Chemoselective H/D Exchange Catalyzed by Nickel Nanoparticles Stabilized by N-Heterocyclic Carbene Ligands

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With this work, we report the synthesis and full characterization of nickel nanoparticles (NPs) stabilized by *N*-heterocyclic carbene (NHC) ligands, namely 1,3-bis(cyclohexyl)-1,3-dihydro-2*H*-imidazol-2-ylidene (ICy) and 1,3-bis(2,4,6-trimethylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene (IMes). Although the resulting NPs have the same size, they display different magnetic properties and different reactivities, which result from ligand effects. In the context of H/D exchange on pharmaceutically relevant heterocycles, Ni@NHC shows a high chemoselectivity, avoiding the formation of undesired reduced side-products and enabling a variety of H/D exchange on nitrogen-containing aromatic compounds. Using 2-phenylpyridine as a model substrate, it was observed that deuteration occurred preferably at the α position of the nitrogen atom, which is the most accessible position for the C-H activation. In addition, Ni@IMes NPs are also able to fully deuterate the *ortho* positions of the phenyl substituents.

Introduction

Hydrogen isotope exchange reactions are presently widely studied since the applications of organic molecules labelled with deuterium and tritium atoms have significantly increased during the last decades.[1] Particularly, deuterium-labelled compounds are of high interest in life sciences,[2] as kinetic isotopic effects can for example significantly influence the pharmacokinetic behavior of drugs or reduce their toxicity.[3] The development of efficient methods to perform such reactions in mild conditions, and to have a good control on reaction selectivity is therefore essential.[4] Thus, C-H activation catalyzed by different metal complexes for H/D exchange has emerged as a powerful tool. For instance, Ir,[5, 6] Ru,[7-9] Rh,[10] Pd[11] or Pt[12] complexes have been described in literature as efficient catalysts for H/D exchange reactions in homogeneous phase. Very recently, Zarate *et al.* have shown that Ni(II)

and Ni(I) complexes functionalized with bulky diimines are active catalysts for H/D exchange reactions in pharmaceuticals.[13, 14] Heterogeneous catalysts have also been widely employed in H/D exchange, with the advantage of an easy removal and recyclability of the catalyst. Amongst different metals, the most employed are Pd, Pt and Ru, all supported on carbon (Pd/C, Pt/C and Ru/C).[15-16] However, to the best of our knowledge, only few examples of H/D exchange catalyzed by metal nanoparticles (MNPs) have been reported to date, while abundant and less costly first row transition metal NPs have never been used for this purpose,[4] although a few examples of H/D exchange catalyzed by Raney Nickel are known.[17, 18]

MNPs have shown to be very efficient catalysts due to their unique electronic properties and the possibility to modulate their size, shape and composition, thus permitting control of their catalytic properties. In addition, upon adjusting the nature of the stabilizing ligands at the surface of the NPs, the reactivity, solubility or selectivity of the system can be easily tuned, which constitutes an advantage over the classical heterogeneous catalysts. MNPs are well-known catalysts for the H-H and D-D activation[19-22] and, therefore, they have been widely employed in catalytic hydrogenation.[23] A more recent development of MNPs reactivity is C-H activation in mild conditions, which may present several potential applications.[24, 25] The combination of these reactivities may render the NPs active catalysts for H/D exchange, which in turn can serve as a good model reaction to understand the surface reactivity and selectivity of the MNPs.[26] For instance, our research groups have already shown that Ru NPs can efficiently catalyze C-H activation reactions leading to selective deuterium incorporation into several nitrogen-containing compounds such as pyridines, indoles, alkylamines, etc.[27, 28] Later on, it was shown that Ru and RuPt NPs are good catalysts for the enantiospecific deuteration of peptides at the α position of nitrogen atoms.[24-29] However, a typical limitation of Ru-based NPs in H/D exchange reactions is their high reactivity towards aromatic rings, leading, in some cases, to the formation of considerable amounts of undesired reduced side-products.[30, 31] In this respect, Ni NPs, less prone to hydrogenate aromatic rings, can appear as a more earth-abundant and less-costly alternative to Ru NPs for H/D exchange reactions.

N-heterocyclic carbenes (NHCs) are versatile ligands that have been widely used for the synthesis of a broad variety of metallic complexes or for the functionalization of metallic surfaces.[32-38] During the last years, NHCs have also shown to be very efficient ligands that strongly coordinate to the surface of MNPs, permitting to modulate their catalytic activity and selectivity.[39-44] MNPs stabilized by NHCs have previously been employed as catalysts in H/D exchange reactions. We have previously observed that Ru NPs stabilized by water-soluble NHC ligands showed a remarkable activity for the enantiospecific deuteration of L-lysine in aqueous solution,[45] as well as for selective labelling of drug candidates and nucleobase derivatives.[46] Recently, Godard and co-workers reported the synthesis of Ni NPs stabilized by NHC ligands through thermal decomposition of a NHC-CO_2 adduct, used as catalysts for alkyne hydrogenation.[47] However, to the best of our knowledge, Ni NPs have never been used as catalysts in H/D exchange reactions so far.

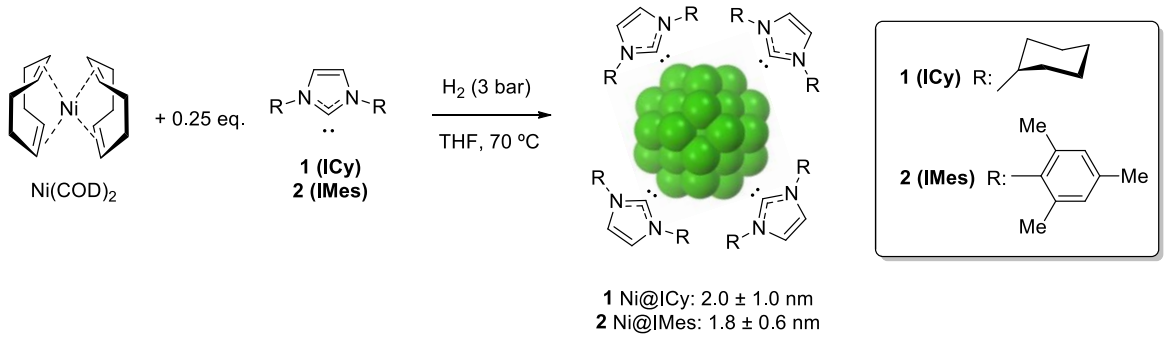
In this work, we have synthesized Ni NPs stabilized by bulky NHC ligands and compared their catalytic activity and selectivity for the deuteration of 2-phenylpyridine. Ni@NHC NPs are used for the first time as catalysts for C-H activation, and it is shown that they can selectively deuterate 2-phenylpyridine without reducing aromatic rings, which is the

most important limitation of Ru@NHC NPs. Finally, deuteration of a substrate scope containing different *N*-heterocycles has been performed, leading to excellent chemoselectivities in all cases.

Results and discussion

Synthesis and characterization of Ni@NHC NPs

Ni@NHC NPs have been synthesized by decomposition of $Ni(COD)_2$ under 3 bar of H_2 in THF at 70 ºC, in the presence of 0.25 equivalents of *free* 1,3-bis(cyclohexyl)-1,3-dihydro-2*H*-imidazol-2-ylidene (ICy – NPs **1**), obtained after deprotonation of the corresponding imidazolium salt with KO^tBu; or in the presence of 0.25 equivalents of 1,3-bis(2,4,6-trimethylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene (IMes – NPs **2**) (Scheme 1). The Ni NPs were characterized by transmission electron microscopy (TEM). TEM micrographs revealed the presence of small Ni@NHC NPs with mean sizes of 2.0 ± 1.0 nm and 1.8 ± 0.6 nm for NPs **1** and **2** respectively (Fig. 1). NPs **1** and **2** were further characterized by Inductively Coupled Plasma-Mass Spectrometry (ICP-MS, see Experimental Section in ESI) and Wide-Angle X-Ray Scattering (WAXS). The diffractograms of NPs **1-2** (Fig. 2) showed peaks corresponding to *fcc*-Ni(0), although few residual traces of NiO were observable in the case of NPs **1**. Radial Distribution Functions (RDF) analyses showed Ni-Ni distances of 0.25 nm for NPs **1-2** in agreement with the *fcc*-Ni(0) structure above proposed (Fig. S1-2).



Scheme 1 Synthesis of Ni@NHC NPs **1** and **2**.

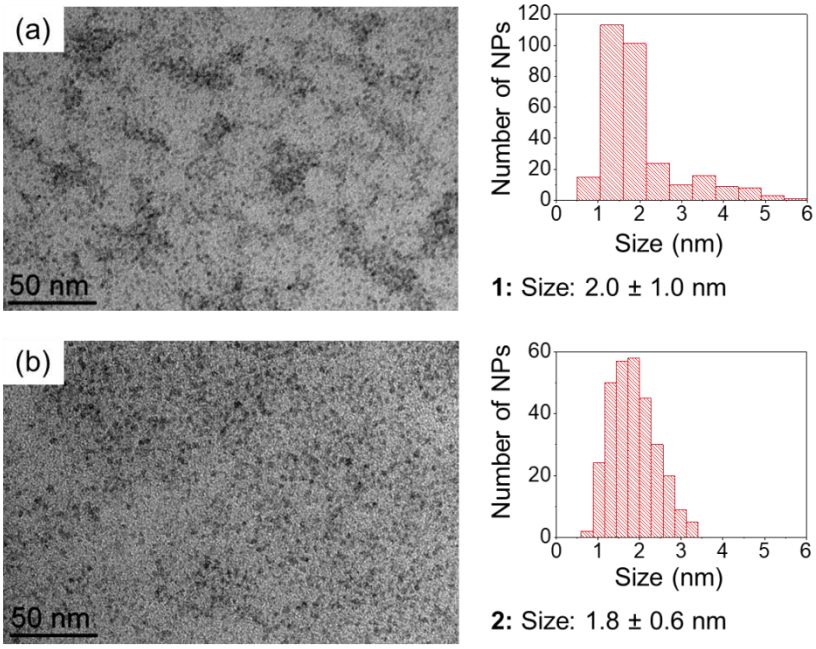


Fig. 1 TEM images and size distributions for NPs (a) Ni@ICy **1** and (b) Ni@IMes **2**.

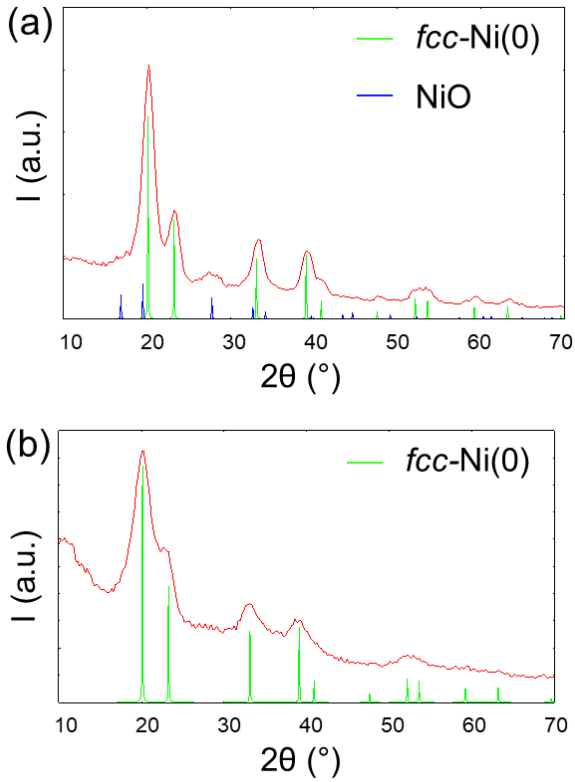


Fig. 2 XRD diffractograms for (a) Ni@ICy NPs **1** and (b) Ni@IMes NPs **2**.

The magnetic properties of NPs **1-2** were determined by Vibrating Sample Magnetometry (VSM). The two systems are superparamagnetic at 300 K and ferromagnetic at 5 K, but display magnetization (*M*) values at a $\mu_0 H$ of 3 T at 300 K below the one reported for Ni bulk (55 $A \cdot m^2 \cdot kg^{-1}$).[48] Indeed, the magnetization vs. applied field curves for Ni@NHC

NPs display a *M* value of 23 A·m^2·kg^{-1} at 300 K at a $\mu_0 H$ of 3 T for NPs **1** whereas it is only of 5 A·m^2·kg^{-1} for NPs **2** (Fig. 3). In both cases, the depletion in the magnetization can be explained by the high surface/magnetic-core ratio resulting from the small size of the Ni NPs, and for which a higher proportion of non-magnetic layers located at the NP surface can be present.[49] The important differences in the *M* values between NPs **1** and **2** at a $\mu_0 H$ of 3 T (23 and 5 A·m^2·kg^{-1} respectively) probably arise from a ligand effect, as the mean sizes measured by TEM for both systems are within the same range. It has previously been observed that the magnetic moment of Ni is highly sensitive to ligand effects. π-acceptor ligands, such as CO, can strongly decrease the *M* value.[50, 51] Therefore, the *M* differences between both systems can serve as an indication of the higher π-acceptor capacity of the IMes ligand with respect to the ICy ligand, which is in agreement with previous observations.[52]

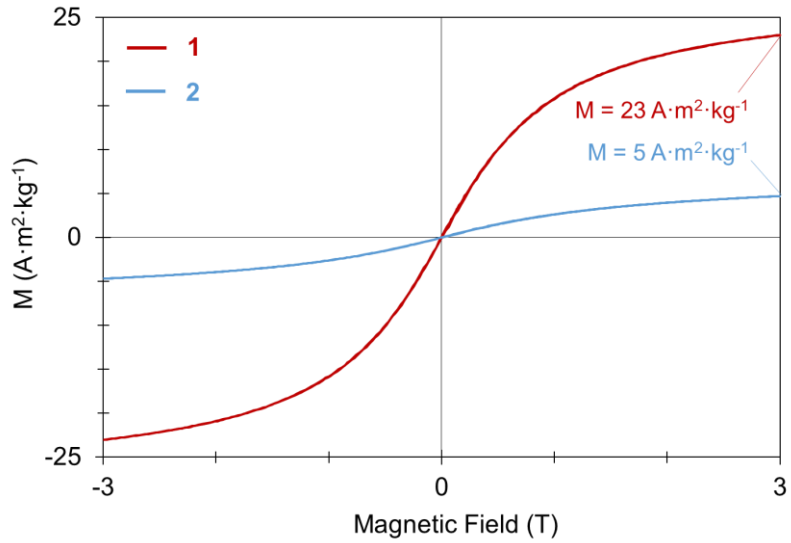
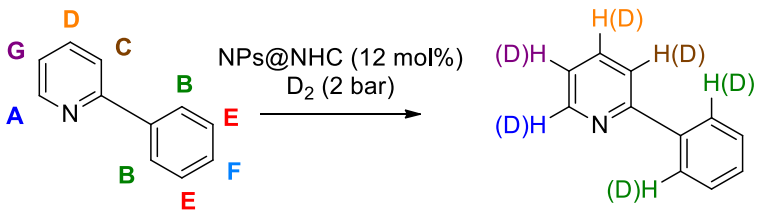


Fig. 3 Comparison of the magnetization *vs.* applied magnetic fields curves for Ni@ICy NPs **1** (red curve) and Ni@IMes NPs **2** (blue curve) at 300 K.

Optimization of the reaction conditions for the deuteration of 2-phenylpyridine

The catalysts **1** and **2** were evaluated for the deuteration of 2-phenylpyridine under 2 bar of D_2 using 12 mol% of catalyst loading (see Table 1). 2-phenylpyridine was chosen as a model substrate because it can coordinate to the surface of the MNPs through the nitrogen donor atom, and it contains two aromatic rings that are susceptible to be reduced under a D_2 atmosphere. For the sake of comparison, Ru NPs are very active catalysts for the hydrogenation of aromatic substrates even at low temperatures. When performing the deuteration of 2-phenylpyridine using the **Ru@ICy** NPs as catalysts at 55 ºC, the total reduction of the aromatic moieties was observed after 24 h (entry 1 and Fig. S3). **Ru@ICy** NPs are thus non-adequate catalysts to perform H/D exchange, as they imply the formation of undesired reduced products in these conditions.

Table 1 Optimization of the reaction conditions for the deuteration of 2-phenylpyridine catalyzed by Ni@NHC.



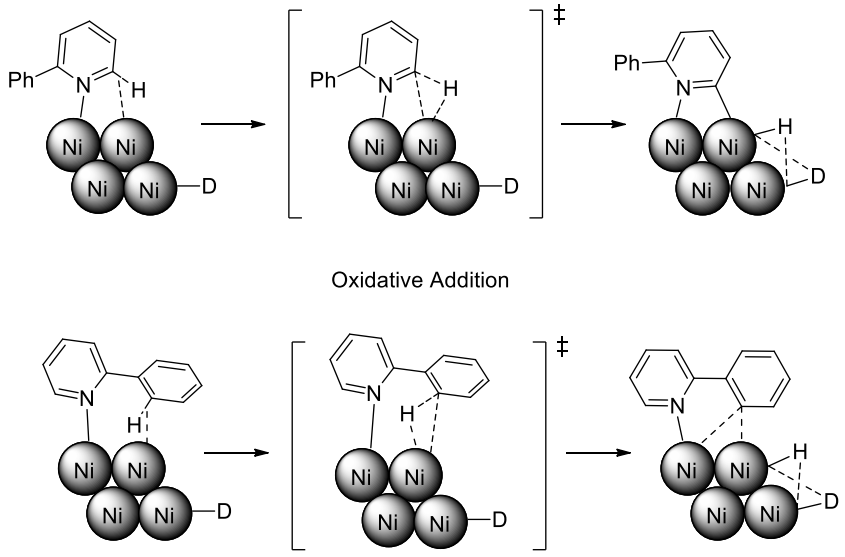
Entry	Catalyst	Solvent	T (ºC)	Time (h)	Isotopic enrichment (%)			
					A	B	C+D[a]	G
1	**Ru@ICy**	THF	55	24	Complete reduction			
2	**1**	THF	55	5	64	4	-	-
3	**1**	THF	55	24	95	12	-	-
4	**1**	THF	rt	24	55	5	-	-
5	**1**	pentane	55	24	96	17	-	-
6	**1**	toluene	55	24	96	14	-	-
7	**2**	THF	55	24	95	99	11	14
8	**2**	THF	55	5	37	40	-	-
9	**3**[b]	THF	55	24	95	75	-	-

General catalytic conditions: 0.15 mmol of the corresponding substrate and 2-3 mg of the NPs (12 mol%) were dissolved in 1 mL of THF in a Fischer-Porter bottle. Then, the reaction mixture was pressurized with D_2 (2 bar) for the indicated time. The conversion and yield were determined by ^{1}H NMR and mass spectrometry. [a] The NMR signals of C and D positions were impossible to distinguish with a 400 MHz NMR spectrometer; the isotopic enrichment is given for both positions. [b] The solution containing the substrate and the catalyst **2** was stirred under air for 5 minutes, and led to the catalyst called **3**, before loading the 3 bar of D_2.

Ni@ICy NPs **1** showed high activity in the deuteration of the 2-phenylpyridine at 55 ºC in THF solution. Indeed, 64% isotopic enrichment at position A was observed after 5 hours (entry 2). After 24 hours, we observed a 95% isotopic enrichment for position A, together with 12% of deuteration for position B (entry 3, Fig. S4-6). Interestingly, the reaction occurred without any reduction of the aromatic rings. The NPs **1** were also active at room temperature (entry 4), and 55% of isotopic enrichment at position A was observed after 24 hours. The reaction is tolerant towards the use of other non-polar solvents, similar deuteration degrees were obtained when performing the reactions in pentane or toluene at 55 ºC (entries 5-6).

The Ni@IMes NPs **2** were more active in H/D exchange on 2-phenylpyridine under similar reaction conditions (entry 7, Fig. S7-8). Indeed, 95% deuteration of position A was accompanied by a complete deuteration of position B. Deuterium incorporations of 11 and 14% were also observed for the C-D and G positions respectively. Similar deuteration proportions were found for the position A and the position B after 5 h of reaction with NPs **2** (entry 8). This behavior contrasts with NPs **1**, where a strong preference for the labelling of position A is observed, regardless the experimental conditions. When the reaction mixture containing the NPs **2** was stirred under air for 5 minutes before loading the 2 bar of D_2 (NPs **3**), almost the same activity was found for position A but decrease of deuteration was observed for position B (entry 9).

Overall, these results first demonstrate that Ni nanoparticles are very active for C-H activation in mild conditions. This property is used for achieving selective H/D exchange reactions, but the scope of this reactivity is likely to be larger. Then, a significant difference of selectivity for deuteration of 2-phenylpyridine can be observed between the catalysts **1** and **2** although they display the same size and contain similar ligands. It has previously been proposed that the mesityl groups of the IMes ligands may interact with metallic Au surfaces through π-interactions, and this can leave enough space for another molecule to approach the NPs surface. [53] This phenomenon is likely to occur with Ni surfaces also. In contrast, ICy ligand would adopt a configuration in which the cyclohexyl substituents are pointing away from the NP and hence can give rise to a more compact organization. In this respect, the steric hindrance induced by the ICy ligand would only allow 2-phenylpyridine to approach the Ni surface of catalyst **1** through the pyridine ring (end-on) whereas the space on the surface could allow side-on coordination or even flat coordination of the aromatic rings on catalyst **2** (Scheme 2). A somewhat similar effect has been observed in hydrogenation reactions involving Ru NPs stabilized long chain NHCs bearing mesityl substituents.[54] The catalytic mechanism is likely to involve oxidative addition in a variety of approaches: (i) a four-membered ring for the deuteration of position A as proposed for Ru(0) NPs[29] for NPs **1** and **2** or (ii) a five- or six-membered ring depending on the number of Ni atoms implied,[55] for the deuteration of position B using NPs **2** (Scheme 2 shows the six-membered metallacycle); and (iii) after π-coordination of the pyridyl ring, a more complex mechanism can act, which has not been elucidated here. It is interesting to note that the other positions of the phenyl ring are not deuterated which probably emphasizes the importance of the coordination through nitrogen atom for the C-H activation to proceed. Interestingly, the system is tolerant to oxygen. Indeed, when a solution of a mixture of catalyst **2** and 2-phenylpyridine was stirred in open air for 5 minutes prior to addition of deuterium (NPs **3**), only a decrease of isotopic enrichment of the position B from 95 to 75% was observed. This system can thus be operated in non-strictly anaerobic conditions.



Scheme 2 Proposed mechanism for the C-H activation catalyzed by Ni(0): C-H activation would follow an oxidative addition into a Ni(0) to give a 4-membered or a 5- or 6-membered metallacycle which would lead to deuteration in positions A or B.

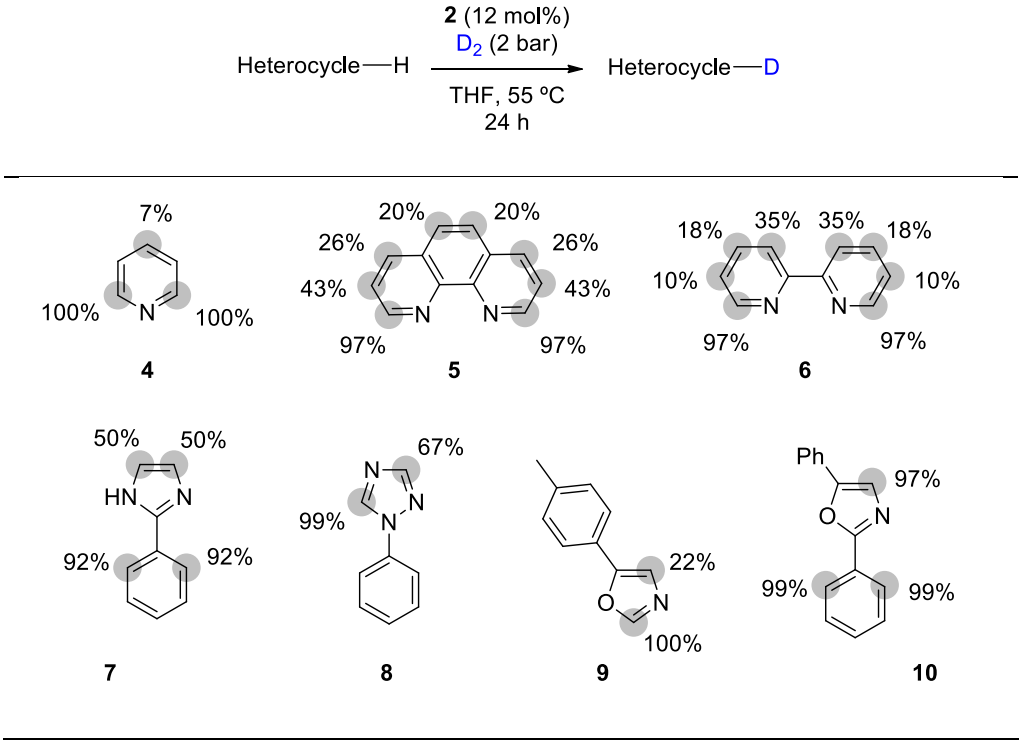
Scope of substrates

After optimization of the reaction conditions for 2-phenylpyridine, the scope of substrates was extended for the most active catalyst, Ni@IMes NPs **2** (12 mol% of catalyst), under 2 bar of D_2 at 55 ºC in THF (Table 2 and Fig. S9-22). In this context, the deuteration of different pharmaceutically relevant heterocycles was explored. In all cases, the deuterium incorporation preferentially took place at the α-positions of the nitrogen atom. For instance, isotopic enrichment was 100 % for pyridine (**4**) in positions 2 and 6. A minor amount of 7% of deuterium uptake was also observed in the position 4. Similarly, an isotopic enrichment of 97% for the α-position of phenantroline (**5**) and 2,2'-bipyiridyl (**6**) was obtained, although some deuterium incorporation was also observed for other positions of the molecules (Table 2). These results obtained with pyridine and phenantroline strongly suggest that, as for 2-phenylpyridine, another mechanism than the classical coordination through the nitrogen atom[27] may also occur, very likely after π-coordination of the substrate. Interestingly, in the case of 2-phenylimidazole (**7**), deuteration was faster for the *ortho*-positions of the aromatic ring (92% of isotopic enrichment) than for the positions of the imidazole ring (50% of isotopic enrichment). 1-phenyl-*1H*-1,2,4-triazole (**8**) was completely deuterated at the 5-position of the triazole ring and 67% of deuteration was obtained for the 3-position. However, in this case, no deuteration was observed on the phenyl substituent, which suggests that coordination occurs preferentially through the 4-N atom of the 1,2,4-triazole unit.

Finally, we studied the isotopic enrichment on other heterocycles also containing oxygen atoms. In the case of 5-(*p*-tolyl)oxazole (**9**), a total deuteration at the most acidic 2-position of the aromatic ring was observed, along with 22% of isotopic enrichment at position 4. The absence of deuteration at the *ortho*-position of the phenyl substituent evidences that

coordination preferentially takes place through the nitrogen atom of this substrate, and not through the oxygen atom. For 2,4-diphenyloxazole (**10**), deuteration was almost complete at position 4 of the aromatic ring as well as at the *ortho*-position of the 2-phenyl substituent, evidencing again that the coordination through nitrogen atom is preferred. Interestingly, no reduced side-product of **10** was detected here, whereas the use of Ru NPs as catalysts on this substrate lead to lower isotopic enrichments and an isolated yield of 25%.[49]

Table 2 Scope of substrates catalyzed by Ni@IMes NPs **2**.



Conclusions

In conclusion, we report here the preparation of Ni@NHC NPs by a controlled decomposition of the corresponding precursor under H_2 in the presence of *free* NHC ligands. Magnetic measurements of the Ni@NHC NPs have been used for the first time to characterize the electronic features of the NHC ligand, showing that the presence of the IMes ligand induces a decrease of the magnetic susceptibility. We propose that this behavior may be linked to the higher π-acceptor ability of IMes. The activity of Ni@NHC NPs in the C-H activation for the selective H/D exchange of 2-phenylpyridine has been explored. Firstly, this system is fully selective for aromatic rings deuteration and does not lead to side-reduction products. This selectivity is of interest for pharmaceutical products in which active principles frequently contain such aromatic rings. It is furthermore possible to control the selectivity of deuteration according to the nature of the NHC ligand, IMes allowing a more extensive deuteration of a variety of molecules than ICy. Finally, the system displays a tolerance to oxygen, which can make it of practical interest. Overall, we propose a catalytic system based on Ni@NHC NPs, which constitutes a less-costly alternative to noble metal catalysts and which displays a high

activity and a controlled selectivity for deuteration reactions. A rapid screening of the scope of substrates shows that Ni@NHC NPs are very promising catalysts for the selective H/D exchange of challenging molecules.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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