Palladium-Catalyzed Nondirected Late-Stage C–H Deuteration of Arenes

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C–H activation, late-stage modification, deuteration, palladium, arenes

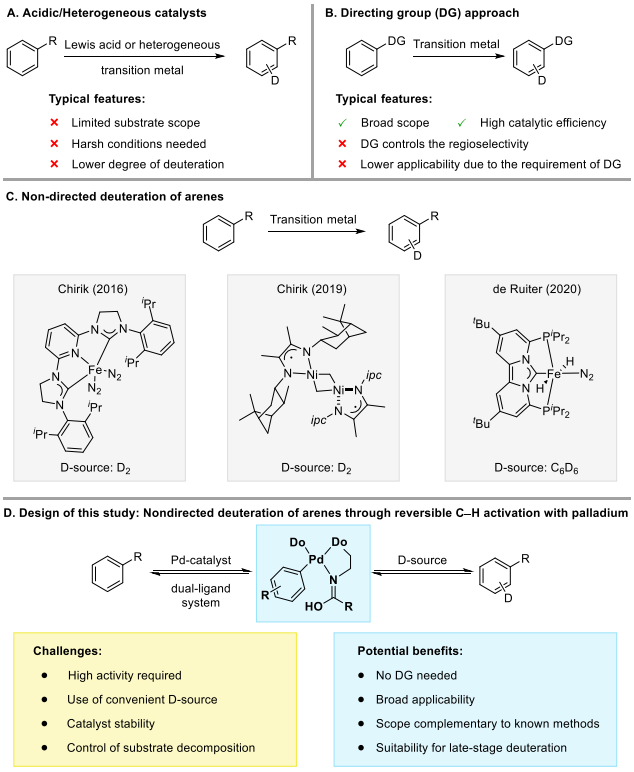
ABSTRACT: We describe a palladium catalyzed non-directed late-stage deuteration of arenes. Key aspects include the use of D_2O as a convenient and easily available deuterium source and the discovery of highly active *N*,*N*-bidentate ligands containing an *N*-acyl sulfonamide group. The reported protocol enables high degrees of deuterium incorporation via a reversible C–H activation step and features an extraordinary functional group tolerance, allowing for the deuteration of complex substrates. This is exemplified by the late-stage isotopic labelling of various pharmaceutically relevant motifs and related scaffolds. We expect that this method, amongst other applications, will prove useful as a tool in drug development processes and for mechanistic studies.

Over the last decades the incorporation of hydrogen atom isotopes into organic molecules has received considerable attention and remains a key research goal in both academic and industrial research.[1] Isotopically labelled compounds feature a broad range of applications, starting from their use in the elucidation of reaction mechanisms[2] or as internal standards in mass-spectrometry studies.[3] Isotopically labelled analogs of bioactive molecules play a critical role in the drug discovery processes, for example in absorption, distribution, metabolism, and excretion (ADME) studies to gain knowledge of their metabolic profile and toxicity.[4] In an increasing number of cases deuterated molecules are marketed as new pharmaceuticals[5] often characterized by improved pharmacokinetic and pharmacodynamic properties. These diverse applications have spurred a continued interest in the development of convenient and robust synthetic methods to incorporate deuterium into complex aromatic scaffolds, which occur in many bioactive molecules and related compounds.[1d,e]

Methods such as the *de novo* synthesis of complex deuterated analogs or the introduction of D/T in pre-functionalized positions often prove to be time consuming and cost-intensive.[6] Efforts have thus been made to establish methods for the direct hydrogen isotope exchange (HIE) of aromatic C–H bonds, that could in principle enable an efficient post-synthetic incorporation of hydrogen isotopes into bioactive molecules.[1d,e,7]

Traditional methods for the direct H/D-exchange of arenes include pH-dependent methods (Scheme 1A), where the incorporation of deuterium is achieved by the use of Brønsted/Lewis-acids mostly via an S_EAr-type mechanism.[8] Examples of base-mediated HIE reactions of arenes are also known.[9] Owing to the typically harsh reaction conditions these methods are usually employed for simple arenes. Heterogenous methods for the HIE of arenes are well developed and high activity could be achieved with many transition metals.[3e,10] This approach offers technical advantages like simple purification,[11] but faces challenges such as undesired side reactions.[12]

Scheme 1. Approaches towards the Deuteration of Arenes



The potential to achieve high selectivities for the HIE under comparably mild conditions and thus enabling a broader functional group tolerance, has spurred research towards homogeneously catalyzed methods.[1b,1d,1e,13] In this context, the use of directing groups (DGs) has proven highly useful.[14] Methods based on various transition metals have been established and feature high efficiencies and broad functional group tolerances (Scheme 1B).[15] While DGs usually lead to a selective deuteration in the ortho position, specialized DGs to achieve meta deuteration have also been described.[16]

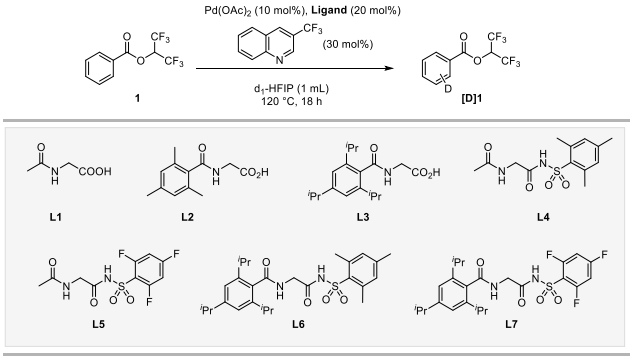
Recent studies have focused on the use of native functional groups rather than designed DG to enable directed late-stage C–H deuteration.[17]

These directed protocols are complemented by non-directed approaches,[18] which offer the potential to address unbiased C–H bonds without requiring a DG on the substrate, thus potentially enabling the H/D exchange on a substantially broader range of substrates. Non-directed methods for the deuteration of simple arenes are well established,[19] but catalysts that enable the non-directed HIE of drug molecules and other similarly complex scaffolds have only recently been described (Scheme 1C).[20] Chirik and co-workers introduced an iron catalyst capable of inducing HIE with a variety of pharmaceuticals using D_2 as deuterium source.[20a] The same group later described a Ni-based catalyst, which delivered deuterated and tritiated drug molecules efficiently using D_2 and T_2 as deuterium source.[20c] Recently, de Ruiter et al. described a Fe-PCP-pincer complex that proves highly active for the non-directed H/D-exchange of arenes using C_6D_6 as deuterium source and tolerates a considerable range of functional groups.[20e] These catalysts provided substantial progress towards the mild and efficient HIE of complex molecules and raised interest in the development of complementary methods.[1e,20f]

Our group has recently developed Pd-catalysts for the non-directed late-stage functionalization of complex (hetero)arenes.[21,22] An extensive mechanistic investigation of our dual ligand-based catalyst system[23] showed that the C–H activation step is reversible (Scheme 1D). We envisioned that a highly active catalyst for the reversible C–H activation of arenes using our dual ligand design could enable a homogenous non-directed method for the Pd-catalyzed late-stage HIE with the potential to complement existing methods based on 3d-metals with regard to the substrate scope and/or deuterium source used.

Based on these considerations, we engaged in detailed optimization studies.[24] Table 1 shows the deuteration of model substrate **1** using different bidentate ligands in d_1-HFIP. Acetyl glycine (**L1**) as ligand resulted in a moderate H/D-exchange (Entry 1). Building upon our recent finding that bulky aryl amides as CMD promoting group in ethylenediamine ligands show superior activity in HIE,[24] we synthesized the analogous glycine derivates **L2** and **L3** (Entries 2 and 3). These α-amino acid derived ligands lead to a significant improvement in deuterium incorporation. An extensive search for novel ligand classes with improved properties regarding activity and regioselectivity led us to discover *N*,*N*-bidentate ligands which feature *N*-acyl sulfonamide groups. Interestingly, introducing this motif instead of the carboxylic acid moiety offers additional potential for ligand diversification by introducing further variable positions. Using mesityl-substituted ligand **L4** gave similar results as acetyl glycine, albeit with less deuteration in the ortho-position, whereas **L5** lead to decreased values (Entries 4 and 5). A significant improvement resulted when the two structural variations were combined in **L6** and **L7** (Entries 6 and 7).

Table 1. Optimization of the Ligand Structure.[a, b]

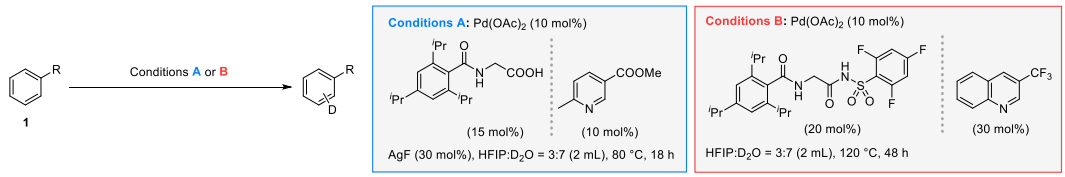


Entry	Ligand	Yield (%)	D-content (%, NMR)			Total D-content (MS)
			Ortho	Meta	Para	
1	**L1**	99	11	50	23	1.66
2	**L2**	95	22	73	41	2.42
3	**L3**	97	24.5	79	47	2.65
4	**L4**	98	4	46	23	1.27
5	**L5**	98	7	35	21	1.05
6	**L6**	97	5	72	46	2.08
7	**L7**	97	17	90	74	2.87
8[c]	**L7**	95	39	95	84	3.51
9[c,d]	**L7**	99	34	60	32	2.15
10[c]	**No L7**	98	0	0	0	0
11[c,e]	**L7**	94	62	95	95	4.05

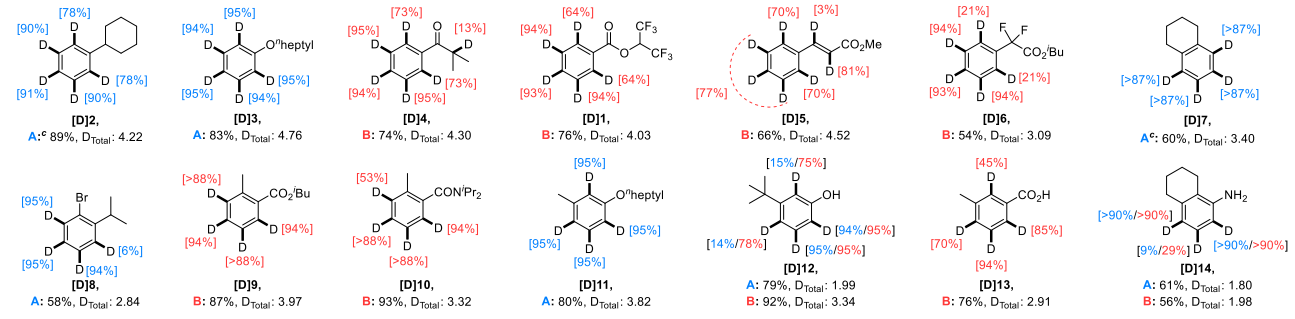
[a] Reactions were performed on a 0.1 mmol scale. [b] Yields and degrees of deuteration were determined by ^{1}H-NMR spectroscopy using mesitylene as internal standard. The total deuterium content was determined by mass spectrometry. [c] Reaction performed with D_2O:HFIP (7:3) as solvent. Note: since D_2O is used as part of the solvent system, this corresponds to an excess of approx. 390 equivalents. [d] No 3-trifluoromethyl quinoline. [e] Reaction performed with 48 h reaction time.

An investigation of alternative, more convenient deuterium sources showed that improved results are obtained with a mixture of D_2O:HFIP (7:3) as solvent (Entry 8). This is particularly attractive since d_1-HFIP, which is comparably costly or needs to be synthesized, can be replaced by a cheap and convenient deuterium source. Control experiments at this stage revealed that both ligands are indeed required to obtain optimal results (Entries 9 and 10). Finally, nearly complete deuteration of the meta and para positions was observed when using **L7** with an increased reaction time (Entry 11).

Scheme 2. Reaction Scope.[a,b]



Simple arenes



[D]2, A:[c] 89%, D_{Total}: 4.22

[D]3, A: 83%, D_{Total}: 4.76

[D]4, B: 74%, D_{Total}: 4.30

[D]1, B: 76%, D_{Total}: 4.03

[D]5, B: 66%, D_{Total}: 4.52

[D]6, B: 54%, D_{Total}: 3.09

[D]7, A[c]: 60%, D_{Total}: 3.40

[D]8, A: 58%, D_{Total}: 2.84

[D]9, B: 87%, D_{Total}: 3.97

[D]10, B: 93%, D_{Total}: 3.32

[D]11, A: 80%, D_{Total}: 3.82

[D]12, A: 79%, D_{Total}: 1.99; B: 92%, D_{Total}: 3.34

[D]13, B: 76%, D_{Total}: 2.91

[D]14, A: 61%, D_{Total}: 1.80; B: 56%, D_{Total}: 1.98

[D]15, B: 60%, D_{Total}: 3.95

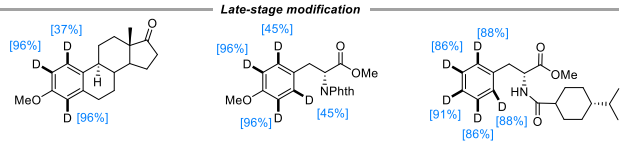
[D]16, B: 53% D_{Total}:[d] 0.56

[D]17, B:[d] 32% D_{Total}: 1.18

[D]18, A:[d] 85% D_{Total}: 0.46

[D]19, B: 69% D_{Total}: 0.89

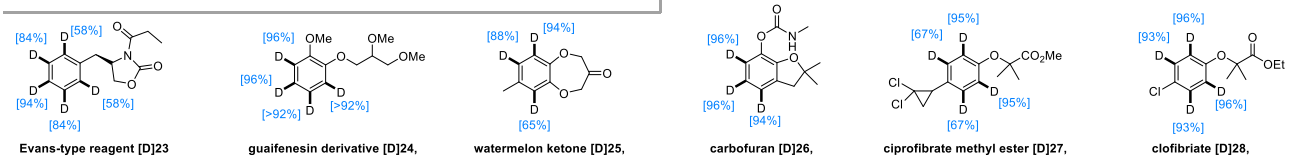
Late-stage modification



estrone methyl ether [D]20, A: 86%, D_{Total}: 2.21

tyrosine derivative [D]21, A: 97%, D_{Total}: 2.80

nateglinide methyl ester [D]22, A: 92%, D_{Total}: 4.42



Evans-type reagent [D]23 A: 98%, D_{Total}: 3.63

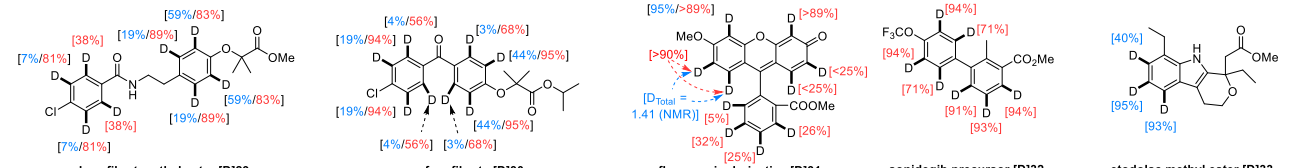
guaifenesin derivative [D]24, A: 91%, D_{Total}: 3.85

watermelon ketone [D]25, A: 86%, D_{Total}: 2.44

carbofuran [D]26, A: 85%, D_{Total}: 2.86

ciprofibrate methyl ester [D]27, A: 76%, D_{Total}: 3.23

clofibriate [D]28, A: 60%, D_{Total}: 3.71



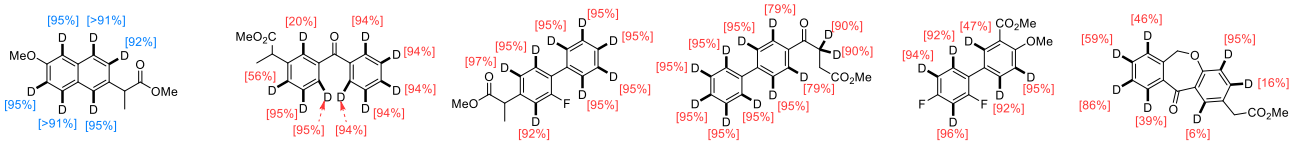
bezafibrat methyl ester [D]29, A: 99%, D_{Total}: 1.77; B: 98%, D_{Total}: 5.96

fenofibrate [D]30, A: 91%, D_{Total}: 1.18; B: 92%, D_{Total}: 6.12

fluorescein derivative [D]31, A: 86%, D_{Total}: 2.49; B: 88%, D_{Total}: 4.57

sonidegib precursor [D]32, B: 89%, D_{Total}: 6.06

etodolac methyl ester [D]33, A: 78%, D_{Total}: 2.31



naproxen methyl ester [D]34, A: 80%, D_{Total}: 5.54

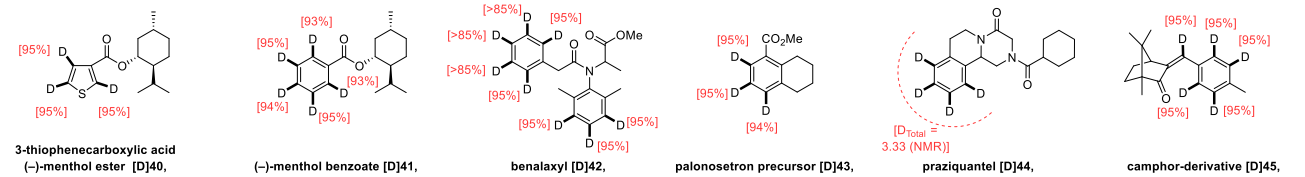
ketoprofen methyl ester [D]35, B: 63%, D_{Total}: 7.25

flurbiprofen methyl ester [D]36, B: 82%, D_{Total}: 7.57

fenbufen methyl ester [D]37, B: 60%, D_{Total}: 9.88

diflunisal derivative [D]38, B: 91%, D_{Total}: 5.10

isoxepac methyl ester [D]39, B: 75%, D_{Total}: 3.46



3-thiophenecarboxylic acid (–)-menthol ester [D]40, B: 83%, D_{Total}: 2.86

(–)-menthol benzoate [D]41, B: 86%, D_{Total}: 4.68

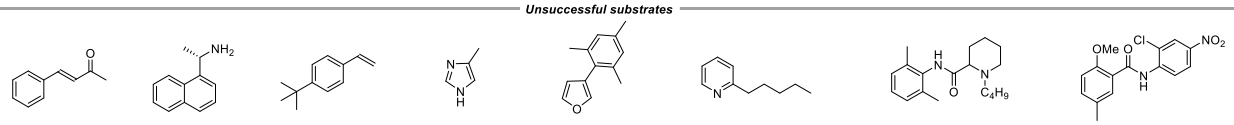
benalaxyl [D]42, B: 95%, D_{Total}: 7.70

palonosetron precursor [D]43, B: 90%, D_{Total}: 2.85

praziquantel [D]44, B: 60%, D_{Total}: 3.38

camphor-derivative [D]45, B: 92%, D_{Total}: 4.74

Unsuccessful substrates



46 decomposition

47 decomposition

48 decomposition

49 decomposition

50 decomposition

51 no reaction

52 no reaction

53 no reaction

[a] Reactions were performed on a 0.2 mmol scale. [b] Positions with less than 10% D incorporation are typically not depicted explicitly but reflected in the D_{Total} value (For experimental details: see the SI). [c] Reaction performed at 40 °C for 72 h. [d] Determined by ^{1}H-NMR spectroscopy.

Interestingly, the seemingly sterically most hindered ligand enables the highest deuteration in the ortho-position. This can be explained by two factors. Firstly, the steric bulk does not point towards the substrate in the key C–H activation step,[23] and secondly, the ligand enables the highest overall activities, such that even the least reactive site on the substrate is deuterated, although still substantially slower than the other positions (Entries 8 and 11). Since the conditions developed in Table 1 (Conditions B in Scheme 2) were found using a particularly challenging electron-poor substrate, we hypothesized that more electron-rich substrates might be deuterated under milder conditions. A re-optimization (see the SI for details) delivered a second set of reaction conditions using **L3** and AgF as an additive at lower temperatures (Conditions A in Scheme 2)

Having established two sets of conditions we evaluated the scope (Scheme 2). We initiated our investigation by using simple arenes to assess the general functional group tolerance when applying our catalyst systems. The yields of the re-isolated substrates were in general good to excellent. The use of alkylated arene **2** under very mild conditions resulted in high H/D-exchange in the arene moiety (D_{Total}=4.22). Excellent degrees of deuteration were also observed for the anisole derivative **3**. Notably, our protocol tolerates ketones (**4**), a functional group that is challenging for many literature methods. This observation is of particular importance due to the presence of this functionality in a wide range of bioactive molecules. Using Conditions B, in addition to the deuteration on the arene core, butyrophenone **4** underwent little but measurable isotope exchange in the relatively acidic α-position, presumably via an acid-base mechanism. The electron-poor arenes **1**, **5**, and **6** were likewise subjected to Conditions B, leading to very high degrees of deuteration, especially in the meta and para positions. Di-alkyl substituted substrate **7** smoothly underwent H/D exchange in the arene moiety. Interestingly, halogenated arene **8** was well tolerated under Conditions A giving the re-isolated substrate in good yield and with a high overall degree of deuteration. Further di-substituted arenes containing ester-, amide-, ether-, and free hydroxy groups (**9**-**12**) gave high levels of deuterium incorporation (up to D_{Total}=3.97). Aniline-derivatives (**14**), aldehydes and extended p-systems (**15**) are likewise tolerated under the reaction conditions. Finally, we probed whether our protocol can be used for heterocycles. The comparably electron-rich heteroarenes pyrrole **16**, oxazole **17**, and thiazole **18** could be deuterated in moderate to good yields and with appreciable levels of deuterium incorporation. The deuteration of pyridine-derivative **19** confirmed that this substrate class is in principle amenable if the *N*-atom is sufficiently shielded to avoid catalyst poisoning.

We proceeded to evaluate the suitability of our method for the late-stage deuteration of bioactive molecules and related scaffolds. Subjecting estrone derivative **20** to Conditions A delivered the deuterated compound **[D]20** in very good yield and a high degree of deuteration on the arene moiety. Interestingly, the sterically most congested position underwent H/D-exchange to a reduced extent. Similarly, with tyrosine derivative **21** the deuterium incorporation into the sterically more hindered position was lower than ortho to the methoxy-group. Furthermore, nateglinide methyl ester **22**, the Evans-type reagent **23**, guaifenesin derivative **24**, watermelon ketone (**25**), and carbofuran (**26**) were subjected to Conditions A, leading to almost complete deuterium incorporation into the respective arene moieties, thereby demonstrating a functional group tolerance towards amides, esters, ethers, and carbamates.

Representatives of the fibrate class such as cipofibrate methyl ester (**27**), clofibrate (**28**), benzafibrate methyl ester (**29**), and fenofibrate (**30**) were efficiently deuterated. Due to the presence of an electron-poor and a rather electron-rich arene moiety, substrates **29** and **30** were subjected to both Conditions A and B. With the milder reaction Conditions A, a good degree of deuteration on the electron-rich arene was observed, while with Conditions B both arene moieties were efficiently deuterated.

The fluorescein-derivative **31** was also subjected to both catalyst systems. With Conditions A, the electron-rich positions underwent efficient H/D-exchange (D_{Total}=2.49) exclusively, whereas Conditions B lead to a substantially increased overall deuterium incorporation (D_{Total}=4.57). Nearly complete deuteration of the arene moieties occurred using the sonidegib precursor **32**. The etodolac methyl ester (**33**), which contains an indole substructure, likewise underwent an efficient H/D-exchange using Conditions A.

Methyl ester derivatives of naproxen (**34**), ketoprofen (**35**), and flurbiprofen (**36**), as representatives of the profen class of medications were almost completely deuterated at the arene position (up to D_{Total}=7.57). The fenbufen derivative **37** could likewise be deuterated. It should be noted that besides the aromatic core, the α-keto position underwent almost complete deuteration presumably due to an acid/base-type mechanism.

Derivatives of diflunisal (**38**) and isoxepac (**39**) gave high degrees of deuteration using Conditions B. (–)-Menthol esters of 3-thiophenecarboxylic acid (**40**) and benzoic acid (**41**) could both be deuterated efficiently. Finally, subjecting benalaxyl (**42**), the palonosetron precursor **43**, praziquantel (**44**), and camphor-derivative **45** to our catalyst led to nearly complete deuterium incorporation in the arene moieties, as well as the olefinic position of **45**.

Finally, Scheme 2 depicts a number of substrates that could not be deuterated using our method either due to substrate decomposition (**46-50**) or due to an absence of reactivity that presumably originates from catalyst poisoning by the substrate or its insolubility in the reaction medium (**51-53**).

As evidenced by the above scope studies, we have developed a broadly applicable protocol for the non-directed late-stage deuteration of arenes using dual ligand-based palladium catalysts. Enabled by the development of a novel ligand class, a wide variety of bioactive molecules and related structures could be isotopically labelled using D_2O as a cheap and convenient deuterium source. This method is applicable to both electron-rich and electron-poor arenes and tolerates a wide range of functional groups, rendering it complementary to established protocols. We expect that our catalysts will prove useful for isotopic labelling in a variety of fields, with potential applications ranging from mechanistic studies to drug development.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge via the Internet at http://pubs.acs.org. Optimization of reaction conditions, preparative procedures, analytical data for the compounds are described.

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Author Contributions

‡ M.F., and A.M. contributed equally to this work. § S.M. and F.D. contributed equally to this work.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

HFIP, 1,1,1,3,3,3-hexafluoropropan-2-ol.

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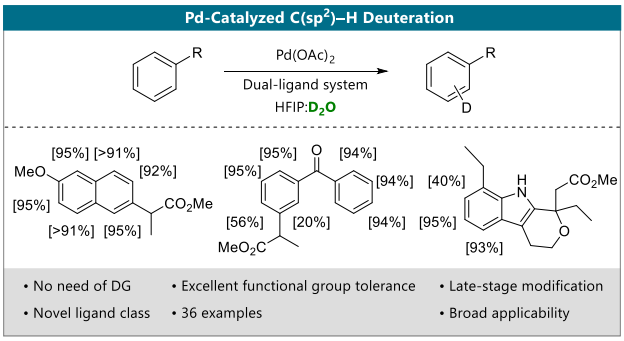
Pd-Catalyzed C(sp2)–H Deuteration
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Dual-ligand system
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• No need of DG
• Novel ligand class
• Excellent functional group tolerance
• 36 examples
• Late-stage modification
• Broad applicability