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Aerobic oxidative amidation of alkynes using titanium oxide encapsulated cuprous iodide nanoparticles (CuI@TiO_2)

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Abstract

A catalyst consisting of titanium oxide encapsulated cuprous iodide nanoparticles was prepared *via* sol-gel method using inexpensive raw material and was harnessed successfully in oxidative amidation of alkynes *via* environmentally benign and sustainable protocol. The mechanism of action for this transformation was thoroughly discussed. The robustness of the catalyst was elucidated by the synthesis of diverse analogues of α-ketoarylamide from variety of electron rich and poor substrates *via* a simple procedure in moderate to high yields, with no generation of toxic by-products, in good recyclability till five cycles, under solvent free and aerobic condition. The chemical nature, morphology and loading of the CuI@ TiO_2 nanocatalyst were investigated by TEM, SEM, XPS, EDX, powder X-Ray, BET, TGA and ICP-MS.

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Introduction

Catalysts play a crucial role in the synthesis of complex organic molecules. Application of catalysts not only favour the economy of a process but also addresses the perils of environmental hazards created through stoichiometric reactions. Hence inventing appropriate catalysts which is selective towards a specific organic transformation have garnered immense attention. Among various catalysts the catalytic activity of nanoparticles (NPs) provides a plethora of scope, diversity and robustness in chemical processes deployed frequently in academia and industry.[1]

By virtue of their enhanced activity owing to high surface area nanoparticles play a crucial role in catalysing various organic transformation. NP catalysts *viz*. graphene based catalysts, magnetic supported nanocatalysts, integrated nanocatalysts, various metal nanostructures and etc. are harnessed in energy conversion, manufacturing, biological applications, storage, environmental protection and many more.[2] This enormous depth and utility of these catalysts facilitated a gamut of synthetic strategies that could afford them either on their own or supported on other metals.[3] Interestingly, NP catalysts generated from metals which are inexpensive and naturally abundant have garnered substantial attention as feasible alternatives to expensive and rare noble metal catalysts.[4] Incidentally, Cu-NPs are exceptionally useful due to their high earth-abundance, low cost and simple synthetic procedures.[5] Recent examples of supported copper nanocatalysts in organic transformation include immobilization of copper as magnetites to catalyse arylation of heteroarenes, Cu-NP/montmorillonite catalysed 1, 3-dipolar cycloaddition of aliphatic azides with terminal alkynes in water, sonogashira coupling of acyl chlorides with terminal alkynes using copper oxide encapsulated copper catalyst, Cu-NP catalysed cross coupling reaction of alkyl bromides and chlorides with organomagnesium reagents and many more.[6]

Despite various applications of metal nanoparticles (NPs) one major disadvantage of these class of materials is their instability towards atmospheric oxidation. To circumvent this disadvantage solid matrix supported nanoparticles has emerged as a useful alternative. It not only enhances their stability towards aerial oxidations and moisture sensitivity but also optimizes their size which in turn is largely responsible for their robustness and catalytic activity in organic transformation. These solid support could be carbon based materials, metal oxides, polymers, zeolites etc.[7] But most of the available strategies to encapsulate the metal

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NPs into solid matrix is associated with tedious preparative techniques and metal leeching.[8] Herein we have reported a simple, robust, cost effective, recyclable and environmentally benign titanium oxide encapsulated cuprous iodide nano catalyst (CuI@TiO_2). They are made from easily available cost effective raw materials (refer *SI*). Their utility is demonstrated by successful use as catalyst in the amidation of alkynes.

By virtue of their ubiquitous presence as biologically active compounds, α-ketoarylamides hold a niche status in the field of medicinal and synthetic organic chemistry. They provide access to important building blocks, diverse natural products, active pharmaceutical ingredients and agrochemicals (Scheme 1).[9] Notable bioactive molecules and marketed drug bearing α-keto amide functionality are FK506 (tacrolimus), rapamycin, varespladib, boceprevir and telaprevir. Besides their therapeutic applications, these class of compounds are also considered as potential building blocks and synthetic precursors for several interesting organic scaffolds such as β-lactum, chiral α-hydroxyamides, 2-oxindoles and etc.[10] The importance of these molecules are further emphasized by assessing the research that underwent for the modification of the chemistry in and around α-ketoarylamides. There are quite a few catalytic strategies to access them. For example, aldehydes and aryl ketones were converted to their corresponding α-ketoarylamides in reactions catalysed by cuprous bromide (CuBr) and cuprous iodide (CuI) in presence of pyridine and under solvent free conditions.[11] Wang and his co-workers have synthesised α-ketoarylamides from ethylarenes under solvent free condition, using CuI as a catalyst.[12] On the other hand terminal alkynes required cupric bromide ($CuBr_2$) and cupric triflate ($Cu(OTf)_2$) as catalysts for similar transformation and finally a metal free iodine catalysed oxidative amidation of alkynes are also reported.[13] In general (apart from the metal free procedure) these strategies suffer from several drawbacks such as poor conversion, toxic solvents (*viz*. pyridine, dichloromethane and toluene), low recyclability, toxic by-products and tedious work-up and isolation procedure of the product. Hence it is high time to identify a suitable catalyst which could alleviate these drawbacks. Accordingly, we envisioned developing an efficient supported metal nano catalysts for this purpose. The legacy of TiO_2 as photocatalytic support prompted us to generate a titanium oxide encapsulated Cu-NPs. Interestingly we observed that this catalyst works fluently enough under normal circumstances without any assistance of light (be it UV or sunlight). A silica supported Cu-NP was also synthesized, but the poor yields and lack of reproducibility of the catalyst directed us to develop this Cu-based titanium oxide (TiO_2) encapsulated, heterogeneous solid supported catalyst. Here in we report application of this catalyst in the

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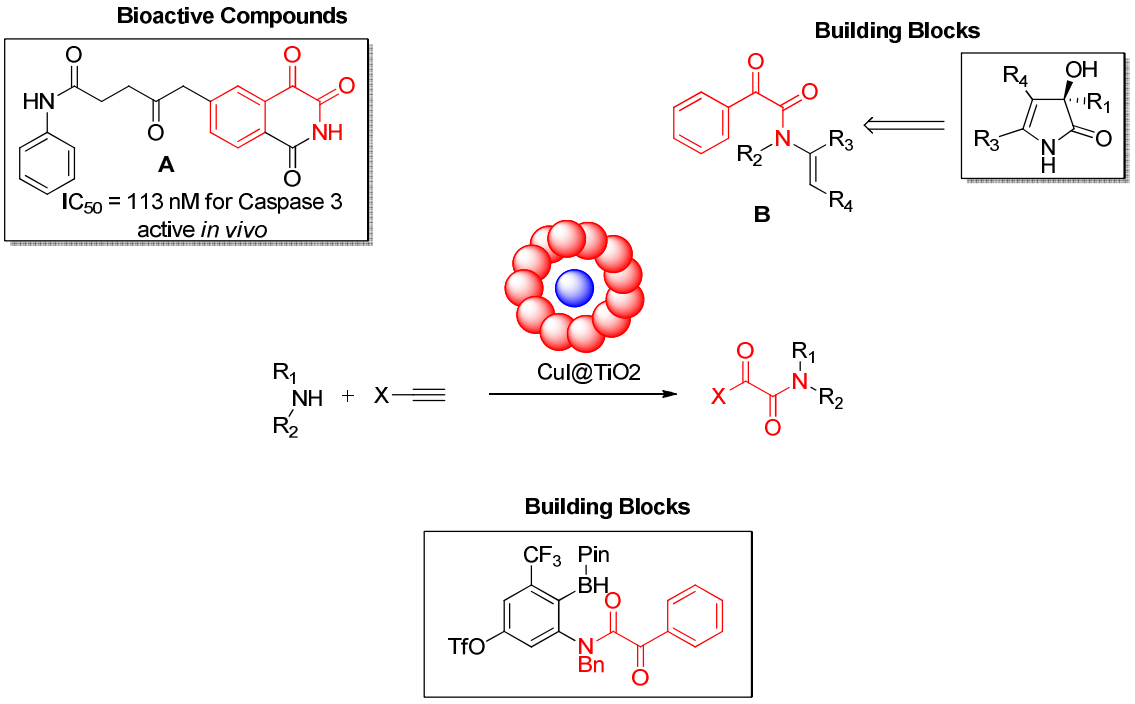
formation of α-ketoarylamide from terminal alkynes and 2°-amines with TEMPO as oxidant under mild solvent free and environmentally benign reaction condition. Control experiments without the catalyst generated no/ low yields of the desired products. These observations further assisted us in proposing the mechanism of the transformation. It is worth mentioning that the catalytic protocol is robust, efficient and devoid of the use of complex ligands which renders it to be simple and economical.



Scheme 1. Catalyst comprising of TiO_2 encapsulated CuI nanoparticles (CuI@TiO_2) for the synthesis of ketoaryl amides (from alkynes) and their representative molecules as building blocks and bioactive compounds

Results and discussion

Synthesis of the catalyst (CuI@TiO_2)

The synthesis of catalyst involved heating a mixture of cuprous iodide (CuI) with nearly hundred equivalents of titanium isopropoxide ($Ti(O^iPr)_4$) in tetraethylene glycol (five equiv) followed by refluxing in water (3 mL per 10g of $Ti(O^iPr)_4$) for nearly 10h before it was filtered, washed with acetone and dried at 100°C (Scheme 2). Cautious addition of water was required as rapid addition provided catalysts with much larger particle size rendering them ineffective towards the reaction (Scheme 2).

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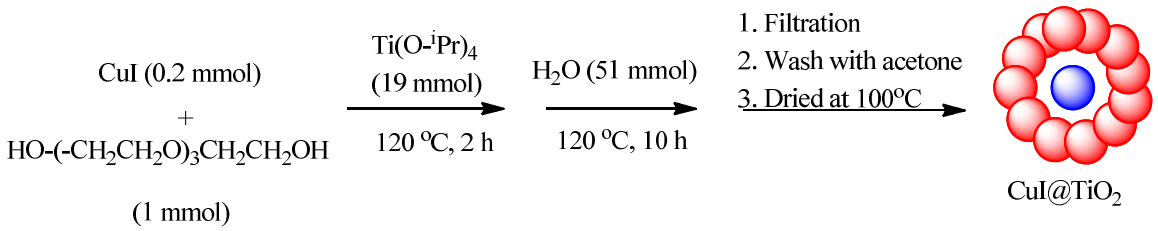

Scheme 2

Characterization of the catalyst

The catalyst comprised of TiO_2 encapsulated cuprous iodide nanoparticles was synthesized in a straightforward fashion (refer *SI*) and the size, morphology and structure of the were determined by transmission electron microscopy (TEM, Tecnai G2 F30) with an accelerating voltage of 300 kV and scanning electron microscopy (Zeiss EVO 18 Special). The elemental analysis of the Cu-catalyst was also done by energy dispersive spectroscopy (EDS) analysis integrated with the same SEM instrument. The X-ray photoelectron spectrometer (Kratos Axis Ultra) equipped with a monochromatic Al KαX-ray source (15 kV, 10 mA) was used to measure the surface properties of the copper-TiO_2 composite catalyst. Binding energies were calculated using maximum intensity of the C 1s signal at 284.8 ev as reference.

XPS study suggests Cu($2p_{3/2}$) peak was related to Cu(I) (Figure 1).[14] Moreover, the shake-up satellite peak of the Cu($2p_{3/2}$) peak which generally shows up at ~9 eV greater than the corresponding major peak for Cu(II) was not observed in our experimental data. This further confirmed that the surface consists of only Cu(I).[14-15]

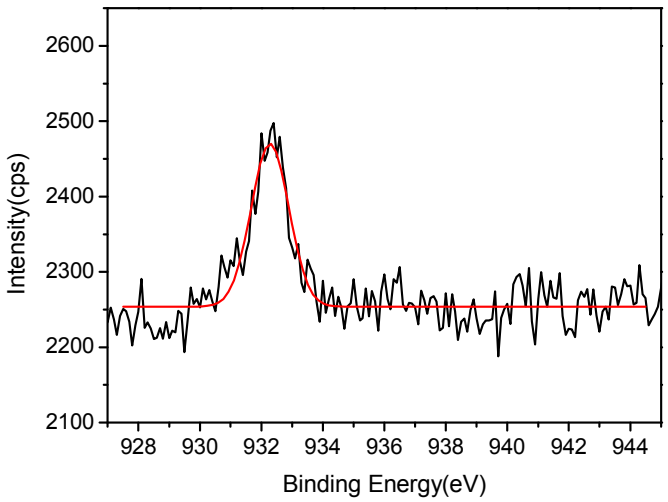

Figure 1. XPS Cu($2p_{3/2}$) peak for the as-made copper-TiO_2 composite catalyst.

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We furthermore carried out XRD analysis (Figure 2) of our catalyst. Peaks at 29.64, 42.42 and 50.09 are characteristic for (110), (200) and (311) planes of CuI. Furthermore, peak at 25.62 is characteristic for the (101) plane of TiO_2 present in anatase phase. These set of data led us to the firm conclusion of the existence of pure cubic phase of copper with F-43m space group (JCDPS No. 77-2391).[16]

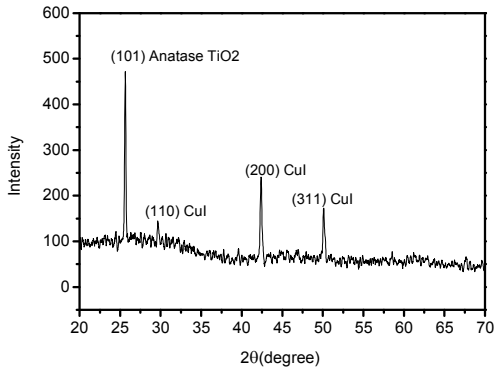

Figure 2. Characterization of the catalyst (CuI@TiO_2) by powder XRD

Figure 3a shows SEM image of copper-TiO_2 composite catalyst where the surface is uneven and irregular-shaped. CuI nano particles are distributed on the TiO_2 crystal. The corresponding EDS spectrum (Figure 3b) demonstrated peaks for titanium (Ti), oxygen (O), copper (Cu) and iodine (I), thereby corroborating the existence of Cu.

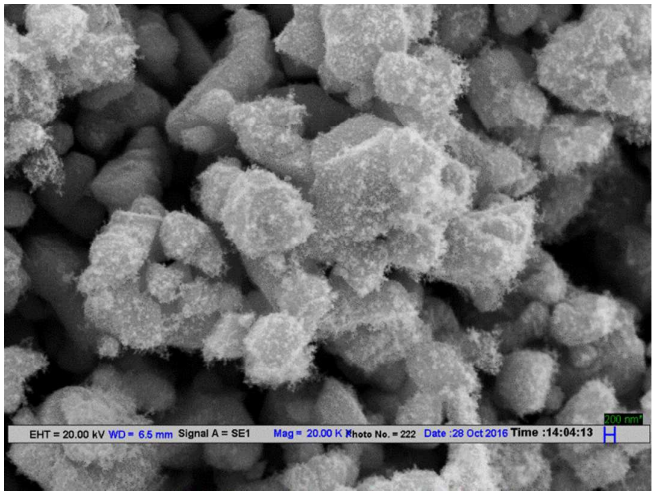

Figure 3a. Characterization of the catalyst (Cu@TiO_2) by SEM for the morphology

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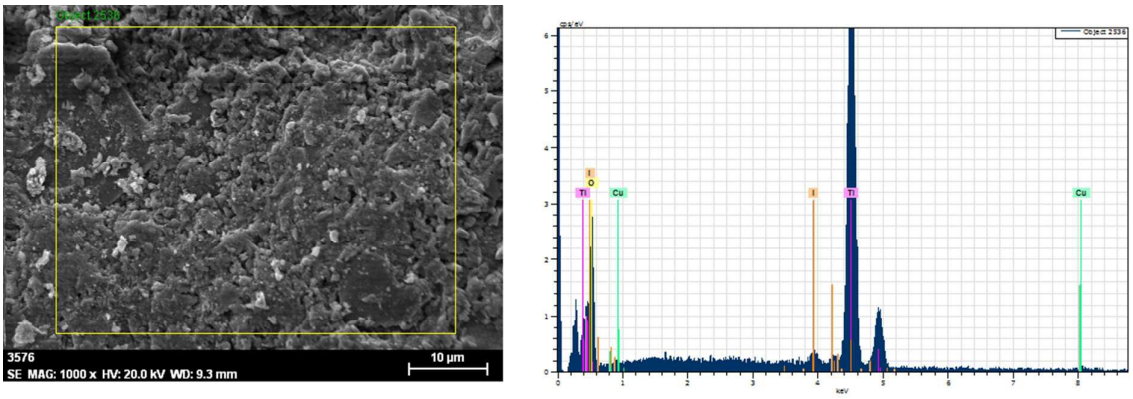

Figure 3b. Characterisation of the catalyst by EDS to ascertain the size of the catalyst.

TEM image of the catalyst revealed that our Cu nanoparticles are well dispersed with a size distribution of 5.8 ± 1.7 nm within the TiO_2 matrix (Figure 4). Histogram of size distributions is provided below.

Inductively coupled plasma analysis further indicated 0.77wt % of Cu on TiO_2.

To find out the surface area of our catalyst we performed BET experiment. From the BET plot (Figure 5) we calculated the surface area of our catalyst (1.765×10^2 m^2/g).

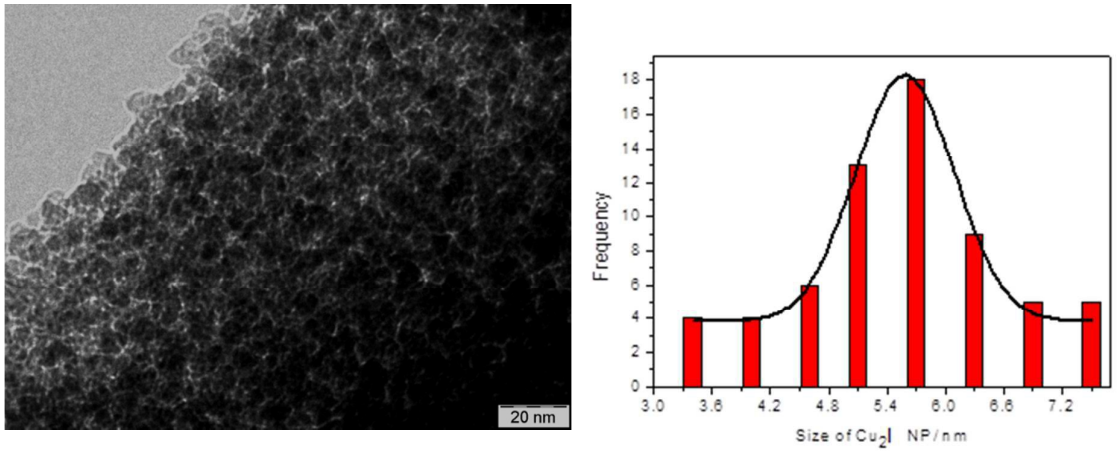

Figure 4. TEM image of the catalyst

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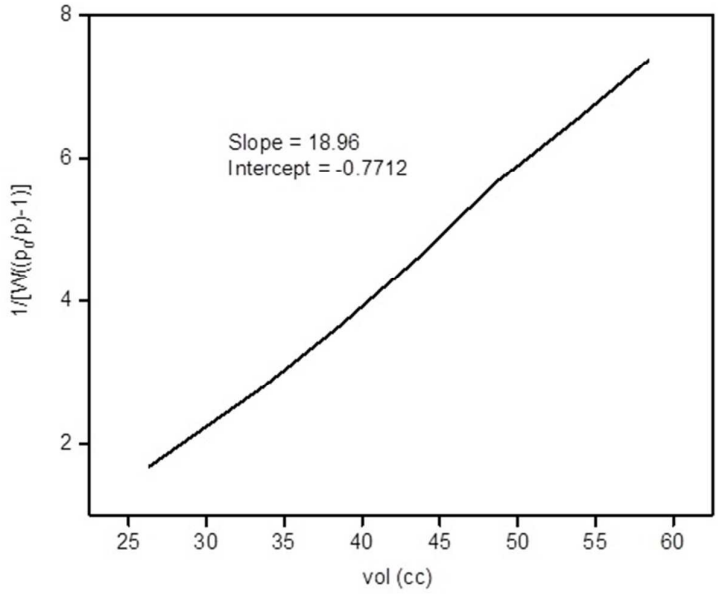

Figure 5. BET analysis plot

Synthesis of α-ketoarylamides from aryl acetylenes

With the catalyst in hand we assessed its utility in the conversion of aryl acetylenes to α-ketoaryl amides by their reactions with secondary amines. Accordingly, phenyl acetylene and pyrrolidine were used as reaction partners for the optimization studies, with five mole% of CuI@TiO_2, sodium carbonate (Na_2CO_3) as base, silver acetate (AgOAc) as oxidant, with toluene as solvent at 70 ºC under oxygen atmosphere (Table 1, entry 1). The desired compound **1a** was obtained in excellent yield (87%) (Table 1, entry 1). Next, the reaction under oxygen and in absence of silver acetate rendered much less yield (42%) (Table 1, entry 2), however the same in presence of silver acetate and in absence of oxygen generated the final compound in slightly poorer yield (34%) (Table 1, entry 3). From these initial experiments it is quite obvious that AgOAc-O_2 combo is required for our catalyst to facilitate the formation of α-arylketoamides from aryl acetylenes. In a bid to discover a "green" protocol with equal or better yields we conducted the reaction with variety of non-metallic oxidants i.e. aq. hydrogen peroxide, tert-butyl hydrogen peroxide (TBHP), 2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO), chloramine-T in "green" solvents like dimethyl sulfoxide and dimethyl formamide. Reactions of aq. H_2O_2 and TBHP failed to provide the desired compound **1a** in any of the solvents (Table 1, entry 4-7). In the reaction with Chloramine-T in DMF, the final product **1a** was generated in moderate yield of 48% (Table 1, entry 8). Finally, to our utmost pleasure the desired compound was obtained in 90% yield

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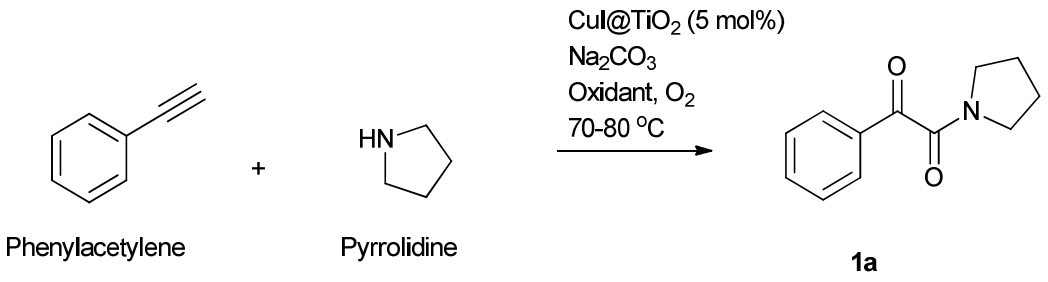
with TEMPO in DMSO at 80 ºC under oxygen atmosphere (Table 1, entry 11). Same reaction in DMF provided **1a** in much lesser yield of 65% (Table 1, entry 10). Finally, to our utmost gratification when the reaction was conducted under solvent free condition, the desired product **1a** was obtained in 91% yield (Table 1, entry 12). Interestingly the reaction under photocatalytic condition provided the desired product is lesser yields compared to the thermal condition (Table 1, entry 13). Hence the optimized protocol for the synthesis of α-ketoarylamide **1a**, involved reaction of 1 equivalent pyrrolidine, with phenyl acetylene, in presence of 5 mol% of CuI@TiO_2, Na_2CO_3 as base with TEMPO (1 equiv.), under oxygen in solvent free condition. It is interesting to note that under this optimized conditions, reaction with cuprous bromide and cuprous acetate as catalysts afforded the desired product **1a** in 15-18% yield. Thin layer chromatography indicated multiple spot formation in the reaction mixture, during the reaction which rendered isolation of **1a** extremely difficult.

Table 1. Optimization of reactions for the synthesis of α-arylketoamides from arylacetylenes



Entry	Oxidant	Solvent	Yield (%)[2]
1	AgOAc	Toluene	87
2	-	"	42
3	AgOAc[1]	"	34
4	Aq. H_2O_2	DMF	0
5	"	DMSO	"
6	TBHP	DMF	"
7	"	DMSO	"
8	Chloramine-T	DMF	48
9	"	DMSO	47
10	TEMPO	DMF	65
11	"	DMSO	90

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12	"	-	91
13[3]	"	-	31

[1] Without oxygen; [2] Isolated yield (reaction scale: 50 mg); [3] In presence of UV light

Catalyst loading induce substantial effect on the yield of the product and consequently on the efficiency of the process. Accordingly, we investigated the optimal loading of our catalyst by executing the model reaction (in table 1) with 0, 1, 2, 3, 4, 5 and 6 mol% of catalyst under optimal condition. As expected no progress of the reaction was observed even after 5h of reaction, without the catalyst. However, we were gratified to observe that the rate of the reaction improved steadily with the increase in the concentration of the catalyst till 5 mol%. Beyond 5 mol%, there was no substantial improvement in the yield (Figure 6).

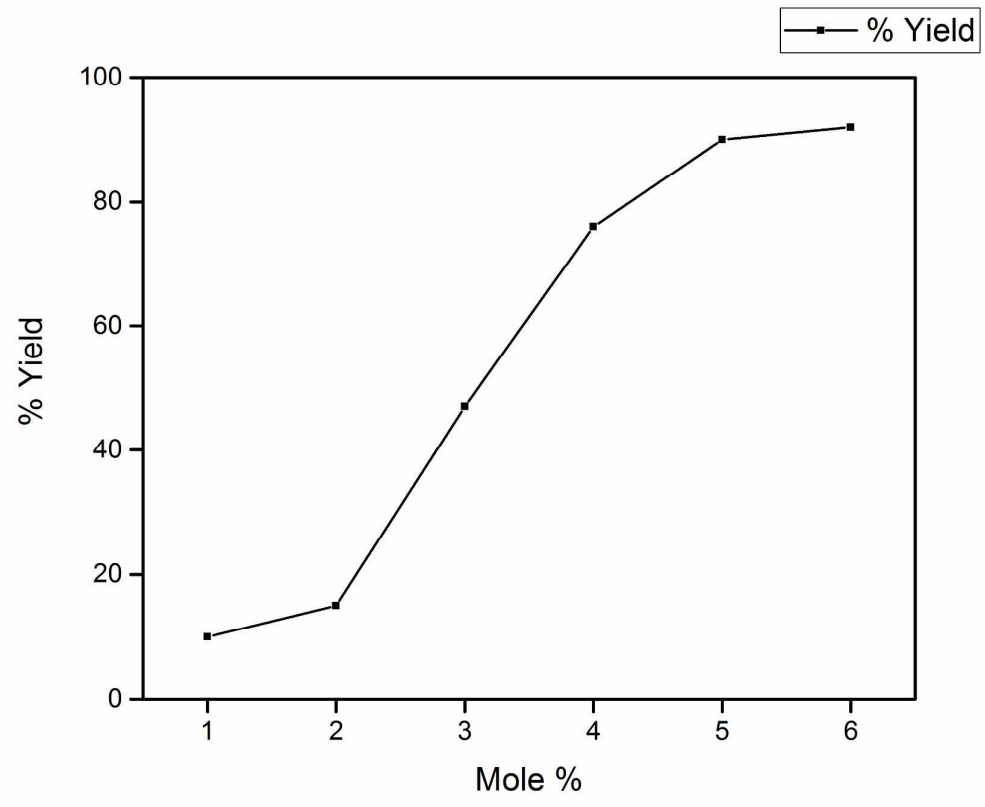

Figure 6. Optimization of catalyst loading

With the optimized condition in hand, several substituted phenyl and a heteroaryl acetylene were reacted with diverse 2º amines, such as pyrrolidine, piperidine, morpholine, N-methylpiperazine, diethyl amine, tetrahydroisoquinoline and piperazine, to afford corresponding α-ketoarylamides **1a** – **1o** in moderate to excellent yield (65 – 88%) (Scheme 3). In general, the yields were best for the electron rich substrates such as 3-methoxyphenyl

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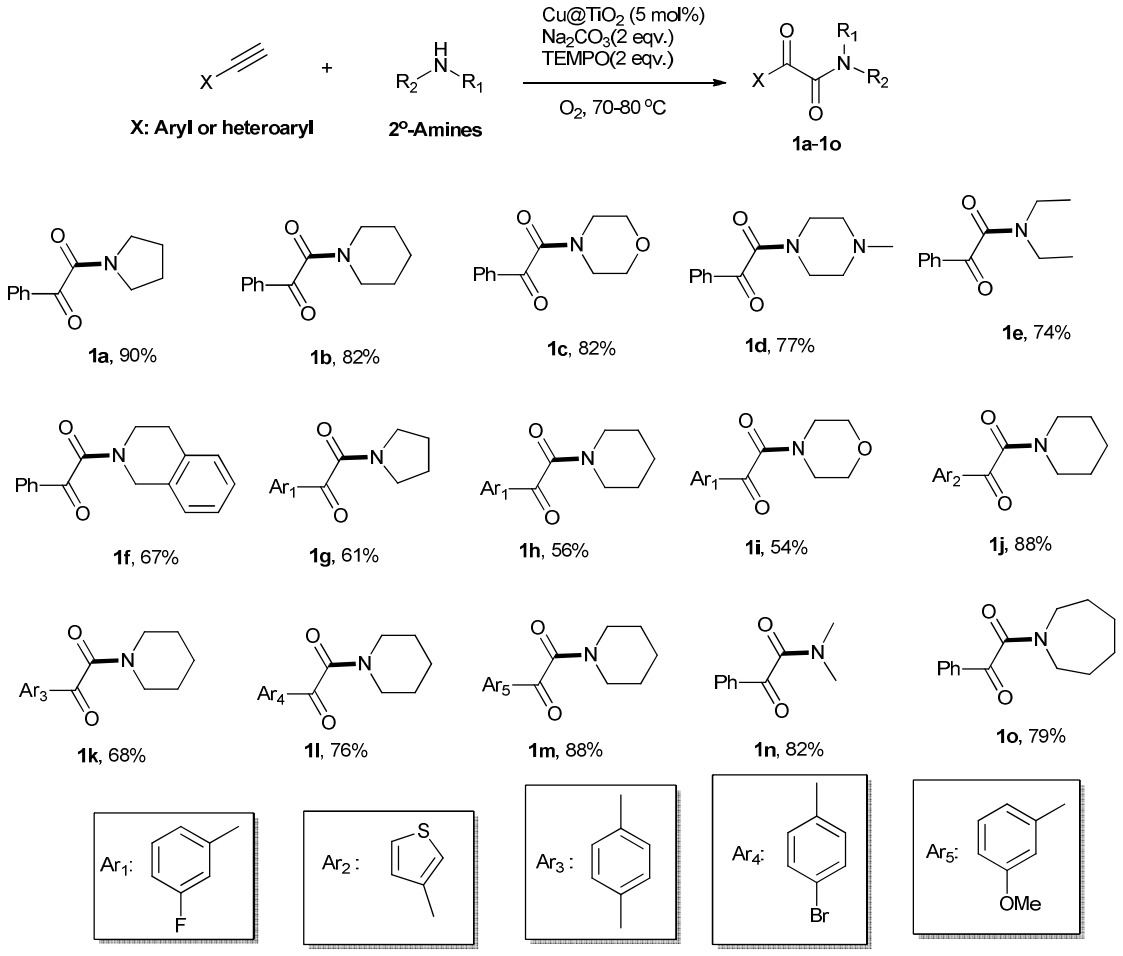
acetylene (**1m**), followed by unsubstituted acetylenes (**1a-1g**) and then the electron poor motifs (**1h-1k**) (Scheme 3). The heteroaromatic 3-thiophenylacetylene yielded the desired compound **1j** in 88% yield (Scheme 3).



Scheme 3. Synthesis of α-ketoarylamides by oxidative amination of (het)arylacetylenes

Control experiments with phenyl acetylene and pyrrolidine as model reaction partners were conducted in absence of catalyst or TEMPO or Na_2CO_3 (Scheme 4a, b and c). As expected there was no or barely minimum product formation without catalyst or the base, however without TEMPO, ~23% of **1a** was formed thereby indicating the utility of the oxygen in the reaction. Reaction of phenyl glyoxal (**D**) with piperidine under standard reaction condition yielded the desired product **1a** in 73% yield (Scheme 4d) which further indicated that **D** is one of the potential intermediates formed in the reaction.

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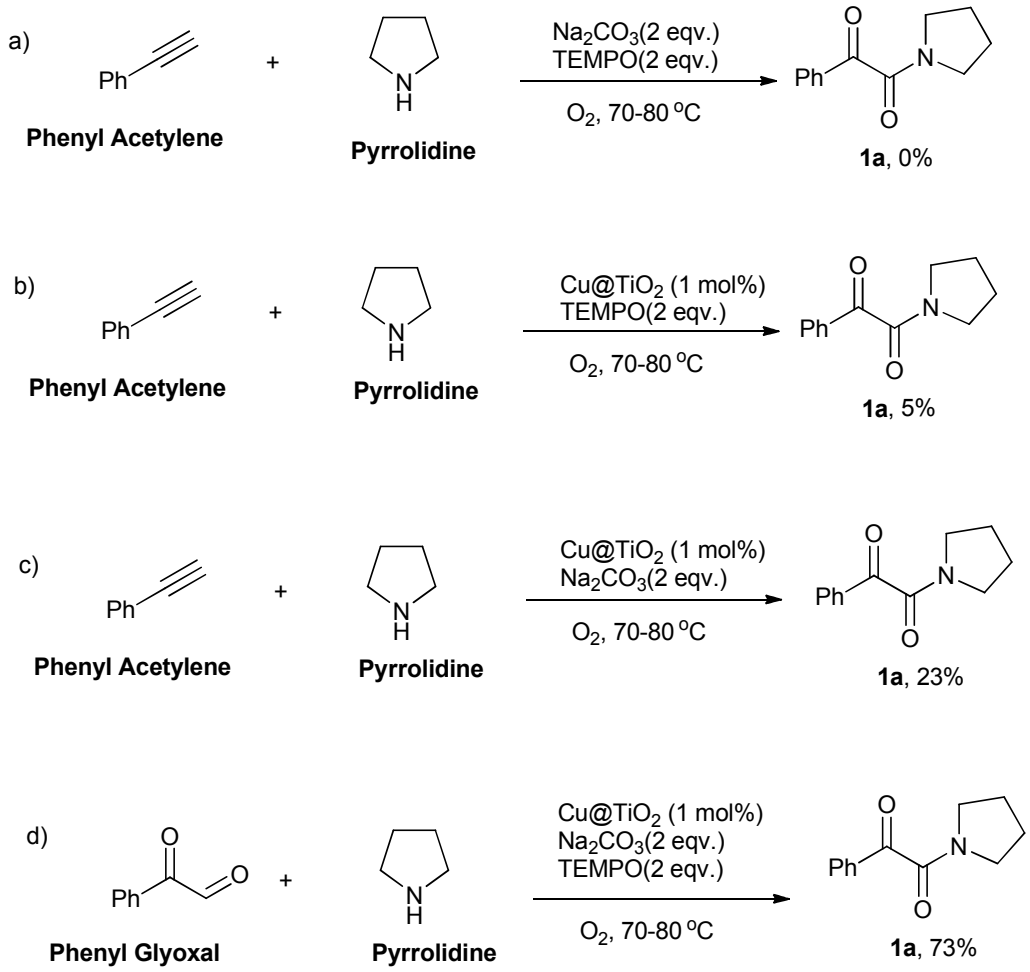

Scheme 4. Control experiments to propose the mechanism

These results and literature precedence of similar reactions prompted us to propose a putative mechanism for this transformation (Scheme 5).[9] We presume, the reaction began with Na_2CO_3 assisted coordination of $CuI@TiO_2$ catalyst with aryl acetylene to generate **A**. Reaction of **A** with appropriate amines furnishes the enamine intermediate **B**, which underwent oxidation to afford **C**. Under the reaction condition amine elimination from **C** provided α-ketoarylaldehyde **D**. Nucleophilic substitution of **D** with available amines generated aminol **E**. Subsequent oxidation of **E** provided the desired products **1a-1o** (Scheme 5).

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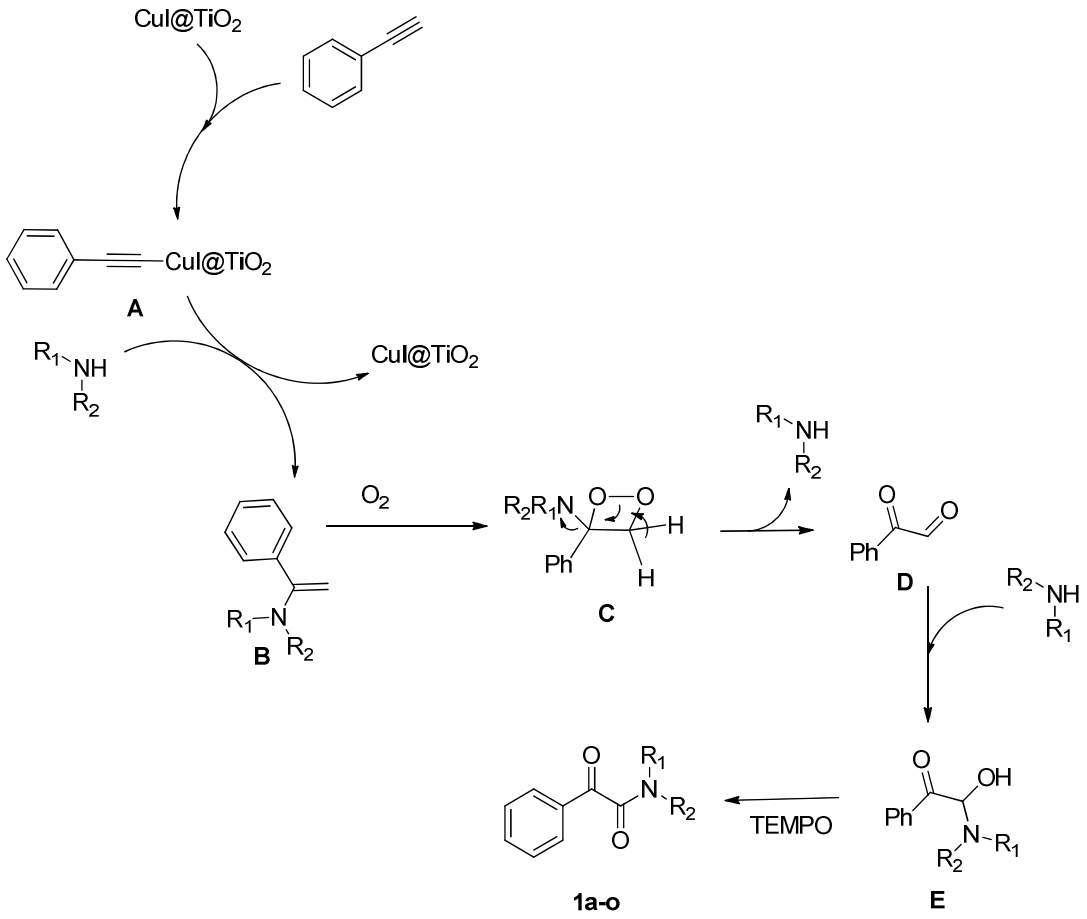

Scheme 5. Mechanism of transformation of aryl/hetarylacetylene to corresponding α-ketoarylamide

Recyclability of the catalyst for the synthesis of α-ketoarylamide

In a bid to evaluate the recyclability of our $CuI@TiO_2$ catalyst in the synthesis of α-ketoarylamides, the catalyst was recycled under standard reaction conditions for the synthesis of **1a** (where phenyl acetylene was reacted with pyrrolidine to generate the desired ketoaryl amide) and **2a**. To our utmost gratification the catalyst demonstrated excellent activity to five cycles for the reaction, where the isolated yields ranged from 90 to 87% (Figure 7).

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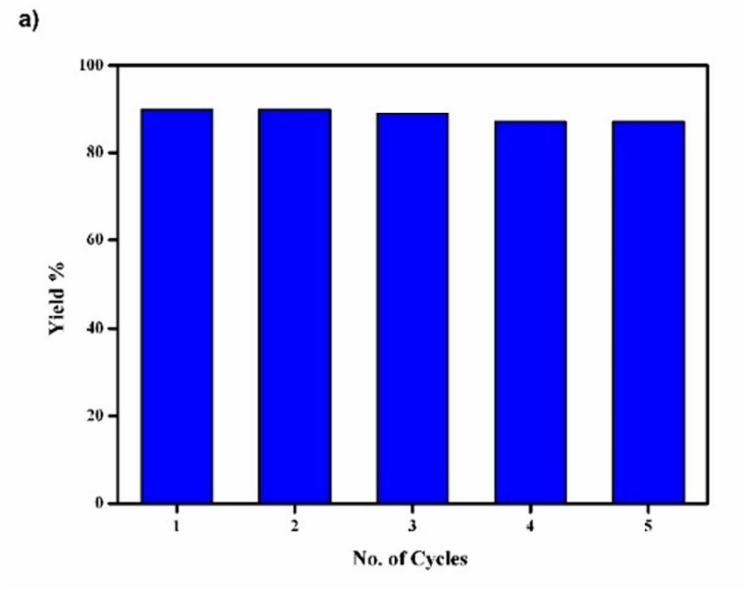

Figure 7. Recyclability of CuI@TiO_2 for the synthesis of ketoaryl amides

Conclusion

In conclusion we have developed a novel catalyst consisting of TiO_2 encapsulated CuI nanoparticles useful for C-C bond forming reactions involving synthesis of α-ketoarylamides. The optimized protocol demonstrated moderate to high yields of the desired products, under solvent free condition and excellent recyclability of the catalyst till five cycles. The catalyst is thoroughly characterized by TEM, SEM, EDS, XPS, XRD and ICP-MS, BET and TGA (refer spectra file) analysis. The reactions pathway was explained through putative mechanisms. This efficient protocol further promotes the importance of metal oxide encapsulated metal catalysts in the generation of relevant bioactive motifs, through interesting organic transformations.

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Notes

The authors declare no competing financial interest

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Experimental

Synthesis of CuI@TiO_2 catalyst

The synthesis of catalyst involved heating a mixture of CuI (0.2 mmol) with $Ti(O^iPr)_4$ (19.0 mmol) in tetraethylene glycol (1 mmol) for two hours followed by addition of water (51.0 mmole) and refluxed at 120^{o}C for nearly 10h. It was then cooled to room temperature and filtered through a cintered glass crucible (G3). The residue was washed with acetone and dried at 100^{o}C.

Synthesis of α-ketoamides

An oven dried round bottomed flask, equipped with magnetic stir bar, was charged with phenylacetylene (200 mg, 1.95 mmole), Na_2CO_3 (415 mg, 3.90 mmole), TEMPO (654 mg, 3.90 mmole), amine (1.95 mmole) and CuI@TiO_2 (100mg, 0.0975 mmole) and allowed to stir under O_2 atmosphere at 70 ^{o}C for 5 hours. Upon completion the crude reaction mixture was cooled to room temp and diluted with EtOAc, then filtered through a plug of celite and washed with EtOAc. It is then extracted with EtOAc (3 X 30 mL).The organic layer was washed with brine and dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude product. It is purified by column chromatography using the indicated eluent.

1-Phenyl-2-(pyrolidin-1-yl)ethane-1,2-dione (1a): EtOAc/*n*-hexane (15%); Yellow gummy solid (76%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (t, *J* = 8 Hz, 2H), 7.63 (d, *J* = 8 Hz, 1H), 7.50 (t, *J* = 8 Hz, 2H), 3.65 (t, *J* = 8 Hz, 2H), 3.42 (t, *J* = 8 Hz, 2H), 1.98-1.95 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.57, 163.92, 133.60, 131.90, 128.88, 127.92, 45.67, 44.24, 24.89, 23.00. . HRMS (EI+) m/z calcd. for $C_{12}H_{14}NO_2$ $[M]^+$: 204.1019, found: 204.1042.

1-Phenyl-2-(piperidin-1-yl)ethane-1,2-dione (1b): EtOAc/*n*-hexane (15%); Yellow gummy solid (76 %), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8 Hz, 2H), 7.65-7.61 (m. 1H), 7.51 (t, *J* = 8 Hz, 2H), 3.70 (s, 2H), 3.28 (t, *J* = 8 Hz, 2H), 1.71-1.68 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.18, 165.48, 134.99, 133.6, 129.70, 129.13, 66.76, 66.69, 46.29, 41.64. HRMS (EI+) m/z calcd. for $C_{13}H_{16}NO_2$ $[M]^+$: 218.1176, found: 218.1164.

1-Morpholino-2-phenylethane-1,2-dione (1c): EtOAc/*n*-hexane (20%); red oily mass (82 %), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 4 Hz, 2H), 7.68 (t, *J* = 8 Hz, 1H), 7.53 (t, *J* = 8 Hz, 2H), 3.80 (s, 4H), 3.66 (t, *J* = 4 Hz, 2H), 3.39 (t, *J* = 4 Hz, 2H). ^{13}C NMR (100 MHz,

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$CDCl_3$) δ 190.95, 164.44, 133.65, 132.24, 128.56, 127.99, 46.03, 41.14, 25.18, 24.43, 23.36. HRMS (EI+) m/z calcd. for $C_{13}H_{16}NO_2$ $[M]^+$: 220.0968, found : 220.0971.

1-(4-methylpipirazin-1-yl)-ethane-1,2-dione (1d): MeOH/ dichloromethane (2 %); brown oily mass (77 %), ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.95 (d, *J* = 8 Hz, 2H), 7.65 (t, *J* = 8 Hz, 1H), 7.52 (t, *J* = 8 Hz, 2H), 3.80 (t, *J* = 4 Hz, 2H), 3.38 (t, *J* = 4 Hz, 2H), 2.52 (t, *J* = 4 Hz, 2H), 2.39 (t, *J* = 4 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.47, 167.53, 165.40, 134.83, 133.14, 129.67, 129.06, 54.90, 54.45, 45.98, 45.77, 41.15. HRMS (EI+) m/z calcd. for $C_{13}H_{17}N_2O_2$ $[M]^+$: 233.1285, found : 233.1282.

N,N-diethyl-2-oxo-2-phenylacetamide (1e): EtOAc/*n*-hexane (20%); red gummy solid (74 %), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8 Hz, 2H), 7.64 (d, *J* = 8 Hz, 1H), 7.51 (d, *J* = 8 Hz, 2H), 3.56 (q, *J* = 8 Hz, 2H), 3.24 (q, *J* = 8 Hz, 2H), 1.29 (t, *J* = 8 Hz, 3H), 1.16 (t, *J* = 8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.58, 166.75, 135.57, 133.26, 129.63, 128.96, 42.13, 38.82, 14.11, 12.84. HRMS (EI+) m/z calcd. for $C_{12}H_{15}NO_2$ $[M]^+$: 206.1176, found : 206.1182.

1-(3,4-Dihydroisoquinolin-2(1H)-yl)-2-phenylethane-1,2-dione (1f): EtOAc/*n*-hexane (15%); red crystalline solid (67 %), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8 Hz, 1H), 7.96 (d, *J* = 8 Hz, 1H), 7.68-7.62 (m, 2H), 7.54-7.47 (m, 2H), 7.24-7.20 (m, 2H), 7.13 (d, *J* = 8 Hz, 1H), 6.94 (d, *J* = 8 Hz, 1H), 4.92 (s, 1H), 4.54 (s,1H), 4.00 (t, *J* = 8 Hz, 1H), 3.63 (t, *J* = 8 Hz, 1H), 3.01 (t, *J* = 8 Hz, 1H), 2.87 (t, *J* = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.53, 191.38, 166.11, 165.80, 134.87, 134.82, 134.21, 133.43, 133.13, 133.05, 131.83, 131.56, 129.76, 129.74, 129.08, 129.05, 129.00, 128.82, 127.24, 126.90, 126.85, 126.71, 126.63, 126.10, 47.36, 43.55, 43.47, 39.40, 29.25, 28.28. HRMS (EI+) m/z calcd. for $C_{17}H_{15}NO_2$ $[M]^+$: 266.1176, found : 206.1172.

1-(3-fluorophenyl)-2-(pyrrolidin-1-yl)ethane-1,2-dione (1g): EtOAc/*n*-hexane (15%); red gummy solid (61%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8 Hz, 1H), 7.72-7.69 (m, 1H), 7.48 (td, 1H), 7.36-7.31 (m, 1H), 3.65 (t, *J* = 8 Hz, 2H), 3.44 (t, *J* = 8 Hz, 2H), 2.00-1.92 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.07, 164.13 (d, *J* = 7 Hz), 161.62, 135.07 (d, *J* = 6 Hz), 130.67 (*J* = 8 Hz), 125.91 (d, *J* = 3 Hz), 121.7 (d, *J* = 22 Hz), 116.30 (d, *J* = 22 Hz), 46.77, 45.42, 25.94, 24.00. HRMS (EI+) m/z calcd. for $C_{12}H_{12}FNO_2$ $[M]^+$: 222.0925, found : 222.0947.

1-(3-fluorophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (1h): EtOAc/*n*-hexane (15%); red oily mass (56 %), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8 Hz, 1H), 7.67-7.64 (m, 1H),

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7.50 (td, 1H), 7.36-7.32 ((m, 1H), 3.71 (d, J = 8 Hz, 2H), 3.29 (t, J = 8 Hz, 2H), 1.70 (t, J = 4 Hz, 4H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.68, 130.76 (d, J = 8 Hz), 125.59, 121.75 (d, J = 21 Hz), 115.88 (d, J = 22 Hz), 47.07, 42.29, 26.24, 25.44, 24.36. HRMS (EI+) m/z calcd. for $C_{13}H_{14}FNO_2$ $[M]^+$: 236.1081, found : 236.1123

1-(3-fluorophenyl)-2-morpholinoethane-1,2-dione (1i): EtOAc/*n*-hexane (15%); brown oily mass (54%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.73 (m,1H), 7.68-7.65 (m, 1H), 7.54-7.48 (m, 1H), 7.38-7.34 (m, 1H), 3.82-3.77 (m, 4H), 3.68-3.66 (m, 2H), 3.40-3.37 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.70, 164.49 (d, J = 62 Hz), 161.70, 135.12 (d, J = 6 Hz), 130.9 (d, J = 8 Hz), 125.71 (d, J = 3 Hz), 122.09 (d, J = 21 Hz), 116.01 (d, J = 23 Hz), 66.74, 66.65, 46.29, 41.75. HRMS (EI+) m/z calcd. for $C_{12}H_{12}FNO_3$ $[M]^+$: 238.0874, found : 238.0861

1-(piperidin-1-yl)-2-(thiophen-3-yl)ethane-1,2-dione (1j): EtOAc/*n*-hexane (15%); yellow oily mass (88 %), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 4 Hz, 1H), 7.58 (d, J = 4 Hz, 1H), 7.38-7.36 (m, 1H), 3.67 (t, J = 8 Hz, 2H), 3.34 (d, J = 8 Hz, 2H), 1.69 (t, J = 4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.39, 165.33, 138.80, 136.19, 127.14, 126.93, 47.13, 42.33, 26.32, 25.49, 24.41. HRMS (EI+) m/z calcd. for $C_{11}H_{13}NO_2S$ $[M]^+$: 224.074, found : 224.0697

1-(piperidin-1-yl)-2-(p-tolyl)ethane-1,2-dione (1k): EtOAc/*n*-hexane (15%); red gummy solid (68%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8 Hz, 2H), 7.30 (d, J = 8 Hz, 2H), 3.69 (bs, 2H), 3.27 (t, J = 8 Hz, 2H), 2.43 (s,3H), 1.69 (t, J = 4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.72, 165.65, 145.89, 130.85, 129.72, 129.70, 47.05, 42.11, 26.21, 25.47, 24.41, 21.92. HRMS (EI+) m/z calcd. for $C_{14}H_{17}NO_2$ $[M]^+$: 232.1332, found : 232.1386

1-(4-bromophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (1l): EtOAc/*n*-hexane (15%); brown oily mass (76 %), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8 Hz, 2H), 7.65 (d, J = 8 Hz, 2H), 3.69 (bt, 2H), 3.28 (t, d, J = 8 Hz, 2H), 1.70-1.64 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.72, 163.87, 131.38, 131.04, 129.94, 129.12, 46.04, 41.24, 25.23, 24.42, 23.32. HRMS (EI+) m/z calcd. for $C_{13}H_{14}BrNO_2$ $[M]^+$: 296.0281, 298.0261, found : 296.0276, 298.0211.

1-(3-methoxyphenyl)-2-(piperidin-1-yl)ethane-1,2-dione (1m): EtOAc/*n*-hexane (15%); red gummy solid (88 %), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.51 (m, 2H), 7.39 (t, J = 8 Hz, 1H), 7.17 (d, J = 4 Hz, 1H), 3.85 (s,3H), 3.64 (t, J = 8 Hz, 2H), 3.40 (t, J = 8 Hz, 2H), 1.97-1.91 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.48, 164.93, 160.02, 134.21, 129.98,

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123.07, 121.57, 112.98, 55.54, 46.68, 45.25, 25.91, 24.04. HRMS (EI+) m/z calcd. for $C_{14}H_{17}NO_3$ $[M]^+$: 248.1281, found : 248.1309

N,N-dimethyl-2-oxo-2-phenylacetamide (1n): EtOAc/*n*-hexane (20%); colorless oily mass (82 %), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 4 Hz, 2H), 7.63 (t, *J* = 8 Hz, 1H), 7.50 (t, *J* = 8 Hz, 2H), 2.95(s, 3H), 3.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.81, 167.04, 134.75, 133.03, 129.66, 129.02, 37.07, 34.01. HRMS (EI+) m/z calcd. for $C_{10}H_{11}NO_2$ $[M]^+$: 178.0863, found: 178.0842

1-(azepan-1-yl)-2-phenylethane-1,2-dione (1o): EtOAc/*n*-hexane (15%); red viscus mass (79 %), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 4 Hz, 2H), 7.63 (t, *J* = 8 Hz, 1H), 7.51 (t, *J* = 8 Hz, 2H), 3.68 (t, *J* = 8 Hz, 2H), 3.34 (t, *J* = 8 Hz, 2H), 1.86-1.82 (m, 2H), 1.69-1.65 (m, 4H), 1.61-1.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.87, 167.20, 134.60, 133.23, 129.66, 128.98, 47.98, 45.17, 29.04, 27.63, 27.22, 26.57. HRMS (EI+) m/z calcd. for $C_{14}H_{17}NO_2$ $[M]^+$: 232.1332, found: 232.1356

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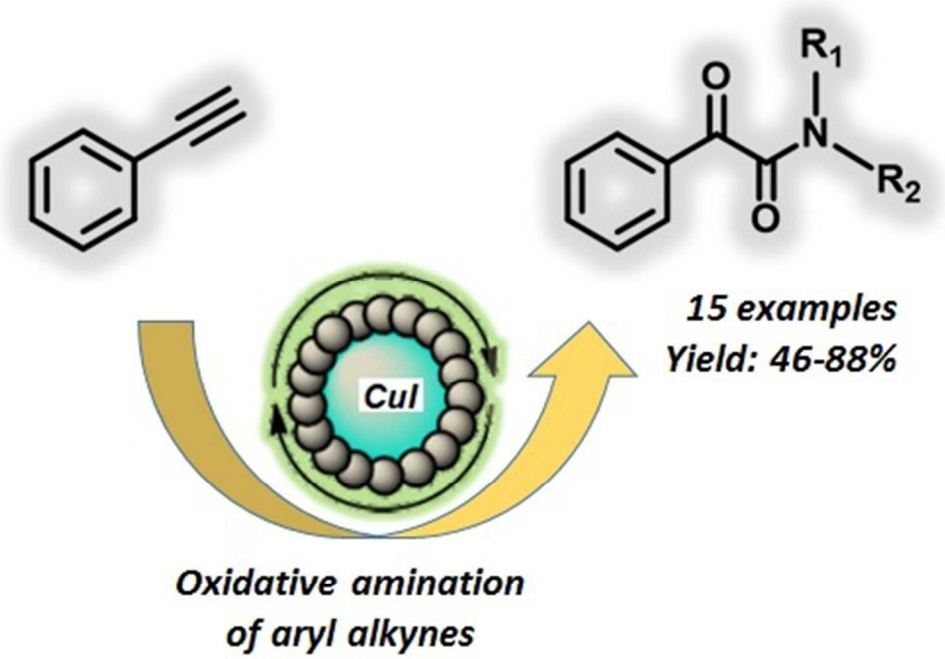

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