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Short Research Article

H/D-exchange reactions with hydride-activated catalysts†

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Abstract: A safe, user friendly and efficient method to provide high deuterium incorporation into a variety of organic substrates was developed. Systematic screening of catalysts and activators revealed that the activation of the Pd- or Rh-catalyst by $NaBD_4$ is essential for the H/D exchange. The feasibility has been demonstrated by the successful application of this method to bi- and tricyclic aromatic compounds as well as chiral natural products like dextrorphan or drugs like formoterol. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: deuterium; palladium; rhodium; heterogeneous catalysis; alkaloids; microwave

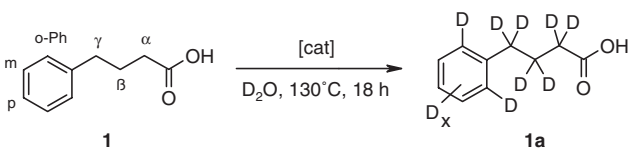
Introduction

Deuterium-labeled compounds are of fast-growing interest due to the widespread application of mass spectrometry as a specific detection and investigation tool in pharmacological, chemical and environmental research. Compared to conventional synthetic approaches starting from small commercially available stable-labeled precursors, the deuterium introduction *via* H/D exchange[1] provides the advantage to circumvent a long and expensive synthesis.[2]

Several new methods for H/D-exchange have been reported in the last couple of years.[3] However, the described procedures for the replacement of hydrogen by deuterium in organic molecules are predominantly limited to activated positions, usually require high amounts of catalyst, the addition of acidic or basic additives, and/or deuterium/hydrogen atmosphere under high temperatures and pressures or even hydrothermal conditions. Especially to improve the heterogeneous metal-catalyzed exchange reaction we considered a significant practical improvement could be achieved by avoiding the handling of gaseous reaction components. For this purpose we reasoned that the pre-activation of the catalyst by addition of hydride donors should be a suitable approach to achieve high deuterium incorporation in complex organic molecules.

Results and discussion

In a model study with phenylbutyric acid **1** (Scheme 1) we examined catalysts and their activation with several hydride/deuteride-donors (Table 1) in D_2O. Under the described reaction conditions (entry 1–3), neither reflux of **1** in D_2O, addition of non-activated Pd/C in D_2O nor $NaBD_4$ without catalyst in D_2O yielded a significant H/D-exchange. Even 5 mol% $NaBD_4$ was already sufficient to activate the transition metal catalyst and to reach a high deuterium content. Surprisingly, in most reactions the hydrogen atoms in γ, β and even in the *ortho*-ring position showed a higher exchange tendency compared to the hydrogen atoms in the α-carbonyl position. Other catalysts sources like $IrCl_3$, $NiCl_2$, $FeCl_3$, $ZnBr_2$, Zn/DCl, PtO_2, Ru/C, Rh/C or Pt/C showed no H/D-exchange activity even after activation with 20 mol% $NaBD_4$. The best results with regard to yield and deuterium incorporation were achieved with Pd/C/$NaBD_4$ (entry 4) or Pd salt/$NaBD_4$ (entry 5). *In situ*-generated rhodium black from $RhCl_3$



1 **1a**

Scheme 1

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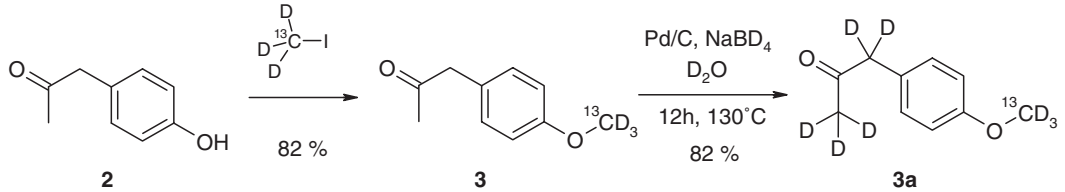
Table 1 Optimization of H/D-exchange reaction of phenyl butyric acid **1** in D_2O[a]

Entry	Catalyst	Activator	**1a** [%][b]	γ [%D][c]	β [%D][c]	α [%D][c]	o-Ph [%D][c]	M^+_{max}[d]
1	—	—	92	—	—	—	—	165
2	Pd/C (10%)	—	87	—	—	—	—	165
3	—	$NaBD_4$	85	—	—	—	—	165
4	Pd/C (10%)	$NaBD_4$	89	97	97	53	93	172
5	$PdCl_2$	$NaBD_4$	93	97	97	32	79	171
6	$RhCl_3$	$NaBD_4$	45	97	97	57	97	172

[a] Conditions: sealed tube with septum, 130°C, 18 h.
[b] Isolated yield.
[c] Determined by NMR.
[d] Determined by LC–MS.



2 **3** **3a**

Scheme 2

and $NaBD_4$ (entry 6) was also active, leading, however, to a higher level of decomposition products in this case.[4]

This method was further applied to the synthesis of racemic [$^{13}C,D_9$]-formoterol **9** which is used as MS standard. (*R,R*)-formoterol (Foradil®), is a very potent β_2 agonist which is used as a bronchodilator in the therapy of asthma and chronic bronchitis.[5] Unfortunately, the described reaction conditions for H/D-exchange lead to decomposition and were not suitable for the labeling of (*R,R*)-formoterol. However, starting from unlabeled 1-(4-hydroxy-phenyl)-propan-2-one **2** the label was introduced by reaction with [$^{13}C,D_3$]-methyl iodide followed by a palladium-catalyzed H/D-exchange reaction in deuterium oxide to yield **3a** in 82% yield (Scheme 2).

Alternative approaches employing basic (2 N NaOD, 2 equiv. KOtBu) or acidic conditions (5 N D_2SO_4) for deuteration of ketone **3** gave low yields (30–65%) mostly due to aldol side reactions. Furthermore, the isolated product **3a** showed in these cases a broader isotope distribution in the MS spectra.

To complete the synthesis of [$^{13}C,D_9$]-formoterol **9** [$^{13}C,D_8$]-labeled ketone **3a** was reacted with benzylamine **4** under reductive conditions with platinum on charcoal and deuterium gas to yield the racemic secondary amine **5** (Scheme 3). Epoxide **6** was synthesized according to the literature.[6] Heating of a 1:1 mixture of racemic **5** and **6** without any solvent yielded [$^{13}C,D_9$]-aminoalcohol **7** as racemic mixture of two diastereomers. Amino alcohol **7** was converted into the desired final compound **9** *via* reduction of the nitro group, subsequent formylation and final debenzylation under reductive conditions. Overall the 5 step synthesis yielded 30% of a racemic mixture of two diastereomers of [$^{13}C,D_9$]-formoterol **9**. Under the used RP HPLC conditions no differences in the retention times of both diastereomers were detected.

We further investigated the influence of the $NaBD_4$-activated Pd- or Rh-catalyzed deuteration on stereogenic centres and the stereoselectivity of the deuterium incorporation. The level of deuterium introduction at the stereocenters of (*S*)-ibuprofen **10** was 96% (determined by NMR). In the H/D-exchange reaction (18 h, 130°C) a significant decrease of optical purity was found (from 99 to 56% see, Scheme 4).

To show the broad generality of the method for labeling more complex aromatic and heteroaromatic structures aromatic ketones (**11**), tetrahydroisoquinolines and tetrahydro-quinolines (**12,13**), indane (**14**) or indole (**15**) derivatives were successfully deuterated. However, it should be mentioned that reaction time, temperature and catalyst need to be optimized for each individual reaction to increase the yield and the deuterium content of the product. All reactions were highly reproducible with respect to deuterium incorporation and position.

In order to reduce the reaction times and to further increase the efficiency, work on microwave-assisted $NaBD_4$-activated Pd- or Rh-catalyzed deuteration has been started. Microwave acceleration was applied for the preparation of the deuterated MS-standard of

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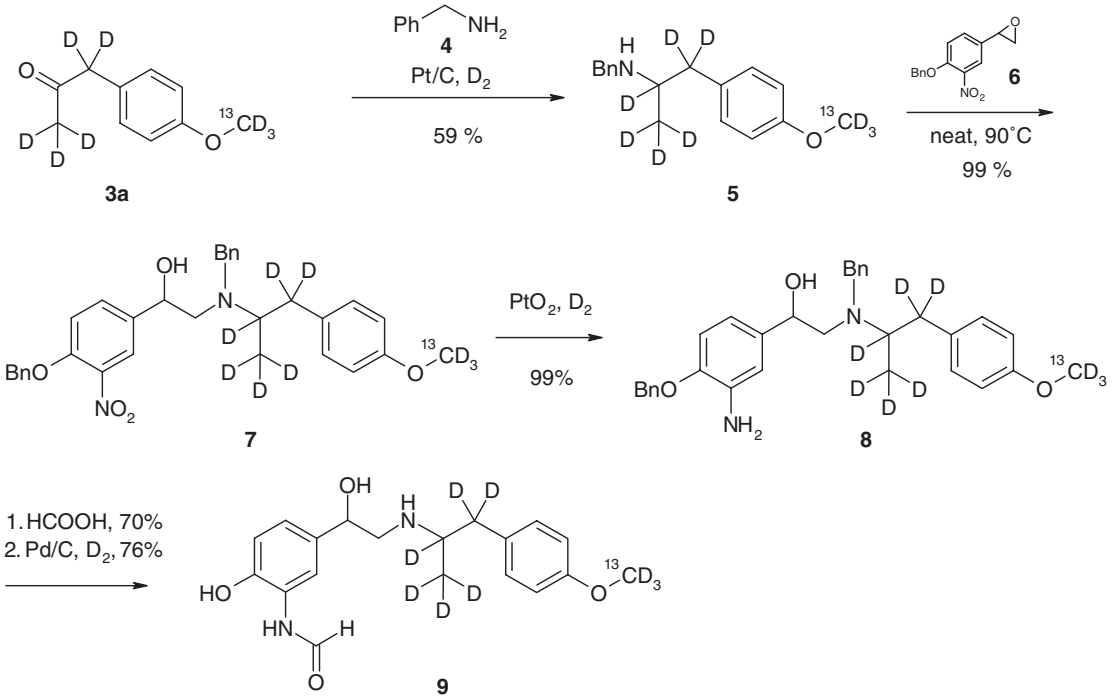
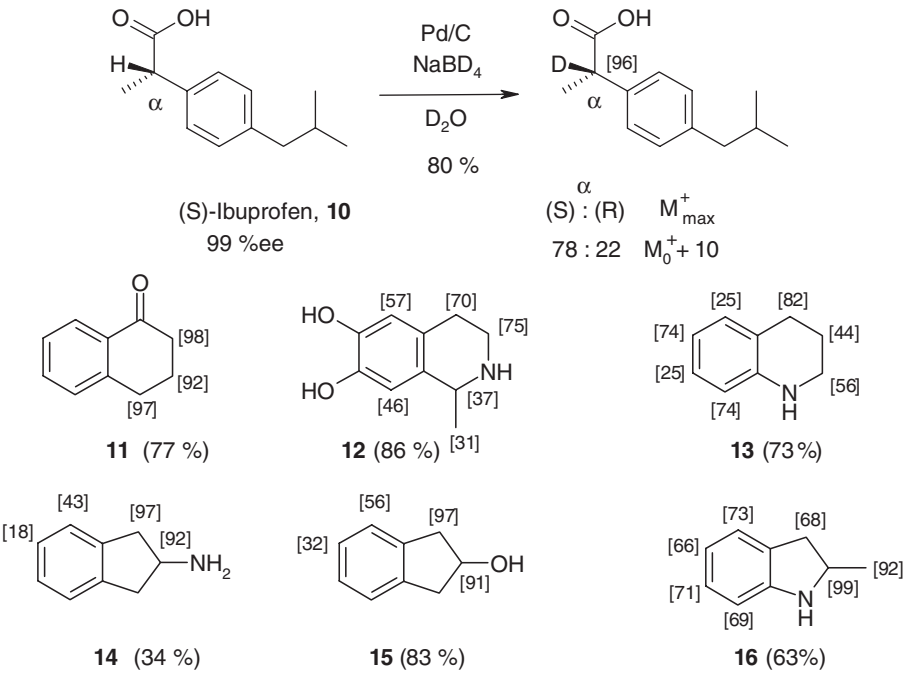


Scheme 3



Scheme 4

dextrorphan **18** (Scheme 5), a compound which is frequently used for enzyme inhibition studies within pharmaceutical drug development. Starting from readily available dextromethorphan **17** the exchange occurred predominantly at the aliphatic positions and after purification the deuterated dextrormethorphan (M_0+9) was obtained in 87% yield. Finally, the *O*-methyl group was removed with HBr and after work up the deuterated dextrorphan **18** (M_0+9) was obtained in 67% yield.

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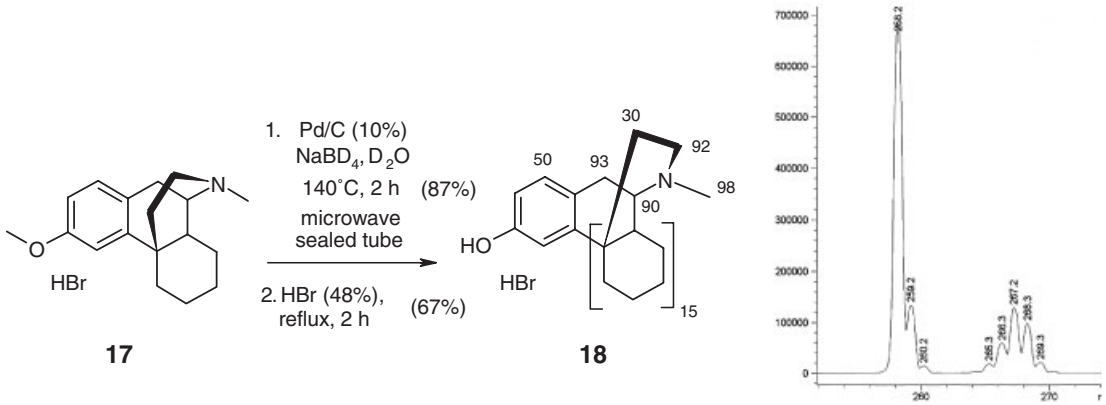

Scheme 5 Synthesis of a MS standard of dextrorphan **18**; MS-spectra of a LC–MS co-injection of dextrorphan and dextrorphan MS standard **18** in the ratio of 3:1 (right side).

Method

Typical thermal reaction conditions

Into a pressure tube filled with argon was placed 1.00 mmol of the organic compound, 10 weight-% 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. Then the reaction mixture was heated to 130°C for 18 h. The mixture was cooled to room temperature and 3 ml acetonitrile were added. The catalyst was removed by filtration. The product was purified by chromatography if necessary and analyzed by NMR and LC–MS.

Typical microwave reaction conditions

Into a pressure tube filled with argon was placed 1.00 mmol of the organic compound, 10 weight-% 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 not closed until bubbling had stopped) and heated to 140°C for 2 h. The mixture was cooled to room temperature and 3 ml acetonitrile were added. The catalyst was separated by filtration. The product was purified by chromatography if necessary and analyzed by NMR and LC–MS.

Conclusion

We have developed a safe and efficient exchange method to provide high deuterium incorporation into a wide variety of substrates employing a catalyst system consisting of Pd/C or a Pd or Rh salt and an activator like $NaBD_4$. The pre-activation of the catalyst by hydride/deuteride donors is essential for high labeling yields. An example was given for the successful application of the microwave-assisted $NaBD_4$-activated Pd- catalyzed deuteration.

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