Au(I)-catalysis Enables Regioselective Hydrogen Isotope Labeling of Indoles

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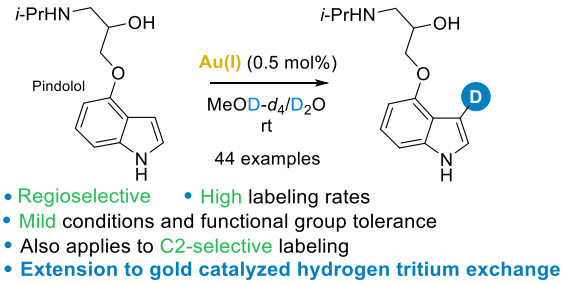
The gold(I)-catalyzed hydrogen isotope exchange reaction on indoles and related heterocycles is described, under mild conditions and low catalyst loadings, using CD_3OD and D_2O as readily available deuterium sources. C3-unsubstituted indoles are labeled at the C3 position with an exquisite regioselectivity, while C3-substituted indoles are labeled at the C2 position. The reaction tolerates a number of chemical functions including amines, alcohols, aldehydes, in addition to the most classical functional groups. This method has been applied to the deuterium labeling of densely functionalized bioactive compounds and to the synthesis of a tritiated analogue of pindolol using tritiated water as isotopic source. Mechanistic study revealed the involvement of aurated indole as key intermediates.



Facilitating synthetic access to complex molecules labeled with hydrogen isotopes is of paramount importance across various scientific domains, from chemistry to drug development and materials science.[1] For example, thanks to the deuterium kinetic primary isotope effect, [2] incorporating deuterium into active pharmaceutical ingredients has the potential to enhance their safety, efficacy, and/or tolerability.[3] Tritium labelled radiotracers also play a crucial role in preclinical Absorption, Distribution, Metabolism, and Excretion (ADME) studies, enabling the investigation of the biodistribution and pharmacokinetics of drug candidates.[1a, 4]

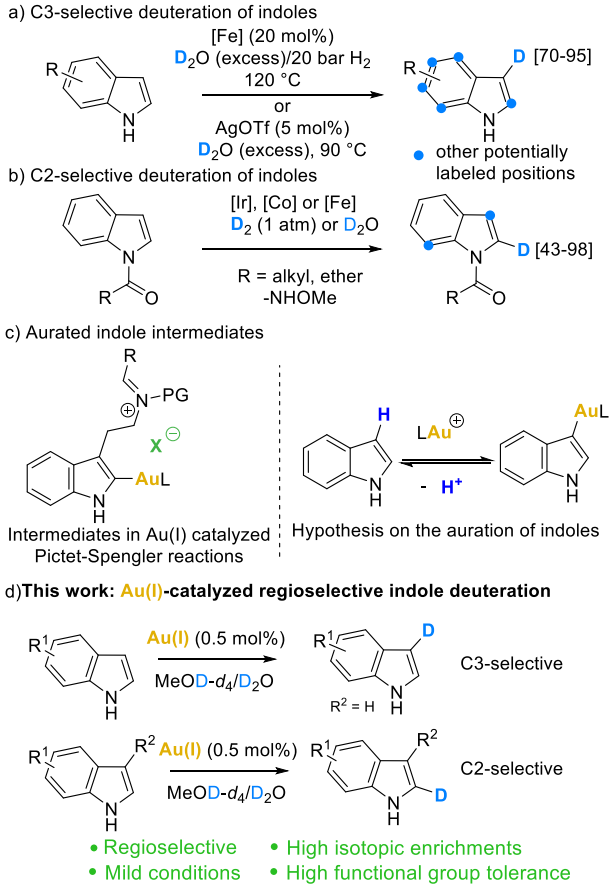
By virtue of their predominance and importance, indole derivatives have been largely studied in the context of hydrogen isotope labeling. For instance, in 1999 the deuterium labeling of indoles using Raney nickel in deuterated solvents was reported, resulting in an efficient but poorly regioselective labeling.[5] Metallic nanoparticles,[6] or highly acidic conditions[7] may also be used generally leading to multiple site deuterium incorporation. Considering the long-known basicity of indoles,[8] regioselective deuteration is possible at C3 of the indole ring using acidic conditions, [9] a method which is however poorly compatible with acid-sensitive compounds or basic chemical groups that will quench the acid necessary to the hydrogen deuterium exchange. Most recent C3-labeling methods include iron[10] or silver catalysis[11] under harsh conditions (Scheme 1a), such as temperatures higher than 90 °C and use of high pressure of H_2 These methods are endowed with poor regioselectivities and are not applicable to C3-substituted indoles for the C2 position labeling.

Strategies for the labelling of C2 position are very efficient and rely mostly on CH-activation strategies using iron,[10] iridium,[12] cobalt,[13] ruthenium[14] or rhodium[13, 15] catalysis which imposes a directing group on the indole nitrogen and either the use of D_2 as the deuterium source or harsh conditions (Scheme 1b), and sometimes lack a total regioselectivity.[14, 16] All these methods constitute a solid arsenal for the hydrogen isotope labeling with deuterium of indoles. However, most perdeuteration methods use harsh conditions that could potentially be poorly tolerant to a large number of chemical functionalities, while the vast majority of very regioselective methods require the introduction of a directing group.

Recently, we developed Pictet-Spengler reactions catalyzed by Au(I) complexes,[17] in which aurated indole intermediates are involved (Scheme 1c). Aiming at probing these species, we became interested in the fundamental issue of the auration of indoles and hypothesized that indoles could act as ligands for Au(I) and potentially be metallated at their C3 position. Interestingly, this was also earlier reported by Shi and Tang,[18] who invoked indolylgold species in the course of cyclizations of indolylcyclopropenes and used deuterodeauration (leading to 18% deuterium incorporation at 80

°C at the C3 position) as a mean to support their hypothesis , without further exploiting this reactivity nor investigating more the nature of the species involved.

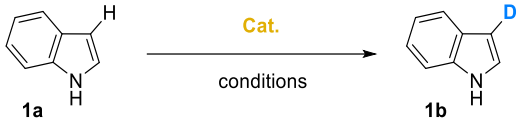
Scheme 1: Selection of common methods for the deuterium labeling of indole derivatives and context of this work



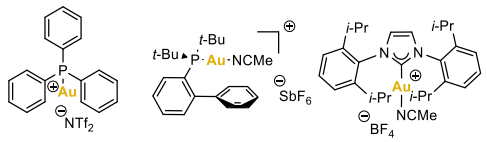
In this paper, we report a full study about the C3-regioselective deuteration of indole derivatives using Au(I) catalysts under mild conditions that operate with a large tolerance to a number of chemical functions (Scheme 1d). The method has also been successfully applied to the C2 regioselective deuteration of indoles and preliminary results indicate that other heterocycles can be labeled under the same conditions. It is finally demonstrated that the method can be applied to the tritiation of indoles using a similar strategy. Mechanistic studies complete this study, shedding light on putative Au(I) complexes intermediates.

We initiated this study by optimizing suitable conditions for the regioselective C3-deuteration of indole **1a** (See the SI pS3 for full optimization). First tests were performed using 5 mol% of the Gagosz complex[19] as the Au(I) catalyst and deuterated methanol as the isotope source (Table 1, entry 1). After 16 h of reaction at room temperature, a deuteration rate of 75% was measured by ^{1}H NMR. The same reaction was performed in a mixture of deuterated methanol and deuterated water (9:1 ratio), which led to a virtually total conversion in a 2 h timespan (entry 2). The decrease of the catalyst charge to 2 mol% however triggered a drop of the isotopic enrichment at the C3-position (entry 3). This was solved by the replacement of the **Cat a** by the JohnPhosAuSbF$_6$.MeCN **Cat b** and IPrAuBF$_4$.MeCN **Cat c** complexes (entries 4-5), which led to an isotopic enrichment >95% . The catalyst loading could be further decreased to 1 and 0.5 mol% with a similar success (entries 6 and 7), leading to the isolation of the target deuterated compound **1b** in 97 and 98% yields, respectively. Control experiments to demonstrate the role of the Au(I) complex were then attempted. While no reaction occurred in the absence of the Au(I) complex (entry 8), it was shown that the reaction proceeds well using a strong acid as the catalyst (entry 9), as expected. However, the combination of the Au(I) complex with a sterically hindered base used as a proton scavenger, made sure that the Au(I) complex is the actual catalyst, instead of the presence of adventitious acid that would form in the reaction mixture (entry 10). In all cases above, a full regioselectivity for the hydrogen-deuterium exchange a position C3 was observed.

Table 1: Optimization of the Au(I)-catalyzed deuterium labeling of indole



entry	cat (mol%)	solvent	reaction time (h)	% D[a]
1	a (5)	$CDCl_3$/MeOD-d_4 (9:1)	16	75
2	a (5)	MeOD-d_4/D_2O (9:1)	2	95
3	a (2)	MeOD-d_4/D_2O (9:1)	2	30
4	b (2)	MeOD-d_4/D_2O (9:1)	2	95
5	c (2)	MeOD-d_4/D_2O (9:1)	2	95
6	c (1)	MeOD-d_4/D_2O (9:1)	2.5	95 (97)
7	c (0.5)	MeOD-d_4/D_2O (9:1)	16	94 (98)
8	-	MeOD-d_4/D_2O (9:1)	2	0
9	$HNTf_2$ (2)	MeOD-d_4/D_2O (9:1)	2	95
10[b]	c (1)	MeOD-d_4/D_2O (9:1)	2	95

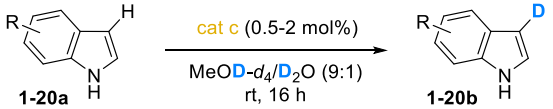


[a] Deuteration rates have been measured by ^{1}H NMR. Numbers given in brackets are isolated yields. [b] Reaction performed in the presence of 1 equiv. of tri-*tert*-butylpyrimidine as an acidic scavenger.

With these conditions in hand, we studied the scope of functionalized commercially available indoles bearing functional groups at diverse positions (Table 2). The reactions were performed at room temperature using optimized catalyst loadings varying from 0.5 to 2 mol%, analyzed by ^{1}H NMR to determine the deuteration rate and purified over deactivated silica gel prior to further NMR analysis. The reaction tolerated a methoxy group at positions 4, 5, 6 and 7

of the indole ring, delivering high isotopic enrichments and yields (entries 2-5). A methyl group at C5 of the indole ring was also compatible with the reaction (entry 6). Reactions performed on chlorinated indoles showed that 4-chloro and 5-chloro indoles **7a** and **8a** are less reactive and necessitate an increased catalyst loading (entries 7-8). A part of the isotopic enrichment was lost during the purification of 4-chloroindole **7b**, despite all precautions, showcasing the lability of the deuterium label in this specific case. The presence of the chlorine atom at positions 6 and 7 did not meet the same limitations (entries 9-10) and high isotopic enrichments were obtained using low catalytic loadings. Reactions performed with a bromine and iodine at C5 proceeded well (entries 11-12), in a similar manner to that using 5-trifluoromethylindole **13a**, demonstrating the compatibility with inductive attractor functions (entry 13). We next screened indole bearing mesomere attractor groups, such as a carboxaldehyde or a nitrile (entries 14-16). These reactions resulted in high deuteration rates but lower isolated yields. It is also worth noting that a higher catalyst loading is necessary. Methyl and benzyl groups were well tolerated on the nitrogen atom, leading to high isotope labeling (entries 17-18). Finally, methyl and phenyl substituents were introduced at C2 of the indole, leading to high yields but a decreased stability of the isotopic labeling upon purification (entries 19-20). This first set of results demonstrates the compatibility of this method with most of the electronically diverse chemical functions.

Table 2: Scope of the Au(I)-catalyzed deuterium labeling of indoles



1-20a **1-20b**

entry	R substituent	cat loading (mol%)	isotopic enrichment (%)[a]	yield (%)[b]
1	H	0.5	94	**1b**, 98
2	4-MeO	0.5	91	**2b**, 99
3	5-MeO	0.5	81	**3b**, 94
4	6-MeO	0.5	95	**4b**, 97
5	7-MeO	0.5	94	**5b**, 99
6	5-Me	0.5	80	**6b**, 93
7	4-Cl	2	30 (87)[c]	**7b**, 94
8	5-Cl	1	82	**8b**, 87
9	6-Cl	0.5	89	**9b**, 96
10	7-Cl	0.5	89	**10b**, 91
11	5-Br	0.5	82	**11b**, 93
12	5-I	0.5	91	**12b**, 88
13	5-CF_3	1	88	**13b**, 97
14	4-CHO	2	94	**14b**, 45
15	2-CHO	0.5	89	**15b**, 60
16	4-CN	2	94	**16b**, 90
17	1-Me	0.5	79 (94)[c]	**17b**, 95
18	1-Bn	5	86 (95)[c]	**18b**, 90
19	2-Me	0.5	33 (93)[c]	**19b**, 92
20	2-Ph	1	43 (93)[c]	**20b**, 92

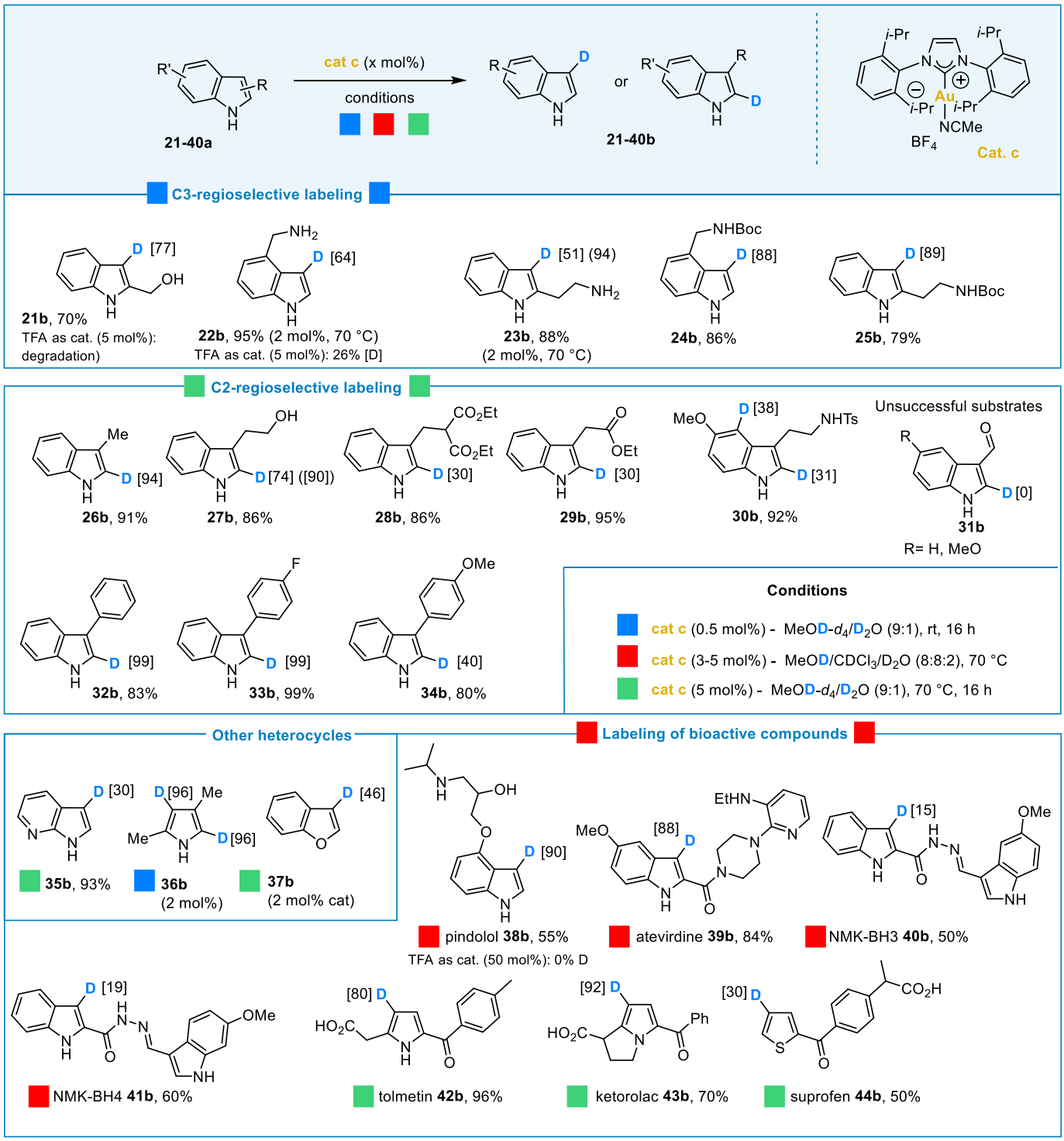
[a] Deuteration rates have been measured by ^{1}H NMR after the purification. [b] Isolated yield after purification on deactivated silica gel. [c] Deuteration rate before purification on silica gel.

We next turned our attention to more functionalized indole derivatives, in order to demonstrate the high level of functional group tolerance of the method. 2-Indolylmethanol **21b** was obtained in 80% yield with isotopic enrichment reaching 77% using a catalyst loading of 0.5 mol%. Considering the known reactivity of indolylmethanol towards acids,[20] this result is highly rewarding and demonstrates the unique mildness of the method. Indeed, the same reaction performed with TFA as catalyst (5 mol%) only led to degradation of the starting material. Isotryptamines **22a** and **23a** also participated in the reaction delivering reasonable deuteration rates. With these compounds, it was necessary to increase the catalyst loading (2%mol) and the temperature to counterbalance the coordination of the amine to the gold complex. Again, control experiment with 5 mol% TFA led to 22b with only 26% deuterium incorporation. The *N*-Boc protected analogues **24b** and **25b** were obtained in high yields and labeling rates restoring the high catalytic activity of the Au(I) complex and avoiding the Boc deprotection that would be triggered if the reaction was performed using acidic conditions.

We next turned our attention towards C3-substituted indoles, in order to achieve C2-regioselective deuteration. Conditions proceeding at 70 °C afforded 3-methylindole **26b** in 91% yield and 94% deuterium labeling at the C2 position, confirming that Au(I) complexes are competent catalysts for C2 deuteration as well, despite a necessary increase of the catalytic loading to 5 mol% (see the SI for more details). Tryptophol **27a** was also well converted to **27b**, even if some deuterium labeling was lost during the purification process. Substrates embedding ester functions such as **28a** and **29a** were labeled with 30% rate. Finally, tryptamine **30a** was submitted to the reaction conditions and led to the corresponding product **30b** with 31% labeling at C2 and, unexpectedly, 38% deuterium incorporation at the C4 position of the indole. It is of note that compounds **31**, incorporating aldehyde function at C3 of the indole ring did not engage in the reaction and remained intact. Finally, 3-arylindoles, known for their antibacterial or antifungal activities,[21] engaged in the reaction and led to the isolation of **32-34-b**. The deuteration rate proved excellent with phenyl or *p*-fluorophenyl groups (99% D, 32-33b), while a methoxy group on the aryl led t a decrease in the labeling rate (40% D, 34b).

We next hypothesized that heterocycles with similar electronic features to those of indoles may also be labeled via similar mechanistic pathways. Indeed, 7-azaindole **35a** reacted as well and furnished **35b** in 98% yield and 94% deuteration rate.

Scheme 2: C3- and C2-regioselective Au(I)-catalyzed deuterium labeling of indole derivatives and bioactive compounds



3,5-Dimethylpyrrole **36a** was labeled on both C2 and C4 positions with high deuterium incorporation (96%). Similarly, benzofurane provided **37b** with 46% deuteration rate. Unfortunately, **36b** and **37b** proved difficult to purify and we were unable to isolate them. This provided at least a proof of concept for the labeling of pyrroles and benzofurane.

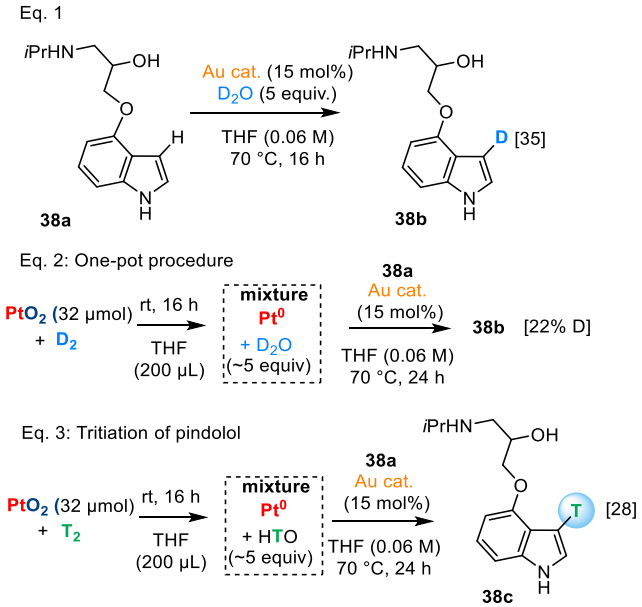
Bioactive compounds embedding different heterocycles were next engaged in the reaction. We first used pindolol **38a** containing both amine and alcohol functional groups. This compound is known for its β-blocker and anti-hypertensive properties and its used as a drug to treat depression.[22] Solubility issues led us to reconsider the solvent system (see the supporting information) and introduce $CDCl_3$

to the solvent mixture. Deuterated pindolol **38b** was obtained in 55% yield and 90% deuteration rate after a 3 days reaction at 70 °C. For comparison purpose, a reaction performed with 50 mol% of TFA as catalyst did not provide any desired product, while an excess (3 equiv) led to a loss of the regioselectivity. Atevirdine **39a**[23] is an anti-HIV compound derived from Delavirdine,[24] used in the treatment of HIV. This compound presents a piperazinamide group and a 3-aminopyridine moiety that represent a challenge for established labelling methods, as well as potentially for our method by reducing the catalytic activity of the gold complex by coordination of both the pyridine and the amines.

Despite these expected difficulties, compound **39b** was obtained in 84% yield and 88% deuteration rate, using toluene instead of chloroform in the solvent system. NMK-BH3 and NMK-BH4 **40a** and **41a** are bis(indolyl)-hydrazide-hydrazone derivatives that have been studied as tubulin-assembly inhibitors, potentially useful in the treatment of lung cancer.[25] Their structure represent a serious challenge for labeling, because of their electron-depleted indole rings and the presence of both C3 and C2 available indole positions. Nevertheless, we obtained **40b** and **41b** with 15-19% deuterium labeling rates, in a full regioselectivity towards the C3 positions. Moderate yields were obtained as a result of purification issues but this achievement is still considerable considering the structure of these compounds and the late stage isotope exchange. Finally, tolmetin **42a**, a pyrrole nonsteroidal anti-inflammatory drug,[26] was selectively mono-deuterated (80%D) on the more electron-rich position. Similarly, ketorolac **43a**, used as a drug for the treatment of pain,[27] incorporated 92% deuterium regioselectively on the pyrrole ring. Finally, thiophene drug suprofen **44a**, used as a topical ophthalmic solution,[28] was deuterated selectively with 30% deuterium incorporation. Not only these last results extended the scope of this gold-catalyzed hydrogen isotope exchange method to pyrroles and thiophene, but also demonstrated exquisite regioselectivity and compatibility with carboxylic acids and ketone functions.

We subsequently explored the possibility to apply this gold-catalyzed methodology to hydrogen tritium exchange, utilizing tritiated water (HTO) as the isotopic source. While the latter is not the most convenient source of tritium (T_2 being clearly preferable), the functional group tolerance and regioselectivity of isotope incorporation demonstrated previously for Au catalyzed deuteration are valuable for synthesizing tritiated analogs of complex pharmaceuticals.Our initial efforts focused on optimizing the reaction conditions for the gold-catalyzed hydrogen-deuterium exchange of pindolol **38a** to minimize the utilization of the isotopic source (first using indole then using pindolol, see the SI page S15). We achieved reasonable deuterium incorporation (0.35 D) by using 13 µmol of pindolol, a catalytic loading of 12.5%, and only 5 equivalents of deuterium oxide (approximately 1.15 µl) in THF (Scheme 3, Eq. 1). Subsequently, this reaction was conducted by generating deuterated water (HDO) through the reduction of platinum oxide under a deuterium atmosphere in tetrahydrofuran (THF), followed by the addition of the gold catalyst and pindolol in the same reaction vessel.[29] This resulted in a 22% isotopic enrichment at the C3 position of the indole substructure of pindolol **38b** (Eq. 2). This one-pot procedure was envisioned not only to simplify the handling of tritiated water (highly contaminant) but also to minimize the erosion of isotopic enrichment of HTO due to tritium-hydrogen exchange during the traditionally conducted filtration of platinum (0) particles formed within the tritiated water production in small scale. Finally, this method was successfully applied the radiosynthesis (using 5 Ci of tritium gas to generate HTO) of ^{3}H-pindolol **38c**, obtained with high radiochemical purity after HPLC purification and a molar activity of 310 GBq.mmol^{-1}. Although the molar activity achieved may be considered as moderate, it is nonetheless adequate to envision the utilization of this tritiated product for biodistribution or pharmacokinetic experiments within ADME studies.

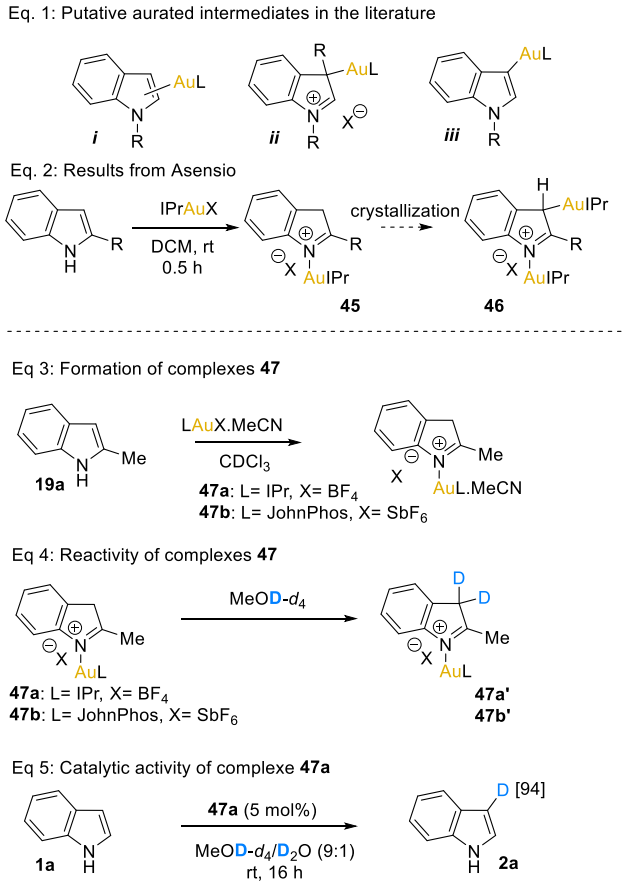
Scheme 3: Towards a method for the regioselective tritiation of indoles



The mechanism of this reaction is intriguing. In our recent work on the enantioselective Au(I)-catalyzed Pictet-Spengler reactions, we reported the intermediacy of such C2-tryptaminyl-gold(I) species, confirmed by DFT calculations.[17b] The Au(I) catalyzed functionalization of indoles is an active field of study,[30] however, irrefutable experimental evidence that indolyl-gold(I) intermediates may form from coordination of indoles are scarce. Examples where the indolyl-gold(I) species is formed from chemical reactions, most often under harsh conditions, have been reported occasionnaly.[31] The direct, unbiased, auration

from unfunctionnalized indoles is however less understood. Both Arcadi[32] and Carbery[33] claimed the intermediacy of C3-indolyl-gold(III) species by reaction of indoles with $AuCl_3$, but the actual species are not documented. Unsworth hypothesized a coordination of indoles to Au(I) complexes and observed by ^{31}P NMR a concentration-dependent chemical shift, without further characterization of potential complexes ***i*** (Scheme 4, eq. 1).[34] Liu also made the hypothesis that indoles intermediate may coordinate a Au(I) complex and form an indolyl-gold(I) species ***ii.*** [35] More importantly, Shi and Tang hypothesized the formation of indolyl intermediates ***iii*** with a C3-Au bond,[18] and indirectly evidenced this hypothesis by exposure to a deurated solvent under harsh conditions, resulting in a low deuteration incorporation though. Asensio reported the most tangible results showing that C2-substituted indoles lead, upon coordination to Au(I) complex to 3*H*-indolyl-σ-*N*-bonded complexes **45**,[36] a phenomenon that was already observed in rhenium, iridium or platinum η^1-complexes of C3-substituted indoles (Scheme 4, eq. 2).[37] These complexes **45** could not be crystallized but instead, crystals of a diaurated species **46** were obtained.

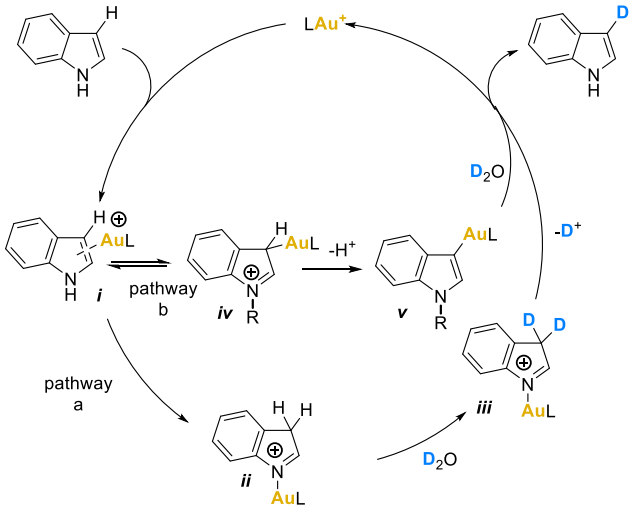
Scheme 4: Known auration of indoles and mechanistic experiments



We reproduced results from Asensio starting from 2-methyl indole **19a** and stoichiometric amounts of $IPrAuBF_4$.MeCN, indeed resulting in the quantitative formation of complex **47a** that could be characterized by NMR techniques (Scheme 4, eq. 3). The structure was unambiguously confirmed in ^{13}C NMR with the signal of the C3 atom which is largely shifted upfield (δ=45.6 ppm) as a CH_2, identified at δ= 3.93 ppm in ^1H NMR. The same experiment performed with JohnPhos ligand complex afforded the complex **47b**, obtained *via* the same coordination pattern. The stability of complexes **47a,b** (both with IPr and JohnPhos ligands, respectively) towards CD_3OD was next studied (Scheme 4, eq. 4). We found that the methylene group was deuterated on both complexes when exposed to protic deuterated solvents. Finally, a catalytic quantity of complexes **47a** was used to attempt to catalyze the deuteration of indole **1a**, in order to determine whether complexes **47** are catalytically active (Scheme 4, eq. 5). Indole was successfully labeled at C3, with 94% deuteration rate. This indicates that both complexes **47** are catalytically active.

On the basis of all information gathered, we pictured a plausible mechanism (Scheme 5). Coordination of the Au(I) complex to indole generates complex complexes as η^2 (***i***) then σ-(*N*)-coordinated form (***ii***), that will evolve to aurated intermediate ***iii*** (pathway a). The latter could then be labeled by hydrogen/deuterium exchange as shown in Scheme 4, eq. 4, followed by elimination and deauration. This pathway **a** however does not account for the successful labeling of *N*-substituted indoles (such as **17a** and **18a**) for which intermediacy of ***ii*** is not anymore an option. These reactions could however be explained by a similar mechanism initiated by η^1-coordination at C3 of the indole ring (intermediate **iv**), elimination (**v**) and deuterodeauration (pathway b). A similar mechanism may be drawn for the deuteration at position 2 of C3-substituted indoles with η^1-coordination at C2 of the indole ring. Noteworthy, the unique mechanism of these transformations with Au(I) catalysts differs totally from most known deuteration reactions reported on indoles, which offers unique opportunities to target selectivity.

Scheme 5: Mechanistic hypothesis



In conclusion, we have shown that indoles can be labeled with deuterium in high regioselectivity at the position 3 or 2 of the ring. High deuteration rates were obtained and the gold-catalyzed reaction proved compatible with a large number of chemical functions, as illustrated by the labeling of densely functionalized bioactive compounds. The reaction conditions compare very favorably with most known methods, in mild conditions, high regioselectivity and easily accessible and cheap deuterium source. Extension of the method to the tritiation of indoles was demonstrated using pindolol as a representative example.

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