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Dehydrogenative coupling reactions catalysed by Rose Bengal using visible light irradiation $\ddagger \$$

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Rose Bengal, an organic dye, was demonstrated to be a photoredox catalyst for dehydrogenative coupling reactions using visible light irradiation. α -Functionalised tertiary amines were obtained with good to excellent yields. Air is essential for this reaction and acts as the terminal oxidant. This is an environmentally friendly C–H functionalisation methodology that avoids the use of metal catalysts and stoichiometric amount of peroxo-compounds.

The dehydrogenative coupling reactions, performed under oxidative conditions, are an important C–C bond formation methodology.¹ As the reactive intermediates are generated *in situ*, it avoids the pre-functionalisation of the substrates. This makes synthetic routes shorter and more atom-economical. This reaction has been utilized to activate α -C–H bonds of tertiary amines and ethers, benzylic and allylic C–H bonds, and alkane C–H bonds.² Current dehydrogenative coupling reactions require transition metal catalyst to activate the C–H bonds and stoichiometric amount of peroxo-compounds as terminal oxidants to complete the catalytic cycle. These reactions can be made more environmentally friendly if we can avoid the use of transition metals and reduce or avoid the consumption of large amount of peroxo-compounds.

Unlike photochemistry using ultraviolet irradiation, photo-induced single electron transfer (SET) processes using visible light are easy to perform, as there is no need for special instrument or apparatus. Furthermore, the reaction conditions are mild, thus attracting increasing attention from synthetic organic chemists.³ Several single electron transfer photoredox catalysts have been shown to work well in numerous reactions that are irradiated by visible light.⁴ In photoredox chemistry, tertiary amines are often used as a reductant to quench the excited state of the photoredox catalyst. Making slight modification to the reaction, Stephenson et al. reported dehydrogenative coupling reactions between cyclic tertiary amines such as N-aryl-tetrahydroisoquinolines and nitroalkanes, catalysed by Ir(ppy)₂(dtbbpy)PF₆.⁵ Subsequently, Rueping et al. reported the reaction of similar cyclic tertiary amine with ketones, catalysed using a dual catalyst system, Ru(bpy)₃Cl₂ and L-proline.⁶ Despite these advancements, the development of dehydrogenative coupling reactions under metal-free conditions is still highly desirable.

Organic dyes are cheap and easier to modify compared to metal photoredox catalysts (Fig. 1). Most recent research on organic dyes has focused on their potential application in dye-sensitizer solar cells.⁷ The potential use of organic dyes



Fig. 1 Absorption wavelength of different organic dyes.^{9c,10}

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[†] Representative procedure for organic dye-catalysed dehydrogenative coupling reaction: *N*-aryl-tetrahydroisoquinoline **1a** and nitromethane **2a**: **1a** (20.9 mg, 0.1 mmol, 1.0 equiv.) was added to a solution of RB (5.0 mg, 0.005 mmol, 5 mol%) in 1.0 ml nitromethane **2a**. The reaction mixture was stirred under green LEDs irradiation at room temperature. After 10 h, the solvent was removed *in vacuo* and the crude product was directly loaded onto a short silica gel column. Flash chromatography was performed using gradient elution with hexane/EA mixtures (40/1–15/1 ratio). After removing solvent, product **3a** (24.7 mg) was obtained as yellow oil in 92% yield.

[‡] Representative procedure for organic dye-catalysed dehydrogenative-Mannich reaction: *N*-aryl-tetrahydroisoquinoline **1a** (20.9 mg, 0.1 mmol, 1.0 equiv.) was added to a solution of RB (5.0 mg, 0.005 mmol, 5 mol%) in 1.0 ml acetone **4a**. This was followed by pyrrolidine (2.5 μ l, 0.03 mmol, 30 mol%) and TFA (2.3 μ l, 0.03 mmol, 30 mol%). The reaction mixture was stirred under green LEDs irradiation at room temperature. After 20 h, the solvent was removed *in vacuo* and the crude product was directly loaded onto a short silica gel column. Flash chromatography was performed using gradient elution with hexane/EA mixtures (40/1 - 15/1 ratio). After removing solvent, product **5a** (24.1 mg) was obtained as pale yellow solid in 91% yield.

[§] Electronic supplementary information (ESI) available: General procedures for dehydrogenative coupling reactions, spectroscopic data, computational details. See DOI: 10.1039/c1gc15489c

Table 1 Dehydrogenative coupling between N-aryl-tetrahydroisoquinoline 1a and nitromethane $2a^a$

	1a 2a organic dye (x mol%) LEDs I, v Ph 1a 2a NO ₂						
Entry	Organic dye	x	LED color	Conv. % ^b			
1	RB	5	Green	100			
2	Rhodamine B	5	Green	40			
3	TPP	5	Violet	<10			
4	Methylene Blue	5	Red	25			
5	Fluorescein	5	Blue	50			
6	Eosin Y	5	Green	70			
7 ^c	RB	5		0			
8 ^d	RB	5	Green	100			
9 ^d	RB	0.1	Green	35			
10^{d}	RB	1	Green	50			
11^{d}	RB	10	Green	100			

"Reaction was performed using 0.05 mmol of 1a in 0.2 ml of 2a. ^b Conversion was determined by ¹H NMR. ^c Reaction was performed in the dark. ^d 0.5 ml of 2a was used. Reaction time was 10 h.

as catalysts for organic reactions was recognized many years before, with high power light source, which requires high energy input and thus undesirable from an environmental point of view.8 Recently, several examples were reported on the use of organic dyes as photoredox catalysts using visible light irradiation from low power source.9 In 2010, our group demonstrated that using irradiation from a 11 W household fluorescence bulb, Rose Bengal (RB) was able to catalyse α -oxyamination of 1,3-dicarbonyl compounds and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) with excellent yields.^{9a} Griesbeck found that nanosized semiconductor particles and lucigenin can also be used as catalysts in photoinduced azidohydroperoxidation of myrtenyl hydroperoxide reaction.96 More recently, Zeitler reported Eosin Y-catalysed dehalogenation and enantioselective α -alkylation reactions, in the presence of both photoredox catalyst and organocatalyst.9c In this manuscript, we wish to report the use of organic dyes as photoredox catalysts in dehydrogenative coupling reactions of tertiary amines using low power light source.

We embarked our investigation by screening a number of organic dyes for photocatalytic activities, using the reaction between N-aryl-tetrahydroisoquinolines 1a and nitromethane 2a (Table 1).⁵ Different Light Emitting Diode (LED, 0.5–5W) colours were used to match the absorption wavelength of the different dyes used. For example, green light was used when Rose Bengal ($E_{red} = +1.04 \text{ V}$ vs. NHE, for the triplet excited state of RB)14 was investigated. Amongst the dyes tested, RB showed the best reactivity, catalysing a complete conversion after 20 h with 5 mol% catalyst (Table 1, entry 1). Eosin Y provided a good conversion of approximately 70% while other dyes gave low conversions, as determined with ¹H NMR (Table 1, entries 2-6). Visible light from the LED was essential for the reaction to proceed. No conversion was observed when the reaction was conducted in the dark (Table 1, entry 7). When the volume of nitromethane was increased, decreasing the concentration of the catalyst and cyclic amine, the reaction rate was increased and the reaction was completed in 10 h. Decreasing the RB loading to 0.1 or 1 mol% led to lower conversion while increasing RB to

	$ \begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $					
Entry	1[Ar]	2 [R]	t (h)	3	Yield % ^b	
$ \begin{array}{c} 1\\2^c\\3^{c,d}\\4\\5\end{array} $	$\begin{array}{l} \textbf{1a}[C_6H_5]\\ \textbf{1a}[C_6H_5]\\ \textbf{1a}[C_6H_5]\\ \textbf{1b}[4\text{-}Br\text{-}C_6H_4]\\ \textbf{1c}[4\text{-}Me\text{-}C_6H_4] \end{array}$	2a[H] 2b[Me] 2c[Et] 2a[H] 2a[H]	10 24 72 48 15	3a 3b 3c 3d 3e	92 82 95 89 85	

" Reaction was performed using 0.1 mmol of 1 in 1.0 ml of 2. b Isolated yield. ^{*c*} dr = $3:2^{d}$ Reaction was performed using 0.1 mmol of 1a and 1.0 mmol of 2c in 1.0 ml CH₃CN as solvent, dr = 3 : 2.

10 mol% did not result an obvious rate enhancement (Table 1, entries 9-11). Hence 5 mol% loading of RB was chosen for the substrate scope evaluation.

Using the established conditions, we evaluated the performance of different N-aryl-tetrahydroisoquinolines 1a-c with nitroalkanes 2a-c in the presence of 5 mol% RB (Table 2). Both nitromethane (Table 2, entries 1, 4 and 5) and nitroethane (Table 2, entry 2) provided desired coupled products with good to excellent yields. Excellent yield was also obtained when 1nitropropane was coupled with cyclic amine 1a in CH₃CN (Table 2, entry 3).

Tertiary amine without a benzyl group is found to give a lower yield under the optimized conditions. Moderate yield was observed when 3 in nitromethane was irradiated with green light (Scheme 1). A small amount of by-product, the bis-addition product, was observed. The lower reactivity of 3 relative to 1a does not lie in their relative ease of oxidation, as density functional theory calculations¹¹ indicate that the oxidation of 3 ($E_{ox} = +1.02$ V vs. NHE)¹⁵ is thermodynamically more favourable than 1a ($E_{ox} = +1.14$ V vs. NHE) by 4.5 kcal mol⁻¹ in nitromethane. The lower reactivity is attributed to the more unfavourable thermodynamics in the formation of the required iminium for 3 relative to 1a (formation of iminium from 1a⁺⁺ is 14.8 kcal mol⁻¹ more favourable than from **3'**⁺).



Scheme 1 Dehydrogenative coupling between 4-methyl N,Ndimethylaniline and nitromethane.

The ability to harness solar energy for chemical reaction is of paramount importance to photochemistry,12 therefore we performed our dehydrogenative coupling reaction between N-aryl tetrahydroisoquinoline 1a and nitromethane 2a with sunlight. A faster reaction was observed and 87% yield of 3a was isolated after 3 h (Scheme 2).

The dehydrogenative-Mannich reaction occurs between a tertiary amine and a ketone. This methodology is potentially more useful than the 'classical' Mannich reaction as the reactive iminium intermediate was generated in situ, compared to the requirement for an extra step to prepare the imine as in Mannich reaction.^{6,13} RB was once again shown to be a good catalyst

 Table 3
 Dehydrogenative-Mannich reaction catalysed by Rose Bengal under visible light^a



^{*a*} Reaction was performed using 0.1 mmol of 1 in 1.0 ml of 4. ^{*b*} Isolated yield.



Scheme 2 Dehydrogenative coupling reaction under ambient sunlight.

for the dehydrogenative-Mannich reaction between *N*-aryltetrahydroisoquinolines **1a–d** and acetone (Table 3, entries 1–4). Pyrrolidine/TFA was used to generate the enamine nucleophiles from acetone. When butanone was subjected to the dual catalysts system, good yield and excellent regioselectivity was obtained (Table 3, entry 5). Cyclohexanone is typically a poor donor for dehydrogenative coupling reactions and gave low yield under standard condition. But by simply changing pyrrolidine/TFA to L-proline and the solvent to CH_3CN , 66% yield of the desired product with 9:1 *dr* could be obtained (Scheme 3). As the enamine catalysis has been well developed for asymmetric organocatalysis, several catalysts including L-proline and derivatives were tested. The highest *ee* value of 15% was achieved for reaction between *N*-aryl-tetrahydroisoquinoline **1d** to acetone **4a** (Scheme 4).



Scheme 3 L-Proline and Rose Bengal co-catalysed dehydrogenative-Mannich reaction.



Scheme 4 Asymmetric dehydrogenative-Mannich reaction between *N*-aryl-tetrahydroisoquinoline 1d and acetone 4a.

We proposed that RB*, the excited state of RB, generated under visible light irradiation, is able to abstract an electron from the tertiary amine *via* a single electron transfer (SET) process (Fig. 2). The photoredox cycle is completed by the oxidation of



Fig. 2 Proposed mechanism for RB-catalysed dehydrogenative coupling.

the RB radical anion back to the ground state RB by dioxygen. The tertiary amine radical cation donates one hydrogen atom to the dioxygen radical anion and results in the formation of an iminium, which could be trapped by nucleophiles under mild conditions, to release the final product. Hydroperoxide anion is also generated in the same process.

Preliminary assessment of the role of dioxygen by performing a control reaction in a glovebox (O_2 at 0.1 ppm) indicated that it is not essential for the reaction to occur, however in the absence of dioxygen, a much lower yield was obtained relative to reaction performed in open air, which is consistent with the observation by Stephenson *et al.*⁵

In conclusion, we have developed an environmentally friendly, metal-free dehydrogenative coupling reaction catalysed by an organic dye, Rose Bengal under visible light irradiation. Both nitroalkanes and ketones can be used as nucleophiles and gave excellent yields under very mild conditions. Organic dye, which is environmentally benign, cheaper, readily available and easy to modify, was demonstrated to be a viable alternative inorganic photoredox catalyst. We are currently carrying out mechanistic studies to understand this reaction and will be reported in due course.

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Notes and references

- 1 C.-J. Li, Acc. Chem. Res., 2008, 42, 335-344.
- 2 (a) Z. Li and C.-J. Li, J. Am. Chem. Soc., 2005, 127, 3672–3673; (b) Y. Zhang and C.-J. Li, J. Am. Chem. Soc., 2006, 128, 4242–4243; (c) Z. Li, L. Cao and C.-J. Li, Angew. Chem., Int. Ed., 2007, 46, 6505–6507; (d) Y. Li and W. Bao, Adv. Synth. Catal., 2009, 351, 865–868; (e) X.-Z. Shu, X.-F. Xia, Y.-F. Yang, K.-G. Ji, X.-Y. Liu and Y.-M. Liang, J. Org. Chem., 2009, 74, 7464–7469; (f) G. Kumaraswamy, A. N. Murthy and A. Pitchaiah, J. Org. Chem., 2010, 75, 3916–3919; (g) F. Yang, J. Li, J. Xie and Z.-Z. Huang, Org. Lett., 2010, 12, 5214–5217; (h) J.-S. Tian and T.-P. Loh, Angew. Chem., Int. Ed., 2010, 49, 8417–8420; (i) J. M. Allen and T. H. Lambert, J. Am. Chem. Soc.

2011, **133**, 1260–1262; (*j*) Y. Zhang, H. Peng, M. Zhang, Y. Cheng and C. Zhu, *Chem. Commun.*, 2011, **47**, 2354–2356.

- 3 (a) K. Zeitler, Angew. Chem., Int. Ed., 2009, 48, 9785–9789; (b) T. P.
 Yoon, M. A. Ischay and J. Du, Nat. Chem., 2010, 2, 527–532; (c) J.
 M. R. Narayanam and C. R. J. Stephenson, Chem. Soc. Rev., 2011, 40, 102–113.
- 4 (a) D. A. Nicewicz and D. W. C. MacMillan, *Science*, 2008, 322, 77–80; (b) R. S. Andrews, J. J. Becker and M. R. Gagné, *Angew. Chem., Int. Ed.*, 2010, 49, 7274–7276; (c) Z. Lu, M. Shen and T. P. Yoon, *J. Am. Chem. Soc.*, 2011, 133, 1162–1164; (d) C. Dai, J. M. R. Narayanam and C. R. J. Stephenson, *Nat. Chem.*, 2011, 3, 140–145; (e) Y. Chen, A. S. Kamlet, J. B. Steinman and D. R. Liu, *Nat. Chem.*, 2011, 3, 146–153.
- 5 A. G. Condie, J. C. González-Gómez and C. R. J. Stephenson, J. Am. Chem. Soc., 2010, 132, 1464–1465.
- 6 M. Rueping, C. Vila, R. M. Koenigs, K. Poscharny and D. C. Fabry, *Chem. Commun.*, 2011, **47**, 2360–2362.
- 7 (a) A. Mishra, M. K. R. Fischer and P. Bäuerle, Angew. Chem., Int. Ed., 2009, 48, 2474–2499; (b) Y. Ooyama and Y. Harima, Eur. J. Org. Chem., 2009, 2009, 2903–2934.
- 8 (a) E. Hasegawa, S. Takizawa, T. Seida, A. Yamaguchi, N. Yamaguchi, N. Chiba, T. Takahashi, H. Ikeda and K. Akiyama, *Tetrahedron*, 2006, **62**, 6581–6588; (b) Y. Yoshimi, S. Hayashi, K. Nishikawa, Y. Haga, K. Maeda, T. Morita, T. Itou, Y. Okada, N. Ichinose and M. Hatanaka, *Molecules*, 2010, **15**, 2623–2630; (c) K. Ohkubo, K. Mizushima, R. Iwata and S. Fukuzumi, *Chem. Sci.*, 2011, **2**, 715–722.

- 9 (a) H. Liu, W. Feng, C. W. Kee, Y. Zhao, D. Leow, Y. Pan and C.-H. Tan, *Green Chem.*, 2010, **12**, 953–956; (b) A. G. Griesbeck, M. Reckenthäler and J. Uhlig, *Photochem. Photobiol. Sci.*, 2010, **9**, 775– 778; (c) M. Neumann, S. Füldner, B. König and K. Zeitler, *Angew. Chem., Int. Ed.*, 2011, **50**, 951–954; (d) A. G. Griesbeck and M. Cho, *Org. Lett.*, 2007, **9**, 611–613.
- 10 (a) G. N. Lewis, O. Goldschmid, T. T. Magel and J. Bigeleisen, J. Am. Chem. Soc., 1943, 65, 1150–1154; (b) M. Lan, H. Zhao, H. Yuan, C. Jiang, S. Zuo and Y. Jiang, Dyes Pigm., 2007, 74, 357–362; (c) C.-C. Chang, Y.-T. Yang, J.-C. Yang, H.-D. Wu and T. Tsai, Dyes Pigm., 2008, 79, 170–175; (d) C. Grotzinger, D. Burget, P. Jacques and J. P. Fouassier, Macromol. Chem. Phys., 2001, 202, 3513–3522.
- 11 (a) M. J. Frisch *et al.*, *Gaussian 09*, Revision A.2, Gaussian Inc, Wallingford CT, 2009; (b) Y. Zhao and D. G. Truhlar, *Theor. Chem. Acc.*, 2008, **120**, 215–41; (c) A. V. Marenich, C. J. Cramer and D. G. Truhlar, *J. Phys. Chem. B*, 2009, **113**, 6378–6396.
- 12 (a) P. Esser, B. Pohlmann and H.-D. Scharf, Angew. Chem., Int. Ed. Engl., 1994, 33, 2009–2023; (b) S. Protti and M. Fagnoni, Photochem. Photobiol. Sci., 2009, 8, 1499–1516.
- 13 (a) Y. Shen, M. Li, S. Wang, T. Zhan, Z. Tan and C.-C. Guo, *Chem. Commun.*, 2009, 953–955; (b) A. Sud, D. Sureshkumar and M. Klussmann, *Chem. Commun.*, 2009, 3169–3171.
- 14 C. Grotzinger, D. Burget, P. Jacques and J. P. Fouassier, *Polymer*, 2003, 44, 3671–3677.
- 15 Y. Fu, L. Liu, H.-Z. Yu, Y.-M. Wang and Q.-X. Guo, J. Am. Chem. Soc., 2005, 127, 7227–7234.