

H/D Exchange at Aromatic and Heteroaromatic Hydrocarbons Using D₂O as the Deuterium Source and Ruthenium Dihydrogen Complexes as the Catalyst**

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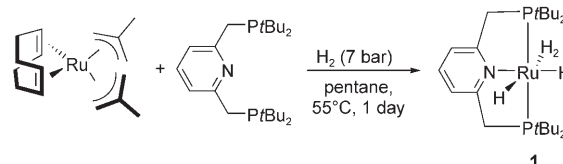
Dedicated to Professor Peter Hofmann on the occasion of his 60th birthday

Hydrogen/deuterium exchange processes are powerful methods to evaluate the potential of a catalyst for the cleavage and formation of a C–H bond.^[1–3] The isotopic exchange reactions can also be of synthetic value, as deuterated and tritiated compounds are used for NMR spectroscopy, for medicinal research, and for drug discovery processes.^[4–6] Furthermore, deuterated polymers have been evaluated for organic light emitting diodes (OLEDs) and are used in optical communication systems.^[7] Therefore, there is increasing interest in mild and selective catalytic H/D exchange processes from both fundamental and application-oriented viewpoints.

Transition-metal-catalyzed H/D exchange processes are usually performed with D₂ or in deuterated organic solvents such as [D₆]benzene or [D₆]acetone, and only in very few cases can deuterium oxide (D₂O) be used.^[4,8–10] In recent years, iridium, rhodium, and ruthenium complexes have shown promising potential, but reaction temperatures are typically well above 100 °C for systems utilizing D₂O as the deuterium source.^[4,8,9a,b] We report herein the efficient and selective H/D exchange between arenes and D₂O at temperatures as low as 50 °C by using the nonclassical hydride complex [Ru(dtbpmp)(η²-H₂)H₂] (**1**, dtbpmp = 2,6-bis((di-

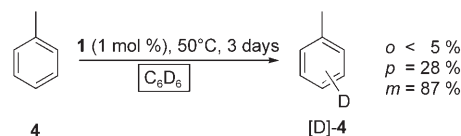
tert-butylphosphino)methyl)pyridine) as the catalyst precursor.

As part of our ongoing interest in the catalytic properties of nonclassical ruthenium hydrides, we have recently synthesized complexes [Ru(IMes)(PCy₃)(η²-H₂)H₂] (**2a**, IMes = 1,3-dimesityl-1,3-dihydro-2H-imidazol-2-ylidene, Cy = cyclohexyl) and [Ru(IMes)₂(η²-H₂)H₂] (**2b**) as carbene analogues of Chaudret's hexahydride [Ru(PCy₃)₂(η²-H₂)H₂] (**3**).^[10] In contrast to **3**, complexes **2a** and **2b** showed a very high activity for H/D exchange between [D₆]benzene and other aromatic compounds. To further evaluate the catalytic properties of this class of compounds we extended the structural motifs of nonclassical ruthenium hydrides to complexes with pincer-type ligands. The complex [Ru-(dtbpmp)(η²-H₂)H₂] (**1**, dtbpmp = 2,6-bis((di-*tert*-butylphosphino)methyl)pyridine) is readily accessible in high yields by using the direct hydrogenation route shown in Scheme 1.^[11]



Scheme 1. Synthesis of the pincer-type nonclassical ruthenium hydride complex **1**.^[11b]

As expected, complex **1** is a very active catalyst for the H/D exchange between [D₆]benzene and aromatic substrates (Scheme 2). At 50 °C, deuterium is effectively transferred



Scheme 2. Deuteration of arenes with C₆D₆ and **1**.

from C₆D₆, which is used as the solvent in these experiments, to toluene with a noticeable regioselectivity for the *meta* position.

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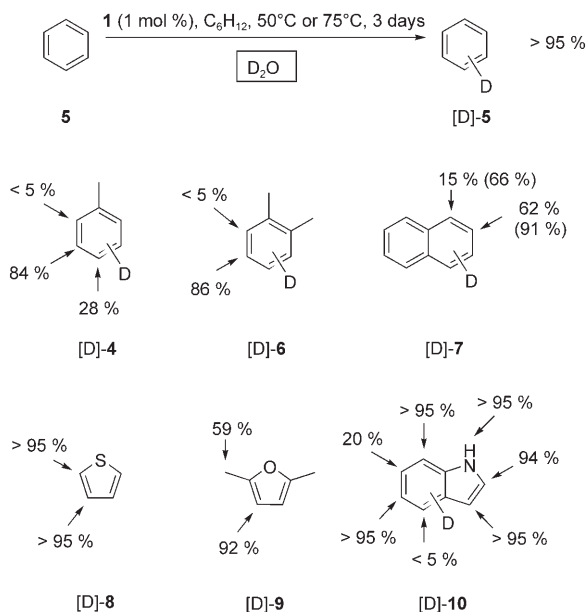
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Most intriguingly, however, we found that **1** is also active at the same temperature for the incorporation of deuterium into aromatic substrates when D₂O is used as a cheap and environmentally benign deuterium source (Scheme 3). The



Scheme 3. Catalytic H/D exchange of aromatic and heteroaromatic compounds using D₂O as the deuterium source and complex **1** as the catalyst. Reaction conditions (under argon): Substrate **4**–**10**: **1**–1.25 mmol; Ru cat. **1** (1 mol %), D₂O (1 mL), C₆H₁₂ (0.7–1.0 mL). *t* = 3 days; reaction temperature: [D]-**4**–[D]-**7**: *T* = 50 °C (75 %); [D]-**8**–[D]-**10**: *T* = 75 °C; see the Supporting Information for details.

exchange occurs in a two-phase system consisting of cyclohexane and D₂O, whereby cyclohexane served as the solvent for the aromatic substrate and the catalyst. Control experiments verified that no deuterium was incorporated into cyclohexane under these reaction conditions. Thus, the H/D exchange can be conveniently monitored by ¹H NMR spectroscopy through observation of the decrease of individual signals in the organic phase relative to the solvent signal (as an internal standard). Deuterium incorporation at the various positions was verified by ²H NMR and ¹³C NMR spectroscopic analysis at the end of the reaction. Values given as “< 5 %” or “> 95 %” indicate that no signals were detected corresponding to the deuterated or non-deuterated species, respectively. Details of the experimental procedure and the NMR spectroscopic analysis are given in the Supporting Information.

As depicted in Scheme 3, benzene (**5**) was deuterated quantitatively using 1 mol % of catalyst **1** at 50 °C within three days. Other aromatic and heteroaromatic compounds were also deuterated effectively under similar mild reaction conditions, and a significant chemo- and regioselectivity was observed in certain cases. For toluene (**4**), incorporation of deuterium occurred with preference for the *meta* position, with 84 % of all these protons replaced. Additionally, 28 % of the *para* protons were exchanged with deuterium, while no incorporation was detected in the *ortho* position. The methyl

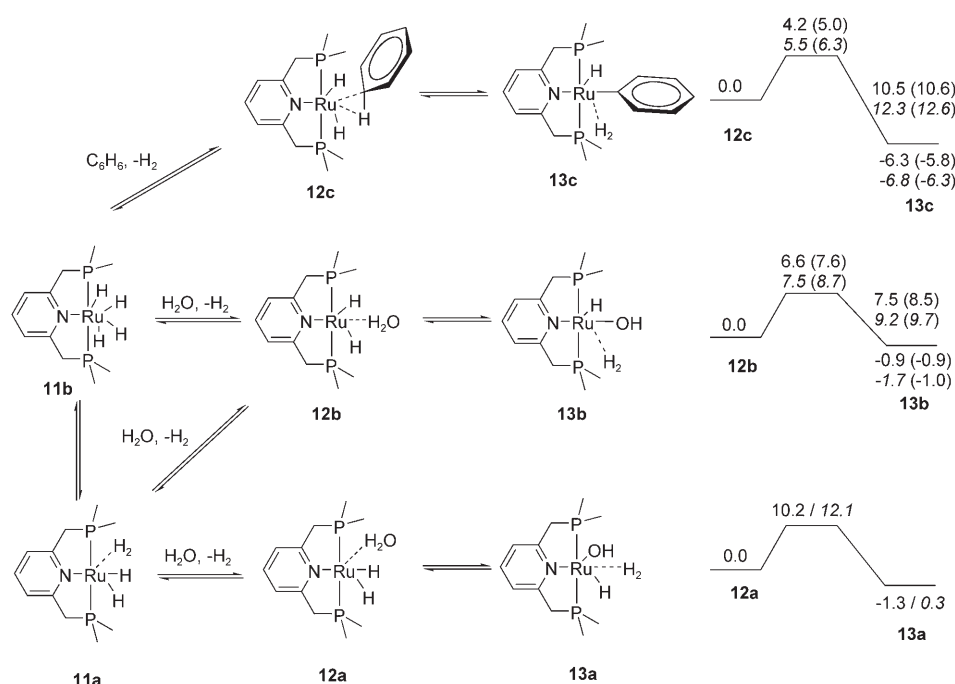
group remained unreactive under these reaction conditions. *ortho*-Xylene (**6**) was deuterated almost exclusively at the β -positions to the methyl groups (86 %), with no significant deuterium incorporation in the α -positions or the methyl groups. Treatment of naphthalene (**7**) under the same conditions resulted preferably in β -deuteration (62 %), with a lower amount of α -deuteration (15 %).

The H/D exchange also occurred readily with heteroaromatic compounds, even when potentially coordinating groups were present. Thiophene (**8**) was fully deuterated in all positions within the standard reaction time at 75 °C. Treatment of 2,5-dimethylfuran (**9**) led to almost quantitative incorporation of deuterium at the sp² carbon atoms (92 %), but there was also noticeable deuteration at the methyl groups (59 %). As no H/D exchange was observed in the alkyl groups of other substrates, this finding might indicate that an activation of the C(sp³)–H bond is directed by pre-coordination to the oxygen atom in the case of **9**. Efficient H/D exchange was observed for indole (**10**), whereby C3 was found to be the least reactive position. The ¹H NMR signal for the proton at C3 overlapped with that of the NH signal, and the combined area decreased by a total of 59 %. ¹³C NMR analysis revealed that the incorporation at C3 was negligible and also that C5 remained largely non-deuterated.

The properties of the catalytic system were studied in more detail using **7** as the benchmark substrate. The long-term stability of the catalytically active species at the end of the standard reaction was tested by removing the D₂O layer and replacing it with H₂O. The amount of deuterium incorporated was found to decrease to 35 % in the β -position and 5 % in the α -position, thus indicating that the exchange was still going on. Increasing the reaction temperature to 75 °C resulted in **7** being deuterated within one day to 81 % in the β -position together with 26 % deuterium incorporation at the α -position. Again, the exchange continues over an extended period of time and leads to greater than 95 % β -[D]-**7** after two days, and reaches 77 % exchange in the α -position after four days. On the other hand, increasing the loading of **1** to 4 mol % and shortening the reaction time to one day still led to a high level of β -deuteration (60 %) without significant α -deuteration at 50 °C.

To investigate a possible contribution of acid-catalyzed H/D exchange under the present conditions a solution of **4** in cyclohexane was treated with concentrated DCl/D₂O (37 %). No incorporation could be detected at 50 °C over an extended period of time. Furthermore, the H/D exchange in the **7**/D₂O system catalyzed by **1** was not influenced significantly by the addition of mercury (Hg/Ru: 10:1, *T*: 50 °C, *t*: 3 days, α : 15 %, β : 55 %), thus indicating, although not proving, that the catalytic cycle involves a molecular organometallic species.^[12] Finally, the choice of the ligand appears to play an important role for the catalytic properties: the use of Chaudret's complex **3** as catalyst for the deuteration of **5** resulted only in 47 % deuterium incorporation within 4.5 days as compared to quantitative incorporation after three days with **1** under otherwise identical conditions.

Scheme 4 shows a plausible reaction scheme that explains the exchange of H and D in the coordination sphere of a pincer-ligated ruthenium center in water and benzene,



Scheme 4. Reaction steps and energy profiles ($\Delta H/\Delta G$ (italics) in kcal mol⁻¹) for H/D exchange processes starting from **11a** as determined by DFT calculations. Values in parenthesis denote relative energies of stationary points for the corresponding D₂O (**12b** and **13b**) and C₆D₆ complexes (**12c** and **13c**).

respectively. The corresponding intermediates and transition states were identified from DFT calculations on model complexes in which the *t*Bu groups at the P centers of **1** were replaced by methyl substituents.^[13] The dihydrogen molecule in precursor **11a** can be replaced by a H₂O molecule to yield **12a**. The aquo complex subsequently reacts through a σ -bond metathesis to give **13a**, again containing an H₂ ligand.^[14] This reaction requires a moderate activation energy ($\Delta G^\ddagger = 12.1$ kcal mol⁻¹). An alternative route (**12b** to **13b**) with the H₂O molecule bound *trans* to the pyridine ring of the ligand is also possible, and has an activation energy of $\Delta G^\ddagger = 7.5$ kcal mol⁻¹. On repeating the calculations for the corresponding D₂O complexes of **12b** and **13b** as well as the corresponding transition states, the activation energy for the forward and the backward reactions were found to be marginally higher, by 1.0 kcal mol⁻¹ ($\Delta G^\ddagger = 8.7$ kcal mol⁻¹,

$\Delta G^\ddagger = 9.7$ kcal mol⁻¹, respectively), thus indicating that the incorporation of deuterium into the metal complex from D₂O is a facile process.

The stationary points for the corresponding benzene-containing complexes were also localized (Scheme 4, Figure 1). In complex **12c**, one H₂ molecule of the parent complex **11a** is replaced by a benzene molecule which binds in a η^2 C-H mode.^[14,15] Complex **12c** can react to give product **13c** and the activation energy for the forward reaction amounts to $\Delta G^\ddagger = 5.5$ kcal mol⁻¹, while the backward reaction requires 12.3 kcal mol⁻¹. Replacement of C₆H₆ by C₆D₆ leads to a slightly higher activation energy for the forward reaction ($\Delta G^\ddagger = 6.3$ kcal mol⁻¹), while the activation energy for the backward reaction remains practically unchanged ($\Delta G^\ddagger = 12.6$ kcal mol⁻¹).

Scheme 5 shows the key steps of the exchange process with the real substitution pattern of catalyst **1** and toluene **4** as the substrate. The C-H activation steps in the *para* and *meta* positions were calculated to have practically the same activation energy ($\Delta G^\ddagger = 12.1$ kcal mol⁻¹ and $\Delta G^\ddagger = 13.1$ kcal mol⁻¹, respectively). The *ortho* position, however, is clearly disfavored, with a much higher activation energy of $\Delta G^\ddagger = 17.9$ kcal mol⁻¹. Considering the statistic preference of the *meta* over the *para* position, these results would predict an approximate 2:1 preference for deuteration in the *meta* over the *para* position in **4**, with no significant incorporation in the *ortho* position. Thus, the general trend of reactivity and regioselectivity is reproduced well by this pathway at the present stage of investigation, although additional electronic control factors clearly come into play, especially for hetero-aromatic substrates.

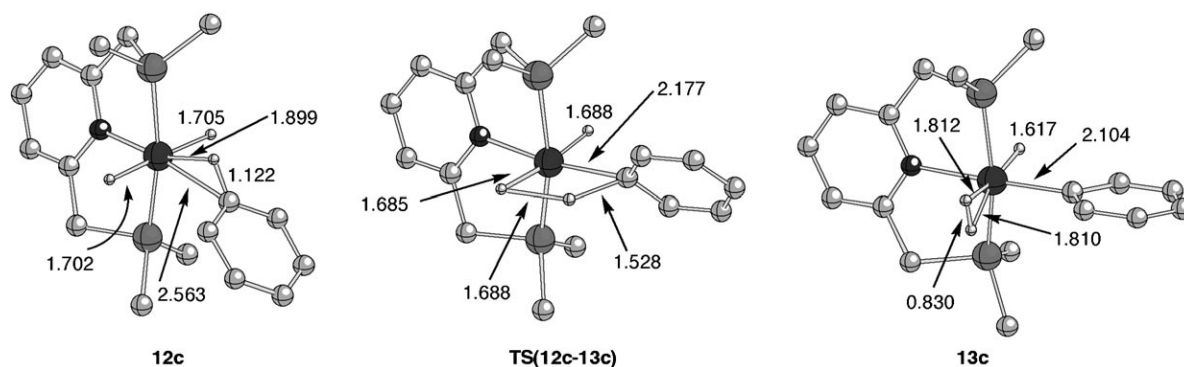
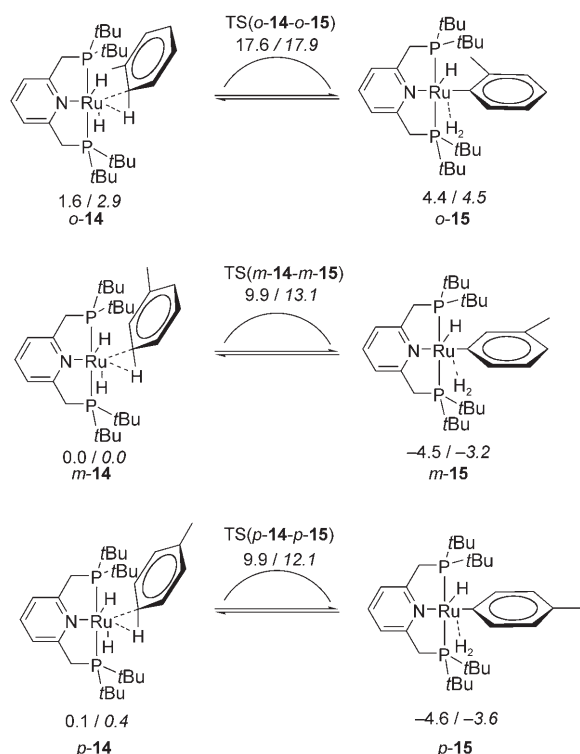


Figure 1. Ball-and-stick-representation of the calculated structures in the C-H exchange of **12c** with selected atom distances [Å]. See Scheme 4.



Scheme 5. Relative energies (ΔH , ΔH^\ddagger ; ΔG , ΔG^\ddagger (in italics), kcal mol⁻¹) of reactants, products, and transition states (not shown) involved in C–H exchange at the *ortho*, *meta*, and *para* positions (top to bottom) of toluene.

In summary, we have shown that the nonclassical ruthenium hydride complex **1** is an effective catalyst for H/D exchange between aromatic substrates and D₂O under unprecedented mild conditions. The incorporation occurs with aromatic and heteroaromatic substrates, with significant chemo- and regioselectively observed in certain cases. DFT calculations support a catalytic cycle comprising σ -bond metathesis as the key step for the exchange processes and with a strong steric component directing the effect. Further preparative and mechanistic studies to explore the catalytic potential of **1** and related complexes are underway.

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