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Amphiphilic methyleneamino synthon through organic dye catalyzed-decarboxylative aminoalkylation†

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The utilization of a photo-induced synthon generated from *N*-phenyl glycine by an organic dye and visible light irradiation is disclosed. The intermediate could be coupled with either a radical or a nucleophile in a simple operation to afford several natural product-like compounds.

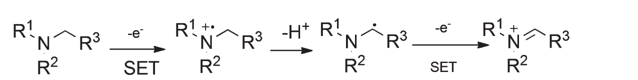
The functionalization of α C–H bonds of amines represents an efficient approach towards the preparation of complex amines.[1] A common system of this methodology is to use the transition metal-catalyzed dehydrogenative coupling using stoichiometric oxidants such as *tert*-butyl hydrogen peroxide (TBHP).[2] The study of visible light photoredox catalysis has made much progress recently,[3,4] and in particular, photoredox aminoalkylation is shown by various groups to be viable.[5] Our groups have also demonstrated that this reaction can be effectively photocatalyzed using organic dyes.[6] The photoredox process begins with the single electron oxidation of the nitrogen centre by the excited state of the photocatalyst (Scheme 1).

The α-amino radical is proposed as an intermediate *via* deprotonation in polar solvents. However, it is difficult to trap the α-amino radical while further oxidation often occurs as the major pathway to form an iminium ion, which is frequently trapped with nucleophiles.[7] Recently, it was found that oxygen could be used as the switch between these two pathways. In the absence of oxygen, α-amino radicals can be formed preferentially and added to electron deficient alkenes.[8]

The photo-decarboxylative radical process was reported using phenanthrene as a stoichiometric sensitizer in the presence of UV light (Scheme 2a).[9] The process is initiated through a single-electron transfer (SET) from the carboxylate ion to generate the cation radical, formed by SET from the singlet excited-state of phenanthrene to 1,4-dicyanobenzene. The α-amino radical generated in this way was shown to attack electron deficient alkenes effectively. At the beginning of this work, we hypothesized that α-amino radical **3** could be obtained through a decarboxylative process, catalyzed by organic dyes in the presence of visible light (Scheme 2b).[6] Under such conditions, *N*-phenyl glycine **1** would undergo SET reaction forming radical cation **2**, and decarboxylation would lead us to α-amino radical **3**. Further oxidation of **3** would lead to iminium **4**. We aimed to manipulate reaction conditions so that a methyleneamino equivalent could be installed in both electrophilic and nucleophilic substrates.

We first investigated the reaction between *N*-phenyl glycine and *N*-phenyl maleimide under visible light irradiation with various organic dyes as catalysts. Decarboxylative annulation product **6aa** was obtained with 30% yield when CH_3CN was used as the solvent and Rose Bengal was the catalyst (Table 1, entry 1). The yield was increased dramatically when water was added as a co-solvent (entry 2). A better result was obtained when Fluorescein was used as the catalyst in MeOH (entry 3). Other organic dyes as well as $Ru(bpy)_3Cl_2$ did not give good yields (entries 4–6). Lowering the Fluorescein loading from 5 mol% to 2 mol% did not affect the reaction rate and yield (entry 7). The slow-addition of glycine was found to improve the reaction yield (entry 8). The slow-addition would possibly suppress the decomposition of the active intermediate. Both light and organic dyes have been proved to be essential for this reaction. However, the reaction showed low conversion to the expected product when preformed under oxygen-free conditions (entry 9).

With the established conditions, we then evaluated the performance of different *N*-aryl glycines and maleimides in the



Scheme 1 Photo-oxidative strategies of generating nitrogen centre intermediates from tertiary amine.

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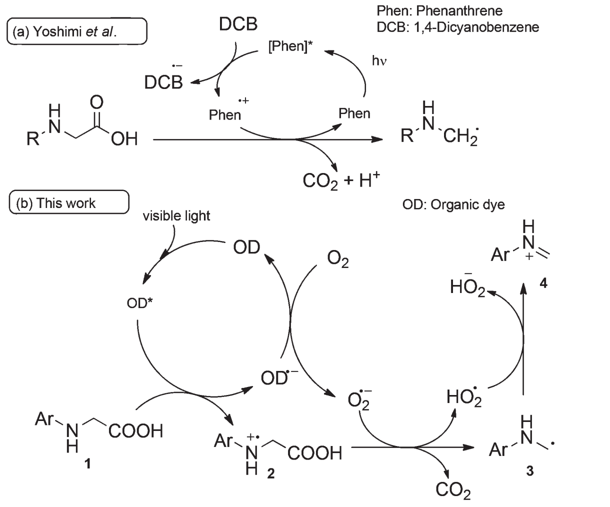
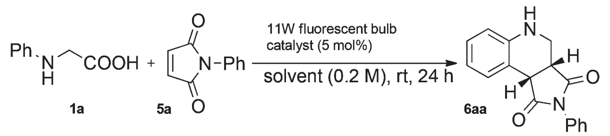


Scheme 2 Photo-oxidative decarboxylative strategies of generating nitrogen centre intermediates.

Table 1 Decarboxylative annulation between *N*-phenyl glycine **1a** and *N*-phenylmaleimide **5a**[a]



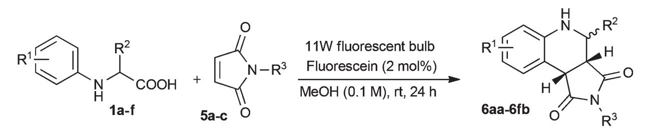
Entry	Catalyst	Solvent	Yield[b] (%)
1	Rose Bengal	CH_3CN	30
2	Rose Bengal	CH_3CN–H_2O (4 : 1)	73
3	Fluorescein	MeOH	82
4	Methylene Blue	MeOH	61
5	Eosin Y	MeOH	42
6	$Ru(bpy)_3Cl_2$	MeOH	46
7[c]	Fluorescein	MeOH	80
8[c,d]	Fluorescein	MeOH	89
9[e]	Fluorescein	MeOH	<10

[a] Reaction was performed using 0.12 mmol of **1a** and 0.1 mmol of **5a** and 5 mol% catalyst in 0.5 mL of a solvent. [b] Isolated yield. [c] 2 mol% Fluorescein. [d] Slow addition for **1a** (see ESI). [e] The reaction was carried out under oxygen-free conditions.

presence of 2 mol% Fluorescein using an 11 W household bulb (Table 2). Substituents on maleimides had little effect on the result (entries 1–3). The α-substituted *N*-aryl glycines were demonstrated to work well under these conditions, but gave slightly lower yields (Table 2, entries 8 and 9) as compared to non-substituted ones (entries 3, 2, 5 and 7). Electron donating substituents on the phenyl ring did not increase the yield significantly while electron withdrawing substituents led to a decrease in yield (entry 10).

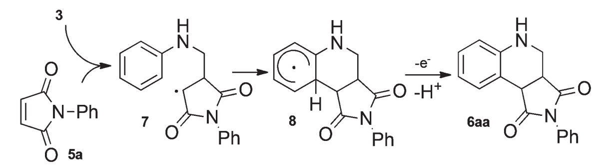
We proposed that after the α-amino radical intermediate **3** formed, *N*-phenyl maleimide then trapped it to generate intermediate **7**. Cyclization onto the aromatic ring led to cyclohexadienyl radical **8**, which would undergo re-aromatization *via* SET and proton elimination to release the annulation product **6aa** (Scheme 3).

Table 2 Decarboxylative annulation between *N*-aryl glycines **1a–f** and maleimides **5a–c**[a]



Entry	1 [R^1]	1 [R^2]	5 [R^3]	6	Yield[b](%)
1	**1a** [H]	[H]	**5a** [Ph]	**6aa**	89
2	**1a** [H]	[H]	**5b** [Et]	**6ab**	88
3	**1a** [H]	[H]	**5c** [Bn]	**6ac**	90
4	**1b** [4-Me]	[H]	**5a** [Ph]	**6ba**	95
5	**1b** [4-Me]	[H]	**5b** [Et]	**6bb**	87
6	**1c** [2-Me]	[H]	**5a** [Ph]	**6ca**	78
7	**1c** [2-Me]	[H]	**5b** [Et]	**6cb**	89
8	**1d** [H]	[Me]	**5b** [Et]	**6db**	73
9	**1e** [4-Me]	[Me]	**5b** [Et]	**6eb**	64
10	**1f** [4-Cl]	[H]	**5b** [Et]	**6fb**	51

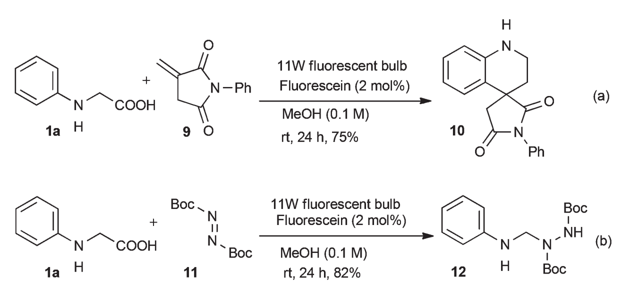
[a] Reaction was performed using 0.12 mmol of **1**, 0.1 mmol of **5** and 2 mol% of Fluorescein in 1.0 mL of MeOH. [b] Isolated yield.



Scheme 3 Proposed mechanism for Fluorescein-catalyzed decarboxylative annulation using visible light.

Similarly, other electron deficient unsaturated systems could be used to trap this α-amino radical. For example, methylene succinimide **9** could react with **1a** under optimized conditions to give the spiro-bicyclic amine **10** (Scheme 4a). Diazo-compound was shown to trap the α-amino radical under similar conditions (Scheme 4b).

We further hypothesized that in the absence of electrophilic substrates, α-amino radical **3** would be further oxidized to iminium **4** (Scheme 2b). Inspired by our previous research,[6a] such iminiums could be excellent acceptors for enamines generated from proline and ketones, providing α-amino-ketone products in good yields (Table 3). Both simple ketones (Table 3, entries 1–7) and cyclohexanone (see ESI†) were suitable substrates for this reaction. This electrophilic iminium



Scheme 4 Nucleophilic transformation of *N*-phenyl glycine **1a**.

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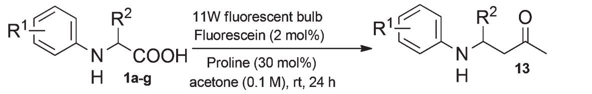
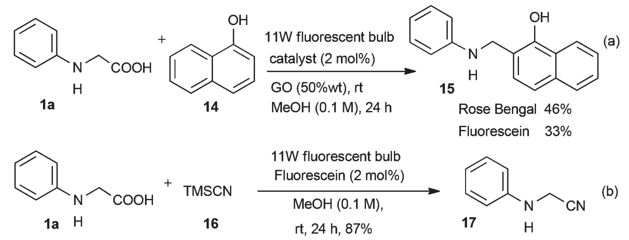
Table 3 Decarboxylative coupling between *N*-aryl glycines **1a–g** and acetone[a]



Entry	1 [R¹]	1 [R²]	13	Yield[b] (%)
1	**1a** [H]	[H]	**13a**	85
2	**1b** [4-Me]	[H]	**13b**	92
3	**1c** [2-Me]	[H]	**13c**	76
4	**1f** [4-Cl]	[H]	**13d**	71
5	**1g** [4-OMe]	[H]	**13e**	88
6	**1d** [H]	[Me]	**13f**	70
7	**1e** [4-Me]	[Me]	**13g**	82

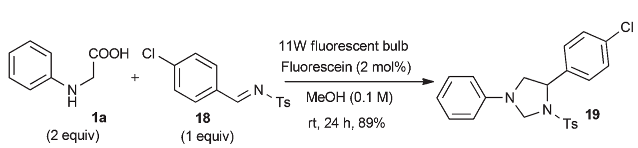
[a] Reaction was performed using 0.12 mmol of **1**, 0.036 mmol of L-proline, and 2 mol% Fluorescein in 1.0 mL of acetone. [b] Isolated yield.



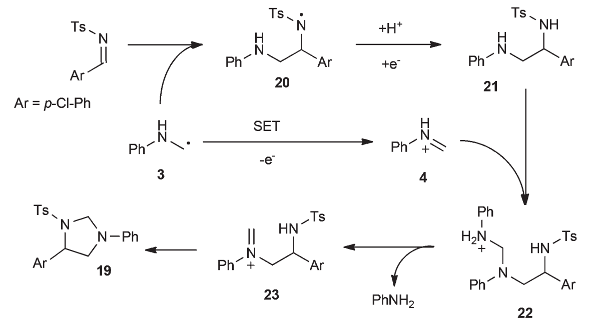
Scheme 5 Electrophilic transformation of *N*-phenyl glycine **1a**.

intermediate could also undergo further transformation such as Frediel–Crafts reaction (Scheme 5a). 1-Naphthol was added to glycine **1a** to give aminoalcohol **15** in moderate yield. For the Frediel–Crafts reaction, graphene oxide (GO) was used as a reaction additive and Rose Bengal performed better as a photocatalyst than Fluorescein.[6b] Other nucleophiles such as TMSCN also worked well to give 2-(phenylamino) acetonitrile **17** in excellent yield (Scheme 5b).

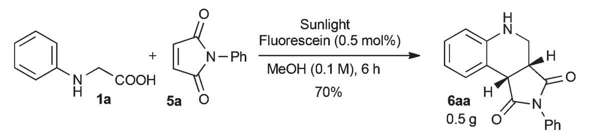
When *N*-tosylimine **18** was utilized as the acceptor, a cyclic compound **19** was formed, instead of the Mannich adduct that we expected (Scheme 6). After some investigations, we found that the Mannich adduct underwent further modifications to give cyclic diamine **19**. A cascade process which contained both radical and ionic pathways was proposed for its formation (Scheme 7). The α-amino radical **3** was added to the *N*-tosylimine **18** to afford a diamine intermediate **21**. This adduct was added to iminium ion **4** to form ammonium intermediate **22**. Losing an aniline led to iminium cation **23**, which cyclized to form product **19**.



Scheme 6 Cascade reaction between *N*-phenyl glycine **1a** and *N*-tosylimine **18**.



Scheme 7 Proposed mechanism for cascade reaction between *N*-phenyl glycine **1a** and *N*-tosylimine **18**.



Scheme 8 Decarboxylative annulation using ambient sunlight.

In order to demonstrate the scalability of this organic dye-catalyzed visible light induced process, we performed the decarboxylative annulation under ambient sunlight (Scheme 8).[10] With only 0.5 mol% of Fluorescein, 0.5 g of **6aa** in 70% yield was isolated after 6 h.

In conclusion, we have developed *N*-phenyl glycine as the reagent for the methyleneamino synthon in an amphoteric manner. Through an organic dye-catalyzed decarboxylation-α-amino-alkylation reaction, both electrophilic and nucleophilic substrates can be used as acceptors, leading to a variety of natural product-like compounds. Application of these methodologies to synthesis is being carried out at the moment.

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