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Metal-Free Visible-Light Induced Cross-Dehydrogenative Coupling of Tertiary Amines with Diazo Compounds

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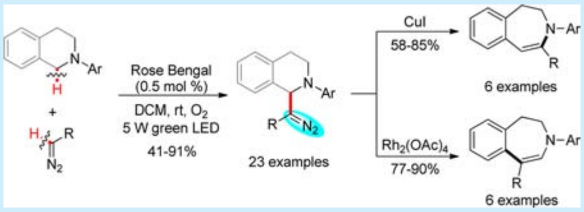
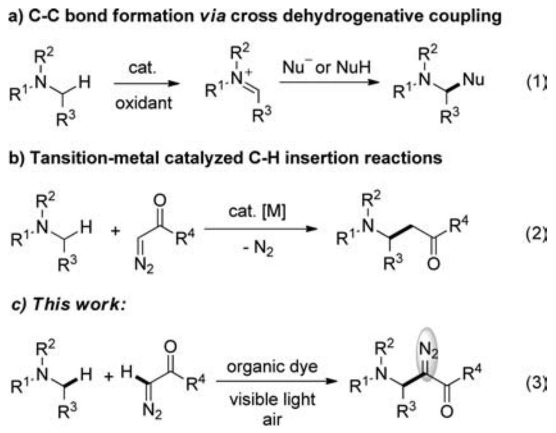
S *Supporting Information*

ABSTRACT: The first visible-light induced cross-dehydrogenative coupling between tertiary amines and diazo compounds is described. The reaction proceeds smoothly under mild and metal-free conditions by using air or O_2 as the oxidant, affording various *β*-amino-*α*-diazo adducts in moderate to good yields with broad substrate scopes. The resulting products were successfully employed for the synthesis of 4- or 5-ester *N*-aryl-2,3-dihydrobenzo[*d*]azepines with high regioselectivity simply switched by the selection of the transition metal catalysts.



Cross-dehydrogenative coupling (CDC) has attracted considerable interest among synthetic organic chemists, because it does not require substrate prefunctionalizations and is thus atom economic. Since the pioneering work of Murahashi[1] and Li,[2] the generation of the reactive iminium intermediate through oxidation of an sp^3 C−H bond adjacent to a nitrogen atom, followed by attack of a carbon nucleophile, has become a powerful strategy for C−C bond formation (Scheme 1, eq 1).[3] Despite the use of a variety of different nucleophiles, the development of new types of nucleophiles is still in high demand.

Scheme 1. C−H Insertion vs CDC Reaction



Diazo compounds, which are generally exploited as carbene precursors, have found wide applications in organic synthesis for several decades.[4] Diazo carbon bears a partial negative charge and thus has considerable nucleophilicity.[5] Nucleophilic addition of diazo compounds to activated imines bearing a strong electron-withdrawing *N*-substituent has been employed in the synthesis of *β*-amino acid derivatives and other valuable products.[6,7] However, to the best of our knowledge, diazo compounds have not been directly used as nucleophiles in cross-dehydrogenative coupling. This limitation is largely due to the harsh reaction conditions and stoichiometric amounts of oxidants, mainly peroxides and transition metals used in most of the CDC reactions, in which diazo decomposition will occur easily. In fact, a typical reaction between tertiary amines and diazo compounds in the presence of a transition metal is the direct C−H insertion involving metal carbenoid intermediates (Scheme 1, eq 2).[8] The recent progress in the field of visible-light photoredox reactions with amines promoted researchers to develop oxidative C−C and C−heteroatom bond formations under mild conditions by using oxygen or air as the oxidant.[9] Moreover, with organic dyes as the photoredox catalysts, the metal-free CDC reactions have also been reported by several groups.[10] Enlightened by these reports and as a continuation of our interest in visible-light photoredox chemistry,[11] we now report the first metal-free, visible-light induced oxidative coupling of tertiary amines with diazo compounds, which affords various *β*-amino-*α*-diazocarbonyl compounds in good yields (Scheme 1, eq 3).

Initially, when *N*-phenyl-tetrahydroisoquinoline (**1a**), ethyl diazoacetate (**2a**), and 1 mol % of eosin Y in MeCN were irradiated with a 5 W green LED at rt for 12 h, the cross-dehydrogenative coupling product **3a** was formed in 35% yield (Table1, entry 1). Encouraged by this result, $Ru(bpy)_3Cl_2$ and other organic dyes such as eosin B, methyl blue, and rose bengal (RB) were examined; among them RB gave the best results (Table 1, entries 2−5). Further optimization of the conditions showed the reaction was significantly affected by the catalyst loading and 0.5 mol % of RB was found to be optimal (Table 1, entry 7). However, the reaction only afforded the desired product in 37% yield when 5 mol % of catalyst was used (Table 1, entry 6). Next, a screening of solvents revealed that the yield of **3a** increased to 85% when the reaction was performed in CH_2Cl_2

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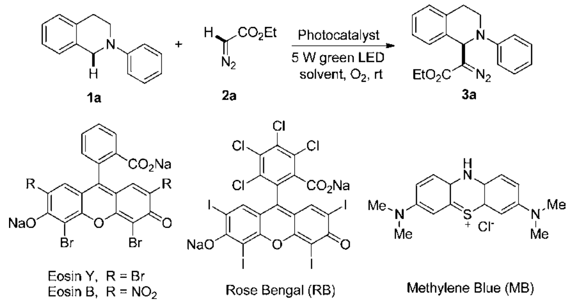
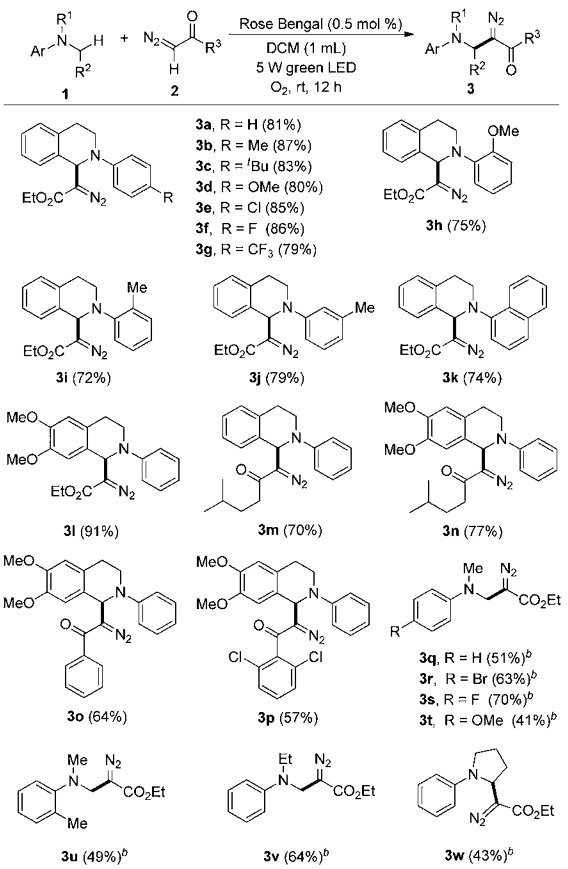
Table 1. Optimization of Reaction Conditions[a]



entry	photocatalyst (mol %)	solvent	yield (%)[b]
1	eosin Y (1)	MeCN	35
2	$Ru(bpy)_3Cl_2$ (1)	MeCN	41
3	eosin B (1)	MeCN	43
4	MB (1)	MeCN	17
5	RB (1)	MeCN	54
6	RB (5)	MeCN	37
7	RB (0.5)	MeCN	61
8	RB (0.5)	DMSO	67
9	RB (0.5)	DMF	51
10	RB (0.5))	1,4-dioxane	72
11	RB (0.5)	toluene	63
12	RB (0.5)	$ClCH_2CH_2Cl$	58
13	RB (0.5)	CH_2Cl_2	85
14[c]	RB (0.5)	CH_2Cl_2	77
15[d]	RB (0.5)	CH_2Cl_2	trace
16[e]	RB (0.5)	CH_2Cl_2	trace
17	none	CH_2Cl_2	N.R.

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), solvent (1 mL), 5 W green LED, rt under O_2 for 12 h. [b]Yield determined by ^1H NMR spectroscopy using mesitylene as the internal standard. [c]DBU (10 mol %) was added. [d]The reaction was carried out under N_2. [e]The reaction was conducted in the dark.

Scheme 2. Visible-Light Introduced CDC Reaction of Tertiary Amines and α-Diazocarbonyl Compounds[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), RB (0.5 mol %), DCM (1 mL), 5 W green LED, rt under O_2 for 12 h, isolated yield. [b] RB (5 mol %), 1,4-dioxane(1 mL) were used, open to air, 24 h.

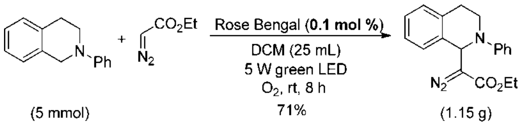
(Table 1, entry 13). Other solvents including DMSO, DMF, 1,4-dioxane, toluene, and DCE were also effective, but they were all not better than CH_2Cl_2 (Table 1, entries 8−12). Although DBU has been reported as a catalyst to promote the nucleophilic addition of diazo compounds to imines,[12] the addition of DBU in this reaction resulted the diminished yield of **3a** (Table1, entry 14). The control experiments showed that the reaction did not take place in the absence of either O_2, visible-light, or the photocatalyst (Table1, entries 15−17).

With the optimized conditions established (Table1, entry 13), we then investigated scopes of this visible-light induced CDC reaction by using various tertiary amines and α-diazocarbonyl compounds. We first examined the substituent effect on the benzene ring connected to the nitrogen atom in the *N*-aryl-tetrahydroisoquinolines (THIQ). As shown in Scheme 2, the substrates bearing electron-donating groups such as methyl, tertiary butyl, methoxyl and electron-withdrawing groups such as chloro, fluoro, trifluoromethyl at the *para*-position underwent smooth reactions with ethyl diazoacetate and afforded the desired products **3b−g** in good yields (79%−87%). *N*-Aryl THIQ bearing methoxyl (**3h**), methyl at the *o*-position (**3i**) and methyl at the *m*-position (**3j**) produced the corresponding diazo esters in slightly low yields. In another case, *N*-naphthalenyl THIQ coupled with ethyl diazoacetate efficiently, affording the desired product **3h** in 74% yield. 6,7-Dimethoxy substituted THIQ was also compatible with the standard reaction conditions and displayed high reactivity (**3l**). Next, several acyl diazo compounds were examined as coupling partners for the reactions under the optimized conditions. We were pleased to find that all the substrates underwent CDC reaction with THIQ, resulting in the corresponding products **3m−p** in 57%−77% yields. To further demonstrate the scope of the reaction, the present protocol was then extended to *N*,*N*-dimethylaniline, a general type of tertary amines. Treatment of ethyl diazoacetate with a series of substituted *N*,*N*-dimethylanilines in the presence of 5 mol % of RB in 1,4-dioxane for 24 h gave the corresponding α-amino diazo compounds **3q−u** in moderate to good yields. Notably, a bromo substituent could survive in the reaction. When *N*-ethyl-*N*-methylaniline was used as the substrate, the coupling reaction occurred on the methyl group specifically, providing diazo compound **3v** as the sole product in 64% yield. Notably, using a cyclic amine also afforded the expected product **3w** with 43% yield.

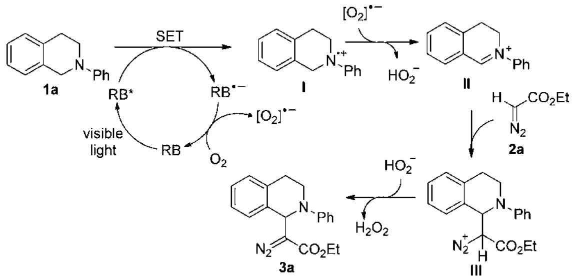
To demonstrate the practical usefulness of this reaction, the CDC reaction has been carried out on a gram scale under the irradiation of visible light. As shown in Scheme 3, the diazo compound **3a** was obtained in slightly diminished yield (71%) on the 1.15 g scale by using 0.1 mol % of RB as the photoredox catalyst.

On the basis of the experimental results and literature reports,[9,10] a plausible reaction mechanism for this photocatalytic CDC reaction is proposed in Scheme 4. Initially, visible light irradiation of Rose Bengal generates the excited species RB*.

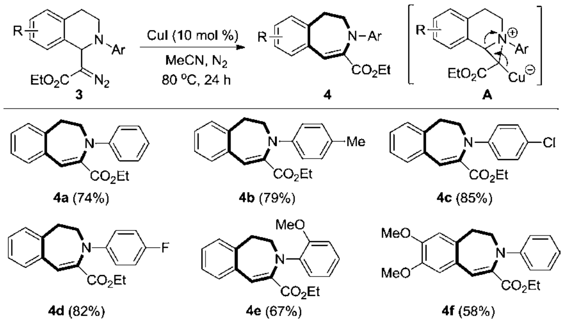
Scheme 3. Gram-Scale Reaction



Scheme 4. Proposed Reaction Mechanism

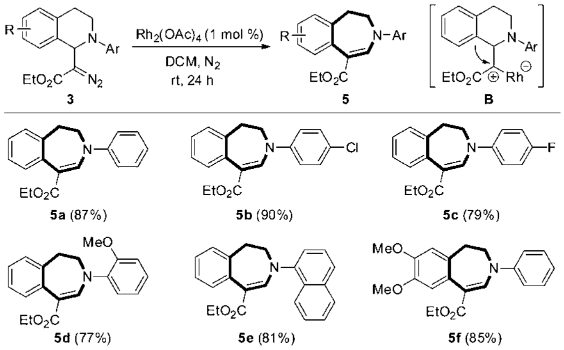


Scheme 5. CuI-Catalyzed Ring Expansion of Diazo Compounds 3[a]



[a]Reaction conditions: **3** (0.2 mmol), CuI (10 mol %), MeCN (2 mL), 80 °C under N_2 for 12 h, isolated yield.

Scheme 6. Rhodium-Catalyzed 1,2-Aryl Shift/Ring Expansion Reaction of 3[a]



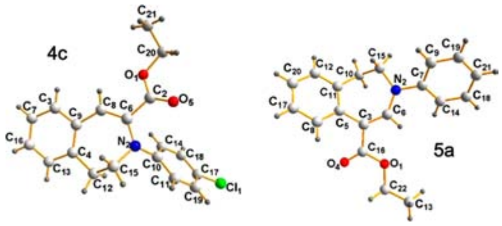
[a]Reaction conditions: **3** (0.2 mmol), $Rh_2(OAc)_4$ (1 mol %), DCM (25 mL), rt under N_2 for 24 h, isolated yield.

Reductive quench of RB* by tertiary amine via a single electron transfer (SET) process to form intermediate **I**. The generated $RB^{\bullet-}$ is then oxidized by oxygen to give a superoxide radical anion with concomitant regeneration of the photocatalyst. Hydrogen atom abstraction of **I** by $O_2^{\bullet-}$ provides the iminium ion **II**, which undergoes nucleophilic attack by a diazo compound to give intermediate **III**. Finally, intermediate **III** is deprotonated by a hydroperoxide anion, leading to the desired α-amino diazo compound **3**. An evaluation of successful nucleophiles in CDC reactions with *N*-phenyl tetrahydroquinoline has been made by Klussmann, in which a nucleophilicity threshold of around 3.8 as a lower limit on the Mayr scale has been determined.[13] The nucleophilicity of the diazo compounds used in the present visible-light induced CDC reaction (for example, 4.91 for ethyl diazoacetate) fits this prediction very well.[5] In addition, it is well-known that the UV irradiation of diazo compounds leads to the loss of nitrogen.[14] However, the nitrogen extrusion was not observed under the present conditions, which may be attributed to the low energy of green light used in this reaction.[15]

Benzoazepines are an important class of seven-membered *N*-heterocycles, which have been extensively studied as dopamine receptor agonists and antagonists.[16] The nucleophilic addition of diazo compounds to quinolinium salts, followed by a ring-expansion reaction in the presence of a copper catalyst, has been reported as an efficient method for the synthesis of benzo[*b*]-azepines.[17] To explore the synthetic potential of the visible-light induced CDC reaction, the obtained compound **3a** was treated with 10 mol % of CuI in MeCN at 80 °C for 24 h. To our delight, the desired ring-expansion product **4a** was obtained in a yield of 74%. As shown in Scheme 5, the reactions worked efficiently with other *N*-aryl substituted substrates, and they all gave good yields of the desired 4-ester *N*-aryl-2,3-dihydrobenzo[*d*]azepines **4a**−**f**. This ring expansion reaction probably proceeds through a tricyclic intermediate **A**.[17b]

Interestingly, when $Rh_2(OAc)_4$ instead of CuI was employed as the catalyst, an exclusive 1,2-aryl shift/ring expansion process was taking place, affording the corresponding 5-ester *N*-aryl-2,3-dihydrobenzo[*d*]azepines **5** in good to excellent yields (Scheme 6). This observation is similar to Wang's report on $Rh_2(OAc)_4$-catalyzed 1,2-aryl migration of *N*-tosyl diazoketamines.[18] However, the strategy has never been used to construct a seven-membered heterocyclic ring. To our knowledge, this is the first report on the synthesis of benzoazepines via a Rh-catalyzed 1,2-aryl shift/ring expansion process. The structures of compounds **4c** and **5a** were further confirmed by their X-ray crystal diffractions (Scheme 7). Thus, the present protocols could provide an efficient method for the synthesis of 4- or 5-ester *N*-aryl-2,3-dihydro-benzo[*d*]azepines with high regioselectivity by simply switching the selection of the transition metal catalysts, both of which are difficult to be obtained by the reported methods.[19]

Scheme 7. X-ray Crystal Structures of 4c and 5a



In conclusion, we have reported the first visible-light induced CDC reaction of tertiary amines and diazo compounds. This protocol supplements a new type of nucleophile, diazo compounds, to the known CDC reactions. The reaction also provides an interesting approach toward β-amino-α-diazo-carbonyl compounds with a wide range of functional group tolerance, which are not easily accessible by conventional methods. Additionally, the resulting products can easily convert to 4- or 5-ester *N*-aryl-2,3-dihydro-benzo[*d*]azepines with high regioselectivity by simply switching the selection of the transition metal catalysts. Further investigations on the application of this reaction and related oxidative coupling processes are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, characterization data, NMR spectra of all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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