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Visible-light-mediated Oxidative Arylation of Vinylarenes under Aerobic Conditions

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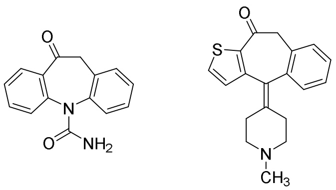
A mild and efficient method for the photocatalytic oxidative arylation of vinylarenes to generate 1,2-diarylated ethanones has been developed. The reaction was catalyzed by $Ru(bpy)_3Cl_2$ at room temperature under aerobic conditions. This protocol realizes a controllable, regioselective 1,2-difunctionalization of carbon-carbon double bonds.

Difunctionalization of vinylarenes is an important subject in organic synthesis, and has been extensively studied in the past decades.[1] Especially, transition-metal-catalyzed reactions including dihydroxylation, diamination, hydroxyacetoxylation, aminoacetoxylation, and oxyalkylation proved to be quite efficient.[2] Among them, the formation of CX–CC bonds to give *α*-aryl-*β*-heterofunctionalized alkanes should have a great synthetic potential.

1,2-Diarylated ethanones (deoxybenzoines), which can be synthesized by oxidative arylation of vinylarenes, are valuable building blocks for the construction of heterocycles.[3] Also, the framework of these compounds can be found in the structure of various nature products and pharmaceuticals, such as the anticonvulsant oxcarbazepine and H_1-antihistamine ketotifen (Scheme 1). A number of approaches have been employed to build these structures. Conventional transformations, like nucleophilic aromatic substitution, often require stoichiometric amounts of metal catalysts, and also have other drawbacks like functional-group compatibility and toxicity of reagent.[4] Recently, palladium-catalyzed arylation of ketones as an appealing method, has been impressively researched by the groups of Buchwald[3c,5] and Hartwig[6]. However, expensive ligands and strong basic conditions are often needed in these reactions.

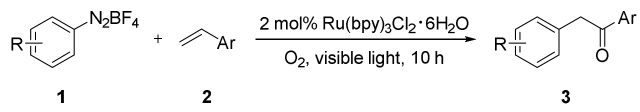


Oxcarbazepine Ketotifen

Scheme 1 Structures containing the framework of 1,2-diarylated ethanones.

Visible light photoredox catalysis has been widely applied in modern catalysis and synthesis,[7] due to its easy availability and environmental friendliness. Great efforts have been made by the research groups of MacMillan,[8] König,[9] Yoon,[10] Rueping,[11] Stephenson,[12] *etc*. Aryl diazonium salts are very facile and able to generate reactive aryl radicals easily *via* single-electron reduction through photoelectron transfer (PET) process. The applications of aryl diazonium salts in photocatalytic arylation of diverse unsaturated componds have been demonstrated by König and co-workers in several recent reports.[9,13] And they also harnessed aryl diazonium salts in the chemical modification of coumarin-functionalized cellulose sheets.[13c] Yet, all these reactions must be conducted under degassed condition without oxygen using the “freeze-pump-method”.

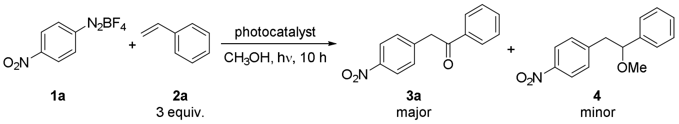
As an “ideal” oxidant, molecular oxygen is clean, nontoxic, and ecosustainable. Utilizing oxygen, the field of photoredox catalysis has opened up a new area. Although ground state triplet oxygen is nonreactive for most closed-shell organic substrate, the reaction can occur by either one-electron oxidation of the substrate or one-electron reduction of oxygen to superoxide.[7e] There have already been several successful examples, including the [2 + 2 + 2] cycloadditions,[14] aerobic oxidations of benzylic halides,[15] and *β*-keto sulfoxidation of alkene[16]. Along this line, we herein describe a mild method for visible-light-mediated oxidative arylation of vinylarenes to generate 1,2-diarylated ethanones. The reaction proceeds smoothly at room temperature using molecular oxygen as the oxidant.



Scheme 2 Photocatalytic approach for oxidative arylation of vinylarenes.

We initiated our work by exploring the reaction between aryl diazonium salt **1a** and styrene **2a** catalyzed by $Ru(bpy)_3Cl_2 \cdot 6H_2O$. The reaction was exposed directly to the air and irradiated with a blue LED at room temperature. The reaction gave the desired product ketone **3a** along with 1-(2-methoxy-2-phenylethyl)-4-nitrobenzene (**4**) as a byproduct. Organic dyes (Table 1, entries 3–5) were evaluated as the catalyst to check whether there is a possibility to replace $Ru(bpy)_3^{2+}$, and the results are listed in Table 1. Comparing to the control reaction without catalyst (entry 2), the organic dyes all have effects on the reaction, but the result shows ruthenium complex remains to be the best catalyst. We also conducted the reaction in the dark (entry 7), little product was generated, which indicates that light is a critical factor for this reaction.

Table 1 Screening of different photocatalysts.[a]

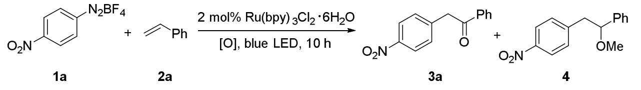


Entry	Catalyst	Mol %	Yield (%)[b]
1	$Ru(bpy)_3Cl_2 \cdot 6H_2O$	2	59 (14[c])
2	None		20
3	Eosin Y	5	36
4	Rose bengal	5	30
5	Eosin B	5	41
6	Rhodamine B	5	42
7[d]	$Ru(bpy)_3Cl_2 \cdot 6H_2O$	2	6

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), MeOH (1 mL), irradiation under an air atmosphere at rt. [b] Isolated yield of product **3a**. [c] Isolated yield of **4**. [d] Experiment was carried out without light.

The effects of oxygen on this reaction were examined. To our delight, the amount of **4** declined sharply when the reaction was performed in an oxygen atmosphere, with product **3a** obtained in 75% yield (Table 2, entry 2). The experiment conducted without oxygen under an atmosphere of argon produced very little product, but gave byproduct **4** in 40% yield (entry 3).[17] Then, different solvents and amounts of **2a** were screened to optimize the reaction conditions. The results are presented in Table 2, and methanol (entry 5) showed to be the best solvent for this reaction.

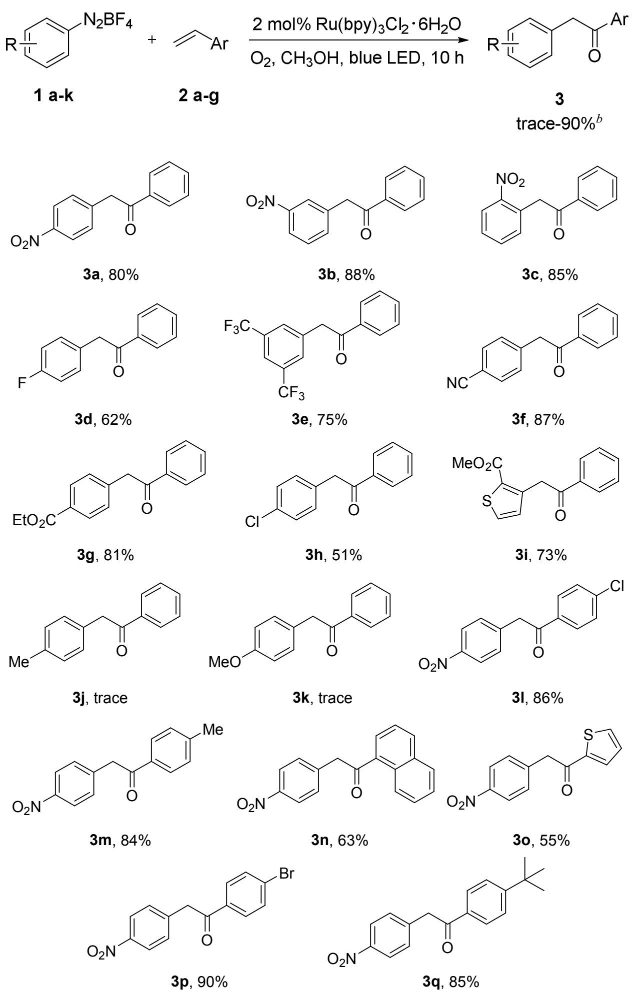
Table 2 Optimization of reaction conditions.[a]



Entry	Conditions	Yield (%)[b]
1	**2a** (3 equiv), air, MeOH	59 (14[c])
2	**2a** (3 equiv), O_2, MeOH	75 (1[c])
3	**2a** (3 equiv), argon, MeOH	2 (40[c])
4	**2a** (1.1 equiv), O_2, MeOH	47
5	**2a** (5 equiv), O_2, MeOH	80
6	**2a** (5 equiv), O_2, DMF	61
7	**2a** (5 equiv), O_2, DCM	10
8	**2a** (5 equiv), O_2, DMSO	51
9	**2a** (5 equiv), O_2, THF	34
10	**2a** (5 equiv), O_2, acetone	46

[a] Reaction conditions: $Ru(bpy)_3Cl_2$ (2 mol%), solvent (1 mL), irradiation with a blue LED at rt. [b] Isolated yield of product **3a**. [c] Isolated yield of **4**.

Table 3 Substrate scope for the oxidative arylation reaction of vinylarene.[a]

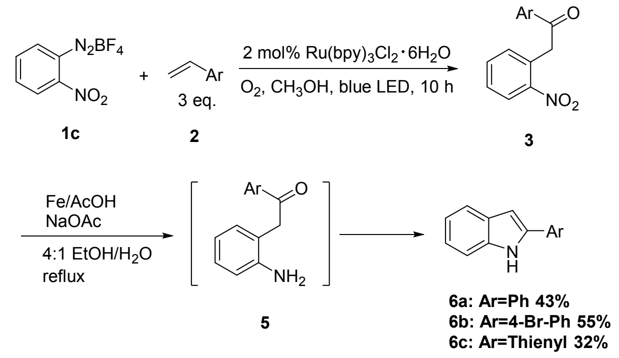


[a] Reaction Condition: $Ru(bpy)_3Cl_2$ (2 mol%), **1** (0.2 mmol), **2** (1.0 mmol), MeOH (1 mL), irradiation with a blue LED under an oxygen atmosphere at rt. [b] Isolated yield.

With the optimized conditions in hand, different aryl diazonium salts were surveyed to investigate the scope of the reaction. Aryl diazonium salts bearing electron-withdrawing and -neutral substituents all reacted smoothly, including heteroaryl diazonium salt **1i**. Electron-donating-substituted diazonium salts, such as *para*-methylbenzene- and *para*-methoxybenzene-diazonium salts, are not good substrates for the reaction, and only trace products were detected. Instead, toluene and anisole were observed. This might be because *para*-donor-substituted aryl radicals are more easily quenched in the presence of dioxygen *via* hydrogen abstraction.[18] Steric effect had only a slight impact on the yields (Table 3, **3a**–**c**).

Then our attention was turned to exploring the scope of the reaction with regard to vinylarene. A variety of vinylarenes were subjected to the reaction conditions, with the corresponding products obtained in moderate to excellent yields. Unsuccessful substrates that were screened included *β*-substituted alkenes such as methyl cinnamate and stilbene.

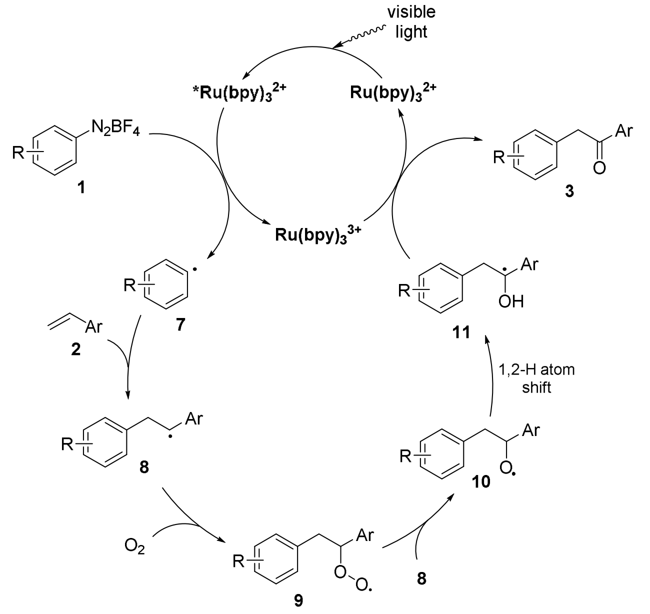
In order to further demonstrate the application of this photocatalytic oxidative arylation reaction, we conducted the synthesis of the 2-substituted indoles[13b]. As shown in Scheme 3 the photocatalytic reaction which gives the ketone **3** carrying an *ortho*-nitro-substituted benzene in the *α*-position serves as a first step, followed by reduction using iron powder. In situ reduction of the nitro group leads to the intermediate amine **5**, which undergoes a condensation to afford indole **6**.



Scheme 3 Synthesis of 2-substituted indoles using arylation products.

To gain insight into the catalytic pathway of the photocatalytic oxidative arylation reaction, some control experiments were conducted. It was found that the reaction was obviously inhibited by addition of 3 equivalent of TEMPO, indicating that the reaction might follow a radical pathway. While the reaction was not quenched either in the presence of 2,3-dimethyl-2-butene (2.0 mol%) or DABCO (2.0 mol%), which suggested that singlet oxygen is not involved in the reaction.[16]

According to the above results and recent reports[13,16,19], a plausible mechanism for the present process was proposed as illustrated in Scheme 4. Initially, the excited state of photocatalyst $Ru(bpy)_3^{2+*}$ is oxidatively quenched by diazonium salt **1**, and aryl radical **7** is formed upon loss of dinitrogen. Addition of aryl radical **7** to the double bond of vinylarene gives radical intermediate **8**, which reacts with dioxygen to give peroxy radical **9** and alkoxy radical **10**, respectively[19a]. Preceded by 1,2-hydrogen atom shift of alkoxy radical **10**, a subsequent SET oxidation yields the final product **3** and completes the catalytic cycle.[19b]



Scheme 4 Proposed mechanism for the photocatalytic oxidative arylation reaction.

Conclusions

A novel visible-light-mediated oxidative arylation of vinylarenes at room temperature has been disclosed. In this chemistry, visible light as a clean source of energy and oxygen as an environmentally-friendly and ecosustainable oxidant, are both successfully utilized in this reaction to generate 1,2-diarylated ethanones. The reaction proceeds smoothly at room temperature without the presence of base and expensive ligands, and the desired products were produced in moderate to excellent yields.

Acknowledgements

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