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Rongalite-Mediated Transition Metal- and Hydride-Free Chemoselective Reduction of α-Keto Esters and α-Keto Amides

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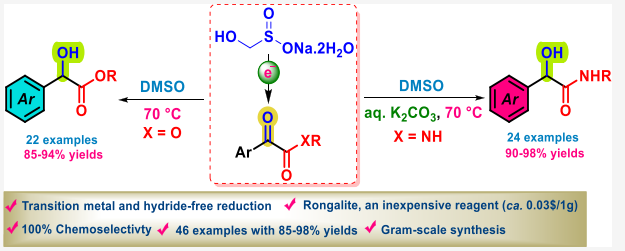
ABSTRACT: A transition metal- and hydride-free protocol has been developed for the chemoselective reduction of α-keto esters and α-keto amides using rongalite as a reducing agent. Here, rongalite acts as a hydride-free reducing agent *via* a radical mechanism. This protocol offers the synthesis of a wide range of α-hydroxy esters and α-hydroxy amides with 85−98% yields. This chemoselective method is compatible with other reducible functionalities such as halides, alkenes, amides, and nitriles. The use of inexpensive rongalite (*ca.* $0.03/1 g), mild reaction conditions, and gram-scale synthesis are some of the key features of this methodology. Also, cyclandelate, a vasodilator drug, has been synthesized in gram scale with 79% yield.



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INTRODUCTION

Chemoselective reduction of the ketone moiety to an alcohol in the presence of other reducible functionalities is a ubiquitous process, and it helps in complex molecule synthesis.[1] The chemoselective reduction of α-keto esters and α-keto amides gives α-hydroxy esters and α-hydroxy amides, respectively, which are important building blocks in many bio-active compounds[2] and agrochemicals[3] (Figure 1)

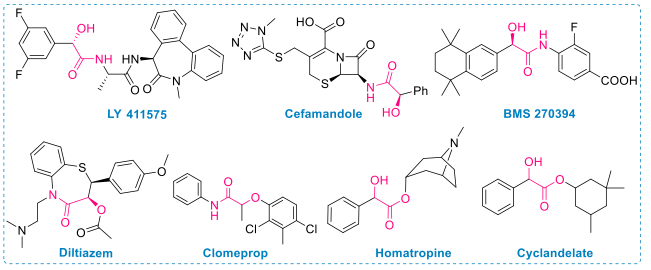
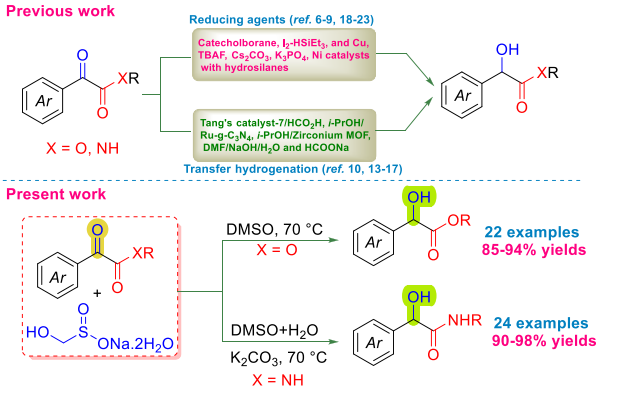


Figure 1. Some of the pharmaceuticals and agrochemicals containing α-hydroxy esters and α-hydroxy amides.

and are also employed as ligands in the metal-catalyzed asymmetric synthesis due to their variable coordinating capabilities.[4] These are versatile synthetic intermediates in organic synthesis, enabling the preparation of a wide range of functionalized compounds.[5]

Many reducing agents are employed for the chemoselective reduction of α-keto esters such as Ru clay-H_2,[6] catecholborane,[7] I_2-$HSiEt_3$,[8] and alkyl phosphines[9] (Scheme 1). Recently, transfer hydrogenation (TH)[10] and electrochemical reduction[11] have become popular alternatives for this chemoselective reduction to avoid hydride-based reducing agents. In

Scheme 1. Chemoselective Reduction of α-Keto Esters and α-Keto Amides



addition to α-hydroxy esters, α-hydroxy amides also received great attention from researchers all around the world. Although many primeval methods are available for the synthesis of α-hydroxy amides,[12] the chemoselective reduction of α-keto amides is one of the most straightforward methods in this category. Mainly three groups, *viz.*, Wu et al., Sekar et al., and Bhanage et al., have made significant contributions *via* (i) transfer hydrogenation using Hantzsch ester,[13] *i*-PrOH/Ru-g-

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C_3N_4,[14] HCOONa,[15] *i*-PrOH/zirconium MOF,[16] and DMF/NaOH/H_2O system[17] and (ii) catalysts such as Cu,[18] TBAF,[19] Cs_2CO_3,[20] K_3PO_4,[21] Ni,[22] and NS-CeO_2[23] with the help of a hydride source (Scheme 1). Although these methods give good results, they suffer from their own set of limitations such as high temperatures, long reaction times, and production of large amounts of silanol-based byproducts.

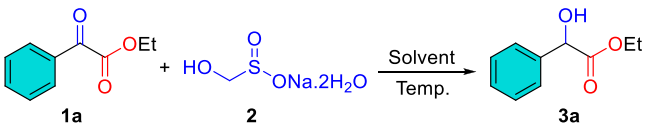
Thus, we sought to develop a novel method for chemoselective reduction of α-keto esters and α-keto amides to circumvent all of the constraints associated with the above methods. In this context, we are developing a transition metal- and hydride-free method using rongalite as a reducing agent.

Sodium hydroxymethanesulfinate dihydrate (SHM), commonly known as rongalite, is a commercially inexpensive (0.03$/1 g) industrial product, and Kotha and co-workers widely used rongalite in organic synthesis.[24,25] It acts as a super-electron donor,[26] a source of C1 unit, and a sulfoxylate dianion (SO_2^{2-}).[27] In continuation of our efforts to explore the synthetic utility of rongalite as an electron source and in hydride-free reduction,[28] herein, we report a chemoselective transition metal- and hydride-free protocol to prepare α-hydroxy esters/amides from the respective α-keto esters/amides by exploring the super-electron-donating nature of rongalite.

RESULTS AND DISCUSSION

In our initial studies, a test reaction was conducted between ethyl 2-oxo-2-phenylacetate **1a** (1 mmol) as a model substrate and rongalite **2** (2 mmol) in EtOH + H_2O to obtain the desired product ethyl 2-hydroxy-2-phenylacetate **3a**, and only the key points are summarized in Table 1 (see Table S1 for more details). At room temperature, only 5% yield of **3a** was observed (Table 1, entry 1). To our delight, the yield of **3a** was dramatically increased to 82% when the same reaction was conducted at 70 °C (Table 1, entry 2). The structure of **3a** was confirmed by ^1H and ^{13}C NMR and HRMS spectral data. Later, screening was continued in polar protic solvents such as H_2O, aq. MeOH, and aq. *i*-PrOH, resulting in low yields (Table 1, entries 3−5). Further, the polar aprotic solvents such as aq. acetone, aq. CH_3CN, and DMF also followed the same trend of polar protic solvents (Table 1, entries 6−8). Fortunately, DMSO gave **3a** in 93% yield within 10 min (Table 1, entry 9). Notably, there was a drop in the yield of **3a** when loading of rongalite was decreased (Table 1, entry 10). Additionally, variants in temperature and increasing equivalent of rongalite did not improve the yield of **3a** (Table 1, entries 11−13). To check the importance of rongalite, we have performed the same reaction with other sulfur-containing reducing agents such as thiourea dioxide and sodium dithionite, which were found to be nonreactive with α-keto esters (Table 1, entries 14 and 15).

Table 1. Optimization of Reaction Conditions for Chemoselective Reduction of α-Keto Esters[a]



1a 2 3a

s. no.	solvent (8:2, v/v)	reagent	temp. (°C)	time	yield (%)[b]
1	EtOH + H_2O	rongalite	rt	24 h	5
2	EtOH + H_2O	rongalite	70	20 min	82
3	H_2O + β-CD	rongalite	70	24 h	trace
4	MeOH + H_2O	rongalite	65	20 min	70
5	*i*-PrOH + H_2O	rongalite	70	20 min	71
6	acetone + H_2O	rongalite	60	8 h	41
7	CH_3CN + H_2O	rongalite	70	20 min	60
8	DMF	rongalite	70	20 min	71
9	DMSO	rongalite	70	10 min	93
10	DMSO	rongalite	70	30 min	75[c]
11	DMSO	rongalite	70	10 min	93[d]
12	DMSO	rongalite	80	10 min	93
13	DMSO	rongalite	60	15 min	91
14	DMSO	thiourea dioxide	70	8 h	n.r.[e]
15	DMSO	sodium dithionite	70	10 h	n.r.[e]

[a]Reaction conditions: ethyl 2-oxo-2-phenylacetate **1a** (1 mmol) and reagent **2** (2 mmol) in different solvent mixtures at variable temperatures. [b]Yield of the isolated product. [c]1.5 equiv of rongalite was used. [d]2.5 equiv of rongalite was used. [e]n.r. = no reaction.

With the optimized reaction conditions in hand (Table 1, entry 9), then we have turned our attention to the testing of the scope of the reaction with diversely substituted α-keto esters (Table 2). Electron-donating groups such as methyl- and methoxy-substituted α-keto esters reacted smoothly with rongalite to furnish **3b−3d** in 89−92% yields (Table 2). This method can also tolerate halogen (F, Cl, and Br) derivatives and afforded the corresponding α-hydroxy esters **3e−3i** in 89−92% yields (Table 2). Biphenyl, naphthyl, and heteroaromatic α-keto esters were also effortlessly involved in the reaction to afford the reduced products **3j−3m** in 90−94% yields (Table 2). α-Keto benzyl esters, which have various substitutions on the benzyl group, also well participated in the reaction and delivered **3n−3q** in 85−92% yields (Table 2). Interestingly, cinnamyl and phthalimide α-keto esters offered the respective reduced products **3r** and **3s** in 85−91% yields with functional groups being intact (Table 2). This methodology is also applicable to α-keto esters that were formed by the secondary alcohols such as isopropyl alcohol and benzhydrol, which furnished **3t** and **3u** in 89−95% yields, respectively (Table 2).

To check the generality and scope of the protocol, we have extended our optimized method to α-keto amides to produce α-hydroxy amides, owing their applications in the synthetic and medicinal chemistry. 2-Oxo-*N*,2-diphenylacetamide **4a** (1 mmol) was treated with rongalite **2** (2 mmol) under optimized reaction conditions, and the formation of 2-hydroxy-*N*,2-diphenylacetamide **5a** in 62% yield was observed, which is lower compared to esters (Table 3, entry 1). Then, the same reaction was conducted in the presence of K_2CO_3, but this did not improve the product yield (Table 3, entry 2). Later, we conducted the reaction with other solvents such as CH_3CN and EtOH (with water to dissolve rongalite) in basic conditions and observed that aq. EtOH gave 76% yield in 2 h (Table 3, entries 3 and 4). Further, we conducted the reaction in DMSO + H_2O (8:2, v/v) with K_2CO_3; surprisingly, the reaction was completed within 15 min and resulted in **5a** with 96% yield (Table 3, entry 5).

Also, reaction was tested with aq. DMSO without a base to know the role of the base in the aqueous condition and found an inferior result (Table 3, entry 6), which indicates that the aq. basic condition was required to produce **5a** in good yield. Further, the ratio of the solvent mixture was also examined and it was observed that the increasing amount of H_2O resulted in

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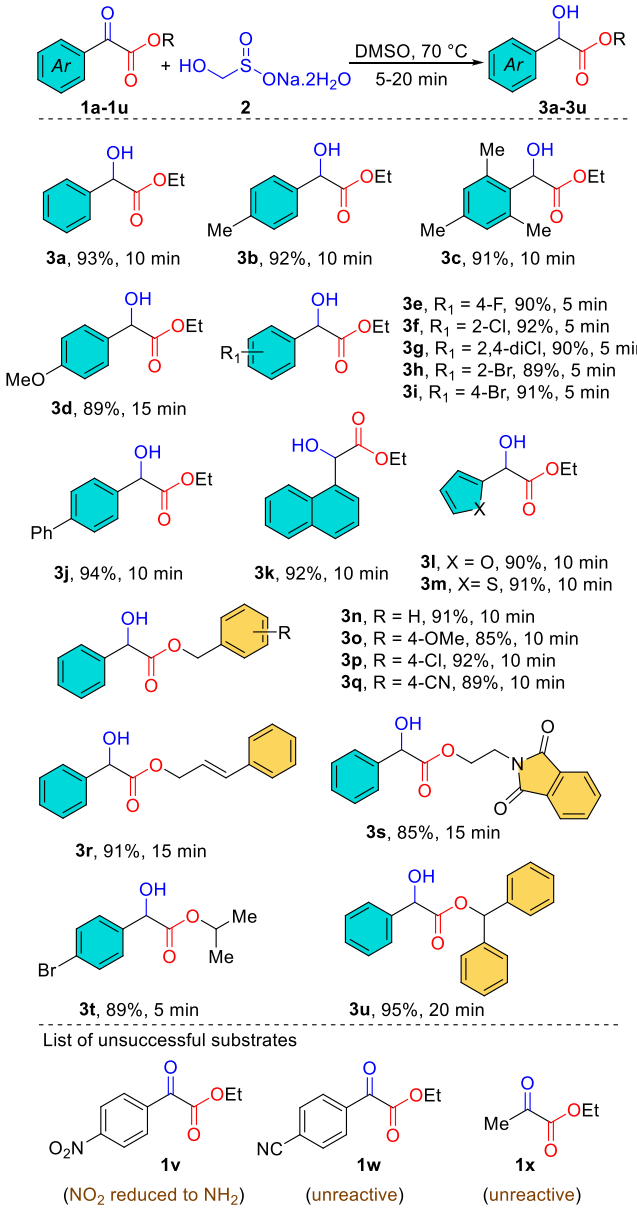
Table 2. Substrate Scope of the Chemoselective Reduction of α-Keto Esters by Rongalite[a,b]

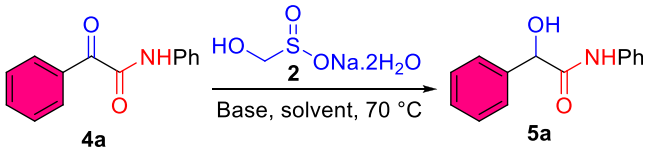


[a]Reaction conditions: α-keto ester **1** (1 mmol) and rongalite **2** (2 mmol) in 2 mL of DMSO at 70 °C. [b]Yield of isolated products.

long reaction times (Table 3, entries 7 and 8). Later, screening was continued with other bases such as Cs_2CO_3, DBU, and 4-DMAP and low yields were observed (Table 3, entries 9−11). Further, the change in the loadings of the base and rongalite also resulted in low yields (Table 3, entries 12 and 13). Therefore, the optimized reaction conditions are 2-oxo-*N*,2-diphenylacetamide **4a** (1 mmol), rongalite **2** (2 mmol), and K_2CO_3 (1.5 mmol) in DMSO + H_2O (8:2, v/v) at 70 °C (Table 3, entry 5).

With the optimized reaction conditions for α-keto amides in hand (Table 3, entry 5), to check the generality of this chemoselective reduction, various α-keto amides were used, and the findings are discussed in Table 4. Electron-donating groups such as methyl- and methoxy-substituted α-keto amides underwent reaction smoothly with rongalite to furnish **5b**, **5c**, **5j**, and **5k** in 90−95% yields (Table 4). This method can also

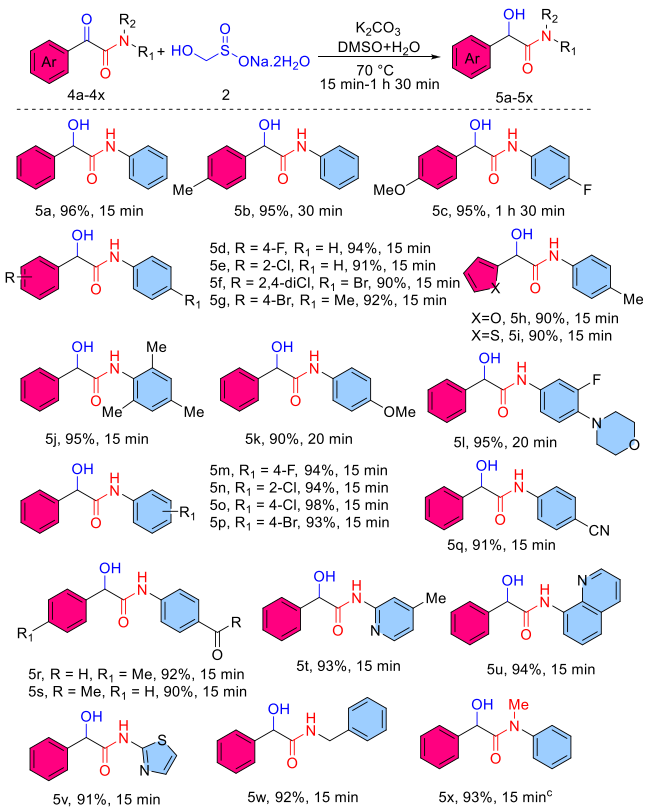
Table 3. Optimization of Reaction Conditions for Chemoselective Reduction of α-Keto Amides[a]



s. no.	solvent	base (equiv)	time	yield (%)[b]
1	DMSO		16 h	62
2	DMSO	K_2CO_3	16 h	60
3	CH_3CN + H_2O (8:2, v/v)	K_2CO_3	8 h	40
4	EtOH + H_2O (8:2, v/v)	K_2CO_3	2 h	76
5	DMSO + H_2O (8:2, v/v)	K_2CO_3	15 min	96
6	DMSO + H_2O (8:2, v/v)		24 h	50
7	DMSO + H_2O (6:4, v/v)	K_2CO_3	30 min	92
8	DMSO + H_2O (1:1, v/v)	K_2CO_3	50 min	90
9	DMSO + H_2O (8:2, v/v)	Cs_2CO_3	15 min	91
10	DMSO + H_2O (8:2, v/v)	DBU	15 min	85
11	DMSO + H_2O (8:2, v/v)	DMAP	15 min	81
12	DMSO + H_2O (8:2, v/v)	K_2CO_3	40 min	89[c]
13	DMSO + H_2O (8:2, v/v)	K_2CO_3	60 min	65[d]

[a]Reaction conditions: 2-oxo-*N*,2-diphenylacetamide **4a** (1 mmol), rongalite **2** (2 mmol), and base (1.5 mmol) in 2 mL of solvent at 70 °C. [b]Yield of isolated products. [c]1.2 equiv of K_2CO_3 was used. [d]1.5 equiv of rongalite was used.

Table 4. Substrate Scope of the Chemoselective Reduction of α-Keto Amides by Rongalite[a,b]



[a]Reaction conditions: α-keto amide **4** (1 mmol), rongalite **2** (2 mmol), and K_2CO_3 (1.5 mmol) in 2 mL of DMSO + H_2O (8:2, v/v) at 70 °C. [b]Yield of isolated products. [c]α-Keto amide **4x** (1 mmol) and rongalite **2** (2 mmol) in DMSO (2 mL) at 70 °C.

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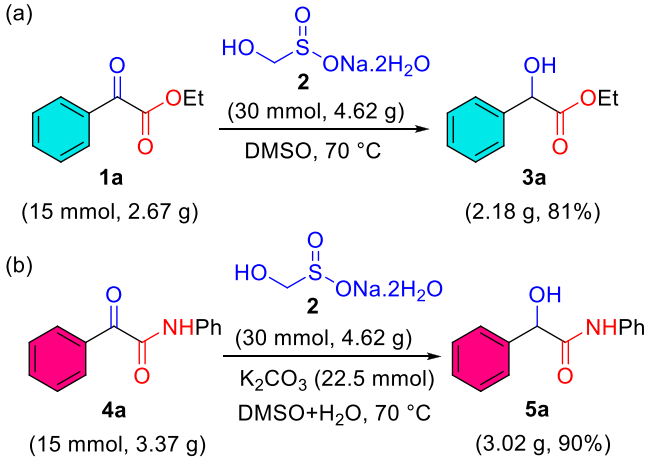
tolerate halogen derivatives (F, Cl, and Br) and afforded the reduced products **5d**−**5g** and **5l**−**5p** in 90−98% yields (Table 4). Electron-withdrawing groups such as cyano-, formyl-, and acetyl-containing α-keto amides were effortlessly involved in the reaction to give **5q**−**5s** in 90−92% yields (Table 4). Also, heteroaromatic α-keto amides delivered the corresponding α-hydroxy amides **5h**, **5i**, and **5t**−**5v** in 90−94% yields (Table 4). Additionally, this protocol is applicable to α-keto amides that were formed by benzyl amine and secondary aniline, which readily gave reduced products **5w** and **5x** in 92−93% yields (Table 4).

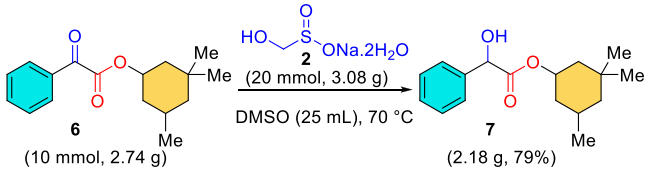
Finally, we have evaluated the synthetic potential of our methodology for gram-scale synthesis, which is more useful in industry. Ethyl 2-oxo-2-phenylacetate **1a** (2.67 g, 15 mmol) and rongalite **2** (4.62 g, 30 mmol) were added in DMSO (15 mL) at 70 °C, resulting in ethyl 2-hydroxy-2-phenylacetate **3a** with 81% yield (Scheme 2a). Similarly, we have prepared 2-hydroxy-*N*,2-diphenylacetamide **5a** in 90% yield using 2-oxo-*N*,2-diphenylacetamide **4a** (3.37 g, 15 mmol), rongalite **2** (4.62 g, 30 mmol), and K_2CO_3 (22.5 mmol) in DMSO + H_2O (8:2, v/v; 15 mL) at 70 °C (Scheme 2b).

Scheme 2. Gram-Scale Synthesis



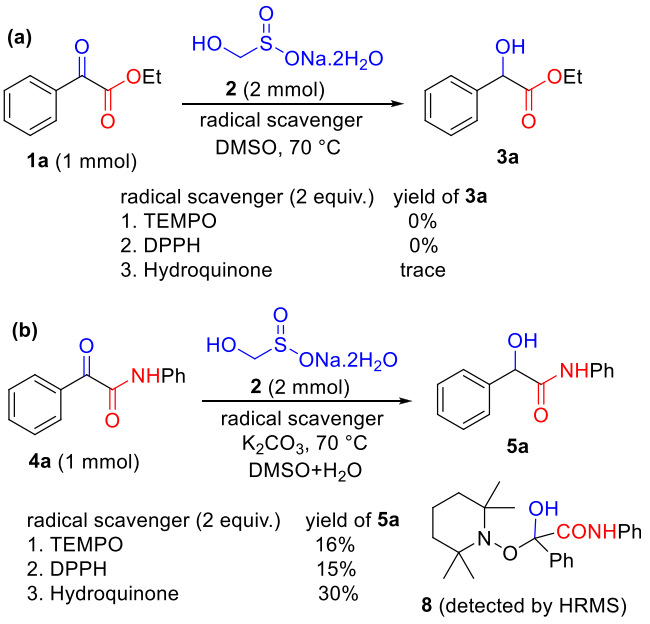
Also, we have synthesized "cyclandelate", a vasodilator drug **7**, which is used to treat heart and blood-vessel diseases and reduces high blood pressure,[2f] using 3,3,5-trimethylcyclohexyl 2-oxo-2-phenylacetate **6** (2.74 g, 10 mmol) and rongalite **2** (3.08 g, 20 mmol) in DMSO (25 mL) at 70 °C in 79% yield (Scheme 3).

Scheme 3. Application of the Protocol for the Synthesis of Cyclandelate



To gain mechanistic insight into these chemoselective reductions, we have conducted some control experiments with radical scavengers such as TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl), DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate), and hydroquinone (Scheme 4). First, control experiments were conducted on α-keto ester by taking ethyl 2-oxo-2-phenylacetate **1a** (1 mmol), rongalite **2** (2 mmol), and TEMPO/DPPH/hydroquinone (2 equiv) in DMSO (2 mL) at 70 °C. No progress of the reaction was observed to provide ethyl 2-hydroxy-2-phenylacetate **3a** in the case of TEMPO and DPPH, and only trace amounts of **3a** were observed in the case of hydroquinone (Scheme 4a).

Scheme 4. Control Experiments



The above results clearly indicate that the reduction of α-keto esters by rongalite is undergoing a radical mechanism. Similarly, some more control experiments were conducted on α-keto amide using 2-oxo-*N*,2-diphenylacetamide **4a** (1 mmol), rongalite **2** (2 mmol), K_2CO_3 (1.5 mmol), and TEMPO/DPPH/hydroquinone (2 equiv) in 2 mL of DMSO + H_2O (8:2, v/v) at 70 °C (Scheme 4b). The product, i.e., 2-hydroxy-*N*,2-diphenylacetamide **5a**, was formed in 15−30% yield, which indicated that the reduction of α-keto amides by rongalite also follows through a radical mechanism. Additionally, the TEMPO adduct with α-keto amide was detected in HRMS analysis (see the Supporting Information, Figure S1). Further, to know the proton source in the hydroxy products, we have conducted a reaction between α-keto ester **1o** (0.05 mmol) and anhydrous deuterated rongalite **2-D** (0.1 mmol) in DMSO-d_6 at 70 °C and observed the incorporation of 28 and 38% deuterium into −CH and −OH groups of α-hydroxy ester, respectively (see the Supporting Information, Figures S3 and S4).

Based on the control experiments and previous literature reports,[26] a plausible mechanism is proposed in Scheme 5. Initially, the reductant rongalite dissociates itself into formaldehyde and HSO_2^-. Later on, a single-electron transfer (SET) takes place from HSO_2^- to α-keto ester/amide to form ketyl radical anion intermediate **I**, which further converts into ketyl radical **II** by protonation. Subsequently, another single-electron transfer occurs at ketyl radical **II** from HSO_2^- to generate intermediate **III**, which finally yields the title compound α-hydroxy ester/amide **IV** by abstraction of proton.

In conclusion, we have developed a transition metal- and hydride-free protocol for the chemoselective reduction of α-keto esters and α-keto amides to produce diversely substituted α-hydroxy esters and α-hydroxy amides with 85−98% yields,

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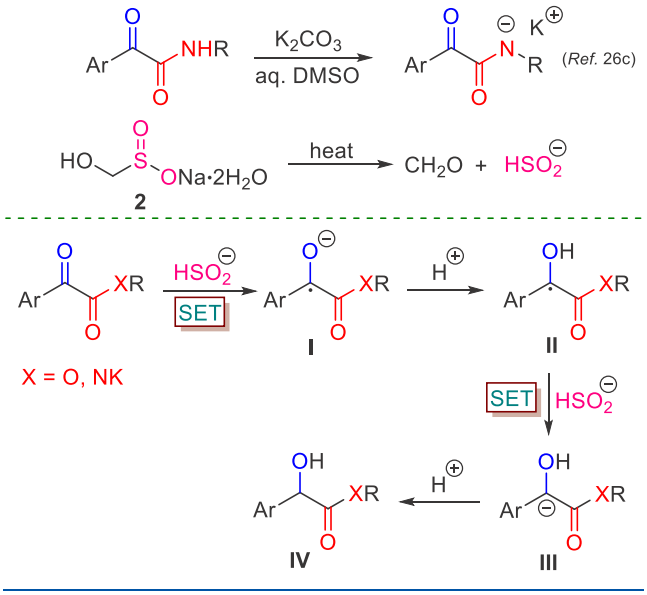
Scheme 5. Plausible Reaction Mechanism



respectively, using rongalite as a reducing agent. Rongalite is an inexpensive industrial product (1 g, 0.03$) found to be a potential radical source of hydride-free reducing agent. This protocol overcomes all the constraints associated with the existing methods such as hazardous byproducts, long reaction times, elevated temperatures, and chemoselectivity problems. Also, we applied our protocol to synthesize cyclandelate, a vasodilator drug, in gram scale with 79% yield.

EXPERIMENTAL SECTION

General Information. All chemicals and solvents were purchased from Alfa Aesar, Spectrochem, SRL, and Finar and used as received. Thin-layer chromatography was performed on 200 μm aluminum-foil backed silica gel plates, and column chromatography was performed using 100−200 mesh silica gel (Merck). The ^{1}H NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer with $CDCl_3$ and DMSO-d_6 as solvents and TMS as an internal standard. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Coupling constants J were reported in Hertz unit (Hz). The $^{13}C\{^1H\}$ NMR spectra were recorded on a Bruker Avance 100/125 MHz spectrometer, and they were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm in reference to the center line of a triplet at 77.16 ppm of chloroform-d (a multiplet at 39.52 ppm of DMSO-d_6). Melting points were determined with a Stuart SMP30 apparatus and were uncorrected. The FT-IR spectra were recorded on a PerkinElmer spectrometer. HRMS data were analyzed with an Agilent Q-TOF 6230.

General Procedure (A) for the Synthesis of α-Hydroxy Esters (3a−3u). An oven-dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with appropriate α-keto ester **1** (1 mmol, 0.5 M), rongalite **2** (2 mmol, 2 equiv), and DMSO (2 mL). The reaction mixture was stirred at 70 °C using an oil bath for the appropriate time (5−20 min). The progress of the reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After the completion of reaction, water was added to the reaction mixture and the organic compound was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried on Na_2SO_4 and evaporated to give a residue that was purified on a short pad of silica gel by column chromatography using hexanes and ethyl acetate as an eluent.

General Procedure (B) for the Synthesis of α-Hydroxy Amides (5a−5x). An oven-dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with appropriate α-keto amide **4** (1 mmol, 0.5 M), rongalite **2** (2 mmol, 2 equiv), K_2CO_3 (1.5 mmol, 1.5 equiv), and DMSO + H_2O (2 mL; 8:2, v/v). The reaction mixture was stirred at 70 °C using an oil bath for the appropriate time (15 min to 1 h and 30 min). The progress of the reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After the completion of reaction, water was added to the reaction mixture and the organic compound was extracted with ethyl acetate (3 × 10 mL). The organic layers were dried on Na_2SO_4 and evaporated to give a residue that was purified on a short pad of silica gel by column chromatography using hexanes and ethyl acetate as an eluent.

*Ethyl 2-Hydroxy-2-phenylacetate (**3a**).*[29] Colorless liquid; yield: 167 mg, 93%. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 10:90). FT-IR (KBr, cm^{-1}): 3456, 3064, 2983, 1737, 1211, 733; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.41 (d, J = 7.6 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 7.2 Hz, 1H), 6.03 (d, J = 5.2 Hz, 1H), 5.12 (d, J = 5.6 Hz, 1H), 4.15−4.01 (m, 2H), 1.13 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 173.0, 140.2, 128.7, 128.3, 127.1, 72.9, 60.9, 14.5; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{10}H_{12}NaO_3$, 203.0684; found, 203.0680.

*Ethyl 2-Hydroxy-2-(p-tolyl)acetate (**3b**).*[9a] White solid; yield: 178 mg, 92%; mp 76−77 °C. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 10:90). FT-IR (KBr, cm^{-1}): 3458, 3091, 2954, 1738, 1215, 791; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.22−7.09 (AB quartet, 4H, J = 8.0 Hz), 5.04 (s, 1H), 4.21−4.05 (m, 2H), 3.32 (s, 1H), 2.27 (s, 3H), 1.15 (d, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.9, 138.2, 135.5, 129.3, 126.5, 72.8, 62.2, 21.2, 14.0.

*Ethyl 2-Hydroxy-2-mesitylacetate (**3c**).*[10a] White crystalline solid; yield: 202 mg, 91%; mp 54−55 °C. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 10:90). FT-IR (KBr, cm^{-1}): 3450, 3092, 2945, 1736, 1218, 802; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.83 (s, 2H), 5.52 (s, 1H), 4.32−4.15 (m, 2H), 3.28 (s, 1H), 2.32 (s, 6H), 2.25 (s, 3H), 1.22 (d, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 174.9, 137.8, 137.2, 131.5, 129.8, 69.1, 62.2, 20.9, 19.9, 14.1; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{13}H_{18}NaO_3$, 245.1154; found, 245.1146.

*Ethyl 2-Hydroxy-2-(4-methoxyphenyl)acetate (**3d**).*[10a] White solid; yield: 187 mg, 89%; mp 51−52 °C. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 10:90). FT-IR (KBr, cm^{-1}): 3455, 2982, 1735, 1713, 1250, 837; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.25−6.80 (AB quartet, 4H, J = 8.6 Hz), 5.03 (s, 1H), 4.21−4.07 (m, 2H), 3.73 (s, 3H), 3.14 (s, 1H), 1.15 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.9, 159.7, 130.7, 127.8, 114.0, 72.5, 62.1, 55.3, 14.1; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{11}H_{14}NaO_4$, 233.0790; found, 233.0785.

*Ethyl 2-(4-Fluorophenyl)-2-hydroxyacetate (**3e**).*[30] White solid; yield: 178 mg, 90%; mp 71−72 °C. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 5:95). FT-IR (KBr, cm^{-1}): 3441, 3095, 2982, 1732, 1387, 1324; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36−7.30 (m, 2H), 7.01−6.94 (m, 2H), 5.06 (s, 1H), 4.22−4.08 (m, 2H), 3.43 (s, 1H), 1.15 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.5, 162.7 (d, $^1J_{C-F}$ = 245.2 Hz), 134.2 (d, $^4J_{C-F}$ = 3.2 Hz), 128.3 (d, $^3J_{C-F}$ = 8.3 Hz), 115.5 (d, $^2J_{C-F}$ = 21.6 Hz), 72.2, 62.4, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): −113.78; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{10}H_{11}FNaO_3$, 221.0590; found, 221.0585.

*Ethyl 2-(2-Chlorophenyl)-2-hydroxyacetate (**3f**).*[31] Colorless liquid; yield: 197 mg, 92%. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 5:95). FT-IR (KBr, cm^{-1}): 3451, 3091, 2925, 1732, 1191, 790; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34−7.30 (m, 2H), 7.21−7.18 (m, 2H), 5.47 (s, 1H), 4.22−4.10 (m, 2H), 3.44 (s, 1H), 1.15 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.2, 136.2, 133.6, 129.9, 129.7, 128.8, 127.1, 70.4, 62.4, 13.9.

*Ethyl 2-(2,4-Dichlorophenyl)-2-hydroxyacetate (**3g**).*[32] White solid; yield: 224 mg, 90%; mp 54−55 °C. The title compound was prepared according to the general procedure (A) described above

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(EtOAc:hexanes = 5:95). FT-IR (KBr, cm^{-1}): 3457, 3095, 2937, 1738, 1218, 1188, 571; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.62 (d, J = 2.0 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.47 (dd, J = 8.4, 2.0 Hz, 1H), 6.45 (d, J = 6.0 Hz, 1H), 5.38 (d, J = 5.6 Hz, 1H), 4.14−4.07 (m, 2H), 1.14 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 171.6, 137.1, 133.7, 133.4, 130.5, 129.1, 128.0, 69.8, 61.3, 14.4.

*Ethyl 2-(2-Bromophenyl)-2-hydroxyacetate (**3h**).* Colorless liquid; yield: 231 mg, 89%. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 5:95). FT-IR (KBr, cm^{-1}): 3440, 3090, 2952, 1735, 1121; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.50 (dd, J = 8.0, 1.2 Hz, 1H), 7.31 (dd, J = 7.6, 2.0 Hz, 1H), 7.25 (td, J = 7.2, 1.2 Hz, 1H), 7.14−7.08 (m, 1H), 5.49 (s, 1H), 4.22−4.10 (m, 2H), 3.35 (s, 1H), 1.15 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.2, 137.9, 133.2, 129.9, 128.8, 127.8, 123.6, 72.4, 62.5, 13.9; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{10}H_{11}BrNaO_3$, 280.9789; found, 280.9783.

*Ethyl 2-(4-Bromophenyl)-2-hydroxyacetate (**3i**).*[31] White solid; yield: 236 mg, 91%; mp 63−64 °C. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 5:95). FT-IR (KBr, cm^{-1}): 3441, 3092, 2986, 1731, 1021, 523; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 5.04 (s, 1H), 4.23−4.07 (m, 2H), 3.42 (s, 1H), 1.16 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.2, 137.4, 131.7, 128.2, 122.4, 72.2, 62.5, 14.0; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{10}H_{11}BrNaO_3$, 280.9789; found, 280.9777.

*Ethyl 2-([1,1′-Biphenyl]-4-yl)-2-hydroxyacetate (**3j**).*[11b] White solid; yield: 241 mg, 94%; mp 117−118 °C. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 5:95). FT-IR (KBr, cm^{-1}): 3456, 3061, 2991, 1731, 1210, 692; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.61−7.57 (m, 4H), 7.49 (d, J = 8.0 Hz, 2H), 7.43 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 5.20 (d, J = 5.6 Hz, 1H), 4.32−4.16 (m, 2H), 3.53 (d, J = 5.6 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 172.6, 140.3, 139.6, 136.4, 127.8, 126.4, 126.3, 126.1, 125.9, 71.6, 61.3, 13.0.

*Ethyl 2-Hydroxy-2-(naphthalen-1-yl)acetate (**3k**).*[33] Colorless liquid; yield: 212 mg, 92%. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 5:95). FT-IR (KBr, cm^{-1}): 3456, 3064, 2983, 1737, 1211, 721; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.03 (d, J = 8.4 Hz, 1H), 7.71−7.63 (m, 2H), 7.38−7.22 (m, 4H), 5.63 (s, 1H), 4.07−3.92 (m, 2H), 3.84 (s, 1H), 0.93 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 172.9, 133.2, 132.9, 129.9, 128.2, 127.6, 125.3, 124.7, 124.6, 124.1, 122.8, 70.3, 60.9, 12.8.

*Ethyl 2-(Furan-2-yl)-2-hydroxyacetate (**3l**).*[34] Colorless liquid; yield: 153 mg, 90%. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 10:90). FT-IR (KBr, cm^{-1}): 3444, 3097, 2984, 1740, 1370, 804; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40−7.38 (m, 1H), 6.38−6.35 (m, 2H), 5.18 (d, J = 6.8 Hz, 1H), 4.32−4.25 (m, 2H), 3.38 (d, J = 6.8 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 171.5, 150.9, 142.9, 110.5, 108.6, 66.9, 62.5, 14.1; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_8H_{10}NaO_4$, 193.0477; found, 193.0469.

*Ethyl 2-Hydroxy-2-(thiophen-2-yl)acetate (**3m**).*[31] Colorless liquid; yield: 169 mg, 91%. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 10:90). FT-IR (KBr, cm^{-1}): 3452, 3097, 2982, 1736, 1664, 1227; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.21 (dd, J = 5.2, 1.2 Hz, 1H), 7.03 (d, J = 3.6 Hz, 1H), 6.91 (dd, J = 5.2, 3.6 Hz, 1H), 5.33 (s, 1H), 4.25−4.17 (m, 2H), 3.43 (s, 1H), 1.22 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 172.5, 141.6, 126.9, 125.7, 125.3, 69.1, 62.6, 14.1; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_8H_{10}NaO_3S$, 209.0248; found, 209.0245.

*Benzyl 2-Hydroxy-2-phenylacetate (**3n**).*[31] White crystalline solid; yield: 220 mg, 91%; mp 95−96 °C. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 10:90). FT-IR (KBr, cm^{-1}): 3445, 3078, 2950, 1955, 1739, 1727, 1211, 724; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43−7.18 (m, 8H), 7.17−7.04 (m, 2H), 5.18−5.03 (m, 3H), 3.28 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.5, 138.2, 135.0, 128.6, 128.6, 128.5, 128.5, 127.9, 126.6, 72.9, 67.7; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{15}H_{14}NaO_3$, 265.0841; found, 265.0839.

*4-Methoxybenzyl 2-Hydroxy-2-phenylacetate (**3o**).* White solid; yield: 231 mg, 85%; mp 66−67 °C. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 10:90). FT-IR (KBr, cm^{-1}): 3377, 3047, 2951, 1712, 1384, 1086; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.42−7.26 (m, 5H), 7.19 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.08 (d, J = 5.2 Hz, 1H), 5.16 (d, J = 5.2 Hz, 1H), 5.06 (d, J = 12.0 Hz, 1H), 5.00 (d, J = 12.0 Hz, 1H), 3.73 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 172.9, 159.6, 140.0, 130.1, 128.7, 128.4, 128.3, 127.1, 114.2, 72.9, 66.1, 55.6; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{16}NaO_4$, 295.0946; found, 295.0941.

*4-Chlorobenzyl 2-Hydroxy-2-phenylacetate (**3p**).*[35] White crystalline solid; yield: 254 mg, 92%; mp 133−134 °C. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 10:90). FT-IR (KBr, cm^{-1}): 3377, 3047, 2954, 1715, 1384, 1086; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34−7.26 (m, 5H), 7.20 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.5 Hz, 2H), 5.14 (s, 1H), 5.06 (t, J = 10.0 Hz, 2H), 3.31 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.4, 138.1, 134.4, 133.5, 129.3, 128.8, 128.7, 128.6, 126.6, 72.9, 66.8; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{15}H_{13}ClNaO_3$, 299.0451; found, 299.0449.

*4-Cyanobenzyl 2-Hydroxy-2-phenylacetate (**3q**).* White solid; yield: 238 mg, 89%; mp 141−142 °C. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 10:90). FT-IR (KBr, cm^{-1}): 3442, 3062, 2924, 2230, 1737, 1728, 896; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.49 (d, J = 8.4 Hz, 2H), 7.35−7.27 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 5.20−5.11 (m, 3H), 3.33 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.3, 140.3, 137.9, 132.4, 128.8, 128.8, 127.9, 126.6, 118.4, 112.3, 73.0, 66.2; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{13}NNaO_3$, 290.0793; found, 290.0791.

*Cinnamyl 2-Hydroxy-2-phenylacetate (**3r**).* White solid; yield: 244 mg, 91%; mp 68−69 °C. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 10:90). FT-IR (KBr, cm^{-1}): 3449, 3031, 2980, 1731, 1493, 1200; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40−7.36 (m, 2H), 7.33−7.14 (m, 8H), 6.42 (dt, J = 15.6, 1.2 Hz, 1H), 6.11 (dt, J = 16.0, 6.4 Hz, 1H), 5.15 (s, 1H), 4.79−4.69 (m, 2H), 3.37 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.5, 138.3, 135.9, 134.6, 128.7, 128.6, 128.6, 128.3, 126.7, 122.0, 73.0, 66.5; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{17}H_{16}NaO_3$, 291.0997; found, 291.1000.

*2-(1,3-Dioxoisoindolin-2-yl)ethyl 2-Hydroxy-2-phenylacetate (**3s**).* White solid; yield: 276 mg, 85%; mp 89−90 °C. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 10:90). FT-IR (KBr, cm^{-1}): 3470, 2959, 1774, 1742, 1712, 529; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.78−7.74 (m, 2H), 7.68−7.65 (m, 2H), 7.28−7.25 (m, 2H), 7.16−7.09 (m, 3H), 5.09 (s, 1H), 4.42−4.36 (m, 1H), 4.28−4.21 (m, 1H), 3.94−3.83 (m, 2H), 3.31 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.3, 167.9, 137.8, 134.1, 131.8, 128.4, 128.3, 126.5, 123.5, 72.9, 63.0, 36.6; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{18}H_{15}NNaO_5$, 348.0848; found, 348.0843.

*Isopropyl 2-(4-Bromophenyl)-2-hydroxyacetate (**3t**).* White crystalline solid; yield: 243 mg, 89%; mp 72−73 °C. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 10:90). FT-IR (KBr, cm^{-1}): 3444, 3091, 2989, 1740, 1108, 513; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40−7.24 (AB quartet, 4H, J = 8.4 Hz), 5.04−4.94 (m, 2H), 3.44 (s, 1H), 1.21 (d, J = 6.4 Hz, 3H), 1.04 (d, J = 6.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 172.7, 137.6, 131.6, 128.1, 122.3, 72.3, 70.5, 21.7, 21.4; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{11}H_{13}BrNaO_3$, 294.9946; found, 294.9937.

*Benzhydryl 2-Hydroxy-2-phenylacetate (**3u**).*[36] White solid; yield: 302 mg, 95%; mp 115−116 °C. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 10:90). FT-IR (KBr, cm^{-1}): 3443, 3095, 2982, 1735, 1265,

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1172; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35−7.20 (m, 10H), 7.11−7.04 (m, 3H), 6.83 (d, J = 6.8 Hz, 2H), 6.80 (s, 1H), 5.20 (s, 1H), 3.39 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 172.8, 139.3, 139.2, 138.1, 128.7, 128.6, 128.6, 128.4, 128.3, 127.9, 127.4, 126.8, 126.3, 78.8, 73.2.

*2-Hydroxy-N,2-diphenylacetamide (**5a**).*[23] White solid; yield: 218 mg, 96%; mp 150−151 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 20:80). FT-IR (KBr, cm^{-1}): 3444, 3064, 2973, 1642, 1563, 880; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.90 (s, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 7.2 Hz, 2H), 7.36 (t, J = 7.2 Hz, 2H), 7.29 (t, J = 7.2 Hz, 3H), 7.05 (t, J = 7.6 Hz, 1H), 6.43 (d, J = 4.8 Hz, 1H), 5.11 (d, J = 4.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 171.6, 141.3, 138.9, 129.1, 128.6, 128.1, 127.0, 124.0, 120.2, 74.5.

*2-Hydroxy-N-phenyl-2-(p-tolyl)acetamide (**5b**).*[23] White crystalline solid; yield: 229 mg, 95%; mp 145−146 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 20:80). FT-IR (KBr, cm^{-1}): 3373, 3092, 2973, 1642, 1557, 1076; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.90 (s, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.34 (t, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.10 (t, J = 7.2 Hz, 1H), 6.39 (d, J = 4.8 Hz, 1H), 5.10 (d, J = 4.4 Hz, 1H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 171.8, 138.9, 138.4, 137.2, 129.1, 129.1, 126.9, 123.9, 120.1, 74.3, 21.2.

*N-(4-Fluorophenyl)-2-hydroxy-2-(4-methoxyphenyl)acetamide (**5c**).* White crystalline solid; yield: 261 mg, 95%; mp 156−157 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 25:75). FT-IR (KBr, cm^{-1}): 3351, 3012, 2842, 1659, 1273, 832; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 9.03 (s, 1H), 7.54−7.48 (m, 2H), 7.36 (d, J = 8.8 Hz, 2H), 6.91 (t, J = 8.8 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 5.87 (s, 1H), 5.04 (s, 1H), 3.71 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 171.1, 159.5, 159.1 (d, $^1J_{C-F}$ = 241.3 Hz), 133.9, 132.5, 128.0, 121.3 (d, $^3J_{C-F}$ = 7.8 Hz), 115.4 (d, $^2J_{C-F}$ = 22.3 Hz), 113.8, 73.8, 55.3; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{15}H_{14}FNNaO_3$, 298.0855; found, 298.0849.

*2-(4-Fluorophenyl)-2-hydroxy-N-phenylacetamide (**5d**).*[23] White crystalline solid; yield: 230 mg, 94%; mp 115−116 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 20:80). FT-IR (KBr, cm^{-1}): 3301, 3095, 1656, 1512, 1231, 1061; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.91 (s, 1H), 7.72−7.67 (m, 2H), 7.59−7.53 (m, 2H), 7.32−7.27 (m, 2H), 7.19 (t, J = 9.2 Hz, 2H), 7.06 (t, J = 7.6 Hz, 1H), 6.49 (d, J = 4.8 Hz, 1H), 5.13 (d, J = 4.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 171.5, 162.1 (d, $^1J_{C-F}$ = 241.8 Hz), 138.9, 137.5 (d, $^3J_{C-F}$ = 11.2 Hz), 129.1 (d, $^4J_{C-F}$ = 4.6 Hz), 128.9, 124.1, 120.2, 115.4 (d, $^2J_{C-F}$ = 21.2 Hz), 73.7.

*2-(2-Chlorophenyl)-2-hydroxy-N-phenylacetamide (**5e**).*[37] White crystalline solid; yield: 238 mg, 91%; mp 158−159 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 20:80). FT-IR (KBr, cm^{-1}): 3300, 3179, 3091, 2915, 1656, 1061; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.02 (s, 1H), 7.75−7.70 (m, 2H), 7.58 (dd, J = 7.6, 2.4 Hz, 1H), 7.48−7.42 (m, 1H), 7.39−7.29 (m, 4H), 7.08 (t, J = 7.6 Hz, 1H), 6.65 (d, J = 5.2 Hz, 1H), 5.49 (d, J = 5.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 170.5, 139.2, 138.9, 133.1, 129.9, 129.7, 129.6, 129.1, 127.7, 124.1, 120.3, 71.6.

*N-(4-Bromophenyl)-2-(2,4-dichlorophenyl)-2-hydroxyacetamide (**5f**).* White crystalline solid; yield: 338 mg, 90%; mp 155−156 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 20:80). FT-IR (KBr, cm^{-1}): 3433, 3061, 2977, 1641, 1556, 1077; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.22 (s, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.66−7.53 (m, 2H), 7.52−7.45 (m, 3H), 6.76 (d, J = 5.2 Hz, 1H), 5.45 (d, J = 5.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 170.3, 138.3, 138.2, 133.9, 133.6, 131.9, 130.9, 129.1, 127.9, 122.3, 115.9, 71.3; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{14}H_{11}BrCl_2NO_2$, 373.9350; found, 373.9323.

*2-(4-Bromophenyl)-2-hydroxy-N-(p-tolyl)acetamide (**5g**).*[17] Off-white crystalline solid; yield: 294 mg, 92%; mp 166−167 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 20:80). FT-IR (KBr, cm^{-1}): 3412, 3062, 2978, 1640, 1557, 1077; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.83 (s, 1H), 7.56 (d, J = 8.4 Hz, 4H), 7.47 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 6.49 (d, J = 4.8 Hz, 1H), 5.09 (d, J = 4.8 Hz, 1H), 2.24 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 170.9, 140.8, 136.4, 133.0, 131.4, 129.5, 129.2, 121.2, 120.2, 73.7, 20.9; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{15}H_{15}BrNO_2$, 320.0286; found, 320.0280.

*2-(Furan-2-yl)-2-hydroxy-N-(p-tolyl)acetamide (**5h**).* White crystalline solid; yield: 208 mg, 90%; mp 163−164 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 20:80). FT-IR (KBr, cm^{-1}): 3286, 3036, 1651, 1602, 1232, 507; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.83 (s, 1H), 7.64−7.56 (m, 3H), 7.11 (d, J = 8.4 Hz, 2H), 6.44 (d, J = 5.6 Hz, 1H), 6.44−6.37 (m, 2H), 5.13 (d, J = 5.6 Hz, 1H), 2.25 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 169.1, 153.8, 143.0, 136.3, 133.1, 129.5, 120.2, 110.9, 108.4, 68.5, 20.9; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{13}H_{13}NNaO_3$, 254.0793; found, 254.0792.

*2-Hydroxy-2-(thiophen-2-yl)-N-(p-tolyl)acetamide (**5i**).*[17] White solid; yield: 222 mg, 90%; mp 172−173 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 20:80). FT-IR (KBr, cm^{-1}): 3344, 3090, 2925, 1651, 1233, 819; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.85 (s, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 5.2 Hz, 1H), 7.15−7.07 (m, 3H), 6.99 (dd, J = 5.2, 4.0 Hz, 1H), 6.69 (d, J = 5.2 Hz, 1H), 5.34 (d, J = 4.8 Hz, 1H), 2.24 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 170.4, 144.6, 136.3, 133.2, 129.5, 127.0, 125.9, 125.3, 120.3, 70.6, 20.9; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{13}H_{13}NNaO_2S$, 270.0565; found, 270.0561.

*2-Hydroxy-N-mesityl-2-phenylacetamide (**5j**).*[38] Off-white crystalline solid; yield: 256 mg, 95%; mp 126−127 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 20:80). FT-IR (KBr, cm^{-1}): 3329, 3036, 2917, 1659, 1440, 1065, 697; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.26 (s, 1H), 7.53 (d, J = 7.2 Hz, 2H), 7.36 (t, J = 7.2 Hz, 2H), 7.28 (t, J = 7.2 Hz, 1H), 6.82 (s, 2H), 6.29 (d, J = 4.4 Hz, 1H), 5.09 (d, J = 4.4 Hz, 1H), 2.19 (s, 3H), 1.96 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 171.5, 141.8, 135.8, 135.5, 132.5, 128.6, 128.4, 127.9, 127.0, 74.4, 20.9, 18.3; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{17}H_{19}NNaO_2$, 292.1313; found, 292.1317.

*2-Hydroxy-N-(4-methoxyphenyl)-2-phenylacetamide (**5k**).*[17] White crystalline solid; yield: 231 mg, 90%; mp 152−153 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 25:75). FT-IR (KBr, cm^{-1}): 3349, 3095, 2942, 1659, 1271, 762; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.82 (s, 1H), 7.64 (d, J = 9.2 Hz, 2H), 7.55 (d, J = 7.2 Hz, 2H), 7.39 (t, J = 7.2 Hz, 2H), 7.33 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 6.42 (d, J = 4.4 Hz, 1H), 5.12 (d, J = 4.8 Hz, 1H), 3.75 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 171.1, 155.9, 141.5, 132.1, 128.5, 128.0, 127.0, 121.7, 114.2, 74.4, 55.6.

*N-(3-Fluoro-4-morpholinophenyl)-2-hydroxy-2-phenylacetamide (**5l**).* Off-white solid; yield: 314 mg, 95%; mp 176−177 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 25:75). FT-IR (KBr, cm^{-1}): 3299, 3091, 2829, 1659, 1652, 1304, 1251; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.98 (s, 1H), 7.63 (dd, J = 14.8, 2.0 Hz, 1H), 7.50 (d, J = 7.6 Hz, 2H), 7.43 (d, J = 8.8 Hz, 1H), 7.35 (t, J = 6.8 Hz, 2H), 7.29 (t, J = 6.8 Hz, 1H), 6.97 (t, J = 9.2 Hz, 1H), 6.46 (d, J = 4.4 Hz, 1H), 5.08 (d, J = 4.8 Hz, 1H), 3.715 (t, J = 4.4 Hz, 4H), 2.93 (t, J = 4.4 Hz, 4H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 171.6, 154.8 (d, $^1J_{C-F}$ = 241.4 Hz), 141.2, 135.9 (d, $^2J_{C-F}$ = 14 Hz), 134.1 (d, $^3J_{C-F}$ = 10.6 Hz), 128.6, 128.1, 127.0, 119.4 (d, $^3J_{C-F}$ = 3.9 Hz), 116.3 (d, $^4J_{C-F}$ = 2.7 Hz), 108.4 (d, $^2J_{C-F}$ = 25.5 Hz), 74.4, 66.6, 51.2 (d, $^4J_{C-F}$ = 2.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): −120.77; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{20}FN_2O_3$, 331.1458; found, 331.1449.

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*N-(4-Fluorophenyl)-2-hydroxy-2-phenylacetamide (**5m**).*[17] White solid; yield: 230 mg, 94%; mp 162−163 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 20:80). FT-IR (KBr, cm^{-1}): 3303, 3100, 1656, 1513, 1236, 1064, 504; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.00 (s, 1H), 7.77−7.70 (m, 2H), 7.52 (d, J = 7.6 Hz, 2H), 7.36 (t, J = 7.2 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 7.13 (t, J = 8.8 Hz, 2H), 6.45 (d, J = 4.8 Hz, 1H), 5.10 (d, J = 4.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 171.6, 158.6 (d, $^1J_{C-F}$ = 238.5 Hz), 141.3, 135.4 (d, $^4J_{C-F}$ = 2.2 Hz), 128.6, 128.1, 127.1, 121.9 (d, $^3J_{C-F}$ = 7.8 Hz), 115.6 (d, $^2J_{C-F}$ = 22.0 Hz), 74.5; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{14}H_{12}FNNaO_2$, 268.0750; found, 268.0747.

*N-(2-Chlorophenyl)-2-hydroxy-2-phenylacetamide (**5n**).*[21] White solid; yield: 245 mg, 94%; mp 167−168 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 20:80). FT-IR (KBr, cm^{-1}): 3299, 3184, 3092, 2842, 1651, 1062; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.65 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.52 (t, J = 8.4 Hz, 3H), 7.40−7.30 (m, 4H), 7.16 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 4.4 Hz, 1H), 5.20 (d, J = 4.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 171.4, 140.8, 134.6, 129.8, 128.7, 128.3, 127.2, 125.9, 124.3, 122.7, 74.1.

*N-(4-Chlorophenyl)-2-hydroxy-2-phenylacetamide (**5o**).*[22] White solid; yield: 256 mg, 98%; mp 164−165 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 20:80). FT-IR (KBr, cm^{-1}): 3317, 3157, 3092, 2842, 1650, 1060; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.08 (s, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.53−7.45 (m, 4H), 7.36 (t, J = 7.2 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 6.47 (d, J = 4.4 Hz, 1H), 5.10 (d, J = 4.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ (ppm): 171.9, 141.1, 138.4, 131.9, 128.6, 128.1, 127.0, 122.2, 115.7, 74.5; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{14}H_{12}ClNNaO_2$, 284.0454; found, 284.0448.

*N-(4-Bromophenyl)-2-hydroxy-2-phenylacetamide (**5p**).*[17] Off-white crystalline solid; yield: 285 mg, 93%; mp 127−128 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 20:80). FT-IR (KBr, cm^{-1}): 3343, 3294, 3091, 2900, 1668, 751; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.65 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.52 (t, J = 8.4 Hz, 3H), 7.41−7.30 (m, 4H), 7.16 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 4.4 Hz, 1H), 5.20 (d, J = 4.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 171.9, 141.1, 138.4, 131.9, 128.6, 128.1, 127.0, 122.2, 115.7, 74.5.

*N-(4-Cyanophenyl)-2-hydroxy-2-phenylacetamide (**5q**).*[21] Off-white crystalline solid; yield: 229 mg, 91%; mp 169−170 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 20:80). FT-IR (KBr, cm^{-1}): 3358, 3092, 2913, 2224, 1667, 1309; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.39 (s, 1H), 7.95−7.76 (AB quartet, 4H, J = 8.8 Hz), 7.52 (d, J = 7.2 Hz, 2H), 7.37 (t, J = 6.8 Hz, 2H), 7.30 (t, J = 7.2 Hz, 1H), 6.57 (d, J = 4.4 Hz, 1H), 5.16 (d, J = 4.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 172.6, 143.3, 140.8, 133.6, 128.7, 128.3, 127.1, 120.3, 119.5, 105.8, 74.6.

*N-(4-Formylphenyl)-2-hydroxy-2-(p-tolyl)acetamide (**5r**).* Off-white solid; yield: 247 mg, 92%; mp 164−165 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 25:75). FT-IR (KBr, cm^{-1}): 3434, 3092, 2976, 1692, 1562, 802; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.29 (s, 1H), 9.87 (s, 1H), 7.94 (d, J = 8.8 Hz, 2H), 7.84 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 6.43 (s, 1H), 5.11 (s, 1H), 2.28 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 192.1, 172.6, 144.6, 137.9, 137.4, 132.0, 131.1, 129.2, 127.0, 119.9, 74.4, 21.2; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{15}NNaO_3$, 292.0950; found, 292.0936.

*N-(4-Acetylphenyl)-2-hydroxy-2-phenylacetamide (**5s**).*[21] White solid; yield: 242 mg, 90%; mp 169−170 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 25:75). FT-IR (KBr, cm^{-1}): 3434, 3092, 2975, 1672, 1644, 1556, 815; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.29 (s, 1H), 7.98−7.89 (m, 4H), 7.57 (d, J = 7.2 Hz, 2H), 7.41 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 6.55 (d, J = 4.8 Hz, 1H), 5.20 (d, J = 4.8 Hz, 1H), 2.56 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 197.1, 172.3, 143.4, 140.9, 132.5, 129.8, 128.6, 128.2, 127.1, 119.5, 74.6, 26.9.

*2-Hydroxy-N-(4-methylpyridin-2-yl)-2-phenylacetamide (**5t**).* White solid; yield: 225 mg, 93%; mp 142−143 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 30:70). FT-IR (KBr, cm^{-1}): 3410, 3056, 2978, 1685, 1647, 1552, 850; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.90 (s, 1H), 8.22 (d, J = 4.8 Hz, 1H), 7.93 (s, 1H), 7.55 (d, J = 7.2 Hz, 2H), 7.40 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 7.03−6.98 (m, 1H), 6.57 (d, J = 4.8 Hz, 1H), 5.26 (d, J = 4.8 Hz, 1H), 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 171.8, 151.5, 149.7, 148.3, 140.9, 128.6, 128.2, 127.0, 121.4, 114.0, 73.8, 21.3; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_2$, 243.1134; found, 243.1127.

*2-Hydroxy-2-phenyl-N-(quinolin-8-yl)acetamide (**5u**).* Off-white crystalline solid; yield: 261 mg, 94%; mp 136−137 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 30:70). FT-IR (KBr, cm^{-1}): 3419, 3071, 2980, 1641, 1554, 881; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.23 (s, 1H), 9.02 (dd, J = 4.4, 1.6 Hz, 1H), 8.70 (dd, J = 7.6, 1.2 Hz, 1H), 8.45 (dd, J = 8.4, 1.6 Hz, 1H), 7.73−7.67 (m, 2H), 7.63−7.55 (m, 3H), 7.41 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 7.08 (d, J = 4.4 Hz, 1H), 5.29 (d, J = 4.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 171.5, 149.7, 141.1, 138.5, 137.2, 134.1, 128.7, 128.3, 128.2, 127.5, 127.1, 122.8, 122.5, 115.9, 74.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{15}N_2O_2$, 279.1134; found, 279.1131.

*2-Hydroxy-2-phenyl-N-(thiazol-2-yl)acetamide (**5v**).* White solid; yield: 213 mg, 91%; mp 150−151 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 30:70). FT-IR (KBr, cm^{-1}): 3432, 3082, 2979, 1645, 1554, 1077; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.07 (s, 1H), 7.60−7.55 (m, 2H), 7.54 (d, J = 3.6 Hz, 1H), 7.41 (t, J = 7.2 Hz, 2H), 7.35 (t, J = 7.2 Hz, 1H), 7.27 (d, J = 3.6 Hz, 1H), 6.38 (s, 1H), 5.37 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 171.6, 157.9, 140.4, 138.2, 128.7, 128.4, 127.1, 114.3, 73.4; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{11}H_{11}N_2O_2S$, 235.0541; found, 235.0538.

*N-Benzyl-2-hydroxy-2-phenylacetamide (**5w**).*[39] White crystalline solid; yield: 222 mg, 92%; mp 110−111 °C. The title compound was prepared according to the general procedure (B) described above (EtOAc:hexanes = 20:80). FT-IR (KBr, cm^{-1}): 3278, 3083, 2976, 1619, 1295, 754; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.52 (t, J = 6.0 Hz, 1H), 7.43 (d, J = 7.6 Hz, 2H), 7.32 (t, J = 7.2 Hz, 2H), 7.29−7.24 (m, 3H), 7.23−7.18 (m, 3H), 6.19 (d, J = 4.8 Hz, 1H), 4.97 (d, J = 4.8 Hz, 1H), 4.33−4.23 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 172.7, 141.8, 140.0, 128.6, 128.4, 127.9, 127.6, 127.1, 127.0, 74.0, 42.2.

*2-Hydroxy-N-methyl-N,2-diphenylacetamide (**5x**).*[21] White crystalline solid; yield: 224 mg, 93%; mp 128−129 °C. The title compound was prepared according to the general procedure (A) described above (EtOAc:hexanes = 30:70). FT-IR (KBr, cm^{-1}): 3423, 3091, 2954, 1656, 1495, 707; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.49−7.38 (m, 3H), 7.30−6.90 (m, 7H), 5.59 (d, J = 6.4 Hz, 1H), 5.06 (s, 1H), 3.22 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 172.2, 143.1, 140.7, 129.9, 128.5, 128.3, 128.2, 128.1, 127.4, 70.6, 37.9; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{15}H_{15}NNaO_2$, 264.1000; found, 264.0995.

*3,3,5-Trimethylcyclohexyl 2-Hydroxy-2-phenylacetate (Cyclandelate) (**7**).*[35] Colorless liquid; yield: 2.18 g, 79%. Cyclandelate was prepared according to the general procedure (A) as a mixture of diastereomers (EtOAc:hexanes = 10:90). FT-IR (KBr, cm^{-1}): 3458, 3091, 2994, 2954, 1738, 1215, 786; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43−7.27 (m, 5H), 5.18−5.13 (m, 0.2 H), 5.12−5.07 (m, 1H), 4.99−4.90 (m, 0.8H), 3.67 (dd, J = 13.2, 5.6 Hz, 0.2H), 3.58 (d, J = 5.6 Hz, 0.8H), 2.05−1.98 (m, 0.4H), 1.81−1.61 (m, 2H), 1.51−1.41 (m, 0.6H), 1.35−1.25 (m, 2H), 0.95−0.82 (m, 9H), 0.77−0.67 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.4, 173.4, 173.3, 173.3, 138.8, 138.8, 138.5, 128.6, 128.5, 128.5, 128.4, 127.0,

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126.7, 126.6, 126.5, 73.8, 73.7, 73.6, 73.4, 73.3, 73.1, 48.0, 47.5, 47.5, 43.9, 43.5, 41.4, 41.2, 40.3, 39.9, 38.5, 38.1, 34.0, 33.8, 33.1, 33.0, 32.5, 32.4, 27.4, 27.2, 27.1, 26.8, 25.6, 25.5, 23.4, 23.1, 22.5, 22.4, 22.3.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c00936.

Experimental procedures for starting materials, ^{1}H, ^{13}C, and ^{19}F NMR copies of all compounds, and HRMS copies of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Y. D. Vankar on the occasion of his 71st birthday.

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