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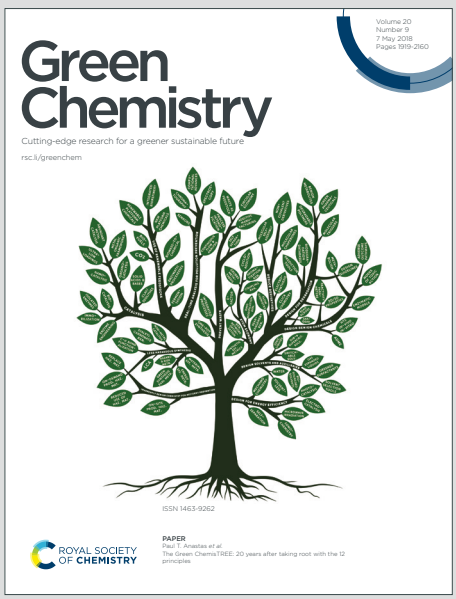

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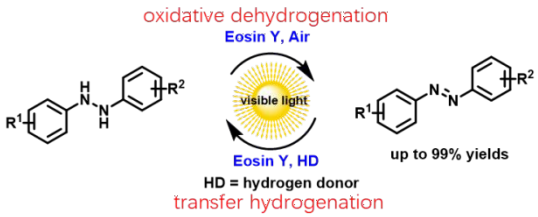

Visible-light-promoted oxidative dehydrogenation of hydrazobenzenes and transfer hydrogenation of azobenzenes are realized using Eosin Y as photo-catalysis

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ARTICLE

Visible-Light-Promoted Oxidative Dehydrogenation of Hydrazobenzenes and Transfer Hydrogenation of Azobenzenes

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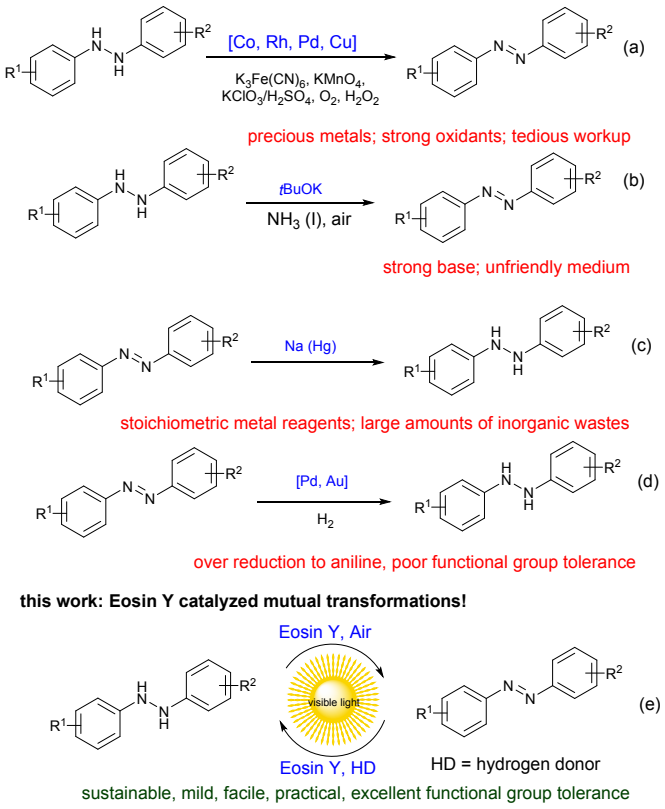
Azo compounds are widely used in the pharmaceutical and chemical industries. Here, we report the use of a non-metal photo-redox catalyst, Eosin Y, to synthesize azo compounds from hydrazine derivatives. The use of visible-light with air as oxidant makes this process sustainable and practical. Moreover, the visible-light-driven, photo-redox-catalyzed transfer hydrogenation of azobenzene is compatible with a series of hydrogen donors such as phenyl hydrazine and cyclic amines. Compared with traditional (thermal/transition-metal) methods, our process avoids the issue of over-reduction to aniline, which extends the applicability of photo-redox catalysis and confirms it as a useful tool for synthetic organic chemistry.

Introduction

Azo compounds are widely used in the chemical industry as dyes and pigments,[1] photo-responsive switches and polymers,[2-4] food additives, and therapeutic agents.[5] In addition, azo compounds have shown potential application in drug delivery[6] and electronics.[7] There exist numerous methods for the preparation of azo compounds, such as oxidative coupling of anilines,[8, 9] reduction of nitroaromatics,[10, 11] coupling of diazo salts with aromatic compounds,[12] and the Mills reaction.[13] Alternatively, the oxidative dehydrogenation of hydrazobenzene (hydrazine) derivatives provides a straightforward route to azobenzenes. In this context, the use of stoichiometric amounts of strong oxidants, such as $K_3Fe(CN)_6$, $KMnO_4$, and $KClO_3/H_2SO_4$, has been reported. Other methods have used O_2 or H_2O_2 as the oxidant, which is believed to be more sustainable; however, transition metals such as Co,[14] Rh,[15] Cu,[16] and Pd[17] were indispensable in these syntheses (Scheme 1a). Recently, Hashimoto and coworkers have reported the oxidative dehydrogenation of hydrazobenzenes using a catalytic amount of *t*BuOK (Scheme 1b). However, use of liquid NH_3 as solvent necessitated an operating temperature of -75°C, which limited its practical application. Thus, the discovery of a novel, environmentally friendly, and practical method for the oxidative dehydrogenation of hydrazobenzenes to azobenzene is keenly pursued.

Apart from serving as precursors for the synthesis of azobenzene, hydrazobenzenes themselves also have plenty of applications: for example, substituted diphenyl hydrazines have potential value for evaluating Alzheimer's disease.[18] Traditionally, hydrazobenzenes were prepared from azobenzene using stoichiometric amounts of metallic reducing reagents such as sodium amalgam,[19] zinc in alcoholic ammonia,[20] and stannous chloride[21] in ethanolic sodium



Scheme 1. Known processes for mutual transformation of azobenzene and hydrazobenzene, and the process reported herein.

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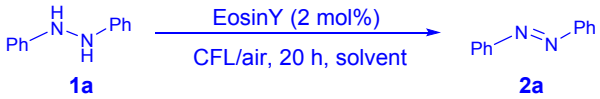
hydroxide, along with concomitant formation of large amounts of inorganic waste (Scheme 1c). Although catalytic hydrogenation of azobenzene by transition metals has also been proposed,[22] it often suffers from over-reduction of azobenzene to anilines (Scheme 1d). Moreover, functional groups such as nitro, iodo, and ester cannot survive the reduction conditions. Thus, the development of a new, mild, and facile method for selective azobenzene-to-hydrazobenzene reduction is highly desirable.

Over the past decade, visible-light photo-redox catalysis has emerged as an enabling platform for the development of novel organic reactions with high synthetic efficiency and functional-group tolerance.[23-29] In this context, photo-redox catalysis has been used to perform oxidation and dehydrogenation reactions. For example, the activation of O_2 for transformation of amines and alkenes using photo-redox catalysis has been comprehensively developed.[30-33] Recently, a range of dual-catalysis systems combining a photo-redox catalyst and a cobalt-based proton-reduction catalyst have been established for dehydrogenation reactions.[34-37] Interestingly, there is only one report of using a Ru–Co dual-metal system for azobenzene synthesis from hydrazobenzene.[37] In the area of azobenzene reduction, Pt/TiO_2 and Au/CeO_2 systems using alcohol as a sacrificial electron-and-proton donor are known.[38, 39] However, the former system needs UV light for catalyst photoexcitation, and the latter needs a strong base and generates aniline as a side product. Herein, we wish to report a facile and practical mutual transformation of azobenzene and hydrazobenzene using Eosin Y as a photo-redox catalyst (Scheme 1e). Our work represents a very rare example of using photo-redox catalysis as the sole catalyst to realize the mutual transformation of two kinds of compound.

Results and Discussion

We focused our initial studies on the oxidative dehydrogenation of diphenyl hydrazine (**1a**, 0.2 mmol) under ambient conditions with a 22 W white compact fluorescent lamp (CFL). We first evaluated different photo-redox catalysts in various solvents (Table 1). With transition metal-based photo-redox catalysts, azobenzene was obtained in yields of 86% with $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ and 62% with $Ir(bpy)_3$ in MeCN (Table 1, entries 1 and 2). Then, different organic photo-redox catalysts were tested. We found that Eosin Y gave the best yield (95%), even better than the transition metal-based photo-redox catalysts (Table 1, entry 5). With Eosin Y as photo-redox catalyst, various solvents were tested. To our delight, all solvents produced azobenzene (**2a**) in moderate to very good yields (54-95%) (Table 1, entries 5-13). However, MeCN was still the best solvent. Notably, even with H_2O as the solvent, a 75% yield of **2a** was still observed (Table 1, entry 13). When the color of the excitation light was changed to green, the amount of **2a** produced was almost unchanged (96%, Table 1, entry 14).

Table 1. Condition optimization for the oxidative dehydrogenation from **1a** to **2a**.[a]



Entries	Catalysts	Solvent	Yields[%][b]
1	$[Ru(bpy)_3]Cl_2{\cdot}6H_2O$	MeCN	86
2	$Ir(bpy)_3$	MeCN	62
3	Rose Bengal	MeCN	54
4	DCA	MeCN	46
5	Eosin Y	MeCN	95
6	Eosin Y	THF	67
7	Eosin Y	DMSO	66
8	Eosin Y	Dioxane	73
9	Eosin Y	Tol	79
10	Eosin Y	DMF	59
11	Eosin Y	EtOH	58
12	Eosin Y	DCM	54
13	Eosin Y	H_2O	75
14[c]	Eosin Y	MeCN	96

[a]the reaction were performed in a 20 mL vial with **1a** (0.2 mmol), photo-redox catalysts (2 mol%), solvents 1.0 mL and the vial were open to air under irradiation using CFL as the light source; [b]yields were determined by ^1H NMR using CH_2Br_2 as internal standard; [c]with green LED light.

With the optimal reaction conditions in hand (0.2 mmol **1**, 2 mol% Eosin Y, CFL, 1 mL MeCN under ambient conditions) we evaluated the oxidative dehydrogenation strategy to synthesize different azobenzene derivatives (Figure 1 and 2). For symmetrical hydrazobenzene derivatives (Figure 1), substrates with both electron-rich and electron-deficient substituents underwent efficient dehydrogenation to afford the corresponding desired products in excellent yields (72-99%, **2a**-**2o**). We found that sterically hindered substrates such as **2b** (2-Me) and **2e** (3-*i*Pr) provided slightly poorer yields (85% and 81%). Substrates with electron-withdrawing groups like -F, -Cl, -Br, and $-CF_3$ reacted well and gave the corresponding azobenzenes in very good yields (up to 93%). The slightly lower yields with electron-withdrawing groups indicated that electronic effects also played a role during the reaction. Furthermore, disubstituted hydrazobenzenes were also suitable substrates for the reaction and afforded the desired products in high yields (84-90%, **2m**-**2o**). The excellent functional-group compatibility and mild conditions favor the implementation of this reaction in late-stage functionalization of complex structural motifs.

Similar to symmetrical hydrazobenzenes, unsymmetrically substituted hydrazobenzenes showed very good reactivity (Figure 2). Substrates with both electron-rich and electron-deficient substituents undertook facile dehydrogenation to afford the corresponding products in excellent yields (up to

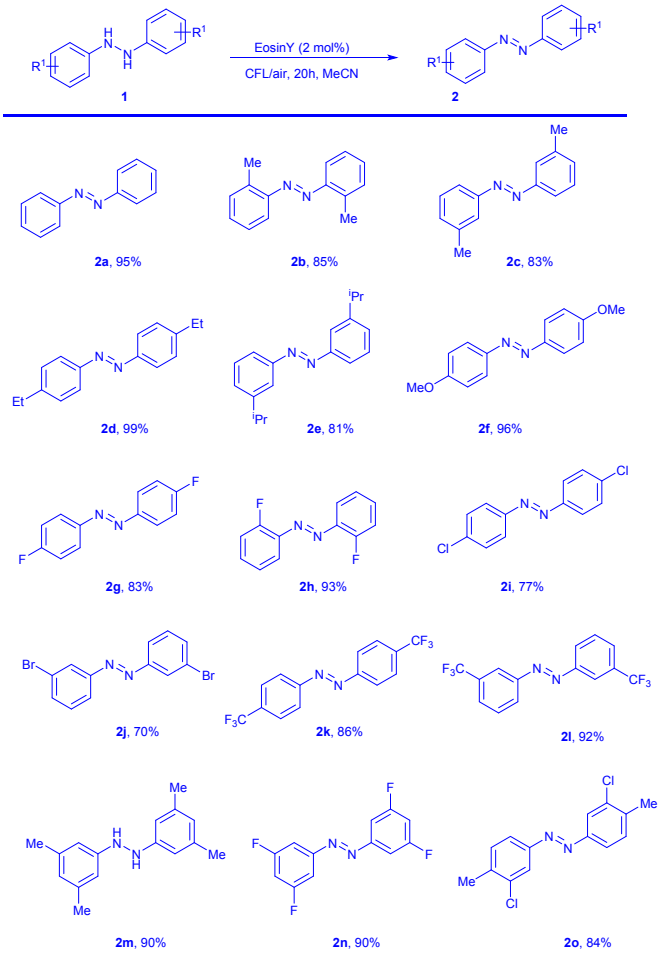


Figure 1. Visible light mediated synthesis of symmetrical azobenzene: the reactions were performed in 20 mL vial with **1** (0.2 mmol), Eosin Y (2 mol%), MeCN 1.0 mL and the vial were placed under ambient conditions with irradiation for 20 h, yields of isolated products are reported.

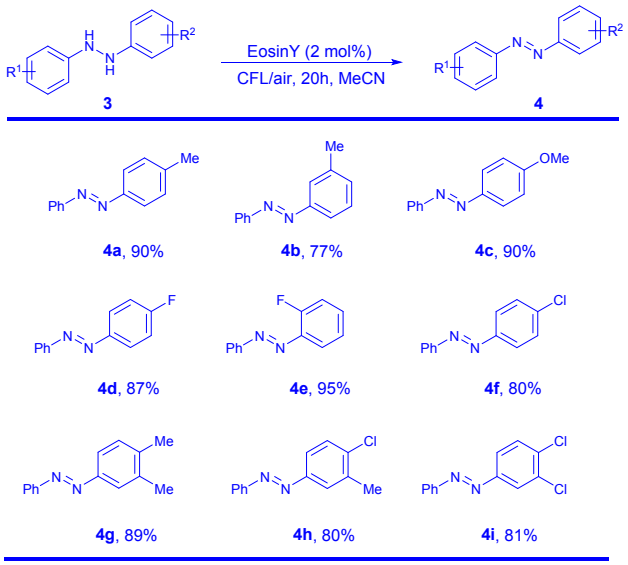
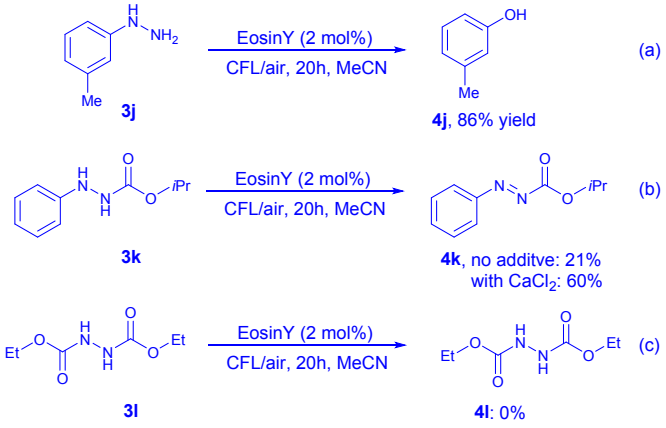


Figure 2. Visible light promoted synthesis of unsymmetrical azobenzene: the reactions were performed in 20 mL vial with **3** (0.2 mmol), Eosin Y (2 mol%), MeCN 1.0 mL and the vial were placed under ambient conditions with irradiation for 20 h, yields of isolated products are reported.

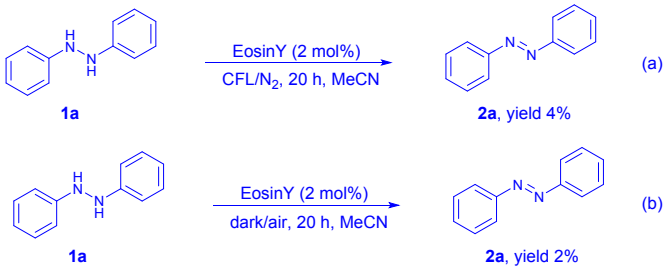
90%). Various substituents such as -Me, -MeO, -F, -Cl, and disubstituted hydrazobenzenes were well tolerated (products **4a**–**4i**), which showed the synthetic value of our process.

Follow-up chemistry was investigated to demonstrate the more general applicability of our strategy. Interestingly, when phenyl hydrazine **3j** was examined, *m*-cresol **4j** was detected as the main product with 86% yield (Scheme 2a). This might because of the further denitrogenative formation of aryl radical quenched by H_2O. Changing one phenyl group of diphenyl hydrazine to a stronger electron-withdrawing ester group (**3k**), we obtained only 21% of the dehydrogenation product **4k** (Scheme 2b), consistent with the lower reactivity of strong electron-withdrawing groups. Thus, unsurprisingly, the use of diethyl hydrazine-1,2-dicarboxylate **3l** resulted in no reaction at all (Scheme 2c). However, by adding 1 equivalent of $CaCl_2$ as an additive, the yield of **4k** was increased to 60%.



Scheme 2. Further extension of our strategy.

To better understand the reaction mechanism, control experiments were performed (Scheme 3). First, standard reaction was performed without Eosin Y, we found that there was only 10% of **2a** produced (Scheme S1). When the reaction with hydrazobenzene was performed under N_2 atmosphere, only an 4% yield of azobenzene was produced, which indicated the key role of air (O_2) for this transformation (Scheme 3a). When the reaction was performed without light, only a 2% yield of azobenzene was detected (Scheme 3b). Those experiments proved the key role of Eosin Y, light and O_2 in the reaction process. Then, in a fluorescence quenching study, we found that hydrazobenzene could efficiently quenched the excited state of Eosin Y (Supporting information, Figure S1a), while the quenching ability of saturated O_2 was barely discernible (Supporting information, Figure S1b).



Scheme 3. Control experiments for mechanism studies.

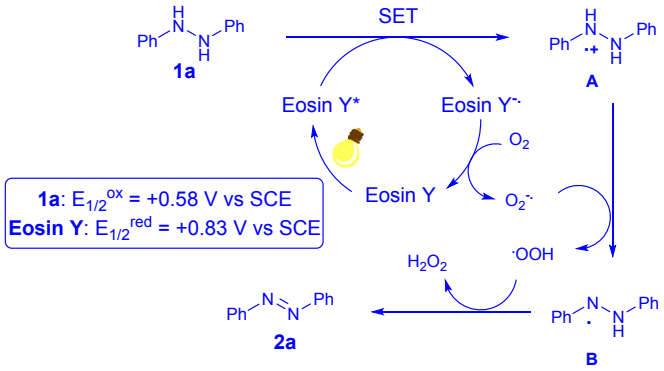


Figure 3. Plausible reaction mechanism for oxidative azobenzene synthesis.

Based on our mechanistic studies and recent literature reports,[37, 40, 41] we proposed a reaction mechanism as depicted in Figure 3. Eosin Y is first excited under visible light to produce its excited state species, Eosin Y*, which undergoes a single electron transfer with hydrazobenzene to form the corresponding radical anion of Eosin Y and radical cation A. The Eosin Y radical anion then relay-transfers one electron to O_2 to form a superoxide anion, and Eosin Y returns to its ground state. Then, the superoxide anion gains one proton from **A** to produce **B** and a peroxide radical. Finally, the peroxide radical reacts with **B** to produce azobenzene and hydrogen peroxide.

Recently, the photo-redox transfer hydrogenation of imines (with polar π bonds) was reported using thiols and triethylamine as hydrogen source and one-electron donor.[42-44] However, no analogous transfer hydrogenation of non-polar π bond-containing azobenzenes (N=N) has been reported. Given the virtual absence of previous examples, we investigated whether Eosin Y was able to catalyze the transfer hydrogenation of azobenzene to hydrazobenzene with the hope of performing the reaction under mild conditions and thus suppressing the over-reduction of hydrazobenzene to aniline. The reaction was performed with 0.1 mmol of azobenzene **2a**, 0.2 mmol of *p*-thiocresol, and 2% of Eosin Y in 1 mL of MeCN under visible light irradiation. We were delighted to find that a 91% yield of hydrazobenzene **1a** was produced (Figure 4). Inspired by this result, a series of potential hydrogen donors were tested. We found that apart from widely used thiols, phenyl hydrazine and hydrazine were also good transfer hydrogenation reagents, producing hydrazobenzene in 82% and 50% yields, respectively. Moreover, cyclic amines were also able to hydrogenate azobenzene to hydrazobenzene with 50% and 56% yields, respectively (Figure 4).

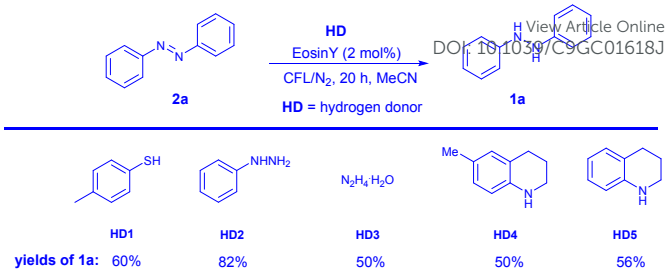


Figure 4. Eosin Y catalyzed transfer hydrogenation of azobenzene using a series of hydrogen donor: the reactions were performed in 20 mL vial with **2a** (0.2 mmol), Eosin Y (2 mol%), MeCN 1.0 mL and the corresponding hydrogen donor (0.42 mmol), the vial were placed under ambient conditions with irradiation for 20 h, yields were determined using by ^{1}H NMR using CH_2Br_2 as internal standard.

Conclusions

In conclusion, we have developed the first visible-light-driven, photo-redox-catalyzed oxidative dehydrogenation of hydrazobenzene to azobenzene using Eosin Y as the catalyst. The use of visible light and air as oxidant make this process sustainable and practical. Thus, a series of symmetrical and unsymmetrical azobenzenes were successfully synthesized in excellent yields (up to 99%) with broad functional-group tolerance. Moreover, the interconversion from azobenzene to hydrazine derivatives was also realized. Thus, the visible-light-driven, photo-redox-catalyzed transfer hydrogenation of azobenzene was developed and found to be compatible with hydrogen donors such as phenyl hydrazine and cyclic amines. Compared with traditional (thermal/transition-metal) catalytic methods, our process avoids over-reduction to aniline, which extends the applicability of photo-redox catalysis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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