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Tuning Triplet Energy Transfer of Hydroxamates as the Nitrene Precursor for Intramolecular C(sp³)-H Amidation

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ABSTRACT: Reported herein is the design of a photosensitization strategy to generate triplet nitrenes and its applicability for the intramolecular C–H amidation reactions. Substrate optimization by tuning physical organic parameters according to the proposed energy transfer pathway led us to identify hydroxamates as a convenient nitrene precursor. While more classical nitrene sources, representatively organic azides, were ineffective under the current photosensitization conditions, hydroxamates which are readily available from alcohols or carboxylic acids are highly efficient in accessing synthetically valuable 2-oxazolidinones and γ -lactams by visible light. Mechanism studies supported our working hypothesis that the energy transfer path is mainly operative.

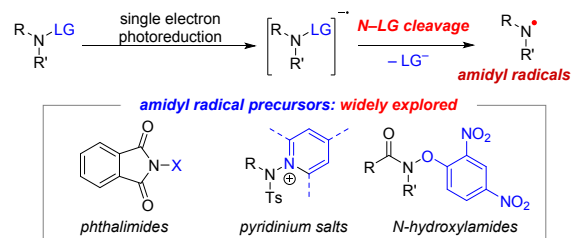
Introduction

Nitrogen-centered reactive intermediates such as amidyl radicals and nitrenes have attracted an increasing interest mainly due to their potential applicability in the construction of C–N bonds.^{1–4} In this context, the development of new synthetic approaches to generate these reactive N-centered intermediates more selectively by identifying effective precursors has been highly desired. Recent advances in visible-light photoredox catalysis allowed for the selective generation of amidyl radicals, and their subsequent amination reactivity toward various substrates has been widely explored.^{5–7} For example, single-electron photoreduction of N-acyloxy(halo)phthalimides,^{8,9} N-aminopyridinium salts^{10–13} and hydroxylamides^{14–18} gives rise to the corresponding amidyl radicals upon heterolytic cleavage of the leaving groups (Scheme 1a).

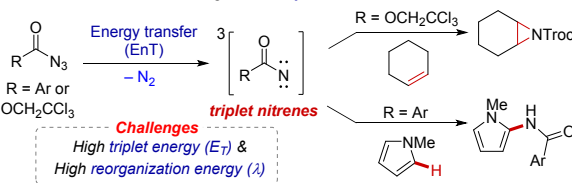
Photosensitization or energy transfer is an efficient strategy to activate ground state substrates into their triplet states.^{19,20} Pioneered by Bach^{21–23}, Yoon^{24–27} and Xiao,²⁸ this energy transfer approach was utilized to excite alkenes to enable elegant [2+2] cycloaddition reactions. More recently, Glorius and coworkers reported the photosensitization of disulfides to lead to sulfur radical species.²⁹ Oxime esters were known to be activated by the energy transfer to furnish iminyl radicals along with alkyl radicals.^{30–32} On the other hand, nitrenes can also be produced via energy transfer catalysis by employing azides^{33–36} or triazoles³⁷ upon release of molecular nitrogen (Scheme 1b). Given that azides are known to absorb UV light to undergo photodecomposition process leading to free organic nitrenes,^{38,39} Yoon and coworkers successfully demonstrated the viability of azide photosensitization. Indeed, by utilizing azidoformates as a triplet nitrene

Scheme 1. Photocatalytic approaches accessing amidyl radicals and nitrenes

(a) Photoredox catalytic approach generating **amidyl radicals**

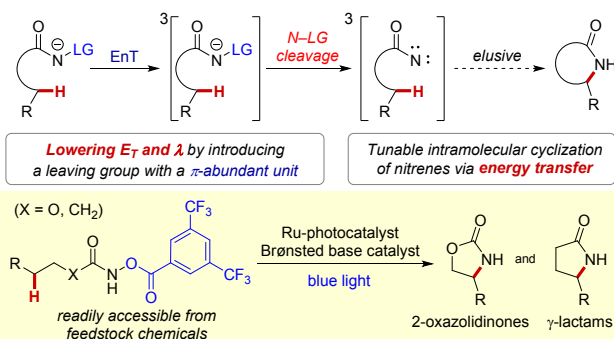


(b) Photosensitization of azides to generate **triplet nitrenes**



(c) **This work**

Identification of nitrene precursors enabling **photosensitized C(sp³)-H amidation**



precursor, aziridination reactivity toward alkenes was explored.³³ They also highlighted the energy transfer of vinyl azides for the formation of pyrrole rings.³⁴ In

addition, König and Brachet showcased the photosensitization of benzoyl azides to achieve C(sp²)-H amidation of heteroarenes³⁶ and olefin cycloaddition affording oxazolines.³⁵

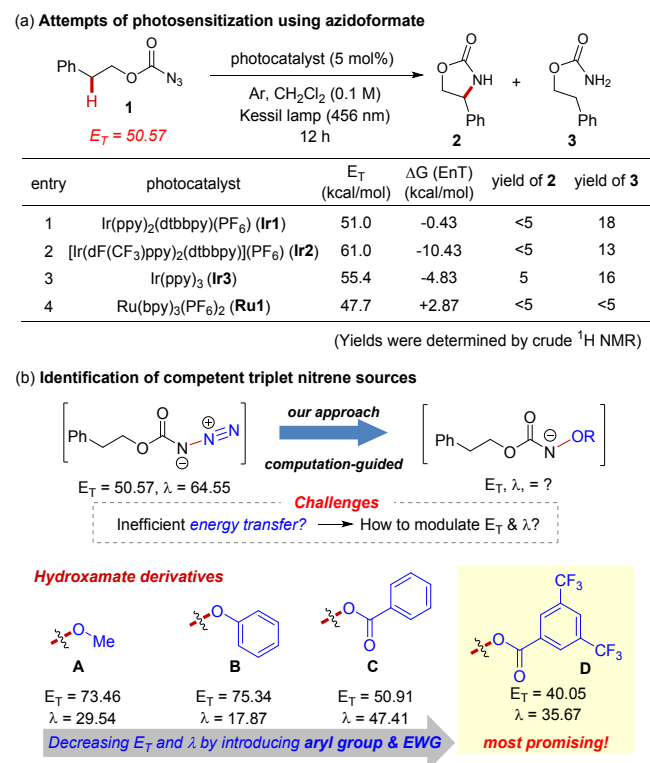
Despite this recent promise, since the azide photosensitization was found to be capricious to the nature of existing substituents, the reactivity of thus generated free organic nitrenes has been rather underexplored especially when compared to that of amidyl radicals. Low efficiency in the energy transfer is another issue often observed in certain azides, and this difficulty can be ascribed to the intrinsically high triplet energy (E_T) and/or reorganization energy (λ) of those azide substrates.

In this regard, we were encouraged to identify photosensitizable organic precursors for generating triplet nitrenes that can efficiently undergo C(sp³)-H amidation, eventually affording azacyclic products (Scheme 1c). Given that we and others recently revealed notable reactivity of metal-acylnitrenoids,⁴⁰⁻⁴⁷ it was highly interesting to examine the viability of the current energy transfer approach for the targeted intramolecular photosensitized C-H amidation reaction. In 1965, Lwowski and coworkers explored the reactivity of azides under UV irradiation, where free nitrenes were shown to undergo C-H amination albeit with low selectivity.^{38,39} Lu and coworkers recently reported the construction of 2-oxazolidinones from *N*-benzoyloxycarbamates using photoredox catalysis, and they proposed the intermediacy of amidyl radicals.¹⁸ To our best knowledge, an energy transfer pathway endowing the reactivity of organic nitrenes for the selective C(sp³)-H amidation has not been explored. Considering the fact that the previous reports were limited mainly to the photoactivation of azidoformates or benzoyl azides, we envisioned to newly explore triplet nitrene precursors to overcome the intrinsic challenges of azides for the photosensitization process. Guided by the combined computational and experimental studies, we identified hydroxamates as highly efficient and convenient sources to effectuate an intramolecular C(sp³)-H amination via energy transfer.

Results and Discussion

Identification of nitrene sources. Inspired by the previous work of Yoon,³³ we initially examined azidoformate **1** as a model substrate for the proposed photosensitization to obtain a cyclic carbamate **2** (Scheme 2a). When visible light was shined in the presence of iridium photocatalysts **Ir1** or **Ir2**, no desired oxazolidinone **2** was detected while carbamate byproduct **3** was observed to form in low yields (entries 1 and 2). In fact, Brown and coworkers previously observed the formation of amide when hexanoyl azide was photosensitized.⁴⁸ Interestingly, the use of homoleptic photocatalyst **Ir3** resulted in a small amount of oxazolidinone **2** (5%), but carbamate **3** was still major. Triplet energies of the above employed iridium photocatalysts are higher than that of **1**, thereby leading the photosensitization event to be exergonic. On the other hand, a ruthenium photocatalyst **Ru1** bearing smaller

Scheme 2. Identification of effective triplet nitrene precursors by combined experimental and computational studies



triplet energy was totally ineffective in converting the starting material (entry 4).

The observed inefficiency of azidoformate toward photoactivation was reasoned to originate from the incompatible triplet sensitization. To check this rationale, we subsequently computed the Marcus energy transfer parameters, triplet energy (E_T) and structural reorganization energy (λ), of the nitrene precursors, as they are critical to the overall energy transfer efficiency (Scheme 2b).²⁴⁻²⁷ The fact that **1** has a high singlet reorganization energy of 64.6 kcal/mol can be ascribed to the significant structural distortion of the azido moiety from linear to bent upon reaching its triplet state (see the supporting information for details). Moreover, since **1** possesses a relatively high triplet energy of 50.6 kcal/mol, the energy transfer to azidoformate is inefficient as experimentally observed (Scheme 2a). This result led us to envision to develop alternative types of triplet acceptors to enable the desired cyclization. In fact, there are several precedents showing the activation of hydroxamates via photoredox catalysis to generate amidyl radicals.¹⁴⁻¹⁸ In addition, hydroxamates were used as a metal nitrenoid precursor by the action of transition metal catalysts.⁴⁴⁻⁴⁹⁻⁵²

As summarized in Scheme 2b, it was calculated that the simplest hydroxamate **A** bearing a *N*-methoxy group exhibits higher triplet energy (E_T , 73.5 kcal/mol) compared to **1** but with lower reorganization energy (λ , 29.5 kcal/mol). *N*-Phenyl derivative **B** shows even smaller λ of 17.9 kcal/mol, yet, E_T is in a similar range. We further scrutinized the impact of a carboxylate leaving group (-

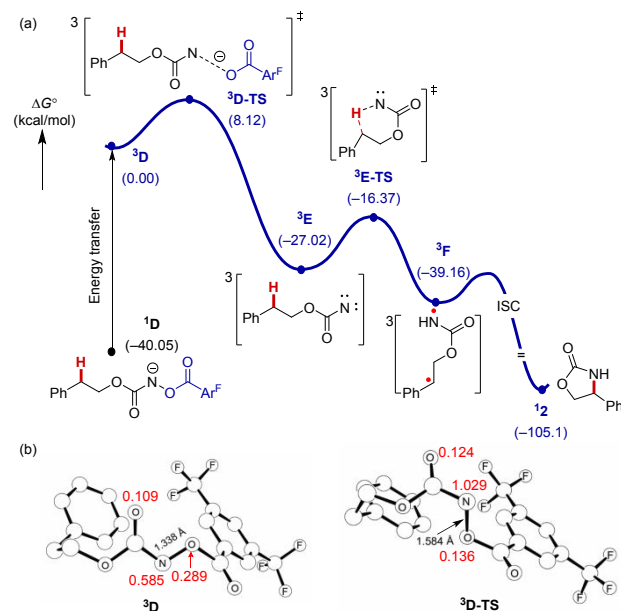


Figure 1. (a) Computed reaction pathway of the photosensitized triplet nitrene formation of ${}^3\text{D}$. (b) Structures and spin densities of ${}^3\text{D}$ and ${}^3\text{D-TS}$. $\text{Ar}^{\text{F}} = 3,5$ -bis(trifluoromethyl)phenyl; ISC = intersystem crossing.

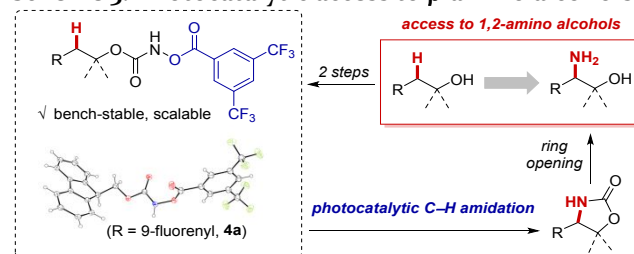
OR) and found that the introduction of a benzoyl substituent (C) decreases the triplet energy to 50.9 kcal/mol. Finally, it was found that the introduction of N-[3,5-bis(trifluoromethyl)benzoyl] group (D) decreases E_{T} to 40.1 kcal/mol with λ of 35.7 kcal/mol.

To check the viability of utilizing hydroxamates as an effective nitrene precursor toward the envisaged photosensitization, a plausible pathway was first evaluated with DFT calculations (Figure 1a). Once anionic hydroxamate ${}^1\text{D}$ is activated to its triplet state ${}^3\text{D}$, it can undergo an N–O bond cleavage by traversing the transition state ${}^3\text{D-TS}$ located at 8.1 kcal/mol to form triplet nitrene ${}^3\text{E}$ which will then induce a hydrogen atom transfer (HAT) with low barrier of 10.7 kcal/mol. A radical recombination is assumed to proceed finally to access the desired oxazolidinone product **2**.

The nature of N–O bond cleavage was further interrogated by analyzing the Mulliken spin density of ${}^3\text{D}$ and ${}^3\text{D-TS}$. Previous studies by the groups of Glorius^{30,31} and Cho³² suggested that N–O bond breaks homolytically when an oxime ester is sensitized into its triplet state.^{30–32} As illustrated in Figure 1b, our calculations revealed that the spin density of the nitrogen core is almost doubled from 0.59 to 1.03 during the bond cleavage event. On the contrary, the nitrogen-bonded oxygen atom of the benzoate decreases its spin density from 0.29 to 0.14, suggesting that the radical character shifts significantly to the nitrogen center. Hence, we concluded that the N–O cleavage of photosensitized hydroxamate (${}^3\text{D}$) is a heterolytic σ -bond cleavage. In contrast to the photosensitization of oxime esters affording iminyl radical,^{30–32} the activated hydroxamate would give a triplet nitrene releasing anionic benzoate. Indeed, an intrinsic reaction coordinate (IRC) analysis on ${}^3\text{D-TS}$ further

supported the formation of triplet nitrene ${}^3\text{E}$ (see the supporting information for detailed computations). On the other hand, an interconversion between the triplet nitrene ${}^3\text{E}$ and its singlet state ${}^1\text{E}$ could also be considered, while ${}^1\text{E}$ is higher than ${}^3\text{E}$ by 8.3 kcal/mol. And subsequent concerted C–H insertion from the presumed singlet nitrene ${}^1\text{E}$ was calculated to proceed with a low barrier of 3.0 kcal/mol (see the supporting information for details).

Scheme 3. Photocatalytic access to β -amino alcohols



Reaction development. The above computational studies suggest that our designed photocatalytic cyclization of hydroxamates would be highly plausible to access synthetically versatile 2-oxazolidinones. We, therefore, envisioned that the current approach can serve as a competent photocatalytic procedure eventually installing an amino group at the β -position of alcohols (Scheme 3).⁵³ Hydroxamate derivatives bearing the 3,5-bis(trifluoromethyl)benzoyl group are easy to prepare from the corresponding alcohols in 2 steps and they are bench-stable crystalline solid in most cases. The structure

Table 1. Optimization of reaction parameters^a

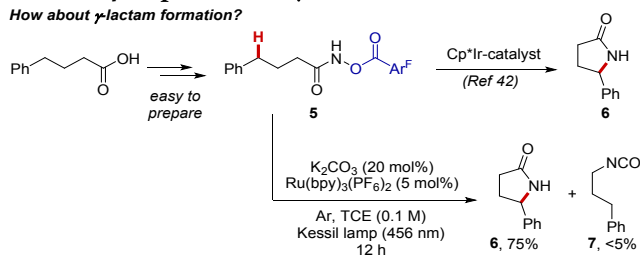
Entry	Change from standard conditions	2 (%)	RSM (%)
1	none	75 (70) ^b	<5
2	without K_2CO_3	<5	>95
3	without $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$	<5	>95
4	in dark condition	<5	>95
5	using 1 equiv of K_2CO_3 (6 h)	70	<5
6	0.05 M instead of 0.1 M	75	<5
7	under air	70	<5
8	CH_2Cl_2 instead of TCE	70	<5
9	CH_3CN instead of TCE	9	25
10	DMF instead of TCE	<5	47
11	using Penn reactor instead of Kessil lamp (450 nm, 3 h)	70	<5

^aReaction conditions: 0.1 mmol scale in a 4 mL glass vial and yields were based on ${}^1\text{H}$ NMR analysis of the reaction mixture using an internal standard (1,1,2-trichloroethane).

^bIsolated yield. TCE: 1,1,2,2-tetrachloroethane, RSM: Remaining starting material.

Scheme 4. Expansion to γ -lactam construction

How about γ -lactam formation?



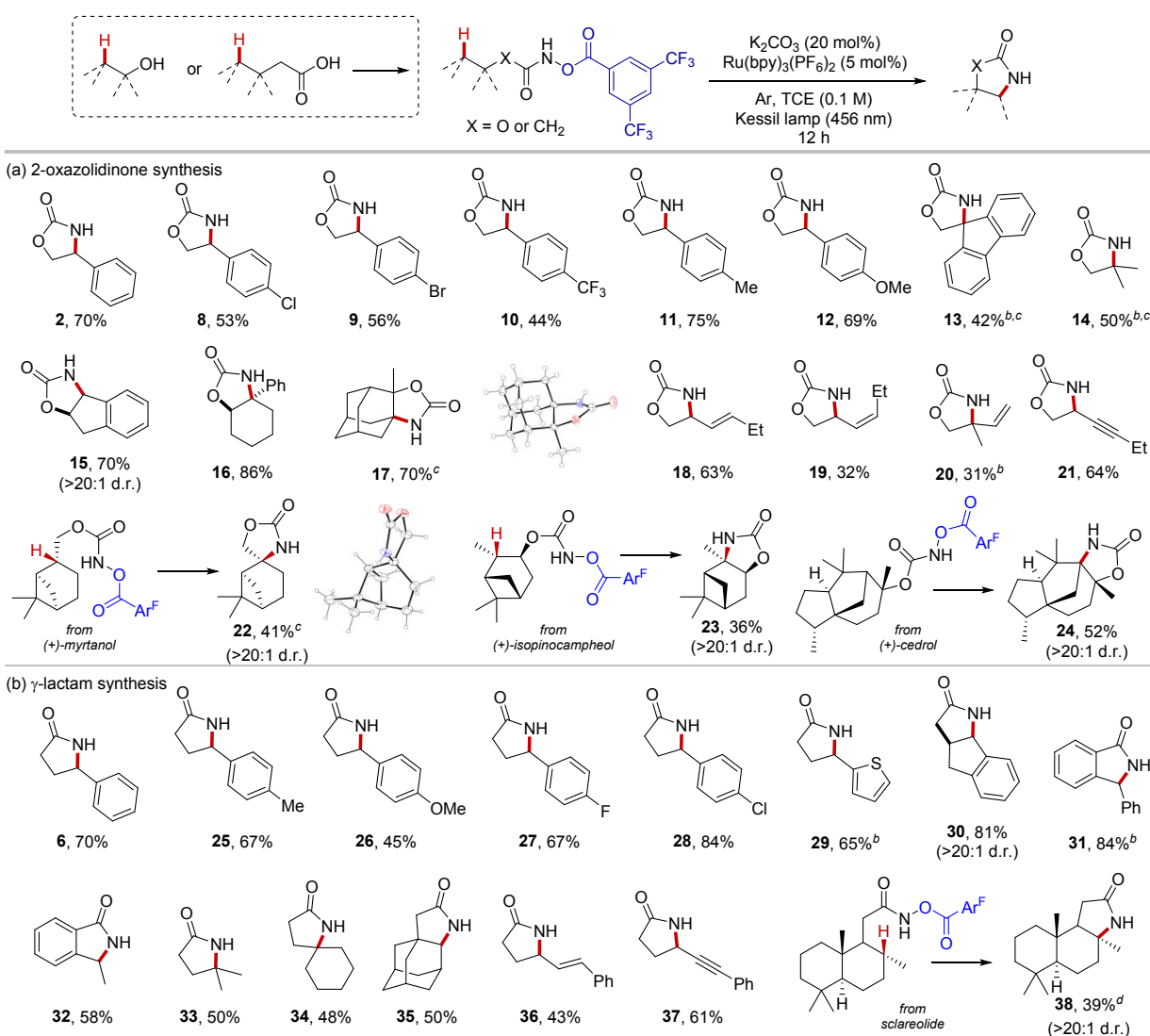
of one substrate **4a** was confirmed by an X-ray crystallographic analysis.

To validate our working hypothesis, we tested a model reaction of **4** using $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$ photosensitizer (**Ru1**, 5 mol%), which carries sufficient triplet energy of 47.7 kcal/mol (Table 1). *N*-Benzoyloxycarbamate **4** was found to cyclize smoothly to form the desired oxazolidinone product **2** in 75% yield upon irradiation of blue light (entry 1). While base was required to induce the reaction

presumably for the deprotonation of carbamate, the use of catalytic amounts was sufficient (20 mol% of powdered K_2CO_3 , entry 2), implying that the energy transfer occurs to anionic carbamate. Indeed, the triplet energy of neutral substrate **4** was calculated to be 71.4 kcal/mol, which is out of the regime that **Ru1** can sensitize. Starting material was remained intact either in the absence of photocatalyst or in dark (entries 3–4). When a stoichiometric amount of base was employed, the reaction proceeded slightly faster (entry 5). Concentration of the reaction solution was observed to be flexible (entry 6). On the other hand, the reaction turned out to be more sensitive to the choice of solvents: while 1,1,2,2-tetrachloroethane (TCE) or dichloromethane were optimal (entries 1 and 7), the use of polar media was less effective (entries 9–10). The cyclization took place with slightly lower efficiency by using a Penn photoreactor (entry 11).⁵⁴

With a promise accessing 2-oxazolidinone starting from *N*-benzyloxycarbamate **4** under the photosensitization

Table 2. Substrate scope of photosensitized construction of azacycles^a



^aIsolated yields. ^bPerformed with a Penn reactor (450 nm, 3 h). ^c1.0 Equiv of K_2CO_3 was used. ^d α,α,α -Trifluorotoluene was used as the solvent instead of TCE.

conditions, we were next wondered whether the present approach can also be applied toward γ -lactam formation from *N*-benzoyloxyamide which is easy to prepare from carboxylic acid (Scheme 4). Pleasingly, the standard reaction conditions also worked well for the intramolecular C–H lactamization and γ -lactam **6** was obtained in 75% yield with effective suppression of a byproduct, isocyanate (**7**) which can be formed by a Lossen rearrangement. While we recently reported a highly efficient Ir-catalyzed nitrene transfer protocol to provide **6** from the same starting material (**5**),⁴⁴ the current approach represents the first example of photocatalytic γ -lactam formation to our best knowledge.

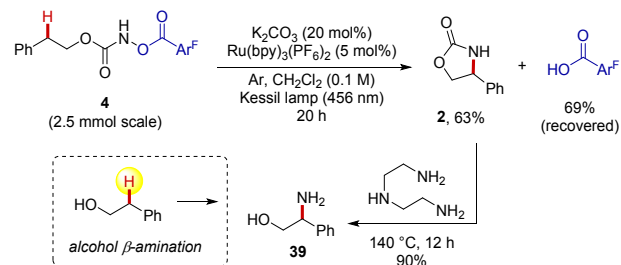
Substrate scope and synthetic utility. With the optimized photosensitization conditions in hand, we subsequently explored the substrate scope to access oxazolidinones and γ -lactams (Table 2). *N*-Benzoyloxy carbamate derivatives with electronic variation on the phenyl moiety all smoothly underwent the cyclization to furnish the corresponding oxazolidinones in moderate to good yields (**8–12**). A substrate possessing the 9-fluorenyl group was also viable for the photosensitized reaction to give a spirocyclic product **13**. Oxazolidinone product (**14**) bearing a quaternary carbon–nitrogen bond could also be obtained. *N*-Benzoyloxy carbamate substrates derived from not only primary alcohols but also secondary (**15** and **16**) and tertiary alcohols (**17**) were fully amenable for the current cyclization protocol. An excellent level of diastereoselectivity was observed in the production of **15**. Interestingly, the cyclization of a substrate bearing two potentially reactive C–H bonds (secondary vs benzylic tertiary) occurred highly selectively at the later position (**16**). It should be emphasized that while the scope of alcohol precursors are broad (1°, 2°, and 3°) in the present approach, the previously reported photoredox-catalyzed intramolecular C–H amination via the amidyl radical intermediacy operates mainly for substrates of tertiary alcohols while those of primary and secondary alcohols were reported to be sluggish.¹⁸ *N*-Benzoyloxy carbamates having β C–H bonds being at the allylic (**18–20**) and propargylic (**21**) position also underwent the desired cyclization. Notably, the stereochemistry of double bonds (*E/Z*) in substrates was not deteriorated during the course of the reaction as exemplified by **18** and **19**.

The applicability of the present photoamination reaction was briefly examined by using substrates prepared from terpene-derived alcohols. Substrate prepared from myrtaanol underwent the desired cyclization exclusively at the tertiary C–H bond (**22**), and the product structure was confirmed by an X-ray crystallographic analysis. The same reactivity pattern towards the quaternary C–N bond formation in the presence of potentially reactive secondary C–H bonds was also observed with substrates derived from isopinocampheol (**23**) and cedrol (**24**) albeit in moderate yields along with free carbamate as a side product.

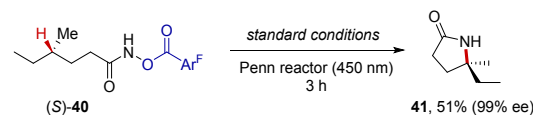
After establishing the photosensitization approach accessing cyclic carbamates, we turned our attention to the γ -lactam synthesis starting from *N*-benzoyloxyamides which can be readily prepared from the corresponding

Scheme 5. Synthetic applicability of the present protocol

(a) Synthetic route to 1,2-aminoalcohol and recovery of released carboxylic acid



(b) Stereoretentive γ -lactam formation

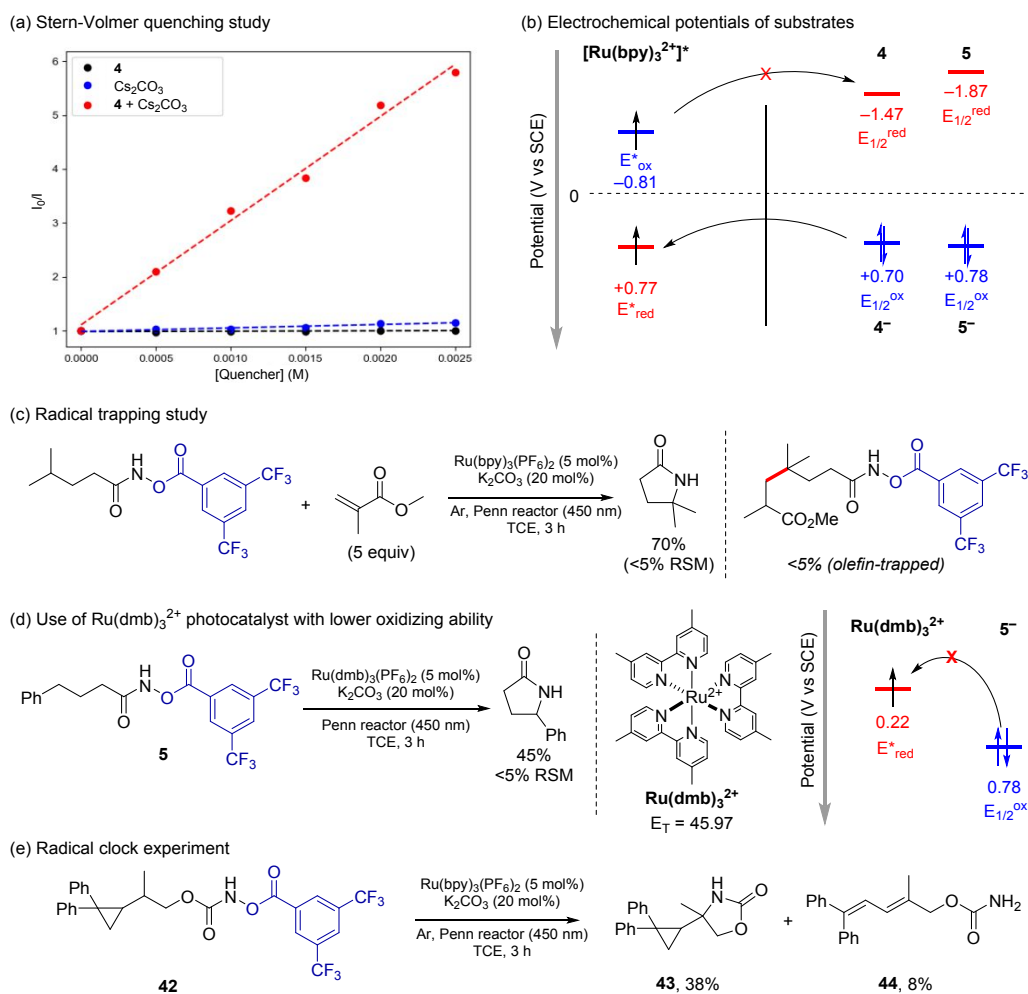


carboxylic acids (Table 2b). This research direction was motivated from our previous reports, where the same lactam products could be obtained by using tailored transition metal catalysts including Ir and Ru species.^{40–44} We were pleased to find that the current photosensitization procedure can also be viable in delivering a broad range of γ -lactams. This reaction was observed to be compatible with methoxy and halide substituents at the phenyl moiety (**26–28**). γ -Lactam product having the thienyl group was obtained in good yield (**29**). Our present system also worked efficiently for the construction of benzofused γ -lactams (**31–32**). Products bearing a quaternary C–N bond were readily obtained (**33–34**). In addition, γ -lactams having allylic (**36**) and propargylic (**37**) chains could be prepared albeit in moderate yield in the former case. Finally, a substrate derived from sclarelolide was cyclized selectively leading to the corresponding γ -lactam (**38**) in moderate yield along with isocyanate as a side product.⁴³ On the other hand, the current amidation was not effective for obtaining 6-membered azacyclic compounds via 1,6-HAT process (see the supporting information for details).

As highlighted in Scheme 5a, the present photosensitization procedure can readily be utilized as a convenient route to 1,2-amino alcohols starting from alcohols.⁵⁵ Importantly, 3,5-bis(trifluoromethyl)benzoic acid was recovered in high efficiency from the cyclization process. In addition, the reaction was observed to proceed in a stereoretentive manner as shown in Scheme 5b (**41**, 99% ee), thus allowing an access to enantioenriched γ -lactams. This result led us to suggest a rapid radical recombination of the postulated 1,4-diradical intermediate before racemization, while an alternative pathway of the singlet nitrene intermediacy cannot be completely ruled out at the present stage.

Mechanistic investigations. To validate our working mode that deprotonated carbamates are a triple acceptor, we carried out a Stern-Volmer quenching experiment. As shown in Scheme 6a, the emission intensity of excited **Ru1** was not changed by the addition of neutral substrate **4**. In stark contrast, in the presence of carbonate base,

Scheme 6. Mechanistic experiments on the triplet energy transfer pathway



luminescence quenching was significantly increased, thus suggesting that the anionic carbamate is active to interact with the excited **Ru**. Moreover, electrochemical potentials of substrates further supported this rationale. The cyclic voltammograms of representative substrates **4** and **5** displayed irreversible reduction features and their half potentials ($E_{1/2}$) were estimated to be -1.47 and -1.87 V vs. SCE, respectively. Since the oxidation potential of the excited **Ru** was known to be -0.81 V vs. SCE,⁵⁶ the single electron reduction of neutral substrates will not be operative as we proposed.

Half potentials of substrates **4** and **5** were measured to be $+0.70$ and $+0.77$ V vs. SCE, respectively, in the presence of KO^tBu base.⁵⁷ Since the reduction potential of excited state of $\text{Ru}(\text{bpy})_3^{2+}$ is 0.77 V vs. SCE,⁵⁶ the obtained electrochemical values indicate that an electron transfer pathway is still a viable alternative working mode in our current photocatalytic reactions. As a result, we next carried out an olefin-trapping experiment which has been generally used as a compelling probe to support the radical intermediacy induced by electron transfer pathways.⁵⁸ When the cyclization was attempted in the presence of an efficient trapping reagent, methyl methacrylate (5.0 equiv), no olefin-coupled compound was observed

(Scheme 6c). This result suggests that an electron transfer pathway cannot be completely ruled out at the present stage, it will be a non-productive process according to our mechanistic studies.

Ruthenium photocatalyst with less oxidizing power was also examined in the current cyclization reaction to gain more mechanistic insights. $\text{Ru}(\text{dmb})_3(\text{PF}_6)_2$ possesses much lower excited state redox potential (0.22 V vs. SCE)⁵⁶ compared to that of **Ru** (0.77 V vs. SCE) while both ruthenium complexes have similar triplet energy ($46 \sim 48$ kcal/mol). When the reaction was performed in the presence of $\text{Ru}(\text{dmb})_3(\text{PF}_6)_2$, the desired lactam product was obtained in 45% yield (Scheme 6d). Considering that fact that this ruthenium photocatalyst $\text{Ru}(\text{dmb})_3(\text{PF}_6)_2$ is insufficient for the oxidation of the deprotonated substrate, the product formation strongly supports that our current amidation operates via an energy transfer pathway.

Unfortunately, our attempts to directly capture triplet nitrene intermediate using an intermolecular reaction of hydroxamate with pyrrole³⁶ or alkene³³ were unsuccessful (see the supporting information for details). On the other hand, when a radical clock experiment was performed, not only cyclization product (**43**) but ring-opened olefinic

compound (**44**) was also formed (Scheme 6e). This result supports our mechanistic proposal that the current cyclization reaction proceeds via stepwise HAT with a fast radical recombination from triplet nitrene although a concerted C–H insertion at the singlet state is not completely ruled out.

Conclusions

Herein, we successfully demonstrated that computationally identified nitrene precursors can be utilized for photosensitized C(sp³)–H amidation reactions. By tuning the key parameters of triplet energy (E_T) and structural reorganization (λ), we could devise readily available hydroxamates bearing N-[3,5-bis(trifluoromethyl)benzoyl] moiety for the photocatalytic production of synthetically valuable 2-oxazolidinones and γ-lactams. The cyclization scope was found to be broad with high functional group compatibility under mild conditions. Mechanistic investigations revealed that the triplet energy transfer pathway is mainly operative. We anticipate that the outlined mechanism-driven strategy to generate reactive organic nitrenes, which are otherwise difficult to access conveniently, will find its broad utility in synthetic chemistry.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures; characterization data; spectra for all new compounds; crystallographic data; Cartesian coordinates of all computed structures (PDF)

Crystallographic data for **4a**

Crystallographic data for **17**

Crystallographic data for **22**

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