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Palladium-Catalyzed H/D Exchange Reaction with 8-Aminoquinoline as the Directing Group: Access to *ortho*-Selective Deuterated Aromatic Acids and *beta*-Selective Deuterated Aliphatic Acids

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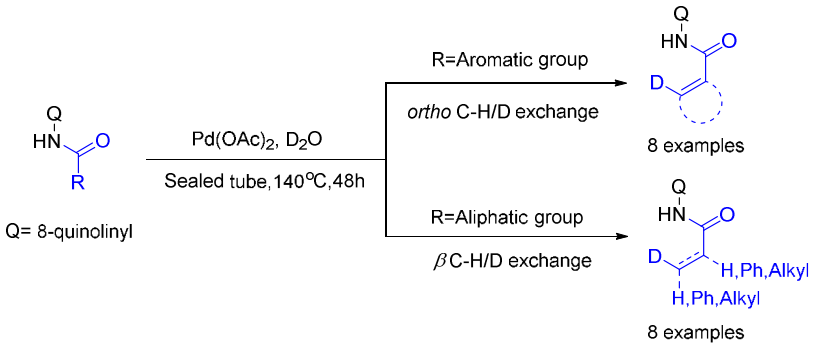
Supporting Information Placeholder



ABSTRACT: We develop a palladium-catalyzed H/D exchange reaction with 8-aminoquinoline as the directing group as well as D_2O as the source of deuterium atom and solvent. This reaction achieves selectively H/D exchange at the *ortho* C-H of aromatic amides and the *beta* C-H of aliphatic amide. *Ortho*-deuterated aromatic acids and *beta*-deuterated aliphatic acids are obtained by removal of the directing group. And a possible mechanism is also proposed.

INTRODUCTION

Metal-catalysed hydrogen isotope exchange labeling has been playing a significant role in the preparation of stable isotopically labeled compounds.[1]The deuterium labeled organic compounds are widely used as internal standards in quantitative LC-MS/MS analysis,[2] mechanistic probes in chemical and biological processes, as well as biologically active compoundsand pharmaceuticals.[3]Therefore, the synthesis of deuterium labeled organic compounds is an increased interest subject. The previous synthetic methods are mainly divided into the following two categories, including the conventional method starting from commercially available, stable deuterium-labeled synthons and the H/D exchange reactions via the direct exchange of hydrogen atom with deuterium atom under the catalytic condition, such as acid, base and metal catalyst (Pd, Pt, Rh, Ru, Ni, Ir).[2a, 4] Though the H/D exchange reaction is highly effective and accessible, the *ortho*-selective H/D exchange reactions are mainly limited to the aromatic compound as substrates and organoiridium as catalysts.[5]Fels investigated the scope and limitation of an iridium-catalysed H/D exchange reaction, and showed that the *ortho*-of benzoic acids was deuterated, but phenylacetic acids was not. [6]Yu achieved the-*ortho*-selective C-H deuteration of phenylacetic acid via palladium-catalyzed *ortho*-selective deuteration and treatment with NaOH for reprotonation of the α-position. And in Yu' works, only [D_4] acetic acidcan be the source of deuterium atom **(**deuterium-containing solvent D_2O was also tested, but no deuterated product was observed.**)** and base is essential.[7]Sawama and Sajiki obtained multi-deuterated saturated fatty acids including valproic acid-d_{15} by Pt/C-catalyzed multi-deuteration method in a mixed solvent of isopropylalcohol and deuterium oxide.[8]Also, the utilization of directing groups to achieve C-H bond functionalization has been widely reported. Daugulis reported they achieved that pyridine-containing auxiliary in the molecule to be activated could result in selective arylation of a variety of classes of organic compounds. Later, they reported palladium-catalyzed arylation and alkylation of C-H in amine derivatives with pyridine or 8-aminoquinoline as a directing group.[9] Chen accomplished the total synthesis of celogetin C using 8-aminoquinoline as an auxiliary group. A method of total synthesis of piperborenined with 8-aminoquinoline directing the C-H activation was reported by Baran.[10]Here, we developed a novel, practical and selective deuteration of carboxylic acids. The approach proceeded using D_2O as the source of deuterium atom and solvent, commercially available 8-aminoquinoline as the directing group and palladiumacetateas the catalyst. The selective H/D exchange at the *ortho* C-H of aromatic amides and the *beta*-C-H of aliphatic amide was achieved in this work (Scheme 1).*Ortho*-deuterated aromatic acids and β-deuterated aliphatic acids

including valproic acid-d_4 were also obtained by the hydrolysis of deuterated amides.

RESULTS AND DISCUSSION

We initiated our studies by using 2-methyl-*N*-(quinolin-8-yl)benzamide and testing different Pd(II) as the catalyst(Table 1, entry 1-3). To our delight, the *ortho*-selective deuteration of aromatic amides was achieved and the deuterium incorporation was up to 81% when $Pd(OAc)_2$ was used as the catalyst(Table 1, entry 3). Then, a cheaper catalyst $Cu(OAc)_2$ was used instead of $Pd(OAc)_2$, but the deuterium incorporation was much lower(Table 1, entry 4). The *ortho* C-H of aromatic amides was deuterated in different degrees, which can easily be seen by the frame area in the Table 1.

And then, in order to confirming the necessity of 8-aminoquinoline as a directing group, we also test the free aromatic acids and changing the directing group to 2-methylpyridine. As shown in table 2, the deuteration of aromatic nucleus can't be abtained removing 8-aminoquinoline.

Scheme 1. H/D Exchange Reactions

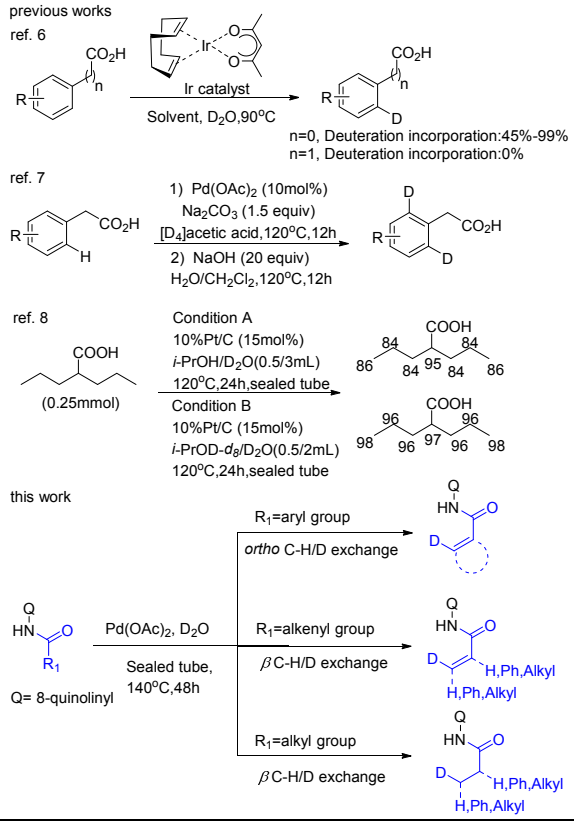
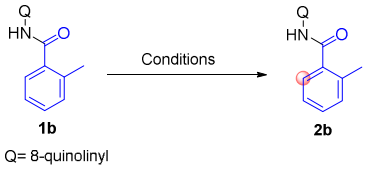


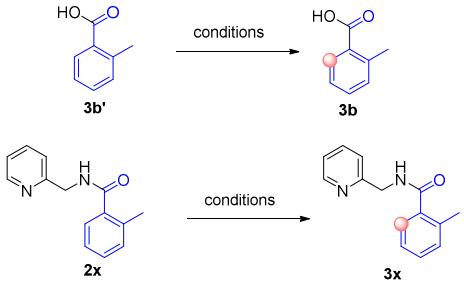
Table 1.Deuteration of 2-Methyl-*N*-(quinolin-8-yl) benzamide (1b) Under the Initial Conditions[a]



Entry	Catalyst(eq.)	T(°C)	Time (h)	Dincorporation[b] (%)
1	$Pd(dppf)_2Cl_2$(0.2)	120	48	78
2	$Pd(pph_3)_4$(0.2)	120	48	48
3	$Pd(OAc)_2$(0.2)	120	48	81
4	$Cu(OAc)_2$(0.2)	120	48	35

[a]Initial conditions: **1b**(1.0 equiv., 0.2 mmol), catalyst (0.2 equiv., 0.04 mmol), D_2O (99.8% D content, 1 mL), in a sealed tube, 120 °C, 48h. [b] D incorporation was determined by ^{1}H NMR.

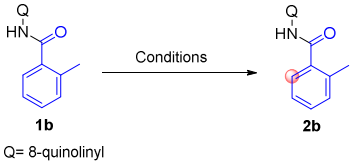
Table 2.Deuteration of 2-Methyl-N-(quinolin-8-yl) benzamide (1b) Under the Conditions[a]



Entry	Directing group	T(°C)	Time (h)	Dincorporation[b] (%)
1	-	140	24	0
2	2-methylpyridine	140	48	0

[a]Reaction conditions: **3b'/2x** (1.0 eq., 0.2 mmol), $Pd(OAc)_2$ (0.2 eq., 0.04 mmol), D_2O (99.8% D content, 1 mL), in a sealed tube.[b] D incorporation was determined by^{1}H NMR.

Table 3.Optimization of the Reaction Conditions with $Pd(OAc)_2$ as the Catalyst[a]

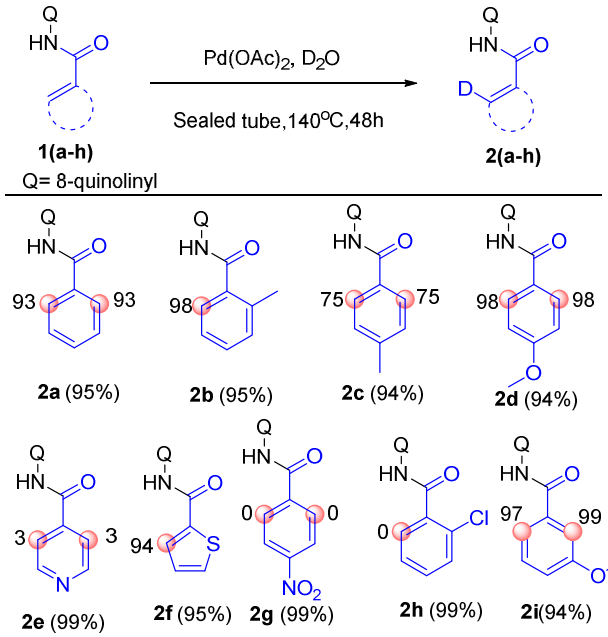


Entry	Catalyst(eq.)	T(°C)	Time (h)	D incorporation[c] (%)
1	$Pd(OAc)_2$(0.2)	120	48	81
2	$Pd(OAc)_2$(0.2)	140	48	98
3	$Pd(OAc)_2$(0.2)	160	48	96
4[b]	$Pd(OAc)_2$(0.2)	reflux	48	96
5	$Pd(OAc)_2$(0.1)	140	48	91
6	$Pd(OAc)_2$(0.3)	140	48	93
7	$Pd(OAc)_2$(0.2)	140	24	85
8	$Pd(OAc)_2$(0.2)	140	72	94
9	_	140	48	0

[a]Reaction conditions: **1b** (1.0 equiv., 0.2 mmol), $Pd(OAc)_2$, D_2O (99.8% D content, 1 mL), in a sealed tube. [b]The reaction was performed in normal pressure reactor with D_2O refluxing. [c]D incorporation was determined by ^{1}H NMR.

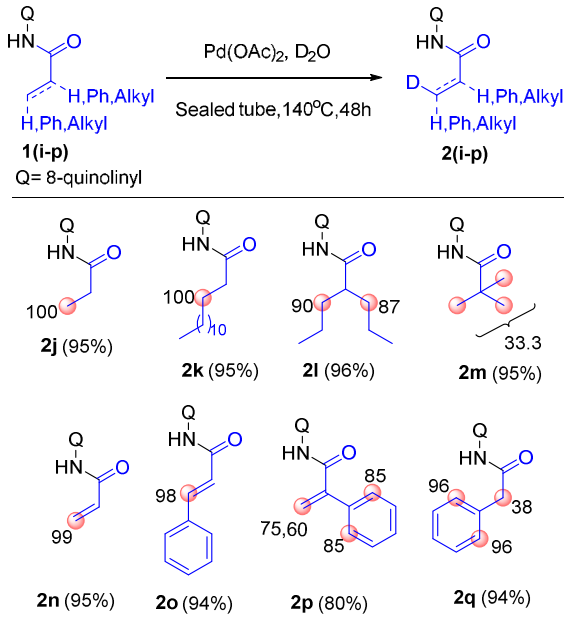
According to the above results, we selected $Pd(OAc)_2$ as the catalyst and other reaction factors were further examined (Table 3). Firstly, the reaction temperature was investigated and 140°C was found to be the best (entry 2). The replacement of sealed tube with normal pressure reactor with D2O refluxing resulted in a slightly lower deuterium incorporation (entry 4). Then, the equivalent of $Pd(OAc)_2$ and reaction time were screened. Compared with entry 2, there was no increase in the deuterium incorporation(entry 5-8). Furthermore, control experiments revealed that no reaction occurred in the absence of $Pd(OAc)_2$ (entry 9 *vs* entry 2). Accordingly, we obtained the optimized reaction conditions: treatment of the substrate(1.0 eq.) with $Pd(OAc)_2$ (0.2 eq.) in D_2O at 140°C for 48h (entry 2). As shown in the Table 3, the *ortho* C-H of aromatic amides of substrate (**1b**) and products (**2b**, Table 3) was framed.

Scheme 2. Scope of the Aromatic Amides [a]



[a]Reaction conditions:**1** (0.4 mmol, 1.0 equiv.), $Pd(OAc)_2$(0.08 mmol, 0.2 equiv.), D_2O (99.8% D content, 2 mL), in a sealed tube, 140 °C, 48h.[b]D incorporation was determined by ^1H NMR. [c]Isolated yields = (Mass of product **2**/Mass of substrate **1**)×100%, as shown in parentheses.

Scheme 3.Scope of the Aliphatic and OlefinicAmides[a]



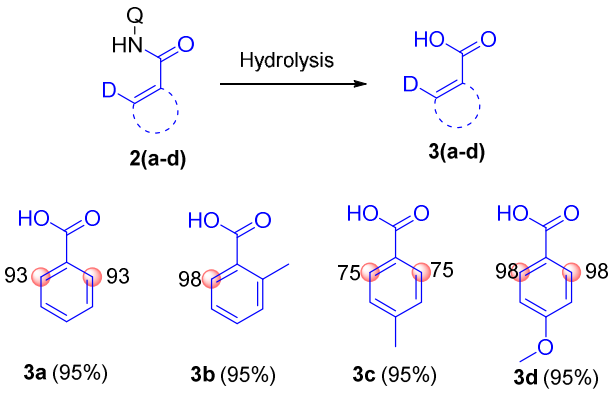
[a]Reaction conditions:1 (0.4 mmol, 1.0 equiv.), Pd(OAc)2(0.08 mmol, 0.2 equiv.), D2O (99.8% D content, 2 mL), in a sealed tube, 140 °C, 48h. [b]D incorporation was determined by 1H NMR. [c]Isolated yields = (Mass of product 2/Mass of substrate 1)×100%, as shown in parentheses.

With the optimized reaction conditions in hand, the deuteration of a number of aromatic amides was investigated. The results were shown in the Scheme 2, which indicated that the applicability of this reaction was related to the electron effect of the aromatic ring. Electron-rich aromatic rings achieved the *ortho*-selective deuteration with good deuterium incorporation, while electron-deficient aromatic rings had no reactions (**2a-2d, 2i***vs***2g-2h**, **2f**vs**2e**). Besides, there is no distinct difference of incorporation between the hindered 2-H and the less hindered 5-H in **2i**.

Furthermore, to explore the scope of this method, a substrate scope study on aliphatic amides was then performed. As shown in Scheme 3, β-C-H selective deuteration of α, β- saturated aliphatic amides (**2j-2l**) and α, β-unsaturated aliphaticamides (**2n-2o**) were achieved with excellent deuterium incorporation except **2m**. The aliphatic amide (**2m**) with three methyl groups at the *beta* position, achieved 33.3% deuterium incorporation of all three methyl groups. Unexpected and reasonable, β-selective deuteration at the propenyl group and *ortho*-selective deuteration at the 2-phenyl group of **2p** was obtained, and *ortho*-selective deuteration at the phenyl group of **2q** was achieved. The amides **2o** and **2p** further demonstrated that this method can achieve selective deuteration at the *ortho* C-H of aromatic amides and the β-C-H of aliphatic amides.

On the basis of the above and to further broaden the application of this synthetic methodology, the 8-quinolylamino directing group was removed[11] and some *ortho*-deuterated benzoic acids were obtained (Scheme 4).

Scheme 4. Removal of the Directing Group by Hydrolysis [a]

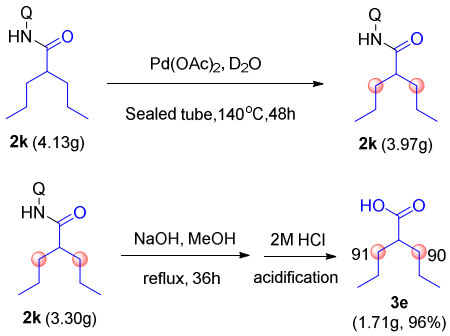


[a]Hydrolysis conditions:**2** (0.45mmol) and 40% H_2SO_4aqueous solution (2 mL), 120 °C, 12h. [b]D incorporation was determined by ^{1}H NMR. [c]isolated yields = (Real mass of **3**/Theoretical mass of **3**according to the 100% D incorporation)×100%,as shown in parentheses.

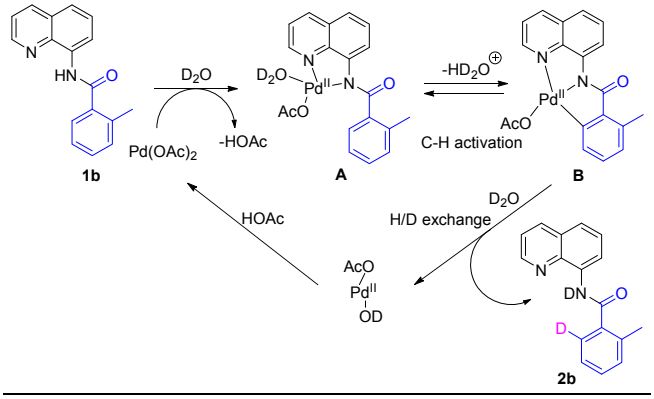
Valproic acid is a widely used antiepileptic drug. Abbott reported that Valproic acid is mainly metabolized by hydroxylated at beta-position. [12]Using β -deuterated Valproic acid as a probe can indicate whether Valproic acid is β -metabolized in a human body by detecting the existent of β -D. In this way, selective β -deuterated Valproic acid can be used in the study of drug metabolism field. The β-deuterated valproic acid was obtained in gram-scale by this catalytic H/D exchange reaction following with the removal of the directing group (Scheme 5). The activity evaluation of β-deuterated valproic acidis also undergoing.

On the basis of the results above, the possible mechanism was proposed and shown in Scheme 6. 2-methyl-*N*-(quinolin-8-yl)benzamide (**1b**)was reacted with palladium acetate to afford the intermediate **A.** Then palladium amide **A** transformed to **B** by achieving the C-H activation with a rapid cyclometalation of phenyl group. Complex **B** was deuterated leading to **2b**. [13]

Scheme 5.Gram-Scale Synthesis and Synthetic Applications



Scheme 6.Possible Mechanism



CONCLUSION

In summary, we have developed an approach resulting inselective H/D exchange reaction. The reaction proceeded using D_2O as the source of deuterium atom and solvent, as well as 8-aminoquinoline as the directing group and palladium acetate as the catalyst. Some *ortho*-deuterated benzoic acids and β-deuterated valproic acid were obtained by the removal of the directing group. A possible reaction mechanism was proposed involving formation of palladium amide, cyclometalation, and deuteration steps.

EXPERIMENTAL SECTION

General Information. ^{1}H NMR were recorded in $CDCl_3$ or DMSO-d_6 at 500 MHz. Tetramethylsilane (TMS) served as internal standard (δ=0) and data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t= triplet, q=quartet, m=multiplet), and coupling constant(s) in Hertz. LC-HRMS data was obtained using Agilent Technologies 6224 TOF LC/MS.

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. All solvents were purified and dried according to standard methods prior to use. Products were purified by flash column chromatography on 200-300 mesh silicagel, SiO_2.

Typical procedure for the preparation of carboxamides 1. All amides **1** were synthesized from the corresponding carboxylic acids or acid chlorides and 8-aminoquinoline referring to literature procedures.[14]

*Synthesis of amides (**1a, 1i, 1j, 1l, 1m, 1p**) from acid chlorides.*[1a-d]

8-Aminoquinoline (1.0 equiv.) was dissolved in anhydrous CH_2Cl_2 (20 mL) and Et_3N (1.2 equiv.) was added under nitrogen atmosphere. The solution was cooled to 0 °C and then acid chloride (1.2 equiv.) was added dropwise. The reaction mixture was stirred over night at room temperature. The reaction mixture was quenched with saturated aqueous solution of sodium bicarbonate and extracted with dichloromethane three times. The combined organic phase was washed with water, brine and dried with Na_2SO_4 and concentrated in vacuum. The crude mixture was purified by silica gel column chromatography to give the carboxamide.

*Synthesis of amides (**1b, 1c, 1d, 1e, 1f, 1g, 1h, 1k, 1n, 1o**) from carboxylic acids.*[1e-j]

To a solution of acid (1.0 equiv.) and catalytic amount DMF (2 drops) anhydrous CH_2Cl_2 under nitrogen atmosphere, ox-

alyl chloride (1.2 equiv.) was added dropwise at 0 °C. After stirring for 3 h at room temperature, the solvent was evaporated under reduced pressure and the resulting acid chloride was used immediately without further purification.

8-Aminoquinoline (1.0 equiv.) was dissolved in anhydrous CH_2Cl_2 (20 mL) and Et_3N (1.2 equiv.) was added under nitrogen atmosphere. The solution was cooled to 0 °C and then the above obtained acid chloride (1.2 equiv.) was added dropwise. The reaction mixture was stirred over night at room temperature. The reaction mixture was quenched with saturated aqueous solution of sodium bicarbonate and extracted with dichloromethane three times. The combined organic phase was washed with water, brine and dried with Na_2SO_4 and concentrated in vacuum. The crude mixture was purified by silica gel column chromatography to give the carboxamide.

General Experimental Procedure for the Synthesis of Deuterated Amides 2. In a sealed tube, amides**1**(0.4mmol, 1.0 equiv.), $Pd(OAc)_2$ (0.08mmol, 0.2 equiv.) and D_2O (99.8% D content, 2 mL) were added. The reaction was stirred at 140 °C for 48 hours. Then, the reaction mixture was cooled to room temperature and extracted with water (15 mL)-ethyl acetate (3×20 mL). The combined organic phase was washed with saturated salt water and dried with Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (Petroleum ether/ethyl acetate=15/1) to give the deuterated amides **2**.

Hydrolysis of deuterated benzoic amides (2a, 2b, 2c, 2d).[15]The deuterated benzoic amide (**2a, 2b, 2c, 2d**) (0.3 mmol) was dissolved in 2mL aq. H_2SO_4 (40%) and stirred at 120 °C for 12h (The reaction is complete by TLC detection). The reaction mixture was cooled to room temperature and extracted with water (10 mL) - ether (3×20 mL). The combined organic phase was washed with saturated salt water and dried with Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give the corresponding ortho deuterated benzoic acid (**3a, 3b, 3c, 3d**).

Gram-scale Synthesis of β-deuterated valproic acid. In *Synthesis of deuterated 2-propyl-N-(quinolin-8-yl)pentanamide **2k***.

In a sealed tube, 2-propyl-N-(quinolin-8-yl)pentanamide **1k** (4.13g, 15.26 mmol, 1.0 equiv.), $Pd(OAc)_2$ (0.68g, 3.05 mmol, 0.2 equiv.) and D_2O (99.8% D content, 8.3 mL) were added. The reaction was stirred at 140 °C for 48 hours. Then, the reaction mixture was cooled to room temperature and extracted with water (20 mL)-ethyl acetate (3×30 mL). The combined organic phase was washed with saturated salt water and dried with Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (Petroleum ether/ethyl acetate=15/1) to give the deuterated 2-propyl-N-(quinolin-8-yl)pentanamide **2k** (3.97g, 95%).

*Hydrolysis of deuterated 2-propyl-N-(quinolin-8-yl)pentanamide **2k**.*[16]

The deuterated 2-propyl-N-(quinolin-8-yl)pentanamide **2k** (3.30g, 12 mmol, 1.0 equiv.) was dissolved in MeOH (17mL) and NaOH (4.80g, 120 mmol, 10.0 equiv.) was added. The reaction mixture was refluxed with stirring for 36h (The reaction is complete by TLC detection). The reaction mixture was cooled to room temperature and extracted with ethyl acetate (30 mL) - water (2×30 mL). The combined aqueous phase was acidified with 2M HCl to pH=2 and extracted with ether (3×30 mL). The combined ether phase was washed with saturated salt water (45 mL) and dried with Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give the β-deuterated valproic acid **3e**(1.71g, 96%).

^{1}H NMR Spectral Dataof Substrates and Products.

*N-(quinolin-8-yl)benzamide**(1a)***. White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.75 (s, 1H), 8.95 (dd, *J* = 7.6, 1.5 Hz, 1H), 8.85 (dd, *J* = 4.2, 1.7Hz, 1H), 8.19 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.13 – 8.07 (m, 2H), 7.62 – 7.53 (m, 5H), 7.48 (dd, *J* = 8.2Hz, 4.2Hz, 1H).

*2-methyl- N-(quinolin-8-yl)benzamide**(1b)***.White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.22 (s, 1H), 8.95 (d, *J* = 7.3 Hz, 1H), 8.78 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.56 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.33 (t, *J* = 8.1 Hz, 2H), 2.61 (s, 3H).

*4-methyl- N-(quinolin-8-yl)benzamide**(1c)***. White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.72 (d, *J* = 7.8 Hz, 1H), 8.94 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.85 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.01 – 7.97 (m, 2H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.53 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.47 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 2H), 2.45 (s, 3H).

*4-methoxyl- N-(quinolin-8-yl)benzamide**(1d)***. White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.92 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.85 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.18 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.08 – 8.04 (m, 2H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.52 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.47 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.07 – 7.02 (m, 2H), 3.89 (s, 3H).

*N-(quinolin-8-yl)isonicotinamide **(1e)***.Pale yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.82 (s, 1H), 8.91 (dd, *J* = 6.4, 2.5 Hz, 1H), 8.88 – 8.85 (m, 3H), 8.21 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.92 – 7.90 (m, 2H), 7.63 – 7.59 (m, 2H), 7.51 (dd, *J* = 8.3, 4.2 Hz, 1H).

*N-(quinolin-8-yl)thiophene-2-carboxamide **(1f)***.White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.60 (s, 1H), 8.87 – 8.82 (m, 2H), 8.19 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.84 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.61 – 7.56(m, 2H), 7.54 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.48 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.19 (dd, *J* = 5.0, 3.7 Hz, 1H).

*3-methoxyl- N-(quinolin-8-yl)benzamide **(1i)***.White solid;^{1}H NMR(500 MHz, CDCl3)δ 10.76 (s, 1H), 8.95 (dd, *J* = 7.5, 0.8 Hz, 1H), 8.90 – 8.84 (m, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 7.67 (d, *J* = 3.4 Hz, 1H), 7.66 (s, 1H), 7.62 (t, *J* = 7.9 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.49 (dt, *J* = 10.2, 5.8 Hz, 2H), 7.17 – 7.12 (m, 1H), 3.94 (s, 3H).

*N-(quinolin-8-yl)propionamide **(1j)***. Pale yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.83 – 8.75 (m, 2H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.49 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.34 (t, *J* = 7.6 Hz, 3H).

*N-(quinolin-8-yl)tetradecanamide **(1k)***. White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.83 – 8.76 (m, 2H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.56 – 7.51 (m, 1H), 7.49 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.58 – 2.54 (m, 2H), 1.86 –1.79 (m, 2H), 1.46 – 1.40 (m, 2H), 1.39 – 1.34 (m, 2H), 1.32 – 1.23 (m, 17H), 0.88 (t, *J* = 7.0 Hz, 3H).

*2-propyl-N-(quinolin-8-yl)pentanamide **(1l)***. Pale yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85 (s, 1H), 8.88 – 8.78 (m, 2H), 8.16 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.54 (t, *J* = 7.9 Hz,

1H), 7.51 – 7.47 (m, 1H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 2.53 – 2.47 (m, 1H), 1.83 – 1.75 (m, 2H), 1.59 – 1.52 (m, 2H), 1.47 – 1.38 (m, 4H), 0.94 (t, *J* = 7.3 Hz, 6H).

N-(quinolin-8-yl)pivalamide ***(1m)***. Pale yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.28 (s, 1H), 8.85 – 8.76 (m, 2H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.56 – 7.51 (m, 1H), 7.49 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 1.43 (s, 9H).

N-(quinolin-8-yl)acrylamide ***(1n)***. Yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.86 (dd, *J* = 7.4, 1.5 Hz, 1H), 8.81 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.57 – 7.54 (m, 1H), 7.52 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.53 – 6.48 (m, 2H), 5.83 (dd, *J* = 8.1, 3.4 Hz, 1H).

N-(quinolin-8-yl)cinnamamide ***(1o)***. Pale yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.92 (dd, *J* = 7.5, 1.2 Hz, 1H), 8.85 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.83 (d, *J* = 15.6 Hz, 1H), 7.63 (dd, *J* = 7.7, 1.4 Hz, 2H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.54 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.48 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.44 – 7.37 (m, 3H), 6.82 (d, *J* = 15.5 Hz, 1H).

2-phenyl-N-(quinolin-8-yl)acrylamide ***(1p)***. Brown liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.26 (s, 1H), 8.90 (dd, *J* = 7.5, 1.4 Hz, 1H), 8.64 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.60 – 7.54 (m, 3H), 7.53 – 7.51 (m, 1H), 7.47 – 7.43 (m, 3H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.33 (d, *J* = 0.9 Hz, 1H), 5.84 (d, *J* = 0.9 Hz, 1H).

2-phenyl-N-(quinolin-8-yl)acetamide ***(1q)***. Pale yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.91 (s, 1H), 8.77 (dd, *J* = 7.4, 1.5 Hz, 1H), 8.73 – 8.66 (m, 1H), 8.12 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.53 – 7.50 (m, 1H), 7.48 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.45 (d, *J* = 7.0 Hz, 2H), 7.43 – 7.39 (m, 3H), 7.36 – 7.32 (m, 1H), 3.90 (s, 2H).

N-(quinolin-8-yl)benzamide-2,6-d_2***(2a)***. White solid; yield: 94.4 mg, 95%;^{1}H NMR (500 MHz, $CDCl_3$) δ 10.75 (s, 0.95H), 8.95 (dd, *J* = 7.6 Hz, 1.5Hz, 1H), 8.85 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.19 (dd, *J* = 8.2, 1.5 Hz, 1H), 8.09 (d, *J* = 7.6 Hz, 0.14H), 7.55–7.61 (m, 5H), 7.48 (dd, *J* = 8.2, 4.2 Hz, 1H).

2-methyl-N-(quinolin-8-yl)benzamide-6-d_1***(2b)***.White solid; yield: 99.7 mg, 95%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.22 (s, 0.94H), 8.96 (d, *J* = 7.6 Hz, 0.43H), 8.78 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 0.02H), 7.59 – 7.62 (m, 1H), 7.56 (d, *J* = 8.3 Hz, 0.66H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.35 – 7.31 (m, 2H), 2.62 (s, 3H).

4-methyl-N-(quinolin-8-yl)benzamide-2,6-d_2***(2c)***. White solid; yield: 98.6 mg, 94%;^{1}H NMR (500 MHz, $CDCl_3$) δ 10.72 (s, 1H), 8.94 (d, *J* = 7.6 Hz, 1H), 8.86 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.19 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 0.50H), 7.60 (t, *J* = 7.9 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.48 (m, 1H), 7.35 (s, 2H), 2.46 (s, 3H).

4-methoxy-N-(quinolin-8-yl)benzamide-2,6-d_2***(2d)***. White solid; yield: 104.6 mg, 94%;^{1}H NMR (500 MHz, $CDCl_3$) δ 10.68 (s, 0.95H), 8.93 (d, *J* = 7.5 Hz, 0.70H), 8.86 (d, *J* = 2.8 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 8.7 Hz, 0.04H), 7.63 – 7.57 (m, 1H), 7.53 (d, *J* = 8.1 Hz, 0.78H), 7.49 – 7.47 (m, 1H), 7.05 (s, 2H), 3.90 (s, 3H).

N-(quinolin-8-yl)isonicotinamide-3,5-d_2***(2e)***.Pale yellow solid; yield: 98.7 mg, 99%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.82 (s, 0.95H), 8.91 (dd, *J* = 6.4, 2.5 Hz, 1H), 8.88 – 8.85 (m, 3H), 8.21 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.92 – 7.90 (m, 1.94H), 7.63 – 7.58 (m, 2H), 7.51 (dd, *J* = 8.2, 4.2 Hz, 1H).

N-(quinolin-8-yl)thiophene-3-d_1*-2-carboxamide* ***(2f)***.White solid; 96.6 mg, yield: 95%;^{1}H NMR (500 MHz, $CDCl_3$) δ 10.59 (s, 1H), 8.87 – 8.82 (m, 2H), 8.19 -8.16(m, 1H), 7.84 (d, *J* = 3.5, 0.06H), 7.60-7.55 (m, 1.66H), 7.53 (d, *J* = 8.0, 1H), 7.47 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.18 (d, *J* = 3.6 Hz, 1H).

3-methoxyl- N-(quinolin-8-yl)benzamide ***(2i).***White solid; yield: 104.7 mg, 94%;^{1}H NMR (500 MHz, CDCl3) δ 10.76 (s, 0.92H), 8.96 (dd, *J* = 7.5, 1.3 Hz, 0.92H), 8.87 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.21 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.68 (s, 0.01H), 7.66 (d, *J* = 2.4 Hz, 0.03H), 7.62 (t, *J* = 7.9 Hz, 1H), 7.57 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.53 – 7.45 (m, 2H), 7.15 (d, *J* = 8.3 Hz, 1H), 3.94 (s, 3H).

N-(quinolin-8-yl)propanamide-3,3,3-d_3***(2j)***.Pale yellow liquid; yield: 76.1 mg, 95%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.82 – 8.76 (m, 1.43H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.49 (d, *J* = 8.3, 1H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.58 (s, 2H).

N-(quinolin-8-yl)tetradecanamide-3,3-d_2***(2k)***.White solid;yield: 134.7 mg, 95%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 0.96H), 8.82 – 8.76 (m, 1H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.56 – 7.51 (m, 1H), 7.49 (dd, *J* = 8.3, 1.4 Hz, 0.97H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 0.82H), 2.58 – 2.54 (m, 2H), 1.46 – 1.40 (m, 2H), 1.39 – 1.34 (m, 2H), 1.32 – 1.23 (m, 17H), 0.88 (t, *J* = 7.0 Hz, 3H).

2-(propyl-1,1-d_2*)-N-(quinolin-8-yl)pentanamide-3,3-*d_2***(2l)***. Pale yellow liquid; yield: 103.8 mg, 96%; ^{1}H (500 MHz, $CDCl_3$) δ 9.84 (s, 1H), 8.85 – 8.80 (m, 1H), 8.19 – 8.14 (m, 1H), 7.54 (m, 1H), 7.51 – 7.47 (m, 1H), 7.48 – 7.43 (m, 0.69H), 2.47 (d, *J* = 5.4 Hz, 1H), 1.80 – 1.74 (m, 0.20H), 1.55 – 1.52 (m, 0.26H), 1.41 (q, *J* = 7.4, 7.0 Hz, 4H), 0.94 (t, *J* = 7.3 Hz, 6H).

2,2-bis(methyl-d_3*)-N-(quinolin-8-yl)propanamide-3,3,3-*d_3***(2m)***. Pale yellow liquid; yield: 86.8 mg, 95%; ^{1}H (500 MHz, $CDCl_3$) δ 10.28 (s, 1H), 8.82 – 8.79 (m, 2H), 8.15 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.55 – 7.51 (m, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 1.43 (s, 6H).

N-(quinolin-8-yl)acrylamide-3,3-d_2***(2n)***. Yellow liquid; yield: 75.3 mg, 95%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.86 (dd, *J* = 7.4, 1.5 Hz, 1H), 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.17 – 8.15 (m, 1H), 7.57 – 7.54 (m, 1H), 7.52 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.47 – 7.45 (m, 1H), 6.48 (s, 1H), 5.81 (d, *J* = 10.3 Hz, 0.02H).

N-(quinolin-8-yl)cinnamamide-3-d_1***(2o)***. Pale yellow solid; yield: 103.1 mg, 94%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.92 (dd, *J* = 7.5, 1.1 Hz, 1H), 8.84 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.18 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.83 (d, *J* = 15.5 Hz, 0.02H), 7.64 – 7.60 (m, 2H), 7.58 (dd, *J* = 7.6, 2.9 Hz, 1H), 7.53 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.48 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.44 – 7.39 (m, 3H), 6.82 (d, *J* = 1.9 Hz, 1H).

2-(phenyl-2,6-d_2*)-N-(quinolin-8-yl)acrylamide-3,3-*d_2***(2p)***.Brown liquid; yield: 87.8 mg, 80%; ^{1}H (500 MHz, $CDCl_3$) δ 10.26 (s, 1H), 8.90 (dd, *J* = 7.5, 1.3 Hz, 1H), 8.65 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.59 – 7.55 (m, 1.30H), 7.52 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.47 – 7.42 (m, 3H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.33 (d, *J* = 0.9 Hz, 0.05H), 6.31 (s, 0.20H), 5.84 (d, *J* = 0.8 Hz, 0.05H), 5.82 (s, 0.35H).

2-(phenyl-2,6-d_2)-N-(quinolin-8-yl)acetamide-2,2-d_2 ***(2q)***.Pale yellow solid; yield: 98.6 mg, 94%; ^{1}H (500 MHz, $CDCl_3$) δ 9.91 (s, 1H), 8.77 (dd, *J* = 7.4, 1.5 Hz, 0.03H), 8.73 – 8.66 (m, 1H), 8.12 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.46 – 7.44 (m, 0.08H), 7.46 – 7.44 (m, 3H), 7.43 – 7.39 (m, 1H), 3.90 (s, 1.24H).

Benzoic acid-2,6-d_2 ***(3a)***. White solid; yield: 34.8mg, 95%;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 8.0, 1.0 Hz, 0.14H), 7.65 – 7.61 (m, 1H), 7.50 (t, *J* = 5.6 Hz, 2H).

2-methylbenzoic acid-6-d_1 ***(3b)***. White solid; yield: 38.8 mg, 95%;^{1}H NMR (500 MHz, $CDCl_3$) δ 12.51 (s, 1H), 8.09 (d, 0.02H), 7.49 – 7.45 (m, 1H), 7.32 – 7.28 (m, 2H), 2.68 (s, 3H).

4-methylbenzoic acid-2,6-d_2 ***(3c).*** White solid; yield: 38.8 mg, 95%;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.2 Hz, 0.5H), 7.28 (t, *J* = 6.6 Hz, 2H), 2.44 (s, 3H).

4-methoxylbenzoic acid-2,6-d_2 ***(3d).***White solid; yield: 43.4 mg, 95%;^{1}H NMR (500 MHz, DMSO-d_6) δ 7.87 (d, *J* = 8.8 Hz, 0.04H), 7.00 (s, 2H), 3.81 (s, 3H).

2-(propyl-1,1-d_2)pentanoic acid-3,3-d_2 ***(3e).*** Colorless liquid; yield: 1.17 g, 96%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (d, 1H), 1.62 – 1.57 (m, 0.18H), 1.44-1.41 (m, 0.20H), 1.40 – 1.28 (m, *J* = 6.7 Hz, 4H), 0.91 (t, *J* = 7.3 Hz, 6H).

ASSOCIATED CONTENT

Supporting Information

Supplementary data (copies of ^{1}H NMR and LC-HRMS Spectral spectra for all products).
The Supporting Information is available free of charge on the ACS Publications website.

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