-[4-[(1*R*,3*R*)-3-methyl-2-(2-methylallyl)-1,3,4,9-tetrahydropyrido[3,4-*b*]indol-1-yl]phenyl]prop-2-enoic acid [128]:



Scheme 22. Synthesis of 16α,17α-[3',4'-3*H*]cyclopentanoprogesterone.

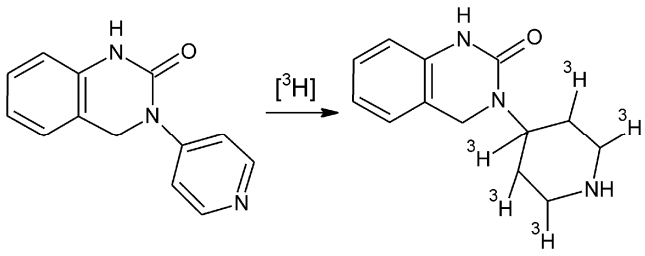
The second case is when it is necessary to introduce the corresponding protecting groups to ensure the required hydrogenation selectivity (Scheme 22) [108].

It is known that selective hydrogenation of one aromatic moiety in the presence of several other moieties (e.g., pyridine or benzyl groups) occurs in solution only at very low pH values pH [109, 129]. Under such conditions, very strong isotope dilution occurs, leading to an appreciable decrease in the molar activity of the labeled product, which was noted, e.g., in synthesis of (cyclohexylmethyl)amine from benzylamine. Considerably lower isotope effects can be expected when using the solid-phase method.

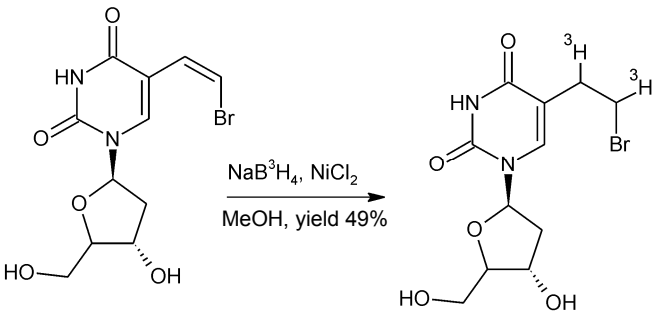
For example, it appeared possible to hydrogenate the pyridine ring without affecting the benzyl ring. Activated tritium species (cations) protonate the pyridine moiety more efficiently than the benzene moiety. In the process, the aromatic structure of the pyridine moiety is disturbed, and its hydrogenation is facilitated. For example, in selective hydrogenation of a compound of such structure, the labeled product contained more than five tritium atoms (174 Ci mmol^{-1}). The content of the desired product in the reaction mixture was seven times higher than the content of all the other productsl; i.e., the process selectivity was high [130] (Scheme 23).

Selective hydrogenation of halogen-containing compounds and selective dehalogenation of unsaturated compounds also strongly depend on the reaction conditions. In the presence of triethylamine or quinoline, the major process is dehalogenation, whereas without these additives the hydrogenation occurs preferentially. Indeed, using 5% Pd/$BaSO_4$ and ethyl acetate [27], we were able to selectively hydrogenate (1*R*,2*R*)-*N*-[2-(4'-methylpiperidylmethyl)cyclohex-4-enyl]-4-amino-5-chloro-2-cyclopropylmethoxybenzamide, and using 10% Pd/$BaSO_4$ and a methanol–triethylamine mixture, Cerny et al. [131] selectively dehalogenated the bromo derivative of cyclosporin.

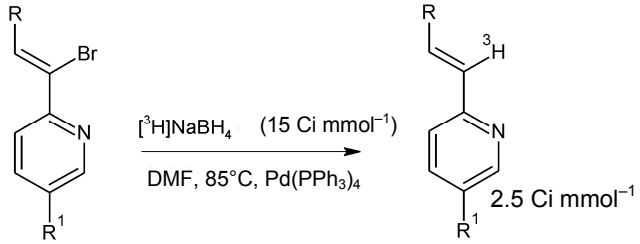
There are also more exotic ways to increase the selectivity of reactions with halogen-containing unsaturated compounds. For example, treatment of $NiCl_2$ with sodium borotritide yields a mixture of products ($^3H_2$, H_3BO_3, $^3HH_2BO_3$, NaCl, Ni_2B, $^3H_2HBO_3$, $^3H_3BO_3$) that selectively hydrogenates carbon–carbon



Scheme 23.



Scheme 24.



Scheme 25.

double bonds without dehalogenation of the organic compound [132] (Scheme 24).

On the contrary, the use of $Pd(PPh_3)_4$ and $[^3H]NaBH_4$ allowed dehalogenation of an unsaturated compound [133] (Scheme 25).

The selectivity of deuterium or tritium incorporation into organic molecules can be increased using homogeneous catalysts. Furthermore, the use of homogeneous catalysts allows in some cases efficient isotope exchange to be performed under milder conditions.

III. INTRODUCTION OF HYDROGEN ISOTOPES INTO ORGANIC COMPOUNDS IN THE PRESENCE OF HOMOGENEOUS CATALYSTS

III.1. Mechanism of Introduction of Hydrogen Isotopes by Hydrogenation of Organic Compounds Using Gaseous Deuterium or Tritium in the Presence of Homogeneous Catalysts

Progress in this field is determined by the development of the chemistry of transition metal coordination compounds exhibiting catalytic effect in a homogeneous system. Some dihydride and monohydride complexes and some adducts formed in the reaction were isolated and characterized by spectroscopic methods [60]. For example, the structures determined for $IrH_2Cl\cdot(CO)(PPh_3)_2$, $RhH_2Cl(PPh_3)_2\cdot CH_2Cl_2$, $RuHCl(PPh_3)_3$, and adduct of 1,3-butadiene with $CoH(CN)_5K_3$ are shown in Scheme 26.

The mechanism of the hydrogenation on the monohydride complex can be illustrated by Scheme 27 [60, 61].

The mechanism of the hydrogenation on the dihydride complexes can be illustrated by Scheme 28 [60] (where S is the solvent molecule).

Examples of using such catalysts are given in Table 10 [70].

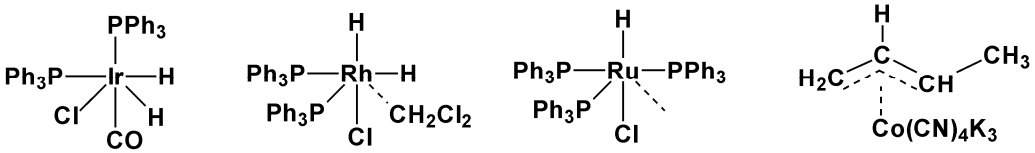
A procedure for labeling in the presence of homogeneous Ir catalysts via formation of a complex of a substrate molecule with two free coordination bonds of the Ir atom (Scheme 29, S = benzophenone) has also been reported [134].

Apparently, the product formed by hydrogenolysis of the Ir–C bond with activated tritium contains the label in the *o*-position.

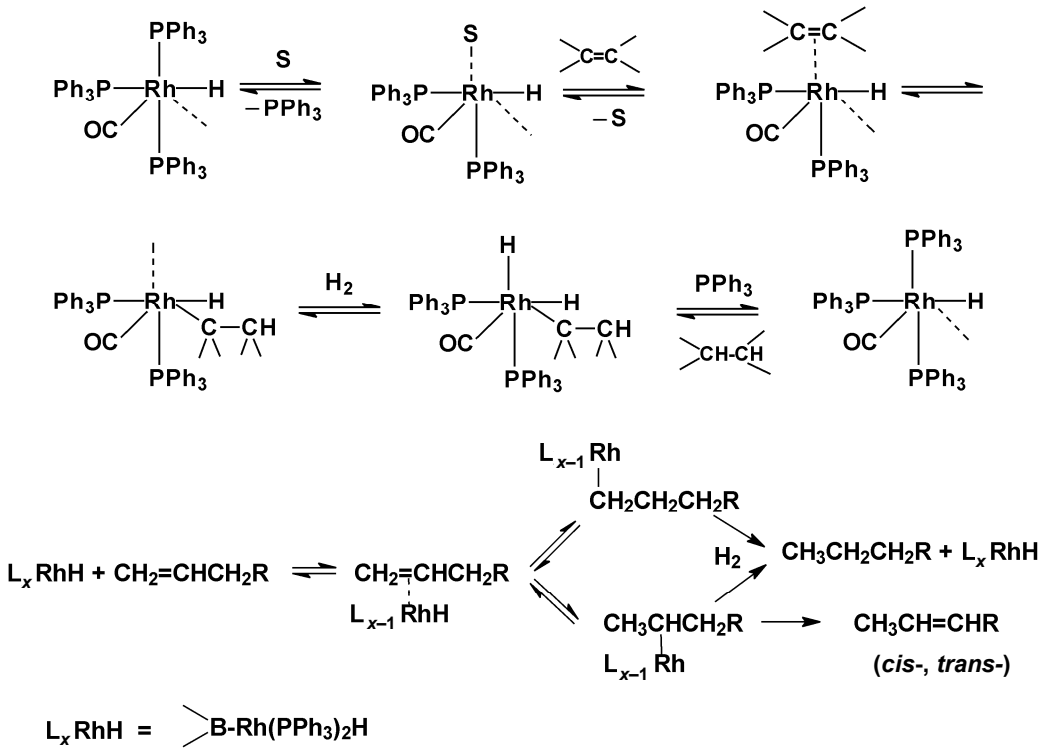
III.2. Mechanism of Isotope Exchange with Deuterium or Tritium in the Presence of Homogeneous Iridium Catalysts

Interesting data concerning processes that occur in labeling via formation of a complex of a substrate molecule with an iridium atom were obtained by Kerr et al. [135–137], who studied how the isotope exchange is influenced by temperature, substituents in benzoic acid or acetophenone, and substituents in iridium catalysts.

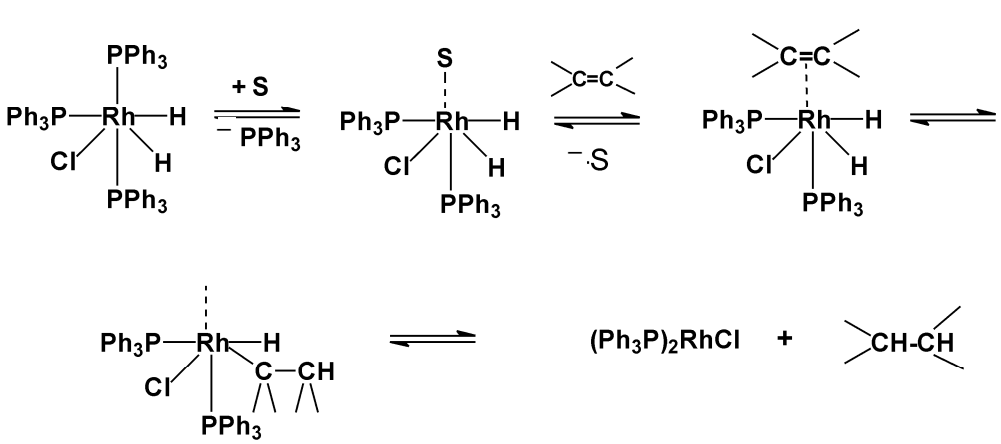
Experiments with benzoic acid and acetophenone derivatives as model compounds demonstrated the effect of steric factors and substituents of the first and second kind on the isotope exchange efficiency and thus furnished additional information on the mecha-



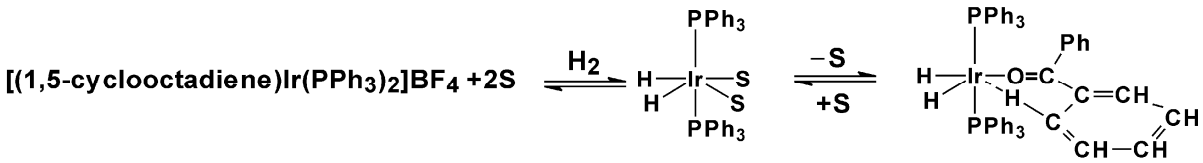
Scheme 26.



Scheme 27.



Scheme 28.



Scheme 29.

nism of the isotope exchange in the presence of iridium catalysts. Iridium catalysts **a**–**c** were used (Scheme 30).

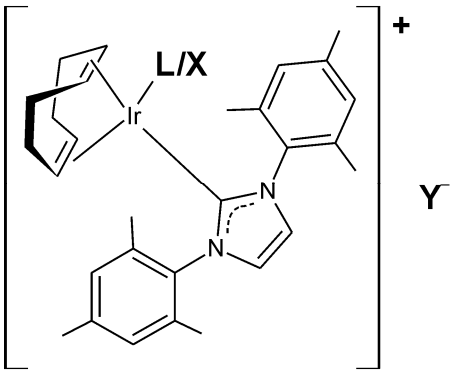
An increase in the temperature from 25 to 40°C leads to an increase in the deuterium incorporation into ethyl (compounds **1**–**3**) and methyl (compounds **4**–**6**) benzoates (Table 11). Experiments were performed with benzoic acid derivatives containing in the

Table 10. Preparation of labeled products by tritiation of the corresponding unsaturated precursors in the presence of $(Ph_3P)_3RhCl$

Starting compound	Yield, %	MA, Ci mmol^{-1}
Bumetanide	37	15.9
2-[*N*-(2,6-Dimethoxyphenoxyethyl)aminomethyl]-1,4-benzodioxin	46	59.9
Egg phosphatidylchloline	87	14.6
Yeast phosphatidylinositol	94	0.8
Ganglioside G_1	51	4.3
Ganglioside G_2	72	3.0
1,11,15-Tri-BDMS-PGE_2	60	51.3
1,11-Di-BDMS 5-fluoro-15-deoxy-PGE_2	60	27.0
1,15-Di-BDMS-PGA_2	40	70.2
2,6-Dimethyl-3,5-di(allyloxycarbonyl)-4-(2'-difluoromethoxyphenyl)-1,4-dihydropyridine	55	109.4

p-position of the phenyl ring protium (H) (compounds **1**, **4**), methyl (compounds **2**, **5**), and trifluoromethyl (compounds **3**, **6**). The reaction was performed in dichloromethane for 1 h in the presence of catalyst **a** (deuterium pressure 1 atm).

It follows from the data obtained (Table 11) that the deuterium incorporation increases with temperature. The substituent influences the isotope exchange between gaseous deuterium and alkyl benzoates differently: The label incorporation at 25°C increases in the series H–CH_3–CF_3 for ethyl esters but decreases for the corresponding methyl esters. Apparently, not only the electron density distribution in the benzene ring but also the steric effects associated with the interaction of the polar group of the substance with the Ir atom play the decisive role in the formation of the complex with the iridium catalyst.



Scheme 30. Iridium catalysts. (PPh_3) Triphenylphosphine, (PBn_3) tribenzylphosphine, and (BArF) tetrakis(bis-3,5-trifluoromethylphenyl)borate. **a**: L = PPh_3, Y = PF_6; **b**: L = PBn_3, Y = PF_6; **c**: L = PPh_3, Y = BArF.

Naturally, this interaction depends not only on the substrate structure, but also on the structure of the iridium catalyst (Tables 12, 13). In this case, iridium catalysts differing in the fragments L = PPh_3 and PBn_3 (catalysts **a** and **b**) and also in counterions Y = PF_6 and BArF (catalysts **a** and **c**) were used. $CH_3OC_6H_4COOR$ was used as a substrate. The reaction was performed at 25°C in dichloromethane for 1 h (deuterium pressure 1 atm).

Along with compounds **1**–**3**, *p*-$ClC_6H_4COOC_2H_5$ (**7**) and *p*-$CH_3OC_6H_4COOC_2H_5$ (**8**) were used in the experiments.

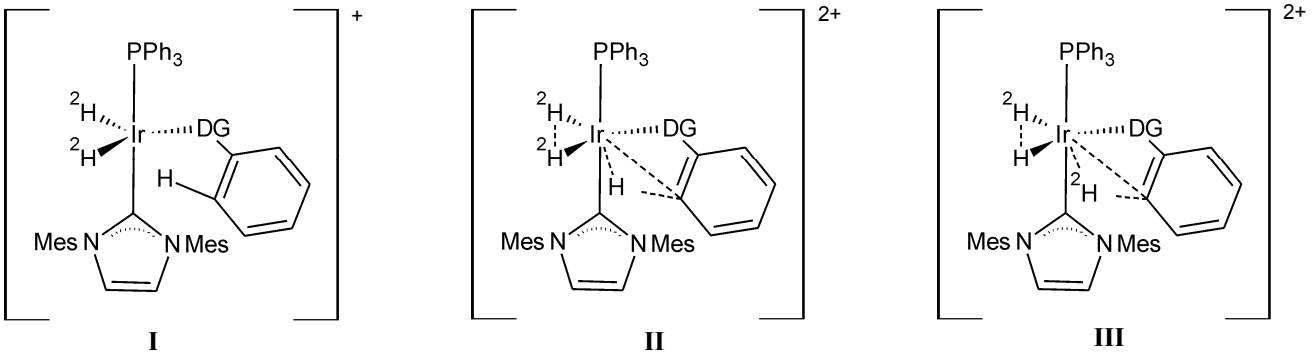
The experiments have shown that not only the alco-

Table 11. Influence of temperature on isotope exchange (^2H, %)

Compound	Temperature, °C	
	25	40
$C_6H_5COOC_2H_5$ (**1**)	23	86
p-$CH_3C_6H_4COOC_2H_5$ (**2**)	68	90
p-$CF_3C_6H_5COOC_2H_5$ (**3**)	77	96
$C_6H_5COOCH_3$ (**4**)	52	76
p-$CH_3C_6H_4COOCH_3$ (**5**)	42	96
p-$CF_3C_6H_5COOCH_3$ (**6**)	32	93

Table 12. Influence of the alcohol moiety in ester molecules and of the counterion Y in the iridium catalyst on the isotope exchange (^2H, %)

R	Catalyst		R	Catalyst	
	a	**c**		**a**	**c**
n-Pr	28	89	*i*-Pr	72	94
CH_2CF_3	8	24	Bzl	61	89
t-Bu	10	41			



Scheme 31. Interaction of an aromatic compound with catalyst **a** (DG is a directing group) [136].

hol moiety of the ester but also the counterions Y and ligands L appreciably influence the isotope exchange efficiency (Tables 12, 13). Apparently, the iridium catalyst containing the more lipophilic counterion (BArF) dissociates in dichloromethane more readily, which facilitates the interaction of the compounds with the Ir atom (Table 12). If the iridium catalyst contains a bulkier substituent, the probability of the complexation with the substrate decreases (Table 13).

With increasing temperature, the differences in the efficiency of the deuterium incorporation into compounds with different ester components containing different substituents in the benzoic acid moiety become less significant. This fact also shows that the major influence on the isotope exchange is exerted by the substrate fragment determining the efficiency of the interaction with the Ir atom (Table 11). Indeed, at a higher temperature the influence of the counterions on the degree of dissociation of iridium catalysts and of differences in the structures of the substrates used becomes less significant.

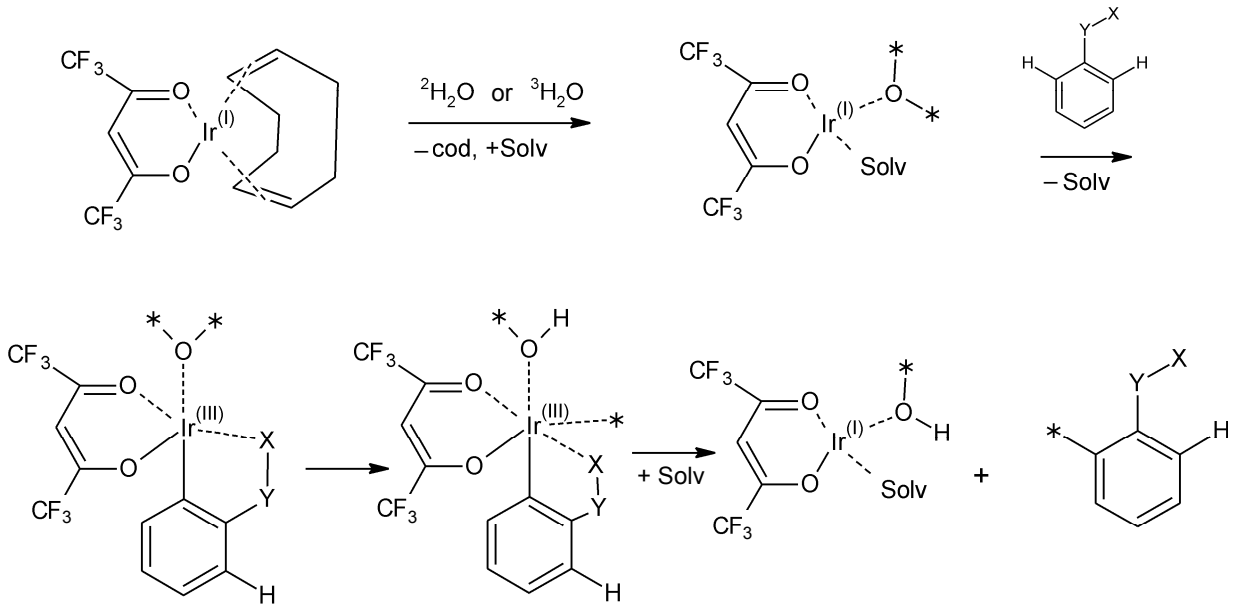
If a compound molecule contains two groups that can be associated with the Ir atom, the competition with them arises. This fact determines the deuterium distribution in the labeled compound. This is confirmed by data on the isotope exchange of deuterium with ethyl *p*-nitrobenzoate, *p*-nitroacetophenone, and *N*,*N*-diethyl-*p*-nitrobenzamide (catalyst **a**, 25°C, dichloromethane, 1 h, deuterium pressure 1 atm). The probability of the deuterium incorporation in the *o*-positions relative to the nitro group in *p*-nitrobenzoic acid is 1.4 times higher than in the *p*-positions relative to the carbonyl group. For *p*-nitroacetophenone, the deuterium incorporation in the *o*-positions relative to the nitro group is 3 times lower than in the *o*-positions relative to the keto group. For *N*,*N*-diethyl-*p*-nitrobenzamide, the deuterium distribution in the *o*-positions oriented by the groups that can be associated with the Ir atom is approximately 50%. This fact indicates that the major influence on the isotope exchange efficiency is exerted by the substrate fragment that interacts with the Ir atom more efficiently (Scheme 31).

Table 13. Influence of the ligand L = PPh_3 and PBn_3 in the iridium catalyst on the isotope exchange efficiency (^2H, %)

Compound	Catalyst	
	a	**b**
1	23	10
2	68	19
3	77	56
p-$ClC_6H_4COOC_2H_5$ (**7**)	95	89
p-$CH_3OC_6H_4COOC_2H_5$ (**8**)	96	62

After the interaction of the polar moiety with the Ir atom (**I**), protium from the *o*-position of the aromatic compound becomes also bound to the Ir atom (**II**). The bond of protium in the *o*-position of the aromatic compound with the phenyl ring becomes weaker, and the C–Ir bond arises (**III**). The break of the C–Ir bond results in the deuterium incorporation into the aromatic compound, with protium remaining bonded to the Ir atom.

By taking advantage of the relationships revealed, it is possible to cardinally change the deuterium distribution in the labeled product. For example, knowing that the amount of deuterium incorporated at 25°C into the *o*-position relative fo the keto group in 4-nitroacetophenone was 3 times larger compared to the *o*-position relative to the nitro groups, Kerr et al. first performed the reaction at 40°C, when all the four protium atoms are replaced by deuterium owing to iso-



Scheme 32. Mechanism of incorporation of hydrogen isotopes into molecules of an organic compound in the presence of an iridium catalyst. Hydrogen isotope source: deuterium or tritium water. (Solv) Solvent and (cod) cyclooctadiene. The ^{2}H or ^{3}H atoms are marked with an asterisk.

tope exchange. Then, the labeled product was treated with gaseous protium at 25°C using the same catalyst. Naturally, deuterium was mainly replaced by protium in the *o*-position relative to the keto group. As a result, the deuterium amount in the *o*-position relative to the nitro group appeared to be 8 times larger than in the *o*-positions relative to the keto group in 4-nitroacetophenone.

The mechanism of the incorporation of hydrogen isotopes into molecules of an organic compound upon treatment with deuterium or tritium water also consists of several steps (Scheme 32). The solvent and water molecules displace the 1,5-cyclooctadiene fragment from the iridium complex. Then, an organic substrate molecule is incorporated into this complex. In the process, the valence of the metal catalyst changes. As a result, isotope exchange occurs between protons of the substrate and hydrogen isotopes from deuterium or tritium water [138].

III.3. Use of Homogeneous Iridium Catalysts for Preparing Labeled Compounds

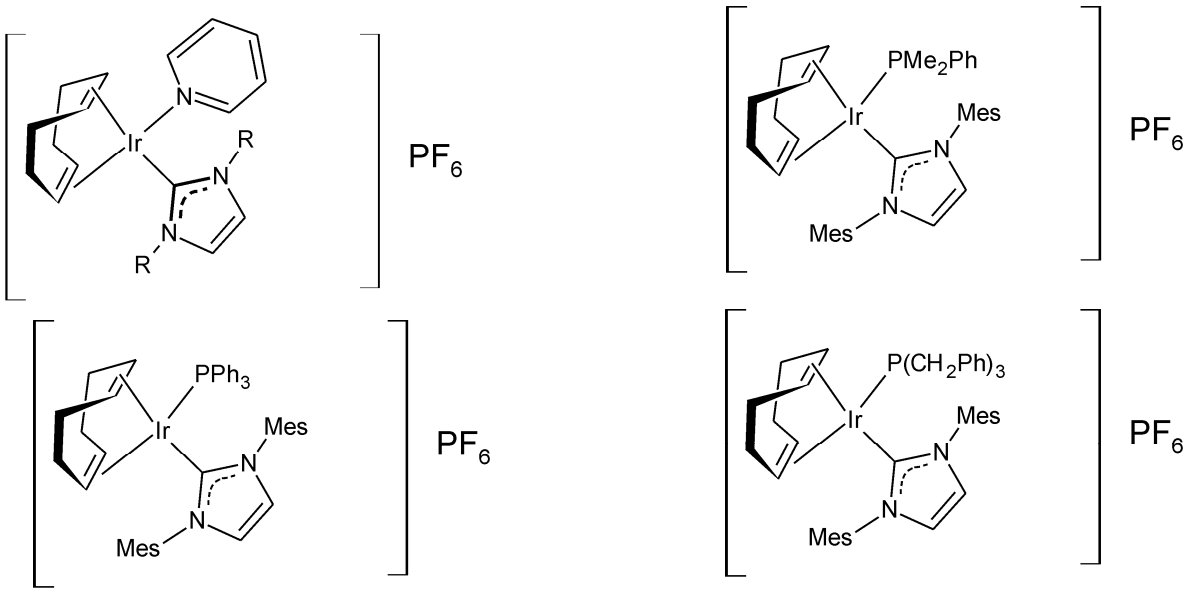
A typical prcocedure for performing such reactions is as follows. A mixture of a substrate, e.g., 5-phenylbenzoic acid (100 mg), was mixed with an iridium catalyst, e.g., (cyclooctadiene)(pentane-1,3-dionato)-iridium(I) (1.2 mg). The mixture was dissolved in DMF (6.6 mL) containing deuterium water (3.3 mL) and heated at 90°C for 2 h. Yield of 4-phenyl[2,6-$^{2}H_2$]-benzoic acid 74%. Two deuterium atoms were incorporated, on the average, into the 4-phenylbenzoic acid molecule [125]. With gaseous tritium, the reaction is usually performed in methylene chloride. In the process, as in the above-considered cases, the use of gaseous tritium as a tritium source allows preparation of products with higher molar activity compared to the use of tritium water.

Diverse iridium catalysts (Scheme 33) were used for preparing labeled products [139–142].

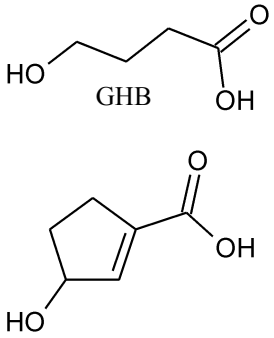
Both commercial catalysts and catalysts prepared directly before the isotope exchange [143] are used today. The catalysts thus prepared, Ir(1,5-cyclooctadiene)$(Ph_3PO)_2BF_4$, Ir(1,5-cyclooctadiene)$(Bu_3PO)_2BF_4$, and Ir(1,5-cyclooctadiene)$(i\text{-}PrPh_2PO)_2BF_4$, were used for introducing deuterium into $PhSO_2NH_2$ and methyl phenyl sulfoxide.

The specific features of the procedures for introducing hydrogen isotopes into organic compounds can be demonstrated and described in detail for the reactions performed with iridium catalysts as examples.

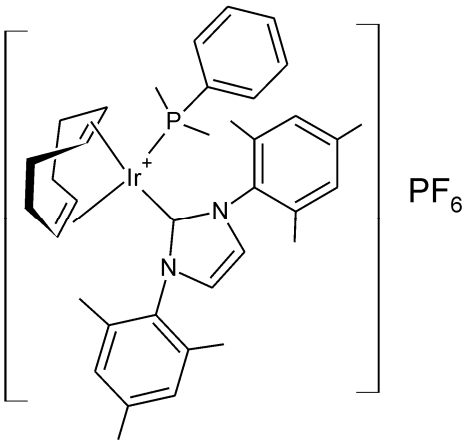
When preparing deuterium-labeled HOCPCA (analog of GHB), which contained the C=C bond [144], it was necessary to find the conditions under which the double bond would be preserved:



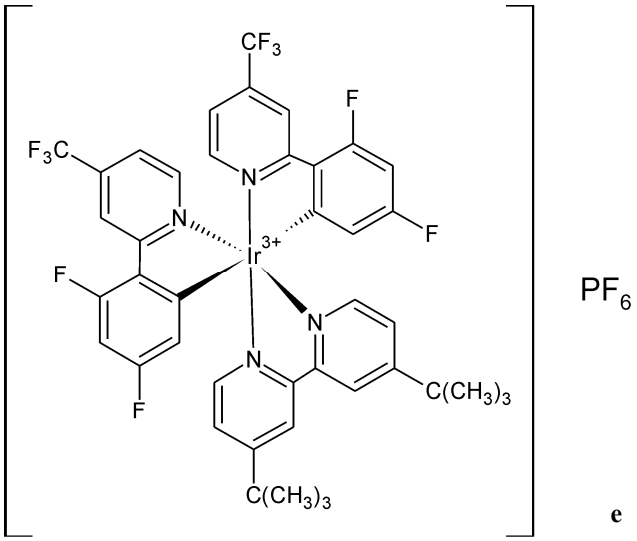
Scheme 33. Structures of iridium catalysts used for activating isotope exchange.



GHB analog (HOCPCA)



d



e

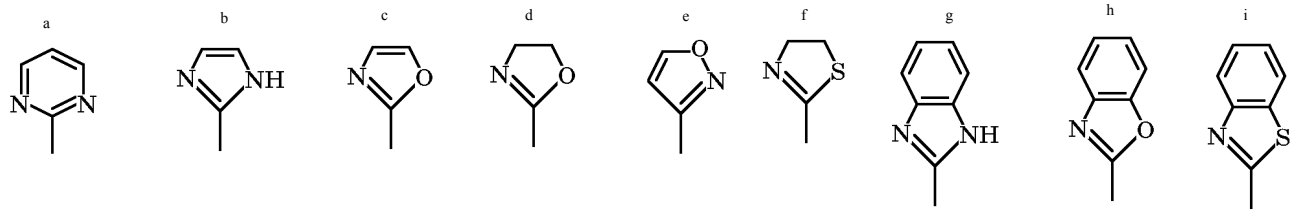
It is known that, when using gaseous hydrogen and iridium complexes, hydrogenation of the double bond occurs concurrently with isotope exchange. Therefore, first, deuterium was introduced not into HOCPCA but into propyl 3-oxocyclopent-1-enecarboxylate; second, different catalysts and solvents were used. The following catalysts were used: (1,5-cyclooctadiene)(pyridine)-(tricyclohexylphosphine)iridium(I) hexafluorophosphate, **a**, **d**, and **e**; CH_2Cl_2, THF, DMF, methanol, acetone, acetonitrile, nitromethane, chloroform, CCl_4, ethyl acetate, and DMSO were used as solvents; the reaction time was varied from 10 min to 72 h (Scheme 34).

When using catalyst **d**, the amount of the hydrogenated product was 3% in 10 min, 10% in 20 min, and 39% in 60 min. When using catalyst **a**, the amount of the hydrogenated product in the respective times was 0, 3, and 7%. HOCPCA was prepared by the re-

Scheme 34. Structures of iridium catalysts **d** and **e**.

Table 14. Dependence of the isotope exchange efficiency (% deuterium, first numeral) and yield (second numeral) on the heterocyclic substituent in the compounds R–[2,6-^{2}H]C_6H_5. Conditions: iridium catalyst, 0.086 mol of substrate, 0.0043 mol of [Ir], 1 mL of CH_2Cl_2, 1 atm of H_2, 25°C, 1 h

Catalyst	Heterocyclic substituent R								
	a	b	c	d	e	f	g	h	i
a	93; 96	89; 94	83; 99	92; 80	82; 89	86; 93	84; 88	90; 94	94; 99
b	42; 93	73; 91	75; 94	79; 79	44; 80	95;100	83; 89	82; 96	60; 93
d	14; 96	70; 95	80; 94	91; 70	72; 98	89; 95	72; 82	80; 95	31; 95

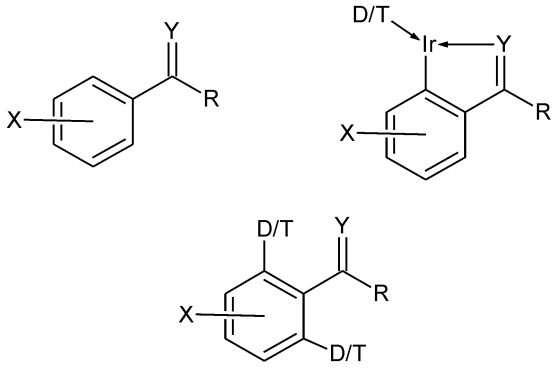


duction of the ketone with sodium borohydride and base hydrolysis.

The influence of the structure of the iridium catalyst on the yield and efficiency of the isotope exchange was demonstrated in a study in which hydrogen isotopes were introduced using catalysts **a**, **b**, and **d** not only into aromatic pharmaceuticals (Scheme 35), but also into pharmaceuticals containing heterorings (Table 14) [145].

As seen from Table 14, the yield and efficiency of the isotope exchange on the same catalyst vary for different substrates within 10%, whereas the efficiency of the isotope exchange for the same substrate on different catalysts can differ by 60–80%.

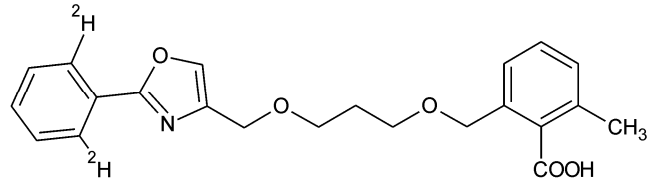
It is interesting that the efficiency of hydrogen isotope labeling using catalyst **a** (1 atm of $^2H_2$, 25°C, 1 h) in dichloromethane and methanol does not differ essentially (Scheme 36). This fact indicates that the labile protons of the solvent do not appreciably participate in the labeling process under these conditions.



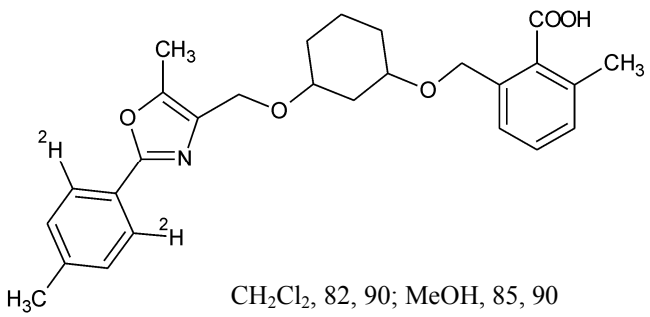
Scheme 35. Assumed mechanism of hydrogen isotope incorporation into aromatic compounds.

The effect of steric factors in reactions involving homogeneous iridium catalysts can be seen from the results of tritium labeling of aromatic aldehydes (Scheme 37) [146]. The reaction was performed in dichloromethane with stirring in a gaseous tritium atmosphere at room temperature for 16 h with (1,5-cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium(I) hexafluorophosphate as a catalyst. Under these conditions, the labeled product with the molar activity of 24 Ci mmol^{-1} was obtained from 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde.

As seen from Scheme 37, steric factors strongly influence the tritium incorporation into an aromatic



CH_2Cl_2, 83, 95; MeOH, 80, 94

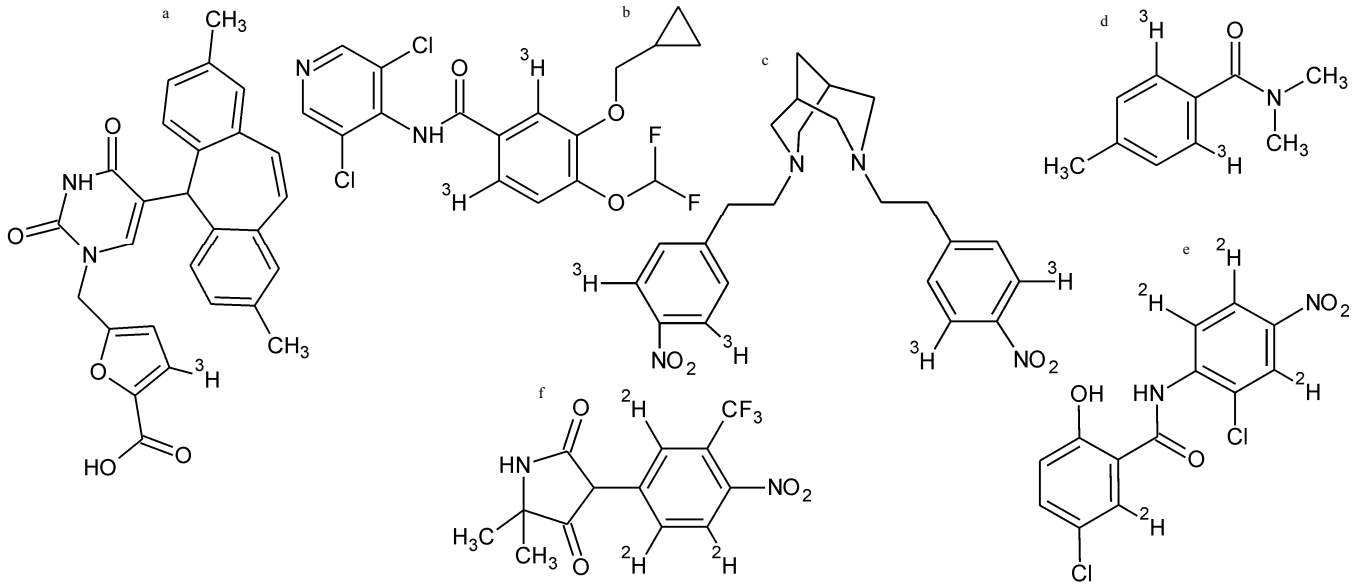


CH_2Cl_2, 82, 90; MeOH, 85, 90

Scheme 36. Isotope exchange efficiency (first numeral, %) and yield (second numeral, %) when using protic and aprotic solvents.

Table 15. Isotope exchange on iridium catalysts

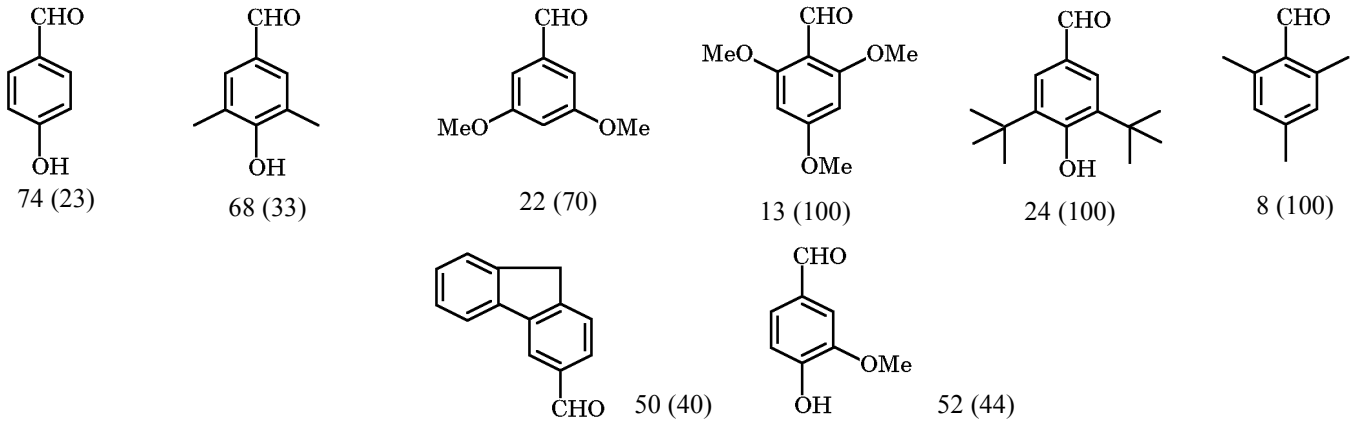
Compound	Reaction conditions
[a], 1.9 Ci mmol^{-1}	DMF, ^3H_2O, 70°C, 20 h [2]
[b], 77.7 Ci mmol^{-1}	$^3H_2$, CH_2Cl_2, 16 h [97]
[c], 79.4 Ci mmol^{-1}	CH_2Cl_2, $^3H_2$, 23°C, 18 h [2]
[d–f]	Gaseous tritium or deuterium, 23°C, 1–2 h, CH_2Cl_2 [139]



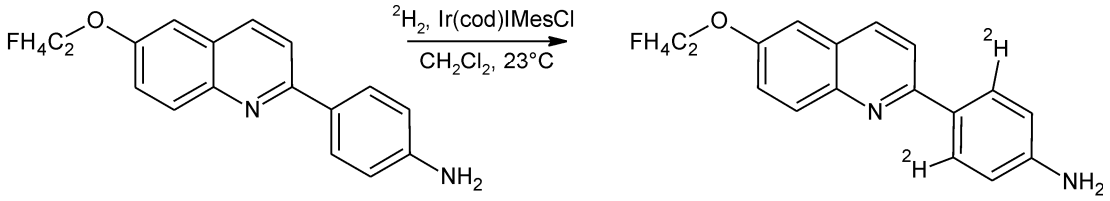
ring. If the *o*- and *p*-positions of the aromatic ring are occupied, the label is incorporated in the formyl group only. Methyl groups decreased the tritium incorporation into the aromatic ring by 19%, and *tert*-butyl substituents in the aromatic ring fully suppressed its labeling.

If a substrate is stable under the conditions of such reactions (Scheme 38), the incorporation of hydrogen isotopes can significantly increase with increasing reaction time [147]. As the reaction time was increased from 1 to 6 days, the deuterium incorporation increased by a factor of approximately 2.

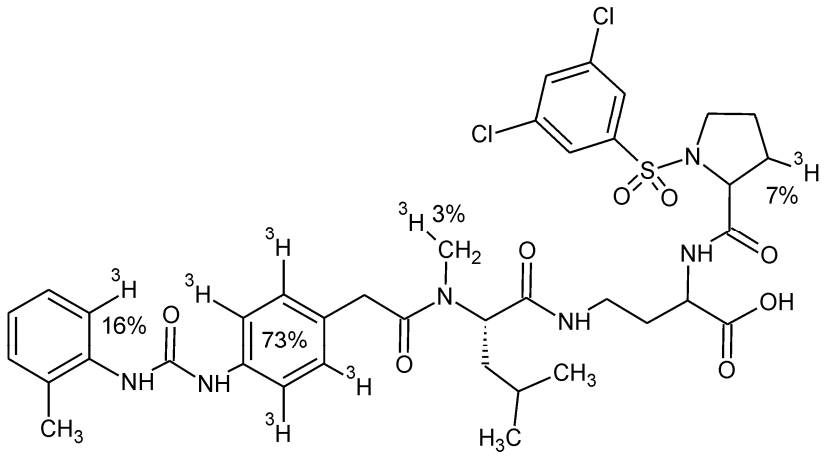
To introduce tritium into SCH Q, the reaction was performed with the methyl ester of SCH Q (3.7 mg) and an equivalent amount of (1,5-cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium(I) hexafluorophosphate (3.7 mg) in an atmosphere of gaseous tritium (850 mCi) with stirring for 16 h. After the saponi-



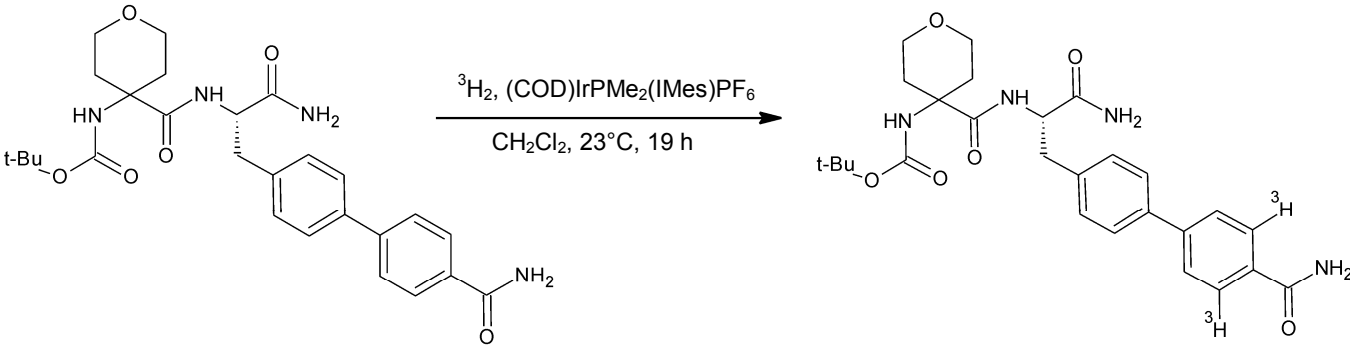
Scheme 37. Influence of steric factors on the tritium distribution in molecules of aromatic aldehydes (first numeral: total molar activity; in parentheses: percent fraction of the label in the formyl group).



Scheme 38. Deuterium incorporation into THK-523 depending on the reaction time (1 day, 50%; 6 days, >95%).



Scheme 39. Structure of SCH Q.



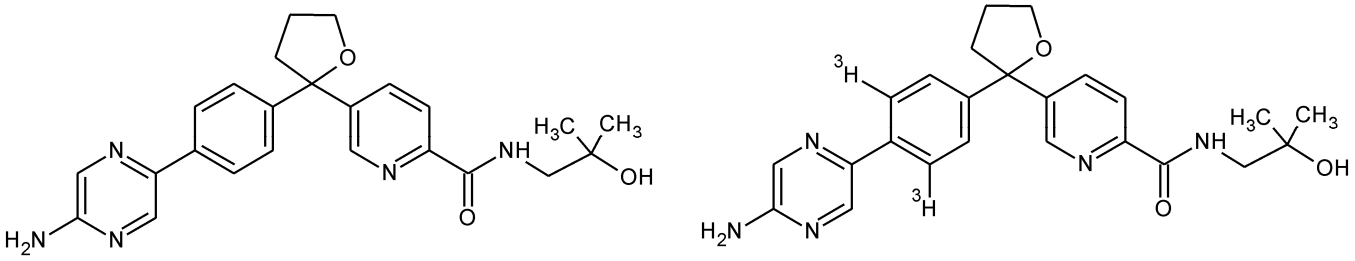
Scheme 40. Conditions of tritium introduction into a carbamoyldiphenyl derivative.

fication, [^{3}H]SCH Q was obtained (Scheme 39) with the molar activity of 20.5 Ci mmol^{-1} [96].

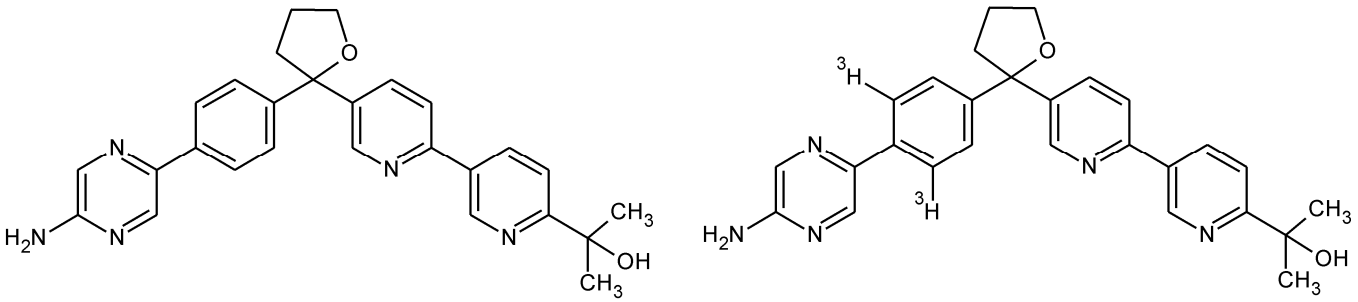
Using (COD)IrPMe$_2$Ph(IMes)PF$_6$, Allen et al. [115] prepared *tert*-butyl *N*-[4-[[(1*S*)-2-amino-1-[[4-(4-carbamoyl[3(5)-^{3}H]phenyl)phenyl]methyl]-2-oxoethyl]-carbamoyl]tetrahydropyran-4-yl]carbamate (Scheme 40) with the molar activity of 13.3 Ci mmol^{-1} in 40% yield.

It is convenient to introduce tritium by this method into compounds containing the same group determining the label incorporation sites. For example, for more detailed studies of the metabolism and pharmacokinetic properties of AZD6642 and its derivatives, showing promise as drugs, it was necessary to prepare their tritium-labeled analogs [148] (Scheme 41). Because the group determining the label distribution was identical in these compounds, tritium was incorporated at the same carbon atoms, which allowed the use of the unified procedure in the biological experiments.

Some other examples of introduction of hydrogen isotopes using iridium catalysts are given in Table 15.

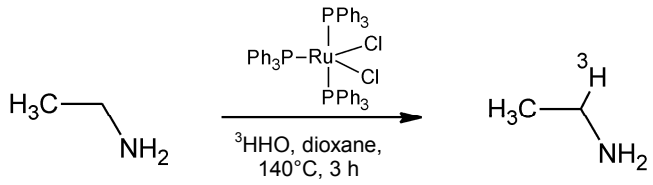


$^3H_2$, catalyst **d**, AZD6642, CH_2Cl_2, 23°C, 2 h (yield 34%, 28.4 Ci mmol^{-1})



$^3H_2$, catalyst **d**, AZD6642 derivative, CH_2Cl_2, 23°C, 3 h (yield 51%, 32.4 Ci mmol^{-1})

Scheme 41. Dependence of the yield and molar activity of AZD6642 on the reaction conditions.

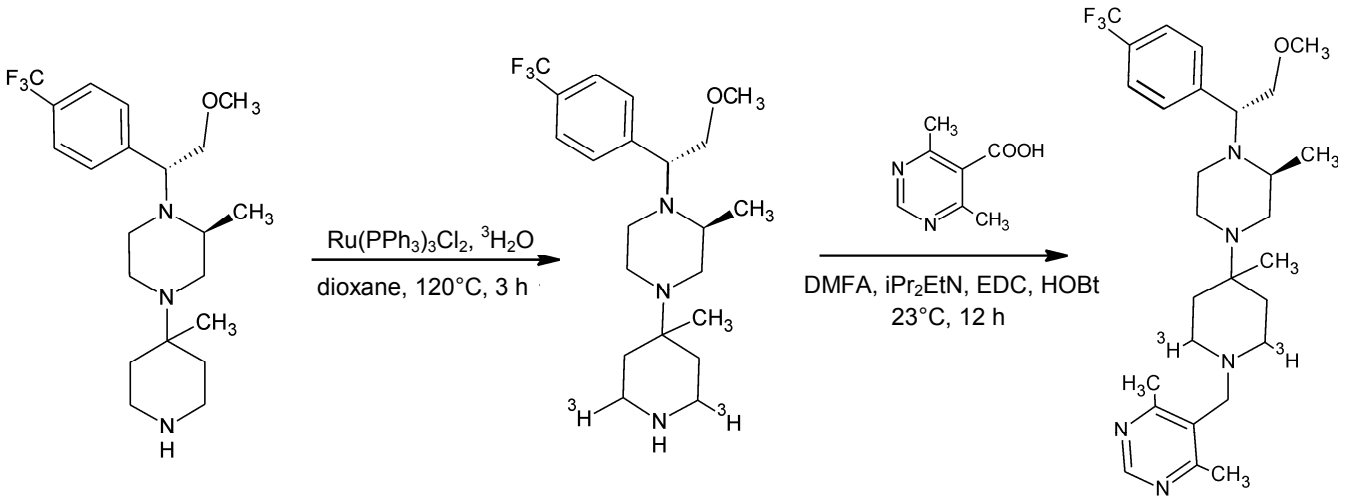


Scheme 42.

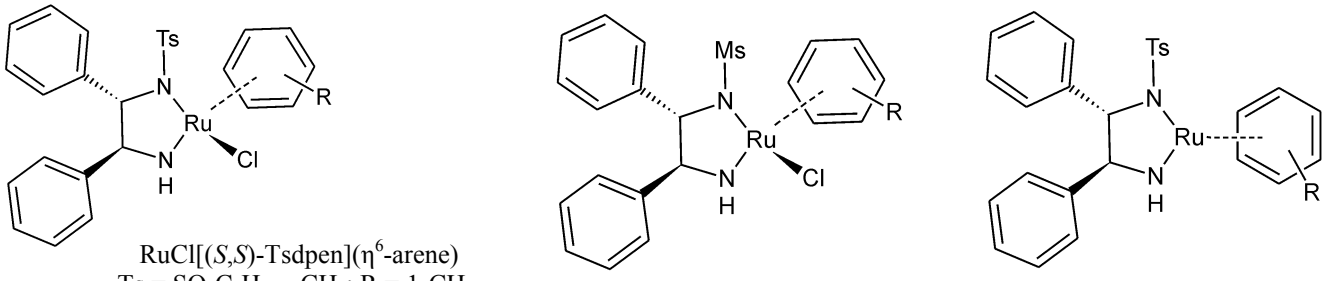
III.4. Use of Homogeneous Ruthenium Catalysts for Preparing Labeled Compounds

The isotope exchange can be performed using ruthenium triphenylphosphine complexes [89] (Scheme 42).

Various procedures for preparing homogeneous ruthenium catalysts for the reduction of ketones and imines have been reported [149, 150]. It is possible to



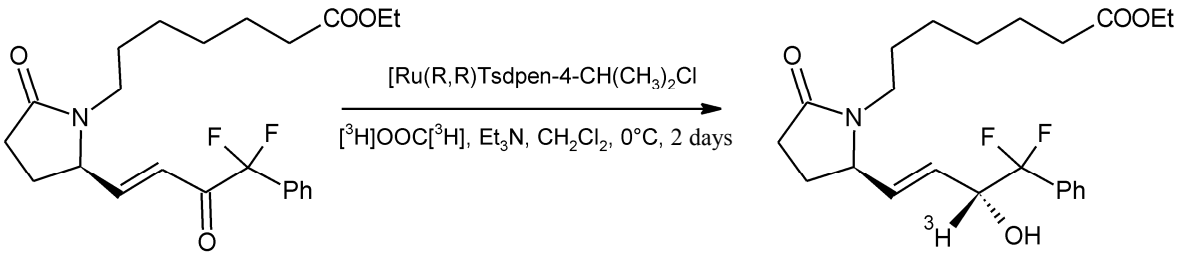
Scheme 43. Synthesis of [^{3}H]SCH 417690 with the molar activity of 16.4 Ci mmol^{-1}. EDC is 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, and HOBt is 1-hydroxybenzotriazole.



RuCl[(*S*,*S*)-Tsdpen](η^6-arene)
Ts = $SO_2C_6H_4$-*p*-CH_3; R = 1-CH_3, 4-$CH(CH_3)_2$, 1,3,5-$(CH_3)_3$ (mesitylene) or 1,2,3,4,5,6-$(CH_3)_6$

RuCl[(*S*,*S*)-Msdpen](η^6-arene)
Ms = SO_2CH_3, R = 4-$CH(CH_3)_2$

Scheme 44. Ruthenium complexes used for asymmetric reduction of ketones and imines.



Scheme 45. Synthesis of an optically active prostaglandin analog (yield 35%, 14.7 mCi mmol^{-1}).

prepare such a catalyst, e.g., RuPVP, by the reaction of polyvinylpyrrolidone with ruthenium chloride.

With $Ru(Ph_3P)_3Cl_2$, the label was introduced into SCH 417690 (Scheme 43), which is a powerful and selective antagonist of the CCR5 receptor and shows promise for treatment of HIV infections.

The use of ruthenium catalysts with asymmetric ligands allows prepararation of optically active compounds as reduction products. For example, (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediamine and (1*S*,2*S*)-(–)-1,2-diphenyl-1,2-ethanediamine with one of the amino groups bonded with $SO_2C_6H_4$-*p*-CH_3 or SO_2CH_3 were used for this purpose. The ruthenium complex also contained alkyl-substituted benzene (Scheme 44). Optically active alcohols [151–160] and amines [161–164] were prepared by the reduction of the corresponding ketones and imines in the presence of such catalysts.

Not only ^3H_2O but also formic acid can serve as a source of hydrogen for the reduction of ketones and imines (Scheme 45) [38].

IV. CONCLUSION

The review discusses the published mechanisms of hydrogen isotope incorporation by isotope exchange, hydrogenation, and dehalogenation using heterogeneous and homogeneous catalysts and various sources of tritium or deuterium. The modern views on the processes influencing the efficiency of the introduction of hydrogen isotopes into organic compounds in the presence of heterogeneous and homogeneous catalysts are presented.

Diverse deuterium and tritium sources can be used. These include not only gaseous hydrogen isotopes and ^2H_2O or ^3H_2O, but also labeled diazomethane, acetic and formic acids, R_3Si^2H or R_3Si^3H, ^3HCHO, $^3HC^3HO$, $^3HCON(CH_3)_2$, $^3HCOOCOCH_3$, $C^3H_3NH_2$, $CH_2{}^3H{\cdot}CH^3HNH_2$, $^3HN{=}N^3H$, *N*-trithioacetoxyphthalimide, agents derived from metal tritides (lithium aluminotritide, sodium borohydride, etc.), and also methyl iodide and its derivatives [41].

The isotope exchange between hydrogen isotopes and the majority of saturated organic compounds, performed at room temperature in solvents, as a rule, does not lead to the formation of labeled products with the molar activities required for studying the reception, and such products can be used only as markers. If the introduction of hydrogen isotopes by reactions performed in the system hydrogen isotope source–catalyst–substrate solution is inefficient, products with high molar activity can be prepared using procedures without solvents.

The previously suggested mechanisms [75] and models [165] of solid-phase reactions were supplemented by the assumption that the hydrogen spillover is preceded by the spillover of electrons, which are known to be capable of transport even through an insulator layer due to tunneling [80]. As a result, the transfer of hydrogen cations from the metal catalyst to the support is facilitated.

When the flux of electrons and activated hydrogen isotope species reaches the substrate applied onto a support, clusters of solvated hydrogen cations and electrons start to be formed in the pool of the organic substrate also. Different ability of even structurally similar compounds to solvate hydrogen cations and electrons can account for significant differences in the efficiency of the incorporation of hydrogen isotopes into these compounds.

Examples of preparing labeled compounds by isotope exchange, hydrogenation, and dehalogenation in solvents and without them are presented. Higher molar activities are reached when using gaseous tritium.

Isotope exchange with tritium water is efficient if about 100 Ci of tritium water with the molar activity close to the maximum possible value (58 Ci $mmol^{-1}$) is used. Usually, even at temperatures higher than 100°C and reaction time of several days, the molar activity of the product does not exceed 40–60% relative to that of tritium water.

Recent achievements in label introduction by selective hydrogenation and dehalogenatoin are noted.

Finally, an attempt is made to attract particular attention to the use of homogeneous catalysts allowing preparation of labeled products with high content of hydrogen isotopes by isotope exchange under very mild conditions. Such catalysts can also be used for preparing optically active compounds.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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