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Palladium-catalyzed site-selective hydrogen isotope exchange (HIE) reaction of arylsulfonamides using amino acid auxiliary

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ABSTRACT

Hydrogen isotope exchange (HIE) is a versatile method for the introduction of deuterium to organic compounds. Herein, regioselective deuteration of sulfonamides is achieved by palladium-Catalyzed HIE reaction. By using amino acid as weakly coordination-directing auxiliary, a variety of sulfonamides are efficiently deuterated at the *ortho*-position. Placing competing directing groups on the aromatic ring does not affect the site-selectivity.

1. Introduction

Deuterium-labeled compounds find widespread application in a range of different scientific fields, such as reaction mechanisms, analytical methods as internal standards, optoelectronics, clinical pharmacology, and drug discovery.[1,2] In particular, Deuterium-labeled compounds have attracted growing interests in pharmaceutical industry because the incorporation of deuterium can change ADME properties of the existing drugs, while retaining their original efficiency and selectivity.[3,4] The first deuterated drug (deutetrabenazine, SD-809), has been approved by FDA in 2017.[5] Usually, isotopically labeled organic compounds can be achieved by multistep syntheses involving functional-group transformation with deuterium reagents. However, the most versatile way to introduce deuterium atoms into organic molecules is through hydrogen-isotope exchange (HIE) reaction, which allows direct incorporation of deuterium and circumvents the need for additional synthetic steps.[1] Recent years, transition metal-catalyzed aromatic HIE reactions have been well established. For example, Homogeneous iridium catalysts have been widely used for selective deuteration *ortho* to directing groups on aromatic rings.[6] More recently, other transition metals, such as Ru,[7] Pd[8] and Fe[9] catalysts, were also employed in aromatic HIE reactions. These catalytic systems were also applicable for tritium labeling, but depending on hydrogen isotope resources. Ir,[6] Fe,[9] and part of Ru catalytic systems,[7a,b] which involve D_2 as hydrogen isotope resource, were perfectly adapted to tritium labeling by using T_2 gas. On the other hand, Pd catalytic systems, which usually using deuterated solvents as hydrogen isotope resources, were still not applicable for catalytic tritation. However, Hoover and coworkers[8e] have successfully achieved Pd mediated C-H tritation in stepwise stoichiometric reaction.

Sulfonamide functional groups have long been acclaimed as an important structural fragment widely existing in drug molecules for the characters of a series of sulfonamide-containing drugs, such as sulfamethoxazole, sumatriptan, and gliclazide.[10] Despite the importance of sulfonamide in pharmaceutical industry, *ortho*-directed deuterium labeling of sulfonamides was rarely explored. Several iridium complexes were reported to catalyzed the HIE reaction of sulfonamides.[11–13] Among them, Kerr's NHC catalyst,[12] Burgess catalyst[13] and Tamm catalyst[14] were reported to catalyze reaction with high deuterium incorporation. However, these protocols still have some limitations. For example, when substrate containing competitive directing groups, such as amino and carbonyl groups, low site-selectivity and decreased deuterium incorporation were observed. Another limitation for further utilization was that Ir catalysts were too expensive. Herein, we report $Pd(OAc)_2$ catalyzed selective *ortho*-deuteration of sulfonamides by using amino acid as weakly coordination-directing auxiliary (Scheme 1). The reaction results in efficient deuterium incorporation as well as excellent site-selectivity.

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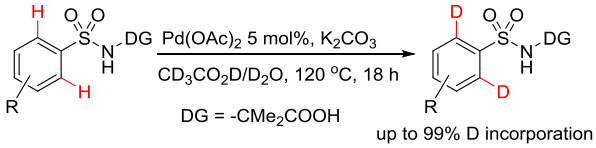


Scheme 1. $Pd(OAc)_2$ catalyzed ortho-deuteration of sulfonamides.

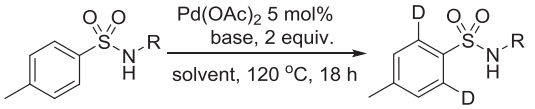
2. Results and discussion

We initiated our studies towards a palladium-catalyzed HIE reaction of sulfonamide by treatment of 4-methylbenzenesulfonamide **1a** in CH_3COOH in the presence of $Pd(OAc)_2$ as catalyst and NaOAc as base. However, no deuterium incorporation was observed when heating of the reaction mixture at 120 °C for 18 h (Table 1, entry 1). By using amino acid as weakly coordination-directing auxiliary,[8a,15] *ortho*-deuteration reaction of sulfonamide derivative **2a** occurred and 45% of D-incorporation was achieved (Table 1, entry 2). Different deuterium-containing solvents (D_2O, CF_3COOD, and CD_3OD) were also tested, but lower D-incorporation were observed in these reactions (Table 1, entries 3–5). Then different bases were investigated, and K_2CO_3 gave the best result (Table 1, entries 2, 6–8). The fact that carbonate bases are prior to acetate bases indicated that small amount of water (generated by reaction of carbonate with acetic acid) may promote the HIE reaction through formation of hydrogen bonds with reaction intermediate. When 3 Å molecular sieve was added, the D-incorporation dropped significantly (Table 1, entry 9). When 0.1 mL of D_2O was added as co-solvent, D-incorporation was increased to 84% (Table 1, entry 10). The D-incorporation was raised to 87% when CD_3COOD was used instead of CH_3COOD (Table 1, entry 11). Finally, when enhancing the steric hindrance of amino acid auxiliary, excellent D-incorporation (97%) was achieved (Table 1, entry 12).[16]

With optimized reaction conditions in hand, variety of sulfonamide derivatives **2** were examined, including both electron-deficient and electron-rich substrates (Scheme 2). Benzenesulfonamide and *para*-substituted benzenesulfonamide derivatives gave the desired di-deuterated products with 46–99% D-incorporation (**3b**-**3j**). In general, substrates with electron-donating groups gave the higher D-incorporation than substrates with electron-withdrawing groups. It is noteworthy that substrates with acetamido, acyl, pyrazolyl, methoxycarbonyl and carbamoyl groups, which usually serve as directing groups in transition metal-catalyzed C-H activation, only gave the *ortho*-deuterated sulfonamides with high site-selectivity (**3f**-**3j**). The selectivity was mainly due to preferring of chelating coordination of palladium with N^O auxiliary. The acetyl groups and pyrazolyl were partially deuterated during the reaction. When *meta*-substituted benzenesulfonamide derivatives were employed, the di-deuterated products were formed in 95–98% D-incorporation, in which C6 position has the slightly higher D-incorporation than C2 position (**3k**-**3l**). *ortho*-Substituted substrates gave mono-deuterated products in 84–97% D-incorporation (**3m**-**3o**). The steric effect has little influence on the deuteration reaction. The HIE reaction was also extended to other aromatic sulfonamides. When 1-naphthylsulfonamide **2p** was employed, the deuteration occurred at C2 and C8 position with 99% and 79% D-incorporation respectively. The result suggested that formation of five-membered palladacycle was preferred over six-membered palladacycle. When 2-naphthylsulfonamide **2q** was employed, the deuteration occurred at C1 and C3 position with 85% and 96% D-incorporation respectively. Deuteration of 2-thiophenesulfonamide gave the products **3r** in 33% and 27% D-incorporation. No reaction was occurred for 3-pyridinesulfamide **2s**. When benzylsulfonamide was employed, 70% of *ortho*-D-incorporation was achieved (**3t**). The Pd-catalyzed HIE reaction of alkylsulfonamide was unsuccessful and no deuterated product was observed with propylsulfonamide **2u**. The Pd-catalyzed *ortho*-deuteration reaction can be scaled up without significant decrease of yield and D-incorporation. For example, we checked 1 mmol reaction for **2b**, **2d**, **2e**, **2f**, **2k**, and **2n**, and the D-incorporation was consistence with that shown in Scheme 2.

The amino acid auxiliary of sulfonamide derivatives can be easily removed by CuO in DMSO to give the *ortho*-deuterated sulfonamides **4** in high yields (Scheme 3). In most cases, no

Table 1
Optimization of palladium-catalyzed ortho-deuteration of sulfonamides.[a]



R = H, **1a**
R = -CHMeCOOH, **2a**
R = -CMe_2COOH, **2b**

3

Entry	substrate	solvent	base	D[b] (%)	Yield[b] (%)
1	**1a**	CH_3COOD	NaOAc	0	0
2	**2a**	CH_3COOD	NaOAc	45	97
3	**2a**	D_2O	NaOAc	23	99
4	**2a**	CF_3COOD	NaOAc	15	95
5	**2a**	CD_3OD	NaOAc	13	99
6	**2a**	CH_3COOD	Na_2CO_3	58	92
7	**2a**	CH_3COOD	K_2CO_3	65	90
8	**2a**	CH_3COOD	KOAc	61	93
9[c]	**2a**	CH_3COOD	K_2CO_3	21	95
10	**2a**	CH_3COOD/D_2O[d]	K_2CO_3	84	93
11	**2a**	CD_3COOD/D_2O[d]	K_2CO_3	87	94
12	**2b**	CD_3COOD/D_2O[d]	K_2CO_3	97	96

[a]Reaction conditions: **1a** or **2** (0.2 mmol), base (0.4 mmol), $Pd(OAc)_2$ (0.01 mmol), deuterated solvent (0.6 mL), 120 °C, 18 h. The reactions were carried out in a 25 mL sealed tube.

[b]Deuterium incorporation and yields was determined by ^1H NMR spectroscopy analysis.

[c]3Å molecular sieve was added.

[d]0.1 mL of D_2O was added as co-solvent.

Entry	substrate	solvent	base	D[b] (%)	Yield[b] (%)
1	**1a**	CH_3COOD	NaOAc	0	0
2	**2a**	CH_3COOD	NaOAc	45	97
3	**2a**	D_2O	NaOAc	23	99
4	**2a**	CF_3COOD	NaOAc	15	95
5	**2a**	CD_3OD	NaOAc	13	99
6	**2a**	CH_3COOD	Na_2CO_3	58	92
7	**2a**	CH_3COOD	K_2CO_3	65	90
8	**2a**	CH_3COOD	KOAc	61	93
9[c]	**2a**	CH_3COOD	K_2CO_3	21	95
10	**2a**	CH_3COOD/D_2O[d]	K_2CO_3	84	93
11	**2a**	CD_3COOD/D_2O[d]	K_2CO_3	87	94
12	**2b**	CD_3COOD/D_2O[d]	K_2CO_3	97	96

[a] Reaction conditions: **1a** or **2** (0.2 mmol), base (0.4 mmol), $Pd(OAc)_2$ (0.01 mmol), deuterated solvent (0.6 mL), 120 °C, 18 h. The reactions were carried out in a 25 mL sealed tube.
[b] Deuterium incorporation and yields was determined by ^1H NMR spectroscopy analysis.
[c] 3 Å molecular sieve was added.
[d] 0.1 mL of D_2O was added as co-solvent.

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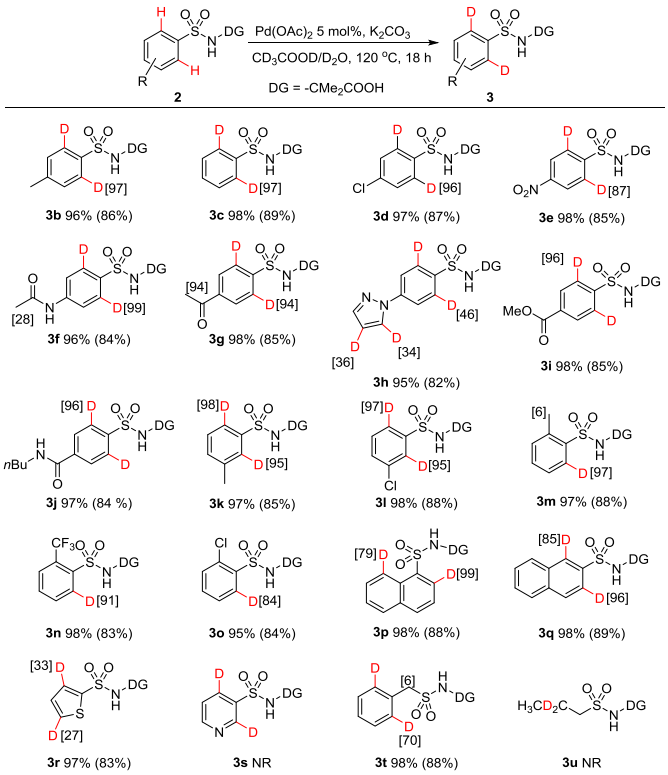
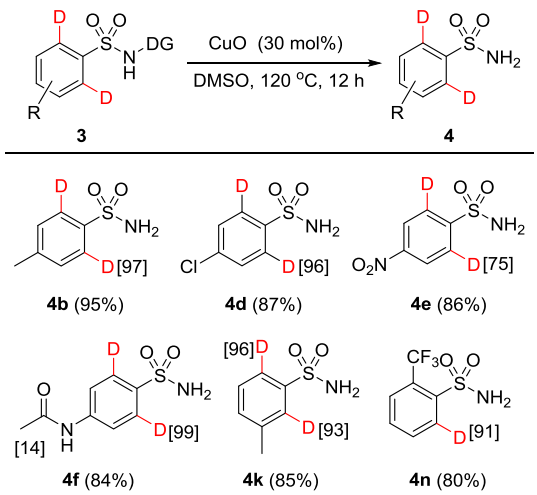


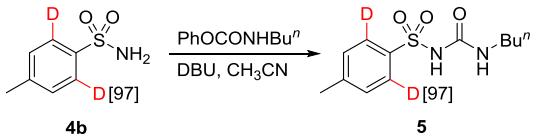
Scheme 2. Pd-catalyzed *ortho*-deuteration of sulfonamide derivatives **2**: **2** (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), and K_2CO_3 (0.4 mmol) in CD_3COOD/D_2O (0.6mL/0.1 mL) at 120 °C for 18 h. Deuterium incorporation was determined by ^1H NMR spectroscopic analysis and given in square brackets. Yields were given as NMR yields, isolated yields were given in parenthesis.

dedeuteration reaction was observed during the reaction. One exception was *para*-nitro-substituted sulfonamide **3e**, in which partial dedeuteration reaction was observed and D-incorporation of **4e** was decreased to 75%. The resulting sulfonamides can be further used for the synthesis of deuterium-labeled sulfa drugs. As an example, treatment of **4b** with phenyl butyl carbamate afforded deuterated tolbutamide **5** in 76% isolated yield (Scheme 4).[17]

Mechanistically, we proposed that the palladium catalyzed HIE



Scheme 3. Removal of auxiliary by CuO catalyst: **3** (0.5 mmol), CuO (0.15 mmol), DMSO (1 mL), 120 °C, 12 h. Deuterium incorporation was determined by ^1H NMR spectroscopic analysis and given in square brackets. Isolated yields were given in parenthesis.



Scheme 4. Synthesis of deuterated tolbutamide.

reaction of sulfamides was preceded via coordination of N^O auxiliary with palladium and subsequent dehydropalladation with the aid of acetate to form C^N^O chelated pallacycle. Depalladation by CD_3COOD afforded the deuterated product (Scheme 5). In a stoichiometric reaction, when sulfonamide **2b** was treated with 1 eq. of $Pd(OAc)_2$ and 2 eq. of K_2CO_3 in THF, intermediate **6** was formed in high yield and characterized by ^1H NMR and ^{13}C NMR. In the NMR spectra, we also observed the formation of *ca* 2 eq. of KOAc, which was consistence of proposed reaction mechanism (Scheme 5).

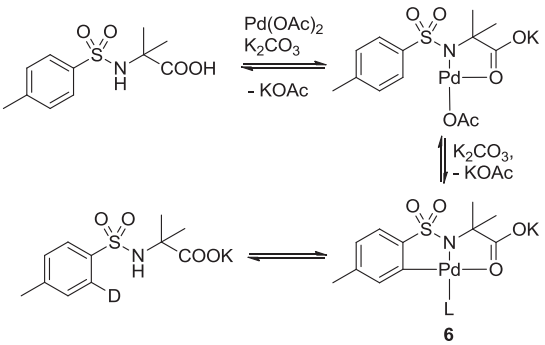
3. Conclusions

In summary, we have developed an efficient method for the site-selective hydrogen isotope exchange (HIE) of sulfonamides by using amino acid as weakly coordination-directing auxiliary. The reaction resulted in efficient deuterium incorporation as well as excellent *ortho*-selectivity with a wide range of functional groups. Placing competing directing groups on the aromatic ring did not affect the site-selectivity. The amino acid auxiliary could be easily removed to afford *ortho*-deuterated sulfonamides, which can be converted to deuterated sulfa drugs such as tolbutamide-d_2 in single step. We proposed one possible mechanism and isolated the reaction intermediate to support the mechanism. Further investigations are still in progress in this area.

4. Experimental section

4.1. General

All manipulations were conducted in sealed tube. ^1H NMR spectra were recorded on Bruker 400 MHz spectrometer and the chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm) for DMSO-d_6. The peak patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, *J*, are reported in Hertz (Hz). ^{13}C NMR spectra were obtained at Bruker 100 MHz and referenced to the internal solvent signals (central peak is 39.96 ppm in DMSO-d_6). Flash column chromatography was performed over silica gel 200–300 mesh. All chemical reagents and deuterated solvent were purchased from Alfa, Acros, Aldrich, TCI,



Scheme 5. Proposed reaction mechanism.

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and J&K and used without further purification. All bases used are anhydrous.

4.2. General procedure for synthesis sulfonamide derivatives

A 50 mL round-bottom flask equipped with a stir bar was charged with amino acid or its derivative (10 mmol) and NaOH aqueous solution (20 mmol, 2 M) and stirred vigorously at 0 °C. When solid was dissolved in water, arylsulfonyl chlorides (20 mmol) were added dropwise over 20 min, then the mixture was allowed to warm to room temperature for 12 h. The reaction mixture was acidified with concentrated HCl at 0 °C to pH 2. After stirring for further 30 min the precipitates were collected by filtration, washed with cold water and dried in vacuo to give the desired product **2a-2g** and **2k-2u** in good to excellent yields.

4.2.1. 2-(4-methyl-benzenesulfonylamino)-propionic acid (**2a**)

^{1}H NMR (400 MHz, DMSO) δ 8.07 (d, J = 8.3 Hz, 1H), 7.68 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 3.74 (quintet, J = 7.2 Hz, 1H), 2.38 (s, 3H), 1.13 (d, J = 7.2 Hz, 3H).

4.2.2. 2-(toluene-4-sulfonylamino)-2-methyl-propionic acid (**2b**)

^{1}H NMR (400 MHz, DMSO) δ 12.54 (s, 1H), 7.91 (s, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 2.37 (s, 3H), 1.25 (s, 6H).

4.2.3. 2-Benzenesulfonylamino-2-methyl-propionic acid (**2c**)

^{1}H NMR (400 MHz, DMSO) δ 12.56 (s, 1H), 8.01 (s, 1H), 7.81 (dd, J = 8.0, 1.3 Hz, 2H), 7.65–7.48 (m, 3H), 1.26 (s, 6H).

4.2.4. 2-(4-Chloro-benzenesulfonylamino)-2-methyl-propionic acid (**2d**)

White solide, m.p. 157.4–160.2 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.11 (s, 1H), 7.80 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H), 1.28 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 175.5, 142.9, 137.2, 129.5, 128.6, 58.4, 26.3. HRMS (ESI-TOF) m/z Calcd for $C_{10}H_{12}ClNO_4S$ $[M+Na]^+$ 300.0074, found 300.0066.

4.2.5. 2-(4-Nitro-benzenesulfonylamino)-2-methyl-propionic acid (**2e**)

^{1}H NMR (400 MHz, DMSO) δ 8.43 (s, 1H), 8.39 (d, J = 8.8 Hz, 2H), 8.04 (d, J = 8.8 Hz, 2H), 1.31 (s, 6H).

4.2.6. 2-(4-Acetamide-benzenesulfonylamino)-2-methyl-propionic acid (**2f**)

White solid, m.p. 105.2–106.5 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.51 (s, 1H), 10.29 (s, 1H), 7.84 (s, 1H), 7.72 (s, 4H), 2.09 (s, 3H), 1.25 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 175.8, 169.4, 142.8, 137.8, 127.8, 118.8, 58.1, 26.2, 24.6. HRMS (ESI-TOF) m/z Calcd for $C_{12}H_{16}N_2O_5S$ $[M+H]^+$ 301.0853, found 301.0842.

4.2.7. 2-(4-Acetyl-benzenesulfonylamino)-2-methyl-propionic acid (**2g**)

White solide, m.p. 161.4–163.5 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.22 (s, 1H), 8.11 (d, J = 8.2 Hz, 2H), 7.93 (d, J = 8.2 Hz, 2H), 2.64 (s, 3H), 1.28 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 197.8, 175.5, 147.8, 139.5, 129.2, 126.9, 58.4, 27.5, 26.3. HRMS (ESI-TOF) m/z Calcd for $C_{12}H_{15}NO_5S$ $[M+Na]^+$ 308.0569, found 308.0563.

4.2.8. Synthesis of 2-(4-(1H-pyrazol-1 yl)benzenesulfonylamino)-2-methyl-propionic acid (**2h**)

Ethyl 2-((4-bromophenyl)sulfonamido)-2-methyl-propionic acid. A 50 mL round-bottom flask equipped with a stir bar was charged with ethyl 2-amino-2-methylpropanoate[18] (1.96 g, 10 mmol) and K_2CO_3 aqueous [2.7 g, 10 mL (H_2O), 2 M] at 0 °C. When solid completely dissolved in water, 4-bromobenzenesulfonyl chloride (2.55 g, 1 mmol) was added dropwise over 30 min. Then the reactant was stirred at rt for 14 h, the precipitate obtained through filtered, washed with cold water. The rude product recrystallized with DCM and PE. The white solid (2.6 g, 74%, m.p. 95.6–97.5 °C) was obtained. ^{1}H NMR (400 MHz, DMSO) δ 8.29 (s, 1H), 7.80 (d, J = 8.7 Hz, 2H), 7.71 (d, J = 8.7 Hz, 2H), 3.94 (q, J = 7.1 Hz, 2H), 1.30 (s, 6H), 1.11 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 173.6, 143.1, 132.5, 128.7, 126.2, 61.1, 58.5, 26.3, 14.2. HRMS (ESI-TOF) m/z Calcd for $C_{12}H_{16}BrNO_4S$ $[M+Na]^+$ 371.9881, found 371.9874.

Ethyl 2-(4-(1H-pyrazol-1-yl*)benzenesulfonylamino)-2-methyl-propionic acid.* A mixture of ethyl 2-((4-bromophenyl)sulfonamido)-2-methyl-propionic acid (339 mg, 0.97 mmol), pyrazol (43.5 mg, 0.64 mmol), Cu_2O (9.2 mg, 0.064 mmol), Cs_2CO_3 (417 mg, 1.28 mmol) were mixed in a dry sealed tube. Under an argon atmosphere anhydroud DMF (1.5 mL) was added. The tube was sealed under argon, and the mixture was heated at 110 °C for 18 h. The reaction was cooled to room temperature. The crude reaction mixture was then concentrated in vacuo to remove DMF. Optional further purification was via silica gel column chromatography (4:1 petroleum ether/ethyl acetate). The white solid (179 mg, 83%, m.p. 124.5–125.9 °C) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 2.5 Hz, 1H), 7.98 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 1.5 Hz, 1H), 6.53 (t, J = 2.0 Hz, 1H), 5.63 (s, 1H), 4.15 (q, J = 7.1 Hz, 2H), 1.47 (s, 6H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 142.8, 142.2, 139.8, 128.7, 126.9, 118.7, 108.8, 62.0, 59.1, 25.7, 14.0. HRMS (ESI-TOF) m/z Calcd for $C_{15}H_{19}N_3O_4S$ $[M+H]^+$ 338.1169, found 338.1171.

A 50 mL round-bottom flask equipped with a stir bar was charged with *ethyl 2-(4-(1H-pyrazol*-1-yl*)benzenesulfonylamino)-2-methyl-propionic acid* (200 mg, 0.6 mmol) and 10% NaOH (5 mL) at room temperature for 12 h. When reaction was complete monitored by TLC, The reaction mixture was acidified with concentrated HCl at 0 °C to pH = 2; solid precipitated out and stirred for further 30min. The crystals were collected by filtration, washed with cold water and dried in vacuo to give the *title compound* **2h** (127 mg, 64%) as a white solid. ^{1}H NMR (400 MHz, DMSO) δ 8.63 (d, J = 2.5 Hz, 1H), 8.05 (s, 1H), 8.04 (d, J = 8.9 Hz, 2H), 7.90 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 1.4 Hz, 1H), 6.62 (t, J = 2.2 Hz, 1H), 1.30 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 175.5, 142.5, 142.3, 141.0, 128.8, 128.4, 118.6, 109.2, 58.3, 26.3. HRMS (ESI-TOF) m/z Calcd for $C_{13}H_{15}N_3O_4S$ $[M+Na]^+$ 332.0681, found 332.0669.

4.2.9. 2-(4-methoxalyl-benzenesulfonylamino)-2-methyl-propionic acid (**2i**)

The reactions were carried out in a one-neck round bottom flask. The corresponding 2-amino-2-methylpropanoic acid (0.88 g, 8.5 mmol) and triethylamine (3.4 g, 34 mmol) were added to a vigorously stirred mixture of water (5 mL) at 0 °C. When solid completely dissolved in water, 4-chlorosulfonyl benzoic acid methyl ester (1 g, 4.3 mmol) was added dropwise over 30 min. Then the reaction was stirred at rt for 12 h, the product was extracted with EtOAc (3 × 50 mL). Combined organic layers were dried over Na_2SO_4, concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH = 30/1) to afford the desired product. Yellow solid, m.p. 170.2–173.6 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.24 (s, 1H), 8.10 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.4 Hz, 2H), 3.88 (s, 3H), 1.28 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 175.5, 165.7, 148.0, 132.9, 130.2, 127.0, 58.4, 53.0, 26.2. HRMS (ESI-TOF) m/z Calcd for $C_{12}H_{15}NO_6S$ $[M+Na]^+$ 324.0518, found 324.0504.

4.2.10. Synthesis of 2-(4-N-butylaminocarbonyl-benzenesulfonylamino)-2-methyl-propionic acid (**2j**)

4-(Butylcarbamoyl)benzenesulfonyl chloride. To a stirred solution of (chlorosulfonyl)benzoyl chloride[19] (2 g, 8.4 mmol) and triethylamine (1.7 g, 16.8 mmol) in CH_2Cl_2 (12 mL) cooled to −78 °C was

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added dropwise *n*-butylamine (0.6 g, 8.4 mmol). The reaction was allowed to warm to room temperature over 1 h and then poured into 15 mL of ice water. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried ($MgSO_4$) and evaporated in vacuo to a white solid. The solid was chromatographed (CH_2Cl_2) to obtain the title compound (1.8 g, 78%). White solid, m.p. 91.3–93.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.5 Hz, 2H), 8.00 (d, J = 8.6 Hz, 2H), 6.42 (br, 1H), 3.49 (q, J = 7.1 Hz, 2H), 1.64 (quintet, J = 7.1 Hz, 2H), 1.43 (sextet, J = 7.4 Hz, 2H), 0.98 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 146.1, 141.1, 128.3, 127.3, 40.2, 31.5, 20.2, 13.8. HRMS (ESI-TOF) *m/z* Calcd for $C_{11}H_{14}ClNO_3S$ $[M+Na]^+$ 298.0281, found 298.0269.

Title compound **2j** as a white solid, m.p. 162.8–165.9 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.64 (t, J = 5.5 Hz, 1H), 8.13 (s, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H), 3.27 (q, J = 6.8 Hz, 2H), 1.51 (quintet, J = 7.0 Hz, 2H), 1.33 (sextet, J = 7.4 Hz, 2H), 1.27 (s, 6H), 0.90 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 175.6, 165.5, 146.1, 138.1, 128.2, 126.6, 58.3, 39.5, 31.6, 26.2, 20.1, 14.2. HRMS (ESI-TOF) *m/z* Calcd for $C_{15}H_{22}N_2O_5S$ $[M+Na]^+$ 365.1147, found 365.1139.

4.2.11. 2-(3-methyl- benzenesulfonylamino)-2-methyl-propionic acid (**2k**)

^{1}H NMR (400 MHz, DMSO) δ 7.94 (s, 1H), 7.60 (d, J = 7.5 Hz, 2H), 7.48–7.37 (m, 2H), 2.38 (s, 3H), 1.26 (s, 6H).

4.2.12. 2-(3-Chloro-benzenesulfonylamino)-2-methyl-propionic acid (**2l**)

White solid, m.p. 161.3–164.2 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.64 (s, 1H), 8.19 (s, 1H), 7.80 (s, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.60 (t, J = 7.9 Hz, 1H), 1.29 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 175.4, 145.9, 133.9, 132.4, 131.5, 126.3, 125.3, 58.5, 26.3. HRMS (ESI-TOF) *m/z* Calcd for $C_{10}H_{12}ClNO_4S$ $[M+Na]^+$ 300.0074, found 300.0067.

4.2.13. 2-(toluene-2-sulfonylamino)-2-methyl-propionic acid (**2m**)

^{1}H NMR (400 MHz, DMSO) δ 8.03 (s, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.48 (t, J = 7.4 Hz, 1H), 7.35 (t, J = 8.2 Hz, 2H), 2.59 (s, 3H), 1.23 (s, 6H).

4.2.14. 2-(2-Trifluoromethyl-benzenesulfonylamino)-2-methyl-propionic acid (**2n**)

White solide, m.p. 143.2–145.6 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.27 (s, 1H), 8.21 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 7.4 Hz, 1H), 7.87 (t, J = 7.5 Hz, 1H), 7.80 (t, J = 7.6 Hz, 1H), 1.31 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 175.8, 142.7, 133.4, 132.9, 130.5, 128.5 (q, $^3J_{C-F}$ = 5.8 Hz), 126.0 (q, $^2J_{C-F}$ = 32.8 Hz), 123.5 (q, $^1J_{C-F}$ = 274.1 Hz), 58.9, 26.0. HRMS (ESI-TOF) *m/z* Calcd for $C_{11}H_{12}F_3NO_4S$ $[M+Na]^+$ 334.0337, found 334.0332.

4.2.15. 2-(2-chloro-benzenesulfonylamino)-2-methyl-propionic acid (**2o**)

^{1}H NMR (400 MHz, DMSO) δ 8.17 (s, 1H), 7.97 (d, J = 8.1 Hz, 1H), 7.66–7.56 (m, 2H), 7.55–7.47 (m, 1H), 1.27 (s, 6H).

4.2.16. 2-(1-Naphthalenesulfonylamino)-2-methyl-propionic acid (**2p**)

White solide, m.p. 171.2–174.3 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.69 (d, J = 8.4 Hz, 1H), 8.34 (s, 1H), 8.17 (dd, J = 12.5, 7.8 Hz, 2H), 8.07 (d, J = 7.8 Hz, 1H), 7.74–7.58 (m, 3H), 1.22 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 176.1, 139.3, 134.2, 133.8, 129.3, 128.0, 128.0, 127.9, 127.1, 125.5, 124.9, 58.4, 25.9. HRMS (ESI-TOF) *m/z* Calcd for $C_{14}H_{15}NO_4S$ $[M+Na]^+$ 316.0620, found 316.0613.

4.2.17. 2-(2-naphthalenesulfonylamino)-2-methyl-propionic acid (**2q**)

White solide, m.p. 167.6–171.1 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.40 (d, J = 9.0 Hz, 1H), 8.13 (d, J = 7.8 Hz, 1H), 8.08 (t, J = 4.3 Hz, 2H), 8.01 (d, J = 7.7 Hz, 1H), 7.83 (d, J = 8.6 Hz, 1H), 7.71–7.61 (m, 2H), 1.26 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 175.7, 141.1, 134.4, 132.1, 129.7, 129.4, 129.0, 128.2, 127.9, 127.0, 122.9, 58.3, 26.2. HRMS (ESI-TOF) *m/z* Calcd for $C_{14}H_{15}NO_4S$ $[M+Na]^+$ 316.0620, found 316.0610.

4.2.18. 2-Thiophenesulfonylamino-2-methyl-propionic acid (**2r**)

^{1}H NMR (400 MHz, DMSO) δ 8.20 (s, 1H), 7.87 (dd, J = 5.0, 1.0 Hz, 1H), 7.56 (d, J = 3.5 Hz, 1H), 7.12 (dd, J = 4.7, 3.9 Hz, 1H), 1.33 (s, 6H).

4.2.19. 3-Pyridinesulfonylamino-2-methyl-propionic acid (**2s**)

Yellow solide, m.p. 162.4–165.7 °C. 1H NMR (400 MHz, DMSO) δ 8.94 (d, J = 2.0 Hz, 1H), 8.78 (d, J = 4.6 Hz, 1H), 8.29 (s, 1H), 8.17 (d, J = 8.1 Hz, 1H), 7.61 (dd, J = 8.0, 4.8 Hz, 1H), 1.31 (s, 6H). 13C NMR (100 MHz, DMSO) δ 175.3, 153.0, 147.2, 140.2, 134.7, 124.4, 58.7, 26.4. HRMS (ESI-TOF) *m/z* Calcd for $C_9H_{12}N_2O_4S$ $[M+Na]+$ 267.0415, found 267.0409.

4.2.20. 2-(Benzylsulfonylamino)-2-methyl-propionic acid (**2t**)

White solide, m.p. 188.6–189.9 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.70 (s, 1H), 7.41–7.34 (m, 5H), 7.29 (s, 1H), 4.34 (s, 2H), 1.39 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 176.2, 131.5, 131.0, 128.7, 128.4, 61.1, 58.9, 26.9. HRMS (ESI-TOF) *m/z* Calcd for $C_{11}H_{15}NO_4S$ $[M+Na]^+$ 280.0620, found 280.0610.

4.2.21. 2-Methyl-2-(propylsulfonamido)propanoic acid (**2u**)

White solide, m.p. 139.3–140.3 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.58 (s, 1H), 7.27 (s, 1H), 2.98 (t, J = 7.6 Hz, 2H), 1.69 (sextet, J = 7.4 Hz, 2H), 1.39 (s, 7H), 0.97 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 176.2, 58.3, 57.1, 26.9, 17.5, 13.2. HRMS (ESI-TOF) *m/z* Calcd for $C_7H_{15}NO_4S$ $[M+Na]^+$ 232.0620, found 232.0611.

4.3. General procedure for Pd-Catalyzed ortho-deuteration

A 25 mL sealed tube equipped with a stir bar was charged with 2-arylsulfonyl-2-methyl-propionic acid (0.2 mmol), K_2CO_3 (0.4 mmol) and palladium acetate (0.01 mmol). The sealed tube and reactants were dried in vacuum. Then 0.6 mL d_4-AcOH and 0.1 mL D_2O were added and the mixture was heated to 120 °C for 18 h. The resulting residue was purified by silica gel column chromatography with the following eluent system: AcOEt → AcOEt (added 5% concentrated hydrochloric acid).

4.3.1. 2-(Toluene-4-sulfonylamino)-2-methyl-propionic acid-d_2 (**3b**)

Yellow solid, 44.2 mg, 86% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 7.90 (s, 1H), 7.34 (s, 2H), 2.36 (s, 3H), 1.25 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 175.8, 142.5, 141.2, 129.7, 126.4 (t, J = 24.8 Hz), 58.1, 26.2, 21.4. HRMS (ESI-TOF) *m/z* Calcd for $C_{11}H_{13}D_2NO_4S$ $[M+Na]^+$ 282.0745, found 282.0738.

4.3.2. 2-Benzenesulfonylamino-2-methyl-propionic acid-d_2 (**3c**)

Yellow solid, 43.3 mg, 89% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 8.00 (s, 1H), 7.63–7.52 (m, 3H), 1.26 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 175.8, 144.0, 132.4, 129.2, 126.3 (t, J = 25.1 Hz), 58.2, 26.2. HRMS (ESI-TOF) *m/z* Calcd for $C_{10}H_{11}D_2NO_4S$ $[M+Na]^+$ 268.0589, found 268.0583.

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*4.3.3. 2-(4-Chloro-benzenesulfonylamino)-2-methyl-propionic acid-d_2 (**3d**)*

Yellow solid, 48.3 mg, 87% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 8.11 (s, 1H), 7.62 (s, 2H), 1.28 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 175.5, 142.7, 137.2, 129.4, 128.4 (t, J = 26.0 Hz), 58.4, 26.3. HRMS (ESI-TOF) *m/z* Calcd for $C_{10}H_{10}D_2ClNO_4S$ $[M+Na]^+$ 302.0199, found 302.0190.

*4.3.4. 2-(4-Nitro-benzenesulfonylamino)-2-methyl-propionic acid-d_2 (**3e**)*

Yellow solid, 49.0 mg, 85% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 8.38 (s, 3H), 1.30 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 175.3, 149.6, 149.2, 127.9 (t, J = 25.7 Hz), 124.6, 58.7, 26.4. HRMS (ESI-TOF) *m/z* Calcd for $C_{10}H_{10}D_2N_2O_6S$ $[M+Na]^+$ 313.0440, found 313.0434.

*4.3.5. 2-(4-Acetamide-benzenesulfonylamino)-2-methyl-propionic acid-d_2 (**3f**)*

Yellow solid, 50.5 mg, 84% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 10.43 (s, 1H), 7.73 (s, 2H), 7.20 (s, 1H), 2.08 (s, 72% of undeuterated CH_3), 1.21 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 177.2, 169.4, 142.8, 138.2, 127.5 (t, J = 20.9 Hz), 118.8, 59.3, 26.4, 24.6. HRMS (ESI-TOF) *m/z* Calcd for $C_{12}H_{14}D_2N_2O_5S$ $[M+Na]^+$ 325.0803, found 325.0800.

*4.3.6. 2-(4-Acetyl-benzenesulfonylamino)-2-methyl-propionic acid-d_2 (**3g**)*

Yellow solid, 48.4 mg, 85% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 8.21 (s, 1H), 8.10 (s, 2H), 2.59 (s, 6% of undeuterated CH_3), 1.28 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 197.9, 175.5, 147.6, 139.5, 129.1, 126.7 (t, J = 24.6 Hz), 58.4, 26.7 (t, J = 19.3 Hz), 26.3. HRMS (ESI-TOF) *m/z* Calcd for $C_{12}H_{13}D_2NO_5S$ $[M+Na]^+$ 310.0694, found 310.0687.

*4.3.7. 2-(4-(1H-pyrazol-1-yl)benzenesulfonylamin o)-2-methyl-propionic acid-d_2 (**3h**)*

Faint yellow solid, 46.3 mg, 82% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 8.62 (s, 66% of undeuterated at pyrazol C5-H), 8.06 (s, 1H), 8.04 (d, J = 9.1 Hz, 54% of undeuterated at phenyl C2-H), 7.91 (t, J = 3.7 Hz, 3H), 7.83 (s, 1H), 6.61 (t, J = 2.3 Hz, 64% of undeuterated at pyrazol C4-H), 1.30 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 175.6, 142.3 (t, J = 11.8 Hz), 141.0, 128.7 (t, J = 9.5 Hz), 128.4, 128.3, 118.6, 109.0 (t, J = 14.8 Hz), 58.2, 26.3. HRMS (ESI-TOF) *m/z* Calcd for $C_{13}H_{13}D_2N_3O_4S$ $[M+Na]^+$ 334.0807, found 334.0789.

*4.3.8. 2-(4-methoxalyl-benzenesulfonylamino)-2-methyl-propionic acid-d_2 (**3i**)*

Yellow solid, 51.2 mg, 85% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 8.25 (s, 1H), 8.11 (s, 2H), 3.88 (s, 4H), 1.28 (s, 7H). ^{13}C NMR (100 MHz, DMSO) δ 175.5, 165.7, 147.8, 132.9, 130.1, 126.8 (t, J = 25.7 Hz), 58.4, 53.0, 26.3. HRMS (ESI-TOF) *m/z* Calcd for $C_{12}H_{13}D_2NO_6S$ $[M+Na]^+$ 326.0644, found 326.0631.

*4.3.9. 2-(4-N-butylaminocarbonyl-benzenesulfonyla mino)-2-methyl-propionic acid-d_2 (**3j**)*

Yellow solid, 57.4 mg, 84% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 8.63 (br, 1H), 8.13 (s, 1H), 7.97 (s, 2H), 3.28 (q, J = 6.2 Hz, 2H), 1.52 (quintet, J = 6.7 Hz, 2H), 1.34 (sextet, J = 7.1 Hz, 2H), 1.27 (s, 6H), 0.90 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 175.6, 165.6, 146.0, 138.1, 128.1, 126.3 (t, J = 25.8 Hz), 58.3, 39.5, 31.6, 26.2, 20.1, 14.1. HRMS (ESI-TOF) *m/z* Calcd for $C_{15}H_{20}D_2N_2O_5S$ $[M+Na]^+$ 367.1273, found 367.1264.

*4.3.10. 2-(3-Methyl-benzenesulfonylamino)-2-methyl-propionic acid-d_2 (**3k**)*

Faint yellow solid, 43.7 mg, 85% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 7.92 (s, 1H), 7.41 (dd, J = 8.6, 7.6 Hz, 2H), 2.37 (s, 3H), 1.27 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 175.8, 144.0, 138.8, 133.0, 129.1, 126.5 (t, J = 26.5 Hz), 123.5 (t, J = 24.1 Hz), 58.2, 26.2, 21.3. HRMS (ESI-TOF) *m/z* Calcd for $C_{11}H_{13}D_2NO_4S$ $[M+Na]^+$ 282.0745, found 282.0733.

*4.3.11. 2-(3-Chloro-benzenesulfonylamino)-2-methyl-propionic acid-d_2 (**3l**)*

Yellow solid, 48.8 mg, 88% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 8.17 (s, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 1.29 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 175.4, 145.8, 133.8, 132.4, 131.3, 126.0 (t, J = 25.6 Hz), 125.0 (t, J = 24.6 Hz), 58.5, 26.4. HRMS (ESI-TOF) *m/z* Calcd for $C_{10}H_{10}D_2ClNO_4S$ $[M+Na]^+$ 302.0199, found 302.0195.

*4.3.12. 2-(Toluene-2-sulfonylamino)-2-methyl-propionic acid-d_1 (**3m**)*

Yellow solid, 45.2 mg, 88% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 7.99 (s, 1H), 7.47 (t, J = 7.4 Hz, 1H), 7.38–7.30 (m, 2H), 2.60 (s, 94% of undeuterated CH_3), 1.24 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 176.1, 142.1, 136.8, 132.6, 132.5, 127.9 (t, J = 24.4 Hz), 126.3, 58.2, 26.0, 20.2. HRMS (ESI-TOF) *m/z* Calcd for $C_{11}H_{14}DNO_4S$ $[M+Na]^+$ 281.0683, found 281.0673.

*4.3.13. 2-(2-Trifluoromethyl-benzenesulfonylamin o)-2-methyl-propionic acid-d_1 (**3n**)*

Yellow solid, 51.6 mg, 83% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 8.25 (s, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.87 (d, J = 7.0 Hz, 1H), 7.80 (t, J = 7.6 Hz, 1H), 1.31 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 175.8, 142.7, 133.3, 132.9, 130.2 (t, J = 27.6 Hz), 128.5 (q, $^3J_{C\text{-}F}$ = 5.8 Hz), 126.0 (q, $^2J_{C\text{-}F}$ = 32.6 Hz), 123.5 (q, $^1J_{C\text{-}F}$ = 274.0 Hz), 58.9, 25.0. HRMS (ESI-TOF) *m/z* Calcd for $C_{11}H_{11}DF_3NO_4S$ $[M+Na]^+$ 335.0400, found 335.0394.

*4.3.14. 2-(2-Chloro-benzenesulfonylamino)-2-methyl-propionic acid-d_1 (**3o**)*

Yellow solid, 46.6 mg, 84% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 8.13 (s, 1H), 7.63–7.59 (m, 2H), 7.51–7.49 (m, 1H), 1.27 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 175.8, 141.2, 134.0, 132.0, 130.9, 129.8 (t, J = 24.7 Hz), 127.8, 58.6, 26.0. HRMS (ESI-TOF) *m/z* Calcd for $C_{10}H_{11}DClNO_4S$ $[M+Na]^+$ 301.0136, found 301.0130.

*4.3.15. 2-(1-Naphthalenesulfonylamino)-2-methyl-propionic acid-d_2 (**3p**)*

Faint yellow solid, 51.6 mg, 88% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 8.33 (s, 1H), 8.17 (d, J = 8.3 Hz, 1H), 8.05 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 6.5 Hz, 1H), 7.67–7.58 (m, 2H), 1.23 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 176.1, 139.2, 134.2, 133.8, 129.3, 127.9 (t, J = 12.3 Hz), 127.9, 127.8, 127.1, 125.3 (t, J = 29.0 Hz), 124.8, 58.4, 25.9. HRMS (ESI-TOF) *m/z* Calcd for $C_{14}H_{13}D_2NO_4S$ $[M+Na]^+$ 318.0745, found 318.0731.

*4.3.16. 2-(2-Naphthalenesulfonylamino)-2-methyl-propionic acid-d_2 (**3q**)*

Yellow solid, 52.2 mg, 89% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 8.15 (d, J = 7.8 Hz, 1H), 8.10 (d, J = 5.1 Hz, 2H), 8.03 (d, J = 8.0 Hz, 1H), 7.72–7.62 (m, 2H), 1.29 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 175.6, 140.9, 134.3, 132.0, 129.5, 129.2, 128.9, 128.2, 127.8, 126.7 (t, J = 28.0 Hz), 122.6 (t, J = 24.3 Hz), 58.2, 26.2. HRMS (ESI-TOF) *m/z*

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Calcd for $C_{14}H_{13}D_2NO_4S$ $[M+Na]^+$ 318.0745, found 318.0736.

*4.3.17. 2-Thiophenesulfonylamino-2-methyl-propionic acid-d_2 (**3r**)*

Faint yellow solid, 41.1 mg, 83% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 8.18 (s, 1H), 7.85 (d, $J=4.9$ Hz, 73% of undeuterated at C5-H), 7.56 (d, $J=3.0$ Hz, 67% of undeuterated at C3-H), 7.11 (m, 1H), 1.33 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 175.7, 145.4 (t, $J=8.7$ Hz), 132.4, 131.6, 127.6 (t, $J=8.8$ Hz), 58.6, 26.0. HRMS (ESI-TOF) *m/z* Calcd for $C_8H_9D_2NO_4S_2$ $[M+Na]^+$ 274.0153, found 274.0146.

*4.3.18. 2-(Benzylsulfonylamino)-2-methyl-propionic acid-d_2 (**3t**)*

White solid, 45.2 mg, 88% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 7.42–7.31 (m, 3H), 7.28 (s, 1H), 4.34 (s, 94% of undeuterated CH_2), 1.39 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 176.2, 131.5, 130.9 (t, $J=8.6$ Hz), 128.6 (d, $J=11.4$ Hz), 128.5 (d, $J=15.9$ Hz), 61.0, 58.9, 26.9. HRMS (ESI-TOF) *m/z* Calcd for $C_{11}H_{13}D_2NO_4S$ $[M+Na]^+$ 282.0745, found 282.0733.

4.4. Removal of directing group to synthesis of sulfonamides

A 25 mL sealed tube equipped with a stir bar was charged with deuterated sulfonamide derivatives (0.5 mmol, 1 equiv), CuO (0.15 mmol, 30 mol%), DMSO (1 mL). The sealed tube was capped and heated to 120 °C. After 12 h, the reaction was cooled to ambient temperature. The reaction solution was then added some water and extracted with EtOAc. The organic layers were collected and dried with Na_2SO_4 concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 3/1) to afford the desired product **4**.

*4.4.1. 4-Methyl-benzenesulfonamide-d_2 (**4b**)*

White solid, 82.3 mg, 95% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 7.37 (s, 2H), 7.29 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 142.4, 141.7, 129.7, 125.8 (t, $J=25.3$ Hz), 21.4. HRMS (ESI-TOF) *m/z* Calcd for $C_7H_7D_2NO_2S$ $[M+Na]^+$ 196.0378, found 196.0371.

*4.4.2. 4-Chloro-benzenesulfonamide-d_2 (**4d**)*

White solid, 84.2 mg, 87% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 7.66 (s, 2H), 7.48 (s, 2H). ^{13}C NMR (100 MHz, DMSO) δ 143.3, 137.1, 129.4, 127.8 (t, $J=25.7$ Hz). HRMS (ESI-TOF) *m/z* Calcd for $C_6H_4D_2ClNO_2S$ $[M+Na]^+$ 215.9831, found 215.9826.

*4.4.3. 4-Nitro-benzenesulfonamide-d_2 (**4e**)*

Yellow solid, 87.7 mg, 86% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 8.42 (s, 2H), 7.76 (s, 2H). ^{13}C NMR (100 MHz, DMSO) δ 149.7, 127.4 (t, $J=26.0$ Hz), 124.9, 124.8. HRMS (ESI-TOF) *m/z* Calcd for $C_6H_4D_2N_2O_4S$ $[M+Na]^+$ 227.0072, found 227.0067.

*4.4.4. 4-Acetamide-benzenesulfonamide-d_2 (**4f**)*

Yellow solid, 90.8 mg, 84% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 10.27 (s, 1H), 7.74 (s, 2H), 7.24 (s, 2H), 2.09 (s, 86% of undeuterated CH_3). ^{13}C NMR (100 MHz, DMSO) δ 169.4, 142.7, 138.4, 126.9 (t, $J=25.9$ Hz), 118.8, 24.6. HRMS (ESI-TOF) *m/z* Calcd for $C_8H_8D_2N_2O_3S$ $[M+Na]^+$ 239.0436, found 239.0429.

*4.4.5. 3-Methyl-benzenesulfonamide-d_2 (**4k**)*

White solid, 73.6 mg, 85% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 7.46 (d, $J=7.6$ Hz, 1H), 7.42 (d, $J=7.6$ Hz, 1H), 7.34 (s, 2H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 144.4, 138.9, 132.8, 129.2, 126.1 (t, $J=28.3$ Hz), 123.0 (t, $J=25.4$ Hz), 21.3. HRMS (ESI-TOF) *m/z* Calcd for $C_7H_7D_2NO_2S$ $[M+Na]^+$ 196.0378, found 196.0369.

*4.4.6. 2-Trifluoromethyl-benzenesulfonamide-d_1 (**4n**)*

White solid, 90.5 mg, 80% yield. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, DMSO) δ 7.95 (d, $J=7.8$ Hz, 1H), 7.90 (d, $J=7.2$ Hz, 1H), 7.81 (t, $J=7.7$ Hz, 1H), 7.75 (s, 2H). ^{13}C NMR (100 MHz, DMSO) δ 142.8, 133.5, 132.9, 129.6 (t, $J=30.5$ Hz), 128.5 (q, $^3J_{C\text{-}F}=5.7$ Hz), 126.0 (q, $^2J_{C\text{-}F}=32.6$ Hz), 123.5 (q, $^1J_{C\text{-}F}=274.0$ Hz). HRMS (ESI-TOF) *m/z* Calcd for $C_7H_5DF_3NO_2S$ $[M+Na]^+$ 249.0032, found 249.0025.

4.5. Synthesis of deuterium tolbutamide

A 25 mL sealed tube equipped with a stir bar was charged with sulfonamide (0.5 mmol, 86.6 mg), carbamate (0.55 mmol, 106.3 mg) in acetonitrile (4 mL), when solid was dissolved, then DBU (0.75 mmol, 114.1 mg) was added and the reaction mixture was refluxed. The reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated in vacuo and then dissolved in ethyl acetate and extracted with 0.1 N HCl and saturated salt solution, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 2/1) to afford the desired product **5**[17] (103.5 mg, 76%) as a white solid. Characterization data for the deuterated compound only: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.32 (s, 2H), 6.55 (t, $J=5.2$ Hz, 1H), 3.22 (q, $J=6.8$ Hz, 2H), 2.45 (s, 3H), 1.46 (quintet, $J=7.2$ Hz, 2H), 1.29 (sextet, $J=7.6$ Hz, 2H), 0.90 (t, $J=7.2$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 144.6, 136.6, 129.7, 126.8 (t, $J=24.9$ Hz), 40.0, 31.6, 21.6, 19.9, 13.7. HRMS (ESI-TOF) *m/z* Calcd for $C_{12}H_{16}D_2N_2O_3S$ $[M+Na]^+$ 295.1062, found 295.1056.

4.6. Synthesis catalyst intermediate **6**

A mixture of sulfonamide **2b** (51.4 mg, 0.2 mmol), $Pd(OAc)_2$ (44.8 mg, 0.2 mmol), K_2CO_3 (55.2 mg, 0.4 mmol) and anhydrous THF (2 mL) were mixed in a dry sealed tube. The mixture was stirred at 100 °C under N_2 for 12 h. The precipitate obtained was filtered, washed with ethyl acetate, and dried in vacuo to afford intermediate **6** (containing *ca.* 2eq. KOAc). ^{1}H NMR (400 MHz, DMSO) δ 7.41 (s, 1H), δ 6.86 (d, $J=9.2$ Hz, 1H), 6.84 (d, $J=8.4$ Hz, 1H), 2.21 (s, 3H), 1.51 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 186.5, 152.4, 138.7, 134.5, 133.9, 125.4, 123.0, 64.7, 30.0, 21.9.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.06.024.

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