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Metal-free synthesis of ketones by visible-light induced aerobic oxidative radical addition of aryl hydrazines to alkenes

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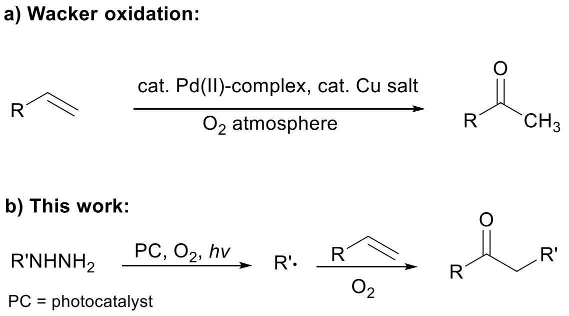
A green and cost-effective method has been developed for the conversion of alkenes to ketones under metal-free conditions. The reaction involves the oxidative addtion of alkenes with aryl radicals, which are generated by visible-light induced aerobic oxidation of arylhydrazines. The key features of this reaction include broad substrate scope, readily available reagents and amenability to gram-scale synthesis.

Carbonyl groups are important moieties for the construction of organic targets and synthetic intermediates.[1] Alkenes are extremely abundant chemical feedstocks which are produced in large quantities from petrochemical sources. As a consequence, they have been exploited as starting materials for the synthesis of a wide range of fine chemicals, and the oxidation of alkenes has evolved to be one of the most straightforward routes for the synthesis of carbonyl compounds. The industrially important oxidation of ethylene to acetaldehyde promoted by the combination of palladium with copper, namely the Wacker process, represents a milestone of alkene utilization.[2-5] Since the discovery of this process, this Pd/Cu catalyst system has been extended to the oxidation of diverse terminal olefins (Wacker–Tsuji oxidation), which provides a powerful method for the synthesis of methyl ketones.[6] More recent developments in this area have focused on the identification of new conditions that enable broader substrate scope and efficient catalytic turnover of the palladium catalyst.[7] However, the Wacker-type reactions generally employs expensive palladium(II) salts as the catalyst and sometimes high catalyst loading is required[8], leading to cost and environmental concerns and limiting their practical utility. Hence, the development of metal-free synthetic methods with improved efficiency and generality for the conversion of alkenes to carbonyl compounds is highly desirable.

The Wacker-type reactions generally rely on the interaction of palladium(II) salts with the π-orbitals of an alkene, as an alternative, visible light photoredox catalysis[9] can engage alkenes in single-electron-transfer (SET) processes leading to the functionalization of the double bond in the presence of radical source. Hydrazines have been reported to generate radical species by treatment with metallic compounds through the formation of diazenes.[10] However, many of these radical reactions were carried out in the presence of toxic transition metals. There are only a few examples using photoredox catalysts to initiate the formation of radical species from hydrazines. For example Zhou and Mao reported the use of organic dye eosin B as an efficient initiator for generation of radical species from hydrazines upon visible-light irradiation in the open air, which were trapped by 2-isocyanobiphenyls to give a series of 6-substituted phenanthridines in good yields.[11] We reported a visible-light photocatalytic aerobic oxidation of hydrazine to diazene followed by its addition to Michael acceptors to form polysubstituted pyrazoles.[12] In this respect we envision that alkenes could be converted to ketones by reaction with radicals generated from the oxidation of hydrazines in the presence of photocatalyst (PC) and dioxygen (Scheme 1).


a) Wacker oxidation:

b) This work:

Scheme 1. Synthetic pathways from alkenes to ketones

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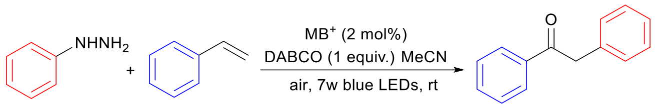
We initiated our studies by examining the model reaction of **1a** and **2a** (Table 1). After examining a wide array of reaction conditions, we determined that the ketone **3aa** can be produced in a good yield (81%) in the presence of methylene blue (MB^+, 2 mol%), DABCO (1 equiv.), and air (open flask) in MeCN at room temperature under the irradiation of 7 W blue LEDs for 8 h (Table 1, entry 1).

Table 1. Effect of Reaction Parameters on the oxidative addition of aryl hydrazines to alkenes[a]



1a **2a** **3aa**

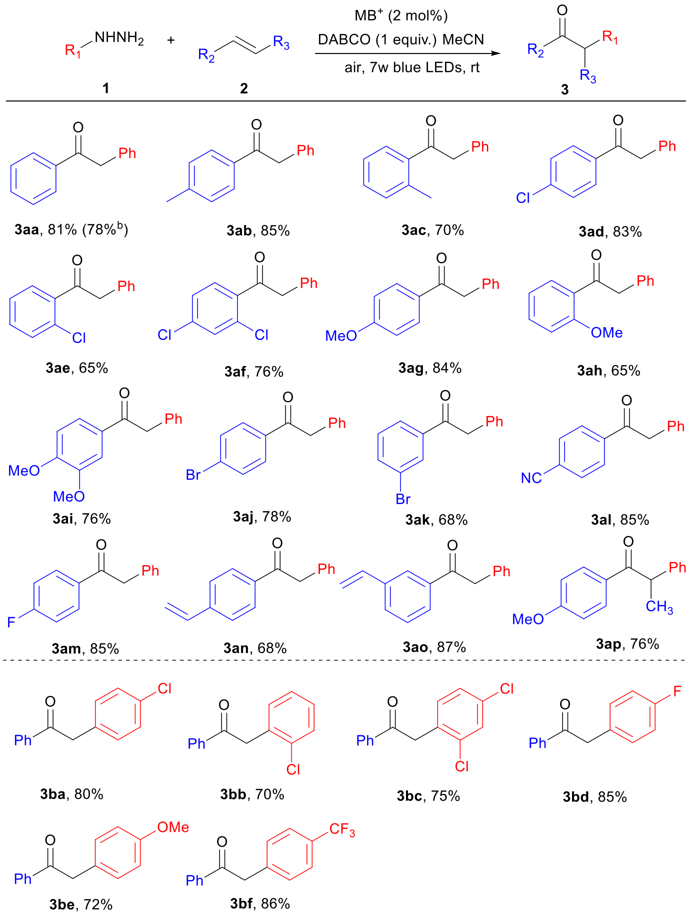
entry	variation from the standard conditions	yield/%[b]
1	none	81
2	no MB^+	0
3	no visible light	0
4	rhodamine B, instead of MB^+	32
5	$Ru^{II}(bpy)_3Cl_2.6H_2O$, instead of MB^+	56
6	eosin Y, instead of MB^+	65
7	no DABCO	10
8	Cs_2CO_3, instead of DABCO	25
9	Et_3N, instead of DABCO	51
10	$^iPr_2NEt$, instead of DABCO	20
11	DBU, instead of DABCO	60
12	MeOH, instead of MeCN	58
13	CH_2Cl_2, instead of MeCN	62
14	DMSO, instead of MeCN	45

[a] Standard conditions: 0.5 mmol of **1a**, 1.5 mmol of **2a**, 0.01 mmol of methylene blue, 0.5 mmol of DABCO, air (open flask), and MeCN (1.5 mL) at room temperature under the irradiation of 7 W blue LEDs; MB^+ = methylene blue, DABCO = 1,4-Diazabicyclo[2.2.2]octane. [b] isolated yield

The data in Table 1 illuminated the effect of a variety of parameters on the reaction efficiency. For example, results of control experiments showed that photocatalyst and visible light are essential for this reaction (entries 2−3). Replacing of methylene blue with other commercially available photocatalysts (i.e., rhodamine B, $Ru^{II}(bpy)_3Cl_2.6H_2O$ and eosin Y), was deleterious to the product yield (entries 4−6). $Ru^{II}(bpy)_3Cl_2.6H_2O$ and eosin Y possess lower oxidation potential [e.g., $E_{1/2}(PC^*/PC^-) = +0.77$ V for $Ru(bpy)_3^{2+}$; $E_{1/2}(PC^*/PC^-) = +0.83$ for eosin Y] than methylene blue [$E_{1/2}(PC^*/PC^-) = +0.97$].[9] Obviously, it is more difficult for $Ru^{II}(bpy)_3Cl_2.6H_2O$ and eosin Y to oxidize hydrazine in this reaction. On the other hand, removal of DABCO from the reaction mixture resulted in a decreased yield (entry 7), indicating that base is necessary for the reaction to achieve a decent yield. Several bases could promote the reaction (entries 8−11), and DABCO was found to be the best. When other solvent, such as MeOH, CH_2Cl_2 or DMSO, was employed as the reaction media to replace MeCN, a notable decrease of yield was observed (Table 1 entries 12-14).

After establishing suitable conditions, the scope of the reaction in terms of hydrazine and alkene was explored (Table 2). Initially, styrene derivatives with various functional groups on the phenyl ring were investigated (**3aa**–**3ap**), and most of the *para*-substituted styrene substrates were found to undergo the desired transformation affording yields greater than 80% (**3ab**, **3ad**, **3ag**, **3al**, and **3am**). But when steric pressure was applied at the *ortho* position (**3ac**, **3ae**, **3af**, and **3ah**), the yield was reduced by 10% approximately. The electronic nature of the substrates was shown to have little influence on the reaction efficiency, and styrenes with electron-donating or electron-withdrawing substituents on the phenyl group could be converted to corresponding ketones in good to excellent yields (**3ag** and **3al**). Interestingly divinylbenzene substrates could react with phenylhydrazine to form mono-ketone selectively in good to excellent yields (**3an** and **3ao**). Notably β-methyl styrene also worked smoothly under current conditions affording a yield of 76%. Furthermore, we turned our attention to the scope of the aryl hydrazine fragment. As shown in bottom line of Table 2, different aryl hydrazines are amenable to this strategy, including those that bearing different groups at different positions on the aromatic ring (**3ba**-**3bf**, 70-86% yield). And steric effect was observed that *ortho*-substituted hydrazines gave slightly lower yields (**3bb** and **3bc**). To demonstrate the synthetic utilities of this strategy, we also conducted a gram-scale reaction of **1a** and **2a**, which provided **3aa** in 78% yield.

Table 2. Substrate scope of the oxidative addition of aryl hydrazines to alkenes[a]



3aa, 81% (78%[b])
3ab, 85%
3ac, 70%
3ad, 83%
3ae, 65%
3af, 76%
3ag, 84%
3ah, 65%
3ai, 76%
3aj, 78%
3ak, 68%
3al, 85%
3am, 85%
3an, 68%
3ao, 87%
3ap, 76%
3ba, 80%
3bb, 70%
3bc, 75%
3bd, 85%
3be, 72%
3bf, 86%

[a] 0.5 mmol of **1**, 1.5 mmol of **2**, 0.01 mmol of methylene blue, 0.5 mmol of DABCO, air (open flask), and MeCN (1.5 mL) at room temperature under the irradiation of 7 W blue LEDs; MB^+ = methylene blue, DABCO = 1,4-Diazabicyclo[2.2.2]octane. [b] 10 mmol of **1a**, 30 mmol of **2a**, 0.2 mmol of methylene blue, 10 mmol of DABCO, air (open flask), and MeCN (30 mL)

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To further understand this transformation, Stern-Volmer fluorescence quenching experiments were performed to gain an insight into the photoredox catalytic cycle. The luminescence of methylene blue with excitation at 664 nm could be readily quenched by **1a** following Stern–Volmer kinetics (Figure 1), and styrene **2a** cannot serve as the emission quenchers. This luminescence quenching is most likely due to photoinduced electron transfer.

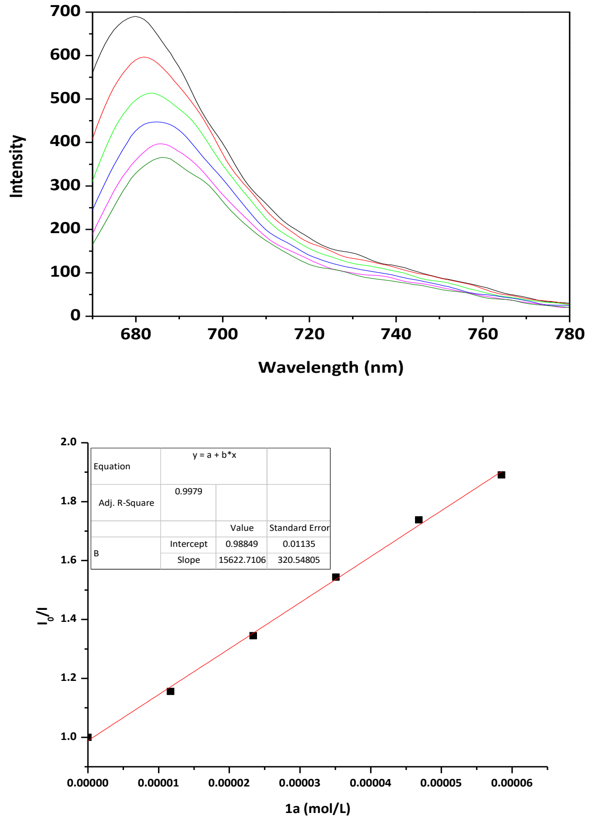
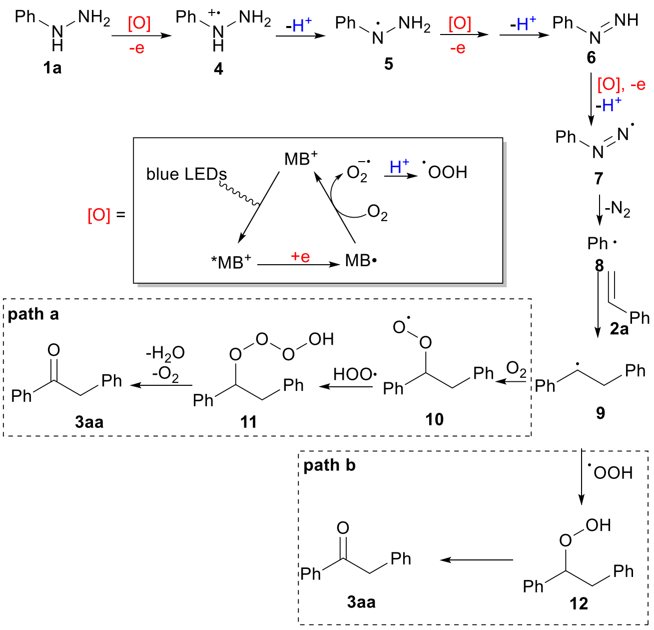


Figure 1. (up) Luminescence quenching of methylene blue with excitation at 664 nm by **1a**. (down) The Stern- Volmer plot.

On the basis of these experimental observations, a plausible mechanism is proposed (Scheme 2). First, methylene blue is irradiated to the excited state $^*MB^+$ using blue LEDs, and this excited state is then reductively quenched by **1a** with concomitant generation of ionic radical **4** and methylene blue radical (MB•). Upon deprotonation, ionic radical **4** is converted to radical **5**, which can also quench the excited state $^*MB^+$ and lose a proton to form diazene **6**. Another single-electron oxidation by $^*MB^+$, followed by deprotonation, leads to the formation of phenyl radical **8**. During the course MB• is oxidized back to MB^+ by molecular oxygen which is reduced to hydroperoxyl radical (HOO•). Furthermore, intermediate **10**, which is generated from the addition of phenyl radical **8** to styrene **2a** followed by incorporation of dioxygen, could react with hydroperoxyl radical to form **11.** Then **11** decomposes to afford the desired product **3aa**, along with the formation of molecular oxygen and water through Russell fragmentation[13]. Another possible pathway from intermediate **9** to **3aa** is the combination of **9** with hydroperoxyl radical to form intermediate **12**, followed by its decomposition to final product **3aa** (path b).

Scheme 2. Proposed Mechanism



Conclusions

In conclusion, we have developed a metal-free protocol for the conversion of alkenes to ketones through oxidative radical addition with arylhydrazines. This reaction avoids the need for the use of aryldiazonium or diaryliodonium which are unstable and may cause some cost and environmental concerns. Instead, by using arylhydrazines as the radical source, this visible-light induced reaction leads to H_2O and N_2 as the by-products. Preliminary mechanistic studies suggested the reaction goes through VLPC-promoted oxidation of arylhydrazine to aryl radical followed by its addition to alkenes. Taken together with its operational simplicity, readily available reagents, broad substrates scope, and amenability to gram-scale synthesis, this green reaction will find practical application for the utilization of alkenes.

Acknowledgments

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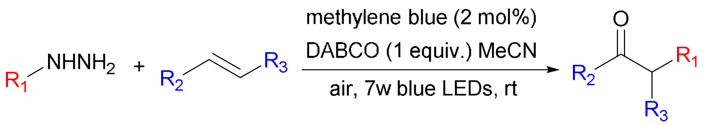

- 20 examples, up to 87% yield
- O_2 as green oxidant
- metal- free