Azetidine synthesis enabled by photo-induced copper catalysis via [3+1] radical cascade cyclization

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GRAPHICAL ABSTRACT

PUBLIC SUMMARY

- Azetidines, four-membered N-heterocyclic compounds, are valuable targets for synthesis
- The first [3 + 1] cyclization approach is enabled by visible-light-induced copper catalysis
- This atom economic synthesis is characterized by double C-H activation
- This technology features operational simplicity, cheap catalyst, and broad substrate scope
Azetidines are an important type of saturated, highly strained, four-membered, nitrogen-containing heterocyclic compound. These compounds serve as important raw materials, intermediates, and catalysts in organic synthesis, as well as important active units in amino acids, alkaloids, and pharmaceutically active compounds. Thus, the development of an efficient and concise method to construct azetidines is of great significance in multiple disciplines. In this work, we reported on the photo-induced copper-catalyzed radical annulation of aliphatic amines with alkenes to produce azetidines. This reaction occurred in a two- or three-component manner. The alkenes efficiently captured photogenerated azaminoalkyl radicals, forming vinyl radicals, which initiated tandem 1,5-hydrogen atom transfer and 4-exo-trig cyclization. Density functional theory calculations indicated that the tertiary radical intermediate was critical for the success of cyclization. In addition, the resulting saturated azetidine scaffolds possessed vicinal tertiary-quaternary and even quaternary-quaternary centers.

INTRODUCTION

Azetidines are four-membered saturated nitrogen heterocycles that are widely used in medicinal chemistry, as they offer rigidification and novel chemical space.6–8 (Figure 1A). Specifically, the incorporation of azetidine blocks has been shown to enable scaffold hopping,16,17 which can result in improved pharmacokinetic properties and metabolic stability.18–21 Thus, the incorporation of rigid scaffolds into drug design may lead to more compounds as drug candidates in the pharmaceutical industry. In addition, azetidines can be used as synthetic building blocks.7–19 Although the introduction of azetidines into complex molecules is highly desirable, this process is often encumbered by the limited number of efficient, robust methods for the generation of highly strained four-membered rings.

Traditional azetidine synthesis methods include the cyclization of a linear precursor, robust methods for the generation of highly strained four-membered rings.6–8 Despite these developments, the intrinsic ring strain and its steric hindrance around C2 possibly broke the 2c-3e interactions and suppressed the 1,5-hydrogen atom transfer (HAT)/intramolecular cyclization process,45–47 while few studies have reported on 5-endotrig cyclization leading to five-membered rings,48 and studies on alternative 4-exo-trig cyclization leading to 4-membered-rings are very limited. We were motivated by the potential utility of the intermolecular [3 + 1] cascade cyclization reaction, which could greatly broaden the substrate scope and substitution patterns of currently available protocols for azetidine synthesis. Thus, in this work, we decided to explore feasible photocatalysts and aliphatic amines.

Photoactive copper (Cu) complexes have advanced beyond their role as a cheap complement to noble metal photosensitizers and have shown unique catalytic properties in many important photochemical reactions.22–24 Notably, Cu exhibits a persistent radical effect due to multiple accessible oxidation states with highly tunable redox properties. Liu recently reported on the efficient synthesis of allylarenes by the photo-induced, Cu-catalyzed cross-coupling of tertiary amines with aromatic alkenes (Figure 1C),25,26 and heteroleptic Cu (I)(Xantphos)(2,9-disopropyl-1,10-phenanthroline)PF6 was used as the photosensitizer. The mechanism study showed that the intermediate of the azaminoalkyl radical27–29 was added to the alkene, followed by vinyl radical 1,5-HAT. The product split out through downstream C-N bond homolytic cleavage. Although efficient, this method was limited to aryl alkenes and linear alkyl amines with an unproductive loss of more valuable amine functionality. We hypothesized that the cleavage of the C1-N3 bond would be the result of favorable two-center-three-electron (2c-3e) interactions between the radicals and adjacent nitrogen lone pair, which strengthened the C1-N2 bond but weakened the C1-N3 bond. The introduction of steric hindrance around C2 possibly broke the 2c-3e interactions and suppressed the C-N bond cleavage pathway, thus offering an opportunity to access novel reactivity.46 As a result, the intramolecular ring-closing reaction could occur, resulting in formal [3 + 1] cyclized products (e.g., azetidine).

In line with our continuing interest in photoredox copper catalysis,30,31 in this work, we reported on the successful implementation of this hypothesis. Under blue-light irradiation, Cu catalyzed the selective annulation of tertiary amines with a large variety of alkenes, which were involved in the functionalization of both C(sp3)-H bonds at the a-position of the nitrogen atom (Figure 1D). This strategy could be successfully extended to the three-component radical tandem cyclization reaction, and the use of different aldehydes could greatly improve the substrate scope of this method. This method constituted a new atom-economic intermolecular cycloaddition strategy for the production of densely substituted but saturated small N-heterocycle azetidines, which have shown potential as saturated polar molecules for drug discovery.41,42 The use of visible light and a cheap photocatalyst would also make this transformation substantially more general and applicable to the pharmaceutical industry. In addition, it could also serve as a novel example for challenging double sp3 C-H activation.43–46

RESULTS

Investigations of the reaction conditions were carried out using 4-ethyl-1,1′-biphenyl (1a) and DiPEA as the sole test substrates for the proof of concept (e.g., cyclization before over-reduction), and the desired radical cascade cyclization product azetidine 4a was formed. After extensive condition optimization, azetidine was isolated with 93% yield, with a negligible quantity of other products (entry 1, Figure 2).
Notably, the most effective Cu(I) photosensitizer was [(DPEphos)(bcp)Cu]PF$_6$, PS$_4$. The product yields of the reactions by other Cu-based photosensitizers, such as dipyridine L$_1$+CuI, tripyridine L$_2$+CuI, homoletic N/N Cu(I) PS$_3$, and heteroleptic P/N Cu(I) photosensitizers (PS$_5$, PS$_6$, and PS$_7$) were generally lower than PS$_4$ (entries 2–7, Figure 2). In addition, the steric hindrance derived from isopropyl substitution on PS$_5$ could weaken the potential interactions of copper with the alkynes through π-acid activation. Azetidine formation was due to the formation of a tertiary alpha-amino carbon-centered radical, which underwent favored 4-exo-tet cyclization rather than C-N bond cleavage. Common photocatalysts, such as Ru(bpy)$_3$Cl$_2$ $\cdot$ 6H$_2$O (entry 8), were inert in this reaction, while for the organic photosensitizers, rose bengal had no catalytic activity in this reaction (entry 9, Figure 2). When Et$_3$N (2 equiv) was used as the reducing and reacting agent, we obtained allylbenzene 3a as the major product (75%) (entry 12, Figure 2). Through systematic screening, we found that when acetonitrile was used as the solvent, the amine to alkyne ratio was crucial for obtaining 3a (entries 10 and 11, Figure 2). Control experiments showed that the photosensitizer and light were essential for double functionalization (entry 14, Figure 2). Of note, the dr ratio of 4a was always greater than 20/1, which was not affected by the noted parameters.

Scope and limitation of the reaction

With the optimized conditions identified (entry 1, Figure 2), we subsequently evaluated the generality of a wide range of alkynes for this radical cascade cyclization reaction (Figure 3). Various arylalkynes could react under the
optimal conditions, giving fully substituted azetidines with good to excellent yields (4b–4n), depending on whether they were electron deficient, with substitutions such as CF₃, CN, sulfonamide, and amide (4c–4g), or electron rich, with substitutions such as Me, t-Bu, and OMe (4h–4j). Of note, the electronic properties and steric hindrance had little effect on the reaction. In addition, the halogen atoms (e.g., Br, Cl, F) were also compatible (4k–4n), thus providing potential opportunities for further functionalization. Furthermore, 2-ethynylpyridine also reacted with DIPEA, allowing for the introduction of heteroaromatics into this system (4o). Trimethylsilylacetylene and ethyl propionate could also react, in addition to arylacetylene, which greatly broadened the functional group scope of this methodology (4p, 4q). When inner alkynes were used, such as arylalkyl alkynes, the [3 + 1] radical cascade cyclization reaction also proceeded well, providing a highly functionalized azetidine ring that contained two adjacent quaternary carbon centers (4r, 4s). Ethyl butyrate was a competent substrate, which further increased the diversity of the products (4t).

We further used more complex alkynes, such as cholesterol and estrone derivatives, and the reactions furnished the desired products 4u and 4v in moderate to good yields, providing the possibility of late-stage modification of complex molecules. Moreover, the anticancer drug molecule erlotinib could be easily converted into an azetidine derivative (4w), showcasing the potential of this method for pharmaceutical agent exploration. We subsequently explored the scope of the amines by varying three substituents of potential tertiary amines (Figure 3). Initial
α-aminoalkyl radical formation required an unsubstituted linear alkane moiety, and in this regard, ethyl, methyl (6a), and benzyl (6b, 6c) were allowed. Further scope studies revealed that one of the other two substituents of amine required a secondary carbon, such as isopropyl or cyclic alkane (6d, 6e). A spiro-structure could also be generated in the system, potentially offering a promising drug architecture.1 Because of ring strain, no [3 + 1] ring-closing reaction could take place in the cyclic tertiary amines. Notably, only alkylamines were feasible substrates under the current conditions, as we did not observe radical initiation in the aryl amines or amides (see supplemental information for more details).

We further assessed the feasibility of a multicomponent reaction with acetylenes, aldehydes, and amines, offering the potential for the uniquely efficient synthesis of azetidines from easily available starting materials (Figure 3). By slightly changing the conditions, the corresponding product 7a could be isolated with an acceptable yield using the Hantzsch ester as the reducing agent. Next, we investigated the scope of the aldehydes, and the results are shown in Figure 3. A range of linear (n-Pen) or branched (i-Pr, c-Hex) aldehydes was compatible with the optimal reaction conditions (7b–7e), and the functional group (e.g., Cl-, MeOOC-, and phenyl- or heteroaryl-) tethered linear aldehydes reacted equally well (7f–7i). Citronellal was also a viable substrate under the current reaction conditions (7j), and the alkynes and amines could be readily varied, resulting in diversified products (7k, 7l).

Figure 3. Substrate scope study
Mechanistic observations

To further understand the reaction mechanism, we carried out several mechanistic experiments (Figure 4). First, the reaction was carried out in the presence of 2 equiv of TEMPO, and the reaction was completely inhibited (Figure 4A). In addition, we did not observe the TEMPO-trapped adduct. Next, when the reaction was carried out under standard conditions in the presence of 2 equiv of D₂O, deuterated 4a with a D enrichment rate of 30% at the benzylic position was isolated with 70% yield (Figure 4B), suggesting that the proton source promoted the final protonation of the active intermediate. Deuterium enrichment of 35% at the 3-position of azetidine was possibly due to copper-assisted deuteration of acetylene-hydrogen under basic conditions.56 This was further supported by the control experiment. In the presence of 2 equiv of D₂O, substrate 8 was isolated with a D enrichment rate of 94% (Figure 4C). Next, when the reaction was carried out under standard conditions in the presence of d₈, the substrate 4a was isolated with 63% deuterium enrichment at the 3-position of azetidine and 24% deuterium enrichment at the benzylic position, possibly from d₈ (Figure 4D). Accordingly,
using alkene as the substrate instead of alkyne in the three-component reaction, the formation of tertiary amine 9 supported the generation of the \( \alpha \)-amino radical, from the secondary amine and aldehyde (Figure 4E). With propargyl amine, the potential cross-dehydrogenative-coupling (CDC) product was subjected to the standard condition, and 4a was not observed, suggesting that the CDC pathway was less likely (Figure 4F).71–73

DFT calculations
To better understand how the different substituents resulted in the distinct reaction pathways, we carried out density functional theory (DFT) calculations. The calculations that used the tertiary radical D revealed that cyclization was kinetically preferred over C-N bond cleavage by 2.4 kcal/mol (Figure 5A), which agreed well with the experimentally observed chemoselectivity. The chemoselectivity was almost completely reversed (cyclization versus C-N bond cleavage), changing from the tertiary D radical to the secondary D• radical. Thus, C-N bond cleavage was favored over cyclization by 2.8 kcal/mol. This reversal in chemoselectivity was largely attributed to the more favorable orbital interactions between the singly occupied molecular orbital (SOMO) and the olefin \( \pi \) orbital in the tertiary radical D, compared to the secondary radical D•. This was likely due to the steric effect, where the tertiary radical was distorted out of the plane of N1C2C3C4, and the SOMO pointed toward the olefin \( \pi \) orbital. Consequently, the tertiary radical was already in the near-attack conformation for cyclization. In sharp contrast, the SOMO pointed away from the olefin \( \pi \) orbital in the secondary radical D•, which strengthened the C1-N2 bond but weakened the C1-N3 bond. Accordingly, the C1-N3 bond cleavage pathway dominated.

DISCUSSION
Based on experimentation and the studies found in the literature,38,40,43,45–51,69,74 we proposed a mechanism for the cycloaddition reaction in this study (Figure 6). First, for the two-component reaction, the excited state of PS4 Cu(I)* \([E_{1/2}(CuI*/Cu0) = +0.63 \text{ V versus SCE}]\) was reduced by diisopropyl ethylamine (0.68 V versus SCE in MeCN), forming amino radical cation species A through a single-electron oxidation process.57 Second, an \( \alpha \)-aminoalkyl radical B was generated through deprotonation. The addition of \( \alpha \)-aminoalkyl radicals to alkynes yielded vinyl radical species C, which further underwent a key 1,5-HAT process that produced a new tertiary radical D. The tertiary carbon radicals underwent 4-exo-trig type cyclization. In addition, azetidine formation occurred with high dr,
thus, favoring the anti-diastereomer. This configuration was rationalized using a steric-based model through the less-strained transition state from D to E. Third, the radical E was reduced by the Cu(0) complex \( E_{1/2}(\text{CuI}/\text{Cu0}) = -1.63 \text{ V versus SCE} \) and protonated to yield the final product 3a. The reaction of the three components proceeded along a similar pathway with slight adjustments. The condensation of different aldehydes and secondary amines led to iminium ions. In the absence of DIPEA, photoexcited [(DPEphos)(bcp)Cu]* was quenched by the Hantzsch ester (0.79 V versus SCE in MeCN), resulting in the Cu(0) complex, which underwent SET with the above iminium ions, leading to the key \( \alpha \)-aminoalkyl radical B.58 Subsequently, a similar process occurred, which finally resulted in the product.

To our knowledge, this was the first study to develop the intermolecular [3 + 1] radical cascade cyclization of tertiary alkylamines with alkynes, involving two \( \alpha \)-amino C(sp\(^3\))-H bonds that were functionalized by photoredox copper catalysis, thereby giving highly functionalized but saturated azetidines. The success of the three-component reaction could further expand the scope of the substrates. This methodology introduced the medicinally relevant N-heterocyclic ring system into the complex molecular environment, thus allowing for the late-stage modification of drugs and natural product derivatives. This methodology could be applied to synthetic and medicinal chemistry.

**MATERIALS AND METHODS**

**Resource availability**

**Lead contact.** Further information and requests for resources should be directed to and will be fulfilled by the lead contact.

**Materials availability.** All materials generated in this study are available from the lead contact without restriction.

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**Figure 6. Proposed reaction mechanism**

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**General procedure for the synthesis of azetidines via visible-light-mediated intermolecular radical cascade cyclization**

In a glove box, a 3-mL sealed vial was equipped with a magnetic stirring bar and was charged with [(DPEphos)(bcp)CuPF\(_6\)] (0.010 mmol, 5 mol%), DIPEA (0.4 mmol, 2.0 equiv), and terminal alkyne (0.2 mmol, 1 equiv). Then, 1 mL of anhydrous CH\(_3\)CN (1.0 mL) was added, and the vial was sealed with screw caps and removed from the glovebox. The reaction mixture was stirred under a nitrogen atmosphere at room temperature under a blue LED for 24 h, where the vial distance from the lamp was about 1–3 cm. The resulting mixture was passed through a silica gel pad and concentrated under reduced pressure. Then, the residue oil was purified by column chromatography and rinsed with hexane/EtOAc to afford the products.

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AUTHOR CONTRIBUTIONS

Conceptualization, G.Z. and J.L.; methodology, J.L.; investigation, J.L, B.C., G.R., and X.M.; writing – original draft, G.Z.; writing – review & editing, G.Z., Y.L., J.L., and X.X.; DFT calculations, X.X. and L.Y.; funding acquisition, G.Z.; supervision, G.Z.

DECLARATION OF INTERESTS

The authors declare no competing financial interests.

DATA AND CODE AVAILABILITY

Characterization and spectra of new compounds are included in the supplemental information.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.xinn.2022.100244.

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