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Communication

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

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Cite This: *J. Am. Chem. Soc.* 2021, 143, 16370–16376 Read Online

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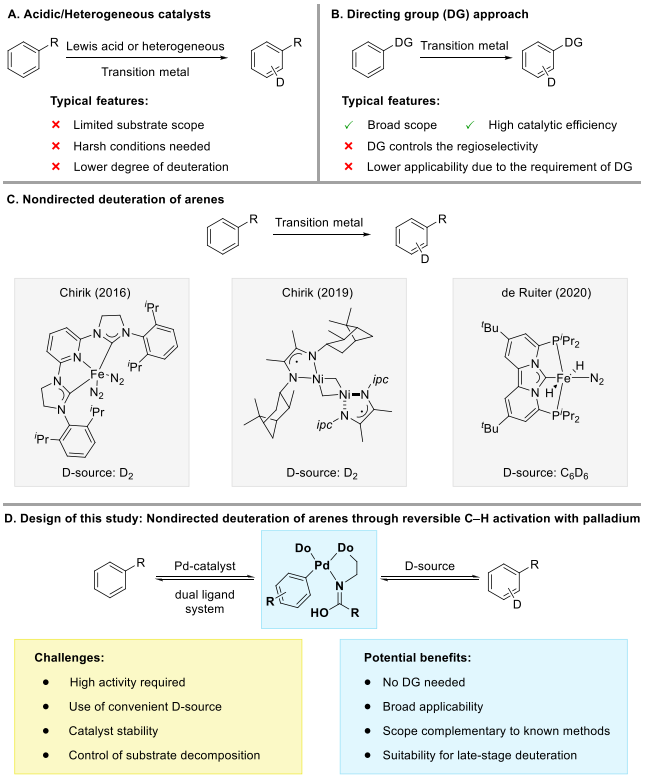
ABSTRACT: We describe a palladium-catalyzed nondirected late-stage deuteration of arenes. Key aspects include the use of D_2O as a convenient and easily available deuterium source and the discovery of highly active N,N-bidentate ligands containing an *N*-acylsulfonamide group. The reported protocol enables high degrees of deuterium incorporation via a reversible C–H activation step and features extraordinary functional group tolerance, allowing for the deuteration of complex substrates. This is exemplified by the late-stage isotopic labeling of various pharmaceutically relevant motifs and related scaffolds. We expect that this method, among 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 labeled 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 labeled analogues of bioactive molecules play a critical role in drug discovery processes, for example in absorption, distribution, metabolism, and excretion (ADME) studies to gain insights into 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 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]

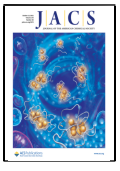
Methods such as the de novo synthesis of complex deuterated analogues and the introduction of D/T in prefunctionalized positions often prove to be time-consuming and cost-intensive.[6] Efforts have thus been made to establish methods for direct hydrogen isotope exchange (HIE) of aromatic C–H bonds that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

Traditional methods for 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 HIE of arenes are well-developed, and high activity can 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 toward the Deuteration of Arenes



Received: August 6, 2021
Published: September 28, 2021



https://doi.org/10.1021/jacs.1c08233
J. Am. Chem. Soc. 2021, 143, 16370–16376

The potential to achieve high selectivities for HIE under comparably mild conditions, thus enabling a broader functional group tolerance, has spurred research toward homogeneously catalyzed methods.[1b,d,e,13] In this context, the use of directing groups (DGs) has proven to be 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 selective deuteration at the ortho position, specialized DGs to achieve meta deuteration have also been described.[16]

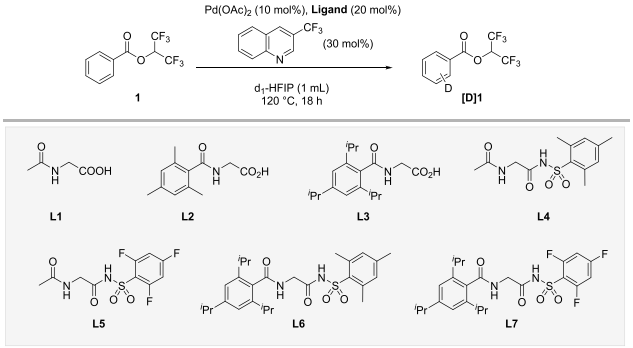
Recent studies have focused on the use of native functional groups rather than designed DGs to enable directed late-stage C−H deuteration.[17]

These directed protocols are complemented by nondirected approaches,[18] which offer the possibility to address unbiased C−H bonds without requiring a DG on the substrate, thus potentially enabling H/D exchange on a substantially broader range of substrates. Nondirected methods for the deuteration of simple arenes are well-established,[19] but catalysts that enable nondirected 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 the deuterium source.[20a] The same group later described a Ni-based catalyst that delivered deuterated and tritiated drug molecules efficiently using D_2 and T_2 as the sources of deuterium and tritium, respectively.[20c] Recently, de Ruiter et al. described an Fe−PCP-pincer complex that proved to be highly active for the nondirected H/D exchange of arenes using C_6D_6 as the deuterium source and tolerated a considerable range of functional groups.[20e] These catalysts provided substantial progress toward 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 nondirected 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 homogeneous nondirected method for 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.

On the basis of these considerations, we engaged in detailed optimization studies.[24] Table 1 shows the deuteration of model substrate **1** using different bidentate ligands in 1,1,1,3,3,3-hexafluoropropan-2-ol-d_1 (d_1-HFIP). *N*-Acetylglycine (**L1**) as the ligand resulted in moderate H/D-exchange (entry 1). Building upon our recent finding that bulky arylamides as concerted metalation−deprotonation (CMD)-promoting groups in ethylenediamine ligands show superior activity in HIE,[24] we synthesized the analogous glycine derivatives **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 that feature *N*-acylsulfonamide 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 **L1**, albeit

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



			D content (%)			
entry	ligand	yield (%)	ortho	meta	para	total D content
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 an internal standard. The total deuterium content was determined by mass spectrometry. [c]The reaction was performed with D_2O/HFIP (7:3) as the solvent. Since D_2O is used as part of the solvent system, this corresponds to an excess of approximately 390 equiv. [d]No 3-trifluoromethylquinoline. [e]The reaction was performed with a reaction time of 48 h.

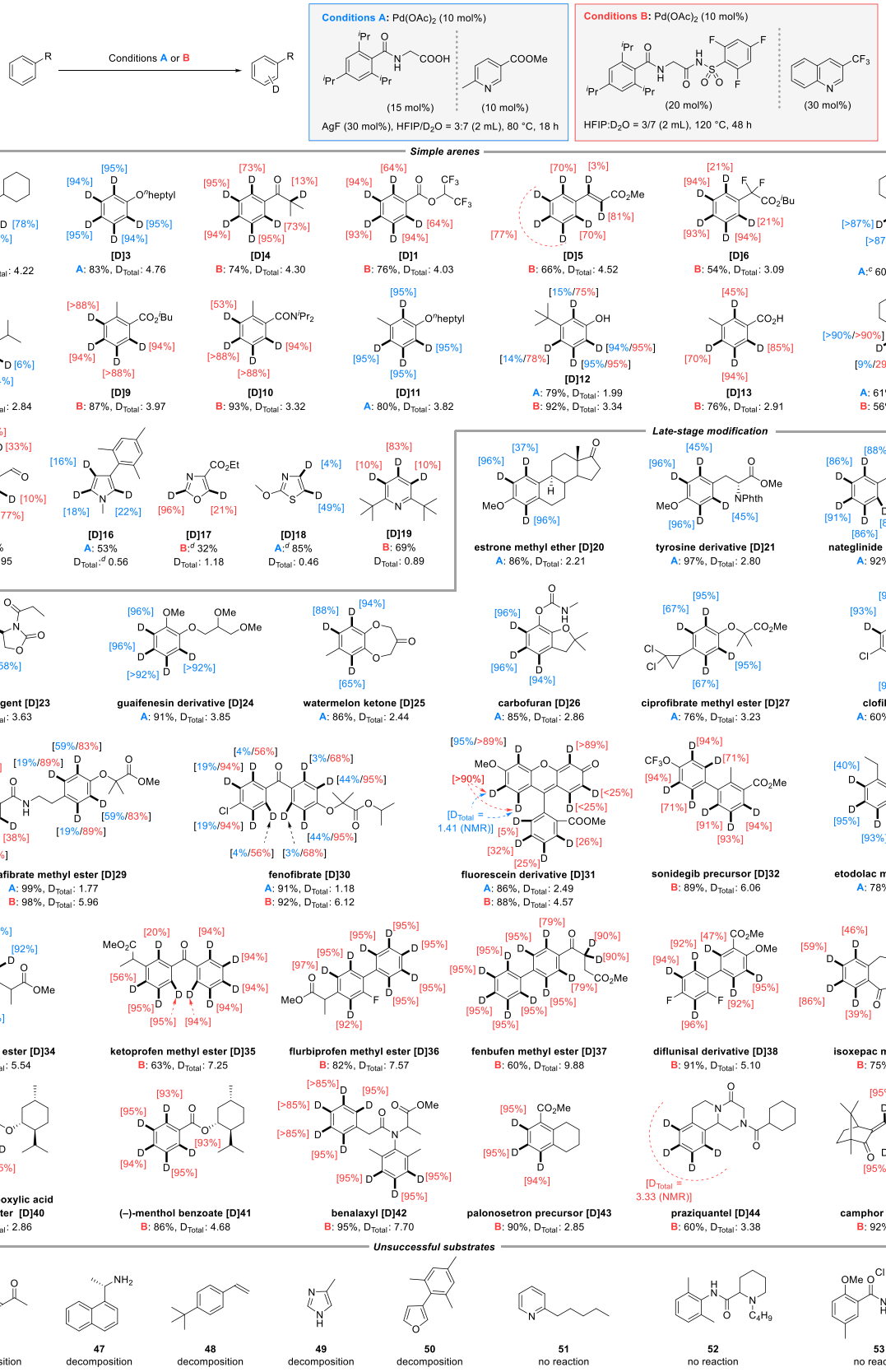
with less deuteration at the ortho position, whereas **L5** led to decreased values (entries 4 and 5). A significant improvement resulted when the two structural variations were combined in **L6** and **L7** (entries 6 and 7).

An investigation of alternative, more convenient deuterium sources showed that improved results are obtained with a 7:3 D_2O/HFIP mixture as the solvent (Table 1, 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 **L7** was used with an increased reaction time (entry 11).

Interestingly, the seemingly sterically most hindered ligand enables the highest deuteration at the ortho position. This can be explained by two factors. First, the steric bulk does not point toward the substrate in the key C−H activation step,[23] and second, the ligand enables the highest overall activities, such that even the least reactive site on the substrate is deuterated. However, it remains 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 reoptimization (see the Supporting Information (SI) for details) delivered a second set

https://doi.org/10.1021/jacs.1c08233
J. Am. Chem. Soc. 2021, 143, 16370−16376

Scheme 2. Reaction Scope[a,b]



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

https://doi.org/10.1021/jacs.1c08233
J. Am. Chem. Soc. 2021, 143, 16370−16376

of reaction conditions using **L3** with AgF as an additive at lower temperatures (conditions A in Scheme 2)

Having established two sets of conditions, we evaluated the scope of our method (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 reisolated 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 anisole derivative **3**. Notably, our protocol tolerates ketones (**4**), a functional group that occurs in a wide range of bioactive molecules, but is challenging for many literature methods. 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 at the meta and para positions. Dialkyl-substituted substrate **7** smoothly underwent H/D exchange in the arene moiety. Interestingly, halogenated arene **8** was well-tolerated under conditions A, giving the reisolated substrate in good yield with a high overall degree of deuteration. Further disubstituted arenes containing ester, amide, and ether, as well as free hydroxy and acid groups (**9**−**13**) gave high levels of deuterium incorporation (up to D_{Total} = 3.97). Aniline derivatives (**14**) as well as aldehydes and extended π 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 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 with 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 at the sterically more hindered position was lower than at the position 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 functional group tolerance toward amides, esters, ethers, and carbamates.

Representatives of the fibrate class such as cipofibrate methyl ester (**27**), clofibrate (**28**), bezafibrate methyl ester (**29**), and fenofibrate (**30**) were efficiently deuterated. Because of 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.

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 led to substantially increased overall deuterium incorporation (D_{Total} = 4.57). Nearly complete deuteration of the arene moieties occurred with sonidegib precursor **32**. Etodolac methyl ester (**33**), which contains an indole substructure, likewise underwent 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). 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 via an acid/base-type mechanism.

Derivatives of diflunisal (**38**) and isoxepac (**39**) gave high degrees of deuteration under conditions B. (−)-Menthol esters of 3-thiophenecarboxylic acid (**40**) and benzoic acid (**41**) could both be deuterated efficiently. Finally, subjecting benalaxyl (**42**), 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 because of either substrate decomposition (**46**−**50**) or an absence of reactivity that presumably originates from catalyst poisoning by the substrate (**51**−**53**).

As evidenced by the above scope studies, we have developed a broadly applicable protocol for the nondirected late-stage deuteration of arenes using dual ligand-based palladium catalysts. Enabled by the development of a novel ligand class, a variety of bioactive molecules and related structures could be isotopically labeled 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 labeling in various fields, with potential applications ranging from mechanistic studies to drug development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c08233.

Optimization of the reaction conditions, preparative procedures, and analytical data for the compounds (PDF)

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https://doi.org/10.1021/jacs.1c08233
J. Am. Chem. Soc. 2021, 143, 16370−16376

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Funding

We acknowledge generous financial support by the DFG (Emmy Noether Programme) and WWU Münster. Additionally, this project received funding from the European Research Council (ERC) under the European Union's Horizon 2020 Research and Innovation Programme (Grant Agreement 946044).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank all of the members of our MS and NMR department for their excellent service, A. Uttry for helpful scientific discussions, and Prof. Dr. Frank Glorius for his generous support.

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