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ARTICLE

Regioselective Ruthenium catalysed H-D exchange using D_2O as the deuterium source

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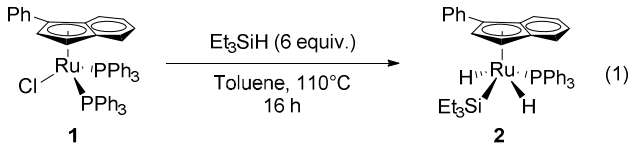
An efficient and convenient ruthenium catalysed method for a regiospecific H/D exchange using D_2O is described. Organic moieties such as pyridine, oxazole, imidazole, pyrazole, ester, ketone and carboxylic acid have been found effective directing groups in this transformation. In addition, the deuteration of the enantiopure (*S*)-Ketoprofen leads to the incorporation of three deuterium atoms with retention of molecular chirality.

Introduction

Isotopically labelled molecules are extremely valuable compounds used in a wide range of applications. These facilitate the study of drug metabolism and biological macromolecules through monitoring of biochemical processes,[1-3] and are useful probes enabling mechanistic and kinetic studies. To these ends, deuterium has been targeted as the alternative, to the more expensive and less abundant known isotopes (^3H, ^{13}C, ^{14}C, ^{18}O and ^{19}F). Hydrogen isotope exchange provides the most straightforward and direct procedure toward the synthesis of labelled molecules.[4] The versatility of deuterium-labelling molecules has attracted the attention in various fields, from protein crystallography,[5] NMR,[6-8] MS,[9] medical imaging[10] to the elucidation of either organic[11] or bioorganic[12,13] reaction mechanisms.[14] Moreover, very recently, deuterated molecules are being studied as possible new drug candidates, incorporating deuterium atoms in the active ingredient.[15] Owing to the usual requirement of multistep synthesis with consequent low yields, as well as the use of costly procedures and isolation problems of deuterating methodologies,[5,16–18] metal-catalysed H/D exchange systems have been developed that operate by activation of a C-H bond using metal-based catalysts (Rh, Ir, Pd and Pt). The main limitations in these practices are low selectivity,[3,19–23] the use of relatively high catalyst loadings,[24,25] the presence of additives,[25,26] as well as the use of deuterium gas[2,27,28] or more expensive deuterating agents.[22-25] Ruthenium has also been found to be active in deuteration processes through C-H bond activation, in the presence of various deuterating agents. Peris has described[29] an arene *ortho* deuteration procedure using a NHC-ruthenium complex, which was only active in the presence of MeOD-d_4. Deuterium oxide (D_2O) is the most attractive isotopic source for the preparation of deuterated substrates due to its combined low cost and low toxicity. However, general procedures for the incorporation of deuterium into the C-H bonds of organic compounds that utilise D_2O are limited and remain undeveloped. A few examples of ruthenium-catalysed deuteration systems have been reported using D_2O as the isotope source with substrates such as alcohols and heterocycles, but these reports are marked by non-selective deuterium incorporation.[13,10,30-32]

With this in mind, we envisioned that the development of a regioselective ruthenium-catalysed deuteration system using D_2O would permit access to practical, easy to handle, and highly cost effective labelling processes. We initially evaluated deuteration reactions using $[RuH_2(SiEt_3)(PPh_3)(3\text{-phenylindenyl})]$ (**2**) that has shown important reactivity in arene borylation[33] through a C-H activation process. Catalyst **2** is easily synthesized in good yield by adding triethylsilane to a commercially available ruthenium complex (Scheme 1). Arylpyridines were selected as model substrates as they are commonly encountered motif in the pharmaceutical industry.[34]

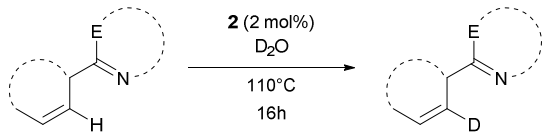


Scheme 1. Synthesis of **2.**

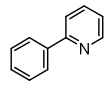
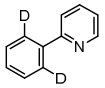
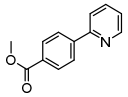
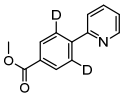
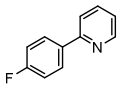
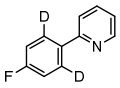
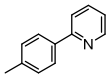
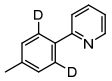
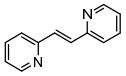
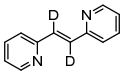
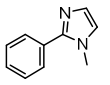
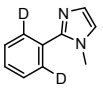
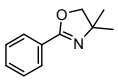
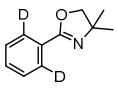
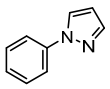
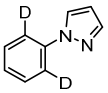
Results and discussion

Complex **2** was found to be highly efficient and selective in the dideuteration of phenylpyridine (**3a**) in the *ortho* positions of the phenyl moiety after 8 h at 110°C, under the optimised conditions (see ESI) in D_2O without use of any additives. In order to evaluate the steric and electronic effects on this transformation, various substituted pyridyl and congeners were tested (Table 1). The system was found to be quite tolerant toward the presence of either electron-donating (Me) or electron-withdrawing groups (F and CO_2Me) in the *para* position of the 2-phenylpyridine, giving excellent conversions to the desired dideuterated products (Table 1, entries 2-4).

Table 1. Scope of the deuteration using *N*-containing directing groups.[a]



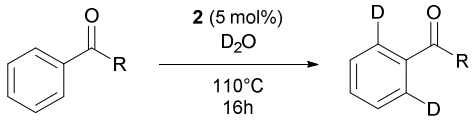
3 E=O,N **4**

Entry	Substrate		Product		Conversion (%)[b]
1		**3a**		**4a**	>95[c]
2		**3b**		**4b**	90
3		**3c**		**4c**	>95[c]
4		**3d**		**4d**	92
5		**3e**		**4e**	94[d]
6		**3f**		**4f**	>95[c]
7		**3g**		**4g**	50[d,e]
8		**3h**		**4h**	>95[d]
9		**3i**		**4i**	>95

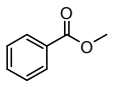
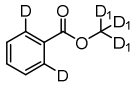
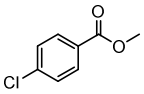
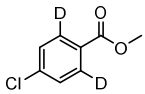
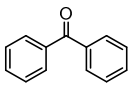
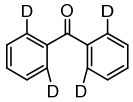
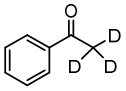
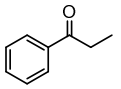
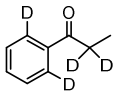
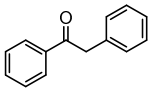
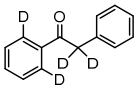
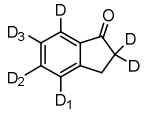
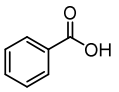
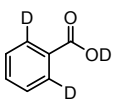
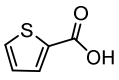
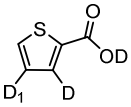
[a] Reaction conditions: **2** (2 mol%), **3** (0.25 mmol) and D_2O (0.5 mL). [b] Conversion determined by ^{1}H-NMR. [c] 8h. [d] **2** (5 mol%). [e] Solvent is toluene: D_2O mixture (1:1).

Interestingly, the presence of an ester group does not affect the selectivity of the transformation, and only deuteration in the *ortho* positions of the pyridine moiety was observed (Table 1, entry 2). A pyridyl group proved to effectively direct the deuteration of an olefinic C-H bond, yielding the deuterated vinyl product (**3e**) (93%) in the presence of a higher catalyst loading (5 mol%) (Table 1, entry 5). The deuteration of benzo[*h*]quinoline (**3f**) proceeded with full conversion (Table 1, entry 6). In order to test this reaction on a broader range of nitrogen-based directing groups, various heterocycles were tested. 4,4-Dimethyl-2-phenyl-2-oxazoline (**3h**) and *N*-phenyl pyrazole (**3i**) achieved selective deuteration in the *ortho* positions with full conversions (Table 1, entries 8 and 9). Deuteration of methylimidazole (**3g**) proved more challenging and only 50% of the labelled product was obtained (Table 1, entry 7). Encouraged by the generality found for the *ortho* selective deuteration protocol using *N*-based directing groups, we further increased the level of versatility of the method by studying oxygen-containing directing groups (Table 2). Surprisingly, and to our delight, complex **2** can successfully catalyse deuteration reactions using several *O*-containing functional groups such as esters, ketones, and carboxylic acids (Table 2). These moieties are often present in biological environments and drug molecules, thus expanding the potential use of this system.

Table 2. Scope of the deuteration using *O*-containing directing groups.[a]



3 **4**

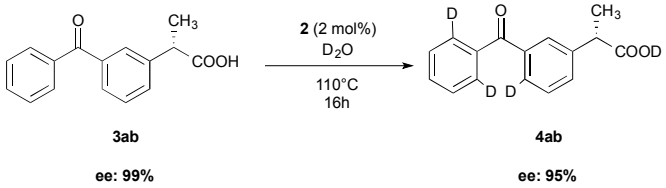
Entry	Substrate		Product		Conversion (%)[b]
1		**3j**		**4j**	70 D_1:22[c]
2		**3k**		**4k**	80
3		**3l**		**4l**	60
4		**3m**		**4m**	0
5		**3n**		**4n**	15
6		**3o**		**4o**	>95
7		**3p**		**4p**	25 D_1: 10 D_2: 15 D_3: 20
8		**3q**		**4q**	>95
9		**3r**		**4r**	>95 D_1:60

[a] Reaction conditions: **2** (5 mol%), **3** (0.25 mmol) and D_2O (0.5 mL). [b] Arene deuteration determined by ^{1}H-NMR. [c] Solvent is a mixture of toluene and D_2O (1:1).

Good conversions to the desired deuterated compounds were obtained with methylbenzoate (**3j**) and methyl 4-chlorobenzoate (**3k**) (Table 2, entries 1 and 2). *Para, meta* or *ortho* substituted methyl

bromobenzoate did not react, and in all cases the starting material was recovered (see ESI). This is probably due to steric hindrance, which can interfere with the formation of the ruthenacycle during the the catalytic reaction. Benzophenone (**3l**) was also tested, resulting in moderate deuteration in the *ortho* positions of both arenes, probably due again to steric hindrance (Table 2, entry 3). Due to the expected tautomerization to the corresponding enolates, acetophenone (**3m**), propiophenone (**3n**) and 1-indanone (**3p**) led to complete deuteration in the α positions of the carbonyl groups (Table 2, entries 4-7). In the case of 2-phenylacetophenone (**3o**), arene *ortho* deuteration was also observed with full conversion (Table 2, entry 7). However, 1-indanone (**3p**), which was tested in order to understand how the strain of the metallacycle could affect the reaction, led to moderate deuteration at all phenyl ring positions (Table 2, entry 6). Unfortunately benzaldehyde did not react and the starting material was recovered unchanged (see ESI). A *S*-containing molecule was also tried: surprisingly, dibenzyl disulfide was partially deuterated (25%) at the CH_2 positions instead of the expected aromatic positions, without the cleavage of the weak S-S bond, showing an unpredicted sp^3 C-H activation (see ESI). Next, more challenging carboxylic acid containing substrates were investigated. To our delight, both *ortho* positions of benzoic acid (**3q**) and β positions of 2-thiophenecarboxylic (**3r**) were fully labelled (Table 2, entries 8 and 9), highlighting the robustness of the catalyst. This system is the first ruthenium-catalysed procedure for *ortho* deuteration with D_2O of arene using carboxylic acids as directing groups. The protocol also avoids additional protection-deprotection steps in the labelling process. Only a handful of catalytic systems have been found active in C-H/C-D exchanges using carboxylic acids as directing groups, although high loadings of expensive metal catalysts (Pd, Rh and Ir) are required in order to efficiently obtain the desired labelled products.[25,35,36]

Finally, in order to exemplify the use of this catalytic system, the pharmaceutical blockbuster molecule Ketoprofen (an anti-inflammatory drug) was subjected to the deuteration conditions. Satisfyingly, we observed complete and selective deuteration of the positions showed in Scheme 2 at 2 mol% catalyst loading (see ESI for further information). This is a more highly deuterated product compared with the commercially available analytical standard tri-deuterated molecule previously reported.[37] Pleasingly, when the enantiomerically pure (*S*)-Ketoprofen was used, only a slight erosion of the enantiomeric excess was observed (from 99% to 95%), when 2 mol % of **2** is used, leading to the desired enantioenriched labelled Ketoprofen (Scheme 2). This compound, to the best of our knowledge, cannot be prepared using conventional methodologies.



Scheme 2. Labelling of (*S*)-Ketoprofen

Conclusions

In conclusion, a new application of the recently reported dihydridosilyl ruthenium catalyst **2** has been developed in the field of hydrogen isotope exchange. This ruthenium catalysed deuteration procedure functions without the use of any additive, and uses D_2O as the co-solvent and deuterium source, A very wide range of substrates featuring *N*- and *O*-containing directing groups, including carboxylic acids, are well tolerated in the deuteration reaction. The complete and regioselective labelling of a drug, Ketoprofen, was achieved without any protection/deprotection steps and providing the first example of metal catalysed deuteration with retention of chirality. The broad generality of the method examined with deuterated water should also, in principal, be applicable to tritium and **2** may become a very useful catalyst in the area of molecule radiolabelling.

Experimental section

Material and instrumentation

Complex **2** was synthesized according to the reported procedure.[33] 2-Phenyl-pyridine, 2-(4-methylphenyl)pyridine, 4,4-dimethyl-2-phenyl-2-oxazoline, 2-(1-methylimidazole)-pyridine, 1-phenylpyrazole, methylbenzoate, methyl 4-chloro-benzoate, 1,2-bis(2-pyridyl)ethylene, 7,8-benzoquinoline, ketoprofen, acetophenone, propiophenone, 2-phenylacetophenone, diphenylketone, benzoic acid, 2-thiophenecarboxylic acid, 1-indanone, dibenzyl disulfide, 4-bromomethylbenzoate, 3-bromomethylbenzoate, 2-bromomethylbenzoate, 3,5-dihydroxymethylbenzoate, 2-vinylpyridine, 8-methylquinoline, ketoprofen and (S)-ketoprofen were purchased from Sigma Aldrich and used as received. D_2O and toluene were purchased from Sigma and were degased prior to use. 2-(4-Fluorophenyl)pyridine and 2-(4-carboxyphenyl)pyridine were synthetized as reported.[38] 2-[4,5-Dihydro-1,3-oxazol-2-yl]pyridine was synthetized as reported.[39] ^1H, ^2H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance 400 or Bruker Avance III 500 Ultrashield NMR spectrometers. Chemical shifts are reported in δ ppm. Mass spectrometry was performed by the EPSRC National Mass Spectrometry Service Centre at Swansea University, Grove building, Singleton Park, Swansea, SA2 8PP, Wales, UK.

General procedure and characterisation

Inside the glovebox, **2** (0.005 or 0.0125 mmol) and the substrate (**3**) (0.25mmol) were placed in a vial fitted with a screw cap. Outside the glovebox, degassed D_2O (0.5 mL) or a mixture of degassed D_2O and toluene (1:1; 0.5 mL) was added. Then, the mixture was stirred at 110ºC for 16h. The reaction was allowed to cool to room temperature; when CH_2Cl_2 was added and a liquid-liquid extraction was performed and the organic phase was passed dried over $MgSO_4$. The solvent was removed and the crude was analysed by NMR spectroscopy.

2-(2,6-Dideuterophenyl)pyridine (4a).
Conversion: >95%. ^1H NMR (500 MHz, $CDCl_3$): 8.70 (d, J = 7.4 Hz, 1H), 7.74 (d, J = 24.4 Hz, 2H), 7.48 (d, J = 7.4 Hz, 2H), 7.42 (d, J = 14.6 Hz, 1H), 7.22 (d, J = 13.3 Hz, 1H). NMR data are consistent with previously reported data.[29]

2-(4-Carboxy-2,6-dideuterophenyl)pyridine (4b).
Conversion: 90%. ^1H NMR (500 MHz, $CDCl_3$): δ 8.73 (d, J = 5.7 Hz, 1H), 8.15 (s, 2H), 7.79 (s, 2H), 7.32 - 7.26 (m, 1H), 3.95 (s, 3H). HRMS (EI+): m/z calcd for $C_{13}H_{10}D_2N_1O_2$: 216.0988, found 216.0985.

2-(2,6-Dideutero-4-fluoro-phenyl)pyridine (4c).
Conversion: >95%. ^1H NMR (500 MHz, $CDCl_3$): δ 8.66 (d, J = 4.7 Hz, 1H), 7.72 (td, J = 7.7, 1.7 Hz, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.21 (dd, J = 7.2, 4.9 Hz, 1H), 7.14 (d, J = 8.6 Hz, 2H). HRMS (EI+): m/z calcd for $C_{11}H_7D_2F_1N_1$: 176.0839, found 176.0834.

2-(4-Methyl-2,6-dideuterophenyl)pyridine (4d).

Conversion: 92.5%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68-8.67 (m, 1H), 7.73-7.69 (m, 2H), 7.29 (s, 2H), 7.20-7.18 (ddd, *J* = 6.6, 4.8, 1.7 Hz 1H), 2.41 (s, 3H). HRMS (EI+): m/z calcd for $C_{12}H_{10}D_2N_1$: 172.1090; found 172.1085.

1,2-Dideutero-1,2-bis(2-pyridyl)ethylene (4e).

Compound **4e** was obtained using 5% of **2** in a mixture of D_2O/toluene (1:1). Conversion: 93.5%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62 (d, *J* = 5.4 Hz, 2H), 7.68 – 7.64 (m, 2H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.17 (ddd, *J* = 7.5, 4.8, 0.9 Hz, 2H). NMR data are consistent with previously reported data.[40]

7,8-(4-Deutero)-benzoquinoline (4f).

Conversion: >95%. ^{1}H NMR (500 MHz, CDCl3): δ 9.01 (dd, *J* = 4.4, 1.7 Hz, 1H), 8.15 (dt, *J* = 8.1, 1.4 Hz, 1H), 7.91 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.76 (d, *J* = 6.8 Hz, 1H), 7.72 – 7.64 (m, 2H), 7.52 – 7.49 (m, 1H). NMR data are consistent with previously reported data.[29]

(5)-Methyl-2-(2,6-dideuterophenyl)-imidazole (4g).

Compound **4g** was obtained using 5% of **2**. Conversion: 50%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61-7.59 (m, 1H), 7.44-7.36 (m, 3H), 7.06 (s, 1H), 6.93 (s, 1H), 3.70 (s, 3H). HRMS (EI+): m/z calcd for $C_{10}H_9D_2N_2$: 161.1042; found 161.1037.

4,4-Dimethyl-4,5-dihydro-2-(2,6-dideuterophenyl) oxazole (4h).

Compound **4h** was obtained using 5% of **2**. Conversion: >95%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 – 7.40 (m, 3H), 4.12 (s, 2H), 1.40 (s, 6H). HRMS (EI+): m/z calcd for $C_{11}H_{12}D_2N_1O_1$: 178.1195; found 178.1192.

1-(2,6-Dideuterophenyl)-1H-pyrazole (4i).

Conversion: >95%. ^{1}H NMR (500 MHz, CDCl3): δ 7.92 (d, *J* = 2.4 Hz, 1H), 7.73 (d, *J* = 1.9 Hz, 1H), 7.45 (d, *J* = 7.4 Hz, 2H), 7.28 (d, *J* = 14.9 Hz, 1H), 6.46 (t, *J* = 2.1 Hz, 1H). NMR data are consistent with previously reported data.[29]

Methyl 2,6-dideuterobenzoate (4j).

Compound **4j** was obtained using 5% of **2** in a mixture of D_2O/toluene (1:1). Conversion: 70%. Partial deuterium incorporation in OCH_3: 22%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07-8.05 (m, 2H), 7.59-7.56 (m, 1H) 7.47-7.45 (m, 2H). NMR data are consistent with previously reported data.[35]

Methyl 4-chloro-2,6-dideuterobenzoate (4k).

Compound **4k** was obtained using 5% of **2** in a mixture of D_2O/toluene (1:1). Conversion: 85%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (s, 2H), 3.93 (s, 3H). HRMS (EI+): m/z calcd for $C_8H_6D_2C_{l1}O_2$: 175.0303; found 175.0302.

2,2',6,6'-Tetradeuteriobenzophenone (4l).

Compound **4l** was obtained using 5% of **2**. Conversion: 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82-7.80 (d, *J* = 7.83, 2H), 7.61-7.59 (m, 2H) 7.50-7.48 (m, 4H). NMR data are consistent with previously reported.[36]

α,α,α-Trideuteromethyl phenyl ketone (4m).

Compound **4m** was obtained using 5% of **2**. Conversion: 0%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97-7.95 (m, 2H), 7.58-7.54 (m, 1H), 7-48-7.44 (m, 2H). NMR data are consistent with previously reported.[41]

α,α-Dideuteroethyl phenyl ketone (4n).

Compound **4n** was obtained using 5% of **2**. Conversion: 15%. 1H NMR (400 MHz, $CDCl_3$): δ 7.97-7.95 (m, 2H), 7.57-7.53 (m, 1H), 7.47-7.44 (m, 2H), 1.23-1.21 (m, 3H). 15% deuterium incorporation at δ 7.87-7.95. NMR data are consistent with previously reported.[42]

2,2-Dideuterio-1,2-diphenyl-ethanone (4o).

Compound **4o** was obtained using 5% of **2**. Conversion: >95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.58 (m, 1H), 7.50-7.48 (m, 2H), 7.38-7.35 (m, 2H), 7.32-7.28 (m, 3H). NMR data are consistent with previously reported.[41]

2,2-Dideuterio-1-indanone (4p).

Compound **4p** was obtained using 5% of **2**. Conversion: >95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.6 Hz, 1H) partial deuteration 25%, 7.60 (t, *J* = 7.4 Hz, 1H) partial deuteration 20%, 7.49 (d, *J* = 7.7 Hz, 1H) partial deuteration 15%, 7.38 (t, *J* = 5.7 Hz, 1H) partial deuteration 10%, 3.14 (s, 2H). NMR data are consistent with previously reported.[43]

2,6-Dideuteriobenzoic acid (4q).

Compound **4q** was obtained using 5% of **2**. Conversion: >95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ7.61-7.59 (m, 1H), 7.48-7.47 (d, *J* = 7.5 Hz, 2H). NMR data are consistent with previously reported.[47]

3-Deuteriothiophene-2-carboxylic acid (4r).

Compound **4r** was obtained using 5% of **2**. Conversion: >95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 5.0 Hz, 1H) partial deuteration 60%, 7.13 (d, *J* = 3.3 Hz, 1H). NMR data are consistent with previously reported.[44]

Bis(1-deuteriobenzyl) disulphide (4z).

Compound **4z** was obtained using 5% of **2**. Conversion: 25%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.27 (m, 10H) 3.64-3.62 (m, 3H). NMR data are consistent with previously reported.[45]

2-(4-Deutero-3-benzoyl-2,6-dideuterophenyl)propionic acid (d3-Ketoprofen)) (4aa).

Compound **4aa** was obtained using 2% of **2**. Conversion: >95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 1.7 Hz, 1H), 7.63 – 7.57 (m, 2H), 7.47 (dd, *J* = 14.0, 7.6 Hz, 3H), 3.80 (q, *J* = 7.2 Hz, 1H), 1.47 (d, *J* = 7.2 Hz, 3H). HRMS (EI+): m/z calcd for $C_{16}H_{12}D_3O_3$: 258.1204, found 258.1189.

(S)-2-(4-Deutero-3-benzoyl-2,6-dideuterophenyl)propionic acid ((S)-d3-Ketoprofen)) (4ab).

Compound **4ab** was obtained using 2% of **2**. Conversion: >95%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 1.9 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.46 (dd, *J* = 13.3, 7.6 Hz, 3H), 3.83 (q, *J* = 7.2 Hz, 1H), 1.57 (d, *J* = 7.2 Hz, 3H). HRMS (EI+): m/z calcd for $C_{16}H_{12}D_3O_3$: 258.1204, found 258.1199.

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