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A simple ketone as an efficient metal-free catalyst for visible-light-mediated Diels–Alder and aza-Diels–Alder reactions†

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Diels–Alder reactions are highly effective between electron-rich dienes and electron-poor dienophiles. However, these reactions with electron-rich dienophiles are limited and require forcing conditions. Based on this, an efficient metal-free homogeneous system has been developed for the Diels–Alder reactions between electron-rich dienophiles and dienes under visible-light conditions. Additionally, this catalyst has shown excellent reactivity for aza-Diels–Alder reactions. This simple catalyst is commercially available, non-toxic, and cheap and has shown excellent reactivity which is comparable to and in some cases even better than the reported metal-based catalysts. Finally, the mechanism of this reaction has been proposed based on the experimental evidence.

Introduction

Diels–Alder (D–A) reactions are the fundamental strategy for the syntheses of versatile cyclohexene derivatives with the formation of new stereogenic centers.¹ These reactions have been well-documented in organic syntheses, in the pharmaceutical industry and in biochemistry.² It should be noted that D–A reactions are highly effective between electron-rich dienes and electron-poor dienophiles, which has been explained based on frontier molecular orbital (FMO) theory.^{3a} To enhance the conversion as well as the stereoselectivity of thermally initiated organocatalytic Diels–Alder reactions, different strategies have been developed. Evans' group established oxazolidinones as chiral organic auxiliaries which sterically hindered the attack of the diene on one face of the dienophile.^{3b} MacMillan and co-workers developed imidazolidinones as highly enantioselective chiral organocatalysts which form iminium species with enones. The iminium species lower the LUMO of the die-

nophile and sterically block one face from being attacked by the diene.^{3c} However, electronically mismatched coupling between dienes and dienophiles is highly challenging and requires strict conditions.^{1,2} These electronically mismatched D–A reactions can be achieved by the formation of radical cation intermediates from dienophiles *via* one electron oxidation by using stoichiometric oxidants such as aminium salts or by photo-initiated electron transfer (PET) with photosensitizers.^{4,5}

In contrast, visible-light-mediated radical cation generation from the electron-rich dienophile is more sustainable and does not require any stoichiometric oxidant (Fig. 1).⁶ Based on this, Yoon and co-workers developed a Ru complex which showed excellent reactivity towards electron-rich dienophiles under visible-light conditions.⁷ In this case the radical cation was generated by the Ru catalyst with the aid of visible-light and air/oxygen was utilized to turn over the catalyst. In fact, they also investigated metal-free photocatalysts, however their efforts were not successful.^{7a} Then, Shores' group and Ferreira's group developed Cr complexes under UV light irradiation.⁸ However, the Cr catalyst required a longer reaction time and an excess of diene (10 equiv.) to achieve full conversion.^{8b}

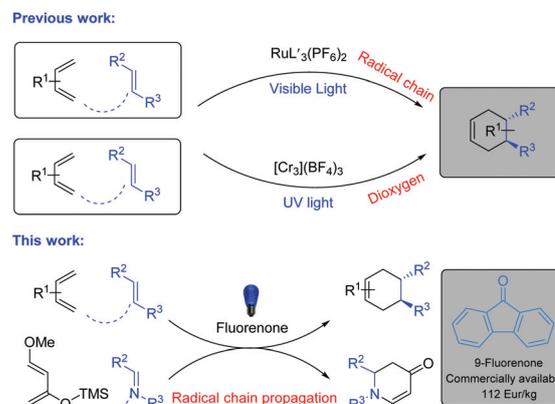


Fig. 1 Homogeneous catalysts for photocatalytic D–A reactions of electron-rich dienophiles.

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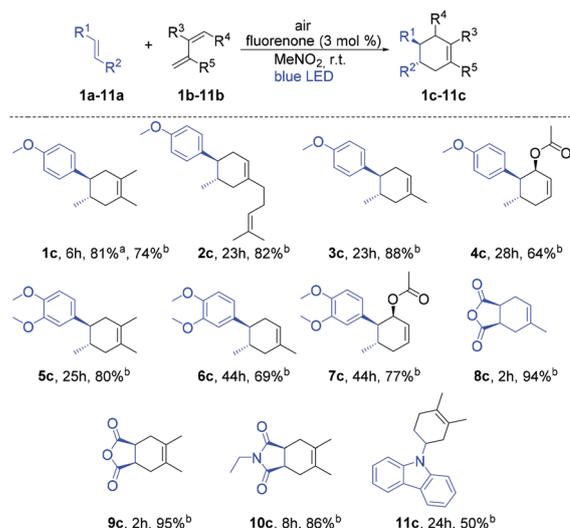


Parallel to the D–A reactions, aza-Diels–Alder reactions are also efficient and powerful approaches for the syntheses of N-heterocycles in a straightforward way.⁹ With the same concept of the generation of radical cation intermediates from electron-rich dienophiles, iminium ions can be generated from imines with the aid of visible light.⁶ Based on this, Zhang, Arai and Ohkuma groups developed visible-light-promoted aza-Diels–Alder reactions with Ru and Cr catalysts.¹⁰ It should be noted that in all the cases of visible-light-mediated D–A or aza-D–A reactions, only transition metal based photocatalysts exist. In contrast, organic dyes are commercially available, cheaper in price, non-toxic in nature and are an interesting avenue to explore.¹¹ Based on all the above information and in continuation of our interest in metal-free catalysis, herein we describe an efficient metal-free homogeneous catalyst for visible-light-mediated Diels–Alder and aza-Diels–Alder reactions.¹²

Results and discussion

At the outset of our reaction, we focused on organic dyes which have a high oxidation potential (*e.g.* in the case of fluorenone +1.7 V *vs.* SCE)^{11a} to generate radical cations from *trans*-anethole (**1a**) (+1.1 V *vs.* SCE).^{7a} We started the optimization using *trans*-anethole (**1a**) as a dienophile and 2,3-dimethyl-1,3-butadiene (**1b**) as a diene under air (Table S1; see the ESI†). Eight different organic dyes were applied using nitromethane (MeNO₂) as the solvent and MgSO₄ as the desiccant under the irradiation of 12 W blue LED for 4 h. Among them, fluorenone showed 81% yield of the corresponding Diels–Alder product. Subsequently, other aprotic polar solvents such as THF, DMF, DMSO and ACN were investigated but did not show any improvement of the yield. Nitromethane was the best solvent in this reaction as aprotic polar solvents with a higher dipole moment at comparable polarities can solvate the formed radical cation intermediate which enhances the product formation.¹³

With these optimized reaction conditions in hand, we extended the scope of this metal-free system to other electron-rich dienophiles and dienes (Scheme 1; entries **1c–11c**). The formation of [4 + 2] cycloadducts proceeded smoothly using 2,3-dimethyl-1,3-butadiene as a diene and other electron-rich dienophiles such as myrcene, isoprene *etc.* (Scheme 1; entries **2c–4c**). In addition to these, 1,2-dimethoxy-4-propenylbenzene was also effectively explored as a dienophile with a series of dienes (Scheme 1; entries **5c–7c**). Furthermore, 2,5-furandione was also suitable in our system and generated corresponding cyclohexene derivatives in excellent yields in 2 h (Scheme 1; entries **8c–9c**). It should be noted that for 2,5-furandione, expensive metal-based catalysts are required to obtain the desired product.¹⁴ However, with our cheap and metal-free fluorenone catalyst, these cyclohexene derivatives can be achieved with excellent yields in only 2 h. Additionally, 9-vinylcarbazole was also capable of acting as a dienophile and gave **11c** with 2,3-dimethyl-1,3-butadiene as a diene.

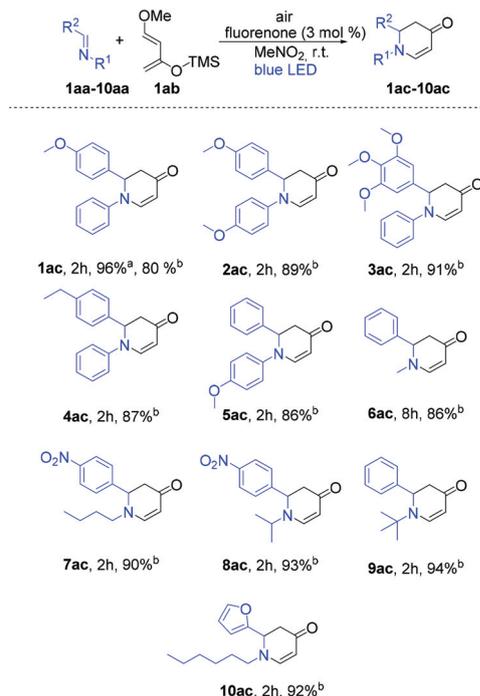


Scheme 1 Scope of the fluorenone-catalyzed Diels–Alder reactions under visible-light irradiation. Reaction conditions: Air, 12 W blue LED, dienophiles (0.5 mmol, 1 eq.), dienes (3 eq.), photocatalyst (3 mol%), 5 mL solvent, room temperature. ^aYield was determined by NMR yield using iodoform as an internal standard. ^bIsolated yields.

Inspired by the excellent reactivity of our catalyst in [4 + 2] cycloaddition reactions, we sought to apply these reaction conditions to aza-D–A reactions. Our main target was to synthesize important N-heterocycles in a straightforward way. For this purpose, we aimed to synthesize 2,3-dihydropyridin-4(1H)-one derivatives as these have wide applications for the treatment of emergent infectious diseases.¹⁵ Additionally, these compounds have been utilized for the syntheses of piperidine containing natural products and bioactive molecule synthesis.¹⁶ In general, syntheses of 2,3-dihydropyridin-4(1H)-one derivatives require either expensive metal based catalysts or a longer reaction time.¹⁷ Gratifyingly, fluorenone showed an excellent yield within 2 h when (*E*)-1-(4-methoxyphenyl)-*N*-phenylmethanimine (**1aa**) as a dienophile and Danishefsky's diene (**1ab**) were applied to synthesize 2-(4-methoxyphenyl)-1-phenyl-2,3-dihydropyridin-4(1H)-one (**1ac**) as the product (Table S2†). Different ratios of diene and dienophile were also investigated and to our delight, with ratio 2:1 the reaction proceeded smoothly with the formation of 96% of the desired product in 2 h.

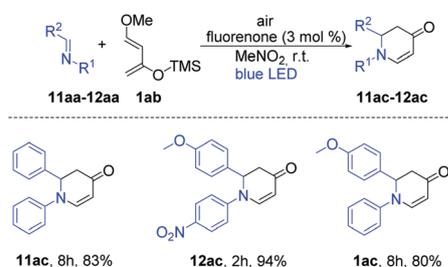
With these optimized reaction conditions, we applied the fluorenone catalyst to other imines to obtain diverse 2,3-dihydropyridin-4(1H)-one derivatives (Scheme 2). Various electron-rich imines showed high reactivities with the formation of desired products in 2 h up to 96% yield. The catalyst showed high tolerance towards alkyl, aryl and heteroaryl substituents (Scheme 2; entries **2ac–10ac**). Additionally, six new 2,3-dihydropyridin-4(1H)-one derivatives have been synthesized whose biological activities should be further investigated considering the promising lead compounds against human infectious diseases (Scheme 2; entries **3ac–4ac**, **7ac–10ac**).¹⁶ Expediently, with this fluorenone catalyst, we have been able to synthesize previously



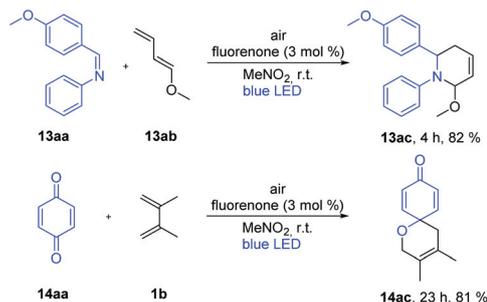


Scheme 2 Scope of the fluorenone-catalyzed aza-Diels–Alder reactions under visible light irradiation. Reaction conditions: Air, 12 W blue LED, imines (0.10 mmol, 1 eq.), diene (2 eq.), photocatalyst (3 mol%), 5 mL solvent, room temperature. ^aYield was determined by NMR yield using iodoform as an internal standard. ^bIsolated yields.

reported bioactive derivatives which were evaluated *in vitro* against a wide spectrum of viruses (Scheme 3; entries **11ac**, **11ac–12ac**).^{15a} The scope of the fluorenone-catalyzed aza-Diels–Alder reaction was not only limited to the synthesis of 2,3-dihydropyridin-4(1*H*)-one derivatives but also applied to synthesize other important heterocycles (Scheme 4). For example, when the Danishefsky's diene was replaced by 1-methoxy-1,3-butadiene, it generated a 1,2,3,6-tetrahydropyridine derivative (Scheme 4; entry **13ac**). In addition to this, 2,3-dimethyl-1,3-butadiene reacted with 1,4-benzoquinone to generate 3,4-dimethyl-1-oxaspiro[5.5]undeca-3,7,10-trien-9-one (Scheme 4; entry **14ac**).



Scheme 3 Syntheses of bioactive derivatives using the fluorenone catalyst. Reaction conditions: Air, 12 W blue LED, imines (0.10 mmol, 1 eq.), diene (2 eq.), photocatalyst (3 mol%), 5 mL solvent, room temperature.



Scheme 4 Fluorenone-catalyzed hetero-Diels–Alder reactions under visible light irradiation. Reaction conditions: Air, 12 W blue LED, imine or 1,4-benzoquinone (0.10 mmol, 1 eq.), dienes (2 eq.), photocatalyst (3 mol%), 5 mL solvent, room temperature.

Considering the broad scope of this catalyst, we sought to enquire the role of the catalyst, air, and light source in this reaction. Control experiments showed no product formation in the absence of light or the photocatalyst (see the ESI[†]). Notably, 60% yield was achieved under nitrogen, which clearly indicates that there is a chain propagation mechanism similar to the earlier report on Ru complexes.^{7a} Singlet oxygen in the air acts as an indispensable electron mediator which further increases the yield. Furthermore, the effect of different quenchers was investigated to recognize the reactive oxygen species from air and possible intermediates (Table 1).^{11c–e} When 2,6-di-*tert*-butyl-4-methylphenol (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) were added to the reaction mixture, the reaction was completely inhibited, which proved a radical pathway. Furthermore, the addition of CuCl₂ to the reaction mixture showed lower yields, which showed the involvement of single electron processes in this photocatalytic system. The addition of sodium azide also showed a decreased yield, indicating the involvement of singlet oxygen, or activated oxygen species.

To acquire further information about the reaction mechanism, Stern–Volmer quenching experiments were carried out (see the ESI[†]). The excited state of the photocatalyst was quenched by *trans*-anethole.¹⁸ As shown in Fig. S3,[†] a clear

Table 1 Quenching experiments for fluorenone catalyzed cyclo-addition reactions

Quencher	Equivalents	Yield [%]	Scavenger for
BHT	1.0	0	Radical
TEMPO	1.0	0	Radical
CuCl ₂	1.0	73	Single electron
NaN ₃	1.0	63	Singlet oxygen

Reaction conditions: Air, 12 W blue LED, 0.5 mmol dienophiles (1 eq.), 1.5 mmol dienes (3 eq.), photocatalyst (3 mol%), 5 mL solvent, room temperature.



decrease of light emission was observed with the increasing concentration of *trans*-anethole (**1a**) and no change was observed with different concentrations of 2,3-dimethyl-1,3-butadiene.

Combining all the mechanistic experiments, we have been able to propose the mechanism for visible-light-mediated D–A and aza-D–A reactions in Fig. 2. At first, the photocatalyst was excited to the photo-excited state by the irradiation of visible light and underwent a single electron transfer (SET) with *trans*-anethole (**1a**). In fact the redox potential value of the catalyst (+1.7 V vs. SCE)^{11a} is enough to oxidize **1a** (+1.1 V vs. SCE).^{7a} The resulting radical cation **1a**^{•+} reacted with the diene *via* [4 + 2] cycloaddition to afford the radical cation product **1c**^{•+}. This product **1c**^{•+} accepted one electron mainly from another equivalent of **1a** in a chain propagation step to form the final product (**1c**).^{7a} Meanwhile, oxygen will also be involved partly in electron donation. Here the role of air/oxygen was to turn over the reduced photocatalyst to the original state. The reported value for the reduction potential of the excited-state fluorenone resides at –0.61 V vs. SCE,^{11d} which is sufficient for the reduction of molecular oxygen to its superoxide radical form (O₂/O₂^{•-}) with the reduction potential residing at –0.56 V vs. SCE.¹⁹

The [2 + 2] cycloaddition also proceeded well *via* SET with the product **1a**^{•+} in the absence of diene.²⁰ In fact, cyclobutane derivatives have wide applications in natural product syntheses and many of them already have become promising candidates as anticancer, antiviral and antifungal drugs.^{20b} Additionally, lignan and neolignan type compounds also contain a cyclobutane motif (Scheme 5a).^{20b} Based on all this information, we applied the fluorenone catalyst to promote [2 + 2] cycloaddition reactions to obtain cyclobutane derivatives (Scheme 5b; entries **1d–2d**). To our delight, the catalyst not only showed the activity for the homodimerization of alkenes (**1d**) but also showed an excellent reactivity towards the heterodimerization of alkene (**2d**).

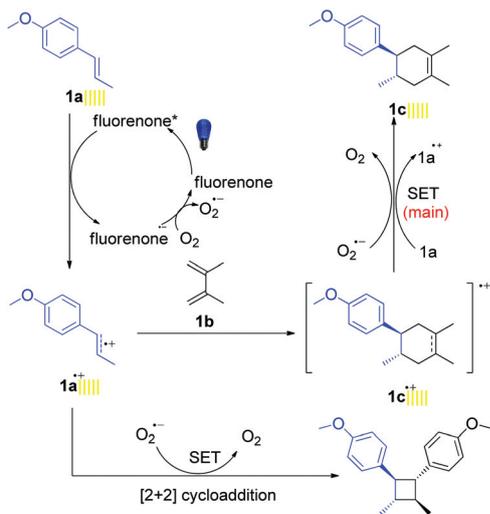
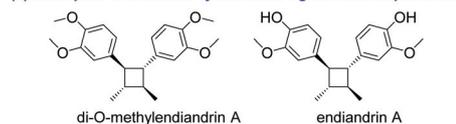
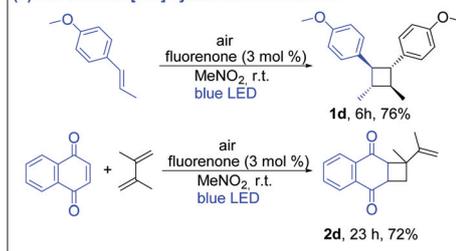


Fig. 2 Proposed reaction mechanism for the fluorenone catalyzed Diels–Alder reactions.

(a) Examples of bioactive cyclobutane lignan natural products



(b) Our work on [2+2] cycloaddition reactions



Scheme 5 (a) Examples of bioactive cyclobutane lignan natural products. (b) Our work on [2 + 2] cycloaddition reactions. Reaction conditions: Air, 12 W blue LED, dienophiles (0.5 mmol, 1 eq.), dienes (3 eq.), photocatalyst (3 mol%), 5 mL solvent, room temperature.

Conclusions

In summary, we have developed fluorenone as a metal-free catalyst for visible-light-mediated cycloaddition reactions. This catalyst is very cheap and commercially available and has shown excellent substrates scope for [4 + 2] and [2 + 2] cycloaddition reactions with electron-rich dienophiles. In addition, we have been able to synthesize bioactive molecules *via* aza-Diels Alder reactions. We believe this protocol can be further applied and extended for the syntheses of pharmaceuticals and natural products. Additionally, detailed mechanistic studies revealed the role of the catalyst and oxygen and led to the proposed mechanism of this reaction.

Conflicts of interest

There are no conflicts to declare.

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