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Visible- Light-Promoted Selective C–H Amination of Heteroarenes with Heteroaromatic Amines under Metal-Free Conditions

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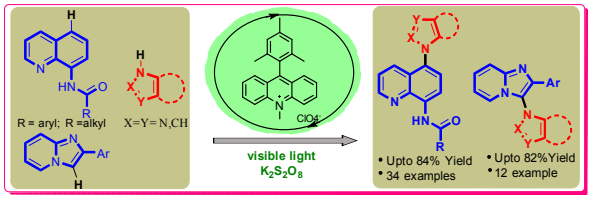
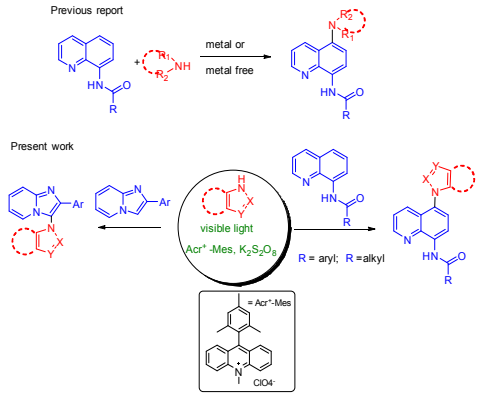
The regioselective C–H amination of quinoline amides (C5) and imidazopyridines (C3) under transition-metal-free conditions at room temperature with a high degree of functional group tolerance is reported. The C–H amination promoted by visible light in presence of photo catalyst with wide range of heteroamines makes the present protocal more sustainable.



Visible light-promoted direct functionalization of C–H bonds is an important transformation in organic synthesis due to its environmentally benign nature.[1] Particularly, C–H amination of heteroarenes is the hot topic of current research, because heteroarylamines are widely exist in many natural products, pharmaceuticals, and functional materials, and much attention has been paid by the synthetic and medicinal chemists.[2] Selective C–H amination is a challenging task to the synthetic and medicinal chemists due to the presence of multiple C–H bonds in heteroarene moiety. This method does not require the use of prefunctionalized substrates, and thus provides an attractive alternative to traditional transition metal-catalysed C–H amination of heteroarenes.[3] In the field of transition metal-catalyzed amination reactions such as Buchwald–Hartwig and Ullmann-type coupling reactions have been emerged as powerful tools.[4]

Among the nitrogen heterocycles, quinoline scaffold is a privileged and prominent chemical entity found in numerous natural products, bioactive molecules, drugs, and materials.[5] Hence there is continuing interest in the development of synthetic methods for the chemical modification of quinolines. In particular C–H amination at C5 position of quinolones[6] is an important scaffold found in many bioactive compounds and exhibit various biological activities. including antimalarial and anticancer properties.[7] However, the above transformations usually require transition metal catalysts. Beyond the metal catalyzed methods, stoichiometric hypervalent iodine reagents such as $PhI(OAc)_2$, DMP, and IBX provided metal-free direct amination avenues.[8] Considering the importance of quinolines and amines, combining these two components into a single entity would be very fascinating for the discovery new lead compounds. Therefore, it is still an attractive to develop simple and efficient methods through the direct C–H amination of quinoline scaffolds at the C5 position under metal-free conditions were rarely explored.[1f]



Scheme 1. Selective C–H amination

In continuation of our research on the development of visible light induced oxidative reactions[9] and metal-free C–H activation for the synthesis of heterocycles, [10-11] herein we report visible light induced selective C–H amination of quinoline amides (C5) and imidazopyridines (C3) under metal-free conditions (Scheme 1).

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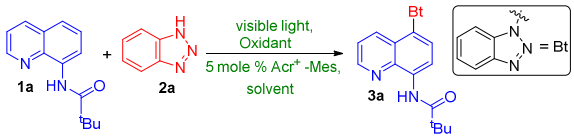
At the outset of our investigation, we selected N-(quinolin-8-yl)pivalamide(1a) and 1H-benzo[d][1,2,3]triazole (**2a**) as model substrates to optimize the reaction conditions. Initially, we evaluated the reaction conditions by subjecting **1a** and **2a** at room temperature using 12W blue LED strips under argon atmosphere and the results are summarized in Table 1. In the presence of 5 mol% 9-mesityl-10-methylacridinium perchlorate (Acr^+-Mes) as photo catalyst with two equivalents of TBHP(aq) as oxidant in dichloroethane at room

Table 1. Optimization of the reaction conditions for **3a**[a]

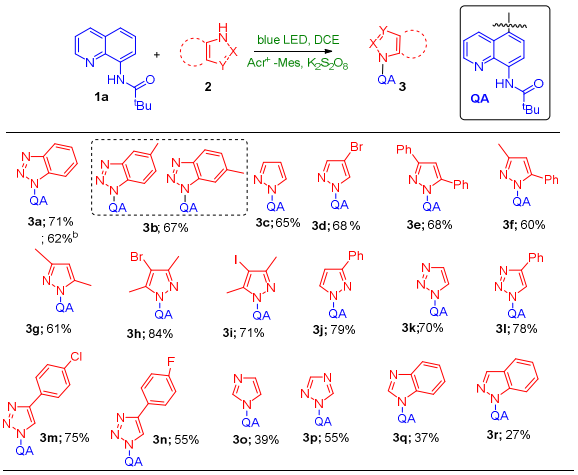


entry	Oxidant (equiv)	solvent	time (h)	**3a** yield (%)
1	TBHP(aq)(2)	DCE	28	20
2	TBHP(decane)(2)	DCE	28	27
3	H_2O_2(2)	DCE	28	16
4	DTBP(2)	DCE	28	30
5	$KHSO_5$(2)	DCE	28	38
6	**$K_2S_2O_8$(2)**	**DCE**	**28**	**71**
7	$K_2S_2O_8$(1)	DCE	28	40
8	$K_2S_2O_8$(1.5)	DCE	28	64
9	$K_2S_2O_8$(2)	DCE	6	39
10	$K_2S_2O_8$(2)	DCE	12	53
11	$K_2S_2O_8$(2)	DCE	18	65
12	$K_2S_2O_8$(2)	THF	28	15
13	$K_2S_2O_8$(2)	Toluene	28	23
14	$K_2S_2O_8$(2)	CH_3CN	28	52
15	$K_2S_2O_8$(2)	DMF	28	0
16	$K_2S_2O_8$(2)	DMSO	28	0
17	$K_2S_2O_8$(2)	Dioxane	28	17
18	$K_2S_2O_8$(2)	EtOH	28	15
19	$K_2S_2O_8$(2)	H_2O	28	10
20	$K_2S_2O_8$(2)	Acetone	28	45
21	$K_2S_2O_8$(2)	DCM	28	63
22	-	DCE	28	7
23[b]	$K_2S_2O_8$(2)	DCE	28	11
24[c]	$K_2S_2O_8$(2)	DCE	28	0
25	O_2 (balloon)	DCE	28	30
26[d]	-	DCE	28	0

[a]Reaction conditions otherwise stated: **1a** (0.20 mmol), **2a** (0.40) mmol, Acr^+ -Mes (5 mole %) and solvent (2.5 mL), at room temperature, argon atmosphere, under irradiation of 12 W blue LED strips for 28 h, isolated yields. [b]Reaction performed without Acr^+ -Mes. [c]Reaction performed under under dark condition condition. [d]Reaction performed without any oxidant under argon atmosphere.

temperature; after 24 h, the desired aminated product N-(5-(1H-benzo[d][1,2,3]triazol-1-yl)quinolin-8-yl)pivalamide (**3a**) was obtained in 20% yield (Table 1, entry 1). Upon performing the same reaction using TBHP in dacane, **3a** was isolated in 27 % yield (Table 1, entry 2). Then, the reaction was performed using different oxidants like, H_2O_2, DTBP, $KHSO_5$, $K_2S_2O_8$, (entries 3–6) among these oxidants tested, **3a** was obtained in 71% yield with $K_2S_2O_8$ as oxidant (entry 6). While decreasing the amount of $K_2S_2O_8$ (entries 7 and 8) and reaction time (entries 9–11) the yield of the product was also decreased. Keeping the optimum amount of oxidant $K_2S_2O_8$ as two equivalents and fixing the reaction time 28 h, we checked the effect of different solvents (THF, toluene, CH_3CN, DMF, DMSO, 1,4-dioxane, EtOH, H_2O, acetone and DCM) for the reaction, but the yield was not improved (entries 12–21). Performing the reaction without oxidant and photo catalyst, the yield of **3a** was enormously dropped (Table 1, entries 22 and 23). No reaction was observed while conducting the reaction under dark conditions (entry 24)[12] and only 30% yield was obtained with oxygen balloon as oxidant (entry 25).

Scheme 2. Scope for C–H amination of **1a** with heteroarenes[a]



[a]Reaction conditions otherwise stated: **1** (0.20 mmol), **2** (0.40) mmol, (0.40 mmol) $K_2S_2O_8$, Acr^+ -Mes (5 mol %) and DCE (2.5 mL), at room temperature, argon atmosphere, under irradiation with 12W blue LED strip, isolated yields. [b]Gram scale synthesis of **3a** (**1a**; 1.00 g, **2a;** 1.04 g**).**

On the basis of the results obtained from the screening of the reaction conditions, the optimized conditions were fixed as 0.2 mmol of **1a**, 0.40 mmol of **2a**, 2.0 equivalents of $K_2S_2O_8$ and 5 mol% of photo catalyst, DCE as solvent at room temperature, 28 h reaction time for further selective C–H amination of **1a** with other heteroarenes (Scheme 2).

Under the optimized conditions the reaction of 1a with 5-methyl-1H-benzo[d][1,2,3]triazole **2a**, the selective C5 aminated product 3b was obtained in 67% yield of two inseparable regioisomers. Purification by column chromatography, these two regioisomers obtained together as confirmed by NMR. Then, the reaction of **1a** with 1H-pyrazole and its halogen, methyl and phenyl substituted derivatives including di- and tri- substituted pyrazoles were subjected to optimized conditions, they all reacted well and provided the corresponding C5 aminated products **3c**–**3j** in good yields (60-84%). Further, the reaction of 1a is compatible with 1H-1,2,3-triazole and arylated triazoles and gave the corresponding

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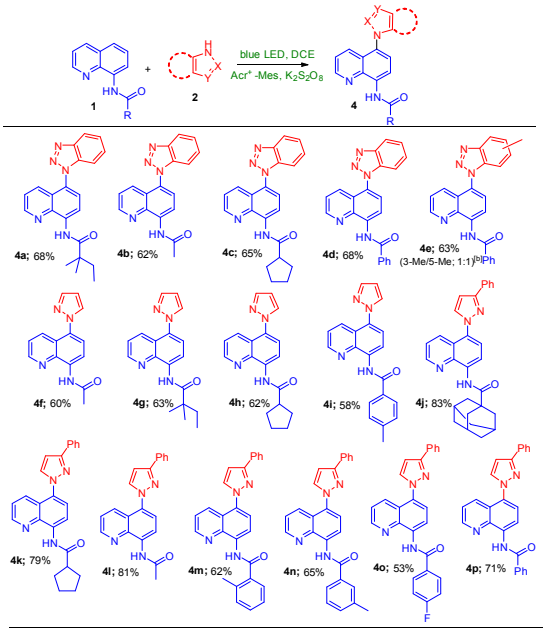
aminated products **3k**–**3n** in good yields. It may be noted that, the halogen (Br, Cl, F and I) substituted derivatives were well tolerated and which could be further applied in traditional cross-coupling reactions. Under the optimized conditions other hetero arenes such 1H-imidazole, 1H-1,2,4-triazole, 1H-benzo[d]imidazole and 1H-indazole were also reacted and afford the products **3o**–**3r** in moderate yields. More over to validate the present protocol, the reaction of **1a** was carried out at gram scale and obtained **3a** in 62% yield.

Further, the present strategy was extended to different 8-amidoquinolines other heteroarene amines, with the optimized conditions to ascertain the scope of our methodology (Scheme 3).

Scheme 3. Substrate scope for C–H amination of 1 with different heteroarenes[a]



[a]Reaction conditions otherwise stated: **1** (0.20 mmol), **2** (0.40) mmol, (0.40 mmol) of $K_2S_2O_8$, Acr+-Mes (5 mol %) and DCE (2.5 mL), at room temperature, argon atmosphere, under irradiation with 12W blue LED strip, isolated yields. [b]Purification by column chromatography, two inseparable regioisomers were obtained as confirmed by NMR.

As evident from the products of scheme 3, variety of amides amides such as acetamide, isobutyramide, 2,2-dimethylbutanamide, cyclopentanecarboxamide and ben-zamide including adamantane-1-carboxamide substituted quinolines underwent selective C–H amination with different arenes (benzotriazole and pyrazole derivatives) and afforded the products **4a–4p** in moderate to good yields (53-83%). One of the products, **4j**, was further confirmed by single-crystal X-ray diffraction (Figure 1).

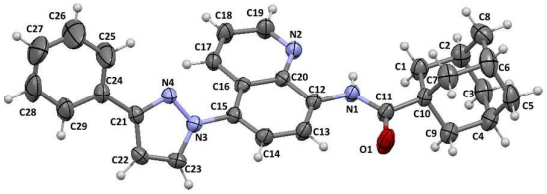
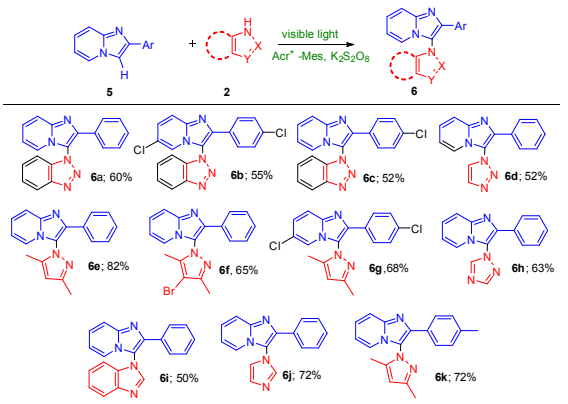


Figure 1. Crystal structure of **4j** (CCDC:1571571).

Further, to expand the scope of the methodology, we extended C–H amination of important but representative imidazopyridines **5** under the optimized conditions with different heteroarenes such as benzotriazole, pyrazole, imidazole, 1H-1,2,4-triazole, 1H-benzo[d]imidazole and 1H-indazole and the corresponding C3 aminated products **6a–k** were obtained in moderate to good yields (Scheme 4). It may be further noted that, the presence of halogenated products were unaffected under the present conditions for the C–H amination.

Scheme 4. Substrate scope for C–H amination of imidazopyridines[a]



[a]Reaction conditions otherwise stated: **5** (0.20 mmol), **2** (0.40) mmol, (0.40 mmol) of $K_2S_2O_8$, Acr+-Mes (5 mole %) and DCE (2.5 mL), at room temperature, atmosphere under irradiation of 12 W blue LED strips for 28 h, isolated yields.

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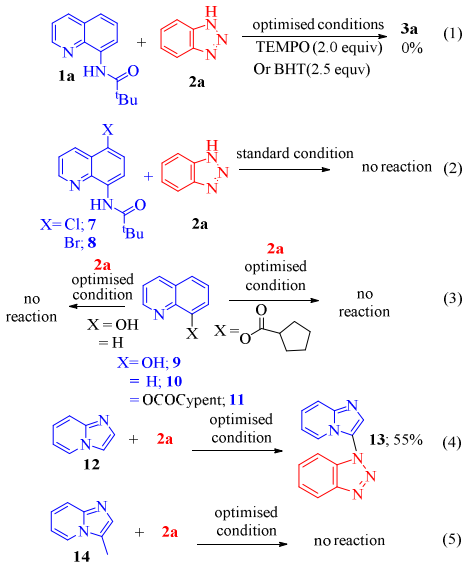
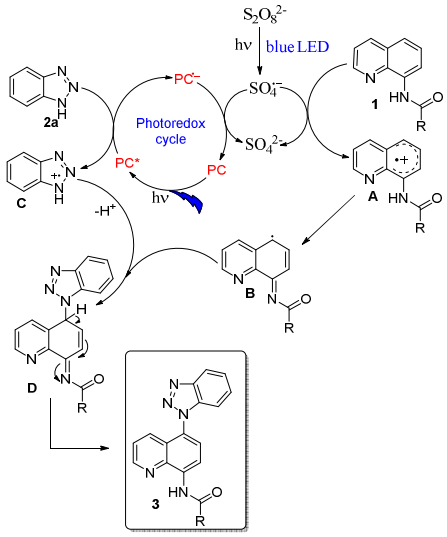


Scheme 5. Control experiments for mechanistic study

To understand the reaction mechanism, some selective and control experiments were performed (Scheme 5). Initially, the reaction of **1a** and **2a** was conducted under the optimized conditions with radical trapping agents TEMPO and BHT, no reaction was observed (Scheme 5, eq. 1). This reaction indicates that, the reaction proceeds via radical pathway. To check the selectivity of C–H amination, the C5 substituted substrates **7** and **8** were subjected to the reaction of **2a** under the optimized conditions, no reaction was observed (Scheme 5, eq. 2).

Further, the substrates **9, 10** and **11** were subjected to the reaction of **2a** under the optimized conditions, no reactions were observed (Scheme 5, eq. 3). These control experiments suggest that, if the C-5 position of quinoline amide 1 is substituted by any group, no reaction takes place to yield the C–H aminated product. Similarly to check the selective C–H amination for imidazopyridines, under the optimized conditions, the reaction of unsubstituted imidazopyridine **12** was subjected with **2a**, the C3 aminated product **13** was obtained in 55% yield (Scheme 5, eq. 4). Further, the C3 substituted imidazopyridine **14** was subjected to the reaction of **2a** under similar conditions, no reaction was observed (Scheme 5, eq. 5). The control experiments (eqs.2–4) suggests the regioselective C–H amination of quinoline amides and imidazopyridines. Based on the above observations and the literature reports,[1d-f, 1j, 3a,13] a plausible reaction mechanism has been proposed for the present protocol (Scheme 6). Initially, photocatalyst, Acr+-Mes (PC) under irradiation with visible light and may reach its excited state (PC^*), it further undergoes single electron transfer excited state (PC^*), it further undergoes single electron transfer by abstracting an electron from **2a** which generates anion radical ($PC^{\bullet-}$) and radical intermediates C. The ground state of PC was regenerated from $PC^{\bullet-}$ by donating an electron to $SO_4^{\bullet-}$. On the other hand **1** was oxidized by $S_2O_8^-$ and may generate the radical intermediate **B** (via intermediate A) under irradiation with visible light. The cross-coupling reaction between intermediates **B** and **C** may furnish another intermediate **D** and its isomerization afford the desired product **3**.



Scheme 6. Plausible mechanism

Conclusions

In conclusion, we have developed an efficient visible light induced regioselective C–H amination of quinoline amides under transition-metal-free conditions at room temperature with a high degree of functional group tolerance. The scope of the methodology has been extended to imidazo[1,2-a]pyridines. Control experiments confirm the applicability for wide range of heteroamines (such as benzotriazoles, benzoimidazoles, triazoles, pyrazoles, imidazoles and indazoles) use of light at room temperature for C–H amination makes the transformation more sustainable.

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