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Visible-light-mediated aerobic Ritter-type C–H amination of diarylmethanes using DDQ/*tert*-butyl nitrite†

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A metal-free photocatalytic Ritter-type C–H amination of unactivated sp^3 carbons using molecular oxygen as a terminal oxidant has been developed. By employing a co-catalytic system of 3-dichloro-4,5-dicyano-1,4-benzoquinone (DDQ) and *tert*-butyl nitrite (TBN), this novel strategy provides a low cost, sustainable and scalable way to synthesise a broad range of secondary amides in moderate to excellent yields under mild conditions.

Introduction

Catalytic transformation of omnipresent C–H bonds to C–N bonds offers an efficient synthetic strategy for the construction of valuable nitrogen-containing compounds.[1–3] As one of the most popular strategies to construct C–N bonds, the Ritter reaction has been established as a powerful tool for the synthesis of amides,[4–6] which widely exist in modern pharmaceutical molecules.[7,8] The classic Ritter reaction involves the generation of a carbocation from a functionalized substrate (*e.g.*, alcohols or alkenes), which then reacts with a nitrile leading to the formation of an amide product (Fig. 1A).[4–6] Recently, much effort has been directed towards the development of catalytic Ritter-type C–H amination, which allows amides to be selectively synthesised from non-functionalized alkanes, with the carbocation intermediate generated from C–H bond oxidation using a variety of oxidants such as ceric ammonium nitrate (CAN),[9] Selectfluor,[10] hypervalent iodine,[11] iodic acid,[12] 3-dichloro-4,5-dicyano-1,4-benzoquinone (DDQ)[13] and sodium persulfate[14] (Fig. 1B). However, these methods still suffer from high loadings of transition metals, high temperature and low sustainability due to unwanted by-products derived from the use of stoichiometric oxidants. Considering the strive for greener chemical production, molecular oxygen (O_2) is the most ideal oxidant as it is inexpensive and environmentally friendly.[15,16] In the past 10 years, important advances have been made in the catalytic aerobic oxidation of $C(sp^3)$–H bonds;[17–21] however, to the best of our knowledge, there is no aerobic Ritter type C–H amination method reported to date.

Therefore, developing an environmentally friendly and low-cost metal-free catalytic system for C–H amination is highly desirable. Herein, we report the first photocatalytic aerobic Ritter-type C–H amination for the synthesis of various amides under mild and metal-free conditions using a DDQ/*tert*-butyl nitrite (TBN) catalytic system (Fig. 1C).

Results and discussion

We began our studies by using the DDQ/TBN/O_2 catalytic system, which has previously been successfully used for the oxidation of $C(sp^3)$–H bonds,[22–25] oxidative C–O coupling[26] and C–N coupling reactions.[27–29] Under the optimal conditions, diphenylmethane (**1a**, 0.5 mmol), DDQ (20 mol%), TBN (20 mol%), H_2O (4 mmol, 8 equiv.) and trifluoroacetic acid (TFA, 5 equiv.) in 2 mL of benzonitrile (**2a**) under an oxygen atmosphere (1 bar) led to the desired product **3aa** in 76% yield under the irradiation of blue LED light for 12 h at room temperature (Table 1, entry 1). When the loading of DDQ was decreased from 20 mol% to 10 mol%, the yield of **3aa** decreased slightly to 74% (Table 1, entry 2). Further decreasing the loading of DDQ or the co-catalyst TBN led to unsatisfactory yields of **3aa** (41–61%, for details see ESI Table S1†). It was found that the solvent played a key role in this catalytic reaction. Attempts to replace benzonitrile with other organic solvents (*e.g.*, dichloroethane, toluene, THF, dioxane) led to poor yields (Table 1, entries 3–6), and no amide product was observed when the reaction was carried out in dimethylformamide (DMF, Table 1, entry 7) and dimethoxyethane

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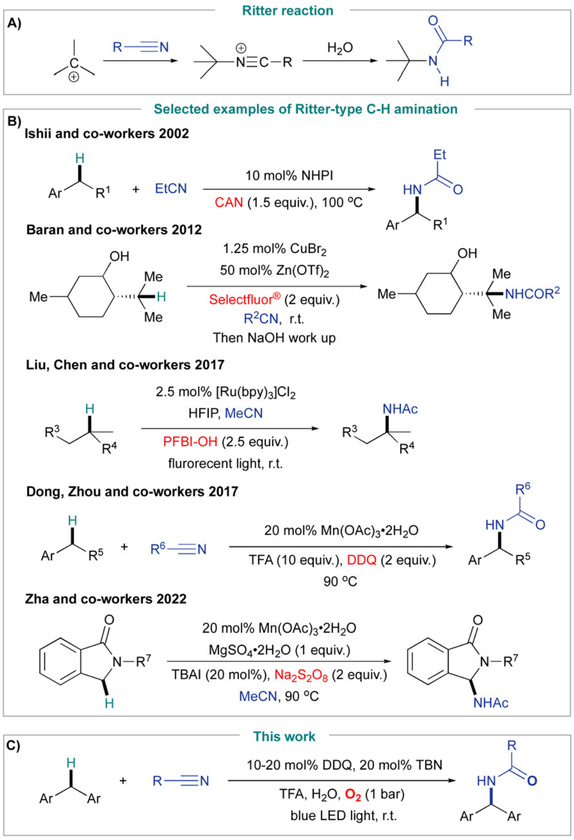
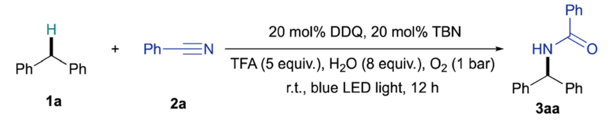


Fig. 1 (A) Ritter reaction with a carbocation as an intermediate. (B) Representative examples of catalytic Ritter-type amination methods with stoichiometric oxidants. (C) This work: metal-free aerobic photocatalytic Ritter-type C–H amination.

Table 1 Optimization of reaction conditions



Entry	Variation from the standard conditions	Yields[a] [%]
1	**None**	**76**
2	10 mol% DDQ	74
3[b]	DCE as the solvent + 15 equiv. of **2a**	61
4[b]	Toluene as the solvent + 15 equiv. of **2a**	42
5[b]	THF as the solvent + 15 equiv. of **2a**	13
6[b]	Dioxane as the solvent + 15 equiv. of **2a**	<1
7[b]	DMF as the solvent + 15 equiv. of **2a**	N.D.[c]
8[b]	DME as the solvent + 15 equiv. of **2a**	N.D.[c]
9	No DDQ	N.D.[c]
10	No TBN	32
11	No TFA	21
12	CH_3COOH instead of TFA	52
13[d]	HCl instead of TFA	28
14[e]	H_2SO_4 instead of TFA	11
15	Under N_2 instead of O_2	16
16	Dark environment	8

Standard conditions: the reaction was performed with **1a** (0.5 mmol), **2a** (2 mL, as a reagent/solvent), DDQ (20 mol%, 0.10 mmol), TBN (20 mol%, 0.10 mmol), TFA (5 equiv., 2.5 mmol), and H_2O (4 mmol, 8 equiv.) with blue LED light and an oxygen balloon at room temperature for 12 h. [a] Yields were determined by GC using biphenyl as an internal standard. [b] 10 mol% DDQ with a specified solvent (2 mL) was used. [c] N.D. implies that no product could be detected by GC-MS and GC. [d] 35 wt% aq. HCl was used. [e] 98 wt% H_2SO_4 was used.

(DME, Table 1, entry 8). Both DDQ and TBN were essential for this catalytic system. No desired product was formed in the absence of DDQ (Table 1, entry 9), whereas a lower yield of **3aa** (32%) was obtained when TBN was omitted or replaced by other NO donors (Table 1, entry 10 and Table S2 in the ESI†). Control experiment also confirmed that the absence of TFA or replacing TFA with other acids (*e.g.*, acetic acid, aq. HCl, H_2SO_4) resulted in lower yields of **3aa** (11–21%, Table 1, entries 11–14), which clearly shows the importance of TFA as an additive. Attempts to carry out the reaction under a N_2 atmosphere or without blue LED light led to a yield of 16% and 8% of **3aa**, respectively (Table 1, entries 15 & 16; for further light source and temperature screening, see Table S2 in the ESI†).

With the optimized reaction conditions in hand, the applicability of these conditions to a range of diarylmethanes was explored (Fig. 2). We found that with 10–20 mol% DDQ and 20 mol% TBN, we could obtain the desired amides in good yields. Having methyl/*tert*-butyl substituents at the *ortho*-, *para*-, and *meta*-positions of diphenylmethane led to the corresponding amide in 64–85% yields (**3ba–3ga**). Unfortunately, diphenylmethane bearing a methoxy group did not participate in the reaction (**3ha**), as the substrate was preferentially oxidized to its corresponding ketone under the optimized conditions. It was found that fluoro-, chloro-, and bromo-substituted diphenylmethanes were successfully transformed to their desired amides in fair to good yields (58–76%, **3ia–3oa**). Notably, strong electron withdrawing substituents (*e.g.*, CF_3– and NO_2–) were well tolerated in the catalytic system and afforded amides in moderate yields (**3pa**, **3qa**). Although benzylheteroarene was not suitable in our reaction system (**3ra**), benzylnaphthalenes showed good activities, affording the desired products (**3sa**, **3ta**) in 67% and 64% yields, respectively.

In previous related Ritter-type C–H amination reports,[4–9,30] the scope of nitriles was less studied and often limited to acetonitrile and benzonitrile. With a broad range of diarylmethanes examined, we tested the system on a variety of nitriles. Excellent functional group tolerance was exhibited by a wide range of nitriles as shown in Fig. 3. We were delighted that benzonitriles bearing an electron donating group (CH_3–) and halogens (F–, Cl–, Br–) could participate in the reaction to furnish their corresponding amides in good to very good yields (**3ab–3ad**, **3ae–3ag**). Furan and thiophene derivatives (*e.g.*, **3ah** and **3ai**) could also be prepared, albeit in moderate yields, highlighting the applicability of this method to synthesize substituted heterocycles. It was found that α,β-unsaturated nitriles could also react successfully, as exemplified by the preparation of **3aj** and **3ak**. Additionally, this system was applied to aliphatic nitriles; they were transformed into their corresponding *N*-benzhydryl amides (**3al**, **3am**, **3an**) in good yields.

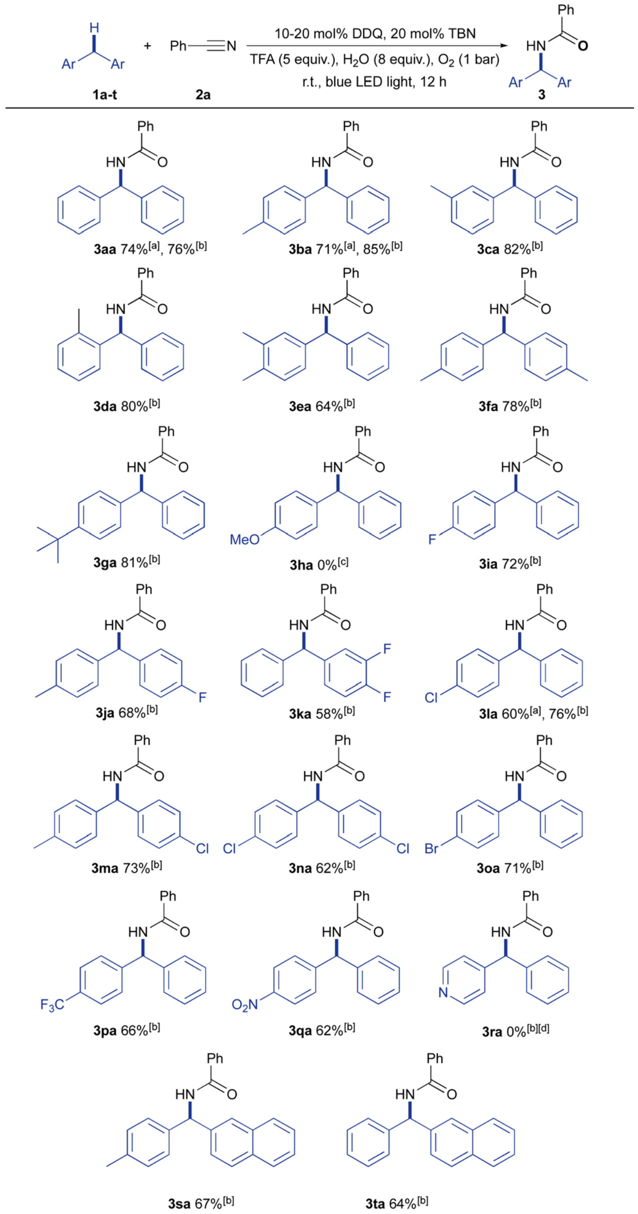


Fig. 2 Scope of diarylmethanes for the aerobic photocatalytic Ritter-type C–H amination reaction using the DDQ/TBN system. Reaction conditions: **1** (0.5 mmol), **2a** (2 mL, as a reagent/solvent), DDQ (10–20 mol% as specified), TBN (20 mol%, 0.10 mmol), TFA (5 equiv., 2.5 mmol) and H_2O (8 equiv., 4 mmol) with blue LED light and an oxygen balloon at room temperature for 12 h. Unless otherwise noted, isolated yields are shown. [a] 10 mol% DDQ was used. [b] 20 mol% DDQ was used. [c] (4-Methoxyphenyl)(phenyl)methanone was isolated in 89% yield. [d] 87% **1r** was recovered.

To further explore the utility of our Ritter-type amination method, we expanded the reaction to a gram scale under the optimized conditions with 10 mol% DDQ and 20 mol% TBN as the co-catalyst (Fig. 4). This work thus far highlights the improved performance of the system compared with the previous system, given the low cost of the catalyst, sustainable mild reaction conditions, and the absence of any metal salts and stoichiometric oxidants.

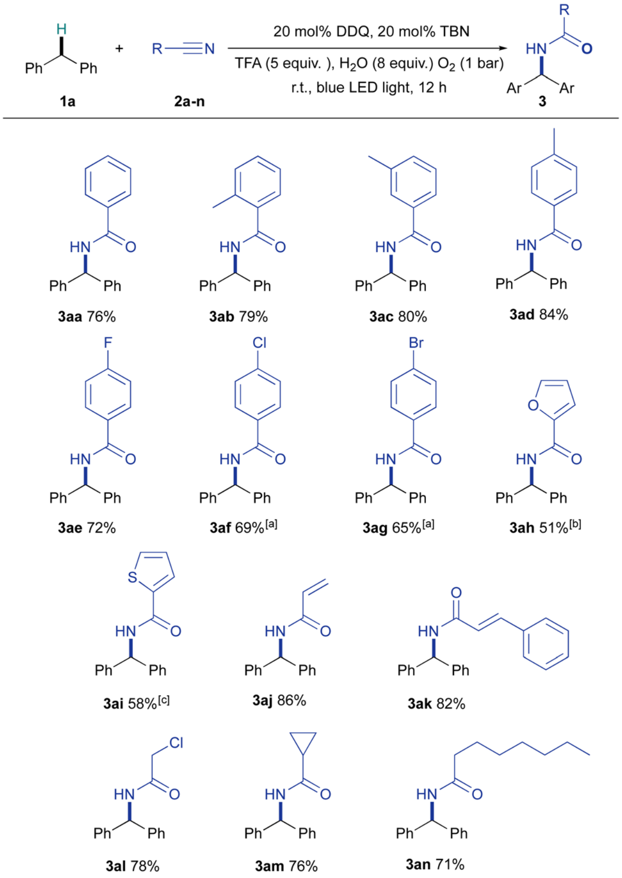


Fig. 3 Scope of nitriles for the aerobic photocatalytic Ritter-type C–H amination reaction using the DDQ/TBN system. Standard conditions: **1** (0.5 mmol), **2** (2 mL, as a reagent/solvent), DDQ (20 mol%, 0.10 mmol), TBN (20 mol%, 0.10 mmol), TFA (5 equiv., 2.5 mmol) and H_2O (8 equiv., 4 mmol) with blue LED light and an oxygen balloon at room temperature for 12 h. Unless otherwise noted, isolated yields are shown. [a] Reaction was carried out with 15 equiv. of the corresponding nitrile in 2 mL of DCE. [b] 42% **1a** was recovered. [c] 40% **1a** was recovered.

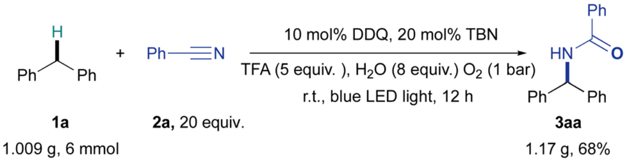
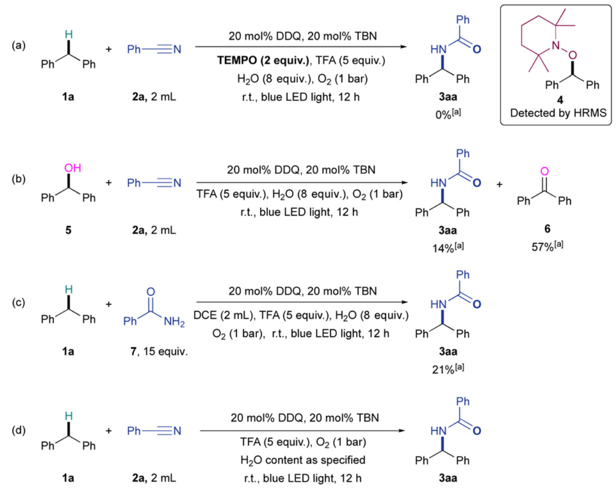


Fig. 4 Gram scale reaction.

To gain insights into the reaction mechanism, several control experiments were carried out (Fig. 5). When 2 equiv. of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) were added as a radical scavenger, the photocatalytic oxidation reaction was completely inhibited and an adduct (**4**) of the N-radical from **1a** with TEMPO was observed by HPLC-MS analysis (Fig. 5a and Fig. S1 in the ESI†). These results suggested that the reaction involved a radical pathway with a carbon centered radical being involved as a key intermediate, which agrees with the mechanism proposed for previously reported Ritter type C–H amination methods.[9–14]



Entry	Water content[c]	Yield[a]
1[b]	0.32 equiv.	55%
2	8 equiv.	76%

Fig. 5 Control experiments. [a] Yields were determined by GC using biphenyl as an internal standard. [b] Reaction was carried out using 3 Å molecular sieves pre-dried **1a**, **2a** and TBN without the addition of H_2O. [c] Water content was determined by Karl-Fischer titration.

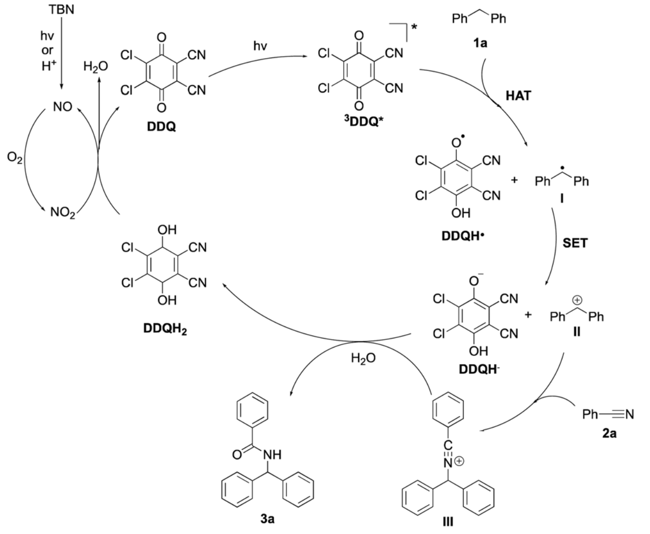


Fig. 6 The proposed mechanism of the aerobic photocatalytic Ritter-type C–H amination using the DDQ/TBN system.

It was reported that the DDQ/TBN system could be employed for visible-light photocatalytic aerobic benzylic C(sp^3)–H oxygenations with alcohols being formed as either intermediates or final products,[31] which could then serve as substrates for the Ritter reaction.[4–6] In addition, it was found that a small amount of **2a** could be hydrolysed to benzylamide (**7**) under the standard reaction conditions (Fig. S2 in the ESI†). To investigate the roles of alcohols and amides, **1a** was first replaced with diphenylmethanol (**5**) as the starting material, which led to only 14% yield of **3aa** with benzophenone (**6**) formed as the major product in 57% yield (Fig. 5b). In addition, the catalytic reaction with benzamide (**7**) instead of **2a** as the starting material led to a sluggish reaction with 21% yield of **3aa** obtained (Fig. 5c). These observations indicate that alcohols or amides generated *in situ* are not involved as the major intermediates during the catalytic cycle. Consistent with previous reports,[14] it was found that the amount of water also played an important role in the catalytic cycle. When the amount of water in the catalytic system was decreased from 8 equiv. to 0.32 equiv., the yield of **3aa** decreased to 55% (Fig. 5d).

According to the above experimental results and literature reports,[14,28,31,32] a mechanism exemplified by the reaction of diphenylmethane (**1a**) with benzonitrile (**2a**) is proposed as shown in Fig. 6. Initial photolysis and acidolysis of TBN liberate NO, which can be readily oxidised to NO_2 by O_2.[31,33,34] Under visible light irradiation, DDQ is excited to its triplet excited state (^{3}DDQ*).[35] The hydrogen atom transfer (HAT) reaction between **1a** and ^{3}DDQ* generates DDQH$^•$ and an alkyl radical (**I**),[36,37] which undergoes subsequent single electron transfer (SET) and leads to the formation of diphenylmethylium (**II**) and DDQH$^-$.[31,37] The carbocation (**II**) then reacts with **2a** to give the nitrilium ion intermediate (**III**), which undergoes hydrolysis to the corresponding amide (**3a**). Meanwhile, DDQH$^-$ is protonated to the hydroquinone DDQH$_2$, which can be re-oxidized to DDQ by NO_2.[38,39]

Conclusions

In summary, by using the DDQ/TBN catalytic system, we have developed the first photocatalytic metal-free Ritter-type C–H amination method with molecular oxygen as a green oxidant. With high functional group tolerance and improved nitrile substrate scope, this protocol provides a simple, sustainable, and scalable method for the construction of secondary C–N bonds under mild conditions with moderate to excellent selectivities. We expect this new protocol to complement existing amination methods and to expand the toolbox for C–H functionalization of unreactive C(sp^3)–H bonds.

Author contributions

ZS and ML conceived the project. ZS, ML and QC designed the methodology and supervised the project. TL, JY, XY, JS, MH and XX performed synthetic and catalytic experiments. TL, QC and ZS analysed the data and wrote the manuscript.

Conflicts of interest

CN Patent CN113943199A by Z. Shen *et al.* contains intellectual property described in this article. The other authors (*e.g.*, J. Yang, X. Yin, J. Shi, Q. Cao, M. Hu and X. Xu) have no conflict of interest to declare.

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