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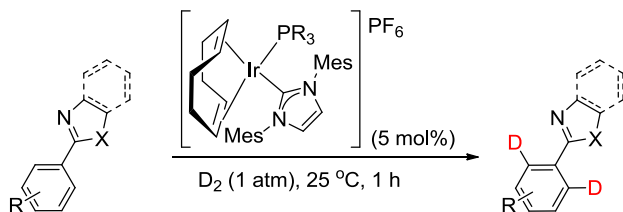
+ 12 examples   + Labelling of drug-like molecules
+ Up to 95% D   + Competition studies
+ Excellent yields

Expanded applicability of iridum(I) NHC-phosphine catalysts in hydrogen isotope exchange processes with pharmaceutically-relevant heterocycles

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ABSTRACT

An assessment of emerging C-H activation catalysts of the type $[(COD)Ir(IMes)(PR_3)]PF_6$ in the deuteration of N-heterocycles is divulged. Substrate scope, competition experiments, and labelling of drug type molecules have revealed $PR_3 = PPh_3$ provides a broadly more applicable and widely effective catalyst system compared to other available complexes in the present series.

1. Introduction

The synthesis and supply of isotopically-labelled molecules has a sustained importance in the study of preparative chemistry, reaction mechanisms, and metabolic processes, with documented uses spanning a range of physical organic, organometallic, and pharmaceutical chemical sciences.[1] In one particularly active branch of such research, hydrogen isotope exchange (HIE) is commonly employed to deliver deuterium (D) or radioactive tritium (T) to pharmaceutical drug candidates in one synthetic step.[2] As well as circumventing the requirement for isotopically-enriched starting materials in synthesising tritiated drug candidates,[2f,g] HIE can also provide deuterated analogues for use as internal standards for mass spectrometry,[3] for kinetic isotope studies,[1] and for the alteration of reaction pathways in total syntheses.[4]

Recently, one of our laboratories has focused on the development and understanding of ortho-directed HIE C-H activation processes using homogeneous iridium(I) complexes of the type 1 (Fig. 1).[5] Owing to the steric bulk and electron-donating power of the NHC/phosphine combination, these complexes have been shown to be significantly more active in the direct introduction of both D and T[5a,c] and produce less radioactive waste[2c] than in tritiations with commonly-used Crabtree's catalyst, $[(COD)Ir(PCy_3)(py)]PF_6$, 5.
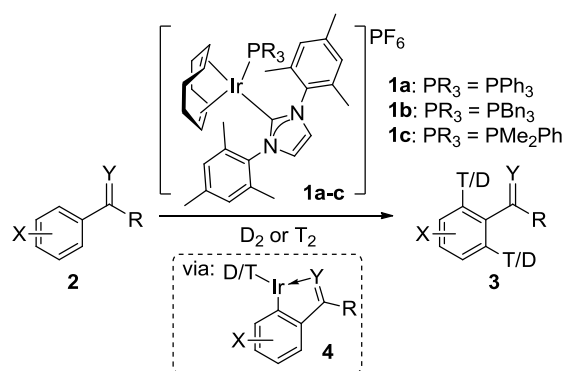

Fig. 1. HIE catalysts bearing an NHC-phosphine ligand sphere.

1a: $PR_3 = PPh_3$
1b: $PR_3 = PBn_3$
1c: $PR_3 = PMe_2Ph$

Although we have shown these catalysts to be compatible with a range of directing groups routinely present in drug-like compounds, the focus has been mainly on ketones, amides, and nitro compounds.[5a,c] To date, we have explored comparatively few N-heterocyclic directing groups,[5c] despite the prevalence of such moieties in drug candidates. In this contribution, we explore the compatibility of complexes 1a-c with an appreciably enhanced array of N-heterocyclic directing groups for the ortho-deuteration of pharmaceutically-relevant aromatic compounds.

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1a: 93%; 96%
1b: 42%; 93%
1c: 14%; 96%

(6)

1a: 89%; 94%
1b: 73%; 91%
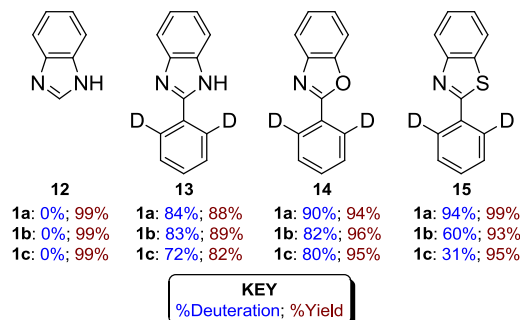**1c**: 70%; 95%

(7)

1a: 92%; 80%
1b: 79%; 79%
1c: 91%; 70%

(8)

1a: 83%; 99%
1b: 75%; 94%
1c: 80%; 94%

(9)

1a: 86%; 93%
1b: 95%;100%
1c: 89%; 95%

(10)

1a: 82%; 89%
1b: 44%; 80%
1c: 72%; 98%

(11)

KEY
%Deuteration; %Yield
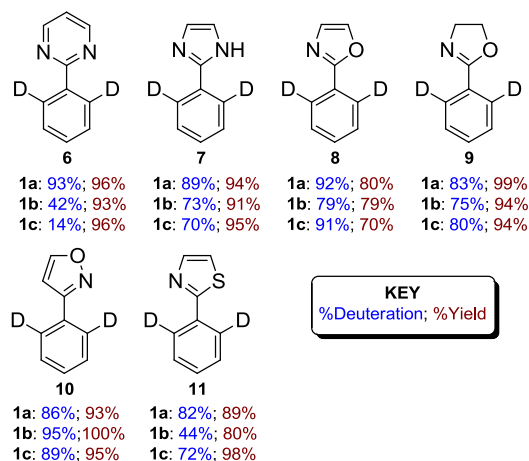
Fig. 2. Deuteration of phenyl *N*-heterocycles with catalysts **1a–c**. Conditions: Substrate (0.086 mmol), [Ir] (0.0043 mmol, 5 mol%), DCM (1 mL), D₂ (1 atm), 25 ºC, 1 h. Deuterium incorporation measured by ^{1}H NMR and LC-MS (see ESI for details). The results shown are an average of two independent reaction runs.

2. Results and Discussion

Our studies began with the application of heteroaryl functionalised benzene derivatives, **6–11**, with complexes **1a–c** under the mild reaction conditions developed for use with these catalyst systems (Figure 2). We were encouraged to find that, in all cases, at least one catalyst from **1a–c** was able to install >80%D in the phenyl ring adjacent to the *N*-heterocyclic directing group. Importantly, all isotopically labelled products were recovered in excellent yields. In the pyrimidine, **6**, catalyst **1a** was able to deliver excellent 93% deuteration to the expected *ortho*-positions, with this Ir species being found to be significantly more efficient than catalysts **1b** and **1c**. For imidazole **7**, oxazole **8**, oxazoline **9**, isoxazole **10**, and thiazole **11**, all three catalysts delivered moderate to excellent levels of deuterium incorporation. Again, catalyst **1a** was found to be the most efficient, except in the case of isoxazole **10**, where complex **1b** was most productive.

To further expand the substrates compatible with catalysts **1a–c** for effective HIE, we studied the deuteration of benzannulated compounds, **12–15** (Figure 3). For benzimidazole, **12**, no deuterium incorporation was detected in the absence of a phenyl substituent. However, the 2-phenyl-substituted benzimidazole, **13**, -benzoxazole, **14**, and -benzothiazole, **15**, were all deuterated with good to excellent levels of incorporation using one of catalysts **1a–c**. Once again, it was clear that **1a** (containing the comparatively least electron-rich phosphine ligand, PPh₃)[6] was the most efficient and most generally applicable Ir catalyst. It should also be noted that, across the new substrates deuterated, catalyst series **1a–c** was shown to be more active than Crabtree's catalyst, **5**, in eight of nine examples (see Experimental and ESI for details). In line with our previous studies,[5a,c] this serves to show that the NHC/phosphine ligand sphere on these iridium(I) catalysts is more generally effective in such homogeneous HIE processes when compared to the pyridine/phosphine ligand sphere of classical catalyst, **5**.

Regio- and chemoselectivity is of fundamental and practical importance to the broadest range of C–H activation processes.[7] As such, the penultimate part of our study aimed to rank the relative electronic directing group capabilities of the *N*-heterocycles employed within this programme. To achieve this, we conducted a series of competition experiments, employing

12
1a: 0%; 99%
1b: 0%; 99%
1c: 0%; 99%

13
1a: 84%; 88%
1b: 83%; 89%
1c: 72%; 82%

14
1a: 90%; 94%
1b: 82%; 96%
1c: 80%; 95%

15
1a: 94%; 99%
1b: 60%; 93%
1c: 31%; 95%

KEY
%Deuteration; %Yield

Fig. 3. Deuteration of benzannulated *N*-heterocycles with catalysts **1a–c**. Conditions: Substrate (0.086 mmol), [Ir] (0.0043 mmol, 5 mol%), DCM (1 mL), D₂ (1 atm), 25 ºC, 1 h. Deuterium incorporation measured by ^{1}H NMR and LC-MS (see ESI for details). The results shown are an average of two independent reaction runs.

Table 1
Competition experiments with phenyl *N*-heterocycles employing catalyst **1a**.[a]

A \ B	7	8	9	10	11
6	78 / 28	87 / 88	80 / 77	30 / 87	52 / 52
7		16 / 76	81 / 81	14 / 84	73 / 70
8			90 / 90	78 / 86	88 / 84
9				43 / 82	84 / 85
10					75 / 63
11					

[a]Numbers inside diagonalised cells represent overall %D for each substrate in competition experiments as determined by LC-MS.

two substrates in one reaction vessel, along with the most generally active catalyst, **1a**. Applying this methodology to simple *N*-heterocycles **6–11**, we have estimated the relative directing group strength to be in the order: **7 > 9 ∼ 11 > 6 > 8 > 10** (Table 1) using a simple scoring system.[8] This order is approximately proportional to the relative base strength of each substrate as determined by their pKₐH values.[9] However, the predicted order based on the collective was inconsistent with individual competition experiments, showing that each case of directing group competition must be treated separately rather than as part of an ensemble.

excellent isolated yields, employing at least one of the commercialised catalysts **1a-c**.[11] From these studies, catalyst **1a** has proven to be the most versatile and most broadly applicable. Employing this catalyst, competition studies between simple phenyl *N*-heterocycles revealed that directing group selectivity has to be considered on a case by case basis and cannot be predicted using a scoring system for the ensemble of competition experiments. This is especially important when considering multifunctional, drug-like compounds, as was demonstrated in the labelling of compound **18**. Similar competition experiments employing benzannulated heterocycles revealed these species to compete equally with their parent heterocylce in reaction with the catalyst, such that: imidazole ~ benzimidazole; oxazole ~ benzoxazole; and thiazole ~ benzothiazole. As part of our future work, we are expanding this fundamental analysis of chemoselectivity to the deuterium and tritium labelling of a broader series of multifunctional drug compounds.

4. Experimental section

4.1. General information

All substrates, catalysts, and solvents were obtained from commercial suppliers and used without further purification. All labelling reactions were carried out on a Heidolph Synthesis 1 Liquid 16 device. Flash column chromatography was carried out using Merck kieselgel 60 silica gel (particle size: 63-200). [1]H (300, 500 MHz) and ^{13}C (75, 125 MHz) NMR spectra were obtained on Bruker spectrometers in the solvents indicated. Chemical shifts are reported in ppm. Coupling constants are reported in Hz and refer to $^3J_{\text{H-H}}$ couplings, unless otherwise stated. The distribution of hydrogen isotopes in the products was determined by a liquid chromatography-mass spectrometry (LC-MS) system with a Symmetry Shield RP18 column, 3.9 x 150 mm, with a gradient program. Column conditions are given in the ESI.

4.2. General Procedures

4.2.1. General Procedure A for Hydrogen Isotope Exchange with Simple Substrates 6 - 15

The water inlet for the carousel reflux system was turned on prior to any further reaction set up. To a carousel tube was added the substrate of choice (0.086 mmol, unless otherwise stated) and iridium(I) catalyst (0.0043 mmol, 5 mol%, unless otherwise stated) under air. The desired solvent (1 mL) was added, rinsing the inner walls of the tube. The tube was then sealed at the screw cap (with gas inlet left open) under air before initiating the carousel shaking motion (720 rpm) and setting the reaction temperature (25 or 50 °C). The flask was twice evacuated and flushed with deuterium *via* a balloon. The carousel tube gas inlet was then closed, creating a sealed atmosphere of deuterium. After sealing the flask, the reaction timer was started, and a quick red to clear/yellow colour change was observed. The reaction mixture was stirred for 1 h before removing excess deuterium and replacing with air. The yellow solution was then washed with DCM and transferred to a single necked flask before removing the solvent under reduced pressure. The residue was filtered through a short plug of silica, eluting with ethyl acetate (2 x 3 mL), and 2% MeOH where necessary, depending on the substrate of choice. An LC-MS sample (~2 μL) was taken directly from the combined filtered fractions. The solvent was evacuated again and the residue analysed directly by ^{1}H NMR spectroscopy. The level and regioselectivity of deuterium incorporation in the substrate was determined by ^{1}H NMR spectroscopy (for detail, see the ESI). Yields and %D incorporation are the averages of two reaction runs.

4.2.2. General Procedure C for Hydrogen Isotope Exchange with Pharmaceuticals 16-18 with Catalyst 1a

Following General Procedure A, each substrate was employed using 22 μmol in conjunction with 1.1 μmol of catalyst **1a** (1.1 mg, 5 mol%) and 1 mL solvent

4.3. Hydrogen Isotope Exchange Experiments

4.3.1. Hydrogen Isotope Exchange with Simple Substrates 6 – 15

2-Phenylpyrimidine 6

Following General Procedure A, exchange of 2-phenylpyrimidine **6** (13.4 mg) in the presence of catalyst **1a** (4.4 mg) gave [2',6'-²H$_2$]-**6** (12.8 mg, 96%, 93%D).

Following General Procedure A, exchange of 2-phenylpyrimidine **6** (13.4 mg) in the presence of catalyst **1b** (4.6 mg) gave [2',6'-²H$_2$]-**6** (12.4 mg, 93%, 42%D).

Following General Procedure A, exchange of 2-phenylpyrimidine **6** (13.4 mg) in the presence of catalyst **1c** (3.8 mg) gave [2',6'-²H$_2$]-**6** (12.8 mg, 96%, 14%D).

Following General Procedure A, exchange of 2-phenylpyrimidine **6** (13.4 mg) in the presence of catalyst **5** (3.4 mg) gave [2',6'-²H$_2$]-**6** (11.6 mg, 86%, 28%D).

δ_H (400 MHz, CDCl$_3$): 8.80 (d, 2H, J = 4.8 Hz), 8.44-8.41 (m, 2H), 7.49-7.47 (m, 3H), 7.17 (t, 1H, J = 4.8 Hz).

Incorporation expected at δ 8.44-8.41.

Incorporation determined against δ 7.17.

2-Phenylimidazole 7

Following General Procedure A, exchange of 2-phenylimidazole **7** (12.4 mg) in the presence of catalyst **1a** (4.4 mg) gave [2',6'-²H$_2$]-**7** (11.7 mg, 94%, 89%D).

Following General Procedure A, exchange of 2-phenylimidazole **7** (12.4 mg) in the presence of catalyst **1b** (4.6 mg) gave [2',6'-²H$_2$]-**7** (11.2 mg, 91%, 73%D).

Following General Procedure A, exchange of 2-phenylimidazole **7** (12.0 mg) in the presence of catalyst **1c** (3.8 mg) gave [2',6'-²H$_2$]-**7** (12.8 mg, 95%, 70%D).

Following General Procedure A, exchange of 2-phenylimidazole **7** (12.4 mg) in the presence of catalyst **5** (3.4 mg) gave [2',6'-²H$_2$]-**7** (12.2 mg, 98%, 76%D).

δ_H (300 MHz, DMSO-d$_6$) 12.48 (bs, 1H), 7.94-7.92 (m, 2H), 7.43 (t, 2H, J = 7.6 Hz), 7.32 (t, 1H, J = 7.3 Hz), 7.13 (bs, 2H).

Incorporation expected at δ 7.94-7.92.

Incorporation determined against δ 7.32.

2-Phenyloxazole 8

Following General Procedure A, exchange of 2-phenyloxazole **8** (12.4 mg) in the presence of catalyst **1a** (4.4 mg) gave [2',6'-²H$_2$]-**8** (10.0 mg, 80%, 92%D).

Following General Procedure A, exchange of 2-phenyloxazole **8** (12.4 mg) in the presence of catalyst **1b** (4.6 mg) gave [2',6'-$^2H_2$]-**8** (9.8 mg, 79%, 79%D).

Following General Procedure A, exchange of 2-phenyloxazole **8** (12.0 mg) in the presence of catalyst **1c** (3.8 mg) gave [2',6'-$^2H_2$]-**8** (8.6 mg, 70%, 91%D).

Following General Procedure A, exchange of 2-phenyloxazole **8** (12.4 mg) in the presence of catalyst **5** (3.4 mg) gave [2',6'-$^2H_2$]-**8** (6.4 mg, 52%, 87%D).

δ_H (300 MHz, MeOD-d_4) 8.03-7.97 (m and overlapping s, 3H), 7.50-7.48 (m, 3H), 7.29 (s, 1H).

Incorporation expected at δ 8.03-7.97.

Incorporation determined against δ 7.50-7.48.

2-Phenyloxazoline *9*

Following General Procedure A, exchange of 2-phenyloxazoline **9** (12.6 mg) in the presence of catalyst **1a** (4.4 mg) gave [2',6'-$^2H_2$]-**9** (12.4 mg, 99%, 83%D).

Following General Procedure A, exchange of 2-phenyloxazoline **9** (12.6 mg) in the presence of catalyst **1b** (4.6 mg) gave [2',6'-$^2H_2$]-**9** (11.8 mg, 94%, 75%D).

Following General Procedure A, exchange of 2-phenyloxazoline **9** (12.6 mg) in the presence of catalyst **1c** (3.8 mg) gave [2',6'-$^2H_2$]-**9** (11.8 mg, 94%, 80%D).

Following General Procedure A, exchange of 2-phenyloxazoline **9** (12.6 mg) in the presence of catalyst **5** (3.4 mg) gave [2',6'-$^2H_2$]-**9** (2.8 mg, 23%, 76%D).

δ_H (300 MHz, CDCl$_3$) 7.95-7.92 (m, 2H), 7.49-7.24 (m, 3H), 4.37 (t, 2H, $J = 9.6$ Hz), 4.00 (t, 2H, $J = 9.6$ Hz)

Incorporation expected at δ 7.95-7.92.

Incorporation determined against δ 4.37.

5-Phenylisoxazole *10*

Following General Procedure A, exchange of 5-phenylisoxazole **10** (12.4 mg) in the presence of catalyst **1a** (4.4 mg) gave [2',6'-$^2H_2$]-**10** (11.6 mg, 93%, 86%D).

Following General Procedure A, exchange of 5-phenylisoxazole **10** (12.4 mg) in the presence of catalyst **1b** (4.6 mg) gave [2',6'-$^2H_2$]-**10** (12.4 mg, 100%, 95%D).

Following General Procedure A, exchange of 5-phenylisoxazole **10** (12.4 mg) in the presence of catalyst **1c** (3.8 mg) gave [2',6'-$^2H_2$]-**10** (12.0 mg, 95%, 89%D).

Following General Procedure A, exchange of 5-phenylisoxazole **10** (12.4 mg) in the presence of catalyst **5** (3.4 mg) gave [2',6'-$^2H_2$]-**10** (9.0 mg, 73%, 54%D).

δ_H (300 MHz, DMSO-d_6) 9.01 (d, 1H, $J = 1.7$ Hz), 7.91-7.88 (m, 2H), 7.56-7.50 (m, 3H), 7.16 (d, 1H, $J = 1.7$ Hz).

Incorporation expected at δ 7.91-7.88.

Incorporation determined against δ 7.16.

2-Phenylthiazole *11*

Following General Procedure A, exchange of 2-phenylthiazole **11** (13.8 mg) in the presence of catalyst **1a** (4.4 mg) gave [2',6'-$^2H_2$]-**11** (12.2 mg, 89%, 82%D).

Following General Procedure A, exchange of 2-phenylthiazole **11** (13.8 mg) in the presence of catalyst **1b** (4.6 mg) gave [2',6'-$^2H_2$]-**11** (11.0 mg, 80%, 44%D).

Following General Procedure A, exchange of 2-phenylthiazole **11** (13.8 mg) in the presence of catalyst **1c** (3.8 mg) gave [2',6'-$^2H_2$]-**11** (13.6 mg, 98%, 72%D).

Following General Procedure A, exchange of 2-phenylthiazole **11** (13.8 mg) in the presence of catalyst **5** (3.4 mg) gave [2',6'-$^2H_2$]-**11** (10.8 mg, 78%, 59%D).

δ_H (300 MHz, DMSO-d_6) 7.97-7.93 (m, 3H), 7.78 (d, 1H, $J = 3.3$ Hz), 7.54-7.48 (m, 3H).

Incorporation expected at δ 7.97-7.93.

Incorporation determined against δ 7.54-7.48

Benzimidazole *12*

Following General Procedure A, exchange of benzimidazole **12** (10.2 mg) in the presence of catalyst **1a** (4.4 mg) gave benzimidazole **12** (10.0 mg, 99%, 0%D).

Following General Procedure A, exchange of benzimidazole **12** (10.2 mg) in the presence of catalyst **1b** (4.6 mg) gave benzimidazole **12** (10.0 mg, 99%, 0%D).

Following General Procedure A, exchange of benzimidazole **12** (10.2 mg) in the presence of catalyst **1c** (3.8 mg) gave benzimidazole **12** (10.0 mg, 99%, 0%D).

Following General Procedure A, exchange of benzimidazole **12** (10.2 mg) in the presence of catalyst **5** (3.4 mg) gave benzimidazole **12** (10.0 mg, 99%, 0%D).

δ_H (300 MHz, DMSO-d_6) 8.15 (s, 1H, H^3), 7.62-7.59 (m, 2H, H^2), 7.29-7.23 (m, 2H, H^1).

No incorporation expected.

2-Phenylbenzimidazole *13*

Following General Procedure A, exchange of 2-phenylbenzimidazole **13** (16.8 mg) in the presence of catalyst **1a** (4.4 mg) gave [2',6'-$^2H_2$]-**13** (14.8 mg, 88%, 84%D).

Following General Procedure A, exchange of 2-phenylbenzimidazole **13** (16.8 mg) in the presence of catalyst **1b** (4.6 mg) gave [2',6'-$^2H_2$]-**13** (14.9 mg, 89%, 83%D).

Following General Procedure A, exchange of 2-phenylbenzimidazole **13** (16.8 mg) in the presence of catalyst **1c** (3.8 mg) gave [2',6'-$^2H_2$]-**13** (13.8 mg, 82%, 72%D).

Following General Procedure A, exchange of 2-phenylbenzimidazole **13** (16.8 mg) in the presence of catalyst **5** (3.4 mg) gave [2',6'-$^2H_2$]-**13** (15.3 mg, 91%, 72%D).

δ_H (300 MHz, DMSO-d_6) 12.90 (s, 1H), 8.19-8.17 (m, 2H), 7.60-7.47 (m, 5H), 7.23-7.18 (m, 2H).

Incorporation expected at δ 8.19-8.17.

Incorporation determined against δ 7.23-7.18.

2-Phenylbenzoxazole **14**

Following General Procedure A, exchange of 2-phenylbenzoxazole **14** (16.8 mg) in the presence of catalyst **1a** (4.4 mg) gave [2',6'-^{2}H$_2$]-**14** (15.2 mg, 94%, 90%D).

Following General Procedure A, exchange of 2-phenylbenzoxazole **14** (16.8 mg) in the presence of catalyst **1b** (4.6 mg) gave [2',6'-^{2}H$_2$]-**14** (16.2 mg, 96%, 82%D).

Following General Procedure A, exchange of 2-phenylbenzoxazole **14** (16.8 mg) in the presence of catalyst **1c** (3.8 mg) gave [2',6'-^{2}H$_2$]-**14** (16.0 mg, 95%, 80%D).

Following General Procedure A, exchange of 2-phenylbenzoxazole **14** (16.8 mg) in the presence of catalyst **5** (3.4 mg) gave [2',6'-^{2}H$_2$]-**14** (16.2 mg, 96%, 96%D).

δ_H (300 MHz, MeOD-d$_4$) 8.23-8.20 (m, 2H), 7.73-7.70 (m, 1H), 7.67-7.64 (m, 1H), 7.59-7.53 (m, 3H), 7.43-7.36 (m, 2H).

Incorporation expected at δ 8.23-8.20.

Incorporation determined against δ 7.43-7.36.

2-Phenylbenzothiazole **15**

Following General Procedure A, exchange of 2-phenylbenzothiazole **15** (18.2 mg) in the presence of catalyst **1a** (4.4 mg) gave [2',6'-^{2}H$_2$]-**15** (18.0 mg, 99%, 94%D).

Following General Procedure A, exchange of 2-phenylbenzothiazole **15** (18.2 mg) in the presence of catalyst **1b** (4.6 mg) gave [2',6'-^{2}H$_2$]-**15** (17.0 mg, 93%, 60%D).

Following General Procedure A, exchange of 2-phenylbenzothiazole **15** (18.2 mg) in the presence of catalyst **1c** (3.8 mg) gave [2',6'-^{2}H$_2$]-**15** (17.2 mg, 95%, 31%D).

Following General Procedure A, exchange of 2-phenylbenzothiazole **15** (18.2 mg) in the presence of catalyst **5** (3.4 mg) gave [2',6'-^{2}H$_2$]-**15** (17.2 mg, 95%, 81%D).

δ_H (300 MHz, CDCl$_3$) 8.10-8.05 (m, 3H), 7.90 (d, 1H, J = 9.0 Hz), 7.50-7.46 (m, 4H), 7.40-7.35 (m, 1H).

Incorporation expected at δ 8.10-8.05.

Incorporation determined against δ 7.40-7.35.

4.3.2. Hydrogen Isotope Exchange of Drug-like Heterocycles 16-18 with Catalyst 1a

Oxazole **16**

Following General Procedure C, exchange of pharmaceutical **16** (8.4 mg) in the presence of catalyst **1a** (1.1 mg) in DCM (1 mL) at 25 °C gave [^{2}H$_2$]-**16** (8.0 mg, 95%, 83%D; see Table 3 for position of D incorporation).

Following General Procedure C, exchange of pharmaceutical **16** (8.4 mg) in the presence of catalyst **1a** (1.1 mg) in MeOH (1 mL) at 25 °C gave [^{2}H$_2$]-**16** (7.9 mg, 94%, 80%D; see Table 3 for position of D incorporation).

Following General Procedure C, exchange of pharmaceutical **16** (8.4 mg) in the presence of catalyst **1a** (1.1 mg) in THF (1 mL) at 50 °C gave [^{2}H$_2$]-**16** (6.1 mg, 73%, 95%D; see Table 3 for position of D incorporation).

δ_H (300 MHz, DMSO-d$_6$) 13.08 (s, 1H), 8.13 (s, 1H), 7.99-7.95 (m, 2H), 7.54-7.52 (m, 3H), 7.29-7.16 (m, 3H), 4.47 (s, 2H), 4.40 (s, 2H), 3.54 (t, 2H, J = 6.5 Hz), 3.45 (t, 2H, J = 6.5 Hz), 2.29 (s, 3H), 1.78 (quintet, 2H, J = 6.5 Hz).

Incorporation expected at δ 7.99-7.95.

Incorporation determined against δ 2.29.

Oxazole **17**

Following General Procedure C, exchange of pharmaceutical **17** (9.9 mg) in the presence of catalyst **1a** (1.1 mg) in DCM (1 mL) at 25 °C gave [^{2}H$_2$]-**17** (8.9 mg, 90%, 82%D; see Table 3 for position of D incorporation).

Following General Procedure C, exchange of pharmaceutical **17** (9.9 mg) in the presence of catalyst **1a** (1.1 mg) in MeOH (1 mL) at 25 °C gave [^{2}H$_2$]-**17** (8.9 mg, 90%, 85%D; see Table 3 for position of D incorporation).

Following General Procedure C, exchange of pharmaceutical **17** (9.9 mg) in the presence of catalyst **1a** (1.1 mg) in THF (1 mL) at 50 °C gave [^{2}H$_2$]-**17** (9.2 mg, 93%, 95%D; see Table 3 for position of D incorporation).

δ_H (300 MHz, DMSO-d$_6$) 13.06 (s, 1H), 7.81 (d, 2H, J = 8.2 Hz), 7.33-7.16 (m, 5H), 4.53 (s, 2H), 4.39 (s, 2H), 2.37-2.36 (overlapping singlets, 6H), 2.29 (s, 3H).

Incorporation expected at δ 7.81.

Incorporation determined against δ 2.29.

Thiazole-oxadiazolone **18**

Following General Procedure C, exchange of pharmaceutical **18** (10.2 mg) in the presence of catalyst **1a** (1.1 mg) in DCM (1 mL) at 25 °C returned **18** (7.7 mg, 75%, 0%D).

Following General Procedure C, exchange of pharmaceutical **18** (10.2 mg) in the presence of catalyst **1a** (1.1 mg) in MeOH (1 mL) at 25 °C gave [^{2}H]-**18** (7.9 mg, 77%, 66%D; see Table 3 for position of D incorporation).

Following General Procedure C, exchange of pharmaceutical **18** (10.2 mg) in the presence of catalyst **1a** (1.1 mg) in THF (1 mL) at 50 °C gave [^{2}H]-**18** (9.3 mg, 91%, 82%D; see Table 3 for position of D incorporation).

δ_H (300 MHz, DMSO-d$_6$) 12.79 (s, 1H), 8.13 (d, 2H, J = 8.1 Hz), 7.86 (d, 2H, J = 8.1 Hz), 7.67 (d, 1H, J = 8.7 Hz), 7.44 (d, 1H, J = 2.5 Hz), 7.23 (dd, 1H, ^3J = 8.7 Hz, ^4J = 2.5 Hz), 5.51 (s, 2H), 2.50 (s, ~3H, overlapping with residual DMSO).

Incorporation possible at δ 7.67 (observed as detailed by that shown in Table 3, Entries 7 – 9), and 8.13.

Incorporation determined against δ 7.23.

References and notes

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10. For a recent account on the synthetic relevance of competition experiments, see: Collins, K. D.; Glorius, F. *Nature Chem.* **2013**, *5*, 597.

11. All three catalyst species **1a-c** are available from Strem Chemicals.

Supplementary Material

Full experimental details and associated analyses for all compounds are provided in the Supplementary Material.