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Visible-light-mediated α-amino alkylation of ketimines and aldimines for the synthesis of 1,2-diamines†

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A visible-light-mediated protocol to prepare 1,2-diamines has been successfully explored based on the photoredox/Brønsted acid co-catalyzed α-amino alkylations of imines with tertiary amines. Both ketimines and aldimines are applicable to this transformation. Various 1,2-diamines with different functional groups were produced in moderate to excellent yields. Moreover, this approach could be performed on a gram scale, showing its practicality.

Introduction

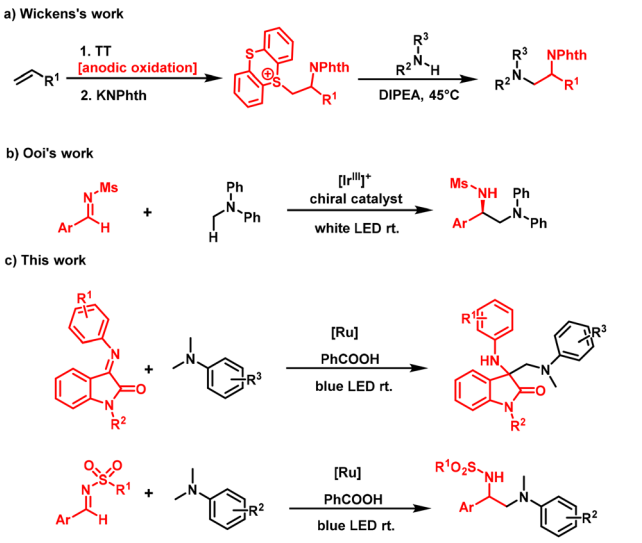
The structural moieties of 1,2-diamines have broad applications in the fields of medicine and synthetic chemistry,[1,2] such as in anti-cancer drugs (*e.g.* spermine[3] and (−)-agelastatin A[4]) and antiviral drugs (*e.g.* Tamiflu[5]), and as auxiliary ligands[6] and as chiral catalysts[7,8] in asymmetric synthesis. The synthesis of 1,2-diamines has attracted much attention in synthetic chemistry, and several methods have been reported such as the classical representative Mannich reactions.[9–13] However, due to the involvement of the harsh conditions of low temperatures,[9–13] stoichiometric amounts of metals[14] and dangerous reagents such as triethyl boron[15] in these reactions, the exploration of mild strategies is essential. Recent advances have been made to make up for these deficiencies; for example, Wickens reported an electrochemical one-pot unsymmetrical diamination reaction[16] (Scheme 1a).

Apart from electrocatalysis, visible-light-mediated construction of C–C bonds[17–20] has also become prominent as a mild strategy in recent years. In this context, the direct functionalization of C–H bonds[21–24] of tertiary amines has been strategically implemented for constructing C–C bonds under visible light irradiation. There are many elegant protocols[25–29] for activating the C–H bonds of tertiary amines, such as visible-light-mediated reactions with electron-deficient olefins,[30–33] maleimides,[34] α,β-unsaturated amides,[35] esters,[36] and imines.

The α-amino alkylation reactions of imines, in particular, are applicable to preparing 1,2-diamines. Ooi successfully realized the asymmetric coupling of secondary α-amino radical anions and *N*-arylaminomethanes to prepare chiral 1,2-diamines[37] (Scheme 1b).

Rueping's group developed a visible-light-mediated approach for the α-amino alkylation of aldimines, the radical coupling reaction of ionic radicals produced by tertiary amines with imines and aldehydes.[38]

Besides, Paixão and co-workers expanded the range of radical α-amino alkylations toward azomethine iminium ions.[39] In addition, Singh successfully prepared α,β-diamino esters using *N*,*N*-dimethylbenzamine and glyoxal oxime ether



Scheme 1 Strategies for preparing 1,2-diamines.

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as substrates.[40] Given that 3-aminooxindoles bearing a stereo carbon center at the 3-position are valuable in the biomedical field,[41] herein we report a protocol for the α-amino alkylation of isatin-derived ketimines with tertiary amines under visible light irradiation to prepare 1,2-diamines (Scheme 1c).

Results and discussion

Initially, 1-methyl-3-(phenylimino)indolin-2-one **1a** and 4,*N*,*N*-trimethylaniline **2a** were selected as the model substrates to screen the conditions of this reaction (Table 1).

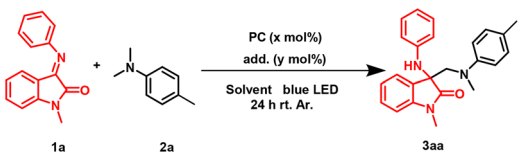
Firstly, this reaction was carried out with **1a** and **2a** in the presence of the photocatalyst $Ru(bpy)_3Cl_2$ in MeCN under the irradiation of a 30 W blue LED lamp at room temperature for 24 h. To our delight, the desired product **3aa** was obtained in 43% yield (Table 1, entry 1). Subsequently, other photocatalysts, such as 4CzIPN, $Ir(ppy)_3$ and $[Ru(bpy)_3](PF_6)_2$, were employed, and $[Ru(bpy)_3](PF_6)_2$ was the best one (Table 1, entries 2–4). Unlike previous relevant reports,[39,40] adding a basic additive such as NaOAc was detrimental to this reaction (Table 1, entry 5).

Nevertheless, the presence of Brønsted acid benefited the reaction (Table 1, entries 6 and 7), and the effect of PhCOOH was superior to that of CF_3COOH. Furthermore, MeCN was the ideal solvent for this transformation (Table 1, entries 7–9). Moreover, the yield was improved up to 83% by increasing the amount of $[Ru(bpy)_3](PF_6)_2$ and PhCOOH (Table 1, entry 10). In addition, control experiments confirmed that a photocatalyst and visible light were essential in this protocol (Table 1, entries 11 and 12). Besides, in the radical quenching experiment with the addition of TEMPO, **3aa** could not be detected (Table 1, entry 13).

Under the optimal conditions, the scope of the α-amino alkylation process was investigated. When the substituents on the *N*-aryl of ketimines were varied, substrates with electron-donating and electron-withdrawing groups reacted smoothly with 4,*N*,*N*-trimethylaniline **2a**, resulting in moderate to excellent yields (Table 2, **3aa–3ea** and **3ga–3la**). The substituents at the *ortho* position influenced this system due to their close location to the reaction site, and enhanced the steric hindrance that existed for the substrates (Table 2, **3ca** and **3ea**).

Unfortunately, when the cyano group was at the *para* position of *N*-aryl, only a trace amount of product **3fa** was detected. It might be that the strong electron-withdrawing effect decreased the density of the electron of imines, which had a negative impact on the protonation process (Scheme 3). Besides, substrates with two substituents of the ketimines

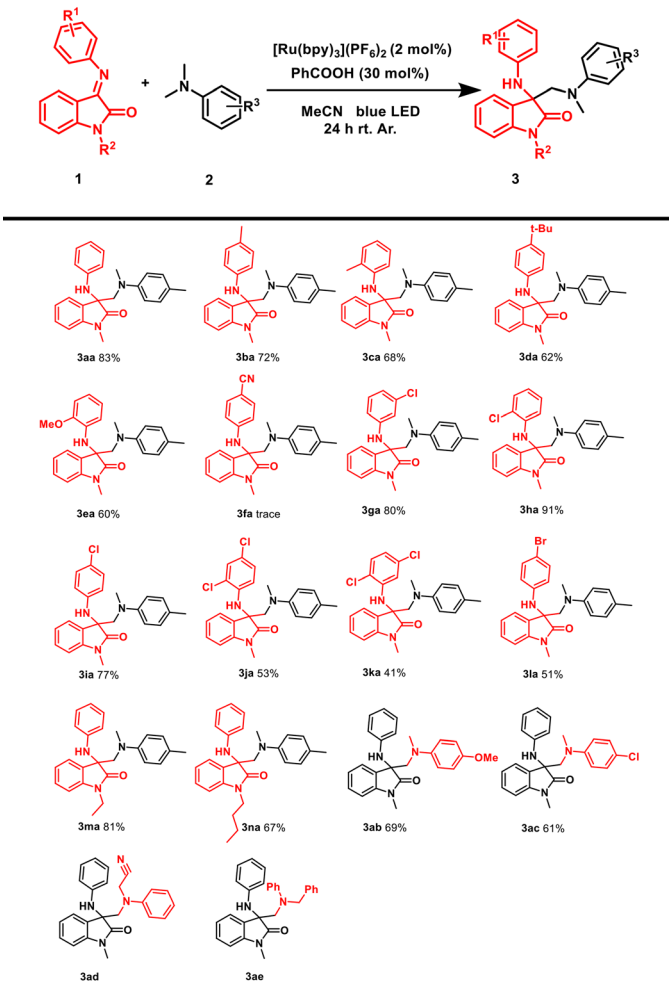
Table 1 Optimization of the reaction conditions



Entry	PC	Add.	Sol.	Yield (%)
1	$Ru(bpy)_3Cl_2$	—	MeCN	43
2	4CzIPN	—	MeCN	n.d.
3	$Ir(ppy)_3$	—	MeCN	36
4	$[Ru(bpy)_3](PF_6)_2$	—	MeCN	51
5	$[Ru(bpy)_3](PF_6)_2$	NaOAc	MeCN	35
6	$[Ru(bpy)_3](PF_6)_2$	CF_3COOH	MeCN	67
7	$[Ru(bpy)_3](PF_6)_2$	PhCOOH	MeCN	73
8	$[Ru(bpy)_3](PF_6)_2$	PhCOOH	DMSO	66
9	$[Ru(bpy)_3](PF_6)_2$	PhCOOH	CH_2Cl_2	63
10[a]	$[Ru(bpy)_3](PF_6)_2$	PhCOOH	MeCN	83
11	—	PhCOOH	MeCN	n.d.
12[b]	$[Ru(bpy)_3](PF_6)_2$	PhCOOH	MeCN	n.d.
13[c]	$[Ru(bpy)_3](PF_6)_2$	PhCOOH	MeCN	n.d.

All reactions of **1a** (0.1 mmol) with **2a** (0.3 mmol) were carried out in the presence of a photocatalyst (1 mol%) and an add. (20 mol%) in solvent (0.5 mL) under an Ar atmosphere at room temperature and irradiated with a blue LED (30 W). Isolated yields. [a] $[Ru(bpy)_3](PF_6)_2$ (2 mol%), PhCOOH (30 mol%). [b] Reaction performed without light. [c] Reaction performed with TEMPO (4 eq.) being added.

Table 2 Scope of ketimines and *N*,*N*-dimethylbenzamines



Reaction of ketimines–anilines. Reaction conditions: **1** (0.1 mmol), **2** (0.3 mmol), $[Ru(bpy)_3](PF_6)_2$ (2 mol%), PhCOOH (30 mol%), and MeCN (0.5 mL) under an Ar atmosphere at room temperature and irradiated with a blue LED (30 W) for 24 h.

were also converted into the corresponding products **3ja** and **3ka** in moderate yields. The lower yields were likely due to the electron-withdrawing effect of the isatin ketimines **1j** and **1k**. In addition, the substituents on the nitrogen atom in isatin had little effect on this reaction, for example, isatin ketimines with *N*-Et/*n*-Bu groups were transformed in good yields (Table 2, **3ma** and **3na**). Moreover, we tested the *N*,*N*-dimethylbenzamine analogs with the methoxy group and chlorine group at the *para* position of the aryl ring, respectively, and obtained the target products in good yields (Table 2, **3ab** and **3ac**). In addition, unsymmetrical anilines were tested; however, only trace amounts of **3ad** were detected and **3ae** was not detected (Table 2, **3ad** and **3ae**).

In order to further explore the application scope, the α-amino alkylation of *N*-sulfonyl aldimines was also realized (see the ESI† for more details). On the basis of the optimized conditions, the scope of *N*-sulfonyl aldimines was evaluated by using 4,*N*,*N*-trimethylaniline **2a** as well (Table 3). *N*-Sulfonyl aldimines with various substituents, irrespective of their substitution patterns and electronic properties, were smoothly converted into the corresponding 1,2-diamines **5**. The alkyl, methoxy and halogenated groups of aromatic *N*-sulfonyl aldimines were competent partners, and gave the corresponding products in good yields (Table 3, **5aa**–**5ga** and **5ia and5ka**). Significantly, the substrate with multi-substituents of methoxy groups was transformed into the desired product **5ga** in an excellent yield due to the enhanced electron-donating effect. Gratifyingly, this approach could be extended to polyaromatic aldimines, leading to **5ha** in 75% yield. A moderate yield was obtained for **5la** with the influence of cyano group at benzene ring (Table 3, **5la**), which was similar to the **3fa**. Likewise, when the Ms group was replaced with the Ts group at the nitrogen atom, the corresponding product **5ma** was obtained in a moderate yield. We also attempted to replace the phenyl group of the aldimine with other heterocycles, such as the pyridine ring, but no target product (**5na**) was detected. Moreover, we further evaluated the *para*-substituted dimethylaniline derivatives with the methoxy and chlorine groups, which presented good yields (Table 3, **5ab** and **5ac**).

In order to investigate the practical potential of this approach, gram scale syntheses of **3aa** and **5aa** were performed under the optimal conditions, respectively (Scheme 2).

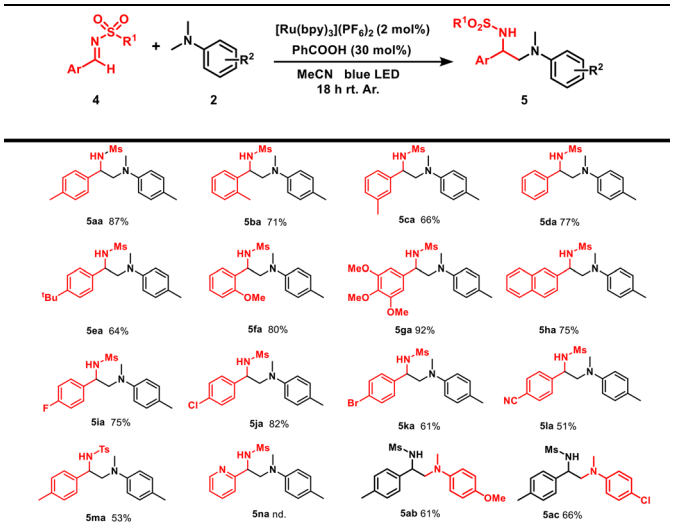
When 4.24 mmol of **1a** and 5.08 mmol of **4a** were alkylated, respectively, with **2a** under the optimal conditions, good yields of **3aa** (72%, 1.13 g) and **5aa** (79%, 1.33 g) were obtained (see the ESI† for more details). The gram-scale synthesis of 1,2-diamines showed the practicality of the α-amino alkylations of both ketimines and aldimines.

The reaction mechanism we forecasted is shown in Scheme 3. To gain further insight into the mechanism, we used TEMPO to perform radical quenching experiments by using **1a** and **2a** and **4a** and **2a** as substrates, respectively. The target products **3aa** and **5aa** were not detected (Table 1, entry 13), with 85% of ketimine **1a** and 80% of aldimine **4a** being recovered, thus indicating that radical processes took place. Besides, fluorescence quenching experiments indicated that **2a** could lead to fluorescence quenching.

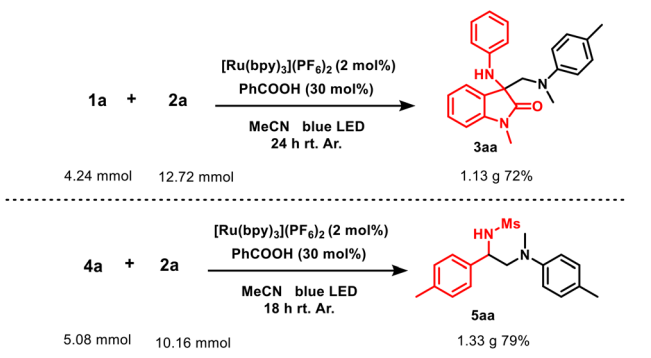
Based on our research studies and related reports,[38,39] we proposed that these radical alkylation reactions could proceed through two plausible mechanisms: (A) the mechanism of radical addition and (B) the mechanism of radical–radical coupling (Scheme 3).

As shown in Scheme 3, in pathway A, the excited-state photocatalyst $^*Ru(bpy)_3^{2+}$ species can oxidize **2** to produce the radical species **6**. The radical species **6** undergoes direct addition to imine **1** or **4** to give the *N*-centered radical species **7**. Then, with the assistance of protons, the radical species **7** is reduced by $Ru(bpy)^+$ to give the final 1,2-diamine **3** or **5** with the regeneration of $Ru(bpy)_3^{2+}$. In pathway B, after producing the radical species **6** similarly, imine **1** or **4** is reduced by $Ru(bpy)_3^+$ with the assistance of protons to give the radical species **8**. And the final product **3** or **5** is produced by the coupling of radical species **8** with radical species **6**. Given that

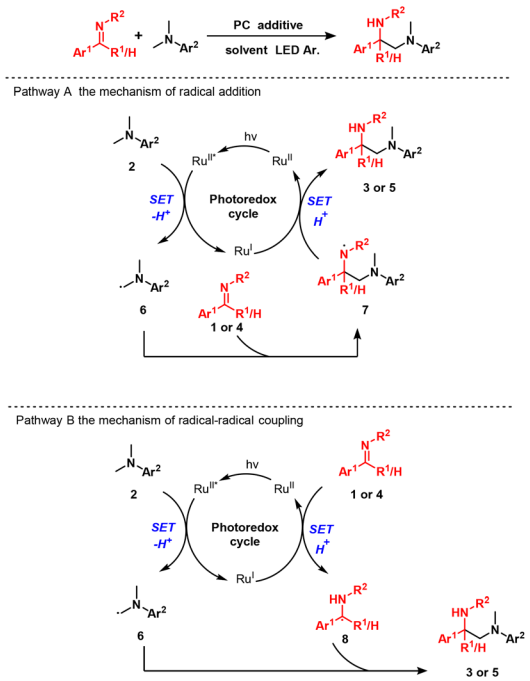
Table 3 Scope of aldimines and *N*,*N*-dimethylbenzamines



Reaction of aldimines–anilines. Reaction conditions: **4** (0.3 mmol), **2** (0.6 mmol), $[Ru(bpy)_3](PF_6)_2$ (2 mol%), PhCOOH (30 mol%), and MeCN (0.6 mL) under an Ar atmosphere at room temperature and irradiated with a blue LED (30 W) for 18 h.



Scheme 2 Gram-scale preparation of **3aa** and **5aa**.



Scheme 3 Proposed mechanistic pathways.

the pathway A is a radical propagation process, which is more advantageous than the pathway B. Therefore, pathway A might be the primary route and pathway B is a limited secondary process. Pathway B can't be ruled out completely at present.

Conclusions

In conclusion, a mild, scalable, and efficient method has been developed for the α-amino alkylation of isatin-derived ketimines with *N*,*N*-dimethylanilines. In particular, this method is also applicable to *N*-sulfonyl aldimines. Based on the photoredox/Brønsted acid co-catalyzed strategy, a wide range of functional groups are tolerated in this method. A series of 1,2-diamines are produced in up to 92% yields under visible light irradiation. Moreover, this method can be performed on a gram scale, providing more prospects and diversity for the synthesis of 1,2-diamines.

Conflicts of interest

There are no conflicts to declare.

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