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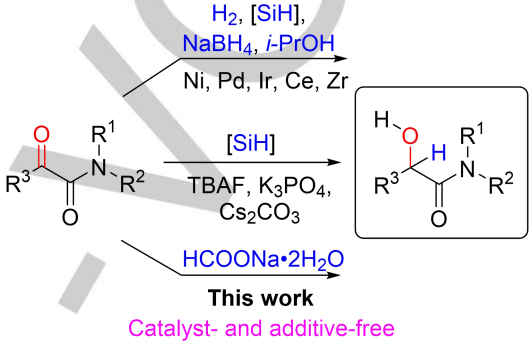
Catalyst- and Additive-free Chemoselective Transfer Hydrogenation of α-Keto Amides to α-Hydroxy Amides by Sodium Formate

Feiyue Hao,[a] Zhenyu Gu,[a] Guyue Liu,[a] Wubing Yao,[a] Huajiang Jiang,[a] and Jiashou Wu*,[a]

Abstract: A catalyst- and additive-free chemoselective transfer hydrogenation of α-keto amides to α-hydroxy amides is easily achieved by using sodium formate as a hydrogen source. The utility of this method is demonstrated by gram-scale synthesis and transformation of the resultant α-hydroxy amides into polysubstituted acetamides and 2-arylindole derivatives. Control experiments suggest that the NH group of α-keto amides is crucial for the chemoselective reduction via the formation of hydrogen bonding.

Introduction

α-Hydroxy amides are important structural motifs in a large number of biologically active compounds exhibiting a wide spectrum of pharmacological properties, such as antibiotic,[1] anticonvulsant,[2] antituberculosis,[3] and γ-secretase inhibitory activities.[4] Besides, α-hydroxy amides also serve as valuable synthetic intermediates in organic synthesis owing to their versatile transformations into a variety of functionalized compounds with structural diversity, including α-alkoxy/aryl/amino amides,[5-8] 1,2-aminoalcohols,[9] and other structurally complex molecules.[10] Hence, the development of efficient methods for the preparation of α-hydroxy amides has attracted considerable attention among organic chemists.[11]
Among preparative methods for α-hydroxy amides, the chemoselective reduction of α-keto amides is the most efficient approach from a practical viewpoint, as it requires only simple experimental manipulations (Scheme 1). Conventional methods for chemoselective hydrogenation of the ketone group of α-keto amides into a hydroxy group involve the use of reducing agents such as H_2, hydrosilanes, $NaBH_4$ or isopropanol, along with a metal catalyst including iridium,[12] nickel,[9] palladium,[13] ceria nanosphere[14] or zirconium-based metal-organic framework.[15] However, these methods suffer from their own limitations, such as the use of a high loading of reducing agents and the employment of expensive noble metals together with inert atmosphere and essential ligands. Despite metal-free chemoselective reduction of α-keto amides employing different hydrosilanes as hydrogen sources has also been developed, additives covering tetrabutylammonium fluoride (TBAF),[16] K_3PO_4,[17] and Cs_2CO_3,[18] are still needed and can not be recycled. Therefore, from the practical and economical viewpoint, the development of a catalyst- and additive-free chemoselective reduction of α-keto amides is of great interest.



Scheme 1. Chemoselective reduction of α-keto amides

Formate derivatives are regarded as an important class of hydrogen storage today, because of their decomposition into H_2 and CO_2 with high efficiency.[19] The hydrogenation of unsaturated functional groups using formate derivatives as a hydrogen source has been extensively investigated, among which transition metal-catalyzed transfer hydrogenation of the ketone functionality is a subject of current interest.[20] Unexpectedly, there is no report on metal-free hydrogenation of the ketone functionality by formates, even though this protocol avoids the use of costly metal catalysts and ligands, and is more environmentally benign. As part of our continuing interest in the development of metal-free transformations, herein for the first time we demonstrate a facile and efficient chemoselective transfer hydrogenation of the ketone group of α-keto amides by employing sodium formate as a hydrogen donor without using any catalyst or additive.

Results and Discussion

To evaluate the potential for chemoselective transfer hydrogenation of α-keto amides, initially, 2-oxo-2-phenyl-*N*-(*p*-tolyl)acetamide **1a** was chosen as the model substrate to react with $HCOONa·2H_2O$ in DMF at 100 ℃ for 10 h, affording α-hydroxy amide **2a** in 44% yield, along with the recovery of **1a** in 54% yield (Table 1, entry 1). Next, different solvents were screened, and the best result was obtained in the reaction using DMSO as the solvent (entries 2–8). A better transformation of **1a** was observed in the case of prolonged reaction time (entry 9). Compared to a higher loading of $HCOONa·2H_2O$, higher temperature was found to be more effective for this reaction,

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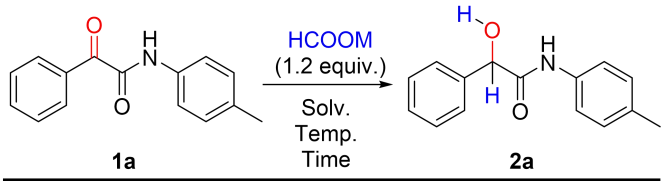
Characterization data including copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the internet at https://doi.org/10.1002/ejoc.201901073R1.

giving **2a** in 93% yield (entries 10 and 11). Moreover, HCOONa, $HCOOLi·H_2O$, and $HCOONH_4$ were also screened, affording **2a** in a comparable yield, respectively (entries 12–14). However, the employment of HCOOK led to a low yield, which might be due to the stronger basicity that facilitated the deprotonation of NH group to cause the tautomerization between α-keto amide and iminone, leading to the low electrophilicity of the ketone group (entry 15).[15] Indeed, the reaction involving HCOOH did not proceed at all (entry 16). Overall, reaction conditions utilized in entry 11 were determined to be optimal.

Table 1. Optimization of reaction conditions



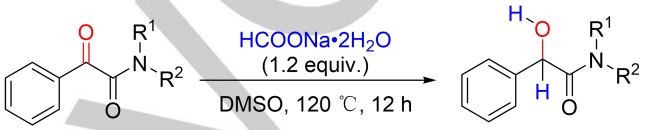
1a **2a**

Entry	Solv.	HCOOM	Temp. (℃)	Time (h)	Yield[a]
1	DMF	$HCOONa·2H_2O$	100	6	44
2	DMSO	$HCOONa·2H_2O$	100	6	70
3	1,4-dioxane	$HCOONa·2H_2O$	100	6	11
4	MeCN	$HCOONa·2H_2O$	100	6	trace
5	*i*-PrOH	$HCOONa·2H_2O$	100	6	0
6	H_2O	$HCOONa·2H_2O$	100	6	0
7	toluene	$HCOONa·2H_2O$	100	6	0
8	DCE	$HCOONa·2H_2O$	100	6	0
9	DMSO	$HCOONa·2H_2O$	100	12	78
10[b]	DMSO	$HCOONa·2H_2O$	100	12	83
11	**DMSO**	**$HCOONa·2H_2O$**	**120**	**12**	**93**
12	DMSO	HCOONa	120	12	82
13	DMSO	$HCOOLi·H_2O$	120	12	80
14	DMSO	$HCOONH_4$	120	12	78
15	DMSO	HCOOK	120	12	15
16	DMSO	HCOOH	120	12	0

[a]Isolated yield. [b]1.5 Equiv. of $HCOONa·2H_2O$ was used.

With the optimized reaction conditions in hand, we started to explore the scope of the substrates. We firstly screened a wide array of α-keto amides with different functional groups on the benzene ring attached to the amide moiety (Table 2). As depicted, α-keto amides **1a**–**j** bearing electron-donating Me, *t*-Bu, MeO, and $(Me)_2N$ groups or weakly electron-withdrawing halo groups successfully gave the corresponding α-hydroxy amides **2a**–**j** in good to excellent yields, regardless of their positions (entries 1–10). Although strongly electron-withdrawing groups, CF_3 and CN, were well tolerated in this protocol, the substrate with a NO_2 group produced a complex mixture, which might be caused by the potential reduction of the NO_2 group into other functionalities under the current reaction conditions (entries 11–13).[19a] As expected, the replacement of phenyl group with naphthyl group did not cause any influence on the yield (entry 14). Furthermore, the substrate with an aliphatic amide moiety was investigated as well. While the secondary amide **1o**–**q** with a benzyl, butyl or cyclohexyl group afforded the target product efficiently, the tertiary amide **1r** with double ethyl groups did not show any conversion, implying that NH group might play an important role in the reduction process (entries 15–18).

Table 2. Investigation on the amide moiety of α-keto amides



1 **2**

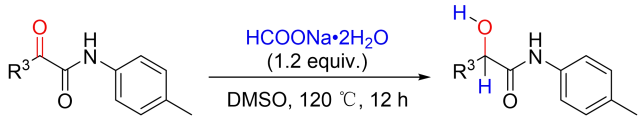
Entry	R^1	R^2		Yield[a]
1	$4\text{-}MeC_6H_4$	H	**a**	93
2	$2\text{-}MeC_6H_4$	H	**b**	96
3	$4\text{-}t\text{-}BuC_6H_4$	H	**c**	85
4	$4\text{-}MeOC_6H_4$	H	**d**	89
5	$3\text{-}MeOC_6H_4$	H	**e**	91
6	$4\text{-}(Me)_2NC_6H_4$	H	**f**	84
7	C_6H_4	H	**g**	91
8	$4\text{-}ClC_6H_4$	H	**h**	92
9	$3\text{-}ClC_6H_4$	H	**i**	90
10	$4\text{-}FC_6H_4$	H	**j**	94
11	$4\text{-}NCC_6H_4$	H	**k**	88
12	$4\text{-}F_3CC_6H_4$	H	**l**	92
13	$3\text{-}O_2NC_6H_4$	H	**m**	c.m.[b]
14	1-naphthyl	H	**n**	89
15	benzyl	H	**o**	90
16	Bu	H	**p**	88
17	cyclohexyl	H	**q**	87
18	Et	Et	**r**	0

[a]Isolated yield. [b]Complex mixture.

Next, the scope of this protocol was expanded to other α-keto amides with diverse functional groups on the aromatic ring attached to the keto moiety (Table 3). As described, both electron-donating and electron-withdrawing groups showed good tolerance with this reaction, affording the corresponding

products **2s**–**w** in high yields, respectively (entries 1–5). In addition, the α-keto amide with naphthyl or thienyl group was also usable as the substrate to afford the desired product in an excellent yield (entries 6 and 7). Furthermore, this protocol was compatible with the methyl-substituted α-keto amide as well, which afforded α-hydroxypropionamide **2z** in 75% yield (entry 8).

Table 3. Study on the ketone moiety of α-keto amides



1 **2**

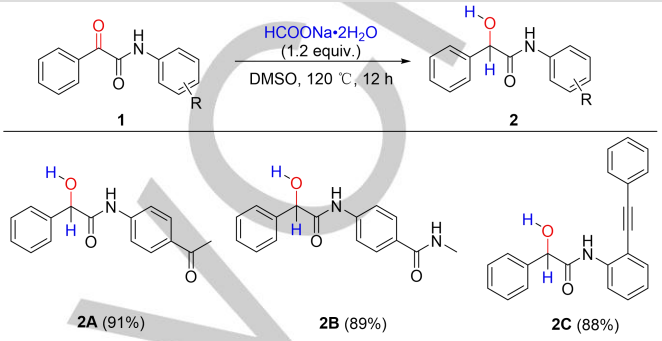
Entry	R^3		Yield[a]
1	4-MeC_6H_4	**s**	89
2	4-$MeOC_6H_4$	**t**	90
3	4-ClC_6H_4	**u**	87
4	4-BrC_6H_4	**v**	88
5	2-BrC_6H_4	**w**	86
6	2-naphthyl	**x**	83
7	2-thienyl	**y**	93
8	Me	**z**	75

[a]Isolated yield.

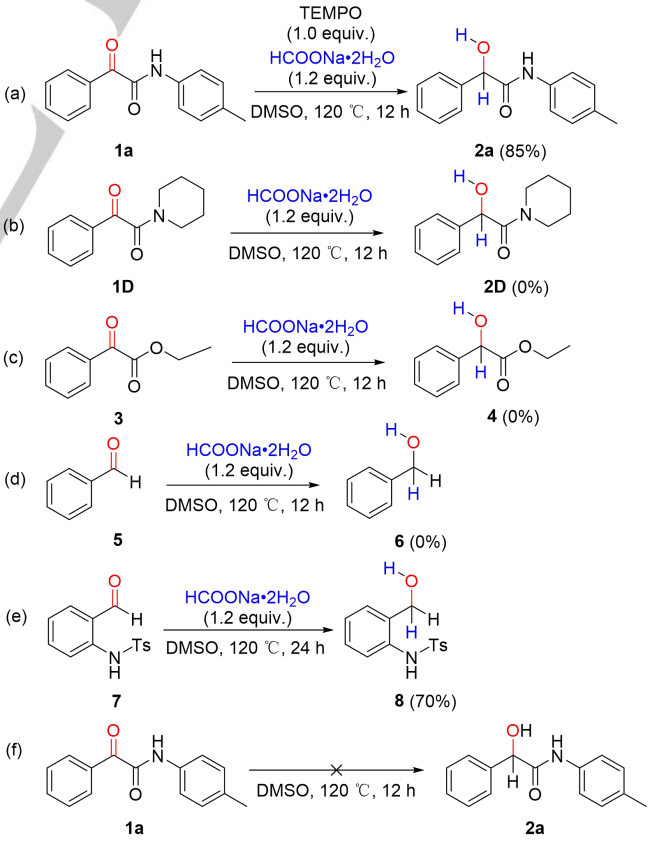
To examine the chemoselectivity of the developed method, we further extended the scope of this transfer hydrogenation to the simple ketone, and the α-keto amides containing additional unsaturated groups. When α-keto amide **1A** or **1B** having an isolated keto or amide group on the benzene ring was subjected to this transformation, α-ketone group was selectively reduced with no effect on the isolated keto or amide group (Table 4). In these chemoselective reductions, the ketone group of α-keto amides should be more electrophilic and active than the isolated ketone or amide group because of the electron-withdrawing effect of the adjacent carbonyl group. Additionally, the NH group of α-keto amide might also facilitate the chemoselective reduction of the ketone group. Furthermore, the reduction only took place on the α-keto amide moiety despite of the introduction of an unsaturated alkynyl group into the substrate. Unfortunately, the reaction using β-keto amide as the substrate did not occur even at higher temperature with longer time, which might be caused by the low reactivity of the ketone group due to the poor eletrophilicity and the keto-enol tautomerism under basic conditions.

In order to elucidate the mechanism of this transformation, several control experiments were carried out (Scheme 2). The addition of TEMPO had a slight influence on the transformation, suggesting that radical intermediates were not involved in this process (eq. a). Piperidyl substituted α-ketone amide **1D** and α-ketone ester **3**, in both of which NH group was absent, failed to produce the corresponding products (eq. b and c). Although the highly reactive benzaldehyde **5** could be easily reduced by metal-catalyzed transfer hydrogenation using HCOONa as a hydrogen donor,[21] it did not yield even a trace amount of the reduced product under the current reaction conditions (eq. d).

Table 4. Chemoselective hydrogenation of the keto group of α-keto amides in the presence of other unsaturated groups

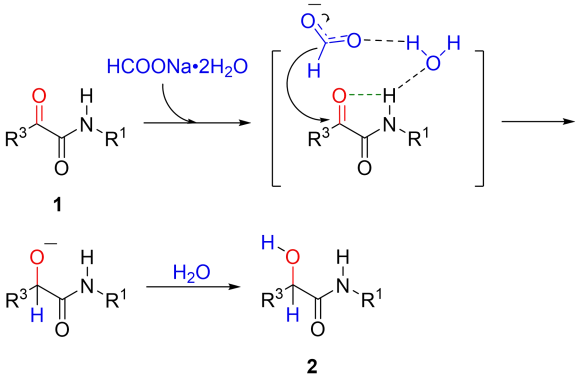


Overall, the result of the above control experiments indicates that NH group is crucial for the reduction of the ketone group of α-keto amides, which was further verified by the smooth hydrogenation of the CHO group having a TsNH group at the adjacent position on the benzene ring (eq. e). Furthermore, the reaction in the absence of HCOONa did not occur, which unambiguously showed that the H atom at the α-position of α-hydroxy amides comes from HCOONa (eq. f).



Scheme 2. Control experiments

Based on the abovementioned results, a plausible mechanism of this transformation is illustrated in Scheme 3. The ketone group of α-keto amide **1** should be activated by the neighbouring carbonyl and NH group through the electron-withdrawing and intramolecular hydrogen bonding effect,[22] respectively. Then, the H_2O-mediated intermolecular hydrogen bonding with NH group and formate anion promotes the reduction of the α-ketone group through a ring transition state that decreases the activation energy.[23] Next, the hydride from formate attacks the electrophilic ketone carbon atom followed by the protonation with H_2O to afford the target α-hydroxy amide **2**.[14]

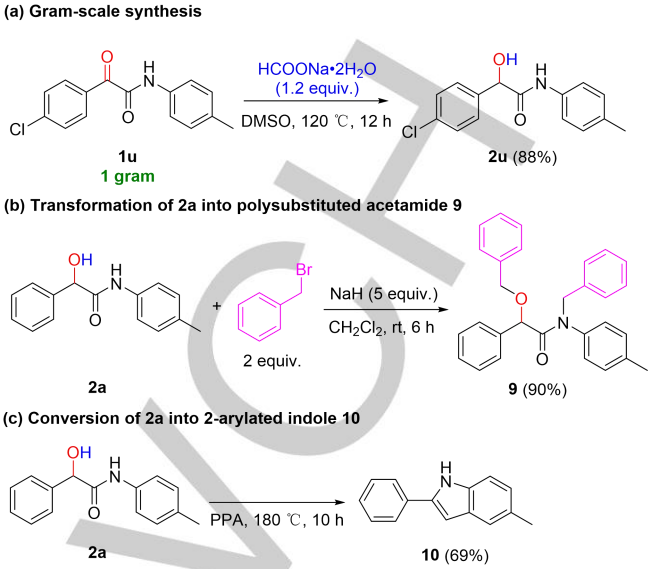


Scheme 3. A plausible mechanism for transfer hydrogenation

Finally, to illustrate the scalability and synthetic utility of the developed protocol, the chemoselective reduction of α-keto amide **1u** was conducted in a gram-scale, and the yield was not influenced in comparison with the reaction in a milligram-scale, which implied that this protocol could be further developed for large-scale production (Scheme 4, a). Next, the conversion of the resulting α-hydroxy amides into other useful synthetic building blocks was investigated. As shown, treatment of α-hydroxy amide **2a** with benzyl bromide in the presence of sodium hydride afforded novel polysubstituted acetamide **9** in a good yield (Scheme 4, b). In addition, the intramolecular cyclization of α-hydroxy amide **2a** into 2-arylated indole **10** in the presence of polyphosphoric acid was achieved, providing a new and useful access to 2-arylindole derivatives (Scheme 4, c).[24]

Conclusions

In conclusion, an operationally simple and metal-free chemoselective transfer hydrogenation of α-keto amides to α-hydroxy amides was developed by using sodium formate as a hydrogen source. The synthetic utility was demonstrated by gram-scale synthesis and transformation of the obtained α-hydroxy amides into other useful compounds. Several control experiments revealed that the NH group of α-keto amides is crucial for the chemoselective reduction via the formation of hydrogen bonding. Further investigations on the application of this protocol for synthesizing structurally diverse compounds are currently in progress in our group.



Scheme 4. Scalability and synthetic utility of this protocol

Experimental Section

General information

The melting points were determined on Buchi M-565 Automated Melting Point System, and are uncorrected. The ^{1}H NMR spectra were measured on a Bruker Ascend-400 at 400 MHz with tetramethylsilane as an internal standard. The ^{13}C NMR spectra were measured on a Bruker Ascend-400 at 100 MHz, and assignments of ^{13}C NMR spectra were performed by DEPT experiments. The high-resolution mass spectra were measured on SYNAPT-G2-Si. The IR spectra were recorded on a JASCO FT/IR-4200 spectrometer. All the reagents and solvents were commercially available and used as received.

General procedure for preparation of α-keto amides 1

Oxalyl chloride (6.4 mmol) was added dropwise to a mixture of benzoyl formic acid (5.0 mmol) and a drop of DMF in CH_2Cl_2 (20 mL), and the reaction mixture was stirred at room temperature for 2 h. Then, a mixture of amine (7.2 mmol) and Et_3N (14.4 mmol) in CH_2Cl_2 (10 mL) was added dropwise, and the resultant mixture was stirred at room temperature for further 4 h. Next, water (30 mL) was added to the reaction mixture, and the organic layer was separated. After concentration under reduced pressure, the obtained residue was purified through silica gel cloumn chromatography (eluted with petroleum ether/ethyl acetate = 5/1) to afford α-keto amides **1**.

General procedure for synthesis of α-hydroxy amides 2

To a solution of α-keto amide **1** (0.21 mmol) in DMSO (2 mL), was added $HCOONa·2H_2O$ (0.25 mmol), and the resultant mixture was stirred at 120 ℃ for 12 h. Then, the mixture was cooled to the room temperature, and water (5 mL) was added. The obtained mixture was extracted with CH_2Cl_2 (5 mL × 2) and dried over Na_2SO_4. After concentration under reduced pressure, the residue was subjected to column chromatography on silica gel to isolate **2** (eluted with petroleum ether/ethyl acetate = 3/1).

2-hydroxy-2-phenyl-*N*-(p-tolyl)acetamide (2a)[17]

White solid (46.7 mg, 0.19 mmol, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.31 (s, 3H), 3.43 (d, *J* = 3.2 Hz, 1H), 5.18 (d, *J* = 3.2 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.34−7.43 (m, 5H), 7.48 (d, *J* = 8.0 Hz, 2H), 8.00 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9 (CH_3), 74.7 (CH), 119.8 (CH), 126.9 (CH), 128.9 (CH), 129.0 (CH), 129.5 (CH), 134.4 (C), 134.5 (C), 139.0 (C), 169.7 (CO).

2-hydroxy-2-phenyl-*N*-(*o*-tolyl)acetamide (2b)[13]

White solid (48.2 mg, 0.20 mmol, 96%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.12 (s, 3H), 3.80 (br s, 1H), 5.16 (s, 1H), 7.05 (t, *J* = 7.2 Hz, 1H), 7.14−7.20 (m, 2H), 7.33−7.42 (m, 3H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 1H), 8.02 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.4 (CH_3), 74.7 (CH), 122.1 (CH), 125.3 (CH), 126.8 (CH), 126.9 (CH), 128.5 (C), 128.9 (CH), 129.0 (CH), 130.5 (CH), 134.9 (C), 139.2 (C), 170.1 (CO).

***N*-[4-(*tert*-butyl)phenyl]-2-hydroxy-2-phenylacetamide (2c)**

White solid (49.4 mg, 0.18 mmol, 84%). Mp 129.1−130.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (s, 9H), 3.42 (d, *J* = 3.2 Hz, 1H), 5.18 (d, *J* = 3.2 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.35-7.49 (m, 7H), 8.01 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.3 (CH_3), 34.4 (C), 74.7 (CH), 119.5 (CH), 125.9 (CH), 126.9 (CH), 128.9 (CH), 129.0 (CH), 134.4 (C), 139.1 (C), 147.8 (C), 169.7 (CO); IR (ATR/cm^{-1}) ν 3313, 3206, 2962, 2904, 2867, 1655; HRMS (ESI/TOF) Calcd for $C_{18}H_{21}NO_2Na$ [(M+Na)$^+$]: 306.1470, found306.1474.

2-hydroxy-*N*-(4-methoxyphenyl)-2-phenylacetamide (2d)[17]

White solid (47.6 mg, 0.19 mmol, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.52 (d, *J* = 3.2 Hz, 1H), 3.78 (s, 3H), 5.16 (d, *J* = 3.2 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 7.34−7.48 (m, 5H), 7.47 (dd, *J* = 1.6 Hz, 8.0 Hz, 2H), 8.03 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.5 (CH_3), 74.7 (CH), 114.2 (CH), 121.6 (CH), 126.9 (CH), 128.9 (CH), 129.0 (CH), 130.2 (C), 139.1 (C), 156.7 (C), 169.7 (CO).

2-hydroxy-*N*-(3-methoxyphenyl)-2-phenylacetamide (2e)[13]

White solid (48.9 mg, 0.20 mmol, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.35 (br s, 1H), 5.20 (s, 1H), 6.68 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.98 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.33 (dd, *J* = 1.2, 2.0 Hz, 1H), 7.37−7.43 (m, 3H), 7.48 (d, *J* = 7.6 Hz, 2H), 8.15 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.3 (CH_3), 74.8 (CH), 105.3 (CH), 110.7 (CH), 111.8 (CH), 126.9 (CH), 128.9 (CH), 129.0 (CH), 129.7 (CH), 138.3 (C), 138.9 (C), 160.3 (C), 169.8 (CO).

***N*-[4-(dimethylamino)phenyl]-2-hydroxy-2-phenylacetamide (2f)**

White solid (47.2 mg, 0.18 mmol, 84%). Mp 173.3−174.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.91 (s, 6H), 3.65 (br s, 1H), 5.14 (s, 1H), 6.69 (d, *J* = 8.4 Hz, 2H), 7.33−7.41 (m, 5H), 7.45−7.48 (m, 2H), 7.88 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 41.0 (CH_3), 74.6 (CH), 96.2 (C), 113.1 (C), 116.4 (C), 121.5 (CH), 127.0 (CH), 128.8 (CH), 129.0 (CH), 139.3 (CH), 169.6 (CO); IR (ATR/cm^{-1}) ν 3309, 3218, 2797, 1656; HRMS (ESI/TOF) Calcd for $C_{16}H_{17}N_2O_2$ [(M-H)$^-$]: 269.1290, found 269.1290.

2-hydroxy-*N*,2-diphenylacetamide (2g)[17]

White solid (42.9 mg, 0.19 mmol, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.46 (d, *J* = 2.8 Hz, 1H), 5.18 (d, *J* = 2.8 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.36−7.42 (m, 3H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.52 (d, *J* = 7.6 Hz, 2H), 8.14 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 74.7 (CH), 119.8 (CH), 124.7 (CH), 126.9 (CH), 128.9 (CH), 129.0 (CH), 129.1 (CH), 137.1 (C), 139.0 (C), 169.9 (CO).

***N*-(4-chlorophenyl)-2-hydroxy-2-phenylacetamide (2h)**[17]

White solid (50.1 mg, 0.19 mmol, 92%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.11 (d, *J* = 4.8 Hz, 1H), 6.49 (d, *J* = 4.8 Hz, 1H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.34-7.38 (m, 4H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.76 (d, *J* = 9.2 Hz, 2H), 10.1 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 74.5 (CH), 121.8 (CH), 127.0 (CH), 127.6 (C), 128.1 (CH), 128.6 (CH), 128.9 (CH), 138.0 (C), 141.1 (C), 171.9 (CO).

***N*-(3-chlorophenyl)-2-hydroxy-2-phenylacetamide (2i)**[18]

White solid (48.9 mg, 0.19 mmol, 90%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.12 (d, *J* = 4.4 Hz, 1H), 6.51 (d, *J* = 4.4 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.28-7.38 (m, 4H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.92 (s, 1H), 10.1 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 74.5 (CH), 118.6 (CH), 119.6 (CH), 123.7 (CH), 127.0 (CH), 128.2 (CH), 128.6 (CH), 130.7 (CH), 133.4 (C), 140.5 (C), 141.0 (C), 172.1 (CO).

***N*-(4-fluorophenyl)-2-hydroxy-2-phenylacetamide (2j)**[25]

White solid (48.0 mg, 0.20 mmol, 94%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.34 (d, *J* = 3.2 Hz, 1H), 5.20 (d, *J* = 3.2 Hz, 1H), 7.01 (t, *J* = 8.4 Hz, 2H), 7.35−7.43 (m, 3H), 7.48−7.51 (m, 4H), 8.17 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 74.7 (CH), 115.7 (d, $^2J_{CF}$ = 22.0 Hz, CH), 121.6 (d, $^3J_{CF}$ = 8.0 Hz, CH), 126.9 (CH), 129.0 (CH), 129.1 (CH), 133.1 (C), 138.9 (C), 159.6 (d, $^1J_{CF}$ = 243.0 Hz, CF), 169.8 (CO).

***N*-(4-cyanophenyl)-2-hydroxy-2-phenylacetamide (2k)**[17]

White solid (46.1 mg, 0.18 mmol, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.49 (d, *J* = 3.6 Hz, 1H), 5.21 (d, *J* = 3.6 Hz, 1H), 7.35−7.42 (m, 3H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 8.65 (br s, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 74.6 (CH), 105.8 (C), 119.5 (C), 120.2 (CH), 127.0 (CH), 128.2 (CH), 128.7 (CH), 133.6 (CH), 140.8 (C), 143.3 (C), 172.6 (CO).

2-hydroxy-2-phenyl-*N*-[4-(trifluoromethyl)phenyl]acetamide (2l)[17]

White solid (56.5 mg, 0.19 mmol, 92%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.15 (d, *J* = 4.4 Hz, 1H), 6.54 (d, *J* = 4.4 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.53 (d, *J* = 7.2 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 2H), 10.32 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 74.5 (CH), 120.1 (CH), 124.0 (q, $^2J_{CF}$ = 31.8 Hz, C), 124.8 (q, *J* = 269.8 Hz, CF_3), 126.3 (q, $^3J_{CF}$ = 3.5 Hz, CH), 127.0 (CH), 128.2 (CH), 128.6 (CH), 141.0 (C), 142.6 (C), 172.4 (CO).

2-hydroxy-*N*-(naphthalen-1-yl)-2-phenylacetamide (2n)[17]

White solid (51.3 mg, 0.185 mmol, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.95 (d, *J* = 3.2 Hz, 1H), 5.23 (d, *J* = 3.2 Hz, 1H), 7.33−7.52 (m, 8H), 7.62−7.64 (m, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.82−7.85 (m, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 8.73 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 74.9 (CH), 119.9 (CH), 120.2 (CH), 125.7 (CH), 125.9 (CH), 126.0 (CH), 126.4 (CH), 126.7 (C), 126.9 (CH), 128.8 (CH), 128.9 (CH), 129.0 (CH), 131.4 (C), 134.0 (C), 139.2 (C), 170.7 (CO).

***N*-benzyl-2-hydroxy-2-phenylacetamide (2o)**[16]

White solid (45.2 mg, 0.19 mmol, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.64 (s, 1H), 4.41 (dd, *J* = 5.6, 15.2 Hz, 1H), 4.46 (dd, *J* = 5.6, 15.2 Hz, 1H), 5.06 (s, 1H), 6.49 (br s, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.24−7.42 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 43.5 (CH_2), 74.3 (CH), 126.7 (CH), 127.5 (CH), 127.6 (CH), 128.7 (CH), 128.8 (CH), 128.9 (CH), 137.7 (C), 139.4 (C), 172.1 (CO).

N-butyl-2-hydroxy-2-phenylacetamide (2p)[18]

White solid (42.3 mg, 0.18 mmol, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.28 (tq, *J* = 7.2, 7.6 Hz, 2H), 1.45 (tt, *J* = 7.2, 7.6 Hz, 2H), 3.19-3.31 (m, 2H), 3.75 (br s, 1H), 4.99 (s, 1H), 6.12 (br s, 1H), 7.31-7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7 (CH_3), 19.9 (CH_2), 31.5 (CH_2), 39.4 (CH_2), 74.1 (CH), 126.9 (CH), 128.6 (CH), 128.9 (CH), 139.6 (C), 172.0 (CO).

N-cyclohexyl-2-hydroxy-2-phenylacetamide (2q)[13]

White solid (42.3 mg, 0.18 mmol, 87%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.02-1.18 (m, 3H), 1.25-1.38 (m, 2H), 1.56-1.69 (m, 3H), 1.81-1.87 (m, 2H), 3.69-3.77 (m, 1H), 3.87 (br s, 1H), 4.95 (s, 1H), 6.09 (br s, 1H), 7.30-7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.6 (CH_2), 24.7 (CH_2), 25.4 (CH_2), 32.8 (CH_2), 48.4 (CH_2), 74.1 (CH), 126.9 (CH), 128.5 (CH), 128.8 (CH), 139.7 (C), 171.2 (CO).

2-hydroxy-*N*,2-di(*p*-tolyl)acetamide (2s)[14]

White solid (47.4 mg, 0.19 mmol, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3H), 2.35 (s, 3H), 3.43 (d, *J* = 1.6 Hz, 1H), 5.12 (d, *J* = 1.6 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 8.00 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9 (CH_3), 21.2 (CH_3), 74.5 (CH), 119.8 (CH), 126.9 (CH), 129.5 (CH), 129.7 (CH), 134.3 (C), 134.6 (C), 136.1 (C), 138.8 (C), 170.0 (CO).

2-hydroxy-2-(4-methoxyphenyl)-*N*-(*p*-tolyl)acetamide (2t)[14]

White solid (50.7 mg, 0.19 mmol, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3H), 3.44 (d, *J* = 2.8 Hz, 1H), 3.80 (s, 3H), 5.10 (d, *J* = 2.8 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 7.2 Hz, 2H), 7.39 (d, *J* = 7.2 Hz, 2H), 8.03 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9 (CH_3), 55.4 (CH_3), 74.2 (CH), 114.4 (CH), 119.8 (CH), 128.4 (CH), 129.5 (CH), 131.2 (C), 134.3 (C), 134.6 (C), 160.0 (C), 170.1 (CO).

2-(4-chlorophenyl)-2-hydroxy-*N*-(*p*-tolyl)acetamide (2u)

White solid (50.0 mg, 0.18 mmol, 87%). Mp 160.2−162.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.31 (s, 3H), 3.67 (br s, 1H), 5.12 (s, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.33−7.41 (m, 6H), 8.17 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9 (CH_3), 73.9 (CH), 119.8 (CH), 128.2 (CH), 129.1 (CH), 129.6 (CH), 134.3 (C), 134.6 (C), 134.7 (C), 137.5 (C), 169.3 (CO); IR (ATR/cm^{-1}) ν 3288, 3043, 1670, 1636; HRMS (ESI/TOF) Calcd for $C_{15}H_{14}NO_2NaCl$ [(M+Na)$^+$]: 298.0611, found 298.0614.

2-(4-bromophenyl)-2-hydroxy-*N*-(*p*-tolyl)acetamide (2v)

White solid (58.4 mg, 0.18 mmol, 88%). Mp 162.9−163.8 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.24 (s, 3H), 5.09 (d, *J* = 4.8 Hz, 1H), 6.52 (d, *J* = 4.8 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 4H, overlap), 9.86 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 20.9 (CH_3), 73.7 (CH), 120.2 (CH), 121.2 (C), 129.2 (CH), 129.4 (CH), 131.4 (CH), 133.0 (C), 136.4 (C), 140.8 (C), 170.9 (CO); IR (ATR/cm^{-1}) ν 3346, 3143, 1655; HRMS (ESI/TOF) Calcd for $C_{15}H_{13}NO_2Br$ [(M-H)$^-$]: 318.0130, found 318.0131.

2-(2-bromophenyl)-2-hydroxy-*N*-(*p*-tolyl)acetamide (2w)

White solid (57.0 mg, 0.18 mmol, 86%). Mp 150.3−152.4 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.31 (s, 3H), 4.07 (d, *J* = 4.4 Hz, 1H), 5.63 (d, *J* = 4.4 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.21 (ddd, *J* = 1.6, 7.6, 8.0 Hz, 1H), 7.35 (ddd, *J* = 0.8, 7.6, 8.0 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.49 (dd, *J* = 1.6, 8.0 Hz, 2H), 7.60 (dd, *J* = 0.8, 8.0 Hz, 1H), 8.06 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9 (CH_3), 72.7 (CH), 119.9 (CH), 122.9 (C), 128.3 (CH), 128.9 (CH), 129.6 (CH), 130.3 (CH), 133.1 (CH), 134.4 (C), 134.6 (C), 138.7(C), 169.2 (CO); IR (ATR/cm^{-1}) ν 3346, 3143, 1655; HRMS (ESI/TOF) Calcd for $C_{15}H_{13}NO_2Br$ [(M-H)$^-$]: 318.0130, found 318.0131.

2-hydroxy-2-(naphthalen-2-yl)-*N*-(*p*-tolyl)acetamide (2x)

White solid (50.4 mg, 0.17 mmol, 83%). Mp 209.2−209.9 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.23 (s, 3H), 5.27 (s, 1H), 6.56 (br s, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.49-7.54 (m, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.67 (dd, *J* = 1.6, 8.8 Hz, 1H), 7.89-7.93 (m, 3H), 8.01 (s, 1H), 9.90 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 20.9 (CH_3), 74.6 (CH), 120.2 (CH), 125.2 (CH), 125.7 (CH), 126.4 (CH), 126.7 (CH), 128.0 (CH), 128.1 (CH), 128.3 (CH), 129.4 (CH), 132.9 (C), 133.0 (C), 133.1 (C), 136.5 (C), 138.9 (C), 171.3 (CO); IR (ATR/cm^{-1}) ν 3275, 2919, 2851,1648; HRMS (ESI/TOF) Calcd for $C_{19}H_{16}NO_2$ [(M-H)$^-$]: 290.1181, found 290.1182.

2-hydroxy-2-(thiophen-2-yl)-*N*-(*p*-tolyl)acetamide (2y)

White solid (47.8 mg, 0.19 mmol, 93%). Mp 169.9−171.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.32 (s, 3H), 3.66 (d, *J* = 3.6 Hz, 1H), 5.46 (d, *J* = 3.6 Hz, 1H), 7.02 (dd, *J* = 3.6, 4.8 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 3.6 Hz, 1H), 7.33 (d, *J* = 4.8 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 8.08 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9 (CH_3), 70.6 (CH), 119.9 (CH), 126.3 (CH), 126.5 (CH), 127.1 (CH), 129.6 (CH), 134.3 (C), 134.6 (C), 141.9 (C), 168.6 (CO); IR (ATR/cm^{-1}) ν 3310, 3146, 2921, 2841, 1670; HRMS (ESI/TOF) Calcd for $C_{13}H_{13}NO_2NaS$ [(M+Na)$^+$]: 270.0565, found 270.0567.

2-hydroxy-*N*-(*p*-tolyl)propanamide (2z)[25]

Colorless oil (27.9 mg, 0.16 mmol, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.29 (s, 3H), 3.94 (br s, 1H), 4.28 (q, *J* = 6.4 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 8.55 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9 (CH_3), 21.1 (CH_3), 68.7 (CH), 120.0 (CH), 129.5 (CH), 134.3 (C), 134.5 (C), 173.0 (CO).

***N*-(4-acetylphenyl)-2-hydroxy-2-phenylacetamide (2A)**[9]

White solid (50.8 mg, 0.19 mmol, 91%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.52 (s, 3H), 5.15 (d, *J* = 4.8 Hz, 1H), 6.52 (d, *J* = 4.8 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.86 (d, *J* = 8.8 Hz, 2H), 7.91 (d, *J* = 8.4 Hz, 2H), 10.32 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 26.9 (CH_3), 74.5 (CH), 119.5 (CH), 127.0 (CH), 128.2 (CH), 128.6 (CH), 129.8 (CH), 132.4 (C), 141.0 (C), 143.4 (C), 172.3 (CO), 197.1 (CO).

4-(2-hydroxy-2-phenylacetamido)-*N*-methylbenzamide (2B)

White solid (52.7 mg, 0.19 mmol, 89%). Mp 203.9−205.1 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.76 (d, *J* = 4.0 Hz, 3H), 5.13 (s, 1H), 6.52 (br s, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.52 (d, *J* = 7.6 Hz, 2H), 7.52 (s, 4H, overlap), 8.32 (d, *J* = 4.0 Hz, 1H), 10.14 (br s, 1H); ^{13}C

NMR (DMSO-d_6, 100 MHz) δ 26.7 (CH_3), 74.5 (CH), 119.4 (CH), 127.0 (CH), 128.1 (CH), 128.2 (CH), 128.6 (CH), 129.8 (C), 141.1 (C), 141.4 (C), 166.5 (CO), 172.0 (CO); IR (ATR/cm^{-1}) ν 3377, 3277, 1655, 1650; HRMS (ESI/TOF) Calcd for $C_{16}H_{15}N_2O_3$ [(M-H)$^-$]: 283.1083, found 283.1082.

2-hydroxy-2-phenyl-*N*-[2-(phenylethynyl)phenyl]acetamide (2C)

White solid (59.8 mg, 0.18 mmol, 88%). Mp 134.7−135.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.84 (d, *J* = 3.2 Hz, 1H), 5.16 (d, *J* = 3.2 Hz, 1H), 7.06 (t, *J* = 8.4 Hz, 1H), 7.25-7.32 (m, 4H), 7.35-7.37 (m, 3H), 7.44-7.49 (m, 3H), 7.52-7.55 (m, 2H), 8.39 (d, *J* = 8.4 Hz, 1H), 9.29 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 75.0 (CH), 84.0 (C), 96.7 (C), 112.6 (C), 119.1 (CH), 122.4 (C), 123.9 (CH), 126.9 (CH), 128.5 (CH), 128.8 (CH), 128.9 (CH), 129.0 (CH), 129.7 (CH), 131.5 (CH), 131.6 (CH), 138.2 (C), 138.9 (C), 170.3 (CO); IR (ATR/cm^{-1}) ν 3331, 3219, 2250, 1650; HRMS (ESI/TOF) Calcd for $C_{22}H_{16}NO_2$ [(M-H)$^-$]: 326.1181, found 326.1181.

Synthesis of *N*-[2-(hydroxymethyl)phenyl]-4-methylbenzenesulfonamide 8[26]

To a solution of *N*-(2-formylphenyl)-4-methylbenzenesulfonamide **7** (57.5 mg, 0.21 mmol) in DMSO (2 mL), was added HCOONa·2H_2O (26.1 mg, 0.25 mmol), and the resultant mixture was stirred at 120 ℃ for 24 h. Then, the mixture was cooled to the room temperature, and water (5 mL) was added. The obtained mixture was extracted with CH_2Cl_2 (5 mL × 2) and dried over Na_2SO_4. After concentration under reduced pressure, the residue was subjected to column chromatography on silica gel to isolate **8** (eluted with petroleum ether/ethyl acetate = 3/1) as a white solid (40.5 mg, 0.15 mmol, 70%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.19 (br s, 1H), 2.38 (s, 3H), 4.39 (s, 2H), 7.06-7.10 (m, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.23-7.28 (m, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.90 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6 (CH_3), 63.9 (CH_2), 123.5 (CH), 125.4 (CH), 127.1 (CH), 129.3 (CH), 129.1 (CH), 129.6 (CH), 131.7 (C), 136.4 (C), 136.9 (C), 143.8 (C).

Synthesis of polysubstituted acetamide 9

To a solution of **2a** (50.0 mg, 0.21 mmol) and benzyl bromide (71.0 mg, 0.42 mmol) in CH_2Cl_2 (2 mL), was added NaH (60% dispersion in mineral oil, 41.5 mg, 1.05 mmol), and the resultant mixture was stirred at room temperature for 12 h. Then, water (2 mL) was added to the reaction mixture, and the organic layer was separated. After concentration under reduced pressure, the obtained residue was purified through silica gel cloumn chromatography (eluted with petroleum ether/ethyl acetate = 5/1) to afford polysubstituted acetamide **9** as a colorless oil (39.2 mg, 0.10 mmol, 90%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (s, 3H), 4.33 (d, *J* = 11.6 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 4.62 (d, *J* = 14.4 Hz, 1H), 4.62 (d, *J* = 14.4 Hz, 1H), 4.74 (s, 1H), 4.87 (d, *J* = 14.4 Hz, 1H), 6.41 (d, *J* = 7.6 Hz, 2H), 6.85 (d, *J* = 7.6 Hz, 2H), 7.04-7.22 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1 (CH_3), 53.4 (CH_2), 70.6 (CH_2), 77.3 (CH), 127.3 (CH), 127.7 (CH), 128.1 (CH), 128.3 (3CH, overlap), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.9 (CH), 129.8 (CH), 136.6 (C), 137.2 (C), 137.7 (C), 138.0 (C), 138.2 (C), 169.9 (CO); IR (ATR/cm^{-1}) ν 3051, 2928, 2876, 1646; HRMS (ESI/TOF) Calcd for $C_{29}H_{28}NO_2$ [(M+H)$^+$]: 422.2120, found 422.2123.

Synthesis of 5-methyl-2-phenyl-*1H*-indole 10[24]

A solution of **2a** (50.0 mg, 0.21 mmol) in PPA (1 mL) was heated at 180 ℃ for 10 h. Then, the mixture was cooled to the room temperature, and water (2 mL) was added. The obtained mixture was extracted with CH_2Cl_2 (5 mL × 2) and dried over Na_2SO_4. After concentration under reduced pressure, the residue was subjected to column chromatography on silica gel to isolate **10** (eluted with petroleum ether/ethyl acetate = 30/1) as a white solid (29.3 mg, 0.14 mmol, 69%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H), 6.67 (d, *J* = 1.2 Hz, 1H), 6.94 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.17-7.25 (m, 2H), 7.33-7.37 (m, 3H), 7.55-7.58 (m, 2H), 8.17 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6 (CH_3), 99.6 (CH), 110.7 (CH), 120.4 (CH), 124.1 (CH), 125.2 (CH), 127.7 (CH), 129.1 (CH), 129.5 (C), 129.6 (C), 132.6 (C), 135.3 (C), 138.1 (C).

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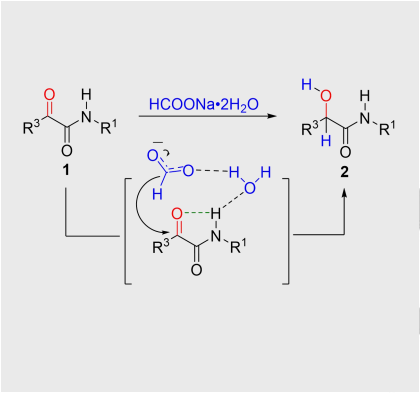

Practicality and Chemoselectivity

*Feiyue Hao, Zhenyu Gu, Guyue Liu, Wubing Yao, Huajiang Jiang, and Jiashou Wu**

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