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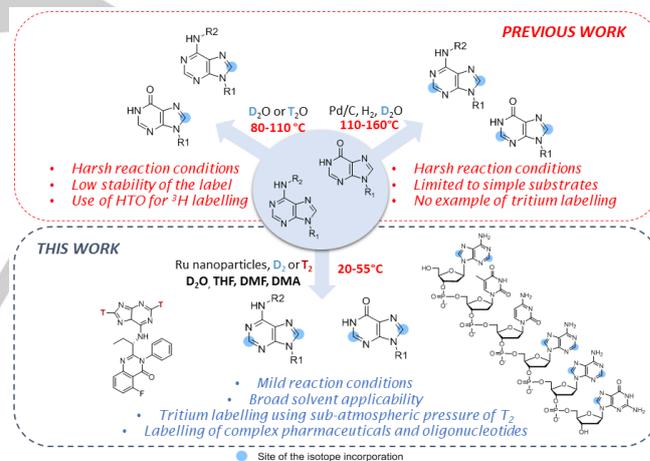
# Efficient access to deuterated and tritiated nucleobase pharmaceuticals and oligonucleotides using hydrogen isotope exchange

Alberto Palazzolo,<sup>[a]</sup> Sophie Feuillastre,<sup>\*[a]</sup> Viktor Pfeifer,<sup>[a]</sup> Sébastien Garcia-Argote,<sup>[a]</sup> Donia Bouzouita,<sup>[b]</sup> Simon Tricard,<sup>[b]</sup> Céline Chollet,<sup>[a]</sup> Elodie Marcon,<sup>[a]</sup> David-Alexandre Buisson,<sup>[a]</sup> Sophie Cholet,<sup>[c]</sup> François Fenaille,<sup>[c]</sup> Guy Lippens,<sup>[d]</sup> Bruno Chaudret,<sup>[b]</sup> Grégory Pieters<sup>\*[a]</sup>

**Abstract:** A general approach for the efficient hydrogen isotope exchange of nucleobase derivatives is described. Catalyzed by ruthenium nanoparticles, using mild reaction conditions and involving D<sub>2</sub> or T<sub>2</sub> as isotopic sources, this reaction possesses a wide substrate scope and a high solvent tolerability. This novel method facilitates the access to essential diagnostic tools in drug discovery and development: tritiated pharmaceuticals with high specific activities and deuterated oligonucleotides suitable to be used as internal standards for LC-MS quantification.

Nucleobases are one of the most important chemical building blocks of life. They can be divided into two groups: purines containing adenine and guanine; and pyrimidines including cytosine, thymine and uracil. These nitrogen-containing heterocycles are involved in many biological processes such as transmission of genetic information, energetic processes or cell communication. Therefore, a myriad of nucleobase derivatives have been found to be potent drugs for the treatment of major public health concerns like HIV, asthma or cancer.<sup>[1]</sup> More recently, RNA interference has emerged as an experimental tool to inhibit the expression of genes and gave birth to, respectively, antisense oligonucleotides<sup>[2]</sup> and small interfering RNA (siRNA),<sup>[3]</sup> which are under intensive studies as high potential therapeutic agents.<sup>[4]</sup> Due to their complex and particularly fragile nature, performing selective chemical transformations on these molecules represents an important challenge. Among those transformations, the development of efficient and selective hydrogen isotope exchange (HIE) reactions, allowing late stage deuterium and tritium labelling of nucleobase derivatives, is of paramount importance.<sup>[5]</sup> Indeed, tritiated analogues of drug candidates, are essential tools for investigating the *in vivo* fate of substances within absorption, distribution, metabolism and excretion (ADME) studies.<sup>[6]</sup> Deuterated molecules are also

widely employed in various life-science fields, such as metabolomics and proteomics, as stable isotopically labelled internal standards (SILS) for quantitative GC- or LC-MS analyses.<sup>[7]</sup> In the case of oligonucleotides, the synthetic access to SILS is particularly problematic due to their complexity and relative instability. Up to now, the nucleobase hydrogen isotope labelling is mainly achieved by multistep synthesis starting from precursors such as halogen, ketone or aldehyde derivatives followed by, respectively, catalytic dehalogenation using D<sub>2</sub>/T<sub>2</sub> gas<sup>[8]</sup> or reduction with labelled reagents<sup>[9]</sup> (NaBD<sub>4</sub> or LiAlT<sub>4</sub> for instance). Nevertheless, methods involving hydrogen isotope exchange have also been reported for such substructures based on the acido-basic exchange of the position 8 of purine derivatives<sup>[10]</sup> or on Pd/C catalyzed HIE in deuterated water (see Figure 1).<sup>[11]</sup> In both cases, the high temperature required to obtain good isotopic enrichments drastically limits the application of such reactions for the labelling of complex and fragile nucleobase-containing molecules.



**Figure 1:** State-of-the-art HIE for purine derivatives and their features compared to our new method using Ru nanocatalysts

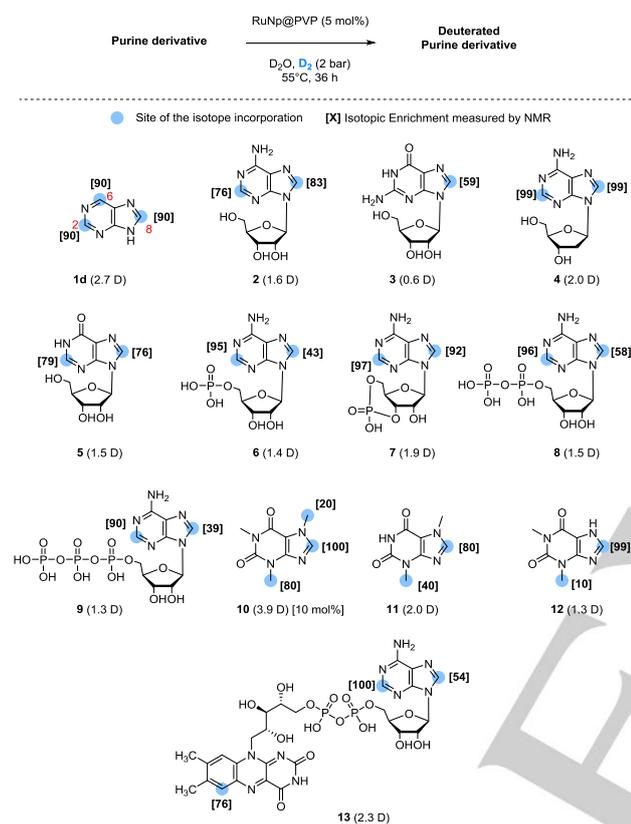
Moreover, methods previously described for tritium labelling are not particularly suited because use of hazardous tritiated water as isotopic source is required. In this communication, we present a wide-spectrum method for the deuterium and tritium labelling of purine substructures using Ru nanoparticles (RuNp) as catalyst and deuterium or tritium gas as isotopic sources (Figure 1). This new method allows the regioselective incorporation of hydrogen isotopes in complex biologically relevant substrates including pharmaceuticals and biomolecules under mild reaction conditions. Moreover, we show that our protocol can be used for the synthesis of radioactive tracers employing a sub-atmospheric pressure of T<sub>2</sub> gas, and of deuterated oligonucleotides suitable to be used as SILS for quantitative LC-MS analyses.

At an early stage of this study, by screening different types of catalysts for HIE, we found that ruthenium nanoparticles embedded in a PVP polymer matrix (RuNp@PVP) may have a

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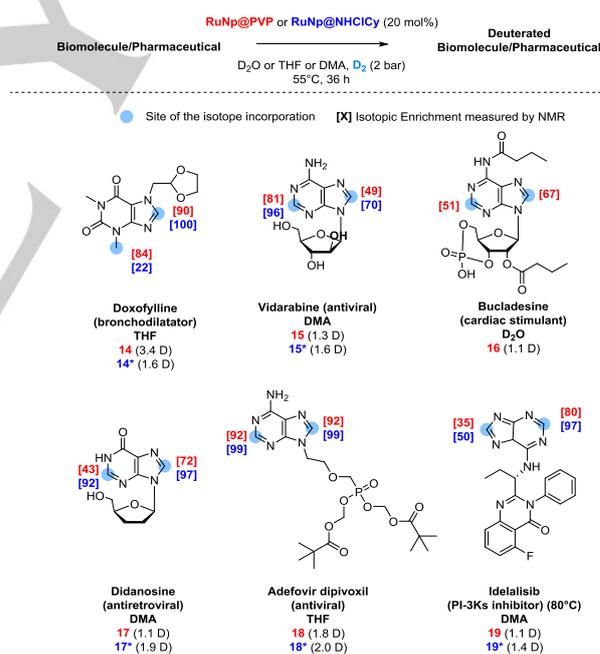
great potential for the labelling of purine derivatives.<sup>[12]</sup> Using optimized reaction conditions (5 mol% of catalyst, 2 bar of D<sub>2</sub> and D<sub>2</sub>O as solvent at 55°C), purine **1** was labelled, with an isotope incorporation at each available position  $\alpha$  to a nitrogen atom (isotopic enrichments of 90%) leading to a high deuterium uptake of 2.7 D without any secondary reactions otherwise observed (see SI). Encouraged by this preliminary result we moved forward to the labelling of purine-based natural substrates such as nucleosides, nucleotides and analogues (see Figure 2).



**Figure 2:** RuNp catalyzed deuterium labelling of representative purine derivatives

Beside the numerous applications evoked in the introduction, deuterated nucleotides are also widely used in biochemistry and molecular biology to suppress non-essential proton resonance in NMR structural studies and for atom transfer experiments with DNA damaging agents.<sup>[13]</sup> Adenosine **2** and Guanosine **3** were selectively deuterated on the purine core using the same conditions described above. To ensure that the labelling was due to the combined action of Ru nanoparticles and D<sub>2</sub> as isotopic source, control experiments using only D<sub>2</sub>O were performed. As expected, a weak to average labelling of the most acidic position 8 was obtained without the presence of Ru nanoparticles and D<sub>2</sub> gas. Interestingly, the attractive position 2, known to not be prone to back-exchange during biodistribution studies, is efficiently labelled in the case of Adenosine **2** using our method. Furthermore, the broad scope of this transformation was demonstrated by the labelling of Deoxyadenosine **4**, Inosine **5** and nucleotides such as AMP **6**, c-AMP **7**, ADP **8** and ATP **9**. Remarkably, despite the coordination ability of phosphate groups for metallic nanoparticles, both selectivity and deuterium incorporation remained very high even in the case of ATP which contains a triphosphate moiety. Interestingly, only slight

changes in deuterium incorporation were observed depending on the pH of the solution for ATP **9** (see Table S1 in SI) highlighting the robustness of this new catalytic process. Analogues like deuterated xanthenes **10**, **11** and **12**, widely used as internal standards in qualitative or quantitative isotope dilution mass-spectrometry for anti-doping controls,<sup>[14]</sup> were also obtained with a good deuterium incorporation and isotopic enrichment on the purine core (1.3 to 3.9 D incorporated). For those compounds, the additional labelling of the methyl group can be explained by a remote C-H activation process facilitated by the proximity of the sp<sup>3</sup>-hybridized carbon center to the surface of the Ru nanocluster after the coordination of the nitrogen in position 9. Gratifyingly, the adoption of a slightly higher catalytic loading (10 mol%) allowed the synthesis of a highly deuterated Caffeine **10**, commonly used as SILS for quantitative LC-MS analyses in anti-doping tests.<sup>[14]</sup> Flavin adenine dinucleotide (FAD) **13** was also labelled both at the purine and the flavin cores, thus demonstrating the usefulness of the method for the labelling of fragile and structurally complex substrates. Complex purine-based drugs Doxofylline **14** (bronchodilator), Vidarabine **15** (antiviral), Bucladesine **16** (phosphodiesterase inhibitor), Didanosine **17** (antiretroviral), Adefovir **18** (reverse transcriptase inhibitor) and Idelalisib **19** (kinase inhibitor) (see Figure 3), were successfully labelled using our HIE protocol, exemplifying its broad applicability relative to harsh labelling conditions described previously in the literature.<sup>[15]</sup> Moreover, due to the high solvent tolerability of this method, the best aprotic solvent could be chosen for each compound depending on its solubility.

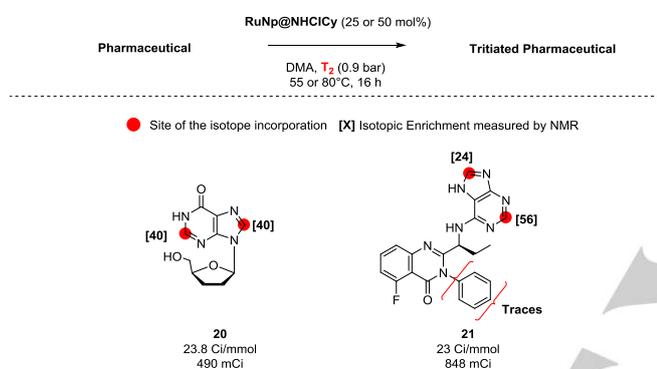


**Figure 3:** Deuterium labelling of pharmaceuticals. In red, isotopic enrichment obtained with RuNp@PVP and with RuNp@NHClCy in blue.

For the compounds shown in Figure 3, higher deuterium uptakes were obtained using ruthenium nanoparticles stabilized by organosoluble carbenes (RuNp@NHClCy), highlighting the importance of nanoparticle engineering to enhance the activity for C-H activation processes.<sup>[16]</sup> Moreover, their higher metal content (in weight) led to an easier work-up and deuterated products purification. Only in the particular case of **14**, a lower deuterium incorporation into the labelled methyl was obtained

using RuNp@NHCiCy instead of RuNp@PVP. This may be explained by the higher steric hindrance at the surface of the catalyst induced by the carbene ligand. All in all, these complex deuterated compounds were obtained with high yields and good to excellent isotopic enrichments (from 50% to 99% for position 2 and from 67% to 100% for position 8). Each experiment was repeated at least twice using different batches of catalyst to ensure the reproducibility of the method.

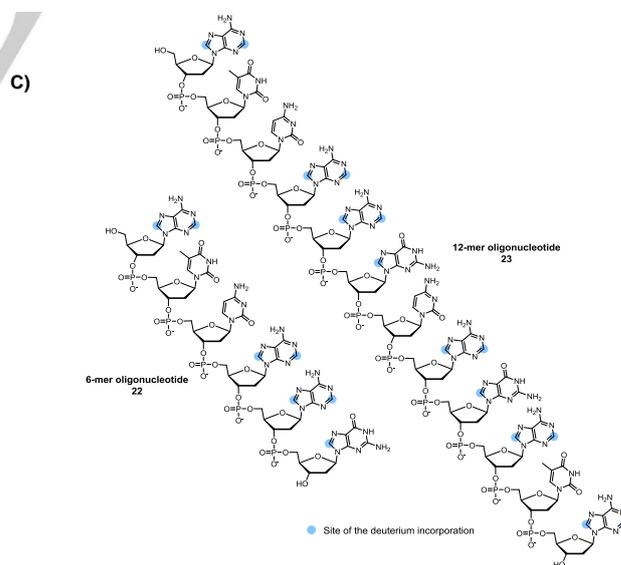
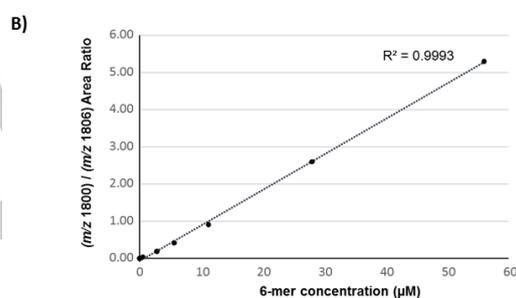
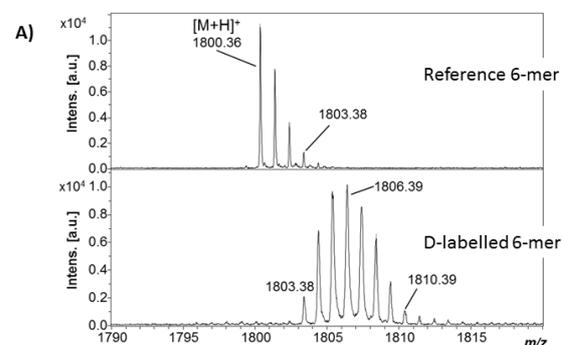
We then have optimized our reaction conditions to perform tritium labelling which provide compounds with high specific activities using a lower pressure of T<sub>2</sub> gas (in order to limit the amount of radioactivity handled). Here, tritiated Didanosine **20** and Idelalisib **21** were synthesized in a single step using sub-atmospheric pressure of T<sub>2</sub> gas and higher catalytic loadings (see Figure 4). The high specific activities (> 23 Ci/mmol) obtained, exceeding the standards required for ADME studies (15 Ci/mmol), highlight the potential of this novel HIE protocol to facilitate access to essential diagnostic tools in drug discovery and development.<sup>[17]</sup>



**Figure 4:** Tritium labelling of pharmaceuticals

DNA- and RNA-based therapeutics have a prominent place in the pharmaceutical industry, with at least 20 siRNA-based drugs that have entered clinical trials for more than a dozen diseases.<sup>[18]</sup> Regarding drug development process, quantitative analysis of oligonucleotide therapeutics in biological matrices is crucial for preclinical and clinical stages.<sup>[19]</sup> Published bioanalytical methods devoted to the quantification of oligonucleotides by MS-based approaches commonly overcome the lack of isotope-labelled versions of oligonucleotides by the use of different physico-sequences as internal standard (i.e. with slightly different physico-chemical properties).<sup>[20]</sup> There is no doubt that using D-labelled oligonucleotides would greatly benefit to such quantitative analytical methods, thereby offering both high quantification accuracy and high precision with systematic errors arising from sample preparation and MS detection being largely eliminated. The method described in this paper can be applied to gain a rapid access to deuterated oligonucleotides as internal standards. Regarding such particularly complex macromolecules, optimization studies have demonstrated that the use of 1 equivalent of Ru nanoparticles was necessary to obtain adequate isotopic enrichments for SILS purpose. With regard to the value of the resulting labelled compounds, this stoichiometric use of Ru nanoparticles was not considered as a limiting preparative issue. In this case, the use of Ru nanoparticles stabilized by hydrosoluble carbenes (RuNp@NHCPriPr) has allowed a high deuterium incorporation to be obtained.<sup>[16a]</sup> This can be explained by their higher water solubility and their better colloidal stability compared to RuNp@PVP. The best conditions developed were applied to the labelling of a model 6-mer

oligonucleotide **22** [RuNp@NHCPriPr (1 eq) in D<sub>2</sub>O (80 mM) under D<sub>2</sub> gas (2 bar), 36 h]. MALDI-TOF MS data (see Figure 5A) showed that an average of 5.5 D atoms can be introduced into the 6-mer oligonucleotide backbone after 3 iterative runs. The location of up to 7 distinct D atoms was obtained by NMR, and demonstrated, as expected, preferential labelling of the purine core.



**Figure 5. A)** MALDI-TOF mass spectra of native and deuterium-labelled 6-mer oligonucleotide, non-overlapping isotope massifs were observed after D-labelling; **B)** Calibration curve obtained for the native 6-mer from 0.56  $\mu\text{M}$  to 56  $\mu\text{M}$ , using a deuterium-labelled 6-mer concentration set at a constant value of 280  $\mu\text{M}$  (overall concentration). Most intense isotopes were used for

native and D-labelled species ( $m/z$  1800.36 and  $m/z$  1806.39, respectively); **C**) Structures of the labelled oligonucleotides.

Of note, labelling was accompanied by a complete conservation of the structure while no reduction of the pyrimidine base was observed. Monitoring the MS intensity ratio between the ions of native and corresponding labelled species is a common practice in state-of-the-art quantitative bioanalysis to correct for any particular experimental or analytical bias. The relationship between the 6-mer concentration and the MS intensity ratio of unlabeled/labelled 6-mer oligonucleotides proved linear over at least two orders of magnitude (0.56–56  $\mu\text{M}$ ) with a coefficient of determination  $R^2 > 0.99$  (Figure 5B), thus underlining the value of the labelled 6-mer as a relevant internal standard. The implemented labelling method was also successfully applied to a more complex 12-mer oligonucleotide **23** with an average deuterium atom uptake of 7.7 (Figure S115 in SI) without any apparent compound degradation.

In summary, we have developed an efficient and convenient general approach for the hydrogen isotope labelling of nucleobase derivatives. Using gentle reaction conditions, this method exhibits broader substrate scope and solvent tolerability than previously published labelling procedures using direct HIE. We have also shown that nanoparticles can be judiciously engineered to significantly increase the efficacy of C-H isotopic exchanges. Modifying the ligand at the nanoparticle's surface allows changes in the catalyst solubility, thus, leading to an increased efficiency of the labelling process. In terms of applications, this work represents an important advance, providing easy access to tritiated analogues of drug candidates which are essential tools in drug discovery and development processes, and to SILS for quantitative purposes notably for metabolomics.

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**Keywords:** C-H activation • Isotopic labelling • Nanoparticles • Hydrogen isotope exchange • Oligonucleotides

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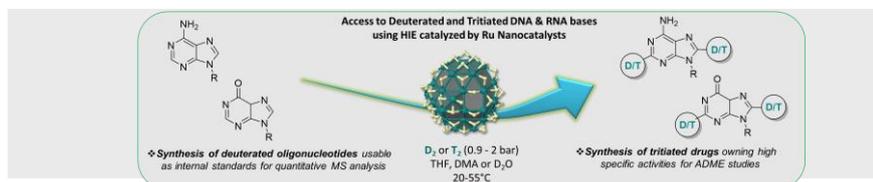
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Layout 2:

## COMMUNICATION



A general approach for the late stage hydrogen isotope exchange of nucleobase derivatives is described. Catalyzed by ruthenium nanoparticles using mild reaction conditions and involving D<sub>2</sub> or T<sub>2</sub> as isotopic sources, this reaction possesses a wide substrate scope and a high solvent tolerability.

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