Undirected, Pd-catalyzed deuteration of indoles with programmable regioselectivity.

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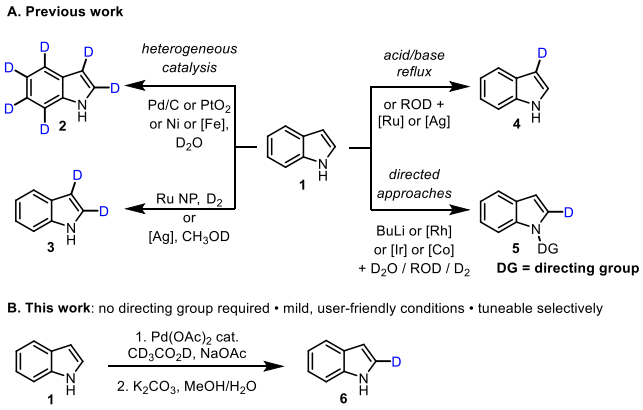
Deuteration, isotope labeling, palladium catalysis, indole, organic synthesis.

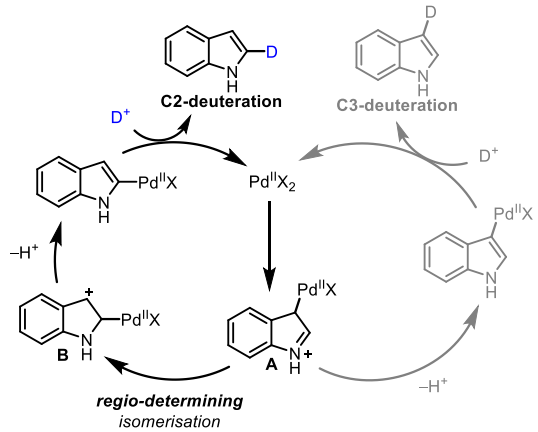
ABSTRACT: Methods for programmable, regioselective deuterium-incorporation into drug-like molecules have become extremely valuable due to the commercial and biological importance of deuterated compounds. Selective C2-deuteration of indoles currently requires the installation of directing groups on nitrogen. Herein, we report the directing group free, $Pd(OAc)_2$ catalyzed, C2-selective deuteration of indoles with CD_3CO_2D in high yields and selectivity. Modification of the reaction conditions also allows selective access to C3- as well as C2-and-C3-deuterated indoles, providing a user-friendly, programmable deuteration strategy.

Deuteration is a crucial tool for drug ADME studies and biomolecular analysis techniques.[1] It can improve the metabolic stability, pharmacokinetics and toxicity profile of drugs.[2,3] The landmark ruling by the U.S. Food and Drug Administration (FDA) classing deuterated drugs as new chemical entities (NCEs) has also added significant commercial importance to these compounds.[4] The development of new methods to selectively incorporate deuterium into drug molecules has therefore become an important field of study. A substrate class of particular interest in this area are nitrogen heterocycles – including indoles – due to their importance in many small-molecule drugs.[5–7]



Scheme 1. Regioselectivity in indole-deuteration reactions.

Given the importance of deuterated indoles, a significant amount of work has gone into developing strategies for their deuteration (Scheme 1A):[8] Heterogeneous catalysis generally affords global deuteration of all free positions (**2**);[9–12] more recently a metal-free approach has also been reported.[13] Deuteration on the pyrrole moiety (C2 and C3, **3**) has been achieved with ruthenium nanoparticles,[14] rhodium,[15] or under homogeneous Ag_2CO_3 catalysis.[16] Under acid/base-mediated conditions, selective deuterium-incorporation at C3 is controlled by the molecule's intrinsic reactivity (**4**).[17–20] Similar reactivity has been achieved using organocatalysts,[21] $Ru_3(CO)_{12}$,[22] or AgOTf.[23] Selective deuteration at C2 can currently only be achieved using directed approaches (**5**): *ortho*-lithiation[17] or transition-metal catalyzed methods requiring a directing group on the indole nitrogen.[24–26] Directing group removal is not always straightforward,[27] and – crucially – can cause isotopic dilution if strong acidic or basic conditions are required.[26,28] Therefore, a directing group free method for C2-deuteration would be highly beneficial. Herein, we report a directing group free, palladium-catalyzed C2-selective deuteration, using an air-stable, readily available palladium catalyst and a user-friendly source of deuterium (Fig. 1B).

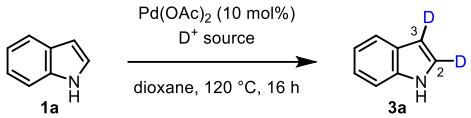


Scheme 2. Proposed strategy for C2-selective deuteration (left) and competing C3-deuteration (right).

Reaction Development

We hypothesized that homogeneous palladium catalysis could provide directing group free deuteration with high levels

of C2-selectivity under mild conditions if competing C3-deuteration could be suppressed (Scheme 2).[1,29–31] We aimed to achieve this by fine-tuning of the reaction pH to favor migration of palladium from C3 (complex **A** in Scheme 2) to C2 (complex **B**) in the carbopalladated intermediate prior to rearomatization, as reported by Gaunt *et al.*[32]

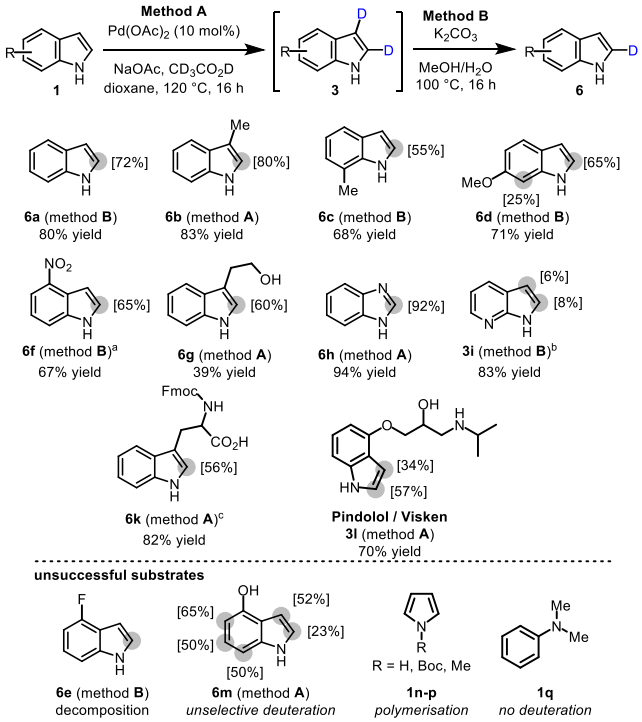


Entry	D^+ Source	Additive	C2-deuteration [%]	C3-deuteration [%]
1	CD_3CO_2D (1.14 mL)	–	40	52
2	CD_3CO_2D (1.14 mL)	NaOAc (1.5 equiv)	81	72
3	CD_3CO_2D (0.6 mL)	NaOAc (1.5 equiv)	80	70
4	CD_3CO_2D (0.3 mL)	NaOAc (1.5 equiv)	70	25
5	CH_3CO_2D (0.6 mL)	NaOAc (1.5 equiv)	37	65
6	D_2O (1 mL)	NaOAc (1.5 equiv)	41	84
7	CD_3CO_2D (0.6 mL)	NaOAc (15 equiv)	80	0
8[a]	**CD_3CO_2D (0.6 mL)**	**NaOAc (1.5 equiv), then: K_2CO_3 (1 equiv), MeOH/H_2O**	**81**	**0**
9[b]	CD_3CO_2D (0.6 mL)	NaOAc (1.5 equiv)	0	50

Table 1. Reaction Optimization.

Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), deuterium source, 1,4-dioxane (1.5 mL), NaOAc (1.5 equiv), 120 °C, 16 h. Deuterium incorporation determined by ^{1}H NMR (see ESI). [a] Reaction conditions: (i) **1a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), deuterium source, 1,4-dioxane (1.5 mL), NaOAc (1.5 equiv), 120 °C, 16 h; (ii) K_2CO_3 (1 equiv.), MeOH/H_2O (0.5 mL / 1 mL), 100 °C, 12 h. [b] No Pd catalyst.

Initially, both C2- and C3-deuteration were observed: when indole was reacted in the presence of 10 mol% $Pd(OAc)_2$ in an anhydrous dioxane/CD_3CO_2D solvent mixture at 120 °C for 16 h, we observed 40% C2-deuteration and 52% C3-deuteration by ^{1}H NMR, with no hydrogen isotope exchange at any other position (Table 1, entry 1). Deuterium incorporation increased at both positions in the presence of NaOAc to 81% (C2) and 72% (C3) respectively (entry 2). Reducing the amount of deuterated acetic acid (entries 3–4) only had a small effect on C2-deuteration, but saw a significant reduction of the undesired deuterium incorporation at the C3 position. The use of CH_3CO_2D significantly reduced deuteration at C2 compared with CD_3CO_2D (entry 5 cf. entry 3) – presumably due to proton exchange between the methyl and hydroxyl positions in acetic acid. Low C2-deuteration was also observed with D_2O (entry 6). Lower reaction temperatures, alternative solvents and a reduced reaction time all had a negative effect on the reaction outcome (see ESI, Table S2). Given the effect of CD_3CO_2D concentration on C2/C3-deuteration ratio (entries 2–4), and the mechanistic hypothesis in Scheme 2, we wondered if careful balancing of pH would allow for selective deuteration on the C2 position only. Indeed, addition of a large excess of NaOAc (15 equiv.) afforded complete protonation at C3 while deuterium incorporation at C2 remained high (80%, entry 7). Due to the impracticalities of using a large excess of base on scale, we wanted to reduce this amount. Indeed, further optimisation revealed that a similar result could be obtained with a telescoped approach using milder conditions: indole was reacted with 10 mol% $Pd(OAc)_2$ in anhydrous CD_3CO_2D/dioxane at 120 °C for 16 h. After filtration through silica and removal of solvents *in vacuo*, 1 equiv. K_2CO_3 and protic solvents (MeOH/H_2O) were added and reacted for a further 16 h (entry 8), resulting in 81% deuterium incorporation at C2 (with no isotopic labelling at C3). A control reaction confirmed that the palladium catalyst was necessary for C2-deuteration: in the absence of $Pd(OAc)_2$, only C3-deuteration was observed (entry 9), as expected from indole's intrinsic acid/base reactivity.

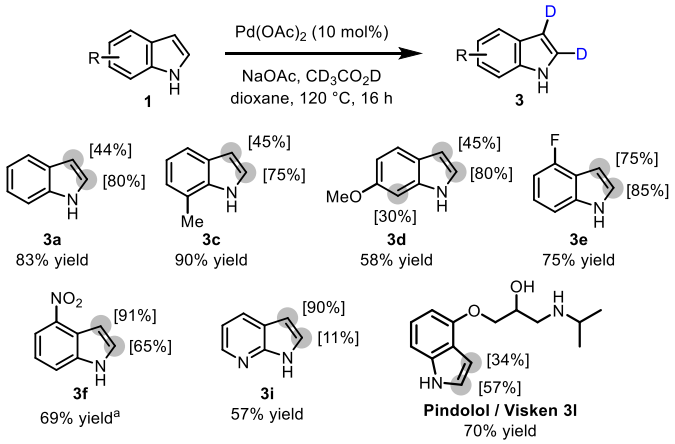


Scheme 3. Selective C2-deuteration of indoles.

Conditions Method A: **1** (0.4 mmol), $Pd(OAc)_2$ (10 mol%), NaOAc (0.6 mmol), CD_3CO_2D/dioxane (1.2 mL/3 mL), 120 °C, 16 h. Method B: (i) **1** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), NaOAc (0.3 mmol), CD_3CO_2D/dioxane (0.6 mL/1.5 mL), 120 °C, 16 h. (ii) K_2CO_3 (0.2 mmol), MeOH/H_2O (1.2 mL / 0.4 mL), 100 °C, 12 h. Grey circles show the labelling positions, with values in square brackets denoting isotope incorporation, as determined by ^{1}H NMR. Yields are of isolated products. [a] Step 1: reaction time = 32 h. [b] Step 2 was carried out twice. [c] From Fmoc-Trp(**Boc**)-OH. Reaction proceeded with deprotection of *N*-Boc group.

With optimized conditions in hand, we explored the substrate scope of indoles amenable to this selective C2-deuteration methodology (Scheme 3). Indoles with no substituent on the pyrrole ring were submitted to palladium-catalyzed deuteration, followed by reaction with K_2CO_3 in MeOH/H_2O after purification (method B), while indoles with a substituent on C3 did not require this second step (method A). Consistently high deuterium incorporation at C2 was achieved in good yields for unsubstituted indole (**6a**), as well as indoles bearing electron-donating methyl and methoxy substituents (**6b**–**6d**). Some unselective background deuteration was observed for more electron-rich indoles: 6-methoxyindole (**6d**) underwent 17% C7-deuteration, while 4-hydroxyindole showed unselective deuteration on all

free positions (**6m**). Similarly, the methodology could not be extended to highly electron-rich pyrrole **1n-p** (with or without protecting groups on nitrogen) which polymerized under the reaction conditions, or other electron-rich aromatics such as *N*,*N*-dimethylaniline **1q**, which was recovered without any deuteration. For electron-poor 4-nitroindole, lower levels of deuterium incorporation were observed (**6f**: 32%), but this result could be improved (to 68%) by increasing the reaction time of step 1 to 32 h. To the best of our knowledge, there are no other examples of selective C2-deuteration of electron-poor 4-nitroindole in the literature. Initial screening results for 4-fluoroindole looked promising (79% deuterium incorporation), but the compound decomposed in our hands. Free hydroxyl groups were tolerated, albeit with lower levels of deuterium incorporation (**6g**: 60%) and yields (39%). Benzimidazole showed high deuterium incorporation at C2 under these conditions (**6h**: 95%). However, this result is comparable to results obtained under palladium-free conditions (see Scheme 5 below), suggesting that simple acid-mediated H/D exchange may be taking place. For 7-azaindole, C2 incorporation was low, possibly due to coordination of the palladium catalyst to the nitrogen heterocycle or protonation: **3i** was formed with only 9% deuterium incorporation at C2 and 47% at C3, with C3-deuteration reduced to 6% when submitted to K_2CO_3 twice. To further demonstrate the utility of our methodology for late-stage functionalization, we submitted two high-value products to our deuteration conditions. The Boc/Fmoc-protected amino acid tryptophan showed 54% deuteration at C2 (**6k**) with concomitant Boc deprotection, a promising result for the use of this methodology on indole alkaloid natural products. Efficient C2-and-C3-deuteration of the clinically approved beta blocker pindolol/Visken[33] was achieved (**3l**: 28%), however no reduction of C3 deuteration was observed after treatment with K_2CO_3, even when 3 equivalents of the base were used.



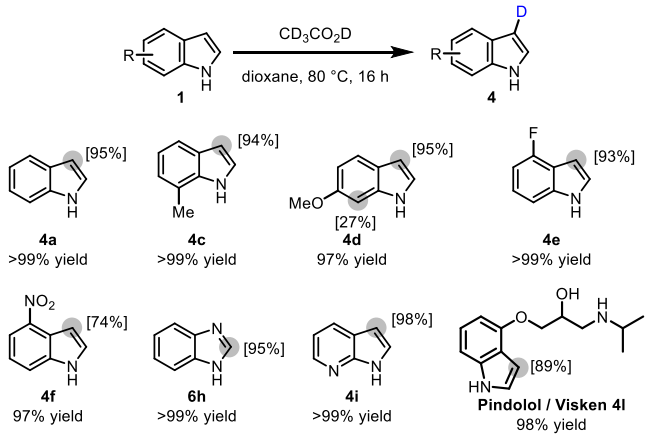
Scheme 4. Selective C2-and-C3-deuteration of indoles.

Reaction conditions: **1** (0.4 mmol), $Pd(OAc)_2$ (10 mol%), NaOAc (0.6 mmol), CD_3CO_2D (1.2 mL), 1,4-dioxane (3 mL), 120 °C, 16 h. Grey circles show the labelling positions, with values in square brackets denoting isotope incorporation, as determined by ^{1}H NMR. Yields and deuteration values are given for purified products; higher C3-deuteration levels were observed before purification by silica flash column chromatography (see ESI Table S4). [a] Reaction time = 36 h.

Many of the C2-and-C3 deuterated intermediates **2** have not previously been reported in the literature. If these compounds are desired, they can easily be isolated after the palladium-catalyzed deuteration step (Scheme 4). C3-Deuteration under these conditions was very high (75-95%) for all substrates, however purification by silica flash column chromatography was required which reduced the deuterium content at C3 to the values shown in Scheme 4 (e.g. from 70% to 46% for **2a**). This effect was less pronounced for electron-poor indoles **3e**, **3f** and **3i**. Deuteration of pindolol was achieved in 57% and 34% at C2 and C3, respectively. The use of anhydrous dioxane was of the utmost importance to avoid isotopic dilution at C3 (see ESI, Table S4). As discussed above, when submitted to K_2CO_3 in $MeOH/H_2O$, the isolated compounds **2** were cleanly transformed to the C2-deuterated compounds **6** shown in Scheme 3.

As seen in Table 1, no C2-deuteration occurs in the absence of palladium. Selectively C3-deuterated indoles can thus be obtained in quantitative yields by treatment with CD_3CO_2D under palladium-free conditions (Scheme 5). The products from this palladium-free method did not require purification by column chromatography, which resulted in high C3-deuteration values (75-98%) across the board.

With only small modifications to the reaction conditions, selective access to C2-, C3- or C2-and-C3-deuterated indoles has been achieved, providing a user-friendly, programmable scaffold for selective late-stage deuteration.



Scheme 5. Selective C3-deuteration of indoles.

Reaction conditions: **1** (0.4 mmol), CD_3CO_2D (1.2 mL), 1,4-dioxane (3 mL), 80 °C, 16 h. Grey circles show the labelling positions, with values in square brackets denoting isotope incorporation, as determined by ^{1}H NMR. Yields are given for isolated products.

Conclusion

We have described a regiodivergent methodology for the selective deuteration of indoles. Directing-group-free palladium-catalysis in the presence of deuterated acetic acid allows for hydrogen isotope exchange at the C2 and C3 position with high levels of deuterium incorporation. Reaction of these compounds with K_2CO_3 and a protic solvent selectively yields C2-deuterated products. Metal-free, acid-mediated deuteration instead affords selective isotope incorporation at C3 only. The methodology not only allows for selective, regiodivergent late-stage deuteration of drug targets (as demonstrated on pindolol/Visken). On a more fundamental level, the selectivity observed in the palladium-catalyzed transformations may guide the development of more complex C–H activation methodology on indoles and other nitrogen heterocycles.

ASSOCIATED CONTENT

Supporting Information.
Experimental procedures and characterization data for the new compounds reported herein are available free of charge.

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Author Contributions

LSF: conceptualisation, methodology, investigation, analysis, writing – original draft, review and editing; RMcN: methodology, investigation, analysis; AG: investigation, validation, analysis; MOD: conceptualisation, methodology, writing – original draft, review and editing.

ACKNOWLEDGMENTS

The authors would like to thank the University of Nottingham, NUI Galway, CÚRAM Centre for Research in Medical Devices, the Science Foundation Ireland (SFI) and the European Regional Development Fund for financial support (studentship to LSF, grant number 13/RC/2073 and 17/RCPhD/3480).

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