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Intermolecular oxidative amination of unactivated alkenes by dual photoredox and copper catalysis†

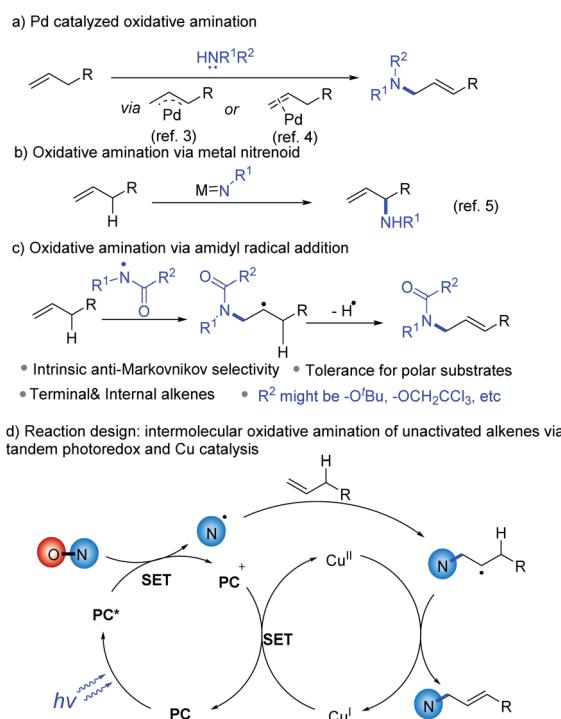
Xiangli Yi and Xile Hu  *

Oxidative amination of alkenes *via* amidyl radical addition is potentially an efficient method to generate allylic amines, which are versatile synthetic intermediates to bioactive compounds and organic materials. Here by combining photochemical generation of amidyl radicals with Cu-mediated β -H elimination of alkyl radicals, we have developed an intermolecular oxidative amination of unactivated alkenes. The reaction relies on tandem photoredox and copper catalysis, and works for both terminal and internal alkenes. The radical nature of the reaction and the mild conditions lead to high functional group tolerance.

Oxidative amination of alkenes¹ is a versatile method to synthesize allylic amines and related nitrogen-containing compounds, which are prevalent in bioactive molecules and organic materials.² Pd-catalyzed allylic C–H activation is an efficient approach to synthesize allylic amines (Scheme 1a), yet so far only mono-substituted terminal alkenes are suitable substrates.³ Anti-Markovnikov oxidative amination *via* amino-palladation⁴ is another potentially versatile method (Scheme 1a), but at this stage chain-walking is a problem for many substrates. Allylic amines can also be prepared by allylic C–H insertion of metal-nitrenoid of alkenes typically with a branch selectivity (Scheme 1b).⁵ These methods have generally limited tolerance for substrates containing highly polar or nucleophilic moieties. Addition of amidyl radical, typically stabilized by an electron-withdrawing group, to an alkene followed by elimination of β -H provides an alternative strategy to effect the oxidative amination (Scheme 1c). This strategy has intrinsic anti-Markovnikov selectivity, is potentially suitable for internal alkenes and the radical nature of the reaction is compatible with polar substrates, which are important for industrial applications.⁶

Amidyl radical addition to alkenes for intramolecular cyclization⁷ and the intermolecular addition to activated alkenes⁸ have been well explored. Unactivated alkenes are more challenging substrates for intermolecular amidyl radical addition because the carbon radical formed upon addition are not stabilized by a heteroatom or aryl group as in the case of activated alkenes. The high reactivity of these radical intermediates makes selective further functionalization harder. Elegant approaches have been developed to trap such C-radicals by

a hydrogen donor⁹ or a SOMophile¹⁰ or a Cu(II)–CF₃ species¹¹ for further functionalization. However, oxidative amination of unactivated alkenes *via* amidyl radical addition is rarely applied for the synthesis of allylic amines. During the preparation of this manuscript, the group of Ritter reported an elegant method for allylic amination through addition of aminium radicals generated from energy transfer between a photocatalyst and iminothianthrenes under illumination to alkenes.¹² Radical–radical cross-coupling between the resulting carbon radical and



Laboratory of Inorganic Synthesis and Catalysis, Institute of Chemical Sciences and Engineering, École Polytechnique Fédérale de Lausanne (EPFL), Lausanne 1015, Switzerland. E-mail: xile.hu@epfl.ch

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persistent thianthrenium radical followed by elimination, or oxidation of the carbon radical by thianthrenium radical followed by deprotonation furnishes the products. Here we report an alternative approach based on synergistic photoredox and Cu catalysis.

Cu has been reported to mediate β -H elimination of alkyl radicals to produce alkenes.¹³ Recent reports described facile generation of an amidyl radical *via* reduction of a hydroxyl-amine precursor by an excited state of a photoredox catalyst.^{7f,14} In this context, we envisioned synergistic photoredox and Cu catalysis for oxidative amination of unactivated alkenes (Scheme 1d). The photochemically generated amidyl radical adds to an alkene to give an alkyl radical, which is trapped by a Cu species. The latter undergoes β -H elimination to give the desired allylic amine and a reduced Cu species, which can be oxidized back to the initial Cu catalyst by the oxidized photocatalyst. Here we describe the successful development of such a process.

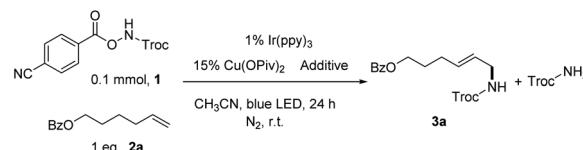
Studer and co-workers showed that oxidation of α -amido-oxy acids by a photoexcited catalyst gave a carboxyl radical, which transformed into an amidyl radical after CO_2 and aldehyde/ketone fragmentation.^{9a,10b,e} They also showed that these electrophilic amidyl radicals could add to unactivated alkenes for eventual amidofluorination and carboamination.^{9a,10b,e} Inspired by these studies we explored various *N*-(benzoyloxy)carbamates as sources of amidyl radicals under photoredox conditions (Scheme S1†). We found that **1**, with a Troc-protection (Troc = 2,2,2-trichloroethoxycarbonyl), could react with alkene **2a** to afford the allylic amine derivative **3a** in 38% yield (Table 1, Entry 1), when 1% of Ir(ppy)₃ (ppy = 2-(2-pyridinyl)phenyl) was used as a photocatalyst and 15% of Cu(2-ethylhexanoate)₂ was used as a metal catalyst. Troc-NH₂ was the main side product and diamination was not observed. The reaction conditions were

then optimized (Tables S1–S4, ESI†). A summary is provided in Table 1. The use of Cu(OPiv)₂ as metal catalyst improved the yield to 42% (Entry 2), while Cu(OTf)₂ was not able to catalyze the reaction (Entry 3). Addition of 1 equiv. of Zn(OPiv)₂ (Entry 4) or Mg(OPiv)₂ (Entry 5) decreased the yield, yet 1 equiv. of Mg(OPiv)₂ and H₂O slightly increased the yield to 44% (Entry 6). Notably, the addition of H₂O resulted in a precipitate during the reaction, which was analyzed as mainly Mg(4-cyanobenzoate)₂ \cdot xH₂O. The replacement of Ir(ppy)₃ by Ir(dfppy)₂(ppy) (dfppy = 2-(2-pyridinyl)-3,5-difluorophenyl) further increased the yield to 49% (Entry 7). Increasing the amount of alkene to 2 equiv. and 3 equiv. increased the yield to 59% and 64%, respectively (Entries 8 and 9). A slow generation of the amidyl radical by slow addition of **1** to the reaction mixture improved further the yield of **3a** to 77% (70% after isolation, Entry 10).

Based on the optimal conditions, we examined the scope of terminal alkenes (Fig. 1). Remote electrophilic functionalities such as bromide (**2b**), iodide (**2c**), and terminal epoxide (**2d**) were all tolerated to afford the products in good yields (**3b**–**3d**, 66–75%). Alcohol (**2e**) and amide (**2f**) were also compatible. A range of alkenes containing a terminal carboxylic acid group were tested. 9-Decenoic acid (**2g**), 5-hexenoic acid (**2h**) and 4-pentenoic acid (**2i**), but not 3-butenoic acid, were successfully aminated. The products were isolated after methylation as methyl esters in moderate yields (50–53%). Polar substrates (**2j**, **2k**), derived from L-phenylalanine and L-threonine, respectively, were also viable for this reaction. When a more electron-deficient alkenyl group was present in the internal position (**2l**, **2m**), amination of the terminal alkenyl group was dominant, consistent with electrophilic nature of the amidyl radical.^{14a}

Next, alkenes with various substitutions at the C3 position were examined. A bulky substituent, such as cyclohexyl (**2n**),

Table 1 A brief summary of reaction optimizations^a



Entry	Variations	Additives	Yield ^b /%
1	Cu(2-ethyl hexanoate) ₂ instead of Cu(OPiv) ₂	—	38
2	—	—	42
3	Cu(OTf) ₂ instead of Cu(OPiv) ₂	—	0
4	—	1 eq. Zn(OPiv) ₂	21
5	—	1 eq. Mg(OPiv) ₂	38
6	—	1 eq. Mg(OPiv) ₂ + 1 eq. H ₂ O	44
7	Ir(dfppy) ₂ (ppy) instead of Ir(ppy) ₃	1 eq. Mg(OPiv) ₂ + 1 eq. H ₂ O	49
8	Ir(dfppy) ₂ (ppy) instead of Ir(ppy) ₃ , 2 eq. 2a	1 eq. Mg(OPiv) ₂ + 1 eq. H ₂ O	59
9	Ir(dfppy) ₂ (ppy) instead of Ir(ppy) ₃ , 3 eq. 2a	1 eq. Mg(OPiv) ₂ + 1 eq. H ₂ O	64
10 ^c	Ir(dfppy) ₂ (ppy) instead of Ir(ppy) ₃ , 3 eq. 2a , 10% Cu(OPiv) ₂	1 eq. Mg(OPiv) ₂ + 1 eq. H ₂ O	77 (70 ^d)

^a Conditions: all reagents of indicated amount dissolved in 1 mL CH₃CN in a glass vial (*d* = 2 cm), blue LED radiation for 24 h. ^b NMR yield with mesitylene as an internal standard. ^c Slow addition procedure: 0.02 mmol **1** and all other reagents were dissolved in 0.2 mL CH₃CN; the rest of **1** (0.08 mmol) was dissolved in 0.4 mL CH₃CN; the latter was added at 1.2 $\mu\text{L min}^{-1}$ to the former after reaction starts. ^d Isolated yield.



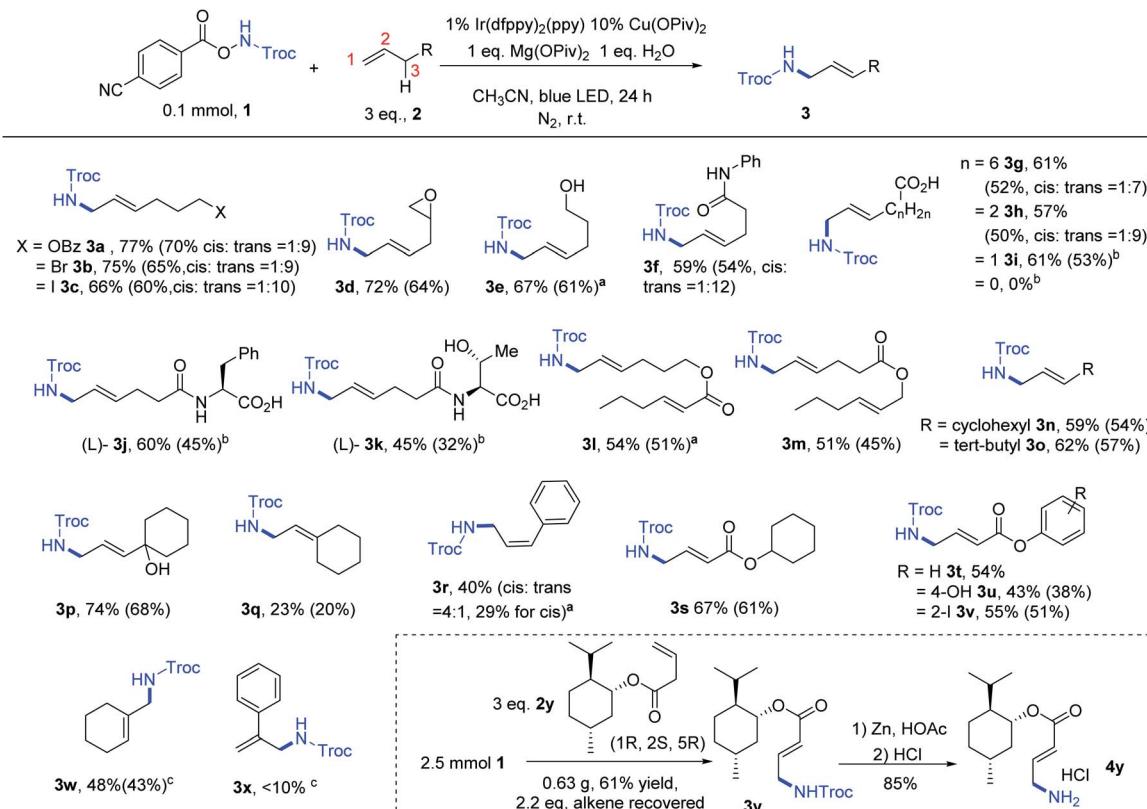


Fig. 1 Scope of terminal alkenes for the oxidative amination. Reaction conditions: same as Table 1, Entry 10. NMR yields and isolation yields (in the bracket) are shown. ^a Reaction conditions: same as Table 1, Entry 9. ^b Reaction conditions: same as Table 1, Entry 2. Products were isolated after methylation as esters. ^c Reaction conditions: based on Table 1, Entry 9, acetone as solvent.

tert-butyl (2o) and 1-hydroxycyclohexyl (2p), didn't deteriorate the reaction yield. However, double substitutions at C3 decreased the yield (3q, 23%). In the case of a phenyl substitution (2r), 3r was obtained in 40% yield, with the *cis*-alkene as the major isomer.¹⁵ Although 3-butenoic acid was not a suitable substrate, the esters of 3-butenoic acid could be used for the generation of α,β -unsaturated esters (3s–3v). 4-Hydroxyl (2u) and 2-iodo (2v) groups on the phenyl substituent were tolerated against potential oxidation or dehalogenation. The reactions of 1,1-disubstituted alkenes gave lower yields of the target products (48% for 3w, <10% for 3x). The reaction of 2y was successfully scaled up to 2.5 mmol, giving 0.63 g of 3y as product (61% yield). The latter can be easily deprotected to give the primary amine 4y. Notably, the majority of the excess alkene 2y could be recovered (1.23 g, 2.2 equiv.).

The oxidative amination method was then applied on internal alkenes (Fig. 2). The transformation was effective when the alkenes were symmetrically substituted, such as cyclohexene (2z), cyclopentene (2aa), and 4-octene (2ab). The reactions of *trans*-4-octene and *cis*-4-octene gave similar yields of 3ab. The reaction of an unsymmetrically substituted alkene, *e.g.*, 2-octene, had a good yield but poor regioselectivity (3ac–1 : 3ac–2 = 1.4 : 1). When 2-hexen-1-ol was used as the substrate, amination at the 2 position (3ad) was dominant (58% yield) compared to amination at the 3 position (5ad, 16% yield). Analogous allylic alcohols (2ae–2ag) were aminated, with

modest to good yields (33% to 61%). The diastereoselectivity was low despite having a bulky substituent adjacent to the alcohol group. The reaction of a trisubstituted alkene 2ah gave 3ah in 51% yield. The allylamine derivative 2ai reacted to give 3ai in 60% yield. Esters (2aj and 2ak) reacted to give both allylic amines (3aj and 3ak) and aziridines (6aj, 6ak) in similar yields.

A preliminary mechanistic study was conducted for the reaction. First, the fluorescence quenching of Ir(dfppy)2(ppy) by different reagents was probed (Fig. S1†). Among all reagents used in the reaction, only 1 and Cu(OPiv)2 could significantly quench the excited photocatalyst. In the corresponding Stern–Volmer plots (Fig. S2 and S3†), the slopes, which are proportional to the quenching coefficients, are 9955 M^{-1} and 2438 M^{-1} for 1 and Cu(OPiv)2, respectively, suggesting 1 as a more efficient quencher. Additionally, according to cyclic voltammetry (Fig. S5†), the reduction potential of 1 ($E_{\text{red}}(1) = -1.43\text{ V vs. SCE}$) is less negative than the oxidation potential of the excited photocatalyst ($E(\text{Ir}^{\text{IV}}/\text{Ir}^*) = -1.56\text{ V}$), indicating that oxidative quenching of the excited state of Ir(dfppy)2(ppy) by 1 is thermodynamically downhill. To probe the possibility of energy transfer between 1 and the excited photocatalyst, we tested the oxidative amination using Ir(dfCF₃ppy)₂(dtbbpy)PF₆ (dfCF₃ppy = 3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-N]phenyl, dtbbpy = 4,4'-di-*tert*-butyl-bipyridine) or 4CzIPN (1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene) as the photocatalyst (Scheme 2a). These complexes have similar triplet energies to



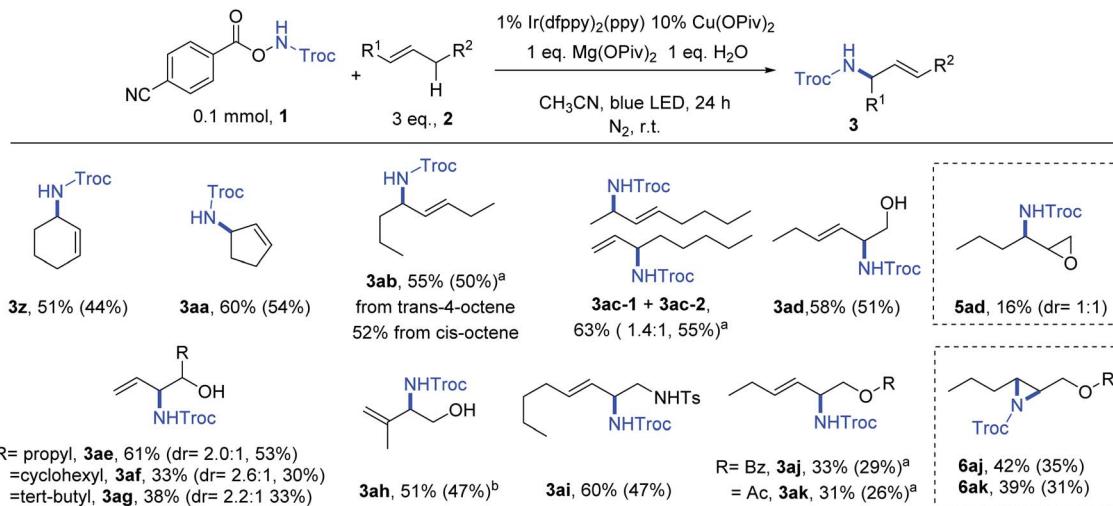
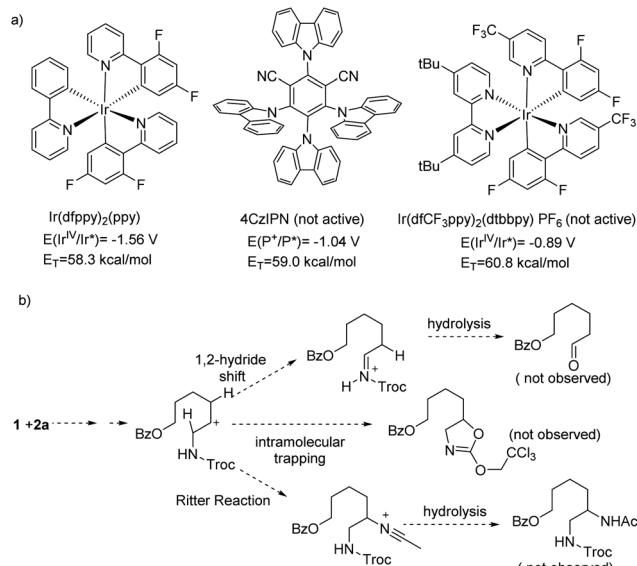


Fig. 2 Scope of internal alkenes for oxidative amination. Reaction conditions: same as Table 1, Entry 10. NMR yields and isolation yields (in the bracket) are shown. ^a Reaction conditions: same as Table 1, Entry 9. ^b Reaction conditions: based on Table 1, Entry 9, acetone as solvent.

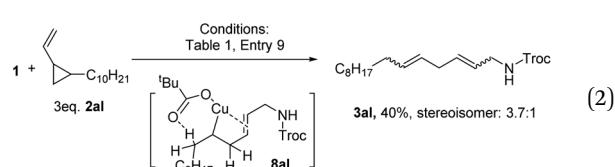
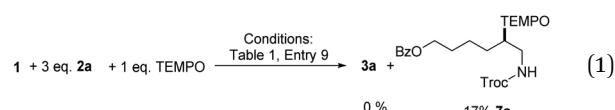


Scheme 2 (a) Comparison of oxidative quenching potentials and triplet energies of several photocatalysts. (b) Absence of possible subsequent reactions with a possible carbocation intermediate in the reaction of 1 with 2a.

Ir(dfppy)₂(ppy) but they have a less reducing excited state (-0.89 V (ref. 16) and -1.04 V,¹⁷ respectively). No oxidative amination was observed using these two photosensitizers. This result indicates energy transfer is not the likely pathway for the generation of the amidyl radical.

To verify the radical nature of this reaction, 1 equiv. of TEMPO (TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl) was added to the reaction mixture of 1 and 2a (eqn (1)). The oxidative amination product 3a was not obtained, but the TEMPO adduct 7a was isolated in 17% yield. Additionally, the reaction of substrate 2aI containing a cyclopropyl substituent, which served as a radical clock, yielded product 3aI where the

cyclopropyl ring was opened (eqn (2)). These results indicate the formation of a carbon radical upon amidyl radical addition. It is conceivable that this carbon radical is further oxidized to a carbon cation en route to alkene. Nevertheless, in the reaction of 1 with 2a, we did not observe products that would arise from 1,2-hydride shift,¹⁸ intramolecular nucleophilic trapping, or Ritter reaction of a carbon cation intermediate (Scheme 2b). This result suggests a free carbon cation is an unlikely intermediate.

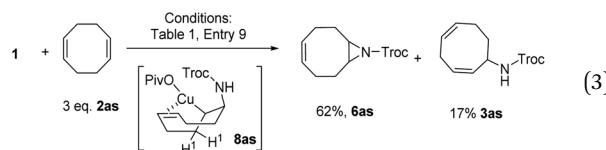


During the investigation of reaction scope, we observed a competition between elimination of β -H and cyclization for substrates with a pendant nucleophilic group ($-\text{OH}$ or $-\text{NHTs}$, 2am–2ar; Scheme 3). When there is one carbon between the alkene and nucleophilic groups, only cyclization was observed (5am, 5ap). When there are two carbons, only elimination was observed (3an, 3aq). When there are 3 carbons, cyclization was favored (5ao, 5ar), yet the product of elimination (3ar) was still obtained if the nucleophilic group was $-\text{OH}$. Cu^{II} species have been reported to mediate cyclization of alkyl radical with a nucleophile.¹⁹ In the present case, we envisage a Cu–alkyl species 8 in which the nucleophilic group coordinates to Cu as the intermediate to cyclization after reductive elimination. The observation of cyclization products supports the formation of

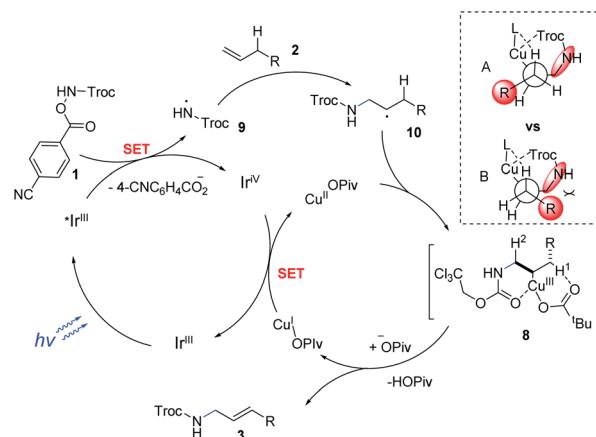


a Cu-alkyl intermediate upon trapping of the carbon radical by a Cu species.

Interestingly, when cyclooctadiene **2as** was applied as a substrate (eqn (3)), aziridine **6as** was obtained as the main product (62%) instead of **3as** (17%). This result might be rationalized by the coordination of Cu in **8as** by the alkene moiety. The coordination could shield H¹ from accessing the Cu center so that elimination of H¹ is suppressed. Consequently C–N reductive elimination to give the aziridine product **6as** is favored. This rational might be applicable to explain the generation of **6aj** and **6ak** as in these cases the ester group of the alkenes could act as a coordinating group. The coordination of Cu by an internal alkene moiety as in intermediate **8al** (eqn (2)) might rationalize the generation of a skipped diene **3al** instead of a conjugated diene in the reaction of **1** with **2al**.



Taking into account the above results, we proposed a plausible catalytic cycle (Scheme 4). The reaction starts from the oxidative quenching of the excited photocatalyst by **1**, which generates the amidyl radical **9** while releasing a carboxylate. The addition of **9** to the alkene **2** leads to the alkyl radical **10**, which is then trapped by a Cu^{II}-pivolate species to give a formal Cu^{III}-alkyl species **8**. The latter undergoes elimination of β-H to form the allylic amine **3** and a Cu^I species¹³ which is oxidized back to the starting Cu^{II} by the oxidized photocatalyst Ir^{IV}. Note that the alkene formation has an exclusive *E*-selectivity. This selectivity can be attributed to the higher stability of the A conformer over the B conformer of the Cu-alkyl intermediate (Scheme 4, right).^{13a} Based on precedents,^{13b,13e} we propose that the elimination step is assisted by the pivolate ligand. To explain the regioselectivity for H elimination in **8**, we propose that the



Scheme 4 The proposed reaction mechanism.

coordination of the Troc group to Cu^{III} prevents the H² to be accessed by the carboxylate so that elimination of H¹ dominates.^{13b} The influence of intramolecular coordination to the reaction selectivity was evidenced by the products of several substrates (e.g., **2al**, **2as**).

Conclusion

In summary, by integrating photochemical generation of amidyl radicals with Cu-mediated β-H elimination of alkyl radical *via* a tandem photoredox and copper catalysis, we developed an intermolecular oxidative amination of unactivated alkenes. The method can be used to synthesize a wide range of allylic amines, from readily available alkenes, with high functional group tolerance. The work broadens the scope of oxidative amination of alkenes *via* amidyl radical addition.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Scheme 3 Reactions of substrates with a tethered nucleophilic group: competition between cyclization and elimination. Conditions: same as Table 1, Entry 9.



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