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# Oxyamination of Alkenes Enabled by Direct Photoexcitation of Fluorenone Oxime Derivatives

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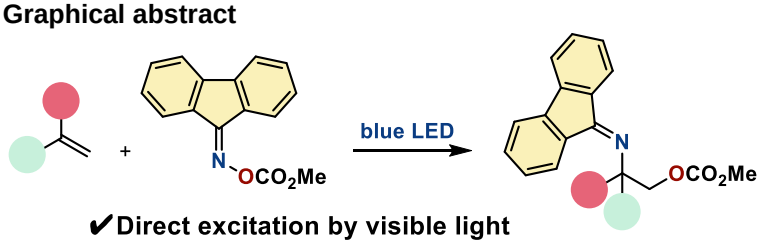
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## Abstract

Visible-light-induced oxyamination of alkenes was developed using fluorenone oxime carbonate as a photoactivatable agent. The nitrogen atom was selectively incorporated at the internal position, constructing a sterically congested α-tertiary amine moiety. The reaction proceeded without any photocatalyst and in the presence of various additives with different functional groups, highlighting the simplicity and robustness of the protocol. Moreover, the fluorenone oxime motif proved effective for visible-light-induced decarboxylative carboamination and diamination of alkenes.

*Keywords*: aminoalcohol, photoexcitation, alkene

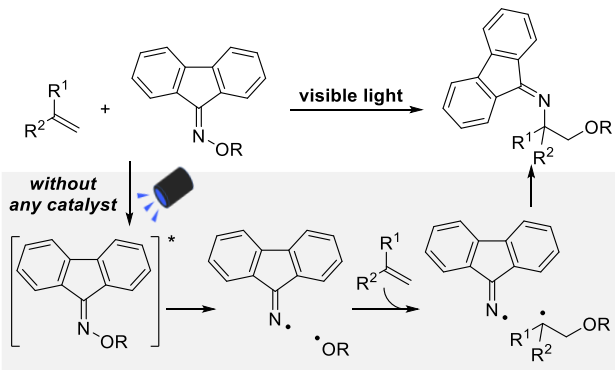
## Graphical abstract




The 1,2-aminoalcohol moiety is a privileged motif in organic chemistry, present in miscellaneous molecules including pharmaceuticals, agrochemicals, and other biologically relevant compounds. Over the past decades, numerous synthetic methods have been developed to access this valuable structure.[1] Among these methods, the oxyamination of alkenes is one of the most powerful approaches, enabling rapid construction of the 1,2-aminooxy structure from readily available alkenes by simultaneously installing an oxygen atom and a nitrogen atom on either side of the double bond. Since the groundbreaking work of Sharpless on osmium-catalyzed hydroxyamination of alkenes,[2] transition metals have played a pivotal role in this field.[3] In addition, visible-light-induced radical reactions using either photoredox catalysts[4] or energy transfer catalysts[5] have recently gained significant attention. Upon visible light irradiation, a photoredox catalyst induces single electron reduction of a specifically designed redox-active reagent, producing a nitrogen radical or oxygen radical. This radical reacts with an alkene, followed by single electron oxidation of the resulting carbon radical to install the other functional group. This method usually generates stoichiometric waste derived from the redox-active reagents. In contrast, energy transfer catalysis, using benzophenone oxime carbonate derivatives as reagents, is particularly effective in incorporating all the atoms of the reagents into the products. Energy transfer from the photo-excited sensitizer to the oxime esters induces homolytic cleavage of the labile N–O bond, generating both iminyl and oxyl radicals, which are then trapped by alkenes.

We previously reported visible-light-induced aminochlorination of alkenes using *N*-chloro-fluorenone imine.[6] The reaction circumvented the use of any photocatalyst by leveraging direct photoexcitation of the *N*-chloro-fluorenone imine with blue LED irradiation. Since the fluorenone imine scaffold was responsible for the direct photoexcitation, we envisioned that the photocatalyst-free method could be extended to related fluorenone oxime derivatives, where a labile N–O bond homolysis might occur upon visible-light irradiation (Scheme 1). Herein, we developed an oxyamination of alkenes using a fluorenone oxime carbonate. The reaction proceeded efficiently with blue LED irradiation without the need for a photocatalyst. The fluorenone oxime scaffold also proved capable of

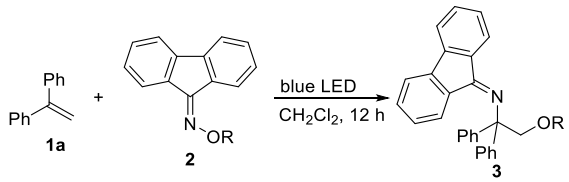
promoting carboamination and diamination by incorporating decarboxylation processes during radical generation.




**Scheme 1.** Working hypothesis for oxyamination of alkenes with a fluorenone oxime derivative.

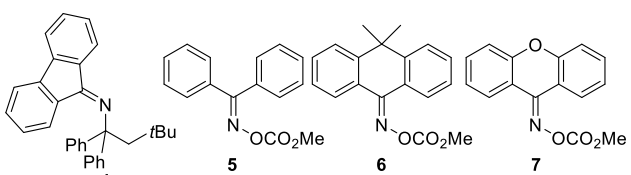
Investigation of the *O*-substituent of fluorenone oxime was performed with 1,1-diphenylethylene (**1a**) as a substrate in $CH_2Cl_2$ under blue LED ($\lambda_{max}$ = 460 nm) irradiation conditions (Table 1). To our delight, oxime carbonates were reactive, affording oxyamination products with the carbonate group at the terminal position and the fluorenone imine group at the internal position (entries 1 and 2). The alkyl group of the oxime carbonates affected the yields, with the methyl group (entry 1, **2a**, 70%) being superior to the benzyl group (entry 2, **2b**, 32%). Although dioxygenation or diamination was expected as the primary side reactions, no notable formation of such products was observed. Attempts to isolate any side products were in vain due to the generation of miscellaneous unidentified products including insoluble materials. These outcomes indicate the high reactivities of the radical intermediates, which likely result in various side reactions. Other carbonyl-based substituents were not effective. Oxime carbamate **2c** (entry 3) was unreactive, with a significant recovery of unreacted **2c**, suggesting low efficiency in the homolytic cleavage of the N–O bond. When oxime ester **2d** was used, the corresponding oxyamination product was not obtained. Instead, a carboamination product **4** was obtained in 31% yield, possibly via *tert*-butyl radical generation through decarboxylation (entry 4). In contrast, the reaction became considerably complex and unmanageable with benzoyl-type oxime ester **2e** (entry 5). Oxime carbonates derived from benzophenone **5** (0% yield), 10,10-dimethylanthracenone **6** (0% yield), and xanthone **7** (13% yield) were not effective, highlighting the importance of the fluorene scaffold.

**Table 1.** Optimization of *O*-substituent of fluorenone oxime **2**.[a]




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

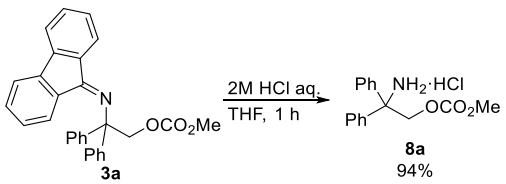
| entry | R | **3**[b] (%) |
|---|---|---|
| 1 | $CO_2Me$ (**2a**) | 70 (63) |
| 2 | $CO_2Bn$ (**2b**) | 32 |
| 3 | $CONMe_2$ (**2c**) | trace |
| 4 | $CO$*t*Bu (**2d**) | 0 |
| 5 | COPh (**2e**) | - |



**4** **5** **6** **7**

[a]**1a** (0.1 mmol), **2** (0.2 mmol), $CH_2Cl_2$ (0.05 M), 12 h. [b]Yields were determined by $^1$H NMR analysis using triphenylmethane as an internal standard. Yield of the isolated product is reported in parentheses.

To obtain a synthetically versatile primary amine, hydrolysis of **3a** was explored (Scheme 2). The desired reaction proceeded smoothly under aqueous HCl conditions, providing **8a** in 94% yield.




**3a** **8a** 94%

**Scheme 2.** Hydrolysis of oxyamination product.

The UV-Vis spectra of oxime derivatives (Fig. 1) confirmed that the fluorenone oxime moiety is a competent scaffold for photoexcitation under blue LED irradiation conditions, regardless of the oxygen substituent. Regarding other oxime derivatives, benzophenone and anthracenone carbonates (**5** and **6**) were unable to absorb the light, while the absorption of the xanthone oxime carbonate **7** slightly overlapped with the emission wavelength of the LED.

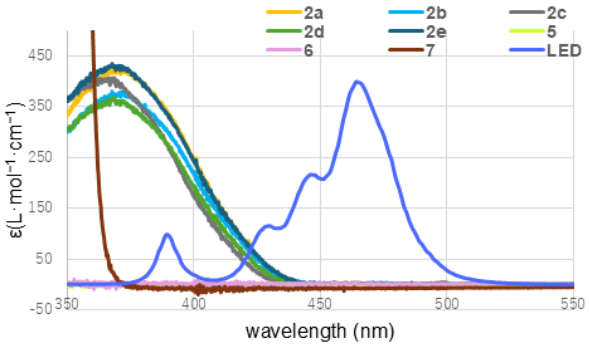
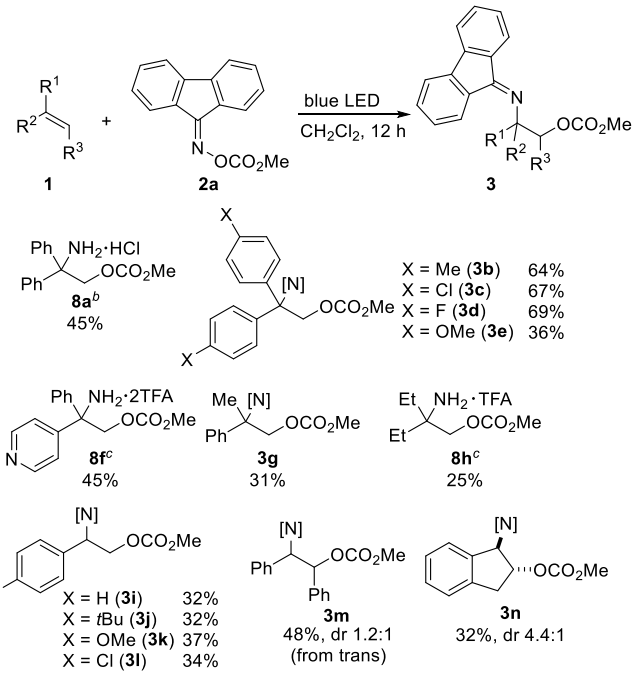



**Fig. 1.** UV-Vis spectra of oxime derivatives and emission spectra of blue LED. UV-Vis spectra of oxime derivatives in $CH_2Cl_2$ (0.1 mM).

With the optimized conditions in hand, the scope of the reaction was assessed (Table 2). The 1 mmol scale reaction of **1a** proceeded, and the HCl salt of free amine **8a** was obtained in 45% yield by successive hydrolysis with HCl in THF/$H_2O$. 1,1-Diphenylethylene derivatives bearing *para*-substituents (**1b**-**1e**) were competent substrates, constructing sterically congested α-tertiary amine motifs. Substrates with *para*-methyl (**1b**) and *para*-halogen (**1c**, **1d**) substituents were compatible to afford the corresponding products in good yields (**3b**, 64%; **3c**, 67%; **3d**, 69%). An electron-donating *para*-methoxy substituent (**1e**), however, decreased the yield to 36%. A pyridine group was tolerated, and the TFA salt of the free amine **8f** was isolated in 45% yield after hydrolysis of the imine moiety, followed by purification with HPLC. Although the reactivity was lower than 1,1-diarylethylenes, α-methylstyrene (**1g**) was applicable (**3g**, 31%). The reaction of 2-ethylbutene (**1h**), bearing no aryl substituent, proceeded, and **8h** was isolated in 25% yield after hydrolysis. Styrene derivatives were also reactive, giving α-secondary amines in moderate yields (**3i**, 32%; **3j**, 32%; **3k**, 37%; **3l**, 34%). *para*-Methoxy substituent (**1k**) did not adversely affect the yield in this case. As an internal alkyne, *trans*-stilbene (**1m**) was applicable, and **3m** was obtained in 48% yield with 1.2:1 diastereoselectivity. A cyclic alkene, indene (**1n**), produced **3n** in 32% yield with 4.4:1 diastereoselectivity.

To assess the functional group tolerance of the reaction, we applied Ohshima's evaluation method using a functional group evaluation kit (FGE-kit).[8] The FGE-kit contains 26 compounds bearing various functional groups with a chlorophenyl group as a common motif. All experiments were conducted twice, and the average yields of **3d**, along with the recovered yields of the additives, were summarized using three icons, green, yellow, and red, to indicate the influence of the additives (Table 3). Green icons indicate that the yield of **3d** or the recovered yield of the additive was comparable to the control experiments. Yellow icons indicate a statistically meaningful decrease in yield, but still more than half of the average of the control

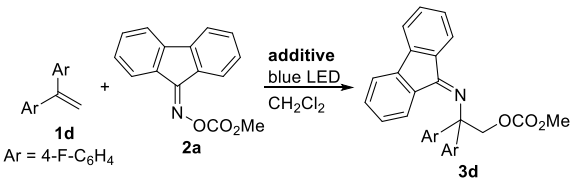
**Table 2.** Substrate scope.[a]




[a]**1a** (0.1 mmol), **2** (0.2 mmol), $CH_2Cl_2$ (0.05 M), 12 h. Yields of isolated products. Diastereomeric ratios were determined by the $^1$H NMR analyses of the crude materials. [b]1 mmol scale reaction. Product was isolated after hydrolysis of the imine by HCl in THF/$H_2O$. [c]After hydrolysis of the imine by HCl in THF/$H_2O$, the products were purified by reversed-phase HPLC using a C18 column with 0.1% TFA aq./MeCN eluent.

**Table 3.** Functional group tolerance assessment.[a]

experiments. Red icons are used for results with yields lower than half of the control experiments. First, the reaction with 1-chloro-4-methylbenzene **A0** was conducted to confirm that the chlorophenyl group had no undesired effect on the reaction outcome. The reaction proceeded without meaningful impact on the yield of **3d** in the presence of a broad range of additives (12 additives showing green icons for the yield of **3d**), including an aliphatic carboxylic acid **A1**, an alcohol **A2**, an amide **A6**, an epoxide **A14**, and a potentially reactive alkyne **A11**. A statistically meaningful decrease in yields, although marginal, was observed with seven additives (yellow icons for the yield of **3d**). Notably, the presence of the aliphatic alkene **A10** did not cause a significant decrease in **3d** production. Meanwhile, the presence of electron deficient alkene **A15** decreased the yield of **3d** to 55%. Although $^1$H NMR analysis of the crude mixture did not indicate the presence of any particular side product derived from **A15**, an independent reaction between **2a** and **A15** demonstrated that oxyamination of **A15** is feasible. This suggests that **A15** could compete with **1d** to capture a radical species generated from **2a** in the reaction mixture, resulting in suppression of **3d** formation. The reaction was completely suppressed by the addition of naphthol **A13**. Instead of




± Comparable to the control

— Statistically significant reduction, equivalent to, or greater than half of the average of the control

X Statistically significant reduction, less than half of the average of the control

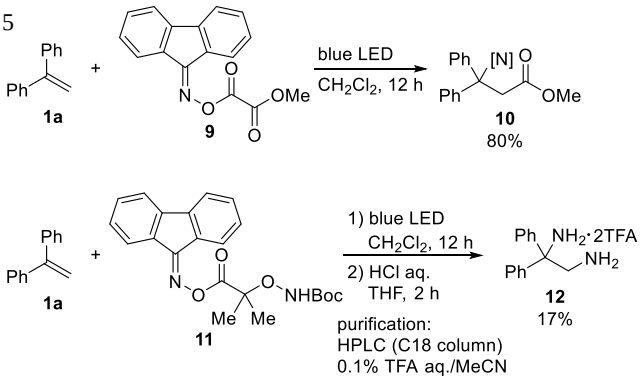
$Ar^1$ = 4-Cl-$C_6H_4$

| additive | **3d** (%) | recovered additive (%) |
|---|---|---|
| none | 89 | - |
| **A0** | 84 | >99 |
| **A1** | 81 | 96 |
| **A2** | 85 | 88 |
| **A3** | 87 | >99 |
| **A4** | 72 | 96 |
| **A5** | 75 | 66 |
| **A6** | 79 | >99 |
| **A7** | 0 | - |
| **A8** | 78 | >99 |
| **A9** | 77 | 90 |
| **A10** | 71 | 64 |
| **A11** | 79 | 95 |
| **A12** | 74 | 90 |
| **A13** | 0 | 0 |
| **A14** | 82 | >99 |
| **A15** | 55 | 61 |
| **A16** | 92 | >99 |
| **A17** | 69 | - |
| **A18** | 87 | - |
| **A19** | 0 | 0 |
| **A20** | 84 | >99 |
| **A21** | 0 | 42 |
| **A22** | 27 | 10 |
| **A23** | 79 | >99 |
| **A24** | 78 | >99 |
| **A25** | 11 | 46 |
| under air | 78 | - |

[a] **1d** (0.1 mmol), **2a** (0.2 mmol), additive (0.1 mmol), $CH_2Cl_2$ (0.05 M), 12 h. Yields were determined by $^1$H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

producing **3d**, two major products which did not contain any fragment of alkene **1d** were detected, indicating the high reactivity of the naphthol as a radical acceptor. Efforts to isolate and identify these products are ongoing. The addition of thiol **A19** also inhibited the oxyamination. Despite the full consumption of **A19**, no significant side product could be isolated. In addition to these, the reaction seems to be susceptible to electron-rich NH functional groups (**A7**, **A21**, **A22**), while amide **A6** and Boc-protected amine **A24** were compatible. Although $^1$H NMR of the crude mixture showed signs of a side product derived from indole **A21**,[9] isolation of the corresponding compound was unsuccessful. In the presence of sulfide **A25**, the reaction was significantly inhibited, with a new peak at 3.46 ppm ($J$ = 3.6 Hz) appearing. Identification of this product is currently in progress. Besides the evaluation of functional group tolerance using the FGE-kit, the influence of oxygen, a typical triplet quencher, was tested by conducting the reaction under air. Although the yield of **3d** dropped slightly to 78%, the decrease was only moderate compared to the significant decrease observed in the reported method involving an energy transfer catalyst.[5a] The marginal tolerance to the oxygen is likely due to the direct excitation of **2a**, which circumvents intermolecular energy transfer from the excited photocatalyst to the oxime derivative. Subsequent N–O bond homolysis, an intramolecular process, would outcompete intermolecular energy transfer to oxygen.

The visible-light-induced N–O cleavage of fluorenone oxime derivatives could be extended to efficient carboamination using **9** as a reagent (Scheme 3).[9,10] Photoinduced N–O cleavage of **9** and subsequent decarboxylation was expected to generate an iminyl radical and a carbon radical for the carboamination. Indeed, the reaction of **1a** and **9** proceeded smoothly under blue LED irradiation, yielding **10** in 80% yield, with the imine moiety at the internal position. In addition, diamination of **1a** was possible using **11**, in which generation of the iminyl radical and an amidyl radical was conceived by consecutive decarboxylation and extrusion of acetone.[11] Since the crude material showed sluggish $^1$H NMR and the isolation of the product was not possible at this stage, hydrolysis of the fluorenone imine moiety and cleavage of the Boc group under acidic conditions were carried out successively. As a result, the TFA salt of diamine **12** was obtained in 17% yield by HPLC purification.




**Scheme 3.** Carboamination and diamination. **1a** (0.1 mmol), **9** or **10** (0.2 mmol), $CH_2Cl_2$ (0.05 M), 12 h. Yields of isolated products.

To gain the mechanistic insights, DFT calculations were conducted for the reaction between **1a** and **2a** using the Gaussian 16 C.01 package[12] at the UωB97X-D/6-31+G(d,p) level of theory with the solvation model (SMD: dichloromethane) and "guess=mix" keyword (Fig. 2). The photoinduced homolytic cleavage of N–O bond was assessed (Fig. 2a). The N–O bond of **2a*** **(triplet)**, which is generated through photoexcitation and intersystem crossing, is oriented perpendicular to the π-plane of the fluorene backbone, and the N–O homolysis proceeded through **TS1** with a small barrier of 8.3 kcal/mol, producing an *N*-centered iminyl radical **A** and a oxyl radical **B** in an exergonic process. The addition of the oxyl radical **B** to **1a** proceeds in a barrierless manner to produce $\beta$-oxy-benzyl radical **C**. In contrast, the addition of the iminyl radical **A** requires 21.2 kcal/mol to afford an aminomethylated benzyl radical **D**. The considerable energy barrier for the iminyl radical addition is consistent with the observation of complete regioselectivity of the reaction, incorporating oxygen atom at the terminal position.

Regarding the incorporation of the imine moiety, we examined two pathways (Fig. 2b): radical-radical coupling between the benzyl radical **C** and the iminyl radical **A** (path a), and addition of **C** to **2a** followed by elimination of oxyl radical **B** for a chain reaction (path b). For the path a, we failed to locate a transition state as expected due to the general difficulty of computations for radical-radical coupling processes. In path b, the transition state (**TS2**) for the addition of **C** to **2a** is 28.8 kcal/mol higher in Gibbs free energy relative to **C**. Subsequent elimination of the oxyl radical **B** from a fluorenyl radical **E** requires only 13.5 kcal/mol to propagate a radical chain process. Considering the high reactivity of the radical-radical coupling (path a) alongside the relatively high energy barrier for the addition of benzyl radical to the oxime (path b), it suggests that path a would likely be the operative pathway in this reaction.

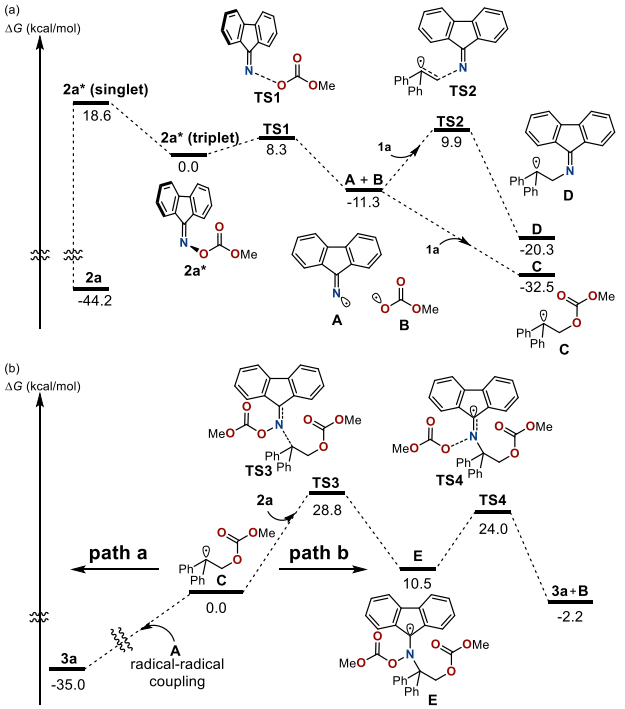



**Fig. 2.** Energy diagrams for the oxyamination.

In summary, we have developed a visible-light-induced oxyamination of alkenes using fluorenone oxime derivative **2a**. Photoexcitation of **2a**, without any photocatalyst, induced homolytic cleavage of the N–O bond, producing 1,2-aminoalcohol derivatives with a nitrogen atom at the internal position. Extensive assessment of functional group tolerance using the FGE-kit revealed the robustness of the reaction. In addition, the fluorenone oxime motif proved effective for carboamination and diamination, demonstrating its versatility as a platform for visible-light-induced aminodifunctionalization of alkenes.


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## Supplementary data

Supplementary material is available at *Chemistry Letters*


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*Conflict of interest statement.* None declared.

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