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COMMUNICATION

Selective amidation by a photocatalyzed umpolung reaction

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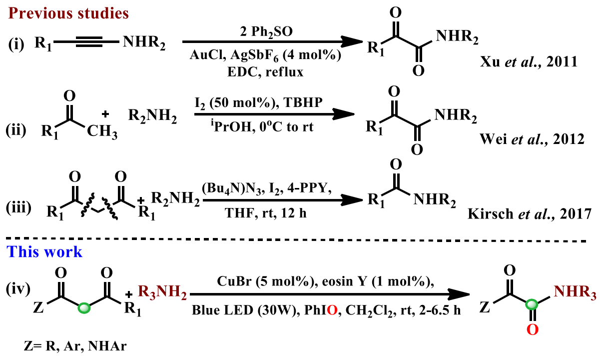
A metal-catalyzed organic transformation merged with another organophotocatalyst has been developed under mild conditions for production of α-ketoamides. CuI-catalyzed highly selective and rapid $COCH_2$-amidation in the presence of electrophilic C_α=O bonds, which is synchronized by an eosin Y (EY)-photocatalysis to furnish a wide range of labile α-ketoamides, unsymmetrical oxalamides and chiral analogues on the treatment of 1,3-dicarbonyls with amines, PhIO and LED light at room temperature. The current strategy opens up a new avenue to photocatalysis for making it a common synthetic tool for the large-scale production in academia and industry.

The photocatalytic organic synthesis emerged as an active area, and several methods were introduced in the synthetic chemistry utilizing Ultra Violet (stronger energy), abundant sunlight, light emitting diode (LED) and other light sources.[1] However, the light-activated photocatalysis is not viable for large-scale and industrial processes mainly because of their critically unsafe nature due to the generation of large quantity of accident-prone radical intermediates,[2] and inability to access labile and/or chiral compounds. The dual photocatalysis is encouraging, such as Cu^I-Fe^{II} for CO_2-reduction,[3a] Ir^{II}-Ni^{II} for C-C cross-coupling,[3b] Ni^{II}/Cu^{II}-organophotocatalyst for hydroxylation,[3d] halofunctionalization,[3c] and decarboxylative olefination.[3e] Herein, we have attempted a dual photocatalysis-assisted direct amidation of –CO-$\boldsymbol{CH_2}$-, which is unknown in the literature. Despite the conventional perception of the radical mechanism of λ^3-hypervalent iodanes[4a,d] mediated reactions; we[4b,c] and others[4e,f] observed that these Lewis acid like oxidants are also capable of switching between radical to ionic mechanism depending on reaction conditions, electronic demands and/or the presence of catalyst. α-Ketoamides were synthesized using pre-functionalized aryl acetylene amines, Ph_2SO, and AuCl-$AgSbF_6$ catalysts (eq. i, Scheme 1),[5a] and through coupling of ketomethyl-amine (eq. ii) with iodine and TBHP (excess).[5b] It is challenging to perform amidation of a $\boldsymbol{CH_2}$-moiety with an amine-nucleophile in the presence of electrophilic C_α=O centers, which is more susceptible for amidation. For instance, Kirsch and co-workers utilized $(nBu_4N)N_3$ and I_2 for coupling of RNH_2 to –CO-CH_2-CO-, and amidation occurred to both the carbonyl groups (eq. iii).[5c] The discovery of a general metal-catalysis merged with organophotocatalytic reaction under mild conditions is displayed in eq. iv, which rapidly produced α-ketoamides, unsymmetrical oxalamides, and chiral analogues.

Scheme 1. Synthesis of α-ketoamides and amides



α-Ketoamides, chiral analogues, and oxalamides are widely distributed in Nature, and are found as invaluable lead drugs, a photoaffinity label, intermediates, pharmaceuticals, antiepileptic drugs, anti-HIV agents, MR2B antagonists, Caspase inhibitors, useful ligands and synthons.[6-10] The widely used α-ketoamide syntheses include coupling of amines with α-ketoacids or acyl halides, oxidation of α-hydroxyamides and α-aminoamides, dual carbonylative amidation, oxidative amination, and Henry cascade and oxygenative alkyne-amine coupling.[6a,b,8] Oxalamides were synthesized through condensation of amines to activated α-amido carboxylic acids, oxidative carbonylation, coupling of the

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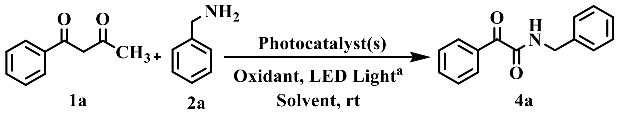
isocyanides with carboxamide lithium or trichloroacetic anhydride-amine, and transamination of 2,2,2-trifluoroethyl chlorooxoacetate.[10]

The initial attempts for photocatalytic reaction between 1-phenyl butane-1,3-dione (**1a**) with benzylamine (**2a**) was studied utilizing 5 mol% of commonly used metallaphoto-catalyst of higher and moderate oxidation state, such as Cu(II), Ru(III) or Au(III) along with organophotocatalyst eosin Y under LED light (5 W), and product *N*-benzyl-2-oxo-2-phenylacetamide (**4a**, entries 1-3, Table 1) was not detected.

Table 1. Survey for developing selective-amidation photocatalysis[a]



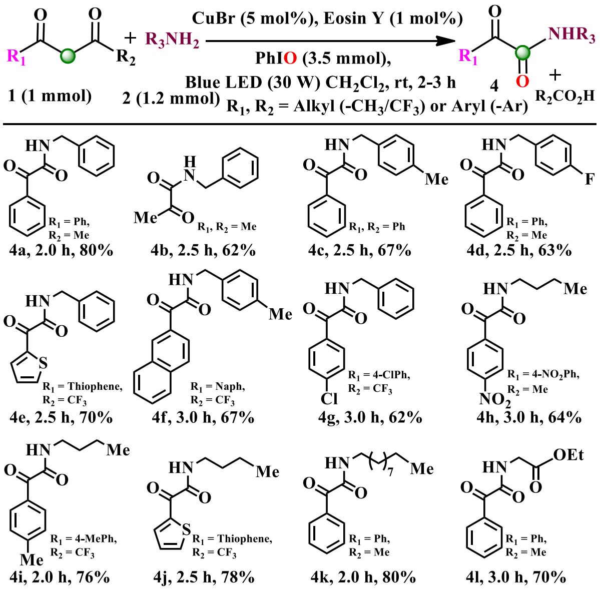
Entry	Metal Catalyst[b]	Reagent[c]	Photocatalyst[d]	Solvent[e]	Time (h)	4a,Yield (%)[f]
1	Cu(OTf)$_2$	PhIO	eosin Y[g]	CH_2Cl_2	24	nd[h]
2	$RuCl_3$	PhIO	eosin Y[g]	CH_2Cl_2	24	nd
3	$AuCl_3$	PhIO	eosin Y[g]	CH_2Cl_2	24	nd
4	AgOTf	PhIO	eosin Y[g]	CH_2Cl_2	24	25
5	AuCl	PhIO	eosin Y[g]	CH_2Cl_2	24	30
6	Ir(cod)Cl	PhIO	eosin Y[g]	CH_2Cl_2	24	nd
7	CuBr	PhIO	eosin Y[g]	CH_2Cl_2	24	40
8	**CuBr**	**PhIO**	**eosin Y**	**CH_2Cl_2**	**02**	**80**
9	CuBr	PhI(OAc)$_2$	eosin Y	CH_2Cl_2	02	50
10	CuBr	TBHP	eosin Y	CH_2Cl_2	02	45
11	CuBr	$K_2S_2O_8$	eosin Y	CH_2Cl_2	02	30
12	CuBr	*m*CPBA	eosin Y	CH_2Cl_2	02	50
13	CuBr	PhIO	rose bengal	CH_2Cl_2	12	30
14	CuBr	PhIO	Phe-PDI-Phe	CH_2Cl_2	24	nd
15	CuBr	PhIO	Trp-PDI-Trp	CH_2Cl_2	24	32
16	CuBr	PhIO	Ir(PPy)$_3$	CH_2Cl_2	24	55
17	CuBr	PhIO	Ir(tpy)(bpy)Cl	CH_2Cl_2	24	52
18	CuBr	PhIO	-	CH_2Cl_2	24	15
19	CuBr	PhIO	eosin Y[i]	CH_2Cl_2	24	15
20	-	PhIO	eosin Y	CH_2Cl_2	24	nd
21	CuBr	-	eosin Y	CH_2Cl_2	24	nd
22	CuBr	PhIO	eosin Y	H_2O	24	nd
23	CuBr	PhIO	eosin Y	CH_3OH	24	10
24	CuBr	PhIO	eosin Y	CH_3CN	24	52
25	CuBr	PhIO	eosin Y	THF	24	60
26	CuBr	PhIO	eosin Y	$PhCH_3$	24	68
27	CuCl	PhIO	eosin Y	CH_2Cl_2	24	48
28	CuI	PhIO	eosin Y	CH_2Cl_2	02	70
29	CuCN	PhIO	eosin Y	CH_2Cl_2	24	65

1a (1 mmol) and **2a** (1 mmol).[a]Blue LED (30 W, 475 nm).[b]5mol%.[c](3.5 mmol).[d]1mol%.[e]5 mL, [f]Purified by column chromatography. [g]5 W LED light source. [h]Not detected. [i]No LED light.

To our delight, using relatively lower oxidation state Ag(I)-eosin Y combined photocatalysis furnished the desired product (**4a**) in low yield (25%) at ambient temperature using neutral oxidant PhIO (entry 4). Replacement of the metal catalyst by AuCl led to the marginal improvement of yield (30%, entry 5), and low valent Ir(I) was inefficient (entry 6). Relatively inexpensive CuBr produced **4a** with a modest yield (40%, entry 7). The yield and reaction rate (2 h) were magnificently enhanced (80%) on improving the power of the LED from 5 W to 30 W (entry 8). PhI(OAc)$_2$, TBHP, $K_2S_2O_8$ and, *m*CPBA did not improve the yield (entries 9-12). The rose bengal, synthesized Phe-PDI-Phe or Trp-PDI-Trp was not useful (entries 13-15). The combination of metal-catalyst and metallaphotocatalyst[3a,b] such as CuBr-Ir(PPy)$_3$, and CuBr-Ir(tpy)(bpy)Cl was not effective (entries 16, 17). The yield and reaction rate was drastically reduced in the absence of organic photocatalyst eosin Y or active LED source (entries 18, 19). These observations indicate the metal-organic dual photocatalytic system is essential for CO-$\boldsymbol{CH_2}$ amidation with C-C cleavage. The photocatalysis was completely arrested on carrying out the reaction without any CuBr or PhIO (entries 20, 21). The photocatalysis was examined in water, methanol, MeCN, THF and $PhCH_3$ (entries 22-26) without improvement in yield. CuBr is found as a smart catalyst over other Cu(I) salts (entries 27-29). We screened visible light and blue LED of 475 nm was found as the best for the dual catalysis (Figure 1S).

The general scope of the combo-photocatalytic reaction among 1,3-diketones (**1**) with different aliphatic primary amines (**2**) was investigated to synthesize labile α-ketoamides (**4**) under mild conditions (Scheme 2). Interestingly, 1,3-diketones (**1**) smoothly proceeded to a large number of structurally diverse α-ketoamides (**4a-l**) through C-C cleaved-coupling of amines (**2**) and sacrificed its acyl, trifluoroacyl and benzoyl residues. The phenyl (**4a**, **c**, **d**, **k**, **l**), substituted phenyl (**4g**, **h**, **i**), aromatic heterocyclic (**4e**, **j**), naphthyl (**4f**) and aliphatic (**4b**) substituents are sustainable under this the reaction conditions. Introduction of electron withdrawing substituent into the aromatic residue slightly reduced the yield of the corresponding products (**4g**, **h**). Almost all types of aliphatic amines were structurally fit to do this job, and aromatic amines were in vain probably due to their oxidation in the presence of

Scheme 2. Synthesis of substituted α-ketoamides



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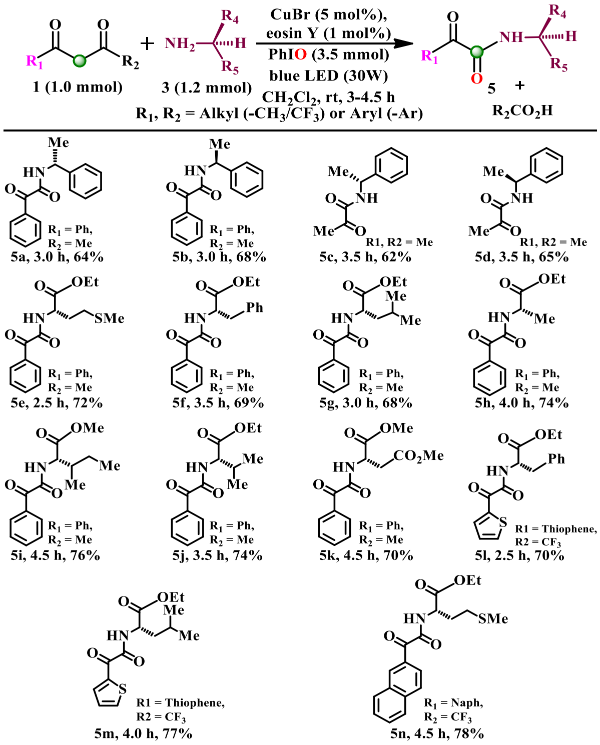
hypervalent iodine. Simple aliphatic amine possessing hydrocarbon chain, aromatic residue and ester functionality were tolerated to achieve desired products (**4a**-**l**) in high yield (62-80%) and shorter reaction time (2-3.0 h). All the synthesized new compounds were fully characterized and the structural skeletal of **4h** was confirmed with the help of single crystal XRD data analyses.[11]

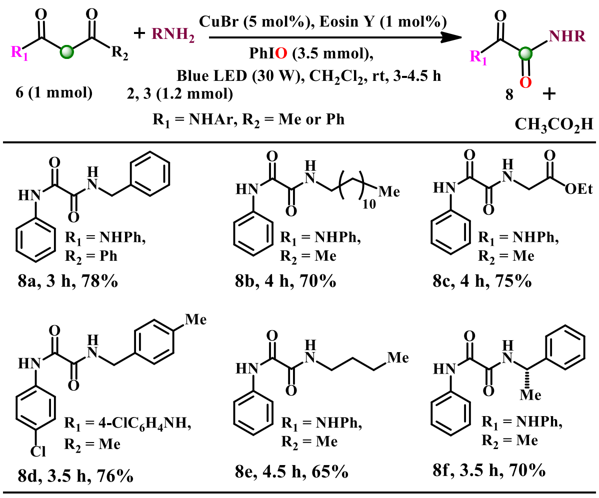
The bio-utilities and other application of chiral α-ketoamides analogues (**5**) led us to target their synthesis utilizing readily available chiral amines and α-aminoacid esters (**3**, Scheme 3). Optically pure α-methyl benzylamines (**3a**,**b**) furnished corresponding pure enantiomer of α-ketoamides (**5a**-**d**). A variety of L-aminoacid esters (**3c**-**i**) was successfully utilized to produce rapidly (2.5-4.5 h) amino acid-based chiral α-ketoamides (**5e**-**n**) with good yield (68-78%) under the unchanged conditions. Existence of pure enantiomer (**5**) was verified using a semipreparative chiral HPLC column and also by recording the optical rotation of all products including a known compound (**5b**).[6a]

Scheme 3. Asymmetric synthesis of α-ketoamides



Next, we turned out attention to expand the scope of the metal-organic synergic-photocatalytic approach for the synthesis of valuable oxalamide derivatives (**8**, Scheme 4) from 1,3-ketoamide substrates (**6**). Gratifyingly, an important observation was experienced in this connection as labile oxalamides (**8a**-**f**) were efficiently obtained in the presence of external amine **2** or **3** under the unchanged conditions. Amide functionality of acetoacetalinide did not hamper the progress of the dual photocatalysis process, which addressed the chemoselective nature of the reaction. Herein, the unsymmetrically substituted amides were constructed very easily. The reported synthetic methods to oxalamides are conventionally produced symmetrical compounds because most of them were derived from activated oxalic acid or oxalal chloride and it is very difficult to control condensation with two different amines.[10]

Scheme 4. Synthesis of unsymmetrical oxalamides



Apart from normal aliphatic amines (**2a**,**b**,**d**), long chain (**2e**) and ethyl glycinate (**2f**) were adequate for this purpose. The diversity of the mild photocatalysis was validated through synthesis of optically pure (-)-(S)-N1-phenyl-N2-(1-phenylethyl)oxalamide (**8f**) using chiral amine (S)-1-phenylethylamine (**3b**). The overall yield of the synthesized oxalamides (**8a**-**f**) is quite high (65-78%) and obtained in shorter reaction time (3-4.5 h).

In order to shed light on regioselectivity we performed two separate control experiments; one with electron withdrawing chlorine substituent containing 1-(4-chlorophenyl)-3-phenyl-1,3-propanedione (eq. i, Scheme 5) and another with electron donating methyl substituent containing 1-(4-methylphenyl)-3-phenyl-1,3-propanedione (eq. ii). In both the cases, we got a mixture of products with unequal proportions. For the first reaction, the ratio of **4a** and **4**g is 5:2 whereas in the second case, the ratio of **4a** and **4m** is 3:4 which is a clear indication that the presence of electron withdrawing group in the phenyl residue allows its carbonyl portion to get oxidize easily as compared to it is a counterpart. The possibility of transforming -*CH_2*- or/and C_α=O to amide of 1,3-dicarbonyl substrate was confirmed utilizing C^{13}-labelled 1,3-diphenyl-propane-1,3-dione (C^{13}-1c, eq. i, Scheme 5). The ESI-MS analyses of the reaction mixture revealed a larger symbolic peak at 241.1053 (M+H$^+$) for C^{13}-**4a** relative to 240.1058 (M+H$^+$) of **4a** (ESI). The source of the 'O'-atom in the amide functionality is PhIO, which was confirmed by formation of the O^{18}-**4a** (e/m 242.1067), using PhIO^{18} (eq. ii). Thus, amidation occurred selectively at CO-*CH_2* utilizing oxygen of PhIO. The reaction was failed to produce the desired product **11** on using CH_2-blocked cyclopropane substrate (**10**, eq. iii).[12] Quenching the reaction in the middle, we found the traces of **12** (eq. vi, Scheme 5), which might be generated due to the coupling of amine (**3a**). Benzoic acid (**14a**) was isolated and fully characterized (ESI) from the reaction between **1a** and **2a** (eq. viii). Right now, exact mechanism is unknown to us and a proposed path for the umpolung (step 2) and ionic mechanism (step 1 and 3) is depicted in Scheme 6 on the basis of experiments performed.

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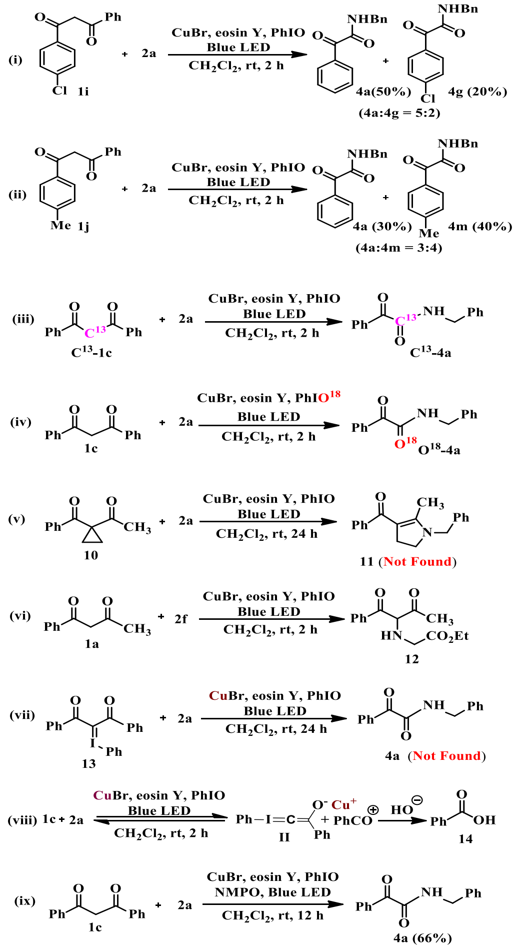
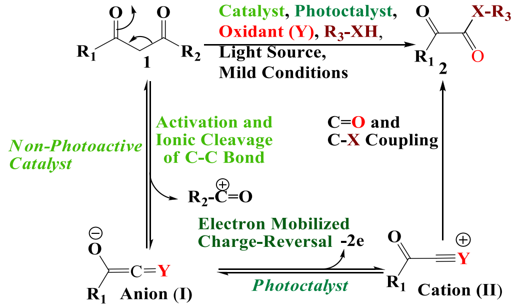
Scheme 5. Control experiments



Scheme. **6** Proposed electron-reversal dual catalysis



In conclusion, a new umpolung Cu^{I}-organophotocatalysis is established for rapid synthesis of valuable α-ketoamides, unsymmetrical oxalamides, and chiral analogues at ambient temperature and solved a long pending issue of photocatalytic organic transformation through highly concentrated ionic intermediates merged with a weaker radical pathway.

Conflicts of interest

"There are no conflicts to declare".

Acknowledgements

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