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Article

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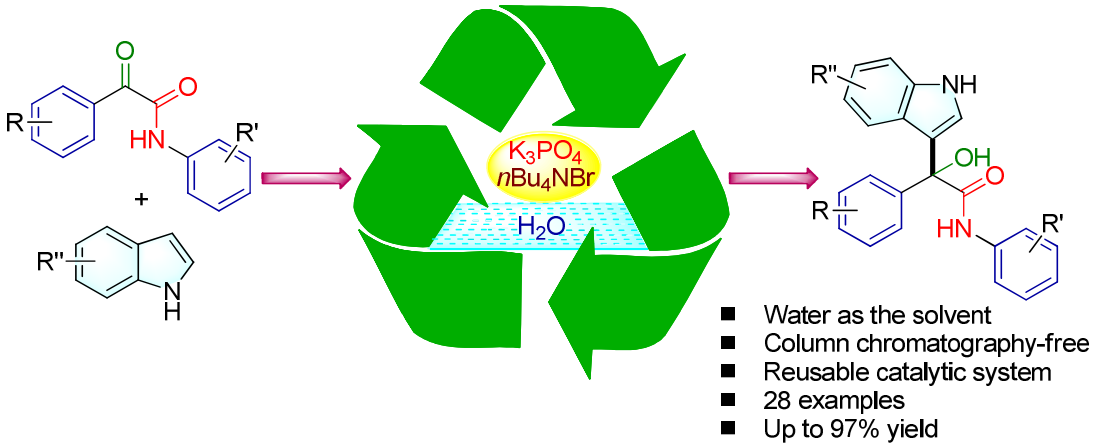
Friedel-Crafts Hydroxyalkylation of Indoles with α-Keto Amides using Reusable K_3PO_4/*n*Bu_4NBr Catalytic System in Water

Alagesan Muthukumar and Govindasamy Sekar*

Department of Chemistry, Indian Institute of Technology Madras, Chennai-600036, Tamilnadu, India



ABSTRACT: A mild and operationally simple Friedel-Crafts hydroxyalkylation of indoles with α-keto amides is developed for the first time by using catalytic amount of K_3PO_4 and *n*Bu_4NBr in water as solvent through a solid-liquid interface formation. The transition-metal-free protocol does not demand column chromatography purification and results in highly pure indole fused α-hydroxy amides in good to excellent yields. Reusability of the catalytic system up to five cycles and extension to a gram-scale reaction are the key advantages of this transformation. The mechanistic study involving ^{1}H-NMR experiments reveal that the reaction proceeds *via* ion exchange pathway.

KEYWORDS: *Monoindolylation; α-keto amide; reusable catalysts; water solvent; chromatography-free*

INTRODUCTION

Indole core containing molecules are present in many natural products and show biological activities.[1] Derivatives of indole with C3 substitution are generally more attractive for the construction of pharmaceutically and agriculturally useful molecules, of which 3-indolyl alcohols play a vital role in organic synthesis as key precursors to synthesize complex molecules and in pharmaceuticals as drugs.[2] Likewise, α-hydroxy amides are the important structural units that exhibit medicinal and pesticidal properties.[3] Considering the importance of 3-indolyl alcohols and α-hydroxy amides, the combination of these two units together in a single molecular framework could be of promising synthetic and biological importance (Figure 1).

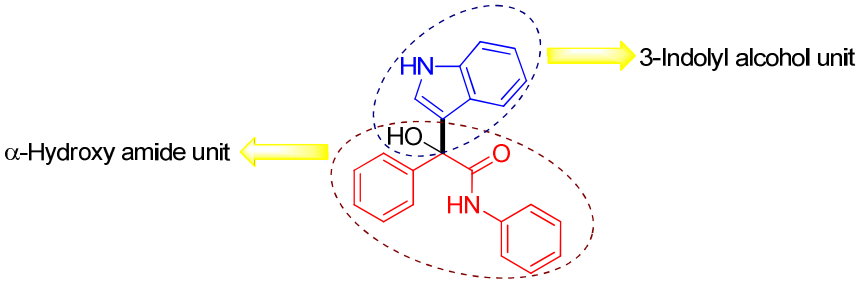
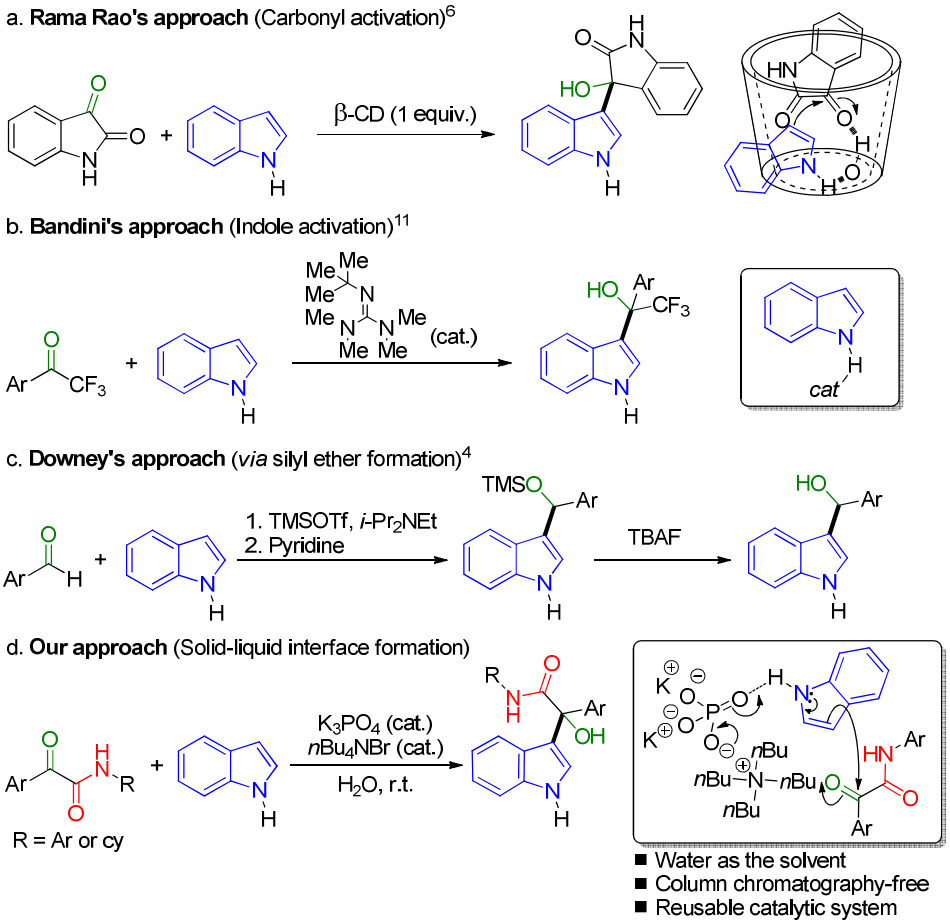


Figure 1. Target motif bearing of 3-indolyl alcohol and α-hydroxy amide units

Selective Friedel-Crafts reaction of indole with carbonyl compounds provides a platform to 3-indolyl alcohols. For instance, mono-addition of indole to aldehyde was reported using stoichiometric TMSOTf/*i*-Pr_2NEt[4] and Cs_2CO_3.[5] Hydroxyalkylation of indole with activated keto group of isatin was explored using β-cyclodextrin catalyst,[6] urea-choline chloride deep eutectic solvent,[7] DABCO-base ionic liquids,[8] bovine pancreas (BPC) enzyme catalyst[9] and chincona-derived squaramide catalyst[10] etc. Similarly, trifluoromethyl ketone was utilized as electrophile for indole hydroxyalkylation using guanidine,[11] Cs_2CO_3,[12] dinuclear zinc,[13] chincodine catalysts[14] and catalyst-, solvent-free condition.[15] In addition, hydroxyalkylation with α-carbonyl and pyruvate esters was reported using Solkane® 365mfc solvent,[16] stoichiometric K_2CO_3[17] and catalytic SmI_2,[18] scandium,[19] cobalt,[20] and quinine/quinidine systems.[21] Based on the literature reports, the mono addition of indole to carbonyl functionality is limited to few electrophiles. Most of the protocols involved through the activation of carbonyl group, activation of indole N-H bond or deprotection of *in-situ* generated silyl ether to form the corresponding 3-indolyl alcohols (Scheme 1a-c) which were meticulously purified by flash chromatography or else it could cause decomposition of the

products. Thus finding of an alternate protocol with simple purification method is much desired.

α-Keto amides have recently gained attention among organic chemists as they own not only biological properties, but also serve as useful synthetic intermediates due to the presence of potential active sites such as ketone and amide functionalities.[22] In this context, our group has contributed to the functionalization of α-keto amides through hydrosilylation and C(sp^3)-H alkylation of 2-alkyl azaarenes.[23] Since there is no significant example known for the fuctionalization of indoles with α-keto amides and in connection with our interest in development of green organic transformations,[24] we herein report a first K_3PO_4/nBu$_4$NBr-catalyzed hydroxyalkylation of indole with α-keto amide in aqueous medium through the formation of an interface between solid organic and aqueous phases (Scheme 1d). We intended to use water as the solvent due to the insolubility of α-hydroxy amides in water that makes the purification easier through a simple filtration technique.



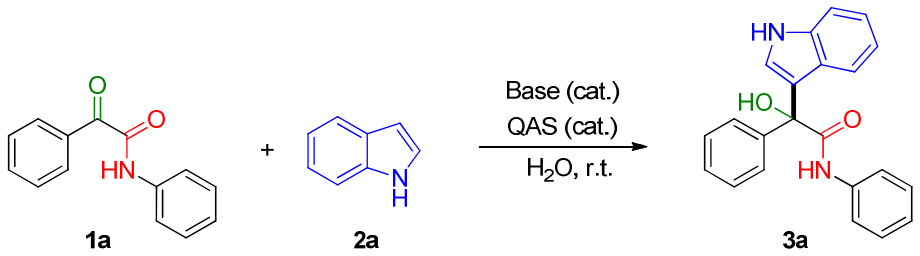
Scheme 1. Hydroxyalkylation of indole

RESULTS AND DISCUSSION

The optimization studies were carried out with 0.5 mmol of α-keto amide, 2-oxo-*N*-2-diphenylacetamide **1a** and 0.6 mmol of indole **2a** as the model substrates in distilled water and the results are depicted in Table 1. Initially, 20 mol% of K_2CO_3 was used as the base (entry 1). No product formation was observed which can be identified by the resulted yellow coloured solid reaction mass of unreacted **1a** (Figure 2A). From this observation, it is understood that the reactants remained insoluble in water. Albeit water has many ecological advantages over other organic solvents,[25] the major concern of water mediated reactions is the solubility of substrates. Thus insolubility of the reactants **1a** and **2a** in water could be overcome by the addition of a quaternary ammonium salt in to the reaction mixture which could form an interface between the solid phase and aqueous phase and thereby assist the progress of reaction. To our delight, when a combination of 20 mol% of K_2CO_3 and 20 mol% of nBu$_4$NBr was tested, it resulted in 81% of the indole addition product, 2-hydroxy-2-(1*H*-indol-3-yl)-*N*,2-diphenylacetamide **3a** in 9 h (entry 2). During the course of reaction, the reactants underwent pasty agglomeration (Figure 2B) which resulted in **3a** as white solid upon vigorous stirring (Figure 2C). The indole fused α-hydroxy amide **3a** was isolated using filtration method and confirmed by X-ray analysis (CCDC 1569315, see Supporting Information for detailed crystallography data). The sticky agglomeration of reactants confirms the formation of an interface between the solid phase and the aqueous phase. Noteworthy, the reaction failed to proceed only in the presence of 20 mol% of nBu$_4$NBr (entry 3) and resulted in a yellow oily mass (Figure 2D). Thus, the combination of both base and quaternary ammonium salt (QAS) is crucial for the progress of reaction.

When the catalytic loading of nBu$_4$NBr was reduced to 10 mol% and 5 mol% (entries 4 and 5), the reaction with 10 mol% of nBu$_4$NBr gave better yield of **3a**. When the activity of other alkali metal carbonates such as Na_2CO_3 and Cs_2CO_3 was tested, the former provided modest yield and the later failed to produce the product **3a** (entries 6 and 7). The use of hydroxide bases like KOH and NaOH did not improve the reaction yield (entries 8 and 9). Interestingly, when K_3PO_4 was used as the base, the reaction yield was increased to 95% and the reaction time reduced to 4 h (entry 10). But, no significant increase in the yield of **3a** was observed when Na_3PO_4 was used as the base (entry 11). After screening various bases, K_3PO_4 was chosen as the catalyst for this transformation.

Table 1. Optimization of the reaction conditions[a]



Entry	Base (mol%)	QAS (mol%)	Time (h)	Yield[b] (%)
1	K_2CO_3 (20)	--	24	0
2	K_2CO_3 (20)	nBu$_4$NBr (20)	9	81
3	--	nBu$_4$NBr (20)	24	0
4	K_2CO_3 (20)	nBu$_4$NBr (10)	19	83
5	K_2CO_3 (20)	nBu$_4$NBr (5)	24	71
6	Na_2CO_3 (20)	nBu$_4$NBr (10)	36	78
7	Cs_2CO_3 (20)	nBu$_4$NBr (10)	24	0
8	KOH (20)	nBu$_4$NBr (10)	6	81
9	NaOH (20)	nBu$_4$NBr (10)	9	79
10	K_3PO_4 (20)	nBu$_4$NBr (10)	4	95
11	Na_3PO_4•12H_2O (20)	nBu$_4$NBr (10)	6	83
12	K_3PO_4 (20)	nBu$_4$NF (10)	4	80
13	K_3PO_4 (20)	nBu$_4$NCl (10)	5	82
14	K_3PO_4 (20)	nBu$_4$NI (10)	8	79
15[c]	**K_3PO_4 (15)**	**nBu$_4$NBr (10)**	**8**	**95 (92)**
16	K_3PO_4 (10)	nBu$_4$NBr (10)	39	84
17	--	--	48	0

[a]Reaction conditions: **1a** (0.5 mmol) and **2a** (0.6 mmol) in 8 mL of distilled water. [b]In all the cases, **3a** was isolated by simple filtration without further column chromatographic purification. [c]Yield of **3a** in tap water.

Screening of other QASs having different halide counter anions such as nBu$_4$NF, nBu$_4$NCl and nBu$_4$NI, did not provide a better yield as compare to nBu$_4$NBr (entries 12-14). When the amount of K_3PO_4 was reduced to 15 mol%, 95% of **3a** was isolated in 8 h (entry 15). Further decrease of the catalyst loading to 10 mol% slowed down the reaction rate and 84% of **3a** was isolated in 39 h (entry 16), which suggests that the combination of 15 mol%

of K_3PO_4 and 10 mol% of nBu$_4$NBr is suitable catalytic system for this protocol. As anticipated, no product formation was observed in the absence of both K_3PO_4 and nBu$_4$NBr (entry 17).

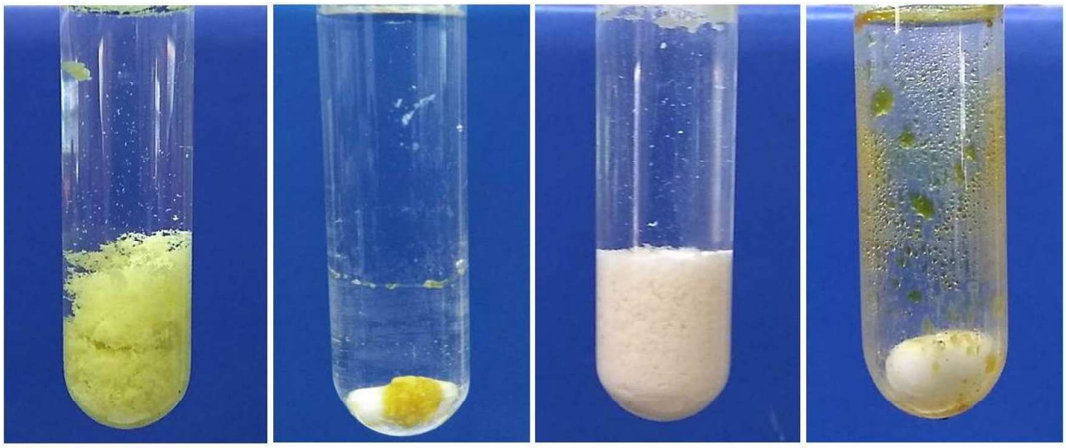


Figure 2. Pictorial representations of the reactions having a mixture of (A) **1a**, **2a** and 20 mol% of base after 24 h. (B) Agglomeration of the reaction mixture in 1-2 h when **1a**, **2a**, 20 mol% of base and 20 mol% of QAS were used. (C) Formation of the product **3a** after 9 h. (D) Formation of oily mass after 24 h when **1a**, **2a** and 20 mol% of QAS were used.

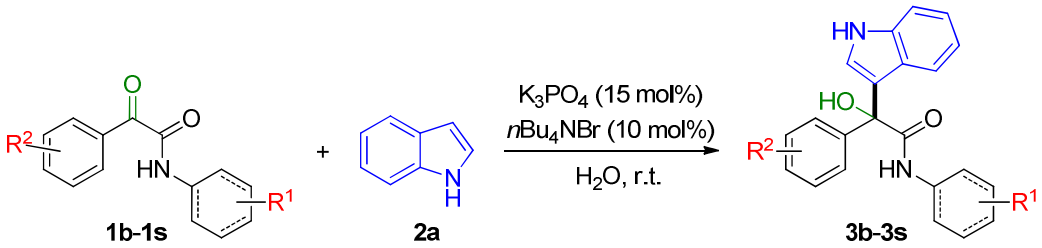
Having the optimized conditions in hand, the scope of the reaction was explored with different α-keto amides and the results are summarized in Table 2. 4-Methyl substituted α-keto amide gave 83% yield of the corresponding product **3b** in 11 h (entry 1). Similarly, α-keto amide having methoxy group substitution at *ortho*-, *meta*- and *para*-positions of the anilide ring provided the corresponding indole fused mandelamides **3c**, **3d** and **3e** in 79%, 73% and 82% yields, respectively (entries 2-4). 2,6-Dimethyl aniline derived α-keto amide resulted in 97% of the indole addition product **3f** in 12 h (entry 5). Likewise, α-keto amide tethered to halo substituents such as chloro, bromo and iodo afforded the corresponding indole bearing α-hydroxy amides **3g-3j** in 81-96% yields, respectively (entries 6-9).

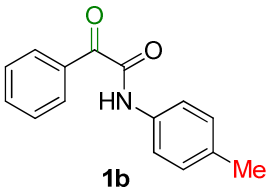
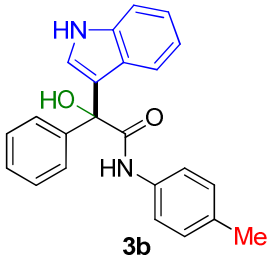
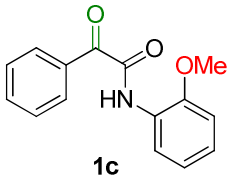
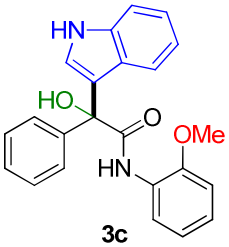
When acetyl and nitro tethered α-keto amides were subjected to reaction, the reactants became sticky mass and further proceeding of the reactions was failed to produce the corresponding products **3k** and **3l** (entries 10 and 11). Even when the reactions were performed in H_2O/EtOH mixture, they resulted in no product formation. The reason could be the deprotonation of α-keto amide to form α-keto amidate which upon conjugation might diminish the electrophilicity of ketone. Interestingly, other electron withdrawing groups like

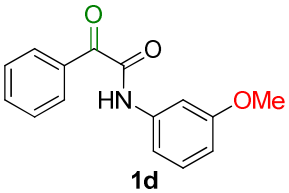
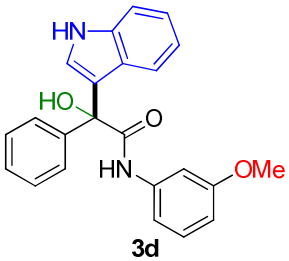
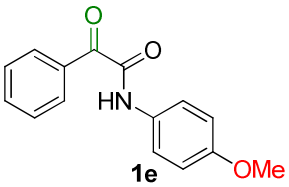
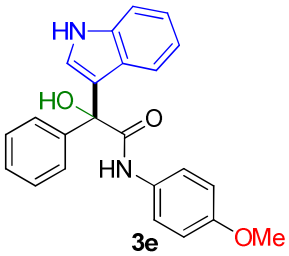
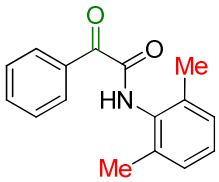
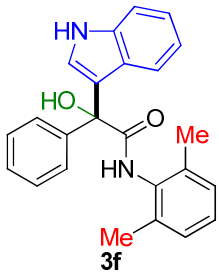
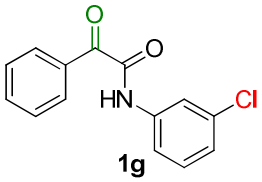
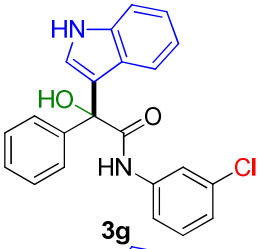
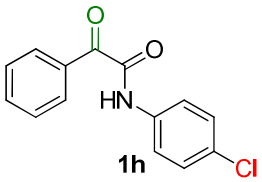
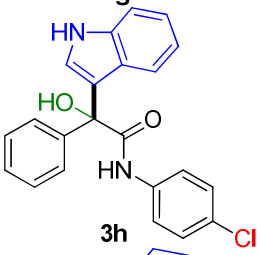
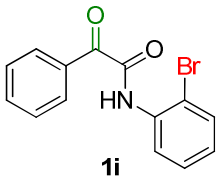
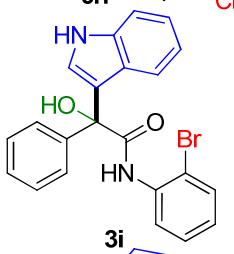
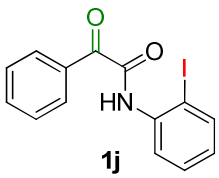
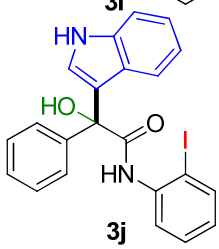
trifluoromethyl and cyano containing α-keto amides underwent smoothly to provide the 3-indolyl alcohol analogues **3m** and **3n** in 83% and 87% yields, respectively (entries 12 and 13). Importantly, aliphatic amine i.e., cyclohexyl amine derived α-keto amide also gave the product **3o** in 84% yield (entry 14).

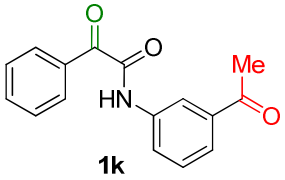
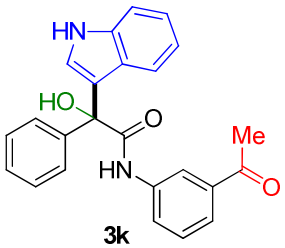
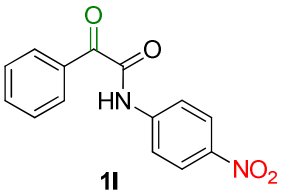
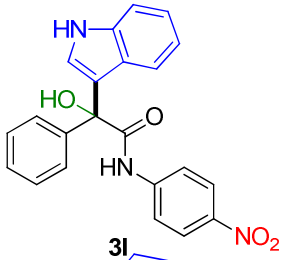
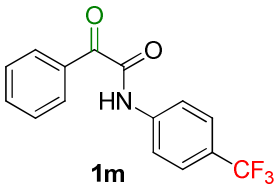
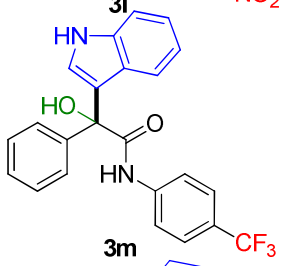
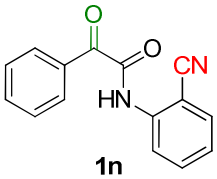
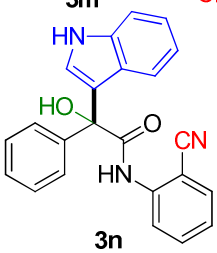
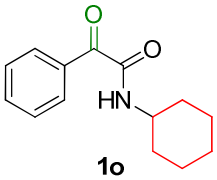
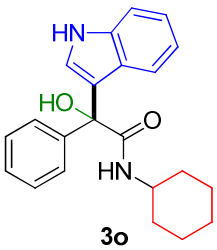
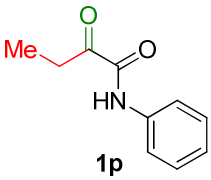
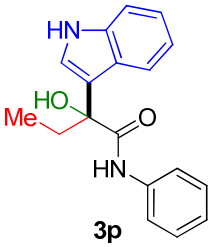
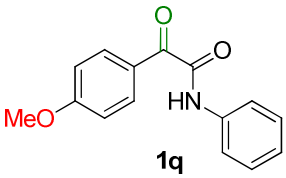
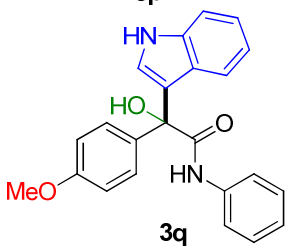
However, α-keto amides with aliphatic ketone failed to provide the corresponding products **3p** and **3s** even after 24 h (entries 15 and 18). The inactiveness of the aliphatic α-keto amides could be either due to the absence of electron withdrawing aryl group or the presence of enolizable protons alpha to the keto group in basic medium which reduces the electrophilicity of the keto functionality. Also, the α-keto amide bearing methoxy group *para* to benzoyl ring underwent reaction smoothly to render the respective product **3q** in 80% yield (entry 16). In addition, 1-naphthyl amine derived α-keto amide provided the corresponding indole fused α-hydroxy amide in 65% yield (entry 17).[26]

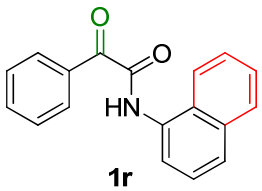
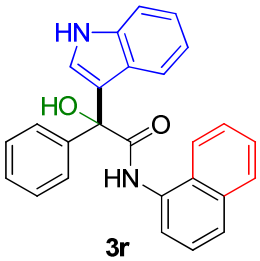
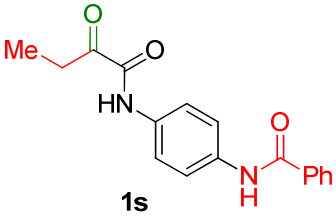
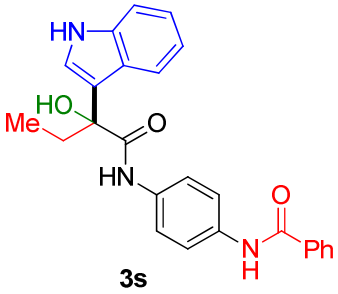
Table 2. Scope of α-keto amide[a]



Entry	α-Keto amide	Product	Time (h)	Yield[b] (%)
1			11	83
2			10	79

3	 **1d**	 **3d**	10	73
4	 **1e**	 **3e**	10	82
5	 **1f**	 **3f**	12	97
6	 **1g**	 **3g**	12	81
7	 **1h**	 **3h**	15	75
8	 **1i**	 **3i**	11	85
9	 **1j**	 **3j**	9	96

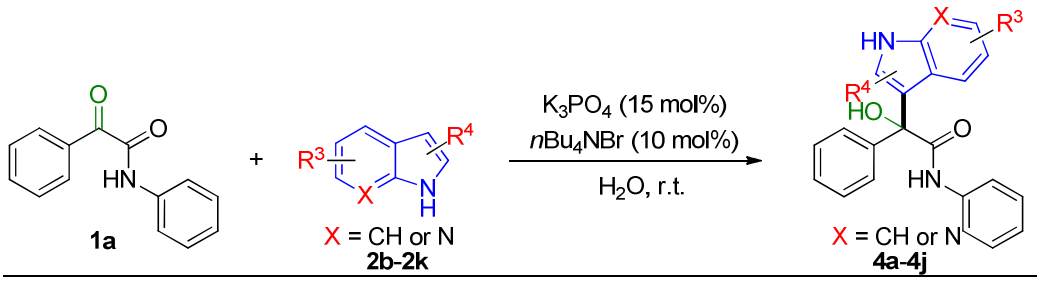
10	 **1k**	 **3k**	24	0
11	 **1l**	 **3l**	24	0
12	 **1m**	 **3m**	15	83
13	 **1n**	 **3n**	15	87
14	 **1o**	 **3o**	10	84
15	 **1p**	 **3p**	24	0
16	 **1q**	 **3q**	12	80

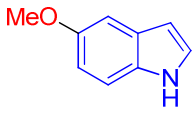
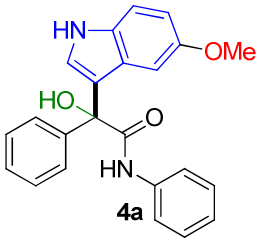
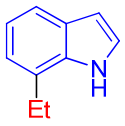
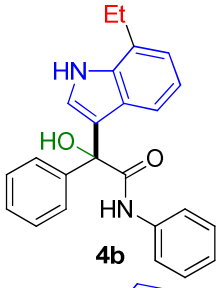
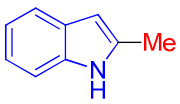
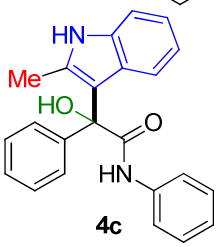
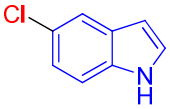
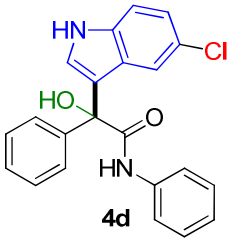
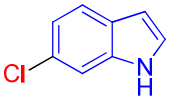
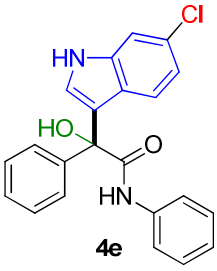
17[c]	 **1r**	 **3r**	24	65
18	 **1s**	 **3s**	24	0

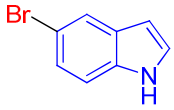
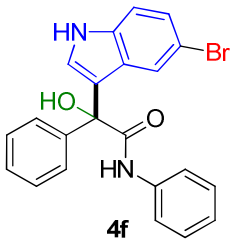
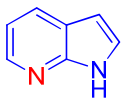
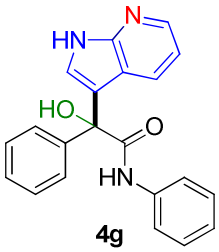
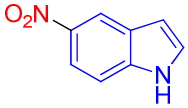
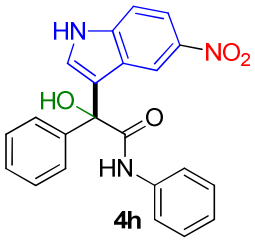
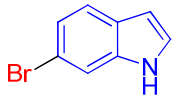
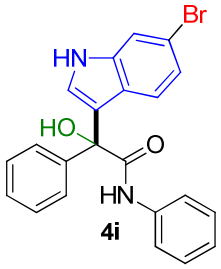
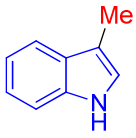
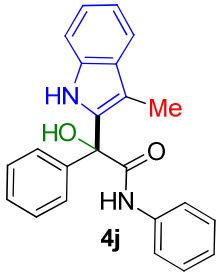
[a]Reaction conditions: **1** (0.5 mmol) and **2a** (0.6 mmol) in 8 mL of distilled water. [b]Isolated yield after purification using filtration. [c]6:2 ratio of water and ethanol was used.

Next, the scope of indole having different substituents was studied with α-keto amide **1a** and the results are shown in Table 3. In the case of 5-methoxy indole, the corresponding hydroxy alkylated product **4a** was isolated in 80% yield in 24 h (entry 1). When 7-ethyl indole was subjected for reaction, it resulted in 81% of the respective product **4b** in 24 h (entry 2). The reaction with sterically demanding 2-methyl indole proceeded well and rendered **4c** in 87% of yield (entry 3). In addition, indole with halo substitutions such as 5-chloro, 6-chloro, 5-bromo and 6-bromo gave the corresponding products **4d**, **4e**, **4f** and **4i** in good yields (entries 4-6 and 9). Noteworthy, when 1*H*-pyrrolo[2,3-*b*]pyridine was utilized, the mono addition product **4g** was isolated in 79% of yield (entry 7). However, the reaction failed to proceed when weak nucleophilic nitro group substituted indole with was used **4h** (entry 8). Furthermore, when 3-methyl indole was tested, the reaction failed to provide the C2 addition product **4j** (entry 10).

Table 3. Scope of Indole[a]



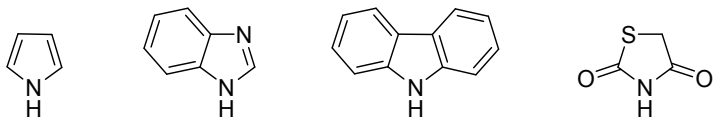
Entry	Indole	Product	Time (h)	Yield[b] (%)
1	 **2b**	 **4a**	24	80
2[c]	 **2c**	 **4b**	24	81
3	 **2d**	 **4c**	8	87
4	 **2e**	 **4d**	10	74
5	 **2f**	 **4e**	10	76

6[c]	 **2g**	 **4f**	15	70
7	 **2h**	 **4g**	16	79
8	 **2i**	 **4h**	24	0
9[c]	 **2j**	 **4i**	24	74
10	 **2k**	 **4j**	24	0

[a]Reaction conditions: **1a** (0.5 mmol) and **2** (0.6 mmol) in 8 mL of distilled water. [b]Isolated yield after purification using filtration. [c]6:2 ratio of water and ethanol was used.

The applicability of other heterocyclic systems such as pyrrole **5**, benzimidazole **6**, carbazole **7** and thiazolidine-2,4-dione **8** was tested with α-keto amide **1a** (Figure 3). But,

they failed to provide the corresponding products under the standard reaction conditions and even after enhancing the catalysts loading.[27]



5 **6** **7** **8**

Figure 3. Reactivity of other heterocycles with α-keto amide

Having the successful development of the hydroxyalkylation of indoles with α-keto amides by using K_3PO_4/*n*Bu_4NBr catalysts, next the possibility of recyclability of catalytic system was investigated using a reaction of 1.0 mmol of α-keto amide **1a** with 1.2 mmol of indole **2a** using 0.15 mmol of K_3PO_4 and 0.1 mmol of *n*Bu_4NBr in 16 mL of distilled water at room temperature in 10 h reaction time. After the completion of first cycle, the indole hydroxyalkylated product **3a** was filtered off and the resultant filtrate was recovered and reused for the successive alkylation reactions. Interestingly, the catalytic system was well active up to four cycles and furnished **3a** in excellent yields. However, in the fifth cycle, the reaction did not proceed for the complete consumption of starting materials and afforded 61% of **3a** (Figure 4). However, the yield of **3a** was increased up to 76% if the reaction time was prolonged to 48 h.[28]

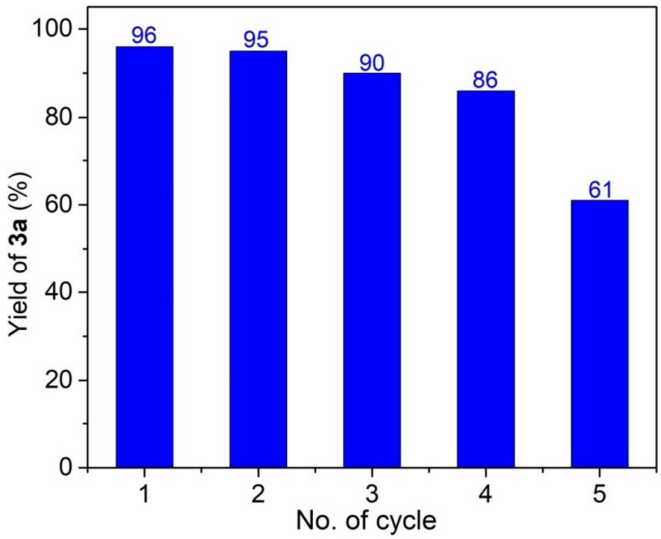


Figure 4. Recovery and recyclability of K_3PO_4/*n*Bu_4NBr catalytic system for the hydroxyalkylation of indole **2a** with α-keto amide **1a** in 10 h reaction time.

As the activity of the catalytic system diminished in the fifth cycle, we focused on the investigation of initial reaction kinetics of hydroxyalkylation of indole with α-keto amides. First, the progress of the reaction was monitored and the ratio of disappearance of α-keto amide **1a** and the formation of product **3a** were determined using HPLC (Figure 5A). The initial reaction rates were deduced from the experimental curves of **3a** concentration versus reaction time by determination of the slope at the origin. Taking into account of the total volume of the reaction mixture, the initial rates were then converted into mmol L^{-1} min^{-1} units. The initial reaction rate for the first cycle was found to be 4.54 x 10^{-2} mmol L^{-1} min^{-1} (Figure 5B). Whereas, the initial reaction rate for the fifth cycle was found as 2.95 x 10^{-2} mmol L^{-1} min^{-1} (Figure 5C). This implies that the catalysts gradually loose the activity in the fifth cycle.

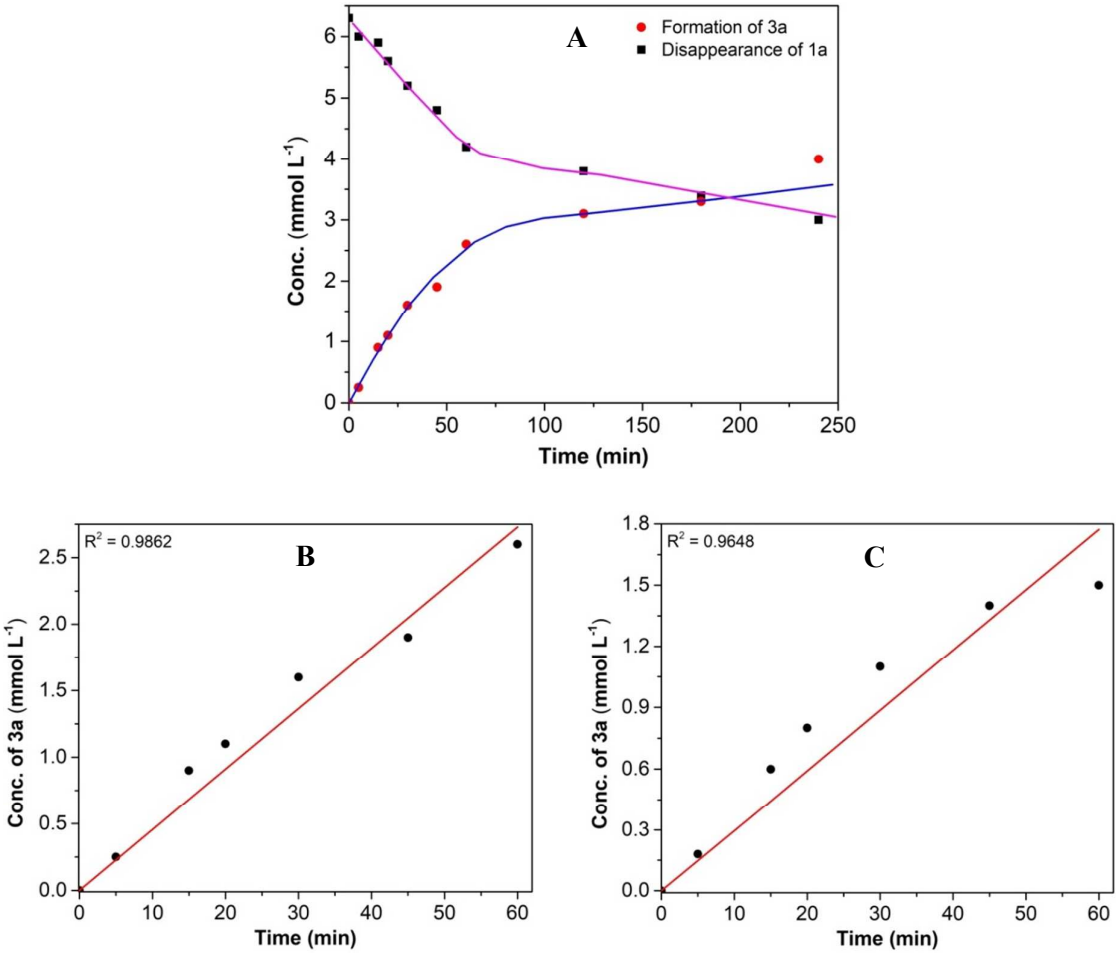
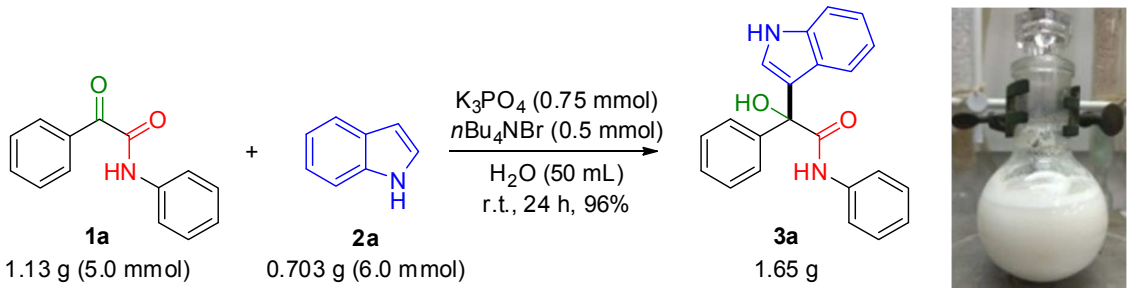


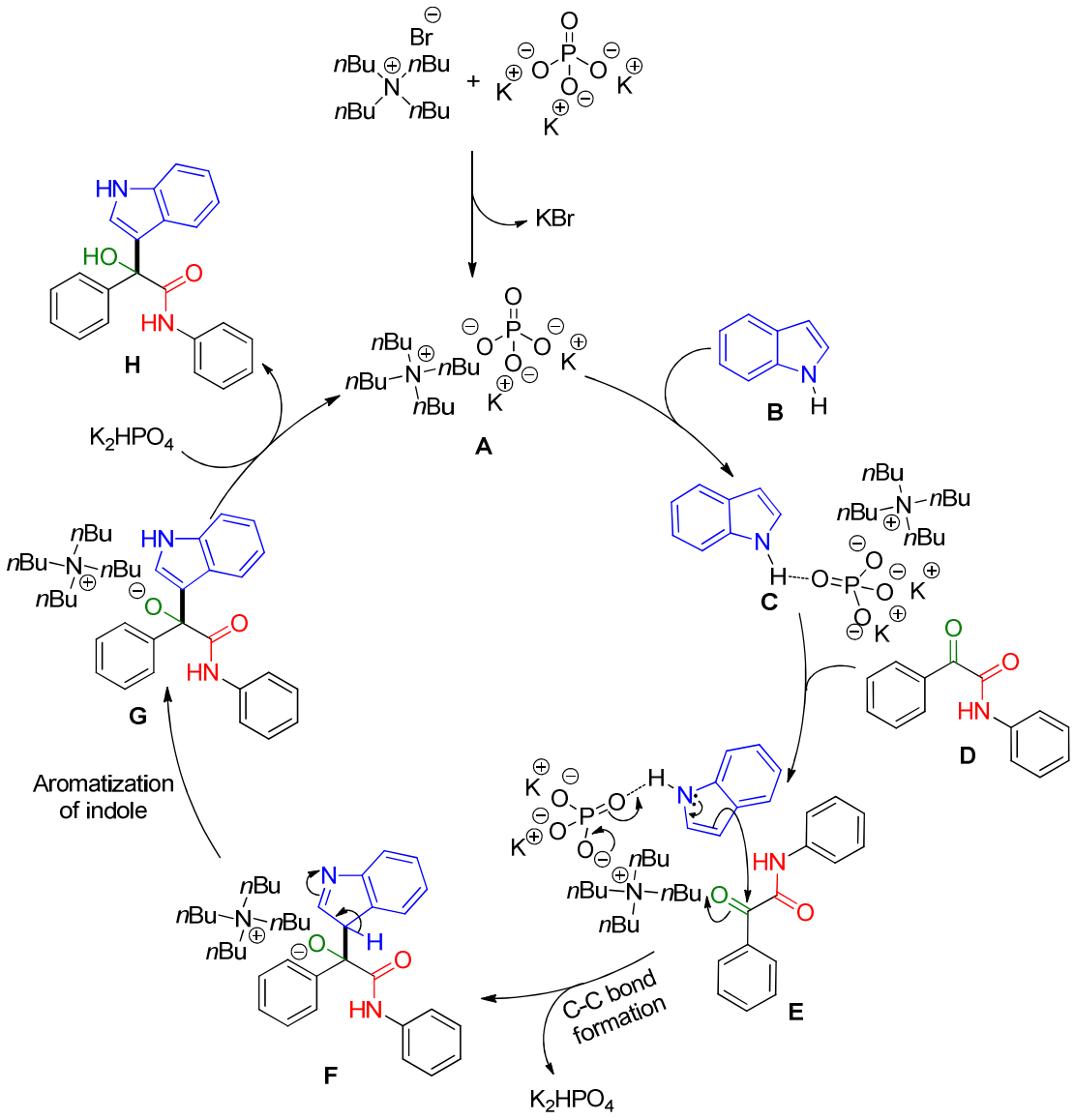
Figure 5. A) Plot for the disappearance of **1a** and formation of **3a**. B) Progress of the formation of **3a** in the first catalytic cycle. C) Progress of the formation of **3a** in the fifth catalytic cycle.

After exploring the recyclability of catalytic system, the efficiency of Friedel-Crafts reaction was further attempted on a gram-scale reaction. For this purpose, 1.13 g (5.0 mmol) of the α-keto amide **1a** was subjected to reaction with 0.703 g (6.0 mmol) of indole **2a** by using 0.75 mmol of K_3PO_4 and 0.5 mmol of nBu$_4$NBr in 50 mL of water at ambient temperature for 24 h (Scheme 2). The reaction afforded 96 % of the selective addition product **3a**.



Scheme 2. Gram-scale reaction

Next, a plausible mechanistic pathway for this transformation is proposed in Scheme 3. Initially, an interaction between nBu$_4$NBr and K_3PO_4 gave rise to the QAS nBu$_4$N$^+$K$_2$PO$_4^-$ **A**.[29] It is important to mention that from the optimization study (Table 1, Entries 10 and 11), it is found that K_3PO_4 provided better yield than Na_3PO_4. The observation can be correlated with Fajan's rule, that is, as the size of the cation increases, the ionic character of the salt increases. Thus, the lowered activity of Na_3PO_4 may be due to less ionic nature than K_3PO_4 which suppresses the rate of the ion metathesis process.[30] Then the QAS **A** would interact with indole **B** through hydrogen bonding to form the adduct **C**. Then, the adduct **C** led to the formation of **E** up on interaction with α-keto amide **D**. The QAS **E** would assist the formation of an interface[31] and undergo indolylation of keto group. Formation of C-C bond between C3-position of indole with α-keto amide resulted in QAS **F**, which further underwent aromatization of indole ring to form **G**. Protonation of **G** would lead to the formation of the product **H** by expelling **A** for the next catalytic cycle.



Scheme 3. Plausible mechanistic proposal for the hydroxyalkylation of indole with α-keto amide

In order to support our mechanistic hypothesis, the interaction between QAS, base and indole was studied using ^{1}H-NMR experiment in D_2O as the solvent and the results are represented in Figure 6. Initially, the ^{1}H-NMR of nBu$_4$NBr was recorded (Figure 6A). Next, a 1:1.5 mixture of nBu$_4$NBr and K_3PO_4 was stirred in D_2O and the resulting solution was analyzed (Figure 6B). Interestingly, the peaks with respect to nBu$_4$N$^+$ slightly shifted towards upfield region. This may imply the formation of the intermediate **A** (Scheme 3) by the interaction between nBu$_4$NBr and K_3PO_4. In order to confirm the chemical shift difference, the ^{1}H-NMR for a 1:1.5 mixture of nBu$_4$NBr and KCl was recorded and this resulted in a

downfield shift (Figure 6C). Moreover, the peaks corresponding to nBu$_4$NCl also appeared almost in the downfield region (Figure 6D). This implies that the observed chemical shift changes could be majorly due to the exchange of anions in aqueous medium. Then, a 1:1.5:1.5 combinations of nBu$_4$NBr, K_3PO_4 and indole were stirred in D_2O and the resulting mixture was analyzed. An upfield shift of peaks corresponding to nBu$_4$N$^+$ was observed which could be due to the effect of indole ring (Figure 6E). This depicts that the formation of the adduct **C** (Scheme 3) might have taken place. In all the cases, the slight shift of peaks towards upfield or downfield regions indicate the effect of the counter anions[32] such as Cl^-, Br^-, and $K_2PO_4^-$ with variable electron density which will have different electrostatic interaction with nBu$_4$N$^+$. Comparing the differences between the chemical shift values of nBu$_4$N$^+$, the increase of shielding capacities of the anions can be ordered as follows: $Cl^- < Br^- < K_2PO_4^-$.

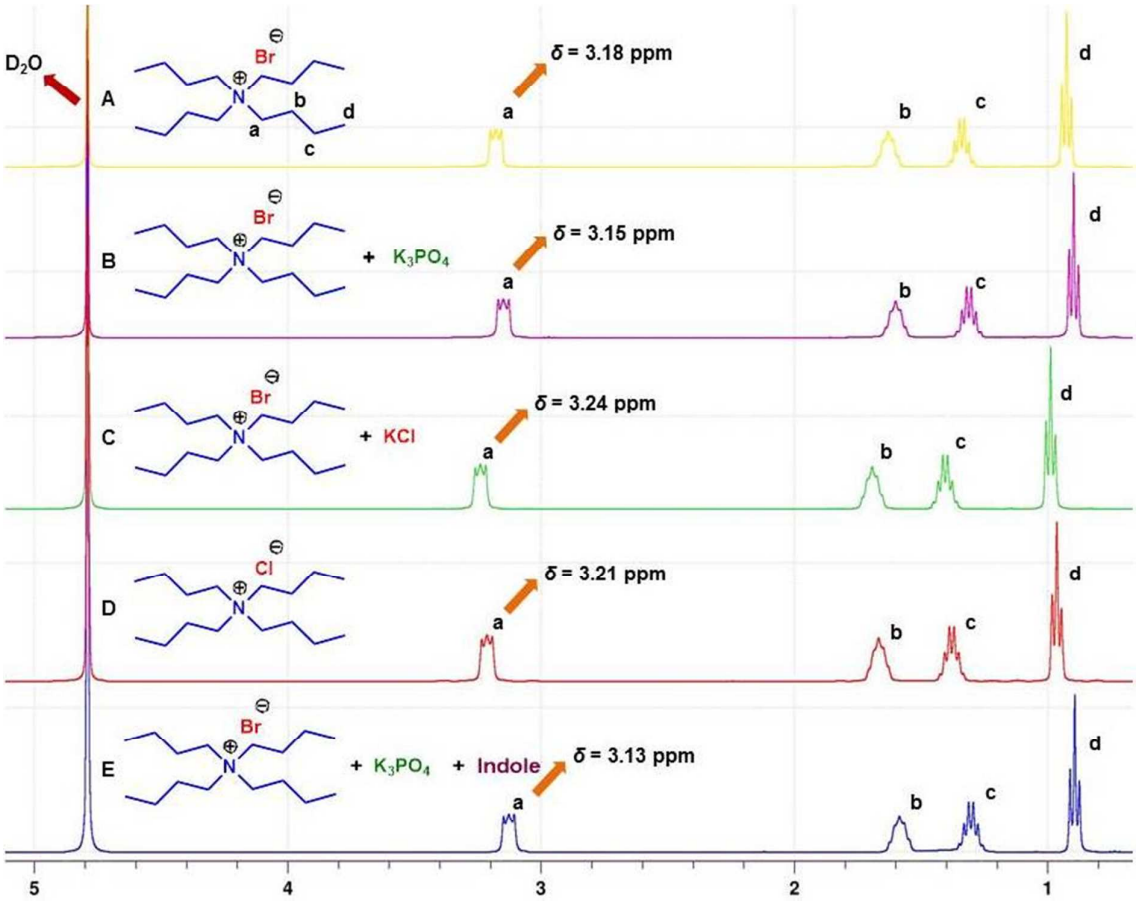
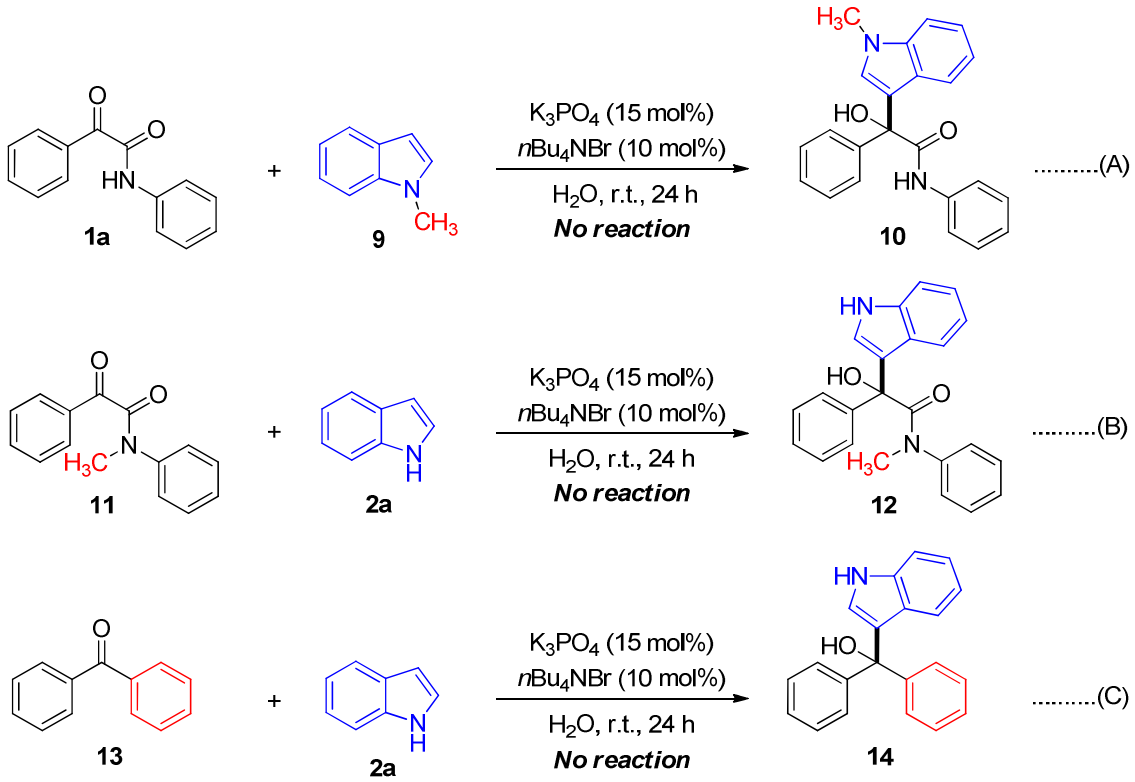


Figure 6. ^{1}H NMR spectra of (A) nBu$_4$NBr (B) nBu$_4$NBr and K_3PO_4 (C) nBu$_4$NBr and KCl (D) nBu$_4$NCl (E) nBu$_4$NBr, K_3PO_4 and indole in D_2O with residual solvent peak calibration at δ = 4.79 ppm (400 MHz)

Further evidence to support the mechanistic proposal, a reaction of *N*-protected indole **9** was carried out with α-keto amide **1a** under the standard reaction conditions. It is noteworthy to mention that the reaction failed to proceed in the absence of indole having free -NH functionality. This shows that the reaction proceeds through the deprotonation of indole (Scheme 4A). Next, in order to find out the necessity of free -NH of α-keto amide, a reaction was performed between *N*-methyl substituted tertiary α-keto amide **11** and indole **2a**. The failure of the reaction implies that the essence of free -NH of α-keto amide perhaps due to interaction with the catalyst[33] or to diminish the steric crowding of keto group (Scheme 4B). In order to understand the importance of amide functionality, a reaction between a non-enolizable ketone i.e., benzophenone **13** and indole **2a** was carried out (Scheme 4C). The failure of reaction depicts the role of amide group for enhancing the electrophilicity of the ketone of α-keto amide. Moreover, the development of this Friedel-Crafts reaction, biological activity of the indole fused α-hydroxy amides and extension to asymmetric hydroxyalkylation are under progress.



Scheme 4. Control experiments

CONCLUSION

In conclusion, we have developed an efficient and practical Friedel-Crafts hydroxyalkylation of indoles with α-keto amides using inexpensive K_3PO_4/*n*Bu_4NBr in water as the solvent. Both aromatic and aliphatic amine derived α-keto amides were well tolerated and provided the indole tethered α-hydroxy amides in good to excellent yields. It is noteworthy that the reaction involves simple filtration method by avoiding column chromatography method to purify the products. The recovery and reusability of the catalytic system was attested up to five consecutive cycles which denote the process is green and economic. In addition, the efficacy of the reaction has been further tested with a gram-scale reaction. The mechanistic study shows that the reaction could proceed *via* the exchange of ions between the base, QAS and indole which has been demonstrated using the counterion effect in ^{1}H-NMR spectroscopy and control experiments.

EXPERIMENTAL SECTION

1. General Considerations

All reactions were carried out in oven-dried reaction tubes. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} pre-coated plates (0.25 mm) and visualized by UV fluorescence quenching. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 and 500 MHz instruments. ^{1}H NMR spectra were reported relative to residual DMSO (δ 2.50 ppm) with tetramethylsilane (TMS, δ = 0.00 ppm) as the internal standard. ^{13}C NMR was reported relative to DMSO-d_6 (δ = 39.52 ppm). Chemical shifts were reported in parts per million (ppm) and multiplicities are as indicated: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet) and bs (broad singlet). Coupling constants (*J*) are reported in Hertz. Melting points were recorded on a Guna capillary melting point apparatus and were corrected with benzoic acid as reference. Infrared spectra were recorded on a FTIR 4000 Series Spectrometer using dry KBr pellet. The wave numbers of recorded IR signals were quoted in cm^{-1}. High resolution mass spectra (HR-MS) were recorded on Q-Tof Micro mass spectrometer and 6545 Accurate-Mass Q-Tof LC/MS instrument. In order to determine the initial reaction rate, the progress of the reaction was monitored and the ratio of α-keto amide and the product was determined in Shimadzu HPLC systems using Luna® 5 μm Silica (2) 100 Å, LC Column 250 x 4.6 mm.

CCDC-1569315 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Solvents used for extraction and column chromatography were laboratory grade and used as received. Reaction solvents used were obtained from Fischer Scientific, India Pvt. Ltd. and Spectrochem Pvt. Ltd. All the anilines were purchased from Alfa-aesar, Sigma-Aldrich Company, Avra synthesis, Spectrochem Pvt. Ltd. and TCI chemicals. α-Keto acids were purchased from Sigma-Aldrich Company and Spectrochem Pvt. Ltd. Indoles were purchased form Spectrochem Pvt. Ltd. and Alfa-aesar. K_3PO_4 was purchased from Sigma-Aldrich Company and nBu$_4$NBr was purchased from Spectrochem Pvt. Ltd.

2. Experimental conditions

2.1 General experimental procedure for synthesis of α-keto amides[23]

To an oven dried RB flask equipped with magnetic bar, benzoyl formic acid (2.0 mmol) in CH_2Cl_2 (10 mL) was added and the RB flask was cooled to 0 ^oC under nitrogen atmosphere. Next, triethyl amine (4.0 mmol) was added and stirred for 15 min. Then, thionyl chloride (4.0 mmol) was added drop wise to the reaction mixture and stirring was allowed for 20 min. A solution of corresponding amine (2.0 mmol) in CH_2Cl_2 (10 mL) was added slowly to the reaction mixture at 0 ^oC. The stirring was continued at room temperature and the completion of reaction was monitored by TLC. The reaction mixture was diluted with CH_2Cl_2 and the organic layer was washed with water (2 x 20 mL) followed by a saturated aqueous solution of $NaHCO_3$ (2 x 20 mL) or until no effervescence was observed. The separated organic layer was washed with water (2 x 20 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The pure α-keto amide was isolated as solid using silica gel column chromatography.

2.2 General experimental procedure for Friedel-Crafts hydroxyalkylation of indoles with α-keto amides using K_3PO_4/nBu$_4$NBr Catalytic System

To an oven dried reaction tube equipped a 12mm x 6mm (length x diameter) sized magnetic bar, 0.5 mmol of α-keto amide **1** and 0.6 mmol of indole **2** were added. To which 8 mL water was added and the reaction was allowed to stir for 5 minutes. Next, 0.075 mmol of K_3PO_4 and 0.05 mmol of nBu$_4$NBr were added. Initially the reaction mixture underwent

agglomeration which further allowed for vigorous stirring (if the reaction mixture turned to a sticky mass, few drops of ethanol can be added for a better stirring) resulted in indole incorporated α-hydroxy amide **3** or **4** formation as a white or off-white solid. The resulting residue was filtered through Whatman Filter Paper Grade No. 1-Size 125mm using Büchner filtrations funnel and washed with hexanes. Further purification using column chromatography was not required.

2.3 Spectroscopic and physical data of products

2-Hydroxy-2-(1*H*-indol-3-yl)-*N*,2-diphenylacetamide (3a)

White solid; 154 mg, 90% yield; mp = 174-176 ^{o}C; R_f = (hexanes : ethyl acetate, 70 : 30 v/v); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 11.03 (bs, 1H), 9.96 (bs, 1H), 7.77 (d, J = 7.6 Hz, 2H), 7.67 (d, J = 7.2 Hz, 2H), 7.24-7.42 (m, 7H), 7.15 (d, J = 2.4 Hz, 1H), 7.01-7.11 (m, 2H), 6.83-6.93 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ = 172.1, 143.5, 138.6, 136.7, 128.6, 127.5, 127.1, 126.8, 125.8, 124.8, 123.6, 121.1, 120.8, 119.9, 118.5, 118.3, 111.5, 77.6; IR (KBr) v = 3424, 3340, 3052, 3031, 1666, 1596, 1519, 1434, 1049, 740, 691 cm^{-1}; HR-MS (*m/z*): [M+Na]$^{+}$ calcd. for $C_{22}H_{18}N_2O_2Na$, 365.1266; found, 365.1265.

2-Hydroxy-2-(1*H*-indol-3-yl)-2-phenyl-*N*-(*p*-tolyl)acetamide (3b)

White solid; 148 mg, 83% yield; mp = 200-202 ^{o}C; R_f = 0.65 (hexanes : ethyl acetate, 70 : 30 v/v); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 11.02 (bs, 1H), 9.87 (bs, 1H), 7.57-7.73 (m, 4H), 7.22-7.44 (m, 5H), 7.08-7.18 (m, 3H), 7.05 (t, J = 7.2 Hz, 1H), 6.79-6.93 (m, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ = 171.9, 143.6, 136.7, 136.0, 132.5, 129.0, 127.5, 127.1, 126.8, 125.8, 124.7, 121.0, 120.8, 119.8, 118.5, 118.4, 111.5, 77.5, 20.5; IR (KBr) v = 3403, 3329, 3052, 3027, 1663, 1511, 1305, 1168, 1034, 817, 740 cm^{-1}; HR-MS (*m/z*): [M+Na]$^{+}$ calcd. for $C_{23}H_{20}N_2O_2Na$, 379.1422; found, 379.1433.

2-Hydroxy-2-(1*H*-indol-3-yl)-*N*-(2-methoxyphenyl)-2-phenylacetamide (3c)

White solid; 147 mg, 79% yield; mp = 206-208 ^{o}C; R_f = 0.42 (hexanes : ethyl acetate, 70 : 30 v/v); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 11.06 (bs, 1H), 9.94 (bs, 1H), 8.33 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 7.2 Hz, 2H), 7.23-7.45 (m, 5H), 7.00-7.20 (m, 5H), 6.82-6.98 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ = 171.5, 148.1, 143.3, 136.7, 127.6, 127.2, 127.1, 126.8, 125.7, 124.8, 123.8, 121.1, 120.6, 118.6, 118.3, 118.0, 111.6, 110.9, 77.6, 56.0; IR

(KBr) v = 3378, 3318, 3115, 3066, 2961, 2834, 1656, 1596, 1526, 1248, 1115, 1034, 740, 695 cm^{-1}; HR-MS (*m/z*): $[M+Na]^+$ calcd. for $C_{23}H_{20}N_2O_3Na$, 395.1372; found, 395.1362.

2-Hydroxy-2-(1*H*-indol-3-yl)-*N*-(3-methoxyphenyl)-2-phenylacetamide (3d)

Off-white solid; 136 mg, 73% yield; mp = 126-128 ^oC; R_f = 0.59 (hexanes : ethyl acetate, 70 : 30 v/v); ^1H NMR (400 MHz, DMSO-d_6) δ = 11.03 (bs, 1H), 9.94 (bs, 1H), 7.66 (d, J = 7.6 Hz, 2H), 7.49 (s, 1H), 7.24-7.43 (m, 6H), 7.20 (t, J = 8.0 Hz, 1H), 7.14 (s, 1H), 7.05 (t, J = 7.2 Hz, 1H), 6.82-6.95 (m, 2H), 6.58-6.69 (m, 1H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.2, 159.5, 143.5, 139.8, 136.7, 129.4, 127.5, 127.1, 126.9, 125.8, 124.8, 121.1, 120.7, 118.5, 118.3, 112.0, 111.5, 109.3, 105.3, 77.6, 55.0; IR (KBr) v = 3386, 3318, 3059, 2958, 2834, 1670, 1603, 1547, 1027, 838, 754, 695 cm^{-1}; HR-MS (*m/z*): $[M+Na]^+$ calcd. for $C_{23}H_{20}N_2O_3Na$, 395.1372; found, 395.1386.

2-Hydroxy-2-(1*H*-indol-3-yl)-*N*-(4-methoxyphenyl)-2-phenylacetamide (3e)

White solid; 153 mg, 82% yield; mp = 200-202 ^oC; R_f = 0.38 (hexanes : ethyl acetate, 70 : 30 v/v); ^1H NMR (400 MHz, DMSO-d_6) δ = 11.01 (bs, 1H), 9.86 (bs, 1H), 7.02-7.62 (m, 4H), 7.24-7.41 (m, 5H), 7.13 (d, J = 2.4 Hz, 1H), 7.05 (t, J = 7.4 Hz, 1H), 6.84-6.92 (m, 3H), 6.80 (s, 1H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ =171.7, 155.5, 143.7, 136.6, 131.7, 127.4, 127.0, 126.8, 125.8, 124.7, 121.4, 121.0, 120.8, 118.5, 118.4, 113.7, 111.5, 77.4, 55.2; IR (KBr) v = 3406, 3333, 3059, 2965, 2834, 2824, 2348, 1659, 1515, 1406, 1245, 1042, 831, 751 cm^{-1}; HR-MS (*m/z*): $[M+Na]^+$ calcd. for $C_{23}H_{20}N_2O_3Na$, 395.1372; found, 395.1373.

***N*-(2,6-Dimethylphenyl)-2-hydroxy-2-(1*H*-indol-3-yl)-2-phenylacetamide (3f)**

White solid; 180 mg, 97% yield; mp = 210-212 ^oC; R_f = 0.57 (hexanes : ethyl acetate, 70 : 30 v/v); ^1H NMR (400 MHz, DMSO-d_6) δ = 11.00 (bs, 1H), 9.47 (bs, 1H), 7.67 (d, J = 7.2 Hz, 2H), 7.25-7.46 (m, 5H), 7.22 (s, 1H), 6.96-7.11 (m, 4H), 6.88 (t, J = 7.6 Hz, 1H), 6.74 (s, 1H), 2.03 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.0, 144.0, 136.7, 135.5, 135.2, 127.6, 127.4, 126.9, 126.7, 126.3, 125.9, 124.7, 121.1, 121.0, 118.3, 118.2, 111.4, 77.7, 18.0; IR (KBr) v = 3452, 3365, 3249, 3052, 2961, 2915, 1670, 1498, 1091, 768, 743, 698 cm^{-1}; HR-MS (*m/z*): $[M+Na]^+$ calcd. for $C_{24}H_{22}N_2O_2Na$, 393.1579; found, 393.1581.

***N*-(3-Chlorophenyl)-2-hydroxy-2-(1*H*-indol-3-yl)-2-phenylacetamide (3g)**

Off-white solid; 153 mg, 81% yield; mp = 168-170 ^oC; R_f = 0.62 (hexanes : ethyl acetate, 70 : 30 v/v); ^1H NMR (400 MHz, DMSO-d_6) δ = 11.04 (bs, 1H), 10.22 (bs, 1H), 8.02 (s, 1H),

7.59-7.78 (m, 3H), 7.24-7.43 (m, 6H), 7.09-7.18 (m, 2H), 7.05 (t, J = 7.4 Hz, 1H), 6.82-6.96 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.7, 143.3, 140.1, 136.7, 133.0, 130.2, 127.5, 127.2, 126.8, 125.8, 124.8, 123.3, 121.1, 120.7, 119.4, 118.6, 118.5, 118.2, 111.5, 77.6; IR (KBr) v = 3421, 3343, 3129, 3080, 3059, 1659, 1648, 1592, 1526, 1421, 1329, 740, 695 cm^{-1}; HR-MS (*m/z*): [M+Na]$^+$ calcd. for $C_{22}H_{17}N_2O_2{}^{35}ClNa$, 399.0876; found, 399.0863.

_N_-(4-Chlorophenyl)-2-hydroxy-2-(1*H*-indol-3-yl)-2-phenylacetamide (3h)

White solid; 141 mg, 75% yield; mp = 194-196 ^{o}C; R_f = 0.63 (hexanes : ethyl acetate, 70 : 30 v/v); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.03 (bs, 1H), 10.15 (bs, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 7.2 Hz, 2H), 7.22-7.45 (m, 7H), 7.14 (s,1H), 7.05 (t, J = 7.2 Hz, 1H), 6.79-6.95 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.4, 143.4, 137.6, 136.7, 128.5, 127.6, 127.3, 127.2, 126.7, 125.8, 124.8, 121.6, 121.1, 120.8, 118.6, 118.3, 111.6, 77.6; IR (KBr) v = 3435, 3326, 3095, 3056, 3027, 1666, 1589, 1511, 1400, 1042, 828, 736 cm^{-1}; HR-MS (*m/z*): [M+Na]$^+$ calcd. for $C_{22}H_{17}N_2O_2{}^{35}ClNa$, 399.0876; found, 399.0874.

_N_-(2-Bromophenyl)-2-hydroxy-2-(1*H*-indol-3-yl)-2-phenylacetamide (3i)

White solid; 179 mg, 85% yield; mp = 190-192 ^{o}C; R_f = 0.6 (hexanes : ethyl acetate, 70 : 30 v/v); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.09 (bs, 1H), 10.10 (bs, 1H), 8.30 (d, J = 8.0 Hz, 1H), 7.56-7.77 (m, 3H), 7.24-7.47 (m, 7H), 7.18 (s, 1H), 7.06 (t, J = 7.4 Hz, 2H), 6.88 (t, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.0, 142.9, 136.7, 135.6, 132.6, 128.5, 127.7, 127.4, 126.8, 125.7, 125.6, 124.9, 121.2, 121.1, 120.6, 118.7, 117.5, 113.6, 111.6, 77.7; IR (KBr) v = 3368, 3329, 3112, 3063, 1680, 1586, 1509, 1294, 1031, 751, 695 cm^{-1}; HR-MS (*m/z*): [M+Na]$^+$ calcd. for $C_{22}H_{17}N_2O_2{}^{79}BrNa$, 443.0371; found, 443.0372.

2-Hydroxy-2-(1*H*-indol-3-yl)-_N_-(2-iodophenyl)-2-phenylacetamide (3j)

White solid; 224 mg, 96% yield; mp = 184-186 ^{o}C; R_f = 0.62 (hexanes : ethyl acetate, 70 : 30 v/v); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.08 (bs, 1H), 9.97 (bs, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 7.6 Hz, 2H), 7.24-7.45 (m, 7H), 7.18 (s, 1H), 7.06 (t, J = 7.6 Hz, 1H), 6.81-6.96 (two d, J = 7.6, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.1, 143.0, 139.0, 138.4, 136.7, 129.0, 127.7, 127.3, 126.8, 126.0, 125.7, 124.9, 121.2, 120.8, 120.7, 118.7, 117.6, 111.6, 90.8, 77.7; IR (KBr) v = 3382, 3322, 3112, 3059, 1670, 1571, 1519, 1428, 1284, 1034, 761, 701 cm^{-1}; HR-MS (*m/z*): [M+Na]$^+$ calcd. for $C_{22}H_{17}N_2O_2INa$, 491.0232; found, 491.0239.

2-Hydroxy-2-(1*H*-indol-3-yl)-2-phenyl-*N*-(4-(trifluoromethyl)phenyl)acetamide (3m)

White solid; 170 mg, 83% yield; mp = 174-176 ^{o}C; R_f = 0.52 (hexanes : ethyl acetate, 70 : 30 v/v); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 11.05 (bs, 1H), 10.38 (bs,1 H), 8.03(d, J = 8.4 Hz, 2H), 7.59-7.75 (m, 4H), 7.24-7.44 (m, 5H), 7.15 (s, 1H), 7.05 (t, J = 7.6 Hz, 1H), 6.96 (s, 1H), 6.87 (t, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ = 172.9, 143.3, 142.3, 136.7, 127.6, 127.2, 126.9, 125.9 (q, J = 3.0 Hz), 125.8, 124.8, 121.1, 120.7, 120.0, 118.6, 118.1, 111.6, 77.7; IR (KBr) v = 3438, 3329, 3101, 3059, 3027, 1676, 1515, 1406, 1333, 1171, 845, 743, 691 cm^{-1}; HR-MS (*m/z*): [M+Na]$^{+}$ calcd. for $C_{23}H_{17}N_2O_2F_3Na$, 433.1140; found, 433.1137.

***N*-(2-Cyanophenyl)-2-hydroxy-2-(1*H*-indol-3-yl)-2-phenylacetamide (3n)**

White solid; 160 mg, 87% yield; mp = 184-186 ^{o}C; R_f = 0.37 (hexanes : ethyl acetate, 70 : 30 v/v); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 11.10 (bs, 1H), 10.35 (bs, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.84 (dd, J = 6.4, 1.4 Hz, 1H), 7.62-7.72 (m, 3H), 7.26-7.42 (m, 6H), 7.17-7.25 (m, 2H), 7.02-7.10 (m, 1H), 6.84-6.92 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ = 172.5, 143.0, 140.2, 136.7, 134.1, 133.0, 127.6, 127.4, 126.9, 125.7, 125.04, 124.95, 122.7, 121.2, 120.7, 118.6, 117.6, 116.7, 111.6, 104.9; IR (KBr) v = 3424, 3322, 3098, 3059, 3031, 2213, 1680, 1575, 1515, 1449, 1294, 1042, 736 cm^{-1}; HR-MS (*m/z*): [M+Na]$^{+}$ calcd. for $C_{23}H_{17}N_3O_2Na$, 390.1218; found, 390.1230.

***N*-Cyclohexyl-2-hydroxy-2-(1*H*-indol-3-yl)-2-phenylacetamide (3o)**

White solid; 146 mg, 84% yield; mp = 182-184 ^{o}C; R_f = 0.41 (hexanes : ethyl acetate, 70 : 30 v/v); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 10.94 (bs, 1H), 7.72 (d, J =8.4 Hz, 1H), 7.57 (d, J = 7.2 Hz, 2H), 7.18-7.43 (m, 5H), 6.94-7.11 (m, 2H), 6.86 (t, J = 7.4 Hz, 1H), 6.43 (s, 1H), 3.48-3.70 (bs, 1H), 1.50-1.90 (m, 5H), 1.00-1.45 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ = 172.1, 144.0, 136.6, 127.3, 126.8, 126.75, 125.8, 124.5, 121.0, 120.9, 118.7, 118.3, 111.4, 77.0, 47.6, 32.4, 32.2, 25.2, 24.6; IR (KBr) v = 3406, 3322, 3056, 2922, 2849, 1648, 1530, 1034, 747, 701 cm^{-1}; HR-MS (*m/z*): [M+Na]$^{+}$ calcd. for $C_{22}H_{24}N_2O_2Na$, 371.1735; found, 371.1732.

2-Hydroxy-2-(1*H*-indol-3-yl)-*N*-(4-methoxyphenyl)-2-phenylacetamide (3q)

White solid; 149 mg, 80% yield; mp = 202-204 ^{o}C; R_f = 0.36 (hexanes : ethyl acetate, 70 : 30 v/v); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 11.01 (d, J = 1.6 Hz, 1H), 9.92 (bs, 1H), 7.75 (d, J

= 8.0 Hz, 2H), 7.55 (t, *J* = 8.8 Hz, 2H), 7.36 (t, *J* = 6.8 Hz, 2H), 7.30 (t, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 2.4 Hz, 1H), 7.01-7.09 (m, 2H), 6.84-6.93 (m, 3H), 6.78 (s, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.4, 158.4, 138.6, 136.7, 135.6, 128.6, 128.1, 125.8, 124.7, 123.6, 121.0, 120.8, 119.8, 118.53, 118.49, 112.8, 111.5, 77.2, 55.0; IR (KBr) v = 3378, 3322, 3112, 3066, 2947, 2831, 1663, 1603, 1536, 1515, 1248, 1034, 831, 754, 704 cm^{-1}; HR-MS (*m/z*): $[M+Na]^+$ calcd. for $C_{23}H_{20}N_2O_3Na$, 395.1372; found, 395.1377.

2-Hydroxy-2-(1*H*-indol-3-yl)-*N*-(naphthalen-1-yl)-2-phenylacetamide (3r)

White solid; 128 mg, 65% yield; mp = 183-185 ^{o}C; R_f = 0.5 (hexanes : ethyl acetate, 70 : 30 v/v); ^{1}H NMR (500 MHz, DMSO-d_6) δ = 11.06 (bs, 1H), 10.26 (bs, 1H), 7.95 (d, *J* = 7.0 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.69-7.87 (m, 4H), 7.28-7.61 (m, 8H), 7.25 (s, 1H), 7.01-7.20 (m, 2H), 6.90 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 172.5, 143.6, 136.7, 133.7, 133.1, 128.3, 127.5, 127.4, 127.1, 126.8, 126.1, 126.08, 125.8, 125.6, 125.1, 124.7, 121.6, 121.1, 120.8, 120.4, 118.5, 118.0, 111.5, 77.9 ; IR (KBr) v = 3385, 3335, 3136, 3056, 2955, 2842, 1669, 1612, 1516, 1254, 1039, 845, 756, 718 cm^{-1}; HR-MS (*m/z*): $[M+Na]^+$ calcd. for $C_{26}H_{20}N_2O_2Na$, 415.1422; found, 415.1437.

2-Hydroxy-2-(5-methoxy-1*H*-indol-3-yl)-*N*,2-diphenylacetamide (4a)

Off-white solid; 149 mg, 80% yield; mp = 174-176 ^{o}C; R_f = 0.67 (hexanes : ethyl acetate, 70 : 30 v/v); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.89 (bs, 1H), 9.99 (bs, 1H), 7.77 (d, *J* = 7.2 Hz, 2H), 7.69 (d, *J* = 6.8 Hz, 2H), 7.21-7.42 (m, 6H), 7.00-7.15 (m, 2H), 6.84 (d, *J* = 12.0 Hz, 2H), 6.72 (d, *J* = 8.0 Hz, 1H), 3.55 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.2, 152.7, 143.4, 138.5, 131.8, 128.6, 127.5, 127.1, 126.9, 126.2, 125.4, 123.6, 119.9, 118.1, 112.1, 110.8, 102.9, 77.5, 55.1; IR (KBr) v = 3424, 3337, 3316, 3056, 2989, 2939, 2824, 1631, 1533, 1438, 1031, 901, 796, 695 cm^{-1}; HR-MS (*m/z*): $[M+Na]^+$ calcd. for $C_{23}H_{20}N_2O_3Na$, 395.1372; found, 395.1372.

2-(7-Ethyl-1*H*-indol-3-yl)-2-hydroxy-*N*,2-diphenylacetamide (4b)

White solid; 150 mg, 81% yield; mp = 172-174 ^{o}C; R_f = 0.6 (hexanes : ethyl acetate, 70 : 30 v/v); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.01 (bs, 1H), 9.95 (bs, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 7.2 Hz, 2H), 7.23-7.39 (m, 5H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.01-7.12 (m, 2H), 6.75-6.93 (m, 3H), 2.85 (q, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.2, 143.5, 138.6, 135.3, 128.7, 127.5, 127.1, 126.92, 126.85, 125.7, 124.4, 123.6, 119.8, 118.9, 118.8, 118.5, 77.6, 23.8, 14.6; IR (KBr) v = 3421, 3294, 3052, 2965,

2930, 2862, 1670, 1596, 1526, 1438, 1038, 743, 695 cm^{-1}; HR-MS (*m/z*): $[M+Na]^+$ calcd. for $C_{24}H_{22}N_2O_2Na$, 393.1579; found, 393.1564.

2-Hydroxy-2-(2-methyl-1*H*-indol-3-yl)-*N*,2-diphenylacetamide (4c)

Pale yellow solid; 155 mg, 87% yield; mp = 194-196 ^oC; R_f = 0.74 (hexanes : ethyl acetate, 70 : 30 v/v); ^1H NMR (400 MHz, DMSO-d_6) δ = 10.96 (bs, 1H), 9.99 (bs, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 7.2 Hz, 2H), 7.27-7.41 (m, 5H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 6.93 (t, *J* = 7.2 Hz, 1H), 6.62-6.80 (m, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.5, 144.0, 138.6, 134.7, 134.3, 128.7, 127.52, 127.46, 127.2, 127.1, 123.6, 119.8, 119.7, 118.2, 113.5, 110.3, 77.7, 13.2; IR (KBr) *v* = 3414, 3329, 3080, 3063, 3031, 1666, 1592, 1519, 1438, 1160, 1031, 751, 695 cm^{-1}; HR-MS (*m/z*): $[M+Na]^+$ calcd. for $C_{23}H_{20}N_2O_2Na$, 379.1422; found, 379.1425.

2-(5-Chloro-1*H*-indol-3-yl)-2-hydroxy-*N*,2-diphenylacetamide (4d)

White solid; 139 mg, 74% yield; mp = 174-176 ^oC; R_f = 0.56 (hexanes : ethyl acetate, 70 : 30 v/v); ^1H NMR (400 MHz, DMSO-d_6) δ = 11.26 (bs, 1H), 9.98 (bs, 1H), 7.76 (d, *J* = 7.6 Hz, 2H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.25-7.45 (m, 8H), 7.02-7.12 (m, 2H), 6.97 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.0, 143.3, 138.5, 135.2, 128.7, 127.7, 127.3, 126.9, 126.8, 126.5, 123.7, 123.1, 121.0, 120.0, 119.9, 118.0, 113.1, 77.5; IR (KBr) *v* = 3442, 3340, 3301, 3087, 3059, 3031, 1642, 1596, 1522, 1434, 1305, 1105, 751, 695 cm^{-1}; HR-MS (*m/z*): $[M+Na]^+$ calcd. for $C_{22}H_{17}N_2O_2{}^{35}ClNa$, 399.0876; found, 399.0878.

2-(6-Chloro-1*H*-indol-3-yl)-2-hydroxy-*N*,2-diphenylacetamide (4e)

Off-white solid; 143 mg, 76% yield; mp = 192-194 ^oC; R_f = 0.6 (hexanes : ethyl acetate, 70 : 30 v/v); ^1H NMR (400 MHz, DMSO-d_6) δ = 11.17 (bs, 1H), 9.97 (bs, 1H), 7.76 (d, *J* = 7.6 Hz, 2H), 7.63 (d, *J* = 7.2 Hz, 2H), 7.43 (s, 1H), 7.15-7.41 (m, 7H), 7.06 (t, *J* = 6.8 Hz, 1H), 6.85-7.01 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.0, 143.3, 138.5, 137.1, 128.6, 127.6, 127.2, 126.8, 125.9, 124.6, 123.7, 122.1, 119.9, 118.9, 118.5, 111.1, 77.5; IR (KBr) *v* = 3449, 3347, 3308, 3081, 3062, 3038, 1656, 1596, 1530, 1445, 1322, 1231, 1027, 898, 754, 736, 695 cm^{-1}; HR-MS (*m/z*): $[M+Na]^+$ calcd. for $C_{22}H_{17}N_2O_2{}^{35}ClNa$, 399.0876; found, 399.0868.

2-(5-Bromo-1*H*-indol-3-yl)-2-hydroxy-*N*,2-diphenylacetamide (4f)

White solid; 147 mg, 70% yield; mp = 174-176 ^{o}C; R_f = 0.47 (hexanes : ethyl acetate, 70 : 30 v/v); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.27 (bs, 1H), 9.98 (bs, 1H), 7.76 (d, J = 7.2 Hz, 2H), 7.61 (d, J = 6.4 Hz, 2H), 7.48 (s, 1H), 7.23-7.43 (m, 7H), 7.17 (d, J = 7.6 Hz, 1H), 7.07 (t, J = 6.4 Hz, 1H), 6.98 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 171.9, 143.3, 138.4, 135.4, 128.6, 127.7, 127.6, 127.3, 126.8, 126.3, 123.7, 123.5, 123.0, 120.0, 117.9, 113.6, 111.2, 77.5; IR (KBr) ν = 3442, 3343, 3312, 3091, 3066, 3024, 1642, 1592, 1526, 1449, 1098, 754, 691 cm^{-1}; HR-MS (*m/z*): $[M+Na]^+$ calcd. for $C_{22}H_{17}N_2O_2{}^{79}BrNa$, 443.0371; found, 443.0369.

2-Hydroxy-*N*,2-diphenyl-2-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acetamide (4g)

White solid; 136 mg, 79% yield; mp = 196-198 ^{o}C; R_f = 0.26 (hexanes : ethyl acetate, 50 : 50 v/v); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.61 (bs, 1H), 9.99 (bs, 1H), 8.18 (dd, J = 4.4, 1.2 Hz, 1H), 7.76 (d, J = 7.6 Hz, 2H), 7.65-7.71 (m, 1H), 7.62 (d, J = 7.2 Hz, 2H), 7.24-7.40 (m, 6H), 7.07 (t, J = 7.2 Hz, 1H), 7.02 (s, 1H), 6.96 (dd, J = 8.0, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 171.9, 148.8, 143.2, 142.6, 138.5, 128.9, 128.6, 127.7, 127.4, 126.8, 124.8, 123.7, 120.0, 118.2, 117.1, 115.2, 77.6; IR (KBr) ν = 3393, 3203, 2992, 2930, 2884, 1670, 1596, 1526, 1442, 1308, 1059, 736 cm^{-1}; HR-MS (*m/z*): $[M+Na]^+$ calcd. for $C_{21}H_{17}N_3O_2Na$, 366.1218; found, 366.1204.

2-(6-Bromo-1*H*-indol-3-yl)-2-hydroxy-*N*,2-diphenylacetamide (4i)

White solid; 156 mg, 74% yield; mp = 191-193 ^{o}C; R_f = 0.57 (hexanes : ethyl acetate, 70 : 30 v/v); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.16 (bs, 1H), 9.95 (bs, 1H), 7.75 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.57 (s, 1H), 7.25-7.37 (m, 6H), 7.23 (s, 1H), 7.00-7.09 (m, 2H), 6.94 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 171.9, 143.3, 138.5, 137.5, 128.6, 127.6, 127.2, 126.8, 125.7, 124.9, 123.6, 122.5, 121.4, 119.9, 118.5, 114.0, 113.9, 77.5; IR (KBr) ν = 3448, 3356, 3310, 3082, 3064, 3018, 1656, 1599, 1517, 1452, 1010, 746, 695 cm^{-1}; HR-MS (*m/z*): $[M+Na]^+$ calcd. for $C_{22}H_{17}N_2O_2{}^{79}BrNa$, 443.0371; found, 443.0372.

2.4 Procedure for recovery and reusability of catalytic system

To an oven dried reaction tube equipped with a magnetic bar, 1.0 mmol of α-keto amide **1a**, and 1.2 mmol of indole **2a** were weighed. To which 18 mL water was added and the reaction was allowed to stir for 5 minutes. Next, 0.15 mmol of K_3PO_4 and 0.1 mmol of nBu$_4$NBr were

added. After 10 h, the reaction mass was filtered off and resulted in 95% of indole incorporated α-hydroxy amide **3a**. The resulting filtrate was used for next catalytic cycles.

2.5 Determination of initial reaction rate

The initial reaction rate of the catalytic cycles has been determined by using HPLC method. However, we faced a major challenge which was the solubility of reactants. The yellow colored solid component α-keto amide unevenly distributed in the water medium. Thus, withdrawing of sample was not feasible for every given time interval.

Hence we carried out separate reactions for the given time interval (each in 0.25 mmol scale of α-keto amide **1a** 0.3 mmol of indole **2a** with 15 mol% of K_3PO_4 and 10 mol% of *n*Bu4NBr in 4 mL of distilled water) in order to determine the reaction rate of the first cycle. The progress of the reactions was monitored through the formation of product **3a** using HPLC method by extracting the reaction mixture with 10 mL of ethyl acetate. 1 mL of the organic layer was evaporated and dissolved in 4 mL of acetonitrile and from which 5 μL of sample was injected for HPLC studies.

In the meantime, a bulk reaction of 1.0 mmol scale of α-keto amide **1a** in 32 mL of water was carried out. The filtrate received from the fourth catalytic cycle was utilized for the initial reaction rate studies for the fifth cycle each reaction having 4 mL of water containing the catalysts (See the ESI for further details).

2.6 Procedure for mechanistic study using ^{1}H-NMR spectroscopy

Initially, ^{1}H-NMR spectrum for *n*Bu_4NBr was recorded. Next, a 1:1.5 mixture of *n*Bu_4NBr and K_3PO_4 was taken in a reaction tube having D_2O solvent. The reaction mixture was stirred for 1 h and analyzed using ^{1}H-NMR spectroscopy. Then, a reaction tube containing a mixture of *n*Bu_4NBr, K_3PO_4 and indole in 1:1.5:1.5 ratios were stirred in D_2O solvent for 1 h, and the reaction mass was analyzed using ^{1}H-NMR spectroscopy (See the ESI for further details).

SUPPORTING INFORMATION

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Catalyst reusability study, initial reaction rate determination, NMR study, X-ray crystallographic data of **3a**, ^{1}H and ^{13}C NMR spectra for all compounds

AUTHOR INFORMATION

Corresponding Author

***E-mail:** gsekar@iitm.ac.in, Phone: (+91)44-2257 4229, Fax: (+91)44-2257-4202.

Notes

The authors declare no competing financial interest.

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26. As per the reviewer's suggestion, the reaction of **1a** and **2a** was carried out under previously reported reaction conditions ^{t}BuTMG (10 mol%)[11] and TMSOTf, Pyridine, -78^{o}C/TBAF. [4] In the case of catalytic ^{t}BuTMG, no formation of product **3a** was observed. However, when the reaction was carried out in stoichiometric ^{t}BuTMG (1 equivalent), 78% of **3a** was isolated in 24 after column chromatography purification. In the case of TMSOTf, Pyridine, -78^{o}C/TBAF, the reaction mass led to the formation of complex reaction mixture.
27. The reaction of **1a** and **2a** was carried out by replacing nBu$_4$NBr with chiral QAS derived from chinconin and benzylbromide. To our disappointment, the reaction did not proceed due to the formation of sticky reaction mass. However, when the solvent was changed to ethanol, the reaction provided 90% of the product **3a**. But no asymmetric induction was found.
28. The diminish in catalytic activity might be due to the dilution of filtrate by adding 1 mL of water in each cycle for washing the product present in the RB flask. Thus accumulation of extra added water solvent might slowdown the reaction rate in the fifth cycle.
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