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

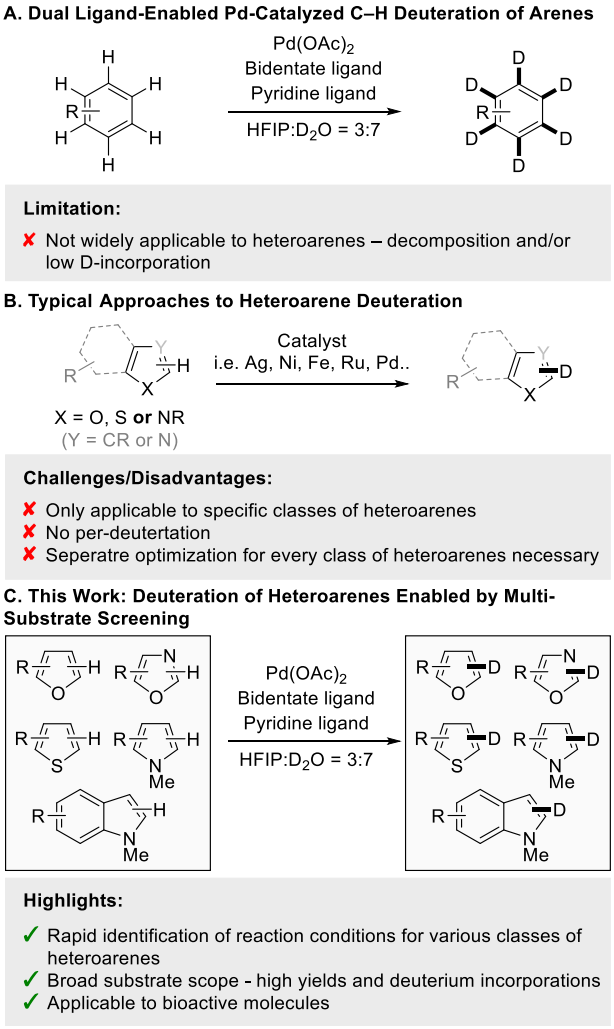
Jyotirmoy Dey[†, a], Simon Kaltenberger[†, a], and Manuel van Gemmeren*[a]

[a] Jyotirmoy Dey, Simon Kaltenberger, Prof. Dr. Manuel van Gemmeren
Otto-Diels-Institut für Organische Chemie
Christian-Albrechts-Universität zu Kiel
Otto-Hahn-Platz 4, 24098 Kiel (Germany)
E-Mail: vangemmeren@oc.uni-kiel.de
[†] These authors contributed equally to this work
Supporting information for this article is given via a link at the end of the document.

Dedicated to Prof. Dr. Rainer Herges on the occasion of his retirement.

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).

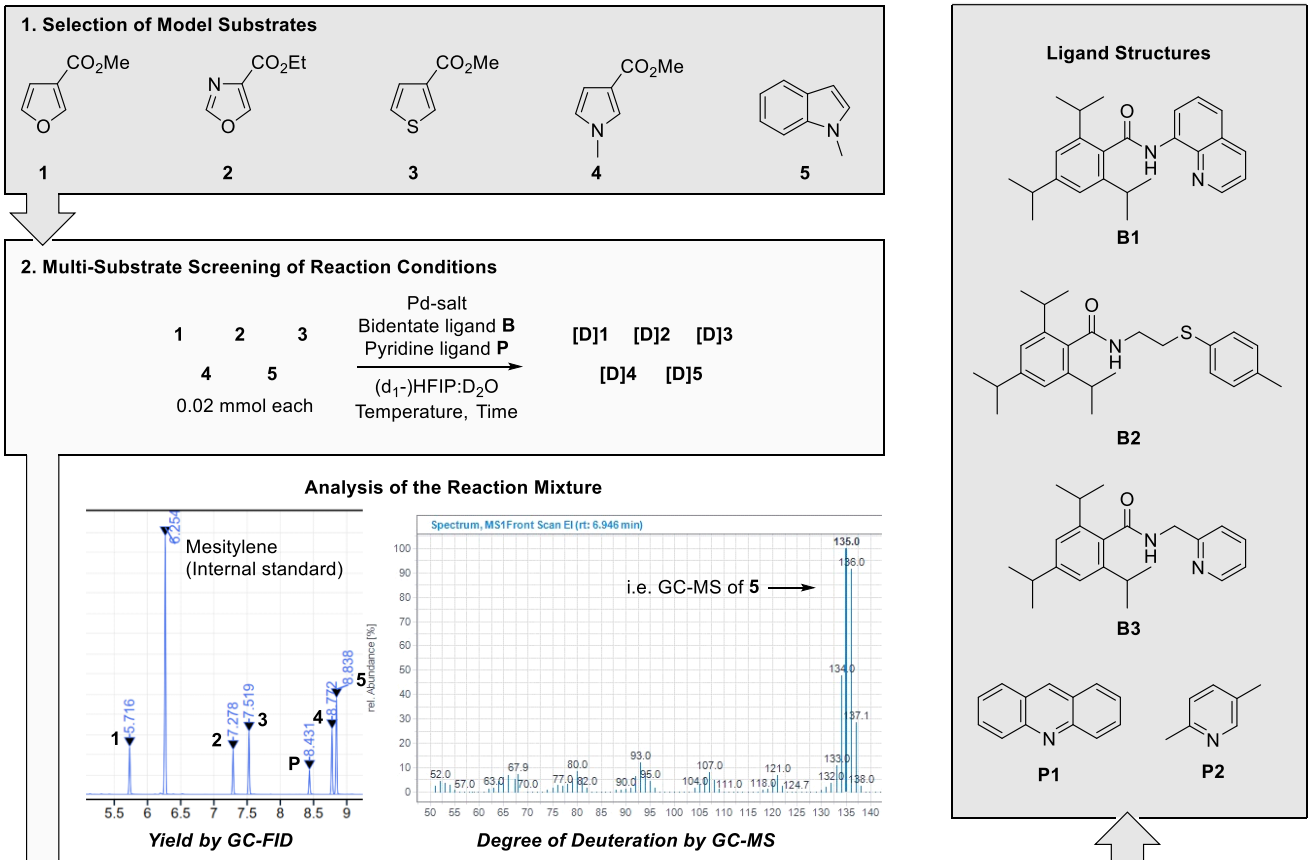
While being applicable to a wide range of arenes, including several bioactive molecules, the method could not be applied on a broad spectrum of heteroarenes, as many such substrates decomposed under the reaction conditions and/or gave low

deuterium incorporations. Joo recently described a Pd-catalyzed method for the (per-)deuteration of arenes that could also be applied to selected heteroarenes.[9] High degrees of deuteration are reported, albeit without the associated yields. Despite these advances, broadly applicable protocols for the per-deuteration of several important classes of heteroarenes, like for example furans and indoles, remained unaddressed by literature methods. 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,[13,14], Ru[15], Pd[16] and further catalytically active metals (Scheme 1B).[17] While some of these protocols, like for example from Sajiki[16], Hartwig[11d] and other groups[17], show occasional examples of per-deuteration of simple substrates, 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 be required to cover a broad substrate scope. In order to avoid the excessive experimentation associated with the multiple optimization campaigns 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,[18] and Jackson et al.[19] as a means to efficiently optimize the stereoselectivity of a reaction for a broad scope of substrates.[20,21] Here, multiple substrates, ideally covering the whole range of properties expected in the scope of the method, are combined in one reaction vessel during the optimization campaign. At the same time the number of substrates should remain small enough to ensure reproducibility and reliable analytics. As long as neither interactions between the substrates themselves nor catalyst poisoning 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 asymmetric catalysis.[20,21] The approach has also been used to obtain scope information or mechanistic information for existing synthetic methods.[22] Furthermore, Plenio used multi-substrate screening to optimize the reaction conditions of Sonogashira reactions.[23] In this study, we probed the utility of this approach for the optimization of C–H activation methods and in the field of isotopic labelling.

The work-flow of our reaction optimization is shown in Scheme 2. First we selected model substrates for our reaction (Substrates **1-5**, 1. Scheme 2). The choice of these substrates was based on the general principles of multi-substrate screening outlined above, since these substates reflected the breadth of steric and electronic properties expected to occur in the desired scope of our method while keeping the total number of components at an acceptable level. 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.[24] 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 cases D_2O serves as deuterium source and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as co-solvent to solubilize organic compounds and assist in the C–H activation (for challenging substrates d_1-HFIP as co-solvent instead of HFIP further improved the reaction outcome). As in our previous studies, bidentate ligands carrying a bulky 2,4,6-triisopropylbenzamide moiety gave the best results.[7,25] For substrates **1**-**3** a ligand combination consisting of 8-aminoquinoline-derivative **B1**[26] and acridine (**P1**) proved to be optimal (conditions A and B), however the use of $Pd(TFA)_2$ and a reaction temperature of 130 °C was found to be crucial for efficient deuteration of relatively electron-poor oxazole-derivative **2**. The deuteration of pyrroles, such as **4** (conditions C), proceeded best in the presence of thioether **B2**[27] as a single ligand. These conditions are milder than the other protocols to avoid decomposition of sensitive substrates and use the relatively high reactivity of pyrroles to still achieve high deuteration.[28] Optimal results for indole-derivative **5** were obtained with picolinamine-derivative **B3**, [29] and 2,5-lutidine (**P2**, conditions D), which offer the best balance of reactivity and mildness to prevent indole decomposition. Finally, we validated the optimized conditions in single-substrate reactions (4. Scheme 2) and obtained essentially equal results as in the multi-substrate screening. Indole-derivative **5** even provided a higher yield in single-substrate settings compared to the multi-substrate reactions, presumably because the larger metal:substrate ratio in the multi-substrate screening caused increased decomposition of this sensitive compound during the optimization process. It is noteworthy that preliminary substrate scope information is already available from the optimization campaign, such as the incompatibility of indole moieties with conditions B. Additionally, the information how each substrate class reacts under the other sets of reaction conditions can prove valuable when adjusting to challenges encountered during the scope studies.

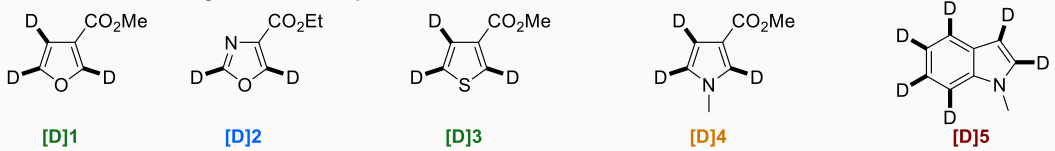
With optimized conditions in hand, we investigated the scope of our protocol (Scheme 3). Throughout the scope studies and in accordance with the mechanistic investigations reported by our group,[30] we observed that our catalysts preferentially activate electron-rich positions,[31] while electron-poorer positions show lower degrees of deuteration. As expected, the protocol proved sensitive to steric effects, leading to reduced deuteration in hindered positions. Furthermore, some Lewis-basic moieties acted as directing-groups leading to increased deuteration in their vicinity.



3. Identification of Optimal Conditions for Each Model Substrate

	Conditions A: **1**,**2**,**3**,**4**,**5** (total = 0.1 mmol), $Pd(OAc)_2$ (3 mol%), **B1** (6 mol%), **P1** (9 mol%), $HFIP:D_2O$ = 3:7 (0.1 M), 90 °C, 18 h		Conditions B: **1**,**2**,**3**,**4**,**5** (total = 0.1 mmol), $Pd(TFA)_2$ (5 mol%), **B1** (15 mol%), **P1** (20 mol%), d_1-$HFIP:D_2O$ = 3:7 (0.06 M), 130 °C, 18 h		Conditions C: **1**,**2**,**3**,**4**,**5** (total = 0.1 mmol), $Pd(OAc)_2$ (3 mol%), **B2** (6 mol%), $HFIP:D_2O$ = 3:7 (0.1 M), 60 °C, 18 h		Conditions D: **1**,**2**,**3**,**4**,**5** (total = 0.1 mmol), $Pd(OAc)_2$ (3 mol%), **B3** (6 mol%), **P2** (18 mol%), $HFIP:D_2O$ = 3:7 (0.1 M), 100 °C, 18 h	
Substrate	Yield [%]	Deuteration [%]	Yield [%]	Deuteration [%]	Yield [%]	Deuteration [%]	Yield [%]	Deuteration [%]
1	quant.	95	97	98	quant.	29	quant.	69
2	91	46	73	90	quant.	12	93	53
3	91	95	86	98	97	55	89	92
4	93	96	85	97	quant.	95	92	95
5	65	74	7	87	68	66	76	87

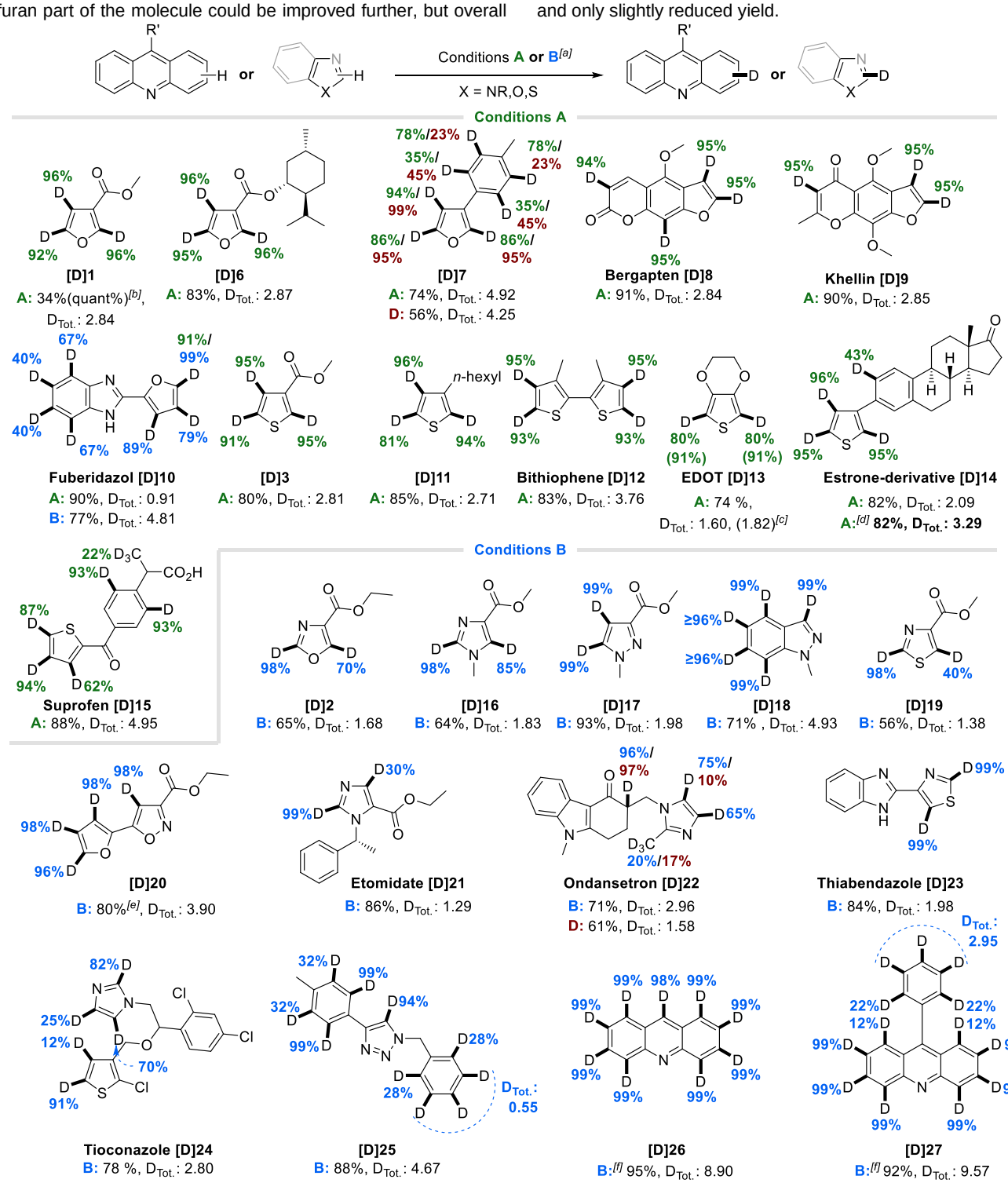
4. Validation of Optimal Conditions in Single-Substrate Experiments[a]



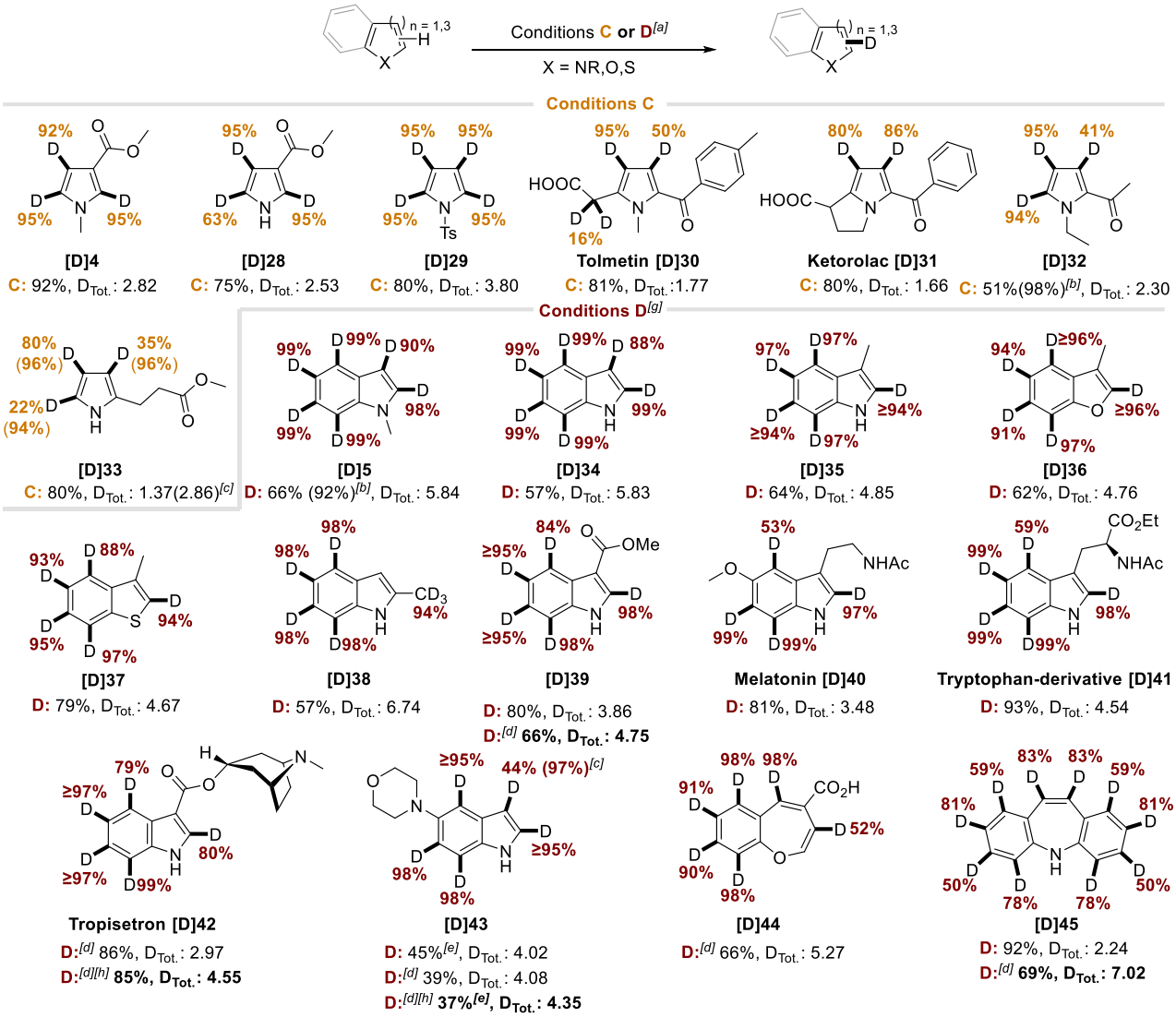
	[D]1	[D]2	[D]3	[D]4	[D]5
Yield [%]	**quant. (34[b])**	**68 (65)**	**96 (80)**	**98 (92)**	**92 (66[b,c])**
Deuteration [%]	**97 (95)**	**84 (84)**	**96 (94)**	**95 (94)**	**86 (97[c])**

Scheme 2. Optimization of the reaction conditions using a one-pot multi-substrate screening approach. [a] Yields and degrees of deuteration of isolated products are shown in parentheses, [b] Partial loss of product due to the volatility, [c] Isolated from a reaction in d_1-$HFIP:D_2O$ = 3:7.

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. 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 natural products **8** and **9** were deuterated to high degrees in all aromatic C–H-bonds and the olefinic C–H bond next to the ketone. Fuberidazol **10** did not undergo significant deuteration under conditions A. The information from multi-substrate screening proved valuable here: since furane-derivative **1** remained stable even under the most forcing conditions B, we opted to employ **10** under these conditions. Gratifyingly, **[D]10** could be obtained with high deuteration in the heteroaromatic part and only slightly reduced yield.



Scheme 3.



Scheme 3 continued. Substrate scope. [a] $D_{Tot.}$ values and the deuteration values in individual positions were determined by ^{1}H-NMR-spectroscopy (positions with ≥10% of deuteration are labelled). [b] Partial loss of product due to the volatility, GC-FID yield given in parenthesis. [c] Degree of deuteration in parenthesis determined by crude ^{1}H-NMR-spectroscopy. [d] Reaction performed at 120 °C. [e] Yield determined by ^{1}H-NMR-spectroscopy. [f] $Pd(TFA)_2$ (5 mol%), **B1** (15 mol%), **26** or **27** (1.0 equiv), d_1-HFIP:D_2O = 3:7 (0.06 M), 130 °C, 48 h [g] Reactions performed in d_1-HFIP:D_2O = 3:7. [h] Trifluoroacetic acid (1 equiv.) added.

Thiophene-derivative **[D]3** could be isolated in good yield and high levels of deuteration in all positions. Likewise, electron-rich thiophenes **11-13** could be employed in the reaction. Estrone-derivative **14** gave slightly lower values of deuteration, which could be attributed to steric hinderance and/or low solubility of the substrate. At this temperature, deuteration was exclusively observed in the heteroaromatic part of the molecule while the aromatic C–H bonds did not react. When the temperature was increased to 120 °C deuteration significantly increased and minor deuteration was also observed at the sterically least hindered arene C–H bond. Free carboxylic acids are tolerated under the reaction conditions, as evidenced by the deuteration of Suprofen **15**. 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- (**16**), pyrazole- (**17**), indazole (**18**) and thiazole- (**19**) derivatives showed good to very high values of deuterium incorporation. Substrate **20**, containing a furan and an isoxazole moiety, underwent full deuteration in both parts. Etomidate **21** 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 **22** a slight preference for the 5-position was observed. Conditions D also gave no significant deuteration in the indole part and overall resulted in lower deuteration of **22**. Interestingly, no deuterium incorporation was observed in the aromatic positions of **22** and the benzyl group of **21**, showing that the conditions are selective for heteroaromatic C–H bonds. Thiabendazole **23** underwent nearly quantitative deuteration in the thiazole part of the molecule. We also tested if the unreactive arene parts of molecule **14** and **21**-**23** can be deuterated with our previously developed arene-deuteration protocol,[7] in order to obtain per-deuterated compounds. However, as expected based on our previous work, these methods either lead to minor

deuteration in the arene and/or inferior overall results compared to the conditions described herein (see SI). Tioconazole **24** could be deuterated to high degrees in the 5-position of both rings, whereas the electron-poorer 4-positions remained nearly untouched. Note, that the acidic 2-position is, whenever occupied by a H-atom, nearly quantitatively deuterated. However, control experiments showed that deuterium is incorporated in this position via a background reaction. Finally, 1,2,3-triazole-derivative **25**, a common motive obtained from click-chemistry, gave high deuteration in the triazole part of the molecule as well as, due to directed C–H activation, in the ortho-positions. In contrast to compounds **21-23**, a moderate deuterium incorporation was observed in the arene moieties of **25**. During screening we also observed that **P1** is nearly quantitatively deuterated when used as a ligand above 120 °C. We hypothesized that **P1** could be acting as monodentate ligand and as substrate at the same time in analogy to a recent report by the Yu group.[32] Accordingly, acridine-derivatives **26** and **27** could be deuterated in very high degrees using slightly modified reaction conditions.

Next, pyrrole-derivatives were investigated using conditions C. Model substrate **4** was isolated in high yield and with very high degrees of deuteration. Unprotected pyrrole **28** could equally be used in the reaction, however deuteration was found to be slightly lower in the 5-position. *N*-tosylpyrrole **29** 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 **30** and Ketorolac **31** were deuterated effectively. Molecule **32**, containing a ketone moiety, was deuterated giving very high deuterium incorporation in two positions and a reduced level of deuteration in the most electon-poor position neighboring the electron-withdrawing group. Alkyl-substituted pyrrole **33** was also effectively deuterated. However, due to the electron-rich character of this substrate significant de-deuteration was observed during isolation.

Turning our attention to indole-derivatives, we first investigated model-substrate **5** using conditions D. Except the 3-position, excellent degrees of deuteration were overserved in the isolated product. The D-atom at the 3-position is labile and easily de-deuterated during purification. In analogy to similar protocols[33], deuteration in this position is therefore often diminished in the isolated products. The same trend was observed in unprotected indole **34**. 3-Methylindole **35** underwent almost quantitative deuteration in all positions. Likewise, 3-methylbenzofurane **36** and 3-methylbenzothiophene **37** could be deuterated. 2-Methylindole **38** again showed no deuteration in 3-position, but almost quantitative deuteration in the methyl group next to nitrogen. This reactivity of methyl-groups in *N*-heterocycles is well known and is also observed in other protocols.[14,34] When an electron-withdrawing ester group is present, as in **39**, only moderate degrees of deuteration could be achieved at 100 °C. Since multi-substrate screening showed that indole-substrates are incompatible with the other reaction conditions, we opted to increase the temperature rather than changing reaction conditions to increase deuteration in this case. At 120 °C the deuteration significantly increased and only the 4-position did not reach full deuterium incorporation. Melatonin **40** and tryptophane-derivative **41** could be recovered in high yields with, moderate deuteration in the 4 positions and very high degrees of deuteration in all other positons. Tropisetron **42** was deuterated to a moderate degree at 120 °C. We hypothesized that the free tertiary amine in this molecule could act as a catalyst poison. Accordingly, 1.0 equivalents of trifluoroacetic acid (TFA) were added, leading to a significantly increased deuterium incorporation. In contrast aniline-type substrate **43** did not require higher reaction temperatures or the addition of TFA and was already effectively deuterated at 100 °C. However, a positive influence of these two reaction parameters was still observed. Oxepine-derivative **44**, containing a seven-membered heterocycle, could be deuterated to very high degrees in the arene part and, via directed C–H activation, in two olefinic positions. Likewise, azepine-derivative **45** was deuterated effectively in all parts of the molecule at 120 °C.

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. Notably, the conditions feature low palladium and ligand loadings while at the same time leading to high yield and per-deuteration of several common heteroarene scaffolds. 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.[35-46]

Acknowledgements

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 programme (grant agreement No 946044). We thank the members of the NMR- and MS-department for their excellent service, Fritz Deufel, Gitta Kohlmeyer-Yilmaz and Prof. Dr. Frank Sönnichsen for providing help in data analysis, as well as Sourjya Mal and Fritz Deufel for helpful scientific discussions. Markus Luft is acknowledged for recording IR-spectra and melting points. S.K. thanks the Studienstiftung des deutschen Volkes for a doctoral fellowship.

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

References:

[1] a) A. E. Mutlib, *Chem. Res. Toxicol.* **2008**, *21*, 1672; b) J. Atzrodt, V. Derdau, W. J. Kerr, M. Reid, *Angew. Chem. Int. Ed.* **2018**, *57*, 1758; c) R. D. Jansen-van Vuuren, L. Jedlovčnik, J. Košmrlj, T. E. Massey, V. Derdau, *ACS omega* **2022**, *7*, 41840.

[2] a) E. Stokvis, H. Rosing, J. H. Beijnen, *Rapid Commun. Mass Spectrom.* **2005**, *19*, 401; b) A. Damont, A. Legrand, C. Cao, F. Fenaille, J.-C. Tabet, *Mass Spec Rev.* **2023**, *42*, 1300.

[3] E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 3066.

[4] a) T. G. Gant, *J. Med. Chem.* **2014**, *57*, 3595; b) C. S. Elmore, R. A. Bragg, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 167.

[5] R. M. C. Di Martino, B. D. Maxwell, T. Pirali, *Nat. Rev. Drug Discov.* **2023**, *22*, 562.

[6] S. H. DeWitt, B. E. Maryanoff, *Biochemistry* **2018**, *57*, 472.

[7] M. Farizyan, A. Mondal, S. Mal, F. Deufel, M. van Gemmeren, *J. Am. Chem. Soc.* **2021**, *143*, 16370.

[8] S. Kaltenberger, M. van Gemmeren, *Acc. Chem. Res.* **2023**, *56*, 2459.

[9] a) E. Kang, J. E. Jeon, S. Jeong, H. T. Kim, J. M. Joo, *Chem. Commun.* **2021**, *57*, 11791; b) S. J. Yun, J. Kim, E. Kang, H. Jung, H. T. Kim, M. Kim, J. M. Joo, *ACS Catal.* **2023**, *13*, 4042.

[10] a) D. K. Dalvie, A. S. Kalgutkar, S. C. Khojasteh-Bakht, R. S. Obach, J. P. O'Donnell, *Chem. Res. Toxicol.* **2002**, *15*, 269; b) P. Jeschke, *ChemBioChem* **2004**, *5*, 571; c) A. Gomtsyan, *Chem Heterocycl Comp* **2012**, *48*, 7; d) R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845; e) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257.

[11] a) M. D. Lotz, N. M. Camasso, A. J. Canty, M. S. Sanford, *Organometallics* **2017**, *36*, 165; b) E.-C. Li, G.-Q. Hu, Y.-X. Zhu, H.-H. Zhang, K. Shen, X.-C. Hang, C. Zhang, W. Huang, *Org. Lett.* **2019**, *21*, 6745; c) B. Dong, X. Cong, N. Hao, *RSC Adv.* **2020**, *10*, 25475; d) A. Tlahuext-Aca, J. F. Hartwig, *ACS Catal.* **2021**, *11*, 1119; e) G.-Q. Hu, J.-W. Bai, E.-C. Li, K.-H. Liu, F.-F. Sheng, H.-H. Zhang, *Org. Lett.* **2021**, *23*, 1554; f) F.-F. Sheng, E.-C. Li, J.-W. Bai, C.-X. Wang, G.-Q. Hu, K.-H. Liu, Z.-Y. Sun, K. Shen, H.-H. Zhang, *Org. Biomol. Chem.* **2022**, *20*, 1176; g) J. Tang, J. Kong, H. Xu, Z.-J. Jiang, Y. She, J. Bai, B. Tang, J. Chen, Z. Gao, K. Gao, *J. Org. Chem.* **2023**, *88*, 1560.

[12] a) W.-M. Yau, K. Gawrisch, *J. Labelled Cpd. Radiopharm.* **1999**, *42*, 709; b) H. Yang, C. Zarate, W. N. Palmer, N. Rivera, D. Hesk, P. J. Chirik, *ACS Catal.* **2018**, *8*, 10210; c) C. Zarate, H. Yang, M. J. Bezdek, D. Hesk, P. J. Chirik, *J. Am. Chem. Soc.* **2019**, *141*, 5034; d) D. Bouzouita, J. M. Asensio, V. Pfeifer, A. Palazzolo, P. Lecante, G. Pieters, S. Feuillastre, S. Tricard, B. Chaudret, *Nanoscale* **2020**, *12*, 15736.

[13] a) R. P. Yu, D. Hesk, N. Rivera, I. Pelczer, P. J. Chirik, *Nature* **2016**, *529*, 195; b) S. Garhwal, A. Kaushansky, N. Fridman, L. J. W. Shimon, G. de Ruiter, *J. Am. Chem. Soc.* **2020**, *142*, 17131; c) J. Corpas, P. Viereck, P. J. Chirik, *ACS Catal.* **2020**, *10*, 8640; d) L. Britton, J. H. Docherty, J. Sklyaruk, J. Cooney, G. S. Nichol, A. P. Dominey, S. P. Thomas, *Chem. Sci.* **2022**, *13*, 10291; e) F. Bourriquen, K. Junge, M. Beller, *Synlett* **2023**, *34*, 332.

[14] W. Li, J. Rabeah, F. Bourriquen, D. Yang, C. Kreyenschulte, N. Rockstroh, H. Lund, S. Bartling, A.-E. Surkus, K. Junge, A. Brückner, A. Lei, M. Beller, *Nat. Chem.* **2022**, *14*, 334.

[15] a) G. Pieters, C. Taglang, E. Bonnefille, T. Gutmann, C. Puente, J.-C. Berthet, C. Dugave, B. Chaudret, B. Rousseau, *Angew. Chem. Int. Ed.* **2014**, *53*, 230; b) V. H. Mai, O. B. Gadzhiev, S. K. Ignatov, G. I. Nikonov, *Catal. Sci. Technol.* **2019**, *9*, 3398; c) V. Pfeifer, M. Certiat, D. Bouzouita, A. Palazzolo, S. Garcia-Argote, E. Marcon, D.-A. Buisson, P. Lesot, L. Maron, B. Chaudret, S. Tricard, I. Del Rosal, R. Poteau, S. Feuillastre, G. Pieters, *Chem. Eur. J.* **2020**, *26*, 4988.

[16] a) H. Esaki, N. Ito, S. Sakai, T. Maegawa, Y. Monguchi, H. Sajiki, *Tetrahedron* **2006**, *62*, 10954; b) Y. Sawama, Y. Monguchi, H. Sajiki, *Synlett* **2012**, *23*, 959.

[17] a) J. Atzrodt, V. Derdau, W. J. Kerr, M. Reid, *Angew. Chem. Int. Ed.* **2018**, *57*, 3022; b) M. Daniel-Bertrand, S. Garcia-Argote, A. Palazzolo, I. Mustieles Marin, P.-F. Fazzini, S. Tricard, B. Chaudret, V. Derdau, S. Feuillastre, G. Pieters, *Angew. Chem. Int. Ed.* **2020**, *59*, 21114; c) J. B. Roque, T. P. Pabst, P. J. Chirik, *ACS Catal.* **2022**, *12*, 8877; d) S. Kopf, F. Bourriquen, W. Li, H. Neumann, K. Junge, M. Beller, *Chem. Rev.* **2022**, *122*, 6634; e) Q.-K. Kang, H. Shi, *Synlett* **2022**, *33*, 329; f) G. Prakash, N. Paul, G. A. Oliver, D. B. Werz, D. Maiti, *Chem. Soc. Rev.* **2022**, *51*, 3123.

[18] X. Gao, H. B. Kagan, *Chirality* **1998**, *10*, 120.

[19] C. Gennari, S. Ceccarelli, U. Piarulli, C. A. G. N. Montalbetti, R. F. W. Jackson, *J. Org. Chem.* **1998**, *63*, 5312.

[20] T. Satyanarayana, H. B. Kagan, *Adv. Synth. Catal.* **2005**, *347*, 737.

[21] M. S. Fogel, K. Koide, *Org. Process Res. Dev.* **2023**, *27*, 1235.

[22] a) J.-P. Goddard, J.-L. Reymond, *J. Am. Chem. Soc.* **2004**, *126*, 11116; b) M. an der Heiden, H. Plenio, *Chem. Commun.* **2007**, 972; c) C. Yan, J. W. Schmidberger, F. Parmeggiani, S. A. Hussain, N. J. Turner, S. L. Flitsch, P. Barran, *Analyst* **2016**, *141*, 2351; d) K. Yan, V. Triana, S. V. Kalmady, K. Aku-Dominguez, S. Memon, A. Brown, R. Greiner, R. Derda, *Chem. Sci.* **2021**, *12*, 14301.

[23] M. Schilz, H. Plenio, *J. Org. Chem.* **2012**, *77*, 2798.

[24] The computer software UMC (Universal Mass Calculator) was used to simulate isotope patterns, evaluate the degree of deuteration/labelling, evaluate elemental compositions. UMC V3.11.0.27, Dr. Matthias C. Letzel, WWU Münster, Org.-Chem. Institut, Germany. https://www.uni-muenster.de/Chemie.oc/ms/downloads.html.

[25] A. Uttry, S. Mal, M. van Gemmeren, *J. Am. Chem. Soc.* **2021**, *143*, 10895.

[26] a) C.-H. Ying, S.-B. Yan, W.-L. Duan, *Org. Lett.* **2014**, *16*, 500; b) M. I. Morja, P. M. Chauhan, K. H. Chikhalia, *Res. Chem. Intermed.* **2021**, *47*, 4513.

[27] a) Z. Zhuang, C.-B. Yu, G. Chen, Q.-F. Wu, Y. Hsiao, C. L. Joe, J. X. Qiao, M. A. Poss, J.-Q. Yu, *J. Am. Chem. Soc.* **2018**, *140*, 10363; b) Z. Zhuang, J.-Q. Yu, *J. Am. Chem. Soc.* **2020**, *142*, 12015; c) Z. Zhuang, A. N. Herron, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2021**, *60*, 16382; d) Y. Wang, X. Xu, B. Pang, L. Hao, G. Wu, Y. Ji, *Org. Lett.* **2022**, *24*, 6734; e) M. Tomanik, S. Qian, J.-Q. Yu, *J. Am. Chem. Soc.* **2022**, *144*, 11955; f) Z. Zhuang, S. Liu, J.-T. Cheng, K.-S. Yeung, J. X. Qiao, N. A. Meanwell, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2022**, *61*, e202207354.

[28] H. Chen, M. Farizyan, F. Ghiringhelli, M. van Gemmeren, *Angew. Chem. Int. Ed.* **2020**, *59*, 12213.

[29] a) G. Chen, W. Gong, Z. Zhuang, M. S. Andrä, Y.-Q. Chen, X. Hong, Y.-F. Yang, T. Liu, K. N. Houk, J.-Q. Yu, *Science* **2016**, *353*, 1023; b) M. S. Andrä, L. Schifferer, C. H. Pollok, C. Merten, L. J. Gooßen, J.-Q. Yu, *Chem. Eur. J.* **2019**, *25*, 8503.

[30] P. Wedi, M. Farizyan, K. Bergander, C. Mück-Lichtenfeld, M. van Gemmeren, *Angew. Chem. Int. Ed.* **2021**, *60*, 15641.

[31] a) S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 10848; b) S. Pratihar, S. Roy, *J. Org. Chem.* **2010**, *75*, 4957; c) D. Lapointe, T. Markiewicz, C. J. Whipp, A. Toderian, K. Fagnou, *J. Org. Chem.* **2011**, *76*, 749; d) J. Clayden, N. Greeves, S. G. Warren, *Organic chemistry*, Oxford University Press, Oxford, New York, **2012**; e) S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Org. Chem.* **2012**, *77*, 658; f) M. Kruszyk, M. Jessing, J. L. Kristensen, M. Jørgensen, *J. Org. Chem.* **2016**, *81*, 5128.

[32] G. Meng, Z. Wang, H. S. S. Chan, N. Chekshin, Z. Li, P. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2023**, *145*, 8198.
[33] L. S. Fitzgerald, R. L. McNulty, A. Greener, M. L. O'Duill, *J. Org. Chem.* **2023**, *88*, 10772.
[34] M. Liu, X. Chen, T. Chen, S.-F. Yin, *Org. Biomol. Chem.* **2017**, *15*, 2507.
[35] G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Goldberg, *Organometallics* **2010**, *29*, 2176.
[36] C. Messina, L. Z. Douglas, J. T. Liu, P. Forgione, *Eur. J. Org. Chem.* **2020**, *2020*, 5182.
[37] J. Barluenga, F. Andina, M. A. Fernández-Rodríguez, P. García-García, I. Merino, E. Aguilar, *J. Org. Chem.* **2004**, *69*, 7352.
[38] H. Wang, H. Shao, A. Das, S. Dutta, H. T. Chan, C. Daniliuc, K. N. Houk, F. Glorius, *Science* **2023**, *381*, 75.
[39] X.-Y. Chen, X.-X. Nie, Y. Wu, P. Wang, *Chem. Commun.* **2020**, *56*, 5058.
[40] H. Khatua, S. Das, S. Patra, S. K. Das, S. Roy, B. Chattopadhyay, *J. Am. Chem. Soc.* **2022**, *144*, 21858.
[41] S. K. Das, S. Das, S. Ghosh, S. Roy, M. Pareek, B. Roy, R. B. Sunoj, B. Chattopadhyay, *Chem. Sci.* **2022**, *13*, 11817.
[42] C. A. Riedl, L. S. Flocke, M. Hejl, A. Roller, M. H. M. Klose, M. A. Jakupec, W. Kandioller, B. K. Keppler, *Inorg. Chem.* **2017**, *56*, 528.
[43] Y. M. A. Yamada, S. M. Sarkar, Y. Uozumi, *J. Am. Chem. Soc.* **2012**, *134*, 9285.
[44] C. Jones, M. Waugh, *J. Organomet. Chem.* **2007**, *692*, 5086.
[45] M. Weber, S. Jautze, W. Frey, R. Peters, *Chem. Eur. J.* **2012**, *18*, 14792.
[46] B. Soliman, N. Wang, G. Zagotto, S. Pockes, *Arch Pharm Chem Life Sci.* **2019**, *352*, e1900107.

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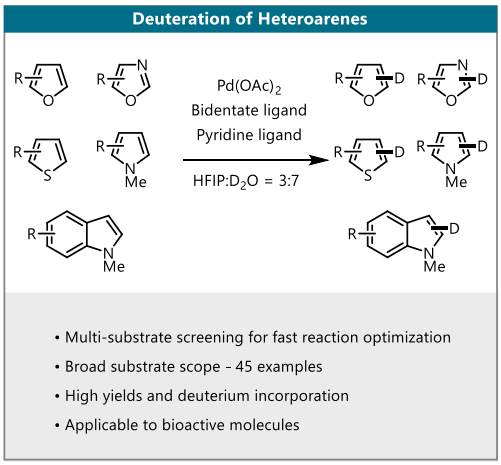

We describe a method for the Pd-catalyzed deuteration of a variety of five-membered heteroarenes. Reaction optimization was performed using a multi-substrate screening approach, which allowed for the identification of optimal reaction conditions for different classes of heteroarenes from a minimal number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

Institute and/or researcher Twitter usernames: @vangemmerenlab @kieluni