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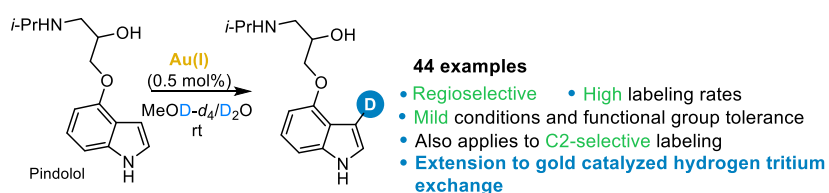
Au(I)-catalyzed Regioselective Hydrogen Isotope Labeling of Indoles

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Supporting Information Placeholder



ABSTRACT: The gold(I)-catalyzed hydrogen isotope exchange reaction on indoles and related heterocycles is described, under mild conditions and low catalyst loadings, using CD₃OD and D₂O as readily available deuterium sources. C3-unsubstituted indoles are labeled at the C3 position with exquisite regioselectivity, while C3-substituted indoles are labeled at the C2 position. The method is also applicable to the regioselective tritiation of indoles. Mechanistic studies revealed the involvement of auroated indoles as key intermediates.

Synthetic access to complex molecules labeled with hydrogen isotopes¹ is of paramount importance across various scientific domains, from chemistry to drug development and materials science.² For example, thanks to the deuterium kinetic primary isotope effect,³ incorporating deuterium into active pharmaceutical ingredients has the potential to enhance their safety, efficacy, and/or tolerability.⁴ 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.^{2a, 5} By virtue of their importance, indole derivatives have been largely studied in the context of hydrogen isotope labeling. A large number of transition metal-catalyzed methods targeting C3-regioselective labeling have been reported various complexes⁶ (Scheme 1a). Most methods, however, proceed under harsh conditions (>90 °C), use high pressure of D₂ and are endowed with poor regioselectivities. Strategies for the labelling of the C2 position are very efficient but rely mostly on CH-activation strategies,^{6b, 7} a biased strategy which imposes a directing group on the indole nitrogen and either the use of D₂ as the deuterium source or harsh conditions. Highly acidic conditions may also be used generally leading to multiple site deuterium incorporation and potential chemoselectivity issues under harsh conditions.^{6f, 8}

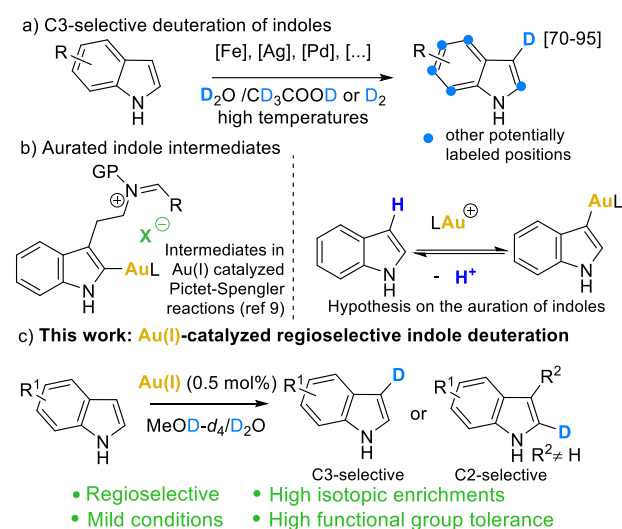
Recently, we developed Au(I)-catalyzed Pictet-Spengler reactions⁹ involving auroated indole intermediates (Scheme 1b). We became interested in the fundamental issue of the auration of indoles and hypothesized that indoles could act as ligands for Au(I) and be metalated at their C3 position. Interestingly, this was also earlier reported

by Shi and Tang,¹⁰ who invoked similar species and used deutero-deauration as a means to support their hypothesis.

In this paper, we report the regioselective deuteration of indole derivatives using Au(I) catalysts under mild conditions with a large tolerance of chemical functions (Scheme 1c). The method was applied to a number of indole derivatives, including bioactive drugs (44 examples). It is finally demonstrated that the method can be applied to the tritiation of indoles using a similar strategy.

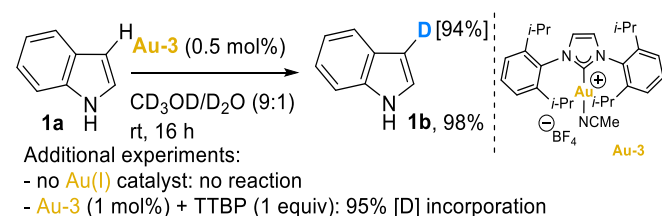
We initiated this study by optimizing the regioselective C3-deuteration of indole **1a** (Scheme 2, see the SI for full optimization).

Scheme 1: Context of this work



First tests performed using 5 mol% of $\text{Ph}_3\text{PAuNTf}_2$ **Au-1** and $[\text{JohnPhosAu}(\text{MeCN})]\text{SbF}_6$ **Au-2** and CD_3OD and D_2O as isotopic sources (9:1 ratio) led to virtually total conversions in a 2 h timespan. Further optimization led to the use of $[\text{IPrAu}(\text{MeCN})]\text{BF}_4$ **Au-3** (0.5 mol%) as catalyst, which furnished **1b** in 98% yield with 94% deuterium labelling at C3. Control experiments assessed the role of the Au(I) complex since no reaction occurred in the absence of the Au(I) complex. Moreover, the combination of the Au(I) complex with a sterically hindered base used as a proton scavenger supports that the Au(I) complex is the actual catalyst.

Scheme 2. Optimization of the reaction.



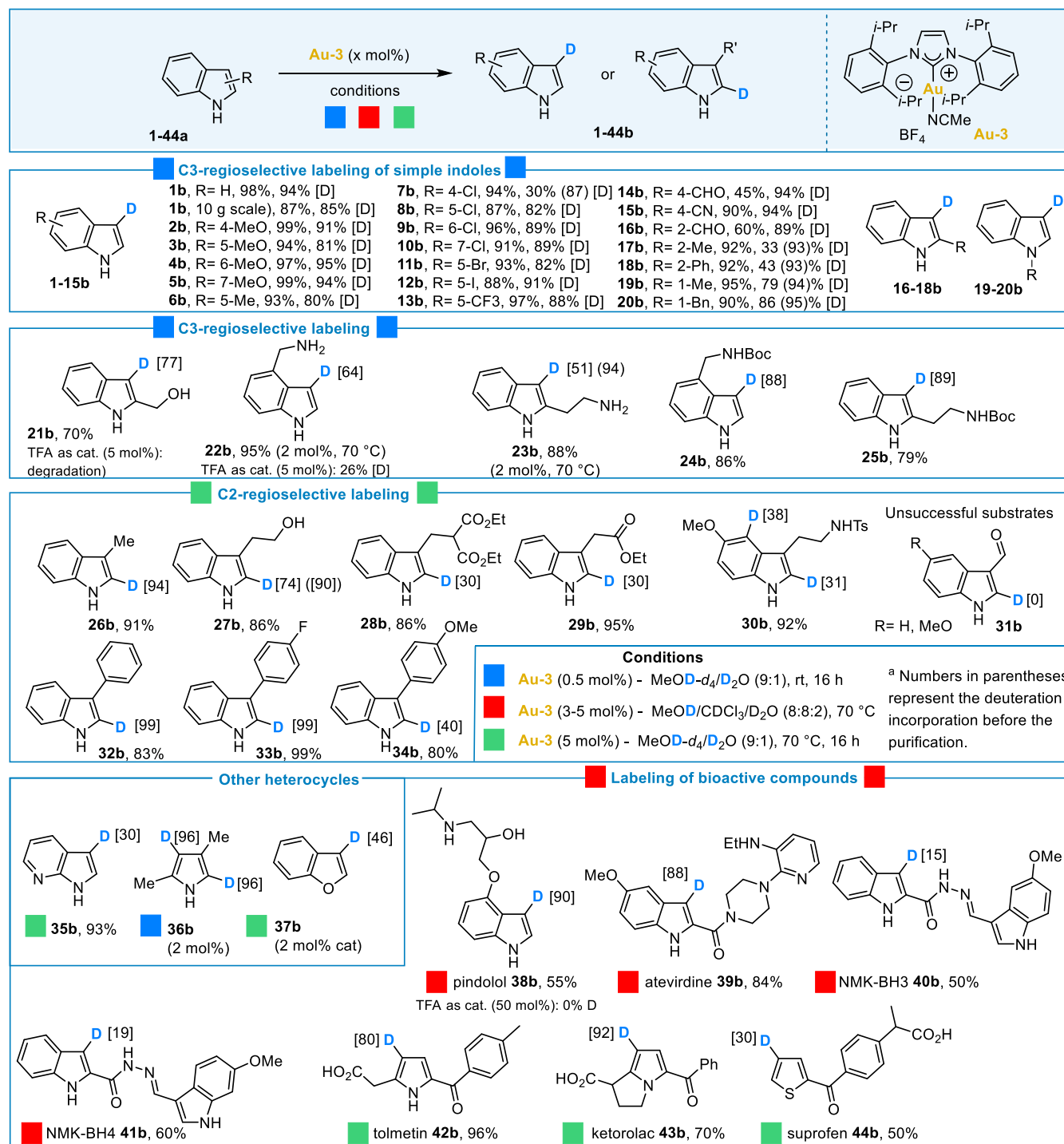
With these conditions in hand, we studied the scope of commercially available indoles **1a-20a** at room temperature using 0.5 mol% catalyst (Scheme 3). This screening (20 compounds) showed that the reaction is very versatile, fully C3-regioselective and tolerates EWGs and EDGs at most positions of the indole ring. Substituents at positions 1 (**19b**, **20b**) and 2 (**17b-18b**) led to high deuteration incorporation, which are however partially lost during the purification. This first set of results demonstrates the compatibility of this method with most of the electronically diverse chemical functions, including on bigger scale (**1b**, 10 mmol scale, 84% [D] incorporation). 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,¹¹ 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. Amines **22a** and **23a** also participated in the reaction delivering reasonable deuteration incorporation. Again, a 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 investigated 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**. 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. Aldehyde **31** did not engage in the reaction and remained intact. Finally, 3-arylindoles, known for their antibacterial or antifungal activities,¹² engaged in the reaction and led to the isolation of **32-34b**. The deuteration incorporation, however, decreased with a methoxy group on the aryl (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 incorporation. 3,5-Dimethylpyrrole **36a** was labeled on both C2 and C4 positions (96% D). Similarly, benzofuran provided **37b** with 46% deuteration incorporation. 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 benzofuran. Bioactive compounds¹³ embedding different heterocycles were next engaged in the reaction. We first used β -blocker and anti-hypertensive^{13a} pindolol **38a** containing both amine and alcohol functional groups. 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 incorporation after a 3 days reaction at 70 °C. For comparison purposes, a reaction performed with 50 mol% of TFA as catalyst did not provide any desired product, while 3 equiv TFA led to a loss of the regioselectivity.

Scheme 3: C3- and C2-regioselective Au(I)-catalyzed deuterium labeling of indole derivatives and bioactive compounds*

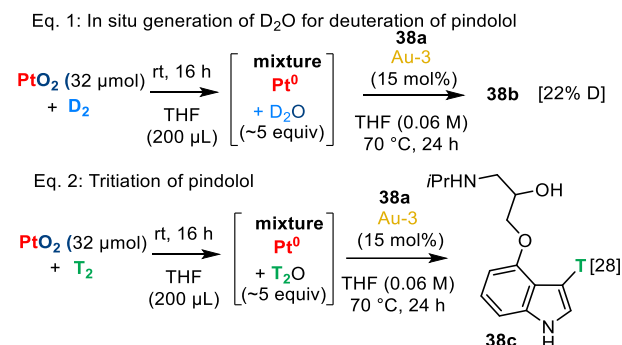


The method was applied to challenging anti-HIV compound Atevirdine **39a**,^{13b} which led to **39b** in 84% yield and 88% deuteration incorporation. Finally, bis(indolyl)-hydrazide-hydrazones tubulin-assembly inhibitors^{13c} NMK-BH3 and NMK-BH4 **40a** and **41a** have been labeled with 15-19% deuterium labeling rates, with regioselectivity towards the C3 positions. Tolmetin **42a**, a pyrrole nonsteroidal anti-inflammatory drug,^{13d} was selectively mono-deuterated (80% D) on the more electron-rich position. Similarly, ketorolac **43a**, used as a drug for the treatment of pain,^{13e} incorporated 92% deuterium regioselectively on the pyrrole ring. Finally, thiophene drug suprofen **44a**, used as a topical ophthalmic solution,^{13f, 13g} was

deuterated selectively with 30% deuteration incorporation. Not only did these last results extend 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 super heavy water (HTO) as the isotopic source (Scheme 4). After optimization (see the SI), deuterated water (HDO) was first generated *in situ* through the reduction of platinum oxide in THF under D₂ atmosphere in tetrahydrofuran (THF), followed by the addition of the gold catalyst and pindolol in

the same reaction vessel.¹⁴ This resulted in a 22% isotopic enrichment at the C3 position of pindolol **38b** (Eq. 1). The method was then successfully applied to the radiosynthesis (using 5 Ci of tritium gas to generate HTO) of ³H-pindolol **38c** (Eq. 2), obtained with high radiochemical purity after HPLC purification and a molar activity of 333 GBq.mol⁻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.

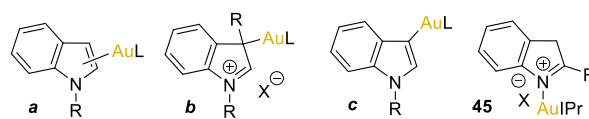
Scheme 4: Towards a method for the regioselective tritiation of pindolol



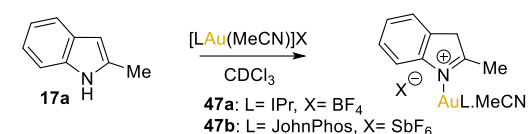
The mechanism of this reaction is intriguing. The Au(I) catalyzed functionalization of indoles is an active field of study.¹⁵ However, irrefutable experimental evidence that indolyl-gold(I) intermediates may form from coordination of indoles are scarce (Scheme 5, eq. 1).¹⁶ The direct, unbiased, auration from unfunctionalized indoles is poorly understood.¹⁷ Intermediates such as **a**^{17c} or **b**^{17d} have been suggested but lack direct evidence. Shi and Tang hypothesized the formation of indolyl intermediates **c** with a C3-Au bond,¹⁰ indirectly evidenced by poorly efficient deutero-deauration. 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**,¹⁸ a phenomenon that was already observed in rhenium, iridium or platinum η¹-complexes of C3-substituted indoles.¹⁹ We prepared **47a** by reacting **17a** with stoichiometric amounts of [IPrAu(MeCN)]BF₄ as reported¹⁸ (eq. 2). The structure was unambiguously confirmed in ¹³C NMR with the signal of the C3 atom which is largely shifted upfield (δ=45.6 ppm) as a CH₂, identified at δ= 3.93 ppm in ¹H NMR. The same experiment performed with JohnPhos ligand complex afforded the similarly coordinated complex **47b**. The stability of complexes **47a,b** towards CD₃OD was next studied. We found that the methylene group was deuterated on both complexes when exposed to protic deuterated solvents (eq. 3). Finally, a catalytic quantity of complex **47a** was used to catalyze the deuteration of indole **1a**, in order to determine whether complexes **47** are catalytically active (eq. 4). Indole was successfully labeled at C3, with 94% deuteration incorporation. This indicates that complexes **47** are catalytically active.

Scheme 5: Known auration of indoles, mechanistic experiments and catalytic cycle

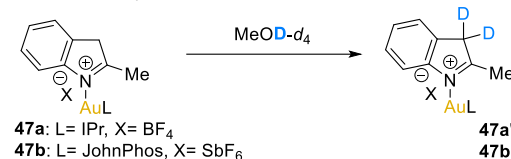
Eq. 1: Putative aurred intermediates in the literature



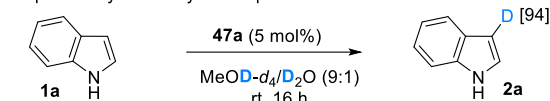
Eq 2: Formation of complexes **47**



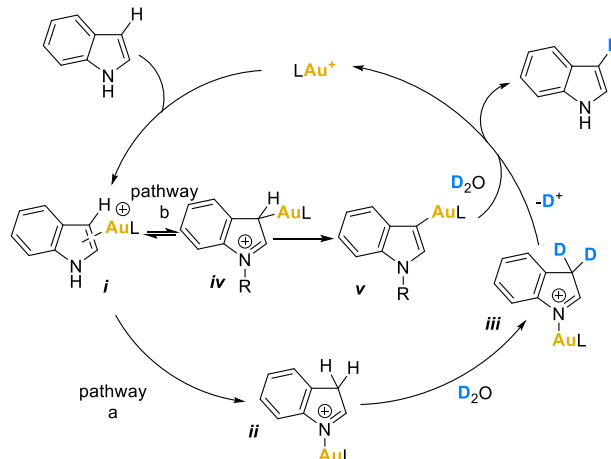
Eq 3: Reactivity of complexes **47**



Eq 4: Catalytic activity of complex **47a**



Eq 5: Catalytic cycle



On the basis of all information gathered, we pictured a plausible mechanism (eq. 5).²⁰ Coordination of the Au(I) complex to indole generates species as η² (**i**) then σ-*N*-coordinated form (**ii**), that will evolve to aurred intermediate **iii** (pathway a).²¹ The latter could then be labeled by hydrogen/deuterium exchange followed by elimination and deauration. This pathway **a**, however, does not account for the successful labeling of *N*-substituted indoles (such as **19a** and **20a**) for which intermediacy of **ii** is no longer an option. These reactions could however be explained by a similar mechanism initiated by η¹-coordination at C3 of the indole ring (intermediate **iv**), aromatization of **iv** to aurred species **v**, followed by deutero-deauration. A similar mechanism may be drawn for the deuteration at position 2 of C3-substituted indoles with η¹-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.

In conclusion, we have shown the Au(I)-catalyzed regioselective deuteration of indoles. High deuteration incorporations were obtained and the method showed broad scope, 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.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information .

Supporting Information

Details of the experimental procedures, ¹H and ¹³C NMR spectra. The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

All authors have given approval to the final version of the manuscript.

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20. See the Supporting Information for a clearer overview of all mechanistic pathways.

21. The deuteration could also occur during the two-steps formation of intermediate ii from intermediate i by simple N-H to N-D exchange. See, for instance: Greb, L.; Tamke, S.; Paradies, J., Catalytic metal-free Si–N cross-dehydrocoupling. *Chem. Commun.* **2014**, *50*, 2318.