Synlett J. Dey et al. THIEME OPEN ACCESS Account

Late-Stage C–H Deuteration of Organic Compounds via Ligand-Enabled Palladium-Catalyzed Hydrogen Isotope Exchange

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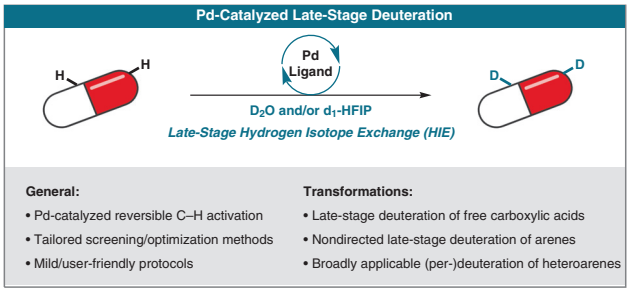
Published as part of the Cluster
Isotopic Labeling



Received: 05.12.2023
Accepted after revision: 15.01.2024
Published online: 22.03.2024 (Version of Record)
DOI: 10.1055/s-0042-1751566; Art ID: ST-2023-12-0535-A

Abstract Over the past years our lab has established a research program towards the late-stage introduction of deuterium into organic molecules using Pd-catalyzed reversible C–H activation as a means to affect hydrogen isotope exchange. Through catalyst design, including the introduction of novel ligand scaffolds, as well as the use of strategically chosen optimization and screening approaches, e.g., exploiting microscopic reversibility by first optimizing de-deuteration processes or using a multi-substrate screening approach, our studies have resulted in a number of synthetically useful labelling protocols and are described herein from a personal perspective.

Key words deuteration, hydrogen isotope exchange (HIE), catalysis, ligand design, labelling

1 Introduction

Due to the importance of deuterium labelled compounds in many research areas, hydrogen isotope exchange (HIE) is a key technology that has received considerable attention in both academic and industrial laboratories.[1] Deuterated compounds display marked differences in their physical and chemical properties when compared to their non-deuterated analogs. The most important differences result from the fact that deuterium has a two-fold larger mass than hydrogen. As a consequence, the C–D bond is associated with a reduced vibrational stretching frequency in comparison to the C–H bond, a lower ground-state energy, and thus a greater activation energy for the bond cleavage (1.2–1.5 kcal mol^{-1}). This difference in reactivity is quantified as the so-called kinetic isotope effect (KIE),[2] which corresponds to the ratio of the rate constants (k_H/k_D) when a deuterated and non-deuterated compound are engaged in an otherwise equal reaction (Figure 1A). Furthermore, deuterated compounds feature a reduced lipophilicity and slightly altered pK_a values. Deuterium labelled compounds are for example used to elucidate reaction mechanisms,[2d] to create unique isotope patterns in mass spectrometry,[3] and to study bioactive molecules in terms of their absorption, distribution, metabolism, and excretion (ADME) properties,[4] thereby gaining insights into their metabolic profile and toxicity (Figure 1B).[5] In addition to this, deuterium incorporation can help to improve the pharmacokinetic and/or toxicity profile of bioactive molecules, potentially translating into improvements in the efficacy and the safety of these drugs.[6] In 2017, deutetrabenazine, the first deuterium-labeled drug, was approved by the FDA for the treatment of chorea associated with Huntington's disease (Figure 1B).[7] Later, in 2022, the FDA approved the de novo deuterated drug deucravacitinib, an allosteric tyrosine kinase 2 inhibitor used for psoriasis (Figure 1B).[8] While these approved drugs feature N/O-CD$_3$ motifs, it should be noted that molecules with other deuteration patterns, e.g., deuteration on (hetero)aromatic C(sp^2) positions or on varied aliphatic chains are currently at different stages of clinical investigations.[1e]

For simple molecules with lower molecular complexity, traditional approaches have been utilized to incorporate deuterium in pre-functionalized starting materials.[1a,c] However, these approaches have major limitations in applicability due to substrate availability, often resulting in

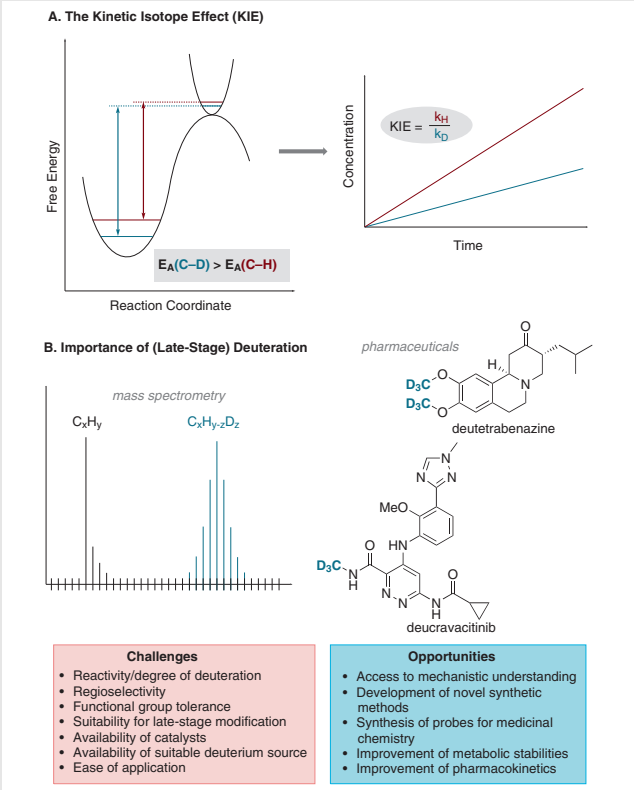


Figure 1 The kinetic isotope effect (A). The importance of deuterated organic compounds alongside the challenges and opportunities of deuteration methods (B).

time-consuming and cost-intensive multistep synthetic protocols. The increasing demand for deuterium labelled complex organic molecules has raised interest in methods that enable the direct late-stage incorporation of deuterium, thereby bypassing the need for pre-functionalized starting materials.[9] Traditional methods for direct deuteration via HIE include the use of Lewis/Brønsted acids/bases,[1a,9a] which can enable efficient HIE but typically remain limited to comparably simple substrates due to the harsh conditions typically required that result in low functional group tolerance (Scheme 1A). In this context, reversible C–H activation has been recognized as an elegant tool to enable direct HIE.[9] Heterogeneously catalyzed methods have been used to deuterate various substrates and high catalytic activities can be achieved with many transition metals.[9c–e,10] These methods offer advantages with respect to the high levels of deuterium incorporation that can be reached and simple purification protocols, but also typically require harsh reaction conditions, leading to low functional group tolerance and undesired side reactions (Scheme 1B). The use of homogeneous transition-metal catalysis in conjunction with directing groups (DGs) on the substrate has proven highly useful for the regioselective deuteration of complex substrates under mild reaction conditions, enabling broader functional group tolerance and applications in late-stage functionalization (Scheme 1C).[9] Notably, this approach is suitable for regioselective deuteration, but in turn cannot be used for per-deuteration of the respective substrates, since the reactivity remains limited to positions to

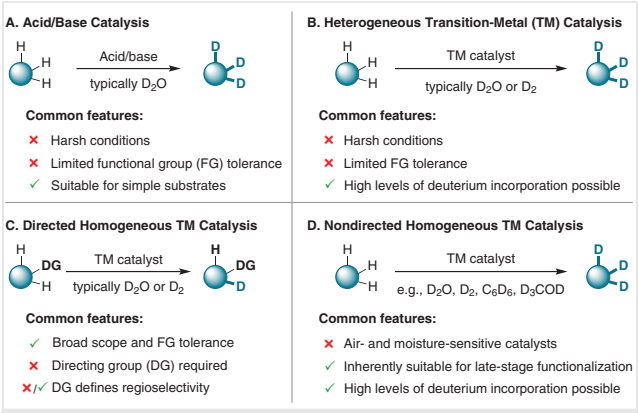
Biographical Sketches

Jyotirmoy Dey received his B.Sc. degree in chemistry (honors) from Ramakrishna Mission Residential College (RKMRC), Narendrapur (affiliated to the University of Calcutta). He obtained his M.Sc. degree in chemistry from the Indian Institute of Technology Kanpur. In 2021, he began his doctoral studies in the research group of Prof. Dr. Manuel van Gemmeren at the University of Münster. In 2022, the van Gemmeren research lab moved to Kiel University, where Jyotirmoy is continuing his research studies focused on Pd-catalyzed nondirected C–H activation/functionalization of arenes.

Manuel van Gemmeren conducted his doctoral studies in the lab of Prof. Benjamin List (completed in 2014), followed by postdoctoral studies in the group of Prof. Rubén Martín. He led an independent research group at the University of Münster from 2016 to 2022, before he moved to Kiel University as a professor of organic chemistry. Research in the van Gemmeren lab focusses on the development of novel synthetic methods, typically based on C–H activation, that enable challenging transformations to proceed with catalyst-controlled reactivity and selectivity

which the DG directs the catalyst. These directed methodologies are complemented by nondirected approaches that offer the potential to access unbiased C–H bonds without requiring a DG on the substrate.[11] This can in principle be used to affect the late-stage per-deuteration of structurally diverse substrates, although many of the catalyst systems reported to date are moisture- and air-sensitive and have proven to be incompatible with a range of common organic functional groups,[9b] raising the need for further catalyst development (Scheme 1D). Besides C–H activation, recent reports in the field of late-stage deuteration have also used various complementary approaches.[12]

In this context, we initiated a research program aiming to develop catalysts for late-stage HIE that would either rely on a directed C–H activation with a widespread, native directing group, or would enable a non-directed HIE with broad applicability.

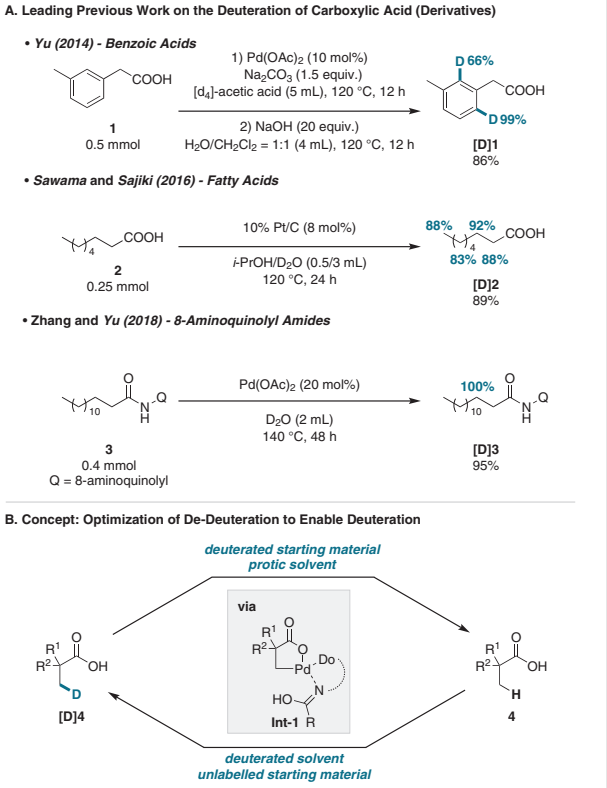


Scheme 1 Strategies towards hydrogen isotope exchange (HIE): Acid/base catalysis (A), heterogeneous transition-metal catalysis (B), homogeneous directed C–H activation (C) and nondirected homogeneous C–H activation (D)

2 β-C(sp³)–H Deuteration of Free Carboxylic Acids

Carboxylic acids are abundant in bioactive molecules and are thus highly attractive substrates in catalysis.[13] Various research groups have developed catalysts for the regioselective and/or enantioselective C–H activation of free carboxylic acids, thereby enabling a wide range of useful transformations.[14] Carboxylic acids and their derivatives have also been used as directing groups for HIE processes.[15]

In 2014, Yu and co-workers described a Pd-catalyzed ortho deuteration of phenylacetic acid using (d_4)-acetic acid as a source of deuterium (Scheme 2A).[16] For example, 2-(*m*-tolyl) acetic acid (**1**) was fully deuterated at the sterically accessible ortho position, while the sterically more hindered ortho position reached 66% deuteration. The authors also observed deuteration of the benzylic position α to the carboxylic acid, presumably occurring through a deprotonation/reprotonation mechanism. In 2016, building on previous related reports,[17] Sawama and Sajiki developed a method for the deuteration of saturated fatty acids.[18] For example, caprylic acid (**2**) reached high levels of deuterium incorporation at all positions in good yield using heterogeneous Pt/C in an ^{i}PrOH/D_2O solvent mixture. The authors also demonstrated that the degree of deuteration could be increased by using a fully deuterated ^{i}PrOD/D_2O solvent mixture. In 2018, Zhang and Yu developed a Pd-catalyzed regioselective HIE reaction using 8-aminoquinoline as a DG.[19] With this protocol the authors could access *ortho*-selective deuterated aromatic acids and β-deuterated aliphatic acids using D_2O as the main source of deuterium. For example, 8-aminoquinolyl amide **3** was fully β-deuterated with an excellent yield.



Scheme 2 Selected precedents on the C–H deuteration of carboxylic acids and their derivatives (A). Concept of exploiting microscopic reversibility for reaction optimization (B).

In light of these advances and our own experience in the direct C–H activation of free carboxylic acids, the development of a regioselective deuteration of such free carboxylic substrates, ideally suitable for late-stage HIE, seemed highly attractive. We became aware of this potential during the mechanistic investigation of our method for the γ-olefination of a free carboxylic acid, where we found that the C–H activation step was in principle reversible.[20] The key mechanistic experiment in this context was the de-deuteration

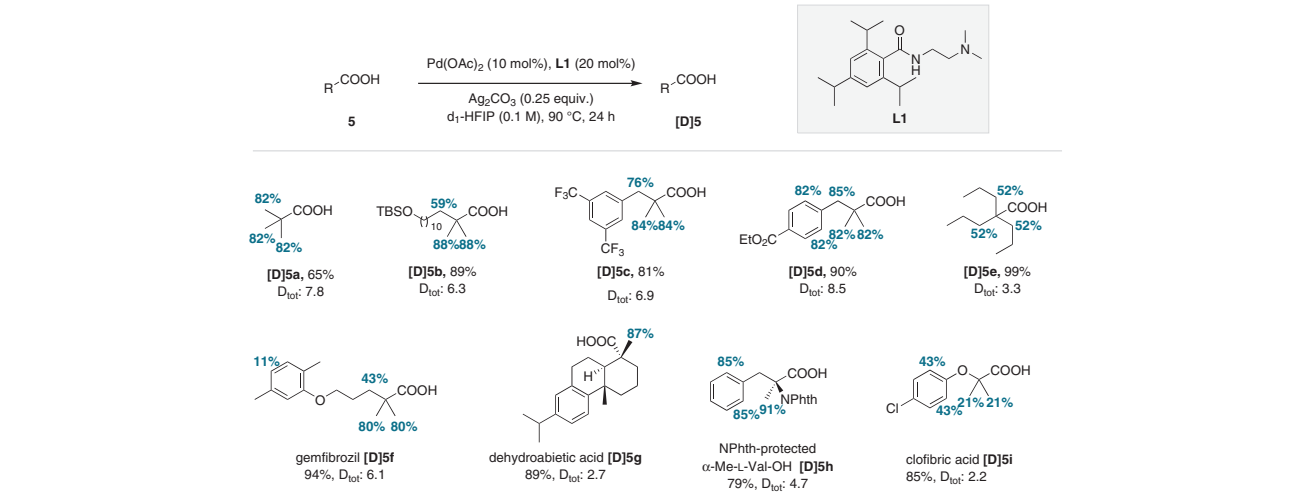
of a deuterated starting material when exposed to the reaction conditions. De-deuteration experiments are commonly used to probe reversibility in C–H activation methods, and we argued that it should be possible to exploit the principle of microscopic reversibility to enable the deuteration of free carboxylic acids (Scheme 2B).[21] Such a method would proceed via the same intermediate (**Int-1**) also involved in the de-deuteration, but with two key changes: a native substrate **4** would be exposed to the reaction conditions with a deuterated solvent rather than placing the deuterated substrate **[D]4** in the protic solvent.

We realized that the development of such a method would require an efficient reversible formation of **Int-1** without decomposition of the starting material. Regarding **Int-1**, the general ligand structure depicted in Scheme 2B merits some attention. Building upon Yu's original discovery of *N*-acylamino acids as ligands for Pd-catalyzed C–H activation processes, it has been shown more generally that bidentate ligands bearing one donor site, which can be a neutral L-type donor or an anionic X-type donor, and one anionic internal base site with the ability to promote the concerted metalation–deprotonation (CMD) step, are privileged motifs for catalyst design in the field of Pd-catalyzed C–H activation.[22]

We furthermore realized that a successful method development would also require careful control of all possible sources of protons, e.g., from the base used, the ligand, the acidic protons of the substrate, etc. We questioned if there could be a strategically better approach to the optimization studies. At this stage, the van Gemmeren lab was closely associated with the Glorius group, who had developed a mechanism-based screening strategy,[23] where the feasibility of new transformations is probed by studying a single key step in the alleged mechanism. By combining this line of thought with the microscopic reversibility mentioned above, we hypothesized that it might be possible to optimize the de-deuteration of a deuterated substrate **[D]4** and later change the direction of the transformation. This would offer the advantage that during method development no issues with unknown sources of protons could arise and that the optimization studies would require only a deuterated starting material instead of a deuterated solvent. We also realized that the later change of direction would actually benefit from a kinetic isotope effect, since in the deuteration protocol the kinetically more accessible C–H bond would need to be activated while in the de-deuteration the less reactive C–D bond would need to react. Thus, if a difference were to be expected at the end of the optimization studies, the deuteration should in fact work better than the previously optimized de-deuteration.

During our optimization studies we found that, as expected from previous experience, 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) performed best as the reaction solvent.[24] Considering the high costs of deuterated HFIP from commercial suppliers, we developed a reliable method for the large-scale synthesis of d_1-HFIP from cheap starting materials in parallel to our further optimization work. We also discovered that ethylenediamine-derived ligands, first described by Yu,[22b,c] gave the most promising results. Further optimization studies revealed that replacing the acetamide group in this class of ligands with a sterically demanding 2,4,6-tri-isopropyl (TRIP) benzamide as the CMD-promoting group gave optimal results (see **L1** in Scheme 3). Notably, benzamides without ortho substituents gave virtually no catalytic activity, presumably due to an intramolecular C–H activation within the ligand.

Furthermore, by blocking both ortho positions of the benzamide moiety, the arene is forced out of the amide plane, which is expected to have a strong influence on the ability of this motif to engage in the CMD step.[25]

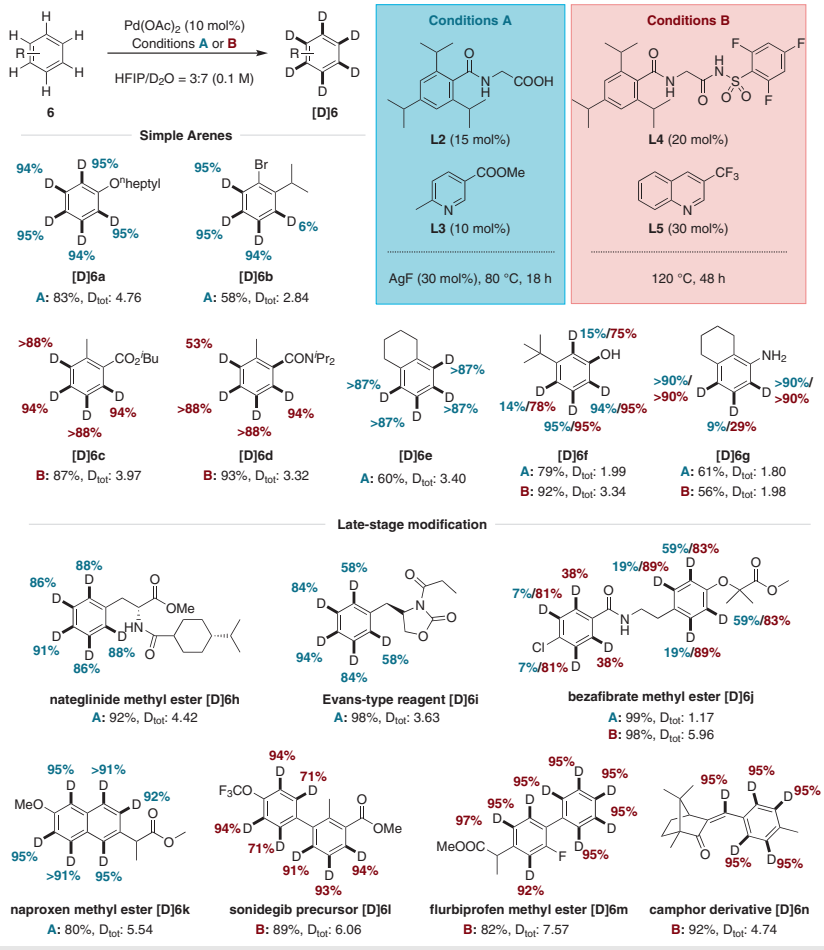


Scheme 3 Selected examples from our studies on the deuteration of free carboxylic acids

Having identified the optimal reaction conditions, we started to investigate the substrate scope of this protocol. The majority of substrates were reisolated in high to excellent yields. Selected examples are shown in Scheme 3. Pivalic acid (**5a**) resulted in high D-incorporation (D_{tot} = 7.8). Substrate **5b** bearing a TBS-protected alcohol on the side chain led to an interesting finding. Besides the expected deuteration in the methyl group, we also observed significant deuterium incorporation at the β-methylene position. This is remarkable, since this constituted the first report on Pd-catalyzed β-methylene C–H activation/functionalization of a free carboxylic acid. With 3,5-trifluoromethylated substrate **5c** H/D exchange was observed exclusively in the aliphatic positions, while in substrate **5d**, deuterium incorporation also occurred at the ortho positions of the arene (D_{tot} = 8.5), presumably through a carboxylate-directed pathway. The high activity of our catalyst system toward β-methylene positions was also observed in 2,2-dipropylpentanoic acid (**5e**). Later, we applied our method to the late-stage deuteration of various bioactive molecules. For example, compounds **[D]5f**–**[D]5i** gave moderate to high deuterium incorporation with excellent yields, highlighting the functional group tolerance of our method.

3 Nondirected C–H Deuteration of Arenes

In the context of nondirected C–H activations on arenes, our lab has introduced a catalyst system that, alongside a contemporary report, enabled such reactions to occur with the arene as the limiting reagent.[26] The key to success in our case was the use of two cooperatively acting ligands, an electron-poor *N*-heterocycle and a bidentate ligand analogous to those used in aliphatic C–H activation. These dual-ligand-based catalysts are substantially more active than the respective mono-ligand systems and mimic the steric/electronic environment of directed C–H activation processes. This design has enabled us to, for example, develop



Scheme 4 Selected examples from our protocol for the nondirected C–H deuteration of arenes

nondirected olefinations, cyanations, alkynylations, and iodinations of arenes.[26] During extensive mechanistic studies on our dual-ligand-based catalyst system for the nondirected C–H activation of arenes, we found that the C–H activation step is also reversible in this case.[26g] Aromatic motifs are ubiquitous in bioactive molecules and it is widely recognized that C–H bonds can be considered the Achilles heel of drug candidates with respect to undesirably fast metabolization.[9] In the context of nondirected C–H deuterations,[27] Chirik and co-workers developed an iron catalyst capable of inducing HIE using D_2 as the deuterium source.[28] The same group later developed a Ni-based catalyst that enabled the deuteration and tritiation of drug molecules using D_2 and T_2.[29] Furthermore, de Ruiter et al. described an Fe-PCP-pincer complex that catalyzes HIE using C_6D_6 as the deuterium source.[30] Despite these developments, challenges remained, for example, due to the sensitivity of the catalysts employed and limitations in the substrate scope. Thus, novel methods for the incorporation of deuterium into aromatic scaffolds remain highly attractive and we wondered if we could utilize the reversibility of C–H activation with our catalysts to obtain such a method.

After extensive optimization, two sets of conditions were developed: one for electron-rich arenes and the other for electron-poor arenes (Scheme 4).[31] Based on our previous studies we knew that the sterically demanding TRIP-benzamide group is useful to achieve high rates and degrees of deuteration. Glycine-derived **L2** was found to be best for electron-rich arenes (conditions A) while for electron-poor substrates, a novel *N*,*N*-bidentate ligand featuring an *N*-acyl sulfonamide motif instead of a carboxylate as an X-type donor site (**L4**) proved to be optimal (conditions B). Notably, cheap and easy to handle D_2O was used as a source of deuterium alongside regular HFIP as a co-solvent.

With these reaction conditions, we explored the substrate scope of our deuteration protocol. Yields were generally good to excellent. Excellent degrees of deuteration were observed in anisole derivative **6a** as well as the disubstituted arenes **6b** and **6e** under conditions A. Further, disubstituted arenes containing electron-withdrawing ester and amide groups (**6c** and **6d**) showed high degrees of deuteration under conditions B. A free hydroxy group (**6f**) or amine group (**6g**) were also well tolerated, and even challenging positions in these substrates were deuterated when using conditions B. We later proceeded to evaluate the suitability of our method for the late-stage isotopic labelling of bioactive molecules. Nateglinide methyl ester **6h**, the Evans-type reagent **6i**, and naproxen methyl ester **6k** all gave high levels of deuterium incorporation under conditions A. Bezafibrate methyl ester **6j** underwent efficient deuteration on both arene moieties when it was subjected to conditions B. Sonidegib precursor **6l**, flurbiprofen methyl ester **6m**, and the camphor derivative **6n** also underwent efficient deuteration under conditions B. The decomposition of the above-mentioned complex substrates generally remained low, highlighting the broad functional group tolerance of our protocol.

4 Nondirected C–H Deuteration of Heteroarenes

A drawback of our method for the deuteration of arenes remained that it was not generally applicable to heteroarenes, giving low degrees of deuterium incorporation or leading to substrate decomposition.[31] Methods for nondirected deuteration of heteroarenes have been reported using Fe,[10c,28,30,32] Ni,[29,33] Ag,[34] Ru[35] and other catalytically active metals,[9] and typically induce a site-specific deuteration at inherently more reactive positions. Additionally, these methods are specifically optimized for particular classes of heteroarenes. Since heteroarenes are common motifs in pharmaceuticals and agrochemicals,[36] we were interested to further develop our catalyst systems towards a Pd-catalyzed nondirected late-stage deuteration of heteroarenes.[37] However, we realized that due to the extremely broad spectrum of chemical reactivities encountered within the envisaged scope of substrates, several sets of reaction conditions would most likely be required to obtain good results. In order to avoid the tedious work associated with conducting various extensive optimization campaigns, we turned our attention to the efficient yet underutilized strategy of multi-substrate screening.[38] This approach was first introduced in 1998 by Gao and Kagan[39] and by Jackson et al.[40] in asymmetric catalysis as an efficient alternative to high throughput experimentation. Despite its efficiency, this ap-

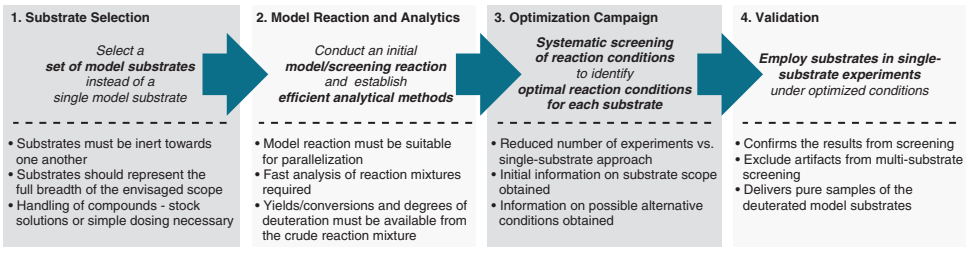


Figure 2 Workflow and strategic considerations for a multi-substrate screening towards a broadly applicable C–H deuteration of heteroarenes

proach has rarely been used outside the field of asymmetric catalysis and had, to the best of our knowledge, not been used in the context of C–H activation and/or HIE catalysis. Our envisaged workflow is outlined in Figure 2 alongside strategic considerations for each step.

First, multiple substrates were to be chosen that together cover the whole range of chemical properties encountered in the envisaged substrate scope (Figure 2, step 1). These substrates should then be employed together in a single reaction vessel for the optimization campaign. Thus, these substrates needed to be inert to one another, such that their reactivity could be considered as independent from the other substrates in the mixture. From a practical point of view, the handling of the substrates needed to be convenient, either as stock solutions or as solids, to guarantee a reproducible experimentation, even with very small compound quantities. Next, the reference conditions for a model reaction and the respective analytical methods needed to be established (step 2). The conditions had to be suitable for parallel screening during the optimization campaign and the analytical method(s) employed had to deliver the yield and degree of deuteration of all substrates without a tedious sample preparation/purification. Now, a systematic variation of all relevant reaction parameters would lead to optimal conditions for each model substrate from a single optimization campaign (step 3). Additionally, the multi-substrate screening approach would provide information regarding how each substrate would behave under the optimal conditions developed for the other substrates, which could prove valuable when adjusting reaction conditions to challenging substrates in the application of the method. Finally, the optimized conditions needed to be validated in single-substrate experiments (step 4). This validation would confirm the absence of positive or negative interference between the substrates, as well as the applicability of each set of conditions at the intended reaction scale.

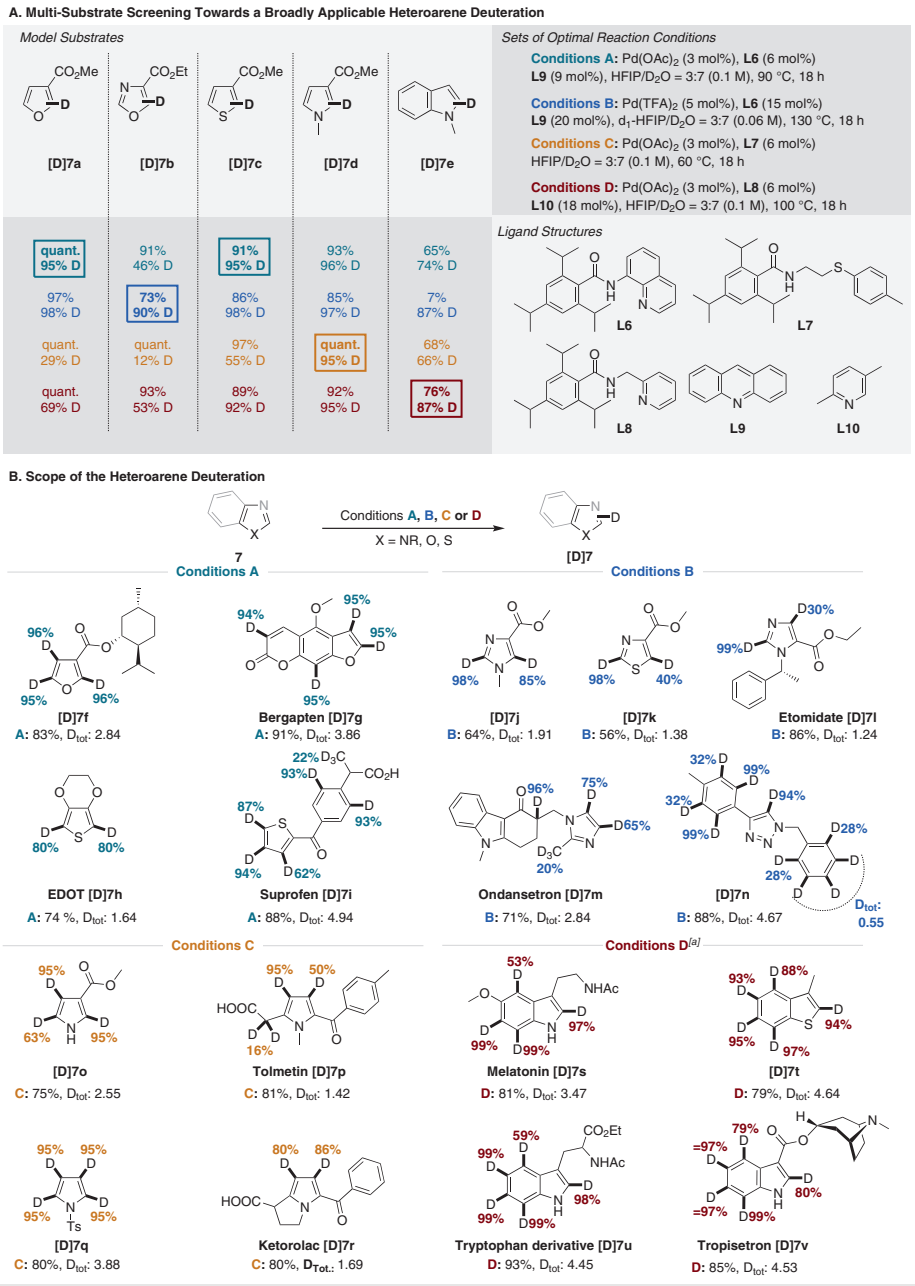
Scheme 5A shows our realization of this strategy.[41] Using substrates **7a–e** as a mixture during the optimization campaign, we developed four sets of reaction conditions, each ideal for one or two of the substrates respectively. The reaction conditions differ in the choice of ligands, temperature, and Pd source. Notably, low catalyst loadings are used and D_2O serves as the source of deuterium under all four sets of conditions. Based on our previous deuteration studies discussed above, we expected that bidentate ligands bearing a bulky TRIP-benzamide group would be highly efficient. TRIP-protected 8-aminoquinoline **L6**[42] together with acridine **L9** proved to be optimal for substrates **7a–c**. Notably, these ligand combinations follow our dual ligand design with the variation that an L-type donor is present in the bidentate ligand instead of an X-type donor. For substrate **7d**, a single TRIP-protected thioether ligand **L7**[43] delivered the best deuteration result. Finally, for substrate **7e**, TRIP-protected 2-picolylamine **L8**[44] together with 2,5-lutidine **L10** proved optimal. These results could all be validated in single substrate experiments. Notably, the results from multi-substrate screening enable first predictions regarding the substrate scope. For example, the incompatibility of **7e** with conditions B precludes the use of indole motifs under these conditions.

With the optimized conditions in hand, we started to investigate the substrate scope of our protocol (Scheme 5B). Using conditions A, an excellent deuterium incorporation was achieved in the menthol-substituted furan **7f**. Electron-rich bergapten (**7g**) was deuterated to high degrees at all aromatic C–H positions along with the reactive olefinic C–H bond. Di-alkoxy substituted EDOT **7h** was well-tolerated and gave high deuterium incorporation. With suprofen (**7i**) as the substrate, directed C–H activation led to a deuteration in proximity to the carboxylate moiety in addition to the expected heteroarene deuteration, at the same time demonstrating that carboxylic acids are well-tolerated in this protocol. Under conditions B, imidazole **[D]7j** and thiazole **[D]7k** showed high deuterium incorporation. Etomidate (**7l**) gave reduced deuteration at the less reactive 4-position. Notably, we observed that for such substrates deuteration at the 2-position occurs in a background reaction. Ondansetron (**7m**) gave high deuteration at both the 4 and 5 positions of the heteroarene moiety. Both in **[D]7l** and **[D]7m** the deuteration occurred selectively in the heteroarene unit, while the arene C–H bonds remained unaffected. 1,2,3-Triazole derivative **7n** underwent moderate deuteration on the arene rings. Using conditions C, an unprotected pyrrole was well tolerated, giving **[D]7o** with slightly reduced deuteration at the 5-position. *N*-Tosylpyrrole **7q** delivered excellent results. Pyrrole-containing drug molecules like tolmetin (**7p**) and ketorolac (**7r**) also gave high deuterium incorporation. Since under these conditions no additional monodentate ligand was employed, the aromatic C–H bonds of simple arenes remained untouched. Finally, under conditions D, 3-methylbenzothiophene (**7t**) gave excellent deuterium incorporation. Melatonin (**7s**) and tryptophan derivative **7u** were also efficiently deuterated, albeit with a slightly lower degree of deuteration at the 4-position. Electron-poor tropisetron (**7v**) was efficiently deuterated when the reaction conditions were slightly adjusted, heating to 120 °C and adding 1.0 equivalent of trifluoroacetic acid to prevent catalyst poisoning by the tertiary amine scaffold.

5 Conclusion

Over recent years, our lab has established a research program towards the palladium-catalyzed HIE in complex organic molecules through reversible C–H activation. The research towards these methods led us to discover new structural variations that can be introduced into common ligand scaffolds, such as the use of bulky benzamide units to affect concerted metalation–deprotonation. Strategic

considerations regarding the optimization of reaction conditions, such as the exploitation of microscopic reversibility and the implementation of multi-substrate screening enabled us to identify highly efficient catalyst systems and reaction conditions. Overall, our research has led us to discover methods suitable for the late-stage deuterium incorporation into free carboxylic acids, the nondirected deuteration of arenes, and a broadly applicable nondirected deuteration of heteroarenes. In all cases, the applicability to a wide range of complex organic molecules such as pharmacologically active substances was demonstrated. Together with the simple protocols and easily available deuterium sources, these protocols are expected to find widespread application and inspire further research in our own group and elsewhere. Future research in our lab will aim to complement our current methods for (per-)deuteration with regioselective systems that exploit differing modes of selectivity, such as distance control for carboxylic acids or ste-



Scheme 5 Results of the multi-substrate screening approach for the deuteration of heteroarenes (A) and selected examples from the respective scope studies (B). [a] Reactions were performed in d_1-HFIP/D_2O = 3:7.

ric/electronic control for (hetero)arenes. Another key area of development will be directed towards the development of highly active catalyst systems that deliver good results at low catalyst loadings, as well as silver-free reaction conditions, two essential prerequisites for applications on a large scale.[45]

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

We thank Kiel University for generous support. This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (Grant No. 946044).

Acknowledgment

We thank Simon Kaltenberger for helpful scientific discussions.

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