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Site-Selective Deuteration of *N*-Heterocycles via Iridium-Catalyzed Hydrogen Isotope Exchange

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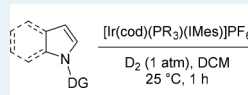
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S *Supporting Information*

ABSTRACT: The application of iridium(I) NHC/phosphine catalysts has delivered highly selective deuteration of indole, azaindole, and pyrrole *N*-heterocycles, which represent an important and relatively underexplored class of labeling substrates. Common *N*-protecting groups have been used to selectively direct C−H activation and can be removed under mild conditions with retention of the deuterium label. The method is exemplified by the labeling of the drug molecule sumatriptan. Complementary DFT studies have been conducted to facilitate the rationalization of the very good selectivity offered by the mild and convenient labeling process.

- 18 examples
- Up to 99% deuterium incorporation
- High regioselectivity
- Removable directing groups
- Drug molecule example
- Computational studies

KEYWORDS: *iridium, catalysis, indoles, isotope labeling, C−H activation, heterocycles*

INTRODUCTION

Isotopic labeling plays a key role in the drug discovery process by offering an unparalleled insight into the metabolic pathways of a potential drug molecule.[1] In recent years, hydrogen isotope exchange (HIE), via metal-catalyzed C−H activation, has been widely adopted as a key method for the synthesis of isotopically labeled compounds, allowing late-stage incorporation of deuterium or tritium (²H or ³H), thus avoiding the need for expensive, labeled starting materials.[2]

Until recently, the industry standard catalyst for HIE was an Ir(I) complex developed by Crabtree, **1**[3] (Figure 1); however, there are some drawbacks associated with its use. Specifically, complex **1** has limited functional group compatibility, is thermally unstable, and often has to be used in stoichiometric or superstoichiometric quantities. Studies within our laboratory have resulted in the development of a range of HIE catalysts of the type **2** (Figure 1), bearing a combination of bulky phosphine and *N*-heterocyclic carbene ligands.[4−13] These complexes exhibit high activity as deuteration catalysts under mild reaction conditions, displaying appreciable efficiency and selectivity at low catalyst loadings. Complexes **2** have been shown to effect HIE directed by a broad range of functional groups, including a number of heterocyclic systems.[4,7,9,11]
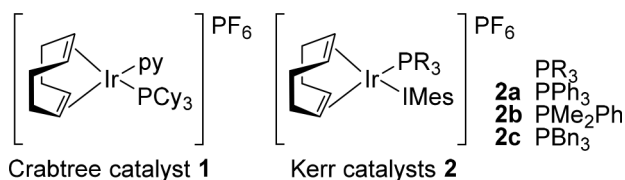
As privileged structures in both the pharmaceutical and agrochemical industries, indoles and related *N*-heterocycles have received increased attention over the last few decades, and the indole moiety now represents one of the most important scaffolds in modern drug discovery.[14] With regard to the HIE of indoles[15] via metal-catalyzed C−H activation,[16,17] previous work in this area has required elevated temperatures or resulted in either moderate levels of labeling or labeling at multiple sites.[18−20] Herein, we report our studies which further expand the scope of our HIE methodology to the indole and pyrrole classes of *N*-heterocycles, to deliver a mild, selective, and preparatively simple labeling method delivering high levels of deuterium incorporation (Figure 2).

Our previous work has shown that C−H activation with catalysts **2** usually occurs preferentially via a five-membered metallacyclic intermediate (5mmi) over a 6mmi.[4,7] We therefore proposed that common *N*-protecting groups could be used as functional handles to direct C−H activation selectively to the C2 position of indole (Figure 3).[21]

RESULTS AND DISCUSSION

To initiate our studies, indole was protected with a selection of amide and carbamate protecting groups, giving derivatives **3−6**. These substrates were evaluated under mild HIE conditions (1 atm of D₂, DCM, 25 °C, 1 h) with 5 mol % of our developed catalyst [(COD)Ir(IMes)(PPh₃)]PF₆ (**2a**)[4,7] and, for comparison, Crabtree's catalyst [(COD)Ir(py)(PCy₃)]PF₆ (**1**) (Table 1). With *N*-acetylindole (**3**), use of catalyst **2a** resulted in labeling exclusively at the C2 position, with an excellent 94%

Figure 1. Ir(I) catalysts for hydrogen isotope exchange.

You and Lan (2013)[18a]
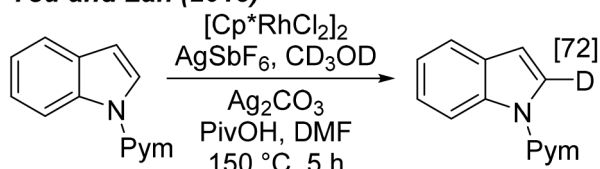
Chaudret and Rousseau (2014)[18b]
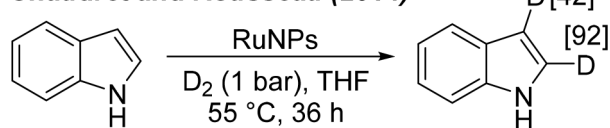
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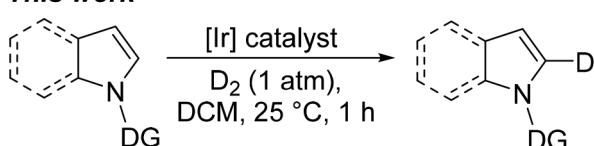
Figure 2. C−H activation and HIE on indole systems.

5mmi   **6mmi**
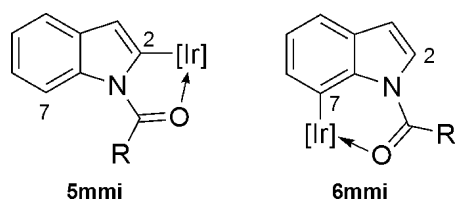
Figure 3. Metallacyclic intermediates formed during metal-catalyzed C−H activation.

Table 1. Deuteration of N-Acylindoles
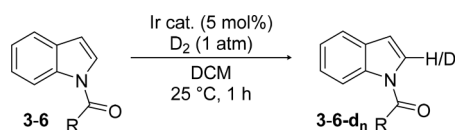
entry	substrate	R	catalyst	D (%)[a]
1	3	Me	2a	94
2	3	Me	1	22
3	4	tBu	2a	82
4	4	tBu	2b	93
5	4	tBu	1	18
6	5	OEt	2a	94
7	5	OEt	1	7
8	6	OtBu	2a	12
9	6	OtBu	2b	73
10	6	OtBu	1	5

[a]Deuterium incorporations are an average of two reaction runs.

deuterium incorporation (entry 1). In comparison, under the same conditions only 22% labeling was observed at C2 with catalyst **1** (entry 2). With the bulkier directing group in *N*-pivaloylindole (**4**), labeling with **2a** was reduced slightly to 82% (entry 3), but the high levels of labeling could be recovered by switching to catalyst **2b**, which bears a less sterically demanding phosphine ligand (entry 4). Again, however, Crabtree's catalyst **1** gave a low 18% incorporation (entry 5). A similar trend was observed with ethyl carbamate derivative **5**, with catalyst **2a** delivering 94% labeling (entry 6), in comparison to only 7% with **1** (entry 7). With the more hindered *tert*-butoxy carbamate

6, both **2a** and **1** gave only low levels of labeling (entries 8 and 10, respectively), but again, higher levels of deuterium

Table 2. Selective Deuteration of N-Benzoylindole
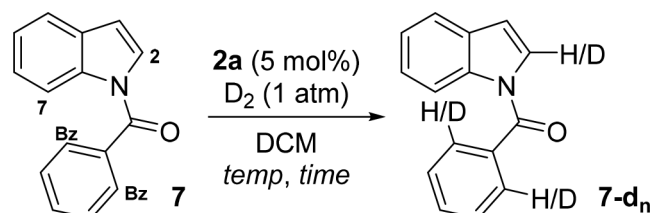
entry	temp (°C)	time (h)	C2 D (%)[a]	Bz D (%)[a]
1	25	1	73	2
2	25	24	90	6
3	40	1	80	4

[a]Deuterium incorporations are an average of two reaction runs.

incorporation could be restored by employing complex **2b** (entry 9).

We next investigated the preference for labeling the heterocycle versus a competing aromatic site. In this regard, *N*-benzoylindole (**7**) was selected as a suitable substrate since, in addition to the indole C2 position, the ortho positions of the benzoyl group can also be accessed via a 5mmi. When catalyst **2a** was employed in the labeling of **7**, rather remarkable selectivity was observed for labeling at the C2 position of the indole over the aromatic ortho sites in the benzoyl group (Table 2, entry 1). Through tuning of the reaction conditions, deuterium incorporation at C2 was increased to 80−90%, maintaining only minimal labeling on the benzoyl group (entries 2 and 3).

To understand the origins of this notable selectivity, the reaction was studied computationally, in order to establish the relative energies of binding and C−H activation for each of the possible labeling sites. In compounds containing more than one directing group, the binding energy for each group can play a key role in determining the selectivity.[13a] In *N*-benzoylindole **7**, however, all three potential labeling sites are accessed from the same directing group. In this case, the relative C−H activation energies for each bound conformer might be expected to influence the selectivity. Figure 4 shows the three potential energy surfaces (PESs) for C−H activation. At the initial binding phase, the conformer leading to C7 deuteration is the lowest in free energy (G_{rel} = 0.0 kcal mol^{-1}), albeit only marginally more stable than the conformer for benzoyl activation (+0.4 kcal mol^{-1}). In contrast, the conformer leading to activation of the C2 position is significantly destabilized (+4.5 kcal mol^{-1}). However, given that the C2 position is the preferred labeling site, these energy differences suggest that the more stable binding modes are not the most reactive. This observation is in contrast to previous studies with multiple directing groups within a substrate, which showed that the binding mode stability has the ability to directly determine the labeling selectivity.[13a] Instead, calculation of the energy barriers to the respective C−H activations reveals that the free energy barrier to activation of the C2 position is by far the lowest of the three processes and is the only exothermic reaction coordinate of the three. We, therefore, conclude that the higher kinetic barrier to C−H activation of the C7 and benzoyl positions is the source of the appreciable labeling selectivity observed with *N*-benzoylindole (**7**). These results are in accord
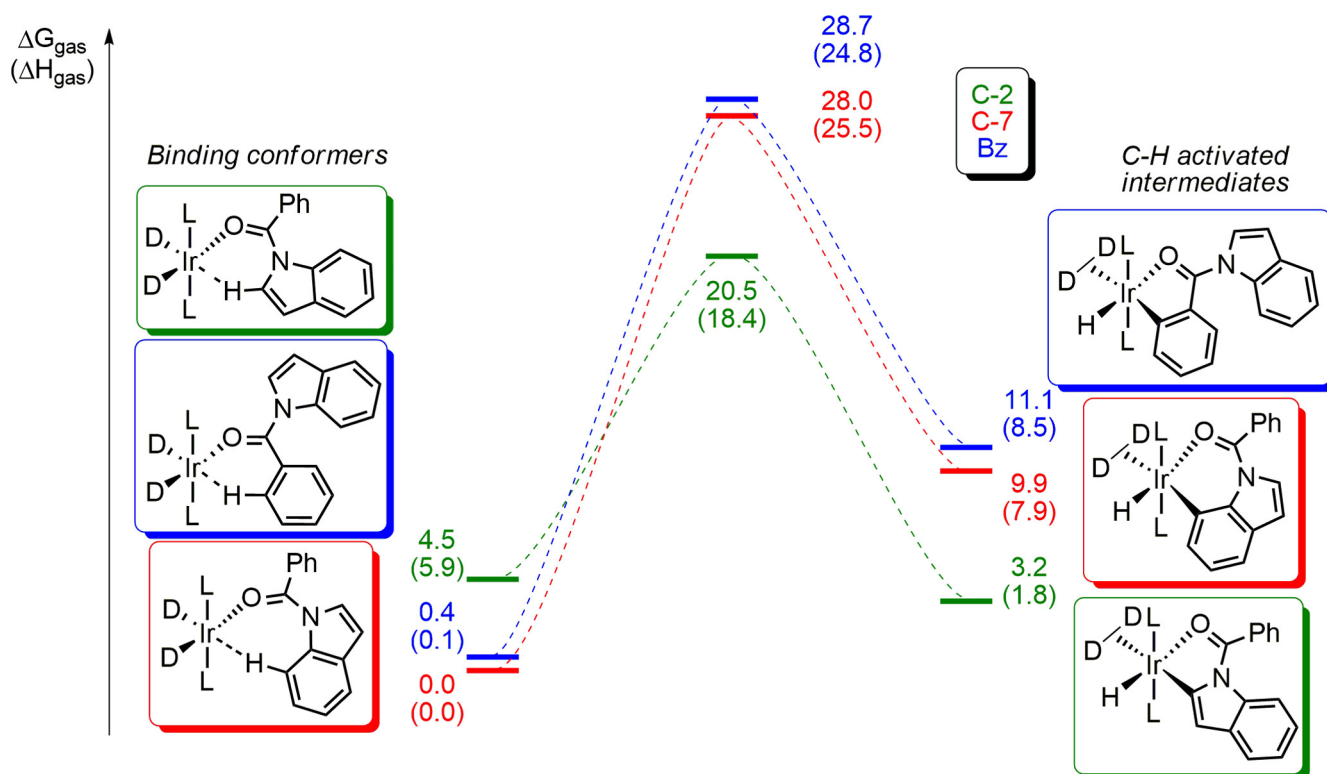
Figure 4. Potential energy surfaces (PESs) for C−H activation of the three potential labeling sites of *N*-benzoylindole (**7**).

with our experimental observations for the labeling of benzanilide, where two labeling sites are accessed via a single directing group.[4,7] Additionally, in terms of the C−H activation calculations, the extremely low levels of benzoyl-directed incorporation are indistinguishable from the lack of C7 labeling at the semiquantitative levels of the methods employed. The absolute free energy barriers to C−H activation of the three possible labeling sites are summarized in Table 3.

Table 3. Free Energy Barriers for the C−H Activation of *N*-Benzoylindole (7)

entry	binding conformer	ΔG°_{init} [a]	$\Delta G^{\ddagger}$ [a]	ΔG°_{prod} [a]
1	C7	0.0	28.0	9.9
2	Bz	0.4	28.7	11.1
3	C2	4.5	20.5	3.2

[a]All energies are in kcal mol^{-1} normalized against the C7 binding conformer; values were calculated using M06/6-31G* in the gas phase. Additional details are provided in the Supporting Information.

Having established an efficient method for the C2 labeling of acyl-protected indoles, we next explored the use of alternative modes of direction (Scheme 1). For example, beginning with substituents at the C3 position of the indole moiety, the Weinreb amide group in substrate **8** was able to act as a functional handle, directing labeling to the C2 position with 99% deuterium incorporation. For 3-formylindole (**9**), selectivity was observed for deuteration of the C2 over the formyl position, though with only a moderate 29% incorporation at C2. When **9** was protected as the ethyl carbamate to give **10**, however, deuteration at the C2 position increased to 97%, with the level of aldehyde labeling remaining low. Turning to alternative heterocyclic units with acyl direction, for isomeric *N*-acetylazaindole substrates **11** and **12**, the presence of an
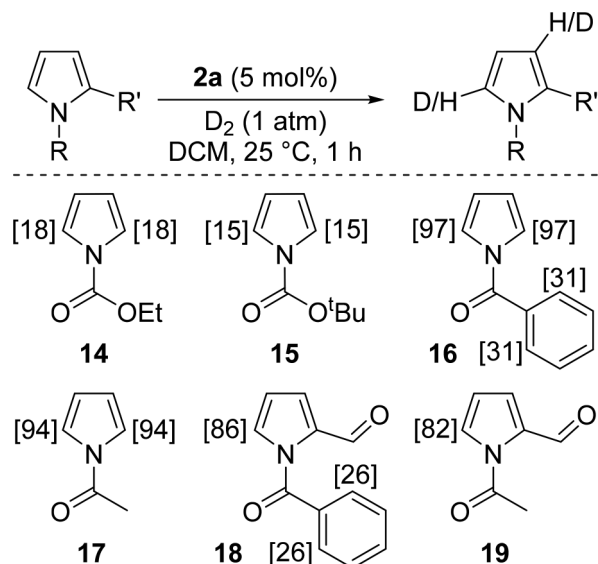
Scheme 1. Scope of *N*-Heterocycle Deuteration
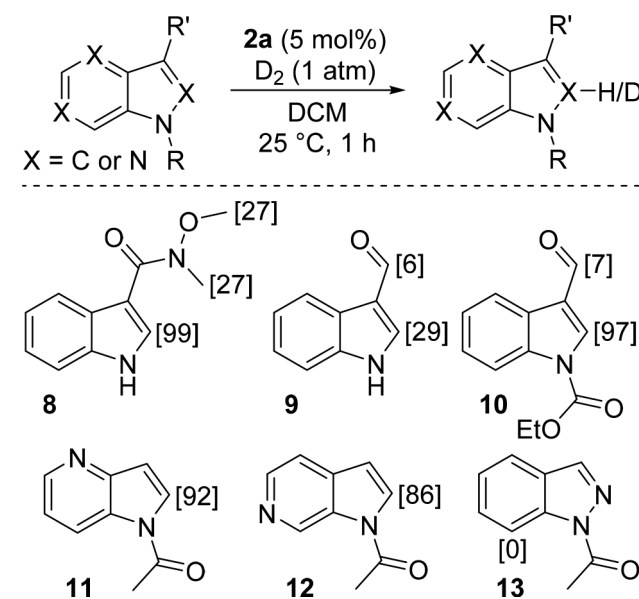
additional nitrogen atom had no negative effects on coordination, with excellent levels of C2 labeling being delivered for both substrates. In an attempt to bias the system toward labeling at C7, *N*-acetylbenzopyrazole (**13**) was subjected to our labeling conditions. In this case, however, no labeling was observed.

In a further extension of the substrate scope, a range of substituted pyrroles[17d,e,22,23] was subjected to our labeling conditions (Scheme 2). While the ethyl and *tert*-butyl carbamate protected pyrroles **14** and **15** did not mediate effective levels of labeling, we were pleased to see that acetyl-

Scheme 2. Deuteration of Substituted Pyrroles

Scheme 4. Labeling of the Migraine Drug Sumatriptan[a]

[a]Legend: (a) EtOCOCl, NaH, DCM, 53%; (b) **2a** (5 mol %), D$_2$ (1 atm), DCM, room temperature, 36 h, 99%; (c) NaOH, EtOH, room temperature, 16 h, 87%.

and benzoylpyrroles **16** and **17**, respectively, were labeled with high deuterium incorporation. Further, the corresponding formylpyrroles **18** and **19** were also labeled efficiently, with no decarbonylation or aldehydic labeling observed.

In order to increase the general utility of these deuteration protocols, conditions for removal of two of the more effective directing groups were investigated. Pleasingly, both acetyl and ethyl carbamate protected indoles **3** and **5**, respectively, could be deprotected under basic conditions to yield C2-deuterated indole **20** with retention of the deuterium label (Scheme 3).
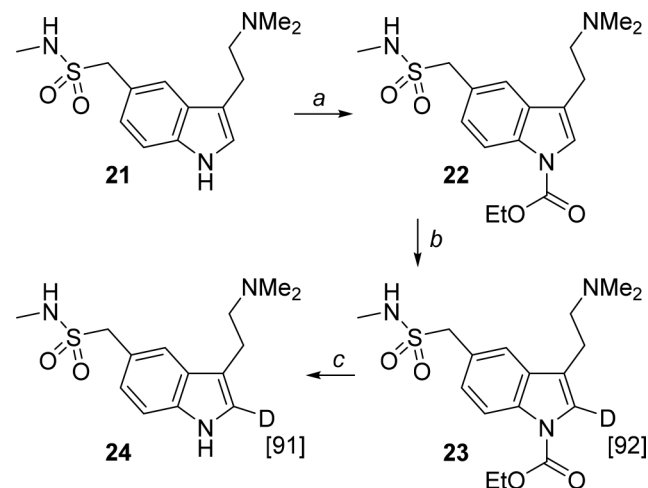
Scheme 3. Deprotection of Deuterated Indoles
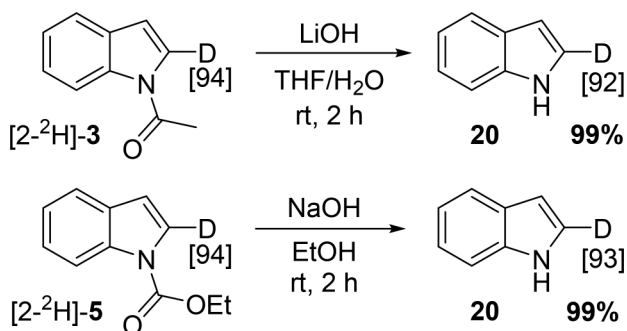
As a final example, and to highlight the application of our developed methodology in an industrially relevant context, the deuterium labeling of sumatriptan (**21**),[24] a 5HT-receptor drug used to treat migraines and cluster headaches, was investigated (Scheme 4). Ethyl carbamate protection, labeling, and deprotection reactions proceeded to yield 2-deuterosumatriptan ([2-^{2}H]-**21**) in a 46% yield over three steps. Importantly, an excellent 92% deuterium incorporation was obtained, with negligible isotopic degradation observed during deprotection.

Notable selectivity for C—H activation via a 5mmi is observed, and the C2 position can be selectively labeled in the presence of benzoyl groups. The labeling and subsequent deprotection of the commercial migraine drug sumatriptan serve to further highlight the applicability and effectiveness of the developed, preparatively simple catalytic process for use by pharmaceutical partners engaged in drug discovery endeavors.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.7b02682.

> Details of all experimental procedures, compound characterization, and DFT calculations (including optimized Cartesian coordinates) (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

HIE, hydrogen isotope exchange; Cy, cyclohexyl; py, pyridine; Mes, mesityl; Pym, 1-(pyrimidin-2-yl); NPs, nanoparticles; DCM, dichloromethane; mmi, membered metallacyclic intermediate; COD, 1,5-cyclooctadiene; PES, potential energy surface

■ CONCLUSIONS

To conclude, we have established a mild and general method for the C2 deuteration of indole, azaindole, and pyrrole N-heterocycles. Through the use of common directing groups as removable functional handles, high levels of deuterium incorporation have been achieved for a range of substrates.

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