C–H Activation

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NHC-Stabilized Iridium Nanoparticles as Catalysts in Hydrogen Isotope Exchange Reactions of Anilines

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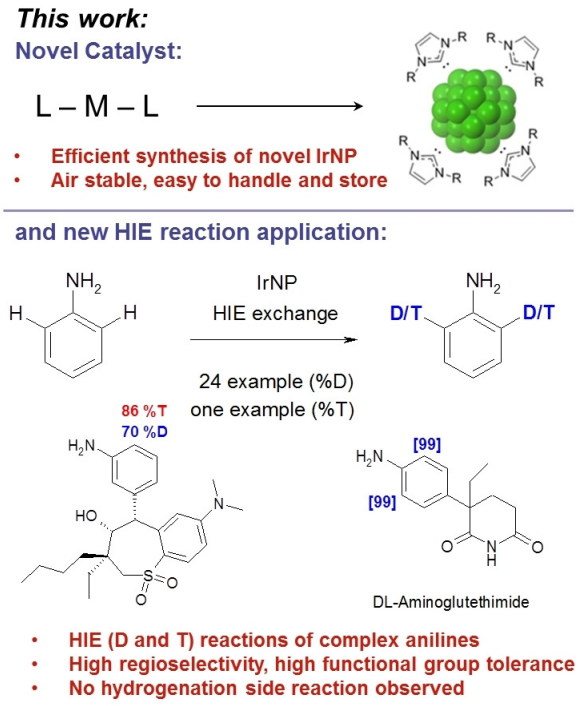
Abstract: *The preparation of N-heterocyclic carbene-stabilized iridium nanoparticles and their application in hydrogen isotope exchange reactions is reported. These air-stable and easy-to-handle iridium nanoparticles showed a unique catalytic activity, allowing selective and efficient hydrogen isotope incorporation on anilines using D_2 or T_2 as isotopic source. The usefulness of this transformation has been demonstrated by the deuterium and tritium labeling of diverse complex pharmaceuticals.*

Metal nanoparticles (MNPs) possess unique physical and chemical properties, crossing the barriers of homogeneous and heterogeneous catalysis and paving the way to new applications in life sciences and medicine.[1] To enhance their performance in catalysis, N-heterocyclic carbenes (NHCs) are employed as ligands to stabilize the nanoparticles and to induce selectivity.[2] These ligands were used for the preparation of Au,[3] Pd,[4] Ni,[5] and also Ru[6] nanoparticles. Recently, Pieters and Chaudret et al. demonstrated the usefulness of metal nanocatalysts (Ru) in the context of hydrogen isotope exchange (HIE),[7] which is widely known as the most fundamental of all C–H functionalization processes.[8] HIE has become the state-of-art strategy for the incorporation of deuterium or tritium atoms into complex organic molecules.[9,10] In life sciences, isotopically labeled compounds[11] are experiencing a renaissance owing to the highly improved mass spectrometry applications utilizing labeled mass spectrometry (MS) standards[12,13] and to the limitations of ^{14}C labeling, such as high cost and synthesis duration. In this context, we were interested in the synthesis of new NHC-stabilized IrNPs and the study of their catalytic properties in HIE reactions (Scheme 1).



Scheme 1. Overview of the presented work.

While there have been numerous homogeneous iridium-catalyzed methods described in the last 40 years[9,14] and some HIE catalysts are commercially available, such as the Crabtree,[15] Kerr[16,17] or Burgess[18] catalysts, heterogeneous HIE applications with iridium are overall overlooked. To the best of our knowledge, there is only one report on the stabilization of IrNPs using imidazolium-based ionic liquids.[19] An ongoing active research for C(sp^3)–H activation by HIE,[11e,20,21] especially protocols with deuterations in the vicinity of N heteroatoms (for example, primary, secondary, and tertiary amines or N-heterocycles) have already been successful. Regarding C(sp^2)–H activation by HIE there are still some challenges which still wait to be overcome. One of

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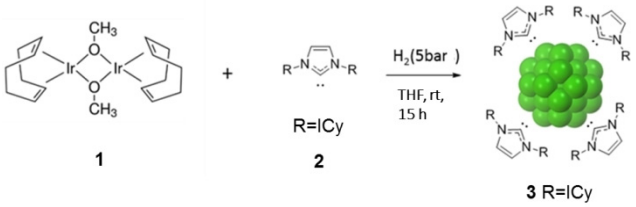
these examples is the labeling of anilines. Indeed, the best results for unselective aniline labeling with deuterium were described by Lautens or Jung using strong acids like DCl[22] or TFA[23] in large excess at temperatures above 100 °C, giving access to 99 %D labeled simple anilines. Junk described complete exchange (99 %D) for the synthesis of [D_7]aniline in D_2O/NaOD at 400 °C (600 bar) over 10 h.[24] Recently Bagley reported an unselective deuteration of aniline and aminopyridines in neutral D_2O at 190 °C (high pressure, 16 bar) with up to 25 %D of isotopic enrichment for all C(sp^2)–H aniline positions.[25] Unfortunately, all these methods are difficult to transfer to tritium chemistry, yielding mainly low specific activity[26] or are incompatible with some functional groups due to the harsh conditions used. Another approach reported by Garnett starting from nitrobenzene reacting over Raney nickel (alternatively platinum or palladium) with D_2 or D_2O (or T_2 or HTO respectively) at a temperature lower than 75 °C over days allows the corresponding deuterated/tritiated anilines to be obtained in low %D or %T unless a very large excess of isotope source is used.[27] Alternatively Tashiro et al. started from brominated anilines and exchanged the halogen by deuterium with a Raney copper–aluminum alloy in a basic D_2O/THF media.[28] However, both pathways might need an involved precursor synthesis. A direct HIE approach for the *ortho*-deuteration of anilines was studied using several transition metals like Co, Ni, or Pt leading up to 34 %D at the *ortho* position but requiring temperatures above 300 °C and along with the reduction of the aromatic ring.[29] Schou studied the synergistic effect of a heterogeneous and homogeneous catalysts mixture such as rhodium black and Crabtree catalyst (1 atm of D_2, 4 h, rt) reaching 36 %D in the *ortho* position of unsubstituted aniline.[30] Furthermore Lockley et al. reported labeling of anilines with a homogeneous iridium catalyst.[31] Even though there are already some examples published, there is still no simple and general method for the deuteration/tritiation of complex anilines. This is due to the fact that the conjugated amino group may be a too strong a metal ligand, or the pH can cause reactivity or solubility issues. This motivated us to search for an easy to handle, mild, and generally applicable HIE method applying our newly synthesized iridium nanoparticle (IrNP) catalysts. This way we could notably improve the tritiated compound supply in a compound class where moderately useful methods have been developed for over the last 50 years.

Trying to label aniline substructures using RuNPs[7] have led to unsatisfactory results. Depending on the model substrate used and the nature of the stabilizing agent very poor isotopic enrichments or complete reduction of the aniline rings were observed. To circumvent this issue, we reasoned that the use of metallic nanoparticles less prone to reduce aromatic rings might allow developing a convenient approach to label aniline substructure in complex molecules. In this context, we hypothesized that Ir could be a good substitute to Ru since ligated Ir complexes are very efficient for H/D exchange,[8,9] presumably because of a low barrier for C–H activation.[16,17] Furthermore, these catalysts are generally poor hydrogenation catalysts.[18] We therefore turned to synthesize novel IrNPs stabilized by the same ligands found in RuNPs, namely NHCs since these ligands have demonstrated their strong binding abilities to various transition metal NPs. It is noteworthy that there is no precedent for IrICy NPs although such NHC binding to IrNPs has been proposed in ionic liquids to explain their stabilization.[19]

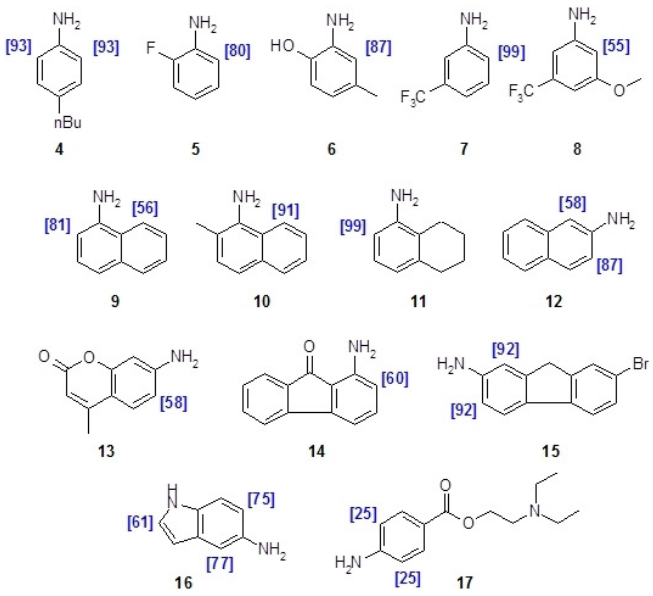
The reaction of the precursor [(COD)Ir(MeO)]$_2$ (COD = 1,5 cyclooctadiene) **1** with 5 bar of H_2 (Scheme 2) over 15 hours in the presence of N-heterocyclic carbene ligand **2** (ICy = 1,3-dicyclohexylimidazole) produces very small NPs of



Scheme 2. Synthesis of NHC-stabilized iridium nanoparticles **3** (IrICy).

1.1 to 1.3 nm mean size and of good size dispersity as observed by TEM analysis. The NPs **3** adopt the face-centered cubic (fcc) structure of bulk Ir as determined by X-ray diffraction (XRD) analysis (for a detailed characterization of the NPs, see the Supporting Information). We demonstrated also a high reproducibility of different IrICy **3** batches with compound **4**. The NPs can be handled without the need for an inert atmosphere as there are consistent levels of deuterium incorporation from run to run. The NPs can be isolated as a black powder and can be redissolved in organic solvents, for example, tetrahydrofuran (THF). The metal content of the isolated powder depends upon the initial ligand/metal ratio and was found between 40 and 90 wt %. Interestingly, the NPs **3** displaying a metal content of 90 wt % are stable, which demonstrates the strong coordination of the NHC at the surface of Ir. X-ray photoelectron spectroscopy (XPS) (N 1s) on NPs prepared with 0.125 equiv ICy clearly showed two signals corresponding, respectively to free ICy ligand and to a high-energy shift, which has been previously attributed to coordinated ICy ligand in the case of Pd NPs.[32]

After optimization and identification of the best HIE conditions (solvent screening, catalyst, catalyst amount, time, temperature; for details see the Supporting Information), we observed satisfactory to excellent isotopic enrichments (55–99 %D) for simple anilines **4**–**8** (Scheme 3). Neither electron-withdrawing functional groups (**5, 7, 8**) nor electron-donating ones (**4, 6**) seemed to have a significant influence on the outcome of the HIE reaction. Instead we identified steric interactions as the major driving force of the IrNP-catalyzed HIE reactions. For example, we found no deuteration in the *ortho* position (**7, 8**) of CF_3 groups at all, and in the HIE reaction of naphthalenes **9**–**12** we observed different %D for position 2 and 8 in 1-amino-naphthalenes **9**–**11**. Interestingly the C(sp^2)–H is significantly more reactive than the C(sp^3)–H as shown by comparison of 1-amino-naphthalenes **9** and **11**. Furthermore we studied the scope of this reaction with more complex anilines **13**–**17** containing other functional groups. The reaction conditions tolerate halogens, phenols, indoles,



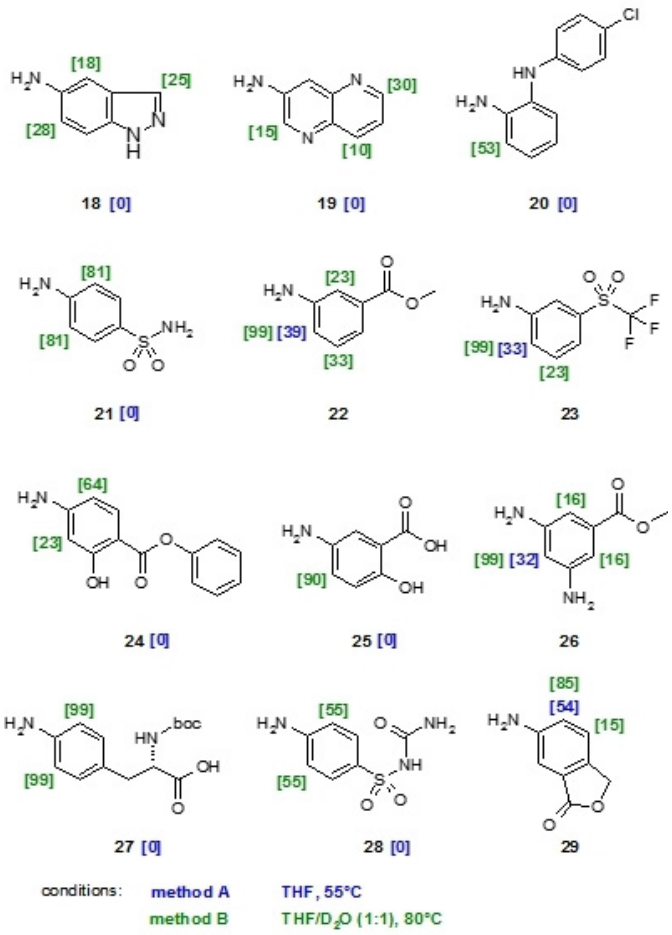
Scheme 3. HIE reaction with various anilines **4**–**17**. Conditions: substrate (22 µmol), IrICy **3** (4 mol%, 1.5 mg), solvent (3 mL), D_2 (1 bar), 3 h, 55 °C, THF.

esters, and ketones without any influence on selectivity or evidence of side reactions.

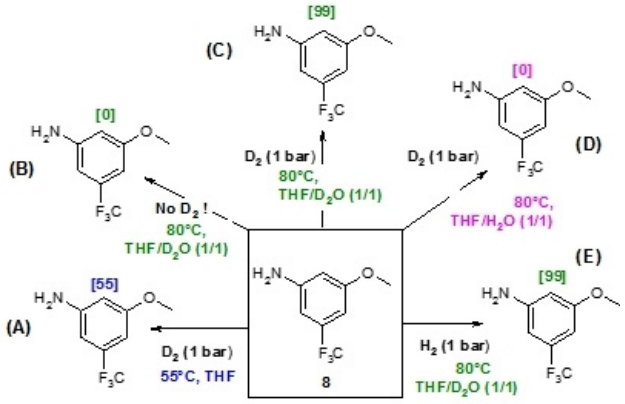
Nevertheless, we observed for a group of anilines **18**–**29** that the prior optimized conditions yield low deuterium incorporation (Scheme 4). We concluded that due to the high polarity of the amino moiety we would need a stronger donating co-solvent like D_2O, which would also allow us to run the reaction at higher temperature. Thus, performing the HIE with a THF/D_2O 1:1 solvent mixture at 80 °C permits successful exchange for anilines **18**–**29** with high deuterium incorporation and regioselectivity. However, in the case of N-heterocycles an additional labeling takes place in the *ortho* position of the nitrogen atom(**16, 18, 19**) as well and in three cases we have also observed the labeling in the *meta* position of aniline moieties (**22, 23, 29**).

We questioned ourselves if the role of D_2O is just as simple polar co-solvent or if there are other effects we did not understand so far. Therefore, we initiated a series of experiments to further investigate the role of the co-solvent. Firstly, without substrate we placed a solution of IrICy in THF containing ca. 1% water under an atmosphere of D_2 (5 bar) and monitored the reaction by ^2H NMR. Initially, we only saw the natural abundance signals of THF. Rapidly we observed both, a) the fast appearance of a signal corresponding to D_2O as well as b) a signal for dissolved D_2 confirming a very fast HIE between gas phase D_2 and water (likewise between H_2 and D_2O).

As shown in Scheme 5, a second set of experiments were conducted with **8** as substrate holding the reaction time, temperature and gas pressure (if used) constant. If the reaction was carried out in THF under D_2 and in the absence of D_2O (**A**), we observed 55% of isotopic enrichment whereas if the reaction was performed in THF/D_2O in the absence of H_2 or D_2, no deuteration was found in **8** (**B**). However, if the deuteration was carried out in the presence of



Scheme 4. HIE reaction with various anilines **18**–**29**. Conditions: substrate (22 µmol), IrICy **3** (4 mol%, 1.5 mg), solvent (3 mL), D_2 (1 bar), 3 h, method A: 55 °C, THF; method B: 80 °C, THF/D_2O (1:1).

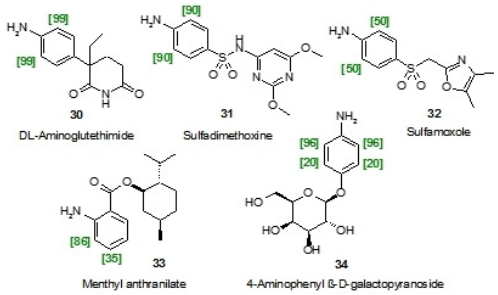


Scheme 5. HIE reaction with aniline **8**. Conditions: substrate (22 µmol), IrICy **3** (4 mol%, 1.5 mg), solvent (3 mL), 3 h.

D_2 and in a THF/D_2O mixture (**C**), the deuterium introduction increased to 99% D. Thus, we hypothesized that upon fast equilibrium for HIE between gas and aqueous phase D_2O may serve as kind of a reservoir to replenish the consumed D_2 in the gas phase. To verify this assumption, we conducted two complementary experiments: (**D**): THF/H_2O under D_2 and

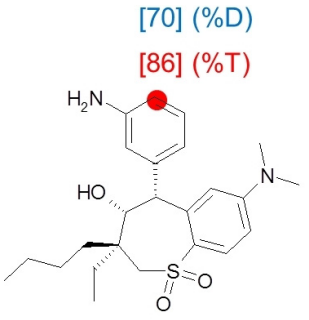
(**E**): THF/D_2O under H_2 resulting in 0 and 99% D deuteration, respectively.[33] We propose that the HIE exchange between water and the catalyst is much faster than the exchange of the catalyst with the substrate, resulting in 0% D (**D**) even though there is D_2 in the system. Interestingly this catalytic system does not require an additional supply of D_2 gas but can conveniently be carried out under H_2 in D_2O/THF mixtures as well. And it is likely that similar conditions could be also applied for other HIE reactions in D_2O/ organic solvent mixtures.[34]

We were able to show that the developed conditions could be applied to more complex structures, like the drugs aminoglutethimide **30**, sulfadimethoxine **31**, sulfamoxole **32**, menthyl anthranilate **33** (sunscreening agent), or saccharose 4-aminophenyl-*beta*-D-galactopyranoside **34**. In all of the examples, excellent selectivity and moderate to good HIE reactivity was achieved (Scheme 6).



Scheme 6. HIE reaction with complex aniline compounds **30**–**34**. Conditions: substrate (22 µmol), IrICy **3** (4 mol%, 1.5 mg), THF/$D_2$0 1:1 (3 mL), 80°C, 3 h.

Next, we demonstrated that the late-stage tritiation of complex pharmaceuticals can be realized using this novel IrNp catalyzed HIE. The use of T_2 gas as an isotopic source is a clear advantage because it is the cheapest and easiest raw material to handle for tritium labeling. Typically, reactions involving T_2 gas are conducted using a sub-atmospheric pressure of T_2 to minimize the risk of leakage and radioactivity release. For these reasons, we have optimized our reaction conditions using Volixibat **35** aniline pharmacophore as substrate (Scheme 7).[35] This complex molecule is a medication under development for cholestatic liver disease. Using a catalytic loading of 80 mol% of Ir NPs, the tritiated pharmacophore of Volixibat **35** was obtained utilizing sub-atmospheric pressure of tritium gas ($p = 0.8$ bar, 10 Ci)[36] within a relatively short reaction time (3 h). In terms of regioselectivity, the labeling of the less sterically encumbered *ortho* position of the NH_2 group was mainly observed (as demonstrated by the isotope incorporation observed for deuterium experiments and using ^3H NMR spectroscopy; see the Supporting Information). Typically, a specific activity between 10–20 Ci mmol^{-1} is considered as suitable for the use of tritiated molecules in the context of absorption, distribution, metabolism, and excretion studies. The high specific activity of 25 Ci mmol^{-1} obtained here (calculated by mass spectrometry) clearly demonstrate the high potential of this



Scheme 7. Tritiation of the pharmacophore of Volixibat **35** catalyzed by IrNps **3** in a 0.8 bar tritium atmosphere.

novel method for late-stage labeling of complex pharmaceuticals containing aniline substructures.

In conclusion, we have developed a new method for a selective HIE of anilines. The method is fully adaptable to the specific requirements of tritium chemistry, which is demonstrated by direct tritium labeling of the volixibat pharmacophore with a high selectivity and specific activity of 25 Ci mmol^{-1}. The new IrNPs are simple to prepare, easy-to-handle, and air-stable. No hydrogenation side products have been observed.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: C–H activation · C–H functionalization · heterogeneous catalysis · hydrogen isotope exchange · iridium nanoparticles

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