Late-Stage β-C(sp^3)–H Deuteration of Carboxylic Acids

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ABSTRACT: Carboxylic acid moieties are highly abundant in bioactive molecules. In this study we describe the late-stage β-C(sp^3)–H deuteration of free carboxylic acids. Based on our finding that the C–H activation with our catalyst systems is reversible, the de-deuteration process was first optimized. The resulting conditions involve a novel type of ligands, which, amongst other positions, for the first time enables the functionalization of non-activated methylene β-C(sp^3)–H bonds and can be used to achieve the desired deuteration when using a deuterated solvent. The reported method allows for the functionalization of a wide range of free carboxylic acids with diverse substitution patterns, as well as the late-stage deuteration of bioactive molecules and related frameworks.

Synthetic methods to introduce heavy hydrogen isotopes into organic molecules are a key technology. Despite the apparent simplicity of such exchanges, efficient methods for the late-stage deuteration of complex substrates are still scarce.[1] Deuterated analogs are important in the drug discovery process with applications including absorption, distribution, metabolism, and excretion (ADME) studies.[2] Isotopically labeled compounds are used as internal standards[3], for the elucidation of reaction mechanisms[4], as a design element in pharmacologically active compounds to lower metabolism rates,[5] and in a wide range of further fields, like the investigation of proteomics[6] or medicinal imaging[7].

Compared to the introduction of deuterium into aromatic positions the number of methods available for aliphatic positions is limited and especially the regioselective late-stage introduction of deuterium is still a substantial challenge.[1b] For small target molecules with limited molecular complexity traditional synthesis using pre-functionalized substrates in multistep, time consuming procedures can be used to introduce deuterium. Such traditional methods include the isotope exchange in acidic postions[8], reductive methods using deuterium gas[9] or metalldeuterides[10], or enolization followed by introduction of a deuterated methyl group.[11] However, these approaches are limited in their applicability to complex molecules such as pharmacophores. In this context, the late-stage deuteration of bioactive molecules becomes highly attractive, since it inherently avoids the above-mentioned drawbacks (Figure 1A), which is for example evidenced by recent reports on photo-catalyzed deuterations based on HAT processes and transition metal-catalyzed protocols.[12] Further recent work towards this goal includes the stereo retentive α-deuteration of amino acids or the selective stereo-retentive deuteration of C(sp^3)–H bonds in benzylic positions.[13]

The carboxylic acid moiety is amongst the most common functional groups present in drug molecules as well as in organic molecules in general.[14] Consequently, methods for the regioselective late-stage hydrogen-isotope-exchange of carboxylic acids poses tremendous application potential.

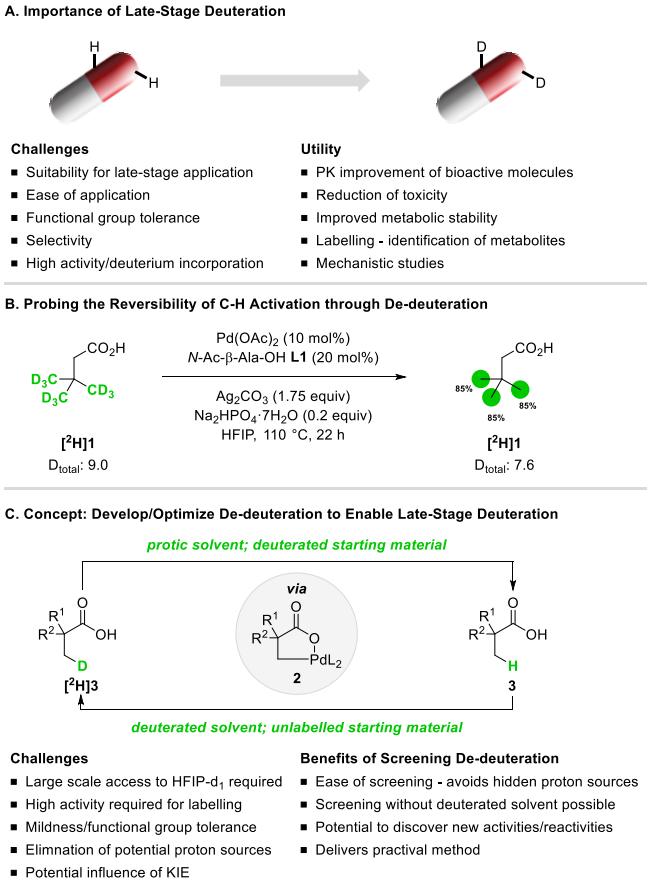


Figure 1. A. Importance of late-stage deuteration; B. Reversibility of the C–H activation; C. Design of the study.

With carboxylic acids as directing groups (DG), the only reports for the deuterations of C(sp^3)–H bonds have remained limited to heterogeneously catalyzed protocols for simple fatty acid, enabling an unselective deuteration under harsh conditions.[15] Carboxylates have also been used as directing

groups to enable the ortho deuteration of aromatic substrates.[16] The first regioselective C(sp^3)–H deuteration of carboxylic acid derivatives was achieved indirectly via the introduction of the 8-aminoquinoline (8-Aq) moiety as an exogenous directing group,[17] but direct regioselective deuterations of free carboxylic acids have remained elusive to date.

Recently, palladium-catalyzed C(sp^3)–H activations/ functionalizations of free carboxylic acids have emerged as an attractive alternative to the use of exogenous DG, demonstrating that careful catalyst design can be used to overcome the particular challenges associated with this directing group.[18] During mechanistic studies concerning our catalysts for the γ-olefination of carboxylic acids we found that the C–H activation step is in principle reversible as evidenced in a de-deuteration experiment (Figure 1B). Using nona-deutero 2,2-dimethylbutyric acid (**[^{2}H]1**) in the absence of a coupling partner we could experimentally observe a decrease of the overall deuteration degree of the recovered starting material.[19]

Based on this observation we reasoned that the reverse should be possible and we might be able to develop an efficient technique for the deuteration of aliphatic carboxylic acids (Figure 1C). Key to such a method would be to reversibly form the C–H activated palladacycle **2** in a highly efficient manner while at the same time avoiding side reactions leading to catalyst or substrate decomposition. We expected that the use of HFIP (1,1,1,3,3,3-hexafluoropropan-2-ol) as solvent would be required, due to its well-documented unique suitability to enable challenging C–H activation processes.[20]

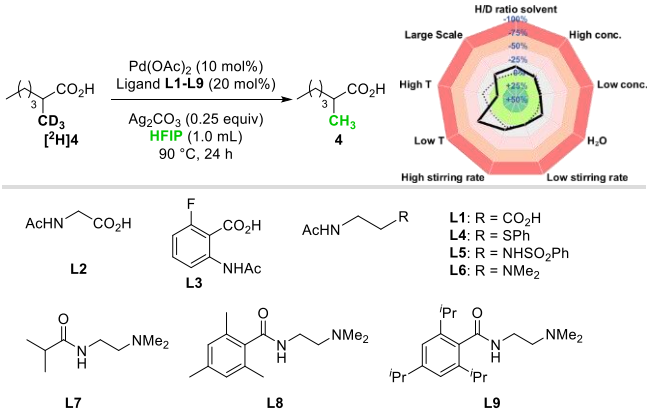
Considering the correlation between a deuteration of regular substrates in a deuterated solvent and the reverse de-deuteration of labelled substrates in regular solvents (Figure 1C)[21], we furthermore reasoned that it should be possible as a general technique to optimize de-deuteration processes when ultimately aiming to develop a method for deuteration. This strategy would offer substantial advantages compared to studying the deuteration directly. In particular, the optimization studies would not require deuterated solvent and would be more robust, because potential contaminations with proton sources such as water and the acidic proton of the substrate would exert no detrimental effect. Another attractive feature of this approach is that it could be used to uncover new catalytic activities. Since the C–H activation step is separated from any subsequent transformation, the discovery of catalyst systems that activate challenging positions is not affected by the ability of the same catalyst to facilitate the subsequent steps in the model reaction. Such single step screenings for active catalysts have been used successfully in the discovery of new photochemical transformations[22] and are expected to prove useful in C–H activation.

When employing this strategy, the possible effects of the kinetic isotope effect (KIE) must be considered. When the deuterated acid **[^{2}H]3** is de-deuterated to **3** the KIE disfavors the isotope exchange, since in partially deuterated intermediates the C–H bonds already present are activated preferentially over the remaining C–D bonds. Conversely, in the deuteration process, the KIE is expected to favor the reaction. Thus, a higher catalytic efficiency is expected in the deuteration process than in the de-deuteration, which implies that catalysts optimized for the de-deuteration will perform better when the direction of the reaction is reversed.

Being aware that the application of our method would require the availability of d_1-HFIP in substantial quantities, a convenient method for its synthesis from cheap starting materials was developed.[23]

Encouraged by these conceptual considerations, we initiated our investigation by screening common ligands classes **L1**–**L6** which have been employed in C(sp^3)–H activation processes of carboxylic acids (Table 1). The ligands **L1**–**L5** gave low but measurable levels of de-deuteration. However, this reactivity could not further be improved (entries 2-6). Ligand **L6** derived from ethylenediamine gave the first encouraging result, leading to an overall de-deuteration of 11% (entry 7).

Table 1. Ligand Screening and Reaction Condition Based Sensitivity Assessment.[a]



Entry	Ligand	Yield 4 (%)[b]	De-Deuteration (%)[b]
1	**n**	82	<5
2	**L2**	87	<5
3	**L3**	91	<5
4	**L1**	87	<5
5	**L4**	92	<5
6	**L5**	91	<5
7	**L6**	89	11
8	**L7**	90	32
9	**L8**	93	73
10	**L9**	93	80

[a] Conditions: Reactions were performed on a 0.1 mmol scale. Radar diagram: Solid line = deviation from de-deuteration under standard conditions; Dotted line = deviation from the yield under standard conditions. [b] Yields and degrees of de-deuteration were determined by ^{1}H-NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

Based on this observation, we prepared a series of novel ethylenediamine-based ligands. While in related studies the NHAc-protecting group was used to facilitate the concerted-metalation-deprotonation (CMD) step, we discovered that the reactivity for the de-deuteration could be significantly increased by changing this group to a more bulky isopropyl substituent **L7** (entry 8). Further systematic variation of the group resulted in the highly active ligands **L8** and **L9** enabling the de-deuteration with high efficiency (entries 9–10). Substitution on the backbone or at the tertiary amine of the ligands gave no further improvements (For details see the SI). Finally, we performed a reaction condition based sensitivity assessment.[24] We chose a set of parameters that, based on our experience with related C–H activation methods, could potentially be relevant

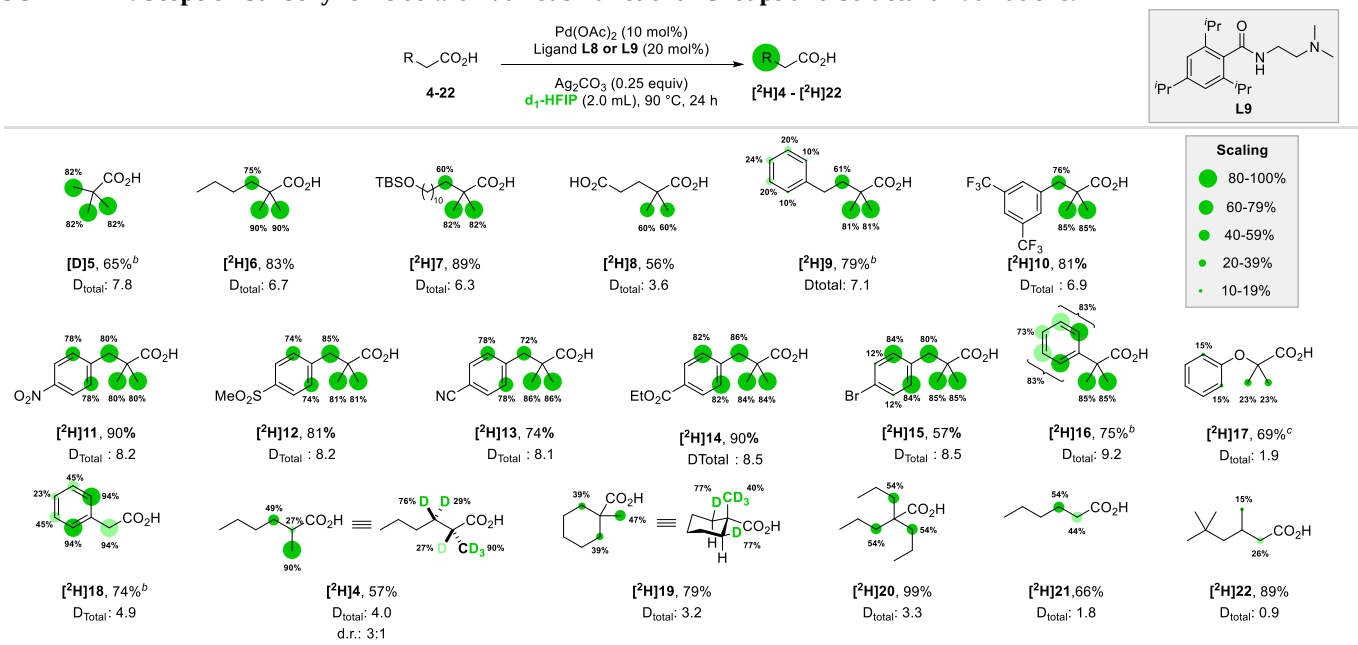
for the reproducibility of our protocol. Amongst these factors, only lowering the reaction temperature resulted in a significant loss of reactivity. A higher reaction temperature is not beneficial, since an increased activity for isotope exchange is counterbalanced by a growing decomposition of the carboxylic acid.

Having optimized conditions in hand we began to investigate the scope of our reaction (Scheme 1). Throughout the scope studies the carboxylic acid substrates were generally re-isolated in good to excellent yields, the majority of products being obtained in yields above 70%. We began our investigation with pivalic acid (**5**) and found that the conditions identified in the de-deuteration screening indeed enabled us to incorporate very high amounts of deuterium (D_{total}=7.8). Moving to a substrate with a longer alkyl chain **6** revealed an interesting observation. Besides the expected methyl groups, we could observe additional deuterium incorporation in the β-methylene position with almost same efficiency. This is remarkable, since such non-activated methylene positions are typically outside the range of carboxylate-directed C–H activation catalysts. In fact, to the best of our knowledge, this constitutes the first report on a Pd-catalyzed β-methylene C–H activation/functionalization of an unbiased carboxylic acid.

We continued to investigate the compatibility of typical functional groups. An OTBS-protected alcohol **7** and a remote second carboxylic acid moiety **8** were well tolerated under the reaction conditions. For the substrate bearing a phenyl residue **9** we observed that besides the expected deuteration in the β-methyl- and β-methylene positions, a C–H deuteration also occurred on the arene to a small extend. Employing a substrate bearing two trifluoromethyl groups in 3,5-position **10** only aliphatic C–H deuteration was observed. Various other carboxylic acids bearing different aromatic EWG substituents (**11**–**15**) were well tolerated under the reaction conditions. We observed high levels of deuterium incorporation (up to D_{total}=8.5) for these substrates. Deuterium incorporation occurred in the ortho positions of the arene, presumably resulting from a carboxylate directed pathway involving the formation of a seven membered palladacycle.c,[25] In these cases, the efficiency of remote carboxylate directed deuteration can outcompete weak to moderate directing groups directly attached to the arene (**12**, **14**, **15**). The Phenylacetic acid derivative **16** was deuterated with very high efficiency even in remote positions of the arene (D_{Total}=9.2). The lactic acid derivative **17** was chosen as a model substrate since this is a common structural motif of numerous drug molecules of the fibrate class. For this substrate, a silver free protocol was required to control the degradation of the starting material. In this way, we could obtain the deuterated compound **[^{2}H]17** in 69% yield.

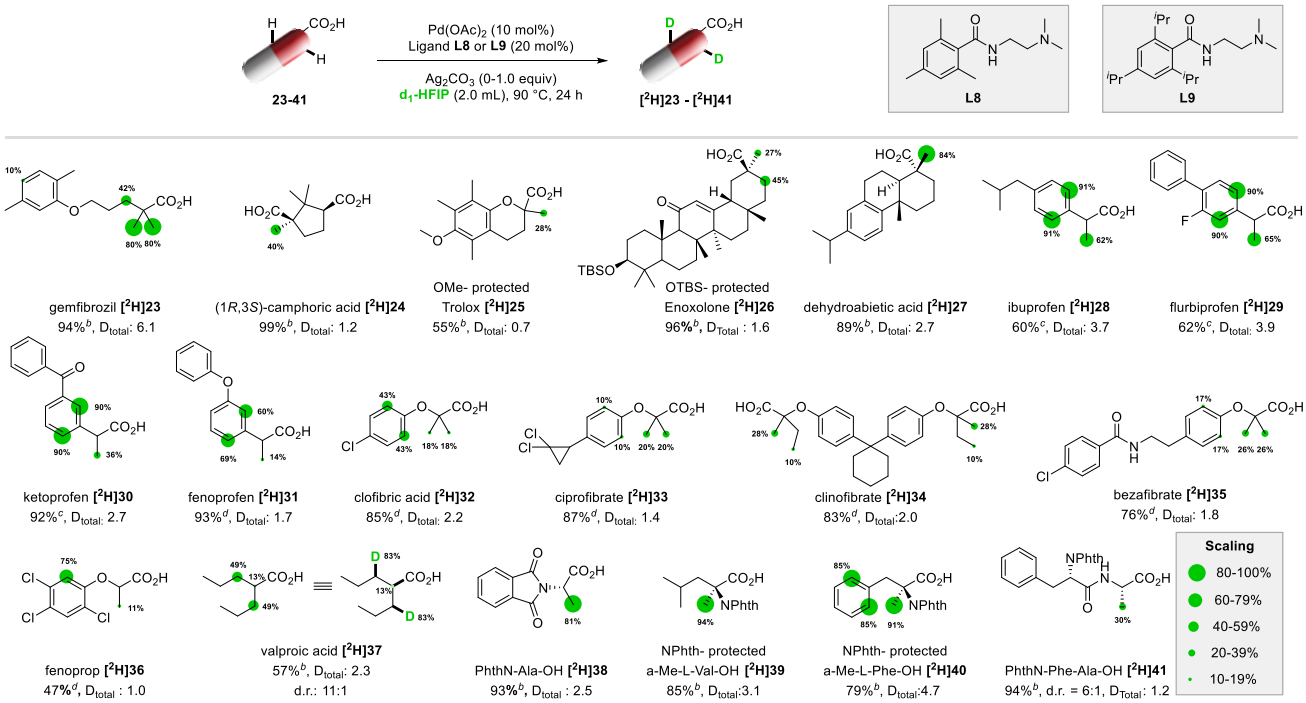
Phenylacetic acid (**18**) underwent the isotope exchange with high levels of deuterium incorporation in the ortho positions alongside an undirected deuteration as well as deuteration of the relatively acidic α-position of the carboxylic acid.[16c] The model substrate 2-methylhexanoid acid (**4**) used for the de-deuteration reaction showed, that the deuteration of the protons in the β-methylene position occurs diastereoselectively, with the preferential product resulting from the reaction proceeding via the sterically less encumbered palladacycle (d.r. = 3:1). A very similar trend was observed for 1-methyl-1-cyclohexanecarboxylic acid (**19**), where only the geometrically easily accessible β-methylene protons underwent H/D exchange. Encouraged by the high activity of our system towards β-methylene positions, we used 2,2-dipropylpentanoic acid (**20**) to achieve deuteration exclusively in such positions. Even for the completely unbiased hexanoic acid (**21**) high levels of deuterium incorporation were observed. Finally, we used the isononanoic acid **22** to investigate the reactivity towards γ-C(sp^3)–H positions and could achieve a proof of principle for this type of reactivity, albeit with a moderate deuterium incorporation.

SCHEME 1. Scope of Carboxylic Acids with Various Functional Groups and Structural Variations.[a]



[a] Positions with less than 10% D incorporation are not explicitly depicted but are reflected in the D_{Total} value (For experimental details: see SI). [b] isolated as the corresponding ester. [c] no Ag_2CO_3.

SCHEME 2. Scope of Bioactive Compounds.[a]



[a] Positions with less than 10% D incorporation are not explicitly depicted but are reflected in the D_{Total} value (For experimental details: see SI). [b] Conditions: Ligand **L9,** Ag_2CO_3 (0.25 equiv). [c] Conditions: Ligand **L8,** Ag_2CO_3 (1.0 equiv) [d] Conditions: Ligand **L9**, no Ag_2CO_3.

Having investigated the general reactivity of our catalytic system we applied our method to the late-stage deuteration of bioactive molecules and related frameworks, for which an alternative *de novo* synthesis of a deuterated analog would be highly challenging (Scheme 2). Using gemfibrozil (**23**), an oral lipid lowering agent, we obtained the deuterated compound **[^{2}H]23** in good yield and deuteration efficiency. For (+)-camphoric acid (**24**) we observed deuteration exclusively in the most proximate methyl group. The ether derivative of Trolox (**25**), a water-soluble vitamin E derivative, could be employed and showed good regioselectivity. The pentacyclic triterpenoid enoxolone, with a variety of interesting biological properties, could be deuterated in its OTBS-protected form **26**. Interestingly, we observed the deuteration exclusively in the methyl and only in the less hindered methylene position. Dehydroabietic acid (**27**), a diterpenoid obtained from tree resins, was selectively deuterated at the β-methyl position.

Next, we became interested in the deuteration of nonsteroidal anti-inflammatory drugs. Ibuprofen **28** could be deuterated under slightly modified conditions using the less active ligand **L8** in combination with an increased silver loading. Notably, by applying mild conditions we could deuterate the ibuprofen analogues flurbiprofen (**29**), ketoprofen (**30**), and fenoprofen (**31**) with moderate to high degrees of deuterium incorporation (D_{total} up to 3.9). Clofibric acid (**32**), ciprofibrate (**33**), clinofibrate (**34**) and bezafibrate (**35**) were chosen as representatives for the fibrate class and showed moderate but useful deuterium incorporation (D_{total} = 1.4 – 2.2). The phenoxy-type herbicide fenoprop (**36**) could also be deuterated. Valproic acid (**37**), a drug used against epilepsy, was employed and the β-methylene all-*cis* deuterated compound **[^{2}H]37** was obtained as the major diastereoisomer.

Finally, we concluded our investigation using amino acids. Starting from (*S*)-*N*-phthaloyl-protected alanine (**38**) we observed a high degree of β-methyl deuteration, without substantial loss of stereochemical information. α-Methylated amino acids, which show interesting pharmacological properties[26] can be used in our deuteration reaction, as showcased by the valine- and phenylalanine-derivatives **39**–**40**. Finally using a simple dipeptide as model compound **41**, it could selectively be deuterated at the C-terminus (the d.r. of 6:1 remained unaffected during the course of the reaction)

In summary, we have achieved the first regioselective late-stage C(sp^3)–H deuteration of free carboxylic acids using d_1-HFIP as a source of deuterium. The reaction was developed using a screening approach in which we first optimized the reverse reaction, a strategy that we expect will prove useful for the development of other challenging transformations. Importantly, we designed a novel ligand class based on an ethylenediamine backbone that enables unprecedented β-methylene C(sp^3)–H activations of unbiased carboxylic acids. The late-stage deuteration method developed in this study enables the isotope labelling of diverse bioactive molecule frameworks and is thus expected to prove valuable in medicinal chemistry and organic synthesis.

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, and analytical data for the compounds are described

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Author Contributions

All authors have given approval to the final version of the manuscript.

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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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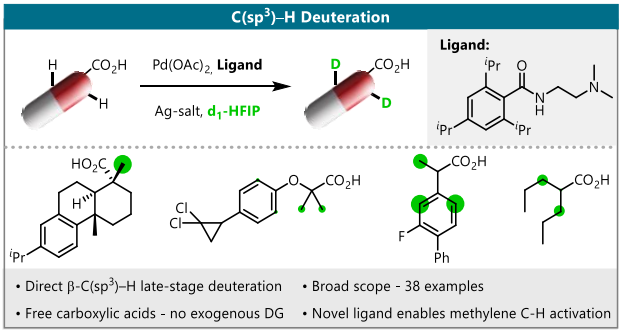

SYNOPSIS TOC. We report the late-stage β-C(sp^3)–H deuteration of free carboxylic acids. Using a novel ligand and d_1-HFIP as solvent, the deuterium labelling of bioactive carboxylic acids via C–H activation was achieved. We expect that our method will prove useful in drug development processes and further applications by avoiding cumbersome de novo synthesis of isotopically labelled molecules.