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Hydrogen–Deuterium Exchange Reactions of Aromatic Compounds and Heterocycles by $NaBD_4$-Activated Rhodium, Platinum and Palladium Catalysts

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Abstract: Conventional thermal and microwave conditions were compared for hydrogen–deuterium (H/D) exchange reactions of aminobenzoic acids catalysed by $NaBD_4$-activated Pd/C or $RhCl_3$ with D_2O as the deuterium source. We also investigated different $NaBD_4$-activated metal catalysts (including Pd/C, $RhCl_3$ and Pt/C) under microwave conditions for an efficient H/D exchange of aromatic and heterocyclic compounds. Even higher deuterium incorporations were obtained for Pd/C and Pt/C catalyst mixtures due to the previously observed synergistic effect. Finally, we have applied these optimised conditions for one-step syntheses of the MS standards of several pharmaceutically active compounds.

Keywords: C–H activation · deuterium · hydrogen–deuterium exchange · microwave chemistry

Introduction

The rapid development of tandem mass spectrometry in combination with liquid chromatography (LC-MS/MS) and its widespread application for the investigation of samples originating from environmental, animal and human studies in the life sciences has considerably increased the demand for isotopically labelled internal standards.[1] Usually, internal standards can be prepared with very high isotope abundance starting from commercially available labelled precursors by conventional synthesis. However, hydrogen–deuterium (H/D) exchange can be a cost- and time-efficient alternative approach if it can be carried out directly on the target molecule or an advanced intermediate.[2] On the other hand, disadvantages of H/D exchange include the non-specific labelling of the molecule (mixtures of different isotopomers and isotopologues[3]), leading to isotope clusters and the potential risk of batch-to-batch variations in the composition of these mixtures. Nonetheless, materials with narrow isotope clusters formed by H/D exchange can be fit for use as an internal standard for LC-MS/MS investigations as long as the value of M_0 is negligible and less than 0.5% (to reduce cross-signal overlapping to a minimum) and a representative mass peak is present in the mixture that can be used as the reference mass of the internal standard (see Figure 1). Typically, for small molecules without chlorine, bromine or sulfur-containing functionalities, an incorporation of three to five deuterium atoms is necessary. In spite of recent methodological improvements, H/D exchange still often either leads to an insufficient deuterium incorporation, results in a very broad isotope cluster, or leads to decomposition of the compound. Key requirements for stable labelled internal standards, essential in drug development programs in the pharmaceutical industry, have not been completely addressed and there is still an unmet need for the development of specific H/D exchange methods that provide labelled materials with a narrow isotopologue distribution.[4]

Results and Discussion

Based on pioneering work by Sajiki et al.,[5] we have recently developed a safe and efficient H/D exchange method with hydride-activated Pd and Rh catalysts and D_2O as the deuterium source.[6] Compared with existing heterogeneous transition-metal-catalysed H/D exchange methods, a small but significant practical improvement is the avoidance of

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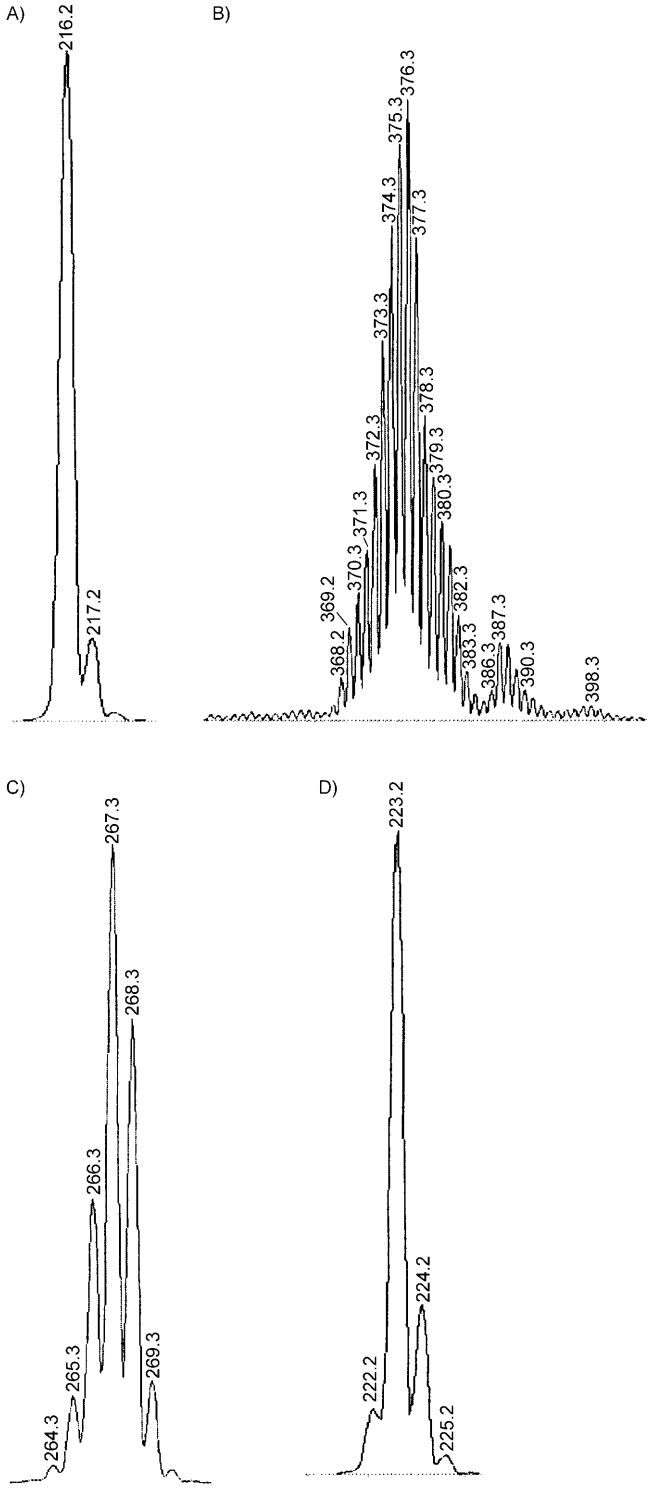
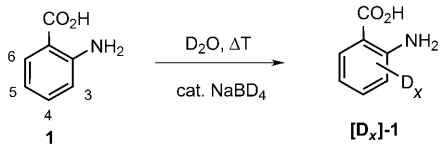


Figure 1. A) Natural MS isotope distribution of a hydrocarbon. B) Broad isotope cluster after an unselective H/D exchange. C) Moderately broad isotope cluster with a representative mass peak. D) MS isotope distribution after a highly selective H/D exchange.

gaseous reaction components, which allows safe and easy handling and the utilisation of automated high-throughput devices or microwave instruments. Initial trials in our laboratory have already suggested a higher efficiency of the deuterium incorporation under microwave conditions, but a systematic investigation has not yet been conducted. To compare conventional thermal and microwave conditions (Table 1) and to gain more insights into the scope and limitations of this reaction, we initiated studies using $NaBD_4$-activated Pd/C and $RhCl_3$ catalysts for the H/D exchange of aminobenzoic acids **1** and **2**. Besides an improved efficiency in deuterium uptake, the selective formation of products with the required small mass distribution pattern for internal standard synthesis was of particular interest (see Figure 1).

Table 1. Deuteration of 2-aminobenzoic acid (**1**) under thermal and microwave heating conditions.



1 [Dx]-1

Entry	Cat.	T [°C]	t [h]	Yield [%]	%D[a] C3	C4	C5	C6	D_{max}[b]
1	Pd/C	150	2	61	76	78	86	0	D_3
2	Pd/C	150, mw	2	46	95	93	92	0	D_3
3	$RhCl_3$	150	2	42	24	0	24	0	D_0
4	$RhCl_3$	150, mw	2	31	93	0	95	0	D_2

[a] Measured by ^{1}H NMR spectroscopy. [b] Measured by LC-MS.

To this end, we have performed H/D exchange reactions with $NaBD_4$-activated palladium and rhodium catalysts under classical heating conditions and under microwave conditions (at 150 °C for 2 h). In both cases, an incorporation of up to three deuterium atoms was observed for **1** with Pd/C (Table 1, entries 1 and 2), but the H/D exchange under thermal conditions was less specific, leading to a broader isotope cluster. Compared with classical heating, an even higher deuterium efficiency under microwave conditions was observed for the $RhCl_3$-catalysed H/D exchange of the same substrate (Table 1, entries 3 and 4).[7] Interestingly, only the protons at C3 and C5 were exchanged selectively, whereas with the Pd/C catalyst high deuterium incorporation was also obtained at the C4 position. Similarly, a higher deuterium uptake under microwave conditions was observed for **2** (Table 2, entries 2 and 4), although with $RhCl_3$ this effect

Table 2. Deuteration of 3-aminobenzoic acid (**2**) under thermal and microwave heating conditions.

2 [Dx]-2

Entry	Cat.	T [°C]	t [h]	Yield [%]	%D[a] C2	C4	C5	C6	D_{max}[b]
1	Pd/C	150	2	61	88	76	45	11	D_2
2	Pd/C	150°C, mw	2 h	57	97	96	95	53	D_4
3	$RhCl_3$	150	2	65	92	93	89	12	D_3
4	$RhCl_3$	150, mw	2	67	91	92	88	12	D_3

[a] Measured by ^{1}H NMR spectroscopy. [b] Measured by LC-MS.

was less pronounced. Again, the deuterium incorporation was considerably higher at sites *ortho* to amino groups than *ortho* to a carboxyl function. Thus, we concluded that the kinetics and equilibria of the H/D exchange reaction at each carbon atom are largely controlled by electronic factors.

From an industrial perspective, microwave systems are simple to handle, safe and also provide the option of a better process automation and standardisation. Due to the higher and even more specific deuterium incorporation observed, we decided to use microwave conditions (150 °C, 2 h) as the standard reaction procedure for all further investigations. To understand more about the selectivity of the pre-activated catalysts we further examined *para*-substituted anilines for H/D exchange (Table 3). Two general trends were observed. Firstly, the electronic influence of amino or substituted amino groups on the H/D exchange of *ortho*-positions of compounds **3**–**9** was particularly pronounced. In comparison with other functional groups present, the deuterium uptake at these positions was considerably higher. Secondly, $RhCl_3$ usually gave slightly higher deuterium incorporations at aromatic centres (Table 3, entries 2, 8, 12 and 14), but, in contrast to Pd/C, was almost ineffective for the H/D exchange of aliphatic protons (Table 3; entries 12 and 13). In almost all experiments (Table 3), the H/D exchange reactions afforded only a small number of isotopologues, one of which being the most abundant. In the mass spectra this was reflected by a narrow-to-moderate mass distribution pattern and one major mass peak.

Next, we studied palladium and rhodium catalysts in the H/D exchange of substituted pyridines (Table 4), which are common structural fragments of pharmaceutical drugs. 3-Aminopyridine (**10**) was completely deuterated by using Pd/C as catalyst (Table 4, entry 1) in moderate yield. Although only very narrow mass spectrometric distribution patterns were observed for pyridines **10** and **12**, pyridines **11** and **13** gave broader clusters, as a result of incomplete H/D exchange of both aromatic and aliphatic protons. Pd/C gave much better results than $RhCl_3$ in terms of higher deuterium incorporation. Except for pyridine **11**, for which it might be difficult to assign a representative mass spectrometric peak as a reference mass, all other pyridines **10**, **12** and **13** could be employed as deuterated precursors for the synthesis of more complex stable isotope-labelled internal MS standards.

In the course of ongoing pharmaceutical development programs, a series of deuterated hetero- and bicyclic compounds (Table 5) were required as precursors for the synthesis of stable isotope-labelled internal standards. Almost quantitative deuterium incorporations and very small isotopic clusters were obtained for **14**, **16** and **19** by applying Pd/C-catalysed H/D exchange under standard microwave conditions (Table 5). In contrast, the deuterium uptake for electron-poor aromatic heterocycles was not sufficient to use these materials as precursors for an internal standard synthesis. Compared with the Pd/C-catalysed exchange, deuterium uptake catalysed by $RhCl_3$ was generally lower. Although not very efficient in our initial trials,[6] Pt/C was found to be highly active in Sajiki's H/D exchange protocol[8] especially towards aromatic hydrogen atoms. Moreover, Sajiki also reported a synergistic effect when mixing Pd/C and Pt/C together,

Table 3. H/D-exchange reaction of *para*-substituted anilines **3**–**9** under microwave conditions (cat. $NaBD_4$, 150 °C, 2 h, sealed vial) in deuterium oxide.

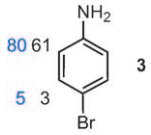
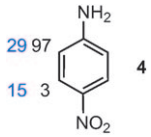
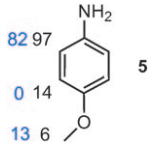
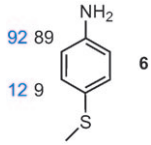
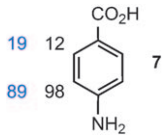
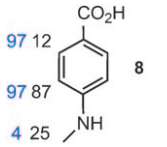
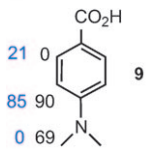
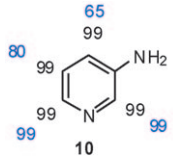
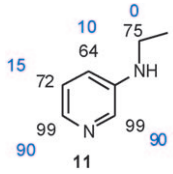
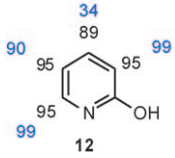
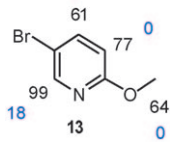
Entry	Product	Cat.	Yield [%]	%D_x						
				D_0	D_1	D_2	D_3	D_4		
1		Pd/C	50	15	44	39	2	0		
2	**3**	$RhCl_3$	33	0	22	72	3	0		
				D_0	D_1	D_2	D_3	D_4		
3		Pd/C	63	0	3	90	6	0		
4	**4**	$RhCl_3$	74	33	48	19	0	0		
				D_0	D_1	D_2	D_3	D_4		
5		Pd/C	30	0	2	58	32	8		
6	**5**	$RhCl_3$	51	0	15	77	8	0		
				D_0	D_1	D_2	D_3	D_4		
7		Pd/C	80	0	3	86	8	3		
8	**6**	$RhCl_3$	72	0	4	89	8	0		
				D_0	D_1	D_2	D_3	D_4		
9		Pd/C	72	0	3	79	17	2		
10	**7**	$RhCl_3$	44	1	6	64	23	6		
				D_0	D_1	D_2	D_3	D_4	D_5	D_6
11		Pd/C	67	1	19	67	11	1	0	0
12	**8**	$RhCl_3$	57	0	0	1	8	75	16	0
				D_0	D_1	D_2	D_3	D_4	D_5	D_6
13		Pd/C	29	0	0	3	7	13	21	25
14	**9**	$RhCl_3$	45	4	9	77	8	0	0	0

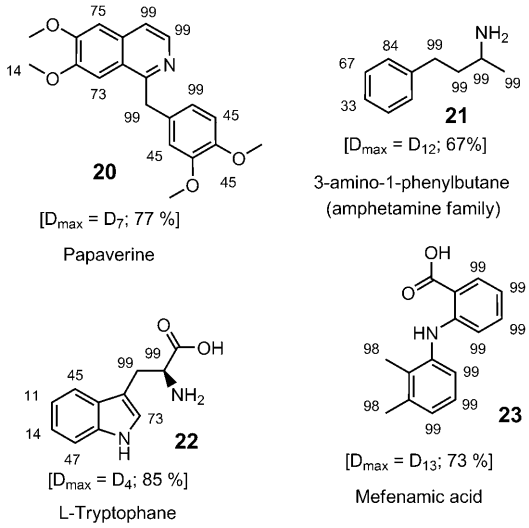
Table 4. H/D-exchange reaction of substituted pyridines **10–13** under microwave conditions (cat. $NaBD_4$, 150 °C, 2 h, sealed vial) in deuterium oxide.

Entry	Product	Cat.	Yield [%]	%D_x						
				D_0	D_1	D_2	D_3	D_4		
1		Pd/C	50	0	0	0	1	99		
2	**10**	$RhCl_3$	61	0	0	0	15	85		
				D_0	D_1	D_2	D_3	D_4	D_5	D_6
3		Pd/C	44	0	0	0	8	36	38	15
4	**11**	$RhCl_3$	68	3	19	58	16	4	0	0
				D_0	D_1	D_2	D_3	D_4		
5		Pd/C	64	0	0	0	9	91		
6	**12**	$RhCl_3$	87	0	0	4	75	21		
				D_0	D_1	D_2	D_3	D_4	D_5	D_6
7		Pd/C	48	0	0	4	21	39	26	10
8	**13**	$RhCl_3$	30	91	9	0	0	0	0	0

Pd/Pt/C-catalysed H/D exchange of **20**, a phosphodiesterase inhibitor that was frequently used for treatment of erectile dysfunction prior to the introduction of Viagra, yielded an internal MS standard with seven additional mass units as the major isotopologue. Under the same reaction conditions, both **21** (a compound of the amphetamine family) and **22** (a second-generation antidepressant agent) were sufficiently deuterated to obtain MS standards (for example, for doping tests). Finally, the H/D exchange reaction of **23**, a non-steroidal anti-inflammatory agent that is applied for treatment of rheumatoid arthritis, yielded a convenient MS standard (major isotopologue M_0+13) in one single reaction step.[10]

resulting in higher deuterium incorporations compared with those obtained with a single catalyst.[9] To increase the deuterium efficiency, especially for electron-poor heterocycles, we decided to test Pt/C in single runs and also in combination with Pd/C under microwave conditions. In fact, the mixture of Pd/Pt/C yielded, in most cases, a significantly higher deuterium uptake under the same reaction conditions (Table 5, entries 4, 8, 12 and 16).

For quinoline **14**, an almost complete deuteration was achieved by using the Pd/Pt/C catalyst mixture, and in contrast to Pd/C alone (Table 5, entry 1), a representative peak at $M+9$ could also be identified (Table 5, entry 4). An even more significant synergistic effect could be observed for **15** (Table 5, entry 8), **16** (Table 5, entry 12) and **17** (Table 5, entry 16). In all cases, the poor deuterium incorporation obtained with Pd/C, Pt/C or $RhCl_3$ could be increased by using the Pd/Pt/C catalyst mixture, resulting in the formation of the required stable labelled precursors with a narrow mass distribution. In contrast, no further improvement was observed for furan **18** and triazole **19** using the Pd/Pt/C mixture (Table 5, entries 20 and 24) than with Pd/C alone (Table 5, entries 17 and 21). For all hetero- and bicyclic compounds investigated, $RhCl_3$ and Pt/C alone resulted in only limited deuterium incorporations, whereas Pd/C often yielded acceptable results. However, because generally the best results were obtained with the mixture of Pd/C and Pt/C, we have further applied this catalyst system for the preparation of the required internal MS standards of several pharmaceutically active compounds by H/D exchange of the drug material itself (Scheme 1).

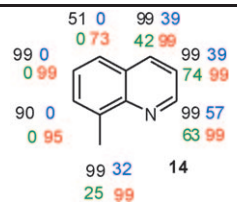
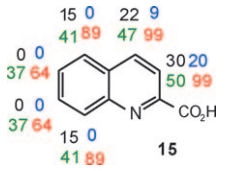
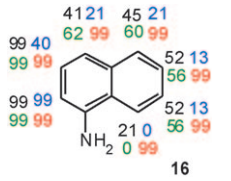
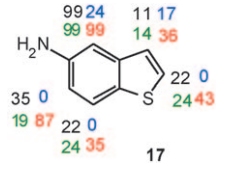
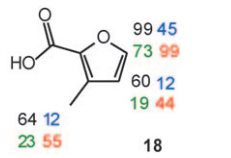
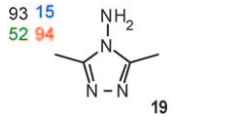


Scheme 1. H/D exchange of pharmaceutically active compounds by using $NaBD_4$-activated Pd/Pt/C as catalyst in D_2O.

Conclusion

We have demonstrated that microwave-enhanced $NaBD_4$-activated metal-catalysed H/D exchange is a useful synthetic method that allows access to a variety of stable isotopically labelled compounds. Initially, activated Pd/C proved to be the most efficient catalyst for the deuteration of several aromatic and heterocyclic compounds, but even better results were obtained for Pd/C and Pt/C catalyst mixtures due to an

Table 5. H/D-exchange reaction of substituted quinolines **14** and **15**, aminonaphthalene **16**, benzothiophene **17**, furan **18** and triazole **19** under microwave conditions (cat. $NaBD_4$, 150 °C, 2 h, sealed vial) in deuterium oxide.

Entry	Product	Cat.	Yield [%]	%D_x								
				D_0	D_1	D_2	D_3	D_4	…	D_7	D_8	D_9
1		Pd/C	86	0	0	0	0	0		5	47	48
2		$RhCl_3$	75	54	33	10	3	0		0	0	0
3		Pt/C	53	18	29	25	17	8		0	0	0
4		Pd/Pt/C	46	0	0	0	0	0		6	29	59
	14											
				D_0	D_1	D_2	D_3	D_4	D_5	D_6		
5		Pd/C	86	48	35	14	3	0	0	0		
6		$RhCl_3$	75	89	11	0	0	0	0	0		
7		Pt/C	53	7	25	32	22	11	3	0		
8		Pd/Pt/C	46	0	0	0	3	14	35	43		
	15											
				D_0	D_1	D_2	D_3	D_4	D_5	D_6	D_7	
9		Pd/C	52	0	0	0	0	0	15	54	31	
10		$RhCl_3$	44	0	0	55	25	11	6	3	0	
11		Pt/C	84	0	0	10	22	29	26	11	2	
12		Pd/Pt/C	86	0	0	0	0	0	0	11	80	
	16											
				D_0	D_1	D_2	D_3	D_4				
13		Pd/C	95	0	50	40	8	2				
14		$RhCl_3$	91	76	19	5	0	0				
15		Pt/C	82	4	60	28	6	2				
16		Pd/Pt/C	91	4	60	28	6	2				
	17											
				D_0	D_1	D_2	D_3	D_4	D_5			
17		Pd/C	96	0	7	19	31	29	14			
18		$RhCl_3$	95	53	32	6	8	0	0			
19		Pt/C	91	39	39	11	11	0	0			
20		Pd/Pt/C	91	0	24	43	21	8	4			
	18											
				D_0	D_1	D_2	D_3	D_4	D_5	D_6	D_7	
21		Pd/C	95	0	0	0	0	0	11	80	9	
22		$RhCl_3$	97	70	23	5	2	0	0	0	0	
23		Pt/C	98	24	26	18	15	8	5	3		
24		Pd/Pt/C	91	0	0	0	0	0	10	79	11	
	19											

observed synergistic effect. These conditions were successfully applied in a one-step deuteration of complex molecules and pharmaceutically active compounds to give products with a very narrow isotopologue distribution, which proved to be applicable as deuterated MS standards.

Experimental Section

General methods: ^1H (300, 500 MHz) and ^{13}C (75, 125 MHz) NMR spectra were obtained on Bruker spectrometers Avance 300 and 500 in the solvents indicated. Column chromatography was carried out by using Merck kieselgel 60 silica gel (particle size: 63–200). The purity of the products was determined by an LC-MS system with a symmetry Shield RP18 column, 3,9*150 mm with gradient program; conditions: mobile phase: A: water (900 mL), acetonitrile (100 mL), trifluoroacetic acid (TFA) (1 mL) mobile phase B: water (100 mL), acetonitrile (900 mL), TFA (0.75 mL), flow 0.6 mL min^{-1}, detection UV 254 nm and UV 210 nm. Commercially available chemicals and solvents were used as received. Deuterated water (D_2O) was purchased from Aldrich. Dry Pd/C (10% on charcoal; AB121364) was purchased from Degussa (lot 1022260). Depending on the batch or supplier of the catalyst, significant changes in catalyst reactivity were observed. Dry Pt/C was purchased from Hereaus (MP 60/04 Cat Box; batch K0101). The percentage of deuteration at each CH position was determined by using tartaric acid as an internal standard in ^1H NMR spectroscopy experiments.

Typical thermal reaction conditions: A pressure tube filled with argon was charged with the organic compound (1.00 mmol), catalyst (10 wt%), $NaBD_4$ (5 mol%; 98% D), and D_2O (6 mL; 99% D). The tube was sealed and put into an oil bath and heated at 150 °C for 2 h under stirring. The mixture was cooled to room temperature and acetonitrile (3 mL) was added. The catalyst was separated by filtration and the product was isolated by lyophilisation. Purification (if necessary) was performed by column chromatography and the compounds were analysed by ^1H NMR spectroscopy and LC-MS.

[D]-1: a) 85 mg (0.61 mmol, 61%) colourless solid; cat. Pd/C; ^1H NMR (300 MHz, DMSO): δ=12.43 (brs, 1H; CO_2H), 7.68 (d, J=8.5 Hz, 1H; 3-H, 24% H), 7.61 (dd, J=8.5, 8.3 Hz, 1H; 5-H, 14% H), 7.31 (dd, J=8.5, 8.3 Hz, 1H; 4-H, 22% H), 6.90 (d, J=8.3 Hz, 1H; 6-H, 100% H), 5.58 ppm (brs, 2H; NH_2); LC-MS (ESI): m/z (%): 138 (1) $[M_0+H]^+$, 139 (11), 140 (36), 141 (46), 142 (5); purity (UV, 254 nm) 97%. b) 58 mg (0.42 mmol, 42%) colourless solid; cat. $RhCl_3$; ^1H NMR (300 MHz, DMSO): δ=12.38 (brs, 1H; CO_2H), 7.68 (d, J=8.5 Hz, 1H; 3-H, 76% H), 7.61 (dd, J=8.5, 8.3 Hz, 1H; 5-H, 76% H), 7.31 (dd, J=8.5, 8.3 Hz, 1H; 4-H, 100% H), 6.90 (d, J=8.3 Hz, 1H; 6-H, 100% H), 5.58 ppm (brs, 2H; NH_2); LC-MS (ESI): m/z (%): 138 (47) $[M_0+H]^+$, 139 (41), 140 (10), 141 (2); purity (UV, 254 nm) 91%.

[D]-2: a) 84 mg (0.61 mmol, 61%) colourless solid; cat. Pd/C; ^1H NMR (300 MHz, DMSO): δ=12.14 (brs, 1H; CO_2H), 8.03 (s, 1H; 2-H, 12% H), 7.91 (d, J=8.5 Hz, 1H; 6-H, 89% H), 7.45 (dd, J=8.5, 8.3 Hz, 1H; 5-H, 55% H), 6.91 (d, J=8.5 Hz, 1H; 4-H, 14% H), 5.58 ppm (brs, 2H; NH_2); LC-MS (ESI): m/z (%): 138 (3) $[M_0+H]^+$, 139 (26), 140 (42), 141 (23), 142 (6); purity (UV, 254 nm) 96%; b) 89 mg (0.65 mmol, 65%) colourless solid; cat. $RhCl_3$; ^1H NMR (300 MHz, DMSO): δ=12.14 (brs, 1H; CO_2H), 8.03 (s, 1H; 2-H, 8% H), 7.91 (d, J=8.5 Hz, 1H; 6-H, 88% H), 7.45 (dd, J=8.5, 8.3 Hz, 1H; 5-H, 11% H), 6.91 (d, J=8.5 Hz, 1H; 4-H, 7% H), 5.58 ppm (brs, 2H; NH_2); LC-MS (ESI): m/z (%): 138 (0) $[M_0+H]^+$, 139 (9), 140 (38), 141 (43), 142 (10); purity (UV, 254 nm) 91%.

Typical microwave reaction conditions: A pressure tube filled with argon was charged with the organic compound (1.00 mmol), catalyst (10 wt%), $NaBD_4$ (5 mol%; 98% D) and D_2O (6 mL; 99% D). The mixture was stirred for approximately 30 s and the tube was sealed (note: the reaction vessel was not closed until effervescence had stopped) and heated at 150 °C for 2 h. The mixture was cooled to room temperature and acetonitrile (3 mL) was added. The catalyst was separated by filtration and the product was isolated by lyophilisation. Purification (if necessary) was performed by chromatography and the compounds analysed by ^{1}H NMR spectroscopy and LC-MS.

[D]-1: a) 63 mg (0.46 mmol, 46%) colourless solid; cat. Pd/C; ^{1}H NMR (300 MHz, DMSO): δ=12.43 (brs, 1H; CO_2H), 7.68 (d, J=8.5 Hz, 1H; 3-H, 5% H), 7.61 (dd, J=8.5, 8.3 Hz, 1H; 5-H, 8% H), 7.31 (dd, J=8.5, 8.3 Hz, 1H; 4-H, 7% H), 6.90 (d, J=8.3 Hz, 1H; 6-H, 100% H), 5.58 ppm (brs, 2H; NH_2); LC-MS (ESI): m/z (%): 138 (0) $[M_0+H]^+$, 139 (1), 140 (14), 141 (77), 142 (8); purity (UV, 254 nm) 94%; b) 43 mg (0.31 mmol, 31%) colourless solid; cat. $RhCl_3$; ^{1}H NMR (300 MHz, DMSO): δ=12.43 (brs, 1H; CO_2H), 7.68 (d, J=8.5 Hz, 1H; 3-H, 7% H), 7.61 (dd, J=8.5, 8.3 Hz, 1H; 5-H, 5% H), 7.31 (dd, J=8.5, 8.3 Hz, 1H; 4-H, 100% H), 6.90 (d, J=8.3 Hz, 1H; 6-H, 100% H), 5.58 ppm (brs, 2H; NH_2); LC-MS (ESI): m/z (%): 138 (1) $[M_0+H]^+$, 139 (11), 140 (79), 141 (8), 142 (1); purity (UV, 254 nm) 91%.

[D]-2: a) 78 mg (0.57 mmol, 57%) colourless solid; cat. Pd/C; ^{1}H NMR (300 MHz, DMSO): δ=12.14 (brs, 1H; CO_2H), 8.03 (s, 1H; 2-H, 3% H), 7.91 (d, J=8.5 Hz, 1H; 6-H, 47% H), 7.45 (dd, J=8.5, 8.3 Hz, 1H; 5-H, 5% H), 6.91 (d, J=8.5 Hz, 1H; 4-H, 4% H), 5.58 ppm (brs, 2H; NH_2); LC-MS (ESI): m/z (%): 138 (0) $[M_0+H]^+$, 139 (1), 140 (9), 141 (38), 142 (53); purity (UV, 254 nm) 95%; b) 91 mg (0.67 mmol, 67%) colourless solid; cat. $RhCl_3$; ^{1}H NMR (300 MHz, DMSO): δ=12.14 (brs, 1H; CO_2H), 8.03 (s, 1H; 2-H, 9% H), 7.91 (d, J=8.5 Hz, 1H; 6-H, 89% H), 7.45 (dd, J=8.5, 8.3 Hz, 1H; 5-H, 12% H), 6.91 (d, J=8.5 Hz, 1H; 4-H, 8% H), 5.58 ppm (brs, 2H; NH_2); LC-MS (ESI): m/z (%): 138 (1) $[M_0+H]^+$, 139 (2), 140 (20), 141 (68), 142 (9), purity (UV, 254 nm) 87%.

[D]-3: a) 87 mg (0.50 mmol, 50%) colourless oil; cat. Pd/C; ^{1}H NMR (300 MHz, DMSO): δ=7.22 (d, J=8.3 Hz, 2H; 2-H, 97% H), 6.74 ppm (d, J=8.3 Hz, 2H; 3-H, 39% H); LC-MS (ESI): m/z (%): 173 (15) $[M_0+H]^+$, 174 (44), 175 (39), 176 (2); purity (UV, 254 nm) 98%; b) 57 mg (0.33 mmol, 33%) colourless oil; cat. $RhCl_3$; ^{1}H NMR (300 MHz, DMSO): δ=7.22 (d, J=8.3 Hz, 2H; 2-H, 95% H), 6.74 ppm (d, J=8.3 Hz, 2H; 3-H, 20% H); LC-MS (ESI): m/z (%): 173 (3) $[M_0+H]^+$, 174 (22), 175 (72), 176 (3); purity (UV, 254 nm) 94%.

[D]-4: a) 88 mg (0.63 mmol, 63%) yellow oil; cat. Pd/C; ^{1}H NMR (300 MHz, DMSO): δ=8.08 (d, J=7.9 Hz, 2H; 2-H, 97% H), 6.91 ppm (d, J=7.9 Hz, 2H; 3-H, 3% H); LC-MS (ESI) m/z (%): 139 (0) $[M_0+H]^+$, 140 (3), 141 (90), 142 (6); purity (UV, 254 nm) 97%; b) 103 mg (0.74 mmol, 74%) yellow oil; cat. $RhCl_3$; ^{1}H NMR (300 MHz, DMSO): δ=8.08 (d, J=7.9 Hz, 2H; 2-H, 85% H), 6.91 ppm (d, J=7.9 Hz, 2H; 3-H, 71% H); LC-MS (ESI): m/z (%): 139 (33) $[M_0+H]^+$, 140 (48), 141 (19); purity (UV, 254 nm) 91%.

[D]-5: a) 38 mg (0.30 mmol, 30%) yellow oil; cat. Pd/C; ^{1}H NMR (300 MHz, DMSO): δ=6.92 (d, J=8.8 Hz, 2H; 2-H, 86% H), 6.76 (d, J=8.8 Hz, 2H; 3-H, 3% H), 3.73 ppm (s, 3H; CH_3); LC-MS (ESI): m/z (%): 124 (0) $[M_0+H]^+$, 125 (2), 126 (58), 127 (32), 128 (8); purity (UV, 254 nm) 96%; b) 64 mg (0.51 mmol, 51%) yellow oil; cat. $RhCl_3$; (^{1}H NMR (300 MHz, DMSO): δ=6.92 (d, J=8.8 Hz, 2H; 2-H, 100% H), 6.76 (d, J=8.8 Hz, 2H; 3-H, 13% H), 3.73 ppm (s, 3H; CH_3); LC-MS (ESI): m/z (%): 124 (0) $[M_0+H]^+$, 125 (15), 126 (77), 127 (8); purity (UV, 254 nm) 96%.

[D]-6: a) 113 mg (0.80 mmol, 80%) yellow oil; cat. Pd/C; ^{1}H NMR (300 MHz, DMSO): δ=7.09 (d, J=8.3 Hz, 2H; 2-H, 81% H), 6.66 (d, J=8.3 Hz, 2H; 3-H, 11% H), 2.45 ppm (s, 3H; CH_3); LC-MS (ESI): m/z (%): 140 (0) $[M_0+H]^+$, 141 (3), 142 (86), 143 (8), 144 (3); purity (UV, 254 nm) 97%; b) 102 mg (0.72 mmol, 72%) yellow oil; cat. $RhCl_3$; ^{1}H NMR (300 MHz, DMSO): δ=7.09 (d, J=8.3 Hz, 2H; 2-H, 88% H), 6.66 (d, J=8.3 Hz, 2H; 3-H, 8% H), 2.45 ppm (s, 3H; CH_3); LC-MS (ESI): m/z (%): 140 (0) $[M_0+H]^+$, 141 (4), 142 (89), 143 (8); purity (UV, 254 nm) 95%.

[D]-7: a) 100 mg (0.72 mmol, 72%) colourless solid; cat. Pd/C; ^{1}H NMR (300 MHz, DMSO): δ=12.32 (brs, 1H; CO_2H), 7.72 (d, J=8.5 Hz, 2H; 2-H, 88% H), 6.90 (d, J=8.5 Hz, 2H; 3-H, 2% H), 5.61 ppm (brs, 2H; NH_2); LC-MS (ESI): m/z (%): 138 (0) $[M_0+H]^+$, 139 (3), 140 (79), 141 (17), 142 (2); purity (UV, 254 nm) 92%; b) 61 mg (0.44 mmol, 44%) colourless solid; cat. $RhCl_3$; ^{1}H NMR (300 MHz, DMSO): δ=12.32 (brs, 1H; CO_2H), 7.72 (d, J=8.5 Hz, 2H; 2-H, 81% H), 6.90 (d, J=8.5 Hz, 2H; 3-H, 11% H), 5.61 ppm (brs, 2H; NH_2); LC-MS (ESI): m/z (%): 138 (1) $[M_0+H]^+$, 139 (6), 140 (64), 141 (23), 142 (6); purity (UV, 254 nm) 94%.

[D]-8: a) 103 mg (0.67 mmol, 67%) colourless solid; cat. Pd/C; ^{1}H NMR (300 MHz, DMSO): δ=12.11 (brs, 1H; CO_2H), 7.78 (d, J=8.8 Hz, 2H; 2-H, 88% H), 6.90 (d, J=8.8 Hz, 2H; 3-H, 13% H), 2.65 ppm (s, 3H; CH_3, 75% H); LC-MS (ESI): m/z (%): 152 (1) $[M_0+H]^+$, 153 (19), 154 (67), 155 (11); purity (UV, 254 nm) 93%; b) 88 mg (0.57 mmol, 57%) colourless solid; cat. $RhCl_3$; ^{1}H NMR (300 MHz, DMSO): δ=12.11 (brs, 1H; CO_2H), 7.78 (d, J=8.8 Hz, 2H; 2-H, 3% H), 6.90 (d, J=8.8 Hz, 2H; 3-H, 3% H), 2.65 ppm (s, 3H; CH_3, 96% H); LC-MS (ESI): m/z (%): 154 (1), 155 (8), 156 (75), 157 (16); purity (UV, 254 nm) 94%.

[D]-9: a) 50 mg (0.29 mmol, 29%) colourless solid; cat. Pd/C; ^{1}H NMR (300 MHz, DMSO): δ=12.11 (brs, 1H; CO_2H), 7.77 (d, J=7.6 Hz, 2H; 3-H, 10% H), 6.70 (d, J=7.6 Hz, 2H; 2-H, 100% H), 2.98 ppm (s, 6H; CH_3, 31% H); LC-MS (ESI): m/z (%): 166 (0) $[M_0+H]^+$, 169 (7), 170 (13), 171 (21), 172 (25); purity (UV, 254 nm) 97%; b) 76 mg (0.45 mmol, 45%) colourless solid; cat. $RhCl_3$; ^{1}H NMR (300 MHz, DMSO): δ=12.11 (brs, 1H; CO_2H), 7.77 (d, J=7.6 Hz, 2H; 3-H, 15% H), 6.70 (d, J=7.6 Hz, 2H; 2-H, 79% H), 2.98 ppm (s, 6H; CH_3, 100% H); LC-MS (ESI): m/z (%): 166 (4) $[M_0+H]^+$, 167 (9), 168 (77), 169 (8); purity (UV, 254 nm) 90%.

[D]-10 x **HCl**: a) Addition of 2 N HCl (3 mL) to the filtrate, 65 mg (0.50 mmol, 50%) brown solid; cat. Pd/C; ^{1}H NMR (300 MHz, DMSO): δ=7.91 (s, 1H; 2-H, 1% H), 7.82 (d, J=6.9 Hz, 1H; 6-H, 1% H), 6.99 (dd, J=6.9, 6.9 Hz, 1H; 5-H, 1% H), 6.85 (d, J=6.9 Hz, 1H; 4-H, 1% H), 5.30 ppm (brs, 2H; NH_2); LC-MS (ESI): m/z (%): 95 (0) $[M_0+H]^+$, 98 (1), 99 (99); purity (UV, 254 nm) 97%; b) addition of 3 mL 2 N HCl to the filtrate, 80 mg (0.61 mmol, 61%) brown solid; cat. $RhCl_3$; ^{1}H NMR (300 MHz, DMSO): δ=7.91 (s, 1H; 2-H, 1% H), 7.82 (d, J=6.9 Hz, 1H; 6-H, 1% H), 6.99 (dd, J=6.9, 6.9 Hz, 1H; 5-H, 20% H), 6.85 (d, 1H; 6.9 Hz, 4-H, 35% H), 5.30 ppm (brs, 2H; NH_2); LC-MS (ESI): m/z (%): 95 (0) $[M_0+H]^+$, 98 (15), 99 (85); purity (UV, 254 nm) 97%.

[D]-11: a) 54 mg (0.44 mmol, 44%) brown oil; cat. Pd/C; ^{1}H NMR (300 MHz, DMSO): δ=8.25–8.19 (m, 2H; 2-H, 6-H, 1% H), 7.45 (dd, J=6.9, 6.9 Hz, 1H; 5-H, 18% H), 7.09 (d, J=6.9 Hz, 1H; 4-H, 36% H), 2.55 (q, J=5.3 Hz, 2H; CH_2CH$_3$ 25% H), 2.41 ppm (t, J=5.3 Hz, 3H; CH$_2$CH_3 100% H); LC-MS (ESI): m/z (%): 123 (0) $[M_0+H]^+$, 126 (8), 127 (36), 128 (38), 129 (15); purity (UV, 254 nm) 89% b) 83 mg (0.68 mmol, 68%) brown oil; cat. $RhCl_3$; ^{1}H NMR (300 MHz, DMSO): δ=8.25–8.19 (m, 2H; 2-H, 6-H, 10% H), 7.45 (dd, J=6.9, 6.9 Hz, 1H; 5-H, 85% H), 7.09 (d, J=6.9 Hz, 1H; 4-H, 90% H), 2.55 (q, J=5.3 Hz, 2H; CH_2CH$_3$, 100% H), 2.41 ppm (t, J=5.3 Hz, 3H; CH$_2$CH_3 100% H); LC-MS (ESI): m/z (%): 123 (3) $[M_0+H]^+$, 124 (19), 125 (58), 126 (16), 127 (4); purity (UV, 254 nm) 94%.

[D]-12·*x*HCl: a) Addition of 2 N HCl (3 mL) to the filtrate, 84 mg (0.64 mmol, 64%) colourless solid; cat. Pd/C; ^{1}H NMR (300 MHz, DMSO): δ=9.80 (brs, 1H; OH), 8.15 (d, J=6.0 Hz, 1H; 3-H, 5% H), 8.11 (d, J=5.9 Hz, 6-H, 1H; 5% H), 7.23–7.06 ppm (m, 2H; 4-H 11% H, 5-H 5% H); LC-MS (ESI): m/z (%): 96 (0) $[M_0+H]^+$, 99 (9), 100 (91); purity (UV, 254 nm) 96%; b) Addition of 3 mL 2 N HCl to the filtrate, 114 mg (0.87 mmol, 87%) colourless solid; cat. $RhCl_3$; ^{1}H NMR (300 MHz, DMSO): δ=9.80 (brs, 1H; OH), 8.15 (d, J=6.0 Hz, 1H; 3-H, 1% H), 8.11 (d, J=5.9 Hz, 1H; 6-H, 1% H), 7.23–7.06 ppm (m, 2H; 4-H 65% H, 5-H 10% H); LC-MS (ESI): m/z (%): 96 (0) $[M_0+H]^+$, 98 (4), 99 (75), 100 (21); purity (UV, 254 nm) 96%.

[D]-13: a) 90 mg (0.48 mmol, 48%) colourless oil; cat. Pd/C; ^{1}H NMR (300 MHz, DMSO): δ=8.25 (s, 1H; 6-H, 1% H), 7.89 (d, J=6.8 Hz, 1H; 4-H, 39% H), 6.82 (d, J=6.8 Hz, 1H; 3-H, 23% H), 3.87 ppm (s, 3H; OMe, 36% H); LC-MS (ESI): m/z (%): 189 (0) $[M_0+H]^+$, 191 (4), 192 (21), 193 (39), 194 (26), 195 (10); purity (UV, 254 nm) 97% b) 56 mg

(0.30 mmol, 30%) colourless oil; cat. $RhCl_3$; ^1H NMR (300 MHz, DMSO): $\delta = 8.25$ (s, 1H; 6-H, 72% H), 7.89 (d, $J = 6.8$ Hz, 1H; 4-H, 100% H), 6.82 (d, $J = 6.8$ Hz, 1H; 3-H, 100% H), 3.87 ppm (s, 3H; OMe, 100% H); LC-MS (ESI): m/z (%): 96 (91) $[M_0+H]^+$, 97 (9); purity (UV, 254 nm) 98%.

[D]-14: a) 123 mg (0.86 mmol, 86%) yellow solid; cat. Pd/C; ^1H NMR (300 MHz, DMSO): $\delta = 8.82$ (d, $J = 7.5$ Hz, 1H; 2-H, 1% H), 8.35 (d, $J = 7.5$ Hz, 1H; 4-H, 1% H), 7.90 (d, $J = 7.5$ Hz, 1H; 5-H, 27% H), 7.78 (d, 7.5 Hz, 1H; 7-H, 5% H), 7.62–7.55 (m, 2H; 3-H, 6-H, 1% H), 2.70 ppm (s, 3H; CH_3, 1% H); LC-MS (ESI): m/z (%): 144 (0) $[M_0+H]^+$, 151 (5), 152 (47), 153 (48); purity (UV, 254 nm) 94%; b) 107 mg (0.75 mmol, 75%) yellow solid; cat. $RhCl_3$; ^1H NMR (300 MHz, DMSO): $\delta = 8.82$ (d, $J = 7.5$ Hz, 1H; 2-H, 43% H), 8.35 (d, $J = 7.5$ Hz, 1H; 4-H, 61% H), 7.90 (d, $J = 7.5$ Hz, 1H; 5-H, 100% H), 7.78 (d, $J = 7.5$ Hz, 1H; 7-H, 100% H), 7.62–7.55 (m, 2H; 3-H, 6-H, 61% H), 2.70 ppm (s, 3H; CH_3, 68% H); LC-MS (ESI): m/z (%): 144 (54) $[M_0+H]^+$, 145 (33), 146 (10), 147 (3); purity (UV, 254 nm) 85%; c) 75 mg (0.53 mmol, 53%) yellow solid; cat. Pt/C; ^1H NMR (300 MHz, DMSO): $\delta = 8.82$ (d, $J = 7.5$ Hz, 1H; 2-H, 27% H), 8.35 (d, $J = 7.5$ Hz, 1H; 4-H, 58% H), 7.90 (d, $J = 7.5$ Hz, 1H; 5-H, 100% H), 7.78 (d, $J = 7.5$ Hz, 1H; 7-H, 100% H), 7.62–7.55 (m, 2H; 3-H, 6-H, 26% H), 2.70 ppm (s, 3H; CH_3, 75% H); LC-MS (ESI): m/z (%): 144 (18) $[M_0+H]^+$, 145 (29), 146 (25), 147 (17); purity (UV, 254 nm) 92%.d) 66 mg (0.46 mmol, 46%) yellow solid; cat. mixture of Pd/C and Pt/C (ratio 2:1); ^1H NMR (300 MHz, DMSO): $\delta = 8.82$ (d, $J = 7.5$ Hz, 1H; 2-H, 1% H), 8.35 (d, $J = 7.5$ Hz, 1H; 4-H, 1% H), 7.90 (d, $J = 7.5$ Hz, 1H; 5-H, 27% H), 7.78 (d, $J = 7.5$ Hz, 1H; 7-H, 5% H), 7.62–7.55 (m, 2H; 3-H, 6-H, 1% H), 2.70 ppm (s, 3H; CH_3, 1% H); LC-MS (ESI): m/z (%): 151 (6), 152 (29), 153 (59); purity (UV, 254 nm) 98%.

[D]-15: a) 145 mg (0.84 mmol, 84%) yellow solid; cat. Pd/C; ^1H NMR (300 MHz, DMSO): $\delta = 13.24$ (brs, 1H; CO_2H), 8.66 (d, $J = 7.5$ Hz, 1H; 4-H, 78% H), 8.20–8.03 (m, 3H; 3-H, 5-H, 8-H, 70% H), 7.89 (dd, $J = 7.5$, 7.5 Hz, 1H; 7-H, 100% H), 7.73 ppm (dd, $J = 7.5$, 7.5 Hz, 1H; 6-H, 100% H); LC-MS (ESI): m/z (%): 174 (48) $[M_0+H]^+$, 175 (35), 176 (14), 177 (3); purity (UV, 254 nm) 96%; b) 160 mg (0.93 mmol, 93%) yellow solid; cat. $RhCl_3$; ^1H NMR (300 MHz, DMSO): $\delta = 13.24$ (brs, 1H; CO_2H), 8.66 (d, $J = 7.5$ Hz, 1H; 4-H, 81% H), 8.20–8.03 (m, 3H; 3-H, 5-H, 8-H, 80% H), 7.89 (dd, $J = 7.5$, 7.5 Hz, 1H; 7-H, 100% H), 7.73 ppm (dd, $J = 7.5$, 7.5 Hz, 1H; 6-H, 100% H); LC-MS (ESI): m/z (%): 174 (89) $[M_0+H]^+$, 175 (11); purity (UV, 254 nm) 95%; c) 172 mg (0.98 mmol, 98%) yellow solid; cat. Pt/C; ^1H NMR (300 MHz, DMSO): $\delta = 13.24$ (brs, 1H; CO_2H), 8.66 (d, $J = 7.5$ Hz, 1H; 4-H, 53% H), 8.20–8.03 (m, 3H; 3-H, 5-H, 8-H, 50% H), 7.89 (dd, $J = 7.5$, 7.5 Hz, 1H; 7-H, 63% H), 7.73 ppm (dd, 7.5, 7.5 Hz, 1H; 6-H, 63% H); LC-MS (ESI): m/z: 174 (7) $[M_0+H]^+$, 175 (25), 176 (32), 177 (22), 178 (11); purity (UV, 254 nm) 97% d) 163 mg (0.91 mmol, 91%) yellow solid; cat. mixture of Pd/C and Pt/C (ratio 2:1) ; ^1H NMR (300 MHz, DMSO: $\delta = 13.24$ (brs, 1H; CO_2H), 8.66 (d, $J = 7.5$ Hz, 1H; 4-H, 1% H), 8.20–8.03 (m, 3H; 3-H, 5-H, 8-H, 11% H), 7.89 (dd, $J = 7.5$, 7.5 Hz, 1H; 7-H, 36% H), 7.73 ppm (dd, 7.5, 7.5 Hz, 1H; 6-H, 36% H); LC-MS (ESI): m/z (%): 177 (3), 178 (14), 179 (35), 180 (43), purity (UV, 254 nm) 99%.

[D]-16: a) 77 mg (0.52 mmol, 52%) yellow solid; cat. Pd/C; ^1H NMR (300 MHz, DMSO): $\delta = 8.06$ (d, $J = 7.5$ Hz, 1H; 8-H, 79% H), 7.88 (d, $J = 7.5$ Hz, 1H; 5-H, 55% H), 7.39–7.32 (m, 2H; 6-H, 7-H, 48% H), 7.19 (d, $J = 7.5$ Hz, 1H; 4-H, 59% H), 7.06 (dd, $J = 7.5$, 7.5 Hz, 1H; 3-H, 60% H), 6.68 (d, $J = 7.5$ Hz, 1H; 2-H, 1% H), 5.81 ppm (brs, 2H; NH_2); LC-MS (ESI): m/z (%): 144 (0) $[M_0+H]^+$, 148 (15), 149 (54), 150 (31); purity (UV, 254 nm) 95%; b) 63 mg (0.44 mmol, 44%) yellow solid; cat. $RhCl_3$; ^1H NMR (300 MHz, DMSO): $\delta = 8.06$ (d, $J = 7.5$ Hz, 1H; 8-H, 100% H), 7.88 (d, $J = 7.5$ Hz, 1H; 5-H, 79% H), 7.39–7.32 (m, 2H; 6-H, 7-H, 87% H), 7.19 (d, $J = 7.5$ Hz, 1H; 4-H, 79% H), 7.06 (dd, $J = 7.5$, 7.5 Hz, 1H; 3-H, 60% H), 6.68 (d, $J = 7.5$ Hz, 1H; 2-H, 1% H), 5.81 ppm (brs, 2H; NH_2); LC-MS (ESI): m/z (%): 145 (55), 146 (25), 147 (11), 148 (6); purity (UV, 254 nm) 90%; c) 123 mg (0.84 mmol, 84%) yellow solid; cat. Pt/C; ^1H NMR (300 MHz, DMSO): $\delta = 8.06$ (d, $J = 7.5$ Hz, 1H; 8-H, 100% H), 7.88 (d, $J = 7.5$ Hz, 1H; 5-H, 40% H), 7.39–7.32 (m, 2H; 6-H, 7-H, 44% H), 7.19 (d, $J = 7.5$ Hz, 1H; 4-H, 38% H), 7.06 (dd, $J = 7.5$, 7.5 Hz, 1H; 3-H, 1% H), 6.68 (d, $J = 7.5$ Hz, 1H; 2-H, 1% H), 5.81 ppm (brs, 2H; NH_2); LC-MS (ESI): m/z (%): 145 (10), 146 (22), 147 (29), 148 (26), 149 (11); purity (UV, 254 nm) 92%; d) 129 mg (0.86 mmol, 86%) yellow solid; cat. mixture of Pd/C and Pt/C (ratio 2:1); ^1H NMR (300 MHz, DMSO): $\delta = 8.06$ (d, $J = 7.5$ Hz, 1H; 8-H, 1% H), 7.88 (d, $J = 7.5$ Hz, 1H; 5-H, 1% H), 7.39–7.32 (m, 2H; 6-H, 7-H, 1% H), 7.19 (d, $J = 7.5$ Hz, 1H; 4-H, 1% H), 7.06 (dd, $J = 7.5$, 7.5 Hz, 1H; 3-H, 1% H), 6.68 (d, $J = 7.5$ Hz, 1H; 2-H, 1% H), 5.81 ppm (brs, 2H; NH_2); LC-MS (ESI): m/z (%): 150 (11), 151 (80), 152 (9); purity (UV, 254 nm) 96%.

[D]-17: a) 143 mg (0.95 mmol, 95%) yellow solid; cat. Pd/C; ^1H NMR (300 MHz, DMSO): $\delta = 7.78$–7.72 (m, 2H; 2-H, 7-H, 78% H), 7.21 (d, $J = 7.4$ Hz, 1H; 3-H, 89% H), 7.01 (s, 1H; 4-H, 1% H), 6.75 (d, $J = 7.4$ Hz, 1H; 6-H, 65% H), 5.10 ppm (brs, 2H; NH_2); LC-MS (ESI): m/z (%): 150 (0) $[M_0+H]^+$, 151 (50), 152 (40), 153 (8), 154 (2); purity (UV, 254 nm) 91%; b) 135 mg (0.91 mmol, 91%) yellow solid; cat. $RhCl_3$; ^1H NMR (300 MHz, DMSO): $\delta = 7.78$–7.72 (m, 2H; 2-H, 7-H, 100% H), 7.21 (d, $J = 7.4$ Hz, 1H; 3-H, 83% H), 7.01 (s, 1H; 4-H, 76% H), 6.75 (d, $J = 7.4$ Hz, 1H; 6-H, 100% H), 5.10 ppm (brs, 2H; NH_2); LC-MS (ESI): m/z (%): 150 (76) $[M_0+H]^+$, 151 (19), 152 (5); purity (UV, 254 nm) 96%; c) 123 mg (0.82 mmol, 82%) yellow solid; cat. Pt/C; ^1H NMR (300 MHz, DMSO) $\delta = 7.78$–7.72 (m, 2H; 2-H, 7-H, 76% H), 7.21 (d, $J = 7.4$ Hz, 1H; 3-H, 86% H), 7.01 (s, 1H; 4-H, 1% H), 6.75 (d, $J = 7.4$ Hz, 1H; 6-H, 81% H), 5.10 ppm (brs, 2H; NH_2); LC-MS (ESI): m/z (%): 150 (4) $[M_0+H]^+$, 151 (60), 152 (28), 153 (6), 154 (2); purity (UV, 254 nm) 98%; d) 138 mg (0.91 mmol, 91%) yellow solid; cat. mixture of Pd/C and Pt/C (ratio 2:1); (^1H NMR (300 MHz, DMSO): $\delta = 7.78$–7.72 (m, 2H; 2-H, 7-H, 57% H), 7.21 (d, $J = 7.4$ Hz, 1H; 3-H, 64% H), 7.01 (s, 1H; 4-H, 1% H), 6.75 (d, $J = 7.4$ Hz, 1H; 6-H, 13% H), 5.10 ppm (brs, 2H; NH_2); LC-MS (ESI): m/z (%): 151 (4), 152 (26), 153 (48), 154 (18); purity (UV, 254 nm) 98%.

[D]-18: a) 124 mg (0.96 mmol, 96%) yellow solid; cat. Pd/C; ^1H NMR (300 MHz, DMSO): $\delta = 12.85$ (brs, 1H; CO_2H), 7.83 (d, $J = 7.3$ Hz, 1H; 5-H, 1% H), 6.52 (d, $J = 7.3$ Hz, 1H; 4-H, 40% H), 2.33 ppm (s, 3H; CH_3, 36% H); LC-MS (ESI): m/z (%): 127 (0) $[M_0+H]^+$, 128 (7), 129 (19), 130 (31), 131 (29), 132 (14); purity (UV, 254 nm) 97%; b) 120 mg (0.95 mmol, 95%) yellow solid; cat. $RhCl_3$; ^1H NMR (300 MHz, DMSO): $\delta = 12.85$ (brs, 1H; CO_2H), 7.83 (d, $J = 7.3$ Hz, 1H; 5-H, 55% H), 6.52 (d, $J = 7.3$ Hz, 1H; 4-H, 88% H), 2.33 ppm (s, 3H; CH_3, 88% H); LC-MS (ESI): m/z (%): 127 (53) $[M_0+H]^+$, 128 (32), 129 (6); purity (UV, 254 nm) 87%; c) 116 mg (0.91 mmol, 91%) yellow solid; cat. Pt/C; ^1H NMR (300 MHz, DMSO): $\delta = 12.85$ (brs, 1H; CO_2H), 7.83 (d, $J = 7.3$ Hz, 1H; 5-H, 27% H), 6.52 (d, $J = 7.3$ Hz, 1H; 4-H, 81% H), 2.33 ppm (s, 3H; CH_3, 77% H); LC-MS (ESI): m/z (%): 127 (39) $[M_0+H]^+$, 128 (39), 129 (11), 130 (11); purity (UV, 254 nm) 93%; d) 116 mg (0.91 mmol, 91%) yellow solid; cat. mixture of Pd/C and Pt/C (ratio 2:1); ^1H NMR (300 MHz, DMSO): $\delta = 12.85$ (brs, 1H; CO_2H), 7.83 (d, $J = 7.3$ Hz, 1H; 5-H, 1% H), 6.52 (d, $J = 7.3$ Hz, 1H; 4-H, 56% H), 2.33 ppm (s, 3H; CH_3, 45% H); LC-MS (ESI): m/z (%): 128 (24), 129 (43), 130 (21), 131 (8), 132 (4); purity (UV, 254 nm) 96%.

[D]-19: a) 112 mg (0.95 mmol, 95%) yellow solid; cat. Pd/C; ^1H NMR (300 MHz, DMSO): $\delta = 5.79$ (s, 2H; NH_2), 2.22 ppm (s, 6H; CH_3, 7% H); LC-MS (ESI): m/z (%): 113 (0) $[M_0+H]^+$, 118 (11), 119 (80), 120 (9); purity (UV, 254 nm) 97%; b) 109 mg (0.97 mmol, 97%) yellow solid; cat. $RhCl_3$; ^1H NMR (300 MHz, DMSO): $\delta = 5.79$ (s, 2H; NH_2), 2.22 ppm (s, 6H; CH_3, 85% H); LC-MS (ESI): m/z (%): 113 (70) $[M_0+H]^+$, 114 (23), 115 (5), 116 (2); purity (UV, 254 nm) 98%; c) 111 mg (0.98 mmol, 98%) yellow solid; cat. Pt/C; ^1H NMR (300 MHz, DMSO): $\delta = 5.79$ (s, 2H; NH_2), 2.22 ppm (s, 6H; CH_3, 48% H); LC-MS (ESI): m/z (%): 113 (24) $[M_0+H]^+$, 114 (26), 115 (18), 116 (15), 117 (8); purity (UV, 254 nm) 98%; d) 107 mg (0.91 mmol, 91%) yellow solid; cat. mixture of Pd/C and Pt/C (ratio 2:1); ^1H NMR (300 MHz, DMSO): $\delta = 5.79$ (s, 2H; NH_2), 2.22 ppm (s, 6H; CH_3, 6% H); LC-MS (ESI): m/z: 118 (10), 119 (79), 120 (11); purity (UV, 254 nm) 98%.

[D]-20 papaverine: 261 mg (0.77 mmol, 77%) colourless solid; cat. mixture of Pd/C and Pt/C (ratio 2:1); ^1H NMR (300 MHz, DMSO): $\delta = 8.36$ (d, $J = 5.2$ Hz, 1H; 3-H, 1% H), 7.49 (d, $J = 5.2$ Hz, 1H; 4-H, 1% H), 7.46 (d, $J = 5.2$ Hz, 1H; 8-H, 27% H), 7.33 (s, 1H; 5-H, 27% H), 6.98 (s, 1H; 7′-H, 1% H), 6.71–6.66 (m, 2H; 3′-H, 6′-H, 55% H), 4.44 (s, 2H; 1′-H, 1% H), 3.98 (s, 6H; OCH_3, 86% H) 3.67 ppm (s, 6H; OCH_3, 55%

H); LC-MS (ESI): *m/z* (%): 340 (0) $[M_0+H]^+$, 345 (11), 346 (19), 347 (25), 348 (20), 349 (14) 350 (9), 351 (2); purity (UV, 254 nm) 99%.

[D]-21: 100 mg (0.67 mmol, 67%) colourless oil; cat. mixture of Pd/C and Pt/C (ratio 2:1); ^{1}H NMR (300 MHz, DMSO): δ=7.26 (d, J=7.5 Hz, 2H; 3-H, 33% H), 7.20–7.17 (m, 3H; 2-H, 4-H, 16/67% H), 2.81 (dd, J= 6.1, 6.9 Hz, 1H; 3′-H, 1% H), 2.56 (d, J=7.2 Hz, 2H; 1′-H, 1% H), 1.55 (dd, J=6.9, 7.2 Hz, 2H; 2′-H, 1% H), 1.15 ppm (d, J=6.9 Hz, 3H; 4′-H, 1% H); LC-MS (ESI): *m/z* (%): 150 (0) $[M_0+H]^+$, 159 (3), 160 (11), 161 (29), 162 (38); 163 (17), 164 (2); purity (UV, 254 nm) 92%.

[D]-22 L-tryptophan: 173 mg (0.85 mmol, 85%) colourless solid; cat. mixture of Pd/C and Pt/C (ratio 2:1); ^{1}H NMR (300 MHz, DMSO): δ=11.42 (brs, 1H; CO_2H), 7.62 (d, J=8.0 Hz, 1H; 4-H, 55% H), 7.44 (s, 1H; 2-H, 27% H), 7.33 (d, J=7.6 Hz, 1H; 7-H, 53% H), 7.07 (dd, J=7.6, 8.0 Hz, 1H; 6-H, 86% H), 6.98 (dd, J=7.8/8.0 Hz, 1H; 5-H, 89% H), 4.15 (d, J=7.6 Hz, 1H; 2′-H, 1% H), 3.67 (brs, 2H; NH_2), 3.11 ppm (d, J= 7.6 Hz, 2H; 1′-H, 1% H); LC-MS (ESI): *m/z*: 205 (0) $[M_0+H]^+$, 208 (3), 209 (53), 210 (38), 211 (6); purity (UV, 254 nm) 97%.

[D]-23 mefenamic acid: 186 mg (0.73 mmol, 73%) colourless solid; cat. mixture of Pd/C and Pt/C (ratio 2:1); ^{1}H NMR (300 MHz, DMSO): δ= 13.24 (brs, 1H; CO_2H), 7.63 (dd, J=7.5, 7.4 Hz, 1H; 4-H, 1% H), 7.54 (d, J=7.4 Hz, 1H; 6-H, 1% H), 7.36 (dd, J=7.5, 7.5 Hz, 1H; 5-H, 1% H), 7.06 (d, J=7.5 Hz, 1H; 3-H, 1% H), 6.92 (dd, J=7.5, 7.5 Hz, 5′-H, 1% H), 6.82–6.77 (m, 4′-H, 6′-H, 1% H), 2.23 (s, 3H; CH_3, 2% H), 2.15 ppm (s, 3H; CH_3, 2% H); LC-MS (ESI): *m/z* (%): 242 (0) $[M_0+H]^+$, 253 (3), 254 (16), 255 (72), 256 (9); purity (UV, 254 nm) 98%.

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[10] The yields reported are isolated yields. Low to moderate yields were found for reactions with significant decomposition and/or low solubility of the product in acetonitrile/water/methanol mixtures.

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