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Visible light-promoted copper catalyzed regioselective acetamidation of terminal alkynes by arylamines†

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Herein, we describe a copper photoredox catalyzed synthesis of acetamide *via* regioselective C–N coupling of arylamines with terminal alkynes using molecular oxygen (O_2) as an oxidant at room temperature under visible light irradiation (47 examples). Unique simultaneous formation of both amide and ester functionalities occurs *via* intramolecular cyclization in a single-step reaction in the case of anthranilic acids using inexpensive copper as a catalyst and eco-friendly O_2 as an oxidant and reagent. Different substrates undergo different reaction pathways to generate similar acetamide products, as evidenced by $^{18}O_2$ labelling experiments. The current protocol was also applied for the rapid, few step preparation of biologically active inhibitors (BACE-1 and PDE4). This process can be readily scaled up to a gram scale, and calculations of green metrics suggest the economic feasibility and eco-friendly nature of the current photoredox approach.

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Introduction

Amide functionalities are important and ubiquitous structural motifs found in natural products, pharmaceutical drugs, and polymeric materials, and they represent important synthetic intermediates that can be utilized for further construction of complex molecules.[1] Traditional methods for the synthesis of amides include; (i) condensation of amines with carboxylic acids at high temperatures,[2] (ii) nucleophilic addition of amines to activated carbonyl moieties, such as water-sensitive acyl chlorides and anhydrides,[3] (Scheme 1a), and (iii) coupling reaction of acids and amines using stoichiometric coupling reagents (typically used in excess)[4] (Scheme 1b). Transition-metal-catalysis has emerged as a powerful and alternative attractive approach for amide bond construction.[5] In this regard, Chang *et al*. reported that inexpensive copper catalysis has successfully facilitated amide bond formation, wherein terminal alkynes and TsN_3 were employed as coupling partners (Scheme 1c).[6] Consequently, Jiao *et al*. recently reported Au/Ag-co-catalyzed nitrogenation of alkynes *via* C_{sp^2}–C_{sp} cleavage at elevated temperatures to synthesize amides using $TMSN_3$ (Scheme 1d).[7] Despite indisputable advances, these transformations necessitate the use of stoichiometric unstable azides (*e.g.*, TsN_3 or $TMSN_3$) as coupling partners with terminal/internal alkynes for amide bond formation. Moreover, several other methods have been developed including amidation of alcohols at high temperature using expensive Ru/Rh-catalysts.[8] As such, the development of a new method for amide bond construction using commercially available stable arylamines to couple with terminal alkynes using inexpensive catalysts (*e.g.*, copper) under low energy visible light irradiation would be a desirable goal in contemporary organic synthesis.

In recent years, photoredox catalysis has enabled the development of a wide range of challenging chemical transformations *via* outer-sphere single electron transfer (SET) processes.[9] Unlike expensive photoredox catalysts (Ru- and Ir-complexes),[9b] Earth-abundant cheaper copper-based photoredox catalysts can be much more feasible in various transformations[10] *via* an outer-sphere[10a,b] or inner-coordination-sphere mechanism.[10c,d]

Herein, we report the first visible light-induced acetamidation of terminal alkynes by arylamines and molecular O_2 using copper as a catalyst that opens a new synthetic route to acetamides.[11] The reaction proceeds at room temperature using an inexpensive catalyst (5 mol% CuCl), K_2CO_3 as a base, and O_2 as an oxidant, without the use of additional oxidants and ligands (Scheme 1e). Notably, the current work represents the first literature method for mono-ketonation/amidation of terminal alkynes by arylamines, which is complementary to the reported copper-catalyzed process for diketonation/amidation

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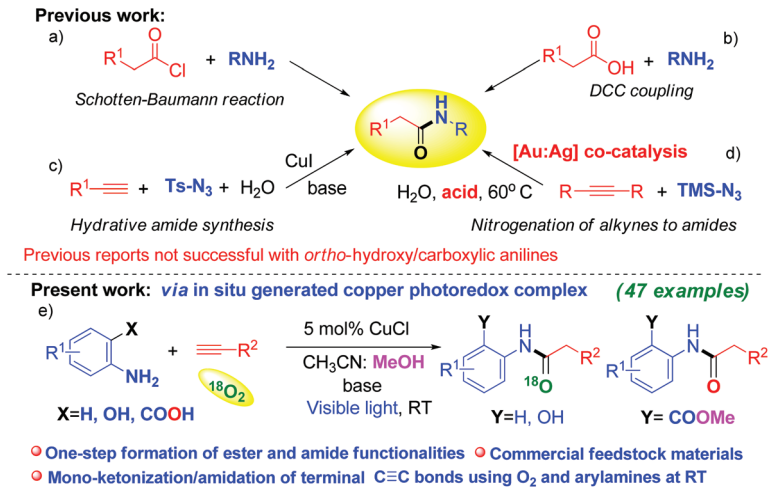


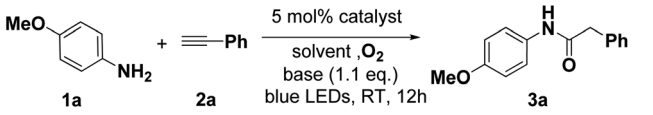
Scheme 1 Different synthetic approaches for amide formation.

of terminal alkynes.[11,12] The notable key features of the current method include: (a) avoiding the use of protecting groups in the cases of 2-aminophenol and anthranilic acid to synthesize acetamide, which would be an important task in organic synthesis,[13a] (b) simultaneous single-step formation of amide and ester functionalities in the case of anthranilic acids, which are not possible by using previously reported literature methods,[13b] and (c) as compared to the previous unstable azide (Ts-N_3 or TMS-N_3) protocol,[6] the current method achieves mono-ketonization/amidation using simple anilines and eco-friendly O_2 (as an oxidant and reagent) in a clean manner under sustainable conditions.

Results and discussion

Inspired by our previous work where α-ketoamides were obtained by C–N coupling of anilines and terminal alkynes under neutral conditions,[11c,14] we were delighted to find that the presence of an inorganic base drives the reaction to a different pathway, leading to the formation of acetamides, instead of α-ketoamides, as dominant products (for mechanistic comparison, please see Scheme S6 in the ESI†). Although the current reaction conditions (the presence of an additional base) are only slightly different from our previous work,[11c] the chemistry (*i.e.*, mono-ketonation amidation), reaction mechanisms, and products are totally different from our previous diketonation/amidation reaction under neutral conditions.[11c] Visible light irradiation of 4-methoxyaniline **1a** and phenylacetylene **2a** in the presence of Cs_2CO_3 (1.1 equiv.) with 5 mol% CuCl in CH_3CN–MeOH (1 : 1 v/v) afforded acetamide **3a** in 68% yield (Table 1, entry 1) with yield being improved to 82% when K_2CO_3 was used as a base (entry 2). After screening different solvents, CH_3CN : CH_3OH (1 : 1 v/v) turned out to give the best yields, whilst alternative Cu-salts (CuBr & $CuCl_2$) were scrutinized and showed inferior results. A series of control experiments were then carried out. Exclusion of either base, light, O_2, or [Cu]-catalyst all resulted in no product formation (entries 6–9) (for detailed optimization, please see Table S1, ESI†).

Table 1 Optimization of the reaction conditions[a]

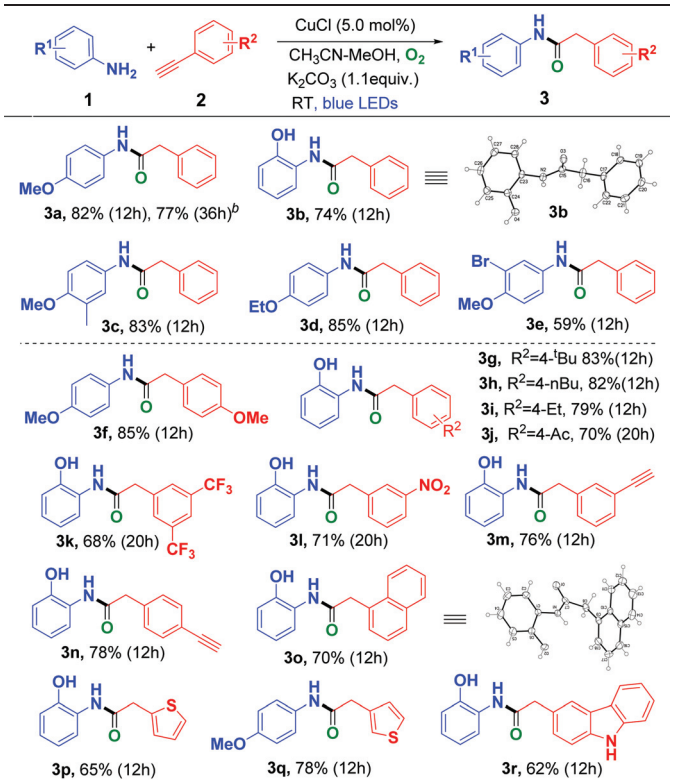


Entry	Cu [catalyst]	Base	Solvent	[Yield %][b]
1	CuCl	Cs_2CO_3	CH_3CN–MeOH	68
2	**CuCl**	**K_2CO_3**	**CH_3CN–MeOH**	**82**
3	Other Cu-salts	K_2CO_3	CH_3CN–MeOH	<65
4	CuCl	K_2CO_3	ACN or ACN–DMF	0
5[c]	CuCl	K_2CO_3	CH_3CN–MeOH	78
6[d]	CuCl	None	CH_3CN–MeOH	0
7[e]	None	K_2CO_3	CH_3CN–MeOH	n.r.
8[f]	CuCl (dark)	K_2CO_3	CH_3CN–MeOH	0
9[g]	CuCl	K_2CO_3	CH_3CN–MeOH	0

[a] Unless otherwise noted, the reaction conditions are as follows; **1a** (0.50 mmol), **2a** (0.7 mmol), base (1.1 equiv.), [Cu]-catalyst (5 mol%), and solvents (8 mL) in 1 : 1 v/v. The reaction mixture was irradiated with blue LEDs (40 mW cm^{-2} at 460 nm) for 12 h under O_2 (1 atm). [b] Yield of the isolated product. [c] Under 1 atm. air. [d] In absence of a base. [e] In absence of a copper catalyst. [f] Under dark conditions at 70 °C. [g] Under a N_2 atm. n.r = no reaction.

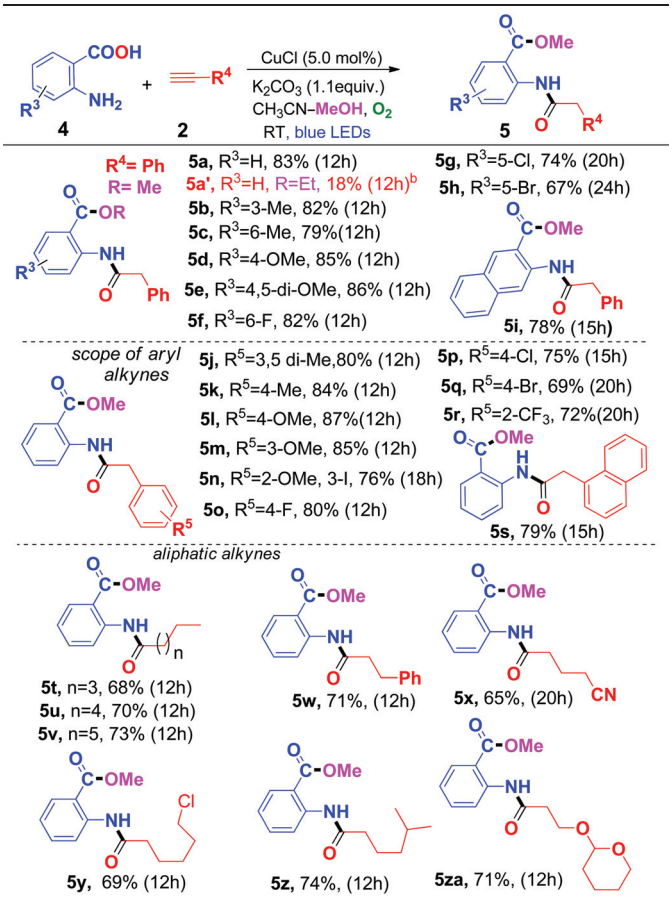
Under the optimized conditions, the scope of this reaction with various arylamines **1** and terminal alkynes **2** was explored (Table 2). Arylamines containing electron-donating groups, in general, facilitate the transformation to afford their corresponding acetamides in high yields (**3a–3e**). In addition, a gram scale reaction of **1a** with **2a** generates acetamide **3a** in 77% yield. Notably, when 2-aminophenol **1b** was used to couple with **2a** (affording **3b** in 74%), there was no need of pre-protection and deprotection of the phenolic OH group. However, electron poor anilines fail to produce acetamides, probably due to their weaker nucleophilic nature and thus poor interaction with Cu(II)-phenylacetylide. Consequently, the C–N

Table 2 Substrate scope of aryl amines and terminal alkynes[a]



[a] Standard reaction conditions. Isolated yields after purification by column chromatography on silica gel. [b] Reaction performed on the 10.0 mmol scale.

Table 3 Substrate scope of anthranilic acids and terminal alkynes[a]



[a] Standard reaction conditions. Isolated yields after purification by column chromatography on silica gel. [b] ACN–EtOH was used as a co-solvent. When longer chain alcohols, such as propanol and butanol, were used to mix with ACN as a co-solvent, no product was observed.

bond formation step might be very slow or difficult to achieve. As compared to anilines, aliphatic amines and 2° aryl, alkylamines do not work in the current protocol, probably due to their stronger tendency to compete with alkynes and form complexes with the Cu(I) ion, forbidding the formation of the key Cu(I)-phenylacetylide photoredox light absorbing species.[15]

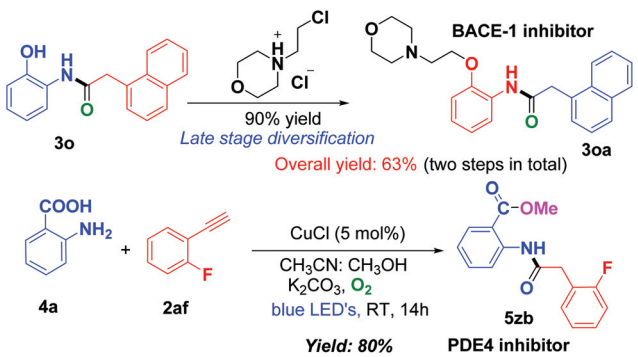
Next, the scope of terminal alkynes in the current oxidative C–N coupling reactions was explored. Aryl alkynes bearing butyl, ethyl, and methoxy groups performed well (**3f–3i**, 79–85% yields, Table 2). Moreover, a diverse array of electron withdrawing phenylacetylenes (–NO_2, di-CF_3, and acyl) was found to be competent substrates with **1b** (**3j–3l**, 68%–71% yields). 1,3- and 1,4-Di-alkynes work well to generate the corresponding acetamides (**3m** & **3n**). Bulky 1-ethynylnaphthalene also showed good reactivity with **1b** to generate **3o** in 70% yield. Notably, heterocyclic alkynes, such as ethynylthiophenes (**2p** & **2q**) and carbazole alkynes (**2r**) which are usually sensitive to oxidative conditions, however, reacted smoothly in the current protocol to generate the desired acetamides in good yields (**3p–3r**).

Furthermore, 2-aminobenzoic acid **4a** could react with phenylacetylene **2a** to produce **5a** in 83% yield (Table 3), demonstrating a single step simultaneous formation of amide and ester functionalities from the co-solvent methanol. Anthranilic acids bearing electron-rich groups (–OMe & –Me) and halogen substituents (F, Cl & Br) react well with **2a** to furnish the corresponding acetamides (**5a–5e** & **5f–5h**) in good to moderate yields. In addition, amino naphthoic acid couples with **2a** effectively to afford **5i** in 78% yield. However, no desired products were obtained when anthranilamide, 2-aminobenzenesulfonamide and orthanilic acids were used as starting materials, instead of anthranilic acid. Finally, a wide range of terminal alkynes including electron-rich and electron withdrawing groups were employed to react with 2-aminobenzoic acid **4a**, furnishing their acetamides in good yields (Table 3). Aryl alkynes bearing –Me, –OMe, halogen substituents (F, Cl, Br & I), an electron withdrawing group (–CF_3), and naphthyl alkyne showed excellent tolerance in the current transformation (**5j–5s**) in 69% to 87% yields. Notably, acetamides bearing halogen substituents can be used in late-stage functionalization. Furthermore, aliphatic terminal alkynes were also successfully employed in this photoredox transformation. Long-chain terminal alkynes, such as hexyne, heptyne and octyne, performed well. Linear-chain terminal alkynes bearing a benzyl group, electron withdrawing groups (–CN and

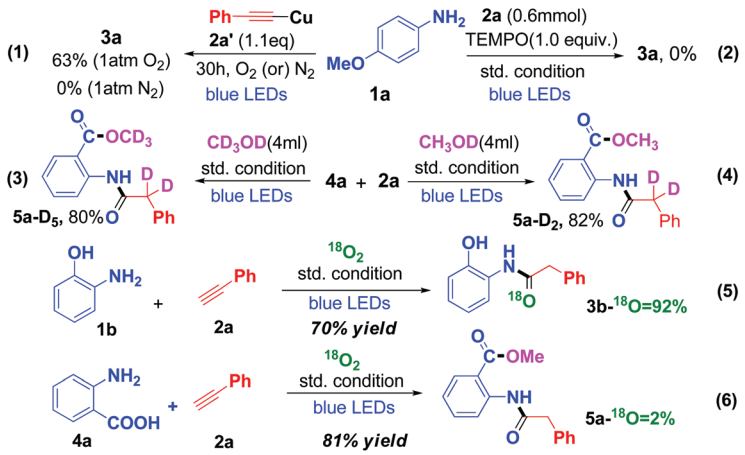
–Cl), and branched aliphatic alkyne smoothly underwent the reaction to furnish the corresponding acetamides (**5t–5z**) without having any side reactions. Structurally labile tetrahydro-2*H* pyran type alkyne underwent regioselective C–N coupling with **4a** to produce acetamide **5za** in 76% yield without having oxidation at the α-methyne/methylene C–H bonds. Additionally, we found that there is a dramatic decrease in the yield of product **5a** to 18% when methanol was replaced by ethanol and used as a co-solvent. When methanol was replaced by other longer-chain alcohols (*i.e.* propanol, butanol, and isopropyl alcohol), no product formation was detected. Methanol is a less hindered, better nucleophile as compared to ethanol and other long-chain alcohols (bulky hindered nucleophiles). Thus, a methoxide anion (MeO^-) would attack more easily on the six-membered cyclic anhydride type intermediate **15** (see, the proposed mechanism in Scheme 4) than other longer-chain counterparts, which leads to higher product yields. The structures of **3b**, **3o** and **3q** were confirmed by single crystal X-ray diffraction (Fig. S5–S7, ESI†).

Finally, the current methodology can be applied to synthesize pharmacologically active drugs, such as BACE-1 **3oa**[13a] and PDE4 **5zb** (Scheme 2).[13b] The BACE-1β-secretase inhibitor **3oa** was successfully synthesized *via* late-stage functionalization of **3o**, which evades the use of unwanted protection and de-protection steps,[16] demonstrating the practical application of the current protocol. The PDE4 phosphodiesterase inhibitor **5zb** was synthesized *via* simultaneous formation of ester and amide bonds in a single-step reaction, which is unprecedented (see Schemes S3 and S4, ESI†). Furthermore, **3p** and **3q** are potential anti-tubercular agents.[17] We further evaluated the calculations of green metrics for the synthesis of **3oa** and made a comparison with those obtained from the existing literature methods. Our current photoredox process to synthesize **3oa** (overall yield of 63%) with an overall *E*-factor of 48.6, atom-economy of 94.5% and 84.2% in two steps, and with a 100% overall carbon efficiency is better in comparison with thermal literature procedures that involve multistep processes (4 steps) to synthesize **3oa** (overall yield of 41%) (see the detailed green metric calculations in the ESI†).

To gain mechanistic insight, several control experiments were carried out (Scheme 3, eqn (1)–(6)). First, pre-synthesised Cu(I) phenylacetylide **2a′** was used as a stoichiometric starting material in the absence of CuCl to react with **1a**, which afforded **3a** in 63% yield after 30 h irradiation (see eqn (1)), suggesting that *in situ* generated Cu(I) phenylacetylide is most probably the key light-absorbing photocatalyst.[11b,c] Next, when the reaction of **1a** with **2a** was carried out in the presence of a radical scavenger TEMPO (1.0 equiv.), the formation of acetamide product **3a** was completely inhibited (see eqn (2)), which is in line with the radical intermediate nature of the transformation. Thereafter, we carried out the reaction of **4a** and **2a** using deuterated methanol solvents (CD_3OD and CH_3OD) under standard conditions (see eqn (3) & (4)), which successfully afforded deuterated products **5a-D$_5$** and **5a-D$_2$**. Physical mixing of acetamide **5a** with CD_3OD or in the presence of K_2CO_3 does not lead to H/D exchange at the methylene protons. These control experiments suggest that the source of the methylene protons is H^+/D^+ from water, which undergoes H/D exchange with deuterated methanol. When *o*-aminophenol was used as a substrate, instead of **4a**, in eqn (4), similar deuteration at the methylene protons was also



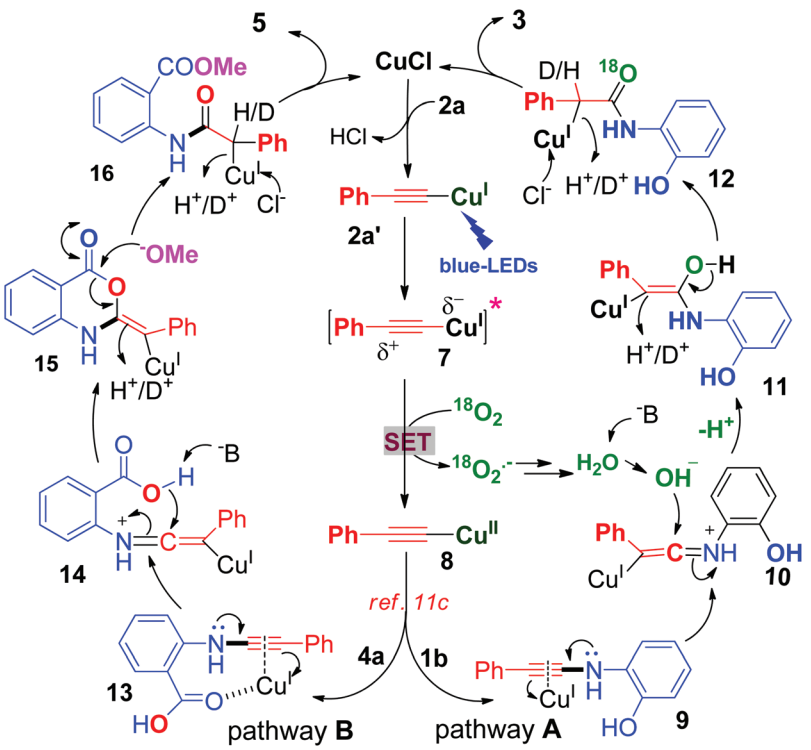
Scheme 2 Synthesis of pharmacologically active inhibitors.



Scheme 3 Mechanistic control studies.

observed for product **3b-D$_2$** (for details, see the ESI†). Finally, we carried out the reaction using **1b** and **4a** under a labelled $^{18}O_2$ (98%) atmosphere (see eqn (5) & (6)). Mass spectra measurements show that 92% of $^{18}O_2$ was incorporated into acetamide **3b**, but only 2% of $^{18}O_2$ was incorporated into product **5a** (Schemes S7 and S8, ESI†). Thus, these results reveal that the carbonyl oxygen in acetamide **5a** originates from the *ortho*-carboxylic acid group *via* intra-molecular nucleophilic addition of a carboxylic anion to imine carbon, followed by the addition of methanol (see the mechanism in Scheme 4). Note that in the reaction with aniline substrates bearing the *o*-carboxylic acid moiety, molecular O_2 does not get incorporated into the final products, but simply acts as an electron acceptor to initiate the reaction *via* a SET process. More precisely, aniline derivatives bearing *o*-hydroxy/-carboyxlic acid moieties undergo different reaction pathways to generate similar acetamide products. Furthermore, the reduction potential of photo-excited copper(I)-phenyl acetylide **2a′** is −2.048 V_{SCE} in CH_3CN, which is sufficiently higher than that of O_2 ($E_{1/2}$ = +0.98 V_{SCE}). Therefore, the SET process from the triplet excited state **2a′** to O_2 is exothermic and occurs spontaneously.[11c]

Based on the above results and our previous studies,[11] we propose a reaction mechanism (Scheme 4) as below. Photoexcitation of *in situ* formed Cu(I)-phenylacetylide (λ_{abs} = 476 nm) by visible light generates a long-lived triplet excited state Cu(I)-phenylacetylide **7**,[11a] which then undergoes a facile SET event with O_2 to generate Cu(II)-phenylacetylide **8** and a superoxide radical anion, as evidenced by EPR measurements (Fig. S1, ESI†).[11c] A superoxide radical anion eventually becomes H_2O_2, and then H_2O *via* metal ion induced decomposition of H_2O_2.[11c,18] In the next step, nucleophilic addition by anilines, either **1b** or **4a**, with **8** (at the α C-site of terminal alkynes), followed by electron transfer to molecular oxygen generated an amine-Cu(III)-phenylacetylide species (not shown in the mechanism cycle, as we already showed this step in our previous studies, ref. 11*c*). Coordination of amine to Cu(II)-phenylacetylide could facilitate the oxidative conversion of the Cu(II)-phenylacetylide to the Cu(III) state.[19] Subsequent reductive elimination of amine-Cu(III)-phenylacetylide leads to the formation of highly reactive Cu(I)-π coordinated ynamine intermediates **9** and **13**, in which the *ortho* group *i.e.*, the carboxylic group would be in chelation with the Cu(I) ion.[11c,20] Acetamides **3** and **5** were formed from different pathways **A** and **B**, respectively. In the presence of a base, a hydroxyl anion will be formed and it would attack the electron deficient imine carbon centre **10** to form Cu(I)-coordinated hydroxyl intermediate **11**, which abstracts a H^+/D^+ from water to form the amide carbonyl (C═O) bond **12**, and finally affords the desired product **3** acetamide and regenerates the CuCl catalyst. In path **B**, a carboxylic acid proton was abstracted by a base, followed by a subsequent intramolecular nucleophilic attack of the carboxylic anion on the electrophilic imine carbon centre **14**, resulting in the formation of a six-membered cyclic intermediate **15**. Further nucleophilic attack by the methoxy group (from methanol solvent) on the carbonyl carbon of **15** leads to the transfer of acid oxygen to ketone and the formation of acetamide **5** with concomitant regeneration of CuCl. Notably,



Scheme 4 Plausible reaction mechanisms.

path **B** allows a simultaneous formation of both ester (C–OMe) and amide carbonyl (C═O) functionalities, which is not possible using previously reported literature methods.[13b] The $^{18}O_2$ experiment confirms that the carbonyl oxygen in **5** is from the *o*-carboxylic acid (CO–**O**H) group, instead of molecular O_2 (see eqn (6)).

Conclusion

In summary, we report the first literature example of photoredox copper catalyzed regioselective acetamidation, including both mono-ketonization and amidation, of terminal alkynes by arylamines using molecular O_2 as a sustainable oxidant at room temperature (47 examples) which can be readily scaled up to a gram scale. The presence of an inorganic base drives a subtle change in the reaction pathway from diketonization–amidation (under neutral conditions)[11c] to mono ketonization–amidation (under basic conditions) of terminal alkynes under visible light irradiation. The current method achieves unprecedented single-step formation of both ester and amide functionalities which are not possible using previously reported literature thermal methods, and evades the need of pre-protection and de-protection of *ortho*-hydroxyl/-carboxylic acid groups in the synthesis of acetamides. The photoredox chemistry reported here was never disclosed by any previous literature work. Mechanistic studies illustrated that different substrates, such as anthranilic acid and 2-aminophenol, undergo different reaction mechanisms to produce the same acetamide core structure. The current protocol was applied to synthesize two biologically active inhibitors with fewer steps (2 steps for BACE-1 inhibitor **3oa** and 1 step for PDE-4 inhibitor **5zb**) without using water-sensitive ($SOCl_2$) reagents, and is more practicable than the literature reported thermal methods.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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References

1 J. M. Humphrey and A. R. Chamberlin, *Chem. Rev.*, 1997, **97**, 2243.
2 A. Ojeda-Porras, A. Hernández-Santana and D. Gamba-Sánchez, *Green Chem.*, 2015, **17**, 3157.
3 (*a*) D. H. B. Ripin and M. Vetelino, *Synlett*, 2003, 2353; (*b*) A. Temperini, R. Terlizzi, L. Testaferri and M. Tiecco, *Synth. Commun.*, 2009, **40**, 295.
4 (*a*) E. Valeur and M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606; (*b*) V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471.
5 (*a*) R. M. de Figueiredo, J.-S. Suppo and J.-M. Campagne, *Chem. Rev.*, 2016, **116**, 12029; (*b*) H.-Q. Do, S. Bachman, A. C. Bissember, J. C. Peters and G. C. Fu, *J. Am. Chem. Soc.*, 2014, **136**, 2162.
6 (*a*) S. H. Cho, E. J. Yoo, I. Bae and S. Chang, *J. Am. Chem. Soc.*, 2005, **127**, 16046; (*b*) S. H. Cho and S. Chang, *Angew. Chem., Int. Ed.*, 2007, **46**, 1897.
7 C. Qin, P. Feng, Y. Ou, T. Shen, T. Wang and N. Jiao, *Angew. Chem., Int. Ed.*, 2013, **52**, 7850.
8 (*a*) A. O. Gálvez, C. P. Schaack, H. Noda and J. W. Bode, *J. Am. Chem. Soc.*, 2017, **139**, 1826; (*b*) N. D. Schley, G. E. Dobereiner and R. H. Crabtree, *Organometallics*, 2011, **30**, 4174; (*c*) X. Wang, T. Gensch, A. Lerchen, C. G. Daniliuc and F. Glorius, *J. Am. Chem. Soc.*, 2017, **139**, 6506; (*d*) C. Gunanathan, Y. Ben-David and D. Milstein, *Science*, 2007, **317**, 790; (*e*) I. Kim and C. Lee, *Angew. Chem., Int. Ed.*, 2013, **52**, 10023; (*f*) J. Zhang, Y. Hou, Y. Ma and M. Szostak, *J. Org. Chem.*, 2019, **84**, 338; (*g*) L. Hie, N. F. F. Nathel, X. Hong, Y.-F. Yang, K. N. Houk and N. K. Garg, *Angew. Chem., Int. Ed.*, 2016, **55**, 2810.
9 (*a*) M. H. Shaw, J. Twilton and D. W. C. MacMillan, *J. Org. Chem.*, 2016, **81**, 6898; (*b*) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322; (*c*) A. Sagadevan and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2019, **58**, 9826.
10 (*a*) O. Reiser, *Acc. Chem. Res.*, 2016, **49**, 1990; (*b*) A. C. Hernandez-Perez and S. K. Collins, *Acc. Chem. Res.*, 2016, **49**(8), 1557; (*c*) J. M. Ahn, T. S. Ratani, K. I. Hannoun, G. C. Fu and J. C. Peters, *J. Am. Chem. Soc.*, 2017, **139**, 12716; (*d*) A. Hazra, M. T. Lee, J. F. Chiu and G. Lalic, *Angew. Chem., Int. Ed.*, 2018, **57**, 5492; (*e*) A. Hossain, A. Bhattacharyya and O. Reiser, *Science*, 2019, **364**, eaav9713; (*f*) R. Kancherla, K. Muralirajan, A. Sagadevan and M. Rueping, *Trends Chem.*, 2019, **1**, 510.
11 (*a*) A. Sagadevan, A. Ragupathi and K. C. Hwang, *Angew. Chem., Int. Ed.*, 2015, **54**, 13896; (*b*) A. Sagadevan, V. P. Charpe, A. Ragupathi and K. C. Hwang, *J. Am. Chem. Soc.*, 2017, **139**, 2896; (*c*) A. Sagadevan, A. Ragupathi, C.-C. Lin, J. R. Hwu and K. C. Hwang, *Green Chem.*, 2015, **17**, 1113; (*d*) A. Sagadevan, V. K. K. Pampana and K. C. Hwang, *Angew. Chem., Int. Ed.*, 2019, **58**, 3838; (*e*) D. K. Das, V. K. K. Pampana and K. C. Hwang, *Chem. Sci.*, 2018, **9**, 7318.
12 C. Zhang and N. Jiao, *J. Am. Chem. Soc.*, 2010, **132**, 28.
13 (*a*) W. Huang, H. Yu, R. Sheng, J. Li and Y. Hu, *Bioorg. Med. Chem.*, 2008, **16**, 10190; (*b*) Y.-D. Cheng, T.-L. Hwang, H.-H. Wang, T.-L. Pan, C.-C. Wu, W.-Y. Chang, Y.-T. Liu, T.-C. Chu and P.-W. Hsieh, *Org. Biomol. Chem.*, 2011, **9**, 7113.
14 In the absence of a base, the reaction produces α-ketoamide as a major product; see ref. 11*c*.
15 J.-P. Wan, S. Cao and Y. Jing, *Appl. Organomet. Chem.*, 2014, **28**, 631.
16 G. Sartori, R. Ballini, F. Bigi, G. Bosica, R. Maggi and P. Righi, *Chem. Rev.*, 2004, **104**, 199.

17 M. C. S. Lourenço, F. R. Vicente, M. G. M. O. Henriques, A. L. P. Candéa, R. S. B. Gonçalves, T. C. M. Nogueira, M. L. Ferreira and M. V. N. Souza, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 6895.
18 H. W. Richter and W. H. Waddell, *J. Am. Chem. Soc.*, 1982, **104**, 4630.
19 (*a*) A. King, L. M. Huffman, A. Casitas, M. Costas, X. Ribas and S. Stahl, *J. Am. Chem. Soc.*, 2010, **132**, 12068; (*b*) A. E. Wendlandt, A. M. Suess and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2011, **50**, 11062.
20 J. Li and L. Neuville, *Org. Lett.*, 2013, **15**, 1752.