Review Article

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Pd- and Pt-catalyzed H/D exchange methods and their application for internal MS standard preparation from a Sanofi-Aventis perspective

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This review addresses method developments both homogeneous and heterogeneous Pd- and Pt-catalyzed exchange, including catalyst activation principles and recent practical applications together with example procedures. Specific requirements for isotopically labelled internal MS standard preparation are discussed from a Sanofi-Aventis perspective on recent examples.

Keywords: H/D exchange; deuterium; catalysis; palladium; platinum

Introduction

Both palladium and platinum are widely applied, highly active catalysts for H/D(T) exchange labelling of organic compounds.[1,2] Although a number of homogeneous methods[3] utilizing Pd and Pt salts, such as K_2PtCl_4[4,5] or *N*-heterocyclic carbene Pd(II) complexes, have been described,[6] most of the methods developed for isotopic exchange use heterogeneous Pd or Pt catalysts.

Platinum-catalysed reactions appear to show a greater involvement of a dissociative π-complex mechanism,[7] whereas for palladium the competing associative mechanism[8] seems to be preferred.[9] Nevertheless, the basic exchange reaction is similar and the same activation principles apply to both systems.[10] The optimization of methods for the activation of platinum[11] or palladium[12] is of particular importance to achieve high deuterium incorporation in the H/D exchange process, it has been the subject of numerous fundamental investigations.[13] Besides prior hydrogenation,[14] catalyst activation is also possible by the so-called "*self-activation*" process[15] involving a reduction of the catalyst surface with organic compounds such as benzene.[16] Additionally, PtO_2 has also been activated by UV irradiation or by γ-rays.[17] Existing practical exchange methods often involve harsh reaction conditions. They may also require a pre-reduction or an *in-situ* activation of the catalyst. Moreover, they differ between the two metals with respect to substrate selectivity, rate of exchange, and reaction conditions. Platinum catalysts generally have a higher selectivity for exchange at aromatic rather than aliphatic positions, whereas palladium displays the opposite preference.[18]

Specific requirements for isotopically labelled internal MS standard preparation – A Sanofi-Aventis perspective

In recent years, liquid chromatography coupled with tandem mass spectroscopy detection (LC-MS/MS) has become the most powerful bioanalytical tool for the investigation of samples originating from animal and human toxicological, metabolism and pharmacokinetic studies.[19] For a quantitative LC-MS/MS analysis of new drug candidates or relevant metabolites in complex matrices (like blood, urine, bile etc.), stable isotopically labelled internal standards are considered essential.[20]

In order to avoid matrix effects,[21] such as ion suppression, stable isotopically labelled internal standards are particularly advantageous due to the similarity of the physical and chemical properties of the analyte and its standard. Both can be extracted from biological samples to the same extent, usually have identical retention times in chromatographic methods[22] and ionization behavior in the LC/MS, but differ on account of their molecular masses. If this mass difference is large enough to avoid cross signal overlapping as a result of the natural isotope pattern, quantitative determination is possible. Today, quantitative bioanalytical assays are developed and validated for most new drug candidates very early in the pharmaceutical development programme. Consequently, not only the number of compounds for which stable isotope labelling is required, but also the need for their efficient and fast preparation has increased considerably.

Compared with a conventional synthesis starting from a suitable commercially available stable labelled precursor, H/D exchange can be a cost- and time-efficient alternative approach if it can be carried out directly on the target molecule or an advanced intermediate. On the other hand, the disadvantages of H/D exchange can include unspecific labelling of the molecule (giving mixtures of different isotopomers and isotopologues[23]),

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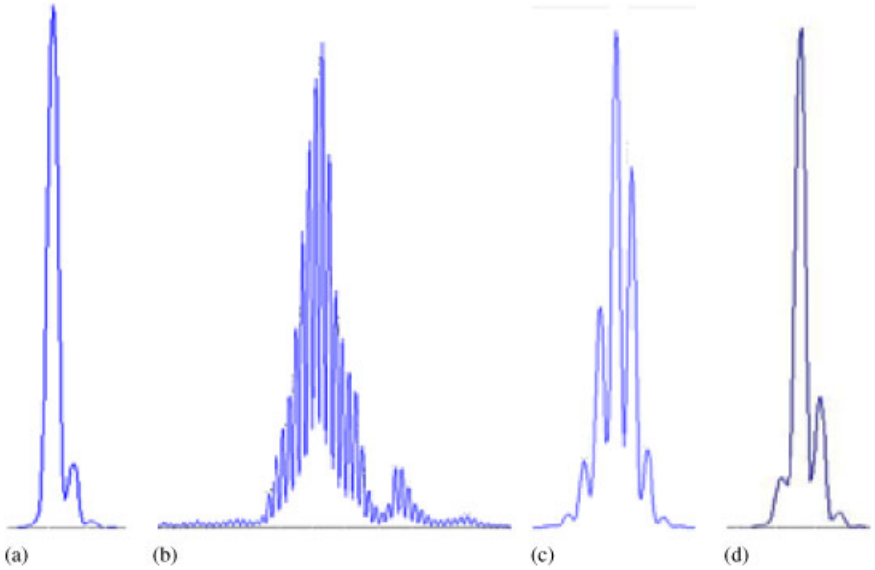


Figure 1. Examples of typical MS pattern from different compounds: (a) natural MS isotope distribution of a hydrocarbon; (b) broad isotope cluster after an unselective H/D exchange; (c) moderately broad isotope cluster with a representative mass peak; (d) MS isotope distribution after a highly selective H/D exchange.

leading to isotope clusters and the potential risk of batch to batch variations of the composition of these mixtures. Nonetheless, materials with narrow isotope clusters can be fit for use as an internal standard as long as the content of D_0 material is less than 0.5% to reduce cross signal overlapping to a minimum and that a representative mass peak is present in the mixture, which can be used as the reference mass of the internal standard (Figure 1). Typically, for small molecules without chlorine, bromine or sulfur-containing functionalities, an incorporation of 3–5 deuterium atoms is considered adequate. In spite of recent methodological improvements, H/D exchange still often either leads to insufficient deuterium incorporation, results in a very broad isotope cluster, or leads to decomposition of the compound. Often, method development has been conducted with simple model substrates only, therefore predictions regarding the position and number of hydrogen atoms exchanged in drug molecules are still difficult to make. Hence, a key motivation for the isotope synthesis group at Sanofi-Aventis was the development of safe and efficient methods for the rapid preparation of high quality stable isotope-labelled compounds suitable for use as MS internal standards.

Pd- and Pt-catalyzed H/D exchange under hydrothermal conditions

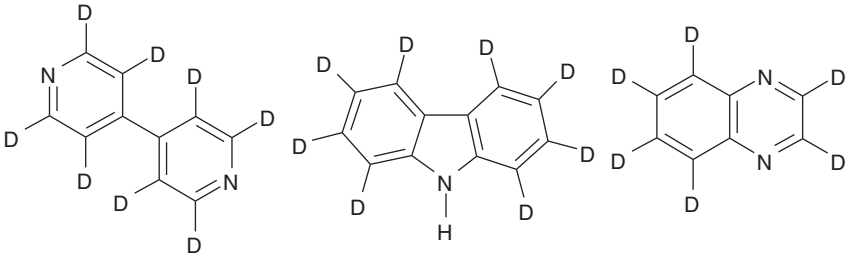
Under hydrothermal conditions, water dissociates a thousand times more rapidly than at room temperature,[24] thus Pd^0 or Pt^0 can be oxidatively inserted into the D-OD bond.[25] The resulting D-M-OD complex dissociates with the formation of the cationic $D\text{-}M^+$, which can interact with an organic substrate and finally result in H/D exchange.[26] For example, in 1990 Möbius and Schaaf[27] reported a hydrothermal method for the deuteration of aliphatic hydrocarbons (>95% D) catalyzed by Pd/C at temperatures up to 290°C, and a very high deuterium incorporation was also observed for cyclodecene by applying a similar method.[28] Hydrothermal reaction conditions (250°C, 4–5 MPa) were also found to be effective for decarboxylation of free carboxylic acids and decarbonylation of aldehydes, thus leading to highly deuterated aromatic or aliphatic hydrocarbons.[29] Different mechanisms are discussed for both processes.[30] For the first, a reductive decarboxylation via an alkylidene-palladium species and subsequent CO_2 elimination at the metal surface is postulated, whereas for the latter a hydride transfer from an intermediate acyl–palladium complex formed after direct C–H bond insertion is discussed. However, the use of a lower reaction temperature (200°C) leads to a complete deuteration of 4-aminobenzoic acid without decarboxylation, which formed the basis of a synthesis of deuterated folic acid derivatives.[31]

While, as mentioned above, Pd has a much higher preference for the exchange of aliphatic hydrogen atoms, arenes are efficiently deuterated with Pt.[32] Accordingly, high degrees of deuteration could be achieved both for substituted arenes such as dibenzo[18]crown-6, triphenylphosphine, and ferrocene, and also for heteroarenes, e.g. 4,4′-dipyridine (**1**), carbazole (**2**) and quinoxaline (**3**), as shown in Scheme 1.[33] Microwave-enhanced reactions were found to proceed with significantly shorter reaction times and with fewer side reactions.[34] Depending on the electronic nature of the substituent, arenes were deuterated selectively in the *meta* (for example, benzoic acid) or in the *ortho* position (for example aniline).

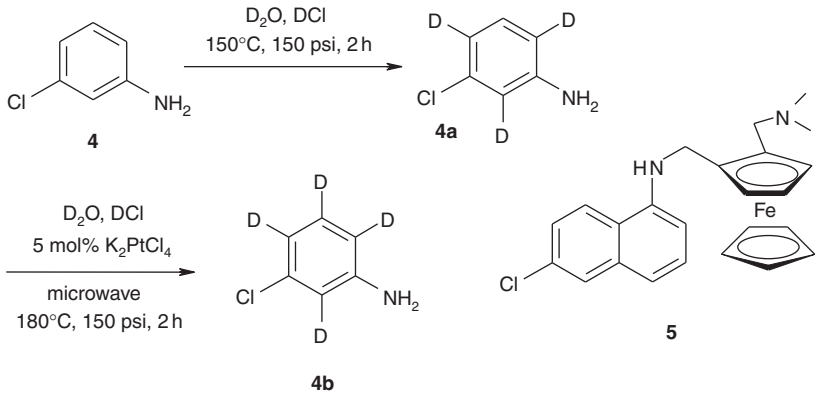
Pd- and Pt-catalyzed H/D exchange without specific catalyst activation

Since the pioneering work of Garnett et al.,[35] homogeneous K_2PtCl_4-catalyzed H/D exchange has been frequently applied for the selective exchange of specific aromatic positions often with a different or even higher selectivity when compared with heterogeneous methods.[36]

In a recent example, Ilyas *et al.* reported a complete deuteration of 3-chloroaniline (**4**, Scheme 2). This fully deuterated intermediate was needed to provide an analytical MS standard (with a mass difference of at least M_0+4) for ferroquine (**5**, SSR97193), which is presently being developed as anti-malarial drug at Sanofi-Aventis.[37] In an initial reaction step, all activated aromatic protons of 3-chloroaniline (**4**) were exchanged under acidic conditions in concentrated DCl.



Scheme 1. Pt-catalyzed hydrothermal H/D exchange of 4,4′-dipyridine (**1**), carbazole (**2**) and quinoxaline (**3**).



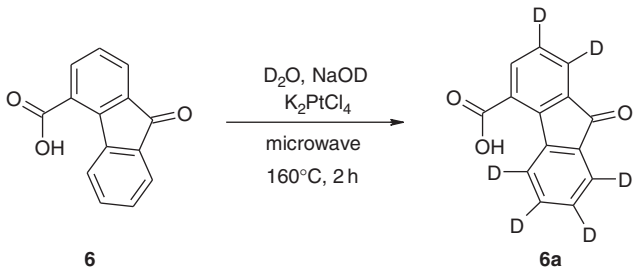
Scheme 2. H/D exchange of 3-chloroaniline (**4**) under acidic and Garnett conditions in the microwave.

Subsequently, the undeuterated *meta*-hydrogen of aniline **4a** was completely exchanged by treatment with K_2PtCl_4 in D_2O under microwave conditions at 180°C for 2 h (2 runs).[38]

*Example procedure, 3-chloro[2,4,5,6-$^2H_4$]aniline (**4b**): 3-Chloroaniline (4; 3.311 g, 26 mmol) was dissolved in D_2O (20 mL) in an 80 mL microwave vessel and 35% DCl solution (3 mL) was added dropwise with stirring. The homogeneous solution was then irradiated in the microwave using the following parameters; solvent – water, standard mode, power – 300 W, temperature 200°C, pressure 150 psi, ramp 10 mins, hold 30 mins, stir on, cooling off. The reaction mixture was then concentrated in vacuo and redissolved in D_2O (20 mL). 5% K_2PtCl_4 catalyst (0.540 g in 4.5 mL) and DCl (0.6 mL) were added and the mixture was irradiated once again following the parameters detailed above. This step was repeated. After irradiation, the reaction mixture was partitioned between diethyl ether and NaOH (10 mL, 2 M) and the aqueous layer was washed with more diethyl ether. The organic extracts were combined, dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford 3-chloro[2,4,5,6-$^2H_4$]aniline (**4b**) (2.011 g, 15.4 mmol, 60% yield).*

Another Sanofi-Aventis internal H/D exchange example using Garnett's conditions was performed by Holla *et al.*. In the reaction of fluoren-9-one-4-carboxylic acid (**6**), the highest deuterium introduction was achieved under the basic Garnett-conditions (K_2PtCl_4, D_2O, NaOD) in the microwave at 160°C. The isotopologue distribution of the raw material was determined by LC-MS as 60% D_6, 30% D_5 and 10% of a mixture of D_4, D_7 and D_8 (Scheme 3).[39]

Further interesting H/D exchange results have been reported using Adams' catalyst ($PtO_2 \cdot H_2O$). With this catalyst, the exchange selectivity of the α-hydrogen atoms of aliphatic amines and amino acids shows a strong dependency upon



Scheme 3. H/D exchange of fluoren-9-one-4-carboxylic acid (**6**) under Garnett conditions in the microwave.

the number and steric demand of the *N*-substituents. From these results, it appears that the nitrogen atom binds to the surface of the catalyst. The exchange efficiency decreases in the series tertiary>secondary>primary.[40]

Hydrogen-activated Pd- and Pt-catalyzed H/D exchange

In early studies on heterogeneously catalyzed H/D exchange reactions, gaseous deuterium was frequently used in combination with Pd catalysts.[41] In the method developed by Azran *et al.*, the catalyst surface (10% Pd/C) was freed from adsorbed hydrogen and protic compounds by repeated purging with deuterium gas prior to use. With this pre-activated catalyst, benzylic hydrogen atoms could be substituted selectively within 1 h at room temperature. The deuterium transfer was strongly influenced by solvent, substrate structure and catalyst/substrate ratio.[42]

The catalyst system established by Hardacre *et al.* was activated by hydrogen reduction prior to its use for the deuteration of substituted imidazoles and imidazole salts. The substrate dissolved in D_2O was then added and the reaction mixture degassed by several freeze/thaw cycles.[43]

This pre-activation principle, by initial charging the catalyst surface with hydrogen gas, has been known for some time in exchange reactions,[14,44] and was further taken up by Hirota and Sajiki and developed into a one-pot method with *in-situ* catalyst activation.[45,46] Consistently, without activation, no H/D exchange took place with the model compound diphenylmethane (**7**) with 10 wt% Pd/C (10% Pd) in D_2O (Scheme 4).

In contrast, the catalyst activity increased dramatically in a hydrogen atmosphere, resulting in 95% deuterium content for the benzylic positions of **7** even at room temperature within 3 days. The method tolerated differently substituted benzyl derivatives, e.g. sodium 4-ethylbenzoate (**8**) and cyclohexylbenzene (**9**). Moreover, especially for amine substrates such as 2-phenethylamine (**10**) and 2-benzylaniline (**11**) the deuterium efficiency was considerably enhanced by mild heating at 50°C. In order to suppress a competing hydrogenolysis observed for benzylic ethers, Pd/C(en) (Pd/C-ethylenediamine complex) was used instead of Pd/C, most efficiently in a solvent mixture of D_2O/THF at 50°C.[48] Under these conditions, 3β-benzyloxycholestane (**12**) and *N*-Boc-*O*-benzyl-L-serine (**13**) were selectively deuterated at the benzylic position in excellent yields of 79 and 96%, respectively (Scheme 4).

Further investigations by Sajiki *et al.* on 5-phenylvaleric acid (**14**) found a considerable influence of the reaction temperature on the regioselectivity and deuterium incorporation in H/D exchange reactions.[49] The benzylic hydrogen atoms were selectively deuterated at room temperature, whereas as at 160°C not only the less reactive α-positions but also β, γ and aromatic hydrogens were also involved, so that multiply deuterated products were formed.

The reaction conditions described were compatible with numerous functional groups such as carboxy **15**, keto **16** or hydroxy groups **17** (Scheme 5), but the process remained restricted to substrates with aryl-linked aliphatic compounds with a strong preference for deuteration in the aliphatic side chain compared with the aromatic positions in the molecule.[50] With the same method, moderate to good deuterium incorporations could be also achieved for pyridines **18**, indoles **19**, pyrimidines **20**, pyrazoles **21**,[51] pyrimidine bases such as uracil (**22**)[52] and nucleosides such as adenosine (**23**) and inosine (**24**)[53] (see also Scheme 6).

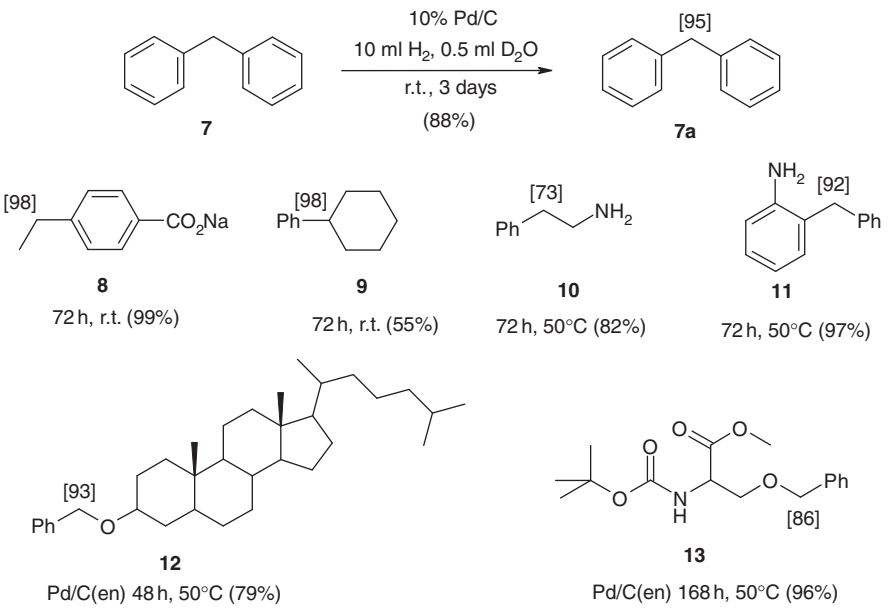
Another preparatively useful application of the Pd/C–H_2-D_2O system is the selective deuteration of the β-position of L-phenylalanine (**25**) shown in Scheme 7, which takes place at 110°C (6 h, 96% D) without racemization.[54] At 160°C, the α-position is also accessible for H/D exchange, but under these conditions racemization occurred (17% ee).

General procedure:[49] *The substrate (500 mg) and 10% Pd/C (50 mg, 10 wt% of the substrate) in D_2O (17 mL) were stirred at a temperature of (110– 160°C) in a sealed tube under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with methanol (20 mL) and the mixture was filtered through a filter paper to remove the catalyst. The filtered catalyst was washed with methanol (2 × 5 mL) and the filtrate was concentrated in vacuo.*

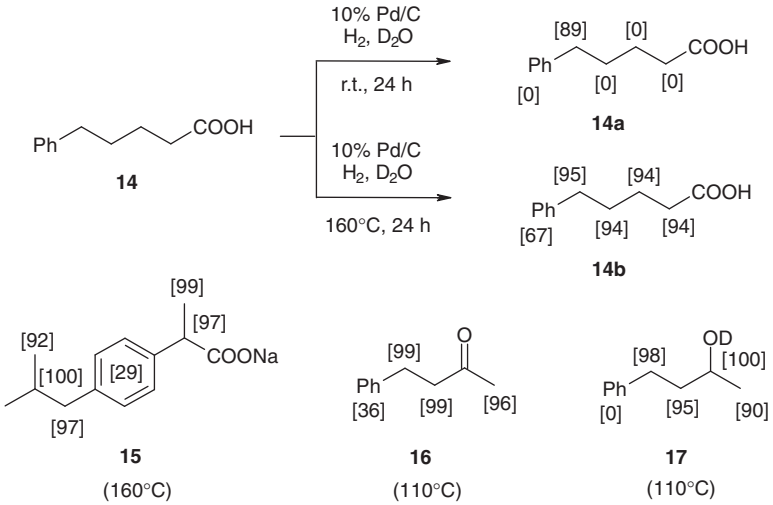
Faigl and co-workers achieved a significantly higher exchange efficiency for the benzylic hydrogen atoms of the piperidine derivative **26** with Pd/C–H_2–D_2O in the presence of deuterated alcohols and DCl.[55] Stock and Ofosu-Asante used deuterated acetic acid as a deuterium source with Pd/C in a D_2 atmosphere for the selective benzylic deuteration of the tetrahydronaphthalene carboxylic acid (**27**) (Scheme 8).[56]

In a comparative study, Sajiki *et al.* were able to demonstrate that platinum catalysts generally have a higher selectivity for the deuteration of aromatic positions, whereas palladium catalysts preferentially exchanged aliphatic hydrogen atoms.[57] The deuteration of phenol (**28**) was achieved almost quantitatively with 5% Pt/C even at room temperature; in contrast, the palladium-catalyzed reaction had to be heated to 180°C for realization of a comparable degree of deuteration.

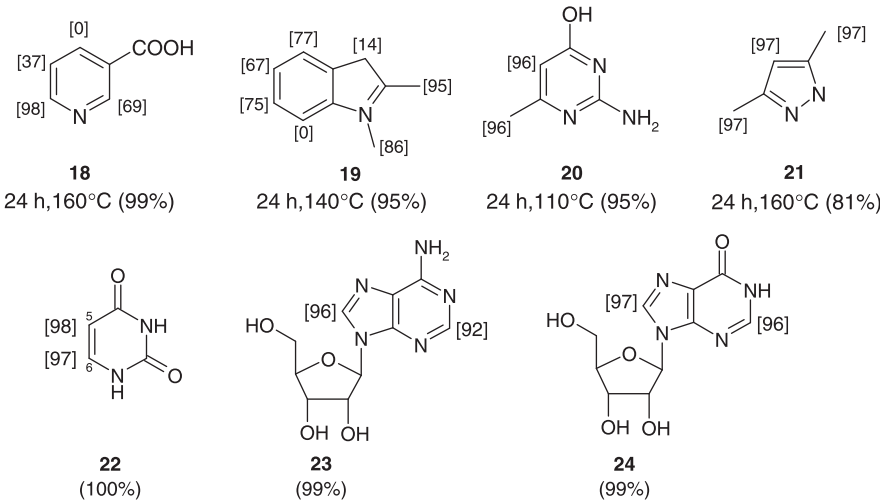
Mild heating at 80°C for aniline (**29**) and biphenyl (**30**) is sufficient to give almost quantitative deuterium incorporation



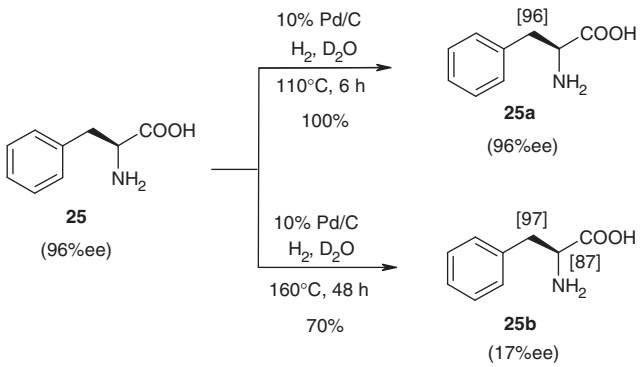
Scheme 4. H/D exchange of benzylic hydrogen atoms with *in-situ*-activated Pd-catalyst. The number in brackets gives the percentage fraction of deuterium [% D][47].



Scheme 5. Influence of the temperature on the deuterium uptake and regioselectivity of Pd-catalyzed H/D exchange and examples for multi deuterium introduction under heating conditions.



Scheme 6. Pd/C-catalyzed H/D-exchange of heterocyclic compounds, pyrimidine bases and nucleosides.



Scheme 7. Deuteration of L-phenylalanine (**25**). Influence of temperature on deuterium uptake and stereochemistry of H/D exchange.

with Pt/C. However, more drastic conditions (180°C) have to be applied for aromatic compounds possessing electron-withdrawing groups, such as benzoic acid (**31**) to obtain similar deuterium levels (Scheme 9). In the case of strong electron withdrawing functionalities, such as nitrobenzene and bromobenzene, even at 180°C almost no deuterium uptake could be observed. Pt/C-catalyzed H/D exchange was also applied for the labelling of 2-aminophenol (**32**), which was later used as a precursor for the synthesis of an internal MS standard of the PPAR α agonist (*R*)-K-13675.[58]

On a preparative scale, the different selectivity of the two metals was used for the stepwise deuteration of ibuprofen (**15**) as shown in Scheme 10, which led to an almost completely labelled product. Initially, all protons on the aromatic ring were exchanged with 5% Pt/C, followed by deuteration of the remaining protons on the aliphatic residue in a second step with 10% Pd/C.[59]

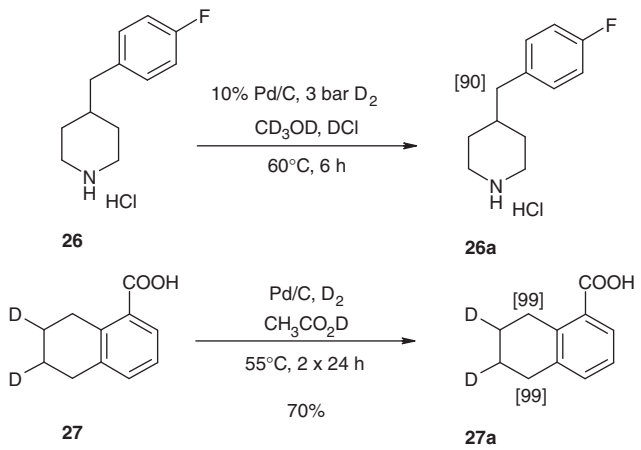
Metal hydride-activated Pd-and Pt-catalyzed H/D exchange

In order to provide labelled materials with the requested narrow isotopologue distribution and to address key requirements for stable labelled internal MS standards, we became interested in the development of specific H/D exchange methods. Besides the

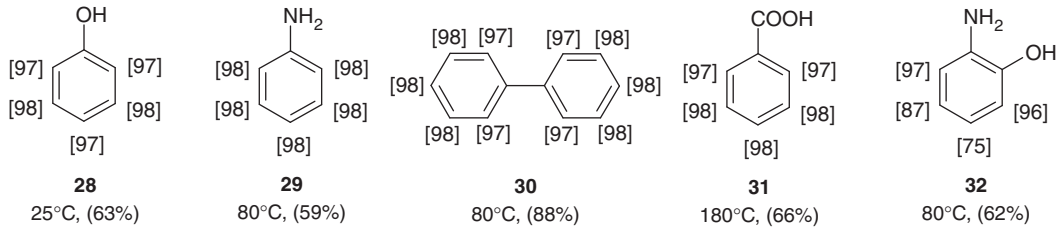
long reaction times and high temperatures, from an industrial user perspective another limitation of the Sajiki protocol is the handling of gaseous hydrogen both from a safety aspect but also with respect to a potential utilisation of automated high-throughput devices or microwave instruments. Therefore, compared with the Sajiki protocol, a small but significant practical improvement was achieved by the utilization of hydride donors for the necessary catalyst pre-activation.[13,60]

For the Sanofi-Aventis development candidate AVE3085 (**33**), a potential eNOS enhancer developed for treatment of cardiovascular disorders, no significant H/D exchange was observed under basic or acidic conditions, or by refluxing in D_2O, or by addition of non-activated Pd/C in D_2O, or with $NaBD_4$ in D_2O without the catalyst (Figure 2). However, even 5 mol% $NaBD_4$ was sufficient to activate the transition metal catalyst and to reach high deuterium incorporations in the product. Although the uptake was reduced from 8 to 5 deuterium atoms, the addition of THF as a co-solvent led to a much higher selectivity of the deuteration and therefore these conditions were also used for the internal MS standard preparation of AVE3085 (**33a**). It is notable that the exchange reaction took place without any side reactions, and thus no chromatographic purification was necessary to obtain the internal standard with $>99\%$ purity.

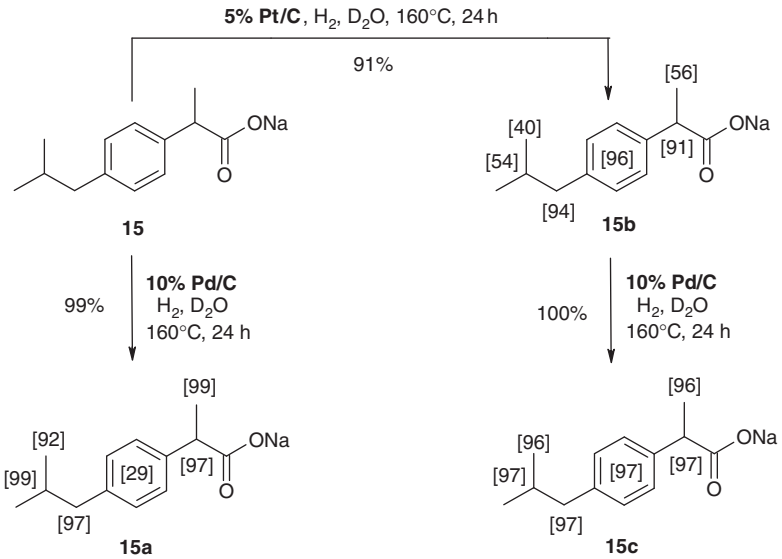
Encouraged by these results, the scope and limitations of this method were further studied. Besides Pd/C, palladium salts such as $PdCl_2$ or $Pd(OH)_2$ and also $RhCl_3$ have been successfully applied as catalysts. Both carbocyclic compounds such as 1-tetralone (**34**) and substituted heterocycles such as 1*H*-pyrrolo[2,3-*b*]pyridin-5-ylamine (**35**), tetrahydroquinoline (**36**) or the highly substituted piperidine derivative **37** proved to be suitable as substrates (Scheme 11) for the hydride activated exchange at 160°C.[58]



Scheme 8. H/D exchange of piperidine **26** and tetrahydronaphthalenecarboxylic acid (**27**).



Scheme 9. Pt-catalyzed H/D exchange of aromatic compounds.



Scheme 10. Palladium- and platinum-catalyzed H/D exchange of ibuprofen (**15**).

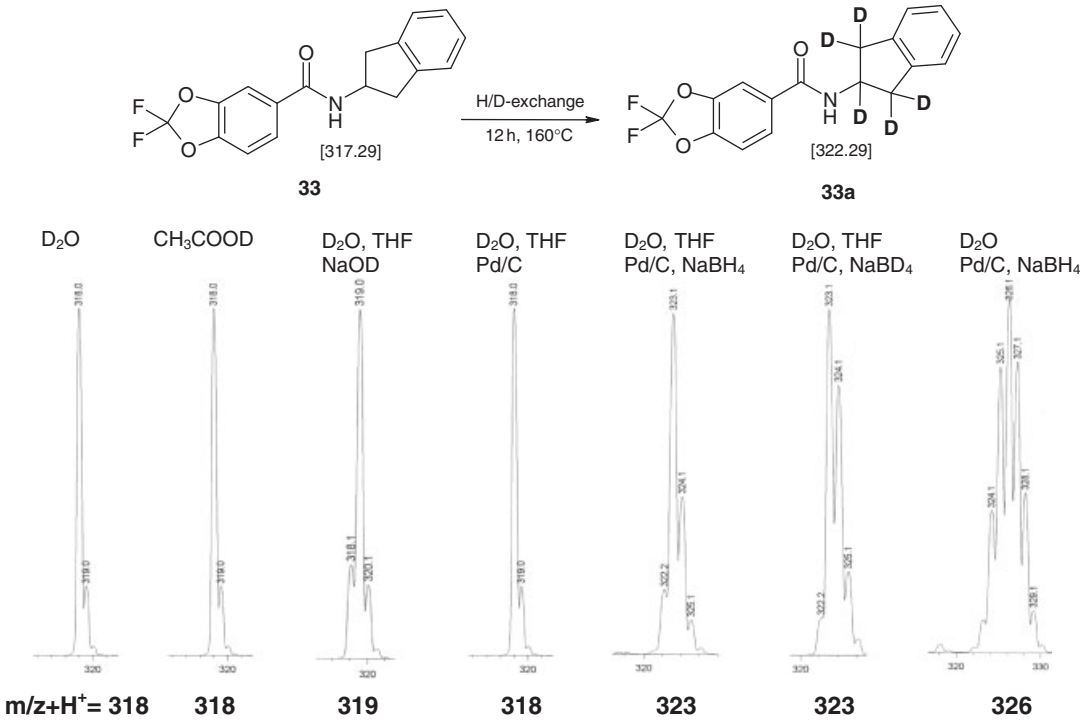
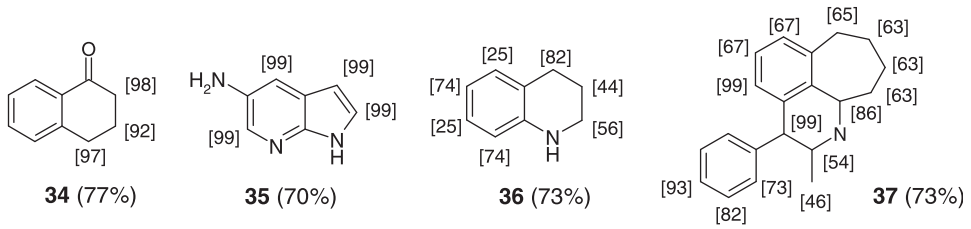


Figure 2. Molecular peak ($M+H^+$) from the MS spectra of AVE3085 (**33**) after H/D exchange under several reaction conditions.



Scheme 11. Application of $NaBD_4$-activated Pd/C-catalyzed H/D exchange for the deuteration of 1-tetralone (**34**) 1*H*-pyrrolo[2,3-*b*]pyridin-5-ylamine (**35**), tetrahydroquinoline (**36**) and piperidine derivative **37**.

The method was further applied to the synthesis of a MS standard of racemic [^{13}C, $^{2}H_9$]Formoterol (**39**) (Foradil®, 1:1 of (*R,R*)- and (*S,S*)-Formoterol), a very potent β_2 agonist which is used as a bronchodilator in the therapy of asthma and chronic bronchitis.[61] Unfortunately, the H/D exchange method was not suitable for labelling of commercially available Formoterol (**39**) directly due to decomposition of the molecule. However, Pd/C-catalyzed H/D exchange was successfully applied to 1-(4-[^{13}C,D_3]methoxy-phenyl)-propan-2-one (**38**) to obtain **38a** in 82% yield; this intermediate was then used as a precursor for the synthesis of racemic [^{13}C, $^{2}H_9$]Formoterol (**39**) (Scheme 12). Alternative H/D exchange methods, e.g. under acidic or basic conditions led to aldol side reactions and a broader isotope distribution in the MS spectra.[62]

Similar results were reported by Sajiki *et al.* in a mechanistic study of H/D exchange reactions of ketones. However, H_2-activated 10% Pd/C-catalyzed exchange resulted in partial hydrogenation and thus the formation of mixtures of the ketone and the corresponding secondary alcohol.[63]

General procedure:[60] *Into a pressure tube filled with argon was placed 1.00 mmol of the organic compound, 10 wt% catalyst, 5 mol% $NaBD_4$ (98% D), and 3 mL D_2O (99% D). The mixture was heated to 50°C and the tube was sealed after effervescence had ceased. Then the reaction mixture was heated to 130–180°C for 18 h. The mixture was cooled to room temperature and 3 mL acetonitrile were added. The catalyst was removed by filtration and if necessary the product was purified by chromatography.*

From an industrial user's perspective, microwave systems are safe, simple to handle and provide the option for effective process automation and standardization. The H/D exchange of various aminobenzoic acid model substrates has been studied using $NaBD_4$-activated Pd. The results show higher and more specific deuterium incorporations when microwave heating rather than classical heating is used.[64] Thus, the long reaction times of 16 h with conventional heating (150°C) could be reduced to 2 h (150°C) by microwave irradiation. This method was successfully applied to the labelling of substituted pyridines such as 3-amino-pyridine (**40**) and even proved to be effective for the deuteration of aromatic compounds like 4-nitro-aniline (**41**) or 4-amino-benzoic acid (**42**) (Scheme 13).

A first useful synthetic application of this convenient method was the fast preparation of the deuterated MS-standard of dextrorphan

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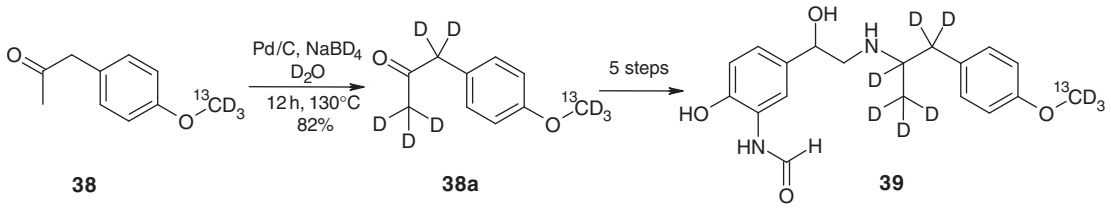
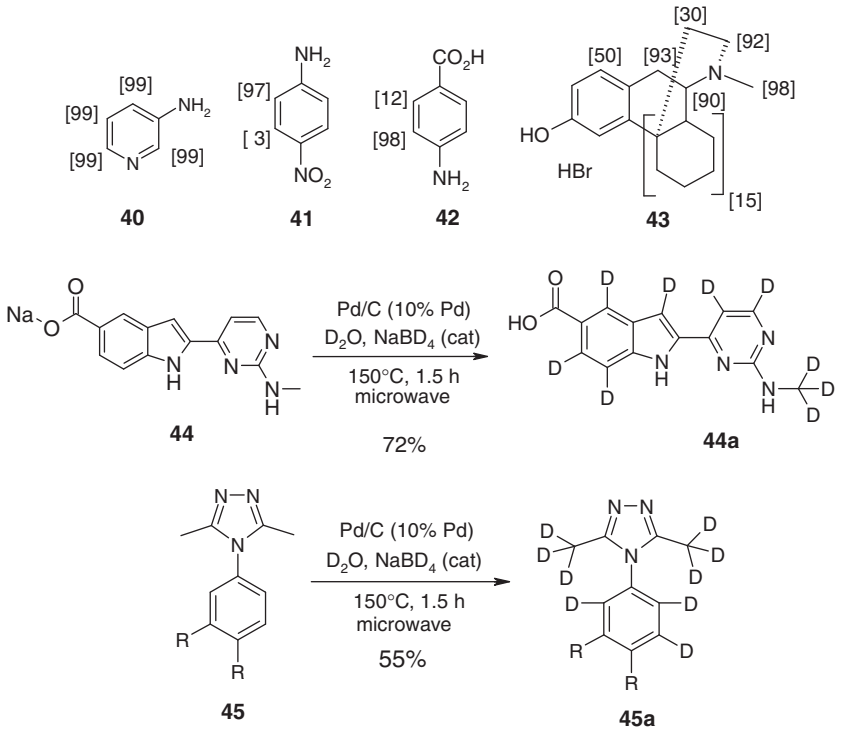


Scheme 12. $NaBD_4$-activated Pd/C-catalyzed H/D exchange as key step for the synthesis of [^{13}C, $^{2}H_9$]Formoterol (**39**).



Scheme 13. Microwave-enhanced $NaBD_4$-activated Pd/C-catalyzed H/D exchange.

(**43**) (Scheme 13), which is frequently used for enzyme inhibition studies within pharmaceutical drug development.

$NaBD_4$-activated H/D-exchange under microwave conditions has become a standard method for fast stable isotope labelling of new drug development candidates. For example, the pyrimidine-indole-5-carboxylic acid derivative **44** was almost completely deuterated with the introduction of nine deuterium atoms. The product **44a** was then successfully converted into the labelled drug development candidate in only two additional synthetic steps. Compared with the free acid, the carboxylate **44** was more soluble in D_2O and therefore resulted in higher and more specific deuterium incorporation. In the case of the triazole derivative **45** the candidate itself was stable under the exchange conditions and thus a highly selective labelling was achieved in just one step (Scheme 13).

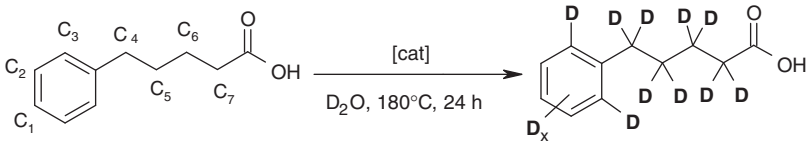
Typical procedure: Into a pressure tube filled with argon was placed 1.00 mmol of the organic compound, 10 wt% catalyst, 5 mol% $NaBD_4$ (98% D) and 6 mL D_2O (99% D). The mixture was stirred for approximately 30 s and the tube was sealed (remark: the reaction vessel was sealed after effervescence had ceased) and heated to 140°C for 2 h. The mixture was cooled to room temperature and 3 mL acetonitrile was added. The catalyst was separated by filtration. The product was purified by chromatography if necessary and analyzed by NMR and LC-MS.

Pd–Pt catalyst mixtures – the synergistic effect

In 2006 Sajiki *et al.* reported a synergistic effect observed when using catalyst mixtures of Pd/C and Pt/C for H/D exchange reactions.

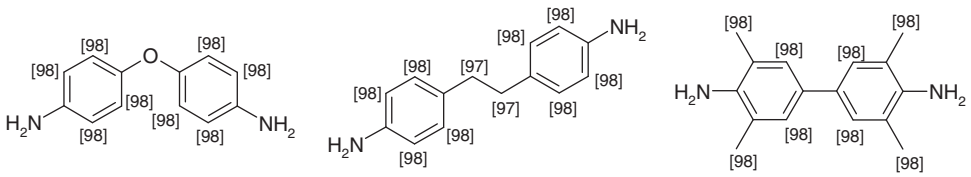
Employing 5-phenylvaleric acid (**14**) as a model substrate, the deuterium incorporation for the H/D exchange in the *ortho* position of **14** was only 14% with Pd/C (entry 1, Table 1) and only 19% with Pt/C alone (entry 2). If the reaction was performed in a stepwise manner with Pd/C-catalyzed exchange first, followed after work up by a second run with Pt/C, the deuterium uptake was only slightly increased to 30% (entry 3). However, if the catalysts were mixed together an almost complete deuteration of 97% could be observed in just one single exchange reaction (entry 4). Similar findings were observed for other substrates as well, implying a synergistic effect of Pd/C and Pt/C catalyst mixtures for the H/D exchange reaction,

Table 1. The synergistic effect of Pd-Pt catalyst mixtures



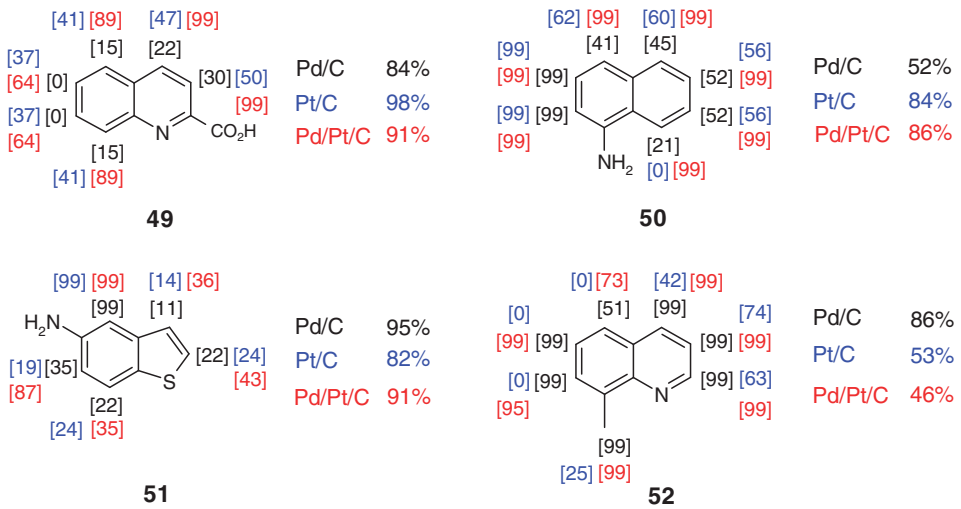
14 14a

Entry	Catalyst	(%)	C_1	C_2	C_3	C_4	C_5/C_6	C_7
1	10% Pd/C	88	96	96	14	98	96	96
2	5% Pt/C	92	97	97	19	28	8	0
3	10% Pd/C, 5% Pt/C, stepwise	84	97	97	30	97	97	97
4	10% Pd/C, 5% Pt/C	94	97	97	97	97	97	94



46 47 48

Scheme 14. Pd/Pt/C-catalyzed exchange of anilines.



49 50 51 52

Scheme 15. Synergistic effect in the $NaBD_4$-activated microwave-induced H/D exchange.

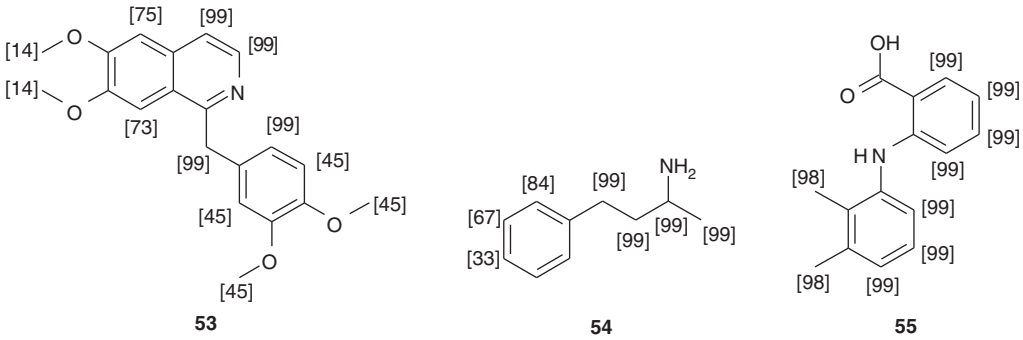
although the mechanism of this remains unexplained.[65] Further extension of this catalyst mixture revealed an almost quantitative deuteration of a number of aniline derivatives investigated, e.g. 4,4′-diaminodiphenylether (**46**), 4,4′-diaminodiphenylethane (**47**) and 3,3′,5,5′-tetramethylbenzidine (**48**) (Scheme 14).[66]

The synergistic effect was also observed after metal-hydride activation of the catalyst, resulting in significantly higher deuterium incorporations for Pd/Pt/C mixtures compared with those obtained with the individual catalysts in the microwave-induced H/D exchange of heterocycles.[62]

For example, a significant synergistic effect could be observed for quinoline-2-carboxylic acid (**49**), 1-aminonaphthalene (**50**) and 5-aminobenzothiophene (**51**) (Scheme 15). For the quinoline **52** an almost complete deuteration was achieved with the Pd/Pt/C catalyst mixture and, in contrast to Pd/C alone a representative peak at M+9 could be identified, making the material suitable as precursor for internal MS standard preparation.

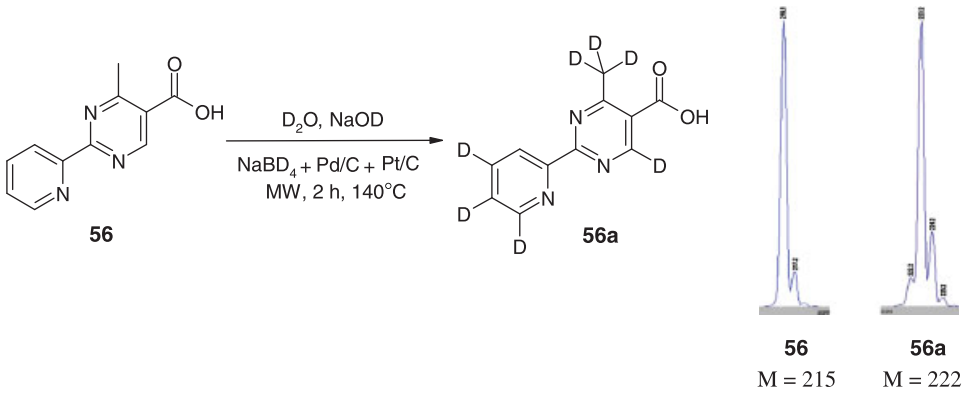
This method was further applied for the preparation of the required internal MS standards of several pharmaceutically active compounds by H/D exchange of the drug material itself.

Pd/Pt/C-catalyzed H/D exchange of papaverine (**53**), a phosphodiesterase inhibitor frequently used for treatment of erectile dysfunction prior to the introduction of Viagra, yielded an internal MS standard with seven additional mass units as the



53 **54** **55**

Scheme 16. Pd/Pt/C-catalyzed H/D exchange of pharmaceutically active compounds.



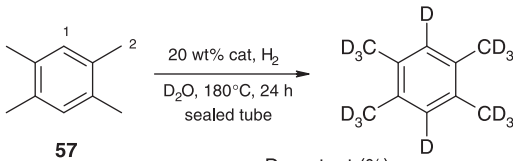
Scheme 17. Pd/Pt/C-catalyzed H/D exchange.

major isotopologue. Under the same reaction conditions, both 3-amino-1-phenylbutane (**54**), a compound of the amphetamine family, and mefenamic acid (**55**), a non-steroidal anti-inflammatory agent used for treatment of rheumatoid arthritis, were sufficiently deuterated to obtain MS standards in a single reaction step (Scheme 16).

Pd/Pt/C-catalyzed H/D exchange was further used for a highly selective deuteration of 4-methyl-2-pyridin-2-yl-pyrimidine-5-carboxylic acid (**56**) which was subsequently converted to an almost ideal internal MS standard with 7 additional mass units (Scheme 17).

General procedure: Into a pressure tube filled with argon was given 1 mmol of the organic compound, 10 wt% catalyst (mixture of 1:1 ratio of Pd/C; 10% Pd, Degussa and Pt/C; 5%Pt, Hereaus), 5 mol% $NaBD_4$ (98% D) and 6 mL D_2O (99% D). The mixture was stirred for approximately 20 sec and the tube was sealed and heated to 140–180°C for 1.5–2 h. The mixture was cooled to room temperature and 3 mL acetonitrile or methanol were added. The catalyst was separated by filtration. The product was purified by chromatography if necessary and analyzed by NMR and LC-MS.

A synergistic effect was also reported by Sajiki *et al.* for bimetallic platinum-palladium on carbon catalysts produced by various reducing agents. The exchange efficiency was strongly dependent on the reducing agent used to prepare the bimetallic catalysts. Interestingly, the bimetallic catalyst prepared by reduction with $NaBH_4$ showed the highest catalytic activity for the deuteration of 1,2,4,5-tetramethylbenzene (**57**) and was even superior to the one reduced by H_2 (Scheme 18).[67] This result is very similar to and in line with the observations made for hydride-activated exchange and therefore $NaBH_4$ is



57 **57a**

D-content (%)	C1	C2
Pd/Pt/C + $NaBH_4$	[95]	[94]
Pd/C + Pt/C	[96]	[75]
Pd/C (10%)	[97]	[13]
Pt/C (5%)	[93]	[75]

Scheme 18. H/D exchange with bimetallic platinum-palladium-on carbon catalysts.

favoured in terms of catalyst preparation/preactivation and consequently delivers high deuterium incorporations.

Conclusion and outlook

A central element of methodological developments in the field of Pd- and Pt-catalyzed H/D exchange in recent years has been investigated in new or improved catalyst activation methods. Hydride activation seems to have advantages over H_2 catalyst pre-activation not only with respect to a safer handling but also because sometimes higher deuterium incorporations can be observed. Known methods for H/D exchange have been optimized for their applicability under microwave conditions, which often leads to a better exchange efficiency after shorter reaction times and sometimes even to higher yields due to fewer by-products. Catalyst combinations, such as Pd/Pt mixtures, can result in a synergistic effect which leads to higher

deuterium incorporations for the mixture compared with those observed for the single catalyst runs with the same substrate.

From a Sanofi-Aventis perspective the development of new methods for a selective multi-labelling of new drug development candidates or advanced synthesis precursors to produce internal MS standards is of particular interest. Although other methods are used, the combination of hydride catalyst pre-activation and the exploitation of the Pt/Pd synergistic effect under microwave conditions has proved to be highly efficient. Today, H/D exchange is a standard method in our isotope synthesis group. Wherever it is reasonable the approach is utilized, with increasing rates of success, for labelling many drug development candidates or advanced synthetic precursors. The application of this convenient method has contributed to a considerable reduction in costs and delivery times for the preparation of internal MS standards of new drug development candidates within the company.

In future, an improved understanding of C–H activation processes, especially in reactions of non-activated hydrocarbons, will hopefully allow H/D exchange to be used under even milder reaction conditions and thus open this method to a wide range of sensitive classes of substrates, including natural products.

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[23] Isotopologues are compounds with the same chemical structure that differ only in their isotope composition (for example, [1,2-D_2]propane and [1,2,3-D_3]propane). The term isotopomer indicates isotopologues with the same mass, for example, [1,1-D_2]propane and [1,2-D_2]propane. See: A. D. McNaught, A. Wilkinson, IUPAC Compendium of Chemical Terminology, 2nd ed, **1997**.

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