

Easy-to-Implement Hydrogen Isotope Exchange for the Labeling of N-Heterocycles, Alkylamines, Benzylic Scaffolds, and Pharmaceuticals

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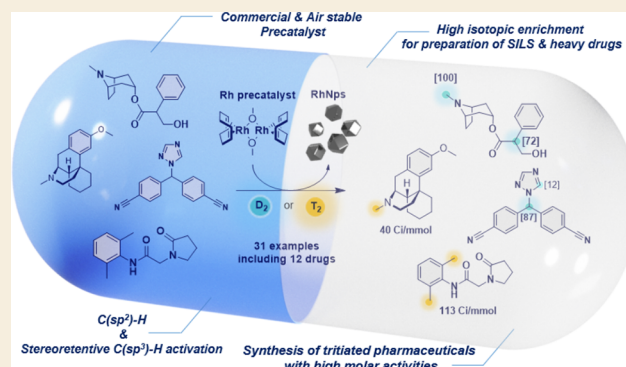
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ABSTRACT: Facilitating access to deuterated and tritiated complex molecules is of paramount importance due to the fundamental role of isotopically labeled compounds in drug discovery and development. Deuterated analogues of drugs are extensively used as internal standards for quantification purposes or as active pharmaceutical ingredients, whereas tritiated drugs are essential for preclinical ADME studies. In this report, we describe the labeling of prevalent substructures in FDA-approved drugs such as azines, indoles, alkylamine moieties, or benzylic carbons by the in situ generation of Rh nanoparticles able to catalyze both C(sp²)-H and C(sp³)-H activation processes. In this easy-to-implement labeling process, Rh nanocatalysts are formed by decomposition of a commercially available rhodium dimer under a deuterium or tritium gas atmosphere (1 bar or less), using the substrate itself as a surface ligand to control the aggregation state of the resulting metallic clusters. It is noteworthy that the size of the nanoparticles observed is surprisingly independent of the substrate used and is homogeneous, as evidenced by transmission electron microscopy experiments. This method has been successfully applied to the one-step synthesis of (1) deuterated pharmaceuticals usable as internal standards for MS quantification and (2) tritiated drug analogues with very high molar activities (up to 113 Ci/mmol).

KEYWORDS: C-H Activation, Nanoparticles, Deuterium, Tritium, Rhodium, Alkylamine, N-Heterocycle, Benzylic position



INTRODUCTION

The development of metal-catalyzed hydrogen isotope exchange (HIE) allowing late-stage incorporation of the two isotopes of hydrogen, namely, deuterium and tritium, has recently attracted considerable attention.¹ This results from the increasing number of important applications of labeled compounds in various scientific areas from drug discovery² to material science^{3–5} and imaging techniques.⁶ Deuterated compounds are of paramount importance as stable isotope-labeled internal standards (SILS) for quantification purposes in all “omic” fields, taking advantage of the mass shift arising from the substitution of hydrogen atoms by deuterium ones in a given molecule.^{2,7} Furthermore, due to the primary kinetic isotope effect, deuterium incorporation at specific positions of a bioactive molecule can decrease its metabolism rate and/or prevent the formation of toxic metabolites.⁸ This has led to the emergence of the so-called “heavy drugs”, which display improved toxicity profiles and longer half-lives, thus enabling the reduction of dosing requirements. Tritiated analogues of drug candidates are essential for absorption, distribution, metabolism and excretion (ADME) studies, a critical step in

drug development allowing insight into drug metabolism and potential interactions. One of the biggest synthetic challenges in this context is to obtain high molar activities (50–100 Ci/mmol), an objective that is often hard to reach using published HIE methods.

Depending on the application, either a multiple incorporation of isotopes (for SILS or tritiated compounds with high molar activities) or a selective one in specific positions is needed (for example, on major metabolism sites for heavy drugs or on photo-oxidation sites for fluorophores). In this context, numerous HIE methods have been developed for the labeling of C(sp²)-H bonds and, to a lesser extent, for C(sp³)-H bonds, using either pH-dependent or metal catalysis.^{9–13}

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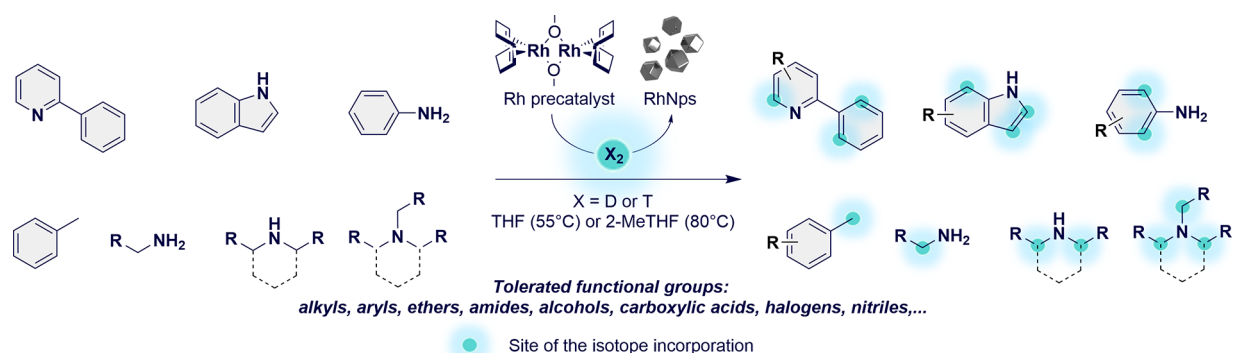


Figure 1. Substrate scope and regioselectivity of the isotope incorporation.

N-Alkylamine moieties and benzylic positions are interesting targets of investigation for the development of HIE methods since, they are common substructures in active pharmaceutical ingredients and are involved in major metabolism pathways through CYP-450 oxidation processes.^{14–16} In material science, deuterated N-alkyl auxochromes are also gaining momentum notably by enhancing device performances, extending lifetimes or improving brightness and photostability of fluorophores.¹⁷ Up to now, only a few efficient and functional group tolerant HIE methods have been described for such important substructures. Deuterated N-alkylamine scaffolds can be obtained via metal-catalyzed HIE using either homogeneous catalysts (Ir¹⁸ or Ru^{19–21}) or Ru nanoparticles.^{22,23} For Ir-catalyzed HIE, very specific directing groups and substitution patterns are mandatory. For Ru-catalyzed HIE processes mediated by Shvo's catalyst¹⁹ or by $[(\eta^6\text{-}p\text{-cymene})\text{RuCl}_2(\mu\text{-H}-\mu\text{-Cl})]$,²⁰ harsh reaction conditions along with the inevitable racemization of chiral amines due to the enamine/imine intermediates involved, prevent their application to the labeling of complex pharmaceuticals. Conversely, the Ru-bMepi complex described by Szymczak et al. allows stereoretentive α deuteration of chiral amines, but with a poor regioselectivity for the isotope incorporation and a limited functional group tolerance (ether and chlorine).²¹ In this framework, our group has demonstrated the usefulness of Ru nanocatalysis in preparing complex deuterated alkylamines.^{22,23} This powerful tool requires, however, the prior synthesis and storage under inert atmosphere of nanoparticles which needs specific skills and equipment. Complex molecules containing labeled alkylamines can also be obtained using photoredox processes, but this approach suffers from the use of HTO as isotopic source for tritiation experiments and leads to moderate molar activities and racemization of chiral compounds.^{24,25} Another method is HSCIE (high-temperature solid-state catalytic isotope exchange), which requires high temperatures and leads to unselective isotope incorporations (both $\text{C}(\text{sp}^2)\text{-H}$ and $\text{C}(\text{sp}^3)\text{-H}$ positions are labeled).^{26–30}

Benzylic positions can be effectively deuterated using either pH-dependent,^{31–33} metal-catalyzed,^{34–42} or photoredox HIE methods.⁴³ pH-dependent HIE methods require, in some cases, high temperatures ($>100^\circ\text{C}$) and the use of strong bases or acids, thus limiting the labeling of fragile pharmaceuticals. Metal-catalyzed HIE uses homogeneous (Co), heterogeneous catalysts (Pd, Pt, Ni) or nanoparticles (Pd). Homogeneous catalysis is restricted to simple substrates (with little to no functionalization), notably due to limited solvent tolerability (alkanes). For heterogeneous or photoredox catalysis, a lack of selectivity is observed along with the use of elevated

temperatures and an incompatibility with basic substrates (using Pd/C³⁸ and photoredox catalysis⁴³). Benzylic positions can also be tritiated using heterogeneous catalysts (Pd/C or pyrophoric Raney Ni), but activation of the catalyst with T_2 gas purge/refill cycles or the use of hazardous HTO as isotopic source is usually needed to obtain acceptable molar activities. Recently, Pd nanocatalysis, which requires the prior synthesis of the nanocatalyst, has been employed for the labeling of benzylic positions leading to deuterated and tritiated benzylic scaffolds.⁴²

Therefore, the development of robust and easy-to-implement HIE methods for the labeling of alkylamines and benzylic scaffolds in complex molecules is still necessary to facilitate access to deuterated drugs and tritiated analogues of pharmaceuticals with high molar activities. To tackle this challenge, we have investigated the in situ formation of Rh nanocatalysts by decomposition of a commercially available Rh dimer under a D_2 or T_2 atmosphere. The coalescence process could be directly controlled by the substrate of the reaction which acted as a surface ligand. Recently, we have demonstrated the potency and advantages of the in situ formation of both Ir complexes and nanoclusters from $[\text{Ir}(\text{OMe})(1,5\text{-COD})]_2$, which led to a remarkable multiple incorporation of hydrogen isotopes in complex pharmaceuticals.⁴⁴ However, this method was limited to the labeling of $\text{C}(\text{sp}^2)\text{-H}$ positions for complex biomolecules.

In this paper, we demonstrate that the in situ formation of Rh nanocatalysts mediates HIE on both $\text{C}(\text{sp}^2)$ and $\text{C}(\text{sp}^3)$ carbon centers (see Figure 1). This easy-to-implement method, which notably selectively targets benzylic positions and/or alkylamine substructures by using mild reaction conditions, permits straightforward access to (1) deuterated pharmaceuticals with high deuterium uptakes (up to 6 deuterium atoms), thus fulfilling SILS requirements; (2) tritiated active pharmaceutical ingredient analogues with extremely high molar activities (up to 113 Ci/mmol) without costly preactivation of the catalyst with tritiated isotopic sources. In addition to these major advances, a systematic study of the in situ generated Rh clusters (size distribution and shape) using transmission electron microscopy (TEM) was carried out. This study points out the relatively surprising homogeneity of catalysts analyzed, despite the wide range of substrates used (heterocycles, primary, secondary and tertiary amines, for instance).

DEUTERATION OF MODEL SUBSTRATES

As a starting point, relevant N-heterocyclic scaffolds were selected to prove the efficiency of Rh species for the $\text{C}(\text{sp}^2)\text{-H}$

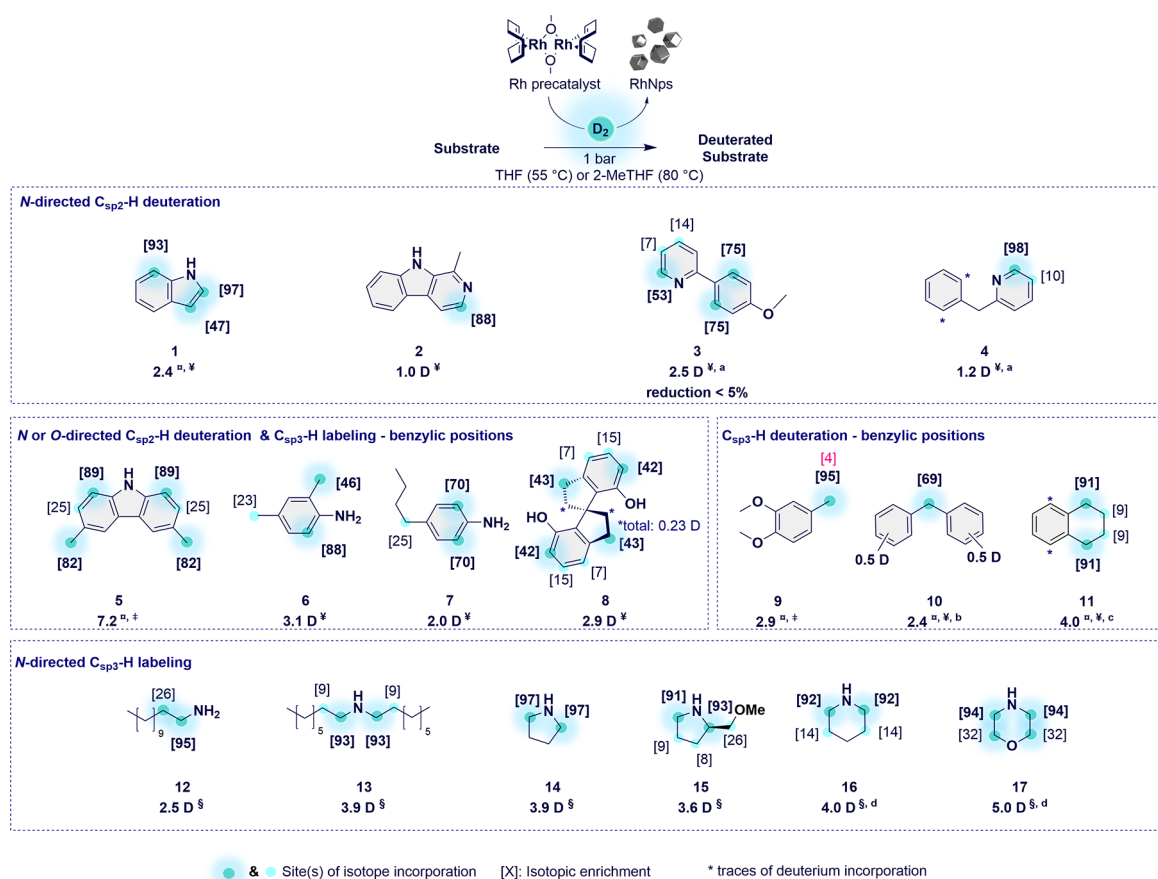


Figure 2. Rh-catalyzed deuteration. Reaction conditions: $[\text{Rh}(\text{OMe})(1,5\text{-COD})]_2$ (2.5 mol %), 0.2 mmol of the substrate in THF (0.1 M, for room temperature and 55 °C experiments) or 2-MeTHF (0.1 M, for 80 °C experiments) at the corresponding temperature (Y: T = room temperature; ‡: T = 55 °C; §: T = 80 °C) under 1 bar of D_2 gas during 24 h; ⁿ: isotopic enrichment determined only by ^1H NMR; a: $[\text{Rh}(\text{OMe})(1,5\text{-COD})]_2$ (1.25 mol %), 1,3-dicyclohexylimidazolium chloride (ICyCl, 2.5 mol %); b: HNET_2 (2 equiv) used as an additive; c: $\text{HN}(\text{Et})_2$ (0.3 equiv) used as an additive; d: $[\text{Rh}(\text{OMe})(1,5\text{-COD})]_2$ (5 mol %), 48 h. For compound 9, the isotopic enrichment indicated in pink has been obtained using $[\text{Ir}(\text{OMe})(1,5\text{-COD})]_2$ as precatalyst.

deuteration process (see Figure 2). Indole 1 and harmine 2 were efficiently labeled at positions α and β (for 1) relative to the nitrogen atoms. It should be noted that the described method gave a total deuterium incorporation which equals that obtained with previously reported Ir catalytic species (2.3 D incorporated), but at a lower temperature.⁴⁴ For easily reducible compounds such as 2-(4-methoxyphenyl)pyridine 3 or 2-benzylpyridine 4, the labeling comes along with reductive deuteration. Based on our previous work on Ru catalysts,⁴⁵ 5 mol % 1,3-dicyclohexylimidazolium (ICy) chloride was added to modify the reactivity of the catalytic surface, leading to a decreased amount of the reduced side-product for 2-benzylpyridine 4. Best results were attained by lowering the catalytic loading to 1.25 mol % and by adding 5 mol % ICy ligand, where deuterated compounds 3 and 4 were obtained with good isotopic enrichments (2.5 and 1.1 deuterium atoms incorporated, respectively) with a negligible amount of reduced side-product (<5%) (see the Supporting Information (SI), Table S1). For carbazole 5 and anilines 6 and 7, both $\text{C}(\text{sp}^2)\text{-H}$ in the close vicinity of a nitrogen atom and benzylic $\text{C}(\text{sp}^3)\text{-H}$ positions were labeled, with a higher isotopic enrichment for N-directed labeling positions. For carbazole 5, an isotopic enrichment of 82% was observed for the benzylic positions compared to 23%, 25%, and 46% for the benzylic positions of anilines 6 and 7 (reactions performed at room

temperature for 6 and 7 instead of 55 °C for 5). Regarding 7, the total number of deuterium atoms incorporated exceeded that obtained with Ir species (2.0 vs 1.6 D),⁴⁴ demonstrating that our method is also of great interest for the labeling of $\text{C}(\text{sp}^2)\text{-H}$ positions. Complex spirocyclic compounds such as spinol 8 were also labeled at $\text{C}(\text{sp}^2)\text{-H}$ positions in close vicinity to an oxygen atom and at benzylic $\text{C}(\text{sp}^3)\text{-H}$ positions. For all compounds, a minimum of two deuterium atoms was incorporated. Labeling of benzylic $\text{C}(\text{sp}^3)\text{-H}$ positions was achieved for 3,4-dimethoxytoluene 9, diphenylmethane 10, and tetralin 11. An impressive isotopic enrichment of 95% was obtained for the electron-rich compound 9 (compared to 4% obtained using $[\text{Ir}(\text{OMe})(1,5\text{-COD})]_2$ as precatalyst), however, under the same conditions, compounds 10 and 11 underwent simultaneous labeling and reduction processes. Adding ICy ligand to the mixture decreased the amount of reduced compound for 10, but the most effective additive proved to be diethylamine (2 equiv) for both 10 and 11 (see Table S2, Figures S38 and S39). The amine ligand may prevent the arene coordination of the aromatic rings while maintaining the accessibility of the benzylic carbon to the catalytic surface, thus promoting almost exclusively the $\text{C}(\text{sp}^3)\text{-H}$ deuteration process of the benzylic carbon. $\text{C}(\text{sp}^3)\text{-H}$ bonds of alkylamines were also efficiently labeled using our new catalytic system. Best results in terms of isotopic

enrichments were obtained using 2-MeTHF as solvent. Deuterated analogues of dodecylamine **12**, dioctylamine **13** and pyrrolidines **14** and **15** were obtained with high isotopic enrichments (from 93% to 97%) in positions α relative to the coordinating nitrogen atom. As expected from our previous work using Ru nanoparticles (RuNps), the C–H deuteration occurred in a totally stereoretentive manner, with full retention of the configuration of the labeled chiral center of **15**.²³ With an extended reaction time (48 h) along with higher catalyst loading (5 mol %), piperidine **16** and pyrrolidine **17** were labeled at positions α and β relative to the nitrogen atom, with an isotopic enrichment greater than 90% in position α and with more than four deuterium atoms incorporated. In comparison, when piperidine **16** was treated with 2.5 mol % of catalyst for 24 h, only 0.9 deuterium atoms were incorporated. These results demonstrate the usefulness of this method, which facilitates access to deuterated alkylamine auxochromes and SILS.

DETERMINATION OF THE CATALYTICALLY ACTIVE SPECIES (TEM EXPERIMENTS)

Upon labeling of the different substrates under the above-mentioned conditions, the final reaction mixture appearance varied quite significantly. In the case of **12** and **13**, a homogeneous brown color was observed, suggesting the formation of stable colloidal Rh particles. Conversely, with substrates **1** and **10**, a black precipitate was formed in the glassware, indicating the potential presence of either Rh black or aggregated nanoparticles. In order to gain insight into the nature of the catalytically active species, morphological assessments were performed by TEM analysis on various representative reaction mixtures. The TEM micrographs obtained reflected the observed colloidal stability, with well-individualized metal particles in the case of stable colloids, aggregated particles in the case of precipitates, or the coexistence of both in some ambiguous cases (see the SI, Table S5). Interestingly, the shape and size of the observed individual nanoparticles formed upon reaction of the Rh dimer precursor under D₂ atmosphere seemed to be independent of the substrate present in the mixture. In fact, for all substrates investigated (and even in the absence of substrate), the aggregation state of the observed particles varied, but their diameter was consistently found to be close to 3 nm (see Figure 3).

These findings led to the conclusion that, under the reaction conditions, the substrate mainly played the role of a stabilizing/dispersing ligand (thus leading to more or less stable colloids) which controlled the aggregation state without affecting the nucleation process. For instance, with alkylamines **12** and **13**, the observed particles were well dispersed and stabilized, whereas in the case of cyclic alkylamines **14** or less coordinating substrates as diphenylmethane **10** aggregated particles were observed. For **10**, the aggregation process might be explained by the lower coordinating ability of the phenyl rings (arene coordination) compared to that of nitrogen atoms (σ -coordination).

By comparison, the nature of the reaction solvent appeared to have an important impact on the morphology and size of the observed particles. For example, the labeling of dodecylamine **12** carried out in 2-MeTHF or dimethylformamide led to the formation of small spherical particles (ca. 3 nm), whereas the same reaction conducted in cyclohexane afforded larger (ca. 5 nm) and more heterogeneously shaped particles (see Figure

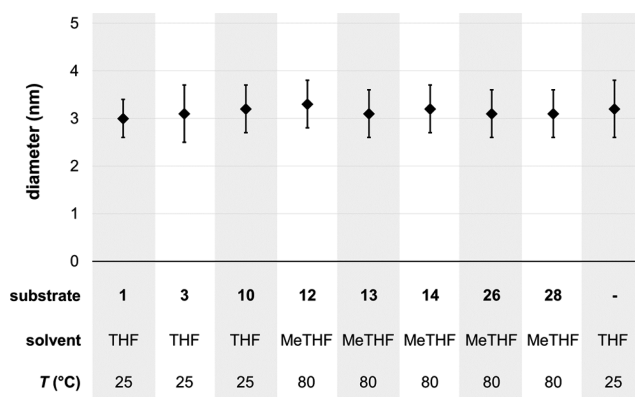


Figure 3. Mean diameter of observed Rh nanoparticles formed upon labeling of various substrates. Reaction conditions: [Rh(OMe)(1,5-COD)]₂ (2.5 mol %), 0.2 mmol of the substrate (0.1 M in corresponding solvent), 1 bar of D₂ gas, corresponding temperature, 24 h. Size statistics obtained from the measurement of 150 particles observed on TEM images taken at 100k $\times$ magnification.

4). The same trend was observed when the Rh dimer precursor was subjected to a D₂ atmosphere without substrate in the different solvents mentioned (see the SI, Table S5).

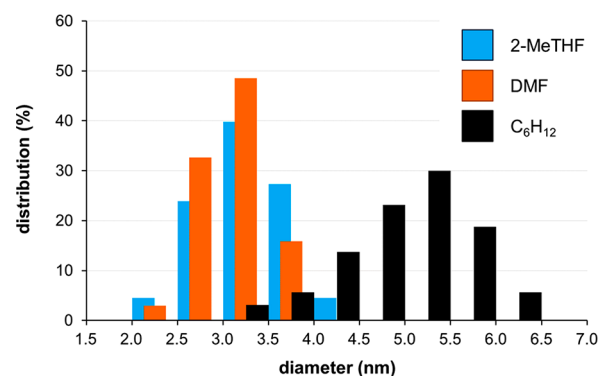


Figure 4. Size distribution of observed Rh nanoparticles formed upon labeling of dodecylamine **12** in 2-MeTHF (blue bars), dimethylformamide (orange bars), and cyclohexane (black bars). Reaction conditions: [Rh(OMe)(1,5-COD)]₂ (2.5 mol %), 0.2 mmol of **12**, 1 bar of D₂ gas, 80 °C, 24 h. Size statistics obtained from the measurement of 150 particles observed on TEM images taken at 100k $\times$ magnification.

DEUTERATION OF PHARMACEUTICALS

Having identified catalytically active species involved in this C–H deuteration process, a variety of relevant pharmaceuticals was labeled to prove the applicability of the developed method to the labeling of complex structures (see Figure 5). Drugs containing N-heterocyclic scaffolds **18**–**22** were efficiently labeled at C(sp²)–H positions. For nicotine **18**, the almost complete deuteration (98% isotopic enrichment) of positions 1 and 5 was achieved and a total number of 2.1 deuterium atoms was obtained (exceeding that previously published using Ir-based catalytic species at a higher temperature). For quinoline-based pharmaceuticals chloroquine **19** and papaverine **20**, the ortho-positions relative to the heterocyclic nitrogen atom were labeled with isotopic enrichments exceeding 90%. For indole-based drugs pindolol **21** and zolmitriptan **22**, C₂-positions of the indole scaffold were labeled with 91% and 55% isotopic

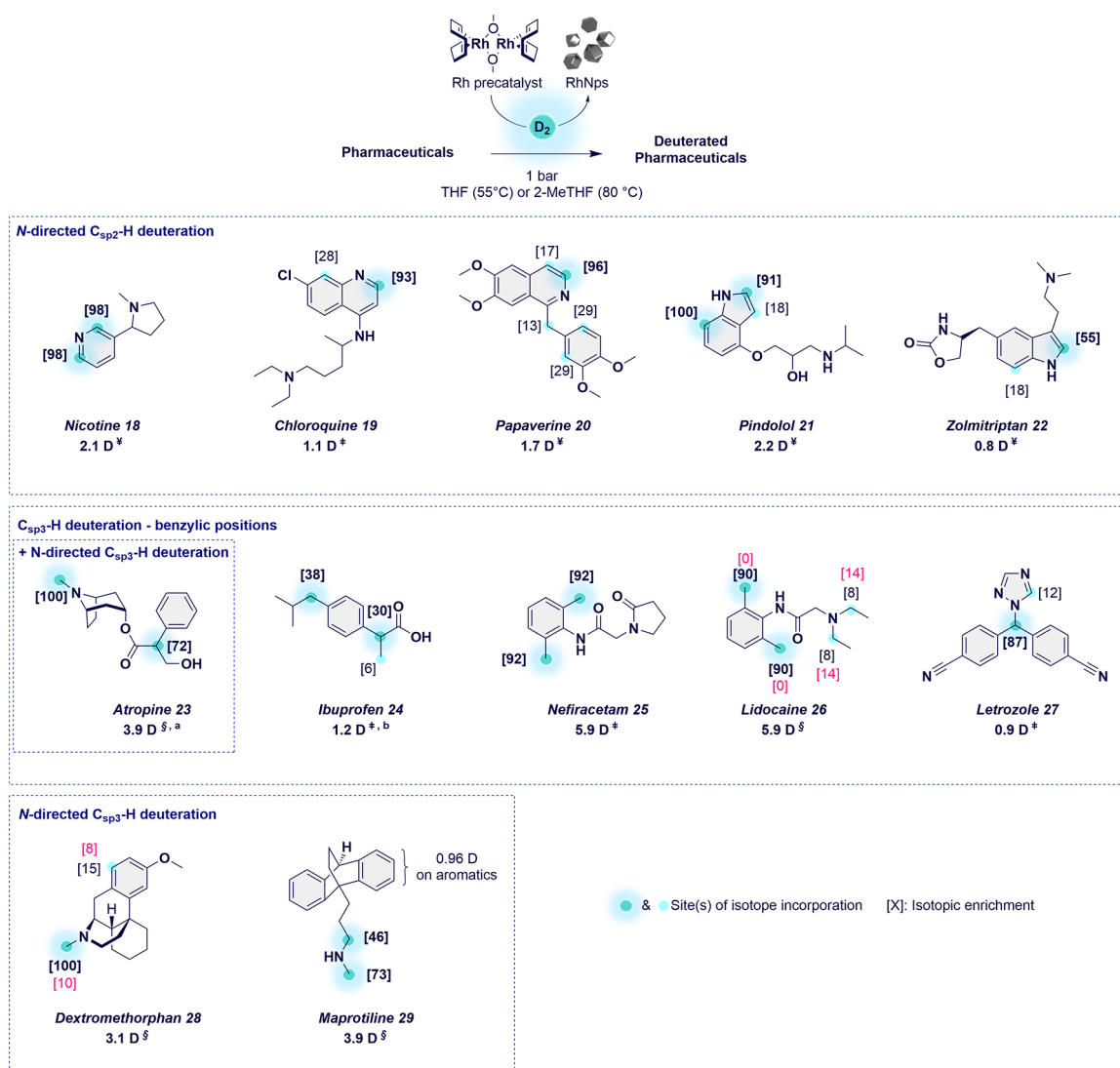


Figure 5. Rh-catalyzed deuteration of pharmaceuticals. Reaction conditions: $[\text{Rh}(\text{OMe})(1,5\text{-COD})]_2$ (2.5 mol %), 0.2 mmol of the substrate in THF (0.1M, for room temperature and 55 °C experiments) or 2-MeTHF (0.1M, for 80 °C experiments) at the corresponding temperature (‡: T = room temperature; †: T = 55 °C; §: T = 80 °C) under 1 bar of D_2 gas during 24 h; a: $[\text{Rh}(\text{OMe})(1,5\text{-COD})]_2$ (5 mol %), 48 h; b: $[\text{Rh}(\text{OMe})(1,5\text{-COD})]_2$ (5 mol %), HNEt_2 (1.3 equiv), 48 h. For compounds 26 and 28 isotopic enrichments indicated in pink have been obtained using $[\text{Ir}(\text{OMe})(1,5\text{-COD})]_2$ as precatalyst.

enrichment, respectively, along with a total hydrogen/deuterium exchange for the C₇-position of 21. The labeling of C(sp³)-H positions was also investigated as benzylic C-H bonds and alkylamines are highly represented in biologically relevant compounds. Indeed, 25% of the 200 top-selling pharmaceuticals contain benzylic C-H bonds.^{16,46} Benzylic position labeling was achieved for ibuprofen 24 using diethylamine as additive to prevent the formation of reduced side-products and degradation. Nefiracetam 25, lidocaine 26, and letrozole 27 were also efficiently labeled, despite the presence of a nitrile moiety in the latter case. For 25 and 26, both possessing two benzylic methyl groups, total incorporations of six deuterium atoms were obtained along with isotopic enrichments greater than 90%, allowing their use as labeled internal standards. It should be noted that previously reported methods for the labeling of 25 and 26 featured significant drawbacks such as laborious synthesis of precursors,^{47,48} mandatory acidification of basic functions,⁴³ or limitation to the complementary labeling of the alkylamine

moieties in the case of 26.⁴⁹ Interestingly, using $[\text{Ir}(\text{OMe})(1,5\text{-COD})]_2$ as precatalyst for the labeling of 26 has only led to a low deuterium incorporation on the two methyls of the trialkylamine substructure ([14]). The lack of reactivity of the Ir active species for the labeling of benzylic scaffolds has also been confirmed using model substrate 9 for which only traces of labeling have been detected (see Figure 2). This exhibits the benefit of using the Rh dimer as precatalyst compared to Ir dimer for the labeling of such sp³ hybridized carbon atoms. For letrozole 27, a challenging substrate in the context of HIE reaction using D_2 as isotopic source due to the presence of two easily reducible nitriles, the labeling takes place at the primary metabolism site. Gaining access to its deuterated counterpart is therefore of great interest since its metabolism pathway might be influenced and it can therefore be studied as a potential “heavy drug”. Atropine 23, which bears both a benzylic position and an alkylamine moiety, was efficiently labeled with a total hydrogen/deuterium exchange on the *N*-methyl group. The same observation was made for dextromethorphan 28 and

to a lesser extent for maprotiline **29** (84% isotopic enrichment on the *N*-methyl and 26% on the *N*-CH₂R moiety). Direct exchange on the *N*-methyl groups of **23** and **29** is of huge interest, since they represent major metabolism sites. Multistep methods for the synthesis of labeled **23** and **28** using demethylation/methylation strategies exist, but lead to low overall yields (32% and 41%, respectively).^{50,51} Once again, performing the labeling experiment on **28** with [Ir(OMe)(1,5-COD)]₂ precatalyst has only led to a low deuterium incorporation ([10] on the *N*-methyl group and [8] on the carbon center in meta position of the methoxy group). In order to confirm the nature of observed catalytically active species found with model substrates, TEM analyses of the reaction mixtures were also performed for pharmaceuticals **26** and **28** (see Figure 3 and the SI). As previously noted, RhNps with a mean diameter of 3 nm were also observed in situ in both cases.

The method described is applicable to the labeling of complex structures and permits the labeling of C(sp²)-H positions and, more importantly, of C(sp³)-H positions for which new strategies are of high interest. The combination of a commercial and therefore readily available precatalyst and mild reaction conditions (1 bar of deuterium gas, room temperature to 80 °C) along with a good functional group tolerance (e.g., chlorine, nitrile moiety) makes this method very attractive for the preparation of new labeled internal standards or heavy drugs. Interestingly, we also successfully recycled the in situ generated RhNps by adding nitrilotriacetate-based amphiphilic ligands at the end of the reaction (see SI page 94 for experimental details). After centrifugation, the resulting black solid was re-engaged in a new run of labeling using *n*-dodecylamine as the substrate. The same regioselectivity and isotopic enrichment (94%) were observed compared to those obtained after a single run of labeling. It should be noted that the labeling ability of the particles was almost identical even after 4 recycling cycles (see the SI, Table S6 and Figure S126).

TRITIATION OF PHARMACEUTICALS

Another major goal to achieve was the preparation of high molar activity tritiated compounds, as they are of paramount importance for ligand binding or autoradiography studies. By increasing the catalyst loading up to 10 mol %, reducing the reaction time to less than 3 h, and using T₂ gas with a pressure below 1 bar, the alkylamine moiety of dextromethorphan and the benzylic positions of nefiracetam were efficiently labeled (see Figure 6).

Respective molar activities of 40.4 and 113 Ci/mmol were obtained, and they exceeded the values recently described in the literature for nefiracetam whose labeling requires the synthesis of a brominated precursor (two steps for the precursor synthesis followed by the reaction with the commercial [³H]methyl naphthalene-1-sulfonate, 79.2 Ci/mmol).⁴⁷

Interestingly here, the formation of metallic nanoparticles in situ, contrary to the use of heterogeneous catalysts or metallic nanoparticles prepared under H₂ atmosphere, avoids the presence of parasitic hydride species on the catalytic surface. Therefore, there is no need for a preactivation step with tritium species (T₂ or HTO) to obtain tritiated compounds with high molar activities.³⁶

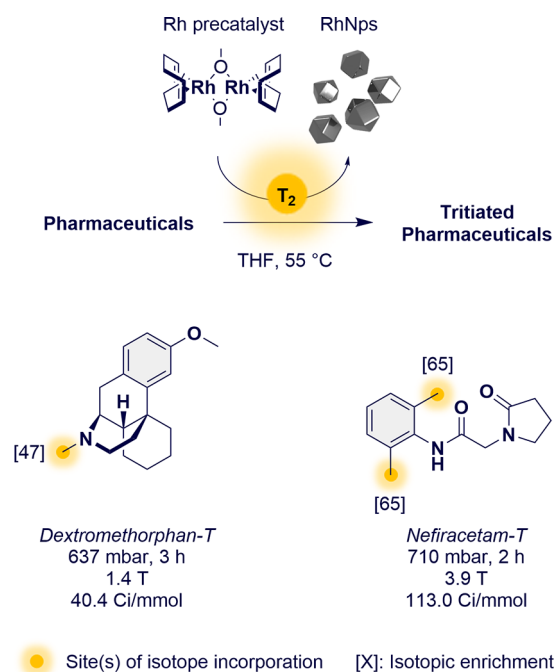


Figure 6. Rh-catalyzed tritiation of pharmaceuticals. Reaction conditions: [Rh(OMe)(1,5-COD)]₂ (10 mol %), 0.02 mmol of the substrate in THF (0.1 M) at 55 °C.

CONCLUSION

In conclusion, we have demonstrated that [Rh(OMe)(1,5-COD)]₂ is a very powerful precatalyst in the mediation of HIE on complex substrates. Under D₂ or T₂ atmospheres, this air stable and commercially available dimer is decomposed to form RhNps in situ with a mean diameter of 3 nm, displaying different aggregation states depending on the nature of the substrate. This robust catalytic system shows unprecedented performances, notably with the ability to catalyze both C(sp²)-H and C(sp³)-H deuteration/tritiation. By analogy with RuNps^{23,52,53} and considering the regioselectivity observed for the *N*-directed C(sp²)-H and *N*-directed C(sp³)-H processes, we propose here that the same catalytic cycle and intermediates are involved for Rh nanocatalysis. Direct access to labeled scaffolds of considerable importance such as various heterocycles (indoles, carbazoles, azines), benzylic carbons, or alkylamines was facilitated and even unlocked, using mild reaction conditions with a high functional group tolerance (e.g., amides, carboxylic acids, nitrile, methoxy, or chloride moieties). The usefulness of this method has been demonstrated by the preparation of deuterated complex compounds usable as stable isotope internal standards or as potential “heavy drugs” and tritiated analogues of pharmaceuticals with very high molar activities (up to 113 Ci/mmol). In addition, with environmental and cost-effectiveness concerns in mind, recyclability studies of the in situ generated nanocatalysts were conducted by adding amphiphilic ligands as stabilizers and their catalytic activity was maintained over four runs. The broad scope of application of the catalytic system described coupled with its ease of implementation and efficiency in terms of isotope incorporation will undoubtedly facilitate the synthesis of tracers essential for ADME studies (SILS, tritiated drug candidates) and access to molecules used in material science (e.g., deuterated dyes for fluorescence imaging).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacsau.1c00503>.

Experimental data and analysis TEM analyses; recyclability studies (PDF)

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Author Contributions

[†]E.L. and K.T. contributed equally. S.F. and G.P. designed the study. E.L., K.T., S.G.-A. and V.P. conducted the labeling experiments. E.G. performed the TEM analyses and supervised the recycling experiments. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

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■ ABBREVIATIONS

ADME, absorption, distribution, metabolism, excretion; HIE, hydrogen isotope exchange; HSCIE, high temperature solid state catalytic isotope exchange; ICy, 1,3-dicyclohexylimidazolium; Np, nanoparticles; SILS, stable isotope labeled internal standards; TEM, transmission electron microscopy; THF, tetrahydrofuran

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