

## RESEARCH ARTICLE

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## High-throughput hydrogen isotope exchange via transfer deuteration

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In recent years, high-throughput experimentation (HTE) has gained significant traction due to the advantages it offers for rapid optimization of reaction conditions. However, there has been little use of deuterium gas in plate format primarily due to practical constraints. We developed a rapid screening protocol based on transfer deuteration conditions with formic acid- $d_2$  as the deuterium source in place of deuterium gas. Here we show that these conditions allow rapid screening of up to 96 hydrogen-isotope-exchange reactions in a controlled and safe manner. In combination with a script, the platform enables fast processing and visualization of analytical data. This ultimately allows for extremely fast screening of conditions for labeling compounds, such as, active pharmaceutical ingredients.

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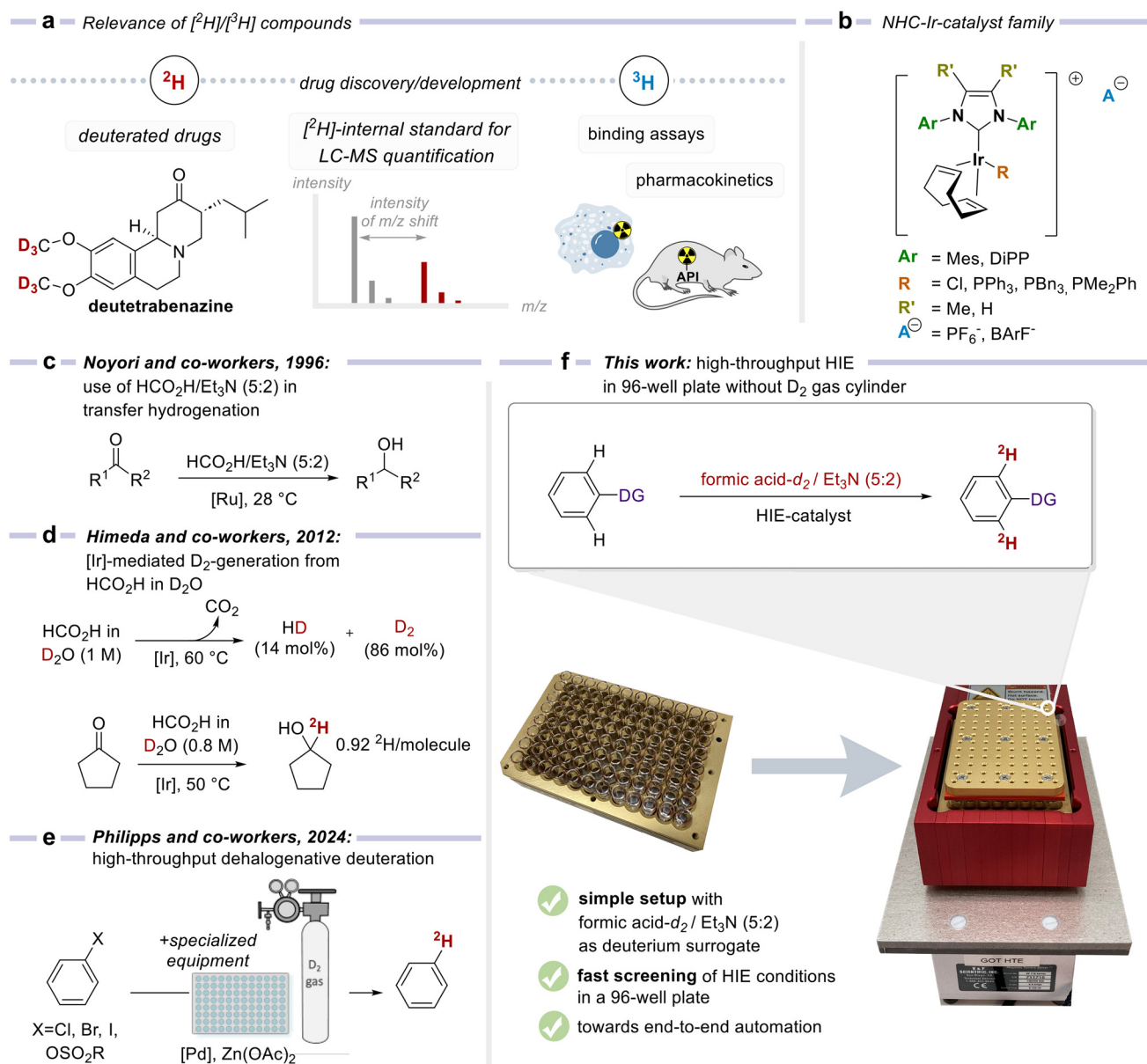
## Introduction

Deuterium labeled compounds have widespread applications, from improving the metabolic stability of drug candidates to mechanistic studies.<sup>1,2</sup> They have particularly gained attention in the last decade due to the development of deuterated drugs (Fig. 1a). The substitution of hydrogen with its heavier stable isotope can have a profound effect on the pharmacokinetic (PK) and metabolic characteristics of a molecule and thereby alter its drug properties. This has been demonstrated, for example, through the approval of deutetrabenazine (the deuterated version of tetrabenazine) by the FDA in 2017 and the approval of deucravacitinib in 2022. The substitution of six protons with deuterium atoms in deutetrabenazine retarded the metabolism of the compound, allowing for reductions in dosage and dosing frequency.<sup>3–5</sup> Deuterium is also frequently used for proof-of-concept labeling before introducing tritium into a molecule and is used to produce stable-isotope-labeled internal standards (SILs) for LC-MS based quantification in bioanalytical studies.<sup>6</sup> Tritiated drug isotopologues are employed in early discovery for binding studies and drug can-

didate profiling including initial metabolism studies. During later drug development tritiated analogs can be used in the preclinical phase with animals to study the pharmacokinetic profile of the drug candidate.<sup>7</sup> Many methods for deuterium and tritium labeling have been developed including double-bond reductions, dehalogenation reactions, as well as, incorporation of hydrogen isotope bearing moieties.<sup>8,9</sup> A valuable and frequently used approach is the transition metal-catalyzed hydrogen isotope exchange (HIE).<sup>10</sup> While this C–H activation approach requires a directing group, it has high functional group tolerance and allows late-stage labeling under mild conditions. This is of particular value for the preparation of deuterated or tritiated drug derivatives as it can save significant amounts of time, cost, and resources. Metal complexes used for this transformation are generally based on Pt,<sup>11,12</sup> Rh,<sup>13</sup> Ru,<sup>14</sup> and Ir.<sup>15,16</sup> In a recent review, Beller and co-workers detail the various catalytic systems that have been developed for HIE reactions,<sup>17</sup> with the most common form being *ortho*-directed aromatic HIE. This is dominated by iridium catalysis, with most examples in recent years using *N*-heterocyclic carbene (NHC)-containing iridium catalysts developed by Kerr and co-workers (Fig. 1b).<sup>18</sup> Generally, these catalysts are cationic phosphine-ligated catalysts bearing a bulky NHC ligand. However, in recent years neutral NHC iridium complexes have been developed, which provide alternative reactivity, *e.g.* for the use of primary sulfonamides as directing groups.<sup>19</sup> Therefore, the choice of catalyst is very substrate dependent.<sup>10</sup>

Deuterium labeling is often carried out with deuterium oxide due to its low cost, ease of use, and accessibility compared to other sources of deuterium,<sup>20–22</sup> although hexafluoro-

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**Fig. 1** (a) Relevance of <sup>2</sup>H/<sup>3</sup>H-labeled drug analogs in drug discovery/development. (b) Depiction of the NHC-Ir-catalyst family. (c) Use of formic acid/Et<sub>3</sub>N (5 : 2) as hydrogen surrogate in transfer hydrogenation of ketones. (d) Deuterium gas generation from HCO<sub>2</sub>H in D<sub>2</sub>O and application to deuterium labeling of ketones. (e) HTE setup using deuterium gas for dehalogenative deuteration. (f) This work: HTE setup using formic acid-*d*<sub>2</sub>/Et<sub>3</sub>N (5 : 2) as the deuterium source in place of deuterium gas for transfer deuteration in HIE.

isopropanol-*d* has been utilized recently to good effect.<sup>23</sup> However, certain reactions require the use of a deuterium gas atmosphere instead of deuterium oxide owing to their mechanism. The HIE catalysts developed by the Kerr group, for example, are used in conjunction with deuterium or tritium gas.<sup>20</sup> Moreover, tritiations are predominantly carried out using tritium gas due to the higher risk associated with the handling of T<sub>2</sub>O and the ease of use of T<sub>2</sub>.<sup>17,24</sup> Tritium gas, unlike T<sub>2</sub>O, is also available at near theoretical molar activity which makes it useful for a wider spectrum of applications. Deuterium gas is often used to test the feasibility of a reaction

as a mimic for T<sub>2</sub> to ensure minimal waste of radioactive material. As a result, deuterium gas was the second most commonly listed deuterium source in publications between 2017 and 2021.<sup>17</sup>

In 1996, Noyori and co-workers reported on the use of formic acid : triethylamine (5 : 2) as a hydrogen source for Ru-catalyzed asymmetric transfer hydrogenation of ketones (Fig. 1c),<sup>25</sup> and formic acid : triethylamine has found use in many different applications.<sup>26–28</sup> Due to the cost of deuterium gas, methods for the laboratory preparation of D<sub>2</sub> have been developed, such as dehydrogenation of HCO<sub>2</sub>H in D<sub>2</sub>O *via* an



iridium catalyst as developed by Himeda and co-workers and applied for transfer deuteration (Fig. 1d).<sup>26</sup>

For radiochemists, reaction optimization of HIE experiments with deuterium gas can be a time-consuming process. If chemists had an apparatus in which different reaction conditions could be tested concurrently, considerable time and effort could be saved. The use of high-throughput chemistry could offer a means to accelerate the reaction optimization, but the use of deuterium gas in parallel synthesis experiments is limited due to the practical considerations of handling D<sub>2</sub>. The main limitations are the handling of a flammable gas, the need to reduce the path length of the plumbing as D<sub>2</sub> is an expensive reagent, and the necessity for specialized equipment to connect a deuterium gas cylinder with the HTE-well plate. Traditionally, HIE reactions with deuterium gas are performed using a deuterium manifold, a D<sub>2</sub>-filled balloon, or a small carousel with a D<sub>2</sub> atmosphere. A two-chamber reactor for the *ex situ* preparation of deuterium gas from heavy water has also been reported by Skrydstrup and co-workers.<sup>29,30</sup> A drawback of these methods is that setting up multiple reactions can be slow and tedious. Therefore, we sought a way to use deuterium gas for iridium catalyzed HIE in a high-throughput format. The use of deuterium gas in an 80-well HTE setup was reported in 2001 by Wilkinson and co-workers. They highlighted however that the setup has no barrier in-between reaction vials, which presents a limitation for volatile substrates or screening different volatile solvents.<sup>31</sup> Phillips and co-workers employed a similar setup for optimizing a dehalogenative deuteration procedure (Fig. 1e). In addition, they reported an automated isotope incorporation calculation using Python.<sup>32</sup> Chirik and co-workers used another specialized setup by pressurizing a 96 well plate with H<sub>2</sub>.<sup>33</sup> Because our facility lacked the specialized equipment to deliver D<sub>2</sub> for HTE, we explored practical alternatives. In this work, we demonstrate that a mixture of formic acid-*d*<sub>2</sub>/Et<sub>3</sub>N (5 : 2) serves as a convenient deuterium surrogate and is compatible for use in a high-throughput format for transfer deuteration in hydrogen isotope exchange reactions. This approach obviates the need to couple an HTE plate to a gas cylinder, allows parallel screening of multiple reactions and paves the work of isotope chemists towards end-to-end automation (Fig. 1f).

## Results and discussion

We initially investigated the hydrogen surrogate formic acid : triethylamine (5 : 2), but using deuterated formic acid-*d*<sub>2</sub> to see how it would perform under standard HIE conditions (Fig. 1f). In addition to avoiding the drawbacks of handling deuterium gas, this method allows for the precise amount of deuterium reagent to be added to the reaction. The initial catalyst used was the iridium catalyst **cat1a** (Fig. 1b, Ar = Mes; R = PBn<sub>3</sub>, R' = Me, A = BARF), which was selected because this class of Ir-NHC catalysts has a broad substrate scope, excellent solubility in a range of solvents, and good bench stability.<sup>34</sup> The HIE reactions using **cat1a** with 2-phenylpyridine at room temperature,

40 °C, 50 °C and 60 °C with both 5 and 50 equivalents of formic acid-*d*<sub>2</sub>:triethylamine gave high levels of deuterium incorporation for all conditions (see SI).

We then moved to a 96-well plate format and chose paradox aluminum blocks as they could both be heated and sealed to avoid the loss of volatiles including solvent and D<sub>2</sub> (if formed). Both 2-phenylpyrimidine and 2-phenylpyridine showed high levels of deuteration for **cat1a** loadings between 5 and 20 mol% and with a slight drop off at 1 mol%; for benzamide, partial deuteration was observed at 20 mol% **cat1a** loading with little incorporation observed at lower catalyst loadings (see SI). A comparison between an HTE plate assembled under inert atmosphere in a glove box and one assembled exposed to air on the benchtop showed no difference; however, to maximize reproducibility between experiments, the plates were prepared under an inert atmosphere for all subsequent reactions. Moreover, we confirmed that there was no difference between using fully deuterated triethylamine-*d*<sub>15</sub> and unlabeled triethylamine for the three substrates, which unsurprisingly demonstrated that no exchange was taking place with the base. The supply of **cat1a** was depleted and the compound was backordered so subsequent work was performed with **cat2** (Fig. 1b, Ar = Mes; R = PME<sub>2</sub>Ph, R' = H, A = BARF). A quick bridging study was conducted in which **cat2** gave similar results to **cat1a** with 2-phenylpyridine.

### Substrate scope – 48 different substrates

To evaluate the scope and reproducibility of the method, we tested 48 substrates (in duplicate) using the formic acid-*d*<sub>2</sub>/triethylamine (5 : 2) mixture with 20 mol% **cat2** loading. The substrates used for this initial screen and the results are depicted in Fig. 2. To facilitate the data interpretation, a Python script was written, which extracts the mass distribution for the molecule of interest from the raw data and determines the isotope distributions using the IsoPat<sup>2</sup> algorithm.<sup>35</sup> With this method, it was easy to compare both positive and negative ionization modes to ensure the robustness of the obtained data. The development of the Python script is described in more detail in the SI.

As expected for this type of C–H activation chemistry, directing groups with an aromatic sp<sup>2</sup> nitrogen performed well (*ca.* 0.73–2.44 <sup>2</sup>H/molecule incorporation, Fig. 2a). Lower incorporations were obtained for pyridine/pyrimidine-indole combinations (Fig. 2b). It is important to bear in mind that the conditions are relatively mild with only 20 mol% loading of **cat2** and 5 equivalents of the deuterium source, compared to reaction conditions which often include the use of stoichiometric catalyst and large excesses deuterium gas when optimizing for tritium-labeling reactions. However, great progress has been made to reduce the amount of deuterium gas and increase the deuterium chemical yield.<sup>36</sup> No incorporation was obtained for triazoles, tetrazoles (Fig. 2c), and amides (Fig. 2d). Tetrazole directing groups are known to give poor HIE under the conditions employed; Kerr and co-workers have reported a general method for use with tetrazoles.<sup>37</sup>



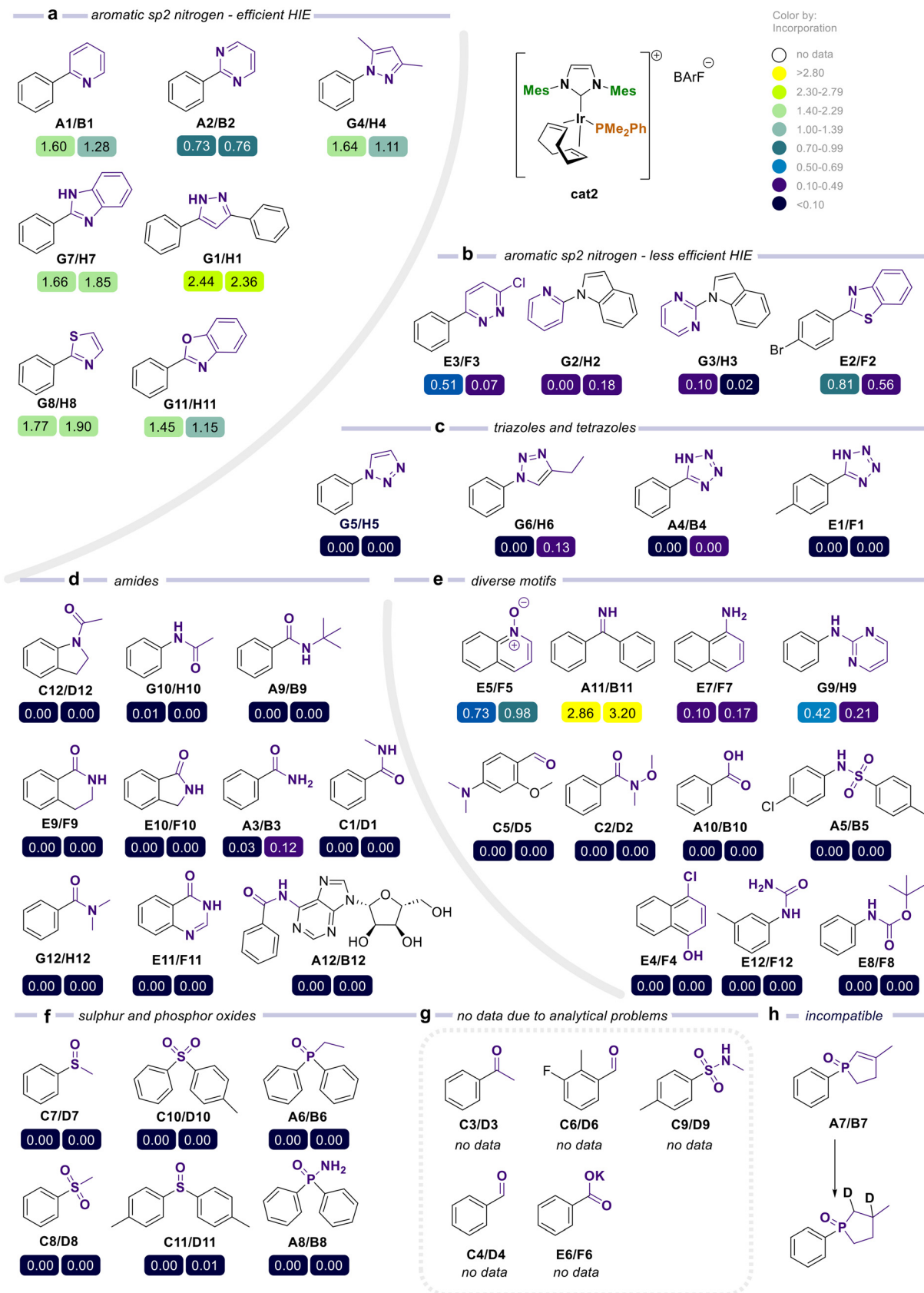


Fig. 2 HTE with 48 different substrates performed in duplicate. The number displays the deuterium incorporation for each molecule. Reaction conditions: substrate (10 μmol, 1 equiv.), cat2 (20 mol%), formic acid-d<sub>2</sub> (5 equiv.), triethylamine (2 equiv.), 2-MeTHF (0.3 mL), RT, overnight.



Within the substrate-subset spanning diverse motifs, interestingly, quinoline *N*-oxide and benzophenone imine worked well under the reaction conditions, while aromatics containing functionalities such as amines, sulfonamide, aldehyde, methoxybenzamide, carboxylic acid, chloro/hydroxy, urea- and carbamates did not incorporate a significant amount of deuterium (Fig. 2e), and neither did sulfoxides or phosphine oxides (Fig. 2f). For five of the substrates, we couldn't analyze the data due to challenging MS-ionization. If needed for a project, these compounds could be analyzed using a different analytical technique. The 2-phospholene oxide compound **A7/B7** partially reacted under the conditions to give the deuterated phospholane (Fig. 2h); the phospholene did not show incorporation of deuterium. Due to the fluctuations observed within duplicates, the chemistry needs to be run at least in duplicate, and a positive result should be confirmed using standard D<sub>2</sub>-manifold chemistry to ensure the appropriateness of the method (if needed, for example for subsequent tritium-labeling applications).

### Inhibition experiments

Having confirmed that the expected directing groups afforded deuterated compounds using the formic acid-*d*<sub>2</sub>/triethylamine (5:2) mixture and that the enrichment could be determined using our Python script, we then set out to determine the impact of other functional groups on the HIE reaction. We selected three substrates that showed excellent exchange in our first reactions: 2-phenylpyridine (**S-A**), 3,5-diphenyl-1*H*-pyrazole (**S-B**), and quinoline *N*-oxide (**S-C**). We then evaluated these three substrates in an HIE reaction in the presence of a competitive substrate **CS1** to **CS16** (Fig. 3). The substrates and catalysts were pre-mixed 30 minutes prior to the addition of the deuteration mixture to allow any potential complexation to the catalyst to occur. With two reactants rather than one being present in the mixture, the equivalents of the formic acid-*d*<sub>2</sub>:triethylamine mixture were increased from 5 to 10. After the reaction, the HIE crude reaction mixtures were analyzed to determine how the competitive compounds impacted the deuteration level of the three substrates. While most compounds did not strongly influence the deuterium incorporation of the substrates, some reduced the efficiency of the reaction. Both **CS1** and **CS7** are aryl nitriles, which are known inhibitors of HIE, and they both had a major impact on the deuterium incorporations for **S-B** and **S-C**.<sup>38</sup> Triazole **CS6** also reduced the deuterium incorporation for **S-B** and **S-C**, while phenyltetrazole **CS13** completely inhibited the deuterium incorporation of **S-A**, **S-B**, and **S-C**. This could indicate that the tetrazole moiety binds to the Ir-catalyst in a non-productive manner, thereby inactivating it and shutting the reaction down. Benzoic acid **CS14** reduced the deuterium incorporation of **S-B**, perhaps indicating a sensitivity to the level of acid present (see SI for detailed isotope incorporations into **CS1** to **CS16**).<sup>37</sup> We did note that our Python script worked well for the substrates, but it did not function well for some of the competitive substrates. Poorly ionizing substrates afforded misleading results, which again highlights the need

to ensure that the analytical technique selected is appropriate.

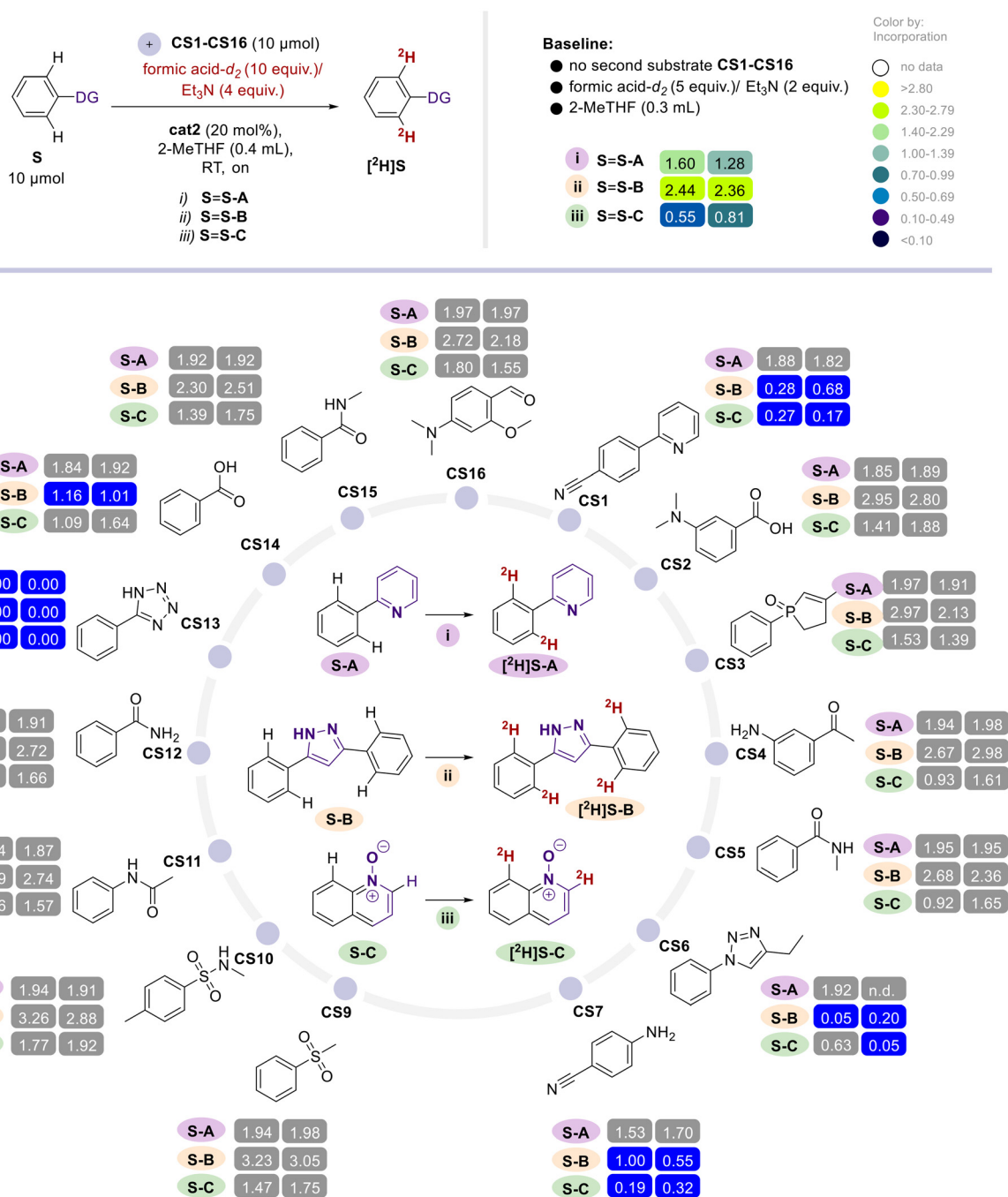
### HTE on 12 different active pharmaceutical ingredients

Having demonstrated the method's utility for building blocks and identified inhibitory motifs, we decided to investigate the platform's use for more heavily functionalized drug molecules. Since it is those molecules we primarily intend to label with deuterium or tritium in our lab, it was important to establish whether the reaction would still work with these and how reproducible it was. We chose the 12 active pharmaceutical ingredients **D-1** to **D-12** (as depicted in Fig. 4), with some of them already previously reported in hydrogen isotope labeled form (lumacaftor (by methylation),<sup>39</sup> rimonabant (by halide reduction),<sup>40</sup> niclosamide (by HIE),<sup>41</sup> tolmetin (by HIE),<sup>42</sup> olaparib (by HIE),<sup>43</sup> aristolochic acid I (by HIE using T<sub>2</sub>O),<sup>44</sup> celecoxib (by methylation and HIE)<sup>36,39,45</sup>).

We ran the reactions in a 96-well plate with each experiment being repeated 8 times. The active pharmaceutical ingredients that were labeled successfully as determined by MS (all except rimonabant **D-3**) were then purified by preparative HPLC and analyzed by <sup>1</sup>H-NMR to understand the deuterium incorporation in more detail. The observed results for all compounds were reasonably similar between all 8 wells, giving us confidence in both the robustness of our method, as well as, its reproducibility. We were unable to determine the regiochemistry of the deuterium label in sildenafil (**D-6**) due to the low level of deuterium incorporation. The regiochemistry of deuterium incorporation for [<sup>2</sup>H]niclosamide (**D-7**),<sup>41</sup> [<sup>2</sup>H]olaparib (**D-9**)<sup>43</sup> and [<sup>2</sup>H]celecoxib (**D-12**)<sup>45</sup> corresponded with that previously reported, and the regiochemistry observed for [<sup>2</sup>H]minaprine (**D-1**), [<sup>2</sup>H]lumacaftor (**D-2**), [<sup>2</sup>H]capmatinib (**D-4**), [<sup>2</sup>H]ataluren (**D-5**), [<sup>2</sup>H]aristolochic acid I (**D-10**), and [<sup>2</sup>H]vismodegib (**D-11**) was as expected. A significant drop in isotope incorporation was observed for **D-7** from the initial LCMS results to isolation prior to preparative HPLC to final isolation (from 2.6 to 1.9 to 1.6 <sup>2</sup>H/molecule). The acidity of the protons of nitroarenes has been described previously.<sup>46</sup> Similarly, the isolation of both [<sup>2</sup>H]capmatinib (**D-4**) and [<sup>2</sup>H]aristolochic acid I (**D-10**) by preparative HPLC resulted in compounds with much lower isotope incorporations than expected from the initial LCMS results (1.25 to 0.17 and 1.70 to 0.85 <sup>2</sup>H/molecule respectively). We suspect this arises from exchange of the deuterium label with solvent during the isolation and purification. The exchange of isotopic hydrogen with solvent during purification or upon storage or during the biological assay is often observed.<sup>47,48</sup>

It needs to be highlighted that the deuterium incorporation into tolmetin (**D-8**) was later demonstrated to occur even without catalyst, likely due to the enolizable carboxylic acid, which can then react with formic acid-*d*<sub>2</sub> to deuterate the methylene (see SI, not further analyzed). This shows the importance of conducting additional <sup>1</sup>H NMR analyses or HIE using D<sub>2</sub> on a deuterium manifold depending on the project, as the use of formic acid-*d*<sub>2</sub> may lead to "false positive" HIE. Although [<sup>3</sup>H]tolmetin has been previously prepared by HIE<sup>42</sup>





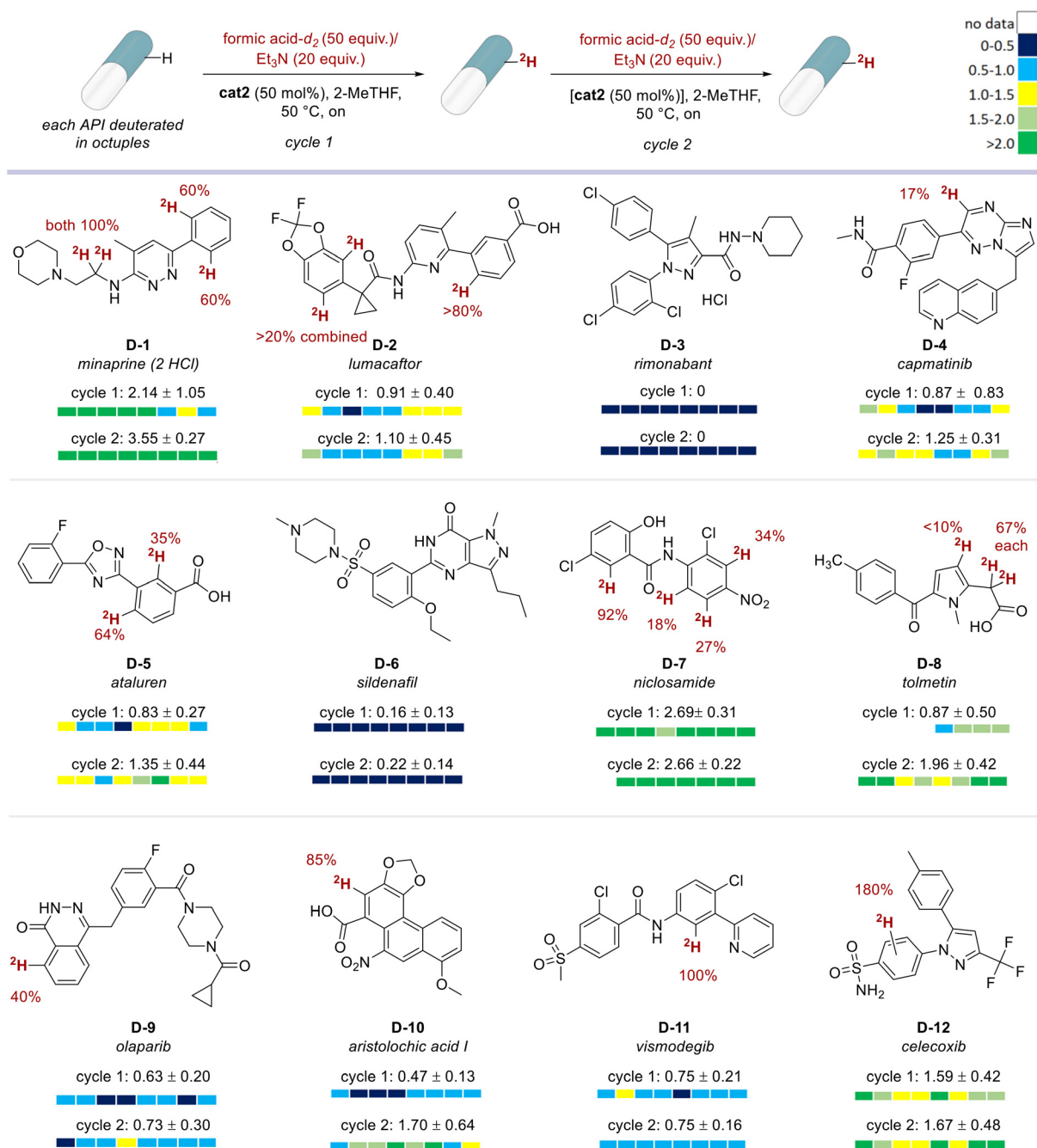
**Fig. 3** Results from the competitive deuteration HTE. Note that results from CS8 are omitted due to uncertainty in the actual substance added. The number displays the deuterium incorporation for each substrate S-A, S-B and S-C (blue highlight indicates significant reduction in the deuterium incorporation).

(see SI), it is likely that our HIE reaction was obscured by the background reaction.

HIE reactions are equilibrium processes which means it is impossible to achieve high isotopic enrichments with near-stoichiometric quantities of deuterium. While there has been a trend to reduce the excess of isotopic hydrogen used in these reactions over recent years,<sup>36</sup> multiple equivalents are nearly always used. Our method allows precise control over the rela-

tive quantities, which means less deuterium can be used for more reactive substances and *vice versa*. Moreover, multiple iterations of these reactions can easily be performed in sequence should sufficient incorporation not have been achieved. Simply adding another aliquot of the deuteration mixture to the well and repeating the reaction improved the degree of deuterium incorporation in many cases (Fig. 4, cycle 2).





**Fig. 4** Results from one and two cycles of HIE reactions. The number displays the mean deuterium incorporation from eight experiments run in parallel, as determined by MS, together with the standard deviation for each molecule and cycle (D-1 to D-12). The color coding visualizes the variability of deuteriation from the eight experiments. The proposed site of deuteriation is indicated based on  $^1H$ -NMR analysis of the successfully labeled molecules.

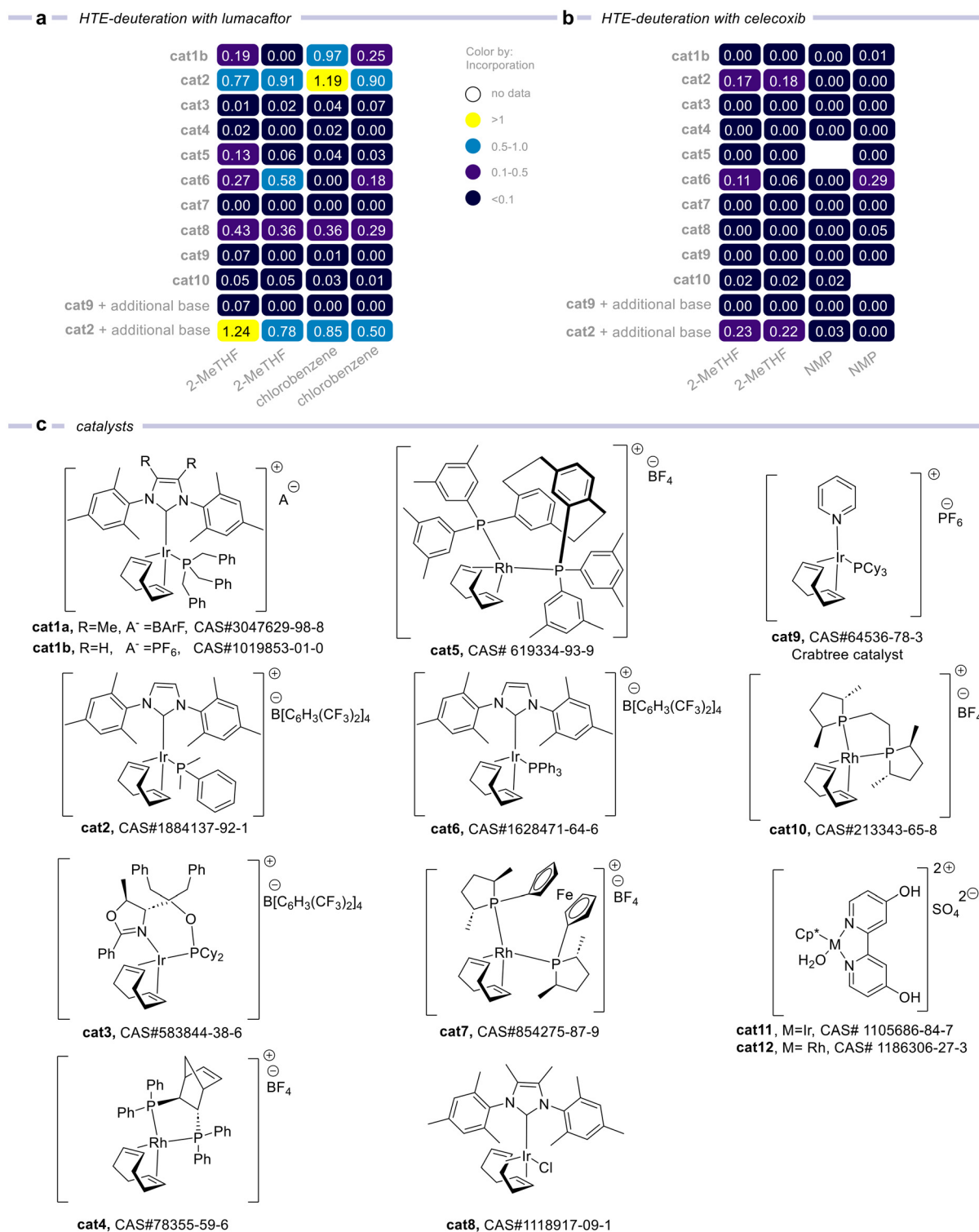
### HTE-catalyst screen

Finally, the applicability of the high-throughput deuteration setup to screen for appropriate HIE conditions was investigated. Being able to test a range of conditions in parallel would accelerate the delivery of  $^2H/^3H$ -labeled compounds. We decided to test lumacaftor (D-2), sildenafil (D-6), tolmetin (D-8), and celecoxib (D-12) from our previous screen, with 10

different catalysts **cat1b**–**cat10** (Fig. 5), some also with additional base, and screening different solvents (2-MeTHF, chlorobenzene and NMP). Adding the ability to rapidly screen different catalysts for HIE reactions should enable us to speed up the delivery of tritium labeled pharmaceuticals.

The HIE reaction for each compound was performed in duplicate. For lumacaftor (Fig. 5a), the four iridium catalysts **cat1b**, **cat6**, **cat8**, and **cat2** showed promise with **cat2** perform-





**Fig. 5** Results of the HIE-conditions screen for (a) lumacaftor (**D-2**) and (b) celecoxib (**D-12**). The number displays the deuterium incorporation for the two compounds. Reaction conditions: substrate **D-2** or **D-12** (4.31  $\mu\text{mol}$ , 1 equiv.), catalyst (50 mol%), formic acid- $\text{d}_2$  (50 equiv.), triethylamine (20 equiv.) vs. additional triethylamine (50 equiv.), 2-MeTHF vs. chlorobenzene or NMP, 50  $^{\circ}\text{C}$ , overnight. (c) List of catalysts **cat1** to **cat12**.

ing the best, and all other catalysts showing minimal HIE. The addition of extra triethylamine to the HIE mixture showed mixed results with **cat2**. For celecoxib, poor exchange was

observed in general, which is in contrast to the previous results. We believe this arises from the acidic nature of the HIE medium interfering with complexation of the iridium to



the pyrazole nitrogen. This may have led to considerable variance of the deuterium exchange (Fig. 4 vs. Fig. 5), but we did not further investigate this. **Cat2** performed the best with or without additional triethylamine and **cat6** also afforded some deuterium incorporation.

The results for sildenafil **D-6** and tolmetin **D-8** are shown in more detail in the SI. Unfortunately, the broader catalyst screen did not result in even a marginal level of deuterium incorporation for sildenafil. Tolmetin on the other hand gave excellent incorporation of deuterium with all the catalysts tested. However, the deuterium incorporation was due to an artifact of the assay and similar levels of deuterium incorporation were observed without catalyst (see SI). The deuterium incorporation may arise *via* reversible enolization of the carboxylic acid; thus, substrates bearing enolizable moieties such as tolmetin would present a limitation of this methodology.

The catalyst screen may also be dependent on the catalyst's ability to generate deuterium gas; meaning that the deuterium incorporations observed by LCMS are dependent upon two distinct reactions both of which are catalyst dependent: 1. dehydrogenation of formic acid- $d_2$  to give  $D_2$  gas and 2. HIE of the arene using either  $D_2$  gas or deuterium from the formic acid- $d_2$ . Himeda has shown that the dehydrogenation of formic acid/formic acid- $d_2$  in  $D_2O/H_2O$  results in dramatic product difference when the metal is changed. With  $HCO_2H$  and  $D_2O$ , iridium catalyst **cat11** forms predominantly  $D_2$  (86%, Fig. 1d) while rhodium catalyst **cat12** forms predominantly HD (91%), each in different rates.<sup>26</sup> Hence, the catalyst-dependent deuterium gas generation, together with the catalyst's individual performance in HIE reactions, could be both responsible for the results in the catalyst screens.

It is critical to recognize that the use of formic acid- $d_2/Et_3N$  (5:2) is not equivalent to using  $D_2$  gas and that tritium labeled formic acid is not a viable option for routine high specific activity reactions. Therefore, additional validation will be required to assess the suitability of any catalyst obtained from the HTE screen for use with  $T_2$  gas in tritium-labeling applications.

## Conclusions

We have demonstrated the use of high-throughput hydrogen-isotope exchange *via* transfer deuteration. Herein, we employ formic acid- $d_2$  as a surrogate for a  $D_2$ -atmosphere which would be otherwise difficult to introduce into a 96-well plate without specialized equipment. This platform has enabled us to quickly screen different substrates and reaction conditions, which previously had to be set up individually. The mild conditions and the ease of reaction set up, with stock solutions, the possibility for ambient atmosphere, and no specialized equipment, makes this method an attractive approach for screening multiple deuteration reactions and conditions. The equivalents of the deuteration reagent (formic acid- $d_2$ ) can be fine-tuned to provide milder or more forcing conditions, depending on the substrate in question. Finally, the end-to-

end automation of the reaction analysis (converting raw LC-MS data into the quantity of deuterium incorporated) was useful to assess isotope incorporation.

## Author contributions

A. Schick: conceptualisation, data curation, investigation, methodology, validation, visualisation, writing: reviewing and editing. C. Bauer: conceptualisation, data curation, software, supervision, writing: reviewing and editing. T. Slagbrand: conceptualisation, investigation, methodology, writing: reviewing and editing. M. Guerzoni: data curation, investigation, methodology, validation, visualisation, writing: reviewing and editing. M. Johansson: investigation, methodology, writing: reviewing and editing. S. Gahlawat: conceptualisation, software, writing: reviewing and editing. M. Johansson: conceptualisation, investigation, methodology, project administration, writing: reviewing and editing. P.-O. Norrby: conceptualisation, methodology, project administration, supervision, writing: reviewing and editing. C. S. Elmore: conceptualisation, data curation, funding acquisition, methodology, project administration, resources, supervision, writing: review & editing. M. Artelsmair: conceptualisation, data curation, investigation, methodology, project administration, validation, visualization, writing – original draft, writing: reviewing and editing.

## Conflicts of interest

AS, CB, TS, MG, MJ, MJ, PN, CE, and MA are or were AstraZeneca employees and may hold shares and/or stock options in the company.

## Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: <https://doi.org/10.1039/d6qo00301j>.

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