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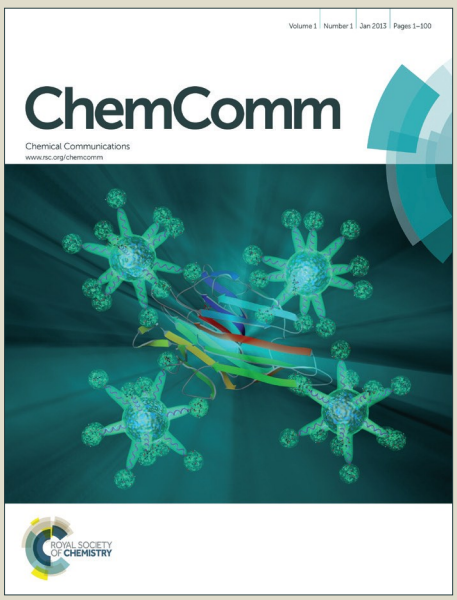




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# Copper(I)-Catalysed Oxidative C-N Coupling of 2-aminopyridine with Terminal alkynes featuring an C≡C bond Cleavage promoted by Visible Light

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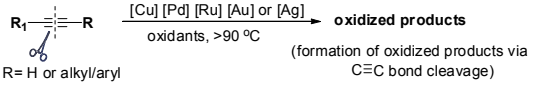
Ayyakkannu Ragupathi, Arunachalam Sagadevan, Chun-Cheng Lin, Jih Ru Hwu, and Kuo Chu Hwang*

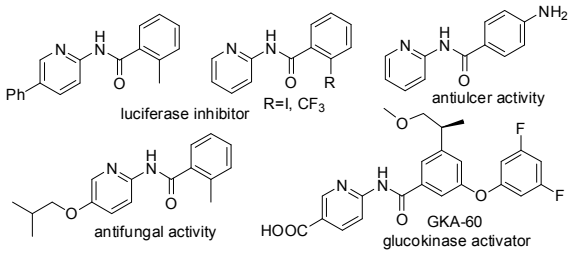
**Facile visible-light promoted copper-catalyzed aerobic oxidative C-N coupling between 2-aminopyridine and terminal alkynes at room temperature via C≡C triple bond cleavage is described. This reaction allows direct synthesis of biologically important pyridyl amides by utilization of commercially available starting materials without the need of bases/external oxidants.**

Reactions involving C≡C triple bond cleavage is of great challenge and fundamentally important in the construction of targeted molecules in organic synthesis.[1] In this regard, most of reports focused on the use of stoichiometric organometallic complexes[2] and catalytic amounts of transition metal complexes (**Scheme 1**) to cleave the tough C≡C triple bond.[1,3] Despite increasing attention of these processes, these methods often suffer from the following drawbacks, such as; a) requirement of specific (stoichiometric) organometallic complex with strong oxidants,[3a] b) often needs of additional promotors (such as; 2-aminopyridine or 2-aminophenol),[3b,g] and c) requirement of high temperature in most of reactions, which sometimes lead to poor control in the selectivity of required products. Although metal-catalysed C≡C triple bond (terminal and internal alkynes) cleavage reaction has been reported, the direct oxidative coupling of 2-aminopyridine with terminal alkynes for the synthesis of heterocyclic amides via C≡C triple bond cleavage remains unexplored.




**Scheme 1** Transition metal-catalysed oxidative C≡C triple bond cleavage.

Nitrogen containing heterocyclic amides represent an important building block in numerous natural products, pharmaceutical, peptides, proteins and organic materials.[4] Typically, pyridyl benzamides are frequently found in a diverse array of bioactive molecules, such as; luciferase inhibitor, antiulcer activity, antifungal activity, glucokinase activator, etc. (see Scheme **2**).[5]




**Scheme 2.** Pyridyl benzamides in pharmaceuticals

As a result, over years many efforts have been devoted to the preparation of pyridyl-amides.[6] Conventionally, preparation of pyridyl-amides heavily relies on reaction of activated carbonyl groups and amines.[6d] Apart from this classical approach, many other methods have also been developed, including; 1) coupling of alkynes with azides,[7] 2) Staudinger reaction,[8] 3) direct oxidative amidation of benzyl alcohols, ketones, aldehyde,[6,9] and 4) other methods.[10] Recently, copper and silver-catalysed coupling reactions involving 2-aminopyridine with alkynes (including activated alkynes) have been reported for the construction of imidazo[1,2-α]pyridines (cyclic products) under harsh conditions.[11] Despite several elegant examples have been described, the alternative platform with combination of copper and light may provide a new opportunity for developing effective process to synthesize N-(pyridine-2-yl)amides through C≡C triple bond cleavage. Recently, photoredox copper-complexes have been proven as an inexpensive catalyst for various coupling reactions, including C-C, C-N, C-S, and C-O cross-coupling reactions.[12] Previously, we reported several examples on visible light-mediated CuCl-catalysed efficient C-C, C-N cross-coupling, and C-H annulation reactions.[13] We demonstrated that these coupling reactions may proceed through the photoexcitation of copper(I) acetylides.[13d] Herein, we report a novel and effective oxidative coupling of terminal alkynes with 2-aminopyridine through C≡C triple bond cleavage under low energy visible light irradiation. The

Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan, R.O.C.
E-mail: kchwang@mx.nthu.edu.tw; Fax: (+886) 35711082.
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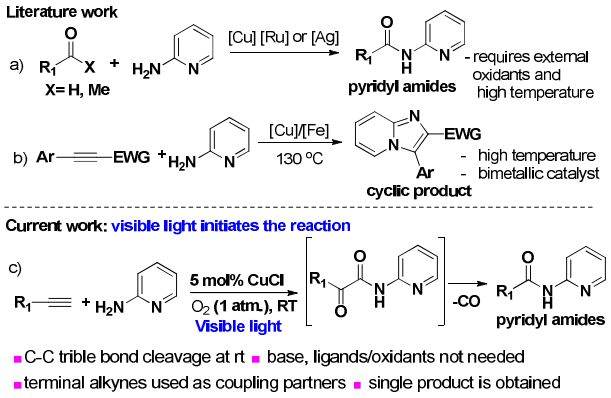
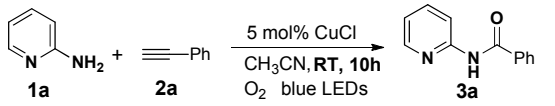
significance of the present chemistry is threefold; a) it is the first example involving both oxidative coupling and cleavage reaction of terminal alkynes, b) this C≡C triple bond cleavage occurs selectively and provides pyridyl-amides, and c) mechanistic investigation illustrates that *in-situ* formation of copper(II)-superoxo or -peroxo complex might be the key catalyst responsible for oxidative cleavage of terminal alkynes.




**Scheme 3** Transition metal-catalysed oxidative coupling reactions of 2-aminopyridine.

**Table 1** Optimization of reaction conditions.[a]

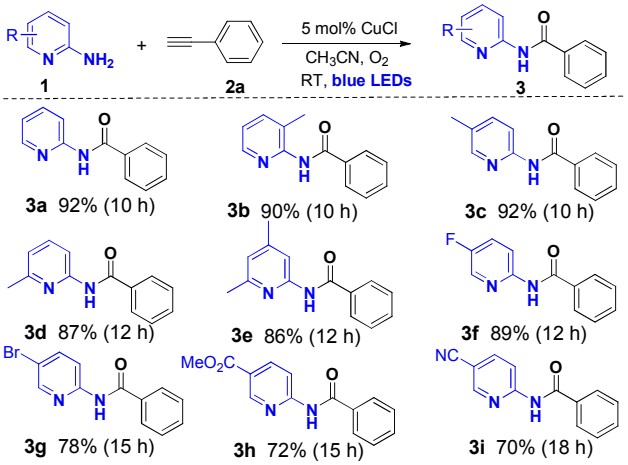



| Entry | [Cu] Catalyst | Solvent | Yield (%)[b] |
|---|---|---|---|
| 1 | CuCl | $CH_3CN$ | 92 |
| 2 | CuBr | $CH_3CN$ | 92 |
| 3 | $CuCl_2$ | $CH_3CN$ | trace |
| 4 | CuCl | $CH_3CN$/MeOH (1:1) | 84 |
| 5 | CuCl | $CH_3OH$ | 64 |
| 6 | CuCl | DMF | 32 |
| 7 | CuCl | THF | trace |
| 8[c] | CuCl | $CH_3CN$ | 10 |
| 9[d] | CuCl | $CH_3CN$ | 10 |
| 10[e] | CuCl | $CH_3CN$ | 36 |
| 11[f] | CuCl | $CH_3CN$ | 80 |
| 12[g] | CuCl | $CH_3CN$ | n.r |
| 13[h] | CuCl | $CH_3CN$ | n.r |
| 14[i] | CuCl | $CH_3CN$ | trace |

[a]Unless otherwise noted, reaction conditions are as follows; **1a** (0.5 mmol), **2a** (0.6 mmol), [Cu] catalyst (5 mol%), and solvent (7 mL). The mixture was irradiated with blue LEDs (power density: 40 mW/cm$^2$ at 460 nm) for 10 h in the presence of $O_2$ atmosphere (1 atm.). [b]Yield of the isolated product. [c]Reaction conducted in the short time irradiation (3h) [d]Reaction conducted with 0.5 equivalent of $K_2CO_3$ [e]0.25 mL water was added. [f]Reaction irradiated with an ambient white light bulb for 15h (power density: 8 mW/cm$^2$ at 460 nm). [g]Reaction conducted in the dark at 80 °C with $O_2$. [h]In the absence of [Cu] catalyst. [i]In the absence of $O_2$. n.r = No reaction, DMF= N, N-dimethylformamide.

The coupling between 2-aminopyridine (**1a**) and phenyl-acetylene (**2a**) was chosen as a model reaction for all optimization studies. In an initial study (Table 1), reaction of 2-aminopyridine (**1a**) (0.5 mmol) and phenylacetylene (**2a**) (0.6 mmol) in the presence CuCl (5 mol%) in $CH_3CN$ affords pyridyl benzamide (**3a**) in 92% yield and 5% pyridyl α-ketoamide (**3aa**) after 10 h irradiation under blue-LEDs. It is worthy to note that, short time irradiation (3-4 h) or reaction in the presence of 0.5 equivalents of base ($K_2CO_3$) accomplished 70% pyridyl α-ketoamide (**3aa**) and trace amount of pyridyl benzamide (**3a**), thus the reaction pathway goes through formation of pyridyl α-ketoamide. In the solvent screening, $CH_3CN$ gives the best yield of the pyridyl-amides (Table 1, entry 1). Other solvents were also tested, but yields are poor (Table 1, entries 4-7). The presence of water dramatically decreases the product yield to 36% (entry 10). In the screening of copper salts, CuX (X: Cl or Br) turns out to be an effective catalyst and affords **3a** in 92% (entries 1 & 2). But, $CuCl_2$ is ineffective for the current reaction (entry 3) and thus copper(I)-salt is responsible for the observed coupling reaction. Control experiments also reveal that the reaction does not occur upon exclusion of light, CuCl or $O_2$ (entries 12-14). Meanwhile, the reaction can be conducted using other light sources (ambient white light; entry 11), however, this light source provided lower yields as compared to blue-LEDs.

**Table 2.** Scope of 2-aminopyridines (**1**).[a]




[a]Standard condition. Isolated yield after purification by column chromatography on silica gel.

With the optimized reaction conditions in hand (see Table 1, entry 1), we have investigated the substrate scope of the 2-aminopyridine derivatives (**1**) with **2a** as a coupling partner (see Table 2). Both electron-rich and electron-neutral groups on 2-aminopyridine ring were well tolerated and produced corresponding amides in good yields 86-92% (**3a-3e**). Importantly, electron-withdrawing groups, such as, ester and nitrile-containing 2-aminopyridines (**1h** & **1i**), are also compatible with phenylacetylene (**1a**), and result in 72 & 70% yields of the corresponding amides (**3h** & **3i**). It was found that current protocol can well tolerate halo-substituted (X= F, Br) 2-aminopyridines, and affords desired amides (**3f** & **3g**) in good yields (89 & 78%), which can be used for further synthetic modification.[14]

Next, the substrate scope of various terminal alkynes was also investigated using **1a** as a coupling partner (see Table 3). Electron-rich phenylacetylenes (**2b-2d**) effectively couple with 2-aminopyridine (**1a**) to afford the corresponding amide products (**4b-4d**) in good yields (Table 3). In addition,

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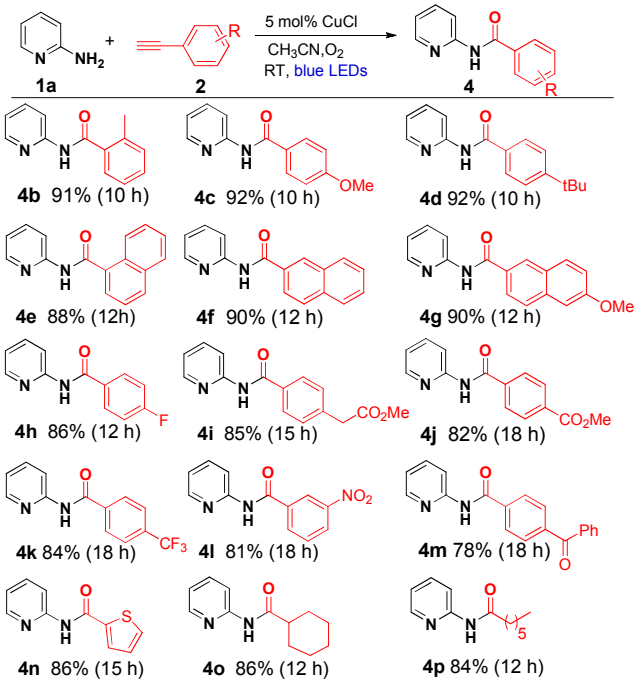
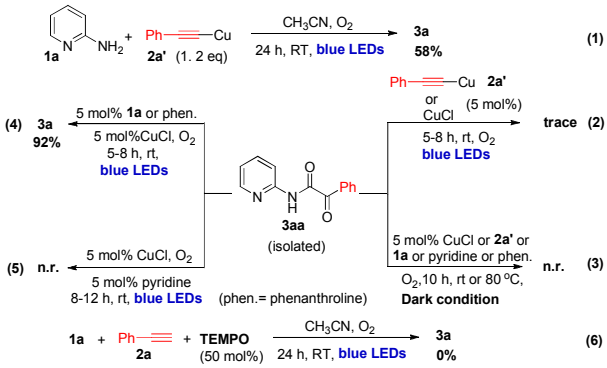
naphthalene moieties (**2e-2g**) as well as aryl alkynes bearing fluoro-substituted group **(2h)** also proceeds with the coupling reaction to furnish the corresponding products **4e-4h** (Table 3). It is worthy to note that the current reaction produces trace or negligible amount of homocoupling 1,3-diyene by-product, in view that most of literature reported reactions involving terminal alkynes always produce 1,3-diynes as homocoupling by-product under aerobic condition.[14b] The electron-deficient phenylacetylenes (**2i-2m**) effectively couple with 2-aminopyridine (**2a**) to afford the desired amide products **4i-4m** in good yields of 78-85%. Moreover, other terminal alkynes, including heteroaryl, cyclohexyl, and octyl alkynes, also successfully underwent the reaction to produce the corresponding pyridyl-amide products (**4n**-**4p**), without any side products. In addition, we have evaluated the green chemistry metrics[13c] for the synthesis of the pyridyl benzamide (**4b**) (see details in S.I.). The structures of **4k** was confirmed by single-crystal X-ray diffraction.[15]

**Table 3.** Scope of terminal alkynes (**2**)

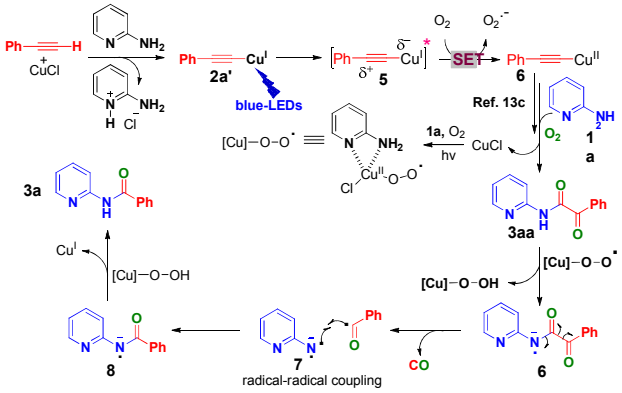



[a]Standard condition. Isolated yield after purification by column chromatography on silica gel.

To gain insights regarding the reaction mechanism, a set of control experiments were carried out [Eq. (1)-(5)]. First, the pre-synthesized copper(I) phenylacetylide (**2a'**)[13d] (1.2 eqv) could react with **1a** and afford the amide product (**3a**) in 58% isolated yield [Eq. (1)]. The reduced yield was attributed to polymeric form of isolated copper(I) phenylacetylide powder.[13c,16] This control experiments show that *in-situ* generated copper(I) phenylacetylide might be the photocatalyst involved in the oxidative coupling reaction.[13d] We have isolated pyridyl α-ketoamide (**3aa**) (after short time irradiation, 3h) and conducted some key control experiments for C≡C triple bond cleavage; first, 5 mol% of CuCl or **2a'** in presence of light and $O_2$ along with **3aa** leads to formation of trace amount of pyridyl benzamide **3a** [Eq. (2)]. Second, we used **3aa** as the starting material and conducted experiments with 5 mol% CuCl in presence of light and $O_2$ along with 5 mol% of 2-aminopyridine or phenanthroline produce the desired product **3a** in 92% yield [Eq. (4)] However, no **3a** product was observed in the dark [Eq. (3)]. In contrast, 5 mol% of pyridine used in the reaction (**3aa**, $O_2$ & light) leads to no reaction, only starting materials were collected [Eq. (5)]. Thus, the *in-situ* generated bidentate ligand coordinated copper(II)-superoxo or -peroxo complex is most probably the key catalyst responsible for oxidative cleavage of pyridyl α-ketoamide to pyridyl benzamide. Indeed, copper(II)-superoxo or peroxo complex could be easily generated by reaction of copper (I)-salt with molecular oxygen in presence of bidentate ligands.[17] Moreover, coupling of **1a** and **2a** in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 50 mol%) was examined under the standard condition. The formation of pyridyl benzamide (**3a**) was completely inhibited [Eq. (6)], suggesting that a radical process might be involved in this reaction.




With respect to mechanistic control experiments and our previous studies,[13c, d] a plausible mechanism was proposed in scheme **4**. Direct Photo-excitation of the *in-situ* generated copper(I) phenylacetylide by blue LEDs (see, uv-visible spectra in figure-**S3**) generates a long lived triplet photoexcited Cu(I)-phenylacetylide[13c,d] via ligand to metal charge transfer (LMCT).[18] The photo-excited Cu(I)-phenylacetylide would undergo a single electron transfer (SET) process to donate an electron to molecular oxygen to generate the Cu(II)-phenylacetylide and superoxide radical anion,[13c,19] which is evidenced by EPR measurements (see, supporting information).




**Scheme 4.** Proposed reaction mechanism.

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Afterward, nucleophilic addition of 2-aminopyridine to Cu(II) phenylacetylide results in the formation of the complex Cu(III) species.[13c,20] Subsequent reductive elimination of Cu(III) to Cu(I) and reaction with molecular oxygen afford pyridine ketoamides and regenerate CuCl.[13c,21] Residual (free) 2-aminopyridine (as a bidentate ligand) could coordinate to $Cu^{I}$. Further photo excitation of the $Cu^{I}$-aminopyridine complex and electron transfer to molecular oxygen leads to the formation of bidentate chelated copper(II) superoxo/-peroxo complex.[17,22] Indeed, copper(II) superoxo/-peroxo complex has a tendency to abstract acidic proton (i.e. pyridyl ketoamides, **3aa**) to form N-centred radical.[12a,23] Radical assisted carbon monoxide elimination and recombination of N-centered radical and carbon centered radical[24] leads to formation of the desired pyridyl benzamides product (**3a**).

In conclusion, we have demonstrated for the first time that C≡C triple bond cleavage and facile synthesis of biologically important pyridyl-amides can be acheived via visible light-initiated copper(I) catalyzed oxidative C-N coupling of 2-aminopyridine with terminal alkynes at room temperature. The current method works well for a wide range of substrates including electron deficient 2-aminopyridines and various terminal alkynes. The mechanistic investigation illustrates that copper(II)-superoxo or -peroxo complex is most probably responsible for oxidative cleavage of C≡C triple bond in terminal alkynes. From the synthetic point of view, exclusion of harsh condition, expensive catalyst, oxidants/base make this method is extremely simple and efficient way to construction of pyridyl-amides under mild conditions.

**Acknowledgments**; this work was supported by the Ministry of Science and Technology, Taiwan.

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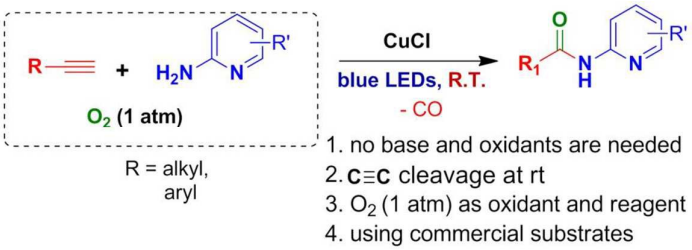
**Graphical Abstract**

# Copper(I)-Catalysed Oxidative C-N Coupling of 2-aminopyridine with Terminal alkynes featuring an C≡C bond Cleavage promoted by Visible Light

Ayyakkannu Ragupathi, Arunachalam Sagadevan, Chun-Cheng Lin, Jih Ru Hwu, and Kuo Chu Hwang*

Department of Chemistry, National Tsing Hua University, Hsinchu 30013, Taiwan. E-mail: kchwang@mx.nthu.edu.tw; Fax: (+886) 35711082.

An efficient and eco-friendly approach to aerobic oxidative C-N coupling of 2-aminopyridine with terminal alkynes for preparation of biologically important priydyl- amides via C≡C triple bond cleavage at room temperature.

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