Pd(II)-Catalyzed Nondirected Late-Stage C(sp^2)–H Deuteration of Heteroarenes Enabled Through a Multi-Substrate Screening Approach

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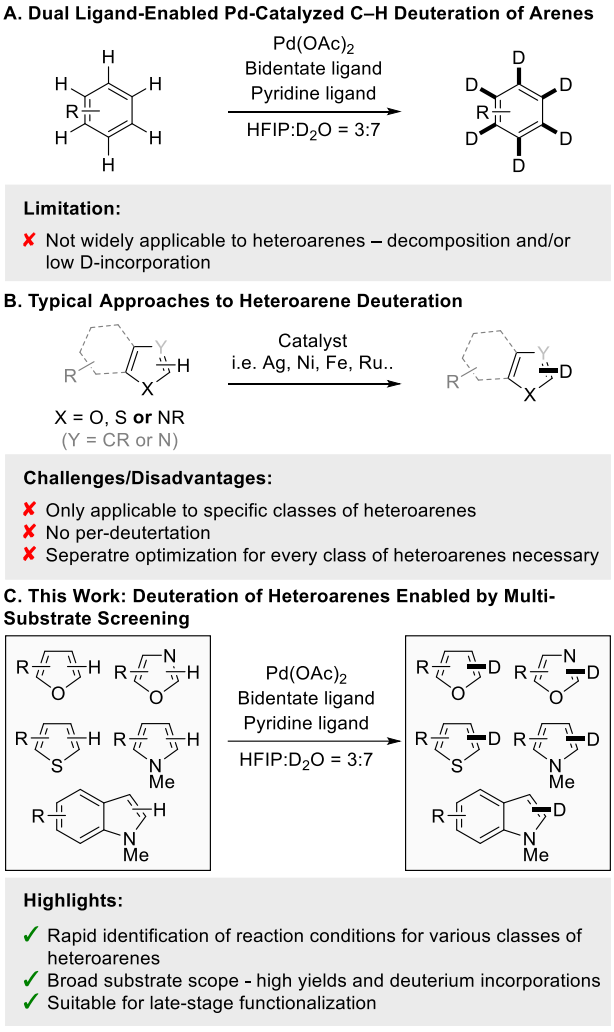
Abstract: The importance of deuterium labelling in a variety of applications, ranging from mechanistic studies to drug-discovery, has spurred immense interest in the development of new methods for its efficient incorporation in organic, and especially in bioactive molecules. The five-membered heteroarenes at the center of this work are ubiquitous motifs in bioactive molecules and efficient methods for the deuterium labelling of these compounds are therefore highly desirable. However, the profound differences in chemical properties encountered between different heteroarenes hamper the development of a single set of broadly applicable reaction conditions, often necessitating a separate optimization campaign for a given type of heteroarene. In this study we describe the use of a multi-substrate screening approach to identify optimal reaction conditions for different classes of heteroarenes from a minimal number of screening reactions. Using this approach, four sets of complementary reaction conditions derived from our dual ligand-based palladium catalysts for nondirected C(sp^2)–H activation were identified, that together enable the deuteration of structurally diverse heteroarenes, including bioactive molecules.

Deuterium labelling holds a privileged position in academic and industrial research due to its broad range of applications in life sciences, drug discovery and beyond.[1] Deuterium labelled compounds are for example used to generate unique isotope patterns in mass spectrometry[2], to gain key mechanistic insights in transition metal catalysis[3] or to study bioactive molecules in terms of their absorption, distribution, metabolism, and excretion (ADME) properties.[4,5] In the latter, the incorporation of deuterium frequently improves physiological properties of drug molecules and a variety of deuterated compounds have been listed as clinical candidates or were approved in recent years.[5,6] Consequently, the development of reliable and efficient methods for the deuteration of organic compounds is of high interest.
We have recently reported a method for the deuteration of simple arenes (Scheme 1A),[7] which is based on the reversibility of the C–H activation step in our dual-ligand enabled systems.[8]



Scheme 1. Previously reported Pd-catalyst for the deuteration of simple arenes (A), typical features of literature methods for the transition metal-catalyzed deuteration of heteroarenes (B) and multi-substrate screening strategy adopted in this work (C).

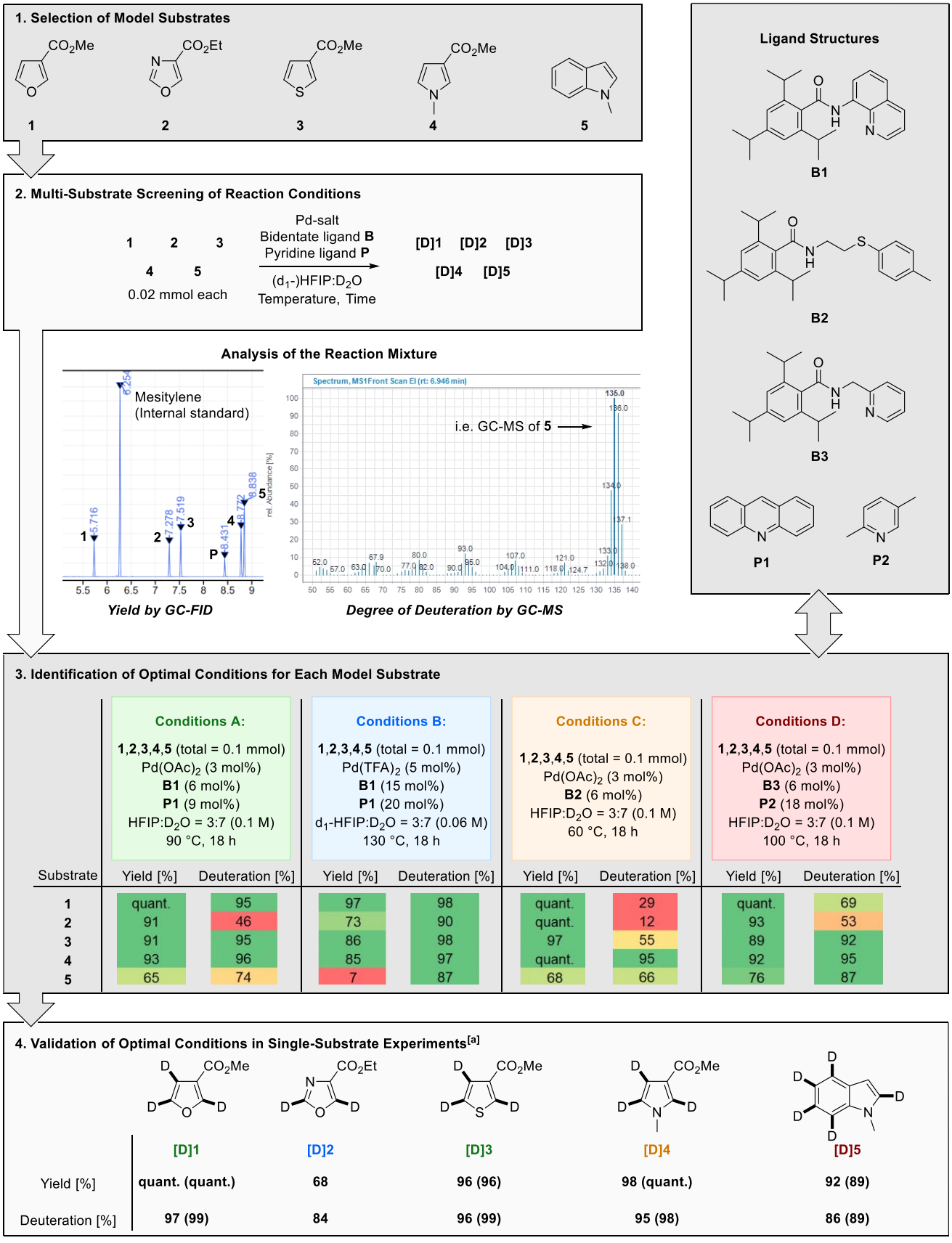
While being applicable to a wide range of arenes, including several bioactive molecules, the method could not be applied on a broad spectrum of heteroarenes, as many such substrates decomposed under the reaction conditions and/or gave low deuterium incorporations. Similarly, related Pd-catalyzed

methods for the (per-)deuteration of arenes that have recently been reported feature a limited scope of heteroarene substrates with good degrees of deuteration, although it should be noted that no information on the yield of these reactions is available.[9] Since heteroarenes are ubiquitous motives in pharmaceuticals, agrochemicals and bioactive molecules in general,[10] we became interested to develop Pd-catalysts for a broadly applicable nondirected deuteration of heteroarenes.

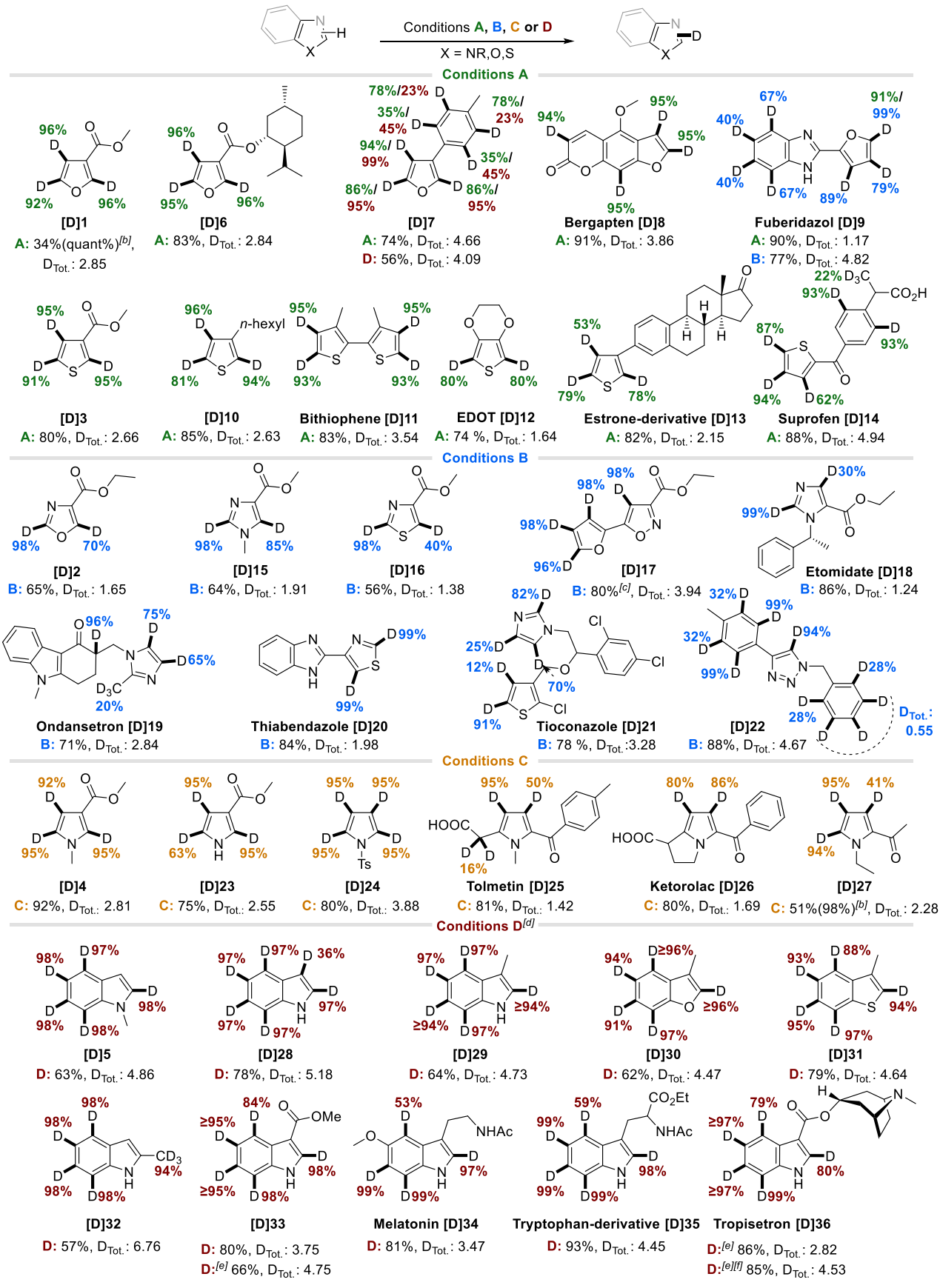
Methods for the nondirected deuteration of heteroarenes have been described using Ag,[11] Ni,[12] Fe,[13], Ru[14] and further catalytically active metals (Scheme 1B).[15] A typical feature of these methods is that specific (inherently more reactive) positions of the heteroarene substrate are deuterated selectively, while other positions in the substrate remain essentially unaffected. Furthermore, these methods are generally suitable for specific classes of heteroarenes and inferior results are obtained with substrates outside the range for which the method was optimized. At the outset of this project, we were confident that due to the remarkable catalytic activity of our dual ligand-based catalysts, high levels of deuterium incorporation could in principle be achieved for various heteroarenes. However, we expected that due to the broad spectrum of chemical properties encountered within such substrates several sets of reaction conditions would most likely be required in order to tailor the catalytic system to the stability and reactivity of the substrate at hand. In order to avoid the excessive experimentation associated with the multiple optimization campaigns that would usually be required in order to identify the optimal conditions for each type of heteroarene, we envisaged to adopt a multi-substrate screening approach (Scheme 1C). This strategy was introduced in 1998 independently by Gao and Kagan,[16] and Jackson et al.[17] in the field of asymmetric catalysis as a means to efficiently optimize the stereoselectivity of a reaction for a broad scope of substrates.[18,19] In this approach, multiple substrates, ideally covering the whole range of properties later to be encountered in the scope of the method under development, are combined in one reaction vessel during the optimization campaign. As long as neither interactions between the substrates themselves nor catalyst poisoning by one or several of the substrates distort the results, data for the performance of the catalyst with each substrate can be obtained from a single reaction. Following these seminal reports, the method was almost exclusively adopted in the field of asymmetric catalysis.[18,19] The approach has also been used to obtain scope information or mechanistic information for existing synthetic methods.[20] Furthermore, Plenio and coworkers have used multi-substrate screening to optimize the reaction conditions of Sonogashira reactions.[21] In this study, we aimed to probe the utility of this approach for the optimization of C–H activation methods and in the field of isotopic labelling that is unprecedented to the best of our knowledge.

The work-flow of our reaction optimization is shown in Scheme 2. We selected suitable model substrates for our reaction covering a broad range of heterocycles and electronic properties (Substrates **1-5**, 1. Scheme 2). Importantly, these substrates could easily be separated by gas chromatography (GC), facilitating the analysis of our screening reactions. The selected substrates were submitted to the optimization campaign on a 0.1 mmol scale (amounting to 0.02 mmol/substrate, 2. Scheme 2). Yields were determined by GC-FID analysis with an internal standard and the overall degree of deuteration was calculated by GC-MS using the universal mass calculator.[22] Through this approach we arrived at four sets of reaction conditions which proved to be optimal for different classes of heteroarenes and differ in the choice of ligands, temperature and Pd-source (3. Scheme 2). In all conditions D_2O serves as deuterium source and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) was used as co-solvent to solubilize organic compounds and assist in the C–H activation step (we observed that for challenging substrates d_1-HFIP could be employed as co-solvent instead of HFIP to further improve the reaction outcome). As in our previously described deuteration studies, bidentate ligands carrying a bulky 2,4,6-triisopropylbenzamide moiety as CMD-group gave the best results.[7,23] For substrates **1**-**3** a ligand combination consisting of 8-aminoquinoline-derivative **B1**[24] and acridine (**P1**) proved to be optimal (conditions A and B). The deuteration of pyrroles, such as **4** (conditions C), was found to proceed best in the presence of thioether ligand **B2**[25] employed as a single ligand, a feature that was also observed when we investigated the olefination of heteroarenes in the past.[26] Optimal results for indole-derivative **5** were obtained with picolinamine-derivative **B3**, [27] and 2,5-lutidine (**P2**, conditions D). Finally, we validated the optimized conditions in single-substrate reactions (4. Scheme 2) and obtained essentially equal results as previously observed in the multi-substrate screening when employed in single-substrate experiments. It is a remarkable feature of the multi-substrate screening approach that preliminary substrate scope information is already available from the optimization campaign. For example, the incompatibility of indole moieties with conditions B precludes the use of such motifs under these conditions. Additionally, the information how each substrate class reacts to the other sets of reaction conditions can prove valuable to adjust to challenges encountered during the scope studies.

With optimized conditions in hand, we investigated the scope of our protocol (Scheme 3). We started with furan-derivative **1**, which was also used in our screening reactions. While overall deuteration was very high ($D_{Tot.}$ = 2.85) and a quantitative GC-yield was observed, isolation proved challenging due to the volatility of this compound. We therefore employed the corresponding menthyl-ester **6**, where a yield of 83% with an equally high degree of deuteration was obtained. 3-aryl substituted furan **7** also provided high yield and deuterium incorporation.



Scheme 2. Optimization of the reaction conditions using a one-pot multi-substrate screening approach. [a] Yields and degrees of deuteration in parentheses were obtained from reactions in d_1-HFIP:D_2O = 3:7.



Scheme 3. Substrate scope. [a] $D_{Tot.}$ values were obtained from EI-MS or HRMS-ESI. The deuteration values in individual positions are derived from ^{1}H-NMR-spectroscopy (positions with ≥10% of deuteration are labelled). [b] Partial loss of product due to the volatility, the yield determined by GC-FID is shown in parenthesis.[c] Yield determined by ^{1}H-NMR-spectroscopy. [d] Reactions were performed in d_1-HFIP:D_2O = 3:7. [e] Reaction was performed at 120 °C. [f] 1.0 equiv of trifluoroacetic acid was added.

Interestingly, when the reaction was performed under conditions D the deuterium incorporation in the furan part of the molecule could be improved further, but overall yield and degree of deuteration were lower than with conditions A. Electron-rich Bergapten **8** was deuterated to high degrees for all aromatic C–H bonds and one of the olefinic C–H bonds. Fuberidazol **9** did not undergo significant deuteration under conditions A. The information from multi-substrate screening proved valuale here: since furane-derivative **1** remained stable even under the most forcing conditions B, we opted to employ **9** under these conditions. Gratifyingly, **[D]9** could be obtained with high deuteration in the heteroaromatic part and only slightly reduced yield. Thiophene-derivative **[D]2** could be isolated in good yield and high levels of deuteration in all positions. Likewise, electron-rich thiophenes **10-12** could be employed in the reaction, although slightly reduced values of deuteration and yield were observed with very electron-rich substrate **12**. Estrone-derivative **13** also gave slightly lower values of deuteration, which could be attributed to steric hinderance and/or low solubility of the substrate. Interestingly, deuteration was exclusively observed in the heteroaromatic part of the molecule while the aromatic C–H bonds did not react. Free carboxylic acids are tolerated under the reaction conditions, as evidenced by the deuteration of Suprofen **14**. Deuteration was observed in the heteroaromatic part of the molecule, as well as in positions that can undergo directed C–H activation.

Using conditions B, oxazole- (**2**), imidazole- (**15**), and thiazole-(**16**) derivatives showed good values of deuterium incorporation. Substrate **17**, containing a furan and an isoxazole moiety, underwent full deuteration in both parts. Etomidate **18** underwent only moderate H/D-exchange, where the low deuterium incorporation in the 4-position can likely be attributed to the electron-poor character of this position. Similarly, in Ondansetron **19** a slight preference for the 5-position was observed. Interestingly, no deuterium incorporation was observed in the aromatic positions of **19** and the benzyl group of **18**, showing that the conditions are selective for heteroaromatic C–H bonds. Thiabendazole **20** underwent nearly quantitative deuteration in the thiazole part of the molecule. Tioconazole **21** could be deuterated to high degrees in the 5-position of both the thiophene- and the imidazole moiety, whereas both 4-positions remained nearly untouched. Note, that the relatively acidic 2-position is, whenever occupied by a H-atom, nearly quantitatively deuterated. Based on our control reactions we concluded that this specific deuterium atom is incorporated in a background reaction. Finally, 1,2,3-triazole-derivative **22**, a common motive obtained from click-chemistry, gave high deuteration in the triazole part of the molecule as well as in the ortho-positions due to directed C–H activation. In contrast to imidazole and thiazole derivatives **18-21**, a moderate deuterium incorporation was observed in the arene moieties of **22**.

Next, pyrrole-derivatives were investigated using conditions C. Model substrate **4** could be isolated in high yield and with very high degrees of deuteration. Unprotected pyrrole **23** could equally be used in the reaction, however deuteration was found to be slightly lower in the 5-position. *N*-tosylpyrrole **24** was equally well suited. Because no pyridine ligand is employed, C–H bonds of simple arenes motifs remained unreactive under conditions C. Drug-molecules Tolmetin **25** and Ketorolac **26** were deuterated effectively. Finally, molecule **27**, containing a ketone moiety, was deuterated giving very high deuterium incorporation in two positions and a reduced level of deuteration in proximity to the electron-withdrawing group.

Turning our attention to indole-derivatives, we first investigated model-substrate **5** using conditions D. We found that the 3-position did not undergo deuteration in our conditions, while excellent degrees of deuterium incorporation were observed in all other positions. A catalyst dependent positional selectivity for the C–H activation of indoles is well documented.[28] The same trend was observed in unprotected indole **28**, although deuteration in the 3-position occurred to a minor degree in this case. 3-Methylindole **29** underwent almost quantitative deuteration in all positions. Likewise, 3-methylbenzofurane **30** and 3-methylbenzothiophene **31** could be deuterated with similar results. 2-Methylindole **32** again showed no deuteration in 3-position, but almost quantitative deuteration in the methyl group next to nitrogen. When an electron-withdrawing ester group is present, as in **33**, only moderate degrees of deuteration could be achieved at 100 °C. Since we know from multi-substrate screening that indole-substrates are incompatible with the other reaction conditions, we opted to increase the temperature rather than changing reaction conditions in order to increase deuteration in this case. Consequently, when the temperature was increased to 120 °C the deuteration significantly increased and only the 4-position did not reach near quantitative deuterium incorporation. Melatonin **34** and tryptophane-derivative **35** could be recovered in high yields and with, apart from slightly reduced values in the respective 4 positions, very high degrees of deuteration. Tropisetron **36** could only be deuterated to a moderate degree at 120 °C. We hypothesized that the free tertiary amine present in this molecule could be acting as a catalyst poison. Accordingly, 1.0 equivalents of trifluoroacetic acid were added, leading to a significantly increased deuterium incorporation.

In conclusion, we have developed a broadly applicable method for the deuteration of various heteroarenes using a rarely utilized but highly efficient screening method. Using a multi-substrate screening approach allowed us to quickly identify several sets of reaction conditions, each optimal for a different subset of heteroarene substrates. Overall, a wide scope of heteroarenes could be deuterium labelled, displaying a broad functional group tolerance and a number of bioactive molecules. We expect that our protocol will prove to be a highly useful addition to the method portfolio in the field of isotopic labelling and at the same time will serve as illustration how multi-substrate screening can be employed in this field.

Supporting Information

The authors have cited additional references within the Supporting Information.[29-40]

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Keywords: Deuterium • Heterocycles • Multi-substrate screening • Catalysis • Ligands

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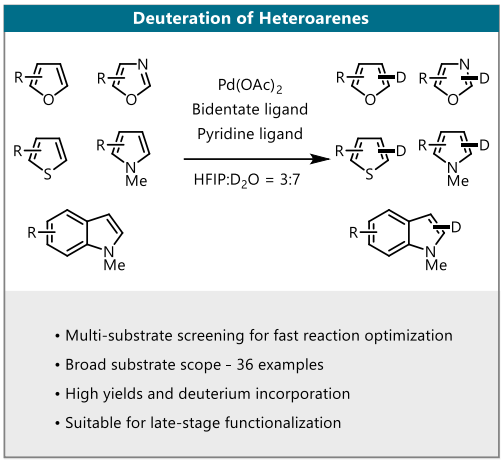

We describe a method for the Pd-catalyzed deuteration of a variety of five-membered heteroarenes. Reaction optimization was performed using a multi-substrate screening approach, which allowed for the identification of optimal reaction conditions for different classes of heteroarenes from a minimal number of screening reactions. We used the obtained conditions for the deuteration of several heteroarenes, including bioactive molecules.

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